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EFFICIENT SYNTHESES OF (*S*)-4-HYDROXY-2-PYRROLIDINONE DERIVATIVES

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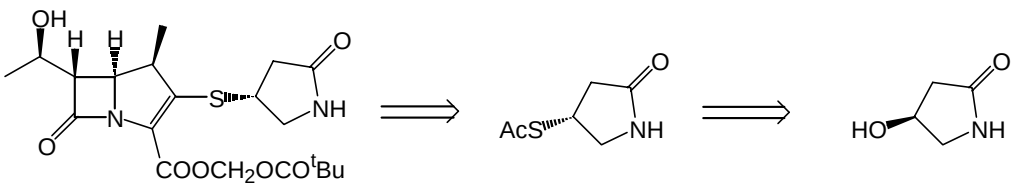
Abstract – Efficient syntheses of (*S*)-4-hydroxy-2-pyrrolidinone ((*S*)-**2**) and (*R*)-4-acetylthio-2-pyrrolidinone (**5**), which are key intermediates of oral carbapenem CS-834, were studied. The most efficient route to (*S*)-**2** from (*S*)-3-hydroxybutyrolactone (**8**) was accomplished in high yield *via* (*S*)-*N*-allyl-3-(1-ethoxy)ethoxy-4-hydroxybutyramide (**14**).

Since 1β-methylcarbapenem was found to enhance renal dehydropeptidase-I (DHP-I) stability compared to 1-H carbapenem,[1] parenteral and oral 1β-methylcarbapenems have been extensively studied.[2] In a preceding paper,[3] we described that a novel oral 1β-methylcarbapenem, CS-834 (**1**), showed excellent antibacterial activity and high DHP-I stability. Moreover, it was interesting that CS-834 was chemically more stable than cephalosphorins in phosphate buffer solution (pH 6.86).[4] CS-834 is undergoing phase II clinical trials as the first oral carbapenem in the world. So we focused our attention on the synthesis of the CS-834 side chain intermediate (*S*)-4-hydroxy-2-pyrrolidinone ((*S*)-**2**) which was known as cyclic γ-aminobutiric acid (GABA) analog.[5] Several methods for the synthesis of optically active compound ((*S*)-**2**) were studied, which involved amination and cyclization[6a,b] of ethyl (*S*)-4-chloro-3-hydroxybutanoate obtained by enzymatic[6b] or asymmetric reduction[7a] of the keto derivative or by microbial optical resolution.[7b] A novel method using (*S*)-malic acid dimethyl ester[8] as stating material were reported very recently. In this paper, we describe efficient syntheses of the key intermediates, (*S*)-4-hydroxy-2-pyrrolidinone ((*S*)-**2**) and (*R*)-4-acetylthio-2-pyrrolidinone (**5**).

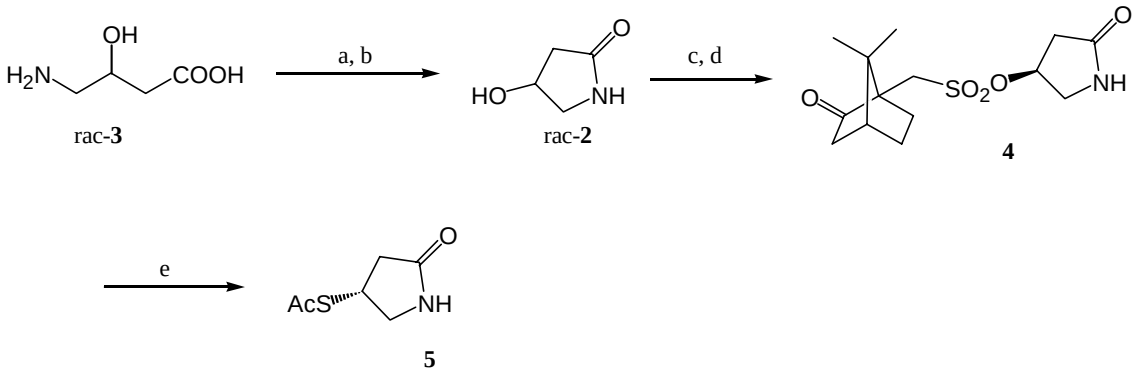


CS-834 (**1**) **5** (*S*)-**2**

Two methods using optical resolution of racemic compounds and chiral starting material were investigated. An optical resolution method was employed first. Racemic 4-hydroxy-2-pyrrolidinone (rac-

2) was prepared from 4-amino-3-hydroxybutyric acid (rac-**3**) by Pellegata's method[9] using hexamethyldisilazane in xylene in the presence of a catalytic amount of chlorotrimethylsilane followed by acidic hydrolysis (Scheme 1). Rac-**2** was converted into (+)-10-camphorsulfonate (**4**: diastereomeric mixture) and then recrystallization of **4** from ethyl acetate gave the desired optically pure isomer (*S*)-**4** in 17% yield. Treatment of (*S*)-**4** with potassium thioacetate afforded (*R*)-4-acetylthio-2-pyrrolidinone (**5**) in 76% yield. Overall yield of **5** from **3** was 10% in five steps.

