resin. The eluents were lyophilized to give the pure peptide **21** (14.5 mg): high-resolution FABMS m/e calcd MH^+ 475.3284 found 475.3280.

PheΨ[CH_2N]ProOBz (24). Trifluoroacetic acid (6.0 mL) was added to an ice-cold solution of *N*-*t*-BOC-PheΨ[CH_2N]ProOBz (100 mg, 0.228 mmol) in dry CH_2Cl_2 (6.0 mL). After the addition was complete, the ice bath was removed and the mixture was stirred at room temperature for 30 min. The volatiles were removed on a rotary evaporator, and the product was washed with hexane (2 × 10 mL). The solid product was dried under reduced pressure to afford the peptide **24** (86.2 mg), which was 95% pure as determined by analytical HPLC: mp 139–140 °C; ^1H NMR (500 MHz, CD_3OD) δ 1.72–1.81 (1 H, m), 1.82–1.96 (2 H, m), 2.11–2.17 (1 H, m), 2.57 (2 H, d, J = 5.0 Hz), 2.73 (1 H, m), 2.75 (1 H, dd, J = 13.5, 8.9 Hz), 2.92 (1 H, m), 2.94 (1 H, dd, J = 13.3, 5.3 Hz), 3.22 (1 H, dd, J = 9.6, 8.5 Hz), 3.73 (1 H, ddd, J = 11.1, 9.0, 5.5 Hz), 4.8 (1 H, d, J = 12.0 Hz), 4.9 (1 H, d, J = 12.0 Hz), 7.22–7.25 (5 H, m), 7.30–7.33 (5 H, m); high-resolution FABMS m/e calcd MH^+ 399.2072, found 399.2035.

PheΨ[CH_2N]ProOH (25). Trifluoroacetic acid (3.1 mL) was added to an ice-cold solution of *N*-*t*-BOCPheΨ[CH_2N]ProOH (40.0 mg, 0.115 mmol) in dry CH_2Cl_2 (3.1 mL). After the addition was complete, the ice bath was removed and the mixture was stirred at room temperature for 30 min. The volatiles were removed on a rotary evaporator, and the product was dissolved in water (5 mL). The aqueous solution was washed with ether (4 × 10 mL) and lyophilized. The crude dipeptide **25** was purified on a Dynamax 300 A, C-18, 12 μm, 10 × 350 mm column. A gradient of 0% CH_3CN–0.1% TFA to 18% CH_3CN–0.1% TFA in 30 min was used at a flow rate of 3 mL/min. The desired fractions were lyophilized, dissolved in water, and filtered through Amberlite IRA-400 (OAc) ion exchange resin. The eluents were lyophilized to give the pure peptide **25** (12.5 mg, 0.05 mmol): mp 189–191 °C; ^1H NMR (500 MHz, CD_3OD) δ 1.70–1.82 (2 H, m), 1.89–1.96 (1 H, m), 2.16–2.24 (1 H, m), 2.53–2.58 (1 H, m), 2.63–2.67 (1 H, dd, J = 13.4, 4.1 Hz), 2.77–2.82 (1 H, dd, J = 13.3, 11.0 Hz), 2.84–2.90 (1 H, m), 2.90 (2 H, dd, J = 9.8, 5.7 Hz), 3.19–3.15 (1 H, ddd, J = 8.7, 6.4, 2.7 Hz), 3.25–3.35 (1 H, m), 7.23–7.35 (5 H m); high-resolution FABMS m/e calcd MH^+ 249.1603 found 249.1599.

Purification of CysThrLeuAsnPheΨ[CH_2N]ProIleSerProIle (3). The crude peptide (5 mg) was purified on a Dynamax 300A, C-18, 12 μm, 10 × 350 mm column. A gradient of 9% CH_3CN–0.1% TFA to 36% CH_3CN–0.1% TFA in 30 min was used at a flow rate of 3 mL/min. The desired fraction was lyophilized, dissolved in water, and filtered through Amberlite IRA-400 (OAc^-) ion exchange resin. The eluents were lyophilized to give the pure peptide **3** (0.25 mg): low-resolution FABMS m/e 1090 (MH^+).

Purification of CysThrLeuAsnPheΨ[CH_2N]ProIleSerProIle (3) and CysThrLeuAsn-D-PheΨ[CH_2N]ProIleSerProIle. The crude peptide (15 mg, from reductive alkylation method) was purified on a Dynamax 300A, C-18, 12 μm, 10 × 350 mm column. Isocratic elution with 24% CH_3CN–0.1% TFA was used at a flow rate of 3 mL/min. The desired fractions were lyophilized, dissolved in water, and filtered through Amberlite IRA-400 (OAc^-) ion exchange resin. The eluents were lyophilized to give the pure L-peptide (5.2 mg) and its D-Phe diastereomer (4.4 mg): low-resolution FABMS calcd MH^+ m/e 1090.58, found 1090.55 for both diastereomers.

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Registry No. 1, 133569-07-0; D-Phe-1, 133773-53-2; **2**, 133673-09-3; **3**, 133673-10-6; D-Phe-**3**, 133773-54-3; **4**, 72155-45-4; **7**, 13734-34-4; **8**, 87694-53-9; **11a**, 2133-40-6; **11b**, 16652-71-4; **12a**, 38017-89-9; **12b**, 70462-58-7; **12c**, 126251-09-0; **13a**, 118447-06-6; **13b**, 128234-82-2; **13c**, 118447-07-7; **14a**, 124869-91-6; **14b**, 133773-52-1; **16**, 133673-14-0; **17**, 133673-15-1; **20**, 133673-17-3; **21**, 133673-18-4; **24**, 133673-21-9; **25**, 133673-22-0; protease, 9001-92-7.

Supplementary Material Available: HPLC analyses of the purified peptides (11 pages). Ordering information is given on any current masthead page.

Synthesis of Four Diastereomeric L-2-(Carboxycyclopropyl)glycines. Conformationally Constrained L-Glutamate Analogues

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To determine what conformations of L-glutamate (L-Glu) activate that compound's different receptors in the mammalian central nervous system, four diastereomeric L-2-(carboxycyclopropyl)glycines, **1–4**, which are conformationally constrained analogues of the extended and folded conformers of L-Glu, were synthesized and subjected to neutrophysiological assay. Compounds **1–4** were efficiently synthesized from chiral amino acids. Cyclopropanation of the (2*S*)-2-amino-3-butenol derivative **5b** gave intermediates for the synthesis of all four diastereomers. Stereoselective cyclopropanation of both the α,β-unsaturated γ-lactam **16** and the δ-lactone **19** gave precursors of (2*S*,1′*S*,2′*R*)-**3** and (2*S*,1′*R*,2′*S*)-**4**, respectively. Neurophysiological assays of **1–4** performed with the newborn rat spinal cord demonstrated that the compounds induced a variety of depolarizing effects. The results of the assays strongly suggested that the *N*-methyl-D-aspartic acid (NMDA) receptor is activated by the folded conformer of L-Glu and that the extended conformer of L-Glu activates the metabotropic L-Glu receptor. The four analogous D-2-(carboxycyclopropyl)glycines (D-**1**–D-**4**), which were synthesized from (2*R*)-**5b**, proved to be NMDA agonists.

Introduction

The neurobiological effects that L-glutamate (L-Glu) induces in the mammalian central nervous system (CNS) are well-documented. L-Glu acts chiefly as an excitatory neurotransmitter, and its excitotoxic effect is closely related to ischemic neuron damage.[1] Also, L-Glu is believed to play a role in the construction of memory and in early

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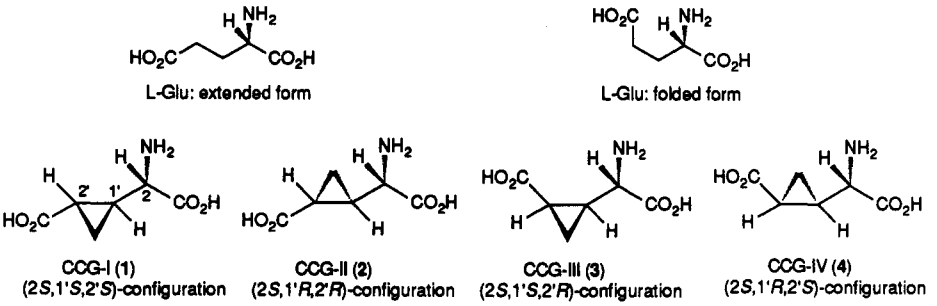
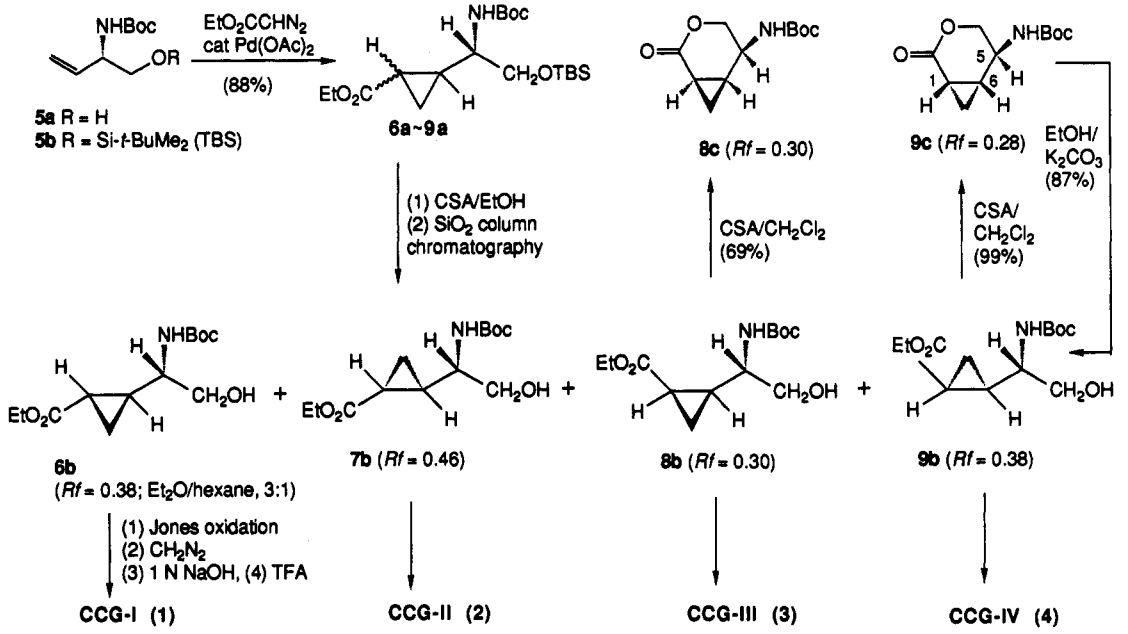


Figure 1.

