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Highly Diastereoselective Synthesis of (3*R*,4*R*)- and (3*R*,4*S*)- β,γ -Diamino Acids from D-Phenylalanine

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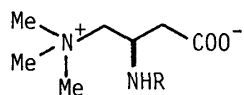
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(2*R*,3*S*)-*N*-Boc-2-Amino-3-hydroxy-1-phenylbutane (**9a**) and (2*R*,3*S*)-*N*-Boc-2-amino-3-hydroxy-1-phenylpentane (**9b**) were converted to (3*R*,4*R*)-*N*³-Boc-3,4-diaminopentanoic acid (**12a**) and (3*R*,4*R*)-*N*³-Boc-3,4-diaminohexanoic acid (**12b**) through *S_N2* type substitution of the hydroxy group to an amino group and oxidation of the phenyl group to a carboxyl group. In a similar way, the (3*R*,4*S*)-isomers (**18a**, **b**) were also synthesized from (2*R*,3*R*)-*N*-Boc-2-amino-3-hydroxy-1-phenylbutane (**15a**) and (2*R*,3*R*)-*N*-Boc-2-amino-3-hydroxy-1-phenylpentane (**15b**), respectively, derived from (2*R*,3*S*)-*N*-Cbz-2-amino-3-hydroxy-1-phenylbutane (**6a**) and (2*R*,3*S*)-*N*-Cbz-2-amino-3-hydroxy-1-phenylpentane (**6b**) by means of the diastereoconversion reaction.

Keywords—diastereoconversion; β,γ -diamino acid; 2-amino alcohol; diastereoselective synthesis; ruthenium tetroxide; cyclocarbamation; oxidation

Recently, stereoselective synthesis of β,γ -diamino acids has received considerable attention because of the wide range of biological activities of these compounds.¹⁻³ Emericedines A (**1a**), B (**1b**), and C (**1c**), new betaines that inhibit long chain fatty acid-oxidation, were isolated and some analogous compounds were synthesized.¹ (3*R*)- β,γ -Diaminobutyric acids without a substituent at the γ -position have been prepared from L-asparagine.¹ Diastereoselective synthesis of γ -substituted β,γ -diamino acids is thus important from both synthetic and pharmacological points of view.² For the preparation of γ -substituted β,γ -diamino acids such as aminostatine (**3**), Michael addition of an amino group to an α,β -unsaturated ester (**2**) is one of the most synthetically useful methods, but the level of diastereoselectivity is known to be low.² We investigated a new, facile method for a diastereoselective synthesis of (3*R*,4*R*)- and (3*R*,4*S*)- β,γ -diamino acids from 2-amino alcohols. Our synthetic strategy for the preparation of β,γ -diamino acids is based on



1a: R=CH₃CO

1b: R=CH₃CH₂CO

1c: R=CH₃CH₂CH₂CO

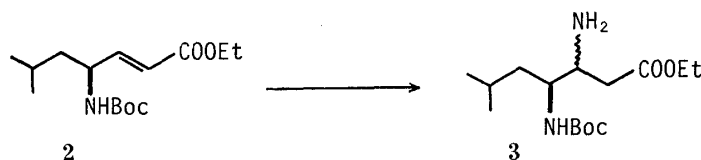


Chart 1

replacement of the hydroxy group of 2-amino alcohols, derived from D-phenylalanine with high diastereoselectivity, with an amino group through an S_N2 type substitution reaction, and the use of the phenyl group as a synthon for a carboxyl group. The results of our studies are described in this paper.

First, (2*R*,3*S*)-*N*-Boc-2-amino-3-hydroxy-1-phenylbutane (**9a**) and (2*R*,3*S*)-*N*-Boc-2-amino-3-hydroxy-1-phenylpentane (**9b**) were prepared as follows. Methylation of the amide (**4**), obtained from *N*-Cbz-D-phenylalanine according to Boutin and Rapoport,⁴⁾ with methyllithium afforded the methyl ketone (**5a**). The use of ethylmagnesium bromide instead of methyllithium yielded the ethyl ketone (**5b**). For reduction of ketones, triethylsilane–titanium tetrachloride⁵⁾ gave the best results among several kinds of reducing agents tested. Reduction of **5a, b** with triethylsilane in the presence of titanium tetrachloride⁵⁾ yielded (2*R*,3*S*)-*N*-Cbz-2-amino-3-hydroxy-1-phenylbutane (**6a**) and (2*R*,3*S*)-*N*-Cbz-2-amino-3-hydroxy-1-phenylpentane (**6b**), with high diastereoselectivity, respectively. Cyclization of **6a, b** with sodium hydroxide gave the corresponding (4*R*,5*S*)-4,5-disubstituted oxazolidin-2-ones (**7a, b**). *tert*-Butoxycarbonylation of **7a, b** with Boc_2O afforded **8a, b**, respectively. Ring cleavage of **8a, b** with lithium hydroxide in aqueous dioxane⁵⁾ gave the corresponding (2*R*,3*S*)-*N*-Boc-2-amino-3-hydroxy-1-phenylbutane (**9a**) and (2*R*,3*S*)-*N*-Boc-2-amino-3-hydroxy-1-phenylpentane (**9b**).

The hydroxyl group of **9a, b** was easily converted to an azide group by treatment with methanesulfonyl chloride in the presence of triethylamine, followed with sodium azide in dimethylformamide. Thus, **10a, b** were obtained from **9a, b**, respectively, with inversion of the hydroxyl group in an S_N2 substitution reaction without contamination by the alternative

