Syntheses of L-Glutamic Acid Analogues for Neuroexcitatory Activity Studies

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Starting from D–serine, (2*S*,3*S*)-, (2*S*,3*R*)-substituted-L-glutamic acids were prepared *via* Claisen rearrangement methodology. A variety of the substituents can be introduced at the C-3 of the L-glutamic acid backbone.

INTRODUCTION

We have reported the syntheses of 4-substituted-L-glutamic acid analogues (Type **A**, Fig. 1) for neuroexcitatory activity studies.[1] It was found that (2*S*,4*R*)-substituted analogues are more potent than their (2*S*,4*S*)-isomers in interacting with L-glutamate receptors both at porcine brain synaptic junctions and on drosophila muscles.[2a] Among synthetic L-glutamate analogues, 4(*R*)-(5′-phenylpentyl)-2(*S*)-glutamic acid (i.e. **A(5)**) shows higher drosophila-paralyzing potency than those of the remaining analogues and even slightly higher than that of quisqualate.[2b,2c] In order to understand the difference of their biological effects between the substituent at 3-(Type **B**) and 4-position (Type **A**) of the glutamate backbone on the nervous system, the preparation of the 3-substituted-L-glutamic acid analogues was needed (Fig. 1). Indeed, four configurational isomers of 3-benzylglutamic acids synthesized by a Michael addition of PhCH(SPh)Li to α,β-unsaturated--γ-amido-δ-lactone or α,β-unsaturated-γ-lactam, followed by desulfurization was reported. They also reported the relative potency of these four stereoisomers in comparison with L-glutamic acid in the rat spinal cord.[3] Here, we describe our work in synthesizing the 3-substituted-L-glutamic acids *via* Claisen rearrangement methodology in enantiomeric pure forms. The phenyl group was jointed to the 3-position of the glutamate backbone by a linker of (CH_2)n, where n is equal to 3, 4 or 5 (Type **B**, Fig. 1).

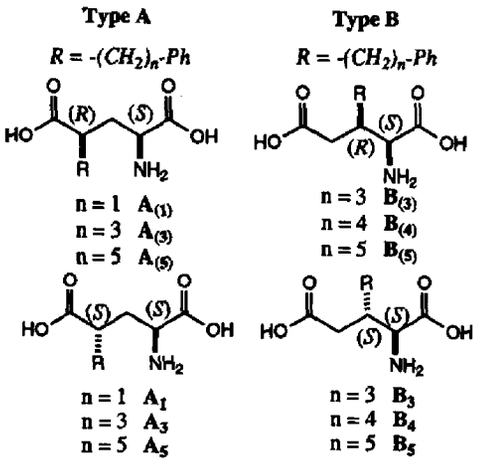


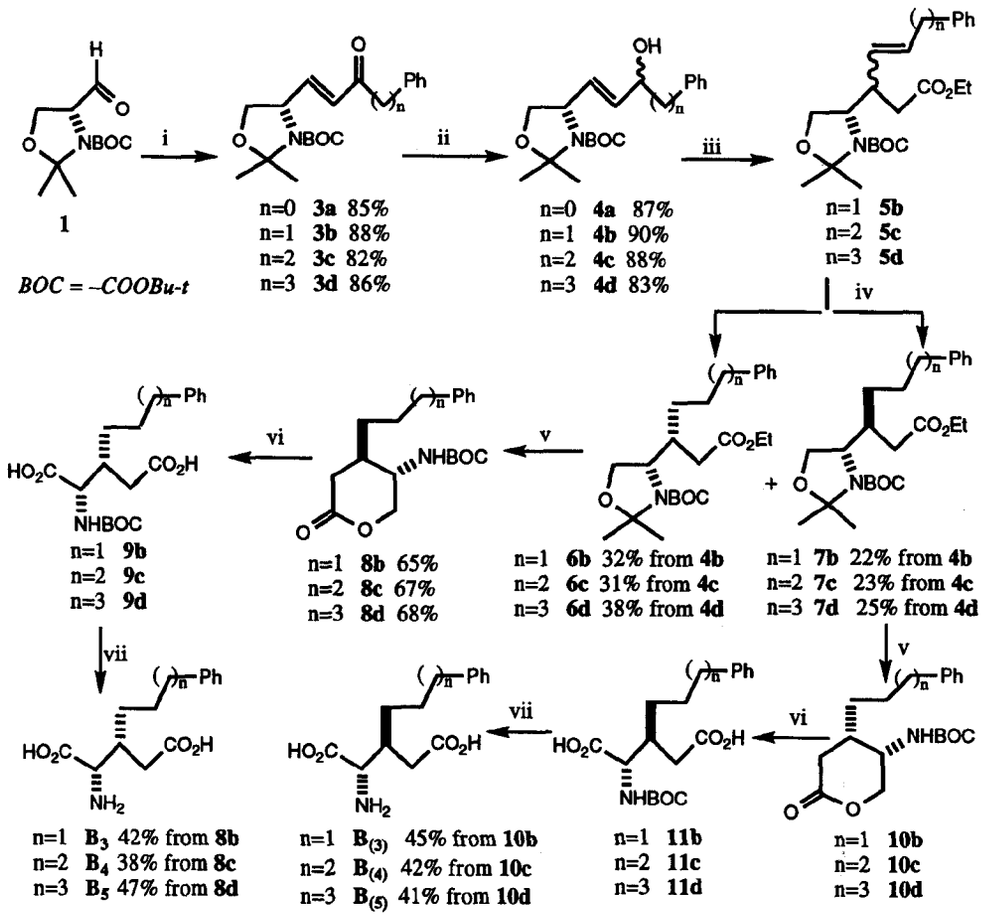
Fig. 1. Four different types of glutamate derivatives.

RESULTS AND DISCUSSION

Chiral molecules constructed by using amino acids is an invaluable source of stereochemically pure molecules.[4] Serine is an α-amino acid that possess a β-hydroxy moiety. To modify the different oxidation state of the hydroxy and carboxyl groups on the serine, we are able to convert it into glutamate. 4(*S*)-Formyl-2,2-dimethyloxazoline-3-carboxylic acid *tert*-butyl ester (**1**) was used as a key intermediate, which was readily prepared from D-serine according to procedures in the literature.[5] The aldehyde (**1**) was treated with several stable phosphonium ylides **2a-2d** in THF under refluxing condition to afford *trans*-α,β-unsaturated ketones **3a-3d** in good yields. Regioselective 1,2-reduction of enones **3a-3d** is achieved with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$[6] to give the corresponding allylic alcohols **4a-4d** as a mixture of two diastereomers in a ratio of 1:1. Treatment of allylic alcohols **4b-4d** with triethyl orthoacetate in the presence of a catalytic amount of propionic acid under heating gave the γ,δ-unsaturated ester **5b-5d**.[7] The double bond on compounds **5b-5d** were reduced by catalytic hydrogenation and the diastereomeric products (**6b** and **7b**; **6c**

Dedicated to the memory of the late Professor Ta-shue Chou

Scheme I

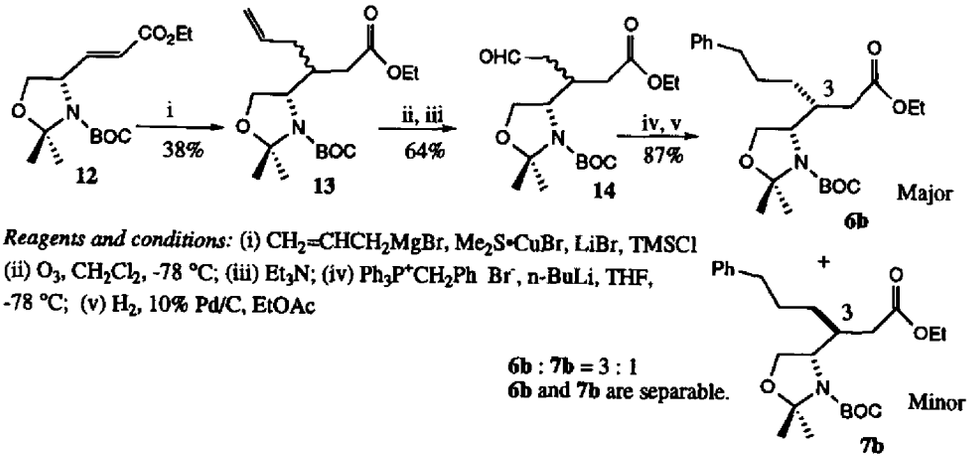


Reagents and conditions: (i) $Ph_3P{=}CHCO(CH_2)_nPh$, CH_2Cl_2, RT, n=0 (**2a**); n=1 (**2b**); n=2 (**2c**); n=3 (**2d**); (ii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$; (iii) $MeC(OEt)_3$, cat. $EtCO_2H$, 130 °C; (iv) H_2, 10% Pd/C, EtOH; MPLC separation; (v) 60% aq. HOAc, 70 °C; (vi) NaOH; $KMnO_4$, Pyridine; (vii) 0 °C, TFA, CH_2Cl_2

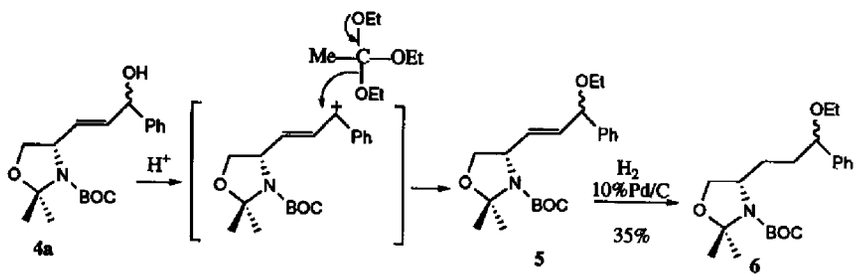
and **7c**; **6d** and **7d**) were separated by medium pressure liquid chromatography (Scheme I). In general, the diastereomeric ratio is about 3:2 in each case, and the major product was the less polar one based on TLC analysis. The stereochemistry of compounds **6b** and **7b** was determined unambiguously by the procedure shown in Scheme II. The *trans*-α,β-unsaturated ester **12**, prepared from aldehyde **1** and $Ph_3P{=}CHCO_2Et$ in 72% yield, underwent diallylcuprate Michael addition to give the 1,4-adduct **13** in 38% yield as a mixture of two inseparable diastereomers.[8] The ozonolysis of compound **13** followed by reaction with triethylamine afforded the corresponding aldehyde **14** in high yield.[9] The aldehyde **14** reacted with benzylidenetriphenyl-phosphorane followed by catalytic hydrogenation to give two separable isomers **6b** and **7b** in a total of 54% yield. The ratio of these two isomers is approximately 3:1, and the major product is also the less polar one on silica gel TLC. The configuration of the C-3 stereogenic center of compound **6b** should be identical to the *syn* isomer of compound **13** because they were not affected during the functional group transformations shown in Scheme II. The *syn* isomer of compound **13** is proposed to be the major product which could be rationalized by the Felkin-Anh model as shown in Fig. 2 where the nucleophilic addition took place from *re* face preferentially.[10] The *syn*-selectivity of the Michael addition has also been reported in a related system.[11] In conclusion, the *syn* isomer is the major product both from Claisen rearrangement (Scheme I) and from Michael addition approach (Scheme II).

