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Synthesis of (+)-carpamic acid from (+)-alanine☆

Yui Masuda,[a] Takuya Tashiro[b] and Kenji Mori[b,*]

[a]*Department of Applied Biological Chemistry, The University of Tokyo, Yayoi 1-1-1, Bunkyo-ku, Tokyo 113-8657, Japan*
[b]*Glycosphingolipid Synthesis Group, Laboratory for Immune Regulation, Research Center for Allergy and Immunology, RIKEN, Hirosawa 2-1, Wako-shi, Saitama 351-0198, Japan*

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Abstract—(+)-Carpamic acid [(2′*R*,5′*S*,6′*S*)-8-(5′-hydroxy-6′-methylpiperidin-2′-yl)octanoic acid, **1**] was synthesized from (*S*)-alanine, employing intramolecular and reductive amination of acyclic amino ketone **8** as the key step to generate the piperidine ring.

1. Introduction

(+)-Carpamic acid [(2′*R*,5′*S*,6′*S*)-8-(5′-hydroxy-6′-methylpiperidin-2′-yl)octanoic acid, **1**][1] is the hydrolysis product of a piperidine alkaloid (+)-carpaine isolated from the Papaw tree (*Carica papaya* L.). (+)-Carpaine is the dimeric macrolactone of **1** as studied by Barger,[2] Robinson,[3] Rapoport,[1] Spiteller-Friedmann,[4] Coke,[5] and others (Fig. 1). (+)-Carpaine shows various bioactivities as a heart poison and an antitumor agent, and has been synthesized by Corey[6] through macrolactonization of *N*-benzyloxycarbonyl(Cbz)-protected (+)-carpamic acid **1**. A review is available on the enantioselective synthesis of bioactive piperidines.[7]

Our experience in sphingolipid chemistry to synthesize penazetidine A, a marine azetidine alkaloid, by cyclization of a sphingosine derivative[8] made us attempt the synthesis of (+)-**1** through a similar cyclization, especially because we had synthesized sphingolipids of human epidermis (ceramide B and ceramide 7) with a hydroxy group at C-6 of the sphingosine moiety.[9] A literature survey on the synthesis of (±)-**1**[10,11] and (+)-**1**[12–15] indicated that all the previous work, except those by Gerlach[11] and Kibayashi,[14] utilized the cyclization of acyclic δ-amino ketone for the genesis of the piperidine ring by means of a palladium-catalyzed hydrogenation.[10,12,13,15] This paper reports a new

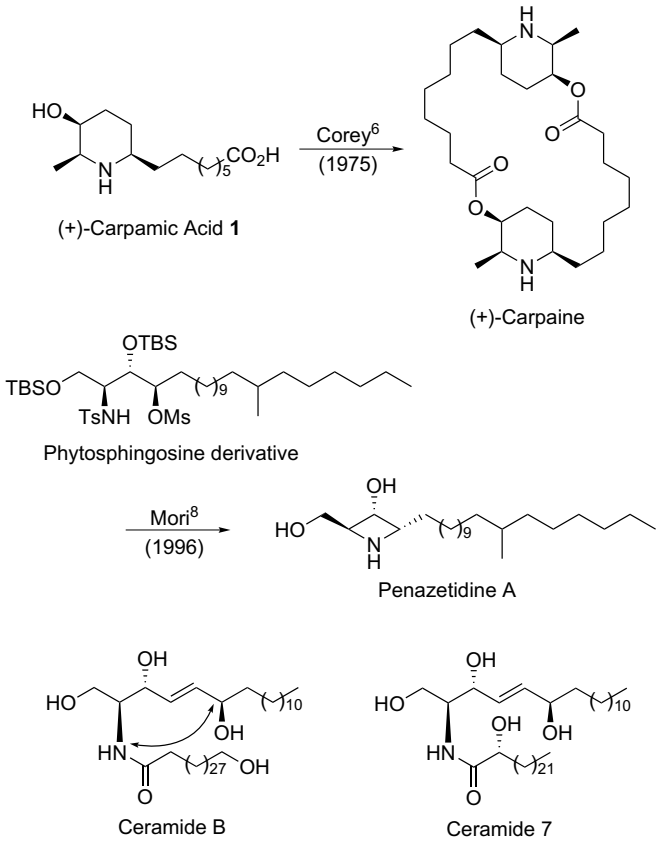

Figure 1. Structures of (+)-carpamic acid **1**, (+)-carpaine, and some sphingolipids.

☆Synthesis of sphingosine relatives, Part 28. For Part 27, see: Ref. 9.

