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Tetrahedron
Tetrahedron 61 (2005) 593–598

# Concise synthetic strategy toward cyclic α,α-disubstituted α-amino acids bearing a δ-nitrogen atom: chiral 1-substituted 4-aminopiperidine-4-carboxylic acids

Makoto Oba, Masakazu Tanaka,* Yukiko Takano and Hiroshi Suemune*

*Graduate School of Pharmaceutical Sciences, Kyushu University, Fukuoka 812-8582, Japan*

Received 20 August 2004; revised 30 October 2004; accepted 4 November 2004

Available online 24 November 2004

**Abstract**—A concise synthetic strategy toward cyclic α,α-disubstituted α-amino acids, 1-substituted 4-aminopiperidine-4-carboxylic acids have been developed. The synthetic route is a reductive amination of dimethyl bis(dioxolanemethyl)malonate with various amines, followed by Curtius rearrangement. This synthetic route is capable of synthesizing 4-aminopiperidine-4-carboxylic acids bearing a bulky substituent and optically active ones bearing a pendent chiral substituent, by the change of condensed amines.


## 1. Introduction

α,α-Disubstituted α-amino acids are non-proteinogenic amino acids,[1] and attract many synthetic, peptide, and medicinal chemists because of their characteristic properties such as biological activities, conformational restriction of side-chains, and the stable secondary structure of their peptides.[2] We have already reported an asymmetric synthesis of α-methylated and α-ethylated α,α-disubstituted α-amino acids,[3] and conformational study of their peptides.[4] Besides acyclic α-alkylated α,α-disubstituted α-amino acids, cyclic α,α-disubstituted α-amino acids (1-amino-cycloalkanecarboxylic acid; $Ac_nc$), in which the side-chain of the amino acids construct a cycloalkane-ring, have been reported.[1b,5] Among cyclic α,α-disubstituted α-amino acids, 4-aminopiperidine-4-carboxylic acid (Pip), which is an achiral α-amino acid bearing a δ-nitrogen atom, has been focused upon because of the anti-microbial activity of its helical peptides.[6] However so far, the Pip derivatives have just been synthesized from piperidone derivative, by the Strecker, or Bücherer–Bergs methods.[7] Herein, we describe a new concise synthetic route for various achiral and chiral 1-substituted 4-aminopiperidine-4-carboxylic acids. Some of them, especially chiral α,α-disubstituted α-amino acids are a new class of optically active cyclic α,α-disubstituted α-amino acids bearing a pendent chiral center, and they could not be easily prepared by the known synthetic route from 4-piperidone,[7] or from heterospirocyclic azirines as synthons (Fig. 1).[8]

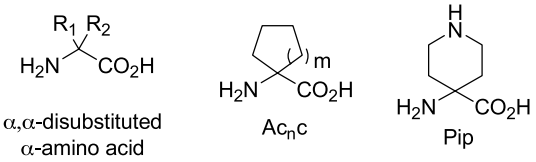


**Figure 1.** Acyclic and cyclic α,α-disubstituted α-amino acids.

## 2. Results and discussion

### 2.1. Synthetic strategy for Pip derivatives

At first, we envisaged that cyclic α,α-disubstituted α-amino acids (Pip derivatives) could be prepared from a bis-(formylmethyl)glycine derivative (ii) by reductive condensation with various amines. Also, it was thought that the dialdehyde (ii) could be prepared from protected intermediate (i). Unfortunately, several attempts to prepare the intermediate (i) from the protected glycines by bisalkylation failed. Next, we thought that cyclic diester intermediate (iv) could be converted into the Pip derivatives by Curtius rearrangement, and diester (iv) may be prepared by a reductive condensation of dimethyl bis(formylmethyl)-malonate (iii) and amines. Preparation of the intermediate (iii) was thought to be easier than that of glycine (ii) because the alkylated dimethyl malonate seemed to be stable (Scheme 1).

*Keywords*: Cyclic α,α-disubstituted α-amino acid; Piperidine; Curtius rearrangement; Unnatural amino acid; Chiral amino acid.
* Corresponding authors. Tel.: +81 92 642 6604; fax: +81 92 642 6545 (M.T.); (H.S.); e-mail addresses: mtanaka@phar.kyushu-u.ac.jp; suemune@phar.kyushu-u.ac.jp

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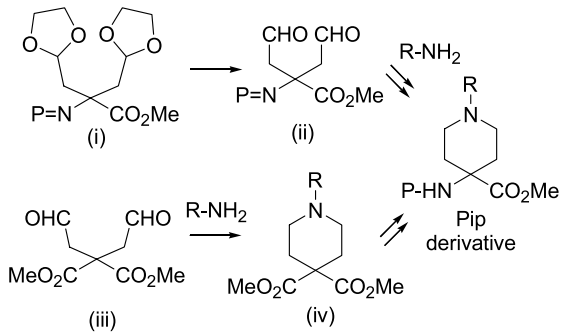
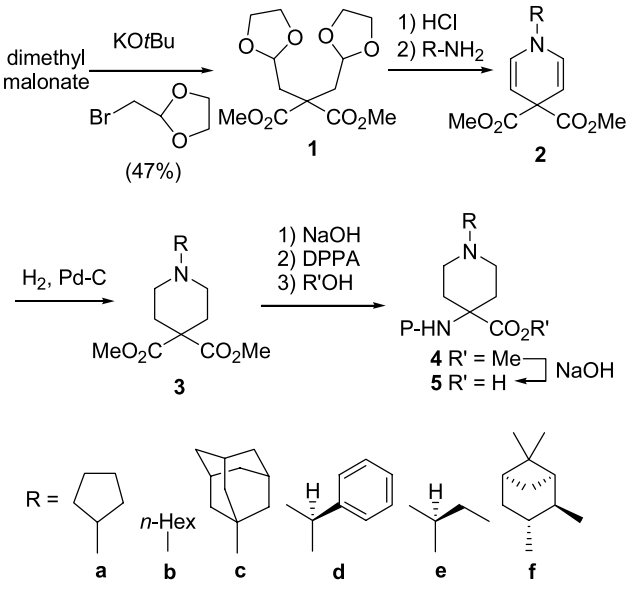
doi:10.1016/j.tet.2004.11.004




