A Rapid Route to Medium to Large Ring Lactones *via* the Thermolysis of Dispiro-1,2,4-trioxane Derivatives

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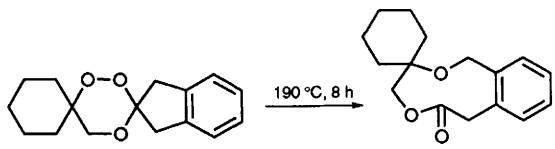
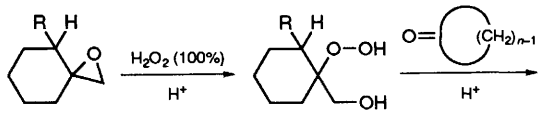
Dispiro-1,2,4-trioxane derivatives **3**, on thermolysis in decane at 190 °C, afford either oxalactones **4**, or ketolactones **5**, or mixtures of both as the predominant ring-expansion products depending on the respective natures of the dispiro substituents.

1,2,4-Trioxanes have attracted considerable recent interest on account of the potent antimalarial activity exhibited not only by the natural product artemisinin (qinghaosu)[1] but also by several simpler trioxane derivatives.[2] In addition to their potential pharmacological properties, several 1,2,4-trioxane derivatives have been shown to undergo selective ring-cleavage reactions to produce in turn α-keto acids,[3] *cis*-diols,[4] 1,2-diol monoesters,[5] benzofurans and benzopyrans[6] as appropriate. Moreover, although thermolysis of several trioxanes had been reported to result in total fragmentation of the peroxide ring,[7,8] a process of limited synthetic utility, the dispiro-trioxane **1** was found to undergo partial ring expansion to give the nine-membered oxalactone **2** in reasonable yield [eqn. (1)].[9] We now report that thermolysis of an extended series of dispiro-substituted trioxane derivatives **3** may give rise to oxalactones **4** or ketolactones **5** depending on the size of ring *C*, and the degree of substitution at the α-position of ring *A*.



1 **2** (50–53%) (1)



3 (2)

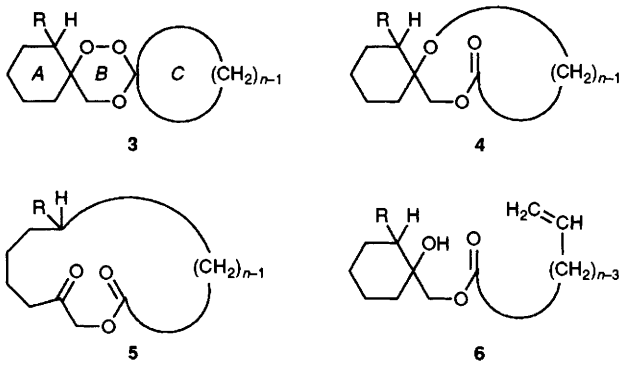


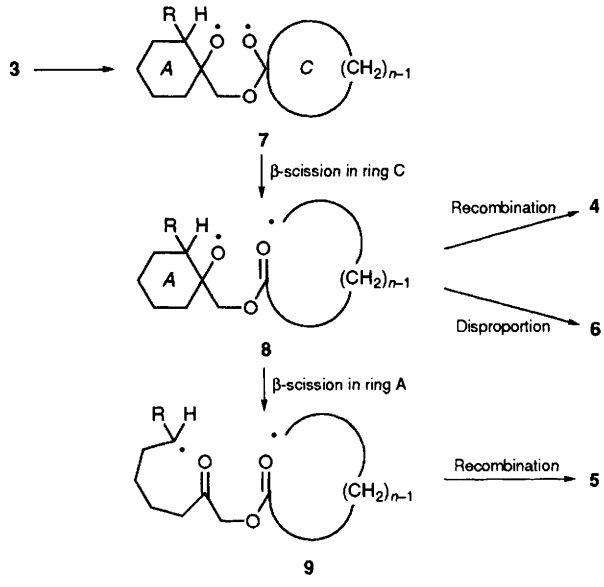
Table 1

Trioxane 3	R	n	Oxalactone 4[a] (%)	Keto-lactone 5 (%)	Hydroxy ester 6 (%)
a	H	5	25 (33)	—	—
b	H	6	24 (32)	—	—
c	H	7	26 (36)	—	—
d	H	12	—	18	—
e	Me	5	15[b]	15	20[b]
f	Me	6	22[b]	15	—
g	Me	7	25[b]	26	6[b]

[a] Figures in parentheses are % yields estimated by quantitative GLC. [b] Inspection of ^1H and ^{13}C NMR spectroscopic data suggests that this compound was isolated as a single diastereoisomer.

