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Efficient and practical asymmetric synthesis of 1-*tert*-butyl 3-methyl (3*R*,4*R*)-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1,3-dicarboxylate, a useful intermediate for the synthesis of nociceptin antagonists

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ABSTRACT

An efficient and practical asymmetric synthesis of 1-*tert*-butyl 3-methyl (3*R*,4*R*)-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1,3-dicarboxylate **1**, a useful intermediate for the synthesis of nociceptin antagonists, has been developed. This method includes the following key steps: (1) diastereoselective reduction of a chiral enaminoester **3** having (*R*)-1-phenylethylamine as a chiral pool constituent with the use of a combined TFA–$NaBH_4$ reduction system and (2) efficient isomerization from 3,4-*cis*-substituted piperidine **8** to 3,4-*trans*-substituted piperidine **1** under basic conditions. The above methods proved to be applicable for large-scale operation and hundred grams of enantiomerically pure compound **1** (>98% ee) was obtained.

1. Introduction

The opioid receptor-like 1 (ORL-1), recently named NOP, was identified in 1994 as a G-protein-coupled receptor that has a high degree of amino acid sequence homology to classic opioid receptors (μ, κ, and δ).[1–9] Since the discovery of nociceptin (orphanin FQ) as an endogenous ligand of ORL-1, many research groups have reported on the possible involvement of the nociceptin/ORL-1 system in pain regulation,[10] cognition,[11–13] anxiety,[14] and in the cardiovascular system.[15,16] Interest in ORL-1 has resulted in an increase of publications in scientific and patent literature on related antagonists.[17,18] A decade ago, we identified a series of potent and selective non-peptide ORL-1 antagonists exemplified by **J-113397** possessing two stereogenic centers on the piperidine ring (Fig. 1).[19,20] There are many publications on biological experiments using **J-113397**, and some critical pharmacological results of nociceptin antagonists were subsequently reported.[21,22] The stereogenic centers on the piperidine ring are very important for potency and selectivity against other classical opioid receptors;[19] however, our initial synthesis of **J-113397** was not effective for further exploration because the separation of both diastereomers and enantiomers was required.[20] There are some reports on the improved synthesis of **J-113397** and its analogues involving base-promoted *cis–trans* isomerization,[21,23] enantiomeric resolution using diastereomeric salt,[22,24] and separation of diastereomers in the late stages.[25] Nevertheless, an efficient and practical asymmetric synthesis of the compounds and their chiral intermediate without using a resolution, chiral HPLC system, or separation of diastereomers is yet to be reported. Therefore, development of a practical asymmetric synthesis of 1-*tert*-butyl-3-methyl-(3*R*,4*R*)-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1,3-dicarboxylate **1**,[26] the key intermediate for the synthesis of nociceptin antagonists with distinct protection of three functional groups, was desired in order to explore further structure–activity relationship (SAR) studies on its analogues. Herein, we report an efficient and practical asymmetric synthetic method for the preparation of **1** starting from commercially available **2**.

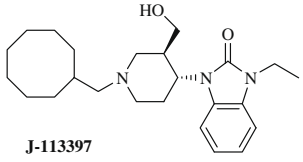

Figure 1.

2. Results and discussion

2.1. Retrosynthesis

We designed **1** as a key intermediate to synthesize **J-113397** analogues, distinctly functionalized with a Boc group, methylester, and proton in order to modify R^1, R^2, and R^3, respectively

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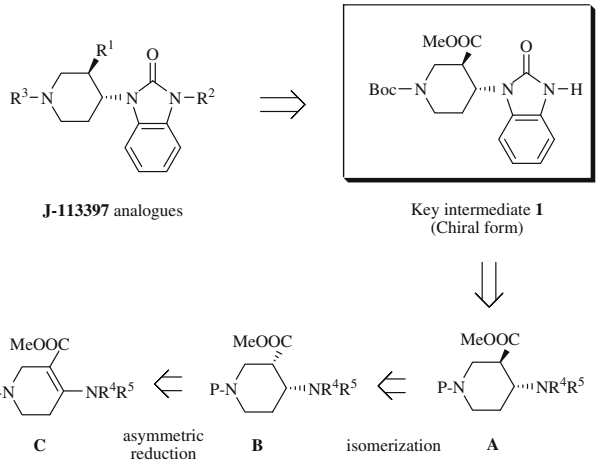


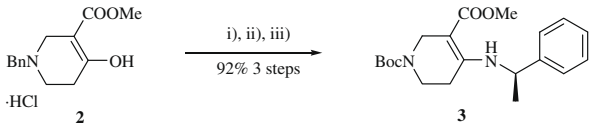
Scheme 1. Retrosynthesis of **1**.

(Scheme 1). We thought that the construction of benzimidazolidinone unit from **A** could be easily accomplished by the previously reported method.[20] The 3,4-*trans* intermediate **A** could be prepared by isomerization of 3,4-*cis* intermediate **B** under basic conditions, as reported by Pollini et al.[23] The stereogenic centers of intermediate **B** would be constructed by stereoselective reduction of enaminoester **C**.

2.2. Stereoselective reduction of 3

To begin, we planned to use chiral enaminoester **3** for the construction of the stereogenic centers according to Palmieri's method[27,28] because of its simplicity and cost effectiveness using (*R*)-1-phenylethylamine. Chiral enaminoester **3** was prepared from commercially available hydroxyl ester **2** in high yield in three steps: deprotection of the benzyl group, followed by Boc protection of the nitrogen atom on the piperidine ring, and formation of an enaminoester with (*R*)-1-phenyethylamine and AcOH (Scheme 2).

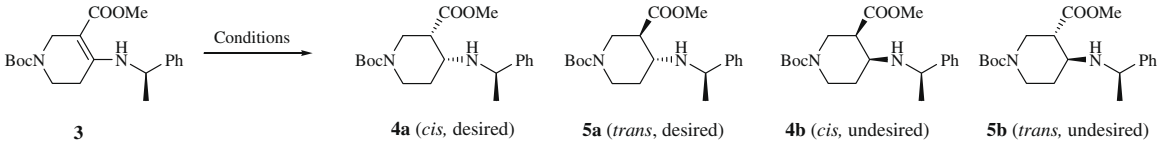
Next we tried diastereoselective reduction using the $NaBH_4$ and AcOH-combined system as reported by Palmieri et al.[27,28] In this reaction, 4 diastereomers (3*S*,4*R*)-*cis*-**4a** (desired form), (3*R*,4*S*)-*cis*-**4b** (undesired form), (3*R*,4*R*)-*trans*-**5a** (desired form), and



Scheme 2. Reagents and conditions: (i) H_2 (1 atm), 10% Pd–C/MeOH, rt; (ii) Boc_2O, $NaHCO_3$/dioxane–H_2O, rt; iii) (*R*)-1-phenylethylamine, AcOH/THF–MeOH, 80 °C.

