Pergamon

Tetrahedron 54 (1998) 9447–9456

TETRAHEDRON

Stereoselective Synthesis of 2,3-Disubstituted Glutamic Acid Derivatives by Conjugate Addition to 3,4-Didehydropyroglutamates

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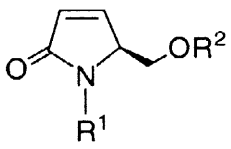
Received 20 January 1998; revised 8 June 1998; accepted 11 June 1998

Abstract: The Michael addition of lithium or magnesium organocuprates and sodium dimethyl malonate to 2-alkylated 3,4-didehydropyroglutamates **7**, prepared from the corresponding 4-substituted sulfoxides pyroglutamates or from benzophenone imine of glycine ethyl ester or nitrile, takes place in a stereoselective manner affording *cis*-2,3-disubstituted pyroglutamates **9**. Final hydrolysis of **9eb** gives *syn*-2,3-disubstituted glutamic acid **10**.

INTRODUCTION

L-Glutamate is the most important excitatory neurotransmitter in the vertebrate central nervous system (CNS) and its excitotoxic effect appears to play a crucial role in certain neurodegenerative disorders.[1] The biological importance of L-glutamic acid has promoted a great effort to modify its structure in order to modulate its activity. Monosubstituted L-glutamates at the C-3[2] or C-4[3] positions have been widely studied. However, disubstituted glutamates have received much less attention due to the dificulties to control the stereoselectivity and only 3,4-[4] and 2,4-disubstituted[5] derivatives have been described.

As part of our interest concerning the synthesis of selective agonist and antagonist for the various glutamate receptors, we report here the stereoselective preparation of *cis*-2,3-dialkylated pyroglutamates precursors of *syn*-2,3-disubstituted glutamic acids. We have recently described the alkylation at the C-2 of ethyl pyroglutamate[5] and the alkylation at the C-3 position has been achieved by Michael addition to 3,4-didehydropyroglutaminol derivatives **1**[6] and **2**.[7] This methodology needs the reduction of the carboxylic group and its regeneration after the alkylation process. However, the didehydropyroglutamate **3**[8] has a big tendency to isomerize to the corresponding 2,3-didehydropyroglutamate and has been only trapped with cyclopentadiene in a Diels-Alder reaction. Our strategy for the preparation of 2,3-dialkylated pyroglutamates is based on the preparation of 2-substituted 3,4-didehydropyroglutamates **4** in which the carbon-carbon double bond can not isomerizes and could be stereoselectively alkylated by Michael addition of nucleophiles at the C-3.



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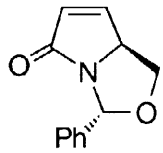

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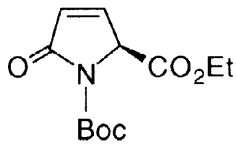

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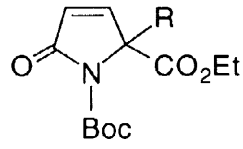

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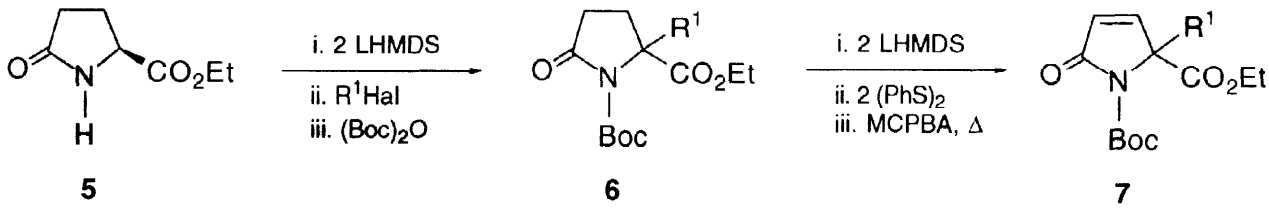
0040-4020/98/$19.00
PII: S0040-4020(98)00573-0

RESULTS AND DISCUSSION

The 2-alkylated derivatives **6**, prepared by double deprotonation of ethyl pyroglutamate (**5**) with lithium hexamethyldisilazide (**LHMDS**) followed by reaction with alkyl halides,[5] were transformed into the corresponding 3,4-didehydropyroglutamates **7** by thermal elimination of the 4-substituted sulfoxides as it was previously described for compound **3**[8] (Scheme 1 and Table 1).



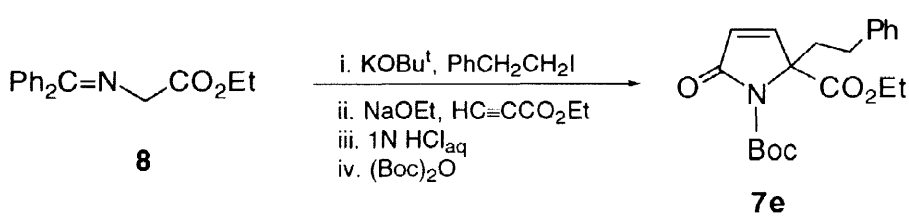
Scheme 1.

