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Efficient stereocontrolled synthesis of sitagliptin phosphate

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ABSTRACT

The synthesis of sitagliptin phosphate **1**, a novel DPP-IV inhibitor for the treatment of type 2 diabetes mellitus has been accomplished starting from the chiral synthon (1,4-bis[(*R*)-1-phenylethyl]piperazine-2,5-dione) **2**, involving highly stereocontrolled (>98%) alkylation as a key step, in a good overall yield of 50% over six steps.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a major and rapidly growing disease, with millions of new cases every year around the world.[1] Dipeptidyl peptidase (DPP-IV) inhibitors are a novel class of anti-hyperglycemic agents for the treatment of T2DM by preserving endogenous glucagon like peptide 1 (GLP-1) from DPP-1V action. GLP-1 is an incretin hormone that stimulates insulin secretion and biosynthesis, inhibits glucagon release in a glucose dependent manner and also does gastric emptying and reducing appetite. GLP-1 is readily degraded by DPP-IV enzyme and the inhibition of DPP-IV improves glucose homeostasis with a low risk of hypoglycemia.[2] Sitagliptin phosphate **1** (Fig. 1) is an orally active, safe, selective, and potent DPP-IV inhibitor for the treatment of T2DM and has been approved by USFDA in October 2006, as a monotherapy (Januvia®) or in combination with metformin (Janumet®).[3,4]

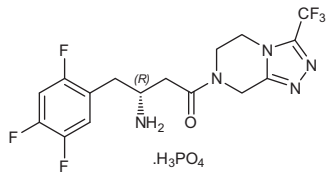

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Figure 1. Structure of sitagliptin phosphate.

The synthesis of sitagliptin phosphate **1** has attracted the attention of several pharmaceutical companies and research groups to report extensive efforts on an asymmetric synthesis and to develop shorter, inexpensive, and environmentally benign routes. The key methods employed to install the correct stereochemistry of **1** in the literature use Schollkopf reagent followed by Arndt–Eistert homologation,[3] and asymmetric hydrogenation[5] of the β-ketoester followed by a Mitsunobu reaction,[5a] enamino derivatives using a PtO_2[5b] or Rh[5c] metals, direct asymmetric reductive amination of a β-ketomide to β-aminoamide using an Ru catalytic system.[5d] The notable disadvantages of these methods are limited atom economy, inherent drawbacks of metal mediated hydrogenation reactions such as specialized high pressure equipments, the use of precious metals, and possible metal contamination of the API. In addition in certain cases, an additional step is required for the upgrade of chemical and enantiopurity of the final product. Recently many methods developed including biocatalytic asymmetric reductive amination of β-ketomide;[6] enzymatic resolution of racemates;[7] diastereoselective conjugate addition of lithium amide,[8] via opening of a chiral aziridine intermediate;[9] and stereoselective reduction of an enamine derivative using $NaBH_4$/HCOOH.[10] Although some of these synthetic routes are straightforward and efficient, given the enormous industrial interest in the molecule, there is still a need for inexpensive, convenient, industrially viable, and greener synthetic routes.

Our synthetic strategy was designed on the basis of a retrosynthetic analysis as outlined in Scheme 1. Sitagliptin phosphate **1** could be obtained by the coupling of fragments **7** and **8**. Compound **7** could be obtained from **5**, which in turn could be derived from cleavage of **4**. It was anticipated that the diastereoselective one pot double alkylation of **2** (Scheme 4) would furnish **4** with a high level of stereoselectivity, as a key step. The main advantage of this synthetic route is that the cleavage of heterocyclic intermediate **4** would produce two units of α-amino acid **5** leaving no waste behind. The high atom economy of these reactions makes the synthetic route greener. Also, this approach is reliable for the