**Scheme 1.** Synthetic strategy for the Pip derivatives.

## 2.2. Preparation of achiral Pip derivatives

Bisalkylation of dimethyl malonate by treatment with KO*t*Bu and 2-bromomethyl-1,3-dioxolane in DMSO at 80 °C afforded a bis(dioxolanemethyl) diester **1** in 47% yield (Scheme 2).




**Scheme 2.** Synthetic scheme of various Pip derivatives.

The dioxolane group in **1** could be deprotected by 10% aqueous HCl to give a dialdehyde, which seemed to be unstable to purification by column chromatography on silica gel. Thus, the crude dialdehyde was subjected to the next reaction without purification. The deprotection of the dioxolane group, followed by condensation of the dialdehyde with cyclopentylamine, *n*-hexylamine, or 1-adamantanylamine afforded cyclic dienamines **2a** (57%), **2b** (55%), and **2c** (36%), respectively. The isolated dienamines **2a–c** were subjected to hydrogenation with Pd-C to afford the desired cyclic diesters **3a–c** in 73, 80 and 82% yields. Hydrolysis of the diester **3a–c** with aqueous NaOH gave monocarboxylic acids, and subsequent Curtius rearrangement using diphenylphosphoryl azide (DPPA),[9,3] followed by quenching with benzyl alcohol afforded Cbz-protected 1-cyclopentyl-Pip-OMe Cbz-**4a** (50%), 1-*n*-hexyl-Pip-OMe Cbz-**4b** (40%), and 1-adamantanyl-Pip-OMe Cbz-**4c** (50%), respectively. Work up with *t*-BuOH afforded a Boc-protected 1-cyclopentyl-Pip-OMe Boc-**4a** in 51% yield, and with 9-fluorenemethanol yielded a Fmoc-protected 1-cyclopentyl-Pip-OMe Fmoc-**4a** in 59% yield (Table 1).

**Table 1.** Preparation of various cyclic α,α-disubstituted α-amino acid; Pip derivatives **4**

| Entry | Amine | Dienamine **2** % yield | Diester **3** % yield | Cbz-protected Pip-OMe **4** % yield |
|---|---|---|---|---|
| 1 | **a** | **2a**: 57 | **3a**: 73 | Cbz-**4a**: 50 |
| 2 | **b** | **2b**: 55 | **3b**: 80 | Cbz-**4b**: 40 |
| 3 | **c** | **2c**: 36 | **3c**: 82 | Cbz-**4c**: 50 |
| 4 | **d** | **2d**: 60 | **3d**: 67 | Cbz-**4d**: 41 |
| 5 | **e** | **2e**: 41 | **3e**: 86 | Cbz-**4e**: 61 |
| 6 | **f** | **2f**: 56 | **3f**: 76 | Cbz-**4f**: 30 |

**a**: cyclopentylamine; **b**: *n*-hexylamine; **c**: 1-adamantanylamine; **d**: (*S*)-phenylethylamine; **e**: (*S*)-(+)-2-aminobutane; **f**: (1*R*,2*R*,3*R*,5*S*)-(−)-isopinocampheylamine.

## 2.3. Preparation of optically active Pip derivatives

The aforementioned strategy was applied to the synthesis of optically active cyclic α,α-disubstituted α-amino acids **4d–f** in which asymmetric carbons exist in the appendant substituent of amines. So far, no such chiral cyclic α,α-disubstituted α-amino acids have been designed, nor synthesized in optically active form. The crude dialdehyde prepared from **1** was condensed with chiral amines (*S*)-phenylethylamine **d**, (*S*)-2-aminobutane **e**, and (1*R*,2*R*,3*R*,5*S*)-(−)-isopinocampheylamine **f** to give dienamines **2d** (60%), **2e** (41%), and **2f** (56%), respectively. Hydrogenation of **2d–f** afforded the corresponding cyclic diesters **3d–f** in 67, 86 and 76% yields. Partial hydrolysis of the diesters, followed by Curtius rearrangement with DPPA[9] afforded optically active 1-substituted Pip-OMe **4d–f**. Work up with benzyl alcohol gave Cbz-protected Pip-OMe Cbz-**4d** (41%), Cbz-**4e** (61%), and Cbz-**4f** (30%), and with *t*-BuOH produced a Boc-protected 1-(*S*)-phenylethyl-Pip-OMe Boc-**4d** (43%). Furthermore, work up with concentrated HCl afforded an N-terminal free amine $H_2N$-1-(*S*)-phenylethyl-Pip-OMe $H_2N$-**4d** in 40% yield. The HPLC analysis of Cbz-(*S*)-**4d** using a chiral column indicated that no epimerization occurred in the synthetic sequences, and the enantiomeric excesses of Cbz-(*S*)-**4d** was >99% ee. Hydrolysis of the ester in Cbz-Pip-OMe **4d** afforded a C-terminal free cyclic α,α-disubstituted α-amino acid Cbz-protected 1-(*S*)-phenylethyl-Pip-OH **5d** (quant.).[10]

