Preparation of a Bicyclic Analogue of Qinghao (Artemisinic) Acid via a Lewis Acid Catalyzed Ionic Diels–Alder Reaction Involving a Hydroxy Diene and Cyclic Enone and Facile Conversion into (±)-6,9-Desdimethylqinghaosu

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Treatment of 6-methylcyclohex-2-enone (**8**) and hexa-3,5-dien-1-ol (**14**) either in dichloromethane at −20 to 0 °C with aluminum chloride (1 equiv) or in acetonitrile at −20 °C with Cu(II) trifluoromethanesulfonate (1 equiv) rapidly provides in a highly stereoselective reaction the hemiacetal Diels–Alder adduct **15**, which with a trans ring junction and anti methyl group is considered to arise via an ionic Gassman-type Diels–Alder reaction involving prior formation of a hemiacetal between the alcohol and enone followed by generation of an allylic cation from the hemiacetal mediated by the Lewis acid. The adduct **15** is then converted in straightforward fashion into the methyl ester of the desdimethyl analogue of qinghao (artemisinic) acid, which upon sequential photosensitized oxygenation and then $Fe(phen)_3(PF_6)_3$/copper(II) triflate catalyzed cleavage–oxygenation provides (±)-6,9-desdimethylqinghaosu.

Introduction

The celebrated qinghao (*Artemisia annua*) has been used in traditional Chinese medicine for the treatment of fever since ancient times.[1] In 1972 a highly active antimalarial compound was isolated from the plant by Chinese chemists.[2] The compound, qinghaosu or artemisinin (**1**, QHS), incorporates a peroxyacetal linked to a lactone; the peroxide is critical for expression of antimalarial activity.[3] QHS and its derivatives are now used in Asia for treatment of chloroquine-resistant falciparum malaria.[4] Because of low availability in the plant (0.01–0.6%), and the need to prepare QHS derivatives which have longer pharmacological half-lives and which are suitable for structure–activity studies, the development of semisynthetic and totally synthetic approaches to QHS and the derivatives is under vigorous examination. Our initial contribution was to develop a procedure[5] for the conversion of dihydroqinghao acid (**3**), readily obtained[6] from the relatively abundant biochemical precursor of QHS, qinghao (artemisinic) acid (**2**, QHA), into QHS. The hydroperoxide **4**, obtained by photooxygenation of **3**, is treated with catalytic copper(II) triflate in CH_3CN–CH_2Cl_2 under an oxygen atmosphere. This transformation embodies a novel cleavage–oxygenation process to provide **1** via an equilibrium mixture of the hydroperoxy ketoaldehyde **5** and peroxyhemiacetal **6**. An effective, closely related approach has been described by Roth and Acton.[7] Through utilization of the abundant quantities of QHA which occur with QHS in *A. annua*, these semisyntheses augment the supply of QHS from this source. While a number of total syntheses of QHS have been reported,[6,8–11] the synthesis described by Avery and co-workers[9] appears best suited for preparation of analogues. In extensive and elegant synthetic studies, his group has prepared a large number of derivatives, and the work provides a basis for development of optimal QHS derivatives.[12,13] In our case, we have semisynthesized QHS derivatives through structural modification of QHA followed by submission of the modified acid to our oxygenation process.[14] This protocol has also been used in conjunction with the Roth–Acton oxygenation.[15] Thus, straightforward total syntheses of QHS and derivatives would be attained through synthesis of dihydroqinghao acid **2** itself or of structurally-modified acids. This approach was recently used by Liu and co-workers, who prepared an unnatural trans-fused

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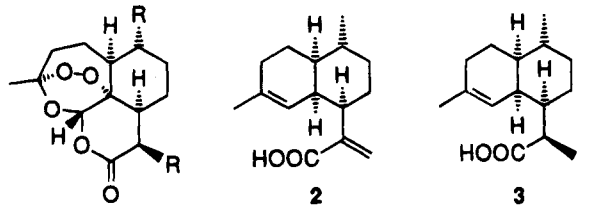
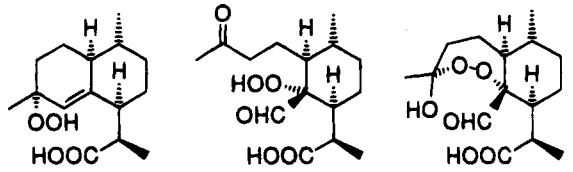
Chart 1



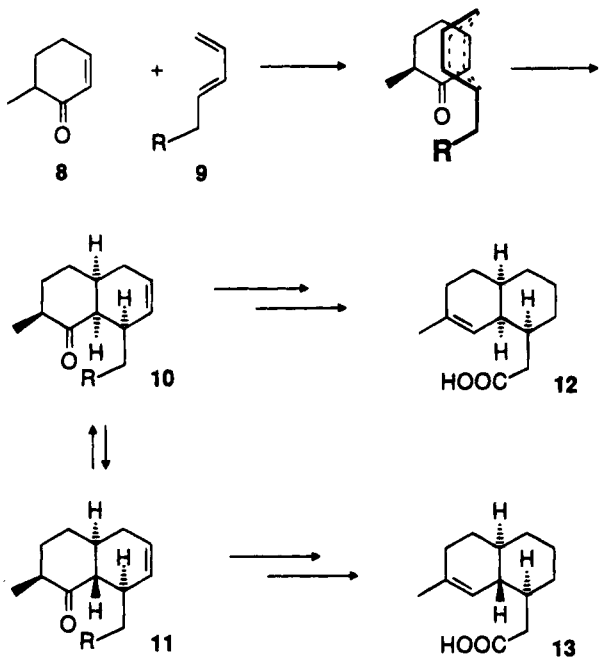
1: R = Me
7: R = H

2 3



4 5 6

Scheme 1

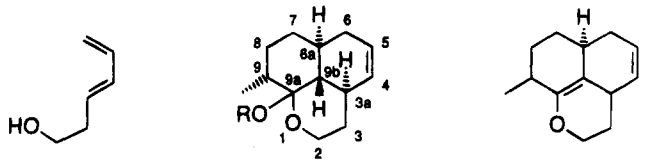


8 9 10 11 12 13

derivative of dihydroqinghao acid methyl ester and converted it into QHS by the Roth–Acton method.[11] We now describe a straightforward preparation of racemic 6,9-desdimethyl-QHS (**7**) which proceeds via the corresponding acid derivative. Racemic **7** has been prepared previously.[12]

