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# A New Synthetic Approach to 1-[(3*R*,4*R*)-1-Cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-benzimidazol-2-one (J-113397), the First Non-peptide ORL-1 Receptor Antagonist

Carmela De Risi,[a] Gian Piero Pollini,[a,*] Claudio Trapella,[a] Ilaria Peretto,[b] Silvano Ronzoni[b] and Giuseppe A. M. Giardina[b]

[a]*Dipartimento di Scienze Farmaceutiche, Università di Ferrara, via Fossato di Mortara 19, 44100 Ferrara, Italy*
[b]*Department of Medicinal Chemistry, SmithKline Beecham SpA, via Zambeletti, 20021 Baranzate di Bollate, Milan, Italy*

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**Abstract**—An efficient approach to 1-[(3*R*,4*R*)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-benzimidazol-2-one (J-113397) **1**, the first non-peptide ORL-1 receptor antagonist described in literature, is outlined. After construction of the piperidine framework through Dieckmann cyclization of the Michael adduct **8** of cyclooctylmethylamine to methyl acrylate, condensation with *o*-phenylendiamine produced the β-enamino ester **2**, which has been conveniently used to construct the benzimidazolone substituent at C-4. Catalytic hydrogenation of intermediate **11** followed by base-promoted *cis–trans* isomerization of the key compound **12** led to the formation of ester **13**, which was converted to the racemic title compound by $LiAlH_4$ reduction. The pure enantiomers were obtained by chiral preparative HPLC separation using a derivatized cellulose-based stationary phase. 

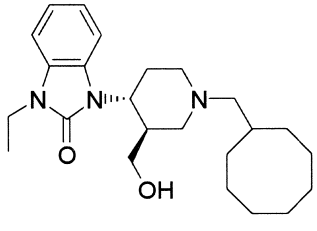
## Introduction

The opioid receptor-like 1 (ORL-1) receptor, discovered in 1994 through cDNA expression cloning techniques,[1] is a member of the G-protein coupled receptor superfamily and shows high sequence homology with the classical δ, μ and κ opioid receptors. Notwithstanding, the classical opioid ligands do not bind to this new receptor with appreciable affinity;[1c] this finding led to the search of the endogenous ligand of the ORL-1 receptor, which was identified as a heptadecapeptide named nociceptin/orphaninFQ.[2] Despite the significant similarity of this peptide with the endogenous κ ligand dynorphinA, nociceptin/orphaninFQ does not bind the other opioid receptors with high affinity.[1,2]

Several experiments have shown that the ORL-1/nociceptin system is involved in many crucial biological functions,[3] but a definitive understanding of its functions has been hampered by the lack of potent and selective non-peptide ligands for this receptor.

Ozaki et al. reported in 1998 the discovery of J-113397, namely 1-[(3*R*,4*R*)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one (**1**), as the first non-peptide ORL-1 receptor antagonist.[4] This compound, which features a *trans*-3,4-disubstituted piperidine nucleus, showed a very interesting in vivo and in vitro pharmacological profile, acting as a potent ORL-1 antagonist with no residual agonist activity and a high selectivity over classical opioid receptors[5] (Fig. 1).

Following our interest in this field, we tried unsuccessfully to prepare **1** through the reported route,[4] probably due to the lack of experimental details in the procedures




**1**

**Figure 1.**

*Corresponding author. Tel.: +39-532-291286; fax: +39-532-291296; e-mail: pol@dns.unife.it

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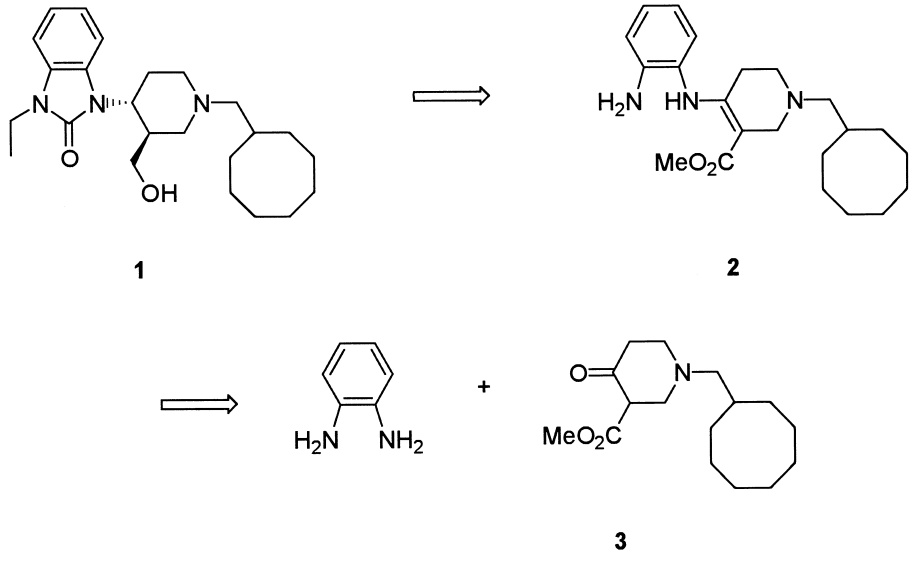
described in the patent, not completely clarified in the recently published full paper.[6] In particular, the introduction of the benzimidazolone moiety seemed to be a capricious operation. Therefore, we decided to develop an alternative synthetic approach to **1**, which relies on the use of the β-enaminoester **2** as the key intermediate for the construction of the benzimidazolone framework at C-4. Compound **2** would in turn be obtained through condensation of *o*-phenylendiamine with β-ketoester **3** (Scheme 1).

