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Synthesis of (+)-Artemisinin and (+)-Deoxoartemisinin from Arteannuin B and Arteannuic Acid

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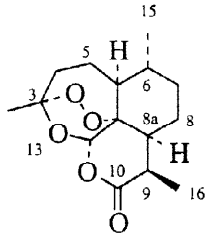
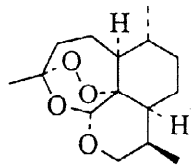
Abstract: (+)-Artemisinin and (+)-Deoxoartemisinin were prepared for the first time from arteannuin B. The synthetic route is short and efficient, making use of the prior art for the final photo-oxygenation/cyclization reaction. A convergent route to each of the above-named products from arteannuic acid is also described. A novel oxidative lactonization reaction was developed for this sequence.

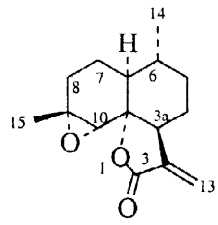
Artemisinin,[1] a sesquiterpene endoperoxide isolated from *Artemisia annua*, is the object of extensive synthetic, mechanistic and pharmacological studies due to its efficacy in the treatment of malaria. This compound is being investigated in response to a renewed sense of urgency for the discovery and development of novel antimalarial agents. Chloroquine has been the primary drug for treatment and prophylaxis of this tropical disease since its discovery during WWII. Current interest in antimalarial therapy was prompted by the emergence of chloroquine-resistant strains of *Plasmodium falciparum*, the protozoan that causes cerebral malaria, some of which show cross-resistance to alternative treatments such as *p*-aminobenzoic acid antagonists and dihydrofolate reductase inhibitors. The discovery of artemisinin was the result of a systematic study initiated by the Chinese government in 1967 to evaluate ethnobotanical practices of the Chinese people. References to the medicinal value of *A. annua* in Chinese literature date back to 168 B.C.[1a]



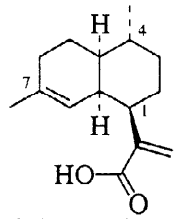
1 Artemisinin



2 Deoxoartemisinin



3 Arteannuin B



4 Arteannuic Acid

The low natural abundance (0.01-0.95% dry weight)[2] of artemisinin together with its complex chemical structure have prompted the development of several successful synthetic strategies. Syntheses have been reported from monoterpenes such as (-)-isopulegol,[4a] *R*-(+)-citronellal,[4b] (+)-pulegone,[4c] (-)-β-pinene,[4d] and (+) -3-carene[4e]. Arteannuic acid, an inactive congener and biochemical precursor of artemisinin, has also been used to synthesize the latter[4f-i].

Reports of promising biological activity have stimulated interest in defining structure activity relationships for artemisinin and developing synthetic derivatives with increased potency.[5a-j] One of the problems with the

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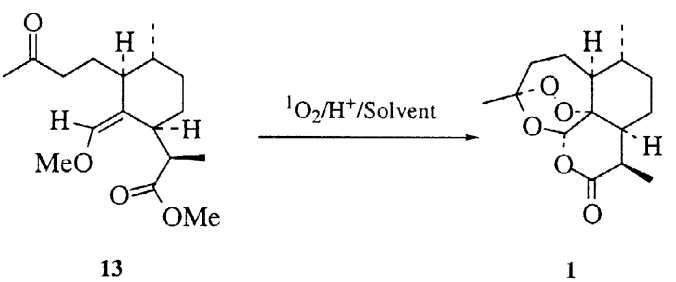
natural product is its low solubility in both water and oil. (+)-Deoxoartemisinin (**2**)[4i] is a more lipophilic synthetic analog with as much as 8 times the *in vitro* activity of artemisinin (although activity appears to be a function of the clone used[5c,11]) against chloroquine-resistant strains of malaria. Preliminary experiments on mice infected with *Plasmodium berghei* confirm increased *in vivo* activity as well.

Our work on artemisinin[6e] evolved from a long-standing interest in the synthesis of sesquiterpene natural products,[6] especially those containing a γ-lactone. The synthesis of Arteannuin B (**3**) was reported by Lansbury and Mojica in 1986.[6c] Arteannuin B is another constituent of *A. annua* having approximately twice the natural abundance of artemisinin. It is a sesquiterpene γ-lactone which lacks the pharmacophoric endoperoxide of artemisinin, but has all of the necessary carbon atoms and three of the seven asymmetric centers. Biosynthetic studies have confirmed that arteannuic acid (**4**) is a natural precursor of both arteannuin B and artemisinin.[7a] The latter has been isolated from cell-free extracts of *A. annua* upon incubation with arteannuin B, suggesting that arteannuin B is a biosynthetic precursor.[7b] The isotope labeling study of Akhila also supports this notion.[7c] Although *in vitro* preparation of arteannuin B from arteannuic acid has been achieved,[8a-e] the only reported attempt to prepare artemisinin from arteannuin B failed.[8f] We were interested in establishing this synthetic link. Our paper details an expeditious route from arteannuin B to both artemisinin and deoxoartemisinin. Also described is a convergent route to the same two products from arteannuic acid, a congener with a natural abundance 8-10 times that of artemisinin.[9,10] Arteannuic acid has the added advantage of facile isolation from the plant via base extraction.

RESULTS AND DISCUSSION

Based on previous synthetic efforts, it is known that enol ethers such as 13 can be converted to artemisinin via singlet oxygen ($^1O_2$) addition and acid-catalyzed rearrangement (Scheme 1).[3,4b] Our challenge was to convert both arteannuin B and arteannuic acid into compound **13**, or some analog thereof.

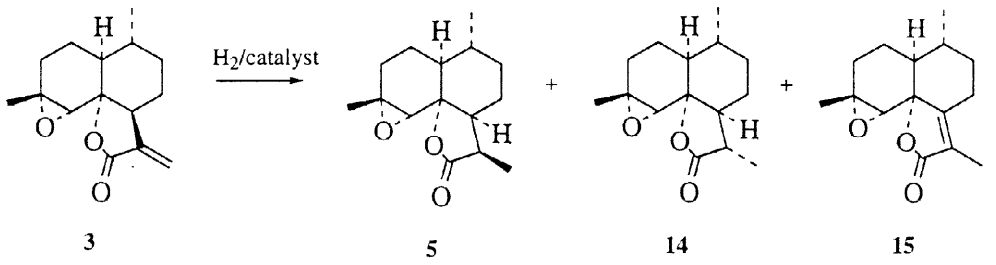


13 **1**

Scheme 1. Zhou's photo-oxygenation reaction

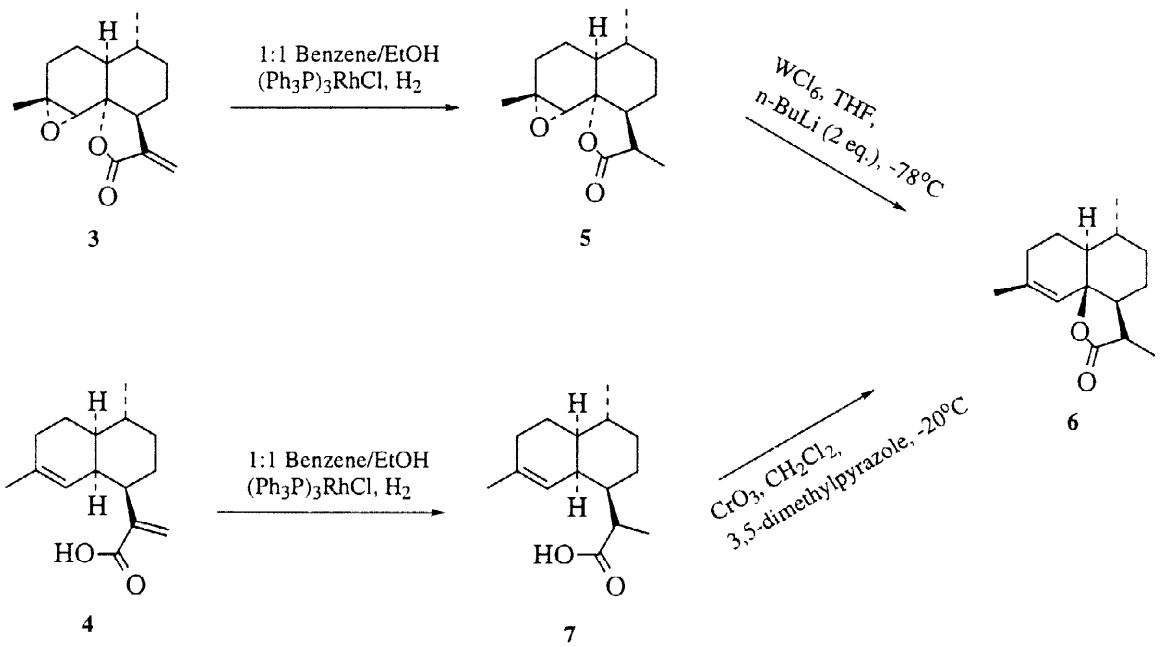
*Preparation of **6** from Arteannuin B*

