Synthesis of Enantiomerically Pure 4-Substituted Glutamic Acids and Prolines: General Aldol Reaction of Pyroglutamate Lactam Lithium Enolate Mediated by $Et_2O{\cdot}BF_3$

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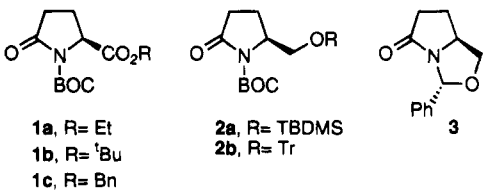
The unnatural amino acids are of considerable biological interest, and two significant examples are substituted prolines and glutamic acids. Thus, substituted prolines have played an important role in the development of novel angiotensin-converting enzyme inhibitors (ACE)[1] and potential mechanism-based inhibitors of proline dehydrogenase.[2] Furthermore, some prolines have been used in protein folding[3] in order to introduce conformational constraints into peptides and allow the study of bioactive conformations.[4] On the other hand, glutamic acid acts as one of the major neurotransmitters at excitatory synapses in the mammalian central nervous system (CNS).[5] This amino acid neurotransmitter and its receptors are implicated in the pathogenesis of many CNS disorders.[6] Several 4-substituted glutamic acid derivatives are natural products,[7] and others with various lengths of the substituents and stereochemistry have been prepared[8] in order to study the structure–activity relationships of excitatory effects on the nervous system. Despite these interests, few efficient methods have been reported to obtain enantiomerically pure 4-substituted prolines[9] or glutamic acids.[8,9a,10]



1a, R= Et
1b, R= ^{t}Bu
1c, R= Bn

2a, R= TBDMS
2b, R= Tr

3

Figure 1.

In this paper we report a quite general, short, and efficient method for the synthesis of both enantiomerically pure 4-substituted prolines and glutamic acids. The key step of the sequence is the aldol reaction of pyroglutamate lithium lactam enolate with carbonyl compounds, both aldehydes and ketones, under $Et_2O{\cdot}BF_3$ catalyst.

It is well known that lactam enolates from variously modified forms of pyroglutamic acid can be generated, in which the carboxylic substituent was reduced to the alcohol and protected with bulky groups[11] **2a,b** or as *O,N*-acetal[12] **3** (Figure 1) in order to remove the acidifying effect on the C2-proton and to ensure the asymmetric induction. More recently it has been shown that lactam enolates of *N*-urethane-protected pyroglutamates **1a-c** can be diastereoselectively functionalized[13] without loss of optical purity.

In the particular case of the aldol reactions of pyroglutamates[14] the scope has been restricted to very reactive aldehydes such as benzaldehydes or α,β-unsaturated aldehydes. In these cases, yields were moderate to good, whereas with other less reactive aldehydes, like alkyl aldehydes, yields were poor or the reaction did not take place. On the other hand, to our knowledge, there is not any report in the literature concerning the aldol condensation of pyroglutamate lactam enolates with ketones.

As a consequence of our interest on the chemistry of pyroglutamic acid,[7c,13,15] and taking into account that 4-alkylprolines **7** and glutamic acids **8** could be obtained from diastereomerically pure 4-substituted pyroglutamates

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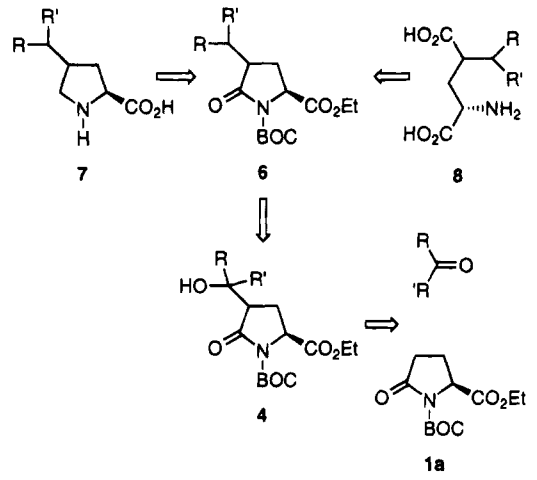
Scheme 1



6, which in turn could be derived from the hydroxy derivatives **4** resulting from the aldol condensation of **1a** (Scheme 1), we decided to carry out a detailed study of this last reaction in order to extend its scope to different carbonyl compounds, aldehydes, and ketones.

L-Ethyl pyroglutamate was prepared from L-glutamic acid[16] and protected as the *N*-BOC derivative.[17] The reaction of **1a** with LiHMDS in anhydrous THF at −78 °C yielded the corresponding lactam lithium enolate, which was further treated with several aldehydes and ketones under different Lewis acids as catalysts. The reaction conducted with $TiCl_4$, $ZnBr_2$, $EtAlCl_2$, and $MgBr_2$ proved to be ineffective, but in the presence of $Et_2O{\cdot}BF_3$ diastereomeric mixtures of the hydroxyalkylated products **4** were obtained (Scheme 2 and Table 1) in good yields.

The reactions with reactive aldehydes (entries a-d, Table 1) take place with better yields than those previously reported[14a,b] in the absence of $Et_2O{\cdot}BF_3$ (entries a, d). High yields were also obtained with alkyl aldehydes (entries e-h) where the presence of the catalyst is mandatory for the reaction to take place. The reaction with ketones (entries i, j) were also successful producing yields of the same order as with aldehydes.

No attempt was made to separate these diastereomeric mixtures **4** as in the following step both chiral centers were going to gain an sp^2 status. Thus, the diasteromeric mixtures of **4** were treated with mesyl chloride in the presence of excess triethylamine in methylene chloride at room temperature for 48 h. Under these reaction conditions the mesylate eliminated giving the 4-alkylidenepyroglutamates **5**. With benzyl aldehydes the newly generated double bond had exclusively the *E* stereochemistry, whereas with alkyl aldehydes different *Z*/*E* mixtures were obtained which were separable by flash chromatography. The 4-alkylidenepyroglutamates **5** were hydrogenated with the aid of platinum oxide as catalyst, giving rise to the *cis* 4-substituted pyroglutamates **6**. The *cis*-relative stereochemistry was confirmed by the ^{1}H-NMR spectra of **6a** and **6b** which were identical in all respects to those prepared by equilibration of the corresponding *trans*-isomers.[13a] It should be noted that hydrogenation took place exclusively on the less hindered face of the pyroglutamate. The same result has been reported in the hydrogenation of the corresponding 4-substituted 3,4-didehydro derivatives of **2a** where the bulkiness of the alcohol protecting group directed hydrogenation.[8] Our results show that it is not necessary to have a bulky ester group to achieve stereoselectivity in this step.[18]

Reduction of the amide carbonyl group on **6** was accomplished using the highly chemoselective reduction method recently reported by us.[19] Thus, partial reduction of the amide into the aminal was accomplished with lithium triethyl borohydride (superhydride) in THF at −78 °C. Without purification, the aminal was reduced directly to the corresponding prolines with triethylsilane and excess of boron trifluoride ethearate in methylene chloride at −78 °C. The Lewis acid is responsible for the generation of an *N*-acyliminium ion intermediate[20] which is reduced by the triethylsilane. Finally, the acidic hydrolysis of the corresponding ethyl prolinate delivered the chiral 4-substituted prolines **7**, which were isolated as zwitterions by treating with propylene oxide a methanolic solution of the hydrochloride. The synthesis of the 4-substituted glutamic acids **8** was also carried out by acidic hydrolysis of **6**, being isolated either as hydrochlorides or zwitterions.

