Convenient Synthesis of Optically Pure α-Mono and α,α-Disubstituted β-Amino Acids

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Optically pure α-mono- and α,α-disubstituted β-amino acids were conveniently prepared in four steps and in 27-40% overall yields from the correspondingly substituted racemic β-hydroxy acids that can be readily obtained from diethyl malonate. In the synthesis, (*S*)-phenylethylamine has been used as a resolving agent and as a source of the amino group in the β-amino acids.

Key Words : α-Monosubstituted β-amino acids, α,α-Disubstituted β-amino acids, β-Lactams, (*S*)-Phenylethylamine

Introduction

β-Amino acids and their cyclyzed derivatives such as β-lactams have received much attention in recent years owing to their interesting biological activities.[1] A variety of pharmacologically important natural products such as paclitaxel,[2] dolastatins,[3] and jasplakinolide[4] contain β-amino acids as a constituent. β-Amino acids are also found in proteins although in much less abundance compared with α-amino acids. Oligomers of β-amino acids have been the subject of intensive research because of their interesting folding patterns.[5] Accordingly, numerous synthetic strategies for the preparation of β-amino acids have been reported.[6]

Recently, we reported a convenient synthesis of optically active α- and β-disubstituted amino acids from the corresponding β-hydroxy carboxylic acids.[7] We now wish to report synthesis of enantiomerically pure α-mono and α,α-disubstituted β-amino acids from the correspondingly substituted racemic β-hydroxy acids that can be readily obtained from diethyl malonate. In the present synthesis, (*S*)-phenylethylamine is employed as a source for the amino group in the β-amino acids and as a resolving agent to yield readily separable diastereoisomeric amide intermediates which can be readily transformed into the target compounds.

The synthetic route is shown in Scheme 1. β-Hydroxy acids (**1**) were coupled at room temperature with (*S*)-phenylethylamine using 1-(dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) in the presence of 1-hydroxybenzotriazole hydrate (HOBT) and triethylamine in methylene chloride solution to give **2** in excellent yield. The amide mixture (**2**) thus obtained in a diastereoisomeric mixture (about 1 : 1 ratio) was separated readily by flash column chromatography to yield **2** in an optically pure form. In the cases of **2a** and **2c**, the diastereomers were more easily separated as β-lactams in the subsequent step. Conversion of **2** into β-lactams **3** was effected in excellent yield by mesylation of the hydroxyl followed by treatment with sodium hydride in DMF. The lactam formation reaction under the Mitsunobu conditions was effective only in the case of **2d** and **2e**. The β-lactams were then hydrolyzed under the acidic conditions using 6 N HCl to give *N*-alkylated β-amino acids that were subjected to hydrogenolysis in methanol containing a small amount of acetic acid and palladium hydroxide on charcoal.[8] The resulting β-amino acids in the form of HCl salt were converted into a salt free form by treatment with DOWEX ion exchange resin. The stereochemical assignments for the β-amino acids thus obtained were made by comparing their specific rotations with those of respective authentic compounds reported in the literature (Table 1), and the stereochemistry of each intermediate in the syntheses was accordingly established. The α-mono and α,α-disubstituted racemic β-hydroxy acids used for the present synthesis were readily prepared, as illustrated in Scheme 2, starting 2-mono or 2,2-disubstituted 1,3-propanediol that were obtained from diethyl malonate.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and were uncorrected. IR spectra were recorded on a Bruker Equinox 55 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker AM 300 (300 MHz) NMR spectrometer using tetramethylsilane as the internal standard. Mass spectral data were obtained with Micro Mass Platform II 8410E spectrometer. Optical rotations were measured on a Rudolp Research Autopol III digital polarimeter. Silica gel 60 (230-400 mesh) was used for flash chromatography and thin layer chromatography (TLC) was carried out on silica coated glass sheets (Merck silica gel 60 F-254). Elemental analyses were performed at Pohang University of Science and Technology, Pohang, Korea.

(2*R*,1'*S*)- and (2*S*,1'*S*)-2-Hydroxymethyl-3-methyl-*N*-(1'-phenylethyl)butyramide ((2*R*,1'*S*)- and (2*S*,1'*S*)- and 2b). 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydro-

