Organic Process Research & Development **2005**, *9*, 634−639

First Generation Process for the Preparation of the DPP-IV Inhibitor Sitagliptin

Karl B. Hansen,* Jaume Balsells, Spencer Dreher, Yi Hsiao, Michele Kubryk, Michael Palucki, Nelo Rivera, Dietrich Steinhuebel, Joseph D. Armstrong III, David Askin, and Edward J. J. Grabowski

Department of Process Research, Merck Research Laboratories, Rahway, New Jersey 07065, U.S.A.

Abstract:

A new synthesis of sitagliptin (MK-0431), a DPP-IV inhibitor and potential new treatment for type II diabetes, suitable for the preparation of multi-kilogram quantities is presented. The triazolopyrazine fragment of sitagliptin was prepared in 26% yield over four chemical steps using a synthetic strategy similar to the medicinal chemistry synthesis. Key process developments were made in the first step of this sequence, the addition of hydrazine to chloropyrazine, to ensure its safe operation on a large scale. The beta-amino acid fragment of sitagliptin was prepared by asymmetric reduction of the corresponding beta-ketoester followed by a two-step elaboration to an *N*-benzyloxy beta-lactam. Hydrolysis of the lactam followed by direct coupling to the triazolopiperazine afforded sitagliptin after cleavage of the *N*-benzyloxy group and salt formation. The overall yield was 52% over eight steps.

Inhibitors of the enzyme DPP-IV are a promising new treatment for type II diabetes.[1] Sitagliptin (MK-0431, **1**) is a potent inhibitor of DPP-IV which is currently being evaluated in clinical trials.[2] Compound **1** was originally synthesized by coupling beta-amino acid **2a** to triazole **3**, which was prepared by hydrogenation of the unsaturated triazolopyrazine **4** (Scheme 1).[3] The synthesis of beta-amino acid **2a** in optically enriched form was carried out using the Schöllkopf chiral auxiliary.[4] The original approach to the preparation of triazolopiperazine **3** could potentially be scaled up for our first large-scale preparation of **1**; however, the use of a chiral auxiliary to prepare the amounts of enantiomerically enriched **2a** we required was not tenable.

A synthesis of the 2,5-difluorophenyl analogue of **2a** has been recently reported by others from these laboratories.[5] Using this method, **2a** could be prepared from lactam **5**, which is derived from an optically enriched beta-hydroxy acid. This method also requires introduction of the amino group as an *O*-benzylhydroxylamine, which we hoped would sufficiently protect the amino group of **2b** during amide formation with triazole **3**. Herein we describe the route used for the first large-scale preparation of **1** using this strategy.

Discussion

The synthesis of triazole **3** began with the alkylation of chloropyrazine **6** with hydrazine (Scheme 2). Refluxing **6** with 5 equiv of hydrazine monohydrate in 2-propanol resulted in complete conversion to hydrazine adduct **7**. Upon cooling to room temperature, **7** crystallized and was isolated directly from the reaction mixture. While this procedure was successful on a laboratory scale, preparation of larger quantities was not possible due to problems with the handling of hydrazine.

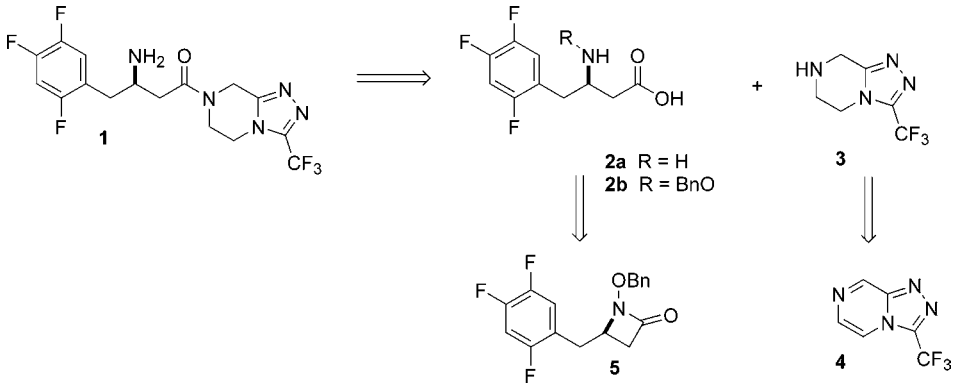
Heating of hydrazine-hydrate in organic solvents, especially solvents which form an azeotrope with water, leads to explosive anhydrous hydrazine in the vapor phase.[6] To ensure that anhydrous hydrazine would not be present, the reaction would need to be carried out on a large scale under aqueous conditions. Unfortunately, performing the reaction with larger concentrations of water present required heating to temperatures over 60 °C to ensure complete reaction. The reaction of **6** with hydrazine was also found to be uncontrollably exothermic at temperatures above 85 °C, so the reaction procedure would need to be modified to ensure that large concentrations of **6** would not build up in the vessel.[7]

A procedure for the preparation of **7** was developed which could be performed safely on large scale. By adding chloropyrazine **6** slowly to a 35 wt % aqueous solution of hydrazine[8] at 60−65 °C, its concentration in the reaction was kept low. This change in the reaction procedure, coupled with careful monitoring of the reaction temperature allowed for it to be performed safely on scale-up.[9] Upon complete consumption of **6**, the reaction mixture was cooled to ambient temperature and extracted with 10% 2-propanol/dichloromethane. By using 10% 2-propanol/dichloromethane as the extraction solvent, the organic extracts contained sufficiently low levels of hydrazine to allow their concentration by distillation, while still obtaining a 79% assay yield of **7**.[10] The organic extracts were distilled in vacuo, replacing them with isopropyl acetate (IPAC) in preparation for the subsequent reaction.