The optical purity of the final products **7** and **8** was investigated. Thus, proline **7a** was transformed into its ethyl ester hydrochloride and subsequently treated with both enantiomers of methoxy-α-(trifluoromethyl)phenylacetyl chloride[21] in the presence of propylene oxide, giving an enantiomeric excess (ee) >95% (detection limit determined by doping experiments). Unfortunately **8a** could not be derivatized to the corresponding Mosher amide as in the proline **7a**. Thus, the glutamic acid **8a** was recyclized to the ethyl *N*-BOC-pyroglutamate under the usual conditions, and reduction of the amide carbonyl group yielded the corresponding proline **7a** displaying the same optical rotation.

As we mentioned before, some 4-alkylideneglutamic acids like **9e** and **9f** (Scheme 3) are naturally-occurring products,[22] and syntheses of these products have been reported recently.[7f] Direct acidic hydrolysis of **5e** and **5f** resulted in the addition of HCl to the double bond. In order to avoid this, compounds **9e** and **9f** were obtained in a two-step hydrolytic sequence. First, basic hydrolysis with LiOH produced the *N*-BOC-protected diacid intermediates which were further hydrolyzed with a saturated solution of HCl in ethyl acetate at room temperature. Both **9e** and **9f** displayed the same spectroscopic data and optical rotation as those described for these natural products indicating that no racemization had taken place in any of the reactions.

The configuration of the C-4 substituent of both **7** and **8** arises from the completely stereocontrolled hydrogenation step. However, the opposite C-4 configuration could be obtained when the pyroglutamates **6** were equili-

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Scheme 2

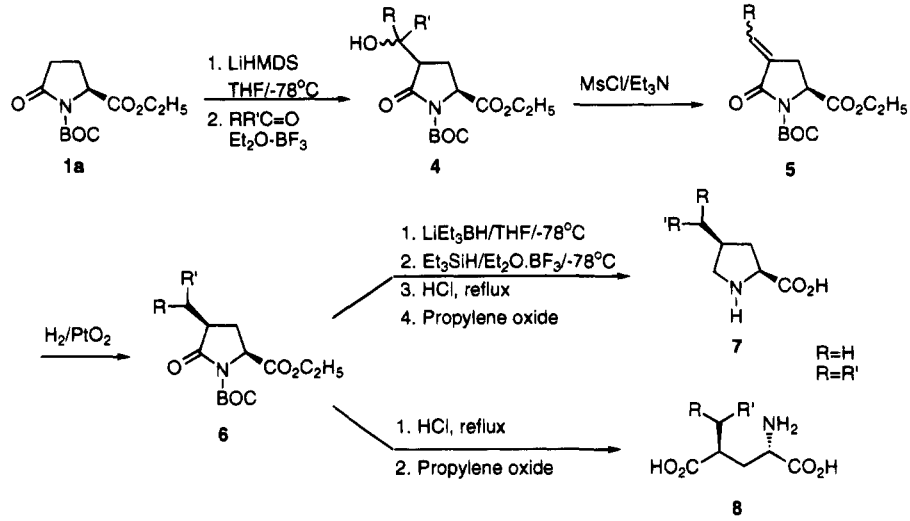
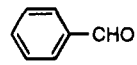
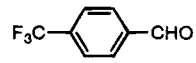
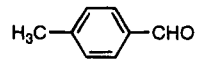
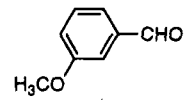
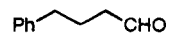
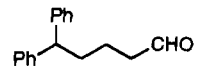
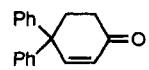
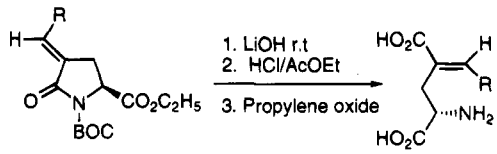


Table 1

Entry	RR'C=O	Yield (%)[a] 4[b]	5	6	7	8
a		72 (69[c])	62	77[d]	64[e]	81[f]
b		--	36[j]	68[d]	70[e]	70[f]
c		81	77	82	--	88[g]
d		61 (58[g])	73	93	54[e]	89[f]
e	CH_3-CHO	67	66	--	--	--
f	CH_3CH_2-CHO	64 (25[c],40[h])	70	--	--	--
g		83	76	72	--	75[f]
h		80	81	90	74[e]	83[f]
i		78	84	92	--	68[g]
j		80	78[j]	92	81[g]	78[g]

[a] Isolated yield. [b] Reported yield in the literature in parentheses. [c] Reference 14a. [d] Reference 13a. [e] Isolated as a zwitterion. [f] Isolated as a hydrochloride. [g] Reference 14b. [h] Reference 14c. [i] This product was obtained as a complex mixture of regioisomers in the double bond and was used without further separation. [j] Overall yield from **1a**.

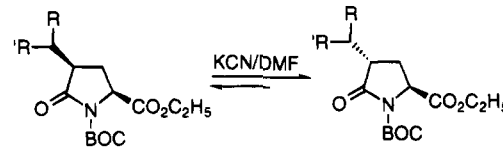
Scheme 3



5e, R=CH_3
5f, R=C_2H_5

9e, R=CH_3
9f, R=C_2H_5

Scheme 4



6 **10**

brated[13a] (Scheme 4) with potassium cyanide in DMF at room temperature for 24 h. In the equilibrium mixture the *trans* diastereoisomers **10** are the major components as they are the thermodynamically favored compounds, and it was possible to separate the 3–2.5/1 *trans*/*cis* mixtures obtained by flash chromatography.

In conclusion, we have reported here a new entry to the synthesis of enantiomerically pure 4-substituted prolines and glutamic acids, based on the general scope

of the $Et_2O{\cdot}BF_3$-catalyzed aldol condensation of pyroglutamate lithium lactam enolate with aldehydes and ketones.

