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TETRAHEDRON: *ASYMMETRY*

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

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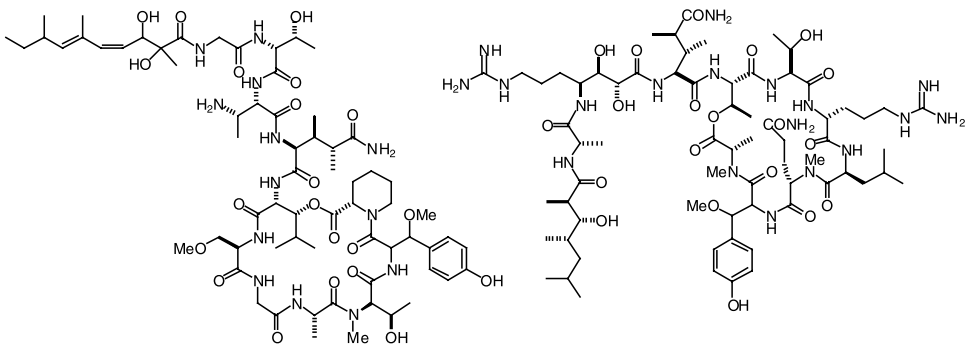
Abstract—(3*S*,4*R*)-3,4-Dimethyl-(*S*)-glutamine, a common component of cyclodepsipeptides, papuamide A and callipeltin A, was stereoselectively prepared from (*S*)-pyroglutamic acid. The stereostructure of natural dimethylglutamine was unambiguously confirmed to be (2*S*,3*S*,4*R*) by comparison of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

1. Introduction

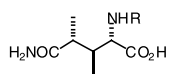
The novel cyclodepsipeptide papuamide A **1** and its congeners[1] were isolated from the marine sponge genus *Theonella*, collected at Papua New Guinea by Boyd et al. These cyclic heptapeptides have a unique structure containing unusual amino acid residues. The structural determination of papuamide 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_{RF} 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,[2] 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-



Papuamide A **1**

Callipeltin A



(3*S*, 4*R*)-dimethyl-(*S*)-glutamine : R = H

2 : R = Boc

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

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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 camphorsultam auxiliary has been reported.[3] 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[4] and was prepared from (*S*)-pyroglutamic acid according to Thottathil's procedure.[5] Introduction of a double bond to the lactam was effected by the method developed by us.[4a,b] 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**.[6]

Treatment of **4** with lithium dimethylcuprate (Me_2CuLi) in the presence of chlorotrimethylsilane[7] at −78°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°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[6] 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.[8] Thus, treatment of *trans*-**6** with LDA at −78°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.[4a,b] 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°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 $RuCl_3$–$NaIO_4$[9] 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.[2] 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°C to give the desired product with recovery of the starting material. The obtained ring-opened product was directly oxidized with $RuCl_3$–$NaIO_4$ 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

