If we assume the usual aggregation number (60) of SLS is unchanged, this indicates ca. 20–30 ions can bind per micelle. From tabulation of bond distances, an approximate surface area for the ions is estimated as ca. 50 Å^2. This indicates a requirement ranging from 900 to 1550 Å^2 for the binding of these ions to the assembly. Various spherical droplet models for micelle structure recently proposed suggest a sphere radius of 18–21 Å for 12-carbon surfactants;[11,38,41] these values yield surface areas of 4070 and 5600 Å^2, respectively. Using combinations of minimum and maximum values, these areas give a range of 16–38% for the proportion of the surface occupied by the ions if it is assumed they bind with the molecular plane of the cation on the surface of the sphere with no interpenetration. In comparison, the recently proposed surfactant block model[38,39] suggests a more-or-less cubic structure having an edge length of 36 Å; this yields a surface area of ca. 7800 Å^2 of which 12–19% would be covered by the ions if the same assumptions are made. A principal difference between the "larger" sphere model[11] and the surfactant block model is the presumed resistance to penetration of the latter model. Thus while the former model should allow some penetration of molecules such as MV^{2+} into gaps, the surfactant block model would suggest the ions should indeed be in one or more of the various sites indicated at the assembly–water interface.

From the above calculations it would seem that the observed results could be accommodated reasonably well by most of the models recently proposed but not by the more classical "two-state" model. The major conclusion from the present results is that the micelle must present a variety of binding sites where ready exchange of ions can occur. Some of these sites are clearly highly hydrophilic such that binding of ions can be largely governed by enthalpy while others are moderately hydrophobic such that entropic effects are predominant.

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Registry No. MV^{2+}, 4685-14-7; Cu, 7440-50-8; RuL_3^{4-}, 78338-26-8.

Synthesis with Tin Templates. A New Family of Diastereomeric Macrocycles

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Abstract: The synthesis and properties of a new family of diastereomeric macrocyclic compounds are described which span two different types of internal cavities. The compounds are characterized by a polylactone ring and functionalized side chains arranged in either a "syn" or an "anti" configuration. The method of synthesis involves the use of cyclic tin–oxygen compounds as covalent templates and provides either of the diastereomers with high regio- and stereospecificity. Extensive spectroscopic data are given (NMR and X-ray analyses) and evidence for the different binding properties of the diastereomers for europium ions. The relationships of these compounds with naturally occurring ionophores is discussed and their possible application for the design of ion carriers or catalysts indicated.

In recent years considerable effort has been made to design synthetic complexing agents for metal ions and charged molecules.[1-4] Major emphasis has been given to systems which span a well-defined environment around the guest ion such as macrocyclic polyethers,[2] cryptands,[3] and spherands.[4] While the crown ethers delineate a two-dimensional environment, the cryptands and spherands span a three-dimensional one, providing systems with high binding efficiency and selectivity. Additional compounds capable of forming three-dimensional cavities have recently been introduced with macrocyclic polyaza- and oxo compounds containing ligating side chains.[5-8] The binding properties of the latter family of compounds are intermediate between those of the crown ethers and cryptands. Specificially, macrocyclic compounds with ligating side chains are more efficient binders than nonfunctionalized marocycles.[5-9] On the other hand, they are likely to show more favorable exchange kinetics than cryptands. In addition, macrocycles with ligating side chains offer themselves for the design of two different types of cavities: considering compounds with two side chains, two diastereoisomers are possible: structures where the side chains assume a "syn" configuration (structure A), and structures where the side chains assume an "anti" configuration (structure B). In the "syn" isomer (A) one

A B

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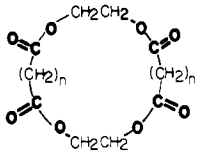
face of the ring remains uncovered and therefore one coordination site of a coordinated ion unsaturated. Such systems may provide structures for the design of catalysts, mimicking the active sites of metalloenzymes.[9] In the "anti" isomer (B), on the other hand, the coordinated ion may be embedded into a closed shell by the opposing side chains. Such systems would be of importance for the design of ion carriers. The synthesis of such compounds requires the introduction of two chiral residues into a macrocyclic ring: two chiral residues of identical configuration giving rise to one diastereomer and chiral residues of opposite configuration leading to the other diastereomer. In this publication we wish to describe the first regio- and stereospecific preparation of either of the diastereomers and wish to provide evidence for their different binding properties and for the participation of the side chains in binding. Carbonyl groups, specifically lactones and amides, have been selected as functional groups, since they are also employed in natural ionophores such as the depsipeptides enniatin and valinomycin[10] and the siderophores enterobactin and dimerum acid.[11]