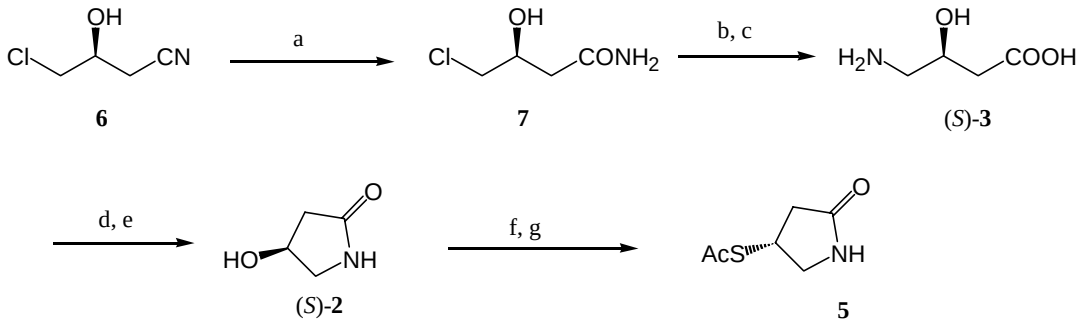
Scheme 1



rac-**3** rac-**2** **4** **5**

Reagents; a) hexamethyldisilazane, TMSCl (cat), reflux in xylene, 8 h; b) 1N-HCl; c) (1*S*)-(+)-10-camphor-sulfonyl chloride; d) recrystallization from EtOAc; e) AcSK / MeCN.

Scheme 2



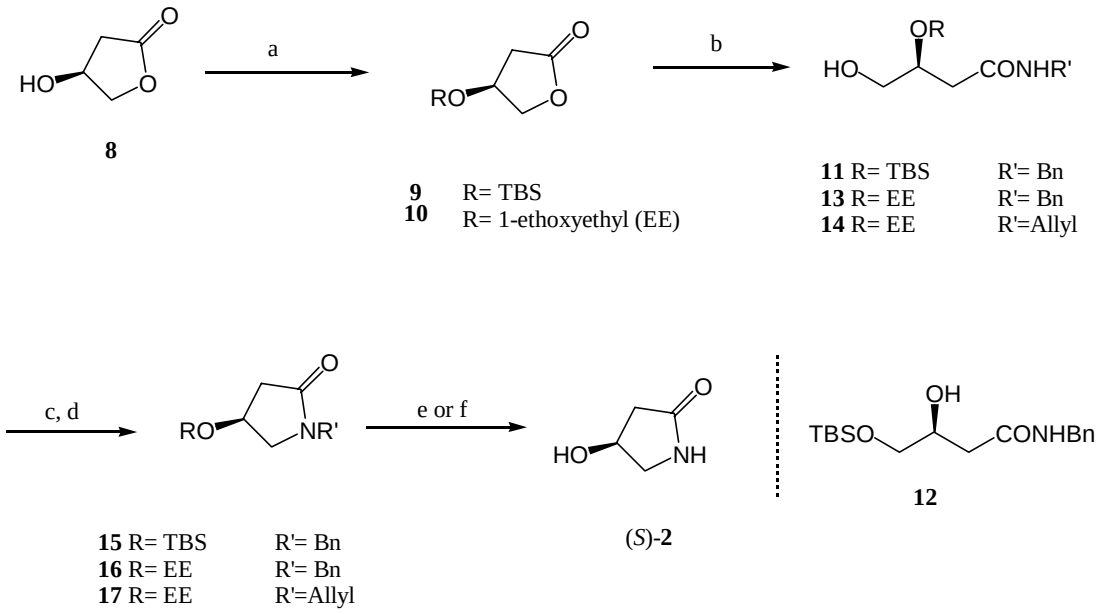
6 **7** (*S*)-**3** (*S*)-**2** **5**

Reagents; a) H_2O_2 / 2 M aq. NaOH; b) 29% aq. NH_3 in a sealed tube, 120 ^oC, 8 h; c) ion-excahnge resin IRA-120 (H^+); d) hexamethyldisilazane, TMSCl (cat), reflux in xylene, 8 h; e) 1N-HCl; f) MsCl / pyridine; g) AcSK / MeCN.

Next, more versatile synthetic routes using chiral starting material were examined. At first, a more efficient method of preparation of optically pure **3** was investigated as shown in Scheme 2, because the optical resolution of rac-**3** using tartaric acid was very low yield and not suitable for large scale preparation. Commercially available (*S*)-4-chloro-3-hydroxybutyronitrile (**6**) was converted into amide compound (**7**) in 55% yield by oxidative hydrolysis. Amination of **7** with aqueous ammmonia and subsequent hydrolysis with ion exchange resin (acid form) gave optically pure (*S*)-4-amino-3-

hydroxybutyric acid ((*S*)-**3**) in 80% yield. The conversion of (*S*)-**3** into (*S*)-**2** was achieved in 88% yield by Pellegata's method.[9] Mesylation of (*S*)-**2** followed by treatment with potassium thioacetate in acetonitrile gave thioacetate (**5**) in 57% yield. The whole conversion yield from **6** to **5** was 22% using this route.

