Tetrahedron: *Asymmetry* 24 (2013) 827–832

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis of the melatonin receptor agonist Ramelteon using a tandem C–H activation–alkylation/Heck reaction and subsequent asymmetric Michael addition

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ARTICLE INFO

Article history:
Received 15 April 2013
Accepted 6 May 2013
Available online 2 July 2013

ABSTRACT

An asymmetric synthesis of the melatonin receptor agonist Ramelteon **1** has been achieved, which involved a tandem C–H activation–alkylation/Heck reaction and subsequent highly diastereoselective asymmetric Michael addition to generate the corresponding chiral intermediate, which was readily converted into Ramelteon **1** in 19% overall yield in 15 linear steps.

1. Introduction

Ramelteon **1** (Rozerem™, (*S*)-*N*-[2-(1,6,7,8-tetrahydro-2*H*-indeno[5,4-*b*]furan-8-yl)ethyl]-propionamide]), developed by Takeda Pharmaceuticals North America, is the first selective agonist for the melatonin MT1/MT2 receptors in the suprachiasmatic nucleus (SCN)[1] for the treatment of circadian rhythm sleep disorders.[2] In contrast to other FDA-approved drugs for this disease, it constitutes as a new class of prescription drugs that do not cause the adverse effects typically associated with the use of benzodiazepine class of drugs, such as learning and memory impairment and drug dependence since it has negligible affinity for the MT3 receptors.[3] It is also the single prescription sleep medication that is not designated as a controlled substance by the US Drug Enforcement Administration (DEA).[4,5]

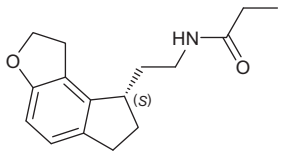
Ramelteon has a simple but unique chemical scaffold containing a furan-fused tricycle ring and an asymmetric center at the benzylic position. Currently, most of the reported total syntheses of Ramelteon involve catalytic asymmetric hydrogenation[6,7] or chiral resolution[8,9] of the corresponding racemic mixtures, which have disadvantages such as low ee values or low yields. Zhang[10] reported a new approach to synthesize Ramelteon **1** from a commercially unavailable starting material, however it is not suitable for industrial production.

Herein, we have developed an efficient synthesis of a tricycle intermediate 1,2,6,7-tetrahydro-8*H*-indeno[5, 4-*b*]furan-8-one based on a tandem C–H activation–alkylation/Heck reaction[11] and subsequent highly diastereoselective asymmetric Michael addition,[12] which is then tested for industrial production. From a medicinal chemistry point of view, a new synthetic approach of Hamilton is presented herein based on our previous exploration (Fig. 1).

2. Results and discussion

In recent decades, tandem reactions have been developed as an efficient and straightforward one-step methodology for the construction of fused heterocyclic compounds. Jafarpour[11] reported on a tandem palladium-catalyzed alkylation/alkenylation process which forms at least three new C–C bonds in excellent yield, using readily accessible starting materials, which inspired us to utilize this method in our synthetic design.

As shown in Scheme 1, commercially available compound **2** was converted into compound **4** by employing Jafarpour's[11] method after diazotization of the amino group, which was subjected to Friedel–Crafts acylation and then recrystallized to afford compound **5** in good yield (47%). Protection of the carbonyl group in **5** was



Ramelteon **1**

Figure 1. Structure of Ramelteon **1**.

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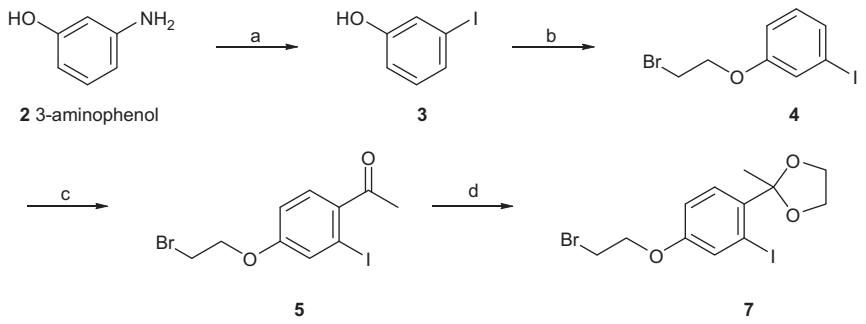
0957-4166/$ - see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tetasy.2013.05.006



