Pergamon

Tetrahedron Vol. 50, No. 4, pp. 957-972, 1994

0040-4020/94 $6.00+0.00

0040-4020(93)E0045-H

Synthesis, Conformational Analysis, and Antimalarial Activity of Tricyclic Analogs of Artemisinin

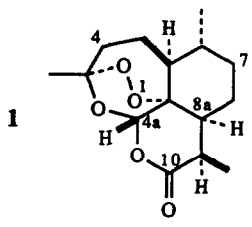
Mitchell A. Avery,*[1] Fenglan Gao,[1] Wesley K.M. Chong,[2a] Thomas F. Hendrickson,[2b] Wayne D. Inman,[4] and Phillip Crews[3]

Department of Chemistry, University of North Dakota, Grand Forks, North Dakota 58202;
Department of Chemistry, University of California, Santa Cruz, California 95064;
BioOrganic Chemistry Laboratory, SRI International, 333 Ravenswood Ave., Menlo Park, California 94025;
Agouron Pharmaceuticals, Inc. 3565 General Atomics Court, San Diego, CA 92121

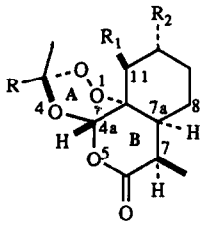
Abstract: Aspects of synthesis, conformational analysis, and antimalarial activity of artemisinin analogs (±)-5-nor-6-desmethyl-4,5-secoartemisinin (**2**), (-)-5-nor-4,5-secoartemisinin (**3**), (+)-4,5-secoartemisinin (**4**), and (+)-4,5-desethano-artemisinin (**5**)[22] are described. The conformations of these multicyclic structures were determined through a combination of X-ray crystallography, NMR, and computational analysis, with an emphasis on the 1,2,4-trioxane geometry. Two major solution conformations for both **2** and **3** were found: all chair forms **2a** and **3a**, and twist-boat/twist-boat/chair forms **2b** and **3b**, respectively. The major solution conformer **2a** matched the solid state structure found via X-ray crystallography. Computations suggest that (+)-4,5-Secoartemisinin (**4**) has three conformations of equal energy: chair/twist-boat/boat, **4a**, twist-boat/twist-boat/chair, **4b**, corresponding to the X-ray crystal structure, and twist boat/chair/chair, **4c**. The 1,2,4-trioxane and lactone rings adopt the twist-boat conformations in **2b**, **3b**, **4a**, and **4c**. When compared to artemisinin, these tricyclic, flexible analogs have different geometry yet retain some *in vitro* antimalarial activity against resistant strains of *Plasmodium falciparum*. Possible structure/activity correlations are discussed.

Artemisinin (**1**, qinghaosu) is a naturally occurring peroxidic sesquiterpene that is effective against drug-resistant *Plasmodium falciparum* malaria.[5] The peroxy group is definitely an essential feature of the ill-defined pharmacophore responsible for the antimalarial activity[6] of **1**, as shown from the lack of activity for 1-deoxyartemisinin. However, other peroxides[9a] such as t-butyl hydroperoxide,[7] cyclic endoperoxides,[8] simple 1,2,4-trioxanes,[5] and 1,2,4,5-tetraoxanes[9b] exhibit relatively weak antimalarial activity. Studies undertaken by Meshnick to define the mode of action of this drug suggest that the molecular mechanism of action involves hemin,[10] a ubiquitous cellular component of *P. falciparum*, at least as an initiator for homolytic cleavage of the peroxy moiety of artemisinin and analogs.[11] Further support for this mechanism is provided by the observation that iron sequestering agents attenuate the activity of this class of molecules,[12] and that iron salts catalyze the decomposition of artemisinin analogs.[13] Our search for the optimal architecture of antimalarial peroxides led to the preparation of diverse analogs,[14] such as 4,5-seco analogs[15] of artemisinin (see Figure I, wherein Chemical Abstract

numbering is employed[16]). These analogs were readily prepared,[15] but many had complex, temperature-dependent ^{1}H NMR spectra that reflected conformational mobility. Although 1,2,4-trioxolanes[17] and 1,3,5-trioxanes[18] have known dynamic behavior, the flexibility of 1,2,4-trioxanes was heretofore unexplored. This study was undertaken to structurally characterize the observed solution conformers and their association with potency with the aim of further defining SAR and improving these antimalarials.



1

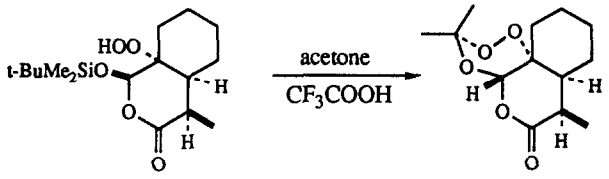


2, R = CH_3; R_1 = R_2 = H;
3, R = CH_3; R_1 = H, R_2 = CH_3;
4, R = R_1 = R_2 = CH_3;
5, R = R_1 = H; R_2 = CH_3

Figure I. Structures of artemisinin (**1**) and 4,5-seco analogs.

RESULTS AND DISCUSSION

Tricyclic **2** was made from our reported hydroperoxy-lactone **6**[14b] as shown below. Treatment of peroxide **6** in acetone with an excess of trifluoroacetic acid afforded 1,2,4-trioxane **2** in 73% yield. Adaptations of this depicted process for the syntheses of (-)-5-nor-4,5-secoartemisinin (**3**), (+)-4,5-secoartemisinin (**4**), and Lee's "desethanoartemisinin" (**5**) have been reported by us,[15] and experimental details for the synthesis of **3-5** outlined in Scheme I are provided.



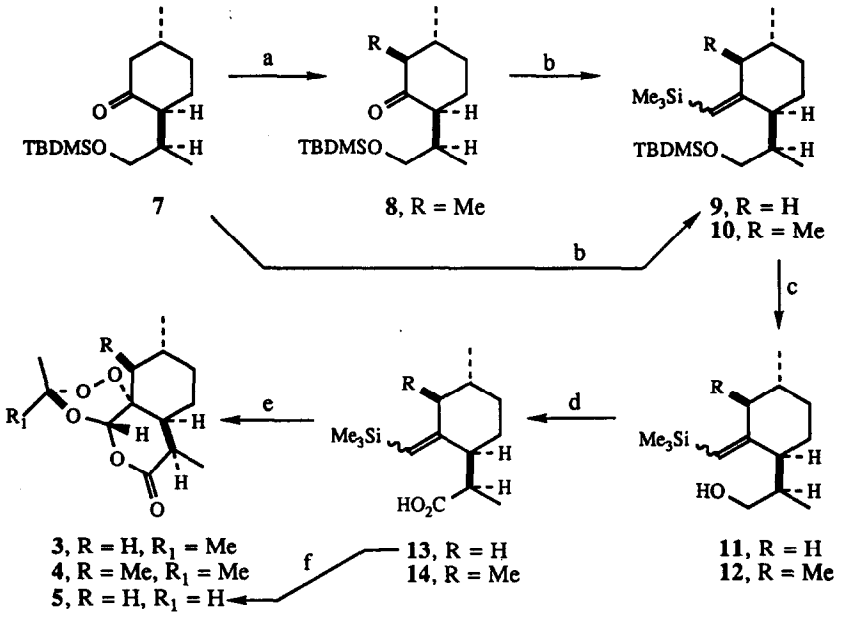
6 **2**

The structures of these analogs **2-5** were examined in solution and/or crystalline states. As a point of reference, examination of the rigid structure of artemisinin (**1**)[6] shows that the trioxane ring is held in a twist-boat conformation by the C4-C5 bridge. In these analogs **2-5**, this restriction is absent and the chair conformation can be adopted by the trioxane ring. For **2** and **3**, multiple solution conformers were observed, analyzed by NMR techniques, and compared to the solid state (X-ray determined structure) when possible.

