(d, J = 7.6 Hz, 1 H). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.51; H, 7.96.

***cis*-3a,8b-Dihydro-3,6,8b-trimethyl-3a-ethyl-1*H*-cyclopenta[*b*]benzofuran (24)**: yield 90 mg (91%) from 100 mg of **30**; ot 110–115 °C (0.06 mmHg); GLC (column II), t_R = 2.31 min at a column temperature of 180 °C; ^{1}H NMR δ 0.84 (t, J = 7.6 Hz, 3 H), 1.33 (s, 3 H), 1.68 (ddd, J = 1.6, 1.0, 0.6 Hz, 3 H), 1.06–2.12 (m, 2 H), 2.27 (s, 3 H), 2.36–2.74 (m, 2 H), 5.54 (br s, 1 H), 6.57 (br s, 1 H), 6.66 (br d, J = 7.5 Hz, 1 H), 7.0 (d, J = 7.5 Hz, 1 H). Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.50; H, 8.99.

Acknowledgment. We graciously thank the CSIR, New Delhi for financial assistance. A.N. also thanks the same agency for a fellowship.

Registry No. (±)-**1**, 21019-65-8; (±)-**2**, 21019-64-7; **13**, 106949-32-0; (±)-**14**, 138629-60-4; (±)-**15**, 138629-61-5; (±)-**16**, 63023-41-6; (±)-**17**, 138629-62-6; (±)-**18**, 138629-63-7; (±)-**19**, 138629-64-8; (±)-**20**, 138629-65-9; (±)-**21**, 138629-66-0; (±)-**24**, 138629-67-1; **25**, 18612-99-2; (±)-**26**, 138629-68-2; (±)-**27**, 138629-69-3; (±)-**28**, 138629-70-6; (±)-**29**, 138629-71-7; (±)-**30**, 138629-72-8; 2-hydroxy-4-methylpropiophenone, 2886-52-4.

Macrocyclic Polylactones by Catalyzed Cyclooligomerization. Tetra[(*S*)-β-butyrolactone][1]

Stefano Roelens*,†

CNR, Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, c/o Department of Organic Chemistry, University of Florence, 50121 Florence, Italy

Antonella Dalla Cort and Luigi Mandolini

CNR, Centro di Studio sui Meccanismi di Reazione and Department of Chemistry, University "La Sapienza", 00185 Rome, Italy

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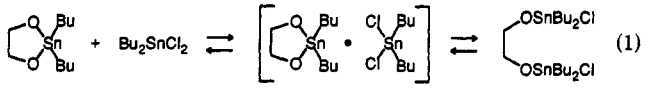
The synthesis of the elusive macrotetrolide **2** of 3-hydroxybutyric acid has been approached by cyclooligomerization of enantiomerically pure (*S*)-β-butyrolactone (**3**), promoted by the catalytic system 2,2-dibutyl-1,3,2-dioxastannolane/dibutyltin dichloride (DOS/DTC). The product has been isolated in 10% yield, demonstrating that it is not inaccessible, and its structure has been proven by X-ray crystal structure analysis. DOS/DTC afforded a thermodynamically controlled cyclooligomerization mixture, which was analyzed by means of a revised version of the Jacobson–Stockmayer theory, providing an evaluation of the effective molarity (EM) parameter for the formation of the tetrameric macrolide. The EM value was found to be five times lower than the corresponding value for tetra(β-propiolactone), its strainless unsubstituted analogue. The observed EM allowed a quantitative measure (1.1 kcal mol^{-1}) of the strain induced in the 16-membered macrotetrolide by the introduction of a methyl group into four homochiral stereocenters of the ring. Such relatively small strain is sufficient to depress to an appreciable extent the yield of **2** that can be expected from a thermodynamically controlled reaction. The possible origin of the observed strain is discussed.

In a previous communication,[1] it has been shown that the catalytic system 2,2-dibutyl-1,3,2-dioxastannolane/dibutyltin dichloride (DOS/DTC) can efficiently induce thermodynamically controlled cyclooligomerization of lactones under mild conditions. In connection with this



(1)

DOS DTC DOS/DTC

discovery, we have recently developed a revised version[2] of the Jacobson and Stockmayer theory[3] in which the product distribution of equilibrated polymeric mixtures is conveniently described in terms of effective molarity (EM) of cyclic compounds and an equilibrium constant (K_{inter}) for the intermolecular polymerization reaction.[4] In the revised presentation, given (or estimated) the EM_n and K_{inter} parameters, the application of the theory to practical cases is straightforward and provides the complete product distribution. Conversely, EM_n and K_{inter} can be evaluated for different systems by fitting the observed product distribution with the theoretical equations.