*Corresponding author. Fax: +81 48 462 1339; e-mail: kjk-mori@arion.ocn.ne.jp

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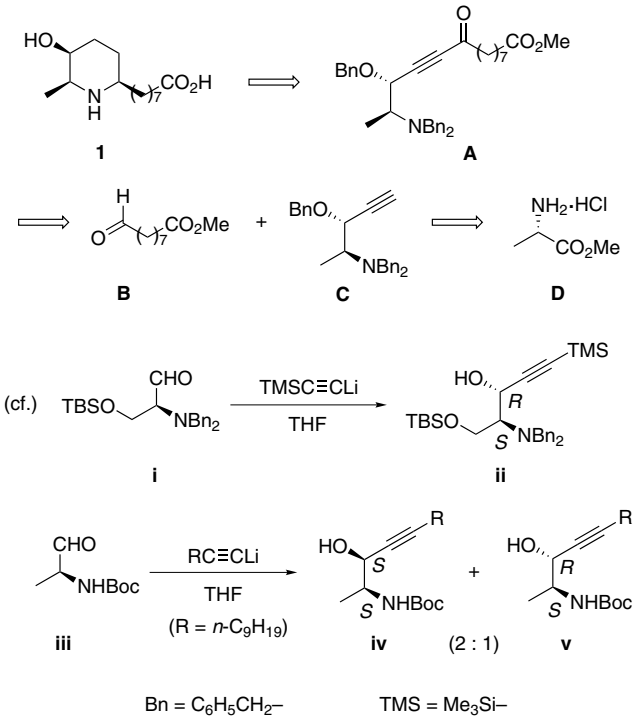
synthesis of (+)-carpamic acid **1** by intramolecular C–N bond formation of an acyclic δ-amino ketone **8**.

2. Results and discussion

2.1. Retrosynthetic analysis

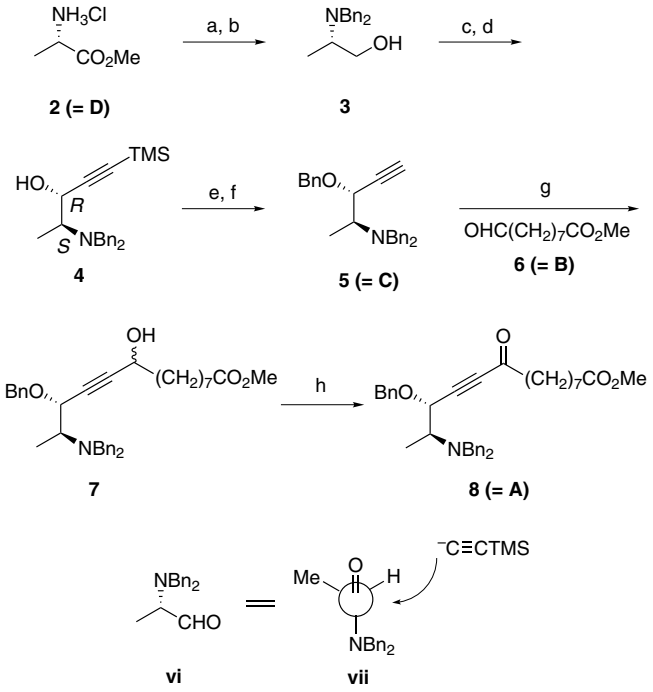
Scheme 1 shows our retrosynthetic analysis of (+)-**1**. Because Hiroya et al.[16] reported that the addition of lithium trimethylsilyl(TMS)acetylide to aldehyde **i** gave (2*S*,3*R*)-**ii** as the major diastereomer (7:1) as generated under Felkin–Anh control,[16] we envisaged **C** as our intermediate, whose anion would add to aldehyde **B** to give **A** after oxidation. Acetylene **C** would be prepared from commercially available hydrochloride **D** of (*S*)-alanine methyl ester. It should be added that *t*-butoxycarbonyl(Boc)-protected (*S*)-alaninal (**iii**) gave (2*S*,3*S*)-**iv** as the major isomer after reaction with lithium 1-undecylide.[17] The resulting 2:1 mixture of **iv** and **v** was hardly separable.



Scheme 1. Retrosynthetic analysis of carpamic acid **1**.

2.2. Synthesis of acyclic δ-amino ketone 8

Scheme 2 summarizes the synthesis of the key intermediate **8**, the substrate for the ring-forming reaction. Commercially available (*S*)-alanine methyl ester hydrochloride (**2**) was treated with sodium hydride and benzyl bromide, and the resulting bis-benzylated alanine methyl ester was reduced with lithium aluminum hydride to give known (*S*)-2-*N*,*N*-dibenzylamino-1-propanol **3**.[18] Swern oxidation of **3** was executed under the Dondoni conditions in the presence of ethyldiisopropylamine to avoid racemization,[19] giving the corresponding aldehyde, which was then treated



