Tetrahedron Letters 51 (2010) 3536–3537

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Chemoenzymatic synthesis of the calcimimetics (+)-NPS R-568 via asymmetric reductive acylation of ketoxime intermediate

Kiwon Han, Yunwoong Kim, Jaiwook Park *, Mahn-Joo Kim *

Department of Chemistry, Pohang University of Science and Technology, San-31 Hyojadong, Pohang 790–784, Republic of Korea

ARTICLE INFO

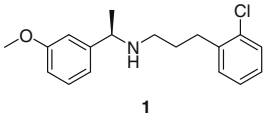
Article history:
Received 12 March 2010
Revised 23 April 2010
Accepted 28 April 2010
Available online 6 May 2010

ABSTRACT

A practical and efficient procedure for the synthesis of a potent calcimimetic (+)-NPS R-568 was developed. This procedure includes as the key step the asymmetric reductive acylation of a ketoxime intermediate catalyzed by a Pd nanocatalyst and a lipase in combination. The target compound was prepared from commercially available 3′-methoxyacetophenone via five steps in overall 63% yield.

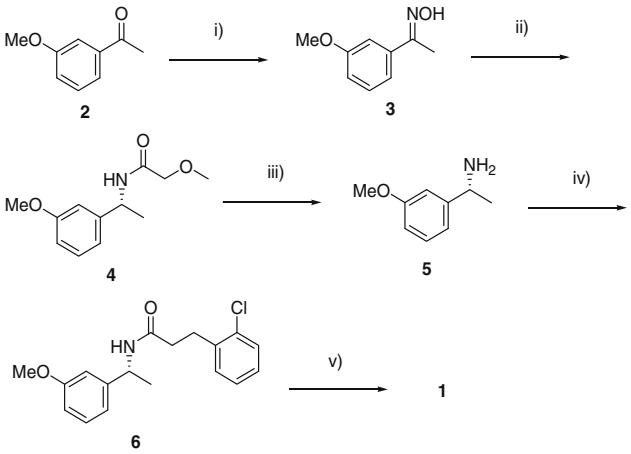
NPS R-568 (**1,** Fig. 1) has a great potential as a novel type of calcimimetics for the treatment of primary and secondary hyperparathyroidism.[1] The clinical studies have shown that the *R* enantiomer of **1** is 10–100 times more potent than the (*S*)-**1**. Several procedures for the enantioselective synthesis of optically active **1** have been developed.[2] In these procedures, the chiral center of **1** was constructed via diastereoselective addition of Grignard or organolithium reagents to imines bearing a chiral auxiliary[2a–c] or asymmetric hydrosilylation of imine.[2d] In this Letter, we wish to report an alternative route to **1**, including the asymmetric reductive acylation of a ketoxime intermediate as the key step for introducing the required chiral center.

The synthesis of **1** started from ketone **2**, which was first converted quantitatively by the reaction with hydroxyl amine to ketoxime **3**[3] (Scheme 1). The ketoxime **3** was then subjected to the asymmetric reductive acylation catalyzed by a lipase–Pd couple[4] to introduce the *R*-chirality. The process comprises three sequential reactions taking place in one-pot: Pd-catalyzed reduction of ketoximes to amines, Pd-catalyzed racemization of amines, and lipase-catalyzed enantioselective acylation of amines to amides (Scheme 2). The last two reactions constitute the dynamic kinetic resolution of primary amimes.[5] Pd/AlO(OH)[6] (palladium nanoparticles entrapped in aluminum oxyhydroxide matrix) and *Candida antarctica* lipase B (CALB; trade name, Novozym 435; immobilized on acrylic resin) were employed as the corresponding catalysts for the process. In a small-scale procedure, the asymmetric reductive acylation of **3** (0.3 mmol) was performed with CALB (30 mg/mmol of substrate) and Pd/AlO(OH) (5 mol % of Pd) in the presence of ethyl methoxyacetate[7] (1.7 equiv) as an acyl donor and 4 Å molecular sieves (500 mg/mmol of substrate) in toluene at 70 °C under 0.1 bar of hydrogen pressure for 48 h to give **4** in 91% isolated yield and 98% ee. The reaction was repeated four times with recovered catalysts, and the yield and ee value of **4** remained practically unchanged up to the 4th recycle[8] (Table 1). These results indicate that the catalysts are thermally stable and can be recycled several times with no significant loss in catalytic efficiency.[9] The reaction was also readily scalable. The reaction performed on a larger scale