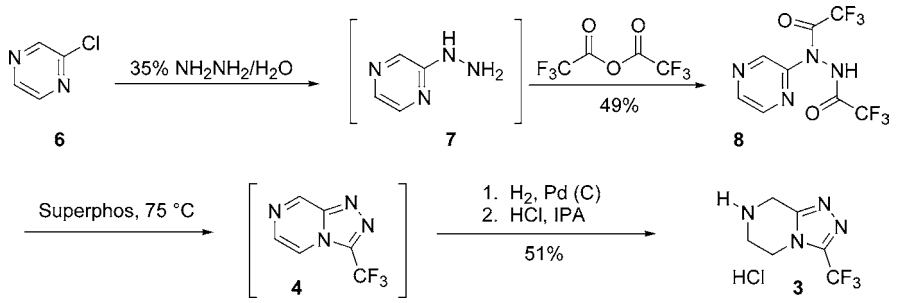
(1) (a) Weber, A. *J. Med. Chem.* **2004**, *48*, 4135−4141. (b) Drucker, D. J. *Exp. Opin. Investig. Drugs* **2003**, *12*, 87−100. (b) Wiedeman, P. E.; Trevillyan, J. M. *Curr. Opin. Investig. Drugs* **2003**, *4*, 412−420.
(2) Kim, D.; Wang, L.; Beconi, M.; et al. *J. Med. Chem.* **2004**, *48*, 141−151.
(3) Nelson, P. J.; Potts, K. T. *J. Org. Chem.* **1962**, *27*, 3243−3248.
(4) (a) Xu, J.; Ok, H. O.; Gonzalez, E. J.; et al. *Biorg. Med. Chem. Lett.* **2004**, *14*, 4759−4762. (b) Schöllkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 798−799.
(5) Angelaud, R.; Zhong, Y.-L.; Maligres, P.; Lee, J. Askin, D. *J. Org. Chem.* **2005**, *70*, 1949−1952.
(6) Information about hydrazine and its safe use can be obtained at http// www.hydrazine.com.
(7) Calorimetry studies of the reaction of hydrazine with **6** display a strong exotherm at temperatures above 85 °C.
(8) 35 wt % hydrazine aqueous solution has no flashpoint.
(9) As a safety precaution, the reaction temperature was carefully monitored upon scale-up. If the temperature of the reaction had exceeded 70 °C, a quench vessel of water was connected to the vessel to quickly stop the reaction. However there was no issue with maintaining the temperature of reaction in the 60−65 °C range.
(10) The hydrazine levels were measured by formation of 3,5-dimethylpyrazole by treating with 2,4-pentanedione and then analyzing by capillary gas chromatography. Levels in the combined extracts were typically ∼2000 ppm.

Published on Web 08/31/2005
10.1021/op0500786 CCC: $30.25

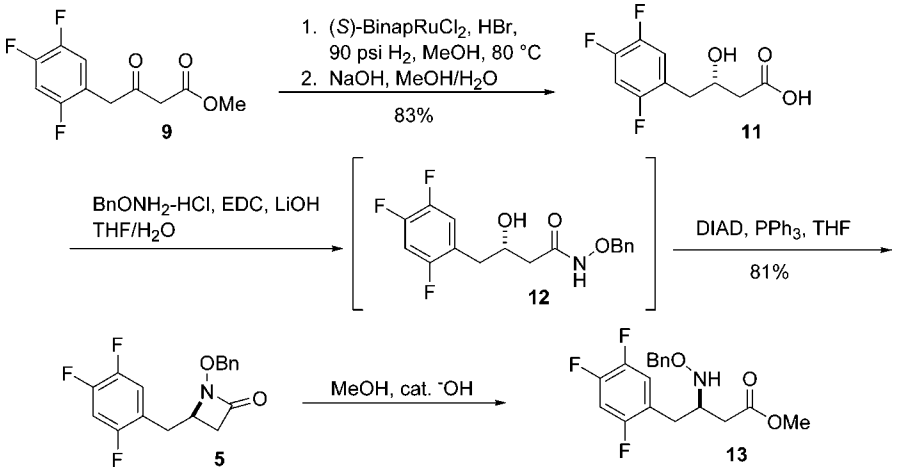
Scheme 1



Scheme 2



Scheme 3



Acylation of **7** with trifluoroacetic anhydride afforded the bis-trifluorohydrazide **8** which was isolated directly from the reaction by adding heptane and filtering. Heating the isolated solids in polyphosphoric acid (PPA) resulted in the cyclization of both compounds to afford triazolopyrazine **4**. Due to the high viscosity of the PPA as well as the strong exotherm associated with quenching PPA with water, superphos,[11] a more hydrated and less viscous form of PPA was used with identical results. Finally, pyrazine **4** was hydrogenated with Pd on carbon to the desired triazolopyrazine which, after filtration to remove the catalyst, was isolated as its HCl salt in 51% yield from **8** (26% yield from chloropyrazine **6**).

