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Synthesis of 3- and 4-Substituted Cyclic α-Amino Acids Structurally Related to ACPD

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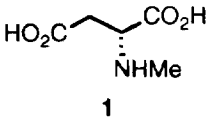
Abstract: The preparation of 3-substituted cyclopentanones **12-16**, 4-substituted cyclohexanones **23-28** and cycloheptanones **38-41** is described. Substituents in the cycloalkanones are carboxylate, phosphonate or tetrazole groups, separated from the ring by a 0, 1, 2, or 3 carbon atoms chain. These cycloalkanones have been transformed into α-amino acids **9-11** by hydrolysis of the corresponding hydantoin derivatives **21**, **37** and **62**, obtained under Bucherer-Bergs reaction conditions.

INTRODUCTION

The excitatory amino acid (EAA) neurotransmitters glutamate and aspartate are mediators of neuronal function in the mammalian central nervous system (CNS)[1]. Several EAA receptor subtypes are known and classified by the agonists which selectively activate them: *N*-methyl-D-aspartic acid (NMDA, **1**), kainic acid (**2**) and L-quisqualic acid (**3**) (AMPA receptor). In addition to these three receptors, two further types have been recognised[2]. One is the receptor activated by the ω-phosphono analogue of glutamate **4** (L-AP4); the other is known as the metabotropic receptor and is selectively activated by (1*S*, 3*R*)-1-aminocyclopentane-1,3-dicarboxylate (**5**) (*trans*-ACPD)[3]. While there are many structure-activity relationship studies on NMDA, kainic and AMPA receptors[4], less attention has been paid to the metabotropic receptor. Thus, conformationally rigid α-amino acids with a second acid function of the type **6a** (n=0[5], 1[6], 2[6c]), **6b** (n=1, 2)[7], **7**[8] and **8**[9] have been prepared to demonstrate the influence of the ring sizes *versus* the activity. As part of a programme for the preparation of cyclic α-amino acids with potential activity against the metabotropic receptor, we describe herein the synthesis of cyclic α-amino acids with a second acidic group (carboxylic, phosphonic or tetrazole group[10]) directly or indirectly attached to a five, six and seven membered ring skeletons of the types **9**, **10** and **11**.



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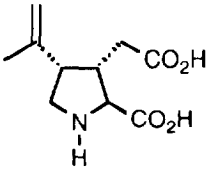

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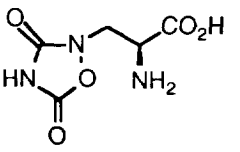

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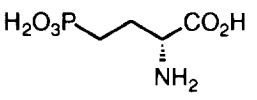

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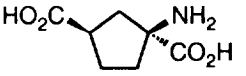

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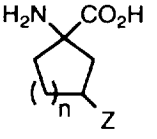
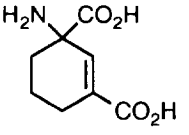


6a; Z=CO_2H
6b; Z=PO_3H_2



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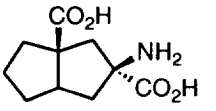

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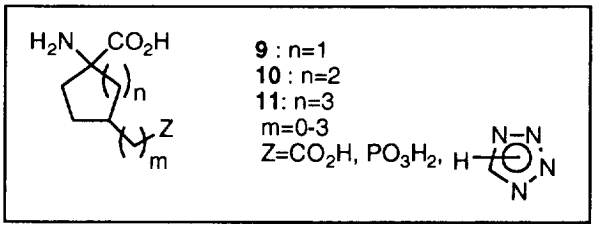
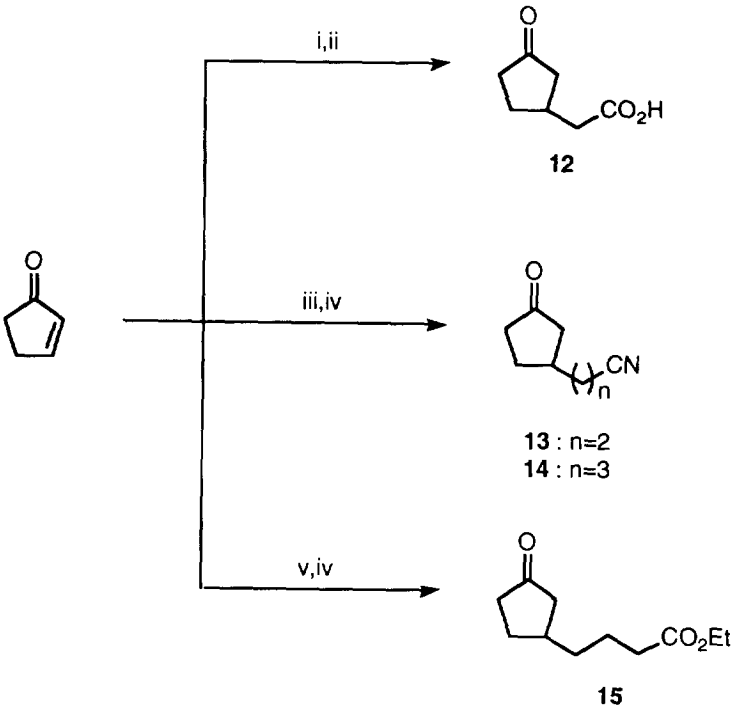


RESULTS AND DISCUSSION

I. Cyclopentane Derivatives

The precursors for α-aminocyclopentanecarboxylic acid derivatives **9** have been prepared starting from 2-cyclopentenone by Michael addition of the corresponding carbanionic intermediates. The synthesis of 3-oxocyclopentylacetic acid (**12**)[11] was carried out by addition of 2-cyclopenten-1-one and trimethylchlorosilane (1:2 molar ratio) to sodium malonate followed by hydrolytic decarboxylation with (20%) H_2SO_4 under reflux, in 50% overall yield (Scheme 1). In the case of the 3-oxocyclopentyl derivatives **13**[12], **14**[13] and **15**, the corresponding mixed copper-zinc reagents (prepared from the corresponding iodides following Knochel methodology[13]) were used, the yields being 36, 73 and 48%, respectively (Scheme 1). The phosphonic ethyl ester **16** could not be prepared by Michael addition of the copper-zinc reagent derived from diethyl 2-iodo-ethanephosphonate to 2-cyclopentenone. The successful route started from 3-oxocyclopentylacetic acid (**12**), which was transformed into the ketal ester **17** by reaction with triethyl orthoformate and ethylene glycol in 45% isolated yield (Scheme 2). Reduction of compound **17** with lithium aluminium hydride (LAH) afforded the alcohol **18** (76%), which was subsequently transformed into the mesylate **19** (94%) and the corresponding bromide. The bromide intermediate was treated *in situ* with diethyl sodium phosphite to give the phosphonate **20**[14] (72%, based on the mesylate **19**), which was finally hydrolysed to ketophosphonate **16** with aqueous (20%) H_2SO_4 in ethanol (85%) (Scheme 2).

Compounds **12-16** were subjected to the standard Bucherer-Bergs[6b,15] reaction conditions [KCN, $(NH_4)_2CO_3$, NH_4Cl in EtOH-H_2O at 60°C][16] to give spirohydantoins **21**, which were isolated as a *ca.* 1:1 mixture of *cis/trans* diastereoisomers (Scheme 3 and Table 1). The hydantoin derived from ketonitrile **14** was transformed into the tetrazole **21c** (see Table 1) by reaction with azidotri-n-butylstannane[10]. Hydrolysis of

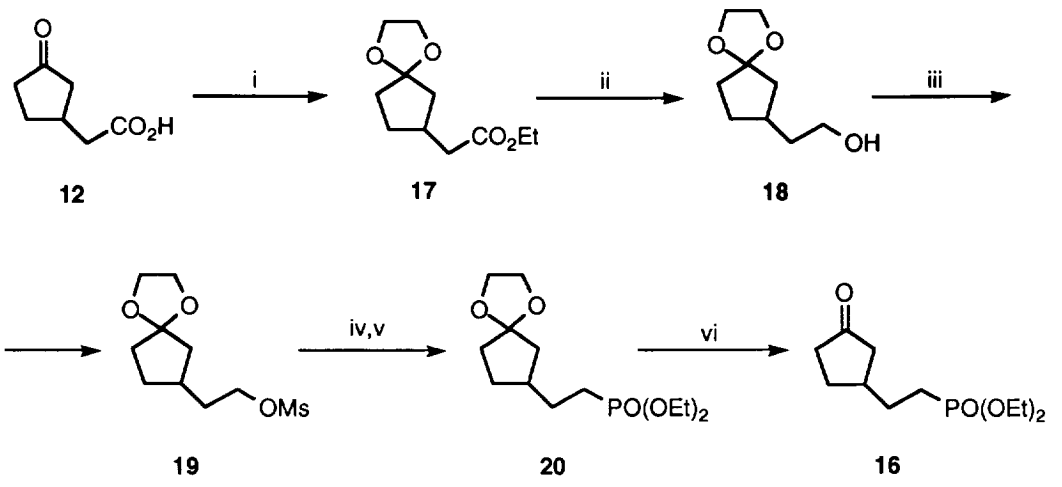


Scheme 1. *Reagents*: i, $CH_2(CO_2Me)_2$, NaOMe, Me_3SiCl; ii, 20% H_2SO_4; iii, $NC(CH_2)_nCu(CN)ZnI$, Me_3SiCl; iv, NH_4Cl; v, $EtO_2C(CH_2)_3Cu(CN)ZnI$, Me_3SiCl.

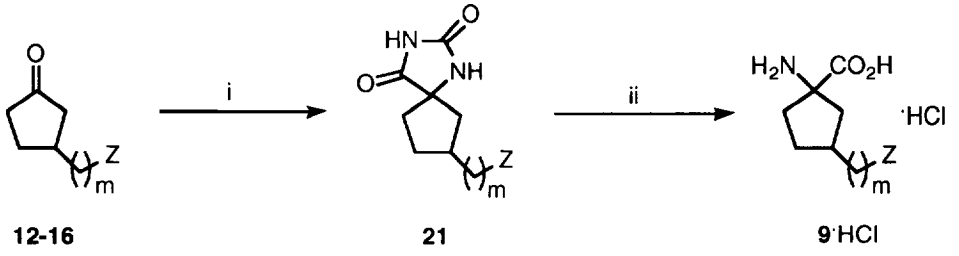
hydantoins[17] **21** was carried out by heating at 150°C in a sealed tube with concd. HCl to give amino acid hydrochlorides **9** (Scheme 3 and Table 1). Only compound **21e** suffered decomposition under the mentioned hydrolytic reaction conditions (Table 1, footnote d).

II. Cyclohexane Derivatives

In order to prepare 4-substituted cyclohexanone derivatives, precursors of amino acids **10**, with m=0 or 1, commercially available ethyl 4-oxocyclohexanecarboxylate[18] (**23**) or 1,4-cyclohexanedione monoethylene ketal (**22**) were used as starting materials, respectively. Ester **24** (Scheme 4) was prepared in a three-step synthesis: reaction of 1,4-cyclohexanedione monoethylene ketal (**22**) with ethyl (triphenylphosphoranylidene)acetate in benzene under reflux for 1 d gave compound **29** (89%), which was hydrogenated in the presence of palladium on carbon in ethyl acetate for 30 min to afford compound **30** (95%) which after final hydrolysis with aqueous 2 M H_2SO_4 in ethanol, gave the expected compound **24** (80%) (Scheme 4). Nitrile **25** was also synthesised from 1,4-cyclohexanedione monoethylene ketal (**22**), which after Wadsworth-Emmons reaction with diethyl cyanomethanephosphonate and sodium hydride in the presence of *N,N'*-dimethylpropyleneurea (DMPU) at room temperature for 12 h afforded quantitatively the nitrile **31**. Hydrogenation catalysed by palladium on



Scheme 2. *Reagents*: i, $HO(CH_2)_2OH$, $HC(OEt)_3$, *p*-TsOH; ii, $LiAlH_4$, THF; iii, MsCl, Et_3N; iv, LiBr; v, $HPO(OEt)_2$, NaH; vi, 20% H_2SO_4, EtOH.

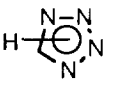
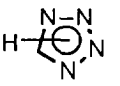


Scheme 3. *Reagents* : i, KCN, $(NH_4)_2CO_3$, NH_4Cl, EtOH, H_2O; ii, HCl.

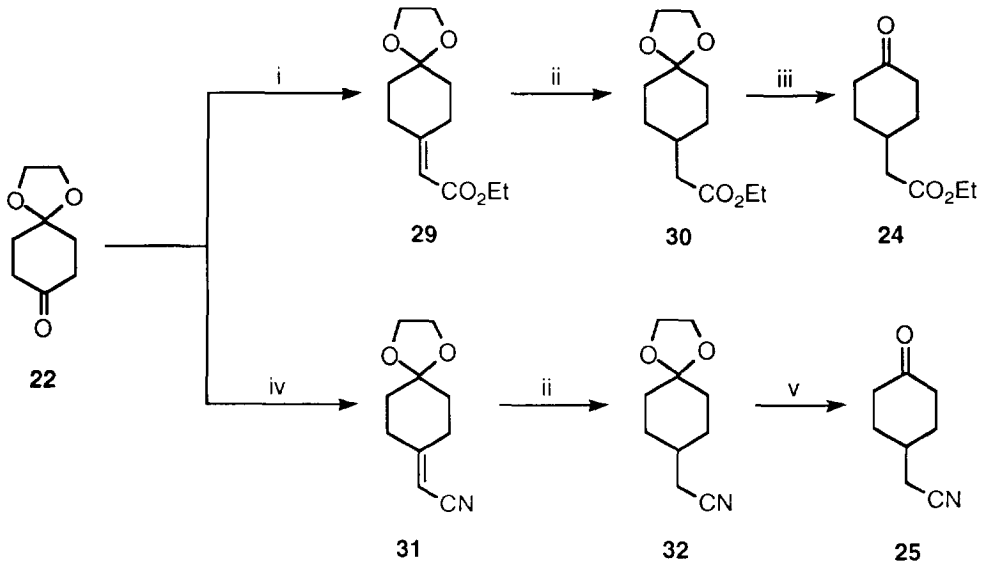
charcoal for 12 h gave compound **32** (87%), which after hydrolysis with aqueous 2 M HCl in ether for 7 h led to nitrile **25** (60%).

