A facile and practical synthesis of (−)-tasimelteon

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An efficient and practical route for the synthesis of (−)-tasimelteon from 2,3-bis(2-hydroxyethyl)phenol has been developed. The product was prepared in seven steps in overall 16.4% yield using highly stereoselective cyclopropanation reaction of the intermediate as the key step.

Keywords: 2,3-bis(2-hydroxyethyl)phenol, 4-vinyl-2,3-dihydrobenzofuran, tasimelteon, synthesis

Tasimelteon **1** is a new kind of oral melatonin receptor agonist. It was developed by the pharmaceutical company Vanda in the United States.[1] Tasimelteon appeared on the market in January 2014, and has a small dosage, strong efficacy and good tolerability. Early in the synthesis of tasimelteon, 4-vinyl-2,3-dihydrobenzofuran **5** was identified as a key intermediate, allowing further manipulation at the vinyl group. It is prepared from 2,3-bis(2-hydroxyethyl)phenol **2** (triol) as the starting material because of its ready availability from the industrial intermediate 5,8-dihydro-1-naphthol *via* ozonolysis and reduction.[2] Therefore, an efficient synthesis of 4-vinyl-2,3-dihydrobenzofuran **5** became essential. A published method for the synthesis of **5** involves the sulfonylation of 2,3-bis(2-hydroxyethyl)phenol **2** with toluenesulfonyl chloride at −40 °C using pyridine as the base, followed by intramolecular cyclisation in the presence of potassium carbonate and then elimination promoted by *tert*-BuOK to form the key intermediate **5**.[3] Rao *et. al.* reported a two-step synthesis of 4-vinyl-2,3-dihydrobenzofuran **5** from 2,3-bis(2-hydroxyethyl)phenol **2** with the Vilsmeier reagent *via* ring closure, chlorination and dehydrohalogenation using a phase-transfer catalyst.[2]

Jacobsen asymmetric epoxidation and Sharpless asymmetric dihydroxylation of 4-vinyl-2,3-dihydrobenzofuran **5** were scaled up to prepare large quantities of the chiral dihydrobenzofuran epoxide.[4] Singh's group developed the cyclopropanation reaction of the chiral epoxide product with the anion of triethylphosphonoacetate.[5] Furthermore, the asymmetric cyclopropanation of **5** with ethyl diazoacetate in the presence of a chiral catalyst has been investigated by Vanda.[6] Subsequently, the cyclopropanation product underwent hydrolysis, aminoacylation and reduction to obtain the optical tasimelteon. Catt's group reported a novel method for the asymmetric synthesis of tasimelteon that involved 2,3-dihydrobenzofuran-4-carbaldehyde as a starting material.[7]

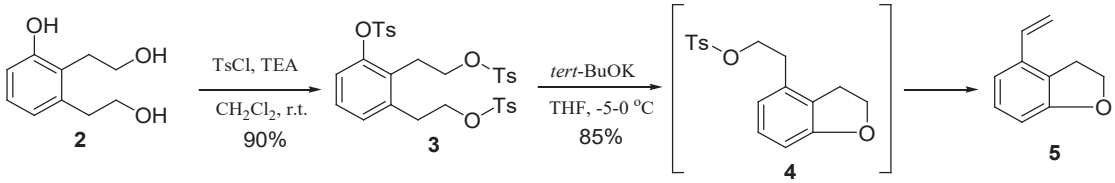
Owing to the lengthy synthetic routes, strict conditions, high cost and difficulties in large-scale preparation, an efficient and practical synthetic method for optically active tasimelteon is desirable. Herein, we report a convenient synthesis of tasimelteon in good yields starting from 2,3-bis(2-hydroxyethyl)phenol **2** *via* a highly selective cyclopropanation reaction of the key intermediate **5**.

