LETTERS

Thiol-Oxygen Cooxidation of Monoterpenes. Synthesis of Endoperoxides Structurally Related to Antimalarial Yingzhaosu A

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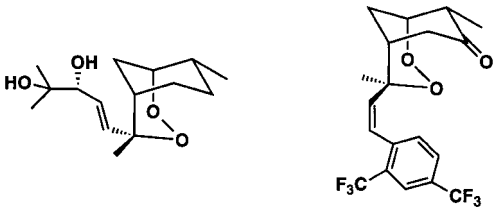
Abstract: The first application of thiol-oxygen cooxidation of 1,5-dienes for the preparation of 6-membered ring endoperoxides is described. Treatment of *S*-(–)-limonene and related monoterpenes with PhSH, dioxygen and a radical initiator, followed by selective reduction of intermediate hydroperoxide-endoperoxides afforded 4,8-dimethyl-4-phenylthiomethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ols.

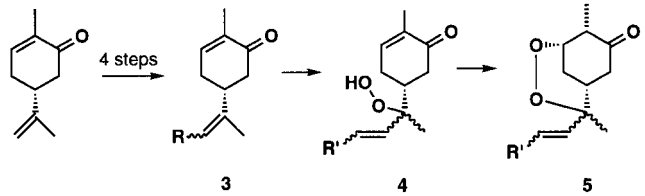
A variety of cyclic peroxides have been studied as potential candidates for the treatment of malaria caused by chloroquine-resistant parasites.[1] Our attention has been given to yingzhaosu A (**1**) and to arteflene (**2**), two endoperoxides characterized by a 2,3-dioxabicyclo[3.3.1]nonane system as a central molecular feature (Figure 1). Yingzhaosu A was isolated from an extract of *Artabotris uncinatus* (Annonaceae) which was used in China as a folk remedy for the treatment of malaria[2] and was subsequently obtained by total synthesis.[3] Arteflene is a representative example of a group of synthetic 4-arylvinyl-2,3-dioxabicyclo[3.3.1]nonan-7-ones,[4] which exhibit potent antimalarial activity against *Plasmodium falciparum* and *Plasmodium berghei*.[5]



1 2

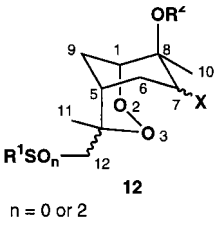
Figure 1

It was postulated that other endoperoxides, which like yingzhaosu A (**1**) and arteflene (**2**), contain the 2,3-dioxabicyclo[3.3.1]nonane system in their molecular backbone may also exhibit antimalarial activity. The only reported synthetic approach to the 2,3-dioxabicyclo[3.3.1]nonane system is based on the transformation of (-)-carvone into a derivative **3** (4 steps), followed by formation of an hydroperoxide **4** and intramolecular Michael addition to give an endoperoxide **5** (Scheme 1).[3-4] In an ongoing study directed toward the development of new antimalarial drugs,[6] a versatile method for the synthesis of new 2,3-dioxabicyclo[3.3.1]nonanes of type **12** was required (Figure 2). The singular array of substituents at positions 7,8, and 12 makes these compounds amenable to chemical manipulations, and thus suitable for structural activities studies.[7]