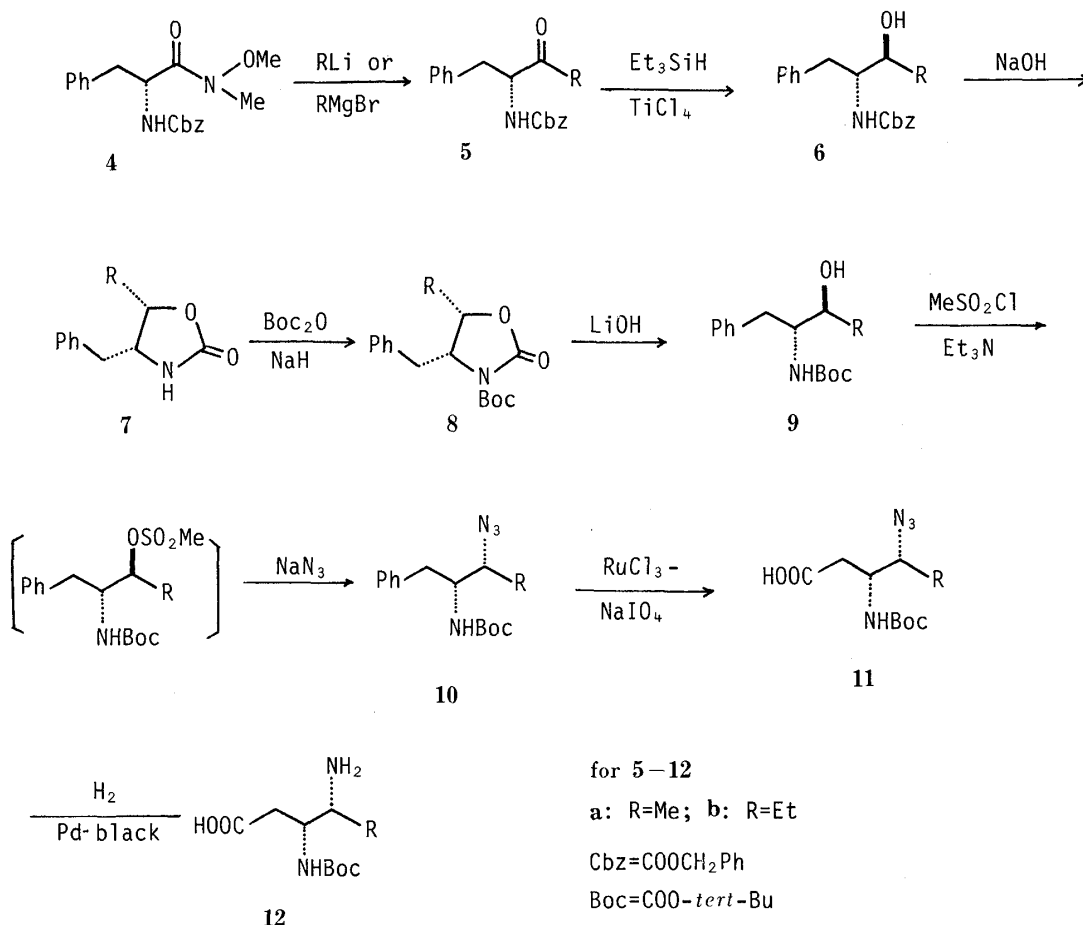


Chart 2

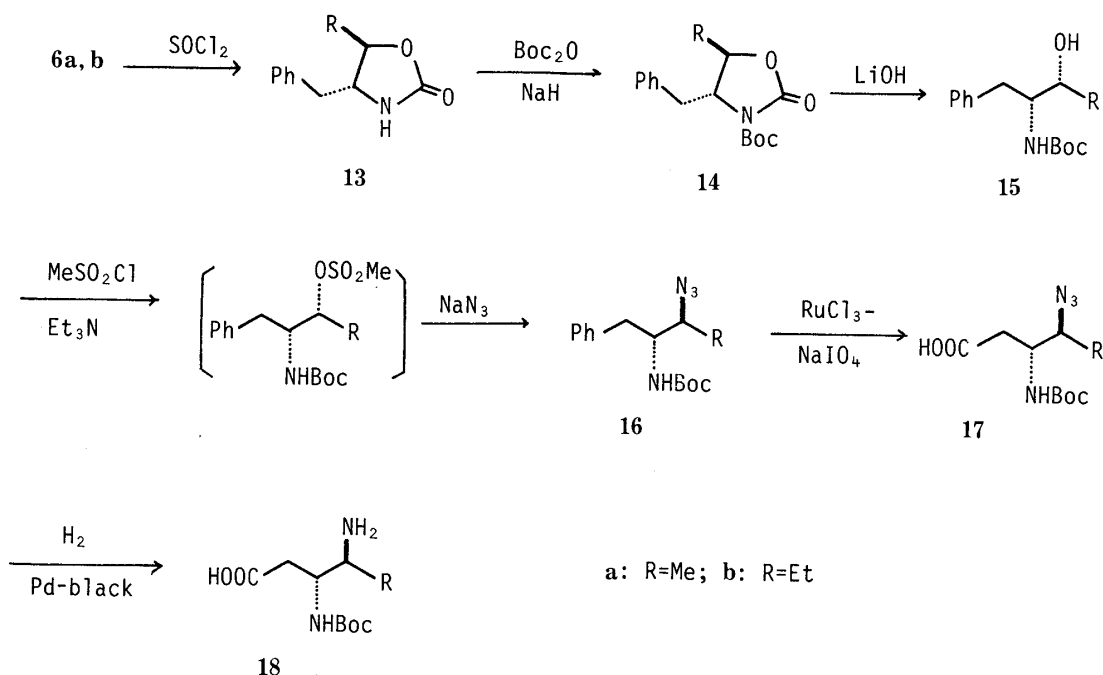


Chart 3

diastereomer. Conversion of the phenyl group to a carboxyl group was successfully achieved by oxidation of **10a, b** with ruthenium chloride–sodium metaperiodate according to Sharpless *et al.*⁶⁾ to give the corresponding *N*-Boc- β -amino- γ -azide acids (**11a, b**). Finally catalytic hydrogenation of **11a, b** over Pd black afforded the (3*R*,4*R*)-*N*³-Boc-3,4-diaminopentanoic acid (**12a**) and (3*R*,4*R*)-*N*³-Boc-3,4-diaminohexanoic acid (**12b**), respectively.

The method was successively applied to a synthesis of (3*R*,4*S*)-*N*³-Boc-3,4-diaminopentanoic acid (**18a**) and (3*R*,4*S*)-*N*³-Boc-3,4-diaminohexanoic acid (**18b**) by using (2*R*,3*R*)-*N*-Boc-2-amino-3-hydroxy-1-phenylbutane (**15a**) and (2*R*,3*R*)-*N*-Boc-2-amino-3-hydroxy-1-phenylpentane (**15b**). We have recently reported a new method for diastereoconversion of chiral 2-amino alcohols with a high degree of stereospecificity.⁵⁾ Compounds **15a, b** were easily obtained from **6a, b** by an application of this method. Treatment of **6a, b** with thionyl chloride gave the corresponding (4*R*,5*R*)-4,5-disubstituted oxazolidin-2-ones (**13a, b**), with inversion of the hydroxyl group, and these products were led to (2*R*,3*S*)-*N*-Boc-2-amino-3-azido-1-phenylbutane (**16a**) and (2*R*,3*S*)-*N*-Boc-2-amino-3-azido-1-phenylpentane (**16b**) by the same reaction sequences through **14a, b** and **15a, b** as in the synthesis of **10a, b** from **7a, b**. The hydroxyl group of **15a, b** was replaced by an azide group as in the preparation of **11a, b** to give **16a, b**, respectively. Oxidation of **16a, b** with ruthenium chloride–sodium metaperiodate, followed by catalytic hydrogenation of the resulting acids (**17a, b**) afforded **18a, b**, respectively.

