4-Alkyl- and 4-Cinnamylglutamic Acid Analogues Are Potent GluR5 Kainate Receptor Agonists

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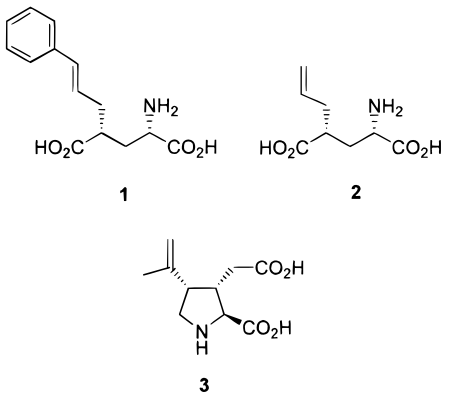
Enantiomerically pure (2*S*,4*R*)-4-substituted glutamic acids were prepared and tested for homomeric GluR5 and GluR6 kainate subtype receptor affinity. Some of the 4-cinnamyl analogues showed high selectivity and potency (K_i < 25 nM) for the GluR5 receptors. The greatest selectivity and potency were achieved with the 3-(2-naphthyl)prop-2-enyl compound. This compound, LY339434, has negligible activity at the AMPA and kainate receptors GluR1, -2, -4 and -6. Although, LY339434 shows agonist activity at NMDA receptors in cultural hippocampal neurons (approximate EC_{50} of 2.5 μM), we consider that LY339434 should be a useful pharmacological tool for the investigation of the functional role of GluR5 kainate receptors.

Introduction

L-Glutamate (Glu) is the major excitatory neurotransmitter in the mammalian central nervous system (CNS). Glutamate receptors are subdivided into ionotropic (GluRs)[1,2] and metabotropic (mGluRs) receptors.[3,4] The ionotropic receptors mediate fast synaptic transmission through ligand-gated ion channels while metabotropic receptors are G protein coupled and have a modulatory role in the CNS. Ionotropic receptors have been subdivided into three classes on the basis of their sensitivity to the ligands NMDA (*N*-methyl-D-aspartate), KA (kainate), and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate), from which they take their names.[5] Expression studies have recently verified that there are further subtypes for each of the aforementioned ionotropic receptors. Five distinct kainate binding proteins have been identified: GluR7, KA1, and KA2 show high affinity for kainate, and GluR5 and -6 show low affinity.[6−13] GluR5, -6 and -7, when expressed homomerically, can form functional ion channels activated by kainate, domoate, or glutamate. By contrast, KA1 or KA2 expressed in homomeric form do not appear to form functional channels. Selective kainate receptor ligands are expected to exhibit distinct pharmacological effects since individual receptor proteins show different distributions within the CNS.[3,14] Recent studies have identified ligands which show selectivity for kainate receptors including ATPA,[15] 5-iodowillardiine,[16] and (2*S*,4*R*)-4-methyl glutamate.[17,18] All of them exhibit high-affinity binding and functional activity at GluR5 kainate receptors. However, none of them are completely selective for kainate. In an earlier paper, we reported that the 4-substituted glutamate analogue LY339434 is a potent homomeric hGluR5 receptor agonist.[19] In this paper we describe the structure−activity relationships for a number of 4-alkyl- and 4-cinnamyl glutamate analogues that are potent GluR5 agonists and show selectivity over other kainate and AMPA receptors examined.

Scheme 1



In an early unpublished study, we found that the 2*S*,4*R* isomers of 4-cinnamyl- (**1**) and 4-allylglutamate (**2**) were active in a tritium-labeled kainate binding assay using a rat forebrain membrane preparation. With the availability of both homomeric hGluR5 and -6 expressing cell lines we decided to retest compounds **1** and **2** since the radioligands themselves were nonselective (many analogues of kainic acid (**3**)) (Scheme 1).[20] Thus, compounds **1** and **2** showed promising subtype selectivity, having at least 30 times greater affinity for hGluR5 than hGluR6 receptors. A highly subtype selective GluR5 ligand would be a very valuable pharmacological tool for the characterization of this receptor. We therefore set out to further improve the selectivity and potency of these ligands. Although we cannot extrapolate the results for homomeric receptors to all kainate receptors found in neuronal tissues, we were able to demonstrate the functional agonist activity of compounds at rat dorsal root ganglion neurons, neurons thought to express GluR5 kainate receptors.

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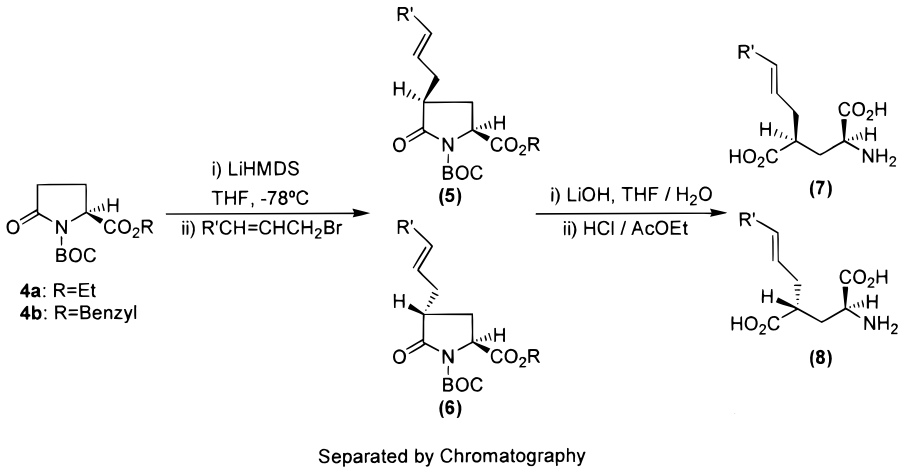
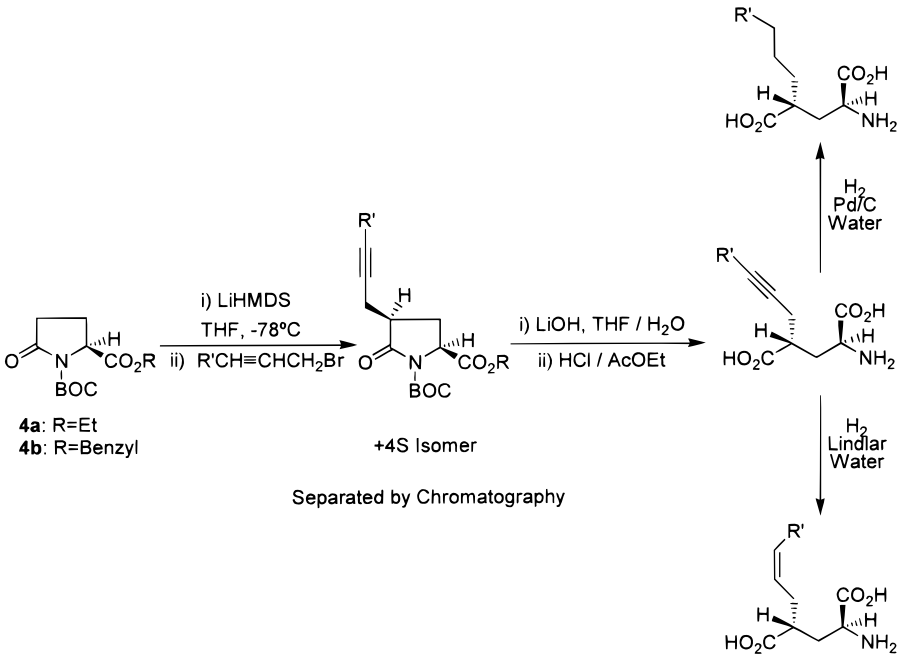
Scheme 2



Scheme 3



Chemistry

The syntheses of (2*S*,4*R*)- and (2*S*,4*S*)-4-substituted glutamic acids (**1**, **2**, **7**, and **8**) were stereoselectively achieved starting from *N*-Boc protected pyroglutamate esters **4** (Scheme 2). Thus, selective generation of the pyroglutamate lactam enolate with LiHMDS in THF at −78 °C and reaction with activated electrophiles (cinnamyl halides) gave rise to thermodynamic equilibrium mixtures of both 4-substituted pyroglutamates **5** and **6**, in moderate to good yields, without affecting the pyroglutamate stereogenic center[21] (Scheme 2). With allyl and propargyl bromides (Scheme 3), we found it necessary to carry out inverse addition of the enolate to 4 equiv of the electrophile. The mixture of diastereomers could then generally be separated by chromatography and their stereochemistry established by NMR (see ref 21 for a detailed discussion). Subsequent deprotection of the individual isomers **5** and **6** yielded the corresponding free amino acids **7** and **8** (Scheme 2). The optical purity of the final amino acids was determined by chemical correlation (see ref 21 for more information).

The procedure used for the final deprotection was dependent on the nature of the substituent at the 4-position. In the case of the cinnamyl derivatives, direct hydrolysis with hydrochloric acid was satisfactory. However, where the 4-substituent had an isolated double bond, it was found that either the hydrochloric acid itself or the 4-carboxy group would add across the bond during the vigorous acid hydrolysis. This problem was overcome by using a two-step hydrolysis procedure, whereby the lactam and ester were cleaved using LiOH in aqueous THF and the BOC group was finally removed under milder acid conditions at room temperature. Even this modified procedure was unsatisfactory for the compounds having electron-rich trisubstituted double bonds. In this case the BOC group of the lactam **5** and **6** was removed thermally, and the lactam and esters were cleaved using aqueous sodium hydroxide. The disadvantage of this latter procedure was that some epimerization occurred.

Attempts to couple phenyl propargyl bromide with protected pyroglutamate failed, so this compound was

prepared by coupling the terminal acetylene with iodobenzene in the presence of a palladium catalyst to give **30**. The cis olefins were prepared by hydrogenation of the acetylenic amino acid in water using Lindlar catalyst. The saturated compounds were prepared by hydrogenation of the acetylenic amino acid using 10% Pd on carbon catalyst at 60 psi (Scheme 3).

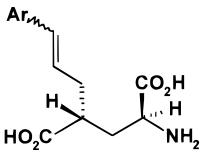
Pharmacology Methods

Ligand Binding Studies at AMPA and Kainate Receptors Expressed in HK293 Cells. Cell membranes were prepared from frozen HEK293 cells expressing either recombinant AMPA[22,23] or kainate[12,13] receptors by resuspending the cells in ice cold distilled water, sonicating, and centrifuging at 50 000*g* for 20 min. The membrane pellets were then washed in >100 × volumes of 50 mM Tris-HCl buffer (pH 7.5) and centrifuged to remove endogenous glutamate. Binding reactions were performed at 4 °C for 60 min in a total volume of 250 μL containing 50 μL of membrane suspension (100−150 μg of protein). For kainate receptor binding (hGluR5 or hGluR6), the reaction mixture consists of 150 μL of 50 mM Tris-HCl (pH 7.5), 25 μL of [^{3}H]-KA (DuPont NEN), and 25 μL of unlabeled competitor (10^{-12}−10^{-3} M). The final [^{3}H]-kainate concentration used in the competitive inhibition experiments was 20 nM. For AMPA binding experiments (hGluR1, hGluR2, or hGluR4), 20 nM [^{3}H]-AMPA (DuPont NEN) was used for each receptor subtype and 100 mM KSCN was added to the Tris-HCl buffer. Following the 60 min incubation, the membranes were centrifuged at 50 000*g* for 20 min to separate bound from free ligand and the pellets washed three times in cold assay buffer. Nonspecific binding was determined by incubation in the presence of 1 mM glutamate. All data were analyzed by GRAFIT 2.0 software.

Electrophysiological Recordings Using HEK293. Whole-cell voltage clamp recordings were made from HEK293 cells stably transfected with hGluR5 or hGluR6 as previously described.[12,13,24] Drugs were applied to cells via bath perfusion with exchange of solutions occurring in less than 20 s. Experiments for both these cell lines were performed in the presence of 2.5 mM concanavalin A to prevent receptor desensitization.[15] Results are expressed as a percentage of the maximum inward current evoked by the ligand. Curve fitting to the data points was based upon the equation $y = R_{max}(D_n/(D_n + EC_{50}{}^n)$, using a slope fixed to a value of 1, where D is the drug concentration. Data for each point were obtained from a minimum of four separate cells.

Electrophysiological Recording in DRG Neurons. Whole-cell voltage clamp recordings were made (Vh = −70 mV) from acutely isolated dorsal root ganglion neurons that were prepared as previously described.[25] All cells were pretreated with 10 mM concanavalin A for 10 min prior to agonist applications. Under these conditions, agonist-induced desensitization is irreversibly removed, and subsequent experiments were performed in the absence of concanavalin A. Comparison of agonist efficacy relative to kainate was obtained by constructing concentration−relationship curves and comparing steady-state current magnitudes to those of 100 μM kainate in the same cell. Data shown represent the mean of at least three values for each concentration obtained from separate cells. Curve fitting was performed as described above.

