Chemoenzymatic Synthesis of 2-Amino-3-(2,2′-bipyridinyl)propanoic Acids†

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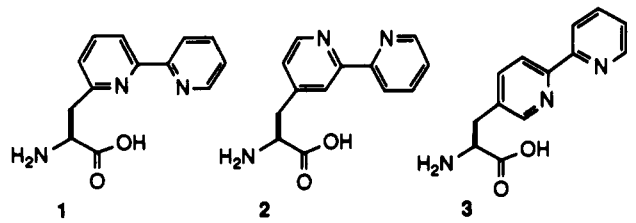
Recently, many authors have reported success in constraining peptide structure through the integration of cooperative properties of amino acids into a rationally designed primary sequence.[1] In an effort to design peptides with structural or functional metal-binding sites we reported the synthesis and peptide incorporation of (*S*)-2-amino-3-(2,2′-bipyridin-6-yl)propanoic acid (**1**).[2] Although peptides containing **1** bind metal ions as expected,[3] it is known that substitution of 2,2′-bipyridine rings at the 6 or 6′ positions has a dramatic effect on the ligand's metal-binding properties.[4] In light of this, we have developed and report herein the syntheses of (*S*)-2-amino-3-(2,2′-bipyridin-4-yl)propanoic acid (**2**) and (*S*)-2-amino-3-(2,2′-bipyridin-5-yl)propanoic acid (**3**). These amino acids contain an unobstructed N–N′ chelation moiety and are expected to provide metal-binding properties complementary to those reported for **1**.[3] The synthesis of **1** relied upon a stereoselective alkylation (53% ee) followed by preferential crystallization of racemic material to afford enantiomerically pure material (>99% ee).[2] However, in attempting to apply an analogous route to the synthesis of **2**, optically pure products could not be obtained due to failure of the crystallization step; thus, alternate strategies were explored. The synthetic routes to **2** and **3** we describe utilize an enzyme-catalyzed hydrolysis to effect the resolution.[5] The enzymatic resolution proved to be not only simple and convenient, but also allowed for *quantitative retrieval* of both enantiomers in high optical purity on preparative scales.

As illustrated in Scheme I (shown for (*S*)-2-amino-3-(2,2′-bipyridin-4-yl)propanoic acid, conditions and yields are similar for (*S*)-2-amino-3-(2,2′-bipyridin-5-yl)propanoic acid), the L-methyl ester can be selectively hydrolyzed



1 **2** **3**

from the racemate of **4** using commercially available alkaline protease.[5] The hydrolysis proceeded smoothly at room temperature and was complete within 2 h. Separation and quantitative recovery of the two enantiomers were accomplished through a simple extraction of the D-amino acid ester **5** (98% ee) with $CHCl_3$ followed by lyophilization of the remaining aqueous layer to afford the L-amino acid (93% ee). The enzyme-catalyzed hydrolysis of these amino acid esters proved to be remarkably reproducible and effective for both regioisomers. As our main goal was to incorporate the residue into peptides, the amino acid was directly N-protected, without purification, as the 9-fluorenylmethoxycarbonyl (FMOC) derivatives. Thus, the crude amino acids[6] were treated with *N*-[(9-fluorenylmethoxycarbonyl)oxy]succinimide in 30% aqueous dioxane containing 10% sodium carbonate (85% yield[7]) to afford the FMOC amino acid **6**.

Synthesis of the racemic amino acid ester **4** is detailed in Scheme II and was accomplished through a route originally described by Erlenmeyer for preparation of aromatic amino acids.[8]

Synthesis of the 5-substituted 2,2′-bipyridine derivative **11** followed the route published for **1**,[2] the key step involving asymmetric alkylation of a commercially available glycine derivative with 5-(bromomethyl)-2,2′-bipyridine, **13**, in the presence of a chiral phase-transfer catalyst.[9] The alkylation proceeded with modest asymmetric induction (40–66% ee) and provided an 85% yield of **15**. Details of the complete synthesis are provided in Scheme III. Alkaline protease catalyzed hydrolysis of the optically enriched methyl ester produced from this synthesis afforded the L-amino acid in >96% ee.

