(n = 6), 10027-07-3; **3** (n = 7), 123-98-8; **3** (n = 8), 111-19-3; **4** (m = 2, R = CH_2Ph, n = 4), 99129-14-3; **4** (m = 2, R = CH_2Ph, n = 6), 99129-15-4; **4** (m = 2, R = CH_2Ph, n = 8), 99129-16-5; **5** (m = 2, R = CH_2CH_3, n = 3), 79265-23-9; **5** (m = 2, R = CH_2Ph, n = 3), 79265-20-6; **5** (m = 2, R = CH_2Ph, n = 5), 79265-21-7; **5** (m = 2, R = CH_2Ph, n = 7), 79265-22-8; **5** (m = 3, R = CH_2CH_3, n = 4), 99129-17-6; **5** (m = 3, R = CH_2CH_3, n = 6), 99129-18-7; **6** (R = Et, n = 3), 99129-19-8; **6** (R = Bz, n = 6), 99129-20-1; *N,N'*-diethylethylenediamine, 111-74-0; *N,N'*-dibenzylethylenediamine, 140-28-3; *N,N'*-diethyl-1,3-diaminopropane, 10061-68-4; bis(diethylamino)dimethylsilane, 4669-59-4; pimeloyl bis(2,4,5-trichlorophenyl) ester, 79265-19-3; glutaroyl bis(*p*-nitrophenyl) ester, 33109-59-0.

Supplementary Material Available: Analytical data and some physical properties of the compounds prepared (Tables VII and VIII (2 pages). Ordering information is given on any current masthead page.

Template Synthesis, Structure, and Binding Properties of Macrocyclic *S,O*-Lactones

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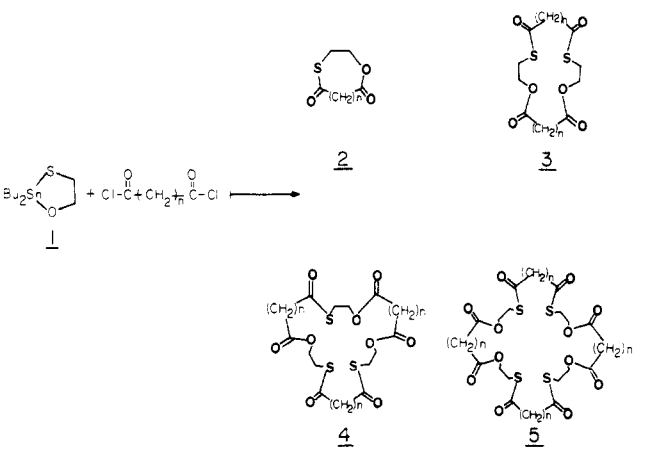
The synthesis, structures, and binding properties of mixed *S,O*-lactones, a new family of macrocyclic carbonyl compounds, are described. The synthesis involves the use of cyclic stannoxathiane (**1**) as a templated mercapto alcohol, which reacts with diacyl dihalides to provide monomeric **2**, dimeric **3**, trimeric **4**, and tetrameric **5** macrocyclic products in good overall yields and high stereospecificity. The dimeric derivatives **3** bind silver nitrate via their thiolactone groups when n is even but do not bind when n is odd. These regularities follow the conformational regularities of these compounds and demonstrate the relationship between conformation and binding. In addition, evidence is provided (crystal structures) that the conformation of the ligating molecule is preserved upon binding. The implications of these findings for the use of carbonyl groups in adjusting the conformation and binding properties of macrocyclic compounds are indicated.

Extensive studies on the crown ethers and related compounds have shown that their binding selectivities may be enhanced by imparting geometric constraints to these molecules. One approach involved the introduction of transannular bridges resulting in the tricyclic cryptands developed by Lehn.[1] Another approach relied on the incorporation of aromatic residues along the ring as exemplified in the spherands introduced by Cram.[2] Considering the abundance of carbonyl groups in naturally occuring ionophores such as the depsipeptides[3] and actins,[4] and the pronounced structural regularities of synthetic macrocyclic polylactones,[5] it occurred to us that carbonyl groups might similarly be used to reduce the conformational mobility. Reduced conformational mobility should then manifest itself by minimal conformational changes upon complexation. In order to examine the feasibility of this approach, we synthesized a new family of macrocyclic carbonyl compounds composed of thiolactone and lactone groups and screened their structures and binding properties. The thiolactone groups were selected to serve as binding sites for heavy metal ions by virtue of their donating sulfur atoms,[6-10] while the carbonyl groups of both lactones and thiolactones were anticipated to impart geometric constraint. In this publication we describe the synthesis of the novel macrocyclic *S,O*-lactones via the tin template method[5] and report on their metal binding properties. The pronounced binding selectivity of some of the compounds is suggested to derive from their defined conformation that is preserved upon binding.