The ^{1}H NMR spectrum of **2** exhibited temperature dependence and conformational interconversion. Slow and fast exchange was observed at -10°C in $CDCl_3$ and 80°C in DMSO-d_6, respectively. At -10°C, two conformers for **2** were evident from the doubled set of proton resonances for H-4a (δ5.69, s, 0.3H;

δ5.62, s, 0.7H) and H-7 (δ3.53, dq, J = 4.5, 7.2 Hz, 0.3H; δ3.09, dq, J = 4.7, 7.2 Hz, 0.7H). X-ray crystallographic analysis of tricycle **2** revealed all-chair conformations for the A, B, and C rings (see Figure II).[19]

For 10-methyl analog **3**, slow interconversion was also seen at -10°C, but it flexed rapidly at 22°C in $CDCl_3$. Like trioxane **2**, the ^1H NMR spectrum of 10-methyl analog **3** at -10°C had two conformers as exhibited in the resonances for H-4a (δ5.70, 0.3H; δ5.61, 0.7H) and H-7 (δ3.55, 0.3H; δ3.10, 0.7H).



Scheme I. *Reagents and conditions:* a) lithium diisopropylamide, tetrahydrofuran, -78°C; then MeI; b) $MeO(Me)_2SiCHLiSi(Me)_3$,[30] pentane; c) Bu_4NF, tetrahydrofuran; d) pyridinium dichromate, N,N-dimethylformamide; e) O_3, CH_2Cl_2, -78°C; then acetone, Amberlyst®-15, 22°C; f) O_3, CH_2Cl_2, -78°C; then acetaldehyde, Amberlyst®-15, 22°C.

By contrast to **2** and **3**, 10,11-dimethyl analog **4** exhibited single proton resonances for H-4a (δ5.66, s) and H-7 (δ3.72, dq) in $CDCl_3$ from -10° through 22°C. An X-ray analysis of **4** revealed a boat/chair/chair conformation (**4b**, Table 2; Figure III) for each of the A, B, and C rings, respectively.[15]

Further study determined the structure of the two solution conformations for **2** by reconciling NMR experimental results with molecular mechanics conformational analysis. Fifteen hundred structures were generated by a Monte Carlo method and subsequently MM2 minimized (see Experimental Section for details). Only eleven conformers were found within 5 kcal/mol of the lowest energy structure (eight of which are described in Table 1), and a simple Boltzmann calculation predicted that only conformations **2a**

and **2b** are significantly populated at room temperature. The next lowest energy calculated conformer **2c** is 2.96 kcal higher in energy and expected to represent less than one percent of the population of

Table 1. Relative Energies and Calculated Distances for Conformers **2a-2h***

Conformer	rel ΔE_{calc} (kcal/mol)	Distance (Å) H-7/Me-3	A/B/C Ring ** Conformation
2a	0.00	2.71	C/C/C
2b	1.08	2.80	B/B/C
2c	2.96	4.09	B/C/C
2d	2.97	2.73	C/B/B
2e	3.85	2.73	B/B/B
2f	3.87	4.75	C/B/B
2g	4.34	2.82	C/C/B
2h	4.77	4.67	C/B/C

* MacroModel[31] (version 4.0), MM2 force field with peroxide parameters.[32] ** C = chair, B = boat (actually twist-boat).

conformers. Experimentally, an observed NOESY correlation between H-7 and Me-13 demonstrated consistency with **2a** and **2b**. The lowest energy calculated conformer **2a** matched the solid state structure derived from X-ray crystallography (Figure II).

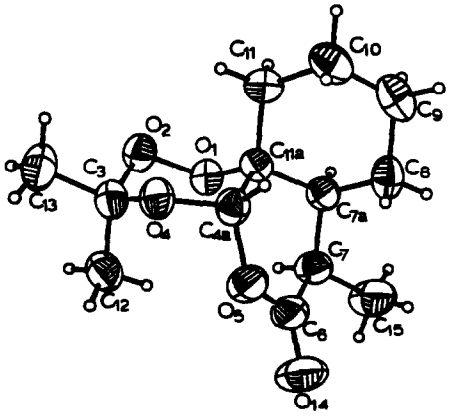


Figure II. Perspective drawing of X-ray structure for **2**. Non-hydrogen atoms are represented by thermal vibration ellipsoids drawn to encompass 50% of their electron density; hydrogen atoms are represented by arbitrarily small spheres that are in no way representative of their true thermal motion.

Also based on the calculated energy (Table 2) and experimental NMR data, the predominant conformation in solution of **3** was predicted to be **3a** (Figure III). An observed NOESY correlation between major resonances for H-7 and Me-3 was consistent with the calculated structure (Table 2). All three rings in **3a** are in the same chair conformation and overlap nicely with the structure for **2** (**2a**).

Analog **4** was apparently one conformer by NMR, but a conformational search provided three conformers (Table 2) that are--if the calculations are accurate--very close in energy and should have almost equal populations in solution. In the solid state, **4** was found in a single conformation matching calculated **4b** (Figure III) that could arise from crystal packing. If there are several conformations so close in energy, perhaps NMR resonances for these conformers were unresolved at the lowest temperature employed, -10°C. However, a NOESY correlation between Me-3 (δ 1.61) and Me-11 (δ 1.10) and not H-7 (δ 3.71) is only consistent with the calculated low energy structure **4b** and its distances between Me-3,

Table 2. Relative Energies and Distances for Conformers of Analogs **2-5**

Analog	Conformer	rel ΔE_{calc} (kcal/mol)*	Distance (Å)		A/B/C Ring Conformation**
			Me-3/H-7	Me-3/Me-11	
3	**3a**	0.00	2.71	-	C/C/C
3	**3b**	1.01	2.80	-	B/B/C
3	**3c**	2.96	4.09	-	B/C/C
3	**3d**	4.16	2.91	-	C/B/B
4	**4a**	0.00	2.55	3.01	B/B/C
4	**4b**	0.11	3.73	2.10	B/C/C
4	**4c**	0.16	2.42	2.98	C/C/C
4	**4d**	2.02	2.70	2.42	C/B/B
4	**4e**	2.06	3.02	4.30	C/B/B
4	**4f**	2.25	2.61	2.19	C/B/C
5	**5a**	0.00	-	-	C/C/C
5	**5b**	4.46	-	-	C/B/B
5	**5c**	4.85	-	-	B/B/C
5	**5d**	6.00	-	-	B/C/C

* MacroModel[31] (version 4.0), MM2 force field with peroxide parameters.[32] ** C = chair, B = boat (actually twist-boat).

H-7 and Me-11 (Table 2). In the case of **4** there is a difference between the conformational analysis, which predicts three low energy structures, and the NMR data that apparently shows the three rings of **4** are in the same boat/chair/chair conformation as the crystalline state.

