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Macrocyclic Polyether Tetralactams I : Synthesis and Cyclization Studies

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Abstract : *:A three-step method for the synthesis of new 18, 21 or 24-membered macrocyclic tetralactams with two dimethyleneoxy moieties is described. The method consists in the ring closure of a bis-secondary amine with a diamide diacid activated by the thiazolidine-2-thione group. The cyclization does not require high dilution techniques and provides the expected tetralactams in good yields, ranging from 42% to 73%. This synthetic pathway leads to dissymmetrical or symmetrical molecules with substituents of variable lipophilicity.*

INTRODUCTION

Neutral ionophores are naturally occurring molecules, the biological function of which being to selectively take up and release essential metal ions (Na^+, K^+, Ca^{2+}) by transport processes across lipidic membranes of living cells. Oxygen atoms of ether, ester and amide groups have been found to serve as binding sites in these natural complexones. Therefore extensive research has been devoted to the design of synthetic compounds having comparable binding properties.

Generally, macrocyclic polyethers (crown ethers) form stable complexes preferably with alkali metal ions.[1] Ligands with high potassium/sodium affinity have been found among these compounds. However, the selectivity of crown ethers for alkaline-earth metal ions is much lower. When the ether groups were successively replaced by lactone ones, the resulting ring systems showed reduced binding affinity. However a good selectivity towards alkaline-earth cations was observed with some polyoxalactones[2]. Of particular interest is the introduction of an amide linkage in the polyether ring. These groups modify the binding properties of the crown compounds in favour of alkaline-earth cations with respect to alkali metal ions[3].

For instance among macrocyclic polylactams, some dilactams[4] with four or five oxygen ether atoms preferentially complex Ca^{2+} vs Na^+, K^+ or Mg^{2+}. Interestingly, the resulting Ca^{2+} complexes often showed the 2:1 (macrocycle : cation) stoichiometry. This property was applied by Kimura[5] to design calcium selective

electrodes. Thus an enhanced calcium ion selectivity is observed in the case of a bicyclic polyether diamide compared to its monocyclic analog. In addition, the most effective neutral carrier-based calcium - selective membranes, extensively studied by Simon, are the two ETH 1001 and ETH 129 open chain diamides[6]. With calcium picrate these ligands also mainly give 2:1 complexes in solution[6a, 7].

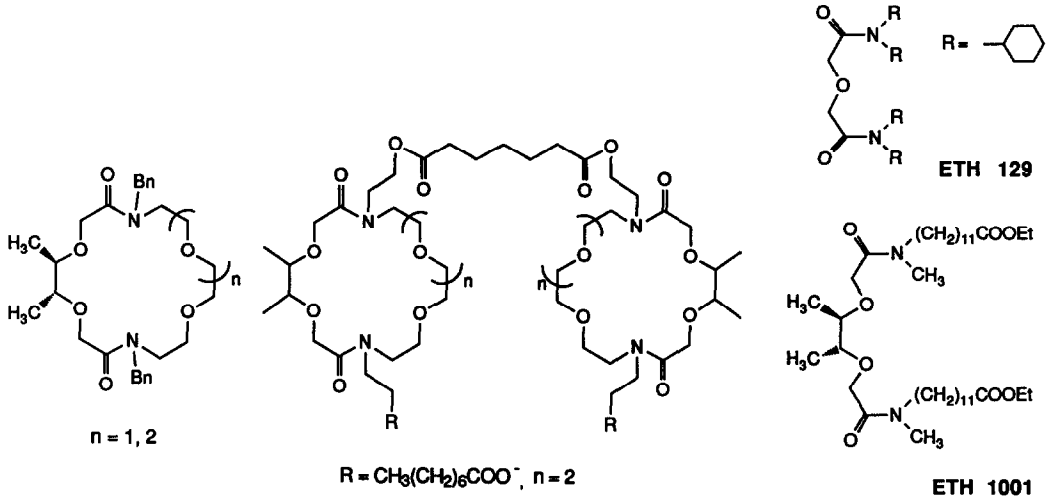


Figure 1 : Representative Dilactams, Bicyclic Polyether Diamide and Ether Diamides Derivatives from the Literature

These observations led us to predict that the incorporation of two ether diamide moieties into a macrocycle with suitable ring size should allow to enhance both selectivity and complexing properties.

In preliminary communications[8] we reported on the synthesis of tetralactams with two dimethyleneoxy moieties which paralleled the linear diamide ETH 129 and showed interesting complexing properties towards alkaline earth cations. This paper is a full account of the synthesis of these macrocyclic tetralactams with 18, 21 and 24 ring atoms. Their structures are represented in Figure 2.

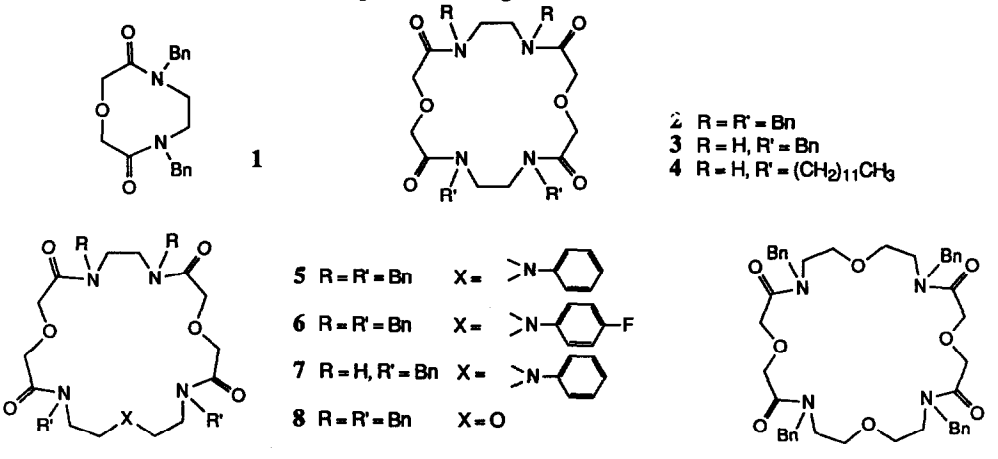


Figure 2 : New Polylactams Compounds

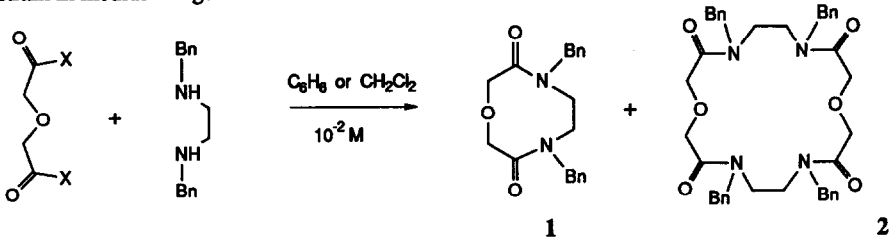
RESULTS and DISCUSSION

. Direct macrocyclization

The reaction of diamines and dicarboxylic acid dichlorides was frequently used for the preparation of tetralactams. Generally mixtures of dilactam (monomer) and tetralactam (dimer) were obtained. Nevertheless when the cyclization to monomer is geometrically restricted, high yields in dimer may be obtained.

