CL-150390 Received: April 24, 2015 | Accepted: May 20, 2015 | Web Released: May 30, 2015

Synthesis of Sitagliptin Phosphate by a $NaBH_4/ZnCl_2$-catalyzed Diastereoselective Reduction

Xianhua Pan,[#] Kun Wang,[#] Wansheng Yu, Ruimin Zhang, Lu Xu, and Feng Liu*
School of Perfume and Aroma Technology, Shanghai Institute of Technology, 100 Haiquan Rd, Shanghai, 201418, P. R. China

(E-mail: liufeng@sit.edu.cn)

A practical asymmetric synthesis of sitagliptin phosphate, from 1-{3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo-[4,3-*a*]pyrazin-7(8*H*)-yl}-4-(2,4,5-trifluorophenyl)butane-1,3-dione, in overall 65.3% yield has been reported. The target compound was synthesized via eneamination, diastereoselective reduction, amine-deprotection, and phosphatization. The key diastereoselective reduction was performed with $NaBH_4$ and $ZnCl_2$, and it gave the product with almost quantitative yield and 68.5% d.e. value after simple work-up and recrystallization with IPA/PE; a high enantiopurity (d.e.% = 99.3%) can also be obtained in 57.1% yield.

Diabetes, a fast growing global epidemic that affects millions of people, is caused by multiple reasons and can be characterized by divided levels of plasma glucose in the rapid or post glucose-challenge state. Two types of diabetes can be generally recognized: Type 1 diabetes mellitus (T_1DM), wherein patients generate none or trace insulin, which cut down glucose, and Type 2 diabetes mellitus (T_2DM), in which patients can generate insulin normally, but this insulin has a poor effect in regulating glucose utilization. In a recent study, inhibitors of dipeptidyl peptidase IV (DPP-IV) could generate fresh therapeutic agents for T_2DM by stimulating GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide) levels, as well as boosting glycemic control for diabetics.

Sitagliptin phosphate **1** (Figure 1), the representative drug for the treatment of T_2DM, was approved by USFDA in 2006, which received almost 4 billion saleroom in 2013, being worthy of the name "heavy bomb drug." Due to the unique structure and good market performance, a large number of synthetic routes of sitagliptin phosphate have been developed in the past decade. Kim et al.[1] reported an ingenious way to obtain the target compound at 2005, but this needs quite strict reaction conditions such as a low temperature (−78 °C) and a dangerous reagent (CH_2N_2). A method to obtain the key intermediate (β-amino acid derivative) of sitagliptin phosphate has been developed by Xiao et al.[2] at 2004, which was carried out by metal-catalyzed asymmetric hydrogenation; however, even if the chiral amidogen were created inventively, the cost of using the expensive ($[Rh(cod)_2]OTf$) limited this process to the laboratory and small

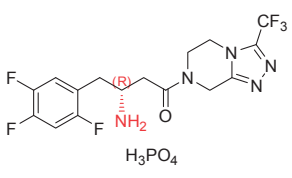
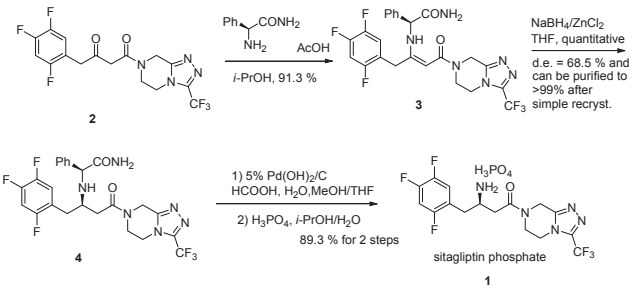


Figure 1. Structure of sitagliptin phosphate.



Scheme 1. Synthesis of sitagliptin phosphate.

scale, so did (*S*-BINAP),[3] $RuCl_2$,[3] [(*R*)-(*R*)-*t*-Bu JOSIPHOS],[4] (R-DM-SEGPHOS),[5] and PtO_2.[6,7] Therefore, applying a cheap, safe, and large-scale method to obtain sitagliptin phosphate or its intermediates has become the scientists' unremitting goal.

