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A Concise Synthesis of (*S*)-*N*-Ethoxycarbonyl-α-methylvaline

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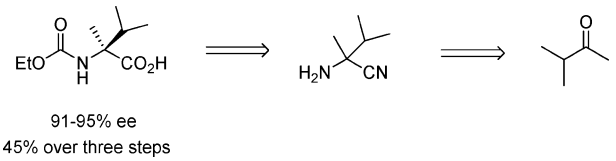

A practical and efficient protocol for the three-step synthesis of (*S*)-*N*-ethoxycarbonyl-α-methylvaline **3** is described which utilizes readily available commercial starting materials. The key transformations involve resolution-crystallization of tartrate salt **6** followed by a one-pot procedure for the preparation of **3** which is isolated as the dicyclohexylamine salt in 45% overall yield and in 91−95% ee.

The preparation of α-methyl-α-substituted amino acids as unnatural amino acid analogues has received considerable interest due to restricted conformational freedom and the tendency to induce 3_{10}-, α-helical, and β-turn-type conformations when incorporated in peptide chains,[1] and these compounds have been incorporated into marketed pharmaceuticals such as Aldomet (L-α-methylDOPA).[2] Since α-methyl-α-substituted amino acids are unable to undergo racemization, these nonproteinogenic building blocks can impart significant changes in biological activities and have found applications in enzyme mimetics and in de novo design of proteins.[3] As α-methyl-α-substituted amino acids are rarely found in nature, the preparation of these increasingly important building blocks in high yield and enantiopure form, by methods that are also amenable to large scale, underscores the importance of developing new methodologies. In particular, α-methylvaline **1** and its amide derivative **2** have been used extensively in the preparation of a range of both medicinal[4] and herbicidal agents (Figure 1).[5] While the asymmetric syntheses of **1** and **2** have been reported,[6] each pose formidable challenges due to starting material availability, length of synthesis, and low-yielding transformations which are most likely due to the sterically hindered nature of **1**. Classical resolution strategies have also been reported;[7] however, complete procedures are scarce since racemic **1** is not readily available and many procedures are only found in published patents which are often difficult to interpret and often lack complete accounts of experimental details. In this paper, we document a full description of an experimentally simplified protocol for the three-step preparation of (*S*)-*N*-ethoxycarbonyl-α-methylvaline **3** which is amenable to large scale and offers significant advantages over currently available methodologies.

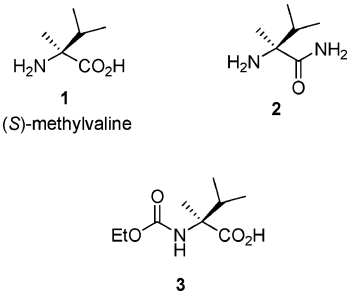

FIGURE 1. Methylvaline and derivatives.

The synthesis of **3** began with the Strecker reaction of 3-methyl-2-butanone **4** (Scheme 1). Reaction of **4** with 0.95 equiv of NaCN in the presence of 0.5 equiv of NH_4Cl and 0.5 equiv of $MgSO_4$ in 7 M NH_3 in MeOH (3.0 equiv) at 30 °C

(1) For leading references, see: (a) Formaggio, F.; Barazza, A.; Bertocco, A.; Toniolo, C.; Broxterman, Q. B.; Kaptein, B.; Brasola, E.; Pengo, P.; Pasquato, L.; Scrimin, P. *J. Org. Chem.* **2004**, *69*, 3849 and references cited therein. (b) Pengo, P.; Broxtermen, Q. B.; Kaptein, B.; Pasquato, L.; Scrimin, P. *Langmuir* **2003**, *19*, 2521. (c) Karle, I. L.; Balaram, P. *Biochemistry* **1990**, *29*, 6747. (d) Mutter, M. *Angew Chem.* **1985**, *97*, 639.

(2) Reinhold, D. F.; Firestone, R. A.; Gaines, W. A.; Chemerda, J. M.; Sletzinger, M. *J. Org. Chem.* **1968**, *33*, 1209 and references cited therein.