Results and Discussion

Synthesis and Structure. The preparation of macrocyclic polycarbonyl compounds represents a difficult synthetic problem since it requires direct condensation reactions to provide ring compounds in preference to

Scheme I



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§ Department of Isotope Research.

(1) Lehn, J. M. *Struct. Bond.* **1973**, *16*, 1. Dietrich, B.; Lehn, J. M.; Simon, J. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 406. Lehn, J. M. *Acc. Chem. Res.* **1978**, *11*, 49.
(2) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1978**, *11*, 8. Cram, D. J. *Science (Washington, D.C.)* **1983**, *219*, 1177.
(3) Ovchinnikov, Yu. A.; Ivanov, V. T. *Tetrahedron* **1975**, *31*, 2177.
(4) Keller-Schierlein, W.; Gerlach, H. In "Progress in the Chemistry of Natural Organic Products"; Zechtmeister, L., Ed.; Springer-Verlag: Vienna, New York, 1968; Vol. 26, p 161.
(5) Shanzer, A.; Libman, J.; Frolow, F. *Acc. Chem. Res.* **1983**, *16*, 60. Shanzer, A.; Mayer-Shochet, N.; Frolow, F.; Rabinovich, D. *J. Org. Chem.* **1981**, *46*, 4662. Shanzer, A.; Libman, L. *Synthesis* **1984**, 140.
(6) The thia ether group has earlier extensively been used as binding site for heavy metal ions as well as for some transition-metal ions,[7-10] while the thiolactones group has so far not been considered.
(7) Rosen, W.; Busch, D. H. *Inorg. Chem.* **1970**, *9*, 262. Travis, K.; Busch, D. H. *J. Chem. Soc., Chem. Commun.* **1970**, 1041.
(8) Izatt, R. M.; Tery, R. E.; Hansen, L. D.; Avondet, A. G.; Bradshaw, J. S.; Dalley, N. K.; Jensen, T. E.; Christensen, J. J. *Inorg. Chim. Acta* **1978**, *30*, 1.

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Table I. Yields and Analytical and Spectroscopic Properties of Macrocyclic S,O-Lactones 2-5

product (n)	yield, %	mp, °C	IR,[a] cm^{-1}	molec[c] formula	mass spec,[b] m/e
2a (4)	19	oil	1735, 1685[1]	$C_8H_{12}SO_3$	188 $(M)^+$
2b (5)	8	oil	1715, 1680[1]	$C_9H_{14}SO_3$	202 $(M)^+$
2c (6)	10	oil	1730, 1690[2]	$C_{10}H_{16}SO_3$	216 $(M)^+$
2d (7)	2	oil	1725, 1680[2]	$C_{11}H_{18}SO_3$	230 $(M)^+$
3a (4)	46.8	oil	1720, 1680[1]	$C_{16}H_{24}S_2O_6$	377 $(M + 1)^+$
3b (5)	25.3	62-64	1730, 1680[1]	$C_{18}H_{28}S_2O_6$	405 $(M + 1)^+$
3c (6)	44.0	49-50	1720, 1670[1]	$C_{20}H_{32}S_2O_6$	433 $(M + 1)^+$
3d (7)	12	50-52	1730, 1685[1]	$C_{22}H_{36}S_2O_6$	461 $(M + 1)^+$
4a (4)	13.8	52-56	1720, 1675[3]	$C_{24}H_{36}S_3O_9$	565 $(M + 1)^+$
4b (5)	8.1	oil	1730, 1685[2]	$C_{27}H_{42}S_3O_9$	607 $(M + 1)^+$
4c (6)	4.9	38-40	1720, 1680[3]	$C_{30}H_{48}S_3O_9$	649 $(M + 1)^+$
4d (7)	2	oil	1725, 1680[2]	$C_{33}H_{54}S_3O_9$	691 $(M + 1)^+$
5a (4)	8.8	75-77	1720, 1675[3]	$C_{32}H_{48}S_4O_{12}$	753 $(M + 1)^+$
5b (5)	4.5	64-66	1735, 1685[2]	$C_{36}H_{56}S_4O_{12}$	809 $(M + 1)^+$
5c (6)	5.3	94-95	1720, 1680[3]	$C_{40}H_{64}S_4O_{12}$	865 $(M + 1)^+$
5d (7)	2.0		1725, 1680[1]	$C_{44}H_{72}S_4O_{12}$	921 $(M + 1)^+$
silver complex **2a**[d]				$C_{16}H_{24}AgNO_9S_2$	

[a] The spectra were measured in Nujol (1), neat (2), or KBr (3). [b] Compounds 2-4 were determined by electron impact mass spectrometry; compound 5 was determined by chemical ionization. [c] Satisfactory combustion analytical data for C, H were obtained for all compounds (±0.4%) except **3a**, **4c**, **5a**, and **5c** (±1.0%). [d] Anal. Calcd: C, 35.13; H, 4.42; S, 11.72; Ag, 19.72. Found: C, 35.32; H, 4.60; S, 11.70; Ag, 20.30%.