Scheme 3



Reagents; a) **9**: TBSCl, imidazole / DMF, 60 ^{o}C, 2 h; **10**: ethyl vinyl ether, PPTS / CH_2Cl_2, rt; b) **11** and **13**: benzylamine 50 ^{o}C, 2 h, neat; **14**: allylamine, 40 ^{o}C, 4 h, neat; c) MsCl, Et_3N / THF, 0 ^{o}C; d) $KN(TMS)_2$, 18-crown-6 (0.2 eq) / THF, -78 ^{o}C or NaH, 18-crown-6 (0.2 eq) / DMF, rt; e) Li, liq. NH_3, -70 ^{o}C, then 0.1M HCl-MeOH; f) $RhCl_3 \cdot 3H_2O$ (2 mol%), reflux in EtOH, 2 h, then reflux in AcOH-H_2O (1:1), 22 h.

On the other hand, another route using commercially available (*S*)-3-hydroxy-γ-butyrolactone (**8**) was studied as shown in Scheme 3. The protection of **8** with *t*-butyldimethylchlorosilane (TBSCl) or ethyl vinyl ether gave protected lactones (**9**) and (**10**) in 99 and 100% yields, respectively. The ring cleavages of **9** and **10** with benzylamine or allylamine afforded amide compounds (**11**, **13** and **14**) in 83, 92 and 92% yields, respectively. In the case of the silyl ether compound (**9**), a considerable amount of silyl migration to the 4-hydroxy group was observed to give a 4-silyl compound (**12**) in 15% yield. Mesylation of **11**, **13** and **14** led to corresponding mesylate and successive cyclization of mesylates using sodium hydride or potassium bis(trimethylsilyl)amide ($KN(TMS)_2$) in the presence of a catalytic amount of 18-crown-6 afforded γ-lactams (**15**, **16** and **17**) in 91, 88 and 84% yields, respectively. The final step in this route was deprotection of the *N*- and *O*-protecting groups. Deprotection of the benzyl group of **16** with Li in liquid NH_3 and subsequent acidic hydrolysis led to (*S*)-4-hydroxy-2-pyrrolidinone ((*S*)-**2**) in 72% yield. *N*-Allyl compound (**17**) was treated with $RhCl_3 \cdot 3H_2O$ in ethanol and successive acidic hydrolysis in aqueous AcOH afforded (*S*)-**2** in 80% yield. In the case of the *N*-allyl and *O*-1-ethoxyethyl protecting groups, the most effective conversion from **8** to (*S*)-**2** was accomplished *via* **14** and **17** in 65% overall yield.

In summary, the most efficient route for (*S*)-4-hydroxy-2-pyrrolidinone ((*S*)-**2**), which is a key intermediate of oral carbapenem CS-834, was achieved in 65% overall yield from (*S*)-3-hydroxybutyrolactone (**8**).

EXPERIMENTAL

General Methods

IR spectra were recorded on a Jasco FT-IR 8300 or 8900 spectrophotometer. NMR spectra were recorded on JEOL EX 270 (270 MHz) or GSX-400 (400 MHz) spectrometer using tetramethylsilane (TMS) or sodium 3-(trimethylsilyl)propionate-d_4 (TSP-d_4) as an internal standard. The melting point was determined using a Yanagimoto micro-melting point apparatus and was not corrected. Optical rotations were obtained with a Jasco DIP-370 polarimeter. Column chromatography was carried out on silica gel 60 (230-400 mesh, Art.9385, Merck) or Cosmosil 75C_{18} PREP (75 μm, Nacalai Tesque, Inc.).

Preparation of (*R*)-4-acetylthio-2-oxopyrrolidine (**5**) from 4-amino-3-hydroxybutyric acid (rac-**3**)

i) 4-Hydroxy-2-oxopyrrolidine (rac-**2**)

4-Hydroxy-2-oxopyrrolidine (rac-**2**) was prepared in 96% yield as crystals according to the following Pellegata's method.[9]