(3) For recent reviews, see: (a) Andrews, M. J. I.; Tabor, A. B. *Tetrahedron* **1999**, *55*, 11711. (b) Venkatraman, J.; Shankaramma, S. C.; Balaram, P. *Chem. Rev.* **2001**, *101*, 3131. (c) Licini, G.; Prins, L.; Scrimin, P. *Eur. J. Org. Chem.* **2005**, 969. (d) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127. (e) Cativiela, C.; Díaz-de-Villega, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569. (f) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406.

(4) For leading references, see: (a) Fitch, D. M.; Evans, K. A.; Chai, D.; Duffy, K. J. *Org. Lett.* **2005**, *7*, 5521. (b) Shen, D.-M.; Shu, M.; Willoughby, C. A.; Shah, S.; Lynch, C. L.; Hale, J. J.; Mills, S. G.; Chapman, K. T.; Malkowitz, L.; Springer, M. S.; Gould, S. L.; DeMartino, J. A.; Siciliano, S. J.; Lyons, K.; Pivnichny, J. V.; Kwei, G. Y.; Carella, A.; Carver, G.; Holmes, K.; Schleif, W. A.; Danzeisen, R.; Hazuda, D.; Kessler, J.; Lineberger, J.; Miller, M. D.; Emini, E. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 941. (c) Tice, C. M.; Hormann, R. E.; Thompson, C. S.; Friz, J. L.; Cavanaugh, C. K.; Michelotti, E. L.; Garcia, J.; Nicolas, E.; Albericio, F. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 475.

(5) (a) Los, M. US Patent 4554013, 1985. (b) Orwick, P. L.; Templeton, A. R. US Patent 4404012, 1983. (c) Los, M. US Patent 4017510, 1977. (d) Gastrock, W. H.; Wepplo, P. J. US Patent 4683324, 1987. (e) Eur. Patent 0,123.830, 1984.

(6) (a) Seebach, D.; Aebi, J. D.; Naef, R.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 144. (b) Obrecht, D.; Spiegler, C.; Schönholzer, P.; Müller, K. *Helv. Chim. Acta* **1992**, *75*, 1666. (c) Obrecht, D.; Bohdal, U.; Broger, C.; Bur, D.; Lehmann, C.; Ruffieuz, R.; Schönholzer, P.; Spiegler, C.; Müller, K. *Helv. Chem. Acta* **1995**, *78*, 563. (d) Cativiela, C.; Díaz-de-Villegas, M. D.; Gálvez, J. A.; Lapeña, Y. *Tetrahedron* **1995**, *51*, 5921. (e) Cooper, T. S.; Laurent, P.; Moody, C. J.; Takle, A. K. *Org. Biomol. Chem.* **2004**, *2*, 265.

(7) (a) Turk, J.; Panse, G. T.; Marshall, G. R. *J. Org. Chem.* **1975**, *40*, 953. (b) Kruizinga, W. H.; Bolster, J.; Kellogg, R. M.; Kamphuis, J.; Boesten, W. H. J.; Meijer, E. M.; Schoemaker, H. E. *J. Org. Chem.* **1988**, *53*, 1826. (c) Boesten, W. H. J.; Peters, P. J. H. Eur. Patent 150854, 1984. (d) Sonke, T.; Kaptein, B.; Boesten, W. H. J.; Broxterman, Q. B.; Schoemaker, W. H. J.; Kamphuis, J.; Formaggio, F.; Toniolo, C.; Rutjes, N. In *Stereoselective Biocatalysis*; Patel, R. M., Ed.; Dekker: New York, 2000; pp 23−58. (e) Kaptein, B.; Boesten, W. H. J.; Broxterman, Q. B.; Peters, P. J. H.; Schoemaker, H. E.; Kamphuis, J. *Tetrahedron: Asymmetry* **1993**, *4*, 1113. (f) Kaptein, B.; Broxterman, Q. B.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Veerman, J. J. N.; Kamphuis, J.; Peggion, C.; Formaggio, F.; Toniolo, C. *Tetrahedron* **2001**, *57*, 6567.