Scheme 1. Reagents and conditions: (a) $NaNO_2$, KI, $CO(NH_2)_2$, HCl (10%), rt, 90%; (b) K_2CO_3, 1,2-dibromoethane, acetone, 55 °C, 92%; (c) $AlCl_3$, CH_3COCl, CH_2Cl_2, 0 °C, 47%; (d) PTS, ethylene glycol, toluene 140 °C, 95%.

achieved by treatment with ethylene glycol (PTS, toluene, 140 °C) to obtain the key intermediate **7** in 95% yield, which was then subjected to a tandem C–H activation–alkylation/Heck reaction process to afford **9** as shown in Scheme 2. To achieve the optimal yield with the lowest production cost, different reaction conditions were carefully investigated as displayed in Schemes 3 and 4 and Table 1. Initially, a direct alkylation/Heck reaction of compound **5** to obtain compound **9** was attempted; unfortunately, the yield was below 20% (Scheme 3). Subsequently, the tandem reaction was tried again after protecting the carbonyl with methanol, but the result was not good (Scheme 4). Compound **5** was treated with ethylene glycol (PTS, toluene, 140 °C) to protect the carbonyl; the next step involving a tandem reaction was completed in a yield of 61%. The base and the catalyst loading were also essential (entries 1, 2, and 4 in Table 1). Finally, the optimal condition was found in entry 4, which afforded compound **8** in high yield (85%).

Fustero[12] reported a new intramolecular asymmetric Michael reaction of *tert*-butanesulfinyl ketimines for the diastereoselective synthesis of indanone derivatives with good yields and high diastereoselectives. Based on the aforementioned result, compound **10** was obtained with high yield (81%) by treatment with (*S*)-*N*-(*tert*-butylsulfinyl)amine ($Ti(OEt)_4$, THF, 60 °C) after deprotection, which was subjected to asymmetric Michael reaction to afford compound **11** in an excellent yield of 98% and with an excellent ee value of over 92% (determined by HPLC after conversion to compound **12**). Subsequently, hydrolysis of the chiral auxiliary in compound **11** afforded chiral ester **12** (Scheme 2). Hydrogenation of compound **12** gave the pure known compound **13**, which was reduced with $LiAlH_4$ (Scheme 5). Chiral amine **15** was obtained from Gabriel reaction of compound **14** (three steps, total 90%). Finally, Ramelteon **1** was obtained with an excellent ee value of over 92% by acylation in the presence of propionyl chloride (Scheme 5).

