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PREPARATION OF (2*R*,4*S*)/(2*S*,4*S*)-4-HYDROXYPIPECOLINIC ACID DERIVATIVES FROM L-(–)-MALIC ACID

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Abstract – Synthetically important 4-hydroxypipecolinic acid derivatives were efficiently prepared from commercially available L-(–)-malic acid. The stereochemistries of the derivatives synthesized by our method were determined by coupling constant analyses with key methine protons on C2 and C4.

Pipecolinic acids, which are not a protenogenic amino acid, are one of synthetically important compounds because of their rigid structural features as seen in some biologically active natural compounds. For examples, representative immunosuppressants such as FK506 (Tacrolimus),[1] rapamycin (Sirolimus)[2] contain a pipecolinic acid fragment as an angle of their characteristic macrocycle. Additionally, oxygenated ones are also incorporated in several natural and unnatural compounds having interesting biological properties. Antibiotic virginiamycin S_2,[3] tumor necrosis factor-α (TNF-α) converting enzyme inhibitor,[4] and peptidemimic HIV protease inhibitor palinavir[5] possess 4-hydroxypipecolinic acid moieties as important backbones (Figure 1). Furthermore, 6-membered pipecolinic acid ring has attracted much attention as a structural replacement of natural 5-membered proline ring in structure-activity relationship studies on pharmaceutical leads.[6] From such interest, many efforts on the syntheses of optically active pipecolinic acid and their substituted congeners have been reported.[7] Among them, synthetic methods for 4-hydroxy derivatives[8] have been well studied because of its high utilities for further derivatization using the hydroxyl group. 4-Amino-,[9] fluoro-,[10] or sulfur-functional groups[11] could be introduced in a few steps from 4-hydroxypipecolinic acids via substitution reaction at C4-position and installation of a carbon side chain[8a] was also possible by oxidation followed by Horner-Wadsworth-Emmons type reaction. We were also interested in the potency of 4-hydroxypipecolinic acids as key synthetic building blocks for biologically active molecules and finally established an efficient synthetic route for them. Herein we

This paper is dedicated to Professor Isao Kuwajima on the occasion of his 77th birthday.

describe the syntheses of (2*R*,4*S*)- and (2*S*,4*S*)-4-hydroxypipecolinic acid derivatives from optically active malic acid, both enantiomers of which are commercially available.

