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STEREOSELECTIVE SYNTHESIS OF MELATONIN RECEPTOR AGONIST RAMELTEON *VIA* ASYMMETRIC MICHAEL ADDITION

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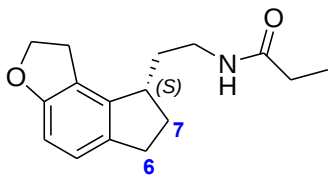
Abstract – Highly enantioselective asymmetric Michael addition was used to synthesize ramelteon and its analogue. The asymmetric strategy provides an efficient approach for the medicinal modification of ramelteon with high *ee* value.

INTRODUCTION

Ramelteon (**1**, Rozerem), developed by Takeda Pharmaceuticals North America, is the first selective agonist for the melatonin MT_1/MT_2 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 derivatives[3] and 7-substituted 1,6-dihydro-2*H*-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 hydrogenation[5] or chiral resolution[6] 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-8*H*-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.



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.

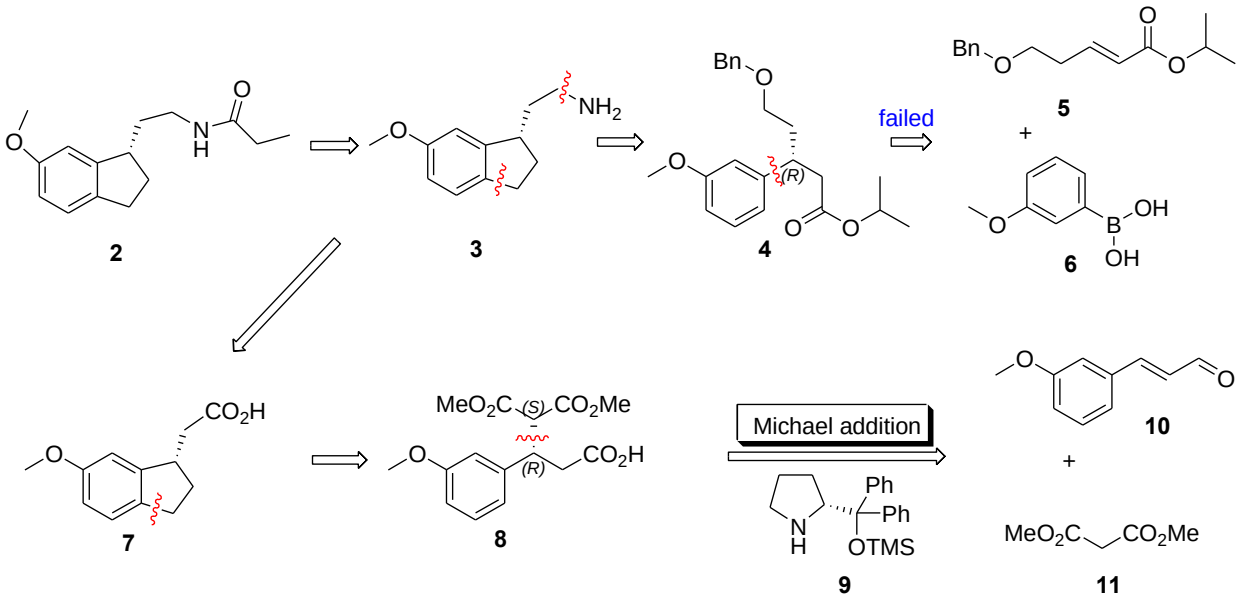


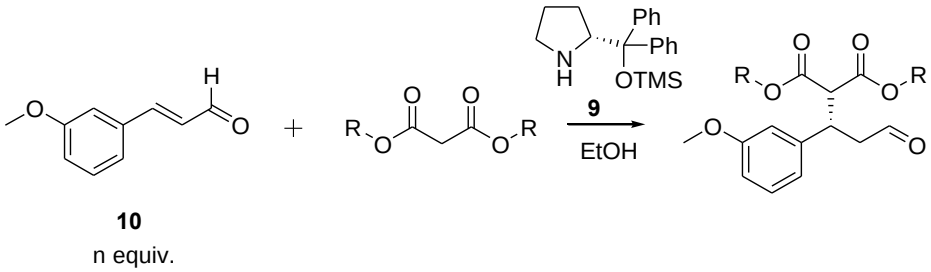
Figure 1. Retrosynthesis of compound **2**

According to Hayashi's work,[8] the rhodium-catalyzed asymmetric 1,4-addition of *α,β*-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 *α,β*-unsaturated aldehyde afforded addition product in good yield and very good to excellent enantioselectivity.[9] Therefore, *α,β*-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*).

