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Iron(II)-Induced Degradation of Antimalarial β-Sulfonyl Endoperoxides. Evidence for the Generation of Potentially Cytotoxic Carbocations

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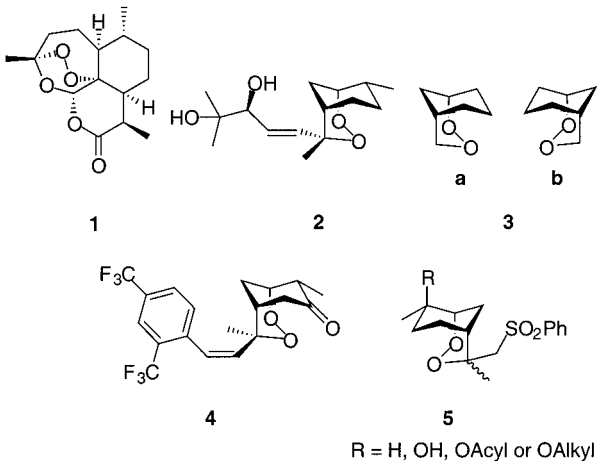
Reactions of antimalarial β-sulfonyl endoperoxides **9** and **10**, which, like yingzhaosu A (**2**), derive from the 2,3-dioxabicyclo[3.3.1]nonane system **3**, with iron(II) salts were studied. Product analysis of the iron(II)-induced degradations provided evidence for the intermediacy of carbon-centered cyclohexyl radicals **20** and **31** and their possible oxidation to the corresponding carbocations **21** and **32**. It is conceivable that the antimalarial activity of β-sulfonyl endoperoxides of type **5** may derive from alkylation of vital intraparasitic biomolecules by free radicals and/or carbocations, generated within the malaria parasite through a similar iron(II)-induced degradation process.

Introduction

A promising approach for treating malaria caused by parasites resistant to chloroquine and other commonly used quinine-related drugs is based on the development of compounds that contain an endoperoxide function in their molecular backbone.[1] The discovery of the natural antimalarial peroxide artemisinin (qinghaosu, **1**)[2] was followed by the development of a variety of semisynthetic and totally synthetic trioxanes as antimalarial drugs and drug candidates.[1] Similarly, the isolation of yingzhaosu A (**2**) from a traditional Chinese antimalarial herbal medicament[3,4] was followed by studies on other antimalarial endoperoxides containing the 2,3-dioxabicyclo[3.3.1]-nonane system **3a**,**b**. Of particular relevance to the present discussion are arteflene (**4**)[5,6] and β-sulfonyl endoperoxides of type **5**.[7−9]



Although the mode of action of endoperoxides as antimalarial agents is not yet fully unfolded, it is widely accepted that they act as pro-drugs that are activated by an iron(II) compound, in a Fenton-type reaction.[1] The iron(II) compound, e.g., heme, originates from hemoglobin, which is digested by the malarial parasite.[10] Indeed, antimalarial peroxides are substantially stable in healthy blood but are rapidly degraded in infected erythrocytes.[11] The Fenton reaction, in which oxygen-centered radicals are generated, is followed by a sequence of events in which a variety of potentially cytotoxic products and transitory reactive species are formed. It has been suggested that these species are responsible for killing

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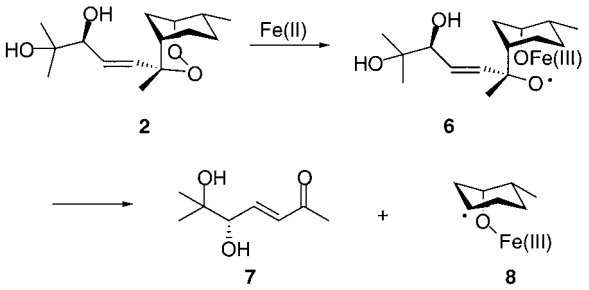
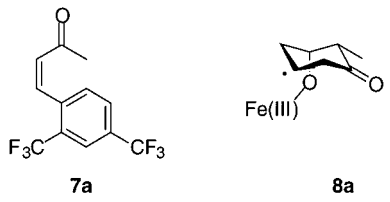
Scheme 1



the parasites through alkylative and/or oxidative processes.[1,11−16] To elucidate the structure and nature of the alkylating and/or oxidizing agents, several research groups have conducted model studies on the reaction of iron(II) salts with artemisinin and structurally related trioxanes.[1,17−24] These studies attribute parasiticidal properties to carbon-centered radicals and high-valent iron species [Fe(IV)═O] as well as to electrophilic reaction products such as epoxides and ketones.[1c,17,20−24]

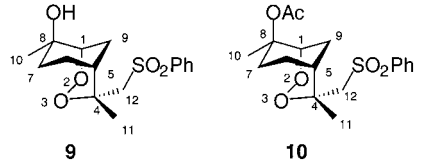
Although the iron(II)-induced degradation of yingzhaosu A (**2**) has not been studied experimentally, it has been suggested that it would result in the formation of two alkylating species: unsaturated ketone **7** and cyclohexyl radical **8** (Scheme 1).[18] Experimental support for such a mechanism was provided in a study on the reaction of arteflene (**4**) with iron(II) chloride, which afforded the unsaturated ketone **7a**. The postulated cyclohexyl radical **8a** was suggested to end up in an "unidentified polymeric substance".[25,26] Very recently, evidence for the generation of cyclohexyl radical **8a** was provided by the use of ESR techniques,[27] and by trapping it, in 6% yield, with TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl).[28]



Recently, we reported on an efficient synthesis[7,9] of highly potent[8,9] antimalarial β-sulfonyl endoperoxides of type **5** that have the 2,3-dioxabicyclononane system **3a**,**b** as a common structural feature with yingzhaosu A (**2**) and arteflene (**4**). Some of these compounds exhibit antimalarial activities comparable to that of artemisinin (**1**) and arteflene (**4**).[8]

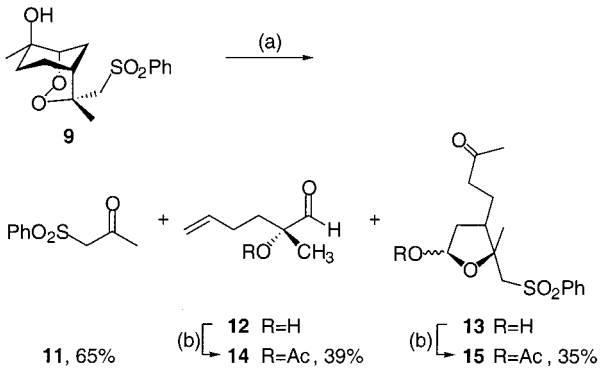
Results and Discussion

In this paper, we describe a study on the reactions of antimalarial β-sulfonyl-endoperoxides **9** and **10** with iron(II) salts.[7−9,29,30] In addition to supporting some of the



suggestions mentioned in the Introduction, analysis of these reactions provides new data that may contribute to a better understanding of the mode of action of antimalarial peroxides. Initially, we adopted the procedure of using iron(II) bromide in THF reported by Posner et al. and Avery et al. in their studies of artemisinin (**1**) and its analogues.[23,24] Endoperoxide **9** was consumed within 12 min upon treatment with catalytic amounts of iron(II) bromide in THF at 0 °C to give compounds **11**−**13**. For purification and characterization purposes, the reaction mixture was acetylated in situ to give compounds **11**, **14**, and **15** (Scheme 2).

Scheme 2[a]



[a] Key: (a) 0.2 equiv of $FeBr_2$, THF, 0 °C; (b) 6 equiv of Ac_2O, 0.25 equiv of DMAP, pyridine, room temperature.