In conclusion, this note demonstrates synthetic routes of two bipyridinyl-substituted amino acids which allow facile generation of gram-scale quantities in high optical purity, suitable for solid-phase peptide synthesis. These synthetic routes, together with that published for the (*S*)-2-amino-3-(2,2′-bipyridin-6-yl)propanoic acid (**1**), provide a powerful array of metal ligands each of which is capable of creating a unique metal coordination environment. The accessibility of these amino acid isomers for polypeptide synthesis should aid in de novo design of metalloproteins where correct programming of both the coordination geometry of the metal center, as well as the orientation of the metal with respect to the polypeptide backbone, is paramount to success.

Experimental Section

^1H and ^{13}C NMR spectra were recorded at 300.2 or 500 MHz and 75.5 MHz, respectively, using TMS or d_5-DMSO as internal standards. Optical rotations were recorded at room temperature

† Contribution No. 8725.

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(5) (a) Chen, S.-T.; Wang, K.-T.; Wong, C.-H. *J. Chem. Soc., Chem. Commun.* **1986**, 1514. Alkaline protease is a very stable and robust enzyme which can be used as supplied by Sigma Chemical Co. (Sigma Type VIII Bacterial Protease from *Bacillus licheniformis*). The preparation is a mixture of proteases, the major component being Subtilisin Carlsberg. The enantioselectivity of the enzyme catalyzed hydrolysis has been consistent with different batches of the enzyme preparation. (b) Chen, S.-T.; Hsiao, S.-C.; Chiou, A.-J.; Wu, S.-H.; Wang, K.-T. *J. Chin. Chem. Soc.* **1992**, *39*, 91.

(6) The amino acids were contaminated with carbonate salts.

(7) Yield based on the amount of L-amino acid methyl ester.

(8) (a) Erlenmeyer, E. *Ann.* **1893**, *275*, 1. (b) Blatt, A. H. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 489.

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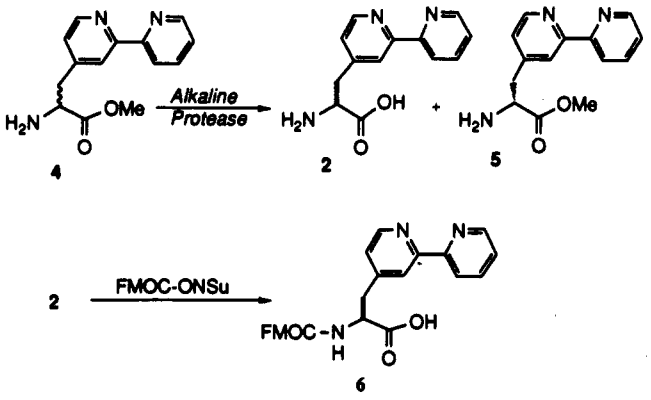
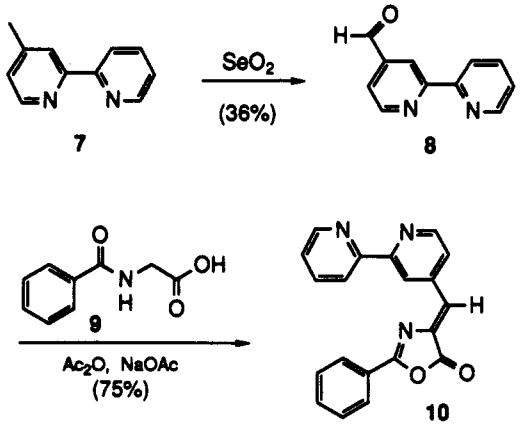
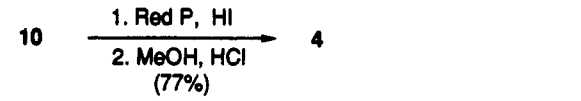
0022-3263/93/1958-1613$04.00/0

