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Efficient Synthesis of 4-Methylene-L-Glutamic Acid and its Cyclopropyl Analogue

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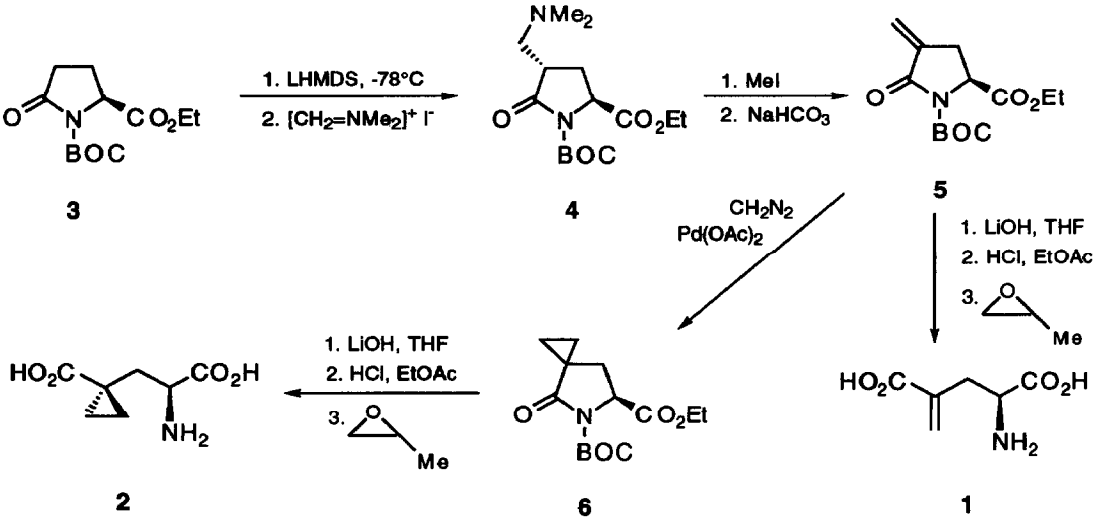
Abstract: 4-Methylene-L-glutamic acid (**1**) and its cyclopropyl analogue **2** were obtained from ethyl *N*-Boc-pyroglutamate (**3**) in 2 and 3 steps, respectively. The key intermediate, ethyl *N*-Boc-4-methylenepyroglutamate (**4**) was prepared by reaction of the lithium lactam enolate with Eschenmoser's salt. Cyclopropyl derivative **2** was also prepared from (S)-2-(*tert*-butyl)-3-methyl-4-imidazolidinone (**7**) in 3 steps. The intermediate **9** was obtained by diastereoselective reaction of the lithium enolate of **7** with butyl (2-tosylmethyl)acrylate (**8**).

INTRODUCTION: 4-Methylene-L-glutamic acid (**1**) was first isolated from germinated peanuts.[1] The same compound has since been found in several other plants[2] and exhibits a potent Central Nervous System (CNS) activity.[3] Preliminary accounts of electrophysiological experiments by Ohfune[4] showed that **1** was 10 times more potent than L-glutamate as a depolarizing agent on the newborn rat spinal cord. The cyclopropyl analogue **2** was twice as potent. This depolarization was due to the activation of NMDA receptors. The biological importance of this natural product has recently attracted attention and synthesis of **1**[4,5] and **2**[4] have recently been reported. Compound **1** has been prepared in optically active form by: (a) reaction of homochiral aziridine-2-carboxylates with stabilized Wittig reagents[5b], (b) a 15 step synthesis starting from *N*-Boc-L-aspartate acid γ-benzyl ester[4] and (c) reduction[5a] of the enaminone[6,7] prepared by reaction of *tert*-butyl *N*-Boc-pyroglutamate with the non-commercially available Bredereck reagent[6,8]. Compound **2** has been obtained by Ohfune methodology[4]. In relation with our program concerned with the synthesis of these amino acids for neurobiological testings, we report here our approach to compounds **1** and **2** through a straightforward three-step synthesis starting from ethyl *N*-Boc pyroglutamate[9] and also other alternative route for compound **2** starting from Seebach's homochiral imidazolidinone derived from glycine.

