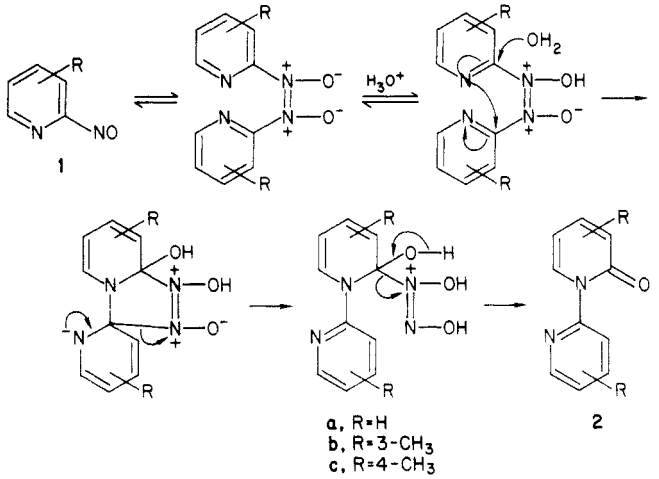
Scheme I



place upon stirring **1a** in 25% dioxane/aqueous phosphate buffer (pH 7.5–8.0) for 7 days; under these conditions, unchanged starting material was recovered in 80% yield.

Analogous transformations of 3-methyl-2-nitrosopyridine (**1b**) and 4-methyl-2-nitrosopyridine (**1c**) to **2b** and **2c**, respectively, proceeded more slowly. For example, no reaction was observed upon stirring aqueous suspensions of **1b** and **1c** in water for 15 days at room temperature. However, refluxing of these aqueous suspensions resulted in slow dissolution and the formation of the 1-(2-pyridyl)-2(1*H*)-pyridones **2b** and **2c**, respectively. In the latter case a small amount of 4-methyl-2(1*H*)-pyridone was also isolated. Once again, the rate of transformation of these methyl-substituted 2-nitrosopyridines to **2b,c** was markedly enhanced by acid. Thus, the addition of one drop of concentrated sulfuric acid to an aqueous solution of the above 2-nitrosopyridines at room temperature resulted in the formation of **2b** and **2c**, respectively, in excellent yield within a matter of 1–2 h.

We suggest that these dimeric "hydrolysis" products are formed by ipso attack of water at the 2-position of the nitrosopyridine dimers[4] as depicted in Scheme I. The electrophilicity of C-2 in these dimers would clearly be enhanced by protonation (presumably on oxygen). 4-Methyl-2(1*H*)-pyridone presumably arises by direct hydrolysis of the monomer **2c**. A possible alternative mechanism for the formation of **2a–c** involving hydrolysis of some of the monomeric 2-nitrosopyridine to the corresponding 2(1*H*)-pyridone, followed by nucleophilic addition of the oxygen of an unchanged molecule of the 2-nitrosopyridine to the lactam carbonyl of the 2(1*H*)-pyridone, was eliminated by the observation that an aqueous acidic solution of a mixture of 2(1*H*)-pyridone and 4-methyl-2-nitrosopyridine gave only **2c**; no trace of a mixed pyridylpyridone could be detected.

Experimental Section

1-(2-Pyridyl)-2(1*H*)-pyridone (2a). A suspension of 0.245 g of recrystallized and powdered 2-nitrosopyridine[2] in 25 mL of water was stirred at room temperature. As the solid slowly dissolved, the solution became first pale green and then yellow. The course of the reaction was monitored by TLC (10% methanol/chloroform); all starting material had disappeared after 8 h of stirring at room temperature. The reaction mixture was extracted with methylene chloride, the extracts were dried ($MgSO_4$) and evaporated, and the residual thick gum was dissolved in ether/petroleum ether (1:1) and passed over silica gel. Evaporation of the eluate gave 0.13 g (66%) of 1-(2-pyridyl)-2-(1*H*)-pyridone. The product can be readily purified either by sublimation (51 °C (0.2 mm)) or by rapid column chromatography on silica gel with 1:1 petroleum ether/ether, followed by recrystallization from petroleum ether: white needles, mp 55.5–56 °C (lit.[3] mp 55–56 °C); IR ($CHCl_3$) 1667, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.30 (t, 1 H), 6.65 (d, 1 H), 7.35 (m, 2 H), 7.90 (m, 3 H), 8.59 (d, 1 H); ^{13}C NMR ($CDCl_3$) δ 162.1, 151.9, 148.9, 140.2, 137.7, 136.1, 123.1, 122.0, 121.4, 106.2. Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.55; H, 4.48; N, 16.00.

