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Synthesis of α,ω-Diamino Acids via Amidocarbonylation Reaction: Novel Synthesis of Lysine, Ornithine, and Their Analogs

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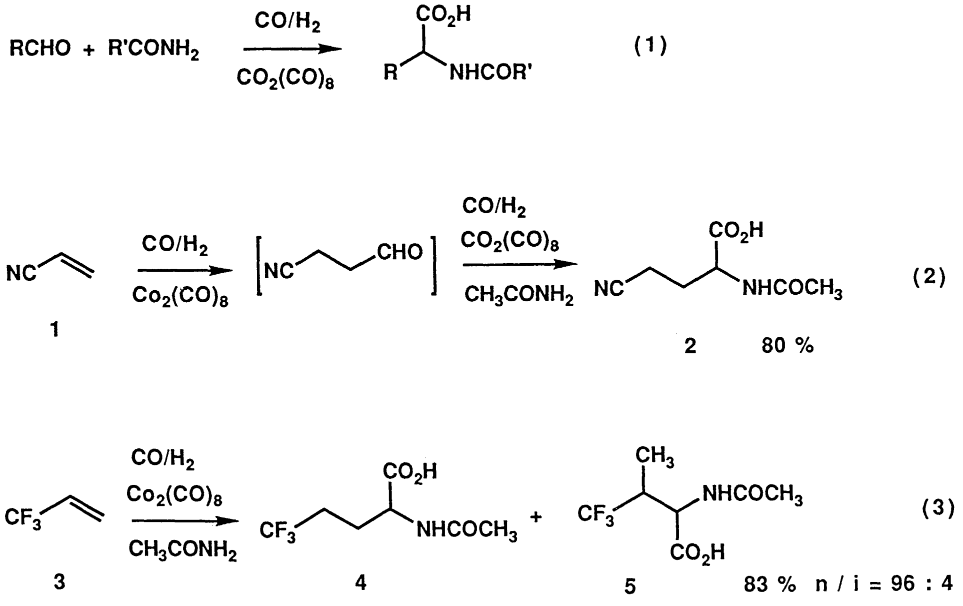
α,ω-Diamino acid derivatives, such as lysine and ornithine, were synthesized via amidocarbonylation (cobalt-catalyzed formation of *N*-acyl α-amino acid from aldehyde, amide and carbon monoxide) of ω-(phthalimido)alkanals in good yield. The phthalimido group was proved to be intact under the conditions of amidocarbonylation. The hydroformylation–amidocarbonylation of *N*-phthaloyl-β,γ- and *N*-phthaloyl-γ,δ-unsaturated amines proceeds very nicely to give α,ω-diamino acid derivatives with good selectivity. Selective deprotection of α-*N*-acyl-ω-*N*-phthaloyl α,ω-diamino acids was achieved using hydrazine for the *N*-phthaloyl group and aminoacylase for the *N*-acetyl group to afford the optically active α,ω-diamino acid, respectively.

The Cobalt-catalyzed amidocarbonylation (Eq. 1) discovered by Wakamatsu et al. in 1971 provides a versatile method for the synthesis of α-amino acids, including a variety of nonproteinogenic α-amino acids, from aldehyde, amide and carbon monoxide.[1] Since the reaction conditions of amidocarbonylation are almost the same as those of hydroformylation, except for the coexistence of an amide, it is possible to combine the two reactions. In fact, 2-acetamido-4-cyanobutyric acid (**2**) was synthesized from acrylonitrile (**1**) in one-pot reactions with high selectivity (Eq. 2).[2] Recently, Ojima et al. also reported that the extremely regioselective hydroformylation of trifluoropropene (**3**) was successfully combined with the amidocarbonylation to give *N*-acetyltrifluoronorvaline (**4**) with 96% selectivity (Eq. 3).[3]

As a continuation of our work directed toward the preparation of nonproteinogenic α-amino acid,[4] we intended to synthesize α,ω-diamino acids, such as lysine, ornithine and their analogs, via the amidocarbonylation of *N*-protected ω-aminoalkanals or the hydroformylation–amidocarbonylation of *N*-protected unsaturated amines.

Results and Discussion

Synthesis of Lysine, Ornithine, and Their Analogs. The choice of the *N*-protecting group was important to successfully achieve the preparation of α,ω-diamino acid derivatives from ω-aminoalkanals or unsaturated amines. We have revealed that the intramolecular amidocarbonylation of ω-(acylamino)alkanals takes place nicely to give *N*-acyl cyclic α-amino acids in good yield.[5] Furthermore, we have found that cobalt-catalyzed carbonylation of *N*-benzoylallylamine (**6**) affords 2-benzamidobutyric acid (**7**) and 3-benzamido-2-methylpropionic acid (**8**) as well as *N*-benzoylproline (**9**) (Eq. 4).[5] The formation of **7** and



Scheme 1.

8 can be explained by the facile migration of the cobalt carbonyl moiety from the β- or γ-position to the α- or β-position of the amido group followed by CO insertion and subsequent hydrolysis.[6] Accordingly, the *N*-acyl group is inadequate as the protecting group of amino group for synthesizing the α,ω-diamino acid.