Scheme I

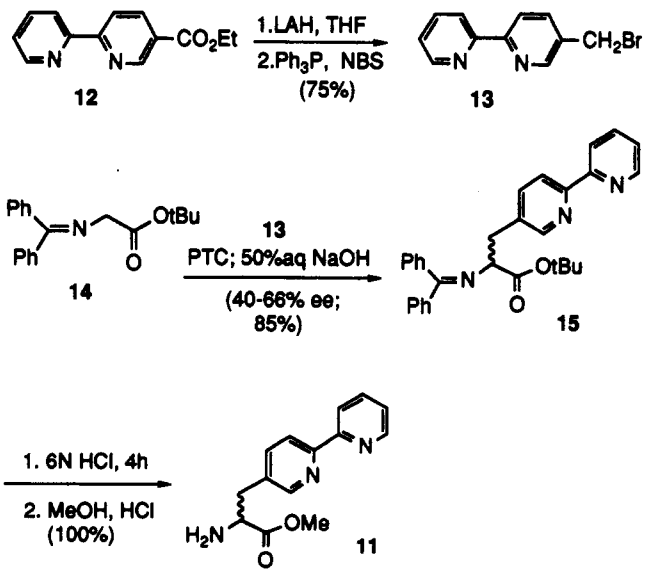


Scheme II





Scheme III



in a microcell, 1-dm path length. Mass spectra were taken on a ZAB mass spectrometer in the fast atom bombardment (FAB) or electron impact (EI) mode. Thin-layer chromatography (TLC) was carried out using EM reagents hard TLC plates with fluorescence indicator (SiO_2 60, F-254). TLC plates were visualized by UV, ninhydrin 0.2% solution in ethanol (followed by heat), or by exposure to an aqueous solution of ferrous ammonium sulphate. Flash column chromatography was carried out according to the procedure of Still[10] using J. T. Baker (~40 μM) flash silica gel.

HPLC analysis to evaluate the optical purity of amino acids and corresponding methyl esters was carried out CrownPak CR (+) analytical column (Daicel).

4-Formyl-2,2′-bipyridine (8). A slurry of 4-methyl-2,2′-bipyridine,[11] 7 (7.68 g, 45.1 mmol), selenium dioxide (7.5 g, 68 mmol), and water (1.2 mL, 67 mmol) in 285 mL of dioxane was refluxed for 2 h. After the slurry was cooled slightly, additional selenium dioxide (7.5 g) and water (1.2 mL) were added and refluxing was continued overnight. The mixture was filtered while still warm, and the filtrate was adsorbed onto silica gel (~10 mL). The resulting solid mixture was purified using flash column chromatography (eluent: CCl_4/EtOAc (2:1)) yielding 3.02 g (36%) of a cream colored solid: mp 84.8–86.0 °C; HRMS [MH^+] calcd for $C_{11}H_9N_2O$ 185.0715, obsd 185.0715; ^1H NMR ($CDCl_3$) δ 7.37 (m, 1 H), 7.73 (m, 1 H), 7.86 (m, 1 H), 8.44 (d, 1 H), 8.73 (d, 1 H), 8.83 (s, 1 H), 8.90 (d, 1 H), 10.18 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 120.8, 121.0, 121.2, 124.4, 137.1, 142.6, 149.3, 150.4, 154.8, 158.0, 191.7; IR (thin film) cm^{-1} 2860, 1704, 1585, 1560, 1458, 1446, 1410, 1388, 1267, 1251, 1231, 1172, 1094, 1061, 988, 908, 839, 788, 739, 664, 649; UV (MeOH) λ_{max} 283 nm ($\epsilon = 13.5 \times 10^3$), 236 nm ($\epsilon = 10.9 \times 10^3$).