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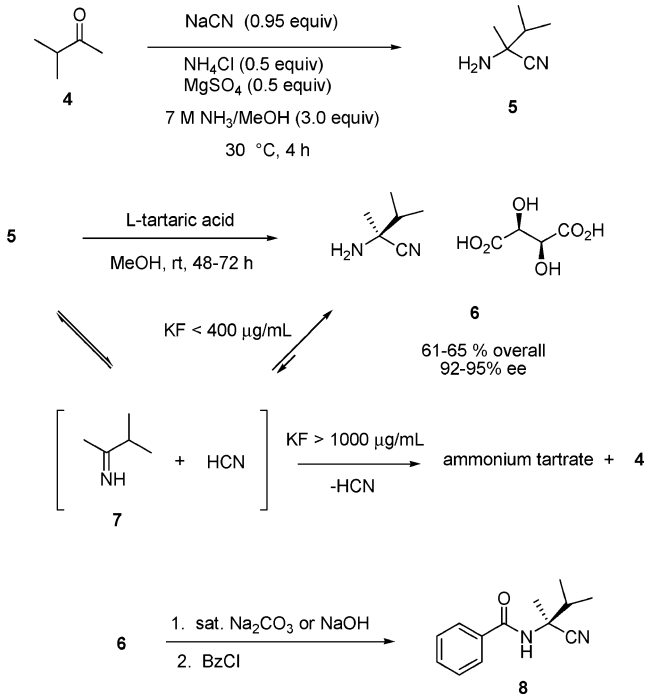
afforded quantitative conversion to crude racemic **5**.[8] The use of an excess of ketone **4** ensured that complete consumption of NaCN occurred. The choice of workup conditions for this reaction was found to be crucial for conversion to enantioenriched **5** (vide infra). The optimal conditions involved concentration of nearly all the NH_3/MeOH from the reaction mixture under reduced pressure and temperature, dilution with MTBE, and filtration of the inorganic solids. This procedure allowed for the complete removal of all inorganic salts without an aqueous workup and provided a means of drying crude **5** by azeotropic distillation under reduced pressure to a KF (by Karl Fisher titration) of <400 μg/mL of water. Crude **5** was then solvent switched back to MeOH by distillation prior to utilization in the next reaction. Initial experiments employed an aqueous workup after filtration of the inorganic salts and were followed by extraction with MTBE. However, difficulties were encountered upon concentration since azeotropic drying of MeOH under reduced pressure, after complete removal of MTBE, was nearly impossible leaving a MeOH solution of **5** which was particularly "wet" with water.[9] In addition, the low boiling point of **5** resulted in significant losses during removal of MeOH when the concentration was conducted at elevated temperatures.[10]

The preparation of enantioenriched **5** involved a resolution−crystallization protocol with L-tartaric acid.[5d] The conversion of racemic **5** to enantioenriched **6** involved the formation of imine **7** and HCN, where upon equilibration, the desired salt **6** was isolated in high enantiopurity. It was discovered through extensive experimentation that careful attention to detail was necessary for the success of this resolution. For example, initial experiments which employed an aqueous workup of crude **5** from the Strecker reaction of **4** led to the formation of significant amounts of ammonium tartrate. In certain cases where the water content of the reaction was high (>1000 μg/mL), ammonium tartrate became the only isolated product. On the other hand, when the optimal conditions for workup of **5** described above were utilized, little ammonium tartrate was formed and good conversion to **6** was observed in excellent enantiopurity and good chemical yield. Successful conditions for conversion to **6** involved addition of crude **5** in MeOH (KF < 400 μg/mL) to a solution of a slight excess (1−1.3 equiv) of L-tartaric acid in MeOH followed by stirring at rt for 48−72 h. In order to minimize loss of HCN during the resolution, the reaction mixture was sealed and vented to an oil bubbler followed by a caustic scrubber which trapped any escaping HCN. The course of the reaction could be monitored by filtration of a small sample, conversion to benzamide **8**, and analyzing by chiral super critical fluid chromatography (SFC). After 24 h, the enantiopurity of **6** was typically 80% ee, and after 48 h, >91% ee was achieved. After filtration, tartrate salt **6** was isolated in 61−65% overall yield for the two-step procedure and in 92−95% ee.

