conditions. The crude reaction product was stirred for 1 h with 5% aqueous sodium carbonate solution, filtered, washed with water, and dried, 2.1 g (56% based on phthalide), mp 183–190 °C.

An analytical sample was obtained by recrystallization from toluene: mp 196–197 °C; NMR 2.65 (s, 3 H), 2.72 (s, 3 H), 3.17 (s, 3 H), 4.00 (s, 3 H), 7.1–8.1 (m, 7 H), 9.18 (s, 1 H); IR (Nujol) 1760, 1630, 1200, 1180, 1010, 860, 810, 800 cm^{-1}.

Preparation of 7-Acetoxy-1,4-dimethylbenz[*a*]anthracene (10b). Beginning with 2.4 g of 3-benzal-4,7-dimethylphthalide, there was obtained, after LAH reduction, Diels-Alder reaction with methyl acrylate, aromatization, and DBU isomerization, 2.3 g of the naphthoate derivative **5b**. Trouble was encountered in attempting to continue the sequence without purification. Therefore 1.1 g of crude **5b** was chromatographed on silica gel, eluting with 1:1 methylene chloride/30–60 °C petroleum ether graded to methylene chloride. After elution of 115 mg of material of uncertain structure, 670 mg of a 3:1 mixture of **5b/6b** (46% yield based on the phthalide) was collected followed by 120 mg of the unaromatized Diels-Alter adduct *endo*-**4b** (8% yield based on the phthalide).

The mixture of **5b** and **6b** was hydrolyzed and cyclized and the crude product washed with dilute $NaHCO_3$ as described to give 0.493 g (71% yield based on the naphthoate ester **5b/6b**) of **10b**, mp 202–204 °C. One recrystallization from toluene, and an additional bicarbonate wash followed by another recrystallization gave the analytical sample: mp 212–214 °C; NMR ($CDCl_3$) 2.61 (s, 3 H) 2.69 (s, 3 H), 3.15 (s, 3 H), 7.3–8.3 (m, 8 H), 9.32 (s, 1 H); IR (Nujol) 1755, 1210, 860, 790, 775, 720 cm^{-1}.

Acknowledgment. This work was financially supported by the Natural Science and Engineering Research Council of Canada.

Registry No. **1a**, 54933-15-2; **1b**, 78963-13-0; **1c**, 78963-14-1; **1d**, 78963-15-2; **2c**, 73194-66-8; **3a**, 54892-75-0; **3b**, 78891-76-6; **3c**, 78891-77-7; **3d**, 78891-78-8; *endo*-**4a**, 73245-14-4; *exo*-**4a**, 73194-98-6; *endo*-**4b**, 78891-79-9; *exo*-**4b**, 78963-16-3; *endo*-**4c**, 78891-80-2; *exo*-**4c**, 78963-17-4; *endo*-**4d**, 78891-81-3; *exo*-**4d**, 78963-18-5; **5a**, 73194-63-5; **5b**, 78891-82-4; **5c**, 78891-83-5; **5d**, 78891-84-6; **6b**, 78891-85-7; **6c**, 78891-86-8; **6d**, 78891-87-9; **8**, 2498-66-0; **9a**, 73194-80-6; **10a**, 25040-01-1; **10b**, 78919-59-2; **10c**, 78919-60-5; **10d**, 78919-61-6; 3-(*p*-methoxybenzal)phthalide, 4767-61-7; methyl acrylate, 96-33-3; 3-benzal-4,7-dimethylphthalide, 78919-62-7; 3-(*p*-methoxybenzal)-4,7-dimethylphthalide, 78919-63-8; 3-(carbomethoxy)-1,4-epoxy-1-(*p*-methoxyyphenyl)-5,8-dimethyl-1,2,3,4-tetrahydronaphthalene, 78919-64-9; 1-(*p*-methoxybenzal)phthalan, 64421-15-4.