3 4 5

Scheme 1

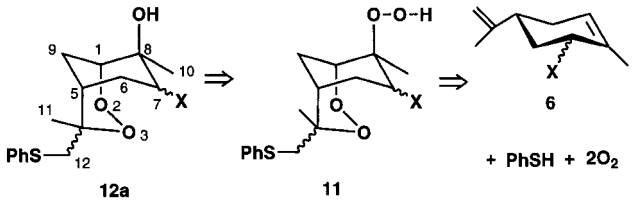


12

n = 0 or 2

Figure 2

A simple retrosynthetic analysis of compound **12a** leads initially to the endoperoxide-hydroperoxide **11**, and then by homolytic cleavage to a monoterpene **6**, benzenethiol, and molecular oxygen (Scheme 2). It was anticipated that the application of the classical thiol-oxygen cooxidation (TOCO) of olefins[8] to substrate **6** may induce a sequential free radical reaction leading to endoperoxide-hydroperoxide **11** in one operation (Scheme 3). Previous studies of the TOCO reaction for the synthesis of cyclic endoperoxides were restricted to five-membered monocyclic 1,2-dioxolane derivatives.[9-14] The formation of endoperoxide **11** in one operation from monoterpenes **6**, PhSH, and O_2, relies on the viability of each step in the sequential process shown in Scheme 3. The unprecedented 6-*exo* addition of peroxy radical **8** to form the 2,3-dioxabicyclo[3.3.1]nonanyl radical **9** was viewed as a potential obstacle in the synthetic plan. A protocol for the synthesis of endoperoxides **17-20** which minimizes undesired competitive reactions of peroxy radical **8** was therefore developed (Scheme 4).

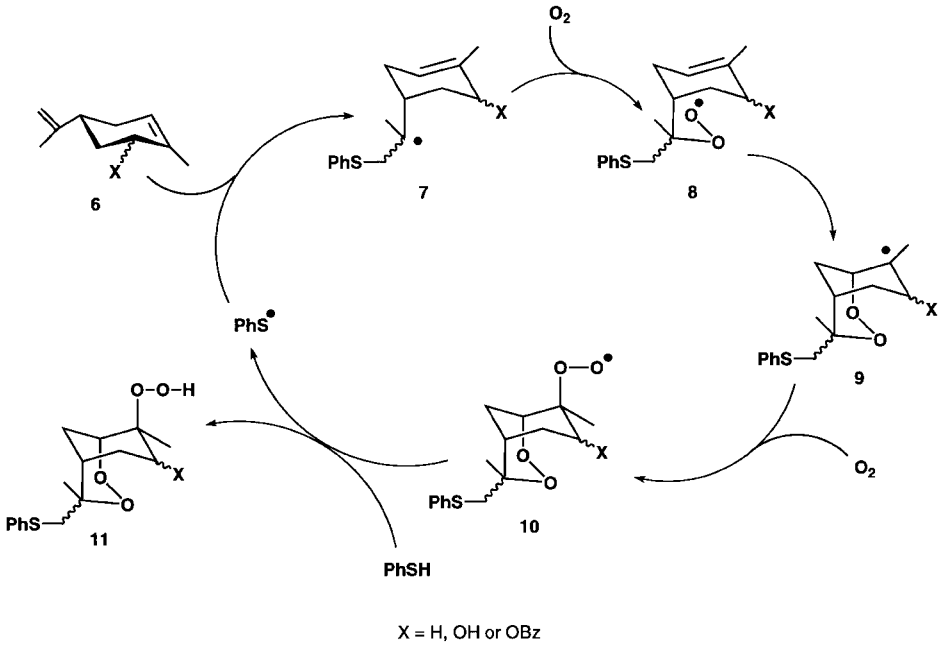


12a 11 6

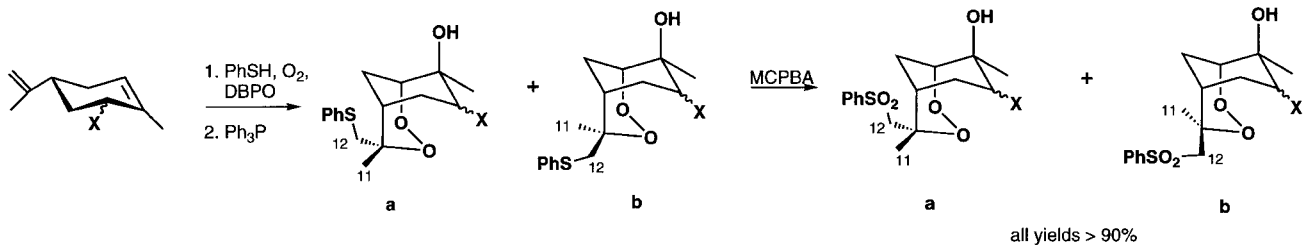
X = H, OH or OBz

Scheme 2

The following general procedure was applied for the preparation of compounds of type **12a**: Oxygen gas is slowly bubbled through a stirred solution of a monoterpene **13-16**[15] (*ca.* 3 equivalents, concentration: 0.02-0.1 M) and di-*tert*- butyl peroxalate radical initiator (DBPO) (0.02-0.04 equivalents) in *n*-heptane-benzene mixture (*ca.* 2:1), at rt, with simultaneous addition of benzenethiol (1 equivalent) in benzene or heptane (concentration: *ca.* 1M) over a period of 12 h (syringe pump). After the addition of thiol is completed, the mixture is kept under oxygen for an additional 12-14 h. It is then cooled to 0-5°C and diluted with CH_2Cl_2, and powdered Ph_3P (1 equivalent) is added. The mixture is stirred for an additional 2 h at 0-5°C and then 1 h at rt. Concentration and flash chromatography affords the corresponding endoperoxides



