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

SHINZO KANO,* TSUTOMU YOKOMATSU, HARUO IWASAWA, and SHIROSHI SHIBUYA

Tokyo College of Pharmacy, 1432–1 Horinouchi, Hachioji, Tokyo 192–03, Japan

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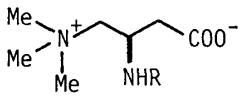
(2*R*,3*S*)-*N*-Boc-2-Amino-3-hydroxy-1-phenylbutane (**9a**) and (2*R*,3*S*)-*N*-Boc-2-amino-3-hydroxy-1-phenylpentane (**9b**) were converted to (3*R*,4*R*)-N^3-Boc-3,4-diaminopentanoic acid (**12a**) and (3*R*,4*R*)-N^3-Boc-3,4-diaminohexanoic acid (**12b**) through *S*N2 type substitution of the 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

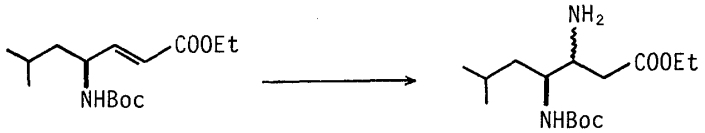
Recently, stereoselective synthesis of β,γ-diamino acids has received considerable attention because of the wide range of biological activities of these compounds.[1-3] Emericedines A (**1a**), B (**1b**), and C (**1c**), new betaines that inhibit long chain fatty acid-oxidation, were isolated and some analogous compounds were synthesized.[1] (3*R*)-β,γ-Diaminobutyric acids without a substituent at the γ-position have been prepared from L-asparaginine.[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=CH_3CO

1b: R=CH_3CH_2CO

1c: R=$CH_3CH_2CH_2CO$



2 3

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 tetrachloride[5] gave the best results among several kinds of reducing agents tested. Reduction of **5a, b** with triethylsilane in the presence of titanium tetrachloride[5] 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 dioxane[5] 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

