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Synthesis of J-113397, the first potent and selective ORL1 antagonist

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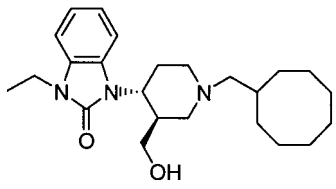
Abstract—The first potent and selective small molecule ORL1 antagonist 1-[(3*R*,4*R*)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one (J-113397) was synthesized. J-113397 is the only available potent and selective ORL1 antagonist, which is a very useful pharmacological tool for elucidating the physiological roles of the nociceptin–ORL1 system. J-113397 was synthesized from ethyl 4-oxo-3-piperidinecarboxylate and a coupling reaction of 2-fluorobenzene with 4-amino-ethoxycarbonylpiperidine is a key step.

1. Introduction

In 1994, the ORL1 receptor was identified as the fourth opioid receptor using a cloning technique.[1] This is a G-protein-coupled receptor having significant sequence homology with the classical opioid receptors (μ, κ, δ), however, none of the classical opioid ligands show significant affinity for the ORL1 receptor. Nociceptin, also termed orphanin FQ (NC/OFQ), is a peptide consisting of 17 amino acids that was identified as an endogenous ligand for the ORL1 receptor in 1995.[2] Although nociceptin has homology with the classical opioid peptide dynorphin A, it has no significant activity at the classical opioid receptors. Nociceptin and ORL1 receptors are widely distributed in the central nervous system. Pharmacological studies using nociceptin and ORL1-deficient mice have shown that the NC/OFQ–ORL1 system may have important roles in the regulation of pain response,[3] morphine tolerance,[4] learning and memory,[5] food intake,[6] anxiety,[7] the cardiovascular system,[8] locomotor activity,[9] and so on.[10] Unfortunately, further pharmacological evaluation of the nociceptin–ORL1 receptor system has been hampered due to the lack of selective ORL1 antagonists. In order to understand the physiological roles of the nociceptin–ORL1 receptor system, development of a potent and selective ORL1 antagonist has been desired. Recently we reported J-113397 to be the first potent and selective small molecule ORL1 antagonist.[11] J-113397 has trisubstituted piperidine and benzimidazolidinone structure and shows high affinity for the ORL1 receptor with a selectivity greater than 600-fold over the opioid μ, κ, and δ receptors (Scheme 1). J-113397 behaves as an antagonist at the ORL1 receptor in in vitro functional assays, as well as in in vivo assays. Since J-113397 is the only available potent and selective small molecule ORL1 antagonist, which is a useful pharmacological tool for elucidating the physiological roles of the nociceptin–ORL1 receptor system, development of an efficient synthetic method is necessary to supply enough of the compound. In this paper, we report the details of the synthesis of J-113397.

2. Results and discussion

Retrosynthetic analysis indicated that J-113397 could be synthesized through a coupling reaction of 2-fluoronitrobenzene **2** with 4-amino-3-alchoxycarbonylpiperidine **3** as a key step. Nothing had been reported about an efficient synthetic method of 4-amino-3-alchoxycarbonylpiperidine when we started the study.[12] We chose commercially available ethyl 4-oxo-3-piperidinecarboxylate **4** as the starting material (Scheme 2).



1 J-113397

Scheme 1.

Keywords: biologically active compounds; coupling reactions; ORL1 receptors.

