Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 240–244

Preparation of enantiomerically pure (*R*)- and (*S*)-3-amino-3-phenyl-1-propanol via resolution with immobilized penicillin G acylase☆

Nitin W. Fadnavis,* Kasiraman R. Radhika and A. Vedamayee Devi

Biotransformations Laboratory, Indian Institute of Chemical Technology, Uppal Road, Habsiguda, Hyderabad 500 007, India

Received 11 November 2005; accepted 29 December 2005
Available online 23 January 2006

Abstract—Ethyl 2,4-dioxo-4-phenylbutyrate, obtained by condensation of acetophenone with diethyl oxalate, was converted to 3-oxo-3-phenyl-1-propanol in 90% yield by reaction with baker's yeast. Reductive amination with sodium cyanoborohydride in the presence of ammonium acetate gave the racemic 3-amino-3-phenyl-1-propanol in 65% yield. Enzymatic resolution of the corresponding *N*-phenylacetyl derivative with penicillin G acylase, immobilized on an epoxy resin gave (*S*)-amide and (*R*)-amino alcohol in high enantiomeric purity (ee >99%) and >45% yields for each enantiomer.

1. Introduction

Enzymes and microbial cells are finding increasing applications in the fine chemical industries such as pharmaceuticals, agrochemicals, and health care products due to their high chemo- and stereospecificity.[1] We have recently described the preparation of ethyl (*R*)-2-hydroxy-4-phenylbutyrate (HPB) ester using ethyl 2,4-dioxo-4-phenylbutyrate **1** with baker's yeast (*Saccharomyces cerevisiae*).[2] During these investigations, the unexpected formation of 3-oxo-3-phenyl-1-propanol **2** was observed as a side reaction. In fact, the compound could be prepared in high yields if the reaction with baker's yeast was allowed to continue for a longer period. The single pot synthesis of **2** in 90% yield is an interesting route since it is an intermediate for the synthesis of enantiomerically pure 1-phenyl-1,3-propanediol, an important intermediate to drugs such as fluoxetine.[3] Since the methodologies of the synthesis of 1-phenyl-1,3-propanediol **3** from **2** and its subsequent conversion to fluoxetine are quite well known,[2,4–8] we did not attempt the synthesis of fluoxetine. Intermediate **2** can also be used for the preparation of chiral 1,3-amino alcohols **6** and **7**. Herein we report the conversion of keto alcohol **2** to the corresponding racemic [*N*-phenylacetyl]amino alcohol **5** and its resolution using immobilized penicillin G acylase (E.C. 3.5.1.11) (Scheme 1).

