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Synthesis of Antimalarial Yingzhaosu A Analogues by the Peroxidation of Dienes with Co(II)/O_2/Et_3SiH

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Co(II)-catalyzed peroxidation of dienes including (*S*)-limonene in the presence of molecular oxygen and triethylsilane provided in each case the corresponding 2,3-dioxabicyclo[3.3.1]nonane derivatives via the intramolecular cyclization of the unsaturated peroxy radical intermediates. The product composition was remarkably influenced by the structure of the dienes, the nature of the solvents, and the concentration of the substrates and the catalyst. Some of the yingzhaosu A analogues obtained in this study showed notable antimalarial activities in vitro.

Introduction

Since malaria parasites are rapidly developing resistance to the most commonly used chemotherapeutic alkaloidal drugs, the antimalarial properties of non-alkaloidal compounds such as artemisinin (**I**), yingzhaosu A (**II**), and their homologues have attracted considerable attention (Figure 1).[1,2]

As part of our interest in the synthesis of novel peroxy compounds having substantial antimalarial activity, we investigated the mechanism of the Co(II)-catalyzed peroxidation of alkenes with molecular oxygen and triethylsilane discovered by Isayama and Mukaiyama[3,4] and found that the reaction of a vinylcyclopropane **1** (an efficient radical clock[5]) provides the 1,2-dioxolane derivative **4** by the intramolecular cyclization of an unsaturated peroxyl radical **3**, which is produced by the rapid ring opening of the cyclopropylmethyl radical **2** followed by reaction with O_2 (Scheme 1).[6] This led us to deduce that the desired cyclic peroxide would be readily produced from an appropriate diene, since selective hydrogen atom transfer to one of the double bonds of the diene from a Co(III)−hydride complex, followed by reaction with an oxygen molecule, is expected to give the unsaturated peroxy radical similar to **3**.[2b,7] We report herein the result of our trials on this line.

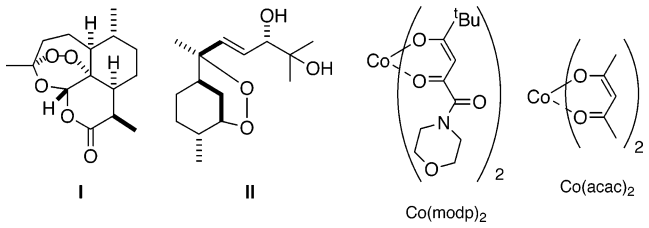

FIGURE 1. The structures of artemisinin (**I**), yingzhaosu A (**II**), and Co(II) complexes.

† Osaka University.
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(1) Artemisinin analogues: (a) Robert, A.; Dechy-Cabaret, O.; Cazelles, J.; Meunier, B. *Acc. Chem. Res.* **2002**, *35*, 167. (b) Haynes, R. K.; Vonwiller, S. C. *Acc. Chem. Res.* **1997**, *30*, 73. (c) McCullough, K. J.; Nojima, M. *Curr. Org. Chem.* **2001**, *5*, 601. (d) Hindley, S.; Ward, S. A.; Storr, R. C.; Searle, N. L.; Bray, P. G.; Park, B. K.; Jill, D.; O'Neill, P. M. *J. Med. Chem.* **2002**, *45*, 1052. (e) Avery, M. A.; Alvim-Gaston, M.; Rodrigues, C. R.; Barreiro, E. J.; Cohen, F. E.; Sabnis, Y. A.; Woolfrey, J. R. *J. Med. Chem.* **2002**, *45*, 292. (f) Posner, G. H.; Jeon, H. B.; Ploypradith, P.; Paik, I.-H.; Borstnik, K.; Xie, S.; Shapiro, T. A. *J. Med. Chem.* **2002**, *45*, 3824.

(2) Yingzahosu A analogues: (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. *Tetrahedron Lett.* **1998**, *39*, 6065. (b) Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Konstantinovski, L.; Posner, G. H.; Bachi, M. D. *Tetrahedron* **2002**, *58*, 2449. (c) Bachi, M. D.; Korshin, E. E.; Ploypradith, P.; Cumming, J. N.; Xie, S.; Shapiro, T. A.; Posner, G. H. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 903. (d) Kim, H.-S.; Begum, K.; Ogura, N.; Wataya, Y.; Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J. *J. Med. Chem.* **2002**, *45*, 4732. (e) Xu, X.-X.; Zhu, J.; Haung, D.-Z.; Zhou, W.-S. *Tetrahedron Lett.* **1991**, *32*, 5785. (f) Bachi, M. D.; Korshin, E. E.; Hoos, R.; Szpilman, A. M.; Ploypradith, P.; Xie, S.; Shapiro, P. A.; Posner, G. H. *J. Med. Chem.* **2003**, *46*, 2516.

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(4) Synthetic application of this methodology: (a) Xu, X.-X.; Dong, H.-Q. *J. Org. Chem.* **1995**, *60*, 3039. (b) Oh, C. H.; Kang, J. H. *Tetrahedron Lett.* **1998**, *39*, 2771. (c) Ito, T.; Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J. *Tetrahedron* **2003**, *59*, 525. (d) Tokuyasu, T.; Masuyama, A.; Nojima, M.; McCullough, K. J.; Kim, H.-S.; Wataya Y. *Tetrahedron* **2001**, *57*, 5979.

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(7) (a) Feldman, K. S. *Synlett* **1995**, 217. (b) Roe, A. N.; McPhail, A. T.; Porter, N. A. *J. Am. Chem. Soc.* **1983**, *105*, 1199. (c) Boukouvalas, J.; Pouliot, R.; Fréchette, Y. *Tetrahedron Lett.* **1995**, *36*, 4167. (d) Ushigoe, Y.; Masuyama, A.; Nojima, M.; McCullough, K. J. *Tetrahedron Lett.* **1997**, *38*, 8753. (e) Yin, H.; Havrilla, C. M.; Morrow, J. D.; Porter, N. A. *J. Am. Chem. Soc.* **2002**, *124*, 7745. (f) Boukouvalas, J.; Haynes, R. K. In *Radicals in Organic Synthesis*; Vol. 2, Applications; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; pp 455−484.

