Available online at www.sciencedirect.com
ScienceDirect
Chinese Chemical Letters 22 (2011) 264–267
CHINESE CHEMICAL LETTERS
www.elsevier.com/locate/cclet

Synthesis of the key intermediate of ramelteon

Shan Bao Yu [a], Hao Min Liu [a], Yu Luo [a], Wei Lu [b,*]

[a] *Department of Chemistry, East China Normal University, Shanghai 200062, China*
[b] *Institute of Drug Discovery and Development, East China Normal University, Shanghai 200062, China*

Received 16 July 2010
Available online 22 December 2010

Abstract

Asymmetric conjugated addition of allylcopper reagents derived from an allyl Grignard reagent and CuBr·Me_2S to chiral α,β-unsaturated *N*-acyl oxazolidinones has been achieved. The synthetic procedure was applied to the preparation of the key intermediate of the novel nonbenzodiazepine hypnotic drug, ramelteon.

Keywords: Ramelteon; Asymmetric Michael addition; Synthesis

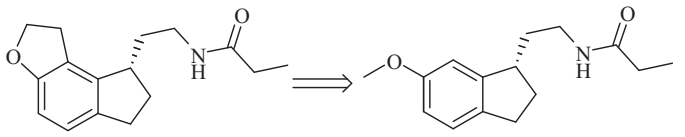
Ramelteon, marketed as Rozerem by Takeda Pharmaceuticals North America, is the first in a new class of sleep agents that selectively binds to the MT1 and MT2 receptors in the suprachiasmatic nucleus (SCN) instead of binding to $GABA_A$ receptors, such as occurs with zolpidem, eszopiclone, and zaleplon [1]. Ramelteon has been approved by the US Food and Drug Administration (FDA) for long-term use for the treatment of insomnia characterized by the difficulty of sleep onset. It is also the first and only prescription sleep medication that is not designated as a controlled substance by the US Drug Enforcement Administration (DEA).

Ramelteon has a unique chemical structure, comprising a three-ring system with an asymmetric center at the benzylic position. Due to the challenging structure, ramelteon has been a popular compound for synthetic chemists. (*S*)-*N*-(2-(6-Methoxy-2,3-dihydro-1*H*-inden-1-yl)ethyl)propionamide **1** (Fig. 1) is the key intermediate for the synthesis of ramelteon. So far, the reported synthesis of compound **1** has mainly been based on catalytic asymmetric hydrogenation [2,3] or resolution [4] of the corresponding racemic mixtures involving difficult procedures. However, known synthetic methods about compound **1** have many defects, involving the use of expensive metal catalysts and phosphorus ligands, or low yield, or low *ee* value. As a part of our research program, we have directed our efforts towards a more practical and efficient strategy to synthesize compound **1** using simple starting materials and reactions.

After having reviewed lots of literature, we found that conjugated addition of various nucleophiles to α,β-unsaturated acid derivatives attached to a chiral auxiliary is an important methodology in asymmetric synthesis. For example, oxazolidinones, which are easily obtained, have been extensively used in related asymmetric fields [5]. Thus, we expected to introduce a stereogenic center *via* an asymmetric Michael addition using (*S*)-4-benzyloxazolidin-2-one **2** as a chiral auxiliary. Herein, we report our synthetic approach to the enantiomerially pure intermediate **1** based on a copper-assisted conjugate addition of a Grignard reagent to chiral α,β-unsaturated *N*-acyl oxazolidinones.

* Corresponding author.
E-mail address: wlu@chem.ecnu.edu.cn (W. Lu).

1001-8417/$ – see front matter
doi:10.1016/j.cclet.2010.10.021



Ramelteon

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

Fig. 1.