Table 1. hGluR5 and hGluR6 Binding Data for the Cinnamyl Series (calculated from an 11 point concentration inhibition curve) (**1**, **9**−**33**)

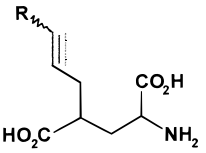


compd no.	Ar	stereochemistry	K_i, nM hGluR5	K_i, nM hGluR6	ratio hGluR6/hGluR5
1	Ph	*E*	44	1580	36
9	Ph	*Z*	157	339	2
10 LY339296	2-OMe-Ph	*E*	26	59	2
11	3-OMe-Ph	*E*	40	6349	161
12	4-OMe-Ph	*E*	284	22340	79
13	2-Cl-Ph	*E*	254	1404	6
14	3-Cl-Ph	*E*	60	1132	19
15 LY339295	4-Cl-Ph	*E*	8	3859	504
16	4-Br-Ph	*E*	30	7216	241
17	4-Me-Ph	*E*	172	4375	28
18	4-F-Ph	*E*	78	559	7
19	4-CF_3-Ph	*E*	52	43929	841
20	4-SMe-Ph	*E*	32	6024	191
21	4-i-Pr-Ph	*E*	58	27532	476
22	4-CN-Ph	*E*	367	4491	12
23	4-CO_2H-Ph	*E*	3590	27280	8
24	4-NO_2-Ph	*E*	59	3845	65
25	4-OCF_3-Ph	*E*	254	11185	44
26	4-Ph-Ph	*E*	133	5650	42
27	3,4-DiCl-Ph	*E*	49	3987	81
28	3,4-DiOMe-Ph	*E*	540	13949	26
29	2,6-DiCl-Ph	*E*	131	1568	12
30	Ph	acetylene	337	1000	3
31	Ph	saturated	1190	>10000	>9
32 LY339434	2-naphthyl	*E*	14	13723	980
33	1-naphthyl	*E*	7	4366	605

Results and Discussion

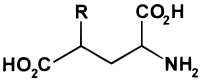
The prepared compounds can be classified in three different categories: the cinnamyl, the straight chain aliphatic, and the branched aliphatic compounds shown in Table 1, 2 and 3, respectively. In all of them the activity resided in the 2*S*,4*R* stereoisomer. In the cinnamyl series (Table 1) it was found that the introduction of a 4-chloro group (**15**) markedly increased the selectivity and potency for the hGluR5 receptor compared to the parent compound **1**. The general trend was that electron-withdrawing groups in the 4-position of the phenyl ring, at least, kept the same range of activity. However, attempts to further enhance the activity with more powerful mesomeric electron-withdrawing groups e.g. the nitrile **22** and the nitro **24** led to a decrease in activity. Another interesting finding was that an ortho substituent on the phenyl ring reduced the selectivity between hGluR5 and hGluR6. This effect was most apparent with the 2-methoxy analogue **10**, where there was little or no selectivity between hGluR5 and hGluR6, but the effect was also detectable with the 2-chloro (**13**) and 2,6-dichloro (**29**) analogues. A similar loss of selectivity was also found with the *Z* isomer **9** and compound **52** with a methyl group. These results may suggest that planarity enhances hGluR5 selectivity. However, there were also some compounds which might be expected to be planar (e.g. 4-F, 4-CN, and 4-CO_2H) which also showed little selectivity, so there may be

Table 2. hGluR5 and hGluR6 Binding Data for the Alkyl Series (calculated from an 11 point concentration inhibition curve) (**34**−**48**)



compd no.	R	stereochemistry	K_i, nM hGluR5	K_i, nM hGluR6	ratio hGluR6/ hGluR5
34	H	2*S*,4*R* acetylene	11.6	160	14
35	H	2*S*,4*R* acetylene	307	823	3
36	Me	2*S*,4*R* acetylene	28.9	1456	50
37	Et	2*S*,4*R* acetylene	831	10247	12
38	nPr	2*S*,4*R* acetylene	3606	68547	19
39 LY310214	H	2*S*,4*R* olefin	48	1840	38
40	H	2*S*,4*R* olefin	1300	13800	11
41	Me	2*S*,4*R*,*Z* olefin	577	5373	9
42	Et	2*S*,4*R*,*Z* olefin	160	22529	141
43 LY339180	Me	2*S*,4*R*,*Z* olefin	21	3258	155
44	Et	2*S*,4*R*,*E* olefin	161	2984	19
45	Cl	2*S*,4*R*,*E* olefin	41	2893	71
46	H	2*S*,4*R* saturated	123	2450	20
47	Et	2*S*,4*R* saturated	267	41152	154
48	nPr	2*S*,4*R* saturated	2376	7207	3

Table 3. hGluR5 and hGluR6 Binding Data for **49**−**52** (calculated from an 11 point concentration inhibition curve)



Compound No	R	Stereo chemistry	hGluR5 Ki nM	hGluR6 Ki nM	Ratio hGluR6/hGluR5
49		2S, 4S/R	1015	42809	42
50		2S, 4S/R	1464	8250	6
51		2S, 4R	670	500	0.75
52	Me	2S, 4R	3	10	3.3

other factors at work here. Compound **31**, in which the double bond was removed, was markedly less potent at hGluR5, as were both the *Z* olefin **9** and acetylene **30**. The greatest selectivity was achieved with the 2-naphthyl compound **32** (LY339434) which showed nearly 1000-fold selectivity for hGluR5 over hGluR6.

In the three aliphatic series, saturated, olefinic, and acetylenic (Table 2), it was found that for R = H the saturated analogue **46** was less active than the equivalent olefinic compound **39**; however, the acetylenic compound **34** was the most active. In the three series the optimum activity occurred with three- or four-carbon atom chains, with a gradual fall off of activity with increasing chain length. Selectivity between GluR5 and GluR6 did vary between the three classes of compounds and with chain length; however, none of the compounds achieved the high selectivity seen with the cinnamyl series. The *E* olefin **43** is more potent and selective that the *Z* isomer **41** when R = Me. However, for R = Et the affinity for the *E* olefin **44** is just the same as that for the *Z* isomer **42**, and the selectivity is reversed. So no clear conclusion can be drawn. Surprisingly, considering the structure of the aliphatic side chain in kainic acid, the trisubstituted olefin **49** (Table 3) was less active than the related disubstituted analogue **43**. It should also be noted that reducing the electron density on the olefin with a chloro group **50** was not beneficial, which is a surprise in the light of the SAR for the cinnamyl series. The previously reported kainate ligand 4-methylglutamate[17,18] **52** was very potent in our hands (hGluR5, K_i = 3 nM) but showed little selectivity (hGluR6, K_i = 10 nM) (Table 3).

In Table 4, we report the binding profiles for three of the more interesting compounds from the cinnamyl series along with the figures for glutamate and kainate. It should be noted that the three new compounds have K_i values of greater than 10 μM on the AMPA receptors GluR1, -2 and -4, making them more selective for kainate receptors than kainate itself. Compounds **15** and **32**, which show greater selectivity between hGluR5 than hGluR6, do have significant hGluR7 activity (K_i = 423 and 617 nM, respectively). The 2-OMe derivative **10** shows no selectivity among hGluR5, -6, and -7, but still lacks AMPA and KA2 activity. Compound **10** could thus be a tool for distiguishing the effects of homomeric GluR5, -6, and -7 compared with homomeric KA2 in biological systems. However, we cannot know to what extent this can be extrapolated to biological heteromeric systems. Additionally, compound **32**, LY339434, was shown to have activity at NMDA receptors with EC_{50} values of 2.5 μM in cultured hippocampal neurons. The functional NMDA receptor activity of the other compounds in this series remains to be evaluated.

In Table 5, we report the electrophysiology data using hGluR5 and -6 expressing cells and acutely isolated rat DRG cells. On the hGluR5 expressing cells the new compounds are all agonists having R_{max} values between 65 and 95% of that observed with kainic acid. On the hGluR6 expressing cells the compounds were again agonists having R_{max} values in the range 110−153% that of kainic acid. It should also be noted that the EC_{50} values are consistently higher than the binding K_i values; however, the rank order of potency is very similar. The data with the DRG cells closely parallels that seen with the hGluR5 expressing cells but not that seen with the hGluR6 expressing cells. We believe these results provide additional evidence that native DRG neurons functionally express GluR5 kainate receptors. Figures 1 and 2 show typical dose−response curves for the compounds listed in Table 4.

Conclusions

The choice of 4-substituent on glutamic acid can profoundly effect the activity of the ligand at hGluR5 and -6 receptors. Although it was not possible to fully understand the structure−activity relationship, we have identified compounds with large planar substituents (compounds **15**, LY339434, and **33**) that can provide very useful selectivity between hGluR5 and -6 receptors. LY339434 has the advantage of no activity at the AMPA receptors hGluR1, 2, and 4, although it showed some NMDA activity.

LY339434 should be a useful pharmacological tools for the investigation of the role of GluR5 receptors in both normal and diseased states. Preliminary studies show that LY339434 does cross the blood−brain barrier following intraparitoneal administration, and its in vivo pharmacology is now being investigated.

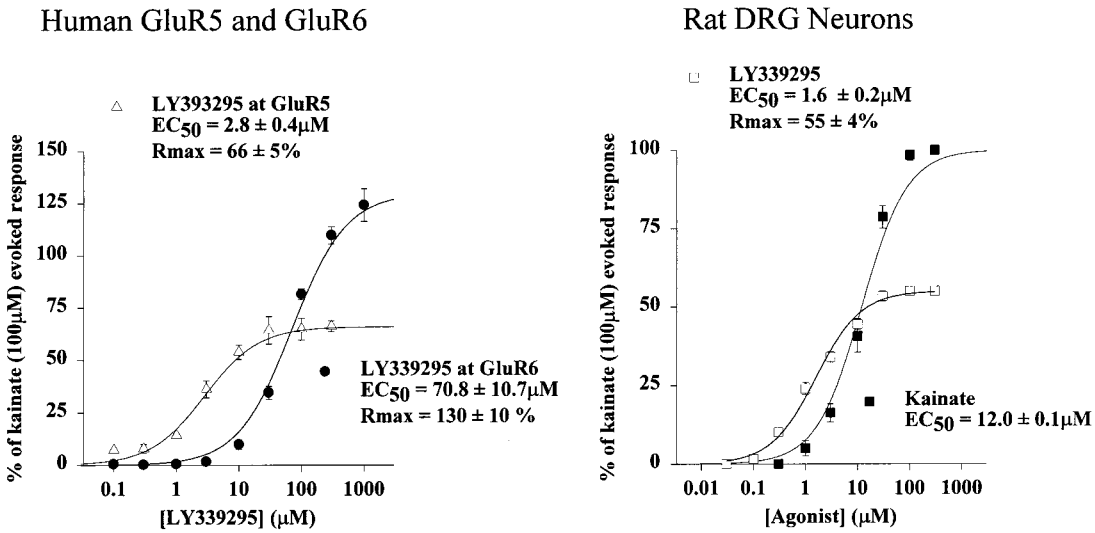


Figure 1. (Left) Concentration−response curves for inward currents evoked by LY339295 at either GluR5 (Δ) or GluR6 (●) expressing HEK293 cells using whole voltage clamp electrophysiology. Approximate R_{max} values and EC_{50} values were generated from the curves for data expressed as a percentage of responses evoked by 100 μM kainate in the same cells. (Right) Concentration−response curves in acutely isolated rat DRG neurons produced by LY339295 (△) and kainate (■).

Table 4. Binding Profiles through the AMPA/Kainate Subreceptors

	K_i, nM[a]						
compd	GluR1	GluR2	GluR4	GluR5	GluR6	KA2	GluR7
kainate (**3**)	7449 ± 2018 (3)	12221 ± 2744 (4)	1714 ± 170 (3)	177 ± 22 (3)	32 ± 13 (4)	8 ± 2 (5)	10 ± 2 (3)
glutamate	1362 ± 257 (3)	940 ± 93 (3)	868 ± 219 (3)	701 ± 46 (3)	1106 ± 159 (3)	750 ± 77 (3)	789 ± 83 (3)
LY339295 (**15**)	>10000 (1)	>10000 (1)	>10000 (1)	8 ± 1 (3)	4649, 3069 (2)	>10000 (1)	423 (1)
LY339296 (**10**)	>10000 (1)	>10000 (1)	>10000 (1)	30 ± 13 (3)	48 ± 4 (3)	>10000 (1)	42 (1)
LY339434 (**32**)	>10000 (1)	>10000 (1)	>10000 (1)	15 ± 13 (2)	15406, 12040 (2)	>10000 (1)	617 (1)

[a] In parentheses are the number of replicates.

