Antimalarial Activity of Yingzhaosu A Analogues

Hye-Sook Kim,[†] Khurshida Begum,[†] Naoki Ogura,[†] Yusuke Wataya,*[,†] Takahiro Tokuyasu,[‡] Araki Masuyama,[‡] Masatomo Nojima,[‡] and Kevin J. McCullough[§]

Faculty of Pharmaceutical Sciences, Okayama University, Tsushima, Okayama 700-8530, Japan, Department of Materials Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan, and Department of Chemistry, Heriot-Watt University, Edinburgh EH14 4AS, Scotland

Received May 14, 2002

Iodonium ion mediated cyclization of unsaturated hydroperoxides **1** afforded the expected yingzhaosu A analogues **2**. In some cases, however, the corresponding cyclic ethers **5** were formed competitively with the cyclic peroxides **2**, the ratios of these two products being a marked function of the structure of the starting materials. Some of the cyclic peroxides **2** showed significant antimalarial activities in vitro and in vivo.

Introduction

Recently, antimalarial activities of artemisinin, yingzhaosu A, and other natural endoperoxides have attracted considerable attention.[1] Total synthesis of yingzhaosu A, possessing the unusual 2,3-dioxabicyclo-[3.3.1]nonane skeleton, has been independently achieved by Xu[2] and Bachi.[3a] In addition, several 2,3-dioxabicyclo-[3.3.1]nonane derivatives with excellent antimalarial activity have been prepared.[3,4] We have also reported the preparation of yingzhaosu A analogues by ozone-mediated cyclization of unsaturated hydroperoxides.[5] As an alternative synthetic approach to this kind of endoperoxide, we report herein the bis(collidine)iodine hexafluorophosphate (BCIH) mediated cyclization of a series of unsaturated hydroperoxides yielding the 4-iodomethyl-substituted 2,3-dioxabicyclo[3.3.1]nonane derivatives and their antimalarial activities.[6]

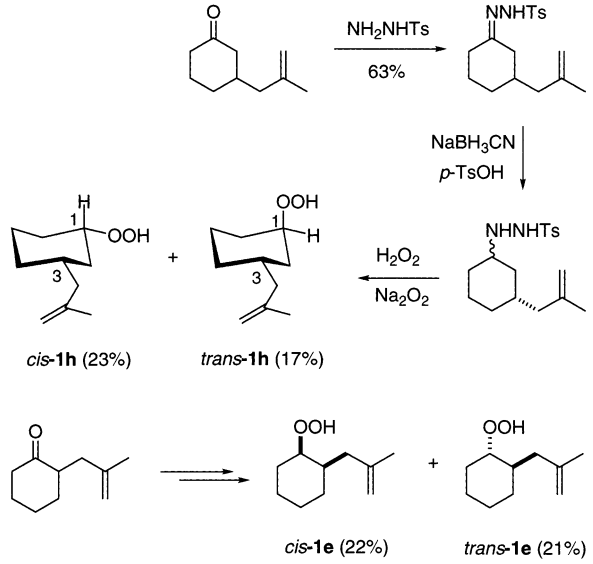
Results and Discussion

Preparation of Unsaturated Hydroperoxides. A variety of unsaturated hydroperoxides **1a**−**j** were used as starting materials for cyclization. The methods for preparation of **1a**−**d**,**f**,**g** have been reported previously.[5] The unsaturated isomeric *sec*-hydroperoxides *cis*-**1h** (23%) and *trans*-**1h** (17%) were prepared from 3-(2-methyl-2-propenyl)cyclohexanone as outlined in Scheme 1.[7] Similarly, the hydroperoxides *cis*- and *trans*-**1e** were prepared from 2-(2-methyl-2-propenyl)cyclohexanone (Scheme 1).

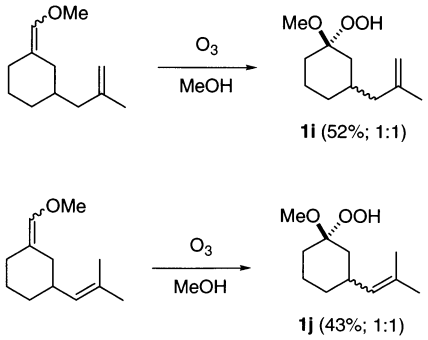
α-Methoxy-substituted hydroperoxide **1i** was obtained as an inseparable mixture of diastereoisomers (52%; 1:1) by the regioselective mono-ozonolysis of the corresponding enol ether in MeOH−CH_2Cl_2 at −70 °C (Scheme 2). Hydroperoxide **1j** was prepared from 1-methoxymethylene-3-(2-methyl-1-propenyl)cyclohexane by a similar method.