Experimental Section

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. ^{1}H-NMR and ^{13}C-NMR data were recorded on a Bruker AC-200P (200 MHz). IR spectra were obtained on Nicolet 510 P-FT (film, KBr, and in solution $CHCl_3$). 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 Servicio Interdepartamental de Investigación (SIdI, Universidad Autónoma de Madrid).

General Procedure for Aldol Reactions on Ethyl *N*-BOC-pyroglutamate and Further Treatment of the Resulting Aldol Mixtures with Methanesulfonyl Chloride and Triethylamine. Synthesis of 4-Alkylidenepyroglutamates. To a solution of ethyl *N*-BOC-pyroglutamate (**1a**) (15.6 mmol) in THF (50 mL) stirred at −78 °C was added a 1 M solution of lithium hexamethyldisilazide in THF (18.7 mL, 18.7 mmol, 1.1 equiv). The reaction mixture was stirred for 1 h at −78 °C prior to the addition of a solution of the aldehyde (17.2 mmol) and $Et_2O{\cdot}BF_3$ (17.2 mmol) in THF (50 mL). The reaction mixture was stirred for 1 h at −78 °C (for aldehydes) or 2.5 h (for ketones), quenched with saturated ammonium chloride solution (100 mL), and extracted with ethyl ether (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated to dryness. Purification of the crude by flash chromatography (hexane/ethyl acetate 2:1) gave a mixture of aldols **4** with the yields shown in Table 1. The aldol mixture **4** was dissolved in CH_2Cl_2 (30 mL) and treated with methanesulfonyl chloride (1.34 mL, 17.2 mmol) and triethylamine (18 mL, 172 mmol). After this solution was stirred for 2 days at room temperature it was quenched with water and extracted with dichloromethane (3 × 50 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure affording the alkylidenepyroglutamates **5** which were purified by flash chromatography (eluent is indicated in each case).

Ethyl (2*S*,*E*)-1-(*tert*-Butoxycarbonyl)-4-(phenylmethylidene)pyroglutamate (5a): Only the *E* isomer was obtained: white needles; mp 109–10 °C (hexane/ethyl acetate 3:1); 62% yield; $[\alpha]_D = -3.2°$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3003, 2980, 1776, 1733, 1318, 1153 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.56 (t, J = 3.0 Hz, 1H), 7.48–7.34 (m, 5H), 4.72 (dd, J = 3.0 and 10.1 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.38 (ddd, J = 3.0, 10.1 and 17.9 Hz, 1H), 2.88 (dt, J = 3.0 and 17.9 Hz, 1H), 1.54 (s, 9H), 1.28 (t, J = 7.1Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.6, 166.5, 149.3, 134.5, 134.1, 129.6 (2C), 129.1, 128.4 (2C), 126.8, 83.0, 61.2, 55.6, 27.4 (4C), 13.6. Anal. Calcd for $C_{19}H_{23}NO_5$: C, 66.07; H, 6.71; N, 4.06. Found: C, 65.71; H, 6.77; N, 4.06.

Ethyl (2*S*,*E*)-1-(*tert*-Butoxycarbonyl)-4-[[*p*-(trifluoromethyl)phenyl]methylidene]pyroglutamate (5b). Only the *E* isomer was obtained; white needles; mp 144–5 °C (hexane/ethyl acetate 3:1); 36% overall yield from **1**; $[\alpha]_D = -7.3°$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3005, 1782, 1740, 1325, 1153 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.68 and 7.55 (AA′, 4H), 7.57 (t, J = 3.0 Hz, 1H), 4.74 (dd, J = 3.0 and 10.1 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.39 (ddd, J = 3.0, 10.1 and 18.1 Hz, 1H), 2.98 (dt, J = 3.0 and 18.1 Hz, 1H), 1.54 (s, 9H), 1.28 (t, J = 7.1Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.7, 166.2, 149.2, 137.6, 132.8, 129.8 (4C), 125.4, 125.3, 123.5 (q, J = 272.3 Hz, 1C), 83.5, 61.5, 55.8, 27.6, 27.5 (3C), 13.7. Anal. Calcd for $C_{20}H_{22}F_3NO_5$: C, 58.11; H, 5.36; N, 3.39. Found: C, 57.77; H, 5.26; N, 3.37.

Ethyl (2*S*,*E*)-1-(*tert*-Butoxycarbonyl)-4-[(*p*-methylphenyl)methylidene]pyroglutamate (5c). Only the *E* isomer was obtained: white needles; mp 172–4 °C (hexane/ethyl acetate 3:1); 77% yield; $[\alpha]_D = +14.6°$ (*c* 1.03, $CHCl_3$); IR (KBr pellet) 2975, 1770, 1740, 1332, 1152 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.53 (t, J = 3.0 Hz, 1H), 7.36 and 7.23 (AA′, 4H), 4.71 (dd, J = 3.0 and 10.1 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.46 (ddd, J = 3.0, 10.1 and 17.8 Hz, 1H), 2.97 (dt, J = 3.0 and 17.8 Hz, 1H), 2.38 (s, 3H), 1.53 (s, 9H), 1.28 (t, J = 7.1Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.9, 166.9, 149.6, 139.8, 134.9, 131.6, 129.9 (2C), 129.4 (2C), 125.7, 83.2, 61.5, 55.9, 27.7, 27.6 (3C), 21.2, 13.8. Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.90; H, 7.09; N, 3.84.

Ethyl (2*S*,*E*)-1-(*tert*-Butoxycarbonyl)-4-[(*m*-methoxyphenyl)methylidene]pyroglutamate (5d). Only the *E* isomer was obtained: yellow solid; mp 72–3 °C (hexane/ethyl acetate 3:1); 73% yield; $[\alpha]_D = -3.6°$ (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 2980, 1780, 1736, 1315, 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.52 (t, J = 3.0 Hz, 1H), 7.38–6.90 (m, 4H), 4.71 (dd, J = 3.0 and 10.0 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 3.37 (ddd, J = 3.0, 10.0, and 17.9 Hz, 1H), 2.98 (dt, J = 3.0 and 17.9 Hz, 1H), 1.54 (s, 9H), 1.28 (t, J = 7.1Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 166.2, 158.9, 148.8, 135.0, 134.1, 129.1, 126.8, 121.6, 114.8, 114.3, 82.6, 60.9, 55.4, 54.5, 27.1 (4C), 13.4; HRMS calcd for $C_{20}H_{25}NO_6$ 375.1681, found 375.1678.