## Results and Discussion

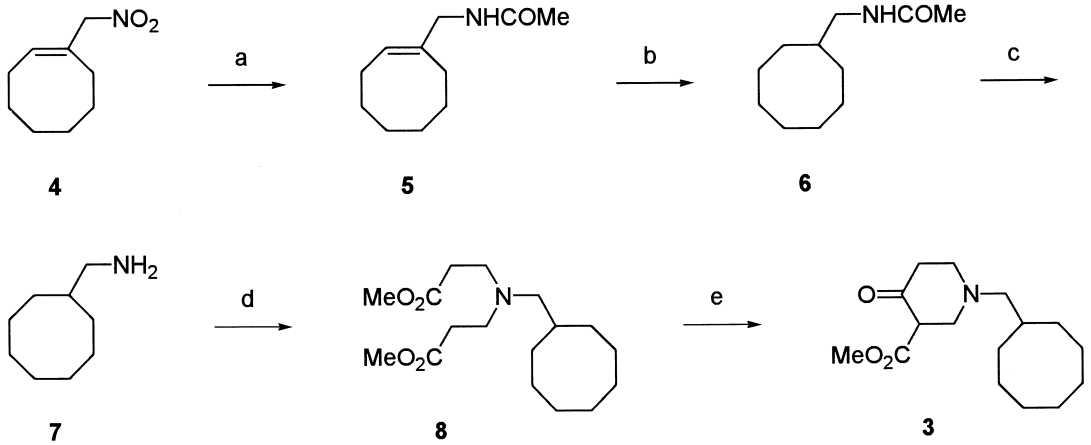
Having established the essential features of the synthetic approach, the preparation of the starting molecule **3** required a suitable source for cyclooctylmethylamine **7**. The most direct route to this compound appeared to be the reduction of the easily available 1-nitromethylcyclooctene **4**.[7] Disappointingly, this reaction proceeded with considerable decomposition, and the desired compound could be obtained only in very low yield. A different approach was eventually found through a rather tedious but convenient procedure which allowed to obtain **7** in 63% overall yield. $LiAlH_4$ reduction of **4** yielded the corresponding allylamine, which was protected as acetamide and subsequently reduced by catalytic hydrogenation to compound **6**; the saturated acetamide **6** was then hydrolyzed in acidic conditions to give the amine **7**. Once **7** was obtained, the preparation of **3** was easily achieved in a high-yield two-step sequence involving Michael addition of **7** to methyl acrylate followed by *t*-BuOK promoted Dieckmann cyclization[8] of the diester adduct **8** (Scheme 2).

A mixture of β-ketoester **3** and *o*-phenylenediamine in benzene was heated at reflux in the presence of a catalytic amount of AcOH and 4 Å molecular sieves to give the stable enamine **2** (Scheme 3).

Attempts to reduce the conjugated double bond in **2** either catalytically or with mild reducing agents, for example, $NaBH_3CN$ proved to be unsuccessful, giving in all cases complex mixtures in which only small traces of the desired reduction product were present. We decided to postpone the reductive step after the introduction




**Scheme 1.**




**Scheme 2.** (a) i: $LiAlH_4$, EtO, 0°C; ii: $Et_3N$, $Ac_2O$, $CH_2Cl_2$, 0°C 78% over two steps. (b) $H_2$, Pd/C 10%, EtOH, 96%. (c) HCl, EtOH/$H_2O$, Δ, 84%. (d) $CH_2$=CH-$CO_2$OMe, MeOH rt, 72%. (e) *t*-BuOK, toluene, rt, 78%.