The formation of compounds **11**−**13** can be rationalized by the all-homolytic mechanism described in Scheme 3. Iron(II)-mediated reductive cleavage of the peroxide bond in **9** leads to oxygen-centered radicals **16** and **17**, which most probably are in equilibrium.[17,18,23] In accord with the mechanism suggested for the analogous ferrous-

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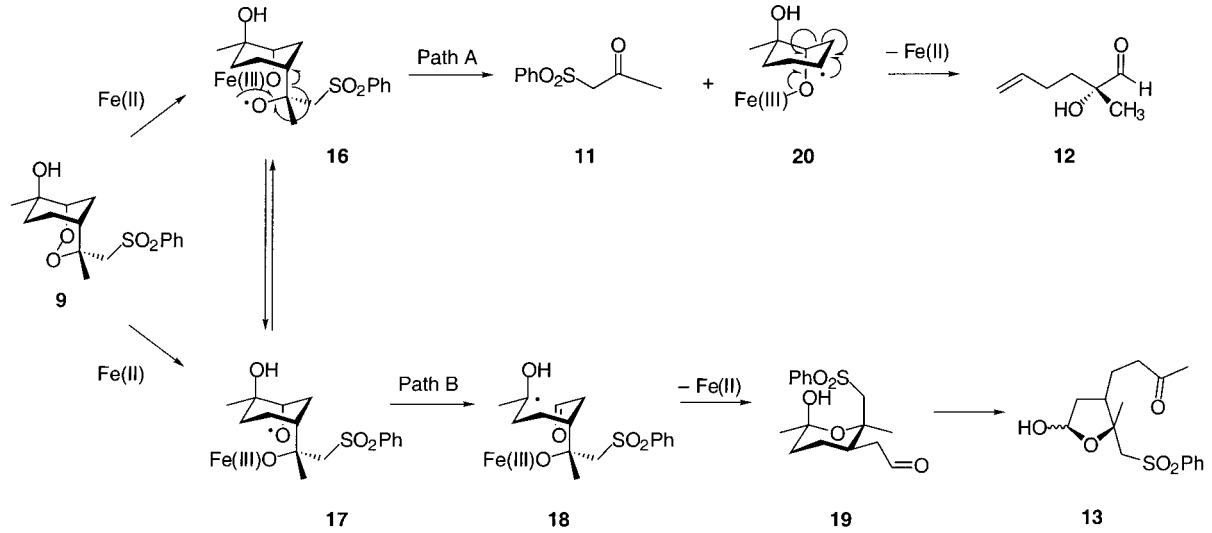
Scheme 3



induced degradation of yingzhaosu A (**2**, Scheme 1)[18] and arteflene (**4**),[25,27] radical **16** undergoes β-scission to give ketosulfone **11** and cyclohexyl radical **20**. It has been reported that the cyclohexyl radical **8a** derived from arteflene (**4**) undergoes polymerization.[25] We have found that radical **20**, as well as similar carbon-centered radical **31** (see Schemes 6 and 10), gives well-defined monomeric products, under the specified reaction conditions. Initially, the formation of these degradation products was rationalized by the radical chain reactions displayed in Scheme 3. Accordingly, cyclohexyl radical **20** undergoes oxidative β-cleavage to give the unsaturated hydroxy aldehyde **12** with concomitant regeneration of iron(II) which continues the chain reaction (path A). β-Cleavage of oxygen-centered radical **17** affords the oxygen-stabilized carbon-centered radical **18**, which undergoes oxidative ring closure to six-membered lactol **19** with regeneration of iron(II). Acid-catalyzed, heterolytic rearrangement then takes place to afford five-membered lactol **13** (path B). Both these compounds contain one masked and one free carbonyl group. Thus, the mechanism described in Scheme 3 accounts for a highly efficient chain reaction in which iron(II) acts as a principal transfer agent.

In discussing the mode of action of other antimalarial peroxides, various authors suggested that carbon-centered radicals may kill the parasite through alkylation of essential parasite biomolecules or Heme (see the Introduction).[1,11,15−17,19] Radical alkylation processes involve addition of the radical to the substrate followed by electron or atom transfer.[19,31] Iron(III) juxtaposed to the incipient radical center, resulting from addition of carbon-centered radical **20** (e.g., to a double bond or an heteroaromatic system), would account for the subsequent oxidative step in which the final alkylated product and iron(II) are formed. An alternative, efficient, alkylating process would result from the involvement of carbocations. A mechanism that accounts for the formation of the compounds shown in Scheme 2 and for the provision of a continuous flux of carbocations is described in Scheme 4. According to this mechanism, carbocation **21** and iron(II) are formed through single-electron transfer (SET) from the carbon-centered radical to iron(III) in **20**. An analogous process would account for the generation of carbocation **22** from carbon-centered radical **18**. The oxidation of carbon-centered radicals to carbocation by iron(III) is detailed in the Conclusion.

In the absence of an effective nucleophile, carbocation **21** undergoes β-cleavage to give the unsaturated hydroxyaldehyde **12** through a classical Grob-type fragmentation (path A).[32] Such a rearrangement is thermodynamically favored and is typical for carbocations that have a β-hydroxy or β-amino substituent in their backbone.[32] In path B, instantaneous proton shift in carbocation **22** results in the dicarbonyl compound **23**, which undergoes spontaneous acid-catalyzed cyclization to five-membered lactol **13**.

Treatment of endoperoxides **9** and **10** with 1 equiv of iron(II) bromide with, or without, 2,6-lutidine afforded the products described in Scheme 5 and Table 1. Diols such as **27** are well-known to derive from two electron-reduction of peroxides[18,25,33] and are not specific to the present study. Degradation of hydroxy endoperoxide **9** with an equimolar amount of iron(II) bromide in the presence of excess 2,6-lutidine (Table 1, entry 1) afforded two epimeric bromides **24** and **25**. In contrast, degradation of its acetoxy derivative, endoperoxide **10** (Table 1, entries 2 and 3), afforded bromide **26** as a single diastereomer. This high stereoselectivity is rationalized by the mechanism detailed in Scheme 6. Accordingly, the incipient carbon-centered radical **31** (X = Br) is oxidized by the adjacent iron(III) to give carbocation **32** (X = Br), which is stabilized by the neighboring acetoxy group as symbolized by structure **33** (X = Br). S_N2 substitution by Br^- from the less hindered side of acetoxonium ion

(29) The in vitro antimalarial activity of compounds **9** and **10** against chloroquine-sensitive *P. falciparum* (NF54) exhibit IC_{50} values of 55 and 17 nM, respectively. For comparison, the IC_{50} of artemisinin (**1**) is 9.3 nM (see ref 8).

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Scheme 4

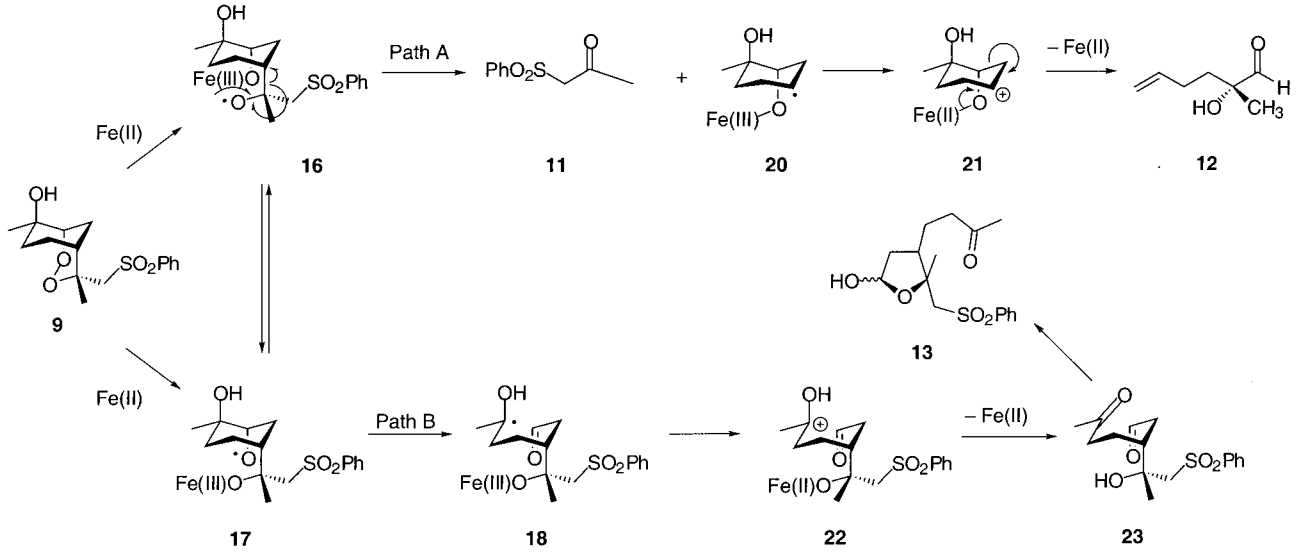
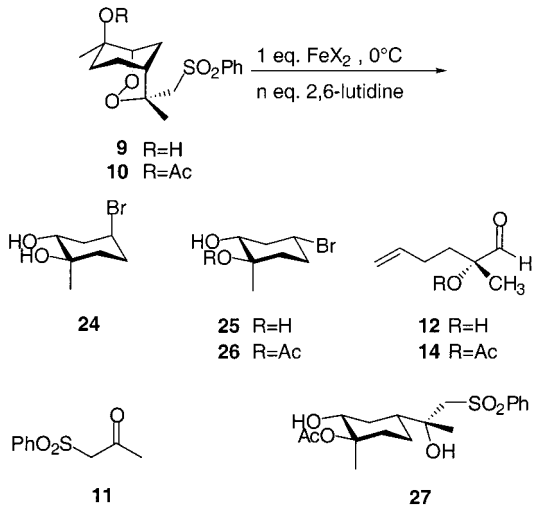


