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Efficient synthesis of sitagliptin phosphate, a novel DPP-IV inhibitor, via a chiral aziridine intermediate

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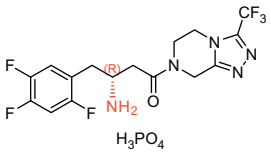
ABSTRACT

Sitagliptin phosphate, a novel DPP-IV inhibitor of T2DM, has been synthesized via 12 linear steps, in an overall yield of 26%. The key step is the coupling reaction of 2,4,5-trifluorophenylmagnesium bromide with a chiral aziridine derivative, which was prepared from L-homo-serine by simple steps.

Type 2 diabetes mellitus (T2DM) is a rapidly growing global epidemic that affects millions of people. A recent study reveals that the number of patients with diabetes has reached 350 million, doubling over the past 30 years. Diabetes and its complications present a serious threat to human health, bringing with it enormously high economic costs, not only to individuals and families, but to global health systems.[1] It was found recently that inhibitors of the dipeptidyl peptidase IV (DPP IV) could form new therapeutic agents for T2DM, by increasing GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic peptide) levels, as well as improving glycemic control for diabetics.[2–5] Sitagliptin phosphate (**1**) (Fig. 1) was approved by the U.S. FDA in October 2006 as a safe and orally active agent for the treatment of T2DM and is marketed by Merck Co., as a monotherapy (Januvia®) or in combination with meiformin (Janumet®).[6–8]

Because of its unique structure and tremendous commercial value, sitagliptin phosphate (**1**) had captured the interest of a number of pharmaceutical companies and synthetic teams. Considerable efforts have been made to identify a shorter, more cost-competitive, and environmentally friendly synthetic route.

Kim et al.[6] synthesized sitagliptin from (*R*)-2-amino-3-(2,4,5-trifluorophenyl)propanoic acid, in which the chiral center was induced from the corresponding Schöllkopf reagent at low temperature. The core β-amino-acid fragment was then synthesized by Arndt–Eistert homologation. However, the strict reaction conditions (−78 °C) and the use of a dangerous reagent (CH_2N_2), had limited this process to the laboratory and small scales.



Sitagliptin phosphate

1

Figure 1. Structure of sitagliptin phosphate.

Xiao et al.[9] described another process for the synthesis of a series of chiral beta amino acid derivatives, including sitagliptin. *S*-Phenylglycine amide was used as a chiral auxiliary to obtain *Z*-enamines from diketones. Finally, the title products were obtained after PtO_2 catalyzed asymmetric hydrogenation, followed by N-deprotection. The shortcoming of this process was the use of precious metals (Pt and Pd), and the enantiomeric excess (ee 90%) of the reduction was less than satisfied.

Dreher and Xiao[10] offered alternative strategies involving the hydrogenation of enamine using rhodium metal complexes with chiral mono or bis phosphine ligands. However, in their processes, the phosphine ligands of the chiral metal catalysts are very difficult

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to prepare and expensive. The reaction was carried out at high pressure and temperature.

Karl and colleagues reported two different asymmetric synthetic routes for sitagliptin[11] in which the β-amino acid moiety was introduced via asymmetric hydrogenation of a keto ester or enamine amide intermediate. These two routes suffer from inadequate stereoselectivity and the product was contaminated with Rh, necessitating an additional purification step at the expense of yield to upgrade both chemical and enantiomeric purities.

Christopher et al. reported an efficient biocatalytic process to prepare sitagliptin.[12] In the presence of the enzyme, transaminase, direct amination of prositagliptin ketone to enantiomeric pure sitagliptin (99.95% ee) was carried out under mild conditions. This biocatalytic route should become an important auxiliary asymmetric synthesis.

As part of our continuing interest in developing efficient and practical processes for the synthesis of active pharmaceutical ingredients (API) and intermediates,[13] we report in this work a novel and efficient approach to the preparation of sitagliptin phosphate (**1**), via the nucleophilic ring-opening reaction of the enantiomeric pure aziridine derivative (**5**)[14–16] with Grignard reagent (**7**) as the key step (Scheme 1).