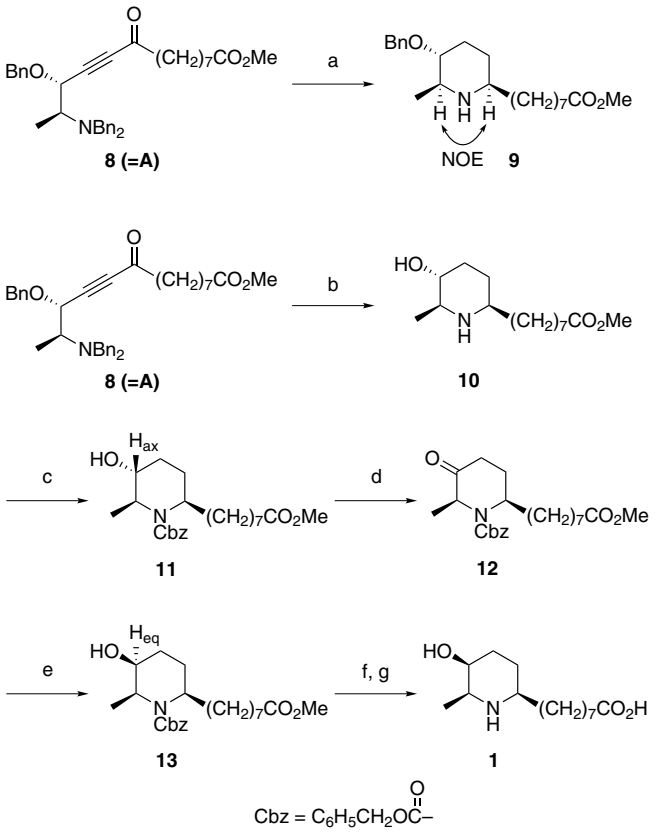
Scheme 2. Synthesis of the key intermediate **8**. Reagents and conditions: (a) NaH, BnBr, THF; (b) $LiAlH_4$, THF, 92% (two steps); (c) $(COCl)_2$, DMSO, CH_2Cl_2, 15 min, −78 °C, then **3**, 30 min, then $(i\text{-Pr})_2NEt$; (d) TMSC≡CLi, THF, HMPA, 6 h, −78 °C to room temperature, 85% (two steps); (e) NaH, BnBr, THF, 6 h, room temperature; (f) TBAF, THF, 1 h, room temperature, 94% (two steps); (g) *n*-BuLi, THF, 1 h, −78 °C, then **6**, 6 h, −78 °C to room temperature, 61%; (h) $(COCl)_2$, DMSO, CH_2Cl_2, 15 min, −78 °C, then **7**, then $(i\text{-Pr})_2NEt$, 81%.

with lithium TMSacetylide to afford acetylenic alcohol **4**. The depicted (3*R*,4*S*)-stereochemistry of **4** was deduced as shown in **vii** in analogy with Hiroya's result.[16] This stereochemical assignment was later proved at the stage of piperidine **9** (vide infra).

Subsequent benzylation of **4** was followed by removal of the TMS group to afford **5**. At this stage, ^1H NMR analysis of **5** clarified the diastereomeric ratio between (3*R*,4*S*)-**5** and its (3*S*,4*S*)-isomer as 9:1. Reaction between the acetylide anion derived from **5** and methyl 9-oxononanoate[20] in THF at −78 °C furnished hydroxy ester **7** in 61% yield. Swern oxidation of **7** under Dondoni conditions[19] gave keto ester **8**, the key substrate for the cyclization reaction. The overall yield of **8** from (*S*)-alanine methyl ester hydrochloride **2** was 37% over eight steps.

2.3. Synthesis of (+)-carpamic acid 1

Scheme 3 shows the reductive cyclization of **8** to piperidine derivatives **9** or **10**, and the conversion of the latter to (+)-carpamic acid **1**. When **8** was hydrogenated over Pearlman's palladium hydroxide in methanol, reduction of the triple bond and removal of the two *N*-benzyl groups followed by formation and reduction of a tetrahydropyridine ring took place to give piperidine **9**. Its ^1H NMR analysis revealed the presence of a nuclear Overhauser effect between the axial protons at C-2′ and C-6′. The benzyloxy



Scheme 3. Synthesis of (+)-carpamic acid **1**. Reagents and conditions: (a) H_2, $Pd(OH)_2$–C, MeOH, 1 h, room temperature, 80%; (b) H_2, $Pd(OH)_2$, MeOH, 1 h, room temperature, then AcOH, 12 h, room temperature, 78%; (c) CbzCl, $NaHCO_3$, 1,4-dioxane, H_2O, 24 h, room temperature, 82%; (d) Dess–Martin periodinane, CH_2Cl_2, 2 h, room temperature, 90%; (e) $NaBH_4$, EtOH, 30 min, 0 °C, quant.; (f) $Ba(OH)_2{\cdot}8H_2O$, MeOH, overnight, 40 °C; (g) H_2, $Pd(OH)_2$–C, MeOH, 1 h, room temperature, 86% (two steps).

group at C-5′ of **9** was equatorially oriented, differing from the axial hydroxy group of target molecule **1**. The *O*-debenzylated product **10** could be secured by adding a small amount of acetic acid to the hydrogenation mixture to increase the rate of hydrogenolysis of the *O*-benzyl group.