## 3. Conclusion

We succeeded in developing a concise synthetic route toward cyclic α,α-disubstituted α-amino acids bearing a δ-nitrogen atom. By using amines, it is possible to synthesize various 1-substituted 4-aminopiperidine-4-carboxylic acid derivatives. In particular, this strategy can be applied to the synthesis of optically active cyclic α,α-disubstituted α-amino acids bearing a pendent chirality,[11] which have not been designed nor synthesized so far. Application of the synthetic route to the combinatorial chemistry, and the use of cyclic α,α-disubstituted α-amino

acids having a pendent chiral moiety for the synthesis of peptide-foldamers[12] are currently underway in our group.

## 4. Experimental

### 4.1. General

$^1$H NMR spectra were determined at 270, 400 or 500 MHz. Infrared spectra were recorded on a NICOLET AVATAR-320 spectrometer. EIMS, FABMS, EI(+)HRMS and FAB(+)HRMS spectra were taken on a JEOL HMS 610H or JEOL SX102 spectrometer.

**4.1.1. Dimethyl 2,2-bis(1,3-dioxolan-2-ylmethyl)malonate (1).** A mixture of dimethyl malonate (4.33 mL, 37.9 mmol) and KO*t*Bu (5.10 g, 45.4 mmol) in DMSO (100 mL) was stirred at room temperature for 1 h. Then, 2-bromomethyl-1,3-dioxolane (4.7 mL, 45.4 mmol) was added, and the mixture was stirred at 80 °C for 12 h. The solution was cooled to room temperature, and then KO*t*Bu (5.10 g, 45.4 mmol) was added, and stirred for 1 h. 2-Bromomethyl-1,3-dioxolane (4.7 mL, 45.4 mmol) was added again, and the solution was stirred at 80 °C for 12 h. The solution was diluted with $H_2O$, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel (40% EtOAc in hexane) to give **1** (5.25 g, 47%) as colorless crystals: mp 36–37 °C; IR (KBr) 2955, 2891, 1738 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.02 (t, $J$=4.8 Hz, 2H), 3.89–3.93 (m, 4H), 3.78–3.82 (m, 4H), 3.71 (s, 6H), 2.45 (d, $J$=4.8 Hz, 4H); EI-MS $m/z$ 305 ($M^+$, 1), 273 (2), 215 (2), 73 (100); FAB(+)HRMS calcd for $C_{13}H_{21}O_8$ ($[M+H]^+$) 305.1236, found 305.1241.

**4.1.2. 1-Cyclopentyl-4,4-bis(methoxycarbonyl)-1,4-dihydropyridine (2a).** A solution of **1** (1.0 g, 3.29 mmol) in 10% aqueous HCl (20 mL) and THF (20 mL) was stirred at room temperature for 12 h. The solution was neutralized with powdered $NaHCO_3$, and then cyclopentylamine (280 mg, 3.29 mmol) in THF (5 mL) was added. After being stirred at room temperature for 3 h, the solution was extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent afforded an oily residue, which was purified by column chromatography on silica gel (15% EtOAc in hexane) to give **2a** (497 mg, 57%) as colorless crystals: mp 41–42 °C; IR (KBr) 2955, 2874, 1734, 1676, 1599, 1433 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.16 (d, $J$=8.1 Hz, 2H), 4.74 (d, $J$=8.1 Hz, 2H), 3.73 (s, 6H), 3.56 (quintet, $J$=7.0 Hz, 1H), 1.85–1.89 (m, 2H), 1.66–1.69 (m, 2H), 1.51–1.60 (m, 4H); FAB(+)HRMS calcd for $C_{14}H_{20}NO_4$ ($[M+H]^+$) 266.1392, found 266.1392.

**4.1.3. 1-Hexyl-4,4-bis(methoxycarbonyl)-1,4-dihydropyridine (2b).** Compound **2b** was prepared from **1** and *n*-hexylamine in a manner similar to that described for the preparation of **2a**. **2b**: 55%. A colorless oil; IR (neat) 2953, 2928, 2858, 1736, 1679, 1600 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.07 (d, $J$=7.9 Hz, 2H), 4.71 (d, $J$=7.9 Hz, 2H), 3.73 (s, 6H), 3.08 (t, $J$=7.2 Hz, 2H), 1.50 (quintet, $J$=6.8 Hz, 2H), 1.26–1.32 (m, 6H), 0.88 (t, $J$=6.8 Hz, 3H); FAB(+)HRMS calcd for $C_{15}H_{24}NO_4$ ($[M+H]^+$) 282.1705, found 282.1710.

