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CYCLIC OLIGOLIDES VIA ACYLKETENE MEDIATED LACTONIZATION: SYNTHESIS AND CHARACTERIZATION.

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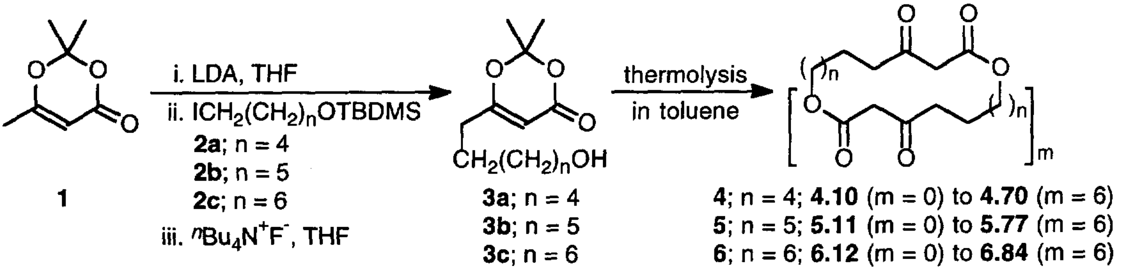
Abstract: An acylketene mediated cyclization protocol delivers a series of cyclic oligolides, the largest characterized cyclic oligolide having a 77-membered ring. 6-(ω-Hydroxyalkyl)dioxinone analogs were prepared and cyclizations were conducted under a variety of conditions in refluxing toluene. ^{1}H-NMR, ^{13}C-NMR, and several different mass spectrometric techniques were employed to verify the cyclic nature of these oligolides. Copyright © 1996 Elsevier Science Ltd

An interesting strategy for macrolide synthesis exploits the 2,2-dimethyl-6-(ω-hydroxyalkyl)-4*H*-1,3-dioxin-4-one derived acylketene which suffers intramolecular addition by the ω-hydroxyl moiety to form a β-ketolactone. General and quite high yielding, this strategy[1] proceeds by thermal decomposition of the "diketene-acetone" adduct[2] in refluxing toluene generating acetone and the highly reactive acylketene.[3,4] Drawing on the work of Boeckman,[5] Petasis,[1] and Ley,[6] we set out to prepare β-ketomacrolides (cf., **4** m = 0) by an acylketene mediated lactonization from **3** (**Scheme 1**), but obtained cyclic oligolides instead.

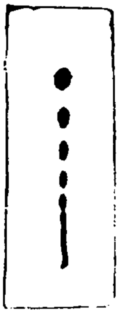
Scheme 1: cyclic oligolide preparation.

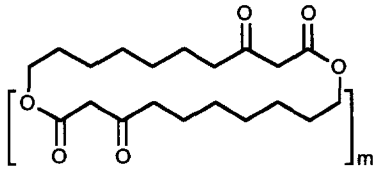


Dioxinone substrates **3a-c** were prepared from commercially available 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**1**) by Cγ-alkylation.[7,8] Two high dilution thermolysis protocols were employed with the goal of obtaining macrolides **4.10**, **5.11**, and **6.12**. In METHOD A, 6-(w-hydroxyalkyl)-dioxinone **3** (~0.2 mmol) was dissolved in toluene (1.7 L; ~10^{-4} M in **3**) and the resulting solution heated to reflux for 3 h. In METHOD B, a toluene solution of **3** (~0.2 mmol; 10^{-3} M in toluene) was added dropwise (over as long as a 5 d period) to refluxing toluene (1.7 L) with continued refluxing for an additional 2 h.

To our initial surprise, thin layer chromatographic (TLC) analysis of the crude reaction mixture (**Figure 1**) indicated formation of a complex mixture of products as evidenced by a strikingly ordered series of TLC spots. This was particularly apparent when a 10^{-1} or 10^{-2} M toluene solution of substrate **3** was thermalized (METHOD C). Preparative TLC of this reaction mixture yielded a series of products, the more polar of which proved increasingly difficult to isolate from neighboring bands. Nevertheless, in the case of **3b** (n=5), six products were isolated. The ^{1}H- and ^{13}C-NMR spectra of these compounds are nearly superimposable indicating that **5.22-5.77** compose an oligomeric series[9] and the symmetry implied by these NMR data preclude a series of oligomeric straight chain compounds.

Figure 1: TLC (42:58::ethyl acetate:hexane) showing the cyclic oligolide series obtained from METHOD C. The top spot is the 22-membered dimer **5.22**. Each successively lower R_f spot represents the addition of one more oligolide unit (e.g., the fifth spot from the top is the 66-membered cyclic hexolide **5.66**).