Hydrolysis of **1a** in water at 62 °C was complete after 2 h (69%), in 25% aqueous dioxane at room temperature after 30 h (79%), and in 25% aqueous dioxane at room temperature with one drop of concentrated sulfuric acid added, after $2^1/_2$ h (72%).

3-Methyl-2-nitrosopyridine (1b). To a cold (0 °C) solution of 13.67 g (0.0794 mol, 80–90%) of *m*-chloroperbenzoic acid in 200 mL of dry methylene chloride was added, all at once, a solution of 7.8 g (0.0464 mol) of *S,S*-dimethyl-*N*-(3-methyl-2-pyridyl)-sulfilimine[5] in 75 mL of methylene chloride. The reaction mixture was stirred at 0–5 °C for 90 min, and then 3 mL of dimethyl sulfide was added. Stirring was continued for an additional 30 min and 300 mL of saturated sodium carbonate added. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to give a yellow solid that was recrystallized from methanol; yield 3.0 g (55%); mp 169–170 °C; ^1H NMR ($CDCl_3$) δ 2.55 (s, 3 H), 7.12, 7.20 (dd, J = 4, 8 Hz, 1 H), 7.65 (d, J = 8 Hz, 1 H), 7.90 (d, J = 4 Hz, 1 H). Anal. Calcd for $C_6H_6N_2O$: C, 59.00; H, 4.91; N, 22.95. Found: C, 58.94; H, 4.89; N, 22.96.

1-(3-Methyl-2-pyridyl)-3-methyl-2(1*H*)-pyridone (2b) was prepared by refluxing 0.2 g of 3-methyl-2-nitrosopyridine in 10 mL of water for 6 h, followed by work-up as described above; yield 55%; mp 87–89 °C (from hexane); IR (KBr) 1645, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.17 (s, 3 H), 2.20 (s, 3 H), 6.18 (m, 1 H), 7.26 (m, 3 H), 7.66 (d, J = 6.5 Hz, 1 H), 8.39 (d, J = 3.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 162.0, 152.7, 146.9, 139.8, 137.3, 134.1, 131.0, 130.6, 124.2, 105.7, 17.3, 17.0. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.98. Found: C, 71.81; H, 6.09; N, 13.81.

1-(4-Methyl-2-pyridyl)-4-methyl-2(1*H*)-pyridone (2c) was prepared analogously by aqueous hydrolysis of 4-methyl-2-nitrosopyridine;[2] yield 46% of light cream-colored crystals; mp 87–88 °C (from hexane); IR (KBr) 1660, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.24 (s, 3 H), 2.43 (s, 3 H), 6.15 (d, J = 8 Hz, 1 H), 6.48 (s, 1 H), 7.12 (d, J = 5 Hz, 1 H), 7.75 (m, 2 H), 8.43 (d, J = 5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 162.1, 152.0, 151.8, 149.1, 148.4, 135.1, 124.1, 121.9, 120.0, 108.8, 21.2, 21.1. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.98. Found: C, 71.98; H, 6.01; N, 13.86.

Further elution of the silica gel column with ether/methanol (10:1) gave a small amount (10%) of 4-methyl-2(1*H*)-pyridone, mp 126–128 °C (lit.[6] mp 130 °C).

Registry No. **1a**, 79917-37-6; **1b**, 99548-31-9; **1c**, 79917-38-7; **2a**, 3480-65-7; **2b**, 99548-29-5; **2c**, 99548-30-8; *S,S*-dimethyl-*N*-(3-methyl-2-pyridyl)sulfilimine, 62135-45-9.

(4) The observation that the rate of hydrolysis decreases markedly with decreasing polarity of the aqueous medium (i.e., upon addition of dioxane) supports the suggestion that the nitroso dimer is the reacting species.

(5) Gilchrist, T. L.; Harris, C. J.; Hawkins, D. G.; Moody, C. J.; Rees, C. W. *J. Chem. Soc. Perkin Trans. 1* **1976**, 2166–2170.

(6) Seide, O. *Chem. Ber.* **1924**, *57*, 791–794.