**4.1.4. 1-Adamantanyl-4,4-bis(methoxycarbonyl)-1,4-dihydropyridine (2c).** Compound **2c** was prepared from **1** and adamantanylamine in a manner similar to that described for the preparation of **2a**. **2c**: 36%. Colorless crystals; mp 155–156 °C (recryst from $CHCl_3$); IR (KBr) 2911, 2852, 1734, 1674, 1595 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.45 (d, $J$=8.3 Hz, 2H), 4.72 (d, $J$=8.3 Hz, 2H), 3.72 (s, 6H), 2.14 (br s, 3H), 1.80 (br d, $J$=2.4 Hz, 6H), 1.68 (br d, $J$=12.1 Hz, 3H), 1.61 (br d, $J$=12.1 Hz, 3H) FAB(+) HRMS calcd for $C_{19}H_{26}NO_4$ ($[M+H]^+$) 332.1862, found 332.1860.

**4.1.5. 1-[(1*S*)-Phenylethyl]-4,4-bis(methoxycarbonyl)-1,4-dihydropyridine (2d).** Compound **2d** was prepared from **1** and (*S*)-phenylethylamine in a manner similar to that described for the preparation of **2a**. **2d**: 60%. A colorless oil; $[\alpha]_D^{28}=-7.53$ (*c* 0.95, $CHCl_3$); IR (neat) 2978, 2954, 2902, 1739 cm$^{-1}$; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 7.22–7.37 (m, 5H), 6.18 (d, $J$=8.0 Hz, 2H), 4.77 (d, $J$=8.0 Hz, 2H), 4.45 (q, $J$=6.9 Hz, 1H), 3.73 (s, 6H), 1.56 (d, $J$=6.9 Hz, 3H); EI-MS $m/z$ 302 ($M^+$+H), 6), 289 (51), 273 (24), 245 (83), 199 (70), 185 (74), 139 (93), 97 (93), 59 (100); FAB(+)HRMS calcd for $C_{17}H_{20}NO_4$ ($[M+H]^+$) 302.1392, found 302.1397.

**4.1.6. 1-[(1*S*)-1-Methylpropyl]-4,4-bis(methoxy-carbonyl)-1,4-dihydropyridine (2e).** Compound **2e** was prepared from **1** and (*S*)-2-aminobutane in a manner similar to that described for the preparation of **2a**. **2e**: 41%. A colorless oil; $[\alpha]_D^{25}=+12.5$ (*c* 0.94, $CHCl_3$); IR (neat) 2967, 2877, 1737, 1677, 1599 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.11 (d, $J$=7.7 Hz, 2H), 4.72 (d, $J$=7.7 Hz, 2H), 3.73 (s, 6H), 3.06 (m, 1H), 1.43–1.53 (m, 2H), 1.16 (d, $J$=6.7 Hz, 3H), 0.86 (t, $J$=7.4 Hz, 3H); FAB(+)HRMS calcd for $C_{13}H_{20}NO_4$ ($[M+H]^+$) 254.1392, found 254.1388.

**4.1.7. 1-[(1*R*,2*R*,3*R*,5*S*)-Isopinocampheyl]-4,4-bis-(methoxycarbonyl)-1,4-dihydropyridine (2f).** Compound **2f** was prepared from **1** and (1*R*,2*R*,3*R*,5*S*)-(−)-isopinocampheylamine in a manner similar to that described for the preparation of **2a**. **2f**: 56%. Colorless crystals; mp 80–81 °C (recryst from $CHCl_3$–MeOH); $[\alpha]_D^{23}=-22.5$ (*c* 0.70, $CHCl_3$); IR (KBr) 2985, 2972, 2935, 2893, 1733, 1675, 1596 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.26 (d, $J$=8.1 Hz, 2H), 4.77 (d, $J$=8.1 Hz, 2H), 3.73 (s, 6H), 3.48 (td, $J$=7.6, 10.1 Hz, 1H), 2.40 (m, 1H), 2.32 (m, 1H), 2.01 (m, 1H), 1.90 (m, 1H), 1.75–1.83 (m, 2H), 1.23 (s, 3H), 1.04 (d, $J$=7.1 Hz, 3H), 1.00 (s, 3H), 0.92 (d, $J$=10.1 Hz, 1H); FAB(+)HRMS calcd for $C_{19}H_{28}NO_4$ ($[M+H]^+$) 334.2018, found 334.2019. Anal. Calcd for $C_{19}H_{27}O_4N$: C, 68.44; H, 8.16; N 4.20. Found: C, 68.21; H, 8.16; N, 4.20.

**4.1.8. 1-Cyclopentyl-4,4-bis(methoxycarbonyl)piperidine (3a).** A mixture of **2a** (213 mg, 0.80 mmol) and 5% Pd-C (100 mg) in MeOH (10 mL) was vigorously stirred under $H_2$ atmosphere for 12 h. The Pd-catalyst was filtered off, and the filtrate was evaporated to leave an oily residue. Purification by column chromatography on silica gel (EtOAc) gave **3a** (159 mg, 73%) as colorless crystals; mp 59–60 °C (recryst from $CHCl_3$); IR (KBr) 3446, 2963, 2869,

2806, 1728 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.73 (s, 6H), 2.40–2.46 (m, 5H), 2.17 (t, $J=5.6$ Hz, 4H), 1.80–1.86 (m, 2H), 1.63–1.71 (m, 2H), 1.50–1.57 (m, 2H), 1.33–1.42 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 171.7, 67.4, 53.2, 52.5, 49.4, 30.8, 30.5, 24.1; FAB(+)HRMS calcd for $C_{14}H_{24}NO_4$ ($[M+H]^+$) 270.1705, found 270.1705. Anal. Calcd for $C_{14}H_{24}O_4N$: C, 62.43; H, 8.61; N 5.20. Found: C, 62.59; H, 8.60; N, 5.09.