In order to invert the incorrect configuration at C-5′ of **10**, there were two options: (i) Mitsunobu inversion or (ii) oxidation to the corresponding ketone and its reduction to the sterically more congested axial alcohol by the approach of a reducing agent from the less hindered α-side. Before attempting these conversions, the amino group of **10** was protected by treatment with benzyloxycarbonyl chloride (CbzCl) to give **11**. Mitsunobu inversion was attempted on **11** under the standard conditions,[21] but was unsuccessful, yielding only the elimination product with a double bond at C-4′(5′). Therefore we turned to the second option. Oxidation of **11** with Dess–Martin periodinane[22] furnished ketone **12**. Its reduction with sodium borohydride cleanly gave the axial alcohol, the Cbz-protected derivative **13** of methyl (+)-carpamate. Finally, alkaline hydrolysis of **13** was followed by hydrogenolytic removal of the Cbz group to give (+)-carpamic acid (**1**) as colorless crystals, mp 219–222 °C, $[\alpha]_D^{24} = +6.0$ (*c* 0.40, MeOH). Its spectral data were identical to those reported previously.[11] Since Cbz-protected (+)-carpamic acid was converted by Corey to (+)-carpaine,[6] our work constitutes its formal synthesis.

3. Conclusion

In conclusion, (+)-carpamic acid **1** was synthesized from (*S*)-alanine methyl ester hydrochloride **2** in 18% overall yield through 14 steps. The present overall efficiency was better than those reported by Singh and Ghosh (4%, 21 steps)[13] and Hanessian and Frenette (9%, 15 steps),[12] but inferior to that reported by Randl and Blechert (24%, eight steps).[15] The modest overall yield in our synthesis was due to the undesired and opposite stereoselectivity in the course of the addition of TMS-protected acetylide anion to the aldehyde. Nevertheless, the present synthesis is straightforward, and further illustrates the usefulness of the reductive cyclization of δ-amino ketones in the synthesis of piperidine alkaloids.

4. Experimental

4.1. General

Melting point (Yanaco MP-S3) is uncorrected. IR spectra were recorded on a Jasco FT/IR-460 spectrometer. ^{1}H NMR spectra were recorded at 300 MHz by a Jeol JNM-AL300 spectrometer or at 500 MHz by a Varian INOVA-AS500 spectrometer. The peaks for TMS (at $\delta = 0.00$), $CDCl_3$ (at $\delta = 7.26$), or CD_3OD (at $\delta = 3.30$) were used as the internal standards. ^{13}C NMR spectrum was recorded at 67.8 MHz by a Jeol JNM-AL270 spectrometer. The peak for CD_3OD (at δ 49.0) was used as the internal standard. Optical rotations were measured on a Jasco P-1010 polarimeter. Mass spectra were measured on a Jeol JMS-SX102A spectrometer. Column chromatography was carried out on Merck Kieselgel 60 Art 1.07734, and TLC analyses were performed on Merck 60F-254 silica gel plates.

4.2. (3*R*,4*S*)-1-Trimethylsilyl-4-(*N*,*N*-dibenzylamino)pent-1-yn-3-ol 4

To a stirred solution of $(COCl)_2$ (2.58 mL, 29.6 mmol) in CH_2Cl_2 (100 mL) was added dropwise a solution of dry DMSO (6.3 mL, 89 mmol) in dry CH_2Cl_2 (30 mL) at −78 °C under Ar. After stirring for 15 min at −78 °C, a solution of (*S*)-*N*,*N*-dibenzylalaninol (**3**, 5.0 g, 20 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to the stirred mixture at −78 °C. After stirring for 30 min at −78 °C, $(i\text{-Pr})_2$NEt (17.2 mL, 98.7 mmol) was added to the mixture. The mixture was stirred for 30 min at room temperature, then poured into water, and extracted with Et_2O. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo to give the corresponding aldehyde (5.21 g, crude) as a yellow oil. This was immediately used in the next step without further purification.

To a stirred solution of trimethylsilylacetylene (2.94 g, 30 mmol) in dry THF (500 mL) was added dropwise a solution of *n*-BuLi (1.60 M in hexane, 19.7 mL, 31.5 mmol) at −78 °C under Ar. After stirring for 1 h at −78 °C, a solution of crude aldehyde (5.21 g) in dry THF (150 mL) was added dropwise to the reaction mixture at −78 °C. The resulting mixture was stirred for 6 h at room temperature. The reaction was then quenched by the addition of an aqueous solution of NH_4Cl. The resulting mixture was extracted with Et_2O. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (100 g, hexane/ethyl acetate = 40:1) to give **4** (5.66 g, two steps, 85%) as a yellow solid; mp 58.0–60.5 °C; $[\alpha]_D^{18} = -24.4$ (*c* 1.50, $CHCl_3$); ν_{max} (Nujol): 3400 (m, OH), 2165 (w, C≡C), 1600 (w, Ar), 1495 (m, Ar), 1250 (s, Si–Me), 845 (s); δ_H (500 MHz, $CDCl_3$): 0.10 (9H, s, $SiCH_3 \times 3$), 1.21 (3H, d, *J* 7.0, 5-H_3), 2.93 (1H, dq, *J* 6.0, 7.0, 4-H), 3.36 (2H, d, *J* 13.5, $PhCH \times 2$), 3.86 (1H, br s, OH), 4.11 (1H, d, *J* 6.0, 3-H), 4.17 (2H, d, *J* 13.5, $PhCH \times 2$), 7.22–7.31 (10H, m, Ar); HRMS calcd for $C_{22}H_{30}NOSi$ [$(M+H)^+$] 352.2097, found 352.2055.