Preparation of *N*-(2-Naphthyl)-2-amino Acids and Esters of High Enantiomeric Purity

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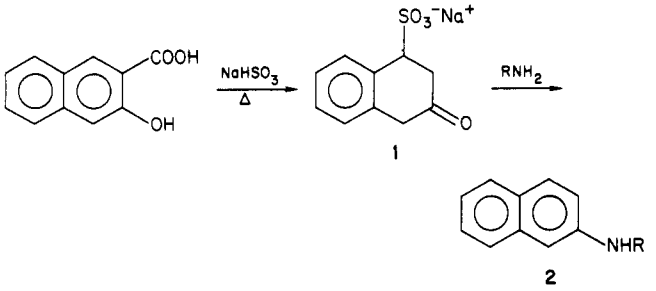
Enantiomers of *N*-(2-naphthyl)-2-amino esters and amides show an unusually high degree of chiral recognition when chromatographed on chiral stationary phases (CSPs) derived from *N*-(3,5-dinitrobenzoyl)-2-amino acids.[1] As

0022-3263/86/1951-0102$01.50/0

Scheme I



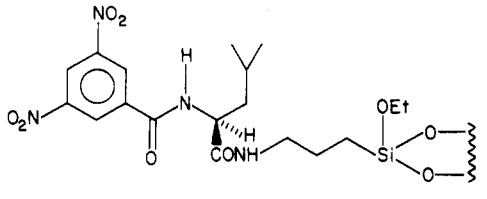
a consequence, "reciprocal" CSPs derived from *N*-(2-naphthyl)-2-amino acids were expected to separate the enantiomers of *N*-(3,5-dinitrobenzoyl)-2-amino acids as well as a variety of related compounds. Indeed, CSPs based on *N*-(2-naphthyl)-2-amino acids show wide applicability in analytical and preparative optical separations.[2] Accordingly, a synthetic approach to enantiomerically pure *N*-(2-naphthyl)-2-amino acids was sought.

A number of racemic *N*-aryl-2-amino acids have been synthesized, but relatively few of these have been resolved. As far as we have been able to ascertain, none has ever been assigned an absolute configuration. McKenzie and Bate[3] resolved the enantiomers of *N*-phenyl-2-phenyl-2-aminoacetic acid through separation of the diastereomeric cinchonine salts. Undavia[4] similarly separated the enantiomers of *N*-phenyl-2-phenyl-2-aminopropionic acid using brucine. Matell[5] and Aberg[6] evaluated the enantiomers of *N*-phenylalanine as auxins and determined the absolute configurations of several *O*-aryl and *S*-aryl analogues by the quasi-racemate method.

Racemic *N*-aryl-2-amino acids can be obtained by alkylation of aryl amines with 2-halo acids or esters. However, this method is not well suited to the preparation of enantiomerically pure *N*-aryl amino acids. Surprisingly, one obvious approach, the Bucherer reaction of 2-naphthol with an enantiomerically pure 2-amino acid, seems not to have been reported. We find this reaction capable of affording *N*-aryl-2-amino acids of high enantiomeric purity and herein describe several such preparations.

Seeboth[7] demonstrated that the Bucherer reaction proceeds through an isolable (as the sodium salt) tetralonesulfonic acid intermediate **1**, which reacts with an amine to afford a naphthylamine (Scheme I).

Following Seeboth's procedure, sulfonate **1** was allowed to react with several enantiomerically pure 2-amino esters to afford the corresponding *N*-(2-naphthyl)-2-amino esters, albeit in rather low yields. Enantiomeric purities were determined by HPLC analysis on CSP **3**. Although these



CSP **3**

results were encouraging, the isolation of intermediate **1** is laborious and the overall yields in the sequence are low. We subsequently found it much easier to prepare the *N*-(2-naphthyl)-2-amino acid directly from the 2-amino acid and 2-naphthol (Scheme II). For this reaction to be successful, the initial pH of the reaction mixture must be adjusted to 8. This was accomplished by diluting equimolar mixtures of 2-naphthol, 2-amino acid, and anhydrous Na_2SO_3 with 5 volumes of saturated $NaHSO_3$ solution. The mixture was then sealed in a pressure vessel capable off being agitated (magnetic stirring, rocking) and heated to 115 °C for 3–5 days. The reaction was monitored visually and stopped when two homogeneous liquid phases were noted. Prolonging the reaction time past this point did not increase yields. The results of several typical preparations are shown in Table I.

Scheme II

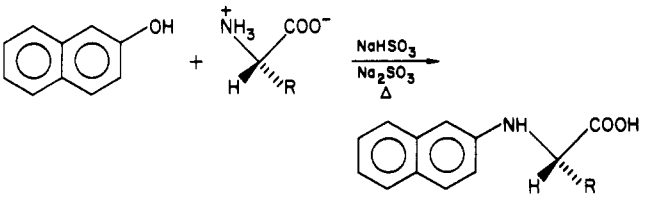


Table I. Products and Yields of Bucherer Reaction between 2-Naphthol and 2-Amino Acids

amino acid	yield, %	reactn time, days	product
D-alanine	25	7	(*R*)-(+)-α-*N*-(2-naphthyl)-alanine (**4a**)
L-serine	8	4	(*S*)-(−)-α-*N*-(2-naphthyl)-serine (**5**)
L-leucine	25	5	(*S*)-(−)-α-*N*-(2-naphthyl)-leucine (**6**)
L-valine	28	5	(*S*)-(−)-α-*N*-(2-naphthyl)-valine (**7**)
L-phenylalanine	19	3	(*S*)-(+)-α-*N*-(2-naphthyl)-phenylalanine (**8**)
L-methionine	33	4	(*S*)-(−)-α-*N*-(2-naphthyl)-methionine (**9**)
D-phenylglycine	23	3	(*R*)-(−)-α-*N*-(2-naphthyl)-phenylglycine (**10**)