**4.1.9. 1-Hexyl-4,4-bis(methoxycarbonyl)piperidine (3b).** Compound **3b** was prepared from **2b** in a manner similar to that described for the preparation of **3a**. **3b**: 80%. A colorless oil; IR (neat) 2952, 2930, 2857, 2812, 1736 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.73 (s, 6H), 2.41 (br m, 4H), 2.27 (t, $J=7.7$ Hz, 2H), 2.16 (t, $J=4.8$ Hz, 4H), 1.45 (m, 2H), 1.27–1.30 (m, 6H), 0.88 (t, $J=7.2$ Hz, 3H); FAB(+)HRMS calcd for $C_{15}H_{28}NO_4$ ($[M+H]^+$) 286.2018, found 286.2014.

**4.1.10. 1-Adamantanyl-4,4-bis(methoxycarbonyl)piperidine (3c).** Compound **3c** was prepared from **2c** in a manner similar to that described for the preparation of **3a**. **3c**: 82%. Colorless crystals; mp 68–69 °C (recryst from $CHCl_3$–MeOH); IR (KBr) 2905, 2849, 1734 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.72 (s, 3H), 3.71 (s, 3H), 2.62 (br s, 4H), 2.14 (br s, 4H), 2.07 (br s, 3H), 1.67 (br s, 6H), 1.64 (br d, $J=12.0$ Hz, 3H), 1.58 (br d, $J=12.0$ Hz, 3H); FAB(+)HRMS calcd for $C_{19}H_{30}NO_4$ ($[M+H]^+$) 336.2175, found 336.2179.

**4.1.11. 1-[(1*S*)-Phenylethyl]-4,4-bis(methoxycarbonyl)-piperidine (3d).** Compound **3d** was prepared from **2d** in a manner similar to that described for the preparation of **3a**. **3d**: 67%. A colorless oil; $[\alpha]_D^{24}=-15.4$ (*c* 0.30, $CHCl_3$); IR (neat) 3026, 2972, 2953, 2811, 1733 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 7.21–7.30 (m, 5H), 3.71 (s, 6H), 3.31 (q, $J=6.7$ Hz, 1H), 2.31–2.47 (m, 4H), 2.12 (t, $J=5.6$ Hz, 4H), 1.32 (d, $J=6.7$ Hz, 3H); EI-MS *m/z* 306 ($M^+$+H, 21), 305 ($M^+$, 14), 291 (59), 290 (100), 228 (52); FAB(+)HRMS calcd for $C_{17}H_{24}NO_4$ ($[M+H]^+$) 306.1705, found 306.1701.

**4.1.12. 1-[(1*S*)-1-Methylpropyl]-4,4-bis(methoxy-carbonyl)piperidine (3e).** Compound **3e** was prepared from **2e** in a manner similar to that described for the preparation of **3a**. **3e**: 86%. A colorless oil; $[\alpha]_D^{28}=+9.91$ (*c* 0.91, $CHCl_3$); IR (neat) 2961, 1736 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.73 (s, 6H), 2.48–2.54 (m, 2H), 2.38–2.46 (m, 3H), 2.10–2.16 (m, 4H), 1.51 (m, 1H), 1.25 (m, 1H), 0.92 (d, $J=6.6$ Hz, 3H), 0.87 (t, $J=7.4$ Hz, 3H); FAB(+)HRMS calcd for $C_{13}H_{24}NO_4$ ($[M+H]^+$) 258.1705, found 258.1710.

**4.1.13. 1-[(1*R*,2*R*,3*R*,5*S*)-Isopinocampheyl]-4,4-bis-(methoxycarbonyl)piperidine (3f).** Compound **3f** was prepared from **2f** in a manner similar to that described for the preparation of **3a**. **3f**: 76%. Colorless crystals; mp 69–70 °C (recryst from $CHCl_3$–MeOH); $[\alpha]_D^{24}=-24.2$ (*c* 1.60, $CHCl_3$); IR (KBr) 2992, 2935, 2873, 1732 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 3.73 (s, 6H), 2.86 (td, $J=6.4$, 9.9 Hz, 1H), 2.51–2.61 (m, 4H), 2.22 (m, 1H), 2.15 (t, $J=5.4$ Hz, 4H), 1.98–2.06 (m, 2H), 1.90 (m, 1H), 1.74–1.80 (m, 2H), 1.18 (s, 3H), 1.06 (d, $J=7.1$ Hz, 3H), 0.97 (s, 3H), 0.87 (d, $J=9.5$ Hz, 1H); FAB(+)HRMS calcd for $C_{19}H_{32}NO_4$ ($[M+H]^+$) 338.2331, found 338.2328. Anal. Calcd for $C_{19}H_{31}O_4N$: C, 67.63; H, 9.26; N 4.15. Found: C, 67.59; H, 9.26; N, 4.14.