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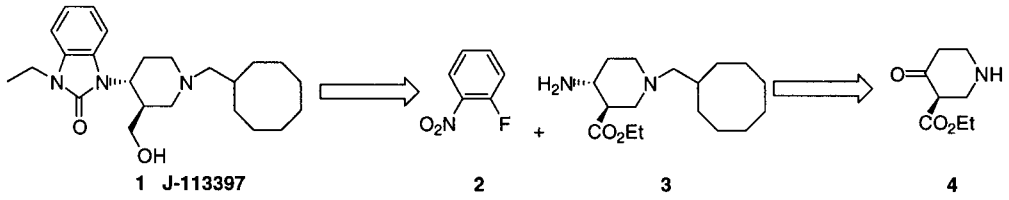
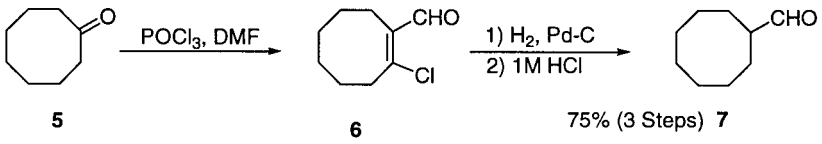
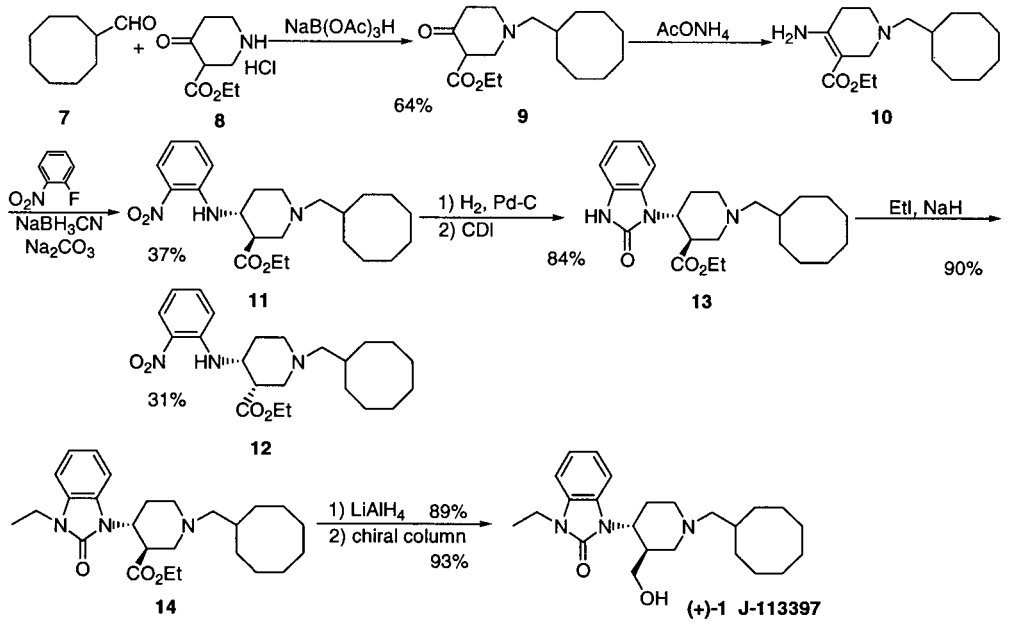


Scheme 2.



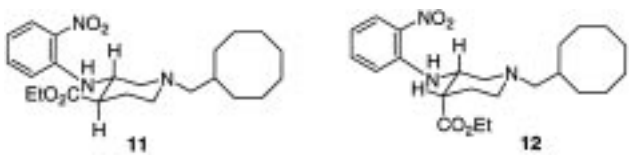
Scheme 3.



Scheme 4.

Cyclooctanecarbaldehyde **7** was prepared from commercially available cyclooctanone according to the known procedure with small modifications as shown in Scheme 3.[13] Thus, vilsmeier formylation of cyclooctanone **5** with $POCl_3$ and DMF at room temperature gave β-chloro-α,β-unsaturated aldehyde **6**. Compound **6** was hydrogenated with Pd–C in MeOH, followed by hydrolysis of the resultant aldehyde dimethyl acetal with aqueous hydrochloric acid in THF after distillation to give the cyclooctanecarbaldehyde **7** in 75% yield.