Table 5. Electrophysiology Data for Selected Compounds

	hGluR5[a]			hGluR6[a]			DRG neurons[a]	
compd	K_i, nM	EC_{50}, μM	R_{max}, %	K_i, nM	EC_{50}, μM	R_{max}, %	EC_{50}, μM	R_{max}, %
kainate (**3**)	177 ± 22 (3)	16.2 ± 1.0 (4)	100	32 ± 13 (4)	0.7 ± 0.1 (6)	100	12.0 ± 0.1 (4)	100
glutamate	701 ± 46 (3)	75.0 ± 7.5 (15)	79 ± 2 (15)	1106 ± 159 (3)	25.0 ± 2.0 (8)	nd	35.2 ± 0.2 (5)	51 ± 10 (5)
LY310214 (**39**)	56, 38 (2)	4.4, 3.7 (2)	65, 96 (2)	1840 (1)	8.3 ± 2.7 (3)	>110 (1)	nd	nd
LY339180 (**43**)	21 ± 3 (3)	4.5 ± 0.8 (6)	86 ± 2 (6)	3258 (1)	58.3 ± 4.2 (4)	138 ± 5 (4)	nd	nd
LY339295 (**15**)	8 ± 1 (3)	2.8 ± 0.4 (6)	66 ± 5 (6)	4649, 3069 (2)	70.8 ± 10.7 (5)	130 ± 10 (5)	1.6 ± 0.2 (4)	55 ± 4 (4)
LY339434 (**32**)	15, 13 (2)	2.5 ± 0.9 (3)	80 ± 1 (3)	15406, 12040 (2)	>100 (5)	nd	0.8 ± 0.2 (6)	57 ± 5 (6)
LY339296 (**10**)	30 ± 13 (3)	3.3 ± 0.4 (3)	95 ± 2 (3)	48 ± 4 (3)	1.3 ± 0.6 (5)	153 ± 2 (5)	nd	nd

[a] In parentheses are the number of replicates.

Experimental Section

Materials and Methods. All solvents and reagents were purchased from commercial sources and used as received, unless otherwise indicated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. All reactions were performed under a positive pressure of argon or nitrogen. ^{1}H NMR and ^{13}C NMR data were recorded on a Bruker AC-200P or Bruker AC-300. IR spectra were obtained on a Nicolet 510 P-FT (film and KBr). High-resolution mass spectra (HRMS) were measured on a VG-Autospec spectrometer. Melting points were determined on a Büchi apparatus and are not corrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter. Analytical TLC was performed on Merck TLC glass plates precoated with F_{254} silica gel 60 (UV, 254 nm and iodine). Chromatographic separations were performed by using 230−400 mesh silica gel (Merck). Elemental analyses were performed by the Universidad Complutense Analytical Centre (Facultad de Farmacia) Madrid.

General Procedure for Preparation of Cinnamyl Bromides. To a −78 °C solution of the corresponding aldehyde (12.8 mmol) in THF (40 mL) was added a 1 M solution of vinylmagnesium bromide in ethyl ether (14.8 mmol) under nitrogen atmosphere. The mixture was warmed to −40 °C and stirred for 2 h. A saturated ammonium chloride solution was added and the aqueous layer was extracted three times with ether. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (8 mL) and 48% HBr (25.6 mmol) and 98% H_2SO_4 (12.8 mmol) were added. The mixture was heated at 60 °C for 30 min. The reaction mixture was washed with a saturated $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The cinnamyl bromide were used without further purification.

Cinnamyl Derivatives (Table 1). General Procedure for Alkylation Reactions of Ethyl or Benzyl *N*-BOC Pyroglutamate Esters with Cinnamyl Bromides. To a solution of pyroglutamate (**4a** or **4b**) (7.77 mmol) in THF (40 mL) stirred at −78 °C was added a 1 M solution of lithium hexamethyldisilazide in THF (8.55 mL, 8.55 mmol, 1.1 equiv). After the reaction mixture was stirred at −78 °C for 1 h, the corresponding cinnamyl bromide (9.30 mmol, 1.2 equiv) in THF (10 mL) was added and stirring continued for 2 h. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL) at −78 °C and extracted with ethyl

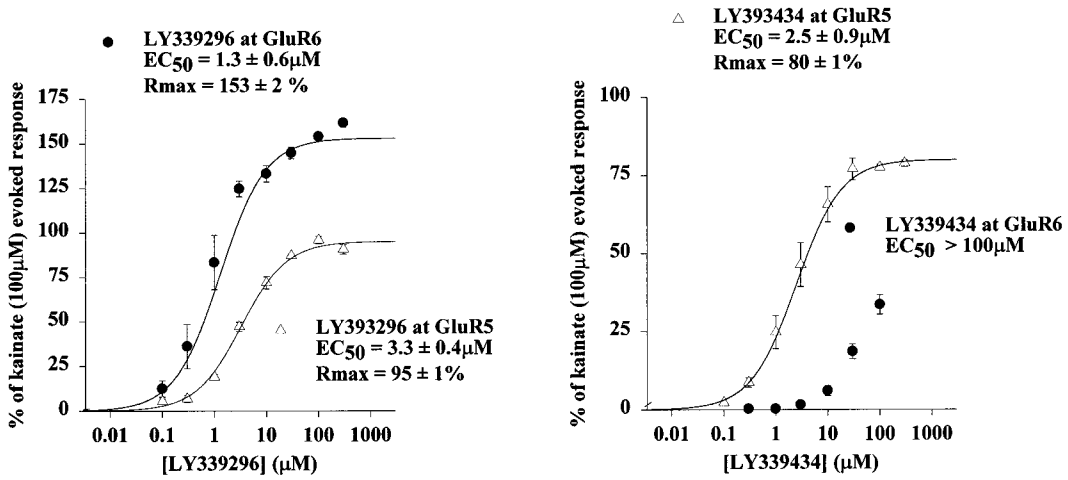


Figure 2. (Left) Concentration−response curves for inward currents evoked by LY339296 at either GluR5 (△) or GluR6 (●) expressing HEK293 cells using whole voltage clamp electrophysiology. Approximate R_{max} values and EC_{50} values were generated from the curves for data expressed as a percentage of responses evoked by 100 μM kainate in the same cells. (Right) Comparison of LY339434 at either GluR5 (△) or at GluR6 (●) expressing HEK293 cells.

ether (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated to dryness. The diastereomers were separated by flash column chromatography using EtOAc/hexane 1:4 as eluent.

General Procedure for the Hydrolysis of 4-Substituted Ethyl or Benzyl *N*-BOC Pyroglutamate Esters. To a solution of the title compounds (2 mmol) in THF (15 mL) was added a 2.5 N aqueous solution of LiOH (14.4 mL, 36 mmol). The mixture was stirred at room temperature for 4 h and then acidified to pH 2 with 1 N HCl solution and extracted with ethyl ether (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give an oily residue which was reacted with a saturated HCl solution in ethyl acetate for 1 h at room temperature. The resulting white solid was triturated with ethyl ether (3 × 20 mL). The final amino acids were isolated as zwitterions by treatment of a methanolic solution of the corresponding hydrochloride with propylene oxide.

Ethyl (2*S*,4*R*,*E*)-*N*-BOC-4-cinnamylpyroglutamate: Hexane/ethyl acetate 3:1. colorless oil. 54% yield. $[\alpha]_D = -33.3$ (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.28−7.09 (m, 5H), 6.37 (d, J = 15.8 Hz, 1H), 6.05 (dt, J = 7.1 and 15.8 Hz, 1H), 4.46 (dd, J = 0.7 and 9.1 Hz, 1H), 4.13 (q, J = 7.2 Hz, 2H), 2.28−2.60 (m, 2H), 2.40−2.20 (m, 1H), 2.20−1.90 (m, 2H), 1.42 (s, 9H), 1.20 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 174.0, 170.8, 148.9, 136.5, 132.5, 128.1, 127.0, 125.7, 125.4, 83.0, 61.2, 56.7, 41.1, 33.1, 27.4, 27.2, 13.8. IR (film): 2980, 1790, 1748, 1317, 1205 cm^{-1}. Anal. ($C_{21}H_{27}NO_5$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-(3-phenylprop-2-enyl)pentanedioic acid (1): 54% yield. Mp: 158−160 °C. $[\alpha]_D = +24.2$ (*c* 0.24, 1 N NaOH). ^{1}H NMR (TFA−acetone-d_6): δ 7.12−6.97 (m, 5H), 6.32 (d, J = 15.8 Hz, 1H), 6.03−5.88 (td, J = 3.0 and 15.8 Hz, 1H), 4.45−4.38 (dd, J = 4.5 and 7.8 Hz, 1H), 2.91−2.87 (m, 1H), 2.62−2.37 (m, 3H), 2.29−2.18 (m, 1H). Anal. ($C_{14}H_{17}NO_4 \cdot H_2O$) C, H, N.

(2*S*,4*R*,*Z*)-2-Amino-4-(3-phenylprop-2-enyl)pentanedioic acid (9): 43% yield. Mp: 143−5 °C. $[\alpha]_D = +12.0$ (*c* 0.15, DMSO). ^{1}H NMR (D_2O−KOD): δ 7.50−7.30 (m, 5H, Ph), 6.55 (d, J = 11.8 Hz, 1H), 5.70 (dt, J = 11.8 and 3.9 Hz, 1H), 3.15 (dd, 1H, J = 9.4 and 4.4 Hz, H-2), 2.60−2.40 (m, 3H), 2.00−1.84 (m, 1H), 1.61−1.47 (m, 1H). ^{13}C NMR (D_2O/MeOH-d_4−KOD): δ 185.0, 183.9, 138.4, 131.7, 130.6, 129.9, 129.5, 128.0, 55.6, 47.4, 39.6, 33.0. IR (KBr): 3447, 2851, 1695, 1585 cm^{-1}. Anal. ($C_{14}H_{17}NO_4 \cdot H_2O$) C, H, N.

Benzyl (2*S*,4*R*,*E*)-*N*-BOC-4-(2-methoxycinnamyl)pyroglutamate: 23% yield. EtOAc/hexane 1:3. ^{1}H NMR ($CDCl_3$): δ 7.41−7.12 (m, 7H), 6.91−6.71 (m, 3H), 6.06 (dt, 1H, J = 15.5 and 7.0 Hz, HC=), 5.16 (AB, 2H, CO_2CH_2), 4.55 (dd, 1H, J = 9.3 and 1.2 Hz, H-2), 3.77 (s, 3H, OCH_3), 2.81−2.65 (m, 2H), 2.44−1.92 (m, 3H), 1.39 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$): δ 174.0, 170.7, 155.8, 148.8, 141.0, 134.6, 128.1 (2C), 128.0 (2C), 127.1, 126.6, 126.0, 125.7, 125.4, 120.1, 110.3, 82.9, 66.7, 59.8, 56.6, 54.8, 41.1, 27.2 (3C), 27.1. Anal. ($C_{27}H_{31}NO_6$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(2-methoxyphenyl)prop-2-enyl]-pentanedioic acid (10): 29% yield. Mp: 171−2 °C. $[\alpha]_D = +4.25$ (*c* 0.4, DMSO). ^{1}H NMR (D_2O/KOD): δ 7.12 (d, 1H, J = 7.2 Hz), 6.92 (t, 1H, J = 8.0 Hz), 6.68−6.60 (m, 2H), 6.33 (d, 1H, J = 15.0 Hz, HC=), 5.89 (dt, 1H, J = 15.0 and 6.9 Hz, HC=), 3.47 (s, 3H, OCH_3), 2.83 (dd, 1H, J = 8.6 and 4.0 Hz, H-2), 2.15−1.96 (m, 3H), 1.62−1.48 (m, 1H), 1.27−1.12 (m, 1H). ^{13}C NMR (D_2O/MeOH-d_4/KOD): δ 183.0, 182.0, 154.8, 129.3, 127.7, 125.8, 125.5, 124.3, 120.5, 111.2, 54.9, 53.8, 45.2, 37.4, 35.8. IR (KBr): 3036, 1686, 1574, 1244 cm^{-1}. Anal. ($C_{15}H_{19}NO_5 \cdot H_2O$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(3-methoxyphenyl)prop-2-enyl]-pentanedioic acid (11): 45% yield. Mp: 148−150 °C. $[\alpha]_D = +17.6$ (*c* 0.3, pyridine). ^{1}H NMR (D_2O/KOD): δ 6.92 (t, 1H, J = 7.8 Hz) 6.70−6.64 (m, 2H), 6.49 (dd, 1H, J = 8.0 and 2.3 Hz), 6.08 (d, 1H, J = 15.9 Hz, HC=), 5.91 (dt, 1H, J = 15.9 and 6.5 Hz, HC=), 3.44 (s, 3H, OCH_3), 2.82 (dd, 1H, J = 9.3 and 4.5 Hz, H-2), 2.15−1.95 (m, 3H), 1.61−1.48 (m, 1H), 1.25−1.11 (m, 1H). IR (KBr):: 1699, 1581, 1489, 1261 cm^{-1}. Anal. ($C_{15}H_{19}NO_5 \cdot H_2O$) C, H, N.