Interestingly, under the standard Claisen rearrangement condition, the allylic alcohol **4a** did not give the desired γ,δ-unsaturated ester but gave the etherification product **5**. Under catalytic hydrogenation conditions, the double bond on compound **5** was reduced to give compound **6** (Scheme III). The formation of compound **5** was rationalized as follows. The protonation of the secondary alcohol of compound **4a**

Scheme II



Scheme III



gave the carbocation intermediate which is stabilized by both the vinyl and phenyl groups. This carbocation intermediate reacts with triethyl orthoacetate to give the allyl ethyl ether **5**.

The β-substituted ester (**6c**) was treated with 60% aqueous acetic acid at 70 °C to give δ-lactone (**8c**). Under refluxing conditions, both isopropylidene and BOC groups were cleaved to give γ-lactam (**8c'**) in moderate yield (Scheme IV). Therefore, the reaction temperature should be controlled caefully. When we compared the ^{1}H-NMR spectra of *anti*-lactones (**8b-8d**) and *syn*-lactones (**10b-10d**), we found that the *anti*-lactones (**8b-8d**) appeared as two well-separated doublets ($\Delta\delta$ = 0.18-0.23 ppm) and the *syn*-lactones (**10b-10d**) appeared as a broad doublet-quartet for the δ-methylene groups (Fig. 3). This trend is consisent with the reported spectral data for *anti*-lactones **8e** and *syn*-lactone **10e** (Fig. 3).[3]

Alkaline hydrolysis of the δ-lactone (**8b**) with 20% aqueous KOH gave the corresponding hydroxy-carboxylate intermediate which was subsequently oxidized by $KMnO_4$ in the presence of pyridine[12] to give the dicarboxylic acid (**9b**) in the same flask. In the absence of pyridine, poor yield of the oxida-

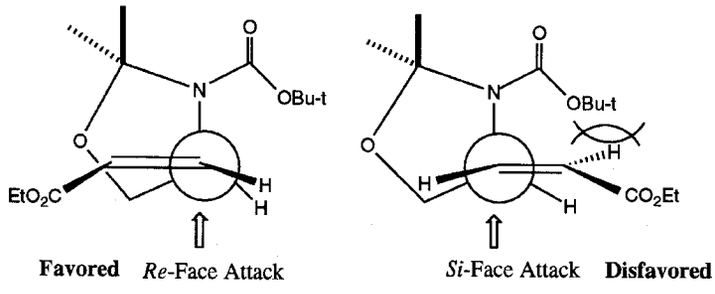
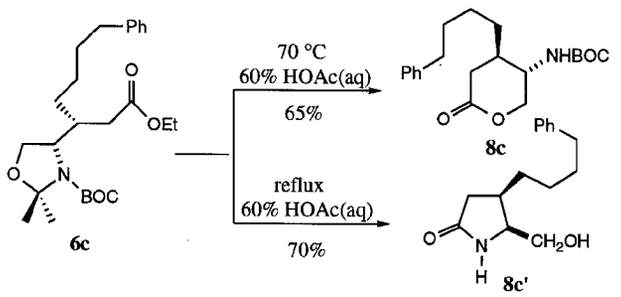


Fig. 2. The facial selectivity for the 1,4-addition of lithium diallylcuprate to α,β-unsaturated ester (**12**).

Scheme IV



tion product was obtained. The deprotection of BOC group by 25% of trifluoroacetic acid in dichloromethane gave 3-substituted-L-glutamic acid $\mathbf{B_3}$ in excellent yield. The glutamate $\mathbf{B_3}$ was then purified by Dowex® ion-exchange resin followed by HPLC (reverse phase column). By employing similar procedures, several 3-substituted-L-glutamic acids ($\mathbf{B_4}$-$\mathbf{B_5}$ and $\mathbf{B_{(3)}}$-$\mathbf{B_{(5)}}$) could also be made (Scheme I).

In summary, we have developed a Claisen rearrangement approach to prepare several 3-substituted-L-glutamic acids. The linker between phenyl and the glutamate backbone longer than three methylene units could be made effectively. The evaluation of the biological activity of these compounds is under investigation.

EXPERIMENTAL

Melting points (Yanaco micro melting point apparatus) are uncorrected. Infrared spectra of dichloromethane solution were recorded on a Pekin-Elmer 882 infrared spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured by a Bruker AC-200 or ACP-300 NMR facility. Tetramethylsilane was used as internal standard in ^{1}H NMR. ^{13}C NMR spectra ($CDCl_3$ central line at 77.0 ppm as internal standard) were recorded at 50 or 75 MHz. The mass spectra and Gas Chromatography-Mass Spectroscopy were recorded by VG 70-250S. The high-resolution mass spectra (HRMS) were recorded on a VG-70-250S spectrometer at an ionizing voltage of 70 eV or 20 eV. The ozonolysis was carried out by a Fisher Ozone Generator (Model 501). 4(*S*)-formyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (**1**) was prepared according to methods in the literature.[5]

(4*S*)-(3′-Oxo-3′-phenylprop-1′(*E*)-enyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (3a)

Compounds **3a-3d** were prepared in a similar manner. The preparation of compounds **3a** is typical. A mixture of 4(*S*)-formyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (**1**) (4.27 g, 18.63 mmol) and (triphenylphosphoranylidene)acetophenone (**2a**) (7.79 g, 20.48 mmol) in 90 mL of THF was heated up to reflux for 12 h. The solution was cooled to room temperature and concentrated *in vacuo*.

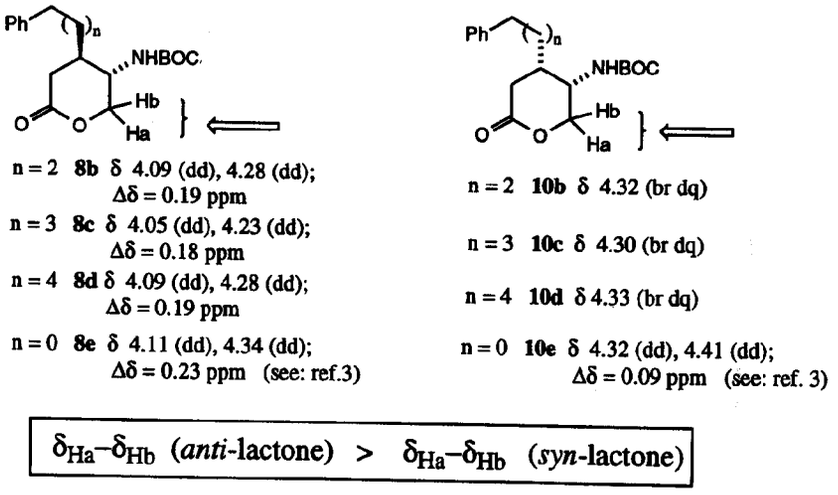


Fig. 3. Comparison of the chemical shift difference of the δ-methylene group in compounds **8** and **10** in ^{1}H-NMR spectra.

Chromatography on silica gel afforded 5.06 g (82%) of α,β-unsaturated ketone (**3a**) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.30-1.75 (m, 15H), 3.86 (dd, J = 9.1 and 2.4 Hz, 1H), 4.13 (dd, J = 9.1 and 6.5 Hz, 1H), 4.32-4.75 (m, 1H), 6.85-6.95 (m, 2H), 7.38-7.65 (m, 3H), 7.88-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.4, 24.5 (-OC($\underline{C}H_3$)$_2$N-), 26.2, 27.1 (-OC($\underline{C}H_3$)$_2$N-), 28.1 (-OC($\underline{C}H_3$)$_3$), 58.2 (-OCH$_2\underline{C}$HRN-), 67.1 (-O$\underline{C}$H$_2$CHRN-), 79.9, 80.0 (-O$\underline{C}$(CH$_3$)$_3$), 93.8, 94.3 (-O$\underline{C}$(CH$_3$)$_2$N-), 125.7 (aromatic), 126.2 (-CH=$\underline{C}$HCOPh), 128.3 (aromatic), 132.7 (aromatic), 137.3 (aromatic), 145.1, 146.1 (-$\underline{C}$H=CHCOPh), 151.4 (-$\underline{C}$OOC(CH$_3$)$_3$), 190.0 (-CH=CH$\underline{C}$OPh).