To a suspension of rac-**3** (5.0 g, 42.0 mmol) in xylene (100 mL), hexamethyldisilazane (10.2 g, 62.9 mmol) and trimethylsilyl chloride (100 μL) were added at rt, and then the mixture was refluxed for 8 h. The reaction mixture was evaporated. The crystals were collected and washed with xylene and diisopropyl ether to afford the trimethylsilyl (TMS) ether of rac-**2** (6.18 g, 85%) as colorless crystals. To a solution of TMS ether of rac-**2** (3.52 g, 20.3 mmol) in MeCN (31.5 mL), water (3.5 mL) and 1N-HCl (35 μL) was added at rt and the mixture was stirred for 0.5 h at the same temperature. After evaporation of the mixture and azeotopic removal of trace of water twice with EtOH, the residue was crystallized from EtOH. Resulting crystals were collected and washed with cooled EtOH to afford rac-**2** (1.97 g, 96%) as colorless crystals. mp 117-118 °C ^{1}H NMR (400 MHz, D_2O) δ 2.28 (1H, dd, J = 17.7, 1.6 Hz), 2.77 (1H, dd, J = 17.7, 6.7 Hz), 3.34 (1H, dd, J = 11.8, 1.0 Hz), 3.72 (1H, dd, J = 11.8, 5.2 Hz), 4.60-4.64 (1H, m).

ii) (*S*)-4-[(1*S*)-10-Camphorsulfonyloxy]-2-oxopyrrolidine (**4**)

To a solution of rac-**2** (1.01 g, 10 mmol) in pyridine (50 mL) was added (1S)-(+)-10-camphorsulfonyl chloride (2.63 g, 10.5 mmol) at 0°C, and then the mixture was stirred for 0.5 h at rt. After this mixture was evaporated, the residue was diluted with ethyl acetate. The organic layer was washed twice with brine and dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc-MeOH 9:1) to give **4** as a crude product. The crude product was recrystallized from EtOAc-MeOH (95:5) to afford the single isomer **4** (262 mg, 17%) as colorless crystals. mp 114-116 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.87 (3H, s), 1.10 (3H, s), 1.47 (1H, ddd, J = 12.7, 9.2, 3.9 Hz), 1.70 (1H, ddd, J = 9.2, 4.6, 3.9 Hz), 1.97 (1H, d, J = 18.5 Hz), 2.00-2.18 (2H, m), 2.33-2.51(2H, m),

2.63 (1H, dd, J = 18.2, 2.6 Hz), 2.80 (1H, dd, J = 18.2, 6.6 Hz), 3.05 (1H, d, J = 14.8 Hz), 3.52 (2H, d, J = 14.8 Hz), 3.66 (1H, dd, J = 11.9, 1.0 Hz), 3.83 (1H, dd, J = 11.9, 6.0 Hz), 5.41-5.49 (1H, m), 6.01 (1H, s). *Anal*. Calcd for $C_{14}H_{21}NO_5S$: C 53.32, H 6.71, N 4.44, S 10.17. Found: C 53.26, H 6.68, N 4.24, S 10.35.

iii) (*R*)-4-Acetylthio-2-oxopyrrolidine (**5**)

To a solution of **4** (160 mg, 0.507 mmol) in acetonitrile (5 mL) was added potassium thioacetate (90 mg, 0.788 mmol) and then the mixture was refluxed for 5 h. After insoluble materials were removed by filtration, the filtrate was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc-MeOH 97:3) to afford **5** (61 mg, 76%) as crystals. mp 58-59 °C; $[\alpha]_D^{25}$ +45.0° (*c* 1.13, MeOH); IR (KBr) cm^{-1} 1689, 1125; ^1H NMR (400 MHz, $CDCl_3$) δ 2.30 (1H, dd, J = 17.4, 6.0 Hz), 2.35 (3H, s), 2.80 (1H, dd, J = 17.4, 9.1 Hz), 3.31 (1H, dd, J = 10.2, 5.1 Hz), 3.89 (1H, dd, J = 10.2, 7.2 Hz), 4.15-4.23 (1H, m), 7.27 (1H, br s). *Anal*. Calcd for $C_6H_9NO_2S$: C 45.27, H 5.77, N 8.80, S 20.14. Found: C 45.18, H 5.81, N 8.84, S 20.22.

Preparation of (*R*)-4-acetylthio-2-oxopyrrolidine (**5**) from (*S*)-4-chloro-3-hydroxybutyronitrile (**6**)

i) (*S*)-4-Chloro-3-hydroxybutyramide (**7**)

To a 35% H_2O_2 aqueous solution (32 mL) was added **6** (5.0 g, 41.8 mmol) at 0°C and then the mixture was stirred for 3 h at the same temperature. The pH of the mixture was adjusted to 8.5 with 2M aqueous NaOH. After an excess amount of H_2O_2 was decomposed with MnO_2, the insoluble materials were removed by filtration and the filtrate was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc-MeOH 97:3) to afford **7** (3.15 g, 55%) as crystals. mp 69-71 °C; IR (KBr) cm^{-1} 3370, 3192; 1656, 1434, 1407, 1113; ^1H NMR (400 MHz, D_2O) δ 2.53 (1H, dd, J = 14.8, 8.1 Hz), 2.59 (1H, dd, J = 14.8, 4.9 Hz), 3.63 (1H, dd, J = 11.7, 5.9 Hz), 3.73 (1H, dd, J = 11.7, 4.0 Hz), 4.26-4.34 (1H, m), 7.27 (1H, br s). *Anal*. Calcd for $C_4H_8NO_2Cl$: C 34.92, H 5.86, N 10.18, Cl 25.77. Found: C 34.56, H 5.90, N 10.01, Cl 25.97.