An improvement of dimer selectivity was observed in the synthesis of some polymethylene tetralactams using a diazasilolidine[9] derived from the diamine in order to take into account the template effect of the silicium atom. However we described in a previous paper[10] that the replacement of methylene groups by oxygen atoms led to a serious drop in the dimer vs monomer selectivity.

We tested this direct macrocyclization process by studying the selectivity monomer (9-membered)/dimer (18-membered) in the condensation of N,N'-dibenzylethylenediamine and activated diglycolic acid. The activation is achieved through formation of the diacid dichloride or the N-acyl thiazolidine 2-thione derivative[11] (Scheme 1). The best result was obtained with this latter coupling reagent yielding 31% of dimer. But the selectivity was not as high as that anticipated from the results of Fujita[11a] on the formation of polymethylene tetralactams. Despite its unfavourable 9-membered size and although high dilution techniques were not used, the recovery of the monomer dilactam in 20% yield may be explained by the presence of one oxygen ether atom reducing the strain in medium rings[12].



1 2

X	yields (%)	
Cl	21.0 (**1**)	20.1 (**2**)
	22.7 (**1**)	31.3 (**2**)

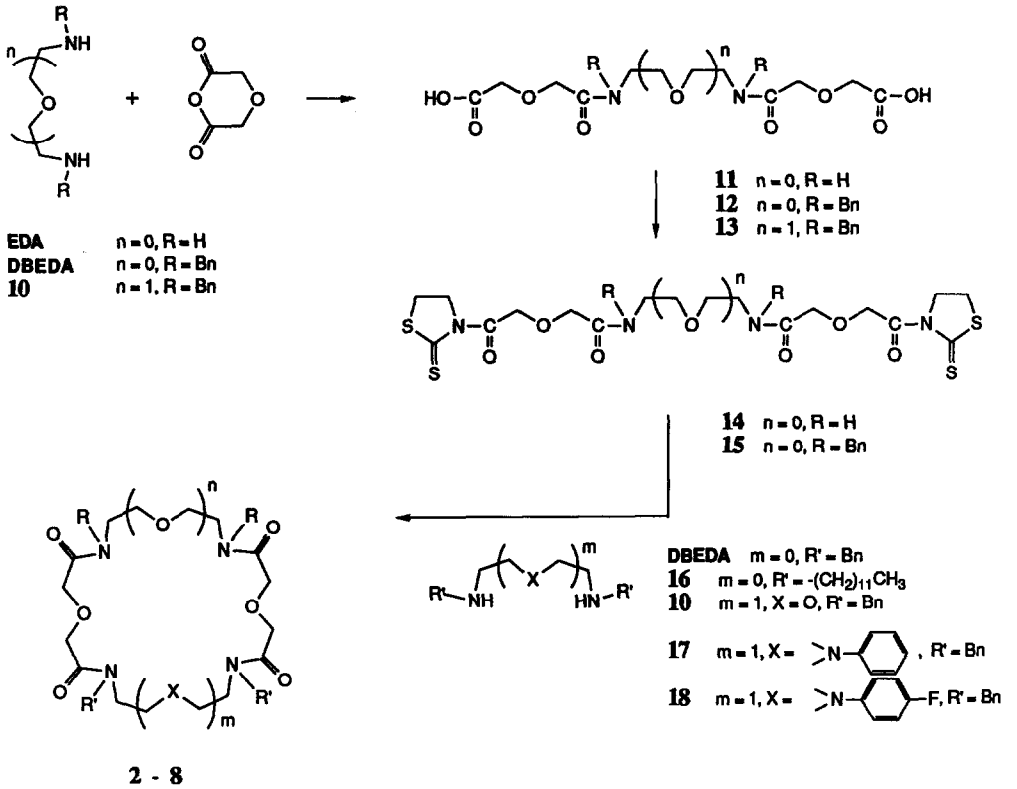
Scheme 1 : Direct Macrocyclization Pathway

Although the yields in tetralactams are acceptable, this direct macrocyclization seems difficult to optimize because of the competition di/tetralactam[13]. In addition this methodology may only provide tetralactams with a C-2 symmetry : it is inappropriate to obtain odd-membered ring macrocycles as well as tetralactams bearing different substituents on nitrogen atoms. Indeed the number of donor atoms, the cavity size and lipophilicity are main factors for binding affinity and cation selectivity. Hence in the development of synthetic models for naturally occuring ionophores, it is useful to have in hand a versatile method of synthesis.

. Stepwise synthesis

The stepwise synthesis developed in this report is outlined in Scheme 2. This method involves an intermediate diamide-diacid prepared from the diglycolic anhydride and a diamine. The resulting acid functions were then activated by the thiazolidine-2-thione group and the cyclization was carried out with a bis-secondary amine leading under low-dilution conditions to the tetralactams. This activating group was selected instead of

the acid chloride one. The reason is that the preparation of diacid dichloride from diamide e.g. **11** or **12** failed with thionyl or oxalyl chloride as previously observed by Izatt and Coll.[15]. The reaction was easily extended to 21- and 24- membered ring macrocycles using the appropriate bis-secondary amines.



Scheme 2 : Stepwise Synthesis Pathway

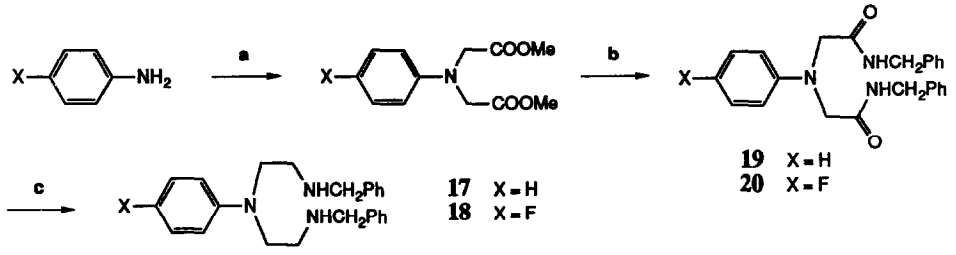
. ***Preparation of bis-secondary amines***

The diamines required to prepare the macrocyclic tetralactams are derived from ethylenediamine (EDA or DBEDA), 1,5-diamino-3-oxapentane and 1,5-diamino-3-azapentane. 1,7-Dibenzyl-4-oxa-1,7-diazaheptane (**10**) was obtained from diglycolyl chloride in a two step synthesis according to Gokel[14].