(4*S*)-(3′-Oxo-4′-phenylbut-1′(*E*)-enyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (3b)

88% yield; pale yellow oil; $[\alpha]_D$ = 52.5 (c 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.25-1.65 (m, 15H), 3.73 (dd, J = 9.1 and 2.2 Hz, 1H), 3.81 (s, 2H), 4.03 (dd, J = 9.2 and 6.4 Hz, 1H), 4.27-4.43 (m, 0.5H), 4.43-4.59 (m, 0.5H), 6.20 (br t, J = 15.6 Hz, 1H), 6.75 (dd, J = 15.6 and 7.1 Hz, 1H), 7.15-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.2, 24.3 (-OC($\underline{C}H_3$)$_2$N-), 26.1, 26.9 (-OC($\underline{C}H_3$)$_2$N-), 28.0 (-OC($\underline{C}H_3$)$_3$), 47.8 (-CO$\underline{C}$H$_2$Ph), 57.9 (-OCH$_2\underline{C}$HRN-), 67.0 (-O$\underline{C}$H$_2$CHRN-), 79.7, 80.3 (-O$\underline{C}$(CH$_3$)$_3$), 93.7, 94.1 (-O$\underline{C}$(CH$_3$)$_2$N-), 126.7 (aromatic), 128.4 (aromatic), 128.7 (aromatic), 129.1 (-CH=$\underline{C}$HCO-), 133.8 (aromatic), 144.1, 144.6 (-$\underline{C}$H=CHCO-), 151.2 (-$\underline{C}$OOC(CH$_3$)$_3$), 196.5 (-CH=CH$\underline{C}$O-); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 2977, 1686 (C=O), 1366, 1171; MS (m/e) (rel intensity) 330 (M^+-15, 3), 289 (12), 272 (18), 230 (100), 154 (30), 96 (49), 84 (65); HRMS Calcd for $C_{20}H_{27}O_4N$-CH_3: 330.1705. Found 330.1709.

(4*S*)-(3′-Oxo-5′-phenylpent-1′(*E*)-enyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (3c)

82% yield; pale yellow oil; $[\alpha]_D$ = 55.1 (c 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.35-1.68 (m, 15H), 2.78-3.02 (m, 4H), 3.73 (dd, J = 9.1, 2.3 Hz, 1H), 4.06 (dd, J = 9.0, 6.4 Hz, 1H), 4.28-4.45 (m, 0.5H), 4.45-4.56 (m, 0.5H), 6.18 (br t, J = 15.7 Hz, 1H), 6.58-6.77 (m, 1H), 7.10-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.2, 24.3 (-OC($\underline{C}H_3$)$_2$N-), 26.1, 26.9 (-OC($\underline{C}H_3$)$_2$N-), 28.0 (-OC($\underline{C}H_3$)$_3$), 29.5 (-$\underline{C}$H$_2$Ph), 41.6 (-CO$\underline{C}$H$_2$-), 57.8 (-OCH$_2\underline{C}$HRN-), 66.9 (-O$\underline{C}$H$_2$CHRN-), 79.7, 80.2 (-O$\underline{C}$(CH$_3$)$_3$), 93.6, 94.0 (-O$\underline{C}$(CH$_3$)$_2$N-), 125.7 (aromatic), 128.0 (aromatic), 128.1 (aromatic), 129.9 (-CH=$\underline{C}$HCO-), 140.7 (aromatic), 143.7 (-$\underline{C}$H=CHCO-), 151.2 (-$\underline{C}$OOC(CH$_3$)$_3$), 198.4 (-CH=CH$\underline{C}$O-); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 2979, 1668 (C=O), 1370, 1169; MS (m/e) (rel intensity) 344 (M^+-15, 3), 303 (16), 244 (36), 200 (5), 84 (100); HRMS Calcd for $C_{21}H_{29}O_4N$-CH_3: 344.1862. Found 344.1672.

(4*S*)-(3′-Oxo-6′-phenylhex-1′(*E*)-enyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (3d)

86% yield; pale yellow oil; $[\alpha]_D$ = 57.2 (c 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.26-1.72 (m, 15H), 1.94 (quin, J = 7.2 Hz, 2H), 2.56 (t, J = 7.3 Hz, 2H), 2.63 (t, J = 7.4 Hz, 2H), 3.76 (dd, J = 9.2, 2.2 Hz, 1H), 4.07 (dd, J = 9.0, 6.4 Hz, 1H), 4.31-4.45 (m, 0.5H), 4.45-4.59 (m, 0.5H), 6.16 (br t, J = 15.3 Hz, 1H), 6.55-6.75 (m, 1H), 7.12-7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.3, 24.4 (-OC($\underline{C}H_3$)$_2$N-), 25.2 (-$\underline{C}$H$_2$CH$_2$Ph), 26.3, 27.1 (-OC($\underline{C}H_3$)$_2$N-), 28.1 (-OC($\underline{C}H_3$)$_3$), 34.8 (-$\underline{C}$H$_2$Ph), 39.2 (-CO$\underline{C}$H$_2$-), 58.0 (-OCH$_2\underline{C}$HRN-), 67.1 (-O$\underline{C}$H$_2$CHRN-), 79.9, 80.4 (-O$\underline{C}$(CH$_3$)$_3$), 93.8, 94.2 (-O$\underline{C}$(CH$_3$)$_2$N-), 125.7 (aromatic), 128.1 (aromatic), 128.2 (aromatic), 130.0 (-CH=$\underline{C}$HCO-), 141.3 (aromatic), 143.2, 143.5 (-$\underline{C}$H=CHCO-), 151.3 (-$\underline{C}$OOC(CH$_3$)$_3$), 199.5 (-CH=CH$\underline{C}$O-); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 2978, 1684 (C=O), 1370, 1165; MS (m/e) (rel intensity) 358 (M^+-15, 1), 317 (10), 258 (27), 200 (37), 144 (36), 100 (100), 84 (15); HRMS Calcd for $C_{22}H_{31}O_4N$-CH_3: 358.2018. Found 358.2030.

(4*S*,3′*RS*)-(3′-Hydroxy-3′-phenylprop-1′(*E*)-enyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (4a)

Compounds **4a-4d** were prepared in a similar manner. The preparation of compounds **4a** is typical. To a mixture of α,β-unsaturated ketone **3a** (5.80 g, 17.53 mmol) in 50 mL of MeOH was added $CeCl_3 \cdot 7H_2O$ (6.53 g, 17.53 mmol) and $NaBH_4$ (663 mg, 17.53 mmol) at 0 °C for 3 h. The reaction was acidified with saturated ammonium chloride and extracted with ethyl acetate (2 × 60 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. Chromatography on silica gel afforded 4.96 g (85%) of allylic alcohol (**4a**) as a mixture of two diastereomers in the form of colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.12-1.65 (m, 15H), 3.62-4.06 (m, 3H), 4.18-4.48 (m, 1H), 5.08-5.22 (m, 1H), 5.65-5.94 (m, 2H), 7.15-7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.5, 24.5 (-OC($\underline{C}H_3$)$_2$N-), 26.7 (-OC($\underline{C}H_3$)$_2$N-), 28.3 (-O$\underline{C}$H$_2$CHRN(-OC($\underline{C}H_3$)$_3$), 58.6 (-OCH$_2\underline{C}$HRN-), 65.2, 68.1-), 74.1 (-CH=CH$\underline{C}$HOH-), 79.6 (-O$\underline{C}$(CH$_3$)$_3$), 94.0 (-O$\underline{C}$(CH$_3$)$_2$N-), 126.2 (aromatic), 127.5 (aromatic), 128.4 (aromatic), 129.5 (-CH=$\underline{C}$HCHOH-), 134.3 (-$\underline{C}$H=CHCHOH), 142.8 (aromatic), 151.8 (-$\underline{C}$OOC(CH$_3$)$_3$).

(4*S*,3′*RS*)-(3′-Hydroxy-4′-phenylbut-1′(*E*)-enyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (4b)

90% yield; colorless oil; $[\alpha]_D$ = 33.9 (c 2.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.22-1.65 (m, 15H), 2.65-3.20 (m, 3H), 3.35-3.88 (m, 1H), 3.88-4.10 (m, 1H), 4.15-4.40 (m, 2H), 5.35-5.75 (m, 2H), 6.95-7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.3, 24.5 (-OC($\underline{C}H_3$)$_2$N-), 26.4, 26.9 (-OC($\underline{C}H_3$)$_2$N-), 28.1 (-OC($\underline{C}H_3$)$_3$), 43.7 (-CO$\underline{C}$H$_2$-), 58.3 (-OCH$_2\underline{C}$HRN-), 64.8, 67.8 (-O$\underline{C}$H$_2$CHRN-), 72.3 (-CH=CH$\underline{C}$HOH-), 79.3, 79.8 (-O$\underline{C}$(CH$_3$)$_3$), 93.5 (-O$\underline{C}$(CH$_3$)$_2$N-), 126.0 (aromatic), 128.0 (aromatic), 129.3 (aromatic), 133.8 (-$\underline{C}$H=CHCHOH-), 137.8

(aromatic), 151.6 (-COOC$(CH_3)_3$); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 3591, 3440 (OH), 2977, 1676 (C=O), 1446, 1376, 1168; MS (m/e) (rel intensity) 332 (M^+-15, 1), 291 (1), 273 (1), 256 (3), 232 (1), 216 (3), 200 (13), 160 (3), 116 (3), 100 (5), 84 (100); HRMS Calcd for $C_{20}H_{29}O_4N$-CH_3: 332.1862. Found 332.1671.

(4*S*,3′*RS*)-(3′-Hydroxy-5′-phenylpent-1′(*E*)-enyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (4c)

88% yield; colorless oil; $[\alpha]_D$ = 24.5 (c 1.34, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.35-1.68 (m, 15H), 1.72-2.02 (m, 2H), 2.54-2.78 (m, 2H), 2.78-3.30 (br, 1H), 3.72 (dd, *J* = 8.8, 2.0 Hz, 1H), 3.96-4.18 (m, 1H), 4.02 (dd, *J* = 8.7, 6.0 Hz, 1H), 4.19-4.45 (m, 1H), 5.58-5.75 (m, 2H), 7.05-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.4, 24.7 (-OC($\underline{C}H_3)_2$N-), 26.6, 27.0 (-OC($\underline{C}H_3)_2$N-), 28.3 (-OC($\underline{C}H_3)_3$), 31.4 (-$\underline{C}H_2$Ph), 38.4 (-CHOH$\underline{C}H_2$-), 58.5 (-OCH$_2\underline{C}$HRN-), 64.2, 65.0, 68.1 (-O$\underline{C}H_2$CHRN-), 71.1 (-CH=CH$\underline{C}$HOH-), 79.5, 80.2 (-O$\underline{C}(CH_3)_3$), 93.8 (-O$\underline{C}(CH_3)_2$N-), 125.6 (aromatic), 128.3 (aromatic), 129.4, 129.5 (-CH=$\underline{C}$HCHOH-), 134.6 (-$\underline{C}$H=CHCHOH-), 141.6 (aromatic), 151.8 (-$\underline{C}$OOC$(CH_3)_3$); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 3597, 3445 (OH), 2979, 1683 (C=O), 1378, 1249, 1171; MS (m/e) (rel intensity) 346 (M^+-15, 3), 305 (3), 287 (6), 246 (10), 228 (17), 216 (6), 200 (8), 160 (6), 144 (12), 116 (14), 100 (17), 84 (100); HRMS Calcd for $C_{21}H_{31}O_4N$-CH_3): 346.2018. Found 346.2028.

