Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: *Asymmetry* 17 (2006) 205–209
Tetrahedron: *Asymmetry*

Application of the asymmetric hydrogenation of enamines to the preparation of a beta-amino acid pharmacophore

Michele Kubryk* and Karl B. Hansen

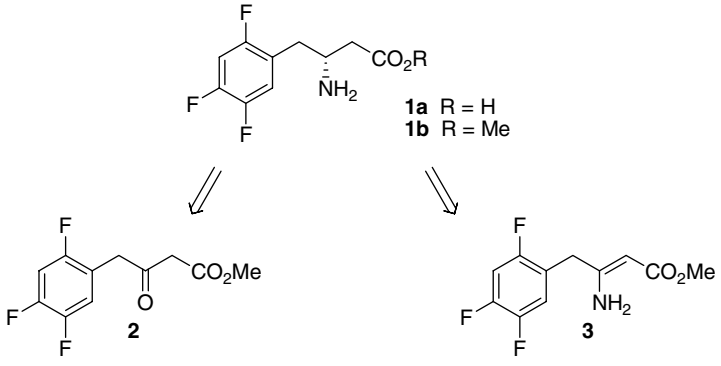
Department of Process Research, Merck Research Laboratories, PO Box 2000, Rahway, NJ 07065, USA

Received 26 October 2005; revised 30 November 2005; accepted 14 December 2005
Available online 23 January 2006

Abstract—(3*R*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoic acid **7a** has been synthesized by an asymmetric hydrogenation of enamine ester **3** using chiral ferrocenyl ligands **I** and **II** in conjunction with $[Rh(COD)Cl]_2$. The direct reduction of **3** provides amino ester **1b** in 93% ee, which was isolated as an (*S*)-camphorsulfonic acid salt to upgrade the enantiomeric excess to >99%. A more concise approach was developed involving the in situ protection of **1b** using di-*tert*-butyldicarbonate. This approach provided the desired *N*-Boc amino ester **7b** directly from the hydrogenation with 97% ee, which was upgraded to >99% ee upon crystallization.

1. Introduction

Beta-amino acids possess biologically interesting properties and their enantioselective synthesis has been the subject of considerable interest.[1] Derivatives of beta-homophenylalanine and in particular those of compound **1** (Scheme 1)[2] have recently been reported to be potential new treatments for type II diabetes.[3] Methods have been developed in these laboratories to prepare compounds such as **1** in enantiomerically pure form by asymmetric reduction of the corresponding beta-keto ester **2**[4] followed by a Mitsunobu reaction. Although this approach has been successfully implemented on large scale, a more direct synthesis of beta-amino acid derivatives was desired. To this end, we recently developed a method for the asymmetric reduction of enamines, which provides unprotected beta-amino amides or esters in high yield and enantioselectivity.[5] This paper describes the application of this methodology to the enantioselective hydrogenation of enamine **3**, conversion of the resultant amine to its *N*-*tert*-butylcarbamate and a crystallization method for the upgrade of the



Scheme 1.

* Corresponding author. E-mail: michele_kubryk@merck.com

0957-4166/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tetasy.2005.12.016

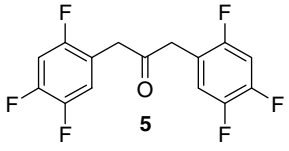
material to near enantiomeric purity. The application of this methodology to the preparation of **1** results in a more efficient and concise preparation of this pharmacophore.

2. Results and discussion

2.1. Synthesis of enamine 3

Enamine ester **3** was prepared in two steps starting from 2,4,5-trifluorophenyl acetic acid **4** (Scheme 2). Activation of carboxylate **4** by the method of Masamune with carbonyldiimidazole (CDI) and reaction with the magnesium enolate of mono-methyl potassium malonate provide beta-keto ester **2**. The enolization procedure (triethylamine, magnesium chloride) was crucial to the success of the reaction on large scale. Charging magnesium chloride to a mixture of triethylamine and the malonate salt resulted in a thick slurry that was difficult to stir and gave inconsistent assay yields of **2**. Addition of the amine base to a mixture of the malonate salt and magnesium chloride resulted in a thinner slurry, which was considerably easier to stir. The malonate slurry was heated to 50 °C for 8 h to ensure complete deprotonation. Shorter age times resulted in incomplete conversion of **4**.