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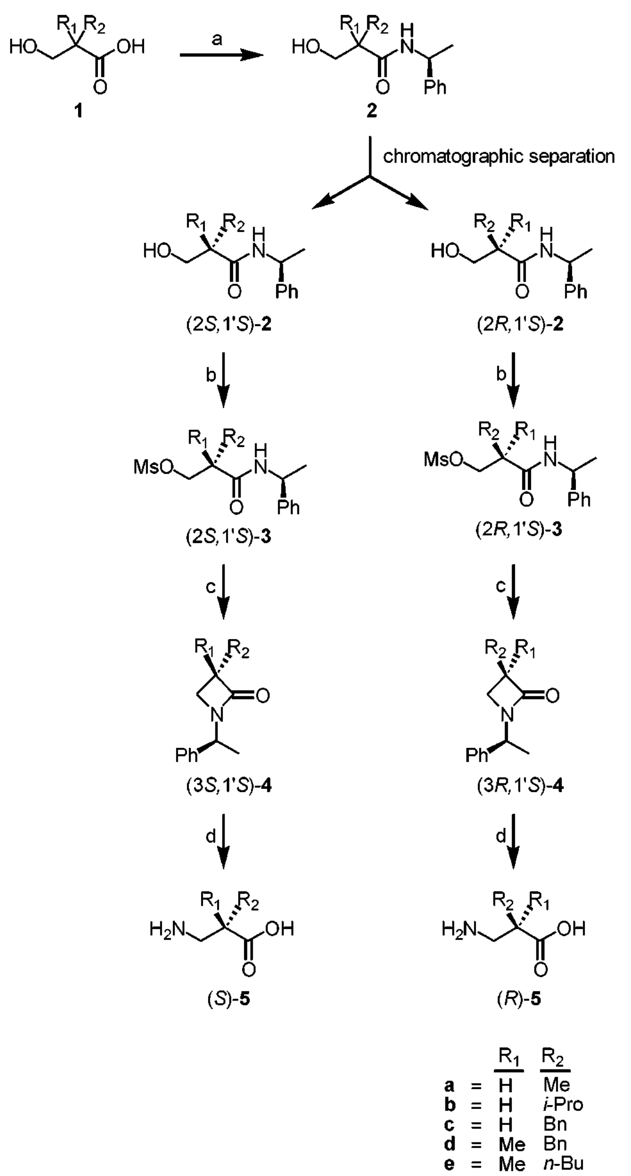


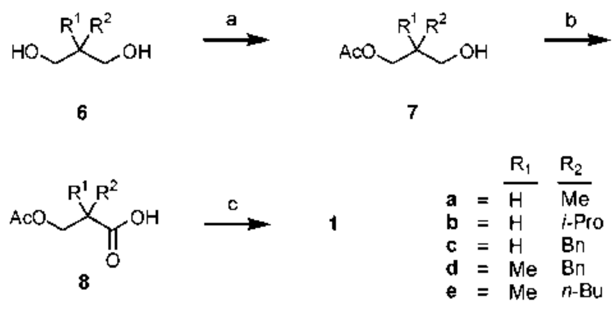
Scheme 1. (a) (*S*)-phenylethylamine, EDCl, HOBT, Et_3N, rt, 1 h, >90%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; (c) NaH, DMF, rt, 4 h, >90% (two steps); (d) (i) 6 N HCl, reflux, 6 h (ii) $Pd(OH)_2$, H_2 (3 atm), $MeOH/H_2O/AcOH$, (iii) DOWEX resin, >86% (three steps).

chloride (1.88 g, 9.8 mmol), 1-hydroxybenzotriazole hydrate (1.32 g, 9.8 mmol), and Et_3N (1.5 mL, 10.8 mmol) were added to the stirred solution of **1b** (1.30 g, 9.8 mmol) in CH_2Cl_2 at 0 °C, and the solution was stirred for 10 min. (*S*)-Phenylethylamine (1.39 mL, 10.8 mmol) was added to the reaction mixture at 0 °C, and the mixture was stirred for 1 h at room temperature. The solution was washed with 10% aqueous solution of citric acid, saturated aqueous $NaHCO_3$ solution, and brine, and the organic layer was dried over $MgSO_4$. The dried solution was concentrated under reduced pressure to give the crude product (2.22 g, 96%) as a white solid in a diastereomeric mixture which was separated into (2*R*,1'S)-**2b** (0.92 g, 40%) and (2*S*,1'*S*)-**2b** (1.05 g, 45%) by flash column chromatography (hexane/EtOAc = 4/1 to 2/1). The analytical samples were prepared by recrystallization

Table 1. Physical properties of final products

Compound	mp (°C) (lit.)	$[\alpha]_D$ (lit.)
(*R*)-**5a**	187-189 (192-194)[a]	−16.5 (−15.4)[a]
(*S*)-**5a**	187-189 (192-194)[a]	−16.4 (+15.4)[a]
(*R*)-**5b**	238-240 (228-230)[b]	−14.3 (−11.4)[b]
(*S*)-**5b**	238-240	+13.5
(*R*)-**5c**	231-233 (224-226)[b]	−19.9 (+17.8)[b]
(*R*)-**5c**	231-233 (224-226)[c]	−18.3 (−11.0)[c]
(*R*)-**5d**	262-264 (205-206)[d]	−24.3 (−17.2)[d]
(*S*)-**5d**	262-264 (205-206)[d]	−24.7 (+17.8)[d]
(*R*)-**5e**	240-242 (187-188)[d]	−8.4 (−6.8)[d]
(*S*)-**5e**	240-242 (187-188)[d]	+81 (−7.0)[d]

[a]Kakimoto, Y. *et al. J. Biol. Chem.* **1961**, *236*, 3283. [b]Jin, Y. *et al. Synlett* **1998**, 1189. [c]Juaristi, E. *et al. Tetrahedron: Asymmetry* **1996**, *7*, 2233. [d]Juaristi, E. *et al. Tetrahedron: Asymmetry* **1998**, *9*, 3881.



Scheme 2. (a) $CH_3C(OCH_3)_3$, *p*-TsOH, CH_2Cl_2, 1 h, >90%; (b) Jones' reagent, acetone, 2 h, >71%; (c) 2 N NaOH, MeOH, reflux, 4 h, >92%.

from the mixed solvent of diethyl ether and hexane.