**4.1.14. Methyl 1-cyclopentyl-4-(benzyloxycarbonyl-amino)piperidine-4-carboxylate (Cbz-4a).** A solution of **3a** (200 mg, 0.743 mmol) and 0.1 N aqueous NaOH (7.43 mL, 0.743 mmol) in MeOH (7 mL) was refluxed for 3 h. After removal of MeOH, the aqueous solution was neutralized with 10% aqueous HCl. Removal of $H_2O$ in vacuo afforded a crude monocarboxylic acid. A solution of the crude acid, diphenylphosphoryl azide (DPPA, 0.192 mL, 0.89 mmol), $Et_3N$ (0.124 mL, 0.891 mmol), and BnOH (0.092 mL, 0.891 mmol) in benzene (7 mL) was refluxed for 6 h. After removal of the solvent, the oily residue was purified by column chromatography (EtOAc) to afford Cbz-**4a** (133 mg, 50%) as colorless crystals: mp 78–79 °C (recryst from $CHCl_3$–MeOH); IR (KBr) 3331, 2951, 2870, 2814, 1735, 1715, 1690, 1526 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.29–7.34 (m, 5H), 5.09 (s, 2H), 5.02 (s, 1H), 3.68 (br s, 3H), 2.75–2.85 (m, 2H), 2.50 (quintet, $J=7.9$ Hz, 1H), 2.15–2.30 (m, 4H), 2.01 (m, 2H), 1.84 (m, 2H), 1.63–1.73 (m, 2H), 1.54 (m, 2H), 1.40 (m, 2H); FAB(+)HRMS calcd for $C_{20}H_{29}N_2O_4$ ($[M+H]^+$) 361.2127, found 361.2128.

**4.1.15. Methyl 1-hexyl-4-(benzyloxycarbonylamino)-piperidine-4-carboxylate (Cbz-4b).** Compound Cbz-**4b** was prepared from **3b** in a manner similar to that described for the preparation of Cbz-**4a**. Cbz-**4b**: 40%. A colorless oil; IR (neat) 3348 (br), 2953, 2930, 2857, 1739, 1716, 1522 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.30–7.34 (m, 5H), 5.09 (s, 2H), 5.02 (s, 1H), 3.68 (br s, 3H), 2.71 (m, 2H), 2.31 (t, $J=7.7$ Hz, 2H), 2.12–2.28 (m, 4H), 2.01 (m, 2H), 1.49 (m, 2H), 1.25–1.36 (m, 6H), 0.88 (t, $J=6.5$ Hz, 3H); FAB(+)HRMS calcd for $C_{21}H_{33}N_2O_4$ ($[M+H]^+$) 377.2440, found 377.2445.

**4.1.16. Methyl 1-adamantanyl-4-(benzyloxycarbonyl-amino)piperidine-4-carboxylate (Cbz-4c).** Compound Cbz-**4c** was prepared from **3c** in a manner similar to that described for the preparation of Cbz-**4a**. Cbz-**4c**: 50%. Colorless crystals; mp 112–113 °C; IR ($CDCl_3$) 3438 (br), 2908, 2853, 1736, 1724 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.30–7.39 (m, 5H), 5.09 (s, 2H), 4.95 (br s, 1H), 3.68 (br s, 3H), 2.90 (m, 2H), 2.42 (br t, $J=10.8$ Hz, 2H), 1.97–2.18 (m, 7H), 1.73 (br s, 6H), 1.68–1.74 (m, 6H), 1.59 (d, $J=12.1$ Hz, 3H), 1.67 (d, $J=12.1$ Hz, 3H); FAB(+)HRMS calcd for $C_{25}H_{35}N_2O_4$ ($[M+H]^+$) 427.2597, found 427.2599.

**4.1.17. Methyl 1-[(1*S*)-phenylethyl]-4-(benzyloxy-carbonylamino)piperidine-4-carboxylate (Cbz-4d).** Compound Cbz-**4d** was prepared from **3d** in a manner similar to that described for the preparation of Cbz-**4a**. Cbz-**4d**: 41%. A colorless oil; $[\alpha]_D^{25}=-23.2$ (*c* 0.49, $CHCl_3$); IR (neat) 3346 (br), 3030, 2952, 2815, 1732, 1710, 1520 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.22–7.37 (m, 10H), 5.02 (s, 2H), 4.91 (br s, 1H), 3.67 (br s, 3H), 3.41 (q, $J=6.4$ Hz, 1H), 2.83 (m, 1H), 2.62 (m, 1H), 2.11–2.25 (m, 4H), 2.05 (m, 1H), 1.93 (m, 1H), 1.36 (d, $J=6.4$ Hz, 3H); EI-MS *m/z* 396 ($M^+$, 5), 381 (57), 319 (8), 291 (47), 273 (12), 140 (97), 105

(41), 91 (100); FAB(+)HRMS calcd for $C_{23}H_{29}N_2O_4$ ($[M+H]^+$) 397.2127, found 397.2126; HPLC analysis: column, Chiralcel OD 0.46$\phi\times$25 cm; eluent, 5% *iso*-PrOH in hexane; flow rate, 1 mL/min; detection, $UV_{254\ nm}$; retention time ($t_R$), Cbz-(±)-**4d**: 36 and 42 min, Cbz-(*S*)-**4d**: 42 min.