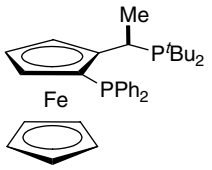
The rate of addition of the CDI adduct to the enolate was also found to be important. Rapid addition resulted in the formation of large amounts of ketone **5**, most likely due to the concentration of the activated carboxylate building up in solution. Slow addition, over several hours, gave consistently high assay yields of **2** with minimal formation of **5** (<1 HPLC area%) after acid quench and aqueous work-up.



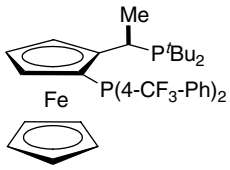
5

Following aqueous work-up, keto-ester **2** could be isolated by crystallization from isopropanol/water but was typically converted directly to enamine **3** without purification. The organic extracts of **2** were switched into methanol by distillation and an excess of ammonium acetate was charged. The mixture was heated at reflux for several hours until complete conversion to **3** was observed.[6] Upon cooling to room temperature, an equivalent of NH_4OH was charged to neutralize the acetic acid formed in situ since enamine formation is reversible under acidic conditions. Solutions treated in this fashion can be subjected to aqueous work-up to remove inorganic salts, however in the case of **3**, the methanol solvent was removed and the mixture dissolved in ethyl acetate to precipitate the excess ammonium acetate, which was removed by filtration. Enamine **3** was then crystallized by switching the solvent by distillation to heptane and cooling to 0 °C. Enamine **3** was isolated in 91% yield with >98 wt % purity and was used directly in the following step.

2.2. Asymmetric hydrogenation of enamine 3



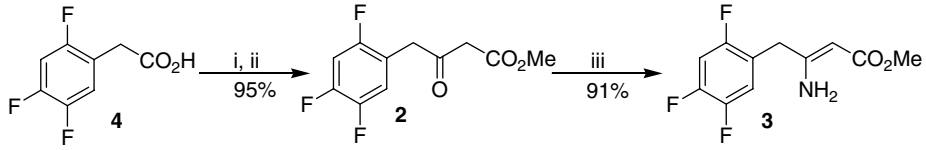
I



II

The direct asymmetric hydrogenation of enamines, such as **3**, is catalyzed by the metal complex generated in situ from $[Rh(COD)Cl]_2$ and chiral ferrocenyl ligands **I** or **II**. Typically, the hydrogenation of enamine-ester substrates requires the use of ligand **II** in conjunction with trifluoroethanol as a solvent. Indeed, reduction with 0.1 mol % **Rh-II** at 40 °C and 200 psig H_2 resulted in the formation of the beta-amino ester **1b** with 93% ee and 89% yield (Table 1, entry 1).

Although the asymmetric hydrogenation yielded beta-amino ester **1b** with enantiomeric purity of 92–94%, material of near enantiomeric purity (99% ee) was desired for further use. Amino ester **1b** was not observed to crystallize at ambient temperatures and was also found to decompose slowly. We wished to find a crystalline salt, which could allow for the isolation of **1b** with an upgrade in enantiomeric purity. After screening several chiral acid salts, it was found that crystallization of the (*S*)-camphorsulfonic acid (*S*-CSA) salt of **1b** resulted in efficient upgrade of its chemical and enantiomeric purity with an overall yield of 70% starting from enamine **3**. The *S*-CSA salt **6** was converted to the *N*-Boc carboxylic acid **7a** in a one-pot procedure by breaking the salt and saponifying the ester with LiOH in THF/water, followed by treatment with di-*tert*-butyldicarbonate (Boc_2O). Following aqueous work-up, the protected amino acid was isolated by crystallization in 90% yield with 97 wt % purity (Scheme 3).

