Tetrahedron Vol. 49, No. 38, pp. 8665-8678, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Stereoselective Reactions of Lithium Enolates Derived from N-BOC Protected Pyroglutamic Esters

Jesús Ezquerra*[1], Concepción Pedregal[1], Almudena Rubio[1], Belén Yruretagoyena[1], Ana Escribano[2] and Francisco Sánchez-Ferrando[3]

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

2.- Departamento de Química Orgánica, Universidad Autónoma de Madrid.
Cantoblanco, 28049 Madrid. Spain.

3.- Departament de Química. Universitat Autònoma de Barcelona.
Bellaterra. 08193-Barcelona. Spain

(*Received in UK* 14 *June* 1993; *accepted* 16 *July* 1993)

Abstract: The lithium enolates of N-Boc protected pyroglutamic ethyl or *tert*-butyl esters react with electrophiles in good yield without epimerization of the chiral centre. With benzyl bromides the process is stereospecific, yielding exclusively the *trans* isomer. However, with other reactive electrophiles a 2:1 *trans/cis* diastereomeric mixture was obtained, regardless of the steric bulk of the ester group.

Natural α-amino acids are useful as starting materials for the synthesis of enantiomerically-pure compounds, the single chiral centre providing a useful building block.[1]

Pyroglutamic acid can be viewed as an internal protection of the γ–carboxyl group of glutamic acid, allowing easy differentiation of the two carboxyl groups. Thus, N-urethane protected pyroglutamates undergo ring opening with Grignard reagents,[2] several heteronucleophiles[3] and lithium carbanions[4] with excellent regioselectivity. In all cases the chiral centre is maintained.

Pyroglutamic acid has been widely used as a starting material for natural product synthesis, for example of (+)-*Deoxynojirimicin*,[5] (-)-*Bulgecinine*,[6](-)-*Domoic acid*,[7] (-)-*Kainic acid*[8] and *1,7a-Diepilalexine*[9]. It has also been used as a chiral building block, in the preparation of 2-(carboxycyclopropyl) glycines,[10] 4-substituted glutamic acid analogs[11] and kainoids,[12] these compounds being pharmacological probes for excitatory amino acid receptors.[13] For all these syntheses it is necessary to functionalize the pyroglutamic ring carbons. Substituents have been introduced into the 4-position in a stereocontrolled manner using the lactam enolate from modified pyroglutamic acid derivatives. The carboxylic substituent was reduced to the alcohol and protected with bulky groups[5,7-12,14] or as O,N-acetal[15] . This procedure being thought necessary to prevent the racemization of the amino acid chiral centre and ensure 1,3 asymmetric induction. More recently, it has been shown that in certain cases the reduction and protection

steps can be avoided. Thus, the lactam enolates derived from N-urethane protected pyroglutamates can be diastereoselectively hydroxylated,[6,16] react with Bredereck's reagent,[17] aldehydes[18] and activated imines[19] without epimerization of the pyroglutamate chiral centre. Baldwin[18a] has studied the reaction of lithium enolates of several N-protected ($Me_2{}^tBuSi$, $PhCH_2OCO$, ^tBuOCO) pyroglutamic esters, with different aldehydes. In this study it was shown that the preferred N-protecting group was a carbamate, the best one being *tert*-butoxycarbonyl. Besides the reaction with aldehydes, the lithium enolate of **1b** reacts diastereospecifically with benzyl bromide delivering *exclusively the trans isomer*. However, other reactive electrophiles such as methyl iodide, cinnamyl or allyl bromide were quoted as giving products resulting from multiple alkylation and ring cleavage.

In this paper we wish to expand on the general scope of the alkylations of pyroglutamate-derived enolates of **1a** and **1b** with activated electrophiles and report the stereochemical outcome of these reactions.

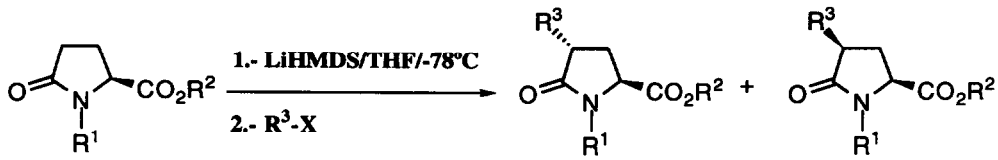
Both (L)-ethyl and tert-butyl pyroglutamates were prepared from (L)-glutamic acid according to literature procedures[20] and protected as N-BOC derivatives.[21] The enolates derived from **1a** and **1b** were generated with LiHMDS[22] in THF at -78°C for one hour and quenched with several electrophiles (Table I), to give the 4-substituted pyroglutamates **2,3a-p**. In all cases, neither C-2 alkylation nor C-4 dialkylation was observed by NMR analysis of the crude reaction mixtures. The reaction proceeds with fairly good yields with a variety of reactive electrophiles such as alkyl halides (entries 1-4), sulfur and selenium electrophiles (entries 5, 6), acyl chlorides (entry 7), allyl halides (entries 8, 9) or benzyl halides (entries 10-16).

These results are in sharp contrast with those previously reported by Baldwin.[18a] Cinnamyl and allyl bromide deliver the alkylated products (entries 8, 9) in 69% and 50% yield as a mixture of *trans/cis* diastereomers in a 2:1 and 3.5:1 ratio respectively. However, with allyl bromide we found it necessary to carry out inverse addition of the enolate to four equivalents of the electrophile. But in neither cases did we observe products resulting from multiple alkylation nor ring cleavage of the pyroglutamate. The use of other reactive alkyl electrophiles such as ethyl bromoacetate or iodoacetonitrile allowed us to obtain the corresponding 4-substituted pyroglutamates (entries 1-4) in good yield as 2:1 *trans/cis* diastereomeric mixtures. The reaction was then extended to sulphur and selenium electrophiles as well as acyl chlorides (entries 5-7). To prepare compounds **2,3e-g**, two equivalents of base were used in order to avoid double substitution of the enolate[23] and to ensure complete reaction. The diastereomeric mixtures were separated by flash chromatography, except for compounds **2,3e-g**. Other tested electrophiles such as propyl or methyl iodide gave poor yields (~10%) after changing the reaction conditions (DME as solvent and HMPA as chelating agent) or the inverse enolate addition to the electrophile. Thus the reaction appears to be restricted only to reactive electrophiles.

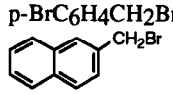
Stereochemical assignments were made on the basis of NOE measurements on compounds **2c** and **3c** (Figure I).

In the *trans* isomer **2c** the proton H_a (dd, 4.63 ppm) exhibits two coupling constants with a different order of magnitude , J_{ab} = 9.5 Hz and J_{ac} = 1.1 Hz. This suggests that H_b (ddd, 2.20 ppm) is *cis* and H_c (ddd, 2.43 ppm) *trans* with respect to H_a. When H_a was irradiated, only H_b gave a significant NOE (9.9%). In addition, H_c can be assigned unambiguously as it shows a geminal coupling of 13.3 Hz, J_{bc}, to H_b. This assignment was confirmed when a 20.9% enhancement to H_c was observed on irradiation of H_b. Finally the *trans* configuration of **2c** was established when the irradiation of H_c gave an NOE on to H_d (m, 2.98 ppm) of 9.0%.