ii) (*S*)-4-Amino-3-hydroxybutyric acid ((*S*)-**3**)

To a solution of **7** (9.5 g, 69 mmol) in water (48 mL) was added 29% aqueous NH_3 (475 mL) over 30 min at rt and then the mixture was stirred for 18 h at the same temperature. After the solvent was evaporated, the residue was dissolved in water (400 mL). The aqueous solution was loaded onto an Amberlite IRA-120B column (H^+ form, 200 mL) and the column was washed with 500 mL more of water to remove HCl. This resin was heated to 68 °C for 9 h and after washing with water (200 mL), the column was eluted with 2 M aqueous NH_3 (700 mL). This eluent was evaporated *in vacuo* and the resulting residue was recrystallized from MeOH-water (4:1) to afford (*S*)-**3** (6.58 g, 80%) as colorless crystals. mp 224-226 °C (lit.,[10] 214 °C); $[\alpha]_D^{25}$ +19.8° (*c* 2.27, H_2O) (lit.,[10] $[\alpha]_D^{22}$ +20.1° (*c* 1.7, H_2O)); IR (KBr) cm^{-1} 3149, 2862, 2757, 2190, 1660, 1576, 1390, 1338, 1055; ^1H NMR (400 MHz, D_2O) δ 2.45 (1H, d, J = 6.6 Hz), 2.97 (1H, dd, J = 13.1, 9.4 Hz), 3.18 (1H, dd, J = 13.1, 3.0 Hz), 4.22 (1H, ddd, J = 9.4, 6.6, 3.0 Hz). *Anal*. Calcd for $C_4H_9NO_3$: C 40.33, H 7.62, N 11.76. Found: C 40.07, H 7.54, N 11.86.

iii) (*S*)-4-Hydroxy-2-oxopyrrolidine ((*S*)-**2**)

Using Pellegata's method,[9] (*S*)-**2** (5.4 g, >99% ee) was prepared from (*S*)-**3** (7.3 g, 61.3 mmol) in 88% yield. The ee of (*S*)-**2** was determined by HPLC analysis. The retention time of (*S*)-**2** was 75.4 min on a CHILALPAK AD (4.6 mmϕ x 250 mm; eluent: n-hexane – EtOH 95:5; flow rate: 1 mL/min.; detection; UV, 220 nm), The retention time of (*R*)-**2** was 69.2 min under the same condition. mp 158-161 °C; $[\alpha]_D^{25}$ -54.2° (*c* 1.00, H_2O); IR (KBr) cm^{-1} 3247, 3145, 1672, 1483, 1446, 1416. *Anal*. Calcd for $C_4H_7NO_2$: C 40.33, H 7.62, N 11.76. Found: C 40.07, H 7.54, N 11.86.

iv) (*R*)-4-Acetylthio-2-oxopyrrolidine (**5**)

To a solution of (*S*)-**2** (1.90 g, 18.8 mmol) in pyridine (100 mL) was added dropwise methanesulfonyl chloride (2.26 g, 19.7 mmol) under ice-cooling. The mixture was stirred at rt for 1.5 h, and then the mixture was concentrated by evaporation under reduced pressure. Saturated aqueous $NaHCO_3$ was then added to the mixture and the mixture was concentrated by evaporation under reduced pressure. A mixture of EtOAc-MeOH (1:1) was then added to the resulting residue. The insoluble portion was removed by filtration and the filtrate was concentrated by evaporation under reduced pressure. The residue was chromatographed on silica gel column with EtOAc-MeOH (9:1 to 4:1) as eluent to give a crystalline powder. The powder was recrystallized from EtOAc-MeOH to afford (*S*)-4-methanesulfonyloxy-2-pyrrolidinone (2.44 g, 72%) as crystals. mp 137-139 °C. $[\alpha]_D^{25}$ –35.5° (*c* 1.09, MeOH). IR (KBr) cm^{-1} 1719, 1697, 1659, 1305, 1177, 1171, 1159, 963. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.28 (1H, dd, J = 17.6, 1.8 Hz), 2.71 (1H, dd, J = 17.6, 6.3 Hz), 3.24 (3H, s), 3.37 (1H, d, J = 11.9 Hz), 3.66 (1H, dd, J = 11.9, 5.3 Hz), 5.31-5.34 (1H, m), 7.85 (1H, br s).

