53. Synthesis of Dipeptides *via* Addition of *N*-(Nitroacetyl)amino-Acid Derivatives to *Michael* Acceptors: Scope, Stereoselectivity, and Absolute Configuration[1])

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Michael addition of *N*-nitroacetyl derivatives **1** of proline esters using KF under phase-transfer catalysis resulted in the formation of adducts **3**–**9** with chemical yields ranging from 40–90% (*Scheme*). Stereoselectivity of up to 51% was obtained on addition of benzyl *N*-(nitroacetyl)-L-prolinate (**1a**). The absolute configuration at the newly created chiral centre was established in the case of **9** by carrying out a reductive acylation and comparing the product **10** with an authentic sample of ethyl *N*-(O^5-ethyl N^2-acetyl-L-glutam-1-yl)-L-prolinate (L,L-**10**).

Introduction. – In the last few years, there has been a spate of research publications on the use of aliphatic nitro compounds as building blocks for the synthesis of various biologically important molecules. The popularity of nitro compounds can be ascribed mainly to two reasons. First, under suitable conditions, it is possible to construct a C–C bond stereoselectively at the C(α) of nitroalkanes: various standard reactions were used for this purpose such as *Michael* addition [1], *Henry* reaction [2], alkylation [3], *etc.* The second important reason is that the NO_2 group can be transformed under mild conditions into other useful functional groups like amine, oxime, hydroxylamine, ketone, carboxylic acid, [4], *etc.* Our own group has been involved in exploring the possibility of using the nitroacetyl group as a peptide synthon [5–7]. The underlying concept is to synthesise *N*-(nitroacetyl)amino-acid derivatives under mild conditions [5] and then to introduce two substituents on the methylene group adjacent to the NO_2 group. Final conversion of the nitro to an amino or acyl amino group completes the synthesis of a dipeptide [6] [7], incorporating a non-proteinogenic amino acid (monoalkyl- or dialkyl-glycine) at the *N*-terminus.

In the present article, we report the diastereoselective addition of *N*-(nitroacetyl)-amino-acid derivatives **1** to various *Michael* acceptors **2**; it also includes the effect of adding achiral and chiral phase-transfer catalysts on the diastereoselectivity of the reaction. Finally, the absolute configuration of the major diastereoisomer obtained by adding *N*-(nitroacetyl)-L-proline ester **1b** to ethyl acrylate (**2c**) is also established.

Results and Discussion. – It was reported that the F^- ion is one of the best catalysts for *Michael* additions involving nitroalkanes [8]. The activation of the nitroalkane by F^- was ascribed to H-bond formation [9]. Our present studies were confined to the use of F^- ion as catalyst for *Michael* additions. The required concentration of F^- in solution was

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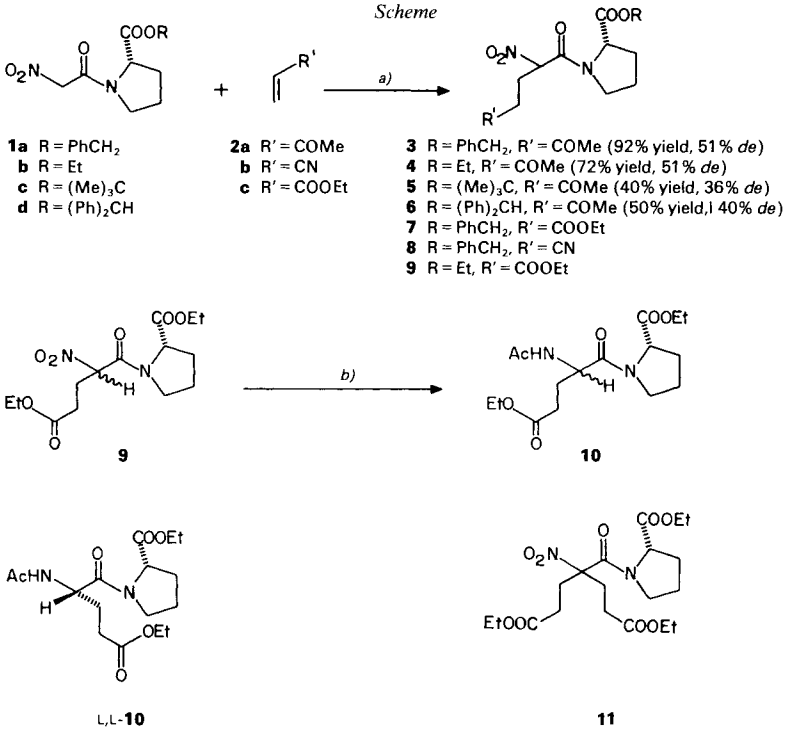
Scheme



a) KF, phase-transfer catalyst, DMF. *b*) Zn/AcOH/Ac_2O, 40–60°.