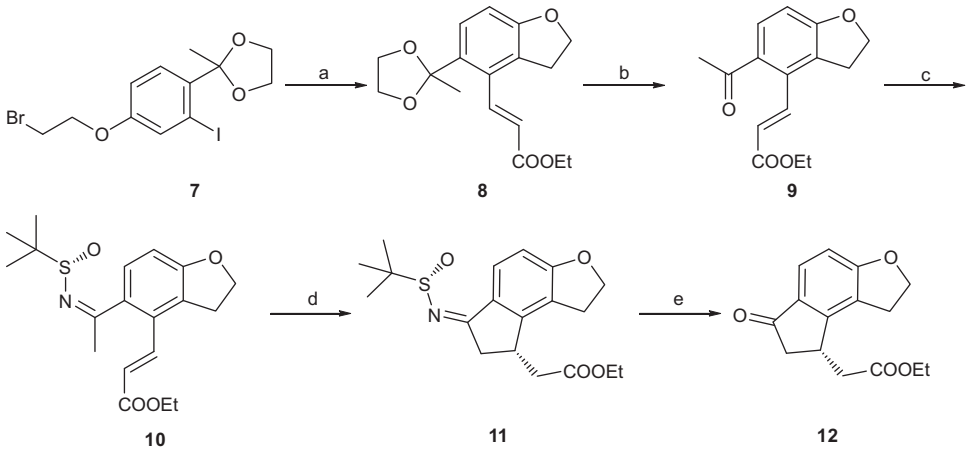
3. Conclusion

In conclusion, we have reported a concise, asymmetric, and stereocontrolled method for the synthesis of Ramelteon **1** via a tandem C–H activation–alkylation/Heck reaction and subsequent highly diastereoselective asymmetric Michael addition, using inexpensive commercially available 3-aminophenol **2** as a starting material. Furthermore, the achieved methodology should be valuable for the medicinal modification of Ramelteon with high ee values in future drug discovery work.

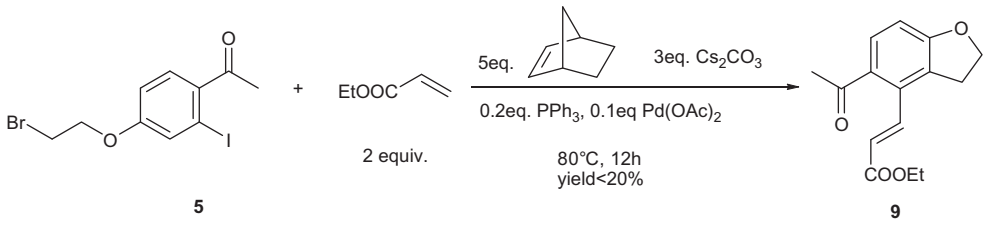
4. Experimental

4.1. General

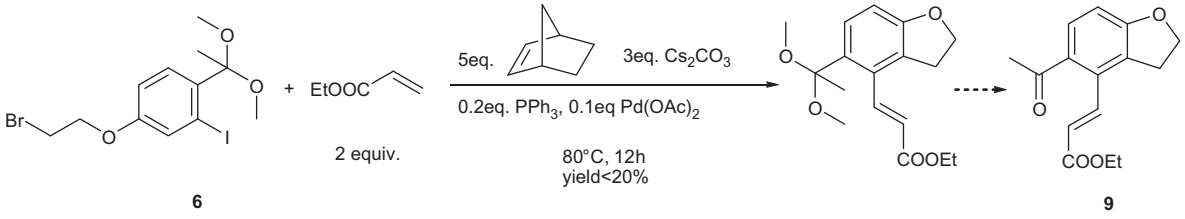
All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (120 °C) which was cooled under argon. Next, THF was distilled from sodium benzophenone ketyl, and DCM was distilled from CaH_2. Column chromatography was performed on Merck silica gel Kieselgel 60 (230–400 mesh). Flash chromatography was carried out using Merck Kieselgel 60 H silica or Matrex silica 60. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$ at 25 °C unless stated otherwise and are reported in parts per million; *J* values are recorded in Hertz and multiplicities are expressed by the usual conventions.



Scheme 2. Reagents and conditions: (a) Norbornene, ethyl acrylate, $Pd(OAc)_2$, PPh_3, K_2CO_3, DME, 80 °C, 85%; (b) HCl (36%), THF:H_2O (2:1), rt, 95%; (c) $Ti(OEt)_4$, (*S*)-*N*-(*tert*-butanesulfinyl)amine, THF, 60 °C, 81%; (d) TBAF (1 M THF), −78 °C, 98%; (e) 3 M HCl, CH_3OH, rt, 88%.

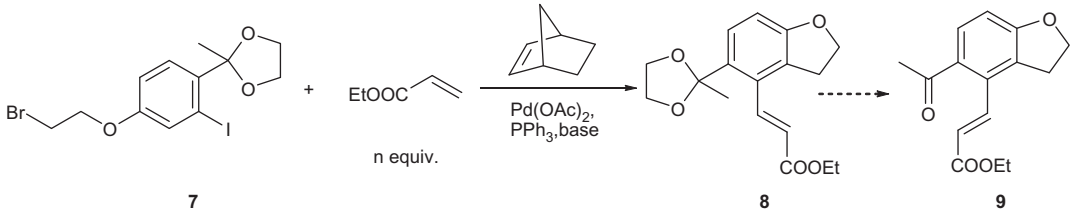


Scheme 3. Conversion of compound **5** to compound **9** directly.