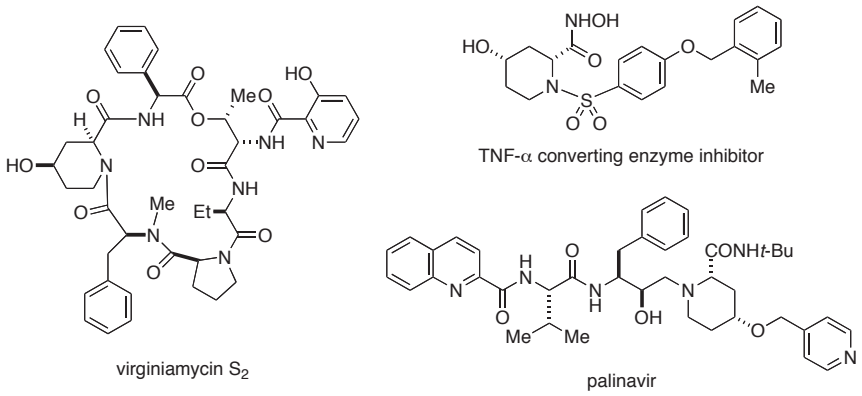
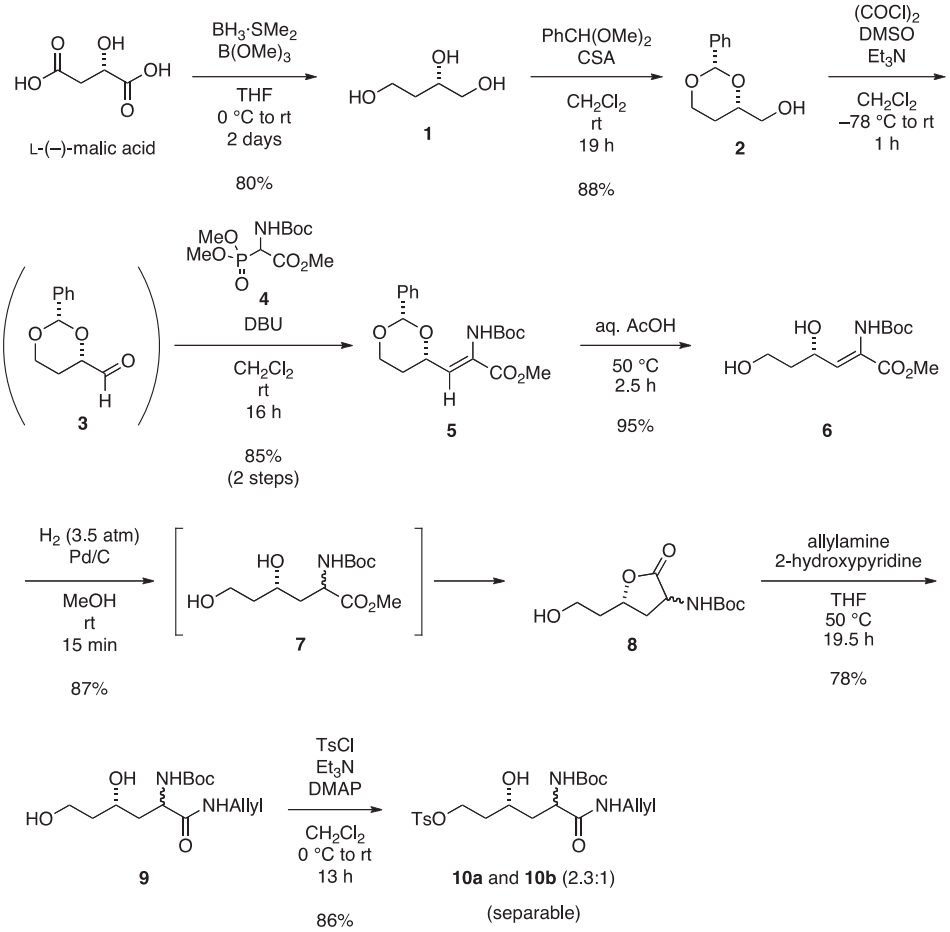


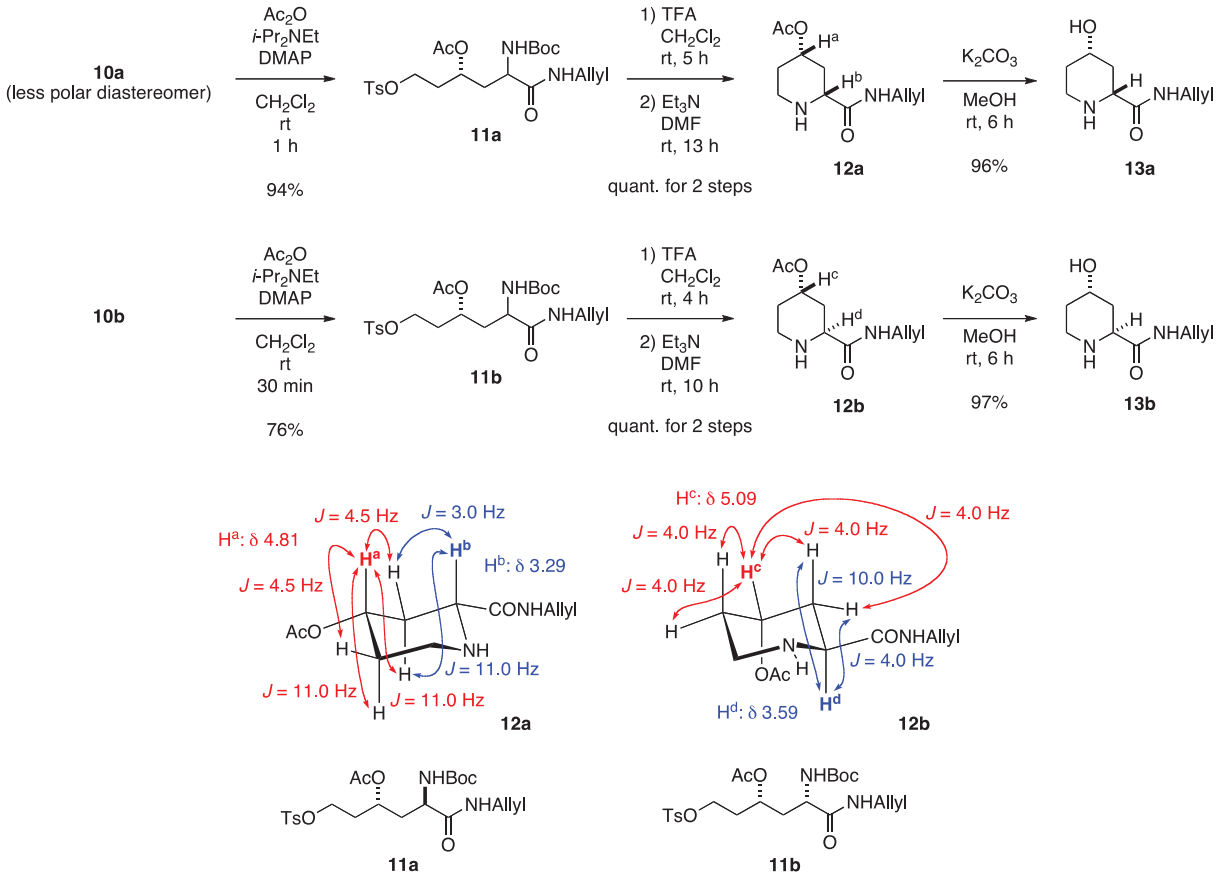
Figure 1. Selected biologically active compounds having 4-hydroxypipecolinic acid fragment



