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A highly stereoselective and efficient synthesis of enantiomerically pure sitagliptin

Sung Kwon Kang [a,b], Gyeong Hi Cho [b], Hyung Joon Leem [b], Bong Kwan Soh [b], Jaehoon Sim [a], Young-Ger Suh [a,*]

[a] College of Pharmacy, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul 151-742, Republic of Korea
[b] Department of Synthetic Chemistry, Chong Kun Dang Research Institute, 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do, Republic of Korea

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ABSTRACT

A highly stereoselective and efficient synthesis of sitagliptin **1** consisting of a chiral β-amino acid unit has been achieved through 6 steps from commercially available 2,4,5-trifluorobenzaldehyde **4**. The chiral antidiabetic drug was obtained with almost perfect enantiomeric purity (>99.9% ee) in 40.9% overall yield. The key feature of the synthesis is the addition of a malonate enolate to a chiral sulfinylimine in more than 99:1 dr. Our synthetic procedure proved to be highly efficient, economical, and sustainable.

1. Introduction

Fluorine-containing compounds have been used in a variety of medicines, such as anti-cancer, anti-hyperlipidemia, anti-diabetes and in many other applications over recent years,[1–3] as shown by the representative drugs in Figure 1. Especially, amino acid motifs containing fluorine[4–7] are of particular interest and medicinal potential in pharmaceutical industry. The representative fluorinated β-amino acid derivative is sitagliptin **1**, which has been approved for the treatment of type 2 diabetes.[8,9]

Sitagliptin inhibits the activity of dipeptidyl peptidase IV (DPP-4) that breaks down incretins,[10] which play a key role in stimulating insulin release and inhibiting glucagon secretion. Since this first dipeptidyl peptidase IV (DPP-4) inhibitor was launched, it has been widely used around the world and has become a leading drug for the treatment of type 2 diabetes. Due to its tremendous value and unique structure, many pharmaceutical companies have been interested in the development of more efficient and economical synthetic routes to sitagliptin.[11–18]

In 2005, the first commercial process[12,19] involved an asymmetric hydrogenation of a β-keto ester using Ru catalyst followed by the Mitsunobu reaction to provide the chiral amino acid unit. However, the reaction conditions, including high pressure for hydrogenation and the use of an expensive ruthenium catalyst, limited this process for commercial production. An improved process[13] included a one-pot, three-step synthesis of a key dehydrositagliptin intermediate and a Rh-catalyzed asymmetric hydrogenation of enamine. However, the requirement of high-pressure equipment for the transition metal-mediated hydrogenation, the unsatisfactory stereoselectivity and an extra procedure to remove the metal catalyst remained as drawbacks for the economical process. Recently, chiral resolution for enantiomerically pure sitagliptin and a highly enantioselective process using an optimal biocatalyst for the direct amination of β-keto amide were also reported although unsatisfactory yields for the resolution, high cost and limited susceptibility to substrates or products remained.[14,20] Thus, there has been continuing interests in the efficient and practical synthesis of sitagliptin.

Herein we report an environmentally friendly, economical, and practical approach for the preparation of optically pure sitagliptin. The key part of our strategy involves a highly stereoselective enolate addition of an malonate derivatives to sulfinyl imine **3** to afford the key amine intermediate **2**, as outlined in Scheme 1.[21–24] The *tert*-butyl sulfinyl aldimine **3**, prepared by direct condensation of aldehyde **4** with *tert*-butanesulfinamide, was anticipated to undergo a facile nucleophilic addition by an enolate for the chiral β-amino acid moiety of sitagliptin. The metal coordination capability of the enantiomerically pure *tert*-butyl sulfinyl moiety was anticipated to induce the diastereoselective addition of an enolate to **3**.[25–27]

2. Results and discussion

We first explored the reactivity of various esters for the enolate addition to sulfinyl imine **3**, which was obtained from commercially available **4**.[28] The experimental investigation for the enolate addition to (*R*)-*tert*-butanesulfinamide **3** is summarized in Table 1.[29] Meldrum's acid **6** and menthyl ester **7** gave poor

* Corresponding author.