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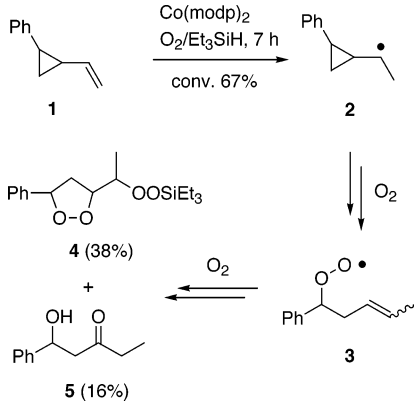
SCHEME 1. Peroxidation of Vinylcylopropane 1



Results and Discussion

When the reaction of (*S*)-limonene **6** (2 mmol) with O_2 and Et_3SiH (4 mmol) was undertaken in 1,2-dichloroethane (DCE; 5 mL) in the presence of bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato)cobalt(II) [$Co(modp)_2$, 5 mol %] at room temperature, a mixture of three triethylsilyl peroxides **11**−**13** (Scheme 2) was obtained, which were easily desilylated into the corresponding hydroperoxides **7**−**9** by treatment with one drop of concentrated HCl in methanol (Table 1). (*S*)-Limonene **6** was completely consumed during 1 h and the unsaturated hydroperoxide **7** was obtained as the major product (36%), together with the desired 2,3-dioxabicyclo[3.3.1]nonane derivative **8** (22%, a single isomer). While the reaction for 24 h resulted in the formation of a bis-hydroperoxide **9** with the concomitant decrease in the yield of a mono-hydroperoxide **7**, the yield of the cyclic peroxide **8** remained intact.

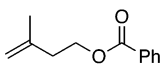
On the basis of our previous work,[6] we propose the probable mechanism for the formation of the endoperoxide **12** (Scheme 2). The first step involves regioselective hydrogen atom transfer from a Co(III)−hydride complex to the less hindered double bond of (*S*)-limonene **6**,[8] which is followed by capture of an oxygen molecule to provide the peroxy radical **10**. There are two modes of decay for this radical **10**. The peroxy radical **10** would be trapped by $Co(modp)_2$ to give the Co(III)−alkylperoxo complex **14**. Subsequently, transmetalation with triethylsilane[9] occurs to yield the triethylsilyl peroxide **11**. Alternatively, the intermediate **10** undergoes an intramolecular cyclization to give the bicyclic alkyl radical **15**. Subsequent capture of the radical **15** by O_2 from the less hindered face provides finally the 2,3-dioxabicyclo[3.3.1]nonane derivative **12** (for the stereochemistry see the structure of the corresponding alcohol **24′** prepared from the stereoisomeric peroxide **12′** in Table 5 and the Experimental Section). In this connection, Bachi and co-workers have proposed a similar mechanism for the stereoselective formation of the yingzhaosu A analogues by the phenylthio radical initiated autoxidation of (*S*)-limonene **6** and the stereoisomeric (*R*)-limonene **6′**.[2b]

The major product from the peroxidation of **6** in the presence of $Co(modp)_2$ in DCE was the unsaturated peroxide **11**. Expecting more efficient production of the cyclic peroxide, we repeated the peroxidation in the presence of bis(acetylacetonate)cobalt(II) [$Co(acac)_2$] in ethanol[4b] (Table 2). A mixture of **11**, **12**, and **8** was produced. The significantly improved yield of the desired bicyclic peroxides, **8** and **12**, demonstrates the usefulness of this methodology in the synthesis of yingzhaosu A analogues. The time-independent product composition suggests that products, **11**, **12**, and **8** were stable under the reaction conditions.

These results imply that on the peroxidation of the diene **6** in ethanol, an additional reaction pathway for the formation of cyclic peroxides, **8** and **12**, seems to participate. That is, in the Co(III)−alkylperoxo complex **14**, ligand exchange with ethanol[10,11] leading to the formation of an unsaturated hydroperoxide **7** may compete with transmetalation with triethylsilane giving the corresponding triethylsilyl peroxide **11** (Scheme 3). The hydroperoxide **7** would be highly reactive under the reaction conditions thereby providing the bicyclic peroxides, **8** and **12**, via the peroxy radical **10**.[12] Consistent with this expectation, treatment of the unsaturated hydroperoxide **7** with $Co(acac)_2/O_2/Et_3SiH$ in ethanol for only 0.5 h resulted in the complete disappearance of **7**, providing the endoperoxides, **8** (25%) and **12** (9%), together with the unsaturated triethylsilyl peroxide **11** (7%).

Even in the absence of the cobalt catalyst the unsaturated hydroperoxide **7** was found to be highly reactive. When the hydroperoxide **7** was kept in a refrigerator for 10 days, a complex mixture was obtained, from which the bicyclic peroxide **8** was isolated in 52% yield (Table 3). Consistent with this, the ^1H NMR spectra of the

(8) This is consistent with the fact that 1,1-disubstituted ethene **28** is ca. three times more reactive than the 1,1,2-trisubstituted compound **29**, as confirmed by the competitive reaction of a mixture of these two alkenes with $Co(modp)_2/Et_3SiH/O_2$ in DCE. See also: Gridnev, A. A.; Ittel, S. D.; Fryd, M.; Wayland, B. B. *J. Chem. Soc., Chem. Commun.* **1993**, 1010.



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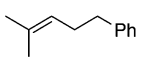

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(9) The example for the related transmetalation: (a) Hays, D. S.; Scholl, M.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 6751. (b) Lipshutz, B. H.; Chrisman, W.; Noson, K. *J. Organomet. Chem.* **2001**, *624*, 367. (c) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892.