Ethyl (2*S*)-1-(*tert*-Butoxycarbonyl)-4-ethylidenepyroglutamate (5e). A 85:15 mixture of *E*/*Z* isomers was obtained. The diastereomers were separated by chromatography (hexane/ethyl acetate 3:1), 66% yield. For the *E* isomer: oil; $[\alpha]_D = -11.6°$ (*c* 0.24, $CHCl_3$); IR ($CHCl_3$) 2990, 1780, 1735, 1325, 1155 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 6.78 (qt, J = 2.8 and 7.1 Hz, 1H), 4.61 (dd, J = 3.7 and 10.2 Hz, 1H), 4.58–4.16 (m, 2H), 3.04–2.87 (m, 1H), 2.66–2.54 (m, 1H), 1.80 (dt, J = 1.8 and 7.1 Hz, 3H), 1.51 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.0, 165.6, 149.6, 133.8, 129.1, 83.0, 61.3, 55.5, 27.5 (3C), 25.2, 14.6, 13.8; HRMS calcd for $C_9H_{13}NO_3$ [$M^+ - CO_2C(CH_3)_3 + 1$] 183.0895, found 183.0891.

For the *Z* isomer: oil; IR ($CHCl_3$) 3000, 1770, 1725, 1315, 1150 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 6.15 (qt, J = 2.2 and 7.3 Hz, 1H), 4.54 (dd, J = 3.5 and 10.2 Hz, 1H), 4.27–4.19 (m, 2H), 3.08–2.91 (m, 1H), 2.65–2.53 (m, 1H), 2.21 (dt, J = 1.8 and 7.3 Hz, 3H), 1.52 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.2, 165.9, 150.2, 138.2, 127.8, 83.3, 61.5, 55.8, 29.2, 27.9 (3C), 14.1, 13.7.

Ethyl (2*S*,*E*)-1-(*tert*-Butoxycarbonyl)-4-propylidenepyroglutamate (5f). A 92:8 mixture of *E*/*Z* isomers was obtained. Isolation of the minor isomer was not possible. Pure *E* isomer was isolated by column chromatography (hexane/ethyl acetate 4:1): oil; 70% yield; $[\alpha]_D = -11.3°$ (*c* 0.76, $CHCl_3$); IR ($CHCl_3$) 3010, 1780, 1735, 1315, 1155 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 6.71 (tt, J = 2.9 and 7.5 Hz, 1H), 4.61 (dd, J = 3.7 and 10.1 Hz, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.04–2.88 (m, 1H), 2.66–2.53 (m, 1H), 2.23–2.07 (m, 2H), 1.51 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H), 1.06 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.2, 165.9, 149.9, 140.6, 127.8, 83.3, 61.5, 55.8, 27.8 (3C), 25.4, 22.7, 14.0, 12.5; HRMS calcd for $C_{10}H_{15}NO_3$ [$M^+ - CO_2C(CH_3)_3 + 1$] 197.1052, found 197.1046.

Ethyl (2*S*)-1-(*tert*-Butoxycarbonyl)-4-(4-phenylbutylidene)pyroglutamate (5g). A 76:24 mixture of *E*/*Z* isomers was obtained. The diastereomers were separated by chromatography (hexane/ethyl acetate 3:1), 76% yield. For the *E* isomer: colorless oil; $[\alpha]_D = +2.5°$ (*c* 1.0, $CHCl_3$); IR (film) 1784, 1748, 1717, 1317, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35–7.10 (m, 5H), 6.74 (tt, J = 2.7 and 7.5 Hz, 1H), 4.60 (dd, J = 3.5 and 10.2 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.02–2.80 (m, 1H), 2.70–2.45 (m, 2H), 2.15 (m, 2H), 1.79 (q, J = 7.5 Hz, 2H), 1.52 (s, 9H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.9, 165.6, 149.5, 141.1, 138.4, 128.5, 128.0, 125.6, 83.0, 61.3, 55.5, 34.8, 29.3, 28.3, 27.5, 25.2, 13.8; HRMS calcd for $C_{22}H_{29}NO_5$ 287.1521, found 287.1521.

For the *Z* isomer: colorless oil; $[\alpha]_D = -10.0°$ (*c* 1.0, $CHCl_3$); IR (film) 1784, 1746, 1717, 1318, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35–7.10 (m, 5H), 6.02 (tt, J = 2.1 and 7.7 Hz, 1H), 4.50 (dd, J = 3.3 and 10.0 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.10–2.75 (m, 3H), 2.70–2.50 (m, 3H), 1.82–1.60 (m, 2H), 1.48 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.1, 165.7, 150.0, 143.1, 142.0, 128.3, 128.2, 128.1, 125.6, 83.2, 61.4, 55.8, 35.4, 30.9, 29.0, 27.8, 26.9, 14.0; HRMS calcd for $C_{22}H_{29}NO_5$ 287.1521, found 287.1522.

Ethyl (2*S*,*E*)-1-(*tert*-Butoxycarbonyl)-4-(5,5-diphenylpentylidene) pyroglutamate (5h). A 92:8 mixture of *E*/*Z* isomers was obtained. Isolation of the minor isomer was not possible. Pure *E* isomer was isolated by column chromatography (hexane/ethyl acetate 4:1): colorless oil; 81% yield; $[\alpha]_D = -1.9°$ (*c* 0.78, CH_2Cl_2); IR (film) 2980, 1784, 1748, 1717, 1317, 1196,

1153 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.26–7.16 (m, 10H), 6.66 (tt, J = 2.9 and 7.7 Hz, 1H), 4.56 (dd, J = 3.6 and 10.2 Hz, 1H), 4.15 (dq, J = 1.8 and 7.1 Hz, 2H), 3.84 (t, J = 7.8 Hz, 1H), 3.00–2.75 (m, 1H), 2.62–2.05 (m, 1H), 2.20–1.95 (m, 4H), 1.48 (s, 9H), 1.48–1.35 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.2, 165.9, 149.9, 144.60, 144.58, 138.9, 128.6, 128.4 (2C), 127.7 (2C), 126.2 (2C), 83.5, 61.6, 55.8, 51.2, 35.2, 29.3, 27.9, 26.7, 25.6, 14.1; HRMS calcd for $C_{29}H_{35}NO_5$ [$M^+ - CO_2C(CH_3)_3 + 1$] 377.1991, found 377.1994.