Although the yields of the β,γ -diamino acids described in this paper were not optimized, the method should be widely applicable to the synthesis of a variety of β,γ -diamino acids such as aminostatine²⁾ and emeramine derivatives.¹⁾

Experimental

All melting points were determined on a Yanagimoto hot-stage apparatus and are uncorrected. Proton nuclear magnetic resonance (¹H-NMR) spectra were recorded on a Varian EM-390 (90 MHz) or a Bruker AM-400 (400 MHz) spectrometer and δ values are quoted relative to tetramethylsilane. The following abbreviations are used: br = broad, d = doublet, dd = doublet of doublets, dq = doublet of quartets, dt = doublet of triplets, m = multiplet, s = singlet, t = triplet. Infrared (IR) spectra were taken on a Hitachi 260-30 spectrophotometer or a Perkin-Elmer FTIR

1710 instrument. Mass spectra (MS) were measured with a Hitachi RMU-7L spectrometer. Benzyloxycarbonyl is abbreviated as Cbz and *tert*-butoxycarbonyl as Boc. Tetrahydrofuran (THF) and ether were distilled from sodium-benzophenone before use. All reactions were carried out under a nitrogen atmosphere except for the preparation of **12a, b** and **18a, b**.

***N*-Methoxy-*N*-methyl-*(R)*-*N*²-Cbz-phenylalaninamide (**4**)**—Ethyl chloroformate (2.6 g, 24 mmol) was added to a stirred mixture of *N*-Cbz-D-phenylalanine (5.98 g, 20 mmol), triethylamine (3.03 g, 30 mmol) and THF (15 ml) under cooling with ice-salt. After 10 min, a solution of *N,O*-dimethylhydroxylamine in THF [prepared from 3.90 g (40 mmol) of *N,O*-dimethylhydroxylamine hydrochloride, 2 ml of H₂O, 11 g (80 mmol) of K₂CO₃ and 50 ml of THF] was added to the reaction mixture. The whole was stirred at the same temperature for 0.5 h, the precipitate was removed by filtration, and the filtrate was diluted with 10% Na₂CO₃ and extracted with ether. The extract was dried (Na₂SO₄) and evaporated to leave **4** (5.61 g, 82% yield) as an oil. ¹H-NMR (CDCl₃) δ: 2.64–3.19 (2H, m, PhCH₂CH–), 3.12 (3H, s, NCH₃), 3.62 (3H, s, OCH₃), 4.82–5.13 (1H, m, NCH–), 5.03 (2H, s, PhCH₂O–), 7.06–7.47 (10H, m, Ar-H). IR (CHCl₃): 3440 (NH), 1715 (C=O), 1655 (NHC=O) cm⁻¹.

***(R)*-*N*-Cbz-2-Amino-1-phenyl-3-butanone (**5a**)**—A solution of **4** (10 g, 29.2 mmol) in THF (20 ml) was added dropwise to a solution of MeLi (88 ml of 1 M ether solution) in THF (250 ml) at –30 °C. After 1 h, the mixture was decomposed with 1 N HCl and extracted with ether. The extract was dried (MgSO₄) and evaporated. The remaining residue was chromatographed on silica gel (70 g) by using hexane–AcOEt (7:1) to give **5a** (5.55 g, 64% yield), mp 79–81 °C (AcOEt–hexane), [α]_D²⁰ –89.9° (c=1.0, chloroform). ¹H-NMR (CDCl₃) δ: 2.09 (3H, s, COCH₃), 2.92 (1H, dd, *J*=7, 14 Hz, PhCH–), 3.13 (1H, dd, *J*=7, 14 Hz, PhCH–), 4.39–4.77 (1H, m, N–CH), 5.08 (2H, s, PhCH₂O–), 7.04–7.52 (10H, m, Ar-H). IR (CHCl₃): 3440 (NH), 1710 (C=O) cm⁻¹. Anal. Calcd for C₁₈H₁₉NO₃: C, 72.70; H, 6.44; N, 4.71. Found: C, 72.75; H, 6.39; N, 4.69.

***(R)*-*N*-Cbz-2-Amino-1-phenyl-3-pentanone (**5b**)**—A solution of EtMgBr (60 ml of 3 M ether solution, 60 mmol) was added to a solution of **4** (5.13 g, 15 mmol) in THF (150 ml) under ice-cooling. After being stirred at the same temperature for 6 h, the mixture was poured into 1 N HCl and extracted with ether. The extract was washed with brine, dried (MgSO₄) and evaporated. The remaining residue was chromatographed on silica gel (60 g) by using hexane–AcOEt (5:1) as an eluant. Removal of the solvent gave **5b** (4.06 g, 87% yield), mp 55–57 °C (ether–hexane), [α]_D²⁰ –64.0° (c=1.1, chloroform). IR (neat): 3320 (NH), 1730 (C=O), 1690 (NHC=O) cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.98 (3H, t, *J*=7 Hz, CH₃CH₂–), 2.35 (2H, q, *J*=7 Hz, CH₃CH₂–), 2.98 (2H, br d, *J*=6 Hz, PhCH₂CH), 4.59 (1H, dt, *J*=7, 7 Hz, NCH–), 5.07 (2H, s, PhCH₂O), 7.04–7.46 (10H, m, Ar-H). Anal. Calcd for C₁₉H₂₁NO₃: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.38; H, 6.83; N, 4.72.