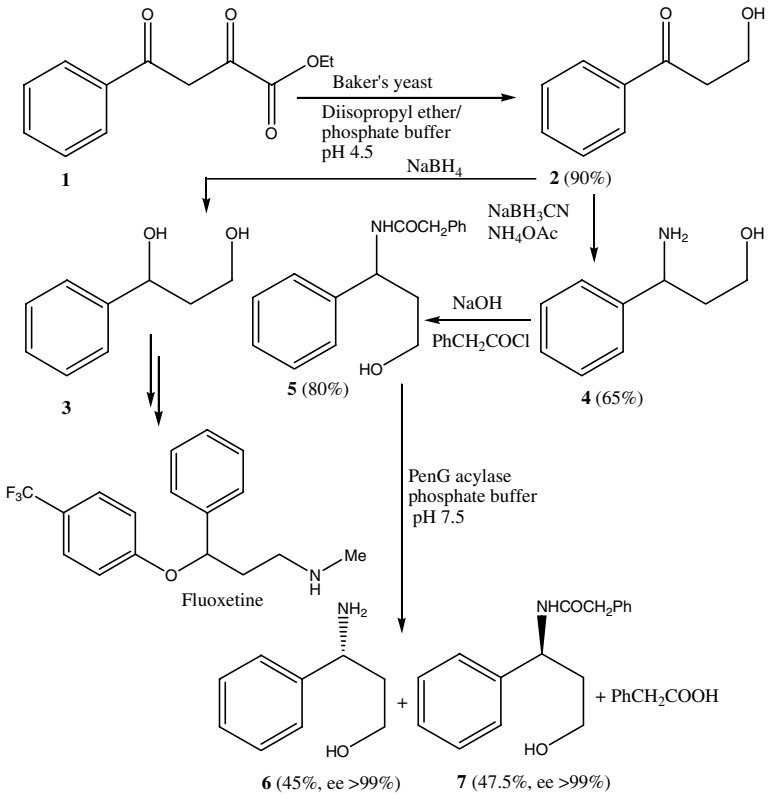
2. Results and discussion

Known methods for the synthesis of **2** include the selective oxidation of 1-phenyl-1,3-propanediol with oxidizing agents;[9] chemoselective reduction of β-keto esters to β-keto alcohols;[10] condensation of acetophenone with formaldehyde;[11] the oxidative ring-opening reaction of a 1,3-dioxane derivative;[12] aldol reaction of silyl enol ethers with aldehydes in the presence of lanthanide catalysts;[13] reduction of epoxides with Bu_3SnH–Bu_3SnI complexes;[14] electron-transfer reactions of aromatic α,β-epoxy ketones,[15] and aldol reaction under high-intensity ultrasound.[16] Compared to the above known methods, the method of preparing **2** by reaction of **1** with baker's yeast in a biphasic system is much simpler. Chiral 1,3-amino alcohols have potential applications both as pharmaceutically active compounds, agricultural chemicals, chiral intermediates, and chiral auxiliary agents. For example, U.S. Pat. No. 3,668,199 describes novel 1,3-amino alcohols having potential applications as anti-diabetic agents and diuretics.[17] The most well-known example is dapoxetine hydrochloride and its derivatives, which are useful for the

☆ IICT Communication No. 051109.

* Corresponding author. Tel.: +91 40 27160123x2631; fax: +91 40 27160512; e-mail addresses: fadnavisnw@yahoo.com; fadnavis@iictnet.org; fadnavis@iict.res.in

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2005.12.022



Scheme 1. Biocatalytic preparation of enantiomerically pure 3-amino-3-phenyl-1-propanol.

treatment of premature ejaculation.[18] Chiral γ-amino alcohols can be prepared by (a) classical resolution of the amino alcohol;[19] (b) reduction of an optically active β-amino acid;[20] (c) reduction of a keto-oxime with a chiral reducing agent such as a metal borohydride complexed to a different optically active amine[21] or a chiral oxaborolidine–BH_3–THF complex;[22] (d) stereoselective oxidation of a 1,4-diol to a γ-lactone using an alcohol dehydrogenase, the conversion of the γ-lactone to the corresponding 4-hydroxyamide, 4-hydroxyhydroxamic acid, or 4-hydroxyhydrazide, followed by stereospecific rearrangement to the corresponding chiral 1,3-amino alcohol,[23] and (e) enzymatic resolution of the amino alcohol using lipases or amino acylases.[24] The processes involving chiral catalysts are expensive and require specialized skills while the methodology of kinetic resolution using a hydrolase is very useful, since it provides both (*R*)- and (*S*)-enantiomers and can be performed easily.

