



# Stereoselective synthesis of (3*S*,4*R*)-3,4-dimethyl-(*S*)-glutamine and the absolute stereochemistry of the natural product from papuamides and callipeltin<sup>†</sup>

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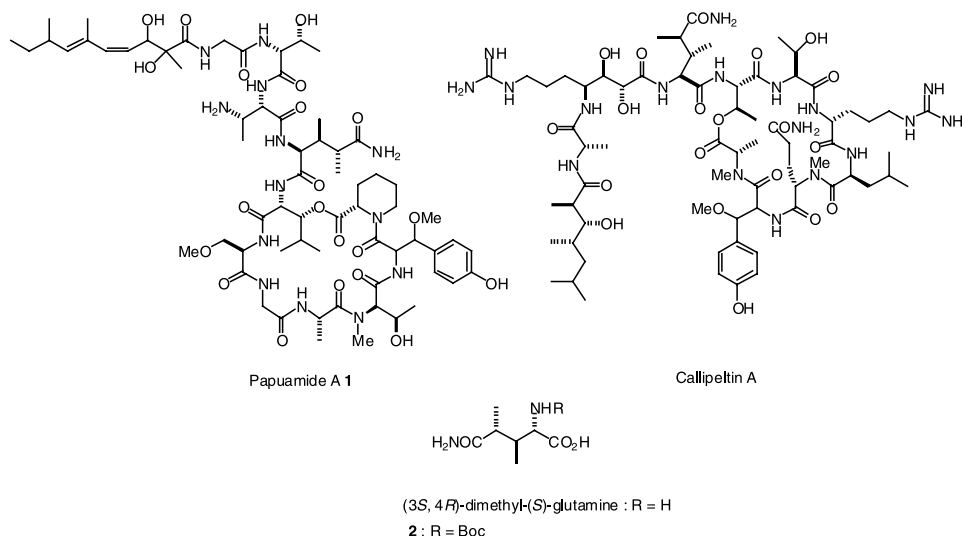
**Abstract**—(3*S*,4*R*)-3,4-Dimethyl-(*S*)-glutamine, a common component of cyclodepsipeptides, papuamide A and callipeltin A, was stereoselectively prepared from (*S*)-pyroglutamic acid. The stereostructure of natural dimethylglutamine was unambiguously confirmed to be (2*S*,3*S*,4*R*) by comparison of the CD and NMR spectra of the synthetic 3,4-dimethylpyroglutamic acid with the hydrolysate of callipeltin A. © 2001 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

The novel cyclodepsipeptide papuamide A **1** and its congeners<sup>1</sup> were isolated from the marine sponge genus *Theonella*, collected at Papua New Guinea by Boyd et al. These cyclic heptapeptides have a unique structure containing unusual amino acid residues. The structural determination of papuamide A has not yet been completed and the stereostructures of some components remain to be defined. Papuamides are known to inhibit the infection of human T-lymphoblastoid cells by HIV-

1<sub>RF</sub> and also exhibit cytotoxicity against a number of human cancer cell lines.

Two unusual amino acids, β-methoxytyrosine and 3,4-dimethylglutamine, of **1** are common components to the cyclodepsipeptide callipeltin A,<sup>2</sup> which was isolated from a sponge collected at New Caledonia, and also shows anti-HIV and cytotoxic activities. The stereostructure of 3,4-dimethylglutamine was determined to be (2*S*,3*S*,4*R*) on the basis of a positive Cotton effect of the hydrolysate, 3,4-dimethylpyroglu-



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<sup>†</sup> Dedicated to Professor Takayuki Shioiri on the occasion of retirement from Nagoya City University.

tamic acid, from callipeltin A. The unique structure and intriguing biological activities of these compounds led us to explore their total synthesis. Herein, we report a stereoselective synthesis of (3*S*,4*R*)-3,4-dimethyl-(*S*)-glutamine (3,4-DiMeGln) in its protected form **2** and the unambiguous determination of the absolute stereostructure of natural 3,4-dimethylglutamine by comparison of the CD spectra of the synthetic 3,4-dimethylpyroglutamic acid with the hydrolysate of callipeltin A. Recently, a synthesis of (3*S*,4*R*)-3,4-dimethyl-(*S*)-glutamine as its protected derivative through asymmetric Michael addition using a camphor-sultam auxiliary has been reported.<sup>3</sup> However, the diastereoselection of the asymmetric synthesis for the desired 3,4-dimethylglutamine is in the ratio 3:1 and remains to be improved.