To a solution of (*S*)-4-methanesulfonyloxy-2-pyrrolidinone (896 mg, 5.00 mmol) in acetonitrile (90 mL) was added potassium thioacetate (857 mg, 7.50 mmol) and the mixture was then refluxed for 2 h. The insoluble material was removed by filtration and the filtrate was concentrated by evaporation under reduced pressure. The residue was chromatographed on silica gel column with EtOAc-MeOH (96:4) as the eluent to give a powder. The powder was recrystallized from EtOAc-cyclohexane to give **5** as crystals (455 mg, 57%). mp 59-60 °C. $[\alpha]_D^{25}$ +47.3° (*c* 1.33, MeOH). IR (KBr) cm^{-1} 1689, 1125. *Anal*. Calcd for $C_6H_9NO_2S$: C 45.27, H 5.70, N 8.80, S 20.14. Found: C 45.23, H 5.62, N 8.82, S 19.51.

Preparation of (*S*)-4-hydroxy-2-oxopyrrolidine ((*S*)-**2**) from (S)-3-hydroxy-γ-butyrolactone (**8**)

(*S*)-3-t-Butyldimethylsilyloxy-γ-butyrolactone (**9**)

To a solution of (*S*)-3-hydroxy-γ-butyrolactone (**8**) (2.0 g, 19.6 mmol) and imidazole (10.7 g, 157 mmol) in dimethylformamide (100 mL) was added the solution of *t*-butyldimethylsilyl chloride (8.86 g, 58.8 mmol) in dimethylformamide (10 mL) and then the mixture was stirred for 2 h at 60 °C. The mixture was evaporated under reduced pressure to give an oily residue. After the residue was diluted with EtOAc, the organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography with hexane-EtOAc (9:1) to afford **9** (4.19 g, 99%) as a colorless powder. $[\alpha]_D^{25}$ –46.4° (*c* 2.28, MeOH), IR (KBr) cm^{-1}

2959, 1759, 1181, 1094, 998. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.09 (6H, s), 0.89 (9H, s), 2.44 (1H, dd, J = 17.8, 2.6 Hz), 2.69 (1H, dd, J = 17.8, 5.9 Hz), 4.18 (1H, dd, J = 9.9, 2.6 Hz), 4.38(1H, dd, J = 9.6, 5.0 Hz), 4.59-4.62(1H, m). *Anal*. Calcd for $C_{10}H_{20}O_3Si$: C 55.52, H 9.32. Found: C 55.45, H 9.37.

(*S*)-3-(1-Ethoxy)ethoxy-γ-butyrolactone (**10**)

To a solution of (*S*)-3-hydroxy-γ-butyrolactone (**8**) (2.0 g, 19.6 mmol) in CH_2Cl_2 (40 mL) was added pyridinium *p*-toluenesufonate (246 mg, 0.196 mmol) and ethyl vinyl ether (7.06 g, 98.0 mmol) at rt. The mixture was concentrated under reduced pressure and the residual oil was purified by silica gel column chromatography with hexane-EtOAc (1:2) as the eluent to afford **10** (3.41 g, 100%) as an oil. IR ($CHCl_3$) cm^{-1} 2981, 1783, 1376, 1172. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, t, J = 7.0 Hz), 1.32 (1/2H, d, J = 2.2 Hz), 1.32 (1/2H, d, J = 2.6 Hz), 2.54-2.62 (1H, m), 2.68-2.77 (1H, m), 3.44-3.53 (1H, m), 3.54-3.64 (1H, m), 4.28-4.34 (1H, m), 4.39 (1H, dd, J = 10.1, 5.2 Hz), 4.44 (1H, dd, J = 9.8, 5.4 Hz), 4.56-4.61 (1H, m), 4.76 (1H, q, J = 5.4 Hz), 4.79 (1H, q, J = 5.7 Hz). *Anal*. Calcd for $C_8H_{14}O_4$: C 55.16, H 8.10. Found: C 55.00, H 8.29.

(*S*)-*N*-Benzyl-3-*t*-butyldimethylsilyloxy-4-hydroxybutyramide (**11**)

(*S*)-*N*-Benzyl-4-*t*-butyldimethylsilyloxy-3-hydroxybutyramide (**12**)

To γ-lactone (**9**) (500 mg, 2.31 mmol) was added benzylamine (980 mg, 9.15 mmol) at rt and then the mixture was stirred for 2 h at 50 °C. The reaction mixture was purified by silica gel column chromatography with hexane-EtOAc (1:1) as the eluent to afford **11** (622 mg, 83%) and **12** (115 mg, 15%) as a viscous oil.

11: $[\alpha]_D^{25}$ –4.7° (*c* 1.12, $CHCl_3$), IR (liquid film) cm^{-1} 3306, 2929. 1648, 1547, 1254, 1114, 837, 779. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.08 (3H, s), 0.09(3H, s), 0.85 (9H, s), 2.28 (1H, t, J = 5.8 Hz), 2.49 (2H, d, J = 5.6 Hz), 3.45-3.51 (2H, m), 4.17-4.25 (1H, m), 4.34 (1H, dd, J = 14.6, 5.3 Hz), 4.52(1H, dd, J = 14.6, 6.0 Hz), 6.15 (1H, br), 7.25-7.37 (5H, m). MS (m/z) 323 [M^+].