BCIH-Mediated Cyclization of Unsaturated Hydroperoxides. The reaction of an unsaturated hydroperoxide **1a** (a 1:1 mixture of isomers) with BCIH in CH_2Cl_2 gave the expected yingzhaosu A analogue **2a** as a 3:2 mixture of diastereoisomers together with the ketone **3a** (Scheme 3); the latter is formed by the intramolecular migration of the methoxy group as discussed previously.[6] From the reaction of **1b** under similar reaction conditions, cyclic peroxide **2b** was obtained in 33% yield as a 5:2 mixture of diastereoisomers together with several unidentified polar products. Under similar conditions for the formation of the endoperoxides **2a**,**b** from **1a**,**b**, the reaction of **1c** with

Scheme 1



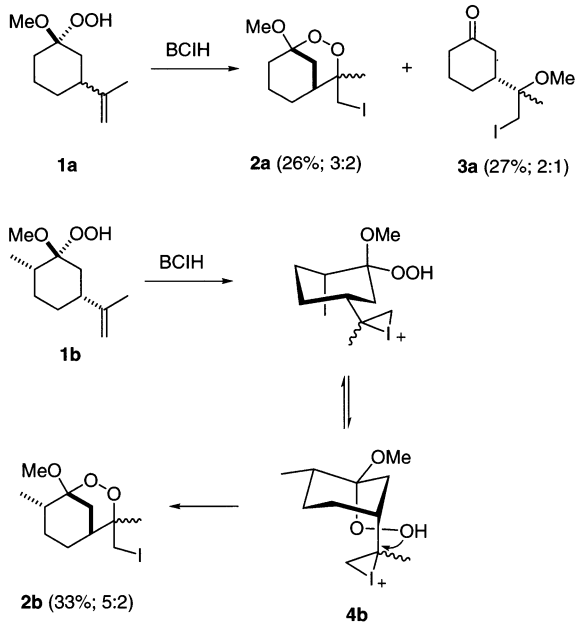
Scheme 2



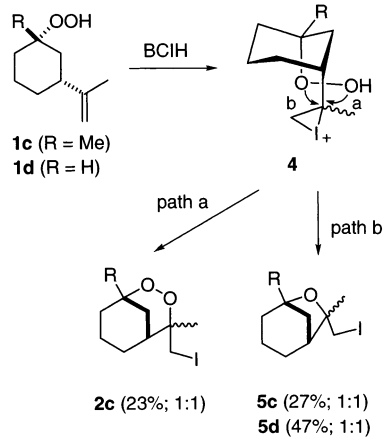
* To whom correspondence should be addressed. Phone: +81-86-251-7976. Fax: +81-86-251-7974. E-mail: wataya@cc.okayama-u.ac.jp
[†] Okayama University.
[‡] Osaka University.
[§] Heriot-Watt University.

10.1021/jm020208q CCC: $22.00
Published on Web 09/11/2002

Scheme 3



Scheme 4

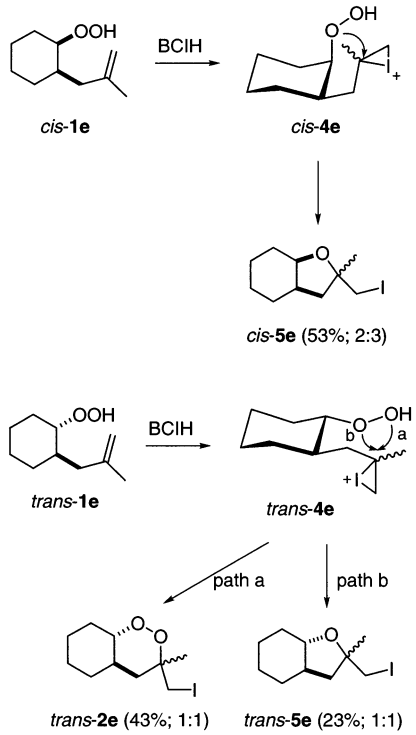


BCIH gave a cyclic ether **5c** (27%), together with the expected cyclic peroxide **2c** (23%) (Scheme 4). From **1d**, the corresponding oxolane **5d** (47%) was obtained exclusively. Regretfully, we failed to identify products resulting from the residual "OH^+".[7]

To realize the intramolecular cyclization of **1a**-**d** to give **2a**−**d**, it is clear that the iodonium ion intermediate **4a**−**d** must adopt a 1,3-synaxial conformation. The formation of **2a**−**c** and **5c**,**d** implies that two competitive cyclization modes (paths a and b in Scheme 4) are in operation. Because of the exclusive formation of the oxolane **5d** from **1d** (R = H), it is tentatively suggested that in the sterically less-congested intermediate **4d**, the inner oxygen of the hydroperoxy group moiety lies relatively close to the iodonium with the more nucleophilic terminal oxygen of the hydroperoxy group directed away from the cyclohexane ring owing to the 1,3-synaxial interactions.

To obtain further insight into the competitive formation of 1,2-dioxanes **2** and oxolanes **5**, the reactions of *cis*- and *trans*-**1e** with BCIH were examined (Scheme 5). It is interesting to note that the reaction of *cis*-**1e** gave exclusively the 7-oxabicyclo[4.3.0]nonane derivative *cis*-**5e** (53% yield), while the reaction of *trans*-**1e** gave mainly the 2,3-dioxabicyclo[4.4.0]decane derivative *trans*-**2e** (43%) together with *trans*-**5e** (23%). These observations are consistent with the notion that in *cis*-**4e** the terminal oxygen of the hydroperoxy group is directed away from the cyclohexane ring, allowing the nucleophilic attack of the inner oxygen to occur predominantly.