1

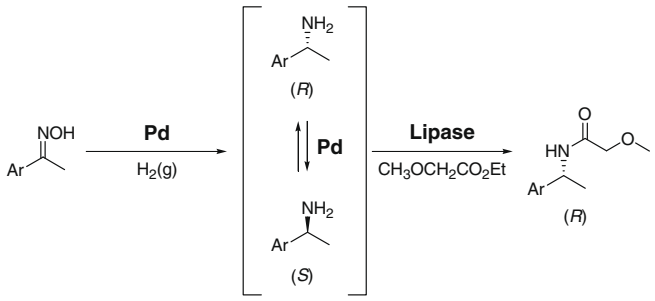
Figure 1. Structure of (+)-NPS R-568 (**1**).



Scheme 1. Synthesis of (+)-NPS R-568 hydrochloride (**1**). Reaction conditions: (i) $NH_2OH{\cdot}HCl$, py, quantitative yield; (ii) CALB, Pd/AlO(OH), $CH_3OCH_2CO_2Et$, H_2 (0.1 bar), 4 Å molecular sieves, toluene, 70 °C, 3 days, 85%, 98% ee; (iii) 3 N HCl in H_2O, 80 °C, 16 h, 94%, 96% ee; (iv) 3-(2-chlorophenyl)-propionic acid (1 equiv), EDCI (1.1 equiv), dry CH_2Cl_2, rt, 12 h, 93%; (v) $LiAlH_4$ (1 equiv), dry Et_2O, rt, 30 h, and then 1 N HCl in H_2O, 85%.

* Corresponding author. Tel.: +82 54 279 2112; fax: +82 54 279 0654.
E-mail address: mjkim@postech.ac.kr (M.-J. Kim).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.04.121



Scheme 2. Asymmetric reductive acylation of ketoximes catalyzed by a lipase–palladium couple.

Table 1
Asymmetric reductive acylation of **3** with recycling of catalysts

# of recycling	Yield[a] (%)	ee[b] (%)
0	91	98
1	88	98
2	89	98
3	89	98
4	90	98

[a] Isolated yield.
[b] Measured by HPLC with a chiral column.

(6 mmol) proceeded smoothly and provided similarly good results (85% isolated yield and 98% ee).[10]

Chiral amide **4** was then hydrolyzed under acidic condition (3 N HCl) at 80 °C for 16 h to give chiral amine **5** with a little loss in enantiomeric excess (94% isolated yield, 96% ee).[11] The conversion of **5** to **1** was achieved by modifying the known procedure.[2b,c] The coupling of **5** with 3-(2-chlorophenyl)propionic acid[12] in the presence of *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDCI) afforded amide **6** in 93% yield.[13,14] Finally, amide **6** was reduced with $LiAlH_4$ to give the target molecule[15] which was isolated as its hydrochloride salt (85% yield) after the treatment with HCl.

We thus accomplished the asymmetric synthesis of the potent calcimimetic (+)-NPS R-568 via five steps from commercially available 3′-methoxyacetophenone in 63% overall yield. This procedure is highlighted by asymmetric reductive acylation of ketoxime as the key step which is cocatalyzed by a lipase and a Pd nanocatalyst with good yield and excellent ee. An advantage of this process is that the catalysts employed are thermally stable and recyclable.

Acknowledgments

This work was supported by National Research Foundation of Korea Grant funded by the Korean Government (2009-0087801). We thank the Korean Government for supporting our graduate program (BK21 Program). This Letter is dedicated to the late Professor Chi Sun Hahn who was an excellent teacher and researcher and made great contributions to organic chemistry of Korea.