Although several methods already exist for preparing enantiomerically pure γ-amino alcohols as described above, we could find only two reported chemo-enzymatic routes to **6**. The one described in the US patent[23] is rather complex needing several steps and NADH recycling strategies. The second route is via reduction of the chiral β-amino acid. The racemic β-amino acid was obtained in 67% yield by refluxing malonic acid, benzaldehyde and ammonium acetate in ethanol.[20d,e] It was then converted to its racemic *N*-phenylacetyl derivative and enantioselectively hydrolyzed with penicillin G acylase to obtain the (*R*)-amino acid,[20f] which can be reduced to obtain **6**. Since penicillin G acylase is commercially available in an immobilized form at a reasonable price and is generally useful for the resolution of amino compounds,[25] we attempted the resolution of racemic γ-amino alcohol **2** to obtain (*R*)-**6** using this enzyme. Herein the synthesis of the enantiomerically pure isomers of both (*R*)- and (*S*)-3-amino-3-phenyl-1-propanol was carried out in the following manner. Reaction of **1** with baker's yeast in a phosphate buffer (pH 4)/diisopropyl ether 2-phase system for 48 h gave **2** in 90% yield in 48 h. Earlier, we had used citrate buffer for the reaction under similar conditions,[2] but it required 4–7 days for the completion of the reaction. The facilitation using a phosphate is unsurprising since we expected the involvement of thiamine pyrophosphate (TPP) adduct in the decarboxylation of a keto acid formed during the reaction.[2,26] Reductive amination of **2** with sodium cyanoborohydride in the presence of ammonium acetate gave the racemic amino alcohol **4** in 65% yield. The amino group was protected with phenylacetyl chloride under Schotten–Baumann conditions to give racemic *N*-phenylacetyl derivative **5** in 80% yield, and then resolved by enantioselective hydrolysis of the racemic amide catalyzed by penicillin G acylase (immobilized on epoxy resin) in phosphate buffer (0.05 M, pH 7.5). The hydrolytic reaction was followed by reverse phase HPLC. The reaction practically stopped at 50% conversion showing very high enantioselectivity. After the reaction, the enzyme was filtered off and the aqueous reaction mixture acidified to convert the (*R*)-amino alcohol into a water soluble hydrochloride. Phenyl acetic acid produced during

hydrolysis and the unreacted (*S*)-amide was extracted with dichloromethane. Separation of the (*S*)-amide and phenylacetic acid was achieved by evaporating the dichloromethane and extracting the phenylacetic acid from the residue with cyclohexane. HPLC analysis on chiral stationary phase (Chiralcel OD, Daicel, Japan) showed that the amide was enantiomerically pure (ee >99%). The (*R*)-amine present in the aqueous reaction mixture after enzymatic hydrolysis and acidification was recovered after basification with 4 M NaOH and extraction with dichloromethane. HPLC analysis on the chiral stationary phase (Crownpack CR(+), Daicel, Japan) showed that the amine was also enantiomerically pure (ee >99%). Thus, from the yields (>45%) and enantiomeric purities (>99%) the reaction was found to be completely enantioselective and only the (*R*)-enantiomer was hydrolyzed by the enzyme.

3. Conclusion

Herein we have provided a simple and environmentally friendly biocatalytic route to both (*R*)- and (*S*)-enantiomers of 3-amino-3-phenyl-1-propanol with high enantiomeric purity (ee >99%) and yield of 45–50% in four steps. The starting materials are easy to prepare while the immobilized enzyme can be recycled several times. Conversion of the amino alcohol to Dapoxetine is currently in progress.

4. Experimental

Immobilized penicillin G acylase (150 units/g) was a gift from M/s KOPRAN, Mumbai. Preparation of diketo ester **1** and baker's yeast mediated synthesis of keto-alcohol **2** has been described earlier.[2] Sodium cyanoborohydride was obtained from Fluka. All other reagents were obtained from SD Fine Chem, India. HPLC analyses were carried out on a Hewlett Packard HP1090 unit with diode array detector and HP Chem Station software.

4.1. 3-Phenyl 3-oxo propanol 2

Yeast cells (20 g) were suspended in sodium phosphate buffer (0.05 M, pH 4.5, 50 mL) containing glucose (5 g). The cells were allowed to activate for 3 h, then diisopropyl ether was added (200 mL) followed by the addition of phenacyl chloride (150 mg) dissolved in diisopropyl ether (10 mL). The contents were vigorously stirred on a magnetic stirrer at room temperature for 3 h. Substrate **1** was prepared from the condensation of diethyl oxalate with acetophenone, as described previously,[1] (2.2 g, 0.1 mol) dissolved in diisopropyl ether (50 mL) was added and the contents were stirred for 48 h at room temperature with intermittent addition of glucose (2 g/day). The starting ester disappeared and the decomposition of intermediate 2-hydroxy ester to form the keto alcohol **2** was complete in 48 h. The cells were centrifuged at 10,000 rpm, the aqueous phase and the yeast cells were separately extracted with ethyl acetate (3×50 mL). The combined organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated on rotavapor to give a yellow viscous oil consisting mainly of keto alcohol **2**. This was purified by column chromatography using hexane–ethyl acetate (25%) as the eluent. The alcohol **2** was obtained as a fraction eluting with rf = 0.31 (1.35 g, 90%); IR (neat) ν (cm^{-1}) 460, 580, 665, 720, 780, 810, 880, 940, 1000, 1040, 1155, 1200, 1240, 1340, 1410, 1595, 1705, 3045, 3495. ^{13}C NMR ($CDCl_3$, 200 MHz): δ_{ppm} 200, 136, 132, 128, 57, 40. ^{1}H NMR ($CDCl_3$, 200 MHz): δ_{ppm} 3.2 (t, 2H, $J_{1,2} = 7.00$ Hz, $J_{1,3} = 9.0$ Hz), 4.00 (t, 2H, $J_{1,2} = 7.5$ Hz, $J_{1,3} = 9.5$ Hz), 7.45–7.62 (m, 3H), 8.01 (d, 2H, $J = 8$ Hz).

