Stereoselective Double Alkylation of Ethyl *N*-Boc-pyroglutamate

Jesús Ezquerra,* Concepción Pedregal, and Almudena Rubio

Centro de Investigación Lilly, S. A., Paraje de la Cruz S/N, 28130 Valdeolmos, Madrid, Spain

Juan José Vaquero, María Paz Matía, Justina Martín, Adolfo Diaz, and José Luis García Navío*

Departamento de Química Orgánica, Universidad de Alcalá, 28871 Alcalá de Henares, Madrid, Spain

Jack B. Deeter

X-Ray Department, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285

Received February 28, 1994

The use of natural α-amino acids as starting materials for the synthesis of enantiomerically-pure compounds has gained a lot of interest in recent times because the single chiral center provides a useful building block.[1] L-Glutamic acid is the least expensive of all the amino acids and, because of its versatility as a chiral synthon and its availability, is one of the most used amino acids. Its transformation into the γ-butyrolactone-γ-carboxylic acid (**1**), with nitrous acid in aqueous solution,[2] or ethyl pyroglutamate (**2**), by treatment with thionyl chloride in refluxing ethanol,[3] has served to prepare valuable starting materials for natural product syntheses.

Thus, the protected alcohol (**3**) derived from the γ-butyrolactone-γ-carboxylic acid (**1**) provides a template where it is possible to control the relative and absolute stereochemistry in the construction of tertiary[4] and quaternary[5] carbon centers contiguous to the lactone carbonyl group. The same approach for creating an unsymmetrical environment has been applied to the pyroglutamate. Substituents have been introduced into the 4-position in a stereocontrolled manner using the lactam enolate from the modified pyroglutamic acid derivatives **4**, in which the carboxylic substituent was reduced to the alcohol and protected with bulky groups[6] or as the *O,N*-acetal.[7] This procedure was thought necessary to prevent the racemization of the amino acid chiral center and ensure 1,3 asymmetric induction.

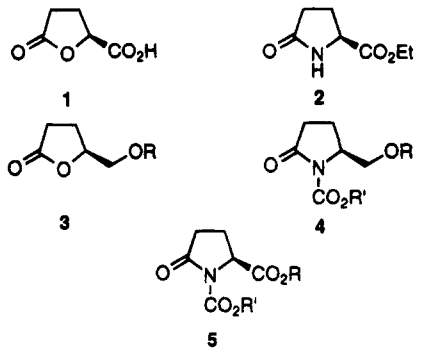


Figure 1.

More recently, it has been shown that lactam enolates derived from hindered esters of *N*-urethane-protected pyroglutamates **5** can be diastereoselectively functionalized[8] without loss of optical purity. The common feature for these syntheses is again the use of bulky ester groups in order to achieve stereoselectivity in the pyroglutamate functionalization. We have shown that this assumption cannot be generalized since *N*-Boc-protected ethyl pyroglutamate reacts with a variety of reactive electrophiles[9] delivering adducts where the stereochemistry depends on the nature of the electrophile, rather than on the ester group bulkiness.

The creation of an asymmetric quaternary center is one of the most challenging problems in synthetic organic chemistry.[10] While the stereoselective double alkylation of **3** is well documented,[5] there is not precedent in the literature for the stereoselective double alkylation of either pyroglutamate esters **5** or its derivatives **4**.[11] Thus, as a part of our interest on the chemistry of pyroglutamic acid,[12] we decided to explore the double alkylation of the ethyl *N*-Boc-pyroglutamate lithium enolate, both with the same and different electrophiles.

(1) (a) Willians, R. M. *Aldrichim. Acta* **1992**, *25*, 11. (b) Coppola, G. M.; Schuster, H. F. In *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*; John Wiley & Sons, Inc.: New York, 1987. (c) Martens, J. *Top. Curr. Chem.* **1984**, *125*, 165.

(2) (a) Eguchi, C.; Kakuta, A. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1704. (b) Taniguchi, M.; Koga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547.

(3) Silverman, R. B.; Levy, M. A. *J. Org. Chem.* **1980**, *45*, 815.

(4) Examples of the synthesis of: (a) (*R*)-(+)-Sulcatol: Mori, K. *Tetrahedron* **1978**, *34*, 1449. (b) (+)-Brefeldin A: Kitahara, T.; Mori, K.; Matsui, M. *Tetrahedron Lett.* **1979**, *20*, 3021. (c) (−)-Stenogenone: Robin, J. P.; Gringore, O.; Brown, E. *Tetrahedron Lett.* **1980**, *21*, 2709.

(5) Precursors in the synthesis of: (a) Gibbane: Takano, S.; Kasahara, C.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1981**, 637. (b) (+)- and (−)-Quebrachamine: Takano, S.; Yonaga, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1981**, 1153. (c) (+)-Eburnamine, (−)-Eburnamenine, and (−)-Eburnamonine: Takano, S.; Yona ga, M.; Morimoto, M.; Ogasawara, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 305 and references cited therein for other natural products.

(6) Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron Lett.* **1993**, *34*, 5743 and references cited therein.