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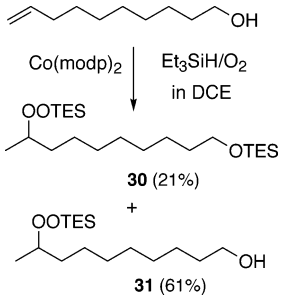
(11) As indirect evidence of the ligand exchange, the reaction of 9-decenol (2 mmol) with $Co(modp)_2$ (5 mol %) and Et_3SiH (4 mmol) in DCE (5 mL) under an oxygen atmosphere for 4 h gave 10-[(triethylsilyl)oxy]decan-2-yl triethylsilyl peroxide (**30**) (21%) together with 2-[(triethylsilyl)dioxy]decanol (**31**) (61%). In the absence of the Co(II) catalyst, however, 9-decenol remained intact.



(12) The key intermediate **10** is most likely to be produced by electron transfer from the hydroperoxide **7** to the adventitious Co(III) complexes, followed by deprotonation. Goldstein, S.; Meyerstein, D. *Acc. Chem. Res.* **1999**, *32*, 547.

SCHEME 2. Mechanism of Peroxidation of (*S*)-Limonene 6 in DCE

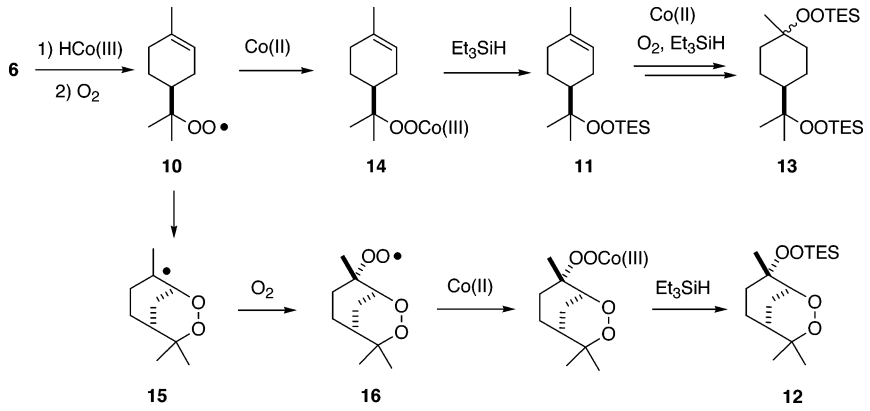
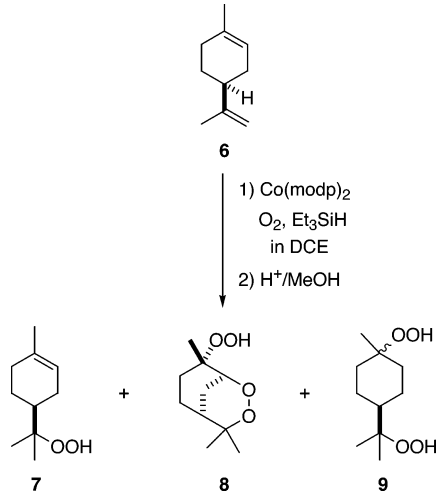


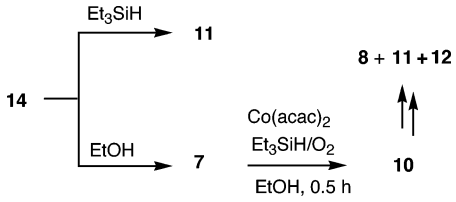
TABLE 1. Peroxidation of (*S*)-Limonene 6 in 1,2-Dichlorethane (DCE)



	products,[b] %		
reaction time, h[a]	**7**	**8**	**9**
1	36	22	
24	8	23	17

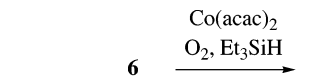
[a] The reaction of **6** (2 mmol) in the presence of $Co(modp)_2$ (5 mol %) and Et_3SiH (4 mmol) in DCE (5 mL) at room temperature. [b] The hydroperoxides **7**−**9** were obtained by treatment of the corresponding triethylsilylperoxides **11**−**13** (Scheme 2) with HCl/MeOH.

SCHEME 3. $Co(acac)_2$-Catalyzed Transformation of a Hydroperoxide 7 to the Yingzhaosu A Analogues, 8 and 12, in Ethanol



solution of **7** in $CDCl_3$, when allowed to stand in contact with the atmosphere (see the Experimental Section), showed slow transformation of **7** to **8**. After 1 week the bicyclic peroxide **8** was isolated in 44% yield. When the same reaction was conducted in the presence of a small amount of 2,6-di-*tert*-butyl-4-methylphenol (BHT; an efficient inhibitor of radical chain reaction), however, the transformation was completely suppressed, suggesting

TABLE 2. Peroxidation of (*S*)-limonene 6 in Ethanol[a]



	products, %		
reaction time, h	**8**	**11**[b]	**12**[b]
1	22	9	18
5	23	7	21

[a] The reaction of **6** (2 mmol) in the presence of Co(II) (5 mol %) and Et_3SiH (4 mmol) in EtOH (5 mL) at room temperature. [b] See footnote *b* in Table 1.

TABLE 3. Spontaneous Transformation of a Hydroperoxide 7 to the Yingzhaosu A Analogue 8

reaction conditions	**8**, %	recovered **7**, %
7 °C, 10 days, neat	52	
rt, 7 days in $CDCl_3$	44[a]	34
rt, 7 days in $CDCl_3$[b]		∼100