RESULTS AND DISCUSSION: The deprotonation of ethyl *N*-Boc pyroglutamate (**3**), prepared by standard procedures[10], with LHMDS (2 equiv.) at -78°C in THF for 1 h afforded the lithium lactam enolate[9], which reacted with commercially available Eschenmoser's salt between -78°C and rt to give compound **4** (Scheme 1). Subsequent *in situ* quaternization with methyl iodide in MeOH followed by elimination with $NaHCO_3$[11] led to ethyl *N*-Boc-4-methylenepyroglutamate (**5**) in 46% overall yield. Adduct **4** was isolated in 65% yield as a single diastereomer with *trans* stereochemistry.[12]

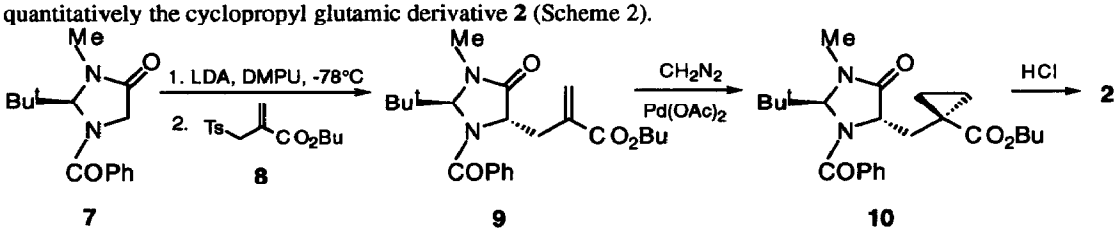


Scheme 1

4-Methylene-L-glutamic acid (**1**) was isolated as its hydrochloride salt after hydrolysis of compound **5** with LiOH[13] in THF followed by treatment with saturated HCl in EtOAc at rt[14]. Final reaction of **1**·HCl with propylene oxide in MeOH at rt gave 4-methylene-L-glutamic acid (**1**) in 80% yield, $[\alpha]_D$ = +12.8 (c = 0.53, 5M HCl).[15]

Cyclopropanation[4] of ethyl *N*-Boc-4-methylenepyroglutamate (**5**) was performed with a freshly prepared ethereal solution of diazomethane in the presence of $Pd(OAc)_2$ (1%) for 1 d at rt, yielding the spyrocyclopropyl pyroglutamate **6** (82%). The cyclopropyl analogue **2** of compound **1** was obtained, following the same hydrolysis procedure above described for compound **5**, in 54% yield: $[\alpha]_D$ = +13.0 (c = 0.50, H_2O).[16]

Compound **2** has been also prepared by alternative route starting from the commercially available homochiral glycine derivative **7**[17]. When lithium enolate of imidazolidinone **7** (2 equiv.), generated with LDA at -78°C in THF, was allowed to react with butyl 2-(tosylmethyl)acrylate (**8**)[18,20] for 1 h in the presence of DMPU[17c] between -78°C and -50°C compound **9** with 98% of d.e. (capillary GC analysis)[22] was obtained. Purification of **9** (flash chromatography) afforded only the *trans* diastereoisomer in 56% yield[24] and starting imidazolidinone **7** was recovered (60%)[25] (Scheme 2). Compound **9** could not be transformed into amino acid **1** by standard hydrolysis conditions with HCl[14]. Cyclopropanation of compound **9** with CH_2N_2 catalysed by $Pd(OAc)_2$ led to the formation of product **10** (50%), which after treatment with 6N HCl under reflux gave quantitatively the cyclopropyl glutamic derivative **2** (Scheme 2).



Scheme 2

We conclude that the procedures described here for the synthesis of compounds **1** and **2** have advantage over other published routes due to the shortness, simplicity and accessibility of starting materials.