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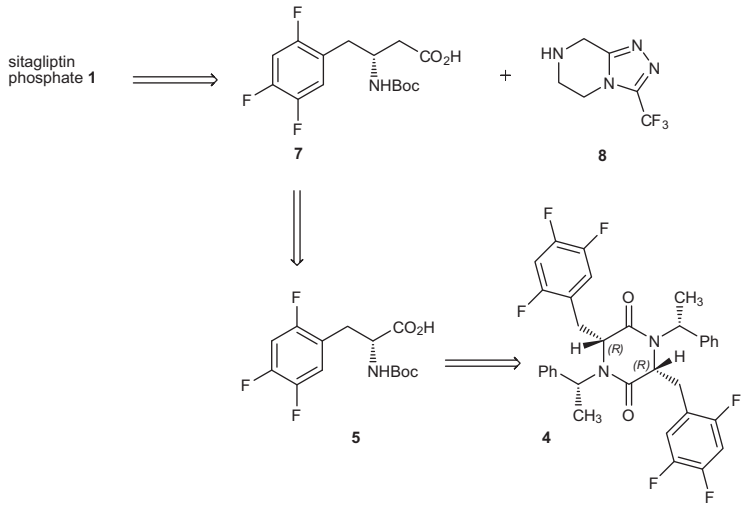
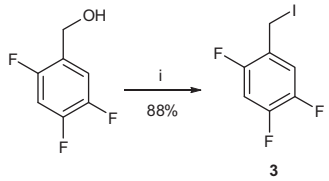


Scheme 1. Retrosynthetic analysis for sitagliptin phosphate **1**.

multi-gram scale synthesis of target compound **1**. In addition, this method uses inexpensive starting materials which could substantially cut the cost of the commercial synthesis of sitagliptin phosphate **1**.



Scheme 2. Synthesis of iodo derivative **3**. Reagents and conditions: (i) $BF_3{\cdot}Et_2O$, KI, rt, 48 h.

2. Results and discussion

2,4,5-Trifluorobenzyliodide **3** was prepared from commercially available 2,4,5-trifluorobenzylalcohol using $BF_3{\cdot}Et_2O$ and KI at room temperature for 48 h in 88% yield (Scheme 2).[11] Chiral synthon **2** was easily prepared in two steps from chloroacetyl chloride and (*R*)-phenylethanamine using phase transfer catalysis (Scheme 3).[14] The one pot double alkylation of chiral synthon **2**[12] using 2.4 equiv of LHMDS and 2.2 equiv of iodo derivative **3** at −78 °C afforded *cis*-dialkyl derivative (3*R*,6*R*)-**4** in 73% yield as a single diastereomer (Scheme 4), which was confirmed by the ^{1}H NMR spectra of the crude reaction mixture.

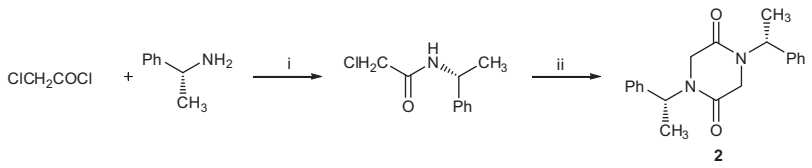
The high diastereoselectivity is due to the steric bias created by the chiral substituents of synthon **2** at both (N-1) and (N-4) in conjunction with the bulk of iodo derivative **3** along with 1,4-*cis* induction.[12i] Cleavage of chiral synthon assembly **4** was achieved by refluxing in 57% HI for 3 h. The amine group was protected using 2.3 equiv of $(Boc)_2O$ at 0 °C to give two units of α-amino acid **5** in near quantitative yield (Scheme 4). The ^{1}H NMR and ^{13}C NMR spectra of compound **4** showed half signals representing a C_2 symmetry axis. The absolute configuration of the intermediate **4** was assigned on the basis of the pseudotriplet observed at 3.93 ppm, which resulted from the shielding effect induced on (C-3)-H and (C-6)-H by the phenyl of the chiral inductor bound to each of the N-atoms, as the same phenomenon was observed for a very similar substrate.[12c] The absolute configuration of the newly created stereocentres on **4** was also confirmed by the specific rotation value of **5** which was in agreement with that reported in the literature {$[\alpha]_D^{25.3}$ = −1.5 (*c* 0.12, CH_3OH); lit.[16] $[\alpha]_D^{20}$ = −3.5 (*c* 1.0, CH_3OH)}.

Next, Arndt–Eistert homologation of α-amino acid **5** (Scheme 4) upon treatment with isobutylchloroformate followed by excess diazomethane gave diazo ketone **6**. Sonication of diazo ketone **6** using a silver benzoate in 1,4-dioxane/water (5:1) provided β-amino acid **7** in 94% yield.[13] Coupling of **7** with triazolopiperazine **8** using EDC/HOBT afforded **9** in 92% yield (Scheme 4).