Although the product yields are modest, starting materials are inexpensive and a simple workup readily affords pure products. Unreacted starting material can be recovered and recycled if desired. Unreacted 2-naphthol was recovered by adjusting the reaction mixture to pH 8.5–9.0 and extracting the naphthol into dichloromethane. Adjustment of the raffinate to pH 3 precipitates the *N*-(2-naphthyl)-2-amino acid in nearly pure form. Racemization was noted only when the reaction temperature exceeded 140 °C for a period of several days. This reaction has been successfully conducted on a multimolar scale in a rocking hydrogenation vessel. Continuous extraction was employed during workup of the large-scale reactions.

Although most of the 2-amino acids tried afford the expected products, aspartic acid gave no product isolable under the usual conditions and tyrosine yielded a dense polymeric material that is barely soluble in hot alkali.

Experimental Section

All reagents were of pharmaceutical or reagent grade and were used without further purification. The pH of solutions were determined by using a Sargent-Welch Model PBL pH meter at 20 °C. All ^1H NMR and ^{13}C NMR spectra were obtained using a Varian XL-200 FTNMR with a switchable probe. All ^1H and ^{13}C resonances are reported relative to tetramethylsilane. All ^{13}C NMR spectra were obtained under broad-band decoupling conditions. Infrared spectra were obtained using a Perkin-Elmer

(1) Pirkle, W. H.; Pochapsky, T. C.; Mahler, G. S.; Field, R. M. *J. Chromatogr.* **1985**, *348*, 89–96.
(2) Pirkle, W. H.; Pochapsky, T. C., *J. Am. Chem. Soc.*, in press.
(3) McKenzie, A.; Bate, S. C. *J. Chem. Soc.* **1915**, 1681.
(4) Undavia, N. K.; Dhanani, M. L.; Thaker, K. A. *J. Indian Chem. Soc.* **1977**, *54* (8), 792.
(5) Matell, M. *Acta Chem. Scand.* **1953**, *7*, 228–29.
(6) Aberg, B. *Kgl. Langbruks-Hogskolan Ann.* **1953**, *20*, 241.
(7) Seeboth, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6* (4), 307.

Model 137 NaCl prism spectrophotometer or an IBM IR32 FTIR. UV/vis spectra were obtained on a Perkin-Elmer Lambda 3 digital spectrophotometer. Low-resolution mass spectra were obtained using a Varian MAT CH-5 spectrometer by electron-impact ionization. High-resolution mass spectra were obtained on a Varian 731 spectrometer using electron-impact ionization. All chromatographic analyses were performed using an Altex 100A pump and an Altex 152 UV detector operating at 254 nm in series with a Rudolph Autopol III digital polarimeter equipped with a 20-cm flow cell. Medium-pressure liquid chromatography was performed using a Crane Chem/Meter pump and an Instrumentation Specialties Model 226 UV detector operating at 254 nm. Optical rotations were obtained using a Rudolph Autopol III digitial polarimeter operating at 589 nm (sodium D line) equipped with a 10-cm cell. Elemental analyses were performed by J. Nemeth and associates of the University of Illinois microanalytical service. Melting points were obtained using a Buchi melting point apparatus and are uncorrected.

Enantiomeric purities of the product acids were established by chromatography of their ethyl esters on commercial columns containing stationary phases derived from L-*N*-(3,5-dinitrobenzoyl)leucine or D-*N*-(3,5-dintrobenzoyl)phenylglycine (Baker L-DNBleu and D-DNBPG, respectively) using 5% 2-propanol in hexane as a mobile phase. It should be noted that the elution order of enantiomers of any of the compounds described herein differ on the D-DNBPG column and the L-DNBleu column. This allows either enantiomer to be cleanly separated from front-running impurities, facilitating the accurate determination of enantiomeric purity even if it is quite high. The ethyl esters used for analysis were prepared from the parent acids by heating the acids in absolute ethanol containing hydrogen chloride. The samples were then prepared for chromatography by neutralization with 5% $NaHCO_3$ solution, extraction of the ester into dichloromethane, back-washing of the extract with water, and finally, filtration of the extract through anhydrous $MgSO_4$. Coinjection with samples of genuine racemate established the identity of the product peak(s). Chromatographic separation of the enantiomers of *N*-aryl amino esters is discussed elsewhere.[1]

Racemates were prepared by several methods. In some instances, racemic 2-amino acids were subjected to the Bucherer reaction. Alternatively, 2-bromo esters were used to alkylate aryl amines according to literature procedures.