***(2R,3S)*-*N*-Cbz-2-Amino-3-hydroxy-1-phenylbutane (**6a**)**—A solution of TiCl₄ (18.3 ml of 3 M solution in CH₂Cl₂, 54.9 mmol) was added to a stirred mixture of **5a** (5.45 g, 18.3 mmol), Et₃SiH (4.25 g, 36.6 mmol) and CH₂Cl₂ (180 ml) under ice-cooling. After being stirred at the same temperature for 1 h, the mixture was poured into 1 N HCl and extracted with CHCl₃. The extract was washed with brine, dried (Na₂SO₄) and evaporated. Recrystallization of the resulting residue from AcOEt–hexane afforded **6a** (4.51 g, 82% yield), mp 139–141 °C, [α]_D²⁰ +42.4° (c=1.1, chloroform). IR (CHCl₃): 3560 (NH or OH), 3450 (NH or OH), 1705 (NHC=O) cm⁻¹. MS *m/z*: 299 (M⁺). ¹H-NMR (CDCl₃) δ: 1.22 (3H, d, *J*=6 Hz, CH₃CH–), 2.70 (1H, dd, *J*=8, 14 Hz, PhCH–), 2.93 (1H, dd, *J*=5, 14 Hz, PhCH–), 3.74–4.07 (2H, m, 2-H and 3-H), 5.04 (2H, s, PhCH₂O–), 7.09–7.47 (10H, m, Ar-H). Anal. Calcd for C₁₈H₂₁NO₃: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.33; H, 7.03; N, 4.67.

***(2R,3S)*-*N*-Cbz-2-Amino-3-hydroxy-1-phenylpentane (**6b**)**—This compound was obtained from **5b** (5.69 g, 18.3 mmol) in 62% yield (3.55 g) according to the same procedure as used for the preparation of **6a**, mp 166–167 °C (AcOEt–hexane), [α]_D²⁰ +32.5° (c=0.9, chloroform). IR (CHCl₃): 3310 (NH and OH), 1685 (NHC=O) cm⁻¹. CI-MS *m/z*: 314 (M⁺ + 1). ¹H-NMR (CDCl₃) δ: 1.00 (3H, t, *J*=7 Hz, CH₃CH₂–), 1.39 (2H, m, CH₃CH₂–), 2.72 (1H, dd, *J*=9, 14 Hz, PhCH–), 2.96 (1H, dd, *J*=5, 14 Hz, PhCH–), 3.49–3.79 (1H, m, 2-H), 3.79–4.07 (1H, m, 3-H), 5.02 (2H, s, PhCH₂O–), 7.06–7.62 (10H, m, Ar-H). Anal. Calcd for C₁₉H₂₃NO₃: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.80; H, 7.24; N, 4.38.

***(4R,5S)*-4-Benzyl-5-methyloxazolidin-2-one (**7a**)**—A mixture of **6a** (4.49 g, 15 mmol), 7.5 N NaOH (15 ml), THF (60 ml) and MeOH (30 ml) was stirred at room temperature for 3 h and the solvent was evaporated off. The remaining residue was diluted with H₂O and extracted with CHCl₃. The extract was washed with brine, dried (Na₂SO₄) and evaporated. The resulting residue was chromatographed on silica gel by using AcOEt–hexane (1:2) as an eluant. Removal of the solvent gave **7a** (2.06 g, 72% yield), mp 97–99 °C (ether–hexane), [α]_D²⁰ +138.1° (c=1.2, chloroform). IR (CHCl₃): 3460 (NH), 1750 (C=O) cm⁻¹. CI-MS *m/z*: 192 (M⁺ + 1). ¹H-NMR (CDCl₃) δ: 1.42 (3H, d, *J*=6 Hz, 5-CH₃), 2.64 (1H, dd, *J*=10, 13 Hz, PhCH–), 2.90 (1H, dd, *J*=5, 13 Hz, PhCH–), 3.97 (1H, ddd, *J*=5, 8, 10 Hz, 4-H), 4.80 (1H, dq, *J*=6, 8 Hz, 5-H), 7.07–7.44 (5H, m, Ar-H). Anal. Calcd for C₁₁H₁₃NO₂: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.80; H, 6.92; N, 7.62.

***(4R,5S)*-4-Benzyl-5-ethyloxazolidin-2-one (**7b**)**—This compound was obtained from **6b** (4.70 g, 15 mmol) in 84% yield (2.58 g) according to the same procedure as used for the preparation of **7a**, mp 58–60 °C (ether–hexane), [α]_D²⁰ +108.3° (c=1.6, chloroform). IR (neat): 3270 (NH), 1760 (C=O) cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.10 (3H, t, *J*=7 Hz, CH₃CH₂–), 1.51–2.07 (2H, m, CH₃CH₂–), 2.64 (1H, dd, *J*=10, 13 Hz, PhCH–), 2.89 (1H, dd, *J*=5, 13 Hz, PhCH–), 3.45–3.83 (1H, m, 4-H), 4.36–4.68 (1H, m, 5-H), 7.02–7.44 (5H, m, Ar-H). Anal. Calcd for C₁₂H₁₅NO₂:

C, 70.22; H, 7.37; N, 6.82. Found: C, 70.33; H, 7.49; N, 6.81.

(4R,5R)-4-Benzyl-5-methyloxazolidin-2-one (13a)—A mixture of **6a** (3.29 g, 11 mol) and SOCl_2 (12 ml) was heated at 50 °C for 24 h. The mixture was poured into H_2O under ice-cooling, made basic with 10% Na_2CO_3 and extracted with CHCl_3 . The extract was washed with brine, dried (Na_2SO_4) and evaporated. The resulting residue was chromatographed on silica gel by using AcOEt –hexane (1 : 2) as an eluant. Removal of the solvent gave **13a** (1.81 g, 86% yield), mp 114–116 °C (AcOEt –hexane), $[\alpha]_{\text{D}}^{20} + 71.1^\circ$ ($c = 0.9$, chloroform). IR (CHCl_3): 3460 (NH), 1750 ($\text{C}=\text{O}$) cm^{-1} . CI-MS m/z : 192 ($\text{M}^+ + 1$). $^1\text{H-NMR}$ (CDCl_3) δ : 1.23 (3H, d, $J = 7$ Hz, 5-CH_3), 2.73 (1H, dd, $J = 7$, 15 Hz, PhCH_2), 2.90 (1H, dd, $J = 7$, 15 Hz, PhCH_2), 3.60 (1H, dd, $J = 6$, 7 Hz, 4-H), 4.36 (1H, dq, $J = 6$, 6 Hz, 5-H), 7.06–7.44 (5H, m, Ar-H). Anal. Calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.28; H, 6.82; N, 7.59.