(4*S*,3′*RS*)-(3′-Hydroxy-6′-phenylhex-1′(*E*)-enyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (4d)

83% yield; colorless oil; $[\alpha]_D$ = 23.2 (c 1.04, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.28-1.87 (m, 19H), 2.22-2.75 (m, 3H), 3.73 (dd, *J* = 8.8, 1.7 Hz, 1H), 4.00 (dd, *J* = 8.7, 6.0 Hz, 1H), 4.02-4.18 (m, 1H), 4.18-4.46 (m, 1H), 5.55-5.78 (m, 2H), 7.15-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.4, 24.7 (-OC($\underline{C}H_3)_2$N-), 26.6 (-OC($\underline{C}H_3)_2$N-), 27.1 (-$\underline{C}H_2CH_2$Ph), 28.3 (-OC($\underline{C}H_3)_3$), 35.6 (-$\underline{C}H_2$Ph), 36.7 (-CHOH$\underline{C}H_2$-), 58.5 (-OCH$_2\underline{C}$HRN-), 65.5, 68.1 (-O$\underline{C}H_2$CHRN-), 71.8 (-CH=CH$\underline{C}$HOH-), 79.5, 80.1 (-O$\underline{C}(CH_3)_3$), 93.7 (-O$\underline{C}(CH_3)_2$N-), 125.6 (aromatic), 128.1 (aromatic), 128.3 (aromatic), 129.2, 129.5 (-CH=$\underline{C}$HCHOH-), 134.9 (-$\underline{C}$H=CHCHOH-), 142.1 (aromatic), 151.8 (-COOC$(CH_3)_3$); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 3600, 3435 (OH), 2934, 1682 (C=O), 1379, 1248, 1166; MS (m/e) (rel intensity) 360 (M^+-15, 2), 319 (2), 301 (4), 260 (9), 242 (12), 216 (9), 200 (12), 160 (9), 144 (10), 116 (27), 100 (28), 84 (100); HRMS Calcd for $C_{22}H_{33}O_4N$-CH_3: 360.2175. Found 360.2185.

(4*S*,3′*RS*)-(3′-Ethoxy-3′-phenylpropyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (6)

A mixture of allylic alcohol (**4a**) (4.85 g, 14.58 mmol), triethyl orthoacetate (11.83 g, 72.92 mmol) and propionic acid (0.11 g, 1.46 mmol) was heated to 138 °C for 2 h and the solvent was concentrated *in vacuo*. The crude products and 10% Pd/C (0.78 g, 0.73 mmol) were dissolved in 50 mL of ethyl acetate and the hydrogenation was carried out at 60 psi. After being shaken at 25 °C for 12 h the mixture was filtered through Celite. The filtrate was concentrated and separated by silica gel column chromatography to give 1.82 g of compound **6** in 35% yield as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.12 (t, *J* = 7.0 Hz, 3H), 1.22-1.94 (m, 19H), 3.20-3.45 (m, 2H), 3.62-4.03 (m, 3H), 4.10-4.42 (m, 1H), 7.18-7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.3 (-$CO_2CH_2\underline{C}H_3$), 23.2 (-OC($\underline{C}H_3)_2$N-), 26.7, 27.4 (-OC($\underline{C}H_3)_2$N-), 28.3 (-OC($\underline{C}H_3)_3$), 29.8 (-$\underline{C}H_2CH_2$CHRPh), 34.8, 35.1 (-$CH_2\underline{C}H_2$CHRPh), 57.3, 57.5 (-OCH$_2\underline{C}$HRN-), 63.9 (-OCH$_2\underline{C}$HRN-), 66.8 (-O$\underline{C}H_2CH_3$), 79.3, 79.7 (-O$\underline{C}(CH_3)_3$), 81.9 (-R$\underline{C}$HOEt), 93.5 (-O$\underline{C}(CH_3)_2$N-), 126.4 (aromatic), 127.3 (aromatic), 128.2 (aromatic), 142.8 (aromatic), 151.8 (-COOC$(CH_3)_3$).

(4*S*,1′*R*)-(1′-Ethexycarbonylmethyl-4′-phenylbutyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (6b) and (4*S*,1′*S*)-(1-Ethoxycarbonylmethyl-4-phenylbutyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (7b)

Compounds **6b-6d** and **7b-7d** were prepared in a similar manner. The preparation of compounds **6b** and **7b** is typical. A mixture of allylic alcohol (**4b**) (4.63 g, 13 mmol), triethyl orthoacetate (10.82 g, 67 mmol) and propionic acid (0.1 g, 1.3 mmol) was heated to 138 °C for 2 h and the solvent was concentrated *in vacuo*. The crude products and 10% Pd/C (0.73 g, 0.68 mmol) were dissolved in 50 mL of ethyl acetate and the hydrogenation was carried out at 60 psi. After being shaken at 25 °C for 12 h the mixture was filtered through Celite. The filtrate was concentrated and separated by medium presure liquid chromatography to give compounds **6b** (34%) and **7b** (22%) as colorless oils.

Compound **6b** is a less polar isomer: $[\alpha]_D$ = 13.2 (c 0.98, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.18 (t, *J* = 9.9 Hz, 3H), 1.38-1.52 (m, 15H), 1.52-1.81 (m, 4H), 1.98-2.20 (m, 1H), 2.46-2.72 (m, 4H), 3.68-4.00 (m, 3H), 4.10 (q, *J* = 7.1 Hz, 2H), 7.10-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1 (-$CO_2CH_2\underline{C}H_3$), 22.5, 23.8 (-OC($\underline{C}H_3)_2$N-), 26.1 (-OC($\underline{C}H_3)_2$N-), 28.3 (-OC($\underline{C}H_3)_3$), 28.9 (-$CH_2\underline{C}H_2CH_2$Ph), 31.5 (-$\underline{C}H_2CH_2CH_2$Ph), 34.7 (-$\underline{C}H_2CO_2$Et), 35.9 (-$\underline{C}H_2$Ph), 36.6 (-R$\underline{C}$H$(CH_2)_3$Ph), 58.7 (-OCH$_2\underline{C}$HRN-), 60.2 (-O$\underline{C}H_2CH_3$), 63.6 (-O$\underline{C}H_2$CHRN-), 80.0 (-O$\underline{C}(CH_3)_3$), 94.2 (-O$\underline{C}(CH_3)_2$N-), 125.6 (aromatic), 128.2 (aromatic), 142.0 (aromatic), 152.5 (-$\underline{C}$OOC$(CH_3)_3$), 172.2 (-$\underline{C}O_2$Et); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 2980, 1724 (C=O), 1683 (C=O), 1365, 1201, 1174; MS (m/e) (rel intensity) 404 (M^+-15, 12), 318 (13), 304 (100), 288 (29), 274 (28), 260 (10), 244 (31), 216 (4), 200 (11), 174 (8), 144 (29), 100 (20); HRMS Calcd for $C_{24}H_{37}O_5N$-CH_3: 404.2437. Found 404.2449.

For compound **7b**: $[\alpha]_D$ = 24.4 (c 0.67, $CHCl_3$); ^1H NMR

($CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3H), 1.44-1.78 (m, 19H), 2.11-2.54 (m, 3H), 2.54-2.75 (m, 2H), 3.68-4.02 (m, 3H), 4.10 (q, J = 7.1 Hz, 2H), 7.12-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1 (-$CO_2CH_2\underline{C}H_3$), 22.7, 24.3 (-OC($\underline{C}H_3)_2$N-), 26.0, 26.8 (-OC($\underline{C}H_3)_2$N-), 28.4 (-OC($\underline{C}H_3)_3$), 28.7 (-$CH_2\underline{C}H_2CH_2$Ph), 29.7 (-$\underline{C}H_2CH_2CH_2$Ph), 35.9 (-$\underline{C}H_2CO_2$Et), 36.5 (-$\underline{C}H_2$Ph), 37.6 (-R$\underline{C}H(CH_2)_3$Ph), 59.9 (-$OCH_2\underline{C}$HRN-), 60.3 (-O$\underline{C}H_2CH_3$), 64.8 (-O$\underline{C}H_2$CHRN-), 80.0 (-O$\underline{C}(CH_3)_3$), 94.3 (-O$\underline{C}(CH_3)_2$N-), 125.7 (aromatic), 128.2 (aromatic), 128.3 (aromatic), 142.1 (aromatic), 152.4 (-$\underline{C}OOC(CH_3)_3$), 172.9 (-$\underline{C}O_2$Et); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 3011, 1713 (C=O), 1679 (C=O), 1364, 1219, 1170; MS (m/e) (rel intensity) 404 (M^+-15, 8), 363 (3), 318 (100), 304 (75), 288 (12), 274 (11), 258 (25), 244 (15), 216 (12), 200 (32), 156 (12), 144 (34), 100 (85); HRMS Calcd for $C_{24}H_{37}O_5N$-CH_3: 404.2437. Found 404.2449.

(4*S*,1′*R*)-(1′-Ethoxycarbonylmethyl-5′-phenylpentyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (6c) and (4*S*,1′*S*)-(1′-Ethoxycarbonylmethyl-5′-phenylpentyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (7c)

Compounds **6c** (31%) and **7c** (23%) were obtained as colorless oils.