**4.1.18. Methyl 1-[(1*S*)-1-methylpropyl]-4-(benzyloxycarbonylamino)piperidine-4-carboxylate (Cbz-4e).** Compound Cbz-**4e** was prepared from **3e** in a manner similar to that described for the preparation of Cbz-**4a**. Cbz-**4e**: 61%. A colorless oil; $[\alpha]_D^{25}=+8.75$ (*c* 1.0, $CHCl_3$); IR (neat) 3350 (br), 2961, 1739, 1715, 1523 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.31–7.35 (m, 5H), 5.09 (s, 2H), 4.93 (br s, 1H), 3.69 (br s, 3H), 2.60–2.65 (m, 2H), 2.42–2.51 (m, 2H), 2.36 (m, 1H), 2.10–2.20 (m, 2H), 1.98–2.01 (m, 2H), 1.54 (m, 1H), 1.26 (m, 1H), 0.96 (d, $J=6.6$ Hz, 3H), 0.88 (t, $J=7.4$ Hz, 3H); FAB(+)HRMS calcd for $C_{19}H_{29}N_2O_4$ ($[M+H]^+$) 349.2127, found 349.2130.

**4.1.19. Methyl 1-[(1*R*,2*R*,3*R*,5S)-isopinocampheyl]-4-(benzyloxycarbonylamino)piperidine-4-carboxylate (Cbz-4f).** Compound Cbz-**4f** was prepared from **3f** in a manner similar to that described for the preparation of Cbz-**4a**. Cbz-**4f**: 30%. Colorless crystals; mp 106–107 °C (recryst from MeOH); $[\alpha]_D^{24}=-21.7$ (*c* 0.89, $CHCl_3$); IR (KBr) 3356, 2952, 2920, 1735, 1712, 1531 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.31–7.36 (m, 5H), 5.09 (s, 2H), 4.97 (br s, 1H), 3.69 (br s, 3H), 2.90 (td, $J=6.4$, 4.5 Hz, 1H), 2.78 (br t, $J=11.4$ Hz, 2H), 2.47 (td, $J=10.9$, 21.8 Hz, 2H), 2.13–2.25 (m, 3H), 1.92–2.09 (m, 6H), 1.76–1.84 (m, 2H), 1.19 (s, 3H), 1.08 (d, $J=6.9$ Hz, 3H), 0.97 (s, 3H), 0.88 (d, $J=9.6$ Hz, 1H); FAB(+)HRMS calcd for $C_{25}H_{37}N_2O_4$ ($[M+H]^+$) 429.2753, found 429.2758.

**4.1.20. Methyl 1-cyclopentyl-4-(t-butoxycarbonylamino)piperidine-4-carboxylate (Boc-4a).** A solution of **3a** (254 mg, 0.943 mmol) and 0.1 N aqueous NaOH (9.43 mL, 0.743 mmol) in MeOH (10 mL) was refluxed for 3 h. After removal of MeOH, the aqueous solution was neutralized with 10% aqueous HCl. Removal of $H_2O$ in vacuo afforded a crude monocarboxylic acid. A solution of the crude acid, DPPA (0.447 mL, 2.08 mmol), $Et_3N$ (0.158 mL, 1.13 mmol) in *t*-BuOH (10 mL) was refluxed for 6 h. After removal of the solvent, the oily residue was purified by column chromatography (4% MeOH in $CHCl_3$) to afford Boc-**4a** (156 mg, 51%) as a colorless oil: IR (neat) 3354 (br), 2956, 1732, 1716 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 4.68 (br s, 1H), 3.72 (s, 3H), 2.80 (br d, $J=12.2$ Hz, 2H), 2.54 (quintet, $J=7.8$ Hz, 1H), 2.29 (m, 2H), 2.18 (dt, $J=3.1$, 12.2 Hz, 2H), 1.97 (br d, $J=12.7$ Hz, 2H), 1.82–1.89 (m, 2H), 1.64–1.72 (m, 2H), 1.49–1.59 (m, 2H), 1.37–1.45 (m, 2H), 1.43 (s, 9H); FAB(+)HRMS calcd for $C_{17}H_{31}N_2O_4$ ($[M+H]^+$) 327.2284, found 327.2279.

**4.1.21. Methyl 1-[(1*S*)-phenylethyl]-4-(*t*-butoxycarbonylamino)piperidine-4-carboxylate (Boc-4d).** Compound Boc-**4d** was prepared from **3d** in a manner similar to that described for the preparation of Boc-**4a**. Boc-**4d**: 43%. A colorless oil; $[\alpha]_D^{26}=-18.2$ (*c* 0.68, $CHCl_3$); IR (neat) 3367 (br), 2975, 2813, 1740, 1705, 1495 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.30 (d, $J=4.3$ Hz, 4H), 7.23 (m, 1H), 4.61 (br s, 1H), 3.71 (s, 3H), 3.38 (q, $J=6.6$ Hz, 1H), 2.84 (m, 1H), 2.59 (m, 1H), 2.08–2.26 (m, 4H), 1.97 (m, 1H), 1.87 (m, 1H), 1.42 (s, 9H), 1.34 (d, $J=6.6$ Hz, 3H); FAB(+)HRMS calcd for $C_{20}H_{31}N_2O_4$ ($[M+H]^+$) 363.2284, found 363.2282.

