Structure−Activity Relationships of the Antimalarial Agent Artemisinin. 3. Total Synthesis of (+)-13-Carbaartemisinin and Related Tetra- and Tricyclic Structures

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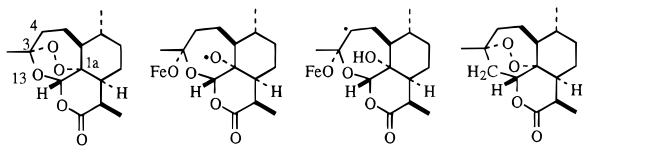
Provided by total synthesis, endoperoxides **18**, **20**, and **22** underwent intramolecular oxymercuration−demercuration leading respectively to formation of an isomeric tetracycle, (1a*S*,3*S*,5a*S*,6*R*,8a*S*,9*R*,12*S*)-10-deoxo-13-carbaartemisinin (**19**), (+)-10-deoxo-13-carbaartemisinin (**21**), and (+)-13-carbaartemisinin (**4**). Structure assignment to **19** and **21** was based on single-crystal X-ray crystallographic analysis. Tricyclic endoperoxide **20** was converted to methyl and benzyl ethers **23** and **24** and reduced to saturated analog **25** which was also converted to ethers **26** and **27**. *In vitro* antimalarial screening of both tri- and tetracyclic analogs was conducted using the W-2 and D-6 clones of *Plasmodium falciparum*. Neither target **4** nor **21** displayed substantial antimalarial potency *in vitro* against *P. falciparum*, but the diastereomeric peroxide **19** possessed good antimalarial potency *in vitro*. Tricyclic analogs were uniformly impotent. Iron(II) bromide-promoted rearrangement of **21** gave, in 79% yield, the unique tetracyclic alcohol **35**, while **19** provided ring-opened cyclohexanone **41** (39%) along with the tricyclic epoxide **42** (20%). Neither **41** nor **42** possessed *in vitro* antimalarial activity, suggesting that epoxide-like intermediates are not responsible for the mode of action of this subclass of antimalarials. Rearrangement of 10-deoxoartemisinin (**43**) with $FeBr_2$ gave a major product (79%) not encountered in the rearrangement of artemisinin that resulted from unraveling of the tetracyclic system cyclohexanone **46**. Minor amounts of 1,10-dideoxoartemisinin (**49**) (8%) were also produced in this reaction.

Much effort has been expended to develop new antimalarial drugs based on the natural product lead (+)-artemisinin (**1**).[1−3] The unusual peroxy moiety of this cadinane sesquiterpene was found to be essential for antimalarial activity,[4] and prompted by Meshnick's observation of the reaction of hemin with **1**,[5] Posner has suggested that carbon-centered radical chemistry surrounds the mode of antimalarial action of this class of drugs.[6] In *in vitro* studies, cleavage of the oxygen−oxygen bond of structures such as **1** by Fe(II) leads to an intermediate oxygen radical (e.g., **2**) which then abstracts, in an intramolecular 1,5-fashion, a hydrogen atom from C-4.[7] The fate of this resultant carbon radical **3** is not as yet understood, although Meshnick's group continues to study the biochemical course of reaction of **1** *in vivo*.[8] The importance of intermediate carbon radicals in the mechanism of action of simpler artemisinin analogs has also been demonstrated by Jefford.[9,10]



1, (+)-Artemisinin **2** **3** **4**, (+)-13-Carbaartemisinin

Structure−activity relationship studies continue to accumulate in the artemisinin area. For example, the peroxide moiety is accepted as essential for activity, while the lactone carbonyl can be removed[11−14] or a lactam ring can be substituted for the customary lactone ring without detriment to antimalarial activity.[15−17] The effect of ring substitution has been examined at several positions of both the intact tetracyclic system[18,19] as well as many tricyclic analogs.[13,20−22] While the antimalarial activity of numerous peroxides has been explored,[23,24] replacement of the nonperoxidic trioxane ring oxygen in artemisinin by a methylene unit had not been carried out until recently.[25] Other carba-modified but nonperoxidic artemisinin-like ring systems have been reported.[26]

Due to the rigid nature of the artemisinin ring system, carba modification (**4** for **1**) would not be expected to significantly modify the shape of the resultant homolog **4**. In fact, simple energy minimization and overlap of **1** and **4** revealed very little difference in shape.[27] Thus, the antimalarial activity of **4** relative to **1** can be ascribed in a general sense to the importance of the 1,2,4-trioxane substructure within the artemisinin tetracycle.