Synthesis of J-113397 is summarized in Scheme 4. Reductive alkylation reaction of commercially available ethyl 4-oxo-piperidine-3-carboxylate **8** with the cyclooctanecarbaldehyde **7** in the presence of $NaB(OAc)_3H$ was achieved at room temperature in THF in 64% yield. The resultant ketoester **9** was treated with 10-fold excess ammonium acetate in MeOH at room temperature to give the corresponding enamine **10**. Because the enamine **10** is very stable, the desired amine was not obtained under usual reduction conditions ($NaBH_3CN$/MeOH, $NaBH_4$/EtOH and hydrogenolysis). We found that the reduction of the enamine **10** was achieved with $NaBH_3CN$ in *n*-BuOH at reflux temperature for 1 h. By adding fluoronitrobenzene and sodium carbonate to the reaction mixture, the reduction and coupling were achieved in a one-pot manner. Thus, a solution of the enamine **10**, fluoronitrobenzene, the $NaBH_3CN$, and Na_2CO_3 in *n*-BuOH was heated at reflux temperature for 3 h, affording compounds **11** and **12** as a mixture of *cis*- and *trans*-isomers. The isomers were easily separated by silica gel column chromatography by eluting with 5% AcOEt–hexane to give **11** as a less-polar isomer in



Scheme 5.

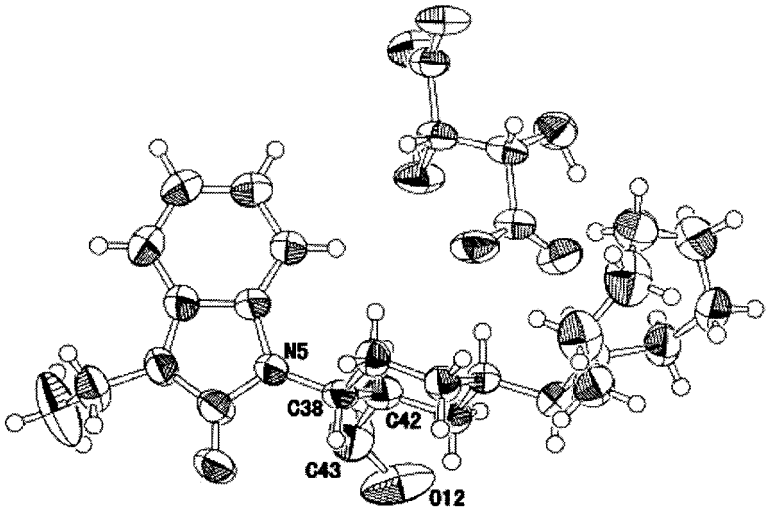


Figure 1. ORTEP drawing of (+)-**1** J-113397 D-tartaric salt.

37% yield and **12** as a polar isomer in 31% yield, respectively. The *trans* configuration of compound **11** was determined by ^{1}H NMR. The coupling constant of the methyne proton at the 3-position of the piperidine of the less-polar isomer showed triplet of doublet (J_d=3.7 Hz and J_t=9.2 Hz), suggesting that the relationship between protons at the 3- and 4-positions to be di-axial (Scheme 5). The *trans*-isomer **11** was hydrogenated in the presence of Pd–C in MeOH and $CHCl_3$, and the resultant phenylene diamine was cyclized with carbonyldiimidazole (CDI) in $CHCl_3$ at room temperature to give benzimidazolidinone **13** in 84% yield.[14] Treatment of imidazolidinone **13** with NaH and ethyliodide in DMF at room temperature gave **14** in 90% yield. Reduction of **14** with $LiAlH_4$ at 0°C afforded **1** as a racemate in 89% yield. Optical resolution of the racemate **1** was achieved by using chiral column CHIRALPAK® AD (hexane/2-propanol/Et_2NH=800/200/1) to give (+)-1-[(3*R*,4*R*)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one, J-113397.

The absolute configuration of the active enantiomer J-113397 was determined to be 3*R* and 4*R* by X-ray crystallography of its D-tartaric salt (Fig. 1).

