A Facile Method for the Asymmetric Synthesis of α-Methyltryptophan

Lijun Zhang* and John M. Finn

Agricultural Research Division, American Cyanamid Company, Princeton, New Jersey 08543

Received March 6, 1995

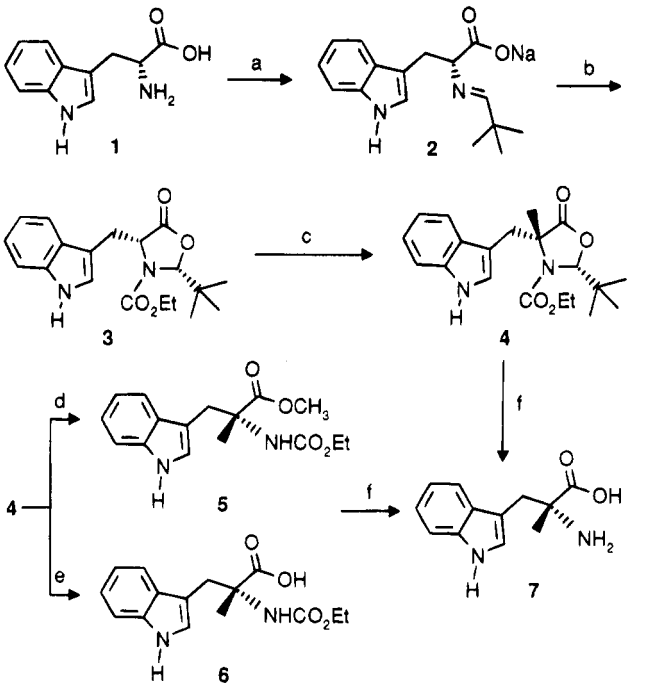
Peptides containing α-substituted-α-amino acids may have special bioactivitives, owing to their tendency to favor specific conformations[1] and dramatic increases in their resistance to hydrolysis.[2] For this reason, the asymmetric synthesis of α-substituted-α-amino acids has recently attracted much attention.[3,4]

In a recent synthetic program, we required optically pure (*R*)-α-methyltryptophan derivatives **5** and **6**. Several literature methods are available for the asymmetric synthesis of α-methyltryptophan.[5] One of the more attractive is Seebach's "chiral self-reproduction" procedure.[5b] However, this synthesis utilizes 1-(*tert*-butoxycarbonyl)-3-(bromomethyl)indole which is commercially unavailable. Another approach was reported by Crich and co-workers.[5c] This method uses tryptophan derivatives as the original source of chirality, but requires several steps including protection and deprotection of the indole nitrogen. In this paper, we describe a new, simpler method for the asymmetric synthesis of α-methyltryptophan. We take advantage of Seebach's principle[6] of "self-reproduction of chirality", using readily available tryptophan as starting material. In this procedure, the protection on the indole moiety is not necessary. The synthetic route is outlined in Scheme 1.

The first step in the synthetic scheme is the synthesis of oxazolidinone **3.** Following Seebach's general procedure for preparation of oxazolidinone derivatives,[7] the sodium salt of D-tryptophan was condensed with pivaladehyde in methylene chloride with azeotropic removal of water to give the Schiff base **2**, which was then cyclized by treatment with ethyl chloroformate at or below room temperature. Oxazolidinone **3** was obtained in 35% yield and 96:4 stereoselectivity.[8] The major isomer was assigned as cis by NOE measurement. This assignment was further confirmed by the measurement of the specific rotation of final product α-methyltryptophan (**7**). The major byproduct of the reaction was identified as N^{α}-(ethoxycarbonyl)tryptophan. We reasoned that the byproduct was the result of incomplete conversion of tryptophan into Schiff base **2** because of the low solubility of the sodium salt of tryptophan in methylene chloride.[9] To solve this problem, methanol instead of methylene chloride was used as solvent in the first step and water generated from this reaction was removed with 4 Å molecular sieves. After removal of methanol, the dried Schiff base **2** was then treated with ethyl chloroformate in methylene chloride to give **3** in 67% yield, maintaining the same degree of stereoselectivity.

