Articles

Synthesis of a C,D-Ring Fragment of Artemisinin

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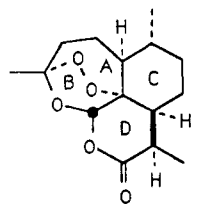
A multistep preparation is described for carboxyvinylsilane **6**, which upon reaction with ozone initially gave dioxetane **8** as a transient intermediate in a highly stereoselective manner. Subsequent rearrangement at ambient temperature resulted in cyclization to (±)-hexahydroisochroman-3-one **2**, whose relative stereochemistry was determined by X-ray crystallographic analysis and found to resemble the C,D-ring portion of the antimalarial artemisinin (**1**).

(+)-Artemisinin, commonly referred to as qinghaosu, is an effective antimalarial agent isolated from *Artemisia annua L.* An X-ray crystallographic analysis has shown that artemisinin possesses the unusual tetracyclic structure **1**.[1]



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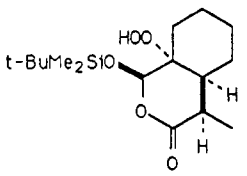

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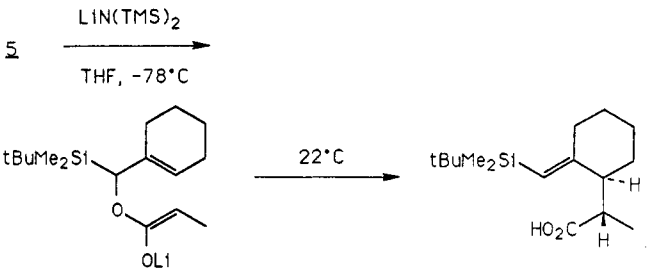
The promising antiparasitic activity of **1** against drug-resistant strains of malaria, combined with its synthetically challenging structure, has prompted total syntheses by Zhou[2] and Hofheinz,[3] an unsuccessful approach by Jung,[4] and a model study by Clark.[5] Despite these synthetic efforts, antimalarial activity has only been examined among derivatives in which the structure of artemisinin is almost wholly preserved.[1] We recently reported a stereoselective synthesis of (+)-artemisinin (**1**)[6] and have now used similar methodology to synthesize isolated structural portions in our ongoing program to identify the essential structural features of a putative antimalarial pharmacaphore and design improved analogues of **1**. We report herein the preparation of the ring fragment **2**, which resembles the C/D rings of artemisinin, as shown in Scheme I.

Reduction of commercially available carbomethoxycyclohexene **3** with vitride in THF at 0 °C gave cyclohexenylmethanol in 82% yield after distillation. Subsequent silylation with *tert*-butyldimethylsilyl chloride in CH_2Cl_2 utilizing *N*-ethyl-*N*,*N*-diisopropylamine and catalytic amounts of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) afforded the silyl ether **4** in 90% yield after distillation. The silyl ether **4** was deprotonated in a mixture of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and THF at −78 °C with *sec*-butyllithium. Three hours after warming to −30 °C, the resultant Brook rearrangement product anion was cooled to −78 °C and quenched with acetic acid. After flash chromatography, the desired α-silyl alcohol was obtained in 52% yield but proved unstable; it was therefore immediately acylated with a mixture of propionic anhydride, pyridine, and DMAP in ether to give the ester **5** in 99% yield after purification. The desired carbon skeleton was established by a modification of the Ireland–Claisen ester–enolate rearrangement.[7] Accordingly, the ester **5** was kinetically deprotonated to the *Z* enolate with lithium *N*-isopropylcyclohexylamide (LICA) in THF at −78 °C and, after 18 h at 22 °C, rearranged to provide **6** in 68% yield after flash chromatography, along with the isomeric contaminant **7** in 6% yield. By contrast, the thermodynamic *E* enolate generated from **5** (**5a**) with lithium hexamethyldisilazane[7] gave **7** as the major product and **6** in trace amounts. Thus,



5a **7**

the minor product **7** is assumed to be isomeric with **6** at the position α to the carboxyl group of the side chain. The *E* geometry about the double bond of **6** was determined via ^1H NMR NOE experiments.[8] The relative stereochemistry about C-2 and the propionate side chain was

