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PRACTICAL AND ECONOMICAL APPROACH TO SYNTHESIZE SITAGLIPTIN

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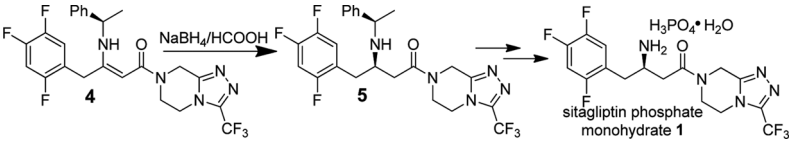
GRAPHICAL ABSTRACT



Abstract *Economic syntheses of sitagliptin phosphate monohydrate, acknowledged as the first dipeptidyl peptidase 4 (DPP-4) inhibitor, have been achieved in an overall yield of 42.4% in four steps from 1-{3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a] pyrazin-7(8H)-yl}-4-(2,4, 5-trifluorophenyl)butane-1,3-dione. The key stereoselective reduction of this process was carried out by $NaBH_4$/HCOOH instead of expensive and toxic catalysts or ligands.*

[Supplementary materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *for the following free supplemental resource(s): Full experimental and spectral details.]*

Keywords Chiral synthesis; DPP-4 inhibitor; sitagliptin

INTRODUCTION

Diabetes is establishing itself as a serious epidemic disease of the 21st century. Type 2 diabetes (T2D), formerly non-insulin-dependent diabetes, accounts for at least 90% of all cases of the disease. Inhibition of dipeptidyl peptidase 4 (DPP-4) has proven to be an effective treatment for improving glycemic control in type 2 diabetic patients.[1] DPP-4 cleaves to a wide range of peptides to modulate their biological activity. One of these peptides is glucagon-like peptide 1 (GLP-1), which plays an important role in the regulation of blood glucose level.[2] GLP-1 is released after food ingestion and stimulates insulin biosynthesis and secretion. GLP-1 also inhibits glucagon release, delays gastric emptying, and induces pancreatic β-cell proliferation.[3]

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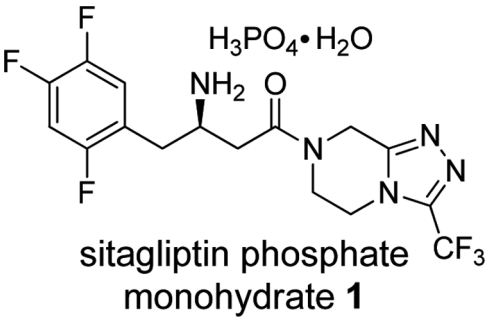


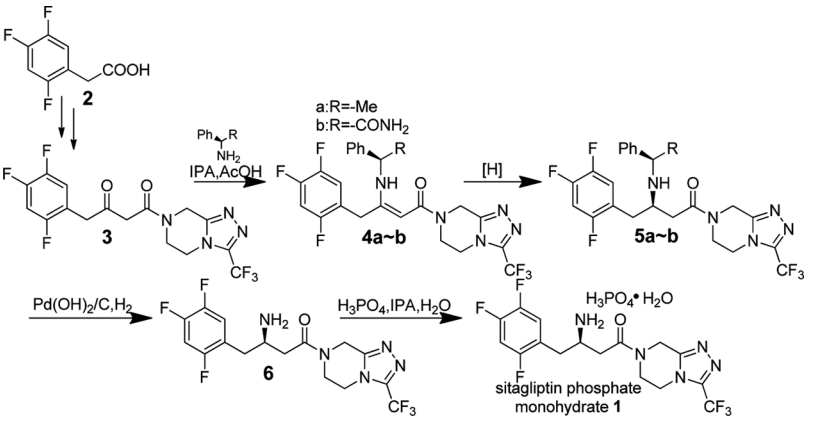
Figure 1. Structure of sitagliptin.