(2*R*,1'*S*)-**2b**: Mp 110-111 °C; $[\alpha]_D$ −82.2° (*c* 0.98, $CHCl_3$); IR (KBr) 3275, 2962, 1674, 1556 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$) δ 0.88 (d, 3H), 0.94 (d, 3H), 1.50 (d, 3H), 1.92 (m, 1H), 2.05 (m, 1H), 2.80 (br, 1H), 3.82 (m, 2H), 5.15 (m, 1H), 6.03 (br, 1H), 7.24-7.37 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 20.56, 21.43, 22.09, 27.87, 49.13, 56.12, 62.18, 126.29, 126.56, 127.74, 129.04, 143.44, 174.53; Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.26; H, 9.05; N, 6.00.

(2*S*,1'*S*)-**2b**: Mp 135-136 °C; $[\alpha]_D$ −101.9° (*c* 1.32, $CHCl_3$); IR (KBr) 3315, 2973, 1643, 1549 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$) δ 0.97 (d, 6H), 1.49 (d, 3H), 1.91 (m, 1H), 2.07 (m, 1H), 2.86 (br, 1H), 3.77 (m, 2H), 5.15 (m, 1H), 6.12 (br, 1H), 7.23-7.36 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 20.63, 21.44, 22.13, 27.76, 49.01, 56.12, 62.18, 126.30, 126.49, 127.74, 129.07, 143.47, 174.59; Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.47; H, 9.09; N, 5.93.

(2*R*,1'*S*)- and (2*S*,1'*S*)-2-Hydroxymethyl-3-phenyl-*N*-(1'-phenylethyl)propionamide ((2*R*,1'*S*)- and (2*S*,1'*S*)-2c) were similarly prepared from **1c** in 46% and 47% yield, respectively. The analytical samples were prepared by recrystallization from the mixed solvent of diethyl ether and hexane.

(2*R*,1'*S*)-**2c**: Mp 130-132 °C; $[\alpha]_D$ −102.2° (*c* 1.00, $CHCl_3$); IR (KBr) 3261, 2966, 1644, 1569 cm^{-1}; ^1H NMR

300 MHz ($CDCl_3$) δ 1.22 (d, 3H), 2.50 (m, 1H), 2.82 (dd, 1H), 2.96 (dd, 1H), 3.03 (dd, 1H), 3.74 (m, 2H), 4.99 (m, 1H), 5.76 (br, 1H), 7.16-7.33 (m, 10H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 21.98, 35.78, 49.01, 50.98, 63.69, 126.40, 126.98, 127.72, 129.05, 129.40, 139.63, 143.37, 173.91; Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.29; H, 7.52; N, 5.00.

(2*S*,1'*S*)-**2c**: Mp 108-110 °C; [α]$_D$ −73.5 ° (*c* 1.03, $CHCl_3$); IR (KBr) 3328, 2972, 1645, 1557 cm^{-1}; ^{1}H NMR 300 MHz ($CDCl_3$) δ 1.40 (d, 3H), 2.54 (m, 1H), 2.80 (dd, 1H), 2.94 (dd, 1H), 3.04 (dd, 1H), 3.77 (m, 2H), 5.04 (m, 1H), 5.89 (br, 1H), 7.00-7.25 (m, 10H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 22.11, 35.61, 48.97, 50.97, 63.78, 126.44, 126.83, 127.58, 128.93, 129.00, 139.43, 143.13, 173.84; Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 75.99; H, 7.53; N, 5.34.

(2*R*,1'*S*)- and (2*S*,1'*S*)-2-Hydroxymethyl-2-methyl-3-phenyl-*N*-(1'-phenylethyl) propionamide ((2*R*, 1'*S*)- and (2*S*,1'*S*)-2d) were similarly prepared from **1d** in 44% and 47% yield, respectively. The analytical samples were prepared by recrystallization from the mixed solvent of diethyl ether and hexane.

(2*R*,1'*S*)-**2d**: Mp 129-131 °C; [α]$_D$ −50.8° (*c* 1.89, MeOH); IR (KBr) 3250, 2915, 1635, 1545 cm^{-1}; ^{1}H NMR 300 MHz ($CDCl_3$) δ 1.05 (s, 3H), 1.34 (d, 3H), 2.80 (d, 1H), 3.03 (d, 1H), 3.53-3.61 (m, 3H), 5.06 (m, 1H), 6.20 (br, 1H), 7.14-7.31 (m, 10H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 19.72, 22.13, 42.26, 47.70, 49.03, 68.94, 126.35, 127.03, 127.68, 128.56, 129.08, 130.80, 137.44, 143.66, 176.40; Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.82; H, 7.88; N, 4.73.

(2*S*,1'*S*)-**2d**: Mp 95-97 °C; [α]$_D$ −81.5° (*c* 1.34, MeOH); IR (KBr) 3292, 2929, 1631, 1545 cm^{-1}; ^{1}H NMR 300 MHz ($CDCl_3$) δ 1.04 (s, 3H), 1.45 (d, 3H), 2.80 (d, 1H), 3.03 (d, 1H), 3.30 (dd, 1H), 3.59 (m, 2H), 5.10 (m, 1H), 6.09 (br, 1H), 7.07-7.32 (m, 10H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 19.66, 22.06, 42.20, 47.71, 49.07, 69.08, 126.57, 126.89, 127.69, 128.52, 129.01, 130.71, 137.29, 143.29, 176.27; Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.80; N, 4.71. Found: C, 76.73; H, 7.82; N, 4.73.