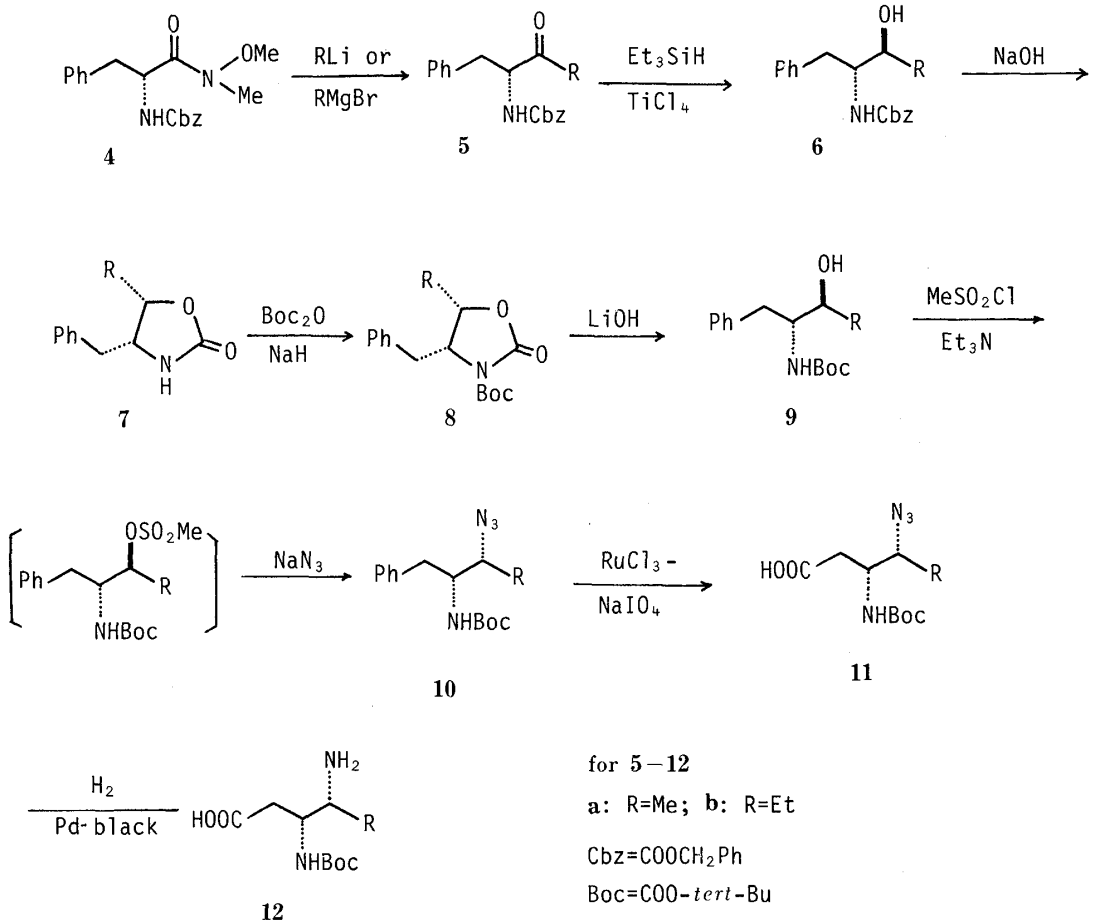
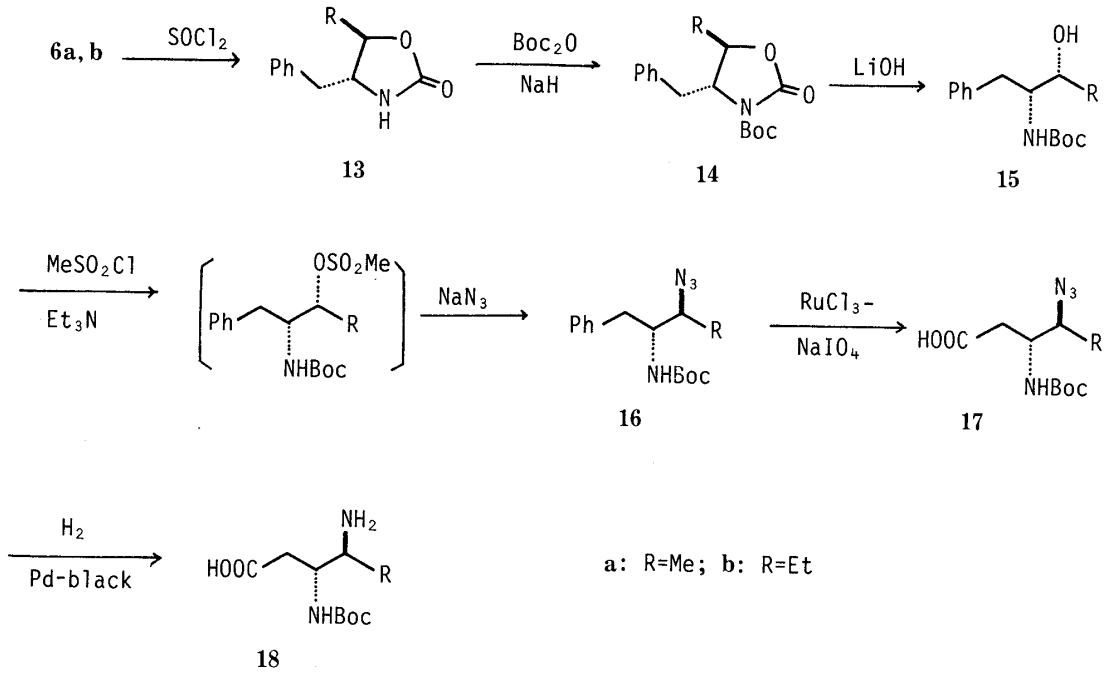


Chart 2



13 14 15 16 17 18

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 aminostatine[2] and emeriamine derivatives.[1]