In recent years, a number of DPP-4 inhibitors, such as sitagliptin, vildagliptin, saxagliptin, alogliptin, and linagliptin, have been launched and showed great efficacy in patients with T2D. Sitagliptin (Fig. 1), the first launched DPP-4 inhibitor, was approved by the U.S. Food and Drug Administration in 2006. Most of existing routes to synthesize sitagliptin focus on the asymmetric synthesis by the chiral catalyst[4–6] or chiral auxiliary.[7,8] However, all the ways to form the chiral center have some deficiencies: They need some expensive and toxic catalysts or ligands such as (*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (*S*-BINAP),[4] $RuCl_2$,[4] (*R*)-(+)-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethyldi-*tert*-butylphosphine [(*R*)-(*R*)-t-Bu JOSIPHOS],[5] [$Rh(COD)_2OTf$],[5] (*R*)-(+)-5,5′-bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole (*R*-DM-SEGPHOS),[6] $Ru(OAc)_2$,[6] or PtO_2.[7,8] We herein report an economic route for practical preparation of sitagliptin without the expensive metal catalyst.

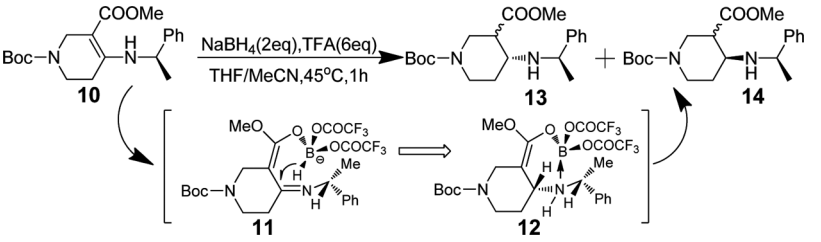
RESULTS AND DISCUSSION

Retrosynthetic analysis suggests that the chiral center can be induced through the commercially available auxiliary *R*-α-methylbenzylamine or *S*-phenylglycinamide. The key intermediate **4** was prepared from β-carbonylamide **3**, which was synthesized from 2,4,5-trifluorophenylacetic acid **2**. In this paper, a stereoselective reduction system was explored to avoid the using of expensive and toxic agents.

The synthesis commenced with β-carbonylamide **3**, prepared from 2,4,5-trifluorophenylacetic acid **2** by two steps, according to previously described procedures[5,9] (Scheme 2). The enaminoamide **4a** was obtained by dehydration condensation with *R*-α-methylbenzylamine in AcOH/iso-propyl alcohol. On the subsequent stereoselective reduction, a recent publication by Jona et al.[10] revealed that the compound **13** could be obtain through enaminoester **10** according to the reported mechanism: The hydride at the complex substrate **11** attacked the side with less steric hindrance to form the chiral center (Scheme 2). Following that idea (Scheme 3), the stereoselective reduction of **4a** with $NaBH_4$ and aliphatic acid to get compounds **5a** was designed (Table 1). At first, a nonselective reduction with $NaBH_4$ in 37 equiv AcOH at room temperature (entry 1 in Table 1) was carried out to get a pair of diastereomers (compounds **5a** and **9a**) for the establishment of

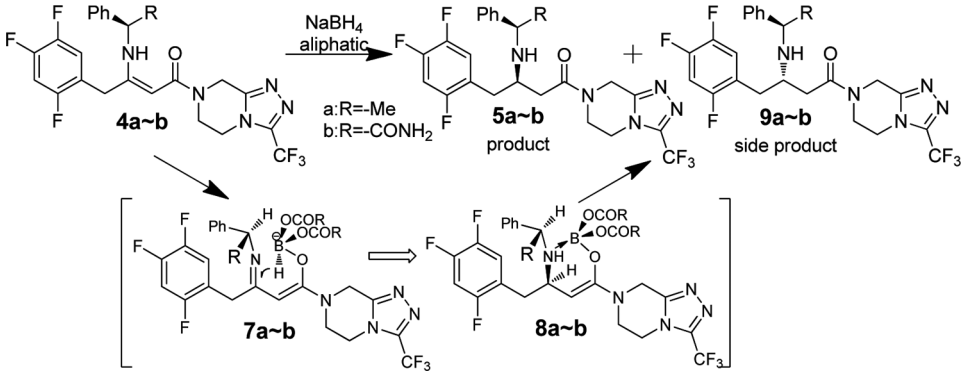


Scheme 1. Synthesis of sitagliptin phosphate monohydrate.



