Efficient Synthesis of (*R*)- and (*S*)-α-(Hydroxymethyl)pyroglutamic Acid Esters from L-Proline

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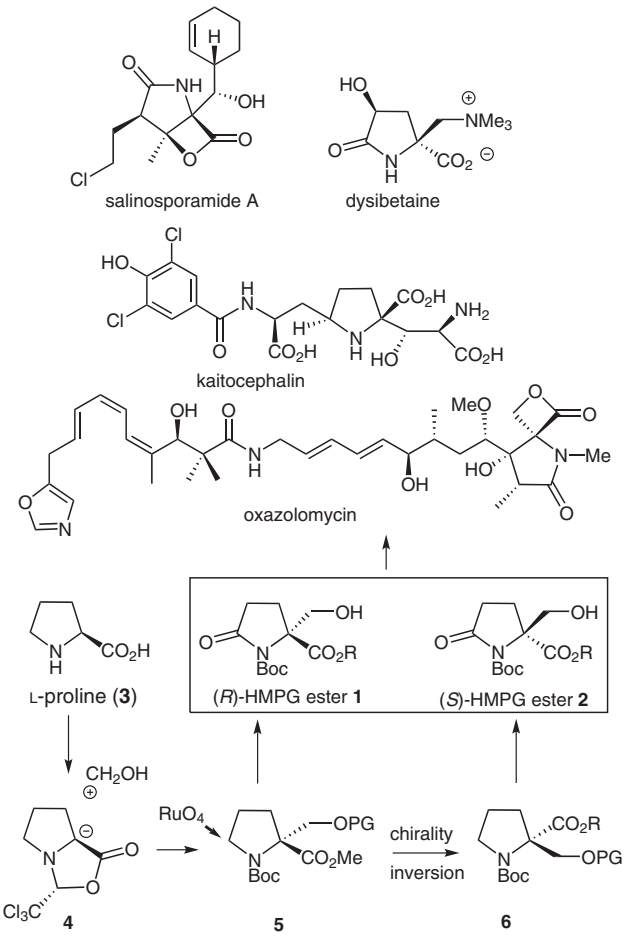
Abstract: An efficient synthesis of (*R*)- and (*S*)-α-(hydroxymethyl)pyroglutamic acid esters from L-proline has been achieved. Each step was carried out on a decagram scale to access the N-protected (*R*)-ester in a highly efficient manner (44% overall yield from a proline-derived bicyclic substrate).

Key words: amino acids, α-substituted proline, pyroglutamic acid esters, stereoselective synthesis, alkylations

Several natural products possessing α,,α-disubstituted pyrrolidine (or α-substituted pyroglutamic acid) as their core unit have attracted much attention because of their synthetically challenging structures and potent biological activities.[1] Much synthetic effort has been dedicated to the enantio- and diastereoselective total syntheses of such compounds and structure–activity relationship studies to explore their bioactivities and modes of action.[2–5] The stereoselective construction of the highly substituted pyrrolidine core is key to their synthesis. We envisaged that optically active α-(hydroxymethyl)pyroglutamic acid esters (HMPGs)[6] **1** and **2** could be useful synthetic intermediates to achieve the above goals (Scheme 1); HMPGs are α-(hydroxymethyl) derivatives of pyroglutamic acid esters, which are widely employed in the synthesis of pyrrolidine-containing natural products and biologically active compounds.[7] The potent utilities of compounds **1** and **2** have been demonstrated in the synthesis of kaitocephalin,[4c] dysibetaine,[5c] and omuralide.[8] However, there remain improvements to be made to the existing syntheses of such substrates; for example, 3 grams of a derivative of (*S*)-HMPG **2**, used as the key intermediate for the total synthesis of kaitocephalin, were synthesized in 12 steps using the asymmetric Strecker synthesis starting from levulinic acid (50 g) resulting in 4% overall yield.[4c] In this report, we describe a practical method for the synthesis of both enantiomers of the HMPGs from L-proline (**3**).

Seebach et al.'s self asymmetric center regeneration method using L-proline (**3**)[9] was adopted to generate the amino group attached chiral center (Scheme 1). Chiral trichloromethyl-containing *N*,*O*-acetal **4**,[10] which can be isolated as a white powder, stored under ambient conditions, and exhibits almost the same reactivity and stereoselectivity compared to those of the moisture-sensitive *tert*-butyl-containing *N*,*O*-acetal, was chosen as the self chirality transferring substrate for the large-scale alkylation reaction. The ruthenium(VIII) oxide (RuO_4) oxidation of *N*-(*tert*-butoxycarbonyl)-substituted (*N*-Boc) pyrrolidine **5** would produce HMPGs.[11] Although enantiomer **2** could be accessed from D-proline along these lines too, this substrate is five times more expensive than L-proline. In this study, an alternative route involving inversion of the *R*-chiral center of **5** to give *S*-product **6** was attempted to access enantiomer **2**.