Preparation of desdimethyldihydroqinghao acid (**12**) logically starts through Diels–Alder (DA) reaction of 6-methylcyclohex-2-enone (**8**) with a six-carbon diene such as 3,5-hexadienoic acid (**9**, R = COOH) (Scheme 1). While under thermal conditions, cyclic enones are poor dienophiles, Lewis acid-catalyzed DA reactions are efficient, and the primary cis-fused cycloadducts may be isolated in many cases from reactions catalyzed by $AlCl_3$.[16,17] Catalyzed addition of 1-alkyl 1,3-dienes to 6-methylcyclohexenone provides the syn 1-adduct.[16] Thus,

Chart 2



14 15: R = H 17

16: R = 3,5-hexadienyl

through employment of the (3*E*)-3,5-hexadienoic acid, the correct stereochemical and regiochemical relationship (*cf.* **3**) between the side chain and the ring junction would be assured for a reaction proceeding through an endo transition state. Stereochemistry at the methyl group in the adduct is inconsequential. Interconversion of the primary cis-adduct **10** into the trans-adduct **11** is not a problem, as configuration at the ring junction in the trans-acid **13** derived from **11** is not crucial to the outcome of the synthesis. This is discussed further below.

Results and Discussion

(*E*)-Hexa-3,5-dienoic acid, its methyl ester, and (*E*)-hexa-3,5-dien-1-ol (**14**) failed to react with enone **8** under most thermal or acid-catalyzed conditions, including high pressure, reported to provide adducts in optimum yields.[16–18] However, the dienol **14** in the presence of $AlCl_3$ (1 equiv) in CH_2Cl_2 at −20 to 0 °C, with **8** at a 9–10 mmol scale during 2 h, provided the trans hemiacetal adduct **15** in an isolated, purified yield of 30% and compounds identified on the basis of spectroscopic data as acetal **16** (6%) and enol diene **17** (6%). Products **15** (42%) and variable amounts of **16** (to 8%) were also obtained with copper(II) triflate (1 equiv) in MeCN in 2 h at −20 °C. In general, competing polymerization of the dienol **14** usually took place in the reaction mixtures. Crystalline **15** contained *ca.* 2% and compound **16** contained *ca.* 20% of the epimeric hemiacetal and acetal, respectively. **17** was a 1:1 mixture of diastereomers. Other products, both less and more polar than the foregoing, were also formed and have yet to be identified.

The ^1H NMR proton assignments of **15** were made by DQF 2D COSY at 600 MHz, and in conjunction with NOE experiments (supplementary material), the relative configuration of the product was thereby determined. No enhancement between H9b and each of H3a and H6a was observed. Strong enhancement of 9-CH_3 is observed upon preirradiation of H9b; this delineates the cis relationship of these protons. H9b appears as a dd, with $^4J_{9b,6a} = {}^4J_{9b,3a} = 11.5$ Hz, which indicates a trans relationship between H9b and each of H6a and H3a. Lack of IR carbonyl stretching absorptions, and a signal due to a quaternary C at 96.7 ppm in the ^{13}C NMR spectrum, pinpoints the acetal carbon 9a, although its configuration could not be established.

While formation of **15** may conceivably proceed via the primary "open" cis-adduct followed by Lewis acid-catalyzed epimerization and hemiacetal formation, other cases in which epimerization of primary adducts takes

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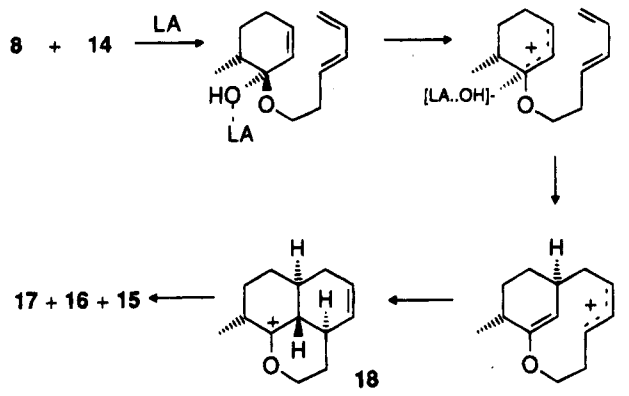
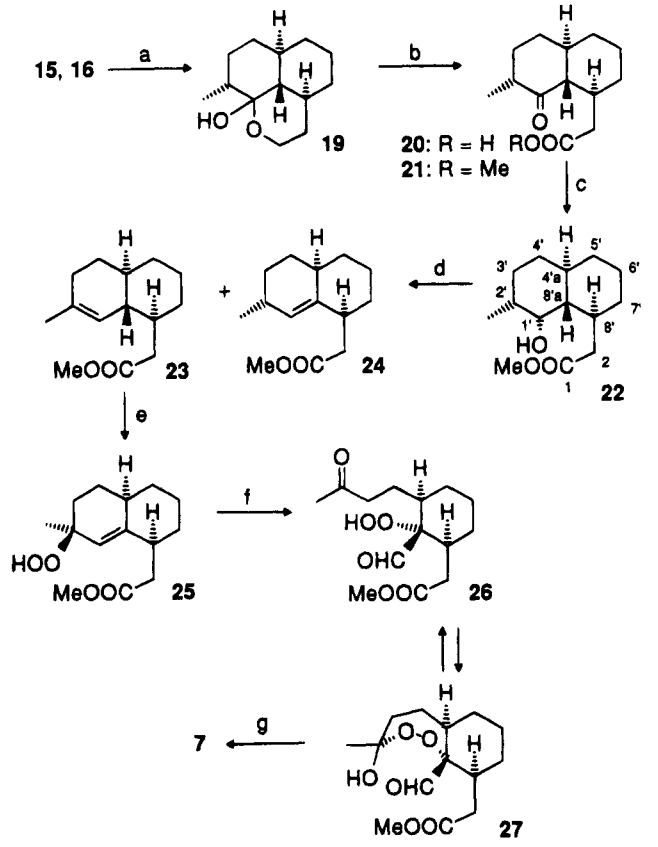
Scheme 2