(4R,5R)-4-Benzyl-5-ethyloxazolidin-2-one (13b)—This compound was obtained from **6b** (3.44 g, 11 mmol) according to the same procedure as used for the preparation of **13a** in 77% yield (1.74 g), mp 75–77 °C (ether–hexane), $[\alpha]_{\text{D}}^{20} + 82.8^\circ$ ($c = 1.0$, chloroform). IR (neat): 3280 (NH), 1740 ($\text{C}=\text{O}$) cm^{-1} . CI-MS m/z : 206 ($\text{M}^+ + 1$). $^1\text{H-NMR}$ (CDCl_3) δ : 0.88 (3H, t, $J = 7$ Hz, CH_3CH_2), 1.26–1.80 (2H, m, CH_3CH_2), 2.76 (1H, dd, $J = 6$, 15 Hz, PhCH_2), 2.93 (1H, dd, $J = 6$, 15 Hz, PhCH_2), 3.64 (1H, dd, $J = 6$, 6 Hz, 4-H), 4.18 (1H, dd, $J = 6$, 6 Hz, 5-H), 7.09–7.42 (5H, m, Ar-H). Anal. Calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.08; H, 7.41; N, 6.79.

(4R,5S)-4-Benzyl-3-Boc-5-methyloxazolidin-2-one (8a)—A solution of **7a** (1.15 g, 6 mmol) in THF was added to a stirred suspension of NaH (720 mg of 60% suspension in oil, used after being washed with pet. ether) in THF (10 ml) under ice-cooling. After 1 h, a solution of Boc_2O (1.96 g, 9 mmol) in THF (5 ml) was added. Stirring was continued at the same temperature for 10 min and further at room temperature for 6 h, then the mixture was poured into aqueous NH_4Cl and extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and evaporated. The remaining residue was chromatographed on silica gel (30 g) by using AcOEt –hexane (1 : 9) as an eluant. Removal of the solvent yielded **8a** (1.4 g, 80% yield), mp 109–111 °C (ether–hexane), $[\alpha]_{\text{D}}^{20} + 33.4^\circ$ ($c = 1.1$, chloroform). IR (CHCl_3): 1805 ($\text{C}=\text{O}$), 1715 ($\text{C}=\text{O}$) cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.33 (3H, d, $J = 6$ Hz, 5-CH_3), 1.43 (9H, s, $-\text{C}(\text{CH}_3)_3$), 2.91–3.08 (2H, m, $4\text{-CH}_2\text{Ph}$), 4.40–4.86 (2H, m, 4-H and 5-H), 7.17–7.43 (5H, m, Ar-H). Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.57; H, 7.37; N, 4.84.

(4R,5S)-4-Benzyl-3-Boc-5-ethyloxazolidin-2-one (8b)—This compound was obtained from **7b** (1.23 g, 6 mmol) in 84% yield (1.54 g) according to the same procedure as used in the synthesis of **8a**, mp 89.5–90.5 °C (ether–hexane), $[\alpha]_{\text{D}}^{20} + 13.3^\circ$ ($c = 0.93$, chloroform). IR (neat): 1805 ($\text{C}=\text{O}$), 1720 ($\text{C}=\text{O}$) cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.93 (3H, t, $J = 7$ Hz, CH_3CH_2), 1.30–2.13 (2H, m, CH_3CH_2), 1.42 (9H, s, $-\text{C}(\text{CH}_3)_3$), 2.97 (2H, d, $J = 7$ Hz, $4\text{-CH}_2\text{Ph}$), 4.30–4.69 (2H, m, 4-H and 5-H), 7.30 (5H, s, Ar-H). Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.88; H, 7.40; N, 4.59.

(4R,5R)-4-Benzyl-3-Boc-5-methyloxazolidin-2-one (14a)—This compound was obtained from **13a** (1.15 g, 6 mmol) in 73% yield (1.27 g) according to the same procedure as described for the synthesis of **8a**, mp 69–71 °C (ether–hexane), $[\alpha]_{\text{D}}^{20} + 1.6^\circ$ ($c = 1.3$, chloroform). IR (neat): 1810 ($\text{C}=\text{O}$), 1715 ($\text{C}=\text{O}$) cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.16 (3H, d, $J = 6$ Hz, 5-CH_3), 1.58 (9H, s, $-\text{C}(\text{CH}_3)_3$), 2.72 (1H, dd, $J = 9$, 14 Hz, 4-CHPh), 3.31 (1H, dd, $J = 4$, 14 Hz, 4-CHPh), 3.90–4.13 (1H, m, 4-H), 4.18–4.48 (1H, m, 5-H), 7.09–7.49 (5H, m, Ar-H). Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 66.04; H, 7.26; N, 4.77.

(4R,5R)-4-Benzyl-3-Boc-5-ethyloxazolidin-2-one (14b)—This compound was obtained from **13b** (1.23 g, 6 mmol) in 95% yield (1.74 g) according to the same procedure as used for the preparation of **8a**, mp 78–79 °C (ether–hexane), $[\alpha]_{\text{D}}^{20} + 8.8^\circ$ ($c = 2.0$, chloroform). IR (neat): 1820 ($\text{C}=\text{O}$), 1725 ($\text{C}=\text{O}$) cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 0.71 (3H, t, $J = 7$ Hz, CH_3CH_2), 1.09–1.77 (2H, m, CH_3CH_2), 1.58 (9H, s, $-\text{C}(\text{CH}_3)_3$), 2.73 (1H, dd, $J = 9$, 13 Hz, 4-CHPh), 3.29 (1H, dd, $J = 4$, 13 Hz, 4-CHPh), 3.96–4.18 (2H, m, 4-H and 5-H), 7.10–7.48 (5H, m, Ar-H). Anal. Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.35; H, 7.59; N, 4.54.