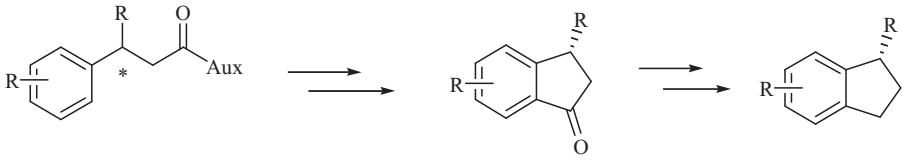
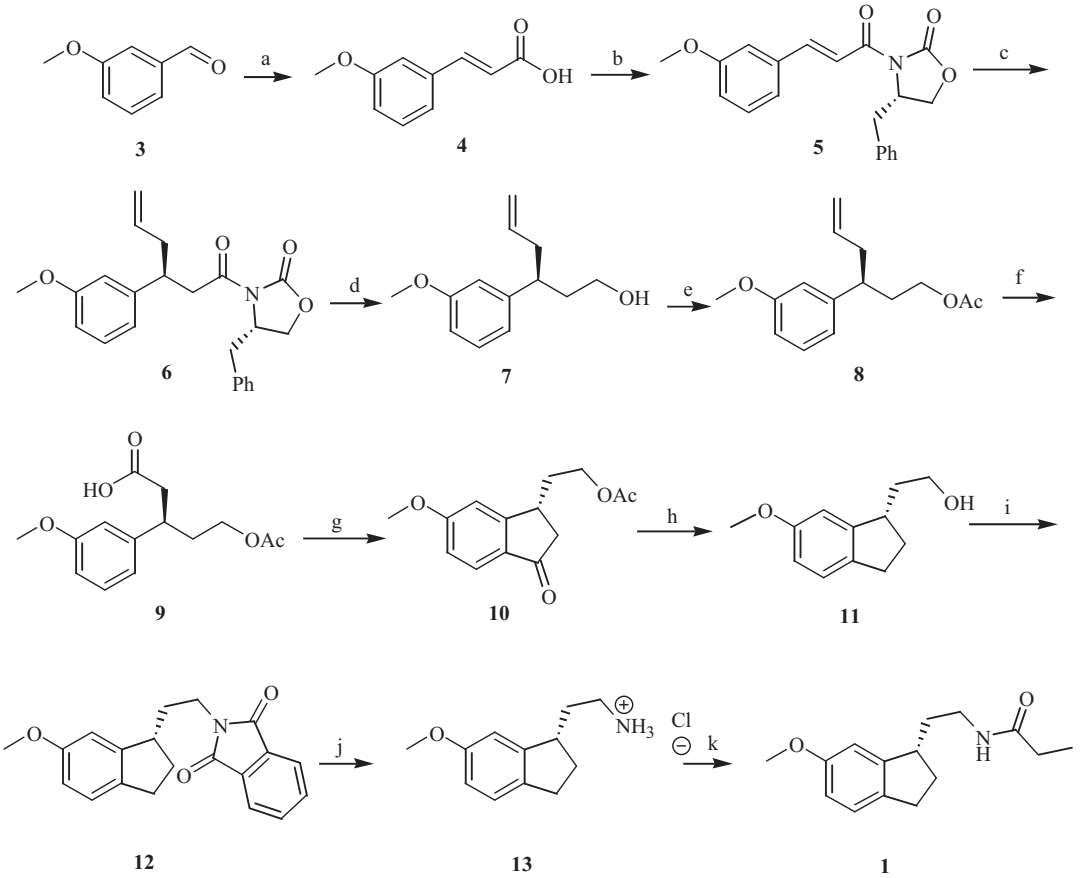


Fig. 2.

Since we were not able to find any chiral 1-substituted indans with a known absolute configuration prepared from 3-substituted indanones in the literature, we focused our attention on developing a novel synthetic strategy that would allow for the synthesis of the enantiopure intermediate **1** with a predetermined absolute configuration. The synthetic procedure we designed consisted of the decarbonylation of chiral 3-substituted indanones (Fig. 2). Optically active 3-



Scheme 1. (a) Malonic acid, piperidine, pyridine. (b) $(COCl)_2$, DMF, CH_2Cl_2; (*S*)-4-benzyloxazolidin-2-one **2**, LiCl, Et_3N, CH_2Cl_2. (c) Allylmagnesium chloride, CuBr. Me_2S, THF. (d) $LiAlH_4$, THF. (e) AcCl, Et_3N, CH_2Cl_2. (f) $NaIO_4$, $KMnO_4$, Me_2CO, H_2O. (g) $(COCl)_2$, DMF, CH_2Cl_2; $SnCl_4$, CH_2Cl_2. (h) Pd/C, H_2, H_2SO_4, EtOH. (i) MsCl, Et_3N, CH_2Cl_2; phthalimide potassium salt, DMF. (j) NH_2NH_2, EtOH. (k) $(CH_3CH_2CO)_2O$, NaOH, THF, H_2O.

