

Efficient Photochemical Transformation of Spiro[4.*n*]-2,5-diones to γ -Alkylidene γ -Butyrolactones: its Relevance to Photostability of Fredericamycin A†

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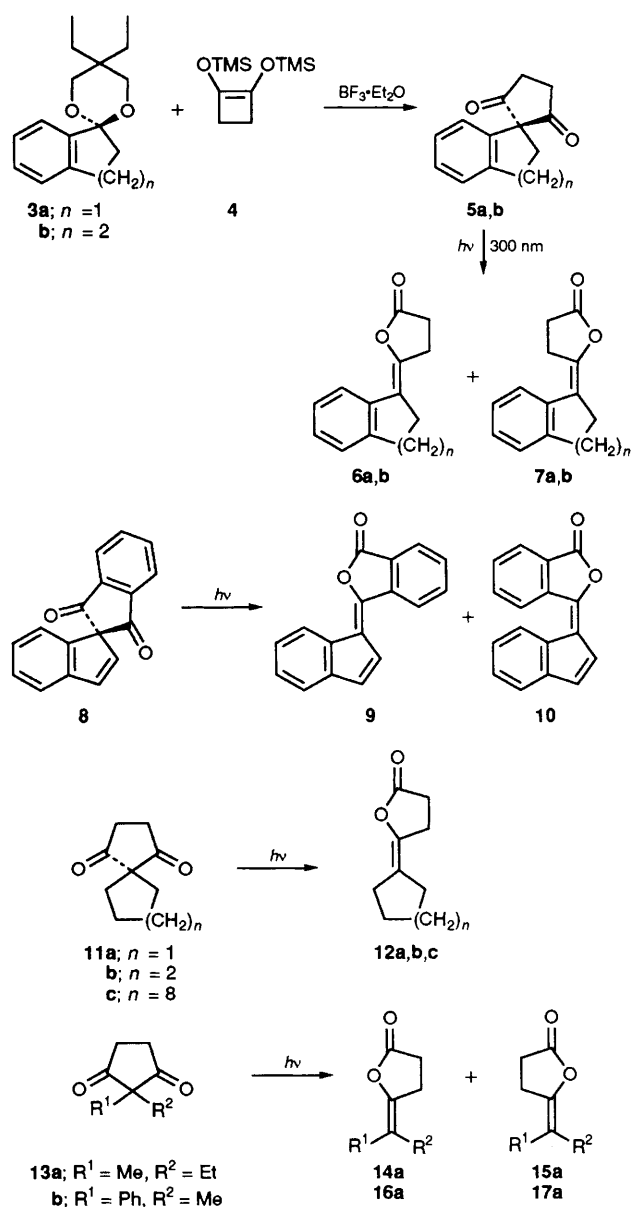
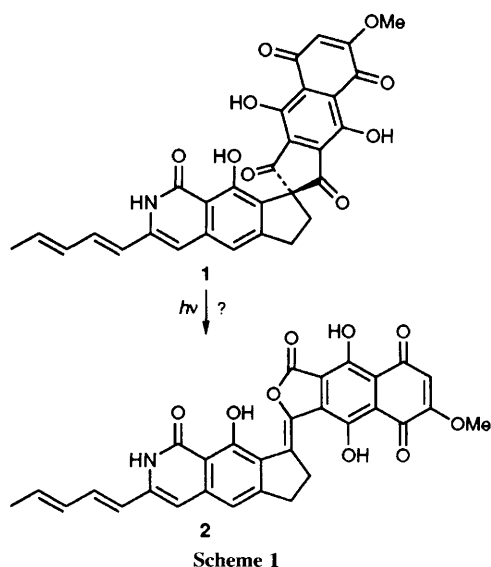
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Irradiation of a variety of model spirodiones related to the antitumour antibiotic Fredericamycin A in various solvents at 300 nm furnishes quantitative yields of γ -alkylidene γ -butyrolactones; its relevance to the typical shape alteration, photostability and consequent biological response of Fredericamycin is discussed.

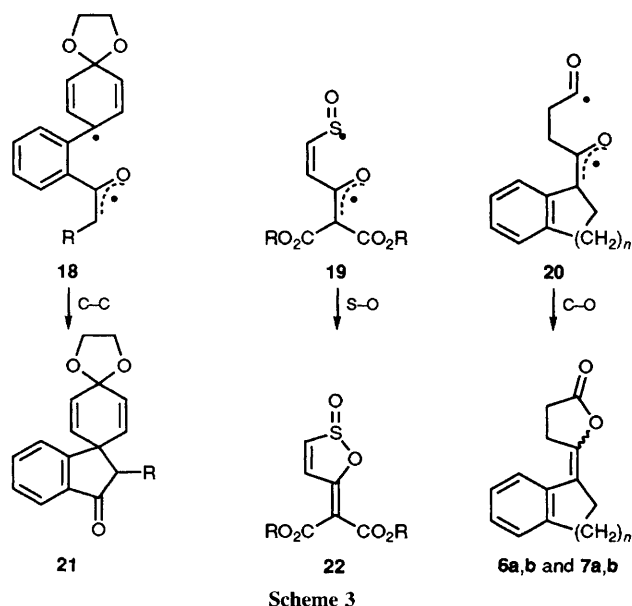
As a part of a programme for the total synthesis of the recently discovered antitumour antibiotic Fredericamycin A **1**, we became interested in the various methodologies for spirodione creation and allied chemistry (Scheme 1).^{1–5} Indeed the typical L-like molecular architecture of **1** is due to its spiro juncture and much of the synthetic efforts were directed towards the creation of this skeleton.^{1,6} Since photostability of biologically relevant compounds is one of the premier concerns of organic chemists,^{7,8} we have investigated the phototransformations of a variety of model spirodiones at 300 nm, which seem to be quite relevant for the shape of Fredericamycin (from L-shape to near planar) and its consequent biological response.⁹ This communication describes efficient phototransformation of a variety of spirodiones and related 2,2-disubstitutedcyclopentane-1,3-diones to synthetically and biologically useful¹⁰ γ -alkylidene γ -butyrolactones and mechanistically contrasts the observation of a series of recent publications from Swenton's group,¹¹ where C–C bond formation is preferred over C–O bond formation, from very similar biradicals in the excited state manifold.