A. Preparation of Racemates. (*RS*)-Ethyl α-*N*-(2-naphthyl)valinate (11) was prepared by the method of Bischoff.[8] To 1.0 g (7 mmol) of 2-naphthylamine (*Caution*! Potent Carcinogen!) was added 1.46 g (7 mmol) of ethyl α-bromoisovalerate and 0.74 g (7 mmol) of Na_2CO_3 (anhydrous) in a one-neck 50-mL round-bottom flask equipped with a magnetic stirring bar. The mixture was heated with stirring under a nitrogen atmosphere for 2 h at 140 °C. After 1 h, solid began to form and, after 2 h, the mixture was completely solidified. The cooled solids were crushed and triturated with 1 N acetic acid, and the residual material was recrystallized from CCl_4–hexane. The yield of **11** was 1.66 g (88%): mp 69 °C; ^1H NMR ($CDCl_3$) δ 1.00 (d, J = 6 Hz, 6 H), 1.18 (t, J = 6 Hz, 3 H), 2.03 (m, J = 8, 6 Hz, 1 H), 3.92 (d, J = 8 Hz, 1 H), 4.10 (q, J = 6 Hz, 2 H), 6.64–7.59 (m, 7 H); IR (film) 3051 (w), 2962 (s), 2933 (w), 1730 (s), 1631 (s), 1604 (w), 1532 (s), 1469, 1393 (d, s) cm^{-1}; MS, m/e (relative intensity) 271 (M^+, 22), 228 (14), 199 (16), 198 (100). Anal. Calcd for $C_{17}H_{21}NO_2$: C 75.25; H, 7.80; N, 5.16. Found: C, 75.31; H, 7.78; N, 5.04.

Preparation and Chromatographic Separation of the Enantiomers of (*RS*)-Ethyl α-*N*-(2-Naphthyl)phenylglycinate (12). Following Baker's procedure,[9] 2.63 g (11 mmol) of ethyl 2-bromo-2-phenylacetate in 10 mL of ethanol was added to a 50-mL one-neck round-bottom flask equipped with a reflux condenser followed by 1.55 g (11 mmol) of 2-naphthylamine (*Caution*! Potent Carcinogen!) and 1.47 g of sodium acetate. The mixture was heated to reflux overnight. After cooling, the mixture was triturated with 10 mL of 5% Na_2CO_3 and the solids were collected by filtration, washed with water, and dried. After recrystallization from CCl_4, 3.5 g (95%) of crystalline **12** (mp 98 °C) was obtained. One gram of this racemate was chromatographed on 250 g of CSP **3** using 1% 2-propanol/hexane as a mobile phase. The enantiomers were completely separated, the *R*-(−) enantiomer being first eluted.

(*R*)-(−)-Ethyl α-*N*-(2-naphthyl)phenylglycinate [(*R*)-12]: mp 93.5 °C; ^1H NMR ($CDCl_3$) δ 1.21 (t, J = 6 Hz, 3 H), 4.20 (q, J = 6 Hz, 2 H), 5.06 (br, 1 H), 5.11 (s, 1 H), 6.62–7.76 (m, 12 H); MS (10 eV), m/e (relative intensity) 305 (M^+, 29), 265 (11), 264 (50), 263 (15), 248 (11), 232 (100), 221 (28); IR (film) 3061 (w), 2980 (w), 1718 (s), 1611 (s), 1360 (s), 1253 (s), 1213, 1193 (d,s), 1020 (s), 827 (s) cm^{-1}; $[\alpha]^{20}_D$ −104.4° (*c* 1.0, THF). Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.63; H, 6.21; N, 4.46.