Scheme 5

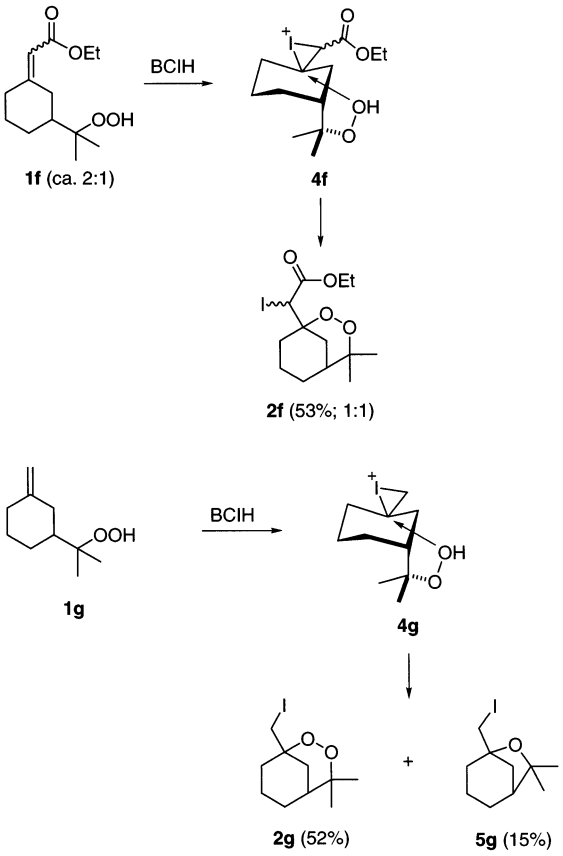


With these notions in mind, we designed unsaturated hydroperoxides **1f**,**g**. In the reactions of these substrates, the resulting iodonium ion intermediates **4f**,**g** should cyclize through sterically less hindered conformations with only one axial substituent. Moreover, the flexibility of the tethered hydroperoxy group in **4f**,**g** should favor nucleophilic attack of the terminal oxygen on the iodonium ion moiety. Consistent with this proposal, the reaction of **1f** with BCIH afforded the expected endoperoxide **2f** in a moderate yield (53%; 1:1 mixture of diastereoisomers). In an analogous manner, the endoperoxide **2g** (52% yield) was obtained as the predominant product from **1g** (Scheme 6).

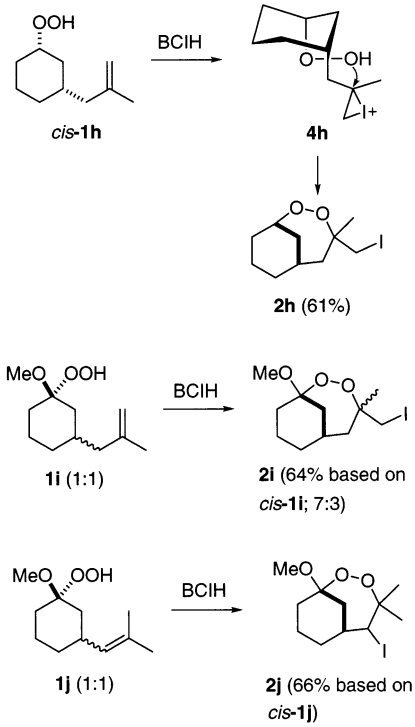
Finally, the reactions of unsaturated hydroperoxides **1h**−**j**, each having a homologated side chain with BCIH, were investigated. In each case, the bicyclic 1,2-dioxepanes **2h**−**j** were obtained in moderate yield (ca. 60%) with no evidence for the formation of the corresponding bicyclic ethers (Scheme 7). A priori, it is presumed that the ease of formation of the bicyclic 1,2-dioxepanes **2h**−**j** must lie in the lower ring strain in the bicyclo[4.3.1]-decane system compared to that of the bicyclo[3.3.1]-nonane structure.

Antimalarial Activity of Yingzhaosu A Analogues in Vitro. With several types of endoperoxides in hand, their antimalarial activity and cytotoxicity were tested against *P. falciparum* and FM3A cells,[8] respectively (Table 1). The data showed the following characteristics. First, of several 2,3-dioxabicyclo[3.3.1]-nonane derivatives **2a**−**d** and **2f**,**g**, **2c**,**f**,**g** exhibited

Scheme 6



Scheme 7



significant antimalarial activities similar to those for arteflene[4b] and the related β-sulfonyl endoperoxides.[3] Thus, although a minor change in the structure affects remarkably the activities, yingzhaosu A analogues are potentially promising as candidates of antimalarial drugs. Second, the related 2,3-dioxabicyclo[4.3.1]decanes **2h**−**j** and 2,3-dioxabicyclo[4.4.0]decane *trans*-**2e** were relatively inactive. This may imply that the presence of ring strain within the 2,3-dioxabicyclo[3.3.1]nonane structure is essential for antimalarial activity. Finally, the activities of the cyclic ethers **5c**, *trans*-**5e**, and **5g** were much lower than those of the corresponding cyclic peroxides **2c**, *trans*-**2e**, and **2g**, as expected.[1b]

Table 1. In Vitro Antimalarial Activities of Yingzhaosu A Analogues against *P. falciparum* and Cyctotoxicities against FM3A Cells[a]

peroxide	EC_{50} (μM) *P. falciparum*[b]	EC_{50} (μM) FM3A[c]	selectivity[d]
2a	1.7	>70 (19%)[e]	>41
2b	2.0	>54 (8%)[e]	>27
2c	0.013	>84 (10%)[e]	>6462
trans-**2e**	1.5	66	44
2f	0.011	3.1	282
2g	0.040	68	1700
2h	3.0	>96 (47%)[e]	>32
2i	2.5	>80 (6%)[e]	>32
2j	15	>64 (10%)[e]	>4
5c	1	>48 (0%)[e]	>48
trans-**5e**	120	>210 (34%)[e]	>2
5g	5.8	>84 (10%)[e]	>14
artemisinin	0.01	10	1000

[a] In vitro antimalarial activities and cytotoxicities were determined by a previously reported protocol.[8] [b] Chloroquine-sensitive (FCR-3 strain). [c] Mouse mammary tumor FM3A cells in culture as a control for mammalian cell cytotoxicity. [d] Selectivity = (mean of EC_{50} value for FM3A cells)/(mean of EC_{50} value for *P. falciparum*). [e] No activity at 10 μM. The value in parentheses is the growth inhibition (%) in each concentration.