Scheme 3[a]



[a] Key: (a) H_2, Pd/C, EtOAc, 99%; (b) (i) H_2CrO_4, acetone, 58%; (ii) CH_2N_2, ether, 93% (to **21**); (c) $NaBH_4$, MeOH, N_2, 96%; (d) $POCl_3$, pyridine, 86% (**23**:**24** = 5:2); (e) Rose Bengal, MeOH, O_2, $h\nu$ (tungsten lamp, 500 W); (f) $Fe(phen)_3(PF_6)_3$ (0.02 equiv) then $Cu(OTf)_2$ (0.10 equiv), MeCN, O_2, −30 °C; (g) *p*-TsOH (0.20 equiv), CH_2Cl_2, 34% from **23**.

place usually provide mixtures which do not necessarily favor the trans isomer.[16] The mildness of the conditions, especially those in the copper triflate catalyzed reaction, are noteworthy, and contrast with those required for Lewis acid catalyzed DA reactions of 2-cyclohexenones.[16,17] The anti relationship between the 9-methyl and the "side chain" attached to C3 is also contrary to that in products of the normal reaction, as outlined above.[16,17] It thus appears likely that the reaction proceeds via *prior* formation of a hemiacetal in which the incoming alcohol adds on the carbonyl face away from the enone methyl. While such tethering provides the necessary stereochemical bias for the DA reaction, it also deactivates the dienophile and it is unlikely that under the reaction conditions a normal DA reaction would take place.[19,20] However, formation of an allyl cation–ion pair in the presence of the Lewis acid then enables cation-mediated ring closure to occur (Scheme 2), a process classified as an ionic DA reaction and one which proceeds rapidly at low temperature.[21,22] Thus, we appear to have here a new variation of the Gassman ionic DA reaction which involves *in situ* formation of the precursor of the allylic cation.

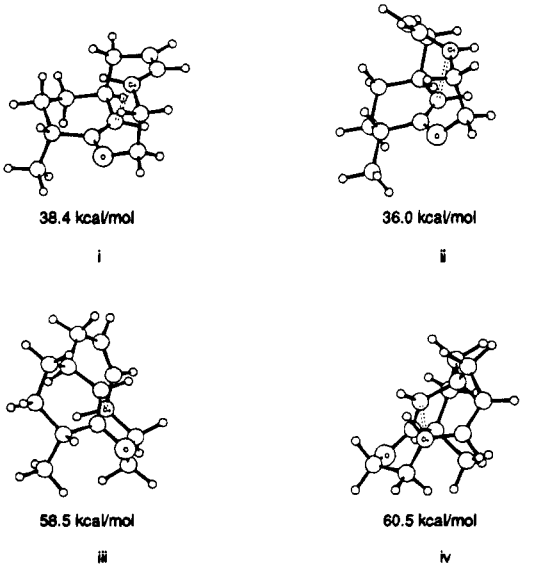
Hydrogenation of each of **15** and **16** over Pd/C in EtOAc provided saturated hemiacetal **19** (Scheme 3), which with Jones' reagent in acetone at room temperature gave keto acid **20** (58%). The acid was converted into ester **21** and then reduced stereoselectively with $NaBH_4$ to provide the hydroxy ester **22** (96%). The ^1H NMR proton assignments in **22** were made by DQF 2D COSY at 600 MHz. With H8a appearing as a ddd, with $^4J_{8'a,1'} = 2.1$ Hz, and $^4J_{8'a,4'a} = {}^4J_{8'a,8'} = 10.9$ Hz, the stereochemical relationship of the ring junction with the newly-introduced stereogenic

(19) Examples of successful tethered DA reactions require an active dienophile—usually an acrylate derivative—and reaction conditions far more vigorous than those described here: Narasaka, K.; Shimada, S.; Osoda, K.; Iwasawa, N. *Synthesis* **1991**, 1171. Gillard, J. W.; Fortin, R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R. *Tetrahedron Lett.* **1991**, *32*, 1145. Shea, K. J.; Zandi, K. S.; Staab, A. J.; Carr, R. *Tetrahedron Lett.* **1990**, *31*, 5885.

(20) The single case in which hemiacetal formation is likely to precede the DA reaction involves a hydroxy diene reacting with a quinonoid dienophile generated *in situ*; in this case, an activated enone component remains after hemiacetal formation: Fleck, A. E.; Hobart, J. A.; Morrow, G. W. *Synth. Commun.* **1992**, 179.