12: IR (liquid film) cm^{-1} 3307, 2929, 1648, 1549, 1254, 1122, 837, 779. ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.89 (9H, s), 2.35-2.47 (2H, m), 3.30 (1H, d, J = 3.8 Hz), 3.53 (1H, dd, J = 10.0, 6.5 Hz), 3.61 (1H, dd, J = 10.0, 4.8 Hz), 3.98-4.12 (1H, m), 4.46 (2H, d, J = 5.8 Hz), 6.50 (1H, br), 7.21-7.41 (5H, m); MS m/z: 323 [M^+].

(*S*)-*N*-Benzyl-3-(1-ethoxy)ethoxy-4-hydroxybutyramide(**13**)

To γ-lactone (**10**) (1.0 g, 5.74 mmol) was added benzylamine (1.23 g, 11.5 mmol) at rt and then the mixture was stirred for 2 h at 50 °C. The reaction mixture was purified by silica gel column chromatography with EtOAc as the eluent to afford **13** (1.48 g, 92%) as a viscous oil. IR ($CHCl_3$) cm^{-1} 3446, 2985, 1668, 1518, 1054, 964; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 -1.32 (6H, m), 2.33-2.58 (2H, m), 3.41-3.69 (4H, m), 4.09-4.15 (1H, m), 4.37-4.51 (2H, m), 4.68 (1/2H, q, J = 5.2 Hz), 4.79 (1/2H, q, J = 5.3 Hz), 6.09 (1/2H, br), 6.60 (1/2H, br), 7.26-7.35 (5H, m). *Anal*. Calcd for $C_{15}H_{23}NO_4$: C 64.04, H 8.24, N 4.98. Found: C 63.65, H 8.23, N 4.94.

(*S*)-*N*-Allyl-3-(1-ethoxy)ethoxy-4-hydroxybutyramide (**14**)

To γ-lactone **10** (850 g, 4.88 mmol) was added allylamine (557 mg, 9.76 mmol) at rt and then the mixture was stirred for 4 h at 40 °C. The reaction mixture was purified by silica gel column chromatography with EtOAc-MeCN (5:1 to 4:1) as the eluent to afford **14** (1.04 g, 92%) as a viscous oil. IR ($CHCl_3$) cm^{-1} 3450, 2989, 1668, 1519, 1127, 1093, 1054; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (3/2H, t, J = 7.3 Hz), 1.23 (3/2H, t, J = 7.3 Hz), 1.31 (3/2H, d, J = 5.2 Hz), 1.35 (3/2H, d, J = 5.3 Hz), 2.46-2.56 (1H, m), 2.60 (1H, t, J = 6.3 Hz), 2.58-2.70 (1H, m), 3.48-3.74 (4H, m), 3.79 (3H, s), 4.14-4.20 (1H, m), 4.75 (1/2H, q, J = 5.2 Hz), 4.86 (1/2H, q, J = 5.2 Hz), 6.34-6.87 (2H, m), 7.38-7.45 (2H, m). *Anal*. Calcd for $C_{11}H_{21}O_4N$: C 57.12, H 9.15, N 6.06. Found: C 56.84, H 9.56, N 5.83.

(*S*)-*N*-Benzyl-4-*t*-butyldimethylsilyloxy-2-oxopyrrolidine (**15**)

To a solution of **11** (100 mg, 0.309 mmol) in THF (2 mL) was added triethylamine (47 mg, 0.464 mmol) and methanesulfonyl choloride (46 mg, 0.402 mmol) at 0^oC, and then the mixture was stirred for 0.5 h at the same temperature. The precipitates were removed by filtration and washed with THF (3mL). To the filtrate was added 18-crown-6 (16 mg, 0.062 mmol) and 55% NaH (15 mg, 0.618 mol, hexane-washed) at 0^oC and the mixture was stirred for 4 h at rt. The reaction mixture was quenched with saturated aqueous NH_4Cl and diluted with EtOAc (30 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with hexane-EtOAc (3:2) as the eluent to afford **15** (95 mg, 91%) as an oil. $[\alpha]_D^{20}$ +7.7° (*c* 0.58, MeOH), IR ($CHCl_3$) cm^{-1} 2957, 2932, 2858, 1682, 1336, 1096, 1006, 838; ^1H NMR (270 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.85 (9H, s), 2.40 (1H, dd, J = 16.9, 3.3 Hz), 2.67 (1H, dd, J = 17.0, 6.4 Hz), 3.12 (1H, dd, J = 10.4, 2.8 Hz), 3.45 (1H, dd, J = 10.4, 5.9 Hz), 4.37(1H, d, J = 15.1 Hz), 4.41-4.53 (1H, m), 4.59 (1H, d, J = 15.1 Hz), 7.22-7.39 (5H, m). *Anal*. Calcd for $C_{17}H_{27}NO_2Si$: C 66.84, H 8.91, N 4.59. Found: C 66.44, H 8.99, N 4.57.