Table 2. In Vivo Antimalarial Activities of Yingzhaosu A Analogues against *P. berghei* Infected Mice[a]

	intraperitoneal administration		intramuscular administration	
	growth inhibitoin (%) at 100 mg kg^{-1} day^{-1}	survival[b] (days)	growth inhibitoin (%) at 100 mg kg^{-1} day^{-1}	survival[b] (days)
2f	20	6.5	80	9.8
2g	32	7.0	99	9.6

[a] The test compounds were prepared in olive oil, and these compounds were administered to groups of five mice once a day starting on day 0 and continuing on days 1−3. Growth inhibition was determined on the day following the last treatment (on day 4). The details of the experimental procedure are described in ref 8. [b] On average, mice in the control group survived for 6.0 days after infection.

Antimalarial Activity of Yingzhaosu A Analogues in Vivo.[8] In vivo antimalarial activities against *P. berghei* NK 65 strain[8] were then determined for the bicyclic peroxides **2f**,**g**, which had shown such notable activities in vitro. As indicated in Table 2, compounds **2f**,**g** exhibited significant antimalarial activities (ED_{50} was 69 mg kg^{-1} day^{-1} for **2f** and 50 mg kg^{-1} day^{-1} for **2g**) on intramuscular (im) administration. In contrast, the activities of **2f**,**g** on intraperitoneal (ip) administration at a dose of 100 mg kg^{-1} day^{-1} were comparatively poor. These results tend to suggest that most of the iodo-substituted compounds **2f**,**g** administered intraperitoneally must have been metabolized in the liver into compounds having little or no antimalarial activity by a detoxification pathway.[9] On the other hand, compounds **2f**,**g** administered into the thigh muscle of mice (im) must have been delivered without modification into the blood stream and consequentially retained substantial antimalarial activity.[9] The survival times of the *P. berghei* infected mice treated with **2f**,**g** (im, 100 mg kg^{-1} day^{-1}) were found to be approximately 1.6 times longer

than those of the untreated ones. In addition, the sample of mice treated with **2f**,**g** (ip or im administration) did not exhibit either any of the usual effects of toxicity (e.g., diarrhea, weight loss, convulsion) or significant deviations from normal behavior. These results led us to deduce that significant modification of the functionalization of this series of bicyclic peroxides **2** would lead to the development of an attractive antimalarial drug candidate. As a first approach, we are now trying to transform the labile iodo group in **2f**,**g** into other functional groups such as hydroxyl and carboxyl.

Summary

The BCIH-mediated cyclization of unsaturated hydroperoxides via the iodonium ion intermediates has been found to provide the corresponding 2,3-dioxabicyclo-[3.3.1]nonane or 2,3-dioxabicyclo[4.3.1]decane derivatives. Some of the 2,3-dioxabicyclo[3.3.1]nonane derivatives show significant antimalarial activity in vitro, suggesting that the strained structure with a peroxide bond in the ring is the essential factor for the appearance of notable activity. The study in vivo demonstrates that substantial modification of the functionalization of this series of bicyclic peroxides **2** would be required in order to produce a significant antimalarial drug candidate.

Experimental Sections

General Procedures. ^{1}H (270 MHz) and ^{13}C (67.5 MHz) NMR spectra were obtained in $CDCl_3$ solution with $SiMe_4$ as the internal standard. The preparation of unsaturated hydroperoxides **1a**−**d**,**f**,**g** was previously reported.[5]

BCIH-Mediated Cyclization of Unsaturated Hydroperoxides. The reaction of the unsaturated hydroperoxide **1c** is representative. To CH_2Cl_2 (5 mL) were concurrently added a CH_2Cl_2 (5 mL) solution of the unsaturated hydroperoxide **1c** (100 mg, 0.59 mmol) and a CH_2Cl_2 (5 mL) solution of BCIH (500 mg, 0.97 mmol) over 30 min, and then the reaction mixture was stirred at room temperature for 2 h (the flask was covered with aluminum foil). The reaction mixture was poured into aqueous $Na_2S_2O_3$ (20 mL) and extracted with ether (30 mL × 2). The combined organic layer was washed with 0.2 N HCl (50 mL) and aqueous sodium bicarbonate (30 mL) in turn and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the product was isolated by column chromatography on silica gel. Elution with diethyl ether−hexane (2:98) gave a mixture of the 1,2-dioxane **2c** and the oxolane **5c**. These two products were separated by subsequent column chromatography on alumina. Elution with diethyl ether−hexane (0.3:99.7) gave the oxolane **5c** (45 mg, 27%) as a 1:1 mixture of two stereoisomers. Subsequent elution with diethyl ether−hexane (0.4:99.6) gave the 1,2-dioxane **2c** (40 mg, 23%) as a 1:1 mixture of two stereoisomers.

