Organic Process Research & Development **2001**, *5*, 23–27

An Expedient Method for Resolution of 3-Amino-3-(3′-pyridyl)propionic Acid and Related Compounds

Heinz Boesch,[†] Sergio Cesco-Cancian,[‡] Leonard R. Hecker,[||] William J. Hoekstra,[||] Michael Justus,[†] Cynthia A. Maryanoff,[§] Lorraine Scott,[§] Rekha D. Shah,[§] Guenter Solms,[†] Kirk L. Sorgi,[‡] Stephen M. Stefanick,[‡] Urs Thurnheer,[†] Frank J. Villani, Jr.,[§] and Donald G. Walker*[,‡]

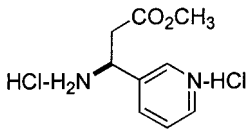
Cilag AG, Hochstrasse 201, CH-8205 Schaffhausen, Switzerland, The R.W. Johnson Pharmaceutical Research Institute, New Product Research, Department of Chemical Development, 1000 Route 202, P.O. Box 300, Raritan, New Jersey 08869-0602, U.S.A., The R.W. Johnson Pharmaceutical Research Institute, New Product Research, Department of Chemical Development, Welsh & McKean Roads, Spring House, Pennsylvania 19477-0776, U.S.A., and The R.W. Johnson Pharmaceutical Research Institute, Drug Discovery, Welsh & McKean Roads, Spring House, Pennsylvania 19477-0776, U.S.A.

Abstract:

Preparation of methyl (*S*)-3-amino-3-(3′-pyridyl)propionate dihydrochloride in high enantiomeric purity by selective crystallization of a diastereomeric salt of a carboxylic acid precursor (*N*-BOC-protected) with (1*R*,2*S*)-(−)-ephedrine is described. Further demonstration of the usefulness of this procedure to resolve other 3-amino-3-[(substituted)pyridyl]propionic acids is also described.

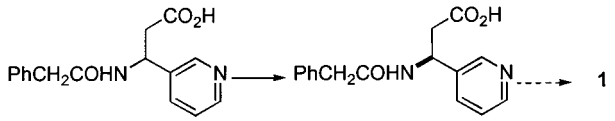
Introduction

A recent project[1,2] required rapid development of a synthetic methodology for access to kilogram quantities of chiral, nonracemic methyl (*S*)-3-amino-3-(3′-pyridyl)propionate dihydrochloride (**1**).



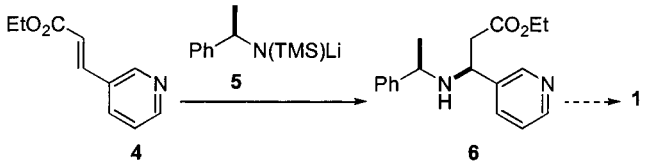
1

We considered several known literature methods[3] for preparing **1** including: (1) enzymatic resolution of racemic amide **2**;[1−4]



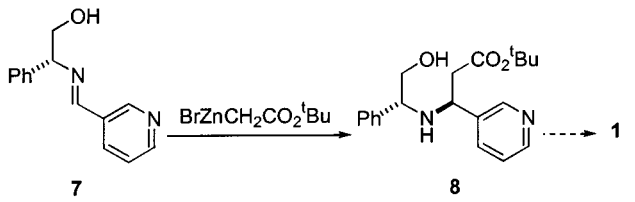
2 **3**

(2) diastereoselective Michael addition of amide **5** to acrylate **4** giving ester **6** in >92% de;[5]



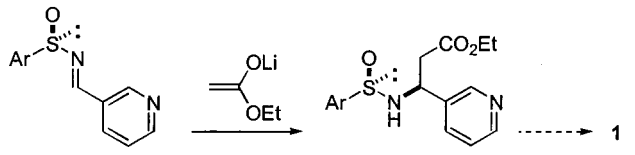
4 **6**

(3) addition of the Reformatsky reagent derived from *tert*-butyl bromoacetate to imine **7** to give ester **8** as a single diastereomer followed by removal of the chiral auxiliary;[6]



7 **8**

(4) addition of a lithium enolate to chiral, nonracemic sulfinimine **9** to give adduct **10** (78% de) followed by hydrolysis;[7]



9 **10**

Ar = 2-methoxy-1-napthyl

[†] Cilag AG.