3. Summary

We achieved the synthesis of a potent and selective ORL1 antagonist J-113397 from commercially available cyclooctanone and ethyl-4-oxo-piperidine-3-carboxlate.

4. Experimental section

4.1. Materials and methods

^{1}H NMR spectra were recorded on a Varian VXR 300 spectrometer and JEOL JNM-A500, and the abbreviations for the signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded on a Varian INOVA 600. Chemical shifts were recorded in ppm (δ) and are reported relative to the solvent peak of TMS. IR spectra were measured on a Horiba FT-200 spectrometer. High-resolution mass spectra were recorded on a JEOL JMS-SX102A spectrometer. Column chromatography separations were carried out using Merck silica gel 60 (mesh 63–200 nm).

4.1.1. Cyclooctanecarbaldehyde (7). Phosphorous oxychloride (115 ml, 1.2 mol) was added dropwise to DMF (200 ml, 2.6 mol) at 0°C, and the mixture was stirred for 0.5 h at the same temperature. Cyclooctanone **5** (100 g, 0.8 mol) in DMF (140 ml) was added dropwise to the mixture at 0°C and stirred for 1 h at room temperature. The reaction mixture was partitioned between AcOEt and water. The organic layer was washed with 1M NaOH and brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give a crude 2-chloro-1-cyclooctene-1-carbaldehyde **6**. To a solution of crude **6** in MeOH (1 l) was added 10% Pd–C (10 g) and pyridine (65 ml). The mixture was stirred under a hydrogen atmosphere for 20 h. The catalyst was filtered off and washed with MeOH. The eluent was concentrated in vacuo, and the residue was partitioned between AcOEt and 1M HCl. The organic layer was concentrated in vacuo to give a crude aldehyde dimethylacetal. To a solution of the acetal in THF (1 l) was added 1M HCl (50 ml) at room temperature, and the reaction mixture was stirred for 3 h and concentrated in vacuo. The residue was partitioned between AcOEt and 1M NaOH, and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was purified by distillation (90°C, 20 mmHg) to give 84 g (yield: 75%) of **7** as a colorless oil.

IR (film): 2852, 1726, 1469, 1446 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.40–1.84 (m, 12H), 1.88–2.05 (m, 2H), 2.33–2.42 (m, 1H), 9.61 (s, 1H).

4.1.2. Ethyl 1-cyclooctylmethyl-4-oxo-3-piperidinecarboxylate (9). To a solution of ethyl 4-oxo-3-piperidinecarboxylate hydrochloride **8** (100 g, 0.48 mol) in THF (1 l) was added cyclooctanecarbaldehyde (82 g, 0.58 mol) and $NaB(OAc)_3H$ (155 g, 0.72 mol) at 0°C. The reaction mixture

was warmed up to room temperature and stirred for 5.5 h. The mixture was partitioned between AcOEt and water, and the organic layer was washed with 1M NaOH and brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=50/1) to give 90.8 g (yield: 64%) of **9** as a colorless oil.

IR (film): 2927, 2917, 2910, 1718, 1653 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.29 (t, J=7.5 Hz, 3H), 1.42–1.95 (m, 15H), 2.20 (d, J=7.2 Hz, 2H), 2.38–2.43 (m, 2H), 2.57 (t, J=6.0 Hz, 2H), 3.09 (t, J=1.5 Hz, 2H), 4.21 (q, J=7.5 Hz, 2H), 11.98 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.2, 25.4, 25.4, 26.3, 27.0, 27.1, 29.4, 30.6, 30.6, 34.9, 49.2, 50.3, 60.0, 65.2, 96.9, 170.2, 171.0. HRMS(FAB) $(M+H)^+$ calculated for $C_{17}H_{30}NO_3$ 296.2226, found 296.2221.