N,N'-didodecyl ethylenediamine was prepared by reaction of N,N'-ditosyl ethylenediamine with 1-bromododecane in DMF solution in the presence of sodium methylate. After removal of the tosyl groups by H_2SO_4 compound **16** was obtained in an overall yield of 24% from the starting ethylenediamine (35% for the deprotection step).

The reactions used to prepare the triamines **17** and **18** are shown in Scheme 3. The starting anilines were easily dialkylated by methyl bromoacetate. The amidation of the resulting diesters by benzylamine afforded excellent yield for **19** (91%) for which the reaction was optimized. $H_3B.THF$ or $H_3B.SMe_2$ reduction of bis-amides finally leads to the expected bis-secondary amines. We also found that reduction with LAH despite prolonged reaction times gave mainly monoamines (35%) besides diamines (10%). These resulting

diamines were purified by column chromatography and their purity checked by HPLC. At last, overall yields of 40% for **17** and **18** were thus obtained.



a. $BrCH_2COOMe$ / Na_2HPO_4 / NaI - b. $PhCH_2NH_2$ / $CH_3O^-Na^+$ - c. $H_3B.THF$ or $H_3B.SMe_2$

Scheme 3 : Synthesis of the Triamines

. ***Preparation of thiazolidine-2-thione derivatives***

The diacid diamides **11-13** were obtained by reacting diamines with diglycolic anhydride in dry tetrahydrofuran solutions. The replacement of benzene[8a] by THF increased the yield of **11** from 32% to 70%. Thiazolidine-2-thione derivatives **14** and **15** were prepared following the procedure described by Fujita[11a]. Thus, compounds **11, 12** were condensed with thiazolidine-2-thione in the presence of dicyclohexylcarbodiimide and of a catalytic amount of 4-dimethylaminopyridine. The resulting activated derivatives **14** and **15** were at first purified by chromatography on a silica gel column with 46 and 39% yields respectively[8a]. A main problem with this purification method consisted in the instability of these compounds using silica gel. Alternatively a work up in dichloromethane afforded activated compounds with excellent purities and much higher yields (70%).

. ***Macrocyclization step***

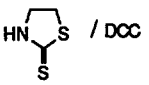
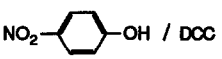
A large variety of coupling agents useful for the preparation of amides is known. In a preliminary study, the effect of some reagents on the yield of the macrolactamization reaction was investigated with the formation of the tetralactam **2** as model reaction (Table 1). The coupling agents selected were already used for the preparation of macrolactams or cyclopeptides[11, 16, 17]. The activation by N,N' carbonyldiimidazole (CDI) of diamide diacid **12** failed in our hands. Insoluble material was only obtained. Among the other coupling reagents studied, activation achieved through thiazolidine-2-thione appears to be the most effective one, though the activated intermediate amide was purified and isolated. A yield of 70% (cyclization) and an overall yield of 49% (activation and cyclization) was thus obtained. Condensation with the bis(4-nitrophenyl ester) derivative of compound **12** or use of "in situ" activating coupling agent (DEPC, BOP) gave lower yields. After our preliminary communication[8a], Mertes[18] reported a 58% yield for tetralactam **2** by an analogous sequence using an excess of diphenylphosphoryl azide (DPPA) as in situ activating-coupling agent.

The thiazolidine-2-thione mediated cyclization was used for preparing tetralactams presented in this paper, except for **9** where BOP reagent was employed. The reactions were carried out in dichloromethane, at room temperature under low dilution conditions (5.10^{-3} M). Purification of the tetralactams was effected on silica gel. It is noteworthy that the purification of tetralactams prepared using this stepwise method was easier than the isolation of the same compounds obtained from the one step procedure. The yields in macrocyclization

were quite acceptable : 70% for the 18-membered rings **2-4** and 42-62% for the 21-membered rings **5-8** (see Table 2)

Long reaction times were observed for these macrocyclization reactions (2-3 days). For the synthesis of tetralactam **5** the progress of the reaction was monitored spectrophotometrically in CH_2Cl_2 solution by the disappearance at 305 nm of the acylating agent **15**. It was found that 0.1 equivalent is consumed after 3 hrs and 0.7 equivalent after 24 hrs. On the contrary, the aminolysis rate of compound **15** by N-benzylmethylamine parallels what was observed by Fujita[19] for the reaction of 3-hexadecanoylthiazolidine-2-thione with the same secondary amine (reaction time 8', yield 95%). On the other hand, for the preparation of **5**, the presence of an isosbestic point (289 nm) in the observed absorption spectra and the study of the evolution of the reaction by thin layer chromatography indicated that the intermediate species resulting from the aminolysis of one activated carboxylic function does not accumulate during the reaction. These data suggest that for the macrocyclization reaction the first step is slow whereas the cyclization step might be fast. This kinetic behaviour could explain the high yields of macrocyclic products obtained without the use of high dilution techniques.

Table 1 : Coupling Agent-Promoted Cyclizations of Tetralactam **2**

Reagent a)	reactions conditions		yield % b)
	solvent	time (h)	
 / DCC	CH_2Cl_2	72	(49)
	CH_2Cl_2	72	29
DEPC	DMF	2	28
BOP	CH_3CN	2	44 (35)

a) abbreviations used : DEPC = diethylphosphorocyanidate, BOP = benzotriazol-1-yl-tris(dimethylamino) phosphonium hexafluorophosphate ; b) Overall yields (activation and macrocyclization) determined by HPLC and isolated yields in brackets.

The structures proposed for the macrocyclic compounds are consistent with data derived from infrared and proton nuclear magnetic resonance spectra in addition to satisfactory combustion analyses and molecular weights determined by mass spectrometric analyses. All macrocyclic lactams are characterized by a carbonyl absorption at 1641-1665 cm^{-1} and a proton NMR pattern consistent with the presence of cyclic lactams. The NMR spectra of these compounds appeared complex due to the phenomenon of hindered internal rotation around the carbon-nitrogen bond of each of the four amide moieties. Therefore these macrocyclic tetralactams display several slow interconverting conformations. For instance, at 250 MHz in CD_3CN compound **7** exhibits twelve peaks in the area related to CH_2O and CH_2Ph groups whereas only three peaks are expected for one isomer. This set of signals coalesces into the three peaks at ca 80°C. The NMR data are summarized in Table 2. The mass spectra of **2-9** compounds performed by fast atomic bombardment (FAB) or desorption - chemical ionization (DCI/NH_3) techniques showed quasi molecular ion $[M+H]^+$ according to the molecular weight expected for each ligand. These molecular ion peaks constitute base peaks in every case.

