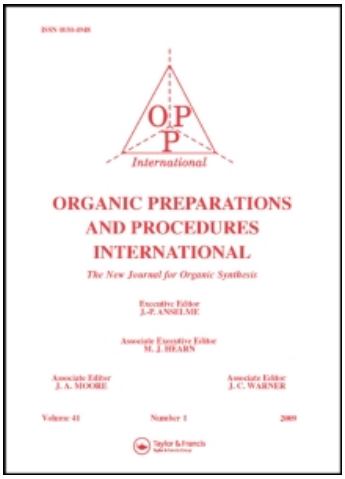

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An Efficient Synthesis of 1,2,6,7-Tetrahydro-8*H*-indeno[5,4-*b*]furan-8-one

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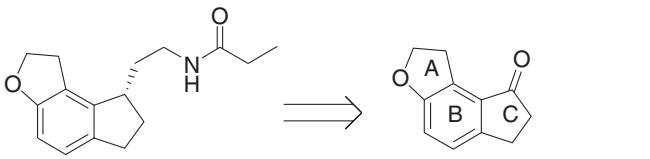
Millions of people worldwide suffer from insomnia. Recently a new drug named *Ramelteon* has been approved by FDA for the treatment of insomnia.[1] In contrast to the present sleep agents, *Ramelteon* works by a completely new mechanism, specifically targeting two receptors in the brain, MT1 and MT2.[2–5] Moreover, human studies have shown that *Ramelteon* has no risk of drug dependence and abuse, which are often associated with other FDA-approved drugs. However, the reported synthesis of *Ramelteon* involves rather inconvenient procedures,[3] especially for the preparation of the key intermediate 1,2,6,7-tetrahydro-8*H*-indeno[5,4-*b*]furan-8-one (**6**). As a part of our exploration of a facile synthesis of *Ramelteon*, we have developed an efficient preparation of compound **6** from commercially available 6-methoxyindan-1-one (**7**). Herein we report the detail of our investigations.



Ramelteon

1,2,6,7-tetrahydro-8H-indeno[5,4-b]furan-8-one (**6**)

Figure 1

To the best of our knowledge, the only synthetic route to 1,2,6,7-tetrahydro-8*H*-indeno[5,4-*b*]furan-8-one (**6**) involves nine steps from 2,3-dihydrobenzofuran (**1**).[6–10] Thus, a more convenient synthesis for ketone (**6**) was needed. Retrosynthetic analysis indicated that this tricyclic compound might be synthesized *via* two strategies, namely construction of the cyclopentanone moiety (C ring) or construction of tetrahydrofuran moiety (A ring).

Our first approach was to construct the cyclopentanone ring (C ring) from 2,3-dihydrobenzofuran (**1**), as illustrated in *Scheme 1*. First, starting material **1** was transformed

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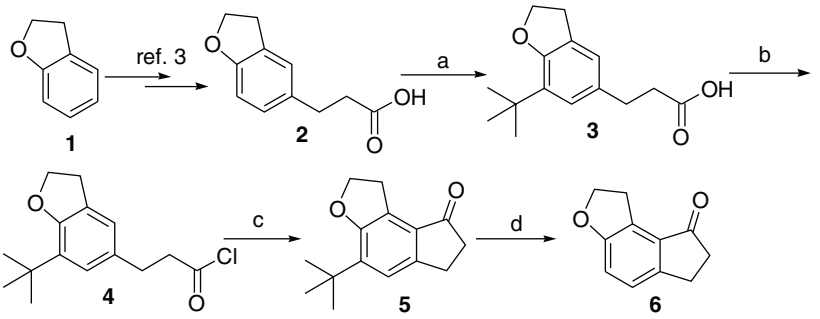
into **2** according the reported procedure,[10] which was treated with *tert*-butyl alcohol under acidic conditions to give compound **3** in 85% yields. Subsequently, **3** was subjected to Friedel-Crafts acylation to afford compound **5**. The regioselectivity of acylation reaction was probably dominated by the steric hindrance of the bulky *tert*-butyl group. Unfortunately, removal of the *tert*-butyl group proved to be rather difficult. Indeed, under several conditions, such as $AlCl_3$, $FeCl_3$ and $AlCl_3$/dry HCl, the yield of the last step was still quite low, with most of the compound **5** being recovered. The best yield was only 20%.



