Organotin-Mediated Synthesis of Macrocyclic Tetraesters: Regio- and Stereochemistry[1]

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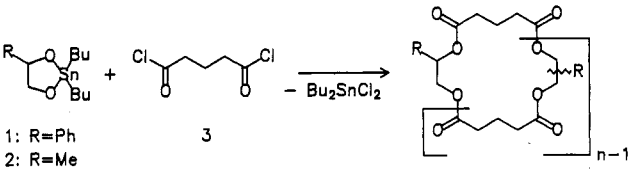
The reaction of 4-phenyl- and 4-methyl-substituted dioxastannolanes (1 and 2, respectively) with glutaryl chloride has been investigated to provide a clear description of the regio- and stereochemistry of the organotin-mediated synthesis of macrocyclic tetraesters. In contrast with previous reports, the reaction does not exhibit the described regio- and stereospecificity, affording all possible isomers in substantial amounts, in line with the expected product distribution for a thermodynamically controlled reaction. The regioisomeric preference, that has been observed to some extent for the phenyl derivatives, appears to be unpredictably dependent on the substituent nature. Although experimental conditions can be optimized for reasonable yields of dimeric tetraester, the regio- and stereochemical outcome of this reaction cannot be readily predicted.

The so called "Covalent Template Method" has received increasing attention for the synthesis of macrocyclic carbonyl compounds because of its remarkable selectivity features.[2] For example, the reaction of cyclic dioxastannanes with diacyl chlorides has been recommended as the method of choice for the stereospecific one-step synthesis of biomimetic macrocyclic tetraesters.[2a] Such method has been described to take advantage of a covalent tin-template effect to assemble preorganized reacting fragments of the final tetraester structure.[2]

It has recently been shown,[3] however, that the reaction of 2,2-di-*n*-butyl-1,3,2-dioxastannolane with diacyl dichlorides is actually a thermodynamically controlled cyclooligomerization, which takes place under very mild conditions. The absence of tin-template effects and the occurrence of an equilibrated mixture of oligomeric macrocyclic esters was unequivocally demonstrated by NMR, gel-permeation chromatography (GPC), and MS-FAB product analysis,[1] which showed no evidence of specific selectivity toward the tetraester. Accordingly, the reaction cannot be expected to exhibit regio- and stereospecificity as originally proposed[2a,4] in the case of substituted substrates. Nevertheless, some specific isomer might be more stable than others and thus be preferred in the equilibrium distribution of products, mimicking an apparent selectivity. If this were the case, the reaction may turn out to be truly convenient to synthesize substituted tetraesters of defined regio- or stereochemistry, since experimental conditions can be adjusted to obtain reasonable yields of dimeric products.[1,3] In this context, to assess the validity of the method, it appears crucial to provide a clear description of which isomeric dimers are actually *formed* in the reaction, since conclusions based exclusively on isolated products can be misleading.

4-Phenyl- and 4-methyl-substituted dioxastannolanes (1 and 2, respectively), obtained from enantiomerically pure (*S*)- and racemic (*R,S*)-1-phenyl-1,2-ethanediol and 1,2-propanediol, respectively, were treated with glutaryl chloride (3) in chloroform at 0–5 °C and then allowed to react at room temperature for 24 h, to afford the macrocyclic polyester mixtures 4 and 5, respectively. Concentration was adjusted to 0.03–0.05 M, in which range about 50% of dimeric products was expected.[5] Indeed, 39–52% yield of tetraesters could be isolated (see Table I), while isolation of monomeric diesters, which were monitored in 9–17% amount, was difficult due to their marked tendency to hydrolytic decomposition during workup.[6]



1: R=Ph
2: R=Me

3

4: R=Ph
5: R=Me

In principle, starting from racemic diols, four diastereomeric tetraesters could be produced: two chiral dimers of C_{2y} and C_{2z} symmetry (*Z-trans* and *E-cis*) and two achiral dimers of C_S (*Z-cis*) and C_i (*E-trans*) symmetry.[7] Only the two chiral structures could obviously be obtained from enantiomerically pure diols.

The choice of glutaryl chloride is particularly convenient for isomer identification: the two central carbons of the alkyl chain (β to the carbonyl), which can unambiguously be assigned in the ^{13}C NMR spectrum, are different in the *Z* but identical in the *E* isomers, thus in principle distinguishable by NMR spectroscopy.

