

A New Approach to the Synthesis of the Nonpeptide NOP Receptor Antagonist J-113397

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Abstract: A new synthesis that eliminates the need for chromatographic separation in order to obtain multigram quantities of J-113397, a competitive antagonist of the N/OFQ-NOP receptor system, is reported. *N*-Benzyl protected 4-oxopiperidinecarboxylate was used as the starting material to obtain an *N*-benzyl intermediate that could be resolved at a relatively early stage in the synthesis. The crucial step in the synthesis was reduction of the double bond of the β -enaminoester functionality of 1-benzyl-4-(3-ethyl-2-oxo-2,3-dihydrobenzimidazol-1-yl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid methyl ester, since Pd/C reduction gave inseparable mixtures. It could be reduced and epimerized to the desired *trans* diastereoisomer in a one-pot reaction by treatment with magnesium metal in methanol.

Key words: NOP antagonist, receptor, synthesis, enantiomeric resolution, β -enaminoester reduction

The fourth opioid receptor, called opioid receptor-like 1 (ORL1), or the NOP receptor, was identified¹ in 1994 through cDNA expression cloning techniques. It was found to be a member of the G-protein coupled receptor superfamily and shares a high sequence homology with the well-known μ -, κ - and δ -opioid receptors. However, none of the classical opioid ligands showed significant affinity for the NOP receptor. An endogenous ligand for the NOP receptor was identified as a 17-amino acid neuropeptide called nociceptin² or orphanin FQ,³ shortly thereafter. Despite the similarity of this peptide, now called the N/OFQ peptide (NOP) receptor,⁴ with the opioid ligand, dynorphin A, nociceptin does not bind to the classical opioid receptors with high affinity. A number of studies have indicated that the NOP receptor might be an important new molecular target for the development of novel therapeutics for various human disorders.^{5,6} The N/OFQ and its receptor have been implicated in several physiological pathways including morphine tolerance, neurotransmitter release, inhibition of learning and memory, modulation of cardiovascular and respiratory function, food intake, anxiety and locomotion. It has also been found to play a direct role on pain perception. However, the precise effect of N/OFQ on nociceptive sensitivity is still unclear.

Recently, several small-molecule ligands for the NOP receptor have been reported in the literature.^{6,7} A highly potent and selective agonist (Ro 64-6198)⁸ and a few antagonists (J-113397,⁹ JTC-801¹⁰) were among these. These ligands have been instrumental in the pharmacological evaluation of the N/OFQ-NOP receptor system. The antagonist J-113397⁹ [*trans*-1-(1-cyclooctylmethyl-3-hydroxymethyl-4-piperidyl)-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one, Figure 1], acts as a high affinity, selective and competitive antagonist of the NOP receptor.¹¹ However, it also appears to have pharmacological actions that are independent of the NOP receptor. In particular, J-113397 has been found to stimulate mesolimbic dopamine release and to have a rewarding effect in mice by a non-NOP mechanism.¹²

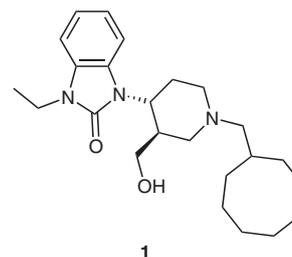


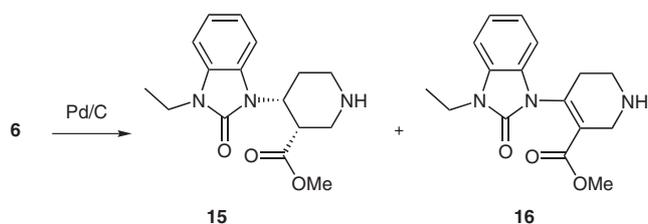
Figure 1 Structure of NOP receptor antagonist J-113397 (1)

Our interest in this opioid field led us to consider further pharmacological investigation of the N/OFQ-NOP receptor system but, in order to do that, we needed a relatively large quantity of the unavailable NOP antagonist, J-113397. Although some total syntheses of J-113397 have been developed over the past few years,^{13,14} these methods have significant drawbacks. A major disadvantage is the necessity of using chromatographic methods in the purification process as well as for the separation of the enantiomers of (\pm)-1. This is problematic in large-scale syntheses, and we preferred to develop synthetic procedures that would obviate the necessity for chromatographic separation. Also, most of the intermediates are oils and some of these were found to be unstable in our hands. Thus, it was important to develop an alternative, more general synthetic procedure. We now wish to report an efficient and non-chromatographic synthesis of J-113397 using 1-benzyl-4-oxo-3-piperidinecarboxylate (**3**) as the starting material. Our synthesis utilizes compound **7** as an early chiral intermediate (Scheme 1). The enantiomers of

compound **7** were obtained via optical resolution. The secondary amine **8** could prove useful as an intermediate for the future synthesis of new *N*-substituted analogues of J-113397. The capability of the new synthetic route to **1** was demonstrated on a multigram scale.