Having identified optimal conditions for the preparation of enantioenriched **6**, our attention turned to the preparation of (*S*)-methylvaline **1** and suitable conditions for isolation. Since **1** is highly soluble in water, efforts were focused on the preparation of ethyl carbamate **3** which would not only facilitate its isolation by extraction into an organic solvent but also allow the ethyl

SCHEME 1



carbamate to serve as an easily removable protecting group. Due to severe steric interactions, basic hydrolysis of amino nitrile **5** is sluggish and low conversion to amide intermediate **2** or the corresponding amino acid **1** is observed. The conversion of **6** to amide **2** has been described[5d] and involves conversion of **6** to the free amino nitrile **5** followed by hydrolysis in conc. H_2SO_4; however, conversion of **6** to (*S*)-methylvaline **1** or any of its other derivatives has not been described. It was envisioned that acid hydrolysis of **5** under more forcing conditions followed by conversion to ethyl carbamate **3** could be effected in a one-pot procedure after conversion of **6** to free aminonitrile **5**.

The salt-break of **6** to **5** in the presence of either NaOH or NH_4OH has been studied,[4d,11] and solutions of **5** in certain solvents are chemically stable for prolonged periods of time without any loss of enantiopurity.[10a] Armed with this data, slurrying **6** in CH_2Cl_2 followed by the addition of 3.2 equiv of 5 N NaOH provided a homogeneous biphasic solution (Scheme 2). Separation of the layers and analyzing both layers by ^{1}H NMR revealed that quantitative extraction of **5** into the organic layer had occurred and all the tartrate remained in the aqueous layer. Although the organic layer could be concentrated under reduced pressure and used without further purification, simple extraction of the organic extract with 50% v/v H_2SO_4 (6 equiv) was also quantitative, leaving virtually no detectable amounts of **5a** in the organic layer as revealed by ^{1}H NMR analysis of each layer. Hydrolysis of **5a** in 50% H_2SO_4 was conducted at 100 °C for 18−24 h to provide a crude aqueous solution of α-methylvaline **1**.[12] Attempts to use this crude hydrolysis mixture for the direct conversion to **3** by adjusting the pH to 8.5−9.0 and addition of 1.2 equiv of ethyl chloroformate resulted in the formation of at least three products of which **3** was the major component (80%). Interestingly, urethane **9** was identified as a significant reaction product which suggested that

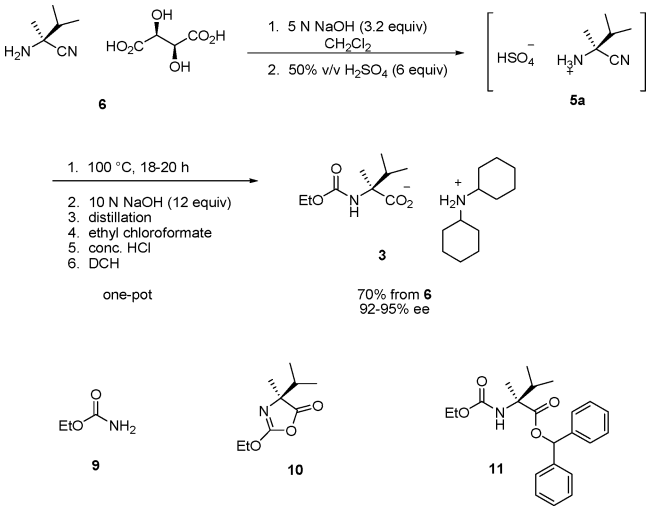
(8) (a) Deng, S. L.; Liu, D. Z. *Synthesis* **2001**, 2445. (b) Christjohannes, J.; Heimgartner, H. *Helv. Chim. Acta* **1986**, *69*, 374. (c) Piper, J. R.; Stringfellow, C. R.; Johnston, T. P., Jr. *J. Med. Chem.* **1966**, *9*, 911.

(9) Horsley, L. H. *Azeotropic Data III*; American Chemical Society: Washington, DC, 1973.

(10) The reported bp of **5** is 71 °C/13 mmHg (see ref 7c) and 43−47 °C/3 mmHg (see ref 7a).