Upon careful separation of the polyester mixture by flash chromatography, monomeric and dimeric cyclic esters, identified by their MS-FAB spectra, could be isolated from higher oligomers; the tetraesters exhibited isomeric distributions that were in excellent agreement with those detected by ^1H NMR directly from the crude reaction mixture (Table I). Assignment of the ^1H NMR signals was accomplished by comparison with spectra of pure isomers, obtained directly from chromatographic fractions or by subsequent crystallization when necessary. Unambiguous

(1) Group 14 Organometallic Reagents. 8. Part 7: Mandolini, L.; Montaudo, G.; Roelens, S.; Scamporrino, E.; Vitalini, D. *Macromolecules*, in press.

(2) (a) Lifson, S.; Felder, C. E.; Shanzer, A.; Libman, J. In *Progress in Macrocyclic Chemistry*; Izatt, R. M., Christensen, J. J., Eds.; Wiley: New York, 1987; Vol. 3, p 245. (b) Shanzer, A.; Libman, J.; Frolow, F. *Acc. Chem. Res.* **1983**, *16*, 60. (c) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 658.

(3) Roelens, S. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1617.

(4) (a) Shanzer, A.; Libman, J.; Gottlieb, H. E.; Frolow, F. *J. Am. Chem. Soc.* **1982**, *104*, 4220. (b) Shanzer, A.; Libman, J.; Gottlieb, H. E. *J. Org. Chem.* **1983**, *48*, 4612.

(5) From preliminary experiments at various concentrations, effective molarity values for dimeric glutarates were estimated in the order of (3–5) $\times 10^{-2}$ M, and those for the monomeric diester 1 order of magnitude smaller. For a definition of the effective molarity parameter and its relevance to cyclization reactions, see: Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1.

(6) Extensive precipitation of glutaric acid was observed during the elaboration of the isolated cyclic diester fractions. For methyl derivatives, polymerization observed onto the FAB target of the mass spectrometer further underlined the lability of the medium-ring diesters.

(7) In this paper, stereoisomers with respect to the plane of the molecule are indicated as cis and trans, while regioisomers with respect to the orthogonal plane bisecting the diol moieties are indicated as *Z* and *E*.

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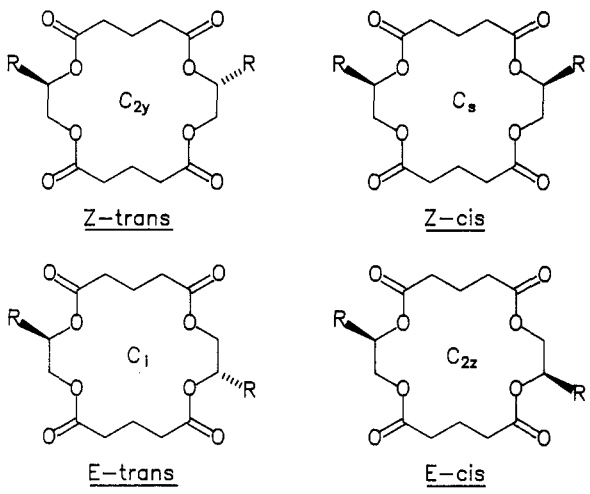

structure assignment for each isomer was straightforward: splitting of the β carbon signal in the ^{13}C NMR spectrum was observed only for one of the two tetraesters obtained from enantiomerically pure diols and for two of the four isolated from racemic diols, which were thus assigned as the *Z* regioisomers.

The key result that appears from the above data (Table I) is the formation in substantial amount of *all* isomeric tetraesters: this evidence rules out the regio- and stereospecificity features ascribed to the investigated reaction.[8] While no significant cis–trans selection was revealed in any case, the 6–7:1 preference toward the *Z* over the *E* isomer, observed for the phenyl derivatives (4), could apparently simulate some regioselectivity. However, going to the methyl derivatives (5), such preference drops to a *Z*/*E* ratio of 1.4–2:1, indicating a strong dependence on the nature of substituents.