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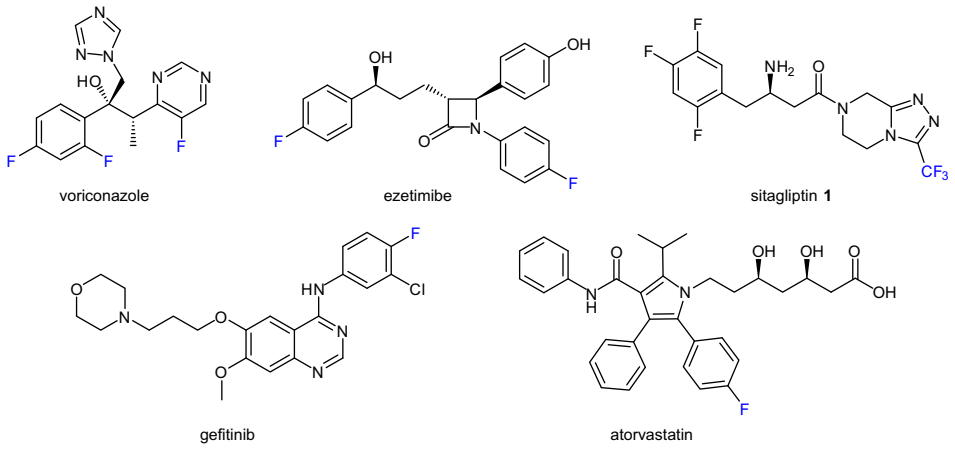
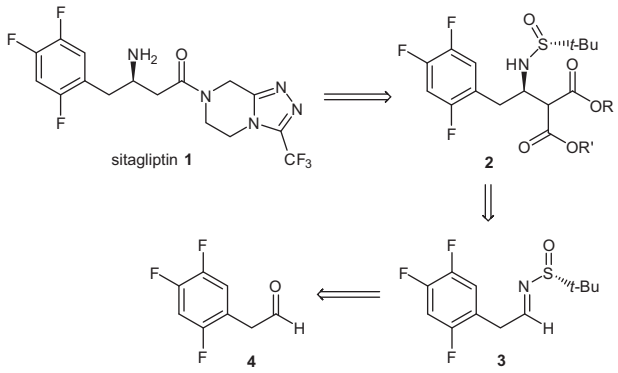


Figure 1. Fluorine-containing pharmaceutical drugs.



Scheme 1. Synthetic strategy for the synthesis of sitagliptin.

conversions, while *tert*-butyl acetate **5** afforded a high conversion. Diethyl malonate **8** provided the best yield of 96.4%, which is likely due to the steric hindrance and geometry of enolates and the low pKa of the malonate.

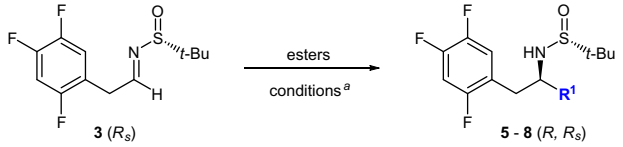
Next, we focused on the optimization of the malonate addition to **3**, as summarized in Table 2. In order to develop a sustainable and economical process, we explored the effect of the base, temperature, and additives at the solvent-free condition in reference to the previously reported literature.[23] All bases afforded high diastereoselectivities of greater than 90.9% dr with high conversions (entries 1–4). However, a relatively long reaction time was required to complete the addition reaction for $NaHCO_3$ and $KHCO_3$.

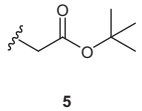
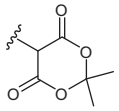
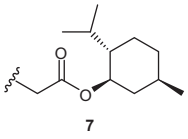
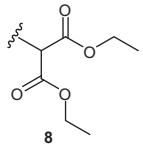
The reaction temperature significantly affected the diastereoselectivity, although the reactions generally produced the desired products in good yields. The diastereoselectivity decreased as the reaction temperature increased (entries 4–8). Considering the satisfactory diastereoselectivities and conversions, we attempted to improve the rate of the addition reaction using a rate accelerating additive. It is noteworthy that the diastereoselectivity dramatically improved to 99.4% upon the addition of NaI (entries 9 and 10). We further confirmed the crucial coordination effect of the metal ion for high diastereoselectivity with the help of the cation-capturing ability of crown ether (entries 11 and 12). A plausible transition state for the highly stereoselective enolate addition is depicted in Figure 2.

With the chiral sulfinamide **8**, acid-catalyzed hydrolysis followed by decarboxylation with 2 M HCl was attempted to obtain the β-amino ester **10**. However, small amounts of by-products **11** (3%) and **12** (1%) were consistently detected (Scheme 2). We assumed that the presence of the acid by-product causes instability in the sulfinamide group. Thus, complete separation of the by-products was considered crucial because even small amounts of by-products influence the purity of the final sitagliptin. In order to overcome the decarboxylation problem, we investigated the Pd-catalyzed decarboxylation of the 1,3-diester consisting of an allyl ester.[21,30] We anticipated that the functional groups of **8** were tolerable in the presence of palladium catalysts and triethylamine-formic acid salt.