Scheme I



learning.[2] At the present time, the excitatory amino acid receptors are believed to be of at least three types, those which have a particular affinity for *N*-methyl-D-aspartic acid (NMDA), kainic acid (KA), or quisqualic acid (QA), respectively. These receptors are associated with ion channels.[3,4] In addition to these ionotropic receptors, recent studies have demonstrated the existence of a metabotropic L-Glu receptor which is associated with phosphatidyl inositol metabolism.[5,6]

It remains uncertain why acyclic neurotransmitters can activate the different receptors that are associated with a variety of physiological functions. Structure–activity studies have revealed that the alteration of any of the functional groups of L-Glu results in a significant decrease in, or even the complete loss of, L-Glu's excitatory capability. Thus, we have been much interested in what conformations of L-Glu molecule activate L-Glu's receptors.[7]

We synthesized four stereoisomeric L-2-(carboxycyclopropyl)glycines (CCG-I–IV; 1–4), conformationally restricted L-Glu analogues in which the presence of a cyclopropyl group fixes the glutamate chain in either an extended or a folded form (Figure 1). Moreover, the effects induced by each set of CCGs (1 and 2, and 3 and 4) may provide information about the steric requirements of the receptors, because each CCG possesses a different configuration of the cyclopropane ring. The isomers 1 and 3 have been isolated by Fowden[8] from the immature fruits of *Aesculus parviflora* and *Blighia sapida*. These fruits are known to induce the symptoms of hypoglycemia in animals.[8] Thus, described herein are efficient syntheses of the diastereomers 1–4 and stereoselective synthesis of the folded isomers 3 and 4.[9] The marked and selective

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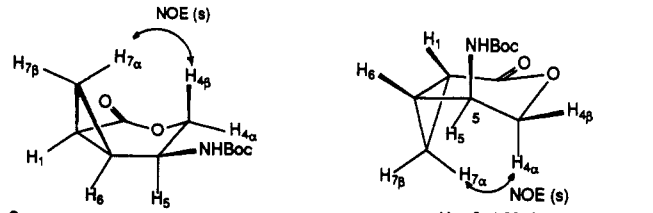
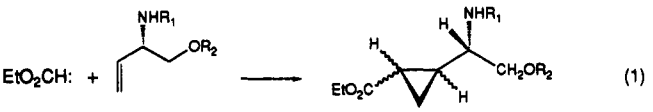


Figure 2. Observed NOEs (NOESY) of the compounds 8c and 9c were as follows. The strength of the NOE in parentheses is designated strong (s), medium (m), or weak (w). 8c: $H_{4\alpha}$–$H_{4\beta}$ (s); $H_{4\beta}$–NH (m); $H_{4\alpha}$–$H_{7\alpha}$ (s); H_1–H_6 (w); H_1–$H_{7\beta}$ (w); H_6–$H_{7\beta}$ (w); $H_{7\alpha}$–$H_{7\beta}$ (s). 9c: $H_{4\alpha}$–$H_{4\beta}$ (s); $H_{4\alpha}$–$H_{7\alpha}$ (s); H_1–$H_{7\beta}$ (m); H_6–$H_{7\beta}$ (m); $H_{7\alpha}$–$H_{7\beta}$ (w).

depolarizing effects that the isomers induce in the glutamate receptors in the rat spinal cord suggested that the L-Glu receptors can differentiate the extended and folded conformations of L-Glu.[10]

Results and Discussion

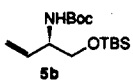
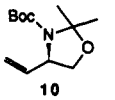
Synthesis of CCG-I–IV (1–4). The intermolecular cycloaddition of ethyl diazoacetate to the carbon–carbon double bond of a derivative of a chiral 2-amino-3-butenol represented an efficient method for preparing intermediates which could be used for the synthesis of all diastereomers, because the reaction was expected to proceed nonstereoselectively (eq 1).



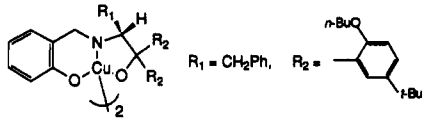
(1)

(2*S*)-2-((*tert*-Butoxycarbonyl)amino)-1-((*tert*-butyldimethylsilyl)oxy)but-3-ene (**5b**), a chiral amino alcohol derivative prepared from L-methionine,[11] was allowed to react in diethyl ether (Et_2O) with ethyl diazoacetate in the presence of a catalytic amount of $Pd(OAc)_2$.[12] The reaction was performed by simultaneously adding Et_2O solutions of ethyl diazoacetate and the catalyst drop by drop to the olefin at room temperature. A mixture of cycloadducts **6a–9a** was produced in 88% yield (Scheme I). The cycloadducts were chromatographically inseparable. However, desilylation of the cycloadducts gave products that were separable. Analysis by TLC (Merck silica gel coated glass plates; Et_2O/hexane, 3:1) showed the mixture of desilylated products to consist of at least three components, R_f = 0.30, 0.38, and 0.46, respectively.[13] Upon silica gel column chromatography of the mixture, it was found that the components of R_f = 0.30 and 0.46 each corresponded to a single diastereomer. The component of R_f = 0.38 proved to be a mixture of two diastereomers (as determined by ^{1}H NMR). Treatment of the latter mixture in CH_2Cl_2 with a catalytic amount of *dl*-camphorsulfonic acid (CSA) gave two products, which could be separated by TLC (Et_2O/hexane, 3:1), one of R_f = 0.38 and the other of R_f = 0.28. The result of the acid treatment suggested that the less polar compound was an extended isomer (**6b** or **7b**) and that the molar polar compound was a δ-lactone (**8c** or **9c**) derived from a folded isomer (**8b** or **9b**). The structure of the more polar compound was established by ^{1}H NMR. The results of NOE experiments showed it to be the δ-lactone **9c**, which possessed 1*S*,5*S*,6*R* stereochemistry (Figure 2). Compound **9c** was reconverted to **9b** by ethanolysis ($EtOH/K_2CO_3$). Thus, all four diastereomers **6b–9b** could be prepared and isolated using chromatographic and chemical methods. The folded isomer **8b** was identified by treating the compounds of R_f = 0.30 and 0.46 individually with CSA/CH_2Cl_2. The more polar isomer was dehydrated to the δ-lactone **8c** under the reaction conditions. The structure of **8c** was unambiguously established by ^{1}H NOE experiments and is depicted in Figure 2. The less polar isomer remained unchanged upon treatment with CSA, indicating that it was an extended isomer (**6b** or **7b**). Finally, the structures of **6b** and **7b** were established by converting them to **1** and **2**, respectively (vide infra).

Table I. Cyclopropanation of the 2-Amino-3-butenol Derivatives[a]

substrate	catalyst	yield (%)	product ratio 6b:7b:8b:9b
 5b	$Pd(OAc)_2$	88	1.2:3.5:1.0:1.0
	(R)-7644[a]	23	5:5:1:1
 10	$Pd(OAc)_2$	14[b]	3.3:1.8:2.2:1.0
	(R)-7644	7[c]	5:5:1:1

[a] Structure of (R)-7644.



[b] 85% of **10** was recovered. [c] 80% of **10** was recovered.

The conversion of **6b–9b** to CCG-I–IV (1–4) was effected in four steps: (1) Jones oxidation of the primary alcohol, (2) CH_2N_2 esterification of the resulting carboxyl group, (3) hydrolysis of the ester groups with 1 *N* NaOH, and (4) removal of the Boc group by treatment with trifluoroacetic acid (TFA). The aqueous solution of the resulting TFA salt was then passed through a column filled with Dowex 50Wx4 ion-exchange resin (elution with 1 *N* aqueous NH_3). The pH of the eluate containing the ammonium salt of the acid was adjusted to 3 with 1 *N* aqueous HCl to precipitate the free acid as colorless crystals.

The structures of the synthetic CCGs were established by comparing their physical properties, especially spectra, with those of authentic natural CCG-I (**1**) and -III (**3**). Because synthetic **1** was identical in all respects with natural **1**, the structure of **2** derived from **7b** was unambiguously shown to be as depicted. Also, the spectra and other physical properties of synthetic **3** were identical with those of natural **3**. Cycloaddition gave a 1.2:3.5:1:1 mixture of **6b**, **7b**, **8b**, and **9b** (determined by HPLC).[14] Because the conformation that olefin **5b** assumed in the transition state of cyclization was flexible and the olefin's mode of coordination with palladium was not known, why (2*S*,1′*R*,2′*R*)-**7a** was the major product cannot be explained at this point.

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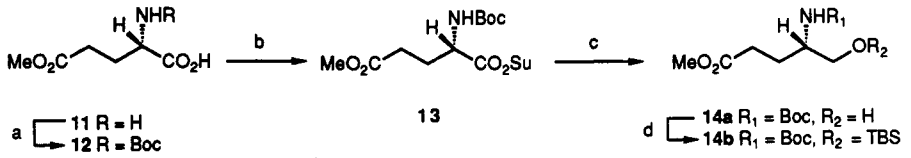
(13) The cycloadducts that were produced from methyl diazoacetate showed the same R_f (0.28) and could not be separated by column chromatography on silica gel.

(14) Column, Develosil ODS-5 (Nomura Chemical, Nagoya, Japan); flow rate, 2 mL/min; eluent, MeOH/H_2O, 1:1. Retention times: **6b**, 32.2 min; **7b**, 34.4 min; **8b**, 26.6 min; **9b**, 29.0 min.

Scheme II[a]



[a] Boc_2O, $NaHCO_3$, 1:1 dioxane/H_2O; (b) HOSu, DCC, AcOEt; (c) $NaBH_4$, 3:1 THF/EtOH, 0 °C, 15 min (83% from 11); (d) TBSCl, imidazole, DMF, room temperature, 14 h (92%).

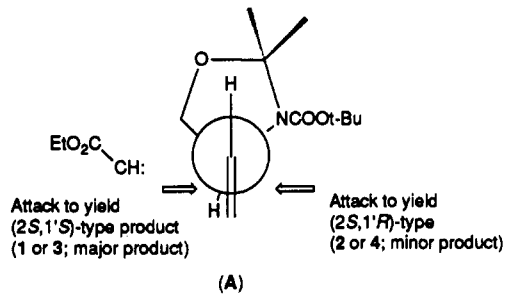


Figure 3.