Compound **6c** is a less polar isomer: $[\alpha]_D$ = 13.2 (c 1.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.22 (t, J = 7.1 Hz, 3H), 1.28-1.72 (m, 21H), 1.96-2.22 (m, 1H), 2.42-2.66 (m, 4H), 3.69-3.95 (m, 3H), 4.10 (q, J = 7.1 Hz, 2H), 7.08-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.0 (-$CO_2CH_2\underline{C}H_3$), 22.3, 23.7 (-OC($\underline{C}H_3)_2$N-), 25.9 (-OC($\underline{C}H_3)_2$N-), 26.7 (-$\underline{C}H_2CH_2CH_2$Ph), 28.2 (-OC($\underline{C}H_3)_3$), 31.3 (-$\underline{C}H_2CH_2CH_2$Ph), 31.7 (-$\underline{C}H_2(CH_2)_4$Ph), 34.5 (-$\underline{C}H_2CO_2$Et), 35.5 (-$\underline{C}H_2$Ph), 36.6 (-R$\underline{C}H(CH_2)_3$Ph), 58.5, 59.3 (-$OCH_2\underline{C}$HRN-), 60.0 (-O$\underline{C}H_2CH_3$), 63.5 (-O$\underline{C}H_2$CHRN-), 79.8 (-O$\underline{C}(CH_3)_3$), 94.0 (-O$\underline{C}(CH_3)_2$N-), 125.4 (aromatic), 128.0 (aromatic), 128.1 (aromatic), 142.1 (aromatic), 152.3 (-$\underline{C}OOC(CH_3)_3$), 173.1 (-$\underline{C}O_2$Et); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 2933, 1721 (C=O), 1681 (C=O), 1365, 1253, 1167; MS (m/e) (rel intensity) 418 (M^+-15, 12), 404 (1), 375 (4), 332 (69), 318 (100), 302 (8), 288 (8), 275 (9), 230 (9), 200 (74), 188 (6), 156 (3), 144 (17), 100 (22); HRMS Calcd for $C_{25}H_{39}O_5N$-CH_3: 418.2593. Found 418.2585.

For compound **7c**: $[\alpha]_D$ = 21.7 (c 0.67, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 1.38-1.76 (m, 21H), 2.18-2.46 (m, 3H), 2.60 (t, J = 7.6 Hz, 2H), 3.72-3.98 (m, 3H), 4.10 (q, J = 7.1 Hz, 2H), 7.10-7.44 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.2 (-$CO_2CH_2\underline{C}H_3$), 22.7, 24.3 (-OC($\underline{C}H_3)_2$N-), 26.1 (-OC($\underline{C}H_3)_2$N-), 26.5 (-$\underline{C}H_2CH_2CH_2$Ph), 28.4 (-OC($\underline{C}H_3)_3$), 29.4 (-$\underline{C}H_2CH_2$Ph), 31.6 (RCH$\underline{C}H_2(CH_2)_3$Ph), 35.7 (-$\underline{C}H_2CO_2$Et), 36.5 (-$\underline{C}H_2$Ph), 37.8 (-R$\underline{C}H(CH_2)_4$Ph), 59.9 (-$OCH_2\underline{C}$HRN-), 60.2 (-O$\underline{C}H_2CH_3$), 65.0 (-O$\underline{C}H_2$CHRN-), 80.0 (-O$\underline{C}(CH_3)_3$), 94.3 (-O$\underline{C}(CH_3)_2$N-), 125.6 (aromatic), 128.2 (aromatic), 128.3 (aromatic), 142.4 (aromatic), 152.8 (-$\underline{C}OOC(CH_3)_3$), 173.0 (-$\underline{C}O_2$Et); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 3015, 1724 (C=O), 1680 (C=O), 1365, 1204, 1178; MS (m/e) (rel intensity) 418 (M^+-15, 9), 375 (12), 332 (100), 318 (88), 302 (18), 288 (17), 275 (28), 258 (7), 230 (13), 200 (41), 188 (8), 156 (10), 144 (26), 100 (17); HRMS Calcd for $C_{25}H_{39}O_5N$-CH_3: 418.2593. Found 418.2583.

(4*S*,1′*R*)-(1′-Ethoxycarbonylmethyl-6′-phenylhexyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (6d) and (4*S*,1′*S*)-(1′-Ethexycarbonylmethyl-6′-phenylhexyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (7d)

Compounds **6d** (38%) and **7d** (25%) were formed as colorless oils.

Compound **6d** is a less polar isomer: $[\alpha]_D$ = 14.0 (c 0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H), 1.29-1.68 (m, 23H), 1.98-2.25 (m, 1H), 2.42-2.68 (m, 4H), 3.72-4.10 (m, 3H), 4.11 (q, J = 7.2 Hz, 2H), 7.11-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1 (-$CO_2CH_2\underline{C}H_3$), 22.5, 23.9 (-OC($\underline{C}H_3)_2$N-), 26.0 (-OC($\underline{C}H_3)_2$N-), 27.2 (-$\underline{C}H_2CH_2CH_2$Ph), 28.4 (-OC($\underline{C}H_3)_3$), 29.5 (-$\underline{C}H_2(CH_2)_3$Ph), 31.3 (-$\underline{C}H_2CH_2$Ph), 32.0 (-$\underline{C}H_2(CH_2)_4$Ph), 34.7 (-$\underline{C}H_2CO_2$Et), 35.8 (-$\underline{C}H_2$Ph), 36.7 (-R$\underline{C}H(CH_2)_5$Ph), 58.7 (-$OCH_2\underline{C}$HRN-), 60.2 (-O$\underline{C}H_2CH_3$), 63.7 (-O$\underline{C}H_2$CHRN-), 80.0 (-O$\underline{C}(CH_3)_3$), 94.2 (-O$\underline{C}(CH_3)_2$N-), 125.6 (aromatic), 128.2 (aromatic), 128.3 (aromatic), 142.6 (aromatic), 152.5 (-$\underline{C}OOC(CH_3)_3$), 173.4 (-$\underline{C}O_2$Et); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 3025, 2931, 1716 (C=O), 1682 (C=O), 1367, 1201; MS (m/e) (rel intensity) 432 (M^+-15, 12), 389 (8), 346 (58), 332 (100), 316 (11), 302 (12), 289 (15), 244 (10), 200 (38), 156 (4), 144 (35), 100 (91); HRMS Calcd for $C_{26}H_{41}O_5N$-CH_3: 432.2750. Found 432.2765.

For compound **7d**: $[\alpha]_D$ = 24.0 (c 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H), 1.28-1.68 (m, 23H), 2.15-2.45 (m, 3H), 2.59 (t, J = 7.9 Hz, 2H), 3.73-4.02 (m, 3H), 4.11 (q, J = 7.1 Hz, 2H), 7.08-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1 (-$CO_2CH_2\underline{C}H_3$), 22.7, 24.2 (-OC($\underline{C}H_3)_2$N-), 25.8 (-OC($\underline{C}H_3)_2$N-), 26.7 (-$\underline{C}H_2CH_2CH_2$Ph), 28.3 (-OC($\underline{C}H_3)_3$), 29.4 (-$\underline{C}H_2(CH_2)_3$Ph), 30.1 (-$\underline{C}H_2CH_2$Ph), 31.3 (-$\underline{C}H_2(CH_2)_4$Ph), 35.8 (-$\underline{C}H_2CO_2$Et), 36.5 (-$\underline{C}H_2$Ph), 37.8 (-R$\underline{C}H(CH_2)_5$Ph), 59.8 (-$OCH_2\underline{C}$HRN-), 60.2 (-O$\underline{C}H_2CH_3$), 65.0 (-O$\underline{C}H_2$CHRN-), 79.9 (-O$\underline{C}(CH_3)_3$), 94.3 (-O$\underline{C}(CH_3)_2$N-), 125.5 (aromatic), 128.1 (aromatic), 128.3 (aromatic), 142.6 (aromatic), 152.4 (-$\underline{C}OOC(CH_3)_3$), 173.0 (-$\underline{C}O_2$Et); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 2975, 2931, 1718 (C=O), 1681 (C=O), 1366, 1245, 1213, 1165; MS (m/e) (rel intensity) 432 (M^+-15, 6), 389 (10), 346 (90), 332 (76), 302 (12), 289 (23), 244 (9), 200 (34), 156 (7), 144 (37), 100 (100); HRMS Calcd for $C_{26}H_{41}O_5N$-CH_3: 432.2750. Found 432.2760.

(5*S*)-Hydroxymethyl-(4*R*)-(5-phenylbutyl)pyrrolidin-2-one (8c′)

A mixture of compound **6c** (2.2 g, 5 mmol) in 60% of aqueous acetic acid was heated to reflux for 4 h. The reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography to give 0.9 g of γ-lactam (**8c'**) in 70% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.18-1.74 (m, 8H), 2.01-2.66 (m, 5H), 3.48-4.10 (m, 4H), 7.06-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 28.1 (C$H(CH_2)_2$Ph), 29.2, 29.3 (-C$H_2(CH_2)_3$Ph), 29.7 (-CH_2CH_2Ph), 31.3 (-RCHC$H_2(CH_2)_4$Ph), 35.8 (-CH_2Ph), 36.5 (-CH_2CO_2NH), 37.5 (RC$H(CH_2)_5$Ph), 58.5 (-CHRCH_2OH), 62.4 (-CHRCH_2CH), 125.7 (aromatic), 128.2 (aromatic), 128.3 (aromatic), 142.6 (aromatic), 179.1 (-CH_2CO_2NH).

(5*S*)-*N*-(*tert*-Butoxycarbonyl)-(4*R*)-(3′-phenylpropyl)-tetrahydropyran-2-one (8b)

Compounds **8b-8d** and **10b-10d** were prepared in a similar manner. The preparation of compound **8b** is typical. A mixture of compound **6b** in 60% of aqueous acetic acid was heated to 80 °C for 1 h. The reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography to give 1.069 g of δ-lactone (**8b**) in 65% yield as a colorless oil. $[\alpha]_D$ = -43.1 (c 5.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.24-1.96 (m, 14H), 2.20 (dd, *J* = 16.6 and 9.4 Hz, 1H), 2.59 (t, *J* = 7.2 Hz, 2H, -CH_2Ph), 2.66 (dd, *J* = 16.6 and 6.2 Hz, 1H), 3.58-3.79 (br, 1H), 4.09 (br dd, *J* = 11.6 and 5.0 Hz, 1H), 4.28 (dd, *J* = 11.6 and 4.3 Hz, 1H), 5.03 (d, *J* = 7.6 Hz, 1H), 7.08-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.7 (-CH_2CH_2Ph), 28.1 (-OC(C$H_3)_3$), 33.2 (-C$H_2(CH_2)_2$Ph), 33.7 (-CH_2CO_2Et), 35.4 (-CH_2Ph), 36.8 (-RC$H(CH_2)_5$Ph), 49.3 (-OCH_2CHRN-), 69.7 (-OCH_2CHRN), 79.6 (-OC(C$H_3)_3$), 125.7 (aromatic), 128.1 (aromatic), 141.5 (aromatic), 155.1 (-COOC$(CH_3)_3$), 171.4 (-CCO_2Et); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 3434, 2978, 2937, 1744 (C=O), 1709 (C=O), 1492, 1365, 1229, 1159; MS (m/e) (rel intensity) 277 (M^+-56, 20), 260 (4), 233 (3), 216 (8), 176 (6), 156 (10), 140 (4), 112 (4), 84 (100); HRMS Calcd for $C_{19}H_{27}O_4$N-CH_3: 277.1314. Found 277.1323.