Further NMR analysis provided additional information for determining the minor conformations of **2** and **3**. Two possibilities for **2** belonged to one family with only partial ring reversal occurring in one or two rings, or that total ring reversal occurred in all three rings. The answer was provided, in part, by low temperature NOESY experiments (-10°C in $CDCl_3$) because magnetization transfer correlations[20] were observed between the major and minor resonances for H-4a, H-7, and H-11. The initial ^1H NMR spectrum displayed H-11 major (δ2.69) and minor (δ2.01) resonances that were broad doublets (J = 13.5 Hz), possibly due to geminal or vicinal coupling of H-10_{ax} with H-11_{ax}. However, decoupling experiments revealed both resonances had similar environments: each had large geminal coupling between equatorial and axial protons at C-11 (H-11_{eq}/H-11_{ax}) and two small vicinal coupling (<3 Hz) to H-10_{ax} and H-10_{eq}. Thus the stereochemistry of H-11_{eq} in **2a** is constrained in a 1,4-diaxial arrangement with two lone pairs of oxygens 0-2 and 0-4 and is diagnostically shifted downfield to δ 2.7,[21] as also seen with H-11 for both solution conformers. Therefore H-11 in each conformer was in the equatorial position (H-11_{eq}), ring reversal does not occur in the C ring and both the conformers seem to be **2a** and **2b**. Finally, the ^1H NMR NOESY interaction between H-7 and Me-3 minor resonances correlated calculated energies and distances between H-7 and Me-13 (Table 1) and implicated **2b** as the minor solution conformer.

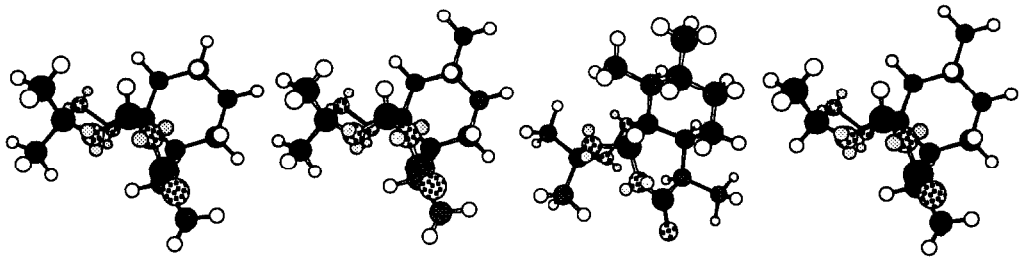


Figure III. From left to right, conformations **2a**, **3a**, **4b**, and **5a**.

Analogously the minor conformer of **3** was determined to be **3b** because of conformer search results and NMR behavior similar to **2**.

Complimentary NMR experiments insured and completed our assignments in the complicated spectra of these analogs. ROESY experiments pinpointed the spectral peaks for the C-3 methyl groups of major and minor conformers of these analogs in both chair and boat conformers. Chemical exchange correlations were found for the axial methyl in the major chair conformer at δ1.63 and the minor equatorial methyl at δ1.42. A similar correlation is seen for equatorial methyl in the chair at δ1.40 correlation to the minor axial methyl at δ1.56. Based on this information, X-ray data, and the modeling results, key proton chemical shifts for these analogs are assigned in Table 3.

The data in Table 3 also provides insight for the prediction of conformational behavior in other similar analogs. For example, Lee reported the related analog **5**,[22] whose structure lacks methyl groups compared to **2-4** (Figure 1). We interpreted the reported ^{1}H NMR data[22] to anticipate **5** in the single all-chair conformation **5a**, related to the **2a** and **3a** conformers. The absence of an axial methyl group raised the calculated relative

Table 3. Key Proton Chemical Shifts for Conformers of **2**, **3**, and **4**

	2		**3**		**4**	
Proton	C/C/C	B/B/C	C/C/C	B/B/C	C/C/C	B/C/C
Me-3	1.63ax	1.43eq	1.64ax	1.41eq	-	1.40eq
Me-3	1.40eq	1.56ax	1.41eq	1.57ax	-	1.61ax
H-4a	5.60	5.69	5.61	5.70	-	5.66
H-7	3.09	3.53	3.10	3.56	-	3.71
Me-7	1.18	1.24	1.19	1.23	-	1.23
Me-10	-	-	1.01	1.00	-	1.00
Me-11	-	-	-	-	-	1.10

energy of a chair/boat/boat conformer **5b**. We independently prepared analog **5**[15] and the ^{1}H NMR indeed displayed no temperature dependency. A thorough conformational search concurred that a single conformation should exist at room temperature, since the closest conformation **5b** was 4.46 kcal/mol higher in energy than the lowest energy all chair conformer (Table 2).

The antimalarial activity of these analogs were assessed *in vitro* in parasitized whole human blood with drug-resistant strains of *P. falciparum* at the Walter Reed Army Institute of Research[23] using a modification of the procedure of Desjardins[24] wherein the uptake of tritiated hypoxanthine is measured. Two *P. falciparum* malaria parasite clones, designated as Indochina (W-2) and Sierra Leone (D-6), were utilized in susceptibility testing. The antimalarial activity of these analogs relative to that of artemisinin (ratio of IC_{50}'s) are listed in Table 4. As shown, the analogs still retained antimalarial potency, and most notably analog **3** was as effective as artemisinin (**1**) in the D-6 clone.

These studies demonstrate that a distribution of conformations exist in solution for analogs **2** and **3**, with the major conformation corresponding to an all chair arrangement. Analogs **4** and **5**, on the other hand, are relatively rigid, in boat/chair/chair and all-chair conformations, respectively. None of the predominant solution conformers overlapped well with the natural product **1** and might be manifested in

the antimalarial potency. These relationships are further complicated by the unexplained variation in antimalarial activities of conformationally restrained, but artemisinin-like, 8a,9-seco analogs of artemisinin.[25,26] In an effort to reconcile these complex structure-activity relationships, we are currently engaged in the study of quantitative structure-activity relationships (QSAR) amongst artemisinin analogs.[27,28] These conformational studies will allow for the inclusion of the analogs **2-5** into a QSAR model.

Table 4. Percent Relative Activity of Artemisinin Analogs*

Structure	W-2	D-6
Artemisinin (**1**)	100	100
2	6	20
3	75	108
4	14	7
5	0	0

*(IC_{50} analog/IC_{50} artemisinin) × 100, *in vitro* against *P. falciparum*

EXPERIMENTAL METHODS

Computational Methods. All calculations were performed on a Silicon Graphics Indigo Elan 3000 workstation. Conformational analysis was performed using the molecular modeling program MacroModel[31] (Version 4.0). The MM2 force field was used, with the addition of specific parameters developed for peroxides[32] that reasonably agreed with the limited experimental data. The partial atomic charges used were those generated from the bond dipole moments in the force field parameter set. Conformations were generated by a previously described Monte Carlo method.[33] For each molecule, 1500 conformations were generated and subsequently minimized to a low r.m.s. gradient (< 0.05 kJ/Å). Since the fused ring somewhat restricts these molecules conformationally, the lowest energy structures were found numerous times during a single search procedure, giving us some assurance that the lowest energy structures found are true global minima. Further minimization of all structures found within 50 kJ of the global minimum (<20 in all cases) with an implicit chloroform solvation model did not change the energy rankings of each conformer set, but slightly affected the relative energy between conformers in each set. The relative energies reported here are from the gas phase calculations.

