Tetrahedron Vol. 48, No. 39, pp. 8471-8490, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Synthesis and CCK-B Binding Affinities of Cyclic Analogues of the Potent and Selective CCK-B Receptor Antagonist CI-988.

Eric Didier, David C. Horwell and Martyn C. Pritchard*
Parke Davis Neuroscience Research Centre, Addenbrookes Hospital Site,
Hills Road, Cambridge CB2 2QB, U.K.

(*Received in UK 9 July* 1992)

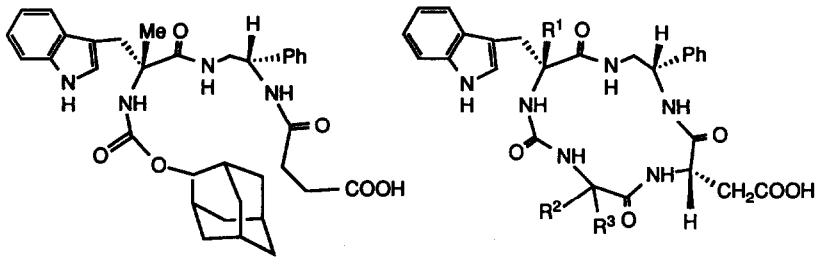
Abstract: A selected series of 14-membered macrocyclic compounds (**2**) has been prepared as potential CCK-B receptor selective ligands. The efficiency of a number of cyclising reagents has also been evaluated.

Introduction: Cholecystokinin (CCK) is one of the most widely distributed members of the brain-gut family of peptides. It is found in a number of mammalian species where it is putatively involved in the modulation of many physiological processes[1]. Although CCK occurs in a variety of molecular forms it is the sulphated C-terminal octapeptide CCK-26-33 that predominates in the mammalian CNS[2].

Our approach[3] to the design of small molecule "peptoid" analogues of CCK- 26-33 has led to the synthesis of potent and selective CCK-B antagonists displaying antigastrin[4] and anxiolytic[5] properties. A representative member of this series, CI-988 (**1**) (***Figure 1***) has high affinity (1.7nM) and selectivity (CCK-A/B ratio 2500:1) for the CCK-B receptor and is currently undergoing clinical trials.

Extensive ^{1}H NMR spectroscopy carried out on this compound exhibited an nOe between the proton on the adamantyl ring adjacent to oxygen and the proton(s) α to the amide group of the succinate side chain. This close through space proximity of the adamantyl and succinate moieties was further substantiated by X-ray crystallography[6]. The interatomic distance between the respective carbon atoms on the adamantyl and succinate groups in the X-ray was measured at 4.56 Å. In order to investigate whether the conformation seen in solution (^{1}H NMR) and in the solid state (X-ray) is that adopted at the receptor site, we designed a 14-membered macrocyclic analogue (**2e**) that covalently links the adamantyl and succinate groups. Computer asssisted molecular modelling suggested that the macrocycle (**2e**) closely overlays the X-ray of CI-988 (the urea moiety is prefered over the corresponding urethane found in CI-988 due to ease of synthesis). In addition to (**2e**), we intended to synthesize further cyclic analogues (**2a-d**)(**Figure 1**)of CI-988. These componds would help determine the role of the α-methyl and adamantyl moieties in receptor binding.

This paper describes the synthesis of these selected macrocyclic compounds and also investigates the effectiveness of a variety of reagents used for macrolactamisations.



(1) (2)

(2a) R^1=H R^2,R^3= H

(2b) R^1=Me R^2,R^3= H

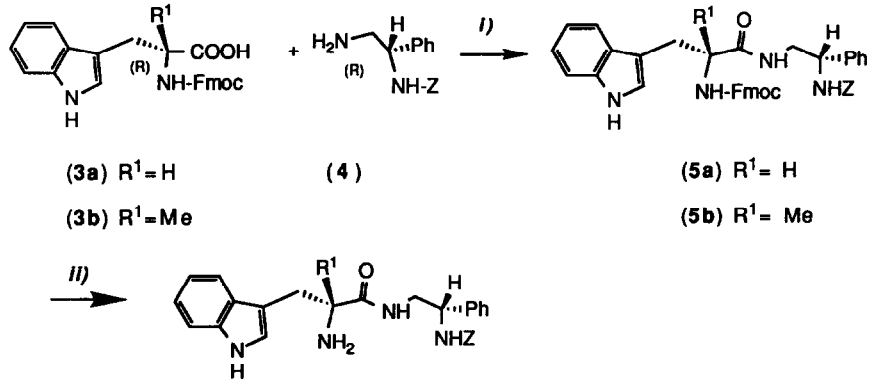
(2c) R^1=H R^2,R^3= cyclohexyl

(2d) R^1=Me R^2,R^3= cyclohexyl

(2e) R^1=Me R^2,R^3= adamantyl

Figure 1

Synthesis of acyclic precursors. As described in ***Scheme 1*** the first step involved the coupling reactions of the N-Fmoc-(R)-tryptophan derivatives (**3a**) and (**3b**) with the N-benzyloxycarbonyl-(R)-diamine (**4**)[3] by the DCC/HOBt method to afford (**5a**) and (**5b**) in 89 and 97 % yields respectively. Deprotection of the Fmoc group was achieved by piperidine in DMF to give the compounds (**6a**) and (**6b**) in 80 and 89% yields respectively.



(**3a**) R^1=H (**4**) (**5a**) R^1= H

(**3b**) R^1=Me (**5b**) R^1= Me

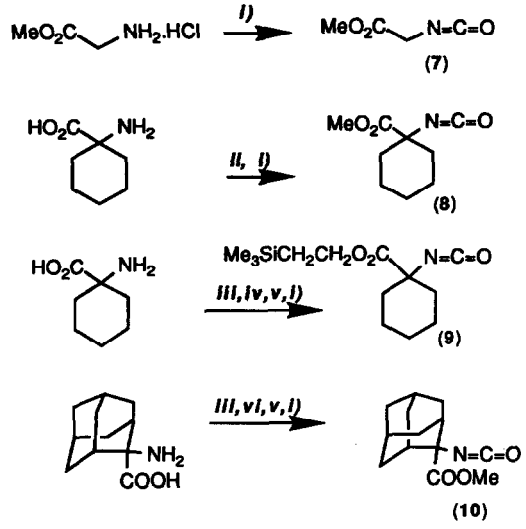
(**6a**) R^1=H

(**6b**) R^1=Me

Scheme 1

Reagents and conditions: *i) DCC, HOBt, EtOAc-THF; ii) piperidine, DMF.*

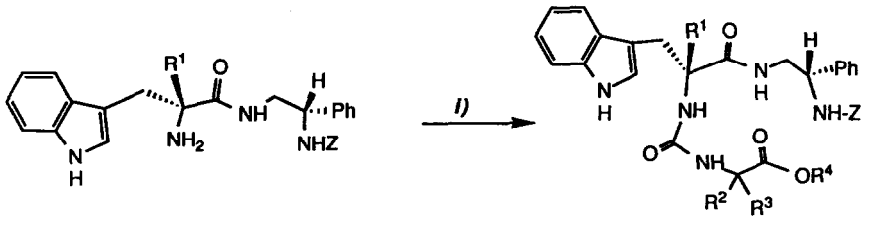
Z=PhCH$_2$OCO-



Scheme 2

Reagents and conditions: *i) bis (trichloromethyl)carbonate, Et_3N, CH_2Cl_2 or THF, 25°C or reflux ; ii) $SOCl_2$, MeOH, reflux; iii) $PhCH_2OCOCl, NaOH_{aq.}$; iv) trimethysilylethanol, DCC, DMAP, acetonitrile/DMF; v) H_2, 45 -60 psi, 20% Pd (OH) $_2$ /C , isopropanol, 25 -60°C; vi) diazomethane, THF, 0°C.*

In the next steps, the methyl or trimethylsilylethanol[7] ester isocyanates (**7**),(**8**),(**9**) and (**10**), prepared as shown in ***Scheme 2***, were reacted with the amines (**6a**) and (**6b**) to give the corresponding ureas (**11a-f**) in good yields (***Scheme 3***, ***Table 1***). Reactions with the volatile isocyanate (**7**) had to be performed in a closed vessel.



(**6a-b**) (**11a-f**)

Scheme 3

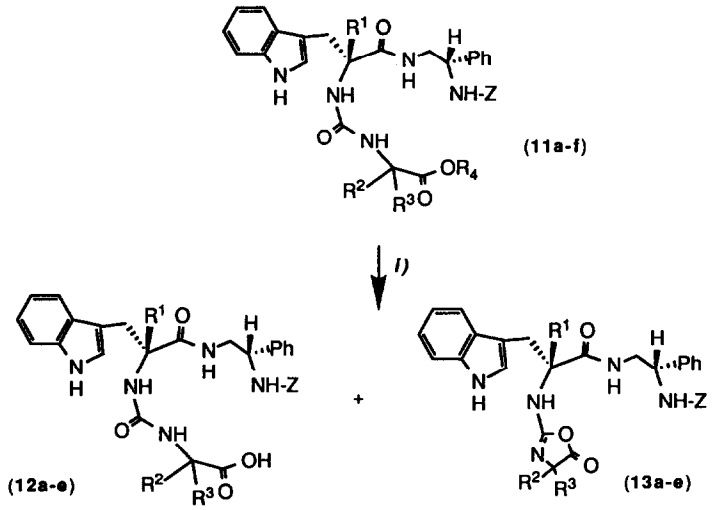
Reagents and conditions: *i) isocyanate (7), (8) , (9) or (10),toluene or THF, 80-100°C.*

Table 1: Preparation of Ureas (11a-f) from Amines (6a) and (6b)

Amine	Isocyanate	Urea	R^1	R^2	R^3	R^4	Yield
(6a)	(7)	(11a)	H	H	H	Me	83%
(6b)	(7)	(11b)	Me	H	H	Me	79%
(6a)	(8)	(11c)	H	cyclohexyl		Me	87%
(6b)	(8)	(11d)	Me	cyclohexyl		Me	87%
(6a)	(9)	(11f)	H	cyclohexyl		Tmse[a)]	81%
(6b)	(10)	(11e)	Me	2-adamantyl		Me	92%

a) Tmse: 2-(trimethylsilyl)ethyl.

Hydrolysis of the methyl esters (**11a-e**) (***Scheme 4***) was achieved using lithium hydroxide in THF/water or methanol/water as indicated in ***Table 2***. In the case of R^2,R^3 geminally substituted derivatives, formation of the corresponding 5-(4H)-oxazolones (**13c-e**) by intramolecular cyclisation was observed. Thus, alkali promoted hydrolysis of the methyl ester (**11d**) in THF/water at 25°C, gave a mixture of the acid (**12d**) and oxazolone (**13d**). The acid/oxazolone ratio was found to increase with temperature in THF/water indicating that the acid is the thermodynamic product. Hydrolysis at 0°C as well as the use of methanol/water as solvent system afforded exclusively the oxazolone (**13d**) (kinetic product).



Scheme 4

Reagent: i) LiOH (see Table 2 for conditions).