In the case of the precursors for the cyclohexane amino acids **10** with m=2 (compounds **24-28**) the protected ketoester **30** was used as starting material. Reduction of the ester **30** with LAH in THF under reflux for 15 h gave the alcohol **33** (93%), which was transformed into the nitrile **35** by reaction with NaCN in DMSO at 120°C for 1 d (74%). Deprotection of the ketal **35** with (20%) H_2SO_4 in EtOH for 9 h gave 3-(4-oxocyclohexyl)propanenitrile (**26**) in 92% yield. Hydrolysis of compound **35** with aqueous 25% NaOH in EtOH under reflux for 1 d followed by acidification with aqueous (20%) H_2SO_4 gave also quantitatively 3-(4-oxocyclo-hexyl)propionic acid (**27**)[19] (Scheme 5).

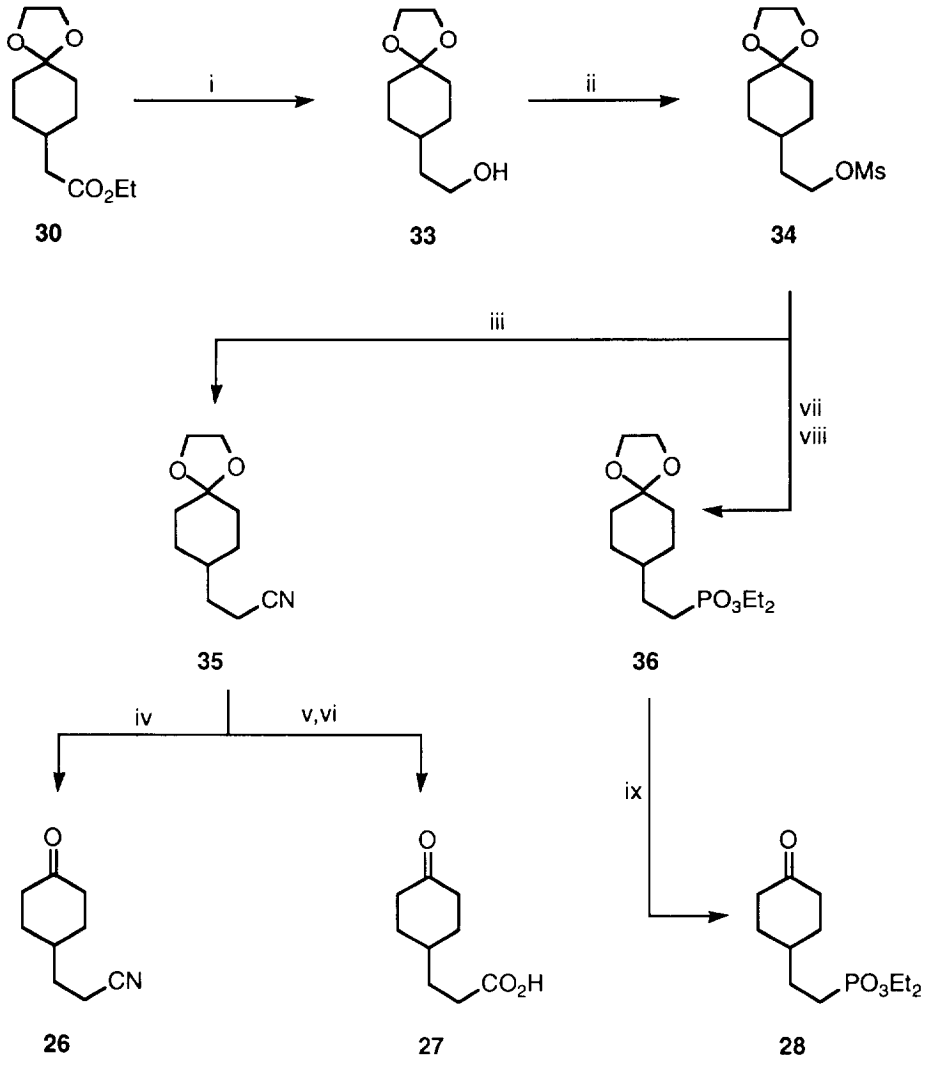
Table 1. Synthesis of Cyclopentane Hydantoins **21** and Amino Acids **9**·HCl

Starting ketone	Hydantoin **21**				Amino acid **9**·HCl		
	no.	m	Z	yield (%)[a]	no.	Z	yield (%)[b]
12	**21a**	1	CO_2H	40	**9a**	CO_2H	59
13	**21b**	2	CN	47	**9b**	CO_2H	44
14	**21c**	3		34[c]	**9c**		47
15	**21d**	3	CO_2Et	79	**9d**	CO_2H	45
16	**21e**	2	PO_3Et_2	54	**9e**	PO_3H_2	-[d]

[a] Based on the starting ketone. [b] Based on hydantoin **21**. [c] Hydantoin with Z=CN, 47% yield; 73% yield in the transformation into the corresponding tetrazole. [d] Decomposed.



Scheme 4. *Reagents*: i, $Ph_3P{=}CHCO_2Et$, PhH; ii, H_2, Pd-C, EtOAc; iii, 20% H_2SO_4; iv, $(EtO)_2P(O)CH_2CN$, NaH, DMPU, THF; v, HCl.

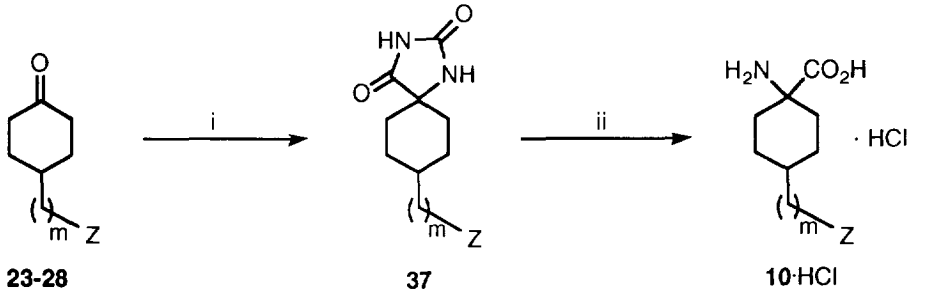


Scheme 5. *Reagents*: i, $LiAlH_4$, THF; ii, MsCl, Et_3N; iii, NaCN, DMSO; iv, 20% H_2SO_4, EtOH; v, 25% NaOH, EtOH; vi, 20% H_2SO_4; vii, LiBr; viii, $HPO(OEt)_2$, NaH; ix, HCl, EtOH.

For the preparation of phosphonate **28**, the mesylate **34** was first transformed into the corresponding bromide and then into the diethylphosphonate **36** (88%) following the same methodology described in Scheme 2 for compound **16**. Final hydrolysis of compound **36** with 2 M HCl in EtOH afforded diethyl 2-(4-oxocyclohexyl)ethanephosphonate **28** in 70% yield (Scheme 5).

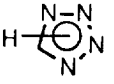
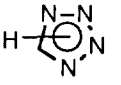
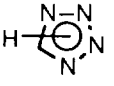
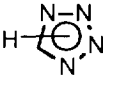
Cyclohexane spirohydantoins **37** derived from cyclohexanone derivatives **23-28** were also prepared under Bucherer-Bergs reaction conditions described for cyclopentane hydantoins **21** and were obtained as a mixture of

cis/trans diastereomers[20] (Scheme 6 and Table 2). The hydantoin derived from ethyl 4-oxocyclohexanecarboxylate (**23**) was hydrolysed with aqueous 5 M sodium hydroxide in methanol and finally acidified to give the hydantoin **37a** (see Table 2).



Scheme 6. *Reagents*: i, KCN, $(NH_4)_2CO_3$, NH_4Cl, EtOH, H_2O; ii, HCl (Method A) or NaOH (Method B).

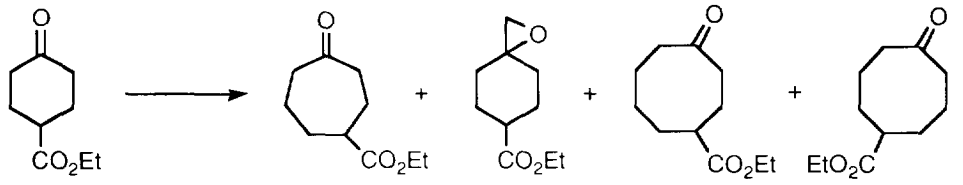
Table 2. Synthesis of Cyclohexane Hydantoins **37** and Amino Acids **10**·HCl

Starting ketone	Hydantoin **37**					Amino acid **10**·HCl			
	no.	m	Z	yield (%)[a]	*cis/trans*	no.	Z	method	yield (%)[b]
23	**37a**	0	CO_2H	80	10/1	**10a**	CO_2H	B	36
24	**37b**	1		42[c]	-[e]	**10b**		A	86
25	**37c**	1	CO_2Et	73	3/1	**10c**	CO_2H	A	80
26	**37d**	2		22[d]	-[e]	**10d**		A	40
27	**37e**	2	CO_2H	70	-[e]	**10e**	CO_2H	A	83
28	**37f**	2	PO_3Et_2	32	7/1	**10f**	PO_3H_2	A	87

[a] Based on the starting ketone **23-28**. [b] Based on hydantoin **37**. [c] Hydantoin with Z=CN, 52% and 80% yield for the transformation into the corresponding tetrazole. [d] Hydantoin with Z=CN, 74% and 30% yield for the transformation into the corresponding tetrazole. [e] Only the *cis* diastereomer was detected (300 MHz ^1H NMR).

III. Cycloheptane Derivatives

The strategy to prepare precursors **38-41** of 4-substituted α-aminocycloheptanecarboxylic acid derivatives **11** is based on the ring enlargement[21] of cyclohexane derivatives by means of diazomethane or trimethylsilyldiazomethane. Ethyl 4-oxocycloheptanecarboxylate (**38**) was prepared starting from ethyl 4-oxocyclohexanecarboxylate (**23**) either by reaction with diazomethane in ether and ethanol[22] or with trimethylsilyldiazomethane in the presence of boron trifluoride[23] (Scheme 7). In both cases compound **38** was obtained together with epoxide **42** and ethyl 4- and 5-oxocyclooctanecarboxylate **43** and **44** (Scheme 7). The best yield for compound **38** was achieved with the silylated reagent at -30°C, a 60% yield after purification by column chromatography being obtained.



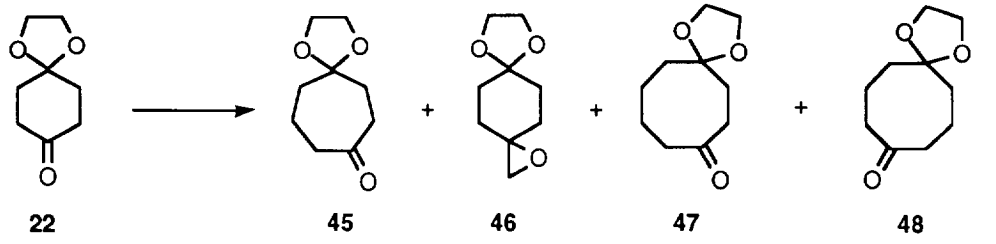
CH_2N_2 (61% conversion):	64%	16%	20%
Me_3SiCHN_2 (85% conversion):	82%	6%	12%

Scheme 7.

Cycloheptane derivatives precursors of amino acids **11** with m=1 (compounds **39** and **40**) were synthesised from 1,4-cycloheptanedione monoethylene ketal (**45**). This ketone **45** was obtained by reaction of 1,4-cyclohexanone monoethylene ketal (**22**) with diazomethane in ether (Scheme 8). In this enlargement the first method, with diazomethane, gave the best yield on compound **45**, which after purification by column chromatography (silica gel) was obtained in 45% yield. The reaction with trimethylsilyldiazomethane gave poorer yields (<15%) for the same process.

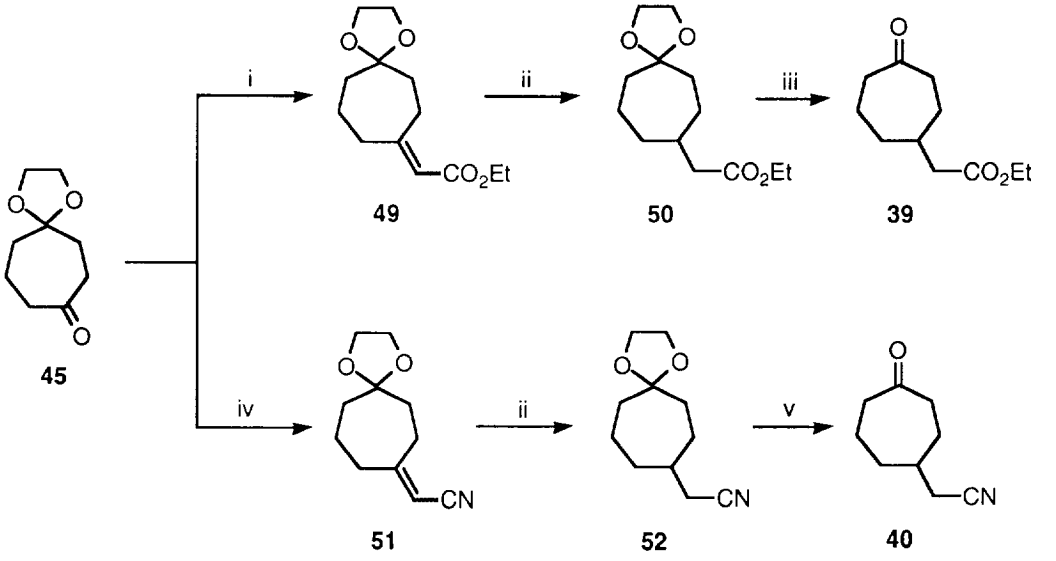
Starting from monoprotected diketone **45** and using the same methodology described in Scheme 4, we prepared the unsaturated ester **49** (80% as mixture of diastereomers) and the saturated one **50** (99%), which was hydrolysed to give compound **39** in 90% yield (Scheme 9). The nitrile **40** was also synthesised according to the methodology described for compound **25** (Scheme 4): first, the unsaturated nitrile **51** was isolated (95% as mixture of diastereomers) and then the saturated nitrile **52** (90%), which after final hydrolysis gave compound **40** (88%) (Scheme 9).