Beginning with arteannuin B, the initial task was to reduce of the exocyclic methylene group to establish the correct *R*- configuration at C-3. Although 1,4-reduction of this α-methylene lactone has been reported previously,[8f] ($NaBH_4/CoCl_2$), the major product is 3-*S*-dihydroarteannuin B (**14**, Scheme 2, 70%). The same report detailed preparation of the desired diastereomer as the minor component of a three product mixture resulting from hydrogenation of arteannuin B over Pd/C. Along with **5** (5%), the product mixture contained 3-*S*-diastereomer **14** (36%), and butenolide **15** (38%), resulting from double bond migration. Formation of **14** can be rationalized on thermodynamic grounds; molecular modeling calculations[12] predict the 3-*S* -diastereomer to be ~5 Kcal/mol more stable than the desired product. Ruesch and Mabry developed reaction conditions favoring formation of the less stable reduction product from coronopilin, another α-methylene-γ-lactone.[13] Using this method (pre-reduced $(PPh_3)_3RhCl$, H_2, Benzene/ethanol), we prepared 3-R-dihydroarteannuin B from **3**. The crude product was purified by chromatography and then fractional recrystallization (diethyl ether) giving an unoptimized yield of 57%. Butenolide **15** (14%) and C-3 epimer **14** (8%), were the by-products.



Scheme 2. Hydrogenation of arteannuin B

Preparation of **6** (Scheme 3) by deoxygenation of epoxide **5** proved to be a formidable task. The trisubstituted epoxide, situated on the convex face of a *cis*-fused decalin ring system, is inaccessible to backside attack by conventional nucleophilic reagents. With this in mind, we attempted to deoxygenate dihydroarteannuin B using electrophilic reagents.[14] Success was ultimately achieved using WCl_6/n-BuLi in THF, a procedure developed by Sharpless for deoxygenation of hindered epoxides.[15a,b] Our initial work was done on 3-S-dihydroarteannuin B (**14**) due to increased availability. Under conditions in which the ratio of n-BuLi to WCl_6 was 3:1, the expected product (**16**, Figure 1), was obtained in 81% yield. The stereochemistry of the product was determined by comparison with spectral data reported in the literature.[16]

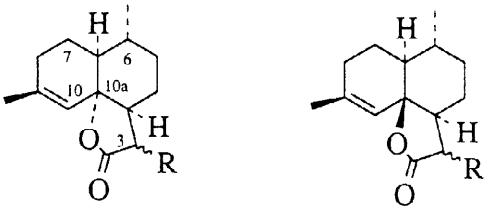


Scheme 3. Synthesis of **6** from arteannuin B and arteannuic acid.

Epimerization occurred when **16** was exposed to silica gel during chromatographic purification yielding a mixture of C-10a epimers in the ratio of 1.1:1. Compound **18** was identified using a combination of ^{1}H-NMR spectroscopy (including homonuclear decoupling experiments), and molecular modeling calculations.[12] Energy minimization of *trans*-fused lactone **16** produced a structure for which the dihedral angle between H-3a and H-3 is predicted to be 170.1°. The theoretical coupling constant of 12.6 Hz is in agreement with the experimentally-determined value of 13.2 Hz. Inversion of configuration at C-10a gave *cis*-fused lactone **18** having a predicted dihedral angle of 15.4°, resulting in a theoretical coupling constant of 7.0 Hz. The experimental value for **18**

was 2.1 Hz.

The conditions used for deoxygenation of **14** did not work for 3-R-dihydroarteannuin B (**5**). The reaction was extremely slow and the desired product was contaminated with unidentified olefinic by-products. We determined that the deoxygenation could be achieved by decreasing the ratio of n-BuLi/WCl_6 to 2:1; however, the resultant product was *cis*-fused lactone **6**, not the expected *trans*-fused **17**. Compound **6** formed as a result of deoxygenation followed by epimerization at C-10a. **No trace** of **17** was observed by ^{1}H-NMR analysis of the crude product (*even prior to exposure to silica gel*).



16 R = *S*-Me
17 R = *R*-Me

18 R = *S*-Me
6 R = *R*-Me

Figure 1. Isomers of Deoxydihydroarteannuin B

Compound **6** was tentatively identified by ^{1}H and ^{13}C-NMR spectroscopy, NOE experiments and molecular modeling. The four stereoisomers resulting from inversion of configuration at either C-10a or C-3 can be distinguished by evaluating NOE's between the respective vinyl protons and the substituents at C-3. The vinyl proton of the 3-*S* epimer containing a *cis*-fused lactone (as in **18**) is in close proximity to the *methyl* group attached to C-3 and therefore exhibits a strong NOE with the methyl protons. Conversely, the vinyl proton of the 3-*S*-*trans*-fused lactone (**16**) is near the *proton* attached to C-3. These relationships are reversed for the 3-*R* diastereomers. Since the respective ^{1}H -NMR signals are unencumbered, NOE measurements were easily made to estimate distances. Atomic distances predicted from modeling studies[12] and experimentally-determined

Table I: Correlation of theoretical interatomic distances with experimentally-determined NOE's

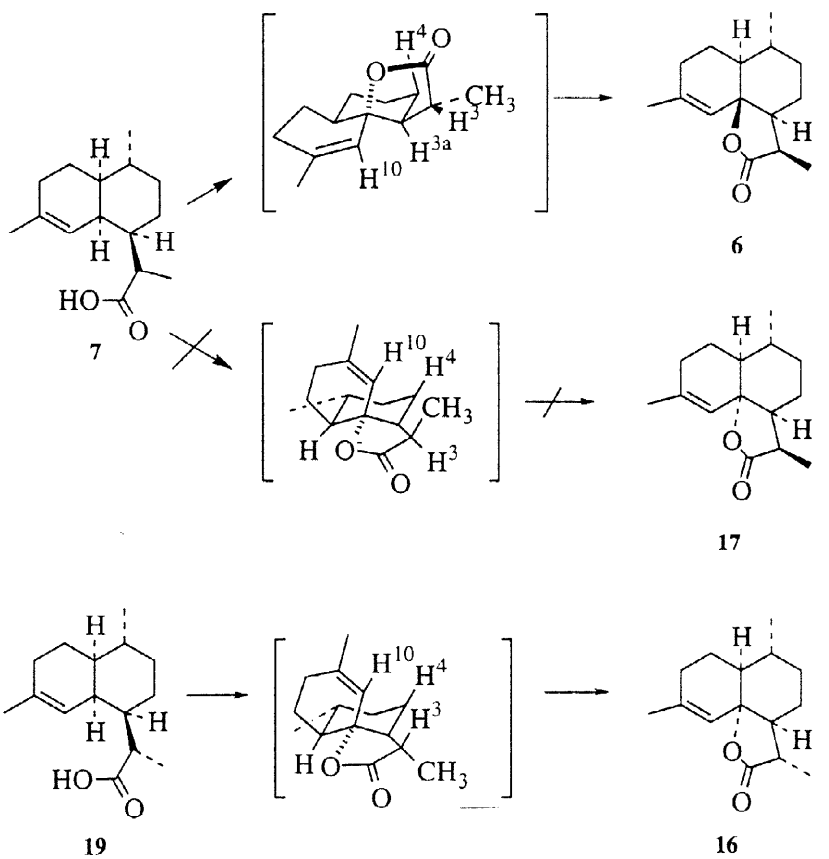
Compound Number	H-10/H-3 Distance[12]	H-10/H-3 NOE	H-10/CH_3-3 Distance[12]	H-10/CH_3-3 NOE
16	2.4Å	14%	4.9Å	6%
18	4.1Å	6%	2.1Å	25%
17	4.3Å	no data	2.2Å	no data
6	2.2Å	14%	4.7Å	6%

NOE data are found in Table I. The experimental data correlate well with the predicted results, the largest NOE values corresponding to the smallest predicted interatomic distances. The structure of **6** was later confirmed by X-ray crystallographic analysis of the ozonolysis product, and has subsequently been isolated from *Artemisia annua* at a level of 4 ppm by G. D. Brown.[16] Brown refers to this compound as dihydro-epideoxyarteannuin B. Epimerization at C-10a is thermodynamically driven. Modeling studies predict an energy difference of 8.8 Kcal/mol between **17** and **6**, favoring the *cis*-fused lactone. Similarly for the C-3 epimers, **18** is predicted to be 4.3 Kcal/mol more stable than **16**. The C-9 double bond presumably facilitates epimerization, allowing for formation of an allylic carbocation intermediate. In addition, the possibility exists for Lewis acid catalysis of ring opening by the tungsten reagent. Inversion of stereochemistry at C-10a was not problematic since the chirality at this center was eliminated in a subsequent reaction. The desired C-10a stereochemistry was

ultimately generated via stereospecific photo-oxygenation toward the end of the synthesis. Conversion of **6** to artemisinin is described later in this report.