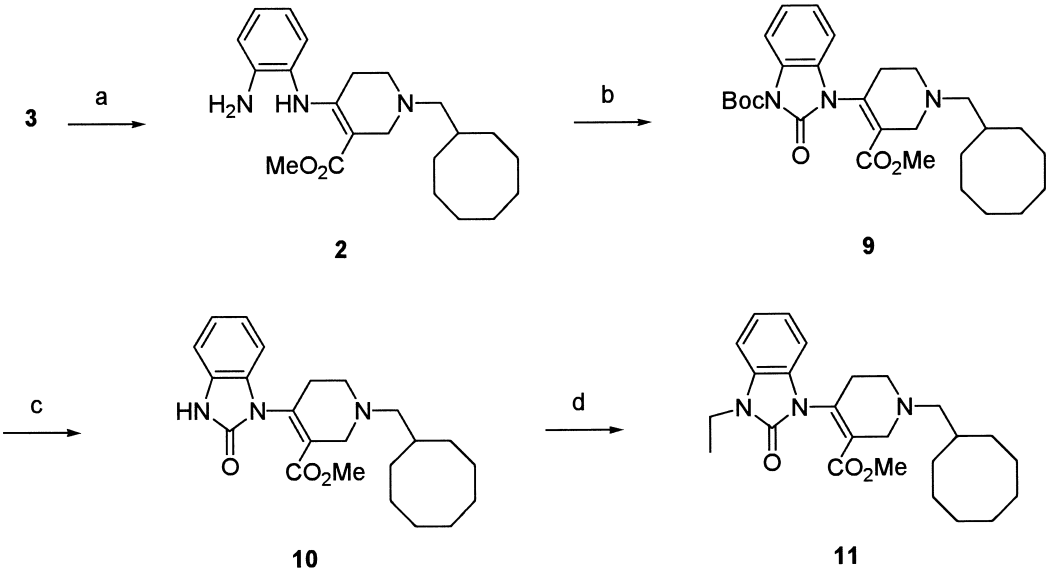
of the benzimidazolone moiety. This operation proceeded smoothly at room temperature by treatment of **2** with di-*tert*-butyldicarbonate ($Boc_2O$) and DMAP yielding **9** in 89% yield, the N-3 nitrogen atom being concomitantly protected. After removal of the *tert*-butoxycarbonyl protecting group by treatment with TFA, the intermediate **10** was transformed into the key compound **11** by treatment with NaH and ethyl bromide.

The next synthetical step required the reduction of the double bond of the β-enaminoester functionality of **11** (Scheme 4).

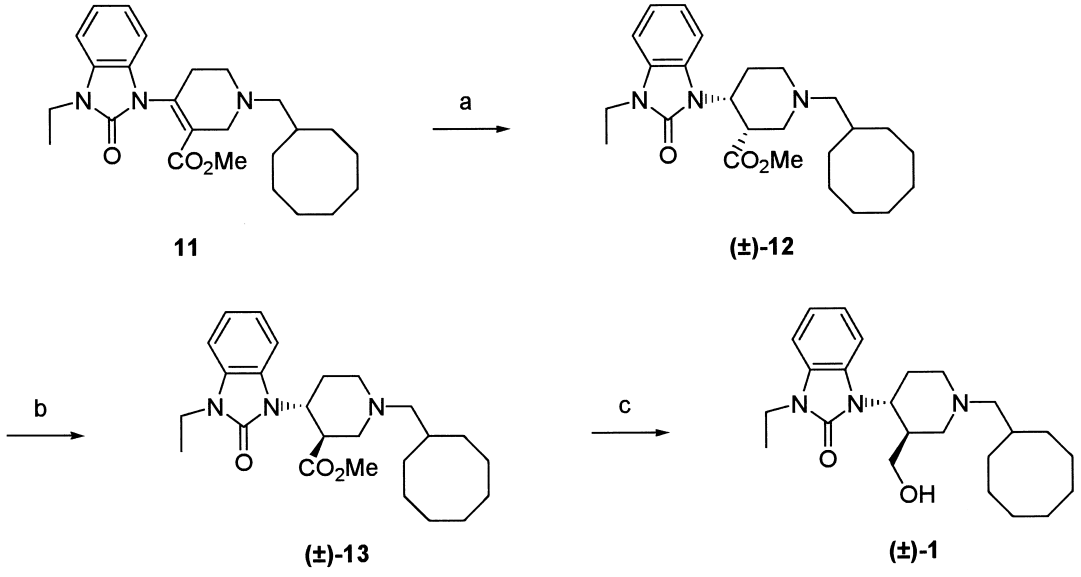
While reduction of **11** with hydrides (e.g., $NaBH_3CN$) was unsuccessful, catalytic hydrogenation in presence of 10% Pd/C allowed us to obtain in moderate yield (50%) the expected derivative (±)-*cis*-**12**; purification by silica gel column chromatography was necessary to separate the side-products, probably arising by palladium-promoted β-elimination processes.

