Thermal Cycloreversion of 2,2-Dimethyl-6-(ω-hydroxyalkyl)-4*H*-1,3-dioxin-4-ones: Mono-, Di-, and Trimeric Macrocyclic β-Keto Lactones by Intramolecular Trapping of (ω-Hydroxy)acylketenes

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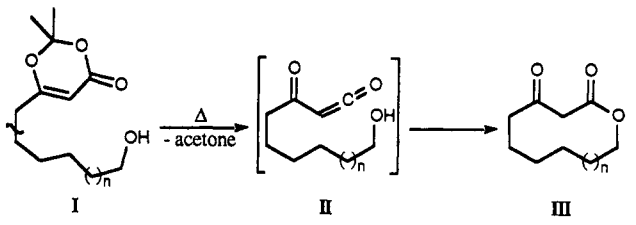
Prompted by the discovery of numerous macrolide antibiotics,[2] development of methodology for the preparation of macrolides has received much synthetic attention.[3] One interesting strategy developed by Boeckman[4] and co-workers exploits thermal cycloreversion of a 2,2-dimethyl-6-(ω-hydroxyalkyl)-4*H*-1,3-dioxin-4-one to form a highly reactive acylketene intermediate which suffers intramolecular addition by the ω-hydroxyl moiety to form a macrocyclic β-keto lactone. This general and quite high yielding strategy[5] proceeds, as outlined in Scheme I, by thermal decomposition of the "diketene–acetone" adduct[6] **I** in refluxing toluene to generate acetone and a highly reactive acylketene **II**.[7] Under suitable high dilution condition, acylketene **II** is preferentially trapped by intramolecular hydroxyl addition to deliver the corresponding monomeric macrolide **III**.

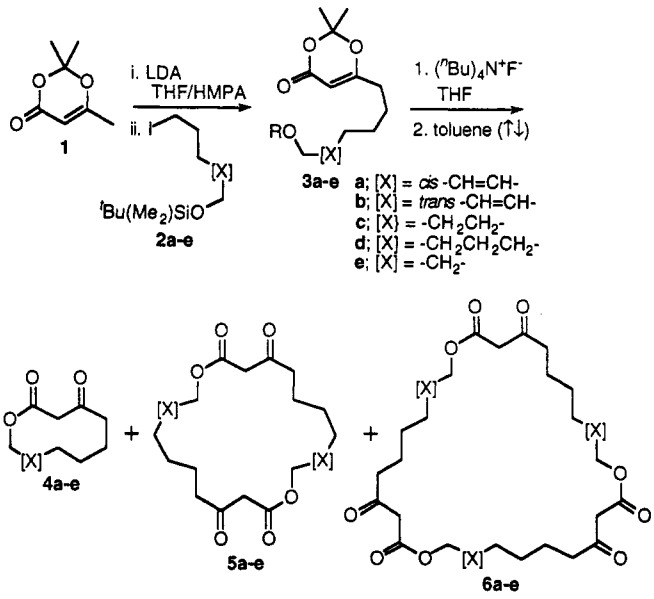
We were intrigued by the potential of this macrolide-forming strategy in connection with another synthetic method project ongoing in our laboratory and thus set out to incorporate **I** → **III** as the key step in our synthesis of macrocyclic β-keto lactones. Smith *et al.*'s report that the lithio anion of an β-alkoxy-α,β-unsaturated ester undergoes Cγ-alkylation[8] led us to consider preparing analogs of **I** by forming the indicated Cγ–Cδ bond.

Thus, our first target, dioxinone **3a**, required 2,2,6-trimethyl-1,3-dioxin-2-one (**1**) and iodoalkene **2a** as starting materials. The former is commercially available[9] and the latter was readily prepared as follows. The dianion of propargyl alcohol[10] was alkylated with 1-chloro-3-iodopropane to give 6-chloro-4-hexyn-1-ol (55%) which