*Preparation of **6** from arteannuic acid*

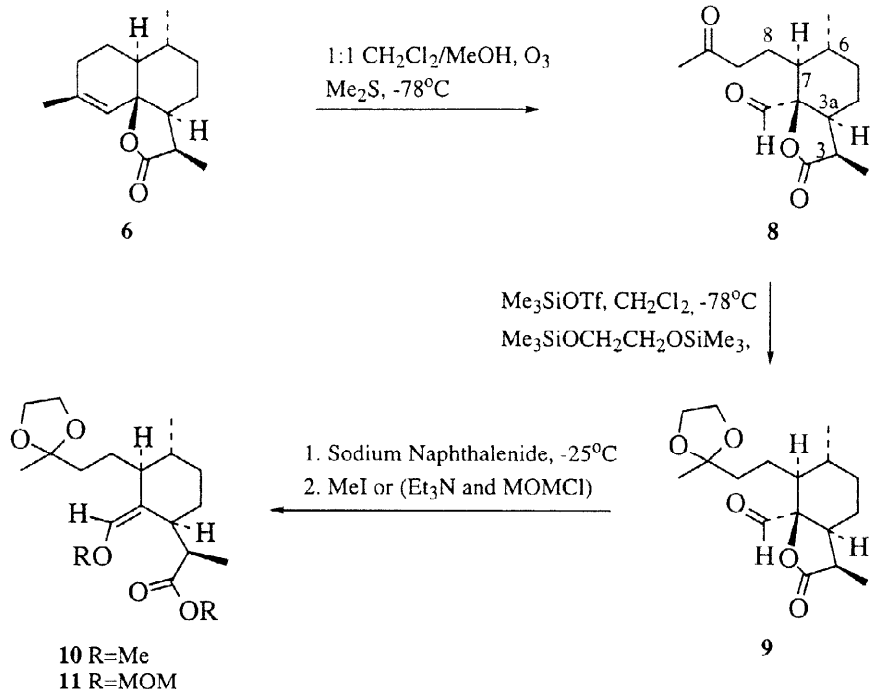
We have devised a two-step sequence by which arteannuic acid can be converted to **6** (Scheme 3). The first step, stereoselective reduction of the exocylic methylene group, was reported by Zhou ($NaBH_4/NiCl_2.6H_2O$ in MeOH).[4b] The product is a mixture of C-3 epimers in the ratio of 85:15, favoring the desired *R*-dihydroarteannuic acid (**7**). Compound **7** was converted directly to **6** by a novel oxidative lactonization reaction developed in our laboratory. The design was to effect allylic oxidation at C-10a followed by trapping of the incipient cation (or radical) by the carboxyl oxygen. Although allylic methyl, methylene and methine carbons exist in the molecule, it was proposed that the thermodynamic preference for oxidation at a tertiary center[17a,b] would prevail, and that *in situ* trapping would prevent subsequent rearrangement of the hydroxyl group to the methylene position. We also anticipated that formation of an adduct between the reagent and the carboxyl group that could direct oxidation to the methine position. To our delight, oxidation of the 85:15 mixture of dihydroarteannuic acid C-3 epimers (CrO_3/DMP in CH_2Cl_2 at -20 to -10°C) yielded a 4:1 mixture of diastereomeric lactones in an unoptimized yield of 59%. The reaction exhibits complete stereoselectivity, with the 3-*R* epimer (**7**) closing to form *cis*-fused lactone **6** and the 3-*S* epimer (**19**) cyclizing to *trans*-fused lactone **16**. We believe that the stereoselectivity results from unfavorable steric interactions (Scheme 4). For **7**, the transition state leading to **17** would involve unfavorable interactions between the β-methyl group at C-3 and the protons at C-10 and C-4. These interactions are absent in the transition state leading from **7** to **6**. *Trans*-lactone **16** *is* accessible from **19** because CH_3-3 is on the α face.



Scheme 4. Oxidative lactonization

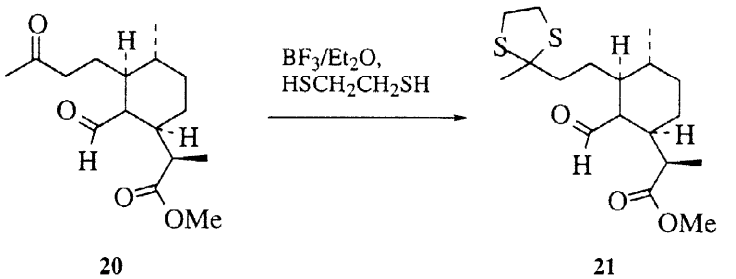
*Preparation of **10** from **6***

Having described two routes to intermediate **6**, what remains is to discuss the conversion **6** to **10** (Scheme 5), and the subsequent conversion of **10** to artemisinin and deoxoartemisinin (Scheme 8). Oxidative cleavage of **6** to ketoaldehyde **8** was accomplished in 93% yield by ozonolysis in a 1:1 mixture of dichloromethane/ methanol, followed by reduction with dimethyl sulfide. We made several attempts to rearrange the ozonide of **6** directly to artemisinin, but were unsuccessful.[18] Compound **8** was eventually converted to **10** via reductive cleavage of the α-acyloxyaldehyde followed by *in situ* trapping of the incipient enolate. However, ketone protection was first necessary before executing the reductive elimination step.



Scheme 5. Synthesis of photo-oxygenation substrates

The propensity for intramolecular aldol condensation of ketoaldehyde **8** mandated mild conditions for installation of the protecting group. Zhou confronted a similar obstacle converting **20** to **21** (Scheme 6); he protected the ketone as a dithiane. Although **21** was the major product (55-65%), by-products resulting from



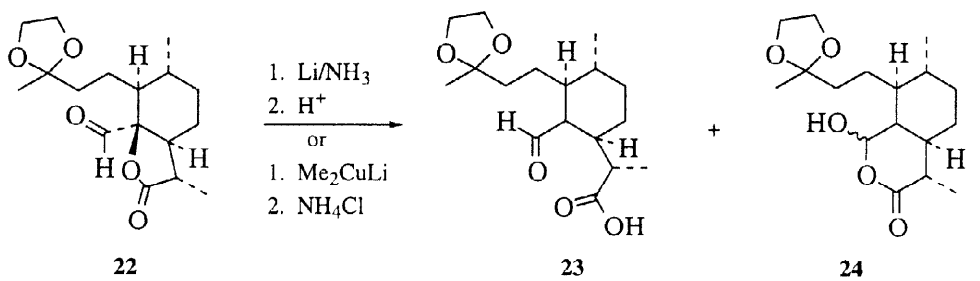
Scheme 6. Zhou's ketone protection

selective protection of the aldehyde and protection of both the aldehyde and ketone were formed. Moreover, the use of a dithiane required a separate deprotection step ($HgCl_2/CaCO_3/CH_3CN$) to regenerate the ketone

subsequent to manipulation of the aldehyde. We overcame this obstacle by protecting the ketone of **8** as a dioxolane. This proved to be a judicious choice for two reasons: 1) reagents exist that allowed for tight regiocontrol of the ketalization, and 2) the acid-labile group could be removed *in situ* during acid-catalyzed rearrangement of the singlet oxygen product in the last step of the synthesis.

Alkoxytrimethylsilanes can reportedly be used to prepare dioxolanes under very mild conditions. A combination of 1,2-bis(trimethylsilyloxy)ethane (BTSE) and trimethylsilyltriflate (TMSOTf) has been used to selectively protect the most accessible site in dicarbonyl compounds.[19a-c] This reaction exhibits kinetic control when run at low temperatures and thermodynamic control when the temperature is increased. Compound **8** is well-suited for a reaction controlled by steric factors since the ketone is relatively unhindered whereas the aldehyde is neopentyl. Upon ketalization with BTSE/TMSOTf in CH_2Cl_2, dioxolane **9** was formed as the sole reaction product in 96% yield at a conversion of 90%. Attempts to achieve 100% conversion were unsuccessful, and due to the instability **9** to chromatography, unreacted **20** was not removed prior to subsequent steps. Reversed regioselectivity was observed when the reaction was run at 0°C. The *in situ* deprotection is described later in this discussion.