Direct methylation of **3** was successfully achieved by treatment of **3** with 2 equiv of LDA followed by 1 equivalent of iodomethane in THF at −78 °C. No protection of the indole moiety was required.[10] The first equivalent of LDA deprotonated the indole NH to give a

Scheme 1[a]



[a] Reagents: (a) NaOH/Me_3CCHO/MeOH/4 Å molecular sieves, 20 °C, or NaOH/Me_3CCHO/CH_2Cl_2, reflux; (b) $ClCO_2Et$/CH_2Cl_2, 0 to 20 °C; (c) 2 equiv of LDA/1 equiv of MeI/THF, −78 °C; (d) LiOH·H_2O/MeOH, 40 °C; (e) LiOH·H_2O/MeOH/H_2O, 45 °C; (f) 6 N HCl, reflux.

(1) (a) Paul, P. K. C.; Sukumar, M.; Bardi, R.; Piazzesi, A. M.; Valle, G.; Toniolo, C.; Balaram, P. *J. Am. Chem. Soc.* **1986**, *108*, 6363 and references cited therein. (b) Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238 and references cited therein. (c) Toniolo, C.; formaggio, F.; Crisma, M.; Valle, G.; Boesten, W. H. J.; Schoemaker, H. E.; Kamphuis, J.; Temussi, P. A.; Becker, E. L.; Precigoux, G. *Tetrahedron* **1993**, *17*, 3641 and references cited therein.

(2) (a) Turk, J.; Panse, G. T.; Marshall, G. R. *J. Org. Chem.* **1975**, *40*, 953. (b) Khosla, M. C.; Stachowiak, K.; Smeby, R. R.; Bumpus, F. M.; Piriou, F.; Lintner, K.; Fermandjian, S. *Proc. Natl. Acad. Sci., U.S.A.* **1981**, *78*, 757.

(3) For reviews, see: (a) O'Donnell, M. J., Ed. α-Amino Acid Synthesis. *Tetrahedron* **1988**, *44*, 5253. (b) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989.

(4) For example, see: (a) Fadel, A.; Salaun, J. *Tetrahedron Lett.* **1987**, *28*, 2243. (b) Schollkopf, U.; Westphalen, K.-O.; Schroder, J.; Horn, K. *Liebigs Ann. Chem.* **1988**, 781. (c) Zydowsky, T. M.; de Lara, E.; Spanton, S. G. *J. Org. Chem.* **1990**, *55*, 5437. (d) Ojima, I.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.* **1990**, *112*, 770. (e) Williams, R. M.; Im, M.-N. *J. Am. Chem. Soc.* **1991**, *113*, 9276. (f) Ihara, M.; Takahashi, M.; Taniguchi, N.; Yasui, K.; Niitsuma, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 525. (f) Roos, E. C.; Lopez, M. C.; Brook, M. A.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1993**, *58*, 3259.

(5) (a) Schollkopf, U.; Lonsky, R.; Lehr, P. *Liebigs Ann. Chem.* **1985**, 413. (b) Gander-Coquoz, M.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 224. (c) Bourne, G. T.; Crich, D.; Davies, J. W.; Horwell, D. C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1693. (d) Cativiela, C.; Diaz de Villegas, M. D.; Galvez, J. A. *Synlett* **1994**, 302.

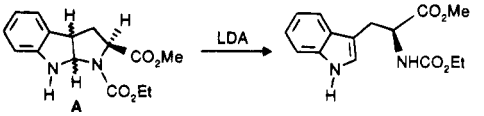
(6) Seebach, D.; Imwinkelried, R.; Weber, T. *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer Verlag: Heidelberg, 1986; Vol. 4, p 125.

(7) (a) Seebach, D.; Fadel, A. *Helv. Chim. Acta* **1985**, *68*, 1243. (b) Altmann, E.; Nebel, K.; Mutter, M. *Helv. Chim. Acta* **1991**, *74*, 800.

(8) The ratio of cis:trans was determined by ^1H NMR analysis.