More specific issues we hoped to address were as follows. (1) Can the process whereby radical intermediates such as **2**/**3** undergo intramolecular collapse be inhibited by replacement of the O-13 atom by CH_2? Perhaps this modification would lead to longer lived intermediate radicals that would have greater activity. The facility with which this process occurs could presumably be determined by observation of the Fe(II)-catalyzed fragmentation pathway of **4**. (2) In light of an earlier assertion that 4β-methyl-substituted tricyclic artemisinin analogs were more potent antimalarials

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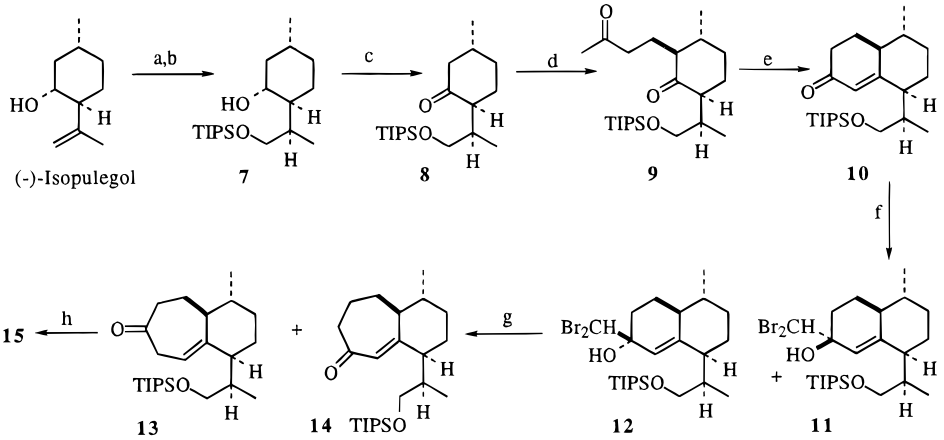
Scheme 1[a]

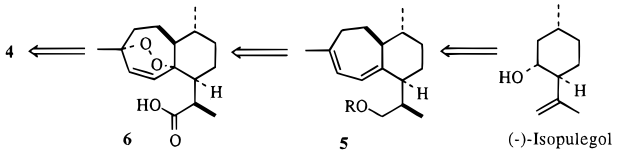


[a] Key: (a) BH_3−THF, then H_2O_2, NaOH; 40%; (b) *i*-Pr_3SiCl, DMAP, Et_3N; 96%; (c) $(COCl)_2$, DMSO, Et_3N; 95%; (d) LDA, 3-(trimethylsilyl)-3-buten-2-one, then pH 2; 73%; (e) *l*-proline, MeOH; 43%; (f) Br_2CH_2, LDA, −95 °C; 88%; (g) BuLi, THF, −95 °C; 53% **13**; (h) KH, DME, Tf_2NPh; 89%.

than artemisinin due to C-4 radical stabilization,[6] replacement of C for O at the C-13 position should lead to a more stable C-4 radical because of the destabilizing effect of the β-oxygen would be removed. (3) Although not an immediate goal of this research, replacement of O-13 by CH_2 might eventually furnish analogs whose hydrolytic stability relative to artemisinin could provide access to congeners with improved oral activity.

Chemistry

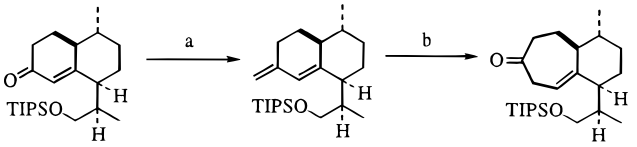
Synthesis of the Tetracyclic System. We set about the synthesis of **4** from a chiral pool, specifically (−)-isopulegol, as outlined retrosynthetically below:



(−)-Isopulegol was envisaged as a suitable precursor for Robinson annelation; ensuing ring expansion and appropriate manipulation of functionality would then furnish the diene **5**. Addition of singlet oxygen to provide **6** followed by an intramolecular oxymercuration would then complete the sequence leading to **4**.

As shown in Scheme 1, manipulation of (−)-isopulegol as described previously[28] provided smooth access to the Robinson precursor: Hydroboration of (−)-isopulegol with oxidative workup followed by selective protection provided alcohol **7**, Swern oxidation of which then gave **8**.[29] Generation of the kinetic enolate of **8** with LDA at low temperature followed by Michael addition to 3-(trimethylsilyl)-3-buten-2-one gave, after mild *in situ* hydrolysis of the α-silyl group, diketone **9**. Aldol cyclization and elimination of water from **9** to generate bicyclic enone **10** was much more difficult than anticipated due to facile epimerization of the propanol side chain. It was found that this epimerization could be inhibited to some extent upon treatment of **9** with 1.5 equiv of *l*-proline, leading directly to the bicyclic enone **10**. Addition of dibromomethyllithium at low temperature afforded a mixture of diastereomers **11** and **12**. The mixture of **11** and **12** was then ring expanded upon treatment with butyllithium at −95 °C and furnished a mixture of β,γ-unsaturated enone **13** along with α,β-unsaturated enone **14** (3:1 mixture of **13**:**14**). It was later found that only isomer **12** underwent the desired ring expansion. Dienol triflate **15** was then regiospecifically formed upon treatment of enone **13** with KH in THF followed by addition of Tf_2NPh. The triflate **15** was just stable enough to be chromatographed rapidly over silica gel; it had to be utilized directly for the next reaction.