Table 1. Synthesis of 3,4-Didehydropyroglutamates **7**.

	product			
R^1Hal	no.	R^1	yield %)[a]	R_f[b]
CH_3I	**7a**	CH_3	23	0.50
$CH_2=CHCH_2Br$	**7b**	$CH_2=CHCH_2$	15	0.50
$(CH_3)_2CHCH_2I$	**7c**	$(CH_3)_2CHCH_2$	32	0.38
$PhCH_2Br$	**7d**	$PhCH_2$	61	0.35
$PhCH_2CH_2I$	**7e**	$PhCH_2CH_2$	42	0.48

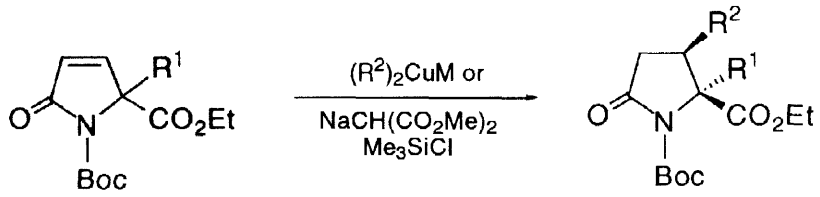
[a] Based on compound **6**, after column chromatography on silica gel. [b] Hexane/EtOAc: 2/1.

Alternatively, compound **7e** was prepared from benzophenone imine glycine ethyl ester (**8**) by successive alkylation with 2-phenylethyl iodide and potassium *tert*-butoxide as base and Michael addition to ethyl propiolate with sodium ethoxide as base, followed by final hydrolysis with aqueous 1N HCl at room temperature for 1 d[9] and protection as *N*-Boc with di-*tert*-butyl dicarbonate (Scheme 2). The overall yield, around 15%, is similar to the route of pyroglutamate but in less number of steps.



Scheme 2.

Michael addition of lithium or magnesium alkylcuprates, prepared in ether, to didehydropyroglutamates **7** was carried out in THF at -30°C in the presence of trimethylsilyl chloride to afford stereoselectively compounds **9** (Scheme 3 and Table 2). In the case of lithium diphenylcuprate the reaction failed and with the magnesium cuprate low yields were obtained even when the reaction was carried out at 0°C (Table 2, entries 5 to 7). With allyl- and propyl-cuprates the more accesible Grignard reagents were used. The reaction with sodium dimethyl malonate, prepared with sodium hydride in THF, took place at room temperature and also in the presence of trimethylsilyl chloride.



7 **9**

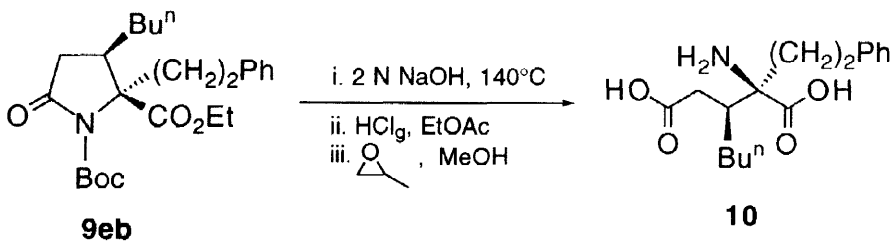
Scheme 3.

Table 2. Michael Addition to 3,4-Didehydropyroglutamates **7**.

entry	didehydro pyroglutamate	nucleophile[a]	T (°C)	product no.	R^1	R^2	yield %)[b]	mp (°C) or R_f[c]
1	**7d**	Me_2CuLi	-30	**9da**	$PhCH_2$	Me	73	76-79[d]
2	**7e**	Me_2CuLi	-30	**9ea**	$PhCH_2CH_2$	Me	75	0.26
3	**7d**	Bu^n_2CuLi	-30	**9db**	$PhCH_2$	Bu^n	76	0.57
4	**7e**	Bu^n_2CuLi	-30	**9eb**	$PhCH_2CH_2$	Bu^n	78	90-92[e]
5	**7d**	Ph_2CuLi	-30	**9dc**	$PhCH_2$	Ph	0	
6	**7d**	$Ph_2CuMgBr$	-30	**9dc**	$PhCH_2$	Ph	28[f]	0.54
7	**7d**	$Ph_2CuMgBr$	0	**9dc**	$PhCH_2$	Ph	21[f]	0.54
8	**7d**	$(allyl)_2CuMgBr$	0	**9dd**	$PhCH_2$	allyl	41[g]	79-81[h]
9	**7e**	$Pr^n_2CuMgBr$	-30	**9ee**	$PhCH_2CH_2$	Pr^n	58[i]	0.50
10	**7e**	$NaCH(CO_2Me)_2$[j]	rt	**9ef**	$PhCH_2CH_2$	$CH(CO_2Me)_2$	74[g]	0.25

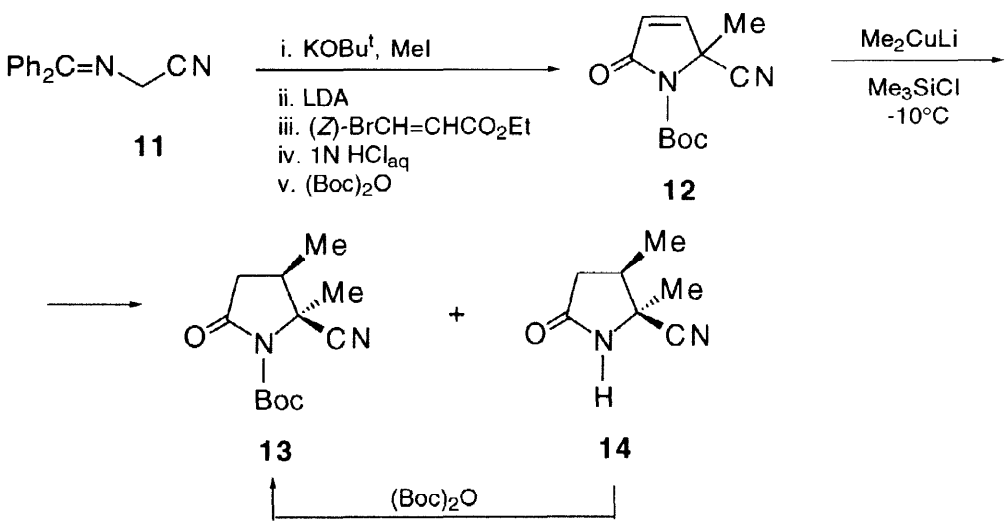
[a] Five equiv were used. [b] Isolated pure yield of pure product, based on compound **7**. [c] Hexane/EtOAc: 2/1. [d] CH_2Cl_2. [e] EtOAc. [f] A 30% of starting product **7d** was also isolated. [g] After column chromatography. [h] Hexane/EtOAc. [i] A 35% of starting product **7e** was also isolated. [j] Generated with NaH in THF.