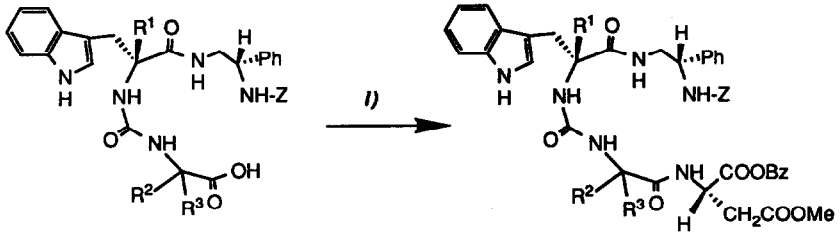
Table 2: Ester Hydrolysis [(11a-f) → (12a-e) + (13a-e)]

	R^1	R^2	R^3	R^4	Conditions	Isolated yields (%)
(**11a**)	H	H	H	Me	2 eq. LiOH,H_2O:THF: 1:3, 25°C	(**12a**)95;(**13a**)--
(**11b**)	Me	H	H	Me	2 eq. LiOH,H_2O:THF: 1:2, 25°C	(**12b**)92;(**13b**)--
(**11c**)	H	cyclohexyl		Me	2.1 eq. LiOH,H_2O:THF:1:2, 25°C	(**12c**)--;(**13c**)93
(**11d**)	Me	cyclohexyl		Me	1.0 eq. LiOH,H_2O:THF:1:3, 0°C	(**12d**)--;(**13d**)95
					2.1 eq. LiOH,H_2O:THF:1:3,25°C	(**12d**)45;(**13d**)55
					1.1 eq. LiOH,H_2O:THF:1:3, 40°C	(**12d**)69;(**13d**)29
					1.0 eq, LiOH. H_2O:MeOH:1:3,25°C	(**12d**)--;(**13d**)95
(**11f**)	H	cyclohexyl		Tmse	1.0 eq. (n-Bu)$_4$NF,1M in THF,0°C	(**12c**)--;(**13c**)95
					10 eq. TFA, CH_2Cl_2, 25 °C	(**12c**)95;(**13c**)--
(**11e**)	Me	2-adamantyl		Me	1.1 eq. LiOH,H_2O:THF:1:3,25°C	(**12e**)--;(**13e**)95
					1.1 eq. LiOH,H_2O:THF:1:3,60°C	(**12e**)--;(**13e**)95

Alkali promoted hydrolysis of methyl esters (**11c**) and (**11e**) and neutral tetra-butyl ammonium fluoride promoted hydrolysis of the trimethylsilylethanol ester (**11f**) afforded exclusively the corresponding oxazolone (**13c**), whereas the trifluoroacetic acid mediated hydrolysis of the ester (**11f**) gave exclusively the desired carboxylic acid (**12c**). However, when R^2,R^3 is hydrogen (**11a** and **11b**), the hydrolysis proceeded smoothly to yield exclusively the corresponding carboxylic acids (**12a**) and (**12b**).

These results suggest that in basic or neutral conditions, disubstitution at R^2,R^3 tends to place the terminal carboxyl group and the urea carbonyl group in close proximity, thus favouring cyclisation to an oxazolone by the "*gem*-dialkyl"[8] or "Thorpe-Ingold" effect. Further attempts to obtain the carboxylic acid (**12e**) from the methyl ester (**11e**) using iodotrimethylsilane[9], lithium iodide/NaCN in DMF[10] or enzymes like pig liver esterase and α-chymotrypsin proved unsuccessful.

The carboxylic acids (**12a-d**) were then coupled to 4-methyl-1-(phenylmethyl)-L-aspartate (**14**) using benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate (BOP reagent)[11] in DMF to give the corresponding amides (**15a-d**) (**Scheme 5, Table 3**) without detectable loss of optical purity as indicated by high field ^{1}H NMR.



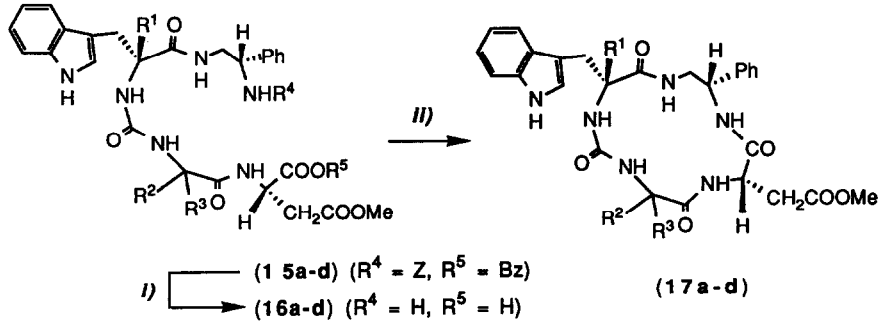
Scheme 5

Reagents and conditions: *i) 4-methyl-1-(phenylmethyl)-L-aspartate (14),BOP, diisopropylethylamine,DMF.*

Table 3: Coupling Reactions [(12a-d) + (14) → (15a-d)].

Acid	R^1	R^2	R^3	Yield
(12a)	H	H	H	(15a) 83%
(12b)	Me	H	H	(15b) 77%
(12c)	H	cyclohexyl		(15c) 80%
(12d)	Me	cyclohexyl		(15d) 90%

Macrolactamisations: After concomitant removal of the N- and C-terminal protecting groups of (**15a-d**) by catalytic hydrogenation, the amino acids (**16a-d**) were cyclized using a variety of reagents (***Scheme 6 ,Table 4***).



Scheme 6

Reagents and conditions:i) *H_2, 45 psi, 20% Pd(OH) $_2$/C , EtOH ; ii) macrolactamization ; (See Table 4) .*

Macrolactamizations of the amino-acid (**16b**) (1mM in DMF) to give (**17b**) using five different reagents, show that diphenylphosphoryl azide (DPPA)[12] (***run 3***) and BOP[13] reagents (***run 6***) are the

most efficient. Cyclisation using DCC or Mukaiyama's 2-chloro-1-methylpyridinium iodide [14] gave only moderate yields (***runs 7,8***). The use of bis(trichloromethyl) carbonate as a precursor of phosgene[15] proved to be the least satisfactory reagent (***run 9***).

With the DPPA reagent, concentrations in the range of 8 to 10 mM resulted in the highest yields (63 to 71 %, ***runs 5,10,12,13***). Increasing the concentration to 20mM resulted in a much poorer yield (26%, ***run 14***) and in lower diastereoselectivity.

Table 4 : Macrolactamizations [(16a-d) → (17a-d)].

Run	Reaction	R^1	R^2	R^3	Method	Conc.(M)	Yield	d.e.[a]
1	**(16a)→(17a)**	H	H	H	A[b]	0.008	- - -	- - -
2					B[b]	0.008	- - -	- - -
3	**(16b)→(17b)**	Me	H	H	A	0.001	54 %	99%
4					A	0.008	50 %	- - -
5					A	0.01	71%	99%
6					B	0.001	49 %	- - -
7					C	0.001	40 %	98%
8					D	0.001	31 %	95%
9					E	0.001	12 %	- - -
10	**(16c)→(17c)**	H	cyclohexyl		A	0.008	71 %	52%
11					B	0.008	63 %	88%
12	**(16d)→(17d)**	Me	cyclohexyl		A	0.008	68%	95%
13					A	0.01	63 %	- - -
14					A	0.02	26 %	- - -
15					B	0.008	61 %	98%
16					c[c]	0.001	48 %	- - -
17					E	0.001	20 %	- - -

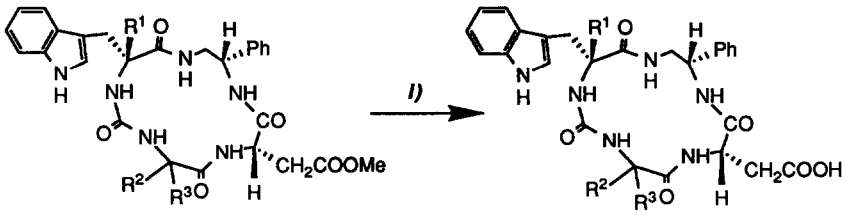
Methods: A) DPPA, $NaHCO_3$, DMF, 0°C, 72h.; B) BOP, diisopropylethylamine, DMF, 72 h.; C) 2-chloro-1-methylpyridinium iodide, Et_3N, DMF, 24 h.; D) DCC, HOBt, DMF, 72h.; E) bis (trichloromethyl) carbonate, THF, 24h.

a) determined by HPLC ; b) detected by mass spectra (FAB); c) as method C) in THF.

Comparison between the BOP and DPPA reagents shows that BOP reagent consistently gives slightly inferior yields to DPPA for a given concentration (***runs 6,11,15***) but less epimerisation was observed with BOP. Thus cyclisation of (**15c**) gave a diastereoisomeric mixture in both cases but a better diastereoselectivity was obtained with BOP (d.e.=88%, ***run 11***) than with DPPA (d.e.=54%, ***run 10***). Cyclisation of (**16a**) with BOP or DPPA proved unsuccessful yielding a poor mixture containing only minor quantities of the desired macrolactam (**17a**). (detected by mass spectroscopy (FAB)).

These results suggest that disubstitution at R^2,R^3 and/or substitution on the α-C center of the tryptophan residue favours the desired macrolactamisations.

Finally, the methyl esters (**17b-d**) were hydrolyzed by lithium hydroxide in THF/water to give the corresponding target carboxylic acids (**2b-d**) (***Scheme 7, table 5***).



(**17b-d**) (**2b-d**)

Scheme 7

Reangent and conditions i) *1.1 eq. LiOH, THF/H_2O: 3/1, 0-25°C.*

Table 5: Hydrolysis [(17b-d) → (2b-d)].

	R_1	R_2	R_3	Yield	d.e.[a]
(**2b**)	Me	H	H	68%	67 %
(**2c**)	H	cyclohexyl		71%	50 %
(**2d**)	Me	cyclohexyl		60%	67%

a) d.e. (R,R,S) of the crude product determined by ^1H NMR at 300Mhz.

Under these conditions, there was detectable amount of epimerisation at the α-carbon of the aspartate residue, presumably due to direct acidic α-proton abstraction by the base. In the case of hydrolysis of (**17d**), the (R,R,R)-diastereoisomer (**2g**) has been separated and obtained in pure form.

Biological Data: CCK-B binding data from the four macrocyclic compounds synthesized (***Table 6***) shows them all to have considerably lower binding affinity for the CCK-B receptor than the acyclic parent CI-988. The optimum compound in this series has a binding affinity approximately three orders of magnitude less than CI-988. We were unable to synthesize the adamantyl analogue (**2e**) using these procedures.

Table 6: CCK-B Binding Data[a)]

Compound	R^1	R^2	R^3	$IC_{50}(\mu M)$
IC-988 (1)	Me	-	-	0.0017
(2b)	Me	H	H	IA at 10^{-6}M
(2c)	H	cyclohexyl		IA at 10^{-6}M
(2d)	Me	cyclohexyl		4.1
(2g)[b)]	Me	cyclohexyl		7.8

a) IC_{50} represents the concentration producing half-maximal inhibition of specific binding of [^{125}I] Bolton-Hunter CCK-8 to CCK receptors in the mouse cerebral cortex. b) R configuration at the Asp residue.

Conclusion: In this paper, we have synthesized a number of 14-membered macrocyclic compounds as CCK-B ligands. We have employed several different methods for the macrolactamisation steps and have found BOP to be the optimum reagent for these reactions.

We can, of course, only speculate on the reasons for the low CCK-B receptor affinities of the macrocyclic compounds prepared. However, these results appear not to support the hypothesis that the conformation seen in solution (^{1}H NMR) and in the solid state (X-ray) of CI-988 is similar to the conformation adopted at the CCK-B receptor site.

