A LEWIS ACID MEDIATED INTRAMOLECULAR [2+2] CYCLOADDITION OF 3-(9-METHYLUNDECA-7,9-DIENYL)-9-METHYLENE-2,8-DIOXABICYCLO-[4.3.0]NONANE-5,7-DIONE

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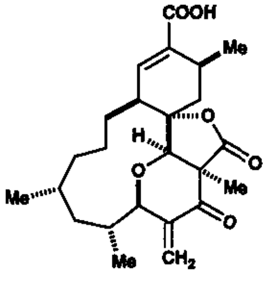
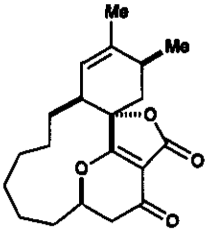
Abstract - Treatment of 3-(9-methylundeca-7,9-dienyl)-9-methylene-2,8-dioxabicyclo[4.3.0]nonane-5,7-dione (**3**) with $SnCl_4$ in CH_2Cl_2 at -80°C produced intramolecular [2+2] cycloadducts (**6a-d**) rather than intramolecular Diels-Alder adducts.

In a project directed toward the synthesis of the antibiotic okilactomycin (**1**),[1] we have been interested in utilizing an intramolecular Diels-Alder technique for a simultaneous construction of the macro-ring as well as the spirolactone system having the correct stereochemistries. Conceptually, the same strategy has previously been employed in our total synthesis of chlorothricolide.[2] This report describes a model cycloaddition study performed with compound (**3**), resulting in formation of the intramolecular [2+2] cycloadducts (**6a-d**), rather than the desired Diels-Alder adduct (**2**).



1



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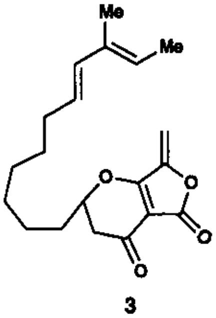
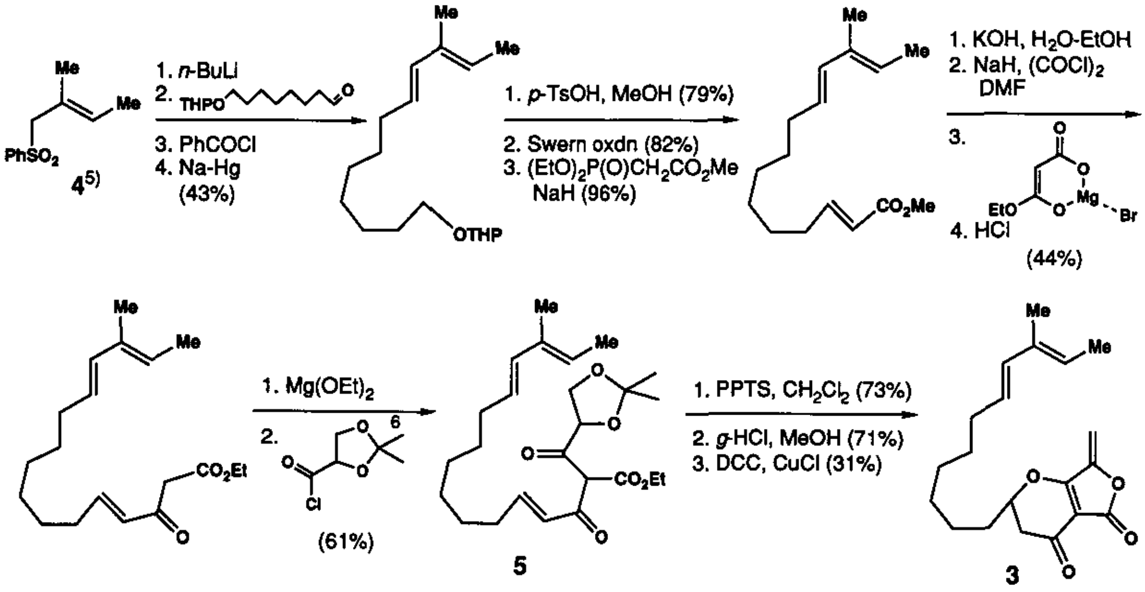