Synthesis with Tin Templates: Preparation of Macrocyclic Tetralactones

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A new approach toward the preparation of macrocyclic lactones is introduced. The method is based on the use of tin derivatives as covalent templates. The latter are capable of directing the condensation of acyclic diols and diacyl dihalides to provide macrocyclic tetralactones as the sole ring products. The usefulness of the method is demonstrated by the preparation of a series of symmetric (**6–9**) as well as mixed (**10**) lactones in high yields. The mechanistic implications of the method will be discussed as will the structural regularities of the newly synthesized compounds.

Polyfunctional macrocyclic compounds are receiving increasing attention because they may selectively bind a large range of metal ions.[1,2] Macrocyclic compounds are therefore being used as catalysts in synthesis (capable of solubilizing salts in organic solvents) and as key components in various metal separation techniques. The growing need for macrocyclic ligands has stimulated extensive research efforts toward their efficient preparation and much progress has been made in this field.[3] Yet, the synthesis of polyfunctional macrocycles still poses serious difficulties and generally provides mixtures of cyclic and acyclic products. The preparation of one class of polyfunctional systems, polylactones, has hitherto been achieved by two major methods: by condensation of dibasic acid derivatives with glycols or dihalides using high dilution techniques[4] or by depolymerization of linear polyesters.[5] Both methods provide mixtures of macrocyclic dilactones and tetralactones, the ratio of which is determined by the relative stability of the two ring systems. In this publication we introduce a new method for the preparation of macrocyclic lactones which yields tetralactones as sole ring products. In addition, we describe the structural regularities of the synthesized polyfunctional systems.

In an attempt to provide an efficient method for the preparation of macrocyclic polylactones, we undertook the use of tin derivatives as covalent templates. The use of a template was believed to favor ring formation, and the choice of tin as the template was based on its chemical properties. Tin, like other metalloids, does readily react with difunctional organic residues to give heterocyclic intermediates such as cyclic stannoxanes. The latter are highly reactive chemical entities which are expected to condense efficiently with difunctional organic substrates to provide ring products.[6] This expectation was indeed realized. By use of a series of four different cyclic stan-

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Table I. Analytical and Spectroscopic Properties of Tetralactones 6 and 10

compd[e]	mp, °C	% yield[c]	IR,[a] cm^{-1} CO	IR,[a] cm^{-1} COC	IR,[a] cm^{-1} CH_2O	NMR,[b] δ CH_2CO	NMR,[b] δ $-(CH_2)_n-$	mass spectrum, m/e (% base peak) M	M/2 + 1	M/2
6a (n = 3)	144	42	1720	1200, 1170, 1150	4.25 (s)	2.40 (t)	2.0 (quin)	316 (7.0)	159 (100)	158 (3.6)
6b (n = 4)	56	28	1735	1180	4.32 (s)	2.39 (m)	1.70 (m)	344 (36)	173 (100)	172 (2.5)
6c (n = 5)	147	35	1725	1170	4.30 (s)	2.36 (t)	1.62 (m)	372 (40)	187 (100)	186 (5.3)
6d (n = 6)	54	35	1715	1270, 1170	4.32 (s)	2.35 (t)	1.40 (m), 1.70 (m)	400 (9)	201 (40)	200 (3)
6e (n = 7)[d]	147	53	1720	1160	4.20 (s)	2.25 (t)	1.35 (m), 1.70 (m)	428 (54)	215 (100)	214 (2.5)
6f (n = 8)[d]	80	65	1730	1170	4.23 (s)	2.32 (t)	1.30 (m), 1.60 (m)	456 (35)	228 (45)	227 (1.5)
10	122	80	1730	1170	4.29 (s)	2.32 (t)	1.35 (m), 1.60 (m)	414 (20)	215 (30), 201 (18)	214 (2), 200 (4)