The required *trans*- stereochemistry between the substituents at C-3 and C-4 was quantitatively achieved under very mild conditions by stirring (±)-*cis*-**12** with MeONa in methanol at room temperature, yielding (±)-*trans*-**13**, which was eventually converted to racemic **1** through $LiAlH_4$ reduction.

The separation of the enantiomers of (±)-**1** was achieved by preparative chiral HPLC, performed on a cellulose-based chiral column (Chiralcel OD). The elution was isocratic, employing a mixture of hexane and 2-propanol (100:2). The separation of the two peaks (see Fig. 2) allowed to obtain both the enantiomers with enantiomeric excess greater than 99% (other enantiomer not detectable under the utilized analytical conditions).




**Scheme 3.** (a) *o*-phenylenediamine, AcOH, molecular sieves, benzene, Δ, 83%. (b) $(Boc)_2O$, DMAP, $CH_2Cl_2$, 0°C, 89%. (c) TFA, $CH_2Cl_2$, rt, 97%. (d) NaH, EtBr, DMF, rt, 75%.




**Scheme 4.** (a) $H_2$, Pd/C 10%, MeOH, 50%. (b) MeONa, MeOH, rt, 92%. (c) $LiAlH_4$, $Et_2O$, 0°C, 80%.

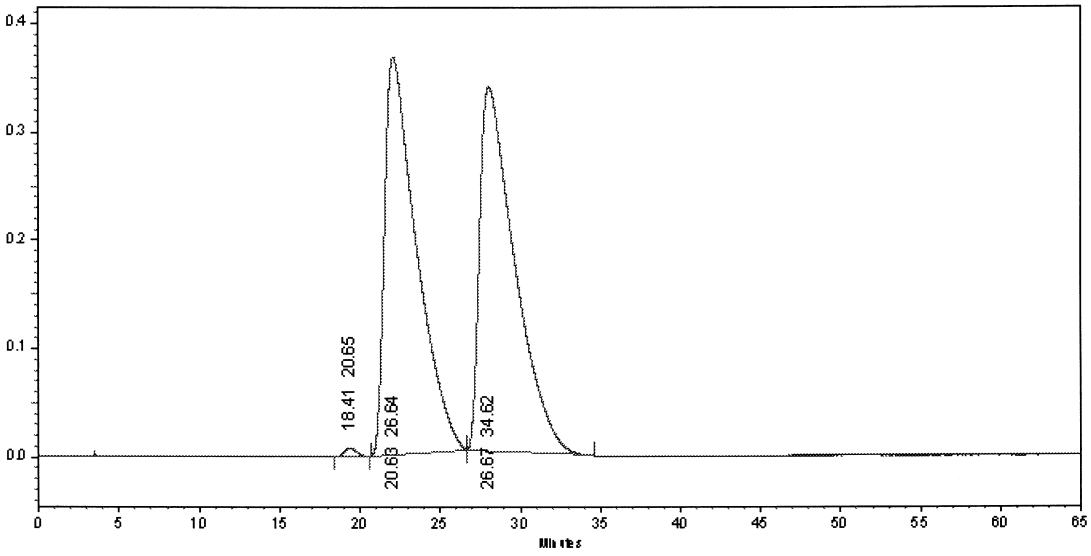



**Figure 2.**

NMR and MS data for the enantiomers thus obtained were consistent with the data reported in literature[4] and with the data measured for the racemate (±)-**1**.

On the basis of literature data and in-house binding studies in CHO cell membranes stably expressing the human ORL-1 receptor (displacement of $^3$[H]-nociceptin), the faster running (+)-enantiomer was established to be J-113397.

## Conclusions

In summary, an alternative approach to 1-[(3*R*,4*R*)-1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl]-3-ethyl-1,3-dihydro-benzimidazol-2-one (J-113397) **1**, which could open the way to the enantioselective synthesis of the target compound or to structurally modified analogues for pharmacological studies, has been described. A major advantage of this approach is represented by the possibility to obtain pure compounds, which may be useful tools for structure–activity relationship studies, having both *cis*- and *trans*- relationship between the substituents at C-3 and C-4 carbon atoms of the piperidine framework, thus avoiding their chromatographic separation.