Scheme 2[a]



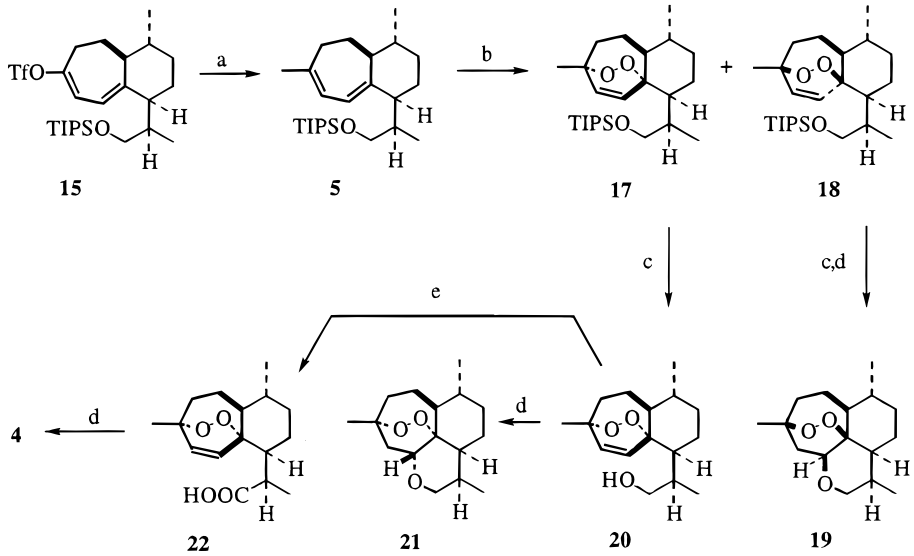
[a] Key: (a) Tebbe reagent, THF, 0 °C; 95%; (b) $Tl(NO_3)_3$, MeOH, $CHCl_3$; 72%.

While this approach to ring expansion yielded the desired product **13** in an overall yield of 47%, photochemical (room lights) and thermal sensitivity (room temperature) of the dibromomethyl intermediates inspired the development of an alternate approach. As shown in Scheme 2, the decalenone **10** could be smoothly methylenated with Tebbe reagent to provide diene **16** in excellent yield. Clean and reproducible oxidative ring expansion could then be effected with thallium trinitrate to furnish enone **13** in 62% overall yield (unoptimized).

The final steps in the overall sequence were then carried out as demonstrated in Scheme 3. Coupling of the enol triflate with dimethylcopper lithium provided the diene **5** in excellent yield. Singlet oxygenation of **5** was then investigated with a variety of dyes in different solvents. We were surprised to find that a mixture of diastereomeric peroxides were obtained, only varying slightly with conditions, and that the desired peroxide **17** could only be obtained in about 30% yield. The unexpected predominant diastereomer **18**, obtained in 54% isolated yield, was carried through the sequence of silyl group deprotection and Hg(II) cyclization (Scheme 3) to arrive at the diastereomeric peroxide **19**.[25] The desired peroxide **17** was then deprotected with tetrabutylammonium fluoride in THF to give the alcohol **20**.

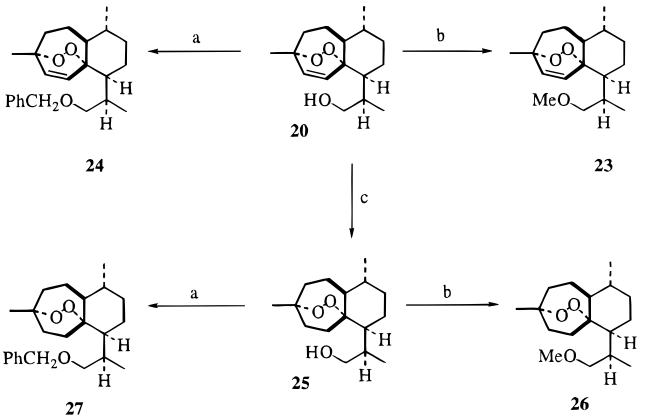
Oxymercuration of the alcohol **20** was readily accomplished using mercuric trifluoroacetate in THF; the

Scheme 3[a]



[a] Key: (a) Me_2CuLi, Et_2O; 94%; (b) O_2, EtOAc, rose bengal salt; 30% **17**, 54% **18**; (c) Bu_4NF, THF; 89% **20**, 70% alcohol from **18**; (d) $Hg(OTFA)_2$, THF, then $NaBH_4$/NaOH; 76% **21**, 78% **19**, 60% **4**; (e) CrO_3, AcOH, H_2O; 64%.

Scheme 4[a]



[a] Key: (a) $PhCH_2Br$, NaH, THF; 70−80%; (b) MeI, NaH, THF; 87−95%; (c) $KO_2CN{=}NCO_2K$, HOAc, CH_2Cl_2; 60%.