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EXPERIMENTAL PART: General. Melting points were obtained with a Reichert Thermovar apparatus and are uncorrected. Optical rotations were measured using a Optical Activity AA-10 polarimeter. IR spectra were obtained as films on a Pye Unicam SP3-200 spectrophotometer. ^{1}H and ^{13}C spectra were recorded on a Bruker AC-300 spectrometer with $SiMe_4$ as internal standard and using $CDCl_3$ as solvent. ^{13}C-NMR assignments were made on the basis of DEPT experiments. MS spectra were measured in a Hewlett-Packard 5988A (EI, 70eV). High resolution mass spectra were measured at the University of Zaragoza. Elemental analyses were performed by the Microanalyses Service of the University of Alicante. Chromatographic analysis (GC) were determined with a Hewlett-Packard HP-5890 instrument equipped with a 25 m WCOT capillary column (0.22 mm diam., 0.2mm film thickness OV-101 stationary phase) using nitrogen (2 ml/min) as the carrier gas, Tinjector=270°C, Tcolumn=60°C, and 60-270 (15°C/min). Thin layer chromatography (TLC) was carried out on Schleicher &Schuell F1500/LS 254 plates coated with a 0.2 mm layer of silica gel and UV visualization. Column chromatography was performed using silica gel 60 of 230-400 mesh. All starting materials were commercially available (Aldrich, Fluka, Janssen) of the highest purity and were used without further purification. THF and ether were dried with $LiAlH_4$ under argon atmosphere.

Synthesis of Ethyl (2S, 4S)-1-(*tert*-Butoxycarbonyl)-4-(dimethylaminomethyl) pyroglutamate (4). To a solution of $(Me_3Si)_2NH$ (0.215 mL, 1 mmol) in dry THF (0.5 mL) at -78°C was added a 1.6 M of BuLi (0.625 mL, 1 mmol). After 10 min a solution of ethyl *N*-Boc-pyroglutamate (0.129 g, 0.5 mmol) in THF (1.5 mL) was added and stirred for additional 40 min at -78°C. Then, Eschenmoser's salt (0.189 g, 1 mmol) was added and, after 15 min at -78°C, the reaction mixture was allowed to rise rt overnight. The resulting solution was hydrolysed with H_2O and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and evaported (15 Torr) to give 0.102 g (65%) of pure compound **4** as oil[26]: $[\alpha]_D^{25}$ = -20.1 (c = 1.1, $CHCl_3$); Rf 0.13 (hexane/EtOAc:1/1); ν (film) 1790, 1740 and 1720 cm^{-1} (C=O); δH ($CDCl_3$) 1.30 (t, J= 7.1 Hz, 3H, $CH3CH_2$), 1.59 [s, 9H, $(CH_3)_3C$], 2.15-2.57 (m with 2s at 2.18 and 2.24, 11H, $2xCH_3N$ and CH_2CHCH_2), 4.21 (q, J= 7.1 Hz, 2H, CH_2O) and 4.62 (dd, J= 8.4, 5.6 Hz, 1H, CH); δC ($CDCl_3$) 14.0 (CH_3CH_2), 27.7 [$(CH_3)_3C$], 28.05 (CH_2CHN,CHCON), 47.15, 47.7 ($2xCH_3N$), 57.1 ($CHCH_2N$), 61.05 (CH_2N), 62.85 (CH_2O), 82.95 (CO_2C), 149.25 (NCO_2), 171.45 ($NCHCO_2$) and 177.05 (CHCON); *m/z* 313 (M^+, 0.5%), 58 (100) and 57 (22).