Scheme 1. Preparation of diastereomeric intermediates

As shown in Scheme 1, we started the synthesis of 4-hydroxypipecolinic acid derivatives from inexpensive L-(–)-malic acid. According to the literature methods,[12] we obtained the aldehyde **3** in three

steps via reduction of two carboxyl groups, transacetalization of **1** with benzaldehyde dimethyl acetal followed by oxidation of remained primary hydroxy group in **2**. This aldehyde **3** was coupled with the phosphonate **4**,[13] readily prepared from the known *N*-Cbz precursor, to give dehydroamino acid methyl ester **5** as a single isomer. After cleavage of benzylidene acetal on **5** in weakly acidic media, resultant diol **6** was exposed to hydrogenation reaction under medium pressure (3.5 atm) to afford Boc-protected α-amino acid derivative **7**, which immediately cyclized to give the inseparable diastereomixture of lactone **8**[14] within 87% yield. A cleavage of the lactone ring with allylamine and 2-hydroxypyridine followed by selective tosylation gave the diastereomers **10a** and **10b** (2.3:1), which were easily separated on silica gel column chromatography (R_f = 0.5 and 0.4 respectively with hexanes/AcOEt = 1:2 as eluent).



Scheme 2. Transformation into pipecolinic acid derivatives

After protection of hydroxy group as acetate and subsequent removal of Boc group, less polar diastereomer **10a** was successfully cyclized into a pipecolinic acid derivative **12a** by exposure to Et_3N in DMF (Scheme 2). These conversions proceeded quite effectively in almost quantitative yield for three steps. Similarly, **10b** was uneventfully transformed into **12b**. At this time, the relative stereochemistries of the substituents on **12a** and **12b** were elucidated by coupling constant analyses in the ^{1}H NMR spectra.

For pipecolinic acid **12a**, the coupling constants of methine proton H^a, resonating at 4.81 ppm, appeared as 11.0 and 4.5 Hz. Furthermore, the methine proton H^b, resonating at 3.29 ppm, was observed as a double doublet with *J* values of 11.0 and 3.0 Hz. Thus, these evidences clearly suggested that the protons H^a and H^b occupied axial position in chair conformation; namely **12a** had (2*R*,4*S*)-configurations. On the other hand, methine proton H^d in **12b** appeared at 3.59 ppm coupling with adjacent methylene protons as double doublet with *J* values 10.0 and 4.0 Hz. These protons also coupled with H^c with *J* values 4.0 and 4.0 Hz, respectively. Thus, the proton H^c was equatorially oriented and H^d occupied axial orientation in chair conformation, that is, the configurations for **12b** were determined as (2*S*,4*S*). Finally hydrolysis of **12a** and **12b** correspondingly afforded the 4-hydroxy derivatives **13a** and **13b** which would be applicable for further transformations.