Scheme I



Scheme II



was then partially hydrogenated to (*Z*)-6-chloro-4-hexen-1-ol (Lindlar catalyst, H_2;[11] 96%). Subsequent hydroxyl protection with *tert*-butyldimethylsilyl chloride[12] (98%) and halogen exchange (Cl → I; excess sodium iodide in acetone)[13] delivered **2a** in excellent yield (48% overall). Treating the lithio anion of **1**, generated by subjecting 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one to HMPA complexed LDA in THF,[14] with **2a** afforded dioxinone **3a** (OR = OSi(ᵗBu)Me; 32–54%) which was then deprotected (OSi(ᵗBu)Me_2 → OH; 87%). When the resulting (ω-hydroxyalkenyl)-dioxinone **3a** (OR = OH) was thermally activated (dioxinone → acylketene) in refluxing toluene under dilute condition (≃10^{-4} M) for a period of 3 h (method A), two products were obtained (separated by flash chromatography on silica gel). The product with higher R_f (0.39, 3:1 EtOAc/hexanes) readily recrystallized from hexane to give white crystals in fair yield (56%). Unexpectedly, single crystal X-ray diffraction revealed that this compound was the 22-membered ring dimeric macrocyclic **5a** ([X] – *cis*-CH=CH-; see Table I). The lower R_f (0.20, 3:1 EtOAc/hexanes) product, a pale yellow oil, was isolated in 20% yield. Fast atom bombardment (FAB) mass spectrometry [$(M + H)^+$ = 547] showed that this compound was the 33-membered ring trimeric product **6a**, not the monomeric β-keto lactone **4a**. Indeed, **4a** was not detected in the crude reaction mixture from **3a** (R = H).

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Table I. Crystallographic Data and Refinement Parameters for 5a, 5b, 5c, and 5e

	5a	5b	5c	5e
crystal system	monoclinic	monoclinic	triclinic	monoclinic
space group	$P2_1/n$	$P2_1/n$	$P\bar{1}$	$P2_1/n$
Z	2	2	1	2
a, Å	5.366(2)	12.702(6)	5.531(1)	4.601(2)
b, Å	18.174(4)	5.159(2)	8.053(1)	24.207(3)
c, Å	9.789(2)	15.022(6)	11.724(1)	8.242(2)
β, deg	99.63(2)	99.01(3)	100.27(2)	104.32(2)
crystal size, mm	0.075 × 0.075 × 0.30	0.08 × 0.08 × 0.50	0.52 × 0.56 × 0.56	0.04 × 0.04 × 0.48
λ, Å	0.71073	0.71073	0.71073	1.54178
2θ, deg	0.0–50.0	0.0–45.0	–0.0–55.0	0.0–108.5
collected reflections	1923	1508	2232	1668
unique reflections	1674	1277	2232	1082
obsd reflections	1326	889	1942	878
final R indices	0.0622	0.0672	0.0428	0.0382

Surprised at this outcome and in an attempt to favor formation of **4a**, this thermal cycloreversion/macrocyclization was conducted by slow addition (syringe pump; 2 h addition time) of a dilute xylene solution of **3a** (OR = OH) to refluxing xylene (125–132 °C) with rapid stirring (method B).[15] Under these conditions,[16] the concentration of reactive acylketene intermediate was always $\ll 10^{-4}$ M and still there was no evidence for formation of **4a**; dimeric macrolide **5a** and trimeric macrolide **6a** were formed in 51 and 18% yield, respectively.

These unexpected results with **3a** led us to investigate macrocyclization reactions for other (ω-hydroxyalkyl)-dioxinones. Our first thought was that perhaps the *endo*-(*Z*) configuration of the (ω-hydroxyalkenyl)acylketene derived from **3a** precluded its adopting a conformation which could lead to monomacrolactonization.[17] In an attempt to probe this issue, the second target we selected for study was dioxinone **3b** in which the carbon–carbon double bond now had the (*E*)-configuration. The requisite iodoalkene **2b** was synthesized as described for **3a** with the exception of how the carbon–carbon triple bond was partially reduced. Thus, 6-chloro-4-hexyn-1-ol was reduced with lithium aluminum hydride[18] to give (*E*)-6-chloro-4-hexen-1-ol (43%). Subsequent silylation, halogen exchange, and Cγ-alkylation of dioxinone 1 delivered **3b**. Again, high-dilution thermal cycloreversion/macrocyclization produced no monomeric macrolide (**4b**). Rather, the 22-membered ring dimeric macrolide **5b** (white crystals; see X-ray in Table I) was obtained in 48 and 50% yields from methods A and B, respectively, and the 33-membered ring trimeric macrolide **6b** (oil) was isolated in 18% yield from both methods.