Scheme 1

The treatment of bicyclic compound **4** with lithium diisopropylamide followed by the addition of benzyl chloromethyl ether gave **7a** in 67% yield (Scheme 2). The use of chloromethyl methyl ether and [2-(trimethylsilyl)eth-

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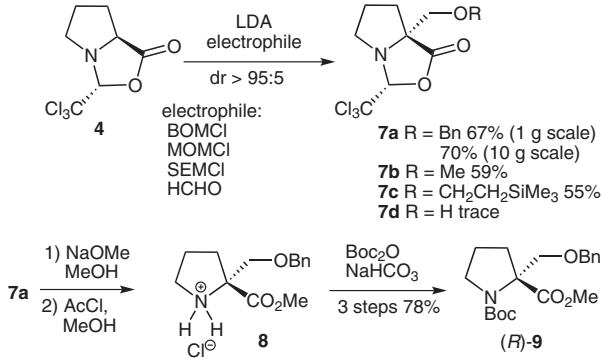
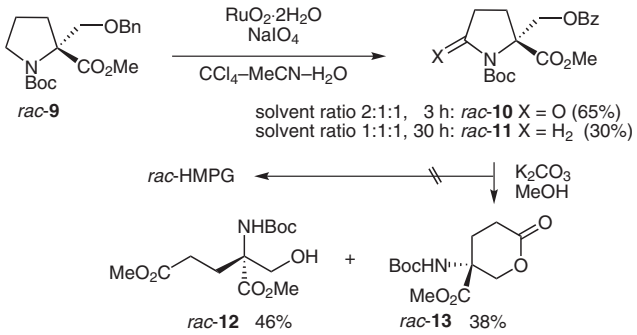
oxy]methyl chloride afforded the corresponding alkylated products **7b** and **7c**, respectively, in moderate yields. The direct hydroxymethylation reaction with formaldehyde (solid paraformaldehyde or gaseous HCHO generated by the thermolysis of paraformaldehyde) was not satisfactory, resulting in almost full recovery of starting material **4**. Based on the above results, as well as the consideration of the protecting group manipulation required in later steps, the scaling up of the synthesis was implemented with benzyl derivative **7a**. The synthesis was found to be reproducible and could be extended on a decagram scale to give 18.5 grams of product **7a** in 70% yield. Benzyl ether **7a** was then converted into *N*-Boc derivative (*R*)-**9** in a manner similar to the reported method.[10] Thus, benzyl ether **7a** was subjected to initial methanolysis using sodium methoxide in methanol to give a mixture of the corresponding amino methyl ester and its formamide. The mixture was successively exposed to AcCl/MeOH to remove the *N*-formamide furnishing the ammonium salt **8**. The installation of the *N*-Boc group gave N-protected product (*R*)-**9** in 78% yield from substrate **7a** in three steps.



Scheme 2

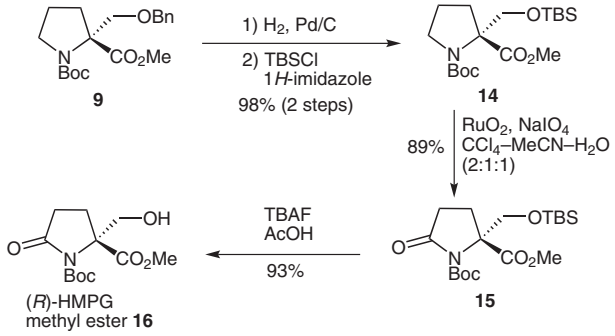
We postulated that the dual oxidation reaction of the pyrrolidine ring and the benzyl group of (*R*)-**9** with RuO_4 (generated in situ from RuO_2 and $NaIO_4$) to produce a benzoyl lactam, followed by the chemoselective removal of the benzoyl group should provide the corresponding (*R*)-HMPG. The feasibility of this synthesis was tested with *rac*-**9**. The desired *rac*-(benzoyloxy)methyl-substituted lactam *rac*-**10** was obtained in 65% yield when protected pyrrolidine *rac*-**9** was subjected to RuO_4 oxidation in tetrachloromethane–methyl cyanide–water (CCl_4–MeCN–H_2O, 2:1:1) (Scheme 3). The chosen solvent ratio was essential for this oxidation reaction. On decreasing the quantity of CCl_4, i.e. using a solvent ratio of 1:1:1, the reaction was found to be sluggish and provided 2-(benzoyloxy)methylpyrrolidine *rac*-**11** in 30% yield along with a trace amount of **10** and recovery of starting material *rac*-**9**, probably because of the poor solubility of *rac*-**9** under this condition. We next attempted the selective removal of the benzoyl group of *rac*-**10**; however, a lactam-opening reaction predominantly occurred. Thus, the treatment of *rac*-**10** with potassium carbonate in methanol



Scheme 3

gave a mixture of lactam-opening products *rac*-**12** and *rac*-**13** in 46 and 38% yield, respectively.

