The asymmetric synthesis of Sitagliptin, a selective dipeptidyl peptidase IV inhibitor for the treatment of type 2 diabetes

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An efficient asymmetric synthesis of Sitagliptin, a new DPP-IV inhibitor for the treatment of type 2 diabetes mellitus has been developed. The beta-amino acid fragment of Sitagliptin was prepared by asymmetric Michael addition of the corresponding α, β-unsaturated ester to (R)-(α-methylbenzyl)benzylamine followed by a two-step elaboration to obtain N-boc beta-amino ester. Hydrolysis of the ester and coupling with the triazolopiperazine afforded Sitagliptin after cleavage of the N-boc group and salt formation. The overall yield was 31% over nine steps.

Keywords: Sitagliptin, diabetes, Michael addition, asymmetric synthesis, β-amino acid.

Diabetes mellitus type 2 or type 2 diabetes (T2DM) is a global epidemic that is characterised by high blood glucose in the context of insulin resistance and relative insulin deficiency.[1] The number of reported cases has doubled over the past 15 years. [2] It has been found that inhibitors of the enzyme DPP-IV were promising new treatments for T2DM.[3–5] Sitagliptin (**1**) has recently been reported to be a potent inhibitor of DPP-IV and is currently being evaluated in clinical trials.[6] As the first selective DPP-IV inhibitor on the market, Sitagliptin (**1**) represents a new class of oral antihyperglycaemic agents. It has been shown to be an orally active and safe agent for the treatment of type 2 diabetes. Monotherapy or combination with meiformin or piogitazone is efficacious and well tolerated in patients with type 2 diabetes.[7]

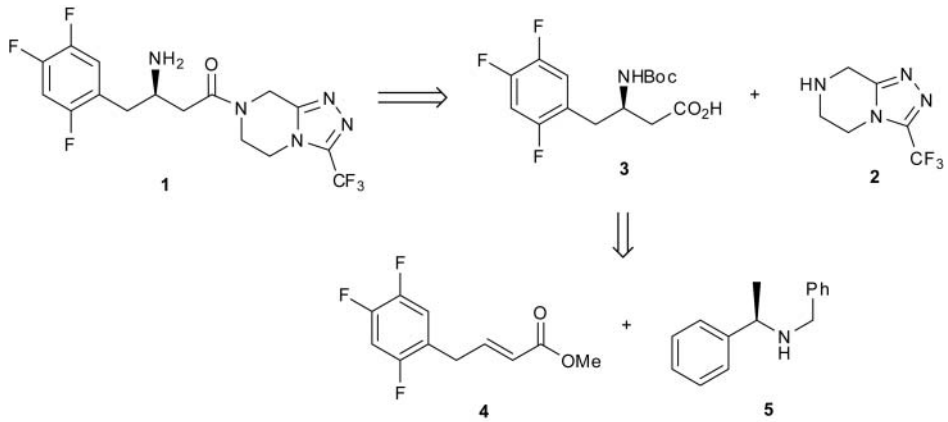
Over the past 10 years, several laboratories have synthesised of Sitagliptin(**1**). Methods had been developed to prepare the β-amino acid fragment, such as the asymmetric hydrogenation of enamino derivatives using a Rh catalyst[8] or PtO_2,[9] reduction of the corresponding β-keto ester followed by a Mitsunobu reaction[10] and Arndt–Eistert homologation of the amino acid.[11] In all the synthetic routes, the key point is the formation of the chiral β-amino acid. In 1994, Davies *et al*. had developed a highly stereo-selective procedure that involved the conjugate nucleophilic addition of lithium N-benzyl-N-α-methylbenzyl-amide to α, β-unsaturated esters affording a versatile asymmetric synthesis of β-amino acids.[12] The advantage of Davies' procedure is the absence of the precious metals, which could cut the cost of commercial syntheses.

Here we describe a new synthetic route using the asymmetric Michael addition as the key step. Sitagliptin (**1**) was originally synthesised by coupling triazole **2** to beta-amino acid **3**, which was prepared by asymmetric Michael addition of (E)-methyl 4-(2,4,5-trifluorophenyl)but-2-enoate **4** and (R)-(α-methylbenzyl)benzylamine **5**(Scheme 1).

The synthesis of the β-amino acid ester **3** started from the reduction of the β-keto ester **6**[13] (Scheme 2). The reduction was carried out using 0.25 equiv. of $NaBH_4$ in methanol at 0 °C, to give **7** in 92% yield. The use of a more reductive reagent or a higher temperature resulted in the by-product 1,3-diol instead of the anticipated product **7**. Acetylation of **7** followed by treatment with *tert*-BuOK in ethyl ether at low temperature yielded the elimination product **4**.