(3*R*,1'*S*)- and (3*S*,1'*S*)-3-Methyl-1-(1'-phenylethyl)-azetidin-2-one ((3*R*,1'*S*)- and (3*S*,1'*S*)-4a). 1-Ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (2.20 g, 11.5 mmol), 1-hydroxybenzotriazole hydrate (1.55 g, 11.5 mmol), and Et_3N (1.77 mL, 12.7 mmol) were added to the stirred solution of **1a** (1.20 g, 11.5 mmol) in CH_2Cl_2 at 0 °C, and the solution was stirred for 10 min. (*S*)-Phenylethylamine (1.63 mL, 12.7 mmol) was added to the reaction mixture at 0 °C, and the mixture was stirred for 1 h at room temperature. The solution was washed with 10% aqueous solution of citric acid, saturated aqueous $NaHCO_3$ solution, and brine, and the organic layer was dried over $MgSO_4$. The dried solution was concentrated under reduced pressure to give the crude product in a diastereomeric mixture which was purified by flash column chromatography (hexane/EtOAc = 4/1 to 2/1) to afford **2a** (2.15 g, 90%) as a colorless oil. Methanesulfonyl chloride (0.96 mL, 12.4 mmol) and Et_3N (1.74 mL, 12.4 mmol) were added to the stirred solution of **2a** (2.15 g, 10.4 mmol) in CH_2Cl_2 at 0 °C and the solution was stirred for 10 min. The reaction mixture was washed with 1 N HCl and the organic layer was dried over $MgSO_4$. The dried solution was concentrated under reduced pressure to give a mesylated product in a white solid. The product was dissolved in DMF and the solution was cooled to 0 °C. To the solution, NaH (0.50 g, 12.4 mmol, 60% dispersion in mineral oil) was added and the reaction mixture was stirred for 4 h. The solution was diluted with EtOAc, and washed with 5% aqueous $Na_2S_2O_3$ solution to remove DMF. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product (1.80 g, 92%) in a diastereomeric mixture. The diastereomeric mixture was separated by flash column chromatography (hexane/EtOAc = 8/1 to 4/1) to give (3*R*, 1'*S*)-**4a** (0.87 g, 44%) and (3*S*,1'*S*)-**4a** (0.67 g, 34%) as colorless oil.

(3*R*,1'*S*)-**4a**: [α]$_D$ −83.8° (*c* 1.19, $CHCl_3$); IR (neat) 2968, 1743 cm^{-1}; ^{1}H NMR 300 MHz ($CDCl_3$) δ 1.30 (d, 3H), 1.58 (d, 3H), 2.82 (dd, 1H), 3.09 (m, 1H), 3.18 (t, 1H), 4.91 (q, 1H), 7.25-7.38 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 14.01, 18.92, 43.63, 45.10, 51.63, 127.09, 127.92, 129.07, 141.16, 171.01; MS (EI) *m/z* 189 (M$^+$).

(3*S*,1'*S*)-**4a**: [α]$_D$ −136° (*c* 0.5, $CHCl_3$); IR (neat) 2969, 1743 cm^{-1}; ^{1}H NMR 300 MHz ($CDCl_3$) δ 1.25 (d, 3H), 1.57 (d, 3H), 2.63 (dd, 1H), 3.13 (m, 1H), 3.36 (t, 1H), 4.94 (q, 1H), 7.25-7.39 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 13.89, 18.71, 43.66, 44.99, 51.47, 127.07, 127.90, 129.07, 141.14, 170.98; MS (EI) *m/z* 189 (M$^+$).

(3*R*,1'*S*)- and (3*S*,1'*S*)-3-Butyl-3-methyl-1-(1'-phenylethyl)azetidin-2-one (3*R*,1'*S*)- and (3*S*,1'*S*)-4e) were similarly prepared from **1e** in 44% and 39% yield, respectively.

(3*R*,1'*S*)-**4e**: [α]$_D$ −70.6° (*c* 0.89, $CHCl_3$); IR (neat) 2958, 1744 cm^{-1}; ^{1}H NMR 300 MHz ($CDCl_3$) δ 0.91 (dd, 3H), 1.22 (s, 3H), 1.34 (m, 4H), 1.57 (d, 3H), 1.60 (m, 2H), 2.69 (d, 1H), 3.06 (d, 1H), 4.95 (q, 1H), 7.26-7.38 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 14.36, 18.76, 19.73, 23.44, 27.30, 34.75, 49.70, 50.90, 53.61, 127.13, 127.89, 129.05, 141.06, 173.47; MS (EI) *m/z* 246 (M$^+$).

(3*S*,1'*S*)-**4e**: [α]$_D$ −75.7° (*c* 0.94, $CHCl_3$); IR (neat) 2957, 1743 cm^{-1}; ^{1}H NMR 300 MHz ($CDCl_3$) δ 0.84 (dd, 3H), 1.23 (m, 4H), 1.28 (s, 3H), 1.52 (m, 2H), 1.56 (d, 3H), 2.87 (dd, 2H), 4.94 (q, 1H), 7.27-7.38 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 14.32, 18.59, 19.89, 23.40, 27.31, 34.72, 49.76, 50.92, 53.62, 127.18, 127.90, 129.02, 141.11, 173.56; MS (EI) *m/z* 246 (M$^+$).