Chemistry. All solvents were HPLC grade and when appropriate, distilled from calcium hydride prior to storage over molecular sieves. Solvent and reagent transfers were accomplished through dried syringe or cannula, and all reactions were routinely conducted under an atmosphere of argon, unless otherwise indicated. Flash chromatography was done with silica gel (Kieselgel 60, 230-400 mesh). Thin-layer chromatography used Analtech 250 micron plates with F-256. NMR spectra were recorded with a GN-300 (300 MHz for ^1H and 75 MHz for ^{13}C), Varian XL 400, or Varian VXR 300 spectrometer. Standard pulse sequences were used in the ^1H-^1H COSY, NOESY, and ROESY experiments.[29] IR spectra were recorded with a Perkin-Elmer 1310 or 1610. UV spectra were recorded on a Perkin-Elmer 552. CIMS were obtained with a Reibermag R-10-10-C. Elemental analyses were determined by Desert Analytics, Tucson, AZ.

(±)-Hexahydro-3,3,7-trimethyl-4aH,6H-1,2,4-trioxino[6,5-jl][2]benzopyran-6-one (2).

To a solution of the hydroperoxide 6[14b] (133 mg, 0.403 mmol) in dry, distilled acetone (6 mL) was added trifluoroacetic acid (0.54 mL). The mixture stirred overnight at ambient temperature, poured into sat aq $NaHCO_3$ (25 mL), and extracted with Et_2O (3 × 25 mL). The combined organic layers were combined, washed with H_2O (40 mL) and sat aq NaCl (40 mL), dried over $MgSO_4$, filtered, and evaporated *in vacuo* to provide crude product, which was purified via preparative TLC on silica gel and elution with 20% EtOAc/hexane. Tricycle 2 was obtained as a white solid (75 mg, 73% yield), which crystallized from hexane, mp 111-112° C, and suitable for subsequent X-ray crystallographic analysis.[19] IR (CCl_4): 2960, 2880, 1755, 1460, 1390, 1220, 1180, 1100, 1020 cm^{-1}. ^1H NMR ($CDCl_3$) at 40° C: δ 5.69 (s, 0.3H), 5.62 (s, 0.7H), 3.53 (dq, J = 4.5, 7.2, 0.3H), 3.09 (dq, J = 4.8, 7.2, 0.7H), 2.69 (d, J = 13.5, 1H), 2.01 (d, J = 13.5, 0.3H), 1.62 (s, 3H), 1.39 (s, 3H), 1.17 (d, J = 7.2, 3H), 0.9 (m, 1.3H). CIMS (DCI-NH_3): 274 (M-NH_4^+), 257 (M-H^+), 198, 181, 170, 153. Calculated for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 61.04; H, 7.93.

2S-(1'-t-Butyldimethysilyloxy-2'R-propyl)-5R-methylcyclohexanone (7).

To a solution of the purified diol 2S-(1'-hydroxy-2'R-propyl)-5R-methylcyclohexan-1R-ol[34] (1.00 g or 5.81 mmol) in dry CH_2Cl_2 (50 mL) was added 4-N,N'-dimethylaminopyridine (28 mg or 0.04 eq.) followed by dry triethylamine (0.9 mL or 1.1 eq.). The resultant solution was cooled to 0°C, t-butylchlorodimethylsilane (963 mg or 1.1 eq.) was added, and the solution allowed to warm to ambient temperature. After 18 hours, the resultant solution was washed with 3% aq. HCl (2 X 25 mL), and then with sat. aq. sodium bicarbonate (2 X 25 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo* to give a clear oil. Flash chromatography over silica gel (50 g) with 10% EtOAc/hexane gave the desired intermediate 2S-(1'-t-Butyldimethylsilyloxy-2'R-propyl)-5R-methylcyclohexan-1R-ol (1.29 g, 83% yield) as a colorless oil. $[\alpha]_D^{20}$ = -10.9° (c = 14.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.062 (s, 3H), 0.065 (s, 3H), 0.92 (s, 9H), 0.92 (d, 3H, J = 6.4 Hz), 0.93 (d, 3H, J = 7.0 Hz), 1.19 (dq, 1H, J = 3.5, 12.6 Hz), 1.28 (m, 1H), 1.38 (br m, 1H), 1.51 (dq, 1H, J =

3.3, 12.8 Hz), 1.60 (m, 2H), 1.84 (ddddd, 1H, J = 2.5, 2.5, 7.4, 7.4, 12.4 Hz), 2.00 (dddd, 1H, J = 2.0, 4.0, 4.0, 12.4 Hz), 3.41 (ddd, 1H, J = 4.2, 9.9, 9.9 Hz), 3.61 (AB, 1H, J = 2.8, 10.0 Hz), 3.67 (AB, 1H, J = 5.4, 10.0 Hz). IR (neat): 3400, 2960, 2910, 2860, 1460, 1260, 1090, 1050, 840, 780 cm-^{1}. DCIMS (NH_3): m/z 287 (M+H), 269. Anal. Calcd for $C_{16}H_{34}SiO_2$: C, 67.07; H, 11.96. Found: C, 67.03; H, 12.22. Also obtained from the above chromatography in later fractions was the undesired regioisomer 1R-t-Butoxydimethylsiloxy-2S-(1'-hydroxy-2'R-propyl)-5R-methylcyclohexane (247 mg, 15% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.04 (s, 6H), 0.83 (d, 3H, J = 7.1 Hz), 0.88 (s, 9H), 0.89 (d, 3H, J = 6.5 Hz), 1.28 (ddq, 1H, J = 2.7, 7.2, 14 Hz), 1.6 (m, 4H), 1.96 (m, 2H), 3.39 (ddd, 1H, J = 4.4, 10, 10 Hz), 3.48 (AB, 1H, J = 7.2, 10 Hz), 3.55 (AB, 1H, J = 5.6, 10 Hz). DCIMS (NH_3): m/z 287 (M+H), 269.

Swern oxidation of the desired intermediate secondary alcohol was accomplished as follows: To a solution of dry dimethylsulfoxide (3.8 mL, 53.8 mmol or 2.4 eq.) in dry CH_2Cl_2 (100 mL) at -78°C was added oxalyl chloride (2.35 mL or 1.2 eq.). After 15 min, a solution of the alcohol 2S-(1'-t-Butyldimethylsilyloxy-2'R-propyl)-5R-methylcyclohexan-1R-ol (6.41 g or 22.4 mmol) in dry CH_2Cl_2 (50 mL) was added via cannula. After 1 hr at -78°C, dry triethylamine (7.80 mL, 56.0 mmol or 2.5 eq.) was added, and the resultant suspension was allowed to warm to ambient temperature. After 15 min, the brown suspension was treated with brine (75 mL), acidified with 10% aq. HCl, and the layers were then separated. The organic layer was washed with brine (2 X 100 mL), dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo* to provide 5.99 g of an orange oil which was purified by flash chromatography over silica gel (200 g) eluting with 5% EtOAc/hexane. The desired product **7** was obtained as a clear oil (5.52 g or 87% yield) as well as recovered starting alcohol (310 mg). $[\alpha]_D^{20}$ = -12.1° (c = 1.63, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.89 (s, 9H), 0.96 (d, 3H, J = 6.8 Hz), 1.01 (d, 3H, J = 6.3 Hz), 1.30 (m, 1H), 1.40 (dq, 1H, J = 3, 12.7 Hz), 1.7-2.4 (m, 5H), 3.48 (AB, 1H, J = 5.7, 9.8 Hz), 3.54 (AB, 1H, J = 5.1, 9.8 Hz). IR (neat): 2950, 2910, 2860, 1715, 1460, 1260, 1090, 1050, 850, 780 cm-^{1}. EIMS: m/z 284 (weak), 283 (M-H), 269 (M-Me), 269 (M-C_4H_9). Anal. Calcd for $C_{16}H_{32}SiO_2$: C, 67.55; H, 11.34. Found: C, 67.38; H, 11.52.