## 2. Results and discussion

As the starting material for the synthesis of (3*S*,4*R*)-3,4-dimethyl-(*S*)-glutamine, we chose **3** as a chiral synthon derived from (*S*)-glutamic acid. Bicyclic lactam **3** is a versatile synthon in the synthesis of a variety of natural products<sup>4</sup> and was prepared from (*S*)-pyroglutamic acid according to Thottathil's procedure.<sup>5</sup> Introduction of a double bond to the lactam was effected by the method developed by us.<sup>4a,b</sup> We first attempted the sequential introduction of two methyl groups to **4** by conjugate addition with Gilman's reagent followed by trapping of the resulting enolate. However, the introduction of the second methyl group completely failed. Therefore, a stepwise procedure was employed for the introduction of methyl groups at the 6- and 7-positions of the bicyclic lactam **4**.<sup>6</sup>

Treatment of **4** with lithium dimethylcuprate ( $\text{Me}_2\text{CuLi}$ ) in the presence of chlorotrimethylsilane<sup>7</sup> at  $-78^\circ\text{C}$  preferentially provided the 6-methylated product **5** in 86% yield in a ratio of 19:1. After removal of the unwanted diastereomer by chromatography, methylation of the bicyclic lactam **5** at the 7-position was carried out by treatment with LDA at  $-78^\circ\text{C}$  followed by alkylation with iodomethane to afford *trans*-dimethyl lactam **6** in 96% yield with stereoselection of 97:3. These results are not in accordance with those of Hanessian's report<sup>6</sup> regarding the selectivities of the conjugate addition and methylation at the 7-position and also the values of specific rotation of **5** and **6**. The structures of **5** and **6** were unequivocally confirmed by

spectroscopic methods and elemental analyses. In particular, NOE experiments disclosed the stereostructures of **5** and **6** as shown in Fig. 1. Conversion of the *trans*-product to the desired *cis*-dimethyl lactam **7** was achieved by deprotonation with LDA followed by stereoselective protonation.<sup>8</sup> Thus, treatment of *trans*-**6** with LDA at  $-78^\circ\text{C}$  followed by slow addition of saturated aqueous ammonium chloride gave the *cis*-product **7** in 77% yield. To deprotect the benzylidene group, we first attempted transfer hydrogenolysis conditions, which had already been applied for the reported synthesis of AI-77-B.<sup>4a,b</sup> Unfortunately, the deprotection was low yielding using this procedure and the starting material was recovered in 46% yield with 38% yield of the desired **8**. The benzylidene was eventually found to be efficiently cleaved by exposure to excess trifluoroacetic acid at  $20^\circ\text{C}$  over 13 hours and using this procedure **8** was formed in quantitative yield (Scheme 1).

To confirm the absolute stereostructure of the naturally occurring 3,4-dimethylglutamine, the lactam **8** was converted into 3,4-dimethylpyroglutamic acid, which was obtained from the degradation product of callipeltin A. The hydroxyl group of **8** was therefore oxidized with  $\text{RuCl}_3\text{--NaIO}_4$ <sup>9</sup> to provide the desired product **9** in 80% yield. In the CD spectrum the synthetic 3,4-dimethylpyroglutamic acid showed a positive Cotton effect at 208 nm ( $\theta = +20054$ ) in accordance with that of the natural product. Additionally, its NMR spectrum was completely identical with that of the natural product.<sup>2</sup> The above results unambiguously show that the absolute configuration of the 3,4-dimethylglutamine unit in the natural products is (2*S*,3*S*,4*R*).