The synthesis of **2b** started with the asymmetric hydrogenation of beta-ketoester **9** (Scheme 3).[12] The reduction of **9** was carried out using (*S*)-BinapRuCl$_2$-triethylamine complex in methanol at 90 psi H_2 and 80 °C.[13] The use of a catalytic amount of HBr allowed the loading of the catalyst to be reduced to <0.1 mol % without affecting the ee or yield of beta-hydroxy ester **10**.[14] Following the reduction, the ester was hydrolyzed and the carboxylic acid **11** was isolated in 83% yield and 94% ee. Lactam **5** was then prepared in a two-step sequence from **11**. First, hydroxamate **12** was formed by coupling the carboxylic acid with $BnONH_2$−HCl using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC). Upon complete consumption of **11**, amine byproducts were removed by aqueous workup and the organic extracts were dried azeotropically

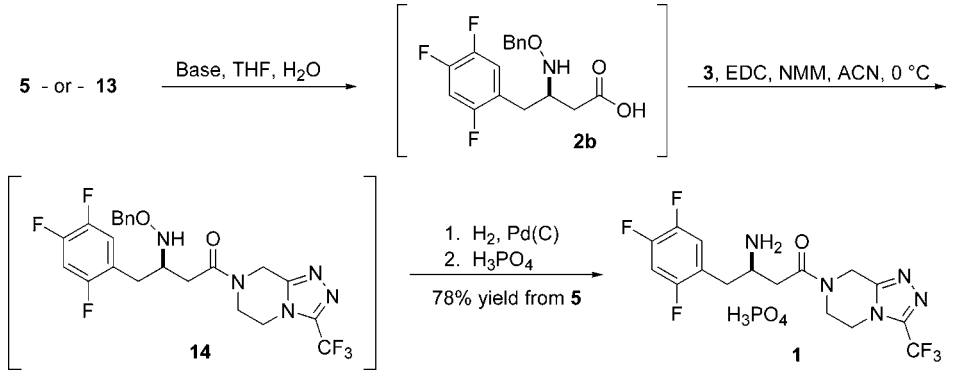
(11) Superphos contains 105% equivalent H_3PO_4, whereas polyphosphoric acid is 115% H_3PO_4.

(12) Brooks, D. W.; Lu, L. D.-L.; Masamune, S. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 72−73.

(13) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Kkutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.

(14) King, S. A.; Thompson, A. S.; King, A. O. Verhoeven, T. R. *J. Org. Chem.* **1992**, *55*, 6689−6691.

Scheme 4



for direct use in the subsequent reaction. The cyclization to form **5** was carried out directly in the solution of **12** using di-isopropyl azodicarboxylate (DIAD) and PPh_3.[15] Optimum results were obtained when the azeotropically dried THF solution of **12** was added to a mixture of PPh_3 and DIAD cooled to 0 °C. The reaction was assayed after complete addition of **12**, and typically less than one HPLC area % of starting material was observed. The product was isolated in 81% yield by crystallizing from methanol/water. An upgrade of the optical purity of **5** to >99% ee was observed in the crystallization when the ee of **11** used in the two-step sequence was at least 94% ee.

Control of the optical purity of **5** was deemed to be crucial at this point of the synthesis. Crystallization of **1** as its desired phosphoric acid salt with ee below the final desired specification did not upgrade its optical purity, and we intended to process **5** to **1** in a through-process with only a final isolation. The isolation of **5** was performed several times on a kilo scale with excellent results; however upon piloting, a large batch of **5** was observed to completely form methyl ester **13** during a solvent switch by distillation to the methanol crystallization solvent. To process the remaining batches of lactam, conditions needed to be developed which would ensure its stability during the distillation of the solvent.

Crude solutions of **5**, which had been tested to be slightly acidic following the reaction, had been stressed by heating in methanol, and none of methyl ester **13** was observed to form. The addition of as little as 0.1 mol % NaOH resulted in the formation of **13** at the temperature the distillation was carried out. The addition of strong acid resulted only in formation of amounts of methyl ester corresponding to the charge of acid. However, solutions charged with acetic acid were found to be stable for days at elevated temperatures. The exact cause of the methanolysis was not determined; however these stability experiments suggest that lactam **5** is most likely methanolyzed due to adventitious base in the reaction.[16] To protect future batches of **5** from methanolysis, a small amount of acetic acid was added to the distillation of solvent to ensure that the pH of the solution would remain low. This modification to the procedure resulted in complete prevention of methanolysis, even when experiments were challenged with aliquots of NaOH prior to and during distillation. The presence of HOAc did not affect the performance of the crystallization, and the lactam was isolated in identical purity and yield as when it was not present.