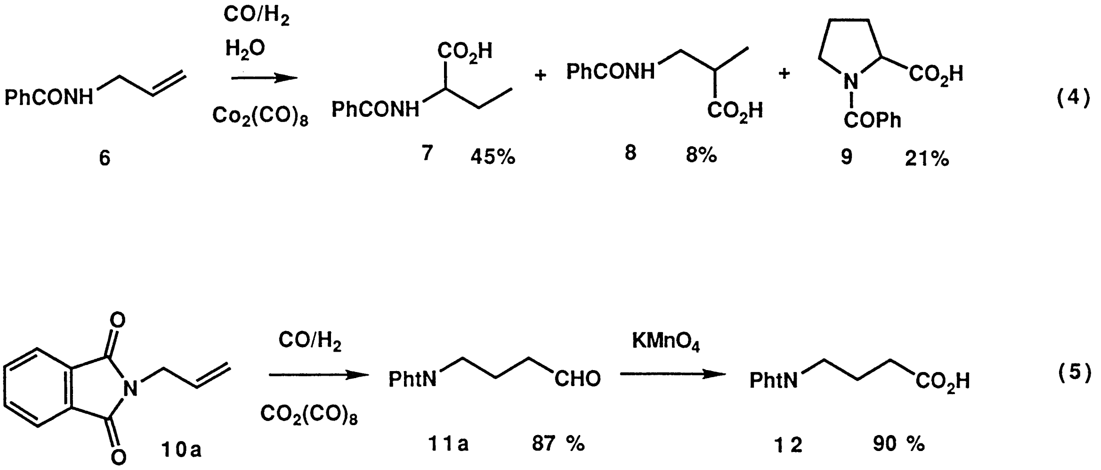
On the other hand, hydroformylation of *N*-phthaloylallylamine was previously studied by some groups,[7] in which such side reactions as migration or cyclization have not been observed. Moreover, Sato has reported that the hydroformylation of *N*-phthaloylallylamine (**10a**) took place regioselectively to give linear aldehyde, 4-phthalimidobutanal (**11a**) as the sole product.[7a] We therefore examined the synthesis of α,ω-diamino acid from ω-aminoalkanals by choosing the phthaloyl group as the N-protecting group. The results are given in equation 6.

It was thus found that the phthalimido group was intact under the conditions of amidocarbonylation and the derivatives of lysine (**13b**) and ornithine (**13a**) were obtained in moderate yield, regardless of the length of the alkyl chain and the kind of amide used.

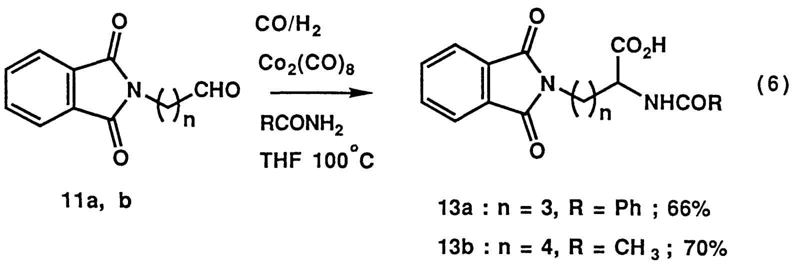
Next, we examined the synthesis of α,ω-diamino acid derivatives from *N*-phthaloyl unsaturated amines (**10**) via hydroformylation followed by subsequent amidocarbonylation (Eq. 7). The results are shown in Table 1.

As Table 1 shows, the cobalt-catalyzed carbonylation of *N*-phthaloylallylamine (**10a**) in the presence of benzamide (initial pressure at 25 °C: CO, 65 atm; H_2, 60 atm) at 100 °C for 6 h gave α-*N*-benzoyl-δ-*N*-phthaloylornithine (**13a**) with more than 80% selectivity in 71% yield (Run 1). The reaction of the longer homolog, *N*-phthaloyl-3-butenylamine (**10b**) afforded α-*N*-acyl-ε-*N*-phthaloyllysine (**13b,c**) in similar yield (Runs 3 and 4). As shown in the previous cases, linear isomers were obtained in good selectivity, regardless of the length of the alkyl chaines and the kind of amide. The introduction of a substitution group at the 1- or 2-position of the allyl moiety of **10a** remarkably improved the selectivity (Runs 6 and 7) to give methyl substituted ornithine derivatives. Similarly, the reaction of methyl 2-phthalimido-4-pentenoate (*N*-phthaloylallylglycine methyl ester) gave the 2,6-diaminoheptandioic acid derivative with more than 95% selectivity (Run 5). As shown in the entries, since *N*-phthaloylallylamine derivatives did not give isomerization-carbonylation products, the difference in the phthalimido and acylamino groups in the cobalt-catalyzed carbonylation was revealed.

Sato exclusively obtained a linear aldehyde (**11a**) during the hydroformylation of *N*-phthaloylallylamine,[7a] whereas, in the hydroformylation-amidocarbonylation of the same substrate, we obtained a linear



Scheme 2.

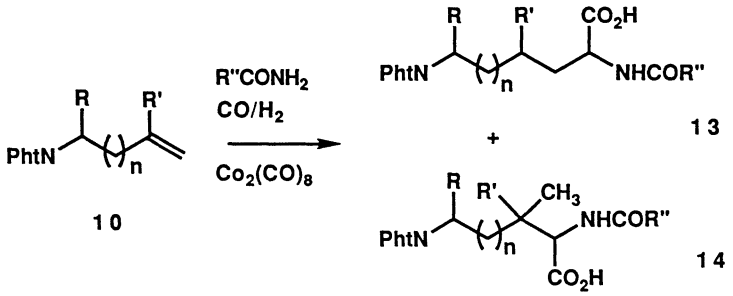


13a : n = 3, R = Ph ; 66%

13b : n = 4, R = CH_3 ; 70%

Scheme 3.

Table 1. Synthesis of α,ω-Diamino Acids

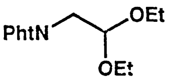
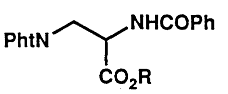
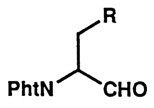
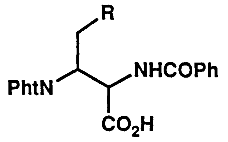
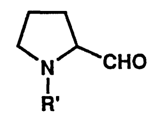
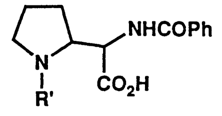


(7)

Run	10			Amide	Products	
	R	R′	*n*	R″	**13**:**14**[a]	Yield (**13**+**14**)[b]/%
1	H	H	0	Ph	5:1	71 (**a**)
2[c]	H	H	0	Ph	12:1	56 (**a**)
3	H	H	1	Ph	6:1	68 (**c**)
4	H	H	1	CH_3	5:1	76 (**b**)
5	CO_2CH_3	H	1	Ph	>20:1	66 (**d**)
6	H	CH_3	0	Ph	>100:1	24 (**e**)
7	CH_3	H	0	Ph	>20:1	63 (**f**)
8	CH_3	H	1	Ph	>10:1	60 (**g**)

a) Determined by ^{1}H NMR and/or GC-MS. b) Isolated yield after esterification with CH_2N_2. c) Stepwise reaction; hydroformylation (100 °C, 3h), amidocarbonylation (100 °C, 3h).