References and notes

1. (a) Nagano, N. *Pharmacol. Therap.* **2006**, *109*, 339–365; (b) Joy, M. S.; Kshirsagar, A. V.; Franceschini, N. *Ann. Pharmacother.* **2004**, *38*, 1871–1880; (c) Cohen, A.; Silverberg, S. J. *Curr. Opin. Pharmacol.* **2002**, *2*, 734–739; (d) Goodman, W. G. *Curr. Opin. Nephrol. Hypertens.* **2001**, *10*, 575–580; (e) Coburn, J. W.; Maung, H. M. *Curr. Opin. Nephrol. Hypertens.* **2000**, *9*, 123–132; (f) Nemeth, E. F.; Fox, J. *Trends Endocrinol. Metab.* **1999**, *10*, 66–71.
2. (a) Fernández, I.; Valdivia, V.; Khiar, N. *J. Org. Chem.* **2008**, *73*, 745–748; (b) Atobe, M.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **2004**, *69*, 5595–5607; (c) Yamazaki, N.; Atobe, M.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 5029–5032; (d) Hansen, M. C.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2033–2034; (e) Barmore, R. M.; Logan, S. R.; VanWagenen, B. C. *Tetrahedron Lett.* **1998**, *39*, 3451–3454.
3. Larock, R. C. *Comprehensive Organic Transformation*; VCH Publishers: New York, 1989.
4. (a) Han, K.; Park, J.; Kim, M.-J. *J. Org. Chem.* **2008**, *73*, 4302–4304; (b) Choi, Y. K.; Kim, M. J.; Ahn, Y.; Kim, M.-J. *Org. Lett.* **2001**, *3*, 4099–4101.
5. For recent studies on the DKR of primary amines, see: (a) Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 668–669; (b) Parvulescu, A.; De Vos, D.; Jacobs, P. *Chem. Commun.* **2005**, 5307–5309; (c) Martin-Matute, B.; Edin, M.; Bogar, K.; Kaynak, F. B.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 8817–8825; (d) Veld, M. A. J.; Hult, K.; Palmans, A. R. A.; Meijer, E. W. *Eur. J. Org. Chem.* **2007**, 5416–5421; (e) Parvulescu, A. N.; Jacobs, P. A.; De Vos, D. E. *Chem. Eur. J.* **2007**, *13*, 2034–2043; (f) Kim, M.-J.; Kim, W.-H.; Han, K.; Choi, Y. K.; Park, J. *Org. Lett.* **2007**, *9*, 1157–1159; (g) Parvulescu, A. N.; Jacobs, P. A.; De Vos, D. E. *Adv. Synth. Catal.* **2008**, *350*, 113–121; (h) Andrade, L. H.; Silva, A. V.; Pedrozo, E. C. *Tetrahedron Lett.* **2009**, *50*, 4331–4334.
6. Pd/AlO(OH) was prepared according to the procedure previously reported in the literature: (a) Kwon, M. S.; Kim, N.; Seo, S. H.; Park, I. S.; Cheedrala, R. K.; Park, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6913–6915; (b) Kwon, M. S.; Kim, N.; Park, C. M.; Lee, J. S.; Kang, K. Y.; Park, J. *Org. Lett.* **2005**, *7*, 1077–1079.
7. Ethyl methoxyacetate is an excellent acyl donor for the enzymatic acylation of primary amines at elevated temperature (70 °C). More active esters such as trifluoroethyl acetate lead to spontaneous acylation while less reactive esters such as ethyl acetate require a significantly larger amount of enzymes or much longer reaction times.[5f] For the use of methoxyacetate in the enzymatic acylations of amines, see: (a) González-Sabín, J.; Gotor, V.; Rebolledo, F. *Tetrahedron: Asymmetry* **2004**, *15*, 481–488; (b) González-Sabín, J.; Gotor, V.; Rebolledo, F. *Tetrahedron: Asymmetry* **2005**, *16*, 3070–3076; (c) Torre, O.; Gotor-Fernández, V.; Gotor, V. *Tetrahedron: Asymmetry* **2006**, *17*, 860–866.
8. *Procedure for recycling the catalysts*: A solution containing **3** (0.3 mmol), CALB (Novozym 435, 30 mg/mmol of substrate), Pd/AlO(OH) (5 mol % of Pd), ethyl methoxyacetate (1.7 equiv), and 4 Å molecular sieves (500 mg/mmol of substrate) in dry and degassed toluene was stirred and heated at 70 °C under 0.1 bar of hydrogen pressure. After 48 h, the reaction mixture was cooled to room temperature and filtered through a glass filter. Filtrate was concentrated and analyzed by ^{1}H NMR spectroscopy and HPLC (Whelk-O1, *n*-hexane/2-propanol = 80/20, flow rate = 0.50 mL/min, UV 217 nm). The separated catalysts were washed with ethyl acetate, dried in vacuo, and then reused for next run.