4.3. (3*R*,4*S*)-3-Benzyloxy-4-(*N*,*N*-dibenzylamino)pent-1-yne 5

To a stirred solution of **4** (500 mg, 1.4 mmol) in dry THF (10 mL) were added NaH (60%; 85 mg, 2.1 mmol) and BnBr (0.33 mL, 2.8 mmol) at 0 °C. After stirring for 6 h at room temperature, the resulting mixture was poured into water and extracted with Et_2O. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo to give the corresponding benzyl ether (620 mg, crude) as a yellow oil. This compound was immediately used in the next reaction without further purification.

To a stirred solution of this crude benzyl ether (650 mg) in dry THF (10 mL) was added a solution of TBAF (1.0 M in THF, 1.5 mL, 1.5 mmol) at 0 °C. After stirring for 1 h at room temperature, the mixture was poured into water and extracted with Et_2O. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (40 g, hexane/ethyl acetate = 50:1) to give **5** (493 mg, two steps, 94%, 9:1 diastereomeric mixture) as a yellow oil. Diastereomer ratio was determined by ^1H NMR analysis (500 MHz); $n_D^{24} = 1.5158$; $[\alpha]_D^{26} = -85.9$ (*c* 1.05, $CHCl_3$); ν_{max} (film): 3290 (s, C≡C–H), 2110 (w, C≡C), 1600 (w, Ar), 1495 (m, Ar), 1070 (s), 745 (s), 700 (s); δ_H (500 MHz, $CDCl_3$): 3*R*-isomer: 1.22 (3H, d, *J* 7.0, 5-H_3), 2.50 (1H, dd, *J* 0.5, 2.0, 1-H), 3.09 (1H, br quint.-like, *J* 7.0, 4-H), 3.60 (2H, d, *J* 14.0, $PhCH \times 2$), 3.76 (2H, d, *J* 14.0, $PhCH \times 2$), 4.25 (1H, dd, *J* 2.0, 7.0, 3-H), 4.50 (1H, d, *J* 12.0, PhCH), 4.81 (1H, d, *J* 12.0, PhCH), 7.18–7.38 (10H, m, Ar); 3*S*-isomer: 1.23 (3H, d, *J* 7.0, 5-H_3), 2.52 (1H, dd, *J* 0.5, 2.0, 1-H), 3.12 (1H, br quint.-like, *J* 6.5, 4-H), 3.57 (2H, d, *J* 14.0, $PhCH \times 2$), 3.83 (2H, d, *J* 14.0, $PhCH \times 2$), 4.24 (1H, dd, *J* 2.0, 5.5, 3-H), 4.47 (1H, d, *J* 12.0, PhCH), 4.78 (1H, d, *J* 12.0, PhCH), 7.18–7.38 (10H, m, Ar); HRMS calcd for $C_{26}H_{28}NO$ [$(M+H)^+$] 370.2171, found 370.2168.

4.4. Methyl (9*RS*,12*R*,13*S*)-12-benzyloxy-13-(*N*,*N*-dibenzylamino)-9-hydroxy-10-tetradecynoate 7

To a stirred solution of **5** (3.92 g, 10.6 mmol) in dry THF (200 mL) was added dropwise a solution of *n*-BuLi (1.58 M in hexane, 7.1 mL, 11 mmol) at −78 °C under Ar. After stirring for 1.5 h at −78 °C, a solution of **6** (1.80 g, 9.66 mmol) in dry THF (150 mL) was added dropwise to the mixture at −78 °C. The resulting mixture was stirred overnight at 0 °C, then poured into an aqueous solution of NH_4Cl, and extracted with Et_2O. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (80 g, hexane/ethyl acetate = 10:1) to give **7** (3.60 g, 61%, 9:1 diastereomeric mixture) as a yellow oil; $n_D^{28} = 1.5161$; $[\alpha]_D^{22} = -69.1$ (*c* 1.05, $CHCl_3$); ν_{max} (film): 3450 (m, OH), 1735 (s, CO), 1605 (w, Ar), 1495 (m, Ar), 1065 (s), 745 (s), 700 (s); δ_H (500 MHz, $CDCl_3$): (12*R*)-isomer: 1.21 (3H, d, *J* 6.5, 14-H_3), 1.27–1.50 (9H, m, 4-, 5-, 6-, 7-H_2, OH), 1.59–1.65 (2H, m, 3-H_2), 1.69–1.76 (2H, m, 8-H_2), 2.30 (2H, t, *J* 7.5, 2-H_2), 3,06 (1H, quint.-like, *J* 6.5, 13-H), 3.58 (2H, d, *J* 14.0, $PhCH \times 2$), 3.67 (3H, s, CO_2CH_3), 3.75 (2H, d, *J* 14.0, $PhCH \times 2$), 4.26 (1H, d, *J* 6.5, 12-H), 4.42 (1H, q-like, *J* 6.5, 9-H), 4.48 (1H, d, *J* 11.5, PhCH), 4.76 (1H, d, *J* 11.5, PhCH), 7.18–7.40 (15H, m, Ar); HRMS calcd for $C_{36}H_{46}NO_4$ [$(M+H)^+$] 556.3427, found 556.3397.