The origin of the observed *Z* preference is not yet understood. The larger stability of the *Z* with respect to the *E* isomers for the phenyl derivatives cannot be explained by mutual interaction of substituents, which, according to molecular models and to published crystallographic and calculated molecular structures,[9] appears to be lacking in such large-ring macrocyclic tetraesters. More likely, the effect might be related to conformational preference next to the ester groups, which were all found to be in the more stable trans conformation[10] in this class of compounds: interaction between the substituent and the carbonyl group may arise as a consequence of the unusual torsion angles displayed by these tetraesters.[10] Indeed, the unusually large downfield shifts observed for the C*H*R ester protons (see the Experimental Section) strongly supports such an interaction, which is probably significant for the phenyl group. However, these conformational effects have been shown to be small and largely unpredictable,[9,10] and thus may well account for the present low isomeric preferences. As a matter of fact, calculated structures of analogous tetraesters exhibit very similar stabilities for conformations of C_i and C_{2z} symmetry.[9]

In conclusion, the reaction of substituted dioxastannolanes with glutaryl chloride does not exhibit the regio- and stereospecificity expected for a template reaction under kinetic control, as previously described. Instead, it affords distributions of isomeric products as expected for equilibrated mixtures. Isomeric preference, that has been observed to some extent for the phenyl derivatives, appears to be unpredictably dependent on the substituent nature. Although this method can be of practical value for the synthesis of macrocyclic tetraesters, in the light of the present findings, its regio- and stereochemical outcome is not readily predictable.

Experimental Section

Materials, Instruments, and Techniques. Preparation and purification of dioxastannolanes, glutaryl dichloride and chloroform, as well as experimental details on the reaction, have been described in previous papers.[3,11] The anhydrous, ethanol-free chloroform used in the reactions was kept in the dark over 13× activated molecular sieves. $CDCl_3$ (Merck, 99.8%) stored on Ag foil and activated molecular sieves was used for NMR spectra. Melting points are uncorrected. EI mass spectra were obtained at 70 eV. MS-FAB spectra were performed in positive mode on a VG 70-70 EQ instrument, equipped with the standard FAB source (argon, 7 kV), using 3-nitrobenzyl alcohol (3-NBA) matrix. NMR spectra were obtained on a Varian VXR 300 instrument. ^1H and ^{13}C NMR δ values (from Me_4Si, using $CHCl_3$ and $CDCl_3$ as internal secondary reference at δ 7.26 and 77.00, respectively) for tetraesters are referred to solutions of all four isomers. ^{13}C NMR spectra were recorded under broadband proton noise decoupling. ^1H NMR data (digital resolution 0.001 ppm, PW < 30°, 3.8-s acquisition) are reported only for signals that have been used for the identification and the analysis of isomers; δ and *J* values for ABX systems have been obtained by computer simulation with the LAOCOON III program. Flash chromatography separations were performed on silica gel 60 (Merck, 230–400 mesh) columns of 20 cm × 40 mm diameter.

Reaction with (*R*,*S*)-4-Phenyl-2,2-dibutyl-1,3,2-dioxastannolane [(*R*,*S*)-1]. General Procedure. A solution of glutaryl chloride (253 mg, 1.5 mmol) in $CHCl_3$ (20 mL) was added dropwise with a syringe through a septum cap to a solution of (*R*,*S*)-1 (553 mg, 1.5 mmol) in $CHCl_3$ (20 mL) cooled with ice and stirred under nitrogen, at such a rate as to maintain the temperature at 0–5 °C. The solution was then allowed to warm to room temperature and, after 24 h of stirring, was poured into petroleum ether (50 mL) until the precipitation of a white solid was complete. The mixture was filtered; the solid was washed with petroleum ether, and dried under vacuum. Only polyesters were detected in the solid while the mother liquors contained dibutyltin dichloride together with small amounts of polyesters, which were recovered by evaporation of the solvent and washing of the residue with petroleum ether. The combined solid portions afforded 363 mg of polyesters mixture, an aliquot of which (324 mg) was then separated by flash chromatography (petroleum ether–ethyl acetate, 2:1), identifying oligomeric fractions by their MS-FAB spectra; 10 mg of monomeric diester (3%; MS-FAB *m*/*e* 235 (M + 1)), 167 mg of dimeric tetraesters (52%; MS-FAB *m*/*e* 469 (M + 1), 235), 55 mg of trimeric hexaesters (MS-FAB *m*/*e* 703 (M + 1), 469, 235), and higher oligomers were obtained. The collected fractions of dimeric tetraesters contained mainly the single isomers. Isomeric distribution was obtained by ^1H NMR at 300 MHz. Crystallization from chromatographic eluant afforded the pure isomers in most cases.