(2R,3S)-N-Boc-2-Amino-3-hydroxy-1-phenylbutane (9a)—A mixture of **8a** (1.46 g, 5 mmol), dioxane (40 ml), H_2O (4 ml) and $\text{LiOH} \cdot \text{H}_2\text{O}$ (0.84 g, 20 mmol) was stirred at room temperature for 8 h, then poured into H_2O and extracted with ether. The extract was washed with brine, dried (MgSO_4) and evaporated. The remaining residue was chromatographed on silica gel by using AcOEt –hexane (1 : 9) as an eluant. Removal of the solvent gave **9a** (1.11 g, 84% yield), mp 139–141 °C (AcOEt –hexane), $[\alpha]_{\text{D}}^{20} + 35.5^\circ$ ($c = 1.3$, chloroform). IR (CHCl_3): 3540, 3440 (OH and NH), 1690 ($\text{C}=\text{O}$) cm^{-1} . CI-MS m/z : 266 ($\text{M}^+ + 1$). $^1\text{H-NMR}$ (CDCl_3) δ : 0.89 (3H, d, $J = 6$ Hz, 3-CH_3), 1.38 (9H, s, $-\text{C}(\text{CH}_3)_3$), 2.70–2.94 (2H, m, PhCH_2), 3.62–4.11 (2H, m, 2-H and 3-H), 7.12–7.51 (5H, m, Ar-H). Anal. Calcd for $\text{C}_{15}\text{H}_{23}\text{NO}_3$: C, 67.89; H, 8.74; N, 5.28. Found: C, 68.15; H, 8.67; N, 4.98.

(2R,3S)-N-Boc-2-Amino-3-hydroxy-1-phenylpentane (9b)—This compound was obtained from **8b** (1.53 g, 5 mmol) in 77% yield (1.07 g) according to the same procedure as used for the preparation of **9a**, mp 164–165 °C (AcOEt –hexane), $[\alpha]_{\text{D}}^{20} + 31.7^\circ$ ($c = 0.9$, chloroform). IR (neat): 3350 (NH and OH), 1680 ($\text{C}=\text{O}$) cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.00 (3H, t, $J = 7$ Hz, CH_3CH_2), 1.34 (9H, s, $-\text{C}(\text{CH}_3)_3$), 1.36–1.70 (2H, m, CH_3CH_2), 2.66 (1H, dd, $J = 9$, 14 Hz, PhCH_2), 2.89 (1H, dd, $J = 5$, 14 Hz, PhCH_2), 3.46–3.98 (2H, m, 2-H and 3-H), 7.22 (5H, s, Ar-H). Anal. Calcd for $\text{C}_{10}\text{H}_{25}\text{NO}_3$: C, 68.78; H, 9.02; N, 5.01. Found: C, 68.87; H, 8.90; N, 5.08.

(2R,3R)-N-Boc-2-Amino-3-hydroxy-1-phenylbutane (15a)—This compound was obtained from **14a** (1.46 g, 5 mmol) in 71% yield (941 mg) according to the same procedure as used for the synthesis of **9a**, mp 95–97 °C (hexane), $[\alpha]_{\text{D}}^{20} + 28.2^\circ$ ($c = 1.2$, chloroform). IR (CHCl_3): 3560 (OH or NH), 3450 (OH or NH), 1700 ($\text{C}=\text{O}$) cm^{-1} .

¹H-NMR (CDCl₃) δ: 1.18 (3H, d, *J* = 6 Hz, CH₃CH–), 1.38 (9H, s, –C(CH₃)₃), 2.89 (2H, d, *J* = 7 Hz, PhCH–), 3.49–3.97 (2H, m, 2-H and 3-H), 7.23 (5H, s, Ar-H). Anal. Calcd for C₁₅H₂₃NO₃: C, 67.89; H, 8.74; N, 5.28. Found: C, 68.07; H, 8.65; N, 5.56.

(2R,3R)-N-Boc-2-Amino-3-hydroxy-1-phenylpentane (15b)—This compound was obtained from **14b** (1.53 g, 5 mmol) in 63% yield (879 mg), mp 69–70 °C (hexane), [α]_D²⁰ + 24.0° (*c* = 0.97, chloroform). IR (neat): 3430 (OH and NH), 1690 (C=O) cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.89 (3H, t, *J* = 7 Hz, CH₃CH₂–), 1.33–1.69 (2H, m, CH₃CH₂–), 1.40 (9H, s, –C(CH₃)₃), 2.88 (2H, d, *J* = 7 Hz, PhCH₂CH–), 3.42 (1H, dt, *J* = 3, 7 Hz, 2-H), 3.58–3.94 (1H, m, 3-H), 7.30 (5H, s, Ar-H). Anal. Calcd for C₁₆H₂₅NO₃: C, 68.78; H, 9.02; N, 5.01. Found: C, 68.62; H, 9.06; N, 4.96.

(2R,3R)-N-Boc-2-Amino-3-azido-1-phenylbutane (10a)—Methanesulfonyl chloride (0.55 g, 4.8 mmol) was added to a stirred mixture of **9a** (1.06 g, 4 mmol), Et₃N (606 mg, 6 mmol) and CH₂Cl₂ (20 ml) under ice-cooling. After being stirred at the same temperature for 0.5 h, the mixture was poured into H₂O and extracted with ether. The extract was washed with brine, dried (MgSO₄) and evaporated. A mixture of the resulting residue, NaN₃ (5.2 g, 80 mmol) and dimethylformamide (DMF) (20 ml) was heated at 50 °C under stirring for 16 h. The mixture was diluted with H₂O and extracted with ether. The extract was washed with brine, dried (MgSO₄) and evaporated. The remaining residue was chromatographed on silica gel (30 g) by using ether–hexane (1 : 9) as an eluant. Removal of the solvent gave **10a** (603 mg, 52% yield), mp 61.5–63 °C (hexane), [α]_D²⁰ – 30.3° (*c* = 1.1, chloroform). IR (CHCl₃): 3450 (NH), 2110 (N₃), 1710 (C=O) cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.27 (3H, d, *J* = 6 Hz, CH₃CH–), 1.42 (9H, s, –C(CH₃)₃), 2.73 (1H, dd, *J* = 8, 14 Hz, PhCH–), 2.79 (1H, dd, *J* = 6, 14 Hz, PhCH–), 3.54 (1H, dq, *J* = 2, 6 Hz, –CHN₃), 3.66–4.04 (1H, m, –CHNH₂Boc), 7.10–7.48 (5H, m, Ar-H). Anal. Calcd for C₁₅H₂₂N₄O₂: C, 62.04; H, 7.64; N, 19.30. Found: C, 61.91; H, 7.65; N, 19.47.

