STEREOSELECTIVE SYNTHESIS OF MELATONIN RECEPTOR AGONIST RAMELTEON VIA ASYMMETRIC MICHAEL ADDITION

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Abstract – Highly enantioselective asymmetric Michael addition was used to synthesize ramelteon and its analogue. The asymmetric strategy provides an efficient approach for the medicinal modification of ramelteon with high ee value.

INTRODUCTION

Ramelteon (1, Rozerem), developed by Takeda Pharmaceuticals North America, is the first selective agonist for the melatonin MT₁/MT₂ receptors in the suprachiasmatic nucleus (SCN) for the treatment of circadian rhythm sleep disorders.¹ In contrast to other FDA-approved drugs for this disease, it has shown no risk of drug dependence and abuse because it has negligible affinity for the MT3 receptors.² Ramelteon has a unique chemical scaffold containing a furan-fused tricyclic ring and an asymmetric center. To date, many ramelteon derivatives have been investigated, such as tricyclic indan derivatives³ and 7-substituted 1,6-dihydro-2H-indeno[5,4-b]furan derivativs.⁴ However, the structure activity relationship (SAR) of 6- and 7-positions is still unclear comparing with those of the dihydrofuran ring. Currently, all reported total synthesis of ramelteon mainly involved catalytic asymmetric hydrogenation⁵ or chiral resolution⁶ of the corresponding racemic mixtures, which have unavoidable defects such as expensive metal and phosphorus ligands, complicated procedures, low ee value and low yield. Moreover, it is very difficult to synthesize 6- or/and 7-substituted derivatives with multi-chiral centers through present known methods. Therefore, it is necessary to find an efficient approach for the medicinal modification of ramelteon with high ee value. Recently, we have reported an efficient synthesis for a tricyclic intermediate 1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one,⁷ which has been successfully applied to the industrial production. From a medicinal chemistry point of view, a new synthetic approach
of ramelteon was presented herein based on our previous exploration.

\[
\text{ramelteon (1)}
\]

RESULTS AND DISCUSSION

Compound 2 (Figure 1) was an important ramelteon derivative with good biological profiles and always served as a standard compound for evaluating other ramelteon derivatives.\(^3\) As an advanced intermediate of ramelteon, it was thus chosen to verify the feasibility of the synthetic design first.

![Figure 1. Retrosynthesis of compound 2](image)

According to Hayashi’s work,\(^8\) the rhodium-catalyzed asymmetric 1,4-addition of \(\alpha,\beta\)-unsaturated ester (5) and organometallic reagent (6) to form carbon-carbon bond was initially tried (Figure 2). Unfortunately, this approach was abolished because addition product 4 turned out to be almost completely racemic in a 70\% yield.

In recent decades, asymmetric Michael addition has been developed as an efficient methodology for the construction of chiral carbon-carbon bond. Since recyclable chiral auxiliaries were employed, this approach was believed to be more economical and eco-friendly than other traditional methods, which intrigued us to utilize this method\(^9,10\) in our new synthetic design. Jørgensen reported that organocatalytic
enantioselective conjugate addition of malonate to an aromatic \( \alpha,\beta \)-unsaturated aldehyde afforded addition product in good yield and very good to excellent enantioselectivity.\(^9\) Therefore, \( \alpha,\beta \)-unsaturated aldehyde 10\(^{11}\) was subjected to asymmetric Michael addition (Figure 2). To obtain optimal yield and \( ee \) value, different reaction conditions were carefully investigated as displayed in table 1. Compared with dimethyl malonate (11), diethyl malonate decreased the reaction efficiency probably because of its steric effects (entries 1 and 2). Maintaining molar the ratio of 10 to dimethyl malonate as 2 : 1 has a positive impact on the reaction yield (entries 1, 3 and 4). Temperature and percent of catalyst were also essential in this step (entries 1, 5, 6 and 7). Finally, the optimal condition was found in entry 7, which afforded addition product 12 in a good yield (94%) and high enantioselectivity (96% \( ee \)).

Table 1. Optimization of Michael addition

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>n (equiv)</th>
<th>Temp.</th>
<th>catalyst (mol%)</th>
<th>yield (%)(^{[a]})</th>
<th>( ee ) (%)(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>2</td>
<td>0-5 °C, 12h</td>
<td>10</td>
<td>88</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>2</td>
<td>0-5 °C, 12h</td>
<td>10</td>
<td>&lt; 30</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>0.9</td>
<td>0-5 °C, 12h</td>
<td>10</td>
<td>44</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>0.5</td>
<td>0-5 °C, 12h</td>
<td>10</td>
<td>&lt; 30</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>2</td>
<td>rt, 12h</td>
<td>10</td>
<td>74</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>2</td>
<td>&lt; -5 °C, 12h</td>
<td>10</td>
<td>&lt; 30</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>2</td>
<td>0-5 °C, 48h</td>
<td>20</td>
<td>94</td>
<td>96</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Isolated yield;
\(^{[b]}\) The enantiomeric excess was determined by HPLC after conversion to the corresponding lactone.\(^9\)