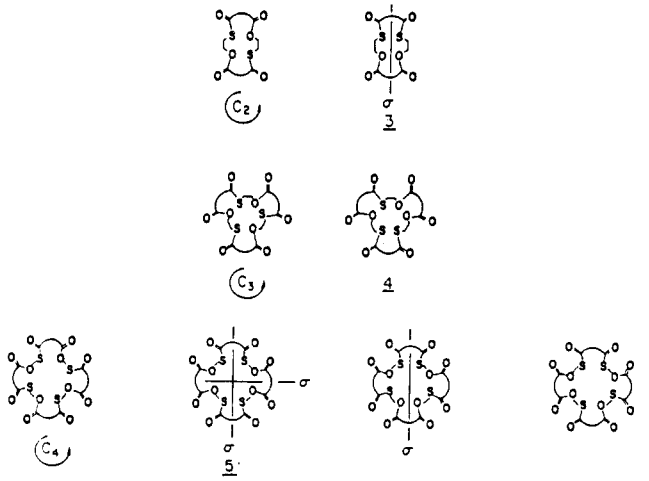
polymeric products. In an attempt to overcome this problem we recently introduced the use of cyclic organotin derivatives as templates.[5] This template approach relies on converting diprotic substrates (i.e., diols) to their cyclic tin derivatives (i.e., stannoxanes) and subsequently reacting them with diacyl dihalides to macrocyclic products. In the reactions of cyclic tin–oxygen derivatives with diacyl dihalides dimeric macrocyclic products, tetralactones, were obtained as sole ring products in high regio- and stereospecificity.[11] This high specificity was shown to derive from the intermediacy of dimeric associates between the tin–oxygen compounds, held together by noncovalent interactions between tin and oxygen.[12] Making use of this experience, we selected cyclic tin compounds derived from mercaptoethanol as tools for the preparation of the mixed macrocyclic derivatives. Since these tin compounds have been found to also associate to molecular complexes,[12] they were anticipated to preferentially provide dimeric macrocyclic products when condensed with diacyl dihalides. These expectations were indeed realized.

Treatment of the organotin compound 1[13] derived from 2-mercaptoethanol with a series of diacyl dihalides provided as major macrocyclic products the dimeric macrocycles **3**, in addition to minor amounts of the corresponding monomeric **2**, trimeric **4**, and tetrameric **5** derivatives (Scheme I).

The yields of the products and their IR and mass spectra are summarized in Table I. NMR data are given in Tables II and III (supplementary material).

The infrared spectra of all the products showed the presence of two types of carbonyl groups, thiolactone and lactone groups, by absorptions at 1680 and 1730 cm^{-1}, respectively. The 1:1 ratios of the mercaptoethanol and diacyl components in all the products were demonstrated by their ^{1}H NMR spectra, which showed well-resolved signals for each of the components whose integration fitted a 1:1 ratio. The mass spectra of the macrocyclic products established their monomeric **2**, dimeric **3**, trimeric **4**, and tetrameric **5** natures by showing molecular ion peaks or molecular ion peaks plus one mass unit $(M + 1)^+$. The fragmentation pattern proved to be highly regular. The tetrameric compound **5** gave rise to fragments corresponding to the trimeric, dimeric, and monomeric subunits. The trimeric **4** and dimeric **3** compounds similarly fragmented into their consecutive subunits. In addition to this general pattern, loss of ethylene sulfide (m/e 60) was observed from each molecular ion and submolecular fragment.

A priori, two isomeric dimers **3**, two isomeric trimers **4**, and four isomeric tetramers **5** could have been formed, with the mercaptoethanol units assuming all head-to-tail, all head-to-head, or both types of arrangements in the same molecule.