[‡] The R.W. Johnson Pharmaceutical Research Institute, New Product Research, Raritan, NJ.

[§] The R.W. Johnson Pharmaceutical Research Institute, New Product Research, Spring House, PA.

[||] The R.W. Johnson Pharmaceutical Research Institute, Drug Discovery, Welsh & McKean Roads, Spring House, PA.

(1) Hoekstra, W. J.; Maryanoff, B. E.; Damiano, B. P.; Andrade-Gordon, P.; Cohen, J. H.; Costanzo, M. J.; Haertlein, B. J.; Hecker, L. R.; Hulshizer, B. L.; Kauffman, J. A.; Keane, P.; McComsey, D. F.; Mitchell, J. A.; Scott, L.; Shah, R. D.; Yabut, S. C. *J. Med. Chem*. **1999**, *42(25)*, 5254.

(2) Hoekstra, W. J.; Maryanoff, B. E.; Andrade-Gordon, P.; Cohen, J. H.; Costanzo, M. J.; Damiano, B. P.; Haertlein, B. J.; Harris, B. D.; Kauffman, J. A.; Keane, P. M.; McComsey, D. F.; Villani, F. J., Jr.; Yabut, S. C. *Bioorg. Med. Chem. Lett*. **1996**, *6(20)*, 2371.

(3) Hoekstra, W. J., Ed. The Chemistry and Biology of *β*-Amino Acids. *Curr. Med. Chem*. **1999**, *6(10)*, 905−1004.

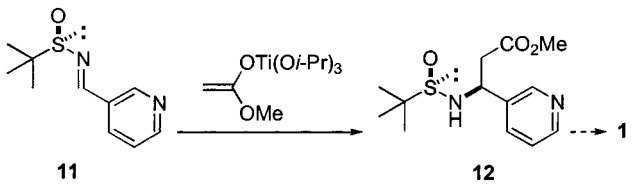
(4) Soloshonok, V. A.; Fokina, N. A.; Rybakova, A. V.; Shishkina, I. P.; Galushko, S. V.; Sorochinsky, A. E.; Kukhar, V. P.; Savchenko, M. V.; Svedas, V. K. *Tetrahedron: Asymmetry* **1995**, *6*, 1601.

(5) Rico, J. G.; Lindmark, R. J.; Rogers, T. E.; Bovy, P. R. *J. Org. Chem*. **1993**, *58*, 7948.

(6) Behling, J. R.; Boys, M. L.; Cain-Janicki, K. J.; Colson, P.-J.; Doubleday: W. W.; Duran, J. E.; Farid, P. N.; Knable, C. M.; Muellner, F. W.; Nugent, S. T.; Topgi, R. S. PCT Int. Appl. WO 98/02410, Jan 22, 1998; *Chem. Abstr*. **1998**, *128*, 154379).

10.1021/op990192m CCC: $20.00
Published on Web 10/26/2000

and (5) addition of a titanium enolate to chiral, nonracemic sulfinimine **11** to give adduct **12** (90% de) followed by removal of the chiral auxiliary.[8]