(21) In this case, closure provides the trans-fused product directly; such products appear characteristic of ionic DA reactions providing 6,5- and 6,6-fused ring systems: Gassman, P. G.; Gorman, D. B. *J. Am. Chem. Soc.* **1990**, *112*, 8623. Gassman, P. G.; Gorman, D. B. *J. Am. Chem. Soc.* **1990**, *112*, 8624 and previous papers.

(22) Although a stepwise process, the ionic DA reaction must involve addition of the diene in an s-cis conformation to the incipient cation to provide the 10-membered cation precursor to **18**, whose configuration will be as depicted in Scheme 2. Preliminary modeling studies (MMX, PCMODEL 4.0, Serena Software) indicate that the most important minimum energy conformations are i, ii, iii, and iv leading to cis-trans, cis-cis, trans-trans, and trans-cis ring fusions, respectively. While iii would give rise to the observed product **18**, calculations indicate that approach of the allylic cation from above the plane of the enol ether, as in i and ii, is energetically more favored than approach from below. However, although iii and iv are similar in energy, the energy increase in bringing the reacting centers together is much greater in iv; while iii experiences essentially no nonbonded interactions there are several eclipsing interactions in iv. Despite an apparent preference for products derived from i and ii an electrostatic effect involving the counterion produced during formation of the incipient cation may favor closure from iii. The situation is intriguing and requires further work to clarify both the overall mechanism and the finer stereochemical details.



center at C-1′ is clearly defined. Dehydration of **22** with $POCl_3$–pyridine gave the trans-analogue **23** of desmethyldihydroqinghao acid methyl ester as an inseparable 5:2 mixture with its allylic regioisomer **24** (86%). Attempts to improve the regioselectivity of this reaction under a wide variety of conditions failed.

It remained to convert the methyl ester **23** into desdimethyldihydroqinghao acid (**7**). In all previous cases, we have photooxygenated QHA derivatives with the natural cis ring junction.[5,14] With a trans ring junction, photooxygenation of **23** will involve abstraction of the allylic proton which projects from the β-face to give the hydroperoxide **25** with configuration opposite to that (**4**) derived from DQHA **3**. However, the configuration of the hydroperoxide will be lost in the ensuing cleavage–oxygenation, in which addition of dioxygen should be directed through the α-face by the flanking β-configured side chains.[23] While the photooxidation of **3** is normally carried out with Rose Bengal in MeCN to optimize formation of the tertiary hydroperoxide **4**, in the present case MeOH was a superior solvent for conversion of **23** into **25**; use of MeCN led to the formation of considerable amounts of secondary hydroperoxides. The allylic regioisomer **24** did not react under these conditions. Hydroperoxide **25** in MeCN was treated initially with $Fe(phen)_3(PF)_6$ (0.02 equiv) followed immediately with $Cu(OTf)_2$ (0.10 equiv) at −20 °C under O_2. After 2 h, the crude products, an equilibrium mixture of the hydroperoxy ketoaldehyde **26** and peroxyhemiacetal **27**, were treated with TsOH in dichloromethane to give desdimethyldihydroqinghao acid (**7**) in an overall yield of 34% from **23**, which is comparable to that obtained for the conversion of dihydroqinghao acid **3** into QHS **1**.[5]

When a free carboxylic acid functionality is present in the hydroperoxide substrate, efficient cleavage–oxygenation proceeds in the presence of $Cu(OTf)_2$ alone. In the present case, the Fe(III) catalyst must be used in conjunction with the Cu(II) species to enhance oxygenation. In the absence of the Fe(III) species, yields of the oxygenation products are somewhat depressed. However, use of the Fe(III) catalyst alone results in exclusive cleavage. This is consistent with earlier studies on the conversion of QHA methyl ester into QHS **1** and underscores the electron-transfer character of the processes leading up to oxygenation.[5,24]

The highly stereoselective outcome of the DA reaction is noteworthy, and, apart from providing a very straightforward route to a QHS derivative which is an active antimalarial, it clearly has the potential to provide new, highly effective stereoselective routes to a number of polycyclic natural products including qinghaosu and its derivatives. We are currently examining the scope of the DA reaction.

Experimental Section

Organic extracts were dried over anhydrous sodium sulfate. Flash chromatography was carried out on Merck silica gel 60. IR spectra were recorded in $CHCl_3$ solution. ^1H NMR spectra were recorded at 200 MHz unless otherwise stated, and all ^{13}C NMR spectra were recorded at 50 MHz. All NMR samples were in $CDCl_3$ solution. 6-Methylcyclohex-2-enone (**8**) was prepared from 2-methylcyclohexanone by trapping the kinetic enolate with TMSCl,[25] brominating the resultant silyl enol ether with NBS,[26] and then dehydrobrominating over MgO.[27] (*E*)-3,5-Hexadien-1-ol (**14**)[28] was prepared by deconjugating sorbic acid[29] and reducing the resultant dienyl acid with $LiAlH_4$.

