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Synthesis of Macrocyclic Polyhydroxy Tetralactams derived from L-Tartaric Acid and β-Hydroxyglutaric Acid

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Abstract: The synthesis of new 16-, 18-, 19- or 20-membered secondary tetralactams with L-tartaric acid or β-hydroxyglutaric acid moieties is investigated. The stepwise synthesis with an intermediate diamide diamine provides overall good yields (30-55%) compared with other processes using an intermediate diamide diacid or direct macrocyclization. This synthetic pathway leads to symmetrical or unsymmetrical polyhydroxytetralactams with variable hydroxyl group number. Use of mild acylating agents in this approach allows to avoid the protection-deprotection steps of hydroxyl groups.

INTRODUCTION

There is continuing interest in the synthesis of macrocyclic polylactams. The polyamido macrocycles have complexation properties that are complementary to all-oxygen crowns, which strongly complex alkali metal ions and to all-nitrogen cyclams, which strongly complex heavy metal cations.[1] In the polylactam series, tetralactams are important ligands for interaction of a variety of metal cations and organic substrates. These ligands form strong complexes with transition metal ions[2] through a linkage between the metal ion and the deprotonated amide nitrogen atoms and also with cations of high charge density (alkaline-earth or lanthanide ions)[3] where the cation interacts with the carbonyl oxygen atoms. The tetralactam ligands act also as hydrogen-bond donors and hydrogen-bond acceptors and can complex neutral molecules of biological interest.[4]

The most popular method for the preparation of tetralactams consists in reacting a diacid dichloride with a diamine in a 2:2 process.[5] Progresses in the application of these compounds in order to study their binding properties, however, rely critically on versatile methods for their synthesis. We have recently reported the access to tetralactams derived from dibenzylethylenediamine[6] and 1,2-diaminobenzene[7] and were interested to investigate synthetic routes towards tetralactams starting from primary aliphatic diamines, more reactive than their secondary aliphatic or primary aromatic diamines counterparts.

On the another hand introduction of the tartaric unit in a macrocyclic framework is of particular interest. Polycarboxylic crown ethers or related compounds derived from tartaric acid have been the subject of numerous studies and display selective ion complexation[8] or ion transport,[9] chiral recognition[10] and molecular catalysis[11] through central anchoring in the macrocyclic cavity and lateral interaction with the side chains. It is also worth noting that acyclic tartramide derivatives were used as resolving agents[12] or as chiral auxiliaries in asymmetric synthesis.[13]

In this paper we describe the access to a series of new symmetrical and unsymmetrical tetralactams with 16, 18, 19 or 20 ring atoms derived from 1,2-diaminoethane or 1,3-diaminopropane. Their structures are represented in Figure 1. The target molecules were intended to include one or two (R,R)-tartaric acid or β-

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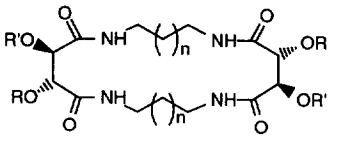
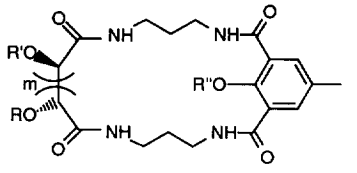
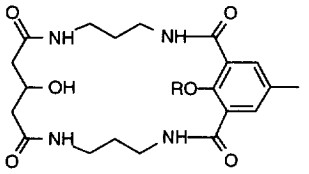
hydroxyglutaric acid residues to study their effect on their metal-ion complexing behaviour related to the features discussed above.



1a n = 0 R, R' = $C(CH_3)_2$
1b n = 0 R = R' = H
2a n = 1 R, R' = $C(CH_3)_2$
2b n = 1 R = R' = H



R, R' = $C(CH_3)_2$ R'' = CH_3 **3a** m = 1 **4a** m = 2
R = R' = H R'' = CH_3 **3b** m = 1 **4b** m = 2
R = R' = R'' = H **3c** m = 1



5a R = CH_3
5b R = H

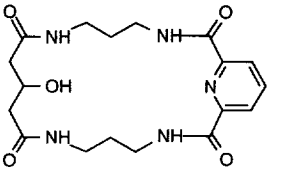


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Figure 1 : New Polylactam Compounds

RESULTS AND DISCUSSION

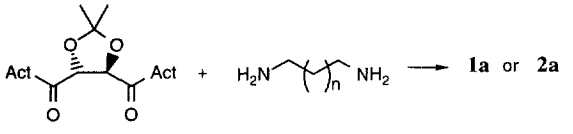
Three synthetic strategies involving amide bond formation may be used for the construction of macrocyclic tetralactams with amide functions in a head-to-head arrangement.

Route I is the most common and conventional procedure for the preparation of cyclic tetramides and requires direct condensation of diamines and dicarboxylic acid derivatives. This 2:2 cyclization process leads to the formation of four amide bonds between four substrates and may be favoured over 1:1 cyclization when reactants contain rigid units[14] or would form strained 8-11-membered dilactam rings in the 1:1 cyclization process.[15] In these conditions the reaction is usually carried out under high-dilution techniques. To a lesser extent template chemistry has been used to build tetramido macrocycles in a 2:2 cyclization process under normal dilution conditions. Template effects have been thus achieved via internal hydrogen bond,[16] metal-cation [17] or from cyclic silicon-nitrogen compounds (covalent template effect)[18] and consequently require respectively cooperative conformational effects, the existence of specific binding sites in the substrates or the use of secondary diamines.

An alternative approach to this direct macrocyclization strategy consists in performing the reaction in successive steps. Two stepwise methods can be considered as involving either an intermediate diamide diacid (Route II) or a diamide diamine (Route III). These intermediates can be obtained by using protection and deprotection techniques or directly from starting materials. These strategies have been investigated with success by us and other research groups for the preparation of tetralactams derived from secondary aliphatic diamines (Route II[3c, 6, 19] and Route III[20]) or primary aromatic diamines (Route III[7, 21]). These two stepwise approaches can lead to symmetrical molecules and can be used to improve the tetralactam yields when a competition di/tetralactam occurs in the direct macrocyclization method. They can be also used to provide unsymmetrical tetralactams with different diamine or diacid units, while the direct macrocyclization method is restricted to the obtention of symmetrical tetralactams.

Tetralactams derived from (R,R)-Tartaric acid. The three routes described above were investigated for the preparation of 16, 18-membered tetralactams **1a**, **2a**.

Route I: Direct Macrocyclization (Scheme 1). First of all we tested the direct macrocyclization process by studying the selectivity of 8- or 9-membered dilactam versus 16- or 18-membered tetralactam formation in a high dilution condensation of 2,3-*O*-isopropylidene-L-tartaric acid dichloride with the appropriate diamine. As a matter of fact the acylation of an amine with an acid chloride meets the high dilution requirements very well. The compounds involved combine extremely rapidly so that there can be no build-up of unreacted materials in the reaction mixture. Reaction was carried out under high dilution conditions as described by Dietrich *et al*[22] (final concentration 0.015 M, 25 °C) in dry benzene by simultaneous addition of reactants via constant-rate addition funnels during 8 hours. Twofold molar excess of diamine was used to neutralize HCl formed in the reaction. The 2:2 cyclization was the main cyclization process observed in these reactions and tetralactams **1a** and **2a** of dimeric structure were isolated by chromatography on silica by using dichloromethane/ methanol 95:05 as eluent with 6% and 17% yield respectively. Although no 1:1 cyclization products were observed, the low yields for compounds **1a** and **2a** were somewhat disappointing in the light of the excellent yields (~80%) obtained for same sized analogous polymethylene tetralactams by using a direct high dilution macrocyclization method.[15]