4.2. 3-Amino-3-phenyl-1-propanol 4

To a stirred solution of **2** (2.0 g, 10 mmol) and ammonium acetate (10.2 g, 0.10 mol) in absolute ethanol (35 mL) was added sodium cyanoborohydride (570 mg, 9 mmol) in one portion at room temperature. The resulting solution was stirred at room temperature for 36 h. Concentrated HCl (1 mL) was added carefully in a fume cupboard, ethanol evaporated, and the resulting white residue dissolved in water (25 mL). The aqueous solution was extracted with diethyl ether to remove unreacted starting materials (3×10 mL). The aqueous phase was then basified with powdered KOH to pH >10, saturated with NaCl and extracted with dichloromethane (3×10 mL). The combined extracts were dried over sodium sulfate and evaporated to dryness to obtain a semi-solid, which was recrystallized from chloroform–hexane to yield **4** as a pale yellow solid (1.3 g, 65%, mp 72–73 °C; lit.[27] mp 72–73 °C). IR (neat) (cm^{-1}): 3282, 1610, 1595, 1059, 755. ^{1}H NMR: ($CDCl_3$ + DMSO-d_6, 200 MHz) δ_{ppm} 1.70–1.90 (m, 2H), 3.4–3.6 (m, 2H), 4.19 (t, 1H), 7.20 (m, 5H). Mass: 151 (M^+).

4.3. 3-[*N*-(Phenylacetyl)amino]-3-phenyl-1-propanol 5

Phenylacetyl chloride (2.6 mL, 19 mmol) and 2 M NaOH (21 mL) were alternately added dropwise to a stirred solution of **4** (2 g, 13 mmol) in ice cold 2 M NaOH (21 mL). The reaction mixture was stirred for a further 4 h at room temperature. The reaction mixture was then cooled to 0 °C, acidified with 10% aqueous HCl to pH ~ 2 and extracted with ethyl acetate (2×25 mL). The combined organic layer was washed with water and brine, dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The crude residue was extracted several times with cyclohexane to remove phenylacetic acid and the crude product was recrystallized from ethyl acetate–hexane to afford the solid racemic 3-phenyl-3-(*N*-phenylacetyl)-1-propanol **5** (4.3 g, 80%, mp 124.5–125 °C). IR (neat) (cm^{-1}): 3310, 3235, 3062, 2946, 2884, 1641, 1559, 1232, 1061, 761, 701, 564. ^{1}H NMR: ($CDCl_3$ + DMSO-d_6, 200 MHz) δ_{ppm} 1.71–2.10 (m, 2H), 3.31–3.61 (m, 4H), 4.0–4.20 (m, 1H), 4.90–5.10 (m, 1H), 7.0–7.40 (m, 10H), 7.9 (br s, 1H, NH).

^{13}C NMR: ($CDCl_3$ + DMSO-d_6, 200 MHz) δ_{ppm} 170, 141, 136, 129, 128.7, 128.1, 127.9, 126.7, 126.1, 57, 50, 43, 38. Mass: 270 (M+1).