(7) (a) Herdeis, C.; Hubmann, H. P.; Lotter, H. *Tetrahedron: Asymmetry*, **1994**, *5*, 119. (b) Griffart-Burnet, D.; Langlois, N. *Tetrahedron Lett.* **1994**, *35*, 119.

(8) Hydroxylations: (a) Ohta, T.; Hosoi, A.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 329. (b) Avent, A. G.; Bowler, A. N.; Doyle, P. M.; Marchand, C. M.; Young, D. W. *Tetrahedron Lett.* **1992**, *33*, 1509. Reaction with Bredereck's reagent: (c) Danishefsky, S.; Morris, J.; Clizbe, L. A. *J. Am. Chem. Soc.* **1981**, *103*, 1602. (d) Attwood, M. R.; Carr, G. M.; Jordan, S. *Tetrahedron Lett.* **1990**, *31*, 283. (e) August, R. A.; Khan, J. A.; Moody, C. M.; Young, D. W. *Tetrahedron Lett.* **1992**, *33*, 4617. (f) Moody, C. M.; Young, D. W. *Tetrahedron Lett.* **1993**, *34*, 4667. Aldehydes: (g) Baldwin, J. E.; Miranda, T.; Moloney, M. *Tetrahedron* **1989**, *45*, 7459. (h) Dikshit, D. K.; Panday, S. K. *J. Org. Chem.* **1992**, *57*, 1920. (i) Tamura, N.; Matsushita, Y.; Iwama, T.; Harada, T.; Kishimoto, S.; Itoh, K. *Chem. Pharm. Bull.* **1991**, *39*, 1199. Activated imines: (j) Bowler, A. N.; Doyle, P. M.; Hitchock, P. B.; Young, D. W. *Tetrahedron Lett.* **1991**, *32*, 2679. Reaction with Eschemosher's salt: (k) Ezquerra, J.; Pedregal, C.; Micó, I.; Nájera, C. *Tetrahedron: Asymmetry* **1994**, *5*, 921.

(9) Ezquerra, J.; Pedregal, C.; Rubio, A.; Escribano, A.; Sánchez-Ferrando, F. *Tetrahedron* **1993**, *49*, 8665.

(10) For reviews see: (a) Fuji, K. *Chem. Rev.* **1993**, *115*, 2037. (b) ApSimon, J. W.; Collier, T. L. *Tetrahedron* **1986**, *42*, 5157. (c) Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(11) (a) In the approach to the synthesis of cytochalasans, the synthesis of 1-*tert*-butyl 3-methyl 5(*R*)-[[(*tert*-butyldimethylsilyl)oxy]-methyl]-2-oxo-3-(phenylseleno)pyrrolidine-1,3-dicarboxylate is described as a mixture of diastereoisomers. This product is used to generate a double bond after oxidation–selenoxide *syn* elimination; see: Achermann, J.; Matthes, M.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 122. (b) Dialkylation products using 1-*tert*-butyl 5(*R*)-[[(*tert*-butyldimethylsilyl)oxy]methyl]-2-oxopyrrolidine lithium enolates reacting with benzyl and allyl bromides at −25 °C have been described by: Hon, Y.-S.; Chang, Y.-C.; Gong, M.-L. *Heterocycles* **1990**, *31*, 191.

(12) (a) Ezquerra, J.; de Mendoza, J.; Pedregal, C.; Ramirez, C. *Tetrahedron Lett.* **1992**, *38*, 5589. (b) Molina, M. T.; del Valle, C.; Escribano, A. M.; Ezquerra, J.; Pedregal, C. *Tetrahedron* **1993**, *49*, 3808. (c) Ezquerra, J.; Rubio, A.; Pedregal, C.; Sanz, G.; Rodriguez, J. H.; García Ruano, J. L. *Tetrahedron Lett.* **1993**, *34*, 4989. (d) Ezquerra, J.; Pedregal, C.; Rubio, A.; Valenciano, J.; García Navio, J. L.; Alvarez-Builla, J.; Vaquero, J. J. *Tetrahedron Lett.* **1993**, *34*, 6317.

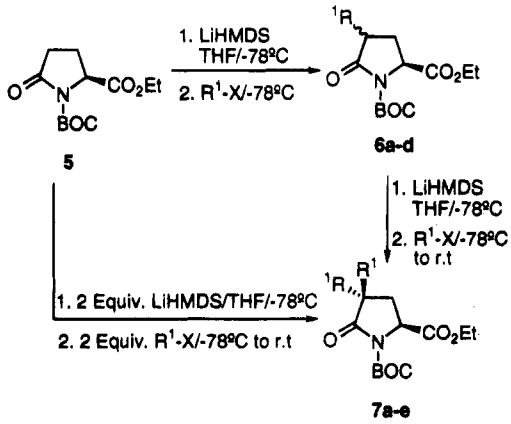
0022-3263/94/1959-4327$04.50/0

Table 1

entry	R^1X	compd	6, % yield	compd	7, % yield[a]
1	$BrCH_2C_6H_5$	**6a**[b]	45	**7a**	69 (89)
2	$BrCH_2CH{=}CHC_6H_5$	**6b**[c]	50	**7b**	50 (70)
3	$BrCH_2CO_2C_2H_5$	**6c**[d]	94	**7c**	47
4	$BrCH_2CH{=}CH_2$	**6d**[d]	40	**7d**	44 (50)
5	ICH_3			**7e**	(68)

[a] Isolated yield for the one-pot reaction is in parentheses. [b] Only the *trans* isomer. [c] A 3.5:1 *trans/cis* diastereomeric mixture. [d] A 2:1 *trans/cis* diastereomeric mixture.