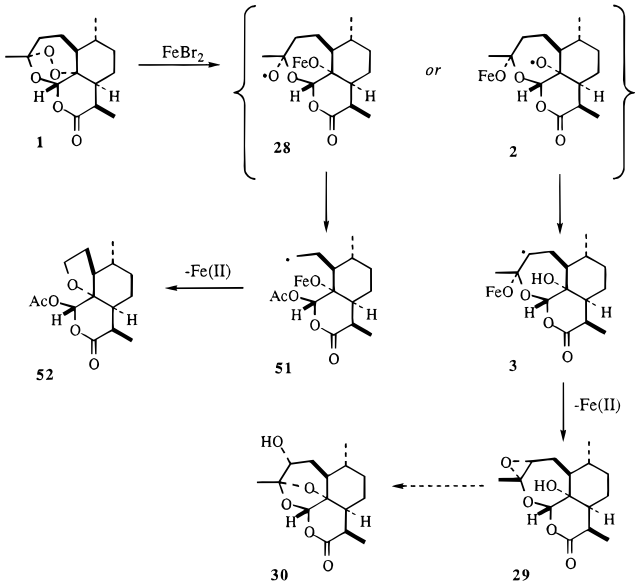
organometallic product could then be carefully demercurated with sodium borohydride to provide (+)-10-deoxy-13-carbaartemisinin (**21**).[25] Attempted oxidation of alcohol **20** directly to acid **22** using pyridinium dichromate in DMF was not successful as the intermediate aldehyde could not be further oxidized with this reagent. However, alcohol **20** could be oxidized directly to the acid **22** using chromium trioxide in acetic acid. Oxymercuration−demercuration then gave the title compound **4**. The structures of **19** (Figure 3) and **21** (Figure 1) were unambiguously determined by single-crystal X-ray crystallographic analysis, while the structure of **4** was reasonably extrapolated from **21**.

Tricyclic Analog Syntheses. Having successfully assembled the desired tetracyclic system, examination of corresponding tricyclic systems derived from synthetic precursor **20** was relatively straightforward. Smooth access to the lipophilic methyl and benzyl ethers **23** and **24**, respectively, was accomplished via S_N2 reaction of the sodium alkoxide, derived from alcohol **20** and NaH, with either methyl iodide or benzyl bromide (Scheme 4). It seemed prudent that the same ethers be examined in the absence of potentially labile functionality; thus removal of unsaturation in **23** and **24** was considered. Hydrogenation of **20** over Pd/C or Pt was unsuccessful; in either case reduction of the peroxide group was problematical. Hydrogenation over Wilkinson's catalyst gave a new product but with the unsaturation retained. While selective alkene hydrogenation can sometimes be achieved in the presence of a peroxide bond, the double bond of **20** was apparently too hindered in this case. Diimide, on the other hand, worked reasonably well for this reduction. Thus, treatment of **20** in dichloromethane solution with potassium azodicarboxylate followed by addition of acetic acid led, after several days, to roughly 60% conversion of **20** to the saturated version **25**. Now, ether formation as before provided the saturated methyl and benzyl ethers **26** and **27**, respectively, in good yields.

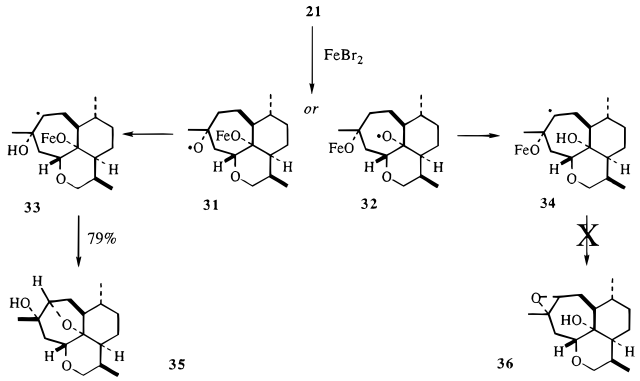
Rearrangement Chemistry. As *Plasmodium falciparum* is rich in hemin, hemozoin, and free iron, the Fe(II)-stimulated rearrangement of artemisinin and several tricyclic artemisinin analogs has been studied with the hope of defining a mechanistic feature that could be exploited in analog design.[6,22,31] On the basis of studies with labeled tricyclic analogs of **1**, it has been suggested that upon Fe(II)-promoted fragmentation, two possible radicals result (Scheme 5): **28** and **2**. Of these, only **2** possesses optimal structure for 1,5-H atom transfer and more stable carbon-based radical formation, i.e., **3**. It has been suggested that the antimalarial activity of structures such as **1** was dependent on formation of radicals such as **3**. It has been further suggested that collapse of **3** to an epoxide might provide an active alkylator (e.g., **29**) that is in fact responsible for the antimalarial action and protein-alkylating properties of this class of drugs.

