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Regioselective radical cyclization initiated by the reaction of allylic hydroperoxides with iron(II) sulfate

Araki Masuyama,[a,*] Tomohiro Sugawara,[a] Masatomo Nojima[a] and Kevin J. McCullough[b,*]

[a]*Department of Materials Chemistry, Graduate School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan*
[b]*Department of Chemistry, Heriot-Watt University, Edinburgh EH14 4AS, Scotland, UK*

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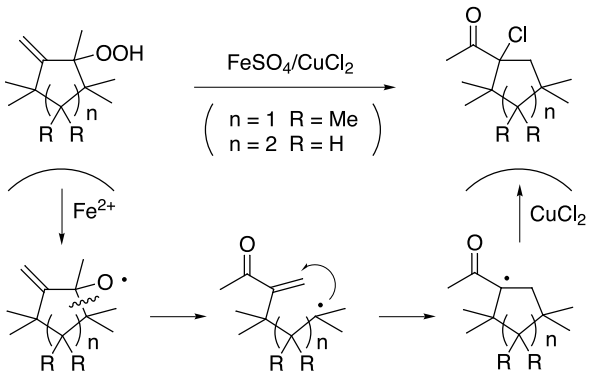
Abstract—Treatment of 1-methyl-2-methylene-1-cyclohexyl hydroperoxide with a mixture of $FeSO_4/CuCl_2$ yielded 1-(1-chlorocyclohexyl)ethanone as the major product consistent with 6-*endo-trig* cyclization of the intermediate 5-acetylhex-5-enyl radical. This strategy was extended to the ring enlargement of a series of 1-isopropenylcycloalkyl hydroperoxides. Regioselective 7- or 8-*endo-trig* cyclization reactions could be achieved by treatment of the corresponding cyclopentyl or cyclohexyl hydroperoxides with either a mixture of $FeSO_4/CuCl_2$ or with $FeSO_4$ only. The influence of substituents on the efficiency of the 8-*endo-trig* cyclization process was also explored. © 2003 Published by Elsevier Science Ltd.

1. Introduction

The regioselectivities of cyclization reactions arising from the intramolecular additions of radical intermediates to double or triple carbon–carbon bonds have been extensively studied.[1] Consequently, a variety of methods have been developed to control the regioselectivities of such radical cyclization reactions.[2] In connection with this, we previously reported efficient 5-*endo-trig* or 6-*endo-trig* cyclizations of carbon-centered radicals.[3] Thus, treatment of polymethylated 2-methylene-cyclopentyl (or hexyl) hydroperoxides with $FeSO_4/CuCl_2$[4] afforded polymethylated 1-(1-chlorocyclopentyl [or hexyl])ethanone as outlined in Scheme 1.



Scheme 1.

In this paper, we report further examples of 6-, 7- and 8-*endo-trig* cyclization reactions of intermediate carbon-centered radicals generated by the sequential reductive cleavage of the O–O bond of an allylic hydroperoxide followed by β-scission of an adjacent C–C ring bond. A key feature of this process is the intermediacy of carbon-centered radicals possessing an α,β-unsaturated carbonyl functionality. In additional, ring substituents of the 1-isopropenylcyclohexyl hydroperoxides are found to exert a significant influence on the efficiency of 8-*endo-trig* cyclization reaction.

2. Results and discussion

2.1. Preparation of allylic hydroperoxides

A series of allylic hydroperoxides **17**–**32**, required as substrates for our studies, could be prepared in satisfactory to moderate yield by choosing one of the following methods as appropriate: the ene reaction between alkenes and singlet oxygen (Method A),[3,5] the acid-catalyzed reaction of 1-isopropenylcycloalkanol with hydrogen peroxide (Method B),[6] and the reaction of isopropylidenecycloalkanes with triphenylphosphite ozonide (Method C).[7] The results are summarized in Table 1.

The hydroperoxides **17**–**32** were isolated by column chromatography on silica gel with diethyl ether/hexane as

Keywords: *endo-trig* radical cyclization; ring enlargement; allylic hydroperoxide; iron(II) sulfate.

* Corresponding authors. Tel.: +81-131-451-8029; fax: +81-131-451-3180; e-mail: k.j.mccullough@hw.ac.uk

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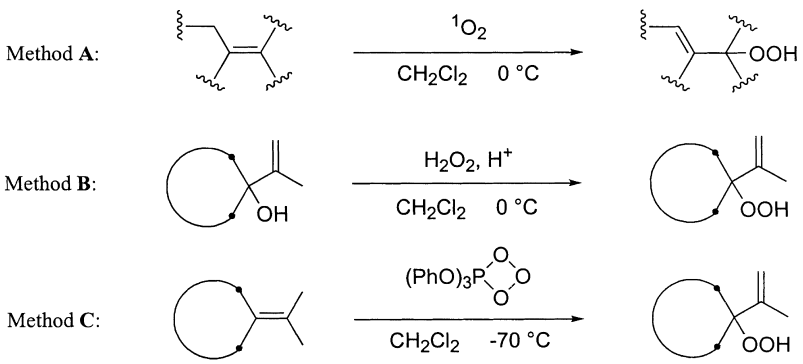
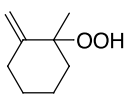
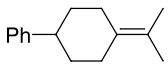
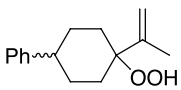
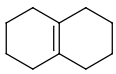
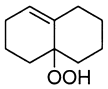
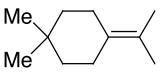
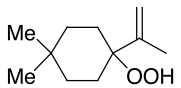
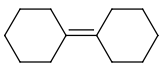
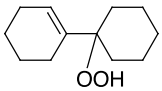
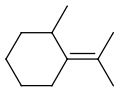
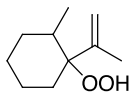
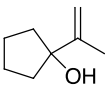
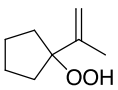
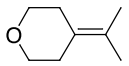
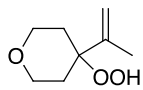
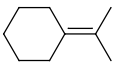
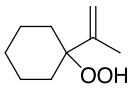
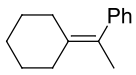
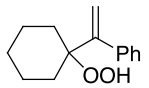
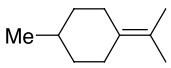
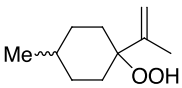
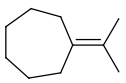
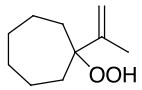
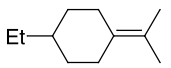
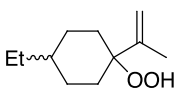
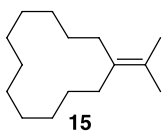
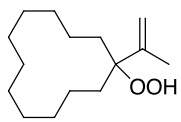
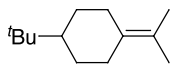
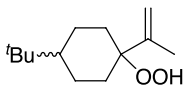
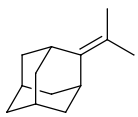
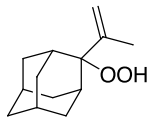
Table 1. Preparation of allylic hydroperoxides **17**–**32**



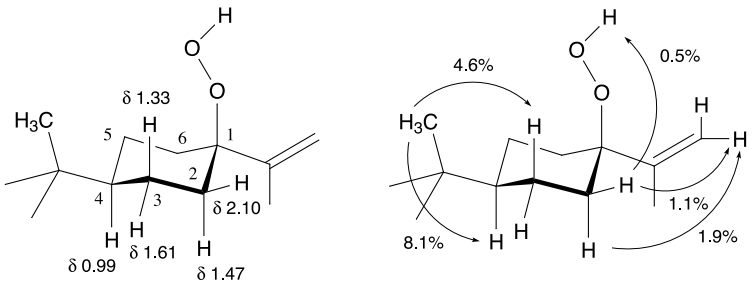
Alkene	Method	Hydroperoxide (yield)	Alkene	Method	Hydroperoxide (yield)
 **1**	A	 **17** (65%)	 **9**	A	 **25** (45%)
 **2**	A	 **18** (56%)	 **10**	A	 **26** (57%)
 **3**	A	 **19** (49%)	 **11**	C	 **27** (52%)
 **4**	B	 **20** (17%)	 **12**	A	 **28** (46%)
 **5**	C	 **21** (63%)	 **13**	A	 **29** (27%)
 **6**	A	 **22** (22%)	 **14**	C	 **30** (46%)
 **7**	A	 **23** (30%)	 **15**	C	 **31** (96%)
 **8**	C	 **24** isomer 24a (26%) isomer 24b (22%)	 **16**	A	 **32** (98%)

[a] Two stereoisomers could be separated by column chromatography on silica gel; isomer **24a** was a solid (mp 54–55°C), whereas isomer **24b** was an oil.

eluent. In the case of hydroperoxide **24**, the two stereoisomers **24a** and **24b** could be separated. The structure of the isomeric hydroperoxide **24a** was determined from the results of a series of HMQC, HMBC and NOE experiments. In general, the chemical shift assignments and NOE results are consistent with a chair-like conformation of the cyclohexane ring with a 1,4-*cis*-relationship between the *tert*-butyl and the hydroperoxide groups as indicated in Figure 1.

2.2. Reaction of allylic hydroperoxides 17–19 with $FeSO_4/CuCl_2$ or with $FeSO_4$ only

Treatment of a solution of 1-methyl-2-methylene-1-cyclohexyl hydroperoxide (**17**) in acetonitrile with an aqueous solution of $FeSO_4$ and $CuCl_2$ (1:3 equiv.) at room temperature gave a mixture of 3-methylene-7-chloroheptan-2-one (**35**) and 1-(1-chlorocyclohexyl)ethanone (**36**). The absence of 1-(1-chlorocyclopentyl)ethanone (**37**)



C-2 and C-6, δ 32.19; C-3 and C-5, δ 22.34; C-4, δ 47.62

Figure 1. Assignment and NOE enhancement of compound **24a**.

as a significant component of the product mixture suggests that the 6-*endo-trig* cyclization is much faster than the alternative 5-*exo-trig* mode (Scheme 2) as observed previously for the reaction of 1,3,3,6,6-pentamethyl-2-methylene-1-cyclohexyl hydroperoxide (n=2 and R=H in Scheme 1) with $FeSO_4/CuCl_2$.[3]

The ratio of the cyclic to acyclic product, **36** and **35** respectively, was found to depend on the initial concentration of hydroperoxide **17**. Thus, both **36** and **35** were isolated (24 and 12%, respectively) from the reaction in which the initial concentration of **17** was 60 mM, whereas only the cyclized product **36** (58%) was isolated when the initial concentration of **17** was reduced to 5 mM.