Conversion of **9** to **10** and **11** was expeditiously achieved by reductive cleavage of the α-acyloxy aldehyde followed by *in situ* enolate trapping. The use of dissolving metal reductions and dialkylcuprate salts (Li or Ca/NH_3, Me_2CuLi) for reductive elimination of α-acetoxy ketones has been reported in the literature.[20a-f] We ran model experiments using the C-3 epimer of **9** (**22**, Scheme 7) due to increased supply. Although treatment with Me_2CuLi followed by NH_4Cl did effect the desired cleavage, compound **23** was not formed and hemiacetal **24** was produced in just 25% yield. Attempts to trap the dianion with MeI were unsuccessful. Reductive elimination with Li/NH_3 produced a mixture of **23** and **24** in a combined yield of 83%, but the logistics of the experiment were cumbersome due to the necessity to titrate the substrate with a stoichiometric amount of the reagent.



22 **23** **24**

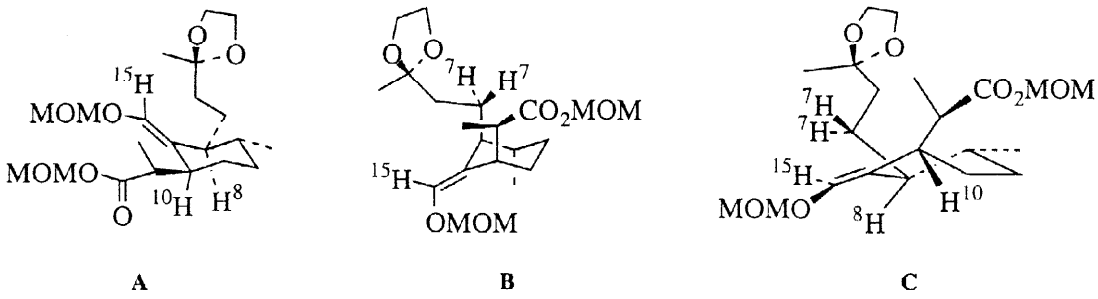
Scheme 7. Reductive cleavage

Sodium naphthalenide[21] serves as an alternative source of electrons that is stable at room temperature, easily standardized, and readily transferable. Exactly two equivalents of sodium naphthalenide in THF were added to a solution of **9** in THF. The resulting dianion was alkylated with excess MeI/DMSO giving the dimethylated product (**10**) in 46% yield. An additional 26% was obtained by methylation (diazomethane) of the carboxylic acid analog of **10**. DMSO was added in order to promote O-alkylation of the enolate.[20b] Alternatively, alkylation with excess chloromethyl methyl ether produced bis-methoxymethyl analog **11** in 82% yield. In each instance, a single diastereomer was obtained. Monoalkylation of the enolate oxygen was achieved by brief exposure (1-2 hours) of the dianion to an excess of MeI in the absence of DMSO. The preference for O-alkylation in the absence of a cation solvator emphasizes the steric hindrance at the ring junction. The success of the reductive alkylation validated our previous assumption that the inverted stereochemistry at C-10a of **6** was of no consequence.

The conformation of the cyclohexane ring in photo-oxygenation substrates such as **10** and **11** can have a profound effect on product distribution.[5i,22,28] Efficient preparation of artemisinin via photo-oxygenation requires dioxetane formation without competing ene reactions. Ene reactions are favored by axial allylic

protons.[5i] We therefore devoted significant effort to the conformational analysis of our photo-oxygenation substrates. Compound **11** was chosen as the model.

Faced with repeated failure in attempts to obtain crystals of **11** suitable for X-ray analysis, we turned to ^{1}H-^{1}H coupling constants and NOE data to assess conformation. The first task was to identify the configuration of the double bond. A difference NOE spectrum collected upon irradiation of the vinyl proton revealed a single interaction at δ 1.13 ppm corresponding to H-8. This was indicative of a Z double bond configuration. The three conformational isomers considered to be most probable for **11** are shown in Figure 2. Chair conformation **A**, in which the side chains are equatorial, was ruled out due to the absence of allylic coupling expected for the axial protons (H-8 and H-10). This conformation would be expected to suffer from $A^{1,3}$ strain.[23] Inverted chair **B** would likely exhibit 1,3-diaxial interactions between the side chains. Furthermore, NOE data indicate that H-15 is near H-7 in compound **11**, these data cannot be explained by **B**. We consider twist-boat **C** to be the most probable for **11**, and by analogy, for **10**; it alleviates both $A^{1,3}$ and diaxial interactions, in addition to being consistent with NOE data. Ene reactions would not be expected for this conformation due to the absence of axial allylic protons.



A B C

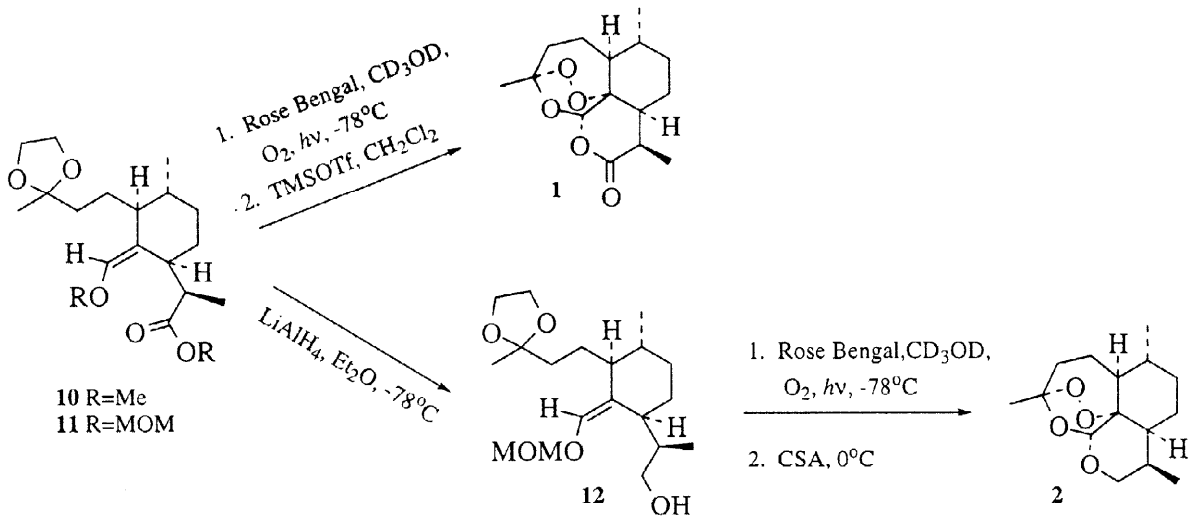
Figure 2. Conformational possibilities for **11**

Regeneration of the ketone from dioxolane **10** was carried out using mild conditions (acetone/H_2O, pyridinium tosylate), producing Zhou's photo-oxygenation substrate (**13**, Scheme 1) in 80% yield. We had thus completed a formal synthesis of artemisinin from arteannuin B and arteannuic acid.

Preparation of artemisinin and deoxoartemisinin

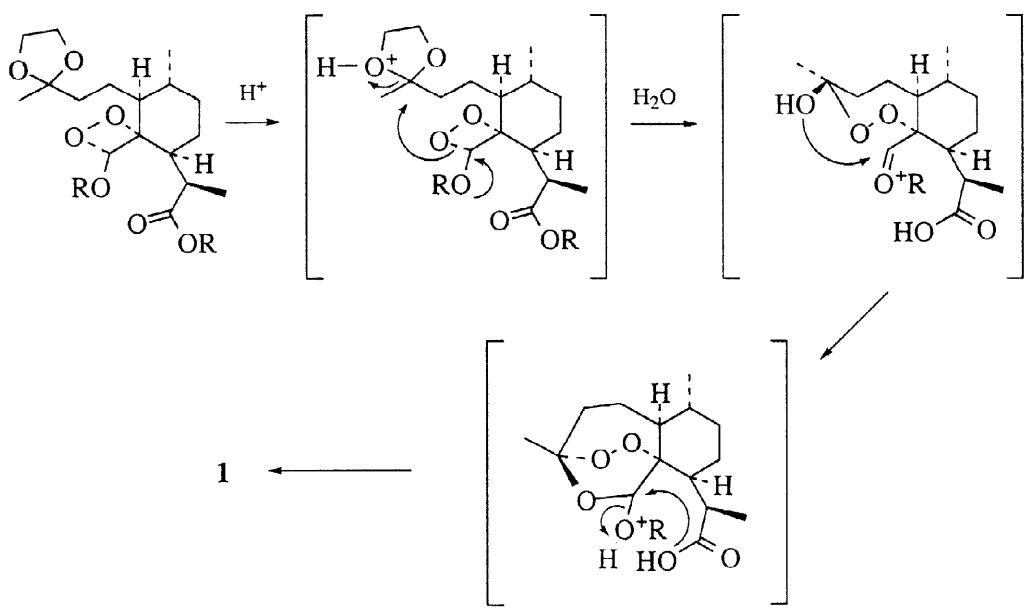
Conversion of **13** to artemisinin (Scheme 8) was accomplished using conditions similar to those described by Zhou.[4b] The photo-oxygenation/acid-catalyzed cyclization was run in deuterated solvents both to prolong the lifetime of singlet oxygen[24a-d] and to allow for intermittent cryogenic NMR analysis. Rose bengal was the sensitizer. Compound **13** was photo-oxygenated in $CD_3OD/(CD_3)_2CO$, 3:1, at -78°C; the solution was then treated with anhydrous hydrogen chloride gas and allowed to warm to room temperature over a period of several hours. Artemisinin was isolated in 15% yield upon purification by chromatography on silica gel. ^{13}C NMR analysis of the crude photo-oxygenation product indicated the presence of a single dioxetane diastereomer.