(1) Klayman, D. *Science* **1985**, *228*, 1049.
(2) Zhou, W. *Pure Appl. Chem.* **1986**, *58*, 817.
(3) Schmid, G.; Hofheinz, W. *J. Am. Chem. Soc.* **1983**, *105*, 624.
(4) Jung, M.; ElSohly, H.; Croom, E.; McPhail, A.; McPhail, D. *J. Org. Chem.* **1986**, *51*, 5417.
(5) Clark, G.; Nikado, M.; Fair, C.; Lin, J. *J. Org. Chem.* **1985**, *50*, 1494.
(6) Avéry, M. A.; Jennings-White, C.; Chong, W. K. M. *Tetrahedron Lett.* **1987**, *28*, 4629.
(7) Ireland, R.; Varley, M. *J. Am. Chem. Soc.* **1984**, *106*, 3668.
(8) A 400-MHz ^1H NMR NOE experiment revealed the following results for compound **6**. The propionate methine proton was assigned to the signal at δ 2.75 (dq, J = 6.8, 11.2 Hz, 1 H); subsequent irradiation confirmed an assignment of the C-2 proton signal at δ 2.35 (overlapping ddd, J = 4.0, 4.0, 11.2 Hz, 1 H) due to the resultant decoupling observed. The vinyl proton signal occurred at δ 5.19 (s, 1 H). On irradiation of the C-1′ vinyl proton signal, an NOE enhancement of 10% was observed solely for the C-2 proton signal, which established the syn relationship of these two hydrogens.

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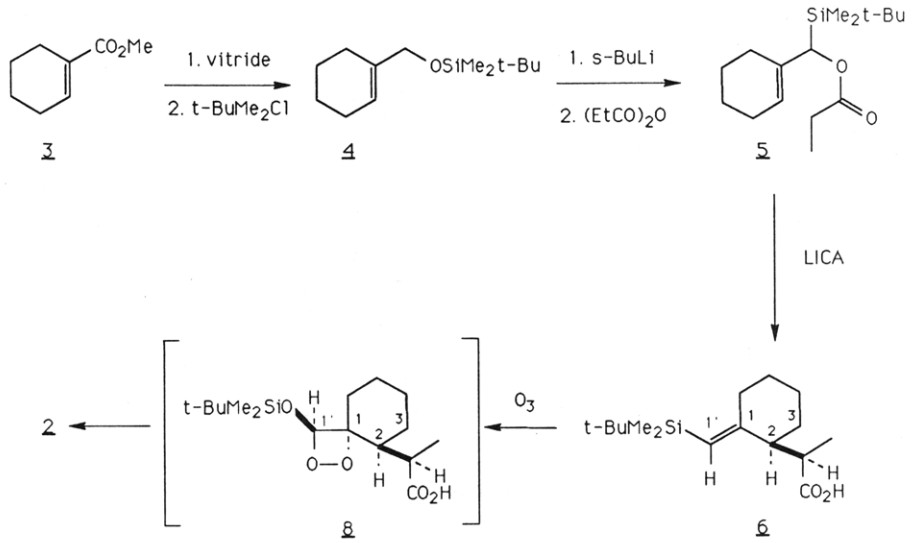
Scheme I



deduced vide infra from an X-ray crystallographic analysis of the reduction product **9**, which was in turn prepared from **2** as shown. The carbon framework was now in place, and penultimate introduction of the crucial oxygen functionality remained. Upon treatment of **6** with ozone in methanol at −78 °C and subsequent evaporation of the solvent at low temperature (ca. 0 °C), we found that the dioxetane **8** was produced by analogy to the observation made by Büchi,[9] and as a single diastereomer, as seen in the initial NMR spectrum ($CDCl_3$, δ 6.35, s, 1 H). However, upon standing at room temperature as a neat oil, the conversion of **8** was witnessed by TLC or in the NMR over several hours to provide **2** as a major product in 57% yield after flash chromatography. The hydroperoxy lactone **2** (IR: 1740 cm^{-1}) is a relatively stable substance that can be stored for long periods at −20 °C. However, for the purpose of further structural elucidation, **2** was reduced with triphenylphosphine in ethanol to give **9** in high yield. Flash chromatography of **9** and crystallization from benzene afforded material suitable for crystallographic analysis by single-crystal X-ray diffraction techniques.