Results and Discussion

The preparation of macrocyclic structures has been achieved by high dilution techniques,[13] double activation methods,[14] mercury salts,[15] metal templates,[16] the incorporation of sulfur as a bridge,[17] and consecutive ring enlargement with a "zipper"-type mechanism.[18] We have recently reported an alternative method which utilizes derivatives of silicon[19] or tin[20,21] as *covalent templates* and have applied the method for the preparation of macrocyclic tetralactones of the general formula **1**.[20] The procedure involved



1

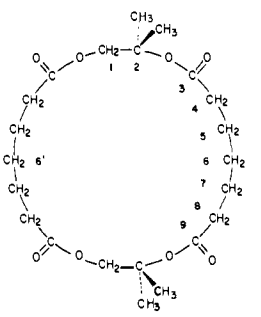
converting diols into cyclic tin–oxygen compounds and then treating them with diacyl dihalides or cyclic anhydrides. The efficiency of this method encouraged us to apply it to the synthesis of diastereomeric tetralactones with functionalized side chains. In the following discussion we wish (i) to demonstrate the feasibility of the method for the stereospecific preparation of chiral macrocyclic compounds using asymmetric diols as chemical probes, (ii) to describe the stereospecific synthesis of functionalized macrocycles with either "syn" or "anti" configuration employing asymmetric diacids, and (iii) to report on the interactions of these macrocycles with europium ions.

Three diols were used as chemical probes: (i) D-diethyl tartrate, (ii) 2-methyl-1,2-propanediol, and (iii) racemic 1,2-propanediol.

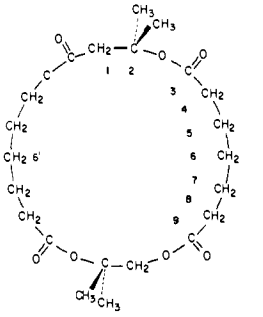
The first compound, the tartrate, was used in order to establish the feasibility of the method for the preparation of chiral compounds without competitive racemization. D-Diethyl tartrate seemed a particularly suitable probe for this purpose, since any racemization results in the formation of the meso diastereomer which can readily be detected by proton NMR analysis. D-diethyl tartrate[22] was thus converted to the cyclic tin derivative **2** by treatment with dibutyl tin diethoxide and then reacted with pimeloyl dichloride to form stereospecifically a single macrocyclic product, the tetralactone **3** (Scheme I).

The optical purity of the tetralactone **3** was established by NMR analysis. Should racemization have occurred, some of the tartaric acid residues would have isomerized to the meso diastereoisomers, which should exhibit a different NMR spectrum than the optical active isomers. The presence of a sharp signal for the proton at α-position to the carbethoxy group in the isolated compound **3** is indicative of a single diastereoisomer and thereby excludes the occurrence of racemization.

The second compound, 2-methyl-1,2-propanediol, was chosen in order to establish the regiospecificity of the method. A priori 2-methyl-1,2-propanediol may form with diacids two diastereomeric tetralactones: one in which the two diol residues are arranged in a parallel orientation (**5a**) and the other in which the diol components are arranged in an antiparallel manner (**5b**).



5a



5b

Treatment of the stannoxane **4** derived from 2-methyl-1,2-propanediol with pimeloyl dichloride gave the tetralactone **5b** as sole macrocyclic product, demonstrating the regiospecificity of the method (Scheme II). The configuration of **5** was established by carbon-13 NMR analysis. Inspection of formulae **5a** and **5b** shows that in the former structure carbon atoms C6 and C6′ are different, while in the latter, **5b** they are identical. The carbon-13 NMR spectrum of tetralactone **5** showed a single signal for C6 and C6′ (Table II). This signal appeared as a sharp singlet which did not undergo resolution or broadening upon the addition of lanthanide shift reagents, indicative of structure **5b**.

In order to establish the stereospecificity of the method, racemic 1,2-propanediol was used as chemical probe. A priori, this diol can form four diastereomeric tetralactones with diacids: two diastereomers with parallel arrangement of the diols (structures **7a** and **7b**) and two diastereomers with antiparallel arrangement of the of the diols (structures **7c** and **7d**).

Cyclic stannoxane **6**[23] derived from racemic 1,2-propanediol was thus prepared and condensed with pimeloyl dichloride to also provide a sole macrocyclic product. The structure of the compound was shown to be **7d** by both NMR and X-ray analyses (Scheme III).

The structures with a parallel arrangement of diols (**7a** and **7b**) should have two carbon-13 signals for carbons C6 and C6′ the structures with an antiparallel arrangement (**7c** and **7d**) a single signal. Carbon-13 NMR analysis of the isolated compound gave an eight-line spectrum with a sharp signal for carbon C6 and C6′ (Table II), suggesting structures **7c** or **7d**. Distintion between the meso form (**7d**) and the chiral form (**7c**) was sought by using chiral shift reagents: addition of a chiral shift reagent should have caused a shift of the signals only in the meso form (**7d**) and should have resolved all carbon-13 signals in the case of the chiral structure (**7c**). Since no resolution of the signals was observed, the structure of the isolated compound was assumed to be **7d**.