Scheme 2. Mechanism of the stereoselective reduction by chiral auxiliary.

high-performance liquid chromatography (HPLC). Reducing the amount of AcOH to 6 equiv caused the reduction not occur (entry 2). The reaction went well with $NaBH_4$ in TFA (trifluoroacetic acid) at $-30\,^{\circ}C$, but the stereoselectivity was not very good and it was not improved when the reaction was performed at $-70\,^{\circ}C$ (entries 3 and 4). Next, HCOOH was applied to lower the reduction ability with an expectation



Scheme 3. Mechanism of the stereoselective reduction of substrates **4a** and **4b**.

Table 1. Reduction of compound **4a**

Entry	Reducing agent (molar equiv)[a]	Product ratio (**5a**:**9a**)[b]
1	$NaBH_4$(3), AcOH(37), rt, 3 h	54:46
2	$NaBH_4$(2), AcOH(6), rt, 6 h[c]	—
3	$NaBH_4$(2), TFA(6), −70 °C, 3 h	68:32
4	$NaBH_4$(2), TFA(6), −30 °C, 3 h	67:33
5	$NaBH_4$(2), HCOOH(6), −30 °C, 16 h	73:27
6	$NaBH_4$(2), HCOOH(7), −30 °C, 15 h	72:28
7	$NaBH_4$(2), HCOOH(12), −30 °C, 3 h	75:25
8	$NaBH_4$(2), HCOOH(12), −78 °C, 3 h[c]	—
9	$NaBH_4$(5), t-BuCOOH(50), rt, 24 h	59:41
10	$NaBH(OCOCH_3)_3$, −30 °C–rt, 6 h[c]	—
11	$NaBH(OCOH)_3$, −30 °C–rt, 20 h	63:37
12	$NaBH_4$, ZnI_2, 0 °C–rt, 5 h	64:36

[a]Reducing agent was prepared in THF.
[b]The ratios were determined by HPLC analysis.
[c]At the end of reaction, the enaminoamide **4a** was detected as the biggest spot by TLC.

of better stereoselectivity. The results in entries 5–7 proved the concept although 6 or 7 equiv of HCOOH did not complete the reaction (entries 5 and 6). Increasing the amount of HCOOH could convert **4a** completely with the selectivity of 75:25 (entry 7), whereas at −78 °C the enaminoamide remained (entry 8). The t-BuCOOH with bigger steric hindrance gave nonstereoselectivity (entry 9). Instead of using $NaBH_4$/aliphatic acid, the reagents such as $NaBH(OCOCH_3)_3$ or $NaBH(OCOH)_3$ lacked enough reduction ability to finish the reaction (entries 10 and 11). Lewis acid (ZnI_2), which could take the place of aliphatic acid in some cases, did not show better results (entry 12).

In addition, another auxiliary (*S*-phenylglycinamide) was studied in this work. It seemed that the reduction of **4b** was easier than that of **4a** (Table 2). $NaBH_4$ (2 equiv) and 6 equiv HCOOH at −30 °C could complete the reaction in 16 h with a stereoselectivity of 75:25 (entry 13). Meanwhile $NaBH_4$ plus TFA gave a similar result at −70 °C (entry 14). Because the reduction of **4b** did not reach a better stereoselective level than **4a** and phenylacetamide, derived from the debenzylation of **5b**, should be more difficult to remove than ethylbenzene from **5a, 5a** was chosen for the following preparation.