achieved by the use of KF in conjunction with [18]crown-6 [10] or other phase-transfer catalysts of the quarternary-ammonium type. *N*-Nitroacetyl derivatives **1** of L-proline esters were prepared by the method described by us earlier [5]. Addition of the benzyl *N*-(nitroacetyl)-L-prolinate (**1a**) to methyl vinyl ketone (**2a**) as the acceptor (KF, [18]crown-6, DMF, 20–30°, 8 h; final acidification at −20°) gave the crude product **3** in more than 90% yield (*Scheme*). The adduct **3** was divested of impurities by passing through a short silica column and characterised completely by ^{1}H- and ^{13}C-NMR spectroscopy. The NMR spectra showed two sets of signals corresponding to two diastereoisomers. The relative intensities of the corresponding signals allowed to estimate the diastereomeric excess (*de*) of the product to be 43%.

The replacement of the phase-transfer catalyst [18]-crown-6 by (benzyl)-triethylammonium bromide did not substantially alter either the chemical yield (84%) of **3** or the *de* (43.7%). This, therefore, enabled us to study the effect of chiral phase-transfer catalysts on the *de* of the products. Cinchona alkaloids are known to catalyze *Michael* additions with high diastereoselectivity [11]. The use of *N*-benzylquinidinium chloride as the chiral phase-transfer catalyst in our reaction (KF, *N*-benzylquinidinium chloride, DMF, −20°, 13 h; acid workup at −20°) gave **3** in 92% chemical yield with a *de* of 51%. Under the same conditions, the use of *N*-benzylquininium chloride led to **3** in 70% yield with a *de* of 37%. In all the above reactions, the same diastereoisomer was obtained as the major product, as shown by the NMR spectra.

Concerning the solvent, we found that DMF gave the best results (KF, *N*-benzylquinidinium chloride, −20°, 13 h) in terms of yield (92% of **3**) and *de* (51%); the use of EtOH gave a 72% yield of **3** (*de* 44%), whereas MeCN led to 77% of **3** (*de* 33%).

It is reasonable to expect that the electrophile (the *Michael* acceptor) in these reactions approaches the carbanion from the face opposite to the ester group of proline, the steric bulk of the ester group might, therefore, influence the diastereoselectivity of the addition. Keeping all other factors constant (KF, *N*-benzylquinidinium chloride, DMF, −20°, 13 h), the diastereoselectivity in the addition of the esters **1b–d** of *N*-(nitroacetyl)-L-proline to **2a** was then examined (→**4–6**; see *Scheme*).

The addition of benzyl *N*-(nitroacetyl)-L-prolinate (**1a**) was extended to other *Michael* acceptors under the standard conditions (KF, *N*-benzylquinidinium chloride, DMF, −20°). Ethyl acrylate (**2c**) gave 89% yield of adduct **7** with 41% *de*, whereas acrylonitrile (**2b**) gave **8** with 45% yield and 39% *de*.

The absolute configuration of the newly created chiral centre of the two diastereoisomers **9** formed in the *Michael* addition of ethyl *N*-(nitroacetyl)-L-prolinate (**1b**) to ethyl acrylate (**2c**) was established as follows. The diastereoisomer mixture **9** could not be separated by chromatography. Hence it was reduced as such with Zn in $AcOH/Ac_2O$ to give a mixture **10** of the two diastereoisomers of ethyl *N*-(O^5-ethyl N^2-acetylglutam-1-yl)-L-prolinate (**10**). The ^1H- and ^{13}C-NMR spectra of this mixture were compared with those of an authentic sample of ethyl *N*-(O^5-ethyl N^2-acetyl-L-glutam-1-yl)-L-prolinate (L,L-**10**) prepared from O^5-ethyl hydrogen N^2-[(benzyloxy)carbonyl]-L-glutamate and L-proline ethyl ester. This clearly indicated that the major component of the diastereoisomer mixture **10** had the L,L-configuration. This was further confirmed by spiking the mixture with a predetermined amount of the authentic sample and redetermining the *de*.