Table 1. Iron(II)-Induced Degradation of Endoperoxides 9 and 10 (See Scheme 5)[a]

entry	compd	FeX_2 (equiv)	solvent	equiv[b] of 2,6-lutidine	yield (%) 11	14	24	25	26	27
1[d]	9	$FeBr_2$ (1)	THF	4	76		20	14		
2	10	$FeBr_2$ (1)	THF	0	68[c]	37			24[c]	
3	10	$FeBr_2$ (1)	THF	4	89				53	10
4	10	$Fe(BF_4)_2 \cdot 6H_2O$ (1)	NMP[f]	0	75	34[e]				
5	10	$Fe(BF_{44})_2 \cdot 6H_2O$ (1)	$MeOH/CH_2Cl_2$ 7:1	0	96	29[e]				

[a] All reactions were complete in less than 30 min. Unless otherwise noted, specified yield refers to isolated compounds. [b] Equivalents relative to peroxide **9** or **10**. [c] The compounds were not separated, and the yields are based on the ^1H NMR spectra of the mixture. [d] Aldehyde **12** was observed by TLC during the reaction but decomposed on workup. [e] The compound was partially lost on workup. [f] *N*-Methylpyrrolidinone.

Scheme 5



33 (X = Br) affords intermediate **34** and, after workup, the *trans*-acetoxybromide **26**. The lack of stereoselectivity in the experiment with hydroxy endoperoxide **9** is then logically attributed to the absence of the carbocation-stabilizing acetoxy group. Whereas 1,4-interactions of acyloxy groups with carbocations are well documented,[34] it is not likely that an analogous interaction would occur with carbon-centered radicals.

An alternative, theoretically possible mechanism would involve a stereospecific direct intramolecular bromine atom transfer from the iron(III)-coordinated bromide in radical **31** (X = Br) to the radical center at C(5)[35] to give *trans*-acetoxy bromide **26** as the only isomer (Scheme 6). The formation of epimeric bromides **24** and **25** in the experiment with hydroxyendoperoxide **9** would then be attributed to conformational changes resulting from iron chelating to the C(8) hydroxy group in radical **20**. However, comparison of entries 2 and 3 (Table 1) provides additional indications in favor of cationic intermediates **32** and **33** in the degradation of acetoxy endoperoxide **10**. In the absence of 2,6-lutidine (entry 2), *trans*-acetoxy bromide **26** was accompanied by a comparable amount of unsaturated aldehyde **14**. In principle, this compound can be obtained both through a Grob-type heterolytic cleavage of carbocation **32** or via a homolytic β-cleavage of cyclohexyl radical **31** (Scheme 6). However, the fact that formation of **14** was inhibited on addition of 2,6-lutidine (entry 3) does not conform with an all-homolytic process, which should not be significantly influenced by addition of 2,6-lutidine. On the other hand, the basic 2,6-lutidine increases the availability of bromide ions, thus accelerating the formation of acetoxy bromide **26** through an S_N2 reaction with acetoxonium ion **33**. This reaction competes with the β-cleavage to such an extent that formation of aldehyde **14** is not observed. In the absence of effective nucleophiles, as in the reaction of acetoxy endoperoxide **10** with iron(II) tetrafluoroborate in *N*-

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(35) Numbering of atoms is correlated to that of endoperoxide **10**.

Scheme 6

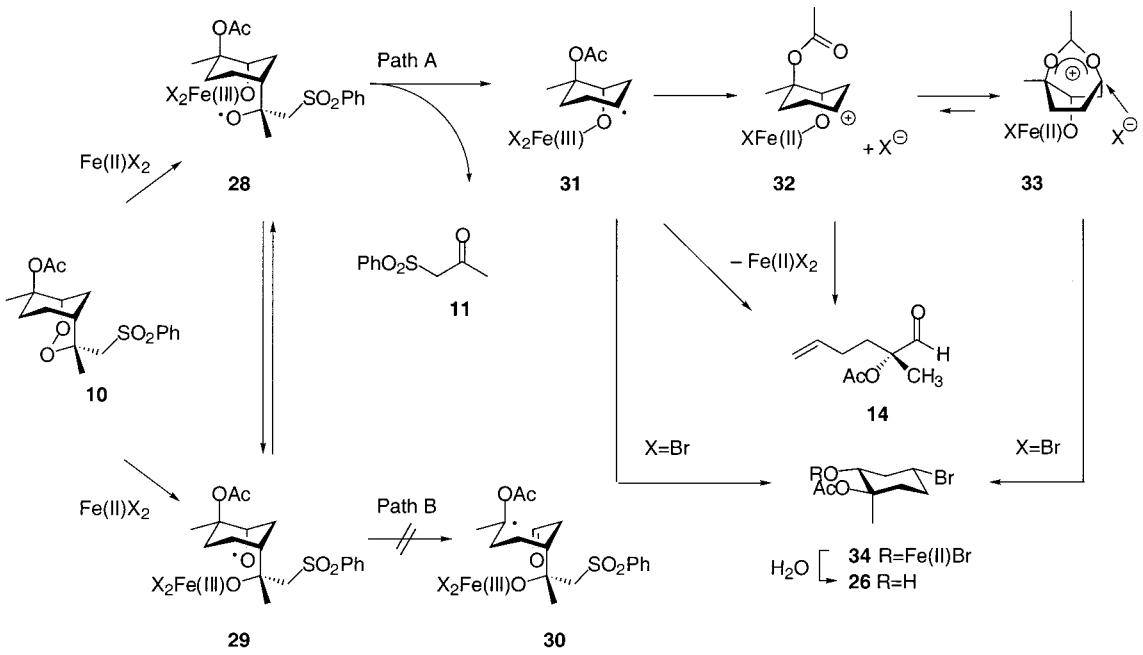


Table 2. Degradation of Peroxide 10 with Iron(II) Acetate (See Scheme 7)[a]

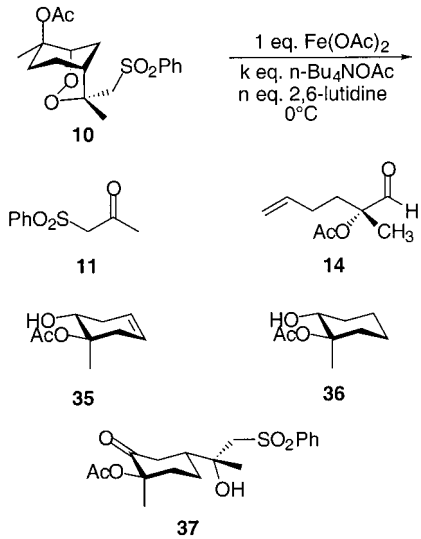
entry	solvent	equiv[b] of 2,6-lutidine	equiv[b] of Bu_4NOAc	mode of addition	reaction time (min)	isolated yield (%) 11	14	35	36[e]	37
1	NMP/THF 1:7	4	5	single portion[d]	15	18		12		43
2	NMP	0	5	syringe pump[c]	85	55		46	10	15
3	NMP	4	5	syringe pump[c]	70	49		44		7
4	NMP	0	0	syringe pump[c]	70	80	70			

[a] All the reactions were carried out at 0 °C in the presence of 1 equiv of $Fe(OAc)_2$. [b] Relative to the amount of endoperoxide **10**. [c] A solution of endoperoxide **10** was added during 40 min to the solution of iron(II) acetate by means of a syringe pump. [d] A solution of endoperoxide **10** was added to a solution of iron(II) acetate in a single portion. [e] See ref 38.

methylpyrrolidinone (NMP) or methanol (Table 1, entries 4 and 5), the Grob-type rearrangement becomes the dominant pathway and the "cyclohexyl moiety" is exclusively degraded to the acetoxy unsaturated aldehyde **14**. The discrepancy between the yields of ketosulfone **11** and unsaturated aldehyde **14** may be due to the relative instability of the latter; indeed, yields vary with reaction and workup conditions. Aldehyde **12** originating from degradation of peroxide **9** could be isolated only after in situ acetylation to **14** (Scheme 2). Possibly the formation of polymeric products reported for the iron(II) chloride-induced degradation of arteflene (**4**)[25] and of other 2,3-dioxabicyclononanes[26] derives from polymerization of unsaturated aldehydes structurally related to **12** and **14**.