Although tertiary alkyl radicals are generally considered to be more reactive than primary alkyl radicals towards electron-deficient alkenes as a consequence of more favorable FMO interactions,[8] 6-*endo-trig* cyclization appears, however, to proceed effectively in the case of the intermediate primary alkyl radical **33** derived from hydroperoxide **17**.

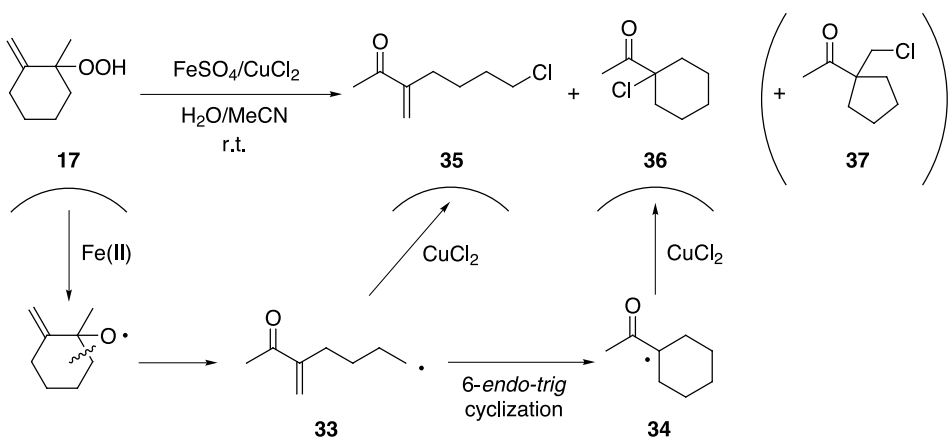
Further confirmation of this predominance of the 6-*endo-trig* mode of cyclization for alkyl radical **33** was evident when the iron(II)-catalyzed decomposition of hydroperoxide **17**, carried out in the absence of $CuCl_2$, yielded a new crystalline compound **38** as the sole isolable product (28%). By X-ray crystallographic analysis, compound **38** was shown to be the centrosymmetrical dimer of the 6-*endo-trig* cyclized radical **34** (Fig. 2). The formation of analogous dimeric products has also been observed in the preparation of macrolides using similar procedures.[4b]

By analogy with the results described above, treatment of the bicylic hydroperoxide **18**, derived from octahydronaphthalene **2**, with $FeSO_4/CuCl_2$ (1:3 equiv.) afforded the corresponding 6-*endo-trig* cyclization product **39**, as a mixture of *cis*- and *trans*-isomers, in good yield (67%) (Scheme 3). Although the reaction of hydroperoxide **19** with $FeSO_4/CuCl_2$ (1:3 equiv.), as described above, gave a complex mixture of unidentified products, the reductive decomposition of hydroperoxide **19** using only $FeSO_4$ (2 equiv.) was relatively clean and yielded the bicyclic product **40** (21%) arising from the novel 8-*endo-trig* mode of cyclization[2e] along with the acyclic reduction product **41** (33%).

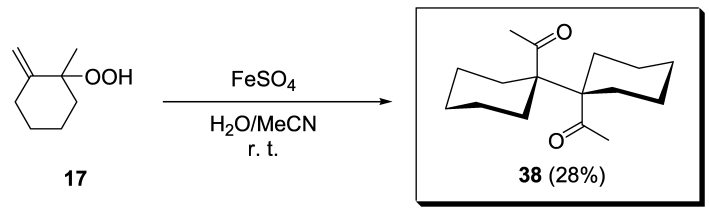
In most cases, the reactions described above also afforded additional highly polar, intractable, tarry products, the nature of which was not investigated further.

2.3. Ring enlargement of 1-isopropenylcycloalkyl hydroperoxides 20,21,30,31 and 32 by this radical cyclization method: scope and limitations

Alkoxy radicals, derived from 1-ethenylcycloalkanols or their related compounds, are key intermediates in a two-carbon ring expansion protocol.[9] By analogy, the above results encouraged us to explore further the ring enlargement reactions of 1-isopropenylcycloalkyl hydroperoxides as potential precursors of medium-sized carbocycles.



Scheme 2. *Reaction conditions*: compound **17**/$FeSO_4/CuCl_2$=1:1:3 (molar ratio), in H_2O/MeCN (2:1, v/v) at room temperature for 2 h.



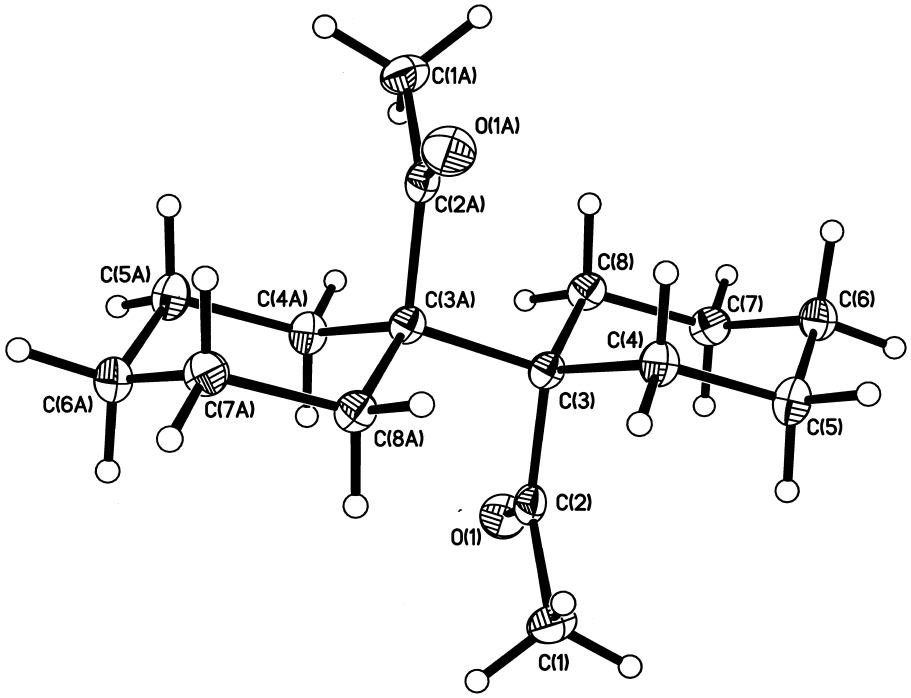


Figure 2. The X-ray crystal structure of compound **38** (ORTEP, 50% probability ellipsoids).

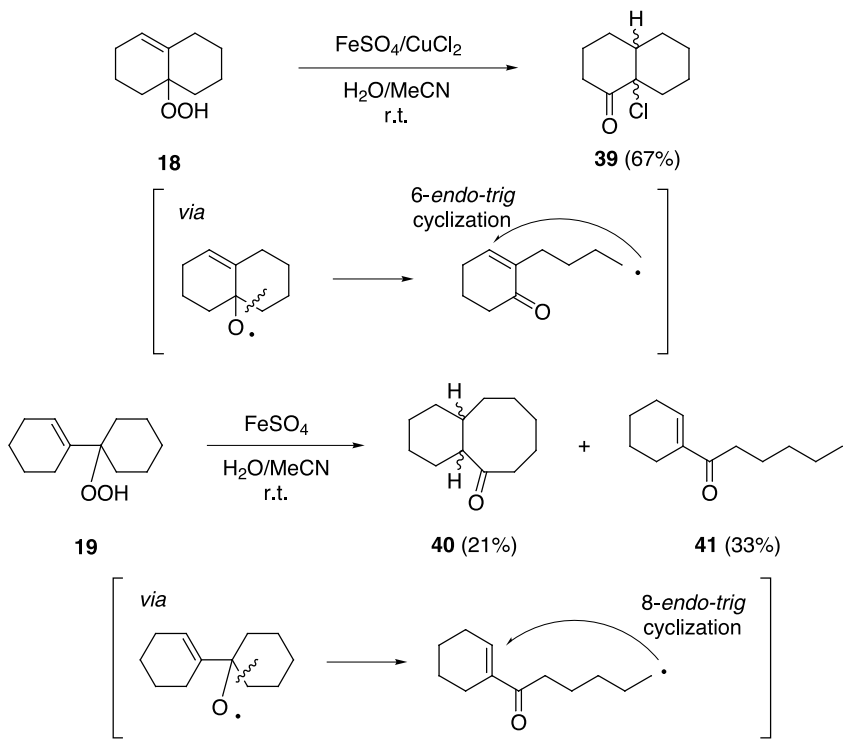
It was expected that induced decomposition of an *n*-membered 1-isopropenylcycloalkyl hydroperoxide with $FeSO_4$ followed in quick succession by β-scission and (*n*+2)-*endo-trig* cyclization of the intermediate alkyl radical would result in the formation of an (*n*+2)-membered carbocycle after appropriate termination (Scheme 4). First, the reaction of the corresponding cyclopentyl hydroperoxide **20** with $FeSO_4$ (3 equiv.) in H_2O/MeCN afforded 1,1′-dimethylbicycloheptyl-2,2′-dione (**42**) (24%) as a mixture of stereoisomers (*meso* and *dl* forms). Similarly, when the hydroperoxide **20** was reacted with a mixture of $FeSO_4$/ $CuCl_2$ (2:3 equiv.), 2-chloro-2-methylcycloheptanone (**43**) was obtained as the sole isolable product. Analysis of the product mixture by NMR spectroscopy indicated that the 6-*exo-trig* cyclization product, 2-chloromethyl-2-methylcyclohexanone, had not been formed in significant quantities (<5%).