In conclusion, we achieved the novel preparation of (2*R*,4*S*)- and (2*S*,4*S*)-4-hydroxypipecolinic acid derivatives starting from commercially available inexpensive L-(–)-malic acid. The synthetic route disclosed in this study is very concise and high-yielding. Because of the importance of the pipecolinic acid derivatives, further investigations on the stereoselective synthesis and applications to natural product syntheses are ongoing in our laboratory.

EXPERIMENTAL

Materials were obtained from commercial suppliers and used without further purification unless otherwise noted. Anhydrous THF and CH_2Cl_2 were purchased from Kanto Chemical Co., Inc. Anhydrous Et_2O, DMF, DMSO, and MeOH were purchased from Wako Pure Chemical Industries and kept on dried Molecular sieves. Anhydrous *i*-Pr_2NH and Et_3N were dried and distilled according to the standard protocols. Otherwise noted, all reactions were performed using oven-dried glassware, sealed with a rubber septum under a slight positive pressure of argon. Flash column chromatography was carried out using Kanto silica gel 60N (spherical, neutral, 40–50 μm). Analytical TLC was performed on Merck 60 F_{254} glass plates precoated with a 0.25 mm thickness of silica gel. IR spectra were measured on a JASCO FT/IR-460Plus spectrometer. NMR spectra were measured on a VARIAN GEMINI300 spectrometer or a VARIAN UNITY-plus500 spectrometer. For ^1H spectra, chemical shifts were expressed in parts per million (ppm) downfield from internal tetramethylsilane (δ 0), relative internal $CHCl_3$ (δ 7.26 in $CDCl_3$) or internal methanol (δ 3.30 in CD_3OD). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. *J* values were in hertz. For ^{13}C spectra, chemical shifts were expressed in ppm, relative to the central line of a triplet at 77.0 ppm for internal $CDCl_3$. Mass spectra were recorded on a JEOL JMS-GCmate II or JEOL JMS-AX505HAD spectrometer.

(2*S*)-1,2,4-Butanetriol (1).[11] To a stirred solution of $BH_3 \cdot SMe_2$ (16.9 mL, 178 mmol) in THF (37 mL) was added trimethylborate (18.2 mL, 163 mmol) at 0 °C. After stirring for 15 min at the same temperature, L-(–)-malic acid (7.42 g, 55.3 mmol) was added to the solution at 0 °C and the stirring was continued for 2 days at room temperature. After the reaction was quenched with MeOH at 0 °C, the mixture was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH = 10:1) to give the triol **1** (4.67 g, 80%) as a colorless oil. ^{1}H NMR spectrum of this triol was identical with that reported.[11] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (2H, br s), 3.98–3.40 (5H, m), 1.79–1.61 (3H, m).

(2*S*,4*S*)-4-(Hydroxymethyl)-2-phenyl-1,3-dioxane (2).[11] To a stirred solution of triol **1** and benzaldehyde dimethyl acetal (5.31 mL, 35.4 mmol) in CH_2Cl_2 (120 mL) was added CSA (384 mg, 6.10 mmol) at room temperature. After stirring for 19 h at the same temperature, the reaction was quenched with Et_3N and the reaction mixture was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 2:1) to give the acetal **3** (5.65 g, 88%) as a colorless oil. ^{1}H NMR spectrum of this acetal was identical with that reported.[11] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54–7.32 (5H, m), 5.54 (1H, s), 4.30 (1H, dd, *J* = 5.1, 1.2 Hz), 4.03–3.97 (2H, m), 3.68–3.65 (2H, m), 2.17 (1H, br s), 2.00–1.76 (1H, m), 1.48–1.45 (1H, m).