It was concluded that the major diastereoisomer formed in the *Michael* addition of *N*-(nitroacetyl)-L-proline ester to *Michael* acceptors had the (*S*)-configuration at the newly created chiral centre. It is worth recalling that the Pd^0-catalysed allylation of ethyl *N*-(nitroacetyl)-L-prolinate (**1b**) also led to the product with the (*S*)-configuration at the new centre for the major diastereoisomer [6].

The *Michael* adduct **9** was reacted with another molecule of ethyl acrylate (**2c**) to produce the bis-adduct **11** in 87% yield. We demonstrated earlier [7] that such tertiary nitro derivatives could be reductively acetylated to generate dipeptides with an α,α-disubstituted glycine residue.

Experimental Part

General. IR Spectra (cm^{-1}): *Perkin-Elmer-Infracord* spectrometer; NaCl optics. ^1H- and ^{13}C-NMR Spectra: *Bruker-WH-90* (*Spectrospin*), *Bruker-AC-200*, *Bruker-MSL-300*, or *Varian-FT-80A* instrument; tetramethylsilane as internal standard, values in ppm; for mixtures of diastereoisomers, values within parentheses refer to the minor diastereoisomer. MS: *Finnigan-MAT-1020B* spectrometer.

Michael *Addition of the* N-*Nitroacetyl Derivative of Proline Esters: General Procedure.* To a soln. of the phase-transfer catalyst (0.01 equiv.) and dry solid KF (1 equiv.) in DMF, stirred for 3–4 h, *N*-(nitroacetyl)-L-proline ester **1** (100 mg) was added and cooled to −20°. After 5 min, the *Michael* acceptor **2a–c** (1 equiv.) was added. The temp. was maintained at −20° and the reaction monitored by TLC. After 12–13 h, the mixture was acidified with 5% aq. HCl soln. and extracted with benzene the org. layer washed with H_2O and brine, dried (Na_2SO_4), and evaporated, and the pale yellow compound passed through a small filter column (silica gel, 60–120 mesh, petroleum ether/AcOEt).

Benzyl N-*(2-Nitro-5-oxohexanoyl)*-L-*prolinate* (**3**). Yield 92%. IR (neat): 3000*w*, 1760*s*, 1720*s*, 1680*s*, 1570*s*, 1450*m*, 1370*m*, 1190*s*. ^{1}H-NMR ($CDCl_3$): 1.68–2.67 (*m*, CH_2(3), CH_2(4), CH_2CH_2CO, CH_2CH_2CO, CH_3CO); 3.57–3.80 (*m*, CH_2(5)); 4.48–4.64 (*m*, CH(2)); 5.1 (*s*, $PhCH_2$); 5.44–5.66 (*m*, $CHNO_2$); 7.2 (*s*, $PhCH_2$). ^{13}C-NMR ($CDCl_3$): 23.40, 24.28, 28.62 (C(3), C(4), CH_2CH_2CO); 29.35 (CH_3CO); 37.36 (37.80) (CH_2CH_2CO); 47.26 (47.00) (C(5)); 58.98 (59.23) (C(2)); 66.52 (66.38) ($PhCH_2O$); 84.22 (85.06) ($CHNO_2$); 127.55, 127.62, 127.77, 128.92, 128.11, 135.12 (135.22) (Ph); 162.39 (CO); 170.67 (170.45) (CO); 207.25 (CO). MS: 362 (M^+), 316, 256, 227, 204, 181, 108, 91, 70. Anal. calc. for $C_{18}H_{22}N_2O_6$ (362): C 59.70, H 6.07, N 7.73; found: C 59.81, H 6.40, N 8.07.