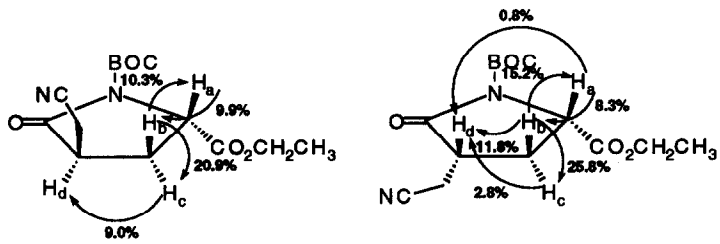
TABLE I



1a, R^1= BOC, R^2= Et **2a-p** **3a-p**
1b, R^1= BOC, R^2= ^{t}Bu

Entry	R^2	R^3-X	Product	Yield [a](%)	Ratio **2:3**
1	Et	$BrCH_2CO_2Et$	**2,3a**	45	2:1
2	^{t}Bu	$BrCH_2CO_2Et$	**2,3b**	70	2:1
3	Et	ICH_2CN	**2,3c**	65	2:1
4	^{t}Bu	ICH_2CN	**2,3d**	73	2:1
5	Et	$(C_6H_5S)_2$	**2,3e**	76	2:1
6	Et	$ClSeC_6H_5$	**2,3f**	60	2:1
7	Et	$ClCOC_6H_5$	**2,3g**	75	1:1
8	Et	$BrCH_2CH{=}CH_2$	**2,3h**	50	2:1
9	Et	$BrCH_2CH{=}CHC_6H_5$	**2,3i**	69	3.5:1
10	Et	$C_6H_5CH_2Br$	**2j**	59	1:0[b]
11	^{t}Bu	$C_6H_5CH_2Br$	**2k**	41	1:0[b]
12	Et	p-$CH_3C_6H_4CH_2Br$	**2l**	57	1:0[b]
13	Et	p-$CNC_6H_4CH_2Br$	**2m**	57	1:0[b]
14	Et	p-$CF_3C_6H_4CH_2Br$	**2n**	53	1.0[b]
15	Et	p-$BrC_6H_4CH_2Br$	**2o**	36	1.0[b]
16	Et		**2p**	55	1:0[b]

[a] Isolated yield. [b] The *cis* isomer could not detected in the crude product by NMR.



2c 3c

Figure I

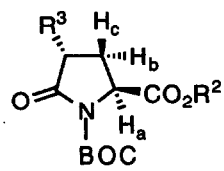
For the assignment of the *cis* isomer, proton H_a (dd, 4.52 ppm) was again taken as the starting point. In this case, H_a exhibits two similar vicinal coupling constants, J_{ab} = 8.4 Hz and J_{ac} = 7.0 Hz. The assignment of H_c (ddd, 1.84 ppm) was made on the basis that one of the coupling constants to this proton is 7.0 Hz. A further experiment was required to assign H_b and H_d prior to performing NOE experiments to establish the relative *cis/trans*, orientation of the H_a and H_c protons. The assignment of H_b (ddd, 2.70 ppm) was made from a COSY experiment, it being the only proton, other than H_c, to show a correlation to H_a. It was also possible to differentiate H_d (m, 2.91 ppm) which overlapped with one of the methylene protons of the ester side chain. When H_a was irradiated, a substantial NOE (8.3%) was observed to H_b and a small NOE (0.8%) to H_d. The irradiation of H_b gave an NOE to H_d (11.8%) confirming the *cis* relationship to H_d.

The coupling constants J_{ab} and J_{ac} reported by Baldwin[18a] and Dikshit[18b] for compound **2k** are not in agreement (Table II, footnote b) and the values in neither publication correspond to those we observe. In order to clarify this point, a comparative study of ^1H NMR spectroscopic data of all the compounds prepared was undertaken (Table II).

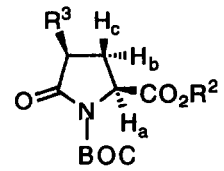
From the results shown in table II, a pattern can be established to predict the assignment of configuration of 4-substituted pyroglutamates **2** and **3**. H_a is always at lower field in the *trans* isomers **2** than in the *cis* compounds **3**. Furthermore, in the *trans* isomers both protons in the methylene group, H_b and H_c, resonate below 2 ppm, their chemical shifts being very similar (almost equivalent in the benzyl derivatives). In contrast, for the *cis* isomers, the H_c proton is always to high field of 1.90 ppm whilst H_b is shifted downfield to at least 2.20 ppm. Finally, for all the *trans* compounds, the coupling constants J_{ab} and J_{ac} are very different from one another, unlike the *cis* isomers where these values are similar. This pattern appears to be quite general and can be extended to all the 4-substituted pyroglutamates examined.

Recently it has been reported by Langlois[24] that the N-methoxycarbonyl pyroglutamic benzyl ester is alkylated with methyl and *tert*-butyl bromoacetates for the synthesis of (2*S*, 4S) 2-carboxy-4-pyrrolidine acetic acid, a conformationally constrained 2-aminoadipic acid. From the spectroscopic data given in this paper it became obvious to us that the stereochemical assignment, based on NOE experiments, [25] was wrong and surprisingly in this case the *trans/cis* ratio was favoured to the *cis* diastereoisomer.

TABLE II



2

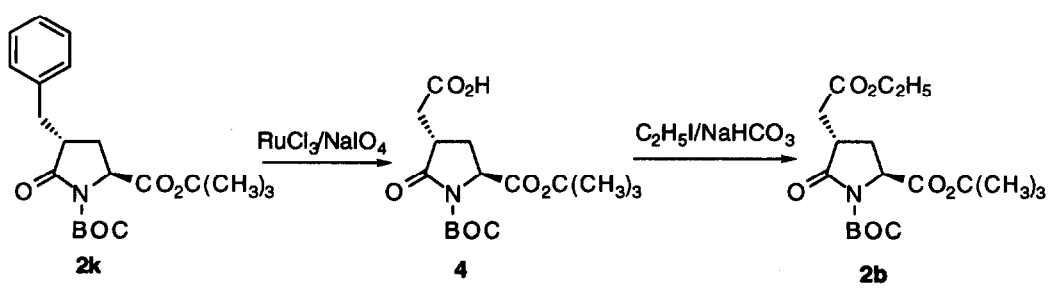


3

R^2	R^3	**2** δH_a(ppm)	**3** δH_a(ppm)	**2** J_{ac}; J_{ab}(Hz)	**3** J_{ac}; J_{ab}(Hz)	**2** δH_b;δH_c	**3** δH_c;δH_b
Et	CH_2CO_2Et	4.52	4.46	1.2; 9.7	7.9; 7.9	2.05; 2.40	1.64; 2.40
^{t}Bu	CH_2CO_2Et	4.42	4.36	1.1; 9.5	6.9; 8.6	2.05; 2.40	1.60; 2.40
Et	CH_2CN	4.63	4.52	1.1; 9.5	7.0; 8.4	2.20; 2.43	1.84; 2.70
^{t}Bu	CH_2CN	4.47	4.39	0.7; 9.2	6.5; 8.6	2.20; 2.40	1.80; 2.60
Et	$CH_2CH{=}CH_2$	4.51	4.46	1.8; 9.4	6.8; 8.8	1.95; 2.10	1.70; 2.20
Et	$CH_2CH{=}CHC_6H_5$	4.46	4.42	0.6; 9.1	6.8; 8.9	2.05; 2.10	1.70; 2.40
Et	$CH_2C_6H_5$	4.43	4.43	3.7; 7.6	6.8; 8.7	2.00[a]	1.70; 2.30
^{t}Bu	$CH_2C_6H_5$	4.31	---	3.7; 7.4[b]	---	1.90[a]	---

