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Yingzhaosu A analogues: synthesis by the ozonolysis of unsaturated hydroperoxides, structural analysis and determination of anti-malarial activity

Takahiro Tokuyasu,[a] Araki Masuyama,[a] Masatomo Nojima,[a,*] Kevin J. McCullough,[b,*] Hye-Sook Kim[c] and Yusuke Wataya[c,*]

[a]*Department of Materials Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan*
[b]*Department of Chemistry, Heriot-Watt University, Edinburgh EH14 4AS, Scotland, UK*
[c]*Faculty of Pharmaceutical Sciences, Okayama University, Tsushima-naka 1-1-1, Okayama 700-8530, Japan*

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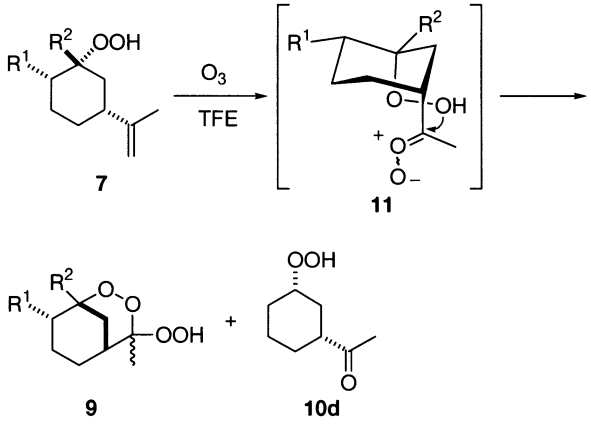
Abstract—Ozone-mediated cyclization of a series of unsaturated hydroperoxides **7**, prepared from dienes **2**, afforded the corresponding yingzhaosu A analogues **9** in moderate to high yield. X-Ray crystallographic analysis of two yingzhaosu A analogues, *endo*-**9f** and **13**, showed that the 2,3-dioxabicyclo[3.3.1]nonane system adopts a chair–boat arrangement. Subsequent treatment of endoperoxides **9** with Ag_2O/MeI afforded the expected methyldioxy-substituted cyclic peroxides **14**, several of which showed notable anti-malarial activity against *P. falciparum* in vitro.

1. Introduction

Since malaria parasites are rapidly developing resistance to the most commonly used chemo-therapeutic alkaloidal drugs, the anti-malarial properties of nonalkaloidal compounds such as artemisinin, yingzhaosu A and other related endoperoxides have attracted considerable attention.[1] In this respect, new methods for the synthesis of 1,2,4-trioxanes[2,3] and 1,2-dioxanes[4–6] have been developed. Among these endoperoxides, yingzhaosu A, possessing the unusual 2,3-dioxabicyclo[3.3.1]nonane framework, was an attractive target. The total synthesis of this endoperoxide has been independently achieved by Xu and Bachi,[7] and several derivatives have been also synthesized.[8,9] We previously reported that ozonolysis of unsaturated hydroperoxy acetals in protic solvent provided a useful synthetic route to hydroperoxy-substituted 1,2-dioxanes and 1,2-dioxepanes.[5] In this paper, we report further application of this methodology to the synthesis of 2,3-dioxabicyclo[3.3.1]-nonane derivatives.[9]



2. Results and discussion

2.1. Preparation of unsaturated hydroperoxides 7

Olefination of ketones **1a**,**b** by the Horner–Emmons reaction (Scheme 1) gave the required dienes **2a**,**b** and **4** which were subsequently transformed into the corresponding α-methoxy-substituted hydroperoxides **7a**,**b**,**f** by regioselective mono-ozonolysis in methanol as outlined in Scheme 2.

Since ozone is a highly electrophilic reagent, it was expected to react selectively at the more electron-rich

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* Corresponding authors. Tel./fax: +81-6-6879-7928; e-mail: nojima@ap.chem.eng.osaka-u.ac.jp

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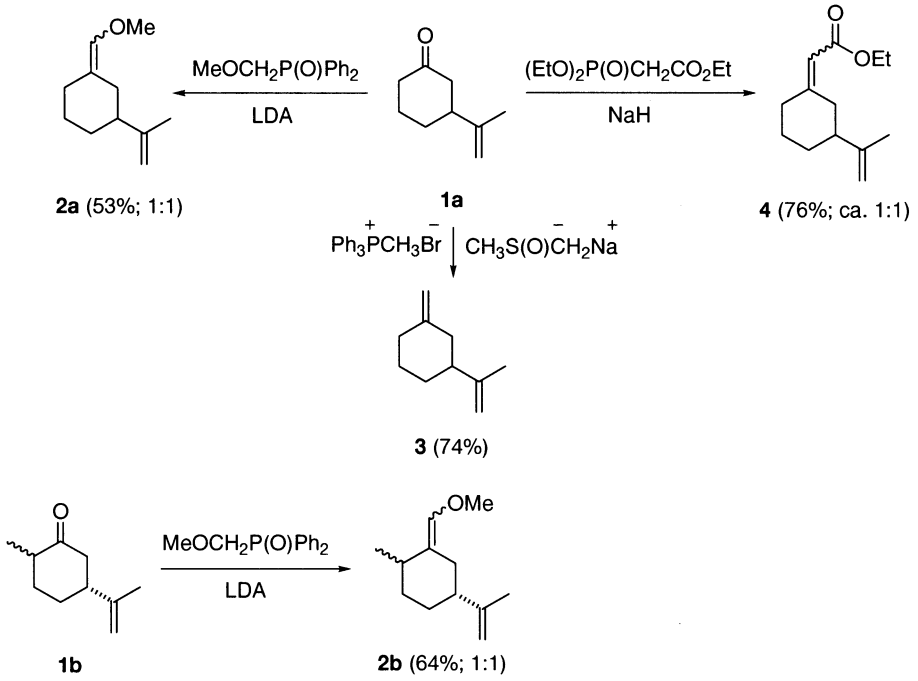


Scheme 1.

C=C double bond in diene substrates **2a**,**b** and **4**.[3,4g] In accordance with this notion, the reaction of diene **2a** with 1 equiv. of ozone in MeOH–CH_2Cl_2 at −70°C, followed by column chromatography on silica gel, gave the unsaturated hydroperoxide **7a** as an inseparable 1:1 mixture of two stereoisomers in 67% yield. Also, mono-ozonolysis of diene **4**, in which electron-withdrawing ester group was introduced into the alkene moiety, afforded a ca. 3:3:3:1 mixture of four unsaturated hydroperoxides **7f** (94%). From the reaction of diene **2b** (prepared from the commercially available dihydrocarvone as a 1:4 mixture of *cis*- and *trans*-isomers), however, only two isomeric hydroperoxides *trans*-**7b** (49%) and *cis*-**7b** (11%), separable by column chromatography on silica gel, were obtained (Scheme 2).

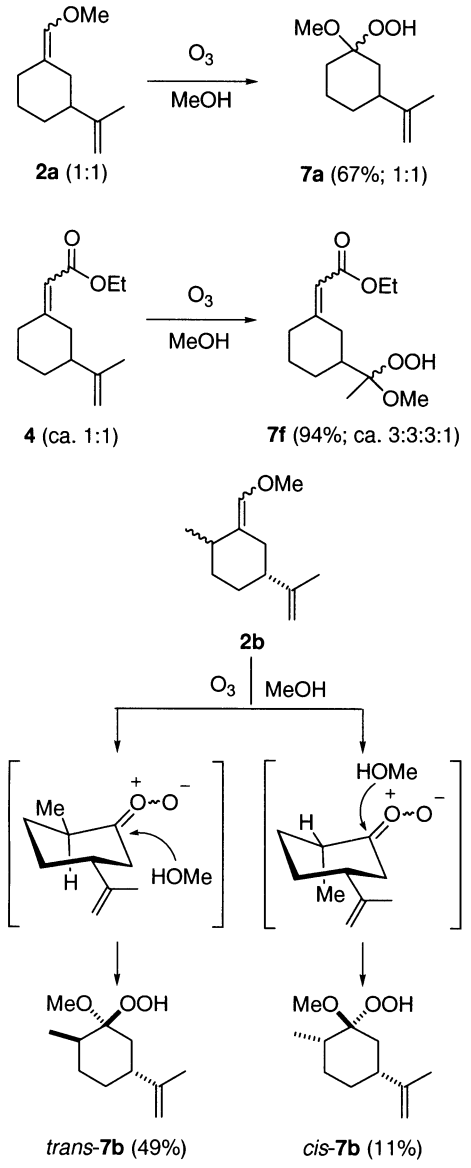
To determine the structure of the isomeric hydroperoxide *trans*-**7b**, a series of DEPT, COSY, HMQC and NOE experiments were conducted on the corresponding benzyl derivative **8**, obtained by the Ag_2O-mediated alkylation with benzyl bromide (Scheme 3). In the NOE experiment on **8**, irradiation at the methoxy group signal (δ 3.46, s) resulted in the enhancement of the C-6 hydrogen signals: H-6eq (δ 2.57, ddd) (3.2%) and H-6ax (δ 1.19, t) (1.2%). Also, irradiation at the C-2 methyl group signal (δ 1.00, d) induced the enhancement of the signals of the hydrogen atoms at C-3: H-3eq (δ 1.5–1.6, m) (2.7%) and H-3ax (δ 1.37, qd) (2.4%). In addition, irradiation of the hydrogen H-3ax signal resulted in enhancement of the H-5ax (δ 2.11, tt) (3.0%) signal. No NOE was observed between H-2ax and H-3ax (Fig. 1). These results are consistent with a *trans*-relationship between the methoxy and the methyl groups in hydroperoxide *trans*-**7b**. Thus, the corresponding intermediate carbonyl oxide must have been selectively captured by methanol from the less hindered face anti to the methyl group as observed previously (Scheme 2).[6] A similar stereochemical relationship is likely to be developed in the isomeric hydroperoxide *cis*-**7b**.