Compounds **39** and **40** can be alternatively prepared by ring enlargement of cyclohexane derivatives **24** and **25**, respectively. Compound **39** was obtained by reaction of compound **24** with trimetylsilyldiazomethane (Scheme 10), the overall yield being similar to that of the route from the protected ketone **45** (Scheme 9). However, it was easier to purify ester **39** in the first case.



CH_2N_2 *in situ* (93% conversion):	66%	7%	27%
CH_2N_2, ether (84% conversion):	41%	46%	3%

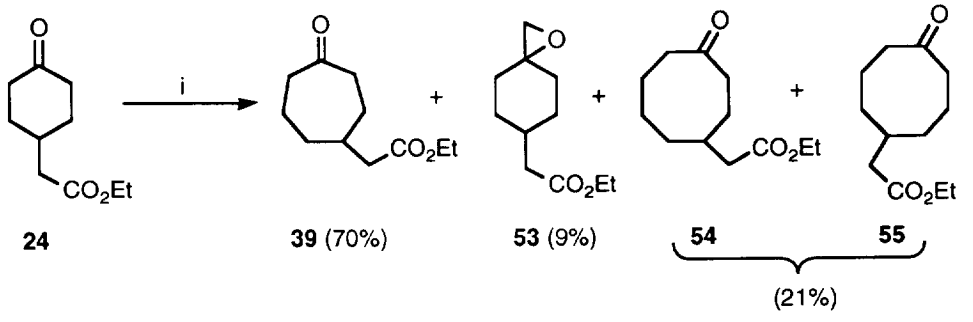
Scheme 8.



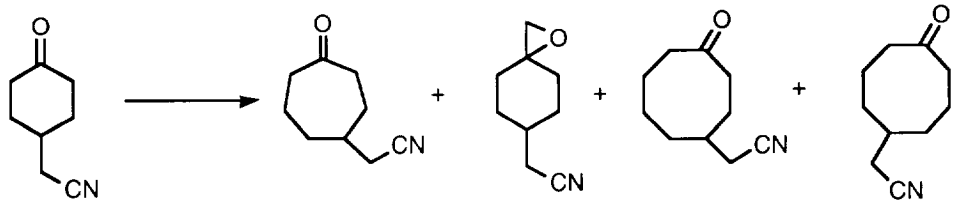
Scheme 9. *Reagents*: i, $Ph_3P{=}CHCO_2Et$, PhH; ii, H_2, Pd-C; iii, 20% H_2SO_4; iv, $(EtO)_2P(O)CH_2CN$, NaH, DMPU; v, HCl.

Nitrile **40** can be also prepared by reaction of cyclohexane nitrile **25** with diazomethane or better with trimethylsilyldiazomethane; after treatment with sodium hydrogen sulfite it was obtained in 46% isolated yield (Scheme 11). Overall yields for both procedures were 34 and 24%, respectively. For both compounds **39** and

38 it was more convenient to start from the cycloheptanedione derivative **45**.



Scheme 10. *Reagents*: i, Me_3SiCHN_2 (82% conversion).



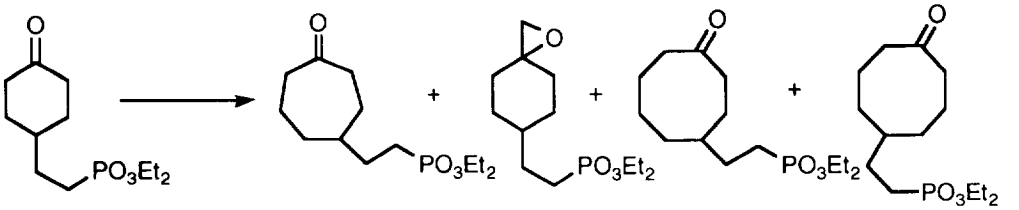
CH_2N_2 (64% conversion):	53%	31%	16%
Me_3SiCHN_2 (84% conversion):	77%	10%	13%

Scheme 11.

Finally, the phosphonate **41** has been prepared starting from the cyclohexanone derivative **28** by ring enlargement with trimethylsilyldiazomethane or diazomethane *in situ* generated (see *supra*), the first method being the most convenient (Scheme 12). Compound **41**, purified by treatment of the reaction mixture with sodium hydrogen sulfite, was isolated in 36% yield.

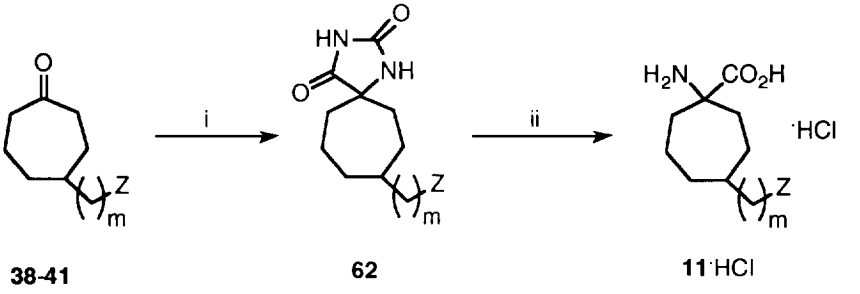
Cycloheptane ketones **38-41** were finally transformed into hydantoins **62** under Bucherer-Bergs reaction conditions and were obtained as *cis/trans* diastereoisomeric mixtures (*ca.* 1:1) (Scheme 13 and Table 3). The hydantoin derived from nitrile **40** was transformed into the tetrazol **62c** by treatment with azidotri-n-butylstannane[10]. Final hydrolysis of hydantoins **62** with concentrated hydrochloric acid afforded amino acid hydrochlorides **9** as *cis/trans* diastereoisomers mixture (*ca.* 1:1) (Table 3).

Work is in progress in order to evaluate physiological activity of the obtained amino acids against excitatory amino acid receptors, particularly the metabotropic receptors.



	28	41	59	60	61
CH_2N_2 *in situ* (56% conversion):	54%		0%	46%	
Me_3SiCHN_2 (78% conversion):	60%		13%	27%	

Scheme 12.

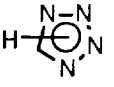
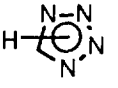


Scheme 13. *Reagents*: i, KCN, $(NH_4)_2CO_3$, NH_4Cl, EtOH, H_2O; ii, HCl.

EXPERIMENTAL SECTION

General. Melting points were obtained with a Reichert Thermovar or on a Büchi and are uncorrected. IR spectra were obtained as films on a Pye Unicam SP3-200 or on Nicolet 510 P-FT spectrophotometers as neat liquids or as indicated. ^1H and ^{13}C spectra were recorded on a Bruker AC-300 and AC-200P spectrometers with $SiMe_4$ as internal standard and using $CDCl_3$ as solvent (unless otherwise stated). ^{13}C-NMR assignments were made on the basis of DEPT experiments. MS spectra were measured in a HP5988A (EI, 70eV) and in a VG7070E (DC, FAB). High resolution mass spectra were measured in the Mass Spectrometry Services at the Universities of Zaragoza and Autónoma of Madrid. Elemental analyses were performed by the Microanalyses Service of the University of Alicante or by the Analytical Centre at the University Complutense of Madrid (Facultad de Farmacia). Chromatographic analyses (GLC) were determined with a Hewlett-Packard HP-5890 instrument equipped with a 25 m WCOT capillary column (0.22 mm diam., 0.2μm film thickness OV-101 stationary phase) using nitrogen (2 ml/min) as the carrier gas, $T_{injector}$=270°C, T_{column}=100°C, and 100-270 (10°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 or iodine visualization. Column chromatography was performed using silica gel 60 of 200-400 mesh and hexane/ether as eluant. All starting materials were commercially available (Aldrich, Fluka, Janssen) of the best grade and were used without further purification. THF was dried with $LiAlH_4$ under an argon atmosphere.

Table 3. Synthesis of Cycloheptane Hydantoins **62** and Amino Acids **11**·HCl

Starting ketone	Hydantoin **62**				Amino acid **11**·HCl		
	no.	m	Z	yield (%)[a]	no.	Z	yield (%)[b]
38	**62a**	0	CO_2Et	70	**11a**	CO_2H	80
39	**62b**	1	CO_2Et	99	**11b**	CO_2H	65
40	**62c**	1		38[c]	**11c**		-[d]
41	**62d**	2	PO_3Et_2	81	**11d**	PO_3H_2	66

[a] Based on the starting ketone. [b] Based on hydantoin **62**. [c] Hydantoin with Z=CN, 57% yield; 66% yield in the transformation into the corresponding tetrazole. [d] Decomposed.

Synthesis of 2-(3-Oxocyclopentyl)acetic Acid (12)[11]: To a solution of sodium diethyl malonate (7.5 mmol) in dry methanol (5 mL) a mixture of 2-cyclopenten-1-one (0.51 mL, 5.7 mmol) and chlorotrimethylsilane (1.45 mL, 11.4 mmol), under argon, was added over 30 min at 60°C and then refluxed for 1 h. The reaction mixture was cooled to room temperature and water (20 mL) was added. The resulting solution was extracted with CH_2Cl_2 (3x20 mL) and the organic layer was dried (Na_2SO_4) and evaporated at reduced pressure (15 Torr). The residue was dissolved in (20%) aqueous H_2SO_4 and heated under reflux for 1 d. After cooling, NaCl was added and the reaction mixture was extracted with EtOAc (3x20 mL). The organic layer was dried (Na_2SO_4) and evaporated at reduced pressure (15 Torr) to give 0.40 g (50% yield) of compound **10**: R_T 5.46 min; ν 3500-2400 (OH) and 1720 cm^{-1} (C=O)[7]; δ_H 1.90-2.80 (m, 9H, 4xCH_2, CH) and 8.50 (br s, 1H, OH)[7]; δ_C 28.8, 38.0, 38.9 (3xCH_2), 30.5 (CH), 44.2 (*C*H_2CO), 175.3 (CO_2) and 218.5 (CO); *m/z* 142 (*M*+, 5%), 85 (26), 83 (36), 55 (45), 54 (14), 53 (31), 52 (10), 51 (18), 50 (14), 45 (100), 42 (69) and 41 (50).

Reaction of 2-Cyclopenten-1-one with Organocopper Reagents. Synthesis of Compounds 13-15: To a suspension of zinc powder (2.32 g, 35.6 mmol) in dry THF (4 mL) 1,2-dibromoethane (0.122 mL, 1.42 mmol) was added and the resulting mixture heated at 65°C for 1 h. Then chlorotrimethylsilane (0.139 mL, 1.12 mmol) was added at room temperature and after stirring for 15 min a solution of the corresponding alkyl iodide (56 mmol) was added in dry THF (10 mL) at 30°C under argon. The reaction mixture was stirred at 40°C for 1 d and then anhydrous copper(I) cyanide (2.71 g, 30 mmol) and lithium chloride (2.60 g, 60.2 mmol) were added at -10°C. The reaction mixture was stirred at 0°C for 10 min, cooled to -78°C and then a mixture of cyclopentenone (2.04 mL, 22.8 mmol) and chlorotrimethylsilane (6.94 mL, 54.4 mmol) was added over 30 min . The reaction was warmed to room temperature and after 12 h 20% aqueous NH_4OH (25 mL) was added and filtered. The filtrate was extracted with ether (3x50 mL) and evaporated *in vacuo* (15 Torr) and the residue purified by flash chromatography (silica gel, hexane/ether) to afford compounds **13-15**.

3-(3-Oxocyclopentyl)propanenitrile **(13)**[12]: 36% yield; R_T 5.01 min; ν 2240 (C≡N) and 1730 cm^{-1} (C=O); δ_H 1.56, 1.87, 2.30 and 2.50 (4 m, 11H, 5xCH_2, CH); δ_C 15.25 (*C*H_2CN), 28.4, 30.4 (*C*H_2CH*C*H_2), 35.7 (CH), 37.9, 43.8 (2x*C*H_2CO), 119.9 (C≡N) and 217.4 (CO); *m/z* 138 (*M*++1, 3%), 137 (*M*+, 35), 108 (60), 83 (46), 55 (100) and 41 (57).

4-(3-Oxocyclopentyl)butanenitrile **(14)**[13]: 73% yield; R_T 6.61 min; ν 2240 (C≡N) and 1730 cm^{-1} (C=O); δ_H 1.70, 2.25 (m, 11H, 5xCH_2, CH) and 2.41 (t, *J*=6.8 Hz, 2H, CH_2CN); δ_C 16.8 (*C*H_2CN), 23.3,

28.9, 34.1, 37.9, 44.4 (5xCH_2), 36.0 (CH), 119.2 (C≡N) and 218.2 (CO); *m/z* 152 (*M*+1, 4%), 151 (*M*+, 37), 122 (58), 83 (83), 55 (100) and 41 (33).

Ethyl 4-(3-Oxocyclopentyl)butanoate **(15)**: 48% yield; R_T 7.89 min; R_f 0.80 (hexane/EtOAc: 2/1); ν 1730 cm^{-1} (C=O); δ_H 1.26 (t, *J*=7.1 Hz, 3H, CH_3), 1.50, 1.75 (2m, 6H, 3xCH_2), 2.27 (m, 5H, 2xCH_2CO, CH), 2.33 (t, *J*=7.3 Hz, 2H, CH_2CO_2) and 4.13 (q, *J*=7.1 Hz, 2H, CH_2O); δ_C 14.0 (CH_3), 23.0, 29.1, 34.0, 34.8 (4xCH_2CH), 36.7, 44.8 (2xCH_2CO), 38.1 (CH), 60.0 (CH_2O), 173.1 (CO_2) and 199.4 (CO); *m/z* 199 (*M*+1, 1%), 198 (*M*+, 10), 125 (32), 88 (50), 83 (100), 82 (39), 55 (58) and 41 (35) (Found: *M*+, 198.1259. $C_{11}H_{18}O_3$ requires 198.1256).