Would a side-chain saturated dioxinone lead to a monomeric macrolide? To answer this question, (ω-hydroxyalkyl)dioxinone **3c** was prepared by alkylating 1 with iodoalkane **2c**, in turn prepared by reacting 1,6-hexanediol sequentially with concentrated hydriodic acid[19] (52% yeld) and *tert*-butyldimethylsilyl chloride. When dioxinone **3c** was cyclized under condition identical to those employed for **3a** and **3b**, only crystalline dimeric (22-membered) and liquid trimeric (33-membered) macrolides were obtaned (i.e., **5c** and **6c** were isolated in 49 and 13% yield, respectively; see X-ray data for **5c** in the Table I). As with **3a** and **3b**, **3c** gave no monomeric macrolide which leads us to conclude that 11-membered ring macrolides are not accessible by this thermal cycloreversion/macrocyclization method.

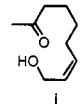
The last two substrates investigated in this series were (ω-hydroxyalkyl)dioxinones **3d**, a potential 12-membered ring precursor, and **3e**, a potential 10-membered ring precursor. These dioxinones were prepared in a fashion parallel to that described for **3c**, but starting with 1,7-heptanediol and 1,5-pentanediol, respectively.

Refluxing **3d** in toluene under dilute condition ($\simeq 10^{-4}$ M; method A), produced three products which were isolated by flash chromatography on silica gel. The compound with highest R_f (0.57; 3:1 EtOAc/hexanes) was a colorless oil obtained in 28% yield. FAB mass spectrometry [$(M + H)^+$ = 199.1333] established this compound as the monomeric 12-membered ring macrolide **4d**. The second fraction (R_f = 0.38; 3:1 EtOAc/hexanes) delivered a white crystalline compound in 41% yield which proved to be the dimeric 24-membered ring macrolide **5d** [$(M + H)^+$ = 397.2602]. Fraction three (R_f = 0.26; 3:1 EtOAc/hexanes) produced a pale yellow oil in 12% yield and FAB characterization established it to be the 36-membered ring trimeric macrolide **6d**. Slow addition of a dilute toluene solution of **3d** into refluxing toluene (method B) gave monomer **4d** in 50% yield, dimer **5d** in 26% yield, and trimer **6d** in 9% yield.[20,21]

Like **3a–c**, subjecting dioxinone **3e** (OR = OH) to method B cyclization conditions resulted in dimer (20-membered **5e**; see X-ray data in Table I) and trimer (30-membered

(15) Dimeric macrolactones resulting from photogenerated hydroxyketenes have been reported: Quinkert, G.; Billhard, U.-M.; Jakob, H.; Fischer, G.; Glenneberg, J.; Nagler, P.; Autze, U.; Heim, N.; Wacker, M.; Schwalbe, T.; Kurth, Y.; Bats, J. W.; Dürner, G.; Zimmermann, G.; Kessler, H. *Helv. Chim. Acta* **1987**, *70*, 771–862.

(16) When the addition time was prolonged to 4.5 days, the decarboxylation product [*cis*-(7-hydroxy-5-hepten-1-yl)methyl ketone results. Trace water contamination in this macrolactonization reactions leads to the formation of hydroxy ketone i and is presumably the consequence of water intercepting the acylketene intermediate to give the corresponding b-keto-ω-hydroxy carboxylic acid which undergoes subsequent thermal decarboxylation to i: IR (neat) 3415 (br OH), 17.12 (C=O) cm^{-1}; ^{1}H-NMR δ 1.29–1.44 (m, 2 H), 1.52–1.65 (m, 2 H), 2.04 (s, 3 H), 2.08 (q, 2 H, J = 7 Hz), 2.43 (t, 2 H, J = 7 Hz), 4.19 (m, 2 H), 5.43–5.66 (m, 2 H), (note: OH proton not observed); ^{13}C-NMR δ 23.21, 27.09, 28.98, 29.88, 43.43, 58.47, 128.80, 132.34, 209.12] was isolated in 40% yield together with trace amounts of the monomeric β-keto lactone **4a** [^{1}H-NMR: δ 1.43–1.52 (m, 2 H), 1.60–1.70 (m, 2 H), 2.11 (dt, 2 H, J = 6.5, 7), 2.56 (t, 2 H, J = 7), 3.40 (s, 2), 4.66 (d, 2 H, J = 4.5), 5.72–5.84 (m, 2 H)] and the yields of **5a** and **6a** were decreased to 31 and 4%, respectively.



i

(17) Indeed, the free energy difference between *endo*-(*E*)- and *endo*-(*Z*)-cycloundecene in acetic acid at 373.6 K is +0.67 kcal/mol. See: Cope, A. C.; Moore, P. T.; Moore, W. R. *J. Am. Chem. Soc.* **1959**, *81*, 3153.