Single crystals of **9** are at 20 ± 1 °C, monoclinic, space group $P2_1/n$ (an alternate setting of $P2_1/c$-C_{2h}^5 (No. 14)) with a = 7.268 (1) Å, b = 10.247 (2) Å, c = 24.115 (5) Å, β = 03.51 (2)°, V = 1792.6 (7) Å^3, and Z = 4 (d_{calcd} = 1.165 g cm^{-3}, μ_a (Mo Kα) = 0.14 mm^{-1}). A total of 2879 independent reflections having $2\theta_{MoK\alpha} < 48.3°$ were collected on a computer-controlled four-circle Nicolet autodiffractometer using full ω scans (0.90° wide); the structure was solved using the "direct methods" techniques incorporated in the Nicolet SHELXTL software package as modified at Crystalytics Co. on a Data General Eclipse S200 or S230 computer. A structural model that utilized anisotropic thermal parameters for all C, O, and Si atoms and isotropic thermal parameters for all H atoms has been refined to convergence [R_1(unweighted, based on F) = 0.040 for 1858 independent reflections having $2\theta_{MoK\alpha} < 48.3°$ and $I > 3\sigma(I)$] using counterweighted cascade block-diagonal least-squares techniques.[10]

The relative stereochemistry at C-1, C-4, C-4a, and C-8a of **9** is as shown in Figure 1, and thus corresponding assignments were made in the depiction of hexahydroisochroman-3-one (**2**). Note that all centers except C-1 are identical with those of the C/D fragment of the natural

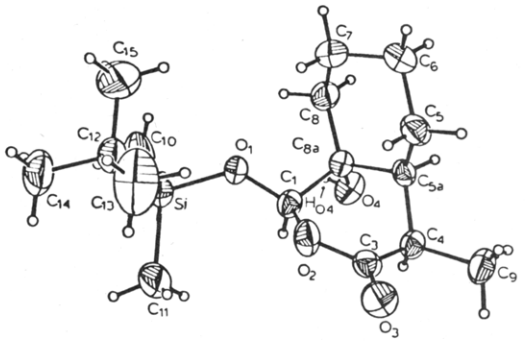
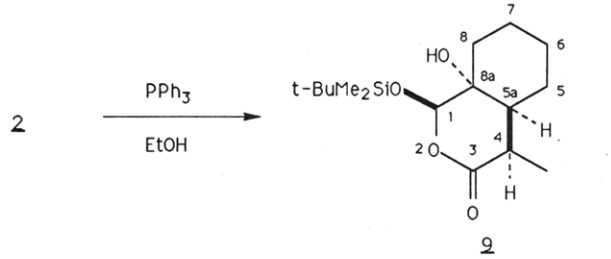


Figure 1. Perspective drawing of $C_{16}H_{30}O_4Si$. Non-hydrogen atoms are represented by thermal vibration ellipsoids drawn to encompass 50% of their electron density; hydrogen atoms are represented by arbitrarily small spheres that are in no way representative of their true thermal motion.

product **1**. Why the C-1 silyloxy substituent becomes oriented in the less stable β-configuration[11] in the product **2** may be a matter of speculation. However, that the dioxetane **8** is obtained as a single diastereomer that, upon rearrangement, produces only a single tractable substance, **2**, suggests that the carboxylate group is involved in an intramolecular cyclization whose outcome is dictated by the relative stereochemistry of the starting dioxetane **8**. Thus, we have indicated the relative stereochemistry at C-1′ in **8** that is consistent with this mechanism.



Although the C/D-ring fragment **2** does not show substantial in vitro antimalarial activity compared with the natural product **1**, we are pursuing the conversion of **2** into new analogues of **1** that may have desired biological activity.

(9) Büchi, G.; Wuest, H. *J. Am. Chem. Soc.* **1978**, *100*, 294.
(10) See the supplementary material.
(11) MM2 calculations showed that **2** (silyloxy substituent β) was *less* stable than the corresponding axial isomer (silyloxy substituent α) by at least 1.5 kcal/mol.

Experimental Section

All melting points were determined on a Thomas capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a JEOL FX90 and a Varian XL400 spectrometer with $CDCl_3$ as solvent unless otherwise stated. IR spectra were recorded on a Perkin-Elmer 1310 instrument. Mass spectral data were obtained through the use of a CEC 21-110B, high-resolution, double-focusing spectrometer. Elemental analyses were determined by Desert Analytics, Tucson, AZ.