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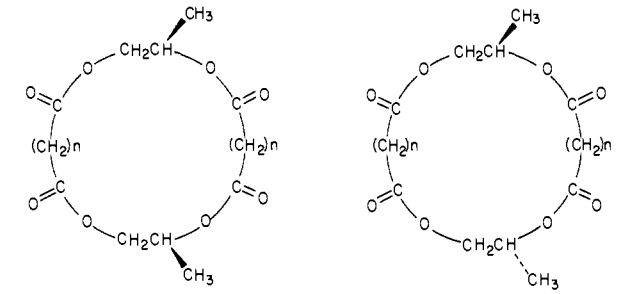
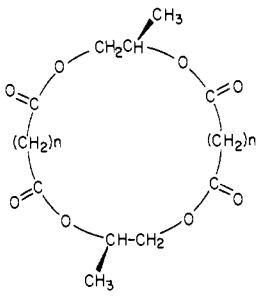


meso

7a

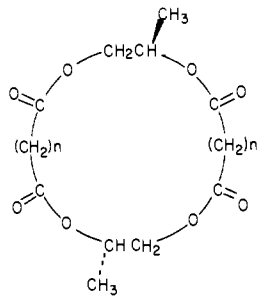
racemic

7b



racemic

7c

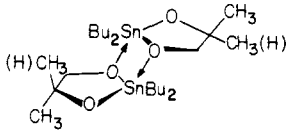


meso

7d

In order to obtain direct evidence for the configuration of the isolated compound, we performed an X-ray diffraction analysis. The X-ray structure of **7d** is shown in Figure 1.[24] Inspection of Figure 1 shows that the two methyl groups are indeed located at diagonal positions and that they assume an "anti" configuration, pointing to opposite faces of the rings surface. It may also be seen that the conformation of the tetralactone **7d** is analoguous to that observed in related tetralactones with acyl residues bearing an odd number of methylene groups:[20] one pair of carbonyl groups point in opposite directions, above and below the plane of the ring, whereas the other pair of carbonyl groups are in the general plane of the ring.

The stereospecificity observed in these reactions may be explained by the presence of dimeric complexes of stannoxanes **4** and **6**. The association in solution of organic compounds con-



taining tin–oxygen bonds has been demonstrated to be a general phenomenon by ebullioscopic and cryoscopic methods[25] as well as by tin-119 NMR analysis.[26] The structures of these associates are likely to be as indicated in the scheme above, where the methyl substituents assume the most distant positions due to the bulkiness of the butyl groups at the tin element. Reaction of such complexes with diacyl dihalides may then occur from either the back or the front face. In the case of the dimethylated derivative, compound

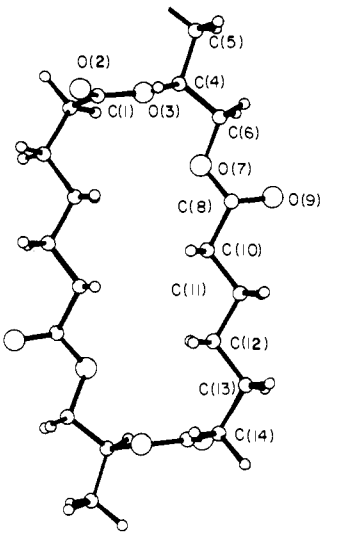
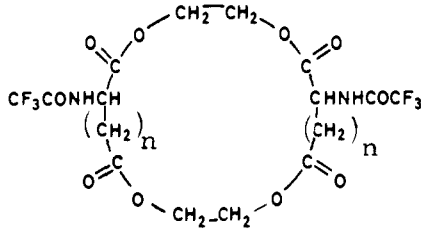


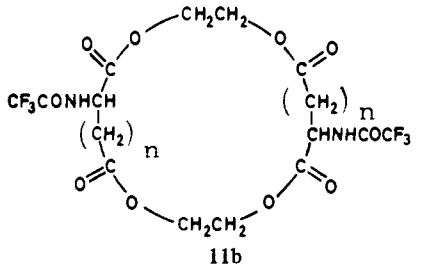
Figure 1.

5b is then formed regiospecifically, in the case of the monomethylated derivative, compound **7d** stereospecifically.