Despite having a solution to the problem of methanolysis of **5**, we also needed to process the methyl ester **13** which had formed to **1**. The optical purity of the lactam had not eroded during its transformation to **13**; however a new isolation needed to be developed to upgrade the ee prior to elaboration to **1**. In addition to the undesired enantiomer, the solution of **13** contained triphenylphosphine oxide and reduced DIAD byproducts from the cyclization.[17] Methyl ester **13** exists as an oil and could not be isolated directly; however its HCl salt was found to be a crystalline solid. Crystallization of the HCl salt **13** from IPAC/heptane resulted in an upgrade of the optical purity to >99%, with an overall yield which was nearly identical to the lactam isolation.

The synthesis of **1** was completed using a four-step through-process (Scheme 4). Lactam **5** or ester **13** was hydrolyzed to amino acid **2b** with LiOH[18] in THF/water by either stirring at room temperature or, in the case of **13**, heating to 40 °C. While the benzyloxy group of **2b** could be cleaved by hydrogenation and then protected with Boc_2O to prevent side reactions during the coupling to triazole **3**, the benzyloxy group of **2b** was found to sufficiently protect the amino group to allow the desired amide to be formed. Thus, triazole **3** was coupled to **2b** at 0 °C using EDC−HCl and *N*-methylmorpholine (NMM) as base to afford **14** in >99% assay yield. Following an aqueous workup, the organic extracts were distilled into ethanol and the solution was subjected to hydrogenation with 10% Pd on carbon. The presence of water in the hydrogenation was found to be crucial to the reaction success; anhydrous solutions of **14** hydrogenated with dry Pd on carbon proceeded only to low levels of conversion to **1**, and addition of water to these reductions resulted in restored performance of the catalyst. Following hydrogenation, the catalyst was removed by filtration to provide an ethanol solution of **1**. Sitagliptin was isolated in >99.5% purity as its anhydrous phosphoric acid salt by crystallizing from aqueous ethanol.

(15) Miller, M. J.; Mattingly, P. G.; Morrison, M. A.; Kerwin, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 7026−7032.
(16) Detergents used to clean vessels and transfer lines can have a very high pH. A small amount of basic soap catalyzes the formation of **13** from **5**.
(17) Solutions of **13** were measured to be only ~25 HPLC area % purity at 210 nm.
(18) NaOH or KOH could be used instead of LiOH with no effect on reaction performance.

The large-scale synthesis of sitagliptin, which prepares this important new drug candidate in 60% yield over eight steps from keto-ester **9** and triazole **3**, has been described. Triazole **3** was prepared in 26% yield by transforming the route used for the discovery of **1** into a process which can be run safely on multi-kilogram scale. While this route allowed for the preparation of large quantities of **3**, the difficulty with the alkylation of chloropyrazine with hydrazine coupled with the low overall yield has resulted in the development of a more efficient process for its preparation.[19] Beta-amino acid **2b**, prepared in five steps, was coupled directly to **3** to afford sitagliptin after deprotection. While this route allowed for the preparation of multi-kilogram quantities of **1**, the number of steps required to form the beta-amino acid moiety has led us to develop alternative methodology for its preparation.[20] The application of this methodology to the synthesis of **1** will be published shortly.

Experimental Section

Melting points were determined on an open capillary apparatus and are uncorrected. HPLC assays were carried out using a C-18 reversed-phase column eluted with acetonitrile and 0.1% H_3PO_4 (aq). GC assays were carried out using a 30 m RTX-5 capillary column (1.0 μM thickness). Assay yields were obtained by HPLC or by GC using pure compounds as standards. All reagents and solvents were used as received without further purification.

(1,2)-Bis-trifluoroacetyl-1-pyrazinylhydrazide (8). 2-Chloropyrazine (3.9 L, 5.0 kg, 43.7 mol, 1 equiv) was added dropwise to 22.2 L of 35 wt % aqueous solution of hydrazine (245 mol, 5.6 equiv) at 63−65 °C over 4 h. **The addition rate was carefully monitored to ensure that the reaction temperature did not exceed 65 °C.** Following the addition, the reaction mixture was aged for 11−13 h at 65 °C, at which point <1% chloropyrazine was observed by GC area percent assay. The reaction mixture was cooled to 30 °C and then extracted 5 times with 10% (v/v) 2-propanol/CH_2Cl_2. The combined extracts were assayed to contain 3.88 kg (35.3 mol, 81% assay yield) of **6**. The extracts were then concentrated by distillation and flushed with IPAc until <1 vol % of IPA remained as judged by GC assay. The solution was diluted with IPAC to a total volume of 51 L at which point the mixture was a slurry of white solids. The solution was cooled to 5 °C, and trifluoroacetic anhydride (19.6 L, 29.2 kg, 139.1 mol, 3.94 equiv) was added while maintaining the reaction temperature below 20 °C by controlling the addition rate (~1 h total addition time). Upon complete addition, the reaction was assayed by HPLC and contained <1 area percent **7**. Heptane (22 L) was added to the slurry, and the product was isolated by filtration. The solids were washed with 9 L of 10% (v/v) IPAC/heptane. After drying at ambient temperature under a vacuum/nitrogen sweep, 6.44 kg of a yellow solid (61% yield from **7**, 49% yield over both steps) was isolated. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.30 (s, 1H), 9.30 (s, 1H), 8.66 (d, J = 2 Hz, 1H), 8.64 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 157.6 (q, J_{C-F} = 37.8 Hz), 157.3 (q, J_{C-F} = 37.6 Hz), 146.1, 143.6, 143.1, 139.3, 115.4 (q, J_{C-F} = 288 Hz). ^{19}F NMR (DMSO-d_6, 376 MHz) δ −74.5, −71.3.