We examined the reactivity and selectivity of the enolate addition for various allyl malonates (Table 3). All substrates produced

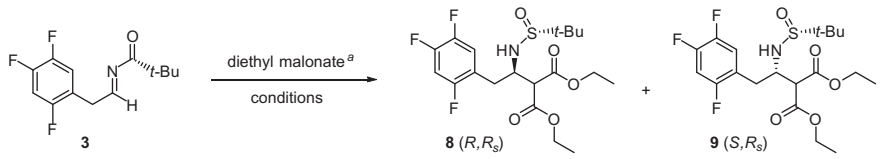
Table 1
Pre-screening results for enolate addition to sulfinyl imine **3** with various esters



R^1=	 5	 6	 7	 8
Conversion[b]	88.0%	Trace	Trace	96.4%

[a] Reaction conditions: **3** (1.0 equiv, 1.08 mmol), LHMDS (10.0 equiv, 10.8 mmol), esters (10.0 equiv, 10.8 mmol), −78 °C, THF.
[b] Conversion is given based on the disappearance of the starting compound by HPLC analysis.

Table 2
Optimization of the enolate addition reactions



Entry	Base (equiv)	Temperature (°C)	Additive (equiv)	Time (h)	Conversion[b]	dr[c] (**8**:**9**)
1	$NaHCO_3$ (5)	40	—	20	80	98.0:2.0
2	$KHCO_3$ (5)	40	—	22	91	97.2:2.8
3	Na_2CO_3 (5)	40	—	12	91	97.5:2.5
4	K_2CO_3 (5)	40	—	1.5	98	90.9:9.1
5	K_2CO_3 (5)	25	—	0.5	94	96.2:3.8
6	K_2CO_3 (5)	5	—	2.5	94	97.8:2.2
7	K_2CO_3 (5)	0	—	4	94	97.9:2.1
8	Na_2CO_3 (5)	0	—	17.5	94	98.8:1.2
9	K_2CO_3 (5)	0	NaI (0.1)	4	94	99.4:0.6
10	Na_2CO_3 (5)	0	NaI (0.1)	12.5	90	99.7:0.3
11	Na_2CO_3 (5)	0	15-Crown-4	4	84	74.3:25.7
12	K_2CO_3 (5)	0	18-Crown-6	1	96	46.8:53.2

[a] Diethyl malonate was used as solvent (5.0 equiv, 18.0 mmol).
[b] Conversion is given based on the disappearance of the starting compound by HPLC analysis.
[c] Diastereoselectivity was determined by HPLC analysis of crude reaction mixture.

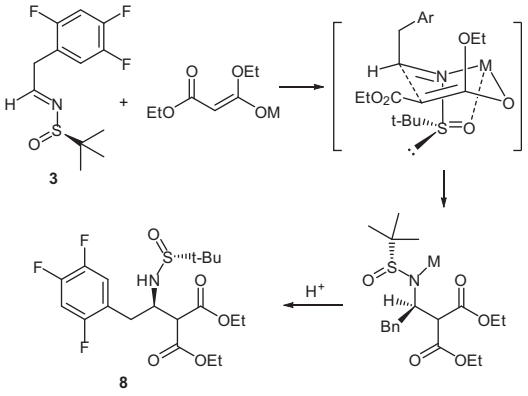
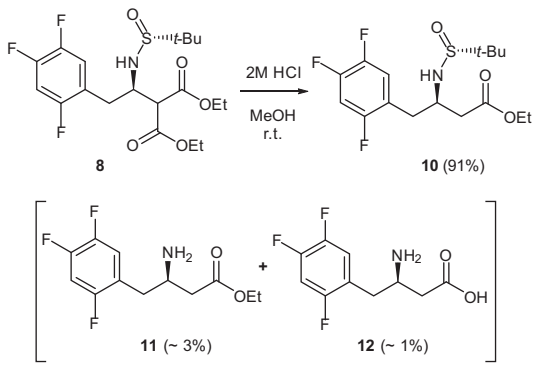


Figure 2. The enolate addition reaction of **3** through the chelate-controlled transition state.

the desired products with high diastereoselectivities greater than 99.3% and in high conversions. Allyl ethyl malonate afforded the best results in terms of selectivity and reactivity (entry 2).

As shown in Scheme 3, enantiomerically pure chiral sulfinamide **14**, prepared by the selective enolate addition, was subjected to Pd-catalyzed decarboxylation to provide the β-amino ester **10** with excellent diastereoselectivity. Hydrolysis of the terminal ester afforded pure β-amino acid **16**. Coupling of **16** with the piperazine unit with the assistance of HBTU produced amide **17**. To complete the synthesis, the sulfinyl chiral auxiliary was removed by HCl to produce sitagliptin **1**, which exhibited almost perfect enantioselectivity (>99.9% ee). We did not detect the enantiomeric sitagliptin.



Scheme 2. Acid-catalyzed hydrolysis and decarboxylation.

3. Conclusion

In conclusion, a highly stereoselective and concise synthesis of enantiomerically pure sitagliptin was accomplished in 40.9% overall yield over six steps from the commercially available aldehyde **4**. The key step of the synthesis includes elaboration of the chiral β-amino acid moiety of sitagliptin via a highly stereoselective enolate addition of allyl ethyl malonate to the chiral sulfinyl imine **3**. Our synthetic procedure proved to be highly efficient, economical, and environmentally friendly. We believe that it could be widely utilized by synthetic and medicinal chemists.