[a] Overlapped signals. [b] J_{ac}; J_{ab} = 8.3; 10.7 Hz in *ref.* 18a. J_{ac}; J_{ab} = 5.0; 6.6 Hz in *ref* 18b

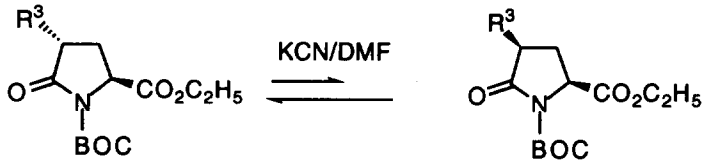
In order to confirm our stereochemical assignment compound **2k**,[26] for which Baldwin[18a] describes its X-ray structure, was subjected to phenyl ruthenium oxidation[27] affording **4** (57% yield based on recovered starting material), which was ethylated to furnish **2b** (71% yield) displaying the same optical rotation ($[\alpha]_D$ = -20° (c 1.0, $CHCl_3$)) and spectroscopical data as the one prepared by direct akylation of **1b** with ethyl bromoacetate (Scheme 1).



Scheme 1

Pyroglutamic benzyl and *tert*-butyl esters have been commonly used as substrates for stereocontrolled electrophilic attack, probably due to the steric effect of these bulky ester groups in the asymmetric induction.[28] To evaluate the influence of the ester groups, pyroglutamic ethyl **1a** and *tert*-butyl **1b** esters were reacted with some electrophiles (Table I, entries 1- 4, 10, 11) under the same reaction conditions. Surprisingly, the same diastereomeric ratio was obtained, regardless of the bulkiness of the ester moiety.[29]

When benzyl bromides were used (entries 10-16), exclusively the *trans* 4-benzyl substituted pyroglutamates were obtained as previously reported by Baldwin[18a] for compound **2k**. Compounds **2j, n, p** were isomerized when treated with KCN in DMF for 18 hours at room temperature (Scheme 2).



2j, n, p **3j, n, p**

Scheme 2

Under these conditions it was possible to isolate a 2.5:1 mixture of the corresponding diastereomers **2j, n, p** and **3j, n, p** respectively. To ensure that the epimerization took place exclusively at the four position, a parallel experiment was run on **2j** in the presence of D_2O. Under these conditions no deuterium incorporation was observed at the amino acid chiral centre, being exclusively deuterated in the four position of the pyroglutamic ring system. As the diastereomeric mixture obtained under these equilibrating conditions was about the same as in the case of the rest of the non-benzylic electrophiles, it was possible to consider that epimerization might have taken place in the reaction medium in this latter case. In order to clarify this assumption **2c** and **2j** were treated with 0.1 equivalents of LiHMDS under the reaction conditions but no appreciable epimerization was observed (NMR analysis). These results suggest that the stereochemical outcome of this process is exclusively dependent on the steric bulkiness of the electrophile.

In summary, the introduction of substituents in the 4-position of the pyroglutamic ring system is possible without first reducing the ester. The reaction is succesful with a variety of reactive electrophiles. The stereochemical outcome of this reaction does not depend on the bulk of the ester group, but is dependent on the nature of the electrophile. Under kinetic control conditions, benzyl bromides afforded exclusively the *trans* isomer whereas the rest of the electrophiles tested gave a *trans/cis* mixture as a result of steric control. Finally a spectroscopic patterm to assess the relative configuration of 4-substituted pyroglutamates has been stated.

ACKNOWLEDGEMENTS. This research was supported by the Spanish FARMA II programme (Ministerio de Industria). We would like to thank Mr. Ivan Collado for his helpful collaboration. A. E. thanks Lilly, S. A. for a fellowship. We are also grateful to Dr. S. R. Baker (Lilly Research Centre, U. K.) for useful suggestions.

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. ^{1}H-NMR and ^{13}C-NMR data were recorded on a Bruker AC-200P (200 MHz and 400MHz). IR spectra were obtained on 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 alkylation reactions on ethyl and t-butyl N-BOC pyroglutamate (1a and 1b). Synthesis of 4-substituted pyroglutamates. To a solution of pyroglutamate **1a** or **1b** (7.77 mmol) in THF (40 ml) stirred at -78°C was added a 1M 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 hour, the electrophile (9.30 mmol, 1.2 equiv) in THF (10 mL) was added and stirring was continued for 2h. The reaction mixture was quenched with saturated ammonium chloride solution (50 mL) at -78°C and extracted with ethyl ether (3 x 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 (the eluent is indicated in each case).

Ethyl (2S, 4S)-1-(*tert*-butoxycarbonyl)-4-(ethoxycarbonylmethyl)pyroglutamate (2a): (hexane/ethyl acetate: 2/1). 30% yield. Colorless oil. $[\alpha]_D$ = -17.5° (c 1.26, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 4.52 (dd, J = 1.2 and 9.7 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.05 (q, J = 7.1 Hz, 2H), 2.97 (m, 1H), 2.83 (dd, J = 3.8 and 17.1 Hz, 1H), 2.40 (dd, J = 8.6 and 17.1 Hz, 1H), 2.32 (ddd, J = 1.2, 8.7 and 17.7 Hz, 1H), 2.05 (ddd, J = 9.7, 11.8 and 13.1 Hz, 1H), 1,43 (s, 9H), 1.23 (t, J = 7.2 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 173.6, 171.1, 171.0, 149.2, 83.5, 61.6, 60.8, 57.0, 38.2, 34.4, 28.2, 27.7, 14.1, 14.0; IR (KBr pellet) 1784, 1736, 1369, 1317, 1153 cm^{-1}. FABMS (M^++H) calcd 344.17, found 344.28.

Ethyl (2S, 4R)-1-(*tert*-butoxycarbonyl)-4-(ethoxycarbonylmethyl)pyroglutamate (3a): This compound was characterized from a 1:1 mixture of **2a** and **3a**. ^{1}H NMR ($CDCl_3$) δ 4.46 (t, J = 7.9 Hz, 1H), 4.3 -4.0 (m, 4H), 3.1-2.9 (m, 2H), 2.65 (dt, J = 8.5 and 14.0 Hz, 1H), 2.40 (m, 1H), 1.64 (dt, J = 7.9 and 17.0 Hz, 1H), 1.43 (s, 9H), 1.23 (t, J = 7.2 Hz, 6H). ^{3}C NMR ($CDCl_3$) δ 173.7, 171.2, 171.0, 149.1, 83.8, 61.6, 60.9, 57.4, 39.2, 35.4, 27.9, 27.8, 14.1, 14.0.