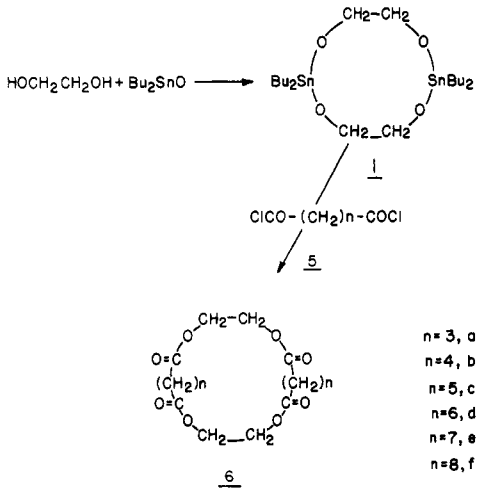
[a] The IR spectra have been recorded in either KBr pellets or Nujol. [b] The NMR spectra have been measured on a Varian A-60 instrument in $CDCl_3$ solution; the chemical shifts given are relative to internal Me_4Si. [c] The yields given are for pure isolated materials. [d] See reference 5. [e] Satisfactory analytical data (±0.3% for C and H) for all compounds were submitted for review.

Table II. Physical and Spectroscopic Properties of Tetralactones 7–9

compd[d]	mp, °C	% yield[c]	IR,[a] cm^{-1} CO	IR,[a] cm^{-1} COC	NMR,[b] δ CHO	NMR,[b] δ CH_2CO	NMR,[b] δ CH_2-CH_2CO	NMR,[b] δ CH_2	NMR,[b] δ CH_3	mass spectrum, m/e (% base peak) M	M/2 + 1	M/2
7	133	38.5	1720	1260, 1170	4.95 (m)	2.28 (2t)	1.60 (m)	1.35 (m)	1.20 (d)	456 (11)	229 (34)	
8	90	48.6	1720	1270, 1190, 1165, 1120	3.88 (s)	2.32 (t)	1.63 (quin)	1.34 (quin)	0.97 (s)	456 (17.5)	229 (99.8)	
9	97	21	1720	1190	4.12 (t)	2.34 (t)	1.71 (m)	1.71 (m)		400 (4)	201 (12)	200 (5)

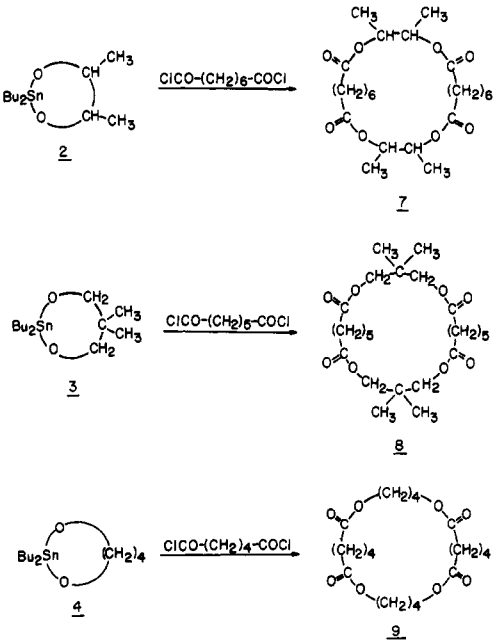
[a] Thr IR spectra have been recorded in Nujol. [b] The NMR spectra have been measured on a 270-MHz Bruker instrument in $CDCl_3$ solution; the chemical shifts given are relative to internal Me_4Si. [c] The yields given are for pure, isolated material. [d] Satisfactory analytical data (±0.3% for C and H) for all compounds were submitted for review.

noxanes, **1–4**, as templated diol precursors and a large range of diacyl dihalides, **5**, as condensing agents, symmetric and mixed macrocyclic tetralactones were prepared in good yields.



The first stannoxane employed was the cyclic distannoxane 1. The latter compound, which may be regarded as templated ethylene glycol, has been described in the literature and may readily be prepared by treatment of ethylene glycol with dibutyltin oxide.[7] Condensation of **1** with diacyl dihalides **5a–f** in boiling chloroform provided the corresponding tetralactones **6a–f** as the sole ring products. The yields range between 30% and 85% and are significantly better than our earlier reported values, which were obtained in carbon tetrachloride solution[8] (Table I).