Reaction of the cyclohexyl hydroperoxide **21** with $FeSO_4$ gave 1,1′-dimethylbicyclooctyl-2,2′-dione (**44**) (41%), whereas the acyclic product, 8-chloro-2-methyloct-1-ene-3-one (**45**), was predominantly obtained from the $FeSO_4$/ $CuCl_2$ reaction. This suggests that the rate of 8-*endo-trig* cyclization of intermediate alkyl radical is appreciably slower than that of chlorine atom transfer.

Ring enlargement of cycloheptyl and cyclododecyl hydroperoxides **30** and **31** was not achieved under the reaction conditions employed in this work. Reaction of these hydroperoxides with $FeSO_4$ gave complex, intractable mixtures. However, acyclic chloroketones **46** and **47** were isolated in 55 and 72% yields, respectively, when these hydroperoxides were treated with a mixture of $FeSO_4$/-$CuCl_2$. In the reaction of adamantyl hydroperoxide **32** with $FeSO_4$/$CuCl_2$, the corresponding epoxide derivative **49** was isolated in 6% yield besides the allylic alcohol **48** (40%) as a result of reduction of **32**. This result suggests that the adamantyl ring system is reluctant to undergo β-scission and 3-*exo-trig* cyclization of the intermediate alkoxy radical is also possible.

2.4. Effect of some structural factors of 1-isopropenylcyclohexyl hydroperoxides on the efficiency of 8-*endo-trig* cyclization

The occurrence of 8-*endo-trig* cyclization had been clearly demonstrated by the formation of the 2-methylcyclooctanone dimer **44** in the reaction of hydroperoxide **21** with $FeSO_4$ even though the corresponding cyclized product was not detected in the $FeSO_4$/$CuCl_2$ reaction system. Since the rate of radical cyclization is significantly influenced by



Scheme 3. *Reaction conditions*: hydroperoxide/$FeSO_4$/$CuCl_2$=1:1:3 (molar ratio), in H_2O/MeCN (2:1, v/v) at room temperature for 2 h.

substituents on the skeleton of parent radicals,[1,8,10] the possibility of 8-*endo-trig* cyclization in the $FeSO_4$/$CuCl_2$ system was pursued by structural modification of the parent substrate **21**.

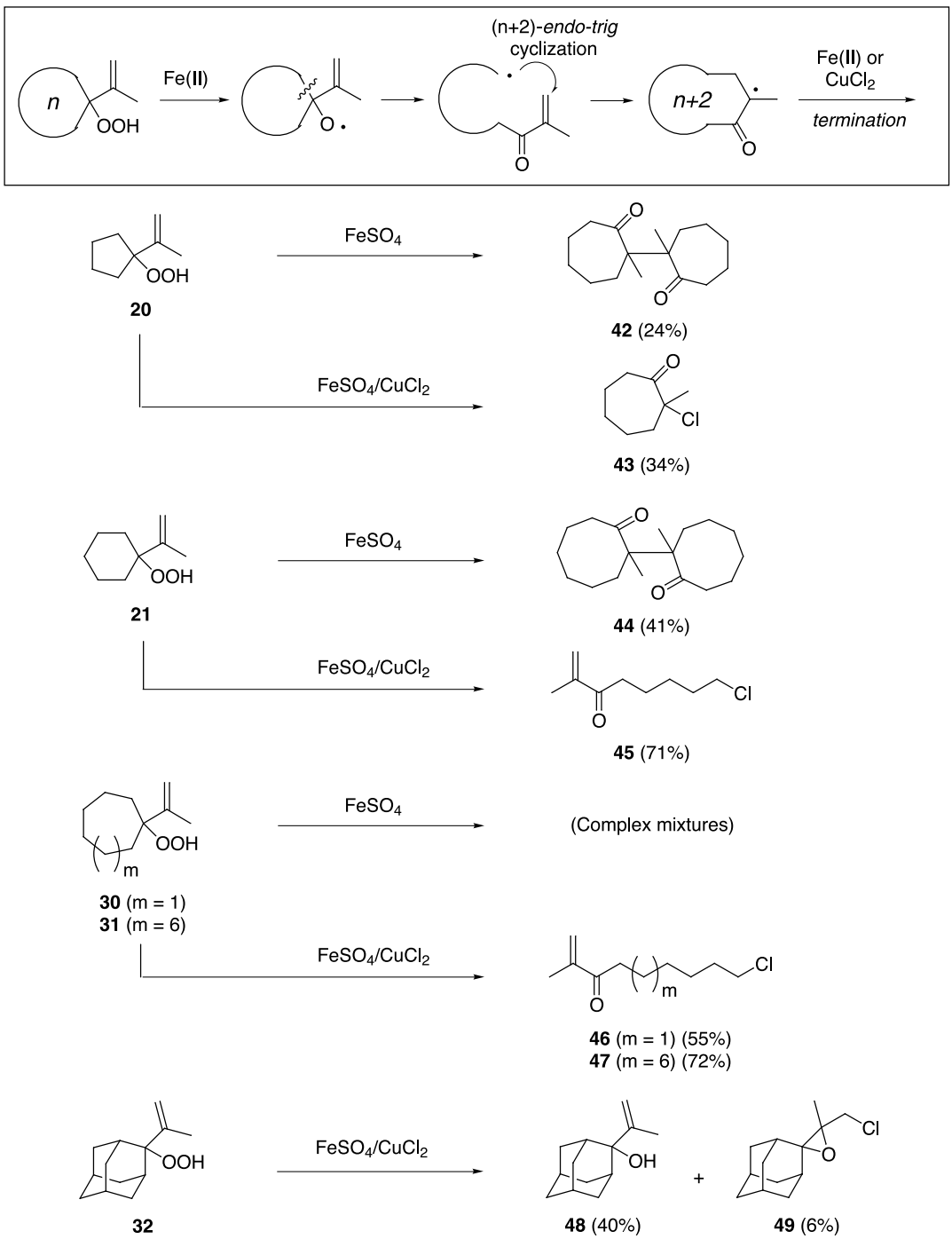
Beckwith et al. have reported the beneficial effect of a *tert*-butyl substituent on 5-*exo-trig* cyclization of 5-hexenyl radicals.[11] In our work, treatment of one isomer of 4-*tert*-butyl-1-isopropenylcyclohexyl hydroperoxide (**24a**) with a mixture of $FeSO_4$/$CuCl_2$ afforded the corresponding chloro-substituted 8-*endo-trig* cyclization products (60%) as a separable mixture of two stereoisomers **53a** and **53b** (5:1). The structure of the crystalline minor isomer **53b** was shown unambiguously by X-ray crystallographic analysis to be *c*-6-*tert*-butyl-*r*-2-chloro-2-methylcyclooctanone (Fig. 3). The crystal structure of compound **53b** is unusual because there are four independent molecules clustered together in the asymmetric unit. Each molecule has a slightly distorted boat-chair conformation and they show only minor differences in the positions of corresponding ring atoms (r.m.s. deviation <0.03 Å). Although the major isomer **53a** did not provide single crystals suitable for X-ray analysis, this isomer was assigned to the corresponding *trans* form. Another hydroperoxide isomer **24b** also gave a mixture of **53a** and **53b** (61%) under the same reaction conditions. In addition, the reduction product **64** was isolated (12%) (Scheme 5). This alcohol was not detected by TLC and ^{1}H NMR analysis as a component of the crude product mixture obtained from substrate **24a**.

Since the 4-*tert*-butyl substituent in hydroperoxides **24a** appeared to enhance the efficiency of cyclization in the $FeSO_4$/$CuCl_2$ reaction system, the effects of other substituents and substitution patterns on the 8-*endo-trig* radical cyclization process were investigated further. The results obtained for hydroperoxides **21**–**27** are summarized in Table 2.

In general, the yields of the cyclized products tended to increase as those of the acyclic products decreased with increasing the size of 4-alkyl substituent, except that the 4-phenyl group did not favor cyclization at all. It was found that the yield (17%) of cyclooctane **51** derived from hydroperoxide **22** bearing a 4-methyl substituent was more than double that of cyclized product **55** from substrate **26** having a *gem*-dimethyl moiety at the same position. Although positive *gem*-dimethyl group effects have been observed on the rate of *n*-membered lactonization of ω-bromoalkanoate ions (particularly n=6 and 9) in DMSO,[12] the comparatively low yield of cyclic product suggests that this effect is less pronounced in 8-*endo-trig* radical cyclization reactions.

Decomposition of the 2-methyl substituted hydroperoxide **27** resulted in the formation of the 2-chlorocyclooctanone **56** in 26% yield as well as the acyclic chloride **63** (17%). When compared to the corresponding reaction involving the parent compound **21**, these products indicate that the introduction of 2-methyl substituent resulted in a selective cleavage of the cyclohexyl ring and promoted rather than inhibited 8-*endo-trig* cyclization.

The replacement of a ring carbon by an oxygen atom is known to improve the efficiency of cyclization in certain cases.[8,13] The reaction of hydroperoxide **28** with $FeSO_4$/$CuCl_2$ afforded the chlorinated 6-oxacyclooctanone **65** in 22% yield accompanied by the corresponding acyclic chloride **66** (10%) and reduction product **67** (10%) (Scheme 6). Finally, treatment of hydroperoxide **29**, bearing a 1-phenylvinyl group, with $FeSO_4$/$CuCl_2$ afforded a



Scheme 4. *Reaction conditions*: hydroperoxide/$FeSO_4$=1:3 or hydroperoxide/$FeSO_4$/$CuCl_2$=1:2:3 (molar ratio), in H_2O/MeCN (2:1, v/v) at room temperature for 2 h.

mixture of 1-phenylvinylcyclohexanol (**68**) and 8-chloro-2-phenyloct-1-ene-3-one (**69**) in 42 and 48% yield, respectively. The latter acyclic chloride **69** was transformed quantitatively into crystalline 1,1′-diphenylbicylooctyl-2,2′-dione (**70**) on standing overnight at room temperature under an atmosphere of argon and illuminated by artificial light. Compound **70** could also be isolated from the reaction of hydroperoxide **29** with $FeSO_4$ (3 equiv.) in 26% yield. This unexpected transformation of compound **69** into **70** did not occur to any appreciable extent in the dark or in solution. An investigation is in progress to clarify the mechanism of this successive cyclization and dimerization process.