Experimental section

General:
Melting points and boiling points are uncorrected. Melting points were determined with a Reichert Thermovar hot-stage apparatus. Bulb-to-bulb distillations were performed on a Büchi GKR-50 apparatus. Optical rotations were measured on a Perkin Elmer Model 241 polarimeter.
Flash chromatography was performed on Silica Gel 60 (Merck, 230-400 mesh), analytical TLC on Silica Gel 60 F_{254} (Merck), reversed phase silica gel chromatography on Lichroprep RP 18 (230-400 mesh, Merck 13900) and HPLC on Spherisorb 5 ODS 2 (Technical) using gradiant of acetonitrile/ water-TFA 0.1 %. as eluant. The organic solutions were dried using $MgSO_4$.
IR spectra were recorded with the compound on a sodium chloride disk and a Perkin Elmer 1750 FT-IR spectrophotometer, ^{1}H NMR spectra on Bruker AM 300 spectrometer and mass spectra (FAB) on a Finnigan 4500 spectrometer (accurate mass of $(M+H)^+$ or $(M+Na)^+$ is given with relative intensity). Elemental analysis were determined by CHN Analysis Limited, Leicester,UK.

Experimental procedures and characterisation of products:
9H-Fluoren-9-ylmethyl [R-(R*,R*)]- 3-(1H-Indol-3-ylmethyl)-4,9-dioxo-7,11,-diphenyl-10-Oxa-2,5,8-triazaundecanoate (5a): To a solution of commercialy available Fmoc-(R)-Trp-OH (4.90g,11.5 mmol) in EtOAc (100ml) and THF (10ml), was added hydroxybenzotriazole hydrate (HOBt.H_2O) (1.70g,12.6mmol), followed by the dropwise addition of dicyclohexylcarbodiimide (DCC)(2.70g,11.9mmol) in EtOAc (30ml). The resulting solution was stirred at 25°C for 2 hours. The dicyclohexylurea (DCU) was filtered off and the amine (4)[3)] (3.10g, 11.5 mmol) was added to the

solution. The solution was stirred for 17 hours at 25°C, filtered and the solid dried to give (**5a**) (6.95, 89%) which was directly used in the next step. An aliquot was purified by chromatography in THF/hexane for analysis. M.p. 183-184°C; $[\alpha]^{23}_D$ = -11.0° (c=0.40,THF); IR (film): 3320 cm^{-1} (NH), 1694 cm^{-1} (NCOO), 1658 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6) δ : 2.80-3.03 (m,2H,C$\underline{H}_2$-NH); 3.24-3.58 (m,2H, C$\underline{H}_2$-Ind.); 4.07-4.34 (m, fluorenyl-C$\underline{H}_2$ + C$\underline{H}$-Ar$_2$ + C$\underline{H}$); 4.74 (m,1H,C$\underline{H}$-Ar); 4.98 (s,2H,Ar-C$\underline{H}_2$-O); 6.92-7.94 (m,25H, Ar-$\underline{H}$ + CON$\underline{H}$); 8.07 (s,1H,CON$\underline{H}$); 10.79 (s,1H,N$\underline{H}$-Ind.); MS (FAB): m/z calcd for ($C_{42}H_{38}N_4O_5$ + H)$^+$: 679.8026; found: 679.2920 (100).

9H-Fluoren-9-ylmethyl[R-(R*,R*)]3-(1H-indol-3-ylmethyl)-3-methyl-4,9-dioxo-7,11-diphenyl-10-Oxa-2,5,8-triazaundecanoate (5b): was prepared from Fmoc-(R)-α-methyl-Trp-OH (13.5g,36.7mmol) in the same manner as for (**5a**): (20.6g,97%); M.p. 85-87°C; $[\alpha]^{23}_D$ = -2.5° (c=0.99,MeOH); IR (film): 3343 cm^{-1} (NH), 1705 cm^{-1} (NCOO), 1660 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6) δ : 1.15 (s,3H,C$\underline{H}_3$): 3.05-3.41 (m,4H,C$\underline{H}_2$-NH + C$\underline{H}_2$-Ind.); 4.17 (m,2H, fluorenyl-C$\underline{H}_2$); 4.40 (m,1H,C$\underline{H}$); 4.73 (m,1H,C$\underline{H}$-Ar); 4.95 (s,2H,Ar-C$\underline{H}_2$-O); 6.85-7.95 (m,26H, Ar-$\underline{H}$ +CON$\underline{H}$); 10.80 (s,N$\underline{H}$-Ind.); $C_{43}H_{40}N_4O_5$ (692.82); MS (FAB): m/z calcd for ($C_{43}H_{40}N_4O_5$ + H)$^+$: 693.8296; found 693.3077 (35).

Phenylmethyl[R-(R*,R*)]-[2[[2-amino-3-(1H-indol-3-yl)-1-oxopropyl]amino]-1-phenylethyl]-carbamate(6a): The N-Fmoc derivative (**5a**) (5.87g, 8.65mmol) was dissolved in DMF (100ml) and cooled to 0°C. Piperidine (0.74g, 8.65mmol) in DMF (10ml) was added dropwise over 15 minutes at 0°C and stirred for 17 hours. The DMF was evaporated and the residue was dissolved in EtOAc. After washing with brine, drying and evaporating, the crude product was purified by column chromatography in CH_2Cl_2/MeOH 5% to give (**6a**) as a foam (3.80g,89%).

M.p.123.5°C; $[\alpha]^{22}_D$ = -30.2° (c=0.30,MeOH); IR (film): 3320 cm^{-1} (NH), 1706 cm^{-1} (NCOO), 1652 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6) δ: 1.59 (s,N$\underline{H}_2$); 2.61 (m,1H,C$\underline{H}_2$-NH); 3.02 (m,1H,C$\underline{H}_2$-NH); 3.20-3.47 (m,3H, C$\underline{H}_2$-Ind. + C$\underline{H}$); 4.69 (m,1H,-C$\underline{H}$); 5.00 (m,2H,Ar-C$\underline{H}_2$-O); 6.90-7.40 (m,14H, Ar-$\underline{H}$); 7.50 (d,J=7.5Hz,1H,Ar-$\underline{H}$); 7.83 (d,J=8Hz,CON$\underline{H}$) 8.00 (s,CON$\underline{H}$); 10.80 (s,N$\underline{H}$-Ind.); Anal. found: C,69.92; H,6.06; N,11.93; Calcd for $C_{27}H_{28}N_4O_3$: C,71.03; H,6.18; N,12.27.

Phenylmethyl[R-(R*,R*)]-[2[[2-amino-3-(1H-indol-3-yl)-2-methyl-1-oxopropyl]amino]-1-phenylethyl]-carbamate(6b): was prepared from (**5b**) (20.5g, 29.6mmol) in the same manner as for (**6a**): (11.2g,80%); M.p. 59-62°C; $[\alpha]^{22}_D$ = + 82° (c=1.0,$CHCl_3$); IR (film): 3320 cm^{-1} (NH), 1703 cm^{-1} (NCOO), 1648 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6) δ : 1.16 (s,3H,C$\underline{H}_3$)1.67 (s,2H,N$\underline{H}_2$); 2.78 (m,1H,C$\underline{H}_2$-NH); 3.06 (m,1H,C$\underline{H}_2$-NH); 3.32 (s,2H,C$\underline{H}_2$-ind.); 4.68 (m,1H, C$\underline{H}$); 5.00 (m,2H,Ar-C$\underline{H}_2$-O); 6.90-7.15 (m,3H,Ar-$\underline{H}$); 7.15-7.50(m,11H, Ar-$\underline{H}$); 7.52 (d,J= 8Hz 1H,Ar-$\underline{H}$); 7.78 (d,J=7.5Hz,CON$\underline{H}$) 7.98 (m,CON$\underline{H}$); 10.83 (s,1H,N$\underline{H}$-Ind.) $C_{28}H_{30}N_4O_3$; Anal. found: C,70.45; H,6.42; N,11.56; Calcd for $C_{28}H_{30}N_4O_3$: C,71.47; H,6.43; N,11.91.

Methyl α-isocyanato ethanoate(7): Glycine methylester hydrochloride (12.0g,100mmol) was refluxed in THF (200ml) in the presence of triethylamine (14ml,100mmol) for 30 minutes. Then bis(trichloromethyl) carbonate (10.0g,33.7mmol) in THF (100ml) was added dropwise and the mixture refluxed for 3 hours. Et_3N (28ml) in THF (50ml) was added and the mixture was refluxed for an additional hour. After filtration and evaporation of the solvent, the crude oil was bulb-to-bulb distilled to give (7) as a colorless oil (6.2g, 54%). B.p. 50°C / 1mbar; IR (film): 2256 cm^{-1} (N=C=O), 1752 cm^{-1} (COO); ^1H NMR (300Mhz, $CDCl_3$) d 5.30 (s,5H,C$\underline{H}_2$ + C$\underline{H}_3$); Anal. found: C,41.49; H,4.38; N,12.17; Calcd for $C_4H_5NO_3$: C,41.75; H,4.38; N,12.17.

Methyl 1-isocyanato-1-cyclohexane carboxylate (8): 1-Amino-1-cyclohexane carboxylic acid (25g,174mmol) was dissolved in methanol and thionyl chloride (35ml,552mmol) was added dropwise at -10°C. The mixture was refluxed for 4 hours and the solvent removed *in vacuo*. The residue was slurried in $NaHCO_3$ sol. and extracted with EtOAc to yield a crude colorless oil (20.5g,75%). The crude amino ester (20.5g,130mmol) was dissolved in dichloromethane (500ml). Et_3N (18.2ml,130mmol), bis(trichloromethyl) carbonate (12.8g,43mmol) were added at 0°C. The mixture was stirred overnight at

25°C and the solvent was removed *in vacuo*. The residue was redissolved in EtOAc and the precipitate was filtered off. After evaporating, the product was purified by bulb-to-bulb distillation to yield (8) as a colorless oil (10.2g, 55mmol,32 %).

B.p. 68-70°C/ 2 mbar; IR (film): 2255 cm^{-1} (N=C=O), 1741 cm^{-1} (COO); ^1H NMR (300Mhz, $CDCl_3$) δ : 1.52-1.90 (m,10H,C$\underline{H}_2$cycl.);3.80 (s,3H,C$\underline{H}_3$); Anal. found: C,58.84; H,7.06; N,7.44; Calcd for $C_4H_5NO_3$: C,59.00; H,7.15; N,7.65.