Ethyl (2*S*,4*R*,*E*)-*N*-BOC-4-(4-methoxycinnamyl)pyroglutamate: 30% yield. EtOAc/hexane 1:4. A pale yellow oil. $[\alpha]_D = -18.3$ (*c* 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.18 (d, J = 8.7 Hz, 2H), 6.76 (d, J = 8.7 Hz, 2H), 6.31 (d, J = 15.8 Hz, 1H), 5.90 (dt, J = 14.4 and 7.3 Hz, 1H), 5.19 (s, 2H), 4.47 (dd, J = 1.9 and 9.0 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.72 (s, 3H), 2.85−2.59 (m, 2H), 2.40−1.92 (m, 3H), 1.42 (s, 9H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 174.4, 171.2, 158.9, 149.2, 132.3, 129.6, 127.1, 123.3, 113.8, 83.4, 61.6, 57.1, 55.2, 41.6, 33.4, 27.7, 14.0. IR (film): 1790, 1748, 1512, 1316, 1250, 1154. Anal. ($C_{22}H_{29}NO_6$) C, H, N.

(2*S*,4*R*,6*E*)-2-Amino-4-[3-(4-methoxyphenyl)prop-2-enyl]-pentanedioic acid (12): 15% yield. Mp: 159 °C (dec). $[\alpha]_D = +25.0$ (*c* 0.08, 12N HCl). ^{1}H NMR (D_2O−KOD): δ 7.00 (d, J = 8.5 Hz, 2H), 6.55 (d, J = 8.5 Hz, 2H), 6.03 (d, J = 16.0 Hz, 1H), 5.75 (dt, J = 6,5 and 16.0 Hz, 1H), 3.40 (s, 3H), 2.78 (dd, J = 4.5 and 9.1 Hz, 1H), 2.10−1.90 (m, 3H), 1.50 (m, 1H), 1.15 (m, 1H). ^{13}C NMR (MeOH-d_4/Pyr-d_5/KOD): δ 184.2, 183.0, 160.1, 132.0, 131.6, 128.2, 127.8, 114.8, 56.4, 55.8, 47.8, 40.6, 38.6. IR (KBr): 3420, 1703, 1586, 1512, 1246 cm^{-1}. Anal. ($C_{15}H_{19}NO_5 \cdot H_2O$) C, H, N.

Benzyl (2*S*,4*R*,*E*)-*N*-BOC-4-(2-chlorocinnamyl)pyroglutamate: 53% yield. EtOAc/hexane 1:4. White solid. Mp: 82−4 °C. $[\alpha]_D = -31.0$ (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.47−7.13 (m, 4H), 7.33 (s, 5H), 6.78 (d, J = 15.8 Hz, 1H), 6.08 (dt, J = 14.4 and 7.2 Hz, 1H), 5.18 (s, 2H), 4.59 (dd, J = 1.9 and 9.2 Hz, 1H), 2.91−2.70 (m, 2H), 2.51−2.02 (m, 3H),

1.40 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.2, 171.1, 149.3, 135.0, 132.6, 129.6, 128.7, 128.5, 126.8, 83.7, 67.4, 57.1, 41.4, 33.6, 27.8. IR (KBr): 1780, 1734, 1306 cm^{-1}. Anal. ($C_{26}H_{28}ClNO_5$) C, H, N.

(2*S*,4*R*,6*E*)-2-Amino-4-[3-(2-chlorophenyl)prop-2-enyl]-pentanedioic acid (13): 20% yield. Mp: 140−1 °C. $[\alpha]_D$ = +8.5 (*c* 0.42, DMSO). ^{1}H NMR (pyr-d_5−D_2O): δ 7.25 (m, 1H), 7.6−7.3 (m, 3H), 6.95 (d, *J* = 16.2 Hz, 1H), 6.44 (m, 1H), 4.19 (dd, *J* = 3.5 and 9.2 Hz, 1H), 3.10−2.25 (m, 5H). ^{13}C NMR (pyr-d_5−D_2O): δ 181.7, 174.0, 134.5, 131.3, 130.5, 128.9, 127.9, 127.0, 126.6, 126.4, 53.0, 44.4, 35.8, 32.2. IR (KBr): 3400, 1699, 1584, 1418, 1200 cm^{-1}. Anal. ($C_{14}H_{16}ClNO_4\cdot H_2O$) C, H, N.

Benzyl (2*S*,4*R*,*E*)-*N*-BOC-4-(3-chlorocinnamyl)pyroglutamate: 50% yield. EtOAc/hexane 1:7. ^{1}H NMR ($CDCl_3$): δ 7.35 (broad s, 5H), 7.30−7.13 (m, 4H), 6.36 (d, 1H, *J* = 15.8 Hz, HC═), 6.11 (dt, 1H, *J* = 15.8 and 7.0 Hz, HC═), 5.19 (AB system, 2H, CO_2CH_2), 4.60 (dd, 1H, *J* = 9.3 and 1.8 Hz, H-2), 2.87−2.66 (m, 2H), 2.44−1.94 (m, 3H), 1.42 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$): δ 174.0, 170.9, 149.1, 138.6, 134.8, 134.2, 131.5, 129.6, 128.5 (2C), 128.4, 128.3 (2C), 127.3, 127.1, 125.8, 124.2, 83.5, 67.2, 56.9, 41.3, 33.2, 29.5, 27.6 (3C). IR (film): 1777, 1744, 1314, 1182 cm^{-1}. Anal. ($C_{26}H_{28}ClNO_5$) C, H, N.

(2*S*,4*R*,6*E*)-2-Amino-4-[3-(3-chlorophenyl)prop-2-enyl]-pentanedioic acid (14): 50% yield. Mp: 146−8 °C. $[\alpha]_D$ = +1.7 (*c* 0.41, DMSO). ^{1}H NMR (D_2O−KOD): δ 7.20−6.90 (m, 4H), 6.22−5.94 (m, 2H), 2.96 (d, *J* = 4.3 and 9.2 Hz, 1H), 2.35−2.15 (m, 3H), 1.70 (m, 1H), 1.32 (m, 1H). ^{13}C NMR (D_2O−KOD): δ 184.3, 183.4, 140.0, 134.4, 130.8, 130.6, 130.3, 127.4, 126.3, 125.0, 55.3, 46.5, 38.9, 36.8. IR (KBr): 3450, 1698, 1593, 1481, 1203 cm^{-1}. Anal. ($C_{14}H_{16}ClNO_4\cdot H_2O$) C, H, N.

Ethyl (2*S*,4*R*,*E*)-*N*-BOC-4-(4-chlorocinnamyl)pyroglutamate: 43% yield. EtOAc/hexane 1:6. Mp: 86−8 °C. $[\alpha]_D$ = −30.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.26 (s, 4H), 6.41 (dt, 1H, *J* = 15.8 and 0.9 Hz, HC═), 6.11 (dt, 1H, *J* = 15.8 and 7.0 Hz, HC═), 4.55 (dd, 1H, *J* = 9.3 and 1.9 Hz, H-2), 4.23 (q, 2H, *J* = 7.1 Hz, CO_2CH_2), 2.90−2.68 (m, 2H), 2.46−1.97 (m, 3H), 1.50 (s, 9H, $C(CH_3)_3$), 1.29 (t, 3H, *J* = 7.1 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 174.2, 171.2, 149.3, 135.3, 132.9, 131.7, 128.6 (2C), 127.3 (2C), 126.5, 83.6, 61.7, 57.0, 41.5, 33.4, 27.8 (3C), 27.7, 14.1. IR (film): 1779, 1720, 1315, 1149 cm^{-1}. Anal. ($C_{21}H_{26}ClNO_5$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(4-chlorophenyl)prop-2-enyl]-pentanedioic acid (15): 70% yield. Mp: 167−9 °C. $[\alpha]_D$ = +7.8 (*c* 0.6, DMSO). ^{1}H NMR (MeOH-d_4−KOD): δ 7.30 and 7.19 (AA′BB′, 4H), 6.42−6.17 (m, 2H, HC═), 3.20 (dd, 1H, *J* = 9.5 and 3.7 Hz, H-2), 2.57−2.41 (m, 2H), 2.36−2.24 (m, 1H), 2.08−1.94 (m, 1H), 1.25−1.44 (m, 1H). ^{13}C NMR: δ (MeOH-d_4−KOD) 184.1, 183.3, 137.9, 133.3, 131.2, 130.9, 129.5 (2C), 128.5 (2C), 56.5, 47.6, 40.6, 38.6. IR (KBr): 2999, 2924, 1697, 1585, 1491 cm^{-1}. Anal. ($C_{14}H_{16}ClNO_4\cdot H_2O$) C, H, N.

Benzyl (2*S*,4*R*,*E*)-*N*-BOC-4-(4-bromocinnamyl)pyroglutamate: 58% yield. EtOAc/hexane 1:3. White solid. Mp: 131−2 °C. $[\alpha]_D$ = − 27.5 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.33 (s, 5H), 7.17 (d, *J* = 8.5 Hz, 2H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.08 (dt, *J* = 14.2 and 7.1 Hz, 1H), 5.18 (s, 2H), 4.57 (dd, *J* = 1.8 and 9.3 Hz, 1H), 2.89−2.63 (m, 2H), 2.44−1.92 (m, 3H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.1, 171.0, 149.2, 141.7, 135.8, 134.9, 131.6, 128.6, 128.5, 127.6, 126.6, 121.1, 83.7, 67.4, 57.0, 41.4, 27.7. IR (KBr): 1779, 1738, 1316, 1188 cm^{-1}. Anal. ($C_{26}H_{28}BrNO_5$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(4-bromophenyl)prop-2-enyl]-pentanedioic acid (16): 21% yield. Mp: 158 °C (dec). $[\alpha]_D$ = +3.1 (*c* 0.65, DMSO). ^{1}H NMR (D_2O−KOD): δ 7.11 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 6.06 (d, *J* = 15.8 Hz, 1H), 5.90 (m, 1H), 3.40 (s, 3H), 2.80 (dd, *J* = 4.4 and 9.0 Hz, 1H), 2.20−1.90 (m, 3H), 1.50 (m, 1H), 1.15 (m, 1H). ^{13}C NMR (MeOH-d_4−D_2O−KOD): δ 184.9, 184.0, 137.8.1, 132.7, 131.0, 130.8, 128.9, 121.3, 55.9, 47.1, 39.5, 37.4. IR (KBr): 3420, 1698, 1586, 1487 cm^{-1}. Anal. ($C_{14}H_{16}BrNO_4\cdot H_2O$) C, H, N.