When potassium bis(trimethylsilyl)amide was used, after the filtration, the mesylate intermediate was treated with 1.3 eq. potassium bis(trimethylsilyl)amide for 1 h in THF at –78 °C (96% yield).

(*S*)-*N*-Benzyl-4-(1-ethoxy)ethoxy-2-oxopyrrolidine (**16**)

By a similar manner as that described for the preparation of **15** from **11**, **16** (124 mg, 88%) was prepared as an oil from **13** (150 mg, 0.533 mmol). IR ($CHCl_3$) cm^{-1} 2993, 2933, 1683, 1443, 1265, 1128, 838; ^1H NMR (400 MHz, $CDCl_3$, TMS) δ 1.14 (3/2H, t, J = 7.0 Hz), 1.17 (3/2H, t, J = 7.0 Hz), 1.27 (3/2H, d, J = 5.1 Hz), 1.28 (3/2H, d, J = 4.6 Hz), 2.50 (1/2H, dd, J = 17.0, 4.0 Hz), 2.54 (1/2H, dd, J = 17.0, 3.9 Hz), 2.69 (1/2H, dd, J = 17.1, 7.3 Hz), 2.73 (1/2H, dd, J = 17.3, 7.3 Hz), 3.19-3.28 (1H, m), 3.35-3.59 (3H, m), 4.38-4.54 (3H, m), 4.67-4.74 (1H, m), 7.23-7.35 (5H, m). MS m/z: 264 $[M+H]^+$.

(*S*)-*N*-Allyl-4-(1-ethoxy)ethoxy-2-oxopyrrolidine (**17**)

By a similar manner as that described for the preparation of **15** from **11**, **17** (77 mg, 84%) was prepared as an oil from **14** (100 mg, 0.432 mmol). IR ($CHCl_3$) cm^{-1} 2991, 2915, 1683, 1444, 1269, 1128; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (3H, t, J = 7.2 Hz), 1.31 (3H, d, J = 5.4 Hz), 2.46 (1/2H, dd, J = 17.3, 4.0 Hz),

2.60 (1/2H, dd, J = 17.4, 4.0 Hz), 2.66 (1/2H, dd, J = 14.8, 7.3 Hz), 2.70 (1/2H, dd, J = 15.0, 7.3 Hz), 3.29-3.36 (1H, m), 3.44-3.64 (3H, m), 3.84-3.98 (2H, m), 4.41-4.47 (1H, m), 4.73-4.78 (1H, m), 5.18-5.23 (2H, m), 5.68-5.78 (1H, m). MS m/z: 214 $[M+H]^+$.

(*S*)-4-Hydroxy-2-oxopyrrolidine ((*S*)-**2**) from **16**

Liquid NH_3 (*ca*.10 mL) was trapped in the solution of **16** (250 mg, 0.949 mmol) in THF (2 mL) and EtOH (0.56 mL) at –70 °C, and Li (52 mg, 7.49 mmol) was added to this solution at the same temperture. After 30 min, NH_4Cl (802 mg, 15.0 mmol) and EtOH (5 mL) were added to the solution and the mixture was concentrated under the reduced pressure. The resulting residue was extracted with CH_2Cl_2 (50 mL) and the organic layer was dried over Na_2SO_4. The solvent was evaporated *in vacuo* to give (*S*)-4-(1-ethoxy)ethoxy-2-oxopyrrolidine (119 mg, 0.687 mmol, 72%) as an oil. This product (20 mg, 0.115 mmol) was diluted with 0.1M HCl-MeOH (2 mL) and the solution was stirred for 1 h at room temperture. The mixture was concentrated under reduced pressure to afford (*S*)-**2** (12.0 mg, 100%) as colorless crystals. mp 158-159 °C; $[\alpha]_D^{25}$ –57.5° (*c* 0.780, H_2O) (lit.[8] $[\alpha]_D^{20}$ –57.8° (*c* 0.780, H_2O)). NMR, mp and HPLC of this compound were identical with those of (*S*)-**2** obtained from (*S*)-**3**.

(*S*)-4-Hydroxy-2-oxopyrrolidine ((*S*)-**2**) from **17**

To a solution of **17** (200 mg, 0.938 mmol) in EtOH (5 mL), $RhCl_3 \cdot 3H_2O$ (4.9 mg, 0.02 mmol) was added and the mixture was refluxed for 2 h. After EtOH was removed by evaporation, AcOH (4 mL) and H_2O (4 mL) were added to the residue and the mixture was refluxed for 22 h. The mixture was concentrated under reduced pressure and the residue was washed with $CHCl_3$. The insoluble portion in $CHCl_3$ was purified by HPLC (column: Nacalai tesque $5C_{18}$-AR 250 mm x 20 mm; eluent H_2O) to afford (*S*)-**2** (76 mg, 80%) as colorless crystals. mp 156-158 °C; $[\alpha]_D^{25}$ –54.4° (*c* 0.825, H_2O); NMR and HPLC of this compound were identical with those of (*S*)-**2** obtained from (*S*)-**3**.

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