A Short Synthesis of 6,9-Desmethyldeoxoartemisinin and Its Isomer

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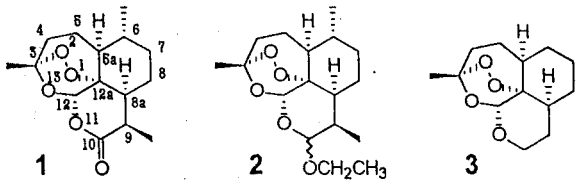
Received March 22, 1996

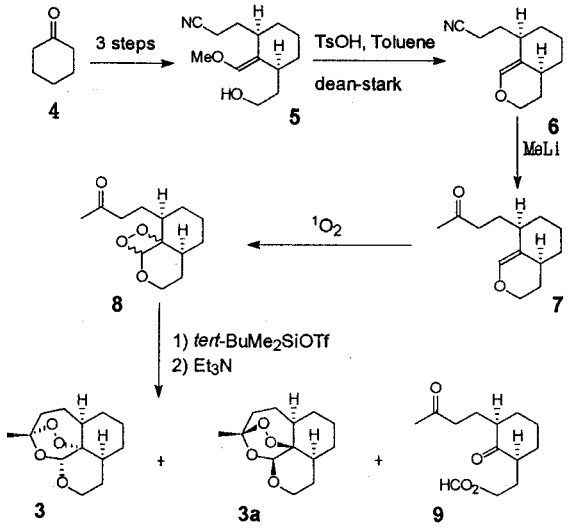
Artemisinin (**1**), isolated from the Chinese herbal medicine Qinghao (*Artemisia annua* L.) as a non-alkalodial endoperoxide natural product, has been clinically used for treatment of malaria worldwide.[1] The outstanding antimalarial activities, the novel structure, and low natural supply of artemisinin (Quinghaosu) have prompted extensive synthetic efforts for artemisinin and its analogs and model studies aimed at securing routes to the biologically crucial 1,2,4-trioxanes.[2] The complete synthesis of artemesinin has been achieved by several groups after Schmid and coworkers reported the first total synthesis starting from (-)-isopulegol in 13 steps.[3] Given the synthesis of artemisinin and its semi-synthetic derivatives, recent efforts have been focused on the synthesis of structurally simple 1,2,4-trioxanes.[4] Structure activity analysis reveals that the minimum requirements for a synthetic peroxide are the 1,2,4-trioxane ring and a second ring. Several synthetic trioxanes, synthesized by some of us, were shown to be as active as arteether (2) against multi-drug resistant *Plasmodium falciparum* in Aotus monkeys.[5]



1 **2** **3**

Many attempts have been made to photooxygenate a cyclic enol ether, but only one successful synthesis was reported from naturally occurring artemisinic acid as a starting material.[6] With structurally similar substrates, the Jung and the Wallace groups reported their unsuccessful results.[7] In connection with our interest in developing new potent antimalarial 1,2,4-trioxanes, we have studied the photooxygenation of a enol ether using our methodology and now report a short synthesis of a tetracyclic trioxane **3** structurally similar to artemisinin (**1**). Our attention has been devoted to the photooxygenation of the cyclic enol ether **7** which is easily prepared and also easily derivatized into other interesting compounds. Scheme 1 outlines our synthesis.

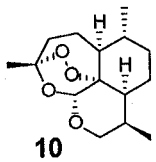
The compound **5** was stereoselectively prepared from cyclohexanone (**4**) in three steps, bis-alkylation, Wittig reaction, and reduction, according to the previously reported procedure.[5] The compound **5** was refluxed in toluene in the presence of catalytic amount of *p*-toluenesulfonic acid to form the cyclic enol ether, compound **6**, in 90% yield. Addition of methylithium to the compound **6** was performed in ether to form the corresponding methyl ketone, compound **7**. The transformation of the compound **7** to the corresponding trioxane **3** was the key step of this study as noted above. The photooxygenation of the cyclic enol ether **7** was quite slow at −78 ℃, but occurred completely at elevated temperature (−40 ℃) presumably to form the corresponding 1,2-dioxetane **8** as a non-isolable intermediate.[8] The final solution was treated quickly with *tert*-butyldimethylsilyl triflate at −78 ℃, stirred for 5 h, and treated with triethylamine to form three major products. Silica gel chromatography followed by HPLC separation provided a dioxetane-cleavage product (**9**), two pure isomeric trioxanes (**3** and **3a**) in 35, 15 and 3% yields, respectively.[9] ^{1}H NMR spectra of the two trioxanes were very similar except for the acetal H (H^{12}) region.



Scheme 1.