Diels–Alder Reaction. i. 6-Methylcyclohex-2-enone (**8**) (1.00 g, 9.09 mmol) was added dropwise to a stirred suspension of $AlCl_3$ (1.21 g, 9.09 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 10 °C under nitrogen. After being stirred at room temperature for 15 min the solution became yellow in color. The mixture was cooled to −20 °C, and a solution of (*E*)-3,5-hexadien-1-ol (**9**) (1.34 g, 13.6 mmol, 1.5 equiv) in CH_2Cl_2 (2 mL) was added dropwise. Stirring was continued at 0 °C for 2 h, during which time the solution became deep red in color. The reaction mixture was poured onto saturated NH_4Cl solution (100 mL), and the products were extracted into ether (3 × 40 mL). The combined ether extracts were washed with water (2 × 150 mL) and brine (2 × 100 mL) and dried. Removal of solvent under reduced pressure left a brown oil which was submitted to flash chromatography with 1:19 ethyl acetate–petroleum ether. The major product was a colorless oil which crystallized under high vacuum. The solid was washed with cold petroleum ether to give (3a*RS*,6a*SR*,9*RS*,9a*SR*,9b*RS*)-9a-hydroxy-9-methyl-2,3,3a,6,6a,7,8,9,9a,9b-decahydro-1-oxa-1*H*-phenalene (**15**) (567 mg, 30%) as colorless needles, mp 73–74 °C, containing a trace of another diastereomer (<2%) as detected by ^1H NMR spectroscopic analysis at 600 MHz: IR 3474 br w, 3010 m, 2926 vs, 2850 m, 1702 w, 1453 w, 1393 w, 1317 w, 1267 w, 1236 w, 1168 w, 1146 m, 1114 m, 1090 w, 1069 s, 1047 m, 935 m, 918 m, 882 w, 681 m cm^{-1}; ^1H NMR (600 MHz) δ 0.91 (d, J = 6.7 Hz, 3H), 1.02 (dddd, J = 4.1, 10.8, 13.3, 13.3 Hz, 1H), 1.08 (dd, J = 11.5, 11.5 Hz, 1H), 1.39 (dddd, J = 3.8, 13.2, 13.2, 13.2 Hz, 1H), 1.42 (dddd, J = 4.9, 12.7, 12.7, 12.7 Hz, 1H), 1.52 (dddd, J = 3.9, 3.9, 3.9, 13.4 Hz, 1H), 1.62–1.72 (m, 3H), 1.77 (dddd, J = 3.9, 3.9, 3.9, 13.4 Hz, 1H), 1.81 (s, 1H), 2.14–2.20 (m, 2H), 2.45–2.51 (m, 1H), 3.71 (ddd, J = 1.2, 5.0, 11.3 Hz, 1H), 4.04 (ddd, J = 2.8, 11.3, 13.1 Hz, 1H), 5.46 (dddd, 1H, J = 2.1, 2.1, 2.1, 10.0 Hz, 1H), 5.57 (dddd, J = 2.4, 2.4, 4.8, 9.9 Hz, 1H); ^{13}C NMR δ 12.8, 30.7, 31.3, 32.1, 33.1, 33.3, 33.5, 40.6, 50.6, 61.4, 96.7, 125.8, 130.7; MS *m/z* 208 (M, 11), 190 (52), 163 (16), 151 (100), 133 (22), 123 (19), 105 (33), 91 (42), 79 (50), 67 (12), 55 (20), 41 (41), 28 (54). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.00; H, 9.65.

A less polar acetal identified as (3a*RS*,6a*SR*,9*RS*,9a*SR*,9b*RS*)-9a-[(*E*)-3′,5′-hexadienyloxy]-9-methyl-2,3,3a,6,6a,7,8,9,9a,9b-decahydro-1-oxa-1*H*-phenalene (**16**) (157 mg, 6%) was isolated as a colorless oil: IR 3013 m, 2961 s, 2926 vs, 2871 s, 1649 w, 1602 w, 1452 w, 1377 w, 1262 m, 1234 w, 1170 m, 1146 s, 1104 s, 1080 s, 1045 s, 1000 s, 986 m, 931 w cm^{-1}; ^1H NMR δ 1.00 (d, J = 7.1 Hz, 3H), 1.1–1.4 (m, 3H), 1.4–1.9 (m, 6H), 2.0–2.2 (m, 2H), 2.36 (dt, 2H, J = 6.8, 6.8 Hz, 2H), 2.4–2.6 (m, 1H), 3.40 (t, J = 6.8 Hz, 2H), 3.6–3.8 (m, 2H), 4.9–5.2 (m, 2H), 5.4 (d, J = 10.2 Hz, 1H), 5.5–5.6 (m, 1H), 5.8 (dt, J = 7.1, 15.1 Hz, 1H), 6.1–6.5 (m, 2H); ^{13}C NMR δ 13.6, 27.4, 27.7, 30.8, 31.8, 31.9, 32.9, 33.3, 33.5, 44.5, 57.6, 61.6, 100.0, 115.2, 125.7, 130.5, 131.4, 132.0, 132.5, 137.2; MS *m/z* 288 (M, 2), 231 (8), 191 (100), 175 (8), 151 (41), 133 (14), 119 (10), 105 (22), 91 (28), 81 (60), 67 (16), 55 (20), 41 (31), 28 (16); HRMS *m/z* calcd for $C_{19}H_{28}O_2$ M^+ 288.2089, found M^+ 288.1469.

In addition, a 1:1 mixture of dienol ethers tentatively identified as (3a*RS*)- and (3a*SR*,6a*SR*,9*RS*)-9-methyl-2,3,3a,6,6a,7,8,9-octahydro-1-oxa-1*H*-phenalene (**17**) (104 mg, 6%) was

(23) The recent preparation of QHS from a *trans*-dihydroqinghao acid derivative by Liu and co-workers (ref 11) bears this out, although no rationalization is given for the successful outcome of their oxygenation cleavage. It would seem that the original synthetic plan called for formation of the cis-fused acid but that isomerization in the transformation in ref 11 of intermediate **6** into **7** could not be avoided.

(24) Our original proposals for the cleavage-oxygenation process (ref 5) have been subject to criticism based on an extrapolation of aqueous Fenton-type chemistry to the aprotic cases: Courtneidge, J. L., *J. Chem. Soc., Chem. Commun.* **1992**, 381. Results already published prior to the appearance of the Courtneidge paper are sufficient to discount the criticism: see ref 5 and: Haynes, R. K.; Vonwiller, S. C. *J. Chem. Soc., Chem. Commun.* **1990**, 1102.