Ethyl N-*(2-Nitro-5-oxohexanoyl)*-L-*prolinate* (**4**)[2]. Yield 72%. IR (neat): 3000*m*, 1750*s*, 1730*s*, 1660*s*, 1570*s*, 1450*m*, 1200*s*, 1040*m*. ^{1}H-NMR ($CDCl_3$): 1.22 (*t*, CH_3CH_2O); 1.77–2.68 (*m*, CH_2(3), CH_2(4), CH_2CH_2CO, CH_2CH_2CO, CH_3CO); 3.6–3.77 (*m*, CH_2(5)); 4.11 (*q*, CH_3CH_2O); 4.4–4.6 (*m*, CH(2)); 5.44–5.64 (*m*, $CHNO_2$). ^{13}C-NMR ($CDCl_3$): 13.6 (CH_3); 23.61, 24.20, 28.61 (C(3), C(4), CH_2CH_2O); 29.36 (CH_3CO); 37.36 (37.74) (CH_2CH_2O); 47.19 (46.98) (C(5)); 58.88 (59.2) (C(2)); 60.81 (60.69) (CH_3CH_2O); 84.05, (84.86) ($CHNO_2$); 162.18 (161.68) (CO); 170.73 (170.47) (CO); 207.24 (206.80) (CO). MS: 254, 227, 181, 142, 123, 111, 96, 84, 70, 55.

tert-*Butyl* N-*(2-Nitro-5-oxohexanoyl)*-L-*prolinate* (**5**)[2]. Yield 40%. IR (neat): 3500*m*, 3000*s*, 1750*s*, 1730*s*, 1670*s*, 1580*s*, 1450*s*, 1170*s*. ^{1}H-NMR ($CDCl_3$): 1.05–1.3 (*m*, 3 CH_3); 1.79–2.6 (*m*, CH_2(3), CH_2(4), CH_2CH_2CO, CH_2CH_2CO, CH_3CO); 3.32–3.71 (*m*, CH_2(5)); 4.12–4.33 (*m*, CH(2)); 5.3–5.5 (*m*, $CHNO_2$). ^{13}C-NMR ($CDCl_3$): 23.64, 24.31 (C(3), CH_2CH_2CO); 27.54, 27.63 (3 CH_3); 28.77 (C(4)); 29.43 (CH_3CO); 37.67 (37.99) (CH_2CH_2CO); 47.33 (47.15) (C(5)); 59.82 (59.94) (C(2)); 81.32 ((CH_3)$_3CO$); 84.35 (85.11) ($CHNO_2$); 162.1 (161.47) (CO); 170.11 (169.96) (CO); 206.7 (207.1) (CO). MS: 282, 255, 227, 182, 114, 91, 83, 77, 70, 57, 43.

Diphenylmethyl N-*(2-Nitro-5-oxohexanoyl)*-L-*prolinate* (**6**). Yield 50%. IR ($CHCl_3$): 3020*m*, 1750*s*, 1720*s*, 1670*s*, 1570*s*, 1500*w*, 1450*s*, 1370*s*, 1190*s*. ^{1}H-NMR ($CDCl_3$): 1.8–2.6 (*m*, CH_2(3), CH_2(4), CH_2CH_2CO, CH_2CH_2CO, CH_3CO); 3.3–3.7 (*m*, CH_2(5)); 4.5–4.7 (*m*, CH(2)); 5.4–5.5 (*t*, $CHNO_2$); 6.76 (*s*, $(Ph)_2CH$); 7.15–7.28 (*m*, 2 Ph). ^{13}C-NMR ($CDCl_3$): 24.01, 24.81, 29.05 (C(3), C(4), CH_2CH_2CO); 30.03 (CH_3CO); 38.00 (38.40) (CH_2CH_2CO); 47.80 (47.06) (C(5)); 59.58 (59.92) (C(2)); 78.21 ($(Ph)_2CH$); 84.63 (85.54) ($CHNO_2$); 127.10, 127.17, 127.30, 127.45, 128.14, 128.36, 128.67, 128.76, 138.55, 139.87 (2 Ph); 162.78 (CO); 170.55 (170.33) (CO); 208.05 (CO). MS: 263, 227, 167, 157, 149, 139, 111, 105, 91, 78, 70, 55. Anal. calc. for $C_{24}H_{26}N_2O_6$ (438): C 65.78, H 5.93, N 6.38; found: C 65.70, H 6.32, N 6.37.