4. Experimental

4.1. General

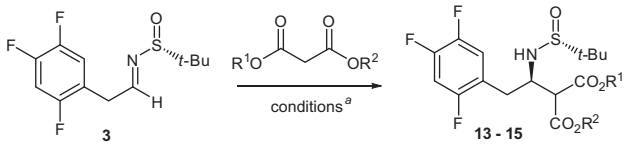
^{1}H NMR spectra and ^{13}C NMR spectra were measured using a Bruker DPX 400 Spectrometer. All purity values were obtained by HPLC analysis. HPLC was 1200 Series available from Agilent Technologies. Melting points were determined on an open capillary apparatus. All NMR spectra were measured using 400 UltraShield NMR in $CDCl_3$, NMR chemical shifts are reported in ppm referenced to the solvent peaks of $CDCl_3$ (7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C, respectively). High resolution mass spectra were obtained with Synapt G2 instrument.

4.2. Preparation of compounds

4.2.1. (*R*,*E*)-2-Methyl-*N*-[2-(2,4,5-trifluorophenyl) ethylidene] propane-2-sulfinamide 3

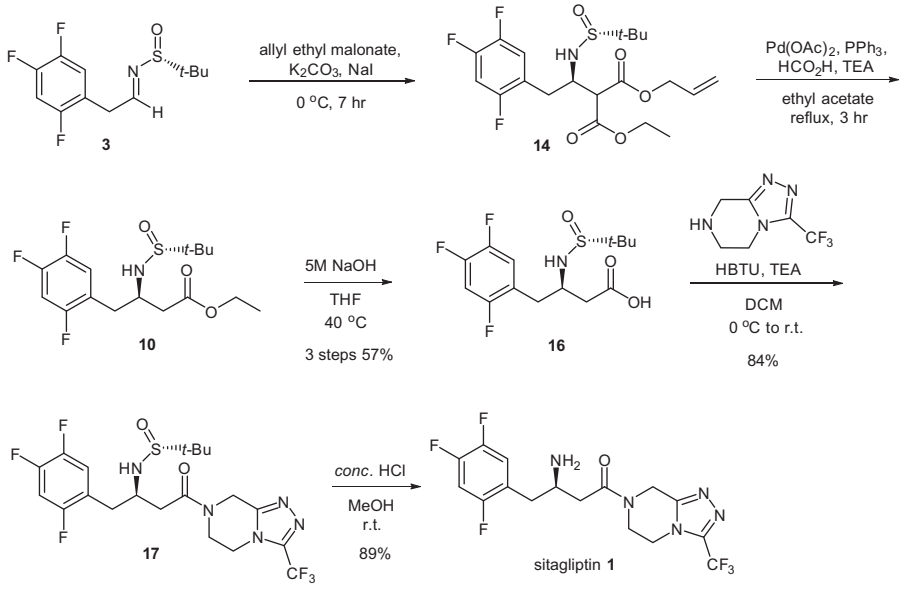
To a suspension of compound **4** (45.8 g, 262.9 mmol) in DCM (115 mL) were added (*R*)-(+)-2-methyl-2-propanesulfinamide

Table 3
Stereoselective enolate addition to sulfinyl imine **3** with allyl malonates



Entry	R^1	R^2	Time	Conversion[b]	dr[c]
1 **13**[d]	Allyl	Methyl	4	89.1	99.3:0.7
2 **14**[d]	Allyl	Ethyl	7	94.0	99.5:0.5
3 **15**	Allyl	Allyl	4	91.6	99.3:0.7

[a] Reaction conditions: **3** (1.0 equiv, 3.6 mmol), K_2CO_3 (5.0 equiv, 18.0 mmol), NaI (0.1 equiv, 0.4 mmol), 0 °C, malonates were used as solvent (5.0 equiv, 18.0 mmol).
[b] Conversion is given based on the disappearance of the starting compound by HPLC analysis.
[c] Diastereoselectivity was determined by HPLC.
[d] Compounds **13** and **14** were obtained as a 1:1 mixture of a-diastereomers.



Scheme 3. Completion of sitagliptin synthesis.

(33.4 g, 276.1 mmol), pyridinium-p-toluenesulfonic acid (3.30 g, 13.1 mmol), and anhydrous sodium sulfate (186.8 g, 1.32 mol) and then stirred for 16 h at room temperature. The completion of the reaction was confirmed by TLC. To the reaction mixture was added DCM (230 mL), after which it was filtered with Celite, and washed with DCM (90 mL × 2). The filtered DCM solution was concentrated to give compound **3** as yellow oil (70.0 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (s, 9H), 3.79 (d, 2H, J = 4.2 Hz), 6.92–6.94 (m, 1H), 6.96–6.98 (m, 1H), 8.09 (t, 1H, J = 4.3 Hz). HRMS: Calcd for $C_{12}H_{14}F_3NOS$ $[M+H]^+$ 278.0826; Found 278.0827.

