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Iron(II)-mediated Rearrangement of 1,2,4-Trioxanes into 1,2-Diol Monoesters via 1,5-Hydrogen Transfer

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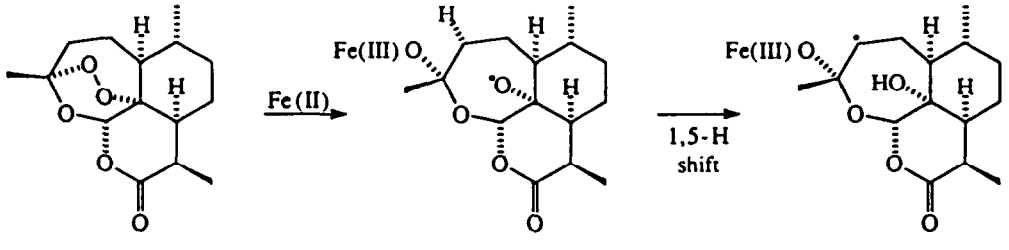
Abstract: Five 3-alkyl- or 3-aryl-5,5,6,6-tetramethyl-1,2,4-trioxanes **4** upon treatment with iron(II) sulfate in aqueous acetonitrile under nitrogen for 12-72h are cleanly isomerised into the corresponding 2,3-dimethylbutan-2,3-diol monoesters **5**; it is suggested that the reactions involve reduction to oxyl radicals followed by 1,5-hydrogen transfer, a sequence that has recently been implicated in the molecular mechanism of action of the antimalarial artemisinin.

As resistance in malaria parasites to traditional drugs continues to grow, so too does the importance of artemisinin **1** and related 1,2,4-trioxanes as alternative chemotherapeutic agents. Not surprisingly, therefore, the molecular basis of the antimalarial activity of these peroxidic drugs is currently the subject of intense investigation.[1-6] Although the precise identity (or identities) of the (possibly several) cytotoxic species involved remains unclear, some key features of the process by which they are generated from the 1,2,4-trioxanes have emerged. Thus, it is generally agreed that the initial step is a one-electron reduction by the heme which is produced as the parasites digest the hemoglobin of the host cell. For artemisinin (Scheme 1), the resultant oxyl radical **2** is then converted into a carbon-centred radical **3** by 1,5-hydrogen transfer.[1-3] Carbon-centred radicals may be the lethal agents[6], but ß-scission of the C-OFe(III) bond in radical **3** produces an iron-oxo species and rebound epoxidation gives an epoxide, both of which could reasonably be responsible for the parasiticidal activity.[3]

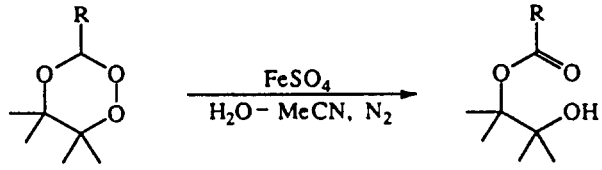


1 **2** **3**

Scheme 1

We report herein that iron(II) smoothly effects the isomerisation of 3,5,5,6,6-pentasubstituted 1,2,4-trioxanes[7] into 1,2-diol monoesters. Not only does this provide a convenient preparation of compounds which are related to many natural products and for which few synthetic routes exist[8], but it also provides evidence to support the emerging molecular mechanism described above by showing that 1,2,4-trioxanes are reduced by iron(II) to give oxyl radicals which can undergo 1,5-hydrogen transfer.

3-Alkyl- and 3-aryl-5,5,6,6-tetramethyl- 1,2,4-trioxanes **4**, prepared by intramolecular oxymercuriation of the hemiperoxyacetals formed from the requisite aldehydes RCHO and 2,3-dimethylbut-1-en-3-yl hydroperoxide followed by sodium borohydride reduction,[7] were treated with 2 mol equivalents of iron(II) sulfate in aqueous acetonitrile under nitrogen. When all the 1,2,4-trioxane had been consumed (12-72h), extraction with dichloromethane followed by purification by silica chromatography gave analytically pure 2,3-dimethylbutan-2,3-diol monoesters **5** in yields typically of 50% (Scheme 2).



4 **5**

R	Me	Pr	Bu^t	2-$NO_2C_6H_4$	4-ClC_6H_4
Reaction time (h)	12	12	72	48	48
Yield of 5 (%)	73[a]	35	50	50	50

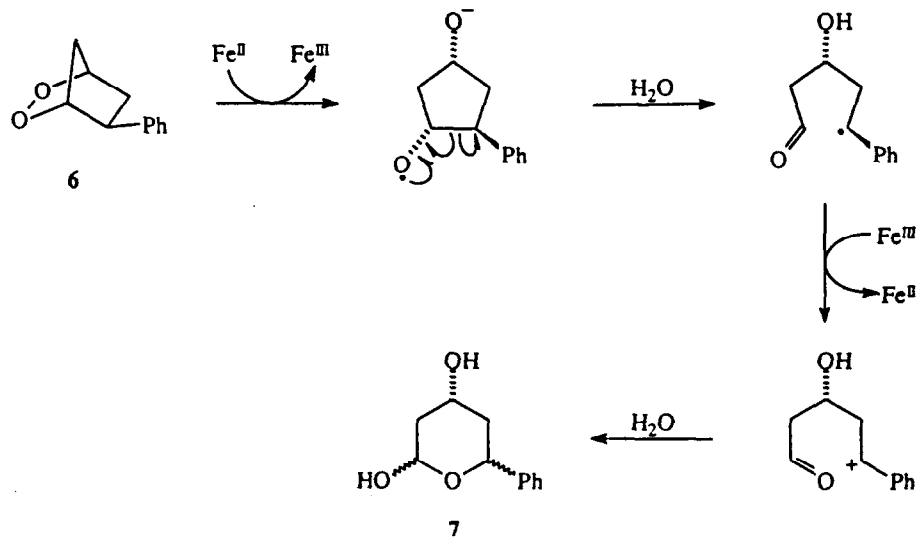
([a] Crude but spectroscopically pure product identical with the analytically pure compound prepared by photolysis of the 1,2,4-trioxane)