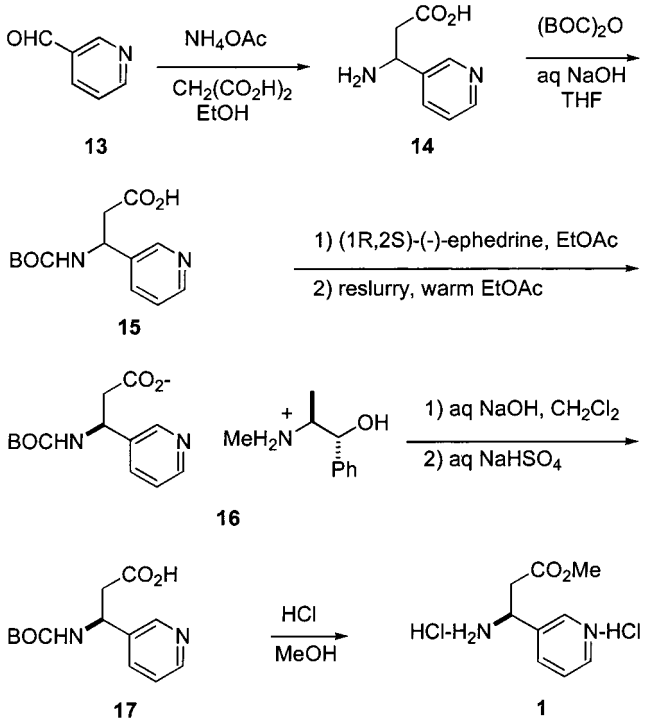
One other approach we considered centered around the stereoselective cyclization of appropriately *N*-substituted proline amides.[9]

Since these approaches used costly materials, moisture-sensitive reagents, or chromatographic purifications, or gave intermediates in unacceptable % de, we pursued an alternative method for synthesizing ester **1** involving a classical resolution strategy. Herein we describe the results of this effort and report an expedient method for the synthesis of kilogram quantities of **1** in >98% ee (HPLC) based on fractional crystallization of a diastereomeric salt intermediate prepared by reaction of an *N*-BOC-protected carboxylic acid precursor with (1*R*,2*S*)-(−)-ephedrine.

Results and Discussion

Using a classical approach, synthesis of *N*-BOC-protected acid **15** (Scheme 1, nonoptimized results) was pursued, with the expectation of selectively crystallizing a diastereomeric salt prepared from reaction of acid **15** with chiral, nonracemic amines. Thus, pyridine-3-carboxaldehyde (**13**) was reacted with excess malonic acid and ammonium acetate in refluxing ethanol to yield the racemic amino acid **14** (42%).[10−14] Further reaction of **14** with aqueous NaOH (1 equiv) in THF followed by excess di-*tert*-butyl dicarbonate (1.5 equiv) and aqueous NaOH (1.5 equiv) and work-up (acidification to pH ∼3.8, concentration, CH_2Cl_2 extraction) gave the desired BOC-protected acid **15**[15−20] as an unstable oil (83%), which was used immediately without further purification. Conversion to salt **16** was performed by reaction of **15** with (1*R*,2*S*)-(−)-ephedrine in warm ethyl acetate. Almost immediately,

Scheme 1

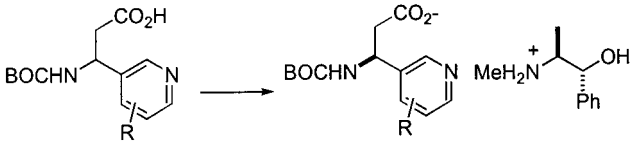


this resulted in the precipitation of a salt,[21] HPLC analysis[22,23] of which showed it to contain >95% of the desired salt **16**.[24] A single reslurry of this material in hot ethyl acetate further improved the diastereomeric purity to the desired level of >98% de (HPLC)[22,23] in 42% yield from acid **15**. Conversion of salt **16** to the (*S*)-*N*-BOC-acid **17** was performed by neutralization of **16** with aqueous base, exhaustive extraction of (1*R*,2*S*)-(−)-ephedrine into CH_2Cl_2 and crystallization of **17** by careful acidification of the aqueous phase to pH ∼3.8 with solid $NaHSO_4-H_2O$ (85%). Finally, reaction of (*S*)-*N*-BOC-acid **17** with excess HCl in MeOH resulted in an 82% isolated yield of methyl (*S*)-3-amino-3-(3′-pyridyl)propionate dihydrochloride (**1**). By HPLC analysis, this material was >98% ee.[22]