(11) (a) Gastrock, W. H.; Wepplo, P. J.; Kremer, K. A. M.; Drabb, T. W. Eur. Patent 1050529B1. (b) Kremer, K. A. M. International Patent WO 01/47856A1.

SCHEME 2



competitive reaction of ammonia, liberated during the hydrolysis of amide intermediate **2**, with ethyl chloroformate was occurring. Also identified in the crude reaction mixture was oxazolinone **10**.[13] The formation of **10** could be explained by acylation of both the nitrogen atom and the carboxylate ion followed by intramolecular cyclization to **10** and represents an unusual case of formation of an oxazolinone under Schotten−Baumann reaction conditions.[14] After extensive examination of all of the reaction parameters, it was discovered that optimal conditions for the one-pot conversion of **5a** to **3** required heating in 50% H_2SO_4 (6 equiv) at 100 °C for 18−24 h followed by adjusting the pH to 12 by the addition of 10 N NaOH (12 equiv). In order to effectively remove ammonia from the reaction mixture and eliminate the competitive formation of urethane **9**, distillation of ammonia from the crude mixture was conducted at 100−104 °C at atmospheric pressure.[15] The removal of approximately 1/4 of the total reaction volume was required to completely remove ammonia from the reaction mixture.[16] Once the distillation was complete, the reaction mixture was cooled to 20−25 °C, 0.90 equiv of ethyl chloroformate was added, and the pH of the mixture was maintained around 10.0 by the portionwise addition of 10 N NaOH over 1−2 h. These conditions also suppressed the formation of **10** and resulted in an extremely clean reaction profile. Finally, the pH of the reaction mixture was readjusted to 2.2 with conc. HCl and the mixture was filtered to remove the precipitated Na_2SO_4 formed during the neutralization of H_2SO_4 with NaOH. After extraction with MTBE and drying, carbamate **3** was isolated in analytically pure form as the dicyclohexylamine (DCH) salt in 70% overall yield from **6** and in 92−95% ee. The final ee determination of **3** was conducted by conversion to benzhydryl ester **11** with diphenyldiazomethane[17] and analyzing by chiral SFC.

In conclusion, we have established a rapid, practical, and efficient method for the three-step preparation of (*S*)-*N*-ethoxycarbonyl-α-methylvaline **3** which proceeds in 45% overall yield from readily available bulk chemicals, requires no chromatographic separations, and provides **3** in 92−95% ee. A clear understanding of the reaction parameters, which can greatly affect the outcome of each transformation, allows for successful preparation of **3**. The formation of tartrate salt **6** under anhydrous conditions and removal of ammonia prior to formation of carbamate **3** were necessary in order to obtain reproducible yields. The use of D-tartaric acid would also provide access to the enantiomer of **3** using the present methodology. Application of this methodology for the preparation of other α,α-disubstituted amino acids may be possible and could aid in the discovery and development of a wide range of structurally intriguing compounds.

Experimental Section

Caution: The potential for HCN release is present. These reactions should be effectively scrubbed with either a caustic or bleach scrubber, and adequate protective equipment should be worn at all times to prevent exposure.

Preparation of (*S*)-2-Amino-2,3-dimethylbutyronitrile (2*R*,3*R*)-Tartrate (6). In a 75 L round-bottom flask equipped with a mechanical stirrer, condenser, and thermocouple was added 2.79 kg (23.2 mol) of $MgSO_4$, 1.24 kg (23.2 mol) of NH_4Cl, and 2.16 kg (44.1 mol) of NaCN. The solids were slurried in 26.5 L (185.6 mol) of 7 M NH_3 in MeOH and cooled to −5 to −10 °C. The internal temperature of the slurry was −5 °C and rose to 8 °C after stirring for 10 min as some of the solids dissolved. To the resulting suspension was added in one portion (4.00 kg, 46.4 mol) of 3-methyl-2-butanone **4**. The internal temperature slowly rose from 8 to 35 °C over the course of 1 h, at which point it slowly decreased to 30 °C and was held at this temperature for 3 h (total reaction time 4 h). The reaction was judged complete by GC analysis at this point. The solvent was then removed under reduced pressure (∼ 30 mmHg) while maintaining the internal temperature <30 °C until nearly all of the MeOH and ammonia were removed. The resulting slurry of inorganic salts and the product was diluted with 30 L of MTBE, stirred at rt for 30 min, and filtered. The inorganic wet cake was washed with 4 L of MTBE. The filtrate was then charged to a 75 L round-bottom flask equipped with a thermocouple, mechanical stirrer, and a vacuum distillation apparatus. The solvent was concentrated under reduced pressure (∼30 mmHg) while maintaining the internal temperature <20 °C and solvent switched to a final volume of 20 L of MeOH for use in the next step without further purification. The KF of the solution was 373 μg/mL of water, and the final ^{1}H NMR assay was 4.3 kg of **5** (87%).