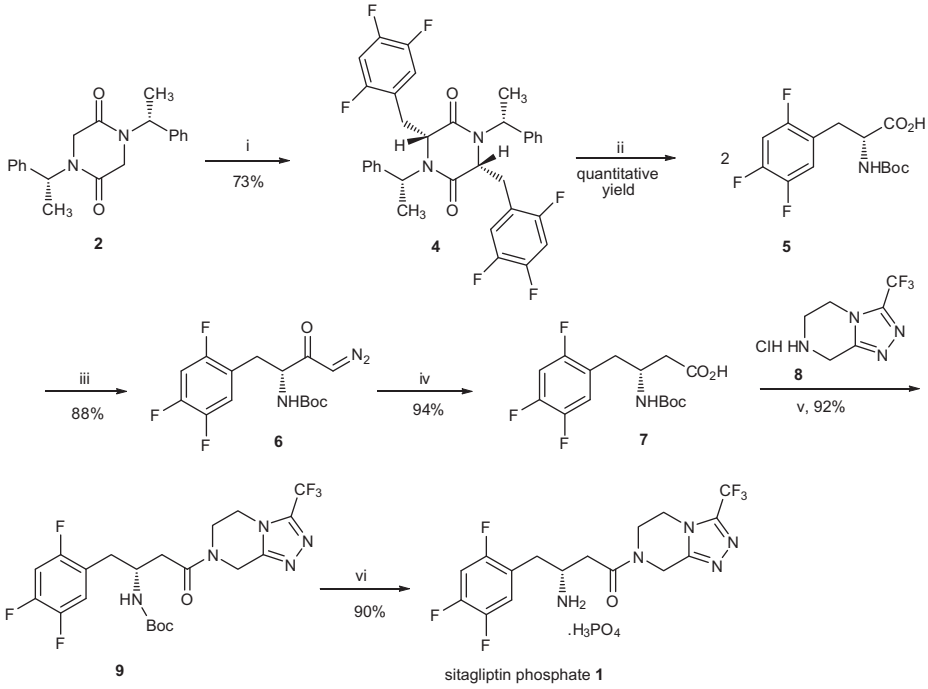
The *N*-Boc protection was removed by treatment of compound **9** with concentrated HCl and MeOH at ambient temperature. Subsequent treatment of the resultant free amine with phosphoric acid at 80 °C for 30 min afforded sitagliptin phosphate **1** in 90% yield. The spectroscopic data for this compound were found to be in excellent agreement with those for the compound originally reported in the literature {$[\alpha]_D^{25.2}$ = −73.1 (*c* 0.13, H_2O); lit.[5a] $[\alpha]_D^{20}$ = −74.4 (*c* 1.0, H_2O)}.

3. Conclusion

In conclusion we have developed an efficient route for the synthesis of sitagliptin phosphate **1**. The approach gives high overall yield with good atom economy via the generation of two equiva-



Scheme 3. Synthesis of chiral synthon **2**. Reagents and conditions: (i) $Na_2CO_3{\cdot}10H_2O$, in water/acetone;[12a] (ii) TEBA (10%), aq NaOH, CH_2Cl_2, rt, 48 h.[14]



Scheme 4. Synthesis of sitagliptin phosphate **1**. Reagents and conditions: (i) 2.4 equiv of LHMDS in THF at −78 °C and 2.2 equiv of **3** (see Scheme 2); (ii) 57% HI at reflux for 3 h, $(Boc)_2O$, Na_2CO_3, 1,4-dioxane, water; (iii) Et_2O, Et_3N, *iso*-butyl chloroformate, −20 °C, diazomethane; (iv) silver benzoate, 1,4-dioxane/H_2O (5:1), sonication, rt; (v) EDC/HOBT, DIPEA, DCM, 0 °C to rt, 24 h; (vi) concd HCl, MeOH, $NaHCO_3$, H_3PO_4.

lents of chiral intermediates from one equimolar chiral synthon with two working sites. In addition, the highly diastereoselective alkylation as a key step, makes this synthetic route simple and practical from an inexpensive chiral synthon.