2-(Trimethylsilyl)ethyl-1-isocyanato-1-cyclohexane carboxylate(9): 1-Amino-1-cyclohexane carboxylic acid (15g,105mmol) was treated with benzyloxychloroformate (18g,105mmol) according to the usual procedure[16] to give the N-protected derivative (15g,52%): M.p.: 138-139°C (CH_2Cl_2:n-hexane); IR (film): 3330 cm^{-1} (OH,NH); 1713 cm^{-1} (COO); 1H NMR (300 Mhz, DMSO-d_6) : δ 1.10-1.72 (m,8H, C$\underline{H}_2$cycl.); 1.87-2.06 (m,2H,C$\underline{H}_2$cycl.); 5.00 (s,2H,OC$\underline{H}_2$); 7.26-7.45 (m,6H,Ar-$\underline{H}$ + CON$\underline{H}$); 12.20(s,COO$\underline{H}$); Anal. found: C,64.96; H,6.84; N,5.06; Calcd for $C_4H_5NO_3$: C,64.97; H,6.91; N,5.05. The intermediate (9.3g,33mmol) was suspended in acetonitrile (20ml) and DMF was added to complete dissolution. Then DCC (7.6g,37mmol), 4-dimethylaminopyridine (DMAP) (0.42g,34mmol) and 2-(trimethylsilyl) ethanol (4.9ml,34mmol) were added and the solution stirred at room temperature for 24 hours. The solution was filtered, the precipitate washed with EtOAc and after evaporation of the solvents, the residue was dissolved in EtOAc. The solution was successively washed with 2N HCl, saturated aqueous $NaHCO_3$ solution and brine. After drying and evaporating the crude product was purified by flash chromatography in EtOAc:n-hexane 1:4 to give the crystalline ester (8.7g, 68%) : M.p.: 62°C; IR (film): 3353 cm^{-1} (NH);1733 cm^{-1} (COO);1717 cm^{-1} (NCOO); 1H NMR(300 Mhz, DMSO-d_6) : d 0.01 (s,9H,C$\underline{H}_3$): 0.85 (m,2H,C$\underline{H}_2$-Si): 1.20 -1.90 (m,10H, C$\underline{H}_2$cycl.); 4.05 (m,2H,Ar-C$\underline{H}_2$-O); 5.00 (s,2H,Ar-C$\underline{H}_2$-O); 7.30 (m,5H,Ar-$\underline{H}$); 7.50 (s, CON$\underline{H}$); $C_{20}H_{31}NO_4Si$;Anal. found: C,63.66; H,8.19; N,3.72; Calcd for $C_{20}H_{31}NO_4Si$: C,63.63; H,8.28; N,3.71. The derivative (8.7g,23mmol) was hydrogenated in isopropanol (250ml) at 45 psi and 25 °C for 17 hours in the presence of 20% $Pd(OH)_2$/C (1g) to give the title ester(9) (5.5g,99%) as an oil: B.p.: 150°C/0.1 mbar; IR (film): 3370 cm^{-1} (NH);1724 cm^{-1} (COO); 1H NMR(300 Mhz, DMSO-d_6)δ: 0.01 (s,9H,C$\underline{H}_3$): 0.90 (m,2H,C$\underline{H}_2$-Si): 1.15 -1.85 (m, C$\underline{H}_2$cycl. + N$\underline{H}_2$); 4.08 (m,2H, OC$\underline{H}_2$); Anal. found: C,58.93; H,10.20; N,5.73; Calcd for $C_{12}H_{25}NO_{2Si}$: C,59.21; H,10.35; N,5.75. The oil (2.9g,12mmol) was treated with bis(trichloromethyl) carbonate (2.4g,8mmol) and Et_3N (5ml,36mmol) in THF (100ml) at 25°C . After filtration and evaporation, the crude product was purified by flash chromatography in EtOAc: hexane 1:3 to give the isocyanate (9)(3.1g,96%).

M.p.: 37-38°C; IR (film): 2250 cm^{-1}(N=C=O), 1736 cm^{-1} (COO); 1H NMR (300 Mhz, DMSO-d_6): d 0.02 (s,9H,Si-C$\underline{H}_3$); 0.95 (m,2H,C$\underline{H}_2$-Si); 1.10-1.80 (m,10H, C$\underline{H}_2$cycl.); 4.20 (m,2H,O-C$\underline{H}_2$); Anal. found: C,58.21; H,8.62; N,4.97; Calcd for $C_{13}H_{23}NO_3Si$: C,57.96; H,8.60; N,5.20.

Methyl-2-isocyanato-2-adamantane carboxylate (10):2-Amino 2-adamantane carboxylic acid[17] (12.8g,65.8mmol) was treated with benzyloxychloroformate (11.2g,65.8mmol) in a mixture of NaOH aqueous solution and dioxan to give the N-benzyloxycarbonyl derivative (3.5g, 16%): M.p.: 161-162°C; IR (film): 3392 cm^{-1} (OH,NH); 1709 cm^{-1} (COO); 1H NMR (300 Mhz, DMSO-d_6): δ 1.40-2.50 (m,14H,$\underline{H}$-adamant.); 5.00 (s,2H,OC$\underline{H}_2$); 7.30 (m,6H,Ar-$\underline{H}$ + CON$\underline{H}$); 12.11(s,COO$\underline{H}$); Anal. found: C,69.04; H,6.89; N,4.26; Calcd for $C_{13}H_{23}NO_3Si$: C,69.26; H,7.04; N,4.25. The N-protected intermediate (3.5g,10.6mmol) was dissolved in dry THF (100ml) and cooled to 0°C. A solution in Et_2O of a slight excess of diazomethane[18] was added and the solution was stirred at 25°C for an hour. After evaporation of the solvent, the crude product was purified by flash chromatography in EtOAc:n-hexane 1:3 to give the compound as a viscous oil (3.0g,82%): B.p.: > 250°C/ 0.5 mbar; IR (film): 3332 cm^{-1} (NH); 1747 cm^{-1}(COO);1710 cm^{-1} (NCOO); 1H NMR (300 Mhz, DMSO-d_6): δ 1.45-2.48 (m,14H, C$\underline{H}_2$ + C$\underline{H}$); 3.55 (s,3H,C$\underline{H}_3$);5.00 (s,2H,OC$\underline{H}_2$); 7.30 (m,5H,Ar-$\underline{H}$); 7.52 (s, CON$\underline{H}$); Anal. found: C,69.95;H,7.34; N,4.08; Calcd for $C_{20}H_{25}NO_4$: C,69.59; H,7.50; N,4.09. The methyl ester (2.80g,8.15mmol) was hydrogenated for 24 hours at 60°C and 60psi in isopropanol(50ml), in the presence of 20% $Pd(OH)_2$/C (0.28g) to give after purification by flash chromatography in EtOAC:n-hexane 1:1 the corresponding

amine (1.6g,93%): M.p.: 58 °C (n-hexane); IR (film): 3335 cm^{-1} (NH); 1718 cm^{-1} (COO); 1H NMR (300 Mhz, DMSO-d_6): δ 1.30-2.90 (m,16H, H-adamant. + NH_2); 3.60 (s,3H,CH_3); Anal. found: C,68.80; H,9.36; N,6.65; Calcd for $C_{12}H_{19}NO_2$: C,68.86; H,9.15; N,6.69. The amine (1.5g,7.3mmol) was treated with bis (trichloromethyl) carbonate (1.4g,4.9mmol) and Et_3N (4.1ml,15mmol) in THF (150ml) at 25°C for four hours to give after purification by flash chromatography in EtOAc:n-hexane 1:3 the corresponding isocyanate (**10**) as an oil (1.7g,98%): B.p.:170°C/ 0.5 mbar; IR (film): 2251 cm^{-1} (N=C=O); 1746 cm^{-1} (COO); 1H NMR (300 Mhz, DMSO-d_6): δ 1.40-2.52 (m,14H, H-adamant.); 3.76 (s,3H,CH_3); Anal. found: C,66.58; H,7.36; N,5.74; Calcd for $C_{13}H_{17}NO_3$: C,66.36; H,7.28; N,5.95.

General procedure for the reaction of amines (6a) and (6b) with the isocyanates (7),(8),(9) and (10) (see Table 1):

In a sealed bomb, the amine (1eq.) and the isocyanate (1.3eq.) were dissolved in toluene and if necessary THF was added to complete dissolution. After heating for 16 hours at 80-100°C, the solution was cooled and the precipitate filtered, washed with toluene and dried *in vacuo*. For compounds (**11c,e,f**) the solution was evaporated *in vacuo* and the residue was purified by flash chromatography in CH_2Cl_2: MeOH 5%.

Methyl[R-(R*,R*)]-6-(1H-indol-3-ylmethyl)-4,7,12-trioxo-10,14-diphenyl-13-oxa-3,5,8,11-tetraazatetradecanoate (11a): (1.5g,83%); M.p. 189-91°C; $[\alpha]^{22}_D$ = - 33.0° (c=0.47,THF); IR (film): 3330 cm^{-1}(NH), 1737 cm^{-1} (COO) , 1706 cm^{-1} (NCOO), 1643 cm^{-1} (CONH); ^{1}H NMR (300Mhz, DMSO-d_6) δ: 2.74-3.00 (m,2H, CH_2-NH); 3.21-3.43 (m,2H,CH_2-Ind.); 3.60 (s,3H, $COOCH_3$); 3.78(d,J=7Hz,2H,NH-CH_2-COO); 4.35 (m,1H,CH); 4.70 (m1H,CH); 5.00 (m,2H,Ar-CH_2-O); 6.31-6.50 (m,2H,NH-CONH); 6.90-7.15 (m,3H,Ar-H); 7.15-7.45 (m,11H,Ar-H); 7.50 (d,J=8Hz,1H,Ar-H); 7.78 (d,J=8Hz,CONH); 8.00 (m,CONH); 10.78 (s,1H,NH-Ind.); Anal. found: C,64.90; H,5.87; N,12.27; Calcd for $C_{31}H_{33}N_5O_6$: C,65.14; H,5.82; N,12.25.

Methyl[R-(R*,R*)]-6-(1H-indol-3-ylmethyl)-6-methyl-4,7,12-trioxo-10,14-diphenyl-13-oxa-3,5,8,11-tetraazatetradecanoate (11b): (2.3g,79%); M.p. 161-162°C; $[\alpha]^{22}_D$ = + 18.9° (c=0.51,MeOH); IR (film): 3346 cm^{-1} (NH), 1745 cm^{-1} (COO), 1715 cm^{-1} (NCOO), 1665 cm^{-1} (CONH); ^{1}H NMR (300Mhz, DMSO-d_6) δ: 1.15 (s,3H,CH_3;) 3.10-3.50 (m,4H, CH_2-Ind. + CH_2-NH); 3.65 (s,3H,CH_3); 3.85 (m,2H,NH-CH_2-CO); 4.75 (m,1H,NH-CH-CO); 5.00 (m,2H,Ar-CH_2-O); 6.25 (s,1H,NH-CONH); 6.50 (m,1H, NHCO-NH) 6.85-7.15 (m,4H,Ar-H); 7.15-7.40 (m,10H,Ar-H); 7.45 (d,J=8Hz,1H,Ar-H); 7.60-7.80 (m,2H,CONH); 10.9 (s,1H,NH-Ind.); Anal. found: C,65.57; H,5.99; N,11.89; Calcd for $C_{32}H_{35}N_5O_6$: C,65.63; H,6.02; N,11.96.

Phenylmethyl[R-(R*,R*)]4-(1H-indol-3-ylmethyl)-1-[1-(methoxycarbonyl)cyclohexyl]-2,5-dioxo-8-phenyl-1,3,6,9-tetraazadecan-10-oate(11c): (4.4g,87%); M.p. 96-97°C; $[\alpha]^{23}_D$ = -14.7° (c=0.34,MeOH); IR (film): 3320 cm^{-1} (NH), 1733 cm^{-1} (COO), 1705 cm^{-1} (NCOO), 1636 cm^{-1} (CONH); ^{1}H NMR (300Mhz, DMSO-d_6) δ : 1.20 (m,1H,CH_2cyc.); 1.30-1.70 (m,7H, CH_2cyc.); 1.83 (m,2H,CH_2cyc); 2.74-3.02 (m,2H,-CH_2-NH); 3.30 (s,2H, CH_2Ind.); 3.50 (s,3H,CH_3); 4.42 (m,1H,-CH-NHCONH); 4.68 (m,1H, -CH-NHCO); 4.99 (m,2H, O-CH_2-Ar); 6.11 (d,J=8Hz,NHCO-NH-CH); 6.44 (s, NH-CONH); 6.88-7.08 (m,3H,Ar-H); 7.12-7.47 (m,11H,Ar-H); 7.47 (d,J=7Hz, 1H,Ar-H); 7.78 (d,J=7.5Hz, NH-COO); 8.02 (s,CONH); 10.78 (s, NH-Ind.); Anal. found: C,67.51; H,6.37; N,10.90; Calcd for $C_{36}H_{41}N_5O_6$: C,67.59; H,6.46; N,10.95.