Results and discussion

The starting point for the synthetic route development is outlined in Scheme 1. This approach involved the preparation of 4-vinyl-2,3-dihydrobenzofuran **5** in a three-step sequence from 2,3-bis(2-hydroxyethyl)phenol **2** as the starting material. Compound **2** was dissolved in CH_2Cl_2 and triethylamine, which was followed by dropwise addition of toluenesulfonyl chloride in CH_2Cl_2. The unknown tosylated compound **3** was provided in high yield (90%) and further utilised into the next step without purification. The synthesis of 4-vinyl-2,3-dihydrobenzofuran **5** is described in Scheme 1. Initially, compound **3** was treated with 2.0 equiv. of *tert*-BuOK, which mainly gave intermediate **4** in anhydrous THF at −5–0 °C. Interestingly, we observed that elimination of intermediate **4** was easily carried out and subsequently converted into 4-vinyl-2,3-dihydrobenzofuran **5** by increasing the amounts of *tert*-BuOK. A one-pot reaction of compound **3** treated with 5.0 equiv. of *tert*-BuOK gave the key compound **5** in 85% yield. The sulfonate, compound **3**, was susceptible to elimination, forming an irreversible diene byproduct, and the intermediate product **4** could not be obtained. We investigated a variety of bases, such as NaOMe, EtONa, *tert*-BuOK, *tert*-BuONa and sodium *tert*-amyl alcohol. Of the various screened bases, *tert*-BuOK was found to be the best base in terms of yield and selectivity.

With compound **5** in hand, it was first subjected to epoxidation using 30% hydrogen peroxide and 2,2,2-trifluoroacetophenone.[8] Unfortunately, the epoxide **6** was not obtained. We succeeded in epoxidising compound **5** using 30% hydrogen peroxide as an oxidant in the presence of sodium bicarbonate in acetonitrile under mild conditions in 75% yield.[9] Subsequently, we focused on investigating the cyclopropanation of epoxide **6**.

The reaction of epoxides with the anion of triethyl phosphonoacetate in the synthesis of cyclopropane derivatives has been known for over four decades.[10,11] Singh developed a practical, safe and high-yielding process for the cyclopropanation of a chiral epoxide such as **6** using triethyl phosphonoacetate and *tert*-BuONa.[6] Herein, we tried the cyclopropanation reaction of epoxide **6** using diethyl cyanomethylphosphonate under similar conditions, but a low yield was provided (Scheme 2). To evaluate the scalability of this reaction, we systematically



Scheme 1

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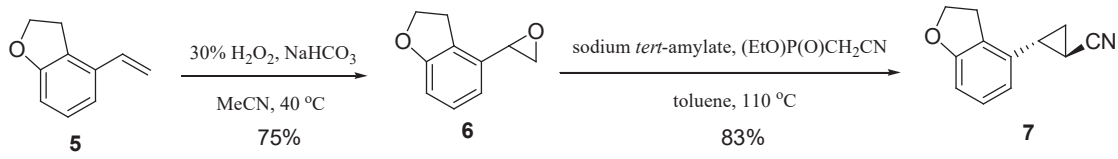
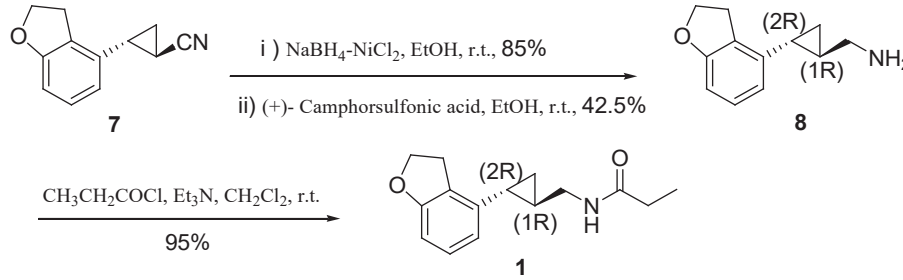


Scheme 2



Scheme 3

studied the effect of base, solvent and temperature on the extent of reaction completion. The results are listed in Table 1.

Initial experiments were carried out with sodium *tert*-amylate (STA) in different solvents and at different temperatures because it is a very common and inexpensive base. By screening various solvents, we found that toluene is the best solvent for this reaction (Table 1, entry 9). Moderate yield was given in DMSO (Table 1, entry 6). Low yields were given in dioxane and DMF (Table 1, entries 4 and 5). No reactions were observed in THF, DME and 2-MeTHF (Table 1, entries 1–3). It is worth noting that the reaction temperature has an obvious effect on the rate and conversion of the cyclopropanation reaction. The reaction rate was considerably slow at temperatures below 100 °C. It was efficiently conducted at 110 °C and good yield was obtained (Table 1, entry 9). As the anion of TEPA can be formed by almost any base (hydrides, alkoxides and alkyllithiums), we screened several common bases in toluene. The cyclopropanation reaction did not work well in toluene at 110 °C with CH_3ONa, *tert*-BuONa, *tert*-BuOK, NaH and LiHMDS as bases (Table 1, entries 12–16). In addition, sufficient reaction time was necessary for conversion to the desired product **7**. With the improved reaction conditions in hand, STA was selected for further scale-up work due to its ease of handling, low hazards and low cost.