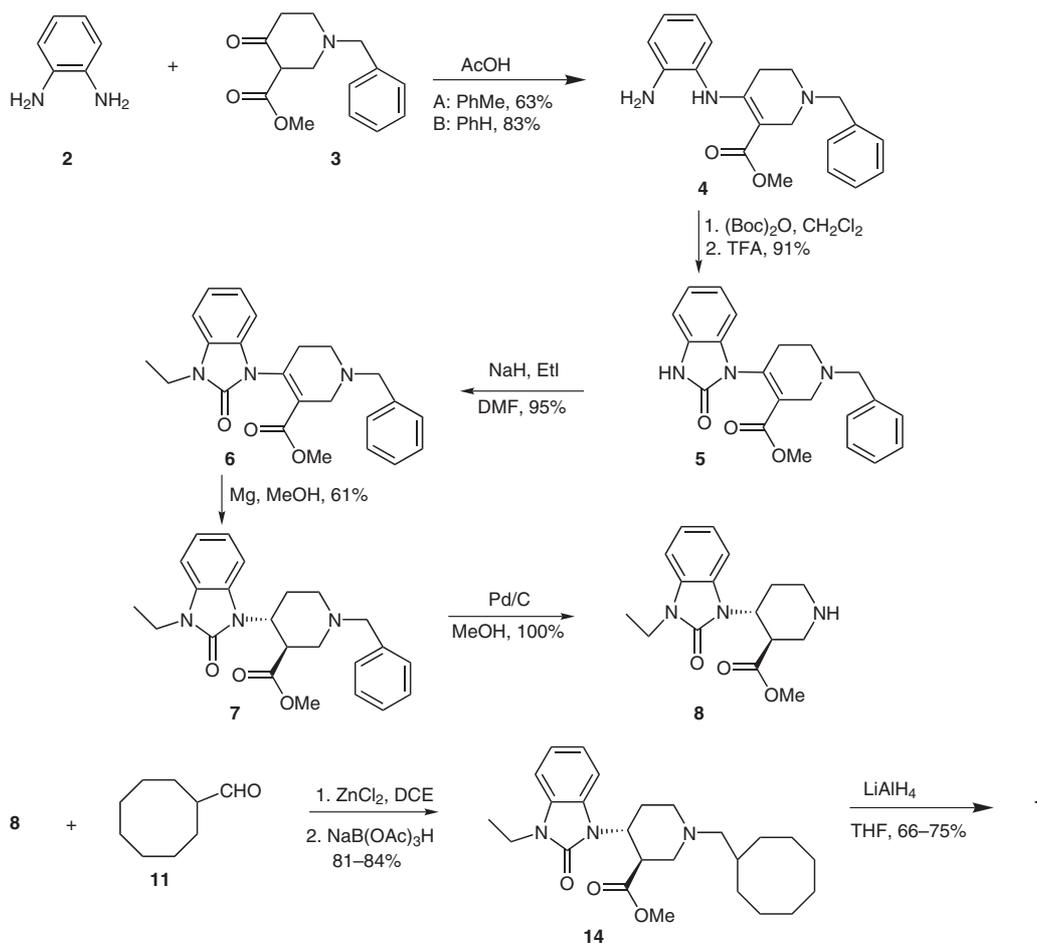
The outline of the synthetic pathway to J-113397 is shown in Scheme 1. In order to access the chiral *N*-nor intermediate (e.g., **8**) we decided to use *N*-benzyl protected 4-oxopiperidinecarboxylate **3** as the starting material. Accordingly, condensation of *o*-phenylenediamine (**2**) with **3** in toluene (Method A) under reflux in the presence of a catalytic amount of AcOH gave the enamine **4**. Fewer impurities were formed and a better yield was obtained under the same reaction conditions using benzene as a solvent (Method B). The benzimidazolone core in **5** was derived by treatment of the enamine **4** with a 2.2-fold excess of di-*tert*-butyl dicarbonate (Boc₂O) followed by subsequent hydrolysis of the resulting *N*-Boc derivative with TFA. *N*-Alkylation of intermediate **5** with ethyl iodide in the presence of NaH furnished **6** in high yield.

The crucial step of the synthesis was reduction of the double bond of the β-enaminoester functionality of **6**. In the first attempt we used catalytic hydrogenation in the presence of Pd/C, which gave an inseparable mixture of desired **15** and *N*-deprotected enamine **16** (Scheme 2).



Scheme 2

Different solvent systems were tried and different amounts of catalyst, as well as different temperatures, without success. Apparently, compound **16**, with its unsaturated bond is stable and could not be easily hydrogenated under these conditions. It was found, however, that **6** could be reduced and epimerized to the desired *trans*-isomer **7** in a one-pot reaction by treatment with magnesium metal in methanol under reflux.¹⁵ The *cis*-isomer was not obtained in pure form. The *trans*- and *cis*-isomers of **7** could be distinguished by NMR spectroscopy. The *cis/trans*-isomer mixture had peaks at $\delta = 1.96$ – 1.99 (m), 2.43 – 2.47 (m), and 7.55 (br s) that were not found in the spectra of pure *trans*-**7**. The intermediate **7** was then smoothly transformed to **8** by catalytic hydrogenation in the presence of Pd/C. NMR spectra and TLC indicated that the crude product **8** was pure enough for the next step



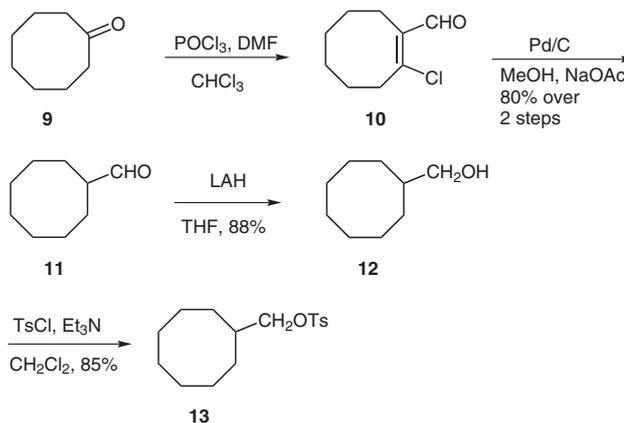
Scheme 1 Synthesis of J-113397 (**1**)

without need for additional purification. It is noteworthy that the direct conversion of **6** into **8** or into **7** was unsuccessful under Birch reduction with lithium metal in liquid ammonia¹⁶ providing a complex mixture of products.