Reaction with (*S*)-4-Phenyl-2,2-dibutyl-1,3,2-dioxastannolane [(*S*)-1]. Reaction of 738 mg (2.0 mmol) of (*S*)-1 and 338 mg (2.0 mmol) of glutaryl chloride in $CHCl_3$ (40 mL) gave 468 mg of polyesters mixture. The separation of 324 mg of the crude ester mixture by flash column chromatography (petroleum ether–ethyl acetate, 2:1) afforded 1.2 mg of monomeric diester (1%; MS-FAB *m*/*e* 235 (M + 1)), 165 mg of dimeric tetraesters (39%; MS-FAB *m*/*e* 469 (M + 1), 235), 66 mg of trimeric hexaesters (MS-FAB *m*/*e* 703 (M + 1), 469, 235), and higher oligomers.

Reaction with (*R*,*S*)-4-Methyl-2,2-dibutyl-1,3,2-dioxastannolane [(*R*,*S*)-2]. Reaction of 461 mg (1.5 mmol) of (*R*,*S*)-2 and 253 mg (1.5 mg) of glutaryl chloride in $CHCl_3$ (40 mL) gave

(8) Such specificities have been previously inferred on the basis of the structure of isolated and crystallized products, which may likely reflect solubility more than selectivity (see ref 4). Indeed, in the case of the phenyl derivatives, the trans isomers have been found to be less soluble than the cis isomers and crystallized spontaneously from chromatographic eluant, even the minor *E-trans* isomer.

(9) See ref 2a, p 271–275.

(10) Dale, J.; Groth, P.; Schwartz, J. E. *Acta Chem. Scand.* **1986**, *B40*, 568.

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Table I. Yields and Isomeric Distributions of Monomeric and Dimeric Cyclic Glutarates[a]

		tetraester				
			isomeric distribution, %			
reagent	diester yield, %	yield, %	*Z-trans*	*Z-cis*	*E-cis*	*E-trans*
1a[b]	9 (1)	(39)	88 (90)		12 (10)	
1b[c]	12 (3)	(52)	44 (46)	42 (43)	7 (5)	7 (6)
2a[c]	17 (12)	(43)	59 (59)		41 (41)	
2b[c]	14 (4)	(50)	32 (29)	30 (33)	22 (22)	16 (16)

[a] Data are obtained by ^{1}H NMR spectroscopy at 300 MHz. Isolated product yields and distributions are reported in parentheses. [b] Reaction run at 5.0×10^{-2} M initial concentration. [c] Reaction run at 3.9×10^{-2} M initial concentration.

282 mg of solid, impure of traces of dibutyltin dichloride of which were eliminated by washing with petroleum ether. The separation of 168 mg of the crude ester mixture by flash column chromatography (petroleum ether–ethyl acetate, 2:1) afforded 6 mg of monomeric diester (4%; MS-FAB, polymerizes on target), 86 mg of dimeric tetraesters (50%; MS-FAB *m/e* 345 (M + 1), 173), 37 mg of trimeric hexaesters (MS-FAB *m/e* 517 (M + 1), 345, 173), and higher oligomers.

Reaction with (*S*)-4-Methyl-2,2-dibutyl-1,3,2-dioxastannolane [(*S*)-2]. Reaction of 461 mg (1.5 mmol) of (*S*)-**2** and 253 mg (1.5 mmol) of glutaryl chloride in $CHCl_3$ (40 mL) gave 265 mg of polyesters mixture. The separation of 181 mg of the crude mixture by flash column chromatography (petroleum ether–ethyl acetate, 2:1) afforded 21 mg of monomeric diester (12%), 77 mg of dimeric tetraester (43%; MS-FAB *m/e* 345 (M + 1), 173), 26 mg of trimeric hexaesters (MS-FAB *m/e* 517 (M + 1), 345, 173), and higher oligomers.

Products. 8-Phenyl-1,7-dioxacyclononane-2,6-dione (4, *n* = 1): solid; mp 59–63 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ OCH_2CHO (AMX), A 4.021, M 4.994, X 6.177; $\Delta\nu_{AM}$ = 292 Hz; J_{AM} = 11.1 Hz, J_{AX} = 6.3 Hz, J_{MX} = 9.9 Hz; IR (KBr, cm^{-1}) 1742, 1732 (C=O); MS (EI) *m/z* (relative intensity) 234 (M^+, 29), 148, 128, 115, 104, 98 (100), 91, 70, 55. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.70; H, 6.11.