Treatment of cyano compound **7** with $NaBH_4$–$NiCl_2$ in EtOH provided the primary racemic amine. After completion, the reaction was quenched by 2 mol L^{-1} HCl aqueous solution. Ethyl acetate was added and the aqueous phase was separated. This aqueous was adjusted to pH = 12 using 2 mol L^{-1} NaOH aqueous and extracted with ethylacetate. The enantiomer mixture was found to be efficiently separated as the salt or complex with a resolving agent such as (+)-10-camphorsulfonic acid. The most favourable separation was achieved when 0.5 equiv. of resolving agent is mixed with the enantiomer mixture. The optical compound **8** was obtained in 42.5% yield (based on the racemic compound) with 95.6% e.e. Finally, the target product tasimelteon **1** was successfully obtained by the acylation of compound **8** with propionyl chloride in the presence of triethylamine at room temperature.

Conclusion

The one-pot, two-step process for the synthesis of 4-vinyl-2,3-dihydrobenzofuran **5** was fulfilled *via* compound **3**, which was not isolated. A practical, safe and high-yielding process for the cyclopropanation of epoxide **6** using the inexpensive and nonhazardous reagents diethyl cyanomethylphosphonate and sodium *tert*-amylate was developed as the key step. (+)-10-Camphorsulfonic acid was selected as the optimal resolving agent.

Table 1 Optimisation of cyclopropanation reaction conditions of epoxide **6** with diethyl cyanomethylphosphonate[a]

Entry	Base	Solvent	Temperature/°C	Time/h	Product **7** yield/%[b]
1	STA	THF	65	5.0	–
2	STA	DME	85	5.0	–
3	STA	2-MeTHF	80	5.0	–
4	STA	1,4-dioxane	101	5.0	14
5	STA	DMF	125	5.0	47
6	STA	DMSO	127	5.0	60
7	STA	toluene	90	5.0	24
8	STA	toluene	100	5.0	31
9	STA	toluene	110	5.0	83
10	STA	toluene	110	3.0	65
11	STA	toluene	110	2.0	60
12	CH_3ONa	toluene	110	5.0	25
13	*tert*-BuONa	toluene	110	5.0	41
14	*tert*-BuOK	toluene	110	5.0	38
15	NaH	toluene	110	5.0	50
16	LiHMDS	toluene	110	5.0	15

[a]The reaction was carried out by the condensation of epoxide **6** (10 mmol) and diethyl cyanomethylphosphonate (15 mmol) in the presence of base (18 mmol) under the above reaction conditions.

[b]Isolated yield by silica gel flash column chromatography.

Experimental

The purification of the products by flash column chromatography utilised silica gel (200–300 mesh) and light petroleum ether (PE, b.p. 60–90 °C). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-500 spectrometer at 500 and 125 MHz, respectively, in $CDCl_3$ solution using Me_4Si as an internal standard. The reactions were monitored by TLC on silica-gel polygram SILG/UV 254 plates. FTIR spectra were recorded on a Bruker Tensor 27 spectrometer. EI-MS spectra were determined on a Perkin Elmer spectrometer. HRMS(EI) was carried out on Waters GCT Premier GC/TOF instrument. ESI-MS and HRMS(ESI) were determined on a Therm LCQ TM Deca XP plus spectrometer. HPLC analysis was conducted using an Agilent 1200, and an OJ-H chiral column was used for chiral analysis. All compounds were identified by ^{1}H NMR and the data are in good agreement with those reported. Melting points were measured on a BUCHI B-540 and are uncorrected.

2,3-Bis(2-tosyloxyethyl)phenyl 4-methylbenzenesulfonate (**3**)