Scheme 1



L-Ethyl pyroglutamate (**2**) was prepared from L-glutamic acid[3] and protected as the *N*-Boc derivative.[13] Double alkylations of **5** using one electrophile to prepare 4,4-disubstituted pyroglutamates **7** were made using two different procedures: a two-step sequence or in a one-pot reaction. The 4-substituted pyroglutamates **6a–d** (Table 1) were obtained from the lithium enolate of **5** as we previously reported.[9]

To prepare the 4,4-disubstituted pyroglutamates **7a–d**, compounds **6a–d** were treated with 1 equiv of base (LiHMDS) in THF at −78 °C for 1 h, quenched with the corresponding electrophile, and allowed to warm to room temperature. Pyroglutamates **7a–d** were obtained with moderate yields (44–69%). These yields can be improved by running the reaction in one pot. Thus, when **5** was treated with 2 equiv of LiHMDS at −78 °C in THF for 1 h and then with 2 equiv of the electrophile and allowed to reach room temperature, compounds **7a–e** were obtained in good yields (50–89%). These results show that while the first alkylation happens at −78 °C the second one takes place at higher temperature as no dialkylated product was obtained when the reaction was quenched at −78 °C using an excess of base and electrophile. In neither was alkylation at C-2 of the pyroglutamate observed.

Double alkylation using different electrophiles can be done starting from the 4-substituted pyroglutamates **6** (Table 2) in good yields.

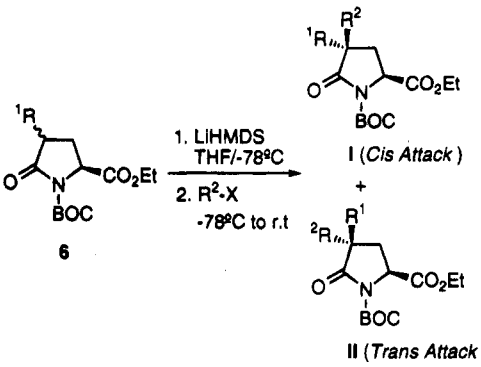
The stereochemistry of the newly generated chiral center is dependent on the order in which the electrophiles are reacted with **5**. Starting from a 4-substituted pyroglutamates **6** and following the same experimental conditions as in the step-by-step alkylation procedure used to obtain compounds **7**, several mixtures of diastereoisomers of structure **I** and **II** were isolated. The diastereomeric ratio between **I** (*cis* attack) and **II** (*trans* attack) depends on the bulkiness of the electrophile introduced on **6**. Thus, bulky electrophiles such as benzyl bromide or cinnamyl bromide add *trans* respect to the ester group of pyroglutamates **6** giving rise to structure **II** as the major diastereoisomer with a de ≥ 80% (Table 2, entries 2, 4–6), it being 100% for compounds **14–17**. With other less steric demanding electrophiles (Table 2, entries 1, 3) is not possible to achieve significant facial differentiation in the addition. These results are in agreement with those previously reported by us[9] for the monoalkylation of *N*-urethane-protected pyroglutamates where the stereoselectivity of the addition depends only on the bulkiness of the electrophile and not on the nature of the ester group moiety of the pyroglutamate.

Table 2

entry	R^1	R^2	I:II ratio[a]	yield (%)
1	$C_6H_5CH_2$	$CNCH_2$	50:50 (**8**:**9**)	60
2	$CNCH_2$	$C_6H_5CH_2$	10:90 (**9**:**8**)	55
3	$C_6H_5CH_2$	$CH_2{=}CHCH_2$	33:66 (**10**:**11**)	45
4	$CH_2{=}CHCH_2$	$C_6H_5CH_2$	10:90 (**11**:**10**)	60
5	$C_6H_5CH_2$	$C_6H_5CH{=}CHCH_2$	5:95 (**12**:**13**)	40
6	$C_6H_5CH{=}CHCH_2$	$C_6H_5CH_2$	5:95 (**13**:**12**)	81
7	C_6H_5S	$C_6H_5CH_2$	0:100 (**14**)	42
8	C_6H_5S	$C_6H_5CH{=}CHCH_2$	0:100 (**15**)	67
9	$C_6H_5CH_2$	$4\text{-}NO_2C_6H_4CH_2$	0:100 (**16**)	41
10	$4\text{-}NO_2C_6H_4CH_2$	$C_6H_5CH_2$	0:100 (**17**)	48

[a] Determinated by NMR analysis of the crude reaction mixture. Compounds in parentheses.