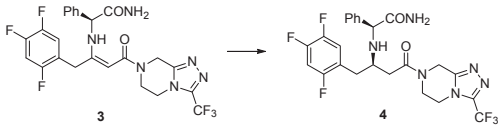
In 2013, a novel method that achieved the intermediate of sitagliptin phosphate in a certain chiral purity (d.e.% = 50%) by using a cheap reductant ($NaBH_4$ and aliphatic acid) was developed by Lin and colleagues,[8] which revealed that a cheap and simple reductive system can also catalyze the substrate controlled diastereoselective reduction to a certain extent.

As a part of our interests in developing practical and simple approaches for the synthesis of sitagliptin phosphate and other active pharmaceutical ingredients (API) as well as the intermediates,[9] we report here an efficient approach to the synthesis of sitagliptin phosphate **1** (Scheme 1) by a $NaBH_4$/Lewis acid-catalyzed diastereoselective reduction reaction[10] and the following work-up.[11–14]

The synthesis began from compound **2**,[2] after treating it with (*S*)-phenylglycine amide in the presence of AcOH in IPA, compound **3** was obtained in good yield (91%) and high HPLC purity (99%).

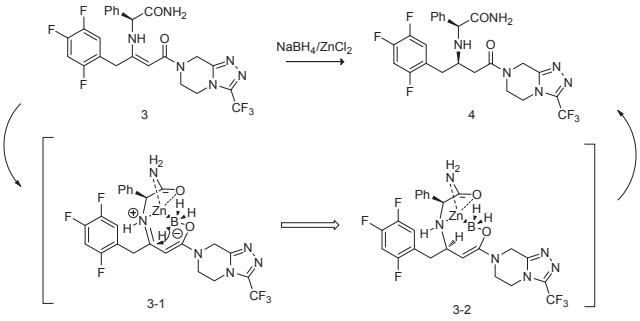
Then, with the key intermediate, enamine compound **3** in hand, the Lewis acid-catalyzed diastereoselective reduction was examined carefully. As indicated in Table 1, it could be easily found that $NaBH_4$–$ZnCl_2$ has better catalytic ability among the four different $NaBH_4$–Lewis acids (Entries 1–4) at 0 °C in THF, resulting in 59.4% yield and 51.7% diastereomeric excess. Then, the reaction mixture was frozen to −60 °C to enhance the chiral selectivity, and a better yield and enantioselectivity were obtained (Entry 5). We were happy to find that on decreasing the loading of $ZnCl_2$ to 0.7 equiv (Entry 6), the diastereomeric pair of **4** could be quantitatively obtained with a satisfactory diastereoselectivity (d.e.% = 68.5%). However, unfortunately, further decreasing $ZnCl_2$ to 0.35 equiv gave us a worse result, and both the yield and d.e. value were reduced (Entry 7). We then tried to adjust the reaction temperature to a moderate level in order to reduce the energy consumption, but with the increase in the temperature, the reaction yield decreased, and the stereoselectivity was less than satisfactory (Entries 8–10).

Table 1. Influence of the sort of Lewis acid, equivalent and temperature on reaction[a]



Entry	Lewis acid	equiv	Temp. /°C	Yield[b] /%	d.e. /%
1	$CoCl_2$	1.5	0	38.6	30.0
2	$MnCl_2$	1.5	0	—[c]	—[c]
3	$CaCl_2$	1.5	0	—[c]	—[c]
4	$ZnCl_2$	1.5	0	59.4	51.7
5	$ZnCl_2$	1.5	−60	74.1	54.9
6	$ZnCl_2$	0.7	−60	100	68.5[d]
7	$ZnCl_2$	0.35	−60	60.4	46.8
8	$ZnCl_2$	0.7	−35	81.6	59.6
9	$ZnCl_2$	0.7	−15	90.2	58.3
10	$ZnCl_2$	0.7	0	60.4	57.5

[a]All reactions were run under the following conditions unless otherwise noted: **3** (0.93 mmol) in 15 mL THF, $NaBH_4$ (1.86 mmol.), 4 h. [b]Yields calculated by HPLC. [c]Trace product. [d]After work up and recrystallization, a white powder was gained with the yield of 57.1%, and d.e.% = 99.3%.



Scheme 2. Proposed mechanism of the reduction.