Other cyclic stannoxanes proved equally suitable for the preparation of macrocyclic tetralactones. Condensation of the stannoxanes **2**,[9] **3**,[10] and **4**[9] with suberyl chloride (**5d**), pimelyl chloride (**5c**), and adipyl chloride (**5b**) provided the 12-membered macrocyclic tetralactones **7–9** in unoptimized yields ranging between 21% and 49%. No formation of the corresponding macrocyclic dilactones was observed.



(7) W. J. Considine, *J. Organomet. Chem.*, **5**, 263 (1966).
(8) A. Shanzer and N. Mayer-Snochet, *J. Chem. Soc., Chem. Commun.*, 176 (1980).
(9) J. C. Pommier and J. Valade, *J. Organomet. Chem.*, **12**, 433 (1968).
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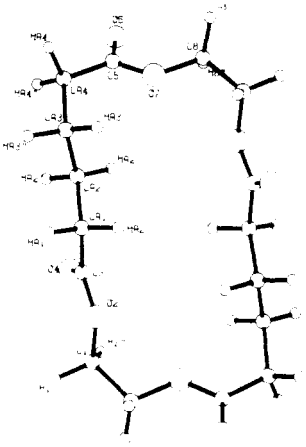
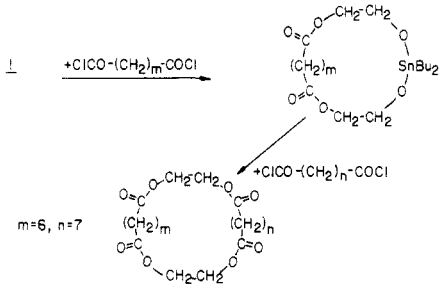


Figure 1. X-ray structure of tetralactone **6b** (n = 4).

The formation of macrocyclic tetralactones in preference to dilactones may be rationalized by proposing a stepwise condensation reaction between stannoxanes and acyl halides. The isolation of monoacylated diols when such stannoxanes were treated with benzoyl or acetyl chloride is compatible with such a reaction pathway.[11] Indirect



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evidence for a stepwise process was also obtained by isolating the mixed tetralactone **10** as major product upon successive addition of 1 equiv of suberyl chloride (**5d**) and azelyl chloride (**5e**) to stannoxane **1**.

All macrocyclic tetralactones were characterized by their analytical and spectroscopic properties which were in agreement with the assigned structures (Tables I and II).

Mass spectral data proved most indicative, showing in each case a weak molecular ion peak and a strong fragment corresponding to M/2 + 1. The latter fragment is visible in both the symmetric tetralactones **6–9** and the mixed tetralactone **10**. The mixed tetralactone **10** gave rise to two such fragments, one of each of the acyl residues. Such a fragmentation pattern is characteristic for macrocyclic tetralactones.[12] The IR spectra of all macrocycles invariably indicated the presence of lactone functions by absorptions in the 1725-cm^{-1} range. The NMR spectra of the lactones **6** showed three groups of protons corresponding to the glycol residue, the methylene adjacent to the carbonyl functions, and the aliphatic methylene chain. The 1,4-butanediol derivative **9** also gave three groups of signals, which were assigned to the methylene protons adjacent to the ether and the carbonyl groups and to the aliphatic methylene chains. High-resolution NMR spectroscopy (270 MHz) of the 2,3-butanediol derivative **7** and 2,2-dimethyl-1,3-propanediol derivative **8** showed five groups of protons corresponding to the protons adjacent to the ether oxygen, the methylene protons at the α- and

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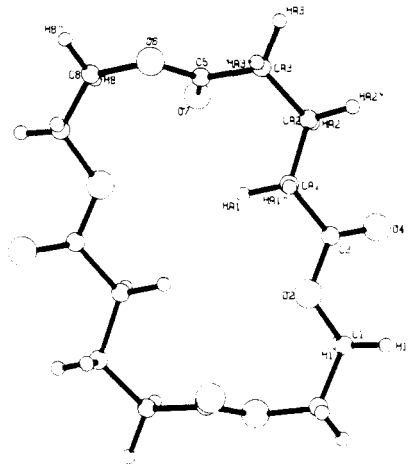

Figure 2. X-ray structure of tetralactone **6a** (n = 3).