Scheme 2



When a comparative study of the ^{1}H-NMR spectra (NOE and phase-sensitive COSY) of the pyroglutamates **8–17** was performed, it was observed that in compounds **8**, **10**, **12** and **17**, where the benzyl substituent of the C-4 position was *trans* respect to the ester group, the proton α to the ester is shielded by 0.5–1.0 ppm relative to the other diastereoisomers **9**, **11**, **13**, and **16**. This observation helped us to establish the stereochemistry of the newly generated quaternary carbon. However, in order to confirm this assumption an X-ray analysis was made on compound **8** (Figure 2).[17]

To demonstrate that the chirality of the pyroglutamate was preserved during the dialkylation process, compound **18** was prepared and transformed into the corresponding methyl 4,4-dimethyl-*N*-Boc-prolinate **20** which has been previously reported[14] in chiral form (Scheme 3).

Reduction of the lactam carbonyl group on **18** to give the corresponding ethyl prolinate **20** was accomplished using the highly chemoselective reduction system recently reported by us.[15] Thus, treatment of **18** with $LiEt_3BH$ in THF at −78 °C provided the hemiaminal **19**.

(13) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424.

(14) Soucy, F.; Wernic, D.; Beaulieu, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2885.

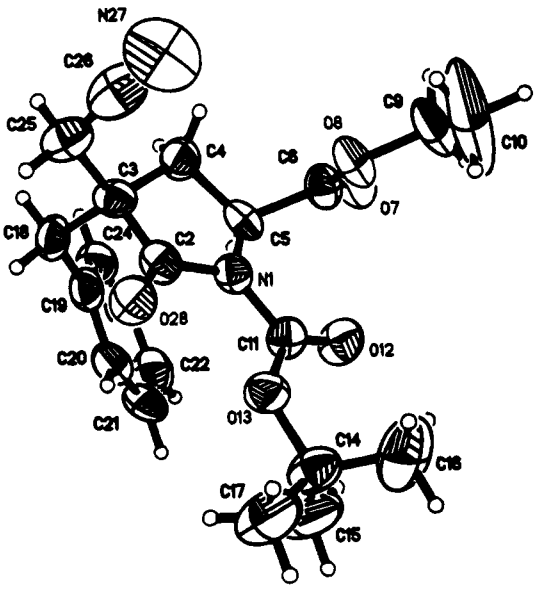
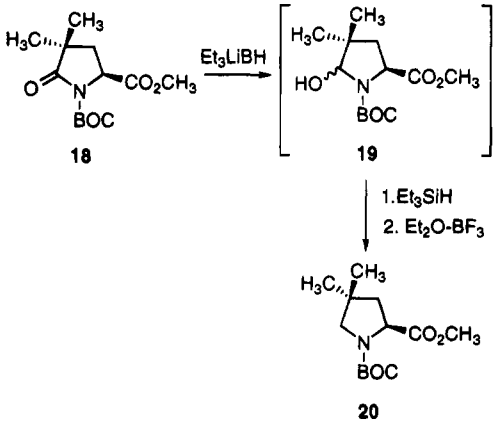


Figure 2.

Scheme 3



Without purification, **19** was further reduced to the corresponding prolinate, using 2 equiv of Et_3SiH–$Et_2O{\cdot}BF_3$ in methylene chloride at −78 °C for 2 h (68% overall yield). Compound **20** displayed the same optical rotation ($[\alpha]_D = -68°$ (c = 1, $CHCl_3$)) and spectroscopic data as the one previously reported.[14] Additionally, compound **20** was deprotected and treated with (*R*)-(−)-methoxy-α-(trifluoromethyl)phenylacetyl chloride[16] in the presence of pyridine, giving an enantiomeric excess (ee) ≥ 95% based on careful ^{1}H-NMR analysis of the corresponding Mosher amide.

In summary, double alkylations of *N*-Boc-protected ethyl pyroglutamates can be performed without epimerization even when the ester moiety has not been reduced. Using the same electrophile the reaction provides better yields in one pot. When two different substituents are to be introduced the stereochemistry of the newly generated chiral center depends on the order in which these electrophiles are introduced. Thus, excellent diastereomeric excess can be obtained when bulky electrophiles (benzyl or cinnamyl) are introduced last, as they add *trans* with respect to the ester moiety of the 4-substituted pyroglutamates.

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) or a Varian Unity (300 MHz). IR spectra were obtained on a Perkin-Elmer 1310 Nicolet 510 P-FT (film or KBr pellet). 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 de Alcalá de Henares Analytical Centre.

General Procedure for Dialkylation of Pyroglutamate 5. Step-by-Step Procedure. Synthesis of 4-Substituted Pyroglutamates.[9] To a solution of pyroglutamate **5** (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 had been stirred at −78 °C for 1 h, the electrophile (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 ether (3 × 20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and evaporated to dryness. The products were separated by flash column chromatography from the unreacted pyroglutamate **5** and used for the next step.

Synthesis of 4,4-Disubstituted Pyroglutamates. To a solution of the 4-substituted pyroglutamate (0.67 mmol) in dry THF (4 mL) stirred at −78 °C was added a 1 M solution of lithium hexamethyldisilazide in THF (0.7 mL, 0.7 mmol). After the reaction mixture had been stirred at −78 °C for 1 h, the electrophile (0.67 mmol) dissolved in dry THF (1 mL) was added also at −78 °C, and the mixture was stirred for 15 min at this temperature and 2 h at 25 °C. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated to dryness. The products were purified by silica gel chromatography, the columns being eluted with hexane/EtOAc with the proportions adjusted for each case.