3-Trifluoromethyl-[1,2,4]triazolo[4,3-a]piperazine (3). 4.8 kg (15.8 mol, 1 equiv) of **8** were charged to 19.2 L of superphosphoric acid. The viscous slurry was heated to an internal temperature of 75 °C at which point the color became dark red and the mixture became homogeneous. After 5 h, the reaction was cooled to 30 °C and sampled for conversion by HPLC. Water (19.2 L) was added over 1.5 h to the reaction mixture while maintaining the temperature below 40 °C. NH_4OH (28.8 L) was carefully added to the mixture (gas evolution and strong exotherm) while keeping the temperature below 40 °C, until a pH of 8−9 was achieved. The slurry was extracted with 2 × 29 L and then 1 × 14 L of IPAC. The solids present were partitioned with the aqueous phase during each separation. The combined organic layers were treated with 0.5 kg of DARCO KB for 1 h and then filtered through cellulose. The waste cake was washed with 9.6 L of IPAC. The combined filtrate and wash were assayed to contain 2.11 kg of **4** (71% HPLC assay yield).

The combined organic extracts were then solvent switched into EtOH by vacuum distillation, and upon complete removal of IPAC, the volume was adjusted to 36 L with EtOH. The solution was then hydrogenated in three 12 L batches using 200 g of 10% Pd/C (each batch) at 50 psig H_2 and 45 °C. The combined hydrogenation mixtures were then treated with 200 g of DARCO G-60 and then filtered through cellulose. The cake was washed with ethanol, and the combined filtrate and wash was assayed to contain 1.87 kg of piperazine **3** (9.76 mol, 87% yield from **4**).

The solvent was then switched into IPA by vacuum distillation until <2 vol % ethanol remained. The volume was adjusted to 8 L, and then 2.4 L of a 3.7 M solution of HCl in IPA (8.8 mol, 1.01 equiv, prepared by diluting concentrated HCl with IPA, charge based on assay yield of **3**) were charged with cooling. IPAC (29 L) was added to the slurry, and the mixture was aged for 1 h at 20 °C and then filtered. The cake was washed with 4 L of 13 vol % IPA in IPAC and then dried under vacuum with a nitrogen sweep. 1.8 kg (8.01 mol, 51% yield from **8**) of **3-HCl** as a white solid were obtained.[21]

4-(2,4,5-Trifluorophenyl)-3(*S*)-hydroxybutanoic Acid (11). A solution of ketoester **9** (2.5 kg, 10.2 mol) and HBr (115 mL, 48 wt % solution in water, 1.01 mol, 0.1 equiv) in 11.5 L of methanol was degassed by bubbling N_2 through the solution for 20 min and then transferred to a stirred autoclave. 21.5 g of (*S*)-BinapRuCl$_2$ triethylamine complex was dissolved in 1 L of methanol which had been degassed as above and transferred to the autoclave. Following addition of the catalyst solution, the entire reaction solution was further degassed by five vacuum purge/N_2 back-fill cycles. The mixture was then subjected to 90 psig H_2 at 80 °C for 10 h at which point <1% ketoester remained by HPLC assay. The solution was removed from the vessel with a methanol

(19) Balsells, J.; DiMichele, L.; Kubryk, M.; Hansen, K.; Armstrong, J. D. *Org. Lett.* **2005**, *7*, 1039−1042.

(20) (a) Hsiao, Y.; Krska, S.; Rivera, N.; Rosner, T. et al. *J. Am. Chem. Soc.* **2004**, *126*, 9918−9919. (b) Ikemoto, N.; Tellers, D.; Rivera, N. et al. *J. Am. Chem. Soc.* **2004**, *126*, 3047−3048.

(21) Complete characterization of **3-HCl** can be found in ref 19.

rinse. The solution was assayed to contain 2.51 kg of **10** (99.3% yield) which was 90.8% ee by chiral HPLC analysis (Chiracel AD-H, 95% hexanes, 5% IPA, 1% TFA, 1 mL/min, 35 °C, t_r = 12.3 min (*S*-**10**), 15.7 (*R*-**10**).