The intrinsic instability of **29** makes its existence difficult to prove; intramolecular closure to 4-hydroxy-1-deoxyartemisinin (**30**) or simple aqueous hydrolysis leads to its destruction. If the epoxide **29** or related epoxides in analogous structures were the agent(s) through which the artemisinin class exerted its antimalarial effect, then replacement of O-13 by CH_2 might give an isolable intermediate epoxide whose activity could be separately ascertained.

Scheme 5



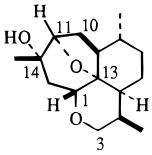
Scheme 6



After reproducing the reported rearrangement chemistry of artemisinin itself with $FeBr_2$ or hemin,[31] we moved on to the study of analogs **19** and **21**. Upon treatment of these analogs at ambient temperature in THF with 2 equiv of $FeBr_2$, products were isolated by flash chromatography. In all cases, these reactions gave the same results either with hemin/PhSH or with $FeBr_2$ and were complete within 10 min.

The only tractable product from rearrangement of **21** was the alcohol **35**, isolated in 79% yield as shown in Scheme 6. Alcohol **35** was isomeric with **21** by HRMS and contained no carbonyl by IR. The structure of **35** was determined by extensive NMR studies. Of two mechanistically sound possibilities (Scheme 4), ether alcohol **35** could be chosen over epoxide **36**, in part, on the basis of the carbon NMR APT/DEPT spectra. For **35**, relevant carbon atoms were observed at δ 68.9 (C-3), 70.2 (C-14), 70.5 (C-1), 79 (C-13), and 83 (C-11). No carbon atoms were observed in the region expected for an isolated epoxide (e.g., 55−65 ppm). Ultimately, HMBC and HSQC experiments confirmed the connectivity shown for **35**. For example, the C-11 proton at δ 3.98 (ddd, J = 2, 2, 8 Hz) showed a strong HMBC correlation to C-13, a quaternary C assigned to δ 79; C-14 at δ 70.2; C-15 at δ 35; and C-9 at δ 55.

From a mechanistic standpoint, it would seem that radical **33** is a probable precursor to **35**, while it is less clear how **33** is derived from **21** (Scheme 6). Homolysis



of the peroxide bond of **21** could lead to either **31** or **32**. If C-4 H atom abstraction from **32** were to occur giving radical **34**, then it would be more difficult to explain the product **35**. In fact, a more reasonable product of radical **34** might be the epoxide **36** which was, however, not formed in this reaction. If proton transfer occurs from C-4 to radical **31**, then **33** would result directly. The later, more direct pathway unfortunately proceeds through a 4-membered transition state (TS) which would be predicted to occur at a much slower rate than the 6-membered TS leading to **34**.

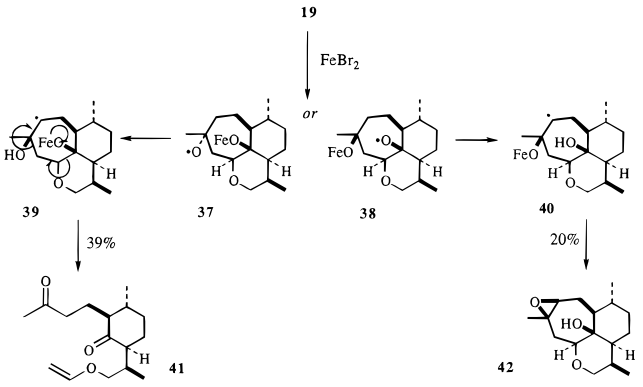
Rearrangement of the isomeric β-oriented peroxide **19** under identical conditions with those used for **21** provided **41** and **42** (Scheme 7) in 39% and 20% yields, respectively. Both products were isomeric with **19** by MS; **41** displayed strong carbonyl and alkene stretching in the IR at 1708 and 1635 cm^{-1}, while **42** was clearly only hydroxylic. In the NMR, the vinyl ether of **41** showed characteristic 1H patterns for the vinyl group at δ 6.47 (dd, J = 6.8, 14.4 Hz), 4.17 (dd, J = 1.9, 14.4 Hz), and 3.97 (dd, J = 1.9, 6.8 Hz), while the presence of a methyl ketone was clearly indicated as a 3H singlet at δ 2.13. In addition to connectivity determined by HMBC and HSQC experiments, **42** (in contrast to **35**) had ^{13}C NMR shifts consistent with an epoxide at δ 61.9 (methine) and 57.4 (quaternary).

As the rearrangement products of the carba-modified 10-deoxo analogs (D-ring tetrahydropyran) where somewhat different from the products from rearrangement of artemisinin (**1**) (D-ring lactone), we felt that it would be worthwhile to explore the rearrangement of 10-deoxoartemisinin (**43**). Upon exposure of **43** with 2.5 equiv of $FeBr_2$ in THF at room temperature (Scheme 8), reaction was complete within minutes and gave, after purification, the products **46** and **49** in 79% and 8% yields, respectively. Several other products were present in minor amounts, but their structure elucidation was not vigorously pursued.