substituted indanones with a known stereochemistry have been reported in the literature, and have been prepared using a classical cyclohydration from the corresponding chiral 3-substituted cinnamic acid, which can be obtained using asymmetric synthesis procedures with a high enantiomeric purity [6–8]. The synthesis of (*S*)-*N*-(2-(6-methoxy-2,3-dihydro-1*H*-inden-1-yl)ethyl)propionamide using this methodology is outlined in Scheme 1.

As shown in Scheme 1, the cinnamic acid **4** was easily obtained from 3-methoxybenzaldehyde **3** in a 95% yield, and was condensed with (*S*)-4-benzyloxazolidin-2-one **2** through cinnamoyl chloride to form the chiral unit **5**. Then, the asymmetric conjugate addition of an allylcopper reagent derived from commercially available allylmagnesium chloride and $CuBr{\cdot}Me_2S$ (allylMgCl/Cu 1:1) to the chiral cinnamic unit **5** furnished the intermediate **6** with a high enantiomeric purity. High-pressure liquid chromatography (HPLC) analysis of the reaction mixture suggested a high diastereomeric excess (>99%). This was confirmed in the final step. Removal of the chiral auxiliary ($LiAlH_4$ in THF) yielded the alcohol **7**, which was protected by the acetyl group to result in compound **8** in a 90% yield. Subsequent oxidation of the allyl compound with $NaIO_4/KMnO_4$ (6:1) gave the acid **9** in high yields without further purification. Treating **9** with oxalyl chloride, followed by a Lewis acid-promoted Friedel–Crafts acylation afforded the indanone **10**. Then, pure indanol **11** was obtained through deprotection and reduction in a one-pot procedure with Pd/C catalytic hydrogenation in concentrated sulfuric acid in ethanol. Subsequent amination of the indanol **11** *via* a Gabriel synthesis gave the indanamine **12**, which, after salification (4 M HCl/EtOH), yielded the indanamine hydrochloride **13**. Finally, the reaction of this compound with propionic anhydride under alkaline conditions afforded the key target **1**. HPLC analysis [2,9] revealed an *ee* > 99%. At last, all the prepared compounds gave satisfactory analytical data [10].

In conclusion, an efficient enantioselective synthesis of (*S*)-*N*-(2-(6-methoxy-2,3-dihydro-1*H*-inden-1-yl)ethyl)-propionamide with an absolute configuration has been achieved. Our methodology appears to be suitable for preparing various chiral 3-substituted indanones and 1-substituted indan derivatives.

Acknowledgments

We gratefully acknowledge the Shanghai Municipal Natural Science Foundation (No. 10ZR1409600). We also thank Lab of Organic Functional Molecules, the Sino-French Institute of ECNU for supports.