4.4. Enzymatic hydrolysis of 5

A solution of **5** (1.0 g, 3.7 mmol) dissolved in ethanol (3 mL) was added to phosphate buffer (0.05 M, pH 7.5, 20 mL) and immobilized penicillin G acylase (1 g, 150 units). The reaction mixture was shaken in a conical flask at 80 rpm (25 °C) and the reaction followed by reverse phase HPLC analysis. The reaction virtually stopped at 50% hydrolysis (1 h). The enzyme was filtered and washed with water (5 mL). The aqueous phase was acidified with concd HCl to pH ~2 and extracted with dichloromethane (3 × 5 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a mixture of unreacted (*S*)-amide and phenylacetic acid. The crude residue was extracted with cyclohexane (4 × 5 mL), in which only phenylacetic acid was highly soluble. The crude amide residue was recrystallized from ethyl acetate–hexane to afford (*S*)-**7** {0.48 g, 95%; $[\alpha]_D^{25} = -51.6$ (*c* 1, ethanol)}. Amide **7** was hydrolyzed by refluxing with 6 M HCl (10 mL), liberated phenylacetic acid removed by extraction with cyclohexane and the amino alcohol recovered as a hydrochloride after evaporation of the aqueous solution under vacuum in quantitative yields {$[\alpha]_D^{25} = +30.5$ (*c* 1, ethanol)}. To isolate the free (*S*)-amino alcohol, it was dissolved in distilled water (10 mL) and the aqueous layer basified with 4 M NaOH (2 mL) to liberate the free amine, which was extracted with dichloromethane. After evaporation of the solvent, the residual oil was recrystallized from chloroform–hexane to obtain (*S*)-3-amino-3-phenyl-1-propanol {0.26 g, 95%; $[\alpha]_D^{25} = -2.75$ (*c* 0.57 ethanol), lit.[27] $[\alpha]_D^{25} - 2.8$ (*c* 0.57, ethanol) for the (*S*)-enantiomer}. The acidic aqueous extract of the enzymatic reaction exclusively contained the (*R*)-amino alcohol **6**. It was isolated after basification with NaOH and extraction with dichloromethane as described above for the (*S*)-enantiomer {252 mg, 90%. $[\alpha]_D^{25} = +2.8$ (*c* 0.57, ethanol)}. The amine was converted to its hydrochloride for storage {$[\alpha]_D^{25} = -30.6$ (*c* 1, ethanol)}.

4.5. Reverse phase HPLC analysis

The disappearance of dioxo ester **1** was followed by reverse phase HPLC. Column C-18 (250 × 5 mm), Chrompack, The Netherlands. Mobile phase was 70% acetonitrile–water containing 0.2% formic acid; flow rate was 0.7 mL/min; detection wavelength 316 nm; and retention times **1**: 9.3 min. The formation of product **2** was monitored on the same column at 246 nm with a mobile phase of 40% acetonitrile–water containing 0.2% formic acid. Retention time **2**: 7.0 min. The hydrolysis of **5** catalyzed by penicillin G acylase was followed by monitoring a decrease in the peak height of amide **5** and an increase in a peak height of phenylacetic acid on a reverse phase HPLC column C-18 (250 × 5 mm), Chrompack, The Netherlands. Mobile phase: 50% acetonitrile–water containing 0.1% trifluoroacetic acid; flow rate 0.4 mL/min; detection wavelength 210 nm; and retention times: phenylacetic acid 9.64 min, **5**: 10.4 min.

4.6. HPLC with chiral stationary phase

The enantiomeric purity of amino alcohol **6** was determined by HPLC analysis on Crownpack CR(+) column (150 × 4 mm), Daicel Chemical Industries, Japan. Mobile phase: water containing 0.1% perchloric acid; flow rate 0.7 mL/min; detection wavelength 210 nm; retention times: (*S*)-amino alcohol 7.98 min, (*R*)-amino alcohol 9.32 min. The enantiomeric purity of the amide **7** was determined by HPLC analysis on Chiralcel OD column (250 × 5 mm), Daicel Chemical Industries, Japan. Mobile phase: 10% isopropanol in hexane containing 0.1% trifluoroacetic acid; flow rate: 0.7 mL/min; and detection wavelength 210 nm. Retention times: (*S*)-amide 28.87 min, (*R*)-amide 30.31 min.

Acknowledgements

We thank CSIR, New Delhi, for grant of SRF to K.R.R. and financial support.