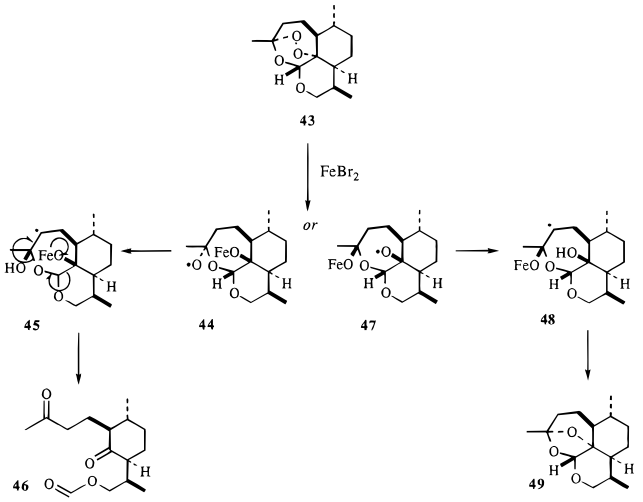
Assignment of structure to **49** was based initially on spectral evidence: No carbonyl or alcohol group was present in the infrared spectra, and the proton NMR data were consistent, for example, with a ketal methyl group (δ 1.55) and a acetal methine (δ 5.5). In the final analysis, however, comparison with authentic 1,10-dideoxoartemisinin provided the required assurance: Thus, reductive cleavage of 10-deoxoartemisinin with zinc metal followed by acid-catalyzed ring closure gave cleanly material that matched **49** in all respects (Scheme 9).

The major product **46** showed strong carbonyl absorption in the IR and was confirmed in the proton NMR spectra which indicated the presence of a formate ester (δ 8.06) and methyl ketone (δ 2.12). A remarkable spectral similarity was seen between **46**, the enol ether **41**, and the silyl ether **9**. For example, all three showed methyl ketone singlets between 2.09 and 2.13 ppm. Ultimately, however, the interrelatedness of these materials was demonstrated by conversion of these materials to the same ketone, **50**. Removal of the silyl

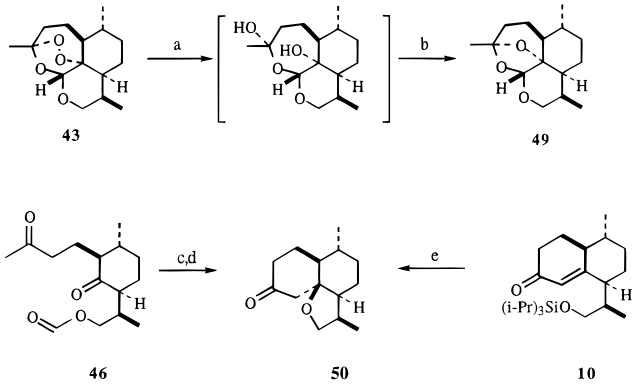
Scheme 7



Scheme 8



Scheme 9[a]



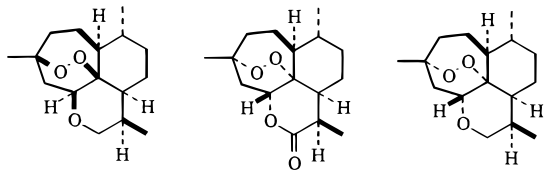
[a] Key: (a) Zn, HOAc, THF; (b) *p*-TsA, $CHCl_3$; 73%; (c) $NaHCO_3$, MeOH; (d) *p*-TsA, CH_2Cl_2; (e) Bu_4NF, THF.

protecting group from **10** (tetrabutylammonium fluoride, THF) led primarily to the tricyclic ketone **50** via intramolecular Michael addition of the liberated alcohol group. Deformylation of **46** ($NaHCO_3$, MeOH) provided a complex mixture that could be coalesced to a major product upon exposure to Amberlyst-15 and was identical in all aspects with **50**. Finally, **50** was observed upon acid treatment of the enol ether **41**.

Biological Evaluation

Artemisinin (**1**) and the analogs **4** and **19**−**21** were tested *in vitro* in parasitized whole blood (human) against drug-resistant strains of *P. falciparum* at the Walter Reed Army Institute of Research by the Milhous

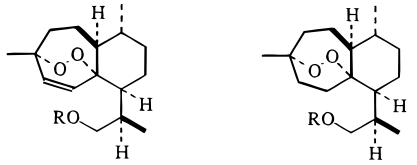
Table 1. Relative *in Vitro* Antimalarial Activity of 13-Carbaartemisinin Analogs against *P. falciparum*



	IC_{50} (ng/mL)		relative activity[a]		
structure	D-6	W-2	D-6	W-2	anal. (C,H)
1 (artemisinin)	0.97	0.48	100	100	
4	38.8	12.63	2.5	3.8	$C_{16}H_{24}O_4$
4[b]	6	20	23.3	11	
19	1.72	0.78	53	58	$C_{16}H_{26}O_3$
21	2.87	2.79	32	16	$C_{16}H_{26}O_3$

[a] Relative activity = 100 × [IC_{50} artemisinin (control value)/IC_{50} of analog](MW of analog/MW artemisinin); Milhous−Desjardins *in vitro* screen. [b] Makler parasite LDH *in vitro* screen; artemisinin IC_{50} = 1.4 (D-6) and 2.2 (W-2) ng/mL.