	Act =	Cl	OMe	O-N
yield %	**1a**	6	6	-
	2a	17	8	5

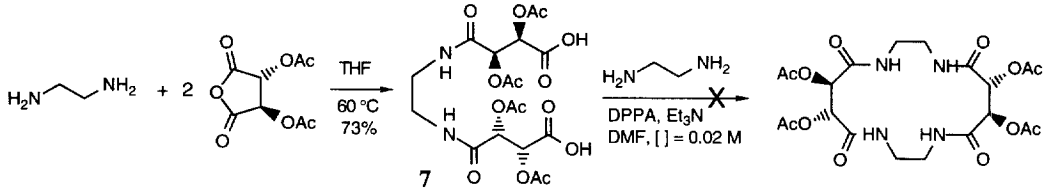
Scheme 1 : Route I - Direct Macrocyclization Pathway (see discussion for experimental conditions)

Recently, Jurczak *et al*[23] have reported that, consistent with earlier findings of Tabushi *et al*[24] and Morphy *et al*,[25] dimethyl α,ω-dicarboxylates react under normal dilution conditions in methanol with α,ω-diamines to form the macrocyclic dilactams in good yields. Thus, taking into account that the cyclization to 8,9-membered monomeric dilactams corresponding to tetralactams **1a**, **2a** would be unfavoured, we used dimethyl esters in place of the more reactive diacid dichlorides. Treatment of dimethyl 2,3-*O*-isopropylidene-L-tartrate with 1 equiv. of 1,2-diaminoethane or 1,3-diaminopropane under usual conditions (methanol as a solvent, 25 °C, 10 days, reagent concentrations 0.1 M) gave only 6% and 8% yields of isolated compounds **1a** and **2a** respectively. Better results were not obtained by carrying out the reaction at higher temperature (reflux). These yields were substantially low and the reaction mixtures were highly contaminated with low Rf polymeric compounds. This is believed to be due to a poor preorganization of intermediate linear amido compounds in alcohol which should favour polymerization versus cyclization in such reactions.[23, 26]

The disuccinimido ester mediated cyclization was also investigated for this direct macrocyclization pathway but was found to give a very poor yield. The reaction was performed following the procedure described by Oussaid *et al*[27] for the successful preparation of thiophene-containing tetralactams (dichloromethane as solvent, 25 °C, 4 days, reagent concentrations 0.14 M).

Route II: Stepwise Synthesis through an intermediate diamide diacid (Scheme 2). This stepwise approach is attractive owing to its successful use for the access to tetralactams derived from secondary aliphatic diamines.[3c, 6] In that case, activation of diamide diacid by diphenylphosphoryl azide (DPPA)[28] or through thiazolidine-2-thione derivatives[6] appeared to be the most effective for the macrocyclization reaction.

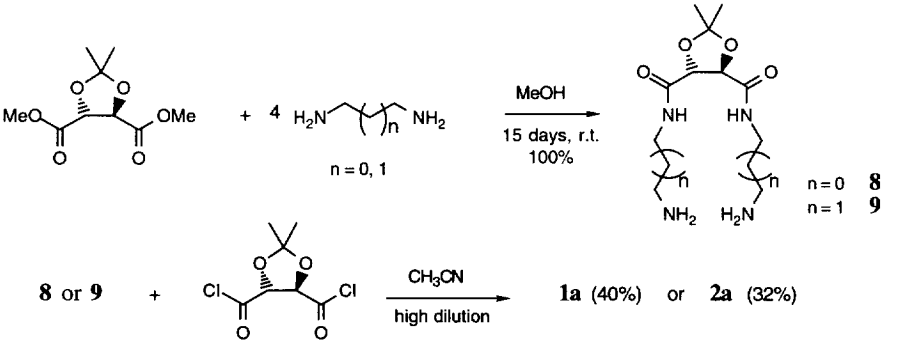
In a first step (Scheme 2) the condensation of commercially available diacetyl-L-tartaric anhydride, with 1,2-diaminoethane (molar ratio 2:1) led to the intermediate diamide diacid **7**. The resulting acid functions were then activated using DPPA reagent as *in situ* activating-coupling agent. This activating group was selected instead of the N-acyl thiazolidine-2-thione one. The reason is related to the fact that the preparation of the bis(thiazolidine-2-thione) derivative of **7** failed with the DCC, DMAP method[29] and cannot be performed via the acid chloride method owing to the destruction of the diamide function when the diacid is reacted with thionyl chloride or oxalyl chloride.[6, 30]



Scheme 2 : Route II - Stepwise Synthesis Pathway (intermediate diamide diacid)

No cyclocondensation product was obtained when 1,2-diaminoethane was reacted with **7** in presence of DPPA. It is also noteworthy that no intramolecular cyclization process of activated diamide diacid giving imide derivatives occured in this reaction, unlike for the diamide diacids derived from primary aromatic diamines.[7]

Route III: Stepwise Synthesis through an intermediate diamide diamine (Scheme 3). This strategy was much more successful. The key diamide diamine intermediates were obtained directly without using a protection-coupling-deprotection sequence. According to the study of Jacobson *et al*[31] on the monoacylation of symmetrical aliphatic diamines showing that a decrease of the reactivity of the acylating agents leads to increased yields of monoacylated diamine, the condensation of a diester with an excess of diamine gives the diamide diamine compound. However, when the reaction was carried out with a large excess of the diamine or using it as a solvent, the major problem was the complete removal at room temperature of this excess.[32] On the another hand we found that the use of a stoichiometric amount of diamine (2 equiv.) led to the formation of unidentified by-products easily evidenced by ^{13}C NMR and making difficult to purify the reaction mixture. The preparation of **8** and **9** was therefore performed by mixing dimethyl 2,3-*O*-isopropylidene-L-tartrate and the appropriate diamine (4 equiv.) in methanol and allowing to react 15 days at room temperature. Methanol and excess of diamine were evaporated under reduced pressure to give quantitatively **8** and **9**.



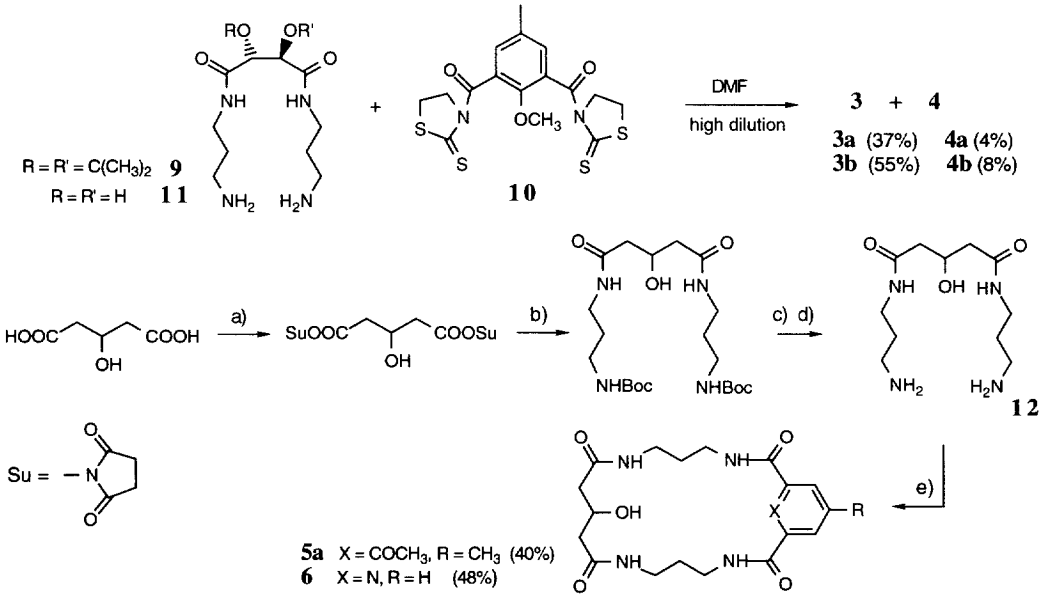
Scheme 3 : Route III - Stepwise Synthesis Pathway (intermediate diamide diamine)

The cyclocondensation between twofold molar excess of diamide diamine compounds **8** or **9** and L-tartaric acid dichloride was carried out at high dilution to prevent polymerization and afforded the corresponding tetralactams **1a** and **2a** in fairly good yields (40 and 32% respectively).