(18) Grant, B.; Djerassi, C. *J. Org.* **1974**, *39* (7), 968–70.

(19) Vogel, A. I. *J. Chem. Soc.* **1943**, 636–47.

6e) formation in 60 and 26% yields, respectively. None of the monomeric product 4e was detected.

It appears that (ω-hydroxyalkylketenes derived from substrates like 3 are quite sensitive to transition-state conformational effects as manifested by "ring" size.[22] Even under high dilution condition ($<10^{-4}$ M) only 3d produces monomeric product 4d (12-membered ring); 3a–c and 3e give only dimeric (5; 22- and 20-membered rings, respectively) and trimeric (6; 33- and 30-membered rings, respectively) products. Further implications of this chemistry will be reported in due course.

Experimental Section

General. Tetrahydrofuran (THF) and toluene were refluxed over and distilled from sodium–potassium immediately prior to use. Hexamethylphosphoric triamide (HMPA) was distilled from and stored over CaH_2. 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one was distilled under vacuum (63–64 °C/1–2 mm) and stored at −4 °C. All reactions were conducted under a nitrogen or argon atmospheres and normal workup consisted of washing extracts with water and brine, drying over $MgSO_4$, filtration, and concentration on a rotary evaporator at water aspirator pressure. Flash chromatography refers to the procedure of Still *et al.*[23] Preparative TLC was performed on 0.25 × 200 × 200 mm general-purpose, precoated silica gel glass plates. Melting points are uncorrected. All NMR spectra were measured in $CDCl_3$ unless otherwise noted. ^{1}H- and ^{13}C-NMR spectra were measured at 300 and 75 MHz, respectively, and chemical shifts are reported in ppm downfield from internal tetramethylsilane. Elemental analyses were performed at the MidWest Microlab, Indianapolis. Mass spectra were obtained with VG TRIO2 (high resolution; VG-11-250 data system) and VG ZAB-HS-2F (FAB) analytical instruments by Dr. Dan Jones (Facility for Advanced Instrumentation, University of California, Davis). X-ray crystallographic data were collected on automated Siemens R3m/V (5a–5c) or P4RA (5e) diffractometers and the structures were solved by direct methods and refined by the full-matrix least-squares method with the aid of SHELXTL PLUS programs.[24]

General Procedure. Preparation **of 6-(ω-Hydroxyalk-1-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3a–e).** A solution of lithium diisopropylamide in THF/heptane/ethylbenzene (0.75 mL; 2.0 M, 1.5 mmol) at 0 °C was diluted with THF (2 mL) and HMPA (296 mg, 1.65 mmol). 2,2,6-Trimethyl-4*H*-1,3-dioxin-4-one (1; 213 mg, 1.5 mmol, in 1mL THF) was added dropwise over a period of 5 min and the resulting light orange solution was stirred at 0 °C for 30 min. A solution of iodoalkyl silyl ether 2 (1 mmol) in THF (1 mL) was added dropwise over 10 min and the mixture was allowed to slowly warm to room temperature and stirred an additional 14 h. The mixture was concentrated by rotary evaporation and the residue partitioned between ether (10 mL) and satuated NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with ether (2 × 5 mL), acidified to pH 6, and extracted again (ether; 2 × 5 mL). Normal workup of the combined ethereal layers gave a yellow oil which was purified by flash chromatography on silica gel (1:8 EtOAc/hexanes) to give silyl-protected dioxinone 3 (OR = OSi(ᵗBu)Me_2; 25–54% yield).