4.5. Methyl (12*R*,13*S*)-12-benzyloxy-13-(*N*,*N*-dibenzylamino)-9-oxo-10-tetradecynoate 8

To a stirred solution of $(COCl)_2$ (0.57 mL, 7.0 mmol) in CH_2Cl_2 (50 mL) was added dropwise a solution of dry DMSO (1.5 mL, 21 mmol) in dry CH_2Cl_2 (25 mL) at −78 °C under Ar. After stirring for 15 min at −78 °C, a solution of **7** (2.6 g, 4.7 mmol) in dry CH_2Cl_2 (25 mL) was added dropwise to the mixture at −78 °C. The resulting mixture was stirred for 30 min at −78 °C, then $(i\text{-Pr})_2NEt$ (4.1 mL, 24 mmol) was added to it. The mixture was stirred for 30 min at room temperature, then poured into water, and extracted with Et_2O. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (50 g, hexane/ethyl acetate = 40:1) to give **8** (2.11 g, 81%, 9:1 diastereomeric mixture) as a yellow oil; $n_D^{28} = 1.5162$; $[\alpha]_D^{23} = -80.5$ (*c* 1.05, $CHCl_3$); ν_{max} (film): 2205 (m, C≡C), 1735 (s, CO), 1675 (s, CO), 1605 (w, Ar), 1495 (m, Ar), 1170 (br s), 745 (s), 700 (s); δ_H (500 MHz, $CDCl_3$): 1.22 (3H, d, *J* 7.0, 14-H_3), 1.28–1.35 (6H, m, 4-, 5-, 6-H_2), 1.58–1.69 (4H, m, 3-, 7-H_2), 2.30 (2H, t, *J* 7.0, 2-H_2), 2.57 (2H, t, *J* 7.5, 8-H_2), 3,14 (1H, quint.-like, *J* 6.5, 13-H), 3.57 (2H, d, *J* 14.0, $PhCH \times 2$), 3.66 (3H, s, CO_2CH_3), 3.72 (2H, d, *J* 14.0, $PhCH \times 2$), 4.34 (1H, d, *J* 6.5, 12-H), 4.48 (1H, d, *J* 11.5, PhCH), 4.77 (1H, d, *J* 11.5, PhCH), 7.19–7.37 (15H, m, Ar). HRMS calcd for $C_{36}H_{44}NO_4$ [$(M+H)^+$] 554.3270, found 554.3318.

4.6. Methyl (2′*R*,5′*R*,6′*S*)-8-(5′-benzyloxy-6′-methylpiperidin-2′-yl)octanoate 9

Pearlman's $Pd(OH)_2$–C (20%, 12 mg) was added to a solution of **8** (200 mg, 0.361 mmol) in MeOH (2 mL). The

mixture was stirred under H_2 (balloon) for 1 h at room temperature. An additional amount of $Pd(OH)_2$–C (20%, 120 mg) was then added to the mixture, and the resulting mixture was stirred under H_2 (balloon) for 6 h at room temperature. The mixture was then diluted with MeOH and filtered through a bed of Celite. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel (4 g, $CHCl_3$/MeOH = 50:1) to give 104 mg (80%) of **9** as a yellow oil. Its 5′-epimer could be removed at this stage; $n_D^{28} = 1.4981$; $[\alpha]_D^{23} = -41.8$ (*c* 1.05, $CHCl_3$); ν_{max} (film): 3610 (w, NH), 1735 (s, CO), 1495 (w, Ar), 1095 (br s), 735 (s), 700 (s); δ_H (300 MHz, $CDCl_3$): 1.07–1.39 (13H, m, 3′-, 4′-H_a, 4-, 5-, 6-, 7-, 8-H_2, NH), 1.20 (3H, d, *J* 6.0, 6′-CH_3), 1.55–1.80 (3H, m, 3′-H_b, 3-H_2), 2.20 (1H, dq, *J* 3.6, 12.3, 4′-H_b), 2.30 (2H, t, *J* 7.5, 2-H_2), 2.46–2.55 (1H, m, 2′-H), 2.63 (1H, dq, *J* 6.0, 8.7, 6′-H), 2.95 (1H, ddd, *J* 4.5, 8.7, 10.5, 5′-H), 3.67 (3H, s, CO_2CH_3), 4.47 (1H, d, *J* 11.7, PhCH), 4.64 (1H, d, *J* 11.7, PhCH), 7.27–7.35 (5H, m, Ar); NOE was observed between the protons at C-2′ and C-6′. HRMS calcd for $C_{22}H_{36}NO_3$ $[(M+H)^+]$ 362.2695, found 362.2675.