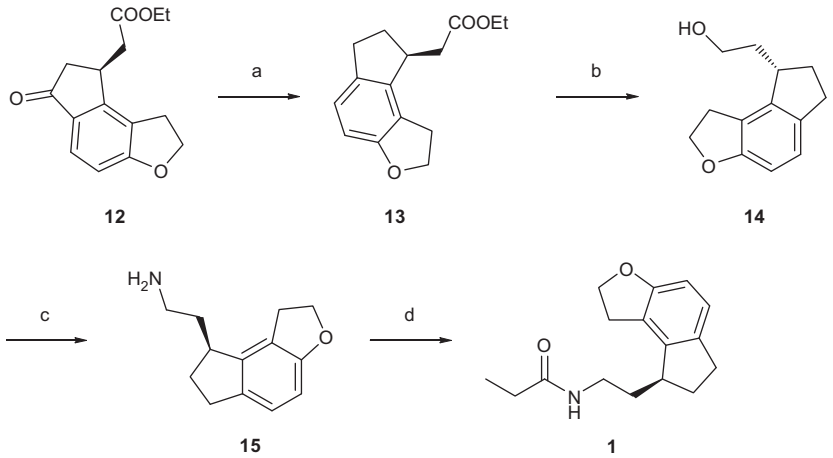
Scheme 4. Conversion of compound **6** (protected with methanol) to compound **9**.

Table 1
Conversion of compound **7** to compound **8**



Entry	*n* (equiv)	Base	Temp	Catalyst (mol %)	Yield[a] (%)
1	2	Cs_2CO_3	80 °C, 12 h	10	61
2	2	K_2CO_3	80 °C, 12 h	10	60
3	5	K_2CO_3	80 °C, 12 h	10	70
4	5	K_2CO_3	80 °C, 12 h	3	85

[a] Isolated yield.



Scheme 5. Reagents and conditions: (a) Pd–C, H_2, EA:AcOH (1:1), 40 °C, 98%; (b) $LiAlH_4$, THF, rt, 97%; (c) (i) MsCl, Et_3N, CH_2Cl_2, rt; (ii) phthalimide potassium salt, DNF, 100 °C; (iii) hydrazine hydrate, EtOH, 80 °C, 90% (three steps); (d) CH_3CH_2COCl, Et_3N, DCM, rt, 95%.

4.2. 3-Iodophenol 3

To a suspension of 3-aminophenol (1 kg, 9.16 mol) in 10% hydrochloric acid (600 mL) was added a solution of sodium nitrite (948 g, 13.75 mol) in water (300 mL) at 0 °C dropwise and then stirred at 0 °C for 30 min. To the mixture was added urea (440 g, 7.33 mol) slowly portionwise, and then stirred at 0 °C for 1 h, after which in a separate flask, potassium iodide (3.04 kg, 18.33 mol) suspended in water (1 L) and 1,2-dichloroethane (1 L) were added to the suspension. This mixture was cooled to 0 °C, and then

poured slowly into the diazonium mixture. The reaction was stirred for 30 min at 0 °C, then allowed to warm to room temperature and stirred for another 2 h. The reaction mixture was filtered through Celite and the solid was rinsed with dichloromethane. The organic phase was washed with water and dried over anhydrous Na_2SO_4, then concentrated in vacuo to provide the product 3-iodophenol.