**4.1.22. Methyl 1-cyclopentyl-4-[(9-fluorenylmethoxycarbonyl)amino]piperidine-4-carboxylate (Fmoc-4a).** A solution of **3a** (124 mg, 0.460 mmol)) and 0.1 N aqueous NaOH (4.60 mL, 0.460 mmol) in MeOH (10 mL) was refluxed for 3 h. After removal of MeOH, the aqueous solution was neutralized with 10% aqueous HCl. Removal of $H_2O$ in vacuo afforded a crude monocarboxylic acid. A solution of the crude acid, DPPA (0.119 mL, 0.553 mmol), and $Et_3N$ (0.077 mL, 0.553 mmol) in benzene (3 mL) was refluxed for 1 h. Then, 9-fluorenylmethanol (108 mg, 0.553 mmol) was added, and the solution was refluxed for 5 h. After removal of the solvent, the oily residue was purified by column chromatography (4% MeOH in $CHCl_3$) to afford Fmoc-**4a** (121 mg, 59%) as colorless crystals; mp 160 °C (decomp.); IR (KBr) 3371 (br), 2953, 2867, 1729, 1605, 1448 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.76 (br d, $J=7.5$ Hz, 2H), 7.59 (br d, $J=7.5$ Hz, 2H), 7.40 (br t, $J=7.5$ Hz, 2H), 7.31 (br t, $J=7.5$ Hz, 2H), 4.93 (s, 1H), 4.42 (d, $J=6.5$ Hz, 2H), 4.23 (t, $J=6.5$ Hz, 1H), 3.68 (br s, 3H), 2.71–2.82 (m, 2H), 2.51 (quintet, $J=8.0$ Hz, 1H), 2.11–2.29 (m, 4H), 1.91–2.09 (m, 2H), 1.84–1.86 (m, 2H), 1.65–1.73 (m, 2H), 1.54–1.60 (m, 2H), 1.35–1.44 (m, 2H); FAB(+)HRMS calcd for $C_{27}H_{33}N_2O_4$ ($[M+H]^+$) 449.2440, found 449.2436.

**4.1.23. Methyl 1-[(1*S*)-phenylethyl]-4-aminopiperidine-4-carboxylate ($H_2$N-4d).** A solution of **3d** (200 mg, 0.655 mmol) and 0.1 N aqueous NaOH (6.55 mL, 0.655 mmol) in MeOH (8 mL) was refluxed for 3 h. After removal of MeOH, the aqueous solution was neutralized with 10% aqueous HCl. Removal of $H_2O$ in vacuo afforded a crude monocarboxylic acid. A solution of the crude acid, DPPA (0.169 mL, 0.786 mmol), and $Et_3N$ (0.110 mL, 0.786 mmol) in benzene (5 mL) was refluxed for 2 h. Removal of the solvent afforded an oily residue, which was dissolved in 10% aqueous HCl (3 mL), and stirred at room temperature for 1 h. Then, the solution was diluted with 5% aqueous $NaHCO_3$, extracted with EtOAc, and dried over $MgSO_4$. Removal of the solvent and purification by column chromatography afforded $H_2$N-**4d** (69 mg, 40%) as a colorless oil: $[\alpha]_D^{26}=-14.9$ (*c* 1.70, $CHCl_3$); IR (neat) 3375 (br), 3305 (br), 2951, 2816, 1729, 1600 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.21–7.32 (m, 5H), 3.70 (s, 6H), 3.41 (q, $J=6.7$ Hz, 1H), 2.60 (m, 1H), 2.42–2.52 (m, 3H), 2.03–2.15 (m, 2H), 1.63 (br s, 2H), 1.48–1.57 (m, 2H), 1.36 (d, $J=6.7$ Hz, 3H); FAB(+)HRMS calcd for $C_{15}H_{23}N_2O_2$ ($[M+H]^+$) 263.1760, found 263.1758.

**4.1.24. 1-[(1*S*)-Phenylethyl]-4-(benzyloxycarbonylamino)piperidine-4-carboxylic acid (5d).** 0.1 N Aqueous NaOH solution (1.6 mL) was added to the stirred solution of Cbz-**4d** (41 mg, 0.105 mmol) in MeOH (1 mL), and the whole was refluxed for 6 h. After evaporation of MeOH, the aqueous solution was washed with hexane, neutralized with 5% aqueous HCl, and the solution was concentrated in vacuo. The residue was dissolved in MeOH, and filtered. Evaporation of MeOH afforded an acid **5d** (40 mg, quant.) as a yellowish powder: $[\alpha]_D^{25}=-25.8$ (*c* 0.66, $CHCl_3$); IR

(KBr) 3307 (br), 1705, 1588 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$ 7.21–7.40 (m, 10H), 5.01 (s, 2H), 3.45 (q, $J$= 6.9 Hz, 1H), 2.89 (m, 1H), 2.60 (m, 1H), 2.20–2.35 (m, 2H), 1.90–2.20 (m, 4H), 1.39 (d, $J$=6.9 Hz, 3H); FAB(+)MS *m/z* 405 ($[M+Na]^+$), 383 ($[M+H]^+$); FAB(+)HRMS calcd for $C_{22}H_{27}N_2O_4$ ($[M+H]^+$) 383.1971 found 383.1952.

## Acknowledgements

This work was partly supported by a Grant-in-Aid for Scientific Research (C) from Japan Society for the Promotion of Science, and also supported by a grant from the Takeda Science Foundation.

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