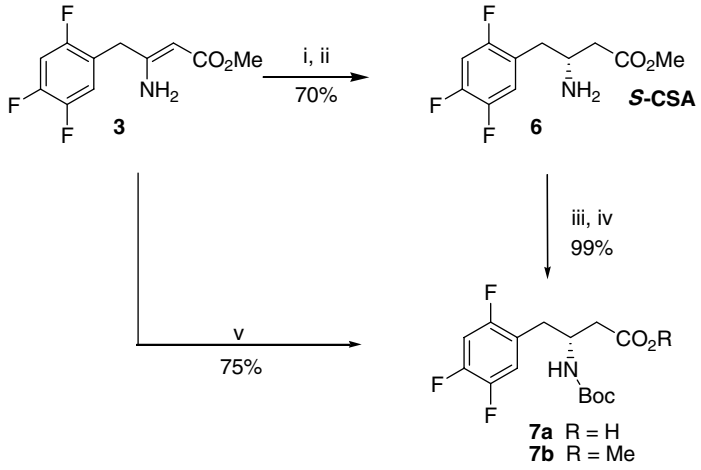


Scheme 2. Reagents and conditions: (i) 1-1′-carbonyldiimidazole, CH_3CN; (ii) mono-methyl potassium malonate, Et_3N, $MgCl_2$, CH_3CN, 30 °C; (iii) NH_4OAc, MeOH, reflux.

Table 1. Asymmetric hydrogenation of enamine ester **3**

Entry	Ligand	Catalyst loading (mol %)	Solvent	Pressure (psig)	Yield (%)[a]	ee (%)
1	**II**	0.1	TFE	200	89	93
2	**I**	1.0	MeOH	90	80	93
3[b]	**I**	0.6	MeOH	90	88	97

[a] HPLC assay (LCAP).
[b] Reaction performed with 1.1 equiv of Boc_2O at 25 °C.



Scheme 3. Reagents and conditions: (i) 0.1 mol % $[Rh(COD)Cl]_2$, 0.1 mol % **II**, 200 psig H_2, trifluoroethanol, 40 °C; (ii) (1*S*)-(+)-10 camphorsulfonic acid, isopropanol; (iii) LiOH–H_2O, THF, water; (iv) 1.1 equiv Boc_2O, LiOH–H_2O; (v) 0.6 mol % $[Rh(COD)Cl]_2$, 0.6 mol % **I**, 1.1 equiv Boc_2O, 90 psig H_2, MeOH, 25 °C.

While our initial goal of applying asymmetric hydrogenation to the synthesis of **1** had been achieved, several aspects of the process could be improved. First, the reduction conditions required the use of trifluoroethanol as a solvent, which is considerably more expensive than methanol. The catalyst derived from ligand **I** can be used with methanol as a solvent, however, higher loadings of this catalyst were required to achieve yields comparable to the **Rh-II**/TFE system (Table 1, entry 2). Additionally, the crystallization of **1b** as its *S*-CSA salt was necessary to upgrade its enantiomeric purity. A more efficient process would involve a single isolation of the desired *N*-Boc amino acid or ester directly without the use of a chiral acid.

We recently reported that product inhibition occurs in the asymmetric reduction of enamines and that it can be largely eliminated by in situ protection of the product with $(Boc)_2O$.[7] In addition to increasing the efficiency of catalyst **Rh-I**, application of these conditions to the reduction would avoid the use of trifluoroethanol as a solvent, as well as provide the desired *N*-Boc amino ester **1b** in a single step. Thus, reduction of **3** using 0.6 mol % catalyst at 90 psig H_2 at room temperature resulted in 90% conversion to **1b**. The enantioselectivity under these conditions increased to 97% upon reduction of the reaction temperature. In contrast to amino ester **1b**, carbamate **7b** is a crystalline solid and was isolated directly from the reaction mixture in 75% yield. The enantiomeric purity of **7b** was gratifyingly increased to >99% when it was isolated in this fashion.