4.3. 1-(2-Bromoethoxy)-3-iodobenzene 4

The preparation of 1-(2-bromoethoxy)-3-iodobenzene was carried out according to the literature.[11]

4.4. 1-(4-(2-Bromoethoxy)-2-iodophenyl)ethanone 5

To a solution of **4** (100 g, 306 mmol, 1 equiv) in anhydrous DCM (200 mL) was added acetyl chloride (28.8 g, 367 mmol, 1.2 equiv) at 0 °C. Then $AlCl_3$ (53 g, 398 mmol, 1.3 equiv) was added portionwise to this stirred mixture over a period of 30 min, and the mixture was stirred at ambient temperature for 2 h. After the reaction was completed, the mixture was poured slowly into ice-water and extracted with DCM (3 × 100 mL). The organic layer was washed with 1 M NaOH (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to obtain crude **5**, which was recrystallized by a mixed solvent of petroleum ether/ethyl acetate (5:1) to provide 64 g of **5** (47%) as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 8.1 Hz, 1H), 7.39 (dd, J = 8.2, 1.5 Hz, 1H), 7.24 (d, J = 1.3 Hz, 1H), 4.5–4.28 (m, 2H), 3.71 (dd, J = 6.0, 5.3 Hz, 2H), 2.66 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.8, 159.8, 134.9, 130.8, 127.6, 113.9, 92.8, 68.0, 28.8, 28.4. HRMS (EI-quadrupole) m/z: $[M]^+$ Calcd for $C_{10}H_{10}O_2BrI$ 367.8909; Found 367.8907.

4.5. 2-(4-(2-Bromoethoxy)-2-iodophenyl)-2-methyl-1,3-dioxolane 7

To a mixture of **5** (66 g, 179 mmol, 1 equiv) and toluene (240 mL) were added ethane-1,2-diol (55.5 g, 894 mmol, 5 equiv) and *p*-toluenesulfonic acid (3.12 g, 17.9 mmol, 0.1 equiv). Next, the reaction mixture was stirred at 140 °C to remove the water by a Dean–Stark Trap. After the reaction was completed, it was quenched by adding 10% $NaHCO_3$, then concentrated under reduced pressure to remove the solvent, after which the residue was dissolved in ethyl acetate (100 mL). The organic layer was separated, washed with water (50 mL) followed by brine (50 mL), dried, concentrated, and purified by flash chromatography (10:1 petroleum ether/ethyl acetate) to provide 70 g (95%) of **7** as a clear colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.7 Hz, 1H), 7.49 (d, J = 2.6 Hz, 1H), 6.87 (dd, J = 8.7, 2.6 Hz, 1H), 4.26 (t, J = 6.1 Hz, 2H), 4.03 (td, J = 6.1, 4.4 Hz, 2H), 3.69 (dt, J = 9.2, 4.0 Hz, 2H), 3.62 (t, J = 6.1 Hz, 2H), 1.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 136.8, 128.0, 128.0, 113.9, 108.4, 92.8, 67.9, 64.5, 63.8, 28.8, 25.5. HRMS (EI-quadrupole) m/z|: $[M]^+$ Calcd for $C_{12}H_{14}O_3BrI$ 411.9171; Found 411.9168.

4.6. (*E*)-Ethyl 3-(5-(2-methyl-1,3-dioxolan-2-yl)-2,3-dihydrobenzofuran-4-yl) acrylate 8

Compound **7** (11 g, 26.63 mmol, 1 equiv), ethyl acrylate (13.33 g, 133 mmol, 5 equiv), norbornene (12.54 g, 133 mmol, 5 equiv), K_2CO_3 (11 g, 80 mmol, 3 equiv), $Pd(OAc)_2$ (179 mg, 799 μmol, 3% equiv), and PPh_3 (699 mg, 2.66 mmol, 10% equiv) were dissolved in 80 mL of degassed dry DME. The mixture was flushed with Ar and heated at 80 °C for 16 h. After cooling at rt, the mixture was diluted with diethyl ether, washed with water, dried over anhydrous Na_2SO_4, and purified by flash chromatography on silica gel (15:1 petroleum ether/ethyl acetate) to furnish 6.8 g (85%) of **8** as a clear colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 16.3 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.05 (d, J = 16.3 Hz, 1H), 4.55 (t, J = 8.6 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 4.00 (t, J = 6.9 Hz, 2H), 3.72 (t, J = 6.9 Hz, 2H), 3.29 (t, J = 8.6 Hz, 2H), 1.65 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.6, 159.9, 143.4, 134.2, 129.9, 126.70, 121.0, 109.3, 77.6, 76.5, 75.3, 71.1, 63.1, 60.0, 30.9, 27.3, 14.5. HRMS (EI-quadrupole) m/z: $[M]^+$ Calcd for $C_{17}H_{20}O_5$ 304.1311; Found 304.1310.