Peroxide degradation through path B (Schemes 3 and 4) was observed only in the experiment in which the hydroxy endoperoxide **9** was treated with a catalytic amount of iron(II) bromide in the absence of 2,6-lutidine (Scheme 2). The fact that no evidence for path B was provided in the degradation of hydroxy endoperoxide **9** with a stoichiometric amount of iron(II) bromide and excess of 2,6-lutidine may derive from decomposition of reactive intermediates such as six-membered lactol **19** or keto-aldehyde **23** during the reaction or workup. As radicals **16** and **17** are in equilibrium, the reaction pattern, i.e., path A versus path B, is determined by the ratio of the rate of degradation of **16** to **11** + **20** and the rate of degradation of **17** to **18**, and for the case of acetoxy endoperoxide **10** (Scheme 6) by the ratio of the rates of degradation of **28** to **11** + **31** and of **29** to **30**. Since the

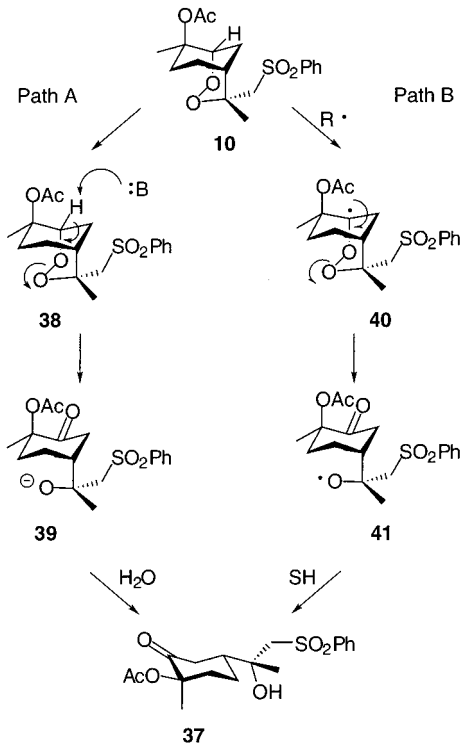
Scheme 7



stabilizing effect of the hydroxyl group in radical **18** is superior to that of the acetoxy group in radical **30**, the rate of degradation of **29** to **30** should be lower than that of **17** to **18**. This may account for the fact that no evidence for path B was observed in any of the reactions of acetoxy endoperoxide **10** (Tables 1 and 2).

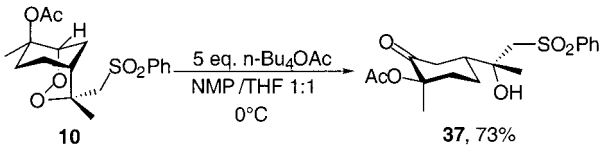
Acetoxy endoperoxide **10** was found to be more amenable than hydroxy endoperoxide **9** for further studying the postulated involvement of carbocations in the iron(II) degradation, and it was used in the experiments

Scheme 8[a]



[a] Key: R = any radical including oxygen-centered radicals. SH = any hydrogen atom donor. B = base.

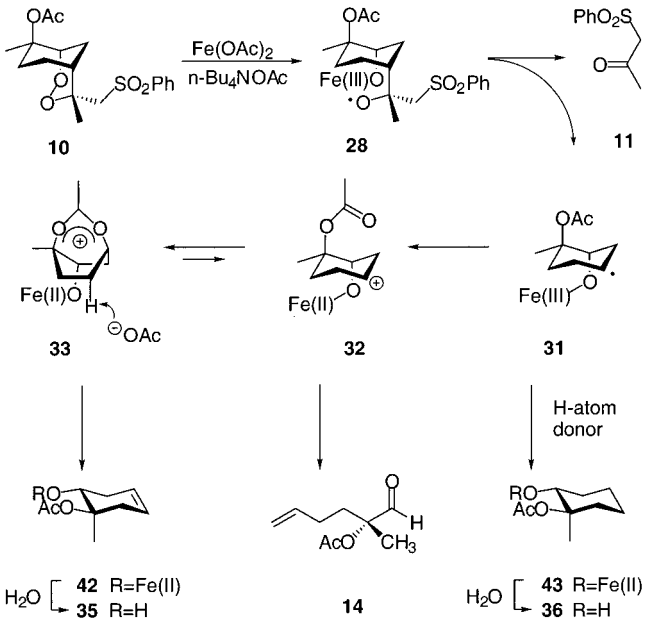
Scheme 9



described in Scheme 7 and Table 2. To avoid possible participation of the counteranion of iron(II) in homolytic processes, iron(II) acetate was selected. To amplify possible involvement of the counteranion in heterolytic processes, the experiments were performed in a dipolar aprotic solvent and part of them in the presence of tetrabutylammonium acetate.

Table 2 and Scheme 7 describe the degradation of acetoxy endoperoxide **10** with iron(II) acetate in the presence or absence of tetrabutylammonium acetate. Probably most of cyclohexanone **37** (Table 2, entries 1−3) is formed by a Kornblum reaction[36] induced by basic tetrabutylammonium acetate (Scheme 8, path A). In fact **37** was obtained as the major product on fast mixing of peroxide **10** with iron(II) acetate and tetrabutylammonium acetate in NMP/THF (Table 2, entry 1). Iron(II) acetate has low solubility in this solvent mixture making the Kornblum reaction competitive with degradation by iron(II). Indeed, when acetoxy endoperoxide **10** was subjected to similar conditions, in the absence of iron(II) acetate, it was converted into cyclohexanone **37** in less than 1 h at 0 °C (Scheme 9). Possibly, a minor amount of **37** is formed through the radical mechanism described in Scheme 8, path B.[37] In the experiment described in

Scheme 10



entries 2−3 of Table 2 and Scheme 7, the availability of a soluble iron(II) salt was guaranteed by slow addition of endoperoxide **10** to a solution of iron(II) acetate in NMP. Under these conditions, formation of **37** is significantly reduced, and the major products are **11** and **35**. 2,6-Lutidine does not play any significant role in these reactions (compare Table 2, entries 2 and 3). When acetoxy endoperoxide **10** was reacted with an equimolar amount of iron(II) acetate *in the absence* of tetrabutylammonium acetate (Table 2, entry 4), ketosulfone **11** and aldehyde **14** were obtained in high yield whereas, no cyclohexene **35** was obtained. This observation is consistent with the intermediacy of cations **32**/**33** which, in the absence of basic tetrabutylammonium acetate, undergo a Grob-type fragmentation to aldehyde **14**, while with an excess of tetrabutylammonium acetate they lose a proton to give cyclohexene **35**. Formation of cyclohexene **35** (Table 2, entries 2 and 3) through a radical mechanism would require a bimolecular radical−radical reaction that, under the employed reaction conditions, cannot be considered a major reaction path. Furthermore, such a mechanism would not conform with the cardinal role of tetrabutylammonium acetate as seen by comparison between entries 3 and 4 of Table 2. Clearly, formation of **35** by a radical mechanism would not be affected by the presence or absence of tetrabutylammonium acetate.

The results obtained in this series of experiments led us to propose the mechanism described in Scheme 10. Oxygen-centered radical **28**, deriving from iron(II) acetate degradation of *β*-sulfonyl endoperoxide **10**, yields in the first fragmentation process ketosulfone **11** and cyclohexylradical **31**. Iron(III) oxidation of the carbon-centered radical leads to carbocation **32**, which is stabilized by the C(8) acetoxy group to give the conformationally restricted acetoxonium ion **33**. Each of these postulated reactive intermediates may undergo additional secondary reactions. Hydrogen atom transfer from the solvent or other hydrogen donors to cyclohexyl radical **31** is a minor reaction path. Indeed, cyclohexane **36** was only isolated

(36) Original review: (a) Kornblum, N.; DeLamare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880−881. For examples, see: (b) Sengul, M. E.; Ceylan, Z.; Balci, M. *Tetrahedron* **1997**, *53*, 10401−10408. (c) Pansare, S. V.; Vederas, J. C. *J. Org. Chem.* **1987**, *52*, 4804−4810.

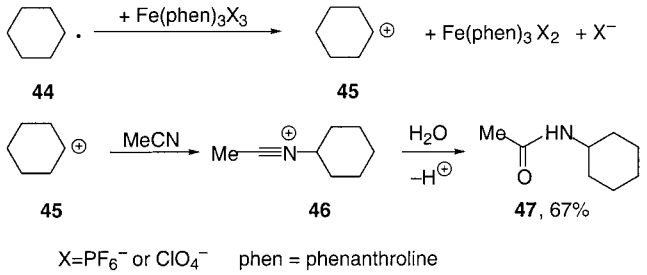
(37) Pryor, A. W.; Huston, D. M.; Fiske, T. R.; Pickering, T. L.; Ciuffarin, E., *J. Am. Chem. Soc.* **1964**, *86*, 4237−4243.

in one experiment (Table 2, entry 2).[38] Degradation of cationic intermediates **32**/**33** leading to compounds **14** and **35** accounts for the major reaction path. The regioselectivity of double bond formation (**33** → **35**) derives from the particular structure of intermediate **33**. Due to steric and electrostatic factors, out of the three hydrogen atoms that are anti-periplanar to the acetoxonium group, only the hydrogen at C(6)[35] is abstracted by the acetate anion.