Inspection of these structures reveals that, in the isomers of all head-to-tail arrangements, only one type of acyl residues is present, flanked by one lactone and one thiolactone group. In the all head-to-head arrangements, two types of acyl residues flanked by two lactone or two thiolactone groups, respectively, do occur. And in the structures with mixed arrangements, more than two types of acyl residues are recognizable. Relying on the ample NMR data on macrocyclic lactones and thiolactones,[5] high-resolution proton and carbon NMR spectrometry were selected as analytical tools to determine the nature of acyl residues present in each of the macrocylic products.

Considering the dimeric derivatives **3**, when n is odd (either 5 or 7), the central methylene carbons of each of

(9) Weber, E.; Voegtle, F. *Ann. Chem.* **1976**, 891.
(10) Arnaud-Neu, F.; Schwing-Weill, M. J. *Inorg. Nucl. Chem. Lett.* **1975**, *11*, 131, 655.
(11) Shanzer, A.; Libman, J.; Gottlieb, H.; Frolow, F. *J. Am. Chem. Soc.* **1982**, *104*, 4220.
(12) Herber, R. H.; Shanzer, A.; Libman, J. *Organometallics* **1984**, *3*, 586.
(13) Sukhani, D.; Gupta, V. D.; Mehrotra, R. C. *Aust. J. Chem.* **1968**, *21*, 1175.

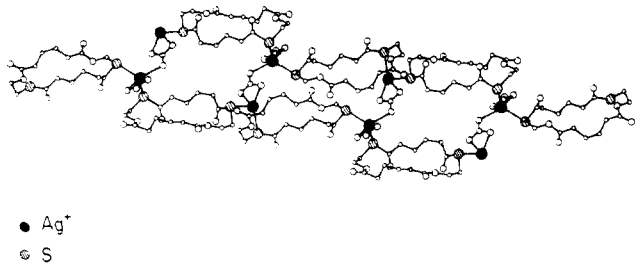


Figure 1. Crystal structure of the $AgNO_3$ complex with *S,O*-lactone **3a**.

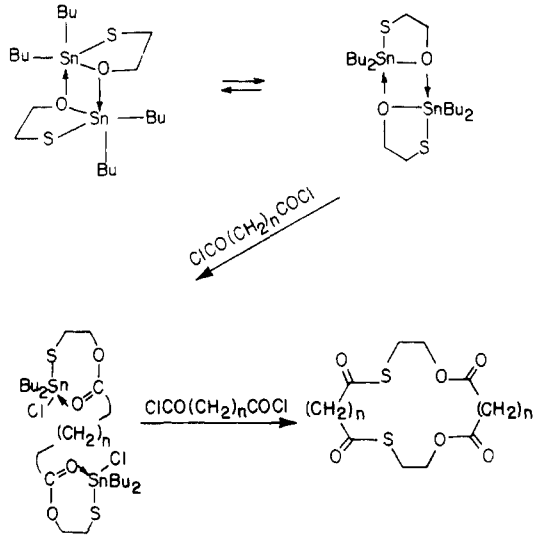
the two diacyl residues should be identical in the head-to-tail isomer but different in the head-to-head structure. Carbon-13 NMR analysis (Table III, supplementary material) of the isolated macrocyclic pimelate **3b** (n = 5) and azelate **3d** (n = 7) showed two different signals for the central methylene groups (δ 28.48, 27.33 for **3b**; δ 28.89, 28.01, 28.48 for **3d**), indicating the presence of two types of acyl residues, compatible with structures **3**. The trimeric product **4b** revealed three signals for the central methylene carbons (δ 28.47, 27.90, 28.21) in agreement with the nonsymmetric structures with both head-to-head and head-to-tail arrangements. The tetrameric product **5b** showed two types of central methylene carbons (δ 28.53, 28.11), in compliance with an all head-to-head arrangement.

For the macrocyclic series with even n (either 4 or 6), proton NMR spectrometry and selected decoupling experiments were chosen to differentiate between the possible alternatives. Starting the analysis with dimers **3** in the head-to-head structure, the methylene protons at β-position to the lactone group should not couple with the methylene protons at β-position to the thiolactone group but should couple with each other in the head-to-tail structure. Irradiation of the protons in the α-position to the lactone (δ 2.32 (t, J = 6.5 Hz)) resulted in a collapse of the β-protons (δ 1.68 (t, J = 6.5 Hz)) to a singlet. Similarly, irradiation of the protons in α-position to the thiolactone group (δ 2.59 (t, J = 6.5 Hz)) converted the β-protons (δ 1.74 (t, J = 6.5 Hz)) to a singlet, indicating the presence of the head-to-head structure **3a**. The same results were obtained with tetramer **5a**, confirming its structure to posses an all head-to-head arrangement. For comparison, in the monomer **2a**, the same type of double irradiation experiment gave rise to triplets for the β-protons, as expected. For the trimer **4a**, irradiation of the α-methylenes gave rise to overlaps of singlets and multiplets for the β-protons. In addition, the signal corresponding to the CH_2S groups is split in **4a** into three closely overlapping, but distinct, triplets. This is consistent only with the asymmetric structure, with mixed mercaptoethanol arrangements.