3. Conclusion

Several of the allylic hydroperoxides **17**–**32** examined in this study readily decomposed on treatment with either $FeSO_4$ or $FeSO_4$/$CuCl_2$ under mild conditions producing carbon-centered radicals via reductive cleavage of the O–O bond followed by successive C–C bond β-scission. The

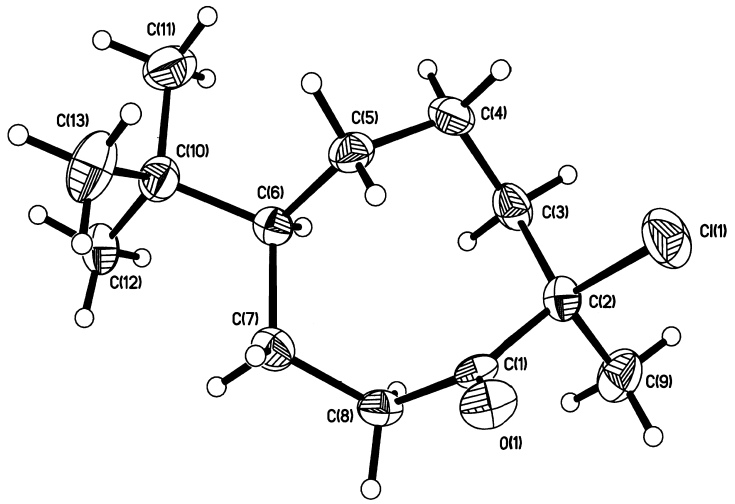
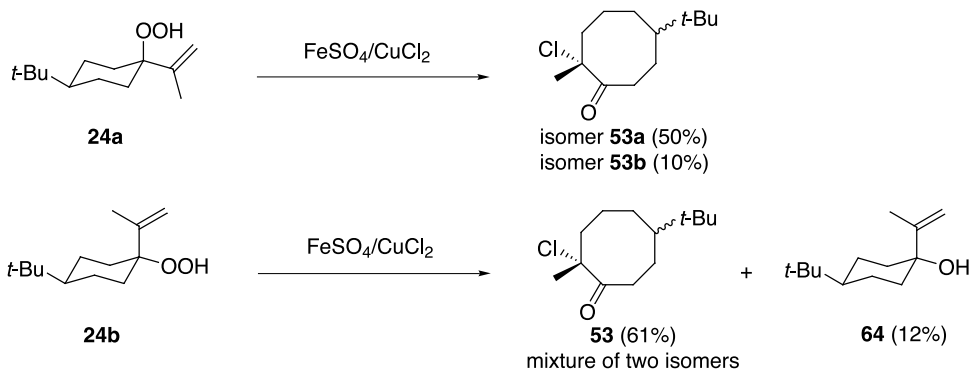


Figure 3. The X-ray crystal structure of compound **53b** (ORTEP, 50% probability ellipsoids).

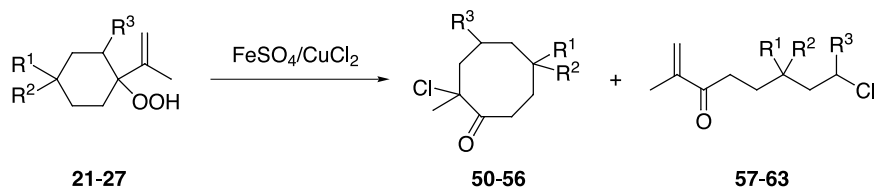


Scheme 5. *Reaction conditions*: hydroperoxide/$FeSO_4$/$CuCl_2$=1:2:3 (molar ratio), in H_2O/MeCN (2:1, v/v) at room temperature for 2 h.

structures of the isolated products indicated that the resulting radical intermediates had undergone subsequent regioselective cyclization reactions via 6-, 7- or 8-*endo-trig* modes as appropriate.

This radical fragmentation–cyclization procedure was applied to the ring expansion of 1-isopropenylcycloalkyl hydroperoxides. Although cycloheptanone derivatives, arising from 7-*endo-trig* cyclization, were readily obtained by reaction of the corresponding cyclopentyl substrate **20** with either $FeSO_4$ or $FeSO_4$/$CuCl_2$, 1-isopropenylcyclohexyl hydroperoxide **21** was only transformed into a 8-*endo-trig* cyclization product on reaction with $FeSO_4$. Cyclooctanone derivatives were, however, isolated in

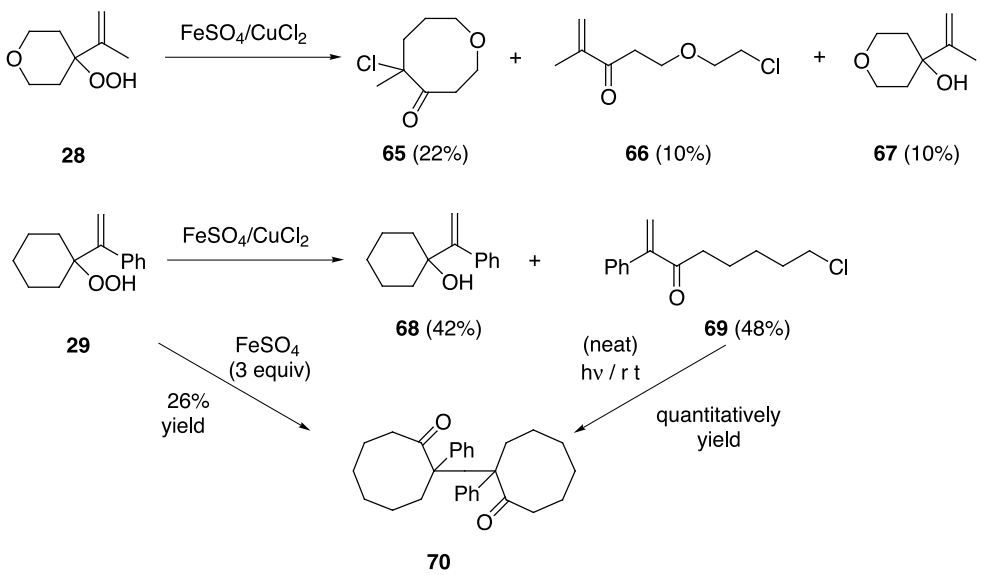
Table 2. Reaction of 1-isopropenylcyclohexyl hydroperoxides **21**–**27** with $FeSO_4$/$Cucl_2$



21-27 **50-56** **57-63**

Hydroperoxide				Products			
	R^1	R^2	R^3		Yield (%)		Yield (%)
21	H	H	H	**50**	0	**57**	71
22	Me	H	H	**51**	17	**58**	38
23	Et	H	H	**52**	29	**59**	24
24a	*t*-Bu	H	H	**53**	60	**60**	0
25	Ph	H	H	**54**	0	**61**	71
26	Me	Me	H	**55**	8	**62**	48
27	H	H	Me	**56**	26	**63**	17

Reaction conditions: hydroperoxide/$FeSO_4$/$CuCl_2$=1:2:3 (molar ratio), in H_2O/MeCN (2:1, v/v) at room temperature for 2 h.



Scheme 6. *Reaction conditions*: hydroperoxide/$FeSO_4$/$CuCl_2$=1:2:3 (molar ratio), in H_2O/MeCN (2:1, v/v) at room temperature for 2 h.

varying amounts from the reactions of cyclohexyl hydroperoxides **22**–**27** bearing ring substituents in the 2- and 4-positions with $FeSO_4$/$CuCl_2$. Best yields of cyclooctanones (ca. 60%) were obtained from hydroperoxides **24** which had a 4-*tert*-butyl group on the cyclohexyl ring.

4. Experimental

4.1. General procedures

^{1}H (270 MHz for routine measurements and 400 MHz for HMQC, HMBC and NOE measurements) and ^{13}C (67.5 MHz or 100 MHz) NMR spectra were measured in $CDCl_3$ solution with $SiMe_4$ as the internal standard. IR spectra were recorded with a HORIBA FT-720 instrument. High-resolution MS (HRMS) spectra were recorded with a JEOL JMS-DX-303 mass spectrometer.

A series of alkenes **1**–**16** as starting compounds for preparation of hydroperoxides were prepared by literature procedures. 1,2-Dimethylcyclohexene (**1**) and 1-isopropenylcyclopentanol (**4**) were prepared by treatment of the corresponding ketones with the Grignard reagents, methyl- or isopropenylmagnesium iodide followed by appropriate work-up.[7b,14] 1,2,3,4,5,6,7,8-Octahydronaphthalene (**2**) and cyclohexylidenecyclohexane (**3**) were synthesized by the established methods reported in Organic Syntheses.[15,16] Cyclohexylideneethylbenzene (**13**) was derived from cyclohexyl magnesium chloride and acetophenone followed by dehydration.[15,17] Other 1-isopropylidenecycloalkanes **5**–**12**,**14**–**16**[18] were prepared by the reaction of the corresponding ketone with lithiated phenyl isobutyrate at −78°C followed by decarboxylation of the resulting β-lactone at 110°C.[19] All alkenes were purified by silica gel column chromatography. Alkenes **7** and **10** were new compounds.

4.1.1. 1-Isopropylidene-4-ethylcyclohexane (7). An oil; ν_{max} (liquid film) 2960, 2880, 1465 cm^{-1}; ^{1}H NMR δ 0.87 (t, J=7.1 Hz, 3H), 1.15–1.50 (m, 7H), 1.67 (s, 6H), 2.55–2.71 (m, 4H); ^{13}C NMR δ 11.61, 19.95, 29.49, 29.63, 33.86, 39.57, 120.11, 132.09. HRMS (EI) calcd for $C_{11}H_{20}$: 152.1565. Found: 152.1567.

4.1.2. 4-Isopropylidene-1,1-dimethylcyclohexane (10). An oil; ^{1}H NMR δ 0.93 (s, 6H), 1.22–1.33 (m, 4H), 1.65 (s, 6H), 2.10–2.21 (m, 4H); ^{13}C NMR δ 19.95, 25.97, 28.30, 30.17, 40.40, 120.22, 131.75. HRMS (EI) calcd for $C_{11}H_{20}$: 152.1565. Found: 152.1577.