Benzyl (2*S*,4*R*,*E*)-*N*-BOC-4-(4-methylcinnamyl)pyroglutamate: 35% yield. EtOAc/hexane 1:3. White solid. Mp: 88−9 °C. $[\alpha]_D$ = − 33.1 (*c* 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.33 (s, 5H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 6.38 (d, *J* = 15.9 Hz, 1H), 6.03 (dt, *J* = 14.3 and 7.2 Hz, 1H), 5.18 (s, 2H), 4.57 (dd, *J* = 2.0 and 9.1 Hz, 1H), 2.90−2.65 (m, 2H), 2.45−1.96 (m, 3H), 2.31 (s, 3H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.3, 171.1, 149.2, 137.2, 135.0, 134.1, 132.8, 129.2, 128.6, 128.5, 126.0, 124.6, 83.6, 67.3, 57.1, 41.6, 33.4, 27.8, 27.7, 21.1. IR (KBr): 1775, 1742, 1704, 1366, 1316, 1192, 1160 cm^{-1}. Anal. ($C_{27}H_{31}NO_5$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(4-methylphenyl)prop-2-enyl]-pentanedioic acid (17): 25% yield. White solid. Mp: 155−6 °C (dec). $[\alpha]_D$ = + 42.8 (*c* 0.5, 1 N HCl). ^{1}H NMR (D_2O−pyr-d_5): δ 7.44 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.86−6.46 (m, 2H), 4.35 (dd, *J* = 3.2 and 9.5 Hz, 1H), 3.20−2.41 (m, 5H), 2.41 (s, 3H). ^{13}C NMR (D_2O−pyr-d_5): δ 184.2, 176.4, 150.2, 136.5, 133.3, 131.1, 129.0, 128.0, 126.1, 55.6, 47.2, 38.5, 34.9, 22.4. IR (KBr): 3023, 2921, 1699, 1586, 1514 cm^{-1}. Anal. ($C_{15}H_{19}NO_4$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(4-fluorophenyl)prop-2-enyl]-pentanedioic acid (18): 35% yield. Mp: 164−6 °C. $[\alpha]_D$ = +2.4 (*c* 0.42, DMSO). ^{1}H NMR (MeOH-d_4−D_2O−KOD): δ 7.45 (m, 2H), 7.10 (m, 2H), 6.50 (d, *J* = 15.9 Hz, 1H), 6.22 (m, 1H), 3.22 (dd, *J* = 4.4 and 9.3 Hz, 1H), 2.60−2.30 (m, 3H), 1.98 (m, 1H), 1.60 (m, 1H). ^{13}C NMR (MeOH-d_4−D_2O−KOD): δ 185.0, 183.9, 162.8 (d, *J* = 245 Hz, C−F), 134.8 (d, *J* = 3 Hz), 131.0, 129.5, 128.7 (d, *J* = 8.1 Hz), 116.4 (d, *J* = 21.5 Hz), 55.8, 47.2, 39.4, 37.3. IR (KBr): 3410, 1705, 1586, 1508, 1231, 1208 cm^{-1}. Anal. ($C_{14}H_{16}FNO_4\cdot H_2O$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(4-trifluoromethylphenyl)prop-2-enyl]pentanedioic acid (19): 43% yield. Mp: 166−8 °C. $[\alpha]_D$ = +17.5 (*c* 0.83, DMSO). ^{1}H NMR (MeOH-d_4−D_2O−KOD): δ 7.62 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 6.53 (d, *J* = 17.3 Hz, 1H), 6.40 (m, 1H), 3.22 (dd, *J* = 4.8 and 9.3 Hz, 1H), 2.60−2.30 (m, 3H), 1.96 (m, 1H), 1.58 (m, 1H); ^{13}C NMR (MeOH-d_4−D_2O−KOD): δ 185.0, 183.9, 142.3, 132.5, 130.9, 129.0 (c, *J* = 31.7 Hz), 127.3, 126.5 (c, *J* = 4 Hz), 125.3 (c, *J* = 267 Hz, CF_3), 55.8, 47.0, 39.4, 37.3. IR (KBr): 3410, 1705, 1586, 1327, 1169, 1124 cm^{-1}. Anal. ($C_{15}H_{16}F_3NO_4\cdot H_2O$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(4-methylthiophenyl)prop-2-enyl]pentanedioic acid (20): 42% yield. Mp: 173−4 °C (dec). $[\alpha]_D$ = +6.3 (*c* 0.52, DMSO). ^{1}H NMR (MeOH-d_4−KOD): δ 7.40 (d, *J* = 8 Hz, 2H), 7.27 (d, *J* = 8 Hz, 2H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.28 (dt, *J* = 6.5 and 16.0 Hz, 1H), 3.22 (dd, *J* = 4.2 and 9.1 Hz, 1H), 2.50 (s, 3H), 2.60−2.35 (m, 3H), 1.95 (m, 1H), 1.57 (m, 1H). ^{13}C NMR (MeOH-d_4−KOD): δ 185.0, 184.1, 137.3, 135.8, 131.4, 129.6, 127.8, 127.7, 55.9, 47.2, 39.5, 37.5, 15.9. IR (KBr): 3410, 1705, 1586, 1497, 1445, 1208 cm^{-1}. Anal. ($C_{15}H_{19}NO_4S\cdot H_2O$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(4-isopropylphenyl)prop-2-enyl]-pentanedioic acid (21): 38% yield. Mp: 163−4 °C. $[\alpha]_D$ = +2.2 (*c* 0.32, DMSO). ^{1}H NMR (MeOH-d_4−KOD): δ 7.37 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.43 (d, *J* = 15.9 Hz, 1H), 6.23 (dt, *J* = 6.5 and 15.9 Hz, 1H), 3.21 (dd, *J* = 3.9 and 9.3 Hz, 1H), 2.80 (sept, *J* = 7 Hz, 1H), 2.60−2.25 (m, 3H), 1.95 (m, 3H), 1.57 (m, 3H). ^{13}C NMR (MeOH-d_4−KOD): δ 184.9, 184.0, 149.4, 136.3, 131.8, 129.0, 127.8, 127.2, 55.9, 47.3, 39.7, 37.6, 34.0.4, 24.4. IR (KBr): 3410, 1703, 1584, 1497, 1451, 1208 cm^{-1}. Anal. ($C_{17}H_{23}NO_4\cdot H_2O$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(4-cyanophenyl)prop-2-enyl]-pentanedioic acid (22): 54% yield. Mp: 162−4 °C. $[\alpha]_D$ = +1.43 (*c* 0.28, DMSO). ^{1}H NMR (DMSO): δ 7.78 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 6.60−6.30 (m, 2H), 3.32 (m, 1H), 2.80 (m, 1H), 2.50 (m, 2H), 2.10 (m, 1H), 1.70 (m, 1H). IR (KBr): 3410, 1694, 1605, 1576, 1414 cm^{-1}. Anal. ($C_{15}H_{16}N_2O_4\cdot H_2O$) C, H, N.

Benzyl (2*S*,4*R*,*E*)-*N*-BOC-4-(4-carboxymethylcinnamyl)-pyroglutamate: 34% yield. EtOAc/hexane. Oil. $[\alpha]_D$ = −15.7 (*c* 4.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.97 (d, 2H, *J* = 8.4 Hz), 7.38 (d, 2H, *J* = 8.4 Hz), 6.45 (d, 1H, *J* = 15.8, HC═), 6.25 (dt, 1H, *J* = 15.8 and 6.9 Hz, HC═), 5.23 (AB system, 2H, *J* = 12.2 Hz, CH_2Ph), 4.61 (dd, 1H, *J* = 9.2 and 1.6 Hz, H-2), 3.91 (s, 3H), 2.87−2.71 (m, 2H), 2.48−2.02 (m, 3H), 1.42 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$): δ 174.1, 171.0, 166.8, 149.2, 141.3, 134.9, 129.8, 128.7, 128.6, 128.5, 126.0, 121.6, 83.6, 67.4, 57.0, 52.0, 41.4, 33.5, 27.7 (3C). Anal. ($C_{23}H_{29}NO_7$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(4-carboxyphenyl)prop-2-enyl]-pentanedioic acid (23): 29% yield. Mp: >200 °C. $[\alpha]_D$ = +42.1 (*c* 0.21, 1 N HCl). ^{1}H NMR (D_2O−pyr-d_5): δ 8.9 (d, *J* = 7.8 Hz, 2H), 7.56 (d, *J* = 7.8 Hz, 2H), 6.68 (d, 15.8 Hz, 1H), 6.54 (dt, *J* = 6.2 and 15.8 Hz, 1H), 4.18 (m, 1H), 3.10−2.20 (m, 5H); ^{13}C NMR (D_2O−pyr-d_5): δ 184.4, 176.7, 176.6, 141.9, 136.9, 133.1, 131.6, 127.8, 126.2, 55.6, 47.1, 38.5, 34.9. IR (KBr): 3420, 1698, 1609, 1586 cm^{-1}. Anal. ($C_{15}H_{17}NO_6$·H_2O) C, H, N.

Benzyl (2*S*,4*R*,*E*)-*N*-BOC-4-(4-nitrocinnamyl)pyroglutamate: 52% yield. Colorless oil. $[\alpha]_D$ = −37.5 (*c* 0.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 8.16 (d, *J* = 8.7 Hz, 2H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.35 (s, 5H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.34 (dt, *J* = 16.0 and 6.8 Hz, 1H), 5.20 (s, 2H), 4.61 (dd, *J* = 1.6 and 7.8 Hz, 1H), 2.90−2.70 (m, 2H), 2.55−2.30 (m, 1H), 2.30−2.00 (m, 2H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 173.5, 170.4, 150.4, 146.3, 143.0, 134.5, 130.8, 128.3, 128.2, 127.9, 127.7, 126.4, 123.6, 83.7, 67.1, 56.7, 40.9, 33.2, 27.9, 27.4. Anal. ($C_{26}H_{28}N_2O_7$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(4-nitrophenyl)prop-2-enyl]pentanedioic acid (24): 61% yield. Mp: 171−2 °C. $[\alpha]_D$ = +51.0 (*c* 1, 1 N HCl). ^{1}H NMR (D_2O−pyr-d_5): δ 8.13 (d, *J* = 7.6 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 2H), 6.80 (m, 2H), 4.37 (m, 1H), 3.30−2.50 (m, 5H). ^{13}C NMR (D_2O−pyr-d_5): δ 184.1, 176.5, 147.7, 146.6, 136.0, 131.9, 128.8, 125.8, 55.8, 47.1, 38.7, 35.2. IR (KBr): 3410, 1692, 1597, 1522, 1429, 1342 cm^{-1}. Anal. ($C_{14}H_{16}N_2O_6$·H_2O) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(4-trifluoromethoxyphenyl)-prop-2-enyl]pentanedioic acid (25): 54% yield. Mp: 168−9 °C. $[\alpha]_D$ = +2.0 (*c* 0.2, DMSO). ^{1}H NMR (MeOH-d_4−KOD): δ 7.49 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 6.51 (d, *J* = 15.9 Hz, 1H), 6.30 (m, 1H), 3.25 (dd, *J* = 4.2 and 9.3 Hz, 1H), 2.65−2.37 (m, 3H), 1.98 (m, 1H), 1.60 (m, 1H). ^{13}C NMR (MeOH-d_4−KOD): δ 184.9, 184.0, 148.8, 137.6, 130.8, 130.7, 128.5, 122.3, 121.4 (c, *J* = 250 Hz, CF_3), 55.9, 47.1, 39.5, 37.4, 34.0.4, 24.4. IR (KBr): 3410, 1705, 1584, 1508, 1275, 1219 cm^{-1}. Anal. ($C_{15}H_{16}F_3NO_5$·H_2O) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(4-phenylphenyl)prop-2-enyl]-pentanedioic acid (26): 50% yield. Mp: 192−3 °C. $[\alpha]_D$ = +13.4 (*c* 0.5, 1 N NaOH). ^{1}H NMR (D_2O−KOD): δ 7.55−7.10 (m, 9H), 6.35−5.94 (m, 2H), 2.95 (m, 1H), 2.32−2.00 (m, 3H), 1.70 (m, 1H), 1.32 (m, 1H). ^{13}C NMR (D_2O−KOD): δ 184.0, 183.0, 140.2, 139.2, 137.0, 130.5, 129.2, 127.7, 127.2, 126.8, 54.8, 46.2, 38.4, 36.4. IR (KBr): 3420, 1701, 1583, 1485, 1206 cm^{-1}. Anal. ($C_{20}H_{21}NO_4$·H_2O) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(3,4-dichlorophenyl)prop-2-enyl]-pentanedioic acid (27): 60% yield. Mp: 145−6 °C. $[\alpha]_D$ = +30.9 (*c* 0.42, DMSO). ^{1}H NMR (MeOH-d_4−D_2O−KOD): δ 7.52−7.20 (m, 3H), 6.50−6.13 (m, 2H), 3.26 (dd, *J* = 4.5 and 9.2 Hz, 1H), 2.60−2.30 (m, 3H), 1.98 (m, 1H), 1.58 (m, 1H). ^{13}C NMR (MeOH-d_4−D_2O−KOD): δ 185.0, 183.9, 138.9, 132.6, 131.7, 131.3, 130.6, 129.9, 128.6, 126.6, 55.8, 47.0, 39.4, 37.3. IR (KBr): 3436, 1696, 1588, 1474 cm^{-1}. Anal. ($C_{14}H_{15}Cl_2NO_4$·H_2O) C, H, N.

Benzyl (2*S*,4*R*,*E*)-*N*-BOC-4-(3,4-dimethoxycinnamyl)-pyroglutamate: 46% yield. EtOAc/hexane 1:3. A pale yellow oil. $[\alpha]_D$ = − 28.0 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.31 (s, 5H), 7.29−6.74 (m, 3H), 6.33 (d, *J* = 15.8 Hz, 1H), 5.94 (dt, *J* = 14.5 and 7.2 Hz, 1H), 5.16 (s, 2H), 4.56 (dd, *J* = 2.0 and 8.9 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 2.90−2.61 (m, 2H), 2.45−1.98 (m, 3H), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.3, 171.0, 149.2, 148.9, 148.5, 134.9, 132.6, 129.9, 128.6, 128.4, 123.5, 119.1, 110.9, 108.2, 83.5, 67.3, 57.1, 55.7, 41.5, 33.3, 27.6. IR (film): 1788, 1748, 1717, 1514, 1314, 1264, 1152 cm^{-1}. Anal. ($C_{28}H_{33}NO_7$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(3,4-dimethoxyphenyl)prop-2-enyl]pentanedioic acid (28): 31% yield. Mp: 156−8 °C. $[\alpha]_D$ = +35.3 (*c* 0.34, 1 N HCl). ^{1}H NMR (D_2O−KOD): δ 7.70−6.45 (m, 3H), 5.96 (d, *J* = 16.3 Hz, 1H), 5.81−5.63 (m, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 2.75 (dd, *J* = 4.1 and 10.0 Hz, 1H), 2.09−1.85 (m, 3H), 1.48 (m, 1H), 1.12 (m, 1H). ^{13}C NMR (D_2O−pyr-d_5): δ 184.5, 178.6, 150.2, 150.0 133.2, 132.9, 128.3, 121.4, 113.4, 110.8, 57.4, 57.3, 55.6, 47.3, 38.4, 34.9. IR (KBr): 3420, 1705, 1586, 1516, 1264, 1138 cm^{-1}. Anal. ($C_{16}H_{21}NO_6$·H_2O) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(2,6-dichlorophenyl)prop-2-enyl]-pentanedioic acid (29): 45% yield. Mp: 184 °C. $[\alpha]_D$ = −16.0 (*c* 0.05, 1 N NaOH). ^{1}H NMR (D_2O−KOD): δ 7.08 (d, *J* = 8.0 Hz, 2H), 6.86 (t, *J* = 8.0 Hz, 1H), 6.12 (d, *J* = 16.9 Hz, 1H), 5.88 (m, 1H), 2.91 (m, 1H), 2.40−2.00 (m, 3H), 1.64 (m, 1H), 1.33 (m, 1H). ^{13}C NMR (D_2O−pyr-d_5): δ 138.6, 136.0, 135.6, 130.2, 130.1, 127.1, 55.5, 42.0, 39.0, 34.9. IR (KBr): 3410, 1705, 1586, 1504, 1429, 1208 cm^{-1}. Anal. ($C_{14}H_{15}Cl_2NO_4$·H_2O) C, H, N.