Table 2. Synthesis of α,β-Diamino Acids

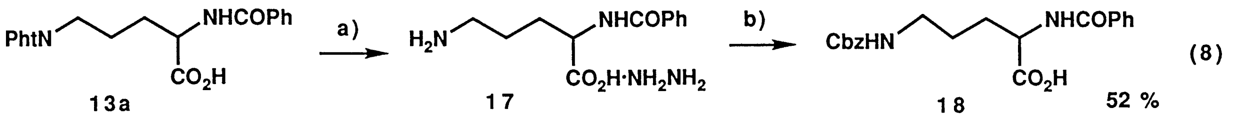
Run	Aldehyde **15** (yield/%)[a]		Product **16** (yield/%)[b]	
1				**a**; R=H (50) R=Et (8)
2 3		R=^{i}Pr (25) R=Ph (35)		**b**; R=^{i}Pr (32) **c**; R=Ph (42)
4 5[c]		R′=CO_2Ph (70) R′=COPh (35)		**d**; R′=CO_2Ph (30) **e**; R′=COPh (31)

a) Determined by ^{1}H NMR. Obtained by oxydation of alcohols with DMSO-SO_3·Py-Et_3N. b) Isolated yield after esterification with CH_2N_2. c) *N*-Benzoyl-2-piperidinecarboxylic acid (20%) and α,ε-*N*,*N*′-dibenzoyllysine (3%) were also obtained.

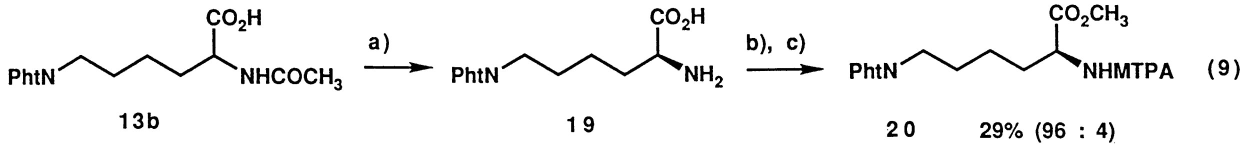
(**13**) and branched (**14**) product (derived from a terminal and internal hydroformylated intermediate, respectively) in the ratio of *ca.* 5:1 (Run 1). We thought that the decrease in regioselectivity during the hydroformylation step should be attributed to the coexistence of the amide. To confirm our estimation, after the hydroformylation was almost completed acetamide was added and the reaction resumed (Run 2). The ratio of the linear and branched products was increased to 12:1. It is presumed that the property of the cobalt hydridocarbonyl catalyst or the solvent may be affected by the coexistence of the amide, which resulted in the decrease of the regioselectivity of hydroformylation. A similar result was previously observed in the hydroformylation-amidocarbonylation of isobutene.[6]

Since *N*-phthaloyl unsaturated amines (**10**) are easily obtained from the corresponding unsaturated alcohols or unsaturated amines, the hydroformylation-amidocarbonylation of **10** revealed a useful method for the synthesis of nonproteinogenic α-amino acid analogs of lysine and ornithine.

Synthesis of α,β-Diamino Acid Derivatives. We also examined the synthesis of α,β-diamino acid via



Reagents : a) 2eq NH_2NH_2, MeOH, Δ ; b) CbzCl, $NaHCO_3$, H_2O-ether.



Reagents : a) acylase ; b) MTPACl, Na_2CO_3 ; c) CH_2CN_2.

Scheme 4.

amidocarbonylation starting from N-protected α-aminoalkanals (**15**), which are easily obtained from α-amino acids.[8] The preparation of β-functionalyzed α-amino acid via the amidocarbonylation of an α-functionalyzed aldehyde, such as 2-acetoxypropanal, has not yet been successful.[6] The results are shown in Table 2.

The yield of α,β-diamino acid derivatives (**16**) was not very satisfactory when compared with the α,ω-diamino acid derivatives (**13**). This low yield would be ascribed to the liability of the N-protected α-aminoalkanal (**15**) under the reaction conditions. Also, α-(phthalimido)alkanals, *N*-benzoyl- and *N*-benzyloxycarbonyl-2-pyrrolidinecarbaldehyde gave the corresponding α,β-diamino acid derivatives. However, except for the 2-pyrrolidinecarbaldehyde derivatives, the reactions of the *N*-benzoyl or *N*-benzyloxycarbonyl derivatives of acyclic α-aminoalkanal were unsuccessful. The choice of the protective group was also important to successfully achieve the preparation of α,β-diamino acid derivatives. Disappointingly, α,β-diamino acid derivatives were a diastereoisomeric mixture, in spite of the fact that optically active *N*-protected α-aminoalkanals were used; thus, the 1,2-asymmetric induction was not achieved in this process.

Selective Deprotection of α,ω-Diamino Acid Derivatives. The α,ω-diamino acid derivatives, thus obtained, should be very useful compounds, since the two amino groups are protected by different groups which can be selectively removed by conventional methods. Equation 8 shows the selective removal of the ω-phthaloyl group. The treatment of **13a** with hydrazine in methanol gave the α-*N*-benzoyl, ω-free diamino acid derivative (**17**), which was further transformed into α-*N*-benzoyl-ω-*N*-benzyloxycarbonylornithine (**18**).