4.2. Preparation of allylic hydroperoxides 17–32

Each hydroperoxide was prepared by the most appropriate method A–C as indicated in Table 1. All the hydroperoxides were readily isolated by column chromatography on silica gel at room temperature. Hydroperoxides **17**–**22** and **32** are known compounds.[7b,18b,1,20] Spectral data obtained for hydroperoxides newly prepared in this work are as follows.

4.2.1. 4-Ethyl-1-isopropenylcyclohexyl hydroperoxide (23). An oil; ^{1}H NMR δ 0.89 (t, J=7.5 Hz, 3H), 1.20–1.70 (m, 9H), 1.80 (s, 3H), 1.99–2.12 (m, 2H), 4.97 (d, J=0.7 Hz, 1H), 5.01 (d, J=0.7 Hz, 1H), 7.38 (s, 1H); ^{13}C NMR δ 11.47, 18.76, 27.60, 29.53, 31.61, 38.73, 84.44, 111.61, 148.57. Anal. calcd for $C_{11}H_{20}O_2$: C, 71.10; H, 10.94. Found: C, 71.41; H, 10.96.

4.2.2. 4-*tert*-Butyl-1-isopropenylcyclohexyl hydroperoxide (separable isomer-24a). The title compound was isolated by column chromatography on silica gel eluting with diethyl ether/hexane (3:97, v/v). Yield: 26% as a colorless solid, mp 54–55°C (from hexane); ν_{max} (KBr) 3350, 2960, 2880, 1650, 1150 cm^{-1}; ^{1}H NMR (400 MHz; Fig. 1 indicates the assignment of chemical shifts based on its HMQC, HMBC and NOE results) δ 0.88 (s, 9H), 0.90–2.07 (m, 1H), 1.27–1.39 (m, 2H), 1.41–1.55 (m, 2H), 1.57–1.65 (m, 2H), 1.80 (s, 3H), 2.04–2.15 (m, 2H), 4.96 (d, J=0.7 Hz, 1H), 5.00 (d, J=0.7 Hz, 1H), 7.55 (s, 1H); ^{13}C NMR δ 18.74, 22.34, 27.51, 32.19, 32.35, 47.62, 83.94, 111.50, 148.68. Anal. calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.40; H, 11.23.

4.2.3. 4-*tert*-Butyl-1-isopropenylcyclohexyl hydroperoxide (separable isomer-24b). The title compound was isolated by column chromatography on silica gel eluting with diethyl ether/hexane (5:95, v/v) eluent. Yield: 22%. An oil; ^{1}H NMR δ 0.85 (s, 9H), 0.95–1.95 (m, 7H), 1.82 (s, 3H), 2.06–2.15 (m, 2H), 5.11 (s, 1H), 5.23 (s, 1H), 7.44 (s, 1H); ^{13}C NMR δ 23.99, 24.08, 27.41, 31.75, 32.06, 47.73, 83.37, 116.89, 142.17. Anal. calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 72.99; H, 11.19.

4.2.4. 1-Isopropenyl-4-phenylcyclohexyl hydroperoxide (25). An oil; ν_{max} (liquid film) 3350, 3005, 2965, 2875, 1650, 1605, 1493, 1460, 1155 cm^{-1}; ^{1}H NMR δ 1.42–1.95 (m+s, 6H+3H), 2.08–2.25 (m, 2H), 2.45–2.58 (m, 1H), 5.01 (s, 1H), 5.06 (s, 1H), 7.15–7.37 (m, 5H+1H); ^{13}C NMR δ 18.76, 29.04, 31.95, 43.76, 83.81, 111.97, 125.97, 126.83, 128.28, 146.92, 148.21. Anal. calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.54; 8.93.

4.2.5. 1-Isopropenyl-4,4-dimethylcyclohexyl hydroperoxide (26). An oil; ^{1}H NMR δ 0.90 (s, 3H), 0.95 (s, 3H), 1.16–1.23 (m, 2H), 1.49–1.90 (m+s, 6H+3H), 5.02 (s, 1H), 5.05 (s, 1H), 7.22 (s, 1H); ^{13}C NMR δ 18.78, 24.85, 27.68, 29.47, 31.43, 34.41, 84.49, 112.60, 147.44. Anal. calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.74; 10.76.

4.2.6. 1-Isopropenyl-2-methylcyclohexyl hydroperoxide (27). Colorless solid, mp 50–51°C (from hexane); ^{1}H NMR δ 0.85 (d, J=7.6 Hz, 3H), 1.25–1.70 (m, 7H), 1.80 (s, 3H), 1.83–1.95 (m, 1H), 2.09 (m, 1H), 4.95 (s, 1H), 5.08 (s, 1H), 6.98 (s, 1H); ^{13}C NMR δ 18.74, 21.78, 25.68, 31.77, 84.87, 112.65, 147.62. Anal. calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.27; H, 10.41.

4.2.7. 4-Isopropenyltetrahydropyran-4-yl hydroperoxide (28). An oil; ^{1}H NMR δ 1.80 (s, 3H), 1.85–2.00 (m, 4H), 3.76 (dd, J=7.6, 3.3 Hz, 4H), 5.03 (s, 1H), 5.07 (s, 1H), 8.23 (br, 1H); ^{13}C NMR δ 18.04, 31.70, 63.52, 81.53, 113.08, 146.42. Anal. calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.33; H, 8.93.

4.2.8. 1-(1-Phenylvinyl)cyclohexyl hydroperoxide (29). An oil; ^{1}H NMR δ 1.21–1.69 (m, 8H), 1.92 (m, 2H), 5.29 (s, 1H), 5.46 (s, 1H), 7.26–7.38 (m+s, 5H+1H); ^{13}C NMR δ 21.91, 25.52, 32.76, 85.05, 117.40, 127.12, 127.85, 128.54, 141.04. Anal. calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.36; H, 8.33.

4.2.9. 1-Isopropenylcycloheptyl hydroperoxide (30). An oil; ^{1}H NMR δ 1.35–1.76 (m, 8H), 1.81 (s, 3H), 1.85–1.92 (m, 4H), 4.97 (s, 1H), 4.99 (s, 1H), 7.53 (s, 1H); ^{13}C NMR δ 18.80, 22.54, 30.07, 34.61, 89.65, 111.81, 148.52. HRMS (EI) calcd for $C_{10}H_{18}O_2$: 171.1373. Found: 171.1138.

4.2.10. 1-Isopropenylcyclododecyl hydroperoxide (31). Colorless solid, mp 49–50°C (from hexane); ^{1}H NMR δ 1.20–1.55 (m, 20H), 1.68–1.81 (m+s, 2H+3H), 4.93 (s, 1H), 5.03 (s, 1H), 7.38 (s, 1H); ^{13}C NMR δ 18.67, 19.28, 21.82, 22.12, 26.13, 27.62, 88.66, 113.30, 147.31. Anal. calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.85; H, 11.87.

Caution. Because organic hydroperoxides are potentially hazardous compounds, they must be handled with due care. Avoid exposure to strong heat or light, mechanical shock, oxidizable organic materials or transition metal ions. No particular difficulties were experienced in handling any of the organic hydroperoxides prepared in this work using reaction scales and procedures described below, together with any safeguard mentioned above.

4.3. Reaction of allylic hydroperoxide 17 with either $FeSO_4/CuCl_2$ or with $FeSO_4$ only

To a solution of $FeSO_4{\cdot}7H_2O$ (1 equiv.) and $CuCl_2$ (3 equiv.) in H_2O (75 mL) was added dropwise a solution of 1-methyl-2-methylene-1-cyclohexyl hydroperoxide (**17**) (0.58 or 6.9 mmol) in MeCN (40 mL) during 45 min via syringe pump. After stirring at room temperature for an additional 2 h, the reaction mixture was extracted with diethyl ether (3×50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent removed by rotary evaporation under reduced pressure. In the case of the reaction in which the initial concentration of hydroperoxide **17** was ca. 5 mM (at the moment after addition of aqueous metal solutions), purification of the crude product by column chromatography on silica gel with diethyl ether/hexane (5:95, v/v) as eluent gave 1-(1-chlorocyclohexyl)ethanone (**36**) (58%) as the sole isolated compound. At higher initial concentrations of hydroperoxide **17** (60 mM), an acyclic chlorinated product **35** (12%) was also isolated on elution with a diethyl ether/hexane (9:91, v/v) eluent in addition to the cyclized compound **36** (isolated yield: 24%).

In the case of reaction of hydroperoxide **17** with $FeSO_4$ (2 equiv.) only, a solution of compound **17** (284 mg, 2.0 mmol) in MeCN (25 mL) was added dropwise to an aqueous solution of $FeSO_4{\cdot}7H_2O$ (50 mL, 0.8 M) during 10 min. After 2 h of stirring, the reaction mixture was worked up as described above and purified by column chromatography; elution with diethyl ether/hexane (15:85, v/v) gave the cyclized dimer **38** (70 mg, 28%) as the only isolable compound.

4.3.1. 3-(4-Chlorobutyl)but-3-en-2-one (35). An oil; ν_{max} (liquid film) 2960, 2880, 1675, 1625, 1205, 805 cm^{-1}; ^{1}H NMR δ 1.45–1.90 (m, 4H), 2.15–2.40 (m, 5H), 3.55 (t, J=6.6 Hz, 2H), 5.80 (s, 1H), 6.05 (s, 1H); ^{13}C NMR δ 25.57, 25.79, 29.62, 32.10, 44.71, 125.28, 148.41, 199.53. HRMS (EI) calcd for $C_8H^{13}ClO$: 160.0665. Found: 160.0625.

4.3.2. 1-(1-Chlorocyclohexyl)ethanone (36). An oil; ^{1}H NMR δ 1.20–1.42 (m, 2H), 1.57–2.05 (m, 8H), 2.35 (s, 3H); ^{13}C NMR δ 21.93, 24.30, 24.82, 35.38, 75.13, 204.67; IR (neat) ν 2980, 1720 cm^{-1}. HRMS (EI) calcd for $C_8H^{13}ClO$: 160.0665. Found: 160.0647.