A solution of **10** (5.00 kg, 20.15 mol) in 25 L of methanol was charged to a round-bottom flask equipped with an overhead stirrer, steam bath, and thermocouple. A solution of aqueous NaOH (0.89 kg, 22.16 mol, 1.1 equiv) dissolved in 25 L of water was charged to the methanol solution. The mixture was aged for 1 h at which point HPLC assay indicated complete consumption of ester starting material. The methanol was removed by distillation in vacuo, and the resulting solution was transferred to an extractor. 12 N HCl (3.8 L, 34.3 mol, 1.7 equiv) and 15 L of MTBE were added to the solution with cooling. The layers were separated, and the aqueous layer was back-extracted with 15 L of MTBE. The combined MTBE layers were switched to toluene by distillation at 50−60 °C, and upon complete removal of MTBE, the volume was adjusted to 50 L. The solution was then allowed to cool to room temperature. At ∼37 °C the product began to crystallize from solution. The mixture was aged overnight at room temperature (∼18 h). The crystals were isolated by filtration and washed with 5 L of toluene. Following drying at 40 °C, 4.08 kg of hydroxy acid **11** which was 94% ee and 96.7 wt % pure were isolated in 83% yield. (Chiracel AD-H, 95% hexanes, 5% IPA, 1% TFA, 1 mL/min, 35 °C, t_r = 20.3 min (*S*-**11**), 22.9 (*R*-**11**)). Mp: 84 °C. ^{1}H NMR: ($CDCl_3$, 400 MHz) δ 7.11 (m, 1H), 6.92 (m, 1H), 4.27 (m, 1H), 2.82 (d, J = 6.1 Hz, 2H), 2.61 (dd, J = 3.4, 16.8 Hz, 1H), 2.52 (dd, J = 8.7, 16.8 Hz, 1H). ^{13}C NMR: (CD_3OD, 100 MHz) δ 173.7, 156.3 (dd, J_{C-F} = 9.3, 243.1 Hz), 148.7 (ddd, J_{C-F} = 12.8, 27.3, 248.0 Hz), 146.2 (ddd, J_{C-F} = 3.6, 12.4, 242.5 Hz), 122.1 (ddd, J_{C-F} = 4.4, 5.4, 18.3 Hz), 119.2 (dd, J_{C-F} = 6.2, 19.3 Hz), 104.7 (dd, J_{C-F} = 21.1, 29.3), 67.6, 41.1, 35.1. ^{19}F NMR: ($CDCl_3$, 376 MHz) −119.7 (dd, J_{F-F} = 3.2, 15.5 Hz), −136.0 (dd, J_{F-F} = 3.2, 21.0 Hz), −133.3 (dd, J_{F-F} = 15.5, 21.0 Hz). $[\alpha]_D$ = +16.3° (c = 1.0, $CHCl_3$). Anal. Calcd for $C_{10}H_9F_3O_3$: C, 51.29; H, 3.87. Found: C, 50.59; H, 3.62.

***N*-Benzyloxy-4(*R*)-[1-methyl-(2,4,5-trifluorophenyl)]-2-oxoazetidine (5).** To a slurry of hydroxyacid (4.0 kg, 17.1 mol, 1.0 equiv), *O*-benzylhydroxy amine hydrochloride (3.0 kg, 18.8 mol, 1.1 equiv), and LiOH (0.72 kg, 17.1 mol, 1.0 equiv) in 10 L of THF and 30 L of water at 20 °C was added EDC−HCl (4.26 kg, 22.2 mol, 1.3 equiv). The solution was aged for 1 h at which point <1% hydroxy acid was present by HPLC assay. 32 L of MTBE were added, and the phases were separated. The organic layer was then vacuum distilled and dried by flushing first with MTBE and then with THF until all of the MTBE had been removed and the water content was <2000 ppm as judged by Karl Fisher titration. The final volume was adjusted to 17 L, and the solution was then used directly in the next step. In a separate vessel, DIAD (3.70 L, 18.8 mol, 1.1 equiv) was charged slowly via addition funnel to a solution of PPh_3 (4.93 kg, 18.8 mol, 1.1 equiv) at 0 °C such that the temperature did not rise above 10 °C. A slurry of white solids formed during the addition. The THF solution of hydroxamate **12** was then added slowly to the slurry keeping the reaction temperature below 10 °C. Upon completion of the addition, the reaction was warmed to 20 °C and then aged overnight (18 h). The reaction was assayed by HPLC at which point <1% area percent starting material remained. Acetic acid (51.6 g, 0.86 mol) was charged to the solution which was then solvent switched to methanol. Crystals formed upon complete removal of THF. The final volume of the mixture was adjusted to 43 L with methanol, and then water (2.8 L) was added. The mixture was heated to 35 °C to redissolve all of the solids and then slowly cooled to −20 °C. After 1 h at −20 °C, the slurry was filtered and then washed with 2 × 4.5 L of 10% v/v water/methanol cooled to −20 °C. 4.7 kg of **5** (93 wt % purity by HPLC) were isolated as a crystalline solid after drying at room temperature in vacuo (82% yield over two steps). The material was assayed by chiral HPLC to be 99.7% ee. (Chiracel AD-RH, 60% CH_3CN/40% H_2O, 0.6 mL/min, 20 °C, t_r = 9 min (*R*-**5**), 11 min (*S*-**5**). Mp: 80 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37 (m, 5H), 6.90 (m, 2H), 4.92 (m, 2H), 3.63 (m, 1H), 2.86 (dd, J = 5.0, 14.3 Hz, 1H), 2.67 (m, 2H), 2.33 (dd, J = 2.2, 13.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ 163.6, 155.9 (dd, J_{C-F} = 10.6, 244.2 Hz), 149.1 (dd, J_{C-F} = 12.5, 250.9 Hz), 146.6 (ddd, J_{C-F} = 3.7, 12.5, 231.3 Hz), 135.3, 129.3, 129.1, 128.6, 119.7 (ddd, J_{C-F} = 4.4, 5.1, 18.4 Hz), 118.8 (dd, J_{C-F} = 6.5, 19.2 Hz), 105.5 (dd, J_{C-F} = 20.8, 28.5 Hz), 78.2, 57.0, 37.6, 31.0. ^{19}F NMR ($CDCl_3$, 377 Hz): δ −119.4 (dd, J_{F-F} = 3.2, 15.1 Hz), −135.5 (dd, J_{F-F} = 3.2, 21.6 Hz), −147.7 (dd, J_{F-F} = 14.9, 21.5 Hz). $[\alpha]_D$ = + 26.2° (c = 1.04, $CHCl_3$). Anal. Calcd for $C_{17}H_{14}F_3NO_2$: C, 63.55; H, 4.39; N, 4.36. Found: C, 63.55; H, 4.27; N, 4.33.