It is worth noting that an enantioselective hydrolysis of **13b** can be achieved by an enzyme (aminoacylase) to give ω-phthaloyl-L-lysine (**19**) in moderate yield, as shown in Eq. 9. Its optical purity proved to be more than 92% by ^{1}H NMR and HPLC studies after transformation to **20** by a treatment with Mosher's acid chloride, followed by esterification.

In conclusion, the synthesis of α,ω-diamino acid derivatives was achieved via the amidocarbonylation of the ω-(phthalimido)alkanals and the hydroformylation-amidocarbonylation of *N*-phthaloyl unsaturated amines. A new application of amidocarbonylation to the preparation of nonproteinogenic α-amino acid was represented.

Experimental

^{1}H NMR spectra were measured with a Varian XL 300 spectrometer and chemical shifts are given as δ ppm relative to tetramethylsilane (TMS) or sodium 3-trimethylsilylpropionate-2,2,3,3-d_4 (TPS) as an internal standard. Infrared (IR) spectra were recorded on a Hitachi 260-10 spcctrophotometer with samples as neat liquid or in KBr disks. Mass spectra (MS) were recorded with a JEOL DX-300 instrument by using the FAB technique. The melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. GC-MS was performed on a HP 5890A-5970B with a high-performance capillary column (cross-linked methyl silicone). The thin-layer chromatographic system employed on silica gel (Merck Art. 7515). PTLC was performed with a Whatman PLK 5F. HPLC was performed on a GILSON 303 with a YMC-A312 (ODS 6×150 mm) column with a mobil phase composed of 70% MeOH-H_2O, at 25 °C. The elution rate was 0.5 ml min^{-1} and detection was carried out at ultraviolet (UV) 254 nm.

Amidocarbonylation of ω-(Phthalimido)alkanals (11). A typical procedure is described for the reaction of 4-phthalimidopentanal (**11b**) catalyzed by $Co_2(CO)_8$.

4-Phthalimidopentanal (**11b**) (1.28 g, 5.56 mmol), acetamide (328 mg, 5.56 mmol), and $Co_2(CO)_8$ (100 mg, 0.29 mmol) were heated in a 100 ml stainless-steel autoclave with a 1 : 1 mixture of carbon monoxide and hydrogen (total pressure 120 atm, measured at room temperature) at 100 °C for 3.5 h. The autoclave was then cooled to ambient temperature and carbon monoxide and hydrogen purged out. After the solvent was removed under reduced pressure, the residue was dissolved in AcOEt (50 ml) and the insoluble material filtered off. The filtrate was extracted with 10% aqueous $NaHCO_3$ (50 ml) and the extract washed with AcOEt. Then, the aqueous phase was acidified with concentrated HCl and extracted with AcOEt (50 ml). The organic layer was washed with brine and dried over $MgSO_4$. After concentration, the residue was washed with hexane-AcOEt (1 : 1, v/v) to give α-*N*-acetyl-ε-*N*-phthaloyllysine (**13b**) as a solid (1.24 g, 3.90 mmol, 70.1%).

α-*N*-Acetyl-ε-*N*-phthalylolysine (13b): ^{1}H NMR (300 MHz, DMSO-d_6) δ=1.28—1.40 (2H, m, CH_2), 1.50—1.75 (4H, m, CH_2), 1.80 (3H, s, CH_3), 3.55 (2H, t, *J*=7.0 Hz, CH_2), 4.07—4.15 (1H, m, CH), 7.82—7.89 (4H, m, aromatic H), 8.05 (1H, d, *J*=7.6 Hz, NH); IR (KBr) 3300, 3050, 2940, 1770, 1700, 1645, 1540, 1395, 1370, 1295, 1155, 1050, 720 cm^{-1}; mp 170—172 °C (from hexane-AcOEt) ; High mass (FAB) *m*/*z* Calcd for $C_{16}H_{18}N_2O_5$+H: 319.1294. Found: 319.1301.

α-*N*-Benzoyl-δ-*N*-Phthaloylornithine (13a): ^{1}H NMR (300 MHz, DMSO-d_6) δ=1.60—1.85 (4H, m, CH_2), 3.62 (2H, t, *J*=5.9 Hz, CH_2), 4.35—4.45 (1H, m, CH), 7.43—7.57 (4H, m, aromatic H), 7.80—7.89 (5H, m, aromatic H), 8.57 (1H, d, *J*=7.7 Hz, NH); IR (KBr) 3350, 2940, 1780, 1710, 1645, 1520, 1400, 1050, 720 cm^{-1}; mp 190—193 °C (from hexane-AcOEt); High mass (FAB) *m*/*z* Calcd for $C_{20}H_{18}N_2O_5$+H: 367.1294. Found; 367.1294.

Hydroformylation-Amidocarbonylation of *N*-Phthaloyl Unsaturated Amines (10). A typical procedure is described for the reaction of *N*-phthalyl-3-butenylamine (**10b**) catalyzed by $Co_2(CO)_8$.

N-Phthalyl-3-butenylamine (**10b**) (1.0 g, 4.97 mmol), benzamide (602 mg, 4.97 mmol), and $Co_2(CO)_8$ (100 mg, 0.29 mmol) in THF (20 ml) were heated in a 100 ml stainless-steel autoclave with a 1 : 1 mixture of carbon monoxide and hydrogen (total pressure 120 atm, measured at room temperature) at 100 °C for 6 h. The autoclave was then cooled to ambient temperature and carbon monoxide and hydrogen purged out. After the solvent was removed under reduced pressure, the residue was dissolved in AcOEt (50 ml) and the insoluble material filtered off. The filtrate was extracted with 10% aqueous $NaHCO_3$ (50 ml) and the extract washed with AcOEt. The aqueous phase was acidified with concentrated HCl and then extracted with AcOEt (50 ml). The organic layer was washed with brine and dried over $MgSO_4$. After concentration, the residue was esterified with etherial CH_2N_2 to give α-*N*-benzoyl-ε-*N*-phthaloyllysine methyl ester (methyl ester of **13c**) (1.33 g, 3.36 mmol, 67.6%) as a solid.