To a stirred solution of 2,3-bis(2-hydroxyethyl)phenol **2** (1.82 g, 10.0 mmol) in CH_2Cl_2 (10 mL) and triethylamine (5.53 mL, 40.0 mmol), a solution of *p*-toluenesulfonyl chloride (5.80 g, 30.5 mmol) in CH_2Cl_2 (10 mL) was added dropwise at room temperature. The mixture was stirred for 8 h at room temperature and filtered. The organic phase was washed with 2 mol L^{-1} HCl, water and brine, and then dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography on silica gel to give compound **3** as: Brown viscous oil; yield 5.83 g (90%); R_f = 0.38 (PE:EtOAc, 3:1); FTIR (film) (ν cm^{-1}): 759, 815, 965, 1096, 1175, 1359, 1456, 1598, 1737, 2892, 2925, 2961, 3067; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.44 (s, 3H), 2.48 (s, 3H), 2.82 (t, *J* = 7.2 Hz, 2H), 2.93 (t, *J* = 6.9 Hz, 2H), 4.04 (t, *J* = 7.2 Hz, 2H), 4.10–4.15 (m, 2H), 6.94–6.99 (m, 2H), 7.09 (t, *J* = 8.0 Hz, 1H), 7.28–7.32 (m, 4 H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.65–7.69 (m, 4H), 7.73–7.75 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.8, 145.8, 144.9, 144.7, 137.8, 130.0, 129.9, 129.8, 128.2, 128.0, 127.7, 127.6, 120.8, 69.6, 68.6, 32.0, 26.3, 21.7, 21.6; MS (ESI) *m*/z (%): 667 (100) $[M + Na]^+$; HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{31}H_{32}NaO_9S_3$: 667.1106; found: 667.1096.

4-Vinyl-2,3-dihydrobenzofuran (**5**)[4]

To a stirred solution of *tert*-BuOK (9.6 g, 86.1 mmol) in THF (20 mL) under nitrogen, a solution of compound **4** (9.20 g, 14.3 mmol) in THF (20 mL) was added dropwise over 0.5 h at −5–0 °C. After addition, the reaction mixture was stirred for 3 h at room temperature. The resulting precipitate was filtered and washed with EtOAc (150 mL). The filtrate was washed with water (3 × 30 mL) and then concentrated under reduced pressure to give a brown liquid. The residue was purified by flash column chromatography on silica gel to give compound **5** as: Colourless oil; yield 1.77 g (85%); R_f = 0.62 (PE:EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.28 (t, *J* = 8.7 Hz, 2H), 4.62 (t, *J* = 8.7 Hz, 2H), 5.38 (d, *J* = 11.2 Hz, 1H), 5.74 (d, *J* = 17.7 Hz, 1H), 6.72–6.78 (m, 2H), 7.03 (d, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H).

4-(Oxiran-2-yl)-2,3-dihydrobenzofuran (**6**)[5]

4-Vinyl-2,3-dihydrobenzofuran **5** (10.0 g, 68.5 mmol) was dissolved in acetonitrile (50 mL). 30% hydrogen peroxide (125 mL, 411 mmol) and $NaHCO_3$ (23.0 g, 274 mmol) was added. After stirring for 24 h at 40 °C, the mixture was filtered and the filtrate was extracted with EtOAc (2 × 100 mL). The organic layer was washed with saturated $NaHSO_3$ aqueous, water and brine. After concentration, the residue was purified by flash column chromatography on silica gel to give compound **6** as: Colourless oil; yield 8.3 g (75%); R_f = 0.32 (PE:EtOAc, 10:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.84 (dd, *J* = 2.6, 5.6 Hz, 1H), 3.14 (dd, *J* = 4.2, 5.6 Hz, 1H), 3.27 (t, *J* = 8.7 Hz, 2H), 3.85 (dd, *J* = 2.8, 4.0, 1H), 4.60 (t, *J* = 8.8 Hz, 2H), 6.71–6.76 (m, 2H), 7.12 (t, *J* = 7.9 Hz, 1H).

2-(2,3-dihydrobenzofuran-4-yl)cyclopropane-1-carbonitrile (**7**)

To a solution of the epoxide compound **6** (14.0 g, 86.4 mmol) in toluene (150 mL), diethyl cyanomethylphosphonate (22.9 g, 129.4 mmol) and sodium *tert*-amylate (17.1 g, 155.5 mmol) were added. The reaction mixture was refluxed at 110 °C under nitrogen for 5 h. After cooling to room temperature, water (100 mL) and EtOAc (300 mL) were added. The organic phase was separated and concentrated under reduced pressure to give a yellow oil. The residue was purified by flash column chromatography on silica gel to give compound **7** as: White solid; m.p. 47.3–47.8 °C; yield 13.3 g (83%); R_f = 0.20 (PE:EtOAc, 10:1); FTIR (KBr) (ν cm^{-1}): 773, 985, 1237, 1457, 1478, 1592, 1612, 2237, 2898, 2970; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46–1.49 (m, 1H), 1.54–1.58 (m, 1H), 1.60–1.64 (m, 1H), 2.52–2.56 (m, 1H), 3.27–3.31 (m, 2H), 4.63 (t, *J* = 8.8 Hz, 2H), 6.39 (d, *J* = 7.8 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 7.07 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 134.1, 128.4, 126.8, 120.9, 115.9, 108.3, 71.0, 28.3, 22.7, 14.3, 5.4; MS (EI) *m*/z (%): 185 (100) $[M]^+$; HRMS (EI) *m/z* $[M]^+$ calcd for $C_{12}H_{11}NO$: 185.0841; found: 185.0826.