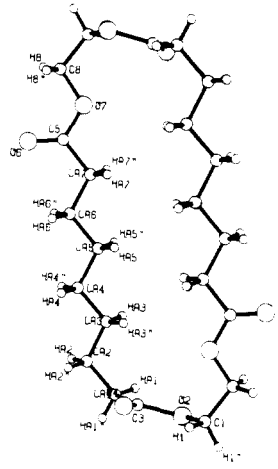

Figure 3. X-ray structure of tetralactone **6e** (n = 7).

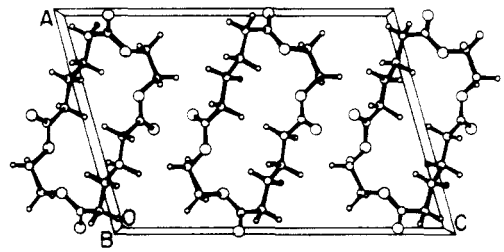

Figure 4. Packing arrangement of the even tetralactones (**6b**, n = 4).

β- positions of the carbonyl group, and the aliphatic methylene and methyl protons.

Inspection of Table I reveals that there are striking regularities in the melting points of the tetralactones. The ring systems incorporating an even number of methylene groups exhibit significantly lower melting points than those incorporating an odd number of methylene groups. These observations were suggestive of different arrangements of the two families of compounds in the solid state. X-ray diffraction analyses confirmed these expectations.

Diffraction studies showed that the "even" tetralactone **6b** forms a different packing arrangement than the "odd" tetralactones **6a** and **6e**. The former disclosed a layer-type pattern and the latter a herring-backbone pattern (Figures 4 and 5). In addition, the conformation and particularly the arrangement of the carbonyl groups were found to also follow a different pattern in the two systems, as evident from Figures 1–3. (For supplementary material on the X-ray data see the paragraph at the end of the paper.) Inspection of the figures shows, that in the "even" tetra-

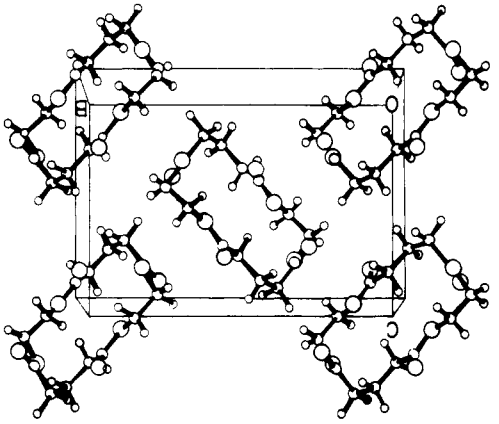

Figure 5. Packing arrangement of odd tetralactones (**6a**, n = 3).

lactone **6b** one pair of adjacent carbonyl groups (originating from the same acyl halide residue) points below the plane of the ring and the other pair above the plane of the ring. In the "odd" tetralactones **6a** and **6e** one pair of oppositely located carbonyl groups is oriented outside the plane of the ring and the other pair alternatingly above and below the plane of the ring.

The observed regularities are at this stage not accounted for. It seems, however, relevant to recall that structural studies on macrocyclic diketones also indicated conformational regularities which were dependent on the chain length of the interlinking methylene residues.[13]

The here-described successful preparation of both symmetric and mixed tetralactones, via the use of cyclic stannoxanes as covalent templates, introduces a new synthetic method for the preparation of macrocyclic compounds. The outstanding features of the method are specificity (only tetrafunctional ring compounds are being obtained), good yields, and ease of performance and workup. Of particular interest are the observed structural regularities in the macrocyclic carbonyl compounds. Macrocyclic carbonyl compounds such as valinomycin and enniatin are naturally occurring ion carriers of alkali and alkaline earth ions.[14] Their specific binding properties are believed to be derived from the nature, number, and spacial distribution of their binding sites. Realizing the relevance of structural features, one can see that the observed regularities in the solid state arrangement of macrocyclic tetralactones may provide the first guidelines toward the design of synthetic ion carriers that would approach the properties of natural ones by approaching their arrangements.