(3*S*,4*S*)-*trans*-**5b** (undesired form) were produced as given in Table 1, with the desired products **4a** and **5a** having the same (*R*) orientation at the 4-position. We first tried diastereoselective reduction using 4 equivalents of $NaBH_4$ and 20 equiv of AcOH in MeCN at 0 °C, which gave a mixture of **4** and **5** in high yield (entry 1). As expected, we obtained **4a** and **5a** as major products with moderate diastereoselectivity (desired **4a+5a**:undesired **4b+5b** = 3.4:1). Next, we reduced the amounts of AcOH to verify its reactivity and selectivity (entry 2). In this case, the diastereoselectivity was improved to 4.7:1 while the starting material **3** remained. Thus, the combination of 12 equiv of AcOH and 4 equiv of $NaBH_4$ afforded better stereoselectivity than the use of 20 equiv of AcOH. We next examined various carboxylic acids such as formic acid, propionic acid, butanoic acid, pivalic acid, and TFA (entries 3–7). Among them, TFA gave the best result in high diastereoselectivity with a 9.8:1 ratio of desired products **4a** and **5a** to the undesired products **4b** and **5b** in high yield (entry 7). Even at −45 °C using 2 equiv of $NaBH_4$ and 6 equiv of TFA, the stereoselective reduction proceeded smoothly to give **4a** as a major product in high yield (entries 8 and 9). Unfortunately, when we examined the experiment on a 10 g scale with reaction conditions similar to those of entry 9, a large amount of the starting material remained. We considered that MeCN would be partially reduced during the preparation of the reducing agent, and the reducing agent would be consumed before use in substrate reduction in this large scale due to the time required when compared to smaller scale experiments. Therefore, we screened the above reaction with solvents other than MeCN. Finally, we found that the use of THF for reducing agent preparation was efficient, while the addition of MeCN solution of the substrate was also beneficial in this reduction to afford the desired products with high diastereoselectivity and in high yield (entry 10 vs 9). It should be noted that when we used only THF as a solvent in this reaction, no reaction was observed. This result indicates that MeCN plays an important role in this reduction system to enhance

Table 1
Stereoselective reduction of **3**



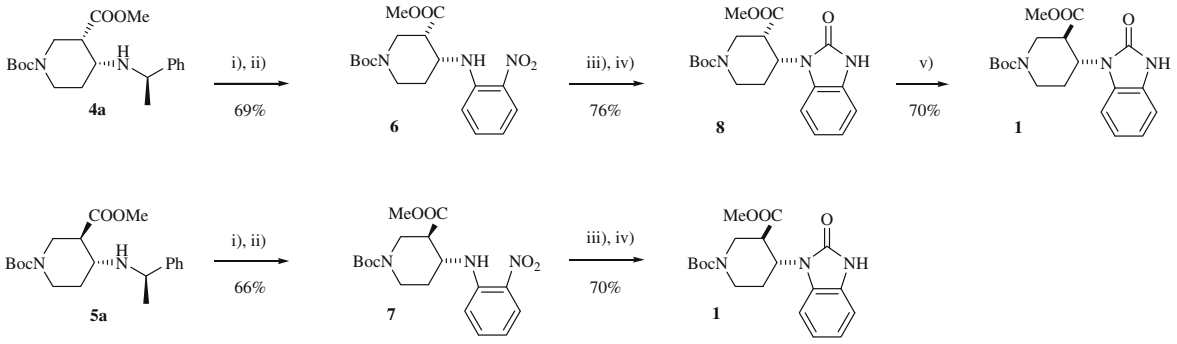
Entry[a]	Reducing agent (molar equiv)[b]	Solvent	Temperature	**4** and **5** (Yield%)	**3** (Yield%)	Desired:undesired[c] (*cis*-**4a**:*trans*-**5a**)
1	$NaBH_4$ (4) + AcOH (20)	MeCN	0 °C, ON	92	0	3.4:1 (3.4:1)
2	$NaBH_4$ (4) + AcOH (12)	MeCN	0 °C, ON	64	25	4.7:1 (4.4:1)
3	$NaBH_4$ (4) + HCOOH (12)	MeCN	0 °C, ON	70	16	4.9:1 (4.4:1)
4	$NaBH_4$ (4) + EtCOOH (12)	MeCN	0 °C 1 h, rt ON	50	30	2.6:1 (2.5:1)
5	$NaBH_4$ (4) + *i*PrCOOH (12)	MeCN	0 °C 1 h, rt ON	20	41	2.0:1 (1.7:1)
6	$NaBH_4$ (4) + *t*BuCOOH (12)	MeCN	0 °C 1 h, rt ON	57	35	2.7:1 (2.5:1)
7	$NaBH_4$ (4) + **TFA** (12)	MeCN	0 °C, 1 h	94	0	9.8:1 (9.6:1)
8	$NaBH_4$ (4) + **TFA** (12)	MeCN	−45 °C, 1 h	96	0	19:1 (18:1)
9	$NaBH_4$ (2) + **TFA** (6)	MeCN	−45 °C, 1 h	92	0	19:1 (19:1)
10	$NaBH_4$ (2) + **TFA** (6)	THF–MeCN[d]	−45 °C, 1 h	95	0	28:1 (26:1)

[a] 1 mmol of **3** was used.
[b] The standard compound was the starting material **3**.
[c] The ratios were determined by chiral HPLC analysis after purification.
[d] Reducing agent was prepared in THF (3 ml) for 1 h and MeCN (1 ml) solution of **3** was added thereto.

reactivity. Furthermore, it was revealed that the optimized reaction conditions (entry 10) could be applicable for the large-scale preparation of **1** in Scheme 5. All peaks of the isomers were separable by chiral HPLC (CHIRALPAK AD-H) and the ratio was determined after isolation. The *cis*- and *trans*-stereoconfigurations of the products were determined by ^{1}H NMR spectroscopy. Moreover, the absolute stereochemistry of **4a** and **5a** was determined by conversion into **1** independently, as described later in Scheme 3.

2.3. Toward key intermediate 1

After major products **4a** and **5a** were separated by chiral column, the transformation of **4a** and **5a** to the key intermediate **1** was performed independently in order to confirm the absolute stereochemistry and establish the synthetic route (Scheme 3). Deprotection of the (*R*)-1-phenyethyl group of **4a** was examined in the presence of 10% Pd–C in an H_2 atmosphere, and was followed by



Scheme 3. Reagents and conditions: (i) H_2 (1 atm), 10% Pd–C/MeOH, rt; (ii) 2-fluoronitrobenzene, Na_2CO_3 /DMF, 100 °C; (iii) H_2 (1 atm), 10% Pd–C/MeOH; (iv) carbonyldiimidazole/$CHCl_3$, rt; (v) Na_2CO_3 /MeOH reflux.

In this reaction, the major product **4a** proved to have the same *cis*-(*R*) orientation as the products reported by Palmieri et al.[27,28] The reaction mechanism is not yet clear but the possible mechanistic pathway for the high stereoselectivity could be explained in accordance with Palmieri's proposed mechanism in Figure 2 (replacement of AcOH with TFA). TFA is a bulky carboxylic acid and stronger than the other acids given in Table 1; therefore, the boron atom could tightly combine to the enol oxygen so that the bulky boron complex could effectively release a hydride from the less-hindered side of the phenylethylimine moiety. Protonation of the enolate from the less-hindered face could afford the desired *cis* = isomer predominantly. In addition, we speculated that the essential reducing agent would be $NaBH_2(TFA)_2$ because gas evolution and exothermic reaction were observed when up to 2 equiv of TFA was added to the $NaBH_4$ suspension in THF but not with the last 1 equiv of TFA, which might be required for reduction, that is, 2 equiv of TFA might be consumed for the production of $NaBH_2(TFA)_2$ and the remaining 1 equiv of TFA could serve for the activation of enaminoester **3** and as a proton source for the reaction.