The synthesis of various spirodiones was accomplished as per our recently published methodology involving coupling of 1,2-disilyloxycyclobutene **4** with ethylene glycol ketals of corresponding ketones, in the presence of an excess of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at -78°C (Scheme 2).⁵ However, since the ethylene glycol ketal formation of indan-1-one and α -tetralone is a highly inefficient reaction, the formation of spirodiones **5a** and **5b** involved the coupling of **4** with 2,2-diethylpropane-1,3-diol ketals **3a** and **3b**. To examine the photostability of spirodiones of **5a** or **5b**, irradiation was performed at 300 nm Rayonet (*ca.* 0.1 mol dm^{-3} in dry benzene) for 2 h and quantitative conversion to γ -alkylidene γ -butyrolactones *Z*-**6a,b** (60%) and *E*-isomer **7a,b** (40%) was observed. Indeed, the spiro-

[4.*n*]-2,5-diones to γ -alkylidene γ -butyrolactones phototransformation was found to be quite a general and efficient process. Thus, irradiation of **8**, under identical conditions, furnished a photostationary mixture of **8** (20%), **9** (50%) and **10** (20%). Similarly, other spirodiones *e.g.* **11a,b** and **c** gave >90% isolated yields of **12a**, **12b** and **12c**, respectively after 2–4 h of photolysis in 0.05–0.1 mol dm^{-3} benzene at 300 nm. In continuation, the photolysis of 2,2-disubstitutedcyclopentane-1,3-dione *e.g.* **13a** and **13b** was also examined under identical concentration and irradiation conditions and quantitative conversion to butyrolactones **14a** + **15a** (95%) and **16a**



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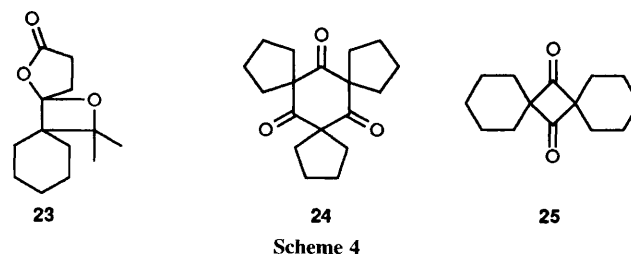


+ **17a** (96%) with *Z* to *E* ratio of 60:40, was observed (Scheme 2). The structures of spirodiones and corresponding *E* and *Z*-butyrolactones were established based on chemical, analytical and spectroscopic evidence.

With a view to enhance the efficiency and gain some mechanistic insight, the progress of phototransformation was examined, (i) by varying solvents *e.g.* benzene, cyclohexane, acetonitrile, methanol, ethanol and *n*-hexane, (ii) by varying concentration of substrates between 0.005 to 0.1 mol dm⁻³, (iii) by examining the effect of variation in irradiation wavelength *e.g.* 254, 300 and 350 nm Rayonet and duration of photolysis, (iv) by using quenchers *e.g.* piperylene and cyclohexa-1,3-diene, and (v) by employing sensitizers *e.g.* acetone, acetophenone and benzophenone.

Thus, the best yields of phototransformation were obtained in the experimental conditions described above. From sensitization and quenching studies, the reaction appears to go from singlet manifold. The mechanism of phototransformation can be visualized as initial efficient α -cleavage,¹² and subsequent bond reorganisation to the biradical **20**, from starting materials **5a** or **5b**, which recombine to form preferentially a C-O bond to yield **6a,b** and **7a,b**, respectively (Scheme 3). Interestingly, in a series of publications from Swenton's group,¹¹ where intermediacy of **18** type biradicals are invoked, preferential C-C bond formation has been proposed, whereas in Margaretha's studies¹³ of similar photochemically generated biradicals **19**, S-O bond formation is preferred. One can argue that the biradicals involving nucleophilic and electrophilic centres similar to Swenton's examples *e.g.* in **18**, recombine to give the preferred C-C bond, whereas the biradicals with both electrophilic termini *e.g.* in our **20** and Margaretha's examples **19**, recombine to give C-O and S-O bonds, respectively (Scheme 3). During sensitization studies of phototransformation of **11b** to **12b** with acetone, a highly efficient chemo- and regio-selective oxetane **23** formation was observed (Scheme 4). It is interesting to note that similarly related spirodiones *e.g.* **24** and **25**, gave decarbonylated products on photolysis and no rearrangement to γ -alkylidene γ -butyrolactones was observed (Scheme 4).¹⁴⁻¹⁶

In conclusion, efficient phototransformation of a variety of model spirodiones related to Fredericamycin A **1**, to γ -alkylidene γ -butyrolactone has been established. Interestingly this efficient phototransformation fits well with the Trost's recently published and highly environmentally desirable concept of developing reactions with 'atom economy selectivity'.¹⁷



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