We identified several improvements while developing the process which further improved operational aspects during scale-up. For example, we found that in preparing *N*-BOC acid **15**, all of the aqueous NaOH (2.5 equiv) could be

(7) Davis, F. A.; Szewczyk, J. M.; Reddy, R. E. *J. Org. Chem.* **1996**, *61*, 2222.
(8) Tang, T. P.; Ellman, J. A. *J. Org. Chem*. **1999**, *64*, 12.
(9) Chung, X. X. *Tetrahedron: Asymmetry* **1997**, *8*, 5.
(10) Johnson, T. B.; Livak, J. E. *J. Am. Chem. Soc*. **1936**, *58*, 299 and refs 3−5 therein.
(11) Castle, R. N.; Burger, A. *J. Am. Pharm. Assoc*. **1954**, *43*, 163; procedure 1 and ref 12 therein.
(12) Profft, V. E.; Becker, F.-J. *J. Prakt. Chem*. **1965**, *30(1−2)*, 18.
(13) Secor, H. V.; Edwards, W. B., III. *J. Org. Chem*. **1979**, *44*, 3136.
(14) Shih, Y.-E.; Wang, J.-S.; Chen, M.-L.: Liu, L.-K. *Bull. Inst. Chem., Acad. Sin.* **1989**, *36*, 35.
(15) Zablocki, J. A.; Tjoeng, F. S.; Bovy, P. R.; Miyano, M.; Garland, R. B.; Williams, K.; Schretzman, L.; Zupec, M. E.; Rico, J. G.; Lindmark, R. J.; Toth, M. V.; McMackins, D. E.; Adams, S. P.; Panzer-Knodle, S. G.; Nicholson, N. S.; Taite, B. B.; Salyers, A. K.; King, L. W.; Campion, J. G.; Feigen, L. P. *Bioorg. Med. Chem. Lett*. **1995**, *3(5)*, 539. Since no preparation of **15** was given, adaptation of methods for preparation of the isomeric *N*-BOC-3Pal were applied (see refs 16−19).
(16) Rivier, J. E.; Porter, J.; Rivier, C. L.; Perrin, M.; Corrigan, A.; Hook, W. A.; Sigiganian, R. P.; Vale, W. W. *J. Med. Chem*. **1986**, *29*, 1846 (preparation of *N*-BOC derivative of D-3Pal).
(17) Spencer, J. R.; Antonenko, V. V.; Delaet, N. G. J.; Goodman, M. *Int. J. Pept. Protein Res*. **1992**, *40*, 282.
(18) Zablocki, J. A.; Rico, J. G.; Garland, R. B.; Rogers, T. E.; Williams, K.; Schretzman, L. A.; Rao, S. A.; Bovy, P. R.; Tjoeng, F. S.; Lindmark, R. J.; Toth, M. V.; Zupec, M. E.; McMackins, D. E.; Adams, S. P.; Miyano, M.; Markos, C. S.; Milton, M. N.; Paulson, S.; Herin, M.; Jacqmin, P.; Nicholson, N. S.; Panzer-Knodle, S. G.; Haas, N. F.; Page, J. D.; Szalony, J. A.; Taite, B. B.; Salyers, A. K.; King, L. W.; Campion, J. G.; Feigen, L. P. *J. Med. Chem*. **1995**, *38*, 2378.
(19) Khalil, E. M.; Subasinghe, N. L.; Johnson, R. L. *Tetrahedron Lett.* **1996**, *37(20)*, 3441.
(20) The authors gratefully acknowledge helpful discussions with Drs. M. Sreenivasan and P. Knutson of SyntheTech, Albany, OR, regarding this chemistry.
(21) In this instance, precipitation of the desired (*S*)-salt **16** was achieved using (1*R*,2*S*)-(−)-ephedrine, in contrast to the use of (1*R*,2*S*)-(+)-ephedrine for the selective precipitation of a salt of an (*S*)-3-vinyl containing *β*-amino acid; see ref 18.
(22) Kersten, B. S. *J. Liq. Chromatogr*. **1994**, *17*, 33.
(23) Due to a salt exchange during analysis, the HPLC chromatogram showed only the amount of each *β*-amino acid enantiomer present in the sample.
(24) Precipitation of the (1*R*,2*S*)-(−)-ephedrine salt of the (*S*)-enantiomer **16** was proven by conversion to **1** and comparison (HPLC) to **1** prepared by an enzymatic route.[1,2]