Experimental

All melting points were determined on a Yanagimoto hot-stage apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-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 H_2O, 11 g (80 mmol) of K_2CO_3 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% Na_2CO_3 and extracted with ether. The extract was dried (Na_2SO_4) and evaporated to leave **4** (5.61 g, 82% yield) as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.64—3.19 (2H, m, $PhC\underline{H}_2CH$–), 3.12 (3H, s, $NC\underline{H}_3$), 3.62 (3H, s, $OC\underline{H}_3$), 4.82—5.13 (1H, m, $NC\underline{H}$–), 5.03 (2H, s, $PhC\underline{H}_2O$–), 7.06—7.47 (10H, m, Ar-$\underline{H}$). IR ($CHCl_3$): 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 exact was dried ($MgSO_4$) 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), $[\alpha]_D^{20}$ −89.9° (c=1.0, chloroform). ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s, $COC\underline{H}_3$), 2.92 (1H, dd, J=7, 14 Hz, $PhC\underline{H}$–), 3.13 (1H, dd, J=7, 14 Hz, $PhC\underline{H}$–), 4.39—4.77 (1H, m, N–$C\underline{H}$), 5.08 (2H, s, $PhC\underline{H}_2O$–), 7.04—7.52 (10H, m, Ar-$\underline{H}$). IR ($CHCl_3$): 3440 (NH), 1710 (C=O) cm^{-1}. *Anal.* Calcd for $C_{18}H_{19}NO_3$: 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 ($MgSO_4$) 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), $[\alpha]_D^{20}$ −64.0° (c=1.1, chloroform). IR (neat): 3320 (NH), 1730 (C=O), 1690 (NHC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, t, J=7 Hz, $C\underline{H}_3CH_2$–), 2.35 (2H, q, J=7 Hz, $CH_3C\underline{H}_2$–), 2.98 (2H, br d, J=6 Hz, $PhC\underline{H}_2CH$), 4.59 (1H, dt, J=7, 7 Hz, $NC\underline{H}$–), 5.07 (2H, s, $PhC\underline{H}_2O$), 7.04—7.46 (10H, m, Ar-$\underline{H}$). *Anal.* Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.38; H, 6.83; N, 4.72.

(2*R*,3*S*)-*N*-Cbz-2-Amino-3-hydroxy-1-phenylbutane (6a)——A solution of $TiCl_4$ (18.3 ml of 3 M solution in CH_2Cl_2, 54.9 mmol) was added to a stirred mixture of **5a** (5.45 g, 18.3 mmol), Et_3SiH (4.25 g, 36.6 mmol) and CH_2Cl_2 (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 $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4) and evaporated. Recrystallization of the resulting residue from AcOEt–hexane afforded **6a** (4.51 g, 82% yield), mp 139—141 °C, $[\alpha]_D^{20}$ +42.4° (c=1.1, chloroform). IR ($CHCl_3$): 3560 (NH or OH), 3450 (NH or OH), 1705 (NHC=O) cm^{-1}. MS m/z: 299 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.22 (3H, d, J=6 Hz, $C\underline{H}_3CH$–), 2.70 (1H, dd, J=8, 14 Hz, $PhC\underline{H}$–), 2.93 (1H, dd, J=5, 14 Hz, $PhC\underline{H}$–), 3.74—4.07 (2H, m, 2-$\underline{H}$ and 3-$\underline{H}$), 5.04 (2H, s, $PhC\underline{H}_2O$–), 7.09—7.47 (10H, m, Ar-$\underline{H}$). *Anal.* Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.33; H, 7.03; N, 4.67.

(2*R*,3*S*)-*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), $[\alpha]_D^{20}$ +32.5° (c=0.9, chloroform). IR ($CHCl_3$): 3310 (NH and OH), 1685 (NHC=O) cm^{-1}. CI-MS m/z: 314 (M^++1). ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7 Hz, $C\underline{H}_3CH_2$–), 1.39 (2H, m, $CH_3C\underline{H}_2$–), 2.72 (1H, dd, J=9, 14 Hz, $PhC\underline{H}$–), 2.96 (1H, dd, J=5, 14 Hz, $PhC\underline{H}$–), 3.49—3.79 (1H, m, 2-$\underline{H}$), 3.79—4.07 (1H, m, 3-$\underline{H}$), 5.02 (2H, s, $PhC\underline{H}_2O$–), 7.06—7.62 (10H, m, Ar-$\underline{H}$). *Anal.* Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.80; H, 7.24; N, 4.38.

(4*R*,5*S*)-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 H_2O 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 **7a** (2.06 g, 72% yield), mp 97—99 °C (ether–hexane), $[\alpha]_D^{20}$ +138.1° (c=1.2, chloroform). IR ($CHCl_3$): 3460 (NH), 1750 (C=O) cm^{-1}. CI-MS m/z: 192 (M^++1). ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, d, J=6 Hz, 5-$C\underline{H}_3$), 2.64 (1H, dd, J=10, 13 Hz, $PhC\underline{H}$–), 2.90 (1H, dd, J=5, 13 Hz, $PhC\underline{H}$–), 3.97 (1H, ddd, J=5, 8, 10 Hz, 4-$\underline{H}$), 4.80 (1H, dq, J=6, 8 Hz, 5-$\underline{H}$), 7.07—7.44 (5H, m, Ar-$\underline{H}$). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 68.80; H, 6.92; N, 7.62.