In a separate 100 L round-bottom flask equipped with a thermocouple and mechanical was added 6.79 kg (46.4 mol) of L-tartaric acid and 45 L of MeOH. The resulting homogeneous solution was cooled to an internal temperature of 8 °C, and the above crude solution of amino nitrile **5** in MeOH was added over 45 min. After approximately 2 L of the crude amino nitrile solution was added, the solution was seeded with 100 g of **6** which was 95% ee. The reaction mixture should not be placed under a positive pressure of nitrogen as this will remove HCN from the reaction mixture and only ammonium tartrate will be isolated. The reaction mixture was sealed and vented only to an oil bubbler followed by

(12) Hydrolysis of **5** with 6 N HCl at 100 °C to α-methylvaline **1** required heating for 24−36 h and **1** could be isolated in ∼80 % yield after concentration under reduced pressure. Unfortunately, isolated amino acid **1** was contaminated with significant amounts of ammonium chloride. Attempts to convert crude aqueous solutions of **1** to **3** by the method describe above were complicated by the formation of numerous unidentified byproducts.

(13) Fiammengo, R.; Licini, G.; Nicotra, A.; Modena, G.; Pasquato, L.; Scrimin, P.; Broxterman, Q. B.; Kaptein, B. *J. Org. Chem.* **2001**, *66*, 5905.

(14) The individual components of the crude reaction mixture were identified by analysis of the crude NMR and were not separated from one another.

(15) Removal of ammonia from water is most effectively accomplished at the boiling point of water, see: *Perry's Chemical Engineers' Handbook*, 6th ed.; McGraw Hill Book Co.: New York, 1984.

(16) The course of the ammonia distillation was monitored by acidification of a small sample, dilution with DMSO-d_6, and analysis for the ammonium triplet at 7.3−7.6 ppm.

(17) Kumar, S.; Murray, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 1041.

a caustic solution. The resulting slurry was stirred at rt for 72 h, at which point, after conversion to the benzamide **8**, the ee of **6** was found to be 92%. The reaction slurry was filtered, and the wet cake was washed with 10 L of MTBE and dried under vacuum/N_2 sweep for 3 h to give 8.66 kg (82 wt %, 61% overall yield) of **6** as a MeOH solvate and a white solid which was sufficiently pure for use in the next reaction without further purification:[18] ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.90 (d, 3H, J = 6.8 Hz), 0.92 (d, 3H, J = 6.8 Hz), 1.27 (s, 3H), 1.69 (m, 1H), 3.13 (s, MeOH), 4.23 (s, 2H), 6.42 (br s, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 17.6, 17.7, 24.5, 37.1, 49.0 (MeOH), 54.4, 72.6, 124.6, 173.8.