4.7. (*E*)-Ethyl 3-(5-acetyl-2,3-dihydrobenzofuran-4-yl)acrylate 9

To a solution of **8** (8.2 g, 27 mmol, 1 equiv) in THF (40 mL) and water (20 mL) was added dropwise 36% HCl (3.4 mL, 40.5 mmol, 1.5 equiv) at 0 °C, and the mixture was stirred at ambient temperature for 2 h, which was then neutralized by adding saturated aqueous $NaHCO_3$, then extracted with ethyl acetate (3 × 40 mL). The organic layer was washed with saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to obtain crude **9**, which was recrystallized by a mixture solvent of petroleum ether and ethyl acetate (3:1) furnished 6.66 g of **9** (95%) as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 16.3 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.16–5.92 (m, 1H), 4.65 (t, J = 8.7 Hz, 2H), 4.27 (q, J = 7.2 Hz, 2H), 3.31 (t, J = 8.7 Hz, 2H), 2.53 (s, 3H), 1.31 (t, J = 8.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7, 166.3, 163.1, 144.1, 133.5, 132.0, 130.2, 127.0, 121.7, 109.3, 71.8, 60.5, 29.4, 28.3, 13.8. HRMS (EI-quadrupole) m/z: $[M]^+$ Calcd for $C_{15}H_{16}O_4$ 260.1049; Found 260.1051.

4.8. (*E*)-Ethyl 3-(5-(1-(*S*)-((*tert*-butylsulfinyl)imino)ethyl)-2,3-dihydrobenzofuran-4-yl) acrylate 10

A solution of **9** (4 g, 15.4 mmol, 1 equiv) and 66% $Ti(OEt)_4$ (21.3 g, 61.5 mmol, 4 equiv) in anhydrous THF (40 mL) was stirred for 10 min at 0 °C. To the resulting solution was added (*S*)-*N*-(*tert*-butylsulfinyl)amine (2.05 g, 16.9 mmol, 1.1 equiv) and stirred at 60 °C for 24 h. Next, saturated aqueous $NaHCO_3$ was added at 0 °C until white titanium salts precipitated. The suspension was filtered through a short pad of Celite washing with small portions of ethyl acetate. The filtrate was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated to give crude **10**, which was purified by flash chromatography on silica gel (3:1 petroleum ether/ethyl acetate) to give 4.5 g (81%) of **10** as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.84 (m, 1H), 7.36 (d, J = 8.3 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.06 (dd, J = 16.3, 9.5 Hz, 1H), 4.73–4.53 (m, 2H), 4.24 (t, J = 7.2 Hz, 2H), 3.45–3.22 (m, 2H), 2.71 (s, 3H), 1.30 (q, 3H), 1.25 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.4, 166.2, 162.0, 143.6, 133.9, 131.1, 129.6, 127.0, 121.6, 109.3, 71.8, 60.7, 56.5, 30.2, 29.3, 22.3, 14.2. $[\alpha]_D^{25} = -4.1$ (c 1.0, $CHCl_3$). HRMS (EI-quadrupole) m/z: $[M]^+$ Calcd for $C_{19}H_{25}NO_4S$ 363.1504; Found 363.1502.