We next envisioned optical resolution of intermediates **7** or **8** taking advantage of the amine functionality. Screening of twenty different acids resulted in a diastereomeric salt of **7** with (*R*)-(-)-3-chloromandelic acid. The isolated free base from the diastereomer showed 94.7% ee. Recrystallization from a mixture of ethanol and propan-2-ol (5.6:1) furnished optically pure (-)-**7**, [α]_D²⁰ -33.1 (*c* = 1.26, MeOH). The purity of the separated enantiomer was evaluated by chiral analytical HPLC. The analysis was performed on a Shimadzu analytical instrument using a mixture of hexane–propan-2-ol–Et₂NH (85:15:0.2) as the eluent system. The enantiomers of **7** were found to be >98% ee. A 98:2 enantiomeric mixture was easily estimated by HPLC. Once we had obtained optically pure amine (-)-**7** as the free base, we were able to use (*R*)-(-)-mandelic acid to generate the salt [(-)-**7**·(*R*)-(-)-mandelic acid], and it crystallized from propan-2-ol. This approach allowed us to change the protocol for the optical resolution of (±)-**7** to a more practical procedure utilizing both enantiomers of mandelic acid itself, since (*S*)-(+)-3-chloromandelic acid is not commercially available. Thus, treatment of racemic amine (±)-**7** with (*S*)-(+)-mandelic acid gave the enantiomeric salt [(+)-**7**·(*S*)-(+)-mandelic acid] that, after reconversion into the base, provided (+)-**7**, [α]_D²⁰ +33.5 (*c* 0.98, MeOH). All attempts to obtain diastereomeric salts of (±)-**8** with various chiral acids failed, affording mostly viscous oils.

The last two steps of the synthesis involved reductive amination of compound **8** and the reduction of the ester group in **14** to a primary alcohol, as shown in Scheme 1. For the addition of the cyclooctylmethyl substituent of **14**, different approaches were used, including reductive alkylation with aldehyde **11** and N-alkylation with tosyl derivative **13** (Scheme 3) in the presence of K₂CO₃ (3 equiv) in DMF at 80 °C (data not published). The reductive amination was found to be more efficient and was further explored. For reductive alkylation different borohydride reducing agents, as well as different additives such as molecular sieves or Lewis acids were tried.

Compound **14** was obtained under mild conditions, in good yield by reductive alkylation of **8** with aldehyde **11** and NaBH(OAc)₃ in the presence of ZnCl₂¹⁷ and molecular sieves in 1,2-dichloroethane (DCE). The addition of ZnCl₂ was found to be essential for the formation of **14** (Scheme 1). Intermediate **11** was prepared from commercially available cyclooctanone (**9**) according to the known procedure¹³ with a few modifications as shown in Scheme 3. Conversion of **9** into β-chloro-α,β-unsaturated aldehyde **10** proceeded via Vilsmeier formylation with phosphorus oxychloride and DMF in CHCl₃.¹⁸ Reductive dehalogenation of **10** over Pd/C catalyst in MeOH using NaOAc·3H₂O as a hydrogen chloride scavenger afforded **11** in 87% yield over two steps. The tosyl derivative **13** was obtained via reduction of aldehyde **11** to primary al-



Scheme 3

cohol **12** with LiAlH₄, which was then converted into **13** in a reaction with *p*-toluenesulfonyl chloride in the presence of triethylamine.

The target compound **1** was obtained by reduction of the ester group of **14** with LiAlH₄ described previously.^{13,14} Using 30% excess LiAlH₄ and a low temperature (0 °C) we were able to obtain the desired product **1** in high yield (93–96%) on a small scale (up to 1 g). Since the reaction conditions were not optimized for the multigram scale, the yield was somewhat lower, in the range of 66–75%. The NMR spectra of **1** were in good agreement with the published ¹H and ¹³C NMR spectra of J-113397.^{13,14} The elemental analysis of the compound was consistent with the structure of **1**, as was the HRMS spectra. The optical purity of both enantiomers was evaluated by chiral analytical HPLC. The specific rotation was comparable to literature data.¹⁴

TLC analyses were carried out on Analtech silica gel GHLF 0.25 mm plates with UV and I₂ detection. Melting points were determined in open glass capillaries on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses (C,H,N) were performed by Atlantic Microlabs, Norcross, GA and were within ± 0.3% of the theoretical values. ¹H NMR and ¹³C NMR spectra were recorded on a Varian Gemini spectrometer at 300 MHz and 75 MHz, respectively. For ¹H NMR, 0.1% v/v tetramethylsilane was used as an internal standard. Chemical shifts (δ) are given in parts per million (ppm), coupling constants *J* values are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. The accurate mass Electrospray Ionization (ESI) and Atmospheric Pressure Chemical Ionization (APCI) mass spectra were obtained on a Waters LCT Premier time-of-flight (TOF) mass spectrometer. The chiral HPLC analysis was performed on a Shimadzu LC-6A analytical instrument equipped with UV detector SPD-6AV using Chiralcel OD column (manufactured by Daicel), 250 × 4.6 mm. The samples for HPLC analyses were dissolved in mixture of hexane–propan-2-ol (6:4). Gradient grade quality solvents for HPLC were employed. The specific rotation was measured with a PerkinElmer 341 polarimeter.