4-Iodomethyl-1,4-dimethyl-2,3-dioxabicyclo[3.3.1]-nonane (2c). An oil (a 1:1 mixture of two stereoisomers); ^{1}H NMR δ 0.99 (s) + 1.02 (s) + 1.24 (s) + 1.48 (s) (6H), 1.3−2.3 (m, 9H), 3.07 (s) + 3.08 (s) + 3.40 (d, J = 10.4 Hz) + 3.73 (d, J = 10.4 Hz) (2H); ^{13}C NMR δ 10.15, 13.43, 20.46, 21.06, 22.48, 22.96, 25.81, 25.97, 26.41, 26.79, 31.00, 33.21, 34.73, 35.65, 36.24, 36.28, 76.82, 77.15, 80.41, 80.68; HRMS (EI) m/z calcd for $C_{10}H_{17}IO_2$ 296.0273, found 296.0276. Anal. Calcd for $C_{10}H_{17}IO_2$: C, 40.56; H, 5.79. Found: C, 40.77; H, 5.75.

7-Iodomethyl-5,7-dimethyl-6-oxabicyclo[3.2.1]octane (5c). An oil (a 1:1 mixture of two stereoisomers); ^{1}H NMR δ 1.2−2.2 (m, 8.5H), 1.20 (s) + 1.22 (s) + 1.39 (s) + 1.46 (s) (6H), 2.3−2.5 (m, 0.5H), 3.12 (d, J = 9.9 Hz) + 3.20 (d, J = 9.9 Hz) + 3.24 (d, J = 9.6 Hz) + 3.51 (d, J = 9.6 Hz) (2H); ^{13}C NMR δ 11.47, 18.24, 19.14, 19.86, 20.40, 25.82, 26.67, 27.21, 27.37, 27.98, 37.47, 37.83, 41.44, 43.16, 43.34, 43.61, 82.10, 82.98, 83.33, 83.45; HRMS (EI) m/z calcd for $C_{10}H_{17}IO$ 280.0324, found 280.0304. Anal. Calcd for $C_{10}H_{17}IO$: C, 42.87; H, 6.12. Found: C, 42.96; H, 6.18.

4-Iodomethyl-1-methoxy-4-methyl-2,3-dioxabicyclo-[3.3.1]nonane (2a). An oil (a 3:2 mixture of two stereoisomers); ^{1}H NMR δ 1.2−2.5 (m, 9H), 1.35 (s, major) + 1.43 (s) (3H), 3.3−3.5 (m, major) + 3.63 (s) + 3.66 (s) (2H), 3.38 (s) + 3.39 (s, major) (3H); ^{13}C NMR δ 11.56 (CH_2), 12.22 (CH_2), 20.45 (CH_2), 20.94 (CH_3), 21.46 (CH_2), 24.82 (CH_2), 24.87 (CH_3), 26.13 (CH_2), 31.36 (CH_2), 31.81 (CH_2), 31.86 (CH_2), 32.51 (CH_2), 35.92 (CH), 37.97 (CH), 49.15 (CH_3), 49.38 (CH_3), 81.47 (C), 82.07 (C), 103.11 (C), 104.19 (C). Anal. Calcd for $C_{10}H_{17}IO_3$: C, 38.48; H, 5.49; I, 40.66. Found: C, 38.39; H, 5.37; I, 40.64.

4-Iodomethyl-1-methoxy-4,8-dimethyl-2,3-dioxabicyclo-[3.3.1]nonane (2b) (Major Isomer). Mp 95−97 °C (ethyl acetate−hexane); ^{1}H NMR δ 0.91 (d, J = 6.2 Hz, 3H), 1.2−2.0 (m, 6H), 1.36 (s, 3H), 2.3−2.6 (m, 2H), 3.31 (d, J = 10.9 Hz, 1H), 3.43 (s, 3H), 3.65 (d, J = 10.9 Hz, 1H); ^{13}C NMR δ 11.49 (CH_2), 13.91 (CH_3), 25.29 (CH_3), 25.39 (CH_2), 29.27 (CH_2), 30.86 (CH_2), 38.12 (CH), 39.89 (CH), 49.56 (CH_3), 81.85 (C), 104.89 (C). Anal. Calcd for $C_{11}H_{19}IO_3$: C, 40.51; H, 5.87; I, 38.91. Found: C, 40.45; H, 5.77; I, 38.63.

2b (Minor Isomer). The minor isomer was obtained as an admixture with 71% of the major one and is obtained as an oil. ^{1}H NMR δ 0.97 (d, J = 5.6 Hz, 3H), 1.43 (s, 3H), 3.29 (d, J = 10.4 Hz, 1H), 3.39 (s, 3H), 3.46 (d, J = 10.4 Hz, 1H); ^{13}C NMR δ 12.19 (CH_2), 13.98 (CH_3), 20.81 (CH_3), 26.49 (CH_2), 29.33 (CH_2), 29.85 (CH_2), 36.07 (CH), 39.75 (CH), 49.76 (CH_3), 81.17 (C), 103.85 (C).