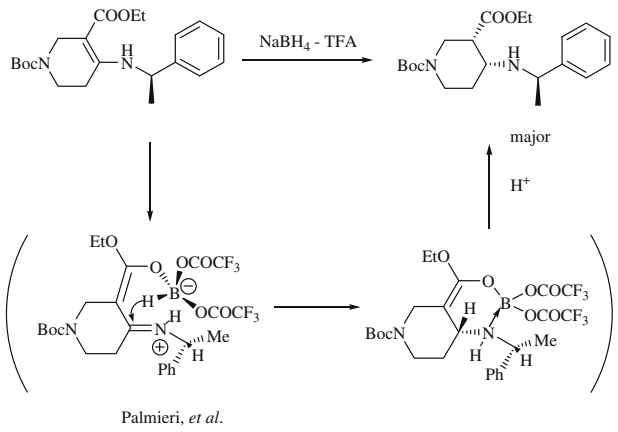
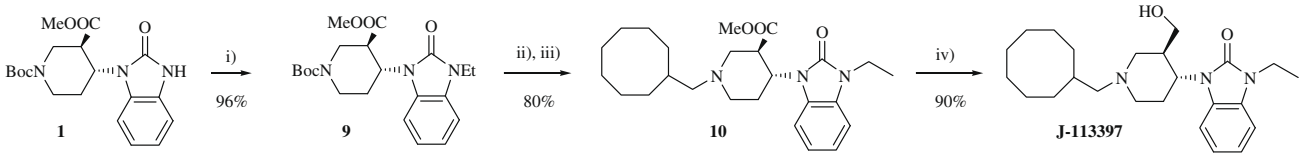


Figure 2. Putative reaction mechanism.

a substitution reaction with 2-fluoronitrobenzene in the presence of Na_2CO_3 to afford*cis*-**6** in good yield. Then, reduction of the nitro group and subsequent cyclization using carbonyldiimidazole (CDI) were carried out to give *cis*-**8**. Finally, the isomerization reaction of **8** was attempted according to the modified conditions of Giardina's method[21,23] by using Na_2CO_3 instead of NaOMe as a base to exclusively furnish the key intermediate *trans*-**1** in 70% yield. When we used NaOMe as a base in this reaction, a significant hydrolysis reaction was observed. Thus the obtained compound **1** was proved to be enantiomerically pure and to have the desired (4*R*)-stereoconfiguration. In the same manner, transformation of **5a** to **1** was performed. Deprotection of the (*R*)-phenylethyl group of **5a** by hydrogenolysis followed by substitution with 2-fluoronitrobenzene afforded *trans*-**7** in high yield. The transformation of **7** to **1** was carried out via reduction of the nitro group and cyclization with CDI. Thus the obtained compound **1** from **5a** was also proved to be enantiomerically pure and to have the desired (4*R*)-stereoconfiguration as described later in Scheme 4.

It should be noted that *cis*-**8** was the appropriate substrate for the isomerization reaction rather than *cis* **6** (Fig. 3). When we used **8** as the starting material for the reaction, perfect isomerization to **1** was observed under basic conditions using Na_2CO_3 in MeOH. On the other hand, isomerization using *cis*-**6** did not work well and only afforded **6**–**7** in a 2:3 ratio. The above phenomenon is well explained considering the heat of formations of each compound (MOPAC, AM1). As shown in Figure 3, the ΔE of **8** versus **1** was large compared to the ΔE of **6** versus **7** so that the isomerization of *cis*-**8** proceeded smoothly to afford the corresponding *trans*-**1** exclusively.

The absolute stereoconfiguration of **1** was determined by sequential conversion to **J-113397** as follows (Scheme 4): alkylation of nitrogen with EtI and K_2CO_3 followed by deprotection of the Boc group, reductive alkylation with cyclooctylcarboxaldehyde,[24] and reduction of the methylester using LAH afforded **J-113397** in 69% overall yield which was specifically identified by its retention time in chiral HPLC analysis and its specific rotation.[20,24] The absolute stereoconfiguration of **1 was** proved to be (3*R*,4*R*)-orientation on the piperidine ring which was the desired stereochemistry.



Scheme 4. Reagents and conditions: (i) EtI, K_2CO_3 /DMF, rt; (ii) 4 N HCl in dioxane/MeOH, rt; (iii) cyclooctylcarboxaldehyde, $NaHB(OAc)_3$ /DMF, rt; (iv) LAH/THF, −78 to 0 °C.

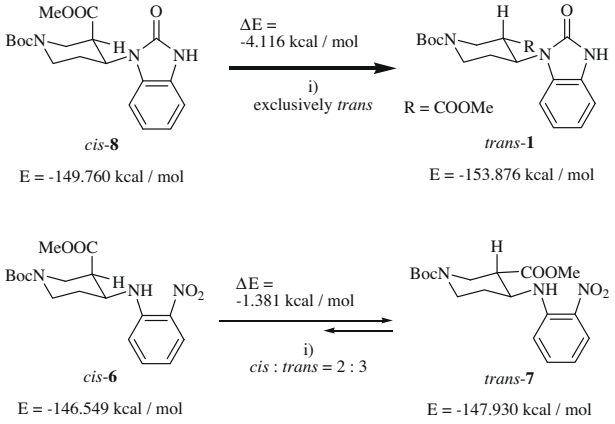


Figure 3. Heat of formation (MOPAC: AM1). Reagents and conditions: (i) Na_2CO_3 (1.5 equiv)/MeOH, 70 °C, 20 h.

2.4. Large-scale preparation of 1

Now that we had established an efficient asymmetric synthetic method for **1**, the large-scale preparation of **1** was finally performed subsequent to the optimization of each reaction step (Scheme 5). Starting from 1.5 kg of commercially available **2**, **3** was prepared by transformation of the protecting group from Bn to Boc followed by enaminoester formation with (*R*)-1-phenyethylamine. Next, the stereoselective reduction of **3** was performed. Combined reducing agent TFA (×6)–$NaBH_4$ (×2) was prepared in THF below 10 °C, MeCN solution of **3** was then added dropwise at a range of −70 °C to −20 °C, and further stirred for 1 h to afford the desired *cis* **4a** as a major product, as determined by NMR spectroscopy. Deprotection of the phenylethyl group and the subsequent substitution reaction with 2-fluoronitrobenzene in basic conditions were carried out to predominantly give *cis*-**6**. Reduction of the nitro group of **6** followed by cyclization with CDI afforded **8** as a major product. In the last stage, the isomerization of **8** using Na_2CO_3 was successfully carried out and gave crude **1** with 95% ee. This result indicated that the asymmetric reduction of **3** proceeded with high diastereoselectivity. Purification of the crude product by crystallization afforded 614 g of pure **1** in 26% overall yield with >98% ee. It is noteworthy that the above sequential procedures do not need any chromatography or resolution methods.

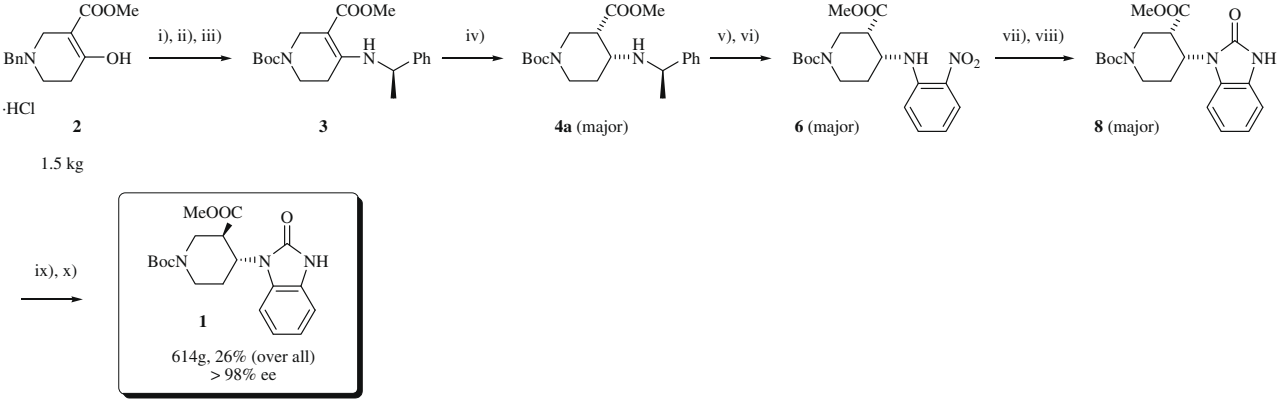
3. Conclusion

In conclusion, we have developed an efficient and practical asymmetric synthesis of 1-*tert*-butyl 3-methyl (3*R*,4*R*)-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)-1,3-piperidinedicarboxylate **1** with a distinct protecting group, a useful intermediate for the synthesis of nociceptin antagonists. The essential stereocenters were constructed by diastereoselective reduction of the chiral enaminoester **3** having (*R*)-1-phenylethylamine as a chiral constituent with the use of a TFA–$NaBH_4$ combined reduction system and afforded *cis*-**4a** predominantly. The efficient isomerization of 3,4-*cis*-substituted piperidine **8** to 3,4-*trans*-substituted piperidine **1** was also accomplished using Na_2CO_3 as a base. In addition, it should be noted that the above methods were proved to be applicable for large-scale operation and a hundred grams of enantiomerically pure compound **1** (>98% ee) was obtained in 26% overall yield without silicagel column chromatography and resolution methods.