To complete the synthesis of 3,4-dimethylglutamine, the hydroxyl and amine functions of the lactam were respectively protected with *tert*-butyldimethylsilyl (TBS) and *tert*-butoxycarbonyl (Boc) groups in good yields. After deprotection of the silyl group, ring-opening of lactam **10** into the carboxamide was carried out by ammonolysis. Alcohol **10** was treated with 2.4% ammonia-methanol for 24 hours at  $55^\circ\text{C}$  to give the desired product with recovery of the starting material. The obtained ring-opened product was directly oxidized with  $\text{RuCl}_3\text{--NaIO}_4$  to give *N*-Boc-3,4-dimethylglutamine **2** in 81% yield without epimerization (Scheme 2).

In summary, we have demonstrated the stereoselective synthesis of (3*S*,4*R*)-dimethyl-(*S*)-glutamine **2** from

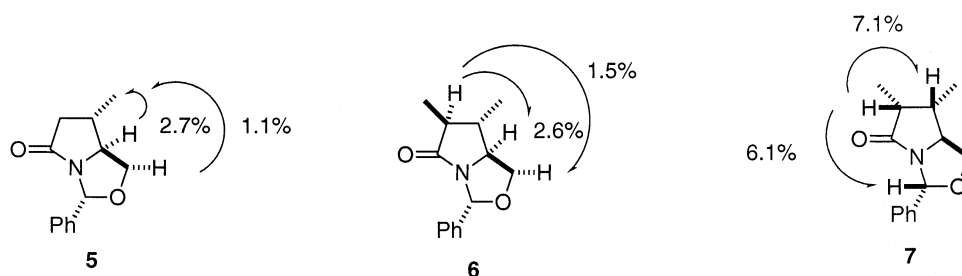
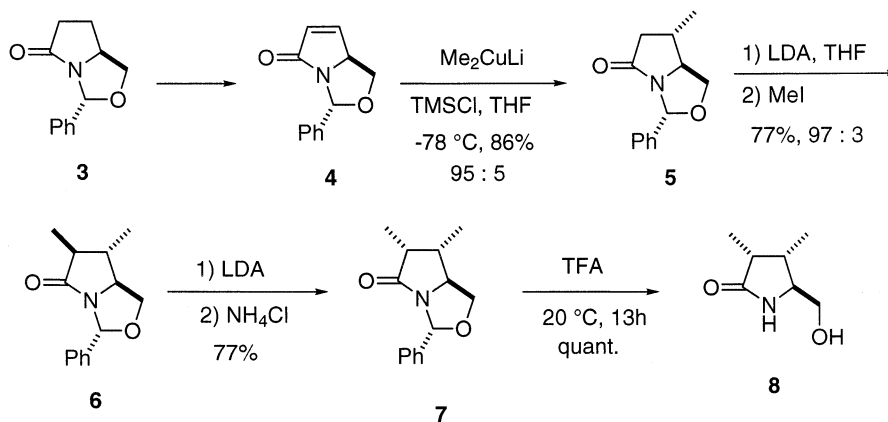
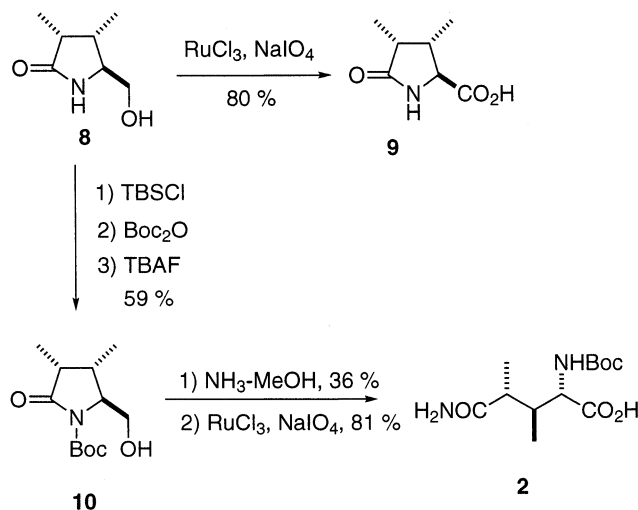


Figure 1.