4.3.3. 1,1′-Diacetylbicyclohexyl (38). Colorless solid, mp 133–135°C; MS (EI) *m/e* (relative intensity) 250 (M^+, 4), 232 (11), 207 (11), 190 (54), 177 (15), 163 (21), 126 (46), 43 (100); ν_{max} (KBr) 2960, 2880, 1715 cm^{-1}; ^{1}H NMR δ 1.05–1.15 (m, 6H), 1.30 (dt, J=2, 13 Hz, 4H), 1.60–1.75 (m, 6H), 2.18 (s, 6H), 2.20–2.30 (m, 4H); ^{13}C NMR δ 24.03, 24.09, 25.56, 29.64, 29.69, 58.36, 212.22. Anal. calcd

for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.65; H, 10.67.

4.4. Reaction of hydroperoxide 18 with $FeSO_4/CuCl_2$ and reaction of hydroperoxide 19 with $FeSO_4$ only

The reaction of hydroperoxide **18** (150 mg, 0.9 mmol) with $FeSO_4·7H_2O$ (1 equiv.) and $CuCl_2$ (3 equiv.) was carried out as described above. Analysis of the crude product by GC indicated the presence of the bicyclic chloroketone **39** as the major product along with other four minor products. Subsequent purification of the crude residue by column chromatography (elution with diethyl ether/hexane, 2:98, v/v) gave **39** as a mixture of two diastereomers (111 mg, 67%).

The reduction of a solution of hydroperoxide **19** (85 mg, 0.43 mmol) in MeCN (30 mL) with $FeSO_4·7H_2O$ (2 equiv.) in H_2O (70 mL) was also conducted as described above. GC analysis of the crude product showed the presence of compounds **40** and **41** as the two major components along with other four minor contaminants. Purification of the residue by column chromatography (elution with diethyl ether/hexane, 2:98, v/v) gave non-cyclized product **41**[21] (26 mg, 33%) and, on further elution with diethyl ether–hexane (5:95), the second component **40** as one of two possible diastereomers (16 mg, 21%).

4.4.1. 1-Chlorobicyclo[4.4.0]decan-2-one (39). An oil; ^{1}H NMR δ 1.21–2.36 (m, 8H), 2.37–2.46 (m, 4H), 2.57–2.64 (m, 1H), 2.98–3.23 (m, 2H); ^{13}C NMR δ 21.08, 21.76, 24.46, 25.05, 25.16, 25.57, 26.54, 27.64, 29.22, 33.21, 36.34, 36.52, 47.05, 47.38, 76.64, 204.81, 205.66. Anal. calcd for $C_{10}H_{15}ClO$: C, 64.34; H, 8.10; Cl, 18.99. Found: C, 64.36; H, 8.16; Cl, 19.10.

4.4.2. Bicyclo[6.4.0]dodecane-2-one (40). An oil; ^{1}H NMR δ 0.95–1.50 (m, 8H), 1.55–1.92 (m, 8H), 2.12–2.20 (m, 1H), 2.32 (dt, J=3, 12 Hz, 1H), 2.67–2.75 (m, 2H); ^{13}C NMR δ 21.33, 24.78, 25.78, 26.53, 29.87, 30.03, 32.58, 33.43, 39.77, 53.87, 218.20. HRMS (EI) calcd for $C_{10}H_{20}O$: 180.1514. Found: 180.1508.

4.5. Reaction of a series of 1-isopropenylcycloalkyl hydroperoxides 20–28,30–32 or 1-phenylvinylcyclohexyl hydroperoxide (29) with either $FeSO_4/CuCl_2$ or $FeSO_4$ only

The reaction of 1-isopropenylcyclopentyl hydroperoxide (**20**) is representative. To a solution of $FeSO_4·7H_2O$ (1 equiv.) and $CuCl_2$ (3 equiv.) in H_2O (100 mL) was added via syringe pump a solution of hydroperoxide **20** (346 mg, 2.4 mmol) in MeCN (50 mL) during 40 min. After stirring for an additional 2 h at room temperature, the reaction mixture was extracted with diethyl ether (3×100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent removed by rotary evaporation under reduced pressure. Subsequent purification of the crude residue by column chromatography (silica gel, elution with diethyl ether/hexane, 3:97, v/v) gave 2-chloro-2-methylcycloheptanone (**43**) as the only isolable product (130 mg, 34%).

In the case of the reaction of hydroperoxide **20** with $FeSO_4$ (3 equiv.), a solution of compound **20** (240 mg, 1.7 mmol) in MeCN (50 mL) was added dropwise to an aqueous solution of $FeSO_4·7H_2O$ (1.4 g, 150 mL) over 40 min. After 2 h, the reaction mixture was extracted with diethyl ether as described above. Purification of the residue by column chromatography (silica gel, elution with diethyl ether/hexane, 6:94, v/v) gave one stereoisomer of dimeric cycloheptanone **42** (minor isomer, 20 mg, 10%) and, on further elution with diethyl ether/hexane (8:92, v/v), the other stereoisomer **42** (major isomer, 30 mg, 14%) was obtained.

4.5.1. 1,1′-Dimethylbicycloheptyl-2,2′-dione (42) (minor isomer). Colorless solid, mp 102–103°C (from hexane); ^{1}H NMR δ 1.08 (s, 6H), 1.13–1.37 (m, 6H), 1.61–1.95 (m, 10H), 2.26–2.33 (m, 2H), 2.39–2.48 (m, 2H); ^{13}C NMR δ 17.31 (CH_3), 24.23, 27.64, 30.21, 32.37, 44.21, 58.13 (C), 217.20 (C=O). Anal. calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.63; H, 10.48.

4.5.2. 1,1′-Dimethylbicycloheptyl-2,2′-dione (42) (major isomer). Colorless solid, mp 91–92°C (from hexane); ^{1}H NMR δ 1.06 (s, 6H), 1.10–1.33 (m, 6H), 1.60–1.91 (m, 10H), 2.36–2.43 (m, 2H), 2.58–2.68 (m, 2H); ^{13}C NMR δ 19.25, 24.23, 27.21, 30.41, 32.72, 44.64, 55.80, 217.18.

4.5.3. 2-Chloro-2-methylcycloheptanone (43). An oil; ^{1}H NMR δ 1.26–1.88 (m, 6H), 1.60 (s, 3H), 2.07–2.15 (m, 2H), 2.47 (dt, J=3.2, 10.4 Hz, 1H), 2.86 (dt, J=3.2, 6.1 Hz, 1H); ^{13}C NMR δ 25.02, 25.88, 27.06 (CH_3), 29.45, 39.10, 41.48, 72.58 (C), 206.88 (C=O). HRMS (EI) calcd for $C_8H_{13}ClO$: 160.0655. Found: 160.0650.

4.5.4. 1,1′-Dimethylbicyclooctyl-2,2′-dione (44). Derived by the reaction of hydroperoxide **21** with $FeSO_4$. Isolated by silica gel column chromatography with a diethyl ether/hexane (4:96, v/v) eluent. Yield: 41%. Colorless solid, mp 116–117°C (from hexane); ^{1}H NMR δ 0.79–0.98 (m, 2H), 1.04 (s, 6H), 1.16–1.35 (m, 2H), 1.40–1.88 (m, 14H), 2.03–2.16 (m, 2H), 2.28–2.38 (m, 2H), 2.81 (dt, J=3.3, 12.5 Hz, 2H); ^{13}C NMR δ 16.79 (CH_3), 24.21, 25.50, 26.60, 28.63, 30.75, 41.28, 55.81 (C), 220.36 (C=O). Anal. calcd for $C_{18}H_{30}O_2$: C, 77.64; H, 10.87. Found: C, 77.49; H, 10.89.

4.5.5. 8-Chloro-2-methyloct-1-en-3-one (45). Obtained by the reaction of **21** with $FeSO_4/CuCl_2$ and isolated by column chromatography on silica gel with diethyl ether/hexane (4:96, v/v) as eluent. Yield: 71%. An oil; ^{1}H NMR δ 1.40–1.53 (m, 2H), 1.58–1.70 (m, 2H), 1.75–1.87 (m, 2H), 1.87 (s, 3H), 2.71 (t, J=7.3 Hz, 2H), 3.55 (t, J=6.8 Hz, 2H), 5.77 (s, 1H), 5.96 (s, 1H); ^{13}C NMR δ 17.58, 23.60, 26.49, 32.38, 37.07, 44.84, 124.46, 144.42, 201.76. HRMS (EI) calcd for $C_9H_{15}ClO$: 174.0811. Found: 174.0806. Anal. calcd for $C_9H_{15}ClO$: C, 86.45; H, 13.55. Found: C, 86.20; H, 13.61.

4.5.6. 9-Chloro-2-methylnon-1-en-3-one (46). Produced by the reaction of hydroperoxide **30** with $FeSO_4/CuCl_2$ and isolated by silica gel column chromatography (silica gel, diethyl ether/hexane (3:97, v/v) eluent). Yield: 55%. An oil; ^{1}H NMR δ 1.26–1.87 (m, 8H), 1.87 (s, 3H), 2.67 (t, J=10.2 Hz, 2H), 3.54 (t, J=6.7 Hz, 2H), 5.77 (s, 1H), 5.96

(s, 1H); ^{13}C NMR δ 17.56, 24.19, 26.60, 28.41, 32.29, 37.13, 44.94, 124.40, 144.38. HRMS (EI) calcd for $C_{10}H_{17}ClO$: 188.0968. Found: 188.0956. Anal. calcd for $C_{10}H_{17}ClO$: C, 63.63; H, 9.09. Found: C, 63.44; H, 8.88.

4.5.7. 14-Chloro-2-methyltetradec-1-en-3-one (47). Obtained by the reaction of hydroperoxide **31** with $FeSO_4/CuCl_2$ and isolated by column chromatography on silica gel with diethyl ether/hexane (3:97, v/v) as eluent. Yield: 72%. An oil; ^{1}H NMR δ 1.16–1.39 (m, 14H), 1.50–1.58 (m, 2H), 1.66–1.81 (m, 4H), 1.81 (s, 3H), 2.62 (t, J=6.6 Hz, 2H), 5.70 (s, 1H), 5.90 (s, 1H); ^{13}C NMR δ 17.54, 24.48, 26.74, 28.75, 29.20, 29.31, 32.53, 37.32, 45.02, 124.19, 144.40, 202.17. HRMS (EI) calcd for $C_{15}H_{27}ClO$: 258.1750. Found: 258.1734.