Table 2. Relative *in Vitro* Antimalarial Activity[a] of Tricyclic 13-Carbaartemisinin Analogs against *P. falciparum*



		IC_{50} (ng/mL)		
structure	R	D-6	W-2	anal. (C,H)
1 (artemisinin)		1.4	2.2	
20	H	1000	NA	$C_{16}H_{26}O_3$
23	Me	920	NA	$C_{17}H_{28}O_3$
24	CH_2Ph	NA	NA	$C_{23}H_{32}O_3$
25	H	300	1500	$C_{16}H_{28}O_3$
26	Me	310	700	$C_{17}H_{30}O_3$
27	CH_2Ph	290	660	$C_{23}H_{34}O_3$

[a] Relative activity = 100 × [IC_{50} of artemisinin (control value)/IC_{50} of analog](MW of analog/MW of artemisinin); Makler parasite LDH *in vitro* screen. NA = not active.

modification[32] of the procedure of Desjardins[33] involving uptake of tritiated hypoxanthine (Table 1). Two *P. falciparum* malaria parasite clones, designated as Indochina (W-2) and Sierra Leone (D-6), were used in susceptibility testing. The W-2 clone is chloroquine-resistant and mefloquine-sensitive, while the D-6 clone is chloroquine-sensitive and mefloquine-resistant. The relative potencies for the analogs (Table 1) were derived as follows: (IC_{50} of artemisinin divided by the IC_{50} of analog) × 100% (i.e., the relative activity of artemisinin = 100%).

The analogs **23**−**27** were tested *in vitro* against the D-6 and W-2 strains of *P. falciparum* at the University of Mississippi using the parasite lactate dehydrogenase (pLDH) assay developed by Makler (Table 2).[34,35] This assay is based on the ability of pLDH enzyme of *P. falciparum* to reduce APAD to APADH and has been shown to display slightly different relative potencies than the Milhous assay.[17] This reaction is carried out at a slow rate by human red blood cell LDH. The formation of APADH was monitored colorimetrically by the addition of nitroblue tetrazolium which was reduced to a blue formazan product. The relative potencies for

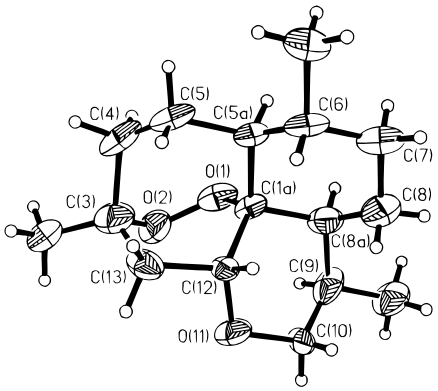


Figure 1. Thermal ellipsoid plots of **21** at 50% probability level drawn from the coordinates derived from X-ray diffraction.

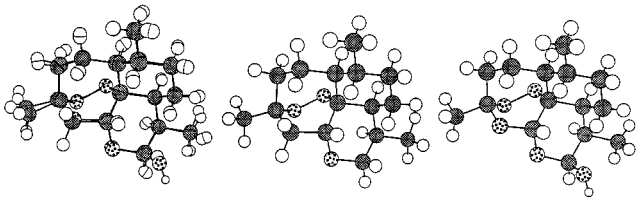


Figure 2. Stereosuperposition (left) of the X-ray crystal structures of **21** (middle) and dihydroqinghaosu (right).

the analogs (Table 2) were derived as described for Table 1. Also, because these particular tricyclic analogs were found to be relatively inactive, minor differences between the two assays were not considered to be important.

X-ray Crystallography

The X-ray crystal structure of **21** confirms that all of the chiral centers have the identical configuration as in artemisinin. Although the X-ray experiment does not distinguish between the configuration shown in Figure 1 and its mirror image, **21** can be placed into the illustrated configuration since the chirality of the starting materials is known. The overall conformation of **21** is essentially the same as the conformation of the X-ray crystal structure of dihydroqinghaosu[36] (Figure 2). In dihydroqinghaosu, the C-13 methylene group of **21** is replaced by an oxygen atom and a hydroxyl group is attached to C-10. The endoperoxide O1−O2 bond length in **21** is 1.433 ± 0.027 Å compared to 1.479 Å in dihydroqinghaosu. The C1a−O1−O2−C3 and C1a−C12−C13−C3 torsion angles in **21** are 41.7 ± 2.2° and 22.7 ± 2.5°, respectively, and in dihydroqinghaosu are 44.2° and 27.1°, respectively. The nonbridged 6-membered rings are in normal chair conformations. Thus, the substitution of a methylene group for an oxygen atom at position 13 did not affect the overall conformation of **21**.