α-*N*-Benzoly-ε-*N*-phthaloyllysine Methyl Ester (Methyl Ester of 13c): ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.35—2.10 (6H, m, CH_2), 3.70 (2H, t, *J*=7.2 Hz, CH_2), 3.78 (3H, s, CH_3), 4.75—4.83 (1H, m, CH) , 6.75 (1H, d, *J*=7.2 Hz, NH), 7.40—7.55 (4H, m, aromatic H), 7.65—7.85 (5H, m, aromatic H), minor isomer 1.04 (1.5H, d, *J*=6.6 Hz, CH_3), 1.10 (1.5H, d, *J*=6.6 Hz, CH_3); IR (KBr) 3320, 2950, 1770, 1745, 1710, 1635, 1395, 1335, 1215, 1160, 720 cm^{-1}; GC-MS *m*/*z* 335 (M^+−59); mp 112—114 °C (from hexane-AcOEt); High mass (FAB) *m*/*z* Calcd for $C_{22}H_{22}N_2O_5$+H: 395.1607. Found; 395.1611.

α-*N*-Acetyl-ε-*N*-phthaloyllysine Methyl Ester (Methyl Ester of 13b): ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.25—1.90 (6H, m, CH_2), 3.68 (2H, t, *J*=7.0 Hz, CH_2), 3.73 (3H, s, CH_3), 4.53—4.61 (1H, m, CH), 6.15 (1H, d, *J*=7.3 Hz, NH), 7.68—7.88 (4H, m, aromatic H), minor isomer 0.95 (1.5 H, d, *J*=6.8 Hz, CH_3), 1.02 (1.5 H, d, *J*=6.8 Hz, CH_3); IR (KBr) 3300, 3080, 2950, 2860, 1765, 1740, 1700, 1645, 1540, 1435, 1400, 1375, 1345, 1295, 1220, 1155, 1055, 720 cm^{-1}; GC-MS *m*/*z* 300 (M^+−18); 289 (M^+−29), 273 (M^+−45); mp 117—119 °C (from hexane-AcOEt); High mass (FAB) *m*/*z* Calcd for $C_{17}H_{20}N_2O_5$+H: 333.1451. Found 333.1445.

α-*N*-Benzoyl-δ-*N*-phthaloylornithine Methyl Ester (Methyl Ester of 13a): ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.70—2.05 (4H, m, CH_2), 3.72 (2H, br. t, *J*=6.6 Hz, CH_2), 3.76 (3H, s, CH_3), 4.83—4.90 (1H, m, CH), 6.75 (1H, d, *J*=7.8 Hz, NH), 7.40—7.55 (4H, m, aromatic H), 7.65—7.90 (5H, m, aromatic H), minor isomer 0.98 (1.5 H, d, *J*=6.9 Hz, CH_3), 1.13 (1.5H, d, *J*=6.9 Hz, CH_3); IR (neat) 2950, 1770, 1740, 1700, 1650, 1520, 1440, 1395, 1210, 1040 cm^{-1}; GC-MS *m*/*z* 321 (M^+−59); High mass (FAB) *m*/*z* Calcd for $C_{21}H_{20}N_2O_5$+H: 381.1451. Found: 381.1434.

Dimethyl 2-Benzamido-6-phthalimidoheptandioate (Methyl Ester of 13d): ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.30—2.35 (6H, m, CH_2), 3.72 (6H, s, CH_3), 4.70—4.90 (2H, m, CH), 6.64 (1H, br. t, *J*=7.0 Hz, NH), 7.35—7.55 (4H, m, aromatic H), 7.70—7.85 (5H, m, aromatic H); IR (neat) 2950, 1770, 1740, 1710, 1640, 1520, 1430, 1380, 1240 cm^{-1}; GC-MS *m*/*z* 393 (M^+−59); High mass (FAB) *m*/*z* Calcd for $C_{24}H_{24}N_2O_7$+H: 453.1662. Found: 453.1636.

α-*N*-Benzoyl-ε-methyl-ε-*N*-phthaloyllysine Methyl Ester (Methyl Ester of 13g): ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.46 (1.5 H, d, *J*=6.8 Hz, CH_3), 147 (1.5 H, d, *J*=6.9 Hz, CH_3), 1.69—2.20 (6H, m, CH_2), 3.70 (1.5H, s, CH_3), 3.71 (1.5H, s, CH_3), 4.38—4.40 (1H, m, CH), 4.70—4.80 (1H, m, CH), 6.65 (1H, br.s, NH), 7.35—7.55 (4H, m, aromatic H), 7.63—7.85 (5H, m, aromatic H); IR (neat) 2950, 2860, 1770, 1740, 1710, 1360, 1325, 1210, 1160, 1040 cm^{-1}; GC-MS *m*/*z* 408 (M^+), 373 (M^+−32), 349 (M^+−59); High mass (FAB) *m*/*z* Calcd for $C_{23}H_{24}N_2O_5$+H: 409.1763. Found: 409.1781.

α-*N*-Benzoyl-δ-methyl-δ-*N*-phthaloylornithine Methyl Ester (Methyl Ester of 13f): ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.46 (1.5H, d, *J*=6.8 Hz, CH_3), 1.47 (1.5H, d, *J*=6.8 Hz, CH_3), 1.80—1.91 (2H, m, CH_2), 2.14—2.35 (2H, m, CH_2), 3.73 (1.5H, s, CH_3), 3.77 (1.5H, s, CH_3), 4.30—4.42 (1H, m, CH), 4.78—4.88 (1H, m, CH), 6.70 (0.5H, d, *J*=7.7 Hz, NH), 6.76 (0.5H, d, *J*=7.5 Hz, NH), 7.40—7.55 (4H, m, aromatic H), 7.68—7.85 (5H, m, aromatic H); IR (KBr) 3320, 2950, 1770, 1740, 1695, 1630, 1520, 1385, 1360, 1200, 1050, 720 cm^{-1}; GC-MS *m*/*z*: 394 (M^+), 362 (M^+−32), 335 (M^+−59); mp 120—124 °C (from hexane-AcOEt); High mass (FAB) *m*/*z* Calcd for $C_{22}H_{22}N_2O_5$+H: 395.1607. Found: 395.1594.