4.5.8. 2-Hydroxy-2-isopropenyladamantane (48). Obtained by treatment of hydroperoxide **32** with $FeSO_4/CuCl_2$ and isolated by column chromatography on silica gel with diethyl ether/hexane (4:96, v/v) as eluent. Yield: 40%. Mp 50–51°C (from hexane); ^{1}H NMR δ 1.25–1.35 (m, 2H), 1.57–1.79 (m, 9H), 1.80 (s, 3H), 2.11 (br s, 2H), 2.22–2.32 (m, 2H), 4.97 (s, 1H), 5.03 (s, 1H); ^{13}C NMR δ 18.53 (CH_3), 26.90 (CH), 27.12 (CH), 32.78 (CH_2), 34.49 (CH_2), 37.63 (CH_2), 76.01 (C), 119.10 (CH_2), 148.48 (C). Anal. calcd for $C_{13}H_{20}O$: C, 81.18; H, 10.49. Found: C, 80.89; H, 10.54.

4.5.9. Tricyclo[3.3.1.1^{3,7}]decane-2-spiro-2′-(3′-chloromethyl-3′-methyl)oxirane (49). Obtained along with compound **48** by treatment of **32** with $FeSO_4/CuCl_2$ and isolated by column chromatography (silica gel, eluting with diethyl ether/hexane (2:98, v/v)). Yield: 6%. An oil; ^{1}H NMR δ 1.48 (s, 3H), 1.76–1.93 (m, 14H), 3.57 (d, J=14 Hz, 1H), 3.63 (d, J=14 Hz, 1H); ^{13}C NMR δ 15.82 (CH_3), 26.76 (CH), 32.24 (CH), 32.65 (CH), 34.88 (CH_2), 34.93 (CH_2), 36.25 (CH_2), 36.86 (CH_2), 47.35 (CH_2), 65.16 (C), 119.10 (CH_2), 148.48 (C). HRMS (EI) calcd for $C_{13}H_{19}ClO$ (m+1)/z: 227.1203. Found: 227.1212.

4.5.10. 2-Chloro-2,6-dimethylcyclooctanone (51). Obtained from the reaction of hydroperoxide **22** with $FeSO_4/CuCl_2$ and isolated by column chromatography (silica gel, eluting with diethyl ether/hexane (2:98, v/v)). Yield: 17%. An oil; ^{1}H NMR δ 0.93 (d, J=6.3 Hz, 3H), 1.25–1.68 (m, 6H), 1.63 (s, 3H), 1.84–1.95 (m, 1H), 2.09–2.18 (m, 1H), 2.31–2.38 (m, 1H), 2.58–2.69 (m, 1H), 3.10–3.20 (m, 1H); ^{13}C NMR δ 22.88, 24.51, 25.05, 32.04, 32.58, 35.55, 38.26, 38.33, 71.86, 209.04. HRMS (EI) calcd for $C_{10}H_{17}ClO$: 188.0968. Found: 188.0965.

4.5.11. 8-Chloro-2,6-dimethyloct-1-en-3-one (58). Obtained along with compound **51** by treatment of **22** with $FeSO_4/CuCl_2$ and isolated by column chromatography (silica gel, eluting with diethyl ether/hexane (4:96, v/v)). Yield: 38%. An oil; ^{1}H NMR δ 0.93 (t, J=6.3 Hz, 3H), 1.42–1.88 (m, 5H), 1.90 (s, 3H), 2.65–2.75 (m, 2H), 3.50–3.66 (m, 2H), 5.78 (s, 1H); ^{13}C NMR δ 17.59, 18.78, 29.96, 30.80, 34.77, 39.41, 42.97, 124.40, 144.33, 201.89. HRMS (EI) calcd for $C_{10}H_{17}ClO$: 188.0968. Found: 188.0971. Anal. calcd for $C_{10}H_{17}ClO$: C, 63.65; H, 9.08. Found: C, 63.62; H, 8.89.

4.5.12. 2-Chloro-6-ethyl-2-methylcyclooctanone (52). Obtained by the reaction of hydroperoxide **23** with $FeSO_4/CuCl_2$ and isolated by column chromatography (silica gel, eluting with diethyl ether/hexane (2:98, v/v)). Yield: 29%. An oil; ^{1}H NMR δ 0.88 (d, J=7.1 Hz, 3H), 1.15–1.76 (m, 8H), 1.64 (s, 3H), 1.83–1.97 (m, 1H), 2.10–2.18 (m, 1H), 2.33–2.41 (m, 1H), 2.59–2.70 (m, 1H), 3.13 (dt, J=4.3, 12.7 Hz, 1H); ^{13}C NMR δ 11.41, 22.79, 25.00, 29.85, 31.31, 35.53, 36.21, 38.15, 39.39, 71.75, 209.04. HRMS (EI) calcd for $C_{11}H_{19}ClO$: 202.1124. Found: 202.1135.

4.5.13. 8-Chloro-6-ethyl-2-methyloct-1-en-3-one (59). Obtained along with compound **52** by treatment of **23** with $FeSO_4/CuCl_2$ and isolated by column chromatography (silica gel, eluting with diethyl ether/hexane (4:96, v/v)). Yield: 24%. An oil; ^{1}H NMR δ 0.88 (t, J=7.2 Hz, 3H), 1.18–2.01 (m, 10H), 2.62–2.74 (m, 2H), 3.56 (t, J=7.1 Hz, 2H), 5.78 (s, 1H), 5.96 (s, 1H); ^{13}C NMR δ 10.41, 17.65, 25.25, 27.12, 34.52, 36.10, 36.17, 43.06, 129.42, 144.42, 201.49. HRMS (EI) calcd for $C_{11}H_{19}ClO$: 202.1124. Found: 202.1124. Anal. calcd for $C_{11}H_{19}ClO$: C, 65.17; H, 9.45. Found: C, 65.08; H, 9.46.

4.5.14. 6-*tert*-Butyl-2-chloro-2-methylcyclooctanone (separable isomer-53a). Obtained by reaction of hydroperoxide **24a** with $FeSO_4/CuCl_2$ and isolated by column chromatography (silica gel, eluting with diethyl ether/hexane (2:98, v/v)). Yield: 50%. Colorless solid, mp 71–72°C (from hexane); ^{1}H NMR δ 0.85 (s, 9H), 0.90–1.12 (m, 2H), 1.32–1.74 (m, 7H), 2.01–2.19 (m, 2H), 2.38–2.45 (m, 1H), 2.63–2.75 (m, 1H), 3.01–3.12 (m, 1H); ^{13}C NMR δ 22.61 (CH_3), 25.70 (CH_2), 26.42 (CH_2), 27.10 (CH_3), 31.81 (CH_2), 34.14 (C), 35.85 (CH_2), 37.74 (CH_2), 48.02 (CH), 71.57 (C), 209.29 (C=O). Anal. calcd for $C_{13}H_{23}ClO$: C, 67.66; H, 10.05; Cl, 15.36. Found: C, 67.38; H, 9.96; Cl, 15.15.

4.5.15. *c*-6-*tert*-Butyl-*r*-2-chloro-2-methylcyclooctanone (separable isomer-53b). Obtained along with compound **53a** by treatment of **24a** with $FeSO_4/CuCl_2$ and isolated by column chromatography (silica gel, eluting with a diethyl ether/hexane (4:96, v/v)). Yield: 10%. Colorless solid, mp 90–91°C (from hexane); ^{1}H NMR δ 0.85 (s, 9H), 1.17–1.74 (m, 7H), 1.65 (s, 3H), 2.00–2.11 (m, 2H), 2.45–2.72 (m, 2H); ^{13}C NMR δ 25.47 (CH_2), 26.87 (CH_2), 27.10 (CH_3), 29.09 (CH_3), 31.34 (CH_2), 34.09 (CH_2), 35.85 (CH_2), 36.39 (CH_2), 38.56 (CH_2), 48.25 (CH), 76.78 (C), 210.40 (C=O). HRMS (EI) calcd for $C_{13}H_{23}ClO$: 230.1437. Found: 230.1439. The relative configuration of **53b** was determined by its X-ray crystallographic analysis (vide infra).

4.5.16. 4-*tert*-Butyl-1-isopropenylhexanol (64). Obtained along with a mixture of stereoisomers **53a** and **53b** by the reaction of hydroperoxide **24b** with $FeSO_4/CuCl_2$ and isolated by column chromatography (silica gel, eluting with diethyl ether/hexane (8:92, v/v)). Yield: 12%. Colorless solid, mp 34–35°C (from hexane); ^{1}H NMR δ 0.82 (s, 9H), 0.90–1.68 (m, 8H), 1.79 (s, 3H), 2.14–2.20 (m, 2H), 4.97–5.06 (m, 2H); ^{13}C NMR δ 18.69, 24.67, 27.53, 32.13, 36.71, 47.62, 73.66, 113.05, 146.58. Anal. calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.39; H, 12.14.

4.5.17. 8-Chloro-2-methyl-6-phenyloct-1-en-3-one (61). Obtained by treatment of hydroperoxide **25** with $FeSO_4/$

$CuCl_2$ and isolated by column chromatography (silica gel, eluting with diethyl ether/hexane (2:98, v/v)). Yield: 71%. Colorless solid, mp 98–99°C (from hexane); ^{1}H NMR δ 1.68–2.84 (m, 7H), 1.81 (s, 3H), 3.18–3.28 (m, 1H), 3.36–3.45 (m, 1H), 5.66 (s, 1H), 5.75 (s, 1H), 7.14–7.33 (m, 5H); ^{13}C NMR δ 17.50 (CH_3), 30.62 (CH_2), 35.19 (CH_2), 39.55 (CH_2), 42.34 (CH), 42.93 (CH_2), 124.46 (CH_2), 126.65 (CH), 128.63 (CH), 142.77 (C), 144.17 (C), 201.65 (C=O). HRMS (EI) calcd for $C_{15}H_{19}ClO$: 250.1124. Found: 250.1125.