4. Experimental

4.1. General

All of the reagents and solvents were purchased from commercial sources and used without purification. NMR spectra were recorded with a 400, 500 MHz spectrometer for ^1H and 100, 125 MHz for ^{13}C. Chemical shifts are reported relative to the residual signals of tetramethylsilane in $CDCl_3$ or deuterated solvent $CDCl_3$/DMSO-d_6 for ^1H and ^{13}C NMR spectroscopy, respectively. Multiplicities are reported as follows: singlet (s), doublet (d), broad singlet (br s), doublet of doublets (dd), doublet of triplets (dt), triplet (t), quartet (q), and multiplet (m). HRMS was performed using QToF mass spectrometer. Melting points were recorded on an electrically heated melting point apparatus and are uncorrected. All of the reactions were monitored by TLC. Dry tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Column chromatography was performed with silica gel (100–200 mesh) as the stationary phase.

4.2. 2,4,5-Trifluorobenzyliodide 3

2,4,5-Trifluorobenzylalcohol (2.26 g, 14 mmol) was dissolved in dry 1,4-dioxane (30 mL) and to that $BF_3{\cdot}Et_2O$ (1.98 g, 14 mmol) and KI (2.32 g, 14 mmol) were added and the resulting mixture was stirred for 48 h at room temperature. The reaction mixture was poured into cold water and extracted with diethyl ether. The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with 10% ethyl acetate in hexane to give **3** (3.35 g, 88%) as a brown liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 4.34 (s, 2H), 6.93–6.86 (m, 1H), 7.21–7.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.78, 106.0, 106.2, 106.2, 106.4, 118.3, 118.5, 123.1, 145.7, 148.1, 148.7, 151.2, 154.2, 156.6.

4.3. 1,4-Bis[(*R*)-1-phenylethyl]piperazine-2,5-dione 2

Off-white solid; 83% yield; mp: 115–118 °C; $[\alpha]_D^{23.4}$ = +342.0 (*c* 0.13, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (d, *J* = 7.1 Hz, 6H), 3.52 (d, *J* = 16.4 Hz, 2H), 3.86 (d, *J* = 16.4 Hz, 2H), 5.95 (q, *J* = 7.1 Hz, 2H), 7.37–7.25 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 138.3, 128.8, 128.1, 127.4, 50.2, 44.7, 15.1; MS (ESI) *m*/*z*: 323.0 $(M+H)^+$. HRMS (ESI) $(M+H)^+$: calcd for $C_{20}H_{22}N_2O_2$: 323.1754; found: 323.1752.

4.4. (3*R*,6*R*)-1,4-Bis[(*R*)-1-phenylethyl]-3,6-bis(2,4,5-trifluorobenzyl)piperazine-2,5-dione 4

Chiral synthon **2** (1.64 g, 5.0 mmol) was dissolved in dry THF (20 mL) after which was added a 1 M solution of LHMDS (12 mL, 2.4 equiv) at −78 °C under nitrogen atmosphere. After 90 min, the iodo derivative **3** (3 g, 2.2 equiv) in dry THF (5 mL) was slowly added dropwise, after which the reaction was stirred for approximately 2 h. The reaction mixture was allowed to room temperature then quenched with water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum to dryness. The crude product was purified by column chromatography eluting with 10% ethyl acetate in hexane to give **4** as a colorless oil (2.27 g, 73%); $[\alpha]_D^{24.6}$ = −36.7 (*c* 0.14, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.65 (d, *J* = 7.2 Hz, 6H), 3.11–3.05 (m, 2H), 3.27–3.23 (m, 2H), 3.93–3.89 (m, 2H), 5.72 (q, *J* = 7.2 Hz, 2H), 6.96–6.89 (m, 4H), 7.19–7.17 (m, 4H), 7.36–7.32 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 34.7, 52.9, 57.9, 105.2, 105.5, 105.5, 105.7, 118.5, 118.7,

119.4, 119.6, 127.3, 128.4, 129.0, 138.5, 145.5, 147.9, 148.0, 150.5, 154.9, 157.3, 165.6; MS (ESI) *m*/*z*: 610.9 $(M+H)^+$. HRMS (ESI) $(M+H)^+$: calcd for $C_{34}H_{28}F_6N_2O_2$: 611.2128; found: 611.2121.