Table 2 : Cyclization Yields and Physical Properties of Macrocyclic Tetralactams **2** - **9**
(see Scheme 2 for synthesis and Fig. 2 for structures of the macrocycles)

	Starting Materials [a]		Yield %	mp °C	^{1}H NMR Spectra (80 and 250 MHz, $CDCl_3$, δ) [b]
2	DBEDA	**12**	70	214-218	3.36-3.73 (m, 8H, CH_2N), 4.23-4.69 (m, 16H, CH_2O, CH_2Ph), 7.0-7.45 (m, 20H, Ar)
3	DBEDA	**11**	73	150-152	3.25-3,76 (m, 8H, CH_2N), 3.87-4.64 (m, 12H, CH_2O, CH_2Ph), 6.90-7.38 (m, 10H, Ar)
4	**16**	**11**	70	74-75	0.69-1.78 (m, 46H, CH_3-$(CH_2)_{10}$-), 2.85-3.60 (m, 12H, CH_2N), 3.95-4.40 (m, 8H, CH_2O)
5	**17**	**12**	58	119-120	3.13-3.67 (m, 12H, CH_2N), 4.22-4.60 (m, 16H, CH_2O, CH_2Ph), 6.30-6.77 (m, 3H, Ar), 7.11-7.35 (m, 22H, Ar)
6	**18**	**12**	42	122-124	3.16-3.73 (m, 12H, CH_2N), 4.20-4.78 (m, 16H, CH_2O, CH_2Ph), 6.04-6.92 (m, 2H, Ar), 6.96-7.54 (m, 22H, Ar)
7	**17**	**11**	62	95-97	3.25-3.55 (m, 12H, CH_2N), 3.86-4.63 (m, 12H, CH_2O, CH_2Ph), 6.36-6.84 (m, 3H, Ar), 7.05-7.41 (m, 12H, Ar)
8	**10**	**12**	48	94-95	3.17-3.65 (m, 12H, NCH_2CH_2O), 4.10-4.82 (m, 16H, CH_2O, CH_2Ph), 7.16-7.36 (m, 20H, Ar)
9	**10**	**13**	23 [c]	114-115	3.08-3.84 (m, 16H, NCH_2CH_2O), 3.90-4.85 (m, 16H, CH_2O, CH_2Ph), 6.96-7.49 (m, 20H, Ar)

a) DBEDA = N,N'-dibenzylethylenediamine ; b) 80 MHz for **2** - **4**, **9** ; CD_3CN for **5**, **7**, **8** ; c) BOP used as activating coupling agent.

CONCLUSION

Comparative overall yields obtained for preparing **2** by using the stepwise approach with the thiazolidine-2-thione as coupling agent and the direct macrocyclization indicate that the first method is more efficient despite the greater number of steps involved (47% vs 31%).

Thus we have shown that tetralactams with two dimethyleneoxy moieties can be synthesized by a three-step method leading to dissymmetrical or symmetrical molecules. The advantages of this method are as follows: (i) high yields of cyclization- typically 42-73% - without high dilution techniques ; (ii) ease of purification ; (iii) synthetic versatility. This allows to provide even or odd membered tetralactams with flexible lipophilicity and donor number.

A study of an another pathway independent of the availability of the starting cyclic anhydride is in progress.

EXPERIMENTAL SECTION

Melting points were determined on a Kofler apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 883 spectrophotometer in potassium bromide discs or in 0.05 M chloroform solutions using NaCl 0.5 mm cells. ^{1}H magnetic resonance spectra (80 MHz unless otherwise indicated) and ^{13}C magnetic resonance spectra (22.6, 50.3 or 62.9 MHz) were recorded on Bruker AC 80, WH 90, AC 200 or AC 250 spectrometers and are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported in the following order : chemical shift, spin multiplicity (s = singulet, d = doublet, t = triplet, m = multiplet), integration and assignment. Mass spectra (MS) were performed with a NERMAG R10-10C spectrometer using the Fast Atom Bombardment (FAB, MNBA matrix) or desorption-chemical ionization (DCI/NH_3) techniques. UV-Vis spectra were obtained from a Perkin-Elmer Lambda 17 spectrophotometer. Elemental analyses were carried out by the "Service Commun de Microanalyse élémentaire UPS-INP" in Toulouse. Analytical HPLC was performed on a Kratos 400 chromatograph with a Microbondapack C18 column (300 x 4.6 mm, 10 μ). Precoated sheets (Merck silicagel 60F-254) were used for TLC analyses.

Compounds were detected with UV light (254 nm) and/or iodine chamber. rf values refer to relative mobilities on TLC plates. Preparative chromatography columns were packed with Amicon silica gel 60 (70-200 mesh). Commercially available chemicals were used as purchased without further purification, except for solvents, which were purified and dried before use by standard methods.
The following compounds were prepared as described in the literature : diglycolic anhydride[20], diglycolic acid dichloride[21], 1,7-dibenzyl-4-oxa-1,7-diazaheptane[14], N,N'-bis(p-tolylsulfonyl)ethylenediamine[22].

Preparation of bis secondary amines

- N,N'-didodecyl ethylenediamine 16

Alkylation of N,N'-bis(p-tolylsulfonyl)ethylenediamine : To a stirred, cooled solution of 4.08 g (75.6 mmol) of freshly prepared sodium methoxide in 70 ml of methanol was added 13.96 g (37.8 mmol) of solid N,N'-bis(p-tolylsulfonyl)ethylenediamine. The clear solution was then flash evaporated and the white residue taken up with 120 ml of DMF. To the stirred solution heated at 80 °C was added dropwise 18.79 g (75.4 mmol) of 1-bromododecane . This mixture was stirred at 80 °C for 2 hrs. When cooled, the dialkylated product precipitated from the reaction mixture, or crystallized out by evaporation of a part of the solvent under reduced pressure. White needles were collected on a filter and washed with water, methanol and ether. A small sample was recrystallized from methanol. 22.9 g (86.0%) ; m.p. 80-82 °C ; IR (KBr) 1349 (SO_2), 1154 cm^{-1} (SO_2) ; ^1H NMR ($CDCl_3$, 60 MHz), δ 0.87 (t, 6H, J = 4 Hz, CH_3), 1.30 (broad s, 40H, -$(CH_2)_{10}$-), 2.43 (s, 6H, CH_3Ts), 3.10 (t, 4H, J = 7 Hz, -CH_2N-), 3.23 (s, 4H, NCH_2CH_2N), 7.26 (d, 4H, J = 4 Hz, Ts), 7.66 (d, 4H, J = 4 Hz, Ts).
Detosylation : the previous compound (5g, 7.1 mmol) was suspended in concentrated sulfuric acid (97%, 15 ml) and stirred at 100 °C for 72 hrs. The solution was then cautiously neutralized with sodium hydroxyde solution while cooling. The precipitated sodium sulfate was removed by filtration and the mother liquor extracted with dichloromethane.The CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give white crystals of compound **16**, which was not further purified. 1.1 g (39%) ; m.p. 58-60 °C ; IR (KBr) 3245 cm^{-1} (NH) ; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.90 (t, 6H, J = 4 Hz, CH_3),1.30 (broad s, 40H, -$(CH_2)_{10}$-), 1.47 (s, 2H, NH), 2.61 (t, 4H, J = 7 Hz, CH_2N), 2.72 (s, 4H, NCH_2CH_2N) ; ^{13}C NMR ($CDCl_3$, 50.3 MHz), δ 14.1 (CH_3), 22.7, 27.4, 29.4, 29.6, 29.65, 29.7, 30.2, 31.9 (-$(CH_2)_{10}$-), 49.5 and 50.0 (CH_2N).