The conjugate addition of (R)-(α-methylbenzyl)benzylamine **5** to the α, β-unsaturated ester **4** was achieved in THF at –78 °C and provided the β-amino acid ester **9** in good yield and high enantioselectivity(Scheme 3). Deprotection of **9** by $Pd(OH)_2/C$ catalysed hydrogenation and Boc_2O protection of the resultant amine lead to the β-amino ester **11** (83% for two steps). The methyl ester **11** was hydrolysed to the amino acid **3** with NaOH in EtOH/water by stirring at 0 °C in 91% yield. Then, the triazole **2** was coupled with the amino acid **3** at 0 °C using HOBT-EDCI, to afford **13** in 95% yield. The Boc group was removed by stirring **13** in the presence of MeOH and conc. HCl at room temperature. After neutralisation with aq. ammonia and work up, the crude product crystallised from toluene. Sitagliptin (**1**) was isolated in 90% yield and its anhydrous phosphoric acid salt was obtained in 99.2% HPLC purity and 99.5% ee after crystallisation from aqueous ethanol.

In summary, we had devised a new convergent route for the total synthesis of Sitagliptin **1.** Since the chiral β-amino group was introduced by an asymmetric Michael addition, the use of an expensive Rh or Pt catalyst could be avoided here, the simple procedure and economical operation provides a new access to Sitagliptin which is of current interest.



Scheme 1 Strategy for the synthesis of Sitagliptin.

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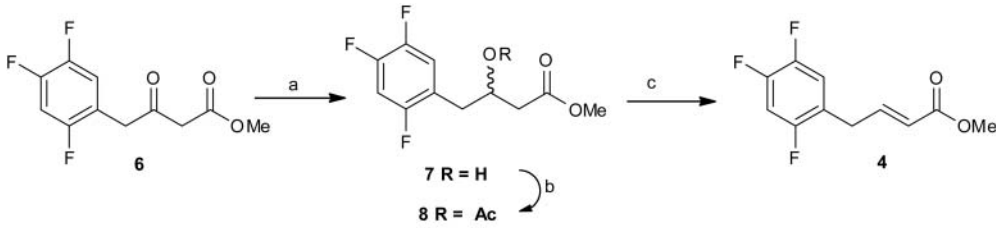
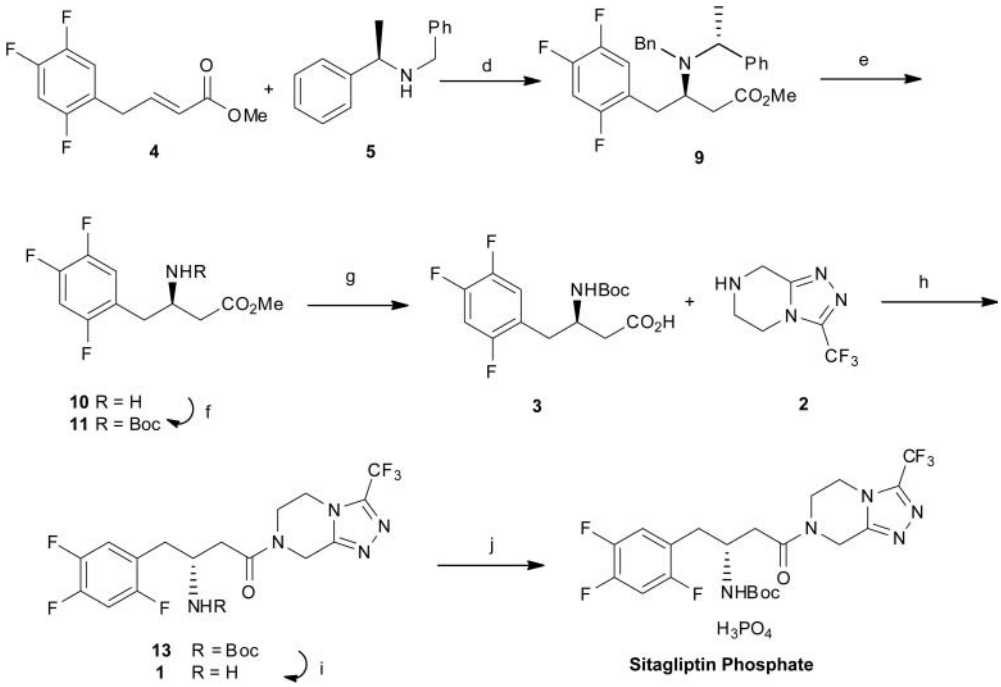


Reagents and conditions: (a) NaBH4, MeOH, 0°C to room temperature, 92%;
(b) Ac_2O, Py. 80°C, 90%;
(c) *t*-BuOK, Et_2O, -60 °C, 80%.