One-Pot Synthesis of 4,4-Disubstituted Pyroglutamates. To a solution of ethyl (2*S*)-1-(*tert*-butoxycarbonyl)pyroglutamate (0.67 mmol) **5** in dry THF (10 mL) stirred at −78 °C under argon atmosphere was added a 1 M solution of lithium hexamethyldisilazide in THF (1.4 mL, 1.4 mmol). The mixture was stirred at −78 °C for 15 min. The electrophile (1.34 mmol) dissolved in dry THF (1 mL) was added at −78 °C, and the mixture was then stirred for 15 min at this temperature and 2 h at 25 °C. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated to dryness. The products were purified by silica gel chromatography, the columns being eluted with hexane/EtOAc with the proportions adjusted for each case.

Ethyl (2*S*)-1-(*tert*-butoxycarbonyl)-4,4-dibenzylpyroglutamate (7a): oil; $[\alpha]_D = -8.35°$ (c = 2.00, $CHCl_3$); IR ($CHBr_3$) 3024, 2980, 1785, 1739, 1705, 1694, 1663 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.08 (t, 3H, J = 7.1 Hz), 1.37 (s, 9H), 1.90 (dd, 1H, J = 13.6 and 7.5 Hz), 2.18 (dd, 1H, J = 13.5 and 9.3 Hz), 2.60 (d, 1H, J = 13.2 Hz), 2.80 (d, 1H, J = 13.7 Hz), 3.17 (d, 1H, J = 13.0 Hz), 3.24 (d, 1H, J = 13.7 Hz), 3.22–3.30 (m, 1H), 3.93–3.98 (m, 2H), and 7.12–7.33 (m, 10H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 13.8, 27.8, 28.7, 43.2, 44.6, 52.0, 56.3, 61.1, 83.1, 126.8, 127.1, 128.4, 129.8, 130.5, 136.1, 136.5, 148.6, 171.1, and 176.7; HRMS [$M^+ - CO_2C(CH_3)_3$] calcd 337.1677, found 337.1674.

Ethyl (2*S*)-1-(*tert*-butoxycarbonyl)-4,4-dicinnamylpyroglutamate (7b): $[\alpha]_D = -5.9°$ (c = 0.55, $CHCl_3$); mp = 118–

(15) Ezquerra, J.; Pedregal, C.; Escribano, A.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron Lett.* **1994**, *35*, 2053.
(16) Dak, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(17) The author has deposited atomic coordinates for **8** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

120 °C; IR ($CHBr_3$) 2980, 2258, 1784, 1740, 1449 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.72 (t, 3H, J = 7.2 Hz), 1.46 (s, 9H), 2.00 (dd, 1H, J = 15.0 and 5.4 Hz), 2.34 (dd, 1H, J = 12.0 and 9.0 Hz), 2.43–2.60 (m, 4H), 4.10 (q, 2H, J = 7.2 Hz), 4.44 (dd, 1H, J = 9.0 and 5.7 Hz), 6.03–6.28 (m, 2H), 6.38 (d, 1H, J = 22 Hz), 6.47 (d, 1H, J = 22 Hz), and 7.18–7.40 (m, 10H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 13.9, 27.8, 29.7, 40.3, 40.8, 49.7, 56.3, 61.5, 83.6, 123.8, 124.3, 126.2, 127.4, 127.5, 128.4, 128.5, 134.4, 134.6, 136.8, 136.9, 149.1, 171.4, and 176.5. Anal. Calcd for $C_{30}H_{35}NO_5$: C, 72.55; H, 7.18; N, 3.02. Found: C, 72.80; H, 7.35; N, 3.05.

Ethyl (2*S*)-1-(*tert*-butoxycarbonyl)-4,4-bis[(ethoxycarbonyl)methyl]pyroglutamate (7c): oil; $[\alpha]_D$ = +12.7° (c = 0.90, $CHCl_3$); IR ($CHBr_3$) 2984, 2940, 1794, 1726 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.21–1.31 (m, 9H), 1.48 (s, 9H), 2.24 (dd, 1H, J = 14.1 and 4.0 Hz), 2.54 (dd, 1H, J = 10.7 and 3.4 Hz), 2.58–2.90 (m, 4H), 4.09 (q, 2H, J = 7.1 Hz), 4.11 (q, 2H, J = 7.1 Hz), 4.22 (q, 2H, J = 7.2 Hz), 4.60 (dd, 1H, J = 10.6 and 4.0 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 13.5, 13.6, 13.7, 27.3, 27.7, 29.6, 39.5, 40.4, 44.7, 55.9, 60.3, 61.1, 83.0, 148.6, 169.5, 170.0, 171.3, 174.8; HRMS [$M^+ - CO_2C(CH_3)_3$] calcd 329.1474, found 329.1478.