Preparation of (*S*)-2-Ethoxycarbonylamino-2,3-dimethylbutyric Acid Dicyclohexylamine Salt (3). In a 100 L cylindrical extractor was added 25 L of CH_2Cl_2 followed by 7.32 kg of 82 wt % (6.00 kg by assay, 22.9 mol) of **6**. The sides of the extractor were rinsed with 5 L of CH_2Cl_2. To the slurry of **6** was added 14.5 L (73.3 mol) of 5 N NaOH. Within 15 min, a biphasic homogeneous solution formed and the layers were allowed to separate. The bottom organic layer was separated, and the top aqueous layer was discarded. The extractor was washed with water, and the organic layer was added back into the extractor. To the organic layer was added 15.0 L (26.9 mol) of 50% v/v of H_2SO_4, and the layers were well mixed for 15 min and allowed to settle. The bottom aqueous layer was separated and placed into a 100 L round-bottom flask equipped with a thermocouple, mechanical stirrer, and reflux condenser. The reaction mixture was then heated to 100 °C for 18−20 h. The reaction mixture was allowed to cool to rt, and the pH was adjusted to 12 by the addition of 27.5 L (275 mol) of 10 N NaOH while keeping the internal temperature <100 °C. After all the NaOH was added, the internal temperature was increased to 103−104 °C, and the distillate containing aqueous ammonia was collected. This atmospheric distillation was also conducted with effective scrubbing to a 5 N HCl solution in order to prevent release of ammonia. A total of 5.5 L of distillate was collected, and ^{1}H NMR analysis of a small sample of the reaction mixture, re-acidified with H_2SO_4, revealed that all the ammonia was removed. Characteristic ammonium peaks in the ^{1}H NMR of DMSO-d_6 appear as a triplet at ∼7.3−7.6 ppm. After the distillation of ammonia was complete the reaction mixture was allowed to cool to 25 °C, and 1.96 kg (18.1 mol) of ethyl chloroformate was added over the course of 1 h. After the addition of ethyl chloroformate, the pH of the reaction mixture was maintained between 9.8 and 10.2 by the portionwise addition of ∼1.5 L of 10 N NaOH. After 2.5 h, the pH of the reaction mixture stabilized at 10 and the reaction was complete. The reaction mixture was diluted with 12 L of MTBE, and the pH of the reaction mixture was back adjusted to 2.2 by the addition of 2.65 L of conc. HCl. The resulting biphasic slurry was filtered and the inorganic wet cake washed with 10 L of MTBE. The biphasic filtrate was transferred to a 100 L extractor, and the layers were allowed to separate. The aqueous layer was back extracted with 10 L of MTBE. The combined MTBE extracts were dried over 600 g of $MgSO_4$ for 1.5 h, filtered, and added to a 50 L round-bottom flask equipped with a mechanical stirrer, thermocouple, and a vacuum distillation apparatus. The solvent was concentrated to a final volume of 12−13 L under reduced pressure (∼30 mmHg) while maintaining the internal temperature <20 °C. To the concentrated solution was added 3.28 kg (18.1 mol) of dicyclohexylamine over the course of 2 h while maintaining the internal temperature <30 °C, and the slurry was stirred overnight at rt. The slurry was diluted with 12 L of heptane, stirred for 45 min, and filtered. The wet cake was washed with 5 L of heptane and dried under vacuum/N_2 sweep for 6 h to give 5.044 kg (73%, 92%ee) of **3** as an analytically pure colorless solid: mp 129−130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (d, 3H, J = 6.8 Hz), 0.97 (d, 3H, J = 6.8 Hz), 1.21 (m, 9H), 1.45 (q, 4H, J = 11.5 Hz), 1.61 (m, 5H), 1.76 (m, 4H), 1.97 (m, 4H), 2.32 (m, 1H), 2.92 (m, 2H), 4.04 (m, 2H), 6.44 (s, 1H), 9.50 (br s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8, 18.3, 18.6, 21.3, 24.8, 25.3, 28.9, 34.6, 52.4, 59.6, 63.3, 155.1, 177.4. Anal. Calcd for $C_{21}H_{40}N_2O_4$: C, 65.59; H, 10.48; N, 7.28. Found: C, 65.60; H, 10.62; N, 7.12.

Acknowledgment. We thank Mirlinda Biba of Merck & Co., Inc., for assistance with chiral HPLC analysis and Dr. Robert A. Reamer for valuable NMR assistance.

Supporting Information Available: Experimental details for the preparation of **8** and **11**, analytical details for ee determination of **6** and **3**, as well as copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **6**, **8**, **3**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Satisfactory elemental analysis could not be obtained for tartrate salt **6** due to the presence of MeOH and trace amounts of ammonium tartrate present in the isolated solid.