Based upon mechanistic considerations (potential mechanism in Scheme 9), we suspected that removal of the dioxolane in **10** prior to treatment with singlet oxygen was unnecessary. Our hypothesis was confirmed when artemisinin was formed upon photo-oxygenation of **10** in $CD_3OD/(CD_3)_2CO$ followed by treatment with camphorsulfonic acid monohydrate (CSA). The yield was estimated at 20-30%.



Scheme 8. Preparation of artemisinin and deoxoartemisinin

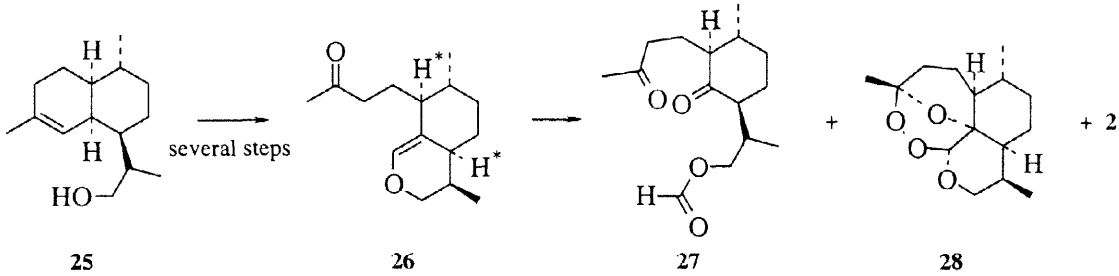
Artemisinin decomposes in the presence of strong acid[9,25] making it desirable to facilitate rapid formation and product isolation. We assumed that rearrangement of the photo-oxygenation product of **11** (methoxymethyl enol ether, MOM) would proceed faster than the analogous methyl enol ether. The MOM group would facilitate opening of the endoperoxide, and rapid hydrolysis of the MOM ester would increase the rate of γ-lactone formation. Upon photo-oxygenation of **11** and subsequent acidification, artemisinin was rapidly formed, sometimes within 30 minutes of acid treatment. The identity of the acid did affect yield;[26] the best results were obtained from treatment of the photo-oxygenation product with TMSOTf followed by aqueous CSA. Artemisinin was formed in 32% yield.[27]



Scheme 9. Acid-catalyzed rearrangement of the dioxetane intermediate

Prior to our work, there were two reported syntheses of deoxoartemisinin; both began with conversion of arteannuic acid to olefin **25** (Scheme 10). Jung prepared deoxoartemisinin in 18% yield by direct photo-

oxygenation of **25** followed by treatment with Dowex resin.[4i] This reaction presumably proceeds by way of an initial ene reaction followed by subsequent rearrangement and further oxidation. Wu's route involves photo-oxygenation and acid-catalyzed cyclization of cyclic enol ether **26**. Several steps were required to prepare **26** from **25**, and the reported yield for the final cyclization reaction was 62%.[4g] Although no mechanism was proposed, a sequence involving initial dioxetane formation followed by acid-catalyzed ring opening and rearrangement is conceivable. The formation of formate **27** can be explained as a dioxetane cleavage product. The isolation of regioisomeric peroxide **28** may indicate a competing ene pathway, as might be expected due to the axial allylic hydrogens (H*) in **26**.



25 **26** **27** **28**

Scheme 10. Prior syntheses of deoxoartemisinin

Our route is similar to that of Wu, but our photo-oxygenation substrate is devoid of axial allylic hydrogens. Enol ether **12** (Scheme 8), was prepared from **11** in 90% yield by reduction with lithium aluminum hydride in diethyl ether. As noted for compounds **10** and **11**, no allylic coupling is observed between H-15 and H-8 or H-15 and H-10 of **12**, suggesting a twist-boat conformation (see conformational analysis of **11**). Compound **12** was photo-oxygenated in CD_3OD at -78°C in the presence of Rose Bengal and then stirred with CSA at 0°C for 15 hours. Analysis of the product mixture revealed formation of deoxoartemisinin in 65% yield.[27]

CONCLUDING REMARKS

We have established a synthetic link between arteannuin B and artemisinin, and also developed a new route to artemisinin from readily available arteannuic acid. The latter synthesis makes use of a novel, stereoselective, oxidative lactonization and regioselective protection of the ketone with a group that can be removed *in situ* during acid-catalyzed rearrangement of the photo-oxygenation product. Yields for the photo-oxygenation reaction leading to artemisinin are comparable to those reported in previous syntheses; however, we observed no "ene" products, presumably because there are no axial allylic protons in our substrates. The yield for the photo-oxygenation to form deoxoartemisinin (65%) is extraordinary, comparable to yields obtained by Avery from the ozonolysis/cyclization of vinylsilanes[32]. We attribute this result to: 1) the enhanced rate of cyclization of alcohol **12** (as compared to that for esters **10** and **11**), thus minimizing the opportunity for dioxetane cleavage, and 2) the absence of competing ene reactions. The efficient synthesis of artemisinin and deoxoartemisinin from readily available precursors should facilitate rapid preparation of other synthetic analogs such as C-9 and C-10 alkylated derivatives.

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EXPERIMENTAL METHODS

General:

Infrared spectra were run on a Perkin Elmer 727B prism spectrometer. The 1601 cm^{-1} band of polystyrene was used for calibration purposes. Proton nuclear magnetic resonance spectra (^1H NMR) were run on Varian Gemini 300 and Varian VXR-400S spectrometers. Samples were run in either chloroform-*d* or methanol-*d*. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane. Peak multiplicities are abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Coupling constants (*J*) are reported in Hertz. Mass spectra were recorded on a VG 70-SE high resolution magnetic sector instrument. Isobutane was used as the carrier gas. Melting points were determined using a Fisher-Johns melting point apparatus and are uncorrected.

All moisture-sensitive reactions were run in flame-dried glassware under a blanket of argon. Reagents were purified prior to use by standard procedures,[29] unless otherwise noted. Alkyllithium reagents were standardized prior to use by titration of diphenylacetic acid. Thin layer chromatography was carried out on 250 micron, pre-coated plates (GHLF silica gel, Analtech, Inc.) which were visualized by spraying with a solution of sulfuric acid and cobalt chloride followed by scorching.

Sodium naphthalenide was typically prepared one day in advance of its use. Naphthalene (1.89g, 14.7 mmol) was dissolved in THF (25 ml). Sodium was added (0.32 g, 13.9 mmol) and the solution was stirred at room temperature under argon for 16 hours. Prior to use, the solution was standardized. An aliquot was added to water and titrated with 0.1000N HCl, using phenolphthalein as the indicator.