2S-(1'-t-Butyldimethysilyloxy-2'R-propyl)-5R,6S-dimethylcyclohexanone (**8**).

To a solution of dry N-isopropylcyclohexylamine (3.49 mL, 21.2 mmol) in THF (100 mL) at 0°C was added dropwise a 1.60M solution of butyllithium in hexane (13.3 mL, 21.3 mmol). After 10 min, the solution was cooled to -20°C and a solution of the ketone **7** (5.04 g, 17.7 mmol) in THF (40 mL) was added via cannula. The resultant yellow solution was allowed to warm to ambient temperature over 30 min. After 45 min at ambient temperature, methyl iodide (2.51 mL, 38.9 mmol) was added rapidly. After 25 min, the mixture was poured into a mixture of sat. aq. NH_4Cl (150 mL)/10% aq. HCl (5 mL). The mixture was extracted with ether (3 x 120 mL), and the combined organic layers were washed in succession with sat. aq. NH_4Cl (150 mL)/10% aq. HCl (5 mL); 5% aq. sodium thiosulfate (3 x 100 mL); and brine (2 x 100 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent evaporated under reduced pressure to afford 5.88 g of a brown oil. Flash chromatography over silica gel (150 g)

with 1% EtOAc/hexane gave the desired product **8** (3.04 g, 58% yield) as a yellow oil. $[\alpha]_D^{22}$ = -9.67° (c = 1.50, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 0.03 (s, 6H), 0.89 (s, 9H), 0.95 (d, 3H, J = 6.8 Hz), 1.00 (d, 3H, J = 6.45 Hz), 1.05 (d, 3H, J = 6.06 Hz), 1.45 (m, 3H), 1.85 (m, 1H), 1.95 (dddd, 1H, J = 1.5, 6.6, 6.6, 11.6 Hz), 2.00-2.13 (m, 2H), 2.38 (dddq, 1H, J = 1.5, 4.9, 5.6, 6.4 Hz), 3.53 (AB, 1H, J = 4.9, 9.8 Hz), 3.59 (AB, 1H, J = 5.6, 9.8 Hz). IR: 2955, 1709, 1468, 1253, 1089, 838, 776 cm^{-1}. EIMS: (m/z) 298 (M^+, weak), 284 (M-Me), 255, 244, 241, 242, 223, 211. Anal. Calcd for $C_{17}H_{34}SiO_2$: C, 68.40; H, 11.48. Found: C, 68.75; H, 11.23.

2S-(1'-t-Butyldimethysilyloxy-2'R-propyl)-5R-methyl-1-E/Z-trimethylsilylmethylenecyclohexane (**9**).

To a solution of dry pentane (200 mL) and (dimethyl(methoxy)silyl)trimethylsilylmethane[30] (4.5 mL, 20 mmol) at -78°C was added 1.7 M t-butyllithium in pentane (11.8 mL, 20 mmol). The mixture was allowed to warm to 23°C, stirred 120 min, recooled to -78°C, and treated with a solution of ketone **7** (5.6 g, 18 mmol) in pentane (50 mL). The mixture was allowed to warm slowly to 23°C while stirring overnight. The reaction mixture was poured into sat. aq. NH_4Cl (500 mL). The organic layer was separated, washed with additional portions of NH_4Cl (2 x 500 mL), dried over $MgSO_4$, filtered, and evaporated to give a light yellow oil. Gradient elution flash chromatography on silica gel (150 g) with 5 ⇒ 20% EtOAc/hexane gave the desired product **9** (1.21 g, 19% yield) as a colorless oil. While the product **9** was routinely used as a 60:40 E/Z mixture, the isomers were separated by SiO_2 PTLC eluting with hexane. In this manner, 380 mg of **9** gave 203 mg of isomer **9a** and 127 mg of **9b**. For **9a**, ^1H NMR (400 MHz, $CDCl_3$): δ 0.06 (s, 6H), 0.10 (s, 9H), 0.84 (d, 3H, J = 6.8 Hz), 0.91 (s, 9H), 1.22 (br dddd, 1H, J = 2.4, 4.1, 4.5, 13.3 Hz), 1.61 (ddd, 1H, J = 4.1, 4.1, 13.8 Hz), 1.67 (m, 1H), 1.74 (br d, 1H, J = 13.0 Hz), 1.82 (dddd, 1H, J = 4.7, 4.7, 13.7, 13.7 Hz), 1.97 (m, 1H), 2.07 (m, 1H), 2.34 (br d, 1H, J = 10.6 Hz), 2.52 (ddd, 1H, J = 1.3, 5.3, 12.5 Hz), 3.54 (AB, 1H, J = 5.7, 9.9 Hz), 3.65 (AB, 1H, J = 3.2, 9.9 Hz), 5.15 (d, 1H, J = 1.1 Hz). IR: 1615, 1260, 1120, 1100, 875, 850, 780 cm^{-1}. EIMS: (m/z) 354 (M^+), 339 (M-CH_3), 297 (M-tBu), 222, 211, 209, 182. Anal. Calcd for $C_{20}H_{42}Si_2O$: C, 67.72; H, 11.93. Found: C, 68.01; H, 12.17. For isomer **9b**, ^1H NMR (400 MHz, $CDCl_3$): δ 0.047 (s, 6H), 0.10 (s, 9H), 0.9 (s, 9H), 0.91 (d, 3H, J = 6.6 Hz), 0.93 (d, 3H, J = 6.6 Hz), 1.05-1.25 (m, 2H), 1.66 (m, 1H), 1.76 (dd, 1H, J = 8.8, 12.6 Hz), 1.83 (m, 2H), 1.90 (dq, 1H, J = 3.5, 6.6 Hz), 2.41 (ddd, 1H, J = 1.1, 4.2, 12.5 Hz), 3.42 (AB, 1H, J = 6.8, 9.7 Hz), 3.68 (AB, 1H, J = 3.5, 9.7 Hz), 5.14 (s, 1H). IR: 1615, 1250, 1100, 840, 780 cm^{-1}. EIMS: (m/z) 354 (M^+), 339 (M-CH_3), 297 (M-tBu), 251, 222, 211, 209, 182. Anal. Calcd for $C_{20}H_{42}Si_2O$: C, 67.72; H, 11.93. Found: C, 67.19; H, 12.07.