B. Scheme I. Preparation of Enantiomerically Pure *N*-(2-Naphthyl) α-Amino Esters. 3-Tetralone-1-sulfonic acid sodium salt (1) was prepaed by using Seeboth's procedure.[6] 3-Hydroxy-2-naphthoic acid (Aldrich) (9.4 g, 50 mmol), along with 2 g of NaOH pellets, was stirred into 133 g of 38% $NaHSO_3$ solution in a 500-mL round-bottom flask equipped with a stirrer and reflux condenser. The mixture was heated to 90 °C for 12 h, filtered, diluted with 2.5 volumes of ethanol, and, after being allowed to stand overnight, filtered again. The volume of the filtrate was reduced to 50 mL under vacuum and at a temperature of 40 °C. The resulting concentrate was filtered, 12 mL of concentrated HCl added, and nitrogen bubbled through the solution for several hours. After again filtering, the solution was washed twice with 50-mL portions of diethyl ether and dried under vacuum at 45 °C. The solid residue was crushed and washed three times with 100-mL portions of ethanol. The crude sulfonate salt was precipitated from the combined ethanol washes by the addition of diethl ether. After collection by filtration, the crude **1** was used "as is" for the reactions with the 2-amino esters.

A typical preparation of *N*-(2-naphthyl) amino esters of high enantiomeric purity is illustrated by the following synthetic procedure.

(*R*)-(−)-Ethyl α-*N*-(2-Naphthyl)phenylglycinate [(*R*)-12]. To 0.5 g of crude tetralonesulfonate **1** in a screw-top vial was added 0.5 g of (*R*)-(−)-ethyl phenylglycinate hydrochloride and 5 mL of ethanol. The mixture was adjusted to pH 6 with 5% Na_2CO_3; the vial was closed and heated to 60 °C overnight. After the vial cooled, 5 mL of water was added and the solution was acidified with several drops of 6 N HCl and then twice extracted with 2-mL portions of CCl_4. The organic phase was washed sequentially with 2 mL of 1 N HCl, 2 mL of 5% $NaHCO_3$, and 2 mL of brine. After further drying over anhydrous Na_2SO_4 and filtration through Celite, the organic phase was concentrated and the residual oil was purified by medium-pressure liquid chromatography on cyanopropyl-derivitized silica gel using a 1% 2-propanol–hexane mobile phase. The reulting material (0.2 g 28% yield) is chromatographically and spectroscopically identical with the enantiomer of **12** least retained on CSP **3**.

C. Scheme II. A typical Bucherer reaction is demonstrated by the preparation of **(*S*)-(−)-α-*N*-(2-Naphthyl)leucine (6).** A mixture of 10 g (76 mmol) of L-leucine (Sigma), 11 g (76 mmol) of β-naphthol (Aldrich), and 9.6 g (76 mmol) of anhydrous Na_2SO_3 was placed in a pressure vessel equipped with a magnetic stirring bar. Saturated $NaHSO_3$ solution (60 mL) was added; the bottle was sealed and heated slowly to 115 °C while being stirred. After 1 day, two homogeneous layers formed. Heating and stirring was continued for 3 additional days. After being cooled, the bottle was emptied into a 1000-mL beaker and rinsed with alternate 5% $NaHCO_3$ and acetone washes. The combined washes and reaction mixture were diluted to 500 mL with water, the pH was adjusted to 8.5–9.0 with saturated Na_2CO_3 solution, and the mixture was washed twice with 60-mL portions of dichloromethane. The organic phase was back-washed with two 60-mL portions of 5% $NaHCO_3$ solution, which were combined with the original aqueous phase. The 2-naphthol-containing organic phase may then be discarded, or the unreacted 2-naphthol may be recovered. The aqueous phase was adjusted to pH 3 with 6 N hydrochloric acid (SO_2 and CO_2 are evolved!). The resultant white precipitate was collected and washed with 50 mL of ethyl acetate. The aqueous phase was extracted with two 50-mL portions of ethyl acetate and was then either discarded or evaporated to recover unreacted amino acid. The combined ethyl acetate extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness. The remaining solids were recrystallized from 95% ethhanol to afford

(8) Bischoff, C. A.; Hausdorfer, A. *Chem. Ber.* **1892**, *25* (Part 2), 2298.
(9) Baker, W.; Ollis, W. D.; Poole, V. D. *J. Chem. Soc.* **1949**, Part 1, 307.