5.11; m = 0 (11-membered macrolide)
5.22; m = 1 (22-membered oligolide)
5.33; m = 2 (33-membered oligolide)
5.44; m = 3 (44-membered oligolide)
5.55; m = 4 (55-membered oligolide)
5.66; m = 5 (66-membered oligolide)
5.77; m = 6 (77-membered oligolide)

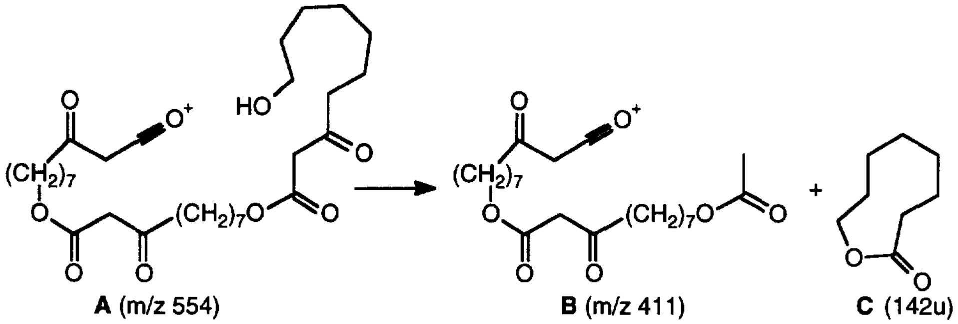
Though ^{1}H- and ^{13}C-NMR data are consistent with cyclic oligolide structures, verification required fast atom bombardment (FAB) mass spectral analysis. In the thermolysis of **3b**, the highest R_f product proved to be cyclic diolide **5.22** (22-membered cyclic oligolide; X-ray structure).[7] Monomeric macrolide **5.11** (11-membered macrolide) was not obtained using METHODS A, B, or C. The lowest isolable R_f product from **3b** proved to be 77-membered heptolide **5.77** (TLC band six)! Bands 2 through 5 proved to be 33- (i.e., **5.33**) through 66-membered (i.e., **5.66**) cyclic oligolides, respectively.

To further characterize these cyclic oligolides, collisionally induced dissociation (CID) experiments were undertaken. While the fragmentation patterns discussed below are mirrored in the FAB experiments, CID fragments clearly come from one parent molecular ion. These experiments, using argon or nitrogen as the collision gas, show several fragmentation patterns consistent with cyclic oligolide structures. One key CID fragmentation is loss of one or more monomeric units ($C_{10}H_{16}O_3$, 184u) from the molecular ion; another is the loss of one or two water molecules. For example, CID analysis of **5.44** (44-membered cyclic tetrolide; MH^+ = m/z 737.5) shows daughter ions at m/z 553.5 [MH^+ - ($C_{10}H_{16}O$)], m/z 369 [MH^+ -

$2x(C_{10}H_{16}O)]$, and m/z 185 [MH^+ - $3x(C_{10}H_{16}O)$]. Each daughter ion loses one or two neutral water molecules; i.e., m/z 554 leads to fragments of m/z 536 and m/z 517.

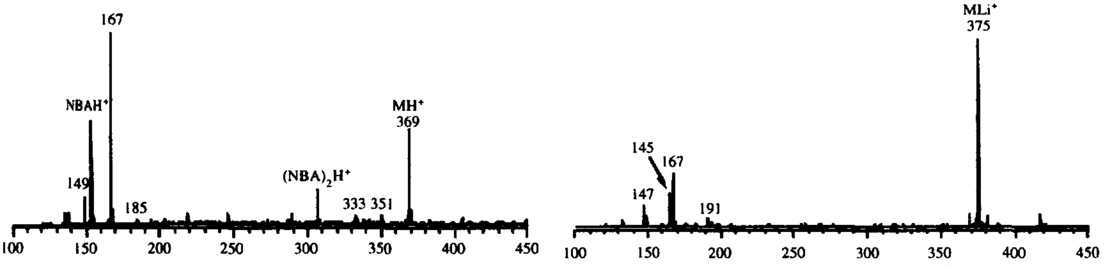
A third fragmentation addressed the unlikely possibility of catenane products. This third process results from attack of an intermediate ω-OH (see ion **A**) on the nearest ketone carbonyl which leads to C—C bond fragmentation to give fragment ion **B** together with a neutral lactone moiety (**C**; **Scheme 2**). For example, CID on **5.44** (MH^+ = m/z 738) gives fragmentation peaks at m/z 596, m/z 411, and m/z 227 representing the loss of a neutral lactone fragment (142u; $C_8H_{14}O_2$) from the molecular ion m/z 738 (→ m/z 596) as well as from daughter ions m/z 554 (→ m/z 411) and m/z 369 (→ m/z 227). This is illustrated in **Scheme 2** for daughter ion **A** (m/z 554) fragmenting to ion **B** (m/z 411) and neutral lactone **C** (142u). Dissociation of the two rings of a catenane would result in loss of one β-ketolactone unit (184u), not the observed loss of a lactone unit (142u).[10]

Scheme 2: fragmentation leading to neutral lactone fragment **C** (142u).



In the course of these mass spectrometry studies, we noticed that a number of these oligomacrolides exhibited intriguing metal trapping capabilities. **Figure 2** shows the FAB mass spectra of 22-membered dimeric cyclic oligolide **5.22** collected in the absence and presence of added lithium cation. In addition to the expected $[M+H]^+$ peak at m/z 369 in this spectrum, the base peak in this spectrum is the $[M+Li]^+$ ion at m/z 375. Additional interesting oligomacrolide dependent results were observed in the mass spectrometry data of oligomacrolides **4-6** in the presence of lithium as well as other metal cations.[11]

Figure 2: FAB mass spectra collected in the absence (left) and in the presence (right) of lithium cation.



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