The thermolyses of the trioxanes **3**,† prepared from the appropriate methylenecyclohexane oxide as indicated in eqn. (2), were carried out in decane solution (2–5% m/v, scaled tubes, 10 h) at 190 °C. Following removal of solvent by distillation under reduced pressure, the non-volatile rearrangement products‡ were isolated by column chromatography (Table 1). A mechanism, outlined in Scheme 1, based on stepwise radical-scission pathways satisfactorily accounts for the formation of the various rearrangement products **4–6**.

Since trioxanes **3a–3c** produced the corresponding oxalactones **4a–4c** as the sole isolable rearrangement product in each case, the decomposition mechanism should be similar to that for **1**. Thus, after the initial O–O bond homolysis, the resulting dioxyl diradical **7** must have undergone selective β-scission in ring *C* to give the corresponding diradical **8** which in turn rapidly recombined in the solvent cage to provide **4** before ring *A* could open up.§ On the other hand, the formation of the twenty-membered ketolactone **5d** from **3d** suggests that diradical **8d** must have been less confined by the solvent cage and hence had sufficient lifetime to allow the second β-scission process in ring *A* to take place.



Scheme 1

Since the corresponding macrocyclic ketolactones **5e–5g** were obtained as significant components of the product mixture, substitution at the α-position in ring *A* of trioxanes **3e–3g** appeared to have resulted in an increase in the rate of opening of ring *A* in diradicals **8e–8g** as compared to **8a–8c**.¶ In-cage recombination of the diradicals **8e–8g**, producing the oxalactones **4e–4g** as above, remains, nonetheless, a competitive process. Moreover, the formation of the hydroxy esters **6e** and **6g** indicates that the oxyl radical centres in intermediates **8e** and **8g** can participate in long-range hydrogen abstraction processes, presumably facilitated by restrictions on the conformational mobility of the intermediate biradicals imposed by the solvent cage.‖

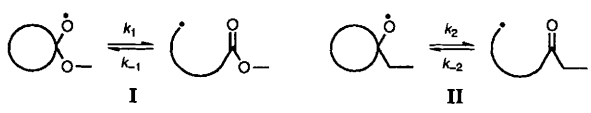
Since naturally occurring macrocyclic lactones exhibit a range of attractive pharmacological and, in simple systems, olfactory properties, considerable effort has been expended in developing synthetic routes to these compounds. Macrocyclic ketolactones similar to **5** have been prepared by conventional methods[14,15] and used as models for the stereochemically controlled introduction of additional functionality.[15]

† All trioxane derivatives, which were either viscous oils or low melting solids, were satisfactorily characterised by ^1H and ^{13}C NMR spectroscopy, and high resolution mass spectrometry.

‡ 1,2,4-Trioxanes **3** were found to have undergone complete decomposition under the reaction conditions specified (*cf.* ref. 10); no starting material was recovered from the corresponding thermolysate. The isolated rearrangement products **4–6** were satisfactorily characterised by ^1H and ^{13}C NMR spectroscopy, and high resolution mass spectrometry. Fragmentation of the central trioxane ring would result in the formation of three carbonyl fragments (*cf.* ref. 7), *e.g.* cyclohexanone, cyclopentanone and formaldehyde would be expected from **3a**. The cycloalkanones in the thermolysate were generally identified qualitatively by GLC in comparison to authentic samples, but were not quantified or isolated since considerable quantities were lost on removal of the decane solvent.

§ Story and coworkers reported that decomposition products obtained from the thermolysis of the corresponding dispiro-1,2,4,5-tetroxane derivatives were more consistent with simultaneous opening in both rings after the initial O–O homolysis (see ref. 11).

¶ Formation of the oxalactones **4** and the hydroxy esters **6** provides circumstantial evidence that the decomposition pathway of trioxanes **3** is stepwise in nature hence suggesting that the overall rate of ring opening of oxyl radicals **I** is significantly greater than that of **II**. Although there are no data available, to our knowledge, on radicals **I**, studies on radicals **II** indicate that the rate of ring opening and the position of the equilibrium between cyclic and acyclic forms, which favours the latter, are dependent on ring size (see ref. 12). The thermolysis results reported above suggest that the differences in relative stability between the cyclic and acyclic forms must be greater for radicals **I** than **II** though an explanation for this apparent difference is unclear. We are currently investigating the natures of radicals **I** and **II** by *ab initio* calculations.



‖ Although oxyl radicals generally participate in intramolecular 1,5-hydrogen abstraction processes *via* kinetically favoured six-membered transition states, several examples of 1,8- and 1,9-hydrogen abstractions have been reported recently (see ref. 13).

Although the yields of totally ring expanded products **5** are modest, this ring expansion approach *via* dispirotrioxanes **3**, derived from readily available epoxides and carbonyl compounds, could provide rapid entry to a variety of medium- to large-ringed lactones once the rules governing the ring-opening processes (**7** → **8** → **9**) have been more fully established.

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