Benzyl N-*(*O^5*-Ethyl 2-Nitroglutar-1-yl)*-L-*prolinate* (**7**). Yield 89%. IR (neat): 2900*s*, 1750*s*, 1670*s*, 1560*s*, 1450*s*, 1200*m*. ^{1}H-NMR ($CDCl_3$): 1.2 (*t*, CH_3CH_2O); 1.73–2.57 (*m*, CH_2(3), CH_2(4), CH_2CH_2CO, CH_2CH_2CO); 3.55–3.77 (*m*, CH_2(5)); 4.06 (*q*, CH_3CH_2O); 4.44–4.66 (*m*, CH(2)); 5.08 (*s*, $PhCH_2O$); 5.4–5.68 (*m*, $CHNO_2$); 7.2 (*s*, $PhCH_2$). ^{13}C-NMR ($CDCl_3$): 13.54 (CH_3); 24.08, 24.48, 28.41, 28.83 (C(3), C(4), CH_2CH_2COOEt, CH_2CH_2COOEt); 47.01 (46.9) (C(5)); 58.88 (59.08) (C(2)); 60.17 (CH_3CH_2O); 66.3 (66.19) ($PhCH_2O$); 84.17 (84.71) ($CHNO_2$); 127.37, 127.47, 128.09, 128.27, 128.47, 134.97 (135,06) (Ph); 162.06 (161.54) (CO); 170.36 (170.23) (CO); 171.70 (171.55) (CO). MS: 347, 301, 257, 211, 204, 124, 116, 91, 70, 55. Anal. calc. for $C_{19}H_{24}N_2O_7$ (392): C 58.19, H 6.12, N 7.14; found: C 58.37, H 6.53, N 7.63.

Benzyl N-*(4-Cyano-2-nitrobutyryl)*-L-*prolinate* (**8**): Yield 45%. IR (neat): 3500 (br.), 2900*m*, 2260*m*, 1750*s*, 1680*s*, 1580*s*, 1450*s*, 1200*m*. ^{1}H-NMR ($CDCl_3$): 1.66–2.53 (*m*, CH_2(3), CH_2(4), CH_2CH_2CN, CH_2CH_2CN); 3.55–3.82 (*m*, CH_2(5)); 4.4–4.6 (*m*, CH(2)); 5.0 (*s*, $PhCH_2O$); 5.15–5.42 (*m*, $CHNO_2$); 7.2 (*s*, $PhCH_2$). ^{13}C-NMR ($CDCl_3$): 22.30, 23.97, 25.08, 28.29 (C(3), C(4), CH_2CH_2CN, CH_2CH_2CN); 47.10 (46.91) (C(5)); 58.89 (59.10) (C(2)); 66.43 (66.22) ($PhCH_2O$); 82.75 (83.48) ($CHNO_2$); 117.70 (117.55) (CN); 127.28, 127.47, 127.79, 127.93, 128.06, 134.59 (134.75) (Ph); 160.78 (160.22) (CO); 170.14 (169.92) (CO). MS: 345, 299, 238, 210, 164, 124, 91. Anal. calc. for $C_{17}H_{19}N_3O_5 \cdot 1.5\ H_2O$ (372): C 54.87, H 5.91, N 11.28; found: C 55.04, H 6.34, N 10.8.

Ethyl N-*(*O^5*-Ethyl 2-Nitroglutar-1-yl)*-L-*prolinate* (**9**). Yield 90%. IR ($CHCl_3$): 3050*m*, 1750*s*, 1680*s*, 1570*s*, 1450*m*, 1230*s*. ^{1}H-NMR ($CDCl_3$); 1.24 (*t*, 2 CH_3CH_2O); 1.8–2.55 (*m*, CH_2(3), CH_2(4), CH_2CH_2COOEt, CH_2CH_2COOEt); 3.66–3.86 (*m*, CH_2(5)); 4–4.31 (*m*, 2 CH_3CH_2O); 4.4–4.62 (*m*, CH(2)); 5.48–5.73 (*m*, $CHNO_2$). ^{13}C-NMR ($CDCl_3$): 13.40, 13.52 (2CH_3CH_2O); 24.13, 24.67, 28.47, 28.56, 28.99 (C(3), C(4), CH_2CH_2COOEt, CH_2CH_2COOEt); 47.09 (46.93) (C(5)); 59.0 (59.25) (C(2)); 60.16 (CH_3CH_2O); 60.64 (60.52) (CH_3CH_2O); 84.24 (84.8) ($CHNO_2$); 161.97 (161.37) (CO); 170.52 (170.34) (CO); 171.65 (171.5) (CO). MS: 284, 257, 239, 211, 188, 142, 116, 70. Anal. calc. for $C_{14}H_{22}N_2O_7$ (330): C 50.94, H 6.66, N 8.48; found: C 51.19, H 7.05, N 8.16.