Scheme 1.



Scheme 2.

(*S*)-pyroglutamic acid and unambiguously determined that the naturally occurring 3,4-dimethylglutamine residue in papuamides and callipeltins has (2*S*,3*S*,4*R*) stereochemistry. Further investigation of other components of the papuamides and callipeltins and their total synthesis is actively under way.

### 3. Experimental

Melting points are uncorrected. IR spectra were recorded on a JASCO FT/IR-230 spectrometer. NMR spectra were recorded on JEOL JNM GSX400A, JNM GSX500A and JNM ECP400 spectrometers. FAB mass spectra were obtained with a JEOL JMS-HX-110A spectrometer. Optical rotations were determined on a JASCO DIP-140 polarimeter. The CD spectrum was recorded on a JASCO J-720WI spectrometer. Column chromatography was carried out with silica gel BW-820MH (Fuji silysia).

#### 3.1. (2*R*,5*S*,6*S*)-6-Methyl-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-8-one 5

To a suspension of CuI (11.4 g, 59 mmol) in THF (344 mL) was added a solution of MeLi in ether (0.8 M, 105 mL, 59 mmol) at  $-78^\circ\text{C}$  and the mixture was stirred at  $0^\circ\text{C}$  for 30 min. The resulting colorless solution was cooled to  $-78^\circ\text{C}$  and a solution of TMSCl (7.57 mL, 59 mmol) and the enone 4 (4 g, 19 mmol) in THF (30 mL) was added. After stirring for 1 h the reaction mixture was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (250 mL). The aqueous phase was extracted with ether (3 $\times$ 120 mL). The combined organic extracts were washed with saturated aqueous  $\text{NH}_4\text{Cl}$  (3 $\times$ 100 mL), water (100 mL) and saturated brine (150 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. The residue was purified by column chromatography on silica gel (120 g, *n*-hexane-ethyl acetate=2:1) to give 5 as a colorless oil (3.78 g, 86%):  $[\alpha]_D^{22} = +228$  (*c* 0.64,  $\text{CHCl}_3$ ) (lit.<sup>6</sup> (6*R*)-enantiomer:  $[\alpha]_D = -2.3$  (*c* 1.47,  $\text{CHCl}_3$ )); IR (neat) 2962,

1710, 1453, 1350  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.22 (3H, d,  $J=6.8$  Hz), 2.33–2.39 (1H, m), 2.46–2.69 (2H, m), 3.60 (1H, dd,  $J=7.0, 8.0$  Hz), 3.62–6.77 (1H, m), 4.20 (1H, dd,  $J=6.3, 8.3$  Hz), 6.35 (1H, s), 7.30–7.44 (5H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  19.16, 34.77, 42.31, 66.04, 70.77, 87.08, 125.95, 128.38, 128.49, 138.5, 177.5. HRMS (FAB, NBA) calcd for  $\text{C}_{13}\text{H}_{16}\text{NO}_2$ : 218.1181 ( $\text{M}+\text{H}^+$ ). Found: 218.1185.