The head-to-head orientation in dimeric **3** was further confirmed by X-ray diffraction analysis of the representative **3d** (n = 6). Its crystal structure is given in Figure 1. It is interesting to note that the structure of the dimer **3d** closely resembles that observed for the corresponding analogous all-oxygen tetralactone,[5] having two carbonyl groups pointing above the face of the ring and two carbonyl groups below the face of the ring.

The preferential formation of dimeric macrocycles **3**, independent of the nature of the diacyl dihalide employed, and the head-to-head orientation of their components are in agreement with the intermediacy of dimeric tin–oxygen compounds in these reactions as illustrated in Scheme II. The formation of such intermediates is supported by Mössbauer studies,[12] which demonstrated the presence of

Scheme II



dimeric species with sp^3d hydridized tin noncovalently bound to oxygen. Reaction of these intermediates with 1 equiv of acetyl chloride resulted in predominant Sn–O cleavage, as evidenced by FTIR spectroscopy.[14] Accordingly, with diacyl dihalides, these intermediates are likely to first react with the electrophilic diacyl dihalide through their tin–oxygen linkages and subsequently close with a second diacyl dihalide through their tin–sulfur linkages to the dimeric products of head-to-head configuration. The monomers **2** may be visualized to derive from minor amounts of monomeric species present at equilibrium in solution, the higher homologues **4** and **5** from coupling reactions between monomeric and dimeric intermediate species. A similar reaction pathway is likely to be also involved in the reaction of oxathiastibole with acyl halides.[15]

Binding Properties. The metal ion binding properties of the dimeric macrocycles **3**, whose cavity dimensions appeared most appropriate for binding, were then screened by IR spectrometry. IR spectrometry was selected as analytical tool, since the carbonyl absorption frequency was anticipated to provide a sensitive probe that would tell not only whether binding occurs but also at which sites.

IR spectroscopy of mixtures of each of the dithiolactones **3a–d** with each of the metal salts, lead nitrate, mercury chloride, and silver nitrate, in Nujol mulls indicated no binding of lead and mercury, but binding of silver nitrate to the even members of the dithiolactones, **3a** and **3c** (n = 4, 6). This was shown by the displacement of thiolactone absorption from 1680 cm^{-1} in the free compound to 1720 cm^{-1} in the complex. In compliance with the shift of the thiocarbonyl absorption to higher frequencies, the sulfur atoms of the thiolactone groups appear to act as binding sites in these complexes. Binding to the carbonyl oxygen of the thiolactone group would have resulted in a shift toward lower frequencies.

The dependence of binding in these thiolactones on the length of the acyl residues even vs. odd appeared to derive from conformational effects: the even-membered derivatives **3a** and **3c** differ from the odd-membered derivatives **3b** and **3d**. In the even representatives (n = 4, 6), the two carbonyl absorptions in the IR spectrum are badly resolved

(14) This is in agreement with earlier literature reports. See: Davis, A. G.; Smith, P. J. In "Comprehensive Organometallic Chemistry"; Wilkinson, G., Ed.; 1982; Vol. 2, pp 519–627.

(15) Anchisi, C.; Bonsignore, L.; Corda, L.; Maccioni, A.; Podda, G. *Heterocycles* **1983**, *20*, 1755.

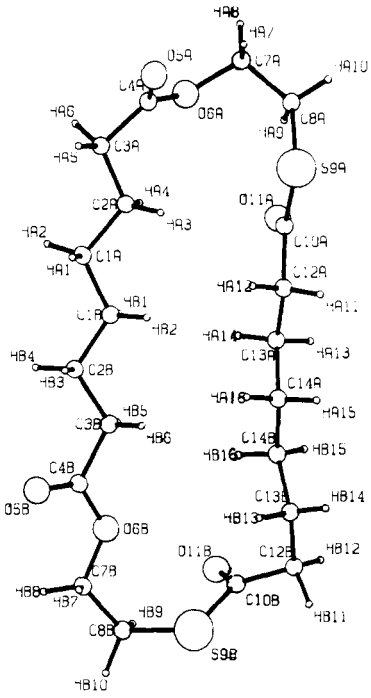


Figure 2. Crystal structure of *S,O*-lactone **3d**.

as are the NMR signals (more second-order character) for the protons adjacent to the carbonyl groups; in the odd representatives (n = 5, 7) the carbonyl absorptions in the IR spectra as well as the NMR signals for the protons adjacent to the carbonyls are well-resolved. These observations suggest that the conformations of the even representatives differ from those of the odd members in being stereochemically more constrained and exhibiting a higher energy barrier toward conformational interconversions.