Having established the feasibility of the method for the stereospecific preparation of macrocyclic compounds, the synthesis of chiral macrocycles with ligating side chains was sought. The acidic amino acids glutamic and aspartic acid were selected as acid components for this purpose and specifically *N*-(trifluoroacetyl)glutamic anhydride (**9**) and *N*-(trifluoroacetyl)aspartic anhydride (**10**).[27] Reaction of *N*-(trifluoroacetyl)glutamic anhydride (L-**9**) with distannoxane **8**[28] (derived from ethylene glycol), provided a sole macrocyclic compound, LL-**11**, containing two amino acid residues of identical configuration. Its spectroscopic data were in agreement with those expected for a ring system containing two ethylene glycol and two glutamic acid residues (Table I). However, as in the case of diols, two diastereomers might have been formed: an isomer with a parallel orientation of the acid residues, structure **11a**, or an isomer with an antiparallel orientation of the acid residues, structure **11b**.



11a



11b

Proton NMR decoupling experiments established the presence of structure **11b**. Irradiation of the methylene protons belonging to the ethylene glycol residue at 3.68 ppm caused collapse of the methylene multiplet at 4.18 ppm to a singlet, and irradiation of the methylene protons at 4.18 ppm caused collapse of the signal

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(24) Compound **7d** crystallizes as monoclinic crystals from hexane: space group $P2_1/c$, $a = 13.437$ (2) Å, $b = 7.680$ (2) Å, $c = 10.997$ (4) Å, $\beta = 107.08$ (2)°, $Z = 2$. Intensity data were collected on a CAD-4 diffractometer (1825 unique reflections, 1151 classed as observed, $\theta \leq 70°$) with Cu K_α Ni-filtered radiation. The structure was solved by direct methods and refined by full-matrix least squares to $R = 0.078$ and $R' = 0.087$.

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Scheme I

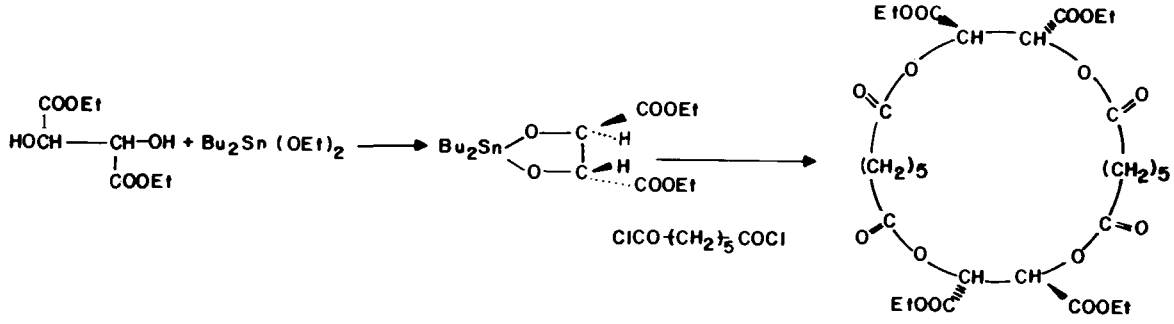


Table I. Yields and Spectroscopic Data of Macrocyclic Tetralactones

compd	yield, %	IR[a] ν, cm^{-1}	MS, *m/e* (%)	^{1}H NMR,[b] δ $^1CH_2O$	^2CHO	CO^4CH	$COCH_2$	(CH_2)	CH_3	OC_2H_5	mol formula	elemental anal. calcd %C	%H	%N	found %C	%H	%N
3[c] (oil)	39	1740 1450	660 (3.3) 331 (72.2)	5.69 (s)	5.69 (s)	2.4 (m)	2.4 (m)	1.6 (m)		4.24 (q, J = 7 Hz) 4.27 (t, J = 7 Hz)	$C_{30}H_{44}O_{16}$	54.54	6.71		54.25	6.90	
5[c] (oil)	24	1730 1150	428 (7.55) 215 (78.8)	4.25 (s)		2.25 (m)	2.25 (m)	1.38–1.79 (m)	1.45 (s)		$C_{22}H_{36}O_8$	61.66	8.47		61.40	8.65	
7[c] (mp 92–94 °C)	29	1730 1250 1175	400 (29.5) 200 (100)	4.32 (dd, 11.5; 1.5[g]) 3.96 (dd, 10.5; 7.5[g])	5.19 (dq, 6.6; 1.5[g])	2.3 (m)	2.3 (m)	1.3–1.8 (m)	1.24 (d, J = 6.5 Hz)		$C_{20}H_{32}O_8$	59.98	8.05		60.10	7.90	
11[d] (oil)	49 (LL) 41 (DL)	3300 1750 1705	... 270 (36)	3.68 (t, J = 5 Hz)	4.18 (m)[f]	4.50 (m)	2.43 (t, J = 7 Hz)	2.20 (dtd, 14; 7; 5[g]) 2.04 (ddt, 14; 9.5; 7[g])			$C_{18}H_{20}N_2O_{10}F_6$	40.15	3.74	5.23	40.30	3.8	5.65
12[e] (mp 76–78 °C)	70	3300 1755 1554	510 (2.09) 256 (99.4)	3.32 (t, J = 5 Hz)	3.8 (t, J = 5 Hz)	4.48 (m)	2.46 (dd, 17; 8[g]) 2.58 (dd, 17; 5[g])				$C_{16}H_{16}N_2O_{10}F_6$	37.66	3.16	5.49	37.50	3.25	5.39