***tert*-Butyl (2S, 4S)-1-(*tert*-butoxycarbonyl)-4-(ethoxycarbonylmethyl)pyroglutamate (2b)**: (hexane/ethyl acetate: 2/1). 47% yield. Colorless oil. $[\alpha]_D$ = -20° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 4.42 (dd, J = 1.1 and 9.5 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.00 (m, 1H), 2.90 (dd, J = 3.8 and 16.9 Hz, 1H), 2.42 (dd, J = 8.6 and 17.0 Hz, 1H), 2.32 (ddd, J = 1.2, 8.8 and 13.3 Hz, 1H), 2.02 (ddd, J = 9.7, 11.8 and 13.3 Hz, 1H), 1.48 (s, 9H), 1.45 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 173.8, 171.1, 170.0, 149.1, 83.2, 82.2, 60.7, 57.6, 38.1, 34.4, 28.3, 27.74, 27.71, 14.0. IR (film) 1794, 1736, 1369, 1154 cm^{-1}. HRMS [M^+-$CO_2C(CH_3)_3$ + 1] calcd 270.1341, found 270.1250.

***tert*-Butyl (2S, 4R)-1-(*tert*-butoxycarbonyl)-4-(ethoxycarbonylmethyl)pyroglutamate (3b)**: m.p.: 102-3° C; $[\alpha]_D$ = -2° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 4.38 (dd, J = 7.0 and 8.6 Hz, 1H), 4.13 (q, J = 7.1 Hz,

2H), 3.10-2.85 (m, 2H), 2.63 (dt, J = 8.8 and 13.1 Hz, 1H), 2.41 (dd, J = 11.2 and 17.6 Hz, 1H), 1.63 (dt, J = 7.1 and 13.1 Hz, 1H) 1.49 (s, 9H), 1.46 (s, 9H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 173.7, 171.2, 170.2, 149.2, 83.5, 82.2, 60.8, 58.0, 39.2, 35.6, 27.82, 27.77, 14.1. IR (KBr pellet) 1755, 1728, 1317, 1189 cm^{-1}. Anal. Calcd for $C_{18}H_{29}NO_7$: C, 58.21; H, 7.87; N, 3.77. Found: C, 58.29; H, 7.64; N, 3.88.

Ethyl (2S, 4S)-1-(*tert* -butoxycarbonyl)-4-(cyanomethyl)pyroglutamate (2c): (hexane ethyl/acetate: 2/1). 43% yield. White needles, m.p.: 140-1°C (Hexane-CH_2Cl_2). $[\alpha]_D$ = -12.4° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 4.60 (dd, J = 1.1 and 9.2 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 3.03-2.74 (m, 2H), 2.57 (dd, J = 8.0 and 13.1 Hz, 1H), 2.40 (dd, J = 9.0 and 13.1 Hz, 1H),2.18 (ddd, J = 9.4, 12.3 and 13.1 Hz, 1H), 1.47 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H), ^{13}C NMR ($CDCl_3$) δ 171.3, 170.5, 148.8, 116.9, 84.2, 62.0, 56.7, 38.4, 27.8, 27.7, 18.1, 14.1. IR (KBr pellet) 2258, 1777, 1738, 1317 cm^{-1}. Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.70; H, 6.75; N, 9.45. Found: C, 56.78; H, 6.53; N, 9.56.

Ethyl (2S, 4R)-1-(*tert*-butoxycarbonyl)-4-(cyanomethyl)pyroglutamate (3c): (hexane/ ethyl acetate: 2/1). 22% yield. m.p.: 67-8°C (Hexane-ethyl ether). $[\alpha]_D$ = +23.2° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 4.53 (dd, J = 7.0 and 8.4Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 3.0-2.8 (m, 2H), 2.73 (dd, J = 8.3 and 13.2 Hz, 1H), 2.57 (dd, J = 10.7 and 17.7 Hz, 1H), 1.86 (ddd, J = 7.0, 7.8 and 13.2 Hz, 1H), 1.48 (s, 9H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 171.4, 170.8, 148.6, 117.1, 84.3, 61.9, 57.1, 39.2, 27.7, 26.8, 18.9, 14.0. IR (KBr pellet) 2253, 1775, 1740, 1290, 1198 cm^{-1}. HRMS [M^+- $CO_2C(CH_3)_3$ + 1] calcd 195.0769, found 195.0732.

***tert*-Butyl (2S, 4S)-1-(*tert*-butoxycarbonyl)-4-(cyanomethyl)pyroglutamate (2d)**: (hexane/ethyl acetate: 2/1). 49% yield. White needles, m.p.: 130°C. $[\alpha]_D$ = -10.8° (c 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 4.47 (dd, J = 0.7 and 9.2 Hz, 1H), 3.02-2.76 (m, 2H), 2.56 (dd, J = 8.0 and 17.0 Hz, 1H), 2.36 (dd, J = 8.6 and 13.3 Hz, 1H), 2.14 (ddd, J = 9.5, 12.9 and 13.3 Hz, 1H), 1.46 (s, 9H), 1.45 (s,9H). ^{13}C NMR ($CDCl_3$) δ 171.5, 169.5, 148.7, 117.0, 84.0, 82.9, 57.3, 38.4, 27.8, 27.7, 18.2. IR (KBr pellet) 2250, 1775, 1734, 1345 cm^{-1}. Anal. Calcd for $C_{16}H_{24}N_2O_5$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.11; H, 7.35; N, 8.57.

***tert*-Butyl(2S, 4R)-1-(*tert*-butoxycarbonyl)-4-(cyanomethyl)pyroglutamate (3d)**: m.p.: 134 °C. $[\alpha]_D$ = -1.5° (c 1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 4.39 (dd, J = 6.5 and 8.6 Hz, 1H), 2.96-2.80 (m, 2H), 2.73-2.48 (m, 2H), 1.79 (dt, J = 7.0 and 13.3 Hz, 1H), 1.46 (s,9H), 1.45 (s,9H). ^{13}C NMR ($CDCl_3$) δ 171.4, 169.9, 148.8, 117.1, 84.1, 82.8, 57.7, 39.2, 27.74, 27.71, 26.7, 19.1. IR (KBr pellet) 2260, 1782, 1738, 1337, 1152 cm^{-1}. Anal. Calcd for $C_{16}H_{24}N_2O_5$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.11; H, 7.28; N, 8.57.

Ethyl (2S, 4S) and (2S, 4R)-1-(*tert*-butoxycarbonyl)-4-phenylthiopyroglutamate (2e and 3e): (hexane/ethyl acetate: 4/1). 76% yield as a 2/1 diastereomeric mixture. A small fraction of the major isomer **2e** was obtained pure by flash chromatography, whereas **3e** was characterized from a 3/1 enriched mixture of **3e** and **2e**.

