

## Unusual Behaviour of Thermally generated Oxygen 1,3-Diradicals from $\beta$ -Peroxylactones: Stereoselective Synthesis of a Tetrahydrofuran Ring by Intramolecular Hydrogen Abstraction

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Thermolysis of the steroidal  $\beta$ -peroxylactone (**3**) gave ether (**4**), produced by intramolecular hydrogen abstraction from a non-activated carbon; the reaction occurs with complete stereoselectivity by abstraction of the  $C_{7-pro-R}$  hydrogen, and a concerted mechanism is proposed, no free radicals seem to be involved in the reaction since when a true free radical hydrogen abstraction was realized with alcohol (**7**) no selectivity was observed and a mixture of ethers (**4**) and (**8**) was obtained.

Recent years have witnessed a remarkable upsurge of interest among synthetic organic chemists in the preparation of five membered rings by radical processes. Two principal strategies are employed: syntheses of cyclopentane rings through hex-5-enyl radical cyclization,<sup>1</sup> and formation of tetrahydrofuran or pyrrolidine rings by intramolecular functionalization of non-activated carbons.<sup>2</sup>

On the other hand, numerous examples of oxygen diradicals (dioxyls) have been postulated as intermediates in the thermal and photochemical decomposition of cyclic peroxides, in particular  $\beta$ -peroxylactones that have been extensively studied by Adam and co-workers.<sup>3</sup> Although, of the three possible processes that can occur *via* the intermediate diradicals

obtained by pyrolysis or photolysis of  $\beta$ -peroxylactones;  $\beta$ -scission, decarboxylation, and hydrogen abstraction, the last one should be of the lowest activation energy,<sup>3,4</sup> no products arising from this process have been reported previously, probably because this reaction has not been tested on an appropriate substrate.

We have recently reported that the photoreaction of lactol (**1**), in the presence of (diacetoxyiodo)benzene and iodine under oxygen atmosphere, gave, after methylation of acid (**2**), the  $\beta$ -peroxylactone (**3**) in good yield.<sup>6</sup> In this reaction a tandem  $\beta$ -fragmentation of the generated alkoxy radical followed by peroxidation of the C-radical formed and subsequent attack on the carboxylic group have taken place. With

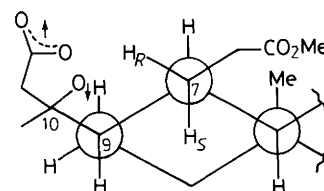
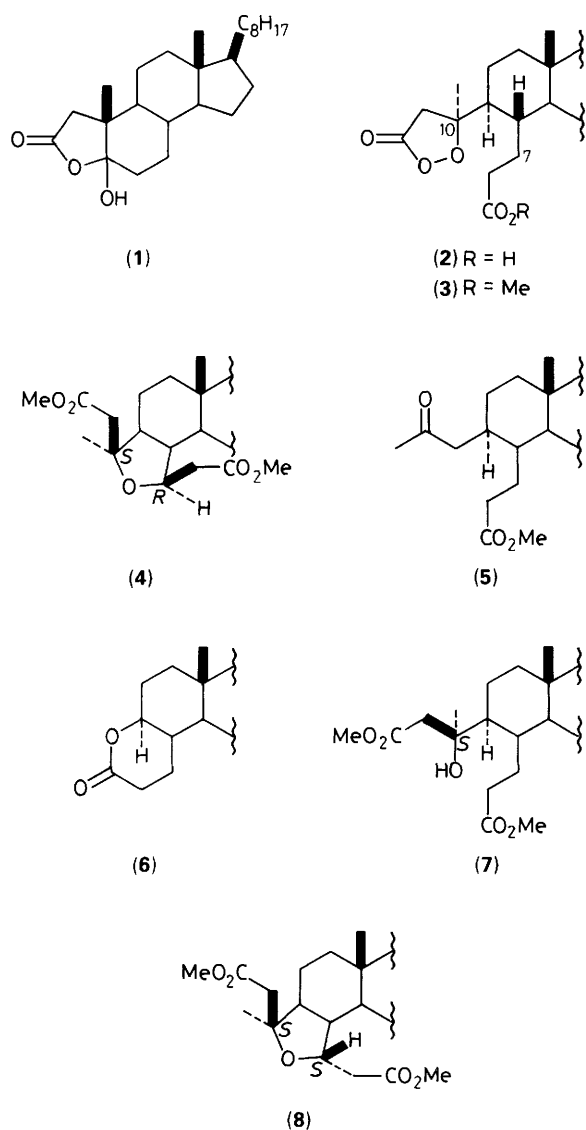


Figure 1

molecular hydrogen abstraction cannot only be observed but is also the principal process, occurring moreover with complete stereoselectivity, which is very surprising for an anticipated free radical reaction.