To prepare unsaturated *tert*-hydroperoxides *cis*-**7c** and **7e**, the Co(II)-catalyzed procedure for the autoxidation of alkenes developed by Mukaiyama[10] was investigated because the resulting triethylsilyl peroxides can be readily desilylated on treatment with hydrochloric acid in MeOH. Certainly, the two-step reaction of diene **3** afforded a mixture of the unsaturated hydroperoxides *cis*- and *trans*-**7c**, **7g** and the dihydroperoxide **7h**, demonstrating that two olefinic double bonds could not be differentiated during the autoxidation process (Scheme 4). Although hydroperoxides *cis*-**7c** and **7g** could be separated by column chromatography on silica gel, hydroperoxide *trans*-**7c** was obtained as an admixture with **7g**. In case of the diene **4**, however, the more electron-rich C=C double bond was selectively peroxidized, thereby yielding the desired mono-hydroperoxide **7e** in 74% yield as a ca. 2:1 mixture of geometrical isomers.

Finally, the *sec*-hydroperoxide *cis*-**7d** was prepared by the method reported by Bloodworth.[11] *N*-Tosylhydrazone **5**, prepared from the corresponding ketone **1a**, was reduced to the hydrazine **6** by $NaBH_3CN$/*p*-TsOH. Subsequent treatment of the crude hydrazine **6** with 30% H_2O_2 and Na_2O_2 afforded a mixture of the desired hydroperoxides *cis*-**7d** (26%) and *trans*-**7d** (19%), which could be separated by column chromatography on silica gel (Scheme 5). Replacement of the aqueous solution of H_2O_2 by a dried solution of H_2O_2 in THF afforded the hydroperoxides *cis*-**7d** and *trans*-**7d** in improved yields of 38 and 25%, respectively.

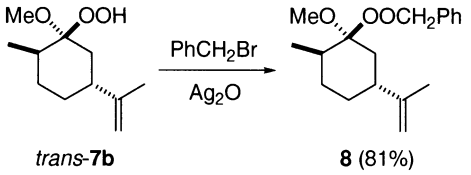
2.2. Ozonolysis of unsaturated hydroperoxides 7 in 2,2,2-trifluoroethanol (TFE)

With a series of the unsaturated hydroperoxides **7** in hand, ozone-mediated cyclizations in 2,2,2-trifluoroethanol (TFE) were conducted. Ozonolysis of the unsaturated hydroperoxide **7a** (a 1:1 mixture of two stereoisomers) afforded



Scheme 2.

the expected hydroperoxy-substituted yingzhaosu A analogue **9a** in 17% yield (34% based on *cis*-**7a**, having a configuration favorable for cyclization), together with the corresponding ketone **10a** (Scheme 6). Also, from the ozonolysis reactions of the *cis*-**7b**, *cis*-**7c** and *cis*-**7d**, the corresponding bicyclic peroxides **9b**–**d** were obtained in 45, 48 and 24% yield, respectively (Table 1). The by-product from the reaction of *cis*-**7b** and *cis*-**7c** was a complex mixture of unidentified, highly polar products in each case. Consistent with the unfavorable configuration of the unsaturated hydroperoxide *trans*-**7b**, the corresponding



Scheme 3.

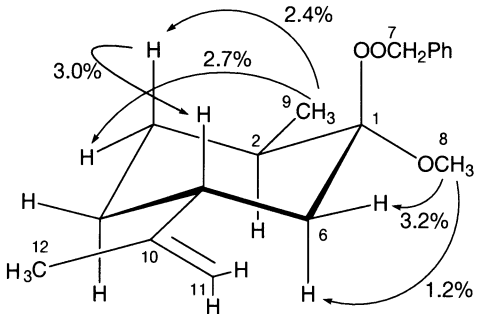


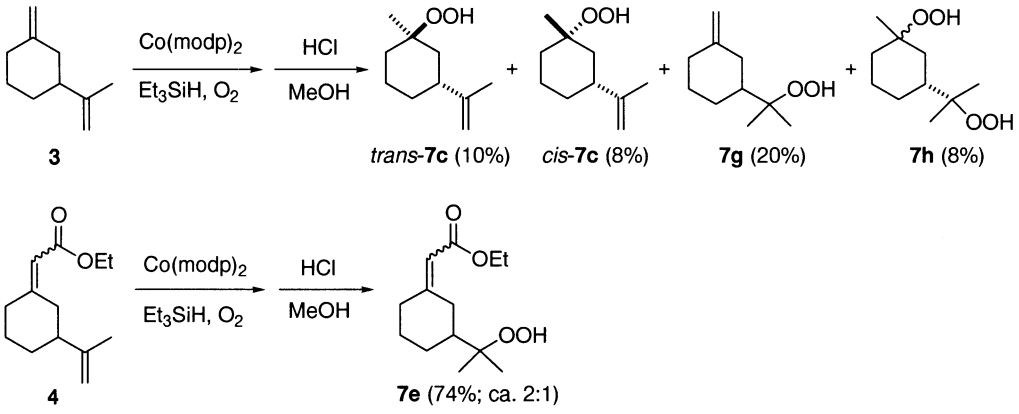
Figure 1. NOE enhancement of **8**.

ketone **10b** (68%) was obtained from *trans*-**7b** as the sole identified product (Scheme 7).

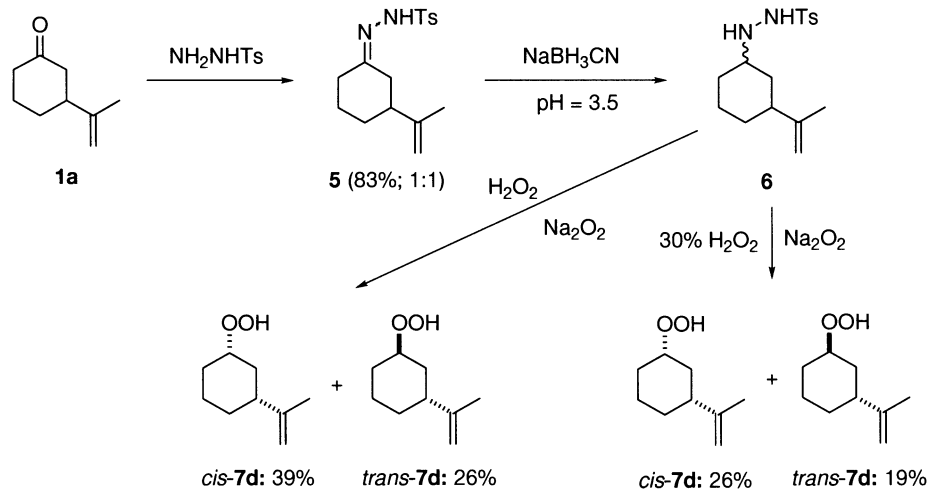
To realize intramolecular cyclization of the carbonyl oxide intermediate **11**, it is clear that the hydroperoxy group and the carbonyl oxide moiety are required to be 1,3-synaxial. Since the yield of the bicyclic peroxide **9b** (45% from *cis*-**7b**) was significantly higher than that of **9a** (34% from *cis*-**7a**), the presence of the methyl group at C-2 in *cis*-**7b** must make the population of the corresponding 1,3-synaxial conformation more favorable. In respect of the nucleophilicity of the hydroperoxy group, the *sec*-hydroperoxide *cis*-**7d** would be expected to capture the carbonyl oxide moiety highly efficiently, thereby producing the bicyclic peroxide **9d** in higher yields than the other cases. In reality, the yield of **9d** (24%) is lower than those of **9a**–**c**, suggesting that the presence of a substituent at the α-position of **7a,c** also facilitates the adoption of the corresponding 1,3-synaxial conformation. Thus, it may be concluded that, in the cyclization process, the ease of population of the appropriate 1,3-synaxial conformation is a significantly more important factor than the nucleophilicity of the hydroperoxy group.