(4*R*,5*S*)-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), $[\alpha]_D^{20}$ +108.3° (c=1.6, chloroform). IR (neat): 3270 (NH), 1760 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J=7 Hz, $C\underline{H}_3CH_2$–), 1.51—2.07 (2H, m, $CH_3C\underline{H}_2$–), 2.64 (1H, dd, J=10, 13 Hz, $PhC\underline{H}$–), 2.89 (1H, dd, J=5, 13 Hz, $PhC\underline{H}$–), 3.45—3.83 (1H, m, 4-$\underline{H}$), 4.36—4.68 (1H, m, 5-$\underline{H}$), 7.02—7.44 (5H, m, Ar-$\underline{H}$). *Anal.* Calcd for $C_{12}H_{15}NO_2$:

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

(4*R*,5*R*)-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), $[\alpha]_D^{20}$ +71.1° (c=0.9, chloroform). IR ($CHCl_3$): 3460 (NH), 1750 (C=O) cm^{-1}. CI-MS m/z: 192 (M^++1). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, d, J=7 Hz, 5-C$\underline{H}_3$), 2.73 (1H, dd, J=7, 15 Hz, PhC$\underline{H}$–), 2.90 (1H, dd, J=7, 15 Hz, PhC$\underline{H}$–), 3.60 (1H, dd, J=6, 7 Hz, 4-$\underline{H}$), 4.36 (1H, dq, J=6, 6 Hz, 5-$\underline{H}$), 7.06—7.44 (5H, m, Ar-$\underline{H}$). *Anal.* Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.28; H, 6.82; N, 7.59.

(4*R*,5*R*)-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), $[\alpha]_D^{20}$ +82.8° (c=1.0, chloroform). IR (neat): 3280 (NH), 1740 (C=O) cm^{-1}. CI-MS m/z: 206 (M^++1). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t, J=7 Hz, C$\underline{H}_3$CH$_2$–), 1.26—1.80 (2H, m, CH$_3$C$\underline{H}_2$–), 2.76 (1H, dd, J=6, 15 Hz, PhC$\underline{H}$–), 2.93 (1H, dd, J=6, 15 Hz, PhC$\underline{H}$–), 3.64 (1H, dd, J=6, 6 Hz, 4-$\underline{H}$), 4.18 (1H, dd, J=6, 6 Hz, 5-$\underline{H}$), 7.09—7.42 (5H, m, Ar-$\underline{H}$). *Anal.* Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.08; H, 7.41; N, 6.79.

(4*R*,5*S*)-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), $[\alpha]_D^{20}$ +33.4° (c=1.1, chloroform). IR ($CHCl_3$): 1805 (C=O), 1715 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, d, J=6 Hz, 5-C$\underline{H}_3$), 1.43 (9H, s, –C(C$\underline{H}_3$)$_3$), 2.91—3.08 (2H, m, 4-C$\underline{H}_2$Ph), 4.40—4.86 (2H, m, 4-$\underline{H}$ and 5-$\underline{H}$), 7.17—7.43 (5H, m, Ar-$\underline{H}$). *Anal.* Calcd for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.57; H, 7.37; N, 4.84.

(4*R*,5*S*)-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), $[\alpha]_D^{20}$ +13.3° (c=0.93, chloroform). IR (neat): 1805 (C=O), 1720 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J= 7 Hz, C$\underline{H}_3$CH$_2$–), 1.30—2.13 (2H, m, CH$_3$C$\underline{H}_2$–), 1.42 (9H, s, –C(C$\underline{H}_3$)$_3$), 2.97 (2H, d, J=7 Hz, 4-C$\underline{H}_2$Ph), 4.30—4.69 (2H, m, 4-$\underline{H}$ and 5-$\underline{H}$), 7.30 (5H, s, Ar-$\underline{H}$). *Anal.* Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.88; H, 7.40; N, 4.59.

(4*R*,5*R*)-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), $[\alpha]_D^{20}$ +1.6° (c=1.3, chloroform). IR (neat): 1810 (C=O), 1715 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, d, J=6 Hz, 5-C$\underline{H}_3$), 1.58 (9H, s, –C(C$\underline{H}_3$)$_3$), 2.72 (1H, dd, J=9, 14 Hz, 4-C$\underline{H}$Ph), 3.31 (1H, dd, J=4, 14 Hz, 4-C$\underline{H}$Ph), 3.90—4.13 (1H, m, 4-$\underline{H}$), 4.18—4.48 (1H, m, 5-$\underline{H}$), 7.09—7.49 (5H, m, Ar-$\underline{H}$). *Anal.* Calcd for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 66.04; H, 7.26; N, 4.77.