This result may partly be caused by the balance between the temperature and the concentration of Zn^{2+}. At the beginning of the reduction process, conjugated imine-enol intermediate state **3-1** has formed in the coordination of $NaBH_4$ and $ZnCl_2$; then, imine was stereoselectively reduced to amine **3-2** as the C–N double bond was linked with the zinc ion at little space steric hindrance (α-face), and then compound **4** was obtained by the reduction of intermediate state **3-2** by treatment with $NaBH_4$ (Scheme 2). During the reduction course, the chiral purity would be reduced while the process temperature is too high or the zinc ion concentration is too high, which would both affect the selective annexation of the zinc ions and imine; meanwhile, when the concentration of zinc ion was too low, a portion of enamine would be reduced by $NaBH_4$ directly instead of stereoselective reducing.

According to the optimized reaction condition in Table 1, compound **4** could be obtained in an excellent yield and a moderate purity (d.e.% = 68.5%); then, after a simple work-up and recrystallization with IPA/PE, a high enantiopurity (d.e.% = 99.3%) can also be obtained in 57.1% yield.

The subsequent synthesis could be carried out by treating **4** with $Pd(OH)_2/C$ and HCOOH aq. in MeOH/THF for 16 h; after a typical work-up, the crude free base was recrystallized from toluene, and sitagliptin was isolated with 95% yield, and then adding 85% H_3PO_4 in IPA/H_2O, a phosphoric acid salt **1** was obtained with 94% yield, 99.2% HPLC purity (single impurity less than 0.1%) and 99.4% e.e. value after recrystallization from *i*-PrOH.

In summary, we have devised a novel asymmetric synthesis of sitagliptin phosphate via a diastereoselective reduction reaction, which was performed by $NaBH_4$ and $ZnCl_2$, giving us the satisfying result with an almost quantitative yield and 68.5% d.e. value. This simple and economical process provides a novel synthesis of sitagliptin phosphate **1**.

This work was supported by the National Natural Science Foundation of China (Grants No. 21302126) and Shanghai Engineering Technology Research Center of Fragrance and Flavor (No. 12DZ2251400).

Supporting Information is available electronically on J-STAGE.

References and Notes

# These two authors (Xianhua Pan and Kun Wang) contributed equally to this work and should be considered as co-first authors.

1 D. Kim, L. Wang, M. Beconi, G. J. Eiermann, M. H. Fisher, H. He, G. J. Hickey, J. E. Kowalchick, B. Leiting, K. Lyons, F. Marsilio, M. E. McCann, R. A. Patel, A. Petrov, G. Scapin, S. B. Patel, R. S. Roy, J. K. Wu, M. J. Wyvratt, B. B. Zhang, L. Zhu, N. A. Thornberry, A. E. Weber, *J. Med. Chem.* **2005**, *48*, 141.

2 Y. Xiao, J. D. Armstrong, III, S. W. Krska, E. Njolito, N. R. Rivera, Y. Sun, T. Rosner, PCT Int. Appl. WO 2004085378, **2004**.

3 K. B. Hansen, J. Balsells, S. Dreher, Y. Hsiao, M. Kubryk, M. Palucki, N. Rivera, D. Steinhuebel, J. D. Armstrong, III, D. Askin, E. J. J. Grabowski, *Org. Process Res. Dev.* **2005**, *9*, 634.

4 K. B. Hansen, Y. Hsiao, F. Xu, N. Rivera, A. Clausen, M. Kubryk, S. Krska, T. Rosner, B. Simmons, J. Balsells, N. Ikemoto, Y. Sun, F. Spindler, C. Malan, E. J. J. Grabowski, J. D. Armstrong, III, *J. Am. Chem. Soc.* **2009**, *131*, 8798.

5 D. Steinhuebel, Y. Sun, K. Matsumura, N. Sayo, T. Saito, *J. Am. Chem. Soc.* **2009**, *131*, 11316.

6 S. D. Dreher, N. Ikemoto, E. Njolito, N. R. Rivera, D. M. Tellers, Y. Xiao, WO 2004085661.

7 P. P. Reddy, I. Babu, P. Srinivas, P. Shailaja, N. Kavitha, R. V. Anand, V. R. Reddy, WO 2009085990.

8 H. Jona, J. Shibata, M. Asai, Y. Goto, S. Arai, S. Nakajima, O. Okamoto, H. Kawamoto, Y. Iwasawa, *Tetrahedron: Asymmetry* **2009**, *20*, 2439.