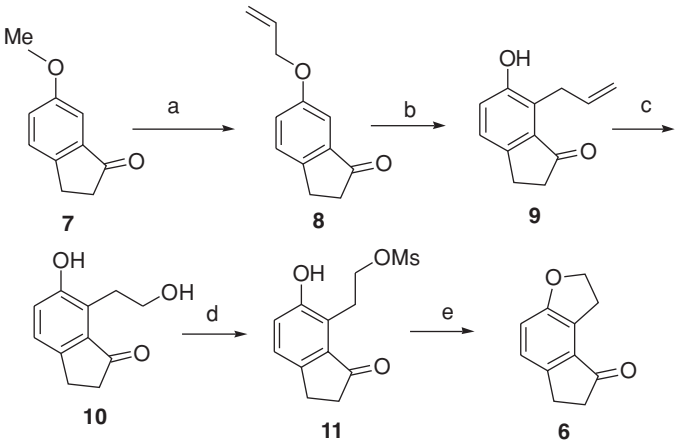
(a) H_3PO_4, t-BuOH, 90%; (b) $(CO)_2Cl_2$, DMF, CH_2Cl_2; (c) $AlCl_3$, CH_2Cl_2, 70% from 13; (d) $AlCl_3$, dry HCl, benzene, 20%

Scheme 1

These unsatisfactory results led us to devise new strategy. It was realized that the construction of the tetrahydrofuran moiety (A ring) deserved careful investigation. Recently, Marsaioli and coworkers[11] reported that 6-allyloxyindan-1-one (**8**) could rearrange to give 6-hydroxy-7-allylindan-1-one (**9**) by heating in sealed ampoules. Although this protocol could not be used in large-scale preparation, it inspired us to develop a novel synthetic procedure of 1,2,6,7-tetrahydro-8*H*-indeno[5,4-*b*]furan-8-one (**6**) (*Scheme 2*).

Commercially available 6-methoxyindan-1-one (**7**) was first converted to compound **8** in good yields according to the published procedures.[11,12] Upon heating in *N,N*-dimethylaniline, complete conversion of **8** into **9** was observed, without other regioisomers. Subsequently, the intermediate **9** was treated with ozone and KBH_4 to afford compound **10** in 85% yields. Esterification of compound **10** at low temperature ($-10\,^{\circ}C$) gave compound **11**. In the final step, **11** was treated with triethylamine to give the tricyclic compound **6** in 65% yields. After crystallization, compound **6** was obtained in better than 99% purity. The effectiveness and reliability of this procedure were undiminished on a preparative scale. At present, the tricyclic compound **6** has been produced in kilogram without loss of purity or yields.

In summary, we have developed a six-step synthesis of the tricyclic compound **6** in 41% overall yield from commercially available 6-methoxyindan-1-one (**7**). The advantages of this procedure include short reaction steps, simple operation and good yields.



(a) (i) $AlCl_3$, toluene; (ii) K_2CO_3, acetone, allyl bromide, 85% (two steps);
(b) *N,N*-dimethylaniline, 180^0C, 88%; (c) O_3, KBH_4, CH_3OH, 85%;
(d) CH_3SO_2Cl, Py, CH_2Cl_2; (e) Et_3N, EtOAc, 65% (two steps).

Scheme 2

Experimental Section

^{1}H NMR spectra were recorded on a Bruker DRX-500 (500 MHz). ^{13}C NMR spectra were obtained on a JNM-EX400 (100 MHz). Mass spectra (MS) were determined on a Finnigan MAT-95 mass spectrometer.

3-(7-tert-Butyl-2,3-dihydrobenzofuran-5-yl)propionic Acid (3)

To a solution of **2** (1.00 g, 5.21 mmol) in concentrated phosphoric acid (10 mL) was added dropwise *t*-BuOH (0.424 g, 5.73 mmol). The mixture was heated at 80°C for 4 h. After cooling to room temperature, the mixture was poured into water (50 mL), and extracted with CH_2Cl_2 (20.0 ml × 2). The organic phase was washed with brine (20 mL × 2), dried with Na_2SO_4, and concentrated to give **3** (1.16 g, 90% yield) as a off-white solid, mp. 126–127°C.

^{1}H NMR ($CDCl_3$): δ 1.33 (s, 9 H), 2.64 (t, J = 8.2 Hz, 2 H), 2.88 (t, J = 7.9 Hz, 2 H), 3.13 (t, J = 8.7 Hz, 2 H), 4.53 (t, J = 8.7 Hz, 2 H), 6.90 (d, J = 15.7 Hz, 2 H), 10.3 (br, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.97, 156.53, 132.74, 131.68, 127.61, 124.64, 122.20, 70.48, 36.20, 34.00, 30.37, 29.69, 29.21. MS (EI): *m/z* 248 (M^+, 37.80), 233 (100.00). HRMS (EI): *m/z* Calcd. for $C_{15}H_{20}O_3$ [M^+]: 248.1412. Found: 248.1413.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.43; H, 8.01.