The cyclic peroxides **9a**,**b**,**d** were obtained in each case as a single isomer. Although compound **9b** was crystalline, the crystals obtained diffracted weakly and decayed substantially during X-ray data collection at 160 K. From the X-ray data obtained, a structural solution was obtained but attempts to refine the structure were unsatisfactory. The structure, as depicted in structural formula **9b**, consists of the chair-like cyclohexane ring and the boat-like 1,2-dioxane ring (cf. X-ray crystal structure of *endo*-**9f** below) with a 1,2-*trans*-diequatorial relationship between the methoxy group and the adjacent methyl group. The hydroperoxy group occupies the *endo*-position, suggesting that compound **9b** could be stabilized by an anomeric effect between the peroxide oxygen non-bonded electron pairs and the exocyclic C–O bond.[12] From its structure, compound **9b** must be selectively formed by path a rather than path b (Scheme 8) which differ only by the orientation of the carbonyl oxide moiety. From the reaction of *cis*-**7c**, however, bicyclic peroxide **9c** was obtained as a 1:1 mixture of stereoisomers. The reason for the notable difference in stereoselectivity between **9b** and **9c** is obscure.

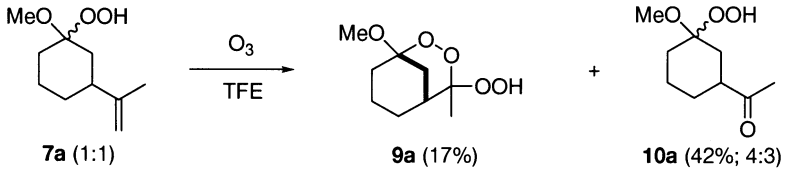
We have previously reported that ozonolysis of unsaturated hydroperoxides in aprotic solvents such as ether resulted in the formation of a complex mixture of products[9] with the



Scheme 4.



Scheme 5.



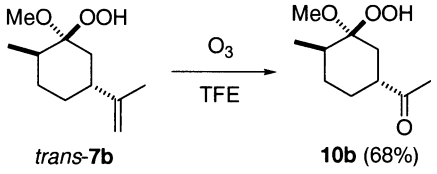
Scheme 6.

concomitant decrease in the yield of the desired cyclic peroxide.[5] In protic solvent such as TFE, however, the analogous reactions proceeded smoothly to afford the bicyclic peroxides in good yield. As indicated in Scheme 8, TFE assist the cyclization of the carbonyl oxide intermediate because solvation enhances the electrophilicity of the carbonyl oxide moiety thereby suppressing the [3+2] cycloaddition with the co-produced formaldehyde and facilitating the intramolecular capture by the hydroperoxy group.[3]

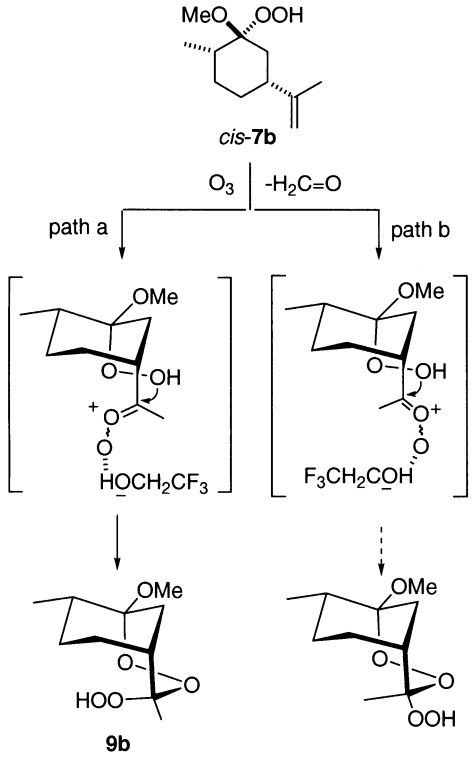
Table 1. Ozonolysis of *cis*-**7b**, *cis*-**7c** and *cis*-**7d** in TFE

Substrate	R^1	R^2	Products (yield)
cis-**7b**	Me	OMe	**9b** (45%)
cis-**7c**	H	Me	**9c** (48%; 1:1)
cis-**7d**	H	H	**9d** (24%), **10d** (33%)

Given that the carbonyl oxide intermediates derived from **7a–d** require 1,3-synaxial arrangements to produce the corresponding bicyclic endoperoxides **9a–d**, it was expected that the unsaturated hydroperoxides **7e**,**f** should undergo cyclization more readily because the resulting carbonyl oxide intermediates (e.g. **12** from **7e**) should cyclize through less sterically hindered conformations with only one axial group. Consistent with this expectation, ozonolysis of the unsaturated hydroperoxides **7e**,**f** proceeded



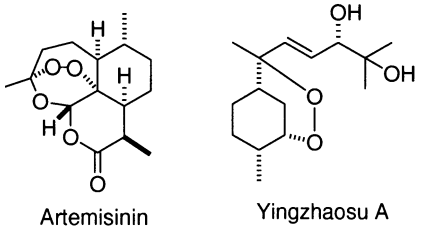
Scheme 7.



Scheme 8.

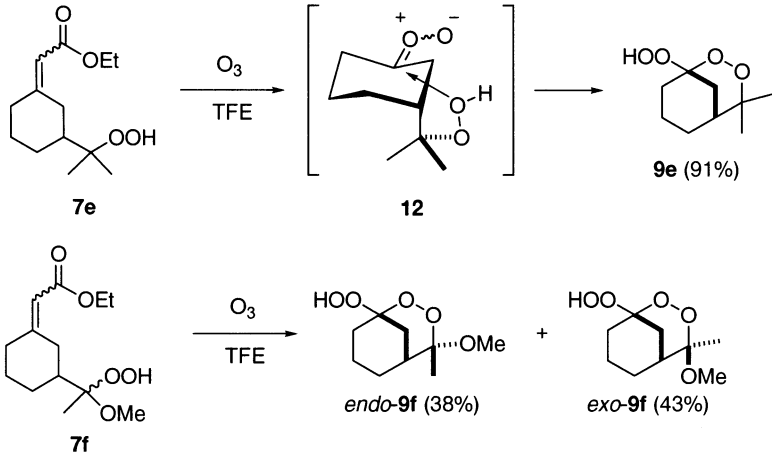
smoothly to afford the corresponding bicyclic peroxides **9e**, and *endo*- and *exo*-**9f**, respectively, in high yield (Scheme 9). The isomeric compounds, *endo*- and *exo*-**9f**, could be separated by column chromatography on silica gel and the structure of the highly crystalline *endo*-**9f** was determined by X-ray crystallographic analysis. The crystal structure of *endo*-**9f** consists of the dioxabicyclo[3.3.1]nonane skeleton with the cyclohexane and 1,2-dioxane rings being in a chair–boat arrangement (Fig. 2). The 1,2-dioxane ring exhibits significant distortion from an ideal boat conformation. The methoxy substituent was located at the *endo*-position which would favor an anomeric interaction analogous to that in endoperoxide **9b**.[12] The other isomer *exo*-**9f**, lacking any stabilizing anomeric effect, was found to be more thermally labile than *endo*-**9f** and underwent extensive decomposition in less than a week on storage at temperatures below 5°C.

The crystal structure of a related bicyclo[3.3.1] *endo*-peroxide **13**, whose synthesis was reported previously,[9] was also determined by X-ray crystallographic analysis (Fig. 3). The molecular skeleton of **13** has the chair–boat conformational arrangement as observed for **9b** and *endo*-**9f**. It is interesting to note that in the crystal structures of yingzhaosu A derivative[7a] and an analogue,[8a] both prepared by intramolecular Michael-type cyclization of hydroperoxycyclohexenone derivatives, the [3.3.1] bicyclic skeleton adopts the alternative chair–chair arrangement.