4. Experimental

4.1. General experimental

In general, reagents and solvents were used as purchased without further purification. The NMR spectra were obtained at 400 MHz on a MERCURY-400 (Varian) or on a JMN-AL400 (JEOL) spectrometer, with chemical shift (δ, ppm) expressed relative to TMS as an internal standard. High resolution mass spectra were recorded with electrospray ionization (ESI) on a micromass Q-Tof-2 instrument. Flash chromatography was carried out with prepacked silica gel columns (KP-Sil silica) from Biotage or (Purif-Pack) from Moritex. Preparative thin layer chromatography



Scheme 5. Large scale preparation of **1.** Reagents and conditions: (i) H_2, 10% Pd–C/MeOH, rt; (ii) Boc_2O, $NaHCO_3$ /dioxane–H_2O; (iii) (*R*)-1phenylethylamine, AcOH/THF–MeOH, 80 °C; (iv) $NaBH_4$, TFA/MeCN–THF, −70 °C to −20 °C; (v) H_2, Pd– C, AcOH/MeOH, rt; (vi) 2-nitrofluorobenzene, Na_2CO_3/DMF, 100 °C; (vii) H_2 (3 atm), 10% Pd–C/MeOH; (viii) carbonyldiimidazole/THF, 0 °C; (ix) Na_2CO_3/MeOH–THF, 60 °C; (x) crystallization.

(TLC) was performed on TLC Silica Gel 60 F (Merck KGaA). Purification by preparative HPLC was carried out on CHIRALPAK AD, AD-H or CHIRALPAK IC, eluting with a gradient of hexane/EtOH with 0.1% Et_2NH or hexane/isopropanol with 0.1% Et_2NH. HPLC analysis was performed on CHIRALPAK AD, AD-H or CHIRALPAK IC, eluting with a gradient of hexane/EtOH with 0.1% Et_2NH or hexane/isopropanol with 0.1% Et_2NH. IR spectra were recorded on SHIMADZU FTIR 8900. Optical rotations were measured with a JASCO P-1020 polarimeter. Melting points were determined with a Tanaco MP-J3 instrument. All calculations were carried out on Silicon Graphics Octane R10000 workstations. Heat of formation was calculated with the semi-empirical method using the AM1 Hamiltonian in MOPAC 6 in Cerius2 (v. 3.8, Molecular Simulations Inc.).

4.2. Asymmetric synthesis of 1-*tert*-butyl 3-methyl (3*R*,4*R*)-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1,3-dicarboxylate 1

4.2.1. 1-*tert*-Butyl 3-methyl 4-{[(1*R*)-1-phenylethyl]amino}-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate 3

To a suspension of methyl 1-benzyl-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate hydrochloride **2** (50.0 g, 176 mmol) in methanol (200 mL) was added 10% Pd–C (5.00 g, 50% wet) and the mixture was stirred under a hydrogen atmosphere (1 atm) at room temperature for 16 h. After replacement of hydrogen with nitrogen, the catalyst was filtered off with a Celite pad, and the solvent was removed under reduced pressure to give methyl 4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate hydrochloride as a crude oil. To a stirred solution of the crude product and $NaHCO_3$ (32.5 g, 387 mmol) in dioxane (150 ml)—H_2O (150 ml) was added dropwise di-*tert*-butyl dicarbonate (BOC_2O, 39.3 g, 180 mmol) and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was poured into EtOAc and H_2O, and extracted with EtOAc. The combined organic layer was washed with brine and dried over $MgSO_4$. The drying agent was filtered off, and the solvent was removed under reduced pressure to give 1-*tert*-butyl 3-methyl 4-hydroxy-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate as a crude oil. To a stirred solution of the crude product in THF (100 mL)–MeOH (100 mL) were added AcOH (13.1 ml, 229 mmol) and (*R*)-methylbenzylamine (25.6 g, 211 mmol), and the reaction mixture was stirred at reflux for 3 h. After removal of the solvent, the mixture was diluted with EtOAc and aqueous NaOH. The organic layer was washed with H_2O and brine, and dried over $MgSO_4$. The drying agent was filtered off, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 80/20) to give 1-*tert*-butyl 3-methyl 4-{[(1*R*)-1-phenylethyl]amino}-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate **3** (58.0 g, 91.5%) as a pale yellow solid. Mp 88–90 °C; $[\alpha]_D^{24} = -277$ (*c* 1.0, $CHCl_3$); IR (KBr): 2976, 1734, 1693, 1601, 1145 cm^{-1}, ^1H NMR ($CDCl_3$) δ: 9.25 (1H, d, *J* = 6.8 Hz), 7.36–7.30 (2H, m), 7.28–7.21 (3H, m), 4.61 (1H, dq, *J* = 6.8, 6.8 Hz), 4.16–3.98 (2H, br m), 3.72 (3H, s), 3.47–3.37 (1H, m), 3.32–3.30 (1H, m), 2.47–2.32 (1H, br m), 2.12–1.98 (1H, br m), 1.50 (3H, d, *J* = 6.8 Hz), 1.43 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 169.4, 157.5, 154.7, 145.1, 128.9, 128.9, 127.1, 125.4, 125.4, 88.1, 79.7, 52.3, 50.5, 41.4, 38.9, 28.4, 28.4, 28.4, 26.2, 25.2; HRMS: (ESI) calcd for $C_{20}H_{29}N_2O_4$ $[M+H]^+$: 361.2127, found, 361.2122.

4.2.2. Stereoselective reduction of 3 (representative method: Table 1, entry 10)

To a stirred suspension of $NaBH_4$ (42.0 mg, 1.11 mmol) in THF (3 ml) were added dropwise TFA (0.256 ml, 3.33 mol) at 0 °C and **3** (200 mg, 0.550 mmol) in MeCN (1 ml) at −45 °C and the mixture was stirred for 1 h at the same temperature. After the reaction mixture was stirred at 0 °C for a further 1 h, 25% aqueous NH_3 (0.270 ml, 4.44 mmol) was added at 0 °C to quench the reaction. The mixture was poured into EtOAc and H_2O, and then extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4. The drying agent was filtered off, and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to give a mixture of **4a** (predominantly), **4b**, **5a,** and **5b** (191 mg, 95.0%) as a colorless oil. The ratios of all isomers given in Table 1 were determined by analytical chiral HPLC (CHIRALPAK AD, 0.46 × 25 cm hexane/*i*PrOH = 40/1 + 0.1% Et_2NH, flow rate = 1 ml/min): **4a** = 12.1 min, **4b** = 11.3 min, **5a** = 13.6 min, **5b** = 15.9 min. Separation of all isomers was performed by Preparative HPLC (CHIRALPAK AD, 2 × 25 cm, hexane/*i*PrOH = 50/1 + 0.1% Et_2NH, flow rate = 15 ml/min).