References

1. (a) *Industrial Biotransformations*; Liese, A., Seelbach, K., Wandrey, C., Eds.; Wiley-VCH: Weinheim, 2005; (b) Faber, K. *Biotransformations in Organic Chemistry*, 5th ed.; Springer: Berlin, 2004; (c) Muller, M. *Curr. Opin. Biotechnol.* **2004**, *15*, 591–598; (d) Straathof, A. J. J.; Panke, S.; Schmid, A. *Curr. Opin. Biotechnol.* **2002**, *13*, 548–556.
2. Fadnavis, N. W.; Radhika, K. R. *Tetrahedron: Asymmetry* **2004**, *15*, 3443–3447.
3. (a) Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 4081–4084; (b) Ratovelomanana-Vidal, V.; Girard, C.; Touati, R.; Tranchier, J. P.; Ben Hassine, B.; Genêt, J. P. *Adv. Synth. Catal.* **2003**, *345*, 261–274.
4. Noboru, S.; Sayo, N.; Kumobayashi, H. U.S. Patent 5,286,888, 1994.
5. Kira, I.; Suzuki, T.; Nakanishi, E.; Oonishi, I. Japanese Patent JP 05219984, 1993.
6. Sano, N.; Sayo, N.; Kumobayashi, H. Japanese Patent JP 05111639, 1993.
7. Kira, I.; Watanabe, K.; Nakanishi, E.; Ban, H.; Ohnishi, N.; Suzuki, T. European Patent EP 542300, 1993.
8. Otsubo, K.; Yamamoto, K. Japanese Patent JP 04271796, 1992.
9. (a) Ueno, Y.; Okawara, M. *Tetrahedron Lett.* **1976**, *50*, 4597–4600; (b) Santaniello, E.; Milani, F.; Casati, R. *Synthesis* **1983**, *9*, 749–751; (c) Kim, K. S.; Song, Y. H.; Lee, N. H.; Hahn, C. S. *Tetrahedron Lett.* **1986**, *27*, 2875–2878; (d) Kim, K. S.; Chung, S.; Cho, I. H.; Hahn, C. S. *Tetrahedron Lett.* **1989**, *30*, 2559–2562; (e) Yamaguchi, M.; Takata, T.; Endo, T. *J. Org. Chem.* **1990**, *55*, 1490–1492; (f) Choudary, B. M.; Durgaprasad, A.; Valli, V. L. K. *Tetrahedron Lett.* **1990**, *31*, 5785–5788.
10. Sobe, K.; Mohri, K.; Sano, H.; Taga, J.; Tsuda, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3029–3032.
11. (a) Mekhtiev, S. D.; Kurbanov, T. M.; Suleimanova, E. T.; Musaev, M. R. *Dokl. Akadem. Nauk USSR* **1971**, *27*, 38–40; (b) Roy A. PCT Int. Appl. WO 1993/10071, 1993.
12. Watanabe, K.; Nakanishi, E.; Suzuki, T.; Izawa, K. European Patent EP 0528244, 1993.
13. (a) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590–3596; (b) Kobayashi, O.; Mukoyama, M. Japanese Patent JP 06166652, 1994.

