Stereoselective Total Synthesis of (+)-Artemisinin, the Antimalarial Constituent of *Artemisia annua* L.

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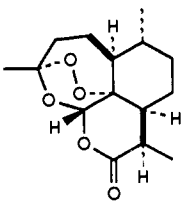
Abstract: A 10-step stereoselective total synthesis of the antimalarial cadinane sesquiterpene (+)-artemisinin (**1**) is described. Elaboration of (*R*)-(+)-pulegone to the known sulfoxide **11** was followed by dianion alkylation and desulfurization to provide the trans-2,3-substituted cyclohexanone **7**. Homologation to the cyclohexenecarboxaldehyde **6** was followed by a diastereoselective silyl anion addition to afford the silyl acetate **15**. Tandem Claisen ester–enolate rearrangement and dianion alkylation furnished the fully functionalized vinylsilane **18** that underwent abnormal ozonolysis and cyclization to provide the natural product **1**.

Increasing resistance of the malaria parasite, *Plasmodium falciparum*, toward contemporary antimalarials is cause for concern.[1] Fortunately, the relative recent isolation and structure determination of the antimalarial constituent of the Chinese medicinal herb Qinghao[2] (*Artemisia annua* L.) yielded the novel natural product (+)-artemisinin (**1**, qinghaosu, QHS). Subsequently, this stable peroxide **1** emerged as a potent antimalarial[3] against resistant strains of *P. falciparum*. The limited availability of the natural product coupled with its modest potency delineated the need for ready synthetic entry to the artemisinin tetracyclic framework. Many valuable contributions to total synthesis[4-6] and congener synthesis[7-9] have appeared in recent years. In this paper we describe our optimized total synthesis.



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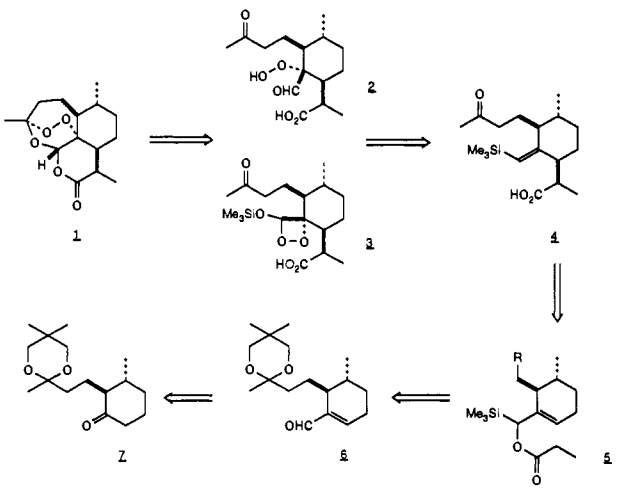
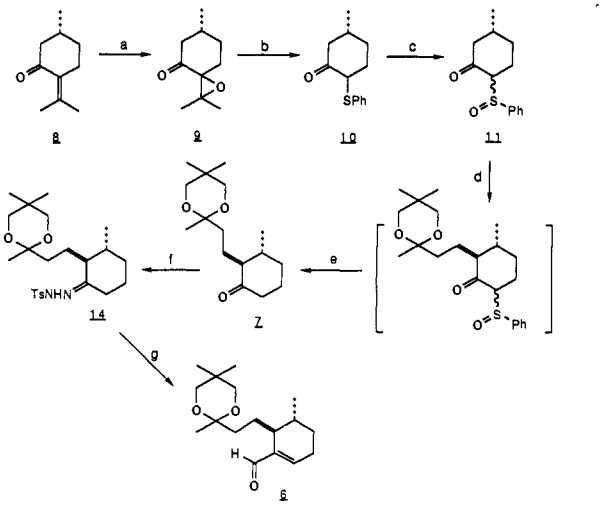
From a retrosynthetic standpoint, we felt that the most obvious intermediate in the production of **1** would be the "unraveled" α-hydroperoxy aldehyde **2** because, in a ketalization-like process, simple cyclodehydration of **2** should readily furnish the tetracyclic natural product **1**. The inherent synthetic challenge for **1** thus lies in the preparation of the unstable aldehyde **2**, and in commendable fashion others have employed enol ether photooxygenation as an entry to that functional arrangement.[4,5] By contrast, we took advantage of the ozonolysis of a vinylsilane, a process reported to furnish the desired α-hydroperoxycarbonyl moiety.[10] Thus, the next intermediate in our analysis was the $2\beta,6\beta$-disubstituted cyclohexanylidenesilane **4** which, according to precedent and the favorable outcome of earlier model studies,[7a-c] was anticipated to afford **2** or the synthetically equivalent dioxetane **3** upon exposure to ozone. Construction of the key vinylsilane **4** via Claisen ester–enolate rearrangement of **5** had precedent in our previous model work.[7a] To complete our retrosynthetic analysis, a plausible route to **5** was conceived, involving straightforward homologation of the $2\beta,3\alpha$-disubstituted cyclohexanone **7** to the cyclohexenecarboxaldehyde **6**, which in turn might undergo silyl anion addition and subsequent acylation, as shown in Scheme I.

The requisite cyclohexanone **7** was synthesized in optically active form. As shown in Scheme II, (*R*)-(+)-pulegone (**8**) was epoxidized[11] with alkaline hydrogen peroxide to pulegone epoxide **9**. Thiophenoxide opening of **9** with concomitant retro-aldol

Scheme I



Scheme II[a]



[a] (a) Alkaline HOOH, THF, 74%. (b) NaSPh, THF, 99%. (c) *m*-CPBA, CH_2Cl_2, −78 °C, 95%. (d) 2 LDA, HMPT or DMTP, THF, −35 °C; then 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane. (e) Al(Hg) amalgam, wet THF, 37–50% overall for d and e. (f) *p*-$CH_3PhSO_2NHNH_2$, neat, 1 mmHg, 86%. (g) 4 *n*-BuLi, TMEDA, 0 °C; then DMF, 70%.

expulsion of acetone[12] yielded regioisomerically pure phenyl thio ketone **10**. Customary peracid oxidation of sulfide **10** afforded

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(1) (a) Marshall, E. *Science* **1990**, *247*, 399. (b) Krogstad, D. J.; Herwaldt, B. L. *N. Engl. J. Med.* **1988**, *319*, 1538. (c) Miller, K. D.; Greenberg, A. E.; Campbell, C. C. *N. Engl. J. Med.* **1989**, *321*, 65.