(13) J. Dale, IUPAC Symposium, Plenary Lectures, 1969, p 469.
(14) Y. A. Ovchinnikov and V. T. Ivanov, *Tetrahedron*, **31**, 2177 (1975).

Experimental Section

Preparation of Tetralactones 6. Preparation of Ethylene Azelate 6e. A 1.74-g (3 mmol) sample of stannoxane **1** was dissolved in 100 mL of dry, boiling chloroform and treated dropwise during 30 min with a solution of 1.34 g (6 mmol) of azelyl chloride (**5e**) in 100 mL of chloroform. Reflux was then continued for 1 h and the reaction mixture allowed to cool. Then 0.96 mL of pyridine was added, and the reaction mixture was concentrated in vacuo and chromatographed (silica gel column, solvent gradient of benzene–ethyl acetate, 100-mL fractions) to give 560 mg of the tetralactone **6e**. Analogous reactions of stannoxane **1** with acyl halides **5a–d,f** afforded the corresponding tetralactones **6a–d,f** in good yields as summarized in Table I.

Preparation of Tetralactones 7–9. A solution of 1.92 g (6.0 mmol) stannoxane **2** in 200 mL of boiling chloroform was treated dropwise with a solution of 1.05 mL (6.0 mmol) of suberyl chloride (**5d**) in 100 mL of chloroform. Reflux was continued for 2.5 h, the reaction mixture was concentrated in vacuo, and the residue was chromatographed on silica gel to provide 527 mg (1.1 mmol) of tetralactone **7**. Analogous reaction of stannoxanes **3** and **4** with pimelyl chloride (**5c**) or adipyl chloride (**5b**) afforded the tetralactones **8** and **9**, respectively. The yields and physical and spectroscopic properties of the ring products are summarized in Table II.

Preparation of Mixed Tetralactone 10. A 2.975-g (5.0 mmol) sample of stannoxane **1** was dissolved in 100 mL of dry chloroform and reacted dropwise with a solution of 0.84 mL (5.0 mmol) of suberyl chloride (**5d**) in 100 mL of chloroform under reflux. Heating was continued for 1 h and then a solution of 0.9 mL (5.0 mmol) of azelyl chloride (**5e**) in 100 mL of chloroform was added dropwise. After being heated for 1 h, the mixture was allowed to cool, neutralized by addition of pyridine, concentrated in vacuo, and chromatographed on silica gel (column). Elution with benzene–ethyl acetate (3:1) provided 1.66 g of the mixed tetralactone **10**.

X-ray Analysis of Tetralactones 6a,b,e. Intensity data for the tetralactones **6a,b,e** were collected on a computer-controlled Enraf-Nonius CAD-4 diffractometer with graphite-monochromated Mo K radiation. The structures were solved by direct methods. Refinement of each compound was carried out by full-matrix least-squares analysis and was checked by a difference Fourier map. Hydrogen atoms were included at calculated positions and then refined. The final difference Fourier map displayed only random fluctuation of the electron density in each case. All calculations were performed with the SHELX-76 (Sheldrick 1976) structure determination system. The crystal parameters and all relevant data are given in the supplementary material (see the paragraph at the end of the paper).

Registry No. **1**, 5271-60-3; **2**, 3590-63-4; **3**, 36887-65-7; **4**, 3590-62-3; **5a**, 2873-74-7; **5b**, 111-50-2; **5c**, 142-79-0; **5d**, 10027-07-3; **5e**, 123-98-8; **5f**, 111-19-3; **6a**, 74783-06-5; **6b**, 64066-17-7; **6c**, 74783-05-4; **6d**, 78837-84-0; **6e**, 74783-04-3; **6f**, 74783-03-2; **7**, 78837-85-1; **8**, 78837-86-2; **9**, 78837-87-3; **10**, 78837-88-4.

Supplementary Material Available: X-ray data and specifically cell dimensions (Table III), atomic parameters and esd's (Table IV), bond parameters (Table V), and torsional angles (Table VI) (4 pages). Ordering information is given on any current masthead page.