The yields obtained by using this diamide diamine strategy indicate that this method is more efficient than the direct macrocyclization method (two or seven fold increased yields) despite the greater number of steps involved. Moreover this stepwise approach made easier the purification of final tetralactam products compared with the one-step method and can be used to provide unsymmetrical tetralactams bearing two different acid moieties as outlined in scheme 4.

When 2-methoxy-5-methyl isophtalic acid bis(2-mercaptothiazolide) **10** is reacted with building block **9**, the 19-membered cyclotetramide **3a** was isolated in a 37% yield along with 4% of cyclic octaamide by-product (result of a 2:2 cyclization). Reaction was carried out under high dilution conditions and by using stoichiometric amounts of reactants because the thiazolidine-2-thione activating group do not yield hydrochloric acid as a by-product. An additional advantage of this stable and mild acylating agent is its extremely high chemoselectivity for the amino group. Hence aminolysis can be performed without protection of hydroxyl group.[33] Thus, the condensation of diol diamine compound **11** with the thiazolidine-2-thione derivative **10** yields the tetralactam **3b** in 55% yield. The 36-membered octalactam **4b** of dimeric structure was also isolated in a 8% yield in this reaction.

Deprotection of the isopropylidene and methyl protected compounds **1a**, **2a**, **3a** by using standard HCl or BBr_3 methods afforded the polyhydroxy tetralactams **1b**, **2b** and **3c** in 80-100% yield.



a) DCC, SuOH; b) BocHN$\sim\sim$NH$_2$, 2 equiv.; c) HCl, AcOEt; d) KOH;
e) **10** or 2,6-Pyridinedicarboxylic acid bis(2-mercaptothiazolide) **13**, DMF, high dilution conditions.

Scheme 4 : Synthesis of Unsymmetrical Tetralactams

Tetralactams derived from β-hydroxyglutaric acid

The stepwise procedure involving the formation of a diamide diamine derivative was used to synthesize the unsymmetrical tetralactams **5**, **6** incorporating one hydroxyglutaric unit.

The diamide diamine **12** was very difficult to purify from the reaction mixture obtained from the condensation of diethyl 3-hydroxyglutarate and 1,3-diaminopropane. Therefore it was prepared through a protection-coupling-deprotection sequence as shown in Scheme 4. Treatment of two equivalents of N-hydroxysuccinimide with 3-hydroxyglutaric acid in the presence of two equivalents of 1,3-dicyclohexylcarbodiimide provided readily an active ester without requiring the protection of the hydroxyl function. Reaction of this succinimido ester with tert-butyl N-(3-aminopropyl)carbamate and removal of the Boc group (HCl/AcOEt) followed by a base treatment afforded **12** in 62% overall yield (from starting diacid). Subsequent macrocyclization of **12** with bis(2-mercaptothiazolide) derivatives **10** or **13** in DMF solutions led to the corresponding 20-membered rings **5a**, **6** in 40-50% yield. Finally, free phenol ligand **5b** was obtained by action of BBr_3 with **5a**.

CONCLUSION

No general synthetic method can be used widely for the synthesis of macrocyclic tetralactams with head to head arrangements. The direct macrocyclization between activated diacid derivatives is limited to the obtention of symmetrical tetralactams and strongly depends on the substitution of the hydrocarbon backbone. The most flexible stepwise synthesis via an intermediate diamide diacid is successful when this intermediate is reacted with secondary aliphatic diamines. The stepwise approach developped in this study, based on the formation of an intermediate diamide diamine gives good results for the obtention of secondary tetralactams and allows the structural dissymmetrization of the tetralactams dicarboxylic moieties.

EXPERIMENTAL SECTION

General. Melting points were determined on a Kofler apparatus. Infrared spectra were recorded on a Perkin-Elmer 883 spectrophotometer (ν cm^{-1}) in potassium bromide unless otherwise indicated. ^1H magnetic resonance spectra (200 MHz unless otherwise indicated) and ^{13}C magnetic resonance spectra (50.3 MHz) were recorded (DMSO-d6 unless otherwise indicated) on Bruker AC-80 or AC-200 spectrometers. Data are reported in the following order: chemical shift in ppm, spin multiplicity (s = singulet, d = doublet, t = triplet, q = quadruplet, q_i = quintuplet, m = multiplet), integration and assignment. Mass spectra (MS) were performed with a NERMAG R10-10C spectrometer using the Fast Atom Bombardment (FAB; following abbreviations are used: mNBA (3-nitrobenzyl alcohol), gly (glycerol), thiogly (thioglycerol), TCA (trichloroacetic acid)) or Desorption Chemical Ionization (DCI/NH_3) techniques. Optical rotations were measured at room temperature (22± °C) with a Perkin Elmer 141 polarimeter. Elemental analyses were carried out by the "Service Commun de Microanalyse élémentaire UPS-INP" in Toulouse (the presence of H_2O indicated in the elemental analyses of polylactams was quantified by ^1H NMR). Chromatographic purifications were performed by filtration through Merck silicagel (15 µm), by column chromatography (Amicon silicagel 70-200 µm) or by high pressure chromatography (Amicon silicagel 6-35 µm, Jobin-Yvon miniprep LC apparatus). Precoated sheets (Merck silicagel 60F-254) were used for TLC analyses.

Synthesis of reactants

- ***Preparation of diacids***

– **2,3-*O*-isopropylidene-L-tartaric acid**: the disodium salt of the title compound was prepared by treating dimethyl-2,3-*O*-isopropylidene-L-tartrate (Aldrich) with NaOH in hot ethanol, according to the procedure described by Klotz and coworkers[34] (97%). This neutralization with 2 equivalents of aqueous 2N HCl provided the title compound (84%). White solid; m.p. 92 °C (lit.[34], 80-86 °C).

– **2-methoxy-5-methyl isophtalic acid**: this compound was prepared in three steps by using procedures described in the literature.[35, 36] Hydroxymethylation[35] of p-cresol with formaldehyde in the presence of base gave 2,6-bis(hydroxymethyl)-4-methylphenol (89%), which was selectively methylated[36] ($(CH_3)_2SO_4$) to give 2,6-bis(hydroxymethyl)-4-methylanisole (88%). The two hydroxymethyl groups were then converted with $KMnO_4$ to the carboxylic groups (85%) in accordance with the procedure described by Ullmann and Brittner.[35] White solid; m.p. 172 °C (lit.[35], 177 °C).

– **β-Hydroxyglutaric acid**: this material was prepared in two steps. Reduction[37] of dimethyl 3-oxoglutarate

(Aldrich) with $NaBH_4$ provided dimethyl 3-hydroxyglutarate (54%). The hydroxy diester was then converted to the dicarboxylic acid by the following procedure: Dimethyl 3-hydroxyglutarate (55 g, 0.31 mol) and KOH pellets (40.2 g, 0.72 mol) were stirred in 150 mL of methanol for 2 h. The reaction mixture was then concentrated in vacuo and the solid residue was dissolved in a minimum amount of water. The solution was brought to pH 1.5 with concd HCl and extracted with ethyl acetate. The extract was dried with $MgSO_4$, filtered, and then concentrated in vacuo to afford 43.6 g of the title compound (95%). White solid; m.p. 93 °C. IR: 3455 (νO-H alcohol); 3050 (νO-H acid); 1700 (νC=O). ^{1}H NMR: δ 2.31 and 2.41 (A_2B_2 part of an A_2B_2X syst, J_{AB} = 15.2 Hz, J_{AX} = 5.3 Hz, J_{BX} = 7.6 Hz, 4H, CH_2); 4.22 (X part of an A_2B_2X syst, 1H, C<u>H</u>OH). ^{13}C NMR: δ 41.9 (CH_2); 64.4 (CH); 172.5 (CO).