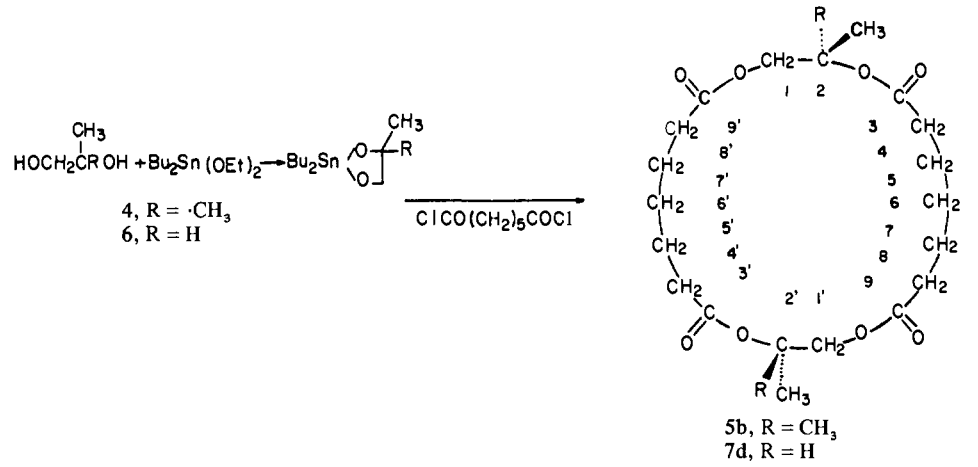
[a] The IR spectra were recorded in Nujol. [b] The NMR chemical shifts are in ppm from internal Me_4Si; the spectra were run at the frequencies and in the solvents indicated. [c] 80 MHz, $CDCl_3$. [d] 270 MHz, CD_3CN. [e] 270 MHz, CD_3OD. [f] ABX_2 system; J_{gem} = 11 Hz, J_{vic} = 5 Hz, ν_{AB} = 12 Hz (0, 044 ppm). [g] Hz.

Table II. ^{13}C NMR Data of Macrocyclic Tetralactones[a]

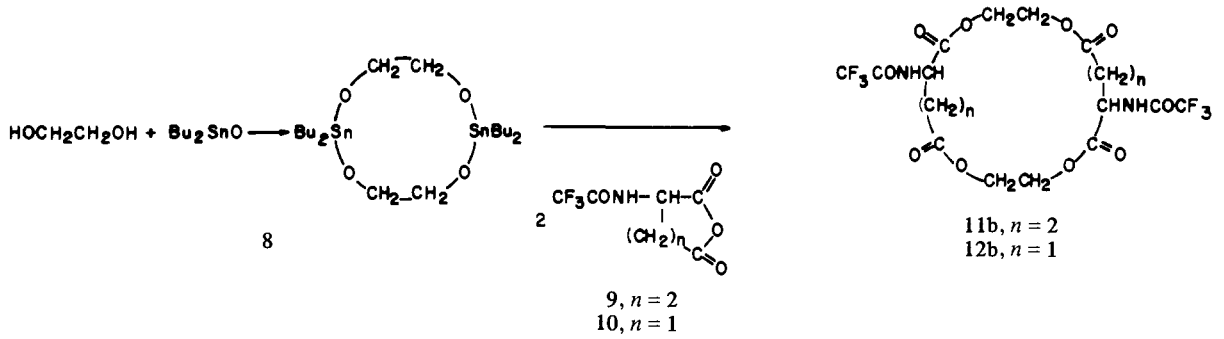
compd	O^1CH_2	^2CO	O^3CO	CO^4C	$^5CH_2$	$^6CH_2$	$^7CH_2$	$^8CH_2CO$	^9COO	2-CH_3	$COCF_3$[f]	COCF
1[b] (n = 5)	62.0	62.0	173.3	34.2	24.8	28.4	24.8	34.2	173.3			
5[b,c]	68.5 (1.7)	79.6 (1.7)	172.7 (1.3)	35.6 (2.0)	25.1 (1.3)	28.6 (0.9)	24.8 (1.0)	34.4 (1.6)	172.9 (1.2)	23.3 (0.9)		
7[b,c]	66.0 (1.5)	68.0 (1.5)	172.8 (0.7)	34.5 (1.6)	24.9 (1.0)	28.5 (0.7)	24.8 (0.9)	34.3 (1.4)	173.1 (1.0)	16.3 (0.5)		
1[b] (n = 3)	62.0	62.0	172.6	33.2	20.4			33.2	172.6			
11[d]	58.9	66.8	173.7	52.0	25.3			29.9	170.4		156.8	115.8
1[b] (n = 2)	62.4	62.4	172.1	28.9				28.9	172.1			
12[e]	60.3	67.8	173.0	50.3				35.5	170.2		158.4	116.8