- 1,7-Dibenzyl-4-phenyl-1,4,7-triazaheptane : 17 (Scheme 3) :

Dialkylation of aniline : 1.86 g (20 mmol) of aniline, 8.42 g (55 mmol) of methyl bromoacetate, 7.8 g (55 mmol) of anhydrous Na_2HPO_4 and 1.5 g (10 mmol) of sodium iodide in 35 ml of acetonitrile were stirred and refluxed under argon for 18 hrs. The cooled reaction was diluted with water until dissolution of inorganic salts. The reaction mixture was then extracted with four 50 ml portions of toluene. The combined organic extracts were dried with Na_2SO_4, filtered and evaporated. The residue was chromatographed on silica with dichloromethane - ethyl acetate / 95-5 (v/v) eluent. 4.74 g of expected diester was thus obtained (100%) ; brown thick oil ; rf = 0.44 (CH_2Cl_2-AcOEt / 95-5) ; IR ($HCCl_3$) 1735 cm^{-1} (C=O) ; ^1H NMR ($CDCl_3$), δ 3.73 (s, 6H, CH3), 4.17 (s, 4H, CH2), 6.37-7.40 (m, 5H, Ar) ; ^{13}C NMR ($CDCl_3$, 22.6 MHz), δ 52.0 (CH_2), 53.2 (CH_3), 112.4 (Ar-C_o), 118.3 (Ar-C_p), 129.3 (Ar-C_m), 147.8 (Ar-C_i), 171.3 (C=O).

Amidation of the previous diester : To a stirred suspension of 5.9 g (0.11 mol) of freshly prepared sodium methoxide in 100 ml of dry benzene were added successively 10.7 g (0.1 mol) of benzylamine then a solution of 11.9 g (50 mmol) of the previous diester in 15 ml of benzene. The reaction mixture was stirred at 80°C overnight, then cooled to 0°C and poured into 100 ml of 1N HCl. The suspension was diluted with 100 ml of pentane and filtered. The precipitate was washed with pentane and dried under vacuum. Recrystallization from boiling benzene afforded 19.4 g of expected diamide **19** (91%) ; m.p. 176-178 °C ; rf = 0.33 ($HCCl_3$-CH_3COCH_3 70-30) ; IR ($HCCl_3$) 3432 (free NH), 3267 (associated NH), 1662 cm^{-1} (C=O) ; ^1H NMR ($CDCl_3$), δ 3.96 (s, 4H, CH_2CO), 4.42 (d, 4H, J = 5.9 Hz, $\underline{CH_2}Ph$), 6.40-7.53 (m, 15H, Ar), 8.10 (t, 2H, J = 5.9 Hz, NH) ; ^{13}C NMR ($CDCl_3$, 50.3 MHz), δ 43.5 ($\underline{CH_2}NPh$), 57.2 ($\underline{CH_2}CO$), 111.9 (Ar-C_o), 118.5 (Ar-C_p), 127.4 (Bn-C_p), 127.7 (Bn-C_o), 128.6 (Bn-C_m), 129.5 (Ar-C_m), 138.1 (Bn-C_i), 146.2 (Ar-C_i), 171.0 (C=O).

Compound **17** : A solution of 4.84 g (12.5 mmol) of the previous diamide in 125 ml of dry THF was slowly added to a stirred solution of BH_3-THF complex (100 ml, 1.0 M) at 0 °C. After addition the reaction mixture was stirred under reflux for 20 hrs. It was then cooled to 0 °C, and excess of borane was destroyed by cautious addition of water (7-8 ml). When the liberation of H_2 was stopped, the mixture was concentrated in vacuo and 6N HCl (40 ml) was added. The aqueous solution was heated at reflux for 6 h, cooled, and adjusted to pH 10 with 15% NaOH solution. The aqueous solution was then extracted with $HCCl_3$ (4 x 30 ml). The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (CH_2Cl_2-CH_3OH-$(C_2H_5)_3N$ / 90-10-0.5) gave the triamine **17** (2.2 g, 49%) as an oil ; rf = 0.29 (CH_2Cl_2-CH_3OH-$(C_2H_5)_3N$ / 90-10-0.5) ; IR ($HCCl_3$) 3300 cm^{-1} (NH) ; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.3 (broad s, 2H, NH), 2.85 (t, 4H, J = 7 Hz, $\underline{CH_2}NH$), 3.48 (t, 4H, J = 7 Hz, $\underline{CH_2}$-N-Ph), 3.78 (s, 4H, $\underline{CH_2}$-Ph), 6.50-7.47 (m, 15H, Ar) ; ^{13}C NMR ($CDCl_3$, 22.6 MHz), δ 46.7 (CH_2NH), 51.7 ($\underline{CH_2}$-N-Ph), 53.9 ($\underline{CH_2}Ph$), 112.7 (Ar-C_o), 116.6 (Ar-C_p), 127.0 (Bn-C_p), 128.0 (Bn-C_o), 128.4 (Bn-C_m), 129.3 (Ar-C_m), 140.0 (Bn-C_i), 148.3 (Ar-C_i).