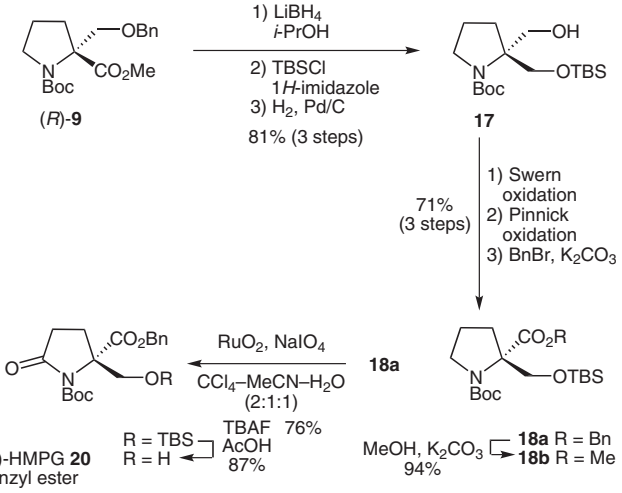
We reported the synthesis of (*R*)-HMPG **16** by the mild desilylation reaction (TBAF, AcOH) of lactam **15** during the total synthesis of (–)-kaitocephalin.[4c] Moreover, the compatibility of a *tert*-butyldimethylsilyl (TBS) ether with RuO_4 oxidation conditions was confirmed during the first total synthesis of trideoxytetrodotoxin.[11] Based on these results, we turned our attention to the synthesis of silyl ether **15** from benzyl ether (*R*)-**9** (Scheme 4). The benzyl group of (*R*)-**9** was initially exchanged for a TBS group under the conventional reaction conditions: (i) hydrogenation with hydrogen and palladium on carbon, and (ii) silylation with TBSCl in the presence of 1*H*-imidazole. The RuO_4 oxidation of 2-(siloxymethyl)pyrrolidine **14** in CCl_4–MeCN–H_2O (2:1:1) gave (*R*)-lactam **15** in excellent yield. The mild desilylation reaction of silyl ether **15** produced (*R*)-HMPG **16** without any undesired ring-opening reaction. Each step could be practically carried out on a decagram scale (44% overall yield starting from **4**).



Scheme 4

The synthesis of the related *S*-isomer **20** from (*R*)-**9** via the chirality switching of the quaternary amino carbon center was attempted. The chirality switching was achieved using the following sequence of reactions: (i) reduction of the ester moiety, (ii) protection of the resulting alcohol with the TBS group, (iii) removal of the benzyl group, and (iv) conversion of hydroxymethyl derivative **17** into benzyl ester **18a** (Scheme 5). The optical purity of **18a** was confirmed by the comparison of the optical rotation of the corresponding methyl ester **18b** with that of *R*-enantiomer

14. These results indicated that the TBS group did not migrate during the hydrogenation reaction. Benzyl ester **18a** was converted into (*S*)-HMPG **20** (1.8 g) in two steps according to the procedure for the formation of (*R*)-HMPG **16**. The synthesis of benzyl ester **20** turned out to be beneficial, allowing the option of further protecting groups at the carboxylate moiety in HMPGs.



Scheme 5

In summary, we have established an efficient synthesis of (*R*)- and (*S*)-HMPGs from L-proline. Further synthetic applications starting from HMPGs on the synthesis of glutamate analogues and pyrrolidine ring containing natural products are now in progress.

All reagents and solvents were purchased from Sigma-Aldrich, Nacalai Tesque, or the Tokyo Chemical Industry and were used without further purification unless otherwise indicated. Solvents of anhydrous grade were used. Optical rotations were recorded on a Jasco Polarimeter P-1030. Fourier transform infrared spectra were measured on a Jasco FT/IR-6200 infrared spectrophotometer. ^{1}H NMR spectra were recorded on either a Jeol JNM-LA400 (400 MHz) or Bruker Avance 300M (300 MHz) spectrometer; chemical shifts are reported in ppm relative to the residual peak of $CHCl_3$ (δ = 7.26) in $CDCl_3$. ^{13}C NMR spectra were recorded on either a Jeol JNM-LA400 (100 MHz) or Bruker Avance 300 (75 MHz) spectrometer; chemical shifts are reported in ppm relative to $CDCl_3$ (δ = 77.0). HRMS was performed on a Jeol JMS-AX-500 instrument using FAB and CI techniques. All reactions were monitored by TLC, which was performed with precoated plates (silica gel 60 F-254, 0.25-mm layer thickness, manufactured by Merck); TLC visualization was accomplished using a UV lamp (254 nm) or a charring solution (ethanoic phosphomolybdic acid). Daisogel IR-60 1002W (40/63 mm) was used for flash column chromatography on silica gel.

(3*R*,7a*R*)-7a-[(Benzyloxy)methyl]-3-(trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (7a); Typical Procedure

To a solution of *i*-Pr_2NH (14.1 mL, 101 mmol) and THF (200 mL) in a flame-dried, 500-mL round-bottomed flask was added 1.63 M *n*-BuLi in hexane (62.0 mL, 101 mmol) at –78 °C under argon. The mixture was stirred for 30 min at –78 °C. To the resulting LDA solution was added a cooled solution (0 °C) of bicyclic compound **4**[10] (17.7 g, 72.5 mmol) in THF (80 mL) via cannula at –78 °C under argon. The mixture was stirred for 15 min at –78 °C. To the mixture was added BOMCl (18.0 mL, 130 mmol), and the solution was allowed to warm to –40 °C over 4 h. The mixture was then quenched with H_2O (300 mL) and extracted with EtOAc (3 × 300 mL). The combined organic layers were dried (anhyd $MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (Et_2O–hexane, 1:7) to give **7a** as a yellow oil. Yield: 18.5 g (70%); $[\alpha]_D^{24}$ +7.86 (*c* 1.08, $CHCl_3$).