4.5. (*R*)-2-(*tert*-Butoxycarbonylamino)-3-(2,4,5-trifluorophenyl) propanoic acid 5

The heterocyclic intermediate **4** (690 mg, 1.13 mmol) was refluxed in 57% HI (10 mL) for 3 h. The reaction mixture was evaporated under vacuum, after which water (23 mL) containing Na_2CO_3 (1.6 g, 15 mmol) was added (reaction mixture pH should be basic), and cooled to 0 °C. Di-*tert*-butyl dicarbonate (567 mg, 2.3 equiv) in 1,4-dioxane (14 mL) was added slowly and stirred for 12 h, then slowly warmed up to rt. Water was added to the reaction mixture and extracted with ether. The aqueous layer was acidified with aqueous citric acid solution up to pH 2 and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The crude product was purified by column chromatography eluting with 30% ethyl acetate in hexane and afforded a white powder in about quantitative yield. Mp: 107–110 °C; $[\alpha]_D^{25.3} = -1.5$ (*c* 0.12, CH_3OH); {lit.[16] $[\alpha]_D^{20} = -3.5$ (*c* 1.0, CH_3OH)}; ^1H NMR (400 MHz, CD_3OD) δ 1.37 (s, 9H), 2.87–2.82 (m, 1H), 3.31–3.22 (m, 1H), 4.38–4.34 (m, 1H), 7.23–7.07 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 27.2, 30.4, 30.7, 53.2, 54.5, 79.2, 80.1, 104.6, 104.8, 104.8, 105.1, 118.9, 119.0, 119.1, 121.1, 121.3, 145.1, 145.2, 147.5, 147.6, 150.0, 150.1, 150.2, 155.2, 155.3, 155.5, 156.2, 157.6, 157.7, 173.1; MS (ESI) *m*/*z*: 219.9 (M+1H−*t*-Boc)$^+$. HRMS (ESI) (M+1H−*t*-Boc)$^+$: calcd for $C_{14}H_{16}F_3NO_4$: 220.0585; found: 220.0576.

4.6. (*R*)-3-(*tert*-Butoxycarbonylamino)-4-(2,4,5-trifluorophenyl) butanoic acid 7

To a solution of (*R*)-2-(*tert*-butoxycarbonylamino)-3-(2,4,5-trifluorophenyl)propanoic acid **5** (465 mg, 1.45 mmol) in 12 mL of diethyl ether at −20 °C were added sequentially 0.214 mL (1.54 mmol) of triethylamine and 0.200 mL (1.54 mmol) of isobutylchloroformate, and stirred for 15 min. A cooled solution of diazomethane was added until a yellow color persisted and stirring was continued for 1 h. The excess diazomethane was quenched by the dropwise addition of acetic acid. The reaction mixture was diluted with ethyl acetate, and washed sequentially with saturated aqueous sodium bicarbonate solution and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuum. The crude product was purified by column chromatography eluting with 20% ethyl acetate in hexane to afford diazoketone **6** (440 mg, 88%). To a solution of diazoketone (440 mg, 1.27 mmol) in 15 mL of 1,4-dioxane/water (5:1) was added 30 mg (0.127 mmol) of silver benzoate. The resultant solution was sonicated for 90 min before diluting with ethyl acetate and being washed sequentially with 1 M hydrochloric acid and brine, dried over sodium sulfate, and concentrated under vacuum. The crude product was purified by column chromatography eluting with 25% ethyl acetate in hexane to afford **7** as a white powder (400 mg, 94%). Mp: 121–124 °C; {lit.[15] mp: 124–125 °C}; $[\alpha]_D^{24.3} = +27.8$ (*c* 0.13, $CHCl_3$); {lit.[15] $[\alpha]_D^{20} = +32.3$ (*c* 1.0, $CHCl_3$)}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 9H), 2.66–2.57 (m, 2H), 2.88 (d, *J* = 4.9 Hz, 2H), 4.14 (br s, 1H), 5.07 (br s, 1H), 6.94–6.87 (m, 1H), 7.09–7.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.2, 29.6, 32.9, 33.9, 37.9, 38.4, 47.6, 48.8, 79.9, 81.3, 105.1, 105.3, 105.4, 105.6, 119.0, 119.1, 121.3, 145.3, 145.4, 147.5, 147.7, 150.0, 150.2, 150.3, 155.0, 155.2, 156.9, 157.5, 175.1, 176.2; MS (ESI) *m*/*z*: 355.9 $(M+Na)^+$. HRMS (ESI) $(M+Na)^+$: calcd for $C_{15}H_{18}F_3NO_4Na$: 356.1080; found: 356.1068.