Methyl (*Z*)-2-(*tert*-butoxycarbonylamino)-3-[(2*S*,4*S*)-2-phenyl-1,3-dioxan-4-yl]acrylate (5). To a stirred solution of $(COCl)_2$ (0.107 mL, 1.27 mmol) in CH_2Cl_2 (6.0 mL) was added DMSO (0.181 mL, 2.55 mmol) at –78 °C. After stirring for 10 min at the same temperature, a solution of the acetal **3** (165 mg, 0.850 mmol) in CH_2Cl_2 (2.0 mL) was added to the reaction mixture at –78 °C. After stirring for 30 min at –60 °C, Et_3N (0.540 mL, 3.83 mmol) was added to the reaction mixture. After removal of the cooling bath, the mixture was stirred for 30 min. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous NH_4Cl and water. The organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure to give a crude aldehyde **3**[11] as a pale yellow oil. The crude aldehyde was directly subjected to the next reaction without further purification. ^{1}H NMR spectrum of this crude aldehyde was identical with that reported.[11] ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (1H, s), 7.55–7.34 (5H, m), 5.61 (1H, s), 4.38–4.33 (2H, m), 4.02 (1H, td, *J* = 12.0, 2.6 Hz), 2.02–1.78 (2H, m).

To a stirred solution of phosphonate **4** (278 mg, 0.935 mmol) in CH_2Cl_2 (5.0 mL) was added DBU (0.133 mL, 0.893 mmol) at room temperature. After stirring for 10 min at room temperature, a solution of the above crude aldehyde **3** in CH_2Cl_2 (4.0 mL) was added to the reaction mixture. After stirring for 16 h at room temperature, the mixture was diluted with AcOEt and washed with 1 M aqueous H_2SO_4. The organic phase was dried over $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by

flash column chromatography on silica gel (hexane/AcOEt = 1:1) to give the ester **5** (263 mg, 85% for 2 steps) as a colorless oil. $[\alpha]_D^{20}$ +85.7 (*c* 0.320, $CHCl_3$); IR (neat) 3658, 2928, 1708, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50–7.30 (5H, m), 6.64 (1H, s), 6.28 (1H, d, *J* = 6.3 Hz), 5.58 (1H, s), 4.78–4.84 (1H, m), 4.30 (1H, dd, *J* = 11.7, 4.8 Hz), 4.04 (1H, td, *J* = 11.7, 2.5 Hz), 2.00 (1H, qd, *J* = 11.7, 4.8 Hz), 1.46 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 152.8, 138.0, 128.7, 128.5, 128.1, 128.0, 101.0, 80.8, 74.2, 66.8, 52.5, 29.7, 28.1; MS (EI) *m*/*z* 363 (M^+); HRMS (FAB) calcd for $C_{19}H_{26}NO_6$ $[M+H]^+$ 364.1760, found 364.1770.

Methyl (*S*)-(*Z*)-2-(*tert*-butoxycarbonylamino)-4,6-dihydroxyhex-2-enoate (6). A solution of the ester **5** (2.28 g, 5.19 mmol) in AcOH/H_2O (100 mL, 9:1 v/v) was stirred for 2.5 h at 50 °C. The mixture was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/AcOEt = 1:3) to give the diol **6** (1.36 g, 95%) as a colorless oil. $[\alpha]_D^{20}$ –3.30 (*c* 2.59, $CHCl_3$); IR (neat) 3326, 1710, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.52 (1H, s), 6.42 (1H, d, *J* = 9.3 Hz), 4.58 (1H, td, *J* = 8.7, 4.4 Hz), 3.88–3.75 (5H, m), 1.98–1.72 (2H, m), 1.47 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.1, 154.2, 133.3, 126.1, 81.4, 66.4, 60.1, 52.6, 37.5, 28.1; MS (EI) *m*/*z* 275 (M^+); HRMS (FAB) calcd for $C_{12}H_{22}NO_6$ $[M+H]^+$ 276.1447, found 276.1441.

***tert*-Butyl (3*R*,5*R*)-5-(2-hydroxyethyl)-2-oxotetrahydrofuran-3-ylcarbamate and *tert*-Butyl (3*S*,5*R*)-5-(2-hydroxyethyl)-2-oxotetrahydrofuran-3-ylcarbamate (8).**[14] Under a hydrogen atmosphere (3.5 atm), a suspension of the diol **6** (195 mg, 0.708 mmol) and 10% palladium on activated carbon (113 mg, 0.107 mmol) in MeOH was stirred for 15 min at room temperature. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (AcOEt only) to give the lactone **8**[13] (151 mg, 87%) as a colorless oil. IR (neat) 3361, 1777, 1659 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.18 (1H, br s), 4.89–4.84 (0.5H, m), 4.68–4.58 (0.5H, m), 4.41 (1H, br s), 3.81 (2H, q, *J* = 7.2 Hz), 2.55–2.33 (1H, m), 2.16–1.81 (4H, m), 1.44 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 172.9, 156.3, 155.2, 80.3, 75.6, 75.3, 58.13, 58.11, 52.4, 52.2, 38.3, 38.1, 37.6, 28.2; MS (EI) *m*/*z* 245 (M^+); HRMS (FAB) calcd for $C_{11}H_{20}NO_5$ $[M+H]^+$ 246.1341, found 246.1309.