9. The catalysts were reused several times without losing any significant activity in the dynamic kinetic resolution of primary amines. See Ref. 5f.
10. A suspension containing **3** (1 g, 6.05 mmol), Pd/AlO(OH) (1.5 g, 2.5 mol % of Pd), CALB (Novozym 435, 151 mg, 25 mg/mmol), 4 Å molecular sieves (3 g, 500 mg/mmol), and ethyl methoxyacetate (1.1 g, 1.5 equiv) in dry and degassed toluene (54 mL, 0.1 M) was stirred at 70 °C under 0.1 bar of hydrogen pressure in a 250 mL round–bottomed flask with a condenser. After 72 h, the reaction mixture was cooled to room temperature and filtered through a glass filter. The filtrate was concentrated and then subjected to flash chromatography (silica gel, *n*-hexane/ethyl acetate = 1/1) to provide oily liquid **4** (1.15 g, 5.14 mmol, 85%, 98% ee): $[\alpha]_D^{20}$ +75.5 (*c* 1.15, $CHCl_3$): HPLC (chiral column = (*R*,*R*) Whelk–O1, *n*-hexane/2–propanol = 80/20, flow rate = 0.5 mL/min, UV 217 nm) (*S*)-**4** = 22.70 min, (*R*)-**4** = 66.50 min. HRMS (EI): $C_{12}H_{17}NO_3$ calcd 223.1208 (M^+), found 223.1206. ^{1}H and ^{13}C NMR data are in good agreement with those of (+/−)-**4** reported in the literature.[16]
11. *Compound* **5**: $[\alpha]_D^{20}$ +26.7 (*c* 1.05, MeOH) (lit.[2c] $[\alpha]_D^{20}$ +23.6 (*c* 0.8, MeOH)); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.27–7.21 (m, 1H), 6.94–6.91 (m, 2H), 6.80–6.76 (m, 1H), 4.12–4.06 (q, *J* = 6.62 Hz, 1H), 3.81 (s, 3H), 1.38 (d, *J* = 6.62 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 159.8, 149.6, 129.5, 118.1, 112.1, 111.4, 55.2, 51.3, 25.6. HRMS (EI): $C_9H_{13}NO$ calcd 151.0997 (M^+), found 151.1001. The % ee was determined by HPLC after converting to the corresponding amide by treatment with a few drops of methoxyacetyl chloride.
12. 3-(2-Chlorophenyl)propionic acid was prepared by hydrogenation of 2-chlorocinnamic acid in the presence of Ru/Al_2O_3 in methanol under 1 bar of molecular hydrogen.
13. *Compound* **6**: Mp 90.7–91.6 °C (lit.[2b] mp 92–92.5 °C); $[\alpha]_D^{20}$ +47.2 (*c* 1.0, $CHCl_3$) (lit.[2b] $[\alpha]_D^{20}$ +45.6 (*c* 1.0, $CHCl_3$)).
14. It is noted that the direct synthesis of **6** from **3** using 3-(2-chlorophenyl)-propionic acid ethyl ester as the acyl donor in the asymmetric reductive acylation was unsuccessful because CALB (Novozym 435) was unreactive toward the ester.
15. *Compound* **1**: $[\alpha]_D^{20}$ +37.9 (*c* 0.7, $CHCl_3$, 96 %ee) (lit.[2d] $[\alpha]_D^{20}$ +38.6 (*c* 1.1, $CHCl_3$)). The % ee was determined by HPLC (chiral column = Kormasil-5-cellcoat, hexane/isopropanol/diethyl-amine = 90/10/0.1, flow rate = 1.5 ml/min, 220 nm): (*R*)-**1** = 4.05 min, (*S*)-**1** = 4.43 min. **1·HCl**: mp 183.3–184.4 °C; $[\alpha]_D^{20}$ +39.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 10.28 (br s, 1H), 9.86 (br s, 1H), 7.32–7.19 (m, 3H), 7.16–7.03 (m, 4H), 6.92–6.89 (m, 1H), 4.14 (br s, 1H), 3.87 (s, 3H), 2.75–2.58 (m, 4H), 2.28–2.18 (quintet, *J* = 7.61 Hz, 2H), 1.86 (d, *J* = 6.81 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 160.4, 137.6, 137.4, 133.8, 130.4, 130.3, 129.5, 127.8, 126.9, 120.0, 115.8, 112.2, 59.0, 55.6, 44.9, 30.4, 25.5, 20.5. HRMS (EI): $C_{18}H_{23}Cl_2NO$ calcd 339.1157 (M^+), found 339.1161.
16. Mangas-Sanchez, J.; Rodriguez-Mata, M.; Busta, E.; Gotor-Fernandez, V.; Gotor, V. *J. Org. Chem.* **2009**, *74*, 5304–5310.