Since the presence of the hydroperoxy group was expected to render the bicyclic endoperoxides **9** highly cytotoxic, they were converted into the corresponding methylated compounds **14** on treatment with a mixture of Ag_2O and methyl iodide (Scheme 10).

With the yingzhaosu A analogues **14** in hand, their anti-malarial activities and cytotoxicities were tested against *P. falciparum* and FM3A cells,[1j] respectively (Table 2). Compound **14b** was found to give the best result, providing an EC_{50} value of 1.0×10^{-7} M against *P. falciparum* [approximately a tenth of the anti-malarial potency of artemisinin ($EC_{50}=7.8\times10^{-9}$ M)]. Moreover, the selectivity determined by the comparison with the 50% inhibitory concentration against FM3A cells (3.3×10^{-5} M) was as high as 330. The other compounds in the series showed only moderate anti-malarial activities, suggesting that significant modification of the structure would be required in order to develop promising candidates as anti-malarial drugs.



Scheme 9.

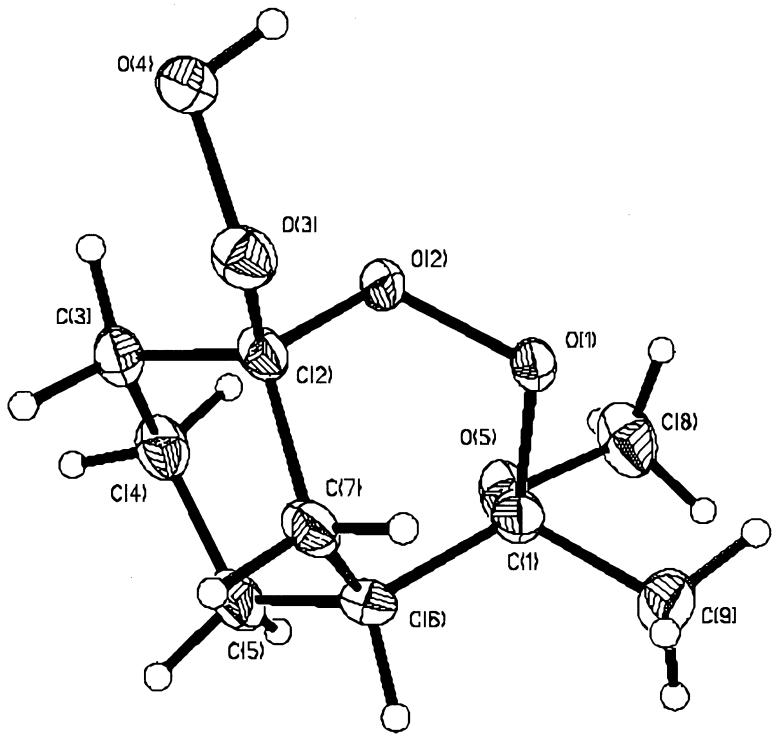


Figure 2. The X-ray crystal structure of the bicyclic endoperoxide *endo*-**9f** (ORTEP[17]).

3. Conclusion

A series of yingzhaosu A analogues were prepared by ozonolysis of the appropriate unsaturated hydroperoxides in TFE. In several cases, the reaction proceeded in a highly stereoselective fashion. The efficiency of cyclization process depends more on the ease of population of a conformation favorable for cyclization than the nucleophilicity of the hydroperoxy group. Consistent with this, structure of unsaturated hydroperoxides significantly affected the yields

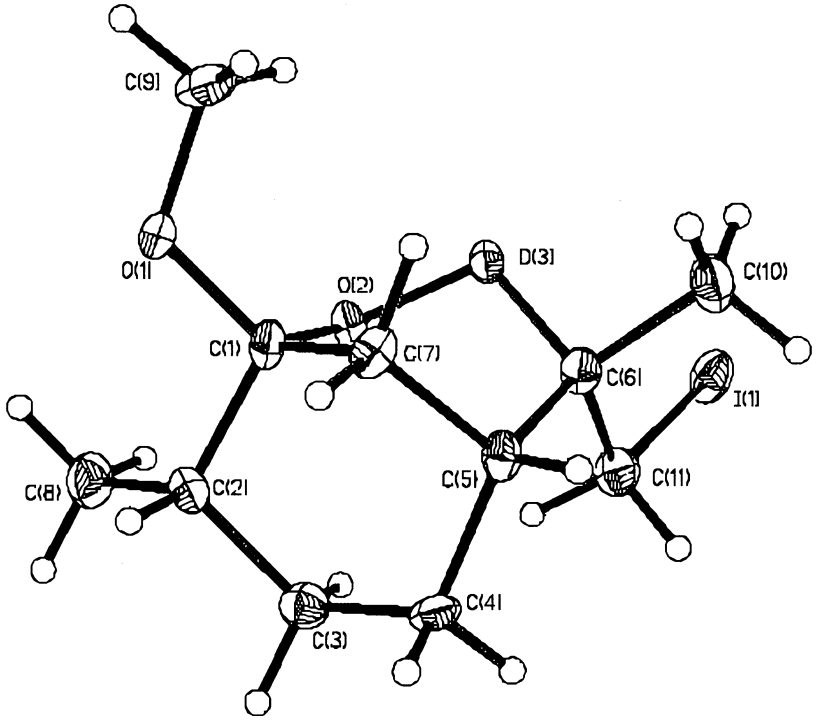
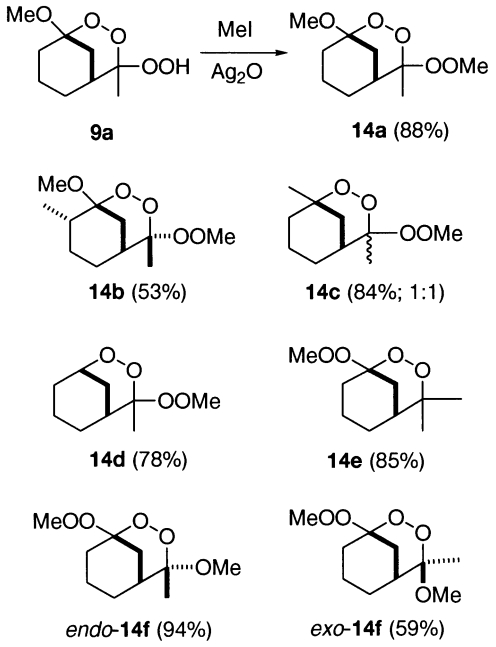


Figure 3. The X-ray crystal structure of the bicyclic endoperoxide **13** (ORTEP[17]).



Scheme 10.

Table 2. In vitro anti-malarial activities of yingzhaosu A analogues **14** against *P. falciparum* and cytotoxicities against FM3A cells

	Ec_{50} values (M)		Select[a]
	P. falciparum	FM3A	
14a	4.6×10^{-6}	1.4×10^{-4}	30
14b	1.0×10^{-7}	3.3×10^{-5}	330
14c	2.9×10^{-5}	4.6×10^{-4}	16
14e	7.0×10^{-5}	6.8×10^{-5}	<1
endo-**14f**	1.7×10^{-5}	4.7×10^{-5}	3
exo-**14f**	1.8×10^{-6}	9.8×10^{-5}	54
Artemisinin	7.8×10^{-9}	1.0×10^{-6}	1280

[a] Select=(EC_{50} value for FM3A cells)/(EC_{50} value for *P. falciparum*).

of the bicyclic endoperoxides. Some of the obtained bicyclic endoperoxides, prepared in this study, showed notable anti-malarial activity in vitro.

4. Experimental

4.1. General procedures

^{1}H (270 MHz; 400 MHz for COSY, HMQC and NOE measurements) and ^{13}C (67.5 MHz) NMR spectra were obtained in $CDCl_3$ solution with $SiMe_4$ as the standard. Unsaturated ketone **1b** was commercial available, and the other unsaturated ketone **1a**[13] and the derivatives **2**[14], **3**[15] and **4**[16] were prepared by literature procedures. The detailed procedures for the determination of antimalarial activities of peroxides in vitro and in vivo have been previously described.[1j]

4.2. Mono-ozonolysis of dienes 2,4 in MeOH–CH_2Cl_2

Ozonolysis of the diene **2b** is representative. Into a solution of **2b** (1.7 g, 9.4 mmol) in CH_2Cl_2 (25 mL) and methanol (5 mL) was passed a slow stream of ozone (1 equiv.) at −70°C. Reaction mixture was poured into aqueous sodium bicarbonate, and extracted with ether (30 mL×2). The combined organic extracts were washed with saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the products were isolated by column chromatography on silica gel. Elution with diethyl ether–hexane (8:92) gave the unsaturated hydroperoxide *trans*-**7b** (920 mg, 49%). Subsequent elution with (15:85) gave the unsaturated hydroperoxy acetal *cis*-**7b** (240 mg, 11%).