Conclusion

Oxidation of carbon-centered radicals by iron(III) salts to carbocations is well documented,[31,39−45] including in the context of iron(II)-mediated degradation of peroxides.[46] In a series of papers on the *intermolecular* oxidation of alkyl radicals by iron(III) salts, Kochi[40−45] identified three distinct *modes* of oxidative processes: (a) oxidation of the alkyl radical by *outer-sphere electron transfer to* iron(III) leading to the formation of intermediate carbocations (or ion pairs) as discrete species that are then transformed through intra- and intermolecular processes into end products;[40−42] (b) homolytic *inner-sphere ligand transfer*;[44] and (c) homolytic *inner-sphere* alkylation of the iron ligand followed by an *intramolecular SET* process to give the alkylated product.[40,43,44] Kochi observed[44,47] that, for oxidation of alkyl radicals by iron(III)X_3 salts where X is a halide, it is possible to distinguish between oxidation through modes a and b only when the carbocation undergoes a distinctive skeletal rearrangements. At the outset of our study on the iron(II)-induced degradation β-sulfonyl endoperoxides **9** and **10**, the generation of carbocation intermediates was not predicted and iron(II) bromide was used in our first series of experiments. Indeed, the two experiments with hydroxy endoperoxides **9** (Schemes 2 and 5; Table 1, entry 1) can be rationalized by an all-homolytic mechanism (Scheme 3) as well as by a mechanism that includes also a carbocation intermediate (Scheme 4). However, the stereospecific iron(II) bromide-induced degradation of acetoxy-endoperoxide **10** to 5,8-*trans*-acetoxy bromide **26**,[35] and the finding that formation of **26**, on account of competitive rearrangement to aldehyde **14**, is accelerated by 2,6-lutidine (Scheme 6; Table 1, entries 2 and 3),

Scheme 11



provided the first significant indication in favor of involvement of a carbocation intermediate. These results are comparable to some of Kochi's mode (a) processes involving skeletal rearrangements and counterion trapping.[40,47] Sound arguments in favor of the involvement of cationic intermediates are provided in the series of experiments described in Table 2 and Schemes 7 and 10. We suggest that the regioselective formation of cyclohexene **35** (Table 2, entries 1−3) requires oxidation of cyclohexyl radical **31** to cyclohexyl carbocation **32** followed by formation of acetoxonium cation **33** and final proton abstraction by basic acetoxy anion (Scheme 10).

This interpretation is in strong agreement with the findings of Kochi[40] exemplified herein by the reaction described in Scheme 11. Kochi proved, through acetonitrile trapping, that cyclohexyl radical **44** is oxidized by tris(phenanthroline)iron(III) hexafluorophosphate to cyclohexyl carbocation **45**. The resulting nitrilium ion **46** was eventually hydrolyzed to *N*-cyclohexyl acetamide **47** in 67% yield.[48]

Previous reports on the mode of action of antimalarial peroxides have attributed the parasiticidal activity to oxidative damage caused by iron(IV) oxide, free-radical alkylation of heme and of vital proteins, and alkylation of vital biomolecules by electrophilic dicarbonyl and unsaturated carbonyl compounds.[1,19] We suggest that, while the first step in which oxygen-centered radicals are generated through iron(II)-induced reductive cleavage of the peroxide bonds is common to all peroxides, the sequence of events that follow this first step is highly dependent on the overall nature of the peroxide molecule. In the present study on iron(II)-induced degradation of β-sulfonyl peroxides of type **5**, no indication for the involvement of iron(IV) oxide was found. The alkylating power of ketosulfone **11**, of aldehydes **12**, **14**, and of masked dicarbonyl compound **13** is comparable to that of previously reported dicarbonyl and unsaturated carbonyl compounds that were considered as intra-parasitic alkylating electrophiles.[20,25] Possible damage to the parasite can result from alkylation by radicals such as **31** and by carbocations such as **32**. Although the present study was not performed under biomimetic conditions, the strong evidence provided here in favor of the major involvement of carbocations in the iron(II)-induced degradation of acetoxy endoperoxide **10** suggests that carbocations such as **32** may be involved in the parasiticidal activity of β-sulfonyl peroxides of type **5**. Product analysis

(38) The experiment in which cyclohexane **36** was isolated (in an amount of 10 mg) was performed at twice the scale of the other experiments described in Scheme 7 and Table 2 (see the Experimental Section). It is possible that some cyclohexane **36** was formed in other experiments as well but escaped detection.

(39) See: Snider, B. B. *Chem. Rev.* **1996**, *96*, 339−363 and references cited therein.

(40) Rollick, K. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 1319−1330.

(41) Wong, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 5593−5603.

(42) Schlesener, C. J.; Kochi, J. K. *J. Org. Chem.* **1984**, *49*, 3142−3150.

(43) Rollick, K. L.; Kochi, J. K. *J. Org. Chem.* **1982**, *47*, 435−444.

(44) Rollick, K. L.; Kochi, J. K. *Organometallics* **1982**, *1*, 725−732.

(45) Fukuzumi, S.; Wong, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 2928−2939.

(46) For examples, see: (a) Abe, M.; Inakazu, T.; Munakata, J.; Nojima, M. *J. Am. Chem. Soc.* **1999**, *121*, 6556−6562. (b) Kishi, M.; Takahashi, K. *Tetrahedron* **1988**, *44*, 4737−4746. (c) Herz, W.; Ligon, R. C.; Turner, J. A.; Blount, J. F., *J. Org. Chem.* **1977**, *42*, 1885−1895. (d) Turner, J. A.; Herz, W. *Ibid.* 1895−1900. (e) Turner, J. A.; Herz, W. *Ibid.* 1900−1904. (f) Jefford, C. W.; Favarger, F. da Graça, M.; Vincente, H.; Jacquier, Y. *Helv. Chim. Acta* **1995**, *78*, 452−458. (g) Porter, N. *Free Rad. Biol.* **1980**, *IV*, 261−295.

(47) (a) Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 856−865. (b) *Organometallic Mechanisms and Catalysis;* Kochi, J. K., Eds.; Academic Press: New York, 1978; pp 1−83.

(48) The alkylation of nitriles by carbocations is commonly known as the Ritter reaction (Ritter, J. J.; Munieri, P. J. *J. Am. Chem. Soc.* **1948**, *70*, 4045−4048). For reviews on the Ritter reaction, see: (a) Beckwith, A. J. In *The Chemistry of Amides*; Zabicky, J. Z., Ed.; Interscience: New York, 1970; pp 119−125. (b) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213−325. (c) Gridnev, I. D.; Gridneva, N. A. *Usp. Khim.* **1995**, *64*, 1091−1105; *Chem. Abstr.* **1996**, *124*, 288342.

reported for iron-induced degradation of artemisinin (**1**) and other structurally related trioxanes could also be rationalized by the intermediacy of analogous carbocations.[1,17,49]

Experimental Section

^{1}H, COSY, ^{13}C, DEPT, and HMQC NMR data were obtained on Bruker Avance-DPX-250 MHz or Avance-400 MHz systems. $CDCl_3$ was used as an internal standard (δ 7.27 and 77.0 for ^{1}H and ^{13}C NMR, respectively). Infrared data was recorded on a Protégé 460 FT-IR instrument. Desorption chemical ionization (DCI) HRMS and MS spectra were recorded on an Autospec mass spectrometer at 70 eV. Melting points were obtained on a Büchi apparatus and are uncorrected. Flash chromatography (FC) was performed on Merck Si 60 silica gel (230−400 mesh) using ethyl acetate/hexane mixtures as the eluent. All reactions were carried out in oven-dried glassware under an atmosphere of dry argon. All reactions were followed by analytical TLC, which was performed on Merck silica gel 60 F_{254} covered aluminum sheets. Nonracemic β-sulfonyl endoperoxides **9** and **10** were used.[7−9] All solvents were dried using standard procedures and deoxygenated before use. $FeBr_2$ was 98% iron(II) and $Fe(BF_4)_2{\cdot}6H_2O$ was 97% iron(II) as stated by the manufacturer (Aldrich). Iron(II) acetate was analyzed by titration and found to contain approximately 83% iron(II). Given yields are in molar percentage of each component respective to the starting material and are calculated after separation and purification by FC. In cases where yields are calculated from the NMR of mixtures, these contained only components that have been individually characterized.