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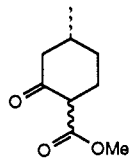
the sulfoxide **11** in good overall yield.[13]

Roush and Walts[14] converted the sulfoxide **11** into its corresponding dianion with lithium diisopropylamide (LDA, HMPA), and then alkylated the anion with *n*-butyl iodide to provide a diastereomerically complex mixture that underwent elimination upon thermolysis to 2-butyl-3(*R*)-methylcyclohex-2-en-1-one (50% yield, 6:1, β/α mixture at C-2). Similarly, we found sulfoxide **11** was alkylated (LDA, HMPA) with 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane,[15] and the resultant complex mixture was desulfurized with an aluminum amalgam to furnish the desired ketone **7** in 50% yield as a 9:1 (β/α) mixture at C-2. Surprisingly, alkylation of this sulfoxide dianion was not improved using 2-(2-iodoethyl)-2,5,5-trimethyl-1,3-dioxane[16] in place of the bromide. The alternate use of the dianion of β-keto ester **12** did not afford improvements in the yield of the alkylation step, and saponification of the alkylation product **13** led to epimerization at C-2 (6:4 β/α mixture). Although we used this approach to **7** via sulfoxide **11**, the construction of the functional arrangement of **7** could probably be optimized further.



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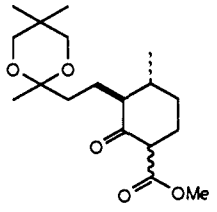

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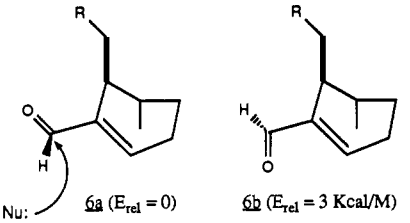
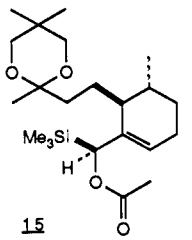


Figure 1. Transoid (**6a**) and cisoid (**6b**) rotamers of the preferred conformer of aldehyde **6**. Nucleophilic attack could be predicted to occur upon the less sterically encumbered α-face of **6a** to provide the C-1′ *S* diastereomer **15**.

With the ketone **7** in hand, we then pursued its homologation to the unsaturated aldehyde **6**. We expected that the corresponding hydrazone of **7** would provide a regioisomerically pure vinyl anion which could be intercepted with dimethylformamide[17] to provide **6**. After considerable experimentation to avoid facile ketal hydrolysis or base-catalyzed epimerization at C-2 of ketone **7**, we found that, if THF and pyridine were simply removed from the reaction mixture under vacuum, quantitative formation of hydrazone **14** was obtained. Subsequent treatment of hydrazone **14** in *N,N,N′,N′*-tetramethylenediamine (TMEDA) with 4 equiv of *n*-butyllithium afforded a red solution of vinyl anion, which was quenched with dimethylformamide to afford the regiochemically pure $\Delta^{1,6}$-unsaturated aldehyde **6** in 70% yield (Scheme II). At this stage, any minor 2α-diasteromer was conveniently removed by chromatography.

Our original plan (Scheme I) to elaborate aldehyde **6** into the propionate ester **5** was accomplished, but it was found that the propionate ester–enolate Claisen rearrangement proceeded in rather poor yield, presumably as a result of steric congestion in the transition state. It was felt that in the rearrangement of acetate ester **15** these constraints would be absent, and thus approaches to the transformation of aldehyde **6** to the silyl acetate **15** were investigated. Early synthetic efforts afforded **15** and **16** as a 1:1



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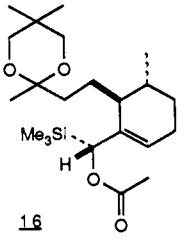

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mixture, of which only isomer **15** underwent Claisen ester–enolate rearrangement to give the desired β-product **17**.[18] This outcome was presumably a result of conformational bias in the Claisen rearrangement toward chairlike transition states with equatorial substituents[19,20] and clearly justified the need for a stereoselective approach to acetate **15**.

Along these lines, molecular mechanics calculations of the unsaturated aldehyde **6** revealed an interesting possibility. A comparison of the lowest energy conformers of **6** demonstrated a definite preference for diaxially oriented **6a** ($\Delta E_{rel} > 3$ kcal/mol). Inspection of this conformer suggested that an incoming nucleophile could approach from one face of the carbonyl to lead to a single product whose relative stereochemistry corresponded

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(14) Roush, W. R.; Walts, A. E. *J. Am. Chem. Soc.* **1984**, *106*, 721.
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(16) See the Experimental Section. Prepared by a modification of the procedure(s) cited in (a) Gil, G. *Tetrahedron Lett.* **1984**, *25*, 3805. (a) Larson, G.; Klesse, R. *J. Org. Chem.* **1985**, *50*, 3627.
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(18) The acetates **15/16** were synthesized as a 1:1 mixture via aldehyde **6** by the following sequene of reactions. Reduction of **6** with DIBAH afforded an allylic alcohol i, which was silylated (TMSCl, pyr) to give ii. Brook rearrangement of ii with *t*-BuLi/THF gave a mixture of α-silyl alcohols iii, which were acetylated (Ac_2O, pyr) to provide **15/16**. Claisen ester–enolate rearrangement of the **15/16** mixture (using LICA) afforded **17** in poor yield (22%). See the supplementary material.
(19) Ireland, R.; Varney, M. *J. Am. Chem. Soc.* **1984**, *106*, 3668.
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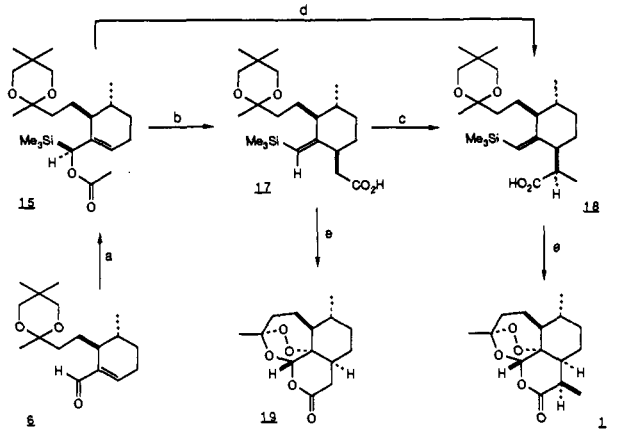
Scheme III[a]



[a] (a) Tris(trimethylsilyl)aluminum etherate, Et_2O, −78 °C; Ac_2O, DMAP, to 23 °C, 88%. (b) 2 LDEA, THF, −78 °C to 23 °C, 63%. (c) 2 LDA, THF, 50 °C; CH_3I, −78 °C, 97%. (d) 3 LDEA, THF, −78 °C to 50 °C; 2.5 LDA, 0 to 45 °C; CH_3I, −78 °C to ambient temperature, 61%. (e) O_3/O_2, CH_2Cl_2, −78 °C; SiO_2; 3 M aqueous H_2SO_4, 35% for **1**, 61% for **19**.

to diastereomer **15**, as depicted in Figure 1. Thus, if the trimethylsilyl anion were used as the nucleophile, then the requisite diastereomer **15** could become available. Of the various counterions, Li^+, Na^+, and K^+ have been examined by others. None of these species was suitable for direct (1,2) addition to carbonyl compounds.[21] However, it has been found that tris(trimethylsilyl)aluminum etherate (TTAE) will undergo direct 1,2-addition to benzaldehydes to furnish α-silylbenzyl alcohols.[24] In our hands, this reagent reacted with cyclohexenecarboxaldehyde at low temperature in ether to afford a stable α-silyl aluminum alkoxide that could be captured with acetic anhydride/4-(*N*,*N*-dimethylamino)pyridine to provide 1-cyclohexenyl-1-(trimethylsilyl)methyl acetate in 90% yield.