4-(2-Aminophenylamino)-1-benzyl-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Methyl Ester (**4**)

Method A: A solution of *o*-phenylenediamine (**2**; 114 g, 1.05 mol) and methyl 1-benzyl-4-oxo-3-piperidinecarboxylate (**3**; 260 g, 1.05 mol) in toluene (1.6 L) was refluxed for 4 h in the presence of AcOH

(14.6 mL, 0.26 mol) with azeotropic removal of H₂O. After cooling, the mixture was quenched with aq sat. NaHCO₃ solution to pH 8.5–9, followed by washing with H₂O (400 mL) and brine (300 mL). The solution was dried and the solvent was evaporated under reduced pressure to give a brown oil (342 g). The crude product was purified by crystallization from a mixture of propan-2-ol and H₂O (6:1, 0.6 L), seeding with crystals from previous experiments to afford 223 g (63%) of white crystals, mp 109–110 °C. An analytical sample was recrystallized from EtOH; mp 112–112.5 °C.

¹H NMR (CDCl₃): δ = 2.26 (t, *J* = 5.77 Hz, 2 H), 2.45 (t, *J* = 5.77 Hz, 2 H), 3.30 (br s, 2 H), 3.62 (s, 2 H), 3.70 (s, 3 H), 3.85 (br s, 2 H), 6.65–6.74 (m, 2 H), 6.96–7.07 (m, 2 H), 7.22–7.36 (m, 5 H), 9.84 (br s, 1 H).

¹³C NMR (CD₃OD): δ = 28.17, 50.21, 51.25, 52.61, 63.57, 91.21, 117.16, 118.98, 125.56, 128.69, 129.24, 129.55, 129.99, 130.84, 138.47, 146.12, 158.76, 171.03.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₀H₂₄N₃O₂: 338.1869; found: 338.1858.

Anal. Calcd for C₂₀H₂₃N₃O₂: C, 71.19; H, 6.87; N, 12.45. Found: C, 70.98; H, 6.78; N, 12.31.

Method B: A solution of *o*-phenylenediamine (**2**; 17.9 g, 0.165 mol) and methyl 1-benzyl-4-oxo-3-piperidinecarboxylate (**3**; 41 g, 0.165 mol) in benzene (0.4 L) was refluxed for 3 h in the presence of AcOH (2.85 mL) with azeotropic removal of H₂O. The mixture was worked up according to the procedure described in method A. The crude solid was purified by crystallization from propan-2-ol affording 46.4 g (83%) of **4** as white crystals; mp 109.5–110 °C.

1-Benzyl-4-(2-oxo-2,3-dihydrobenzimidazol-1-yl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Methyl Ester (**5**)

To a solution of **4** (269 g, 0.8 mol) in CH₂Cl₂ (540 mL) was added di-*tert*-butyl dicarbonate (Boc₂O) (384 g, 1.76 mol) in CH₂Cl₂ (360 mL) followed by addition of a catalytic amount of DMAP (0.98 g). The mixture was stirred under argon for 4 h at 0 °C. TFA (250 mL) was added dropwise and the stirring was continued for 3 h at 0 °C. The second portion of TFA (300 mL) was added and the mixture was kept over night at r.t. The next portion of TFA (150 mL) was added at 0 °C and the mixture was left for 8 h at r.t. The solvent and excess TFA were distilled off under reduced pressure. The residue was quenched with aq sat. Na₂CO₃ solution to pH 8.5–9, and extracted with CHCl₃–MeOH (9:1) (4 × 300 mL). The extracts were dried and the solvents were removed under reduced pressure to afford a crude solid, that was washed with propan-2-ol (0.4 L), collected, and dried to give 264.9 g (91%) of **5**; mp 178.5–179.0 °C.

¹H NMR (CDCl₃): δ = 2.70 (br s, 2 H), 2.79 (br s, 2 H), 3.43 (s, 3 H), 3.49 (br s, 2 H), 3.75 (s, 2 H), 6.86–6.92 (m, 1 H), 7.00–7.11 (m, 3 H), 7.26–7.42 (m, 5 H), 9.41 (br s, 1 H).

¹³C NMR (CDCl₃): δ = 29.92, 48.69, 52.09, 52.89, 61.97, 108.69, 110.09, 121.68, 122.09, 127.54, 127.98, 128.37, 128.61, 129.27, 130.11, 137.91, 138.38, 154.16, 164.94.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₁H₂₂N₃O₃: 364.1661; found: 364.1658.

Anal. Calcd for C₂₁H₂₁N₃O₃: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.20; H, 5.81; N, 11.50.