It appears that the combination of such mathematical treatment with the use of the above catalytic system might represent a powerful tool for achieving the synthesis of molecular targets that are cyclic oligomers of accessible

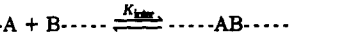
† Address correspondence to CNR, Centro di Studio sulla Chimica e la Struttura dei Composti Eterociclici e loro Applicazioni, Via Gino Capponi 9, 50121 Firenze, Italy.

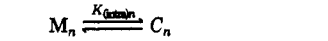
(1) Group 14 Organometallic Reagents. 11. For part 10, see: Roelens, S. *J. Chem. Soc., Chem. Commun.* **1990**, 58.

(2) (a) Ercolani, G.; Mandolini, L.; Mencarelli, P.; Roelens, S. *Proceedings, Giornate di Chimica Organica Fisica e Meccanicistica*, COFEM 90, June 1990, S. Miniato, Italy, p. 29. (b) Roelens, S.; Dalla Cort, A.; Ercolani, G.; Mandolini, L.; Mencarelli, P. *Proceedings, Macrocyclic and Supramolecular Chemistry in Italy*, May 1990, Padova, Italy, p 123.

(3) Jacobson, H.; Stockmayer, W. H. *J. Chem. Phys.* **1950**, *18*, 1600.

(4) K_{inter} is defined as the equilibrium constant relative to the intermolecular reversible reaction between the A and B reactive chain-end of a growing polymer, giving rise to the AB functional group. The thermodynamic effective molarity EM_n relative to the reversible formation of the nth cyclic oligomer C_n from the open chain precursor M_n





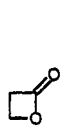
is defined as

$$EM_n = K_{(intra)n}/K_{inter}$$

For a detailed discussion on the EM parameter and its relevance to cyclization processes, see: Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1.

0022-3263/92/1957-1472$03.00/0

monomers. This approach has been successfully applied to the oligomerization of β-propiolactone (1),[5] for which a detailed statistical analysis of the system as a function of conditions has lead to an excellent fit between experimental data and theoretical predictions.



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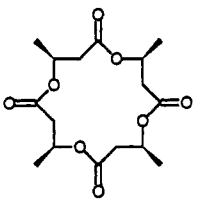


2

In order to establish the practical value of the cyclooligomerization approach, a significant example was sought among the number of naturally occurring and synthetic compounds of interest which are cyclic oligomers. The 16-membered macrotetrolide **2** from 3-hydroxybutyric acid appeared to be an application of interest because of its potential antibiotic activity.[6] The synthesis could be attempted by controlled cyclooligomerization of β-butyrolactone (**3**), accessible from 3-hydroxybutyric acid, which is readily available in enantiomerically pure form of (*R*) configuration by hydrolytic degradation of poly(3-hydroxybutyric acid) (PHB).[7]

The synthesis of **2** appeared to be a real challenge, because it had been attempted unsuccessfully by Seebach and co-workers.[6] The widely used Yamaguchi reaction,[8] reported by the authors as the method of choice for the macrolactonization of (*R*)-3-hydroxybutyric acid, afforded good yields of the cyclic pentamer, hexamer, and heptamer, but no isolable amounts of the desired tetramer. The reason for the absence of the tetrolide remained an open question. In a subsequent paper,[9] the authors reported the results of a careful and detailed investigation on the possible causes for this unexpected result, making use of X-ray molecular structure of the isolated higher cyclooligomers and force-field calculations. No determinant reason could be found, but it was concluded that, although the problem remained open, thermodynamic instability is an unlikely reason for the lack of tetrolide isolation.

On this basis, the synthesis of **2** was undertaken by the DOS/DTC-catalyzed cyclooligomerization strategy, in the belief that this approach would lead either to the preparation of the product itself or to an understanding of the factors that determine its elusive behavior.