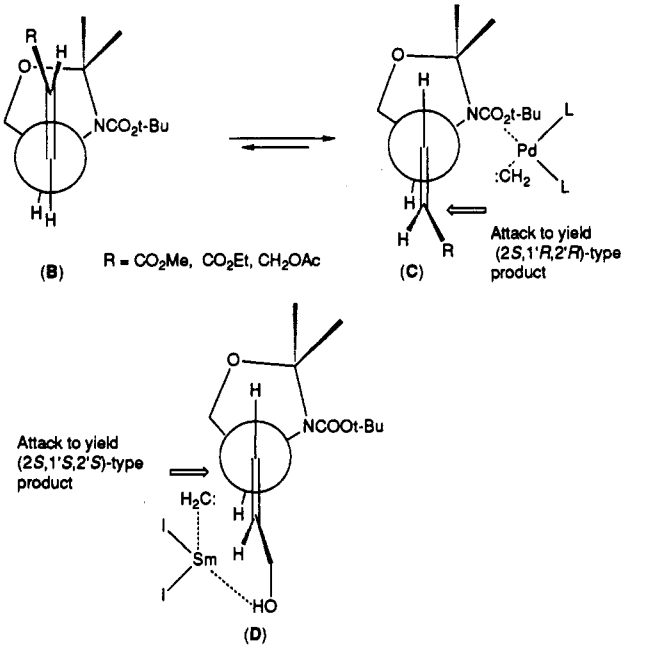


Figure 4.

To provide an alternative route to the four CCG isomers, the cycloaddition of ethyl diazoacetate to the acetonide **10**[15] was examined (Table I). Cycloaddition provided a mixture of adducts in 14% yield (85% of the starting material was recovered). These were converted to the corresponding hydroxy carbamates **6b–9b** by successive treatment with TFA and di-*tert*-butyl dicarbonate (Boc_2O). A 3.3:1.8:2.2:1 mixture of **6b**, **7b**, **8b**, and **9b** was produced. That the 2*S*,1'*S* isomers (**6b** and **8b**) were formed in preference (ca. 2:1) to the 2*S*,1'*R* isomers (**7b** and **9b**) may have been the result of a tendency for the carbene to attack the slightly less hindered face of **10**, as is shown in Figure 3A.

When a chiral copper catalyst[16] was used, higher proportions of the extended isomers (**6b** and **7b**) were formed (**6b**/**7b**/**8b**/**9b** = 5:5:1:1). However, the yield dropped to 7%.

The four analogous D-2-(carboxycyclopropyl)glycines (D-**1**–D-**4**) were synthesized from (2*R*)-**5b** in the same manner as **1**–**4** were synthesized from (2*S*)-**5b**.[17]

Synthesis of CCG-I–IV via the Palladium-Catalyzed Cycloaddition of Diazomethane to the Olefins. (1) Synthesis of CCG-I and -II. The Pd(II)-catalyzed cycloaddition of diazomethane to the carbon–carbon double bond of *E*- or *Z*-olefins[18] provided a useful stereoselective method for the synthesis of precursors of both the extended and folded CCGs (Table II). The $Pd(OAc)_2$-catalyzed reactions of several *E*-olefins with excess CH_2N_2 gave mixtures of both *trans*-cyclopropanes (**1** and **2**; extended forms). In the case of *Z*-olefins, the yields of cycloadducts were extremely low (<10%). *N*- and *O*-methylated species were byproducts. The stereoselectivity of the reaction was only slightly affected by the structure of the olefin. The reaction proceeded with both allyl alcohol and unsaturated esters. The use of *N*,*O*-acetonides (entries 6–8, Table II) gave a slight excess of (2*S*,1'*R*)-type products, which could be converted to **2**. Such products would be produced from the conformer C, which would exhibit less allylic strain than the other conformer and in which the amide carbonyl group could coordinate with the palladium–carbene complex.[19] On the other hand, the use of Sm/CH_2ICl method[20] tended slightly to produce (2*S*,1'*S*)-type products (entry 9), which could be converted to **1**. Inspection of molecular models suggested that the SmI_2–carbene complex D, which could coordinate with the hydroxyl group, would preferentially attack the carbon–carbon double bond from the less hindered side of the olefin (Figure 4D).

(2) Stereoselective Synthesis of CCG-III and -IV. Because approaches to the synthesis of the folded isomers **3** and **4** which involved the cyclopropanation of acyclic *Z*-olefins were not successful, as described in the previous section, the cyclopropanation of the cyclic intermediates **16** and **19** with diazomethane was next examined. L-Glu was the starting material for the synthesis of both **16** and **19**. It provided both a source of chirality and the required carbon framework. The synthetic approach to the intermediates **16** and **19** is shown in Scheme II.

(2-1) Synthesis of (4*S*)-4-Amino-5-hydroxypentanoic Acid. The synthesis of 4-amino-5-hydroxy-

(15) The acetonide **10** was prepared from **5a** in 96% yield (2,2-dimethoxypropane/acetone, CSA, 70 °C, 1 h).

(16) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1982**, *23*, 685. We thank Dr. T. Aratani of Sumitomo Chemical Co. Ltd., Osaka, Japan, for kindly donating the asymmetric catalyst (R)-7644. The reaction of (2*R*)-**5b** in the presence of (R)-7644 gave a mixture of cycloadducts. The proportions of which were the same as the mixture of analogous products derived from (2*S*)-**5b**.

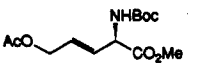
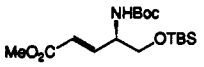
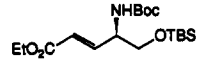
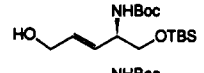
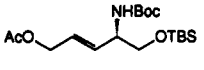
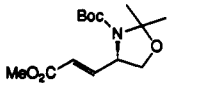
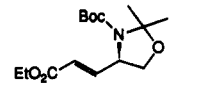
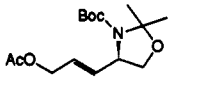
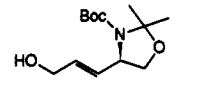
(17) D-**1**: mp 240–242 °C dec; $[\alpha]^{25}_D$ −97.4° (*c* 0.5, H_2O). D-**2**: mp 254–258 °C dec; $[\alpha]_D^{25}$ +21.6° (*c* 0.5, H_2O). D-**3**: mp 202–203 °C; $[\alpha]_D^{25}$ −15.6° (*c* 0.5, H_2O). D-**4**: mp 172–180 °C dec; $[\alpha]_D^{25}$ −86.7° (*c* 0.5, H_2O). Compounds **1**–**4** and D-**1**–D-**4** were analyzed by HPLC [column, optically active CROWNPAK CR(+) (Daicel Chem. Ind. Ltd., Osaka, Japan); column dimensions, 0.4 cm i.d. × 15 cm; flow rate, 0.4 mL/min; eluent, 1% aqueous $HClO_4$]. The retention times were as follows: **1**, 5.3 min; **2**, 4.6 min; **3**, 9.5 min; **4**, 9.4 min; D-**1**, 4.0 min; D-**2**, 3.8 min; D-**3**, 4.3 min; D-**4**, 4.2 min.

(18) For examples of the Pd-catalyzed cyclopropanation of olefins by diazomethane, see: (a) Suda, M. *Synthesis* **1981**, 714. (b) Mende, U.; Raduchel, B.; Skuballa, W.; Vorbrüggen, H. *Tetrahedron Lett.* **1975**, *18*, 629.

(19) Maas, G. *Top. Curr. Chem.* **1987**, *137*, 75.

(20) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525.

Table II. Cyclopropanation of *E* Olefins

entry	substrate	reaction conditions[a]	yield (%)[b]	product ratio[c] 2*S*,1′*S*,2′*S*:2*S*,1′*R*,2′*R*
1		a	68	1:1
2		a	48[d]	1:1
3		a	73	1:3
4		a b	40[d] 39	1:2 3:4
5		a	50[d]	4:3
6		a	87	1.0:2.8
7		a	90	1.0:4.6
8		a	53[d]	1:6
9		b	39	2:1

[a] Reaction conditions: (a) excess CH_2N_2, 0.05 equiv of $Pd(OAc)_2$, room temperature; (b) 4 equiv of Sm powder, CH_2ICl, room temperature. [b] Isolated yield. [c] The stereochemistry of the cycloadducts was determined by converting them to the known diastereomers **6b** and **7b** or the corresponding dimethyl esters. Product ratio was determined after the chromatographic isolation or by ^1H NMR analysis of the product mixture. [d] Determined by ^1H NMR.

pentanoic acid from glutamic acid, via a pyrroglutamic acid derivative, was reported by Silvermann et al.[21] However, this method required multiple transformations and had the added handicap of involving intermediates that were either racemic or water soluble. Also, no efficient method for the regioselective reduction of the α-carboxyl group of L-Glu has been reported. The solution to the problem involved the reduction of the activated ester **13**, which was derived from commercially available L-glutamic acid γ-methyl ester **11**. Thus, after the amino group of **11** was protected with a Boc group, treatment with dicyclohexyl carbodiimide (DCC)/*N*-hydroxysuccinimide (HOSu), followed by treatment with $NaBH_4$/tetrahydrofuran (THF)–EtOH gave the desired alcohol **14a** in 83% yield. That no racemization occurred was ascertained by converting **14a** to the known **15b**.[22]