Synthesis of 2-[3,3-(Ethylenedioxy)cyclopentyl]ethan-1-ol (18): A solution of 2-(3-oxocyclopentyl)acetic acid (**12**) (6.25 g, 44 mmol), ethylene glycol (4.93 mL, 88 mmol), triethyl orthoformate (3.65 mL, 22 mmol) and *p*-toluenesulfonic acid (440 mg, 2.2 mmol) in dry benzene (120 mL) was heated with a Dean-Stark apparatus for 1 d. The solvent was evaporated (15 Torr) and the residue was dissolved in a mixture of ether and an aqueous saturated solution of $NaHCO_3$. The organic layer was washed with water, dried (Na_2SO_4) and evaporated (15 Torr) to give 4.45 g (45% yield) of crude ethyl 2-[3,3-(ethylenedioxy)cyclopentyl]acetate (**17**). To a suspension of $LiAlH_4$ (1.19 g, 31.2 mmol) in dry THF (80 mL) was dropwise added at 0°C a solution of crude compound **17** in THF (20 mL) under argon. The mixture was stirred under reflux for 3 h, then cooled at 0°C and hydrolysed with water. The resulting suspension was filtered off and the filtrate poured into a mixture of ether/water. The organic layer was dried (Na_2SO_4) and evaporated (15 Torr) and the residue purified by flash chromatography to yield 2.70 g (76%) of alcohol **18**: R_T 5.74 min; ν 3400 cm^{-1} (OH); δ_H 1.38, 1.62, 1.85, 2.06 [4m, 9H, $CH_2CH_2CH(CH_2)_2$]; 2.60 (br s, 1H, OH), 3.61 (t, *J*=6.8 Hz, 2H, CH_2OH) and 3.88 (m, 4H, 2xCH_2O); δ_C 30.2, 35.8, 38.6, 42.6 (4xCH_2C), 34.2 (CH), 61.3 (CH_2OH), 63.9, 64.0 (2xCH_2O) and 117.7 (CH_2CO); *m/z* 172 (*M*+, 2%), 143 (40), 127 (39), 113 (10), 100 (11), 99 (100) and 55 (14).

Synthesis of 2-[3,3-(Ethylenedioxy)cyclopentyl]ethyl Mesylate (19): To a solution of alcohol **18** (2.70 g, 15.7 mmol) in dry THF (40 mL) triethylamine (4.43 ml, 31.4 mmol) and a solution of methanesulfonyl chloride (1.85 mL, 23.6 mmol) in THF (10 mL) were added under argon at 0°C . The reaction mixture was stirred at room temperature for 4 h, then an aqueous saturated solution of $NaHCO_3$ (50 mL) and ether (100 mL) were added. The organic layer was dried (Na_2SO_4) and evaporated (15 Torr) to afford 3.69 g (94% yield) of pure compound **19** (>95% GLC): R_T 11.16 min; ν 1360 and 1180 cm^{-1} (SO_2); δ_H 1.41, 1.86, 2.10 [3m, 9H, 4xCH_2, CH), 3.00 (s, 3H, CH_3), 3.88 (m, 4H, 2xCH_2OC) and 4.22 (t, *J*=6.6 Hz, 2H, CH_2OMs); δ_C 30.1, 35.1, 35.9, 42.5 (4xCH_2C), 34.1 (CH), 37.5 (CH_3), 64.2, 64.4 (OCH_2CH_2O), 68.9 (CH_2OMs) and 117.6 (CO); *m/z* 221 (*M*+-29, 11%), 171 (11), 127 (53), 125 (27), 100 (16), 99 (100), 86 (12), 83 (10), 79 (18), 55 (25) and 41 (10).

Synthesis of Diethyl 2-[3,3-(Ethylenedioxy)cyclopentyl]ethanephosphonate (20): A solution of compound **19** (3.69 g, 14.75 mmol) in dry THF (10 mL) was added to a solution of lithium bromide (3.84 g, 44.25 mmol) in dry THF (40 mL) at 0°C under argon. The reaction mixture was stirred at room temperature for 15 h and then was added to a suspension of sodium hydride (1.78 g, 44.25 mmol) and diethyl phosphite (5.67 mL, 44.25 mmol) in dry THF (50 mL). The resulting mixture was stirred under reflux for 10 h, cooled at room temperature, hydrolysed with water and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated (15 Torr) to give 3.1 g (72%) of pure compound **20**: R_T 12.49 min; ν 1240 and 1050 cm^{-1} (PO); δ_H 1.32 (t, *J*=7.1 Hz, 6H, 2xCH_3), 1.84 (m, 11H, 5xCH_2, CH), 3.89 (m, 4H, 2xCH_2OC) and 4.10 (m, 4H, 2xCH_2OP); δ_C 16.4 (d, J_{CP}=6.0 Hz, 2xCH_3), 24.4 (d, J_{CP}=141.0 Hz, CH_2P), 28.3 (d, J_{CP}=5.0 Hz, CH_2CH_2P), 29.7 (CH_2CH_2CH), 37.9, 42.2 (2xCH_2CO), 38.3 (d, J_{CP}=17.0 Hz, CH) , 61.4 (d, J_{CP}=6.0 Hz, 2xCH_2CH_3), 64.0, 64.2 (OCH_2CH_2O) and 117.6 (CH_2CO); *m/z* 263 (*M*+-29, 17%), 152 (27), 138 (10), 137 (14), 127 (100), 125 (32), 109 (16), 100 (11), 99 (60), 86 (11), 81 (12) and 55 (15).

Synthesis of Diethyl 2-(3-Oxocyclopentyl)ethanephosphonate (16): To a solution of compound **18** (3.1 g, 10.6 mmol) in ethanol (50 mL) a 20% aqueous solution of H_2SO_4 (2 mL) was added. The resulting solution was stirred at room temperature for 3 h and then neutralised with $NaHCO_3$ and extracted with ether (3x50 mL). Extracts were washed with water, dried (Na_2SO_4) and freed of solvent. The residue was purified by flash chromatography to give 2.22 g (85%) of compound **16**: R_T 10.63 min; R_f 0.25 (hexane/EtOAc: 1/1); ν 1720 (C=O), 1235 and 1040 cm^{-1} (PO); δ_H 1.34 (t, *J*=7.1 Hz, 6H, 2xCH_3), 1.81,

2.30 (2m, 11H, 5xCH_2, CH) and 4.13 (m, 4H, 2xCH_2OP); δ_C 16.3 (d, J_{CP}=6.0 Hz, 2xCH_3), 23.8 (d, J_{CP}=142.0 Hz, CH_2P), 27.9 (d, J_{CP}=5.0 Hz, CH_2CH_2P), 28.9 (CH_2CH_2CH), 37.5 (d, J_{CP}=17.0 Hz, CH), 38.4, 44.6 (2xCH_2CO), 62.15 (d, J_{CP}=6.0 Hz, 2xCH_2CH_3) and 217.9 (C=O); *m/z* 248 (*M*+, 10%), 166 (37), 165 (28), 152 (100), 139 (15), 138 (38), 137 (17), 125 (86), 111 (37), 110 (11), 109 (31), 108 (23), 97 (25), 82 (16), 81 (19), 65 (11) and 55 (13) (Found: *M*+, 248.1168. $C_{11}H_{21}O_4P$ requires 248.1177).

Synthesis of Ethyl 2-[4,4-(Ethylenedioxy)cyclohexylidene]acetate (29): A solution of 1,4-cyclohexanedione *mono*-ethylene ketal (**22**) (1.5 g, 10 mmol) and ethyl (triphenylphosphoranylidene)acetate (3.83 g, 11 mmol) in dry benzene (20 mL) was refluxed for 1 d under argon. The solvent was removed (15 Torr) and the residue was purified by flash chromatography to give 2.1 g (89%) of compound **29**: R_T 9.27 min; ν 3050, 1645 (C=CH) and 1710 cm^{-1} (C=O); δ_H 1.27 (t, *J*=7.0 Hz, 3H, CH_3), 1.76 (m, 4H, 2xCH_2CO), 2.38, 3.00 (2t, *J*=7.0 Hz, 4H, 2xCH_2C=C), 3.91 (s, 4H, OCH_2CH_2O), 4.08 (q, *J*=7.0 Hz, 2H, CH_2CH_3) and 5.66 (s, 1H, CH=C); δ_C 14.0 (CH_3), 25.75, 34.3, 34.7, 35.5 (2xCH_2CH_2), 59.2 (CH_2CH_3), 64.15 (OCH_2CH_2O), 107.7 (OCO), 114.1 (CH), 158.9 (*C*=CH) and 166.1 (C=O).

Synthesis of Ethyl 2-[4,4-(Ethylenedioxy)cyclohexyl]acetate (30). A suspension of compound **29** (1.56 g, 6.8 mmol) and 10% palladium on charcoal (0.94 g) in ethyl acetate (40 mL) was stirred under a hydrogen atmosphere for 25 min. The reaction mixture was filtered off and the filtrate concentrated to give 1.50 g (95%) of compound **30**: R_T 8.70 min; ν 1720 cm^{-1} (C=O); δ_H 1.22 (t, *J*=7.0 Hz, 3H, CH_3), 1.26, 1.49 (2td, *J*=14.0, 3.0 Hz, 4H, 2xCH_2CH_2C-O), 1.67 (m, 4H, 2xCH_2C-O), 1.75 (m, 1H, CH), 2.15 (d, *J*=7.0 Hz, 2H, CH_2C=O), 3.86 (s, 4H, OCH_2CH_2O) and 4.05 (q, *J*=7.0 Hz, 2H, CH_2CH_3); δ_C 14.2 (CH_3), 29.9, 34.2 (2xCH_2CH_2), 33.4 (CH_2CO), 40.9 (CH), 60.1 (CH_2CH_3), 64.1 (OCH_2CH_2O), 108.5 (OCO) and 172.8 (C=O); *m/z* 228 (*M*+, 1%), 212 (12), 183 (55), 155 (25), 139 (36), 105 (10), 99 (11), 98 (25) 92 (36), 91 (100) and 65 (43).

Synthesis of Ethyl 2-(4-Oxocyclohexyl)acetate (24): Compound **30** (1.50 g, 6.45 mmol) was treated with 20% H_2SO_4 as described for compound **16**. The residue was purified by flash chromatography to afford 0.94 g (80%) of compound **24**: R_T 6.53 min; R_f 0.62 (hexane/EtOAc: 2/1); ν 1710 cm^{-1} (C=O); δ_H 1.27 (t, *J*=7.0 Hz, 3H, CH_3), 1.42, 1.75, 2.12, 2.35 (4m, 11H, 5xCH_2, CH) and 4.16 (q, *J*=7.0 Hz, 2H, CH_2O); δ_C 14.0 (CH_3), 32.0, 40.2 (4xCH_2), 30.9 (CH_2CO), 32.7 (CH), 60.2 (CH_2O), 172.2 (CO_2) and 211.4 (CO); *m/z* 185 (*M*+1, 2%), 184 (*M*+, 22), 139 (29), 97 (65), 96 (100), 88 (24), 70 (20), 61 (27), 60 (28), 55 (68) and 41 (30) (Found: *M*+, 184.1103. $C_{10}H_{16}O_3$ requires 184.1099).

Synthesis of 2-[4,4-(Ethylenedioxy)cyclohexyl]acetonitrile (32): To a solution of diethyl cyanomethanephosphonate (0.72 mL, 4.46 mmol) and DMPU (1.56 mL, 11.5 mmol) in dry THF (4 mL) a suspension of 60% dispersion of sodium hydride in mineral oil (0.165 g, 4.1 mmol) in dry THF (6 mL) and a solution of 1,4-cyclohexanedione *mono*-ethylene ketal (**22**) (0.6 g, 4.0 mmol) in THF (4 mL) were succesively added at 0°C. The mixture was stirred for 12 h and then hydrolysed with water and extracted with ether. The organic layer was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4) and evaporated to yield 0.71 g (99%) of 2-[4,4-(ethylenedioxy)cyclohexylidene]acetonitrile (**31**). This compound was hydrogenated for 12 h following the same procedure described for the synthesis of compound **30**. Crude product **32** was purified by flash chromatography affording 0.62 g (87%) of nitrile **32**: R_T 7.14 min; R_f 0.50 (hexane/EtOAc: 2/1); ν 2220 cm^{-1} (C≡N); δ_H 1.20-1.65 (2m, 4H, 2xCH_2CHCH_2CN), 1.79 (m, 5H, 2xCH_2CO, CH), 2.28 (d, *J*=6.5 Hz, 2H, CH_2CN) and 3.94 (s, 4H, OCH_2CH_2O) ; δ_C 23.75 (CH_2CN), 29.35 (2xCH_2CHCH_2CN), 33.6 (CH), 33.95 (2xCH_2CO), 64.2, 64.3 (OCH_2CH_2O), 107.9 (OCO) and 118.65 (C≡N); *m/z* 182 (*M*+1, 1%), 181 (*M*+, 11), 141 (17), 100 (23), 99 (100), 86 (58), 55 (38), 53 (12), 43 (10), 42 (20) and 41 (16) (Found: *M*+, 181.1100. $C_{10}H_{15}NO_2$ requires 181.1103).