***tert*-Butyl (2*R*,4*R*)-1-(allylamino)-4,6-dihydroxy-1-oxohexane-2-ylcarbamate and *tert*-Butyl (2*S*,4*R*)-1-(allylamino)-4,6-dihydroxy-1-oxohexane-2-ylcarbamate (9).** To a stirred solution of lactone **8** (91.0 mg, 0.371 mmol) in THF (7.4 mL) were added 2-hydroxypyridine (18.0 mg, 0.182 mmol) and allylamine (282 μL, 3.71 mmol) at room temperature. After stirring for 19.5 h at 50 °C, the reaction mixture was evaporated under reduced pressure. The residue was purified by flash column

chromatography on silica gel ($CHCl_3$/MeOH = 10:1) to give the diol **9** (87.0 mg, 78%) as a colorless oil. IR (neat) 3326, 1704, 1646 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 5.88–5.80 (1H, m), 5.24–5.16 (1H, m), 5.09 (1H, d, *J* = 10.2 Hz), 4.28–4.16 (1H, m), 3.87–3.64 (5H, m), 1.87–1.60 (4H, m), 1.44 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 155.5, 133.53, 133.45, 116.0, 80.1, 79.9, 67.8, 67.5, 60.5, 60.3, 41.7, 40.0, 38.7, 28.2; MS (EI) *m/z* 303 (M^+); HRMS (EI) calcd for $C_{14}H_{27}N_2O_5$ (M^+) 303.1920, found 303.1922.

(3*R*,5*R*) and (3*R*,5*S*)-6-(Allylamino)-5-(*tert*-butoxycarbonylamino)-3-hydroxy-6-oxohexyl 4-methylbenzenesulfonate (10a and 10b). To a stirred solution of the diol **9** (292 mg, 0.965 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.41 mL, 2.9 mmol) and DMAP (6.0 mg, 0.048 mmol) at room temperature. After stirring for 10 min at room temperature, TsCl (294 mg, 1.54 mmol) was added to the mixture at 0 °C. After stirring for 13 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl and the aqueous phase was extracted with AcOEt. The combined organic extracts were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (hexane/acetone = 2:1) to give the tosylates **10a** (263 mg, 60%, pale yellow oil) and **10b** (114 mg, 26%, pale yellow oil). **10a**: $[\alpha]_D^{20}$ –10.5 (*c* 2.18, $CHCl_3$); IR (neat) 3302, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 7.8 Hz), 7.33 (2H, d, *J* = 7.8 Hz), 6.37 (1H, br s), 5.84–5.63 (2H, m), 5.19–5.11 (2H, m), 4.32–4.08 (3H, m), 3.86–3.79 (3H, m), 2.44 (3H, s), 1.81–1.63 (4H, m), 1.44 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 156.6, 144.5, 133.5, 132.6, 129.6, 128.7, 127.6, 125.6, 116.1, 80.3, 67.5, 63.8, 51.3, 41.8, 35.9, 29.2, 28.2, 21.6; MS (EI) *m/z* 456 (M^+); HRMS (FAB) calcd for $C_{21}H_{33}N_2O_7S$ $[M+H]^+$ 457.2009, found 457.1970. **10b**: $[\alpha]_D^{20}$ –2.90 (*c* 2.05, $CHCl_3$); IR (neat) 3327, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 8.1 Hz), 7.34 (2H, d, *J* = 8.1 Hz), 6.69 (1H, br s), 5.85–5.76 (1H, m), 5.44 (1H, br s), 5.22–5.11 (2H, m), 4.31–4.08 (3H, m), 3.89–3.87 (3H, m), 2.45 (3H, s), 1.88–1.74 (4H, m), 1.43 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 155.5, 144.6, 133.4, 132.5, 129.6, 128.7, 127.6, 125.6, 116.1, 80.0, 67.5, 64.5, 51.9, 41.7, 40.1, 36.2, 28.2, 21.6; MS (EI) *m/z* 456 (M^+); HRMS (FAB) calcd for $C_{21}H_{33}N_2O_7S$ $[M+H]^+$ 457.2009, found 457.2020.