(3*R*,1'*S*)-3-Isopropyl-1-(1'-phenylethyl)azetidin-2-one ((3*R*,1'*S*)-4b). Methanesulfonyl chloride (0.30 mL, 3.8 mmol) and Et_3N (0.54 mL, 3.8 mmol) were added to the stirred solution of (2*R*,1'*S*)-**2b** (750 mg, 3.2 mmol) in CH_2Cl_2 at 0 °C and the solution was stirred for 10 min. The reaction mixture was washed with 0.1 N HCl, and the organic layer was dried over $MgSO_4$. The dried solution was concentrated under reduced pressure to give a mesylated product as a white solid. The product was dissolved in DMF and the solution was cooled to 0 °C. To the solution was added NaH (0.154 g, 3.8 mmol, 60% dispersion in mineral oil) and the reaction mixture was stirred for 4 h. The solution was diluted with ethyl acetate and washed with 5% aqueous $Na_2S_2O_3$ solution to remove DMF. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc = 8/1 to 4/1) to give (3*R*,1'*S*)-**4b** (630 mg, 91%) as a white solid which was recrystallized from the mixed solvent of diethyl ether and hexane. Mp 57-58 °C; $[\alpha]_D$ −96.5 ° (*c* 1.03, $CHCl_3$); IR (KBr) 2961, 1723 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$) δ 0.95 (d, 3H), 1.05 (d, 3H), 1.58 (d, 3H), 1.97 (m, 1H), 2.90 (m, 2H), 3.03 (t, 1H), 4.92 (q, 1H), 7.27-7.37 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 18.89, 20.25, 20.32, 28.33, 40.85, 51.39, 55.70, 127.16, 127.93, 129.06, 141.04, 169.89; Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.52; H, 8.90; N, 6.41.

(3*S*,1'*S*)-3-Isopropyl-1-(1'-phenylethyl)azetidin-2-one ((3*S*,1'*S*)-4b) was similarly prepared from (2*S*,1'*S*)-**2b** in 93% yield as a colorless oil. $[\alpha]_D$ −87.1 ° (*c* 1.18, $CHCl_3$); IR (neat) 2958, 1743 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$) δ 0.87 (d, 3H), 1.00 (d, 3H), 1.56 (d, 3H), 1.91 (m, 1H), 2.73 (dd, 1H), 2.91 (m, 1H), 3.22 (t, 1H), 4.96 (q, 1H), 7.25-7.37 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 18.53, 20.32, 28.40, 40.78, 51.02, 55.80, 127.17, 127.91, 129.04, 141.08, 169.89; MS (EI) *m/z* 218 (M^+).

(3*R*,1'*S*)-3-Benzyl-1-(1'-phenylethyl)azetidin-2-one ((3*R*,1'*S*)-4c) was similarly prepared from (2*R*,1'*S*)-**2c** in 90% yield as a white solid which was recrystallized from the mixed solvent of diethyl ether and hexane. Mp 82-83 °C; $[\alpha]_D$ −92.3° (*c* 0.88, $CHCl_3$); IR (KBr) 2987, 1721 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$) δ 1.42 (d, 3H), 2.90 (dd, 1H), 2.99 (dd, 1H), 3.06 (m, 2H), 3.37 (m, 1H), 4.83 (q, 1H), 7.15-7.30 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 18.88, 34.61, 42.39, 49.70, 51.92, 126.29, 126.91, 127.05, 127.90, 128.87, 129.05, 129.40, 138.47, 140.94, 169.53; Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.59; H, 7.34; N, 5.29.

(3*S*,1'*S*)-3-Benzyl-1-(1'-phenylethyl)azetidin-2-one ((3*S*,1'*S*)-4c) was similarly prepared from (2*S*,1'*S*)-**2c** in 92% yield as a colorless oil. $[\alpha]_D$ +27.7° (*c* 0.98, $CHCl_3$); IR (neat) 2972, 1743 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$) δ 1.52 (d, 3H), 2.77 (dd, 1H), 2.90 (dd, 1H), 3.06 (dd, 2H), 3.25 (t, 1H), 3.42 (m, 1H), 4.89 (q, 1H), 7.03-7.27 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 18.67, 34.53, 42.29, 49.87, 51.29, 126.31, 126.91, 127.74, 128.08, 128.88, 128.99, 129.35, 138.48, 140.85, 169.48; MS (EI) *m/z* 266 (M^+).

(3*R*,1'*S*)-3-Benzyl-3-methyl-1-(1'-phenylethyl)azetidin-2-one ((3*R*,1'*S*)-4d) was similarly prepared from (2*R*,1'*S*)-**2d** in 93% yield as a colorless oil. $[\alpha]_D$ −69.7° (*c* 1.01, $CHCl_3$); IR (neat) 2967, 1743 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$) δ 1.16 (d, 3H), 1.32 (s, 3H), 2.62 (d, 1H), 2.68 (d, 1H), 3.04 (d, 1H), 3.07 (d, 1H), 4.75 (q, 1H), 7.02-7.07 (m, 2H), 7.24-7.32 (m, 8H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 18.51, 20.54, 40.93, 48.21, 51.32, 54.43, 126.30, 126.99, 127.75, 128.63, 128.95, 130.49, 137.56, 140.90, 172.45; MS (EI) *m/z* 279 (M^+).