Subsequently, compound 12 was oxidized with NaClO\(_2\) to afford chiral acid 8, which was subjected to Friedel-Crafts acylation to give 3-subsituted indanone 13 (scheme 1). Hydrogenation of compound 13 gave pure compound 14, which was decarboxylated in mesitylene at 160 °C to afford compound 7. After reduction with LiAlH\(_4\), indanol 15 was obtained in a 92% yield. Gabriel reaction of compound 15 followed by acylation in the presence of propionic anhydride furnished final compound 2 in a satisfactory yield of 64% and an excellent \( ee \) value of above 99%.
With the expeditious methodology in hand, our endeavor continued toward the total synthesis of ramelteon (1). As shown in scheme 2, compound 17 was chosen as starting material, and was converted to \( \alpha,\beta \)-unsaturated aldehyde 18 according to Cacchi’s method. Based on the aforementioned result, chiral aldehyde 19 was obtained with a good yield (80%) and high enantioselectivity (92% ee) in the presence of catalyst 9. Subsequent oxidation of compound 19 with NaClO2 gave chiral acid 20 in an 89% yield. Treatment compound 20 with thionyl chloride followed by a Lewis acid-promoted cyclization afforded indanone 21. Hydrogenation of compound 21 gave compound 22, which was subjected to hydrolysis and decarboxylation to afford known compound 23. Chiral amine 25 was obtained after amidation and reduction. Finally, ramelteon (1) was prepared with 92% enantiomeric ratios from compound 25 in the presence of propionic anhydride.

**Scheme 1.** Reagents and condition: a) 11, catalyst 9, EtOH; b) NaClO2, NaH2PO4, 2-methyl-2-butene, \( t \)-BuOH, H2O; c) SOCl2, toluene, SnCl4, DCM; d) Pd/C, H2, EtOH; e) NaOH (aq), EtOH, mesitylene; f) LiAlH4, THF; g) MsCl, Et3N, CH2Cl2, phthalimide potassium salt, DMF; h) hydrazine hydrate, EtOH; i) propionic anhydride, NaOH (aq), THF.

**Scheme 2.** Reagents and condition: a) 1,1-diethoxy-2-propene, Pd(OAc)2, \( n \)-Bu4NOAc, KCl, K2CO3, DMF; b) 11, catalyst 9, EtOH; c) NaClO2, NaH2PO4, 2-methyl-2-butene, \( t \)-BuOH, H2O; d) SOCl2, toluene, AlCl3, CH2Cl2; e) Pd/C, H2, MeOH; f) NaOH, H2O, MeOH; mesitylene; g) SOCl2, toluene, NH3, CH2Cl2; h) LiAlH4, THF; i) propionic anhydride, Et3N, CH2Cl2.
CONCLUSIONS
In summary, we have developed a new approach to synthesize ramelteon (1) and its analogue with high efficiency and enantioselectivity via asymmetric Michael addition. Furthermore, the achieved methodology will be valuable for medicinal modification of ramelteons with high ee value in the future drug discovery.

EXPERIMENTAL
General methods.
Melting points were taken on a Fisher-Johns melting point apparatus, uncorrected and reported in degrees Centigrade. $^1$H NMR spectra and $^{13}$C NMR were recorded in CDCl$_3$ and C$_2$D$_6$SO on Bruker DRX-500 (500 MHz) using TMS as internal standard. Chemical shifts were reported as $\delta$ (ppm) and spin-spin coupling constants as $J$ (Hz) values. The mass spectra (MS) were recorded on a Finnigan MAT-95 mass spectrometer.

$(S)$-Dimethyl 2-(1-(3-methoxyphenyl)-3-oxopropyl)malonate (12).
Compound 10 (3.7 g, 23 mmol) and amino catalyst 9 (760 mg, 2.3 mmol) were stirred in EtOH (50 mL) at 0 °C for 30 min, then compound 11 (1.55 g, 11.7 mmol) was added dropwise. The mixture was stirred at 0 °C for 48 h. The reaction mixture was extracted with EtOAc, washed with 1N HCl and brine. Concentration in vacuo gave crude product, which was purified by column chromatography (EtOAc : petroleum ether = 1:5) to give pure 12 as a pale yellow liquid (3.2 g, 94%). $[\alpha]_{20}^{D}$ +32.0 (c 1.0, acetone); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.89-2.94 (m, 2H), 3.54 (s, 3H), 3.74-3.76 (m, 4H), 3.79 (s, 3H), 3.97-4.03 (m, 1H), 6.76 - 6.83 (m, 3H), 7.22 (t, $J = 7.8$ Hz, 1H), 9.60 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 199.9, 168.2, 167.7, 159.6, 141.3, 129.7, 120.0, 113.8, 112.6, 57.1, 55.1, 52.6, 52.4, 47.0, 39.4; HRMS (EI): m/z calcd for C$_{15}$H$_{18}$O$_6$ (M) $^+$: 294.1103, found: m/z = 294.1108. The enantiomeric excess of 12 was determined by HPLC as > 96% after conversion to the corresponding lactone. [column, CHIRALPAK OD-H (4.6mm × 250mm), room temperature; eluent, 2-propanol/ hexane 20/80; flow rate, 1.0 mL/min; $t_R$ of (S)-12, 27.2 min; $t_R$ of (R)-12 (enantiomer of (S)-12), 43.7 min, detection at 214 nm].

