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Fragmentation of Peroxyhemiacetals. Stereoselective Synthesis of 1,2-Dioxolanes

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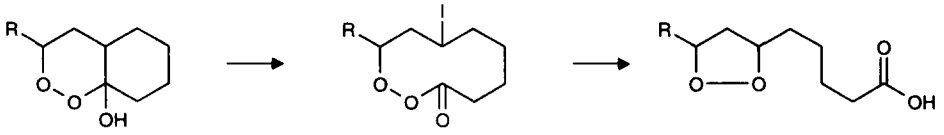
Abstract: A new and efficient approach to the synthesis of 1,2-dioxolanes by β-fragmentation of alkoxy radicals from readily available peroxyhemiacetals, under mild conditions, is described. The radical reaction proceeds in a diastereoselective manner providing a sole 1,2-dioxolane.

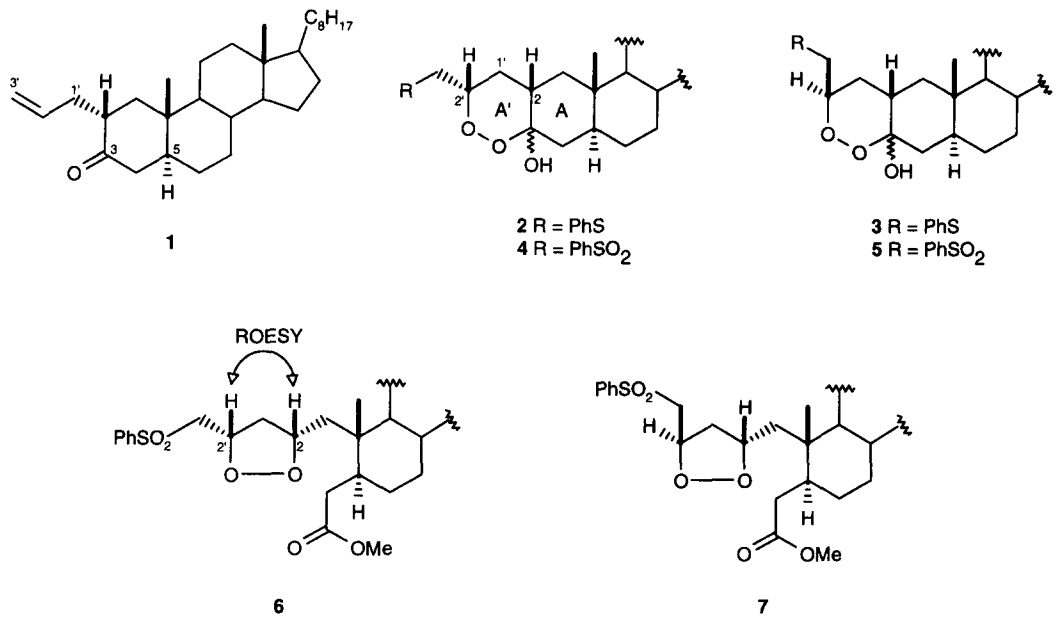
Five-membered ring peroxides, 1,2-dioxolanes, are found in oxidized lipids,[1] and recently, in the structure of antifungal marine natural products.[2] To date, only a limited number of methods have been reported for the preparation of 1,2-dioxolanes. Basically, they rely upon the cyclization of a functionalized hydroperoxide and dioxygenation of cyclopropane rings,[3] although recently reported approaches are 1,3-dipolar addition of carbonyl oxides and hydroperoxycarbenium ions to alkenes.[4] Dioxolanes are adequate precursors of 1,3-diols through reductive cleavage of the oxygen-oxygen bond.[5] The synthesis of 1,3-diols in a stereocontrolled manner has considerable interest because these subunits are present in naturally occurring substances such as polyene macrolides,[6] which possess significant physiological activity.