(4*R*,5*R*)-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), $[\alpha]_D^{20}$ +8.8° (c=2.0, chloroform). IR (neat): 1820 (C=O), 1725 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.71 (3H, t, J=7 Hz, C$\underline{H}_3$CH$_2$–), 1.09—1.77 (2H, m, CH$_3$C$\underline{H}_2$–), 1.58 (9H, s, –C(C$\underline{H}_3$)$_3$), 2.73 (1H, dd, J=9, 13 Hz, 4-C$\underline{H}$Ph), 3.29 (1H, dd, J=4, 13 Hz, 4-C$\underline{H}$Ph), 3.96—4.18 (2H, m, 4-$\underline{H}$ and 5-$\underline{H}$), 7.10—7.48 (5H, m, Ar-$\underline{H}$). *Anal.* Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.35; H, 7.59; N, 4.54.

(2*R*,3*S*)-*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 LiOH·H_2O (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), $[\alpha]_D^{20}$ +35.5° (c=1.3, chloroform). IR ($CHCl_3$): 3540, 3440 (OH and NH), 1690 (C=O) cm^{-1}. CI-MS m/z: 266 (M^++1). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, d, J=6 Hz, 3-C$\underline{H}_3$), 1.38 (9H, s, –C(C$\underline{H}_3$)$_3$), 2.70—2.94 (2H, m, PhC$\underline{H}_2$–), 3.62—4.11 (2H, m, 2-$\underline{H}$ and 3-$\underline{H}$), 7.12—7.51 (5H, m, Ar-$\underline{H}$). *Anal.* Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28. Found: C, 68.15; H, 8.67; N, 4.98.

(2*R*,3*S*)-*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), $[\alpha]_D^{20}$ +31.7° (c=0.9, chloroform). IR (neat): 3350 (NH and OH), 1680 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7 Hz, C$\underline{H}_3$CH$_2$–), 1.34 (9H, s, –C(C$\underline{H}_3$)$_3$), 1.36—1.70 (2H, m, CH$_3$C$\underline{H}_2$–), 2.66 (1H, dd, J=9, 14 Hz, PhC$\underline{H}$–), 2.89 (1H, dd, J=5, 14 Hz, PhC$\underline{H}$–), 3.46—3.98 (2H, m, 2-$\underline{H}$ and 3-$\underline{H}$), 7.22 (5H, s, Ar-$\underline{H}$). *Anal.* Calcd for $C_{10}H_{25}NO_3$: C, 68.78; H, 9.02; N, 5.01. Found: C, 68.87; H, 8.90; N, 5.08.

(2*R*,3*R*)-*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), $[\alpha]_D^{20}$ +28.2° (c=1.2, chloroform). IR ($CHCl_3$): 3560 (OH or NH), 3450 (OH or NH), 1700 (C=O) cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, d, J=6 Hz, CH_3CH–), 1.38 (9H, s, –C(CH_3)$_3$), 2.89 (2H, d, J=7 Hz, PhCH_2–), 3.49—3.97 (2H, m, 2-H and 3-H), 7.23 (5H, s, Ar-H). *Anal.* Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28. Found: C, 68.07; H, 8.65; N, 5.56.

(2*R*,3*R*)-*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), $[\alpha]_D^{20}$ +24.0° (c=0.97, chloroform). IR (neat): 3430 (OH and NH), 1690 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7 Hz, CH_3CH_2), 1.33—1.69 (2H, m, CH_3CH_2–), 1.40 (9H, s, –C(CH_3)$_3$), 2.88 (2H, d, J=7 Hz, PhCH_2CH–), 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 $C_{16}H_{25}NO_3$: C, 68.78; H, 9.02; N, 5.01. Found: C, 68.62; H, 9.06; N, 4.96.