4.2.2. Pre-screening results for enolate addition to sulfinimine (sulfinylimine) 3 with various esters (Table 1)

4.2.2.1. General procedure for the synthesis of compound 5, 6, 7 and 8. To a reaction flask were added ester (10.8 mmol), and THF (15.0 mL). The reaction mixture was cooled to −78 °C, and then was slowly added dropwise LHMDS (10.8 mmol) in droplet. The reaction mixture was stirred for 1 h at −78 °C. To the reaction slurry was added a solution of compound **3** (1.08 mmol) dissolved in THF (9.0 mL), and the reaction mixture was stirred for 3 h at −78 °C. Approximately 1.0 mL of the reaction sample was subjected to HPLC analysis.

HPLC methods. Kromasil C18, 4.6 mm × 250 mm (5 μm), λ = 268 nm, flow rate 1.2 mL/min, column temperature: 25 °C, mobile phase: water/acetonitrile.

Time (min)	Water (%)	Acetonitrile (%)
0	48	52
15.5	30	70
20.5	5	95
20.6	48	52
27	48	52

4.2.2.2. *tert*-Butyl-(*R*)-3-[((*R*)-*tert*-butylsulfinyl)amino]-4-(2,4,5-trifluorophenyl)butanoate 5. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (s, 9H), 1.38 (s, 9H), 2.30–2.34 (m, 2H), 2.89 (dd, 1H, J = 7.5, 6.5 Hz), 3.07 (dd, 1H, J = 8.5, 5.4 Hz), 3.74 (d, 1H, J = 8.4 Hz), 3.82–3.87 (m, 1H), 6.87 (q, 1H, J = 9.4 Hz, 6.8 Hz), 7.04 (q, 1H, J = 8.7 Hz, 7.8 Hz). HRMS: Calcd for $C_{18}H_{26}F_3NO_3S$ $[M+H]^+$ 394.1664; Found 394.1664.

4.2.2.3. Diethyl-2-{(*R*)-1-[((*R*)-*tert*-butylsulfinyl)amino]-2-(2,4,5-trifluorophenyl)ethyl}malonate 8. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.26–1.33 (m, 6H), 2.92 (d, 2H, J = 7.3 Hz), 3.89 (d, 1H, J = 3.6 Hz), 3.97–4.01 (m, 1H), 4.23–4.29 (m, 4H), 4.57 (d, 1H, J = 10.0 Hz), 6.85–6.91 (m, 1H), 7.02–7.08 (m, 1H). HRMS: Calcd for $C_{19}H_{26}F_3NO_5S$ $[M+H]^+$ 438.1562; Found 438.1563.

4.2.3. Optimization of the enolate addition reactions (Table 2)

4.2.3.1. General procedure for the synthesis of compound 8 (entries 1–4). To a reaction flask were added compound **3** (3.60 mmol), diethyl malonate (18.0 mmol), and bases (18.0 mmol) and then stirred at 40 °C. The completion of the reaction was confirmed by HPLC and TLC. The solution was cooled to room temperature, and then purified water (10 mL) was added to the reaction mixture. The slurry was extracted with ethyl acetate (10 mL) and the organic layer was vacuum distilled to afford compound **8** as a yellow oil.

4.2.3.2. General procedure for the synthesis of compound 8 (entries 5–7). To a reaction flask were added compound **3** (3.60 mmol), diethyl malonate (18.0 mmol), and K_2CO_3 (18.0 mmol) and then stirred. The completion of the reaction was confirmed using HPLC and TLC. Purified water (10 mL) was then added to the reaction mixture. The slurry was extracted with ethyl acetate (10 mL) and the organic layer was vacuum distilled to afford compound **8** as a yellow oil.

4.2.3.3. Synthesis of compound 8 (entry 8). To a reaction flask were added compound **3** (1.0 g, 3.60 mmol), diethyl malonate (2.74 mL, 18.0 mmol), and Na_2CO_3 (1.91 g, 18.0 mmol) and then stirred for 17.5 h at 0 °C. The completion of the reaction was confirmed using HPLC and TLC. The solution was allowed to return to room temperature, and then purified water (10 mL) was added to the reaction mixture. The slurry was extracted with ethyl acetate (10 mL) and the organic layer was vacuum distilled to afford compound **8** as a yellow oil.

4.2.3.4. General procedure for the synthesis of compound 8 (entries 9, 10). To a reaction flask were added compound **3** (3.60 mmol) and diethyl malonate (18.0 mmol), and then the reaction mixture was cooled to 0 °C. Base (18.0 mmol) and NaI (53.0 mg, 0.36 mmol) were added to the reaction mixture and stirred at 0 °C. The completion of the reaction was confirmed using HPLC and TLC. The solution was allowed to room temperature, and then purified water (10 mL) was added to the reaction mixture. The slurry was extracted with ethyl acetate (10 mL) and the organic layer was vacuum distilled to afford compound **8** as a yellow oil.