For **2e**: Colorless oil. $[\alpha]_D$ = +23.2° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 7.56-7.51 (m, 2H), 7.30 (m, 3H), 4.37 (dd, J = 3.3 and 9.0 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.92 (dd, J = 8.9 and 9.7 Hz, 1H), 2.30 (m, 2H), 1.46 (s, 9H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 170.5, 170.2, 148.4, 132.2, 131.3, 128.8, 128.2, 83.4, 61.3, 56.5, 47.5, 28.7, 27.4, 13.6. IR (film) 1798, 1748, 1475, 1310 cm^{-1}. HRMS calcd for $C_{18}H_{23}NO_5S$ 365.1297, found 365.1285.

For **3e**: ^{1}H NMR ($CDCl_3$) δ 7.56-7.51 (m, 2H), 7.30 (m, 3H), 4.53 (dd, J = 5.0 and 9.0 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.88 (dd, J = 5.9 and 14.9 Hz, 1H), 2.74 (dt, J = 8.9 and 13.9 Hz, 1H), 2.15 (m, 1H), 1.48 (s,

9H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 170.5, 170.4, 148.5, 133.2, 132.3, 128.8, 128.7, 83.5, 61.4, 56.4, 47.4, 28.7, 27.4, 13.7.

Ethyl (2S, 4S) and (2S, 4R)-1-(*tert*-butoxycarbonyl)-4-phenylselenopyroglutamate (2f and 3f): (hexane/ethyl acetate: 7/3). 60% yield. as a 2/1 diastereomeric mixture. A small fraction of the major isomer **2f** was obtained pure by flash chromatography, whereas **3f** was characterized from a 6/1 enriched mixture of **3f** and **2f**.

For **2f**: $[\alpha]_D$ = -68.4° (c 0.84, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.65 (m, 2H), 7.40-7.20 (m, 3H), 4.19 (dd, J = 5.6 and 7.9 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.89 (t, J = 8.2 Hz, 1H), 2.36 (m, 2H), 1.44 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 171.6, 170.8, 148.9, 136.0, 129.0, 126.2, 83.8, 61.7, 57.6, 40.1, 29.9, 27.8, 14.1. IR (film) 1790, 1748, 1723, 1310 cm^{-1}. HRMS calcd for $C_{18}H_{23}NO_5Se$ 413.0741, found 413.0715.

For **3f**: ^1H NMR ($CDCl_3$) δ 7.63 (m, 2H), 7.40-7.20 (m, 3H), 4.56 (dd, J = 3.4 and 9.3 Hz, 1H), 4.20 (dq, J = 2.2 and 7.1 Hz, 2H), 3.94 (dd, J = 4.6 and 9.0 Hz, 1H), 2.78 (dt, J = 9.1 and 14.4 Hz, 1H), 2.20 (td, J = 3.7 and 14.4 Hz, 1H), 1.48 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 171.7, 170.7, 149.4, 135.1, 129.3, 128.6, 128.2, 83.8, 61.9, 57.6, 40.7, 29.9, 27.8, 14.1.

Ethyl (2S, 4S) and (2S, 4R)-1-(*tert*-butoxycarbonyl)-4-phenylcarbonylpyroglutamate (2g and 3g): (hexane/ethyl acetate: 1/1). 75% yield as 1:1 diastereomeric mixture. Diastereomer separation was not possible. They were characterized in the mixture. ^1H NMR (DMSO-d_6) δ 8.05 (m, 2H), 7.80-7.40 (m, 3H), 4.98 (2dd, 1H), 4.80-4.60 (2dd, 1H), 4.30-4.10 (2q, 2H), 2.80 (dt, J = 9.4 and 13.2 Hz, 0.5H), 2.60 (dt, J = 9.2 and 13.0 Hz, 0.5H), 2.39 (td, J = 5.6 and 13.0 Hz, 0,5H), 2.20 ddd, J = 2.7, 9.0 and 13.2 Hz, 0.5H), 1.47 (s, 9H), 1.25 (2t, J = 7.1 Hz, 3H). ^{13}C NMR (DMSO-d_6) δ 194.8, 193.8, 171.0, 170.7, 169.2, 168.6, 148.7, 135.8, 135.4, 134.0, 133.9, 129.6, 129.4, 128.7, 128.6, 82.9, 82.8, 61.4, 61.2, 57.2, 56.9, 50.8, 49.7, 32.1, 29.6, 27.4 (2C), 24.3, 23.9, 10.0 (2C). IR (film) 1790, 1746, 1682, 1312 cm^{-1}. HRMS calcd for $C_{19}H_{23}NO_6$ 361.1525, found 361.1497.

Ethyl (2S, 4R)-1-(*tert* -butoxycarbonyl)-4-allylpyroglutamate (2h): (Hexane/ethyl acetate: 4:1). 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.

Ethyl (2S, 4S)-1-(*tert*-butoxycarbonyl)-4-allylpyroglutamate (3h): (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.

Ethyl (2S, 4R)-1-(*tert*-butoxycarbonyl)-4-cinnamylpyroglutamate (2i): (Hexane/ethyl acetate: 3:1). Colorless oil. 54% yield. $[\alpha]_D$ = -33.3° (c 1, $CHCl_3$). ^1H 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. Calcd for $C_{21}H_{27}NO_5$: C, 67.47; H, 7.22; N, 3.75. Found: C, 67.20; H, 7.15; N, 3.77.

Ethyl (2S, 4S) -1-(*tert*-butoxycarbonyl)-4-cinnamylpyroglutamate (3i): Colorless oil. 15% yield. $[\alpha]_D$ = +55.0° (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.40-7.10 (m, 5H), 6.33 (d, J = 15.7 Hz, 1H), 6.05 (dt, J = 6.8 and 15.7 Hz, 1H), 4.42 (dd, J = 6.8 and 8.9 Hz, 1H), 4.42 (q, J = 7.1 Hz, 2H), 2.28-2.60 (m, 2H), 2.55-2.20 (m, 2H), 1.85-1.60 (m, 1H), 1.43 (s, 9H), 1.20 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 174.3, 171.1, 148.9, 136.5, 132.5, 128.2, 127.0, 125.7, 83.2, 61.2, 57.1, 42.0, 34.0, 27.5, 26.2, 13.7. IR (film) 2980, 1790, 1748, 1717, 1317 cm^{-1}. MS. Repeated attempts to obtain satisfactory high resolution mass spectra (FAB and EI) were unsuccessful. 317 (4), 173 (99), 200 (36), 143 (35), 129 (14), 117 (100), 115 (23), 102 (38), 91 (29), 57 (38).