1-Benzyl-4-(3-ethyl-2-oxo-2,3-dihydrobenzimidazol-1-yl)-1,2,5,6-tetrahydropyridine-3-carboxylic Acid Methyl Ester (**6**)

To a suspension of compound **5** (263 g, 0.72 mol) in DMF (0.6 L) was added 60% NaH (32 g, 0.79 mol) portionwise at 0 °C. After 40 min, EtI (63 mL, 0.79 mol) was added dropwise. The temperature was allowed to warm to r.t., and the mixture was allowed to stand overnight. The mixture was poured onto ice and extracted with CHCl₃ (4 × 300 mL). The organic layer was washed with brine (300 mL), dried and evaporated. The crude oily product was purified by

crystallization with oxalic acid (64 g) from acetone (0.6 L) affording 325.6 g of **6** as a salt; mp 107–108 °C. Cleavage of the oxalic salt with base gave 267 g (95%) of free base as an oil that could be crystallized from a mixture of EtOH and propan-2-ol (2:1); mp 116–116.5 °C.

¹H NMR (CDCl₃): δ = 1.35 (t, *J* = 7.14 Hz, 3 H), 2.68 (br s, 2 H), 2.78 (br s, 2 H), 3.39 (s, 3 H), 3.50 (br s, 2 H), 3.73 (s, 2 H), 3.95 (q, *J* = 7.14 Hz, 2 H), 6.87–6.92 (m, 1 H), 6.98–7.12 (m, 3 H), 7.26–7.42 (m, 5 H).

¹³C NMR (CDCl₃): δ = 13.72, 29.83, 36.03, 48.66, 51.91, 52.86, 61.86, 107.82, 108.57, 121.35, 121.63, 127.34, 127.48, 128.55, 129.17, 129.21, 129.43, 137.91, 138.78, 152.30, 164.86.

HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₃H₂₆N₃O₃: 392.1974; found: 392.1984.

Anal. Calcd for C₂₃H₂₅N₃O₃: C, 70.57; H, 6.44; N, 10.73. Found: C, 70.74; H, 6.41; N, 10.75.

(±)-*trans*-1-Benzyl-4-(3-ethyl-2-oxo-2,3-dihydrobenzimidazol-1-yl)piperidine-3-carboxylic Acid Methyl Ester (**7**)

Mg turnings (120 g, 4.95 mol) were added portionwise to a solution of **6** (128 g, 0.33 mol) in MeOH (2 L) at 0–5 °C. When the exothermic reaction was completed, the mixture was refluxed under argon until the epimerization was accomplished (5–6 h). The resulting suspension was cooled and quenched by careful addition of aq 10% HCl (ca. 4 L). The mixture was brought to pH 8 by addition of NH₄OH and extracted with CHCl₃ (4 × 500 mL). The organic layer was washed with brine (400 mL), dried, and evaporated in vacuo. The crude product was purified by crystallization from (*i*-Pr)₂O, furnishing 79.9 g (61%) of **7** as white crystals; mp 117–118 °C.

¹H NMR (CDCl₃): δ = 1.32 (t, *J* = 7.14 Hz, 3 H), 1.74–1.84 (m, 1 H), 2.23 (dt, *J* = 11.95, 2.34 Hz, 1 H), 2.32 (t, *J* = 11.26 Hz, 1 H), 2.62 (dq, *J* = 12.64, 3.57 Hz, 1 H), 2.98–3.08 (m, 1 H), 3.17–3.25 (m, 1 H), 3.40 (s, 3 H), 3.61 (s, 2 H), 3.65–3.78 (m, 1 H), 3.92 (q, *J* = 7.14 Hz, 2 H), 4.35–4.50 (m, 1 H), 6.95–7.01 (m, 1 H), 7.03–7.10 (m, 2 H), 7.15–7.21 (m, 1 H), 7.25–7.40 (m, 5 H).

¹³C NMR (CDCl₃): δ = 13.72, 28.17, 35.89, 44.46, 51.97, 52.73, 53.08, 55.44, 62.35, 107.69, 108.86, 121.07, 121.07, 127.40, 128.54, 128.54, 128.90, 129.13, 129.13, 129.35, 138.30, 153.56, 172.64.

HRMS (ESI): *m/z* [M + H]⁺ calcd for C₂₃H₂₈N₃O₃: 394.2131; found: 394.2149.

Anal. Calcd for C₂₃H₂₇N₃O₃: C, 70.21; H, 6.92; N, 10.68. Found: C, 70.16; H, 6.95; N, 10.73.

Optical Resolution of (±)-**7**

(*R*)-(–)-3-Chloromandelic acid (27.5 mg, 0.147 mM) was added to a solution of amine (±)-**7** (58 mg, 0.147 mol) in a mixture of EtOH and propan-2-ol (5.6:1) (0.5 mL). The mixture was kept at r.t. for 0.5 h, and then in an ice-bath for 10 min. The formed salt (30 mg) was collected [(–)-**7**, 95% ee; mp 133.5–134 °C]. Recrystallization from the same solvent system afforded the pure enantiomer (–)-**7**; yield: 15.1 mg (free base); [α]_D²⁰ –33.1 (*c* = 1.26, MeOH). The purity of the enantiomer was determined by chiral analytical HPLC. A mixture of hexane–propan-2-ol–Et₂NH (85:15:0.2) was used as the eluent system. The faster (+)-enantiomer eluted at 8.50 min and the slower (–)-enantiomer at 10.75 min. The free base of (–)-**7** (29 mg) was then crystallized with (*R*)-(–)-mandelic acid (11.2 mg) from EtOAc to give 34 mg of seed crystals; mp 132.5–133 °C. Treatment of a solution of (±)-**7** (158 g) in propan-2-ol (450 mL) with (*R*)-(–)-mandelic acid (10% excess) with seeds from the previous experiment yielded the diastereomeric salt [(–)-**7**·(*R*)-(–)-mandelic acid]; 93% ee; mp 130–131 °C. Two recrystallizations from propan-2-ol followed by conversion of the diastereomeric salt into its free base with aq sat. solution of NaHCO₃ gave pure (–)-**7**; yield: 73 g (free