### 3.2. (2*R*,5*S*,6*S*,7*S*)-6,7-Dimethyl-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-8-one 6

To a precooled ( $-78^\circ\text{C}$ ) solution of LDA, prepared from *n*-BuLi in hexane (1.6 M solution, 15.1 mL, 4.17 mmol) and di-*iso*-propylamine (3.39 mL, 24 mmol) in THF (40 mL) at  $-78^\circ\text{C}$ , was added a solution of **5** (3.5 g, 16 mmol) in THF (20 mL). After stirring the mixture for 30 min, iodomethane (2 mL, 32 mmol) was added in one portion at  $-78^\circ\text{C}$  and the mixture was stirred at the same temperature for 1 h. The reaction was quenched with saturated aqueous  $\text{NH}_4\text{Cl}$  (30 mL) and extracted with ethyl acetate ( $3\times 40$  mL). The combined organic extracts were washed with saturated brine (40 mL), dried over  $\text{Na}_2\text{SO}_4$  and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (160 g, *n*-hexane–ethyl acetate=3:1) to give **6** (3.59 g, 96%) as a colorless oil:  $[\alpha]_{\text{D}}^{22}=+152$  ( $c$  0.75,  $\text{CHCl}_3$ ) (lit.<sup>5a</sup> (6*R*,7*R*)-enantiomer:  $[\alpha]_{\text{D}}^{22}=-19$  ( $c$  0.7,  $\text{CHCl}_3$ ); IR (neat) 2964, 2929, 1707, 1454, 1351  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.18 (3H, d,  $J=7.1$  Hz), 1.20 (3H, d,  $J=6.6$  Hz), 1.81–1.87 (1H, m), 2.47–2.52 (1H, m), 3.63–3.72 (2H, m), 4.17 (1H, dd,  $J=5.8, 7.8$  Hz), 6.37 (1H, s), 7.29–7.38 (3H, m), 7.42–7.44 (2H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  13.06, 16.83, 45.52, 47.32, 63.99, 70.85, 87.00, 126.1, 128.4, 128.5, 138.4, 179.1. HRMS (FAB, NBA) calcd for  $\text{C}_{14}\text{H}_{18}\text{NO}_2$ : 232.1338 ( $\text{M}+\text{H}^+$ ). Found: 232.1343.

### 3.3. (2*R*,5*S*,6*S*,7*R*)-6,7-Dimethyl-2-phenyl-1-aza-3-oxabicyclo[3.3.0]octan-8-one 7

To a precooled ( $-78^\circ\text{C}$ ) LDA solution prepared from *n*-BuLi in hexane (1.6 M solution, 13.8 mL, 22 mmol) and di-*iso*-propylamine (13.8 mL, 22 mmol) in THF (40 mL) was added a solution of **6** (3.4 g, 14 mmol) in THF (20 mL). After stirring the mixture for 30 min, saturated aqueous  $\text{NH}_4\text{Cl}$  (0.8 mL) was added dropwise and the mixture was stirred at the same temperature for 1 h. The aqueous phase was separated and extracted with ethyl acetate ( $3\times 40$  mL). The combined organic layers were washed with saturated brine (40 mL), dried over  $\text{Na}_2\text{SO}_4$  and concentrated in vacuo. The residue was purified by column chromatography on silica gel (120 g, *n*-hexane–ethyl acetate=2:1) to give **7** as a colorless oil (2.26 g, 67%):  $[\alpha]_{\text{D}}^{22}=+154$  ( $c$  0.42,  $\text{CHCl}_3$ ); IR (neat) 3419, 2967, 1705, 1450, 1352  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.09 (3H, d,  $J=6.8$  Hz), 1.25 (3H, d,  $J=7.6$  Hz), 2.40 (1H, sextet,  $J=7.1$  Hz), 2.69 (1H, quintet,  $J=7.6$  Hz), 3.62 (1H, dd,  $J=7.1, 8.1$  Hz), 3.76 (1H, q,  $J=6.6$  Hz), 4.18 (1H, dd,  $J=6.5, 8.2$  Hz), 6.37 (1H, s), 7.29–7.43 (5H, m);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  11.8, 13.6, 38.0, 44.9, 64.3, 70.4, 86.9, 125.9,

128.3, 128.4, 138.4, 181.4. HRMS (FAB, NBA) calcd for  $\text{C}_{14}\text{H}_{18}\text{NO}_2$ : 232.1338 ( $\text{M}+\text{H}^+$ ). Found: 232.1329.