Ethyl (2*S*)-1-(*tert*-butoxycarbonyl)-4,4-diallylpyroglutamate (7d): oil; $[\alpha]_D$ = −169.7° (c = 0.35, $CHCl_3$); IR ($CHBr_3$) 2981, 2936, 1790, 1744, 1640 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.27 (t, 3H, J = 6.9 Hz), 1.48 (s, 9H), 1.89 (dd, 1H, J = 12.0 and 5.7 Hz), 2.12–2.43 (m, 5H), 4.20 (q, 2H, J = 7.2 Hz), 4.42 (dd, 1H, J = 12.0 and 5.7 Hz), 5.03–5.15 (m, 4H), and 5.67–5.72 (m, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 14.1, 27.9, 29.6, 41.0, 41.4, 48.7, 56.2, 61.5, 83.6, 119.3, 119.7, 132.5, 132.8, 149.3, 171.5, and 176.2; HRMS [$M^+ - CO_2C(CH_3)_3$] calcd 237.1364, found 237.1363.

Ethyl (2*S*)-1-(*tert*-butoxycarbonyl)-4,4-dimethylpyroglutamate (7e): $[\alpha]_D$ = −29.45° (c = 0.73, $CHCl_3$); mp = 45–47 °C; IR (KBr pellet) 3023, 2978, 1786, 1742, 1459 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.16 (s, 3H), 1.17 (s, 3H), 1.25 (t, 3H, J = 6.3 Hz), 1.46 (s, 9H), 1.89 (dd, 1H, J = 10.8 and 5.1 Hz), 2.19 (dd, 1H, J = 13.2 and 9.6 Hz), 4.21 (q, 2H, J = 7.2 Hz), and 4.48 (dd, 1H, J = 9.6 and 6.0 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 14.0, 25.2, 27.8, 30.5, 41.6, 55.9, 61.5, 83.3, 149.6, 171.5, and 177.9. Anal. Calcd for $C_{13}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 59.02; H, 7.89; N, 5.21.

Ethyl (2*S*,4*R*)-4-benzyl-1-(*tert*-butoxycarbonyl)-4-(cyanomethyl)pyroglutamate (8): $[\alpha]_D$ = −39.2° (c = 0.27, $CHCl_3$); mp = 86–88 °C; IR (KBr pellet) 2992, 2950, 1735, 1711, 1496 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.25 (t, 3H, J = 7.1 Hz), 1.43 (s, 9H), 1.95 (dd, 1H, J = 13.9 and 6.4 Hz), 2.52 (dd, 1H, J = 13.9 and 9.3), 2.76 (d, 2H, J = 1.8 Hz), 2.90 (d, 1H, J = 13.4 Hz), 3.15 (d, 1H, J = 13.4 Hz), 3.59 (dd, 1H, J = 9.2 and 6.6 Hz), 4.16 (q, 2H, J = 7.1 Hz), and 7.17–7.32 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 14.0, 26.6, 27.7, 29.9, 42.6, 48.5, 55.9, 61.9, 84.2, 116.6, 127.8, 128.8, 129.8, 134.4, 148.3, 170.9, and 173.7. Anal. Calcd for $C_{20}H_{26}N_2O_5$: C, 64.17; H, 6.95; N, 7.48. Found: C, 64.20; H, 6.81; N, 7.45.

Ethyl (2*S*,4*R*)-4-allyl-4-benzyl-1-(*tert*-butoxycarbonyl)-pyroglutamate (10): oil; $[\alpha]_D$ = −20.0° (c = 0.36, $CHCl_3$); IR ($CHBr_3$) 2928, 1790, 1745, 1369 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.19 (t, 3H, J = 7.0 Hz), 1.39 (s, 9H), 1.85 (dd, 1H, J = 13.6 and 7.2 Hz), 2.16–2.35 (m, 2H), 2.48–2.54 (m, 1H), 2.62 (d, 1H, J = 13.3 Hz), 3.04 (d, 1H, J = 13.2 Hz), 3.40 (dd, 1H, J = 9.3 and 7.3 Hz), 4.10 (q, 2H, J = 7.2 Hz), 5.01–5.23 (m, 2H), 5.64–5.83 (m, 1H) and 7.15–7.30 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 14.1, 27.7, 29.1, 41.9, 43.7, 50.5, 56.2, 61.4, 83.3, 119.7, 127.1, 128.5, 129.8, 132.9, 136.2, 148.8, 171.4 and 176.7; HRMS calcd 387.2046, found 387.2049.

Ethyl (2*S*,4*S*)-4-allyl-4-benzyl-1-(*tert*-butoxycarbonyl)-pyroglutamate (11): oil; $[\alpha]_D$ = +3.9° (c = 0.70, $CHCl_3$); IR ($CHBr_3$) 2980, 1790, 1747, 1720 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.17 (t, 3H, J = 7.1 Hz), 1.46 (s, 9H), 1.92 (dd, 1H, J = 13.7 and 5.9 Hz); 2.03–2.27 (m, 2H), 2.48 (dd, 1H, J = 13.6 and 6.3 Hz), 2.74 (d, 1H, J = 13.7 Hz), 3.04 (d, 1H, J = 13.7 Hz), 4.08 (q, 2H, J = 7.2 Hz), 4.37 (dd, 1H, J = 9.7 and 5.9 Hz), 5.03–5.26 (m, 2H), 5.60–5.84 (m, 1H), and 7.03–7.36 (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 14.0, 27.8, 28.6, 41.8, 42.1, 50.3, 56.3, 61.5, 83.6, 120.1, 126.8, 128.3, 130.5, 132.5, 136.3, 149.1, 171.4, and 176.6; HRMS calcd 387.2046, found: 387.2048.