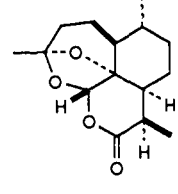
With these encouraging results in hand, we returned to aldehyde **6**. Upon reaction with TTAE and subsequent quenching with acetic anhydride, **6** was transformed to a single diastereomer **15** in 88% yield. Although it was not determined which diastereomer (**15** vs **16**) had actually been produced as this stage, the material underwent ester–enolate rearrangement (2.1 LICA, THF, −78 °C to 23 °C) to a single acid, identical to **17**, in 51% yield on the first attempt. The balance of the material from this reaction corresponded to the competing Claisen condensation product (β-keto ester) and Brook rearranged silyl ether (together with desilylated allylic alcohol), obtained in yields of 12 and 28%, respectively.

Regiochemistry about the vinylsilane moiety in **17** was ascertained by nuclear Overhauser enhancement difference (DNOE) experiments. Decoupling experiments with either downfield methylene proton ajdacent to the carboxylic acid (δ 2.62 (dd, 1 H, J = 9.5, 15.0 Hz) or δ 2.48 (dd, 1 H, J = 5.9, 15.0 Hz)) identified the C-6 proton resonance (δ 2.78 (m, 1 H)). Similarly, the C-2 proton resonance was also located (δ 2.11 (m, 1 H)). Irradiation of the vinylsilane proton sinlget at δ 5.38 led to an enhancement of 10% of the C-6 resonance and none at the C-2 proton resonance, thus demonstrating a syn relationship between the vinyl proton and the C-6 proton. Conversion of the acid **17** to the natural product **1** or (+)-9-desmethylartemisinin **19**[6] (Scheme III) confirmed that a β-oriented side chain had been produced at C-6 and clinched the stereochemistry of **17** as depicted.

With the desired stereocontrol mastered, the preparation of **17** was optimized. With highly hindered lithium bases such as LICA or lithium tetramethylpiperidide (LiTMP), self-condensation products accounted for as much as half of the reaction products. When less bulky amides were used, the rate of deprotonation became more competitive with self-condensation but was instead accompanied by an increased amount of direct displacement by amide anion on the ester carbonyl (low acetoacetate high silyl ether ratio, with attendant acetamide formation). For example, LDA, LICA, lithium diethylamide (LDEA), and lithium pyrrolidinylamide each gave **17** in yields of 25, 40, 63, and 20%, respectively. Thus, we settled for the optimum reached with LDEA, which gave the desired product **7** in 63% yield.

We next examined the methylation of the carboxylic acid **17**. Warming of a THF solution of **17** with 2 equiv of LDA at 50 °C for 2 h led to an orange solution of dianion. Addition of methyl iodide then gave rise to a single, diastereomerically pure homologous acid, **18**, in nearly quantitative yield (Scheme III). The stereochemical identity of **18** was determined as erythro by its conversion to the natural product **1**. Furthermore, substitution of ^{14}C-methyl iodide in this sequence eventually led to the synthesis of (+)-^{14}C-artemisinin. It has also been found that this alkylation is of general utility in that a wide variety of alkyl halides can be employed, furnishing a myriad of analogues of the natural product. The basis for this observed fortuitous stereochemical outcome of the dianion alkylation is currently under investigation. Upon the establishment that the appropriate stereochemistry was provided via alkylation, the final stages of the synthesis were reviewed for improvement. First, if the Claisen rearrangement required excess base and if the dianion formation could be combined at the terminus of the rearrangement, then it was considered possible that the use of several equivalents of base with the acetate **15** would lead directly to the dianion of **17**, which could then be alkylated in situ to provide the homologated acid **18** in one pot. Indeed, successive treatment of **15** with 3 equiv of LDEA (−78 °C to 50 °C) followed by 2.5 equiv of LDA provided the desired dianion of **17** which, upon cooling and admission of methyl iodide, gave the acid **18** in 61% yield.

Finally, the conversion of acid **18** to the natural product **1** was considered. Previously, separate deprotection of the ketal **18** to keto acid **4** (80% yield) was performed prior to ozonolysis. The possibility of a one-pot onzolysis, deprotection, and cyclization sequence was entertained. Thus, ozonolysis of **18** in dichloromethane, when followed by successive addition of aqueous sulfuric acid and silica gel, led in reasonable yield (33–39%) to (+)-artemisinin (**1**), identical in all respects to the authentic natural product. A nonpolar byproduct in this reaction was deoxyartemisinin **20**.



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In optimization studies, various solvents were examined for the sequence **18** to **1**. The use of methanol led to destruction of the tetracycle via lactone ring methanolysis. Other solvents examined for this final sequence (hexane, ethyl acetate, etc.) were poor in comparison to dichloromethane. When a fairly dilute solution of **18** in dichloromethane (0.01 M) was subjected to ozone, a higher yield of artemisinin (**1**) was obtained with a lower proportion of non-peroxidic deoxyartemisinin **20**. Additives such as *tert*-butyl hydroperoxide and *tert*-butyl peroxide were investigated in an attempt to maintain an oxidative environment during acid treatment for ozone exposure, but they had little effect. In fact, the crude product profile was much cleaner by thin-layer chromatography with the addition of *tert*-butylhydroxytoluene (BHT) subsequent to reaction of **18** with ozone and afforded the best yield of artemisinin (35%).

(21) Still, W. *J. Org. Chem.* **1976**, *41*, 3063.
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In summary, we have developed a stereoselective 10-step total synthetic route to the antimalarial sesquiterpene (+)-artemisinin (**1**). The crucial elements of the approach include diastereoselective trimethylsilyl anion addition to the α,β-unsaturated aldehyde **6** and a tandem Claisen ester–enolate rearrangement/dianion alkylation to afford the diastereomerically pure erythro acid **18**. Finally, acid **18** was converted in a one-pot procedure involving sequential treatment with ozone followed by wet acidic silica gel to effect a complex process of dioxetane formation, ketal deprotection, and multiple cyclizations to the natural product (+)-artemisinin (**1**). The route was designed for the late incorporation of a carbon-14 label and the production of a variety of analogues for structure–activity relationship (SAR) studies.