- **1,7-Dibenzyl-4-(4-fluoro)phenyl-1,4,7-triazaheptane 18** (Scheme 3)

Dialkylation of 4-fluoroaniline : Following the procedure described above, the diester was obtained in 88 % yield ; brown oil ; rf = 0.40 (CH_2Cl_2-AcOEt / 95-5) ; IR ($HCCl_3$) 1735 cm^{-1} (C=O) ; ^1H NMR ($CDCl_3$, 60 MHz), δ 3.73 (s, 6H, CH_3), 4.13 (s, 4H, CH_2), 6.40-7.17 (m, 4H, Ar) ; ^{13}C NMR ($CDCl_3$, 22.6 MHz), δ 52.0 (CH_2), 53.7 (CH_3), 114.0 (d, $^3J_{C-F}$ = 7.4 Hz, Ar-C_o), 115.7 (d, $^2J_{C-F}$ = 23.5 Hz, Ar-C_m), 144.6 (Ar-C_i), 156.4 (d, $^1J_{C-F}$ = 235 Hz, Ar-C_p), 171.3 (C=O).

Amidation of the previous diester : Following the procedure described above the diamide **20** was obtained in 65% yield ; m.p. = 180-183 °C ; rf = 0.44 (CH_2Cl_2-CH_3OH / 95-5) ; IR (KBr) 3280, 3220 (NH), 1650 cm^{-1} (C=O); ^1H NMR ($CDCl_3$), δ 3.90 (s, 4H, CH_2CO), 4.37 (d, 4H, J = 7 Hz, $\underline{CH_2}NH$), 6.30-7.43 (m, 14H, Ar), 8.37 (t, 2H, J = 7 Hz, NH) ; ^{13}C NMR ($CDCl_3$, 22.6 MHz), δ 43.5 ($\underline{CH_2}Ph$), 57.5 ($\underline{CH_2}CO$), 112.8 (d, $^3J_{C-F}$ = 7.4 Hz, Ar-C_o), 115.9 (d, $^2J_{C-F}$ = 22.1 Hz, Ar-C_m), 127.4 (Bn-C_p), 127.6 (Bn-C_o), 128.6 (Bn-C_m), 138.0 (Bn-C_i), 142.7 (Ar-C_i), 156.4 (d, $^1J_{C-F}$ = 235 Hz, Ar-C_p), 170.8 (C=O).

Compound **18** : Following the procedure described above the compound **18** was obtained in 51% yield ; oil ; rf = 0.24 (CH_2Cl_2-CH_3OH-$(C_2H_5)_3N$ / 90-10-0.5) ; IR ($HCCl_3$) 3300 cm^{-1} (NH) ; ^1H NMR ($CDCl_3$, 60 MHz), δ 2.07 (broad s, 2H, NH), 2.75 (t, 4H, J = 7 Hz, $\underline{CH_2}NH$), 3.53 (t, 4H, J = 7 Hz, $\underline{CH_2}$-N-Ph), 3.75 (s, 4H, $\underline{CH_2}Ph$), 6.48-7.42 (m, 14H, Ar) ; ^{13}C NMR ($CDCl_3$, 22.6 MHz), δ 46.6 (CH_2NH), 52.4 ($\underline{CH_2}$-N-Ph), 53.9 ($\underline{CH_2}$-Ph), 114.8 (d, $^3J_{C-F}$ = 7 Hz, Ar-C_o), 115.5 (d, $^2J_{C-F}$ = 21 Hz, Ar-C_m), 127.0 (Bn-C_p), 128.0 (Bn-C_o), 128.4 (Bn-C_m), 140.0 (Bn-C_i), 145.3 (Ar-C_i), 155.6 (d, $^1J_{C-F}$ = 235 Hz, Ar-C_p).

Preparation of diamide diacid

To a stirred solution of diglycolic anhydride (24 mmol) in dry THF (20 ml) heated at 50 °C was added dropwise a solution of diamine (12 mmol) in dry THF (10 ml). The mixture was stirred at the same temperature for 12 hrs. Compounds **11** and **12** precipitated from the solution and the crystals were filtered off, washed with THF, $HCCl_3$, ether and dried in vacuo. Compound **13** was obtained after flash evaporation of the solvent and washed as previously.

Compound **11** : **11** was obtained from ethylenediamine in 70% yield ; white solid ; m.p. = 146 °C, IR (KBr) 3390 (NH), 3200-2800 (OH), 1765 (C=O, acid), 1640 cm^{-1} (C=O, amide) ; ^1H NMR ($DMSOd_6$), δ 3.24 (m, 4H, CH_2N), 3.96 (s, 4H, CH_2O), 4.11 (s, 4H, CH_2O), 7.9 (broad s, 2H, NH) ; ^{13}C NMR ($DMSOd_6$, 62.9 MHz), δ 37.9 (CH_2N), 67.8 (CH_2O), 70.0 (CH_2O), 169.0 (CON), 171.3 (COOH).

Compound **12** : **12** was obtained from N,N'-dibenzyl ethylenediamine in 96% yield ; white solid ; m.p. = 135°C, IR (KBr) 3100-2800 (OH), 1720 (C=O, acid), 1605 cm^{-1} (C=O, amide) ; ^1H NMR ($DMSOd_6$, 200 MHz),δ 3.35 (m, 4H, CH_2N), 4.10 (s, 4H, $\underline{CH_2}COOH$), 4.28 (m, 4H, $O\underline{CH_2}CO$), 4.52 (m, 4H, $\underline{CH_2}Ph$), 7.20-7.37 (m, 10H, Ar) ; ^{13}C NMR (DMSO d_6, 62.9 MHz), δ 42.6, 43.0, 44.1, 44.3 (CH_2N), 47.7, 48.0, 49.8, 50.2 ($\underline{CH_2}Ph$), 67.0, 67.5, 67.7, 68.4, 68.7 (CH_2O), 126.6-128.6 (7 peaks, Ar-$C_{o,m,p}$), 137.0, 137.5 (Ar-C_i), 168.7, 168.9, 169.0 (CON), 171.2, 171.3 (COOH).

Compound **13** : **13** was obtained from **10** in 90 % yield ; oily product ; IR ($HCCl_3$) 3200-2800 (OH), 1755 (C=O, acid), 1620 cm^{-1} (C=O, amide) ; ^1H NMR ($CDCl_3$), δ 3.30 (broad s, 4H, CH_2N), 3.51 (broad s, 4H, OCH_2CH_2N), 4.10 (s, 4H, CH_2COOH), 4.23 (m, 4H, OCH_2CO), 4.52 (m, 4H, CH_2Ph), 7.0-7.35 (m, 10H, Ar).

Preparation of thiazolidine-2-thione (t-2-t) derivatives

General procedure : Dicyclohexylcarbodiimide (1.30 g, 6.3 mmol) and a catalytic amount of 4-dimethylaminopyridine were added to a solution of the diacid derivative (2.4 mmol) and thiazolidine-2-thione (1.0 g, 8.4 mmol) in ethyl acetate (35 ml). The mixture was stirred at room temperature for 24 hrs and the precipitate formed in the reaction was collected on a filter. This precipitate was poured in dichloromethane (30 ml) and the organic solution was concentrated in vacuo to give a yellow product with satisfactory purity. Analytical samples were chromatographed on silica gel with dichloromethane-acetone as eluents.