Ethyl (2*S*)-1-(*tert*-butoxycarbonyl)-4-isopropylidenepyroglutamate (5i): white needles; mp 52–3 °C (hexane/ethyl acetate 3:1); 84% yield; $[\alpha]_D = -28.0°$ (c 1.1, $CHCl_3$); IR ($CHCl_3$) 2980, 1775, 1730, 1320, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.54 (dd, J = 3.7 and 10.5 Hz, 1H), 4.27–4.16 (m, 2H), 3.04–2.84 (m, 1H), 2.63–2.51 (m, 1H), 2.28 (t, J = 2.2 Hz, 3H), 1.81 (t, J = 1.3 Hz, 3H), 1.51 (s, 9H), 1.28 (t, J = 7.1Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.1, 165.5, 149.7, 148.9, 120.8, 82.3, 60.9, 54.5, 27.4 (3C), 27.0, 23.6, 19.2, 13.6; HRMS calcd for $C_{15}H_{24}NO_5$ (M + 1) 298.1654, found 298.1650.

General Procedure for Hydrogenation. To a solution of alkene **5** (5 mmol) in 25 mL of ethyl acetate was added 0.5 mmol (0.1 equiv) of platinum(IV) oxide. The reaction was allowed to proceed under hydrogen atmosphere at rt and atmospheric pressure for 4 h. Filtration of the catalyst through Celite gave compounds **6** whose purification was achieved by flash chromatography (the eluent is indicated in each case).

Ethyl (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(*p*-tolylmethyl)-pyroglutamate (6c): white needles; mp 61–3 °C (hexane/ethyl acetate 3:1); 82% yield; $[\alpha]_D = +54.7°$ (c 1.04, $CHCl_3$); IR (KBr pellet) 2975, 1787, 1770, 1745, 1305, 1146 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.10 and 7.02 (AA', 4H), 4.45 (dd, J = 6.6 and 8.6 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.28 (dd, J = 3.8 and 13.6 Hz, 1H), 2.90–2.74 (m, 1H), 2.60 (dd, J = 10.9 and 13.6 Hz, 1H), 2.40–2.29 (m, 1H), 2.31 (s, 3H), 1.76–1.59 (m, 1H), 1.50 (s, 9H), 1.28 (t, J = 7.1Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.8, 170.2, 147.9, 134.4, 134.1, 127.9 (2C), 127.4 (2C), 81.5, 60.0, 56.1, 42.8, 34.8, 26.4 (3C), 25.5, 19.5, 12.8. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.19; H, 7.50; N, 3.81.

Ethyl (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(*m*-methoxybenzyl)pyroglutamate (6d): oil (hexane/ethyl acetate 4:1); 93% yield; $[\alpha]_D = +43.9°$ (c 0.82, $CHCl_3$); IR (film) 2995, 1790, 1745, 1320, 1153 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 7.24–7.16 (m, 1H), 6.79–6.69 (m, 3H), 4.45 (dd, J = 6.9 and 8.9 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.33 (dd, J = 3.8 and 13.6 Hz, 1H), 2.83–2.78 (m, 1H), 2.61 (dd, J = 10.9 and 13.6 Hz, 1H), 2.34 (dt, J = 8.9 and 13.6 Hz, 1H), 1.77–1.64 (m, 1H), 1.50 (s, 9H), 1.29 (t, J = 7.1Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.6, 170.7, 159.0, 148.4, 139.2, 128.8, 120.2, 113.7, 111.0, 82.4, 60.6, 56.6, 54.2, 43.3, 35.8, 26.9 (3C), 26.0, 13.3; HRMS calcd for $C_{20}H_{27}NO_6$ 377.1838, found 377.1833.

Ethyl (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(4-phenylbutyl)-pyroglutamate (6g): oil (hexane/ethyl acetate 4:1); 72% yield; $[\alpha]_D = -5.3°$ (c 1.0, $CHCl_3$); IR (film) 1790, 1748, 1717, 1316, 1151 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35–7.10 (m, 5H), 4.47 (t, J = 8.1 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H), 2.70–2.40 (m, 5H), 2.05–1.40 (m, 6H), 1.50 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.9, 171.2, 149.0, 141.9, 128.0, 127.9, 125.3, 83.0, 61.2, 57.1, 42.2, 35.2, 30.8, 30.5, 27.5, 27.3, 26.3, 13.8; HRMS calcd for $C_{22}H_{31}NO_5$ 289.1678, found 289.1674.

Ethyl (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(5,5-diphenylpentyl) pyroglutamate (6h): oil (hexane/ethyl acetate 4:1); colorless oil; 90% yield; $[\alpha]_D = -7.0°$ (c 1.0, CH_2Cl_2); IR (film) 2937, 1790, 1751, 1717, 1325, 1152, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.25–7.17 (m, 10H), 4.43 (dd, J = 7.1 and 8.3 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.84 (t, J = 7.8 Hz, 1H), 2.44 (m, 2H), 2.00 (m, 2H), 1.90–1.70 (m, 1H), 1.60 (m, 2H), 1.46 (s, 9H), 1.35–1.20 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.9, 171.2, 149.1, 144.8, 144.7, 128.1 (2C), 127.50, 127.48, 125.8 (2C), 83.1, 61.2, 57.2, 50.9, 42.2, 35.1, 30.5, 27.6, 27.4, 27.3, 26.7, 13.8; HRMS calcd for $C_{24}H_{29}NO_3$ (M^+ – BOC) 379.2147, found 379.2148.

Ethyl (2*S*,4*R*)-1-(*tert*-butoxycarbonyl)-4-isopropylpyroglutamate (6i): white needles; mp 52–4 °C (hexane/ethyl acetate 3:1); 92% yield; $[\alpha]_D = -13.0°$ (c 1.0, $CHCl_3$); IR ($CHCl_3$) 2980, 1785, 1740, 1315, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.44 (t, J = 7.8 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 2.57–2.18 (m, 3H), 1.85–1.64 (m, 1H), 1.48 (s, 9H), 1.28 (t, J = 7.1Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.2, 171.3, 149.2, 83.2, 61.3, 57.0, 48.1, 27.8, 27.6 (3C), 23.1, 20.3, 17.8, 13.9. Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found C, 59.89; H, 8.16; N, 4.48.

Ethyl (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(4'-diphenylcyclohexyl)pyroglutamate (6j): white solid; mp 56–8 °C (hexane/ethyl acetate 3:1); 92% yield; $[\alpha]_D = +3.4°$ (c 1.0, $CHCl_3$); IR ($CHCl_3$) 2970, 1780, 1740, 1315, 1145 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36–7.07 (m, 10H), 4.39 (dd, J = 7.0 and 8.6 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 2.74–2.65 (m, 2H), 2.42–2.20 (m, 2H), 2.05–1.89 (m, 4H), 1.62–1.49 (m, 2H), 1.47 (s, 9H), 1.33–1.15 (m, 2H) 1.23 (t, J = 7.1Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.2, 171.2, 150.7, 149.3, 144.7, 128.4, 128.0 (2C), 127.8 (2C), 126.0 (3C), 125.4 (2C), 83.4, 61.3, 57.1, 47.2, 45.6, 37.8, 36.3, 36.0, 27.7 (3C), 27.3, 24.5, 23.9, 14.0. Anal. Calcd for $C_{30}H_{37}NO_5$: C, 73.29; H, 7.59; N, 2.85. Found: C, 72.98; H, 7.62; N, 2.72.