Table 1. **Diastereomeric purities (HPLC) of precipitated salts 19 after reaction of 18 with (1*R*,2*S*)-(−)-ephedrine in EtOAc solution and hot EtOAc reslurry**



18 **19**

compound	R	% de
19a	6-Me	95
19b	5-Br	93
19c	6-Cl	95
19d	5,6-diCl	97

initially charged into the reaction prior to the di-*tert*-butyl dicarbonate addition. Also, we found that isolation of **15** was unnecessary. On scale-up, this material was preferably prepared in situ in EtOAc solution and used "as is" in the next step. Thus, use of CH_2Cl_2 as an extraction solvent and concentration of the stream to dryness was also eliminated. Furthermore, isolation of salt **16** having a diastereomeric purity of >98% de (HPLC) was frequently observed when this resolution process was run at larger scale, thus eliminating the need for a hot EtOAc reslurry step. Last, after neutralization of **16** with aqueous base, CH_2Cl_2 was replaced with toluene for extraction of the (1*R*,2*S*)-(−)-ephedrine from the aqueous stream. By performing the toluene extractions on an aqueous phase heated to 70−80 °C, the number of extractions necessary to completely remove this amine was minimized. With these process modifications, further scale-up of this sequence proceeded smoothly and provided access to kilogram quantities of methyl (*S*)-3-amino-3-(3′-pyridyl)-propionate dihydrochloride (**1**).

The usefulness of this chemical resolution methodology was further extended to include other (substituted)pyridyl-containing β-amino acids **19** (Table 1). The starting *N*-BOC-amino acids **18** were prepared from the appropriate aldehyde as described for the synthesis of **15** from **13**.[1,2,10−14] Given the outcome of the reaction of (1*R*,2*S*)-(−)-ephedrine with *N*-BOC-acid **15**, proven by further conversion of salt **16** to ester **1** and comparison with material derived from an enzymatic resolution,[1,2,4] it was assumed that the absolute stereochemistry of the β-amino acid portion of salts **19** was also (*S*).

In summary, this expedient chemical resolution procedure provides ready access to kilogram quantities of highly enantiomerically enriched methyl esters of 3-amino-3-[(substituted)pyridyl]propionic acids. This method of synthesis complements both enzyme-based[1,2,4] and other known strategies[5−9,25] for preparation of this class of compounds.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Solvents and reagents were used as received from commercial suppliers. All nonaqueous reactions were performed under an inert atmosphere of nitrogen. NMR spectra were recorded on a Bruker 300 MHz spectrometer; chemical shifts are expressed on the δ scale and are reported in ppm downfield from tetramethylsilane (TMS) internal standard. Elemental analysis was performed by QTI (Whitehall, NJ).

Reversed phase HPLC chromatography was performed according to the following conditions. All gradient changes were linear. Analysis of **15**, **17**, **1**: Zorbax SB-C8 column (4.6 × 250 mm); 254 nm; 30 °C; flow = 1 mL/min; mobile phase A = 0.1% trifluoroacetic acid in water (v/v); mobile phase B = 0.1% trifluoroacetic acid in MeOH (v/v); gradient program (time, %A) = 0 min, 100%; 10 min, 60%; 20 min, 10%; 22 min, 0%; 30 min, 0%; 31 min, 100%; sample concentration = 1 mg/mL; run time was 30 min. Observed retention times were about 18.3 min for **15** and **17** and about 7.4 min for **1**.