(9) While triethylamine was used as the base, the yield was increased to 57% and further increased to 77% using THF as the solvent; however, the stereoselectivity (cis:trans) decreased to 70:30 and 67:33, respectively. The two isomers can be separated by careful chromatography on silica gel.

(10) Attempt at direct methylation of Crich's[5c] intermediate **A** was unsuccessful. Treatment of **A** with LDA resulted in ring opening



0022-3263/95/1960-5719$09.00/0

nitrogen anion which was inert to iodomethane at −78 °C. The second equivalent of LDA then deprotonated the α-carbon to generate an enolate which quickly reacted with iodomethane to give **4** in good yield (79%). The reaction is highly stereoselective with the approach of the iodomethane from the opposite face of the *tert*-butyl group,[7] resulting in compound **4** with the cis configuration (cis:trans > 99:1).

α-Methyltryptophan derivatives **5** and **6** were easily obtained in high yield by treatment of **4** with LiOH in MeOH and MeOH/H_2O respectively.

Further hydrolysis of **5** or **6** in refluxing 6 N HCl gave the final product (*R*)-α-methyltryptophan (**7**) in good yield. Direct hydrolysis of **4** in refluxing 6 N HCl also gave **7** in good yield. The enantiomeric excess of **7** was 92% as determined by ^{19}F NMR analysis of its Mosher amide.[11] This is the highest value expected from the 96:4 mixture of **3**.

In conclusion, α-methyltryptophan and its derivatives can be easily obtained in high yield and good enantiomeric purity from readily available starting materials in three steps.

Experimental Section

^1H NMR and ^{13}C NMR spectra were measured at 300 MHz. All reagents and solvents were used without further purification. Melting points are uncorrected. The HPLC was performed on a Whatman Partisil 5 C_8 column, using H_2O/CH_3CN contained 0.2% HCO_2H as the mobile phase in the gradient elution.

(2*R*,4*R*)-2-(*tert*-Butyl)-3-(ethoxycarbonyl)-4-(indol-3-ylmethyl)-1, 3-oxazolidin-5-one (3). D-Tryptophan (5.1 g, 25.0 mmol), pivalaldehyde (3.2 g, 37.5 mmol), and 4 Å molecular sieves (10 g) were added to a solution of NaOH (1.0 g, 25.0 mmol) in anhydrous MeOH (60 mL). The mixture was stirred at 20 °C for 6 h. After removal of molecular sieves by filtration under N_2, the filtrate was evaporated under reduced pressure to give a solid, which was further dried under vacuum for 6 h to give Schiff base **2** as an off-white solid: ^1H NMR (DMSO-d_6) δ 0.73 (s, 9H), 2.90 (dd, *J* = 8.6, 12.0 Hz, 1H), 3.22 (dd, *J* = 3.4, 12.0 Hz, 1H), 3.58 (dd, *J* = 3.4, 8.6 Hz, 1H), 6.80−7.0 (m, 4H), 7,28 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 10.9 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 27.1, 30.6, 36.0, 78.6, 111.7, 112.8, 118.3, 119.3, 121.0, 124.1, 128.4, 136.7, 176.9; IR (Nujol) 3409, 3223, 1657, 1588 cm^{-1}.