Synthesis of 2-(4-Oxocyclohexyl)acetonitrile (25): A solution of compound **32** (0.23 g, 1.25 mmol) and aqueous 2M HCl (4 mL) in ether (4 mL) was stirred for 7 h. The ethereal layer was decanted, washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4) and evaporated (15 Torr). The residue was purified by flash chromatography to yield 0.107 g (67%) of nitrile **25**: R_T 4.94 min; R_f 0.30 (hexane/EtOAc: 2/1); ν 2220 (C≡N) and 1700 cm^{-1} (C=O); δ_H 1.57 (m, 4H, 2xCH_2CH_2CO), 2.15 (m, 3H, CH_2CH_2CO, CH), 2.45 (m, 4H, 2xCH_2CO) and 2.42 (d, *J*=6.5 Hz, 2H, CH_2CN); δ_C 23.4 (CH_2CN), 31.65 (2xCH_2CHCH_2CN),

33.2 (CH), 39.9 (2xCH_2CO), 118.0 (C≡N) and 209.5 (CO); *m/z* 139 (*M*+2, 6%), 138 (*M*+1, 3), 137 (*M*+, 27), 97 (20), 96 (15), 69 (12), 55 (100), 54 (13), 53 (10), 42 (19) and 41 (26) (Found: *M*+, 137.0837. $C_8H_{11}NO$ requires 137.0841).

Synthesis of 2-[4,4-(Ethylenedioxy)cyclohexyl]ethyl Mesylate (34): To a suspension of $LiAlH_4$ (035 g, 9.3 mmol) in dry THF (10 mL) a solution of compound **30** (1.4 g, 6.2 mmol) in THF (10 mL) was added under argon. The reaction mixture was refluxed for 15 h and after work-up (see synthesis of compound **18**) 1.08 g (93% yield) of compound **33** was obtained, which was mesylated following the procedure described for compound **19**. The reaction with mesyl chloride was stirred during 15 h and after work-up, 1.45 g (95% yield) of mesylate **34** was obtained: R_T 12.60 min; R_f 0.36 (hexane/EtOAc: 2/1); ν 1350 and 1170 cm^{-1} (SO_2); δ_H 1.05-2.10 (m, 10H, 5xCH_2C), 2.94 (s, 3H, CH_3), 3.86 (s, 4H, OCH_2CH_2O) and 4.20 (t, *J*=6.5 Hz, 2H, CH_2OS); δ_C 29.65, 34.1 (4xCH_2CH_2), 32.45, 35.2, 37.2 ($SOCH_2CH_2CH$, CH_3), 64.05 (OCH_2CH_2O), 68.1 (CH_2OS) and 108.5 (OCO); *m/z* 264 (*M*+, 0.5%), 185 (30), 99 (100), 86 (19), 79 (12) and 55 (14).

Synthesis of 3-(4-Oxocyclohexyl)propanenitrile (26): A mixture of compound **34** (1.45 g, 5.6 mmol) and NaCN (0.82 g, 16.7 mmol) in dry DMSO (25 mL) was heated at 120°C for 1 d. The resulting reaction mixture was cooled at room temperature and dissolved in ether (50mL), washed with water, dried (Na_2SO_4) and freed of solvent. The residue, 0.80 g (74% yield) of 3-[4,4-(ethylenedioxy)cyclohexyl]-propanenitrile (**35**) was hydrolysed with a 20% aqueous H_2SO_4 solution (15 mL) in ethanol (15 mL) for 9 h and after work-up (see compound **16**) the resulting residue was purified by flash chromatography to give 0.57 g (92%) of compound **26**: R_T 6.55 min; R_f 0.40 (hexane/EtOAc: 2/1); ν 2260 (C≡N) and 1715 cm^{-1} (C=O); δ_H 1.35, 2.00, 2.25 (3m, 9H, 4xCH_2, CH) and 1.63 (q, *J*=7.0 Hz, 2H, CH_2CH_2CN); δ_C 14.85, 30.6, 31.6, 34.6, 40.05 (6xCH_2, CH), 119.25 (C≡N) and 207.6 (CO); *m/z* 151 (*M*+, 34%), 122 (23), 108 (12), 97 (10), 95 (13), 67 (17), 55(100), 54 (11), 53 (16), 42 (12) and 71 (22) (Found: *M*+, 151.0992. $C_9H_{13}NO$ requires 151.0997).

Synthesis of 3-(4-Oxocyclohexyl)propanoic Acid (27)[19]: To a solution of compound **35** (0.5 g, 2.6 mmol) in ethanol (10 mL) an aqueous 25% NaOH solution (10 mL) was added. The resulting mixture was heated under reflux for 1 d and then the ethanol evaporated. The residue was acidified with 20% H_2SO_4 the solution stirred for 2 h at room temperature and extracted with ether. The organic layer was decanted, dried (Na_2SO_4) and evaporated (15 Torr) to afford 0.43 g (99%) of compound **27**: R_T 14.91 min; ν 3600-2300 (OH) and 1700 cm^{-1} (C=O); δ_H 1.30, 2.00, 2.29 (3m, 11H, 5xCH_2, CH) and 1.60 (q, *J*=7.3 Hz, 2H, CH_2CH_2COOH); δ_C 30.15, 31.65, 32.1, 35.1, 40.3 (6xCH_2, CH), 176.4 (CO_2H) and 206.35 (CO); *m/z* 170 (*M*+, 15%), 152 (37), 124 (29), 123 (11), 111 (22), 110 (26), 98 (10), 97 (100), 96 (18), 95 (11), 82 (10), 81 (11), 73 (14), 71 (10), 70 (41), 69 (30), 68 (11), 67 (15), 60 (11), 55 (78), 53 (10), 45 (13), 42 (11) and 41 (23).

Synthesis of Diethyl 2-(4-Oxocyclohexyl)ethanephosphonate (28): A solution of compound **34** (0.25 g, 1 mmol) in dry THF (2 mL) was added to a solution of lithium bromide (0.26 g, 3.0 mmol) in dry THF (3 mL) at 0°C under argon. The reaction mixture was stirred at room temperature for 20 h and then it was added to a suspension of sodium hydride (60% dispersion in mineral oil; 0.13 g, 3.3 mmol) and diethyl phosphite (0.43 mL, 3.3 mmol) in dry THF (5 mL). The resulting mixture was stirred under reflux for 4 h, and with work-up as described for compound **20** to give after flash chromatography 0.27 g (88%) of compound **36** which was hydrolysed with aqueous 2M HCl (3 mL) in ethanol (3 mL) for 1 d. After extractive work-up 0.16 g (70%) of compound **28** was obtained: R_T 12.00 min; R_f 0.32 (hexane/EtOAc: 1/1); ν 1700 (C=O), 1240 and 1040 cm^{-1} (PO); δ_H 1.36 (m, 6H, 2xCH_3), 1.74, 2.08 (2m, 9H, 4xCH_2, CH), 2.38 (br s, 4H, 2xCH_2CO) and 4.13 (m, 4H, 2xCH_2O); δ_C 16.1 (d, J_{CP}=5.8 Hz, 2xCH_3), 23.2 (d, J_{CP}=144.0 Hz, CH_2P), 27.7 (d, J_{CP}=5.0 Hz, CH_2CH_2P), 31.8, 40.1 (4xCH_2), 36.1 (d, J_{CP}=16.0 Hz, CH), 61.1 (d, J_{CP}=6.7 Hz, 2xCH_2O) and 211.1 (C=O); *m/z* 263 (*M*+1, 3%), 262 (*M*+, 19), 166 (46), 165 (100), 152 (66), 139 (19), 138 (39), 137 (29), 129 (54), 111 (27), 109 (32), 108 (14), 97 (21), 91 (10), 82 (12), 81 (25), 67 (13), 65 (14), 55 (31) and 41 (18) (Found: *M*+, 262.1340. $C_{12}H_{23}O_4P$ requires 262.1334).

Ring Enlargement of Cyclohexanone Derivatives. General Procedures.
***In situ* diazomethane:** To a solution of cyclohexanone derivative (3 mmol) and potassium hydroxide

(2.07 g, 37 mmol) in water (1 mL) and methanol (5 mL) during 2 h a solution of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazal®, 1.12 g, 5.25 mmol) in methanol (9 mL) was added at 0°C. The reaction mixture was stirred for an additional h, neutralised with concd. HCl and evaporated under vacuum (15 Torr), the residue was purified by flash chromatography to give the cycloheptanone derivative.

Diazomethane in ether[22]: To a solution of diazomethane (prepared from Diazal® 0.785 g, 3.67 mmol) in ether (6 mL) a solution of cyclohexanone derivative (3 mmol) in ethanol (1.5 mL) was added. The reaction mixture was stirred for 2 h, then acidified with aqueous 2M HCl and the organic layer decanted, dried (Na_2SO_4) and freed of solvent.

Trimethylsilyldiazomethane[23]: To a solution of cyclohexanone derivative (5 mmol) and boron trifluoride etherate (0.69 mL, 5.5 mmol) in dry CH_2Cl_2 (30 mL) was added a 2M hexane solution of trimethylsilyldiazomethane (2.75 mL, 5.5 mmol) at -30°C under argon. After 2 h stirring, water was added, the organic layer was washed with brine, dried (Na_2SO_4) and freed of solvent. In all these procedures the resulting residue was purified by flash chromatography or was dissolved in ether (10 mL) and an aqueous 5.75 M $NaHSO_3$ solution (4 mL) was added. The mixture was stirred for 1 d, the aqueous layer was decanted, Na_2CO_3 (3.0 g) was added and heated at 60°C for 1 h. After cooling at room temperature it was extracted with ether, the organic layer was washed with brine, dried (Na_2SO_4), evaporated (15 Torr) and the residue purified by flash chromatography.

Synthesis of Ethyl 4-Oxocycloheptanecarboxylate (38): The reaction was carried out starting from ethyl 4-oxocyclohexanecarboxylate (**23**) with CH_2N_2/ether and with Me_3SiCHN_2 (see Scheme 7 and General Procedure). By using the second method compound **38** was obtained in 60% yield: R_T 6.40 min; R_f 0.49 (hexane/EtOAc: 2/1); ν 1715 and 1690 cm^{-1} (C=O); δ_H 1.26 (t, *J*=7.0 Hz, 3H, CH_3), 1.90 (m, 6H, 2xCH_2CH_2CO, CH_2CHCO_2), 2.50 (m, 5H, 2xCH_2CO, CH) and 4.15 (q, *J*=7.0 Hz, 2H, CH_2O); δ_C 14.0 (CH_3), 22.8, 26.5, 32.5 (2xCH_2CH_2CO, CH_2CH), 41.3, 43.35 (2xCH_2CO), 46.35 (CH), 60.4 (CH_2O), 174.9 (CO_2) and 213.55 (CO); *m/z* 185 (M^++1, 4%), 184 (M^+, 35), 139 (35), 138 (22), 128 (28), 127 (20), 114 (23), 111 (91), 110 (100), 101 (23), 99 (12), 88 (10), 84 (10), 83 (31), 82 (22), 81 (11), 73 (22), 69 (12), 68 (13), 67 (11), 55 (70), 54 (11), 53 (10), 42 (11) and 41 (24) (Found: M^+, 184.1107. $C_{10}H_{16}O_3$ requires 184.1099).

Synthesis of 1,4-Cycloheptanedione *mono*-Ethylene Ketal (45): From among the three methods described (see Scheme 8), the reaction of 1,4-cyclohexanedione *mono*-ethylene ketal (**22**) with *in situ* generated CH_2N_2 gave the best yield for compound **45** (45%): R_T 5.98 min; R_f 0.30 (hexane/EtOAc: 2/1); ν 1685 cm^{-1} (C=O); δ_H 1.80 (m, 6H, CH_2CH_2CO, 2xCH_2CO_2), 2.49 (m, 4H, 2xCH_2CO) and 3.89 (s, 4H, 2xCH_2O); δ_C 18.85 (CH_2CH_2CO), 33.0, 37.3 (2xCH_2CO_2), 39.1, 43.4 (2xCH_2CO), 64.3, 64.4 (2xCH_2O), 109.8 (OCO) and 213.9 (C=O); *m/z* 171 (M^++1, 4%), 170 (M^+, 42), 142 (29), 114 (10), 113 (43), 100 (17), 99 (98), 86 (100), 55 (27) and 42 (18) (Found: M^+, 170.0938. $C_9H_{14}O_3$ requires 170.0943).

Synthesis of Ethyl 2-[4,4-(Ethylenedioxy)cycloheptylidene]acetate (49): A solution of 1,4-cyclohexanedione *mono*-ethylene ketal (**45**) (1.7 g, 10 mmol) and ethoxycarbonylmethylenetriphenylphosphorane (7.0 g, 20.3 mmol) in dry benzene (40 mL) was refluxed for 5 d. The solution was cooled to room temperature and hexane (50 mL) added, the resulting suspension was filtered off and the filtrate concentrated under vacuum (15 Torr) and purified by flash chromatography to afford 1.92 g (80%) of compound **49** as a mixture 1/1 of *Z*/*E* diastereomers: R_T 10.51, 10.56 min; R_f 0.60 (hexane/EtOAc: 2/1); ν 3060, 1630 (CH=C) and 1705 cm^{-1} (C=O); δ_H 1.24 (t, *J*=7.0 Hz, 3H, CH_3), 1.78 (m, 6H, 2xCH_2CO_2, $CH_2CH_2CO_2$), 2.42, 2.95 (2m, 2H, CH_2C=C), 3.93 (s, 4H, OCH_2CH_2O), 4.13 (q, *J*=7.0 Hz, 2H, CH_2CH_3) and 5.75 (s, 1H, CH); δ_C 14.2 (CH_3), 20.0 (CH_2CH_2C=C), 32.0, 32.4, 37.4, 38.55 (2xCH_2C=C, 2xCH_2CO_2), 59.3 (CH_2CH_3), 64.2, 64.3 (OCH_2CH_2O), 110.4 (OCO), 115.65, 115.7 (2xCH), 165.05 and 165.5 (C=CH, C=O); *m/z* 241 (M^++1, 1%), 240 (M^+, 8), 195 (13), 167 (14), 139 (10), 99 (100), 86 (12) and 55 (13).