In all cases the addition of nucleophiles was stereoselective and compounds **9** beared both substituents R^1 and R^2 in a *trans* relative position determined by NOE difference experiments carried out with compound **9da** in which H-3 gave 2% and 8% enhancement with the methylene and phenyl groups of the benzyl substituent at the 2-position, respectively. Similar stereochemical outcomes have been observed in the addition to pyroglutamates **1**[6] and **2**.[7] Representative product **9eb** was hydrolyzed to the glutamic acid **10** by successive treatment with 2N NaOH at 140°C in a pressure tube, followed by hydrogen cloride in EtOAc and propylene oxide in MeOH in 41% overall yield (Scheme 4).



Scheme 4.

The same stereoselectivity was observed in the alkylation of the didehydropyroglutamate **12** derived from the benzophenone imine glycine nitrile **11**, which was prepared in 43% overall yield by succesive alkylation with methyl iodide and potassium *tert*-butoxide as base and nucleophilic substitution of ethyl (*Z*)-bromoacrylate and LDA as base followed by hydrolysis with 1N HCl at room temperature[10] and *N*-Boc protection with di-*tert*-butyl dicarbonate. The addition was carried out with lithium dimethylcuprate at -10°C providing a mixture of the *cis*-derivative **13** together with deprotected product **14**, which after protection was transformed into compound **13** which was obtained in 60% overall yield (Scheme 5). The relative configuration of both methyl groups in compound **13** was stablished by means of its NOESY spectrum in which H-3 correlates with the methyl group at the 2-position.



Scheme 5.

As conclusion, 2-subsituted 3,4-didehydropyroglutamates bearing a carboxylate or a nitrile function are appropriate substrates for the stereoselective synthesis of *cis*-2,3-dialkylated pyroglutamates, by means of Michael addition at the 3-position of organocuprates and sodium malonate, immediate precursors of *syn*-2,3-dialkylated glutamic acids.

EXPERIMENTAL SECTION

General. Melting points were obtained by a Reichert Thermovar apparatus and are uncorrected. FT-IR spectra were obtained on a Nicolet 400D spectrophotometer as neat liquids. NMR spectra were recorded on a Bruker AC-300 (300 MHz for ^1H and 75 MHz for ^{13}C) using $CDCl_3$ (otherwise stated)as solvent and TMS as internal standard; chemical shifts are given in δ (ppm) and coupling constans (*J*) are measured in Hz. ^{13}C NMR assignments were made on the basis of DEPT experiments. When D_2O was used as solvent, methanol was used as internal standard. Mass spectra (EI, 70 eV) were obtained on a Hewlett-Packard 5988A spectrometer. High resolution mass were measured in the Mass Spectrometry Service at The University of Zaragoza, in all cases compounds lost the *N*-Boc group. Elemental analyses were performed by the Microanalyses Service at the University of Alicante. Thin layer chromatography (TLC) was carried out on a Schleicher & Schuell F1400/LS 254 plates coated with a 0.2 mm layer of silica gel with UV or iodine visualization. Column chromatography was performed using silica gel 60 of 70-230 mesh and hexane/EtOAc as eluant. All starting materials were commercially available (Aldrich, Fluka, Acros), of the best grade and were used without further purification. THF was dried with $LiAlH_4$ under an argon atmosphere and distilled before use.

Synthesis of *N*-BOC α-Alkylated Ethyl Pyroglutamates (6): The synthesis and physical data for compounds **6** are described on the literature[5] with exception of **6b** which was prepared according with the described procedure. Yield and physical, analytical and spectral data follow:

***1-(tert-Butyl) 2-Ethyl 2-Allyl-5-oxo-1,2-pyrrolidinedicarboxylate* (6b):** Yield, 57%; R_f 0.38 (hexane/EtOAc: 1/1); ν 3078 (HC=CH), 1790, 1743 and 1719 cm^{-1} (C=O); δ_H 1.28 (t, J = 7.0, 3H, CH_3), 1.51 [1s, 9H, $(CH_3)_3$], 2.11, 2.54, 3.07 (3m, 6H, $CH_2CH_2CCH_2$), 4.21 (q, J = 7.0, 2H, CH_2CH_3), 5.19 (m, 2H, CH_2=CH) and 5.70 (m, 1H, CH_2=CH); δ_C 13,8 (CH_3), 26.6 (CH_2CO), 27.6 [$(CH_3)_3$], 30.6 (CH_2C), 39.0 (CH_2CH=CH_2), 61.4 (CH_2O), 67.2 (CN), 83.4 (CO), 120.5, 131.0 (CH_2=CH), 149.0 (NCO_2), 172.4 ($NCCO_2$) and 174.0 (CON); *m/z* 224 (M^+-73, 7%), 156 (41), 124 (100) and 41 (14).