Anhydrous CH_2Cl_2 (200 mL) was added to the Schiff base **2** under N_2. The mixture was cooled to 0 °C with an ice−water bath and treated with ethyl chloroformate (3.3 g, 30.0 mmol). The resulting mixture was stirred at 0 °C for 6 h and then at 20 °C overnight. After removal of the precipitate by filtration, the filtrate was concentrated and the residue was purified by chromatography on silica gel to give **3** (5.76 g, 67%, cis:trans = 96:4)[12] as a gum: $[\alpha]^{20}_D$ = +13.9 (*c* = 1.23, $CHCl_3$); ^1H NMR ($CDCl_3$) δ cis-isomer 1.05 (s, 9H), 1.14 (t, *J* = 7.0 Hz, 3H), 3.38 (d, *J* = 6.6 Hz, 2H), 4.12 (q, *J* = 7.0 Hz, 2H), 4.62 (t, *J* = 6.6 Hz, 1H), 5.58 (s, 1H), 7.08−7.20 (m, 3H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 8.28 (s, 1H); trans-isomer 0.91 (s, 9H), 1.22 (br s, 3H), 3.41 (br d, *J* = 16 Hz, 2H), 4.18 (br s, 2H), 4.48 (dd, *J* = 5.0, 2.0 Hz, 1H), 5.22 (br s, 1H), 7.08−7.38 (m, 4H), 7.65 (d, *J* = 7.5 Hz, 1H), 8.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ cis-isomer 14.0, 24.9, 29.1, 36.9, 57.5, 62.4, 96.0, 110.4, 111.2, 118.5, 119.3, 121.8, 123.6, 127.3, 136.1, 156.1, 172.3; trans-isomer 14.2, 24.7, 28.5, 39.4, 58.4, 62.0, 95.0, 107.8, 110.9, 118.5, 119.3, 121.8, 123.6, 127.5, 135.9, 156.1, 173.2; MS (*m*/*z*) 345 (M^+ + 1); IR (neat) 3406, 1793, 1705 cm^{-1}. Anal. Calcd for $C_{19}H_{24}N_2O_4 \cdot {}^1/_2H_2O$: C, 64.57; H, 7.13; N, 7.93. Found: C, 64.83; H, 7.12; N, 7.38.

In a similar fashion, the enantiomer of **3** was prepared from L-tryptophan.

(2*R*,4*R*)-2-(*tert*-Butyl)-3-(ethoxycarbonyl)-4-(indol-3-ylmethyl]-4-methyl-1,3-oxazolidin-5-one (4). A solution of **3** (3.1 g, 9.0 mmol) in anhydrous THF (50 mL) was treated with a solution of LDA (10 mL, 2 N) in THF at −78 °C under N_2. After 0.5 h, a solution of MeI (1.56 g, 11.0 mmol) in anhydrous THF was added. The resulting reaction mixture was stirred at −78 °C for 2 h. The reaction was quenched with AcOH (1.2 g, 20.0 mmol) at −78 °C. The reaction mixture was concentrated and then the residue was purified by chromatography on silica gel to give **4** (2.55 g, 78.9%) as white solid: mp 107−108 °C. $[\alpha]^{20}_D$ = −50.2 (*c* = 1.24, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.51 (s, 9H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.58 (s, 3H), 3.42 (d, *J* = 12.0 Hz, 1H), 3.50 (d, *J* = 12.0 Hz, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 5.42 (s, 1H), 7.02−7.15 (m, 3H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 8.04 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.5, 24.2, 32.6, 37.7, 62.1, 65.2, 72.2, 94.5, 110.5, 111.1, 119.3, 119.6, 121.9, 124.7, 129.0, 135.9, 156.1, 175.4. MS (*m*/*z*) 359 (M^+ + 1); IR (neat) 3409, 1790, 1714 cm^{-1}. Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.83; H, 7.33; N, 7.70.

(*R*)-N^{α}-(Methoxycarbonyl)-α-methyltryptophan Methyl Ester (5). Oxazolidinone **4** (0.80 g, 2.23 mmol) was mixed with a solution of LiOH·H_2O (0.15 g, 3.57 mmol) in MeOH (20 mL) and stirred at 40 °C. The reaction was monitored by HPLC until it was complete (about 6 h). MeOH was removed under reduced pressure. The residue was diluted with H_2O (20 mL) and extracted with Et_2O (3 × 30 mL). Organic phase was dried over $MgSO_4$. After removal of Et_2O, the residue was crystallized from CH_2Cl_2/hexane to give **5** (0.65 g, 95.7%) as a white solid: mp 96.0−98.0 °C; $[\alpha]^{20}_D$ = −42.3 (*c* = 0.70, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3H), 1.68 (s, 3H), 3.38 (d, *J* = 14.0 Hz, 1H), 3.45 (d, *J* = 14.0 Hz, 1H), 3.68 (s, 3H), 4.14 (q, *J* = 7.2 Hz, 2H), 5.45 (br s, 1H), 6.92 (s, 1H), 7.08−7.20 (m, 2H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 8.58 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.4, 23.7, 32.8, 52.7, 60.7, 60.9, 109.8, 111.4, 118.9, 119.6, 122.0, 123.8, 128.2, 136.1, 155.5, 174.9.; MS (*m*/*z*) 305 (M^+ + 1); IR (Nujol) 3360, 1700 cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_2O_4 \cdot {}^1/_2H_2O$: C, 61.31; H, 6.75; N, 8.93. Found: C, 61.31; H, 6.67; N, 8.80.