Preparation of (3R)-Dihydroarteannuin B (**5**): A 500 ml three-neck round-bottom flask was charged with 75 ml of benzene and 75 ml of ethanol. The mixed solvent was degassed using the freeze-thaw technique and then purged with argon. Tris(triphenylphosphine)rhodium(I) chloride (0.47 g, 0.50 mmol) was added and the vessel was filled with hydrogen from a balloon attached to one neck of the flask. The catalyst solution was allowed to stir under the hydrogen atmosphere for 45 minutes. In a separate flask, arteannuin B (1.96 g,7.89 mmol) was dissolved in benzene (16 ml). This solution was added to the pre-reduced catalyst in 1 ml increments over a period of 7 hours. The balloon was refilled with hydrogen as necessary. When no starting material remained as indicated by TLC analysis, the reaction mixture was transferred to a 500 ml round bottom flask and the solvent was distilled under reduced pressure (room temperature). The catalyst was removed by silica gel chromatography with diethyl ether as the eluent. Fractional recrystallization afforded pure **5** (1.12g, 57%) in the form of colorless prisms, mp 128-9°C (lit. 124-126°C[8f]). The remaining fractions consisted of various combinations of **5**, **14**, and **15**[8f]. Respective yields based on ^1H NMR area ratio are estimated at 16%, 8% and 14%. A relatively pure sample of **15** was obtained as an oil by repeated silica gel chromatography (hexane/diethyl ether - gradient elution). Compound **14** was obtained in crystalline form (colorless needles), mp 183-4°C (lit. 178.5-9.5°C[8f]) by $NaBH_4$ reduction of arteannuin B. Compound **5**: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.98 (s, 1 H), 2.72 (m, 1 H, *J* = 8.0, 9.2), 2.19 (m, 1 H, *J* = 8.0, 13), 1.33 (d, 3 H, *J* = 9.2), 1.31 (s, 3 H), 0.90 (d, 1 H, *J* = 6.5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.2, 83.4, 59.8, 58.3, 50.5, 45.9, 38.8, 35.1, 30.7, 24.3, 23.3, 21.7, 18.7, 16.4, 12.7.; IR (NaCl, neat) 1770, 1215 cm^{-1}; R_f = 0.32 (50% Et_2O/Hex, 2 developments). Compound **14**: ^1H NMR ($CDCl_3$ 300 MHz) δ 2.79 (s, 1 H), 2.64 (m, 1 H, *J* = 6.7, 13.3), 1.31 (s, 3 H), 1.18 (d, 3 H, *J* = 6.7), 0.90 (d, 3 H, *J* = 6.5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.3, 81.3, 58.3, 58.3, 55.1, 44.7, 38.0, 34.8, 30.8, 24.6, 23.1, 23.0, 18.7, 16.4, 13.0; IR (NaCl, Neat) 1770, 1120 cm^{-1}; CI-MS *m/z* 251 (MH^+) R_f = 0.37 (50% Et_2O/Hex, 2 developments). Compound **15**: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.78 (m, 1 H), 2.68 (s, 1 H), 1.79 (s, 3 H), 1.34 (s, 3H), 0.90 (d, 3 H); IR (NaCl, Neat) 1745, 1680 cm^{-1}; R_f = 0.26 (50% Et_2O/Hex, dev. twice).

Preparation of (3R,3a,6R,6aS,10aS)-3a,4,5,6,6a,7,8,8a-octahydro-3,6,9-trimethylnaphtho[8a,1-b]furan-2(3H)-one (**6**): Optimum yield for the above reaction requires preparation of the tungsten reagent under conditions of rapid and efficient agitation. For this reason, the reaction scale was kept small (≤1.25 g of WCl_6). Large quantities of product were prepared by running four batches simultaneously and combining the reaction

mixtures prior to workup. Four 100 ml round-bottom flasks, each equipped with a magnetic stir bar and a rubber septum, were flame-dried and filled with argon. To each was added WCl_6 (1.27g, 3.20 mmol) and dry THF (23 ml each). The brown-colored mixtures were cooled to -78°C, n-BuLi was added dropwise *via* syringe (4.18 ml, 6.39 mmol) and the reaction mixtures were allowed to warm to room temperature over a period of 30-60 minutes, with constant rapid stirring. Several color changes occurred during this time. When the solutions reached room temperature, they were homogeneous and very dark green. In a separate flame-dried flask, **5** (1.34g, 5.36 mmol) was dissolved in dry THF (12 ml). A syringe was used to transfer a 3 ml aliquot of the substrate solution (1.34 mmol) to each WCl_6 mixture. The reactions were stirred at room temperature for 1 hour and 45 minutes. Longer reaction times resulted in a severe reduction in yield. Shorter reaction times led to low conversion. All four reaction mixtures were quenched into a single flask containing 2N NaOH (100 ml). The brown mixture was extracted several times with diethyl ether (100 ml aliquots). The first separation was performed quite rapidly to guard against hydrolysis of the lactone. Care was taken to avoid vigorous shaking as emulsions formed readily. With each extraction, fresh NaOH solution was added to dissolve more of the brown solid that formed at the solvent interface. The ether layers were combined and washed with brine until neutral. The product was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by chromatography on florisil (diethyl ether/hexane, gradient elution) afforded **6** (0.47 g, 38%) as an oil and unreacted **5** (0.48 g, 36%) giving an adjusted yield of 59%. Compound **6**[8f]: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.59 (s, 1 H), 3.10 (m, 1 H, J = 5.8, 7.2), 1.63 (s, 3 H), 1.09 (d, 3 H, J = 7.2), 0.88 (d, 3 H, J = 6.6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.1, 142.8, 122.4, 83.6, 46.9, 43.1, 39.9, 32.6, 31.07, 29.9, 23.9, 23.6, 21.2, 19.8, 9.6; IR (NaCl, Neat) 1765, 1660, 1160 cm^{-1}; R_f = 0.58 (50% Et_2O/Hex).

Preparation of (3S,3a,6R,6aS,10aR)-3a,4,5,6,6a,7,8,8a-octahydro-3,6,9-trimethylnaphtho[8a,1-b]furan-2(3H)-one (**16**): A 50 ml round-bottom flask equipped with a magnetic stir bar and rubber septum was flame-dried and filled with argon. To this was added WCl_6 (1.20g, 3.04 mmol) and dry THF (6 ml). The brown-colored mixture was cooled to -78°C, n-BuLi was added dropwise *via* syringe (6.07 ml, 9.11 mmol) and the reaction mixture was allowed to warm to room temperature over a period of 1.6 hours with constant rapid stirring. Several color changes occurred during this time. When the solution reached room temperature it was homogeneous and very dark brown. In a separate flame-dried flask, **14** (0.348g, 1.39 mmol) was dissolved in dry THF (8 ml). This solution was added to the WCl_6 mixture *via* syringe. The reaction was stirred at room temperature for 50 minutes and worked-up as for **6** above. Purification by chromatography on florisil (diethyl ether/hexane, gradient elution) afforded **16**[8f] (0.18 g, 57%) as an oil and unreacted **14** (0.11 g, 30%) giving an adjusted yield of 81%. Compound **16**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.34 (s, 1 H), 2.59 (m, 1 H, J = 7.0, 13.2), 1.64 (s, 3 H), 1.12 (d, 3 H, J = 7.0), 0.90 (d, 3 H, J = 6.1); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.3, 143.3, 118.3, 84.5, 55.0, 46.1, 38.4, 35.3, 30.9, 26.7, 24.0, 23.6, 20.2, 20.0, 13.4; IR (NaCl, Neat) 1765, 1660, 1200 cm^{-1}; CI-MS *m/z* 235 (MH^+); R_f = 0.58 (50% Et_2O/Hex).

Preparation of (3S,3aS,6R,6aS,10aS)-3a,4,5,6,6a,7,8,8a-octahydro-3,6,9-trimethylnaphtho[8a,1-b]furan-2(3H)-one (**18**): Purification of compound **16**, by silica gel chromatography (chromatotron) resulted in partial conversion to **18** (~30%). The mixture of diastereomers was dissolved in hexane and combined with silica gel. After stirring at room temperature for three days, conversion to **18** had reached 48% as determined by NMR peak areas. Although samples enriched with **18** were recovered, this compound was not obtained in pure form, and attempts to push the epimerization reaction to completion were unsuccessful. Compound **18**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.41(s, 1 H), 2.41 (m, 1 H, J = 2.1, 7.8), 1.66 (s, 3 H), 1.42 (d, 3 H, J = 7.8), 0.93 (d, 3 H, J = 5.4); R_f = 0.53 (50% Et_2O/Hex).

Preparation of (3R,3aS,6R,6aS,7aS)-3,6-dimethyl-7a-formyl-7-(3-oxobutyl)-hexahydrobenzo[1,2-b]furan-2(3H)-one (**8**): Compound **6** (80.7 mg, 0.344 mmol) was dissolved in a solution of 1:1 methylene chloride/methanol (40 ml) and cooled to -78°C. Ozone was bubbled through the mixture until a blue color persisted, after which time the solution was purged with argon and allowed to warm to room temperature.

Excess dimethyl sulfide (2 ml, 27 mmol) was added and stirring was continued for an additional 3 hours. The solvents were removed under reduced pressure and the residue was dissolved in diethyl ether, washed several times with distilled water (to remove DMSO), dried with $MgSO_4$ and concentrated *in vacuo* to give **8** as a colorless oil (85.1 mg, 93%). A portion of the crude product was recrystallized from diethyl ether affording colorless needles, mp 106 - 106.5°C: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 9.70(s, 1 H), 2.51 (m, 2 H, J= 6.6, 7.0), 2.36 (m, 2 H), 2.08 (s, 3 H), 1.07 (d, 3H, J = 7.0), 0.96 (d, 3 H, J = 6.5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.9, 203.2, 178.8, 91.2, 43.7, 41.7, 40.9, 39.2, 32.4, 31.2, 30.2, 23.8, 22.2, 20.0, 9.2; IR (NaCl, Neat) 1775, 1730, 1710, 1180 cm^{-1}; CI-MS *m/z* 267 (MH^+); R_f = 0.23 (50% Et_2O/Hex).