4.2.1. (1*S*,2*R*,5*R*)-1-Methoxy-2-methyl-5-(1-methylethenyl)-cyclohexyl hydroperoxide (*trans*-7b). An oil; ^{1}H NMR δ 0.98 (d, J=6.9 Hz, 3H), 1.2–1.8 (m, 6H), 1.74 (s, 3H), 2.2–2.6 (m, 2H), 3.44 (s, 3H), 4.72 (s, 2H), 8.99 (s, 1H); ^{13}C NMR δ 13.87 (CH_3), 21.10 (CH_3), 31.05 (CH_2), 31.37 (CH_2), 34.34 (CH_2), 38.80 (CH), 41.37 (CH), 51.09 (CH_3), 106.92 (C), 108.93 (C), 149.38 (C). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.94: H, 10.07. Found: C, 65.91: H, 10.09.

4.2.2. (1*R*,2*S*,5*R*)-1-Methoxy-2-methyl-5-(1-methylethenyl)-cyclohexyl hydroperoxide (*cis*-7b). An oil; ^{1}H NMR δ 1.03 (d, J=7.3 Hz, 3H), 1.2–2.4 (m, 8H), 1.73 (s, 3H), 3.30 (s, 3H), 4.71 (s, 2H), 7.81 (s, 1H); ^{13}C NMR δ 14.29 (CH_3), 20.81 (CH_3), 25.10 (CH_2), 28.84 (CH_2), 28.95 (CH_2), 32.96 (CH), 41.40 (CH), 48.09 (CH_3), 108.43 (C), 109.00 (C), 148.96 (C). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.94: H, 10.07. Found: C, 65.34: H, 10.00.

4.2.3. 1-Methoxy-3-(1-methylethenyl)cyclohexyl hydroperoxide (7a). An oil (a 1:1 mixture of two stereoisomers); ^{1}H NMR δ 1.0–1.6 (m, 4H), 1.6–1.9 (m, 2H), 1.72 (s, 3H), 2.0–2.3 (m, 3H), 3.30 (s)+3.35 (s) (3H), 4.70 (s, 2H), 8.49 (s, 1H); ^{13}C NMR δ 20.70 (2C), 22.12, 22.28, 30.30, 30.69, 30.82, 30.86, 35.55, 35.99, 41.10, 41.15, 48.12, 48.25, 105.79, 105.93, 108.75, 108.82, 148.95, 149.04. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49: H, 9.74. Found: C, 64.06: H, 9.62.

4.2.4. Ethyl 3-(1-hydroperoxy-1-methoxyethyl)cyclohexyl-ideneacetate (7f). An oil (a 1:1:1 mixture of three major isomers); ^{1}H NMR δ 1.2–2.6 (m, 14H), 3.30 (s)+3.31 (s)+3.47 (s) (3H), 3.8–4.0 (m, 1H), 4.1–4.3 (m, 2H), 5.6–5.7 (m, 1H), 8.58 (s)+8.69 (s)+8.70 (s) (1H); ^{13}C NMR δ 13.95 (CH_3), 14.09 (CH_3), 15.06 (CH_3), 15.47 (CH_3), 22.48 (CH_2), 26.36 (CH_2), 26.52 (CH_2), 27.08 (CH_2), 27.17 (CH_2), 29.29 (CH_2), 30.66 (CH_2), 31.41 (CH_2), 37.45 (CH_2), 38.58 (CH_2), 38.67 (CH_2), 42.86 (CH), 43.63 (CH), 48.56 (CH_3), 48.59 (CH_3), 59.50 (CH_2), 59.55 (CH_2), 107.76 (C), 107.84 (C), 108.00 (C), 113.71 (CH), 113.87 (CH), 114.02 (CH), 161.58 (C), 161.83 (C), 161.90, (C) 166.68 (C), 166.85 (C); the additional following signals were assigned to the minor isomer. ^{1}H NMR δ 3.38 (s, 3H), 9.24 (s, 1H); ^{13}C NMR δ 27.76 (CH_2), 28.66 (CH_2), 32.45 (CH_2), 37.83 (CH_2), 44.96 (CH), 49.00 (CH_3), 60.16 (CH_2), 107.85 (C), 112.47 (CH), 163.72 (C). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45: H, 8.58. Found: C, 60.33: H, 8.71.

4.3. Mono-peroxygenation of dienes 3,4 with Co(II)-catalyst

Mono-peroxygenation of the diene **4** is representative. Into a

two-neck 50 mL flask, charged with dioxygen, the diene **4** (200 mg, 0.96 mmol), bis(1-morpholinocarbamoly-4,4-dimethyl-1,3-pentanedionato)-cobalt(II) ($Co(modp)_2$) (26 mg, 0.048 mmol) and 1,2-dichloroethane (10 mL) were added, and then the flask was again charged with dioxygen. Triethylsilane (220 mg, 1.9 mmol) was added via 1.0 mL gas-tight syringe, and reaction mixture was stirred vigorously under oxygen atmosphere at room temperature. After 1.5 h, the solvent was evaporated under reduced pressure. The components of the residue were separated by column chromatography on silica gel. Elution with diethyl ether–hexane (3:97) gave a mixture of the diene **4** and the corresponding triethylsilyl peroxide. After treatment of the mixture with a drop of conc. HCl in methanol (5 mL), the reaction mixture was poured into aqueous sodium bicarbonate, and extracted with ether (30 mL×2). The combined organic extracts were washed with saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the products were isolated by column chromatography on silica gel. The diene **2c** (60 mg) was recovered by elution with diethyl ether–hexane (3:97). Subsequent elution with diethyl ether–hexane (15:85) gave a ca. 2:1 mixture of the unsaturated hydroperoxide **7e** (120 mg, 74%). This hydroperoxide **7e** was labile even in refrigerator, and decomposition was observed within one week. Therefore satisfactory elemental analysis data could not be obtained. The reduction of **7e** with Ph_3P gave the corresponding alcohol, which gave satisfactory elemental analysis.

4.3.1. Ethyl 3-(1-hydroperoxy-1-methylethyl)cyclohexylideneacetate (7e). An oil (a ca. 2:1 mixture of two stereoisomers); ^{1}H NMR δ 1.0–2.4 (m, 17H), 3.83 (br t, J=12.7 Hz, 1H), 4.0–4.2 (m, 2H), 5.61 (s)+5.63 (s, major) (1H), 7.95 (s, major)+8.87 (s) (1H); ^{13}C NMR (major isomer) δ 14.20, 20.83, 21.91, 26.85, 27.14, 29.42, 38.53, 46.11, 59.55, 84.17, 113.71, 162.77, 166.94; the following additional signals were assigned to the minor isomer in ^{13}C NMR spectrum; δ 19.77, 22.59, 27.89, 28.92, 31.54, 37.83, 46.29, 59.95, 84.12, 112.09, 164.53, 167.67.

4.3.2. Ethyl 3-(1-hydroxy-1-methylethyl)cyclohexylideneacetate. An oil (a ca. 2:1 mixture of two stereoisomers); ^{1}H NMR δ 1.2–2.4 (m, 18H), 3.82 (br t, J=13.5 Hz, major)+3.98 (br t, J=12.2 Hz) (1H), 4.10 (q, J=7.2 Hz, 2H), 5.61 (s, 1H); ^{13}C NMR δ 14.22 (2C), 26.51, 26.79 (2C), 26.96, 27.05 (2C), 27.30, 27.66, 29.31, 30.84, 37.58, 38.71, 50.28, 50.84, 59.44, 59.50, 72.29, 72.42, 113.28, 113.60, 162.93, 163.13, 166.74, 166.81. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99: H, 9.80. Found: C, 68.68: H, 9.90.

4.3.3. *trans*-1-Methyl-3-(1-methylethenyl)cyclohexyl hydroperoxide (*trans*-7c). An oil; the following signals were assigned; ^{1}H NMR δ 1.25 (s, 3H), 1.70 (s, 3H), 4.67 (s, 2H); ^{13}C NMR δ 20.90, 21.49, 25.66, 30.82, 33.86, 39.32, 39.68, 81.49, 108.34, 150.19.