To silyl-protected dioxinone 3 (1 mmol) in THF (1.5 mL) at room temperature was added dropwise of a solution of tetrabutylammonium fluoride (1.0 M in THF, 1.5 mmol, 1.5 mL). After stirring 2 h at room temperature, the mixture was concentrated by rotary evaporation and the residue partitioned between ether (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with ether (6 × 5 mL). Normal workup of the combined ethereal layers gave a yellow oil which was purified by flash chromatography on silica gel (1:2 EtOAc/hexanes) to give dioxinone 3 (OR = OH; 76–87% yield).

***cis*-6-(7-Hydroxy-5-hepten-1-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3a)** was prepared in 45% yield from 2a: IR (neat) 3431 (br), 3002 (m), 2936, 2863, 1728, 1632, 1391 cm^{-1}; ^{1}H-NMR δ 1.36–1.49 (m, 2 H), 1.49–1.63 (m, 2 H), 1.66 (s, 6 H), 2.12 (dt, 2 H, J = 70, 6.0 Hz), 2.22 (t, 2 H, J = 7.5 Hz), 4.21 (d, 2 H, J = 7 Hz), 5.22 (s, 1 H), 5.46–5.56 (m, 1 H), 5.58–5.68 (m, 1 H) [note: OH proton not detected]; ^{13}C-NMR δ 24.70 (*gem*-dimethyls), 24.93, 26.64, 28.53, 33.11, 57.94, 92.83, 106.07, 129.16, 131.17, 161.40, 171.75. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.05; H, 8.39.

***trans*-6-(7-Hydroxy-5-hepten-1-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3b)** was prepared in 30% yield from 2b: IR (neat) 3424 (br), 3001 (w), 2936, 2860, 1727, 1632, 1391 cm^{-1}; ^{1}H-NMR δ 1.28–1.38 (m, 1 H) 1.38–1.49 (m, 2 H), 1.50–1.62 (m, 2 H), 1.67 (s, 6 H), 2.03–2.11 (dt, 2 H *J* = 7.0, 5.8 Hz), 2.21 (t, 2 H, *J* = 7.5 Hz), 4.10 (m, 2 H), 5.22 (s, 1 H), 5.58–5.72 (m, 2 H); ^{13}C-NMR δ 24.73 (*gem*-dimethyls), 24.89, 28.15, 31.46, 33.15, 63.03, 92.82, 106.09, 129.49, 131.47, 161.37, 171.83. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.08; H, 8.44.

6-(7-Hydroxyheptan-1-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3c) was prepared in 28% yield from 2c: IR (neat) 3435 (br), 2999, 2933, 2858, 1728, 1632, 1392 cm^{-1}; ^{1}H-NMR δ 1.30–1.40 (br m, 7 H), 1.49–1.62 (m, 4 H), 1.66 (s, 6 H), 2.20 (t, 2 H, *J* = 7.5 Hz), 3.62 (dt, 2 H, *J* = 3.4, 6.1 Hz) 5.21, (s, 1 H); ^{13}C-NMR δ 24.59 (*gem*-dimethyls), 25.22, 25.27, 28.54, 28.64, 32.18, 33.18, 62.05, 92.60, 105.96, 161.35, 172.01. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.54; H, 9.20.

6-(8-Hydroxyoctan-1-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3d) was prepared in 25% yield from 2d: IR (neat) 3436 (br), 2998, 2930, 2857, 1728, 1633, 1388 cm^{-1}; ^{1}H-NMR δ 1.32 (br m, 8 H), 1.47–1.65 (m, 4 H), 1.67 (s, 6 H), 2.20 (t, 2 H, *J* = 7.6 Hz) 3.63 (dt, 2 H, *J* = 4.8, 6.2 Hz), 5.22 (s, 1 H) [note: OH proton not detected]; ^{13}C-NMR δ 24.81 (*gem*-dimethyls), 25.49, 28.68, 28.95, 29.01, 32.46, 33.38, 62.51, 92.84, 106.10, 161.41, 172.06 [note: two methylene carbons are coincident at δ 25.49 in this ^{13}C spectrum]. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: 65.44; H, 9.44.