(5*S*)-*N*-(*tert*-Butoxycarbonyl)-(4*R*)-(3′-phenylbutyl)tetrahydropyran-2-one (8c)

67% yield; colorless oil: $[\alpha]_D$ = -38.5 (c 4.68, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.16-1.95 (m, 16H), 2.04-2.40 (m, 2H), 2.49-2.80 (m, 3H), 3.48-3.75 (br, 1H), 4.05 (br dd, *J* = 11.4 and 4.8 Hz, 1H, -CH_2OCO), 4.23 (br dd, *J* = 11.4 and 4.1 Hz, 1H, -CH_2OCO), 5.44 (d, *J* = 7.8 Hz, 1H), 7.08-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.3 (-CH_2CH_2CH_2Ph), 27.9 (-OC(C$H_3)_3$), 30.8 (-CH_2CH_2Ph), 33.3 (-C$H_2(CH_2)_3$Ph), 33.5 (-CH_2CO_2Et), 35.2 (-CH_2Ph), 36.5 (-RC$H(CH_2)_4$Ph), 49.2 (-OCH_2CHRN-), 69.5 (-OCH_2CHRN), 79.2 (-OC(C$H_3)_3$), 125.3 (aromatic), 127.9 (aromatic), 141.8 (aromatic), 155.0 (-COOC$(CH_3)_3$), 171.3 (-CO_2Et); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 3435, 2977, 2934, 1735 (C=O), 1709 (C=O), 1490, 1313, 1227, 1162; MS (m/e) (rel intensity) 291 (M^+-56, 100), 274 (17), 247 (8), 230 (55), 216 (24), 188 (6), 170 (21), 128 (18), 91 (25); HRMS Calcd for $C_{20}H_{29}O_4$N-C_4H_8: 291.1471. Found 291.1463.

(5*S*)-*N*-(*tert*-Butoxycarbonyl)-(4*R*)-(5′-phenylpentyl)tetrahydropyran-2-one (8d)

68% yield; colorless oil: $[\alpha]_D$ = -41.3 (c 4.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.20-1.94 (m, 18H), 2.20 (dd, *J* = 16.6 and 9.4 Hz, 2H), 2.59 (t, *J* = 7.9 Hz, 2H, -CH_2Ph), 2.66 (dd, *J* = 16.6 and 7.5 Hz, 1H), 3.52-3.70 (br, 1H), 4.09 (br dd, *J* = 11.6, and 5.0 Hz, 1H, -CH_2OCO), 4.28 (dd, *J* = 11.6 and 4.3 Hz, 1H, -CH_2OCO), 4.22-4.36 (m, 1H), 5.03 (br d, *J* = 7.6 Hz, 1H), 7.11-7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.8 (-C$H_2(CH_2)_2$Ph), 28.2 (-OC(C$H_3)_3$), 28.9 (-C$H_2(CH_2)_3$Ph), 31.0 (-CH_2CH_2Ph), 33.7 (-RCHC$H_2(CH_2)_4$Ph), 33.8 (-CH_2CO_2Et), 35.6 (-CH_2Ph), 37.2 (-RC$H(CH_2)_5$Ph), 49.5 (-OCH_2CHRN-), 69.8 (-OCHCHRN), 79.8 (-OC(C$H_3)_3$), 125.5 (aromatic), 128.1 (aromatic), 128.2 (aromatic), 142.3 (aromatic), 155.1 (-COOC$(CH_3)_3$), 171.5 (-CO_2Et); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 3436, 2977, 2933, 1745 (C=O), 1709 (C=O), 1492, 1226, 1160; MS (m/e) (rel intensity) 305 (M^+-56, 5), 287 (2), 262 (3), 230 (3), 183 (1), 140 (4), 104 (3), 84 (100); HRMS Calcd for $C_{21}H_{31}O_4$N-C_4H_8: 305.1627. Found 305.1633.

(5*S*)-*N*-(*tert*-Butoxycarbonyl)-(4*S*)-(3′-phenylpropyl)tetrahydropyran-2-one (10b)

63% yield; colorless oil: $[\alpha]_D$ = -51.4 (c 2.92, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.10-1.84 (m, 13H), 1.94-2.35 (m, 2H), 2.48-2.68 (m, 3H), 3.79-4.17 (br, 1H), 4.32 (br dq, *J* = 11.8 and 2.3 Hz, 2H, -CH_2OCO), 5.20 (br d, *J* = 7.5 Hz, 1H), 7.08-7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.9 (-CH_2CH_2Ph), 28.2 (-OC(C$H_3)_3$), 30.9 (-C$H_2(CH_2)_2$Ph), 32.4 (-CH_2CO_2Et), 35.1 (-RC$H(CH_2)_3$Ph), 35.6 (-CH_2Ph), 45.6 (-OCH_2CHRN-), 73.2 (-OCH_2CHRN-), 79.8 (-OC(C$H_3)_3$), 125.7 (aromatic), 128.2 (aromatic), 141.7 (aromatic), 155.6 (-COOC$(CH_3)_3$), 169.7 (-CO_2Et); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 3435, 2978, 2935, 1710 (C=O), 1494, 1364, 1230, 1159; MS (m/e) (rel intensity) 277 (M^+-56, 5), 260 (2), 233 (3), 216 (5), 202 (6), 176 (2), 156 (8), 132 (2), 114 (1), 84 (100); HRMS Calcd for $C_{19}H_{27}O_4$N-C_4H_9: 277.1314. Found 277.1323.

(5*S*)-*N*-(*tert*-Butoxycarbonyl)-(4*S*)-(3′-phenylbutyl)tetrahydropyran-2-one (10c)

66% yield; colorless oil: $[\alpha]_D$ = -44.5 (c 3.36, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.08-1.68 (m, 15H), 1.92-2.38 (m, 2H), 2.48-2.67 (m, 3H), 3.80-4.19 (br, 1H), 4.30 (br dq, *J* = 11.8 and

2.4 Hz, 2H, -C$\underline{H}_2$OCO), 5.28-5.58 (br, 1H), 7.06-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.7 (-$\underline{C}H_2CH_2Ph$), 28.0 (-OC($\underline{C}H_3)_3$), 31.0 (-$\underline{C}H_2(CH_2)_2Ph$), 32.2 (-$\underline{C}H_2CO_2Et$), 34.9 (-R$\underline{C}H(CH_2)_4Ph$), 35.4 (-$\underline{C}H_2Ph$), 45.6 (-OCH$_2\underline{C}$HRN-), 73.0 (-O$\underline{C}H_2$CHRN-), 79.5 (-O$\underline{C}(CH_3)_3$), 125.4 (aromatic), 128.0 (aromatic), 142.0 (aromatic), 155.6 (-$\underline{C}OOC(CH_3)_3$), 169.8 (-$\underline{C}O_2Et$); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 3434, 2978, 2934, 1709 (C=O), 1492, 1364, 1230, 1159; MS (m/e) (rel intensity) 291 (M^+-56, 24), 273 (4), 247 (4), 230 (3), 216 (11), 188 (1), 170 (1), 158 (1), 114 (1), 84 (100); HRMS Calcd for $C_{20}H_{29}O_4N$-C_4H_8: 291.1471. Found 291.1468.

(5*S*)-*N*-(*tert*-Butoxycarbonyl)-(4*R*)-(5′-phenylpentyl)tetrahydropyran-2-one (10d)

61% yield; colorless oil: $[\alpha]_D$ = -59.2 (c 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.14-1.72 (m, 17H), 1.92-2.38 (m, 2H), 2.51-2.75 (m, 3H), 3.94-4.12 (br, 1H), 4.33 (br dq, J = 11.6 and 2.4 Hz, 2H, -C$\underline{H}_2$OCO), 5.13 (d, J = 7.5 Hz, 1H), 7.08-7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.0 (-$\underline{C}H_2CH_2Ph$), 28.2 (-OC($\underline{C}H_3)_3$), 28.9 (-CH_2), 31.0 (-$\underline{C}H_2(CH_2)_2Ph$), 31.2 (-$\underline{C}H_2(CH_2)_4$Ph, 32.5 (-$\underline{C}H_2CO_2Et$), 35.1 (R$\underline{C}H(CH_2)_5Ph$), 35.7 (-$\underline{C}H_2Ph$), 45.7 (-OCH$_2\underline{C}$HRN-), 73.2 (-O$\underline{C}H_2$CHRN-), 79.9 (-O$\underline{C}(CH_3)_3$), 125.5 (aromatic), 128.1 (aromatic), 128.2 (aromatic), 142.4 (aromatic), 155.6 (-$\underline{C}OOC(CH_3)_3$), 169.8 (-$\underline{C}O_2Et$); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 3436, 2977, 2933, 2858, 1710 (C=O), 1492, 1364, 1229, 1158; MS (m/e) (rel intensity) 305 (M^+-56, 100), 288 (10), 262 (28), 244 (9), 230 (33), 202 (6), 183 (11), 170 (13), 159 (19), 140 (15), 128 (18), 114 (22), 104 (60), 84 (49); HRMS Calcd for $C_{21}H_{31}O_4N$-CH_3: 305.1627. Found 305.1629.