Phenylmethyl[R-(R*,R*)]-4-(1H-indol-3-ylmethyl)-1-[1-(methoxycarbonyl)cyclohexyl]-4-methyl-2,5-dioxo-8-phenyl-1,3,6,9-tetraazadecan-10-oate(11d): (3.9g,87%); M.p. 166-68°C; $[\alpha]^{23}_D$ =+17.0° (c=0.5,MeOH); IR (film): 3351 cm^{-1}(NH), 1735 cm^{-1} (COO), 1709 cm^{-1} (NCOO), 1671 cm^{-1} (CONH); ^{1}H NMR (300Mhz, DMSO-d_6) δ: 1.10-1.33 (m,5H,CH_3 + CH_2cycl.); 1.33-1.78 (m,8H,CH_2cycl.); 3.12-3.49 (m,4H, CH_2-Ind. + CH_2-NH); 3.57 (s,3H, $COOCH_3$); 4.75 (m,1H,NH-CH-Ar); 4.97 (m,2H,Ar-CH_2-O); 6.03 (s,1H,NH-CONH); 6.51 (s,1H, NHCO-NH) 6.85-7.64 (m,15H,Ar-H); 7.64-7.97 (m,2H,CONH); 10.83 (s,1H,NH-Ind.); Anal. found: C,67.97; H,6.67; N,10.77; Calcd for $C_{37}H_{43}N_5O_6$: C,67.98; H,6.63; N,10.71.

Phenylmethyl[R-(R*,R*)]-4-(1H-indol-3-ylmethyl)-1-[2-(methoxycarbonyl)tricyc

lo[3.3.1.1^{3,7}]-dec-2-yl]-4-methyl-2,5-dioxo-8-phenyl-1,3,6,9-tetraazadecan-10-oate(11e): (1.7g,92%); M.p. 122-124°C; $[\alpha]^{23}_D$ = +14.8° (c=1.05,MeOH); IR (film): 3351 cm^{-1}(NH), 1730 cm^{-1} (COO) 1708 cm^{-1} (NCOO), 1670 cm^{-1} (CONH); ^{1}H NMR (300Mhz, DMSO-d_6) δ: 1.15 (s,3H,C$\underline{H}_3$); 1.42-2.38 (m,14H,adamantyl-$\underline{H}$); 3.15-3.42 (m,4H,C$\underline{H}_2$-NH + C$\underline{H}_2$-Ind.); 3.57 (s,3H,C$\underline{H}_3$); 4.75 (m,1H,C$\underline{H}$); 4.99 (m,2H,Ar-C$\underline{H}_2$-O); 6.15 (s,1H,N$\underline{H}$-CONH); 6.41 (s,1H, NHCO-N$\underline{H}$) 6.85-7.09 (m,3H,Ar-$\underline{H}$); 7.16-7.39 (m,11H,Ar-$\underline{H}$); 7.45 (d,J=8Hz,1H,Ar-$\underline{H}$); 7.78 (m,2H,CON$\underline{H}$);10.87 (s,N$\underline{H}$-Ind.); Anal. found: C,68.32; H,6.81; N,9.32; Calcd for $C_{41}H_{47}N_5O_6.H_2O$: C,68.03; H,6.82; N,9.67.

Phenylmethyl[R-(R*,R*)]-4-(1H-indol-3-ylmethyl)-2,5-dioxo-8-phenyl-1-[1-[[2-(trimethylsilyl)ethoxy]carbonyl]cyclohexyl]-1,3,6,9-tetraazadecan-10-oate(11f) : (3.2g,81%); M.p. 110-112°C; $[\alpha]^{23}_D$ = -12.8° (c=0.49,MeOH); IR (film): 3295 cm^{-1}(NH), 1730 cm^{-1} (COO) 1701 cm^{-1} (NCOO), 1634 cm^{-1} (CONH); ^{1}H NMR (300Mhz, DMSO-d_6) δ :0.0 (s,9H,SiC$\underline{H}_3$) ; 0.90 (m,2H,C$\underline{H}_2$-Si); 1.10-1.95 (m,10H,C$\underline{H}_2$cycl.); 2.91 (m,2H,C$\underline{H}_2$-NH); 3.30 (s,2H, C$\underline{H}_2$-Ind.); 4.03 (m,2H,C$\underline{H}_2$-OCO); 4.35 (m,1H,C$\underline{H}$); 4.70 (m,1H,C$\underline{H}$); 5.00 (s,2H,Ar-C$\underline{H}_2$-O); 6.15 (d,J=7.5Hz,1H,N$\underline{H}$-CONH); 6.95 (s,1H, NHCO-N$\underline{H}$-) 6.90-7.12 (m,3H,Ar-$\underline{H}$); 7.12-7.40 (m,11H,Ar-$\underline{H}$); 7.50 (d,J=8Hz,1H,Ar-$\underline{H}$); 7.80 (d,J=7.5Hz,CON$\underline{H}$); 8.02 (m,1H,CON$\underline{H}$); 10.80 (s,N$\underline{H}$-Ind.); Anal. found: C,65.92; H,7.17; N,9.57; Calcd for $C_{40}H_{51}N_5O_6Si$: C,66.18; H,7.08; N,9.65.

General procedure for the hydrolysis of the esters (11a-e) with LiOH (see Table 2): After reacting the ester with LiOH.H_2O in THF: water or MeOH: water to completion, the solution was concentrated *in vacuo*, and the aqueous phase was acidified with 1N HCl and extracted twice with EtOAc. The organic phase was dried and evaporated *in vacuo*. Compounds (**12a,b**) were obtained by filtration and drying after acidification.

[R-(R*,R*)]-6-(1H-Indol-3-ylmethyl)-4,7,12-trioxo-10,14-diphenyl-13-oxa-3,5,8,11-tetraazatetradecanoic acid (12a): (1.4g,95%); M.p. 196-198°C; $[\alpha]^{22}_D$ = + 3.7° (c=0.21,DMF); IR (film): 3360 cm^{-1}(NH,OH), 1706 cm^{-1} (NCOO), 1645 cm^{-1} (CONH); ^{1}H NMR (300Mhz, DMSO-d_6) δ : 2.70-3.00 (m,2H, C$\underline{H}_2$-NH); 3.30 (m,2H,C$\underline{H}_2$-Ind.); 3.68(s,2H,C$\underline{H}_2$-CO); 4.32 (m,1H,C$\underline{H}$); 4.68 (m1H,C$\underline{H}$); 4.97 (m,2H,Ar-C$\underline{H}_2$-O); 6.36 (m,2H,N$\underline{H}$-CON$\underline{H}$); 6.90-7.10 (m,3H,Ar-$\underline{H}$); 7.16-7.43 (m,11H,Ar-$\underline{H}$); 7.50 (d,J=8Hz,1H,Ar-$\underline{H}$); 7.76 (d,J=8Hz,CON$\underline{H}$); 7.97 (s,CON$\underline{H}$); 10.77 (s,1H,N$\underline{H}$-Ind.); MS(FAB): m/z calcd for ($C_{30}H_{31}N_5O_6$ + H)$^+$: 558.6189; found;558.2353 (50).

[R-(R*,R*)]-6-(1H-Indol-3-ylmethyl)-6-methyl-4,7,12-trioxo-10,14-diphenyl-13-Oxa-3,5,8,11-tetraazatetradecanoic acid (12b): (3.42g,92%); M.p. 106-110°C; $[\alpha]^{23}_D$= -15.9° (c=0.38,MeOH); IR (film): 3360 cm^{-1} (NH,OH), 1717 cm^{-1} (NCOO), 1661 cm^{-1} (CONH); ^{1}H NMR (300Mhz, DMSO-d_6) δ : 1.12 (s,3H,C$\underline{H}_3$); 3.11-3.75 (m,4H, C$\underline{H}_2$-Ind. + C$\underline{H}_2$-NH); 3.75 (m,2H,NH-C$\underline{H}_2$-CO); 4.74 (m,1H,C$\underline{H}$); 4.97 (m,2H,Ar-C$\underline{H}_2$-O); 6.22 (s,1H,N$\underline{H}$-CONH); 6.49 (m,1H,NHCO-N$\underline{H}$) 6.87-7.14 (m,3H,Ar-$\underline{H}$); 7.14-7.56 (m,12H,Ar-$\underline{H}$); 7.70 (m,2H,CON$\underline{H}$); 10.87 (s,1H,N$\underline{H}$-Ind.); MS (FAB): m/z calcd for ($C_{31}H_{33}N_5O_6$ + H)$^+$: 572.64569; found: 572.2509 (100).

Phenylmethyl[R-(R*,R*)]-1-(1-carboxycyclohexyl)-4-(1H-Indol-3-ylmethyl)-4-methyl-2,5-dioxo-8-phenyl-1,3,6,9-tetraazadecan-10-oate(12d): (1.7g,69%); purified by flash chromatography in CH_2Cl_2/MeOH 5%; M.p. 148-152°C; $[\alpha]^{23}_D$ = + 14.1° (c=0.60,MeOH); IR (film): 3336 cm^{-1} (NH,OH), 1700 cm^{-1} (NCOO), 1651 cm^{-1} (CONH); ^{1}H NMR (300Mhz, DMSO-d_6) δ: 1.10 (s,3H,C$\underline{H}_3$); 1.17-2.07 (m,10H, C$\underline{H}_2$cycl.); 3.10-3.45 (m,4H, C$\underline{H}_2$-Ind. + C$\underline{H}_2$-NH); 4.77 (m,1H,C$\underline{H}$); 5.00 (m,2H,Ar-C$\underline{H}_2$-O); 5.88 (s,1H,N$\underline{H}$-CONH); 6.18 (s,1H, NHCO-N$\underline{H}$) 6.87-707 (m,2H,Ar-$\underline{H}$); 7.12-7.40 (m,12H,Ar-$\underline{H}$); 7.49 (d,J=8Hz,1H,Ar-$\underline{H}$); 8.00 (s,2H,CON$\underline{H}$); 10.88 (s,1H,N$\underline{H}$-Ind.); MS (FAB): m/z calcd for ($C_{36}H_{41}N_5O_6$ + H)$^+$: 640.7656; found 640 (weak) .

Phenylmethyl[R-(R*,R*)]-[2-[[3-(1H-indol-3-yl)-2-[(4-oxo-3-oxa-1azaspiro[4,5]dec-1-en-2-yl)amino]1-oxopropyl]amino]-1-phenylethyl]carbamate(13c): (3.3g,93%); purified by flash chromatography in EtOAc/n-hexane 2:1; M.p. 98-99°C; $[\alpha]^{23}_D$ = + 40.4°

(c=0.93,MeOH); IR (film): 3320 cm^{-1} (NH), 1769 cm^{-1} (COO), 1708 cm^{-1} (NCOO), 1660 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6) δ:1.05-1.64 (m,10H, CH_2cycl.); 3.17-3.65 (m,4H, CH_2-Ind. + CH_2-NH); 4.65 (m,1H,CH); 4.76 (m,1H,CH); 5.00 (m,2H,Ar-CH_2-O); 6.85-7.13 (m,4H,Ar-H); 7.13-7.48 (m,10H,Ar-H); 7.52 (d,J=8Hz,1H,Ar-H); 7.80 (d,J=8Hz,CONH); 8.03 (m,CONH); 8.48 (s, N=C-NH); 10.78 (s, NH-Ind.); MS (FAB): m/z calcd for $(C_{35}H_{37}N_5O_5 + H)^+$: 608.7234; found: 608.3560 (35).