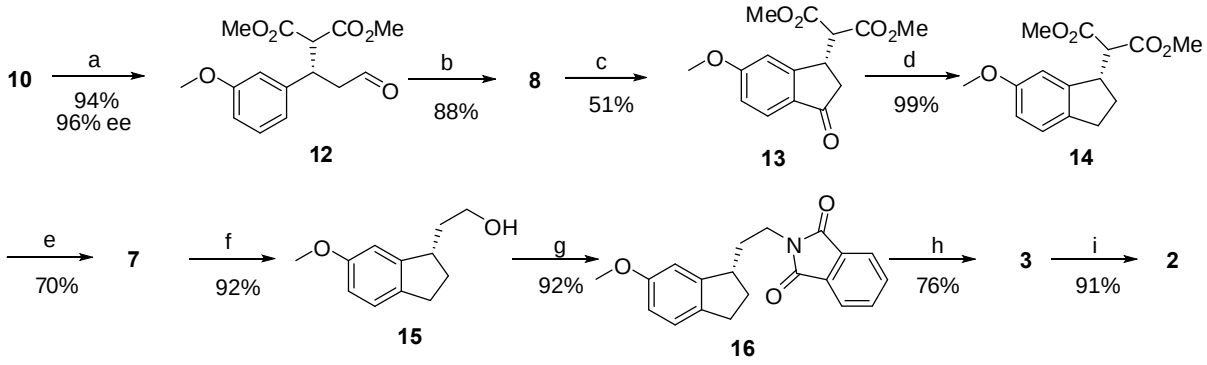
Table 1. Optimization of Michael addition



Entry	R	n (equiv)	Temp.	catalyst (mol%)	yield (%)[a]	*ee* (%)[b]
1	Me	2	0-5 ºC, 12h	10	88	96
2	Et	2	0-5 ºC, 12h	10	< 30	-
3	Me	0.9	0-5 ºC, 12h	10	44	-
4	Me	0.5	0-5 ºC, 12h	10	< 30	-
5	Me	2	rt, 12h	10	74	81
6	Me	2	< -5 ºC, 12h	10	< 30	-
7	Me	2	0-5 ºC, 48h	20	94	96

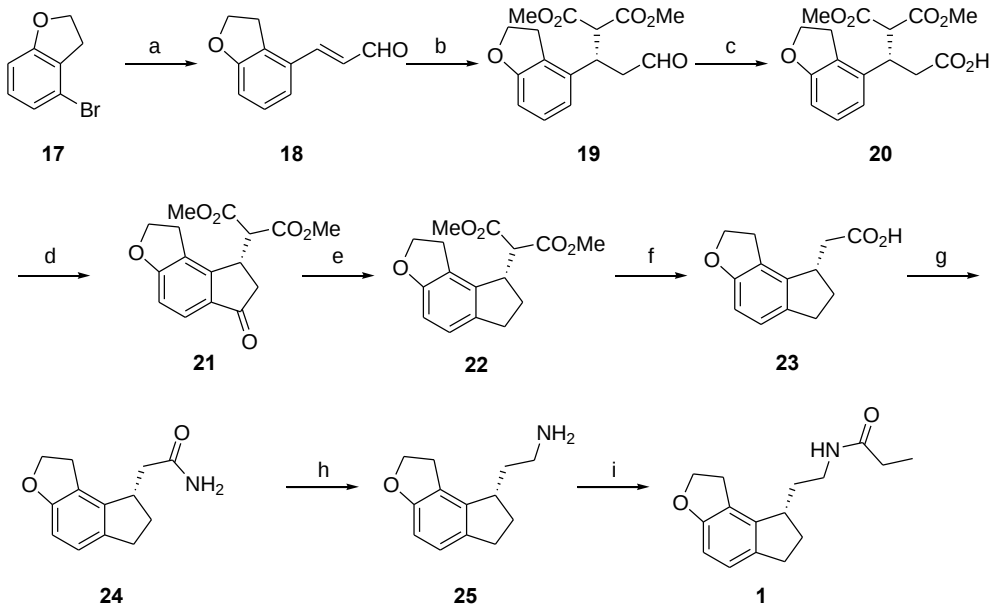
[a] Isolated yield;
[b] The enantiomeric excess was determined by HPLC after conversion to the corresponding lactone.[9]

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 ºC 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%.