***trans*-8,18-Diphenyl-1,7,10,16-tetraoxacyclooctadecane-2,6,11,15-tetrone (4, *n* = 2, *Z-trans*):** solid; mp 146–147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ OCH_2CHO (ABX), A 4.323, B 4.373, X 6.077; $\Delta\nu_{AB}$ = 15 Hz; J_{AB} = 12.1 Hz, J_{AX} = 2.6 Hz, J_{BX} = 9.6 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.13 and 171.74 (*CO*), 135.89 (C_{ipso}), 128.70 and 128.67 ($C_{p,o}$), 126.52 (C_m), 73.38 (*CH*Ph), 66.17 (CH_2O), 33.43 and 33.19 (CH_2CO), 20.28 and 20.26 (CH_2CH_2CO); IR (KBr, cm^{-1}) 1740 (s), 1731, 1726 (C=O); MS (EI) *m/z* (relative intensity) no M^+, 234 (25), 148, 123, 115, 104, 97, 95, 89, 83, 81, 71, 69, 59, 57 (100), 55. Anal. Calcd for $C_{26}H_{28}O_8$: C, 66.66; H, 6.02. Found: C, 66.82; H, 6.22.

***cis*-8,17-Diphenyl-1,7,10,16-tetraoxacyclooctadecane-2,6,11,15-tetrone (4, *n* = 2, *E-cis*):** solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ OCH_2CHO (ABX), AB 4.41–4.29, X 6.130; $J_{AX} \cong 6$ Hz, $J_{BX} \cong 7$ Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.20 and 171.61 (*CO*), 135.76 (C_{ipso}), 128.74 ($C_{p,o}$ unresolv), 126.57 (C_m), 73.16 (*CH*Ph), 66.32 (CH_2O), 33.60 and 33.00 (CH_2CO), 20.33 (CH_2CH_2CO). Anal. Calcd for $C_{26}H_{28}O_8$: C, 66.66; H, 6.02. Found: C, 66.43; H, 6.18.

***cis*-8,18-Diphenyl-1,7,10,16-tetraoxacyclooctadecane-2,6,11,15-tetrone (4, *n* = 2, *Z-cis*):** solid; mp 114–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ OCH_2CHO (ABX), A 4.289, B 4.459, X 6.095; $\Delta\nu_{AB}$ = 51 Hz; J_{AB} = 12.2 Hz, J_{AX} = 8.9 Hz, J_{BX} = 2.6 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.19 and 171.72 (*CO*), 135.95 (C_{ipso}), 128.67 and 128.63 ($C_{p,o}$), 126.51 (C_m), 73.24 (*CH*Ph), 66.08 (CH_2O), 33.33 (CH_2CO), 20.60 and 20.40 (CH_2CH_2CO); IR (KBr, cm^{-1}) 1739, 1729 (C=O); MS (EI) *m/z* (relative intensity) no M^+ 278, 166, 148 (100), 107, 83, 71, 69, 57, 55. Anal. Calcd for $C_{26}H_{28}O_8$: C, 66.66; H, 6.02. Found: C, 66.35; H, 6.27.

***trans*-8,17-Diphenyl-1,7,10,16-tetraoxacyclooctadecane-2,6,11,15-tetrone (4, *n* = 2, *E-trans*):** solid; mp 182–186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ OCH_2CHO (AMX), A 4.227, M 4.498, X 6.135; $\Delta\nu_{AM}$ = 81 Hz; J_{AM} = 12.0 Hz, J_{AX} = 9.3 Hz, J_{MX} = 2.7 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.22 and 171.94 (*CO*), 135.81 (C_{ipso}), 128.74 and 128.70 ($C_{p,o}$), 126.61 (C_m), 73.14 (*CH*Ph), 66.29 (CH_2O), 33.58 and 32.99 (CH_2CO), 20.44 (CH_2CH_2CO); IR (KBr, cm^{-1}) 1736 (s), 1732 (C=O); MS (EI) *m/z* (relative intensity) no M^+, 234 (37), 115, 105, 104 (100), 97, 83, 71, 69, 57, 55. Anal. Calcd for $C_{26}H_{28}O_8$: C, 66.66; H, 6.02. Found: C, 66.52; H, 6.29.