$(S)$-5-Methoxy-4-(methoxycarbonyl)-3-(3-methoxyphenyl)-5-oxopentanoic acid (8).
A solution of compound 12 (2.2 g, 7.6 mmol), sodium chlorite (2.4 g, 26 mmol) and sodium hydrogen phosphate (2.4 g, 20 mmol) in 2-methyl-2-buten (14 mL), $t$-BuOH (60 mL) and water (24 mL) was stirred at room temperature for 1.5 h. The mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na$_2$SO$_4$, and evaporated to dryness to give a white solid, which was crystallized from EtOAc-petroleum ether to afford 2.1 g (88%) of 8 as a white solid. $[\alpha]_{D}^{20}$ +8.0 (c 1.0, acetone); mp 110–112 ºC; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.79 (dd, $J = 16.4, 9.4$ Hz, 1H), 2.89 (dd, $J = 16.4, 4.8$ Hz,
1H), 3.52 (s, 3H), 3.72 (s, 3H), 3.74-3.77 (m, 4H), 3.85-3.89 (m, 1H), 6.75-6.77 (m, 2H), 6.80 (d, J = 7.8 Hz, 1H), 7.19 (t, J = 7.8 Hz, 1H). 13C NMR (100 MHz, CDCl3) δ 176.0, 168.3, 167.8, 159.6, 141.2, 129.6, 120.1, 113.8, 112.8, 56.9, 55.1, 52.7, 52.5, 41.0, 37.9; HRMS (EI): m/z calcd for C15H18O7 (M)+: 310.1053, found: m/z = 310.1045.

(S)-Dimethyl 2-(6-methoxy-3-oxo-2,3-dihydro-1H-inden-1-yl)malonate (13).

Thionyl chloride (1.86 g, 15.6 mmol) was dropped into a solution of compound 8 (1.62 g, 5.2 mmol) in CH2Cl2 (30 mL). The mixture was stirred at room temperature for 6 h. Solvent and thionyl chloride were removed under reduced pressure. Another CH2Cl2 (45 mL) was added into the flask. It was cooled to -25 ºC, then SnCl4 (2.1 mL, 18.3 mmol) was slowly dropped in. After stirred at this temperature for 12 h, it was poured into saturated aqueous NH4Cl. The solution was extracted with CH2Cl2, washed with brine, dried over anhydrous Na2SO4. Concentration in vacuo gave crude product, which was further purified by column chromatography (EtOAc : petroleum ether = 1:5) to give pure 13 as a colorless oil (0.78 g, 51%). [α]D20 -37.3 (c 1.0, acetone); 1H NMR (500 MHz, CDCl3) δ 2.72 (dd, J = 18.9, 3 Hz, 1H), 2.93 (dd, J = 18.9, 8 Hz, 1H), 3.65 (s, 3H), 3.77 (s, 3H), 3.82 (d, J = 6.7 Hz, 1H), 3.87 (s, 3H), 4.05-4.08 (m, 1H), 6.91 (s, 1H), 6.94 (d, J = 9.8 Hz, 1H), 7.69 (d, J = 8.5 Hz, 1H). 13C NMR (100 MHz, CDCl3): 202.6, 168.5, 167.9, 165.2, 156.5, 130.6, 125.4, 115.8, 109.5, 55.6, 55.4, 52.7, 52.6, 41.3, 37.4; HRMS (EI): m/z calcd for C15H16O6 (M)+: 292.0947, found: m/z = 292.0951.

(S)-Dimethyl 2-(6-methoxy-2,3-dihydro-1H-inden-1-yl)malonate (14).