4.2.3.5. General procedure for the synthesis of compound 8 (entries 11, 12). To a reaction flask were added compound **3** (3.60 mmol), diethyl malonate (18.0 mmol), base (18.0 mmol), and additive (18.0 mmol) and then stirred at 0 °C. The completion of the reaction was confirmed using HPLC and TLC. The solution was allowed to room temperature, and then purified water (10 mL) was added to the reaction mixture. The slurry was extracted with ethyl acetate (10 mL) and the organic layer was vacuum distilled to afford compound **8** as a yellow oil. The HPLC method was the same as compound **8**.

4.2.4. Stereoselective enolate addition to sulfinyl imine 3 with allyl malonates (Table 3)

4.2.4.1. General procedure for the synthesis of compound 13, 14 and 15. To a reaction flask were added compound **3** (3.60 mmol) and malonates (18.0 mmol). The reaction mixture was cooled to 0 °C. Next, K_2CO_3 (18.0 mmol) and NaI (53.0 mg, 0.36 mmol) were added to the reaction mixture and then stirred at 0 °C. The completion of the reaction was confirmed using HPLC and TLC. The solution was allowed to room temperature, and then purified water (10 mL) was added to the reaction mixture. The slurry was extracted with ethyl acetate (10 mL) and the organic layer was vacuum distilled to afford the desired products **13**, **14** and **15** as yellow oil. HPLC method was the same as compound **8**.

4.2.4.2. 1-Allyl-3-methyl-{(*R*)-1-[((*R*)-*tert*-butylsulfinyl)-amino]-2-(2,4,5-trifluorophenyl)-ethyl)malonate 13. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (s, 9H), 2.88–2.91 (m, 2H), 3.77 (s, 3H), 3.89–4.02 (m, 2H), 4.50 (dd, 1H, J = 16.8, 9.9 Hz), 4.65–4.69 (m, 2H), 5.21–5.36 (m, 2H), 5.86–5.93 (m, 2H), 6.82–6.88 (m, 1H), 6.99–7.04 (m, 1H). HRMS: Calcd for $C_{19}H_{24}F_3NO_5S$ $[M+H]^+$ 436.1406; Found 436.1405. dr = 99.3:0.7.

4.2.4.3. 1-Allyl-3-ethyl-{(*R*)-1-[((*R*)-*tert*-butylsulfinyl)-amino]-2-(2,4,5-trifluorophenyl)-ethyl}malonate 14. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (s, 9H), 1.31–1.36 (m, 3H), 2.96 (d, 2H, J = 7.2 Hz), 3.97–4.04 (m, 2H), 4.30–4.31 (m, 2H), 4.59 (t, 1H, J = 9.4 Hz), 4.74 (t, 2H, J = 6.0 Hz), 5.31 (t, 1H, J = 10.9 Hz), 5.41 (dd, 1H, J = 9.6, 7.6 Hz), 5.93–5.99 (m, 1H), 6.88–6.94 (m, 1H), 7.05–7.11 (m, 1H). ^{13}C NMR (175 MHz, $CDCl_3$): δ 167.8, 156.8, 155.4, 156.8, 155.4, 149.5, 148.1, 147.2, 145.8, 131.3, 121.6, 119.2, 119.0, 105.4, 66.5, 66.2, 62.1, 61.8, 62.1, 61.8, 60.3, 57.3, 56.1, 55.7, 32.6, 28.0, 22.3, 13.9. HRMS: Calcd for $C_{20}H_{26}F_3NO_5S$ $[M+H]^+$ 450.1562; Found 450.1562. dr = 99.5:0.5.

4.2.4.4. Diallyl-{(*R*)-1-[((*R*)-*tert*-butylsulfinyl)amino]-2-(2,4,5-trifluorophenyl)ethyl}malonate 15. ^{1}H NMR (400 MHz, $CDCl_3$,) : δ 1.06 (s, 9H), 2.93 (d, 2H, J = 7.5 Hz), 3.99–4.04 (m, 2H), 4.52 (d, 1H, J = 9.8 Hz), 4.69–4.72 (m, 4H), 5.25–5.38 (m, 4H), 5.89–5.94 (m, 2H), 6.85–6.91 (m, 1H), 7.01–7.08 (m, 1H). HRMS: Calcd for $C_{21}H_{26}F_3NO_5S$ $[M+H]^+$ 462.1562; Found 462.1561. dr = 99.3:0.7.