– **Diamide diacid 7**: to a stirred solution of diacetyl-L-tartaric anhydride (Aldrich, 2.16 g, 10.0 mmol) in 25 mL of dry THF heated at 60 °C was added dropwise a solution of ethylenediamine (0.3 g, 5.0 mmol) in dry THF (10 mL). The mixture was then stirred at the same temperature for 12 h. The reaction was allowed to cool to room temperature and the solid was collected, washed with diethyl ether and dried to give 0.73 g (29.7%) of product. The filtrate was concentrated in vacuo and the solid residue was dissolved in a minimum amount of methanol. Addition of diisopropyl ether produced a white precipitate which was filtered off and washed with diethyl ether (1.07 g,43.5%). White solid; m.p. 185-190 °C dec. IR: 3360 (νN-H); 2980 (νO-H); 1749 (νC=O ester); 1664 (νC=O acid); 1633 (νC=O amide); 1542 (δNH-CO). ^{1}H NMR: δ 2.08 (s, 6H, CH_3); 2.12 (s, 6H, CH_3); 3.14 (m, 4H, CH_2); 5.48 and 5.50 (AB syst, J_{AB} = 2.7 Hz, 4H, CH); 8.15 (m, 2H, NH). ^{13}C NMR: δ 20.2, 20.5 (CH_3); 38.1 (CH_2); 71.0, 71.6 (CH); 165.6, 167.7 (C=O amide and acid); 169.3, 169.4 (C=O ester).

• ***Preparation of activated diacids***

– **2-methoxy-5-methyl isophthaloyl dichloride**: 2-methoxy-5-methyl isophthalic acid (5.7 g, 27.1 mmol) and thionyl chloride (43 mL) were stirred for 5 h under reflux. The excess of thionyl chloride was removed under reduced pressure and two volumes of 70 mL of dry benzene were then added to evaporate off excess of thionyl chloride. A 6.6 g amount of white solid was obtained (99% yield). m.p. 130-135 °C. IR: 1780 (νC=O).^{1}H NMR (80 MHz, $CDCl_3$): δ 2.46 (s, 3H, CH_3); 3.91 (s, 3H, CH_3-O); 8.00 (s, 2H, arom.).

– **2,3-*O*-isopropylidene-L-tartaric acid dichloride**: the described preparation is a modification of the procedure reported by I.M. Klotz and coworkers.[34] To a suspension of 6.75 g (28.8 mmol) of dry 2,3-*O*-isopropylidene-L-tartaric acid disodium salt in 25 mL of dry benzene was added dropwise oxalyl chloride (15 mL) at 5 °C. After completion of the addition, the reaction mixture was allowed to warm to room temperature, gradually heated at reflux (65 °C) for 1 h and then stirred overnight at room temperature. The solvent and excess reactant were removed by vacuum evaporation. To the solid residue was then added dry CH_2Cl_2 (100 mL), and the suspension was stirred at room temperature for 30 min. Sodium chloride was filtered off quickly and solvent was evaporated. The pale brown solid was then vacuum-dried (6.0 g, 92%); m.p. 39-40 °C (lit. [34], 40-42 °C).

– **di-succinimidyl-2,3-*O*-isopropylidene-L-tartrate**: 2,3-*O*-isopropylidene-L-tartaric acid (0.57 g, 3.0 mmol) and N-hydroxysuccinimide (0.69 g, 6.0 mmol) were dissolved in 10 mL of dry dioxane under argon. After cooling to 11 °C in an ice bath, a solution of 1,3-dicyclohexylcarbodiimide (1.24 g, 6.0 mmol in 7 mL of dry dioxane) was added dropwise over 2 h. The reaction was then warmed to room temperature and stirred for 24 h. The dicyclohexylurea solids were removed by filtration and washed with dioxane. The filtrate was concentrated in vacuo to afford the title compound as a white solid (1.09 g, 95%) and was used as such. IR: 1832, 1790 (νC=O imide), 1735 (νC=O ester). ^{1}H NMR: δ 1.51 (s, 6H, CH_3); 2.86 (s, 8H, CH_2); 5.52 (s, 2H, CH). ^{13}C NMR: δ 25.5 (CH_2); 26.1 (CH_3); 75.25 (CH); 115.2 (<u>C</u>-CH_3); 165.6 (O=C-O); 169.7 (O=C-N).

– **di-succinimidyl-3-hydroxyglutarate**: by the same procedure the title compound was obtained in 92% yield and used as such. White solid. IR: 1814,1782 (νC=O imide); 1742 (νC=O ester). ^{1}H NMR: δ 2.83 (s, 8H, CH_2-CON); 2.94 (m, 4H, CH_2-COO); 4.4 (m, 1H, CH); 5.58 (d, J = 5.7 Hz, 1H, OH). ^{13}C NMR: δ 25.4 (<u>C</u>H_2-CON); 37.8 (<u>C</u>H_2-COO); 63.4 (CH); 166.5 (O=C-O); 170.1 (O=C-N).

– **2-methoxy-5-methyl isophthalic acid bis(2-mercaptothiazolide), 10**: to a stirred solution of 1,3-thiazolidine-2-thione (1.86 g, 15.6 mmol) and triethylamine (2.32 g, 23 mmol) in dry THF (100 mL) was added dropwise 2-methoxy-5-methyl isophthaloyl dichloride (1.92 g, 7.77 mmol) in 30 mL of dry THF at 50 °C. The reaction mixture was stirred for 1 h, then cooled to room temperature. The triethylamine hydrochloride was filtered off, washed with THF and the filtrate was evaporated to dryness. The residue was subjected to column chromatography on silicagel (dichloromethane-methanol 98:02) to give **10** (3.2 g, 92%). Yellow solid; m.p. 176 °C. IR ($CHCl_3$): 1685 (νC=O).^{1}H NMR (80 MHz; $CDCl_3$): δ 2.31 (s, 3H, CH_3-Ar); 3.39 (t, J = 7.2 Hz, 4H, CH_2-S); 3.84 (s, 3H, CH_3-O); 4.56 (t, J = 7.2 Hz, 4H, CH_2-N); 7.22 (d, J = 0.7 Hz, 2H, CH arom.). ^{13}C NMR ($CDCl_3$): δ 20.6 (CH_3-Ar); 29.4 (CH_2-S); 55.8 (CH_2-N); 63.2 (CH_3-O); 128.3 ($C_{1,3}$ arom.); 132.5 ($C_{4,6}$ arom.); 133.5 (C_5 arom.); 152.7 (C_2 arom.); 167.4 (C=O); 200.8 (C=S).

– **2,6-pyridinedicarboxylic acid bis(2-mercaptothiazolide), 13**: using the same procedure the title compound was obtained in 99% yield after purification by filtration through a silicagel pad (dichloromethane-acetone 90:10). Yellow solid; m.p. 104-105 °C. IR: 1687 (νC=O). ^{1}H NMR (80 MHz; $CDCl_3$): δ 3.51 (t, J = 7

Hz, 4H, CH_2-S); 4.58 (t, J = 7 Hz, 4H, CH_2-N); 7.82 (m, 3H, CH arom.). ^{13}C NMR ($CDCl_3$): δ 30.6 (CH_2-S); 56.2 (CH_2-N); 126.5 ($C_{3,5}$ arom.); 138.1 (C_4 arom.); 151.1 ($C_{2,6}$ arom.); 168.3 (C=O); 201.9 (C=S).