Synthesis of Didehydropyroglutamates 7. General Procedure. To a solution of hexamethyldisilazane (0.44 ml, 2.1 mmol) in dry THF (2 ml) at -78°C was added a 1.6M solution of n-butyllithium (1.31 ml, 2.1 mmol) in hexanes. The mixture was stirred for 10 min at -78°C and a solution of product **6** (1 mmol) in THF (2 ml) was added. After 1 h stirring at -78°C, was added a solution of diphenyl disulfide (0.459 g, 2.1 mmol) in THF (1 ml), and the mixture was stirred for an additional hour at -78°C. Then, the reaction mixture was allowed to reach room temperature overnight. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (3x20 ml). The organic layers were washed with brine, dried (Na_2SO_4) and the solvents removed. The residue was purified by column chromatography to yield the corresponding phenylsulfanyl derivative, as a diasteromeric mixture, which was dissolved in chloroform (2 ml) at 0°C and *m*-chloroperbenzoic acid (free of acid, 0.206 g, 1.2 mmol) was added. The reaction was stirred 1 h at 0°C and 1 h at rt, quenched with a saturated solution of $NaHCO_3$ and extracted with EtOAc (3x20 ml), dried (Na_2SO_4) and the solvents removed.

The residue was diluted in toluene (1 ml) and refluxed overnight. The toluene was removed and the residue was purified by column chromatography to give pure products **7**. Yields and physical data are included in Table 1, spectral and analytical data follow:

***1-(tert-Butyl) 2-Ethyl 2-Methyl-5-oxo-2,5-dihydro-1H-1,2-pyrroledicarboxylate* (7a):**[9] ν 3084, 1607 (HC=CH), 1784, 1747 and 1716 cm^{-1} (C=O); δ_H 1.24 (t, *J* = 7.0, 3H, CH_3), 1.53 [s, 9H, $(CH_3)_3$], 1.76 (t, 3H, CH_3), 4.16 (m, 2H, CH_2CH_3), 6.17 and 6.99 (2d, *J* = 6.0, 2H, CH=CH); δ_C 13.9 (CH_3CH_2), 20.7 (CH_3C), 27.9 [$(CH_3)_3$], 62.3 (CH_2CH_3), 70.2 (CN), 83.6 (CO), 126.8 (CHC), 148.5 (CHCO), 149.9 (NCO_2), 168.6 (CON) and 168.8 ($NCCO_2$); *m/z* 270 (M^++1, <1%), 214 (26), 171 (10), 170 (97), 169 (17), 97 (30), 96 (100), 59 (11), 57 (54) and 56 (11).

***1-(tert-Butyl) 2-Ethyl 2-Allyl-5-oxo-2,5-dihydro-1H-1,2-pyrroledicarboxylate* (7b):** ν 3082, 1642 (HC=CH), 1783, 1740 and 1717 cm^{-1} (C=O); δ_H 1.23 (t, *J* = 7.2, 3H, CH_3), 1.53 [s, 9H, $(CH_3)_3$], 2.96 (dd, *J* = 14.5, 6.6, 1H, $HCHCH=CH_2$), 3.17 (dd, *J* = 14.3, 8.2, 1H, $HCHCH=CH_2$), 4.19 (m, 2H, CH_2CH_3), 5.08 (m, 2H, CH_2=CH), 5.45 (m, 1H, $CH_2=CH$), 6.21 and 6.91 (2d, *J* = 5.8, 2H, CH=CH); δ_C 14.0 (CH_3), 28.0 [$(CH_3)_3$], 36.6 (CH_2C), 62.4 (CH_2CH_3), 72.6 (CN), 83.6 (CO), 128.04 (CHC), 148.1 (CHCO), 148.1 (NCO_2), 168.3 (CON) and 168.8 ($NCCO_2$); *m/z* 280 (M^+-15, <1%), 195 (21), 154 (36), 123 (14), 122 (100), 57 (83) and 41 (24) (Found: M^+ 195.0890. Calcd. For $C_{10}H_{13}NO_3$: 195.0895)

***1-(tert-Butyl) 2-Ethyl 2-Isobutyl-5-oxo-2,5-dihydro-1H-1,2-pyrroledicarboxylate* (7c):**[9] ν 3082, 1603 (HC=CH), 1783, 1743 and 1717 cm^{-1} (C=O); δ_H 0.86 [d, *J* = 6.4, 6H, $(CH_3)_2$], 1.23 (t, *J* = 7.2, 3H, CH_3), 1.39 [m, 1H, $CH(CH_3)_2$], 1.52 [s, 9H, $(CH_3)_3$], 2.16, 2.39 (2dd, *J* = 14.8, 6.0, 2H, CH_2CH), 4.15 (m, 2H, CH_2CH_3), 6.21 and 6.94 (2d, *J* = 5.8, 2H, CH=CH); δ_C 13.8 (CH_3), 23.2 (CH), 23.7, 24.6 [$(CH_3)_2$], 27.8 [$(CH_3)_3$], 40.1 (CH_2CH), 62.2 (CH_2CH_3), 73.2 (CN), 83.3 (CO), 127.4 (CHC), 148.4 (NCO_2), 149.2 (CHCO), 168.6 (CON) and 169.3 ($NCCO_2$); *m/z* 256 (M^+- 55, <1%), 212 (29), 211 (15), 159 (10), 139 (12), 138 (100), 96 (92), 57 (47) and 56 (11).

***1-(tert-Butyl) 2-Ethyl 2-Benzyl-5-oxo-2,5-dihydro-1H-1,2-pyrroledicarboxylate* (7d):** ν 3086, 3065, 3003, 1607 (HC=CH), 1789 and 1732 cm^{-1} (C=O); δ_H 1.25 (t, *J* = 7.3, 3H, CH_3), 1.60 [s, 9H, $(CH_3)_3$], 3.51, 3.77 (2d, *J* = 14.2, 2H, CH_2Ar), 4.21 (m, 2H, CH_2CH_3), 5.92, 7.00 (2d, *J* = 6.1, 2H, CH=CH) and 7.08 (m, 5H, ArCH); δ_C 13.7 (CH_3), 27.7 [$(CH_3)_3$], 38.0 (CH_2Ar), 62.2 (CH_2CH_3), 73.1 (CN), 83.3 (CO), 127.0, 127.5, 127.8, 148.6 (ArCH, ArC), 148 (NCO_2), 168.1 ($NCCO_2$) and 168.3 (CON); *m/z* 336 (M^+- 9, <1%), 245 (11), 172 (17), 91 (100), 57 (11) and 41 (12).