white crystals of **(S)-(−)-α-N-(2-naphthyl)leucine (6)** (4.8 g, 25% yield after two crops) that pinken on exposure to air: mp 173 °C; ^{1}H NMR (acetone-d_6) δ 0.92–1.05 (dd, J = 3 Hz, 6 H), 1.7–1.8 (td, J = 3.8, 1 Hz, 2 H), 1.8–2.1 (m, 1 H), 2.5–3.3 (b, 1 H), 4.2 (t, J = 3.8 Hz, 1 H), (naphthyl assignments) 6.85 (d, J = 3 Hz, 1 H), 7.05–7.12 (dd, J = 9, 3 Hz, 1 H), 7.05–7.35 (dt, J = 7 Hz, 2 H), 7.58–7.68 (m, 3 H); ^{13}C NMR (acetone-d_6) δ 22.5, 23.6, 25.8, 42.5, 55.6, (naphthyl assignments) 104.9, 119.4, 122.7, 126.9, 127.1, 128.3, 128.4, 129.5, 136.2, 146.8; IR (Nujol) 3 (b), 3.3–3.8 (s), 6–6.5 (s), 7.4, 7.8 (m), 8.3 (d, m), 8.5 (w), 8.7 (m), 11.5 (m), 12 (s), 13.4 (s), 14.5 (s); UV/vis (CH_3OH) [λ_{max} (ε)] 345 nm (2.18 × 10^3), 289 (6.34 × 10^3), 280 (7.24 × 10^3), 270 (5.63 × 10^3), 245 (3.52 × 10^4); MS (10 eV), m/e (relative intensity) 257 (M$^+$, 100), 213 (71), 212 (100), 170 (80), 156 (99), 154 (93); $[\alpha]^{20}_D$ −127.5° (c 1.0, THF). Enantiomeric purity was determined to be greater than 98% by HPLC of the ethyl ester of **6** on CSP **3**. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; N, 5.44; H, 7.44. Found: C, 74.34; N, 5.26; H, 7.72.

Because of the similarity of structure for all the compounds reported in the following tabulation, only the ^{1}H NMR and ^{13}C NMR resonances that are not assigned to the naphthyl ring system are reported. Complete characterizations will be published in the Ph.D. thesis of T.C.P. In all cases in which rotations are reported, enantiomeric purities have been found to be greater than 98% by HPLC of the derived ester on CSP **3**.

(RS)-α-N-(2-Naphthyl)alanine (4): mp 170 °C; ^{1}H NMR (acetone-d_6) δ 1.51 (d, J = 7.5 Hz, 3 H), 4.23 (q, J = 7.5 Hz, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 18.0, 50.9, 175.7; MS (10 eV) m/e (relative intensity) 216 (M + 1, 20.5), 215 (M$^+$, 100), 171 (92), 170 (100), 156 (62), 128 (42.8), 127 (48.5). Anal. Calcd for $C_{13}H_{13}NO_2$: C 72.54; H, 6.09; N, 6.61. Found: C, 72.56;; H, 6.14; N, 6.42.

(R)-(+)-α-N-(2-Naphthyl)alanine (4a): mp 153 °C, $[\alpha]^{20}_D$ +187.2° (c 0.4, THF). Anal. Calcd for the ethyl ester of **4a** ($C_{15}H_{17}NO_2$): C, 74.05; H, 7.04; N 5.76. Found: C, 73.66; H, 6.83; N, 5.78.

(S)-(−)-α-N-(2-Naphthyl)serine (5): mp 125 °C dec; ^{1}H NMR acetone-d_6) δ 4.22 (d, J = 4 Hz, 2 H), 4.53 (t, J = 4 Hz, 1 H); MS (70 eV) m/e (relative intensity) 232 (M + 1, 8.4), 231 (M$^+$, 53.9), 200 (39.5), 186 (38.6), 168 (34.5), 154 (100), 143 (55), 127 (90); HRESMS for $C_{13}H_{13}NO_3$, calcd 231.0895885, found 231.0895885; $[\alpha]^{20}_D$ −25.7° (c 1.0, THF); ^{13}C NMR of ethyl ester of **5** ($CDCl_3$): δ 44.4, 47.9, 48.5, 91.8, 104.1, 108.5, 110.0, 112.2, 112.3, 113.5, 113.9, 115.1, 120.6, 129.9, 157.9. Anal. Calcd for the ethyl ester of **5** ($C_{15}H_{17}NO_3$): N, 5.40; C, 69.48; H, 6.61. Found: N, 5.29; C, 69.44; H, 6.65.

(S)-(−)-α-N-(2-Naphthyl)valine (7): mp 125 °C; ^{1}H NMR (acetone-d_6) δ 1.05–1.15 (dd, J = 3 Hz, 6 H), 2.13–2.32 (sept, J = 3 Hz, 1 H), 4.0 (d, J = 3 Hz, 1 H); ^{13}C NMR (acetone-d_6) δ 19.2, 19.5, 31.7, 62.8, 174.9; MS (70 eV) m/e (relative intensity) 244 (M + 1, 7.2), 243 (M$^+$, 43.7), 200 (35.8), 198 (95.9), 154 (100), 143 (34.3), 127 (85); HRESMS for $C_{15}H_{17}NO_2$, calcd 243.12551, found 243.12555 $[\alpha]^{20}_D$ −168.7° (c 1.0, THF) for free acid **7**. Anal. Calcd for the ethyl ester of **7** ($C_{17}H_{21}NO_2$): C, 75.25; H, 7.80; N, 5.16. Found: C, 75.33; H, 8.05; N, 4.90.