Ethyl (2*S*,4*S*)-4-benzyl-1-(*tert*-butoxycarbonyl)-4-cinnamylpyroglutamate (12): $[\alpha]_D$ = −127.4° (c = 0.27, $CHCl_3$); mp = 80–82 °C; IR (KBr pellet) 3344, 2976, 1730, 1674, 1600 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.19 (t, 3H, J = 7.1 Hz), 1.43 (s, 9H), 1.98 (dd, 1H, J = 13.6 and 5.9 Hz), 2.17–2.31 (m, 2H), 2.66 (dd, 1H, J = 14.2 and 6.6 Hz), 2.82 (d, 1H, J = 13.4 Hz), 3.10 (d, 1H, J = 13.6 Hz), 4.10 (q, 2H, J = 7.3 Hz), 4.37 (dd, 1H, J = 9.7 and 5.8 Hz), 6.03–6.13 (m, 1H), 6.43 (d, 1H, J = 15.8 Hz), and 7.12–7.30 (m, 10H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 14.0, 27.7, 28.7, 41.1, 42.1, 50.8, 56.3, 61.5, 83.6, 123.8, 126.2, 126.8, 127.6, 128.4, 128.5, 130.5, 134.7, 136.3, 136.7, 148.9, 171.4, and 176.8. Anal. Calcd for $C_{28}H_{33}NO_5$: C, 72.55; H, 7.18; N, 3.02. Found: C, 72.80; H, 7.35; N, 3.05.

Ethyl (2*S*,4*R*)-4-benzyl-1-(*tert*-butoxycarbonyl)-4-cinnamylpyroglutamate (13): $[\alpha]_D$ = −25.14° (c = 0.35, $CHCl_3$); mp = 89–91 °C; IR (KBr pellet) 2983, 1780, 1739, 1698, 1496 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.07 (t, 3H, J = 7.0 Hz), 1.42 (s, 9H), 1.93 (dd, 1H, J = 14.5 and 7.2 Hz), 2.28 (dd, 1H, J = 13.6 and 9.6 Hz), 2.46 (dd, 1H, J = 13.9 and 8.7 Hz), 2.66–2.76 (m, 2H), 3.12 (d, 1H, J = 15.0 Hz), 3.45 (dd, 1H, J = 9.2 and 7.5 Hz), 4.11 (q, 2H, J = 7.2 Hz), 6.09–6.19 (m, 1H), 6.43 (d, 1H, J = 16.2 Hz), and 7.25–7.33 (m, 10H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 13.6, 27.5, 28.9, 40.9, 43.8, 50.6, 56.0, 61.0, 82.9, 124.1, 125.9, 126.8, 127.1, 128.1, 128.2, 129.5, 134.2, 135.8, 136.6, 148.4, 170.9, and 176.4. Anal. Calcd for $C_{28}H_{33}NO_5$: C, 72.55; H, 7.18; N, 3.02. Found: C, 72.55; H, 7.46; N, 3.03.

Ethyl (2*S*,4*S*)-4-benzyl-1-(*tert*-butoxycarbonyl)-4-(phenylthio)pyroglutamate (14): $[\alpha]_D$ = −30.0° (c = 0.18, $CHCl_3$); mp = 85–87 °C; IR ($CHBr_3$) 2258, 1787, 1744, 1674 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.21 (t, 3H, J = 7.1 Hz), 1.45 (s, 9H), 2.15 (dd, 1H, J = 15.5 and 3.8 Hz), 2.49 (dd, 1H, J = 14.3 and 9.5 Hz), 2.90 (d, 1H, J = 13.5 Hz), 3.33 (d, 1H, J = 13.5 Hz), 3.93 (dd, 1H, J = 9.4 and 3.8 Hz), 4.13 (q, 2H, J = 7.1 Hz) and 7.14–7.59 (m, 10H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 14.0, 27.9, 31.6, 42.7, 55.6, 57.8, 61.6, 83.4, 127.2, 128.6, 128.9, 129.7, 129.8, 130.3, 135.5, 137.2, 149.1, 170.5, and 171.4. Anal. Calcd for $C_{25}H_{29}NO_5S$: C, 65.91; H, 6.42; N, 3.07; S, 7.04. Found: C, 66.30; H, 6.31; N, 3.10; S, 6.90.

Ethyl (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-cinnamyl-4-(phenylthio)pyroglutamate (15): $[\alpha]_D$ = +34.0° (c = 1.3, $CHCl_3$); IR ($CHBr_3$) 3412, 3059, 2936, 1787, 1749, 1726, 1557 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.31 (t, 3H, J = 7.3 Hz); 1.50 (s, 9H), 2.27 (dd, 1H, J = 2.4 and 14.2 Hz), 2.56–2.73 (m, 3H), 4.24 (q, 2H, J = 7.3 Hz), 4.56 (dd, 1H, J = 2.4 and 9.5 Hz), 6.08–6.13 (m, 1H), 6.45 (d, 1H, J = 15.7 Hz), 7.20–7.58 (m, 10H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 14.1, 27.9, 32.7, 39.5, 55.6, 56.3, 61.8, 83.4, 123.5, 126.3, 127.6, 128.5, 128.8, 129.1, 129.8, 134.9, 136.7, 137.3, 149.4, 170.6, and 170.9.