(1R, 2R)-[2-(2,3-dihydrobenzofuran-4-yl)cyclopropyl]methanamine (**8**)[12]

To a stirred solution of white solid **7** (3.0 g, 16.2 mmol) in 80 mL ethanol, nickel chloride (2.2 g, 13 mmol) and $NaBH_4$ (4.3 g, 113.4 mmol) were added. The reaction mixture was stirred for 3 h at room temperature. After concentration under reduced pressure, the aqueous was adjusted to pH = 3 by addition of 2 mol L^{-1} HCl aqueous (4 mL). After extraction with EtOAc (30 mL), the aqueous phase was adjusted to pH = 14 by addition of 2 mol L^{-1} NaOH aqueous. The aqueous was then extracted with EtOAc (3 × 40 mL) and concentrated to give a colourless oil in 85% yield (2.6 g). This oil was dissolved in 40 mL of ethanol. (+)-10-Camphorsulfonic acid (1.6 g, 6.9 mmol) was added. The mixture was stirred for 2 h at room temperature, and the precipitated crystals were filtered, rinsed with ethanol and dried to give a white solid. To a stirred solution of this diastereomer complex in 20 mL water, 2 mol L^{-1} NaOH aqueous was added to adjust to pH = 14. The suspension was stirred until it was clear, and then extracted with EtOAc (3 × 40 mL). The organic phase was combined and concentrated to obtain a chiral amine **8** as: Colourless oil; yield 1.1 g (42.5%) (based on the racemic compound) with 95.6% e.e.; [α] = −33.89° (*c* = 10.0 mg mL^{-1}, MeOH); R_f = 0.35 (MeOH:EtOAc, 1:3); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81–0.85 (m, 1H), 0.91–0.95 (m, 1H), 1.27–1.30 (m, 1H), 1.60–1.64 (m, 1H), 1.92 (br s, 2H), 2.72–2.74 (m, 2H), 3.32 (t, *J* = 8.7 Hz, 2H), 4.57 (t, *J* = 8.7 Hz, 2H), 6.37 (d, *J* = 7.8 Hz, 1H), 6.60 (d, *J* = 7.9 Hz, 1H), 7.01 (t, *J* = 7.9 Hz, 1H).

(1R,2R)-N-[[2-(2,3-dihydrobenzofuran-4-yl)cyclopropyl]methyl] propionamide (tasimelteon **1**)[12]

Compound **8** (1.00 g, 5.3 mmol) was dissolved in CH_2Cl_2 (10 mL). Triethylamine (0.95 mL, 6.9 mmol) was added, followed by addition of propionyl chloride (0.54 g, 5.85 mmol) at 0 °C. The reaction mixture was stirred for 2 h and quenched with 2 mol L^{-1} HCl (10 mL). The organic phase was washed with saturated $NaHCO_3$ aqueous (3 × 10 mL), water (3 × 10 mL) and brine (2 × 10 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel to give tasimelteon (**1**) as: Colourless oil; yield 1.23 g (95%) with 96% e.e.; $[\alpha]_D^{25}$ = −37.08 (*c* = 10.0 mg mL^{-1}, $CHCl_3$); R_f = 0.39 (PE:EtOAc, 1:1); FTIR (film) (ν cm^{-1}): 985, 1230, 1459, 1590, 1647 (C=O), 2926, 2974, 3070; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91–0.94 (m, 1H), 0.95–1.00 (m, 1H), 1.18 (t, *J* = 7.6 Hz, 3H), 1.32–1.36 (m, 1H), 1.73–1.76 (m, 1H), 2.22 (q, *J* = 7.6 Hz, 2H), 3.22–3.26 (m, 2H), 3.28–3.37 (m, 2H), 4.60 (t, *J* = 8.7 Hz, 2H), 5.72 (br s, 1H), 6.35 (d, *J* = 7.8 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 7.03 (t, *J* = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8, 159.6, 138.9, 128.2, 126.0, 115.7, 106.8, 71.0, 43.5, 29.7, 28.6, 21.7, 19.7, 13.4, 9.9; MS (ESI) *m*/z (%) = 246 (100) $[M + H]^+$.

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