Synthesis of Ethyl (2S)-1-(*tert*-Butoxycarbonyl)-4-methylenepyroglutamate (5). A solution of compound **4**, prepared according with the above procedure before quenching, was evaporated (15 Torr) and, to the resulting residue, MeOH (2 mL) and an excess of MeI (1.5 mL) were added. The reaction mixture was stirred at rt for 48 h and the solvent was evaporated (15 Torr). To the residue a sat. aqueous solution of $NaHCO_3$ (2mL) was added. The solution was extracted with EtOAc, the organic layer was washed with brine, dried (Na_2SO_4) and evaporated (15 Torr). The residue was purified by flash chromatography (hexane/EtOAc:1/5) to give 0.062 g (46%) of compound **5** as an oil: $[\alpha]_D^{25}$ = -13.9 (c = 1.5, $CHCl_3$); Rf 0.38 (hexane/EtOAc:2/1); ν (film) 3040, 1660 (HC=C), 1780, 1740 and 1710 cm^{-1} (C=O); δH ($CDCl_3$) 1.29 (t, J=

7.2 Hz, 3H, CH_3CH_2), 1.52 [s, 9H, $(CH_3)_3C$], 2.72 (ddt, J=17.4, 3.3, 2.4 Hz, 1H, HCHCN), 3.09 (ddt, J= 17.4, 10.1, 3.0 Hz, 1H, HCHCHN), 4.23 (q, J= 7.2 Hz, 2H, CH_2O), 4.62 (dd, J= 10.1, 3.3 Hz, 1H, CH), 5.53 and 6.23 (2dd, J= 3.0, 2.4 Hz, 2H, CH_2=C); δC ($CDCl_3$) 13.95 (CH_3CH_2), 27.65 ($CHCH_2$), 27.7 [$(CH_3)_3C$], 55.6 (CH), 61,55 (CH_2O), 83.55 (CO_2C), 120.6 (CH_2=C), 136.45 (CH_2=C), 149.65 (NCO_2), 171.35 (CHCO) and 175.15 (CH_2CCO); *m/z* 268 (M^+-15, 0.3%), 97 (14), 96 (67), 69 (11), 68 (15), 57 (100), 54 (11), 52 (12), 43 (20) and 41 (71).

Synthesis of Ethyl (2S)-1-(*tert*-Butoxycarbonyl)-4,4-ethylenepyroglutamate (6). To a suspension of **5** (0.269 g, 1 mmol) and $Pd(OAc)_2$ (2.6 mg, 1%) in ether (1 mL) was slowly added at 0°C an ethereal solution of freshly distilled CH_2N_2 (16 mL, prepared from Diazald®). The reaction mixture was stirred at rt for 1 h and then evaporated (15 Torr). The residue was purified by flash chromatography to give 0.232 g (82 %) of compound **6** as an oil: $[\alpha]_D^{25}$ = -29.3 (c = 1.5, $CHCl_3$); Rf 0.38 (hexane/EtOAc:2/1); ν (liq.) 1780, 1740 and 1710 cm^{-1} (C=0); δH ($CDCl_3$) 0.86, 1.28 (2m, 4H, CH_2CH_2), 1.30 (t, J= 7.0 Hz, 3H, CH_3CH2), 1.51 [s, 9H, $(CH_3)_3C$], 1.96 (dd, J= 13.3, 3.4 Hz, 1H, HCHCN), 2.55 (dd, J= 13.3, 10.0 Hz, 1H, HCHCN), 4.25 (q, J= 7.0 Hz, 2H, CH_2O) and 4.68 (dd, J= 10.0, 3.4 Hz, 1H, CH); δC ($CDCl_3$) 14.0 (CH_3CH_2), 16.9, 22.7 (CH_2CH_2), 27.75 [$(CH_3)_3C$], 29.85 (CH_2CH), 56.55 (CH), 61.45 (CH_2O), 83.25 (CO_2C), 149.35 (NCO_2), 171.35 (CHCO) and 175.15 (CH_2CCO); *m/z* 268 (M^+-15, 0.3%), 210 (13), 110 (100) and 57 (35).