### 3.4. (3*R*,4*S*,5*S*)-3,4-Dimethyl-5-hydroxymethylpyrrolidin-2-one 8

To a stirred solution of benzylidene **7** (2.16 g, 9.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (300 mL) was added trifluoroacetic acid (39 mL) at  $20^\circ\text{C}$ . The mixture was stirred at  $20^\circ\text{C}$  for 16 h. The reaction mixture was concentrated in vacuo. Water (20 mL) was added to the residue and the mixture was stirred at  $20^\circ\text{C}$  for 1 min. Toluene was added to the mixture and removed in vacuo. This procedure was repeated three times. The residue was purified by column chromatography on silica gel (40 g,  $\text{CHCl}_3$ –MeOH=20:1) to give alcohol **8** as a colorless solid (1.33 g, 100%): mp  $76$ – $79^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{24}=+88.0$  ( $c$  0.48,  $\text{CHCl}_3$ ); IR (KBr) 3855, 2977, 1664, 1321, 1074  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.02 (3H, d,  $J=7.3$  Hz), 1.09 (3H, d,  $J=7.6$  Hz), 2.25 (1H, sextet,  $J=7.1$  Hz), 2.54 (1H, quintet,  $J=7.6$  Hz), 3.30–3.35 (1H, m), 3.50 (1H, dd,  $J=7.3, 11.2$  Hz), 3.74 (1H, dd,  $J=2.9, 11.4$  Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  10.7, 13.8, 34.6, 39.8, 62.1, 64.6, 181.4. HRMS calcd for  $\text{C}_7\text{H}_{13}\text{NO}_2$ : 143.0946 ( $\text{M}+\text{H}^+$ ). Found: 143.0950.

### 3.5. (3*R*,4*S*,5*S*)-3,4-Dimethyl-5-*tert*-butyldimethylsilyloxymethylpyrrolidin-2-one

To a stirred solution of alcohol **8** (200 mg, 1.3 mmol) in DMF (1.7 mL) were added TBSCl (232 mg, 1.54 mmol) and imidazole (295 mg, 4.3 mmol) and the mixture was stirred at  $20^\circ\text{C}$  for 48 h. The mixture was diluted with ethyl acetate–*n*-hexane (4:1, 30 mL) and washed with water (10 mL). The aqueous layer was extracted with ethyl acetate–*n*-hexane (4:1, 20 mL $\times 2$ ). The combined organic layer was washed with water, saturated brine, dried over  $\text{Na}_2\text{SO}_4$  and filtered. The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (15 g, *n*-hexane–ethyl acetate=1:1) to give the desired silylether derivative (215 mg, 66%) as colorless solid: mp  $48$ – $49^\circ\text{C}$ ;  $[\alpha]_{\text{D}}^{27}=+54.3$  ( $c$  0.635,  $\text{CHCl}_3$ ); IR (KBr) 3293, 2930, 1654, 1254  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  0.06 (6H, s), 0.89 (9H, s), 1.03 (3H, d,  $J=7.2$  Hz), 1.10 (3H, d,  $J=7.7$  Hz), 2.20 (1H, m), 2.53 (1H, quintet,  $J=7.8$  Hz), 3.28 (1H, m), 3.45 (1H, dd,  $J=8.0, 10.0$  Hz), 3.69 (1H, dd,  $J=4.0, 10.0$  Hz), 5.78 (1H, br s);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  –5.47 –5.46, 10.7, 14.2, 18.2, 25.8, 34.8, 39.4, 61.4, 65.8, 77.3, 180.0. HRMS (FAB, NBA) calcd for  $\text{C}_{13}\text{H}_{28}\text{NO}_2\text{Si}$ : 258.1889 ( $\text{M}+\text{H}^+$ ). Found: 258.1895.

### 3.6. (3*R*,4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-3,4-dimethyl-5-*tert*-butyldimethylsilyloxymethylpyrrolidin-2-one

To a stirred solution of the silylether derivative (192 mg, 0.7 mmol) in acetonitrile (8 mL) were added DMAP (9 mg, 0.07 mmol) and  $(\text{Boc})_2\text{O}$  (0.19 mL, 0.8 mmol). The mixture was stirred for 24 h and diluted with ethyl acetate (60 mL), washed with aqueous citric acid (10%, 10 mL), water (10 mL) and saturated brine (10 mL), dried over  $\text{Na}_2\text{SO}_4$  and filtered. The filtrate was concentrated in vacuo and the residue was purified