Should this notion be correct and the conformations of the dimeric macrocyclic ligands **3** indeed determine their ion-binding properties, their conformation in the free state should be retained in the complex.

In order to test this hypothesis, a crystalline sample of the silver nitrate complex of the thiolactone **3a** (n = 4) was prepared and analyzed by X-ray diffraction.[16] The structure of the complex is given in Figure 2. When the structure of the free molecule (Figure 1) is compared with that of the complex (Figure 2), the retention of the ligands conformation upon binding is well evident: in both samples two carbonyl groups are directed above the mean plane of the ring and two carbonyl groups below the mean plane. As to the nature of the binding, the silver cation is bound to two sulfur atoms in a square-pyramidal coordination, which is complemented by the oxygen atoms of the nitrate anions. The observed Ag^+–S distances, which range between 2.545 and 2.602 Å, are characteristic for covalent bonds and are similar to those observed in macrocyclic thia ethers.[17]

The selective binding properties observed for these macrocyclic dithiolactones are thus likely to derive from the well-defined orientation of the binding sites prior to binding. This behavior is different from that reported for macrocyclic thia ethers, which have been found to be flexible and to bind a series of guest ions in a variety of different geometrical arrangements.[7,9,18,19] We therefore suggest that carbonyl groups may more extensively be considered as tools to reduce conformational mobility of macrocyclic molecules and to thereby enhance their binding selectivity.

Experimental Section

The NMR spectra were measured on FT-80A (Varian, ^1H, 80 MHz), WH-90 (Bruker, ^{13}C, 22.6 MHz), and WH-270 (Bruker, ^1H, 270 MHz) instruments in the Fourier transform mode. All chemical shifts, unless otherwise indicated, correspond to $CDCl_3$ solutions and internal Me_4Si as a reference.

The mass spectra were obtained by direct probe using a Finnigan 4020 quadrupole instrument equipped with a data system. Mass spectrometer operating conditions for electron impact ionization were as follows: emmision current, 0.24 mA; electron multiplier, 1.7 kV; electron energy, 18 eV; inlet temperature, 220–280 °C; source temperature, 280 °C. Chemical ionization condition were as follows: reagent gas, CH_4; electron energy, 60 eV.

IR and mass spectra are summarized in Table I; NMR data are in Tables II and III (supplementary material).

Preparation of Macrocyclic *S,O*-Lactones 2–5. To a boiling solution of 3.087 g (10 mmol) of **1**[13] in 275 mL of dry chloroform was added dropwise a solution of 1.45 mL (10 mmol) of adipoyl chloride in 100 mL of dry chloroform during 30 min. Reflux was then continued for 1 h; the cooled mixture was treated with 1 mL of pyridine and concentrated to dryness (6.25 g). Chromatography of half of the residue through silica gel (Woelm, 63–100) and elution with a mixture of hexane and ethyl acetate (6:4) provided the following: [180 mg (0.9 mmol, 19%) of monomer **2a**] ^1H NMR (270 MHz, $CDCl_3$, ppm) 4.41 (t, J = 5.5 Hz, CH_2O), 3.30 (t, J = 5.5 Hz, CH_2S), 2.59 (t, J = 6 Hz, CH_2COS), 2.39 (t, J = 6 Hz, CH_2COO), 1.95 (quint, J = 6 Hz, CH_2CH_2COS), 1.77 (quint, J = 6 Hz, CH_2CH_2COO); [440 mg (1.17 mmol, 46.8%) of dimer **3a**] ^1H NMR, 4.27 (t, J = 5.5 Hz), 3.19 (t, J = 5.5 Hz), 2.59 (t, J = 6.5 Hz), 2.32 (t, J = 6.5 Hz), 1.74 (t, J = 6.5 Hz), 1.68 (t, J = 6.5 Hz); [135 mg (0.23 mmol, 13.8%) of trimer **4a**] ^1H NMR, 4.22 (t, J = 6 Hz, three close peaks), 3.16 (t, J = 6 Hz), 2.60 (t, J = 6 Hz), 2.34 (t, J = 6 Hz), 1.73 (m), 1.67 (m); [85 mg (0.11 mmol, 8.8%) of tetramer **5a**] ^1H NMR, 4.20 (t, J = 6 Hz), 3.15 (t, J = 6 Hz), 2.60 (t, J = 6 Hz), 2.34 (t, J = 6 Hz), 1.72 (m), 1.67 (m). By applying the same procedure to pimeloyl dichloride, suberoyl dichloride, and azeloyl dichloride the corresponding pimelates, suberates, and azelates were obtained. The yields of these reactions are summarized in Table I.