4.7. Methyl (2′*R*,5′*R*,6′*S*)-8-(5′-hydroxy-6′-methylpiperidin-2′-yl)octanoate 10

Pearlman's $Pd(OH)_2$–C (20%, 30 mg) was added to a solution of **8** (500 mg, 0.904 mmol) in MeOH (5 mL). The mixture was stirred under H_2 (balloon) for 1 h at room temperature. An additional amount of $Pd(OH)_2$–C (20%, 300 mg) was then added to the reaction mixture, and the resulting mixture was stirred under H_2 (balloon) for 6 h at room temperature. To the mixture was added a catalytic amount of AcOH (three drops), the resulting mixture was stirred under H_2 (balloon) for 12 h. The mixture was then diluted with MeOH and filtered through a bed of Celite. The filtrate was concentrated in vacuo, and the residue was chromatographed on silica gel (10 g, $CHCl_3$/MeOH = 20:1) to give 190 mg (78%) of **10** as a colorless waxy semi-solid. Its 5′-epimer could be removed at this stage. This was immediately used in the next step without further purification; $[\alpha]_D^{23} = -11.3$ (*c* 0.90, $CHCl_3$); ν_{max} (Nujol): 3380 (m, OH), 3255 (m, NH), 1740 (s, CO), 1575 (s), 1170 (s), 1060 (m); δ_H (300 MHz, $CDCl_3$): 1.17–1.65 (17H, m, 6′-CH_3, 3′-, 4′-H_a, 3-, 4-, 5-, 6-, 7-, 8-H_2), 1.78–1.85 (1H, m, 3′-H_b), 1.95 (1H, s, NH), 2.02–2.10 (1H, m, 4′-H_b), 2.29 (2H, t, *J* 7.5, 2-H_2), 2.59–2.66 (2H, m, 2′-, 6′-H), 3.28–3.49 (1H, m, 5′-H), 3.66 (3H, s, CO_2CH_3), 4.03 (1H, br s, OH); HRMS calcd for $C_{15}H_{29}NO_3$ (M^+) 271.2147, found 271.2145.

4.8. Methyl (2′*R*,5′*R*,6′*S*)-8-(*N*-benzyloxycarbonyl-5′-hydroxy-6′-methylpiperidin-2-yl)octanoate 11

To a stirred solution of **10** (390 mg, 1.44 mmol) in H_2O (8 mL) and 1,4-dioxane (8 mL) were added $NaHCO_3$ (360 mg, 4.32 mmol) and CbzCl (2.73 g, 14.4 mmol) at 0 °C. After stirring for 24 h at room temperature, the resulting mixture was diluted with water and extracted with CH_2Cl_2. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (8 g, hexane/ethyl acetate = 10:1) to give **11** (479 mg, 82%) as a colorless oil; $n_D^{28} = 1.5008$; $[\alpha]_D^{25} = -2.6$ (*c* 0.60, $CHCl_3$); ν_{max} (film): 3455 (m, OH), 1740 (s, CO), 1690 (s, CO), 1585 (w, Ar), 755 (s), 700 (s); δ_H (500 MHz, $CDCl_3$): 1.19 (3H, d, *J* 7.0, 6′-CH_3), 1.21–1.38 (10H, m, 4-, 5-, 6-, 7-, 8-H_2), 1.40–1.71 (5H, m, 3′-H_a, 4′-H_a, 3-H_2, OH), 1.88 (1H, ddt, *J* 2.5, 3.5, 13.5, 4′-H_b), 2.03 (1H, ddt, *J* 3.5, 6.0, 13.5, 3′-H_b), 2.29 (2H, t, *J* 7.0, 2-H_2), 3.67 (3H, s, CO_2CH_3), 3.77 (1H, br s, 5′-H), 4.15–4.21 (1H, m, 2′-H), 4.30 (1H, br q, *J* 7.0, 6′-H), 5.09–5.17 (2H, m, $PhCH_2$), 7.28–7.38 (5H, m, Ar); HRMS calcd for $C_{23}H_{35}NO_5$ $[(M+H)^+]$ 406.2593, found 406.2568.

4.9. Methyl (2′*R*,6′*S*)-8-(*N*-benzyloxycarbonyl-6′-methyl-5′-oxopiperidin-2′-yl)octanoate 12

To a stirred solution of **11** (20 mg, 0.049 mmol) in CH_2Cl_2 (1 mL) was added Dess–Martin periodinane (24 mg, 0.058 mmol) at 0 °C. After stirring for 2 h at room temperature, the reaction was quenched by the addition of sodium thiosulfate (27 mg, 0.174 mmol). The resulting mixture was poured into saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The extract was successively washed with water, saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (2.5 g, hexane/ethyl acetate = 20:1) to give **12** (18 mg, 90%) as a colorless oil; $n_D^{28} = 1.5029$; $[\alpha]_D^{24} = +53.7$ (*c* 0.25, $CHCl_3$); ν_{max} (film): 1730 (s, CO), 1695 (s, CO), 1495 (w, Ar), 1410 (s, Ar), 1310 (s), 750 (s), 700 (s); δ_H (500 MHz, $CDCl_3$): 1.18–1.46 (8H, m, 4-, 5-, 6-, 7-H_2), 1.39 (3H, d, *J* 7.5, 6′-CH_3), 1.56–1.85 (5H, m, 3′-H_a, 3-, 8-H_2), 2.26–2.32 (1H, m, 3′-H_b), 2.29 (2H, t, *J* 7.5, 2-H_2), 2.43 (1H, dd, *J* 5.5, 10.0, 4′-H_a), 2.45 (1H, br t, *J* 5.5, 4′-H_b), 3.66 (3H, s, CO_2CH_3), 4.10–4.27 (1H, m, 2′-H), 4.54–4.80 (1H, m, 6′-H), 5.10–5.20 (2H, m, $PhCH_2$), 7.31–7.38 (5H, m, Ar); HRMS calcd for $C_{23}H_{34}NO_5$ $[(M+H)^+]$ 404.2437, found 404.2481.