• ***Preparation of diamide diamine compounds 8, 9, 11, 12***

– **Diamide diamine 8:** dimethyl 2,3-*O*-isopropylidene-L-tartrate (2.18 g, 10 mmol) and ethylenediamine (2.40 g, 40 mmol) were mixed in methanol (50 mL) and stirred for 9 days at room temperature. Methanol and excess of ethylenediamine were coevaporated with chloroform and the residue was vacuum-dried (10^{-3} mm Hg) at room temperature to give a pale yellow, oily substance. The 2.75 g of product obtained amounted to approximately 100% of the theoretical yield and was pure according to ^1H nmr analysis. It was used without further purification. IR: 3360, 3300 (broad, νN-H); 1666 (νC=O); 1532 (δ NH-CO). ^1H NMR (80 MHz; $CDCl_3$): δ 1.23 (s, 4H, NH_2); 1.45 (s, 6H, CH_3); 2.80 (t, J = 6 Hz, 4H, C$\underline{H}_2$-NH_2); 3.31 (q, J = 6 Hz, 4H, C$\underline{H}_2$-NH); 4.50 (s, 2H, CH); 7.3 (t, J = 6 Hz, 2H, NH). ^{13}C NMR ($CDCl_3$): δ 26.1 (CH_3); 41.3, 42.0 (CH_2); 77.6 (CH); 112.3 ($\underline{C}$-$(CH_3)_2$); 170.0 (C=O).

– **Diamide diamine 9**: it was obtained by the same procedure in 100% yield as a pale yellow, oily substance. IR ($CHCl_3$): 3426, 3300 (νN-H); 1689, 1660 (νC=O); 1533 (δNH-CO). ^1H NMR (80 MHz): δ 1.38 (s, 6H, CH_3); 1.47 (m, 4H, C-CH_2-C); 1.8 (s, 4H, NH_2); 2.53 (t, J = 6.6 Hz, 4H, C$\underline{H}_2$-NH_2); 3.14 (q, J = 6.6 Hz, 4H, C$\underline{H}_2$-NH); 4.45 (s, 2H, CH); 8.12 (t, J = 6.6 Hz, 2H, NH). ^{13}C NMR: δ 26.1 (CH_3); 32.6 (C-$\underline{C}H_2$-C); 36.4, 39.0 (CH_2-N); 77.6 (CH); 111.5 ($\underline{C}$-$(CH_3)_2$); 168.7 (C=O).

– **Diamide diamine 11**: 4.5 g (14.9 mmol) of **9** were dissolved in 90 mL of 1N HCl. After stirring 2 days at room temperature, the solution was brought to pH 7 with KOH. After lyophilisation, the residual solid was treated with methanol and KCl was eliminated by filtration. Solvent removal afforded the dihydrochloride of **11** (5g, 100%) as a white solid. IR: 3300 (broad, νN-H, νO-H); 2975 (broad, νNH_3^+); 1659 (νC=O); 1540 (δNH-CO). ^1H NMR: δ 1.77 (m, 4H, C-CH_2-C); 2.80 (m, 4H, C$\underline{H}_2NH_2$); 3.18 (m, 4H, C$\underline{H}_2$-NHCO); 4.25 (s, 2H, CH); 7.1 (very broad signal, NH_3^+); 7.95 (m, 2H, NH-CO). ^{13}C NMR: δ 27.0 (C-$\underline{C}H_2$-C); 35.2, 36.2 (CH_2-N); 72.6 (CH); 172.4 (C=O).

11 was prepared by adding KOH (0.67 g, 12 mmol) in methanol (35 mL) to a solution of the dihydrochloride of **11** (2 g, 6 mmol) in methanol (40 mL). The reaction mixture was allowed to stand at room temperature for 2 h, then filtered. The filtrate was concentrated in vacuo to afford **11** (1.57 g, 100%) as a yellow oil. The purity of the crude isolated product was greater than 95%, as determined by ^1H NMR in DMSO-d_6. ^1H NMR: δ 1.49 (m, 4H, C-CH_2-C); 2.51 (m, partly occulted by the solvent, C$\underline{H}_2NH_2$); 3.16 (m, 4H, C$\underline{H}_2$-NHCO); 4.20 (s, 2H, CH); 7.78 (m, 2H, NHCO).

– **Diamide diamine 12** (Scheme 4): A solution of N-Boc-1,3-diaminopropane[38] (3.87 g, 22.2 mmol) in 20 mL of dioxane was added to a stirred solution of disuccinimidyl-3-hydroxyglutarate (3.8 g, 11.1 mmol) in 250 mL of dioxane. After allowing the contents to stir 24 h, solvent was removed under reduced pressure. The oily residue was dissolved in 75 mL of ethyl acetate and the solution was washed with H_2O (2 x 15 mL). The organic phase was dried (Na_2SO_4) and concentrated in vacuo to afford 3.93 g of the bis N-Boc product (77%) as a very hygroscopic white solid. IR: 3310 (νN-H, νO-H); 1705 (νC=O carbamate); 1648 (νC=O amide); 1535 (δNH-CO). ^1H NMR ($CDCl_3$): δ 1.39 (s, 18H, CH_3); 1.61 (q_i, J = 6.4 Hz, 4H, C-C$\underline{H}_2$-C); 2.39 (d, J = 5.3 Hz, 4H, CH_2-CO); 3.12 (q, J = 6.4 Hz, 4H, C$\underline{H}_2$-NHBoc); 3.26 (q, J = 6.4 Hz, 4H, C$\underline{H}_2$-NH-CO); 4.32 (m, 1H, CH); 5.09 (t, J = 6.4 Hz, 2H, NH carbamate); 7.09 (t, J = 6.4 Hz, 2H, NH amide). ^{13}C NMR ($CDCl_3$): δ 28.4 (CH_3); 30.1 (C-$\underline{C}H_2$-C); 36.1 ($\underline{C}H_2$-NHBoc); 37.5 (CH_2-NH amide); 42.1 ($\underline{C}H_2$-CO); 66.1 (CH); 79.4 ($(CH_3)_3\underline{C}$); 156.5 (C=O carbamate); 172.0 (C=O amide).

5.82 g of the previous compound (12.6 mmol) were dissolved in 50 mL of a 2N solution of HCl in ethyl acetate. The reaction mixture was stirred at room temperature for 24 h. At this time the precipitated product was isolated by filtration, washed with dry ethyl acetate and dried under high vacuum (80 °C; 10^{-3} mm Hg). Diamide diamine **12** dihydrochloride (3.69 g, 88%) was obtained as a very hygroscopic pale brown solid. IR: 3300 (νN-H, νO-H); 3000 (broad, νNH_3^+); 1640 (νC=O); 1550 (δNH-CO). ^1H NMR: δ 1.74 (q_i, J = 7.5 Hz, 4H, C-C$\underline{H}_2$-C); 2.25 (d, J = 6.4 Hz, 4H, CH_2-CO); 2.79 (m, 4H, C$\underline{H}_2$-NH_3^+); 3.13 (q, J = 6.4 Hz, 4H, C$\underline{H}_2$-NHCO); 4.20 (m, 1H, CH); 8.11 (m, 8H, NH_3^+ and NH-CO). ^{13}C NMR: δ 27.1 (C-$\underline{C}H_2$-C); 35.4 (CH_2-NH_3^+); 36.5 ($\underline{C}H_2$-NH); 43.1 ($\underline{C}H_2$-CO); 65.2 (CH); 170.8 (C=O).

12 was prepared by adding KOH (0.374 g, 6.7 mmol) in methanol (20 mL) to a solution of the dihydrochloride of **12** (1.11 g, 3.3 mmol) in methanol (20 mL). The reaction mixture was allowed to stand at room temperature for 2 h, then filtered. The filtrate was concentrated in vacuo to afford **12** (0.86 g, 100%) as a pale brown oil. The purity of the crude isolated product was greater than 95%, as determined by ^1H NMR in DMSO. ^1H NMR: δ 1.57 (q_i, J = 6.7 Hz, 4H, C-CH_2-C); 2.21 (d, J = 6.4 Hz, 4H, CH_2-CO); 2.64 (t, J = 6.7 Hz, 4H, C$\underline{H}_2$-NH_2); 3.11 (q, J = 6.7 Hz, 4H, C$\underline{H}_2$-NH-CO); 4.16 (m, 1H, CH); 4.36 (broad s, 5H, NH_2 and OH); 7.94 (t, J = 6.7 Hz, 2H, NH-CO). ^{13}C NMR: δ 30.4 (C-$\underline{C}H_2$-C); 35.7 (CH_2-NH_2); 37.9 ($\underline{C}H_2$-NH-CO); 43.1 ($\underline{C}H_2$-CO); 65.2 (CH); 170.5 (C=O).