Preparation of the $AgNO_3$ Complex of Dithiolactone 3a. Equimolar solutions of silver nitrate and oily adipate **3a** (0.1 mmol each in 50 mL of methanol) were mixed, and the resulting crystalline precipitate was collected. Its IR spectrum was identical with that recorded for the mixture of thiolactone **3a** and silver nitrate, and elemental analysis confirmed the presence of a 1:1 complex. Its crystal structure is given in Figure 2.

X-ray Analyses of Dithiolactone 3c and the Silver Nitrate Complex of 3a. The crystals of the complex are triclinic, space group $P\bar{1}$, a = 11.746 (1) Å, b = 8.931 (3) Å, c = 20.041 (4) Å, α = 90.90 (4)°, β = 97.38 (3)°, γ = 88.67 (4)°, V = 2084.25 Å^3, and Z = 4. A total of 6298 reflections (one hemisphere) was measured by graphite-monochromated Mo K_α radiation up to θ = 23° on a CAD-4 diffractometer with low-temperature setup (T = 83 K). Intensities were corrected for Lorentz and polarization factors, yielding 4449 independent reflections with $F_o > 3\sigma(F_o)$. The structure was solved by direct methods and refined to R = 0.073. All hydrogen atoms were constrained to reasonable geometries. A final difference map possessed no special features. The crystals of the free molecule are orthorombic, space group $P2_12_12_1$, a = 54.041 (2) Å, b = 7.175 (1) Å, c = 5.602 (1) Å, V = 2172 Å^3, and Z = 4. A total of 2878 reflections was measured (one octant hkl)

(16) Comparison between free dithiolactone **3c** and bound dithiolactone **3a** was selected, since free **3a** was obtained as oil and bound **3c** failed to give sufficiently good crystals for X-ray diffraction analysis.

(17) Campbell, M. L.; Dalley, N. K. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1981**, *B37*, 1750.

(18) Louis, R.; Pellisard, D.; Weiss, R. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1976**, *B32*, 1480. Louis, R.; Agnus, Y.; Weiss, R. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1977**, *B33*, 1418.

(19) Louis, R.; Metz, B.; Weiss, R. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1974**, *B30*, 774. Louis, R.; Metz, B.; Weiss, R. *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.* **1974**, *B30*, 1889.

by graphite-monochromated Mo K_α radiation (λ = 0.7114 Å) up to θ = 23° on a CAD-4 diffractometer with low-temperature setup (T = 83 K). Intensities were corrected for Lorentz and polarization factors, yielding 2331 independent reflections with $F_o > 3\sigma(F_o)$. The structure was solved by direct methods and refined to R = 0.0369 and R = 0.045 [$w = 3.0873/[\sigma^2(I_o) + 0.001F^2]$].

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Supplementary Material Available: ^1H and ^{13}C NMR data (Tables II and III, respectively) for all the compounds synthesized, X-ray data for both the dimer **3c** and the silver complex, atom coordinates (Table IV), anisotropic temperature factors (Table V), hydrogen atom coordinates (Table VI), bond distances (Table VII), bond angles (Table VIII), and bond distances and short contacts to silver (Table IX) (15 pages). Ordering information is given on any current masthead page.

Synthesis of Enantiomerically Pure γ-Amino-β-hydroxybutyric Acid Using Malic Acid as the Chiral Precursor