Phenylmethyl[R-(R*,R*)][2-[[3-(1H-Indol-3-yl-2-methyl-2-[(4-oxo-3-oxa-1-azaspiro[4,5]dec-1-en-2-yl)amino]-1-oxopropyl]amino]-1-phenylethyl]carbamate(13d): (0.7g,29%); purified by flas chromatography in CH_2Cl_2/MeOH 5%; M.p.116-119°C; $[\alpha]^{23}_D$ = +18.0° (c=1.0,MeOH); IR (film): 3320 cm^{-1} (NH), 1770 cm^{-1} (COO), 1704 cm^{-1} (NCOO), 1665 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6) δ :0.85 (m,1H,CH_2cycl.); 1.00-1.70 (m,12H, CH_2cycl. + CH_3); 2.95-3.35 (m,4H, CH_2-Ind. + CH_2-NH); 4.80 (m,1H,CH); 5.00 (m,2H,Ar-CH_2-O); 6.87-7.15 (m,3H,Ar-H); 7.15-7.49 (m,12H,Ar-H); 7.58 (d,J=7.5Hz,CONH); 7.71 (m,1H,CONH); 8.51 (s,1H,N=C-NH); 10.86 (s,1H,NH-Ind.);(FAB): m/z calcd for ($C_{36}H_{39}N_5O_5$ + H)$^+$: 622.7442; found: 622.3029 (42)

Phenylmethyl[R-(R*,R*)]-[2-[[3-(1H-Indol-3-yl)-2-methyl-2-[(5-oxo-spiro[oxazole-4-(5H)-2'-tricyclo[3.1.1.1^{3,5}]octan]-2-yl)amino]propyl]amino]-1-phenylethyl]carbamate (13e): (91mg,95%); purified by flash chromatography in EtOAc: n-hexane 1:1; M.p. 128-134°C; $[\alpha]^{23}_D$ = + 23.7° (c=0.49,MeOH); IR (film): 3341 cm^{-1} (NH), 1767 cm^{-1} (COO), 1704 cm^{-1} (NCOO), 1665 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6) δ :1.05-2.47 (m,17H,H-adamant.+ CH_3); 3.01 (d,J=14Hz, 1H,CH_2-N); 3.30 (s,2H, CH_2-Ind.); 3.70 (d,J=14Hz,1H, CH_2-NH); 4.78 (m,1H,CH); 5.01 (m,2H,Ar-CH_2-O); 6.83-7.09 (m,3H,Ar-H); 7.19-7.45 (m,12H,Ar-H); 7.57 (d,J=8Hz,CONH); 7.72 (m,1H,CONH); 8.481(s, 1H,N=C-NH); 10.82 (s, NH-Ind.); MS (FAB): m/z calcd for ($C_{40}H_{43}N_5O_5$ + H)$^+$: 674.8272; found 674.3342 (15).

Phenylmethyl [R-(R*,R*)]-1-(1-carboxycyclohexyl)-4-(1H-Indol-3-ylmethyl)-2,5-dioxo-8-phenyl-1,3,6,9-Tetraazadecan-10-oate(12c): The ester (11f) (2.17g,2.99mmol) was stirred at 25°C for 17 hours in CH_2Cl_2 (50ml) with TFA (3ml,30mmol). After evaporation of the solvent and the excess of reagent, the residue was dissolved in EtOAc. The organic phase was washed with water, dried and concentrated *in vacuo*. Purification by flash chromatography in CH_2Cl_2/ MeOH 5-10% gave (12c)(1.78g,95%): M.p. 153-155°C; $[\alpha]^{23}_D$ = - 16.9° (c=0.4,THF); IR (film): 3340 cm^{-1} (NH,OH), 1704 cm^{-1} (NCOO), 1649 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6) δ: 1.20-2.01 (m,1OH,CH_2cycl.); 2.72-3.13 (m,2H,CH_2-NH); 3.35 (m,2H, CH_2-Ind.); 4.32 (m,1H,CH); 4.71 (m,1H,CH); 5.00 (m,2H,Ar-CH_2-O); 6.09 (s,1H,NH-CONH); 6.38 (s,1H, NHCO-NH) 6.92-7.16 (m,3H,Ar-H); 7.16-7.42 (m,12H,Ar-H); 7.02 (d,J=7.5Hz,1H,Ar-H); 8.00 (s,CONH); 8.12 (s,CONH); 10.82 (s,1H,NH-Ind.); MS (FAB): m/z calcd for $(C_{35}H_{39}N_5O_6$ + H)$^+$: 626.7387; found: 626.2979 (25).

4-Methyl-1-(phenylmethyl)-L-aspartate (14): Commercially available1-(phenylmethyl)-L-aspartate (5.0g,22mmol) was refluxed for 17 hours in MeOH (150ml) in the presence of thionyl chloride (3.3ml, 45mmol). After evaporation of the solvent, saturated aqueous solution of $NaHCO_3$ was added and the solution extracted twice with EtOAc. After drying and evaporating, purification by bulb-to-bulb distillation afforded a colorless oil (4.6g,86%):

B.p.: 220-225°C/0.5 mbar; $[\alpha]^{23}_D$ = - 4.8° (c=1,MeOH); IR (film): 1737 cm^{-1} (COO) ; ^1H NMR (300Mhz, $CDCl_3$) δ :1.80 (s,2H, NH_2); 2.79 (m,2H, CH_2CO); 3.65 (s,3H,CH_3); 3.87 (m,1H,CH); 5.15 (s,2H,Ar-CH_2-O); 7.32 (s,5H,Ar-H); Anal. found: C, 60.43; H,6.28; N, 5.94; Calcd for $C_{12}H_{15}NO_4$: C,60.75; H,6.37; N,3.23.

General procedure for synthesis of compounds (15a-d)(see Table 3): The carboxylic acids (12a-d) (1 eq.) were reacted with BOP reagent (1.5 eq.), diisopropylethylamine (2eq.) and **4 - Methyl-1-(phenylmethyl)-L-aspartate (14)** (1.5 eq.) in dry DMF by stirring at 25°C for 12 hours. After hydrolysis with brine, the solution was concentrated *in vacuo* and extracted twice with EtOAc.

The organic phase was washed successively with 2N HCl,10% $NaHCO_3$ solution and brine, dried and the solvent evaporated.

4-Methyl-1-(phenylmethyl)[R-(R*,R*)]-N-[N-[[[1-(1H-indol-3-ylmethyl)-2-oxo-2-[[2-phenyl-2-[[(phenylmethoxy)carbonyl]amino]ethyl]amino]ethyl]amino]carbonyl]glycyl]-L-aspartate(15a): (1.7g,83%); purified by flash chromatography in EtOAc / THF 5%; M.p. 189-192°C; $[\alpha]^{23}_D$ = -6.8° (c=0.5,MeOH); IR (film): 3340 cm^{-1}(NH), 1730 cm^{-1} (COO) 1700 cm^{-1} (NCOO),1651 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6):δ: 2.68-3.00 (m,4H,CH-C$\underline{H_2}$-CO+C$\underline{H_2}$-NH); 3.30 (s,2H, C$\underline{H_2}$-Ind.); 3.52 (s,3H,C$\underline{H_3}$); 3.65 (m,2H, CO-C$\underline{H_2}$-NH); 4.32 (m,1H,C$\underline{H}$); 4.70 (m,2H,C$\underline{H}$); 4.98 (m,2H,Ar-C$\underline{H_2}$-O); 5.11 (m,2H,Ar-C$\underline{H_2}$-O); 6.38-6.45 (m,2H,N$\underline{H}$CONH); 6.90-7.10 (m,3H,Ar-$\underline{H}$); 7.10-7.40 (m,16H, Ar-$\underline{H}$); 7.52 (d,J=8Hz,1H,Ar-$\underline{H}$); 7.78 (d,J=8Hz, CON$\underline{H}$); 7.98 (s,CON$\underline{H}$); 8.39 (d,J=8Hz,CON$\underline{H}$); 10.77 (s, N$\underline{H}$-Ind.); Anal. found: C,64.08; H,5.71; N,10.79; Calcd for $C_{42}H_{44}N_6O_9$: C,64.94; H,5.71; N,10.82.

4-Methyl-1-(phenylmethyl)[R-(R*,R*)]-N-[N-[[[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-phenyl-2-[[(phenylmethoxy)carbonyl]amino]ethyl]amino]ethyl]amino]carbonyl]glycyl]-L-aspartate(15b): (2.2g,77%); purified by flash chromatography in EtOAc / THF 5%; M.p. 78-80°C; $[\alpha]^{23}_D$ = +7.5° (c=0.62,MeOH); IR (film): 3350 cm^{-1}(NH), 1739 cm^{-1} (COO) , 1652 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6)δ: 1.10 (s,3H,C$\underline{H_3}$); 2.80 (m,2H,CH-C$\underline{H_2}$-CO); 3.08-3.43 (m,4H, C$\underline{H_2}$-Ind. + C$\underline{H_2}$-NH); 3.55 (s,3H,C$\underline{H_3}$); 3.70 (m,2H, CO-C$\underline{H_2}$-NH); 4.77 (m,2H,C$\underline{H}$); 4.98 (m,2H,C$\underline{H_2}$-O); 5.10 (m,2H,C$\underline{H_2}$-O); 6.20 (s,1H,N$\underline{H}$CONH); 6.30 (m,1H,N$\underline{H}$CONH); 6.88-7.51 (m,20H,Ar-$\underline{H}$); 7.70 (m,2H, N$\underline{H}$CO); 8.42 (d,J=8Hz,N$\underline{H}$CO); 10.85 (s, N$\underline{H}$-Ind.); MS (FAB): m/z calcd for $(C_{43}H_{46}N_6O_9 + H)^+$: 791.8888); found: 791.3405 (52).

4-Methyl-1-(phenylmethyl)[R-(R*,R*)]-N-[[1-[[[[1-(1H-indol-3-ylmethyl)-2-oxo-2-[[2-phenyl-2-[[(phenylmethoxy)carbonyl]amino]ethyl]amino]ethyl]amino]carbonyl]amino]cyclohexyl]carbonyl]-L-aspartate (15c): (1.1g,80%); purified by flash chromatography in CH_2Cl_2/MeOH 5%; M.p. 178-181°C; $[\alpha]^{23}_D$ = -10.0° (c=0.36,THF); IR (film): 3339 cm^{-1}(NH), 1731 cm^{-1} (COO), 1651 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6) δ: 1.05-1.89 (m,10H, C$\underline{H_2}$cycl.); 2.55-3.00 (m,4H,CH-C$\underline{H_2}$-CO + C$\underline{H_2}$-NH); 3.25 (s,2H, C$\underline{H_2}$-Ind.); 3.52 (s,3H,C$\underline{H_3}$); 4.30 (m,1H, C$\underline{H}$); 4.62 (m,2H,C$\underline{H}$); 4.98 (s,2H,Ar-C$\underline{H_2}$-O); 5.08 (s,2H,Ar-C$\underline{H_2}$-O); 6.20-6.49 (m,2H,N$\underline{H}$CON$\underline{H}$); 6.87-7.08 (m,3H,Ar-$\underline{H}$); 7.15-7.40 (m,15H,Ar-$\underline{H}$); 7.50 (d,J=8Hz,1H,Ar-H); 7.72 (d,J=8Hz,CON$\underline{H}$); 7.94 (m,2H,CON$\underline{H}$); 10.75 (s, N$\underline{H}$-Ind.); Anal. found: C,65.97; H,6.20; N,9.76; Calcd for $C_{47}H_{52}N_6O_9$: C,66.81; H,6.20; N,9.95.