by column chromatography on silica gel (15 g, *n*-hexane–ethyl acetate=3:1) to give the desired Boc derivative as colorless solid (256 mg, 96%); mp 40–41°C;  $[\alpha]_D^{27} = -46.7$  (*c* 1.12, CHCl<sub>3</sub>); IR (neat) 2931, 1789, 1755, 1712, 1366, 1310, 1159 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.04, (3H, s), 0.06 (3H, s), 0.88 (9H, s), 1.00 (3H, d, *J*=7.3 Hz), 1.09 (3H, d, *J*=7.5 Hz), 1.55 (9H, s), 2.45 (quintet, *J*=7.4 Hz), 2.99 (1H, quintet, *J*=7.6 Hz), 3.68 (1H, m), 3.77 (1H, dd, *J*=2.6, 10.4 Hz), 3.87 (1H, dd, *J*=5.4, 10.4 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ -5.64, 9.97, 15.7, 18.0, 25.7, 28.0, 32.8, 40.5, 62.9, 64.6, 82.5, 150.4, 176.6. HRMS (FAB, NBA) calcd for C<sub>18</sub>H<sub>36</sub>NO<sub>4</sub>Si: 358.2414 (M+H<sup>+</sup>). Found: 358.2395.

### 3.7. (3*R*,4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-3,4-dimethyl-5-hydroxymethylpyrrolidin-2-one 10

To a stirred solution of the Boc derivative (90 mg, 0.25 mmol) in THF (0.27 mL) was added acetic acid (16 μL) and a solution of TBAF in THF (1 M, 0.28 mL, 0.28 mmol). After stirring the mixture for 6 h, the mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel (15 g, *n*-hexane–ethyl acetate=1:3) to give alcohol **10** as a colorless oil (57 mg, 93%);  $[\alpha]_D^{24} = -47.8$  (*c* 1.37, CHCl<sub>3</sub>); IR (neat) 3491, 2976, 1769, 1714, 1370, 1306, 1156 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.02 (3H, d, *J*=7.3 Hz), 1.09, (3H, d, *J*=7.3 Hz), 1.54 (9H, s), 2.39 (1H, quintet, *J*=7.3 Hz), 2.85 (1H, s, OH), 2.91 (1H, quintet, *J*=7.3 Hz), 3.79 (3H, m); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 9.99, 15.3, 28.0, 32.8, 40.6, 63.5, 65.0, 83.3, 151.3, 176.5. HRMS (FAB, NBA) calcd for C<sub>12</sub>H<sub>22</sub>NO<sub>4</sub>: 244.1549 (M+H<sup>+</sup>). Found: 244.1531.

### 3.8. (2*R*,3*S*,4*S*)-4-*tert*-Butoxycarbonylamino-3,4-dimethyl-5-hydroxypentamide

A 5 mL ampoule was charged with alcohol **10** (152 mg, 0.6 mmol) and ammonia in methanol (1.4 M, 3 mL). The ampoule was heated at 55°C for 24 h, then the reaction mixture was concentrated in vacuo. The residue was purified by column chromatography on silica gel (25 g, ethyl acetate–MeOH=20:1) to give the desired amide as a colorless solid (59 mg, 36%); mp 143–144°C;  $[\alpha]_D^{27} = -27.7$  (*c* 0.55, CHCl<sub>3</sub>); IR (KBr) 3407, 3299, 2975, 1693, 1666, 1543 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 0.94 (3H, d, *J*=7.0 Hz), 1.15 (3H, d, *J*=7.0 Hz), 1.47 (9H, s), 1.72–1.67 (1H, m), 2.56 (1H, dq, *J*=2.1, 7.0 Hz), 3.62 (1H, ddt, *J*=3.3, 10.1, 10.2 Hz), 3.72–3.83 (2H, m), 5.36 (1H, d, *J*=9.5 Hz), 5.47 (1H, s), 7.55 (1H, s); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 11.91, 16.25, 28.32, 39.00, 39.39, 54.82, 62.80, 80.08, 157.6, 176.7. HRMS (FAB) calcd for C<sub>12</sub>H<sub>25</sub>N<sub>2</sub>O<sub>4</sub>: 261.1814 (M+H<sup>+</sup>). Found: 261.1799.