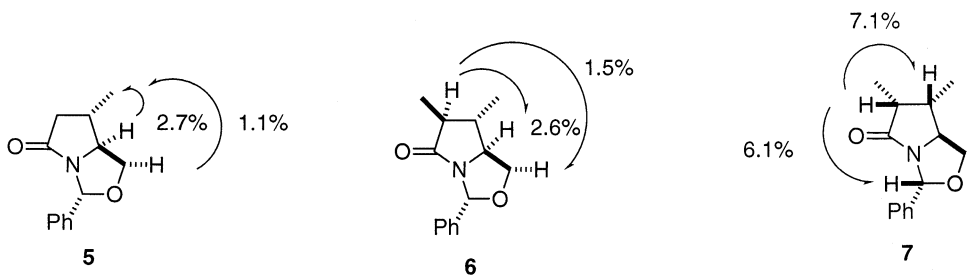
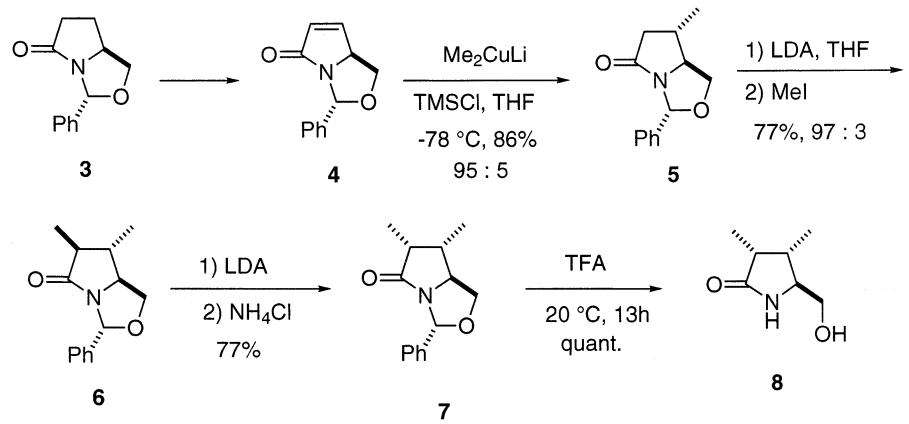
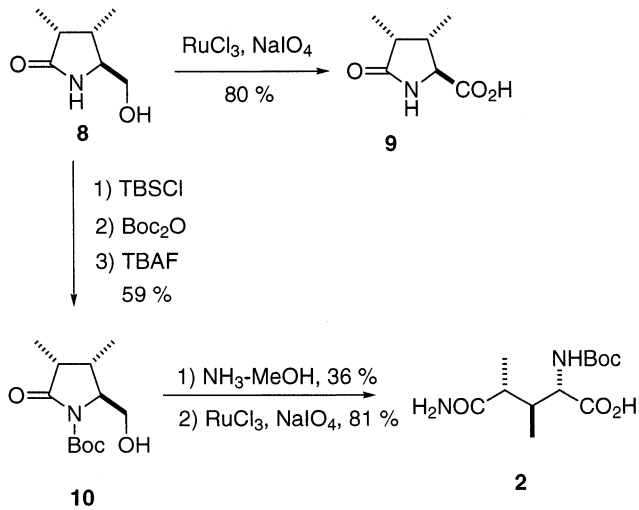


Figure 1.



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°C and the mixture was stirred at 0°C for 30 min. The resulting colorless solution was cooled to −78°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 NH_4Cl (250 mL). The aqueous phase was extracted with ether (3×120 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (3×100 mL), water (100 mL) and saturated brine (150 mL), dried over Na_2SO_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, $CHCl_3$) (lit.[6] (6*R*)-enantiomer: $[\alpha]_D=-2.3$ (*c* 1.47, $CHCl_3$)); IR (neat) 2962,

1710, 1453, 1350 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 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}C NMR (100 MHz, $CDCl_3$): δ 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 $C_{13}H_{16}NO_2$: 218.1181 ($M+H^+$). 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°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°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°C and the mixture was stirred at the same temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (30 mL) and extracted with ethyl acetate (3×40 mL). The combined organic extracts were washed with saturated brine (40 mL), dried over Na_2SO_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: $[\alpha]_D^{22}=+152$ (*c* 0.75, $CHCl_3$) (lit.[5a] (6*R*,7*R*)-enantiomer: $[\alpha]_D=-19$ (*c* 0.7, $CHCl_3$)); IR (neat) 2964, 2929, 1707, 1454, 1351 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 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}C NMR (100 MHz, $CDCl_3$): δ 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 $C_{14}H_{18}NO_2$: 232.1338 ($M+H^+$). 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°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 NH_4Cl (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 (3×40 mL). The combined organic layers were washed with saturated brine (40 mL), dried over Na_2SO_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%): $[\alpha]_D^{22}=+154$ (*c* 0.42, $CHCl_3$); IR (neat) 3419, 2967, 1705, 1450, 1352 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 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}C NMR (100 MHz, $CDCl_3$): δ 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 $C_{14}H_{18}NO_2$: 232.1338 ($M+H^+$). 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 CH_2Cl_2 (300 mL) was added trifluoroacetic acid (39 mL) at 20°C. The mixture was stirred at 20°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°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, $CHCl_3$–MeOH = 20:1) to give alcohol **8** as a colorless solid (1.33 g, 100%): mp 76–79°C; $[\alpha]_D^{24}=+88.0$ (*c* 0.48, $CHCl_3$); IR (KBr) 3855, 2977, 1664, 1321, 1074 cm^{-1}: ^1H NMR (400 MHz, $CDCl_3$): δ 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}C NMR (100 MHz, $CDCl_3$): δ 10.7, 13.8, 34.6, 39.8, 62.1, 64.6, 181.4. HRMS calcd for $C_7H_{13}NO_2$: 143.0946 ($M+H^+$). Found: 143.0950.