***1-(tert-Butyl) 2-Ethyl 5-Oxo-2-phenethyl-2,5-dihydro-1H-1,2-pyrroledicarboxylate* (7e):**[9] ν 3086, 3065, 3027 (HC=CH), 1784, 1743 and 1716 cm^{-1} (C=O); δ_H 1.24 (t, *J* = 7.2, 3H, CH_3), 1.53 [1s, 9H, $(CH_3)_3$], 2.38 (m, 2H, CH_2Ar), 2.53, 2.77 (2m, 2H, CH_2CH_2Ar), 4.17 (m, 2H, CH_2CH_3), 6.23, 6.93 (2d, *J* = 6.0, 2H, CH=CH) and 7.20 (m, 5H, ArCH); δ_C 14.0 (CH_3), 28.0 [$(CH_3)_3$], 29.9 (CH_2Ar), 33.8 (CH_2CH_2Ar), 62.35 (CH_2O), 73.2 (CN), 83.6 [$C(CH_3)_3$], 126.2, 127.95, 128.2, 128.5 (ArCH, CHCO), 140.4 (ArC), 148.4 (CHCCN), 148.5 (NCO_2), 168.45 ($NCCO_2$) and 169.0 (CON); *m/z* 286 (M^+-73, <2%), 156 (11), 155 (100), 91 (55), 57 (71) and 41 (18).

Michael Addition to Didehydropyroglutamates 7. Synthesis of Compounds 9. General Procedure.

A) Addition of Organocuprates: To a suspension of CuI (0.305 g, 1.6 mmol) in dry ether was added at -20°C, the corresponding organolithium or organomagnesium reagent (3.2 mmol). After 15 min, the reaction was cooled at -78°C and a solution of the corresponding didehydro derivative **7** (0.32 mmol) and Me_3SiCl (0.08 ml, 0.64 mmol) in dry THF (3 ml) was added. The mixture was stirred 1 h at -78°C and then, the reaction

was allowed to warm to -30°C and quenched with a saturated solution of NH_4Cl, diluted with ether (20 ml) and the organic layer was washed until the blue colour of the aqueous phase disappeared.

B) Addition of Sodium Dimethyl Malonate: To a suspension of NaH (0.052 g, 1.3 mmol) in THF (2 ml) at 0°C, dimethyl malonate (0.2 ml, 1.3 mmol) was added. The mixture was stirred 30 min and then, a solution of the corresponding compound **7e** (0.26 mmol) and Me_3SiCl (0.52 mmol) in THF (2 ml) was added. The mixture was stirred overnight at rt and then, quenched with a saturated solution of NH_4Cl, extracted with EtOAc (3x20 ml). After drying and evaporation of the organic phase in both cases, the resulting oil was purified by column chromatography to give pure products **9**. Yields and physical data are included in Table 2, analytical and spectral data follow:

***1-(*tert*-Butyl) 2-Ethyl 2-Benzyl-3-methyl-5-oxo-1,2-pyrrolidinodicarboxylate* (9da):** ν 3086, 3063, 3020, 1605 (HC=CH), 1786, 1736 and 1720 cm^{-1} (C=O); δ_H 1.03 (d, J = 6.7, 3H, CH_3C), 1.31 (t, J = 7.1, 3H, CH_2CH_3), 1.59 [s, 9H, $(CH_3)_3$], 2.14 (dd, J = 9.6, 3.2, 2H, CH_2CH), 2.34 (m, 1H, CHAr), 3.20, 3.70 (2d, J= 14.8, 2H, CH_2Ar), 4.27 (q, J= 7.1, 2H, CH_2O), 7.08 and 7.25 (2m, 5H, ArCH); δ_C 14.2, 14.6 (2xCH_3), 27.9 [$(CH_3)_3$], 36.6 (CH_2CH), 37.2 (CH), 38.05 (CH_2Ar), 61.5 (CH_2O), 72.2 (CN), 83.75 (CO), 127.1, 128.5, 130.6 (ArCH), 135.1 (ArC), 149.9 (NCO_2), 171.1 ($NCCO_2$) and 173.8 (CON); *m/z* 361 (M^+,<1%), 305 (10), 188 (49), 170 (100), 91 (53), 57 (34) and 41 (14) (Found: C, 66.75; H, 7.49; N, 3.56. Calcd. for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88).

***1-(*tert*-Butyl) 2-Ethyl 3-Methyl-5-oxo-2-phenethyl-1,2-pyrrolidinedicarboxylate* (9ea):** ν 3086, 3063, 1604 (HC=CH), 1790, 1755 and 1719 cm^{-1} (C=O); δ_H 1.04 (d, 3H, J = 6.1, CH_3CH), 1.27 (t, 3H, J = 7.0, CH_3CH_2O), 1.51 [s, 9H, $(CH_3)_3$], 2.12, 2.49 (2m, 7H, $CH_2CHCCH_2CH_2Ar$), 4.20 (q, 2H, J = 7.0, CH_2O) and 7.23 (m, 5H, ArCH); δ_C 14.3, 14.6 (2xCH_3), 27.9 [$(CH_3)_3$], 29.7 (CH_2CO), 32.1 ($CHCH_3$), 34.2 (CH_2CH), 38.3 (CH_2Ar), 61.4 (CH_2O), 71.5 (CN), 83.6 [$C(CH_3)_3$], 126.1, 128.2, 128.5 (ArCH), 140.8 (ArC), 149.5 (NCO_2), 171.2 ($NCCO_2$) and 174.0 (CON); *m/z* 319 (M^+-56, <2%), 202 (72), 171 (46), 155 (12), 125(39), 105 (29), 92 (10), 91 (100), 57 (93), 43 (12), 42 (10) and 41 (35) (Found: M^+ 275.1523. Calcd. For $C_{16}H_{21}NO_3$: 275.1521)