4.3.4. *cis*-1-Methyl-3-(1-methylethenyl)cyclohexyl hydroperoxide (*cis*-7c). An oil; ^{1}H NMR δ 1.1–2.0 (m, 9H), 1.31 (s, 3H), 1.71 (s, 3H), 4.69 (s, 2H), 7.61 (s, 1H); ^{13}C NMR δ 20.76, 20.94, 23.13, 31.27, 34.22, 39.62, 42.28, 83.63, 108.72, 149.51.

4.3.5. 3-(1-Hydroperoxy-1-methylethyl)methylenecyclohexane (7g). An oil; ^{1}H NMR δ 1.0–1.4 (m, 2H), 1.18 (s, 3H), 1.19 (s, 3H), 1.6–2.0 (m, 5H), 2.2–2.4 (m, 2H), 4.63 (s, 2H), 7.41 (s, 1H); ^{13}C NMR δ 21.19, 21.58, 27.01, 27.39, 34.90, 36.10, 45.66, 84.78, 107.48, 149.18.

4.3.6. 3-(1-Hydroperoxy-1-methylethyl)-1-methylcyclohexyl hydroperoxide (7h). An oil (a 1:1 mixture of two stereoisomers); ^{1}H NMR δ 0.8–2.2 (m, 9H), 1.06 (s)+1.13 (s)+1.17 (s)+1.21 (s)+1.24 (s)+1.28 (s) (9H), 7.99 (s)+8.13 (s)+8.25 (s)+8.26 (s) (2H); ^{13}C NMR δ 20.15, 20.88, 21.17, 21.66, 21.75, 22.55, 22.99, 25.73, 26.85 (2C), 34.31, 34.34, 34.56, 35.51, 38.19, 41.17, 81.65, 83.94, 84.67, 84.75. Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80: H, 9.87. Found: C, 58.72: H, 9.92.

4.4. Preparation of hydrazone 5

Into a 100 mL flask, *p*-tosylhydrazine (13.0 g, 69.9 mmol) and ethanol (20 mL) were added. The flask was warmed to 40–50°C, and then the unsaturated ketone **1a** (9.6 g, 70.0 mmol) was added with stirring. After stirring for 0.5 h, the reaction mixture was poured into water (50 mL), and extracted with diethyl ether (50 mL×2). The combined organic extracts were washed with saturated brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, recrystallization of the residue from ethyl acetate–hexane gave the hydrazone **5** (17.7 g, 83%) as a 1:1 mixture of geometric isomers.

4.4.1. 3-(1-Methylethenyl)cyclohexanone *p*-tosylhydrazone (5). Mp 110–115°C (ethyl acetate–hexane) (a 1:1 mixture of two stereoisomers); ^{1}H NMR δ 1.2–1.5 (m, 2H), 1.6–2.2 (m, 5H), 1.65 (s)+1.67 (s) (3H), 2.3–2.5 (m, 1H), 2.41 (s, 3H), 2.6–2.8 (m, 1H), 4.64 (s, 1H), 4.68 (s, 1H), 7.30 (d, J=8.1 Hz, 2H), 7.86 (d, J=8.1 Hz, 2H), 8.20 (br s, 1H); ^{13}C NMR δ 20.52 (CH_3), 20.61 (CH_3), 21.44 (CH_3, 2C), 24.44 (CH_2), 25.39 (CH_2), 26.33 (CH_2), 30.24 (CH_2), 30.41 (CH_2), 31.59 (CH_2), 34.65 (CH_2), 39.89 (CH_2), 44.05 (CH), 44.94 (CH), 109.27 (CH_2), 109.63 (CH_2), 127.87 (CH, 4C), 128.12 (C), 129.33 (CH, 4C), 129.72 (C), 135.24 (C), 143.65 (C), 147.66 (C), 148.03 (C), 161.69 (C), 161.83 (C). Anal. Calcd for $C_{16}H_{22}N_2SO_2$: C, 62.71: H, 7.24: N, 9.14: S, 10.46. Found: C, 62.57: H, 7.16: N, 9.13: S, 10.44.

4.5. Reduction of the hydrazone 5 to the corresponding hydrazine 6

Into a four-necked flask, equipped with two dropping funnels, the hydrazone **5** (3.6 g, 11.7 mmol) and bromocresol green (ca. 10 mg) were added, and dissolved in THF (50 mL) under a gentle stream of nitrogen. The exit gases were passed through three Dreschel bottles (the first bottle was empty, and the final two bottles contained an aqueous solution of sodium hypochlorite). A solution of sodium cyanoborohydride (3.0 g, 48.1 mmol) in THF (60 mL) was added in one portion from one dropping funnel. From another dropping funnel, a solution of *p*-TsOH·H_2O (4.5 g, 23.9 mmol) in THF (50 mL) was added in small portions to maintain the solution at pH 3.5 (the indicator showed a tan color). After the addition of sodium cyanoborohydride was complete, the reaction

mixture was stirred for additional 4 h. The white precipitate was removed by filtration over Celite, and the filtrate was concentrated under reduced pressure. Water (80 mL) was added to the residue, and extracted with CH_2Cl_2 (50 mL×3). The combined organic extracts were dried over anhydrous $MgSO_4$, and evaporation of the solvent under reduced pressure afforded the crude hydrazine **6** (3.4 g).

4.5.1. *N*-[3-(1-Methylethenyl)cyclohexyl]-*N′*-*p*-tosylhydrazine (6). ^{13}C NMR δ 20.69, 21.53, 24.32, 30.86, 31.04, 36.16, 43.58, 58.74, 108.46, 128.12 (2C), 129.47 (2C), 135.18, 143.88, 149.58.

4.6. Preparation of the unsaturated hydroperoxide 7d

An aqueous solution of H_2O_2 (30%, 250 mL) was extracted with diethyl ether (100 mL×3) [caution!], and the combined organic extracts were dried over anhydrous $MgSO_4$. About 250 mL of diethyl ether was evaporated under reduced pressure. Then, 80 mL of THF was added, and further 80 mL of solvents was evaporated under reduced pressure. This operation was repeated three times. To the cooled (0°C) solution of H_2O_2 in THF was added in turn an additional aliquot of THF (120 mL), followed by the crude hydrazine **6** (3.4 g), and finally an aqueous solution (10 mL) of sodium peroxide (2.3 g, 29.0 mmol). After stirring for 30 h, the reaction mixture was poured into cold water (100 mL) and neutralized with 2N HCl. After extraction with CH_2Cl_2 (70 mL×3), the combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. By column chromatography on silica gel, elution with diethyl ether–hexane (4:96) the unsaturated hydroperoxide *trans*-**7d** was obtained first (460 mg, 25%). Subsequent elution gave the unsaturated hydroperoxide *cis*-**7d** (700 mg, 38%).

4.6.1. *trans*-3-(1-Methylethenyl)cyclohexyl hydroperoxide (*trans*-7d). An oil; ^1H NMR δ 1.3–1.8 (m, 6H), 1.70 (s, 3H), 2.0–2.3 (m, 3H), 4.30 (qi, J=3.0 Hz, 1H), 4.6–4.7 (m, 2H), 8.12 (s, 1H); ^{13}C NMR δ 20.99 (CH_2), 21.31 (CH_3), 28.54 (CH_2), 31.54 (CH_2), 33.80 (CH_2), 39.10 (CH), 80.54 (CH), 108.99 (CH_2), 150.46 (C). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19: H, 10.32. Found: C, 69.10: H, 10.26.

4.6.2. *cis*-3-(1-Methylethenyl)cyclohexyl hydroperoxide (*cis*-7d). An oil; ^1H NMR δ 1.0–1.4 (m, 5H), 1.70 (s, 3H), 1.8–2.2 (m, 4H), 3.98 (tt, J=11.1 and 4.0 Hz, 1H), 4.69 (s, 2H), 8.32 (s, 1H); ^{13}C NMR δ 20.72 (CH_3), 23.83 (CH_2), 30.01 (CH_2), 30.91 (CH_2), 35.35 (CH_2), 43.38 (CH), 84.01 (CH), 108.81 (CH_2), 149.20 (C). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19: H, 10.32. Found: C, 69.68: H, 10.02.

4.7. Preparation of the benzyl peroxide 8 from the hydroperoxide *trans*-7b

Into a solution of *trans*-**7b** (500 mg, 2.5 mmol) and benzyl bromide (430 mg, 2.5 mmol) in CH_2Cl_2 (10 mL), Ag_2O (580 mg, 2.5 mmol) was added. After stirring for 2.5 h, the solid material was removed by filtration over Celite, and the filtrate was concentrated under reduced pressure. The product was isolated by column chromatography on silica gel. Elution with diethyl ether–hexane (2:98) gave the corresponding benzyl peroxide **8** (590 mg, 81%).