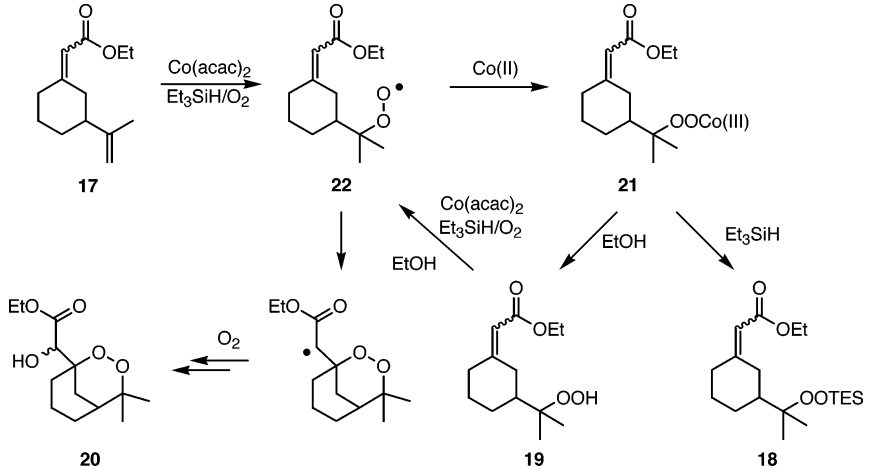
[a] The yield based on the consumed hydroperoxide **7**. [b] In the presence of a small amount of BHT.

that an appropriate initiator such as molecular oxygen facilitates the transformation via a peroxy radical **10**.[13]

To see the scope of the Co(II)-catalyzed peroxidation of diene for the synthesis of the yingzhaosu A analogue, we next tried the peroxidation of a diene **17** in the presence of $Co(modp)_2$ in DCE (run 1 in Table 4; the product yields in Table 4 show those based on the consumed starting material **17**). The reaction of **17** was significantly slower than that of (*S*)-limonene **6** (70% conversion during 2 h). Moreover, the sole isolable product was the unsaturated peroxide **18**.[4d] The reaction of **17** in the presence of $Co(acac)_2$ in ethanol (runs 2 and 3) also gave only the unsaturated peroxides, **18** and **19**. This is in marked contrast to the fact that in the case of **6**, a mixture of the cyclic peroxides, **8** and **12**, was obtained in a reasonable yield. A possible reason is that the intramolecular cyclization of the unsaturated peroxy radical **22** is relatively slow, thereby making capture by the Co(II) complex leading to **18** and **19** predominant. To suppress capture of the unsaturated peroxy radical

(13) Spontaneous rearrangement of allyl hydroperoxides via the corresponding peroxy radical is well-known: (a) Porter, N. A. In *Organic Peroxides*; Ando, W., Ed.; Wiley: New York, 1992; Chapter 2. (b) Dussault, P. H.; Eary, C. T.; Woller, K. R. *J. Org. Chem*. **1999**, *64*, 1789.

TABLE 4. Peroxidaton of Diene 17[a]



run	catalyst	solvent	reaction time, h	converstion, %	products,[b] %		
					18[c]	**19**	**20**
1	$Co(modp)_2$	DCE	2	70[d]	74[d]		
2	$Co(acac)_2$	EtOH	2.5	70	46	31	
3	$Co(acac)_2$	EtOH	7	82	34	18	
4	$Co(acac)_2$	EtOH[e]	6	49	17	47	20
5	$Co(acac)_2$	EtOH[e]	25	78	11	13	29

[a] Unless otherwise noted, the reacton of **17** (1 mmol) was conduced in the presence of Co(II) (5 mmol %) and Et_3SiH (2 mmol) in an appropriate solvent (2.5 mL). [b] The yield based on the consumed starting material **17**. [c] The yield of **18** was determined by transforming into hydroperoxide **19**. [d] Taken from the data in ref 4d. [e] Reaction of **17** (1 mmol) with O_2 and Et_3SiH (2 mmol) in the presence of $Co(acac)_2$ (5 mol %) in EtOH (10 mL).

22 by the Co(II) complex, we next tried the reaction in ethanol under more diluted conditions. That is, the reaction solution was diluted four times compared with the standard one (runs 4 and 5 in Table 4). Under this condition the hydroxy-substituted cyclic peroxide **20**[14,15] was obtained in ca. 25% yield. Perhaps in accordance with this, the reaction of the unsaturated hydroperoxide **19** (0.43 mmol) with O_2 and triethylsilane (0.86 mmol) in the presence of $Co(acac)_2$ (0.022 mmol) in EtOH (1.2 mL) for 5 h (a standard condition) gave only the unsaturated peroxide **18** (27%), while the reaction of hydroperoxide **19** (0.63 mmol), $Co(acac)_2$ (0.031 mmol), and triethylsilane (1.3 mmol) in ethanol (6.3 mL) for 24 h (a more diluted condition) gave the cyclic peroxide **20** (13%) together with **18** (17%).

To understand the notable difference in efficiency of cyclization between the unsaturated peroxy radicals, **10** and **22**, the activation enthalpies and entropies in the cyclization of **10** and **23** (a model of **22**) were calculated at the UB3LYP/6-31G(d) level of theory[16] with the Gaussian 98 package.[17] The results suggested that (i) the cyclization of the peroxy radical **10** seems to proceed via the transition state with a chair-chair conformation, while in the case of the peroxy radical **23** the chair-boat transition state is more favorable,[18] and (ii) the intramolecular cyclization of the unsaturated peroxy radical

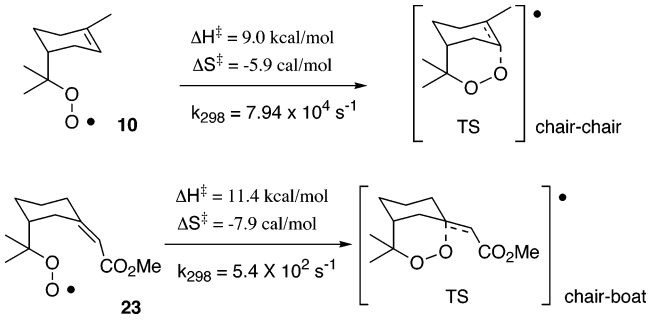


FIGURE 2. Activation enthalopies and entropies in the intramolecular cyclization of unsaturated peroxy radicals, **10** and **23**.