2S-(1'-t-Butyldimethysilyloxy-2'R-propyl)-5R,6S-dimethyl-1-E/Z-trimethylsilylmethylenecyclohexane (**10**).

To a solution of (dimethyl(methoxy)silyl)trimethylsilylmethane[30] (2.7 mL, 12.1 mmol) in pentane (120 mL) at -78°C was added a 1.70 M solution of t-butyllithium in pentane (7.12 mL, 12.1 mmol). The solution was allowed to warm to ambient temperature and stirred 180 min. The resultant yellow solution

was recooled to -78°C and a solution of the ketone **8** (2.40 g, 8.04 mmol) in pentane (60 mL) was added via cannula. The resultant mixture was allowed to warm slowly to ambient temperature and stirred overnight. The reaction solution was washed with sat. aq. NH_4Cl (100 mL) and brine (100 mL). The separated organic layer was dried over sodium sulfate and evaporated in vacuo to provide a yellow oil. Flash chromatography on silica gel (100 g) using a gradient elution with (0.5 ⇒ 1.0% EtOAc)/hexane afforded **10** as a colorless oil, (1.21 g, 41%). Ether **10** was routinely used as a 60:40 mixture of geometrical isomers and reacted identically to the pure isomer in subsequent reactions. An early fraction from chromatography was isomerically pure: $[\alpha]_D^{22}$ = +17.7° (c = 3.16, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.10 (s, 9H), 0.907 (s, 9H), 0.915 (d, 3H, J = 6.6 Hz), 0.922 (d, 3H, J = 7.0 Hz), 1.10 (dq, 1H, J = 4.2, 13.8 Hz), 1.18 (d, 3H, J = 7.6 Hz), 1.28 (m, 4H), 1.57-1.71 (m, 3H), 1.84 (dddd, 1H, J = 4.6, 4.6, 11.9, 13.5 Hz), 1.94 (m, 1H), 2.08 (br dq, 1H, J = 1.9, 7.6 Hz), 2.38 (ddd, 1H, J = 2.2, 5.2, 11.2 Hz), 3.52 (AB, 1H, J = 5.6, 9.9 Hz), 3.64 (AB, 1H, J = 3.1, 9.9 Hz), 5.23 (d, J = 0.6 Hz). IR (film): 2970, 2940, 2900, 1600, 1470, 1255, 1125, 1110, 1070, 1030, 855, 780 cm^{-1}. EIMS: (m/z) 368 (weak M^+), 236 (weak), 223, 196, 181, 162, 147. Anal. Calcd for $C_{21}H_{44}Si_2O$: C, 68.40; H, 12.03. Found: C, 68.39; H, 12.17.

5R,6S-Dimethyl-2S-(2'R-propionyl)-1(E/Z)-trimethylsilylmethylenecyclohexane (**12**).

To a solution of silyl ether **10** (230 mg, 0.623 mmol) in THF (5 mL) at 22°C was added 1.0 M Bu_4NF (0.68 mL) in THF. After 2.5 h at 22°C, the reaction mixture was poured into H_2O (10 mL) and extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (3 x 50 mL), dried over $MgSO_4$, and evaporated to give the crude alcohol **12**. Flash chromatography over silica gel (5 g) with gradient elution EtOAc (5 ⇒ 10%)/hexane provided pure **12** as a 60:40 mixture of diastereomers (140 mg, 88% yield). $[\alpha]_D^{22}$ = +17.0° (c = 7.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): Major diastereomer: δ 0.10 (s, 9H), 0.93 (d, 3H, J = 7.0 Hz), 0.96 (d, 3H, J = 6.8 Hz), 1.19 (d, 3H, J = 7.5 Hz), 3.47 (AB, 1H, J = 6.5, 10.7 Hz), 3.76 (AB, 1H, J = 3.1, 10.7 Hz). Minor diastereomer: δ 0.05 (s, 9H), 0.91 (d, 3H, J = 7.2 Hz), 0.93 (d, 3H, J = 6.8 Hz), 1.02 (d, 3H, J = 6.4 Hz), 3.34 (AB, 1H, J = 8.2, 9.5 Hz), 3.92 (AB, 1H, J = 8.2, 8.2 Hz). IR (film): Mixture: 3320, 2970, 2930, 2880, 1600, 1460, 1370, 1255, 1030, 855 cm^{-1}. EIMS: (m/z) 196, 122. DCIMS (NH_3): m/z 327 (M+TMS), 272 (M+NH_4), 255 (M+H), 239. Anal. Calcd for $C_{15}H_{30}SiO$: C, 70.79; H, 11.88. Found: C, 70.80; H, 12.05.

5R-Methyl-2S-(2'R-propionyl)-1(E/Z)-trimethylsilylmethylenecyclohexane (**13**).

Each isomer **9a** (190 mg, 0.54 mmol) and **9b** (110 mg, 0.31 mmol) were separately placed in THF (5 mL) at 22°C and treated with 1.0 M Bu_4NF in THF (1.1 mL and 0.7 mL, respectively) . After 2.5 h at 22°C, each was poured into water and extracted with Et_2O (3 x 25 mL). For each isomer, the combined organic layers were washed with sat. aq. $NaHCO_3$ (3 x 50 mL), dried over $MgSO_4$, and evaporated to give the crude alcohols **11a** and **11b**, (130 and 75 mg, respectively) which were used without further

purification as follows. The alcohols **11a** and **11b** (130 mg and 75 mg) were each dissolved in dry DMF (6 and 4 mL) at 22°C and treated separately with pyridinium dichromate (700 mg and 400 mg). The mixtures stirred 18 h at 22°C, poured into water (100 mL), and extracted with ether (3 x 25 mL). For each, the combined organic phases were washed with sat. aq. NH_4Cl/5 N HCl (9:1, 2 x 50 mL), and sat. aq. NaCl (2 x 50 mL), dried over $MgSO_4$, and evaporated to give the crude acids **13a** (125 mg) and **13b** (71 mg). Use of acid **13** as a mixture or separate isomer gave identical results, vide infra. PTLC of both acids on 1.5 mm SiO_2 plates with 10% EtOAc/hexane afforded each of the pure acids: **13a** (114 mg, 84%) as a white crystalline solid, mp 75-77°C. ^1H NMR (400 MHz, $CDCl_3$): δ 0.14 (s, 9H), 0.91 (d, 3H, J = 7.0 Hz), 1.09 (d, 3H, J = 6.9 Hz), 1.29 (br d, 1H, J = 15.3 Hz) 1.52 (br d, 1H, J = 12.5 Hz), 1.73 (ddd, 1H, J = 4.5, 4.5, 10 Hz), 1.77 (br d, 1H, J = 12.8 Hz), 1.90 (dddd, 1H, J = 4.2, 4.2, 13.7, 13.7 Hz), 2.10 (br m, 1H), 2.43 (ddd, J = 1.5, 5.3, 12.9 Hz, 1H) 2.73 (br dd, 1H, J = 3.0, 10.0 Hz), 2.91 (br dq, 1H, J = 7.0, 12.0 Hz), 5.25 (s, 1H). Anal. Calcd for $C_{14}H_{26}SiO_2$: C, 66.09; H, 10.30. Found: C, 65.80; H, 10.41. Acid **13b** (62 mg, 78%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 0.11 (s, 9H), 0.93 (d, 3H, J = 6.6 Hz), 1.16 (d, 3H, J = 6.5 Hz), 1.7-1.9 (m, 3H), 2.17 (br t, 1H, J = 8 Hz), 2.37 (dd, 1H, J = 3.9, 12.5), 2.73 (m, 1H), 5.15 (s, 1H). Anal. Calcd for $C_{14}H_{26}SiO_2$: C, 66.09; H, 10.30. Found: C, 65.85; H, 10.32.