4.7.1. (1*S*,2*R*,5*R*)-1-Benzyldioxy-1-methoxy-2-methyl-5-(1-methylethenyl)cyclohexane (8). An oil; ^1H NMR (400 MHz) δ 1.00 (d, J=6.9 Hz, 3H, H-9), 1.19 (t, J=12.9 Hz, 1H, H-6ax), 1.17 (qd, J=12.9 and 4.1 Hz, 1H, H-4ax), 1.37 (qd, J=12.9 and 3.5 Hz, 1H, H-3ax), 1.5–1.6 (m, 1H, H-3eq), 1.6–1.8 (m, 2H, H-2ax and 4-eq), 1.70 (s, 3H, H-12), 2.11 (tt, J=12.9 and 3.3 Hz, 1H, H-5ax), 2.57 (ddd, J=12.9, 3.3 and 2.0 Hz, 1H, H-6eq), 3.46 (s, 3H, H-8), 4.67 (s, 1H, H-11), 4.70 (s, 1H, H-11), 5.02 (s, 2H, H-7), 7.2-7.4 (m, 5H, Ph); ^{13}C NMR (100 MHz) δ 14.27 (CH_3, C-9), 21.07 (CH_3, C-12), 31.15 (CH_2, C-4), 31.71 (CH_2, C-3), 35.24 (CH_2, C-6), 40.90 (CH, C-2), 41.49 (CH, C-5), 51.22 (CH_3, C-8), 77.11 (CH_2, C-7), 106.17 (C, C-1), 108.64 (CH_2, C-11) 128.33 (CH, Ph), 128.40 (CH, Ph, 2C), 129.31 (CH, Ph, 2C), 136.06 (C, Ph), 149.69 (C, C-10). Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45: H, 9.02. Found: C, 74.72: H, 9.07.

4.8. Ozonolysis of the unsaturated hydroperoxides 7 in TFE

The ozonolysis of the unsaturated hydroperoxide **7a** is representative. Into a solution of **7a** (380 mg, 2.0 mmol) in CH_2Cl_2 (25 mL) and 2,2,2-trifluoroethanol (TFE) (5 mL) was passed a slow stream of ozone (1.5 equiv.) at 0°C. The reaction mixture was poured into aqueous sodium bicarbonate, and extracted with ether (30 mL×2). The combined organic layer was washed with saturated brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the products were isolated by column chromatography on silica gel. Elution with diethyl ether–hexane (20:80) gave the bicyclic peroxide **9a** (71 mg, 17%). Subsequent elution with (50:50) gave the ketone **10a** (160 mg, 42%).

4.8.1. 1-Methoxy-4-methyl-2,3-dioxabicyclo[3.3.1]nonan-4-yl hydroperoxide (9a). An oil; ^1H NMR δ 1.2–2.5 (m, 9H), 1.47 (s, 3H), 3.40 (s, 3H), 8.77 (s, 1H); ^{13}C NMR δ 20.33 (CH_3), 21.35 (CH_2), 22.99 (CH_2), 31.23 (CH_2), 31.95 (CH_2), 39.59 (CH), 48.97 (CH_3), 104.64 (C), 110.15 (C). Anal. Calcd for $C_9H_{16}O_5$: C, 52.93: H, 7.90. Found: C, 52.58: H, 7.71.

4.8.2. 1-(3-Hydroperoxy-3-methoxycyclohexyl)ethanone (10a). An oil (a 4:3 mixture of two stereoisomers); ^1H NMR δ 1.1–2.7 (m, 9H), 2.10 (s, major)+2.11 (s) (3H), 3.23 (s)+3.26 (s, major) (3H), 8.75 (s, major)+8.95 (s) (1H); ^{13}C NMR δ 21.35, 21.75, 27.50, 28.07, 29.35, 30.46, 32.51, 32.60, 47.62, 47.67, 48.11, 48.36, 104.83, 105.67, 211.46, 211.82. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43: H, 8.57. Found: C, 57.20: H, 8.47.

4.8.3. (1*R*,4*S*,5*R*,8*S*)-1-Methoxy-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-4-yl hydroperoxide (9b). Mp 161–163°C (from ethyl acetate–hexane); ^1H NMR δ 0.81 (d, J=4.9 Hz, 3H), 1.2–1.8 (m, 6H), 1.39 (s, 3H), 2.2–2.4 (m, 2H), 3.35 (s, 3H), 8.50 (s, 1H); ^{13}C NMR δ 13.71 (CH_3), 20.65 (CH_3), 23.51 (CH_2), 29.18 (CH_2), 30.59 (CH_2), 39.73 (CH), 40.20 (CH), 49.26 (CH_3), 105.34 (C), 110.03 (C).

Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03: H, 8.31. Found: C, 54.95: H, 8.18.

4.8.4. 1-[(1*R*,3*S*,4*R*)-3-Hydroperoxy-3-methoxy-4-methylcyclohexyl]ethanone (10b). An oil; ^{1}H NMR δ 0.98 (d, J=6.9 Hz, 3H), 1.2–2.0 (m, 6H), 2.20 (s, 3H), 2.4–2.6 (m, 1H), 2.7–2.9 (m, 1H), 3.43 (s, 3H), 9.27 (s, 1H); ^{13}C NMR δ 13.76 (CH_3), 27.22 (CH_2), 28.32 (CH_3), 30.40 (CH_2), 30.57 (CH_2), 37.86 (CH), 47.89 (CH), 50.94 (CH_3), 106.20 (C), 211.69 (C). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39: H, 8.97. Found: C, 60.03: H, 9.15.

4.8.5. 1,4-Dimethyl-2,3-dioxabicyclo[3.3.1]nonan-4-yl hydroperoxide (9c). An oil (a 1:1 mixture of two stereoisomers); ^{1}H NMR δ 1.0–2.4 (m, 9H), 1.08 (s)+1.27 (s)+1.42 (s)+1.44 (s) (6H), the quite broad signal, assigned to the signal of the OOH, was observed at 9.2–9.7 ppm; ^{13}C NMR δ 17.67, 19.68, 19.75, 20.42, 22.93, 26.17, 26.48, 27.03, 31.79, 33.77, 34.74, 35.37, 35.93, 37.41, 77.16, 79.12, 107.69, 109.79.

4.8.6. 4-Methyl-2,3-dioxabicyclo[3.3.1]nonan-4-yl hydroperoxide (9d). An oil; ^{1}H NMR δ 1.2–1.6 (m, 4H), 1.47 (s, 3H), 1.8–1.9 (m, 1H), 1.9–2.0 (m, 1H), 2.1–2.3 (m, 3H), 4.62 (t, J=4.8 Hz, 1H), 8.45 (s, 1H); ^{13}C NMR δ 18.45 (CH_2), 20.70 (CH_3), 23.61 (CH_2), 28.82 (CH_2), 29.34 (CH_2), 35.60 (CH), 74.64 (CH), 110.56 (C).

4.8.7. 1-(3-Hydroperoxycyclohexyl)ethanone (10d). An oil; ^{1}H NMR δ 1.2–1.5 (m, 4H), 1.8–2.0 (m, 2H), 2.0–2.1 (m, 1H), 2.20 (s, 3H), 2.2–2.3 (m, 1H), 2.4–2.5 (m, 1H), 3.98 (tt, J=10.2 and 4.0 Hz, 1H), 9.52 (s, 1H); ^{13}C NMR δ 22.75 (CH_2), 27.48 (CH_2), 27.85 (CH_3), 29.36 (CH_2), 31.39 (CH_2), 49.02 (CH), 82.25 (CH), 221.89 (C). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74: H, 8.92. Found: C, 60.33: H, 8.82.

4.8.8. 4,4-Dimethyl-2,3-dioxabicylo[3.3.1]nonyl hydroperoxide (9e). An an oil; ^{1}H NMR δ 1.14 (s, 3H), 1.3–1.6 (m, 3H), 1.36 (s, 3H), 1.6–2.0 (m, 3H), 2.1–2.4 (m, 3H), 8.56 (s, 1H); ^{13}C NMR δ 20.88, 21.84, 25.43, 25.64, 29.40, 30.01, 39.25, 82.61, 108.79. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43: H, 8.57. Found: C, 57.28: H, 8.36.