(2R,3R)-N-Boc-2-Amino-3-azido-1-phenylpentane (10b)—This compound was obtained from **9b** (1.12 g, 4 mmol) in 65% yield (790 mg) as an oil according to the same procedure as used in the synthesis of **10a**, [α]_D²⁰ – 2.9° (*c* = 1.9, chloroform). IR (CHCl₃): 3450 (NH), 2100 (N₃), 1700 (C=O) cm⁻¹. ¹H-NMR (CDCl₃) δ: 0.94 (3H, t, *J* = 7 Hz, CH₃CH₂–), 1.39 (9H, s, –C(CH₃)₃), 1.43–1.84 (2H, m, CH₃CH₂–), 2.74 (1H, dd, *J* = 8, 14 Hz, PhCH–), 2.94 (1H, dd, *J* = 7, 14 Hz, PhCH–), 3.27 (1H, dt, *J* = 2, 7 Hz, –CHN₃), 3.77–4.16 (1H, m, –CHNH₂Boc), 7.10–7.44 (5H, m, Ar-H).

(2R,3S)-N-Boc-2-Amino-3-azido-1-phenylbutane (16a)—This compound was obtained from **15a** (1.06 g, 4 mmol) according to the same procedure as used in the synthesis of **11a** in 62% yield (719 mg), mp 75–77 °C (hexane), [α]_D²⁰ + 65.1° (*c* = 1.1, chloroform). IR (CHCl₃): 3450 (NH), 2100 (N₃), 1700 (C=O) cm⁻¹. CI-MS *m/z*: 291 (*M*⁺ + 1). ¹H-NMR (CDCl₃) δ: 1.31 (3H, d, *J* = 6 Hz, CH₃CH–), 1.33 (9H, s, –C(CH₃)₃), 2.51 (1H, dd, *J* = 8, 14 Hz, PhCH–), 2.91 (1H, dd, *J* = 5, 14 Hz, PhCH–), 3.47–3.96 (2H, m, –CHN₃ and –CHNH₂Boc), 7.11–7.42 (5H, m, Ar-H). Anal. Calcd for C₁₅H₂₂N₄O₂: C, 62.04; H, 7.64; N, 19.30. Found: C, 62.07; H, 7.60; N, 19.62.

(2R,3S)-N-Boc-2-Amino-3-azido-1-phenylpentane (16b)—This compound was obtained from **15b** (1.12 g, 4 mmol) according to the same procedure as used in the synthesis of **10a** in 91% yield (1.06 g), mp 90–91 °C (hexane), [α]_D²⁰ + 43.0° (*c* = 1.0, chloroform). IR (CHCl₃): 3450 (NH), 2100 (N₃), 1700 (C=O) cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.07 (3H, t, *J* = 7 Hz, CH₃CH₂–), 1.34 (9H, s, –C(CH₃)₃), 1.51–1.88 (2H, m, CH₃CH₂–), 2.63 (1H, dd, *J* = 9, 14 Hz, PhCH–), 2.94 (1H, dd, *J* = 5, 14 Hz, PhCH–), 3.37–3.57 (1H, m, –CHN₃), 3.80–4.17 (1H, m, –CHNH₂Boc), 7.13–7.48 (5H, m, Ar-H). Anal. Calcd for C₁₆H₂₄N₄O₂: C, 63.18; H, 7.95; N, 18.41. Found: C, 62.97; H, 7.89; N, 18.31.

(3R,4R)-N-Boc-3-Amino-4-azidopentanoic Acid (11a)—A mixture of **10a** (1.16 g, 4 mmol), CCl₄ (30 ml), CH₃CN (30 ml), H₂O (45 ml), NaIO₄ (17 g, 80 mmol) and RuCl₃ · H₂O (18 mg, 0.088 mmol) was stirred under ice-cooling. Stirring was continued at the same temperature for 0.5 h and at room temperature for 48 h, then isopropanol was added to the reaction mixture and the whole was extracted with CHCl₃. The combined organic layer was extracted with 0.2 N NaOH. The aqueous layer was made acidic with 1 N HCl and extracted with CHCl₃. The extract was washed with brine, dried (Na₂SO₄) and evaporated. The remaining residue was chromatographed on silica gel. Elution with AcOEt–hexane (1 : 4) gave **11a** (568 mg, 55% yield) as an oil, [α]_D²⁰ – 8.2° (*c* = 1.1, methanol). ¹H-NMR (CDCl₃) δ: 1.31 (3H, d, *J* = 6 Hz, CH₃CH–), 1.41 (9H, s, –C(CH₃)₃), 2.57 (2H, d, *J* = 6 Hz, CH₂COOH), 3.64–4.20 (2H, m, –CHN₃ and –CHNH₂Boc). IR (CHCl₃): 3450 (NH), 2750–2400 (OH), 2110 (N₃), 1710 (C=O) cm⁻¹. CI-MS *m/z*: 259 (*M*⁺ + 1).

(3R,4R)-N-Boc-3-Amino-4-azidohexanoic Acid (11b)—This compound was obtained from **10b** in 50% yield (544 mg) according to the same procedure as used in the preparation of **11a**. Oil, [α]_D²⁰ + 19.1° (*c* = 1.0, methanol). ¹H-NMR (CDCl₃) δ: 1.06 (3H, t, *J* = 7 Hz, CH₃CH₂–), 1.44 (9H, s, –C(CH₃)₃), 1.49–1.82 (2H, m, CH₃CH₂–), 2.59 (2H, d, *J* = 7 Hz, –CH₂COOH), 3.33–3.66 (1H, m, –CHN₃), 3.93–4.32 (1H, m, –CHNH₂Boc). IR (neat): 3320 (NH), 2800–2400 (OH), 2100 (N₃), 1700 (C=O) cm⁻¹. CI-MS *m/z*: 273 (*M*⁺ + 1).

(3R,4S)-N-Boc-3-Amino-4-azidopentanoic Acid (17a)—This compound was obtained from **16a** (1.16 g, 4 mmol) in 47% yield (485 mg) according to the same procedure as used in the preparation of **11a**. Oil, [α]_D²⁰ + 47.0° (*c* = 1.4, methanol). ¹H-NMR (CDCl₃) δ: 1.32 (3H, d, *J* = 6 Hz, –CHCH₃), 1.46 (9H, s, –C(CH₃)₃), 2.60 (2H, d, *J* = 5 Hz, CH₂COOH), 3.51–4.09 (2H, m, –CHN₃ and –CHNH₂Boc). IR (CHCl₃): 3440 (NH), 2800–2380 (OH), 2100 (N₃), 1710 (C=O) cm⁻¹. CI-MS *m/z*: 259 (*M*⁺ + 1).