Scheme 2



Reagents and conditions: (d) 2.5M n-BuLi in hexane, THF, -78°C, 76%; (e) $Pd(OH)_2$, 5atm H_2, MeOH, r.t (f) Boc_2O, Et_3N, CH_2Cl_2, r.t., 83% for 2 steps; (g) NaOH, EtOH-H_2O, 0°C, 91%; (h) HOBT, EDCI, CH_2Cl_2, 0°C to r.t., 95%; (i) conc. HCl, MeOH, r.t., 90%. (j) H_3PO_4, EtOH. 96%.

Scheme 3

Experimental

Melting points were determined with a SGW X-4 micro melting point apparatus. IR spectra were determined on a Bruker Vertex 70 spectrophotometer. ^{1}H NMR spectra were recorded using Avance 400 MHz spectrometer. ESI-MS were recorded on Dionex MSOPlus mass spectrometer. EI-MS were recorded on Agilent 5973 mass spectrometer. High resolution mass spectra were recorded on Finnigan MAT XL95 mass spectrometer. HPLC were determined on Dionex Ultimate 3000. Optical rotations were obtained on a Perkin-Elmer 241 Autopol polarimeter.

3-Acetoxy-4-(2,4,5-trifluoro-phenyl)-butyric acid methyl ester (**8**): $NaBH_4$ (6.7 g, 0.175 mol) was added in portions to a stirred solution of 4-(2,4,5-trifluoro-phenyl)-3-oxo-butyric acid methyl ester (**6**) (175 g, 0.7 mol) in MeOH (1000 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, and then water (1000 mL) was added to quench the reaction, followed by aq. citrate to adjust the pH to 7. MeOH was removed under vacuum and then the residue was extracted with EtOAc (2 × 500 mL). The combined organic layers were washed with 5% aq. HCl (500 mL), 5% aq. $NaHCO_3$. (500 mL), saturated NaCl (500 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuum. The resulting oil was dissolved in pyridine (600 mL), acetic anhydride (300 mL) was added in one portion and the reaction mixture was heated to 80 °C and stirred at this temperature for 10 hours. After cooling, the solvent was removed under vacuum and the residue was then diluted with water (1000 mL) and EtOAc (1000 mL). The organic layer was washed with 15% aq. HCl (500 mL), saturated NaCl (500 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by passing through a thin-layer silica gel to afford 168.5 g (83% for two steps) of **8** as a colourless oil. IR (cm^{-1}): 2901, 1738, 1618, 1522, 1355, 1261, 1188, 840. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01–6.92 (m, 1H), 6.88–6.70 (m, 1H), 5.60 (s, 1H), 3.79 (s, 3H), 3.02–2.79 (m, 2H), 2.61 (d, *J* = 17.4 Hz, 2H), 2.01 (s, 3H). ESI-MS *m/z* 291.1(M^+ + 1); HRMS Calcd for $C_{13}H_{13}F_3O_4Na$ (M + Na)$^+$ requires 313.0668, found 313.0662.

4-(2,4,5-Trifluoro-phenyl)-but-2-enoic acid methyl ester (**4**): Compound **8** (168.5 g, 0.58 mol) was dissolved in anhydrous ethyl ether (800 mL) and cooled to –60 °C, *t*-BuOK (112 g, 1 mol) was added in one portion. The reaction mixture was quenched with H_2O (1000 mL) after 10 minutes. The layers were separated, and the organic layer was washed with saturated NaCl (800 mL), dried over anhydrous Na_2SO_4, concentrated and distilled to give the colourless oil **4** (106.7 g, 0.46 mol), bp 96–98 °C (1mm Hg). IR (cm^{-1}): 3030, 2890, 1732, 1631, 1517, 1427, 1334, 1212, 1152, 1101, 880, 844. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (ddd, *J* = 10.9, 8.8, 7.0 Hz, 1H), 6.89 (td, *J* = 9.9, 6.6 Hz, 1H), 6.54 (d, *J* = 16.1 Hz, 1H), 6.30 (dt, *J* = 15.9, 7.1 Hz, 1H), 3.74 (s, 3H), 3.28 (dd, *J* = 7.1, 1.1 Hz, 2H). EI-MS *m/z* (%): 230(M^+ 100), 199(86), 188(17), 177(85), 159(14), 151(81), 145(98), 125(19), 59(22). HRMS Calcd for $C_{13}H_{13}F_3O_4Na$ (M) requires 230.0555, found 230.0550.