Scheme 1. Reagents and condition: a) **11**, catalyst **9**, EtOH; b) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O; c) $SOCl_2$, toluene, $SnCl_4$, DCM; d) Pd/C, H_2, EtOH; e) NaOH (aq), EtOH, mesitylene; f) $LiAlH_4$, THF; g) MsCl, Et_3N, CH_2Cl_2, phthalimide potassium salt, DMF; h) hydrazine hydrate, EtOH; i) propionic anhydride, NaOH (aq), THF.

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 *α,β*-unsaturated aldehyde **18** according to Cacchi's method.[12] 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 $NaClO_2$ 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**.[13] 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 2. Reagents and condition: a) 1,1-diethoxy-2-propene, $Pd(OAc)_2$, *n*-Bu_4NOAc, KCl, K_2CO_3, DMF; b) **11**, catalyst **9**, EtOH; c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O; d) $SOCl_2$, toluene; $AlCl_3$, CH_2Cl_2; e) Pd/C, H_2, MeOH; f) NaOH, H_2O, MeOH; mesitylene; g) $SOCl_2$, toluene, NH_3, CH_2Cl_2; h) $LiAlH_4$, THF. i) propionic anhydride, Et_3N, CH_2Cl_2.

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_2D_6SO on Bruker DRX-500 (500 MHz) using TMS as internal standard. Chemical shifts were reported as δ (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 ºC for 30 min, then compound **11** (1.55 g, 11.7 mmol) was added dropwise. The mixture was stirred at 0 ºC 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%). $[\alpha]_D^{20}$ +32.0 (c 1.0, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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-butene (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_2SO_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, $CDCl_3$) δ 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{15}H_{18}O_7$ $(M)^+$: 310.1053, found: m/z = 310.1045.

(*S*)-Dimethyl 2-(6-methoxy-3-oxo-2,3-dihydro-1*H*-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 CH_2Cl_2 (30 mL). The mixture was stirred at room temperature for 6 h. Solvent and thionyl chloride were removed under reduced pressure. Another CH_2Cl_2 (45 mL) was added into the flask. It was cooled to -25 ºC, then $SnCl_4$ (2.1 mL, 18.3 mmol) was slowly dropped in. After stirred at this temperature for 12 h, it was poured into saturated aqueous NH_4Cl. The solution was extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4. 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%). $[\alpha]_D^{20}$ -37.3 (c 1.0, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{15}H_{16}O_6$ $(M)^+$: 292.0947, found: m/z = 292.0951.

(*S*)-Dimethyl 2-(6-methoxy-2,3-dihydro-1*H*-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%). $[\alpha]_D^{20}$ -18.6 (c 1.0, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 168.7, 158.6, 144.5, 136.1, 125.1, 113.2, 109.9, 55.8, 55.4, 52.5, 52.4, 44.6, 30.5, 29.9; HRMS (EI): m/z calcd for $C_{15}H_{18}O_5$ $(M)^+$: 278.1154, found: m/z = 278.1151.

(*S*)-2-(6-Methoxy-2,3-dihydro-1*H*-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 Na_2SO_4, 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 acidfied with 1N HCl and extracted with EtOAc, washed with brine, dried over anhydrous

Na_2SO_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%). $[\alpha]_D^{20}$ -15.5 (c 1.0, acetone); mp 80–82 ºC, ^{1}H 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). ^{13}C 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-1*H*-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 ºC. 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_2SO_4. Concentration in vacuo afforded pure **15** (0.25 g, 92%) as a colorless oil. $[\alpha]_D^{20}$ -15.0 (c 1.0, $CHCl_3$); ^{1}H 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). ^{13}C 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-1*H*-inden-1-yl)ethyl)isoindoline-1,3-dione (16).