### 3.9. (3*S*,4*R*)-*N*-*tert*-Butoxycarbonyl-3,4-dimethyl-(*S*)-glutamine **11**

To a stirred solution of the alcohol (25 mg, 0.096 mmol) in CH<sub>3</sub>CN (4.4 mL) and CCl<sub>4</sub> (2.2 mL) was added a solution of NaIO<sub>4</sub> (62 mg, 0.298 mmol) in H<sub>2</sub>O (2.9 mL). The mixture was cooled to 0°C and

RuCl<sub>3</sub>·*n*H<sub>2</sub>O (0.4 mg, 0.002 mmol) was added. The mixture was stirred for 8 h gradually warming to 20°C. *iso*-Propanol (1.0 mL) was added and the mixture was stirred at 20°C for 30 min. The resulting brownish oil was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on ODS silica gel with H<sub>2</sub>O–MeOH (2:1) eluent to give *N*-Boc-3,4-dimethylglutamine **11** as colorless solid (21 mg, 81%); mp 146–148°C;  $[\alpha]_D^{21} = +15.0$  (*c* 0.56, MeOH); IR (neat) 3397, 2977, 1671, 1508, 1395, 1169 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O): δ 0.73 (3H, d, *J*=6.8 Hz), 1.02 (3H, d, *J*=6.8 Hz), 1.25 (9H, s), 1.84 (1H, m), 2.34 (1H, m), 3.94 (1H, m); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O): δ 14.31, 15.72, 28.25, 38.89, 43.26, 57.03, 82.11, 158.22, 177.38, 182.05. HRMS (FAB, NBA-NaI) calcd for C<sub>12</sub>H<sub>22</sub>N<sub>2</sub>NaO<sub>5</sub>: 297.1426 (M+Na<sup>+</sup>). Found: 297.1441.

### 3.10. (3*S*,4*R*)-3,4-Dimethyl-(*S*)-pyroglutamic acid **9**

To a stirred solution of **8** (150 mg, 1.048 mmol) in CH<sub>3</sub>CN (4.5 mL) and CCl<sub>4</sub> (2.30 mL) was added a solution of NaIO<sub>4</sub> (609 mg, 3.248 mmol) in H<sub>2</sub>O (3.4 mL). The mixture was cooled to 0°C and RuCl<sub>3</sub>·*n*H<sub>2</sub>O (6.0 mg, 0.023 mmol) was added. The mixture was stirred for 8 h with gradual warming to 20°C. *iso*-Propanol (3.0 mL) was added and the mixture was stirred at 20°C for 0.5 h. The resulting brownish oil was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The residue was purified by ion-exchange chromatography with 2N AcOH eluent to give carboxylic acid **9** as a pale yellow solid (111 mg, 67%); mp 175–176°C;  $[\alpha]_D^{26} = +43.4$  (*c* 0.83, MeOH); CD  $[\theta]_{208\text{ nm}}^{20} +20054$  (*c* 0.001 M, H<sub>2</sub>O) (lit.<sup>2</sup>  $[\theta]_{208\text{ nm}}^{20} +1534$  (*c* 0.001 M, H<sub>2</sub>O)); IR (neat) 3262, 2979, 1719, 1654, 1243 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, pyr-*d*<sub>5</sub>): δ 1.15 (3H, d, *J*=6.7 Hz), 1.18 (3H, d, *J*=7.1 Hz), 2.80 (1H, m), 2.85 (1H, m), 4.14 (1H, d, *J*=3.3 Hz); <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O): δ 0.89 (3H, d, *J*=6.6 Hz), 0.97 (3H, d, *J*=6.2 Hz), 2.53 (2H, m), 3.80 (1H, d, *J*=3.9 Hz); <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O): δ 9.43, 13.69, 37.98, 39.19, 61.38, 176.2, 183.8. HRMS (FAB, NBA) calcd for C<sub>7</sub>H<sub>12</sub>NO<sub>3</sub>: 158.0817 (M+H<sup>+</sup>). Found: 158.0808.

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