3. Conclusion

Two approaches to the enantioselective synthesis of beta amino acid derivative **1** via asymmetric hydrogenation of unprotected enamine **3** have been presented. Direct hydrogenation of enamine **3** using ligand **II** in trifluoroethanol affords the desired amino ester in 93% ee. While this material can be elaborated to a protected and isolable form of **1**, a more concise approach is the in situ protection of **1b** as the desired *N*-Boc carbamate. The use of Boc_2O in the hydrogenation allows for methanol to be used as a solvent and for the reaction temperature to be significantly reduced. These conditions result in a higher enantioselectivity for the reduction and the *N*-Boc amino ester **7b** can be isolated in high enantiomeric and chemical purity directly from the hydrogenation stream.

4. Experimental

4.1. General procedure

Melting points were determined on an open capillary apparatus and were uncorrected. HPLC assays were carried out using a C-18 reverse phase column eluted with acetonitrile and 0.1% $HClO_4$. Assay yields were determined by HPLC using pure compounds as standards. Enantiomeric excess assays were determined by using a Chiralpak AD-H column eluted with isopropanol and *n*-heptane. All reagents and solvents were obtained from

commercial suppliers and used without further purification. All ^{1}H NMR and ^{13}C NMR data were recorded on a 400 and 100 MHz spectrometer, respectively.

4.1.1. Methyl 4-(2,4,5-trifluorophenyl)acetoacetate 2. A solution of 2,4,5-trifluorophenyl acetic acid **4** (3.5 kg, 18.4 mol) in CH_3CN (21 L) was charged to a 50 L flask containing a slurry of 1,1′-carbonyldiimidazole (3.28 kg, 20.2 mol) and CH_3CN (9 L) over 0.5 h. The resulting solution was aged for 3 h. To a separate 100 L flask, mono-methyl malonate potassium salt (3.59 kg, 23 mol), Et_3N (7.8 L, 55.2 mol) and CH_3CN (42 L) were charged followed by a portionwise addition of magnesium chloride (1.9 kg, 20.2 mol). The 100 L reaction slurry was heated to 50 °C and aged for 8 h. The slurry was cooled to 30 °C and was charged with the CDI adduct over 2 h. The combined reaction mixture was aged for 24 h at 30 °C. The reaction was cooled to 0 °C and was charged with 35 L of 3 M HCl over 2 h. Methyl *tert*-butyl ether (MTBE) (25 L) was charged and the biphasic mixture was settled and the aqueous layer discarded. The organic extracts were washed sequentially with 1 M HCl, 7 wt % $NaHCO_3$ and 24 wt % NaCl. The MTBE organic extracts were switched into iPrOH and concentrated to a final volume of 17 L upon which the product crystallized. The slurry was warmed to 30 °C for complete dissolution and was cooled to 20 °C and seeded with 0.1 wt % of **2**.[8] Water (36 L) was charged to the slurry over 6 h. The resulting suspension was filtered and the collected solids were dried under vacuum (temperature <30 °C) to provide **2** (3.94 kg, 84%) as an off-white crystalline solid: mp: 40–41 °C; ^{1}H NMR ($CDCl_3$) δ 7.08 (m, 1H), 6.94 (m, 1H), 3.85 (s, 2H), 3.77 (s, 3H), 3.55 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 197.9, 167.1, 156.9, 154.5, 150.4, 147.9, 145.5, 119.4, 117.0, 105.5, 52.4, 48.3, 41.9; ^{19}F NMR ($CDCl_3$) δ −119.0, −134.7, −143.0; IR (KBr) 3096, 3054, 2945, 1738, 1635, 1522, 1440, 1343, 1236, 1214, 1157, 1091, 995, 948 cm^{-1}; Anal. Calcd for $C_{11}H_9F_3O_3$: C, 53.67; H, 3.68. Found: C, 53.63; H, 3.36.