4.2.2.1. 1-*tert*-Butyl 3-methyl (3*S*,4*R*)-4-{[(1*R*)-1-phenylethyl]amino}piperidine-1,3-dicarboxylate 4a (*cis*, desired). $[\alpha]_D^{24} = +30$ (*c* 1.0, $CHCl_3$); IR (neat): 2972, 1732, 1693, 1427, 1148 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.30–7.26 (4H, m), 7.24–7.17 (1H, m), 3.96 (1H, br s), 3.82 (1H, q, *J* = 6.5 Hz), 3.70–3.67 (1H, br m), 3.68 (3H, s), 3.11 (1H, dd, *J* = 3.9, 13.7 Hz), 2.94 (1H, ddd, *J* = 3.9, 9.4, 13.7 Hz), 2.82–2.70 (1H, br m), 2.80 (1H, ddd, *J* = 3.9, 4.3, 8.6 Hz), 1.77–1.63 (2H, m), 1.46 (9H, s), 1.24 (3H, d, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ: 172.7, 154.5, 145.8, 128.5, 128.5, 127.0, 126.5, 126.5, 79.6, 54.9, 52.5, 51.6, 43.4, 42.2, 41.2, 29.2, 28.4, 28.4, 28.4, 24.9; HRMS: (ESI) calcd for $C_{20}H_{31}N_2O_4$ $[M+H]^+$: 363.2284, found, 363.2274.

4.2.2.2. 1-*tert*-Butyl 3-methyl (3*R*,4*S*)-4-{[(1*R*)-1-phenylethyl]amino}piperidine-1,3-dicarboxylate 4b (*cis*, undesired). $[\alpha]_D^{25} = +47$ (*c* 1.0, $CHCl_3$); IR (neat): 2972, 1730, 1693, 1421, 1146 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.29–7.17 (5H, m), 3.84 (1H, q, *J* = 6.6 Hz), 3.78 (1H, dd, *J* = 7.4, 13.7 Hz), 3.63–3.53 (1H, m), 3.61 (3H, s), 3.35 (1H, dd, *J* = 3.5, 13.7 Hz), 3.16 (1H, ddd, *J* = 3.5, 7.4, 13.3 Hz), 2.74 (1H, ddd, *J* = 3.5, 3.5, 8.2 Hz), 2.60–2.51 (1H, br m), 1.90–1.79 (1H, m), 1.75–1.52 (1H, br m), 1.39 (9H, s), 1.26 (3H, t, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 172.8, 154.6, 145.5, 128.4, 128.4, 126.9, 126.6, 126.6, 79.6, 54.4, 51.5, 50.9, 45.5, 43.0, 40.2, 28.3, 28.3, 28.3, 27.2, 25.2; HRMS: (ESI) calcd for $C_{20}H_{31}N_2O_4$ $[M+H]^+$: 363.2284, found, 363.2274.

4.2.2.3. 1-*tert*-Butyl 3-methyl (3*R*,4*R*)-4-{[(1*R*)-1-phenylethyl]amino}piperidine-1,3-dicarboxylate 5a (*trans*, desired). $[\alpha]_D^{25} = +14$ (*c* 1.0, $CHCl_3$); IR (neat): 2930, 1732, 1693, 1427, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.30–7.23 (4H, m), 7.21–7.16 (1H, m), 4.07–3.89 (2H, br m), 3.75 (1H, q, *J* = 6.6 Hz), 3.71 (3H, s), 2.96–2.75 (1H, br m), 2.84 (1H, ddd, *J* = 4.3, 10.6, 10.6 Hz), 2.63 (1H, ddd, *J* = 2.3, 12.5, 12.5 Hz), 2.27 (1H, ddd, *J* = 3.5, 9.8, 9.8 Hz), 1.76–1.65 (1H, br m), 1.39 (9H, s), 1.23 (3H, d, *J* = 6.6 Hz), 1.13–1.00 (1H, br m); ^{13}C NMR ($CDCl_3$) δ: 173.6, 154.4, 146.5, 128.4, 128.4, 126.9, 126.4, 126.4, 79.9, 55.9, 55.4, 51.8, 49.8, 45.1, 42.8, 32.1, 28.3, 28.3, 28.3, 24.1; HRMS: (ESI) calcd for $C_{20}H_{31}N_2O_4$ $[M+H]^+$: 363.2284, found, 363.2278.

4.2.2.4. 1-*tert*-Butyl 3-methyl (3*S*,4*S*)-4-{[(1*R*)-1-phenylethyl]amino}piperidine-1,3-dicarboxylate 5b (*trans*, undesired). $[\alpha]_D^{25} = +32$ (*c* 1.0, $CHCl_3$); IR (neat): 2930, 1732, 1693, 1427, 1148 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.31–7.25 (2H, m), 7.23–7.17 (3H, m), 4.32–3.93 (2H, br m), 3.90 (1H, q, *J* = 6.6 Hz), 3.65 (3H, s), 2.80–2.63 (1H, br m), 2.59 (1H, ddd, *J* = 3.9, 10.6, 10.6 Hz), 2.57–2.45 (1H, br m), 2.33–2.22 (1H, br m), 2.07–1.97 (1H, br m), 1.39 (9H, s), 1.25 (3H, d, *J* = 6.6 Hz), 1.15–1.03 (1H, m); ^{13}C NMR ($CDCl_3$) δ: 173.0, 154.3, 145.0, 128.3, 128.3, 126.9, 126.5, 126.5, 79.9, 53.9, 53.6, 51.7, 49.5, 45.0, 42.4, 30.6, 28.3, 28.3, 28.3, 25.6; HRMS: (ESI) calcd for $C_{20}H_{31}N_2O_4$ $[M+H]^+$: 363.2284, found, 363.2275.

4.2.3. 1-*tert*-Butyl 3-methyl (3*S*,4*R*)-4-[(2-nitrophenyl)amino]-piperidine-1,3-dicarboxylate 6

To a solution of **4a** (130 mg, 0.359 mmol) in MeOH (2 ml) was added 10% Pd–C (11.5 mg, 50% wet) and stirred under a hydrogen atmosphere (1 atm) at room temperature for 19 h. After replacement of the hydrogen with nitrogen, the catalyst was filtered off and the solvent was removed under reduced pressure to give a crude oil containing 1-*tert*-butyl 3-methyl (3*S*,4*R*)-4-aminopiperidine-1,3-dicarboxylate. To a solution of the crude product in DMF (1 L) were added Na_2CO_3 (45.8 mg, 0.432 mol) and 2-nitrofluorophenol (55.9 mg, 0.396 mmol) at room temperature, and the mixture was stirred at 100 °C for 20 h. The mixture was poured into EtOAc and H_2O, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with H_2O and brine, and dried over Na_2SO_4. The drying agent was filtered off and the solvent was removed under reduced pressure. The residue was purified by thin layer chromatography (hexane/EtOAc = 7/3) to give 1-*tert*-butyl 3-methyl (3*S*,4*R*)-4-[(2-nitrophenyl)amino]-piperidine-1,3-dicarboxylate **6** (94.0 mg, 68.8%) as a yellow oil. $[\alpha]_D^{25} = -60$ (*c* 1.0, $CHCl_3$); IR (neat): 2900, 1732, 1693, 1614, 1504, 1421, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.62 (1H, br s), 8.19 (1H, dd, *J* = 1.5, 8.5 Hz), 7.44 (1H, ddd, *J* = 1.5, 7.1, 8.5 Hz), 6.90 (1H, d, *J* = 8.5 Hz), 6.67 (1H, ddd, *J* = 1.2, 7.1, 8.5 Hz), 4.16 (1H, ddd, *J* = 4.1, 7.8, 12.0 Hz), 4.00 (1H, dd, *J* = 7.3, 14.4 Hz), 3.73–3.59 (1H, m), 3.68 (3H, s), 3.42 (1H, ddd, *J* = 4.4, 7.8, 12.0 Hz), 2.99–2.87 (1H, br m), 2.12–1.98 (1H, br m), 1.92–1.58 (2H, br m), 1.47 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 171.2, 154.4, 144.0, 136.2, 132.6, 127.2, 115.8, 113.6, 80.2, 52.0, 49.3, 44.1, 42.9, 40.3, 28.4, 28.3, 28.3, 28.3; HRMS: (ESI) calcd for $C_{18}H_{26}N_3O_6$ $[M+H]^+$: 380.1822, found, 380.1833; Heat of formation: −146.549 kcal/mol.