Scheme 1

In our continuing effort to expand the synthetic utility of the β-fragmentation reaction of alkoxy radicals,[7] we have found a new and convenient approach to the diastereoselective synthesis of chiral 1,2-dioxolanes by β-fission[8] of 3-hydroxy-1,2-dioxacyclohexanes (peroxyhemiacetals). The iodoperoxylactone initially formed by the β-fragmentation reaction could evolve to the dioxolane derivative (Scheme 1).

The synthesis of alkyl hydroperoxides is a well-documented process.[9] The hydroperoxide function can be intramolecularly trapped with a carbonyl group in a suitable position to give the corresponding peroxyhemiacetal.[10] The steroidal substrates **2** and **3**[11] to be used as models in this study were prepared from the γ,δ-unsaturated ketone **1** following the Yoshida and Isoe procedure[10d] (Scheme 2). At first, the sulfide **2** was



Scheme 2

irradiated with visible light in the presence of (diacetoxyiodo)benzene and iodine at room temperature[12] but, unfortunately, all efforts to apply this β-fragmentation process failed and an inseparable mixture of unidentified products was obtained. Gratifyingly, when the reaction was performed with sulfone **4**, the fragmentation proceeded smoothly under mild conditions and provided, after methylation with diazomethane, *syn*-dioxolane **6** as the sole product in 64% yield.[12] Sulfone **5** afforded the *anti*-derivative **7**, in similar yield (61%). The stereochemical assignment of *syn*- and *anti*-dioxolanes **6** and **7** was established by ROESY experiments in combination with DEPT, HMBC, and HMQC spectra to assign carbons and protons. The stereochemistry of compound **6** has been confirmed by X-ray crystallography[13] (Figure 1).

Sulfones **4** and **5** were obtained in excellent yields by oxidation of sulfides **2** and **3**, respectively, with *m*-chloroperoxybenzoic acid. The versatility of the sulfone moiety in synthesis is noteworthy and enhances the utility of the preceding methodology.

The stereochemistry of peroxyhemiacetals **2-5** deserves a comment. On the basis that in 1,2-dioxanes the chair form is more stable that the boat form,[10e] MMX force field calculations for compounds **2-5**, with A'A rings on chair-chair conformation, indicate that compounds **2** and **4** have a much more favourable *trans*-fused A'A ring system (*trans* is favoured over *cis* by 2.9 and 5.5 Kcal/mol, respectively), while a *cis*-fused structure is more stable for compounds **3** and **5** (*cis* is favoured over *trans* by 1.1 and 1.0 Kcal/mol, respectively). Because in all structures of compounds **2-5** the hydroxyl group at C-3 occupies the axial position, the anomeric effect[14] must not be the factor determining of the relative *trans-cis* A'A junction equilibrium, and therefore steric factors of the neighbouring phenylthiomethyl or phenylsulfonylmethyl at the C-2' group must govern the relative stabilities of the resulting products to leave, preferentially, the C-2' substituent in equatorial position. In fact ^{1}H NMR experiments showed $J_{2'\beta,1'\alpha}$ = 10.3 Hz and $J_{2'\beta,1'\beta}$ = 0-2.1 Hz for compounds **2** and **4** (*trans*-fused), and $J_{2'\alpha,1'\alpha}$ = 0-1.5 Hz and $J_{2'\alpha,1'\beta}$ = 10.6 Hz for compounds **3** and **5** (*cis*-fused), coupling constants being in good agreement with MMX calculations. While the ^{1}H and ^{13}C NMR spectra for compounds **2** and **4** indicate *trans*-fused A'A rings as the sole structure,