4-Methyl-1-(phenylmethyl)[R-(R*,R*)]-N-[[1-[[[[1-(1H-indol-3-ylmethyl)-1-methyl-2-oxo-2-[[2-phenyl-2-[[(phenylmethoxy)carbonyl]amino]ethyl]amino]ethyl]amino]carbonyl]amino]cyclohexyl]carbonyl]-L-aspartate(15d): (2.5g,90%); purified by flash chromatography in EtOAc: n-Hex. 2:1; M.p. 101-103°; $[\alpha]^{23}_D$ = -2.2° (c=0.59,MeOH); IR (film): 3365 cm^{-1}(NH), 1730 cm^{-1} (COO) 1669 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6)δ: 1.05 (s,3H,C$\underline{H_3}$); 1.28-2.05 (m,10H, C$\underline{H_2}$cycl.); 2.70-3.60 (m,9H,CH-C$\underline{H_2}$-CO + C$\underline{H_2}$-NH + C$\underline{H_2}$-Ind. + C$\underline{H_3}$); 4.81 (m,2H,C$\underline{H}$); 4.98 (m,2H,Ar-C$\underline{H_2}$-O); 5.11 (m,2H,Ar-C$\underline{H_2}$-O); 6.06 (s,1H,N$\underline{H}$CONH); 6.10 (s,1H,NHCON$\underline{H}$); 6.87-7.08 (m,3H,Ar-$\underline{H}$); 7.18-7.39 (m,16H,Ar-$\underline{H}$); 7.45 (d,J=8Hz,1H,Ar-H); 7.73 (d,J=8Hz,CON$\underline{H}$); 7.87 (m,CON$\underline{H}$); 8.08 (d,J=8Hz,CON$\underline{H}$); 10.85 (s,1H, N$\underline{H}$-Ind.); MS (FAB): m/z calcd for $(C_{48}H_{54}N_6O_9 + Na)^+$: 881.9904; found: 881.3850 (100).

General procedure for catalytic hydrogenation (15a-d) →(16a-d):

The N-terminal and C-terminal protected derivatives (**15b**), (**15c**) and (**15d**) were hydrogenated at 25°C in EtOH in the presence of 15% in weight of 20% $Pd(OH)_2/C$ under a 45 psi pressure for 12 hours. After filtering off the catalyst using Celite, the solvent was evaporated *in vacuo* to give respectively the amino acids (**16b**),(**16c**) and (**16d**)in quantitative yields. Derivative (**15a**) was hydrogenated at 40°C for 24 hours to give after, purification by reversed phase chromatography in MeOH: water 3:1, (**16a**) in 60% yield.

4-Methyl[R-(R*,R*)]-N-[N-[[[2-[(2-amino-2-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-2-oxo-ethyl]amino]carbonyl]glycyl]-L-aspartate(16a): (0.6g);M.p. 115-

118°C; $[\alpha]^{23}_D$ = +20.1° (c=0.93,MeOH); IR (film): 3284 cm^{-1}(NH,OH), 1729 cm^{-1} (COO), 1642 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6) δ: 2.45-3.88 (m, CH + CH_2 +NH_2); 4.38 (m,2H,CH); 6.49 (m,2H,NHCONH); 6.89-7.37 (m,10H,Ar-H); 7.52 (d,J=8Hz,1H,CONH); 7.82 (d,J=8Hz,1H,CONH); 7.98 (m,1H,CONH); 10.83 (s, NH-Ind.); $C_{27}H_{32}N_6O_7$; Anal found: C,55.29; H,6.48; N,13.58; Calcd for $C_{27}H_{32}N_6O_7.3H_2O$: C,54.46; H,6.31; N,13.85.

4-Methyl[R-(R*,R*)]-N-[N-[[[2-[(2-amino-2-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]amino]carbonyl]glycyl]-L-aspartate(16b): (1.1g);M.p. 162-166° (dec.); $[\alpha]^{23}_D$ = -9.9° (c=0.99,MeOH); IR (film): 3320 cm^{-1}(NH, OH), 1727 cm^{-1} (COO) 1651 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6)δ :1.20 (s,3H,CH_3); 2.50-2.78 (m,2H,CH-CH_2-CO); 3.03-3.70 (m, NH_2 + CH_2-NH + CH_2-Ind. + CH_3); 4.10-4.28 (m,2H,CH); 6.63 (m,2H,NHCONH); 6.89-7.11 (m,3H,Ar-H); 7.20-7.52 (m,7H,Ar-H); 7.84 (d,J=7Hz,NHCO); 7.92 (m,NHCO); 10.93 (s,1H, NH-Ind.); MS (FAB): m/z calcd for $(C_{28}H_{34}N_6O_7 + H)^+$: 567.6272; found: 567.2567 (100).

4-Methyl[R-(R*,R*)]-N-[[1-[[[[2-[(2-amino-2-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-2-oxoethyl]amino]carbonyl]amino]cyclohexyl]carbonyl]-L-aspartate(16c): (1.1g); M.p. 158-162° ; $[\alpha]^{23}_D$ = +14.42° (c=0.31,MeOH); IR (film): 3309 cm^{-1}(NH, OH), 1728 cm^{-1} (COO), 1643 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6) δ: 1.05-1.80 (m,10H,CH_2cycl.); 2.55-3.70 (m,CH-CH_2-CO + NH_2 + CH_2-NH + CH_2-Ind. + CH_3); 3.93 (m,1H,CH); 4.25 (m,2H,CH); 6.21 (d,J=7.5Hz,NHCONH); 6.63 (s,1H, NHCONH); 6.90-7.51 (m,11H,Ar-H + CONH); 7.91 (m,1H,CONH); 10.85 (s,1H, NH-Ind.); MS(FAB): m/z calcd for $(C_{32}H_{40}N_6O_7+H)^+$: 621.7200; found: 621.3037 (60).

4-Methyl[R-(R*,R*)]-N-[[1-[[[[2-[(2-amino-2-phenylethyl)amino]-1-(1H-indol-3-ylmethyl)-1-methyl-2-oxoethyl]amino]carbonyl]amino]cyclohexyl]carbonyl]]-L-aspartate(16d): (1.8g); M.p. 162-166° ; $[\alpha]^{23}_D$ = -3.4° (c=1.08,MeOH); IR (film): 3340 cm^{-1}(NH, OH), 1726 cm^{-1} (COO) 1642 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6)δ: 1.12-2.00 (m,13H,CH_2cycl.+ CH_3); 2.66 (m,2H,CH-CH_2-CO); 3.00-3.75 (m, NH_2 + CH_2-NH + CH_2-Ind. + CH_3); 4.05-4.22 (m,2H,CH); 6.35 (s,NHCONH); 6.53 (s, NHCONH); 6.90-7.15 (m,3H,Ar-H); 7.30-7.58 (m,7H,Ar-H); 7.72 (d,J=8Hz,CONH); 7.87 (m,CONH); 10.97 (s, NH-Ind.);MS (FAB): m/z calcd for ($C_{33}H_{42}N_6O_7$ + H)$^+$: 635.7469; found: 635.3193 (60).

Macrolactamisations (see Table 4):

General procedure for macrolactamisations with diphenyl phosphoryl azide (DPPA) (Method A):

One equivalent of the crude amino acid was treated for 72 hours at 0°C with DPPA (1.5 eq.) and $NaHCO_3$ (5 eq.) at the desired concentration in dried DMF . After addition of water and concentration *in vacuo*, the solution was extracted twice with EtOAc. The combined extracts were washed with 2N aqueous HCl, saturated $NaHCO_3$ solution and twice with brine. After drying and evaporating the solvent *in vacuo*, the crude product was purified by flash chromatography in CH_2Cl_2 / MeOH 5 - 10%.

General procedure for macrolactamisations using BOP reagent (Method B):

One equivalent of the crude amino acid was treated for 72 hours at 25°C with BOP reagent (1.2 eq.) and N,N-diisopropylethylamine (1.2 eq.) at the desired concentration in dried DMF . After addition of saturated brine and concentration *in vacuo*, the solution was extracted twice with EtOAc. The combined extracts were washed with 2N HCl, saturated $NaHCO_3$ solution and twice with brine. After drying and evaporating the solvent *in vacuo*, the crude product was purified by flash chromatography as above.

Typical procedure for macrolactamisation using 2-chloro-1-methylpyridinium iodide (Method C):

The amino acid (**16b**) (80mg,141µmol) was dissolved in DMF (70ml) and triethylamine (59 µl,420µmol) was added. The solution was then added dropwise at 25°C within 2 hours to a solution of 2-chloro-1-methylpyridinium iodide (43mg,170µmol) and triethylamine (38µl,270µl) in dried DMF

(70ml). The solution was then stirred for 24 hours and hydrolyzed with water. After concentration *in vacuo*, the solution was extracted twice with EtOAc, and the organic phase washed with brine, dried and evaporated. The crude product was purified by flash chromatography in CH_2Cl_2/MeOH 5% to give the compound **(17b)** (31mg,40%).

Typical procedure for macrolactamisation using DCC/ HOBt (Method D):
Compound **(16b)** (100mg,176μmol) and HOBt.H_2O (26mg,194μmol) were dissolved in dried DMF (29ml). A solution of DCC (44mg,211μmol) in dried DMF (30ml) was added at 0°C within an hour and the solution was stirred at 25°C for 72 hours. After concentration *in vacuo*, the residue was dissolved in EtOAc and the organic solution washed with 1N HCl, 10% $NaHCO_3$ solution and brine. After drying and evaporating, the crude product was purified by flash chromatography as above to give the compound **(17b)**(30mg,31%).

Typical procedure for macrolactamisation using bis (trichloromethyl) carbonate (Method E):
Compound **(16b)** (100mg,176μmol) was dissolved in dried THF (59ml,0.001 M) and treated with bis (trichloromethyl) carbonate (19mg, 180μmol)and Et_3N (26μl) at 25°C for 72 hours. After addition of water and evaporation of the solvent *in vacuo*, the solution was extracted with EtOAc and the organic solution washed with brine. After drying and evaporating, the crude product was purified by flash chromatography as above to give compound **(17b)** (11.6mg,12%).

Methyl[7S-(7α,10β,14α)]-14-(1H-indol-3-ylmethyl)-2,5,8,13-tetraoxo-10-phenyl-1,3,6,9,12-pentaazacyclotetradecane-7-acetate(17a):MS (FAB): m/z calcd for $(C_{27}H_{30}N_6O_6 + H)^+$: 535.5847; found: 535.2305 (65).

Methyl[7S-(7α,10β,14α)]-14-(1H-indol-3-ylmethyl)-14-methyl-2,5,8,13-tetraoxo-10-phenyl-1,3,6,9,12-pentaazacyclotetradecane-7-acetate(17b):
(256mg,71%); M.p. 164-168°C; $[\alpha]^{23}_D$ = - 40.6° (c=0.43,MeOH); IR (film): 3327 cm^{-1}(NH), 1740 cm^{-1} (COO) · 1651 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6) δ :1.32 (s,3H,C$\underline{H}_3$); 2.40-3.19 (m,4H,CH-C$\underline{H}_2$-CO + C$\underline{H}_2$-NH); 3.30 (s,2H, C$\underline{H}_2$-Ind.); 3.55 (m,5H,C$\underline{H}_3$ + CO-C$\underline{H}_2$-NH); 4.38-4.68(m,2H,C$\underline{H}$); 6.28 (s,1H,N$\underline{H}$CONH); 6.80 (s,1H,N$\underline{H}$CONH); 6.90-7.18 (m,3H,Ar-$\underline{H}$); 7.18-7.49 (m,8H,Ar-$\underline{H}$ + CON$\underline{H}$); 7.71 (d,J=8Hz,1H, CON$\underline{H}$); 8.15 (d,J=8Hz,CON$\underline{H}$); 10.93 (s, N$\underline{H}$-Ind.); MS (FAB): m/z calcd for $(C_{28}H_{32}N_6O_6 + H)^+$: 549.6116; found: 549.2462 (100); Anal. Found: C,59.03; H,5.89; N,14.35; Calcd for $C_{28}H_{32}N_6O_6 .H_2O$: C,59.35; H,6.05; N,14.83

Methyl[10R-(10α,14β,17α)]10-(1H-indol-3-ylmethyl)-8,11,16,19-tetraoxo-14-phenyl-7,9,12,15,18-pentaazaspiro[5,13]nonadecane-17-acetate (17c):(61mg,63%); M.p. 230-232°C; $[\alpha]^{23}_D$ = -62.4° (c=0.53,THF); IR (film): 3306 cm^{-1}(NH), 1730 cm^{-1}(COO) 1659 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6): d 1.11-1.96 (m,10H, C$\underline{H}_2$cycl.); 2.40-3.21 (m,CH-C$\underline{H}_2$-CO + C$\underline{H}_2$-NH + C$\underline{H}_2$-Ind. + C$\underline{H}_3$); 4.15 (m,1H, C$\underline{H}$); 4.75 (m,1H,C$\underline{H}$); 5.15 (m,1H,C$\underline{H}$); 6.22 (d,J=7Hz,1H,N$\underline{H}$CONH); 6.80(s,1H,NHCON$\underline{H}$); 6.91-7.60 (m,11H,Ar-$\underline{H}$ + CON$\underline{H}$); 7.75 (d,J=8Hz,1H,CON$\underline{H}$); 8.02 (m,1H,CON$\underline{H}$); 10.85 (s,1H,N$\underline{H}$-Ind.); MS(FAB): m/z calcd for $(C_{32}H_{38}N_6O_6$ + H)$^+$: 603.7044; found: 603.2931 (100). Anal. found: C,59.83; H,6.31; N,12.82; Calcd for $C_{32}H_{38}N_6O_6.2H_2O$: C,60.17; H,6.63; N,13.15; HPLC: d.e.= 88%.