## Experimental

All reactions were run under nitrogen or argon atmosphere. Organic solutions were dried over anhydrous $MgSO_4$ and evaporated with a rotary evaporator. Light petroleum refers to the fractions boiling in the range 40–60 °C. Flash chromatography was carried out on silica gel (Merck, 230–400 mesh). Melting points were determined on a Büchi–Tottoli apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR Paragon 500 spectrometer. $^1$H NMR spectra were recorded on a Bruker AC spectrometer at 200 MHz. Chemical shifts are given in parts per million upfield from tetramethylsilane as the internal standard. MALDI-TOF mass spectra were recorded on a Hewlett Packard G 2025 A LD-TOF system. Elemental analyses were performed by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara.

***N*-(Cyclooct-1-enylmethyl)-ethanamide (5).** A solution of **4** (12 g, 71 mmol) in $Et_2O$ (40 mL) was added dropwise to a cooled (0 °C) slurry of $LiAlH_4$ (8 g, 213 mmol) in $Et_2O$ (160 mL) and the reaction mixture was stirred at the same temperature for 6 h. Excess hydride was quenched by careful addition of $H_2O$, then the precipitated salts were filtered through a Celite pad and washed with $CH_2Cl_2$ (100 mL). The filtrate was evaporated under reduced pressure to give a yellow oil, which was immediately dissolved in $CH_2Cl_2$ (50 mL). The resulting solution was cooled at 0 °C and treated with $Et_3N$ (10.2 mL, 71 mmol) and acetic anhydride (6.7 mL, 71 mmol). The reaction mixture was kept for 6 h at the same temperature, then the solvent was evaporated and the residue purified by flash chromatography (EtOAc/light petroleum/$NH_4OH$, 1:2:0.1) to afford **5** (10 g, 78%) as a yellowish oil. Anal. calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.91; H, 10.55; N, 7.71. IR (film): 3288, 3080, 1651, 1557 cm$^{-1}$. $^1$H NMR ($CDCl_3$): 5.49 (t, 1H, $J$ = 8.1 Hz), 5.30 (br s, 1H), 3.78 (d, 2H, $J$ = 5.8 Hz), 2.20–2.07 (m, 4H), 1.99 (s, 3H), 1.70–1.40 (m, 8H).

***N*-(Cyclooctylmethyl)-ethanamide (6).** A solution of **5** (8.4 g, 46.40 mmol) in EtOH (100 mL) was hydrogenated in a Parr apparatus at 70 psi for 24 h in the presence of 10% Pd/C (0.5 g). Filtration of the catalyst through Celite pad and solvent evaporation gave **6** (8.2 g, 96%) as a colorless oil, which could be used in the next step without further purification. A small aliquot was purified by flash chromatography (EtOAc/light petroleum/$NH_4OH$, 1:2:0.1) to give a pure sample of **6**.

Anal. calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64. Found: C, 72.04; H, 11.57; N, 7.66. IR (film): 3292, 3087, 1651 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 5.60 (br s, 1H), 3.07 (t, 2H, $J=6.4$ Hz), 1.97 (s, 3H), 1.70–1.20 (m, 15H).

**Methyl 3-[cyclooctylmethyl-(2-methoxycarbonyl-ethyl)-amino]-propanoate (8).** HCl 37% (150 mL) was slowly added to a solution of **6** (8.3 g, 45.35 mmol) in EtOH/$H_2O$ (1:2, 150 mL) and the reaction mixture was refluxed overnight. After cooling, most of the solvent was evaporated in vacuo and the residue brought to pH 12 by careful addition of NaOH 20%. Extraction with EtOAc (5×50 mL) followed by evaporation of the dried organic phases gave **7** (5.4 g, 84%) as a yellowish oil, which was immediately used for the next reaction. A solution of **7** (5 g, 35.46 mmol) in MeOH (20 mL) was added dropwise to a cooled (0 °C) solution of methyl acrylate (7 mL, 78.01 mmol) in MeOH (50 mL). After being stirred for 24 h at rt, the solvent was evaporated and the residue was purified by flash chromatography (EtOAc/light petroleum 1:6) to give **8** (8 g, 72%) as a yellow oil. Anal. calcd for $C_{17}H_{31}NO_4$: C, 65.14; H, 9.97; N, 4.47. Found: C, 65.17; H, 9.95; N, 4.46. IR (film): 1741 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 3.66 (s, 6H), 2.74 (t, 4H, $J=7$ Hz), 2.42 (t, 4H, $J=7$ Hz), 2.11 (d, 2H, $J=7$ Hz), 1.80–1.10 (m, 15H).