Analysis of **16**: Cyclobond I 2000 RSP (4.6 × 250 mm; Advanced Separation Technologies Inc., Whippany, NJ; catalog no. 20324), 218 nm, ambient temperature, flow = 1 mL/min (isocratic analysis, 80% mobile phase A−20% mobile phase B), mobile phase A = 0.1% triethylamine in water (v/v), adjusted to pH 5.0 with 10% acetic acid in water (v/v); mobile phase B = acetonitrile; sample concentration = 5 mg/mL in 1:1 (v/v) acetonitrile−water; run time was 30 min. Observed retention times (for β-amino acid portion of **16** only) were about 14 min for the *S*-enantiomer and about 15 min for the *R*-enantiomer.[23]

Analysis of **1**:[22] Crownpak (CR+) (4.0 × 150 mm; Chiral Technologies Inc., Exton, PA; catalog no. 27014), 200 nm, 5 °C, flow = 0.5 mL/min (isocratic analysis), mobile phase = pH 1.0 perchloric acid (Milli-Q water acidified to pH 1 with 70% perchloric acid), sample concentration = 1 mg/mL, run time was 20 min. Observed retention times were about 5.1 min for the *S*-enantiomer of **14**, about 5.6 min for the *R*-enantiomer of **14**, about 9.0 min for the *R*-enantiomer of **1** and about 10.7 min for the *S*-enantiomer of **1**.

As a representative series of procedures, synthesis of **1** from **14** is described herein. Preparations of **19a**−**d** were performed by an analogous series of reactions.

3-[(*tert*-Butoxy)carbonyl]amino-3-(3′-pyridyl)propionic Acid (15). *Procedure A (Small Scale).* Using the procedure of Rivier et al.,[16] except that 2.10 g (12.6 mmol) of **14**[11,13,14] was substituted for D-3Pal, a total of 2.05 g (54%) of **15** was isolated as a colorless solid from 1:3 (v/v) EtOAc−pet ether (38−59 °C): mp 128−130 °C (gas evolution noted). ^{1}H NMR (d_6-DMSO/TMS) δ 1.35 (s, 9H), 2.64 (dd, 1H), 2.73 (dd, 1H), 4.67 (m, 1H, sharpened after D_2O exchange), 7.36 (m, 1H), 7.56 (d, 1H, exchanged with D_2O), 7.71 (m, 1H), 8.44 (m, 1H), 8.50 (s, 1H), 12.29 (br s, 1H, exchanged with D_2O). MS (ESI) *m*/*z* 267 (MH^+), *m*/*z* 289 (MNa^+). Calcd for $C_{13}H_{18}N_2O_4$: C 58.63, H 6.81, N 10.52. Found: C 58.57, H 6.89, N 10.49.

Procedure B. A flask was charged with 73.00 g (0.44 mol) of **14** and 239.5 g of THF at 15−25 °C. Within 10−

(25) Zhong, H. M.; Cohen, J. H.; Abdel-Magid, A. F.; Kenney, B. D.; Maryanoff, C. A.; Shah, R. D.; Villani, F. A., Jr.; Zhang, F.; Zhang, X. *Tetrahedron Lett.* **1999**, *40*, 7721.