4.1.2. (*Z*)-Methyl 3-amino-4-(2,4,5-trifluorophenyl)but-2-enoate 3. A 1 L flask was charged with **2** (50 g, 0.20 mol), ammonium acetate (78 g, 1.0 mol) and methanol (500 mL).[9] The reaction solution was refluxed for 2 h. The mixture was cooled to 25 °C and the solvent was switched to EtOAc and concentrated to 100 mL. Salts crystallized out during the solvent switch and were filtered. The filtrate was concentrated to 100 mL and heptane (100 mL) was charged. The solution was seeded with 0.1 wt % of **3** and aged for 0.5 h. An additional 200 mL of heptane was charged to the seed bed and the resulting suspension was cooled to 0 °C, filtered and the collected solids were dried under vacuum to provide **3** (45.5 g, 91%) as a white crystalline solid: mp: 70–71 °C; ^{1}H NMR ($CDCl_3$) δ 7.08 (m, 1H), 6.94 (m, 1H), 4.55 (s, 1H), 3.62 (s, 3H), 3.4 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 170.2, 159.4, 156.9, 154.5, 150.5, 148.0, 145.5, 119.8, 118.4, 105.5, 84.7, 50.1, 34.5; ^{19}F NMR ($CDCl_3$) δ −119.5, −135.0, −142.6; IR (KBr) 3490, 3340, 1666, 1559, 1507, 1424, 1167, 773 cm^{-1}; Anal. Calcd for $C_{11}H_{10}F_3NO_2$: C, 53.88: H, 4.11; N, 5.71. Found: C, 53.83; H, 3.84; N, 5.53.

4.1.3. Methyl (3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoate 1b. A hydrogenation vessel under a nitrogen atmosphere was charged with $[Rh(COD)Cl]_2$ (18.5 mg, 0.05 mol %) and Josiphos ligand **II** (51 mg, 0.1 mol %). Enamine **3** (18.4 g, 0.075 mol) was dissolved in degassed trifluoroethanol (150 mL) and charged to the hydrogenation vessel and the entire mixture was degassed by vacuum/N_2 backfill cycles. The vessel was agitated vigorously for 10 min to dissolve the solids and was then hydrogenated at 200 psig H_2 at 40 °C for 24 h. The hydrogenation stream yielded 16.7 g of **1b** (90% assay yield) with an enantiomeric excess of 93%. The enantiomeric excess was determined by treating an aliquot of the crude hydrogenation stream with an excess of 3,5-dinitrobenzoylchloride. The reaction was aged for 30 min and analyzed via HPLC (chiralpak AD-H column, 20% iPrOH/heptane, 1 mL/min, isocratic for 20 min).