Thiazolidine-2-thione derivative of diglycolic acid : it was obtained in 73% yield ; yellow prisms ; m.p. = 145-147 °C ; rf = 0.22 (CH_2Cl_2-CH_3COCH_3 / 98-2) ; IR ($HCCl_3$) 1710 cm^{-1} (C=O) ; ^1H NMR ($CDCl_3$), δ 3.37 (t, 4H, J = 7.5 Hz, CH_2S), 4.61 (t, 4H, J = 7.5 Hz, CH_2N), 5.12 (s, 4H, CH_2O) ; ^{13}C NMR ($DMSOd_6$, 62.9 MHz), δ 29.3 (CH_2S), 55.7 (CH_2N), 71.9 (CH_2O), 171.1 (C=O), 201.9 (C=S).

Compound **14** : **14** was obtained from **11** following the general procedure except for the solvent (CH_3CN vs AcOEt) in 70% yield ; yellow prisms ; m.p. = 147 °C ; rf = 0.25 (CH_2Cl_2-CH_3COCH_3 / 40-60) ; IR ($HCCl_3$) 3420 (NH), 1700 (-C(O)-(t-2-t)), 1670 cm^{-1} (-C(O)N-) ; ^1H NMR ($CDCl_3$, 60 MHz), δ 3.28-3.55(m, 8H, CH_2S, NCH_2-CH_2-N-), 4.11 (s, 4H, CH_2-C(O)NH-), 4.63 (t, 4H, 7.5 Hz, NCH_2CH_2S-), 5.08 (s, 4H, CH_2-C(O)-(t-2-t), 7.35 (s, 2H, NH) ; ^{13}C NMR ($CDCl_3$, 22.6 MHz), δ 29.6 (CH_2S), 38.9 (NCH_2CH_2N), 55.4 (NCH_2CH_2S), 71.4 (CH_2O), 74.8 (CH_2O), 170.9 (C=O), 171.6 (C=O), 201.5 (C=S).

Compound **15** : **15** was obtained from **12** in 71 % yield ; yellow needles ; m.p. = 140-141 °C ; rf = 0.22 (CH_2Cl_2-CH_3COCH_3 / 80-20) ; IR ($HCCl_3$) 1710 (-C(O)-(t-2-t)), 1660 cm^{-1} (-C(O)N) ; UV (CH_2Cl_2) λ 270 (ε_{max} = 29 200), 305 nm (ε = 20 500) ; ^1H NMR ($CDCl_3$), δ 3.22-3.55 (m, 8H, CH_2S, NCH_2CH_2N), 4.30 (s, 4H, CH_2-C(O)-NCH_2Ph), 4.43-4.67 (m, 8H, SCH_2CH_2N, CH_2Ph), 5.05 (s, CH_2-C(O)-(t-2-t)), 7.22-7.28 (m, 10H, Ar) ; ^{13}C NMR ($CDCl_3$, 50.3 MHz), δ 29.6 (CH_2S), 42.2, 43.5, 45.0 (NCH_2CH_2N), 48.7, 50.0, 51.8 (CH_2Ph), 55.5 (SCH_2CH_2N), 69.6, 70.2, 73.3 (CH_2O), 126.7-129.1 (9 peaks, Ar-$C_{o,m,p}$), 136.1, 136.3, 137.1 (Ar-C_i), 168.9, 169.2, 169.6, 171.3, 171.4 (C=O), 201.2 (C=S).

Polylactams 1 and 2 via direct macrocyclization

Method A : To a stirred solution of N,N'-dibenzyl ethylenediamine (0.72 g, 3 mmol) and triethylamine (0.72 g, 7.2 mmol) in anhydrous benzene (300 ml) heated at 50 °C was added a solution of diglycolic acid dichloride (0.513 g, 3 mmol) in 40 ml of anhydrous benzene. After the addition was complete (2 hrs), the reaction was kept along a period of 2 hrs and then cooled to room temperature. The triethylamine hydrochloride formed along the reaction was filtered off and the filtrate evaporated to dryness under vacuum. Chromatography (dichloromethane-acetone / 80-20) afforded polylactams **1** (0.21 g, 21%) and **2** (0.204 g, 20.1%).

Method B : A solution of N,N'-dibenzyl ethylenediamine (0.72 g, 3 mmol) in CH_2Cl_2 (40 ml) was added at room temperature to a stirred solution of thiazolidine-2-thione derivative of diglycolic acid (1 g, 3 mmol) in CH_2Cl_2 (300 ml). The mixture was then stirred for 48 hrs and concentrated in vacuo. Chromatography afforded lactams **1** (0.23 g, 22.7%) and **2** (0.32 g, 31.3%).

Compound **1** : White solid ; m.p. = 139-141 °C ; rf = 0.56 (CH_2Cl_2-CH_3CH_2OH / 96-04) ; IR ($HCCl_3$) 1660 cm^{-1} (C=O) ; ^1H NMR ($CDCl_3$), δ 3.61 (s, 4H, CH_2N), 4.37 (s, 4H, CH_2O), 4.45 (s, 4H, CH_2Ph), 7.15-7.30 (m, 10H, Ar) ; MS (DCI/NH_3) : m/e 339 ($[M+H]^+$, 100%) ; Anal. calcd for $C_{20}H_{22}N_2O_3$: C, 70.99 ; H, 6.55 ; N, 8.28. Found : C, 70.78 ; H, 6.48 ; N, 8.13.

Compound **2** : White solid ; rf = 0.48 (CH_2Cl_2-CH_3CH_2OH / 96-04) ; IR ($HCCl_3$) 1665 cm^{-1} (C=O) ; MS (DCI/NH_3) : m/e 677 ($[M+H]^+$, 100%) ; Anal. calcd for $C_{40}H_{44}N_4O_6$: C, 70.99 ; H, 6.55 ; N, 8.28. Found : C, 70.51 ; H, 6.56 ; N, 8.15.

Tetralactam 2 via stepwise synthesis

Macrocyclization achieved through thiazolidine-2-thione activation (general procedure) : thiazolidine-2-thione derivative (3 mmol) and diamine (3 mmol), each dissolved in dichloromethane (150 ml) were slowly added simultaneously to a stirred dichloromethane (300 ml) solution at room temperature. After the addition was complete the mixture was stirred along a period of 2-3 days. After evaporation of the solution in vacuo, the remaining residue was chromatographed.