4.1.3. Ethyl 4-amino-1-cyclooctylmethyl-1,2,5,6-tetrahydro-3-pyridinecarboxylate (10). To a solution of **9** (90.8 g, 0.31 mol) in MeOH (900 ml) was added $AcONH_4$ (237 g, 3.1 mol) at room temperature, and the reaction mixture was stirred for 1 h and concentrated in vacuo. The residue was partitioned between AcOEt and 1M NaOH, and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated to give 91.0 g (yield: 100%) of **10**.

IR (film): 3442, 3328, 2925, 2910, 1722, 1716, 1672, 1622 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.27 (t, J=7.5 Hz, 3H), 1.38–1.92 (m, 15H), 2.20 (d, J=7.2 Hz, 2H), 2.33 (t, J=6.0 Hz, 2H), 2.51 (t, J=6.0 Hz, 2H), 3.11 (s, 2H), 4.14 (q, J=7.5 Hz, 2H), 5.95 (br, 2H). ^{13}C NMR ($CDCl_3$): δ 14.5, 25.5, 25.5, 26.4, 27.1, 27.1, 30.4, 30.7, 30.7, 34.8, 49.3, 51.7, 58.8, 65.6, 91.4, 154.7, 168.8. HRMS(FAB) $(M+H)^+$ calculated for $C_{17}H_{31}N_2O_2$ 295.2386, found 295.2383.

4.1.4. Ethyl (3*R,4*R**)-1-cyclooctylmethyl-4-(2-nitrophenylamino)-3-piperidinecarboxylate (11).** To a solution of **10** (91.0 g, 0.31 mol) in *n*-BuOH (300 ml) was added 2-fluoronitrobenzene (87.0 g, 0.62 mol), Na_2CO_3 (65.0 g, 0.62 mol) and $NaBH_3CN$ (39.0 g, 0.62 mol) at room temperature, and the reaction mixture was refluxed for 3 h. After cooling, the mixture was partitioned between AcOEt and water, and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=50/1) to give 47.8 g (yield: 37%) of (3*R**,4*R**)-isomer **11** as a yellow oil and 40 g (yield: 31%) of the (3*R**,4*S**)-isomer **12** as a yellow oil.

11: IR (film): 2913, 2923, 1731, 1618, 1576, 1510 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.16 (t, J=7.5 Hz, 3H), 1.17–1.28 (m, 2H), 1.36–1.74 (m, 14H), 2.11 (d, J=6.9 Hz, 2H), 2.15–2.28 (m, 2H), 2.39–2.49 (m, 1H), 2.73 (dt, J=3.7, 9.2 Hz, 1H), 2.75–2.82 (m, 1H), 2.88–2.95 (m, 1H), 3.86–3.97 (m, 1H), 4.06 (q, J=7.5 Hz, 2H), 6.59–6.65 (m, 1H), 6.93 (d, J=8.4 Hz, 1H), 7.38–7.43 (m, 1H), 8.12–8.17 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 14.0, 25.5, 25.5, 26.3, 27.1, 27.1, 30.5, 30.6, 30.9, 34.9, 48.0, 51.0, 51.8, 54.5, 60.8, 65.4, 114.1, 115.4, 126.9, 132.0, 136.0, 144.4, 172.6. HRMS(FAB) $(M+H)^+$ calculated for $C_{23}H_{36}N_3O_4$ 418.2706, found 418.2715.

12: IR (film): 2913, 2848, 1730, 1618, 1571, 1511 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.21 (t, J=7.5 Hz, 3H), 1.12–1.28 (m, 2H), 1.35–1.77 (m, 12H), 1.78–1.92 (m, 2H), 2.03–2.19 (m, 3H), 2.31–2.43 (m, 1H), 2.50–2.66 (m, 2H), 2.90–3.12 (m, 2H), 3.94–4.07 (m, 1H), 4.08–4.19 (m, 2H), 6.58–6.64 (m, 1H), 6.89 (d, J=8.4 Hz, 1H), 7.36–7.43 (m, 1H), 8.16 (br d, J=8.4 Hz, 1H) 8.74 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 14.0, 25.4, 25.5, 26.3, 27.1, 27.1, 29.1, 30.5, 30.6, 34.9, 44.9, 49.4, 51.2, 53.2, 60.7, 65.7, 113.6, 115.0, 127.1, 132.3, 135.9, 144.3, 171.7. HRMS(FAB) $(M+H)^+$ calculated for $C_{23}H_{36}N_3O_4$ 418.2706, found 418.2722.