Synthesis of Ethyl 2-(4-Oxocycloheptyl)acetate (39): A) From compound **49** (2.0 g, 8.3 mmol) by 10% palladium on charcoal (1.3 g) catalysed hydrogenation in AcOEt (50 mL) overnight (see synthesis of compound **30**), 2.02 g of ethyl 2-[4,4-(ethylenedioxy)cycloheptyl]acetate (**50**) (99%) was obtained, which after hydrolysis with 20% aqueous H_2SO_4 solution (10 mL) in ethanol (10 mL) for 1 h, gave 1.48 g (90%) of compound **39**. B) From compound **24** (0.92 g, 5.0 mmol) by reaction with Me_3SiCHN_2 (see General Procedure) followed by treatment of the reaction mixture with $NaHSO_3$, 0.4 g (40%) of compound **39** was

obtained: R_T 7.93 min; R_f 0.50 (hexane/EtOAc: 2/1); ν 1720 and 1690 cm^{-1} (C=O); δ_H 1.26 (t, J=7.0 Hz, 3H, CH_3), 2.20 (m, 13H, CH_2CH_2CO, 2xCH_2CO, 2x$CH_2CHCH_2CO_2$, CH, CH_2CO_2) and 4.14 (q, J=7.0 Hz, 2H, CH_2CH_3); δ_C 14.0 (CH_3), 22.6 (CH_2CH_2CO), 29.8, 36.05 (2x$CH_2CHCH_2CO_2$), 38.0 (CH), 41.65, 41.8, 43.4 (CH_2CO_2, 2xCH_2C=O), 60.15 (CH_2CH_3), 172.3 (CO_2) and 212.2 (CO); *m/z* 199 (M^++1, 2%), 198 (M^+, 14), 125 (14), 124 (13), 111 (100), 110 (60), 107 (12), 97 (10), 95 (13), 88 (12), 83 (11), 81 (11), 55 (32) and 41 (15) (Found: M^+, 198.1263. $C_{11}H_{18}O_3$ requires 198.1256).

Synthesis of 2-[4,4-(Ethylenedioxy)cycloheptylidene]acetonitrile (51): To a solution of diethyl cyanomethanephosphonate (0.72 mL, 4.46 mmol) and DMPU (1.56 mL, 11.5 mmol) in dry THF (4 mL) a suspension of 60% dispersion of sodium hydride in mineral oil (0.165 g, 4.1 mmol) in dry THF (6 mL) and a solution of 1,4-cycloheptanedione *mono*-ethylene ketal (**45**) (0.68 g, 4 mmol) in THF (4 mL) were succesively added at 0°C. The mixture was stirred for 1 h and after work-up (see compound **31**), 0.73 g (95%) of compound **51** was obtained as a *ca.* 1/1 mixture of *Z/E* diastereomers: R_T 8.96 min; R_f 0.55 (hexane/EtOAc: 2/1); ν 3100, 1610 (C=CH) and 2210 cm^{-1} (C≡N); δ_H 1.80 (m, 6H, CH_2CH_2CO, 2xCH_2CO), 2.46, 2.67 (2m, 4H, 2xCH_2C=C), 3.93 (s, 4H, OCH_2CH_2O), 5.13 and 5.16 (2s, 1H, HC=C); δ_C 20.0, 20.7 (CH_2CH_2C=C), 27.9, 30.3, 30.7, 33.9, 35.5, 36.5, 38.0, 38.2 (2xCH_2C=C y 2xCH_2CO), 64.2, 64.25 (OCH_2CH_2O), 94.7, 94.9 (CH), 110.0, 110.1 (CO), 116.6, 116.7 (CN), 169.8 and 169.9 (C=CH); *m/z* 194 (M^++1, 1%), 193 (M^+, 11), 165 (14), 99 (100), 91 (19), 86 (27) and 55 (11) (Found: M^+, 193.1094. $C_{11}H_{15}NO_2$ requires 193.1103).

Synthesis of 2-(4-Oxocycloheptyl)acetonitrile (40): A) From compound **51** (2.0 g, 8.8 mmol) by 10% palladium on charcoal (1.55 g) catalysed hydrogenation in EtOAc (50 mL) overnight (see synthesis of compound **32**), 1.81 g of 2-[4,4-(ethylenedioxy)cycloheptyl]acetonitrile (**52**) (90%) was obtained, which after hydrolysis with 2M HCl solution (20 mL) in THF (10 mL) for 16 h gave 1.1 g (88%) of compound **40**. B) From compound **25** (0.69 g, 5.0 mmol) by reaction with CH_2N_2 or with Me_3SiCHN_2 (see General Procedure) followed by treatment of the reaction mixture with $NaHSO_3$, 0.23 g (29%) or 0.35 g (46%) of compound **39** were, respectively, obtained: R_T 6,53 min; R_f 0,36 (hexane/EtOAc: 2/1); ν 2218 (C≡N) and 1685 cm^{-1} (C=O); δ_H 1.34, 1.64, 2.05 (3m, 7H, CH_2CH_2CO, 2xCH_2CHCH_2CN, CH), 2.37 (d, J=6.5 Hz, 2H, CH_2CN) and 2.55 (m, 4H, 2xCH_2CO); δ_C 22.4, 25.0 (CH_2CN, CH_2CH_2CO), 29.4, 35.7 (2xCH_2CHCH_2CN), 38.3 (CH), 41.4, 43.3 (2xCH_2CO), 118.3 (CN) and 213.2 (C=O); *m/z* 152 (M^++1, 2%), 151 (M^+, 15), 111 (12), 108 (11), 83 (17), 69 (18), 67 (10), 55 (100), 53 (10), 42 (14) and 41 (25) (Found: M^+, 151.0996. $C_9H_{13}NO$ requires 151.0997).

Synthesis of Diethyl 2-(4-Oxocycloheptyl)ethanephosphonate (41): A solution of compound **28** (2.0 g, 6.1 mmol) was treated with *in situ* generated CH_2N_2 or with Me_3SiCHN_2 (see Scheme 12 and General Procedure) followed by treatment of the reaction mixture with $NaHSO_3$: 0.35 g (21%) or 0.61 g (36%) of compound **41** were, respectively, obtained: R_T 13.2 min; R_f 0.36 (hexane/EtOAc: 1/1); ν 1700 (C=O), 1240 and 1040 cm^{-1} (PO); δ_H 1.32 (t, J=7,0 Hz, 6H, 2xCH_3), 1.80 (m, 11H, CH_2P, CH_2CH_2CO, 3xCH_2CH, CH), 2.45 (m, 4H, 2xCH_2CO) and 4.10 (m, 4H, 2xCH_2CH_3); δ_C 16.2 (d, J_{CP}=6.0 Hz, 2xCH_3), 22.6 (CH_2CH_2CO), 23.15 (d, J_{CP}=141.3 Hz, CH_2P), 29.2 (d, J_{CP}=4.7 Hz, CH_2CH_2P), 29.5, 35.6 (2x$CH_2CHCH_2CH_2P$), 41.5 (d, J_{CP}=15.8 Hz, CH), 41.8, 43.4 (2xCH_2CO), 61.3 (d, J_{CP}=6.6 Hz, 2xCH_2CH_3) and 214.0 (C=O); *m/z* 276 (M^+, 3%), 166 (45), 165 (100), 152 (55), 138 (25), 137 (23), 125 (54), 109 (25), 81 (22) and 55 (23) (Found: M^+, 276.1485. $C_{13}H_{25}O_4P$ requires 276.1490).

Synthesis of Hydantoins 21, 37 and 62. General Procedure. A mixture of ketone (5.0 mmol), KCN (0.40 g, 6.0 mmol), $(NH_4)_2CO_3$ (1.06 g, 11 mmol) and NH_4Cl (0.30 g, 5.5 mmol) in ethanol (30 mL) and water (30 mL) was heated at 60°C for 1 d. In the case of hydantoins **19a** and **35e** the keto acid was first neutralised with 20% aqueous NH_4OH solution before the addition of the mentioned salts. After cooling at room temperature the reaction mixture was neutralised with concd. HCl and evaporated under vacuum (15 Torr). The residue was extracted with EtOAc, the organic layer was dried (Na_2SO_4) and the solvent evaporated. The residue was precipitated with ether/methanol and/or recrystallised to afford hydantoins **21**, **37** and **62** as a *ca.* 1/1 molar ratio of *cis/trans* diastereomers for **21** and **62**. Hydantoin **37a** was obtained by hydrolysis with a 5M aqueous solution of NaOH (10 mL) in methanol (10 mL) for 2 h and acidified with concd. HCl . In the case of tetrazol derivatives **21c**, **37b,d** and **62c** a solution of hydantoin-nitrile (5 mmol) and azidotri-n-butylstannane (3.35 g, 10 mmol) was heated at 120°C for 1 d. The mixture was cooled to room

temperature and heated with 2M HCl (25 mL) under reflux. The resulting suspension was cooled to room temperature and filtered off and the solid recrystallised (methanol/ether) to afford hydantoin-tetrazoles **21c**, **37b,d** and **62c**. Yields are included in Tables 1-3, physical, spectral and analytical data follow.

cis/trans-*Hydantoin* 21a: mp 190-191°C (acetone); ν (Nujol) 3600-2400 (OH, NH), 1770 and 1720 cm^{-1} (C=O); δ_H (d^6-DMSO) 1.80 (m, 9H, 4xCH_2, CH), 8.15, 8.25, 10.60, 10.65 (4 br s, 2H, 2xNH) and 12.0 (br s, 1H, OH); δ_C (d^6-DMSO) 31.1, 31.45, 35.3, 35.5, 36.6, 36.9, 40.05, 40.3, 42.7, 43.55 (4xCH_2, CH), 67.83 (*C*CON), 156.3, 156.4 (NCON), 173.8 (CO_2), 179.2 and 179.6 (C*C*ON); *m/z* (FAB) 213 (*M*++1, 6%), 212 (*M*+, 48), 194 (23), 166 (29), 153 (39), 152 (21), 138 (20), 126 (21), 125 (34), 124 (12), 113 (38), 112 (24), 95 (18), 94 (11), 83 (13), 82 (100), 81 (24), 67 (20), 60 (12), 55 (33), 54 (32) and 53 (13) (Found: *M*+, 212.0798. $C_9H_{12}N_2O_4$ requires 212.0797).

cis/trans-*Hydantoin* 21b: mp 1190-191°C (MeOH/ether); ν (KBr) 3200, 3070 (NH), 225 (C≡N), 1780 and 1735 cm^{-1} (C=O); δ_H (d^4-MeOH) 1.95 (m, 11H, 5xCH_2, CH); δ_C (d^4-MeOH) 16.3, 31.6, 31.9, 32.1, 32.6, 37.8, 38.3, 39.9, 40.3, 43.9, 44.5 (5xCH_2, CH), 69.9, 70.3 (*C*CON), 121.1 (C≡N), 158.7 (CNON), 161.3 and 161.6 (C*C*ON).

cis/trans-*Hydantoin* 21c: mp 175-176°C (dec.); ν (KBr) 3190, 3070 (NH), 1780 and 1735 cm^{-1} (C=O); δ_H (d^6-DMSO) 1.65 (m, 13H, 6xCH_2, CH), 8.10, 8.20, 10.50 and 10.60 (2 br s, 2H, NH); δ_C (d^6-DMSO) 22.8, 26.0, 31.2, 31.6, 34.1, 34.2, 36.6, 37.1, 38.5, 38.9, 43.1, 43.8 (6xCH_2, CH), 67.8, 68.3 (*C*CON), 155.9, 156.4 (CNON, CN_4H), 179.3 and 179.7 (C*C*ON); *m/z* (FAB) 265 (*M*++1, 38%), 264 (*M*+, 4), 171 (16), 170 (10), 155 (32), 154 (100), 153 (10), 152 (12), 139 (22), 138 (40), 137 (73), 136 (77), 135 (10), 124 (13), 121 (10), 120 (14), 107 (24), 91 (14), 90 (15), 89 (21), 78 (11) and 76 (20) (Found, FAB+: *M*++1, 265.1417. $C_{11}H_{16}N_6O_2$ requires 265.1413). Anal. calcd. for $C_{11}H_{16}N_6O_2$: C, 49.98; H, 6.11; N, 31.80. Found: C, 50.23; H, 6.00; N, 31.20.

cis/trans-*Hydantoin* 21d: mp 152-155°C (hexane/CH_2Cl_2); ν (KBr) 3190, 3060 (NH), 1770 and 1720 cm^{-1} (C=O); δ_H (d^6-acetone) 1.21 (t, *J*=7.0 Hz, 3H, CH_3), 1.86 (m, 13H, 6xCH_2, CH), 4.09 (q, *J*=7.0 Hz, 2H, CH_2O), 7.40, 7.50 and 9.65 (3 br s, 2H, 2xNH); δ_C (d^6-acetone) 14.5 (CH_3) 24.4, 32.1, 32.5, 34.5, 34.6, 35.2, 35.5 (4x*C*H_2CH), 37.6, 38.0, 44.2, 44.7 (2x*C*H_2CO), 39.8, 40.1 (CH), 60.4 (CH_2O), 69.2, 69.7 (*C*CON), 157.2, 179.3, 179.8 (2xCON) and 173.5 (CO_2); *m/z* (FAB) 269 (*M*++1, 4%), 268 (*M*+, 24%), 223 (46), 222 (36), 205 (10), 182 (15), 181 (100), 156 (23), 154 (20), 153 (10), 152 (10), 138 (12), 126 (18), 125 (21), 123 (13), 113 (30), 112 (10), 111 (35), 110 (76), 108 (15), 101 (10), 97 (15), 95 (14), 88 (27), 83 (18), 81 (67), 80 (19), 79 (10), 78 (10), 72 (10), 70 (11), 69 (22), 68 (23), 67 (25), 61 (12), 60 (17), 55 (35) and 54 (25) (Found: *M*+, 268.1419. $C_{13}H_{20}N_2O_4$ requires 268.1423). Anal. calcd. for $C_{13}H_{23}N_2O_5P$: C, 49.04; H, 7.30; N, 8.80. Found: C, 49.45; H, 6.90; N, 8.85.

