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Synthesis and anti-malarial activity of yingzhaosu A analogues from unsaturated hydroperoxy acetals

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Abstract

Ozonolysis of a vinyl ether **2**, prepared from dihydrocarvone **1** (a 1:4 mixture of *cis*- and *trans*-isomer), in methanol gave two isomeric unsaturated hydroperoxy acetals *cis*- and *trans*-**3**. Iodonium ion- or ozone-mediated cyclizations of the hydroperoxide *cis*-**3** gave the corresponding yingzhaosu A analogues **4** and **6** in moderate yields. The peroxide **8**, obtained by the Ag_2O-mediated methylation of **6**, showed notable anti-malarial activity in vitro ($IC_{50}=1.0\times10^{-7}$ M).

Since malaria parasites are rapidly developing resistance to the most commonly used chemotherapeutic alkaloidal drugs, the anti-malarial properties of non-alkaloidal compounds such as artemisinin and the related endoperoxides have attracted considerable attention.[1,2] As part of our interest in the synthesis of novel peroxide anti-malarial analogues, we considered the possibility of the electrophile-mediated cyclization of unsaturated hydroperoxy acetals such as **3** as an attractive method of producing derivatives of yingzhaosu A (Scheme 1).

Selective monoozonolysis of the electron-rich vinyl ether group of the diene **2**, prepared from the commercially available dihydrocarvone **1** (a 1:4 mixture of *cis*- and *trans*-isomer) by the Horner–Emmons reaction, in methanol[3] gave two isomeric hydroperoxides *cis*-**3** (11%) and *trans*-**3** (49%), which could be separated by column chromatography on silica gel. The structures of two hydroperoxides determined by the HH, CH COSY and NOE measurements suggested that trapping of the carbonyl oxide intermediates by methanol occurs selectively from the direction *anti* to the methyl group (Scheme 1).

Reflecting the difference of the structures, two isomeric hydroperoxides, *cis*- and *trans*-**3**, react with bis(collidine)iodine(I) hexafluorophosphate (BCIH)[4] by different pathways (Schemes 1 and 2). Thus, the reaction of *cis*-**3** gave the iodomethyl-substituted 2,3-dioxabicyclo[3.3.1]nonane **4**[5] (a 5:2 mixture of two isomers; 26%) together with a complex mixture of unidentified oligomeric products. In contrast, the reaction of the isomeric *trans*-**3** under the same conditions resulted in the formation of

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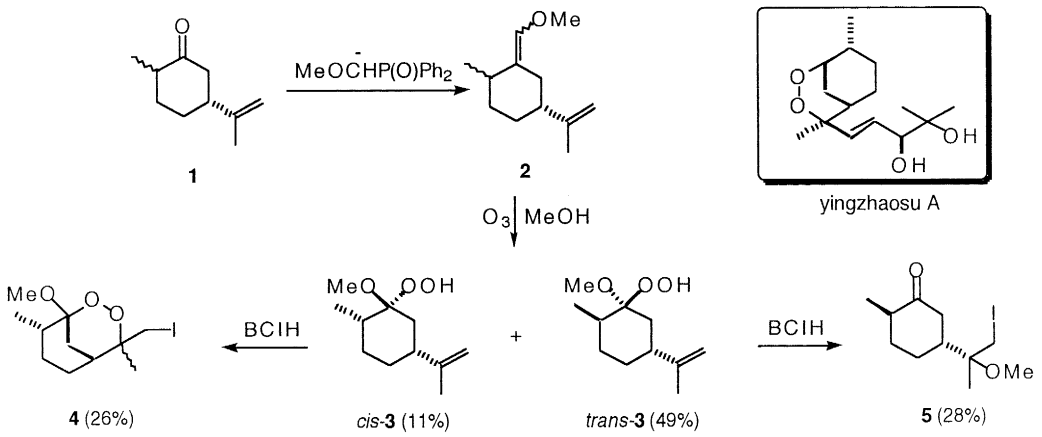
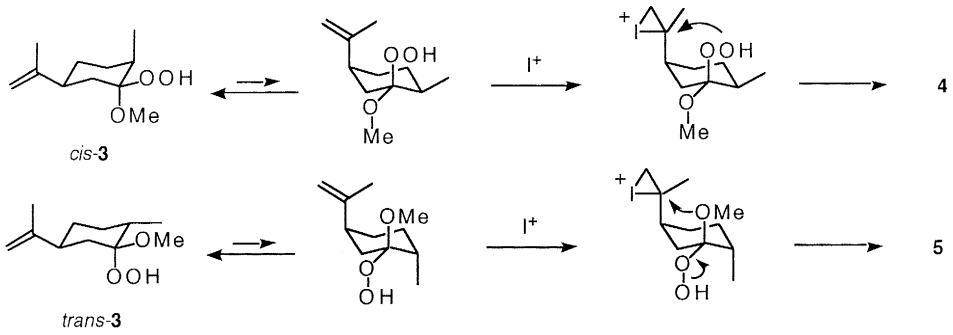