α-*N*-Benzoyl-γ-methyl-δ-*N*-phthaloylornithine Methyl Ester (Methyl Ester of 13e): ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.05 (3H, d, *J*=6.8 Hz, CH_3), 1.70—1.90 (2H, m, CH_2), 2.12—2.25 (1H, m, CH) , 3.58—3.67 (2H, m, CH_2), 3.74 (1.5H, s, CH_3), 3.75 (1.5H, s, CH_3), 4.87—4.95 (1H, m, CH), 6.80 (1H, br.s, NH), 7.18 (1H, br.s, NH), 7.35—7.55 (4H, m, aromatic H), 7.65—7.90 (5H, m, aromatic H); IR (neat) 3060, 2950, 1770, 1740, 1710, 1650, 1530, 1440, 1400, 1360, 1210, 1050 cm^{-1}; GC-MS *m*/*z* 394 (M^+), 362 (M^+−32), 335 (M^+−59); High mass (FAB) *m*/*z* Calcd for $C_{22}H_{22}N_2O_5$+H: 395.1607. Found 395.1604.

Amidocarbonylation of *N*-Protected α-Aminoalkanal

Derivatives (15). A typical procedure is described for the reaction of *N*-(2,2-diethoxyethyl)phthalimido (**15a**) catalyzed by $Co_2(CO)_8$.

N-(2,2-Diethoxyethyl)phthalimido (**15a**) (1.0 g, 3.8 mmol), benzamide (460 mg, 3.8 mmol), and $Co_2(CO)_8$ (100 mg, 0.29 mmol) in THF (20 ml) were heated in a 100 ml stainless-steel autoclave with a 1 : 1 mixture of carbon monoxide and hydrogen (total pressure 120 atm, measured at room temperature) at 100 °C for 6 h. The autoclave was then cooled to ambient temperature and carbon monoxide and hydrogen were purged out. After the solvent was removed under reduced pressure, the residue was dissolved in AcOEt (50 ml) and the insoluble material filtered off. The filtrate was washed with 10% aqueous $NaHCO_3$ (50 ml) and brine. The organic phase was dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue purified by PTLC (hexane : AcOEt=3 ; 5, v/v) to give ethyl 2-benzamido-3-phthalimidopropionate (ethyl ester of **16a**) (113 mg, 0.31 mmol, 8.1%) as an oil. The aqueous $NaHCO_3$ extract was acidified with concentrated HCl and extracted with AcOEt (50 ml). The organic layer was washed with brine and dried over $MgSO_4$. After concentration, the residue was esterified with etherial CH_2N_2 and purified by PTLC (hexane : AcOEt=3 : 5, v/v) to give methyl 2-benzamido-3-phthalimidopropionate (meihyl ester of **16a**) (662 mg, 1.88 mmol, 49.5%) as a solid.

Methyl 2-Benzamido-3-phthalimidopropionate (Methyl Ester of 16a): ^{1}H NMR (300 MHz, $CDCl_3$) δ=3.81 (3H, s, CH_3), 4.20—4.30 (2H, m, CH_2), 5.00—5.10 (1H, m, CH), 7.32 (1H, br.d, *J*=6.7 Hz, NH), 7.40—7.55 (4H, m, aromatic H), 7.70-7.90 (5H, m, aromatic H); IR (KBr) 3300, 2950, 1770, 1710, 1640, 1525, 1425, 1390, 1320, 1215, 1020, 900, 720 cm^{-1}; GC-MS *m/z* 293 (M$^+$−59); mp 123—125 °C (from hexane-AcOEt); High mass (FAB) *m/z* Calcd for $C_{19}H_{16}N_2O_5$+H: 353.1137. Found: 353.1138.

Ethyl 2-Benzamido-3-phthalimidopropionate (Ethyl Ester of 16a): ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.30 (3H, t, *J*=6.8 Hz, CH_3), 4.15—4.30 (4H, m, CH_2), 5.00—5.08 (1H, m, CH), 7.30 (1H, br.d, *J*=6.7 Hz, NH), 7.40—7.55 (4H, m, aromatic H), 7.70—7.90 (5H, m, aromatic H); IR (neat) 3320, 2950, 1765, 1710, 1640, 1525, 1390, 1020 cm^{-1}; GC-MS *m/z* 293 (M$^+$−73).

Methyl 2-Benzamido-5-methyl-3-phthalimidohexanoate (Methyl Eester of 16b): ^{1}H NMR (300 MHz, $CDCl_3$) δ= 0.89—0.96 (6H, m, CH_3), 1.63—1.70 (2H, m, CH_2), 2.13—2.23 (0.5H, m, CH), 2.63 (0.5H, td, *J*=11.7 and 1.8 Hz, CH), 3.66 (1.5H, s, CH_3), 3.79 (1.5H, s, CH_3), 4.80—4.92 (0.5H, m, CH), 5.03—5.12 (1H, m, CH), 5.20 (0.5H, dd, *J*=8.6 and 4.8 Hz, CH), 7.11 (0.5H, d, *J*=7.5 Hz, NH), 7.41—7.56 (3H, m, aromatic H), 7.72—7.89 (5H, m, aromatic H), 7.97—8.00 (1H, m ,aromatic H), 8.39 (0.5H, d, *J*=8.6 Hz, NH); IR (neat) 2950, 1770, 1740, 1705, 1660, 1520, 1360, 1210, 1160, 1065 cm^{-1}; GC-MS *m/z* 377 (M$^+$−31), 349 (M$^+$−59); High mass (FAB) *m/z* Calcd for $C_{23}H_{24}N_2O_5$+H: 409.1763. Found: 409.1739.