base); $[\alpha]_{\text{D}}^{20}$ -33.4 ($c = 0.92$, MeOH); >98% ee. The pooled mother liquor was concentrated in vacuo and the residue dissolved in CHCl_3 (300 mL), treated with aq sat. solution of NaHCO_3 to pH 8.5–9, and the organic solvent was separated and the solvent removed in vacuo. The liberated free base was then treated with (*S*)-(+)-mandelic acid (10% excess) to provide the enriched enantiomeric salt (+)-7-(*S*)-(+)-mandelic acid. The pure free base (+)-7 (70.8 g), was obtained after two recrystallizations of the salt from propan-2-ol; $[\alpha]_{\text{D}}^{20}$ $+33.5$ ($c = 0.975$, MeOH); >98% ee.

(+)- and (–)-trans-4-(3-Ethyl-2-oxo-2,3-dihydrobenzimidazol-1-yl)piperidine-3-carboxylic Acid Methyl Ester [(+)- and (–)-8]

The obtained (+)- or (–)-7 in MeOH (900 mL) was hydrogenated in a Parr apparatus at 50 psi in the presence of Pd/C (5%, 0.2 equiv) overnight. The catalyst was filtered off and washed with MeOH (3 × 100 mL). The solvent was evaporated in vacuo yielding (+)- or (–)-8 as hygroscopic, colorless oil/foam. The crude product (+)- or (–)-8 was used in the next step without further purification. A sample for NMR and mass spectra was prepared by filtration through a short pad of silica gel.

^1H NMR (CDCl_3): $\delta = 1.32$ (t, $J = 7.15$ Hz, 3 H), 2.00–2.11 (m, 1 H), 3.03 (dq, $J = 12.93$, 3.85 Hz, 1 H), 3.20–3.47 (m, 2 H), 3.42 (s, 3 H), 3.70–3.97 (m, 4 H), 4.07 (dt, $J = 11.83$, 3.85 Hz, 1 H), 4.70–4.85 (m, 1 H), 6.96–7.28 (m, 3 H), 7.52 (br s, 1 H).

^{13}C NMR (CDCl_3): $\delta = 13.69$, 26.27, 36.04, 42.00, 44.28, 45.85, 50.87, 52.48, 107.89, 109.53, 121.60, 121.74, 128.01, 129.09, 153.46, 170.47.

(+)-trans-8

Yield: 53.8 g (quant); $[\alpha]_{\text{D}}^{20}$ $+2.0$ ($c = 1.15$, MeOH).

HRMS-TOF (APCI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{22}\text{N}_3\text{O}_3$: 304.1661; found: 304.1658.

(–)-trans-8

Yield: 56 g (quant); $[\alpha]_{\text{D}}^{20}$ -2.4 ($c = 1$, MeOH).

HRMS-TOF (APCI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{22}\text{N}_3\text{O}_3$: 304.1661; found: 304.1674.

2-Chlorocyclooct-1-enecarbaldehyde (10)¹⁸

POCl_3 (57.1 mL, 0.62 mol) was dissolved in CHCl_3 (75 mL) and the solution was added dropwise to a mixture of DMF (48.1 mL, 0.62 mol) and CHCl_3 (145 mL) at 5–10 °C under argon. After 0.5 h, the temperature was allowed to reach r.t. and a solution of cyclooctanone (**9**; 66 g, 0.52 mol) in CHCl_3 (75 mL) was added dropwise. The mixture was reflux for 3 h, cooled to r.t. and quenched with $\text{NaOAc} \cdot 3\text{H}_2\text{O}$ (84.5 g in 200 mL H_2O). The mixture was stirred for 0.5 h. The layers were separated and the aqueous layer was extracted with CHCl_3 (3 × 100 mL). The organic extracts were washed with brine (200 mL) and the solvent was evaporated in vacuo to give 96 g of crude **10**. NMR spectra showed that the crude product **10** was sufficiently pure for the following step.

^1H NMR (CDCl_3): $\delta = 1.40$ –1.60 (m, 6 H), 1.76–1.86 (m, 2 H), 2.42–2.50 (m, 2 H), 2.71–2.79 (m, 2 H), 10.17 (s, 1 H).

^{13}C NMR (CDCl_3): $\delta = 25.48$, 25.93, 26.68, 28.34, 30.17, 37.59, 136.43, 153.83, 191.12.

Cyclooctanecarbaldehyde (11)¹³

A solution of crude **10** (96 g) in a MeOH– H_2O mixture (90:10, 0.5 L) was hydrogenated overnight in a Parr apparatus at 40 psi in the presence of 5% Pd/C (16 g) and $\text{NaOAc} \cdot 3\text{H}_2\text{O}$ (283 g, 2 mol). The catalyst was filtered off and washed with MeOH (3 × 100 mL). The combined extracts were evaporated in vacuo. The residue was dissolved in CHCl_3 (300 mL), washed with H_2O (100 mL), and brine (100 mL) and evaporated to give crude **11** (72.6 g) as a colorless oil.