Scheme 1.

the ketone **5** derived from novel migration of the methoxy group (29%) (Scheme 2).[6] Consistent with the intramolecular migration of the methoxy group, the reaction of *trans*-**3** in the presence of 2 equiv. of CD_3OD provided the ketone **5** (23% yield), which did not contain any deuterium in the methoxy group.

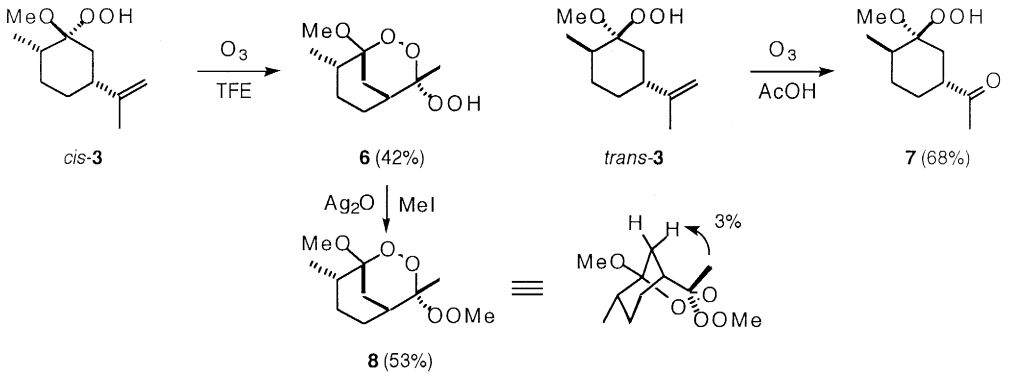


Scheme 2.

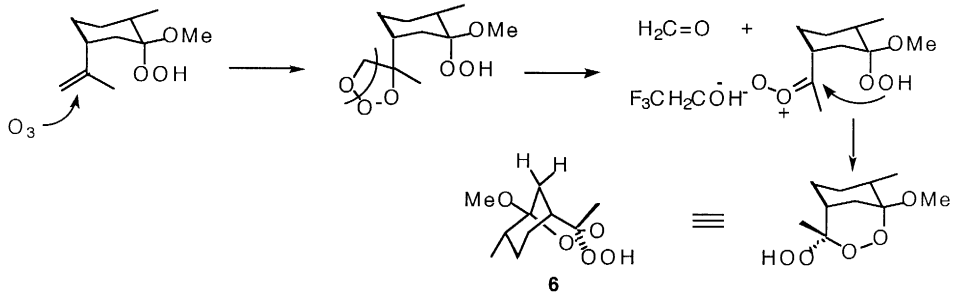
Treatment of *cis*-**3** with ozone in trifluoroethanol (TFE)-CH_2Cl_2[3] gave the expected hydroperoxy-substituted yingzhaosu A analogue **6** in 42% yield (a single isomer).[7] From the reaction of *trans*-**3** in AcOH–CH_2Cl_2, however, the ketone **7** was obtained in 68% yield (Scheme 3). Surprisingly, the reaction of *cis*-**3** in AcOH or the reaction of *trans*-**3** in TFE resulted in the formation of complex mixtures of products. The reason is obscure. Ag_2O-Promoted methylation of the hydroperoxide **6** with MeI proceeded well providing the corresponding methylated product **8** in 53% yield. PM3 calculations suggested that the 1,2-dioxane ring in **8** adopts a boat form. By the HH, CH COSY and NOE measurements, the methyldioxy group was determined to occupy the *endo* position.