10 is much easier than that of **23** (Figure 2; for the details see the Supporting Information). A significantly larger steric congestion in the transition state from **23** should be the reason.[19]

(14) Compound **20** is most likely to be produced from the corresponding hydroperoxide by an oxygen atom transfer to unidentified reductants. In this respect, hydroperoxides with an electron-withdrawing group at the α-position are well-known to oxidize a variety of compounds such as alkene and sulfide.[15]

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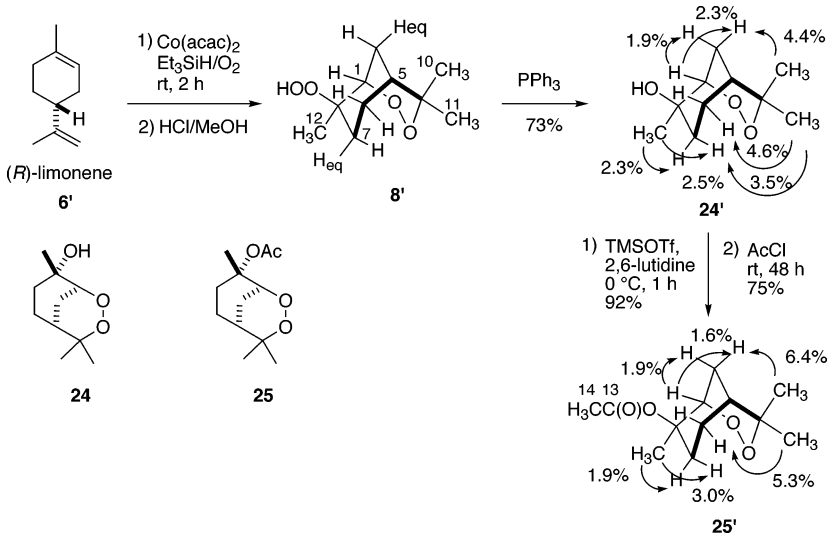
(17) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, Y. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.11; Gaussian, Inc.: Pittsburgh, PA, 2001.

(18) In the case of the peroxy radical **22** the activation enthalpy and entropy leading to the formation of the transition state having a chair-chair conformation were calculated as 14.3 kcal/mol and −7.3 cal/mol, respectively.

TABLE 5. Synthesis and Antimalarial Activity of the Yingzhaosu A Analogues



compd	*P. falciparum* EC_{50}	FM3A EC_{50}	select[a]
25	3.0×10^{-9}	6.5×10^{-7}	217
24′	3.0×10^{-8}	4.8×10^{-6}	160
25′	4.0×10^{-9}	1.5×10^{-6}	375
artemisinin	1.0×10^{-8}	1.0×10^{-5}	1000

[a] Selecivity = mean of the EC_{50} value for FM3A cells/mean of the EC_{50} value for *P. falciparum*.

To undertake a preliminary study of the antimalarial activities of the yingzhaosu A analogues, the hydroperoxide **8** was reduced by triphenylphosphine to the corresponding alcohol **24**. Subsequent transformation of the alcohol **24** to the corresponding acetate **25** was accomplished by the method developed by Bachi and coworkers.[2b] Stereoisomeric alcohol **24′** and acetate **25′** were also prepared from (*R*)-limonene (**6′**) and the structures were determined by ^1H and ^{13}C NMR spectroscopy including NOE (Table 5). The preliminary study on antimalarial activities of these cyclic peroxides against *P. falciparum*[20] showed that the EC_{50} values of the acetoxy derivatives, **25** and **25′**, are better than that of artemisinin. In due course we are studying the activity of these cyclic peroxides in vivo.

Experimental Section

General. ^1H (270 MHz) and ^{13}C (67.5 MHz) NMR spectra were obtained in $CDCl_3$ solution with $SiMe_4$ as the standard. The structures of the alcohol **24′** and the acetate **25′** were determined by ^1H-COSY, NOE-difference, ^{13}C-DEPT, and 2D-HMQC NMR spectra recorded on a 400-MHz spectrometer. The methods in preparation and the physical properties of the diene **17** and the unsaturated hydroperoxide **19** already have been reported.[4d] Triethylsilyl peroxides, **11**−**13** and **18**, were difficult to isolate in pure forms and therefore they were transformed into the corresponding hydroperoxides, **7**−**9** and **19**, respectively. To determine the purity of labile unsaturated hydroperoxides, **7** and **19**, they were converted into the corresponding alcohols, **26** and **27**, respectively, and the elemental analysis data (Analytical Center, Osaka University) were obtained. The catalyst $Co(modp)_2$ was prepared by the reported method.[21] 1,2-Dichloroethane and ethanol were purified by distillation over CaH_2 and CaO, respectively. (*S*)- and (*R*)-limonene, $Co(acac)_2$, and $CDCl_3$ (99.8%) were used as received.

Caution: Since organic peroxides are potentially hazardous compounds, they must be handled with due care; avoid exposure to strong heat or light, or mechanical shock, or oxidizable organic materials, or transition metal ions. No particular difficulties were experienced in handling any of the new peroxides synthesized in this work with use of the reaction scales and procedures described below together with the safeguard mentioned above.

Peroxidation of Dienes with $Co(modp)_2$ in DCE. The reaction of (*S*)-limonene **6** is representative. Into a two-necked 50-mL flask, charged with dioxygen, were added (*S*)-limonene **6** (270 mg, 2.0 mmol), bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato)cobalt(II) [$Co(modp)_2$] (54 mg, 0.10 mmol), and 1,2-dichloroethane (5 mL), and then the flask was again charged with dioxygen. Triethylsilane (490 mg, 4.2 mmol) was added via a 1.0-mL gastight syringe, and the reaction mixture was stirred vigorously under an oxygen atmosphere at room temperature. After the mixture was stirred for 1 h, the solvent was evaporated under reduced pressure. Hexane (10 mL) was added to the residue, and then the precipitated solid materials were removed by filtration over Celite. After concentration of the filtrate, components of the residue were separated by column chromatography on silica gel. Elution with diethyl ether−hexane (2:98) gave a mixture of the triethylsilyl peroxides **11** and **12**. After treatment of this mixture with a drop of concentrated HCl in methanol (2 mL) for 5 min, solid sodium bicarbonate and anhydrous $MgSO_4$ were added. The reaction mixture was stirred for an additional 10 min, and solid materials were removed by filtration over Celite. After evaporation of the solvent under reduced pressure, components of the residue were separated by column chromatography on silica gel. The unsaturated hydroperoxide

(19) The rate of 5-*exo*-cyclization of 5-methyl-5-heptenyl radical is known to be ca. 22 times slower than that of 6-methyl-5-heptenyl radical. Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, Chapter 4.