Tetralactams 1a, 2a via direct macrocyclization

• **Macrocyclization achieved through acid chloride activation** - The following **high dilution technique** was used: dry benzene (500 mL) was placed in a 4 L four-neck flask equipped with a pneumatic mechanical stirrer, two dropping funnels (Normag, Dosiertrichter 8055, 500 mL), and a drying tube ($CaCl_2$). Reactant solutions [(A) 16.0 mmol of 2,3-*O*-isopropylidene-L-tartaric acid chloride in 300 mL of dry benzene and (B) 32.0 mmol of 1,2-diaminoethane or 1,3-diaminopropane in 300 mL of dry benzene] were placed in each dropping funnel. They were introduced dropwise with equivalent rates at room temperature over 8 h under vigorous mechanical stirring (3000 r.p.m.). After the addition was completed, the reaction mixture was stirred for an additional 12 h and filtered. The solvent was evaporated to dryness and the residual mixture was filtered through a silicagel pad to remove polymeric products using dichloromethane-methanol 95:05 as eluent. The further purification was performed by high performance liquid chromatography on silicagel (same eluent) to give **1a** (6%) or **2a** (17%).

• **Macrocyclization achieved through methyl ester activation** - An equimolar 0.1 M methanolic solution (5 mmol) of diamine and dimethyl-2,3-*O*-isopropylidene-L-tartrate was left under magnetic stirring at room temperature for 10 days. The solvent was evaporated, the residue was filtered through a silicagel pad (dichloromethane-methanol 90:10 as eluent) and then subjected to HPLC purification on silicagel eluting with dichloromethane-methanol 96:04 to give **1a** (6%) or **2a** (8%).

• **Macrocyclization achieved through succinimido ester activation** - A solution of di-succinimidyl-2,3-*O*-isopropylidene-L-tartrate (1.129 g, 2.94 mmol) in dry dichloromethane (8 mL) and a solution of 1,3-diaminopropane (0.654 g, 8.82 mmol) in dry dichloromethane (8 mL) were simultaneously added dropwise to dry dichloromethane (5 mL). The resulting mixture was stirred for 4 days and then filtered to remove salts. The organic solution was washed twice with water, dried over Na_2SO_4 and concentrated. The residue was subjected to silicagel HPLC purification (dichloromethane-methanol 96:04) to afford **2a** (0.067 g, 5% yield).

Tetralactam 1a: White solid; m.p. 150 °C. TLC Rf (CH_2Cl_2/MeOH 90/10) = 0.35. $[\alpha]_D$ = +122.4 (c = 0.80, MeOH). IR: 3309 (νN-H); 1671 (νC=O); 1541 (δNH-CO). ^1H NMR: δ 1.45 (s, 12H, CH_3); 3.1-3.4 (m, 8H, CH_2); 4.38 (s, 4H, CH); 7.96 (m, 4H, NH). ^{13}C NMR: δ 26.2 (CH_3); 38.3 (CH_2); 77.7 (CH); 111.6 (C-$(CH_3)_2$); 169.0 (C=O). MS (DCI/NH_3) m/z: 429 [$(MH)^+$, (100)]. Anal. Calcd. for $C_{18}H_{28}N_4O_8$, 0.5 H_2O: C, 49.42; H, 6.68; N, 12.81. Found: C, 49.10; H, 6.92; N, 12.66.

Tetralactam 2a: White solid; m.p.: 138 °C. TLC Rf (CH_2Cl_2/MeOH 90/10) = 0.42. $[\alpha]_D$ = +108.5 (c = 1.16, MeOH). IR ($CHCl_3$): 3413, 3340 (νN-H); 1673 (νC=O); 1540 (δNH-CO). ^1H NMR: δ 1.48 (s, 12H, CH_3); 1.72 (m, 4H, C-CH_2-C); 3.22 (m, 8H, CH_2-N); 4.42 (s, 4H, CH); 7.83 (t, J = 5.9 Hz, 4H, NH). ^{13}C NMR: δ 26.1 (CH_3); 27.6 (C-CH_2-C); 35.6 (CH_2-N); 77.9 (CH); 111.6 (C-$(CH_3)_2$); 168.3 (C=O). MS (DCI/NH_3) m/z: 457 [$(MH)^+$, (100)], 474 [$(MNH_4)^+$, (48)]. MS (FAB, thiogly) m/z: 457 [$(MH)^+$, (100)]. Anal. Calcd. for $C_{20}H_{32}N_4O_8$, 0.5 H_2O: C, 51.60; H, 7.15; N, 12.04. Found: C, 51.98; H, 7.10; N, 12.08.

Tetralactams 1a, 2a via stepwise synthesis

Tetralactam 1a: 2,3-*O*-isopropylidene-L-tartaric acid dichloride (1.14 g, 5.0 mmol) in 200 mL of dry acetonitrile was subjected to cyclization with the diamide-diamine compound **8** (2.74 g, 10.0 mmol) in 200 mL of dry acetonitrile over a 4 h period in 600 mL of dry acetonitrile, using the high dilution procedure described above for the direct macrocyclization via chloride activation. The mixture was then stirred for 12 h and filtered. The filtrate was concentrated and purified through a silicagel pad (dichloromethane-methanol, 95:05) to afford 0.86 g of **1a** (40% yield).

Tetralactam 2a. The same procedure as above was followed using diamide-diamine compound **9** (3.02 g, 10.0 mmol) to yield after HPLC purification (eluent dichloromethane-methanol, 95:05) 0.73 g of **2a** (32% yield).

Polylactams 3a, 3b, 4a, 4b

• **Tetralactam 3a, octalactam 4a:** A solution of 1.27 g (4.2 mmol) of diamide-diamine **9** in 200 mL of dry dimethylformamide and a solution of 1.73 g (4.2 mmol) of bis(2-mercaptothiazolide) derivative **10** in 200 mL of dry dimethylformamide were slowly added simultaneously to a vigorously stirred dry dimethylformamide (500 mL) solution at room temperature. The reaction mixture was then stirred until TLC indicated complete conversion of the bis(2-mercaptothiazolide) derivative (48 h). After evaporation of the solution in vacuo, the remaining residue was purified by filtration through a silicagel pad using dichloromethane-methanol 90:10 as eluent to remove baseline impurities. The filtrate was then chromatographed on silicagel column using dichloromethane-methanol 96:04 as eluent to remove 2-mercaptothiazoline. Compounds **3a**, **4a** were then eluted with dichloromethane-methanol 94:06 as mobile phase. Yields: **3a** 0.739 g, 37%; **4a** 0.08 g, 4%.
Tetralactam 3a: White solid; m.p.: 188-189 °C. TLC Rf (CH_2Cl_2/MeOH 90/10) = 0.36. $[\alpha]_D$ = +33.5 (c = 1.05, MeOH). IR: 3324 (νN-H); 1656 (νC=O); 1529 (δNH-CO). ^1H NMR: δ 1.37 (s, 6H, $(CH_3)_2$-C); 1.75 (m, 4H, C-CH_2-C); 2.32 (s, 3H, CH_3-Ar); 3.25-3.45 (m, 8H, CH_2-N); 3.71 (s, 3H, CH_3-O); 4.42 (s, 2H, CH-O);

7.55 (s, 2H, CH arom.); 8.02 (m, 4H, NH). ^{13}C NMR: δ 20.0 (CH_3-Ar); 25.9 (($\underline{C}H_3)_2$-C); 28.0 (C-$\underline{C}H_2$-C); 37.5, 37.7 (CH_2-N); 63.5 (CH_3-O); 77.3 (CH-O); 111.4 ($\underline{C}$-$(CH_3)_2$); 129.2 ($\underline{C}$-CONH); 132.0 (CH arom.); 133.4 ($\underline{C}$-CH_3); 153.1 ($\underline{C}$-OCH_3); 164.6, 169.2 (C=O). MS (FAB, mNBA) m/z: 477 [$(MH)^+$, (100)]; 499 [$(MNa)^+$, (16)]. Anal. Calcd. for $C_{23}H_{32}N_4O_7$, 0.5 H_2O: C, 56.90; H, 6.85; N, 11.54. Found: C, 56.86; H, 6.75; N, 11.55.