Scheme 4 illustrates the mechanism of formation of the hydroperoxide **6**. TFE assists the cyclization of the carbonyl oxide intermediate; solvation of the carbonyl oxide moiety enhances the electrophilicity, thereby suppressing the [3+2] cycloaddition with the co-produced formaldehyde and facilitating the intramolecular capture by the hydroperoxy group.[3] In accordance with this, the reaction in aprotic solvents such as ether resulted in the formation of a complex mixture of unidentified products.

Ozonolysis of a diene **9** in methanol gave a 1:1 mixture of two unsaturated hydroperoxy acetals, *cis*- and *trans*-**10** (67% yield), which could not be separated by column chromatography on silica gel (Scheme 5). The reaction with BCIH gave the expected bicyclic peroxide **11** (a 3:2 mixture of two isomers; 52%

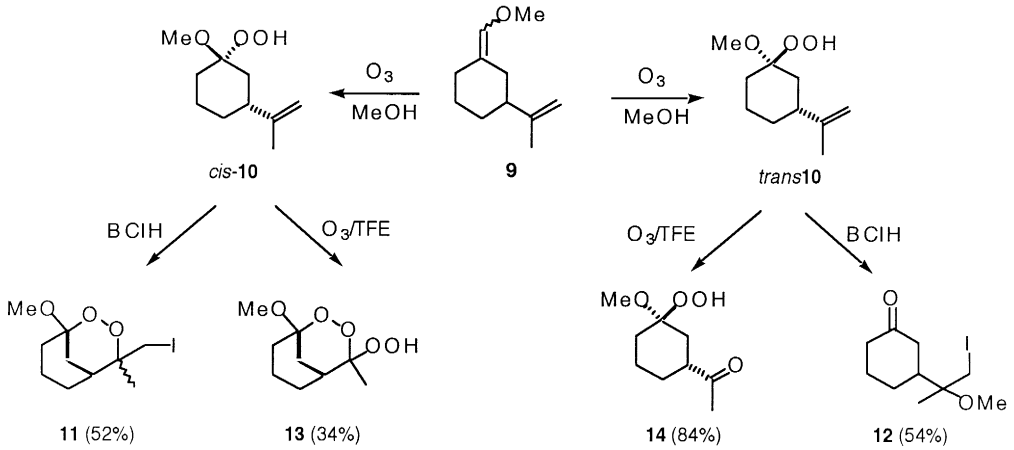


Scheme 3.



Scheme 4.

yield based on *cis*-**10**) together with a ketone **12** (84% based on *trans*-**10**). From the ozonolysis of **10** in TFE–CH_2Cl_2, the bicyclic peroxide **13** (34%; a single isomer) and a ketone **14** (84%) were obtained. The similar trend was observed for the ozonolysis in AcOH–CH_2Cl_2.



Scheme 5.

In a preliminary study of the anti-malarial activities of the derived cyclic peroxides against *P. falciparum*,[8] compound **8** provided IC_{50} value of 1.0×10^{-7} M which are approximately a tenth of the anti-malarial potency of artemisinin ($IC_{50}=7.8\times10^{-9}$ M). Moreover, the selectivity determined by the comparison with the 50% inhibitory concentration against mouse mammary FM3A cells (3.3×10^{-5} M)

was as high as 330, suggesting that this type of cyclic peroxides would be the promising candidate of anti-malarial drugs with low toxicity.

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5. 1-Methoxy-4-iodomethyl-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonane **4** (major isomer): mp 95–97°C (from 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)+3.65 (d, *J*=10.9 Hz) (2 H), 3.43 (s, 3H); ^{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 $C_{11}H_{19}IO_2$: C, 40.51; H, 5.87; I, 38.91. Found: C, 40.45; H, 5.77; I, 38.99.
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7. 1-Methoxy-4,8-dimethyl-2,3-dioxabicyclo[3.3.1]nonan-4-yl hydroperoxide **6**: mp 161–163°C (from ethyl acetate/hexane); ^{1}H 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. 1-Methoxy-4,8-dimethyl-4-(methyldioxy)-2,3-dioxabicyclo[3.3.1]nonane **8**: 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.
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