The structural assignment of each trioxane has been deduced based on the literature spectroscopic data and the mechanism for the formation of 1,2,4-trioxane from the corresponding 1,2-dioxetane.[10] The proton NMR spectrum for deoxoartemisinin (**10**) obtained from the reduction of artemisinin (**1**) showed a signal at 5.20 ppm for the acetal hydrogen.[11] The major isomer **3** showing a singlet peak at 5.19 ppm for the H^{12} has been assigned to have the α-oriented peroxide linkage as the same configuration of natural artemisinin. On the other hand, the other isomer **3a** also showed a singlet peak at 4.79 ppm for the acetal hydrogen; the dramatic shift and the singlet peak for this acetal hydrogen do indicate that the compound has the β-oriented peroxide and the β-oriented ether linkage. Note that other structurally similar 1,2,4-trioxanes having an α-oriented peroxide and a β-oriented ether linkage such as compound **11** have doublets (J=1 to 2 Hz) of H^{12} for acetal hydrogens through the long-range W-type coupling with H^{5a}.[5a,12] These assignments were consistent with the mechanism for the formation of 1,2,4-trioxane.

Although this photooxygenation of the cyclic enol ether **7**, has not been optimized yet, this synthesis has several important features. First, the 1,2,4-trioxanes **3** and **3a** have been synthesized in only 6 steps starting from commercially cheap cyclohexanone. Second, the trioxane **3** is a promising



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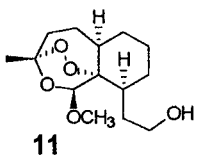

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antimalarial candidate because structurally similar deoxoartemisinin has been shown to be more active than artemisinin both *in vitro* (8 times) and *in vivo*.[11] Third, since the cyclic enol ether **7** can be easily prepared and derivatized, other useful derivatives such as C-4 methylated trioxane are accessible by one additional step. These trioxanes, combined with their antimalarial activities, will be reported in a full paper when ready.

Acknowledgment. This paper was supported by NON DIRECTED RESEARCH FUND (04D0209), Korea Research Foundation.

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9. All synthesized compounds have the following spectroscopic data. Compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (s, 1H), 3.88 (m, 1H), 3.79 (m, 1H), 2.52-2.36 (m, 2H), 2.05-1.90 (m, 4H), 1.85-1.78 (m, 2H), 1.60-1.51 (m, 3H), 1.44 (m, 1H), 1.15 (m, 1H), 0.93 (m, 1H). Compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (s, 1H), 3.87 (m, 1H), 3.78 (m, 1H), 2.58-2.42 (m, 2H), 2.15 (s, 3H), 2.04-1.91 (m, 2H), 1.88-1.72 (m, 5H), 1.59-1.32 (m, 3H), 1.16-1.05 (m, 1H), 0.96-0.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.99, 136.18, 120.00, 63.78, 41.58, 39.39, 35.11, 34.03, 33.18, 30.65, 29.93, 25.93, 25.11. Trioxane **3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (s, 1H), 3.96 (m, 1H), 3.75 (m, 1H), 2.49-2.34 (m, 2H), 2.01 (m, 1H), 1.85-1.52 (m, 8H), 1.44 (s, 3H), 1.41-1.28 (m, 1H), 1.2 (m, 1H), 1.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.04, 91.94, 79.93, 61.26, 46.10, 39.29, 36.41, 32.57, 28.35, 26.96, 26.67, 26.33, 25.00; FT-IR (neat, cm^{-1}) 3013, 2933, 2865, 1453, 1436, 1378, 1088, 1044; Anal calcd for $C_{13}H_{20}O_4$: C, 64.98. H, 8.39. Found: C, 65.04; H, 8.45. Trioxane **3a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.79 (s, 1H), 4.14 (m, 1H), 3.54 (m, 1H), 2.42 (td, J=14.0, 4.0 Hz, 1H), 2.11 (m, 1H), 1.98-1.81 (m, 3H), 1.75-1.67 (m, 2H), 1.45 (s, 3H), 1.42-1.1.29 (m, 5H), 1.26-1.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.30, 97.13, 77.84, 65.65, 43.74, 41.39, 35.14, 28.25, 27.17, 26.40, 26.19, 25.85, 25.21; FT-IR (CHCl3, cm^{-1}) 2978, 2866, 1111, 1076, 1065, 1044, 1016.
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Photopolymerization of Acrylic Acids Initiated by CCl_4/Group VIII Metallocene

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Received March 30, 1996

Photopolymerization technology applicable conveniently is extensively employed this day on a commercial scale in the areas of surface coatings, photoresists, adhesives, and holography.[1] Organometallic photochemistry has drawn a great deal of attention because irradiation of organometallic compounds can lead to catalytically and synthetically useful transformations.[2] In particular, a historically important class of cyclopentadienyl complexes has been plentifully prepared and their photochemical properties have been intensively investigated.[3] Many halogenated organic compounds have been used as effective initiators for the photopolymerization of many vinyl derivatives.[4] Practical problems with halogenated photoinitiators are the corrosion of reactor system and some side reactions caused by acid hydrogen halides which are produced as byproducts during the photopolymerization. The use of ferrocene (Cp_2Fe) as a photopolymerization promotor (to activate the halogenated photoinitiator) and as a halide-radical trap (to prevent the troublesome acid formation) in