Results

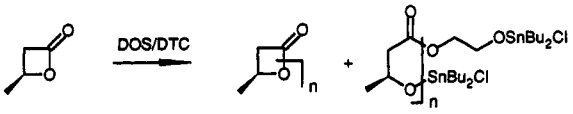
Following Seebach's considerations,[6,9] it was supposed that the "addition" of a methyl group should not introduce particularly severe steric restrictions into the macrotetrolide structure. The strategy for the cyclooligomerization of **3** was thus based on the results obtained for **1**,[1,5] which exhibited a well-behaved distribution of strainless cycles starting from the trimer, deriving in a first approximation from the corresponding statistical analysis an estimate of reasonable parameters and experimental conditions.[10]

Table I. Cyclic Product 4 Distribution for the Catalyzed Oligomerization of (*S*)-β-Butyrolactone (3)[a]

n[b]	M^{+}[c]	rel I[d]	yield, %[e]	$10^3[C_n]$[f]	10^2EM_n (M)[g]
4	345	86.4 (24.4)	13.0	1.53	1.13
5	431	100 (28.2)	15.0	1.41	1.72
6	517	85.5 (24.1)	12.9	1.01	2.03
7	603	43.4 (12.2)	6.5	0.44	1.45
8	689	22.7 (6.4)	3.4	0.20	1.09
9	775	9.9 (2.8)	1.5	0.078	0.70
10	861	4.5 (1.3)	0.7	0.033	0.49
11	947	2.1 (0.6)	0.3	0.013	0.32

[a] $[3]_0 = 0.047$ M; $[DOS/DTC]_0 = 0.0095$ M; reacted in anhydrous $CHCl_3$ for 87 h at 70.0 °C. [b] Oligomerization degree. [c] Mass of the molecular ion monitored in positive FAB-MS spectra. [d] Relative intensity of the FAB-MS molecular ions normalized to the base peak. Relative abundance of oligomers in the cyclic fraction is given in parentheses. [e] Yield of cyclic oligomers calculated from the absolute yield value of **2** (see text). The total yield of cyclic oligomers **4** for $n = 4$–11 is 53.3%. [f] Molar concentration of cyclic oligomers **4** at equilibrium in the reaction solution, calculated from yields. [g] Calculated effective molarity values (see footnote 15).

According to the procedure followed for **1**, (*S*)-**3** was oligomerized at 70 °C in the presence of the required catalytic amount of DOS/DTC to give cyclooligomers **4** and open-chain stannylated esters **5** (eq 2). A check on



(2)

3 4 5

the mixture after 48 h showed that the reaction was complete; however, different runs were never reacted for less than 70 h to ensure complete equilibration even at low substrate and catalyst concentration.

As shown in eq 2, the reaction requires part of the catalyst to be incorporated in the products as end groups. In preliminary kinetic experiments,[11] it has been found that stannylated end groups are incapable of propagating the oligomerization chain, i.e., the active catalyst that effectively promotes the reaction is only that in excess over the amount consumed for end-group generation. This amount of active catalyst at the equilibrium can be calculated from K_{inter} and the initial concentration values for the reagent and the catalyst and can be experimentally measured from the end-group analysis of the oligomerization mixture. This has been done for **1**, for which a $K_{inter} \approx 10$ was found, leading to a consumption of catalyst, under the adopted reaction conditions, of 5–10 mol % ca. with respect to the starting monomer. Assuming an analogous value for K_{inter} of the β-butyrolactone system, as based on the hypothesis that the added methyl group should not affect appreciably the position of the polymerization equilibrium, the catalyst concentration was chosen as 20 mol % with respect to **3**, in order to ensure reasonably fast reaction rates. To select an appropriate substrate concentration, it was assumed that the EM value for the tetrameric macrolide should be lower than the corresponding value for the tetrolide of **1**, which was found to be 5.7×10^{-2} M. Hence, in principle, a monomer concentration lower than 0.05 M would be desirable. In