*3-(7-***tert***-Butyl-2,3-dihydrobenzofuran-5-yl)propionyl Chloride (4)*

A solution of **3** (1.16 g, 4.67 mmol) and DMF (0.47 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0–5°C. To this solution was added dropwise oxalyl chloride (1.20 g, 9.34 mmol). Then the mixture was stirred for 2 h at room temperature, and evaporated to dryness to give crude **4** (1.20 g) as a yellow oil, which was used in the next step without purification.

4-tert-*Butyl-1,2,6,7-tetrahydro-8*H-*indeno[5,4-*b*]furan-8-one (5)*

A mixture of crude **4** (1.20 g) and $AlCl_3$ (1.20 g, 9.00 mmol) in CH_2Cl_2 (20 mL) was stirred room temperature for 4 h. After **4** disappeared, the mixture was quenched with water (40 mL), and extracted with CH_2Cl_2 (20 mL × 2). The organic layer was washed with brine (20 mL × 2), dried with Na_2SO_4 and concentrated to give a residue, which was purified by column chromatography with ethyl acetate/hexane (1:3) to yield **5** (0.75 g, 70% yield from **3**) as a pale yellow solid, mp. 130–132°C.

^{1}H NMR ($CDCl_3$): δ 1.35 (s, 9 H), 2.65 (m, 2 H), 3.15 (d, $J = 6$ Hz, 2 H), 3.45 (t, $J = 8.5$ Hz, 2 H), 4.65 (m, 2 H), 7.15 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.25, 158.29, 147.60, 140.52, 131.50, 123.97, 122.17, 71.65, 37.17, 34.87, 28.96, 28.16, 25.58. MS (EI): *m/z* 230 (M^+, 50.22), 231 (9.20), 216 (15.60), 215 (100.00). HRMS (EI): *m/z* Calcd. for $C_{15}H_{18}O_2$ [M^+]: 230.1307. Found: 230.1310.

Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.02; H, 7.81.

6-Allyloxyindan-1-one (8)

A solution of 6-methoxyindan-1-one (**7**) (20 g, 0.123 mol) and $AlCl_3$ (41.2 g, 0.308 mol) in dry toluene (200 mL) was refluxed for 3 h. After cooling to room temperature, water (200 mL) was added, and the organic layer was separated. The water phase was extracted with ethyl acetate (200 mL × 2). The organic phase was combined, washed with brine (100 mL × 2), dried over Na_2SO_4 and evaporated under reduced pressure to give 17 g of 6-hydroxyindan-1-one (93% yield). Subsequently, to a mixture of 6-hydroxyindan-1-one (17 g, 0.115 mol) and K_2CO_3 (47.6 g, 0.345 mol) in acetone (300 mL), was added allyl bromide (27.8 g, 0.23 mol). After refluxing for 7 h, the mixture was cooled to room temperature and filtered to remove inorganic solid. The filtrate was evaporated under reduced pressure to give 19.5 g of **8** (91% yield) as a pale yellow solid, mp. 50–51°C, after trituration with petroleum ether.

^{1}H NMR ($CDCl_3$): δ 2.70 (t, $J = 6$ Hz, 2 H), 3.05 (t, $J = 6$ Hz, 2 H), 4.56 (d, $J = 4$ Hz, 2 H), 5.29 (d, $J = 11$ Hz, 1 H), 5.41 (d, $J = 17$ Hz, 1 H), 6.05 (m, 1 H), 7.20 (m, 2 H), 7.36 (d, $J = 8$ Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ206.90, 158.23, 148.03, 138.15, 132.69, 127.37, 124.43, 117.93, 105.99, 69.00, 36.95, 25.06. MS (EI): *m/z* 188 (M^+, 74.16).

6-Hydroxy-7-allylindan-1-one (9)

A solution of **8** (10.0 g, 53.2 mmol) in *N*,*N*-dimethylaniline (40 mL) was heated at 180°C for 10 h under nitrogen. After the rearrangement was completed, *N*,*N*-dimethylaniline was evaporated under reduced pressure to give crude **18**, which was recrystallized from ethyl acetate to give 8.80 (88%) g of **9** as a yellow solid, mp. 124–125°C.

^{1}H NMR ($CDCl_3$): δ 2.70 (t, $J = 6$ Hz, 2 H), 3.00 (t, $J = 6$ Hz, 2 H), 4.01 (d, $J = 6$ Hz, 2 H), 5.12 (m, 2 H), 5.27 (s, 1 H), 6.00 (m, 1 H), 7.06 (d, $J = 8$ Hz, 1 H), 7.25 (d, $J = 8$ Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.44, 154.03, 148.68, 135.83, 134.66, 125.28, 124.07, 122.98, 116.04, 37.69, 28.05, 24.37. MS (EI): *m/z* 188 (M^+, 49.80), 173 (100.00). HRMS (EI): *m/z* Calcd. for $C_{12}H_{12}O_2$ [M^+]: 188.0837. Found: 188.0839.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.42; H, 6.34.