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[2]) Analysis data not included as these compounds could not be separated from their bis-adducts.

Reductive Acylation of **9** *to Ethyl* N-*(*O^5-*Ethyl* N^2-*Acetylglutam-1-yl)*-L-*prolinate* (**10**). Prolinate **9** (200 mg) was stirred with Zn dust (250 mg) in AcOH/Ac_2O 1:1 (5 ml). The temp. was maintained at 60° for *ca.* 8–12 h. The white precipitate was filtered off and washed. The filtrate was repeatedly washed with $NaHCO_3$ soln., distilled H_2O, and brine, dried (Na_2SO_4), and evaporated. Purification by column chromatography (silica gel, 60–120 mesh, petroleum ether/AcOEt) yielded 82.5 mg (40%) of the diastereoisomer mixture **10**. IR ($CHCl_3$): 3300 (br.), 3060*m*, 1750*s*, 1660*s*, 1460*m*, 1220*s*. ^{1}H-NMR ($CDCl_3$): 1.2 (*t*, 2 CH_3); 1.7–2.4 (*m*, CH_2(3), CH_2(4), CH_2CH_2COOEt, CH_2CH_2COOEt, CH_3CO); 3.45–3.7 (*m*, CH_2(5)); 4.1 (*q*, 2 CH_3CH_2O); 4.35–4.45 (*m*, CH(2)); 4.75–4.88 (*m*, $CHNHCOCH_3$); 7.22 (*d*, NH). ^{13}C-NMR ($CDCl_3$): 13.64, 13.71 (2 CH_3); 22.28 (22.34) (CH_3CO); 24.43 (24.2) (C(4)); 27.05, 28.59 (28.68), 29.33 (C(3), CH_2CH_2COOEt, CH_2CH_2COOEt); 46.72 (46.67) (CH_2(5)); 49.39 (CH(2)); 58.7 (58.91) ($CHNHCOCH_3$); 60.00, 60.61 (2 CH_3CH_2O); 169.99 (169.7) (CO); 170.07 (CO); 171.22 (CO); 172.38 (CO). MS: 342 (M^+), 255, 200, 172, 142, 130, 84, 70. Anal. calc. for $C_{16}H_{26}N_2O_6 \cdot H_2O$ (360): C 53.36, H 7.77, N 7.77; found: C 53.29, H 7.72, N 7.22.

Ethyl N-{O^5-*Ethyl* N^2-*[(Benzyloxy)carbonyl]*-L-*glutam-1-yl*}-L-*prolinate* (prepared by the mixed anhydride method). IR ($CHCl_3$): 3420*m*, 3020*m*, 1750*s*, 1730*s*, 1660*s*, 1650*s*, 1510*m*, 1450*s*, 1220*s*. ^{1}H-NMR ($CDCl_3$): 1.2 (*t*, 2 CH_3CH_2O); 1.67–2.46 (*m*, CH_2(3), CH_2(4), CH_2CH_2COOEt, CH_2CH_2COOEt); 3.60–3.71 (C(5)); 3.9–4.13 (*m*, CH_3CH_2O); 4.36–4.63 (*m*, H–C(2)); 5.11 (*s*, $PhCH_2$); 5.8 (*d*, NH); 7.23 (*s*, Ph). ^{13}C-NMR ($CDCl_3$): 14.11, 14.19 (2 CH_3); 24.87, 27.63, 28.97, 29.45 (CH_2CH_2COOEt, CH_2CH_2COOEt, C(3), C(4)); 46.95 (C(5)); 51.56 (C(2)); 58.96 ($CHNO_2$); 60.49, 61.14 (2 CH_3CH_2O); 66.79 ($PhCH_2$); 127.94, 128.02, 128.45, 136.41 (Ph); 156.25 (CO); 170.41 (CO); 172.72 (CO); 172.95 (CO). Anal. calc. for $C_{22}H_{30}N_2O_7$ (434): C 60.86, H 6.90, N 6.45; found: C 59.08, H 7.08, N 6.51.