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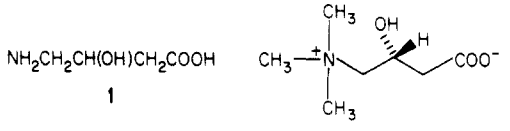
The synthesis of enantiomerically pure γ-amino-β-hydroxybutyric acid using malic acid as the chiral precursor is described. The key step involves the regioselective carboxamidation of the β-carboxyl group (adjacent to the hydroxyl) in malic acid. This was achieved by converting (*S*)-malic acid to its cyclic anhydride **8**, which was then treated with ammonia. Protection of the alcoholic group in the ester amide **9** as a *tert*-butyl ether followed by $LiAlH_4$ reduction gave 3-(*tert*-butyloxy)-4-aminobutanol (**11c**). The amino group in **11c** was protected as the *tert*-butyl carbamate to give (*S*)-3-(*tert*-butyloxy)-4-[((*tert*-butyloxy)carbonyl)amino]butanol (**12c**). The oxidation of the primary alcoholic group was successfully carried out with zinc permanganate to give the desired acid (*S*)-3-(*tert*-butyloxy)-4-[((*tert*-butyloxy)carbonyl)amino]butyric acid (**13c**). Removal of the protecting groups gave (*S*)-(+)-γ-amino-β-hydroxybutyric acid, the optical rotation measurements of which indicated no racemization during the six-step synthesis. The *R* isomer could be synthesized starting from (*R*)-malic acid. Thus a short and efficient route to chirally pure (*R*)- and (*S*)-γ-amino-β-hydroxybutyric acid is presented. Furthermore, this work also highlights zinc permanganate as a useful oxidant for the preparation of carboxylic acids.

γ-Amino-β-hydroxybutyric acid (**1**) is a compound of great pharmacological importance because of its biological function as a neuromodulator in the mammalian central nervous system.[1,2] Of particular interest is the *R*-(−)

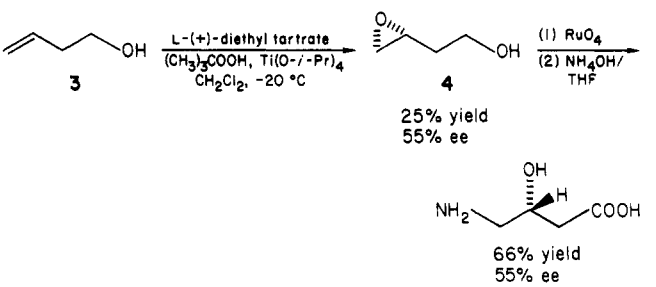


1 **2**

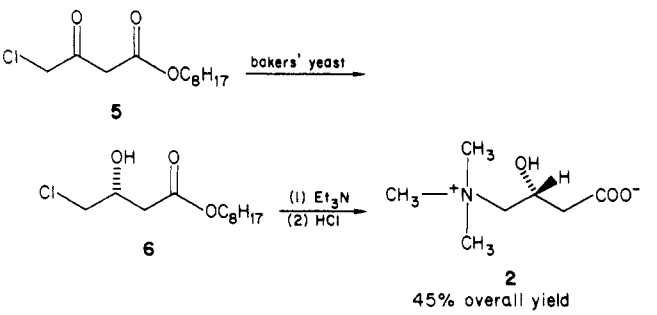
isomer, as it has been shown to have greater biological activity than the *S*-(+) isomer.[3] This γ-aminobutyric acid (GABA) derivative has also been used as a synthetic precursor for certain heterocyclic GABA-receptor agonists.[4] Furthermore, (*R*)-carnitine (**2**), again a compound of considerable biological significance,[5-7] is a derivative of **1**.

An efficient synthetic route leading to optically pure (**1**) is desirable to make the compound more available for biological studies. Our interest in this GABA derivative stems from its possible use in the design of a model of the peptide hormone β-endorphin. We have proposed that the β-endorphin molecule consists of three regions, a specific recognition site which corresponds to the Met-enkephalin sequence, a hydrophilic spacer from residues 6–12, and an

Scheme I



Scheme II



(1) Otsuka, M.; Obata, K.; Miyata, Y.; Yaneka, Y. *J. Neurochem.* **1971**, *18*, 287.
(2) Otsuka, M.; Miyata, Y. "Advances in Biochemical Psychopharmacology"; Raven: New York, 1972; Vol. 6, p 61.
(3) Kurano, Masayasu, Miyaruoto, Shigetoshi, Shigeoka, Satoshi, Mori, and Akitane. Japanese Patent, 1976; *Chem. Abstr.* **1977**, *86*, 89207*u*.
(4) Brehm, L.; Jacobsen, P.; Johansen, J. S.; Krogsgaard-Larsen, P. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1459.
(5) Bremmer, J. *Trends. Biochem. Sci. (Pers. Ed.)* **1977**, *2*, 207.
(6) Fritz, I. B.; Schultz, S. K. *J. Biol. Chem.* **1965**, *240*, 2188.
(7) Roe, C. R.; Bohan, T. P. *Lancet* **1982**, 1411. Chapoy, P. R.; Angelini, C.; Brown, W. J.; Stiff, J. E.; Shug, A. L.; Cederbaum, S. O. W. *Engl. J. Med.* **1980**, *303*, 1389. Borum, P. *Nutr. Rev.* **1981**, *39*, 385.

0022-3263/85/1950-5480$01.50/0