3-R-[(R)-(α-methylbenzyl)benzylamino]-4-(2,4,5-trifluoro-phenyl)-butyric acid methyl ester (**9**): A solution of (R)-(α-methylbenzyl) benzylamine (63.3 g, 0.3 mol) in anhydrous THF (300 mL) was cooled to –78 °C and 2.5M *n*-BuLi (100 mL, 0.25 mol) was added dropwise, the mixture was allowed to warm to –20 °C in 1 hour and cooled down to –78 °C again. The resultant pale pink lithium amide solution was stirred for 45 min whereupon 4-(2,4,5-trifluorophenyl)-but- 2-enoic acid methyl ester (**4**) (57.5 g, 0.25 mol) was added dropwise as a solution in anhydrous THF (300 mL). The resultant deep yellow enolate solution was stirred for a further 30 minutes before saturated aqueous ammonium chloride (100 mL) was added to quench the reaction. The solvent was removed under reduced pressure and the residue was diluted with water (500 mL) and extracted with EtOAc (3 × 300 mL). The combined organic extracts were washed with saturated NaCl (800 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The oily crude product was chromatographed (silica gel; 1:10 ethyl acetate–petroleum ether as eluent) to afford 83.8 g (0.19 mol, 76%) of **9**. $[\alpha]_D^{20} = -9.5$ (c 1.0, $CHCl_3$); IR (cm^{-1}): 3305, 2931, 1744, 1633, 1512, 1400, 1348, 1259, 1214, 833. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.15 (m,10H), 7.11–7.06 (m, 1H), 6.80–6.72 (m, 1H), 3.83 (q, *J* = 5.4 Hz, 1H), 3.66 (s, 3H), 3.59 (d, *J* = 3.3 Hz, 2H), 3.38–3.46 (m, 1H), 2.81–2.73 (m, 2H), 2.44–2.35 (m, 2H), 1.40 (d, *J* = 6.6 Hz, 3H). ESI-MS: 442.2 (M^+ +1). HRMS Calcd for $C_{26}H_{26}F_3NO_2Na$ (M + Na)$^+$ requires 464.1815, found 464.1809.

3-R-tert-Butoxycarbonylamino-4-(2,4,5-trifluorophenyl)butyric acid methyl ester (**11**): **9** (83.8 g, 0.19 mol) was dissolved with absolute MeOH (500 mL) and treated with 20% $Pd(OH)_2$ on activated carbon (5 g). The mixture was then stirred at room temperature overnight under 5 atm. of hydrogen. After removal and recovered of the catalyst by filtration, the solvent was evaporated under reduced pressure. 10% HCl (500 mL) and CH_2Cl_2 (500 mL) was added to the residue and stirred for 10 minutes, the organic layer was discarded. The aqueous layer was neutralised with K_2CO_3, then extracted with CH_2Cl_2 (2 × 500 mL). The combined organic layers were washed with saturated NaCl (800 mL), dried over anhydrous Na_2SO_4 and filtered. To this CH_2Cl_2 solution was added Et_3N (45.5 g, 0.45 mol) and Boc_2O (65.4 g, 0.3 mol) at room temprature. The mixture was stirred for 8 hours before water (500 mL) was added, the layers were separated, the organic layer was washed with saturated NaCl (500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to provide the crude product 62 g, which was 94.5% ee by HPLC analysis. This was recrystallised from toluene to give a pale yellow solid **11** (54.6 g, 0.157 mol), 83% for two steps. $[\alpha]_D^{20} = +13.5$ (c 1.0, MeOH). M.p. 75–78 °C. lit.[11] $[\alpha]_D^{20} = +15.2$ (c 1.0, MeOH). M.p. 88–88.5 °C.} IR (cm^{-1}): 3364, 2980, 1733, 1683, 1519, 1422, 1368, 1332, 1252, 1210, 1155, 1095, 1029, 842. ^{1}H NMR (400 MHz, CDCl3) δ 7.17– 6.97 (m, 1H), 6.97–6.75 (m, 1H), 5.18 (t, *J* = 9.6 Hz, 1H), 4.23–4.05 (m, 1H), 3.70 (s, 3H), 2.85 (d, *J* = 6.9 Hz, 2H), 2.55 (dd, *J* = 10.3, 5.4 Hz, 2H), 1.38 (s, 9H). ESI-MS: 347.7 (M^+ +1).