References

[1] S. Hegde, M. Schmidt, Ann. Report Med. Chem. 41 (2006) 439.
[2] T. Yamano, M. Yamashita, M. Adachi, et al. Tetrahedron: Asymmetry 17 (2006) 184.
[3] M. Yamashita, T. Yamano, Chem. Lett. 38 (2009) 100.
[4] N. Tarui, H. Watanabe, K. Fukatsu, et al. Biosci. Biotechnol. Biochem. 66 (2002) 464.
[5] B.E. Rossiter, N.M. Swingle, Chem. Rev. 92 (1992) 771.
[6] P.G. Andersson, H.E. Schink, K. Österlund, J. Org. Chem. 63 (1998) 8067.
[7] D.L. Romero, P.R. Manninen, F. Han, et al. J. Org. Chem. 64 (1999) 4980.
[8] D.J. Pippel, M.D. Curtis, H. Du, et al. J. Org. Chem. 63 (1998) 2.
[9] O. Uchikawa, K. Fukatsu, R. Tokunoh, et al. J. Med. Chem. 45 (2002) 4222.
[10] **5**: $[\alpha]_D^{20}$ +39.1 (*c*, 1.0, $CHCl_3$); mp 69–71 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.86 (q, 1H, *J* = 9.5 Hz), 3.37 (dd, 1H, *J* = 3.1 Hz, *J* = 13.4 Hz), 3.85 (s, 3H), 4.22 (m, 2H), 4.81 (m, 1H), 6.96 (m, 1H), 7.14 (s, 1H), 7.24–7.36 (m, 7H), 7.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 159.8, 153.4, 146.2, 135.8, 135.3, 129.8, 129.4, 128.9, 127.2, 121.3, 117.2, 116.6, 113.3, 66.1, 55.3, 55.2, 37.8. EI-MS: 337 ($[M]^+$); HR-MS 337.1314 ($[M]^+$, $C_{20}H_{19}NO_4$; Calcd. 337.1315). **6**: $[\alpha]_D^{20}$ +61.6 (*c*, 1.0, $CHCl_3$); mp 66–67 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.45 (m, 2H), 2.66 (m, 1H), 3.29 (dd, 2H, *J* = 4.0 Hz, *J* = 15.0 Hz), 3.20–3.41 (m, 2H), 3.79 (s, 3H), 4.00 (m, 1H), 4.07 (m, 1H), 4.51 (m, 1H), 5.02 (m, 2H), 5.70 (m, 1H), 6.74 (d, 1H, *J* = 8.0 Hz), 6.79 (s, 1H), 6.84 (d, 1H, *J* = 8.0 Hz), 7.16–7.33 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.8, 159.6, 153.4, 145.3, 136.0, 135.3, 129.3, 128.9, 127.3, 120.0, 116.9, 113.4, 113.3, 111.8, 60.1, 55.2, 55.1, 41.4, 40.9, 40.8, 37.8. EI-MS: 379 ($[M]^+$); HR-MS 379.1783 ($[M]^+$, $C_{23}H_{25}NO_4$; Calcd. 379.1784). **7**: $[\alpha]_D^{20}$ +0.3 (*c*, 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.79 (m, 1H), 1.97 (m, 1H), 2.37 (t, 2H, *J* = 7.0 Hz), 3.47 (m, 1H), 3.54 (m, 1H), 3.80 (s, 3H), 4.97 (m, 2H), 5.66 (m, 1H), 6.72–6.78 (m, 3H), 7.21 (t, 1H, *J* = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 146.2, 136.6, 129.3, 120.0, 116.1, 113.6, 111.1, 60.8, 55.0, 42.2, 42.8, 38.5. HR-MS 245.1519 ($[M+Na]^+$, $C_{14}H_{22}O_2Na$; Calcd. 245.1517). **8**: $[\alpha]_D^{20}$ +20.0 (*c*, 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.86 (m, 1H), 1.99 (s, 3H), 2.35 (m, 1H), 2.38 (m, 2H), 2.72 (m, 1H), 3.80 (s, 3H), 3.87 (m, 1H), 3.96 (m, 1H), 4.97 (m, 2H), 5.65 (m, 1H), 6.70 (d, 1H, *J* = 1.4 Hz), 6.74 (m, 2H), 7.21 (t, 1H, *J* = 7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 159.7, 145.6, 136.4, 129.4, 119.9, 116.3, 113.6, 111.3, 62.8, 55.1, 42.5, 41.1, 34.3, 20.8. EI-MS: 248 ($[M]^+$); HR-MS 248.1411 ($[M]^+$, $C_{15}H_{20}O_3$; Calcd. 248.1412). **9**: $[\alpha]_D^{20}$ +11.0 (*c*, 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.87 (m, 1H), 1.96 (s, 3H), 2.01 (m, 1H), 2.65 (d, 2H, *J* = 7.4 Hz), 3.20 (m, 1H), 3.79 (s, 3H), 3.85 (m, 1H), 3.99 (m, 1H), 6.72 (s, 1H), 6.75 (m, 2H), 7.21 (t, 1H, *J* = 7.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.1, 171.1, 159.7, 144.0, 129.7, 119.5, 113.3, 111.8, 62.2, 55.0, 41.0, 38.5, 34.6, 20.7. HR-MS 289.1051 ($[M+Na]^+$, $C_{14}H_{18}NaO_5$; Calcd. 289.1052). **10**: $[\alpha]_D^{20}$ −26.0 (*c*, 1.0, $CHCl_3$); mp 67–68 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.79 (m, 1H), 2.05 (s, 3H), 2.24 (m, 1H), 2.41 (dd, 1H, *J* = 3.4 Hz, *J* = 19.0 Hz), 2.86 (dd, 1H, *J* = 7.6 Hz, *J* = 19.0 Hz),