4-Iodomethyl-4-methyl-2,3-dioxabicyclo[4.4.0]decane (*trans*-2e). An oil (a 1:1 mixture of two isomers); ^{1}H NMR δ 1.0−2.0 (m, 10.5H), 1.27 (s) + 1.54 (s) (3H), 2.1−2.2 (m, 0.5H), 3.12 (s) + 3.58 (d, J = 10.2 Hz) + 3.67 (d, J = 10.2 Hz) (2H), 3.6−3.8 (m, 1H); ^{13}C NMR δ 12.24 (CH_2), 13.75 (CH_2), 21.62 (CH_3), 24.87 (CH_2), 24.91 (CH_2), 25.34 (CH_2), 25.43 (CH_2), 26.51 (CH_3), 28.30 (CH_2), 28.48 (CH_2), 30.37 (CH_2), 30.48 (CH_2), 36.71 (CH), 37.49 (CH_2), 37.63 (CH), 39.30 (CH_2), 78.91 (C), 79.91 (C), 85.36 (CH), 85.50 (CH). Anal. Calcd for $C_{10}H_{17}IO_2$: C, 40.56; H, 5.79. Found: C, 40.61; H, 5.60.

8-Iodomethyl-8-methyl-7-oxabicyclo[4.3.0]nonane (*trans*-5e). An oil (a 1:1 mixture of two isomers); ^{1}H NMR δ 1.0−2.2 (m, 11H), 1.42 (s) + 1.47 (s) (3H), 3.2−3.4 (m, 1H), 3.26 (s) + 3.31 (s) (2H); ^{13}C NMR δ 17.90 (CH_2), 18.85 (CH_2), 24.17 (CH_2), 25.57 (CH_2), 25.64 (CH_2), 27.35 (CH_3), 27.48 (CH_3), 28.79 (CH_2), 28.88 (CH_2), 31.34 (CH_2), 31.52 (CH_2), 42.59 (CH_2), 43.42 (CH_2), 45.57 (CH), 45.97 (CH), 80.20 (C), 80.56 (C), 83.43 (CH) 83.47 (CH); HRMS (CI) m/z calcd for $C_{10}H_{18}IO$ 281.0403, found 281.0405. Anal. Calcd for $C_{10}H_{17}IO$: C, 42.87; H, 6.12. Found: C, 42.75; H, 6.08.

(4,4-Dimethyl-2,3-dioxabicyclo[3.3.1]non-1-yl)iodoacetic Acid Ethyl Ester (2f). An oil (a 1:1 mixture of two stereoisomers); ^{1}H NMR δ 1.2−2.4 (m, 18H), 4.1−4.2 (m, 2H), 4.30 (s) + 4.31 (s) (1H); ^{13}C NMR δ 13.73 (CH_3), 13.77 (CH_3), 20.29 (CH_2), 20.34 (CH_2), 23.04 (CH_3), 23.22 (CH_3), 24.87 (CH_3), 25.05 (CH_3), 25.90 (CH_2), 26.11 (CH_2), 29.04 (CH), 29.45 (CH), 30.71 (CH_2), 31.25 (CH_2), 32.29 (CH_2), 32.76 (CH_2), 35.76 (CH), 36.10 (CH), 61.85 (CH_2), 61.91 (CH_2), 78.47 (C), 78.65 (C), 81.38 (C), 81.58 (C), 168.88 (C), 169.07 (C); LRMS (EI) m/z (rel intens %) 368 (M^+) (8), 241 ($M^+ - I$) (21), 155 ($M^+ - CHICO_2Et$) (61); HRMS (EI) m/z calcd for $C_{13}H_{21}IO_4$ 368.0485, found 368.0483. Anal. Calcd for $C_{13}H_{21}IO_4$: C, 42.41; H, 5.75. Found: C, 42.75; H, 6.00.

1-Iodomethyl-4,4-dimethyl-2,3-dioxabicyclo[3.3.1]-nonane (2g). An oil; ^{1}H NMR δ 1.2−2.4 (m, 9H), 1.22 (s, 3H), 1.39 (s, 3H), 3.10 (s, 1H), 3.11 (s, 1H); ^{13}C NMR δ 13.73 (CH_2), 20.49 (CH_2), 23.42 (CH_3), 24.69 (CH_3), 26.31 (CH_2), 33.57 (CH_2), 34.31 (CH_2), 35.55 (CH), 75.74 (C), 80.67 (C). Anal. Calcd for $C_{10}H_{17}IO_2$: C, 40.56; H, 5.79. Found: C, 40.17; H, 5.59.

5-Iodomethyl-7,7-dimethyl-6-oxabicyclo[3.2.1]octane (5g). Mp 48−49 °C (hexane); ^{1}H NMR δ 1.2−2.1 (m, 8H), 1.28 (s, 3H), 1.36 (s, 3H), 2.2−2.4 (m, 1H), 3.30 (s, 2H); ^{13}C NMR δ 16.64, 19.56, 23.04, 26.62, 30.51, 35.44, 42.21, 44.19, 81.10, 83.81. Anal. Calcd for $C_{10}H_{17}IO$: C, 42.87; H, 6.12. Found: C, 42.82; H, 6.04.

4-Iodomethyl-4-methyl-2,3-dioxabicyclo[4.3.1]decane (2h). An oil; ^{1}H NMR δ 1.2−2.2 (m, 10H), 1.42 (s, 3H), 2.50 (br d, J = 13.9 Hz, 1H), 3.24 (d, J = 10.2 Hz, 1H), 3.30 (d, J = 10.2 Hz, 1H), 4.4−4.5 (m, 1H); ^{13}C NMR δ 10.25 (CH_2), 15.80 (CH_2), 26.45 (CH_3), 28.23 (CH and CH_2, 2C), 30.80 (CH_2), 31.22 (CH_2), 36.30 (CH_2), 79.26 (CH), 84.98 (C); LRMS (EI) m/z (rel intens %) 296 (M^+) (14), 155 ($M^+ - CH_2I$) (100); HRMS (EI) m/z calcd for $C_{10}H_{17}IO_2$ 296.0273, found 296.0270. Anal. Calcd for $C_{10}H_{17}IO_2$: C, 40.56; H, 5.79. Found: C, 40.62; H, 5.76.