(5) Ercolani, G.; Mandolini, L.; Mencarelli, P.; Roelens, S. Manuscript in preparation.
(6) Seebach, D.; Brändli, U.; Schnurrenberger, P.; Przybylski, M. *Helv. Chim. Acta* **1988**, *71*, 155.
(7) Griesbeck, A.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1320.
(8) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
(9) Seebach, D.; Brändli, U.; Müller, H. M.; Dobler, M.; Egli, M.; Przybylski, M.; Schneider, K. *Helv. Chim. Acta* **1989**, *72*, 1704.
(10) The polymerization of racemic β-butyrolactone initiated by an organotin catalyst (tributyltin methoxide) has been reported by H. Kricheldorf and co-workers (Kricheldorf, H.; Scharnagl, N. *J. Macromol. Sci.-Chem.* **1989**, *A26*, 951). The authors described that the formation of poly(β-butyrolactone) promoted by this catalyst is free from byproducts. However, under their conditions (in bulk at 50 °C), no cyclic products were observed by the authors.
(11) Unpublished results from this laboratory.

practice, runs were performed in the 0.03–0.09 M concentration range as a reasonable compromise, since lower values would limit the preparative value of the method.

Under the described conditions the reaction proceeded smoothly to complete consumption of **3**, affording a mixture of cyclic oligomers, together with the expected polymeric stannylated chains, but essentially free from byproducts.[12] Because the present system has a low K_{inter}, open-chain stannylated oligomers constitute a significant but unavoidable part of the equilibrated mixture. The results of a typical experiment, conveniently analyzed by fast-atom bombardment mass spectrometry (FAB-MS), are reported in Table I and Figure S1 (supplementary material). Two main features appear evident from experimental data. First, unlike the case of **1**, the tetramer and not the trimer is the first observed oligomer of the distribution. In order to verify that the molecular peak assigned to the cyclic tetramer was not simply arising from degradation of higher oligomers on the FAB target, the product mixture was spiked with CsI. The resulting spectra (see, for example Figure S2, supplementary material) showed, besides the M + 1 peaks, the molecular ion of all the parent cyclic oligomers bound to cesium, including that of the tetramer. Second, although the pentamer is the most abundant oligomer, the tetramer ranks next in abundance, closely followed by the hexamer. It is worth noting that the tetramer represents nearly 25% of the cyclic products formed in the reaction.

The actual amount of tetramer formed was measured by ^{13}C NMR spectroscopy. The methylene carbon α to the carbonyl exhibits a signal that at high field is resolved enough to be quantitatively integrated with respect to other oligomerization products. Using this technique, a 15% yield of tetramer was detected in the crude reaction mixture. An absolute yield value was independently obtained by adding as internal standard a known amount of **3** to the quenched mixture. Integration of the methylene signal of the tetramer vs that of the standard provided a 13% yield, in good agreement with the previous value. The observation that the open-chain oligomeric material **5** represents 47% of the mixture, while the stannylated end groups are only 5–10% of the starting lactone, indicates that the molecular weight of this fraction is quite disperse and the polymerization degree higher than that of the cyclic fraction. This feature is the typical behavior predicted by the Jacobson–Stockmayer theory[3] and is a drawback for the formation of the cyclic fraction.

Yields obtained from experiments run at different initial monomer concentration in the chosen range did not vary appreciably (9–13%). This result could be anticipated from inspection of simulated product distributions for the cyclooligomerization of **1**,[2] which exhibit a rather shallow variation in the yield of cyclic oligomers with the initial concentration of monomer when K_{inter} is low.

The oligomerization mixture from a run at 0.029 M initial monomer concentration was carefully separated by column chromatography and the tetrameric macrolide was obtained in 10% yield as a white solid, which was recrystallized to provide sharply melting needles in 3% yield. The isolated compound was unambiguously proven to be the desired macrotetrolide by X-ray crystal structure analysis[13] (Figure 1). The latter showed that in the solid

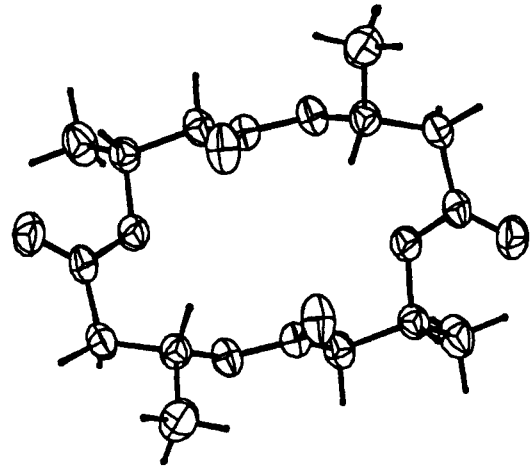


Figure 1. ORTEP projection of the X-ray crystal structure of tetrolide (**2**).