FTIR (neat): 3581, 3064, 3029, 2954, 2897, 2868, 1799, 1454, 1191, 1090, 1024, 837, 746 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 5 H), 4.97 (s, 1 H), 4.62 (d, *J* = 12.2 Hz, 1 H), 4.59 (d, *J* = 12.2 Hz, 1 H), 3.73 (d, *J* = 10.0 Hz, 1 H), 3.71 (d, *J* = 10.0 Hz, 1 H), 3.35–3.20 (m, 2 H), 2.33–2.26 (m, 1 H), 2.14–2.07 (m, 1 H), 1.99–1.94 (m, 1 H), 1.74–1.62 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 137.9, 128.4, 127.6, 127.5, 102.0, 100.4, 73.5, 72.6, 72.5, 58.2, 33.7, 25.1.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}Cl_3NO_3$: 364.0271; found: 364.0278.

(3*R*,7a*R*)-7a-(Methoxymethyl)-3-(trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (7b)

According to the procedure for the synthesis of **7a**, bicyclic compound **4** (147 mg, 0.60 mmol) was alkylated with MOMCl (0.08 mL, 1.07 mmol) to give **7b** as a white solid. Yield: 101 mg (59%); mp 62–63 °C; $[\alpha]_D^{28}$ –0.13 (*c* 1.30, $CHCl_3$).

FTIR (neat): 2900, 1801, 1273, 1188, 1092, 1030, 945, 835, 806, 744, 667, 638 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.99 (s, 1 H), 3.67 (d, *J* = 10.2 Hz, 1 H), 3.63 (d, *J* = 10.2 Hz, 1 H), 3.30 (ddd, *J* = 12.2, 10.0, 5.8 Hz, 1 H), 3.42 (s, 3 H), 3.24 (ddd, *J* = 12.2, 9.8, 3.4 Hz, 1 H), 2.27 (ddd, *J* = 13.2, 9.8, 7.1 Hz, 1 H), 2.12 (dddd, *J* = 13.2, 8.3, 3.9, 1.0 Hz, 1 H), 2.03–1.94 (m, 1 H), 1.76–1.66 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 102.0, 100.3, 75.2, 72.4, 59.8, 58.1, 33.5, 25.1.

HRMS (CI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{12}Cl_3NO_3$: 287.9978; found: 287.9960.

(3*R*,7a*R*)-3-(Trichloromethyl)-7a-{[2-(trimethylsilyl)ethoxy]methyl}tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (7c)

According to the procedure for the synthesis of **7a**, bicyclic compound **4** (137 mg, 563 μmol) was alkylated with [2-(trimethylsilyl)ethoxy]methyl chloride (184 μL, 1.01 mmol) to give **7c** as a colorless oil. Yield: 115 mg (55%); $[\alpha]_D^{29}$ –1.18 (*c* 0.97, $CHCl_3$).

FTIR (neat): 3589, 2954, 2896, 1803, 1250, 1192, 1090, 867, 752 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.99 (s, 1 H), 3.70–3.55 (m, 2 H), 3.67 (s, 2 H), 3.29 (ddd, *J* = 15.4, 9.8, 5.9 Hz, 1 H), 3.23 (ddd, *J* = 15.4, 6.3, 3.4 Hz, 1 H), 2.28 (ddd, *J* = 13.2, 9.8, 7.1 Hz, 1 H), 2.11 (ddd, *J* = 13.2, 8.3, 4.2 Hz, 1 H), 2.02–1.94 (m, 1 H), 1.74–1.63 (m, 1 H), 0.92 (t, *J* = 8.2 Hz, 2 H), 0.00 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 101.9, 100.4, 72.7, 72.6, 72.5, 69.2, 58.1, 33.5, 25.1, 18.3, 18.1, 17.8, –1.2, –1.5, –1.7.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{22}Cl_3NO_3Si$: 374.0530; found: 374.0493.

(*R*)-1-*tert*-Butyl 2-Methyl 2-[(Benzyloxy)methyl]pyrrolidine-1,2-dicarboxylate (9)

A 500-mL, three-necked round-bottomed flask, equipped with a 100-mL pressure-equalizing addition funnel capped by a rubber septum, a reflux condenser fitted with an argon balloon, and a rubber septum, was filled with benzyl ether **7a** (18.0 g, 49.5 mmol) and MeOH (165 mL). To this solution was added NaOMe (1.60 g, 29.6 mmol) over 30 min. The mixture was stirred for an additional 30

min and then was cooled in an ice bath. The pressure-equalizing addition funnel was charged with commercially available AcCl (68.4 mL, 0.96 mol), which was added dropwise to the mixture over 1 h. The funnel was removed and replaced with a rubber septum, and the milky brown solution was refluxed for 20 h. The volatile organics were removed under reduced pressure. The residue was diluted with CH_2Cl_2 (90 mL), and precipitated NaCl was removed by filtration. The filtrate was then poured into sat. Na_2CO_3 (200 mL), and the mixture was extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried (anhyd $MgSO_4$) and concentrated under reduced pressure to give methyl pyrrolidinecarboxylate **8** as a pale red oil. To a solution of this residue in dioxane (114 mL) were successively added sat. $NaHCO_3$ (114 mL) and $(Boc)_2O$ (16.2 g, 74.3 mmol). The mixture was stirred for 24 h and then was concentrated under reduced pressure. The residue was partitioned with EtOAc (200 mL) and H_2O (200 mL), and extracted. The aqueous layer was then extracted with EtOAc (2 × 200 mL). The combined organic layers were dried (anhyd $MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc, 50:1 then 20:1) to give **9** as a colorless oil. Yield: 13.5 g (78%); a 2:3 mixture of rotamers in $CDCl_3$; $[\alpha]_D^{24}$ +37.2 (*c* 1.00, $CHCl_3$).