4.7. (*R*)-*tert*-Butyl 4-oxo-4-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-*a*]pyrazin-7(8*H*)-yl)-1-(2,4,5-trifluorophenyl)-butan-2-ylcarbamate 9

(*R*)-3-(*tert*-Butoxycarbonylamino)-4-(2,4,5-trifluorophenyl)butanoic acid **7** (200 mg, 0.59 mmol) and 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-*a*]pyrazinehydrochloride **8** (115 mg, 0.59 mmol) in anhydrous DCM (3 mL) were cooled to 0 °C. To that solution was added HOBT (96 mg, 0.7 mmol), followed by EDC·HCl (134 mg, 0.7 mmol) and DIEPA (152 mg, 1.18 mmol). After being stirred for 24 h, DCM was evaporated, and the viscous residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography eluting with 80% ethyl acetate in hexane to afford **9** as a white powder (280 mg, 92% yield). Mp: 189–192 °C; {lit.[8a] mp: 188–191 °C}; $[\alpha]_D^{25.1} = +20.8$ (*c* 0.11, $CHCl_3$); {lit.[8a] $[\alpha]_D^{20} = +22.2$ (*c* 1.0, $CHCl_3$)}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 9H), 2.93–2.67 (m, 4H), 4.17–3.97 (m, 5H), 4.92 (s, 1H), 5.07–5.00 (m, 1H), 5.28 (s, 1H), 6.88 (s, 1H), 7.08–7.06 (d, *J* = 6.36 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.2, 32.9, 36.7, 38.0, 39.2, 41.8, 42.6, 43.1, 43.6, 48.2, 48.4, 79.7, 105.2, 105.3, 105.4, 105.5, 117.1, 119.0, 119.1, 121.4, 143.7, 144.0, 145.6, 147.7, 147.9, 149.4, 149.9, 150.2, 155.2, 157.1, 169.5, 169.9; MS (ESI) *m*/*z*: 507.9 $(M+H)^+$. HRMS (ESI) $(M+H)^+$: calcd for $C_{21}H_{23}F_6N_5O_3$: 508.1778; found: 508.1778.

4.8. Sitagliptin phosphate 1

To a solution of **9** (100 mg, 0.19 mmol) in MeOH (2 mL) was added 1 mL of conc. HCl in 2 mL of MeOH at rt. After stirring for 4 h, the solvent was removed under vacuum followed by partitioning between ethyl acetate and 1 M aqueous sodium hydroxide solution. The aqueous layer was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4, and concentrated. The crude product was subjected to column chromatography with CH_2Cl_2/MeOH/NH_4OH (900:50:2.5), then CH_2Cl_2/MeOH/NH_4OH (900:100:5) to give a colorless oil (74 mg, 93%) of sitagliptin as a free base. To a solution of the free base (74 mg, 0.18 mmol) in EtOH (1 mL) was added phosphoric acid (85 wt %, 16.8 mg, 0.17 mmol). The resulting mixture was treated at 80 °C for 30 min. The reaction mixture was allowed to cool to rt and filtered. The solid residue was then recrystallized (^{i}PrOH) to give the title compound as a white powder (88 mg, 96%). Mp: 213–216 °C; {lit.[5a] mp 215–217 °C}; $[\alpha]_D^{25.2} = -73.1$ (*c* 0.13, H_2O); {lit.[5a] $[\alpha]_D^{20} = -74.4$ (*c* 1.0, H_2O)}; ^1H NMR (400 MHz, D_2O) δ 2.88 (ddd, *J* = 17.5, 10.1, 7.5 Hz, 1H), 3.10–2.92 (m, 3H), 4.06–3.93 (m, 3H), 4.27–4.17 (m, 2H), 4.95–4.88 (m, 2H), 7.13–7.03 (m, 1H), 7.26–7.18 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ 30.9, 31.0, 33.7, 33.8, 38.0, 38.7, 41.2, 41.8, 43.1, 43.4, 48.2, 105.5, 105.7, 105.8, 106.0, 113.6, 116.3, 118.4, 118.4, 118.5, 118.5, 118.6, 118.6, 118.9, 119.0, 119.0, 119.1, 119.1, 119.2, 119.3, 121.7, 143.1, 143.5, 143.6, 143.9, 144.0, 145.2, 145.3, 147.6, 147.7, 148.0, 148.1, 150.4, 150.5, 151.0, 155.1, 155.1, 157.5, 157.6, 170.1, 170.2; MS (ESI) *m*/*z*: 408 $(M+H)^+$. HRMS (ESI) $(M+H)^+$: calcd for $C_{16}H_{15}F_6N_5O$: 408.1254; found: 408.1252.

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