1-[[(*tert*-Butyldimethylsilyl)oxy]methyl]cyclohexene (4). To a solution of 1-(hydroxymethyl)cyclohexene (46.6 mL, 44.8 g, 400 mmol) in dry dichloromethane (250 mL) at 0 °C under argon was added *N,N*-diisopropylethylamine (76.6 mL, 440 mmol) followed by a solution of *tert*-butylchlorodimethylsilane (66.3 g, 440 mmol) in dry dichloromethane (100 mL). The mixture was stirred at room temperature for 2 h and poured into ice-cold saturated ammonium chloride solution (100 mL). The organic layer was separated and washed with saturated ammonium chloride solution (100 mL) and brine (100 mL). The aqueous layers were reextracted with dichloromethane (100 mL). The combined organic layers were dried (K_2CO_3) and evaporated in vacuo to give 89.7 g of crude material. This was fractionally distilled under reduced pressure to give the silyl ether **4**[12] (81.8 g, 90%) as a colorless liquid, bp 94–100 °C (6 mmHg). IR (thin film): 3000 (m), 2950 (s), 2930 (s), 2880 (s), 2855 (s), 1680 (w) cm^{-1}. NMR: δ 5.62 (1 H, m), 3.97 (2 H, s), 1.93 (4 H, m), 1.56 (4 H, m), 0.88 (9 H, s), 0.03 (6 H, s). MS (*m/e*): 226 (M^+), 211 (M – Me). Anal. Calcd for $C_{13}H_{26}OSi$: C, 68.96; H, 11.57. Found: C, 69.15; H, 11.65.

1-[1′-(*tert*-Butyldimethylsilyl)-1′-propionoxymethyl]cyclohexene (5). To the silyl ether **4** (26.0 mL, 22.6 g, 100 mmol) in dry THF (250 mL) at −78 °C under argon was added dry TMEDA (24.0 mL, 160 mmol) followed by *s*-BuLi (154 mL of 1.3 M solution in cyclohexane, 200 mmol). The mixture was stirred at −30 °C for 3 h and then recooled to −78 °C. A mixture of acetic acid (20 mL) and THF (80 mL) was slowly added. The mixture was poured onto ice-cold, saturated sodium bicarbonate solution (200 mL), which was extracted with dichloromethane (2 × 300 mL). The organic extracts were washed with brine (200 mL), dried ($MgSO_4$), and evaporated in vacuo to give 26.7 g of crude material. This was purified by flash chromatography on 267 g silica gel 60 (230–400 mesh), eluting with EtOAc/hexane (5:95) → (7:93) to give the product alcohol (11.65 g, 52%) as a colorless oil. IR (thin film): 3580 (w), 3460 (m, broad), 3040 (w), 2940 (s), 2900 (s), 2870 (s), 1670 (w) cm^{-1}. NMR: δ 5.53 (1 H, m), 3.92 (1 H, s), 1.97 (4 H, m), 1.58 (4 H, m), 0.94 (9 H, s), −0.01 (3 H, s), −0.11 (3 H, s). MS (*m/e*): 226 (M^+), 225 (M – H).

To a solution of the alcohol (11.3 g, 50.0 mmol) in diethyl ether (100 mL) at room temperature under argon was added dry pyridine (8.10 mL, 100 mmol) followed by propionic anhydride (7.70 mL, 60.0 mmol). 4-(*N,N*-Dimethylamino)pyridine (610 mg, 5.0 mmol) was added, and the mixture was stirred at room temperature for 16 h. The mixture was poured into ice-cold water (100 mL) and extracted with diethyl ether (2 × 100 mL). The organic extracts were washed with saturated ammonium chloride solution (100 mL), dried ($MgSO_4$), and evaporated in vacuo to give 18.7 g of crude material. This was purified by flash filtration through 100 g of silica gel 60 (230–400 mesh), eluting with 500 mL of EtOAc/hexane (7:93) to give the product (13.9 g, 99%) as a colorless oil. IR (thin film): 3030 (w), 2925 (s), 2885 (m), 2850 (s), 2770 (w), 1740 (s), 1660 (w) cm^{-1}. NMR: δ 5.44 (1 H, m), 5.05 (1 H, s), 2.25 (2 H, q, *J* = 7 Hz), 1.88 (4 H, m), 1.49 (4 H, m), 1.05 (3 H, t, *J* = 7 Hz), 0.83 (9 H, s), −0.03 (3 H, s), −0.12 (3 H, s). MS (*m/e*): 282 (M^+), 253 (M – Et), 225 (M – EtCO). Anal. Calcd for $C_{16}H_{30}O_2Si$: C, 68.03; H, 10.70. Found: C, 67.91; H, 10.72.