Macrocyclization achieved through p-nitrophenyl ester activation : to a stirred solution of diamide-diacid **12** (0.472 g, 1 mmol) in dried dichloromethane (25 ml) was added 4-nitrophenol (0.334 g, 2.4 mmol) and 1-hydroxybenzotriazole (0.378 g, 2.8 mmol). 1,3-Dicyclohexylcarbodiimide (0.454 g, 2.2 mmol) was added to the reaction mixture at 0 °C, which was then stirred for 1 hr at 0 °C and 3 hrs at room temperature. Precipitated urea was then filtered off and the dichloromethane solution was washed with saturated $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was removed in vacuo to give 0.69 g of crude bis(4-nitrophenyl ester) derivative (IR ($HCCl_3$) : 1783 (C=O ester), 1656 cm^{-1} (C=O amide)) which was not further purified. Condensation of crude bis(4-nitrophenyl ester) derivative with N,N'-dibenzylethylenediamine (0.24 g, 1 mmol) was carried out in CH_2Cl_2 as described above. After evaporation of the solution under vacuum the remaining residue was analyzed by chromatography.

Macrocyclization achieved through DEPC activation : to a stirred mixture of diamide diacid **12** (0.472 g, 1 mmol), N,N'-dibenzyl ethylenediamine (0.24 g, 1 mmol) and DEPC (0.358 g, 2.2 mmol) in DMF (200 ml) was added dropwise a solution of triethylamine (0.222 g, 2.2 mmol) in DMF (20 ml) at 0 °C. After the addition the mixture was stirred at 0 °C for 1 hr and then at room temperature for 2 hrs. After evaporation of a part (150 ml) of the solvent under reduced pressure, the reaction mixture was diluted with C_6H_6 (25 ml) and AcOEt (60 ml) and successively washed with 5% HCl, water, saturated $NaHCO_3$ solution and brine. After drying over $MgSO_4$ the evaporation gave a residue which was analysed by HPLC.

Macrocyclization achieved through BOP activation : Diamide diacid **12** (1.42 g, 3 mmol) and N,N' dibenzyl ethylenediamine (0.72 g, 3 mmol), each dissolved in acetonitrile (50 ml) were slowly added simultaneously to a stirred solution of BOP (2.65 g, 6 mmol) and triethylamine (0.6 g, 6 mmol) in acetonitrile (500 ml) at room temperature. The mixture was then stirred for 2.5 hrs, a saturated NaCl solution was added and the mixture was extracted three times with ethyl acetate. The organic phase was washed successively with 2N HCl, water, 5% $NaHCO_3$ solution, and water and dried with $MgSO_4$. The solvent was removed under reduced pressure to give a residue which was analysed by HPLC.

Tetralactams 3-9

Preparation of compounds **3-8** was performed by the stepwise synthesis using thiazolidine-2-thione activation as described above for **2**. **9** was prepared by using the BOP procedure as described for the synthesis of **2**. The yields, melting points and ^1H nmr data are summarized in Table 2. The infrared spectra (in KBr pellets) of compounds **3-9** show a band in the 3500-3300 cm^{-1} range suggesting that lattice water is present in these compounds.

Compound **3** : white solid ; rf = 0.22 (CH_2Cl_2-EtOH / 96-4) ; IR ($HCCl_3$) : 3367 (NH), 1659 cm^{-1} (C=O) ; MS (DCI/NH_3) : m/e 497 $[M+H]^+$, 100% ; Anal. calcd for $C_{26}H_{32}N_4O_6.3/2\ H_2O$: C, 59.64 ; H, 6.74 ; N, 10.70. Found : C, 59.58 ; H, 6.67 ; N, 10.54.

Compound **4** : white solid ; rf = 0.35 (CH_2Cl_2-EtOH / 96-4) ; IR ($HCCl_3$) : 3362 (NH), 1655 cm^{-1} (C=O) ; MS (FAB) : m/e 653 $[M+H]^+$ (100%), 818 $[M+Na^+]$, 834 $[M+K^+]$; Anal. calcd for $C_{36}H_{68}N_4O_6.H_2O$: C, 64.44 ; H, 10.52 ; N, 8.35. Found : C, 64.28 ; H, 10.47 ; N, 8.30.

Compound **5** : white solid ; rf = 0.27 (CH_2Cl_2-CH_3OH / 96-4) ; IR ($HCCl_3$) : 1663 cm^{-1} (C=O) ; MS (FAB) : m/e 796 $[M+H]^+$ (100%), 818 $[M+Na^+]$, 834 $[M+K^+]$; Anal. calcd for $C_{48}H_{53}N_5O_6.1/2\ H_2O$: C, 71.62 ; H, 6.76 ; N, 8.70. Found : C, 71.74 ; H, 6.65 ; N, 8.44.

Compound **6** : white solid ; rf = 0.25 (CH_2Cl_2-CH_3OH / 96-4) ; IR ($HCCl_3$) : 1661 cm^{-1} (C=O) ; MS (FAB) : m/e 814 $[M+H]^+$ (100%), 836 $[M+Na^+]$, 852 $[M+K^+]$; Anal. calcd for $C_{48}H_{52}N_5O_6F.1/2\ H_2O$: C, 70.05 ; H, 6.49 ; N, 8.51. Found : C, 69.67 ; H, 6.14 ; N, 8.21.

Compound **7** : white solid ; rf = 0.21 (CH_2Cl_2-CH_3OH / 96-4) ; IR ($HCCl_3$) : 3419, 3240 (NH), 1654 cm^{-1} (C=O) ; MS (FAB) : m/e 616 $[M+H]^+$ (100%), 638 $[M+Na^+]$, 654 $[M+K^+]$; Anal. calcd for $C_{34}H_{41}N_5O_6.H_2O$: C, 64.44 ; H, 6.83 ; N, 11.05. Found : C, 64.44 ; H, 6.63 ; N, 11.08.

Compound **8** : white solid ; rf = 0.32 (CH_2Cl_2-CH_3OH / 96-4) ; IR ($HCCl_3$) : 1661 cm^{-1} (C=O) ; MS (DCI/NH_3) : m/e 721 $[M+H]^+$ (100%) ; Anal. calcd for $C_{42}H_{48}N_4O_7.1/2\ H_2O$: C, 69.12 ; H, 6.77 ; N, 7.68. Found : C, 69.08 ; H, 6.72 ; N, 7.53.

Compound **9** : white solid ; rf = 0.48 (CH_2Cl_2-EtOH / 96-4) ; IR ($HCCl_3$) : 1641 cm^{-1} (C=O) ; MS (DCI/NH_3) : m/e 765 $[M+H]^+$ (100%), 782 $[M+NH_4^+]$; Anal. calcd for $C_{44}H_{52}N_4O_8.1/2\ H_2O$: C, 68.29 ; H, 6.90 ; N, 7.24. Found : C, 68.20 ; H, 6.83 ; N, 7.16.

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