Benzyl (2*S*,4*R*)-*N*-BOC-4-(3-phenylprop-2-ynyl)pyroglutamate. To a mixture of iodobenzene (0.37 mL, 3.36 mmol) and benzyl (2*S*,4*R*)-*N*-BOC-4-(prop-2-ynyl)pyroglutamate (see below) (1 g, 2.80 mmol) in triethylamine (15 mL) was added bis(triphenylphosphine)palladium dichloride (100 mg, 5%) and copper iodide (33 mg, 2.5%). The reaction mixture was heated at 70 °C under nitrogen atmosphere for 2.5 h. After this time the solvent was evaporated and the residue chromatographed using ethyl acetate/hexane (1:4) as eluent to yield 0.99 g, (82%) as an oil. $[\alpha]_D$ = −26.5 (*c* 0.5, $CDCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.44 (s, 10H), 5.26 (AB system, 2H), 4.65 (m, 1H), 2.90 (m, 2H), 2.65 (m, 1H), 2.43 (m, 2H), 1.45 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 173.2, 171.0, 149.2, 134.9, 131.6, 128.66, 128.63, 128.49, 128.21, 128.02, 123.05, 85.5, 83.8, 82.7, 67.4, 57.1, 41.0, 27.7, 27.6. Anal. ($C_{26}H_{27}NO_5$) C, H, N.

(2*S*,4*R*)-2-(Amino)-4-(3-phenylprop-2-ynyl)pentanedioic acid (30): 71% yield. Mp: 164−6 °C. $[\alpha]_D$ = +13.9 (*c* 0.23, DMSO). ^{1}H NMR (D_2O/KOD): δ 7.52−7.30 (m, 5H), 3.21 (dd, *J* = 2.8, 9.3 Hz, 1H), 2.60 (m, 2H), 2.00 (m, 2H), 1.70 (m, 1H). ^{13}C NMR (DO_2/KOD): δ 183.8, 183.7, 132.7, 129.7, 129.4, 124.0, 89.9, 82.8, 55.8, 46.4, 39.2, 23.8. IR (KBr): 3000, 1697, 1618, 1491, 1404, 1213 cm^{-1}. Anal. ($C_{14}H_{17}NO_5$) C, H, N.

Ethyl (2*S*,4*R*)-*N*-Boc-4-(3-phenylpropyl)pyroglutamate. To a solution of ethyl (2*S*,4*R*,*E*)-*N*-BOC-4-cinnamylpyroglutamate (500 mg, 1.34 mmol) in EtOAc (10 mL) was added PtO_2 (30 mg) and the mixture was stirred under a hydrogen atmosphere at room temperature overnight. The reaction mixture was filtered through a pad of Celite and the solvent evaporated. The crude was purified by chromatography (hexane/ethyl acetate 4:1). 82% yield. Colorless oil. $[\alpha]_D$ = −26.6 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 7.25−7.00 (m, 5H), 4.42 (dd, *J* = 1.4 and 9.5 Hz, 1H), 4.12 (c, *J* = 7.1 Hz, 2H), 2.62−2.45 (m, 3H), 2.20−2.00 (m, 1H), 2.45−1.70 (m, 2H), 1.65−1.20 (m, 3H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.6, 170.9, 149.0, 141.4, 128.0, 127.9, 125.4, 82.9, 61.2, 56.7, 41.1, 35.3, 29.6, 28.3, 28.0, 27.4, 13.8. Anal. ($C_{21}H_{29}NO_5$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-(3-phenylpropyl)pentanedioic acid hydrochloric acid (31): 67% yield. White hygroscopic solid. $[\alpha]_D$ = +19.5 (*c* 1, MeOH). ^{1}H NMR (MeOH-d_4): δ 7.30−7.10 (m, 5H), 3.90 (dd, *J* = 5.6 and 7.8 Hz, 1H), 2.75−2.55 (m, 3H), 2.42−2.20 (m, 1H), 1.95−1.80 (m, 1H), 1.80−1.50 (m, 4H). ^{13}C NMR (MeOH-d_4): δ 178.2, 172.2, 143.1, 129.4, 129.3, 126.8, 53.0, 42.5, 36.6, 33.4, 32.9, 29.8. IR (KBr): 3426, 1717, 1636, 1497 cm^{-1}. Anal. ($C_{14}H_{19}NO_4$.HCl) C, H, N.

Benzyl (2*S*,4*R*,*E*)-*N*-Boc-4-(2-naphthylprop-2-enyl)pyroglutamate: White solid. Mp: 137−8 °C. $[\alpha]_D$ = −24.0 (*c* 1, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 7.90−7.25 (m, 12H), 6.60 (d, *J* = 15.8 Hz, 1H), 6.23 (dt, *J* = 15.8 and 7.1 Hz, 1H), 5.19 (s, 2H), 4.60 (dd, *J* = 1.9 and 9.1 Hz, 1H), 2.95−2.70 (m, 2H), 2.55−2.30 (m, 1H), 2.30−2.00 (m, 2H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 174.3, 171.1, 149.3, 134.9, 134.3, 133.5, 133.1, 132.8, 128.7, 128.6, 128.5, 128.1, 127.8, 127.6, 126.2, 126.1, 125.8, 125.7, 123.4, 83.6, 67.4, 57.1, 41.6, 33.6, 27.8. Anal. ($C_{30}H_{31}NO_5$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(2-naphthyl)prop-2-enyl]pentanedioic acid (32): 77% yield. Mp: 194−5 °C. $[\alpha]_D$ = +4.6 (*c* 0.35, DMSO). ^{1}H NMR (pyr-d_5−D_2O): δ 8.05−7.57 (m, 7H), 6.80 (d, *J* = 15.9 Hz, 1H), 6.65 (m, 1H), 4.28 (dd, *J* = 3.3 and 9.5 Hz, 1H), 3.15−2.35 (m, 5H). ^{13}C NMR (pyr-d_5−D_2O): δ 184.3, 176.5, 137.0, 135.4, 134.5, 133.6, 130.7, 130.1, 129.8, 129.5, 128.4, 127.8, 127.6, 125.6, 55.7, 47.3, 38.6, 35.0. IR

(KBr): 3420, 1703, 1584, 1497, 1208 cm^{-1}. Anal. ($C_{18}H_{19}NO_4 \cdot H_2O$) C, H, N.

Benzyl (2*S*,4*R*,*E*)-*N*-Boc-4-(1-naphthylprop-2-enyl)pyroglutamate: 53% yield. EtOAc/hexane 1:6. Mp: 96−8 °C. $[\alpha]_D = -22.5$ (*c* 0.2, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 8.07−7.98 (m, 1H), 7.81−7.69 (m, 2H), 7.51−7.21 (m, 10H), 7.12 (d, 1H, $J = 15.5$ Hz, HC=), 6.06 (dt, 1H, $J = 15.5$ and 7.1 Hz, HC=), 5.16 (AB, 2H, CO_2CH_2), 4.57 (dd, 1H, $J = 9.4$ and 1.7 Hz, H-2), 2.88−2.72 (m, 2H), 2.51−2.33 (m, 1H), 2.24−1.93 (m, 2H), 1.40 (s, 9H, $C(CH_3)_3$). ^{13}C NMR ($CDCl_3$): δ 173.9, 170.7, 148.9, 134.7, 134.4, 133.1, 130.6, 129.9, 128.8, 128.3 (2C), 128.2 (3C), 128.1, 127.4, 125.7, 125.4, 125.3, 83.1, 66.9, 56.8, 41.2, 33.5, 27.4 (3C), 27.3. IR (film): 1778, 1738, 1311, 1147 cm^{-1}. Anal. ($C_{30}H_{31}NO_5$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-[3-(1-naphthyl)prop-2-enyl]pentanedioic acid (33): 40% yield. Mp: 150−1 °C. $[\alpha]_D = +12.0$ (*c* 0.4, DMSO). ^1H NMR (D_2O−KOD): δ 7.57−7.49 (m, 1H), 7.29−7.13 (m, 2H), 7.03−6.81 (m, 4H), 6.56 (d, 1H, $J = 15.7$ Hz, HC=), 5.71−5.56 (m, 1H, HC=), 2.64 (dd, 1H, $J = 9.5$ and 4.3 Hz, H-2), 2.00−1.81 (m, 3H), 1.47−1.32 (m, 1H), 1.10−0.93 (m, 1H). ^{13}C NMR (D_2O−MeOH-d_4−KOD): δ 185.0, 184.1, 136.2, 134.4, 133.3, 131.7, 129.6, 129.1, 128.6, 127.5, 127.3, 125.0, 124.8, 56.0, 47.4, 39.8, 37.9. IR (KBr): 1697, 1585, 1487, 1203 cm^{-1}. Anal. ($C_{18}H_{19}NO_4 \cdot H_2O$) C, H, N.

Alkyl Derivatives (Table 2). Benzyl (2*S*,4*R*)-*N*-Boc-4-(prop-2-ynyl)pyroglutamate was prepared following the general method for alkylation of pyroglutamates with allyl bromide (see below). 34% Yield. Mp: 102−3 °C. $[\alpha]_D = -31.5$ (*c* 1, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.33 (broad s, 5H), 5.16 (AB system, 2H), 4.62 (m, 1H), 2.90−2.20 (m, 5H), 1.98 (t, $J = 2.7$ Hz, 1H), 1.39 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 172.9, 170.9, 149.1, 134.9, 128.64, 128.62, 128.4, 83.7, 79.9, 70.7, 67.4, 56.9, 40.6, 27.7, 27.3, 19.2 IR (KBr): 3280, 1790, 1744, 1311, 1215, 1148 cm^{-1}. Anal. ($C_{20}H_{23}NO_5$) C, H, N.

(2*S*,4*R*)-2-Amino-4-(prop-2-ynyl)pentanedioic acid (34): 32% yield. Mp: 164−5 °C. $[\alpha]_D = +16.7$ (*c* 0.3, 1 N HCl). ^1H NMR (D_2O−pyr-d_5): δ 4.12 (dd, $J = 2.0$ and 8.4 Hz, 1H), 3.00−2.20 (m, 5H), 2.66 (t, $J = 2.4$ Hz, 1H). ^{13}C NMR (D_2O−pyr-d_5): δ 183.4, 176.5, 84.6, 73.1, 55.4, 46.0, 34.4, 24.0. IR (KBr): 3100, 1697, 1622, 1505, 1406, 1215 cm^{-1}. Anal. ($C_8H_{11}NO_4$) C, H, N.

Benzyl (2*S*,4*S*)-*N*-Boc-4-(prop-2-ynyl)pyroglutamate: 20% Yield. Oil. $[\alpha]_D = +18.7$ (*c* 0.48, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 7.34 (broad s, 5H), 5.12 (s, 2H), 4.53 (dd, $J = 8.5$, 7.3 Hz, 1H), 2.70−2.35 (m, 3H), 2.05−1.90 (m, 2H), 1.40 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 173.0, 171.0, 149.1, 134.7, 128.64, 128.62, 128.5, 83.9, 80.2, 70.5, 67.3, 57.3, 41.7, 27.7, 26.5, 20.1. IR (KBr): 3300, 1790, 1755, 1317, 1254, 1152 cm^{-1}. Anal. ($C_{20}H_{23}NO_5$) C, H, N.

(2*S*,4*S*)-2-Amino-4-(prop-2-ynyl)pentanedioic acid (35): 37% yield. Mp: 167−8 °C. $[\alpha]_D = +10.0$ (*c* 0.2, 1 N HCl). ^1H NMR (D_2O−pyr-d_5): δ 3.92 (dd, $J = 5.3$ and 8.4 Hz, 1H), 2.85 (m, 1H), 2.70 (m, 2H), 2.60 (m, 1H), 2.49−2.20 (m, 2H). ^{13}C NMR (D_2O−pyr-d_5): δ 183.7, 177.1, 84.7, 73.2, 56.5, 47.3, 35.5, 24.2. IR (KBr): 3274, 1589, 1500, 1306 cm^{-1}. Anal. ($C_8H_{11}NO_4$) C, H, N.

Procedure for the Preparation of the Acetylenic Amino Acids. To a solution of **4b** (7.20 g, 22 mmol) in dry tetrahydrofuran (70 mL) under positive nitrogen pressure, and cooled to −78 °C in a dry ice/acetone bath, was added lithium bis(trimethylsilyl)amide (25 mL of 1 M THF solution, 25 mmol). After stirring at −78 °C for 1 h, the reaction mixture was rapidly cannulated under nitrogen pressure into a solution of the corresponding alkynyl bromide (44 mmol) in dry tetrahydrofuran (20 mL), also under positive nitrogen pressure at −78 °C. The resulting mixture was then stirred at −78 °C for 2 h. The reaction mixture was quenched at −78 °C with saturated ammonium chloride solution and then extracted three times with diethyl ether. The combined ethereal extracts were dried over magnesium sulfate, filtered, and evaporated in vacuo to give an oil. The crude oil was purified by flash chromatography on silica (eluent hexane:diethyl ether 2:1).