(±)-*erythro*-2-[(2′*E*)-1-[(*tert*-Butyldimethylsilyl)methylene]cyclohex-2-yl]propionic Acid (6). To dry cyclohexylisopropylamine (2.17 mL, 13.0 mmol) in dry THF (20 mL) at 0 °C under argon was added *n*-BuLi (8.13 mL of 1.6 M solution in hexane, 13.0 mmol). The mixture was stirred at 0 °C for 10 min and then was cooled to −78 °C. The ester **5** (3.08 mL, 2.82 g, 10.0 mmol) was added dropwise, and the mixture was stirred at room temperature for 18 h. The mixture was poured into ice-cold saturated ammonium chloride solution (50 mL) and extracted with diethyl ether (2 × 50 mL). The organic extracts were washed with brine (50 mL), dried ($MgSO_4$), and evaporated in vacuo to give 4.0 g of crude material. This was purified by flash chromatography on 200 g of silica gel 60 (230–400 mesh); eluting with (1% HOAc/EtOAc)/hexane (15:85) → (20:80) gave the desired product **6** (1.70 g, 68%) as a crystalline solid, mp 106–109 °C. IR ($CHCl_3$): 3500 (w), 3030 (m, broad), 2930 (s), 2860 (s), 2650 (m, broad), 1710 (s), 1620 (s) cm^{-1}. NMR (400 MHz): δ 5.19 (1 H, s), 2.75 (1 H, dq, *J* = 6.8, 11.2 Hz), 2.35 (1 H, ddd, *J* = 4.0, 4.0, 11.2 Hz), 2.28 (1 H, ddd, *J* = 4.0, 4.0, 13.7 Hz), 1.72 (1 H, ddd, *J* = 5.0, 5.0, 13.7 Hz), 1.64 (6 H, m), 1.34 (1 H, m), 1.06 (3 H, d, *J* = 6.8 Hz), 0.88 (9 H, s), 0.07 (6 H, s). MS (*m/e*): 257 (M – Me), 255 (M – OH), 225 (M – Bu^t). Anal. Calcd for $C_{16}H_{30}SiO_2$: C, 68.09; H, 10.64; Si, 9.93. Found: C, 68.11; H, 10.45; Si, 9.56. In addition, the threo isomer **7** was obtained (161 mg, 6%) as a white solid, which could be crystallized from cold hexane, mp 105–106 °C. NMR (400 MHz): δ 5.12 (1 H, s), 2.77 (1 H, dq, *J* = 6.9, 9.8 Hz), 2.35 (1 H, ddd, *J* = 5.0, 5.0, 10.5 Hz), 2.29 (1 H, ddd, *J* = 3.8, 3.8, 9.8 Hz), 1.97 (1 H, m), 1.56 (6 H, m), 1.15 (3 H, d, *J* = 6.9 Hz), 0.82 (9 H, s), 0.017 (6 H, s). IR (Nujol): 3100 (broad), 2920 (s), 2880 (s), 2600 (broad), 1710 (s), 1620 (m), 1465 (s), 1380 (m), 1370 (m), 1320 (m), 1295 (m), 1260 (m), 1160 (w), 1090 (w), 1070 (w), 1025 (m), 950 (m), 870 (s), 850 (s), 780 (s). CIMS (*m/e*): 300 (M + NH_4^+), 283 (M + H), 225 (M – C_4H_9).