6-(6-Hydroxyhexan-1-yl)-2,2-dimethyl-4*H*-1,3-dioxin-4-one (3e) was prepared in 28% yield from 2e: IR (neat) 3436 (br), 2996, 2932, 2858, 1728, 1631 cm^{-1}; ^{1}H-NMR δ 1.32–1.37 (m, 4 H), 1.51–1.58 (m, 4 H), 1.65 (s, 6 H), 2.19 (t, 2 H, *J* = 7.5 Hz), 3.61 (t, 2 H, *J* = 6.5 Hz), 5.20 (s, 1 H) [note: OH proton not detected]; ^{13}C-NMR δ 24.67 (*gem*-dimethyls), 25.09, 25.36, 28.42, 32.10, 33.19, 62.06, 92.70, 105.99, 161.26, 171.93. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C 62.98, H 8.81.

General Procedure. Thermal Cycloreversion/Macrocyclization. Method A. A solution of 6-(ω-hydroxyalkyl)-dioxinone 3 (51 mg, 0.2 mmol) in toluene (1.5 L; ≃10^{-4} M) was refluxed for 3 h. The reaction mixture was cooled to room temperature and concentrated by rotary evaporation. The residue was purified either by flash chromatography on silica gel using a stepwise increase in eluent polarity (1:4 → 1:3 → 1:2 EtOAc/hexanes) or preparative TLC (1:2 EtOAc/hexanes).

General Procedure. Thermal Cycloreversion/Macrocyclization. Method B. A solution of 6-(ω-hydroyalkyl)dioxinone 3 (51 mg. 0.2 mmol) in toluene (40 mL) was added dropwise over 2 h to refluxing toluene (1.5 L; xylene was substituted for toluene in the case of 3a) with rapid stirring. The resulting solution was refluxed and stirred for 3 h at which time the reaction mixture was cooled to room temperature and concentrated by rotary evaporation. The residue was purified either by flash chromatography on silica gel using a stepwise increase in eluent polarity (1:4→1:3→1:2 EtOAc/hexanes) or preparative TLC (1:2 EtOAc/hexanes).

***cis*-1,12-Dioxacyclodocosa-9,20-diene-2,4,13,15-tetraone (5a)** was obtained in 56 and 51% yields (method A and method B,

(20) It is interesting to contrast our 12-membered ring macrolactonization results (i.e., 3d → 4d) with those reported using the Corey/Nicolaou (12-membered macrolide in 47% yield and the 24-membered dilide in 30% yield: Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614–6) and Mukaiyama (12-membered macrolide in 61% yield and the 24-membered dilide in 24% yield: Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49–50) methods.

(21) Interestingly, 4d is thermally stable as subjecting this pure monomeric macrolide to the reaction conditions (toluene, 110 °C, 3 h) results in no decomposition and no interconversion to dimer 5d or trimer 6d.

(22) For a review of medium and large ring strains, see: Granik, V. G. *Russ. Chem. Rev.* **1982**, *51*, 119–34.

(23) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–5.

(24) The author has deposited atomic coordinates for 5a-c and 5e with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

respectively): mp 83.6–83.9 °C; IR (KBr) 3024, 2932, 2870, 1728, 1697 cm^{-1}; ^{1}H-NMR (acetone-d_6) δ 1.32–1.47 (m, 4 H), 1.47–1.60 (m, 4 H), 2.14 (dt, 4 H, J = 7.8, 6.0 Hz), 2.56 (t, 4 H, J = 7.5 Hz), 3.50 (s, 4 H), 4.60 (d, 4 H, J = 7.5 Hz), 5.55–5.74 (m, 4 H); ^{13}C-NMR (acetone-d_6) δ 22.80, 27.02, 28.47, 42.27, 49.30, 60.04, 123.54, 137.11, 167.45, 202.60; FAB MS m/e, [M + H]$^+$ = 365. Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74. Found: C, 66.05; H, 7.77. Crystallographic data and refinement parameters for **5a** are given in the Table I.

***cis*-1,12,23-Trioxacyclotritriaconta-9,20,31-triene-2,4,13,-15,24,26-hexaone (6a)** was obtained in 20 and 18% yields (method A and method B, respectively): IR (neat) 3026, 2933, 2863, 1742, 1712 cm^{-1}; ^{1}H-NMR (acetone-d_6) δ 1.32–1.47 (m, 6 H), 1.47–1.65 (m, 6 H), 2.14 (dt, 6 H, J = 7.8, 6.0 Hz), 2.58 (t, 6 H, J = 7.5 Hz), 3.50 (s, 6 H), 4.64 (d, 6 H, J = 7.5 Hz), 5.50–5.73 (m, 6 H); ^{13}C-NMR (acetone-d_6) δ 22.99, 27.16, 28.71, 42.28, 49.28, 49.23, 60.48, 123.88, 135.96, 167.45, 202.62; FAB MS m/e [M + H]$^+$ = 547. Anal. Calcd for $C_{30}H_{42}O_9$: C, 65.92; H, 7.74. Found: C, 66.01; H, 7.89.