(2*S*)-Amino-(3*R*)-(3′-phenylpropyl)pentanedioic acid (B_3)

Compounds $\mathbf{B_3}$-$\mathbf{B_5}$; $\mathbf{B_{(3)}}$-$\mathbf{B_{(5)}}$ were prepared in a similar manner. The preparation of compound $\mathbf{B_3}$ is typical. To a solution of compound **8b** (92 mg, 0.28 mmol) and pyridine (0.19 mL, 2.38 mmol) was added 20% aqueous of KOH (0.8 mL) and $KMnO_4$ (67 mg, 0.42 mmol) sequentially at 0 °C. The reaction mixture was stirred at 0 °C for 4 h and 25 °C for 8 h and was filtered through Celite to remove the manganese salt. The filtrate was acidified by 1N HCl. To the acidic filtrate was added 2 g of sodium chloride and extracted with ethyl acetate (10 mL × 3). The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*. The oil residue was quickly purified by a short column chromatography to remove the inorganic salt. The semi-purified product ($\mathbf{B_3}$) was treated with 25% trifluoroacetic acid in dichloromethane (1.8 mL) at 0 °C for 4 h. The reaction mixture was concentrated *in vacuo* and purified by an an acidic ionic-exchange resin and the detailed procedure is described as follows. The Dowex®-50W ion-exchange resin was washed with 0.1N NaOH aqueous solution and then 0.1 N HCl aqueous solution. This procedure was repeated three times followed by washing with deionized water. The crude product was loaded on the column and eluted with 3.2% of ammonium water (v/v). The fractions with positive ninhydrin test were combined and the ammonium water was removed by freeze dryer. The purified product was repurified by HPLC (RP-18, LiChrosorb, 1 × 25 cm, Merck-Shuchardt). The following condition was applied: Gradient Mobile phase: linear, 0-80% acetonitrile in 0.1% trifluoroacetic acid in 40 Min; Flow rate: 2.0 mL/min; Dectector: UV, 260 nm; Retention time of compound $\mathbf{B_3}$: 19.5 min. The overall yield of compounds $\mathbf{B_3}$ (31 mg) from compound **8b** is 42%. White solid, mp 137-138 °C; $[\alpha]_D$ = 3.1 (c 2.25, 0.2N NH_4HCO_3 in H_2O); ^{1}H NMR (0.2M NH_4HCO_3 in D_2O) δ 1.35-1.47 (m, 2H), 1.57-1.75 (m, 2H), 2.34-2.50 (m, 3H), 2.55-2.70 (m, 2H), 3.76 (s, 1H), 7.23-7.37 (m, 5H); ^{13}C NMR (0.2M NH_4HCO_3 in D_2O) δ 28.5 (-$\underline{C}H_2CH_2Ph$), 28.6 (-$\underline{C}H_2(CH_2)_2Ph$), 34.9 (-$\underline{C}H_2CO_2H$), 36.5 (R$\underline{C}H(CH_2)_3Ph$), 39.8 (-$\underline{C}H_2Ph$), 58.6 (-$\underline{C}H(NH_2)CO_2H$-), 126.0 (aromatic), 128.9 (aromatic), 142.9 (aromatic), 174.2 (-$CH_2\underline{C}OOH$), 180.9 (-CH(NH_2)$\underline{C}O_2H$); IR (KBr): ν_{max} (cm^{-1}) 3431, 3223, 2919, 2852, 1711 (C=O), 1589, 1501, 1420, 1327, 1210; MS (m/e) (rel intensity) 265 (M^+, 8), 228 (63), 213 (16), 167 (12), 149 (40), 135 (28), 117 (44), 99 (60), 84 (100); HRMS Calcd for $C_{14}H_{19}O_4N$: 265.1314. Found 265.1301.

(2*S*)-Amino-(3R)-(3′-phenylbutyl)pentanedioic acid (B_4)

38% yield; retention time, 28.5 min; White solid, mp 136-138 °C; $[\alpha]_D$ = 3.2 (c 4.12, 0.2N NH_4HCO_3 in H_2O); ^{1}H NMR (0.2M NH_4HCO_3 in D_2O) δ 1.30-1.48 (m, 4H), 1.54-1.70 (m, 2H), 2.35-2.43 (m, 3H), 2.63 (t, J = 7.5 Hz, 2H), 3.75 (s, 1H), 7.20-7.40 (m, 5H); ^{13}C NMR (0.2M NH_4HCO_3 in D_2O) δ 26.1 (-$\underline{C}H_2CH_2Ph$), 28.4 (-$\underline{C}H_2(CH_2)_2Ph$), 30.6 (-$\underline{C}H_2(CH_2)_3Ph$), 34.8 (-$\underline{C}H_2COOH$), 36.6 (R$\underline{C}H(CH_2)_4Ph$), 39.8 (-$\underline{C}H_2Ph$), 58.7 (-$\underline{C}H(NH_2)CO_2H$-), 125.9 (aromatic), 128.7 (aromatic), 143.4 (aromatic), 174.4 (-$CH_2\underline{C}OOH$), 181.0 (-CH(NH_2)$\underline{C}O_2H$); IR (KBr): ν_{max} (cm^{-1}) 3434, 3159, 2928, 2854, 1710 (C=O), 1585, 1500, 1431, 1209, 1141; MS (m/e) (rel intensity) 279 (M^+, 10), 265 (30), 247 (6), 228 (22), 213 (5), 167 (33), 149 (100), 129 (17), 111 (18), 99 (41), 84 (56).

(2*S*)-Amino-(3*R*)-(5′-phenylpentyl)pentanedioic acid (B_5)

47% yield; retention time 28.0 min; White solid, mp 126-128 °C; $[\alpha]_D$ = 3.5 (c 2.14, 0.2N NH_4HCO_3 in H_2O); ^{1}H NMR (0.2M NH_4HCO_3 in D_2O) δ 1.25-1.47 (m, 6H), 1.47-1.69 (m, 2H), 2.31-2.43 (m, 3H), 2.63 (t, J = 7.2 Hz, 2H), 3.73 (s, 1H), 7.22-7.38 (m, 5H); ^{13}C NMR (0.2M NH_4HCO_3 in D_2O) δ 26.3 (-$\underline{C}H_2CH_2Ph$), 28.2 (-$\underline{C}H_2(CH_2)_3Ph$), 28.6 (-$\underline{C}H_2(CH_2)_2Ph$), 30.5 (-$\underline{C}H_2(CH_2)_4Ph$), 34.9 (-$\underline{C}H_2CO_2H$), 36.6 (R$\underline{C}H(CH_2)_5Ph$), 39.9 (-$\underline{C}H_2Ph$), 58.7 (-$\underline{C}H(NH_2)CO_2H$-), 125.8 (aromatic), 128.7 (aromatic), 143.6 (aromatic), 174.5 (-$CH_2\underline{C}OOH$), 181.0 (-CH(NH_2)$\underline{C}O_2H$); IR (KBr): ν_{max} (cm^{-1}) 3582, 3448, 2933, 2855, 1698 (C=O), 1582, 1494, 1207;

MS (m/e) (rel intensity) 293 (M^+, 1), 275 (68), 257 (3), 230 (49), 202 (3), 184 (30), 171 (14), 167 (6), 149 (11), 128 (100), 97 (11); HRMS Calcd for $C_{16}H_{23}O_4N$: 293.1627. Found 293.1621.

(2*S*)-Amino-(3*S*)-(3′-phenylpropyl)pentanedioic acid ($B_{(3)}$)

45% yield; white solid, mp 132-133 °C; $[\alpha]_D$ = -5.8 (c 5.0, 0.2N NH_4HCO_3 in H_2O); ^1H NMR (0.2M NH_4HCO_3 in D_2O) δ 1.41-1.62 (m, 2H), 1.62-1.81 (m, 2H), 2.30-2.50 (m, 3H), 2.60-2.75 (m, 2H), 3.77 (s, 1H), 7.25-7.38 (m, 5H); ^{13}C NMR (0.2M NH_4HCO_3 in D_2O) δ 28.5 (-$\underline{C}H_2CH_2Ph$), 29.4 (-$\underline{C}H_2(CH_2)_2Ph$), 34.9 (-$\underline{C}H_2CO_2H$), 36.1 (R$\underline{C}H(CH_2)_3Ph$), 38.1 (-$\underline{C}H_2Ph$), 57.6 (-$\underline{C}H(NH_2)CO_2H$-), 128.0 (aromatic), 128.7 (aromatic), 142.8 (aromatic), 174.5 (-$CH_2\underline{C}OOH$), 180.6 (-$CH(NH_2)\underline{C}O_2H$); IR (KBr): ν_{max} (cm^{-1}) 3477, 3142, 3083, 2926, 2862, 1712 (C=O), 1614, 1505, 1326, 1199; MS (m/e) (rel intensity) 265 (M^+, 8), 240 (3), 228 (16), 221 (17), 202 (70), 185 (44), 167 (13), 149 (31), 128 (24), 115 (10), 97 (32), 84 (99), 69 (100); HRMS Calcd for $C_{14}H_{19}O_4N$: 265.1314. Found 265.1316.

(2*S*)-Amino-(3*S*)-(3′-phenylbutyl)pentanedioic acid ($B_{(4)}$)

43% yield, white solid, mp 139-142 °C; $[\alpha]_D$ = -4.4 (c 1.85, 0.2N NH_4HCO_3 in H_2O); ^1H NMR (0.2M NH_4HCO_3 in D_2O) δ 1.33-1.70 (m, 6H), 2.21-2.45 (m, 3H), 2.67 (t, J = 7.5 Hz, 2H), 3.75 (s, 1H), 7.22-7.40 (m, 5H); ^{13}C NMR (0.2M NH_4HCO_3 in D_2O) δ 26.0 (-$\underline{C}H_2CH_2Ph$), 29.5 (-$\underline{C}H_2(CH_2)_2Ph$), 30.6 (-$\underline{C}H_2(CH_2)_3Ph$), 34.8 (-$\underline{C}H_2CO_2H$), 36.1 (R$\underline{C}H(CH_2)_4Ph$), 38.1 (-$\underline{C}H_2Ph$), 57.4 (-$\underline{C}H(NH_2)CO_2H$-), 125.9 (aromatic), 128.6 (aromatic), 143.3 (aromatic), 174.7 (-$CH_2\underline{C}OOH$), 180.7 (-$CH(NH_2)\underline{C}O_2H$); IR (KBr): ν_{max} (cm^{-1}) 3428, 3098, 2940, 2856, 1711 (C=O), 1694 (C=O), 1614, 1558, 1266, 1205, 1139; MS (m/e) (rel intensity) 279 (M^+, 10), 265 (30), 247 (6), 228 (35), 213 (10), 197 (6), 167 (34), 149 (100), 129 (24), 112 (22), 99 (38), 84 (61), 71 (28).