5R,6S-Dimethyl-2S-(2'R-propionyl)-1-E/Z-trimethylsilylmethylenecyclohexane (**14**).

To a solution of alcohol **12** (122 mg, 0.479 mmol) in dry DMF (5 mL) at ambient temperature was added pyridinium dichromate (631 mg, 1.68 mmol). The mixture was stirred for 18 h, then water (7 mL), 38% HCl (2 mL), and ether (15 mL) were added. The aqueous layer was separated and extracted with ether (2 x 15 mL). The combined organic layers were washed with sat. aq. NH_4Cl (20 mL), 3% sodium thiosulfate (2 x 20 mL), and brine (20 mL), dried over $MgSO_4$, and evaporated in vacuo to provide the crude acid **14**. Flash chromatography over silica gel (7 g) with 5% EtOAc (containing 1% HOAc)/hexane gave pure **14** (102 mg, 79%) as a crystalline solid that recrystallized from hexane, mp 138-140°C. The crystalline material was a single diastereomer by proton NMR but the E/Z mixture could be used for subsequent reactions without adverse effects on yields. $[\alpha]_D^{22}$ = +15.1° (c = 0.735, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 0.15 (s, 9H), 0.92 (d, 3H, J = 7.1 Hz), 1.165 (d, 3H, J = 7.6 Hz), 1.169 (d, 3H, J = 6.9 Hz), 1.43 (dddd, 1H, J = 1.6, 4.2, 4.2, 13.9 Hz), 1.75 (m, 2H), 1.91 (dddd, 1H, J = 4.0, 4.0, 13.2, 13.2 Hz), 2.11 (dq, 1H, J = 1.9, 7.6 Hz), 2.81 (AB, 1H, J = 5.2, 11.9 Hz), 2.91 (AB, 1H, J = 6.9, 11.9 Hz), 5.38 (s, 1H). IR (KBr): 1704, 1600, 1457, 1222, 1008, 954, 838 cm^{-1}. EIMS (m/z): 268 (M+), 253 (M-Me), 196, 183, 161, 150, 135. Anal. Calcd for $C_{15}H_{28}SiO_2$: C, 67.11; H, 10.51. Found: C, 67.13; H, 10.58.

(-)-4aβ,7α,7aα,10β-Hexahydro-3,3,7β,10α-tetramethyl-4aH,6H-trioxino[6,5-jl][2]-benzopyran-6-one (**3**).

Through a solution of acid **13** (260 mg, 1.02 mmol) in methanol (8 mL) at -78°C was bubbled ozonized oxygen from an OREC ozone generator (0.6 L/min, 7 p.s.i, 65 V, 0.7 amps) until a faint blue-

gray color was observed (about 4 min). The -78°C solution was purged with argon until the color was gone, the stir bar was removed and the mixture evaporated to dryness by rotary evaporation (bath temperature < 20°C). The mixture was evaporated to dryness from hexane (2 x 10 mL) and placed under vacuum (0.2 mm Hg) for 30 min. The residual glass was dissolved in CH_2Cl_2 (3 mL), and acetone (3 mL) and Amberlyst®-15 (275 mg) were sequentially added. The mixture stirred at 22°C for 18h and then filtered. The filtrate was evaporated to give crude **3**. Purification on one SiO_2 PTLC plate, eluting with 10% EtOAc/hexane, gave pure **3** (68 mg, 25% yield) as a white solid which was recrystallized from cold hexane, m.p. 109-110°C. $[\alpha]_D^{22}$ = -94.5° (c = 0.145, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) was temperature dependent. At 23°C, the spectra was broad, while at -10°C, a clean 2:1 mixture was observed: d 0.98 and 1.00 (2d, 3H, J = 6.4 Hz), 1.19 and 1.23 (2d, 3H, J = 7.2 Hz), 1.41 and 1.57 (2s, 3H), 1.64 and 1.65 (s, 3H), 2.02 and 2.68 (ddd, 1H, J = 2.0, 4.0, 13.5 Hz), 3.10 and 3.55 (dq, 1H, J = 5.0, 7.2 Hz), 5.61 and 5.70 (2s, 1H). IR (Nujol): 1755, 1215, 1180, 1100, 1030, 1010, 880, 840 cm^{-1}. DCIMS-NH_3: (m/z) 288 (M + NH_4), 271 (M + H), 255, 230, 212, 195, 184, 167. Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 61.90; H, 8.02.

(-)-4aβ,7α,7aα,10β-Hexahydro-3,3,7β,10α,11β-pentamethyl-4aH,6H-trioxino[6,5-i][2]-benzopyran-6-one (**4**).

Through a -78°C solution of acid **14** (185 mg, 0.688 mmol) in methanol (15 mL) was bubbled ozonized oxygen from an OREC ozone generator (0.6 L/min, 7 p.s.i, 65 V, 0.7 amps) until a faint blue-gray color was observed (about 4 min). The -78°C solution was purged with argon until the color was gone, the stir bar was removed and the mixture evaporated to dryness by rotary evaporation (bath temperature < 20°C). The mixture was evaporated to dryness from hexane (10 mL) twice, and placed under vacuum (0.2 mm Hg) for 30 min. The residual glass was dissolved in CH_2Cl_2 (15 mL), and acetone (15 mL) and Amberlyst®-15 (400 mg) were sequentially added. The mixture was stirred at 22°C for 48 h and then filtered. The filtrate was evaporated to give crude **4**. Purification on one SiO_2 PTLC plate, eluting with 10% EtOAc/hexane, gave pure **4** (62 mg, 32% yield) as a white solid which was recrystallized from cold hexane, mp. 102-103°C. $[\alpha]_D^{22}$ = +22.9 (c = 0.520, CH_2Cl_2). NMR (400 MHz, $CDCl_3$) at 22°C: δ 1.00 (d, 3H, J = 6.4 Hz), 1.05 (m, 1H), 1.12 (d, 2H, J = 6.7 Hz), 1.24 (d, 3H, J = 7.2 Hz), 1.41 (s, 3H), 1.61 (s, 3H), 1.77 (br, 1H), 1.91 (br, 2H), 3.72 (br, 1H), 5.66 (s, 1H). At -18°C a single conformer of **4** was observed: δ 0.99 (d, 3H, J = 6.4 Hz), 1.04 (m, 2H), 1.09 (d, 3H, J = 7.2 Hz), 1.20 (m, 1H), 1.24 (d, 3H, J = 7.2 Hz), 1.36 (m, 1H), 1.40 (s, 3H), 1.61 (s, 3H), 1.75 (m, 1H), 1.90 (m, 2H), 3.72 (dq, 1H, J = 4.6, 7.2 Hz), 5.66 (s, 1H).

(-)-4aß,7a,7aα,10ß-Hexahydro-3ß,7ß,10α-trimethyl-4aH,6H-trioxino[6,5-i][2]-benzopyran-6-one (**5**).