4.2.4. 1-*tert*-Butyl 3-methyl (3*R*,4*R*)-4-[(2-nitrophenyl)amino]-piperidine-1,3-dicarboxylate 7

To a solution of **5a** (100 mg, 0.276 mmol) in MeOH (2 ml) was added 10% Pd–C (11.5 mg, 50% wet) and stirred under a hydrogen atmosphere (1 atm) at room temperature for 19 h. After replacement of hydrogen with nitrogen, the catalyst was filtered off and the solvent was removed under reduced pressure to give a crude oil containing 1-*tert*-butyl 3-methyl (3*R*,4*R*)-4-aminopiperidine-1,3-dicarboxylate. To a solution of the crude product in DMF (1 L) were added Na_2CO_3 (35.9 mg, 0.339 mmol) and 2-nitrofluorophenol (43.9 mg, 0.311 mmol) at room temperature, and the mixture was stirred at 100 °C for 18 h. The mixture was poured into EtOAc and H_2O, and the aqueous layer was extracted with EtOAc. The combined organic layer was washed with H_2O and brine, and dried over Na_2SO_4. The drying agent was filtered off and the solvent was removed under reduced pressure. The residue was purified by thin layer chromatography (hexane/EtOAc = 3/1) to give 1-*tert*-butyl 3-methyl (3*R*,4*R*)-4-[(2-nitrophenyl)amino]piperidine-1,3-dicarboxylate **7** (71.0 mg, 66.2%) as a yellow oil. $[\alpha]_D^{25} = -140$ (*c* 1.0, $CHCl_3$); IR (neat): 2900, 1732, 1695, 1614, 1504, 1416, 1136 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.17 (1H, dd, *J* = 1.7, 8.5 Hz), 8.10 (1H, d, *J* = 8.5 Hz), 7.44 (1H, ddd, *J* = 1.7, 7.5, 8.5 Hz), 6.95 (1H, d, *J* = 8.5 Hz), 6.68 (1H, ddd, *J* = 1.0, 7.5, 8.5 Hz), 4.42–3.94 (2H, br m), 4.01 (1H, dddd, *J* = 3.9, 8.5, 10.0, 10.0 Hz), 3.63 (3H, s), 3.35–2.97 (1H, m), 3.03 (1H, ddd, *J* = 2.9, 11.2, 13.9 Hz), 2.64 (1H, ddd, *J* = 4.1, 10.0, 10.0 Hz), 2.22–2.11 (1H, m), 1.48–1.48 (1H, m), 1.48 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 172.3, 154.2, 144.0, 136.3, 132.3, 127.1, 116.0, 114.0, 80.4, 52.2, 51.6, 47.8, 44.7, 41.8, 30.9, 28.3, 28.3, 28.3; HRMS: (ESI) calcd for $C_{18}H_{26}N_3O_6$ $[M+H]^+$: 380.1822, found, 380.1828. Heat of formation: −147.930 kcal/mol.

4.2.5. 1-*tert*-Butyl 3-methyl (3*S*,4*R*)-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl) piperidine-1,3-dicarboxylate 8

To a solution of **6** (62.9 mg, 0.166 mmol) in MeOH (2 ml) was added 10% Pd–C (31 mg, 50% wet) and stirred under a hydrogen atmosphere (1 atm) at room temperature for 2 h. After removal of hydrogen, the catalyst was filtered off and the solvent was removed under reduced pressure to give crude product containing 1-*tert*-butyl 3-methyl (3*S*,4*R*)-4-[(2-aminophenyl)amino]piperidine-1,3-dicarboxylate. To a stirred solution of the crude product in $CHCl_3$ (3 ml) was added CDI (53.8 mg, 0.332 mmol) and the reaction mixture was stirred at room temperature for 2 h. After removal of the solvent, the residue was diluted with EtOAc and H_2O, and extracted with EtOAc. The combined organic layer was washed with brine and dried over $MgSO_4$. The drying agent was filtered off and the solvent was removed under reduced pressure. The residue was purified by thin layer chromatography (hexane/EtOAc = 3/7) to give 1-*tert*-butyl 3-methyl (3*S*,4*R*)-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1,3-dicarboxylate **8** (49.0 mg, 76.0%) as a colorless solid. $[\alpha]_D^{25} = 31$ (*c* 1.0, $CHCl_3$); IR (KBr): 3200, 2978, 1738, 1697, 1481, 1433, 1366, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.79 (1H, br s), 7.30–7.21 (1H, m), 7.07–6.96 (3H, m), 4.69–4.26 (2H, m), 3.39 (3H, s), 3.29–2.77 (4H, m), 1.84–1.72 (2H, br m), 1.44 (9H, s); ^{13}C NMR ($CDCl_3$) δ: 171.8, 155.5, 154.4, 129.5, 127.9, 121.4, 121.2, 110.9, 109.7, 79.9, 54.1, 51.7, 45.6, 43.4, 42.6, 28.4, 28.4, 28.4, 25.3; HRMS: (ESI) calcd for $C_{19}H_{26}N_3O_5$ $[M+H]^+$: 376.1872, found, 376.1881. Heat of formation: −149.760 kcal/mol.

4.2.6. 1-*tert*-Butyl 3-methyl (3*R*,4*R*)-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl) piperidine-1,3-dicarboxylate 1 from 7

To a solution of **7** (71.0 mg, 0.187 mmol) in MeOH (2 L) was added 10% Pd–C (39.8 mg, 50% wet) and stirred under a hydrogen atmosphere (1 atm) at room temperature for 2 h. After removal of hydrogen, the catalyst was filtered off and the solvent was removed under reduced pressure to give the crude product containing 1-*tert*-butyl 3-methyl (3*R*,4*R*)-4-[(2-aminophenyl)amino] piperidine-1,3-dicarboxylate. To a stirred solution of the crude product in $CHCl_3$ (3 ml) was added CDI (36.4 mg, 0.225 mmol) and the reaction mixture was stirred at room temperature for 18 h. After removal of the solvent, the residue was diluted with EtOAc, washed with aqueous 0.5 M HCl and brine, and dried over Na_2SO_4. The drying agent was filtered off and the solvent was removed under reduced pressure. The residue was purified by thin layer chromatography (hexane/EtOAc = 2/1) to give 1-*tert*-butyl 3-methyl (3*R*,4*R*)-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1,3-dicarboxylate **1** (49.0 mg, 69.7%) as a colorless solid. Mp 210–211 °C; $[\alpha]_D^{25} = +50$ (*c* 1.0, $CHCl_3$); IR (KBr): 3246, 2928, 1734, 1713, 1665, 1491, 1433, 1367, 1186, 1163 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 9.79 (1H, br s), 7.30–7.21 (1H, m), 7.07–6.96 (3H, m), 4.69–4.26 (2H, m), 3.39 (3H, s), 3.29–2.77 (4H, m), 1.84–1.72 (2H, br m), 1.44 (9H, s). ^{13}C NMR ($CDCl_3$) δ: 171.7, 155.0, 154.4, 129.3, 127.9, 121.5, 121.3, 109.8, 108.5, 80.5, 52.8, 52.1, 45.7, 44.1, 43.2, 28.4, 28.4, 28.4, 27.9; HRMS (ESI): calcd for $C_{19}H_{26}N_3O_5$ $[M+H]^+$: 376.1872, found, 376.1884. Anal. Calcd for $C_{19}H_{26}N_3O_5$: C, 60.79; H, 6.71; N, 11.19. Found: C, 60.55; H, 6.69; N, 11.07. Heat of formation: −153.876 kcal/mol. The enantiomeric excess was determined by chiral HPLC (CHIRALPAK IC, 0.46 × 25 cm hexane/*i*PrOH = 95/5–50/50 gradient, containing 0.1% Et_2NH, flow rate = 1 ml/min): **1** = 11.0 min, enantiomer of **1** = 13.5 min.