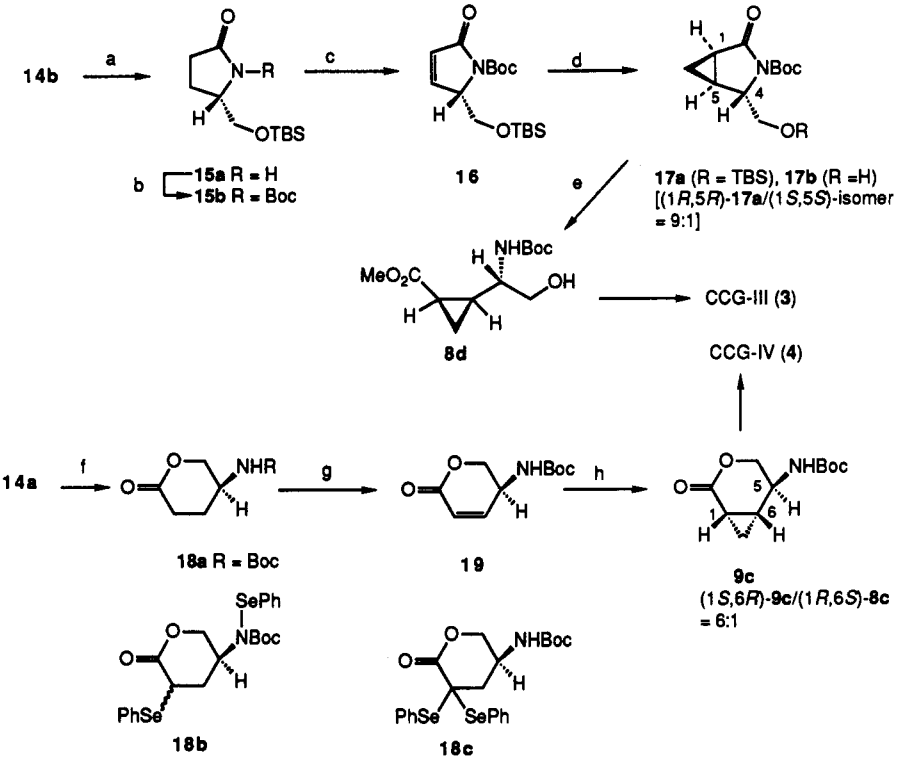
(2-2) Synthesis of L-CCG-III (3). To effect the transformation of **14a** to the γ-lactam **15**, first the primary hydroxyl group of **14a** was protected by a TBS group, to give **14c**. This compound, upon treatment with NaH/THF, yielded the desired cyclized product **15a**. The Boc group was then reintroduced by treatment with Boc_2O/triethylamine/4-(dimethylamino)pyridine (DMAP) to give γ-lactam **15b** in 87% yield. This compound was completely identical with that described previously.[22] Compound **15b** was converted to the known α,β-unsaturated γ-lactam **16** by selenylation–deselenylation.[23] Cyclopropanation of **16** by treatment with diazomethane in the presence of a catalytic amount of $Pd(OAc)_2$ gave, in quantitative yield, a 9:1 mixture of the desired 1*R*,5*R*-**17a** and its 1*S*,5*S* isomer. The two isomers were separated by recrystallization, after removal of the TBS group with CSA/MeOH. The pure alcohol **17b**, upon treatment with LiOH/MeOH, furnished the methyl ester **8d**. This was converted to L-CCG-III (**3**) in the manner described above. The overall yield of **3** was 36% (15 steps from **11**).

(2-3) Synthesis of CCG-IV. The cyclopropanation of the α,β-unsaturated δ-lactone **19** was the key step in the stereoselective synthesis of (2*S*,1′*R*,2′*S*)-**4**. Lactonization of **14a** by treatment with CSA/benzene gave **18a** in 92% yield. Initial attempts to convert **18a** into **19** by selenylation–deselenylation[23] were unsuccessful. Apparently, the *N*-phenylseleno group of the initially formed **18b** migrated to C-2 to give the 2,2-diselenylated product **18c**. Therefore, the requisite double bond was introduced into **18a** by the use of Saegusa's method.[24] Thus, treatment of **18a** with 2 equiv each of lithium hexamethyldisilazane and chlorotrimethylsilane (TMSCl) gave the corresponding *N*-trimethylsilyl *O*-trimethylsilyl enol ether which, upon oxidation with $Pd(OAc)_2$, furnished the desired unsaturated lactone **19** in 70% yield. Cyclopropanation of **19** in the manner described above gave a 6:1 mixture of the desired 1*S*,6*R*-**9c** and the undesired 1*R*,6*S*-**8c** in 46% yield. The cyclopropyl lactone **9c** was then converted to **4** in the manner described above. The overall yield of **4** was 14% (12 steps from **11**). Thus, the folded isomers **3** and **4** were prepared from L-Glu in an efficient manner[25] (see Scheme III).

CCG Isomers 1–4 as Conformational Variants of L-Glu in the Activation of the L-Glu Receptors. L-Glu

(21) Silverman, R. B.; Levy, M. A. *J. Org. Chem.* **1980**, *45*, 815.
(22) Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511.
(23) (a) Reich, H. J.; Reich, J. M.; Renga, J. M. *J. Am. Chem. Soc.* **1973**, *95*, 5813. (b) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137.
(24) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(25) (a) For the synthesis of D-1–D-4 from a vinylglycine derivative, see: Pellicciari, R.; Natalini, B.; Marinozzi, M.; Monahan, J. B.; Snyder, J. P. *Tetrahedron Lett.* **1990**, *31*, 139. (b) For a diastereoselective synthesis of *dl*-**2**, see: Yamaguchi, M.; Torisu, K.; Minami, T. *Chem. Lett.* **1990**, *377*.

Scheme III[a]



[a](a) 1 equiv of NaH, Et_2O, room temperature, 16 h; (b) Boc_2O, Et_3N, 4-DMAP, THF, 4 h (87%); (c) ref 22; (d) CH_2N_2, 0.05 equiv of $Pd(OAc)_2$, Et_2O, room temperature (100%; 17a/1S,5S isomer = 9:1); (e) (1) CSA, MeOH, room temperature, 14 h; (2) LiOH, MeOH, room temperature, 16 h (83%, from 17a); (f) catalytic amount of CSA, benzene, 80 °C, 3 h (92%); (g) (1) 2.2 equiv of TMSCl, 2.2 equiv of $LiN(SiMe_3)_2$, −78 °C, 15 min; (2) 1.2 equiv of $Pd(OAc)_2$, CH_3CN, 20 °C, 45 min (70%); (h) CH_2N_2, 0.2 equiv of $Pd(OAc)_2$, Et_2O, room temperature (46%).

is a conformationally flexible molecule which is capable of nonselectively activating its different receptors. It is reasonable to assume that each of the L-Glu receptors can recognize an optimum conformation of L-Glu. To determine what conformations of L-Glu activate L-Glu's different receptors, the excitatory effects induced by the CCG isomers 1–4 in the mammalian central nervous system were examined. These isomers closely mimic either an extended or folded conformation of L-Glu, if allowances are made for the rotamers that result from hindered rotation of the α-amino acid group. Each of the diastereomers 1–4 induced a variety of depolarizing effects on the motoneurons of the newborn rat spinal cord.[10] The relative intensities of the effects induced by 1–4 and other representative excitatory amino acids were L-Glu (1), 1 (6), 2 (0.5), 3 (0.3), 4 (100), NMDA (40), KA (100), and QA (200).

The use of selective antagonists permitted the classification of compounds 1–4 as either NMDA or non-NMDA agonist.[26] The folded isomers 3 and 4 were classified as NMDA-type agonists, because their effects were almost completely blocked by several NMDA antagonists.[10] All the CCG D isomers (D-1–D-4; Figure 5), which were synthesized from (2R)-5a in the same manner as the L isomers (1–4) synthesized from (2S)-5a were NMDA type agonists.[10a,27] The relative intensities of the effects (L-Glu =

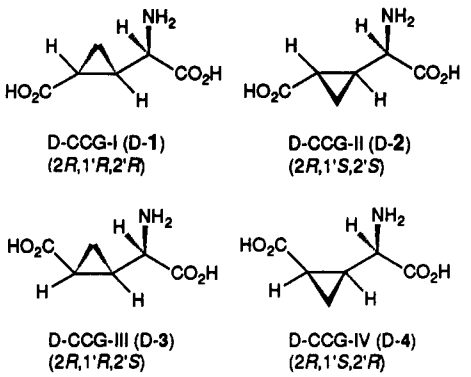


Figure 5. D isomers of diastereomeric 2-(carboxycyclopropyl)-glycines.

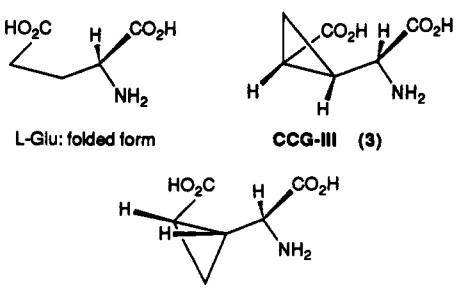


Figure 6. Proposed conformer of L-Glu which activates the NMDA receptor.

1) of the D isomers (D-1–D-4) were D-1 (3), D-2 (200), D-3 (0.1), and D-4 (10).

Among the eight diastereomers of CCG, D-2, which possesses an extended structure, exerted the greatest de-

(26) (a) For information on NMDA antagonists, see: Davies, J.; Evans, R. H.; Herrling, P. L.; Jones, A. W.; Olvermann, H. J.; Pook, P.; Watkins, J. C. *Brain Res.* **1986**, *382*, 169. (b) Non-NMDA antagonist, see: Honoré, T.; Davies, S. N.; Drejer, J.; Fletcher, E. J.; Jacobsen, P.; Lodge, D.; Nielsen, F. *Science* **1988**, *241*, 701.

(27) Before compounds 1–4 and D-1–D-4 were subjected to physiological assay, they were repeatedly recrystallized from water. The enantiomeric purity of each compound was found to be ca. 99% by HPLC (see ref 17).

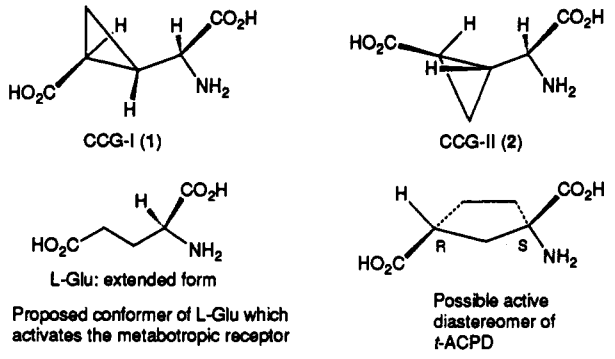


Figure 7. Conformational relationships between 1 and 2 and *dl-t*-ACPD.

polarizing effect. However, radioligand binding assays of the CCG isomers using rat cortical membranes showed 4 to exhibit a binding affinity for the NMDA receptor which was much more than that of D-2.[28a,29] Because the conformation of the L isomer 4 closely mimics the folded conformer of L-Glu and was shown to intensely activate the NMDA receptor both by electrophysiological assay and by receptor binding assay, it is proposed that the conformation of L-Glu which activates the NMDA receptor is the folded form (Figure 6). L-Glu agonists with the D configuration seem to preferentially activate the NMDA receptor. Which conformation(s) of the D isomer activate the NMDA receptor remain(s) to be determined.[30]

Neither NMDA antagonists nor non-NMDA antagonist inhibited the effects of the extended isomers 1 and 2. These effects can be characterized as a selective activation of the metabotropic L-Glu receptor.[5,6,31] The depolarizing effect of 1 was two times greater than that of *trans-dl*-1-amino-1,3-cyclopentanedicarboxylic acid (*t*-ACPD), which is the only known selective agonist of the metabotropic L-Glu receptor.[31a]

On the other hand, only L-CCG-III (3) markedly potentiated the response to L-Glu. However, its depolarizing effect was less than that of L-Glu. The effect was that of an uptake inhibitor of L-Glu in the synaptic environment.[10a,29a,32]

Thus, all the CCG isomers (1–4) markedly affected the L-Glu receptors. From these results, the following conclusions about the conformation of L-Glu that are required to activate L-Glu's receptors were drawn. (1) The folded conformer of L-Glu activates the NMDA receptor. The effect of 4, which has a folded conformation of L-Glu as its substructure, was much greater than those of L-Glu and other known NMDA agonists. The extended isomers 1 and 2 were not NMDA-type agonists. (2) It is possible that the conformation of L-Glu that is required to activate the metabotropic receptor is the extended form, because 1 mimics closely the extended conformation of L-Glu (Figure 7). Although the *t*-ACPD that was used was the racemate,[5,6] that compound's active form should be the 1*S*,3*R* isomer, with the conformation depicted in Figure 7, which closely resembles the conformation of L-Glu substructure of 1 and 2. (3) What conformation of L-Glu is required to activate the non-NMDA receptor remains unclear.[33] (4) A comparison of the depolarizing effects of the extended isomers 1 and 2, and those of the folded isomers 3 and 4 suggests that the cyclopropane ring of 2 and 3 might sterically hinder the approach of the molecules to the receptor surface, because the depolarizing effects of 2 and 3 are much less than those of 1 and 4, respectively (Figures 6 and 7).