Ethyl (2S, 4R)-1-(*tert*-butoxycarbonyl)-4-benzylpyroglutamate (2j): (Hexane/ethyl acetate 4:1). 59% yield. White solid. m.p. 99-100°C (hexane). $[\alpha]_D$ = -38.1° (c 0.84, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.40-7.10 (m, 5H), 4.43 (dd, J = 3.7 and 7.6 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.25 (dd, J = 4.0 and 13.7 Hz, 1H), 3.00-2.82 (m, 1H), 2.63 (dd, J = 9.5 and 13.7 Hz, 1H), 2.05-1.95 (m, 2H), 1.47 (s, 9H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 174.3, 171.1, 149.3, 138.2, 128.9, 128.6, 126.6, 83.5, 61.6, 56.9, 43.4, 36.2, 27.9, 27.8, 14.1. IR (KBr pellet) 1778, 1736, 1286, 1211 cm^{-1}. Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 3.03. Found: C, 65.54; H, 7.06; N, 4.09.

***tert*-Butyl (2S, 4R)-1-(*tert*-butoxycarbonyl)-4-benzylpyroglutamate (2k)**: (Hexane/ ethyl acetate 4:1). 41% yield. White solid. m.p. 129-130°C (hexane). $[\alpha]_D$ = -42.0° (c 1, $CHCl_3$), $[\alpha]_D$ = -38.6° (c 0.44, MeOH). ^1H NMR ($CDCl_3$) δ 7.40-7.10 (m, 5H), 4.43 (dd, J = 3.7 and 7.6 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.25 (dd, J = 4.0 and 13.7 Hz, 1H), 3.00-2.82 (m, 1H), 2.63 (dd, J = 9.5 and 13.7 Hz, 1H), 2.05-1.95 (m, 2H), 1.47 (s, 9H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 174.8, 170.5, 149.6, 138.5, 129.9, 126.8, 83.5, 82.5, 57.9, 43.5, 36.5, 28.1 (in this later signal, the CH_2 carbon of the 3-position of the pyroglutamic ring, is overlapped with the CH_3 carbon atoms of*tert*- butyl groups, as it was determinated by a DEPT experiment). IR (KBr pellet) 1784, 1742, 1340, 1110 cm^{-1}.

Ethyl (2S, 4R) -1-(*tert*-butoxycarbonyl)-4-p-tolylmethylpyroglutamate (2l): (Hexane/ethyl acetate: 4:1). 57% yield. White needles. m.p.: 115-7°C (hexane). $[\alpha]_D$ = -44.3° (c 1.0, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.09-7.02 (AA' BB', J = 10.9 Hz, 4H), 4.42 (dd, J = 7.6 and 7.8 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.2 (dd, J = 3.9 and 13.6 Hz, 1H), 3.90-2.80 (m, 1H), 2.59 (dd, J = 9.4 and 13.6 Hz, 1H), 2.28 (s, 3H), 2.01-1.93 (m, 2H), 1.46 (s, 9H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 174.3, 171.1, 149.2, 136.0, 135.0, 129.2, 128.7, 83.4, 61.5, 56.9, 43.4, 35.6, 27.7, 20.9, 14.0. IR (KBr pellet) 1794, 1782, 1317, 1211 cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.45; H, 7.54; N, 3.87. Found: C, 66.32; H, 7.49; N, 3.96.

Ethyl (2S, 4R)-1-(*tert*-butoxycarbonyl)-4-(p-cyano)benzylpyroglutamate (2m): (Hexane/ethyl acetate: 2:1). 57% yield. White needles. m.p.: 131-2°C (ethyl acetate-hexane). $[\alpha]_D$ = -27.9° (c 1.0, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.56-7.24 (AA'BB', J = 8.0 Hz, 4H), 4.46 (dd, J = 1.9 and 8.9 Hz, 1H), 4.16 (q, J = 7.1 Hz, 2H), 3.26 (dd, J = 4.0 and 13.6 Hz, 1H), 3.0-2.80 (m, 1H), 2.73 (dd, J = 8.8 and 13.5 Hz, 1H), 2.10-1.85 (m, 2H), 1.46 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 173.5, 170.8, 149.0, 143.8, 132.3, 129.7, 118.6, 110.5, 83.7, 61.7, 56.7, 42.8, 35.9, 27.7, 14.0. IR (KBr pellet) 2229, 1784, 1743, 1317 cm^{-1}. Anal. Calcd for $C_{20}H_{24}N_2O_5$: C, 64.49; H, 6.51; N, 7.52. Found: C, 64.42; H, 6.39; N, 7.50.

Ethyl (2S, 4R)-1-(*tert*-butoxycarbonyl)-4-(p-trifluoromethyl)benzylpyroglutamate (2n): Hexane, ethyl acetate 4:1. 53% yield. White needles. m.p.: 119-120°C (hexane). $[\alpha]_D$ = -30.5° (c 1.0, CH_2Cl_2). ^1H NMR

($CDCl_3$) δ 7.54-7.23 (AA'BB', J = 8.0 Hz), 4.45 (dd, J = 2.3 and 8.5 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.28 (dd, J = 3.9 and 13.5 Hz, 1H), 2.95-2.87 (m, 1H), 2.71 (dd, J = 9.1 and 13.5 Hz, 1H), 2.03-1.92 (m, 2H), 1.46 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 173.8, 171.0, 149.2, 142.3 (q, J = 1.3 Hz, 1C), 129.3, 128.9 (q, J = 32.0 Hz, 1C), 125.5 (q, J = 3.7 Hz, 1C), 124.1 (q, J = 271.9 Hz, 1C), 83.7,61.7, 56.9, 43.1, 35.8, 27.8, 14.1. IR (KBr pellet) 1776, 1741, 1329, 1197, 1126 cm^{-1}.Anal. Calcd for $C_{20}H_{24}F_3NO_5$: C, 57.82; H, 5.83; N, 3.37. Found: C, 57.76; H, 5.69; N, 3.43.

Ethyl (2S, 4R)-1-(*tert*-butoxycarbonyl)-4-(p-bromo)benzylpyroglutamate (2o): (Hexane/ethyl acetate 4:1). 36% yield. White needles. m.p.: 135-7°C (hexane). $[\alpha]_D$ = -28.5° (c 1.0, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.39-6.99 (AA'BB', J = 8.3 Hz), 4.42 (dd, J = 5.9 and 8.5 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.15 (dd, J = 4.0 and 13.7 Hz, 1H), 2.89-2.81 (m, 1H), 2.61 (dd, J = 9.0 and 13.7 Hz, 1H), 2.01-1.90 (m, 2H), 1.45 (s, 9H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 173.9, 171.0, 149.1, 137.6, 130.7, 83.5, 61.6, 56.8, 35.3, 27.7, 27.6, 14.0. IR (KBr pellet) 1786, 1751, 1309, 1194 cm^{-1}. Anal. Calcd for $C_{19}H_{24}BrNO_5$: C, 53.52; H, 5.68; N, 3.29. Found: C, 53.32; H, 5.53; N, 3.25.