Experimental Section

All solvents were purchased as HPLC grade and, where appropriate, solvents and reagents were distilled from CaH_2 prior to storage over 4-Å molecular sieves. Solvent and reagent transfers were accomplished via dried syringe or cannula, and all reactions were routinely conducted under an atmosphere of argon, unless otherwise indicated. Flash chromatography was accomplished using silica gel (Kieselgel 60, 230–400 mesh) preparative thin-layer chromatography, utilizing 1-, 1.5-, or 2-mm thick Analtech Uniplates with F-256, and 250-μm silica gel thin-layer chromatography plates also purchased from Analtech. NMR analyses were conducted on either a Varian XL-400 or a JEOL FX90Q and were referenced to a chloroform at δ 7.27. IR spectra were recorded on a Perkin-Elmer 1310 or 1610. UV spectra were recorded on a Perkin-Elmer 552. MS were obtained with a Reibermag R-10-10-C (CIMS) or LKB 9000 (EIMS). Elemental analyses were within ±0.4% as determined by Desert Analytics, Tuscon, AZ.

Pulegone Oxide (9). Pure (*R*)-(+)-pulegone (**8**) (Fluka purum grade, 152 g) was converted to the epoxide, according to the procedure of Katsuhara,[11] to give 119 g of **9** (74%). **Caution**: This reaction is quite exothermic. This material was sufficiently pure by NMR for use in the next reaction. Anal. ($C_{10}H_{16}O_2$) C, H.

5(*R*)-Methyl-2-(phenylthio)cyclohexanone (10). The oxide **9** (119 g) from above was converted to the sulfide **10** by minor modification of a procedure outlined by Caine et al.[12] A 60% oil dispersion of NaH (1.416 mol, 56.64 g) under argon was washed with hexane (3 × 50 mL) in order to remove the oil. Dry THF (1.5 L) was added followed by a solution of thiophenol (1.416 mol, 146.5 mL) in dry THF (1.5 L). The mixture was stirred at ambient temperature for 30 min, and then the epoxide **9** (119 g or 708 mmol) in dry THF (1.0 L) was added. The resulting mixture was heated at reflux for 24 h and allowed to cool. Ice (1 kg) was added and, after stirring for 15 min, the mixture was extracted with Et_2O (2 × 500 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give crude **10** (157 g or ca. 100%), which was sufficiently pure (NMR) for the next reaction. An analytical sample was furnished from column chromatography with silica gel and CH_2Cl_2. A yellow solid, mp 67–68 °C was obtained: UV λ_{max} = 250 nm (log ϵ 3.69). Anal. ($C_{13}H_{16}OS$) C, H, S.

5(*R*)-Methyl-2-(phenylsulfinyl)cyclohexanone (11). The sulfide **10** was oxidized, as described by Oppolzer and Petrizilka,[13] to the sulfoxide **11**. Thus **10** (155.8 g) was converted to crude **11** (241 g). Filtration chromatography on silica gel (723 g of 60–230 mesh) with EtOAc/hex (35 → 80%) gave pure **11** as diastereomeric mixture, 158 g (95%). The sulfoxide was stored under argon in the freezer.

More recently, the sulfide **10** was oxidized with the magnesium salt of monoperoxyphthalic acid hexahydrate (MMPP).[22] To a solution of sulfide **10** (63.58 g, 0.289 mol) in 95% ethanol (1 L) at 0 °C was added a solution of MMPP (256.86 g of 80%, 0.519 mol) in H_2O (1 L) over 30 min. The resultant mixture was stirred with brine (500 mL), saturated with NaCl, and extracted with Et_2O (5 × 150 mL). The combined ethereal layers were washed with saturated aqueous $NaHCO_3$ (2 × 200 mL) and brine (2 × 200 mL), dried over $MgSO_4$, and evaporated to provide **11** as a yellow-orange oil, 62.71 g (91.0%), which was identical to previously obtained **11**, suitable for further use and stored under argon in a freezer. Anal. ($C_{13}H_{16}O_2S$) C, H, S.

2,5,5-Trimethyl-2-[2′-(1″(*R*)-methyl-3″-oxocyclohex-2″-yl)ethyl]-1,3-dioxane (7). 5(*R*)-Methyl-2-(phenylsulfinyl)cyclohexanone (**11**, 48.4 g, 205 mmol) in dry THF (300 mL) was added to a solution of lithium diisopropylamide (prepared from 63.0 mL or 451 mmol of diisopropylamine and 189 mL of 2.5 M solution of *n*-butyllithium in hexane) in dry THF (300 mL) at −78 °C followed by dry 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMTP) (200 mL). The mixture was stirred at −35 °C for 3 h, and then 2-(2′-bromoethyl)-2,5,5-trimethyl-1,3-dioxane[15] (52.7 mL, 226 mmol) was added dropwise. The mixture was stirred at −35 °C for 1 h and then allowed to warm to room temperature over 1 h. The mixture was poured into an ice-cold, saturated NH_4Cl solution (500 mL) and extracted with Et_2O (2 × 500 mL). The organic layers were washed with water (3 × 500 mL) and brine (500 mL), dried over $MgSO_4$, and evaporated in vacuo to give 106 g of the crude alkylation product, which was dissolved in THF (2.5 L). To the solution was added, in succession, water (300 mL) and 60 g of aluminum (−45 + 100 mesh) that was freshly activated by sequential washing with 2% aqueous mercuric chloride for 20 s followed by absolute ethanol and Et_2O. The mixture was stirred at ambient temperature until the temperature reached about 35 °C, whereupon ice was gradually added to a cooling bath to control the exotherm. After 2 h the solids were filtered onto Celite with the aid of reduced pressure and washed with Et_2O (1 L). The filtrate was washed with 5% sodium hydroxide solution (2 × 1 L) and brine (1 L). The aqueous phases were extracted with Et_2O (1 L). The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo to afford 66.0 g of crude material, which was purified by filtration chromatography on 660 g of silica gel 60 (70–230 mesh) and eluted with EtOAc/hex [(5:95) → (25:75)]. In this manner, 16.7 g of the product **7** and 9.2 of mixed fractions were obtained. The mixed fractions were purified by flash chromatography on 184 g of silica gel (230–400 mesh) and eluted with EtOAc/hex [(7:93) → (25:75)] to give an additional 5.0 g of the product **7**. Thus, there was a total yield of 21.7 g (37%) for **7**, which at this scale was typically contaminated with approximately 10% of the inseparable C-2α isomer as determined by NMR (400 MHz) but was suitably pure for further use. When HMPT was substituted for DMTP in this reaction, the yield improved to 50%, with an identical isomeric ratio: ^{1}H NMR δ 3.53 (dd, 2 H, J = 2.2, 11.6 Hz), 3.48 (dd, 2 H, J = 1.4, 11.6 Hz), 2.38 (dddd, 1 H, J = 1.1, 4.5, 4.5, 13.1 Hz), 2.27 (dddd, 1 H, J = 1.0, 5.6, 11.5, 12.0 Hz), 1.95–2.07 (m, 2 H), 1.79–1.92 (m, 2 H), 1.58–1.79 (m, 4 H), 1.45 (dddd, 1 H, J = 3.7, 9.3, 11.2, 11.2, 11.3 Hz), 1.38 (s, 3 H), 1.06 (d, 3 H, J = 6.6 Hz), 0.99–1.04 (m, 1 H), 0.96 (s, 6 H); ^{13}C NMR δ 213.2, 99.1, 70.5, 70.3, 57.1, 41.6, 38.4, 33.5, 33.3, 29.9, 25.6, 22.7, 21.7, 20.8, 20.5; IR 2960, 2940, 2880, 1716 cm^{-1}; EIMS (m/z) 268 (M^+), 253 (M − Me). Anal. ($C_{16}H_{28}O_3$) C, H.