4.9. Ethyl 2-((8S)-6-(((*S*)-*tert*-butylsulfinyl)imino)-2,6,7,8-tetrahydro-1H-indeno[5,4-b]furan-8-yl)acetate 11

To a solution of **10** (5.5 g, 15.1 mmol, 1 equiv) in anhydrous THF (80 mL) was added TBAF (1 M in THF, 18 mL, 18.1 mmol, 1.2 equiv) at −78 °C, and the reaction temperature was allowed to rise until TLC revealed the disappearance of **10**. Next, the reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate (3 × 25 mL). The organic layer was washed with brine (30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to obtain crude **11**, which was purified by flash

chromatography on silica gel (3:1 petroleum ether/ethyl acetate) to give 5.4 g (98%) of **11** as a brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 8.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 4.67 (dd, J = 15.5, 14.1 Hz, 2H), 4.11 (q, J = 7.1 Hz, 2H), 3.69 (d, J = 18.8 Hz, 2H), 3.33–3.12 (m, 2H), 2.99–2.73 (m, 2H), 2.48–2.36 (m, 1H), 1.28 (s, 9H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.1, 171.2, 165.3, 148.9, 132.2, 124.7, 122.2, 110.0, 72.4, 60.4, 57.1, 39.4, 38.2, 37.1, 27.7, 22.4, 14.0. $[\alpha]_D^{25} = +96.9$ (c 1.0, $CHCl_3$). HRMS (EI-quadrupole) m/z: $[M]^+$ Calcd for $C_{19}H_{25}NO_4S$ 363.1504; Found 363.1505.

4.10. (*S*)-Ethyl 2-(6-oxo-2,6,7,8-tetrahydro-1*H*-indeno[5,4-b] furan-8-yl)acetate 12

To a solution of **11** (5.4 g, 14.9 mmol, 1 equiv) in anhydrous MeOH (40 mL) was added 3 M HCl (12 mL, 22.4 mmol, 1.5 equiv) at 0 °C, and then stirred at room temperature for 4 h, after which TLC revealed the disappearance of **11**. The reaction mixture was then quenched with saturated brine, and extracted with ethyl acetate (3 × 30 mL). The organic layer was washed with brine (30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to obtain crude **12**, which was purified by flash chromatography on silica gel (4:1 petroleum ether/ethyl acetate) to give 3.4 g (88%) of **12** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 8.3 Hz, 1H), 4.85–4.60 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.74 (td, J = 7.5, 3.9 Hz, 1H), 3.39–3.18 (m, 2H), 3.05–2.84 (m, 2H), 2.61–2.36 (m, 2H), 1.23 (t, J = 8.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.8, 171.6, 166.6, 153.4, 130.3, 125.0, 122.5, 110.4, 72.6, 60.1, 43.4, 38.4, 33.7, 27.0, 14.2. $[\alpha]_D^{25} = -73.5$ (c 1.0, $CHCl_3$). Chiral HPLC (96:4, $t_{R\,minor}$ = 14.0 min, $t_{R\,major}$ = 17.4 min). HRMS (EI-quadrupole) m/z: $[M]^+$ Calcd for $C_{15}H_{16}O_4$ 260.1049; Found 260.1046. The enantiomeric excess was determined as described in the procedure: Column: AD-H. Solvent: Mobile phase. Mobile phase: Hexane:IPA = 70:30. Concentration: 0.5 mg/mL. Injection volume: 10 μL. Flow rate: 0.5 mL/min. Detection: UV operated at 234 nm. Temp: 30 °C.

4.11. (*S*)-Ethyl 2-(2,6,7,8-tetrahydro-1*H*-indeno[5,4-*b*]furan-8-yl)acetate 13

To a solution of **12** (3 g, 11.53 mmol, 1 equiv) in ethyl acetate (10 mL) and AcOH (10 mL) was added in portions 10% Pd/C (0.6 g, 0.58 mmol, 0.05 equiv), and the mixture was hydrogenated under 40 psi of H_2 and at 45 °C for 24 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to furnish 2.8 g (98%) crude **13** as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 4.63–4.48 (m, 2H), 4.17 (q, J = 7.1 Hz, 2H), 3.63–3.53 (m, 1H), 3.25–3.05 (m, 2H), 2.94–2.84 (m, 1H), 2.82–2.70 (m, 2H), 2.42–2.28 (m, 2H), 1.85 (ddt, J = 13.8, 8.3, 5.6 Hz, 1H), 1.27 (t, J = 7.1 Hz, 3H). $[\alpha]_D^{25} = -58.9$ (c 1.0, $CHCl_3$).