4.2.5. Completion of sitagliptin synthesis (Scheme 3)

4.2.5.1. Ethyl-(*R*)-3-[((*R*)-*tert*-butylsulfinyl)amino]-4-(2,4,5-trifluorophenyl)butanoate 10. To a reaction flask were added compound **14** (113.5 g, 252.4 mmol), palladium acetate (0.23 g, 1.01 mmol), triphenyl phosphine (1.06 g, 4.04 mmol), and ethyl acetate (230 mL). The reaction slurry was stirred until it dissolved clearly at room temperature. To the reaction mixture were added formic acid (11.9 mL, 315 mmol) and triethylamine (45.7 mL, 328 mmol), and then stirred for 3 h at reflux. The completion of the reaction was confirmed using HPLC. The reaction mixture was cooled to room temperature. Subsequently, a 2 M HCl solution (120 mL) was slowly added to the reaction mixture, and then stirred for 5 min. The slurry was extracted with ethyl acetate (565 mL). The organic layer was washed with 20% NaCl solution (565 mL), 5% $NaHCO_3$ solution (565 mL), and 5% NaCl solution (565 mL). Vacuum distillation of the organic layer afforded compound **10** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.08 (s, 9H), 1.27 (t, 3H, J = 7.1 Hz), 2.62–2.92 (m, 4H), 3.74–3.78 (m, 1H), 4.14 (q, 2H, J = 6.1 Hz), 4.25 (d, 1H, J = 8.9 Hz), 6.86–6.92 (m, 1H), 7.00–7.07 (m, 1H). ^{13}C NMR (175 MHz, $CDCl_3$): δ 171.6, 170.7, 169.8, 156.8, 155.4, 149.5, 148.1, 147.2, 145.8, 121.6, 119.2, 106.0, 61.6, 60.9, 59.2, 56.0, 54.3, 49.0, 39.8, 34.9, 34.4, 31.2, 28.1, 22.4, 14.3. HRMS: Calcd for $C_{16}H_{22}F_3NO_3S$ $[M+H]^+$ 366.1351; Found 366.1353. dr = 99.4:0.6.

HPLC methods. Kromasil C_{18}, 4.6 mm × 250 mm (5 μm), λ = 268 nm, flow rate 1.0 mL/min, column temperature: 40 °C, mobile phase: buffer/acetonitrile (buffer: 0.1% $HClO_4$ aqueous solution).

4.2.5.2. (*R*)-3-[((*R*)-*tert*-Butylsulfinyl)amino]-4-(2,4,5-trifluorophenyl)butanoic acid 16. To a reaction flask were added compound **10** (92.2 g, 252.4 mmol), 5 M-NaOH solution (126 mL), and THF (370 mL), and then stirred for 2 h at 40 °C. The completion of the reaction was confirmed using HPLC. The reaction mixture

Time (min)	Buffer (%)	Acetonitrile (%)
0	60	40
10	25	75
12.5	25	75
15	60	40

was cooled to room temperature, after which were added water (370 mL) and *n*-hexane (370 mL) to the solution. The aqueous layer was separated (the organic layer was discarded) and washed with ethyl acetate/hexane solution (1:1, 370 mL). The aqueous solution was adjusted to pH 5.0 with a 2 M HCl solution, and stirred for 2 h at room temperature and then for 1 h at 0 °C. The solid precipitate was filtered, washed with purified water (90 mL), and then dried to give compound **16** as a white solid (48.4 g, 57% for 3 steps). Mp. 117.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (s, 9H), 2.55 (dd, 1H, J = 12.1, 4.9 Hz), 2.83–2.89 (m, 2H), 3.02–3.08 (m, 1H), 3.77 (br, 1H), 5.01 (d, 1H, J = 7.6 Hz), 6.88–6.95 (m, 1H), 7.03–7.09 (m, 1H). ^{13}C NMR (175 MHz, $CDCl_3$): δ 173.4, 156.9 149.5, 147.3, 121.7, 119.3, 56.8, 55.0, 39.0, 34.4, 22.6. HRMS: Calcd for $C_{14}H_{18}F_3NO_3S$ $[M+H]^+$ 338.1038; Found 338.1038. dr = 99.8: 0.2. HPLC method was the same as compound **10**.