General Chemoselective Method for Lactam Reduction of the Pyroglutamates (6). Synthesis of 4-Substituted Prolines (7). A 1.0 M solution of lithium triethylborohydride in THF (1.62 mL, 1.62 mmol) was added to a solution of **6** (1.35 mmol) in THF (10 mL) at −78 °C under nitrogen atmosphere. After 30 min the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2.5 mL) and warmed to 0 °C. Thirty percent H_2O_2 (5 drops) was added, and the mixture was stirred at 0 °C. After 20 min the organic solvent was removed *in vacuo*, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude reaction mixture was used without further purification and dissolved in CH_2Cl_2 (20 mL). After the addition of triethylsilane (0.21 mL, 1.35 mmol) the mixture was cooled to −78 °C. Boron trifluoride etherate (0.18 mL, 1.48 mmol) was added, dropwise under nitrogen atmosphere. After 30 min triethylsilane (0.21 mL) and boron trifluoride etherate (0.18 mL) were added, allowing the reaction to reach room temperature. After being stirred for 30 min at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL), extracted with CH_2Cl_2 (3 × 10 mL), and dried over Na_2SO_4. Evaporation of the solvent and purification by flash chromatography (CH_2Cl_2/MeOH 18:1) yielded proline ethyl esters which were hydrolyzed at 60 °C overnight with 6 N HCl solution (10 mL). The resulting solution was evaporated to dryness, and the solid was triturated with acetone. Finally, the hydrochloride was dissolved in MeOH and an excess of propylene oxide was added. After evaporation of the solvent, the solid was triturated with ethyl ether and filtered.

(2*S*,4*S*)-4-Benzylproline (7a): white solid; mp 190 °C dec; 64% yield; $[\alpha]_D = -39.3°$ (c 0.28, MeOH); IR (KBr pellet) 3428, 1605, 1454 cm^{-1}; ^{1}H NMR (MeOH-d_4/KOD) δ 7.30–7.10 (m, 5H), 3.48 (t, J = 8.3 Hz, 1H), 2.90–2.60 (m, 4H), 2.50–2.10 (m, 2H), 1.45 (m, 1H); ^{13}C NMR (MeOH-d_4/KOD) δ 181.9, 142.4, 129.8, 129.4, 127.0, 63.3, 52.9, 43.4, 40.8, 38.8. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.56; H, 7.88; N, 6.02.

(2*S*,4*S*)-4-[*p*-(Trifluoromethyl)benzyl]proline (7b): white solid; mp >194 °C dec; 70% yield; $[\alpha]_D = -21.9°$ (c 0.41, MeOH); IR (KBr pellet) 3450, 1653, 1622 cm^{-1}; ^{1}H NMR (MeOH-d_4/KOD) δ 754 and 7.38 (AA' system, 4H), 3.49 (t, J = 8.1 Hz, 1H), 2.90–2.70 (m, 4H), 2.45 (m, 1H), 2.25 (m, 4H), 1.48 (td, J = 12.4 and 7.9 Hz, 1H); ^{13}C NMR (MeOH-d_4/KOD) δ 181.7, 147.2, 130.5, 129.2, 126.2, 124.9, 63.2, 52.9, 43.0, 40.4, 38.5. Anal. Calcd for $C_{13}H_{14}F_3NO_4 \cdot 1/2H_2O$: C, 56.05; H, 5.57; N, 4.48. Found: C, 55.83; H, 5.16; N, 4.79.

(2*S*,4*S*)-4-[(*m*-Methoxyphenyl)methyl]proline (7d): white solid; mp >170 °C dec; 54% yield; $[\alpha]_D = -34.3°$ (c 0.3, MeOH); IR (KBr pellet) 3100, 2925, 1600, 1380 cm^{-1}; ^{1}H NMR (MeOH-d_4) δ 7.27–7.19 (m, 1H), 6,83–6.79 (m, 3H), 4.00 (t, J = 8.6 Hz, 1H), 3.80 (s, 3H), 3.37–3.28 (m, 1H), 3.07 (dd, J = 8.4 and 11.5 Hz, 1H), 2.77–2.38 (m, 4H), 1.81 (dt, J = 8.6 and 12.9, 1H); ^{13}C NMR (MeOH-d_4) δ 173.9, 161.4, 142.3, 130.6, 122.0, 115.4, 112.9, 62.6, 55.6, 51.3, 42.0, 39.2, 36.1. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.94; H, 6.81; N, 5.54.

(2*S*,4*S*)-4-(5,5-Diphenylpentyl)proline (7h): white solid; mp 197–9 °C dec; 74% yield $[\alpha]_D = -20.0°$ (c 0.25, DMSO); IR (KBr pellet) 3441, 1620, 1396 cm^{-1}; ^{1}H NMR (MeOH-d_4/KOD) δ 7.30–7.10 (m, 10H), 3.84 (t, J = 8.0 Hz, 1H), 3.45 (t, J = 8.0 Hz, 1H), 2.88 (dd, J = 7.0 and 10.0 Hz, 1H), 2.58 (t, J = 8.4 Hz, 1H), 2.26 (dt, J = 7.4 and 12.1 Hz, 1H), 2.05–1.90 (m, 3H), 1.40–1.25 (m, 7H); ^{13}C NMR (MeOH-d_4/KOD) δ 182.0, 146.7, 129.4, 128.8, 127.1, 63.4, 53.2, 52.6, 41.5, 39.2, 36.8, 34.9, 29.6, 29.3. Anal. Calcd for $C_{22}H_{27}NO_2 \cdot 1/2H_2O$: C, 76.27; H, 8.14; N, 4.04. Found: C, 76.75; H, 8.01; N, 4.16.