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isolated as a colorless oil: ^{1}H NMR (signals due to individual diastereomers are denoted a and b) 1.05 (d, J = 6.7 Hz, 3Ha), 1.11 (d, J = 6.9 Hz, 3Hb), 1.2–1.9 (m, 5H), 1.9–2.1 (m, 3H), 2.1–2.4 (m, 2H), 2.8–3.0 (m, 1Ha), 3.81 (ddd, J = 2.1, 10.5, 10.5 Hz, 1Ha), 3.82 (ddd, J = 1.5, 10.5, 10.5 Hz, 1Hb), 4.13 (dd, J = 2.8, 10.5 Hz, 1H), 5.5–5.6 (m, 1H, H4), 5.6–5.7 (m, 1H, H5); ^{13}C NMR 18.1 (a), 18.6 (b), 23.9, 26.2, 27.0, 28.8, 30.6, 30.7, 31.3, 31.7, 32.1, 32.4, 33.1, 33.2, 33.4, 33.6, 65.1 (a), 65.2 (b), 107.2 (a), 107.5 (b), 126.7, 129.9, 149.1 (a), 149.6 (b).

ii. A solution of the enone **8** (168 mg, 1.75 mmol) and dienol **14** (189 mg, 1.1 equiv, 1.93 mmol) in MeCN (10 mL) under argon was treated with a solution of copper(II) triflate (635 mg, 1.0 equiv, 1.75 mmol) in MeCN (1 mL) at −20 °C. The mixture was stirred at this temperature for 2 h and then poured into saturated aqueous NH_4Cl (100 mL). The products were extracted into ether (3 × 40 mL), and the combined ether extracts were washed with water (2 × 100 mL) and dried. Removal of solvent under reduced pressure left a brown oil, which after flash chromatography and crystallization according to the foregoing conditions provided the adduct **15** (141 mg, 42%).

Hydrogenation of 15. A solution of **15** (709 mg, 3.41 mmol) in EtOAc (20 mL) containing Pd/C (10%, 30.0 mg) was submitted to hydrogenation at room temperature and atmospheric pressure for 3 h. The catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure. The resultant colorless oil was submitted to flash chromatography with 1:14 ethyl acetate–petroleum ether to give (3a*RS*,6a*SR*,9*SR*,9a*RS*,9b*SR*)-9a-hydroxy-9-methyldodecahydro-1-oxa-1*H*-phenalene (**19**) (711 mg, 99%) as a colorless glass with mp 55–56 °C: IR 3482 br w, 2919 vs, 2845 s, 1456 m, 1388 m, 1324 m, 1288 w, 1255 w, 1204 m, 1177 m, 1140 m, 1114 m, 1071 m, 1056 s, 988 m, 924 m, 911 w, 868 w, 830 w, 779 w cm^{-1}; ^{1}H NMR δ 0.8–1.1 (m, 0.88, 4H; d, J = 6.6 Hz, 3H), 1.2–1.5 (m, 7H), 1.5–1.8 (m, 8H), 1.81 (br s, $W_{h/2}$ = 6.8 Hz, 1H), 3.64 (ddd, J = 1.4, 5.0, 11.3 Hz, 1H), 4.00 (ddd, J = 3.0, 12.6, 11.4 Hz, 1H); ^{13}C NMR δ 12.9, 25.1, 30.9, 32.5, 33.3, 33.6 (2 signals), 33.9, 36.6, 40.7, 54.1, 60.7, 96.4; MS *m/z* 210 (M, 1), 193 (47), 153 (46), 107 (23), 93 (27), 81 (46), 67 (53), 55 (87), 43 (98), 41 (100), 29 (53). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.33; H, 10.66.

Oxidation of 19. An excess of Jones' reagent was added dropwise to a stirred solution of **19** (465 mg, 2.21 mmol) in acetone (10 mL) with cooling. The mixture was stirred for 3 h at room temperature, and then EtOH was added dropwise to decompose the excess reagent. The whole was poured onto water (100 mL), and NaCl was added until the solution was saturated. The product was extracted into $CHCl_3$ (3 × 30 mL). The combined $CHCl_3$ extracts were extracted with aqueous Na_2CO_3 solution (5%, 2 × 50 mL). The combined basic layers were acidified with HCl (5 M) and extracted with ether (3 × 30 mL). The combined ether extracts were washed with water (2 × 100 mL) and brine (2 × 80 mL) and dried. The solvent was removed under reduced pressure to leave a yellow solid which was submitted to flash chromatography with 1:1 ethyl acetate–petroleum ether to give a white solid. This was recrystallized from acetonitrile to give (2′*RS*,4a′*RS*,8′*SR*,8a′*SR*)-2-(2′-methyl-1′-oxodecahydronaphthalen-8′-yl)acetic acid (**20**) (289 mg, 58%) as colorless needles, mp 181–186 °C: IR 3011 br w, 2920 vs, 2856 s, 1708 vs, 1698 vs, 1448 m, 1409 w, 1379 w, 1292 m, 1228 m, 1159 w, 1116 w, 1045 w, 1018 w, 952 w cm^{-1}; ^{1}H NMR δ 0.99 (d, J = 6.4 Hz, 3H), 1.1–1.6 (m, 6H), 1.6–1.8 (m, 3H), 1.8–2.0 (m, 1H), 2.0–2.2 (m, 4H), 2.46 (ddq, J = 6.3, 12.3, 12.3 Hz, 1H), 2.5–2.7 (m, 1H); ^{13}C NMR δ 14.4, 25.0, 31.7, 32.6, 33.3, 33.9, 36.7, 39.2, 45.7, 46.3, 59.0, 177.9, 214.3; MS *m/z* 224 (M, 55), 206 (100), 178 (42), 165 (70), 160 (27), 146 (27), 137 (20), 120 (35), 111 (33), 94 (48), 79 (67), 67 (45), 55 (43), 41 (80), 29 (30). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.80; H, 9.26.