A mixture of compound 13 (0.78 g, 2.67 mmol) and 10% Pd/C (78 mg) in EtOH (30 mL) was hydrogenated at room temperature for 13 h. The catalyst was then filtered off and the filtrate was evaporated to dryness to give 14 as a colorless oil (0.75 g, 99%). [α]D20 -18.6 (c 1.0, acetone); 1H NMR (500 MHz, CDCl3) δ 1.95-1.99 (m, 1H), 2.30-2.34 (m, 1H), 2.78-2.90 (m, 2H), 3.59 (d, J = 9.2 Hz, 1H), 3.72 (s, 3H), 3.74 (s, 3H), 3.76 (s, 3H), 3.85-3.87 (m, 1H), 6.6-6.74 (m, 3H), 7.10 (d, J = 8.2 Hz, 1H). 13C NMR (100 MHz, CDCl3): 202.6, 168.5, 167.9, 165.2, 156.5, 130.6, 125.4, 115.8, 109.5, 55.6, 55.4, 52.7, 52.6, 41.3, 37.4; HRMS (EI): m/z calcd for C15H18O6 (M)+: 292.0947, found: m/z = 292.0951.

(S)-2-(6-Methoxy-2,3-dihydro-1H-inden-1-yl)acetic acid (7).

Compound 14 (0.52 g, 1.9 mmol) was dissolved in EtOH (10 mL), then NaOH (0.37 g, 9.3 mmol) in water (10 mL) was added into the flask. The solution was refluxed for 3 h. After cooling to room temperature, it was treated with 1N HCl (15 mL) and extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous Na2SO4, and evaporated to dryness to give a yellow solid (0.49 g). This solid was dissolved in mesitylene (15 mL) and heated to 160 ºC for 1 h under nitrogen atmosphere. It was cooled to room temperature and treated with 5 mL 1N NaOH solution. The aqueous phase was acidified with 1N HCl and extracted with EtOAc, washed with brine, dried over anhydrous
Na$_2$SO$_4$. Concentration in vacuo gave crude product, which was recrystallized in a mixture of EtOAc and petroleum ether to afford pure 7 as white crystal (0.27 g, 70%). \([\alpha]^{20}_D -15.5\) (c 1.0, acetone); mp 80–82 °C, ¹H NMR (500 MHz, CDCl$_3$) δ 1.78-1.82 (m, 1H), 2.43-2.52 (m, 2H), 2.80-2.89 (m, 3H), 3.56-3.58 (m, 1H), 3.79 (s, 3H), 6.73-6.77 (m, 2H), 7.13 (d, \(J = 8.2\) Hz, 1H). ¹³C NMR (100 MHz, CDCl$_3$) δ 177.9, 158.8, 146.9, 135.8, 125.1, 112.6, 109.2, 55.5, 41.3, 39.4, 32.9, 30.3; HRMS (EI): m/z calcd for C$_{12}$H$_{14}$O$_3$ (M)$^+$: 206.0943, found: m/z = 206.0948.

(S)-2-(6-Methoxy-2,3-dihydro-1H-inden-1-yl)EtOH (15).

LiAlH$_4$ (0.11 g, 2.8 mmol) was added into a solution of compound 7 (0.29 g, 1.4 mmol) in THF (10 mL) at 0 °C. The mixture was stirred at room temperature for 5 h, then EtOAc (1 mL) was added to quench the reaction. After stirring for 10 min, the mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na$_2$SO$_4$. Concentration in vacuo afforded pure 15 (0.25 g, 92%) as a colorless oil. \([\alpha]^{20}_D -15.0\) (c 1.0, CHCl$_3$); ¹H NMR (500 MHz, CDCl$_3$) δ 1.38 (s, 1H), 1.68-1.74 (m, 2H), 2.11-2.18 (m, 1H), 2.31-2.35 (m, 1H), 2.74-2.89 (m, 2H), 3.20-3.24 (m, 1H), 3.78-3.83 (m, 5H), 6.70-6.77 (m, 2H), 7.11 (d, \(J = 8.2\) Hz, 1H). ¹³C NMR (100 MHz, CDCl$_3$) δ 158.7, 148.6, 135.8, 124.9, 112.1, 109.3, 61.5, 55.4, 41.7, 37.8, 32.7, 30.6; HRMS (EI): m/z calcd for C$_{12}$H$_{16}$O$_2$ (M)$^+$: 192.1150, found: m/z = 192.1153.

(S)-2-(2-(6-Methoxy-2,3-dihydro-1H-inden-1-yl)ethyl)isoindoline-1,3-dione (16).