FTIR (neat): 3625, 3469, 3380, 2976, 2877, 1741, 1693, 1390, 1238, 1159, 1097, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 5 H), 4.58 (d, *J* = 12.4 Hz, 2/5 H), 4.57 (d, *J* = 12.4 Hz, 3/5 H), 4.55 (d, *J* = 12.4 Hz, 3/5 H), 4.53 (d, *J* = 12.4 Hz, 2/5 H), 4.17 (d, *J* = 10.0 Hz, 2/5 H), 3.95 (d, *J* = 9.8 Hz, 3/5 H), 3.88 (d, *J* = 10.0 Hz, 2/5 H), 3.84 (d, *J* = 9.8 Hz, 3/5 H), 3.74–3.43 (m, 2 H), 3.69 (s, 3 H), 2.45–2.32 (m, 1 H), 2.12–1.82 (m, 3 H), 1.45 (s, 18/5 H), 1.36 (s, 27/5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.7, 173.6, 153.9, 153.2, 138.6, 138.3, 128.3, 128.2, 127.5, 127.4, 127.3, 172.2, 79.9, 79.5, 73.5, 73.4, 71.2, 70.3, 67.9, 67.4, 51.9, 51.8, 48.5, 48.4, 36.2, 34.8, 28.4, 28.2, 23.6, 23.0.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{27}NO_5$: 350.1964; found: 350.1959.

(*R*)-1-*tert*-Butyl 2-Methyl 2-[(*tert*-Butyldimethylsiloxy)methyl]pyrrolidine-1,2-dicarboxylate (14)

To a solution of benzyl ether **9** (13.5 g, 38.7 mmol) in MeOH (192 mL) was added 10% Pd/C (1.30 g). The suspension was stirred for 18 h under hydrogen (balloon), diluted with EtOAc (300 mL), and filtered using a thin Celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc, 12:1 then 6:1) to give the corresponding alcohol as a colorless oil. Yield: 9.92 g (99%); a 4:5 mixture of rotamers in $CDCl_3$; $[\alpha]_D^{25}$ –11.2 (*c* 0.90, $CHCl_3$).

FTIR (neat): 3456, 2978, 2887, 1739, 1691, 1396, 1165, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.09 (d, *J* = 11.7 Hz, 5/9 H), 3.88 (d, *J* = 11.5 Hz, 4/9 H), 3.83 (d, *J* = 11.5 Hz, 4/9 H), 3.88–3.83 (m, 5/9 H), 3.74 (s, 15/9 H), 3.72 (s, 12/9 H), 3.63–3.38 (m, 2 H), 2.49 (dt, *J* = 12.2, 6.8 Hz, 1 H), 2.20–2.05 (m, 2 H), 2.20–1.75 (m, 2 H), 1.44 (s, 45/9 H), 1.38 (s, 36/9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 173.4, 155.6, 153.2, 80.4, 70.4, 67.7, 65.8, 64.1, 52.2, 51.9, 48.5, 48.1, 34.5, 34.3, 28.2, 28.1, 22.5, 22.4.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{21}NO_5$: 260.1495; found: 260.1496.

To a solution of the resulting alcohol described above (9.92 g, 38.3 mmol) in DMF (173 mL) was added 1*H*-imidazole (3.53 g, 51.9 mmol), and then TBSCl (7.82 g, 51.9 mmol) was added at 0 °C with stirring. The mixture was stirred for 18 h at r.t., partitioned with EtOAc (50 mL) and sat. NH_4Cl (200 mL), and extracted. The aqueous layer was then extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with brine, dried (anhyd $MgSO_4$), and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc, 25:1 then 15:1) to give **14** as a colorless oil. Yield: 14.2 g (99%); a 2:3 mixture of rotamers in $CDCl_3$; $[\alpha]_D^{25}$ +34.6 (*c* 1.05, $CHCl_3$).

FTIR (neat): 2954, 2933, 2885, 2858, 1743, 1699, 1471, 1396, 1099, 839, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.31 (d, *J* = 10.2 Hz, 2/5 H), 4.11 (d, *J* = 10.2 Hz, 3/5 H), 3.87 (d, *J* = 10.2 Hz, 2/5 H), 3.84 (d, *J* = 10.2 Hz, 3/5 H), 3.67 (s, 9/5 H), 3.67–3.63 (m, 9/5 H), 3.60–3.53 (m, 2/5 H), 3.48–3.30 (m, 1 H), 2.40–2.27 (m, 1 H), 2.05–1.78 (m, 3 H), 1.41 (s, 27/5 H), 1.38 (s, 18/5 H), 0.86 (s, 9 H), 0.03 (s, 6/5 H), 0.02 (s, 9/5 H), –0.02 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9, 173.8, 153.6, 153.2, 79.8, 79.3, 68.7, 68.2, 64.2, 63.0, 51.8, 51.7, 48.5, 35.9, 34.4, 28.3, 28.2, 25.7, 23.6, 23.0, 18.1, –5.49, –5.56, –5.60, –5.67.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{35}NO_5Si$: 374.2359; found: 374.2362.