Hydrolysis of Pyroglutamate Derivatives 5 and 6. Synthesis of Glutamic Acid Derivatives 1 and 2. General Procedure. To a solution of compounds **5** or **6** (1.2 mmol) in THF (8 mL) was added a 2.5 M aqueous solution of LiOH (7.8 mL, 19.5 mmol). The reaction mixture was stirred for 2 d at rt, then acidified with 2 N HCl until pH = 2 and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and evaporated (15 Torr). To the residue was added a sat. solution of HCl in EtOAc (2mL) and the mixture was stirred for 1 h. The solvent was evaporated (15 Torr) and the residue was washed with ether and filtered off. The solid was dissolved in MeOH (1 mL) and propylene oxide (1ml) was added. The suspension was stirred at rt for 1 h and evaporated. This last treatment was repeated and to the residue a mixture of H_2O and ether was added. The aqueous layer was evaporated (15 Torr) and the residue was washed with absolute EtOH and filtered off to give pure amino acids **1** or **2** (80 or 54% yield, respectively):

2(S)-4-Methylene-L-glutamic acid (1): $[\alpha]_D$ = +12.8 (c = 0.53, 5M HCl), [Lit.[4] $[\alpha]_D$ = +13.2 (c = 0.56, 5M HCl)]. Mp 192-194°C (Lit.[5b] 192-195°C); ν (KBr) 3550-2200 (OH and NH), 1670 and 1590 cm^{-1} (C=O); δH (D_2O/dioxane) 2.55 (dd, J= 14.6, 8.2 Hz, 1H, HCHCH), 2.76 (dd, J= 14.6, 5.0 Hz, 1H, HCHCH), 3.76 (dd, J= 8.2, 5.0 Hz, 1H, CH), 5.66 and 6.24 (2s, 2H, CH_2=C); δC (D_2O/dioxane) 34.35 (CH_2CH), 55.05 (CH), 131.8 (CH_2=C), 136.35 (CH_2=C), 171.7 (CCO) and 174.4 (CHCO); *m/z* (M^+-18, 3%), 98 (12), 96 (100), 74 (10), 68 (18), 52 (49), 43 (33), 44 (26), 43 (10), 42 (10) and 41 (29).

2(S)-4,4-Ethylene-L-glutamic acid (2): $[\alpha]_D$ = +13.0 (c = 0.5, H_2O). [Lit.[4] $[\alpha]_D$ = +13.0 (c = 0.5, H_2O)]. Mp 174-179°C (Lit.[4] 175-185°C); ν (KBr) 3550-2200 (OH and NH), 1690 and 1580 cm^{-1} (C=O); δH (D_2O/dioxane) 0.69, 1.28 (2m, 4H, CH_2CH_2), 2.05 (dd, J= 6.0, 3.9 Hz, 2H, CH_2CN) and 3.90 (t, J= 6.0 Hz, 1H, CH); δC (D_2O/dioxane) 16.7, 17.7 (CH_2CH_2), 22.0 (CCO_2), 35.95 (CH_2CH), 55.3 (CH), 175.45 (CHCO) and 181.35 (CCO); *m/z* (M^+-18, 3%), 111 (17), 110 (100), 82 (21), 81 (14), 80 (13), 67 (27), 55 (21), 54 (13), 53 (23), 45 (29) and 41 (13).

Synthesis of Butyl 2-(Tosylmethyl)acrylate (8)[19,21a] To a solution of butyl methacrylate (4.82 g, 30 mmol) in CH_2Cl_2 (100 mL) was added sodium p-toluenesulfinate (8.82 g, 48 mmol) and iodine (7.61 g, 30 mmol). The reaction mixture was stirred at rt for 3 d and then Et_3N (19 mL, 136 mmol) was added and stirred for 7 d at rt. The reaction mixture was acidified with a 2 N aqueous solution of HCl and the organic layer