[a] Chemical shifts are in ppm from internal Me_4Si unless otherwise stated. [b] Spectra in $CDCl_3$. [c] Values in parentheses are shifts caused by addition of $Eu(tfc)_3$ extrapolated to a 1:1 ratio. [d] Spectrum in Me_2SO-d_6, $\delta(Me_4Si) = \delta(Me_2SO) + 39.5$ ppm. [e] Spectrum in CD_3OD. [f] $^2J_{CF}$ = 38 Hz. [g] $^1J_{CF}$ = 287 Hz.

Scheme II



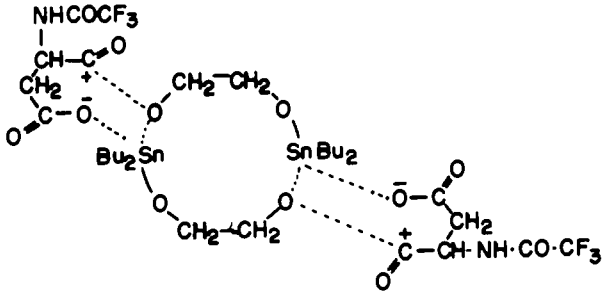
Scheme III



at 3.68 ppm to a singlet (see Table I). The macrocyclic tetralactone LL-**11b** was found to be optically active with an optical rotation of $[\alpha]_D$ −31.8° (*c* 1.8, in ethanol). Hydrolysis of LL-**11b** to its constituents and chromatographic analysis of the glutamic acid formed (as *N*-trifluoroacetyl diisopropyl ester)[29,30] showed the exclusive presence of the L enantiomer, demonstrating the optical purity of LL-**11b**.

L-(Trifluoroacetyl)aspartic anhydride (L-**10**) and D-(trifluoroacetyl)aspartic anhydride (D-**10**) were also reacted with stannoxane **8** to form the analogous tetralactones LL-**12b** and DD-**12b**, respectively, in 70% yield. The optical rotations of the enantiomeric macrocyclic products were found to be $[\alpha]_D$ −26.3° (*c* 1.73, ethanol) and $[\alpha]_D$ + 26.1 (*c* 0.475, in ethanol), respectively.

The formation of macrocyclic tetralactones by condensation of anhydrides with stannoxane may occur via an electrophilic attack of the anhydride carbonyl at the stannoxane oxygen and subsequent elimination of dibutyltin oxide. The loss of dibutyltin oxide has recently been suggested in the tin-catalyzed lactonization of hydroxy acids.[31]



The regiospecific formation of the antiparallel compounds may be due to transannular interactions in distannoxane **8** between tin and oxygen.[32] These transannular interactions are likely to enhance the reactivity of one of the opposite located tin-oxygen bonds relative to the other resulting in the regiospecific attack of the two anhydride molecules at the most distant positions. This attack does not occur simultaneously but in a stepwise manner. Indirect support for the latter point was obtained when reaction of 1 equiv of stannoxane **8** with one instead of 2 equiv of anhydride **9** failed to provide any macrocyclic products.

The macrocyclic glutamate and aspartate compounds described above represent functionalized macrocycles, in which the side chains point to the same direction, i.e., above the plane of the ring (structure A). The design of ring systems with the isomeric configuration, structue B, would require the incorporation of two amino acid residues of opposite configuration. The stepwise nature of the reaction between stannoxane **8** and anhydrides allowed the preparation of the latter systems by this method. Consecutive treatment of stannoxane **8** with 1 equiv each of D-(trifluoroacetyl)glutamic anhydride (D-**9**) and L-(trifluoroacetyl)glutamic anhydride (L-**9**) yielded the meso tetralactone DL-**11b**.

The spectroscopic properties, IR and NMR proton spectra, of the two isomeric tetralactones were indistinguishable (Table I), suggesting that the two acyl residues of the ring do not interact with each other and do not therefore cause any significant chemical shift on each other. Even the carbon-13 NMR spectra of the two diastereomers were identical. The data for the glutamate **11b** and the aspartate **12b** are given in Table II for comparison with those of the nonsubstituted parent compounds, the cyclic glutarate **1** (n = 3) and the cyclic succinate **1** (n = 2).[20] Inspection of these data indicates that the amide proton and the ring lactone at position 3 are probably hydrogen bonded. The proton NMR and the carbon-13 NMR signals for the methylene group at position 2 in **11b** and **12b** are at significantly lower fields than those for the analogous groups in the parent compounds **1**. These low-field

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(30) B. Feibush, *Chem. Commun.*, 544 (1971).
(31) K. Steliou, A. Szczyglielska-Nowasielska, A. Favre, M. A. Poupart, and S. Hanessian, *J. Am. Chem. Soc.*, **102**, 7578 (1980).
(32) We thank one of the referees for drawing our attention to the possibility of transannular interactions in distannoxane **8**.
(33) F. deJong, D. N. Reinhardt, and R. Huis, *Tetrahedron Lett.*, 3985 (1977); D. Laidler and J. F. Stoddart, *J. Chem. Soc. Commun.*, 979 (1976).