4.2.5.3. (*R*)-2-Methyl-*N*-((*R*)-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-yl)propane-2-sulfinamide 17. To a suspension of compound **16** (48.0 g, 142.3 mmol) in DCM (960 mL) were added HBTU (56.6 g, 149.4 mmol), piperazine (34.0 g, 149.4 mmol), and TEA (60.0 mL, 426.0 mmol) at 0 °C. The reaction mixture was allowed to return to room temperature, and stirred for 2 h. The completion of the reaction was confirmed using HPLC. To the reaction mixture was added purified water (960 mL) and then stirred for 20 min. The organic layer was separated and washed with purified water (960 mL). The organic solution was washed with a solution of 0.5% $NaHCO_3$ (960 mL), 0.2 M HCl (960 mL), and purified water (960 mL) and combined using a rotary evaporator. The residue was dissolved with ethyl acetate (480 mL) at reflux. The clear solution was cooled to room temperature, and stirred for 12H, and then stirred for 2 h at 0 °C. The solid precipitate was filtered, and then dried to afford compound **17** as a white solid (61.1 g, 84.0%). Mp 189.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (s, 9H), 2.73–3.02 (m, 4H), 3.84–4.26 (m, 5H), 4.45 (d, 1H, J = 10.4 Hz), 4.91–5.13 (m, 2H), 6.86–6.88 (m, 1H), 7.01–7.08 (m, 1H). ^{13}C NMR (175 MHz, $CDCl_3$): δ 171.5, 170.2, 169.7, 156.8, 155.4, 150.2, 149.6, 148.0, 147.3, 145.9, 143.9, 143.6, 121.8, 120.5, 119.2, 119.1, 119.0, 118.9, 117.4, 115.9, 110.4, 105.4, 64.4, 56.1, 50.0, 55.2, 55.1, 49.0, 43.5, 43.2, 42.5, 41.7, 41.2, 39.1, 38.4, 38.0, 34.7, 22.4. HRMS: Calcd for $C_{20}H_{23}F_6N_5O_2S$ $[M+H]^+$ 512.1555; Found 512.1555. HPLC purity: 99.60%. dr = 99.6:0.4. HPLC method was the same as compound **10**.

4.2.5.4. 7-[(3*R*)-3-Amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-[3-(trifluoromethyl)-1,2,4-triazolo[4,3-*a*] pyrazine 1 (sitagliptin). To a suspension of compound **17** (59.4 g, 116.1 mmol) in methanol (900 mL) was added *conc.* HCl (40 mL) at room temperature for 4 h. The completion of the reaction was confirmed using HPLC. The reaction mixture was vacuum distilled, and then DCM (594 mL) and water (594 mL) were added to the reaction residue. The aqueous layer was separated, and then basified to pH 9.0 with 5 M-NaOH solution. To the solution was added DCM (594 mL), and the organic layer was separated, combined. The residue was dissolved with IPA (180 mL) at 60 °C, and then cooled to room temperature. The solution was stirred for 12 h at room temperature. To the solution was added *n*-hexane (1,200 mL), and stirred for 2 h at room temperature. The solid precipitate was filtered, and then dried to afford compound **1** (sitagliptin) as a white solid (42.1 g, 89.0%). Mp 117.4 °C; $[\alpha]_D^{20} = -22.7$ (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.40–2.56 (m, 2H), 2.64–2.69 (m, 1H), 2.76–2.81 (m, 1H), 3.57 (m, 1H), 3.94–4.21 (m, 4H), 4.92–5.12 (m, 2H), 6.88–6.94 (m, 1H), 7.03–7.09 (m, 1H). ^{13}C NMR (175 MHz, $CDCl_3$): δ 170.5 (major), 170.1 (minor), 156.8 (ddd, J_{C-F} = 243.9, 9.1, 2.1 Hz) 150.3, 149.5 (dt, J_{C-F} = 250.0, 13.0, 13.0 Hz), 146.0 (dd, J_{C-F} = 244.8, 12.2 Hz), 143.7 (q, major, J_{C-F} = 80.2, 40.1 Hz), 143.6 (q, minor, J_{C-F} = 40.1 Hz), 121.6 (d, major, J_{C-F} = 15.5 Hz), 120.6 (d, minor, J_{C-F} = 15.5 Hz), 119.0 (dd, J_{C-F} = 18.8, 5.8 Hz), 117.4 (d, minor), 116.5 (d, major), 105.7 (dd, J_{C-F} = 28.7, 20.6 Hz), 48.5, 43.5 (s, minor), 43.2 (s, major), 42.4 (s, major), 41.6 (s, minor), 40.0, 39.1, 37.99, 36.1. HRMS: Calcd for $C_{16}H_{15}F_6N_5O$ $[M+H]^+$ 408.1259; Found 408.1257. HPLC purity: 99.76%. Enantiomeric sitagliptin: not detected.

HPLC methods (purity). YMC ODS-AM, 4.6 mm × 250 mm (5 μm), λ = 215 nm, flow rate 1.0 mL/min, column temperature: 30 °C, mobile phase: buffer/acetonitrile (buffer: 0.2% H_3PO_4 aqueous solution).

Time (min)	Buffer (%)	Acetonitrile (%)
0	85	15
5	85	15
15	65	35
25	25	75
30	25	75
32	85	15
45	85	15

HPLC methods (enantiomeric purity). Chiralpak IC, 4.6 mm × 250 mm (5 μm), λ = 268 nm, flow rate 1.0 mL/min, column temperature: 25 °C, mobile phase: buffer (*n*-hexane: isopropyl alcohol: ethanol: diethylamine = 70:10:20:0.1).

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