14. Kawakami, T.; Tanizawa, D.; Shibata, I.; Baba, A. *Tetrahedron Lett.* **1995**, *36*, 9357–9360.
15. (a) Hasegawa, E.; Ishiyama, K.; Fujita, T.; Kato, T.; Abe, T. *J. Org. Chem.* **1997**, *62*, 2396–2400; (b) Hardouin, C.; Chevallier, F.; Rousseau, B.; Doris, E. *J. Org. Chem.* **2001**, *66*, 1046–1048; (c) Hasegawa, E.; Chiba, N.; Nakajima, A.; Suzuki, K.; Yoneoka, A.; Iwaya, K. *Synthesis* **2001**, *8*, 1248–1252.
16. Cravotto, G.; Demetri, A.; Nano, G.; Palmisano, G.; Penoni, A.; Tagliapietra, S. *Eur. J. Org. Chem.* **2003**, *22*, 4438–4444.
17. Szmuszkovicz, J.; Mich, K. U.S. Patent 3,668,199, 1972.
18. Sorbera, L. A.; Castaner, J.; Castaner, R. M. *Drugs Fut.* **2004**, *29*, 1201–1205.
19. Kellogg, R. M.; Nieuwenhuijzen, J. W.; Pouwer, K.; Vries, T. R.; Broxterman, Q. B. G.; Reinier, F. P.; Kaptein, B.; La Crois, R. M.; de Wever, E.; Zwaagstra, K.; van der Laan, A. C. *Synthesis* **2003**, *10*, 1626–1638.
20. (a) Review of enantioselective synthesis of β-amino acids: *Enantioselective Synthesis of Beta-Amino Acids*; Juaristi, E., Soloshonok, V. A., Eds.; Wiley-VCH: Weinheim, 2005; (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991–8035; (c) Flores-Sánchez, P.; Jaime, E. J.; Castillo, E. *Tetrahedron: Asymmetry* **2005**, *16*, 629–634; (d) Tan, C. Y. K.; Weaver, D. F. *Tetrahedron* **2002**, *58*, 7449–7461; (e) Rodononow, W. M.; Postovskaja, E. A. *J. Am. Chem. Soc.* **1929**, *51*, 841–847; (f) Cardillo, G.; Gentilucci, L.; Tolomelli, A.; Tomasini, C. *J. Org. Chem.* **1998**, *63*, 2351–2353.
21. Naoto, K.; Yukio, Y.; Yoji, S.; Shinji, N.; Gohfu, S.; Hiroko, S.; U.S. Patent 5,200,561, 1993.
22. Sailes, H. E.; Watts, J. P.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3362–3374.
23. Rozzell, J.; David, J. U.S. Patent 5,916,786, 1999.
24. (a) van Rantwijk, F.; Sheldon, R. A. *Tetrahedron* **2004**, *60*, 501–519; (b) Kaman, J.; van der Eycken, J.; Peter, A.; Fulop, F. *Tetrahedron: Asymmetry* **2001**, *12*, 625–631; (c) Maria, P.; van der Eycken, J.; Gábor, B.; Fülöp, F. *Tetrahedron: Asymmetry* **1998**, *9*, 2339–2347.
25. (a) Watanbe, N.; Anada, M.; Hashimoto, S.; Ikegami, S. *Synlett* **1994**, 1031–1036; (b) Cardillo, G.; Tolomelli, A.; Tomasini, C. *J. Org. Chem.* **1996**, *61*, 8651–8654; (c) Fadnavis, N. W.; Sharfuddin, M.; Vadivel, S. K.; Bhalerao, U. T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3577–3578; (d) Bossi, A.; Cretich, M.; Righetti, P. G. *Biotechnol. Bioeng.* **1998**, *60*, 454–461; (e) Roche, D.; Prasad, K.; Repic, O. *Tetrahedron Lett.* **1999**, *40*, 3665–3668; (f) van Langen, L. M.; Oosthoek, N. H. P.; Guranda, D. T.; van Rantwijk, F.; Svedas, V. K.; Sheldon, R. A. *Tetrahedron: Asymmetry* **2000**, *11*, 4593–4600; (g) Guranda, D. T.; van Langen, L. M.; van Rantwijk, F.; Sheldon, R. A.; Svedas, V. K. *Tetrahedron: Asymmetry* **2001**, *12*, 1645–1650; (h) van Rantwijk, F.; Sheldon, R. A.; van Langen, L. M.; Khimiouk, A. I.; Guranda, D. T.; Svedas, V. K. PCT Int. Appl. WO 2002/20821, 2002; (i) Fadnavis, N. W.; Sharfuddin, M.; Vadivel, S. K. *Tetrahedron: Asymmetry* **1999**, *10*, 4495–4500.
26. (a) Ohta, H.; Sugai, T. In *Stereoselective Biocatalysis*; Patel, R. N., Ed.; Dekker: New York, 2000; pp 487–526; (b) Ward, O. P.; Singh, A. *Curr. Opin. Biotechnol.* **2000**, *11*, 520–526.
27. Koizumi, T.; Hirai, H.; Yoshii, E. *J. Org. Chem.* **1982**, *47*, 4004–4005.