2-(2-Iodoethyl)-2,5,5-trimethyl-1,3-dioxane. Following the procedure of Larson,[16b] to a solution of sodium iodide (36.0 g, 0.240 mol) dissolved in dry acetonitrile (500 mL) and methyl vinyl ketone (19.72 mL, 0.200 mol) was added dropwise trimethylsilyl chloride (30.6 mL, 0.240 mol). After 5 min, 2,2-dimethyl-1,3-propanediol (25.0 g, 0.240 mol) was added. After 5 min the mixture was poured into a stirring mixture of 5% aqueous $NaHCO_3$ (200 mL) and pentane (400 mL). After the solution was thoroughly mixed, the lowermost of three layers was removed. The organic phases were washed with 5% aqueous $Na_2S_2O_3$ (200 mL) and brine (9 × 200 mL) until a single organic layer was obtained. The organic layer was dried over K_2CO_3 and evaporated to provide a yellow oil, which was further purified via column chromatography with alumina. Elution with hexane provided the desired iodide as a colorless oil, 25.7 g (46%), which turned a dark purple color at room temperature but froze to a conveniently storable solid in a −15 °C freezer: ^{1}H NMR (90 MHz) δ 3.52 (q, 4 H, J = 7.2 Hz), 3.36 (ddd, 2 H, J = 3.6, 4.8, 7.2 Hz), 2.30 (ddd, 2 H, J = 3.6, 4.8, 7.2 Hz), 1.40 (s, 3 H), 1.05 (s, 3 H), 0.90 (s, 3 H); IR 2954, 2864, 1253, 1211, 1172, 1117, 1079, 1018, 839 cm^{-1}; EIMS m/z 284, 269, 198, 183, 155, 129. Anal. ($C_9H_{17}IO_2$) C, H.

2,5,5-Trimethyl-2-[2′-(4″-carbomethoxy-1″(*R*)-methyl-3″-oxocyclohex-2″-yl)ethyl]-1,3-dioxane (13).[25] To a solution of cyclohexylisopropylamine (9.1 mL, 55 mmol) in dry THF (100 mL) at 0 °C was added *n*-butyllithium (189 mL of 2.5 M solution in hexane). After 30 min at 0 °C, 2-carbomethoxy-5(*R*)-methylcyclohexanone[23] (**12**, 4.0 mL, 25 mmol) was added. The mixture was stirred at 0 °C for 2 h and cooled to −78 °C, and then in succession 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone (DMTP) (30 mL, 250 mmol) and 2-(2′-bromoethyl)-2,5,5-trimethyl-1,3-dioxane[15] (6.5 mL, 27.5 mmol) were added dropwise. The mixture was allowed to warm to room temperature over 3 h. The mixture was poured into an ice cold, saturated ammonium chloride solution (500 mL) and extracted with diethyl ether (2 × 500 mL). The organic layers were washed with water (3 × 500 mL) and brine (500 mL), dried over $MgSO_4$, and evaporated in vacuo to give 11.9 g of the crude alkylation product, which was purified by flash chromatography with 238 g of silica gel and eluted with a gradient of 10% EtOAc/hexane → 20% EtOAc/hexane. In this manner, 3.5 g (43%) of the product **13** was obtained as a yellow oil: ^{1}H NMR[25] δ 3.70–3.80 (m, 3 H), 3.35–3.55 (m, 3 H), 1.36–1.40 (m, 3 H), 1.11 (dd, 1 H, J = 4.8, 6.3 Hz), 1.06 (dd, 0.6 H, J = 4.2, 6.6 Hz), 0.98–1.04 (m, 3 H), 0.91–0.97 (m, 4 H); IR 2952, 2867, 1746, 1712, 1654, 1614, 1441, 1365, 1212, 1092, 1021, 848 cm^{-1}.

2,5,5-Trimethyl-2-[2′-(1″(*R*)-methyl-3″-oxocyclohex-2″-yl)ethyl]-1,3-dioxane *p*-Tosylhydrazone (14). A mixture of the ketone **7** (41.6 g,

(25) Compounds without accompanying elemental analysies or HRMS have spectral data (NMR) included in the supplementary material.

155 mmol), dry THF (1 L), *p*-toluenesulfonohydrazide (31.8 g, 171 mmol), and dry pyridine (41.6 mL) was rotary-evaporated at 40 mmHg. After 20 h, the crude material was purified by filtration chromatography on 677 g of silica gel 60 (70–230 mesh) and eluted with EtOAc/hex [(20:80) → (40:60)] to give the product **14** (58.0 g, 86%) as a gummy solid that consisted of a 1:1 mixture of syn and anti isomers by NMR (400 MHz) and was routinely used without further purification. Careful flash column chromatography provided each of the slowly interconverting geometrical hydrazone isomers in pure form: first eluted isomer ^{1}H NMR (CD_2Cl_2) δ 7.72 (ddd, 2 H, J = 1.8, 1.8, 8.3 Hz), 7.39 (ddd, 2 H, J = 0.7, 0.7, 8.3 Hz), 3.78 (d, 1 H, J = 11.7 Hz), 3.70 (d, 1 H, J = 11.5 Hz), 3.62 (dd, 1 H, J = 2.6, 11.6 Hz), 3.49 (dd, 1 H, J = 4.4, 11.6 Hz), 3.36 (dd, 1 H, J = 2.6, 11.4 Hz), 2.95 (dd, 1 H, J = 3.8, 12.5 Hz), 2.41 (s, 3 H), 2.00–2.10 (m, 1 H), 1.98 (dddd, 1 H, J = 2.4, 4.2, 12.8, 13.8 Hz), 1.40 (ddd, 1 H, J = 2.4, 6.8, 15.0 Hz), 1.20 (s, 3 H), 1.13 (s, 3 H), 0.90 (d, 3 H, J = 7.2 Hz), 0.80 (s, 3 H); IR ($CHCl_3$) 3120, 2955, 2875, 1735, 1635, 1605, 1500 cm^{-1}; EIMS m/z 437 (M + H$^+$), 421 (M − Me). Anal. ($C_{23}H_{36}H_2O_4S$) C, H, N, S. Last eluted isomer: ^{1}H NMR (CD_2Cl_2) δ 7.81 (ddd, 2 H, J = 1.8, 1.8, 8.3 Hz), 7.59 (br s, 1 H), 7.30 (ddd, 2 H, J = 1.9, 2.6, 8.6 Hz), 3.48 (dd, 1 H, J = 4.4, 11.6 Hz), 3.36 (ddd, 1 H, J = 1.3, 3.9, 11. 4 Hz), 2.40 (s, 3 H), 2.20 (ddd, 1 H, J = 5.5, 8.5, 14.3 Hz), 2.10 (ddd, 1 H, J = 5.0, 7.5, 14.4 Hz), 1.89 (ddd, 1 H, J = 5.9, 7.2, 7.2 Hz), 1.78 (ddd, 1 H, J = 3.1, 8.2, 17.9 Hz), 1.24 (s, 3 H), 0.96 (s, 3 H), 0.88 (d, 3 H, J = 6.91 Hz), 0.87 (s, 3 H); IR ($CHCl_3$) 3120, 2955, 2875, 1735, 1635, 1605, 1500 cm^{-1}; EIMS m/z 437 (M + H$^+$), 421 (M + Me). Anal. ($C_{23}H_{36}N_2O_4S$) C, H, N, S.