(*R*)-N^{α}-(Methoxycarbonyl)-α-methyltryptophan (6). Oxazolidinone **4** (0.80 g, 2.23 mmol) was mixed with a solution of LiOH·H_2O (0.20 g, 4.76 mmol) in MeOH/H_2O (3:1, 20 mL) and stirred at 45 °C. The reaction was monitored by HPLC until it was complete (about 4 h). After removal of MeOH, to the residue was added aqueous HCl (1 N, 10 mL), and it was extracted with Et_2O (4 × 30 mL). The organic phase was dried over $MgSO_4$. After removal of Et_2O, the residue was crystallized from CH_2Cl_2/hexane to give **6** (0.61 g, 94.3%) as a white solid: mp 68.0−70.0 °C; $[\alpha]^{20}_D$ = −9.3 (*c* = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.20 (t, *J* = 7.0 Hz, 3H), 1.66 (br s, 3H), 3.38 (d, *J* = 13.0 Hz, 1H), 3.40 (d, *J* = 13.0 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 5.40 (br s, 2H), 6.90 (s, 1H), 7.02−7.18 (m, 2H), 7.28 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 8.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.1, 23.5, 32.6, 60.7, 61.1, 109.6, 111.4, 118.9, 119.5, 121.9, 124.2, 128.4, 136.1, 156.0, 178.2; MS (*m*/*z*) 291 (M^+ + 1); IR (Nujol) 3420, 1699 cm^{-1}. Anal. Calcd for $C_{15}H_{18}N_2O_4 \cdot {}^1/_4H_2O$: C, 61.11; H, 6.32; N, 9.50. Found: C, 61.16; H, 6.25; N, 9.16.

(*R*)-α-Methyltryptophan (7). Compound **5** (0.40 g, 1.3 mmol) was refluxed in aqueous HCl (6 N, 10 mL) for 16 h. The reaction mixture was cooled to room temperature and washed with CH_2Cl_2 (2 × 10 mL) and then concentrated to give crude **7**·HCl . Pure **7** (0.25 g, 87%, 92% ee) was obtained by cation-exchange chromatography on a Dowex 50 × 8−200 ion-exchange resin (eluted with 3% aqueous NH_3): mp 233−235 °C [lit.[5d] 233 °C]; $[\alpha]^{20}_D$ = +11.6 (*c* = 1.1, H_2O) [lit.[5b] (*S*): −10.6 (*c* = 0.9, H_2O)] or $[\alpha]^{20}_D$ = +15.5 (*c* = 0.95, MeOH) [lit.[5c] (*R*): +16 (*c* = 1.0, MeOH)]; ^1H NMR (D_2O) δ 1.53 (s, 3H), 3.16 (d, *J* = 15.6 Hz, 1H), 3.38 (d, *J* = 15.6 Hz, 1H), 4.70 (s, H_2O), 7.10−7.25 (m, 3H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (D_2O) δ 24.5, 34.7, 64.6, 109.2, 114.0, 120.9, 121.7, 124.2, 127.6, 129.6, 138.2, 179.1; MS (*m*/*z*) 219 (M^+ + 1); IR (Nujol) 3200, 1622 cm^{-1}. **7** was obtained in about 85% yield (determined by HPLC) from **4** under the same conditions.

Acknowledgment. We thank Dr. David W. Ladner for his support and suggestions during the writing of this manuscript.

JO950433Y

(11) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(12) This reaction generally gave **3** in 52−75% yield.