A highly stereoselective and efficient synthesis of enantiomerically pure sitagliptin

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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, as shown by the representative drugs in Figure 1. Especially, amino acid motifs containing fluorine are of particular interest and medicinal potential in pharmaceutical industry. The representative fluorinated β-amino acid derivative is sitagliptin, which has been approved for the treatment of type 2 diabetes.

Sitagliptin inhibits the activity of dipeptidyl peptidase IV (DPP-4) that breaks down incretins, 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 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 sulfynilimine in more than 99:1 dr. Our synthetic procedure proved to be highly efficient, economical, and sustainable.

2. Results and discussion

We first explored the reactivity of various esters for the enolate addition to sulfynil imine 3, which was obtained from commercially available 4. The experimental investigation for the enolate addition to (R)-tert-butanesulfonamide 3 is summarized in Table 1. Meldrum’s acid 6 and menthyl ester 7 gave poor
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 NaHCO3 and KHCO3.

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 (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

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### Table 1

<table>
<thead>
<tr>
<th>R¹</th>
<th>Conversion</th>
<th>R²</th>
<th>Conditions</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>88.0%</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Trace</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Trace</td>
<td>96.4%</td>
<td></td>
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</table>

* 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.
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.

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

1H NMR spectra and 13C 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 CDCl3. NMR chemical shifts are reported in ppm referenced to the solvent peaks of CDCl3 (7.26 ppm for 1H and 77.0 ppm for 13C, 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) ethyldiene]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-propanesulfonamide...
Table 3
Stereoselective enolate addition to sulfinyl imine 3 with allyl malonates

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Time</th>
<th>Conversion&lt;sup&gt;a&lt;/sup&gt;</th>
<th>d&lt;sup&gt;′&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1.13&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Allyl</td>
<td>Methyl</td>
<td>4</td>
<td>89.1</td>
<td>99.3:0.7</td>
</tr>
<tr>
<td>2.14&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Allyl</td>
<td>Ethyl</td>
<td>7</td>
<td>94.0</td>
<td>99.5:0.5</td>
</tr>
<tr>
<td>3.15</td>
<td>Allyl</td>
<td>Allyl</td>
<td>4</td>
<td>91.6</td>
<td>99.3:0.7</td>
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</table>

<sup>a</sup> Reaction conditions: 3 (1.0 equiv, 3.6 mmol), K<sub>2</sub>CO<sub>3</sub> (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).

<sup>b</sup> Conversion is given based on the disappearance of the starting compound by HPLC analysis.

<sup>c</sup> Diastereoselectivity was determined by HPLC.

<sup>d</sup> Compounds 13 and 14 were obtained as a 1:1 mixture of α-diastereomers.

4.2.2.2. tert-Butyl-[(R)-3-[[[(R)-tert-butylsulfinyl]amino]-4-(2,4,5-trifluorophenyl)butanoate 5.](https://en.wikipedia.org/wiki/) 1H NMR (400 MHz, CDCl<sub>3</sub>): 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 = 6.5, 3.4 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<sub>18</sub>H<sub>20</sub>F<sub>3</sub>NO<sub>3</sub>S [M+H]<sup>+</sup> 394.1664; Found 394.1664.

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). The filtered DCM solution was concentrated to give compound 3 as yellow oil (70.0 g, 96%). 1H NMR (400 MHz, CDCl<sub>3</sub>): 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<sub>12</sub>H<sub>14</sub>F<sub>3</sub>NOS [M+H]<sup>+</sup> 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 0 °C, and then was slowly added dropwise LHMDS (10.8 mmol) in droplet. The reaction mixture was stirred for 1 h at 0 °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.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Water (%)</th>
<th>Acetonitrile (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>15.5</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>20.5</td>
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<td>95</td>
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<tr>
<td>20.6</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>27</td>
<td>48</td>
<td>52</td>
</tr>
</tbody>
</table>
4.2.3.2. 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 Na2CO3 (1.91 g, 18.0 mmol) and then stirred for 24 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.