(3R,4S)-N-Boc-3-Amino-4-azidohexanoic Acid (17b)—This compound was obtained from **16b** (1.22 g, 4 mmol) in 45% yield (490 mg) according to the same procedure as described for the preparation of **11a**, mp 100–101 °C

(ether-hexane), $[\alpha]_D^{20} + 21.2^\circ$ ($c = 1.0$, methanol). $^1\text{H-NMR}$ (CDCl_3) δ : 1.07 (3H, t, $J = 7$ Hz, CH_3CH_2-), 1.23—1.90 (2H, CH_3CH_2-), 1.46 (9H, s, $-\text{C}(\text{CH}_3)_3$), 2.55 (2H, d, $J = 5$ Hz, $-\text{CH}_2\text{COOH}$), 3.42—3.64 (1H, m, $-\text{CHNH}_2$), 3.83—4.26 (1H, m, $-\text{CHNHBOc}$), 9.40 (1H, brs, COOH). IR (neat): 3320 (NH), 2700—2400 (OH), 2100 (N_3), 1710 ($\text{C}=\text{O}$) cm^{-1} . Anal. Calcd for $\text{C}_{11}\text{H}_{20}\text{N}_4\text{O}_4$: C, 48.52; H, 7.40; N, 20.58. Found: C, 48.68; H, 7.35; N, 20.67.

(3R,4R)- N^3 -Boc-3,4-Diaminopentanoic Acid (12a)—A mixture of **11a** (774 mg, 3 mmol), MeOH (30 ml) and Pd-black (10 mg) was shaken under 1 atm of hydrogen for 20 h. After removal of the catalyst by filtration, the solvent was evaporated off. The resulting solid was recrystallized from MeOH-ether to give **12a** (315 mg, 42% yield), mp 148—151 $^\circ\text{C}$, $[\alpha]_D^{20} - 4.4^\circ$ ($c = 0.5$, methanol). $^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 1.28 (3H, d, $J = 6.79$ Hz, $4-\text{CH}_3$), 1.45 (9H, s, $-\text{C}(\text{CH}_3)_3$), 2.49 (1H, dd, $J = 4.74, 16.25$ Hz, HOOCCH_2-), 2.57 (1H, dd, $J = 6.82, 16.24$ Hz, HOOCCH_2-), 3.43 (1H, dq, $J = 4.92, 6.80$ Hz, $4-\text{H}$), 3.87—3.90 (1H, m, $3-\text{H}$). IR (neat): 3230 (NH), 2750—2400 (OH), 1685 ($\text{C}=\text{O}$) cm^{-1} . Anal. Calcd for $\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_4 \cdot \text{H}_2\text{O}$: C, 47.98; H, 8.86; N, 11.19. Found: C, 48.45; H, 8.73; N, 11.19.

(3R,4R)- N^3 -Boc-3,4-Diaminohexanoic Acid (12b)—This compound was obtained from **11b** (816 mg, 3 mmol) in 39% yield (288 mg) according to the same procedure as described for the preparation of **12a**, mp 171—173 $^\circ\text{C}$ (MeOH-ether), $[\alpha]_D^{20} + 7.0^\circ$ ($c = 0.9$, methanol). $^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 1.04 (3H, t, $J = 7.44$ Hz, CH_3CH_2-), 1.45 (9H, s, $-\text{C}(\text{CH}_3)_3$), 1.52—1.78 (2H, m, CH_3CH_2-), 2.55 (1H, dd, $J = 4.12, 16.48$ Hz, CHCOOH), 2.64 (1H, dd, $J = 6.72, 16.48$ Hz, CHCOOH), 3.17—3.21 (1H, m, $-\text{CHNH}_2$), 3.98—4.01 (1H, m, $-\text{CHNHBOc}$). IR (neat): 3230 (NH), 2760—2400 (OH), 1700 ($\text{C}=\text{O}$) cm^{-1} . Anal. Calcd for $\text{C}_{11}\text{H}_{22}\text{N}_2\text{O}_4$: C, 53.64; H, 9.00; N, 11.37. Found: C, 53.51; H, 9.00; N, 11.20.

(3R,4S)- N^3 -Boc-3,4-Diaminopentanoic Acid (18a)—This compound was obtained from **17a** (774 mg, 3 mmol) in 39% yield (300 mg) according to the same procedure as described for the preparation of **12a**, mp 179—181 $^\circ\text{C}$ (MeOH-ether), $[\alpha]_D^{20} + 4.0^\circ$ ($c = 1.0$, methanol). $^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 1.24 (3H, d, $J = 6.78$ Hz, CH_3CH_2-), 1.45 (9H, s, $-\text{C}(\text{CH}_3)_3$), 2.42 (2H, d, $J = 6.09$ Hz, CH_2COOH), 3.42—3.48 (1H, m, $-\text{CHNH}_2$), 4.02—4.07 (1H, m, $-\text{CHNHBOc}$). IR (neat): 3390 (NH), 2800—2400 (OH), 1700 ($\text{C}=\text{O}$) cm^{-1} . Anal. Calcd for $\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_4$: C, 51.70; H, 8.68; N, 12.06. Found: C, 51.60; H, 8.59; N, 12.19.

(3R,4R)- N^3 -Boc-3,4-Diaminohexanoic Acid (18b)—This compound was obtained from **17b** (816 mg, 3 mmol) in 15% yield (111 mg) according to the same procedure as described for the preparation of **12a**, mp 151—153 $^\circ\text{C}$ (MeOH-ether), $[\alpha]_D^{20} 0.0^\circ$ ($c = 1.0$, methanol). $^1\text{H-NMR}$ (400 MHz, CD_3OD) δ : 1.04 (3H, t, $J = 7.50$ Hz, CH_3CH_2-), 1.45 (9H, s, $-\text{C}(\text{CH}_3)_3$), 1.52—1.79 (2H, m, CH_3CH_2-), 2.45 (1H, d, $J = 6.12$ Hz, CH_2COOH), 3.20—3.25 (1H, m, $-\text{CHNH}_2$), 4.02 (1H, dt, $J = 5.01, 6.12$ Hz, $-\text{CHNHBOc}$). IR (neat): 3370 (NH), 2800—2400 (OH), 1680 ($\text{C}=\text{O}$) cm^{-1} . Anal. Calcd for $\text{C}_{11}\text{H}_{22}\text{N}_2\text{O}_4$: C, 53.64; H, 9.00; N, 11.37. Found: C, 53.93; H, 8.70; N, 11.21.

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