Mesyl chloride (0.11 mL, 1.35 mmol) and Et_3N (0.19 mL, 1.35 mmol) was added to a solution of compound **15** (0.20 g, 1.04 mmol) in anhydrous CH_2Cl_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_2Cl_2, washed with brine, dried over anhydrous Na_2SO_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 ºC. Then the mixture was poured into water, extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4. Concentration in vacuo afforded **16** as a yellow liquid (0.31 g, 92%), which was used without further purification. ^{1}H 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). ^{13}C 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-1*H*-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_2Cl_2, washed with brine, dried over anhydrous Na_2SO_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 Et_2O, and the solid that precipitated was collected by filtration. The crude solid was recrystallized from EtOH-Et_2O to afford 0.16 g (76% yield) of **3**. $[\alpha]_D^{20}$ -27.0 (c 0.20, H_2O); mp 174–175 ºC, ^{1}H NMR (500 MHz, DMSO-d_6) δ 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) δ 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-1*H*-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 Na_2SO_4. Concentration in vacuoafforded 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 ºC, ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{15}H_{21}NO_2$ $(M)^+$: 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), ^{n}Bu_4NOAc (2.47 g, 8.2 mmol), K_2CO_3 (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 Et_2O and washed with water. The organic layer was dried over Na_2SO_4 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 ºC, ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{11}H_{10}NO_2$ $(M)^+$: 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 (c 0.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{16}H_{18}O_6$ $(M)^+$: 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_R of (*S*)-**19**, 52.3 min; t_R of (*R*)-**19** (enantiomer of (*S*)-**19**), 57.4 min, detection at 220 nm].

(*S*)-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 Na_2SO_4, and evaporated to dryness to give a colorless oil 179mg (89%). $[\alpha]_D^{20}$ +3.5 (c 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 176.9, 168.3, 167.8, 159.8, 136.5, 128.3, 127.0, 117.7, 108.2, 71.0, 56.3, 52.70, 52.4, 37.9, 37.8, 28.6; HRMS (EI): m/z calcd for $C_{16}H_{18}O_7$ $(M)^+$: 322.1053, found: m/z = 322.1057.

(*S*)-Dimethyl 2-(6-oxo-2,6,7,8-tetrahydro-1*H*-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 CH_2Cl_2 (3 mL), the mixture was stirred at 60 ºC for 2 h. Solvent and thionyl chloride were removed under reduced pressure. Another CH_2Cl_2 (3 mL) was added into the flask. It was cooled to 0 ºC, then $AlCl_3$ (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 NH_4Cl. The solution was extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4. 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 (c 0.28, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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*H*-indeno[5,4-*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_3OD) δ 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_3OD) δ 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-Teahydro-1*H*-indeno[5,4-*b*]furan-8-yl)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_2SO_4, and evaporated to dryness to give a yellow solid. This solid was dissolved in mesitylene (6 mL) and heated to 160 ºC for 30 mins under nitrogen atmosphere. It was cooled to room temperature and treated with 5 mL 1N NaOH solution. The aqueous phase was acidfied with 1N HCl and extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_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 ºC, ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.88-1.93 (m, 1H), 2.37-2.47 (m, 2H), 2.77-2.95 (m, 3H), 3.10-3.25 (m, 2H), 3.57-3.60 (m, 1H), 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-Tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl)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 ºC for 2 h. Excess thionyl chloride was distilled off, CH_2Cl_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_2Cl_2. 10 min later, the solution was poured into water, extracted with CH_2Cl_2, washed with brine, dried over anhydrous Na_2SO_4. Concentration in vacuo gave the title compound as a white solid (16 mg, 99%). mp 185–187 ºC, ^{1}H NMR (500 MHz, $CDCl_3$) δ 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-2*H*-indeno[5,4-*b*]furan-8-yl)ethylamine (25).

$LiAlH_4$ (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 Na_2SO_4. Concentration in vacuo gave crude product, which was further purified by column chromatography (CH_2Cl_2 : MeOH = 10:1) to give pure **25** as a yellow oil (11 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) 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-2*H*-indeno[5,4-*b*]furan-8-yl)ethyl]propionamide (1).

Propionic anhydride (8 mg, 0.06mmol) was added to a stirred solution of **25** (10 mg, 0.05 mmol) and Et_3N (15 mg, 0.15 mmol) in CH_2Cl_2 (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 Na_2SO_4. 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 °C, 1H NMR ($CDCl_3$) 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, t_R of (*S*)-**1**, 6.99 min; t_R of (*R*)-**1** (enantiomer of (*S*)-**1**), 7.87 min].

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