(±)-1β-[(*tert*-Butyldimethylsilyl)oxy]-8aα-hydroperoxy-4β-methyl-4aα,5,6,7,8,8aα-hexahydroisochroman-3-one (2). Ozonized oxygen (7.0 psi, 0.4 L/min, 70 V) was bubbled through a sintered-glass frit into a solution of the carboxylic acid **6** (500 mg, 1.77 mmol) in dry methanol (20 mL) at −70 °C for 6 min, 40 s. The mixture was evaporated in vacuo (bath temperature 18 °C) to give 0.651 g of crude material, a small amount of which was examined by TLC and NMR. The initial product, presumably **8**, had ^1H NMR (400 MHz) δ 6.35 (1 H, s), 3.27 (1 H, dq, *J* = 7, 7 Hz), 1.34 (3 H, d, *J* = 7 Hz), 0.93 (9 H, s), 0.13 (3 H, s), 0.10 (3 H, s). After several hours at 22 °C, or after about 18 h at −20 °C, all of **8** had rearranged to crude **2** as witnessed by both TLC and NMR. The crude hydroperoxide **2** was then purified by flash chromatography on 65 g of silica gel 60 (230–400 mesh), eluting with EtOAc/hexane (25:75) to give the product **2** (334 mg, 57%) as a white solid, which was crystallized from EtOAc/hexane, mp 102–103 °C. IR ($CHCl_3$): 3520 (m), 3340 (m, broad), 2950 (s), 2900 (m), 2890 (m), 2870 (s), 1740 (s) cm^{-1}. ^1H NMR (400 MHz): δ 8.06 (1 H, broad), 5.74 (1 H, s), 2.99 (1 H, dq, *J* = 5.7, 7 Hz), 2.22 (1 H, ddd, *J* = 4.1, 4.1, 13.2 Hz), 1.91 (1 H, m), 1.67 (5 H, m), 1.28 (2 H, m), 1.16 (3 H, d, *J* = 7 Hz), 0.92 (9 H, s), 0.20 (3 H, s), 0.17 (3 H, s). ^{13}C NMR: δ 173.6, 138.3, 99.5, 83.2, 41.1, 35.5, 29.2, 25.6 (3 C), 25.5, 23.7, 23.1, 21.0, 17.9, 12.4. MS (*m/e*): 331 (M + H^+), 315 (M – Me), 297 (M – O_2H), 285 (M – CO_2), 273 (M – Bu^t).

(±)-1β-[(*tert*-Butyldimethylsilyl)oxy]-8aα-hydroxy-4β-methyl-4aα,5,6,7,8,8aα-hexahydroisochroman-3-one (9). To a solution of the hydroperoxide **2** (1.2 g, 3.64 mmol) in ethanol (50 mL) at room temperature under Ar was added triphenylphosphine (2.0 g, 7.63 mmol). After 3 h, the solvent was evaporated, and the residue was dissolved in a minimal amount of EtOAc. This crude mixture was applied to a flash column (700 g of silica gel 60, 230–400 mesh) and eluted with 25% EtOAc/hexane to give **9** (1.0 g, 88%) as a white solid, which was crystallized twice from benzene to give needles, mp 98–99 °C. NMR (400 MHz): δ 5.34 (1 H, d, *J* = 1.2 Hz), 3.13 (1 H, dq, *J* = 7.0, 7.0 Hz), 1.94 (1 H, ddd, *J* = 4.8, 4.8, 13.5 Hz), 1.80 (2 H, m), 1.69 (2 H, m), 1.59 (1 H, m), 1.41 (1 H, ddd, *J* = 5.0, 10.8, 13.5 Hz), 1.34 (1 H, m), 1.27 (1 H, m), 1.17 (3 H, d, *J* = 7.0 Hz), 0.90 (9 H, s), 0.19 (3 H, s), 0.15 (3 H, s). IR ($CHCl_3$): 3580 (m), 3350 (br), 2925 (s), 2850 (s), 1735 (s), 1470 (m), 1450 (m), 1380 (m), 1260 (s), 1190 (s), 1170 (s), 1105 (s), 1090 (s), 1000 (s), 820 (s) cm^{-1}. EIMS (*m/e*): 314 (M + H), 299 (M – Me), 257 (M – C_4H_9), 213, 211, 183, 165, 137. The product **9** was analyzed by X-ray crystallographic analysis[10] (Crystalytics Co., Lincoln, NE) and shown to have the structure and relative stereochemistry given in Figure 1. From this information, the structure of **2** can be inferred as shown in Figure 1.

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(12) Detty, M. R.; Seidler, M. D. *J. Org. Chem.* **1981**, *46*, 1283.

to thank Dr. Cynthia Day of Crystalytics Co. (Lincoln, NE) for the crystallographic analysis and Dr. W. Milhous and MRDC staff at the Walter Reed Army Institute of Research for biological screening data.