(2*S*)-Amino-(3*R*)-(5′-phenylpentyl)pentanedioic acid ($B_{(5)}$)

41% yield; white solid, mp 130-132 °C; $[\alpha]_D$ = -9.0 (c 4.91, 0.2N NH_4HCO_3 in H_2O); ^1H NMR (0.2M NH_4HCO_3 in D_2O) δ 1.25-1.47 (m, 6H), 1.47-1.69 (m, 2H), 2.31-2.43 (m, 3H), 2.63 (t, J = 7.4 Hz, 2H), 3.73 (s, 1H), 7.22-7.38 (m, 5H); ^{13}C NMR (0.2M NH_4HCO_3 in D_2O) δ 26.2 (-$\underline{C}H_2CH_2Ph$), 28.2 (-$\underline{C}H_2(CH_2)_3Ph$), 29.6 (-$\underline{C}H_2(CH_2)_2Ph$), 30.6 (-$\underline{C}H_2(CH_2)_4Ph$), 34.9 (-$\underline{C}H_2CO_2H$), 36.1 (R$\underline{C}H(CH_2)_5Ph$), 38.1 (-$\underline{C}H_2Ph$), 57.5 (-$\underline{C}H(NH_2)CO_2H$-), 125.8 (aromatic), 128.7 (aromatic), 143.6 (aromatic), 174.6 (-$CH_2\underline{C}OOH$), 180.7 (-$CH(NH_2)\underline{C}O_2H$); IR (KBr): ν_{max} (cm^{-1}) 3442, 2929, 2855, 1704 (C=O), 1618, 1508, 1405, 1199; MS (m/e) (rel intensity) 275 (M^+-18, 71), 257 (4), 230 (55), 184 (23), 171 (8), 145 (12), 128 (100), 91 (25); HRMS Calcd for $C_{16}H_{23}O_4N$-H_2O: 275.1521. Found 275.1526.

(4*S*)-(1′(*E*)-Ethoxycarbonylvinyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (12)

A mixture of 4(*S*)-formyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (**1**) (1.84 g, 8 mmol) and ethyl (triphenylphosphoranylidene)acetate (2.79 g, 8 mmol) in 40 mL of THF was stirred at 25 °C. After being stirred at 25 °C for 12 h, the mixture was concentrated *in vacuo*. Chromatography on silica gel afforded 1.73 g (72%) of α,β-unsaturated ester (**12**) as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.29 (t, J = 7.1 Hz, 3H), 1.36-1.75 (m, 15H), 3.70-3.88 (m, 1H), 4.04-4.30 (m, 3H), 4.35-4.66 (m, 1H), 5.92 (dd, J = 15.4 and 10.9 Hz, 1H), 6.83 (dd, J = 14.9 and 6.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1 (-$CO_2CH_2\underline{C}H_3$), 23.4, 24.4 (-$OC(\underline{C}H_3)_2N$-), 26.3, 27.1 (-$OC(\underline{C}H_3)_2N$-), 28.2 (-$OC(\underline{C}H_3)_3$), 57.9 (-$OCH_2\underline{C}HRN$-), 60.3 (-$O\underline{C}H_2CH_3$), 67.1 (-$O\underline{C}H_2CHRN$-), 80.0, 80.5 (-$O\underline{C}(CH_3)_3$), 93.9, 94.3 (-$O\underline{C}(CH_3)_2N$-), 122.2 (-$\underline{C}H$=$CHCO_2$), 145.8 (-CH=$\underline{C}HCO_2$-), 151.4 (-$\underline{C}O_2C(CH_3)_3$), 166.0 (-$\underline{C}O_2Et$); IR ($CH_2Cl_2$): ν_{max} (cm^{-1}) 2981, 1752 (C=O), 1685, 1453, 1365, 1279, 1238, 1204, 1165; MS (m/e) (rel intensity) 284 (M^+-15, 12), 244 (13), 228 (12), 184 (100), 144 (59), 100 (17); HRMS Calcd for $C_{15}H_{25}O_5N$-CH_3: 284.1498. Found 284.1489.

(4*S*,1′*RS*)-(1′-Ethoxycarbonylmethyl-but-3′-enyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (13)

To a magnetically stirred mixture of CuBr·Me_2S (1.66 g, 8 mmol), LiBr (1.40 g, 16 mmol) and THF (48 mL) under nitrogen was added allyl magnesium bromide (16 mmol, 16 mL of a 1M solution in THF) dropwise at -78 °C. After 0.5 h, a solution of chlorotrimethylsilane (1.14 mL, 80 mmol) in THF (16 mL) was added, followed by a solution of compound **12** (0.8 g, 2.7 mmol) in THF (24 mL). The dark-colored mixture was stirred at -78 °C for 3 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (25 mL) and extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The oil residue was purified by column chromatography on silica gel to yield compound **13** (0.35 g, 38%) as a mixture of two inseparable diastereomers as well as 0.36 g (*i.e.* 45%) of the recovered starting material **12**. ^1H NMR ($CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 3H), 1.38-2.82 (m, 20H), 3.70-4.00 (m, 3H), 4.11 (q, J = 7.1 Hz, 2H), 4.88-5.15 (m, 2H), 5.56-5.92 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2 (-$CO_2CH_2\underline{C}H_3$), 22.4, 23.9 (-$OC(\underline{C}H_3)_2N$-), 26.2 (-$OC(\underline{C}H_3)_2N$-), 28.3 (-$OC(\underline{C}H_3)_3$), 34.1 (-$\underline{C}H_2CO_2Et$), 36.5 (-R$\underline{C}HCH_2CH$=CH_2), 58.4 (-$\underline{C}H_2CH$=CH_2), 59.3 (-$OCH_2\underline{C}HRN$-), 60.2 (-$O\underline{C}H_2CH_3$), 63.6 (-$O\underline{C}H_2CHRN$-), 80.1 (-$O\underline{C}(CH_3)_3$), 94.2 (-$O\underline{C}(CH_3)_2N$-), 152.9 (-$\underline{C}OOC(CH_3)_3$), 173.1 (-$\underline{C}O_2Et$); IR (CH_2Cl_2): ν_{max} (cm^{-1}) 2980, 1720 (C=O), 1686, 1366, 1172; MS (m/e) (rel intensity) 326 (M^+-15, 5), 264 (2), 244 (23), 226 (38), 185 (20), 160 (31), 144 (100), 128 (11), 100 (50); HRMS Calcd for $C_{18}H_{31}O_5N$-CH_3:

326.1967. Found 326.1954.

(4*S*,1′*RS*)-(1′-Ethoxycarbonylmethyl-3′-oxo-propyl)-2,2-dimethyl-oxazolidine-3-carboxylic acid *tert*-butyl ester (14)

In a 25 mL two-neck flask, equipped with a magnetic stirrer, a drying tube and a gas dispersion tube (with porous fritted tip), were placed 10 mL of dichloromethane and compound **13** (0.32 g, 0.93 mmol). A stream of ozone was bubbled through the solution at -78 °C. Ozone treatment was terminated when the solution assumed a blue color. Excess ozone was removed by a stream of nitrogen. The resulting solution was quenched by the addition of triethylamine (0.19 mL, 1.4 mmol) at -78 °C and then allowed to warm to room temperature over a period of 2 h. The reaction mixture was concentrated *in vacuo* and purified by silica gel column chromatography to give 0.205 g of the corresponding aldehyde (**14**) in 64% yield as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 1.40-1.68 (m, 23H), 2.15-3.08 (m, 5H), 3.76-4.05 (m, 3H), 4.12 (q, J = 7.1 Hz, 2H), 9.74 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9 (-$CO_2CH_2\underline{C}H_3$), 22.3, 23.6 (-OC($\underline{C}H_3)_2$N-), 26.4 (-OC($\underline{C}H_3)_2$N-), 28.1 (-OC($\underline{C}H_3)_3$), 32.2, 32.6, 34.0, 35.1, 45.4, 51.1, 58.9 (-$OCH_2\underline{C}$HRN-), 60.4 (-$O\underline{C}H_2CH_3$), 64.5 (-$O\underline{C}H_2$CHRN-), 80.3 (-O$\underline{C}(CH_3)_3$), 94.2 (-O$\underline{C}(CH_3)_2$N-), 152.2 (-COOC$(CH_3)_3$), 172.1 (-$\underline{C}O_2$Et), 200.8 (-CHO); MS (m/e) (rel intensity) 328 (M^+-15, 6), 299 (17), 242 (11), 228 (100), 212 (22), 199 (26), 182 (8), 140 (33), 100 (71); HRMS Calcd for $C_{17}H_{29}O_6$N-CH_3): 328.1760. Found 328.1753.

Indirect way to determine the stereochemistry of the Claisen rearrangement products

To a suspension of benzyl triphenylphosphonium bromide (0.404 g, 0.93 mmol) in THF (10 mL) was added *n*-BuLi (0.58 mmol, 0.37 mL of 1.6 M in hexane) at 0 °C. To the resulting brick red solution of the phosphorane was added aldehyde (**14**) (86 mg, 0.25 mmol) in THF (5 mL) at -78 °C. The reaction mixture was stirred at this temperature for 2 h and then was allowed to warm to room temperature over a period of 5 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (25 mL) and extracted with ethyl acetate (3 × 30 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The oil residue was purified by column chromatography on silica gel to give 70 mg of the Wittig product in 72% yield. This crude products and 10% Pd/C (13 mg, 1.19 mmol) was dissolved in 5 mL of ethyl acetate and the reduction was carried out by a balloon filled with hydrogen. After being stirred at 25 °C for 24 h the mixture was filtered through Celite. The filtrate was concentrated and separated by medium pressure liquid chromatography to give 47 mg of compounds **6b** (66%) and 16 mg of compound **7b** (21%) as colorless oils.

ACKNOWLEDGMENT

We are grateful to the National Science Council, Republic of China for financial support.

Received September 16, 1999.

Key Words

3-Substituted-L-glutamic acids; Neuroexcitatory activity; Claisen rearrangement; D-Serine.

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