Preparation of (3R,3aS,6R,7S,7aS)-3,6-dimethyl-7a-formyl-7-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-hexahydrobenzo[1,2-b]furan-2(3H)-one (**9**): Compound **8** (0.186 g, 0.699 mmol) was dissolved in methylene chloride (15 ml, freshly distilled from CaH_2) in a flame-dried round bottom flask under an atmosphere of argon. The solution was cooled to -78°C in a cryogenic bath, 1,2-bis(trimethylsilyloxy)ethane (0.218 ml, 0.889 mmol) was added dropwise *via* syringe followed by TMSOTf (0.10 ml, 0.51 mmol) and the solution was stirred at -78°C for 16 hours. Anhydrous pyridine (0.10 ml, 1.2 mmol) was then added and the solution was stirred at -78°C for an additional 15 minutes, allowed to warm to room temperature and quenched into a saturated solution of sodium bicarbonate. The product was extracted into methylene chloride and washed with brine until neutral. Residual pyridine was removed by extraction with saturated $CuSO_4$. The organic layer was washed sequentially with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by rapid chromatography on florisil (Et_2O /hexane, gradient elution) yielding an oily mixture (204.7 mg) containing both **9** and unreacted **8**. The products were present in a molar ratio of 4.1:1 as determined by ^{1}H peak ratios of the aldehyde and methyl ketone protons, giving a conversion of 80% and an adjusted yield of 96%. There was no indication of acetal formation. The mixture was used in subsequent reactions, previous attempts at further purification resulted in significant product loss due to decomposition during chromatographic separation. Compound **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.75(s, 1 H), 3.87 (m, 4 H), 2.54 (m, 1 H, J = 6.3, 7.1), 2.41(m, 1H, J = 6.3), 1.22 (s, 3H), 1.06 (d, 3H, J = 7.1), 0.96 (d, 3 H, J = 6.5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.2, 178.9, 110.3, 91.5, 65.0 (2C), 45.6, 42.3, 39.7, 37.5, 32.6, 31.9, 23.9 (2C), 23.0, 20.0, 9.3; IR (NaCl, neat) 1780, 1735 cm^{-1}; CI-MS *m/z* 311 (MH^+), R_f = 0.30 (50% Et_2O/Hex).

Preparation of 2-(2-(3-((2R)-methoxycarbonylpropyl)-2-methoxylmethylene-(6R)-methylcyclohex-(1S)-yl)ethyl)-2-methyl-1,3-dioxolane (**10**): Sodium naphthalenide (0.43 ml, 0.32 mmol) was charged to a flame-dried round-bottom flask and cooled to -25°C under an atmosphere of argon. A solution of compound **9** (39.2 mg, 0.126 mmol) dissolved in THF (1.5 ml) was added dropwise *via* syringe until the green color of the sodium naphthalenide dissipated. Excess iodomethane (0.1 ml, 1.61 mmol) was then added. The solution was allowed to warm to room temperature and stirred for 16 hours. Ether was added and the solution was extracted sequentially with K_2CO_3, water and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The naphthalene was removed by rapid chromatography through florisil (hexane/diethyl ether, gradient elution) and the crude product (24.6 mg) was isolated as an oil and determined by NMR assay[27] to contain **10** (19.9 mg, 46% yield). Further purification was not accomplished due to product instability. The aqueous layer was acidified with concentrated HCl, extracted with ether, washed with brine until neutral, dried and stripped to give the free acid (10.7 mg, 26% yield) which was readily converted to **10** in quantitative yield by treatment with diazomethane. Compound **10**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.81 (s, 1 H), 3.88 (m, 4 H), 3.64 (s, 3H), 3.49 (s, 3H), 2.97 (m, 1 H , J = 12.2), 2.63 (m, 1H, J = 12.2, 6.8), 1.26 (s, 3H), 1.07 (d, 3H, J = 6.8), 0.86 (d, 3 H, J = 6.7); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.5, 146.2, 115.2, 110.7, 65.0 (2C), 59.6, 51.6, 46.3, 43.4, 38.7, 36.2, 34.0 , 30.8, 24.6, 24.0, 23.9, 19.8, 16.4; IR (NaCl, Neat) 1740, 1660 cm^{-1} R_f = 0.55 (50% Et_2O/Hex).

Preparation of 2-(2-(3-((2R)-methoxymethylcarbonylpropyl)-2-methoxymethyloxymethylene-(6R)-methylcyclohex-(1S)-yl)ethyl)-2-methyl-1,3-dioxolane (**11**): Sodium naphthalenide (0.94 ml, 0.64 mmol) and

THF (2 ml) were charged to a flame-dried round bottom flask and cooled to -25°C under an atmosphere of argon. A solution of compound **9** (73.8 mg, 0.238 mmol) dissolved in THF (3 ml) was added dropwise *via* syringe until the green color of the sodium naphthalenide dissipated. Dry triethylamine (0.3 ml, distilled from sodium metal) was then added followed by chloromethyl methyl ether (0.3 ml, 3.94 mmol) which had been freshly distilled from triethylamine to remove residual HCl. The solution was allowed to warm to room temperature and stirred for 4 hours. Diethyl ether was added and the solution was extracted with brine. The organic layer was washed sequentially with saturated cupric sulfate, water and brine. It was then dried over $MgSO_4$ and concentrated *in vacuo*. The naphthalene was removed by rapid filtration through florisil (hexane/diethyl ether, gradient elution) and crude compound **11** (77.7 mg, 82% yield) was isolated as an oil. Further purification was not accomplished due to product instability. Compound **11**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.09 (s, 1 H), 5.25 (s, 2H), 4.77 (m, 2H), 3.92 (m, 4H), 3.48 (s, 3H), 3.38 (s, 3H), 3.10 (m, 1H, *J* = 12.1), 2.71 (m, 1H, *J* = 4.5, 12.1), 1.31 (s, 3H), 1.18 (d, 3H, *J* = 4.5), 0.91 (d, 3H, *J* = 5.1); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.3, 142.16, 116.7, 110.6, 96.6, 90.5, 65.0 (2C), 57.8, 56.0, 46.4, 43.6, 38.7, 36.3, 33.9, 30.7, 24.5, 24.1, 24.0, 19.8, 16.6; IR (NaCl, Neat) 1740, 1660 cm^{-1}; HRMS calcd for $C_{21}H_{37}O_7$, *m/z* 401.2539, found 401.2526; R_f = 0.35 (50% Et_2O/Hex).

Preparation of (aR,1S,3S,4R)-a,4-dimethyl 2-methoxymethylene-3-(3-oxobutyl)-cyclohexaneacetic acid methyl ester (**13**[4b]): To a solution of acetone (5 ml) and water (1 ml) was added **10** (8.2 mg, 0.024 mmol) and pyridinium tosylate (~1 mg). The mixture was relfuxed for four hours after which time the solvent was removed under reduced pressure. The product was dissolved in diethyl ether and washed several times with brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give 5.7 mg (80% yield) of **13**, isolated as an oil: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 5.81 (s, 1 H), 3.64 (s, 3H), 3.45 (s, 3H), 3.51 (s, 3H), 2.97 (m, 1 H *J* = 11.9), 2.59 (m, 1H, *J* = 7.0, 11.9), 2.10 (s, 3H), 1.07 (d, 3H, *J* = 7.0), 0.87 (d, 3 H, *J* = 6.6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.7, 178.25, 146.4, 114.9, 59.6, 51.7, 45.4, 43.3, 42.9, 36.1, 33.6, 30.2, 24.4, 23.8, 19.8, 16.4, ; IR (NaCl, Neat) 1715, 1660 cm^{-1}; CI-MS *m/z* 297 (MH^+); R_f = 0.52 (50% Et_2O/Hex).