4.1.5. 1-[(3*R,4*R**)-1-Cyclooctylmethyl-3-ethoxycarbonyl-4-piperidyl]-1,3-dihydro-2*H*-benzimidazol-2-one (13).** To a solution of **11** (47.8 g, 0.11 mol) in MeOH (800 ml) and $CHCl_3$ (100 ml) was added 10% Pd–C (8 g) and 10% HCl–MeOH (100 ml), and the mixture was stirred under a hydrogen atmosphere for 22 h. The catalyst was filtered off and washed with MeOH. The eluent was concentrated in vacuo and the residue was partitioned between AcOEt and 2M NaOH. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo to give a brown oil. To a solution of the crude brown oil in $CHCl_3$ (500 ml) was added carbonyldiimidazole (CDI) (27.0 g, 0.17 mol) at room temperature, and the mixture was stirred for 10 h. The mixture was partitioned between AcOEt and water, and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=200/1) to give 38.7 g (yield: 84%) of **13** as a colorless oil.

IR (film): 2913, 2915, 1730, 1701 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.96 (t, J=7.5 Hz, 3H), 1.18–1.30 (m, 2H), 1.44–1.83 (m, 14H), 2.14–2.21 (m, 3H), 2.25 (t, J=11.7 Hz, 1H), 2.48–2.62 (m, 1H), 2.96–3.08 (m, 1H), 3.16–3.23 (m, 1H), 3.58–3.70 (m, 1H), 3.90 (q, J=7.5 Hz, 2H), 4.32–4.48 (m, 1H), 7.02–7.10 (m, 3H), 7.15–7.20 (m, 1H), 8.40 (br, 1H). ^{13}C NMR ($CDCl_3$): δ 13.6, 25.5, 25.5, 26.4, 27.1, 27.1, 28.1, 30.6, 30.7, 35.0, 44.4, 52.8, 53.0, 55.8, 60.5, 65.2, 108.9, 109.3, 121.0, 121.1, 127.8, 129.5, 154.8, 171.9. HRMS(FAB) $(M+H)^+$ calculated for $C_{24}H_{36}N_3O_3$ 414.2757, found 414.2757.

4.1.6. 1-[(3*R,4*R**)-1-Cyclooctylmethyl-3-ethoxycarbonyl-4-piperidyl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one (14).** To a solution of **13** (38.7 g, 94 mmol) in DMF (400 ml) was added 60% NaH (4.5 g, 112 mmol) at 0°C. The reaction temperature was then warmed up to room temperature, and the solution was stirred for 0.5 h. Ethyliodide (15 ml, 188 mmol) was added to the reaction mixture, and the mixture was stirred for 1 h at room temperature. The mixture was partitioned between AcOEt and water, and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt=4/1) to give 37.3 g (yield: 90%) of **14** as a colorless oil.

IR (film): 2913, 1730, 1709, 1495, 1398 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.91 (t, J=7.2 Hz, 3H), 1.91–1.29 (m, 2H), 1.32 (t, J=7.2 Hz, 3H), 1.42–1.80 (m, 13H), 2.14–2.12

(m, 4H), 2.22–2.30 (m, 1H), 2.50–2.64 (1H, m), 2.94–3.04 (m, 1H), 3.13–3.20 (m, 1H), 3.61–3.69 (m, 1H), 3.86 (q, J=7.2 Hz, 2H), 3.91 (q, J=7.2 Hz, 2H), 4.30–4.45 (m, 1H), 6.96–7.00 (m, 1H), 7.04–7.10 (m, 2H), 7.13 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 13.4, 13.6, 25.5, 25.5, 26.3, 27.1, 27.1, 27.9, 30.6, 30.6, 35.0, 35.5, 44.2, 52.9, 53.8, 55.7, 60.3, 64.9, 107.2, 108.5, 120.7, 120.7, 128.8, 129.0, 153.2, 172.1. HRMS(FAB) $(M+H)^+$ calculated for $C_{26}H_{40}N_3O_3$ 442.3070, found 442.3065.