(2S,4S)-4-(4,4-Diphenylcyclohexyl)proline (7j): white solid; mp 183–5 °C dec; 81% yield; $[\alpha]_D = -19.7°$ (*c* 0.46, MeOH); IR (KBr pellet) 3439, 1636, 1559 cm^{-1}; ^1H NMR (MeOH-d_4/KOD) δ 7.40–7.05 (m, 10H), 3.43 (t, J = 8.8 Hz, 1H), 2.91 (t, J = 9.6 Hz, 1H), 2.75–2.65 (m, 3H), 2.25 (dt, J = 7.1 and 11.9, 1H), 2.00–1.60 (m, 5H), 1.40–1.10 (m, 4H); ^{13}C NMR (MeOH-d_4/KOD) δ 1181.9, 152.5, 146.7, 129.5, 129.1, 129.0, 127.2, 126.6, 126.4, 63.4, 51.5, 47.0, 43.2, 37.5, 37.4, 29.7, 29.5. Anal. Calcd for $C_{23}H_{27}NO_2$: C, 71.66; H, 8.11; N, 3.63. Found: C, 71.48; H, 7.84; N, 3.50.

General Procedure for the Hydrolysis of 4-Substituted Ethyl *N*-BOC Pyroglutamates (6). Synthesis of γ-Substituted Glutamic Acids (8). Method A. A mixture of the pyroglutamate **6** (2 mmol) and 1 N HCl solution (25 mL) was refluxed overnight. The resulting solution was evaporated to dryness yielding a white solid which was triturated with ethyl ether (3 × 20 mL).

Method B. To a solution of the pyroglutamate **6** (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 fully hydrolyzed with a saturated HCl solution in ethyl acetate for 1 h at room temperature. After evaporation to dryness, the resulting white solid was triturated with ethyl ether.

The amino acids **8** were isolated either as hydrochlorides or as zwitterions by treatment of a methanolic solution of the hydrochloride with propylene oxide.

(2S,4S)-2-Amino-4-benzylpentanedioic Acid, Hydrochloride (8a). Method A: white solid; mp 66–8 °C; 81% yield; $[\alpha]_D = +11.4°$ (*c* 0.5, MeOH); IR (KBr) 3430, 2926, 1723, 1630, 1497, 1209 cm^{-1}; ^1H NMR (MeOH-d_4) δ 7.35–7.20 (m, 5H), 3.95 (m, 1H), 3.30–2.85 (m, 3H), 2.10–1.95 (m, 2H). ^{13}C NMR (MeOH-d_4) δ 177.5, 139.4, 130.2, 129.6, 127.8, 52.4, 44.5, 39.5, 32.9. Anal. Calcd for $C_{12}H_{16}ClNO_4 \cdot 1/2H_2O$: C, 50.97; H, 6.06; N, 4.95. Found: C, 50.83; H, 5.90; N, 4.71.

(2S,4S)-2-Amino-4-[4-(trifluoromethyl)benzyl]pentanedioic Acid, Hydrochloride (8b). Method A: white solid; mp 89–90 °C; 70% yield; $[\alpha]_D = +12.6°$ (*c* 0.5, MeOH); IR (KBr) 3426, 2926, 1700, 1636, 1250 cm^{-1}; ^1H NMR (MeOH-d_4) δ 7.65–7.45 (AA′ system, 4H), 4.00 (dd, J = 5.6 and 7.8 Hz, 1H), 3.30–2.90 (m, 3H), 2.20–1.80 (m, 2H); ^{13}C NMR (MeOH-d_4) δ 176.9, 171.0, 144.2 , 130.9 (2C), 130.0, 126.4 (3C), 52.3, 44.1, 39.1, 32.9. Anal. Calcd for $C_{13}H_{15}ClF_3NO_4 \cdot H_2O$: C, 43.41; H, 4.76; N, 3.89. Found: C, 43.47; H, 4.38; N, 3.55.

(2S,4S)-2-Amino-4-(4-methylbenzyl)pentadienoic Acid (8c). Method A: white solid; mp 169–170 °C; 88% yield; $[\alpha]_D = +95.7°$ (*c* 0.56, DMSO); IR (KBr) 3400, 2942, 1724, 1640, 1611 cm^{-1}; ^1H NMR (MeOH-d_4/KOD) δ 7.11 and 7.01 (AA′ system, 4H), 3.20 (t, J = 6.6 Hz, 1H), 2.90–2.70 (m, 1H), 2.50–2.60 (m, 2H), 2.24 (s, 3H), 1.76 (t, J = 7.0 Hz, 2H); ^{13}C NMR (MeOH-d_4/KOD) δ 184.5, 183.0, 139.1, 136.3, 130.1, 129.8, 57.1, 49.3, 40.7, 40.5, 21.2. Anal. Calcd for $C_{13}H_{17}NO_4 \cdot H_2O$: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.79; H, 7.06; N, 5.01.

(2S,4S)-2-Amino-4-(3-methoxylbenzyl)pentanedioic Acid, Hydrochloride (8d). Method A: white solid; mp 65–7 °C; 89% yield; $[\alpha]_D = +15.8°$ (*c* 1.0, MeOH); IR (KBr) 3426, 2932, 1717, 1605, 1300 cm^{-1}; ^1H NMR (MeOH-d_4) δ 7.25 (m, 1H), 6.80 (m, 3H), 4.00 (dd, J = 6.6 and 7.8 Hz, 1H), 3.80 (s, 3H), 3.20–2.80 (m, 3H), 2.20–1.80 (m, 2H); ^{13}C NMR (MeOH-d_4) δ 177.5, 173.7, 161.2, 140.9, 130.5, 122.4, 115.7, 113.1, 52.6, 55.5, 44.4, 39.4, 33.0. Anal. Calcd for $C_{23}H_{27}NO_2 \cdot 1/3CH_3OH$: C, 57.23; H, 6.76; N, 4.49. Found: C, 57.40; H, 6.46; N, 5.03.

(2S,4S)-2-Amino-4-(4-phenylbutyl)pentanedioic Acid (8g). Method A: white solid; mp 167 °C dec; 75% yield; $[\alpha]_D = +9.8°$ (*c* 1.0, MeOH); IR (KBr pellet) 3430, 3300–2200 (CO_2H), 1709, 1208 cm^{-1}; ^1H NMR (MeOH-d_4) δ 7.35–7.10 (m, 5H), 3.90 (dd, J = 5.7 and 8.7 Hz, 1H), 2.80–2.55 (m, 3H), 2.20–1.85 (m, 2H), 1.80–1.55 (m, 4H), 1.50–1.30 (m, 2H); ^{13}C NMR (MeOH-d_4) δ 178.0, 171.6, 143.5, 129.4, 129.3, 126.7, 52.3, 42.6, 36.6, 33.44, 33.37, 32.4, 27.2; HRMS calcd for $C_{15}H_{22}NO_4$ ($M^+ + 1 - HCl$) 280.1549, found 280.1551.