(3*S*,1'*S*)-3-Benzyl-3-methyl-1-(1'-phenylethyl)azetidin-2-one ((3*S*,1'*S*)-4d) was similarly prepared from (2*S*,1'*S*)-**2b** in 93% yield as a white solid which was recrystallized from the mixed solvent of diethyl ether and hexane. Mp 98-99 °C; $[\alpha]_D$ +1.4° (*c* 1.16, $CHCl_3$); IR (KBr) 2972, 1734 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$) δ 1.38 (s, 3H), 1.46 (d, 3H), 2.67 (d, 1H), 2.83 (d, 1H), 2.94 (d, 1H), 3.02 (d, 1H), 4.82 (q, 1H), 6.77-6.80 (m, 2H), 7.16-7.29 (m, 8H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 18.68, 20.99, 40.69, 48.01, 50.25, 54.73, 126.72, 127.05, 127.48, 128.78, 128.87, 130.49, 137.48, 140.51, 172.62; Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.70; H, 7.60; N, 5.06.

(*R*)-3-Amino-2-methylpropanoic acid ((*R*)-5a). β-Lactam (3*R*,1'*S*)-**4a** (320 mg, 1.7 mmol) was suspended in 6 N HCl and the mixture was heated under reflux for 6 h. The solvent was removed under reduced pressure and residue was dissolved in MeOH (10 mL) containing water (1 mL) and acetic acid (0.25 mL), and was subjected to hydrogenolysis in the presence of $Pd(OH)_2$ (20 wt.%, 0.2 g) under hydrogen (3 atm) for 24 h at room temperature. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to afford (*R*)-**5a** as a HCl salt which was adsorbed on an acidic ion-exchange resin (Dowex 50WX 8). The resin was washed with distilled water until the washings were neutral, and then the free amino acid was eluted with 1.5 M aqueous NH_4OH solution. Evaporation of the eluent gave crystalline (*R*)-**5a** (150 mg, 86%). Mp 187-189 °C; $[\alpha]_D$ −16.5° (*c* 0.81, H_2O); ^1H NMR 300 MHz (D_2O) δ 0.98 (d, 3H), 2.39 (m, 1H), 2.84 (m, 2H); ^{13}C NMR 300 MHz (D_2O) δ 15.70, 39.78, 43.13, 182.20; MS (EI) *m/z* 103 (M^+).

(*S*)-3-Amino-2-methylpropanoic acid ((*S*)-5a) was similarly prepared from (3*S*,1'*S*)-**4a** in 87% yield as a crystalline solid. Mp 187-189 °C; $[\alpha]_D$ +16.4° (*c* 0.90, H_2O). ^1H and ^{13}C NMR spectra were identical to those of (*R*)-**5a**.

(*R*)-2-Aminomethyl-3-methylbutyric acid ((*R*)-5b) was similarly prepared from (3*R*,1'*S*)-**4b** in 94% yield as a crystalline solid. Mp 238-239 °C; $[\alpha]_D$ −14.3° (*c* 1.03, H_2O); ^1H NMR 300 MHz (D_2O) δ 0.79 (d, 3H), 0.84 (d, 3H), 1.85 (m, 1H), 2.20 (m, 1H), 2.99 (m, 2H); ^{13}C NMR 300 MHz (D_2O) δ 18.91, 20.24, 28.85, 39.26, 52.26, 180.75; MS (EI) *m/z* 132 (M^+).

(*S*)-2-Aminomethyl-3-methylbutyric acid ((*S*)-5b) was similarly prepared from (3*S*,1'*S*)-**4b** in 96% yield as a crystalline solid. Mp 238-239 °C; $[\alpha]_D$ +13.5° (*c* 1.05, H_2O). ^1H and ^{13}C NMR spectra were identical to those of (*R*)-**5b**.

(*R*)-2-Aminomethyl-3-phenylpropanoic acid ((*R*)-5c) was similarly prepared from (3*R*,1'*S*)-**4c** in 92% yield as a crystalline solid. Mp 232-234 °C; $[\alpha]_D$ −18.7° (*c* 0.87, 1N HCl); ^1H NMR 300 MHz (D_2O) δ 2.71 (m, 2H), 2.89 (m, 3H), 7.15-7.28 (m, 5H); ^{13}C NMR 300 MHz (D_2O) δ 36.56, 41.10, 47.51, 127.12, 129.08, 129.35, 138.96, 180.08; MS (EI) *m/z* 179 (M^+).

(*S*)-2-Aminomethyl-3-phenylpropanoic acid ((*S*)-5c) was similarly prepared from (3*S*,1'*S*)-**4c** in 93% yield as a crystalline solid. Mp 232-234 °C; $[\alpha]_D$ +19.9° (*c* 1.19, 1 N HCl). ^1H and ^{13}C NMR spectra were identical to those of

(*R*)-**5c**.

(*R*)-3-Amino-2-benzyl-2-methylpropanoic acid ((*R*)-5d) was similarly prepared from (3*R*,1'*S*)-**4d** in 94% yield as a crystalline solid. Mp 262-264 °C dec.; $[\alpha]_D$ −24.3° (*c* 0.94, H_2O); ^1H NMR 300 MHz (D_2O) δ 1.13 (s, 3H), 2.74 (d, 1H), 2.81 (d, 1H), 2.89 (d, 1H), 3.00 (d, 1H), 7.14-7.31 (m, 5H); ^{13}C NMR 300 MHz (D_2O) δ 21.41, 43.80, 46.43, 46.53, 127.28, 128.83, 130.37, 137.43, 182.14; MS (EI) *m/z* 193 (M^+); Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.16; H, 7.87; N, 7.24.