***1-(*tert*-Butyl) 2-Ethyl 2-Benzyl-3-butyl-5-oxo-1,2-pyrrolidinedicarboxylate* (9db):** ν 3087, 3063, 1604 (HC=CH), 1790, 1743 and 1717 cm^{-1} (C–O); δ_H 0.90 (t, 3H, J = 7.0, $CH_3CH_2CH_2$), 1.00, 1.28 (2m, 9H, $CH_2CH_2CH_2$, CH_3CH_2O), 1.58 [s, 9H, $(CH_3)_3$], 2.20 (m, 3H, CH_2CH), 3.19, 3.70 (2d, J = 14.7, 2H, CH_2Ar), 4.20 (m, 2H, CH_2O), 7.06 and 7.10 (2m, 5H, ArCH); δ_C 13.8, 14.2 (2xCH_3), 22.5, 29.3, 30.0, 36.4, 37.2 ($CH_2CH_2CH_2CHCH_2$, CH_2Ar), 27.9 [$(CH_3)_3$], 35.6 (CH), 61.5 (CH_2O), 71.7 (CN), 83.7 [$C(CH_3)_3$], 127.0, 128.5, 130.7 (ArCH), 135.2 (ArC), 150.0 (NCO_2), 171.3 ($NCCO_2$) and 173.8 (CON); *m/z* 348 (M^+-55, 1%), 303 (11), 230 (63), 212 (100), 138 (15), 91 (42), 57 (60) and 41 (21).

***1-(*tert*-Butyl) 2-Ethyl 3-Butyl-5-oxo-2-phenethyl-1,2-pyrrolidinedicarboxylate* (9eb):** ν 3062, 3027, 1603 (HC=CH), 1791, 1743 and 1720 cm^{-1} (C=O); δ_H 0.90 (t, 3H, J = 6.7, $CH_3CH_2CH_2$), 1.00, 1.28 (2m, 9H, $CH_2CH_2CH_2$, CH_3CH_2O), 1.51 [s, 9H, $(CH_3)_3$], 2.40 (m, 7H, $CH_2CHCCH_2CH_2Ar$), 4.21 (m, 2H, CH_2O) and 7.24 (m, 5H, ArCH); δ_C 13.8 ($CH_3CH_2CH_2$), 14.2 (CH_3CH_2O), 22.5, 29.7, 29.75, 30.1 ($CH_2CH_2CH_2CHCH_2$, CH_2Ar), 27.8 [$(CH_3)_3$], 34.3 (CH_2CH_2Ar), 37.3 (CH), 61.4 (CH_2O), 71.2 (CN), 83.6 [$C(CH_3)_3$], 126.1, 128.2, 128.5 (ArCH), 140.9 (ArC), 149.5 (NCO_2), 171.4 ($NCCO_2$) and 174.0 (CON); *m/z* 402 (M^+-15, <1%), 245 (18), 244 (100), 213 (21), 167 (12), 91 (45), 57 (26) and 41 (10) (Found: M^+ 317.1995. Calcd. For $C_{19}H_{27}NO_3$: 317.1991).

***1-(*tert*-Butyl) 2-Ethyl 2-Benzyl-5-oxo-3-phenyl-1,2-pyrrolidinedicarboxylate* (9dc):** ν 3068, 3030, 3002, 1604 (HC=CH), 1791, 1748 and 1717 cm^{-1} (C=O); δ_H 0.99 (t, J = 7.1, 3H, CH_2CH_3), 1.58 [s, 9H, $(CH_3)_3$], 2.11 (dd, J = 17.7, 9.3, 1H, HCHCON), 2.72 (dd, J = 17.7, 7.5, H, HCHCON), 3.34 (d, J = 15.0, 1H,

HC*H*Ar), 3.52 (t, J = 9.0, 1H, CHAr), 3.73 (m with d at 3.79, J = 15.0, 3H, CH_2CH$_3$, HC*H*Ar) and 7.30 (m, 10H, ArCH); δ_C 13.2 (CH_2CH_3), 27.6 [$(CH_3)_3$], 36.65 (CH_2CO), 38.5 (CHAr), 42.0 (CH_2Ar), 61.1 (CH_2O), 73.6 (CN), 83.6 (CO), 127.0, 127.6, 128.0, 128.5, 130.3, 134.7 (ArCH), 134.7, 136.7 (ArC), 149.4 (NCO_2), 169.9 (NC*C*O$_2$) and 173.1 (CON); *m/z* 350 (M^+-73, 1%), 250 (15), 232 (59), 104 (25), 103 (10), 91 (45), 57 (100) and 41 (26) (Found: M^+ 323.1518. Calcd. For $C_{20}H_{21}NO_3$: 323.1521).