(*R*)-1-*tert*-Butyl 2-Methyl 2-[(*tert*-Butyldimethylsiloxy)methyl]-5-oxopyrrolidine-1,2-dicarboxylate (15)

To a solution of 2-(siloxymethyl)pyrrolidine **14** (13.2 g, 35.4 mmol) in CCl_4–MeCN–H_2O (2:1:1, 230 mL) were added RuO_2 (920 mg, 6.90 mmol) and $NaIO_4$ (37.0 g, 173 mmol) with stirring. The mixture was heated to 40 °C, stirred for 2 h, quenched with *i*-PrOH, and filtered. To the filtrate was added sat. Na_2SO_3 (120 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic layers were washed with brine, dried (anhyd $MgSO_4$), and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc, 50:1 then 10:1) to give **15** as a colorless oil. Yield: 12.9 g (89%); $[\alpha]_D^{26}$ +42.6 (*c* 1.00, $CHCl_3$).

The analytical data of **15** were identical with those of authentic data reported in the literature {$[\alpha]_D^{25}$ +44.6 (*c* 1.10, $CHCl_3$)}.[4c]

(*R*)-1-*tert*-Butyl 2-Methyl 2-(Hydroxymethyl)-5-oxopyrrolidine-1,2-dicarboxylate (16)

According to the procedure in the literature,[4c] silyl ether **15** (13.7 g, 35.3 mmol) was desilylated using TBAF (1 M in THF, 88.3 mL, 88.3 mmol) in the presence of AcOH (15.2 mL, 264.8 mmol) in THF (150 mL) to give (*R*)-HMPG **16**. Yield: 9.0 g (93%); $[\alpha]_D^{25}$ +29.9 (*c* 1.00, $CHCl_3$).

The analytical data of **16** were identical with those of authentic data reported in the literature {$[\alpha]_D^{25}$ +26.2 (*c* 0.65, $CHCl_3$)}.[4c]

(*R*)-*tert*-Butyl 2-[(*tert*-Butyldimethylsiloxy)methyl]-2-(hydroxymethyl)pyrrolidine-1-carboxylate (17)

To a solution of benzyl ether **9** (10.3 g, 29.5 mmol) in anhyd THF (147 mL) was added $LiBH_4$ (1.29 g, 59.0 mmol) and *i*-PrOH (18.0 mL, 236 mmol) in several portions at 0 °C. The mixture was stirred for 24 h at r.t., quenched with sat. NH_4Cl (130 mL), and extracted with EtOAc (3 × 130 mL). The combined organic layers were washed with brine, dried (anhyd $MgSO_4$), and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc, 30:1 then 20:1) to give (*S*)-*tert*-butyl 2-[(benzyloxy)methyl]-2-(hydroxymethyl)pyrrolidine-1-carboxylate as a colorless oil. Yield: 8.77 g (92%); $[\alpha]_D^{25}$ +37.3 (*c* 0.89, $CHCl_3$).

FTIR (neat): 3396, 2974, 2873, 1954, 1666, 1392, 1122, 740 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.26 (m, 5 H), 5.27 (dd, *J* = 8.8, 2.7 Hz, 1 H), 4.61 (d, *J* = 12.2 Hz, 1 H), 4.51 (d, *J* = 12.2 Hz, 1 H), 3.77 (s, 2 H), 3.72–3.67 (m, 2 H), 3.48–3.42 (m, 1 H), 3.36–3.30

(m, 1 H), 2.15 (ddd, *J* = 12.4, 7.1, 2.7 Hz, 1 H), 1.89–1.78 (m, 1 H), 1.73–1.65 (m, 1 H), 1.53–1.48 (m, 1 H), 1.43 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3, 138.7, 128.2, 127.4, 127.33, 127.28, 80.1, 73.4, 69.7, 68.1, 67.3, 49.2, 33.3, 28.4, 21.9.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{27}NO_4$: 322.2015; found: 322.2017.

To a solution of the resulting alcohol described above (8.77 g, 27.3 mmol) in DMF (136 mL) was added 1*H*-imidazole (2.79 g, 41.0 mmol), and then TBSCl (6.17 g, 41.0 mmol) was added at 0 °C. The mixture was stirred for 20 h at r.t., concentrated under reduced pressure, and diluted with EtOAc (50 mL) and sat. NH_4Cl (130 mL). The mixture was extracted with EtOAc (3 × 130 mL). The combined organic layers were washed with brine, dried (anhyd $MgSO_4$), and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc, 70:1 then 30:1) to give (*R*)-*tert*-butyl 2-[(benzyloxy)methyl]-2-[(*tert*-butyldimethylsiloxy)methyl]pyrrolidine-1-carboxylate as a colorless oil. Yield: 12.0 g (100%); a 4:5 mixture of rotamers in $CDCl_3$; $[\alpha]_D^{30}$ –1.92 (*c* 0.83, $CHCl_3$).