The results of the synthetic and neuropharmacological studies of CCG isomers described here provide additional support for the hypothesis that each of the L-Glu receptors is capable of differentiating specific conformers of L-Glu. Thus, these CCG isomers can be expected to be very useful, both as a pharmacological tools for analyzing the mechanisms of glutamate's neurotransmitter function and as starting points for the synthesis of effective L-Glu agonists and antagonists.

Experimental Section

Melting points are uncorrected. ^1H NMR chemical shifts are reported in ppm (δ) relative to $CHCl_3$ (δ = 7.26) in $CDCl_3$ or sodium 3-(trimethylsilyl)propionate-d_4 (δ = 0.00) in D_2O. All reactions were monitored by thin-layer chromatography (TLC), which was performed with precoated TLC plates (Merck). Silica gel (Merck 60) was used for column chromatography. Medium-pressure liquid chromatography (MPLC) was performed with a LiChroprep Si 60 Lobar column (Merck). Yields are of chromatographically and spectroscopically (^1H NMR) pure materials, unless otherwise stated.

(2*S*)-*N*-(*tert*-Butoxycarbonyl)-2-((ethoxycarbonyl)-cyclopropyl)glycinol (6b–9b) and (1*S*,5*S*,6*R*)-5-(*N*-(*tert*-Butoxycarbonyl)amino)-3-oxabicyclo[4.1.0]heptan-2-one (9c). To a solution of $Pd(OAc)_2$ (168 mg, 0.75 mmol) and **5b** (4.34 g, 15 mmol) in Et_2O (150 mL) at room temperature was simultaneously added, drop by drop, a solution of ethyl diazoacetate (17.1 g, 150 mmol) in Et_2O (300 mL) and a solution of $Pd(OAc)_2$ (168 mg, 0.75 mmol) in Et_2O (200 mL) over 3 h. The mixture was filtered. The filtrate was concentrated in vacuo to give a crude oil, which, upon column chromatography on silica gel (Et_2O/hexane, 1:4) gave a mixture of the four diastereomers **6a–9a** as a colorless oil (4.00 g, 88%). The mixture was dissolved in EtOH (100 mL) and was treated with *dl*-10-camphorsulfonic acid (CSA) (5 mg) at room temperature for 16 h. Then the solvent was evaporated under reduced pressure. The residue was purified by medium-pressure column chromatography on silica gel (Et_2O/hexane, 3:1) to give (2*S*,1′*R*,2′*R*)-**7b** (932 mg), (2*S*,1′*S*,2′*R*)-**8b** (175 mg), a mixture of (2*S*,1′*S*,2′*S*)-**6b** and

(28) (a) L-CCG-IV (4) inhibited the binding of [[^{3}H]-3-(2-carboxypiperidin-4-yl)propyl]phosphonic acid ([^{3}H]CPP) to the NMDA receptor which corresponded to 17-fold and 790-fold higher affinity than that of L-Glu and NMDA, respectively. The binding affinity of D-2 was similar to that of L-Glu. See: Kawai, M.; Ishihara, T.; Shimamoto, K.; Ohfune, Y. Submitted to *Eur. J. Pharmacol.* (b) Horikawa, Y.; Kawai, M.; Shimamoto, K. Ohfune, Y.; Ishihara, T. *Jpn. J. Pharm.* **1990**, *52*, 76.

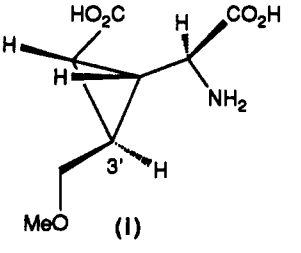
(29) Pellicciari et al. reported that the D isomers of CCG have significant affinity to the NMDA receptor by the binding assay using [^{3}H]-L-glutamic acid as a radioligand.[25a]

(30) Watkins, J. C.; Krogsgaard-Larsen, P.; Honoré, T. *Trends Pharmacol. Sci.* **1990**, *11*, 25.

(31) Activation of the metabotropic receptor by 1 and 2 were determined both by the electrophysiological assay that used rat spinal motoneurons and *Xenopus oocytes*[a] and by the biochemical assay that measured an increase of intracelluler IP_3 formation in rat hippocampal synaptoneurosomes.[b] See: (a) Ishida, M.; Akagi, H.; Shimamoto, K.; Ohfune, Y. Shinozaki, H. *Brain Res.* **1990**, *537*, 311. (b) Nakagawa, Y.; Saitoh, K.; Ishihara, T.; Ishida, M.; Shinozaki, H. *Eur. J. Pharmacol.* **1990**, *184*, 205.

(32) Johnston, G. A. R.; Lodge, D.; Bornstein, J. C.; Curtis, D. R. *J. Neurochem.* **1980**, *34*, 241.

(33) Our recent synthesis of i, which is a C3′ substituted analogue of the most potent NMDA-type agonist 4, showed that its depolarizing effect is of the non-NMDA type which preferentially activates the KA-type receptor. This finding suggests that the active form of L-Glu which acts upon the KA receptor is also the folded form. See: (a) Shimamoto, K.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *31*, 4049. (b) Ishida, M.; Ohfune, Y.; Shimamoto, K.; Shinozaki, H. *Brain Res.*, in press.



(2*S*,1′*R*,2′*S*)-**9b** (363 mg), and a mixture of **6b**–**9b** (197 mg). The mixture of **6b** and **9b** was treated with CSA (5 mg) in CH_2Cl_2 (10 mL) at room temperature for 18 h. The mixture was then washed with aqueous $NaHCO_3$. The organic phase was dried and the solvent was evaporated in vacuo to give an oily residue. This was purified by medium-pressure column chromatography on silica gel (Et_2O/hexane, 3:1) to give unchanged **6b** (190 mg) as a colorless oil and (1*S*,5*S*,6*R*)-δ-lactone **9c** (80 mg) as colorless crystals: (**2*S*,1′*S*,2′*S*)-6b**: oil; $[\alpha]^{25}_D$ +72.9° (*c* 0.50, $CHCl_3$); IR (neat) 3372, 2984, 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.89 (ddd, 1 H, *J* = 4.5, 6.5, 9.0 Hz), 1.20 (ddd, 1 H, *J* = 4.5, 4.5, 9.0 Hz), 1.25 (t, 3 H, *J* = 7.0 Hz), 1.45 (s, 9 H), 1.55 (dddd, 1 H, *J* = 4.5, 6.5, 9.0, 9.0 Hz), 1.76 (ddd, 1 H, *J* = 4.5, 4.5, 9.0 Hz), 2.40 (br s, 1 H), 3.15 (m, 1 H), 3.68 (m, 1 H), 3.76 (m, 1 H), 4.118 (dq, 1 H, *J* = 7.0, 11.0 Hz), 4.120 (dq, 1 H, *J* = 7.0, 11.0 Hz); MS (SIMS) *m*/*z* 274 (M + H)$^+$, 218, 174. Anal. Calcd for $C_{13}H_{23}O_5N$: C, 57.13; H, 8.48; N, 5.12. Found: C, 56.70; H, 8.71; N, 5.02. (**2*S*,1′*R*,2′*R*)-7b**: mp 88.0–89.0 °C; $[\alpha]^{23}_D$ −47.2° (*c* 0.55, $CHCl_3$); IR (neat) 3460, 3028, 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.02 (ddd, 1 H, *J* = 4.5, 6.5, 8.5 Hz), 1.18 (ddd, 1 H, *J* = 4.0, 4.5, 9.0 Hz), 1.26 (t, 3 H, *J* = 7.0 Hz), 1.44 (s, 9 H), 1.54 (dddd, 1 H, *J* = 4.0, 4.0, 6.5, 8.5 Hz), 1.59 (ddd, 1 H, *J* = 4.0, 6.5, 9.0 Hz), 2.35 (br s, 1 H), 3.22 (dddd, 1 H, *J* = 4.0, 5.0, 6.5, 8.5 Hz), 3.68 (ddd, 1 H, *J* = 5.0, 5.0, 10.5 Hz), 3.76 (ddd, 1 H, *J* = 4.0, 6.5, 10.5 Hz), 4.115 (dq, 1 H, *J* = 7.0, 11.0 Hz), 4.120 (dq, 1 H, *J* = 7.0, 11.0 Hz); MS (SIMS) *m*/*z* 274 (M + H)$^+$, 218, 174. Anal. Calcd for $C_{13}H_{23}O_5N$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.19; H, 8.46; N, 5.12. (**2*S*,1′*S*,2′*R*)-8b**: mp 94.0–95.0 °C; $[\alpha]^{23}_D$ −56.0° (*c* 0.48, $CHCl_3$); IR (neat) 3392, 2984, 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.13 (ddd, 1 H, *J* = 5.0, 8.0, 8.5 Hz), 1.18 (ddd, 1 H, *J* = 5.0, 6.0, 7.0 Hz), 1.27 (t, 3 H, *J* = 7.0 Hz), 1.42 (s, 9 H), 1.53 (dddd, 1 H, *J* = 7.0, 7.0, 8.0, 8.5 Hz), 1.78 (ddd, 1 H, *J* = 6.0, 8.5, 8.5 Hz), 3.02 (br s, 1 H), 3.61 (dddd, 1 H, *J* = 3.5, 6.0, 7.0, 10.5 Hz), 3.70 (br m, 1 H), 3.84 (br m, 1 H), 4.13 (dq, 1 H, *J* = 7.0, 11.0 Hz), 4.17 (dq, 1 H, *J* = 7.0, 11.0 Hz); MS (SIMS) *m*/*z* 274 (M + H)$^+$, 218, 174.[28] Anal. Calcd for $C_{13}H_{23}O_5N$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.03; H, 8.45; N, 5.09. (**1*S*,5*S*,6*R*)-δ-Lactone (9c)**: mp 152.0–154.0 °C; $[\alpha]^{23}_D$ −59.4° (*c* 0.46, $CHCl_3$); IR (neat) 3328, 2984, 1734, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.29 (ddd, 1 H, *J* = 6.5, 8.0, 9.5 Hz), 1.38 (ddd, 1 H, *J* = 5.0, 5.0, 6.5 Hz), 1.45 (s, 9 H), 1.88 (dddd, 1 H, *J* = 3.0, 5.0, 7.5, 8.0 Hz), 1.96 (ddd, 1 H, *J* = 5.0, 7.5, 9.5 Hz), 4.12 (dd, 1 H, *J* = 2.5, 13.0 Hz), 4.21 (dddd, 1 H, *J* = 1.5, 2.5, 3.0, 7.0 Hz), 4.28 (dd, 1 H, *J* = 1.5, 13.0 Hz), 4.95 (br d, 1 H, *J* = 7.0 Hz); MS (SIMS) *m*/*z* 228 (M + H)$^+$, 172, 128. Anal. Calcd for $C_{11}H_{17}O_4N$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.08; H, 7.68; N, 6.05.