(20) Kim, H.-S.; Nagai, Y.; Ono, K.; Begum, K.; Wataya, Y.; Hamada, Y.; Tsuchiya, K.; Masuyama, A.; Nojima, M.; McCullough, K. J. *J. Med. Chem.* **2001**, *44*, 2357.

(21) Kato, K.; Yamada, T.; Takai, T.; Inoki, S.; Isayama, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 179.

7 (120 mg, 36%) was isolated by elution with diethyl ether−hexane (10:90). Subsequent elution with diethyl ether−hexane (15:85) gave the hydroperoxides **8** (88 mg, 22%). The hydroperoxide **7** (70 mg, 0.41 mmol), which was labile even in a refrigerator, decomposed within 10 days to afford a complex mixture containing the endoperoxide **8** (43 mg, 52%). Therefore, satisfactory elemental analysis data could not be obtained. The reaction of **7** with Ph_3P (1.2 equiv) in CH_2Cl_2 at 0 °C for 5 min gave the corresponding alcohol, 1-methyl-1-(4-methyl-3-cyclohexenyl)ethanol (**26**) in 94% yield, which showed the expected elemental analysis data.

When the same reaction was conducted for 24 h, followed by column chromatography on silica gel (elution with diethyl ether−hexane, 2:98), a mixture of the triethylsilyl peroxides **11**, **12**, and **13** (459 mg) was obtained. After treatment of the mixture with a drop of concentrated HCl in methanol (2 mL) for 5 min, components of the reaction mixture were separated by column chromatography on silica gel. The unsaturated hydroperoxide **7** (28 mg, 8%) was isolated by elution with diethyl ether−hexane (10:90). Subsequent elution with diethyl ether−hexane (15:85) gave the hydroperoxides **8** (91 mg, 23%). The third fraction (elution with ether−hexane. 25:75) contained 4-(1-hydroperoxy-1-methylethyl)-1-methylcyclohexyl hydroperoxide (**9A**) (36 mg, 9%). Further elution with ether−hexane (25:75) gave the isomeric bis-hydroperoxide **9B** (32 mg, 8%).

1-Methyl-1-(4-methyl-3-cyclohexenyl)ethyl hydroperoxide (7): oil; ^{1}H NMR δ 1.1−1.3 (m, 1 H), 1.19 (s, 6 H), 1.65 (s, 3 H), 1.7−2.1 (m, 6 H), 5.3−5.4 (m, 1 H), 7.48 (s, 1 H); ^{13}C NMR δ 21.0 (CH_3), 21.5 (CH_3), 23.3 (CH_3), 23.9 (CH_2), 26.6 (CH_2), 30.8 (CH_2), 40.3 (CH), 85.0 (C), 120.5 (CH), 134.0 (C).

1-Methyl-1-(4-methyl-3-cyclohexenyl)ethanol (26): oil; ^{1}H NMR δ 1.17 (s, 3 H), 1.19 (s, 3 H), 1.1−1.3 (m, 1 H), 1.4−1.6 (m, 2 H), 1.65 (s, 3 H), 1.7−2.1 (m, 5 H), 5.3−5.4 (m, 1 H); ^{13}C NMR δ 23.3 (CH_3), 23.9 (CH_2), 26.1 (CH_3), 26.8 (CH_2), 27.3 (CH_3), 30.9 (CH_2), 44.9 (CH), 72.7 (C), 120.5 (CH), 133.9 (C). Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.85; H, 11.73.

(1*S*,5*S*,8*S*)-4,4,8-Trimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-yl hydroperoxide (8): oil; ^{1}H NMR δ 1.16 (s, 3 H), 1.42 (s, 3 H), 1.48 (s, 3 H), 1.6−2.0 (m, 5 H), 2.2−2.4 (m, 2 H), 4.1−4.2 (m, 1 H), 7.94 (s, 1 H); ^{13}C NMR δ 21.5 (CH_3), 23.6 (CH_2), 24.4 (CH_2), 24.5 (CH_3), 24.6 (CH_3), 31.6 (CH_2), 32.4 (CH), 77.6 (CH), 81.6 (C), 83.1 (C). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.58; H, 8.94.

4-(1-Hydroperoxy-1-methylethyl)-1-methylcyclohexyl hydroperoxide (9A): colorless solid, mp 78−82 °C (from hexane); ^{1}H NMR δ 1.19 (s, 6 H), 1.29 (s, 3 H), 1.15−1.80 (m, 7 H), 2.01 (br d, J = 10.8 Hz, 2 H), 7.40 (s, 1 H), 7.51 (s, 1 H); ^{13}C NMR δ 20.4, 21.7, 24.2, 34.5, 44.0, 83.0, 84.7. Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80: H, 9.87. Found: C, 58.72: H, 9.92.

Bis-hydroperoxide 9B: colorless solid, mp 85−88 °C (from hexane); ^{1}H NMR δ 1.19 (s, 6 H), 1.10−1.80 (m, 7 H), 1.29 (s, 3 H), 1.78 (br d, J = 10.4 Hz, 2 H), 7.20 (s, 2 H); ^{13}C NMR δ 20.4, 21.7, 24.3, 34.5, 44.0, 83.0, 84.6. Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.80: H, 9.87. Found: C, 58.95: H, 9.70.