4-(2,2′-Bipyridin-4-ylmethylene)-2-phenyl-5(4*H*)-oxazolone (10). 4-Formyl-2,2′-bipyridine, 8 (6.86 g, 37.2 mmol), *N*-benzoyl glycine, 9 (6.86 g, 38.3 mmol), and sodium acetate (3.09 g, 37.7 mmol) were slurried in acetic anhydride (70 mL). Upon heating to 90 °C, the mixture thickened and more acetic anhydride (28 mL) was added. After being stirred at 90 °C for 1 h, the mixture was cooled to room temperature, and the solid was filtered and washed with 12 mL of acetic anhydride. This solid was dried in vacuo yielding 12.6 g of tan solid contaminated with sodium acetate. This solid was stirred in 400 mL of chloroform and filtered. The filtrate was concentrated in vacuo to yield 9.1 g (75%) of a pale tan solid: mp 179.9–180.5 °C; HRMS [MH^+] calcd for $C_{20}H_{14}N_3O_2$ 328.1086, obsd 328.1077; ^1H NMR ($CDCl_3$) δ 7.26 (s, 1 H), 7.35 (m, 1 H), 7.56 (m, 3 H), 7.66 (m, 1 H), 7.85 (m, 1 H), 8.23 (d, 2 H), 8.32 (m, 1 H), 8.42 (m, 1 H), 8.74 (m, 1 H), 8.82 (m, 1 H), 8.85 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 121.4, 123.4, 124.3, 124.8, 125.3, 128.4, 129.1, 129.3, 134.3, 137.2, 137.3, 141.3, 149.6, 150.1, 155.8, 157.3, 165.6, 166.8; IR (thin film) cm^{-1} 1803, 1794, 1654, 1560, 1451, 1397, 1325, 1298, 1230, 1202, 1158, 1112, 1095, 1068, 984, 921, 878, 846, 781, 730, 695, 681, 621; UV (MeOH) λ_{max} 354 nm ($\epsilon = 20.5 \times 10^3$), 278 nm ($\epsilon = 19.3 \times 10^3$), 238 nm ($\epsilon = 26.0 \times 10^3$).

2-Amino-3-(2,2′-bipyridin-4-yl)propanoic Acid Methyl Ester (4). Reductive Cleavage of the Azlactone. The azlactone 10 (3.0 g, 9.2 mmol) and red phosphorous (1.84 g, 59.4 mmol) were stirred in acetic anhydride (15 mL). Hydriodic acid (47%, 12.8 mL, 70.5 mmol) was added dropwise with stirring over 40 min. After being refluxed for 3.5 h the mixture was allowed to cool to room temperature. Unreacted phosphorous was removed by filtration and washed with 8 mL of acetic acid. The filtrate was concentrated under reduced pressure at ~50 °C. Water (10 mL) was added and removed. Water (15 mL) and ether (15 mL) were added to the residue and shaken until all was dissolved. The aqueous layer was isolated and washed with ether, 3 × 10 mL, and concentrated in vacuo to yield a syrupy residue.

Esterification of the Amino Acid. Residual water in the above residue was removed by azeotroping with anhydrous toluene. The resulting residue was dissolved in MeOH (39 mL, dried over and distilled from CaH_2). The solution was cooled to 0 °C, and hydrogen chloride was bubbled through it for ~3 min. After standing overnight, the solution was concentrated in vacuo. The residue was rubbed with Et_2O to yield a solid. This solid was stirred with ether for 2 h, collected by centrifugation, washed with ether, 2 × 25 mL, and dried in vacuo over KOH. The solid residue (in 1-g portions) was partitioned between chloroform and 0.4 M $NaHCO_3$ (100 mL/100 mL). The organic phase was isolated, and the aqueous phase was washed with chloroform, 4 × 100 mL. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo to yield 1.81 g (77%) of a yellow oil: HRMS [MH^+] calcd for $C_{14}H_{16}N_3O_2$ 258.1243, obsd 258.1250;

(10) Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.
(11) Huang, T. L. J.; Brewer, D. G. *Can. J. Chem.* **1981**, *59*, 1689.