4.12. (*S*)-2-(2,6,7,8-tetrahydro-1*H*-indeno[5,4-*b*]furan-8-yl) ethanol 14

To a solution of $LiAlH_4$ (475 mg, 12.5 mmol, 1.1 equiv) in anhydrous THF (10 mL) flushed with Ar was added a solution of **13** (2.8 g, 11.4 mmol, 1 equiv) in anhydrous THF (20 mL) at 0 °C, which was stirred at room temperature for 1 h. The reaction mixture was diluted with THF (20 mL) and then quenched with water (475 mg) at 0 °C, to which was added 15% aqueous NaOH, then water (1.425 g). The reaction mixture was dried over anhydrous $MgSO_4$ after being stirred at room temperature for 15 min and then filtered through a pad of Celite and concentrated under reduced pressure to furnish 2.30 g (97%) of crude **14** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (t, J = 15.9 Hz, 1H), 6.62 (d, J = 7.9 Hz, 1H), 4.66–4.42 (m, 2H), 3.90–3.65 (m, 2H), 3.26 (dt, J = 15.0, 9.7 Hz, 2H), 3.19–3.05 (m, 1H), 2.99–2.82 (m, 1H), 2.83–2.67 (m, 1H), 2.27 (dtd, J = 12.6, 8.3, 6.4 Hz, 1H), 2.11 (dtd, J = 13.5, 7.5, 4.1 Hz, 1H), 1.92–1.74 (m, 1H), 1.68 (dddd, J = 13.4, 10.1, 6.8, 5.4 Hz, 1H). $[\alpha]_D^{25} = -81.4$ (c 1.0, $CHCl_3$).

4.13. (*S*)-2-(2,6,7,8-tetrahydro-1*H*-indeno[5,4-*b*]furan-8-yl) ethanamine 15

To a solution of **14** (2.8 g, 13.7 mmol, 1 equiv) were added mesyl chloride (1.7 g, 15.1 mmol, 1.1 equiv) and Et_3N (2.8 g, 27.4 mmol, 2 equiv) at room temperature. After being stirred for 1 h, the reaction mixture was quenched with a saturated sodium bicarbonate solution (10 mL), extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to furnish a yellow liquid, which was dissolved in DMF (20 mL). Next, phthalimide potassium salt (2.8 g, 15.1 mmol, 1.1 equiv) was added to the solution, and the mixture was heated at 100 °C for 1 h. After the reaction was completed, it was poured into ice-water, extracted with DCM, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to furnish a yellow solid, which was dissolved in EtOH (20 mL). Hydrazine hydrate (1.7 g, 15.1 mmol, 1.1 equiv) was added to the solution, and refluxed for 3 h. The suspension was filtered through Celite and washed with DCM. The filtrate was extracted with DCM and the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated to give crude **15** 2.76 g (90%, three steps), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 2H), 6.93 (d, J = 7.8 Hz, 1H), 6.61 (d, J = 7.8 Hz, 1H), 4.60–4.47 (m, 2H), 3.40–3.11 ((m, 5H), 2.87–2.75 (m, 2H), 2.35–1.95 (s, 2H), 1.89–1.65 (m, 2H). $[\alpha]_D^{25} = -69.2$ (c 1.0, $CHCl_3$).

4.14. Ramelteon 1

The preparation of Ramelteon **1** was carried out according to the literature.[10] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, J = 8.0 Hz, 1H), 6.60 (t, J = 8.0 Hz, 1H), 5.51 (br, 1H), 4.65–4.42 (m, 2H), 3.41–3.28 (m, 2H), 3.29–3.01 (m, 4H), 2.95–2.84 (m, 1H), 2.82–2.70 (m, 1H), 2.34–2.21 (m, 1H), 2.17 (q, J = 7.6 Hz, 2H), 2.08–1.91 (m, 1H), 1.89–1.75 (m, 1H), 1.70–1.56 (m, 1H), 1.14 (t, J = 8.2 Hz, 3H). $[\alpha]_D^{25} = -54.8$ (c 1.0, $CHCl_3$). LC–MS: 260.20$[M+H]^+$.

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