decanted, washed with sat. $NaHCO_3$, dried (Na_2SO_4) and evaporated (15 Torr). The resulting residue was purified by flash chromatography (hexane/EtOAc:18/1) yielding 7.64 g (86%) of compound **8** as yellow oil: Rf 0.28 (hexane/EtOAc: 4/1); ν (film) 3010, 1620, (C=CH), 1315 and 1140 cm^{-1} (S=O); δH ($CDCl_3$) 0.92 (t, J= 7.3 Hz, 3H, CH_3CH_2), 1.33 (m, 2H, CH_3CH_2), 1.53 (m, 2H, CH_2CH_2O), 2.43 (s, 3H, CH_3C=C), 3.98 (t, J= 6.6 Hz, 2H, CH_2O), 4.14 (s, 2H, CH_2S), 5.89, 6.48 (2s, 2H, CH_2=C), 7.32 and 7.72 (2d, J= 7.9 Hz, 4H, ArH); δC ($CDCl_3$) 13.5 (CH_3CH_2), 18.9 (CH_3CH_2), 21.55 (CH_3C=C), 30.25 (CH_2CH_2O), 57.4 (CH_2S), 65.15 (CH_2O), 128.6, 129.5, 135.35, 144.7 (ArC), 129.1 (C=CH_2), 132.95 (CH_2=C) and 164.7 (C=O); *m/z* 232 (M^+-64, 17%), 223 (13), 176 (21), 155 (63), 139 (18), 130 (15), 92 (14), 91 (100), 89 (11), 85 (17), 68 (20), 65 (36) and 41 (26).

Synthesis of (2 S, 5 S) - 1-Benzoyl - 2 - (*tert* - butyl) - 5 - (2 - butoxycarbonyl -2 - propenyl) -3 - methylimidazolidin - 4- one (9). To a solution of $(i\text{-}Pr)_2NH$ (0.427 mL, 2.20 mmol) in dry THF (1.5 ml) was added at 0°C a 1.6 M solution of BuLi (1.38 mL, 2.20 mmol). After stirring for 10 min the solution was cooled at -78°C and a solution of compound **7** (0.526 g, 2 mmol) in dry THF (10 mL) was added. The reaction mixture was stirred for 15 min at -78°C and then a solution of compound **8** (0.296 g, 1 mmol) and DMPU (0.244 mL, 2 mmol) in dry THF (5 mL) was added. The reaction was allowed to warm to -50°C for 1 h and then an aqueous sat. solution of NH_4Cl was added. The solution was extracted with ether, the organic layer was decanted, washed with brine, dried (Na_2SO_2) and evaporated (15 Torr). The resulting residue was purified by flash chromatography (hexane/EtOAc:4/1) to give 0.225 g (56%)[24] of compound **9** as white solid (0.154 g of compound **7** was also recuperated): $[\alpha]_D^{25}$ = +78 (c = 1.5, $CHCl_3$); mp 107-108°C; Tr 20.93 (*trans*) and 21.38 (*cis*)) min; Rf 0.51 (hexane/EtOAc:1/1); ν ($CDCl_3$) 1700 and 1625 cm^{-1} (C=O); δH ($CDCl_3$) 0.85 (t, J= 7.3 Hz, 3H, CH_3CH_2), 0.99 [s, 9H, $(CH_3)_3C$], 1.26 (m, 2H, CH_3CH_2), 1.50 (m, 2H, CH_2CH_2O), 2.17, 2.64 (2d, J= 16,4 Hz, 2H, CH_2C=C), 3.00 (s, 3H, CH_3N), 3.94 (m, 2H, CH_2O), 4.50 (m, 1H, CHCO,) 5.12, 6.05 (2s, 2H, CH=$_2$C), 5.55 (s, 1H, HCN_2) and 7.48 (m, 5H, ArH); δC ($CDCl_3$) 13.65 (CH_3CH_2), 19.1 (CH_3CH_2), 26.35 [$(CH_3)_3C$], 30.5 (CH_2CH_2O), 32.0 (CHCO), 32.15 (CH_2CH), 41.05 ($CCHN_2$), 59.25 (CH_3N), 64.6 (CH_2O), 80.25 (CHN_2), 125.65 (CH_2=C), 127.85, 128.75, 131.65, 135.2 (ArC), 136.45 (CH_2=C), 166.3 (CO_2), 170.7 and 171.05 (CON); *m/z* 385 (M^+-15, 0.5%), 344 (19), 343 (92), 105 (100) and 77 (23).