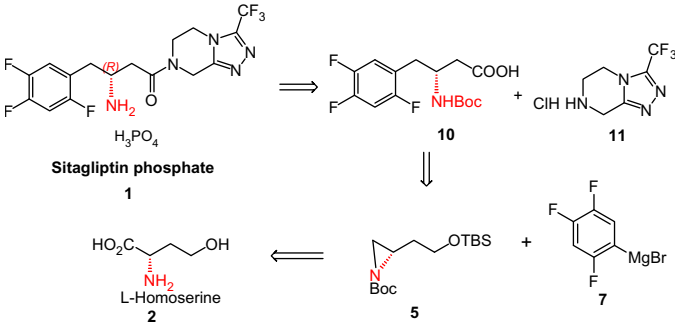
The synthesis begins with the protection of L-homoserine[17] (**2**) (Scheme 2). After treated with TBSCl in the presence of DBU in CH_3CN, silyl ether was formed. This was then treated with Boc_2O to give compound (**3**) with 81% yield in two steps. The Boc-amino-acid (**3**) was then condensed with *N*-hydroxysuccinimide to give the corresponding ester, which was then reduced with 1 equiv of $NaBH_4$ at low temperature to form the diol (**4**) in 84% yield. Compound **4** was then treated with methanesulfonyl chloride followed by subsequent ring closure under basic condition to form aziridine (**5**) in good yield (73%) and high enantio-purity (>99% ee).

With the chiral aziridine (**5**) available, the Grignard reaction, using 2,4,5-trifluoro-phenyl magnesium bromide (**7**), was examined (Scheme 3). Since the direct reaction of Mg and 1-bromo-2,4,5-trifluorobenzene will yield benzyne instead of the anticipated Grignard reagent, we used a bromine–magnesium-exchange reaction.[18] The Br–Mg-exchange of 1-bromo-2,4,5-trifluorobenzene was performed with *i*-PrMgBr at 0 °C in 1 h, monitored by GC to the point at which 1-bromo-2,4,5-trifluorobenzene disappeared. It was found that the reaction of 2,4,5-trifluorobromobenzene Grignard reagents (**7**) and aziridine (**5**) could not be performed smoothly (30%). However, several copper catalysts[19,20] were screened to improve the Grignard reaction yield (Table 1).

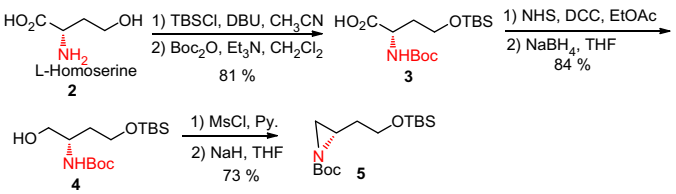
As indicated in Table 1, the addition of cuprous halide significantly improved the Grignard reaction (entries 1–4), and CuBr/Me_2S gave the best result (78%, entry 5).

After the ring-opening reaction, deprotection of the hydroxyl group was carried out by treatment with tetrabutylammonium fluoride in MeOH, to form the amino alcohol (**9**) in 95% yield. After treatment with NaClO and TEMPO, 3-*R*-Boc-amino-4-(2,4,5-trifluorophenyl)butyric acid (**10**) was obtained in good yield (90%). The triazole (**11**)[11a] was then coupled to the amino acid (**10**) at 0 °C using HOBT-EDCI, to provide (**12**) in 95% yield. The Boc group was removed by stirring (**12**) in the presence of concentrated HCl and MeOH at ambient temperature. After a typical work up, the crude product was recrystallized from toluene, and the free base sitagliptin was isolated in 90% yield. Its phosphoric acid salt (**1**) was obtained with 99.2% HPLC purity (single impurity less than 0.1%) and 99.4% ee after recrystallization from *i*-PrOH.