Octalactam 4a: White solid; m.p.> 260 °C. TLC Rf (CH_2Cl_2/MeOH 90/10) = 0.25. IR: 3320 (νN-H); 1650 (νC=O); 1530 (δNH-CO). ^1H NMR (80 MHz): δ 1.40 (s, 12H, $(CH_3)_2$-C); 1.66 (m, 8H, C-CH_2-C); 2.29 (s, 6H, CH_3-Ar); 3.1-3.3 (m, 16H, CH_2-N); 3.75 (s, 6H, CH_3-O); 4.50 (s, 4H, CH-O); 7.42 (s, 4H, CH arom.); 8.25 (m, 8H, NH). MS (FAB, mNBA) m/z: 953 [$(MH)^+$, (63)], 975 [$(MNa)^+$, (67)]. Anal. Calcd. for $C_{46}H_{64}N_8O_{14}$, 2H_2O: C, 55.86; H, 6.93; N, 11.33. Found: C, 55.42; H, 6.88; N, 11.21.

Tetralactam 3b, octalactam 4b: the same procedure as above was followed using diamide-diamine **11** (1.31 g, 5 mmol) and bis(2-mercaptothiazolide) derivative **10** (2.06 g, 5 mmol). After solvent removal, the residue was subjected to HPLC purification on silicagel eluting with dichloromethane-methanol 90:10 to give **3b** (1.2 g, 55%) and **4b** (0.174 g, 8%).

Tetralactam 3b: White solid; m.p. 227-228 °C. TLC Rf (CH_2Cl_2/MeOH 80/20) = 0.45. $[\alpha]_D$ = -42.0 (c = 1.20, DMSO). IR: 3300 (νN-H, νO-H); 1643 (νC=O); 1550 (δNH-CO). ^1H NMR: δ 1.74 (m, 4H, C-CH_2-C); 2.32 (s, 3H, CH_3-Ar); 3.3-3.5 (m, 8H, CH_2-N); 3.80 (s, 3H, CH_3-O); 4.26 (d, J = 7 Hz, 2H, CH-O); 5.32 (d, J = 7 Hz, 2H, OH); 7.51 (s, 2H, CH arom.); 7.68 (t, J = 6 Hz, 2H, NH); 8.04 (t, J = 6 Hz, 2H, NH). ^{13}C NMR: δ 20.0 (CH_3-Ar); 28.6 (C-$\underline{C}H_2$-C); 38.6, 39.0 (CH_2-N); 64.1 (CH_3-O); 72.6 (CH-O); 129.9 ($\underline{C}$-CONH); 131.9 (CH arom.); 133.4 ($\underline{C}$-CH_3); 152.9 ($\underline{C}$-OCH_3); 164.7, 171.5 (C=O). MS (DCI/NH_3) m/z: 437 [$(MH)^+$, (100)]. Anal. Calcd. for $C_{20}H_{28}N_4O_7$, 0.5 H_2O: C, 53.92; H, 6.56; N, 12.58. Found: C, 54.46; H, 6.53; N, 12.61.

Octalactam 4b: White solid; m.p.> 260 °C. TLC Rf (CH_2Cl_2/MeOH 80/20) = 0.20. IR: 3320 (νN-H, νO-H); 1650 (νC=O); 1530 (δNH-CO). ^1H NMR (80 MHz): δ 1.67 (m, 8H, C-CH_2-C); 2.30 (s, 6H, CH_3-Ar); 3.0-3.5 (m, 16H, CH_2-N); 3.78 (s, 6H, CH_3-O); 4.25 (d, J = 7 Hz, 4H, CH-O); 5.51 (d, J = 7 Hz, 4H, OH); 7.45 (s, 4H, CH arom.); 7.88 (t, J = 6 Hz, 4H, NH); 8.33 (t, J = 6 Hz, 4H, NH). MS (FAB, mNBA) m/z: 895 [$(MNa)^+$, (33)]; 911 [$(MK)^+$, (100)]. Anal. Calcd. for $C_{40}H_{56}N_8O_{14}$, 2 H_2O: C, 52.86; H, 6.65; N, 12.33. Found: C, 52.94; H, 6.62; N, 11.91.

Tetralactams 5a, 6

Tetralactam 5a: the bis(2-mercaptothiazolide) derivative **10** (1.36 g, 3.3 mmol) in 250 mL of dry dimethylformamide, was subjected to cyclization with the diamide-diamine **12** (0.858 g, 3.3 mmol) in 250 mL of dry dimethylformamide over a 6 h period, using the procedure described for the preparation of **3a**, **4a**. After evaporation of the solvent in vacuo, the residue was dissolved in water (50 mL). The aqueous phase was extracted with ethyl acetate (3 x 100 mL) and the combined organic phases were dried over $MgSO_4$, and rotary evaporated. The residual oil was chromatographed on silicagel eluting with dichloromethane-methanol 80:20 to provide 0.572 g of **5a** (40%). White solid. m.p.: 218 °C. TLC Rf (CH_2Cl_2/MeOH 80/20) = 0.46. IR: 3300 (νN-H, νO-H); 1646 (νC=O); 1539 (δNH-CO). ^1H NMR: δ 1.72 (m, 4H, C-CH_2-C); 2.27 (m, 4H, CH_2-CO); 2.33 (s, 3H, CH_3); 3.2-3.4 (m, 8H, CH_2-N); 3.69 (s, 3H, CH_3-O); 4.17 (m, 1H, CH-O); 4.8 (broad s, 1H, OH); 7.54 (s, 2H, CH arom.); 7.76 (t, J = 6.0 Hz, 2H, NH); 8.04 (t, J = 6.0 Hz, 2H, NH). ^{13}C NMR: δ 20.0 (CH_3); 28.0 (C-$\underline{C}H_2$-C); 37.2, 37.6 (CH_2-N); 42.8 ($\underline{C}H_2$-CO); 63.2 (CH_3-O); 65.3 (CH-OH); 129.3 ($\underline{C}$-CONH); 132.0 (CH arom.); 133.4 ($\underline{C}$-CH_3); 153.0 ($\underline{C}$-OCH_3); 164.8, 170.8 (C=O). MS (FAB, mNBA) m/z: 435 [$(MH)^+$, (100)]; 457 [$(MNa)^+$, (10)]. Anal. Calcd. for $C_{21}H_{30}N_4O_6$, 0.5 H_2O: C, 56.87; H, 7.05; N, 12.63. Found: C, 56.82; H, 7.00; N, 12.73.