***1-(tert-Butyl) 2-Ethyl 3-Allyl-2-benzyl-5-oxo-1,2-pyrrolidinedicarboxylate* (9dd):** ν 3064, 3028, 1605 (HC=CH), 1790, 1759 and 1718 cm^{-1} (C=O); δ_H 1.32 (t, J = 7.0, 3H, CH_3), 1.59 [s, 9H, $(CH_3)_3$], 1.70 (m, 1H, CH), 2.21 (m, 4H, CH_2CH, CH_2CH=CH), 3.23, 3.72 (2d, J = 14.7, 2H, CH_2Ar), 4.27 (q, J = 7.0, 2H, CH_2O), 5.09 (m, 2H, CH_2=CH), 5.66 (m, 1H, C*H*CH$_2$), 7.07 and 7.26 (m, 5H, ArCH); δ_C 14.2 (CH_3), 14.2 (CH_3CH_2O), 28.0 [$(CH_3)_3$], 34.3 (CH_2C), 35.5 (CH), 36.2 (CH_2CO), 37.6 (CH_2Ar), 61.7 (CH_2O), 71.5 (CN), 83.9 [$C(CH_3)_3$], 117.6 (CH_2=CH), 127.2, 128.6, 130.8 (ArCH), 134.5 (CH_2=CH), 135.1 (ArC), 150.0 (NCO_2), 171.2 (NC*C*O$_2$) and 173.5 (CON); *m/z* 346 (M^+-41, <1%), 287 (10), 246 (59), 214 (33), 196 (71), 172 (11), 122 (21), 91 (55), 57 (100), 43 (13) and 41 (37) (Found: C, 66.12; H, 7.77; N, 3.05. Calcd. for $C_{22}H_{29}NO_5$: C, 66.20; H, 7.54; N, 3.61).

***1-(tert-Butyl) 2-Ethyl 5-Oxo-2-phenethyl-3-propyl-1,2-pyrrolidinedicarboxylate* (9ee):** ν 3063, 3028, 1603 (HC=CH), 1790, 1766 and 1748 cm^{-1} (C=O); δ_H 0.92 (t, 3H, J = 7.1, CH_3CH$_2$CH$_2$), 1.02 (m, 2H, CH$_3$CH_2CH$_2$), 1.27 (t, 3H, J = 7.1, CH_3CH$_2$O), 1.39 (m, 2H, CH$_3$CH$_2$CH_2), 1.52 [s, 9H, $(CH_3)_3$], 2.15, 2.49 (2m, 7H, CH$_2$CHCCH$_2$CH$_2$Ar), 4.20 (m, 2H, CH_2O), 7.19 and 7.30 (2m, 5H, ArCH), δ_C 13.9, 14.2 (2xCH_3), 21.2 ($CH_2CH_2CH_3$), 27.9 [$(CH_3)_3$], 29.7 (CH_2 CH_2CH_3), 32.1 (CH_2CH_2Ar), 34.3 (CH_2CH), 36.8 (CH_2Ar), 37.1 (CH), 61.4 (CH_2O), 71.1 (CN), 83.6 [$C(CH_3)_3$], 126.1, 128.2, 128.5 (ArCH), 140.8 (ArC), 149.4 (NCO_2), 171.4 (NC*C*O$_2$) and 174.1 (CON); *m/z* 330 (M^+-73, <1%), 230 (37), 199 (16), 153 (16), 91 (67), 57 (100), 55 (10) and 41 (44) (Found: M^+ 303.1830. Calcd. For $C_{18}H_{25}NO_3$: 303.1834).

***1-(tert-Butyl) 2-Ethyl 3-[Di(methyloxycarbonyl)methyl]-5-oxo-2-phenethyl-1,2-pyrrolidinedicarboxylate* (9ef):** ν 3063, 3027, 1604 (HC=CH), 1796, 1759, 1744 and 1728 cm^{-1} (C=O); δ_H 1.26 (t, J = 7.1, 3H, CH_3CH$_2$), 1.52 [s, 9H, $(CH_3)_3$], 2.20, 2.39, 2.64 (3m, 6H, CH_2CO, CH_2CH_2Ar), 3.35 [m, 2H, C*H*CH$_2$, CH$(CO_2Me)_2$], 3.75 (s, 6H, 2xCO_2Me), 4.21 (q, J = 7.1, 2H, CH_2CH$_3$) and 7.22, 7.28 (2m, 5H, ArCH); δ_C 14.1 (CH_3), 27.9 [$(CH_3)_3$], 29.7 (CH_2CO), 34.4 (CH_2Ar), 34.6 (CH_2CH_2Ar), 35.2 (CH_2CH), 52.6 [$CH(CO_2Me)_2$], 53.1, 53.15 (CO_2CH_3), 62.1 (CH_2CH_3), 70.8 (CN), 84.2 (CO), 126.2, 128.5 (ArCH), 140.7 (ArC), 149.2 (NCO_2), 167.2, 167.5, 170.8 [CH(CO_2Me)$_2$, NC*C*O$_2$] and 172.1 (CON); *m/z* 393 (M^+-103, 1%), 149 (12), 105 (10), 101 (15), 91 (15), 77 (20), 69 (31), 58 (100), 57 (19), 56 (14), 55 (15), 51 (15), 45 (18), 44 (13), 42 (13) and 41 (20) (Found: M^+ 391.1627. Calcd. For $C_{20}H_{25}NO_7$: 391.1631).