Methyl *N*-Benzyloxy-4-(2,4,5-trifluorophenyl)-3(*R*)-aminobutanoate Hydrochloride (13-HCl). A solution of 3.34 kg of methyl ester **13** (9.44 mol, 1.0 equiv) was charged to a 100 L of RBF equipped with an overhead stirrer, thermocouple, and distillation condenser. Hydrochloric acid (0.89 L, 12 M, 10.7 mol, 1.2 equiv) was added to the solution with cooling. The solution was concentrated in vacuo to 40% of its original volume and then flushed continuously with 50 L of IPAC, while distilling at a constant volume and maintaining the temperature below 45 °C. The solution was checked for methanol content by GC and found to contain <1%. The solution was cooled to room temperature and aged for 1 h at which point a slurry had formed. Heptane (50 L) was added over 0.5 h, and then the mixture was cooled to 0 °C and aged until the HPLC analysis of the supernatant showed a phosphine oxide level of <12% relative to methyl ester at 268 nM (∼12 wt %). The slurry was filtered and washed with 7 L of 90% heptane/IPAC cooled to 0 °C. The solids were dried at ambient temperature in a vacuum oven with a nitrogen sweep to afford 3.02 kg of **13-HCl**. The ee of the methyl ester was assayed to be >99% by hydrolyzing to **2b** using KOH/H_2O (Chiracel OD-H, 95% (0.1% TFA in hexanes)/5% (0.1% TFA in EtOH), 1.0 mL/min, 10 °C, t_r = 11 min (*S*-), 13 min (*R*-). Mp = 123 to 125 °C. ^{1}H NMR ($CDCl_3$, 400 MHZ): δ 7.39 (m, 5H), 7.17 (m, 1H), 6.88 (m, 1H), 5.41 (s, 3H), 4.24 (m, 1H), 3.46 (dd, J = 14.1, 5.0 Hz, 1H), 3.12 (m, 2H), 2.69 (dd, J = 17.1, 6.4 Hz, 1H). ^{13}C

NMR ($CDCl_3$, 100 MHz): δ 169.7, 156.4 (dd, J_{C-F} = 7.0, 245 Hz), 149.5 (ddd, J_{C-F} = 12.9, 14.1, 252.0 Hz), 146.8 (ddd, J_{C-F} = 3.5, 12.4, 249.1 Hz), 132.2, 129.6, 128.7, 119.4 (dd, J = 5.3, 19.4 Hz), 118.3 (ddd, J_{C-F} = 5.0, 9.7, 18.1 Hz), 105.7 (dd, J_{C-F} = 20.1, 28.1 Hz), 76.9, 57.2, 52.2, 33.2, 28.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ −118.3 (dd, J_{F-F} = 3.2, 15.5 Hz), −134.1 (dd, J_{F-F} = 3.2, 22.1 Hz), 142.2 (dd, J_{F-F} = 15.5, 22.1 Hz). $[\alpha]_D$ = + 7.3° (c = 1.0, $CHCl_3$). Anal. Calcd for $C_{18}H_{19}ClF_3NO_3$: C, 55.46; H, 4.91; N, 3.59. Found: C, 55.54; H, 4.69; N, 3.56.