The acid **13** was ozonized as described above for **3**, and treated identically except that acetaldehyde was substituted for acetone and the ensuing cyclization was complete in a few hours. The purified product

5 was crystallized from hexane, mp. 102-103°C (lit.[22] mp. 95-96°C) and had an NMR spectrum as reported.[22] $[\alpha]_D^{22}$ = - 19.3° (c = 0.28, $CHCl_3$).

Acknowledgments. Research support in part from NIH grant number CA47135-01A1 (PC) and U.S. Army Contract No. DAMD17-88-C-8007 (MAA, Contribution No. 1997).

REFERENCES

1. University of North Dakota.
2. a) SRI International. Current address: Agouron Pharmaceuticals, San Diego, CA. b) Agouron Pharmaceuticals, San Diego, CA.
3. University of California, Santa Cruz.
4. University of California, Santa Cruz. Current address: Shaman Pharmaceuticals, South San Francisco, CA.
5. Artemisinin (**1**) exhibits an IC_{50} of 1 ng/mL against chloroquine-susceptible and chloroquine-resistant strains of *Plasmodium falciparum*: Kepler, J.A.; Philip, A.; Lee, Y.W.; Morey, M.C.; Carroll, F.I. *J. Med. Chem.* **1988**, *31*, 713.
6. Klayman, D.L. *Science* **1985**, *228*, 1049.
7. Docampo, R.; Moreno, S.N.J; in *Free Radicals in Biology*; W.A. Pryor, Ed.; Academic Press: New York, 1984, Vol. 6, pp. 243-288.
8. Kepler, J.A.; Philip, A.; Lee, Y.W.; Musallam, H.A.; Carroll, F.I. *J. Med. Chem.* **1987**, *30*, 1505.
9. (a)Vennerstrom, J. L.; Fu, H. N.; Ellis, W. Y.; Ager, A. L.; Wood, J. K.; Andersen, S. L.; Gerena, L.; Milhous, W. K. *J. Med. Chem.* **1992**, *35*, 3023, (b) Vennerstrom, J. L.; Acton, N.; Lin, A. J.; Klayman, D. L. *Drug Design Deliv.* **1989**, *4*, 45.
10. Meshnick, S. R.; Thomas, A.; Ranz, A.; Xu, C. M.; Pan, H. *Mol. Biochem. Parasitol.* **1991**, *49*, 181.
11. Zhang, F.; Gosser, D. K.; Meshnick, S. R. *Biochem. Pharmacol.* **1992**, *43*, 1805.
12. Meshnick, S. R.; Yang, Y.; Lima, V.; Kuypers, F.; Kamchonwongpaisan, S.; Yuthavong, Y. *Antimicrob. Agents Chemother.* **1993**, *37*, 1108.
13. Posner, G. H.; Oh, C. H. *J. Amer. Chem. Soc.* **1992**, *114*, 8328-8329.
14. (a) Avery, M.A.; Jennings-White, C.; Chong, W.K.M. *Tetrahedron Lett.* **1987**, *28*, 4629, (b) Avery, M.A.; Jennings-White, C.; Chong, W.K.M. *J. Org. Chem.* **1989**, *54*, 1789, (c) Avery, M.A.; Jennings-White, C.; Chong, W.K.M. *J. Org. Chem.* **1989**, *54*, 1792.
15. Avery, M.A.; Chong, W.K.M.; Bupp, J.E. *J. Chem. Soc., Chem. Commun.* **1990**, 1487.

16. The atom numbering shown in **2** is numbered according to *Chemical Abstracts* and is used throughout the text. The numbering used in the trivial name 5-nor-6-desmethyl-4,5-secoartemisinin is ascribed according to the artemisinin numbering scheme.
17. Fischer, G.W.; Zimmermann, T. *Comp. Heterocyclic Chem.*, **1984**, *6*, 853-863.
18. Lambert, J.B.; Shruvell, H.; Verbit, L.; Cooks, R.; Stout, G. "Organic Structural Analysis" Macmillan Publishing: New York, **1976**, p. 124. These authors pointed out that many of the oxygenated six-membered ring heterocycles have been studied by dynamic NMR experiments, except for 1,2,4-trioxanes. Heterocycles with noncontiguous oxygens have inversion barriers similar to that of cyclohexane (9-11 kcal/mol) and those with contiguous oxygens have higher barriers (14-16 kcal/mol).
19. The X-ray analysis of **2** was carried out by Crystalytics Co., P.O. Box 82286, Lincoln, NE. Coordinates have been deposited in the Cambridge Crystallographic Data Centre.
20. Sanders, J.K.M.; Hunter, B.K.; in *Modern NMR Spectroscopy, A Guide to Chemists*; Oxford University Press: New York, **1987**, pp. 224-229.
21. A methyl proton is deshielded by a proximal hydroxyl. Examples include: (a) Reference 18, pp. 33-34, (b) Crews, P.; Klein, T.E.; Hogue, E.R.; Myers, B.L. *J. Org. Chem.* **1982**, *47*, 811.
22. Imakura, Y.; Yokoi, T.; Yamagishi, T.; Koyama, J.; Hu, H.; McPhail, D.R.; McPhail, A.T.; Lee, K. *J. Chem. Soc., Chem. Commun.* **1988**, 372.
23. Biological testing was performed by Dr. W. Milhous at the Walter Reed Army Institute of Research.
24. Desjardins, R.E.; Canfield, C.J.; Haynes, D.E.; Chulay, J.D. *Antimicrob. Agents Chemother.* **1979**, *16*, 710.
25. Avery, M. A.; Chong, W. K. M.; Detre, G. *Tetrahedron Lett.* **1990**, *31*, 1799. Selected relative *in vitro* antimalarial potencies for the 8a,9-secoartemisinin analogs reported in this article are (article numbering): **2**, 0.5%; **2b**, 24%; **11**, 37%, **1**, 100%.
26. Posner, G. H.; Oh, C. H.; Gerena, L.; Milhous, W. K. *J. Med. Chem.* **1992**, *35*, 2459.
27. Avery, M. A.; Gao, F.; Chong, W. K. M.; Mehrotra, S.; Jennings-White, C. *Trends in Organic Chemistry*, Research Trends, Trivandrum, India. In press.
28. Avery, M. A.; Gao, F.; Chong, W. K. M.; Mehrotra, S.; Milhous, W. K. *J. Med. Chem.*, Accepted for publication, July **1993**.
29. For reviews see: (a) Kessler, H. ; Gehrke, M.; Griensinger, C. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 490. (b) Schoolery, J. N. *J. Nat. Prod.* **1984**, *47*, 226.
30. Bates, T.; Thomas, R. *J. Org. Chem.* **1989**, *54*, 1784.
31. Mohamadi, F.; Richards, N.J.G.; Guida, W.C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W.C. *J. Comp. Chem.* **1990**, *11*, 440.
32. Chen, K.; Allinger, N.L. *J. Comp. Chem.* **1993**, *14*, 755.
33. Chang, G.; Guida, W.C; Still, W.C. *J. Amer. Chem. Soc.* **1989**, *111*, 4379.
34. Shulte-Elte, K.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 153.

(*Received in USA* 20 *July* 1993; *accepted* 14 *October* 1993)