Table III. Lanthanide-Induced Shifts (LIS) on Macrocyclic Lactones LL-11b and DL-11b (^{1}H NMR Data)[a]

proton	chem shift	LIS for LL-11b[b]	LIS for DL-11b[b]	LL-11b/DL-11b[b]
^{1}CH	3.68	0.30	0.52	0.58
^{2}CH[c]	4.18	0.21	0.35	0.58
^{1}CH	4.51	0.32	0.48	0.67
^{5}CH′	2.04	0.34	0.49	0.69
^{5}CH″	2.20	0.37	0.53	0.69
^{8}CH	2.43	0.31	0.51	0.60

[a] For details see Experimental Section. [b] Extrapolated to a 1:1 Eu(fod)$_3$:substrate ratio; the values are accurate to ±0.03 ppm. [c] Center of multiplet.

signals may be due to the increased electron withdrawal caused by hydrogen bonding of the lactone group and consequently increased polarization of both the C=O and CH—O bonds. The similarity of the NMR spectra of the glutamate **11b** and asparate **12b** indicates that hydrogen bonding of the NH proton occurs with the proximal rather than with the distal lactone function. The difference in configuration of the diastereomeric macrocycles with "syn" or "anti" configuration was shown by the differences in their binding affinity for europium shift reagents.

Gradual addition of Eu(fod)$_3$ to solutions of isomer LL-**11b** or isomer DL-**11b** was found to have two effects: line broadening and a downfield shift of the NMR signals. The line broadening may be attributed to a low rate of exchange between the free and complexed ring system.[33] This explanation for the observed line broadening was confirmed by the decrease in line width at higher temperatures. The line broadening at 330 ± 2 K in the presence of 0.4 equiv of Eu(fod)$_3$ for the ethylene protons was found to be ca. 3 Hz compared with 6 Hz at 296 ± 2 K, and for the methylene protons adjacent to the carbonyl group was found to be 11 Hz, compared with 16 Hz at 296 ± 2 K.

The europium-induced chemical shifts for the isomeric lactone LL-**11b** corresponding to structure A were smaller than for the meso form DL-**11b** corresponding to structure B. The lanthanide induced shifts for the two isomers extrapolated to a 1:1 molar ratio are presented in Table III, which shows that in the chiral isomer LL-**11b** the average shift amounts to only 65% of that found in the meso isomer DL-**11b**. The differences are highest for the protons adjacent to the chiral center. These observations indicated that a different stereochemical environment of the binding sites exists in the two systems and suggests that the chiral residues must contribute significantly to the binding process.

It is interesting to compare the synthetic macrocycles with ligating side chains to some natural ion carriers with ligating side chains such as the iron carriers enterobactin and dimerum acid.[11,12] While the synthetic complexing agents are designed to span a cavity by virtue of both the side chains and the ring backbone, the siderophores enterobactin and dimerum acid[11,12] span octahedral or tetrahedral cavities with the side chains only. The attainment of such cavities requires the substituents to assume a well-defined orientation in space. This orientation could possibly be achieved via hydrogen bonding of the side chains to the lactone or amide backbone. The observed hydrogen bonding between the ligating amides and the ring lactones in compounds **11b** and **12b** support this possibility.

Conclusion

We have introduced diastereomeric macrocyclic lactones with functionalized side chains in either "syn" or "anti" configuration and an efficient method for their preparation. The method of synthesis is based on the use of cyclic tin–oxygen compounds as templates and enables the preparation of the desired diastereomers with high regio- and stereospecificity. The diastereomeric tetralactones have been found to be indistinguishable in their spectroscopic properties, but they differ in their binding affinity to metal ions: the "syn" isomer (structure A) was found to bind europium ions less efficiently than the "anti" isomer (structure B). Although NMR studies using europium ions as a probe do not allow us to identify the location of the guest ion, the different behavior of the two diastereoisomers encourages us to consider the application of such structures for different purposes. Thus, it appears appealing to consider systems with "syn" configuration as ligands for the design of catalysts. On the other hand, systems with "anti" configuration appear promising as specific-ion carriers with variable release profiles.