(2*S*,1′*R*,2′*S*)-*N*-(*tert*-Butoxycarbonyl)-2-((ethoxycarbonyl)cyclopropyl)glycinol (9b). A mixture of **9c** (514 mg, 2.26 mmol), K_2CO_3 (20 mg), and EtOH (30 mL) was stirred at room temperature for 24 h. The mixture was then extracted with EtOAc several times. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated in vacuo. The oily residue was purified by column chromatography on silica gel (Et_2O/hexane, 3:1) to give **9b** as colorless crystals (540 mg, 87%): mp 109.0–110.5 °C; $[\alpha]^{23}_D$ −49.3° (*c* 1.04, $CHCl_3$); IR (neat) 3380, 2984, 2940, 1726 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.10 (ddd, 1 H, *J* = 5.0, 8.0, 8.0 Hz), 1.24 (m, 1 H), 1.27 (t, 3 H, *J* = 7.0 Hz), 1.47 (s, 9 H), 1.50 (m, 1 H), 1.80 (ddd, 1 H, *J* = 5.5, 8.0, 9.0 Hz), 2.85 (br s, 1 H), 3.56 (m, 1 H), 3.67 (m, 2 H), 4.15 (q, 2 H, *J* = 7.0); MS (SIMS) *m*/*z* 274 (M + H)$^+$, 218, 174. Anal. Calcd for $C_{13}H_{23}O_5N$: C, 57.13; H, 8.48; N, 5.12. Found: C, 56.97; H, 8.51; N, 5.03.

(1*R*,5*S*,6*S*)-5-(*N*-(*tert*-Butoxycarbonyl)amino)-3-oxobicyclo[4.1.0]heptan-2-one (8c). A solution of **8b** (100 mg, 0.37 mmol) and CSA (5 mg) in CH_2Cl_2 (5 mL) was stirred at room temperature for 24 h. The mixture was then washed with aqueous $NaHCO_3$. The organic phase was dried and the solvent was evaporated in vacuo to give an oily residue. This was purified by column chromatography on silica gel (Et_2O/hexane, 3:1) to give **8c** (58 mg, 69%) as colorless crystals: mp 123.0–125.0 °C; $[\alpha]^{23}_D$ +70.4° (*c* 0.68, $CHCl_3$); IR (neat) 3348, 2984, 2940, 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.17 (ddd, 1 H, *J* = 6.0, 7.5, 9.5 Hz), 1.45 (s, 9 H), 1.50 (m, 1 H), 1.90 (m, 1 H), 2.02 (ddd, 1 H, *J* = 4.5, 8.0, 9.5 Hz), 3.64 (t, 1 H, *J* = 11.5 Hz), 4.27 (dd, 1 H, *J* = 3.5, 11.5 Hz),4.43 (m, 2 H), 4.49 (m, 1 H); MS (SIMS) *m*/*z* 228 (M + H)$^+$, 172, 128. Anal. Calcd for $C_{11}H_{17}O_4N$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.75; H, 7.52; N, 6.09.

(2*S*,1′*S*,2′*S*)-2-(Carboxycyclopropyl)glycine (1: CCG-I). To a solution of **6b** (1.00 g, 3.66 mmol) in acetone (10 mL) at 0 °C was added a 1.5-fold excess of Jones reagent drop by drop over 5 min. The mixture was stirred at 0 °C for 3 h and then at room temperature for 1.5 h. The excess Jones reagent was destroyed with 2-propanol. The mixture was then extracted with EtOAc several times. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residual oil was dissolved in Et_2O and was treated with an Et_2O solution of CH_2N_2. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 3:1). A solution of the crude product and 1 *N* aqueous NaOH (9 mL, 9 mmol) in MeOH (5 mL) was stirred at 0 °C for 19 h. The mixture was then acidified to pH 2 with 1 *N* aqueous HCl, was saturated with solid NaCl, and was extracted with EtOAc several times. The combined extracts were dried ($MgSO_4$) and concentrated in vacuo to give an oily residue. To a solution of the residue (crude *N*-*t*-Boc 1) in CH_2Cl_2 (2 mL) at 0 °C was added TFA (2 mL). The mixture was stirred for 30 min at room temperature and then was concentrated *in vacuo*. The residue was passed through a column of Dowex 50Wx4 (100–200 mesh) ion exchange resin (H_2O, then 1 *N* aqueous NH_3) to give a solution of the ammonium salt of 1. The eluate was concentrated *in vacuo* and then was dissolved in water (2 mL). The pH of the solution was adjusted to 3 with 1 *N* aqueous HCl. The crystals that precipitated from solution were collected by filtration. They were recrystallized from water to give 1 (228 mg, 39% from **6b**) as colorless crystals: mp 243–247 °C dec; $[\alpha]^{21}_D$ +102.0° (*c* 0.50, H_2O); IR (KBr) 2935, 1688, 1625, 1586 cm^{-1}; ^1H NMR (D_2O, 360 MHz) δ 1.23 (ddd, 1 H, *J* = 5.1, 6.2, 8.7 Hz), 1.32 (ddd, 1 H, *J* = 5.0, 5.1, 9.1 Hz), 1.68 (dddd, 1 H, *J* = 4.1, 6.2, 9.1, 10.2 Hz), 1.76 (ddd, 1 H, *J* = 4.1, 5.0, 8.7 Hz), 3.23 (d, 1 H, *J* = 10.2 Hz); MS (SIMS) *m*/*z* 160 (M + H)$^+$, 142, 115. Anal. Calcd for $C_6H_9O_4N$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.10; H, 5.76; N, 8.65.

(2*S*,1′*R*,2′*R*)-2-(Carboxycyclopropyl)glycine (2: CCG-II). In a manner similar to that used to prepare 1, 2 (75.2 mg, 65%) was prepared from **7b** (200 mg, 0.73 mmol). 2: colorless crystals; mp 255–258 °C dec; $[\alpha]^{25}_D$ −20.2° (*c* 0.51, H_2O); IR (KBr) 3162, 1695, 1628, 1575 cm^{-1}; ^1H NMR (D_2O, 360 MHz) δ 1.10 (ddd, 1 H, *J* = 5.0, 6.5, 9.0 Hz), 1.25 (ddd, 1 H, *J* = 5.0, 5.0, 9.0 Hz), 1.72 (dddd, 1 H, *J* = 4.0, 6.5, 9.0, 9.0 Hz), 1.84 (ddd, 1 H, *J* = 4.0, 5.0, 9.0 Hz), 3.39 (d, 1 H, *J* = 9.0 Hz); MS (SIMS) *m*/*z* 160 (M + H)$^+$, 115. Anal. Calcd for $C_6H_9O_4N$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.21; H, 5.69; N, 8.71.

(2*S*,1′*S*,2′*R*)-2-(Carboxycyclopropyl)glycine (3: CCG-III). In a manner similar to that used to prepare 1, 3 (16.1 mg, 27%) was prepared from **8b** (100 mg, 0.37 mmol). 3: colorless crystals; mp 192–197 °C dec; $[\alpha]^{22}_D$ +20.8° (*c* 0.52, H_2O); IR (KBr) 3141, 1700, 1615, 1578 cm^{-1}; ^1H NMR (D_2O, 360 MHz) δ 1.26 (ddd, 1 H, *J* = 5.0, 6.0, 7.0 Hz), 1.39 (ddd, 1 H, *J* = 5.0, 9.0, 9.0 Hz), 1.61 (dddd, 1 H, *J* = 7.0, 8.0, 9.0, 11.0 Hz), 1.86 (ddd, 1 H, *J* = 6.0, 8.0, 9.0 Hz), 3.89 (d, 1 H, *J* = 11.0 Hz); MS (SIMS) *m*/*z* 160 (M + H)$^+$, 115. Anal. Calcd for $C_6H_9O_4N$: C, 45.28; H, 5.70; N, 8.80. Found: C, 45.19; H, 5.58; N, 8.79.

(2*S*,1′*R*,2′*S*)-2-(Carboxycyclopropyl)glycine (4: CCG-IV). In a manner similar to that used to prepare 1, 4 (159 mg, 61%) was prepared from **9b** (450 mg, 1.65 mmol). 4: as colorless crystals; mp 178–180 °C; $[\alpha]^{28}_D$ +103.4° (*c* 0.50, H_2O); IR (KBr) 3372, 3170, 1712, 1630, 1560 cm^{-1}; ^1H NMR (D_2O, 360 MHz) δ 1.05 (ddd, 1 H, *J* = 5.0, 6.0, 7.0 Hz), 1.20 (ddd, 1 H, *J* = 5.0, 8.5, 8.5 Hz), 1.60 (dddd, 1 H, *J* = 7.0, 8.5, 9.0, 9.0 Hz), 1.93 (ddd, 1 H, *J* = 6.0, 8.5, 9.0 Hz), 3.89 (d, 1 H, *J* = 9.0 Hz); MS (SIMS) *m*/*z* 160 (M + H)$^+$, 110. Anal. Calcd for $C_6H_9O_4N{\cdot}H_2O$: C, 40.68; H, 6.26; N, 7.91. Found: C, 40.53; H, 6.30; N, 7.88.