Degradation of Endoperoxide 9 with Catalytic Amounts of Iron(II) Bromide. To a solution of $FeBr_2$ (21.1 mg; 0.098 mmol; 0.2 equiv) in THF (5 mL) at 0 °C was added a solution of **9**[7−9] (144 mg; 0.44 mmol) in THF (5 mL), and the reaction was stirred at 0 °C. Upon consumption of starting material (12 min), DMAP (14.97 mg; 0.123 mmol), pyridine (3 mL), and acetic anhydride (0.231 mL; 250 mg; 2.45 mmol) were added and the reaction was stirred at room temperature for 22 h. The reaction mixture was poured into 0.333 M HCl (20 mL) and extracted with 25% EtOAc/hexane (8 × 25 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure (0.25 bar, 40 °C). FC gave **14** (29.3 mg; 39%), **11** (57.0 mg; 65%), and **15** (3:2 mixture of epimers, 49.0 mg; 35%).[50]

Degradation of 9 with Iron(II) Bromide and 2,6-Lutidine (Procedure A). $FeBr_2$ (99.7 mg; 0.462 mmol; 1 equiv) was added to a solution of 2,6-lutidine (198 mg; 1.85 mmol; 4 equiv) in THF (11 mL) to give a dark green solution. The solution was cooled to 0 °C, and a solution of **9** (150 mg; 0.4623 mmol) in dry THF (5 mL) was added. The reaction mixture was stirred at 0 °C until all starting material was consumed (15 min). The reaction mixture was poured into a saturated $NaHCO_3$ solution (15 mL) and extracted with 25% EtOAc/hexane (3× 35 mL). The combined organic extracts were washed with 0.333 M HCl (15 mL) and dried (Na_2SO_4), and the solvent was removed under reduced pressure (0.25 bar, 40 °C). FC afforded **24** (19.4 mg; 20%), **25** (13.8 mg; 14%), **11** (70.0 mg; 76%), and 28 mg of an unidentified substance that was active in UV (254 nm) on TLC. This is most probably a decomposition product of aldehyde **12**.

Degradation of 10 with Iron(II) Bromide. The reaction was carried according to procedure A. The only modification was that no 2,6-lutidine was added. Thus, the degradation of 53.7 mg (0.145 mmol) of **10**[7−9] afforded compound **14** (9.2 mg; 37%) and 29.4 mg of a mixture containing **11** and **26** corresponding to 68% and 24%, respectively, as judged by the ^{1}H NMR spectrum.

Degradation of 10 with Iron(II) Bromide in the Presence of 2,6-Lutidine. The reaction was carried out according to procedure A. Thus, the degradation of 107 mg (0.291 mmol) of acetoxy endoperoxide **10** afforded cyclohexyl bromide **26** (39.1 mg; 53%), ketosulfone **11** (51.2 mg; 89%), and diol **27** (10.8 mg; 10%).

Degradation of 10 with Iron(II) Tetrafluoroborate in NMP. To a clear solution of $Fe(BF_4)_2{\cdot}6H_2O$ (95 mg; 0.28 mmol; 1 equiv) in NMP (5 mL) at 0 °C was added a solution of **10** (104 mg; 0.282 mmol) in NMP (3 mL). Upon complete consumption of **10** (15 min), the reaction mixture was poured into a saturated $NaHCO_3$ solution (30 mL) and extracted with 25% EtOAc/hexane (6 × 25 mL). The organic extracts were washed with brine (40 mL) and dried (Na_2SO_4), and the solvent was removed at reduced pressure (0.25 bar, 40 °C). FC afforded aldehyde **14** (16.2 mg; 34% yield) and ketosulfone **11** (41.6 mg; 75% yield).

Degradation of 10 with Iron(II) Tetrafluoroborate in Methanol/Dichloromethane. $Fe(BF_4)_2{\cdot}6H_2O$ (92.2 mg; 0.273 mmol; 1 equiv) was dissolved in methanol (4 mL) to give a clear solution. The solution was cooled to 0 °C, and a solution of **10** (100 mg; 0.273 mmol) in methanol/CH_2Cl_2 (4 mL; 3/1) was added. Upon complete consumption of **10** (15 min), the reaction mixture was poured into a saturated $NaHCO_3$ solution (15 mL) and extracted with 3 × 25 mL of CH_2Cl_2. The organic extracts were washed with brine (30 mL) and dried (Na_2SO_4), and the solvent was removed at reduced pressure (0.25 bar, 40 °C). FC afforded aldehyde **14** (13.4 mg; 29% yield) and ketosulfone **11** (51.7 mg; 96% yield).

Degradation of 10 with Iron(II) Acetate and Tetrabutylammonium Acetate in NMP/THF. $Fe(OAc)_2$ (51.92 mg; 0.299 mmol; 1 equiv) was partly dissolved in a mixture of NMP (2 mL) and THF (2 mL). 2,6-Lutidine (0.116 mg; 1.086 mmol; 4 equiv) and tetrabutylammonium acetate (0.404 g; 1.357 mmol; 5 equiv) were added, and the resulting suspension was cooled to 0 °C. A solution of **10** (98 mg; 0.266 mmol) in THF (4 mL) was added at 0 °C. Upon completion (15 min), the reaction mixture was poured into 0.333 M HCl (15 mL) and extracted with 25% EtOAc/hexane (4 × 35 mL). The combined extract was dried (Na_2SO_4) and the solvent removed under reduced pressure (0.25 bar, 40 °C). FC afforded **35** (5.3 mg; 12%), **11** (9.4 mg; 18%), and **37** (42.1 mg; 43%).

Degradation of 10 with Iron(II) Acetate and Tetrabutylammonium Acetate in NMP Using Slow Addition (Procedure B). $Fe(OAc)_2$ (94.4 mg; 0.54 mmol; 1 equiv) was dissolved in NMP (10 mL). Tetrabutylammonium acetate (0.818 g; 2.71 mmol; 5 equiv) was added, and the resulting solution was cooled to 0 °C. A solution of **10** (200 mg; 0.54 mmol) in NMP (6 mL) was added at 0 °C over 40 min using a syringe pump. The reaction was stirred for an additional 45 min. The reaction mixture was poured into 0.333 M HCl (40 mL) and extracted with 25% EtOAc/hexane (10 × 25 mL). An additional 50 mL of 25% EtOAc/hexane was added, and the combined organic extracts were washed with brine (50 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure (0.25 bar, 40 °C). FC afforded **36** (9.2 mg; 10%), **35** (42.8 mg; 46%), **11** (59.3 mg; 55%), and **37** (31.1 mg; 15%).

Degradation of 10 with Iron(II) Acetate and Tetrabutylammonium Acetate in NMP in the Presence of 2,6-Lutidine Using Slow Addition. The reaction was carried out according to procedure B. The only modification was that 2,6-lutidine (4 equiv) was added to the reaction mixture prior to cooling to 0 °C. Thus, the degradation of acetoxy endoperoxide **10** (96.1 mg; 0.260 mmol) afforded cyclohexene **35** (19.2 mg; 44% yield), ketosulfone **11** (25.2 mg; 49% yield), and cyclohexanone **37** (7.2 mg; 7% yield).

Degradation of 10 with Iron(II) Acetate in NMP Using Slow Addition. The reaction was carried out according to procedure B, but without the addition of tetrabutylammonium-acetate. Thus, the degradation of acetoxy endoperoxide **10** (71.2 mg; 0.193 mmol) afforded aldehyde **14** (23.0 mg; 70%) and ketosulfone **11** (30.5 mg; 80% yield).

Kornblum (Basic) Degradation of 10. To a solution of tetrabutylammonium acetate (110 mg; 0.356 mmol) and 2,6-

(49) Wu, Y.; Yue, Z. Y.; Wu, Y. L. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2580−2582.

(50) The major epimer was isolated in pure form (HPLC) and the structure determined by NMR. The structure of the minor epimer was deduced from the NMR of the mixture of the two epimers.

lutidine (32.4 mg; 0.28 mmol) in THF (1 mL) at 0 °C was added a solution of **10** (26.2 mg; 0.071 mmol) in NMP (1 mL), and the mixture was stirred at 0 °C for 1 h, poured into 0.333 M HCl (10 mL), and extracted with 25% EtOAc/hexane (4 × 25 mL). The combined organic extract was dried (Na_2SO_4) and concentrated at reduced pressure. FC afforded **37** (19.2 mg; 73% yield).

