

A simple synthesis of cytotoxic endoperoxide lactones

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Abstract—A series of dihydrobenzofuran-2-one **3** have been submitted to various dienophiles: whereas maleic anhydride led only to the adducts **4a,b**, singlet oxygen gave the expected new endoperoxide lactones **5a–d**, **6** and **7a,b**, three of them showing interesting cytotoxicity towards various cancer cell lines.

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The one-pot, double nucleophilic addition of bis (TMS) ketene acetals **2** to a carbon–carbon double bond of a series of arene chromium tricarbonyl complexes **1** ($R = H, iPr, tBu, OPh, SiMe_3$) induced successively by $tBuOK$ and I_2 , led in satisfactory yields (from 24% to 71%) to the bi- and tri-cyclic dienes **3**^{1a–c} (Scheme 1).

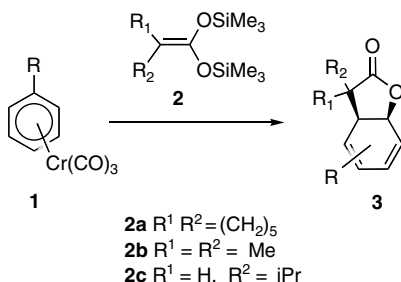
Most of these compounds are however unstable due to the presence of the easy-to-cleave lactone function. They undergo indeed a facile rearomatization to the corresponding arylacetic acids in the presence of weak acids, precluding their purification even by silica gel chromatography. We thought that a way to stabilize these lactones would be to carry out 4 + 2 cycloadditions

involving either olefines or oxygen.^{2,3} If successful, such transformations would not only allow for the preservation of the lactone function, but also give access in the case of oxygen to a potentially important class of compounds, endoperoxide lactones. Indeed, whereas peroxide-containing substrates already show for some of them important cytotoxic properties,⁴ peroxide-containing lactones are among the most active substrates towards *Plasmodium falciparum* malaria parasite,^{5–9} but are now also recognized as potent cytotoxic substrates,¹⁰ inhibitors of the mitochondrial respiratory chain,¹¹ for their activity against fungal pathogens,¹² AIDS opportunistic parasitic infections,¹³ and their antiviral properties.¹⁴

In this letter, we disclose a series of transformations which demonstrate that such reactions can indeed lead to stable cycloadducts, and that moreover, the new polycyclic peroxide lactones revealed interesting cytotoxic properties.

The interaction of the dienes **3** ($R = H, R_1R_2 = C_5H_{10}$ or $R_1R_2 = Me$) with maleic anhydride however did not lead to the expected adducts: whereas no reaction took place at room temperature, decomposition of the dienes into the corresponding acids was observed in refluxing diethyl ether (see Scheme 2).

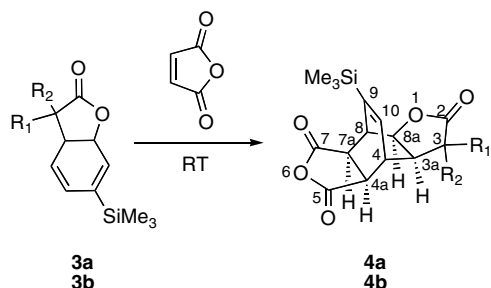
Only the trimethylsilyl-substituted dienes **3a** ($R_1R_2 = C_5H_{10}$) and **3b** ($R_1R_2 = Me$) slowly led, over five days at room temperature, to the adducts **4a** (10%) and **4b**



Scheme 1.

Keywords: Cycloadditions; Endoperoxides; Lactones; Cytotoxicity.

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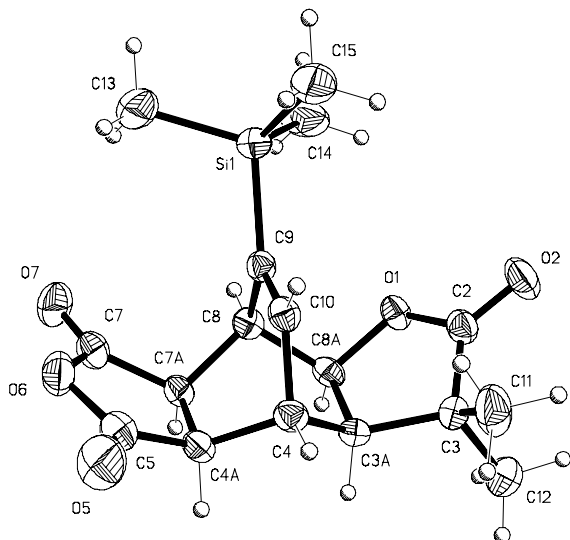
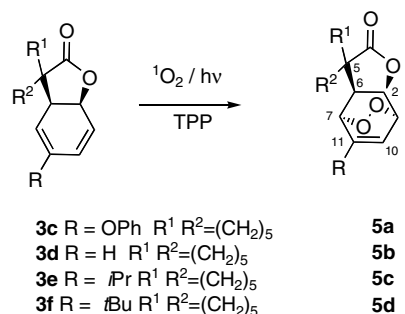


Scheme 2.