General Procedure for the (R)-7644-Catalyzed Cycloaddition of Ethyl Diazoacetate. To a solution of the olefin (0.17 mmol) and (R)-7644 (7.5 mg, 0.01 mmol) in toluene (0.7 mL) was added a solution of ethyl diazoacetate (68 mg, 0.6 mmol) in toluene (2 mL). The mixture was heated at 80 °C until the solution became brown in color. Then a solution of ethyl diazoacetate (500 mg, 4.4 mmol) in toluene (15 mL) was added, drop by drop, at 45 °C over 6 h. The mixture was stirred at 45 °C for 18 h. Then it was concentrated in vacuo to give an oily residue. Purification of the residue by flash column chromatography on silica gel (Et_2O/hexane, 1:1) gave a mixture of cycloadducts. The mixture

of diastereomers was dissolved in EtOH (2 mL). The solution was treated with a catalytic amount of CSA at room temperature for 16 h. The solvent was then evaporated under reduced pressure to give a mixture of **6b–9b**. This was analyzed by HPLC to determine the product ratio.[14] The yields and product ratios are given in Table I.

General Procedure for the Cycloaddition of Diazomethane. To a suspension of the olefin (0.7 mmol), $Pd(OAc)_2$ (8 mg, 0.035 mmol), and Et_2O (10 mL) was added, drop by drop, a solution of CH_2N_2 in Et_2O (200 mL) at room temperature over 30 min. The mixture was then filtered. The filtrate was concentrated *in vacuo* to give an oily residue. This, upon purification by column chromatography on silica gel (Et_2O/hexane, 1:3), gave a mixture of cycloadducts. The yields and product ratios are given in Table II.

General Procedure for Cyclopropanation Catalyzed by Samarium. To a suspension of Sm metal (316 mg, 2.1 mmol) and THF (5 mL) was added a solution of $HgCl_2$ (54 mg, 0.21 mmol) in THF (5 mL). The mixture was stirred for 15 min, and then a solution of the allylic alcohol (0.5 mmol) in THF (2 mL) was added. Freshly distilled CH_2ICl (146 μL, 2.0 mmol) was added drop by drop, and the blue suspension that resulted was stirred for 2 h at room temperature. The mixture was then quenched with aqueous NH_4Cl and was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give an oily residue. This was purified by column chromatography on silica gel (Et_2O/hexane, 3:1) to give the cycloadducts. The yields and product ratios are given in Table II.

Methyl (4*S*)-4-(*N*-(*tert*-Butoxycarbonyl)amino)-5-hydroxypentanoate (14a). To a solution of L-glutamic acid γ-methyl ester **11** (18.4 g, 114 mmol) and $NaHCO_3$ (24 g, 285 mmol) in water (300 mL) was added a solution of Boc_2O (31 mL, 137 mmol) in 1,4-dioxane (300 mL). The mixture was stirred for 16 h at room temperature and then was washed with Et_2O. The aqueous layer was acidified with 1 *N* aqueous HCl to pH 2 and was extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$), and concentrated in vacuo. To a solution of the residue and *N*-hydroxysuccinimide (15.8 g, 137 mmol) in EtOAc (500 mL) was added DCC (28.2 g, 137 mmol) at 0 °C. The mixture was warmed to room temperature and was stirred for 3 h. The mixture was then filtered. The filtrate was washed successively with aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated *in vacuo* to give crude **13** as colorless crystals (51 g). To a solution of crude **13** (20 g, 55 mmol) in THF (150 mL) was added $NaBH_4$ (2.1 g, 56 mmol) at 0 °C. Then EtOH (50 mL) was added. The resulting suspension was stirred for 15 min at 0 °C and then was quenched with aqueous NH_4Cl. The mixture was extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated under reduced pressure to give an oily residue. This, upon column chromatography on silica gel (Et_2O), gave **14a** as colorless crystals. Recrystallization (Et_2O/hexane) gave pure **14a** (11.4 g, 83%): mp 40.5–41.5 °C; $[\alpha]^{23}_D$ −13.2° (*c* 1.00, $CHCl_3$); IR (neat) 3372, 2980, 1708 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.43 (s, 9 H), 1.78 (m, 1 H), 1.88 (ddt, 1 H, *J* = 5.0, 8.0, 8.0, 15.0 Hz), 2.418 (dt, 1 H, *J* = 8.0, 8.0, 16.0 Hz), 2.422 (dt, 1 H, *J* = 8.0, 8.0, 16.0 Hz), 2.51 (br s, 1 H), 3.60 (m, 1 H), 3.65 (m, 2 H), 3.67 (s, 3 H), 4.80 (d, 1 H, *J* = 7 Hz); MS (SIMS) *m/z* 248 (M + H)$^+$, 192, 148. Anal. Calcd for $C_{11}H_{21}O_5N$: C, 53.43; H, 8.56; N, 5.66. Found: C, 53.57; H, 8.76; N, 5.62.

Methyl (4*S*)-4-(*N*-(*tert*-Butoxycarbonyl)amino)-5-((*tert*-butyldimethylsilyl)oxy)pentanoate (14b). To a solution of **14a** (2.95 g, 11.9 mmol) in DMF (15 mL) was added imidazole (1.62 g, 23.9 mmol) and *t*-BuMe$_2$SiCl (2.69 g, 17.9 mmol). The solution was stirred at room temperature for 3 h, then was quenched with MeOH. The mixture was extracted with EtOAc. The extract was washed with water. The extract was then dried ($MgSO_4$) and was concentrated *in vacuo* to give an oily residue. This was purified by column chromatography on silica gel to give **14b** (3.97 g, 92%) as an oil: $[\alpha]^{23}_D$ −21.9° (*c* 2.00, $CHCl_3$); IR (neat) 3468, 2960, 1744, 1722 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 0.05 (s, 6 H), 0.91 (s, 9 H), 1.45 (s, 9 H), 1.84 (m, 2 H), 2.39 (t, 2 H, *J* = 8 Hz), 3.60 (m, 3 H), 3.67 (s, 3 H), 4.64 (br s, 1 H); MS (SIMS) *m/z* 362 (M + H)$^+$, 306, 262, 248. Anal. Calcd for $C_{17}H_{35}O_5N$: C, 56.47; H, 9.76; N, 3.87. Found: C, 56.67; H, 9.83; N, 3.83.

(5*S*)-*N*-(*tert*-Butoxycarbonyl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-pyrrolidone (15b). To a solution of **14b** (1.00 g, 2.76 mmol) in Et_2O (100 mL) was added NaH (83 mg, 2.76 mmol) at 0 °C. The resulting suspension was stirred for 18 h at room temperature, quenched with aqueous NH_4Cl solution, and washed with water. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to give **15a** as an oil. To a solution of **15a** in THF (50 mL) were added Boc_2O (760 μL, 3.31 mmol), Et_3N (460 μL, 3.31 mmol) and DMAP (67 mg, 0.55 mmol). The mixture was stirred for 4 h at room temperature and then was extracted with EtOAc. The extract was washed successively with 5% aqueous citric acid and brine and was dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give an oily residue. This, upon purification by silica gel column chromatography (Et_2O/hexane, 1:1), gave **15b** (796 mg, 87%) as an oil: $[\alpha]^{23}_D$ −62.2° (*c* 1.23, $CHCl_3$); IR (neat) 2960, 1790, 1756, 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.88 (s, 9 H), 1.53 (s, 9 H), 1.90–2.30 (m, 2 H), 2.46 (m, 1 H), 2.66 (m, 1H), 3.68 (dd, 1 H, *J* = 3, 11 Hz), 3.90 (dd, 1 H, *J* = 5, 11 Hz), 4.14 (m, 1 H); MS (SIMS) *m/z* 330 (M + H)$^+$, 274, 236, 230, 216, 172, 156. Anal. Calcd for $C_{16}H_{31}O_4NSi$: C, 58.32; H, 9.48; N, 4.25. Found: C, 58.07; H, 9.40; N, 4.27.

(5*S*)-*N*-(*tert*-Butoxycarbonyl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-pyrrolin-2-one (16). To a solution of **15b** (3.20 g, 9.73 mmol) in THF (5 mL) was added, drop by drop, a solution of Li-*i*-Pr$_2$N [prepared from *i*-Pr$_2$NH (1.58 mL, 11.3 mmol) and *n*-BuLi (1.6 *M* in hexane solution 6.95 mL, 11.1 mmol)] in THF (25 mL) at −78 °C under N_2. The solution was stirred for 30 min at −78 °C. Then a solution of PhSeCl (2.05 g, 10.7 mmol) in THF (15 mL) was added. After 5 min, aqueous NH_4Cl was added. The mixture was allowed to warm to room temperature and then was extracted with Et_2O. The extract was dried ($MgSO_4$) and concentrated in vacuo to give an oily residue. This was purified by a column chromatography on silica gel (Et_2O/hexane, 1:9, then 1:3) to give the phenylselenyl compound as a mixture of diastereomers (4.00 g, 85%). Ozone was passed through the solution of (5*S*)-*N*-(*tert*-butoxycarbonyl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-(phenylseleno)pyrrolidin-2-one (3.2 g, 6.6 mmol) in anhydrous CH_2Cl_2 (80 mL) at −78 °C until the solution became slightly blue in color. Excess ozone was removed from the solution by passing a stream of O_2 through the solution. To the solution was then added NaOAc (6.6 g, 80 mmol). The mixture was allowed to warm to 0 °C and then was stirred for 40 min. The mixture was washed with water, and the organic layer was dried (Na_2SO_4). The solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:4) to give **16** (1.73 g, 87%) as colorless crystals: mp 64.0–65.0 °C; $[\alpha]^{25}_D$ −175.6° (*c* 0.9, $CHCl_3$); IR (neat) 2936, 1768, 1714 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz) δ 0.06 (s, 6 H), 0.88 (s, 9 H), 1.56 (s, 9 H), 3.70 (dd, 1 H, *J* = 7, 10 Hz), 4.15 (dd, 1 H, *J* = 4, 10 Hz), 4.60 (m, 1 H), 6.11 (dd, 1 H, *J* = 2, 6 Hz), 7.24 (dd, 1 H, *J* = 2, 6 Hz); MS (SIMS) *m/z* 328 (M + H)$^+$, 272, 228, 214, 170. Anal. Calcd for $C_{16}H_{29}O_4NSi$: C, 58.68; H, 8.93, N, 4.28. Found: C, 58.68; H, 8.72; N, 4.24.