***trans*-1,12-Dioxacyclodocosa-9,20-diene-2,4,13,15-tetraone (5b)** was obtained in 48 and 50% yields (method A and method B, respectively): mp 93.3–93.8 °C; IR (KBr) 3042, 2945, 2890, 1745, 1711 cm^{-1}; ^{1}H-NMR δ 1.32–1.42 (m, 4 H), 1.52–1.62 (m, 4 H), 2.03 (dt, 4 H, J = 7.2, 7.0 Hz), 2.50 (t, 4 H, J = 7.1 Hz), 3.39 (s, 4 H), 4.56 (d, 4 H, J = 6.4 Hz), 5.49–5.59 (m, 2 H), 5.72–5.82 (m, 2 H); ^{13}C-NMR δ 22.59, 27.94, 31.80, 42.20, 49.89, 65.62, 123.23, 136.74, 166.74, 202.19; FAB MS m/e, [M + H]$^+$ = 365. Anal. Calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74. Found: C, 66.10; H, 7.78.

***trans*-1,12,23-Trioxacyclotritriaconta-9,20,31-triene-2,4,-13,15,24,26-hexaone (6b)** was obtained in 18 and 18% yields (method A and method B, respectively): IR (neat) 3024, 2737, 2859, 1744, 1715 cm^{-1}; ^{1}H-NMR δ 1.35–1.45 (m, 6 H), 1.55–1.65 (m, 6 H), 2.06 (dt, 6 H, J = 7.2, 7.0 Hz), 2.53 (t, 6 H, J = 7.0 Hz), 3.44 (s, 6 H), 4.58 (d, 6 H, J = 6.5 Hz), 5.50–5.60 (m, 3 H), 5.71–5.81 (m, 3 H); ^{13}C-NMR δ 22.68, 27.86, 31.73, 42.58, 49.34, 65.85, 123.48, 136.35, 166.92, 202.54; FAB MS m/e, [M + H]$^+$ = 547. Anal. Calcd for $C_{30}H_{42}O_9$: C, 65.92; H, 7.74. Found: C, 66.30; H, 7.81.

1,12-Dioxacyclodocosane-2,4,13,15-tetraone (5c) was obtained in 49% yield (method A): mp 107.1–107.4 °C; IR (KBr) 29.26, 28.55, 1740, 1711, 1296 cm^{-1}; ^{1}H-NMR δ 1.22–1.40 (br m, 12 H), 1.54–1.66 (m, 8 H), 2.55 (t, 4 H, J = 7.2 Hz), 3.42 (s, 4 H), 4.16 (t, 4 H, J = 6.0 Hz); ^{13}C-NMR δ 23.06, 25.89, 28.36, 28.90, 28.98, 42.68, 49.84, 65.29, 167.03, 202.31; FAB MS m/e, [M + H]$^+$ = 369. Anal. Calcd for $C_{20}H_{32}O_6$: C, 65.19; H, 8.75. Found: C, 65.11; H, 8.75.

1,12,23-Trioxacyclotritriacontane-2,4,13,15,24,26-hexaone (6c) was obtained in 13% yield (method A): IR (CCl_4) 2935, 2835, 1746, 1719, 1231 cm^{-1}; ^{1}H-NMR δ 1.33 (br m, 18 H), 1.56–1.68 (m, 12 H), 2.54 (t, 6 H, J = 7.1 Hz), 3.43 (s, 6 H), 4.14 (t, 6 H, J = 6.0 Hz); ^{13}C-NMR δ 23.17, 25.54, 28.32, 28.68, 42.89, 49.40, 65.31, 167.24, 202.77; FAB MS m/e, [M + H]$^+$ = 553. Anal. Calcd for $C_{30}H_{48}O_9$: C, 65.19; H, 8.75. Found: C, 65.19; H, 8.69.