Benzyl (2*S*,4*R*)-*N*-BOC-4-(but-2ynyl)pyroglutamate: White solid. 22% yield. ^1H NMR ($CDCl_3$): δ 7.36 (s, 5H), 5.22 (d, $J = 12.1$ Hz, 1H), 5.18 (d, $J = 12.1$ Hz, 1H), 4.63 (t, $J = 5.4$ Hz, 1H), 2.77 (m, 1H), 2.59 (m, 1H), 2.43 (m, 1H), 2.26 (m, 2H), 1.75 (t, $J = 2.5$ Hz, 3H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 173.5, 171.1, 149.3, 135.1, 128.7, 128.6, 128.5, 83.7, 78.1, 74.7, 67.4, 57.1, 41.1, 27.8, 27.5, 19.7, 3.5. Anal. ($C_{21}H_{25}NO_5$) C, H, N.

Hydrolysis of Acetylenic Substituted Pyroglutamates. To a solution of the corresponding pyroglutamate (1.1 mmol) in tetrahydrofuran (10 mL) was added 1 M lithium hydroxide (3.3 mL, 3.3 mmol) and the mixture stirred at ambient temperature for 16 h. The reaction mixture was acidified to pH 2 with 1 M hydrochloric acid and extracted three times with diethyl ether. The combined ethereal extracts were dried over magnesium sulfate, filtered, and evaporated in vacuo to give (2*S*,4*R*)-2-(*tert*-butoxycarbonylamino)-4-(alken-2-yn-1-yl) pentanedioic acid as a viscous oil. To a solution of this (400 mg) in moist diethyl ether (10 mL) was added, with ice-bath cooling, trifluoroacetic acid (4 mL). The reaction mixture was then stirred at ambient temperature for 4 h. The reaction mixture was evaporated to dryness in vacuo, redissolved in water, and azeotroped to remove excess trifluoroacetic acid. The resulting white solid was purified by cation-exchange chromatography (Dowex 50 × 8-100). The column was eluted sequentially with water, water/THF 1:1, and water again, and the amino acid was finally eluted with water/pyridine 9:1. The pyridine was removed in vacuo and the residual solid redissolved in water and freeze-dried.

(2*S*,4*R*)-2-Amino-4-(but-2-ynyl)pentanedioic acid (36): 65% yield. Fluffy white solid. Mp: 120 °C. ^1H NMR (D_2O): δ 3.83 (dd, $J = 5.4$ and 8.1 Hz, 1H), 2.74 (m, 1H), 2.53 (m, 2H), 2.33 (m, 1H), 2.06 (m, 1H), 1.78 (t, $J = 2.7$ Hz, 3H). ^{13}C NMR (D_2O): δ 181.4, 176.7, 82.4, 78.6, 55.9, 44.56, 34.47, 24.49, 5.36. Anal. ($C_9H_{13}NO_4$) C, H, N.

Benzyl (2*S*,4*R*)-*N*-Boc-4-(pent-2-ynyl)pyroglutamate: 25% yield. ^1H NMR ($CDCl_3$): δ 7.33 (s, 5H), 5.20 (d, $J = 12.1$ Hz, 1H), 5.16 (d, $J = 12.1$ Hz, 1H), 4.61 (t, $J = 5.2$ Hz, 1H), 2.74 (m, 1H), 2.56 (m, 1H), 2.40 (m, 1H), 2.24 (m, 2H), 2.09 (m, 2H), 1.39 (s, 9H), 1.08 (t, $J = 8.2$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 173.5, 171.2, 149.3, 135.1, 128.7, 128.6, 84.2, 83.6, 74.9, 67.4, 57.2, 41.2, 27.8, 27.4, 19.8, 14.1, 12.4. Anal. ($C_{22}H_{27}NO_5$) C, H, N.

(2*S*,4*R*)-2-Amino-4-(pent-2-ynyl)pentanedioic acid (37): 52% yield. Mp: 198−200 °C. ^1H NMR (D_2O): δ 3.17 (dd, $J = 4.5$ and 9.3 Hz, 1H), 2.44 (m, 1H), 2.30 (m, 2H), 2.13 (q, 2H), 1.88 (m, 1H), 1.59 (m, 1H), 1.05 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (D_2O): δ 185.8, 185.7, 87.4, 81.0, 57.6, 48.5, 40.8 25.0, 16.4, 14.6. Anal. ($C_{10}H_{15}NO_4$) C, H, N.

Benzyl (2*S*,4*R*)-*N*-Boc-4-(hex-2-ynyl)pyroglutamate: 14% yield. ^1H NMR ($CDCl_3$): δ 7.33 (m, 5H), 5.23 (d, $J = 12$ Hz, 1H), 5.19 (d, $J = 12$ Hz, 1H), 4.64 (dd, $J = 4.2$ and 7.8 Hz, 1H), 2.78 (m, 1H), 2.60 (m, 1H), 2.45 (m, 1H), 2.27 (m, 2H), 2.09 (m, 2H), 1.47 (m, 2H), 1.43 (s, 9H), 0.94 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 173.5, 171.1, 149.1, 135.1, 128.7, 128.6, 128.4, 83.6 82.7, 75.7, 67.4, 57.1, 41.2, 27.4, 27.4, 22.3, 20.7, 19.9, 13.4. Anal. ($C_{23}H_{29}NO_5$) C, H, N.

(2*S*,4*R*)-2-Amino-4-(hex-2-ynyl)pentanedioic acid (38): 40% yield. Mp: 200−1 °C. ^1H NMR (D_2O): δ 3.16 (dd, $J = 4.8$ and 9.3 Hz, 1H), 2.43 (m, 1H), 2.30 (m, 2H), 2.09 (m, 2H), 1.87 (m, 1H), 1.58 (m, 1H), 1.43 (m, 2H), 0.90 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (D_2O): δ 185.8, 185.7, 86.0, 81.9, 57.6, 48.5, 40.9, 25.1, 24.7, 22.9, 15.8. Anal. ($C_{11}H_{17}NO_4$) C, H, N.

General Procedure for Alkylation Reactions of Ethyl or Benzyl *N*−BOC Pyroglutamate Esters (4a, 4b) with Allyl Bromides. To a solution of the pyroglutamate (6.26 mmol) in dry tetrahydrofuran (30 mL) under argon was added a 1 M solution of lithium hexamethyldisilazide in dry tetrahydrofuran (7.5 mL, 7.5 mmol) at −78 °C. After 1 h, this solution was cannulated to a previously prepared solution of the corresponding alkyl bromide (25 mmol) in 20 mL of dry tetrahydrofuran at −78 °C, and stirring was continued for 2 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The diastereomeric mixture was evaporated and separated by flash column chromatography.

Ethyl (2*S*,4*R*)-*N*-Boc-4-allylpyroglutamate: Hexane/ethyl acetate: 4:1. Colorless oil. 34% yield. $[\alpha]_D = -31.6$ (*c* 0.76, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 5.80−5.60 (m, 1H), 5.15−5.00 (m, 2H), 4.52 (dd J = 1.9 and 9.4 Hz, 1H), 4.20 (q, J = 7.1 Hz, 1H), 2.80−2.55 (m, 2H), 2.25−1.90 (m, 3H), 1.47 (s, 9H), 1.25 (t, J = 7.1, 3H). ^{13}C NMR ($CDCl_3$): δ 174.4, 171.3, 149.4, 134.3, 117.7, 85.5, 61.6, 57.1, 41.1, 34.4, 27.8, 27.7, 14.1. IR (film): 2980, 1748, 1717, 1319, 1254 cm^{-1}. HRMS: calcd for $C_{15}H_{23}NO_5$ 297.1576, found 297.1590.

(2*S*,4*R*)-2-Amino-4-(prop-2-enyl)pentanedioic acid, hydrochloride (39): 62% yield. White solid, mp 166−7 °C. $[\alpha]_D = +4.5$ (*c* 1.0, H_2O). ^1H NMR (D_2O/MeOH-d_4): δ 5.90−5.70 (m, 1H), 5.20−5.00 (m, 2H), 3.70 (dd, J = 2.0 and 7.0 Hz, 1H), 2.70 (m, 1H), 2.50−2.20 (m, 3H), 1.90 (m, 1H). ^{13}C NMR (D_2O/MeOH-d_4): δ 181.2, 175.0, 135.9, 118.4, 54.2, 43.8, 37.4, 33.0. IR (KBr): 3428−2920, 1697, 1655, 1616, 1342, 1228 cm^{-1}. Anal. (C_8H_{13} NO_4.HCl) C, H, N.

Ethyl (2*S*,4*S*)-*N*-Boc-4-allylpyroglutamate: Hexane/ethyl acetate: 4:1. Colorless oil. 16% yield. $[\alpha]_D = +1.20$ (*c* 2.44, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 5.85−5.60 (m, 1H), 5.15−5.00 (m, 2H), 4.47 (dd J = 6.8 and 8.8 Hz, 1H), 4.21 (q, J = 7.1 Hz, 1H), 2.70−2.55 (m, 2H), 2.55−2.38 (m, 1H), 2.30−2.10 (m, 1H), 1.80−1.60 (m, 1H), 1.48 (s, 9H), 1.28 (t, J = 7.1, 3H). ^{13}C NMR ($CDCl_3$): δ 174.4, 171.3, 149.4, 117.4, 57.3, 41.9, 34.9, 27.6, 26.5, 13.9. IR (film): 2980, 1790, 1755, 1717, 1325, 1198 cm^{-1}. HRMS: calcd for $C_{15}H_{23}NO_5$ 297.1576, found 297.1584.

(2*S*,4*S*)-2-Amino-4-(prop-2-enyl)pentanedioic acid, hydrochloride (40): 24% yield. White solid. Mp 140−2 °C. $[\alpha]_D = +14.0$ (*c* 1.0, H_2O). ^1H NMR (D_2O/MeOH-d_4): δ 5.90−5.70 (m, 1H), 5.20−5.00 (m, 2H), 3.65 (t, J = 7.3 Hz, 1H), 2.70 (m, 1H), 2.36 (t, J = 6.8 Hz, 2H), 2.00 (t, J = 6.8 Hz, 2H). ^{13}C NMR (D_2O/MeOH-d_4): δ 179.9, 174.6, 135.5, 118.5, 54.3, 43.5, 37.3, 33.5. IR (KBr): 3430−2920, 1717, 1642, 1522 cm^{-1}. Anal. ($C_8H_{13}NO_4$·HCl) C, H, N.

Ethyl (2*S*,4*R*,*E*)-*N*-Boc-4-(but-2-enyl)pyroglutamate contaminated with the *Z* isomer: 66% yield. EtOAc/hexane 1:4. $[\alpha]_D = -37.9$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 5.61−5.26 (m, 2H, HC=), 4.54 (dd, 1H, J = 9.3 and 2.1 Hz, H-2), 4.23 (q, 2H, J = 7.1 Hz, CO_2CH_2), 2.77−2.49 (m, 2H), 2.23−1.92 (m, 3H), 1.65 (dq, 3H, J = 6.2 and 1.1 Hz, CHCH_3), 1.50 (s, 9H, C(CH_3)$_3$), 1.29 (t, 3H, J = 7.1 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 174.5, 171.1, 149.1, 128.2, 126.4, 83.1, 61.4, 56.9, 41.3, 32.9, 27.6 (3C), 27.4, 17.4, 13.9. IR (film): 1794, 1747, 1716, 1315, 1153 cm^{-1}. HRMS: calcd for $C_{16}H_{25}NO_5$ 311.1733, found 311.1739.

(2*S*,4*R*,*E*)-2-Amino-4-(but-2-enyl)pentanedioic acid (43): 51% yield. Mp: 149−150 °C. $[\alpha]_D = +14.9$ (*c* 0.85, DMSO). ^1H NMR (MeOH-d_4−KOD): δ 5.47−5.42 (m, 2H, HC=), 3.24−3.21 (m, 1H, H-2), 2.38−2.22 (m, 2H), 2.09−1.90 (m, 2H), 1.60 (d, 3H, J = 4.6 Hz, CHCH_3), 1.57−1.45 (m, 1H). ^{13}C NMR (MeOH-d_4−KOD): δ 184.3, 182.7, 131.0, 130.2 (*Z* isomer), 126.8, 125.4 (*Z* isomer), 56.5, 47.5, 40.4, 38.1, 32.3 (*Z* isomer), 16.1, 13.1 (*Z* isomer). IR (KBr): 1705, 1603, 1581, 1213 cm^{-1}.