^{1}H NMR ($CDCl_3$) δ 1.69 (s, br, 2 H), 2.89 (m, 1 H), 3.16 (m, 1 H), 3.72 (s, 3 H), 3.82 (m, 1 H), 7.16 (m, 1 H), 7.28 (m, 1 H), 7.79 (m, 1 H), 8.27 (s, 1 H), 8.37 (d, 1 H, J = 8.0 Hz), 8.58 (d, 1 H, J = 5.0 Hz), 8.65 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 40.4, 52.0, 55.0, 121.1, 121.6, 123.6, 124.5, 136.8, 147.5, 148.9, 149.1, 155.8, 156.1, 174.9; IR (thin film) cm^{-1} 3372, 3308, 3057, 3006, 2950, 1736, 1604, 1585, 1556, 1460, 1438, 1401, 1271, 1201, 1177, 1017, 992, 793, 746; UV (MeOH) λ_{max} 282 nm (ϵ = 13.3 × 10^3), 238 nm (ϵ = 10.6 × 10^3).

(*S*)-2-Amino-3-(2,2′-bipyridin-5-yl)propanoic Acid Methyl Ester (11). Toluene (20 mL) was added to the amino acid hydrochloride (3) (1.0 g, 3.2 mmol, 40% ee) and removed under reduced pressure. The residue was slurried in dry MeOH (15 mL) and cooled to 0 °C. Anhydrous hydrogen chloride was passed through the mixture for ~3 min. After standing at room temperature overnight, the solvent was removed under reduced pressure. MeOH (~10 mL) was added and removed. The oily residue was rubbed with Et_2O until the residue formed a fine powder. This powder was isolated by centrifugation and washed twice with Et_2O (20 mL). The residual solid was dried under reduced pressure, transferred to a separatory funnel, and then partitioned between $CHCl_3$ (100 mL) and 0.2 M $NaHCO_3$ (100 mL). The organic phase was isolated, and the aqueous phase was washed with $CHCl_3$ (3 × 100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo to yield 591 mg (73%) of an oil which partially solidified upon cooling overnight: HRMS [MH$^+$] calcd for $C_{14}H_{16}N_3O_2$ 258.1250, obsd 258.1239; ^{1}H NMR ($CDCl_3$) δ 1.87 (br s, 2 H), 2.70 (m, 1 H), 2.86 (m, 1 H), 3.46 (s, 3 H), 3.54 (m, 1 H), 7.03 (m, 1 H), 7.44 (m, 1 H), 7.54 (m, 1 H), 8.14 (m, 2 H), 8.31 (m, 1 H), 8.43 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 37.3, 51.4, 54.8, 120.1, 120.3, 123.0, 132.5, 136.2, 137.1, 148.5, 149.3, 154.1, 155.2, 174.3; IR (thin film) cm^{-1} 3368, 3052, 3003, 2949, 1736, 1588, 1573, 1555, 1460, 1436, 1200, 1025, 850, 796, 751; UV (MeOH) λ_{max} 286 nm (ϵ = 17.0 × 10^3), 240 nm (ϵ = 12.6 × 10^3).

***N*-(9-Fluorenylmethoxycarbonyl)-(*S*)-2-amino-3-(2,2′-bipyridinyl)propanoic Acids. General Method for Resolution of Enantiomers and Isolation of L-Amino Acid.** A solution of the protease[5] (30 mg, 200–500 units) in 120 mL of 0.2 M $NaHCO_3$ was added to the amino acid methyl ester (2.33 g, 8 mmol) in a 250-mL Erlenmeyer flask. The mixture was agitated on an orbital shaker at 120–200 rpm and monitored by HPLC at 20-min intervals. When the ratio of the D-amino acid methyl ester to the L-amino acid methyl ester was >50:1 (about 2 h), the mixture was extracted with chloroform, 6 × 110 mL. The aqueous phase was reduced in volume to remove any chloroform and then lyophilized yielding a mixture of amino acid and carbonate salts. The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated. HPLC analysis of the aqueous phase generally shows a 93–95% ee of the L-amino acid (depending on the optical activity of the starting ester), while analysis of the organic residue generally showed 98% ee of the D-amino acid methyl ester.