Synthesis of (2S, 5S) - 1 - Benzoyl - 2 - (*tert*-butyl) - 5 - (2 - butoxycarbonyl- 2- cyclopropylethyl)- 3-methylimidazolidin-4-one (10). To a suspension of compound **9** (0.440 g, 1.1 mmol) and $Pd(OAc)_2$ (4.4 mg, 1%) in ether (2 mL) was slowly added an etheralsolution of freshly destilled CH_2N_2 (18 mL, prepared from Diazald®). After the same work-up as described for compound **6**, 0.228 g of **10** (50%) as white solid were isolated: $[\alpha]_D^{25}$ = +38.67 (c = 1.5, $CHCl_3$); mp 108-110°C; Rf 0.51 (hexane/EtOAc:1/1); ν ($CDCl_3$) 1715, 1695 and 1630 cm^{-1} (C=O); δH ($CDCl_3$) 0.38 (m, 2H, CH_2CH_2C), 0.85 (t, J= 7.3 Hz, 3H,CH_3CH_2), 0.96 [s, 9H, $(CH_3)_3C$], 1.06 (m, 2H, CH_2CH_2C), 1.26 (m, 2H, CH_3CH_2), 1.49 (m, 3H, CH_2CH_2O, HCHCH), 1.83 (dd, J= 14.4, 4.9 Hz, 1H, HCHCH), 2.97 (s, 3H, CH_3N), 3.91 (m, 2H, CH_2O), 4.49 (dd, J= 8.6, 4.9 Hz, 1H, CHCO), 5.56 (s, 1H, HCN_2), 7.43 and 7.60 (2m, 5H, ArH); δC ($CDCl_3$) 13.65 (CH_3CH_2), 14.0, 17.3 (CH_2CCH_2), 19.05 (CH_3CH_2), 20.25 (CCH_2), 26.25 [$(CH_3)_3C$], 30.45 (CH_2CH_2O), 31.75 (CHCO), 36.65 (CH_2CH), 41.1 ($CCHN_2$), 58.4 (CH_3N), 64.25 (CH_2O), 79.9 (CHN_2), 127.55, 128.8, 131.6, 136.6 (ArC), 170.6, 170.95 (NCO) and 173.9 (CO2); *m/z* 399 (M^+-15, 0.1%), 358 (20), 357 (100), 105 (80) and 77 (17).

Hydrolysis of Compound 10. Synthesis of Amino Acid 2. A solution of compound **10** (0.200 g, 0.42 mmol) and 6N HCl (5 mL) was heated under reflux for 3 d. The reaction mixture was extracted with ether and the aqueous layer was evaporated (15 Torr) to give 0.085 g (97%) of compound **2** as its hydrochloride.