(2S,4S)-2-Amino-4-(5,5-diphenylpentyl)pentanedioic Acid, Hydrochloride (8h). Method A: white solid; mp 150–1 °C; 83% yield; $[\alpha]_D = +3.4°$ (*c* 1.0, MeOH); IR (KBr pellet) 3024, 2932, 1725, 1493, 700 cm^{-1}; ^1H NMR (MeOH-d_4) δ 7.30–7.10 (m, 10H), 3.86 (m, 2H), 2.70 (m, 1H) 2.25–1.95 (m, 4H), 1.60 (m, 1H) 1.50–1.20 (m, 5H); ^{13}C NMR (MeOH-d_4) δ 178.2, 172.1, 146.6 (2C), 129.4 (2C), 128.8 (2C), 127.0 (2C), 52.5, 48.6, 42.8, 36.5, 33.7, 33.4, 29.0, 27.6; HRMS calcd for $C_{22}H_{28}NO_4$ ($M^+ + 1 - HCl$) 370.2018, found 370.2018.

(2S,4S)-2-Amino-4-isopropylpentanedioic Acid (8i). Method A: white solid; mp 175–7 °C; 68% yield; $[\alpha]_D = +32.4°$ (*c* 0.21, DMSO); IR (KBr pellet) 3400, 2950, 1707, 1616 cm^{-1}; ^1H NMR (MeOH-d_4/KOD) δ 3.15 (m, 1H), 2.00–1.60 (m, 4H), 0.94 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H); ^{13}C NMR (MeOH-d_4) δ 184.7, 183.0, 57.9, 55.3, 38.3, 32.4, 21.8, 20.9; HRMS calcd for $C_8H_{15}NO_4$ ($M^+ + 1$) 190.1079, found 190.1080.

(2S,4S)-2-Amino-4-(4,4-diphenylcyclohexyl)pentanedioic Acid (8j). Method B: white solid; mp 141–2 °C; 78% yield; $[\alpha]_D = +17.5°$ (*c* 0.28, DMSO); IR (KBr pellet) 3434, 2930, 1628, 1465 cm^{-1}; ^1H NMR (MeOH-d_4/KOD) δ 7.4–6.9 (m, 10H), 3.10 (t, J = 7.0 Hz, 1H), 2.85–2.60 (m, 2H), 2.00–1.00 (m, 10H); ^{13}C NMR (MeOH-d_4/KOD) δ 184.5, 183.0, 152.7, 146.9, 129.4, 129.1, 129.0, 127.2, 126.5, 126.4, 58.0, 54.5, 47.9, 42.1, 38.4, 37.9, 30.8, 29.1, 28.2. Anal. Calcd for $C_{23}H_{27}NO_2 \cdot 2H_2O$: C, 67.39; H, 7.91; N, 3.14. Found: C, 67.58; H, 7.86; N, 2.98.

(2S,*E*)-4-Ethylideneglutamic Acid (9e). Method B: $[\alpha]_D = +22.0°$ (*c* 0.35, H_2O) [lit.[7e] +21° (*c* 0.35, H_2O)]; ^1H NMR (D_2O) δ 7.08 (q, J = 7.2 Hz, 1H), 3.77 (t, J = 7.8 Hz, 1H), 2.91–2.68 (m, 2H), 1.79 (d, 7.2 Hz, 3H); ^{13}C NMR (D_2O) δ 182.5, 177.3, 138.1, 133.7, 57.5, 35.0, 14.4.

(2S,*E*)-4-Propylideneglutamic Acid (9f). Method B: $[\alpha]_D = +11°$ (*c* 0.5, 3N HCl); ^1H NMR (D_2O) δ 6.88 (t, J = 7.6 Hz, 1H), 3.67 (dd, J = 6.1 and 7.7 Hz, 1H), 2.80–2.57 (m, 2H), 2.09 (quintet, J = 7.6 Hz, 2H), 0.87 (t, J = 7.6 Hz, 3H); ^{13}C NMR (D_2O) δ 182.8, 177.4, 141.0, 133.3, 57.4, 35.3, 22.8, 14.3.

Optical Purity Determination. General Procedure.[23] The prolines **7** (5–10 mg) were converted into the corresponding ester hydrochloride salts with a saturated HCl solution in dry MeOH or EtOH. The hydrochlorides were treated with (+)- or (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (1.2 equiv) in THF in the presence of excess propylene oxide at room temperature. After 1 h, the solvent was evaporated and the residue was washed with a saturated $NaHCO_3$ solution and extracted with ethyl ether (3 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness. The crude Mosher amides were analyzed by ^1H-NMR spectroscopy.

(2S,4S,*R*)-Proline (7a)–MTPA amide: ^1H NMR ($CDCl_3$) δ 7.55–6.89 (m, 10H), 4.50 (dd, J = 8.0 and 9.4 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.82 (q, J = 1.9 Hz, 3H), 3.20 (dd, J = 6.4 and 11.2 Hz, 1H), 3.0 (t, J = 11.2 Hz, 1H), 2.64–2.39 (m, 2H), 2.30–1.88 (m, 2H), 1.56–1.29 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H).

(2S,4S,*S*)-Proline (7a)–MTPA amide: ^1H NMR ($CDCl_3$) δ 7.55–6.89 (m, 10H), 4.47 (t, J = 8.0, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.62 (q, J = 1.9 Hz, 3H), 2.88–2.22 (m, 6H), 1.56–1.29 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H).

(2S,4S,*R*)-Proline (7d)–MTPA amide: ^1H NMR ($CDCl_3$) δ 7.50–7.33 (m, 5H), 7.12 (t, J = 8.0 Hz,1H), 6.73–6.69 (m, 1H), 6.47–6.43 (m, 1H), 6.51–6.47 (m, 2H), 4.50 (t, J = 8.2 Hz, 1H), 3.82 (q, J = 1.4 Hz, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 3.20 (dd, J = 6.6 and 11.2 Hz, 1H), 3.01 (t, J = 11.2 Hz, 1H), 2.63–2.39 (m, 2H), 2.29–1.93 (m, 2H), 1.56–1.29 (m, 1H).

(2S,4S,*S*)-Proline (7d)–MTPA amide: ^1H NMR ($CDCl_3$) δ 7.56–7.39 (m, 5H), 7.12 (t, J = 8.0 Hz, 1H), 6.73–6.68 (m, 1H), 6.47–6.43 (m, 1H), 6.51–6.47 (m, 2H), 4.48 (t, J = 8.3 Hz, 1H), 3.77 (s, 3H), 3.74 (q, J = 1.4 Hz, 3H), 3.74 (s, 3H), 2.61–2.18 (m, 6H), 1.56–1.29 (m, 1H).

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Supplementary Material Available: Copies of ^1H and ^{13}CNMR of all compounds lacking elemental analyses (28 pages). This material is contained in libraries on microfiche, inmediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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