Scheme 2

The diol monoesters were unambiguously identified by combustion analyses, FAB mass spectra and NMR spectra. The key common features of the ^1H NMR spectra of **5** were a broad 1H singlet in the region δ 3.3-3.8 corresponding to the OH proton and two sharp 6H singlets in the regions δ 1.35-1.65 and 1.1-1.3 for the methyl protons. In the ^{13}C NMR spectra, the carbonyl carbon was observed in the range δ 164-175, the CO_2CR in the range δ 89-92 and the *C*OH at δ 75. Although the yields of **5** after chromatography were only 35-50%, the reactions appeared to be very clean with no other compounds being detected in the crude products for which yields were much higher (*e.g.* R = Me, 73%; Scheme 3).

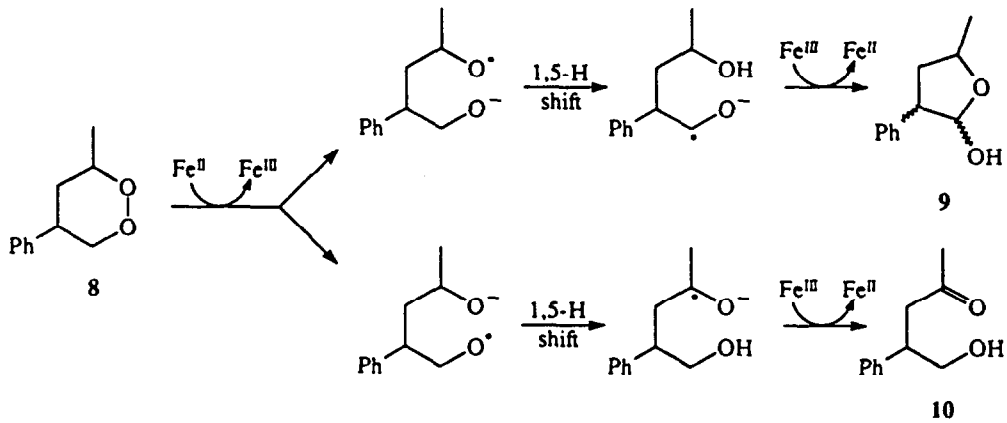
In previous studies of the reaction of 1,2,4-trioxanes with iron(II) reagents, Posner[1,3] used hemin/$PhCH_2SH$ or $FeBr_2$ in THF while Jefford[5] employed $FeCl_2 \cdot 4H_2O$ in acetonitrile. We chose our conditions because they had been used previously in studies aimed at modelling the conversion of prostaglandin

endoperoxides into thromboxanes.[9,10] Thus, Kishi[9] identified the TXB_2-like compound **7** among the products from treating endoperoxide **6** with iron(II) sulfate. The formation of **7** was also rationalised in terms of reduction to an oxyl radical followed by isomerisation to a carbon-centred radical, albeit now by ß-scission rather than 1,5-hydrogen transfer (Scheme 3). A similar ß-scission in a cyclopentyloxyl radical was invoked by Jefford[5] for the generation of carbon-centred radicals from cyclopenteno-1,2,4-trioxanes and iron(II) chloride.



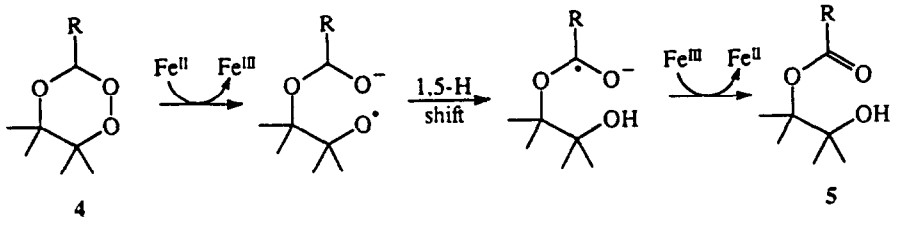
Scheme 3

However, we have shown that under Kishi's conditions the related monocyclic 1,2-dioxane **8** gives solely a 1:1 mixture of products **9** and **10**, 1,5-hydrogen transfer being preferred to the exclusion of ß-scission (Scheme 4).[10]



Scheme 4

A parallel mechanism incorporating the key sequence of reduction to oxyl radical followed by 1,5-hydrogen transfer (Scheme 5) can therefore be proposed with much confidence for the present conversion of 1,2,4-trioxanes into diol monoesters.



Scheme 5

1,5-Hydrogen transfer in the reduced monocyclic peroxides is strongly favoured since the required transition state is set up by simple C-C bond rotation. Furthermore, the subsequent oxidation affords a carbonyl group and if the iron(III) alkoxide is covalently bonded (*cf.* 2) involves the ß-scission of the O-Fe(III) bond rather than a bimolecular process.

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