4.2.7. 1-*tert*-Butyl 3-methyl (3*R*,4*R*)-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl) piperidine-1,3-dicarboxylate 1 from 8

To a solution of a crude **8** (27.8 mg, 0.0710 mmol) in MeOH (1 ml) was added Na_2CO_3 (15.1 mg, 0.143 mmol) and the mixture was stirred at 100 °C for 18 h. The reaction mixture was diluted with EtOAc and H_2O, and extracted with EtOAc. The combined organic layer was washed with aqueous 1 M HCl and brine, and dried over $MgSO_4$. The drying agent was filtered off and the solvent was removed under reduced pressure. The residue was purified by thin layer chromatography (hexane/EtOAc = 3/7) to give 1-*tert*-butyl 3-methyl (3*R*,4*R*)-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl) piper-

idine-1,3-dicarboxylate **1** (19.5 mg, 70.1%) as a colorless solid. All data of **1** were in agreement as before.

4.3. From 1 to J-113397

4.3.1. 1-*tert*-Butyl 3-methyl (3*R*,4*R*)-4-(3-ethyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl) piperidine-1,3-dicarboxylate 9

To a suspension of **1** (300 mg, 0.799 mmol) and K_2CO_3 (221 mg, 1.60 mmol) in DMF (3 ml) was added iodoethane (0.129 ml, 1.60 mmol) at room temperature, and the reaction mixture was stirred for 16 h at 65 °C. The reaction mixture was poured into EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the combined organic layer was washed with H_2O and brine, and dried over $MgSO_4$. The drying agent was filtered off and the solvent was removed under reduced pressure. The residue was purified by silicagel column chromatography (hexane/EtOAc = 1/1) to give 1-*tert*-butyl 3-methyl (3*R*,4*R*)-4-(3-ethyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1,3-dicarboxylate **9** (310 mg, 96.0%) as a colorless solid. $[\alpha]_D^{24} = 50$ (*c* 1.0, $CHCl_3$); IR (KBr): 2978, 1728, 1705, 1682, 1493, 1196, 1161, 1136 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.10–7.05 (3H, m), 7.02–6.97 (1H, m), 4.67–4.17 (3H, br m), 3.92 (2H, q, *J* = 7.2 Hz), 3.56 (1H, ddd, *J* = 4.1, 11.2, 11.2 Hz), 3.42 (3H, s), 3.09–2.74 (2H, br m), 2.57–2.44 (1H, m), 1.86–1.78 (1H, br m), 1.50 (9H, s), 1.32 (3H, t, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ: 171.8, 154.2, 153.2, 129.1, 128.6, 121.1, 121.0, 108.2, 107.6, 80.3, 53.1, 51.9, 45.6, 44.1, 42.8, 35.7, 28.4, 28.4, 28.4, 27.9, 13.5; HRMS (ESI): calcd for $C_{21}H_{30}N_3O_5$ $[M+H]^+$: 404.2185, found, 404.2188.

4.3.2. Methyl (3*R*,4*R*)-1-(cyclooctylmethyl)-4-(3-ethyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-3-carboxylate 10[24]

To a solution of **9** (270 mg, 0.669 mmol) in MeOH (3 ml) was added 4 M HCl in dioxane (3 ml) at room temperature, and the reaction mixture was stirred for 16 h at the same temperature. After completion of the reaction, the mixture was evaporated in vacuo to give a crude oil, which was used in the next step without further purification. To a stirred solution of crude product and cyclooctylcarboxyaldehyde (188 mg, 1.34 mmol) in DMF (3 ml) was added $NaBH(OAc)_3$ (425 mg, 2.01 mmol) portionwise at room temperature, and the reaction mixture was stirred for 3 h at the same temperature. After completion of the reaction, MeOH was added and the mixture was diluted with EtOAc, washed with saturated $NaHCO_3$, H_2O, and brine, and dried over $MgSO_4$. The drying agent was filtered off and the solvent was removed under reduced pressure. The residue was purified by silicagel column chromatography ($CHCl_3$/MeOH = 95/5), and then by thin layer chromatography (hexane/EtOAc = 1/1) to give methyl (3*R*,4*R*)-1-(cyclooctylmethyl)-4-(3-ethyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl) piperidine-3-carboxylate **10** (230 mg, 80.0%) as a colorless solid. $[\alpha]_D^{24} = 24$ (*c* 1.0, MeOH); IR (KBr): 2922, 1730, 1690, 1491, 1194, 1161 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.20–7.15 (1H, m), 7.10–7.05 (2H, m), 7.01–6.95 (1H, m), 4.54–4.28 (1H, br m), 3.92 (2H, q, *J* = 7.2 Hz), 3.79–3.61 (1H, br m), 3.44 (3H, s), 3.21–3.15 (1H, m), 3.03–2.96 (1H, m), 2.64–2.49 (1H, m), 2.29–2.11 (4H, m), 1.81–1.39 (14H, m), 1.32 (3H, t, *J* = 7.2 Hz), 1.28–1.15 (2H, m); ^{13}C NMR ($CDCl_3$) δ: 172.6, 153.3, 129.1, 120.83, 120.80, 108.7, 107.4, 107.4, 65.0, 55.9, 53.0, 53.0, 51.7, 44.2, 35.7, 35.1, 30.7, 30.6, 27.9, 27.2, 27.1, 26.4, 25.6, 25.6, 13.5; HRMS (ESI): calcd for $C_{25}H_{38}N_3O_3$ $[M+H]^+$: 428.2913, found, 428.2920.

4.3.3. 1-[(3*R*,4*R*)-1-(Cyclooctylmethyl)-3-(hydroxymethyl)piperidin-4-yl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one J-113397[20,24]

To a stirred suspension of LAH (33.7 mg, 0.889 mmol) in THF (6 ml) was added **10** (190 mg, 0.444 mmol) in THF (3 ml) at −78 °C and the reaction mixture was gradually warmed to 0 °C. After $Na_2SO_4{\cdot}10H_2O$ was added to the mixture at 0 °C, anhydrous Na_2SO_4 was added and further stirred for 16 h. The drying agent was filtered off, and the solvent was removed under reduced pressure. The residue was purified by thin layer chromatography ($CHCl_3$/MeOH = 9/1) to give 1-[(3*R*,4*R*)-1-(cyclooctylmethyl)-3-(hydroxymethyl)piperidin-4-yl]-3-ethyl-1,3-dihydro-2*H*-benzimidazol-2-one **J-113397** (160 mg, 90.0%) as colorless crystals. $[\alpha]_D^{24} = +7.8$ (*c* 1.0, 2-propanol); IR (KBr): 3398, 2920, 1705, 1684, 1493, 1406, 1377, 1192 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.33 (1H, d, *J* = 7.2 Hz), 7.14–7.03 (3H, m), 4.46–4.33 (1H, br m), 3.98 (1H, dq, *J* = 7.2, 14.6 Hz), 3.96 (1H, dq, *J* = 7.2, 14.6 Hz), 3.39–3.30 (2H, br m), 3.08–2.74 (2H, br m), 2.69–2.53 (1H, m), 2.38–2.00 (6H, m), 1.92–1.84 (1H, m), 1.81–1.39 (13H, m), 1.34 (3H, t, *J* = 7.2 Hz), 1.30–1.18 (2H, m); ^{13}C NMR ($CDCl_3$) δ: 154.6, 129.2, 128.0, 121.1, 121.1, 110.2, 107.9, 66.1, 61.9, 56.4, 53.6, 51.7, 41.0, 36.1, 34.9, 30.9, 30.9, 28.7, 27.2, 27.1, 26.5, 25.6, 25.6, 13.6; HRMS (ESI): calcd for $C_{24}H_{38}N_3O_2$ $[M+H]^+$: 400.2964, found, 400.2967. Confirmation of each isomer was performed by HPLC: CHIRALPAK AD-H, 0.46 × 25 cm, hexane/*i*PrOH = 4/1 + 0.1% Et_2NH, flow rate = 1 ml/min **J-113397**, rt = 10.31 min; its enantiomer, rt = 7.47 min).