(23%) which were characterized both by mass and NMR spectroscopies.¹⁵ The ¹³C NMR spectrum of **4b** confirmed the presence of the anhydride and of the lactone functions with signals at, respectively, δ 171.3, 171.15 and 180.2 ppm. The ¹H NMR spectrum disclosed signals for a vinylic proton at δ 6.57 ppm (d, H₁₀, J = 5.8 Hz), the typical signal at δ 4.86 ppm for the proton geminated to the oxygen of the lactone (dd, H_{8a}, J = 7.4 and 3.6 Hz). The geometry of this adduct was assessed by an X-ray crystal structure determination, an *endo* addition of the double bond to the diene having taken place (Fig. 1).¹⁶

However, singlet oxygen appeared to be a more gratifying reagent since all of the dienes led to rather stable endoperoxides. Thus, irradiation of dichloromethane solutions of the diene **3c** in the presence of catalytic amounts of tetraphenylporphyrin (TPP) and oxygen led after 6 h to a new, more polar crystalline compound which could be purified by silica gel chromatography (58% yield, mp 96–98 °C). Its mass spectrum was in agreement with **5a**, the addition product of molecular oxygen to **3c** (see Scheme 3).

The NMR data of this adduct were in full agreement with structure **5a**.¹⁷ The ¹H NMR spectrum disclosed, besides signals for the aromatic protons, low-field signals for the four protons H₁, H₂, H₇ and H₁₀ whereas

Figure 1. X-ray structure of the adduct **4b**.

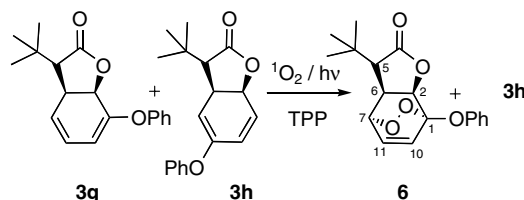
Scheme 3.

the ¹³C NMR spectra confirmed first the presence of a lactone (δ 180.2 ppm), of the double bond of an enol ether with signals at δ 156.9 (C₁₁) and 97.1 (C₁₀), and of three signals for carbons bearing an oxygen atom, at δ 73.1 (C₇), 72.0 (C₁), 70.2 (C₂).

Similarly, the difficult-to-separate 6:5 mixture of the two enolethers **3g** and **3h** was oxidized under the same conditions (see Scheme 4). Fortunate enough, after 1 h of irradiation a complete disappearance of the less polar isomer **3g** was observed leading almost to a single, more polar compound which was easily purified by silicagel chromatography to give a white solid **6** (68% with respect to the starting diene ether), mp 138 °C, **3h** being recovered. The NMR spectra of **6** confirmed the presence of a disubstituted double bond with signals at δ 6.74 (H₁₁, dd, J 9.2 and 5.2 Hz) and 6.47 (H₁₀, d, J = 9.2 Hz) ppm, of signals for two methine groups bearing oxygen at δ 4.80 (H₂, d, J = 7.8 Hz) and 4.66 (H₇, m), the carbon C₁ giving a signal at δ 102.56 confirming thus the presence of two oxygen atoms on the same carbon.¹⁸ The selective addition of oxygen to **3g** rather than to **3h** can be inferred to be due to both electronic and steric factors.^{19,20}

Lactones **3d–f** (R = H, *i*Pr, *t*Bu, R¹R² = C₅H₁₀) led similarly to the lactone peroxides **5b–d** in respectively 95%, 32% and 13% yields. Both their NMR data and their elemental analyses or mass spectra were in agreement with the proposed structures.¹⁷

Finally, the trimethylsilyl-bearing derivatives **3a** and **3b** were also submitted to this transformation: in both cases, satisfactory yields of the expected peroxy lactones **7a** (40%) and **7b** (38%) were obtained (see Scheme 5). For example, the physical data of the crystalline peroxy lactone **7b**, mp 154 °C were in agreement with the suggested structure, the lactone function giving a signal at



Scheme 4.

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