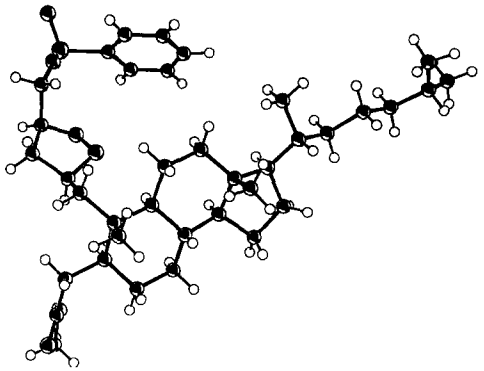
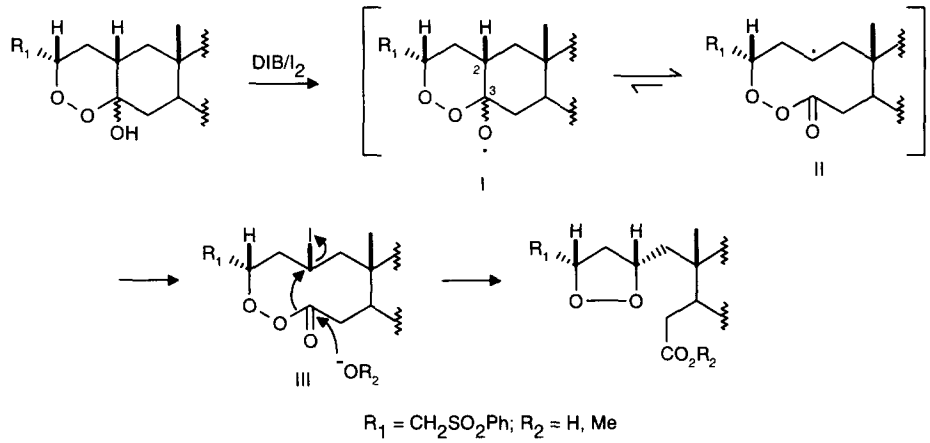


Figure 1. X-Ray structure of compound **6**

compounds **3** and **5** showed major signals for the *cis*-fused conformer accompanied by minor signals for the *trans*-fused one (ca 5:1).

A plausible mechanism for the formation of dioxolane **6** is shown in Scheme 3 and involves the *in situ* generation of the alkoxy radical I which undergoes regioselective C_2-C_3 bond fragmentation to provide the carbon radical II, which abstracts in a stereoselective manner an iodine atom from the medium to give the iodoperoxylactone III. The formation of 1,2-dioxolanes suggests the nucleophilic attack of a hydroxide ion on the acyl carbon[15] of this peroxylactone and that the resulting peroxyanion undergoes intramolecular nucleophilic substitution of the iodoalkane. The formation of methyl esters if the fragmentation reaction is quenched with solution of sodium methoxide instead of water provides a good support for the proposed mechanism.



Scheme 3

It is noteworthy that, despite the sequence occurring, through a radical manifold process, total diastereoselectivity was observed for each iodo-derivative and hence the resulting dioxolanes. Work is in progress in an attempt to extend the method to the preparation of natural 1,2-dioxolanes.

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11. All compounds exhibited spectroscopic (IR, ^{1}H- and ^{13}C-NMR) and analytical (HRMS) data in accord with the assigned structure.
12. A typical experiment is described as follows: a stirring solution of peroxyhemiacetal **4** (0.1 mmol) in CH_2Cl_2 (6 mL) containing (diacetoxyiodo)benzene (1.2 equiv) and iodine (1 equiv) was irradiated with two 80-W tungsten-filament lamps for 15 min at 24-26 °C. The reaction mixture was then poured into water and extracted with CH_2Cl_2 (3x15 mL). The organic layer was washed with aqueous sodium thiosulphate (2x10 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. Rotative chromatography of the residue gave the crude acid that was treated with ethereal diazomethane, and purified. (**6**, 64% overall). Analogously, **5** gave dioxolane **7** in 61% yield.
13. The data were measured on a Philips PW1100 four-circle diffractometer operating with Cu-Kα radiation (λ = 1.5418 Å) monochromated by graphite. Crystal structure data: orthorhombic, space group $P2_12_12_1$, Z = 4, a = 42.945(7), b = 14.524(3), and c = 5.973(2) Å, R(%) 8.8 for 2526 reflections with I>3σ(I). Detailed X-ray crystallographic data are available, on request, from the Director, Cambrige Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, or as standard cif file from the authors at prange@lure.u-psud.fr.
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