3-R-tert-Butoxycarbonylamino-4-(2,4,5-trifluoro-phenyl) butyl]-5,6,7,8-tetrahydro-[3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine (**13**): A solution of **11** (76 g, 0.22 mol) in ethanol 300 mL was placed to a three-necked round-bottomed flask, a solution of 300 mL aqueous NaOH (16 g, 0.4 mol, 1.8 equiv) was added to the ethanol solution at r.t. The mixture was stirred for 2.5 hours at which point TLC assay indicated complete consumption of the ester starting material. The ethanol was removed by distillation in a vacuum, and the resulting solution was transferred to an extractor. 2 N HCl (200 mL, 0.4 mol, 1.8 equiv) and 500 mL of CH_2Cl_2 were added to the solution with cooling. The layers were separated, and the aqueous layer was back-extracted with 500 mL of CH_2Cl_2. The combined organic layers were washed with saturated NaCl (500 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to provide a pale yellow coloured crude product (66 g, 0.2 mol) in 91% yield. The crude acid which was obtained above was mixed with 3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-a] pyrazine hydrochloride (**2**, 45.6 g, 0.2 mol) and dissolved in anhydrous DCM (400 mL). To the above solution was added HOBT (27 g, 0.2 mol) followed by EDCI (38.2 g, 0.2 mol) and Et_3N (60 g, 0.3 mol) at 0 °C. After being stirred at room temperature for 24 h, distilled water (400 mL) was added to the reaction mixture, the layers were separated, the organic phase was washed with distilled water (400 mL) and dried over anhydrous magnesium sulfate. The solution was filtered and concentrated in a vacuum to give a residue that was recrystallised from toluene to give **13** (96.2 g, 0.19 mol) in 95% yield. It was assayed by chiral HPLC to be 98.2% ee. $[\alpha]_D^{20} = +22.2$ (c 1.0, $CHCl_3$). M.p. 188–191 °C. IR (cm^{-1}): 3374, 2897, 1686, 1635, 1519, 1368, 1164, 1128, 1016. ^{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). HRMS Calcd for: $C_{21}H_{23}F_6N_5O_3Na$ (M + Na)$^+$ requires 530.1598, found 530.1604.

(3R)-3-amino-4-(2,4,5-trifluoro-phenyl)butyl]-5,6,7,8-tetrahydro-[3-(trifluoromethyl)- 1,2,4-triazolo[4,3-a]pyrazine (**1**): To a solution of **13** (96.2 g, 0.19 mol) in MeOH (300 mL) was added a mixture of 50 mL conc. HCl and 250 mL MeOH at room temperature. After stirring for 3 hours, the solvent was removed by distillation in a vacuum, and the resulting solution was neutralised with 2 M aq. ammonia to pH 8. The aqueous layer was extracted with EtOAc (300 mL X 3), the combined organic layers were washed with saturated NaCl (500 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and recrystallised from toluene to give the free base **1** (69.2 g, 0.17 mol) in 90% yield. The optical purity was assayed to be >99% ee. $[\alpha]_D^{20} = -22.8$ (c 1.0, $CHCl_3$). M.p. 108–112 °C. IR (cm^{-1}): 3360, 2870, 1644, 1517, 1437, 1342, 1237, 1140, 941, 808. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19–7.02 (m, 1H), 7.02–6.81 (m, 1H) 5.06 (dd, *J* = 50.1, 18.2 Hz, 1H), 4.95 (s, 2H), 4.43–3.77 (m, 5H), 3.60 (s, 1H), 2.92–2.28 (m, 4H). ESI-MS: 408.0 (M^+ +1). HRMS Calcd for: $C_{16}H_{15}F_6N_5ONa$ (M + Na)$^+$ requires 430.1082, found 430.1087.

Sitagliptin phosphate: To the solution of free base **1** (69.2 g, 0.17 mol) in ethanol (1000 mL), phosphoric acid (85 wt%, 10 g) was added in one portion, and the temperature of the solution was raised to 80 °C. After 30 minutes the mixture was cooled to 30 °C, and the white solid which was formed was filtered and recrystallised from *i*-PrOH, Sitagliptin Phosphate (82.4 g, 0.164 mol, 96%) was collected as a white powder, the purity is 99.2%, The ee was assayed to be 99.5%. $[\alpha]_D^{20} = -72.9$ (c 1.0, H_2O). M.p. 213–216 °C. {lit.[10] $[\alpha]_D^{20} = -74.4$ (c 1.0, H_2O). M.p. 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).

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