4-Iodomethyl-1-methoxy-4-methyl-2,3-dioxabicyclo-[4.3.1]decane (2i). An oil (a 7:3 mixture of two stereoisomers); ^{1}H NMR δ 1.4−2.0 (m, 9H), 1.37 (s) + 1.48 (s, major) (3H), 2.2−2.4 (m, 1.3H), 2.4−2.6 (m, 0.7H), 3.18 (d, J = 9.9 Hz, major) + 3.2−3.4 (m) + 3.36 (d, J = 9.9 Hz, major) (2H), 3.31 (s) + 3.32 (s, major) (3H); ^{13}C NMR (major isomer) δ 9.31 (CH_2), 18.12 (CH_2), 27.44 (CH), 28.25 (CH_3), 30.73 (CH_2), 30.78 (CH_2), 34.70 (CH_2), 35.08 (CH_2), 48.47 (CH_3), 85.05 (C), 106.56 (C).

The following additional signals were assigned to the minor isomer. ^{13}C NMR δ 17.22 (CH_2), 18.08 (CH_2), 21.48 (CH_3), 27.69 (CH), 30.57 (CH_2), 30.95 (CH_2), 34.86 (CH_2), 35.00 (CH_2), 48.35 (CH_3), 84.60 (C), 106.42 (C). Anal. Calcd for $C_{11}H_{19}IO_3$: C, 40.51; H, 5.87. Found: C, 40.70; H, 5.76.

5-Iodo-1-methoxy-4,4-dimethyl-2,3-dioxabicyclo[4.3.1]-decane (2j). An oil; ^{1}H NMR δ 1.4−2.2 (m, 7H), 1.52 (s, 3H), 1.56 (s, 3H), 2.7−2.9 (m, 2H), 3.31 (s, 3H), 4.55 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ 18.42 (CH_2), 23.38 (CH_3), 28.81 (CH_2), 29.07 (CH_3), 30.87 (CH_2), 36.50 (CH_2), 40.43 (CH), 42.75 (CH), 48.62 (CH_3), 86.95 (C), 106.11 (C). HRMS (EI) m/z calcd for $C_{11}H_{19}IO_3$ 326.0379, found 326.0393. Anal. Calcd for $C_{11}H_{19}IO_3$: C, 40.51; H, 5.87. Found: C, 40.92; H, 6.02.

In Vitro and in Vivo Antimalarial Activity. In vitro antimalarial activity against *P. falciparum* (FCR-3 strain) and cytotoxicity against mouse mammary cell (FM3A) was determined as described previously.[8] In vivo antimalarial activity was assessed using ICR mice infected with *P. berghei* (NK 65 strain) following the protocol described previously.[8] In brief, various concentrations of the test compounds, prepared in olive oil, were administered daily, ip or im, to groups of five mice for 4 consecutive days beginning on the day of infection (to determine the ED value and survival days). To evaluate the antimalarial activity of the compounds, we prepared tail blood smears and stained them with Giemsa (E. Merck, Germany). A total of 1×10^4 erythrocytes per one thin blood film were examined under a microscope. On day 4, parasitemia of control mice were between 18% and 22%. The suppression of parasitemia for the dose of the **2f**,**g** was calculated by the formula

$$\frac{\text{average \% parasitemia in controls (sham-treated)} - \text{average \% parasitemia in treated mice}}{\text{average \% parasitemia in controls (sham treated)}} \times 100$$

Five infected dimethyl sulfoxide dosed mice were used as a control. The data shown are the mean values from five mice in one test.

Acknowledgment. This work was supported in part by Grant-in-Aid for Scientific Research on Priority Areas (Grants 12307007, 13226079, 13650904, 14021072, and 14021066) from the Ministry of Education, Science, Culture and Sports of Japan.