cis/trans-*Hydantoin* 21e: mp >200°C (MeOH/ether); R_f 0.27 (hexane/AcOEt: 1/1); ν (KBr) 3200, 3040 (NH), 1750, 1720 (C=O), 1240, 1050 and 1030 cm^{-1} (P=O); δ_H (d^4-MeOH) 1.34 (t, *J*=7.0 Hz, 6H, 2xCH_3), 1.93 (m, 11H, 5xCH_2, CH) and 4.10 (m, 4H, 2xCH_2O); δ_C 16.75 (d, J_{CP}=6.0 Hz, 2xCH_3), 24.7 (d, J_{CP}=140.0 Hz, CH_2P), 28.6 (d, J_{CP}=20.0 Hz, *C*H_2CH_2P), 32.3, 32.7, 37.9, 38.3, 41.0, 41.3 (3xCH_2), 44.0, 44.6 (CH), 63.15 (d, J_{CP}=6.0 Hz, 2xCH_2O), 69.8, 70.3 (*C*CON), 158.1, 181.2 and 181.6 (2xC=O); *m/z* 319 (*M*++1, 2%), 318 (*M*+, 13), 290 (20), 207 (14), 206 (50), 193 (14), 191 (11), 166 (43), 165 (100), 152 (81), 150 (10), 139 (20), 138 (97), 137 (44), 125 (89), 124 (15), 122 (11), 113 (10), 111 (55), 110 (19), 109 (57), 108 (29), 97 (49), 96 (35), 93 (25), 91 (33), 83 (21), 82 (75), 81 (61), 80 (30), 79 (10), 77 (11), 69 (13), 68 (15), 67 (25), 65 (44), 55 (45), 54 (38), 53 (17), 45 (13), 44 (15), 43 (18), 42 (13) and 41 (45) (Found: *M*+, 318.1351. $C_{13}H_{23}N_2O_5P$ requires 318.1345).

cis-*Hydantoin* 37a: mp 285°C (H_2O, dec.); ν (Nujol) 3240, 3080 (NH), 1765, 1745 and 1700 cm^{-1} (C=O); δ_H (d^6-DMSO) 1.60-2.20 (m, 5H, 2xCH_2, CH), 2.40 (m, 4H, CH_2CN), 8.40 and 10.10 (2 br s, 2H, 2xNH); δ_C (d^6-DMSO) 23.7 (2x*C*H_2CH), 32.7 (2x*C*H_2CN), 40.8 (CH), 61.8 (CNH), 156.5 (CNON), 176.1 (C*C*ON) and 179.0 (CO_2); *m/z* 213 (*M*++1, 8%), 212 (*M*+, 44), 194 (12), 166 (17), 129 (23), 83 (26), 73 (36), 71 (30), 69 (39), 67 (17), 60 (31), 57 (47), 55 (80), 43 (100) and 41 (98).

cis-*Hydantoin* 37b: mp >200°C (MeOH/ether); ν (KBr) 3240, 3080 (NH), 1765 and 1715 cm^{-1} (C=O); δ_H (d^6-DMSO) 1.55 (m, 9H, 4xCH_2, CH), 2.70 (d, *J*=6.7 Hz, 2H, CH_2CN), 8.50 and 10.60 (2 br s, 2H, 2xNH); δ_C (d^6-DMSO) 26.8, 29.8, 32.8, 35.0 (5xCH_2, CH), 62.0 (*C*CON), 154.3, 156.5 (CNON, CN_4H) and 178.6 (C*C*ON); *m/z* 250 (*M*+, 11%), 207 (24), 168 (10), 167 (100), 166 (20), 139 (20), 138 (15), 137

(14), 136 (12), 126 (23), 125 (54), 124 (13), 123 (16), 113 (36), 112 (29), 111 (12), 110 (11), 109 (10), 108 (12), 107 (10), 97 (20), 96 (47), 95 (26), 94 (18), 93 (11), 92 (10), 91 (19), 85 (10), 84 (53), 83 (23), 82 (36), 81 (26), 80 (17), 79 (24), 77 (17), 69 (46), 68 (24), 67 (34), 65 (13), 60 (10), 57 (14), 56 (17), 55 (56), 54 (76) and 53 (30) (Found: M^+, 250.1180. $C_{10}H_{14}N_6O_2$ requires 250.1178).

cis-*Hydantoin* 37c: mp >200°C (hexane/acetone); ν (KBr) 3200, 3070 (NH), 1775 and 1730 cm^{-1} (C=O); δ_H (d^6-acetone) 1.22 (t, J=7.0 Hz, 3H, CH_3), 1.37, 1.76, 2.18 (3m, 11H, 5xCH_2, CH), 4.10 (q, J=7.0 Hz, 2H, CH_2O), 8.20 and 10.20 (3 br s, 2H, 2xNH); δ_C (d^6-acetone) 14.5 (CH_3), 27.8, 27.9, 33.8, 33.9 (4xCH_2), 41.8 (CH_2CO), 60.4 (CH_2O), 66.4 ($CCON$), 156.8 (CNON), 172.6 (CO_2) and 178.9 ($CCON$); *m/z* 255 (M^++1, 7%), 254 (M^+, 45), 209 (37), 208 (37), 181 (17), 180 (12), 168 (11), 167 (90), 166 (65), 164 (15), 142 (10), 139 (11), 138 (31), 137 (14), 126 (12), 125 (20), 113 (19), 112 (12), 110 (10), 109 (11), 108 (19), 97 (11), 96 (100), 95 (28), 94 (15), 88 (25), 83 (12), 81 (18), 79 (10), 70 (12), 69 (26), 68 (25), 67 (15), 61 (14), 55 (28), 54 (33) and 53 (13) (Found: M^+, 254.1273. $C_{12}H_{18}N_2O_4$ requires 254.1267).

cis-*Hydantoin* 37d: mp >200°C (hexane/acetone); ν (KBr) 3140, 3030 (NH), 1775 and 1700 cm^{-1} (C=O); δ_H (d^6-DMSO) 1.23, 1.55 (2m, 11H, 5xCH_2, CH), 2.88 (t, J=7.5 Hz, 2H, CH_2CN_4), 8.49 and 10.59 (2br s, 2H, 2xNH); δ_C (d^6-DMSO) 20.1, 26.7, 33.0, 34.0, 35.0 (6xCH_2, CH), 62.2 ($CCON$), 156.4 (CNON, CN_4H) and 178.6 ($CCON$); *m/z* 265 (M^++1, 6%), 264 (M^+, 40), 221 (27), 192 (17), 181 (26), 168 (31), 167 (18), 165 (15), 153 (15), 152 (17), 150 (13), 149 (13), 139 (15), 138 (10), 137 (15), 126 (39), 125 (37), 124 (18), 123 (14), 122 (12), 121 (11), 113 (52), 112 (38), 111 (11), 110 (21), 109 (24), 108 (22), 106 (11), 98 (26), 97 (76), 96 (50), 95 (26), 94 (29), 93 (20), 91 (17), 84 (60), 83 (14), 82 (29), 81 (36), 80 (22), 79 (31), 77 (22), 69 (69), 68 (29), 67 (49), 66 (12), 65 (16), 57 (18), 56 (25), 55 (82), 54 (100), 53 (40) and 52 (10) (Found: M^+, 264.1336. $C_{11}H_{16}N_6O_2$ requires 264.1335).

cis-*Hydantoin* 37e: mp >200°C (hexane/CH_2Cl_2); ν (Nujol) 3400-2400 (OH, NH), 1765, 1720 and 1700 cm^{-1} (C=O); δ_H ($CDCl_3$, d^6-DMSO) 1.35, 1.50, 1.70 (3m, 11H, 5xCH_2, CH), 2.25 (t, J=7.5 Hz, 3H, CH_2CO), 8.36 and 10.40 (2br s, 2H, 2xNH); δ_C ($CDCl_3$, d^6-DMSO) 25.5, 29.65, 29.85, 31.5 (4xCH_2), 33.8 (CH), 68.9 ($CCON$), 155.1 (CNON), 173.4 (CO_2) and 179.0 ($CCON$); *m/z* 241 (M^++1, 4%), 240 (M^+, 32), 223 (17), 222 (100), 194 (13), 193 (29), 181 (34), 166 (15), 138 (20), 126 (28), 125 (15), 123 (22), 122 (21), 113 (32), 112 (32), 111 (13), 110 (62), 109 (13), 97 (14), 96 (20), 95 (21), 94 (10), 93 (10), 83 (12), 82 (22), 81 (19), 79 (14), 73 (13), 69 (62), 68 (15), 67 (24), 60 (15), 55 (41), 54 (42) and 53 (16) (Found: M^+, 240.1108. $C_{13}H_{20}N_2O_4$ requires 240.1110).

cis-*Hydantoin* 37f: mp 182-183°C (hexane/CH_2Cl_2); ν (Nujol) 3170-3050 (NH), 1760, 1720 and 1720 cm^{-1} (C=O); δ_H 1.32 (t, J=7.0 Hz, 6H, 2xCH_3), 1.76 (m, 13H, 6xCH_2, CH) 4.10 (m, 4H, 2xCH_2O), 7.90 and 9.40 (2 br s, 2H, 2xNH); δ_C 16.4 (d, J_{CP}=5.0 Hz, 2xCH_3), 22.7 (d, J_{CP}=141.5 Hz, CH_2P), 27.2, 32.9 (4xCH_2), 28.8 (CH_2CH_2P), 36.3 (d, J_{CP}=17.0 Hz, CH), 61.7 (d, J_{CP}=7.0 Hz, 2xCH_2O), 63.4 ($CCON$), 157.4 (CNON) and 178.4 ($CCON$) ; *m/z* 333 (M^++1, 14%), 332 (M^+, 67), 304 (10), 233 (20), 220 (19), 192 (15), 166 (63), 165 (100), 152 (91), 139 (19), 138 (57), 137 (25), 125 (62), 122 (13), 111 (24), 109 (21), 108 (22), 107 (11), 97 (24), 96 (14), 82 (13), 81 (14), 78 (13), 69 (18), 67 (16), 65 (10), 55 (26) and 54 (19) (Found: M^+, 332.1450. $C_{14}H_{25}N_2O_5P$ requires 332.1501).

cis/trans-*Hydantoin* 62a: mp 140-145°C (hexane/CH_2Cl_2); ν (Nujol) 3170, 3050 (NH), 1760 and 1720 cm^{-1} (C=O); δ_H 1.26 (def. t, 3H, CH_3), 1.85 (m, 10H, 5xCH_2), 2.62 (m, 1H, CH), 4.13 (def. q, 4H, CH_2O), 7.54, 7.63 (2 brs, 1H, CONHC) and 9.40 (br s, 1H, CONHCO); δ_C 14.05, 14.1 (CH_3), 20.65, 21.6, 24.4, 31.0, 31.2 (CH_2CH_2CN, 2xCH_2CH), 33.4, 34.4, 36.9, 37.7 (2xCH_2CN), 44.3, 45.0 (CH), 60.4, 60.6 (CH_2O), 65.6 ($CCON$), 157.2, 157.6 (CNON), 175.7, 176.5 (CO_2) and 178.85 ($CCON$) ; *m/z* 254 (M^+, 13%), 209 (23), 208 (45), 181 (33), 180 (100), 138 (39), 126 (24), 113 (27) and 41 (21).

cis/trans-*Hydantoin* 62b: mp 140-145°C (hexane/CH_2Cl_2); ν (Nujol) 3200, 3070 (NH), 1775 and 1725 cm^{-1} (C=O); δ_H 1.26 (t, J=7.0 Hz, 3H, CH_3), 1.87 (m, 11H, CH, 5xCH_2CH_2), 2.27 (t, J=7.0 Hz, 2H, CH_2CO_2), 4.13 (q, J=7.0 Hz, 2H, CH_2CH_3), 7.43, 7.57 (2 br s, 1H, CONHC) and 9.40 (br s, 1H, CONHCO); δ_C 14.05, 14.15 (CH_3), 20.65, 21.8, 27.95, 28.3, 33.6, 34.75, 35.25, 35.55, 36.5, 36.6 (2xCH_2CH_2CN, $CH_2CHCH_2CO_2$, 2xCH_2CN), 37.1, 37.65 (CH), 41.9, 42.05 (CH_2CO_2), 60.3 (CH_2CH_3), 65.9 ($CCON$), 157.4, 157.55 (CNON), 172.85, 173.0 (CO_2), 179.1 and 179.2 ($CCON$) ; *m/z* 269 (M^++1, 9%), 268 (M^+, 45), 223 (62), 222 (100), 221 (12), 220 (34), 195 (36), 194 (27), 182 (13), 181 (86), 180 (71), 178 (23), 169 (22), 165 (10), 153 (11), 152 (17), 151 (14), 139 (17), 138 (31), 126 (25), 125 (27), 124

(23), 123 (24), 122 (36), 115 (11), 114 (12), 113 (52), 112 (14), 111 (63), 109 (47), 108 (39), 101 (15), 100 (19), 97 (16), 96 (22), 95 (32), 94 (14), 93 (15), 91 (11), 88 (22), 83 (25), 82 (55), 81 (30), 80 (21), 79 (23), 76 (10), 70 (14), 69 (26), 68 (33), 67 (34), 61 (15), 60 (17), 56 (10), 55 (43), 54 (39) and 53 (20) (Found: *M*+, 268.1421. $C_{13}H_{20}N_2O_4$ requires 268.1423).

cis/trans-*Hydantoin* 62c: mp 207-209°C (hexane/CH_2Cl_2); ν (KBr) 3235 (NH), 1770 and 1705 cm^{-1} (C=O); δ_H (d^4-MeOH) 1.60 (m, 11H, 5xCH_2, CH), 2.80 and 2.90 (2d, *J*=7.0 Hz, 2H, CH_2CHN); δ_C (d^4-MeOH) 21.7, 22.4, 28.7, 292, 31.5, 31.6, 34.7, 36.4, 36.5, 37.1, 37.7, 38.9, 40.7, 41.3 (6xCH_2, CH), 66.4, 66.8 (*C*CON), 156.7, 158.7 (CNON, CN_4H), 181.6 and 181.8 (C*C*ON). Anal. calcd. for $C_{11}H_{16}N_6O_2 \cdot 1H_2O$: C, 46.78; H, 6.43; N, 29.77. Found: C, 46.54; H, 6.10; N, 29.05.

cis/trans-*Hydantoin* 62d: R_f 0.13 (EtOAc); ν 3210, 3160 (NH), 1760, 1715 (C=O), 1240, 1050 and 1025 cm^{-1} (PO); δ_H 1.32 (t, *J*=7.0 Hz, 6H, 2xCH_3), 1.75 (m, 15H, 7xCH_2, CH), 4.10 (m, 4H, 2xCH_2O), 7.61, 7.84 (2 br s, 1H, CONHC) and 9.77 (br s, 1H, CONHCO); δ_C 16.3 (d, J_{CP}=6.0 Hz, 2xCH_3), 22.5 (*C*H_2CN), 23.25 (d, J_{CP}=141.0 Hz, CH_2P), 27.6, 29.5 (2d, J_{CP}=20.0 Hz, 2x*C*H_2CH_2P), 31.4, 33.4, 34.3, 35.0, 36.7, 37.7 (2x*C*H_2CN, 2xCH_2*C*HCH_2CH_2P), 61.5, 61.55 (2d, J_{CP}=5.0 Hz, 2xCH_2O), 65.5, 65.8 (*C*CON), 157.45, 157.5 (CNON), 179.4 and 179.45 (C*C*ON) ; *m/z* 347 (*M*++1, 1.2%), 346 (*M*+, 7), 247 (12), 166 (13), 165 (52), 152 (100), 138 (24), 137 (12), 125 (49), 111 (17), 109 (21), 108 (14), 97 (20), 82 (14), 81 (17), 55 (11) and 41 (11).