4.1.4. Methyl (3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoate (1*S*)-(+)-10 camphorsulfonic acid 6. A methanol solution of **1b** (18.5 g, 75 mmol) was switched into *i*PrOH and concentrated to 75 mL. (1*S*)-(+)-10-Camphorsulfonic acid (17.4 g, 82.5 mmol) was dissolved in *i*PrOH (30 mL) and charged to **1b** via an addition funnel followed by a 10 mL *i*PrOH rinse. The cloudy solution was seeded with 0.1 wt % of **6** and the title compound crystallized out. The slurry was heated to 40 °C, aged for 3 h and cooled to 20 °C. The solids were filtered, washed with *i*PrOH and dried in a vacuum oven at 50 °C to provide **6** (25.9 g, 72%) as a white crystalline solid with >99% enantiomeric excess. Mp: 137–138 °C; $[\alpha] = +15.7$ (*c* 1.02, $CHCl_3$); ^{1}H NMR (CD_3OD) δ 7.39 (m, 1H), 7.21 (m, 1H), 3.9 (m, 1H), 3.7 (s, 3H), 3.3 (s, 1H), 3.07 (m, 2H), 2.8 (s, 1H), 2.75 (s, 2H), 2.62 (m, 1H), 2.35 (m, 1H), 2.07 (s, 2 H), 1.90 (m, 1H), 1.66 (m, 1H), 1.42 (m, 1H), 1.11 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (DMSO) δ 216.3, 170.4, 157.8, 155.4, 150.1, 147.6, 145.1, 120.1, 106.3, 58.4, 52.0, 47.7, 47.4, 47.2, 42.5, 42.4, 36.2, 31.1, 26.73, 24.5, 20.2, 19.8; ^{19}F NMR (DMSO) δ −118.4, −136.4, −143.9; IR (KBr) 2953, 2097, 1748, 1633, 1522, 1443, 1211, 1048, 850, 818 cm^{-1}; Anal. Calcd for $C_{21}H_{28}F_3NO_6S$: C, 52.6; H, 5.89, N, 2.92. Found: C, 52.53; H, 5.93; N, 2.92.

4.1.5. (3*R*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoic acid 7a. To a 500 mL flask was charged **6** (20 g, 41.7 mmol), THF (100 mL), water (100 mL) and lithium hydroxide monohydrate (5.25 g, 125 mmol). The biphasic mixture was aged for 24 h. Once the ester hydrolysis was complete, the mixture was cooled to 0 °C and was charged with di-*tert*-butyldicarbonate (10 g, 45.9 mmol) and lithium hydroxide monohydrate (1.75 g, 41.7 mmol). The reaction mixture was warmed to ambient temperature and was stirred for 12 h. The reaction was worked-up by adjusting the pH to 2.5 using 10 wt % $NaHSO_4$ and extracting **7a** twice with iPrOAc. The organic extracts were combined, switched into heptane and the final volume was concentrated to 200 mL at which point the product crystallized. The resulting slurry was heated to 50 °C for 2 h and cooled to 20 °C. The solids were collected via filtration and washed with neat heptane to provide **7a** (14 g,

95%) as a white crystalline solid; mp: 124–125 °C; $[\alpha] = +32.3$ (*c* 1.0, $CHCl_3$); ^1H NMR (CD_3OD) δ 7.18 (m, 1H), 7.07 (m, 1H), 4.15 (broad, 1H), 2.93 (dd, $J = 4.7$ and 13.8 Hz, 1H), 2.68 (m, 1H), 2.51 (m, 2H), 1.34 (s, 9H), ^{13}C NMR (CD_3OD) δ 173.1, 157.6, 156.0, 155.1, 149.9, 147.4, 145.1, 122.1, 119.0, 104.6, 78.5, 38.6, 32.9, 27.2, 26.9; ^{19}F NMR (CD_3OD) δ −121.0, −139.6, −146.7; IR (KBr) 3362, 2985, 1693, 1521, 1424, 1274, 1233, 1170, 1054, 840 cm^{-1}; Anal. Calcd for $C_{15}H_{18}F_3NO_4$: C, 54.05; H, 5.44; N, 4.20. Found: C, 54.02; H, 5.42; N, 4.16.