Preparation of (+)-artemisinin (**1**): A sample of **11** (9.4 mg, 66% pure by assay[27] 0.015 mmol) was dissolved in a solution of CD_3OD (1 ml) containing Rose Bengal (0.8 mg) and placed in an NMR tube. The tube was placed in an acetone/dry ice bath. Oxygen was bubbled through the reaction mixture by way of a capillary tube with a microsyringe needle affixed to the end. The solution was irradiated with a tungsten halogen lamp filtered through a solution of $Na_2Cr_2O_7$ in aqueous NH_4Cl/NH_4OH (pH 10) until **11** was no longer visible by TLC (50% Et_2O/hexane). The approximate reaction time was 30 minutes. The reaction mixture was transferred to a round bottom flask and the solvent was removed under reduced pressure. Dry methylene chloride (~4 ml) was added, the solution was cooled to -78°C and 2 drops of trimethylsilyl TMSOTf were added. After stirring for 20 minutes at -78°C the reaction mixture was filtered through florisil, using diethyl ether as the solvent. Proton NMR analysis of the product did not reveal the presence of artemisinin. The product was then dissolved in methylene chloride (5 ml) to which several drops of water and 30 mg CSA had been added. The mixture was stirred at room temperature for 3 hours after which time the organic layer was washed with water, dried and concentrated *in vacuo*. The assay[27] of the resultant crude product (13.9 mg) revealed a 32% yield (1.39 mg) of artemisinin. Several synthetic samples of artemisinin were combined and recrystallized affording white needles, mp 155-156°C. A compound believed to be an intermediate dioxetane was isolated from a similar experiment upon photo-oxygenation and treatment with amberlyst® 15.[30] Compound **1**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.86 (s, 1 H), 3.39 (m, 1H, *J* = 5.5, 6.8), 2.44 (m, 1H), 1.44 (s, 3H), 1.21 (d, 3H, *J* = 6.8), 1.00 (d, 3H, *J* = 5.6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.7, 105.9, 94.2, 79.9, 50.4, 45.3, 37.8, 36.2, 33.9, 33.1, 25.4, 25.1, 23.6, 20.0, 12.7; IR (NaCl, Neat) 1740; CI-MS *m/z* 283 (MH^+); R_f = 0.41 (50% Et_2O/Hex).

Preparation of 2-(2-(3-(3-hydroxy-(2R)-methylpropyl)-2-methoxymethylene-(6R)-methylcyclohex-(1S)-yl)ethyl)-2-methyl-1,3-dioxolane (**12**): Compound **11** (31.1 mg, 0.078 mmol) was dissolved in diethyl ether (20 ml, distilled from $LiAlH_4$) and cooled to -78°C. Excess $LiAlH_4$ (~10 mg, 0.26 mmol) was added and the

solution was stirred at -78°C until the starting material was no longer visible by TLC (~1 hour), after which time the mixture was slowly quenched into cold water. While vigorously stirring the two phase mixture, 10% HCl was added to acidify the aqueous layer. This procedure was done rapidly to prevent hydrolysis of the vinyl ether moiety. The organic layer was washed with brine until neutral, dried over $MgSO_4$ and concentrated *in vacuo*, affording **12** (23.9 mg) as an oil in 90% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.02 (s, 1 H), 4.76(m, 2H), 3.92 (m, 4H), 3.74 (m, 1H, *J* = 3.6, 10.8), 3.51 (m, 1H, *J* = 5.6, 10.8), 3.38 (s, 3H), 2.63 (m, 1H), 1.30 (s, 3H), 0.98 (d, 3H, *J* = 6.8), 0.91 (d, 3H, *J* = 6.8); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.8, 118.9, 110.7, 96.6, 67.3, 64.9 (2C), 55.9 467.0, 38.6, 38.0, 35.5, 34.4, 30.9, 25.4, 24.0, 23.0, 20.3, 16.1; IR (NaCl, Neat) 3450, 1660 cm^{-1}.

Preparation of (+)-deoxoartemisinin (**2**): A sample of **12** (21.4 mg, 55% pure by assay[27], 0.034 mmol) was dissolved in CD_3OD (1 ml) containing Rose Bengal (1.6 mg), and placed in an NMR tube and cooled to -78°C. Oxygen was bubbled through the reaction mixture by way of a capillary tube with a microsyringe needle affixed to the end. The solution was irradiated with a tungsten halogen lamp filtered through a solution of $Na_2Cr_2O_7$ in aqueous NH_4Cl/NH_4OH (pH 10) for 2.2 hours. A ^{1}H NMR spectrum was taken of the photo-oxygenation product (in the CD_3OD solvent) which is believed to be a dioxetane intermediate.[31] Solid (1R)-(-)-10-CSA (44 mg, 0.15 mmol) was then added and the solution was allowed to warm to 0°C over a period of four hours. Unlike the ester analog (**11**), changes were apparent by TLC analysis immediately after addition of the acid (prior to warming to room temperature). The temperature was maintained at 0°C C for ~15 hours, after which time the solution was transferred to a round bottom flask with diethyl ether, and stripped to dryness under reduced pressure. The CSA was separated from the product by filtration of the product through a short column (1/4" x 2") of silica gel using diethyl ether as the eluent. Internal standard ^{1}H NMR analysis[27] of the crude product (16.1 mg) revealed the presence of deoxoartemisinin (6.0 mg) in 65% yield. Crude products from several reactions were combined and purified by chromatography with subsequent recrystallization from petroleum ether, resulting in the isolation of crystalline material, mp 106°C. The purified product exhibited spectral data consistent with literature values reported for deoxoartemisinin[4g,i] The product was also identical to **2** prepared from artemisinin using the method of Jung.[4i] Compound **2**: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 5.20 (s, 1 H), 3.69(m, 1 H, *J* = 4.0, 11.6), 3.41 (m, 1H, *J* = 11.9), 2.59 (m, 1 H), 2.33 (m, 1 H, *J* = 3.9, 14.5), 1.98 (m, 1 H, *J* = 3.4, 14.5), 1.40 (s, 3 H), 0.92 (d, 3H, *J* = 6.2), 0.74 (d, 3H, *J* = 7.3) ; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 104.6, 92.6, 81.2, 66.6, 52.6, 45.2, 37.6, 36.5, 34.3, 28.2, 26.3, 24.9, 20.9, 20.5, 13.2; IR (NaCl, Neat) no noteworthy signals; HRMS calcd for $C_{15}H_{25}O_4$, *m/z* 269.1753, found 269.1736; R_f = 0.43 (50% Et_2O/Hex).

Preparation of (3R,4S,6R,7S,10aS)-3a,4,5,6,6a,7,8,8a-octahydro-3,6,9-trimethylnaphtho[8a,1-b]furan-2(3H)-one: (**6**) (from Arteannuic Acid): A sample of pre-dried CrO_3 (90.5 mg, 0.91 mmol) was combined with CH_2Cl_2 (1 ml). To this was added a solution of 3,5-dimethylpyrazole (87.1 mg, 0.91 mmol) dissolved in CH_2Cl_2 (1.5 ml). The mixture was cooled to -20°C and stirred for 30 minutes. A mixture of **7** and its C-9 epimer (11.1 mg, 0.047 mmol), in a ratio of 83:17 (prepared by reduction of **4**[4b]) was dissolved in CH_2Cl_2 and added to the Cr(VI) mixture. After stirring at -20°C to -10°C for 20 minutes, the solution was poured into aqueous NaOH (1N). The layers were quickly separated and the organic layer was filtered through silica gel to remove the chromium impurities. The eluent was combined with diethyl ether and washed sequentially with saturated $CuSO_4$ and brine, dried over $MgSO_4$, and concentrated *in vacuo* yielding a 4:1 mixture (determined by comparison of peak areas for the C-10 protons in the NMR) of **6** and **16** (6.5 mg, 59%). Subsequent ozonolysis of the product mixture (CH_2Cl_2/MeOH 1:1, -78°) afforded an analogous mixture of **8** and its diastereomer. Spectral data for **6** is cited above

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25. Natural artemisinin was no longer detectable after stirring for several days at room temperature in aqueous perchloric acid.
26. In terms of reaction rate, trimethylsilyl triflate > CSA > Amberlyst® 15.
27. Yield was based on ^1H NMR using triphenylmethane as an internal standard. Quantitation was based on area comparison between the methine proton of triphenylmethane (δ 5.52 ppm) and the C-12 proton of artemisinin (δ 5.83 ppm). Spectra obtained for the purpose of yield determination were run with a delay time of 15 seconds to prevent errors associated with incomplete relaxation.
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31. Dioxetane intermediate for deoxoartemisinin: ^1H NMR (CD_3OD, 400 MHz) δ 5.89 (s, 1 H, H-5), 4.68 (s, 2 H, H-18a,b), 3.90 (s, 4 H, H-16a,b, H-17a,b), 3.34 (s,3 H, CH_3-19) 1.28 (s, 3 H, CH_3-15), 1.13 (d, 3 H, J = 6.8, CH_3-13), 0.96 (d, 3 H, J = 6.8, CH_3). This spectrum was not as clean as the one in the

previous note.
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