Scheme 3



13 X = H	**17** (54%; **a**/**b** = 55:45)	**21a**	**21b**
14 X = β-OBz	**18** (22%; **a**/**b** = 50:50)	**22a**	**22b**
15 X = α-OBz	**19** (6%; **a**/**b** = 65:35)	**23a**	**23b**
16 X = α-OH	**20** (12%; only **a**)	**24a**	

Scheme 4

17a,b-**20a**.[16-19] Reactions were performed using 0.5-15 mmole thiol.

Sulfones **21a**-**24a** and **21b**-**23b** were obtained by oxidation of the corresponding sulfides **17a,b**-**20a** with MCPBA (2.5 equivalents, EtOAc, rt, 4-8 h, monitored by TLC), followed by chromatographic separation into diastereomers **a** and **b**.[16-19]

The one-pot, five-step conversion of *S*-(–)-limonene (**13**) into 2,3-dioxabicyclo[3.3.1]nonan-8-ols (**17a,b**) and their subsequent oxidation to (1*S*,4*S*,5*S*,8*S*)-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (**21a**) (mp 112°C) and (1*S*,4*R*,5*S*,8*S*)-4,8-dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (**21b**) (oil) (Scheme 4) is a rather efficient process. The decrease in yields observed in the reactions with carveol and benzoyl carveols **14**-**16** probably derives from steric interference, at one of the transition states, by substituents at position 7.

The ^{1}H NMR spectrum of isomer **21a** exhibits characteristic signals: CH_3^{11} at 1.51 ppm and $C^{12}H'H$ at 3.27 and 4.23 ppm. The corresponding signals for isomer **21b** are for CH_3^{11} at 1.80 ppm and for $C^{12}H'H$ at 3.14 and 3.33 ppm. Thus the chemical shift of CH_3^{11} of isomer **b** is further downfield than that of isomer **a**, while the chemical shift of $C^{12}H'$ and $C^{12}H$ for isomer **a** is further downfield than that of isomer **b**, also $\Delta_{\text{isomer a}}(\delta H' - \delta H) > \Delta_{\text{isomer b}}(\delta H' - \delta H)$. This pattern which derives from the deshielding effect of the O_2 atom on the juxtaposed CH_2 or CH_3 H-atoms, is common to all sulfone-peroxides **21**-**24** and sulfide-peroxides **17**-**20** and constitutes a simple diagnostic tool to differentiate between epimers **a** and **b** at position-4.[19]

In conclusion, expansion of the scope of thiol-oxygen cooxidation of dienes opens a new avenue for the synthesis of 2,3-dioxabicyclo[3.3.1]nonanes structurally related to antimalarial endoperoxides like **1** and **2**. Compounds of type **12** were found to exhibit significant antimalarial activity.[7]

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References and Notes

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(15) *S*-(-)-Limonene (**13**) and (-)-carvone are commercially available, derivatives **14-16** were obtained by standard methods from (-)-carvone.

(16) Endoperoxides **17-24** are thermally stable at rt for at least 6 months and in solutions of inert organic solvents at 60 °C for at least 5 h.

(17) Caution is to be taken in handling potentially explosive di-*tert*-butyl peroxalate and mixtures of organic solvents and oxygen.

(18) All new compounds were fully characterized by detailed NMR analysis which included NOE difference experiments, 1D - (^{1}H, ^{13}C/DEPT), and 2D-NMR spectra (^{1}H/^{1}H COSY, ^{1}H/^{13}C HMQC). All sulfones (**21a,b-24a**) were additionally characterized by elemental microanalysis or CI HRMS. The 3D-structure of endoperoxide **20a** (crystallized as monohydrate) was determined by X-ray diffraction analysis. The 3D-structure of all other endoperoxides described in this paper was further corroborated by correlation of their NMR spectra with those of **20a** monohydrate.