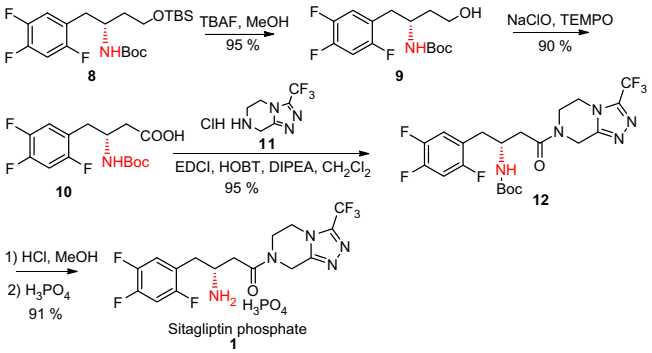
In summary, we have devised a new and convergent route for the synthesis of sitagliptin phosphate (**1**).The chiral β-amino group was introduced via a ring-opening Grignard reaction of the chiral aziridine derivative which was prepared from L-homoserine. The use of expensive Rh or Pt catalysts has been avoided. This simple procedure and economical process provides a novel synthesis of sitagliptin phosphate (**1**).



Scheme 1. Strategy for the synthesis of sitagliptin phosphate.

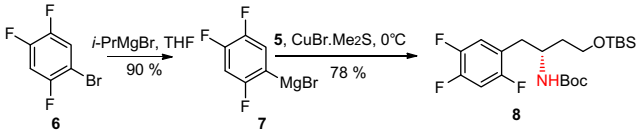


Scheme 2. Synthesis of the chiral aziridine.



Scheme 3. Synthesis of sitagliptin phosphate.

Table 1
Influence of copper catalysts on the Grignard reaction[a]



Entry	Catalyst	Time (h)	Yield[b] (%)
1	Blank	8	30
2	CuCl	2	60
3	CuBr	2	65
4	CuI	2	71
5	CuBr/Me_2S	2	78

[a] Reaction conditions: **7** (0.018 mol) in 40 mL THF, **5** (0.015 mol) in 30 mL THF, catalyst (0.002 mol), 0 °C.
[b] Isolated yield.

Acknowledgments

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Spectral data:

*(S)-2-((tert-Butoxycarbonyl)amino)-4-((tert-Butyl-dimethylsilyl)oxy)-butanoic acid (**3**)* ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 5.86 (d, J = 6.7 Hz, 1H), 4.48–4.15 (m, 1H), 3.90–3.56 (m, 2H), 2.16–1.88 (m, 2H), 1.44 (d, J = 11.4 Hz, 9H), 0.90 (s, 9H), 0.06 (s, 6H); ESI-MS: 334.6 (M^++1).

*(S)-tert-Butyl 4-(tert-butyldimethylsilyloxy)-1-hydroxybutan-2-ylcarbamate (**4**)* $[\alpha]_D^{20}$ −30.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (d, J = 45.0 Hz, 1H), 3.74 (t, J = 5.3 Hz, 2H), 3.70–3.58 (m, 2H), 3.51 (s, 1H), 1.83 (s, 1H), 1.73 (d, J = 6.1 Hz, 1H), 1.44 (s, 9H), 1.26 (d, J = 2.6 Hz, 1H), 0.91 (s, 9H), 0.08 (s, 6H); ESI-MS: 320.3(M^++1).

*(S)-tert-Butyl 2-(2-(tert-butyldimethylsilyloxy)ethyl)aziridine-1-carboxylate (**5**)* $[\alpha]_D^{20}$ −11.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (dd, J = 9.4, 3.7 Hz, 2H), 2.48 (dd, J = 6.0, 4.0 Hz, 1H), 2.28(d, J = 6.1 Hz, 1H), 1.96 (d, J = 3.7 Hz, 1H), 1.81–1.74 (m, 1H), 1.60 (dd, J = 13.7, 6.9 Hz,1H), 1.46 (s, 9H), 0.90 (s, 9H), 0.07 (d, J = 1.9 Hz, 6H); ESI-MS:324.2 (M^++Na); HRMS Calcd for: $C_{15}H_{31}NO_3SiNa$ (M+Na)$^+$ requires 324.1971, found 324.1966.