4.4. Large-scale preparation of 1

4.4.1. Preparation of 1-*tert*-butyl 3-methyl 4-{[(1*R*)-1-phenylethyl]amino}-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate 3

To a suspension of methyl 1-benzyl-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate hydrochloride **2** (763 g, 2.69 mol) in MeOH (2.5 L) was added 10% Pd–C on carbon (157 g, 50% wet) and stirred under a hydrogen atmosphere (3 atm) at room temperature for 4 h. After removal of hydrogen, the catalyst was filtered off with Celite pad and solvent was removed under reduced pressure to give 520 g of crude oil including methyl 4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate hydrochloride. In the same manner, 620 g of crude product was obtained from 747 g of **2**. To a stirred solution of the crude product of methyl 4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate hydrochloride (1.10 kg) in dioxane (3.3 L) H_2O (3.3 L) were added BOC_2O (1.25 L, 5.43 mol) and $NaHCO_3$ (983 g, 11.7 mol), and the reaction mixture was stirred at room temperature for 4 h. The reaction mixture was poured into EtOAc (4 L) and H_2O (3 L), and extracted with EtOAc (4.5 L). The combined organic layer was washed with brine and dried over Na_2SO_4. The drying agent was filtered off, and the solvent was removed under reduced pressure to give 1.48 kg of crude oil containing 1-*tert*-butyl 3-methyl 4-hydroxy-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate. To the stirred solution of the crude product of 1-*tert*-butyl 3-methyl 4-hydroxy-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate (1.48 kg) in THF (3 L) and MeOH (5 L) were added (*R*)-1-phenylethylamine (823 ml, 6.38 mol) and AcOH (396 ml, 6.92 mmol), and the reaction mixture was stirred at reflux for 4 h. After removal of the solvent, the mixture was diluted with EtOAc, washed with H_2O, 0.5 N aqueous NaOH, and brine, and dried over Na_2SO_4. The drying agent was filtered off, and the solvent was removed under reduced pressure to give 1.94 kg of 1-*tert*-butyl 3-methyl 4-{[(1*R*)-1-phenylethyl]amino}-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate **3** as a pale yellow oil.

4.4.2. Stereoselective reduction of 3-methyl 4-{[(1*R*)-1-phenylethyl]amino}-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate 3

To a stirred suspension of $NaBH_4$ (295 g, 7.79 mol) in THF (5.7 L) was added dropwise TFA (1.77 L, 23.0 mol) while keeping below 10 °C for 1.5 h, and then crude **3** (1.42 kg) in MeCN (1.8 L) below −20 °C for 1.5 h. After the reaction mixture was stirred further for 1 h, 25% aqueous NH_3 (1.59 L, 23.4 mol) was added dropwise at −20 °C to quench the reaction. The mixture was poured into EtOAc (11 L) and H_2O (11 L), and extracted with EtOAc (4.3 L). The combined organic layer was washed with brine (11 L) and dried over Na_2SO_4. The drying agent was filtered off, and the solvent was removed under reduced pressure to give 1.66 kg of a green oil

containing 1-*tert*-butyl 3-methyl (3*S*,4*R*)-4-{[(1*R*)-1-phenylethyl]amino} piperidine-1,3-dicarboxylate **4a** as a major product. In the same manner, 660 g of crude product **4a** was obtained from 550 g of **3**.

4.4.3. Deprotection of methylbenzyl group and the introduction of the nitrophenol unit

To a solution of crude **4a** (1.16 kg, 2.69 mol) in MeOH (3.6 L) were added AcOH (238 ml, 4.16 mol) and 10% Pd–C on carbon (293 g, 50% wet) and stirred under a hydrogen atmosphere (3 atm) at room temperature for 16 h. After removal of hydrogen, the catalyst was filtered off with Celite pad and the solvent was removed under reduced pressure. The mixture was diluted with H_2O (4.6 L), washed with methyl-*tert*-butylether (MTBE, 3.5 L), and the organic layer was extracted with H_2O. The combined aqueous layer was neutralized with aqueous 1 M NaOH (4.3 L), extracted with MTBE–THF (2:1), and further with EtOAc (several times). The combined organic layer was washed with brine and dried over Na_2SO_4. The drying agent was filtered off and the solvent was removed under reduced pressure to give 580 g of crude oil containing 1-*tert*-butyl 3-methyl (3*S*,4*R*)-4-aminopiperidine-1,3-dicarboxylate. In the same manner, 520 g of crude oil was obtained from 1.12 kg of crude **4a**. To a solution containing crude product 1-*tert*-butyl 3-methyl (3*S*,4*R*)-4-aminopiperidine- 1,3-dicarboxylate (580 g) in DMF (2.9 L) was added Na_2CO_3 (286 g, 2.69 mol) at room temperature, and the mixture was stirred at 80 °C for 16 h. The reaction mixture was poured into EtOAc (4.5 L) and H_2O (5 L), and the aqueous layer was extracted with EtOAc (3 L). The combined organic layer was washed with H_2O and brine, and dried over Na_2SO_4. The drying agent was filtered off and the solvent was removed under reduced pressure to give 860 g of crude oil containing 1-*tert*-butyl 3-methyl (3*S*,4*R*)-4-[(2-nitrophenyl)amino]piperidine-1,3- dicarboxylate **6** as a major product. In the same manner, 780 g of crude oil was obtained from 500 g of crude **4a**.

4.4.4. Reduction of the nitro group, construction of the benzimidazolidinone unit

To a solution of **6** (860 g) in MeOH (2 L) was added 10% Pd–C on carbon (139 g, 50% wet) and stirred under a hydrogen atmosphere (3 atm) at room temperature for 4 h. After removal of hydrogen, the catalyst was filtered off and the solvent was removed under reduced pressure to give 940 g of crude oil containing 1-*tert*-butyl 3-methyl (3*S*,4*R*)-4-[(2-aminophenyl)amino]piperidine-1,3-dicarboxylate. In a similar manner, 640 g of crude oil was obtained from 780 g of crude **6**. To a stirred solution of the crude product (640 g) in THF (4.5 L) was added CDI (356 g, 2.20 mol) and the reaction mixture was stirred at room temperature for 16 h. After removal of the solvent, the residue was diluted with EtOAc (6 L), washed with aqueous 0.5 N HCl (4.4 L) and brine, and dried over Na_2SO_4 and Wakogel C-300. The drying agent was filtered off and the solvent was removed under reduced pressure to give 720 g of crude brown oil containing 1-*tert*-butyl 3-methyl (3*S*,4*R*)-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl) piperidine-1,3-dicarboxylate **8** as a major product. In the same manner, 960 g of crude product was obtained from 940 g of crude **6**.

4.4.5. Synthesis of 1-*tert*-butyl 3-methyl (3*R*,4*R*)-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl) piperidine-1,3-dicarboxylate 1

To a solution of crude **8** (1.68 kg) in THF (3.4 L)–MeOH (3.4 L) was added Na_2CO_3 (265 g, 2.50 mol) and the mixture was stirred at 70 °C for 16 h. After removal of the solvents, the residue was diluted with THF (3.5 L) and 2-butanone (7.5 L), washed with aqueous 1 N HCl and brine, and dried over Na_2SO_4. The drying agent was filtered off, and the solvent was removed under reduced pressure to give 1.54 kg of crude solid containing 1-*tert*-butyl 3-methyl (3*R*,4*R*)-4-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)piperidine-1,3-dicarboxylate **1** as a major product (94.8% ee). Next, MeOH (4 L) was added to the crude product and stirred at 60 °C for 1 h. After cooling, the precipitate was collected by filtration, washed with MTBE (700 ml × three times), and dried in vacuo to give 509.3 g of **1** in pure form (>99% ee, pale brown solid). In the same manner, the second crop (46.0 g, >99% ee) and the third crop (60.1 g, 98.6% ee) were obtained in high purity (total: 614 g, 25.9% yield over all from **2**, >98% ee). The analytical data of **1 are** the same as those before.

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