4.5.18. 2-Chloro-2,6,6-trimethylcyclooctanone (55). Obtained by treatment of hydroperoxide **26** with $FeSO_4$/$CuCl_2$ and isolated by column chromatography (silica gel, eluting with a diethyl ether/hexane (2:98, v/v)). Yield: 8%. An oil; ^{1}H NMR δ 0.91 (s, 3H), 0.94 (s, 3H), 0.99–1.09 (m, 1H), 1.21–1.81 (m, 4H), 1.67 (s, 3H), 2.03–2.52 (m, 4H), 2.97–3.07 (m, 1H); ^{13}C NMR δ 19.95, 28.11, 28.21, 30.08, 33.86, 36.32, 36.89, 38.03, 43.99, 74.63, 211.48. HRMS (EI) calcd for $C_{11}H_{19}ClO$: 202.1124. Found: 202.1124.

4.5.19. 8-Chloro-2,6,6-trimethyloct-1-en-3-one (62). Obtained along with compound **55** by treatment of **26** with $FeSO_4$/$CuCl_2$ and isolated by column chromatography (silica gel, eluting with a diethyl ether/hexane (4:96, v/v)). Yield: 48%. An oil; ^{1}H NMR δ 0.93 (s, 6H), 1.52–1.58 (m, 2H), 1.66–1.88 (m, 2H), 1.90 (s, 3H), 2.63–2.69 (m, 2H), 4.49–3.55 (m, 2H), 5.78 (s, 1H), 5.97 (s, 1H); ^{13}C NMR δ 17.68, 26.69, 32.15, 32.92, 35.96, 40.97, 44.69, 124.40, 144.38, 201.94. HRMS (EI) calcd for $C_{11}H_{19}ClO$: 202.1124. Found: 202.1134. Anal. calcd for $C_{11}H_{19}ClO$: C, 65.17; H, 9.45. Found: C, 65.36; H, 9.45.

4.5.20. 2-Chloro-2,4-dimethylcyclooctanone (56). Obtained by treatment of hydroperoxide **27** with $FeSO_4$/$CuCl_2$ and isolated by column chromatography (silica gel, eluting with a diethyl ether/hexane (1:99, v/v)). Yield: 26%. An oil; ^{1}H NMR δ 0.94 (d, J=6.9 Hz, 3H), 1.00–1.10 (m, 1H), 1.26–2.07 (m, 7H), 1.65 (s, 3H), 2.29–2.49 (m, 2H), 3.05 (dt, J=3.3, 12.5 Hz, 1H); ^{13}C NMR δ 20.54 (CH_2), 21.60 (CH_3), 23.22 (CH_3), 28.74 (CH), 30.14 (CH_2), 35.96 (CH_2), 36.68 (CH_2), 45.43 (CH_2), 71.63 (C), 208.64 (C=O). Anal. calcd for $C_{10}H_{17}ClO$: C, 63.65; H, 9.08; Cl, 18.79. Found: C, 63.59; H, 9.08; Cl, 18.23.

4.5.21. 8-Chloro-2-methylnon-1-en-3-one (63). Derived by the reaction of **27** with $FeSO_4$/$CuCl_2$ along with compound **56**. Isolated by column chromatography on silica gel with diethyl ether/hexane (3:97, v/v) as eluent. Yield: 17%. An oil; ^{1}H NMR δ 1.26–2.23 (m, 9H), 1.51 (d, J=6.6 Hz, 3H), 2.71 (t, J=6.3 Hz, 2H), 4.00–4.07 (m, 1H), 5.77 (s, 1H), 5.96 (s, 1H); ^{13}C NMR δ 17.59, 23.81, 25.30, 26.31, 37.14, 40.09, 58.52, 124.42, 144.44, 201.81. HRMS (EI) calcd for $C_{10}H_{17}ClO$: 188.0968. Found: 188.0957.

4.5.22. 5-Chloro-5-methyloxocan-4-one (65). Obtained by treatment of hydroperoxide **28** with $FeSO_4$/$CuCl_2$ and isolated by column chromatography (silica gel, eluting with ethyl acetate/hexane (10:90, v/v)). Yield: 22%. An oil; ^{1}H NMR δ 1.54–1.97 (m, 2H), 1.69 (s, 3H), 2.26–2.59 (m, 2H), 2.60–2.70 (m, 1H), 3.17–3.34 (m, 2H), 3.61–4.08 (m, 3H); ^{13}C NMR δ 24.57 (CH_3), 25.93 (CH_2), 36.32 (CH_2), 39.37 (CH_2), 68.25 (CH_2), 71.70 (CH_2), 72.38 (C), 207.47 (C=O). HRMS (EI) calcd for $C_8H_{13}ClO_2$: 176.0604. Found: 176.0609.

4.5.23. 8-Chloro-2-methyl-6-oxaoct-1-en-3-one (66). Obtained along with compounds **65** and **67** by the reaction of **28** with $FeSO_4$/$CuCl_2$ and isolated by column chromatography (silica gel, eluting with ethyl acetate/hexane (8:92, v/v)). Yield: 10%. An oil; ^{1}H NMR δ 1.88 (s, 3H), 3.59–3.86 (m, 6H), 3.71 (t, J=6.4 Hz, 2H), 5.82 (s, 1H), 6.00 (s, 1H); ^{13}C NMR δ 17.41, 37.52, 42.72, 66.47, 71.12, 125.34, 144.51, 199.71. HRMS (EI) calcd for $C_8H_{13}ClO_2$: 176.0604. Found: 176.0599.

4.5.24. 4-Isopropenyltetrahydropyran-4-ol (67). The title compound was isolated by column chromatography on silica gel with ethyl acetate/hexane (20:80, v/v) as eluent. Yield: 10%. An oil; ^{1}H NMR δ 1.24–2.01 (m, 5H), 1.81 (s, 3H), 3.77–3.88 (m, 4H), 4.87 (s, 1H), 5.02 (s, 1H); ^{13}C NMR δ 18.44, 35.96, 63.70, 71.03, 109.85, 150.76. HRMS (EI) calcd for $C_8H_{14}O_2$: 142.0994. Found: 142.0987.

4.5.25. 1-Phenylvinylcyclohexanol (68). Obtained by the reaction of hydroperoxide **29** with $FeSO_4$/$CuCl_2$ and isolated by column chromatography (silica gel, eluting with ethyl acetate/hexane (5:95, v/v)). Yield: 42%. An oil; ^{1}H NMR δ 1.18–1.67 (m, 11H), 5.01 (s, 1H), 5.43 (s, 1H), 7.26–7.36 (m, 5H); ^{13}C NMR δ 22.05, 25.45, 36.61, 73.55, 113.37, 126.86, 127.64, 128.99, 141.58, 156.93. HRMS (EI) calcd for $C_{14}H_{18}O$: 202.1358. Found: 202.1357.

4.5.26. 8-Chloro-2-phenyloct-1-en-3-one (69). The title compound was obtained along with compound **68** by treatment of **29** with $FeSO_4$/$CuCl_2$ and isolated by column chromatography (silica gel, eluting with ethyl acetate/hexane (3:97, v/v)). Yield: 48%. An oil; ^{1}H NMR δ 1.47–1.91 (m, 6H), 2.76 (t, J=6.3 Hz, 2H), 3.53 (t, J=6.6 Hz, 2H), 5.88 (s, 1H), 6.10 (s, 1H), 7.30–7.46 (m, 5H); ^{13}C NMR δ 23.43, 26.38, 32.33, 39.28, 44.78, 124.28, 128.07, 128.18, 128.25, 137.13, 149.34, 201.78.

4.5.27. 1,1′-Diphenylbicyclooctyl-2,2′-dione (70). Obtained quantitatively when a sample of compound **69** was allowed to stand overnight at room temperature under argon and artificial light.

This compound could also be isolated in 26% yield from the reaction of **29** with $FeSO_4$ (3 equiv.) followed by the usual work-up and purification by column chromatography on silica gel. Mp 152–153°C; ^{1}H NMR δ 1.06–2.69 (m, 24H), 6.61–7.32 (m, 10H); ^{13}C NMR δ 23.29 (CH_2), 23.83 (CH_2), 26.69 (CH_2), 27.19 (CH_2), 27.66 (CH_2), 41.94 (CH_2), 67.66 (C), 126.07 (CH), 126.79 (CH), 133.75 (C), 214.46 (C=O). Anal. calcd for $C_{28}H_{34}O_2$: C, 83.54; H, 8.51. Found: C, 83.09; H, 8.52.

4.6. X-Ray crystallographic analysis of compounds 38 and 53b

The X-ray diffraction data were collected on a Brucker AXS P4 diffractometer at 160 K using graphite-monochromated Mo Kα λ=0.71073 Å. The structure was solved by direct methods and refined using least-squares techniques. All crystallographic calculations and preparation of structure

plots and tables were carried out using the SHELXTL PC suite of programs.[22]

Crystal data for dimer **38**. $C_{16}H_{26}O_2$, M=250.37, colorless needles, monoclinic, space group $C2/c$ (No. 15), a=15.4720(10) Å, b=6.0750(10) Å, c=14.2700(10) Å, β=93.690(10)°, U=1338.5(3) Å^3, Z=4, D_c=1.242 g cm^{-3}, $F(000)$=552, μ(Mo Kα)=0.079 mm^{-1}, final discrepancy factors: $R1$=0.035 and wR^2=0.087.

Crystal data for compound **53b**. $C_{13}H_{23}ClO$, M=230.77, colorless needles, triclinic, space group P-1 (No. 2), a=10.902(2) Å, b=10.904(2) Å, c=23.210(3) Å, α=80.290(10)°, β=80.76(2)°, γ=89.890(10)°, U=2683.4(8) Å^3, Z=8, D_c=1.142 g cm^{-3}, $F(000)$=1008, μ(Mo Kα)=0.261 mm^{-1}, final discrepancy factors: $R1$=0.056 and wR^2=0.132.

Crystallographic data (excluding structure factors) for structures of **38** and **53b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 191224 and 191225. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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