Methyl 2-Benzamido-4-phenyl-3-phthalimidobutyrate (Methyl Ester of 16c): ^{1}H NMR (300 MHz, $CDCl_3$) δ=3.21—3.47 (2H, m, CH_2), 3.64 (1.5H, s, CH_3), 3.81 (1.5H, s, CH_3), 5.12 (0.5H, quint, *J*=5.4 Hz, CH), 5.20—5.29 (1.5H, m, CH), 7.10—7.20 (6H, m, NH and aromatic H), 7.40—7.58 (3H, m, aromatic H), 7.67—7.83 (5H, m, aromatic H), 8.03—8.06 (1H, m, aromatic H), 8.53 (0.5H, d, *J*=8.3 Hz, NH); IR (neat) 3030, 2950, 1775, 1740, 1710, 1660, 1520, 1485, 1385, 1360, 1210 cm^{-1}; GC-MS *m/z* 411 (M$^+$−31), 383 (M$^+$−59); High mass (FAB) *m/z* Calcd for $C_{26}H_{22}N_2O_5$+H: 443.1607. Found: 443.1592.

Methyl 2-Benzamido-2-(*N*-benzoylpyrrolidine-2-yl)ethanoate (Methyl Ester of 16e): ^{1}H NMR (300 MHz, $CDCl_3$) δ= 1.40—2.28 (3H, m, CH_2), 2.32—2.45 (1H, m, CH_2), 3.35—3.60 (2H, m, CH_2), 3.78 (1.5H, s, CH_3), 3.83 (1.5H, s, CH_3), 4.25 (0.5H, d, *J*=5.0 Hz, CH), 4.59—5.05 (1.5H, m, CH), 7.35—7.65 (6H, m, aromatic H), 7.70—7.98 (4H, m, aromatic H), 8.20 (0.5H, d, *J*=5.6 Hz, NH), 9.16 (0.5 H, d, *J*=7.9 Hz, NH); IR (neat) 3055, 2950, 1735, 1650, 1575, 1520, 1480, 1415, 1205 cm^{-1}; GC-MS *m/z* 335 (M$^+$−31), 307, (M$^+$−59); High mass (FAB) *m/z* Calcd for $C_{21}H_{22}N_2O_4$+H: 367.1658. Found: 367.1635.

α,ε-*N*,*N′*-Dibenzoyllysine Methyl Ester: ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.38—2.05 (8H, m, CH_2), 3.38—3.52 (2H, m, CH_2), 3.76 (3H, s, CH_3), 4.75—4.85 (1H, m, CH), 6.55 (1H, br.s, NH), 7.00 (1H, d, *J*=7.3 Hz, NH), 7.30—7.55 (6H, m, aromatic H), 7.70—7.88 (4H, m, aromatic H); IR (neat) 3070, 2950, 1753, 1640, 1535, 1490, 1440, 1310, 1210 cm^{-1}; GC-MS *m/z* 368 (M$^+$), 336 (M$^+$−32), 309 (M$^+$−59).

Methyl *N*-Benzoyl-2-piperidinecarboxylate: ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.35—1.85 (4H, m, CH_2), 2.20 (0.5H, br.d, CH_2), 2.35 (1H, br.d, CH_2), 2.85 (0.5H, m,CH_2), 3.25 (1H, br.t, CH_2), 3.65 (1H, br.d, CH_2), 3.78 (3H, br.s, CH_3), 4.45—4.70 (0.5H, m, CH), 5.50 (0.5H, br.s, CH), 7.40 (5H, br.s, aromatic H); IR (neat) 2950, 2860, 1740, 1640, 1420, 1280, 1210 cm^{-1}; GC-MS *m/z* 247 (M$^+$); High mass (FAB) *m/z* Calcd for $C_{14}H_{17}N_1O_3$+H: 248.1287. Found 248.1278.

Methyl 2-Benzamido-2-(*N*-benzyloxycarbonylpyrrolidine-2-yl)ethanoate, (Methyl Ester of 16d): ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.70—2.10 (3H, m, CH_2), 2.20—2.30 (1H, m, CH_2), 3.25—3.65 (2H, m, CH_2), 3.67 (1.5H, s, CH_3), 3.78 (1.5H, s, CH_3), 4.25—4.55 (1.5H, m, CH), 4.84 (0.5H, dd, *J*=7.5 and 2.4 Hz, CH), 5.07—5.22 (2H, m, CH_2), 7.20—7.55 (8H, m, aromatic H), 7.80—7.95 (2H, m, aromatic H), 8.24 (0.5H, br.d, *J*=4.2 Hz, NH), 8.84 (0.5H, d, *J*=7.2 Hz, NH); IR (neat) 2945, 1753, 1690, 1655, 1520, 1480, 1405, 1350, 1330, 1200, 1100 cm^{-1}; GC-MS *m/z* 365 (M$^+$−31), 204 (M$^+$−192); High mass (FAB) *m/z* Calcd for $C_{22}H_{24}N_2O_5$+H: 397.1763. Found 397.1766.

Deprotection of ω-*N*-Phthaloyl Group. α-*N*-Benzoyl-δ-*N*-phthaloylornithine (**13a**) (500 mg, 1.42 mmol) and hydrazine monohydrate (2.84 mmol) in MeOH (10 ml) were heated at 80 °C for 1 h. The solvent was removed under reduced pressure. The residue was dissolved in aqueous HCl and an insoluble material was filtered off. The filtrate was concentrated under reduced pressure and washed with AcOEt to give α-*N*-benzoylornithine hydrazine salt (**17**) (319 mg, 1.19 mmol, 83.8%) as a solid.