Ethyl N-*(*O^5-*Ethyl* N^2-*Acetyl*-L-*glutam-1-yl)*-L-*prolinate* (L,L-**10**). In a *Parr* shaker, 500 mg of the above protected dipeptide was reduced with H_2 (50 psi) over 10% Pd/C (50 mg) in AcOH/Ac_2O 1:1 (10 ml) for 6–7 h at r.t. The catalyst was filtered off (*Celite* pad) and the filtrate evaporated. Purification by column chromatography (silica gel, 60–120 mesh, petroleum ether/AcOEt) yielded 320 mg (82%) of L,L-**10**. IR (neat): 3300 (br.), 3000*m*, 1740*s*, 1760*s*, 1650*s*, 1670*s*, 1220*s*. ^{1}H-NMR ($CDCl_3$): 1.2 (*t*, 2 CH_3CH_2O); 1.7–2.45 (*m*, CH_2(3), CH_2(4), CH_2CH_2COOEt, CH_2CH_2COOEt, CH_3CO); 3.65–3.80 (*m*, CH_2(5)); 4–4.16 (*m*, 2 CH_3CH_2O); 4.38–4.48 (*m*, H–C(2)); 4.73–4.86 (*m*, $CHNHCOCH_3$); 7.22 (*d*, NH). ^{13}C-NMR ($CDCl_3$): 13.74, 13.82 (2 CH_3CH_2O); 22.44 (CH_3CO); 24.53, 27.23, 28.68, 29.41 (C(3), C(4), CH_2CH_2COOEt, CH_2CH_2COOEt); 46.79 (C(5)); 49.48 (CH(2)); 58.76 ($CHNHCOCH_3$); 60.07, 60.69 (2 CH_3CH_2O); 169.89 (CO); 170.38 (CO); 171.29 (CO); 172.47 (CO). MS: 342 (M^+), 297, 269, 255, 242, 200, 172, 142, 130, 84, 70. Anal. calc. for $C_{16}H_{26}N_2O_6 \cdot \frac{1}{2}H_2O$ (351): C 54.73, H 7.68, N 7.97; found: C 54.66, H 7.54, N 7.80.

Ethyl N-{O^5-*Ethyl 2-[2-(Ethoxycarbonyl)ethyl]-2-nitroglutar-1-yl*}-L-*prolinate* (**11**). Yield 87%. IR (neat): 3300*m*, 1750*s*, 1660*s*, 1570*s*, 1210*s*, 1030*m*. ^{1}H-NMR ($CDCl_3$): 1.12–1.25 (*t*, 3 CH_3); 1.8–2.69 (*m*, CH_2(3), CH_2(4), 2 CH_2CH_2COOEt, 2 CH_2CH_2COOEt); 3.15–3.47 (*m*, CH_2(5)); 4–4.16 (*m*, 3 CH_3CH_2O); 4.4–4.5 (*m*, CH_3CH_2O). ^{13}C-NMR ($CDCl_3$): 14.20 (CH_3); 25.54, 28.09, 28.57, 28.91, 30.61 (C(3), C(4), 2 CH_2CH_2COOEt, 2 CH_2CH_2COOEt); 47.098 (C(5)); 60.90 (CH_3CH_2O); 61.19 (C(2)); 61.32 (CH_3CH_2O); 94.72 (CNO_2); 163.57 (CO); 171.48 (CO); 171.72 (CO); 171.91 (CO). MS: 385, 357, 339, 288, 266, 241, 214, 195, 185, 142, 111, 70. Anal. calc. for $C_{19}H_{30}N_2O_9$ (430): C 53.05, H 6.97, N 6.50; found: C 53.26, H 7.25, N 6.01.

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