Characterization. 1-Phenylsulfonylacetone(11):[51] white crystals; R_f = 0.4 (EtOAc/hexane 1:1); mp 52−54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 4.17 (s, 2H), 7.59 (m, 2H, Ar-H), 7.70 (m, 1H, Ar-H); 7.89 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.34 (CH_3), 67.70 (CH_2), 129.36 (CH, 2 Ar-C), 129.41 (CH, 2 Ar-C), 134.31 (CH, Ar-C), 138.58 (C, Ar-C), 195.80 (C=O).

(5*R*)-5-Acetoxy-5-methyl-6-oxo-1,2-hexene (14): colorless oil; R_f = 0.75 (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45(s, 3H), 1.75 (ddd, *J* ≈ 5.7, 10.8, 14.1 Hz, 1H), 1.91 (ddd, *J* ≈ 5.5, 10.9, 14.1 Hz, 1H), 2.08−2.2 (m, 2H), 2.13 (s, 3H), 5.0 (dddd, *J* ≈ 1.1, 1.3, 1.3, 10.2 Hz, 1H), 5.05 (dddd, *J* ≈ 1.5, 1.6, 1.6, 17.0 Hz, 1H), 5.78 (dddd, 6.5, 6.5, 10.2, 17.0 Hz, 1H), 9.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 18.64 (CH_3), 20.91-(CH_3), 27.02(CH_2), 34.37(CH_2,), 84.42(C), 115.37 (CH_2=), 137.23 (CH=), 198.64 (CH=O); IR ($CHCl_3$) *v* 3110 (m), 2937 (m), 2853 (m), 1783 (s), 1641 (m), 1451 (m), 1372 (s), 1257 (m) cm^{-1}; MS (*m*/*z*) 171.10 (M + 1, 99), 141.08 (24), 127.08 (46), 111.08 (100), 99.10 (22); HRMS calcd for $C_9H_{15}O_3$ [M + 1] 171.1021, found: 171.0982 (δ 3.9 mDa).

(4*R*,5*R*)-5-Methyl-4-(3-oxobutyl)-5-phenylsulfonylmethyl-tetrahydro-2-furanyl acetate (15) (3:2 mixture of epimers):[50] oil; R_f = 0.15 (EtOAc/hexane 1:1). Major epimer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.50 (m, 1H), 1.80 (ddd, *J* ≈ 13.0, 13.0, 4.7 Hz, 1H), 1.93 (s, 3H), 2.00−2.08 (m, 1H), 2.14 (dd, *J* ≈ 13.0, 6.8 Hz, 1H), 2.19 (s, 3H), 2.50−2.54 (m, 3H), 3.41 (s, 2H), 6.14 (d, *J* ≈ 4.7 Hz, 1H), 7.56−7.62 (m, 3H, Ar-H), 7.91−7.93 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.31 (CH_3), 21.89 (CH_3), 23.52 (CH_2), 29.90 (CH_3), 37.72 (CH_2), 42.50 (CH_2), 43.65 (CH), 66.51 (CH_2SO_2), 85.14 (C), 96.78 (CH, acetal-C), 127.83 (CH, 2 Ar-C), 129.15 (CH, 2 Ar-C), 133.60 (CH, Ar-C); 142.0 (C, Ar-C), 169.93 (C=O, ester); 207.86 (C=O, ketone); IR (neat) *v* 3618 (w), 3585 (m), 3063 (s), 2980 (m), 2928 (m), 1740 (s), 1716 (s), 1446 (m), 1413 (w), 1377 (m), 1363 (m), 1306 (s), 1238 (s), 1145 (s), 1085 (s), 1014 (s); MS (*m*/*z*) 309.12 (M + 1 − AcOH, 10), 250.07 (10), 199.04 (31), 167.10 (100), 153.09 (56), 149.09 (90), 121.10 (70); HR-MS molecular ion peak absent, calcd for $C_{16}H_{21}O_4S$ [M + 1 − AcOH] 309.1161, found 309.1160 (δ 0.1 mDa). Minor epimer: ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.31 (CH_3), 21.86 (CH_3), 22.48 (CH_2), 29.95 (CH_3), 37.20 (CH_2), 42.31 (CH_2), 44.14 (CH), 66.41 (CH_2SO_2), 84.54 (C), 97.17 (CH, acetal-C), 127.98 (CH, 2 Ar-C), 129.08 (CH, 2 Ar-C), 133.62 (CH, 1 Ar-c), 140.97(C, 1 Ar-C), 169.97 (C=O, ester), 207.95 (C=O).

(1*R*,2*R*,4*S*)-1-Methyl-4-bromo-1,2-cyclohexanediol (24): white needle crystals; R_f = 0.15 (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$, 50 °C) δ 1.23 (3H, s), 1.6 (br, 1 OH), 1.75 (ddd, *J* ≈ 4.1, 7.0, 13.6 Hz, 1H), 1.85 (ddd, *J* ≈ 4.2, 8.8, 13.6 Hz, 1H), 1.90 (br, 1 OH), 1.96 (m, 1H), 2.00 (m, 1H), 2.10 (ddddd, *J* ≈ 1.3, 4.2, 7.0, 6.5, 14.3 Hz, 1H), 2.37 (dddd, *J* ≈ 1.3, 3.8, 6.7, 14.2 Hz, 1H), 3.90 (dd, J≈3.8, 7.8 Hz, 1H), 4.51 (dddd, *J* ≈ 3.8, 3.1, 6.5, 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1 (CH_3, br), 32.74 (CH_2), 34.37 (CH_2), 40.03 (CH_2), 49.43 (CH), 74.00 (CH); IR (KBr) *v* 3330 (s, br), 2920 (m, br.), 2847 (m), 1465 (m), 1433 (m), 1128 (m), 1071 (m), 1040 (m) cm^{-1}; MS (*m*/*z*) 210 (M + 1, ^{81}Br, 1), 208.01 (M + 1, ^{79}Br, 1.5) 192.99 (16), 190.99 (17), 128.08 (100), 111.08 (69), 97.07 (12); HR-MS calcd for $C_7H_{13}O_2{}^{79}Br$ [M + 1] 208.0099, found 208.0085 (δ 1.4 mDa).

(1*R*,2*R*,4*R*)-1-Methyl-4-bromo-1,2-cyclohexanediol (25): white needle crystals; R_f = 0.25 (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 3H), 1.46 (ddd, *J* ≈ 4.0, 13.5, 13.5 Hz, 1H), 1.79 (ddd, *J* ≈ 3.9, 3.9, 13.4 Hz, 1H), 1.83 (m, 1H), 1.89 (ddd, *J* ≈ 11.5, 11.5, 13.0 Hz, 1H), 2.08 (br, 1 OH), 2.22 (ddddd, *J* ≈ 2.0, 4.3, 4.3, 4.0, 13.5 Hz, 1H), 2.46 (br, 1 OH); 2.47 (dddd, *J* ≈ 2.0, 4.3, 4.0, 13.0 Hz, 1H), 3.51 (dd, *J* ≈ 4.0, 11.5 Hz, 1H), 4.01 (dddd, *J* ≈ 4.3, 4.3, 11.5, 11.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.62 (CH_3), 34.68 (CH_2), 37.40 (CH_2), 41.80 (CH_2), 46.12 (CH), 72.83 (C), 75.90 (CH); IR (KBr) *v* 3440 (br, s), 2952 (m), 2923 (m), 2863 (m), 1466 (m), 1437 (m), 1383 (m), 1130 (m), 1071 (s), 1041 (m) cm^{-1}; MS (*m*/*z*) 210 (M + 1, ^{81}Br, 1), 208.01 (M + 1, ^{79}Br, 1), 192.99 (17), 190.99 (13), 128.08 (100), 111.08 (69), 97.07 (12); HRMS calcd for $C_7H_{13}O_2{}^{79}Br$ [M + 1] 208.0099, found 208.0090 (δ 0.9 mDa).