4.8.9. 4-Methoxy-4-methyl-2,3-dioxabicylo[3.3.1]nonyl hydroperoxide (*endo*-9f). Mp 73–74°C (from ethyl acetate–hexane); ^{1}H NMR δ 1.2–1.6 (m, 4H), 1.29 (s, 3H), 1.8–2.1 (m, 3H), 2.2–2.4 (m, 1H), 2.4–2.5 (m, 1H), 3.34 (s, 3H), 8.58 (s, 1H); ^{13}C NMR δ 19.86 (CH_3), 20.94 (CH_2), 24.21 (CH_2), 29.27 (CH_2), 30.28 (CH_2), 40.20 (CH), 49.33 (CH_3), 105.88 (C), 109.11 (C). Anal. Calcd for $C_9H_{16}O_5$: C, 52.93: H, 7.90. Found: C, 52.86: H, 7.76.

4.8.10. 4-Methoxy-4-methyl-2,3-dioxabicylo[3.3.1]nonyl hydroperoxide (*exo*-9f). An oil; ^{1}H NMR δ 1.27 (s, 3H), 1.3–2.0 (m, 5H), 2.1–2.3 (m, 2H), 2.4–2.6 (m, 2H), 3.34 (s, 3H), 8.99 (s, 1H); ^{13}C NMR δ 16.35 (CH_3), 19.27 (CH_2), 26.20 (CH_2), 30.03 (CH_2), 31.14 (CH_2), 38.53 (CH), 48.48 (CH_3), 103.38 (C), 106.29 (C).

4.9. Ag_2O-Mediated methylation of the cyclic peroxides 9

The methylation of the cyclic peroxide **9e** is representative. Into a solution of **9e** (120 mg, 0.64 mmol) in CH_2Cl_2 (10 mL), methyl iodide (200 mg, 1.4 mmol) and Ag_2O (150 mg, 0.64 mmol) was added. After stirring for 1.5 h, the solid material was removed by filtration over Celite, and the filtrate was concentrated under reduced pressure. The product was isolated by column chromatography on silica gel. Elution with diethyl ether–hexane (6:94) gave the methylated cyclic peroxide **14e** (110 mg, 85%).

4.9.1. 4,4-Dimethyl-1-methyldioxy-2,3-dioxabicyclo-[3.3.1]nonane (14e). An oil; ^{1}H NMR δ 1.1–2.3 (m, 9H), 1.15 (s, 3H), 1.34 (s, 3H), 3.91 (s, 3H); ^{13}C NMR δ 20.78, 21.89, 25.48, 25.63, 29.92, 30.48, 39.10, 64.33, 82.05, 108.32. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39: H, 8.97. Found: C, 59.43: H, 9.25.

4.9.2. 1-Methoxy-4-methyl-4-methyldioxy-2,3-dioxabicylo[3.3.1]nonane (14a). An oil; ^{1}H NMR δ 1.1–1.6 (m, 4H), 1.42 (s, 3H), 1.8–2.0 (m, 3H), 2.0–2.2 (m, 1H), 2.3–2.5 (m, 1H), 3.37 (s, 3H), 3.96 (s, 3H); ^{13}C NMR δ 20.54, 21.39, 23.09, 30.91, 32.20, 39.91, 48.93, 64.01, 104.48, 109.45. Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03: H, 8.31. Found: C, 55.53: H, 8.25.

4.9.3. (1*R*,4*S*,5*R*,8*S*)-1-Methoxy-4,8-dimethyl-4-methyldioxy-2,3-dioxabicylo[3.3.1]nonane (14b). An oil; ^{1}H NMR δ 0.84 (d, J=6.3 Hz, 3H), 1.1–1.3 (m, 3H), 1.37 (s, 3H), 1.6–1.8 (m, 3H), 2.2–2.4 (m, 2H), 3.36 (s, 3H), 3.92 (s, 3H); ^{13}C NMR δ 13.75, 20.87, 23.60, 28.92, 30.62, 40.02, 40.27, 49.18, 63.99, 105.12, 109.26. Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88: H, 8.68. Found: C, 56.88: H, 8.60.

4.9.4. 1,4-Dimethyl-4-methyldioxy-2,3-dioxabicylo-[3.3.1]nonane (14c). An oil (a 1:1 mixture of two stereoisomers); ^{1}H NMR δ 1.08 (s)+1.27 (s)+1.42 (s)+1.44 (s) (6H), 1.1–2.6 (m, 9H), 3.98 (s)+3.99 (s) (3H); ^{13}C NMR δ 18.08, 19.79, 19.86, 20.58, 23.09, 26.35, 26.58, 26.99, 32.13, 33.96, 34.76, 35.51, 36.10, 37.74, 64.03, 64.17, 76.48, 78.46, 107.37, 109.40. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39: H, 8.97. Found: C, 59.50: H, 8.91.

4.9.5. 4-Methyl-4-methyldioxy-2,3-dioxabicylo[3.3.1]-nonane (14d). An oil; ^{1}H NMR δ 1.2–1.6 (m, 4H), 1.39 (s, 3H), 1.8–2.0 (m, 2H), 2.0–2.2 (m, 3H), 3.92 (s, 3H), 4.5–4.6 (m, 1H); ^{13}C NMR δ 18.62, 20.69, 23.78, 28.84, 29.47, 35.82, 64.06, 74.43, 109.92. Anal. Calcd for $C_9H_{16}O_4$: C, 57.43: H, 8.57. Found: C, 57.65: H, 8.50.

4.9.6. 4-Methoxy-4-methyl-1-methyldioxy-2,3-dioxabicylo[3.3.1]nonane (*endo*-14f). An oil; ^{1}H NMR δ 1.2–1.6 (m, 4H), 1.29 (s, 3H), 1.8–2.2 (m, 4H), 2.3–2.5 (m, 1H), 3.35 (s, 3H), 3.96 (s, 3H); ^{13}C NMR δ 19.89, 20.81, 24.21, 29.69, 30.68, 40.09, 49.24, 64.15, 105.52, 108.52. Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03: H, 8.31. Found: C, 55.58: H, 8.49.

4.9.7. 4-Methoxy-4-methyl-1-methyldioxy-2,3-dioxabicylo[3.3.1]nonane (*exo*-14f). An oil; ^{1}H NMR δ 1.25 (s, 3H), 1.3–2.0 (m, 5H), 2.1–2.3 (m, 2H), 2.4–2.6 (m, 2H), 3.35 (s, 3H), 3.91 (s, 3H); ^{13}C NMR δ 16.46, 19.37, 26.26, 30.39, 31.57, 38.53, 48.41, 64.62, 102.97, 106.36. Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.03: H, 8.31. Found: C, 55.39: H, 8.34.

4.10. X-Ray crystallographic analysis of the endoperoxides *endo*-9f and 13

The X-ray diffraction data (Mo–K_α λ=0.71073 Å) were collected on a Bruker AXS P4 diffractometer at 160 K. Lorrentz and polarisation corrections were applied to the data. The data from compound **13** were corrected for absorption. The structures were solved by direct methods and refined by full least-squares techniques using anisotropic temperature factors for the non-hydrogen atoms. All crystallographic calculations and preparation of structure plots were carried out using the SHELXTL suite of progams.[17]

4.10.1. Crystal data for *endo*-9f. $C_9H_{16}O_5$, M=204.22, colorless block (data crystal dimensions 0.44×0.68×0.49 mm), monoclinic, space group $P2_1/c$ (No 14), a 8.9418(13), b 10.873 (2), c 10.3033 (19) Å, β 93.175 (12°), U 1000.2 (3) Å^3, Z=4, D_c 1.356 g cm^{-3}, F(000) 440, μ(Mo–K_α) 0.110 mm^{-1}, final discrepancy factors: R=0.037 and $wR2$=0.094 for $I>2\sigma(I)$.

4.10.2. Crystal data for 13. $C_{11}H_{19}IO_3$, M=326.16, colorless block (data crystal dimensions 0.20×0.38×0.48 mm), monoclinic, space group $P2_1$, a 9.5581 (17), b 5.8054 (9), c 11.9491 (19) Å, β 107.613 (13°), U 631.96 (18) Å^3, Z=2, D_c 1.714 g cm^{-3}, F(000) 324, μ(Mo–K_α) 2.521 mm^{-1}, final discrepancy factors: R=0.029 and R_w=0.082 for $I>2\sigma(I)$.

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17. SHELXTL (version 5.1) Sheldrick, G.M., Brucker AXS Inc., Madison, WI, USA. Crystallographic data (excluding structure factors) for the structures of *endo*-**9f** and **13** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 161509 and 161510, respectively. 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.ca.uk].