Mesyl chloride (0.11 mL, 1.35 mmol) and Et$_3$N (0.19 mL, 1.35 mmol) was added to a solution of compound 15 (0.20 g, 1.04 mmol) in anhydrous CH$_2$Cl$_2$ (30 mL) at room temperature. After stirring for 1 h, saturated sodium bicarbonate solution (10 mL) was added in. The solution was extracted with CH$_2$Cl$_2$, washed with brine, dried over anhydrous Na$_2$SO$_4$, and evaporated to dryness to give a yellow liquid, which was dissolved in DMF (8.0 mL). Then phthalimide potassium salt (0.21 mg, 1.15 mmol) was added to the solution, and the mixture was heated for 1 h at 100 °C. Then the mixture was poured into water, extracted with CH$_2$Cl$_2$, washed with brine, dried over anhydrous Na$_2$SO$_4$. Concentration in vacuo afforded 16 as a yellow liquid (0.31 g, 92%), which was used without further purification. ¹H NMR (500 MHz, CDCl$_3$) δ 1.67-1.85 (m, 2H), 2.23-2.25 (m, 1H), 2.40-2.42 (m, 1H), 2.77-2.88 (m, 2H), 3.11-3.12 (m, 1H), 3.77 (s, 3H), 3.81-3.84 (m, 2H), 6.68 (dd, \(J = 8.2, 1.8\) Hz, 1H), 6.79 (s, 1H), 7.08 (d, \(J = 8.2\) Hz, 1H), 7.70-7.85 (m, 2H). ¹³C NMR (100 MHz, CDCl$_3$) δ 168.4, 158.7, 147.8, 135.8, 133.9, 132.2, 124.9, 123.2, 112.6, 108.9, 55.4, 42.6, 36.5, 33.4, 32.4, 30.6.

(S)-2-(6-Methoxy-2,3-dihydro-1H-inden-1-yl)ethanamine hydrochloride (3).

Hydrazine hydrate (0.5 mL) was added to a solution of compound 16 (0.30 g, 0.93 mmol) in EtOH (10 mL), the mixture was refluxed for 3 h. Then it was cooled to room temperature and filtrated, the filtrate was poured into water (40 mL), extracted with CH$_2$Cl$_2$, washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated. The residue was diluted with 1.5 mL EtOH, and 4M HCl/EtOH (1.5 mL) was added in.
To this solution was added Et₂O, and the solid that precipitated was collected by filtration. The crude solid was recrystallized from EtOH-Et₂O to afford 0.16 g (76% yield) of 3. \( [\alpha]_{D}^{20} = -27.0 \) (c 0.20, H₂O); mp 174–175 °C, \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \( \delta \) 1.58-1.71 (m, 2H), 2.05-2.12 (m, 1H), 2.20-2.27 (m, 1H), 2.66-2.86 (m, 4H), 3.10-3.15 (m, 1H), 3.71 (s, 3H), 6.71 (d, \( J = 8.2 \) Hz, 1H), 6.76 (s, 1H), 7.10 (d, \( J = 8.2 \) Hz, 1H), 8.18 (s, 3H). \(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \( \delta \) 158.3, 147.4, 135.0, 124.9, 112.2, 109.1, 55.1, 41.6, 37.1, 31.9, 31.7, 29.9.

(S)-N-(2-(6-Methoxy-2,3-dihydro-1H-inden-1-yl)ethyl)propionamide (2).

Propionic anhydride (0.12 g, 0.9 mmol) and 1M NaOH solution (10 mL) was added into a solution of compound 15 (0.16 g, 0.7 mmol) in THF (30 mL) at room temperature. After stirred at this temperature for 1h, it was poured into water (20 mL) and extracted with EtOAc, washed with brine, dried over anhydrous Na₂SO₄. Concentration in vacuo afforded crude product, which was recrystallized from EtOAc-petroleum ether to afford 0.16 g (91%) of 2 as a white solid. \( [\alpha]_{D}^{20} = -10.0 \) (c 0.20, EtOH); mp 76–77 °C, \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 1.15 (t, \( J = 7.6 \) Hz, 3H), 1.61-1.65 (m, 1H), 1.70-1.74 (m, 1H), 2.04-2.07 (m, 1H), 2.20 (q, \( J = 7.7 \) Hz, 2H), 2.31-2.34 (m, 1H), 2.74-2.88 (m, 2H), 3.10-3.13 (m, 1H), 3.38-3.41 (m, 2H), 3.79 (s, 3H), 5.43 (s, 1H), 6.71 (d, \( J = 8.1 \) Hz, 1H), 6.75 (s, 1H), 7.11 (d, \( J = 8.1 \) Hz, 1H). \(^{13}\)C NMR (100 MHz, CDCl₃) \( \delta \) 173.7, 158.7, 148.1, 135.8, 124.9, 112.3, 109.2, 55.5, 42.7, 37.9, 34.8, 32.5, 30.6, 30.3, 29.8; HRMS (EI): m/z calcd for C₁₅H₂₁NO₂ (M)⁺: 247.1572, found: m/z = 247.1571.

The enantiomeric excess of (S)-2 was determined by HPLC as > 99.9% [column, CHIRALPAK AS-H (4.6mm×250mm), room temperature; eluent, hexane-2-propanol-trifluoroacetic acid (90:10:0.1); flow rate, 1.0 mL/min; detect, 290 nm, \( t_R \) of (S)-2, 34.7 min; \( t_R \) of (R)-2 (enantiomer of (S)-2), 41.3 min].