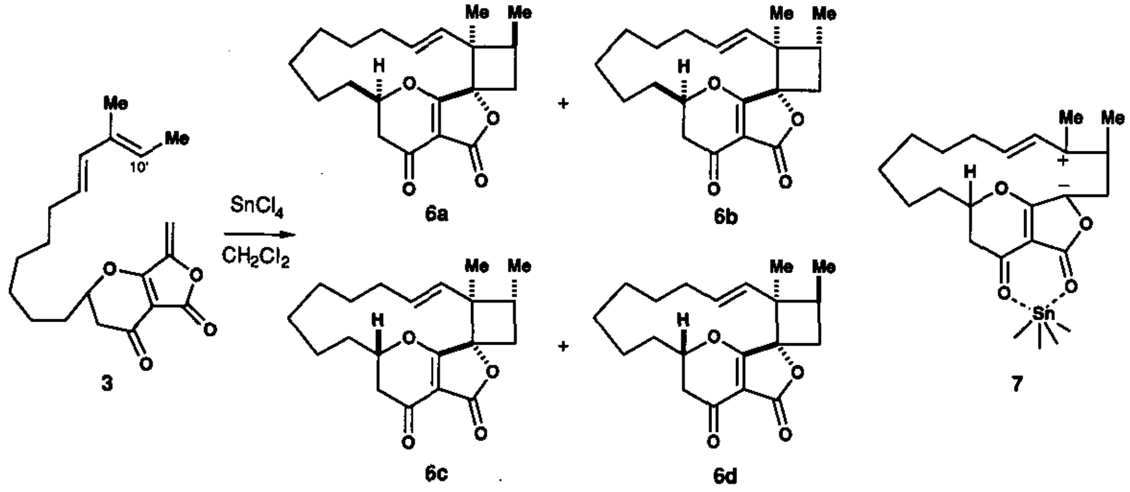
3

The substrate (**3**) was prepared as outlined in Scheme 1, in which formation of the 2,8-dioxabicyclononanedione skeleton was effected by a two-step acid-catalyzed cyclization of γ,δ-unsaturated α-dioxolanylcarbonyl-β-ketoester (**5**) which was obtained according to the Gelin's procedure.[4]



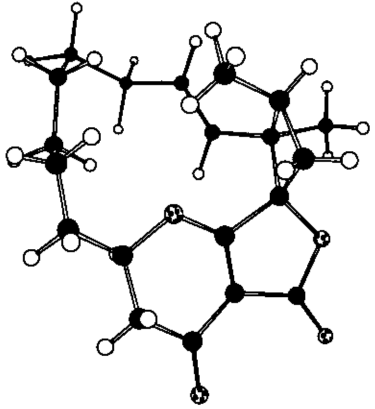
Scheme 1[3]

Since **3** proved to be thermally unstable, readily undergoing polymerization, the cycloaddition was carried out at low temperature (-80°C) in CH_2Cl_2 (8 mM) in the presence of $SnCl_4$ (1 equiv.) for 90 min. Under the conditions, there were produced four diastereomeric [2+2] cycloadducts (**6a-d**) in a ratio of *ca.* 3.5:1:1:1 (*ca.* 30% yield[7]) (Scheme 2).

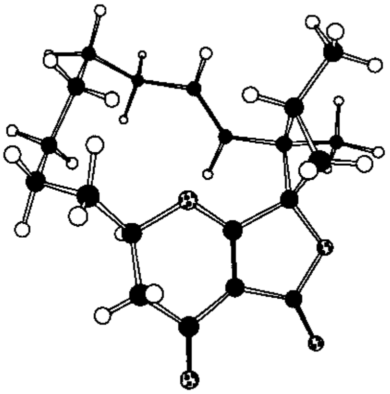


Scheme 2[3]

The unprecedented cyclobutane structures fused to a 13-membered ring were confirmed by a single crystal X-ray analysis[8] on **6a** and **6b**. The structures of **6c** and **6d**, which unfortunately could not be obtained as suitable crystals for X-ray analysis, were determined by comparison of their ^1H nmr spectra with those of **6a** and **6b**. The unexpected formation of [2+2] cycloadducts can be interpreted, as analyzed by molecular models, by an easy access of the C(10') olefinic center and the exo-methylene group of the butenolide without severe distortion of the molecule leading to a stabilized dipolar intermediate (**7**). On the other hand, it seems to be relatively difficult to align the diene and the dienopile in the proper geometry for a concerted [4+2] cycloaddition. There is no reported example[9] where cyclobutane ring is formed in intramolecular [2+2] cycloaddition accompanying by formation of macrocyclic ring. Further studies are underway to define the scope and limitations of this type of intramolecular [2+2] cycloaddition.



6a



6b

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2 K. Takeda, Y. Igarashi, K. Okazaki, and E. Yoshii, *J. Org. Chem.*, 1990, **55**, 3431.
3. All compounds are racemic.
4. P. Pollet and S. Gelin, *Synthesis,* 1978, 142; B. Chantegrel, A-I. Nadi, and S. Gelin, *ibid.,* 1983, 948; S. Gelin and R. Gelin, *Bull. Soc. Chim. Fr.*, 1968, 288.
5. P. J. Kocienski, B. Lythgoe, and I. Waterhouse, *J. Chem. Soc., Perkin Trans. I,* 1980, 1045.
6. A. Tanaka and K. Yamashita, *Agric. Biol. Chem.*, 1980, 44, 199.
7. The main side reactions were polymerization of compound (3).
8. **6a** : FW = 330.42, Monoclinic $P2_1/a$, a = 15.870(1), b = 8.061(1), c = 14.879(1)Å, β = 112.46(1)°, V = 1759.1(2)$Å^3$, Z = 4, Dc = 1.248 Mgm^{-3}, R = 0.048 for 2608 reflections. **6b** : FW = 330.42, Monoclinic A2/a, a = 28.875(4), b = 6.820(2), c = 19.572(2)Å, β = 108.56(1)°, V = 3653(1)$Å^3$, Z = 8, Dc = 1.201 Mgm^{-3}, R = 0.068 for 2724 reflections Detailed crystallographic analyses will be published elsewhere.
9. For non-photochemical [2+2] cycloaddition; see P. G. Gassman and A. C. Lottes, *Tetrahedron Lett.*, 1992, **33**, 157, and references cited therein.

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