(1*R*,4*S*,5*R*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-4-(((*tert*-butyldimethylsilyl)oxy)methyl)bicyclo[3.1.0]hexan-2-one (17a). To a solution of $Pd(OAc)_2$ (14 mg, 0.06 mmol) and **16** (200 mg, 0.609 mmol) in Et_2O (5 mL) was added a solution of CH_2N_2 in Et_2O (30 mL) at room temperature. The resulting suspension was filtered. The filtrate was concentrated in vacuo to give an oily residue. This was purified by column chromatography on silica gel (Et_2O/hexane, 1:1) to give a 9:1 mixture of (1*R*,4*S*,5*R*)-**17a** and its 1*S*,4*S*,5*S* isomer (208 mg, 100%): **(1*R*,4*S*,5*R*)-17a**: an oil; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.72 (dt, 1 H, *J* = 3, 4.5, 4.5 Hz), 0.85 (s, 9 H), 1.13 (dt, 1 H, *J* = 4.5, 8.0, 8.0 Hz), 1.50 (s, 9 H), 1.91 (ddd, 1 H, *J* = 4.5, 6.5, 8.0 Hz), 1.94 (dddd, 1 H, *J* = 1.5, 3.0, 8.0 Hz), 3.76 (dd, 1 H, *J* = 5.5, 10.0 Hz), 3.85 (dd, 1 H, *J* = 2.5, 10.0 Hz), 4.02 (ddd, 1 H, *J* = 1.5, 2.5, 5.5 Hz). **1*S*,4*S*,5*S* Isomer**: ^1H NMR ($CDCl_3$, 360 MHz) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.72 (m, 1 H), 0.85 (s, 9 H), 1.13 (m, 1 H), 1.50 (s, 9 H), 1.91 (m, 1 H), 1.94 (m, 1 H), 3.69 (dd, 1 H, *J* = 2.5, 10.0 Hz), 3.91 (dd, 1 H, *J* = 4.0, 10.0 Hz), 4.16 (ddd, 1 H, *J* = 2,5, 4.0, 7.0 Hz).

(2*S*,1′*S*,2′*R*)-*N*-(*tert*-Butoxycarbonyl)-2-((methoxycarbonyl)cyclopropyl)glycinol (8d). To solution of **17a** (177 mg, 0.517 mmol) in MeOH (5 mL) was added CSA (5 mg). The mixture was stirred at room temperature for 14 h. It was then concentrated in vacuo and was extracted with EtOAc. The extract

was dried ($MgSO_4$) and concentrated in vacuo to give a crystalline residue. This was recrystallized (Et_2O) to give (1*R*,4*S*,5*R*)-**17b** as colorless crystals: mp 99.0–100.0 °C; $[\alpha]^{23}_D$ -39.9° (*c* 0.91, $CHCl_3$); IR (neat) 3436, 2984, 1770, 1718 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz), δ 0.77 (ddd, 1 H, *J* = 3.5, 4.0, 5.0 Hz), 1.19 (ddd, 1 H, *J* = 5.0, 8.0, 9.0 Hz), 1.50 (s, 9 H), 1.88 (ddd, 1 H, *J* = 4.0, 6.0, 8.0 Hz), 2.00 (dddd, 1 H, *J* = 1.5, 3.5, 6.0, 9.0 Hz), 2.31 (t, 1 H, *J* = 6.0 Hz), 3.82 (ddd, 1 H, *J* = 4.0, 6.0, 11.0 Hz), 3.86 (ddd, 1 H, *J* = 4.0, 6.0, 11.0 Hz), 4.11 (dt, 1 H, *J* = 1.5, 4.5, 4.5 Hz); MS (SIMS) *m/z* 228 $(M + H)^+$, 172, 128. Anal. Calcd for $C_{11}H_{17}O_4N$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.04; H, 7.67; N, 6.13. To a solution of **17b** in MeOH (5 mL) was added LiOH (14 mg, 0.57 mmol). The solution was stirred at room temperature for 16 h. Then it was extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated under reduced pressure to give an oily residue. This was purified by column chromatography on silica gel (Et_2O) to give **8d** (111 mg, 83% from **17a**) as a colorless amorphous solid: $[\alpha]^{23}_D$ -52.7° (*c* 1.09, $CHCl_3$); IR (neat) 3384, 2984, 1718 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.14 (ddd, 1 H, *J* = 5.0, 8.0, 9.5 Hz), 1.17 (ddd, 1 H, *J* = 5.0, 5.5, 7.0 Hz), 1.42 (s, 9 H), 1.55 (dddd, 1 H, *J* = 7.0, 7.5, 9.0, 9.5 Hz), 1.80 (ddd, 1 H, *J* = 5.5, 8.0, 9.0 Hz), 2.80 (br s, 1 H), 3.62 (dddd, 1 H, *J* = 3.5, 6.0, 7.5, 7.5 Hz), 3.70 (dd, 1 H, *J* = 6.0, 11.0 Hz), 3.70 (s, 3 H), 3.83 (dd, 1 H, *J* = 3.5, 11.0 hz), 4.93 (br s, 1 H); MS (SIMS) *m/z* 260 $(M + H)^+$, 204, 160. Anal. Calcd for $C_{12}H_{21}O_5N$: C, 55.58; H, 8.16; N, 5.40. Found: C, 55.44; H, 8.29; N, 5.40.

(4*S*)-4-(*N*-(*tert*-Butoxycarbonyl)amino)-5-pentanolide (18a). A solution of **14a** (1.00 g, 4.04 mmol) and CSA (10 mg) in benzene (500 mL) was refluxed for 3 h. The mixture was washed with aqueous $NaHCO_3$ and water and dried ($MgSO_4$). Concentration *in vacuo* gave a crystalline residue. This was crystallized (Et_2O) to give **18a** (799 mg, 92%) as colorless crystals: mp 104.0–104.5 °C; $[\alpha]^{23}_D$ -37.4° (*c* 1.09, $CHCl_3$); IR (neat) 3356, 2984, 1756, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.44 (s, 9 H), 1.87 (m, 1 H), 2.22 (m, 1 H), 2.58 (dt, 1 H, *J* = 7.5, 7.5, 17.0 Hz), 2.66 (dt, 1 H, *J* = 7.0, 7.0, 17.0 Hz), 4.03 (m, 1 H), 4.19 (dd, 1 H, *J* = 5.0, 11.5 Hz), 4.40 (ddd, 1 H, *J* = 0.5, 4.0, 11.5 Hz), 4.72 (br s, 1 H); MS (SIMS) *m/z* 216 $(M + H)^+$, 160, 116. Anal. Calcd for $C_{10}H_{17}O_4N$: C, 55.80; H, 7.96; N, 6.51. Found: C, 55.81; H, 8.03; N, 6.36.

(5*S*)-5-(*N*-(*tert*-Butoxycarbonyl)amino)-5,6-dihydro-2-pyrone (19). To a solution of **18a** (3.00 g, 13.9 mmol) in THF (70 mL) was added, successively, Me_3SiCl (3.85 mL, 30.7 mmol) and lithium hexamethyldisilazide (30.7 mL of a 1 *M* solution in THF, 30.7 mmol) at -78 °C. The solution was stirred for 15 min, then was added to a solution of $Pd(OAc)_2$ (3.74 g, 16.7 mmol) in CH_3CN (80 mL). The mixture was stirred at room temperature for 45 min and then quenched with aqueous NH_4Cl. The resulting suspension was filtered. The filtrate was concentrated *in vacuo* to give an oily residue. This was dissolved in Et_2O (100 mL), and the solution was washed with brine. The Et_2O solution was dried, and the solvent was evaporated *in vacuo* to give an oily residue. This, upon purification by column chromatography on silica gel (Et_2O/hexane, 3:1), gave **19** (2.08 g, 70%) as colorless crystals: mp 128.0–129.0 °C; $[\alpha]^{23}_D$ +113° (*c* 1.07, $CHCl_3$); IR (neat) 3340, 2988, 1724, 1686 cm^{-1}; ^1H NMR ($CDCl_3$, 100 MHz), δ 1.47 (s, 9 H), 4.2–4.6 (m, 3 H), 4.80 (br s, 1 H), 6.70 (d, 1 H, *J* = 10 Hz), 6.86 (dd, 1 H, *J* = 5, 10 Hz); MS (SIMS) *m/z* 214 $(M + H)^+$, 158, 114. Anal. Calcd for $C_{10}H_{15}O_4N$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.15; H, 7.07; N, 6.43.

(1*S*,5*S*,6*R*)-5-(*N*-(*tert*-Butoxycarbonyl)amino)-3-oxabicyclo[4.1.0]heptan-2-one (9c). To a suspension of $Pd(OAc)_2$ (21 mg, 0.094 mmol) and **19** (200 mg, 0.938 mmol) in Et_2O (30 mL) was added, drop by drop, a solution of CH_2N_2 in Et_2O at room temperature over 2 h. The mixture was then filtered. The filtrate was concentrated *in vacuo* to give an oily residue. This, upon purification by flash column chromatography on silica gel (Et_2O/hexane, 3:1), gave **9c** as colorless crystals (98 mg, 46%).

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Nuclear Magnetic Resonance Study of the Kinetics of the Penicillamine/Bis(penicillamine) Selenide Symmetrical Exchange Reaction

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The kinetics of reaction of the thiolate form of D-penicillamine (β,β-dimethylcysteine, PSH) with bis(D-penicillamine)selenide (PSSeSP) have been characterized over a wide pH range in aqueous solution by NMR line broadening techniques. Because of the steric bulk of the substituents on the β-carbon of penicillamine, the rate of nucleophilic reaction at the sulfur of PSSeSP is much less than at selenium, making it possible for the first time to characterize quantitatively the kinetics for reaction of a thiolate at the selenium of the bis(alkylthio) selenide of a biological molecule. Rate constants are reported for reaction of the amino and ammonium forms of PS^- with the various amino protonated forms of PSSeSP, e.g. the rate constant for reaction of the (NH_3^+, CO_2^-, S^-) form of PSH with the (NH_3^+, NH_3^+, CO_2^-, CO_2^-) form of PSSeSP is 9.7×10^5 L/mol·s. The PSH/PSSeSP interchange reactions are approximately 10^6 faster than the analogous reaction of 2-methyl-2-propanethiol with bis(*tert*-butylthio) selenide. The large magnitude of the rate constants suggests that nucleophilic reaction at the selenium of bis(alkylthio) selenides, which are thought to be formed initially in the incorporation of inorganic selenium into living systems, could be important in their conversion to other selenium-containing biomolecules.

Introduction

The reaction of selenious acid with thiol groups to form bis(alkylthio) selenides (or selenotrisulfides) (eq 1) is thought to be one of the principal pathways by which inorganic selenium is initially incorporated into biological systems.[1-6] Once formed, the bis(alkylthio) selenides are consumed by various reactions, although the nature of these reactions is not known. In a study of the reactivity

$$3RSH + H_2SeO_3 \rightarrow RSSeSR + RSSR + 3H_2O \quad (1)$$

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