2,5,5-Trimethyl-2-[2′-((1″*S*)-2″-formyl-6″(*R*)-methylcyclohex-2″-enyl)ethyl]-1,3-dioxane (6).[25] To a solution of the hydrazone **14** (23.8 g, 54.6 mmol) in dry TMEDA (400 mL) at −78 °C was added *n*-butyllithium (136.5 mL of 1.6 M solution in hexane, 218.4 mmol). The mixture was stirred at ambient temperature for 90 min (-N_2) and then cooled to 0 °C. After slow addition of dry DMF (54 mL), the mixture was stirred at 0 °C for 30 min, poured into an ice-cold saturated aqueous NH_4Cl solution (2.0 L), and extracted with EtOAc (2 × 1.0 L). The combined organic layers were washed with a saturated aqueous NH_4Cl solution (1.0 L), water (1.0 L), and brine (1.0 L), dried (Na_2SO_4), and evaporated in vacuo to provide 21.5 g of crude material, which was purified by flash chromatography on 215 g of silica gel 60 (230–400 mesh) and eluted with EtOAc/hex (15:85). In this fashion, the product **6** (10.7 g, 70%) was isolated as a pale yellow oil. The unstable aldehyde was stored for only brief periods in benzene under argon in a freezer (−15 °C) and used as soon as possible: ^{1}H NMR[25] δ 9.42 (s, 1 H), 6.73 (t, 1 H, J = 3.8 Hz), 3.51 (dd, 2 H, J = 1.9, 11.5 Hz), 3.46 (ddd, 2 H, J = 1.3, 4.1, 11.5 Hz), 2.31 (ddd, 2 H, J = 1.3, 3.7, 7.9 Hz), 2.24 (br d, 1 H, J = 8.5 Hz), 1.94 (dddd, 1 H, J = 2.8, 4.0, 8.0, 9.7 Hz), 1.84 (ddd, 1 H, J = 4.0, 8.3, 13.6 Hz), 1.34–1.45 (m, 3 H), 1.31 (s, 3 H), 0.98 (s, 3 H), 0.92 (s, 3 H), 0.89 d, 3 H, J = 6.9 Hz); ^{13}C NMR δ 194.7, 151.2, 99.0, 70.3, 41.6, 37.7, 35.0, 29.9, 28.5, 27.5, 26.1, 23.9, 23.0, 22.7, 21.0, 18.6, 14.1; IR (film) 2960, 2870, 2710, 1685, 1635 cm^{-1}; UV λ_{max} = 230 nm (log ϵ 3.96); EIMS m/z 265 (M − Me).

Tris(trimethylsilyl)aluminum Etherate.[24] A mixture of Fluka aluminum powder (20 g, 100–200 μm), Fluka aluminum granules (5 g, 0.15–1.7 mm), dry Et_2O (200 mL), and iodine (2.0 g) was magnetically stirred in a three-neck, 500-mL round-bottom flask until the iodide color disappeared. Mercury (20 g) was added, followed by freshly distilled chlorotrimethylsilane (120 mL, 945 mmol). The mixture was stirred vigorously at room temperature for 3 h, and clean lithium wire (3.2-mm diam, ~0.01% Na, 1 mol, 7.0 g, 155 cm) was added in small pieces (0.3–0.5 cm). The well-stirred mixture was rigorously maintained at 35–40 °C in an oil bath for 48 h. After allowing to cool and the solids settling, the solution was decanted by cannula, carefully transferring solely clear solution. The decantation procedure was repeated with portions of pentane (2 × 200 mL), and the combined decants were evaporated under vacuum. The residue was dried under high vacuum for 2 h, pentane (50 mL) was added, and the mixture was swirled. After the solids settled, the solution was decanted via cannula and transferred to a new flask under argon. Another portion of pentane (50 mL) was added to the solid material, and the procedure was repeated, finishing with the blending of the two pentane solutions. **WARNING**: A pentane solution of tris(trimethylsilyl)aluminum etherate is highly pyrophoric and, consequently, all operations involving use of this material must be carried out under an inert atmosphere. The solution was indefinitely stable during storage under argon in a freezer. The solution was assayed by reaction with 1-formylcyclohexene that was freshly prepared from 1-(hydroxymethyl)cyclohexene via manganese dioxide oxidation. Typically, the aluminum reagent was added dropwise to 1.0 mmol of 1-formylcyclohexene in dry Et_2O (2 mL) at −78 °C. A transient red color no longer appeared with each drop when the reaction was complete and, when monitored by TLC, the starting material was easily detected in the UV while the product was not, even though the R_f's were similar. For example, with the run following the procedure above, 0.67 mL of the aluminum reagent was required for the assay, indicating a concentration of 1.5 N. The titer of tris(trimethylsilyl)aluminum etherate was highly dependent on the brand and lot of aluminum used.