4.2.3.3. 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 Na2CO3 (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 K2CO3 (0.36 mmol) were added to the reaction mixture and stirred for 17.5 h at 0 °C. The completion of the reaction was confirmed using HPLC. The reaction mixture was cooled to 0 °C, 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 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 the desired products 13, 14 and 15 as yellow oil. HPLC method was the same as compound 8.

4.2.4.3. 1-Allyl-3-ethyl-[[([R]-1)-[[([R]-tert-butylsulfinyl)amino]-2-(2,4,5-trifluorophenyl)-ethyl)malonate 13. 1H NMR (400 MHz, CDCl3): 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), 4.50 (t, 1H, J = 9.4 Hz), 4.74 (t, 1H, 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). 13C NMR (175 MHz, CDCl3): δ 167.8, 156.8, 155.4, 156.8, 149.5, 148.1, 147.2, 145.8, 131.3, 121.6, 119.2, 119.0, 105.0, 66.5, 66.2, 62.1, 61.8, 61.8, 60.3, 57.3, 56.1, 55.7, 32.6, 28.0, 22.3, 13.9. HRMS: Calcd for C19H26F3NO5S [M+H]+ 438.1562; Found 438.1563.

4.2.5. Completion of sitagliptin synthesis (Scheme 3)

4.2.5.1. Ethyl-[[([R]-3)-[[([R]-tert-butylsulfinyl)amino]-2-(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 completely 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% NaHCO3 solution (565 mL), and 5% NaCl solution (565 mL). Vacuum distillation of the organic layer afforded compound 10 as a yellow oil. 1H NMR (400 MHz, CDCl3): 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). 13C NMR (175 MHz, CDCl3): δ 171.6, 170.7, 169.8, 156.8, 149.5, 148.1, 147.2, 145.8, 121.6, 119.2, 106.0, 106.1, 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 C16H24F3NO5S [M]+ 366.1351; Found 366.1353. dr = 99.5:0.5.

4.2.5.2. Diallyl-[[([R]-1)-[[([R]-tert-butylsulfinyl)amino]-2-(2,4,5-trifluorophenyl)ethyl]malonate 14. 1H NMR (400 MHz, CDCl3): 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 C20H26F3NO5S [M+H]+ 450.1682; Found 450.1682. dr = 99:3.7.

4.2.5.3. 1-Allyl-3-ethyl-[[([R]-1)-[[([R]-tert-butylsulfinyl)amino]-2-(2,4,5-trifluorophenyl)ethyl]malonate 15. 1H NMR (400 MHz, CDCl3): 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). 13C NMR (175 MHz, CDCl3): δ 171.6, 170.7, 169.8, 156.8, 149.5, 148.1, 147.2, 145.8, 121.6, 119.2, 106.0, 106.1, 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 C16H24F3NO5S [M]+ 366.1351; Found 366.1353. dr = 99.4:0.6.

HPLC methods. Kromasil C18, 4.6 mm × 250 mm (5 μm), i = 268 nm, flow rate 1.0 mL/min, column temperature: 40 °C, mobile phase: buffer/acetonitrile (buffer: 0.1% HClO4 aqueous solution).
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). The aqueous solution was adjusted to pH 5.0 with a 2 M HCl solution, and stirred for 2 h at room temperature. The completion of the reaction was confirmed using HPLC. The reaction mixture was basified to pH 9.0 with 5 M NaOH solution. 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 (421.1 g, 89.0%).

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/acetoneitrile (buffer: 0.2% H3PO4 aqueous solution).

HPLC methods (enantioselectivity). Chiralpak IC, 4.6 mm × 250 mm (5 μm), λ = 286 nm, flow rate 1.0 mL/min, column temperature: 25 °C, mobile phase: buffer (n-hexane:isopropyl alcohol:ethanol:diethylamine = 70:10:20:1).

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References


29. When ($\text{S}$,$\text{S}$)-($\text{R}$,$\text{S}$)-tert-butanesulfinamide was used as the chiral auxiliary, the enantiomer of compound 8 was the major product.