Ethyl (2*S*,4*R*)-4-benzyl-1-(*tert*-butoxycarbonyl)-4-(*p*-nitrobenzyl)pyroglutamate (16): $[\alpha]_D$ = −25.7° (c = 0.035, $CHCl_3$); mp = 90–92 °C; IR ($CHBr_3$) 3022, 2258, 1786, 1739, 1604, 1520 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.18 (t, 3H, J = 7.1 Hz), 1.41 (s, 9H), 2.02–2.14 (m, 2H), 2.72 (d, 1H, J = 13.2 Hz), 2.90 (d, 1H, J = 13.7 Hz), 3.21 (d, 1H, J = 13.7 Hz), 3.30 (d, 1H, J = 13.0 Hz), 3.58 (dd, 1H, J = 9.6 and 6.4 Hz), 4.08 (q, 2H, J =7.1 Hz), 7.17 (d, 2H, J = 8.4 Hz), 7.24–7.36 (m, 5H), and 8.14 (d, 2H, J = 8.6 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 13.6, 27.4, 27.8, 42.8, 42.9, 51.6, 55.7, 61.2, 83.5, 123.2, 126.8, 128.2, 130.2, 130.6, 135.4, 143.7, 146.9, 148.1, 151.3, 170.5, and 175.6. Anal. Calcd for $C_{26}H_{30}N_2O_7$: C, 64.71; H, 6.26; N, 5.80. Found: C, 65.00; H, 6.45; N, 6.15.

Ethyl (2*S*,4*S*)-4-benzyl-1-(*tert*-butoxycarbonyl)-4-*p*-(nitrobenzyl)pyroglutamate (17): $[\alpha]_D$ = −17.1° (c = 0.35, $CHCl_3$); mp = 38–40 °C; IR ($CHBr_3$) 2980, 2259, 1786, 1742, 1603, 1518 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.04 (t, 3H, J = 7.3 Hz), 1.37 (s, 9H), 1.76 (dd, 1H, J = 13.6 and 7.7 Hz), 2.26 (dd, 1H, J = 13.5 and 9.1 Hz), 2.61 (d, 1H, J = 13.2 Hz), 2.90 (d, 1H, J = 13.5 Hz), 3.18 (d, 1H, J = 13.0 Hz), 3.29 (dd, 1H, J = 9.2 and 7.8 Hz), 3.38 (d, 1H, J = 13.5 Hz), 3.92 (q, 2H, J = 7.3 Hz), 7.14–7.29 (m, 5H), 7.36 (d, 2H, J = 8.8 Hz), and 8.15 (d, 2H, J = 8.8 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 13.8, 27.7, 28.6, 42.7, 44.9, 52.0, 56.1, 61.3, 83.5, 123.5, 127.4, 128.6, 129.7, 131.4, 135.3, 144.3, 147.0, 148.3, 170.8, and 175.9. Anal. Calcd for $C_{26}H_{30}N_2O_7 \cdot H_2O$: C, 62.37; H, 6.45; N, 5.60. Found: C, 62.75; H, 6.70; N, 5.42.

Methyl (2*S*)-1-(*tert*-butoxycarbonyl)-4,4-dimethylprolinate (20). A 1.0 M solution of lithium triethylborohydride in

THF (6.64 mL, 6.64 mmol) was added to a solution of **18** (5.53 mmol, 1.5 g) in THF (30 mL) at −78 °C under a nitrogen atmosphere. After 30 min the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and warmed to 0 °C. H_2O_2 (30%, 1 mL) was added and the mixture stirred at 0 °C. After 20 min the organic solvent was removed in *vacuo* and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude **19** was used without further purification.

A solution of **19** and triethylsilane (0.91 mL, 5.7 mmol) in CH_2Cl_2 (30 mL) was cooled to −78 °C and boron trifluoride etherate (0.79 mL, 6.27 mmol) was then added dropwise under a nitrogen atmosphere. After 30 min, 0.91 mL of triethylsilane and 0.79 mL of boron trifluoride etherate were added. The resulting mixture was stirred for 2 h at −78 °C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (8 mL), extracted with CH_2Cl_2 (3 × 20 mL), and dried over Na_2SO_4. Evaporation of the solvent and purification by flash chromatography (hexane/ethyl acetate (3:1)) yielded 1.04 g (69% overall yield) of pure **20** which was identical in all respects (NMR, IR and optical rotation) with that previously reported.[14]

Acknowledgment. This research has been conducted under the Spanish FARMA II programme (Ministerio de Industria). M.P.M., A.D., and J.M. thank Lilly, S. A. for a fellowship. We are also grateful to Dr. S. R. Baker (Lilly Research Centre, U.K.) for useful suggestions.

Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of **6a**, **6c**, **6d**, **10**, **11**, and **20** (12 pages). This material is contained in libraries on microfiche, immediately 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.