FTIR (neat): 2956, 2931, 2858, 1693, 1389, 1255, 1178, 1097, 829, 775 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.21 (m, 5 H), 4.52 (d, *J* = 12.0 Hz, 4/9 H), 4.50 (br s, 10/9 H), 4.44 (d, *J* = 12.0 Hz, 4/9 H), 4.01 (d, *J* = 9.5 Hz, 5/9 H), 3.80 (d, *J* = 9.5 Hz, 5/9 H), 3.71 (d, *J* = 9.5 Hz, 4/9 H), 3.64–3.57 (m, 2 H), 3.51 (d, *J* = 9.5 Hz, 4/9 H), 3.45–3.20 (m, 2 H), 2.11–2.02 (m, 2 H), 1.77–1.67 (m, 2 H), 1.41 (s, 45/9 H), 1.39 (s, 36/9 H), 0.84 (s, 9 H), –0.02 (br s, 24/9 H), –0.03 (s, 30/9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8, 138.9, 138.4, 128.3, 128.2, 127.42, 127.37, 127.3, 79.2, 78.5, 73.4, 73.3, 72.0, 71.3, 66.9, 66.0, 64.7, 63.6, 49.3, 33.3, 32.0, 28.5, 25.8, 22.3, 21.7, 18.1, –5.45, –5.53, –5.6.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{41}NO_4Si$: 436.2880; found: 436.2885.

To a solution of the resulting silyl ether described above (12.0 g, 27.3 mmol) in MeOH (136 mL) was added 10% Pd/C (1.20 g). The suspension was stirred for 8 h under hydrogen (balloon), diluted with EtOAc (300 mL), and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc, 30:1 then 20:1) to give **17** as a colorless oil. Yield: 8.34 g (88%); $[\alpha]_D^{26}$ –24.4 (*c* 1.20, $CHCl_3$).

FTIR (neat): 3394, 2954, 2931, 2881, 2858, 1920, 1691, 1668, 1392, 1253, 1101, 837, 773 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.25 (dd, *J* = 8.8, 2.4 Hz, 1 H), 4.09 (d, *J* = 10.2 Hz, 1 H), 3.73 (d, *J* = 10.2 Hz, 1 H), 3.72–3.65 (m, 2 H), 3.50–3.35 (m, 2 H), 2.11 (ddd, *J* = 12.7, 7.6, 5.1 Hz, 1 H), 1.95–1.82 (m, 1 H), 1.72–1.66 (m, 1 H), 1.54–1.47 (m, 1 H), 1.45 (s, 9 H), 0.89 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 79.9, 68.3, 62.9, 49.5, 33.3, 28.4, 25.8, 22.0, 18.1, –5.6.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{35}NO_4Si$: 346.2410; found: 346.2417.

(*S*)-2-Benzyl 1-*tert*-Butyl 2-[(*tert*-Butyldimethylsiloxy)methyl]pyrrolidine-1,2-dicarboxylate (18a)

To a solution of oxalyl chloride (1.87 mL, 21.6 mmol) in CH_2Cl_2 (110 mL) was added DMSO (3.20 mL, 43.3 mmol) slowly at –78 °C, and the mixture was stirred for 10 min at the same temperature. To the mixture was added a solution of hydroxymethyl derivative **17** (6.80 g, 19.7 mmol) in CH_2Cl_2 (90.0 mL) at –78 °C. Maintaining this temperature, the mixture was stirred for 45 min and then Et_3N (13.7 mL, 99.0 mmol) was added. After 10 min, the mixture was allowed to warm to r.t. The mixture was quenched with sat. $NaHCO_3$ (150 mL) and extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude aldehyde was subjected to Pinnick oxidation without further purification.

To a solution of the resulting aldehyde in *t*-BuOH (169 mL), H_2O (28.0 mL), and 2-methylbut-2-ene (22.0 mL, 200 mmol) was added NaH_2PO_4 (7.09 g, 59.1 mmol) and $NaClO_2$ (5.32 g, 59.1 mmol) at r.t. The mixture was vigorously stirred at r.t. for 40 min, diluted with H_2O (100 mL), and extracted with EtOAc (3 × 150 mL). The combined organic layers were dried (anhyd $MgSO_4$), filtered, and concentrated under reduced pressure to give the crude acid.

To a solution of the residue in DMF (200 mL) was added K_2CO_3 (3.26 g, 23.7 mmol) and BnBr (2.80 mL, 23.7 mmol) at r.t. The mixture was stirred for 25 min and then was concentrated under reduced pressure. The residue was diluted with EtOAc (150 mL) and H_2O (150 mL), and extracted. The aqueous layer was then extracted with EtOAc (2 × 150 mL). The combined organic layers were washed with brine, dried (anhyd $MgSO_4$), and concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc, 70:1 then 8:1) to give **18a** as a colorless oil. Yield: 6.29 g (71%); a 5:4 mixture of rotamers in $CDCl_3$; $[\alpha]_D^{26}$ –14.6 (*c* 1.25, $CHCl_3$).