α-*N*-Benzoylornithine Hydrazine Salt (17): ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.75—2.08 (4H, m,CH_2), 3.07 (2H, t, *J*=7.5 Hz, CH_2), 4.43 (1H, dd, *J*=8.0 and 5.2 Hz, CH), 7.50—7.70 (3H, m, aromatic H), 7.78—7.84 (2H, m, aromatic H); IR (KBr) 3345, 2950, 1635, 1600, 1530, 1400, 1365, 1300 cm^{-1}; mp 226—228 °C (from H_2O-MeOH); High mass (FAB) *m/z* Calcd for $C_{12}H_{16}N_2O_3$+H: 237.1239. Found: 237.1257.

α-*N*-Benzoylornithine hydrazine salt (**17**) (319 mg), $NaHCO_3$ (706 mg, 8.4 mmol), and benzyloxycarbonyl chrolide (toluene solution, 4.2 mmol) in H_2O (15 ml) and ether (10 ml) were stirred at room temperature for 15 h. The reaction mixture was washed with ether and acidified with concentrated HCl. The solution was extracted with AcOEt and the extract washed with brine, then dried over $MgSO_4$. After concentration, the residue was washed with hexane-

AcOEt to give α-*N*-benzoyl-δ-*N*-benzyloxycarbonylornithine (**18**) (275 mg, 0.74 mmol, 52.2%) as a solid.

α-*N*-Benzoyl-δ-*N*-benzyloxycarbonylornithine (18): ^{1}H NMR (300 MHz, DMSO-d_6) δ=1.45—1.60 (2H, m, CH_2), 1.70—1.90 (2H, m, CH_2), 2.98—3.07 (2H, m, CH_2), 4.30—4.40 (1H, m, CH), 5.00 (2H, s, CH_2), 7.20—7.58 (8H, m, aromatic H), 7.85—7.92 (2H, m, aromatic H), 8.57 (1H, d, *J*=8.1 Hz, NH); IR (KBr) 3310, 2940, 1700, 1680, 1630, 1530, 1250 cm^{-1}; mp 133—135 °C (from hexane-AcOEt); High mass (FAB) *m*/*z* Calcd for $C_{20}H_{22}N_2O_5$+H: 371.1607. Found: 371.1625.

Deprotection of α-*N*-Acetyl Group. A solution of α-*N*-acetyl-ε-*N*-phthaloyllysine (**13b**) (300 mg, 0.90 mmol), $CoCl_2$ (3.9 mg, 0.003 mmol), and aminoacylase (19800 u g^{-1}, 60 mg) in H_2O (30 ml) was adjusted to pH 7.0. The solution was shaken at 38 °C for 4 d. The solution was concentrated under reduced pressure. The residue was dissolved in H_2O (5 ml) and acetone (5 ml). To the solution, 1 equiv $NaHCO_3$ (2 ml) and (−)-MTPACl (methoxytrifluoromethylphenylacetyl chloride) (228 mg, 0.90 mmol) were added at 0 °C; the solution was then stirred at room temperature for 1 h. The solution was acidified with concentrated HCl and extracted with AcOEt (20 ml). The extract was washed with brine and dried over $MgSO_4$. After concentration, the residue was esterified with etherial CH_2N_2 and purified by PTLC (hexane : AcOEt=2 : 1, v/v) to give α-*N*-MTPA-ε-*N*-phthaloyl-L-lysine methyl ester (**20a**) (132 mg, 0.26 mmol, 28.9%, 92%de) as an oil.

Authentic samples of α-*N*-(−)- and -(+)-MTPA-ε-*N*-phthaloyl-L-lysine methyl ester (**20a**, **b**) were prepared starting from α-*N*-benzyloxycarbonyl-L-lysine.

ε-*N*-Phthaloyl-L-lysine (19): ^{1}H NMR (300 MHz, D_2O) δ=1.38—1.50 (2H, m, CH_2), 1.65—1.75 (2H, m, CH_2), 1.85—1.95 (2H, m, CH_2), 3.67 (2H, t, *J*=6.9 Hz, CH_2), 3.73 (1H, t, *J*=6.0 Hz, CH), (4H, m, aromatic H), 7.82 (4H, s, aromatic H); IR (KBr) 2940, 1770, 1710, 1700, 1575, 1500, 1400 cm^{-1}; mp 232—233 °C (from H_2O-MeOH); High mass (FAB) *m*/*z* Calcd for $C_{14}H_{16}N_2O_4$+H: 277.1188. Found: 277.1180.

α-*N*-(−)-Methoxytrifluoromethylphenylacetyl-ε-*N*-phthaloyl-L-lysine Methyl Ester (20a): ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.17—1.30 (2H, m, CH_2), 1.58—1.98 (4H, m, CH_2), 3.54—3.56 (3H, m, CH_3), 3.60 (2H, t, *J*=7.3 Hz, CH_2), 3.76 (3H, s, CH_3), 4.65 (1H, td, *J*=8.2 and 5.0 Hz, CH), 7.08 (1H, d, *J*=8.1 Hz, NH), 7.35—7.74 (3H, m, aromatic H), 7.50—7.56 (2H, m, aromatic H), 7.70—7.74 (2H, m, aromatic H), 7.80—7.84 (2H, m, aromatic H); IR (neat) 3350, 2950, 2850, 1770, 1740, 1710, 1610, 1510, 1440, 1395, 1360, 1265 cm^{-1}; High mass (FAB) *m*/*z* Calcd for $C_{25}H_{25}N_2O_6F_3$+H: 507.1743. Found: 507.1732.

α-*N*-(+)-Methoxytrifluoromethylphenylacetyl-ε-*N*-phthaloyl-L-lysine Methyl Ester (20b): ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.35—1.50 (2H, m, CH_2), 1.62—2.05 (2H, m, CH_2), 3.35—3.38 (3H, m, CH_3), 3.69 (2H, t, *J*=7.1 Hz, CH_2), 3.74 (3H, s, CH_3), 4.61 (1H, td, *J*=8.3 and 5.1 Hz, CH), 7.35—7.43 (4H, m, NH and aromatic H), 7.50—7.58 (2H, m, aromatic H), 7.70—7.74 (2H, m, aromatic H), 7.76—7.83 (2H, m, aromatic H).

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