(E)-3-(2,3-Dihydrobenzofuran-4-yl)acrylaldehyde (18).

To a stirred solution of compound 17 (0.82 g, 4.1mmol) in 20 mL of DMF were added 3,3-diethoxy-1-propene(1.9 mL, 12.5 mmol), \( ^6\)Bu₄NOAc (2.47 g, 8.2 mmol), K₂CO₃ (849 mg, 6.15 mmol), KCl (0.36 g, 4.1 mmol), and Pd(OAc)₂ (30 mg, 0.13mmol). The mixture was stirred at 90 °C for 5 h. After cooling to room temperature, 2 N HCl was slowly added into the mixture. After stirred at room temperature for 10 min, it was diluted with Et₂O and washed with water. The organic layer was dried over Na₂SO₄ and concentrated in vacuo. The crude product was crystallized in a mixture of EtOAc and petroleum ether to afford 0.22 g (31% yield) of 18 as a yellow needle solid. mp 122–124 °C, \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 3.38 (t, \( J = 8.7 \) Hz, 2H), 4.68 (t, \( J = 8.7 \) Hz, 2H), 6.67 (dd, \( J = 16.1, 7.6 \) Hz, 1H), 6.89 (d, \( J = 7.9 \) Hz, 1H), 7.11 (d, \( J = 7.8 \) Hz, 1H), 7.21 (t, \( J = 7.9 \) Hz, 1H), 7.49 (d, \( J = 16.1 \) Hz, 1H), 9.73 (d, \( J = 7.6 \) Hz, 1H). \(^{13}\)C NMR (100 MHz, CDCl₃) \( \delta \) 193.8, 160.8, 150.5, 130.9, 129.9, 128.7, 127.2, 120.3, 111.9, 71.1, 29.4; HRMS (EI): m/z calcd for C₁₁H₁₀NO₂ (M)⁺: 174.0681, found: m/z = 174.0680.
(S)-Dimethyl 2-(1-(2,3-dihydrobenzofuran-4-yl)-3-oxopropyl)malonate (19).

Compound 18 (290 mg, 1.67 mmol) and amino catalyst 9 (54 mg, 0.17 mmol) were stirred in EtOH (5 mL) at 0 ºC for 30 min, then 11 (110 mg, 0.83 mmol) was added dropwise. The mixture was then stirred at 0 ºC for 16 h. The reaction mixture was extracted with EtOAc, washed with 1N hydrochloric acid and brine. Concentration in vacuo gave crude product, which was purified by column chromatography (EtOAc : petroleum ether = 1:5) to give pure 19 as a pale yellow liquid (205 mg, 80%). \[[\alpha]_D^{20} +4.0 \text{ (c 0.4, CHCl}_3; 1\text{H NMR (500 MHz, CDCl}_3) \delta 2.90 (d, J = 6.8 Hz, 2H), 3.32-3.37 (m, 2H), 3.50 (s, 3H), 3.73-3.75 (m, 4H), 3.97-4.03 (m, 1H), 4.58 (t, J = 8.7 Hz, 2H), 6.62-6.64 (m, 2H), 7.05 (t, J = 7.9 Hz, 1H), 9.59 (s, 1H). 13\text{C NMR (100 MHz, CDCl}_3) \delta 199.5, 168.4, 167.8, 160.0, 136.8, 128.5, 126.8, 117.8, 108.2, 71.1, 56.5, 52.8, 52.5, 47.4, 36.3, 28.8; HRMS (EI): m/z calcd for C16H18O6 (M)+: 306.1103, found: m/z = 306.1100. The enantiomeric excess of 19 was determined by HPLC as > 92% after conversion to the corresponding methyl ester.\[^9\] [column, CHIRALPAK OD-H (4.6mm × 250mm), room temperature; eluent, 2-propanol/hexane 2/98; flow rate, 0.5 mL/min; t\text{R of (S)-19, 52.3 min; t\text{R of (R)-19 (enantiomer of (S)-19), 57.4 min, detection at 220 nm}].

(5)-3-(2,3-Dihydrobenzofuran-4-yl)-5-methoxy-4-(methoxycarbonyl)-5-oxopentanoic acid (20).