**1-Cyclooctylmethyl-3-methoxycarbonyl-piperidin-4-one (3).** *t*-BuOK (4.3 g, 38.34 mmol) was added in one portion to a cooled (0 °C) solution of **8** (8 g, 25.56 mmol) in toluene (80 mL) and, after being stirred at the same temperature for 30 min, the reaction mixture was kept at rt overnight. $H_2O$ (100 mL) was added, the phases were separated and the aqueous phase was extracted with EtOAc (3×100 mL). The combined organic extracts were dried and evaporated. Purification of the residue by flash chromatography (EtOAc/light petroleum 1:9) gave **3** (5.6 g, 78%) as an orange oil. Anal. calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.32; H, 9.65; N, 4.97. MALDI-TOF MS: $[MH]^+$ 282. IR (film): 1747, 1722, 1667, 1625 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 11.87 (br s, 1H, enol form), 3.73 (s, 3H), 3.07 (AB system, 2H, $J=10$ Hz), 2.56 (t, 2H, $J=7$ Hz), 2.37 (t, 2H, $J=7$ Hz), 2.19 (d, 2H, $J=7.3$ Hz), 1.85–1.15 (m, 15H).

**Methyl 1-cyclooctylmethyl-4-(*o*-phenylendiamino)-1,2,5,6-tetrahydro-pyridine-3-carboxylate (2).** A solution of **3** (3 g, 10.67 mmol) and *o*-phenylenediamine (1.77 g, 16.43 mmol) in benzene (50 mL) was refluxed overnight in the presence of AcOH (0.3 mL) and 4 Å powdered molecular sieves (1 g), with azeotropic removal of water. After being cooled, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/light petroleum/$NH_4OH$, 1:4:0.1) to yield **2** (3.3 g, 83%) as a white solid (mp 88–90 °C). Anal. calcd for $C_{22}H_{33}N_3O_2$: C, 71.12; H, 8.95; N, 11.31. Found: C, 71.09; H, 8.96; N, 11.33. MALDI-TOF MS: $[MH]^+$ 372. IR (KBr): 3459, 3367, 3265, 1647, 1588, 1503 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 9.83 (s, 1H), 7.12–6.95 (m, 2H), 6.80–6.60 (m, 2H), 3.80 (s, 2H), 3.72 (s, 3H), 3.20 (s, 2H), 2.18 (d, 2H, $J=7.3$ Hz), 2.50–2.20 (m, 4H), 1.90–1.20 (m, 15H).

**1-(1-Cyclooctylmethyl-3-methoxycarbonyl-1,2,5,6-tetrahydro-pyridin-4-yl)-3-*tert*-butoxycarbonyl-1,3-dihydro-*2H*-benzimidazol-2-one (9).** A cooled (0 °C) solution of **2** (2 g, 5.39 mmol) in $CH_2Cl_2$ (40 mL) was treated with di-*tert*-butyldicarbonate (5.88 g, 26.95 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred at the same temperature for 3 h, then the solvent was evaporated in vacuo and the residue purified by flash chromatography (EtOAc/light petroleum, 1:6), yielding **9** (2.4 g, 89%) as an orange oil. Anal. calcd for $C_{28}H_{39}N_3O_5$: C, 67.58; H, 7.90; N, 8.44. Found: C, 67.61; H, 7.88; N, 8.43. MALDI-TOF MS: $[MH]^+$ 498. IR (film): 1742, 1724, 1647, 1580, 1500 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 7.90–7.83 (m, 1H), 7.18–7.08 (m, 2H), 6.90–6.80 (m, 1H), 3.47 (s, 3H), 3.45 (AB system, 2H, $J=15$ Hz), 3.00–2.60 (m, 4H), 2.29 (d, 2H, $J=7.2$ Hz), 1.90–1.20 (m, 24H).

**1-(1-Cyclooctylmethyl-3-methoxycarbonyl-1,2,5,6-tetrahydro-pyridin-4-yl)-1,3-dihydro-*2H*-benzimidazol-2-one (10).** A solution of **9** (2 g, 4.02 mmol) in $CH_2Cl_2$ (20 mL) was cooled at 0 °C and TFA (2.17 mL, 28.14 mmol) was added dropwise. The reaction mixture was kept at rt until completion (8 h), then saturated aq $NaHCO_3$ (20 mL) was carefully added. The phases were separated, the aqueous phase was extracted with $CH_2Cl_2$ (3×20 mL) and the combined organic extracts were dried. Evaporation of the solvent gave **10** (1.54 g, 97%) as a brownish amorphous solid (mp 28–30 °C). Anal. calcd for $C_{23}H_{31}N_3O_3$: C, 69.49; H, 7.86; N, 10.57. Found: C, 69.51; H, 7.85; N, 10.56. MALDI-TOF MS: $[MH]^+$ 398. IR (KBr): 3422, 1707, 1487 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 9.64 (s, 1H), 7.20–7.05 (m, 3H), 7.00–6.85 (m, 1H), 3.60–3.30 (m, 2H superimposed to s, 3H at 3.44), 2.90–2.60 (m, 4H), 2.31 (d, 2H, $J=7.1$ Hz), 1.90–1.20 (m, 15H).