Ethyl (2*S*,4*R*,*E*)-*N*-Boc-4-(pent-2-enyl)pyroglutamate: 45% yield. ^1H NMR ($CDCl_3$): δ 5.50 (dt, 1H, J = 15.4 and 6.2 Hz, HC=), 5.27 (dt, 1H, J = 15.4 and 6.9 Hz, HC=), 4.49 (dd, 1H, J = 9.5 and 1.8 Hz, H-2), 4.18 (q, 2H, J = 7.1 Hz, CO_2CH_2), 2.68−2.46 (m, 2H), 2.15−1.84 (m, 5H), 1.46 (s, 9H, C(CH_3)$_3$), 1.25 (t, 3H, J = 7.1 Hz, CH_2CH_3), 0.92 (t, 3H, J = 7.7 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 174.2, 170.9, 149.1, 135.2, 124.0, 83.0, 61.2, 56.8, 41.3, 32.8, 27.5 (3C), 27.3, 25.1, 13.8, 13.4. EIMS *m*/*e*: 325 (M^+, 0.3), 225 (26), 196 (10), 157 (100), 140 (10), 84 (14), 57 (65). HRMS: calcd for $C_{17}H_{27}NO_5$ 325.1889, found 325.1890.

(2*S*,4*R*,*E*)-2-Amino-4-(pent-2-enyl)pentanedioic acid (44): 30% yield. Mp: 153 °C. $[\alpha]_D = +5.5$ (*c* 0.18, DMSO). ^1H NMR (D_2O−KOD): δ 5.15 (dt, 1H, J = 15.2 and 6.5 Hz, HC=), 4.96 (dt, 1H, J = 15.2 and 6.3 Hz, HC=), 2.71 (dd, 1H, J = 9.2 and 4.5 Hz, H-2), 1.98−1.81 (m, 1H), 1.73−1.34 (m, 5H), 1.06 (ddd, 1H, J = 14.1, 9.6 and 5.3 Hz), 0.48 (t, 3H, J = 7.4 Hz, CH_2CH_3). ^{13}C NMR (D_2O−MeOH-d_4−KOD): δ 185.4, 184.3, 135.8, 127.6, 55.9, 47.5, 39.5, 37.1, 26.2, 14.4. IR (KBr): 1701, 1585, 1485, 1206 cm^{-1}. Anal. ($C_{10}H_{17}NO_4$) C, H, N.

General Procedure for the Hydrogenation of the Acetylenes to *Z* Olefins. A solution of the acetylene amino acid (0.75 mmol) in water (25 mL) was hydrogenated over Lindlar catalyst (100 mg) at 8 psi in a Parr hydrogenation apparatus. After 48 h the reaction mixture was filtered over diatomaceous earth, and the filtrates were evaporated in vacuo to give the product.

(2*S*,4*R*,*Z*)-2-Amino-4-(but-2-enyl)pentandioic acid (41): 80% yield. Mp: 200−2 °C. ^1H NMR (D_2O): δ 5.67 (m, 1H), 5.41 (m, 1H), 3.76 (dd, J = 5.1 and 8.1 Hz, 1H), 2.62 (m, 1H), 2.41 (m, 2H), 2.26 (m, 1H), 1.96 (m, 1H), 1.62 (d, J = 7.5 Hz, 3H). Anal. ($C_9H_{15}NO_4$) C, H, N.

(2*S*,4*R*,*Z*)-2-Amino-4-[pent-2-enyl]pentanedioic acid (42): 72% yield. Mp: 250 °C (dec). ^1H NMR (D_2O): δ 5.54 (m, 1H), 5.35 (m, 1H), 3.7 (dd, J = 3.1 and 8.7 Hz, 1H), 2.41−1.9 (m, 7H), 0.93 (t, J = 7.5 Hz, 3H). ^{13}C NMR (D_2O): δ 185.8, 177.4, 137.3, 128.4, 56.2, 48.0, 35.5, 33.0, 22.9, 16.4. Anal. ($C_{10}H_{17}NO_4$) C, H, N.

Benzyl (2*S*,4*R*,*E*)-*N*-Boc-4-(3-chloroprop-2-enyl)pyroglutamate. 3-Chloro-1-iodoprop-2(*E*/*Z*)-ene (made from commercial available 1,3-dichloroprop-2(*E*/*Z*)-ene by reaction with sodium iodide in acetone) was reacted with benzyl *N*-Boc-4-pyroglutamate using the general procedure described above for the preparation of acetylenic substituted pyroglutamates. The mixture of 4*R* and 4*S* isomers (1:1) was separated by chromatography on a silica column eluted with hexane/ether (3:1). The first eluting 4*R* isomer was then recrystallized from ether twice to give only the *E* isomer (mp: 109−110 °C, yield 13%).

(2*S*,4*R*,*E*)-2-Amino-4-(3-chloroprop-2-enyl)pentandioic acid (45): 45% yield. ^1H NMR (D_2O): δ 6.13 (d, 1H, J = 13.3 Hz), 5.95 (m, 1H), 3.22 (dd, 1H, J = 8.9 and 4.5 Hz), 2.27 (m, 3H), 1.93 (m, 1H), 1.55 (m, 1H). Anal. ($C_8H_{12}ClNO_4$) C, H, N.

Ethyl (2*S*,4*R*)-*N*-Boc-4-propylpyroglutamate: Colorless oil. 99% yield. $[\alpha]_D = -30.0$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 4.52 (dd, J = 1.7 and 9.5 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 2.65 (m, 1H), 2.30−2.10 (m, 1H), 2.05−1.70 (m, 2H), 1.62 (bs, 1H), 1.47 (s, 9H), 1.30 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H), 0.90 (t, J = 7.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 175.2, 171.2, 149.4, 83.2, 61.5, 57.0, 41.3, 32.3, 28.4, 27.7, 20.0, 14.0, 13.8. IR (film): 2990, 1794, 1748, 1719, 1316, 1188, 1153 cm^{-1}. HRMS: calcd for $C_{15}H_{25}NO_5$ 299.1733, found 299.1739.

(2*S*,4*R*)-2-Amino-4-propylpentanedioic acid hydrochloride (46): 83% yield. White solid. Mp: 188−9 °C. $[\alpha]_D = +21.0$ (*c* 1.0, MeOH). ^1H NMR (MeOH-d_4): δ 3.97 (dd, J = 5.6 and 8.3 Hz, 1H), 2.63 (m, 1H), 2.32 (m, 1H), 1.89 (m, 1H), 1.63 (m, 2H), 1.39 (m, 2H), 0.95 (t, J = 7.15 Hz, 3H). ^{13}C NMR (MeOH-d_4): δ 178.1, 171.6, 52.6, 42.3, 35.5, 33.3, 21.0, 14.3. IR (KBr): 3453, 2998, 1740, 1491, 1217 cm^{-1}. Anal. ($C_8H_{15}NO_4$.HCl) C, H, N.

General Procedure for the Hydrogenation of the Acetylenes to Alkanes. A solution of acetylenic amino acid (0.22 mmol) in water (30 mL) was hydrogenated over 10% palladium/charcoal catalyst (20 mg) at 6 psi in a Parr hydrogenation apparatus. After 2 h the reaction mixture was filtered over diatomaceous earth, and the filtrates were evaporated in vacuo to give the product.

(2*S*,4*R*)-2-Amino-4-pentylpentanedioic acid (47): 20% yield. Mp: 160−1 °C. ^1H NMR (D_2O): δ 3.74 (dd, J = 4.8 and 8.7 Hz, 1H), 2.56 (m, 1H), 2.24 (m,1H), 1.94 (m, 1H), 1.61 (m, 2H), 1.32 (m, 6H), 0.89 (t, 3H). ^{13}C NMR (D_2O): δ 184.0, 177.0, 56.2, 45.9, 35.5, 34.9, 33.7, 28.7, 24.6, 16.1. Anal. ($C_{10}H_{19}NO_4$) C, H, N.

(2*S*,4*R*)-2-Amino-4-hexylpentanedioic acid (48): 88% yield. Mp: 194−6 °C. ^1H NMR (D_2O): δ 3.13 (dd, J = 4.4 and 8.8 Hz, 1H), 2.29 (m, 1H), 1.84 (m, 1H), 1.48 (m, 1H), 1.48 (m, 2H), 1.24 (m, 8H), 0.83 (t, 3H). ^{13}C NMR (D_2O): δ 188.2, 186.0, 57.8, 49.1, 42.0, 35.9, 34.0, 31.5, 30.0, 25.0, 16.4. Anal. ($C_{11}H_{21}NO_4$) C, H, N.

Ethyl (2*S*,4*R*)-*N*-Boc-4-(3-methylbut-2-enyl)pyroglutamate: 70% Yield. Oil. EtOAc/hexane 1:3. ^1H NMR ($CDCl_3$): δ 5.10−5.01 (m, 1H, *H*C=C), 4.53 (dd, 1H, J = 9.4 and 1.9 Hz, H-2), 4.22 (q, 2H, J = 7.1 Hz, CO_2CH_2), 2.76−2.46 (m, 2H),

2.24−1.87 (m, 3H), 1.69 (d, 3H, J = 1.1 Hz, CH_3), 1.61 (d, 3H, J = 0.8 Hz, CH_3), 1.50 (s, 9H, $C(CH_3)_3$), 1.32 (t, 3H, J = 7.1 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$): δ 174.6, 171.3, 149.3, 134.6, 119.6, 83.2, 61.5, 56.9, 41.8, 28.2, 27.7 (3C), 27.6, 25.6, 17.7, 14.1. IR (film): 1794, 1747, 1718, 1317, 1155 cm^{-1}. HRMS: calcd for $C_{17}H_{27}NO_5$ 325.1889, found 325.1893.

General Procedure for the Deprotection of Compounds with Branched Alkenyl Chains. The *N*-BOC protected pyroglutamate was heated neat to 150 °C under nitrogen for up to 10 h or until the reaction was complete by TLC. (It was found that the use of higher temperatures (185 °C) led to some epimerization of the 2*S*,4*R* isomers.) The pyroglutamate was then hydrolyzed using 2 M aqueous sodium hydroxide solution under nitrogen. It was found that reaction times and temperature had to be varied for the different substrates. Varying degrees of epimerization were observed which could be reduced by stopping the reaction before competion and separating the amino acid from the lactam acid by ion exchange chromatography using Dowex 50 × 8-100 resin as described earlier. The lactam acid eluted from the column with the THF−water wash.

(2*S*,4*R*)-2-Amino-4-(3-methylbut-2-enyl)pentanedioic acid (49): Mp: >250 °C dec contained 33% of the 4-epimer after hydrolysis for 2 days at 100 °C in 2 M aqueous sodium hydroxide. ^{1}H NMR (D_2O): δ 5.16 (bt, 1H), 3.18 (m, 1H), 2.34−2.16 (m, 2H), 1.89 (m, 1H), 1.77−1.66 (m, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.57−1.48 (m, 1H). Anal. ($C_{11}H_{21}NO_4$) C, H, N.

Benzyl (2*S*,4*S*)-*N*-Boc-4-(2-chloroprop-2-enyl)pyroglutamate: 35% yield. Oil. ^{1}H NMR ($CDCl_3$): δ 7.18 (m, 10H, Ph), 5.10 (AB, 4H, OCH_2), 5.18 (s, 2H), 5.01 (s, 2H), 4.58 (m, 2H, H-2), 2.95 (m, 4H), 2.45 (m, 1H), 2.35 (m, 3H), 2.02 (m, 1H), 1.65 (m, 1H), 1.46 (s, 9H, $C(CH_3)_3$), 1.43 (s, 9H, $C(CH_3)_3$). HRMS: calcd for $C_{20}H_{24}ClNO_5$ 393.1343, found 393.1340.

(2*S*,4*S*)-2-Amino-4-(2-chloroprop-2-enyl)pentanedioic acid (50): 30% yield. Mp: >250 °C dec. ^{1}H NMR (D_2O): δ 5.28 (s, 2H), 3.75 (m, 1H), 3.02−2.89 (m, 1H), 2.71 (m, 1H), 2.62 (m, 1H), 2.28−1.88 (m, 2H). Anal. ($C_8H_{12}ClNO_4$) C, H, N.

(2*S*,4*R*,*E*)-2-Amino-4-(2-methyl-3-phenylprop-2-enyl)-pentanedioic acid (51): 48% yield. Mp: 138−140 C. $[\alpha]_D$ = −14.8 (*c* 0.45, DMSO). ^{1}H NMR (D_2O−KOD): δ 7.06−6.83 (m, 5H, Ph), 5.95 (s, 1H, HC=), 2.81 (dd, 1H, J = 10.5 and 4.1 Hz, H-2), 2.34−2.18 (m, 1H), 2.08−1.84 (m, 2H), 1.61−1.47 (m, 1H), 1.47 (s, 3H, CH_3), 1.22−1.08 (m, 1H). ^{13}C NMR (D_2O−MeOH-d_4−KOD): δ 185.0, 183.9, 139.4, 139.0, 130.0 (2C), 129.4 (2C), 127.4, 127.1, 56.1, 45.9, 45.6, 39.9, 16.3. IR (KBr): 3022, 2926, 1695, 1581, 1489 cm^{-1}. Anal. ($C_{16}H_{23}NO_4$) C, H, N.

Supporting Information Available: Detailed analytical data for the compounds discussed. This material is available free of charge via the Internet at http://pubs.acs.org.

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