A solution of compound 19 (190 mg, 0.62 mmol), sodium chlorite (200 mg, 2.2 mmol) and sodium hydrogen phosphate (200 mg, 1.7 mmol) in 2-methyl-2-butene (1.2 mL), t-BuOH (5 mL) and water (2 mL) was stirred at room temperature for 3 h. The mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na2SO4, and evaporated to dryness to give a colorless oil 179mg (89%). \[[\alpha]_D^{20} +3.5 \text{ (c 0.5, CHCl}_3; 1\text{H NMR (500 MHz, CDCl}_3) \delta 2.67 (dd, J = 16.4, 10.0 Hz, 1H), 2.79 (dd, J = 16.4, 4.4 Hz, 1H), 3.23 (t, J = 8.7 Hz, 2H ), 3.41 (s, 3H), 3.66-3.68 (m, 4H), 3.80-3.85 (m, 1H), 4.45-4.59 (m, 2H), 6.51-6.58 (m, 2H), 6.98 (d, J = 7.8 Hz, 1H). 13\text{C NMR (100 MHz, CDCl}_3) \delta 176.9, 168.4, 167.8, 160.0, 136.8, 128.5, 126.8, 117.8, 108.2, 71.1, 56.5, 52.8, 52.5, 47.4, 36.3, 28.8; HRMS (EI): m/z calcd for C16H18O7 (M)+: 322.1053, found: m/z = 322.1057.\]

(5)-Dimethyl 2-(6-oxo-2,6,7,8-tetrahydro-1H-indeno[5,4-b]furan-8-yl)malonate (21).

Thionyl chloride (96 mg, 0.8 mmol) was dropped into a solution of compound 20 (130 mg, 0.4 mmol) in CH2Cl2 (3 mL), the mixture was stirred at 60 ºC for 2 h. Solvent and thionyl chloride were removed under reduced pressure. Another CH2Cl2 (3 mL) was added into the flask. It was cooled to 0 ºC, then AlCl3 (189 mg, 1.4 mmol) was added. After stirred at this temperature for 1 h, it was warmed to room temperature and stirred for 15 h. Then it was poured into saturated aqueous NH4Cl. The solution was extracted with CH2Cl2, washed with brine, dried over anhydrous Na2SO4. Concentration in vacuo gave crude product, which was further purified by column chromatography (EtOAc : petroleum ether = 1:3) to give pure 21 as a colorless oil (80 mg, 65%). \[[\alpha]_D^{20} -163 \text{ (c 0.28, acetone); } 1\text{H NMR (500 MHz, CDCl}_3) \delta 2.85-2.90 (m,
2H), 3.20-3.29 (m, 2H), 3.46 (s, 3H), 3.76 (s, 3H), 3.97-4.04 (m, 2H), 4.64-4.75 (m, 2H), 6.80 (d, \( J = 8.3 \) Hz, 1H), 7.56 (d, \( J = 8.3 \) Hz, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 202.6, 168.4, 167.4, 166.2, 150.4, 131.2, 125.1, 123.1, 110.5, 72.3, 52.8, 52.4, 52.3, 40.5, 36.8, 27.5; HRMS (EI): m/z calcd for C\(_{16}H_{16}O_6\) (M\(^+\)): 304.0947, found: m/z = 304.0945.

\((S)-\)Dimethyl 2-(2,6,7,8-tetrahydro-1\(\text{H}\)-indeno[5,4-\(\text{b}\])furan-8-yl)malonate (22).

A mixture of compound 21 (44 mg, 0.15 mmol) and 10% Pd/C (5 mg) in MeOH (5 mL) was hydrogenated at room temperature for 5 h. The catalyst was then filtered off and the filtrate was evaporated to dryness to give a colorless oil (36 mg, 86%). \([\alpha]_{D}^{20} -135 \) (c 0.35, MeOH); \(^1\)H NMR (500 MHz, CD\(_3\)OD) \( \delta \) 2.16-2.47 (m, 2H), 2.67-3.17 (m, 4H), 3.56 (s, 3H), 3.70 (s, 3H), 3.85-3.89 (m, 2H), 4.40-4.51 (m, 2H), 6.54 (d, \( J = 8.0 \) Hz, 1H), 6.89 (d, \( J = 8.0 \) Hz, 1H). \(^{13}\)C NMR (100 MHz, CD\(_3\)OD) \( \delta \) 170.8, 170.4, 160.7, 140.6, 137.5, 124.5, 124.0, 109.1, 72.2, 54.9, 53.0, 52.7, 45.4, 31.2, 30.8, 29.5; HRMS (EI): m/z calcd for C\(_{16}H_{18}O_5\) (M\(^+\)): 290.1154, found: m/z = 290.1151.