Retention Times on CrownPak CR (+) Analytical Column (140 × mm). Flow rate 0.7 mL/min, 25 °C, 285 nm, eluent 0.1 M $HClO_4$. 2-Amino-3-(2,2′-bipyridin-4-yl)propanoic acid: D 8.15 min, L 9.73 min. 2-Amino-3-(2,2′-bipyridin-5-yl)propanoic acid: D 9.55 min, L 11.92 min.

General Method for Amine Protection of the L-Amino Acid. The amino acid/carbonate salt mixture from above was dissolved in 25 mL of 10% Na_2CO_3. *N*-[(9-Fluorenylmethoxycarbonyl)oxy]succinimide (1.2 equiv) was dissolved in 15 mL of dioxane and added dropwise to the amino acid solution. The reaction mixture was shaken periodically for 1.5 h and then transferred to a separatory funnel and diluted with 100 mL of water. This mixture was washed with ether, 4 × 60 mL, and transferred to a 250-mL Erlenmeyer flask. After the mixture was cooled to 0 °C and adjusted to pH <2 with concentrated HCl, the precipitate was isolated by centrifugation and washed with water, 3 × 100 mL. The residue was transferred to a round-bottom flask with methanol (~200 mL). The methanol was removed under reduced pressure and replaced with toluene (~80 mL). The resulting toluene/water mixture was azeotroped under reduced pressure. The residue was triturated with ether to yield a solid which was dried in vacuo to afford approximately 85% (yield based on the amount of L-amino acid methyl ester) of the N-protected amino acid.

***N*-(9-Fluorenylmethoxycarbonyl)-(*S*)-2-amino-3-(2,2′-bipyridin-4-yl)propanoic acid:** mp ~167 °C dec (over broad range); HRMS [MH$^+$] calcd for $C_{28}H_{24}N_3O_4$ 466.1779, obsd 466.1783; ^{1}H NMR (DMSO-d_6) δ 8.66 (d, br, 1 H), 8.59 (d, br, 1 H), 8.42 (s, 1 H), 8.39 (d, br, 1 H), 7.97 (m, 1 H), 7.88 (m, 1 H), 7.81 (d, 2 H), 7.55 (m, 2 H), 7.47 (m, 2 H), 7.33 (m, 2 H), 7.17 (m, 2 H), 4.35 (m, 1 H), 4.15 (m, 3 H), 3.24 (m, 1 H), 3.03 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 172.7, 156.0, 153.7, 149.9, 148.9, 148.2, 143.7, 143.6, 140.6, 140.6, 138.0, 127.6, 127.0, 127.0, 125.4, 125.2, 125.1, 124.7, 122.0, 121.1, 120.1, 65.6, 54.5, 46.5, 36.0, 25.2; IR (thin film) cm^{-1} 3315, 3060, 2957, 1731, 1715, 1706, 1696, 1540, 1449, 1255, 1219, 1182, 1152, 1104, 1079, 1046, 1018, 994, 792, 758, 737; $[\alpha]^{28}_D$ −7.4° (c = 0.5, DMSO); UV (MeOH) λ_{max} 299 nm (ϵ = 7.3 × 10^3), 265 nm (ϵ = 19.9 × 10^3).

***N*-(9-Fluorenylmethoxycarbonyl)-(*S*)-2-amino-3-(2,2′-bipyridin-5-yl)propanoic acid:** mp 117 °C dec; HRMS [MH$^+$] calcd for $C_{28}H_{24}N_3O_4$ 466.1767, obsd 466.1779; ^{1}H NMR (DMSO-d_6) δ 8.75 (d, br, 1 H), 8.70 (s, 1 H), 8.49 (d, 1 H), 8.44 (d, 1 H), 8.18 (m, 1 H), 8.07 (m, 1 H), 7.84 (m, 3 H), 7.65 (m, 1 H), 7.58 (m, 2 H), 7.25 (m, 4 H), 4.32 (m, 1 H), 4.17 (m, 3 H), 3.24 (m, 1 H), 3.01 (m, 1 H); ^{13}C NMR (CD_3OD) δ 174.0, 158.3, 150.6, 149.3, 148.8, 147.2, 145.0, 143.4, 142.7, 142.4, 138.4, 128.7, 128.1, 127.3, 126.1, 124.0, 123.5, 120.9, 68.0, 55.7, 35.5; IR (thin film) cm^{-1} 1711, 1531, 1448, 1246, 1045, 759, 739; $[\alpha]^{26}_D$ −2.1° (c = 0.5, DMSO); UV (MeOH) λ_{max} 299 nm (ϵ = 12.5 × 10^3), 288 nm (ϵ = 16.9 × 10^3), 265 nm (ϵ = 22.4 × 10^3), 228 nm (ϵ = 10.7 × 10^3).