20 min a solution of 43.93 g (1.10 mol) of sodium hydroxide in 395.4 g of purified water was added, resulting in a slightly yellowish solution. Within 2−3 h a solution of 143.82 g (0.659 mol) of di-*tert*-butyl dicarbonate in 124.2 g of THF was added. During this addition, the internal temperature did not exceed 30 °C. The pH of the solution decreased during addition of the di-*tert*-butyl dicarbonate solution. The solution was stirred overnight (about 17 h) at 15−25 °C, during which time the pH increased to pH ∼7, and the reaction became heterogeneous. Over 1−2 h a solution of about 167.9 g (1.22 mol) of sodium hydrogen sulphate monohydrate in 160 g of water was added, resulting in a pH of 3.8−3.9. Some solids precipitated, and strong evolution of gas was observed. The suspension was cooled to 5−10 °C, filtered and washed with 50 g of THF. The unified filtrates were reduced by distillation to one-third of their original volume. Thereafter, 102.9 g of EtOAc was added, and an equivalent volume of solvent was distilled off. This solvent replacement procedure was repeated once more using 99.4 g of EtOAc (coevaporation with EtOAc completely removed the THF from the process stream). To the resulting aqueous emulsion was added 64.6 g of sodium chloride and 100.5 g of EtOAc. The phases were separated, and the aqueous phase was washed with EtOAc (3 × 20 g). The unified organic phases were dried over 20 g of anhydrous sodium sulphate, the drying agent was filtered off, and the filter cake was washed with 5 g of EtOAc. The resulting EtOAc solution (about 250 g) containing **15** was used immediately for precipitation of the (1*R*,2*S*)-(−)-ephedrine salt **16**.

By using the process described in this procedure, a total of 30 kg of **14** was processed to 115.8 kg of an EtOAc solution of **15**, which was used immediately for precipitation of the (1*R*,2*S*)-(−)-ephedrine salt **16**.

(*S*)-3-[(*tert*-Butoxy)carbonyl]amino-3-(3′-pyridyl)propionic Acid, (1*R*,2*S*)-(−)-Ephedrine Salt (16). A solution of **15** in EtOAc (250 g, containing about 71.5 g (0.269 mmol) of **15** and 178.5 g of EtOAc) was heated to 60−70 °C. Within 10 min a solution of 48.80 g (0.295 mol) of (1*R*,2*S*)-(−)-ephedrine in 90.0 g of EtOAc was added. The clear solution was slowly cooled to 20−30 °C while the product crystallized as a voluminuous, white solid. After the crystallization of **16** began, 270 g of EtOAc was added to maintain efficient stirring. The suspension was cooled to 15−25 °C, stirred for 3−5 h, and the solids were collected by filtration. The filter cake was washed with 90 g of EtOAc in two portions and dried in vacuo at 70−80 °C to yield 52.72 g **16** as a white solid (28% over two steps from **14**). In addition to **16**, the NMR spectrum showed residual EtOAc which could not be removed by further drying in vacuo. ^{1}H NMR (D_2O) δ 1.01 (d, 3H), 1.24 (s, 9H), 2.47 (dd, 1H), 2.57 (dd, 1H), 2.64 (s, 3H), 3.43 (m, 1H), 4.78 (t, 1H), 5.00 (d, 1H), 7.30 (m, 6H), 7.70 (m, 1H), 8.30 (m, 1H), 8.36 (s, 1H). By HPLC analysis,[23] this material was >98% *S*-enantiomer and <2% *R*-enantiomer (β-amino acid portion of **16** only). MS (ESI, β-amino acid portion only) *m*/*z* 266 (MH^+), *m*/*z* 289 (MNa^+). MS (ESI, (1*R*,2*S*)-(−)-ephedrine portion only) *m*/*z* 166 (MH^+). HRMS results: Calcd for $C_{13}H_{18}N_2O_4$ (β-amino acid portion of **16** only), 267.1345; Found: 267.1341. This material was used immediately as is without further purification.

By using the process described in this procedure, a total of 115.8 kg of an EtOAc solution of **15** was processed to 20.7 kg of **16** (26.6% over two steps from **14**).