Registry No. (±)-**1**, 119241-68-8; (±)-**2**, 119183-85-6; **3**, 18448-47-0; **4**, 76358-53-7; **4** (alcohol), 4845-04-9; (±)**5**, 119183-86-7; (±)-**5** (alcohol), 119183-91-4; (±)-**6**, 119183-87-8; (±)-**7**, 119183-87-8; (±)-**8**, 119183-89-0; (±)-**9**, 119183-90-3.

Supplementary Material Available: Crystal structure analysis report for **9**, Table I (atomic coordinates for non-hydrogen atoms), Table II (anisotropic thermal parameters for non-hydrogen atoms), Table III (atomic coordinates for hydrogen atoms), Table IV (bond lengths), Table V (bond angles), and Table VI (close contacts involving hydrogen atoms) (13 pages). Ordering information is given on any current masthead page.

Simplified Analogues of the Antimalarial Artemisinin: Synthesis of 6,9-Desmethylartemisinin

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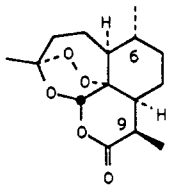
(±)-6,9-Desmethylartemisinin (**8**) was prepared from pyrrolidinocyclohexene and *cis*-1,4-dichloro-2-butene in eight steps. The intermediacy of bicyclic **2** led to a stereocontrolled route to pivotal syn-substituted cyclohexane **5**. Hydrolysate keto acid vinylsilane **7** underwent abnormal reaction with ozone and subsequent acid-catalyzed cyclization to the title compound.

The natural product (+)-artemisinin has exhibited antimalarial activity against chloroquine-resistant *P. falciparum*.[1] The unique peroxide-containing sesquiterpene structure is depicted here by **1**. Despite its use in ancient Chinese medicine and, more recently, structural elucidation in 1980, many details of the molecular basis for antimalarial activity by artemisinin remain unknown. The emergence of quinine-resistant malaria in tropical regions and the challenge of such a target structure for total synthesis have focused attention upon artemisinin from many laboratories,[2] including our own. We have recently reported the total synthesis of (+)-artemisinin[3] and are presently engaged in a program for the synthesis of novel analogues[4] that are intended to identify a responsible pharmacophore for the design of improved antimalarials.



1

(+)- Artemisinin

Reported herein is the synthesis of a simplified analogue of artemisinin that does not have the C6 and C9 substituent methyl groups. The absence of some of the asymmetric centers allowed a much different synthetic approach from that of our other work: as shown in Scheme I, for starting material bicyclo[4.3.1]decenone **2** was prepared from pyrrolidinocyclohexene and *cis*-1,4-dichloro-2-butene as described by Still.[5] The nonenolizable bridging carbonyl of **2**[6] was condensed in straightforward fashion with bis(trimethylsilyl)methyllithium[7] to the vinylsilane **3** in 78% yield after purification. When the diene **3** was submitted to carefully metered delivery of ozone under conditions developed by Schreiber[8] for the production of aldehyde–esters from disubstituted double bonds, surprisingly selective monocleavage to the desired syn-substituted cyclohexane **4** (as a 1:1 mixture of geometrical vinylsilane isomers) was obtained in 64% yield after chromatography. Ozonolysis of the vinylsilane moiety of **3** or **4** under the experimental conditions was never witnessed. The aldehyde of **4** served as a convenient point for elaboration with lithium diphenyl(1-methoxyethyl)phosphine oxide[9] to the diastereomeric methyl enol ethers **5** in 58% yield, which contained all the necessary carbons for the target analogue. Sequential deprotection was carried out by saponification of esters **5** to acids **6**, which were stirred in a suspension with oxalic acid adsorbed on silica gel to provide keto acids **7** and 94% overall yield from **5**. The final construction of the tetracyclic peroxide utilized methodology that coincided with our prior work,[3,4] and, in this manner, ozone was delivered carefully through a solution of keto acids **7** in methylene chloride at −78 °C. In separate experiments, when starting **7** was no longer present by TLC, the solvent was removed in vacuo to give a material that appeared by NMR (90 mHz) to be diastereomeric [(trimethylsilyl)oxy]dioxetanes[10] (δ 6.17 and

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