The product was purified by distillation (ca. 107–110 °C/0.5 Torr) to give **11** (63.4 g, 87% over two steps).

^1H NMR (CDCl_3): $\delta = 1.46$ –1.64 (m, 10 H), 1.64–1.80 (m, 2 H), 1.88–2.05 (m, 2 H), 2.32–2.43 (m, 1 H), 9.61 (s, 1 H).

^{13}C NMR (CDCl_3): $\delta = 25.45$, 25.76, 26.39, 26.92, 50.95, 205.08.

Cyclooctylmethanol (12)

A solution of freshly distilled **11** (2.3 g, 16.4 mmol) in THF (20 mL) was added dropwise to a cooled slurry of LiAlH_4 (0.68 g) in THF (10 mL) under argon. After 2 h, the mixture was quenched with H_2O , filtered through a pad of Celite and extracted with Et_2O (3 × 30 mL). The organic layer was washed with brine (60 mL), dried and evaporated to give **12** (2.25 g) as an oil. The crude product was distilled in vacuo to give pure **12** (2.04 g, 88%); bp 120–123 °C/ca. 0.5 Torr (oil bath ca. 170–200 °C).

^1H NMR (CDCl_3): $\delta = 1.18$ –1.78 (m, 15 H), 3.40 (d, $J = 6.32$ Hz, 2 H).

^{13}C NMR (CDCl_3): $\delta = 25.78$, 25.78, 26.68, 27.13, 27.13, 29.53, 29.53, 40.56, 69.39.

HRMS (ESI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_9\text{H}_{19}\text{O}$: 143.1436; found: 143.1430.

Anal. Calcd for $\text{C}_9\text{H}_{18}\text{O} \cdot 0.05 \text{H}_2\text{O}$: C, 75.52; H, 12.74. Found: C, 75.49; H, 12.65.

Toluene-4-sulfonic Acid Cyclooctylmethyl Ester (13)

To a solution of **12** (0.67 g, 4.7 mmol) in CH_2Cl_2 (5 mL) was added *p*-toluenesulfonyl chloride (0.98 g, 5.17 mmol) in CH_2Cl_2 (7 mL) followed by addition of Et_3N (0.72 mL, 5.17 mmol) at 5–10 °C. The temperature of the mixture was allowed to reach r.t. overnight. The mixture was then treated with aq 1 N HCl and the organic layer was separated, washed with H_2O (15 mL) and brine (15 mL). The solvent was evaporated to give crude **13** (1.18 g, 85%) as an oil. The crude product **13** was pure enough (NMR and TLC) to use in the next step.

^1H NMR (CDCl_3): $\delta = 1.16$ –1.33 (m, 2 H), 1.33–1.77 (m, 12 H), 1.77–1.92 (m, 1 H), 2.45 (s, 3 H), 3.78 (d, $J = 6.59$ Hz, 2 H), 7.32–7.40 (m, 2 H), 7.76–7.83 (m, 2 H).

^{13}C NMR (CDCl_3): $\delta = 21.85$, 25.28, 25.28, 26.44, 26.89, 26.89, 28.95, 28.95, 37.11, 75.96, 128.09, 128.09, 129.99, 129.99, 133.49, 133.49, 144.78.

HRMS-TOF (APCI): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{23}\text{O}_3\text{S}$: 295.1368; found: 295.1377.

(+)- and (–)-trans-1-(1-Cyclooctylmethyl-3-methoxycarbonyl-4-piperidyl)-3-ethyl-1,3-dihydro-2H-benzimidazol-2-one [(+)- and (–)-14]¹⁴

Cyclooctanecarbaldehyde (**11**; 1.1 equiv) was added under argon to (+)- or (–)-**8** (1 equiv, 1 M solution in dichloroethane containing 4 Å MS) and ZnCl_2 (1.5 equiv) at r.t. The mixture was stirred for 0.5 h and then treated portionwise with $\text{NaBH}(\text{OAc})_3$ (1.5 equiv). The stirring was continued for 2 h. The resulting suspension was quenched with aq sat. NaHCO_3 solution to pH 8–8.5, and extracted with CHCl_3 (4 × 200 mL). The organic layer was washed with brine (300 mL) and evaporated to give (+)- or (–)-**14**. The crude product (+)- or (–)-**14** was purified by crystallization from 90% aq acetone to give white crystals.

^1H NMR (CDCl_3): $\delta = 1.14$ –1.28 (m, 2 H), 1.32 (t, $J = 7.29$ Hz, 3 H), 1.38–1.81 (m, 14 H), 2.11–2.30 (m, 4 H), 2.57 (dq, $J = 12.38$, 3.3 Hz, 1 H), 2.95–3.04 (m, 1 H), 3.14–3.23 (m, 1 H), 3.44 (s, 3 H), 3.62–3.76 (m, 1 H), 3.92 (q, $J = 7.29$ Hz, 2 H), 4.31–4.49 (m, 1 H), 6.95–7.02 (m, 1 H), 7.03–7.11 (m, 2 H), 7.14–7.20 (m, 1 H).