Methyl[10R-(10α,14β,17α)]-10-(1H-indol-3-ylmethyl)-10-methyl-8,11,16,19-tetraoxo-14-phenyl-,7,9,12,15,18-pentaazaspiro[5,13]nonadecane-17-acetate(17d):
(66mg,68%); M.p. 177-180°; $[\alpha]^{23}_D$ = -59.8° (c=0.5,MeOH); IR (film): 3300 cm^{-1}(NH), 1728 cm^{-1} (COO), 1651 cm^{-1} (CONH); ^1H NMR (300Mhz, DMSO-d_6) δ :1.10-2.02 (m,13H,C$\underline{H}_3$+ C$\underline{H}_2$cycl.); 2.31-3.20 (m,4H,CH-C$\underline{H}_2$-CO + C$\underline{H}_2$-NH); 3.27 (s,2H, C$\underline{H}_2$-Ind.); 3.51 (s,3H,C$\underline{H}_3$); 4.75 (m,1H,C$\underline{H}$); 4.94 (m,1H,C$\underline{H}$); 6.28 (s,1H,N$\underline{H}$CONH); 6.68 (s,1H,NHCON$\underline{H}$); 6.89-7.45 (m,11H,Ar-$\underline{H}$ + CON$\underline{H}$); 7.78 (d,J=8Hz,CON$\underline{H}$); 7.95 (m,CON$\underline{H}$); 8.08 (d,J=8Hz,CON$\underline{H}$); 10.93 (s,N$\underline{H}$-Ind.); MS(FAB): m/z calcd for $(C_{33}H_{40}N_6O_6$ +H)$^+$: 617.7314; found: 617.3088 (44); Anal. found: C,60.57; H,6.72; N,12.88; Calcd for $C_{33}H_{40}N_6O_6.2H_2O$: C,60.72; H,6.79; N,12.87.

General procedure for hydrolysis of methyl esters (17b-d) to the corresponding carboxylic acids (2b-d) (see table 5):
General procedure: The methyl ester was dissolved in THF and the solution was cooled to 0°C. After dropwise addition of a solution of $LiOH.H_2O$ (1.1 eq.) in water (THF:water 3:1), the solution was allowed to be stirred at 25°C for 17 hours. After evaporation of THF, the solution was acidified with 1N HCl and extracted twice with EtOAc. After drying and evaporating the crude com pound was analyzed and purified.

[7S-(7α,10β,14α)]-14-(1H-Indol-3-ylmethyl)-14-methyl-2,5,8,13-tetraoxo-10-phenyl-1,3,6,9,12-pentaazacyclotetradecane-7-acetic acid (2b): (181mg,68%);^{1}HNMRat 300 Mhz showed two peaks for the α-methyl tryptophan signal at 1.12ppm and 1.30 ppm (relative intensity; 1/2). Two successive reversed phase column purifications of the crude product in MeOH:water 2: 1 isolated the desired diastereoisomer.

M.p. 192-196°C; $[\alpha]^{23}_D$ = - 72.8° (c=0.36,MeOH); IR (film): 3308 cm^{-1}(OH,NH), 1716 cm^{-1} (COO), 1657 cm^{-1} (CONH); ^{1}H NMR (300Mhz, DMSO-d_6) δ: 1.30 (s,3H,C<u>H</u>$_3$); 2.39 (m,1H,C<u>H</u>$_2$CO); 2.70 (m,1H,C<u>H</u>$_2$CO); 2.90-3.20 (m,4H, C<u>H</u>$_2$-NH + C<u>H</u>$_2$-Ind.); 3.55 (m,2H, CO-C<u>H</u>$_2$-NH); 4.68 (m,1H,C<u>H</u>); 4.80 (m,1H,C<u>H</u>); 6.35 (s,1H,N<u>H</u>CONH); 6.82 (s,1H,N<u>H</u>CONH); 6.90-7.55 (m,Ar-<u>H</u> + CON<u>H</u>); 7.75 (d,J=8Hz,1H, CON<u>H</u>); 8.19 (d,J=8Hz,CON<u>H</u>); 10.97 (s,N<u>H</u>-Ind.); MS (FAB):m/z calcd for ($C_{27}H_{30}N_6O_6$ + H)$^+$: 535.5847; found: 535.2305 (100); Anal. found: C,56.02; H,5.80; N,14.47; Calcd for $C_{28}H_{32}N_6O_6$.$2H_2O$: C,56.83; H,6.00; N,14.72.

[10R-(10α,14β,17α)]-10-(1H-Indol-3-ylmethyl)-8,11,16,19-tetraoxo-14-phenyl-7,9,12,15,18-pentaazaspiro[5,13]nonadecane-17-acetic acid (2c): (160mg,71%); ^{1}H NMR at 300 Mhz showed two peaks for the N<u>H</u>-indole signal at 10.87 ppm and 10.83 ppm (relative intensity; 3/1). The desired diastereoisomer was isolated by flash-chromatography in CH_2Cl_2:MeOH 15%.

M.p. 262-263°C; $[\alpha]^{23}_D$ = -5.2° (c=0.23,MeOH); IR (film): 3295 cm^{-1}(OH,NH), 1720 cm^{-1} (COO), 1645 cm^{-1} (CONH); ^{1}H NMR (300Mhz, DMSO-d_6) δ: 1.09-2.18 (m,10H, C<u>H</u>$_2$cycl.); 2.93-3.20 (m,4H,CH-C<u>H</u>$_2$-CO + C<u>H</u>$_2$-NH); 3.30 (s.2H, C<u>H</u>$_2$-Ind.); 4.20 (m,1H, C<u>H</u>); 4.43 (m,2H,C<u>H</u>); 5.43 (m,1H,N<u>H</u>CONH); 6.90(s,1H,NHCON<u>H</u>); 6.93-7.72 (m,10H,Ar-<u>H</u>); 7.85 (d,J=8Hz,1H,CON<u>H</u>); 7.98 (m,1H,CON<u>H</u>); 8.40 (s,CON<u>H</u>); 8.88(s,COO<u>H</u>); 10.85 (s,N<u>H</u>-Ind.); MS (m/z calcd for ($C_{31}H_{36}N_6O_6$ + H)$^+$: 588.6695); found: 589.2603 (100). Anal. found: C,57.67; H,6.37; N,12.68; Calcd for $C_{31}H_{36}N_6O_6.3H_2O$: C,57.93; H,6.58; N,13.06; HPLC> 95% .

(**2d**) and (**2g**): (160mg,60%); After reversed phase chromatography in MeOH:water 2.5:1, both diastereoisomers were isolated separately.

[10R-(10α,14β,17α)]-10-(1H-Indol-3-ylmethyl)-10-methyl-8,11,16,19-tetraoxo-14-phenyl-7,9,12,15,18-pentaazaspiro[5,13]nonadecane-17-acetic acid(2d): M.p. 186-190°; $[\alpha]^{23}_D$ = -67.3° (c=0.21,MeOH); IR (film): 3326 cm^{-1}(OH,NH), 1700 cm^{-1} (COO), 1651 cm^{-1} (CONH); ^{1}H NMR (300Mhz, DMSO-d_6)δ :1.11-2.02 (m,13H,C<u>H</u>$_3$ + C<u>H</u>$_2$cycl.); 2.25-3.21 (m,6H,CH-C<u>H</u>$_2$-CO + C<u>H</u>$_2$-NH + C<u>H</u>$_2$-Ind.); 4.72 (m,1H,C<u>H</u>); 4.93 (m,1H, C<u>H</u>); 6.30 (s,1H,N<u>H</u>CONH); 6.70 (s,1H,NHCON<u>H</u>); 6.88-7.52 (m,11H, Ar-<u>H</u> + CON<u>H</u>); 7.70 (d,J=8Hz,CON<u>H</u>); 7.95 (m,CON<u>H</u>); 10.96 (s, N<u>H</u>-Ind.); MS(FAB): m/z calcd for ($C_{32}H_{38}N_6O_6$ + H)$^+$: 602.6965; found: 603.2931 (100); Anal. found: C,61.77; H,6.42; N,13.11; Calcd for $C_{32}H_{38}N_6O_6.1H_2O$: C,61.92; H,6.49; N,13.54.

[10R-(10α,14a,17α)]-10-(1H-Indol-3-ylmethyl)-10-methyl-8,11,16,19-tetraoxo-14-phenyl-7,9,12,15,18-pentaazaspiro[5,13]nonadecane-17-acetic acid (**2g**): M.p. 198-200°; $[\alpha]^{23}_D$ = -80.0° (c=0.09,MeOH); IR (film): 3326 cm^{-1}(OH,NH) 1700 cm^{-1} (COO) 1651 cm^{-1} (CONH); ^{1}H NMR (300Mhz, DMSO-d_6)δ: 1.11-2.01 (m,13H,C<u>H</u>$_3$ + C<u>H</u>$_2$cycl.); 2.45-2.86 (m,2H,C<u>H</u>$_2$CO); 2.97-3.50 (m,4H, C<u>H</u>$_2$-NH + C<u>H</u>$_2$-Ind.); 4.42 (m,1H,C<u>H</u>); 4.75 (m,1H, C<u>H</u>); 6.19 (s,1H,N<u>H</u>CONH); 6.41 (s,1H,NHCON<u>H</u>); 6.88-7.50 (m,11H,Ar-<u>H</u> + CON<u>H</u>); 7.68 (d,J=8Hz,CON<u>H</u>); 8.21 (d,J=8Hz,CON<u>H</u>); 10.98 (s, N<u>H</u>-Ind.); MS(FAB): m/z calcd for ($C_{32}H_{38}N_6O_6$ + H)$^+$: 602.6965; found: 603.2882 (100); Anal. found: C,61.64; H,6.45; N,13.56; Calcd for $C_{32}H_{38}N_6O_6.1H_2O$: C,61.92; H,6.49; N,13.54.

Acknowledgments: We wish to thank Dr. G. Ratcliffe for his collaboration in the molecular modelling, Dr. D. Hill for the CCK-B binding data ,D. Hunter for excellent technical assistance and Mrs. L. Terry for manuscript preparation.

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