Sitagliptin (1). A solution of lactam (4.65 kg, 93 wt % purity, 13.4 mol, 1.0 equiv) and LiOH monohydrate (0.84 kg, 20 mol, 1.5 equiv) in 14 L of THF and 14 L of water was aged for 1.5 h at 20 °C at which point <1% starting material was present by HPLC assay. Methanesulfonic acid (1.30 L, 20 mol, 1.5 equiv) was slowly added to the reaction with cooling such that the temperature stayed below 20 °C. MTBE (28 L) was charged, and the phases were mixed well and then separated. The organic layer was then concentrated by vacuum distillation and then distilled at constant volume while the solvent was replaced with acetonitrile. The volume was then adjusted to 43 L with acetonitrile. Triazole HCl salt (3.81 kg, 16.7 mol, 1.25 equiv) was charged, and the mixture was then cooled to 0 °C. *N*-Methyl morpholine (1.35 kg, 13.4 mol, 1.0 equiv) was then charged to the slurry followed by EDC−HCl (3.85 kg, 20.07 mol, 1.5 equiv). The reaction was aged for 2 h at 0 °C at which point <1% **2b** remained by HPLC assay. The mixture was quenched with 20 L of water and 40 L of MTBE. After warming to 15 °C, the layers were separated and the organic layer was washed with 1 × 20 L of 10% $KHCO_3$ and 1 × 20 L of 20% NaCl solution. The organic layer was then concentrated by vacuum distillation, and the solvent was switched to ethanol. The volume was adjusted to 36 L with ethanol, and 4 L of water were charged. The solution was hydrogenated at 40 psi and 50 °C with 1.00 kg of 10% Pd on carbon as catalyst. The reactions were complete after 16−18 h as judged by complete consumption of starting material by HPLC assay. The catalyst was removed by filtration of the reaction through cellulose which was washed with ethanol. The combined filtrate and wash was combined and assayed to contain 4.71 kg of MK-431 free base (86% yield).

The ethanol solution was concentrated by vacuum distillation to a volume of 25 L. 5.5 L of water were added, and the mixture was heated to 50°C. Phosphoric acid (85 wt %, 1.33 kg, 11.5 mol, 1.0 equiv) was then added in one portion, and the temperature of the solution raised to 70−74 °C. The solution temperature was lowered to 65 °C, and it was then seeded with sitagliptin H_3PO_4 salt. The slurry was aged for 1 h and then slowly cooled to rt. 75 L of EtOH were added slowly to the slurry, which was then aged for 18 h at room temperature. The crystals were isolated by filtration and washed with 2 × 10 L of ethanol. The solids were dried in a 40 °C vacuum oven with a nitrogen sweep to afford 5.30 kg of **1-H_3PO_4** (78% yield from **5**). The optical purity was assayed to be >99.5% ee. Chiralpak AD-H, 60% (2% H_2O, 2% diethylamine, 96% hexanes), 40% (2% H_2O, 2% diethylamine, 96% EtOH), 0.8 mL/min, 35 °C, t_r = 13 min (*S*-1), 15 min (*R*-1). Mp = 215−217 °C. ^1H NMR (D_2O, 600 MHz) δ 7.06 (m, 1H, major and minor), 6.91 (m, 1H, major and minor), 4.76 (s, 2H, minor), 4.75 (d, J = 17.6 Hz, 1H, major), 4.70 (d, J = 17.6 Hz, 1H, major), 4.11 (m, 2H, major), 4.07 (m, 1H, minor), 4.02 (m, 1H, minor), 3.83 (m, 1H minor and 2H major), 3.79 (m, 2H, major), 2.91 (m, 1H, both), 2.83 (m, 2H, major and minor), 2.79 (dd, J = 17.0, 4.9 Hz, 1H, major), 2.68 (m, 1H, major and minor). ^{13}C NMR: (D_2O, 151 MHz) δ 170.4 (minor), 170.3 (major), 156.5 (m, major and minor), 151.2 (major), 150.7 (minor), 149.4 (m, major and minor), 146.6 (m, major and minor), 144.0 (q, J_{C-F} = 40.6 Hz, minor), 143.9 (q, J_{C-F} = 40.7 Hz, major), 119.3 (m, major and minor), 118.6 (m, major and minor), 117.8 (q, J_{C-F} = 270.1 Hz, major), 117.8 (q, J_{C-F} = 270.2 Hz, minor), 106.0 (dd, J_{C-F} = 28.6, 21.2, major and minor), 48.4 (major and minor), 43.6 (major), 43.3 (minor), 42.0 (minor), 41.3 (major), 38.9 (major), 38.2 (minor), 33.9 (major), 33.8 (minor). $[\alpha]_D$ = −74.4° (c = 1.0, H_2O). Anal. Calcd for $C_{16}H_{18}F_6N_5O_5P$: C, 38.03; H, 3.59; O, 13.86. Found: C, 38.08; H, 3.30; N, 13.77.

Acknowledgment

The authors would like to thank Mr. A. Houck, Mr. C. Bazaral, and Mr. A. Newell of the Merck High Pressure Laboratory for experimental assistance. We also thank Dr. R. Reamer, Dr. P. Dormer, and Ms. L. DiMichele for aid in NMR structure determination.

Received for review May 24, 2005.

OP0500786