Spontaneous Transformation of Unsaturated Hydroperoxide 7 to Endoperoxide 8 in $CDCl_3$. A solution of the unsaturated hydroperoxide **7** (32 mg, 0.18 mmol) was dissolved in $CDCl_3$ (1 mL), and then the ^{1}H NMR spectra of this solution were periodically measured. To make the uptake of the oxygen molecule easy, the cap of the NMR tube was removed (except for the measurement of the NMR spectra) and instead the tube was covered by aluminum foil very loosely. After 7 days the solvent was evaporated and the residue was separated by column chromatography on silica gel. Elution with ether−hexane (8:92) gave the starting material **7** (11 mg, conv 66%). Subsequent elution with ether−hexane (15:85) gave the cyclic peroxide **8** (11 mg, 44% based on the consumed **7**).

Peroxidation of Dienes with $Co(acac)_2$ in EtOH. The reaction of **17** is representative. Into a two-neck 50-mL flask, charged with dioxygen, were added diene **17** (210 mg, 1.0 mmol), bis(acetylacetonato)cobalt(II) (13 mg, 0.050 mmol) and ethanol (10 mL), and then the flask was again charged with dioxygen. Triethylsilane (230 mg, 2.0 mmol) was added via 1.0-mL gastight syringe, and the reaction mixture was stirred vigorously under oxygen atmosphere at room temperature. After the mixture was stirred for 6 h, the solvent was evaporated under reduced pressure. Then, the components of the residue were separated by column chromatography on silica gel. Elution with diethyl ether−hexane (5:95) gave a mixture of the diene **17** and the corresponding triethylsilyl peroxide **18**. Subsequent elution with diethyl ether−hexane (15:85) gave the unsaturated hydroperoxide **19** (55 mg, 47% based on consumed **17**). The hydroxy-substituted 2,3-dioxabicyclo[3.3.1]nonane derivative **20** (26 mg, 20% based on consumed **17**) was obtained from elution with diethyl ether−hexane (25:75). After treatment of the mixture of **17** and **18** with a drop of concentrated HCl in MeOH (1 mL) for 1 min, solid sodium bicarbonate and anhydrous $MgSO_4$ were added. The reaction mixture was stirred for an additional 5 min, and then solid materials were removed by filtration over Celite. After evaporation of the solvent under reduced pressure, components of the residue were separated by column chromatography on silica gel. The diene **17** (106 mg) was recovered by elution with diethyl ether−hexane (5:95) (conv 49%). Subsequent elution with diethyl ether−hexane (15:85) gave the unsaturated hydroperoxide **19** (20 mg, 17% based on consumed **17**). The reduction of **19** with Ph_3P (1 equiv) in benzene gave the corresponding alcohol, [3-(1-hydroxy-1-methylethyl)cyclohexylidene]acetic acid ethyl ester (**27**), quantitatively.

2-Hydroxy-2-(4,4-dimethyl-2,3-dioxabicyclo[3.3.1]nonyl)-acetic acid ethyl ester (20): oil (1:1 mixture of two stereoisomers); ^{1}H NMR δ 1.2−2.4 (m, 18 H), 3.00 (d, J = 8.3 Hz; H−D exchange in D_2O) + 3.05 (d, J = 7.6 Hz; H−D exchange in D_2O) (1 H), 3.90 (d, J = 7.6 Hz; s in D_2O) + 3.95 (d, J = 8.0 Hz; s in D_2O) (1 H), 4.2−4.4 (m, 2 H); ^{13}C NMR δ 14.2 (CH_3), 14.3 (CH_3), 20.2 (CH_2, 2C), 23.5 (CH_3, 2C), 24.9 (CH_3, 2C), 26.4 (CH_2), 26.4 (CH_2), 29.4 (CH_2), 30.2 (CH_2), 30.4 (CH_2), 31.0 (CH_2), 35.25 (CH), 35.29 (CH), 61.8 (CH_2), 62.0 (CH_2), 75.6 (CH), 75.8 (CH), 80.8 (C), 80.9 (C), 81.38 (C), 81.42 (C), 171.7 (C), 171.8 (C); LRMS (EI) *m*/*z* (rel int) 258 (M^+) (14), 155 (M^+ − CH(OH)CO_2Et) (100). Anal. Calcd for $C_{13}H_{22}O_5$: C, 60.45; H, 8.58. Found: C, 60.18; H, 8.44.

[3-(1-Hydroperoxy-1-methylethyl)cyclohexylidene]acetic acid ethyl ester (19): oil (a ca. 2:1 mixture of two stereoisomers); ^{1}H NMR δ 1.0−2.4 (m, 17 H), 3.83 (br t, J = 12.7 Hz, 1 H), 4.0−4.2 (m, 2 H), 5.61 (s) + 5.63 (s, major) (1 H), 7.95 (s, major) + 8.87 (s) (1 H); ^{13}C NMR (major isomer) δ 14.2, 20.8, 21.9, 26.9, 27.1, 29.4, 38.5, 46.1, 59.6, 84.2, 113.7, 162.8, 166.9; the following additional signals were assigned to the minor isomer in the ^{13}C NMR spectrum, δ 19.8, 22.6, 27.9, 28.9, 31.5, 37.8, 46.3, 60.0, 84.1, 112.1, 164.5, 167.7.

[3-(1-Hydroxy-1-methylethyl)cyclohexylidene]acetic acid ethyl ester (27): oil (ca. 2:1 mixture of two stereoisomers); ^{1}H NMR δ 1.2−2.4 (m, 18 H), 3.82 (br t, J = 13.5 Hz, major) + 3.98 (br t, J = 12.2 Hz) (1 H), 4.10 (q, J = 7.2 Hz, 2 H), 5.61 (s, 1H); ^{13}C NMR δ 14.2 (2 C), 26.5, 26.8 (2 C), 27.0, 27.1 (2 C), 27.3, 27.7, 29.3, 30.8, 37.6, 38.7, 50.3, 50.8, 59.4, 59.5, 72.3, 72.4, 113.3, 113.6, 162.9, 163.1, 166.7, 166.8. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.68; H, 9.90.