Ethyl (2S, 4R)-1-(*tert*-butoxycarbonyl)-4-naphtylmethylpyroglutamate (2p): (Hexane/ethyl acetate 4:1). 55% yield. White needles. m.p.:124-4°C (hexane). $[\alpha]_D$ = -19.8° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.78-7.71 (m, 3H), 7.57 (bs,1H), 7.47-7.34 (m, 2H), 7.25 (dd, J = 1.6 and 8.4 Hz, 1H), 7.42 (dd, J = 4.7 and 5.4 Hz, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.38 (dd, J = 3.7 and 13.4 Hz, 1H), 3.06-2.90 (m, 1H), 2.78 (dd, J = 9.3 and 13.4 Hz, 1H), 2.03-1.78 (m, 2H), 1.46 (s, 9H), 1.19 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 174.0, 170.0, 149.0, 135.5, 133.1, 131.9, 128.1, 127.3, 127.23, 127.20, 127.0, 125.3, 83.2, 61.3, 56.7, 43.1, 36.0, 27.6, 13.8. IR (KBr pellet) 1778, 1736, 1334, 1197, 1159 cm^{-1}. Anal. Calcd for $C_{23}H_{26}NO_5$: C, 69.43; H, 6.76; N, 3.52. Found: C, 69.39; H, 6.73; N, 3.52.

[(2S, 5S)-1,5-di-*tert*-Butoxycarbonyl-2-oxo, pyrrolidinyl]-3-acetic acid (4): A flask is charged with a magnetic stirrer, 4.2 ml of CCl_4, 4.2 ml CH_3CN, 6.3 ml of water, 0.792 mg (2.11 mmol) of **2k**, and 1.85 g of $NaIO_4$ (8.65 mmol). To this biphasic solution, 10.5 mg (4.64 mol %) of $RuCl_3.H_2O$ was added, and the entire mixture was stirred vigorously for 9 days at room temperature. Then 20 ml af CH_2Cl_2 were added, and the phases were separted. The upper aqueous phase was extracted three times with CH_2Cl_2. The combined organic extracts were dried and concentrated. the resulting residue was diluted with 20 ml of ethyl ether, filtered through celite path and concentrated. The crude residue was dissolved in CH_2Cl_2 and extracted with 15% $NaCO_3H$ solution. The aqueous phase was acidified with 6N HCl and extracted with CH_2Cl_2. The organic layer was dried and evaporated to dryness to give **4** (92 mg, 13% isolated yield). **2k** (616 mg) was recovered from the organic phase. ^1H NMR ($CDCl_3$) δ 8.45 (bs, 1H), 4.42 (d, J = 9.0 Hz), 3.00-2.80 (m, 2H), 2.53-2.23 (m, 2H), 2.13-1.94 (m, 1H), 1.45 (s, 9H), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 176.1, 174.1, 170.1, 149.2, 83.6, 82.7, 57.7, 38.1, 34.3, 28.3, 27.86 (3C), 27.82 (3C).

General procedure for equilibration of 2j, n, p . A solution of **2j, n, p** (1 mmol) in DMF (8 ml) and KCN (1mmol) was stirred at room temperature overnight. The reaction mixture was diluted with water (15 ml) and extracted with ethyl ether (3x8 ml). The organic layer was dried over Na_2SO_4 and evaporated to dryness. The diastereomeric mixture was separated by flash chromatography using ethyl acetate/hexane 1:4 as movil phase.

Ethyl (2S, 4S)-1-(*tert*-butoxycarbonyl)-4-benzylpyroglutamate (3j): (Hexane/ethyl acetate 4:1). 20% yield. $[\alpha]_D$ = +48.7° (c 0.76, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.40-7.10 (m, 5H), 4.43 (dd, J = 6.8 and 8.7 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.32 (dd, J = 3.7 and 13.6 Hz, 1H), 2.91- 2.75 (m, 1H), 2.61 (dd, J = 11.0 and 13.6 Hz, 1H), 2.30 (dt, J = 8.9 and 13.3 Hz, 1H), 1.75-1.58 (m, 1H), 1.48 (s, 9H), 1.26 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 174.4, 171.4, 149.2, 138.3, 128.7, 128.6, 126.5, 83.6, 61.5, 57.4, 44.4, 36.6, 27.7, 26.8, 14.0. IR (KBr pellet) 1790, 1750, 1717, 1312, 1148 cm^{-1}. HRMS [M^+- $CO_2C(CH_3)_3$ + 1] calcd 246.1130, found 246.1207.

Ethyl (2S, 4S)-1-(*tert*-butoxycarbonyl)-4-(p-trifluormethyl)benzylpyroglutamate (3n): Hexane, ethyl acetate 4:1. 20% yield. $[\alpha]_D$ = +37.5° (c 1.6, CH_2Cl_2). ^1H NMR ($CDCl_3$) δ 7.55-7.23 (AA'BB', J = 8.0 Hz), 4.44 (dd, J = 6.9 and 8.6 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.32 (dd, J = 2.7 and 12.9 Hz, 1H), 2.88-2.79 (m, 1H), 2.73 (dd, J = 10.5 and 12.9 Hz, 1H), 2.33 (dt, J = 8.8 and 13.3 Hz, 1H), 1.70-1.56 (m, 1H), 1.48 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 173.9, 171.2, 149.1, 142.4 (q, J = 1.2 Hz,1C), 129.1, 128.9 (q, J = 32.4 Hz, 1C), 125.5 (q, J = 3.7 Hz, 1C), 124.0 (q, J = 271.9 Hz, 1C), 83.8,61.6, 57.3, 44.0, 36.3, 27.7, 26.8, 14.0. IR (film) 1790, 1750, 1710, 1325, 1155, 1120 cm^{-1}. HRMS [M^+- $CO_2C(CH_3)_3$ + 1] calcd 315.1082, found 315.1077.

Ethyl (2S, 4S)-1-(*tert*-butoxycarbonyl)-4-naphtylmethylpyroglutamate (3p): White solid. m.p.: 112-3°C (Hexane/ethyl acetate) 20% yield. $[\alpha]_D$ = +71.0° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.85-7.74 (m, 3H), 7.55 (bs,1H), 7.53-7.38 (m, 2H), 7.30 (dd, J = 1.6 and 8.5 Hz, 1H), 4.44 (dd, J = 6.8 and 8.7 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.47 (dd, J = 3.2 and 13.1 Hz, 1H), 3.05-2.84 (m, 1H), 2.79 (dd, J = 10.9 and 13.1 Hz, 1H), 2.30 (dt, J = 8.8 and 13.3 Hz, 1H), 1.80-1.55 (m, 1H), 1.49 (s, 9H), 1.24 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 174.4, 171.4, 149.3, 135.9, 134.4, 132.2, 128.4, 127.6, 127.4, 127.3, 126.9, 126.1, 125.6, 83.7, 61.6, 57.4, 44.3, 36.9, 27.8, 26.9, 14.0. IR (film) 1794, 1751, 1721, 1309, 1202 cm^{-1}. Anal. Calcd for $C_{23}H_{26}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.30; H, 6.72; N, 3.63.

REFERENCES AND NOTES

1 (**a**). Martens, J. *Top. Curr. Chem.* **1984**, *125*, 165.(**b**). Coppola, G. M. and Schuster, H. F. in "*Asymmetric Synthesis : Construction of Chiral Molecules Using Amino Acids*"; John Wiley & Sons Inc.: New York.