*(R)-tert-Butyl 4-(tert-butyldimethylsilyloxy)-1-(2,4,5-trifluorophenyl)butan-2-ylcarbamate (**8**)*
$[\alpha]_D^{20}$ +5.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J = 7.0 Hz, 1H), 6.88 (d, J = 6.8 Hz, 1H), 5.24 (s, 1H), 3.97–.74 (m, 2H), 3.73–3.61 (m, 1H), 2.82 (s, 2H), 1.86–1.64 (m, 1H), 1.63–1.47 (m, 1H), 1.39 (s, 9H), 0.91 (s, 9H), 0.06 (d, J = 4.6 Hz, 6H); ESI-MS: 456.20 (M^++Na); HRMS Calcd for: $C_{21}H_{34}F_3NO_3Na$ (M+Na)$^+$ requires 456.2158, found 452.2166.

*(R)-tert-Butyl-4-hydroxy-1-(2,4,5-trifluorophenyl)butan-2-ylcarbamate (**9**)* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 8.3 Hz, 1H), 6.91 (d, J = 6.6 Hz, 1H), 4.56 (d, J = 9.0 Hz, 1H), 4.01 (dd, J = 25.4, 18.8 Hz, 1H), 3.68 (d, J = 6.0 Hz, 2H), 2.82–2.70 (m, 2H), 1.86 (dd, J = 12.4, 7.7 Hz, 1H), 1.67 (d, J = 6.7 Hz, 2H), 1.45–1.37 (m, 9H); ESI-MS: 342.2 (M^++Na).

*(R)-3-(tert-Butoxycarbonyl)-4-(2,4,5-trifluorophenyl)butanoic acid (**10**)* $[\alpha]_D^{20}$ −29.8 (*c* 1.0, $CHCl_3$); mp 123–125 °C. {lit.[21] $[\alpha]_D^{20}$ −32.2 (*c* 1.0, $CHCl_3$). Mp 124–125 °C.} ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 7.8 Hz, 1H), 6.91 (d, J = 6.8 Hz, 1H), 5.23–4.76 (m, 1H), 4.28–3.92 (m, 1H), 2.88 (d, J = 6.9 Hz, 2H), 2.62 (s, 2H), 1.36 (d, J = 23.3 Hz, 9H); ESI-MS: 356.2 (M^++Na).

*(R)-tert-Butyl 4-oxo-4-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1-(2,4,5-trifluorophenyl)butan-2-ylcarbamate (**12**)* $[\alpha]_D^{20}$ +22.1 (*c* 1.0, $CHCl_3$); mp 187–191 °C. {lit.[13a] $[\alpha]_D^{20}$ +22.2 (*c* 1.0, $CHCl_3$). Mp 188–191 °C.} ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.05 (m, 1H), 7.02–6.85 (m, 1H), 5.31 (s, 1H), 5.15–4.76 (m, 2H), 4.43–3.78 (m, 5H), 2.98–2.92 (m, 2H), 2.71–2.61 (m, 2H), 1.36 (s, 9H); ESI-MS: 508.0 (M^++1).

*Sitagliptin phosphate (**1**)* $[\alpha]_D^{20}$ −72.9 (c 1.0, H_2O). Mp 213–216 °C. {lit.[12] $[\alpha]_D^{20}$ −74.4 (*c* 1.0, H_2O). Mp 215–217 °C.} ^{1}H NMR (400 MHz, D_2O) δ 7.23–7.05 (m, 1H), 7.05–6.86 (m, 1H), 4.85–4.80 (m, 2H), 4.16 (d, J = 5.5 Hz, 1H), 4.10 (dt, J = 13.1, 6.0 Hz, 1H), 3.89–3.81 (m, 3H), 3.11–2.76 (m, 3H), 2.73 (ddd, J = 17.5, 10.1, 7.5 Hz, 1H).