FTIR (neat): 3379, 3066, 2954, 2885, 2858, 1738, 1695, 1460, 1392, 1095, 837, 775 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.23 (m, 5 H), 5.21 (d, *J* = 12.4 Hz, 1 H), 5.06 (d, *J* = 12.4 Hz, 5/9 H), 5.03 (d, *J* = 12.4 Hz, 4/9 H), 4.38 (d, *J* = 10.2 Hz, 4/9 H), 4.17 (d, *J* = 10.2 Hz, 5/9 H), 3.92 (d, *J* = 10.2 Hz, 1 H), 3.72–3.65 (m, 5/9 H), 3.60–3.54 (m, 4/9 H), 3.50–3.32 (m, 1 H), 2.40–2.30 (m, 1 H), 2.10–1.78 (m, 3 H), 1.50 (s, 36/9 H), 1.41 (s, 45/9 H), 0.88 (s, 36/9 H), 0.87 (s, 45/9 H), 0.05 (s, 12/9 H), 0.04 (s, 15/9 H), 0.03 (s, 15/9 H), 0.02 (s, 12/9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3, 173.2, 153.6, 153.2, 136.0, 135.5, 128.6, 128.4, 128.2, 128.0, 127.9, 80.0, 79.3, 68.7, 68.3, 66.5, 66.4, 64.1, 63.0, 48.7, 48.6, 35.9, 34.4, 28.4, 28.3, 25.8, 23.7, 23.1, 18.1, –5.4, –5.5, –5.6, –5.7.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{39}NO_5Si$: 450.2672; found: 450.2688.

(*S*)-1-*tert*-Butyl 2-Methyl 2-[(*tert*-Butyldimethylsiloxy)methyl]pyrrolidine-1,2-dicarboxylate (18b)

To a solution of benzyl ester **18a** (59.5 mg, 0.13 mmol) in MeOH (1.3 mL) was added K_2CO_3 (101 mg, 0.73 mmol) at r.t. The mixture was refluxed for 24 h, cooled to r.t., diluted with EtOAc (10 mL), and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc, 25:1 then 15:1) to give **18b** as a colorless oil. Yield: 42.0 mg (94%); $[\alpha]_D^{26}$ –34.1 (*c* 0.80, $CHCl_3$).

The analytical data of **18b** were identical with those of *R*-enantiomer **14**, except for the optical rotation {$[\alpha]_D^{24}$ –34.5 (*c* 1.05, $CHCl_3$)}.

(*S*)-2-Benzyl 1-*tert*-Butyl 2-[(*tert*-Butyldimethylsiloxy)methyl]-5-oxopyrrolidine-1,2-dicarboxylate (19)

To a solution of benzyl ester **18a** (2.44 g, 5.43 mmol) in CCl_4–MeCN–H_2O (27 mL, 2:1:1) were added RuO_2 (143 mg, 1.08 mmol) and $NaIO_4$ (5.81 g, 27.1 mmol). The mixture was stirred for 3.5 h, quenched with *i*-PrOH, and filtered. To the filtrate was added sat. Na_2SO_3 (15 mL) to quench the excess amount of oxidants, and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine, dried (anhyd $MgSO_4$), and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (hexane–EtOAc, 30:1 then 20:1) to give **19** as an amorphous solid. Yield: 1.92 g (76%); $[\alpha]_D^{28}$ –21.3 (*c* 1.07, $CHCl_3$).

FTIR (neat): 2956, 2937, 2887, 2857, 2359, 2341, 1793, 1743, 1715, 1558, 1472, 1456, 1369, 1313 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.39 (m, 5 H), 5.19 (d, *J* = 12.2 Hz, 1 H), 5.13 (d, *J* = 12.2 Hz, 1 H), 4.31 (d, *J* = 10.5 Hz, 1 H), 4.00 (d, *J* = 10.5 Hz, 1 H), 2.69 (ddd, *J* = 17.4, 10.3, 8.7 Hz, 1 H), 2.47 (ddd, *J* = 17.4, 10.6, 4.2 Hz, 1 H), 2.26 (ddd, *J* = 12.8, 10.3, 4.2 Hz, 1 H), 2.05 (ddd, *J* = 12.8, 10.6, 8.7 Hz, 1 H), 1.44 (s, 9 H), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.03 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2. 171.2, 149.4, 135.0, 128.7, 128.6, 128.4, 83.6, 68.9, 67.2, 64.9, 31.6, 27.9, 26.8, 25.8, 18.1, –5.58, –5.60.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{38}NO_6Si$]: 464.2468; found: 464.2473.

(*S*)-2-Benzyl 1-*tert*-Butyl 2-(Hydroxymethyl)-5-oxopyrrolidine-1,2-dicarboxylate (20)

In a similar manner to that reported in the literature,[4c] silyl ether **19** (2.74 g, 5.91 mmol) was desilylated using TBAF (1 M in THF, 14.8 mL, 14.8 mmol) in the presence of AcOH (2.5 mL, 44.3 mmol) in THF (15 mL) to give (*S*)-HMPG **20** as a white solid. Yield: 1.80 g (87%); mp 97–98 °C; $[\alpha]_D^{23}$ –4.50 (*c* 1.10, $CHCl_3$).

FTIR (neat): 3490, 2979, 1784, 1740, 1456, 1370, 1308, 1258 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.28–7.35 (m, 5 H), 5.22 (d, *J* = 12.1 Hz, 1 H), 5.15 (d, *J* = 12.1 Hz, 1 H), 4.17 (d, *J* = 11.5 Hz, 1 H), 3.94 (d, *J* = 11.5 Hz, 1 H), 2.33–2.79 (m, 3 H), 2.01–2.11 (m, 1 H), 1.43 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 172.0, 149.7, 134.7, 128.7, 128.6, 128.4, 84.3, 68.6, 67.5, 64.5, 30.7, 27.8, 25.2.

HRMS (FAB): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{23}NO_6$: 350.1604; found: 350.1597.

Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N: 4.01. Found: C, 61.84; H, 6.63; N: 4.00.

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