$Co(acac)_2$-Catalyzed Transformation of Unsaturated Hydroperoxide 19 to the Endoperoxide 20 in EtOH. A mixture of hydroperoxide **19** (153 mg, 0.63 mmol), $Co(acac)_2$ (8.0 mg, 0.031 mmol), and triethylsilane (146 mg, 1.3 mmol) in ethanol (6.3 mL) was stirred at room temperature for 24 h. After the conventional workup, the mixture of the products was separated by column chromatography on silica gel. Elution with ether−hexane (5:95) gave the peroxide **18** as an admixture with a small amount of contaminants. The hydroperoxide **19** (26 mg) was recovered (conv 83%) from the second fraction (elution with ether−hexane, 15:85). Subsequent elution with

ether−hexane (25:75) gave the cyclic peroxide **20** (17 mg, 13% based on consumed **19**). To evaluate the yield of the triethylsilyl peroxide **18**, the peroxide **18** was treated with a drop of concentrated HCl in methanol (2 mL) to give the unsaturated hydroperoxide **19** (22 mg, 17% based on consumed **19**).

Reduction of Endoperoxides, 8 and 8′, by Ph_3P. The reaction of **8′** is representative. Into a solution of endoperoxide **8′** (600 mg, 3.0 mmol) in CH_2Cl_2 (3 mL) was added triphenylphosphine (856 mg, 3.3 mmol) at 0 °C over 5 min. After evaporation of the solvent, components of the residue were separated by column chromatography on silica gel. Elution with diethyl ether−hexane (25:75) gave the alcohol **24′** (400 mg, 73%).

(1*R*,5*R*,8*R*)-4,4,8-Trimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (24′): oil; ^{1}H NMR δ 1.17 (s, 3 H, Me-11), 1.38 (s, 3 H, Me-12), 1.40−1.44 (m, 1 H, OH; H−D exchange in D_2O), 1.47 (s, 3 H, Me-10), 1.50 (quintet, J = 3.3 Hz, 1 H, H-5), 1.56 (dd, J = 14.3, 5.9 Hz, 1 H, H-7eq), 1.78 (tdd, J = 13.9, 6.2, 3.6 Hz, 1 H, H-6ax), 1.80−1.90 (m, 1 H, H-6eq), 1.99 (ddd, J = 13.6, 3.1, 1.8 Hz, 1 H, H-9ax), 2.24 (dq, J = 13.6, 3.7 Hz, 1 H, H-9eq), 2.34 (td, J = 13.9, 6.2 Hz, 1 H, H-7ax), 3.66 (br dd, J = 3.7, 1.8 Hz, 1 H, H-1); ^{13}C NMR δ 23.4 (C-6), 24.69 (Me-10), 24.74 (Me-11), 24.8 (C-9), 28.0 (Me-12), 32.1 (C-5), 35.1 (C-7), 71.5 (C-8), 81.6 (C-4), 81.8 (C-1). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.54; H, 10.02.

(1*S*,5*S*,8*S*)-4,4,8-Trimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (24): colorless solid, mp 42−43 °C (from hexane). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.71; H, 9.73.

Synthesis of Acetates 25 and 25′ from Alcohols 24 and 24′. The transformation of **24′** is representative. To a cold solution of alcohol **24′** (156 mg, 0.84 mmol) and 2,6-lutidine (250 mg, 2.3 mmol) in dry CH_2Cl_2 (5 mL) was added neat trimethylsilyl trifluoromethanesulfonate (TMSOTf, 397 mg, 1.8 mmol) and the mixture was stirred at 0 °C for 1 h. The mixture was then poured into cold water (50 mL), extracted with EtOAc−hexane (1:4, 2 × 50 mL), washed with cold saturated $NaHCO_3$ (25 mL), dried ($MgSO_4$), and evaporated to give the crude TMS derivative (200 mg, 92%) as an oil; ^{1}H NMR δ 0.13 (s, 9 H), 1.15 (s, 3 H), 1.39 (s, 3 H), 1.42−1.52 (m, 1 H), 1.46 (s, 3 H), 1.59−1.65 (m, 1 H), 1.73−1.78 (m, 2 H), 2.00−2.05 (m, 1 H), 2.20−2.33 (m, 2 H), 3.69 (br s, 1 H). The TMS derivative (200 mg, 0.78 mmol) was treated with acetyl chloride (AcCl, 2.5 mL) and stirred at room temperature for 48 h. The mixture was evaporated and dried under vacuum to give the crude acetate **25′**. Subsequent column chromatography on silica gel (elution with ether−hexane, 15:85) gave the pure **25′** (132 mg, 75%).

(1*R*,5*R*,8*R*)-4,4,8-Trimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-yl acetate (25′): oil; ^{1}H NMR δ 1.17 (s, 3 H, Me-11), 1.47 (s, 3 H, Me-10), 1.49 (quintet, J = 3.3 Hz, 1 H, H-5), 1.66 (s, 3 H, Me-12), 1.68 (tdd, J = 13.8, 6.2, 3.6 Hz, 1 H, H-6ax), 1.77 (ddd, J = 14.3, 3.0, 1.8 Hz, 1 H, H-9ax), 1.82−1.88 (m, 1 H, H-6eq), 2.01 (s, 3 H, Me-14), 2.13 (dd, J = 14.9, 5.8 Hz, 1 H, H-7eq), 2.25−2.35 (m, 2 H, H-7ax + H-9eq), 4.38 (br t, J = 2.2 Hz, 1 H, H-1); ^{13}C NMR δ 22.5 (C-14), 22.6 (C-12), 23.7 (C-6), 24.5 (C-9), 24.6 (C-10), 24.8 (C-11), 32.1 (C-5), 32.8 (C-7), 77.4 (C-1), 81.4 (C-4), 82.9 (C-8), 170.0 (C-13). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.02; H, 8.62.

(1*S*,5*S*,8*S*)-4,4,8-Trimethyl-2,3-dioxabicyclo[3.3.1]nonan-8-yl acetate (25): oil. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.15; H, 8.79.

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Supporting Information Available: Computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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