Thus, we applied *R*-α-methylbenzylamine as auxiliary and the reduction condition of entry 7 in Table 1 to get compound **5a**. The crude product could be purified through recrystallization in a mixture of isopropanol and petroleum ether in 49% yield with 99.4% diastereomer excess. The subsequent debenzylation and salification

Table 2. Reduction of compound **4b**

Entry	Reducing agent (molar equiv)[a]	Product ratio (**5b**:**9b**)[b]
13	$NaBH_4$(2), HCOOH(6), −30 °C, 16 h	75:25
14	$NaBH_4$(2), TFA(6), −70 °C, 3 h	75:25

[a]Reducing agent was prepared in THF.
[b]The ratios were determined by HPLC analysis.

could be carried out by $Pd(OH)_2/C$ in $MeOH/H_2O$ with 94% yield and 85% H_3PO_4 in IPA/H_2O with 95% yield to obtain sitagliptin phosphate monohydrate with a purity of 99.93% and *ee* > 99.94%.

CONCLUSION

In summary, we have disclosed an efficient and economical route to a practical synthesis of sitagliptin phosphate monohydrate starting from 2,4,5-trifluorophenylacetic acid. The key point is use of the cheap reducing agents, $NaBH_4$ plus formic acid, specifically avoiding expensive and toxic agents. The improvement also follows green chemistry principles.

EXPERIMENTAL

(*R,R*)-3-[(1-Phenylethyl)amino]-1-{3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl}-4-(2,4,5-trifluorophenyl)butan-1-one (5a)

$NaBH_4$ (5.40 g, 0.142 mol) was added to THF (240 mL) and cooled to 0–10 °C, and HCOOH (38.5 g, 0.837 mol) was added at 0–10 °C. After stirring for 1 h, the mixture was cooled to −30 °C and enaminoamide **4a** (34.82 g, 0.069 mol, dissolved in 100 mL THF) was added dropwise. After aging for 3 h, saturated Na_2CO_3 (400 mL) was added and extracted with ethyl acetate (3 × 200 mL). The organic layers were combined, washed with brine, dried with Na_2SO_4, and filtered. The solvent was evaporated in vacuo and recrystallized from IPA (70 mL) and petroleum ether (140 mL) to yield 17.5 g white solid (49.9%, *de*: 99.2%).

Sitagliptin Phosphate Monohydrate (1)

Compound **5a** (13 g, 25.4 mmol) was added to MeOH (117 mL), AcOH (3.82 g, 63.7 mmol), and H_2O (13 mL), and 20% $Pd(OH)_2/C$ (1.3 g, 10 wt.%) was added. The mixture was added to a stainless-steel autoclave and heated at 50 °C for 14 h at 1.0 MPa hydrogen. After cooling to room temperature and venting to ambient pressure, the mixture was filtered. After evaporating in vacuo, saturated Na_2CO_3 (200 mL) was added and extracted with CH_2Cl_2 (3 × 200 mL). The organic layers were combined, washed with brine, dried with Na_2SO_4, and filtered. The solvent was evaporated in vacuo and recrystallized from toluene (42 mL) to yield 9.7 g of white solid, **6** (94.0%), with a purity of 99.75% and *ee* of 99.94%.

Compound **6** (8.0 g, 19.7 mmol) was dissolved in IPA (17 mL) and H_2O (7.2 mL), and 85% H_3PO_4 (2.27 g, 19.7 mmol) was added dropwise. The mixture was heated to 75 °C to dissolve the solids. The batch was then cooled to 60–65 °C and seeded with phosphate monohydrate **1**. The batch was aged for 1 h and cooled to ambient temperature for 16 h. IPA (56 mL) was added, and the batch was stirred for 1 h. The batch was filtered, and the wet cake was washed with IPA (5 mL). The wet cake was dry at 60 °C to give 9.83 g of sitagliptin phosphate monohydrate **1** (95.0%) with a purity of 99.93% and *ee* > 99.94%.

SUPPLEMENTARY MATERIAL

Full experimental details and physical and spectral data of the compounds **4a, 5a, 6,** and sitagliptin phosphate monohydrate **1** can be found via the Supplementary Content section of this article's Web page.

ACKNOWLEDGMENT

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