The thermolysis of (3) was studied in some detail under the conditions summarized in Table 1. In neat solvent a mixture of compounds (4), (5), and (6)<sup>†</sup> was obtained after methylation, while in benzene solution at 130 °C only (4) and (5) were observed. Heating in benzene solution at reflux temperature provided a slower but smoother conversion to (4) and (5). Ketone (5) and lactone (6) are the expected compounds of the thermolysis of (3), in accord with Adam's studies.<sup>8</sup>

The structure and stereochemistry of the (7*R*, 10*S*)-epoxy-ester (4)<sup>‡</sup> have been determined by *X*-ray diffraction analysis.<sup>9</sup> The formation of this compound can only be explained by intramolecular hydrogen abstraction by a most unusual concerted mechanism. This explains the observed selectivity in the *pro-R* hydrogen abstraction and also the unobserved decarboxylation of the hypothetical intermediate acyloxy radical.<sup>10</sup>

Adam proposed a singlet-state  $\pi$ -type 1,5-diradical to explain the rearranged ketone [such as (5)] during the thermolysis of  $\beta$ -peroxylactones.<sup>11</sup> If the formation of (4) goes through an intermediate of this type, it would be expected that the alkoxy radical would abstract the hydrogen atom through a favourable six-membered transition state, followed by hydrogen transfer to the acyloxy radical and simultaneous formation of the ether bridge. The direct hydrogen abstraction by the acyloxy radical through an eight-membered transition state seems unlikely. Although it has been claimed that the 1,5-hydrogen abstraction promoted by acyloxy radicals takes place,<sup>10</sup> no supporting evidence has yet been reported in the literature.

The stereoselective abstraction of the  $C_7$ -*pro-R* hydrogen can be explained because the transition state adopts a thermodynamically more stable conformation. In the abstraction of the *pro-S* hydrogen a less stable conformation must be adopted (Figure 1).

Furthermore, free radicals must not be involved in the reaction because when a true free radical hydrogen abstraction was performed starting with the 10*S*-hydroxy compound

Table 1. Thermolysis of  $\beta$ -peroxylactone (3).

Solvent	Conditions <sup>a</sup>		Product yield/% <sup>b</sup>		
	<i>T</i> /°C	<i>t</i> /h	(4)	(5)	(6)
Neat <sup>c</sup>	120	3	51	19	23
Benzene <sup>d</sup>	130	3	53	31	—
Benzene	85–90	90 <sup>e</sup>	59	27	—

<sup>a</sup> All reactions under argon. <sup>b</sup> Yields after methylation with diazomethane and purification by Chromatotron (Harrison Research) chromatography. <sup>c</sup> Büchi glass tube oven. <sup>d</sup> Solution degassed in a borosilicate Griffin–Worden pressure vessel (Kontes K-767100). <sup>e</sup> After this time, starting material (9%) was recovered [yields of compounds (4) and (5), 65 and 29%, respectively, based on conversion].

this  $\beta$ -peroxylactone at hand and in view of our interest in the preparation of tetrahydrofuran<sup>6</sup> and pyrrolidine<sup>7</sup> derivatives by intramolecular radical functionalization of non-activated carbons, we decided to study the chemical behaviour of the oxygen diradical generated therefrom.

In this communication we report that by pyrolysis of a suitably substituted  $\beta$ -peroxylactone, such as (3), the intra-

<sup>†</sup> All new substances exhibited spectroscopic data [IR, <sup>1</sup>H NMR (200 MHz), <sup>13</sup>C NMR (50.3 MHz), and MS] in accord with the assigned structure and provided acceptable high resolution analytical data. Selected spectroscopic data for (7): amorphous, IR 3800, 1720  $cm^{-1}$ ; <sup>1</sup>H NMR  $\delta_H$  1.22 (3H, s, 10-Me), 2.44 and 2.65 (2H, AB, *J* 15.1 Hz, 1-H<sub>2</sub>); <sup>13</sup>C NMR  $\delta_C$  175.64 (C), 174.17 (C), 74.43 (C). For (8): amorphous, IR 1730  $cm^{-1}$ ; <sup>1</sup>H NMR  $\delta_H$  1.43 (3H, s, 10-Me), 2.33 (2H, d, *J* 7.5 Hz, 6-H<sub>2</sub>), 4.48 (1H, q, *J* 7.6 Hz, 7-H); <sup>13</sup>C NMR  $\delta_C$  81.97 (C), 75.90 (CH).

<sup>‡</sup> Steroid numbering is used throughout this communication.

(7)§ through a hypiodite intermediate, generated by reaction of the alcohol with (diacetoxyiodo)benzene and iodine, no selectivity was observed and a mixture of the isomeric ethers (4) (7*R*, 10*S*) and (8) (7*S*, 10*S*) in the ratio 1 : 1.5 (64% yield) was obtained.

To our knowledge, this is the first example of intramolecular hydrogen abstraction realized in a stereoselective manner. Further investigation of the scope and mechanism of this reaction, as well as an exploration of its synthetic applications are underway.

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§ Compound (7) was synthesized by Bu<sup>n</sup><sub>3</sub>SnH/azoisobutyronitrile (AIBN) reduction of (3) and methylation with diazomethane in 58% isolated yield.

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