Esterification of Acid 20. An ethereal solution of diazomethane was prepared by stirring a solution of *N*-methylnitrosourea (130 mg, 1.26 mmol, 2.0 equiv) in ether (10 mL) with aqueous KOH solution (50%, 10 mL) at 0 °C for 30 min. The ether layer was separated and dried over solid KOH and then added dropwise to a stirred solution of **20** (141 mg, 0.629 mmol) in ether (10 mL) at 0 °C. The reaction mixture was stirred at this temperature under nitrogen for 30 min before excess diazomethane was decomposed by the dropwise addition of AcOH. It was then poured onto water (100 mL), and the product was extracted into ether (3 × 30 mL). The combined ether extracts were washed with water (100 mL), aqueous Na_2CO_3 solution (5%, 100 mL), and brine (2 × 80 mL) and dried. Solvent removal under reduced pressure left a colorless oil which was submitted to flash chromatography with 3:47 ethyl acetate–petroleum ether to yield the methyl ester **21** as a white solid, which was recrystallized from MeOH to give colorless needles (140 mg, 93%) with mp 53–55 °C. ^{1}H NMR δ 0.99 (d, J = 6.3 Hz, 3H), 1.1–1.8 (m, 5H), 2.0–2.2 (m, 3H), 2.47 (ddq, J = 6.2, 12.7, 12.7 Hz, 1H), 2.5–2.7 (m, 1H), 3.53 (s, 3H); ^{13}C NMR δ 14.3, 24.9, 31.5, 32.5, 33.3, 33.9, 36.7, 39.0, 45.6, 46.2, 51.2, 58.9, 173.4, 213.7.

Reduction of Methyl Ester 21. $NaBH_4$ (8.5 mg, 0.22 mmol, 0.4 equiv) was added portionwise to a stirred solution of **21** (130 mg, 0.56 mmol) in MeOH (12 mL) with cooling under nitrogen. The reaction was quenched by the dropwise addition of AcOH (1 mL), and the solvent was evaporated to near dryness under reduced pressure. The mixture was poured onto water (80 mL), and the product was extracted into ether (3 × 30 mL). The combined ether extracts were washed with water (100 mL), $NaHCO_3$ solution (5%, 100 mL), and brine (2 × 80 mL) and dried. Removal of solvent under reduced pressure left a yellow oil which was purified by flash chromatography with 2:23 ethyl acetate–petroleum ether to give methyl (1′*RS*,2′*SR*,4a′*SR*,8′*RS*,8a′*RS*)-2-(1′-hydroxy-2′-methyldecahydronaphthalen-8′-yl)acetate (**22**) (130 mg, 96%) as a viscous colorless oil: IR 3510 br w, 3001 w, 2920 vs, 2849 s, 1726 vs, 1438 s, 1412 w, 1372 m, 1348 w, 1289 m, 1269 m, 1190 m, 1175 m, 1129 w, 1048 w, 990 w, 966 m, 915 w cm^{-1}; ^{1}H NMR (600 MHz) δ 0.77 (ddd, J = 2.1, 10.9, 10.9 Hz, 1H), 0.88–1.01 (m, 2H), 0.98 (d, J = 6.6 Hz, 3H), 1.11 (dddd, J = 3.3, 12.7, 12.7, 12.7 Hz, 1H), 1.33 (ddddd, J = 3.7, 3.7, 13.1, 13.1, 13.1 Hz, 1H), 1.35–1.48 (m, 4H), 1.61 (dddd, J = 3.3, 3.3, 3.3, 13.0 Hz, 1H), 1.63–1.67 (m, 1H), 1.67 (ddddd, J = 3.3, 3.3, 3.3, 3.3, 13.1 Hz, 1H), 1.71–1.76 (m, 1H), 1.92 (ddddd, J = 3.3, 6.2, 6.2, 10.4, 12.4 Hz, 1H), 2.10 (br s, $W_{h/2}$ = 24.0 Hz, 1H), 2.15 (dd, J = 5.8, 16.0 Hz, 1H), 2.48 (dd, J = 6.2, 16.0 Hz, 1H), 3.59 (br s, $W_{h/2}$ = 5.0 Hz, 1H), 3.69 (s, 3H); ^{13}C NMR δ 18.8, 25.8, 27.8, 33.9, 34.0 (two signals), 34.3, 34.6, 37.3, 38.8, 51.8, 52.9, 70.1, 175.1; MS *m/z* 240 (M, 5), 222 (12), 208 (14), 183 (12), 166 (10), 148 (100), 107 (17), 93 (22), 81 (28), 74 (75), 69 (13), 55 (31), 41 (33), 28 (14); HRMS *m/z* calcd for $C_{14}H_{24}O_3$ M$^+$ 240.1725, found M$^+$ 240.1725.