4.10. Methyl (2′*R*,5′*S*,6′*S*)-8-(*N*-benzyloxycarbonyl-5′-hydroxy-6′-methylpiperidin-2′-yl)octanoate 13

To a stirred solution of **12** (18 mg, 0.045 mmol) in EtOH (1 mL) was added $NaBH_4$ (1.7 mg, 0.045 mmol) at 0 °C. After stirring for 30 min, the reaction was quenched with aqueous 1 M HCl solution. The resulting mixture was then extracted with diethyl ether. The extract was successively washed with water, saturated aqueous $NaHCO_3$ solution, and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel (400 mg, hexane/ethyl acetate = 10:1) to give **13** (18 mg, quant.) as a colorless oil; $n_D^{28} = 1.5050$; $[\alpha]_D^{25} = -6.9$ (*c* 0.35, $CHCl_3$); ν_{max} (film): 3455 (m, OH), 1740 (s, CO), 1695 (s, CO), 1500 (w, Ar), 1415 (s), 1300 (s), 700 (s); δ_H (500 MHz, $CDCl_3$): 1.09 (3H, d, *J* 7.0, 6′-CH_3), 1.10–1.30 (8H, m, 4-, 5-, 6-, 7-H_2), 1.37–1.66 (8H, m, 3′-H_a, 3-, 4′-, 8-H_2, OH), 1.86–2.01 (1H, m, 3′-H_b), 2.20 (2H, t, *J* 7.5, 2-H_2), 3.58 (3H, s, CO_2CH_3), 3.66–3.71 (1H, m, 5′-H), 3.98–4.05 (1H, m, 2′-H), 4.38–4.44 (1H, m, 6′-H), 5.02 (1H, d, *J* 12.5, PhCH), 5.06 (1H, d, *J* 12.5, PhCH), 7.17–7.28 (5H, m, Ar); HRMS calcd for $C_{23}H_{36}NO_5$ $[(M+H)^+]$ 406.2593, found 406.2553.

4.11. (+)-Carpamic acid 1

To a stirred solution of **13** (18 mg, 0.045 mmol) in MeOH (1 mL) was added $Ba(OH)_2{\cdot}8H_2O$ (70 mg, 0.22 mmol) at room temperature. After stirring overnight at 40 °C, the resulting mixture was poured into aqueous 1 M HCl solution, and extracted with EtOAc. The extract was successively washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo to give the corresponding carboxylic acid (20 mg, crude) as a colorless solid. This compound was immediately used in the next step without further purification.

Pearlman's $Pd(OH)_2$–C (20%, 10 mg) was added to a solution of this carboxylic acid (20 mg) in MeOH (0.5 mL). The mixture was stirred under H_2 (balloon) for 1 h at room temperature. The mixture was then diluted with MeOH and filtered through a bed of Celite. The filtrate was concentrated in vacuo, and the residue was recrystallized from acetone/EtOH to give 10.3 mg (86%, 2 steps) of **1** as a colorless solid; mp 219–222 °C (decomp.) (Ref. 12: mp 225–227 °C); $[\alpha]_D^{24} = +6.0$ (*c* 0.40, MeOH) {Ref. 13: $[\alpha]_D^{21} = +5.1$ (*c* 1.38, MeOH)}; ν_{max} (Nujol): 3330 (m, OH, CO_2H), 3205 (m, NH), 2925 (s, CH), 2850 (s, CH), 1730 (w, CO), 1650 (m), 1555 (s), 1465 (s), 1375 (s), 1100 (w), 840 (m), 665 (m); δ_H (300 MHz, CD_3OD): 1.27–1.50 (8H, m, 4-, 5-, 6-, 7-H_2), 1.30 (3H, d, *J* 6.6, 6′-CH_3), 1.50–1.83 (7H, m, 3-, 8-, 3′-H_2, 4′-H_{eq}), 1.89–1.97 (1H, m, 4′-H_{ax}), 2.14 (2H, t, *J* 7.0, 2-H_2), 2.98–3.10 (1H, m, 2′-H), 3.18–3.27 (1H, m, 6′-H), 3.81 (1H, br s, 5′-H); δ_C (67.8 MHz, CD_3OD): 16.0, 23.7, 26.1, 27.4, 30.0, 30.1, 30.4, 31.1, 34.6, 38.8, 57.4, 58.6, 65.9, 182.3; HRMS calcd for $C_{14}H_{27}NO_3$ (M^+) 257.1991, found 257.1986.

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