(S)-(+)-α-N-(2-Naphthyl)phenylalanine (8): mp 170 °C; ^{1}H NMR (acetone-d_6) δ 3.08–3.38 (dp, J = 8, 3 Hz, 2 H), 4.45 (t, J = 3 Hz, 1 H), 7.15–7.38 (m, 5 H); ^{13}C NMR (acetone-d_6) δ 38.8, 58.2, 126.6, 128.7, 129.2, 129.6, 130.2, 136.3, 174.6; MS (10 eV) m/e (relative intensity) 292 (M + 1, 6.3), 291 (M$^+$, 27.6), 201 (80), 200 (72.0), 154 (100), 127 (62.6)%; $[\alpha]^{20}_D$ +76.7° (c 1.0, THF). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.34; H, 5.90; N, 4.73.

(S)-(−)-α-N-(2-Naphthyl)methionine (9): mp 158 °C; ^{1}H NMR (acetone-d_6) δ 2.08 (s, 3 H), 2.03–2.30 (m, 2 H), 2.68–2.70 (t, J = 7 Hz, 2 H), 4.40 (dd, J = 5, 8 Hz, 1 H); ^{13}C NMR (Me_2SO-d_6) δ 14.9, 30.0, 31.7, 54.5, 175.2; MS (10 eV) m/e (relative intensity) 277 (M + 2, 12.2), 276 (M + 1, 37.4), 275 (M$^+$, 100), 182 (100), 156 (42), 154 (82), 127 (50.4, 61 (100); $[\alpha]^{20}_D$ −31.0° (c 1.0, THF). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09; S, 11.64. Found: C, 65.50; H, 6.23; N, 5.07; S, 11.59.

(R)-(−)-α-N-(2-Naphthyl)phenylglycine (10): mp 173 °C; ^{1}H NMR (acetone-d_6) 5.33 (s, 1 H), 7.20–7.41 (m, 4 H), 7.52 (d, 1 H), (naphthyl assignments) 6.81 (d, J = 3 Hz, 1 H), 7.13 (t, J = 7 Hz, 1 H), 7.22 (dd, J = 9 3 Hz, 1 H), 7.27 (t, J = 7 Hz, 1 H), 7.62–7.70 (m, 4 H); ^{13}C NMR (acetone-d_6) δ 53.6, 98.4, 112 .0, 115.2, 119.3, 119.5, 120.6, 120.8, 121.2, 122.0, 131.9, 138.0, 165.5; MS (10 eV) m/e (relative intensty) 278 (M + 1, 15.0), 277 (M$^+$, 74.0), 233 (70.8), 232 (100), 154 (13.8), 143 (12.9), 127 (47.4); $[\alpha]^{20}_D$ −238.0° (c 1.0, THF). Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.90; H, 5.50; N, 4.98.

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Stereoselectivity of the Reduction of Naltrexone Oxime with Borane

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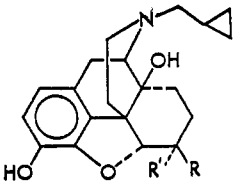
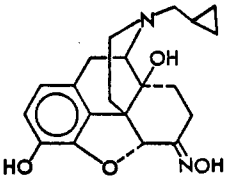
The opiate β-naltrexamine (**1b**)[1,2] is employed as an intermediate in the synthesis of the affinity label β-funaltrexamine (**2**),[3] which is employed widely as a tool in



1a: R = H, R′ = NH_2
1b: R = NH_2, R′ = H
2: R = NHCOHC=CHCOOMe, R′ = H

opioid research.[4] A highly stereoselective synthesis of **1b** has been reported,[2] but its time-consuming nature prompted us to examine a simple alternative approach. In this report, we describe a simple stereoselective method for preparing **1b**. Moreover, this method may have general application in altering the usual stereochemical course of reductive amination in vicinally substituted cyclohexanones.

The route to obtaining **1b** stereoselectively involved the borane reduction of oxime **3**.[5] The choice of borane as



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reducing agent[6] of the oxime group was based on previous studies[2] that suggested that the steric course of reduction at the C-6 center of the opiate is dependent on the conformation of ring C. We had proposed that pseudoallylic strain[7] arising from a disubstituted iminium intermediate (**4a**, **5a**) stabilizes the boat conformation (**5a**), which is more accessible to hydride attack from the α direction. This is in contrast to the unsubstituted iminium intermediate (**4b**, **5b**) that was presumed to be reduced pre-

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