Dehydration of Alcohol 22. $POCl_3$ (76 μL, 0.83 mmol, 4.0 equiv) was added dropwise with cooling to a stirred solution of **22** (50 mg, 0.21 mmol) in dry pyridine (5 mL). The mixture was stirred overnight at room temperature under nitrogen and then quenched by the dropwise addition of water. After being poured onto water (50 mL) the mixture was extracted with ether (3 × 15 mL), and the extracts were washed with water (50 mL), HCl (3 M, 50 mL), and brine (2 × 40 mL) and dried. Evaporation of solvent under reduced pressure left a brown oil which after flash chromatography with 1:99 ethyl acetate–petroleum ether gave methyl (4a′*RS*,8′*SR*,8a′*RS*)-2-(2′-methyl-3′,4′,4a′,5′,6′,7′,8′,8a′-octahydronaphthalen-8′-yl)acetate (**23**) (40 mg, 86%), obtained as a clear colorless oil and as an inseparable 5:2 mixture with its allylic regioisomer **24**: IR 2921 vs, 2852 s, 1740 vs, 1435 m, 1365 w, 1333 w, 1301 w, 1232 w, 1174 m, 1151 m, 1100 w, 1016 w, 864 w cm^{-1}; ^{1}H NMR (**23**) δ 0.9–1.2 (m, 4H), 1.2–1.6 (m, 5H), 1.64 (br s, $W_{h/2}$ = 4.5 Hz, 3H), 1.6–2.1 (m, 4H), 2.03 (dd, J = 8.9, 14.8 Hz, 1H), 2.70 (dd, J = 3.8, 14.8 Hz, 1H), 3.67 (s, 3H), 5.38 (br s, $W_{h/2}$ = 5.6 Hz, 1H). Signals due to **24** were at δ 0.92 (d, J = 7.1 Hz, 3H), 2.20 (dd, J = 8.3, 14.0 Hz, 1H), 2.64 (dd, J = 5.6, 14.1 Hz, 1H), 5.07 (br s, $W_{h/2}$ = 5.6 Hz, 1H); ^{13}C NMR (**23**) δ 23.8, 25.9, 30.7 (two signals), 33.3, 33.4, 38.5, 38.9, 40.2, 46.2, 51.4, 122.2, 135.3, 174.1. Signals due to **24** were at δ 141.7, 123.5; MS *m/z* 223 (M + 1, 8), 220 (9), 206 (4), 191 (6), 163 (19), 148 (50), 121 (15), 105 (34), 91 (48), 79 (41), 55 (49), 43 (100). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.42; H, 10.15.

(±)-6,9-Desdimethylqinghaosu (7). A solution of a 5:2 mixture of **23** and its allylic regioisomer **24** (8.0 mg, 36 μmol) in MeOH (4 mL), containing enough Rose Bengal to impart a

pale pink coloration, was irradiated with white light (500 W) at −20 °C for 24 h under oxygen. After this time, TLC analysis indicated that the majority of the starting material had reacted. The mixture was poured onto saturated $NaHCO_3$ solution (50 mL), and the products were extracted into ether (3 × 15 mL). The sensitizer remained in the aqueous phase. The combined ether extracts were washed with brine (2 × 40 mL) and dried. Removal of solvent under reduced pressure left a colorless gum. This was dissolved in MeCN (4 mL), and the resultant solution was cooled to −20 °C. A solution of $Fe(phen)_3(PF_6)_3$ (0.7 mg, 0.7 μmol, 0.02 equiv) in MeCN (0.5 mL) was added, immediately followed by a solution of $Cu(OTf)_2$ (1.4 mg, 7.2 μmol, 0.10 equiv) in MeCN (0.5 mL). The reaction mixture was stirred at this temperature under an oxygen atmosphere for 2 h during which time TLC analysis revealed polar products, assumed to be the hydroperoxide **26** and hemiacetal **27**. The reaction mixture was quenched with saturated NH_4Cl solution (50 mL), and the products were extracted into ether (3 × 15 mL). The combined ether extracts were washed with water (2 × 50 mL) and brine (2 × 40 mL) and dried. After evaporation of solvent under reduced pressure a colorless oil remained. This was dissolved in CH_2Cl_2 (5 mL), and *p*-TsOH (1.4 mg, 7.2 μmol, 0.20 equiv) was added. The solution was stirred under nitrogen for 2 h at room temperature and then poured onto aqueous saturated $NaHCO_3$ (50 mL). The products were extracted into ether (3 × 15 mL), and the combined ether extracts were washed with water (2 × 50 mL) and brine (2 × 40 mL) and dried. After removal of solvent under reduced pressure the residue was submitted to flash chromatography with 1:4 ethyl acetate−petroleum ether. A colorless gum was obtained which was crystallized from ether−petroleum ether to give 6,9-desdimethylqinghaosu (**7**) (2.2 mg, 34%, based on **23**) as colorless needles, mp 127−129 °C (lit.[12] mp 130−131 °C): ^1H NMR (600 MHz) δ 1.20−1.29 (m, 1H), 1.30−1.42 (m, 2H), 1.47 (s, 3H), 1.50−1.61 (m, 1H), 1.75−1.84 (m, 4H), 1.88−1.92 (m, 1H), 1.92−1.98 (m, 1H), 2.06 (ddd, J = 2.7, 5.0, 14.8 Hz, 1H), 2.28 (dd, J = 1.3, 18.2 Hz, 1H), 2.45 (ddd, J = 3.8, 13.6, 14.8 Hz, 1H), 3.20 (dd, J = 7.1, 18.3, 1H), 5.93 (s, 1H); ^{13}C NMR δ 24.7, 25.5, 26.6, 30.2 (CH_2), 31.6, 32.1, 36.0, 38.4, 44.0, 78.1, 93.2, 105.4, lactone carbonyl not detected. The ^1H and ^{13}C NMR data are in accord with that reported in the literature.[12]

^1H NMR spectroscopic analysis of the nonpolar fraction corresponding to the starting material indicated that it was compound **24** (2.0 mg).

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Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra for compounds **16**, **17**, and **22** and ^1H and ^{13}C NMR data with peak assignments for compounds **7**, **15**, **16**, **17**, **19**, **20**, **21**, **22**, **23**, and **24** (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.