Oxacyclododecane-2,4-dione (4d) was obtained in 28 and 50% yields (method A and method B, respectively): IR (CCl_4) 2936, 2860, 1744, 1715, 1252 cm^{-1}; ^{1}H-NMR δ 1.24–1.40 (m, 6 H), 1.40–1.49 (m, 2 H), 1.62–1.74 (m, 4 H), 2.625 (dd, 2 H, J = 6.2, 6.2 Hz), 3.41 (s, 2 H), 4.16 (dd, 2 H, J = 4.8, 5.7 Hz); ^{13}C-NMR δ 21.73, 23.27, 23.73, 24.78, 26.08, 26.49, 40.47, 50.71, 66.30, 166.73, 202.28. High resolution FAB MS m/e, 199.1333, [M + H]$^+$. Calcd for [$C_{11}H_{18}O_3$ + H]$^+$ 199.1334.

1,13-Dioxacyclotetracosane-2,4,14,16-tetraone (5d) was obtained in 41 and 26% yields (method A and method B, respectively): mp 123.7–124.0 °C; IR (KBr) 2930, 2849, 1746, 1709, 1246 cm^{-1}; ^{1}H-NMR δ 1.24–1.42 (br m, 16 H), 1.55–1.68 (m, 8 H), 2.53 (t, 4 H, J = 7.4 Hz), 3.41 (s, 4 H), 4.15 (t, 4 H, J = 6.0 Hz); ^{13}C-NMR δ 23.58, 25.90, 28.46, 28.77, 28.90, 29.04, 42.68, 49.73, 65.30, 167.00, 202.43. High resolution FAB MS m/e, 397.2602, [M + H]$^+$. Calcd for [$C_{22}H_{36}O_6$ + H]$^+$ 397.2590.

1,13,25-Trioxacyclohexatriacontane-2,4,14,16,26,28-hexaone (6d) was obtained in 12 and 9% yields (method A and method B, respectively): IR (CCl_4) 2932, 2856, 1744, 1717, 1233 cm^{-1}; ^{1}H-NMR δ 1.25–1.38 (br m, 24 H), 1.50–1.70 (m, 12 H), 2.52 (t, 6 H, J = 7.2 Hz), 3.42 (s, 6 H), 4.12 (t, 6 H, J = 6.5 Hz); ^{13}C-NMR δ 23.40, 25.71, 28.46, 28.77, 28.80, 29.00, 42.84, 49.45, 65.46, 167.18, 202.54; FAB MS m/e, [M + H]$^+$ = 595. Anal. Calcd for $C_{33}H_{54}O_9$: C, 66.64; H, 9.15. Found: C, 66.40; H, 9.11.

1,11-Dioxacycloeicosane-2,4,12,14-tetraone (5e) was obtained in 55% yield (method A): mp 117.6–117.8 °C; IR (KBr) 2962, 2853, 1744, 1711 cm^{-1}; ^{1}H NMR δ 1.30–1.41 (m, 8 H), 1.56–1.68 (m, 8 H), 2.53 (t, 4 H, J = 7.5 Hz), 3.42 (s, 4 H), 4.15 (t, 4 H, J = 6.0 Hz); ^{13}C-NMR δ 23.62, 25.65, 28.31, 28.44, 42.54, 49.73, 65.15, 166.96, 202.27; FAB MS m/e, [M + H]$^+$ = 341.

1,11,21-trioxacyclotriacontane-2,4,12,14,22,24-hexaone (6e) was obtained in 22% yield (method A): IR (CCl_4) 2936, 28.60, 1744, 1718, 1230 cm^{-1}; ^{1}H NMR δ 1.30–1.41 (m, 12 H), 1.56–1.68 (m, 12 H), 2.53 (t, 6 H, J = 7.2 Hz), 3.42 (s, 6 H), 4.15 (t, 6 H, J = 6.4 Hz); ^{13}C-NMR δ 23.28, 25.57, 28.33, 28.45, 42.69, 65.22, 167.11, 202.29; FAB MS m/e, [M + H]$^+$ = 511.

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Supplementary Material Available: ^{1}H-NMR data for **4d**, **5d**, **5e**, and **6e**; full details of X-ray crystallographic analyses for compounds **5a–c** and **5e** (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.