REFERENCES AND NOTES

1. Done, J.; Fowden, L. *Biochem. J.* **1952**, *51*, 451-458.
2. (a) Fowden, L. *Ann. Rev. Biochem.* **1964**, *33*, 173-204. (b) Hatanaka, S.; Katayama, H. *Phytochemistry* **1975**, *14*, 1434. (c) Shewry, P. R.; Fowden, L. *Phytochemistry* **1976**, *15*, 1981-1983. (d) Evans, C. S.; Bell, E. A. *Phytochemistry* **1978**, *17*, 1127-1129. (e) Meier, L. K.; Sørensen, H. *Phytochemistry* **1979**, *18*, 1173-1175.
3. Powel, G. K.; Dekker, E. E. *Preparative Biochemistry* **1981**, *11*, 339-350.
4. Ouerfelli, O.; Ishida, M.; Shinozaki, H.; Nakanishi, K.; Ohfune, Y. *Synlett* **1993**, 409-410.
5. (a) Moody, C. M.; Young, D. W.; *Tetrahedron Lett.* **1993**, *34*, 4667-4670. (b) Baldwin, J. E.; Adlington, R. M.; Robinson, N. G. J. *J. Chem. Soc., Chem. Commun.* **1987**, 153-155 and references cited therein for earlier synthesis.
6. (a) Danishefsky, S.; Berman, E.; Clizbe, L. A.; Hirama, M. *J. Am. Chem. Soc.* **1979**, *101*, 4385-4386. (b) Danishefsky, S.; Morris, J.; Clizbe, L. A. *J. Am. Chem. Soc.* **1981**, *103*, 1602-1604.
7. August, R. A.; Khan, J. A.; Moody, C. M.; Young, D. W. *Tetrahedron Lett.* **1992**, *33*, 4617-4620.
8. Bredereck, H.; Simchen, G.; Rebstadt, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41-50.
9. For a previous work using pyroglutamate lactam enolate with different electrophiles, see: Ezquerra, J.; Pedregal, C.; Rubio, A.; Yruretagoyena, B.; Escribano, A.; Sánchez-Ferrando, F. *Tetrahedron* **1993**, *49*, 8665-8678.
10. (a) Ethyl pyroglutamate was prepared as described by: Silverman, R. B.; Levy, M. A. *J. Org. Chem.* **1980**, *45*, 815-818. (b) The *N*-urethane protection was made as described by: Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424-2426
11. This methodology has been applied to the synthesis of α-methylene ketones, esters and lactones: Roberts, J. L.; Borromeo, P. S.; Poulter, C. D. *Tetrahedron Lett.* **1977**, 1621-1624.
12. For NMR studies about *cis/trans* assignments in 4-substituted pyroglutamates see, *ref.* 9.
13. This compound has been hydrolysed by nucleophilic ring opening of **5** with CH_3OLi/THF/-40°C as the use of LiOH was reported[5a] to be ineffective due to the low electrophilicity of the lactam carbonyl group. However, we were able to hydrolise **5** with LiOH under standard conditions (see experimental).
14. Acidic hydrolysis in refluxing HCl gave HCl addition to the double bond.
15. Lit.[4] $[\alpha]_D = +13.2$ (c = 0.56, 5M HCl).
16. Lit.[4] $[\alpha]_D = +13.0$ (c = 0.5, H_2O).
17. See, for instance: (a) Fitzi, R.; Seebach, D. Angew. *Chem. Int. Ed. Engl.* **1986**, *25*, 345-346. (b) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237-261. (c) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277-5292.
18 Prepared by one-pot iodosulfonylation-dehydroiodination[19] of butyl methacrylate in 82% yield (see Experimental Part).
19. Nájera, C.; Baldó, B.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1029-1032.
20. This substitution reaction has been studied with methyl 2-(tosylmethyl)acrylate and *N*-isopropyl-2-(tosylmethyl)acrylamide using Grignard reagents or sodium malonate as nucleophiles and applied to the synthesis of α-methylene esters and amides[21a] and further also with ketones enolates[21b].
21. (a) Nájera, C.; Mancheño, B.; Yus, M.*Tetrahedron Lett.* **1989**, *30*, 3837-3840. (b) Ghera, E.; Yechezkel, T.; Hassner, A. *J. Org. Chem.* **1990**, *55*, 5977-5982.
22. The same reaction with Williams homochiral glycine enolate[23] gave a 33% d.e.
23. Williams, R. M.; Im, M.-N. *Tetrahedron Lett.* **1988**, *29*, 6075-6078.
24. Based on compound **8**.
25. When the homologous methyl ester was used as electrophile it was not possible to separate compound **7** and the methyl derivative of **9**.
26. This compound decomposed partially with silica gel chromatography.

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