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

To a stirred solution of alcohol **8** (200mg, 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°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×2). The combined organic layer was washed with water, saturated brine, dried over Na_2SO_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°C; $[\alpha]_D^{27}=+54.3$ (*c* 0.635, $CHCl_3$); IR (KBr) 3293, 2930, 1654, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 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}C NMR (100 MHz, $CDCl_3$): δ −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 $C_{13}H_{28}NO_2Si$: 258.1889 ($M+H^+$). Found: 258.1895.

3.6. (3*R*,4*S*,5*S*)-*N*-*tert*-Butoxycarbonyl-3,4-dimethyl-5-*tert*-butyldimethylsiloxymethylpyrrolidin-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 $(Boc)_2O$ (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 Na_2SO_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, $CHCl_3$); IR (neat) 2931, 1789, 1755, 1712, 1366, 1310, 1159 cm^{-1}: ^1H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{18}H_{36}NO_4Si$: 358.2414 ($M+H^+$). 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, $CHCl_3$); IR (neat) 3491, 2976, 1769, 1714, 1370, 1306, 1156 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{12}H_{22}NO_4$: 244.1549 ($M+H^+$). 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, $CHCl_3$); IR (KBr) 3407, 3299, 2975, 1693, 1666, 1543 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{12}H_{25}N_2O_4$: 261.1814 ($M+H^+$). 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_3CN (4.4 mL) and CCl_4 (2.2 mL) was added a solution of $NaIO_4$ (62 mg, 0.298 mmol) in H_2O (2.9 mL). The mixture was cooled to 0°C and $RuCl_3 \cdot nH_2O$ (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_2O–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^{-1}; ^1H NMR (400 MHz, D_2O): 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); ^{13}C NMR (100 MHz, D_2O): 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 $C_{12}H_{22}N_2NaO_5$: 297.1426 ($M+Na^+$). 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_3CN (4.5 mL) and CCl_4 (2.30 mL) was added a solution of $NaIO_4$ (609 mg, 3.248 mmol) in H_2O (3.4 mL). The mixture was cooled to 0°C and $RuCl_3 \cdot nH_2O$ (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 $[\theta]_{208\ nm}$ +20054 (*c* 0.001 M, H_2O) (lit.[2] $[\theta]_{208\ nm}$ +1534 (*c* 0.001 M, H_2O)); IR (neat) 3262, 2979, 1719, 1654, 1243 cm^{-1}; ^1H NMR (400 MHz, pyr-d_5): 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); ^1H NMR (400 MHz, D_2O): 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); ^{13}C NMR (100 MHz, D_2O): δ 9.43, 13.69, 37.98, 39.19, 61.38, 176.2, 183.8. HRMS (FAB, NBA) calcd for $C_7H_{12}NO_3$: 158.0817 ($M+H^+$). Found: 158.0808.

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