^{13}C NMR (CD_3OD): $\delta = 13.95$, 26.78, 26.78, 27.68, 28.39, 28.39, 29.07, 32.03, 32.11, 36.34, 36.82, 45.46, 52.41, 54.25, 54.67, 57.11,

66.65, 109.28, 109.28, 110.34, 122.63, 122.71, 130.22, 155.14, 173.88.

(+)-*trans*-14

Yield: 63.1 g (84%); mp 117.5–118 °C; $[\alpha]_{\text{D}}^{20} +27.3$ ($c = 0.765$, MeOH).

HRMS-ESI: m/z $[M + H]^+$ calcd for $\text{C}_{25}\text{H}_{38}\text{N}_3\text{O}_3$; 428.2913; found: 428.2911.

Anal. Calcd for $\text{C}_{25}\text{H}_{37}\text{N}_3\text{O}_3$: C, 70.22; H, 8.72; N, 9.83. Found: C, 70.39; H, 8.72; N, 9.80.

(-)-*trans*-14

Yield: 61.6 g (81%); mp 118–118.5 °C; $[\alpha]_{\text{D}}^{20} -27.4$ ($c = 0.87$, MeOH).

HRMS-ESI: m/z $[M + H]^+$ calcd for $\text{C}_{25}\text{H}_{38}\text{N}_3\text{O}_3$; 428.2913; found: 428.2927.

Anal. Calcd for $\text{C}_{25}\text{H}_{37}\text{N}_3\text{O}_3$: C, 70.22; H, 8.72; N, 9.83. Found: C, 70.04; H, 8.67; N, 9.73.

(+)- and (-)-*trans*-1-(1-Cyclooctylmethyl-3-hydroxymethyl-4-piperidyl)-3-ethyl-1,3-dihydro-2H-benzimidazol-2-one [(+)-(3R,4R)- and (-)-(3S,4S)-*trans*-1]^{13,14}

A 0.7 M solution of (+)- or (-)-**14** in a mixture of Et_2O –THF (1:1) was added dropwise to a slurry of LiAlH_4 (0.75 equiv) in Et_2O at 0–5 °C. The total concentration of (+)- or (-)-**14** in the solution was 0.5 M. The mixture was stirred for 15 min and then decomposed following known procedures.¹⁹ The stirring was continued for 20 min. The resulting precipitate was filtered off and washed with Et_2O (3 × 150 mL). The combined organic washings were evaporated. The residue was dissolved in CHCl_3 (400 mL), washed with brine (150 mL), dried, and the solvent was evaporated. The crude product was crystallized from EtOAc , affording white crystals.

¹H NMR (CDCl_3): $\delta = 1.18$ – 1.30 (m, 2 H), 1.34 (t, $J = 7.28$ Hz, 3 H), 1.40– 1.76 (m, 13 H), 1.83– 1.91 (m, 1 H), 2.02– 2.36 (m, 6 H), 2.60 (dq, $J = 12.36, 3.98$ Hz, 1 H), 2.98– 3.06 (m, 2 H), 3.33 (br s, 2 H), 3.87– 4.04 (m, 2 H), 4.38 (dt, $J = 11.88, 3.75$ Hz, 1 H), 7.03– 7.14 (m, 3 H), 7.31– 7.34 (m, 1 H).

¹³C NMR (CDCl_3): $\delta = 13.78, 25.80, 25.83, 26.67, 27.33, 27.36, 28.95, 31.06, 31.11, 35.06, 36.29, 41.22, 51.94, 53.79, 56.67, 62.08, 66.28, 108.14, 110.44, 121.31, 121.34, 128.22, 129.44, 154.79$.

The purity of the enantiomers was evaluated by chiral analytical HPLC. A mixture of hexane–propan-2-ol– Et_2NH (95:5:0.2) was used as the eluent system. The faster (+)-enantiomer eluted at 9.43 min and the slower (–)-enantiomer at 11.24 min. Since each enantiomer only showed a single peak in the HPLC assay, the enantiomers were estimated to be >98% ee.

(+)-(3R,4R)-*trans*-1

Yield: 42 g (75%); mp 145–145.5 °C; $[\alpha]_{\text{D}}^{20} +8.6$ ($c = 1$, propan-2-ol) {Lit.¹⁴ $[\alpha]_{\text{D}}^{20} +7.6$ ($c = 1$, propan-2-ol)}.

HRMS-TOF (APCI): m/z $[M + H]^+$ calcd for $\text{C}_{24}\text{H}_{38}\text{N}_3\text{O}_2$; 400.2964; found: 400.2955.

Anal. Calcd for $\text{C}_{24}\text{H}_{37}\text{N}_3\text{O}_2$: C, 72.14; H, 9.33; N, 10.52. Found: C, 72.16; H, 9.29; N, 10.41.

(-)-(3S,4S)-*trans*-1

Yield: 37 g (66%); mp 144–145 °C; $[\alpha]_{\text{D}}^{20} -8.5$ ($c = 1.02$, propan-2-ol) {Lit.¹⁴ $[\alpha]_{\text{D}}^{20} -7.2$ ($c = 1$, propan-2-ol)}.

HRMS-TOF (APCI): m/z $[M + H]^+$ calcd for $\text{C}_{24}\text{H}_{38}\text{N}_3\text{O}_2$; 400.2964; found: 400.2969.

Anal. Calcd for $\text{C}_{24}\text{H}_{37}\text{N}_3\text{O}_2$: C, 72.14; H, 9.33; N, 10.52. Found: C, 72.33; H, 9.31; N, 10.44.

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