2,5,5-Trimethyl-2-[2′-[1″*R*-methyl-3″-[(trimethylsilyl)hydroxymethyl]cyclohex-3″-en-2″-yl]ethyl]-1,3-dioxane Acetyl Ester (15). To the aldehyde **6** (10.6 g, 37.9 mmol) in dry Et_2O (100 mL) at −78 °C was added tris(trimethylsilyl)aluminum etherate (40.0 mmol, 100 mL of 0.4 M solution in pentane). After the solution was stirred at −78 °C for 10 min, acetic anhydride (18.9 mL, 200 mmol) and 4-(dimethylamino)-pyridine (200 mg) were added in succession. The mixture was stirred at ambient temperature for 16 h, poured into an ice-cold saturated aqueous sodium potassium tartrate solution (300 mL), and extracted with Et_2O (2 × 300 mL). The combined ethereal layers were washed with saturated sodium potassium tartrate solution (300 mL) and brine (300 mL), dried over $MgSO_4$, and evaporated in vacuo to give 22.2 g of crude material, which was purified by flash chromatography on 222 g of silica gel 60 (230–400 mesh). Elution with EtOAc/hex [(5:95) → (10:90)] gave 13.2 g (88%) of the product **15** as a colorless oil: ^{1}H NMR δ 5.55 (t, 1 H, J = 3.6 Hz), 5.25 (d, 1 H, J = 0.8 Hz), 3.54 (dd, 2 H, J = 1.7, 11.0 Hz), 3.44 (dd, 1 H, J = 1.4, 2.7 Hz), 3.42 (dd, 1 H, J = 1.1, 2.7 Hz), 2.03 (s, 3 H), 1.35 (s, 3 H), 0.98 (s, 3 H), 0.89 (d, 3 H, J = 7.0 Hz), 0.87 (s, 3 H), 0.02 (s, 9 H); IR ($CHCl_3$) 3000, 2960, 2930, 2875, 1725, 1645 cm^{-1}; EIMS m/z 396 (M$^+$), 395 (M − H). Anal. ($C_{22}H_{40}O_4Si$) C, H.

2,5,5-Trimethyl-2-[2′-[4″-(carboxymethyl)-1″(*R*)-methyl-3″-[(trimethylsilyl)methylene]cyclohex-2″-yl]ethyl]-1,3-dioxane (17). To freshly distilled dry diethylamine (10.3 mL, 100 mmol) in dry distilled THF (300 mL) at 0 °C was added *n*-butyllithium (63 mL or 100 mmol of a 1.6 M solution in hexane). The mixture was stirred at 0 °C for 10 min and then was cooled to −78 °C. The ester **15** (19.8 g, 50 mmol) in dry distilled THF (50 mL) was added dropwise over 20 min. The mixture was stirred at −78 °C for 4 h, allowed to warm gradually to ambient temperature, and stirred for 4 days. The resultant mixture was poured into an ice-cold solution of saturated aqueous NH_4Cl (1 L) and 5 N HCl (25 mL) and extracted with $CHCl_3$ (3 × 300 mL). The organic extracts were washed with brine (1 L), dried over $MgSO_4$, and evaporated in vacuo to give 29.8 g of crude material, which was purified by flash chromatography on 400 g of silica gel 60 (230–400 mesh). Elution with (1% HOAc/EtOAc/hexane [(10:90) → (25:75)] provided the product **17** (12.47 g, 63%): ^{1}H NMR δ 5.38 (s, 1 H), 3.56 (d, 2 H, J = 11.4 Hz), 3.44 (ddd, 2 H, J = 1.4, 5.7, 11.4 Hz), 2.78 (m, 1 H), 2.62 (dd, 1 H, J = 9.5, 15.0 Hz), 2.48 (dd, 1 H, J = 5.9, 15.0 Hz), 2.11 (m, 1 H), 1.76–1.94 (m, 4 H), 1.50–1.73 (m, 4 H), 1.40–1.47 (m, 1 H), 1.37 (s, 3 H), 1.10–1.20 (m, 1 H), 1.03 (s, 3 H), d, 3 H, J = 7.1 Hz), 0.90 (s, 3 H), 0.097 (s, 9 H); IR ($CHCl_3$) 3575, 3030, 3000, 2955, 2870, 1710, 1610 cm^{-1}; EIMS m/z 396 (M$^+$), 381 (M − Me); HRMS calcd for $C_{22}H_{40}SiO_4$ 396.260, found 396.270. Anal. ($C_{22}H_{40}SiO_4$) C, H.

[3(*R*)-(3α,5aβ,6β,8aβ,12β,12a(*R*))]-Octahydro-3,6-dimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one ((+)-9-Desmethylartemisinin, 19). Through a solution of acid **17** (2.25 g, 5.68 mmol) in CH_2Cl_2 (200 mL) at −78 °C was bubbled O_3/O_2 from a generator (0.6 L/min, 8.5 psi, 0.8 A, 70 V) for 11 min, whereupon a blue color persisted. The mixture was analyzed by TLC (EtOAc/hex (3:7)) to insure the absence of any starting material, whereupon the mixture was purged with argon and allowed to warm to ambient temperature. BHT (10 mg), silica gel (34.7 g of 70–230 mesh), and 15% aqueous H_2SO_4 (3.3 mL) were added in succession. After the mixture was stirred for 4 days, the solids were filtered off and rinsed with CH_2Cl_2 (2 × 100 mL). The filtrate was concentrated in vacuo to afford an oil, which was purified via flash column chromatography with 25% EtOAc/hex and silica gel. Pure **19** was obtained as colorless crystals that recrystallized from EtOAc/hex, 925 mg (61%): mp 103.0–103.5 °C; $[\alpha]^{22}_D$ = +56.7° (c = 0.150, $CHCl_3$); ^{1}H NMR δ 5.89 (s, 1 H), 3.17 (dd, 1 H, J = 7.1, 18.5 Hz), 2.41 (ddd, 1 H, J = 4.0, 13.0, 14.7 Hz), 2.26 (dd, 1 H, J = 1.5, 18.5 Hz), 2.04 (ddd, 1 H, J = 7.0, 10.1, 14.8 Hz), 1.97 (ddd, 1 H, J = 3.7, 5.7, 13.2 Hz), 1.87 (dddd, 1 H, J = 1.0, 2.8, 6.8, 7.0 Hz), 1.68–1.78 (m, 2 H), 1.43 (s, 3 H), 1.05–1.16 (m, 1 H), 0.98 (d, 3 H, J = 6.0 Hz); IR ($CHCl_3$) 1735, 1105, 1035, 995 cm^{-1}; CIMS m/z (rel intensity) 286 (M + NH_4^+, 89), 269 (M + H$^+$, 28), 258 (48), 251 (30), 240 (57), 223 (88), 195 (59). Anal. ($C_{14}H_{20}O_5$) C, H.

2,5,5-Trimethyl-2-[2′-[4″-(1(*S*)-carboxyethyl)-1″(*R*)-methyl-3″-[(trimethylsilyl)methylene]cyclohex-2″-yl]ethyl]-1,3-dioxane (18). A. Directly from Acid 17. To a solution of diisopropylamine (413 mL, 2.96 mmol) in dry THF (5 mL) at 0 °C was added *n*-butyllithium (2.96 mmol, 1.91 mL of 1.55 M solution in hexane). The mixture was stirred at 0 °C for 15 min and then cooled to −78 °C. The acid **17** (532 mg, 1.34 mmol) in dry THF (2 mL) was added via syringe, and the mixture was allowed to warm to ambient temperature over 30 min and was then heated to 50 °C for 2 h and recooled to 0 °C. Methyl iodide (210 μL,

3.36 mmol) was added via syringe; the mixture was then stirred at room temperature for 1 h, poured into an ice-cold, saturated aqueous NH_4Cl solution (20 mL), and extracted with $CHCl_3$ (2 × 20 mL). The organic layers were washed with brine (20 mL), dried over $MgSO_4$, and evaporated in vacuo to give 640 mg of crude material. This was purified by flash chromatography on 64 g of silica gel 60 (230–400 mesh) and eluted with (1% HOAc/EtOAc)/hexane (20:30) to afford the product (**18**, 535 mg, 97%) as a colorless gum.