(*S*)-3-[(*tert*-Butoxy)carbonyl]amino-3-(3′-pyridyl)propionic Acid (17). A beaker was charged with 25.11 g (0.058 mol) of **16** and 50.0 g of water at 15−25 °C, resulting in a clear solution. Within 10−20 min a solution of 2.63 g (0.066 mol) of NaOH in 23.3 g of water was added. To the resulting clear solution was added 17.4 g of toluene, and the resulting emulsion was heated to 70−80 °C with good stirring. After the stirring was stopped, the phases separated rapidly, and the clear upper organic phase was separated from the slightly turbid lower aqueous phase. The aqueous phase (70−80 °C) was extracted four additional times with 17.4 g of toluene per extraction. The aqueous phase was cooled to 15−25 °C and filtered, and the filtered solids were washed with 2.5 g of water. To the unified filtrates a solution of 9.50 g (0.069 mol) of sodium hydrogen sulphate monohydrate in 12.1 g of water was added. A pH of 3.6−3.9 (preferably 3.8) resulted, and **17** crystallized from solution. The slurry was cooled to 0−5 °C and stirred for 1 h, and the solids were collected by filtration and washed with 5 g of water in two portions. Further drying in vacuo at 40−50 °C gave 11.08 g (72%) **17** as a crystalline solid: mp 87−88 °C (softened), 144−146 °C (d). ^{1}H NMR (d_6-DMSO/TMS) δ 1.35 (s, 9H), 2.64 (dd, 1H), 2.73 (dd, 1H), 4.67 (m, 1H, sharpened after D_2O exchange), 7.36 (m, 1H), 7.56 (d, 1H, exchanged with D_2O), 7.71 (m, 1H), 8.44 (m, 1H), 8.50 (s, 1H), 12.30 (br s, 1H, exchanged with D_2O). MS (ESI) *m*/*z* 267 (MH^+), *m*/*z* 289 (MNa^+). HRMS results: Calcd for $C_{13}H_{18}N_2O_4$, 267.1345; Found: 267.1341. By HPLC analysis, the chemical purity of this material was >99%.

By using the process described in this procedure, a total of 58.4 kg of **16** was processed to 33.2 kg of **17** (92.1%).

Methyl (*S*)-3-Amino-3-(3′-pyridyl)propionate, Dihydrochloride Salt (1). A total of 9.93 g (0.037 mol) of **17** was dissolved in 45.8 g of MeOH, and the resulting milky white solution was cooled to 0−5 °C. Over 2−3 h, 34.2 g (0.938 mol) of hydrogen chloride was bubbled into the solution while maintaining a reaction temperature of <15 °C. During introduction of the HCl, the milky white solution became clear, then became heterogeneous (solid precipitated). After the addition of HCl was complete, the slurry was stirred 2h at 20−25 °C, cooled to 0−5 °C and stirred for 30 min at 0−5 °C. Solids were collected by filtration, washed with 14.2 g of cold MeOH (0−5 °C) in two portions, and dried in vacuo at 20−30 °C to afford 7.86 g (83%) **1** as a white, crystalline solid: mp 187.5−189 °C. ^{1}H NMR (D_2O) δ 3.19 (dd, 1H), 3.28 (dd, 1H), 3.62 (s, 3H), 5.05 (t, 1H), 8.08 (m, 1H), 8.66 (m, 1H), 8.80 (m, 1H), 8.91 (s, 1H). MS (ESI) *m*/*z* 181 (MH^+, free base), *m*/*z* 203 (MNa^+, free base). Calcd

for $C_9H_{14}Cl_2N_2O_2$: C 42.71, H 5.57, N 11.07. Found: C 42.34, H 5.46, N 10.77. By HPLC analysis, this material was >98% *S*-enantiomer and <2% *R*-enantiomer and >99% chemical purity. The chromatographic behavior of this material was identical to that of **1** prepared by an enzymatic resolution route.[1,2]

By using the process described in this procedure, a total of 33.2 kg of **17** was processed to 22.7 kg of **1** (71.9%).

Acknowledgment

We are grateful to Dr. Richard Dunphy of The R.W. Johnson Pharmaceutical Research Institute for compilation of supporting HRMS data.

Received for review May 19, 1999.

OP990192M