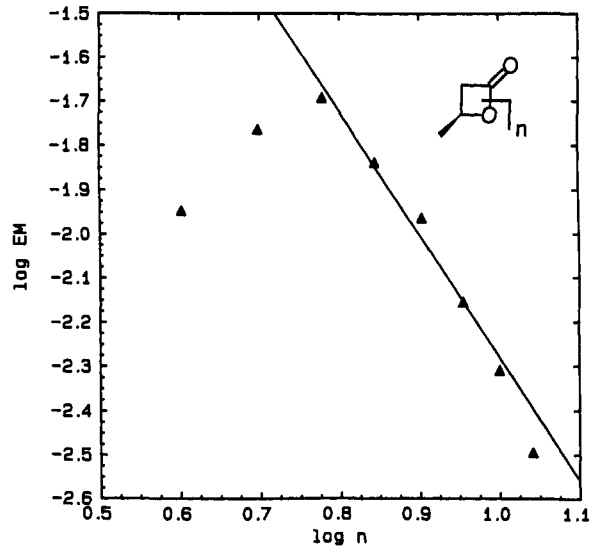


Figure 2. Logarithmic plot of EM_n vs n for cyclooligomers of (*S*)-β-butyrolactone (**4**, n = 4–11). The straight-line fitting data for $n \geq 6$ has a slope = −2.8 ± 0.2.

state the molecule adopts a very regular conformation of C_2 symmetry, which is probably responsible for a favorable packing in the crystal, consistent with its relatively high melting point (175 °C) compared to that of its higher oligomers (pentamer, 103 °C; hexamer, 113 °C; heptamer, 119 °C),[6] as well as with its anomalous chromatographic behavior.[14]

Discussion

The yield of **2**, lower than that expected from the yield obtained for the cyclic tetramer of **1**, is clear evidence that this tetrolide is not strainless, although it is a 16-membered ring. This feature can be quantitatively assessed by comparison between the experimental and the expected EM_4 values. Thermodynamic EM_n values for the cyclic oligomers of **3** can be calculated from the equilibrium concentration of cyclic species in the reaction medium (see Table I), if the reasonable assumption is made that the

(12) Crotonate derivatives are typical byproducts that systematically accompany polymerization reactions of β-butyrolactone. See, for example, ref 10.

(13) Crystal data for **2**: $C_{16}H_{24}O_8$, M = 344.36, C_2/m, a = 19.967 (2) Å, b = 5.606 (1) Å, c = 8.373 (1) Å, Z = 2, V = 896.95 Å^3, d_c = 1.27 g cm^{-3}, R = 0.033 for 921 unique reflections. Details are provided as supplementary material.

(14) On TLC (petroleum ether/methyl formate 2:1) the tetramer exhibited a greater affinity for silica gel than higher oligomers and was eluted with an R_f intermediate between that of the pentamer and of the hexamer. Using Seebach's eluant (ethyl ether/petroleum ether 7:3, see ref 6), such high affinity of the tetramer for silica produces tails that overlap with other oligomers. This might accidentally lead to problems in the isolation of the tetramer.

exponential decay of EM_n for strainless rings is the same as that observed for 1; this means choosing the cyclooligomer distribution of 1 as reference for the cyclooligomerization of 3.[15] A logarithmic plot of EM_n vs n (Figure 2) exhibits a very good linearity for $n \geq 6$, with a slope of -2.8 ± 0.2 very close to the theoretical value of -2.5 and the experimental value of -2.6 for 1 and an evident negative deviation for the tetramer and the pentamer. Comparing the EM values of these two cyclooligomers for the two substrates, it appears that, while the latter is only slightly lower than the reference [$EM_5(1)/EM_5(3) = 1.9$], the former is 5.2 times lower for 3 with respect to 1. Thus, the formation of the tetrolide from 3 is thermodynamically disfavored with respect to its unsubstituted strainless counterpart by a factor of 5, which corresponds to an observed strain energy of 1.1 kcal mol^{-1} at 70 °C.