4.1.6. Methyl (3*R*)-[(*tert*-butoxycarbonyl)amino]-4-(2,4,5-trifluorophenyl)butanoate 7b. A hydrogenation vessel under a nitrogen atmosphere was charged with $[Rh(COD)Cl]_2$ (91 mg, 0.3 mol %) and Josiphos ligand **I** (206 mg, 0.6 mol %). Enamine **3** (15 g, 0.61 mol) was dissolved in degassed methanol (150 mL) and charged to the hydrogenation vessel. The hydrogenator was shaked vigorously for 10 min to dissolve the solids and was hydrogenated at 90 psig H_2 at 30 °C for 24 h. The hydrogenation stream yielded 18.5 g of **7b** (87% assay yield) with an enantiomeric excess of 97% (HPLC, chiralpak AD-H column, 10% isopropanol/heptane, 1 mL/min, isocratic for 15 min). The reaction volume was concentrated to 130 mL of methanol and warmed to 45 °C upon which 45 mL of water was charged to the solution. Aminoester **7b** crystallized and the slurry was cooled to ambient temperature. The solids were collected via filtration and washed with 3:2 methanol/water to provide **7b** (16 g, 75% yield) as a fluffy off-white crystalline solid with a purity of 100 wt % by HPLC and >99% enantiomeric excess. Mp: 88–88.5 °C; $[\alpha] = +15.2$ (*c* 1.0, MeOH); ^1H NMR ($CDCl_3$) δ 7.14 (m, 1H), 6.97 (m, 1H), 5.29 (m, 1H), 4.31 (m, 1H), 3.95 (s, 3H), 3.10 (m, 2H), 2.67 (m, 2H), 1.60 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.1, 154.9, 150.3, 147.5, 145.5, 121.2, 118.9, 105.3, 79.5, 51.7, 47.6, 37.1, 32.9, 28.1; ^{19}F NMR ($CDCl_3$) δ −119.7, −136.3, −143.6; IR (KBr) 3365.8, 3058.7, 2968.7, 1737.6, 1684, 1523.5, 1422, 1253.4, 1160.2, 852.9; Anal. Calcd for $C_{16}H_{20}F_3NO_4$: C, 55.33; H, 5.80; N, 4.03. Found: C, 55.52; H, 5.85; N, 3.96.

References

1. See reviews: (a) Abdel-Magid, A. F.; Cohen, J. H.; Maryanoff, C. A. *Curr. Med. Chem.* **1999**, *6*, 955; (b) Cole, D. C. *Tetrahedron* **1994**, *50*, 32; (c) *Book: Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; (d) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290–4299.
2. Xu, J.; Ok, H. O.; Gonzalez, E. J.; Colwell, L. F.; Habulihaz, B.; He, H.; Leiting, B.; Lyons, K. A.; Marsilio, F.; Patel, R. A.; Wu, J. K.; Thornberry, N. A.; Weber, A. E.; Parmee, E. R. *Biorg. Med. Chem. Lett.* **2004**, *14*, 4759–4762.
3. (a) Weber, A. *J. Med. Chem.* **2004**, *48*, 4135–4141; (b) Drucker, D. J. *Exp. Opin. Investig. Drugs* **2003**, *12*, 87–100; (c) Weideman, P. E.; Trevillyan, J. M. *Curr. Opin. Investig. Drugs* **2003**, *4*, 412–420.
4. Angelaud, R.; Zhong, Y.-L.; Maligres, P.; Lee, J.; Askin, D. *J. Org. Chem.* **2005**, *70*, 1949–1952.
5. Hsiao, Y.; Krska, S.; Rivera, N.; Rosner, T.; Njolito, E.; Wang, F.; Sun, Y.; Armstrong, J.; Grabowski, E. J.; Tillyer, R.; Spindler, F.; Malan, C. *J. Am. Chem. Soc.* **2004**, *126*, 9918–9919.
6. HPLC analysis of the reaction was performed under basic conditions with potassium phosphate buffer and ACN as the diluents since the reaction is reversible under acidic conditions.
7. Hansen, K. B.; Rosner, T.; Kubryk, M.; Dormer, P.; Armstrong, J. D. *Org. Lett.* **2005**, *7*, 4935–4938.
8. Seed was generated by removing an aliquot of the desired compound, cooling to 0 °C and charging antisolvent until the desired compound crystallized out of solution. The slurry was then charged back to the crystallization solution.
9. Through process starting from **4**.