Note: For both derivatives, the optical rotation of the FMOC amino acid derivatives was rather low. We therefore verified that no loss of optical activity had occurred in the processes after the enzyme catalyzed resolution by N-deprotection with saturated methylamine in methanol followed by analysis on the CrownPak CR (+) column. In each case optical purity of the samples was completely preserved.

5-(Bromomethyl)-2,2′-bipyridine (13). To a solution of 5-(ethoxycarbonyl)-2,2′-bipyridine[1b] (12) (2.25 g, 9.9 mmol) in anhydrous THF (50 mL) at −78 °C was added 10 mL (10 mmol) of a 1 M solution of lithium aluminum hydride in THF. The reaction mixture was allowed to warm to −20 °C at which temperature the solution became completely homogeneous. The reaction was stirred at this temperature for 0.5 h and then cooled back down to −78 °C and quenched slowly with 30 mL of 10% aqueous THF. After being warmed to room temperature the reaction mixture was stirred with dry Celite for 15 min and then filtered. The solution was then concentrated under reduced pressure to afford 1.8 g of 5-(hydroxymethyl)-2,2′-bipyridine as a thick orange oil which was used in the subsequent reaction without purification.

The product from the preceding reaction was dissolved in dichloromethane (40 mL) and cooled to 0 °C. To this was added triphenylphosphine (2.75 g, 10.5 mmol) and *N*-bromosuccinimide (1.95 g, 11 mmol). After being stirred for 0.5 h, the reaction mixture was concentrated to approximately one quarter of the original volume and applied directly to a flash silica gel column (eluent: hexanes/diethyl ether (1:1)). Concentration of the pure fractions provided 1.85 g (75% yield over two steps) of 5-(bromomethyl)-2,2′-bipyridine as a pale yellow solid: mp 70–71 °C; HRMS [M$^+$] calcd for $C_{11}H_9N_2Br$ 247.9949, obsd 247.9952; ^{1}H NMR ($CDCl_3$, 300.2 MHz) δ 4.52 (s, 2 H), 7.29 (dd, 1 H, J = 4.8, 7.4 Hz), 7.83 (m, 2 H), 8.39 (d, 2 H, J = 8.1 Hz), 8.67 (d, 2 H, J = 2.3 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 29.9, 121.2, 121.5, 124.2, 133.9, 137.2, 137.8, 149.4, 149.5, 155.7, 156.2; IR (film, cm^{-1}) 610, 650, 750, 798, 834, 858, 992, 1025, 1039, 1061, 1127, 1203, 1253, 1392, 1434, 1461, 1556, 1574, 1597, 1713, 2967, 3050; UV (MeOH) λ_{max} 289 nm (ϵ = 26.7 × 10^3); 244 nm (ϵ = 18.6 × 10^3).

***N*-(Diphenylmethylene)-2-amino-3-(2,2′-bipyridin-5-yl)-propanoic Acid *tert*-Butyl Ester (15).**[12] A solution of *N*-(diphenylmethylene)glycine *tert*-butyl ester (14) (150 mg, 0.5 mmol) and (8*S*,9*R*)-(−)-*N*-benzylcinchonidinium chloride (21 mg, 0.05 mmol) was dissolved in dichloromethane (9 mL). To this was added 0.8 mL of 50% aqueous sodium hydroxide and 5-(bromomethyl)-2,2′-bipyridine (160 mg, 0.64 mmol) in solution