Hydrolysis of 9eb. Synthesis of 2-Amino-3-butyl-2-phenethylpentanedioic acid (10): A solution of 2M NaOH (3.2 ml) was added to compound **9eb** (0.066 g, 0.16 mmol) and heated for 14 h in a pressure tube at 140°C. The reaction was diluted with EtOAc (5 ml) and 0.5M HCl was added until pH<1. The product was extracted with EtOAc (3x20 ml), dried (Na_2SO_4) and the solvents removed. To the residue, EtOAc saturated with $HCl_{(g)}$ (1 ml) was added, and the mixture was stirred 1 h at rt. The solvent was removed and the resulting solid was dissolved in MeOH (2 ml) and propylene oxide (1 ml) was added. The mixture was stirred 1 h at rt. The solvents were removed and the resulting solid was triturated with ether. The suspension was filtered to give 0.020 g of **10** (41% yield) as a white solid: mp 230-234°C (MeOH); ν (KBr) 3219-2366 (NH_3^+, CO_2^-), 3065, 3028, 1602 (HC=CH), 1730 and 1652 cm^{-1} (C=O); δ_H (D_2O) 0.76 (m, 3H, CH_3), 1.09 (5m, 4H, CH_2CH_2CH$_3$), 1.21, 1.47, 1.84, 2.10, 2.51 (5m, 9H, 4xCH_2, CH) and 7.26 (m, 5H, ArCH); δ_C (D_2O) 14.3 (CH_3), 22.3, 30.5, 31.0, 31.6, 36.8, 41.1 (CH_2), 44.1 (CH), 73.4 (C), 127.1, 129.4, 129.7, 143.3 (ArCH, ArC),

179.1 and 181.4 (CO); *m/z* 245 (M^+-62, 11%), 244 (56), 184 (10), 91 (100), 57 (11), 55 (19), 42 (15) and 41 (18) (Found: C, 66.30; H, 8.41; N, 4.27. Calcd. for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56).

Synthesis of *tert*-Butyl 2-Cyano-2-methyl-5-oxo-2,5-dihydro-1*H*-1-pyrrolecarboxylate (12). A solution of *N*-(diphenylmethylene)aminoacetonitrile (0.440 g, 2 mmol) and potassium *tert*-butoxide (0.269 g, 2.4 mmol) in dry THF (5 ml) was stirred at rt for 20 min. Then, a solution of methyl iodide (0.38 ml, 2.6 mmol) in THF (5 ml) was added and the resulting mixture was stirred for 45 min at rt. The reaction was quenched with saturated solution of NH_4Cl and extracted with EtOAc (3x30 ml). The organic layers were washed with water and dried (Na_2SO_4). The solvent was removed and a thick oil was obtained. To a solution of LDA (1.2 mmol, previously prepared) in dry THF at -78°C, was added a solution of the previously obtained oil (0.264 g, 1.1 mmol) in THF (2 ml). The mixture was stirred for 30 min at -78°C and then, a solution of ethyl *cis*-bromoacrylate (1 mmol) in THF (2 ml) was added. The cool bath was removed and the reaction was stirred for 1 h. Water was added and the mixture was extracted with ether (3x30 ml), dried (Na_2SO_4), and the solvents evaporated. To a solution of *cis*-ketimine (1 mmol) in ether (4 ml) at 0°C, was added a solution of 1M HCl (1.1 ml). The mixture was stirred vigorously overnight at rt. The two phases were separated. The aqueous phase was washed with ether (3x20 ml), dried (Na_2SO_4) and the solvents removed. The residue was digested with hexane and then purified by column chromatography. To a solution of the deprotected product in acetonitrile (6 ml), di-*tert*-butyl dicarbonate (0.65g, 3mmol) and 4-(dimethylamino)piridine (0.049g, 0.045 mmol) were added. The reaction mixture was stirred for 12 h and the solvent was removed. Water was added to the residue and the mixture was extracted with EtOAc (3x15 ml). The organic layers were washed sequentially with 1N HCl, saturated $NaHCO_3$ and brine, dried (Na_2SO_4) and the solvents removed to give 0.182 g of product **12** (41% yield): R_f 0.50 (hexane/EtOAc: 2/1); ν 3177 (CN), 3075, 3019, 1611 (HC=CH), 1777 and 1698 cm^{-1} (C=O); δ_H 1.62 [s, 9H, $(CH_3)_3$], 1.92 (s, 3H, CH_3C), 6.29 and 7.14 (2d, 2H, J = 5.6, CH=CH); δ_C 24.0 (CH_3), 27.95 [$(CH_3)_3$], 58.5 (*C*CH), 85.4 (CO), 115.5 (CN), 127.4 (*C*HCO), 147.4 (*C*HC) and 166.6 (CO); *m/z* 207 (M^+-15, 1%), 149 (17), 57 (100), 56 (15), 43 (20) and 41 (31).

Synthesis of *tert*-Butyl 2-Cyano-2,3-dimethyl-5-oxo-1-pyrrolidinecarboxylate (13): Compound **13** was obtained by the procedure above described for the synthesis of product **9**. After extractive work, the product was obtained as a mixture of compounds **13** and **14**. This mixture was submitted to the protection procedure as above to give 0.064 g (60% yield) of **13** after column chromatography: R_f 0.22 (hexane/EtOAc: 2/1); mp 101-104°C (hexane/ EtOAc); ν 1771 and 1728 cm^{-1} (C=O); δ_H 1.35 (d, 3H, J = 6.1, CH_3CH), 1.59 [s, 9H, $(CH_3)_3$], 1.82 (s, 3H, CH_3C), 2.27 (m with dd at 2.29, 2H, J = 16.5, 11.0, C*H*Me, $H_{cis}CH$) and 2.65 (dd, 1H, J =16.5, 6.8, $H_{trans}CH$); δ_C 15.0 (CH_3CH), 24.4 (CH_3C), 27.9, 28.2 [$(CH_3)_3$], 37.6 (CH), 38.0 (CH_2), 85.1 (CO), 117.4 (CN), 148.4 (NCO_2) and 171.5 (NCO); *m/z* 239 (M^++1,<1%), 183 (28), 165 (35), 139 (25), 122 (10), 94 (12), 57 (100), 56 (11), 43 (16), 42 (18) and 41 (32) (Found: C, 60.92; H, 7.70; N, 10.82. Calcd. for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 10.76).

Acknowledgements. This research was supported by a **CDTI** programme (Plan concertado 94/0036) and the Spanish **FARMA III** programme (Ministerio de Industria and Ministerio de Sanidad).

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