Comparing the refined X-ray molecular structure obtained for the tetrolide with one of the models of the structure optimized by force-field calculations,[16] a striking similarity is apparent. It is noteworthy that among the possible minimum energy conformations the one which is in close agreement with the experimental structure is that obtained by adding the methyl substituent with the proper stereochemistry to the X-ray structure of the tetrolide of 1 as starting conformer for the optimization. Since this modification leads to a conformation basically analogous to that of the unsubstituted system, the conclusion that the introduction of four methyl groups on the tetramer ring does not produce significant perturbation seems substantially correct. Such a conclusion is in agreement with the relatively small drop in effective molarity discussed above, which is reasonably related to modest unfavorable energetic contributions, and with the observed yields, which are moderately lower than those expected in the absence of strain.

Further Considerations. A closer inspection of the molecular structure (Figure 1) reveals that methyl groups, which point outward pairwise in opposite directions of the molecular plane, do not seem to exhibit unfavorable interactions either with each other or with adjacent groups. Opposite pairs of carbonyls point instead toward the same side of the plane of the molecule, one equatorial and one axial pair on opposite sides. A van der Waals or dipole–dipole repulsive interaction could be suspected between the two facing axial carbonyls, but the transannular distance between them (C–C, 3.91 Å; O–O, 3.53 Å) and the inspection of the space-filling depiction of the molecule (Figure S3, supplementary material) show clearly that they are too far apart and separated by a well-defined internal "hole" of the macroring. An unfavorable transannular interaction between carbonyls and opposite methine hydrogens seems also unlikely, in view of recent findings demonstrating that these are in fact attractive, hydrogen bond-like interactions.[17] In connection with these findings, it is interesting that the main difference between the calculated model and the experimental structure is a partial twist of the plane of the molecule in the latter that brings facing carbonyls closer to the opposite methine hydrogen of the CHMe groups. Although this phenomenon may be ascribed to conformational selection in the crystal packing, the fact that this twisting is not accounted for by the force-field calculation may suggest the idea of a pair of nonclassical hydrogen bonds as the driving force of twisting. As a matter of fact, the 2.93-Å distance between the carbonyl oxygen and the opposite CHMe hydrogen for both C=O···H—C interactions is markedly shorter than the corresponding 4.7-Å transannular distance between the closest ester oxygens and may be reasonable for a weak hydrogen bond. A second beneficial effect of the plane twisting is that it relieves the short C=O···CH_3 contacts, which have been observed to affect the calculated model.[9] As a check for these hypotheses, the experimental structure has been submitted to energy minimization by force-field calculation. The results show, as expected in consideration that a C=O···H—C hydrogen bond is not parametrized in the force-field, that in the minimum energy conformation opposite C=O and H—C bonds diverge from 2.93 Å to 3.20 Å, while the contiguous C=O···CH_3 distance shortens from 3.23 to 3.02 Å, matching with a torsion angle between these two groups that goes from 72° to 62°.

In conclusion, although experimental evidence demonstrates that the formation of 2 is more hampered than that of the cyclic tetramer of 1, no evidence of constraints could be inferred from the solid-state structure analysis or molecular mechanics calculation. In fact, the observed transannular interactions may even play a favorable role, relieving the intrinsic strain of the ring.

Inspection of ^1H NMR features suggests a possible explanation of the matter. It has been noted[6] that the ^1H NMR spectra of pentamer, hexamer, and heptamer are all strikingly similar, almost superimposable to each other and to those of methyl β-acetoxybutyrate (6) and PHB. This evidence has been taken as an indication that the average conformations around the $CH_3CH(OR)CH_2COOR'$ moieties of these species are very similar. Hence, these cyclic compounds appear to be conformationally free, i.e., strainless, as are their open-chain counterparts. While our EM_n data are perfectly in line with this conclusion for $n \geq 6$ and nearly so for $n = 5$, such is not the case of the tetramer. As can be seen in Figure S6 (supplementary material), the CH_2 signal of the latter, which shows the most evident differences, is appreciably different from that of 6 (and from that of strainless cyclic oligomers) but quite similar to that of 3-hydroxybutyric acid and its methyl ester. Considering that derivatives having the free hydroxyl group are capable of intramolecular hydrogen bonding, while this is not possible when the hydroxyl is esterified, the hypothesis of restricted conformational freedom as the origin of residual strain in the 16-membered ring is suggested. Since relevant unfavorable interactions could not be found, such strain might simply be related to a partial loss of rotational freedom and thus be entropic in origin. If the observed free-energy difference of 1.1 kcal mol^{-1} were entirely ascribed to the entropic factor, it would correspond to 3.3 eu, a value smaller than the entropy that