9 a) F. Liu, W. Yu, W. Ou, X. Wang, L. Ruan, Y. Li, X. Peng, X. Tao, X. Pan, *J. Chem. Res.* **2010**, *34*, 230. b) F. Liu, W. Yu, W. Ou, X. Xu, L. Ruan, X. Wang, Y. Li, X. Peng, X. Tao, J. Mao, J. Wan, X. Pan, *J. Chem. Res.* **2010**, *34*, 517. c) X. Pan, W. Yu, W. Ou, X. Tao, J. Wan, F. Liu, *J. Chem. Res.* **2011**, *35*, 545. d) X. Pan, X. Tao, L. Ruan, Y. Li, W. Ou, F. Liu, *J. Chem. Res.* **2011**, *35*, 729. e) X. Pan, R. Huang, J. Zhang, L. Ding, W. Li, Q. Zhang, F. Liu, *Tetrahedron Lett.*

2012, *53*, 5364. f) X. Pan, X. Li, Q. Lu, W. Yu, W. Li, Q. Zhang, F. Deng, F. Liu, *Tetrahedron Lett.* **2013**, *54*, 6807.
10 a) J. Seyden-Penne, in *Reductions by the Alumino- and Borohydrides in Organic Synthesis*, 2nd ed., ed. by D. P. Curran, Wiley, New York, **1997**. b) S. Narasimhan, S. Madhavan, K. G. Prasad, *J. Org. Chem.* **1995**, *60*, 5314.
11 Compound **2** (10.0 g, 24.6 mmol) and (*S*)-phenylglycine amide (4.1 g, 27.1 mmol) were added into *i*-PrOH (50 mL) successively, then AcOH (0.8 g, 13.3 mmol) was added dropwise into the mixture after warmed to 45 °C. After the addition, the mixture was stirred for another 10 h until the starting material was disappear (determined by TLC). The slurry was filtered and washed with cooled *i*-PrOH (10 mL) carefully after cooled down the mixture to room temperature. 12.0 g of compound **3** (91.3% yield, 99.0% purity) was obtained via drying for 12 h under N_2.
12 Compound **3** (0.5 g, 0.93 mmol) and $ZnCl_2$ (0.09 g, 0.65 mmol) were added into anhydrous THF (15 mL), then $NaBH_4$ (0.07 g, 1.86 mmol) was added into the mixture in several portions after cooled down to −60 °C. After the addition, the mixture was stirred for another 4 h until the starting material was disappear (determined by TLC). The reaction was then diluted with H_2O (15 mL) and extracted with EtOAc (3 × 10 mL). The organic layer was washed with water, sat. $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The Na_2SO_4 was removed by filtration and the volatile removed under reduced pressure to give solid (0.49 g, almost 100% yield, d.e.% = 68.5%). 0.29 g of compound **4** (57.1% yield, d.e.% = 99.3%) was obtained after recrystallized from 1:2 *i*-PrOH/hexane (5 mL).
13 Compound **4** (5.0 g, 18.6 mmol) and 20% $Pd(OH)_2/C$ (0.25 g, 5 wt %) were slurried in 1:1 MeOH/THF (15 mL), then a solution of 98% HCOOH (5.0 mL) in 5.0 mL of H_2O was added dropwise to the mixture. After the addition, the mixture was warmed to 55 °C and stirred for 16 h until the starting material was disappear (determined by TLC). The reaction was cooled to room temperature and filtrated to remove $Pd(OH)_2/C$. After evaporating in vacuo, saturated Na_2CO_3 (50 mL) was added and extracted with DCM (2 × 50 mL). The organic layer was combined and washed with water and brine, then dried over anhydrous Na_2SO_4. The Na_2SO_4 was removed by filtration and the volatile removed under reduced pressure to give a pale yellow solid. 9.5 g of sitagliptin (17.6 mmol, 95.2% yield) was obtained after recrystallized from toluene (40 mL).
14 All sitagliptin obtained above was slurried in 2:1 *i*-PrOH/H_2O (30 mL), 85% H_3PO_4 (2.0 g, 17.6 mmol) was then added dropwise at room temperature. After the addition, the mixture was warmed to 70 °C to dissolve the solids. The reaction was aged for 1 h, then cooled down slowly to 0 °C in about 12 h, a white solid was gained by filtration. Finally 10.5 g of sitagliptin phosphate **1** was obtained with 94% yield, 99.2% HPLC purity (single impurity less than 0.1%) and 99.4% e.e after recrystallization from *i*-PrOH.