8-Methyl-1,7-dioxacyclononane-2,6-dione (5, *n* = 1): solid; mp 86–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ $OCH_2CH(CH_3)O$ ($AFMX_3$), A 3.826, F 4.629, M 5.281, X_3 1.306; $\Delta\nu_{AF}$ = 241 Hz; J_{AF} = 10.8 Hz, J_{AM} = 6.0 Hz, J_{FM} = 9.6 Hz, J_{MX_3} = 6.3 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.46 and 174.43 (*CO*), 67.61 (*CH*Me), 65.26 (CH_2O), 34.54 and 34.42 (CH_2CO), 23.54 (CH_2CH_2CO), 17.29 (CH_3); IR (KBr, cm^{-1}) 1737 (s), 1730 (C=O); MS (EI) *m/z* (relative intensity) no M^+, 148, 128, 98, 71, 70 (100), 57, 55. Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.02. Found: C, 55.50; H, 7.23.

***trans*-8,18-Dimethyl-1,7,10,16-tetraoxacyclooctadecane-2,6,11,15-tetrone (5, *n* = 2, *Z-trans*):** low-melting solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ $OCH_2CH(CH_3)O$ ($AFMX_3$), A 3.996, F 4.248, M 5.178, X_3 1.234; $\Delta\nu_{AF}$ = 76 Hz; J_{AF} = 12.0 Hz, J_{AM} = 8.1 Hz, J_{FM} = 2.4 Hz, J_{MX_3} = 6.6 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.20 and 172.10 (*CO*), 68.20 (*CH*Me), 66.03 (CH_2O), 33.43 and 33.28 (CH_2CO), 20.43 and 20.32 (CH_2CH_2CO), 16.37 (CH_3). Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.80; H, 7.02. Found: C, 55.66; H, 7.01.

***cis*-8,17-Dimethyl-1,7,10,16-tetraoxacyclooctadecane-2,6,11,15-tetrone (5, *n* = 2, *E-cis*):** low-melting solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ $OCH_2CH(CH_3)O$ ($AFMX_3$), A 3.973, F 4.235, M 5.170, X_3 1.226; $\Delta\nu_{AF}$ = 79 Hz; J_{AF} = 12.0 Hz, J_{AM} = 8.4 Hz, J_{FM} = 2.4 Hz, J_{MX_3} = 6.6 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.29 and 171.97 (*CO*), 68.08 (*CH*Me), 66.18 (CH_2O), 33.67 and 32.96 (CH_2CO), 20.39 (CH_2CH_2CO), 16.37 (CH_3). Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.80; H, 7.02. Found: C, 55.58; H, 7.18.

***cis*-8,18-Dimethyl-1,7,10,16-tetraoxacyclooctadecane-2,6,11,15-tetrone (5, *n* = 2, *Z-cis*):** low-melting solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ $OCH_2CH(CH_3)O$ ($AFMX_3$), A 3.936, F 4.327, M 5.170, X_3 1.245; $\Delta\nu_{AF}$ = 117 Hz; J_{AF} = 12.0 Hz, J_{AM} = 7.5 Hz, J_{FM} = 2.4 Hz, J_{MX_3} = 6.6 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.23 and 172.05 (*CO*), 68.15 (*CH*Me), 65.94 (CH_2O), 33.50 and 33.25 (CH_2CO), 20.47 and 20.44 (CH_2CH_2CO), 16.35 (CH_3). Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.80; H, 7.02. Found: C, 55.74; H, 7.03.

***trans*-8,17-Dimethyl-1,7,10,16-tetraoxacyclooctadecane-2,6,11,15-tetrone (5, *n* = 2, *E-trans*):** low-melting solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ $OCH_2CH(CH_3)O$ ($AFMX_3$), A 3.901, F 4.311, M 5.179, X_3 1.237; $\Delta\nu_{AF}$ = 123 Hz; J_{AF} = 12.0 Hz, J_{AM} = 8.1 Hz, J_{FM} = 2.4 Hz, J_{MX_3} = 6.6 Hz; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.24 and 172.17 (*CO*), 68.10 (*CH*Me), 66.08 (CH_2O), 33.67 and 32.95 (CH_2CO), 20.46 (CH_2CH_2CO), 16.32 (CH_3). Anal. Calcd for $C_{16}H_{24}O_8$: C, 55.80; H, 7.02. Found: C, 55.90; H, 7.22.

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