B. Directly from Acetate 15. To a solution of diethylamine (166 μL, 1.61 mmol) in THF (3 mL) at 0 °C was added *n*-butyllithium (1.01 mL of 1.60 M in hex). After 15 min at 0 °C, the solution was cooled to −78 °C and a solution of acetate **15** (212 mg, 0.536 mmol) in THF (1 mL) was added via cannula. The resultant solution was allowed to slowly warm to ambient temperature overnight. After 16 h, the mixture was heated to 45 °C for 2 h and allowed to cool to ambient temperature, and a cold (0 °C) solution of lithium diisopropylamide (from diisopropylamine, 187 μL, 1.34 mmol, and *n*-butyllithium, 0.84 mL of 1.60 M in hex) in THF (2 mL) was added via cannula. The resultant mixture was warmed to 45 °C for 3 h, allowed to cool to ambient temperature, and further cooled to −78 °C; and methyl iodide (233 μL, 3.75 mmol) was then added dropwise via syringe. The resultant yellow suspension was allowed to warm to ambient temperature over 1 h, then stirred with 10% aqueous HCl (2 mL) and saturated aqueous NH_4Cl (15 mL), and extracted with $CHCl_3$ (35 mL). The separated organic layer was washed with saturated aqueous NH_4Cl (20 mL) and 5% aqueous $NaHSO_3$ (2 × 25 mL), dried over Na_2SO_4, and evaporated to afford an orange oil, which was purified via flash column chromatography with silica gel. Elution with 15% (1% HOAc/EtOAc)/hex led to the isolation of **18** as a colorless oil, 133 mg (61%): ^1H NMR δ 5.38 (s, 1 H), 3.57 (d, 2 H, J = 11.5 Hz), 3.45 (ddd, 2 H, J = 1.3, 11.2, 11.2 Hz), 2.74 (dq, 1 H, J = 6.7, 11.4 Hz), 2.40 (ddd, 1 H, J = 3.9, 4.7, 11.0 Hz), 2.09 (dd, 1 H, J = 4.8, 7.0 Hz), 1.37 (s, 3 H), 1.15 (d, 3 H, J = 6.8 Hz), 1.03 (s, 3 H), 0.95 (d, 3 H, J = 7.0 Hz), 0.90 (s, 3 H), 0.07 (s, 9 H); IR ($CHCl_3$) 3600, 3500, 3000, 2950, 2870, 2650, 1705, 1605 cm^{-1}; EIMS m/z 410 (M^+), 395 (M − Me); HRMS calcd for $C_{23}H_{42}O_4Si$ 410.285, found 410.286.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(3″-oxobutyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]propionic Acid (4). To a vigorously stirring suspension of silica gel 60 (70–230 mesh, 500 mg) in CH_2Cl_2 (7 mL) was added 10% aqueous oxalic acid (175 μL). After 15 min, a solution of the ketal **18** (145 mg, 0.350 mmol) in CH_2Cl_2 (3 mL) was added. After 20 h, $MgSO_4$ (1 g) was added, and the suspended solids were filtered off and washed with EtOAc (3 × 10 mL). The filtrate was evaporated to an oil, which was purified via preparative TLC with silica gel. After development in HOAc/MeOH/$CHCl_3$, pure keto acid **4** was obtained as a clear glass, 93 mg (81%): ^1H NMR δ 5.35 (s, 1 H), 2.73 (dq, 1 H, J = 6.8, 12.0 Hz), 2.67–2.80 (br s, 1 H), 2.30–2.58 (br m, 3 H), 2.13 (s, 3 H), 1.10 (d, 3 H, J = 7.2 Hz), 0.92 (d, 3 H, J = 6.8 Hz), 0.087 (s, 9 H); IR ($CHCl_3$) 2925, 1695, 1240 cm^{-1}; CIMS (NH_4^+) m/z (rel intensity) 342 ($M + NH_4^+$, 100), 325 ($M + H^+$, 48), 307 (36), 235 (68). Anal. ($C_{18}H_{32}SiO_3$) C, H.

(+)-Artemisinin (1). A. From Ketal Acid 18. The following reactions were carried out in a hood with its lights off. Into a solution of the ketal acid **18** (170 mg or 0.426 mmol) in CH_2Cl_2 (40 mL) at −78 °C was bubbled a stream of O_3/O_2 (7 psi, 0.4 L/min, 70 V) for 2 min. The mixture was analyzed by TLC (EtOAc/hex (3:7)) to insure the absence of any starting material, whereupon the mixture was purged with argon. To the mixture was added in succession BHT (20 mg), 15% aqueous H_2SO_4 (0.20 mL), and silica gel (70–230 mesh, 2.03 g). The mixture was allowed to warm to 22 °C and stirred efficiently overnight. The suspended solids were filtered and thoroughly rinsed with CH_2Cl_2 (3 × 15 mL) and EtOAc (2 × 10 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ (35 mL), dried over Na_2SO_4, and evaporated to give a yellow oil, 124 mg, which was purified via flash chromatography with silica gel (10 g). Elution with EtOAc/hex (3:7) afforded pure **1** as a white solid, 42 mg (35%), which crystallized from hexane: mp 158–9 °C (lit.[2] mp 156–7 °C) and mixed mp with authentic material, 151–2 °C; observed $[\alpha]^{21}_D$ = +65.2° (*c* 0.900, $CHCl_3$), reported[2] $[\alpha]^{17}_D$ = +66.3° (*c* 1.64, $CHCl_3$). The spectroscopic (NMR, IR, MS) and chromatographic (TLC) properties of this product were identical with an authentic sample of (+)-artemisinin. In addition to **1**, the above chromatography provided a slightly less polar, white crystalline substance, 7 mg (6%), which was identified as (+)-deoxyartemisinin (**20**)[2] by spectroscopic and chromatographic comparison to an authentic sample.

B. From Keto Acid 4. The keto acid **4** (10 mg) was ozonized as above in CH_2Cl_2 (5 mL). After an argon purge, the solvent was evaporated (bath temperature <25 °C), and the resulting oil was dissolved in $CDCl_3$ (1 mL) containing a trace of trifluoroacetic acid (10 μL). Conversion to artemisinin **1** was monitored by NMR. When the reaction was complete after a few hours, the solvent was evaporated and the product purified on TLC plates, eluting with EtOAc/hex (3:7), to afford pure **1** as a white solid (3.5 mg or 39%) as well as deoxyartemisinin (**20**, 1 mg or 11%).

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Supplementary Material Available: Reaction scheme and experimental data for synthesis of **15** and **16** (3 pages). Ordering information is given on any current masthead page.