4.1.7. 1-[(3*R*,4*R*)-1-Cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one (+1). To a solution of **14** (37.3 g, 85 mmol) in THF (750 ml) was added $LiAlH_4$ (3.9 g, 102 mmol) at 0°C. The reaction mixture was then warmed up to room temperature and stirred for 0.5 h. AcOEt was added to the reaction mixture at 0°C, and the mixture was stirred for 5 min. The reaction mixture was partitioned between AcOEt and 2M NaOH, and the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH=150/1) to give 30.0 g (yield: 89%) of (+/−)-**1** as white solids.

Optical resolution was performed by chromatography using CHIRALPAK® AD (hexane/2-propanol/Et_2NH=800/200/1), to give 14.0 g (yield: 93%) of (+)-**1** (J-113397) as white solids.

1: IR (KBr): 3446, 2919, 1704 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.15–1.30 (m, 2H), 1.34 (t, J=7.2 Hz, 3H), 1.40–1.78 (m, 13H), 1.84–1.91 (m, 1H), 2.04–2.33 (m, 6H), 2.54–2.64 (m, 1H), 2.96–3.05 (m, 2H), 3.32–3.36 (m, 2H), 3.91–4.01 (m, 2H), 4.34–4.45 (m, 1H), 7.02–7.13 (m, 3H), 7.29–7.35 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 13.6, 25.6, 25.6, 26.5, 27.1, 27.1, 28.7, 30.9, 30.9, 34.8, 36.1, 41.0, 51.7, 53.6, 56.4, 61.9, 66.1, 108.0, 110.2, 121.1, 121.1, 128.0, 129.2, 154.6. HRMS(FAB) $(M+H)^+$ calculated for $C_{24}H_{38}N_3O_2$ 400.2964, found 400.2979.

The free amine was dissolved in 10% HCl–MeOH and concentrated in vacuo, and the resulting crystalline powder was washed with Et_2O to give hydrochloride salt as a white powder. Mp 218–220°C. Anal. ($C_{24}H_{38}ClN_3O_2\cdot 0.7H_2O$) C, H, N. $[\alpha]_D^{20} = +6.4$ (c=1.0, 0.1N HCl).

4.2. X-Ray crystallography

J-113397 (20 mg, 0.05 mmol) and D-tartaric acid (7 mg, 0.05 mmol) were dissolved in hot AcOEt (2 ml) and MeOH (0.1 ml). After being slowly cooled to room temperature, the mixture was left standing for one day. The precipitates were recrystallized from AcOEt (1.5 ml) and MeOH (0.1 ml) to give colorless plate crystals, triclinic space group $P1$, a=9.778(3) Å, b=14.898(5) Å, c=9.731(3) Å, α=96.90(3)°, β=109.83(2)°, γ=97.02(3)°, V=1303.6(8) Å^3, Z=1, ρ_{calcd}=1.21 g cm^{-3}. The crystallographic data were obtained with a Rigaku AFC-7 four cycle diffractometer (Cu-Kα radiation) at 296.2 K. The structure was solved using direct methods and refined on F^2 using teXsan,[15] SHELXS-86[16] and SHELXL-97,[17] where the final R was 0.051 for 4023 reflections. Atomic coordinates, the thermal parameters, bond lengths and angles have been deposited at Cambridge Crystallographic Data Centre (CCDC 151492).

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