(19) Selected NMR spectra: **(1*S*,4*S*,5*S*,8*S*)-4,8-dimethyl-4-phenylthiomethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (17a) and (1*S*,4*R*,5*S*,8*S*)-4,8-dimethyl-4-phenylthiomethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol (17b):** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.23 (br s, Me^{11}, **17a**), 1.55 (br s, Me^{11}, **17b**), total 3H; 1.37 (s, Me^{10}, **17b**), 1.38 (s, Me^{10}, **17a**), total 3H; 1.58 (m, 1H, H_e^7, **17a** + **17b**); 1.75-1.87 (m, 2H, H_e^6 + H_a^6 , **17a**+ **17b**; H_e^5, **17b**), 1.91 (dddd, $^3J_{5e6e} \approx {}^3J_{5e9e}$ = 6.4 Hz, $^3J_{5e6a} \approx {}^3J_{5e9a}$ = 3.2 Hz, H_e^5 , **17a**), total 3H ; 1.97 (ddd, $^2J_{9a9e}$ = 13.6 Hz, $^3J_{9a5e}$ = 3.2 Hz, $^3J_{9a1e}$ = 2.0 Hz, H_a^9, **17a**) , 2.05 (ddd, $^2J_{9a9e}$ = 13.4 Hz, $^3J_{9a5e}$ = 3.0 Hz, $^3J_{9a1e}$ = 1.8 Hz, H_a^9, **17b**), total 1H; 2.08 (ddd, $^2J_{9e9a}$ = 13.6 Hz, $^3J_{9e5e}$ = 6.4 Hz, $^3J_{9e1e}$ = 3.6 Hz, H_e^9, **17a**), 2.25 (m, $^2J_{9e9a} \approx$ 13.4 Hz, H_e^9, **17b**), total 1H; 2.29-2.39 (m, 1H, H_a^7, **17a** + **17b**); 2.95 (d, ^2J = 12.0 Hz, H^{12}, **17b**), 3.33 (d, ^2J = 12.8 Hz, H^{12}, **17a**), total 1H; 3.02 (br.d, ^2J = 12.0 Hz, H'^{12}, **17b**), 3.69 (dd, ^2J = 12.8 Hz, $^4J_{12,11}$ = 0.4 Hz, H'^{12}, **17a**), total 1H; 3.67 (m, H^1, **17a**), 3.70 (m, H^1, **17b**), total 1H; 7.18-7.24 (m, 1H, H^{16}, **17a** + **17b**); 7.26-7.32 (m, 2H, H^{15}, **17a** + **17b**); 7.35-7.42 (m, 2H, H^{14}, **17a** + **17b**). ^{13}C NMR ($CDCl_3$, 100 MHz) (δ): Isomer **17a**: 21.94 (Me^{11}), 23.66 (C^6H_2), 24.25 (C^9H_2), 28.10 (Me^{10}), 29.32 (C^5H), 35.63 (C^7H_2), 40.81 ($C^{12}H_2$), 71.47 (C^8), 81.65 (C^1H), 83.83 (C^4), 126.20 ($C^{16}H$), 128.92 ($2C^{14}H$), 129.75 ($2C^{15}H$), 136.93 (C^{13}); Isomer **17b**: 21.81 (Me^{11}), 23.38 (C^6H_2), 24.35 (C^9H_2), 28.10 (Me^{10}), 30.61 (C^5H), 35.96 (C^7H_2), 40.86 ($C^{12}H_2$), 71.42 (C^8), 82.09 (C^1H), 83.89 (C^4), 126.40 ($C^{16}H$), 128.98 ($2C^{14}H$), 129.75 ($2C^{15}H$), 136.50 (C^{13}). **(1*S*,4*S*,5*S*,8*S*)-4,8-Dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol, 21a)** ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.35 (s, 3H, Me^{10}), 1.51 (br s, 3H, Me^{11}), 1.60 (br dd, 1H, ^2J = 14.2 Hz, $^3J_{7e6e}$ = 5.6 Hz, H_e^7), 1.86 (dddd, 1H, $^2J \approx {}^3J_{6a7a}$ = 14.2 Hz, $^3J_{6a5e}$ = 6.0 Hz, $^3J_{6a7e}$ = 3.6 Hz, H_a^6), 1.93 (m, 1H, H_e^6), 2.11 (ddd, 1H, ^2J = 13.9 Hz, $^3J_{9a5e}$ = 3.0Hz, $^3J_{9a1e}$ = 2.0 Hz, H_a^9), 2.23 (br ddd, 1H,^2J = 13.9 Hz, $^3J_{9e5e}$ = 6.0 Hz, $^3J_{9e1e}$ = 3.5 Hz, H_e^9), 2.30 (m, 1H, H_e^5), 2.30 (ddd, 1H, ^2J _ $^3J_{7a6a}$ = 14.2 Hz, $^3J_{7a6e}$ = 6.7 Hz, H_a^7), 3.27 (d, 1H, ^2J = 14.3 Hz, H^{12}), 3.67 (m, 1H, $^3J_{1e9e}$ = 3.5 Hz, $^3J_{1e9a}$ = 2.0 Hz, H_e^1), 4.23 (dd, 1H, ^2J = 14.3 Hz, $^4J_{12',11}$ = 0.5 Hz, H'^{12}), 7.58 (m, 2H, $H^{15, 15'}$), 7.67 (m, 1H, H^{16}), 7.95 (m, 2H, $H^{14, 14'}$); ^{13}C NMR (63 MHz, $CDCl_3$, δ): 22.81 (Me^{11}), 23.38 (C^6H_2), 24.57 (C^9H_2), 27.89 (Me^{10}), 30.01 (C^5H), 35.59 (C^7H_2), 60.95 ($C^{12}H_2$), 71.22 (C^8), 81.90 (C^1H), 82.65 (C^4), 127.46 ($2C^{14'}H$), 129.30 ($2C^{15}H$), 133.70 ($C^{16}H$), 140.97 (C^{13}). **(1*S*,4*R*,5*S*, 8*S*)-4,8-Dimethyl-4-phenylsulfonylmethyl-2,3-dioxabicyclo[3.3.1]nonan-8-ol, 21b).** ^{1}H NMR (400 MHz, $CDCl_3$, δ): 1.29 (s, 3H, Me^{10}), 1.58 (br dd, 1H, ^2J = 14.2 Hz, $^3J_{7e6e}$ = 5.4 Hz, H_e^7), 1.80 (br.s, 3H, Me^{11}), 1.86-2.00 (m, 2H, H_e^6 + H_a^6), 2.03 (ddd, 1H, ^2J = 13.6 Hz, $^3J_{9a5e}$ = 3.2 Hz, $^3J_{9a1e}$ = 1.8 Hz, H_a^9), 2.09 (br dddd, 1H, $^3J_{5e6e} \approx {}^3J_{5e9e}$ = 6.4 Hz, $^3J_{5e6a} \approx {}^3J_{5e9a}$ = 3.2 Hz, H_e^5), 2.14 (br ddd, 1H, $^2J \approx {}^3J_{7a6a}$ = 14.2 Hz, $^3J_{7a6e}$ = 6.6 Hz, H_a^7), 2.27 (ddd, 1H, ^2J = 13.6 Hz, $^3J_{9e5e}$ = 6.4 Hz, $^3J_{9e1e}$ = 3.3 Hz, H_e^9), 3.14 (d, 1H, ^2J = 14.0 Hz, H^{12}), 3.33 (br.d, 1H, ^2J = 14.0 Hz, H'^{12}), 3.68 (m, 1H, $^3J_{1e9e}$ = 3.3 Hz, $^3J_{1e9a}$ = 1.8 Hz, H_e^1), 7.58 (m, 2H, $H^{15, 15'}$), 7.67 (m, 1H, H^{16}), 7.93 (m, 2H, $H^{14,14'}$); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 21.71(Me^{11}), 23.46 (C^9H_2), 23.72 (C^6H_2), 27.83 (Me^{10}), 31.53 (C^5H), 35.35 (C^7H_2), 60.55 ($C^{12}H_2$), 71.02 (C^8), 82.35 (C^1H), 82.82 (C^4), 127.52 ($2C^{14}H$), 129.25 ($2C^{15}H$), 133.76 ($C^{16}H$), 141.13 (C^{13}).