**1-(1-Cyclooctylmethyl-3-methoxycarbonyl-1,2,5,6-tetrahydro-pyridin-4-yl)-3-ethyl-1,3-dihydro-*2H*-benzimidazol-2-one (11).** A solution of **10** (1.5 g, 3.78 mmol) in DMF (10 mL) was added dropwise to a stirred suspension of 75% NaH (0.12 g, 3.78 mmol) in DMF (5 mL) at 0 °C. The reaction mixture was stirred for 30 min at the same temperature, then a solution of ethyl bromide (0.31 mL, 4.16 mmol) in DMF (5 mL) was added slowly and stirring was continued at rt overnight. Most of the solvent was evaporated and the residue was diluted with $Et_2O$ (50 mL). The precipitated salts were filtered through a Celite pad, the solvent was removed under reduced pressure and the residue was purified by flash chromatography (EtOAc/light petroleum/$NH_4OH$, 1:4:0.1) to give **11** (1.2 g, 75%) as a yellow oil. Anal. calcd for $C_{25}H_{35}N_3O_3$: C, 70.56; H, 8.29; N, 9.87. Found: C, 70.58; H, 8.28; N, 9.86. MALDI-TOF MS: $[MH]^+$ 426. IR (film): 1714, 1647, 1616, 1493 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 7.10–6.92 (m, 3H), 6.90–6.80 (m, 1H), 3.88 (q, 2H, $J=7.2$ Hz), 3.50–3.30 (m, 2H superimposed to s, 3H at 3.34), 2.80–2.50 (m, 4H), 2.22 (d, 2H, $J=7.2$ Hz), 1.80–1.40 (m, 15H), 1.28 (t, 3H, $J=7.2$ Hz).

**(±)-*cis*-1-(1-Cyclooctylmethyl-3-methoxycarbonyl-4-piperidyl)-3-ethyl-1,3-dihydro-*2H*-benzimidazol-2-one (12).** A solution of **11** (1 g, 2.35 mmol) in MeOH (200 mL)

was hydrogenated in a Parr apparatus at 70 psi for 24 h in the presence of Pd/C 10% (0.1 g). Filtration of the catalyst through Celite pad, solvent evaporation and flash chromatography (EtOAc/light petroleum/$NH_4OH$, 1:4:0.1) of the residue gave **12** (0.5 g, 50%) as a colourless oil. Anal. calcd for $C_{25}H_{37}N_3O_3$: C, 70.23; H, 8.72; N, 9.83. Found: C, 70.26; H, 8.70; N, 9.81. MALDI-TOF MS: $[MH]^+$ 428. IR (film): 1745, 1698, 1616, 1490 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 7.70–7.50 (m, 1H), 7.10–6.95 (m, 3H), 4.39 (dt, 1H, $J=13.3$, 4 Hz), 3.93 (dq, 2H, $J=7$, 2.4 Hz), 3.53 (s, 3H), 3.48–3.20 (m, 2H), 3.15–3.00 (m, 1H), 2.37 (dd, 1H, $J=11.6$, 3 Hz), 2.30–1.90 (m, 5H), 1.80–1.40 (m, 15H), 1.33 (t, 3H, $J=7$ Hz).

**(±)-*trans*-1-(1-Cyclooctylmethyl-3-methoxycarbonyl-4-piperidyl)-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one (13).** A solution of MeONa, freshly prepared dissolving sodium (0.19 g, 8.26 mmol) in MeOH (5 mL), was added in one portion to a cooled (0 °C) solution of **12** (0.5 g, 1.17 mmol) in MeOH (5 mL). The reaction mixture was stirred at rt for 60 h, then adsorbed on silica gel (1 g) and subjected to flash chromatography (EtOAc/light petroleum/$NH_4OH$, 1:4:0.1) to give **13** (0.46 g, 92%) as a white solid (mp 68–70 °C). Anal. calcd for $C_{25}H_{37}N_3O_3$: C, 70.23; H, 8.72; N, 9.83. Found: C, 70.19; H, 8.73; N, 9.85. MALDI-TOF MS: $[MH]^+$ 428. IR (KBr): 1745, 1698, 1616, 1490 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 7.20–7.00 (m, 4H), 4.39 (dt, 1H, $J=12.2$, 5 Hz), 3.91 (q, 2H, $J=7$ Hz), 3.68 (m, 1H), 3.43 (s, 3H), 3.25–3.10 (m, 1H), 3.08–2.90 (m, 1H), 2.56 (dq, 1H, $J=12.5$, 3.9 Hz), 2.30–2.08 (m, 5H), 1.80–1.40 (m, 15H), 1.33 (t, 3H, $J=7$ Hz).