(3*R*,5*S*)-6-(Allylamino)-5-(*tert*-butoxycarbonylamino)-6-oxo-1-(tosyloxy)hexan-3-yl acetate (11a). To a stirred solution of tosylate **10a** (21.5 mg, 0.0471 mmol) in CH_2Cl_2 (0.3 mL) were added *i*-Pr_2NEt (8.3 μL, 0.048 mmol), DMAP (1.0 mg, 0.0080 mmol), and acetic anhydride (7.6 μL, 0.080 mmol) at room temperature. After stirring for 1 h at the same temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was

purified by flash column chromatography on silica gel (hexane/AcOEt = 1:2) to give the acetate **11a** (22.1 mg, 94%) as a colorless oil. $[\alpha]_D^{20}$ +2.10 (*c* 1.20, $CHCl_3$); IR (neat) 3304, 1741, 1716, 1652 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 8.1 Hz), 7.34 (2H, d, *J* = 8.1 Hz), 6.38 (1H, br s), 5.87–5.75 (1H, m), 5.21–4.95 (4H, m), 4.15–4.02 (3H, m), 3.86 (2H, br s), 2.45 (3H, s), 2.15–1.81 (7H, m), 1.43 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.2, 144.7, 133.4, 132.5, 129.7, 127.7, 116.3, 61.2, 66.4, 58.9, 52.2, 41.8, 33.7, 28.2, 21.6, 20.9; MS (EI) *m/z* 498 (M^+); HRMS (FAB) calcd for $C_{23}H_{35}N_2O_8S$ $[M+H]^+$ 499.2114, found 499.2118.

(2*R*,4*S*)-2-(Allylaminocarbonyl)piperidin-4-yl acetate (12a). To a stirred solution of acetate **11a** (19.0 mg, 0.0381 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (124 μL, 1.67 mmol) at room temperature. After stirring for 5 h at the same temperature, the reaction mixture was evaporated under reduced pressure. The residue was diluted with DMF (1.0 mL) and Et_3N (6.4 μL, 0.0046 mmol) was added at room temperature. After stirring for 13 h, the mixture was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel ($CHCl_3$/MeOH = 5:1) to give the piperidine **12a** (11.0 mg, quant.) as a white solid. $[\alpha]_D^{20}$ –19.5 (*c* 0.570, $CHCl_3$); IR (neat) 3291, 1731, 1652 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (1H, s), 5.86–5.78 (1H, m), 5.19–5.12 (2H, m), 4.81 (1H, tt, *J* = 11.0, 4.5 Hz), 3.91–3.84 (2H, m), 3.29 (1H, dd, *J* = 11.0, 3.0 Hz), 3.16 (1H, dt, *J* = 12.5, 4.0 Hz), 2.72 (1H, td, *J* = 12.5, 3.0 Hz), 2.36–2.31 (1H, m), 2.02 (3H, s), 1.99–1.94 (1H, m), 1.49–1.39 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 170.3, 134.0, 116.4, 76.7, 70.5, 58.7, 43.2, 41.4, 35.1, 31.6, 21.2; MS (EI) *m/z* 226 (M^+); HRMS (EI) calcd for $C_{11}H_{18}N_2O_3$ (M^+) 226.1318, found 226.1353.

(2*R*,4*S*)-2-Allylaminocarbonyl-4-hydroxypiperidine (13a). To a stirred solution of acetate **12a** (13.4 mg, 0.0973 mmol) in MeOH (1.0 mL) was added potassium carbonate (9.8 mg, 0.071 mmol) at room temperature. After stirring for 6 h at the same temperature, the reaction mixture was purified directly by flash column chromatography on silica gel (CH_2Cl_2/MeOH = 5:1) to give the alcohol **13a** (8.6 mg, 96%) as a colorless oil. $[\alpha]_D^{20}$ +18.3 (*c* 0.430, $CHCl_3$); IR (neat) 3384, 2928, 1659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.90 (1H, br s), 5.86–5.79 (1H, m), 5.20–5.12 (2H, m), 3.88–3.84 (2H, m), 3.75 (1H, tt, *J* = 11.0, 4.5 Hz), 3.25 (1H, dd, *J* = 11.0, 3.0 Hz), 3.14 (1H, dt, *J* = 12.5, 4.0 Hz), 2.66 (1H, td, *J* = 12.5, 3.0 Hz), 2.31–2.28 (1H, m), 1.91–1.87 (1H, m), 1.44–1.34 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 133.9, 116.3, 68.2, 58.7, 44.2, 41.5, 38.8, 35.0; MS (EI) *m/z* 184 (M^+); HRMS (EI) calcd for $C_9H_{16}N_2O_2$ (M^+) 184.1212, found 184.1215.