(2*R*,3*R*)-*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), Et_3N (606 mg, 6 mmol) and CH_2Cl_2 (20 ml) under ice-cooling. After being stirred at the same temperature for 0.5 h, the mixture was poured into H_2O and extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and evaporated. A mixture of the resulting residue, NaN_3 (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 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 (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), $[\alpha]_D^{20}$ −30.3° (c=1.1, chloroform). IR ($CHCl_3$): 3450 (NH), 2110 (N_3), 1710 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, J=6 Hz, CH_3CH–), 1.42 (9H, s, –C(CH_3)$_3$), 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, –CHN_3), 3.66—4.04 (1H, m, –CHNHBoc), 7.10—7.48 (5H, m, Ar-H). *Anal.* Calcd for $C_{15}H_{22}N_4O_2$: C, 62.04; H, 7.64; N, 19.30. Found: C, 61.91; H, 7.65; N, 19.47.

(2*R*,3*R*)-*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**, $[\alpha]_D^{20}$ −2.9° (c=1.9, chloroform). IR ($CHCl_3$): 3450 (NH), 2100 (N_3), 1700 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7 Hz, CH_3CH_2–), 1.39 (9H, s, –C(CH_3)$_3$), 1.43—1.84 (2H, m, CH_3CH_2–), 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, –CHN_3), 3.77—4.16 (1H, m, –CHNHBoc), 7.10—7.44 (5H, m, Ar-H).

(2*R*,3*S*)-*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), $[\alpha]_D^{20}$ +65.1° (c=1.1, chloroform). IR ($CHCl_3$): 3450 (NH), 2100 (N_3), 1700 (C=O) cm^{-1}. CI-MS m/z: 291 (M^++1). ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6 Hz, CH_3CH–), 1.33 (9H, s, –C(CH_3)$_3$), 2.51 (1H, dd, J=8, 14 Hz, PhCH–), 2.91 (1H, dd, J=5, 14 Hz, PhCH–), 3.47—3.96 (2H, m, –CHN_3 and –CHNHBoc), 7.11—7.42 (5H, m, Ar-H). *Anal.* Calcd for $C_{15}H_{22}N_4O_2$: C, 62.04; H, 7.64; N, 19.30. Found: C, 62.07; H, 7.60; N, 19.62.

(2*R*,3*S*)-*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), $[\alpha]_D^{20}$ +43.0° (c=1.0, chloroform). IR ($CHCl_3$): 3450 (NH), 2100 (N_3), 1700 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, t, J=7 Hz, CH_3CH_2–), 1.34 (9H, s, –C(CH_3)$_3$), 1.51—1.88 (2H, m, CH_3CH_2–), 2.63 (1H, dd, J=9, 14 Hz, PhCH–), 2.94 (1H, dd, J=5, 14 Hz, PhCH–), 3.37—3.57 (1H, m, –CHN_3), 3.80—4.17 (1H, m, –CHNHBoc), 7.13—7.48 (5H, m, Ar-H). *Anal.* Calcd for $C_{16}H_{24}NO_2$: C, 63.18; H, 7.95; N, 18.41. Found: C, 62.97; H, 7.89; N, 18.31.

(3*R*,4*R*)-*N*-Boc-3-Amino-4-azidopentanoic Acid (11a)——A mixture of **10a** (1.16 g, 4 mmol), CCl_4 (30 ml), CH_3CN (30 ml), H_2O (45 ml), $NaIO_4$ (17 g, 80 mmol) and $RuCl_3 \cdot H_2O$ (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 $CHCl_3$. The combined organic layer was extracted with 0.2 N NaOH. The aqueous layer was made acidic with 1 N HCl and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4) 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, $[\alpha]_D^{20}$ −8.2° (c=1.1, methanol). ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6 Hz, CH_3CH–), 1.41 (9H, s, –C(CH_3)$_3$), 2.57 (2H, d, J=6 Hz, CH_2COOH), 3.64—4.20 (2H, m, –CHN_3 and –CHNHBoc). IR ($CHCl_3$): 3450 (NH), 2750—2400 (OH), 2110 (N_3), 1710 (C=O) cm^{-1}. CI-MS m/z: 259 (M^++1).

(3*R*,4*R*)-*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, $[\alpha]_D^{20}$ +19.1° (c=1.0, methanol). ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, t, J=7 Hz, CH_3CH_2–), 1.44 (9H, s, –C(CH_3)$_3$), 1.49—1.82 (2H, m, CH_3CH_2–), 2.59 (2H, d, J=7 Hz, –CH_2COOH), 3.33—3.66 (1H, m, –CHN_3), 3.93—4.32 (1H, m, –CHNHBoc). IR (neat): 3320 (NH), 2800—2400 (OH), 2100 (N_3), 1700 (C=O) cm^{-1}. CI-MS m/z: 273 (M^++1).