6-Hydroxy-7-(2-hydroxyethyl)indan-1-one (10)

A stream of ozone was bubbled through a solution of **9** (8.80 g, 46.8 mmol) in methanol (45 mL) at –40°C until compound **9** disappeared. The excess ozone was removed by purging with nitrogen. Potassium borohydride (2.53 g, 46.8 mmol) was added to decompose ozonide, and the mixture was allowed to warm to room temperature with stirring for 1 h. Then, the mixture was made slight acidic (pH 4–5) by the careful addition of a few drops of 5% HCl. The mixture was extracted into ethyl acetate (20 mL × 3), washed with brine, dried with Na_2SO_4, and concentrated to yield 7.64 g of **10** (85% yield) as a off-white solid, mp. 135–136°C, after trituration with petroleum ether.

^{1}H NMR (DMSO-d_6): δ 2.59 (t, $J = 6$ Hz, 2 H), 2.90 (t, $J = 5.5$ Hz, 2 H), 3.18 (t, $J = 7.5$ Hz, 2 H), 3.44 (m, 2 H), 4.68 (t, $J = 5.5$ Hz, 1 H), 7.08 (d, $J = 8$ Hz, 1 H), 7.19 (d, $J = 8.5$ Hz, 1 H), 9.5 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 207.37, 154.68, 146.62, 134.88, 124.72, 123.50, 121.90, 60.54, 37.20, 27.48, 23.86. MS (EI): *m/z* 192 (M^+, 28.08), 174 (86.22), 173 (100.00). HRMS (EI): *m/z* Calcd. for $C_{11}H_{12}O_3$ [M^+]: 192.0786. Found: 192.0788.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.58; H, 6.11.

6-Hydroxy-7-(2-mesyloxyethyl)indan-1-one (11)

Methanesulfonyl chloride (4.74 g, 41.6 mmol) was added dropwise to a stirred solution of **10** (7.64 g, 39.6 mmol) and pyridine (6.32 g, 80.0 mmol) in CH_2Cl_2 (30 mL) at −10°C. After stirring for 10 h, a solution of 10% HCl (20 mL) was added to the mixture. The organic layer was washed saturated $NaHCO_3$ (20 mL × 2), dried with Na_2SO_4, and concentrated to give crude **11** (10.5 g) as a pale yellow solid, after trituration with petroleum ether; it was used directly in the next step.

^{1}H NMR ($CDCl_3$): δ 2.70 (m, 2 H), 3.00 (s, 3 H), 3.03 (t, $J = 5.6$ Hz, 2 H), 3.56 (t, $J = 6.6$ Hz, 2 H), 4.51 (t, $J = 6.6$ Hz, 2 H), 7.12 (d, $J = 8.2$ Hz, 1 H), 7.26 (d, $J = 8.1$ Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.31, 154.01, 149.00, 135.28, 126.12, 123.36, 121.14, 69.85, 37.57, 37.47, 24.58, 24.41. MS (EI): *m/z* 270 (M^+, 2.98), 204 (100.00). HRMS (EI): *m/z* Calcd. for $C_{12}H_{14}O_5S$ [M^+]: 270.0562. Found: 270.0561.

Anal. Calcd. for $C_{12}H_{14}O_5S$: C, 53.32; H, 5.22; S, 11.86. Found: C, 53.11; H, 5.13; S, 11.72.

1,2,6,7-Tetrahydro-8*H*-indeno[5,4-*b*]furan-8-one (6)

A solution of crude **11** (10.5 g) and triethylamine (7.86 g, 77.8 mmol) in ethyl acetate (50 mL) was refluxed for 3 h, and cooled to room temperature. The mixture was washed with 5% HCl (30 mL × 2), brine (20 mL × 2) and dried with Na_2SO_4. The organic layer was evaporated to give crude product, which was recrystallized from ethyl acetate to afford 4.47 g of **2** (65% yield from **10**) as a off white solid, mp. 132–133°C; *lit.*[10] mp. 133–134°C.

^{1}H NMR ($CDCl_3$): δ 2.68 (t, $J = 6$ Hz, 2 H), 3.07 (t, $J = 5.5$ Hz, 2 H), 3.47 (t, $J = 8.8$ Hz, 2 H), 4.65 (t, $J = 9$ Hz, 2 H), 7.01 (d, $J = 8$ Hz, 1 H), 7.19 (d, $J = 9$ Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.41, 160.22, 147.09, 133.65, 125.59, 123.90, 115.60, 72.32, 37.13, 28.38, 25.37. MS (EI): *m/z* = 174 (M^+, 90.55), 173 (100.00).

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