Experimental Section

Preparation of Cyclic Stannoxanes 2, 4, and 6. A solution of diol (0.01 mol) in 150 mL of benzene was treated with dibutyltin diethoxide (0.01 mol) under reflux overnight with concurrent removal of liberated ethanol as an azeotrope with benzene. The solvent was then removed in vacuo and the dry residue analyzed by IR and NMR spectroscopy. It was found to contain the cyclic stannoxanes **2**, **4**, or **6** as indicated by the absence of hydroxyl groups and was used for further reactions without purification.

Preparation of Macrocyclic Tetralactones 3, 5, and 7. A boiling solution of cyclic stannoxanes **2**, **4**, or **6** (0.01 mol) in 200 mL of dry chloroform was treated dropwise with a solution of 1.5 mL (0.01 mol) of pimeloyl chloride in 200 mL of dry chloroform. When the addition was completed (ca. 30 min), the mixture was refluxed for 2 h more, then cooled to room temperature, treated with 2 mL of pyridine, and concentrated in vacuo. Chromatography of the residue on silicagel (silicagel 60, Merck) and elution with toluene–ethyl acetate (4:1 ratio) yield the corresponding tetralactones **3**, **5**, and **7**. The individual yields, the spectroscopic data, mass spectra, and elemental analyses of the products are summarized in Tables I and II.

Preparation of Tetralactones 11 and 12. A solution of 1.46 g (0.0025 mol) of stannoxane **8** and 1.125 g (0.005 mol) of L-(trifluoroacetyl)-glutamic anhydride L-**9** in 150 mL of dry chloroform was heated under reflux for 2 h. The reaction mixture was then concentrated in vacuo and chromatographed on silicagel (silicagel 60, Merck). Elution with mixtures of benzene and ethyl acetate yielded 669 mg (0.001 24 mol) of the macrocyclic tetralactone LL-**11b**. The aspartic derivatives LL-**12b** and DD-**12b** were prepared by analogous procedures. The meso glutamate DL-**11b** was prepared by refluxing stannoxane **8** (1.464 g, 0.0025 mol) with 562 mg (0.0025 mol) of D-(trifluoroacetyl)glutamic anhydride D-**9** for 2 h and then with 562 mg (0.0025 mol) of L-(trifluoroacetyl)glutamic anhydride (L-**9**) for 2 h. The resulting reaction mixture was concentrated in vacuo and chromatographed on silicagel (silicagel 60 Merck) to form the tetralactone DL-**11b**. The yields, spectroscopic properties, mass spectra, and elemental analyses of the products are summarized in Tables I and II.

Determination of Optical Purity of Lactones LL-11b and LL-12b. Lactones LL-**11b** and LL-**12b** were hydrolyzed to their constituents and the resultant glutamic and aspartic acids derivatized to the corresponding *N*-trifluoroacetyl diisopropyl esters.[29] These derivatives were separated by chromatography on a capillary column coated with a chiral diamide phase[30] and compared with authentic samples of L-glutamic and L-aspartic acid derivatives. Both hydrolyzates (derived from lactones **11b** and **12b**) were found to contain exclusively the L enantiomers.

NMR Measurements. The NMR spectra were measured on FT-80A (Varian, ^{1}H, 80 MHz), WH-90 (Bruker, ^{13}C, 22.6 MHz), and WH-270 (Bruker, ^{1}H, 270 MHz, and ^{13}C, 67.9 MHz) instruments in the Fourier transform mode. The lanthanide-induced shifts on the proton spectra of the lactones LL-**11b** and DL-**11b** were determined by adding known volumes of a stock solution of Eu(fod)$_3$ in CD_3CN to the samples and plotting the peak positions vs. the amounts of shift reagent added and extrapolating the resulting straight lines to a 1:1 molar ratio (Table III). The lanthanide-induced shifts on the C-13 spectra of lactones **5** and **7** were obtained in a similar fashion, with the addition of aliquots of solid tris[3-((trifluoromethyl)hydroxymethylene)-*d*-camphorato]europium (Table II).

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Registry No. 2, 82093-86-5; **3**, 82093-87-6; **4**, 82094-65-3; **5b**, 82093-88-7; **6**, 82112-71-8; **7d**, 82093-89-8; **8**, 5271-60-3; L-**9**, 1535-57-5; D-**9**, 75403-97-3; L-**10**, 777-33-3; D-**10**, 75403-90-6; LL-**11b**, 75494-91-6; DL-**11b**, 82165-89-7; LL-**12b**, 75403-91-7; DD-**12b**, 75443-60-6; i, 13811-71-7; ii, 558-43-0; iii, 4254-16-4; dibutyl tin ethoxide, 1067-41-0; pimeloyl dichloride, 142-79-0.

Supplementary Material Available: Tables of atomic coordinates, anisotropic temperature factors, and bond lengths and angles (3 pages). Ordering information is given on any current masthead page.