(15) In the revised version of the Jacobson–Stockmayer theory, the effective molarity and the equilibrium concentration of the nth cyclic oligomer are simply expressed in the form (see ref 2)

$$EM_n = A \cdot n^{-exp}$$

$$[C_n] = EM_n \cdot X^n$$

where X is defined as the extent of reaction of functional groups in the linear part of the polymer. A complete statistical analysis performed on the oligomerization of 1 gave for exp and the preexponential factor A the values of 2.6 and 2.099, respectively, which provided the whole set of EM_n for the cyclooligomers of 1.[5] Using these figures and introducing the experimental concentration values reported in Table I for C_n in the above expressions, the X value is obtained, which should be constant for strainless cycles following theoretical behavior, as occurs for the reference β-propiolactone system. For 3 this actually occurs for $n \geq 6$, i.e., cycles larger than the hexamer are "well behaved" strainless rings. Introducing the value of X averaged on cyclooligomers with $n \geq 6$ ($X = 0.607$) again in the C_n expression, the set of EM_n reported in Table I is obtained, which differs from the set relative to 1 for the "deviating" EM of the tetramer and the pentamer.

(16) See ref 8, p 1712, Model C.

(17) Wiberg, K. B.; Waldron, R. F.; Schulte, G.; Saunders, M. *J. Am. Chem. Soc.* **1991**, *113*, 971.

can be lost upon freezing the internal rotation about one single bond upon cyclization of a chain molecule.[18] The drop in yield of tetrolide, observed for 3 with respect to 1, might thus be well accounted for, at least in part by a moderate restriction in rotational freedom of the 16-membered ring, caused by the introduction of 4 methyl groups in the backbone, without invoking severely adverse interactions.

Experimental Section

Materials, Instruments, and Techniques. The preparation of (*S*)-(−)-β-butyrolactone [(*S*)-3] from PHB of natural origin (Aldrich, MW 800 000) has been described in detail.[7] Its enantiomeric purity has been independently checked by an NMR method,[19] and the reagent was found to be enantiomerically pure as reported. 2,2-Dibutyl-1,3,2-dioxastannolane (DOS) was prepared according to a known procedure[20] and purified as described previously.[21] Dibutyltin dichloride (DTC, EGA Chemie, mp 39–41 °C) was used as received. Chlorotrimethylsilane (Carlo Erba RPE, bp 57 °C) was purified by distillation over quinoline. $CHCl_3$ (Carlo Erba RPE) was purified by being washed with several portions of distilled water in a separatory funnel and left overnight over anhydrous $CaCl_2$. The solvent was then filtered and kept in the dark over 13 X activated molecular sieves. The treated $CHCl_3$ was free from ethanol and water and could be stored for several weeks without appreciable decomposition. $CDCl_3$ (Merck, 99.8%) stored on Ag foil and activated molecular sieves was used for NMR spectra. Melting points are uncorrected. NMR spectra were obtained at 4.7, 9.4, and 11.7 T. ^1H NMR data were aquired with digital resolution 0.001 ppm, PW < 30°, 3.8-s acquisition, 10-s repetition rate. ^{13}C NMR spectra were recorded under broadband proton noise decoupling. For quantitative measurements, spectra were acquired with a PW ≅ 45°, digital resolution 0.001 ppm, repetition rate ≥ 6 s, in consideration that T_1 values for the α-CH_2 signal of 1 ranged from 0.5 to 1.1 s. EI-MS spectra were obtained at 70 eV ionizing power. FAB-MS spectra were performed in positive mode on an instrument equipped with the standard FAB source (argon, 7 kV), by adding methanolic solutions of the mixture to a tetra(ethylene glycol) matrix. Cationization experiments were carried out by spiking a solution of CsI in methanol to the solution of the mixture on the matrix. Computer graphics and molecular mechanics calculations were performed with ALCHEMY II (Tripos Associates, St. Louis, MO) on a IBM PC.