3.39 (m, 1H), 3.88 (s, 3H), 4.18 (m, 2H), 6.91 (m, 2H), 7.67 (t, 1H, J = 4.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.7, 170.9, 165.4, 160.5, 130.0, 125.4, 115.5, 108.9, 62.6, 55.7, 43.1, 35.3, 34.7, 20.9. EI-MS: 248 ($[M]^+$); HR-MS 248.1047 ($[M]^+$, $C_{14}H_{26}O_4$; Calcd. 248.1049). **11**: $[\alpha]_D^{20}$ −15.0 (*c*, 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.70 (m, 2H), 2.05 (s, 1H), 2.13 (m, 1H), 2.32 (m, 1H), 2.76 (m, 1H), 2.85 (m, 1H), 3.21 (m, 1H), 3.78 (s, 3H), 3.80 (m, 2H), 6.71 (d, 1H, J = 8.2 Hz), 6.77 (s, 1H), 7.26 (d, 1H, J = 8.2 Hz). ^{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. EI-MS: 192 ($[M]^+$); HR-MS 215.1040 ($[M+Na]^+$, $C_{12}H_{16}NaO_2$; Calcd. 215.1043). **12**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.83 (m, 2H), 2.24 (s, 1H), 2.41 (m, 1H), 2.78 (m, 1H), 2.86 (m, 1H), 3.11 (m, 1H), 3.77 (s, 3H), 3.81 (m, 2H), 6.68 (dd, 1H, J = 1.8 Hz, 8.2 Hz), 6.79 (s, 1H), 7.08 (d, 1H, J = 8.2 Hz), 7.71 (m, 2H), 7.84 (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. **13**: $[\alpha]_D^{20}$ −27.0 (*c*, 0.20, H_2O); mp 174–175 °C; ^{1}H NMR (500 MHz, DMSO–d_6): δ 1.66 (m, 2H), 2.09 (m, 1H), 2.24 (m, 1H), 2.70 (m, 1H), 2.80 (m, 3H), 3.12 (m, 1H), 3.71 (s, 3H), 6.71 (d, 1H, J = 8.2 Hz), 6.76 (s, 1H), 7.11 (d, 1H, J = 8.2 Hz), 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. **1**: $[\alpha]_D^{20}$ −10.0 (*c*, 0.20, EtOH); mp 76–77 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (t, 3H, J = 7.5 Hz), 1.60 (m, 1H), 1.70 (m, 1H), 2.02 (m, 1H), 2.19 (q, 2H, J = 7.5 Hz), 2.32 (m, 1H), 2.76 (m, 1H), 2.85 (m, 1H), 3.11 (m, 1H), 3.41 (m, 2H), 3.79 (s, 3H), 5.48 (s, 1H), 6.71 (dd, 1H, J = 2.0 Hz, 8.5 Hz), 6.75 (s, 1H), 7.11 (d, 1H, J = 8.0 Hz). ^{13}C NMR (100 MHz, DMSO–d_6): 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, 29.8, 9.9. EI-MS: 247 ($[M]^+$); HR-MS 247.1572 ($[M]^+$, $C_{15}H_{21}NO_2$; Calcd. 247.1571). The enantiomeric excess of (*S*)-1 was determined by HPLC as >99.9% [column, CHIRALPAK AS-H (4.6 mm × 250 mm), 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*)-1, 30.7 min; t_R of (*R*)-1 (enantiomer of (*S*)-1), 37.1 min].