(1*R*,2*R*,4*R*)-1-Methyl-4-bromo-1-acetoxycyclohexan-2-ol (26): colorless oil; R_f = 0.35 (EtOAc/hexane 3:7); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (d, 3H, *J* ≈ 0.5 Hz), 1.65 (ddd, *J* ≈ 13.5, 13.5, 3.4 Hz, 1H), 1.83 (dddd, *J* ≈ 13.5, 13.4, 11.4, 3.5 Hz, 1H), 1.92 (ddd, *J* ≈ 13.4, 11.0, 11.0 Hz, 1H), 2.04 (s, 3H), 2.18 (ddddd, 13.5, 4.2, 4.2, 3.8, 2.2 Hz, 1H), 2.27 (ddd, *J* ≈ 13.5, 3.5, 3.4 Hz, 1H), 2.51 (dddd, *J* ≈ 13.4, 4.5, 4.2, 2.2 Hz, 1H), 3.78 (dd, *J* ≈ 11.0, 4.5 Hz, 1H), 3.81 (br, s, 1OH), 3.99 (dddd, *J* ≈ 11.4, 11.4, 4.2, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.18 (CH_3), 22.34 (CH_3), 33.78 (CH_2), 34.78 (CH_2), 41.28 (CH_2), 45.43 (CH), 73.74 (CH), 86.07 (C), 171.51 (C=O, ester); IR (neat) *v* 3427 (br, s), 1731 (s), 1416 (m), 1370 (m), 1274 (m), 1245 (m), 1112 (m), 1076 (m), 1046(m), 1024 (m) cm^{-1}; MS (*m*/*z*) 253.03 (M + 1, ^{81}Br 55), 251.03 (M + 1, ^{79}Br, 52), 235.03 (55), 233.77 (52), 192.99 (98), 190.99 (100), 171.10 (31), 111.08 (37); HRMS calcd for $C_7H_{13}O_2{}^{79}Br$ [M + 1] 251.0283, found 251.0338 (δ 5.5 mDa).

(1*R*,2*R*,4*R*)-2-Hydroxy-4-[(1*R*)-1-hydroxy-1-methyl-2-phenylsulfonylethyl]-1-methylcyclohexyl acetate (27): colorless oil; R_f = 0.10 (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.08 (dddd, *J* ≈ 3.3, 12.6, 12.6, 13.5 Hz, 1H), 1.2 (1H, ddd, *J* ≈ 11.5, 12.6, 12.6 Hz, 1H), 1.42 (s, 3H), 1.46 (s, 3H), 1.55 (ddd, *J* ≈ 3.6, 13.5, 13.5 Hz, 1H), 1.76 (ddd, *J* ≈ 3.3, 3.3, 12.6 Hz, 1H), 1.79 (dddd, *J* ≈ 3.3, 3.3, 12.6, 12.6 Hz, 1H), 2.04 (s, 3H), 2.08 (m, 1H), 2.28 (ddd, *J* ≈ 3.3, 3.3, 13.5 Hz, 1H), 3.24 (d, *J* ≈ 14.0 Hz, 1H), 3.34 (d, *J* ≈ 14.0 Hz, 1H), 3.77 (s, 1 OH), 3.79 (dd, *J* ≈ 4.9, 11.5 Hz, 1H), 4.0 (br, 1 OH), 7.60 (m, 2H, Ar-H), 7.68 (1H, m, Ar-H), 7.92 (2H, m, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.63 (CH_3), 22.40 (CH_3), 23.60 (CH_2), 24.29 (CH_3), 31.20 (CH_2), 35.70 (CH_2), 45.63 (CH), 63.42 (CH_2), 73.68 (C), 74.67 (CH), 87.67 (C), 127.48 (CH, 2 Ar-C), 129.47 (CH, 2Ar-C), 133.95 (CH, Ar-C), 141.1 (C, Ar-C), 171.91 (C=O, ester); IR (neat) *v* 3457 (br, s), 3060 (m), 2948 (m), 2874 (m), 1721 (s), 1447 (m), 1370 (m), 1260 (m) cm^{-1}; MS (*m*/*z*) 371.16 (M + 1, 27), 311.14 (19) 293.01 (20), 275.11 (8), 250.07 (12), 199.04 (38), 151.11(100), 133.09 (21); HRMS calcd for $C_{18}H_{27}O_6S$ [M + 1] 371.1528, found 371.1590 (δ 6.2 mDa).

(4*R*,5*R*)-4-Acetoxy-5-hydroxy-4-methylcyclohexene (35): colorless oil; R_f = 0.46 (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 3H), 2.03 (s, 3H), 2.06 (m, 1H), 2.39 (m, *J* ≈ 17.0 Hz, 1H), 2.46 (m, *J* ≈ 3 Hz, 1H), 2.53 (br s, 1 OH), 2.83 (m, *J* ≈ 4.0, 17.0 Hz, 1H), 4.05 (ddd, *J* ≈ 9.0, 5.8, 3.0 Hz, 1H), 5.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.13 (CH_3), 22.48 (CH_3), 31.36 (CH_2), 36.22 (CH_2), 71.25 (CH), 83.94 (C), 123.46 (CH), 124.40 (CH), 170.55 (C=O, Ester); IR (neat) *v* 3455 (s, br), 3031 (w), 2984 (w), 2937 (m), 2856 (w), 1728 (s), 1657 (w), 1437 (m), 1367 (m), 1254 (s), 1080 (s) cm^{-1}; MS (*m*/*z*) 171.10 (M + 1, 6), 153.8 (6) 139.12 (11), 125.08 (20), 110.98 (100); HRMS calcd for $C_9H_{15}O_3$ [M + 1] 171.1021, found 171.1027. (δ 0.6 mDa).

(1*R*,2*R*)-1-Acetoxy-2-hydroxy-1-methylcyclohexane (36): colorless oil; R_f = 0.50 (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25−1.2 (m, 4H), 1.48 (s, 3H), 1.5−1.7 (m, 2H), 1.92 (m, 1H), 2.03 (s, 3H), 2.17 (m, 1H), 3.63 (br s, 1OH), 3.77 (dd, *J* ≈ 4.3, 9.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.51 (CH_3), 22.45 (CH_3), 22.49 (CH_2), 23.09 (CH_2), 30.73 (CH_2), 35.71 (CH_2), 74.40 (CH), 87.70 (C); 171.67 (C=O, ester); MS (*m*/*z*) 173.12 (M + 1, 25), 130.09 (10), 113.12 (100), 112.12 (93), 95.08 (28); HRMS calcd for $C_9H_{17}O_3$ [M + 1] 173.1178, found 173.1180 (δ 0.2 mDa).

(1*R*,4*R*)-4-[(1*R*)-1-Hydroxy-1-methyl-2-phenylsulfonylethyl]-1-methyl-2-oxocyclohexyl acetate (37): oil; R_f = 0.10 (EtOAc/hexane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 3H), 1.51 (s, 3H), 1.52 (dddd, *J* ≈ 3.6, 13.1, 14.0, 14.0 Hz, 1H), 1.92−

(51) The NMR data of **11** match the data reported in the literature: Thomsen, M. W.; Handwerker, B. M.; Katz, S. A.; Belser, R. B. *J. Org. Chem.* **1988**, *53*, 906−907. These authors also report an IR spectrum and a correct elemental analysis.

2.0 (m, 2H), 2.22 (dddd, $J \approx 3.0, 3.0, 11.5, 13.1$ Hz, 1H), 2.32 (dd, $J \approx 13.1, 15.4$ Hz, 1H), 2.34 (ddd, $J \approx 5.1, 14.0, 14.0$ Hz, 1H), 2.66 (ddd, $J \approx 3.0, 3.0, 15.4$ Hz, 1H), 3.24 (d, $J \approx 14.0$ Hz, 1H), 3.33 (d, $J \approx 14.0$ Hz, 1H), 3.81 (br, 1OH), 7.62 (m, 2H, Ar-H), 7.68 (m, 1H, Ar-H), 7.93 (m, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.24 (CH_3), 23.58 (CH_2), 23.64 (CH_3), 23.93 (CH_3), 35.19 (CH_2), 39.52 (CH_2), 46.04 (CH), 63.53 (CH_2), 73.05 (C), 81.93 (C), 127.43 (CH, 2 Ar-C), 129.47 (CH, 2 Ar-C), 133.94 (CH, Ar-C), 140.99 (C, Ar-C), 171.91 (C=O, ester), 205.88 (C=O, ketone); IR (neat) ν 3510 (s, br), 3059 (w), 2986 (m), 2937 (m), 1737 (s), 1720 (s,), 1445 (m), 1370 (m), 1307 (s), 1258 (s), 1141 (s) cm^{-1}; MS (m/z) 369.14 (M + 1, 4), 309.107 (100), 291.09 (84), 199.04 (14); HRMS calcd for $C_{18}H_{25}O_6S$ [M + 1] 369.1372, found 369.1357 (δ 1.4 mDa).

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Supporting Information Available: ^{1}H NMR spectra of compounds **11**, **14**, **15** (a spectra of the mixture of epimers and a spectra of the pure major epimer), **24**−**27**, and **35**−**37** and ^{13}C NMR spectra of **15** (a spectra of the mixture of epimers and a spectra of the pure major epimer). This material is available free of charge via the Internet at http://pubs.acs.org.

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