(3*R*,4*S*)-*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, $[\alpha]_D^{20}$ +47.0° (c=1.4, methanol). ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, d, J=6 Hz, –CHCH_3), 1.46 (9H, s, –C(CH_3)$_3$), 2.60 (2H, d, J=5 Hz, CH_2COOH), 3.51—4.09 (2H, m, –CHN_3 and –CHNHBoc). IR ($CHCl_3$): 3440 (NH), 2800—2380 (OH), 2100 (N_3), 1710 (C=O) cm^{-1}. CI-MS m/z: 259 (M^++1).

(3*R*,4*S*)-*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° (c=1.0, methanol). ^{1}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, –$C(CH_3)_3$), 2.55 (2H, d, J=5 Hz, –CH_2COOH), 3.42—3.64 (1H, m, –CHN_3), 3.83—4.26 (1H, m, –CHNHBoc), 9.40 (1H, br s, COOH). IR (neat): 3320 (NH), 2700—2400 (OH), 2100 (N_3), 1710 (C=O) cm^{-1}. *Anal.* Calcd for $C_{11}H_{20}N_4O_4$: C, 48.52; H, 7.40; N, 20.58. Found: C, 48.68; H, 7.35; N, 20.67.

(3*R*,4*R*)-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 °C, $[\alpha]_D^{20}$ −4.4° (c=0.5, methanol). ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.28 (3H, d, J=6.79 Hz, 4-CH_3), 1.45 (9H, s, –$C(CH_3)_3$), 2.49 (1H, dd, J=4.74, 16.25 Hz, HOOCCH–), 2.57 (1H, dd, J=6.82, 16.24 Hz, HOOCCH–), 3.43 (1H, dq, J=4.92, 6.80 Hz, 4-H), 3.87—3.90 (1H, m, 3-H). IR (neat): 3230 (NH), 2750—2400 (OH), 1685 (C=O) cm^{-1}. *Anal.* Calcd for $C_{10}H_{20}N_2O_4 \cdot H_2O$: C, 47.98; H, 8.86; N, 11.19. Found: C, 48.45; H, 8.73; N, 11.19.

(3*R*,4*R*)-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 °C (MeOH–ether), $[\alpha]_D^{20}$ +7.0° (c=0.9, methanol). ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.04 (3H, t, J=7.44 Hz, CH_3CH_2–), 1.45 (9H, s, –$C(CH_3)_3$), 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, –$CHNH_2$), 3.98—4.01 (1H, m, –CHNHBoc). IR (neat): 3230 (NH), 2760—2400 (OH), 1700 (C=O) cm^{-1}. *Anal.* Calcd for $C_{11}H_{22}N_2O_4$: C, 53.64; H, 9.00; N, 11.37. Found: C, 53.51; H, 9.00; N, 11.20.

(3*R*,4*S*)-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 °C (MeOH–ether), $[\alpha]_D^{20}$ +4.0° (c=1.0, methanol). ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.24 (3H, d, J=6.78 Hz, CH_3CH–), 1.45 (9H, s, –$C(CH_3)_3$), 2.42 (2H, d, J=6.09 Hz, CH_2COOH), 3.42—3.48 (1H, m, –$CHNH_2$), 4.02—4.07 (1H, m, –CHNHBoc). IR (neat): 3390 (NH), 2800—2400 (OH), 1700 (C=O) cm^{-1}. *Anal.* Calcd for $C_{10}H_{20}N_2O_4$: C, 51.70; H, 8.68; N, 12.06. Found: C, 51.60; H, 8.59; N, 12.19.

(3*R*,4*R*)-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 °C (MeOH–ether), $[\alpha]_D^{20}$ 0.0° (c=1.0, methanol). ^{1}H-NMR (400 MHz, CD_3OD) δ: 1.04 (3H, t, J=7.50 Hz, CH_3CH_2–), 1.45 (9H, s, –$C(CH_3)_3$), 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, –$CHNH_2$), 4.02 (1H, dt, J=5.01, 6.12 Hz, –CHNHBoc). IR (neat): 3370 (NH), 2800—2400 (OH), 1680 (C=O) cm^{-1}. *Anal.* Calcd for $C_{11}H_{22}N_2O_4$: C, 53.64; H, 9.00; N, 11.37. Found: C, 53.93; H, 8.70; N, 11.21.

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