\((S)-2-(2,6,7,8-	ext{Teahydro-1}\text{H}-	ext{indeno[5,4-}\text{b}]\text{furan-8-yl})\text{acetic acid (23).}\)

Compound 22 (34 mg, 0.12 mmol) was dissolved in MeOH (2 mL), then NaOH (24 mg, 0.6 mmol) in water (2 mL) was added into the flask. The solution was refluxed for 2 h. After cooling to room temperature, the aqueous phase was treated with 1N HCl (5 mL), then extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous Na\(_2\)SO\(_4\), and evaporated to dryness to give a yellow solid. This solid was dissolved in mesitylene (6 mL) and heated to 160 \(^\circ\)C for 30 mins under nitrogen atmosphere. It was cooled to room temperature and treated with 5 mL 1N NaOH solution. The aqueous phase was acidified with 1N HCl and extracted with EtOAc, washed with brine, dried over anhydrous Na\(_2\)SO\(_4\). Concentration in vacuo gave crude product, which was further purified by column chromatography (EtOAc : petroleum ether = 1:3) to give pure 23 as a white solid (16 mg, 63%). mp 116–118 \(^\circ\)C, \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 1.88-1.93 (m, 1H), 2.37-2.47 (m, 2H), 2.67-3.17 (m, 4H), 3.56 (s, 3H), 3.70 (s, 3H), 3.85-3.89 (m, 2H), 4.50-4.63 (m, 2H), 6.64 (d, \( J = 8.0 \) Hz, 1H), 6.97 (d, \( J = 8.0 \) Hz, 1H).

\((S)-2-(1,6,7,8-	ext{Tetrahydro-2}\text{H}-	ext{indeno[5,4-}\text{b}]\text{furan-8-yl})\text{acetamide (24).}\)

A solution of compound 23 (16 mg, 0.073 mmol) and thionyl chloride (26 mg, 0.22 mmol) in toluene (2mL) was stirred at 60 \(^\circ\)C for 2 h. Excess thionyl chloride was distilled off, CH\(_2\)Cl\(_2\) was added, and again distillation was performed to remove traces of thionyl chloride. Ammonia gas was passed into a solution of the acid chloride in CH\(_2\)Cl\(_2\). 10 min later, the solution was poured into water, extracted with CH\(_2\)Cl\(_2\), washed with brine, dried over anhydrous Na\(_2\)SO\(_4\). Concentration in vacuo gave the title compound as a white solid (16 mg, 99%). mp 185–187 \(^\circ\)C, \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 1.81-1.84 (m, 1H), 2.24-2.35 (m, 2H), 2.61-2.87 (m, 3H), 3.10-3.18 (m, 2H), 3.50-3.70 (m, 1H), 4.48-4.57 (m, 2H), 5.25-5.50 (br, 2H), 6.60 (d, \( J = 8.0 \) Hz, 1H), 6.93 (d, \( J = 8.0 \) Hz, 1H).
(S)-2-(1,6,7,8-Tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethylamine (25).

LiAlH₄ (21 mg, 0.56 mmol) was added into a solution of compound 24 (16 mg, 0.074 mmol) in THF (5 mL) at 0 ºC. The mixture was stirred at room temperature for 16 h, then EtOAc (1 mL) was added to quench the reaction. After stirring for 0.5 h, the mixture was extracted with EtOAc, washed with brine, dried over anhydrous Na₂SO₄. Concentration in vacuo gave crude product, which was further purified by column chromatography (CH₂Cl₂ : MeOH = 10:1) to give pure 25 as a yellow oil (11 mg, 73%). ¹H NMR (500 MHz, CDCl₃) δ 1.55-1.80 (m, 2H), 1.95-2.35 (m, 2H), 2.75-2.87 (m, 4H), 3.11-3.40 (m, 5H), 4.47-4.60 (m, 2H), 6.61 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H).

(S)-N-[2-(1,6,7,8-Tetrahydro-2H-indeno[5,4-b]furan-8-yl)ethyl]propionamide (1).

Propionic anhydride (8 mg, 0.06 mmol) was added to a stirred solution of 25 (10 mg, 0.05 mmol) and Et₃N (15 mg, 0.15 mmol) in CH₂Cl₂ (5 mL) at room temperature. After the mixture was stirred for 1 h at room temperature, EtOAc and water were added. The organic layer was washed with brine and dried over anhydrous Na₂SO₄. The filtrate was concentrated to give a solid, which was further purified by column chromatography (EtOAc : petroleum ether = 2:1) to give pure 1 as a white solid (8 mg, 62%). mp 113–115 ºC, 1H NMR (CDCl₃) δ 1.14 (t, J = 7.6 Hz, 3H), 1.55-2.05 (m, 3H), 2.18 (q, J = 7.6 Hz, 2H), 2.20-2.35 (m, 1H), 2.70-2.99 (m, 2H), 3.05-3.50 (m, 5H), 4.48-4.60 (m, 2H), 5.46 (br, 1H), 6.61 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H). The enantiomeric excess of (S)-1 was determined by HPLC as > 92% [column, CHIRALPAK OD-H (4.6mm × 250mm), room temperature; eluent, hexane-EtOH-MsOH (900:100:0.1); flow rate, 1.0 mL/min; detect, 220 nm, tᵣ of (S)-1, 6.99 min; tᵣ of (R)-1 (enantiomer of (S)-1), 7.87 min].

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