(*S*)-3-Amino-2-benzyl-2-methylpropanoic acid ((*S*)-5d) was similarly prepared from (3*S*,1'*S*)-**4d** in 92% yield as a crystalline solid. Mp 262-264 °C dec.; $[\alpha]_D$ +24.7° (*c* 1.19, H_2O). ^1H and ^{13}C NMR spectra were identical to those of (*R*)-**5d**.

(*R*)-2-Aminomethyl-2-methylhexanoic acid ((*R*)-5e) was similarly prepared from (3*R*,1'*S*)-**4e** in 90% yield as a crystalline solid. Mp 240-242 °C dec.; $[\alpha]_D$ −8.4° (*c* 0.96, H_2O); ^1H NMR 300 MHz (D_2O) δ 1.13 (s, 3H), 2.74 (d, 1H), 2.81 (d, 1H), 2.89 (d, 1H), 3.00 (d, 1H), 7.14-7.31 (m, 5H); ^{13}C NMR 300 MHz (D_2O) δ 21.41, 43.80, 46.43, 46.53, 127.28, 128.83, 130.37, 137.43, 182.14; MS (EI) *m/z* 160 (M^+).

(*S*)-2-Aminomethyl-2-methylhexanoic acid ((*S*)-5e) was similarly prepared from (3*S*,1'*S*)-**4e** in 91% yield as a crystalline solid. Mp 240-242 °C dec.; $[\alpha]_D$ +8.1° (*c* 0.94, H_2O). ^1H and ^{13}C NMR spectra were identical to those of (*R*)-**5e**.

3-Acetoxy-2-methylpropanol (7a). A mixture of 2-methyl-1,3-propanediol (**6a**) (10 mL, 0.11 mol), trimethylorthoacetate (15.3 mL, 0.12 mol), and a catalytic amount (2.28 g, 0.012 mol) of *p*-toluenesulfonic acid monohydrate in CH_2Cl_2 was stirred for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography (EtOAc/hexane = 1/5) to give the product (14.29 g, 96%) as a colorless oil. ^1H NMR 300 MHz ($CDCl_3$) δ 0.96 (d, 3H), 1.98 (m, 1H), 2.08 (s, 3H), 2.36 (br, 1H), 3.52 (m, 2H), 4.08 (m, 2H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 13.89, 21.25, 35.79, 64.79, 66.60, 172.00.

2-Acetoxymethyl-3-methylbutanol (7b) was similarly prepared from **6b**[9] in 93% yield as colorless oil. IR (neat) 3452, 2962, 1740 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$) δ 0.95 (d, 1H), 0.97 (d, 1H), 1.58-1.64 (m, 1H), 1.75-1.85 (m, 1H), 2.07 (s, 3H), 2.81 (br, 1H), 3.57 (dd, 1H), 3.68 (dd, 1H), 4.14 (dd, 1H), 4.26 (dd, 1H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 20.26, 20.56, 21.27, 26.75, 46.58, 61.35, 63.80, 172.04; MS (EI) *m/z* 161 (M^+).

2-Acetoxymethyl-3-phenylpropanol (7c) was similarly prepared from **6c**[10] in 94% yield as a colorless oil. ^1H NMR 300 MHz ($CDCl_3$) δ 2.07 (s, 3H), 2.16 (m, 1H), 2.67 (m, 2H), 3.53 (m, 2H), 4.09 (m, 2H), 7.15-7.31 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 21.30, 34.72, 42.79, 62.30, 64.50, 126.64, 128.90, 129.49, 139.87, 172.16.

2-Acetoxymethyl-2-methyl-3-phenylpropanol (7d) was similarly prepared from **6d**[11] in 90% yield as colorless oil. IR (neat) 3470, 2927, 1737 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$) δ 0.83 (s, 3H), 2.13 (s, 3H), 2.34 (br, 1H), 2.60 (dd, 2H), 3.32 (dd, 2H), 3.95 (dd, 2H), 7.16-7.32 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 18.93, 21.35, 40.33, 40.55, 66.57, 68.08, 126.73, 128.48, 130.99, 137.40, 172.32; MS (EI) *m/z* 223 (M^+).

2-Acetoxymethyl-2-methylhexanol (7e) was similarly prepared from **6e**[12] in 88% yield as colorless oil. IR (neat) 3420, 2957, 1734 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$) δ 0.87-0.91 (m, 6H), 1.25 (m, 6H), 2.09 (s, 3H), 2.21 (br, 1H), 3.32 (dd, 2H), 3.95 (s, 2H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 14.40, 18.92, 21.25, 23.89, 25.63, 34.22, 39.12, 67.22, 68.65, 172.24; MS (EI) *m/z* 189 (M^+).

3-Acetoxy-2-methylpropionic acid (8a). To an ice-cooled acetone solution of **7a** (9.00 g, 68.1 mmol) was added slowly the Jones reagent until brownish color of the solution remains over 20 min, then 2-propanol was added until the solution became clear. The precipitate was filtered and the filtrate was concentrated under reduced pressure. The residue was diluted with ethyl acetate and extracted with saturated aqueous $NaHCO_3$ solution. The aqueous layer was acidified with 6 N HCl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the product (7.07 g, 71%) as a colorless oil. ^1H NMR 300 MHz ($CDCl_3$) δ 1.25 (d, 3H), 2.07 (s, 3H), 2.84 (m, 1H), 4.22 (m, 2H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 14.00, 21.15, 39.32, 65.63, 171.35, 180.42.