(12) We have found this reaction to be most reliable in terms of asymmetric induction in the alkylation step when it is run on a scale of 1 mmol or less. Therefore, when a larger scale is required, the reaction is routinely run in several batches which are pooled for purification..

in dichloromethane (1 mL). The reaction mixture was then stirred at room temperature for 24 h. At this time the organic phase was separated and the remaining aqueous phase washed with an additional aliquot (5 mL) of dichloromethane. The pooled organic phases were then concentrated under reduced pressure and purified by flash chromatography (eluent hexane/ethylacetate (5:1) containing 0.5% triethylamine) to afford 220 mg (85% yield) of pure product. The optical purity of the product was determined to be 66% ee.[13] HRMS [M^+] calcd for $C_{30}H_{30}N_3O_2N$ 464.2338, obsd 464.2333; ^1H NMR ($CDCl_3$, 300.2 MHz) δ 1.45 (s, 9 H), 3.26 (m, 2 H), 4.19 (dd, 1 H, J = 5.34, 8.09 Hz), 6.78 (d, 2 H, J = 6.64 Hz), 7.2–7.6 (m, 9 H), 7.77 (t, 1 H, J = 7.9 Hz), 8.23 (d, 1 H, J = 8.1 Hz), 8.31 (d, 1 H, J = 8.0 Hz), 8.42 (d, 1 H, J = 9.5 Hz), 8.64 (d, 1 H, J = 4.1 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.3, 36.9, 67.4, 81.7, 120.7, 121.2, 123.7, 127.7, 128.3, 128.5, 128.7, 129.0, 130.6, 134.4, 136.4, 137.1, 138.5, 139.4, 149.3, 150.6, 154.4, 170.6, 171.1; IR (film, cm^{-1}) 650, 668, 696, 751, 849, 1029, 1150, 1220, 1253, 1288, 1368, 1392, 1458, 1558, 1575, 1589, 1622, 1732, 2933, 2977, 3056; UV (MeOH) λ_{max} 243 nm (18.9×10^3), 285 nm (18.05×10^3).

2-Amino-3-(2,2′-bipyridin-5-yl)propanoic Acid (3). A suspension of pure *N*-(diphenylmethylene)-2-amino-(2,2′-bipyridin-5-yl)propanoic acid *tert*-butyl ester (1.2 g, 2.6 mmol) was refluxed in 6 N hydrochloric acid (30 mL) for 4 h. The hydrolyzed reaction mixture was then cooled, extracted with ether (3 × 15 mL), and concentrated to dryness. The residual material was lyophilized several times from water to afford 0.72 g (100%) of the amino acid hydrochloride: mp 170 °C dec; HRMS [MH^+] calcd for $C_{11}H_9N_2Br$ 244.1086, obsd 244.1098; ^1H NMR (D_2O, 300.2 MHz) δ 3.33 (t, 2 H, J = 7 Hz), 4.37 (t, 1 H, J = 6.8 Hz), 7.86 (t, 1 H, J = 6.8 Hz), 7.86 (t, 1 H, J = 5.8 Hz), 8.08 (d, 1 H, J = 7 Hz), 8.15 (d, 1 H, J = 8.15 Hz), 8.3–8.5 (m, 2 H), 8.61 (s, 1 H), 8.66 (d, 1 H, J = 5.6 Hz); ^{13}C NMR (D_2O, 75.5 MHz) δ 32.9, 53.4, 123.5, 124.5, 127.6, 134.7, 141.6, 143.2, 145.8, 146.8, 147.2, 149.8, 170.6; UV (H_2O) λ_{max} 238 nm ($\epsilon = 8.44 \times 10^3$); 287 nm ($\epsilon$ 9.996×10^3).

(13) Optical purities were determined by HPLC on a CrownPak CR (+) column after exhaustive hydrolysis in 6 N hydrochloric acid (80 °C,6 h)

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Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra for compounds **4**, **6**, **8**, **10**, **11**, **13**, and **15** and HPLC traces of amino acids **2** and **3** (17 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.