**(±)-1-(1-Cyclooctylmethyl-3-hydroxymethyl-4-piperidyl)-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one ((±)−1).** A solution of **13** (1 g, 2.34 mmol) in $Et_2O$ (20 mL) was added dropwise to a cooled (0 °C) slurry of $LiAlH_4$ (0.19 g, 5.01 mmol) in $Et_2O$ (20 mL). After stirring for 30 min at the same temperature, $H_2O$ (10 mL) was slowly added and the precipitated aluminium salts were filtered through Celite pad. Evaporation of the solvent and purification of the residue by flash chromatography (EtOAc/light petroleum/$NH_4OH$, 1:2:0.1) gave racemic **1** (0.74 g, 80%) as a white solid (mp 93–95 °C). Anal. calcd for $C_{24}H_{37}N_3O_2$: C, 72.14; H, 9.33; N, 10.52. Found: C, 72.18; H, 9.30; N, 10.51. MALDI-TOF MS: $[MH]^+$ 400. IR (KBr): 3435, 1686, 1491 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 7.40–7.30 (m, 1H), 7.20–7.00 (m, 3H), 4.39 (dt, 1H, $J=12.2$, 5 Hz), 3.93 (dq, 2H, $J=7$, 2.2 Hz), 3.34 (br s, 2H), 3.10–2.91 (m, 2H), 2.61 (dq, 1H, $J=12.2$, 3.7 Hz), 2.40–2.00 (m, 6H), 2.10–1.40 (m, 16H), 1.34 (t, 3H, $J=7$ Hz). The spectral data were consistent with those reported by H. Kawamoto et al. for racemic **1**.[4]

**Separation of the enantiomers of (±)-1-(1-Cyclooctylmethyl-3-hydroxymethyl-4-piperidyl)-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one (1) by preparative chiral HPLC.** The separation was performed on a Shimadzu preparative instrument, equipped with UV detector, automated injector and automated fraction-collector system. Gradient grade quality solvents for HPLC (Merck) were employed.

| | |
|---|---|
| Column: | Chiralcel OD (manufactured by Daicel), 250×20 mm, 10 μm; |
| Eluent: | hexane/2-propanol (100:2 v/v); |
| Elution: | isocratic, 20 mL/min; |
| Detection: | UV absorption at 210 nm. |

Typically, 30 mg of racemic sample were dissolved in 100 μL of 2-propanol and injected. The faster enantiomer was eluted typically between 20.6 and 26.6 min, while the slower enantiomer between 26.8 and 34.6 min. Fractions collected between 26.6 and 26.8 min were discarded due to the presence of both the enantiomers. A single purification run typically yielded 13 mg of each enantiomer with ee > 99%.

The purity of the separated enantiomers was evaluated by chiral analytical HPLC. The analysis was performed on a Shimadzu analytical instrument, equipped with automated injector system and UV diode array detector. Gradient grade quality solvents for HPLC (Merck) were employed.

| | |
|---|---|
| Column: | Chiralcel OD (manufactured by Daicel), 250×4 mm, 10 μm; |
| Eluent: | hexane/2-propanol (100:2 v/v); |
| Elution: | isocratic, 0.8 mL/min; |
| Detection: | UV absorption at 210 nm. |

The optical rotation of both the enantiomers was measured with a Perkin-Elmer 341 instrument. 2-propanol Uvasol (Merck) for spectroscopy was employed as solvent.

Faster-running $[\alpha]_D$ (20 °C) = +7.6° ($c=1$, 2-propanol) enantiomer
(J-113397):
Slower-running $[\alpha]_D$ (20 °C) = −7.2° ($c=1$, 2-propanol). enantiomer:

Literature optical rotation data have been obtained for the hydrochloric salts of the two enantiomers: [4]

(J-113397): $[\alpha]_D$ (20 °C) = +6.4° ($c=1$, 0.1 N HCl)
Other enantiomer: $[\alpha]_D$ (20 °C) = −6.2° ($c=1$, 0.1 N HCl).

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