2-Acetoxymethyl-3-methylbutyric acid (8b) was similarly prepared from **7b** in 73% yield as colorless oil. IR (neat) 2967, 1745, 1713 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$) δ 1.04 (dd, 6H), 2.02 (m, 1H), 2.06 (s, 3H), 2.56 (m, 1H), 4.20-4.36 (m, 2H), 10.87 (br, 1H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 20.45, 20.59, 21.15, 28.55, 51.53, 63.73, 171.43, 179.46; MS (EI) *m/z* 175 (M^+).

3-Acetoxy-2-benzylpropionic acid (8c) was similarly prepared from **7c** in 74% yield as colorless oil. ^1H NMR 300 MHz ($CDCl_3$) δ 2.03 (s, 3H), 2.85 (m, 1H), 3.04 (m, 2H), 4.21 (m, 2H), 7.16-7.31 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 21.19, 34.83, 46.61, 63.98, 127.26, 129.09, 129.30, 138.02, 171.33, 179.23.

2-Acetoxymethyl-2-methyl-3-phenylpropionic acid (8d) was similarly prepared from **7d** in 71% yield as a white solid, which was recrystallized from the mixed solvent of diethyl ether and hexane. Mp 98-100 °C; IR (KBr) 2978, 1747, 1699 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$) δ 1.22 (s, 3H), 2.10 (s, 3H), 2.97 (dd, 2H), 4.13 (dd, 2H), 7.13-7.29 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 19.93, 21.12, 41.60, 47.44, 68.22, 127.34, 128.69, 130.55, 136.36, 170.93, 180.03; Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.18; H, 6.82.

2-Acetoxymethyl-2-methylhexanoic acid (8e) was similarly prepared from **7e** in 80% yield as colorless oil. IR (neat) 2958, 1746, 1704 cm^{-1}; ^1H NMR 300 MHz ($CDCl_3$) δ 0.90 (t, 3H), 1.23 (s, 3H), 1.29 (m, 4H), 1.49-1.66 (m, 2H), 2.07 (s, 3H), 4.15 (dd, 2H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 14.16, 19.78, 21.09, 23.40, 26.59, 35.93, 46.37, 69.08, 171.20, 181.73; MS (EI) *m/z* 203 (M^+).

3-Hydroxy-2-methylpropionic acid (1a). Compound **8a**

(4.12 g, 28.2 mmol) was dissolved in MeOH containing 2 N NaOH (28 mL) and the solution was refluxed for 4 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was acidified with 6 N HCl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give the product (2.70 g, 92%) as a colorless oil. ^{1}H NMR 300 MHz ($CDCl_3$) δ 1.20 (d, 3H), 2.72 (m, 1H), 3.75 (d, 2H), 7.00 (br, 1H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 13.55, 21.14, 42.00, 64.66, 180.83.

2-Hydroxymethyl-3-methylbutyric acid (1b) was similarly prepared from **8b** in 96% yield as a colorless oil. ^{1}H NMR 300 MHz ($CDCl_3$) δ 0.99 (dd, 6H), 2.02 (m, 1H), 2.42 (m, 1H), 3.77-3.90 (m, 2H), 6.20 (br, 1H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 20.51, 21.00, 28.11, 54.79, 61.91, 180.00.

2-Hydroxymethyl-3-phenylpropionic acid (1c) was similarly prepared from **8c** in 95% yield as a white solid which was recrystallized from the mixed solvent of diethyl ether and hexane. Mp 60-62 °C (lit.[13] 58-59 °C); ^{1}H NMR 300 MHz ($CDCl_3$) δ 2.83-2.93 (m, 2H), 3.08 (m, 1H), 3.69-3.82 (m, 2H), 7.20-7.33 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 34.42, 49.19, 62.29, 127.10, 129.03, 129.35, 138.60, 180.05.

2-Hydroxymethyl-2-methyl-3-phenylpropionic acid (1d) was similarly prepared from **8d** in 97% yield as a white solid which was recrystallized from the mixed solvent of diethyl ether and hexane. Mp 109-110 °C (lit.[14] 73.5-74.5 °C); ^{1}H NMR 300 MHz ($CDCl_3$) δ 1.14 (s, 3H), 2.95 (dd, 2H), 3.60 (dd, 2H), 7.18-7.30 (m, 5H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 19.60, 40.99, 48.97, 67.03, 127.21, 128.64, 130.81, 136.60, 182.75; Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.10; H, 7.30.

2-Hydroxymethyl-2-methylhexanoic acid (1e) was similarly prepared from **8e** in 93% yield as a colorless oil. IR (neat) 3394, 2958, 1701 cm^{-1}; ^{1}H NMR 300 MHz ($CDCl_3$) δ 0.90 (t, 3H), 1.21 (s, 3H), 1.29 (m, 4H), 1.50-1.62 (m, 2H), 3.52 (d, 1H), 3.75 (d, 1H); ^{13}C NMR 300 MHz ($CDCl_3$) δ 14.28, 19.73, 23.57, 26.65, 35.85, 48.02, 68.36, 183.36; MS (EI) *m/z* 161 (M^+).

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