Tetralactam 6: the bis(2-mercaptothiazolide) derivative **13** (1.70 g, 4.6 mmol) and the diamide-diamine **12** (1.196 g, 4.6 mmol) were treated using the procedure described for the preparation of **3a**, **4a**. After solvent removal, the residual oil was chromatographed on silicagel eluting with dichloromethane-methanol 95:05 to remove 2-mercaptothiazoline. Compound **6** was then eluted with dichloromethane-methanol 85:15. Yield: 0.865 g (48%). White solid; m.p. 221 °C. TLC Rf (CH_2Cl_2/MeOH 80/20) = 0.42. IR: 3300 (broad, νN-H, νO-H); 1671, 1640 (νC=O); 1551, 1530 (δNH-CO). ^1H NMR: δ 1.64 (m, 4H, C-CH_2-C); 2.29, 2.40 (A_2B_2 part of an A_2B_2X syst, J_{AB} = 13 Hz, J_{AX} = 5.4 Hz, J_{BX} = 8.4 Hz, 4H, CH_2-CO); 3.14 (m, 4H, CH_2-N); 3.35 (m, 4H, CH_2-N); 4.18 (X part of an A_2B_2X syst, 1H, CH-O); 5.09 (d, J = 5.4 Hz, 1H, OH); 8.11 (t, J = 6.1 Hz, 2H, NH); 8.17 (s, 3H, arom.); 9.42 (t, J = 6.1 Hz, 2H, NH). ^{13}C NMR: δ 28.8 (C-$\underline{C}H_2$-C); 35.2, 35.4 (CH_2-N); 44.6 ($\underline{C}H_2$-CO); 67.1 (CH-OH); 123.7, 139.6 (CH arom.); 148.5 (C arom.); 162.6, 171.4 (C=O). MS (FAB, Gly-Thiogly-TCA) m/z: 392 [$(MH)^+$, (100)]; 524 [$(MCs)^+$, (4)]. Anal. Calcd. for $C_{18}H_{25}N_5O_5$, H_2O: C, 52.80; H, 6.65; N, 17.10. Found: C, 52.85; H, 6.71; N, 16.87.

Polyhydroxytetralactams 1b, 2b, 3c, 5b

Tetralactam 1b: 0.9 g (2.1 mmol) of **1a** were dissolved in 15 mL of 1N HCl. The solution was stirred for 3 h at room temperature. The pH was adjusted to 6 with 1N NaOH and the resulting suspension was stored in the cold overnight. The mixture was filtered and the solid material washed with acetone (0.645 g, 88%). White solid.

m.p.: 200 °C dec.$[\alpha]_D$ = +50.7 (c = 1.51, DMSO). IR: 3306 (broad, νN-H, νO-H); 1663 (νC=O); 1546 (δNH-CO). ^{1}H NMR: δ 3.0-3.3 (m, 8H, CH_2); 3.98 (m, 4H, CH); 5.48 (m, 4H, OH); 7.91 (m, 4H, NH). ^{13}C NMR: δ 44.0 (CH_2); 78.1 (CH); 177.5 (C=O). MS (FAB, gly) m/z: 349 [$(MH)^+$, (100)]. Anal. Calcd. for $C_{12}H_{20}N_4O_8$, 4 H_2O: C, 34.29; H, 6.71; N, 13.33. Found: C, 34.24; H, 6.70; N, 13.27.

Tetralactam 2b: treatment of compound **2a** according to the procedure described above was used to give **2b** in a quantitative yield. White solid. m.p.: 225 °C dec. $[\alpha]_D$ = +28.7 (c = 1.22, DMSO). IR: 3292 (νN-H, νO-H); 1653 (νC=O); 1567 (δNH-CO). ^{1}H NMR: δ 1.56 (m, 4H, C-CH_2-C); 2.9-3.4 (m, 8H, CH_2-N); 4.13 (s, 4H, CH); 6.05 (s, 4H, OH); 7.82 (t, J = 5.6 Hz, 4H, NH). ^{13}C NMR: δ 28.3 (C-$\underline{C}H_2$-C); 37.5 (CH_2-N); 72.7 (CH); 171.4 (C=O). MS (FAB, gly-thiogly-TCA) m/z: 377 [$(MH)^+$, (61)], 399 [$(MNa)^+$, (18)]. Anal. Calcd. for $C_{14}H_{24}N_4O_8$, H_2O: C, 42.64; H, 6.65; N, 14.21. Found: C, 42.68; H, 6.34; N, 14.16.

Tetralactam 3c: A 10 mL CH_2Cl_2 solution of 10 mmol of BBr_3 was cooled in an ice water bath and compound **3a** (0.619 g, 1.3 mmol) in CH_2Cl_2 (20 mL) was added dropwise under stirring. The contents were allowed to stir 3 h at 0 °C, then the reaction was quenched with 5% $NaHCO_3$ solution (30 mL). The aqueous layer was separated, treated with CH_2Cl_2, neutralized with an aqueous NaOH solution and then taken to dryness. The crude product was then chromatographed on C18 silica reverse phase. Elution with water to remove salts followed by a 80:20 mixture of water and methanol gave **3b** (0.445 g, 81%). White solid. m.p.: 250 °C dec. TLC Rf (CH_2Cl_2/MeOH 80/20) = 0.21. $[\alpha]_D$ = -39.4 (c = 0.79, DMSO). IR: 3400 (broad, νN-H, νO-H); 1647 (νC=O); 1549 (δNH-CO). ^{1}H NMR: δ 1.71 (m, 4H, C-CH_2-C); 2.15 (s, 3H, CH_3-Ar); 2.9-3.2 (m, 4H, CH_2-N); 3.5-3.7 (m, 4H, CH_2-N); 4.31 (s, 2H, CH-O); 6.3 (broad s, 2H, OH); 7.72 (s, 2H, CH arom.); 7.61 (m, 2H, NH); 10.70 (m, 2H, NH). ^{13}C NMR: δ 20.1 (CH_3-Ar); 29.0 (C-$\underline{C}H_2$-C); 37.8, 38.9 (CH_2-N); 73.4 (CH-O); 117.9, 121.4 (C arom.); 133.7 (CH arom.); 167.1, 171.8 (C=O). MS (DCI/NH_3) m/z: 423 [$(MH)^+$, (100)]. Anal. Calcd. for $C_{19}H_{26}N_4O_7$, 2 H_2O: C, 49.78; H, 6.60; N, 12.22. Found: C, 49.55; H, 6.48; N, 12.14.

Tetralactam 5b: Compound **5a** (0.327 g, 0.75 mmol) was treated with BBr_3 according to the procedure described above. After quenching the reaction with 5% $NaHCO_3$ solution, the aqueous layer was separated, taken to dryness and the residue was treated with methanol. The resulting precipitate was removed by filtration and HPLC purification of the filtrate (C18 silica reverse phase, elution with H_2O followed by a 90:10 mixture of water and methanol) gave **5b** (0.254 g, 80%). White solid. m.p.: 275 °C. IR: 3340 (broad, νN-H, νO-H); 1648 (νC=O); 1557 (δNH-CO). ^{1}H NMR: δ 1.68 (m, 4H, C-$\underline{C}H_2$-C); 2.11 (s, 3H, CH_3); 2.23 (m, 4H, CH_2-CO); 3.0-3.3 (m, 8H, CH_2-N); 4.17 (m, 1H, CH-O); 5.04 (s, 1H, OH); 7.63 (s, 2H, arom); 7.79 (t, J = 5.5 Hz, 2H, NH); 11.66 (t, J = 5.5 Hz, 2H, NH). ^{13}C NMR: δ 20.2 (CH_3); 28.1 (C-$\underline{C}H_2$-C); 36.6, 37.4 (CH_2-N); 42.7 ($\underline{C}H_2$-CO); 65.5 (CH-OH); 115.8, 120.8 ($\underline{C}$-CH_3 and $\underline{C}$-CO); 133.2 (CH arom.); 168.0 (C=O); 169.1 (C-OH); 170.4 (C=O). MS (FAB, gly-thiogly-TCA) m/z: 421 [$(MH)^+$, (100)], 443 [$(MNa)^+$, (76)]. Anal. Calcd. for $C_{20}H_{28}N_4O_6$, H_2O: C, 54.78; H, 6.90; N, 12.78. Found: C, 55.05; H, 6.82; N, 12.65.

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