2 Ohta, T.; Hasoi, A.; Kimura, T; Nozoe, S. *Chem. Lett.* **1987**, 2091.

3 Molina, M. T.; del Valle, C.; Escribano, A. M.; Ezquerra, J.; Pedregal, C. *Tetrahedron.* **1993**, *49*, 3801.

4 (**a**). Ohta, T.; Hasoi, A.; Kimura, T.; Sato, N.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 4303. (**b**). Ezquerra, J.; de Mendoza, J.; Pedregal, C.; Ramirez, C. *Tetrahedron Lett.* **1992**, *38*, 5589. (**c**). A synthetic application of this reaction using the lithium p-tolylsulfinyl anion for the synthesis of the *trans* pyrrolidine-2,5-dicarboxylic acid, a constituent of the red alga *Schizymenia dubyi*, Ezquerra, J.; Rubio, A.; Pedregal, C.; Sanz, G.; Rodriguez, J. H.; García Ruano, J. L. *Tetrahedron Lett.* **1993** (in press)

5 Ikota, N. *Heterocycles* **1989**, *29*, 1469.

6 Ohta, T.; Hosoi, A.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 329.

7 Ohfune, Y.; Tomita, M. *J. Am.Chem. Soc.* **1982**, *104*, 3511.

8 Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4978.

9 Ikota, N. *Tetrahedron Lett.* **1992**, *33*, 2553.

10 (a). Shimamoto, K.; Ohfune, Y. *Tetrahedron Lett.* **1989**, *30*, 3803. (b). Shimamoto, K.; Ishida, M.; Shinozaki, H.; Ohfune, Y. *J. Org. Chem.* **1991**, *56*, 4167.

11 (a). Tanaka, K-I.; Yoshifuji, S.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3879. (b). Hon, Y-S.; Chang, Y-C.; Gong, M-L. *Heterocycles* **1990**, *31*, 191.

12 (a). Yanagida, M.; Hashimoto, K.; Ishida, M.; Shinozaki, H.; Shirahama, H. *Tetrahedron Lett.* **1989**, *30*, 3799. (b). Langlois, N.; Andriamialisoa, R. Z. *Tetrahedron Lett.* **1991**, *32* , 3057.

13 Lodge, D. in "*Excitatory Amino Acids in Health and Disease*", John Wiley & Sons, Inc.: New York, **1988**.

14 (a). For a synthesis of (2*R*, 3*S*)-2-Hydroxymethyl-3-hydroxypyrrolidine and the Geissman-Waiss lactone, see. Ikota, N.; Hanaki, A. *Heterocycles* **1988**, *27*, 2535. (b).An approach to the synthesis of cytochalasans, Achermann, J.; Matthes, M.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 122. (c). An enantioselective synthesis of *Monomorium minutum* ant venon alkaloids, Rosset,S.; Célerier, J. P.; Lhommet, G. *Tetrahedron Lett.* **1991**, *32*, 7521. (d). For several hydroxylated derivatives, Woo, K-C.; Jones, K. *Tetrahedron Lett.* **1991**, *32*, 6949. (e). In the synthesis of a potential carbapenem intermediate, Somfai, P.; He, M. H.; Tanner, D. *Tetrahedron Lett.* **1991**, *32*, 283. (f). For the synthesis of *R-Baclofen*, Herdeis, C.; Hubmann, H. P. *Tetrahedron: Asymmetry* **1992**, *3*, 1213.

15 (a). Thottathil, J. K.; Moniot, J. L.; Mueller, R. H.; Wong, M. K. Y.; Kissick, T. P. *J. Org. Chem.* **1986**, *51*, 3140. (b). Hanessian, S.; Ratovelomanana, V. *Synlett.* **1990**, 501. (c). Baldwin, J. E.; Moloney, M. G.; Shim, S. B. *Tetrahedron Lett.* **1991**, *32*, 1379.

16 Avent, A. G.; Bowler, A. N.; Doyle, P. M.; Marchand, C. M.; Young, D. W. *Tetrahedron Lett.* **1992**, *33*, 1509.

17 (a). Danishefsky, S.; Morris, J.; Clizbe, L. A. *J. Am. Chem. Soc.* **1981**, *103*, 1602. (b). Attwood, M. R.; Carr, G. M.; Jordan, S. *Tetrahedron Lett.* **1990**, *31*, 283. (c). August, R. A.; Khan, J. A.; Moody, C. M.; Young, D. W. *Tetrahedron Lett.* **1992**, *33*, 4617.

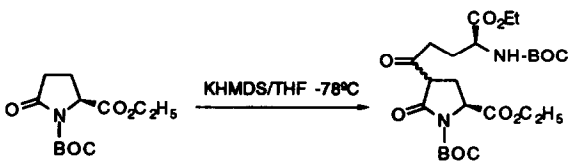
18 (a). Baldwin, J. E.; Miranda, T.; Moloney, M. *Tetrahedron.* **1989**, *45*, 7459. (b). Dikshit, D. K.; Panday, S. K. *J. Org. Chem.* **1992**, *57*, 1920.

19 Bowler, A. N.; Doyle, P.M.; Hitchock, P. B.; Young, D. W. *Tetrahedron Lett.* **1991**, *32*, 2679.

20 (a). Silverman, R. B.; Levy, M. A. *J. Org. Chem.* **1980**, *45*, 815. (b). Yoshifugi, S.; Tanaka, K-I.; Kawai, T.; Nitta, Y. *Chem. Pharm. Bull.* **1986**, *34*, 3873.

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

22 When KHMDS was used to generate the enolate, the pyroglutamate self-condensed. This reaction probably arises because the highly reactive potassium enolate is nucleophilic enough to cause ring opening (see *ref.* 4).



23 Zoretic, P. A.; Soja, P. *J. Org. Chem.* **1976**, *41*, 3587.

24 Langlois, N.; Rojas, A. *Tetrahedron Lett.* **1993**, *34*, 2477.

25 We have repeated the NOE experiments on the same compounds described by Langlois. The wrong assignment was due to a confusion in the correct assignment of the protons α and β of the 3-position in the pyroglutamate ring system.

26 $[\alpha]_D$ values reported by Baldwin[18a] $[\alpha]_D$ = -49.2 (c 0.9, $CHCl_3$), and by Dikshit[18b] $[\alpha]_D$ = -34.09 (c 0.44, MeOH).

27 Carlsen, P. H. J.; Katsuki, T.; Martin V.S.; Sharpless, K. B. *J. Org. Chem.* **1991**, *46*, 3936.

28 Generally to ensure the 1,3-asymmetric induction, pyroglutamates have been reduced to the alcohol and protected with bulky groups (TBDMS, TBDPS, Tr, Bn) *refs.* 5,7-12,14. When the ester moiety was not reduced *refs.* 16-19, bulky ester groups (Bn, ^tBu) have been used, presumably to achieve the same sort of induction, however this has not been reported.

29 Additionally, when the enolate of N-BOC pyroglutamic acid, prepared with two equivalents of LiHMDS, was reacted with iodoacetonitrile the same 2:1 *trans/cis* mixture was obtained.