(3*R*,5*R*)-6-(Allylamino)-5-(*tert*-butoxycarbonylamino)-6-oxo-1-(tosyloxy)hexan-3-yl acetate (11b). According to the same procedure described for **11a**, acetate **11b** was synthesized from **10b** in 0.0672

mmol scale (37.1 mg, 76%, colorless oil). $[\alpha]_D^{20}$ –5.8 (*c* 0.70, $CHCl_3$); IR (neat) 3316, 1739, 1714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.4 Hz), 7.35 (2H, d, *J* = 8.4 Hz), 6.74 (1H, br s), 5.87–5.76 (1H, m), 5.36 (1H, br s), 5.24–5.12 (2H, m), 5.02–4.96 (1H, m), 4.13–3.98 (3H, m), 3.90–3.86 (2H, m), 2.45 (3H, s), 2.04–1.93 (7H, m), 1.43 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 171.2, 144.7, 133.3, 132.3, 129.7, 129.2, 127.7, 116.4, 67.9, 66.0, 58.0, 51.2, 41.8, 37.6, 31.2, 28.3, 21.6, 21.0; MS (EI) *m/z* 498 (M^+); HRMS (FAB) calcd for $C_{23}H_{35}N_2O_8S$ $[M+H]^+$ 499.2114, found 499.2103.

(2*S*,4*S*)-2-(Allylaminocarbonyl)piperidin-4-yl acetate (12b). According to the same procedure described for **12a**, acetate **12b** was synthesized from **11b** in 0.0477 mmol scale (13.8 mg, quant., white solid). $[\alpha]_D^{20}$ +1.7 (*c* 0.41, $CHCl_3$); IR (neat) 3318, 1722, 1660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (1H, br s), 5.87–5.79 (1H, m), 5.20–5.12 (2H, m), 5.09 (1H, quint, *J* = 4.0 Hz), 3.89–3.86 (2H, m), 3.59 (1H, dd, *J* = 10.0, 4.0 Hz), 2.99 (1H, dt, *J* = 12.0, 4.0 Hz), 2.89 (1H, dt, *J* = 12.0, 4.0 Hz), 2.08–2.04 (4H, m), 1.82–1.68 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 169.9, 133.8, 116.2, 67.4, 55.5, 41.4, 40.6, 33.6, 30.2, 21.3; MS (EI) *m/z* 226 (M^+); HRMS (EI) calcd for $C_{11}H_{18}N_2O_3$ (M^+) 226.1318, found 226.1282.

(2*S*,4*S*)-2-Allylaminocarbonyl-4-hydroxypiperidine (13b). According to the same procedure described for **13a**, acetate **13b** was synthesized from **12b** in 0.034 mmol scale (6.3 mg, 97%, colorless oil). $[\alpha]_D^{20}$ –11.1 (*c* 0.330, $CHCl_3$); IR (neat) 3410, 2927, 1644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.13 (1H, br s), 5.86–5.79 (1H, m), 5.19–5.11 (2H, m), 4.04–4.00 (1H, m), 3.88 (2H, t, *J* = 6.0 Hz), 3.70–3.68 (1H, m), 3.11–3.06 (1H, m), 2.79–2.74 (1H, m), 2.04–2.00 (1H, m), 1.84–1.78 (1H, m), 1.75–1.69 (1H, m), 1.55–1.49 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 134.0, 116.2, 64.7, 55.3, 41.5, 40.6, 36.8, 33.7; MS (EI) *m/z* 184 (M^+); HRMS (EI) calcd for $C_9H_{16}N_2O_2$ (M^+) 184.1212, found 184.1216.

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