Cyclooligomerization of (*S*)-β-Butyrolactone (3). The following is a typical procedure. (*S*)-Lactone 3 (108 mg, 1.25 mmol) was dissolved in anhydrous, ethanol-free $CHCl_3$, to a 25-mL volume, and the required catalytic amount of DOS/DTC was added to the solution. The catalytic system was generated in situ by mixing equimolar amounts of 2,2-dibutyl-1,3,2-dioxastannolane (73.5 mg, 0.25 mmol) and dibutyltin dichloride (76 mg, 0.25 mmol) directly in the reaction medium. The solution was then allowed to react in a thermostatic bath for 87 h at 70 °C in a screw-cap bottle. The actual concentrations were 0.047 M in 3 and 0.0095 M in DOS/DTC, taking into account the volume increase of the solvent at 70 °C. The reaction was then quenched with excess Me_3SiCl (137 mg, 1.26 mmol), the solvent was evaporated, and the volatile products were removed under vacuum to constant weight, to obtain 263 mg of crude mixture. Complete oligomerization and absence of the starting material was verified by ^1H NMR spectroscopy. The crude mixture (260 mg) and 47 mg of racemic 3 were dissolved in 1.32 mL of anhydrous $CDCl_3$ in a 5-mm NMR tube and were submitted to proton-decoupled ^{13}C NMR quantitative analysis at 125 MHz. Integration of the tetramer signal vs the internal standard signal gave a 13% (14 mg) absolute yield.

Separation of the Tetramer. An oligomerization mixture from a run with 315 mg (3.66 mmol) of 3 at 0.029 M initial monomer concentration was separated by flash column chromatography. Analytical TLC (eluant: petroleum ether/methyl formate 2:1) exhibited the following R_f values: tetramer, 0.32; pentamer, 0.36; hexamer, 0.28. The crude mixture was separated with this eluant on a 0.015–0.040-mm silica gel 60 column (20-× 4-cm diameter) to give a fraction of 31 mg (10%) of the desired tetrolide as a white solid, which was identified by ^1H NMR, ^{13}C NMR (100 MHz), and FAB-MS spectra. The tetraester was crystallized from diethyl ether/petroleum ether 7:3 and recrystallized from diethyl ether to give 9 mg (3%) of sharply melting fine needles.

(4*S*,8*S*,12*S*,16*S*)-4,8,12,16-Tetramethyl-1,5,9,13-tetraoxacyclohexadecane-2,6,10,14-tetrone (2): white needles (diethyl ether); mp 174.5–175.5 °C; ^1H NMR (200 MHz, 0.02 M in $CDCl_3$) δ 1.30 (d, 3 H, J = 6.4 Hz, CH_3), 2.40–2.67 (m, 2 H, CH_2), 5.24 (m, 1 H, CH); ^{13}C NMR (50 MHz, 0.02 M in $CDCl_3$) δ 19.96 (CH_3), 40.93 (CH_2), 67.50 (CH), 169.64 (CO); MS (EI) m/z (relative intensity) 345 (0.3), 344 (0.05, M^+), 275 (8, $M - C_4H_5O$), 257 (8, $M - C_4H_7O_2$), 191 (6), 173 (13), 171 (13), 155 (58), 154 (20), 128 (12), 103 (7), 87 (25, $C_4H_7O_2$), 70 (9), 69 (100, C_4H_5O). Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.81; H, 7.02. Found: 56.06; H, 7.18.

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Supplementary Material Available: H^+ and Cs^+ FAB-MS spectra of the cyclooligomerization mixture (Figure S1–2), space-filling, labeled representations, and stereoview of 2 (Figure S3–5), ^1H NMR spectral features of 2 and related compounds (Figure S6), and X-ray analysis and crystal data of 2 (Tables S1–6) (13 pages). Ordering information is given on any current masthead page.

(18) The entropy loss per added methylene group on cyclization of alkane chains upon freezing an internal rotation of one C–C bond has been calculated as 4.5–4.8 eu and has been experimentally found to be 4.0 eu. See: Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 23.

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(21) For a general preparation and purification of dioxastannolanes, see: Luchinat, C.; Roelens, S. *J. Am. Chem. Soc.* **1986**, *108*, 4873.