Synthesis of Amino Acid Hydrochlorides 9, 10 and 11. General Procedure. *Method A*: A suspension of hydantoin **21**, **37** and **62** (1 mmol) in concd. HCl (10 mL) was heated at 150°C in a sealed tube overnight. The resulting mixture was cooled and treated with charcoal and filtered through celite. The filtrate was evaporated (15 Torr) and the residue was dissolved in methanol and precipitated with ether to give compounds **9**, **10** and **11** as white solids, which were purified by recrystallisation. *Method B*: A suspension of hydantoin **37a** (1 mmol) in 2 M NaOH solution was heated at 150°C in a sealed tube overnight. The resulting mixture was cooled and acidified with 2 M HCl to pH=1 followed by work-up as described in Method A. Yields are included in Tables 1, 2 and 3; physical, spectral and analytical data follow.

cis/trans-*2-(3-Amino-3-carboxycyclopentyl)acetic Acid Hydrochloride* (9a): mp >270°C (MeOH/ether); ν (KBr) 3500-2500 (OH, NH), 1735, 1720 and 1655 cm^{-1} (C=O); δ_H (d^4-MeOH) 2.00 (m, 9H, 4xCH_2, CH); δ_C (d^4-MeOH) 32.5, 33.1, 36.8, 37.0, 39.3, 39.6, 43.1, 43.7 (4xCH_2), 37.4, 38.1 (CH), 65.5, 65.8 (CN), 174.6, 174.7, 176.0 and 176.1 (2xCO_2); *m/z* (DC, NH_3) 188 (*M*+-Cl+H, 9%), 170 (100), 144 (17) and 126 (23).

cis/trans-*3-(3-Amino-3-carboxycyclopentyl)propanoic Acid Hydrochloride* (9b): mp 124-125°C (MeOH/ether); ν (KBr) 3500-2500 (NH), 1750 and 1710 cm^{-1} (C=O); δ_H (d^6-DMSO) 1.50 (m, 11H, 5xCH_2, CH); δ_C (d^6-DMSO) 29.5, 29.6, 31.0, 31.8, 32.8, 32.9, 39.0, 41.4, 41.9 (5xCH_2), 35.6, 35.9 (CH), 63.6, 64.0 (CN), 173.9, 174.0 and 174.4 (2xCO_2); *m/z* (DC, NH_3) 202 (*M*+-Cl+H, 100%), 201 (26) and 156 (13) (Found: *M*++1, 202.1084. $C_9H_{16}NO_4$ requires 202.1079).

cis/trans-*5-[3-(3-Amino-3-carboxycyclopentyl)propyl]-1H-tetrazole Hydrochloride* (9c): mp 166-168°C (dec., MeOH/ether); ν (KBr) 3500-2500 (OH, NH) and 1740 cm^{-1} (C=O); δ_H (d^4-MeOH) 2.10 (m, 11H, 5xCH_2, CH) and 2.97 (t, *J*=7.0 Hz, 2H, CH_2CN_4); δ_C (d^4-MeOH) 24.1, 24.2, 27.4, 27.5, 32.7, 33.3, 35.0, 40.2, 41.8, 43.4, 44.2 (5xCH_2), 36.9, 37.5 (CH), 65.3, 65.8 (CN), 157.7 (CN_4H), 174.7 and 174.8 (2xCO_2); *m/z* (DC, NH_3) 240 (*M*+-Cl+H, 100%), 222 (10), 197 (15), 196 (32) and 194 (14).

cis/trans-*4-(3-Amino-3-carboxycyclopentyl)butanoic Acid Hydrochloride* (9d): mp 182-183°C (MeOH/ether); ν (KBr) 3500-2500 (OH, NH) and 1720 cm^{-1} (C=O); δ_H (d^4-MeOH) 1.95 (m, 13H, 6xCH_2, CH); δ_C (d^4-MeOH) 24.9, 25.0, 32.8, 33.3, 34.9, 35.2, 40.4, 42.0, 44.2, 43.4 (6xCH_2), 36.9, 37.4 (CH), 65.4, 65.8 (CN), 174.6 and 177.4 (2xCO_2); *m/z* (DC, NH_3) 216 (*M*+-Cl+H, 100%) and 170 (36).

cis-*1-Aminocyclohexane-1,4-dicarboxylic Acid Hydrochloride* (10a): mp 270-271°C (MeOH/ether); ν (KBr) 3500-2500 (OH, NH), 1690 and 1615 cm^{-1} (C=O); δ_H (D_2O) 2.20 (m, 8H, 4xCH_2) and 2.82 (m, 1H, CH); δ_C (D_2O) 23.8, 31.8 (4xCH_2), 41.8 (CH), 63.4 (CN), 177.6 and 183.0 (2xCO_2); *m/z* 216 (*M*+-Cl+H, 100%) and 170 (36); *m/z* (DC, NH_3) 188 (*M*+-Cl+H, 100%), 170 (12) and 142 (10).

cis-*4-Amino-4-[(1H-tetrazol-5-yl)methyl]cyclohexanecarboxylic Acid Hydrochloride* (10b): mp >200°C (MeOH/ether); ν (KBr) 3500-2500 (OH, NH), 1750 and 1730 cm^{-1} (C=O); δ_H (d^4-MeOH) 1.48, 1.78, 2.10 (3m, 9H, 4xCH_2, CH) and 2.98 (d, *J*=7.0 Hz, 2H, CH_2CN_4); δ_C (d^4-MeOH) 26.8, 30.4,

31.7 (3xCH_2), 36.2 (CH), 60.5 (CN), 156.2 (CN_4H) and 173.0 (CO_2); *m/z* (FAB) 226 (*M*+-Cl+1, 76%), 180 (11), 176 (19), 171 (59), 155 (31), 154 (100), 152 (13), 139 (19), 124 (14), 121 (11), 120 (15), 107 (28), 91 (15), 90 (18), 89 (25), 78 (12) and 77 (23) (Found, FAB+: *M*+-Cl+1, 226.1320. $C_9H_{15}N_5O_2$ requires 226.1304).

cis-*2[(4-Amino-4-carboxy)cyclohexyl]acetic Acid Hydrochloride* **(10c)**: mp >270°C (MeOH/ether); ν (KBr) 3500-2500 (OH, NH) and 1735 cm^{-1} (C=O); δ_H (d^4-MeOH) 1.80 (m, 9H, 4xCH_2, CH) and 2.35 (d, *J*=7.0 Hz, 2H, CH_2CO_2); δ_C (d^4-MeOH) 26.9, 31.9, 41.4 (5xCH_2), 34.0 (CH), 60.6 (CN), 174.1 and 176.1 (CO_2); *m/z* (DC, NH_3) 202 (*M*+-Cl+H, 67%), 157 (10) and 156 (100).

cis-*[2-(4-Amino-4-carboxycyclohexyl)ethyl]-1H-tetrazole Hydrochloride* **(10d)**: mp >200°C (MeOH/ether); ν (KBr) 3400-2500 (OH, NH) and 1735 cm^{-1} (C=O); δ_H (d^4-MeOH) 1.25 (m, 11H, 5xCH_2, CH) and 2.71 (t, *J*=7.5 Hz, CH_2CN_4); δ_C (d^4-MeOH) 20.9, 26.64, 31.5 (5xCH_2), 34.0 (CH), 60.9 (CN), 157.9 (CN_4H) and 175.6 (CO_2); *m/z* (DC, NH_3) 240 (*M*+-Cl+H, 94%), 239 (12), 198 (12), 197 (100), 196 (32), 194 (23), 187 (10), 153 (15), 152 (10), 151 (69), 139 (19), 108 (17), 102 (10), 96 (10), 85 (39), 82 (10) and 56 (20).

cis-*3-(4-Amino-4-carboxycyclohexyl)propanoic Acid Hydrochloride* **(10e)**: mp 245-246°C (MeOH/ether); ν (KBr) 3500-2500 (OH, NH), 1750 and 1700 cm^{-1} (C=O); δ_H (d^4-MeOH) 1.20, 1.40, 1.60, 1.75, 2.00, 2.10 (5m, 11H, 5xCH_2, CH) and 2.35 (t, *J*=7.0 Hz, 2H, CH_2CO_2); *m/z* (DC, NH_3) 216 (*M*+-Cl+H, 100%), 184 (11) and 170 (40).

cis-*2(4-Amino-4-carboxycyclohex-1-yl)ethanephosphonic Acid Hydrochloride* **(10f)**: mp > 240°C (MeOH/acetone); ν (KBr) 3500-2500 (OH, NH), 1750 and 1535 cm^{-1} (C=O); δ_H (d^4-MeOH) 1.60 (m, 11 H, 5xCH_2, CH); δ_C (d^4-MeOH) 25.4 (d, J_{CP}=140.0 Hz, CH_2P), 27.0 (2xCH_2CHCH_2CH_2P), 30.4 (d, J_{CP}=4.5 Hz, CH), 32.1 (2xCH_2CN), 37.7 (d, J_{CP}=16.5 Hz, CH_2CH_2P), 60.9 (CN) and 174.4 (CO_2); *m/z* 252 (*M*++1, 18%), 206 (19), 171 (24), 170 (13), 155 (29), 154 (100), 152 (12), 139 (16), 138 (37), 124 (11), 120 (13), 107 (26), 91 (15), 90 (16), 89 (23), 78 (11) and 77 (23) (Found, FAB+: *M*+-Cl+1, 252.1002. $C_9H_{18}NO_5P$ requires 252.1001).

cis/trans-*1-Aminocycloheptane-1,4-dicarboxylic Acid Hydrochloride* **(11a)**: mp 207-209°C (MeOH/ether); ν (KBr) 3500-2500 (OH, NH), 1750 and 1700 cm^{-1} (C=O); δ_H (d^4-MeOH, D_2O) 2.05 (m, 11H, 5xCH_2, CH); δ_C (d^4-MeOH, D_2O) 20.1, 20.5, 23.6, 24.2, 31.7, 31.8, 32.3, 34.3, 34.7 (5xCH_2), 45.2, 45.6 (CH), 62.6, 62.7 (CN), 174.7, 179.9 and 180.1 (2xCO_2); *m/z* (DC, NH_3) 202 (*M*+-Cl+H, 28%), 184 (100) and 156 (56).

cis/trans-*2(4-Amino-4-carboxycycloheptyl)acetic Acid Hydrochloride* **(11b)**: mp 160-162°C (MeOH/ether); ν (KBr) 3500-2500 (OH, NH), 1750, 1710 and 1590 cm^{-1} (C=O); δ_H (d^4-MeOH) 1.75 (m, 13H, 6xCH_2, CH); δ_C (d^4-MeOH) 20.2, 20.7, 27.1, 27.8, 32.4, 32.9, 34.3, 34.9, 35.3, 35.5, 37.2, 37.7 (6xCH_2), 34.3, 34.9 (CH), 62.6, 62.7 (CN), 174.7, 179.9 and 180.1 (2xCO_2); *m/z* (DC, NH_3) 216 (*M*+-Cl+H, 81%), 171 (10) and 170 (100).

cis/trans-*2(4-Amino-4-carboxycycloheptyl)ethanephosphonic Acid Hydrochloride* **(11d)**: mp >200°C (MeOH/ether); ν (KBr) 3500-2500 (OH, NH), 1700 and 1515 cm^{-1} (C=O); δ_H (d^4-MeOH) 1.75 (m, 15H, 7xCH_2, CH); δ_C (d^4-MeOH) 24.5, 25.2, 26.9, 27.1, 29.5, 29.9, 31.1, 31.9, 33.7, 36.8, 37.3, 38.7, 39.3, 39.9, 40.0, 45.3, 45.4, 45.8, 45.9 (very complicated to be assigned), 66.4 (CN) and 177.3 (CO); *m/z* 283 (DC, NH_3) (*M*+-Cl+H, 54%), 184 (50), 170 (30), 160 (70), 156 (100), 148 (10), 142 (20), 118 (18), 114 (34), 104 (10), 72 (19), 70 (19) and 68 (31).

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