Supporting Information Available: Synthetic methods and spectroscopic data of unsaturated hydroperoxides, *cis*- and *trans*-**1e**, *cis*- and *trans*-**1h**, **1i**, and **1j** and spectroscopic data for products **3a**, **5d**, and *cis*-**5e.** This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Haynes, R. K.; Vonwiller, S. C. From Qinghao, Marvelous Herb of Antiquity, to the Antimalarial Trioxane Qinghaosu- and Some Remarkable New Chemistry. *Acc. Chem. Res.* **1997**, *30*, 73−79. (b) Cumming, J. N.; Ploypradith, P.; Posner, G. H. Antimalarial Activity of Artemisinin (Qinghaosu) and Related Trioxanes: Mechanism(s) of Action. *Adv. Pharmacol.* **1997**, *37*, 253−297. (c) Bhattacharya, A. K.; Sharma, R. P. Recent Developments on the Chemistry and Biological Activity of Artemisinin and Related Antimalarials—An Update. *Heterocycles* **1999**, *51*, 1681−1745. (d) Robert, A.; Dechy-Cabaret, O.; Cazelles, J.; Meunier, B. From Mechanistic Studies on Artemisinin Derivatives to New Modular Animalarial Drugs. *Acc. Chem. Res.* **2002**, *35*, 167−174. (e) O'Neill, P. M.; Miller, A.; Bishop, P. D.; Hindley, S.; Maggs, J. L.; Ward, S. A.; Roberts, S. M.; Scheinmann, F.; Stachulski, A. V.; Posner, G. H.; Park, B. K. Synthesis, Antimalarial Acitivity, Biomimetic Iron(II) Chemistry, and in Vivo Metabolism of Novel, Potent C-10-Phenoxy Derivatives of Dihydroartemisinin. *J. Med. Chem.* **2001**, *44*, 58−68. (f) Ma, J.; Weiss, E.; Kyle, D. E.; Ziffer, H. Acid Catalyzed Michael Additions to Artemisitene. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1601−1603. (g) Li, Y.; Zhu, Y.-M.; Jiang, H.-J.; Pan, J.-P.; Wu, G.-S.; Wu, J.-M.; Shi, Y.-L.; Yang, J.-D.; Wu, B.-A. Synthesis and Antimalarial Activity of Artemisinin Derivatives Containing an Amino Group. *J. Med. Chem.* **2000**, *43*, 1635−1640. (h) Posner, G. H.; Jeon, H. B.; Parker, M. H.; Krasavin, M.; Paik, I.-H.; Shapiro, T. A. Antimalarial Simplified 3-Aryltrioxanes: Synthesis and Preclinical Efficacy/Toxicity Testing in Rodents. *J. Med. Chem.* **2001**, *44*, 3054−3058. (i) McCullough, K. J.; Nojima, M. Recent Advances in the Chemistry of Cyclic Peroxides. *Curr. Org. Chem.* **2001**, *5*, 601−636.

(2) Xu, X.-X.; Zhu, J.; Haung, D.-Z.; Zhou, W.-S. Total Synthesis of (+)-Yingzhaosu A. *Tetrahedron Lett.* **1991**, *32*, 5785.

(3) (a) Bachi, M. D.; Korshin, E. E.; Hoos, R.; Szpilman, A. M. Synthesis and Reactions of Antimalarial Bicyclic Peroxides. *J. Heterocycl. Chem.* **2000**, *37*, 639−646. (b) Szpilman, A. M.; Korshin, E. E.; Hoos, B.; Posner, G. H.; Bachi, M. D. Iron(II)-Induced Degradation of Antimalarial β-Sulfonyl Endperoxides. Evidence for the Generation of Potentially Cytotoxic Carbocations. *J. Org. Chem.* **2001**, *66*, 6531−6540.

(4) (a) O'Neill, P. M.; Searle, N. L.; Raynes, K. J.; Maggs, J. L.; Ward, S. A.; Storr, R. C.; Park, B. K.; Posner, G. H. A Carbonyl Oxide Route to Antimalarial Yingzhaosu A Analogues: Synthesis and Antimalarial Activity. *Tetrahedron Lett.* **1998**, *39*, 6065. (b) Hofheinz, W.; Bürgin, H.; Gocke, E.; Jaquet, C.; Masciadri, R.; Schmid, G.; Stohler, H.; Urmyler, H. Ro 42-1611 (Arteflene), a New Effective Antimalarial: Chemical Structure and Biological Activity. *Trop. Med. Parasitol.* **1994**, *45*, 261.

(5) Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J.; Kim, H.-S.; Wataya, Y. Yingzhaosu A Analogues: Synthesis by the Ozonolysis of Unsaturated Hydroperoxides, Structural Analysis and Determination of Anti-malarial Activity. *Tetrahedron* **2001**, *57*, 5979.

(6) A part of this work was published in preliminary form. Tokuyasu, T.; Masuyama, A.; Nojima, M.; Kim, H.-S.; Wataya, Y. Synthesis and Anti-malarial Activity of Yingzhaosu A Analogues from Unsaturated Hydroperoxy Acetals. *Tetrahedron Lett.* **2000**, *41*, 3145−3146. Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J. Halonium Ion-Mediated Unsaturated Hydroperoxy Acetals. Competition between the Formation of Cyclic Peroxide and the Migration of the Methoxy (or Hydroxy) Group. *J. Org. Chem.* **2000**, *65*, 1069−1075.

(7) Formation of a bicyclic ether from the reaction of 5-hydroperoxycyclooctene with *N*-bromosuccinimide via a similar ejection of "OH^+" has already been reported. Bloodworth, A. J.; Melvin, T.; Mitchell, J. C. Oxygen Transfer by Dialkylperoxonium Ions. *J. Org. Chem.* **1986**, *51*, 2612−2613.

(8) Kim, H.-S.; Nagai, Y.; Ono, K.; Begum, K.; Wataya, Y.; Hamada, Y.; Tsuchiya, K.; Masuyama, A.; Nojima, M. McCullough, K. J. Synthesis and Antimalarial Activity of 1,2,4,5-Tetraoxacycloalkanes. *J. Med. Chem.* **2001**, *44*, 2357−2361.

(9) Benet, L. Z.; Kroetz, D. L.; Sheiner, L. W. Pharmacolinetics: The dynamics of drug absorption, distribution, and elimination. In *Goodman & Gilman's the Pharmacological Basis of Therapeutics*, 9th ed.; Hardman, J. G., Limbird, L. E., Eds.; McGraw-Hill Health Professions Division Ltd.: New York, 1996; pp 3−27.

JM020208Q