The X-ray crystal structure of **19** showed this compound to be the isomeric peroxide to **21** (Figure 3). The asymmetric unit contained two independent molecules of nearly the same conformation. The endoperoxide O1−O2 bond length in **19** is 1.466 ± 0.010 and 1.480 ± 0.010 Å for molecules A and B, respectively. The C1a−O1−O2−C3 and C1a−C12−C13−C3 torsion angles in **19** are −33.9 ± 1.1° and −12.5 ± 1.3°, respectively, for molecule A and −36.0 ± 1.1° and −11.1 ± 1.5°, respectively, for molecule B. Again, the nonbridged 6-membered rings are in normal chair conformations.

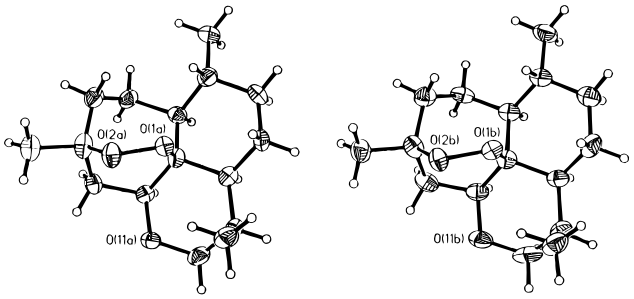


Figure 3. Thermal ellipsoid plots of molecules A and B of **19** at 50% probability level drawn from the coordinates derived from X-ray diffraction (not a stereodiagram).

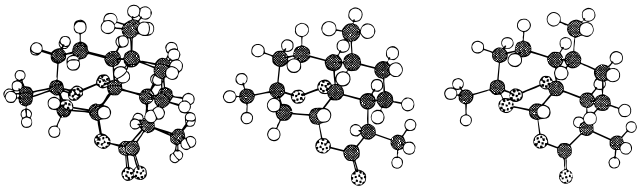


Figure 4. Stereosuperposition of X-ray crystal structure of artemisinin (**1**) with minimum energy structure (AM1) of 13-carbaartemisinin (**4**).[27]

Results and Discussion

As can be seen in Table 1, neither target **4** (∼4%) nor **21** (∼16%) displayed substantial antimalarial potency relative to artemisinin (100%) *in vitro* against the W-2 clone of *P. falciparum*, yet the isomeric peroxide **19** was found to possess good antimalarial activity (∼60%). The 4-fold enhancement in activity of **21** relative to **4** is analogous to the ranking of activities between 10-deoxoartemisinin (**43**) and artemisinin (**1**).[37]

The relative inactivity of **4**, *in vitro*, in comparison to artemisinin is somewhat surprising in that the geometry of these two molecules is very similar. Full geometry optimization of **4** by AM1 calculation provides a structure which overlaps nicely with the reported crystal structure of artemisinin (**1**) (Figure 4).[38] That the crystallographic coordinates of these carba analogs correspond to the natural, oxa series can be seen for **21** whose X-ray structure is very similar to the X-ray structure of 10β-dihydroartemisinin[36] (Figure 2). Thus, while natural product-like architecture is maintained in the analogs **4** and **21**, activity is diminished. This would seem to present clear proof that a 1,2,4-trioxane moiety is essential for good antimalarial potency. This argument is mitigated to some extent by the finding of substantial activity for the novel β-fused diastereomer **19**. Also, it has been reported that a steroidal analog of **43** having a β-fused peroxy group was more effective than artemisinin *in vivo*.[39]

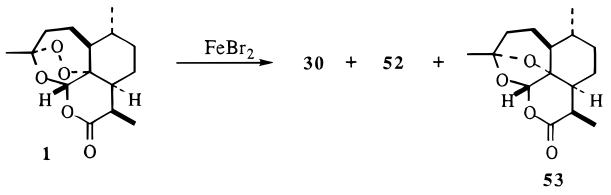
It seems likely that a shift in the details of the mechanism of action has occurred for these carba-modified analogs. It has been suggested that the inactivity of C-4α-substituted artemisinin analogs could be correlated to their inability to undergo C-4 hydrogen atom abstraction. While C-4 radical stability would be predicted to have an impact on antimalarial potency, these results would contradict the notion that improved C-4 radical stability is related, *a priori*, to improved antimalarial activity because the C-4 radical derived from **4** should be more stable than radical **3**. Indeed, more recent studies have shown that within a homologous series, continued stabilization of an intermediate

radical at C-4 leads to decreased antimalarial activity, not increased potency as originally hypothesized.[22] The C-4 radicals derived from **4**, **19**, or **21** would be expected to be more stable than their oxa counterparts (β-destabilization by O), but it is difficult to assess the exact degree of reactivity required for antimalarial potency. Apparently, a careful balance between C-4 radical half-life and C-4 radical reactivity is essential for potency, and this balance is not generally achieved in the 13-carba modification.

An additional step in the radical mechanism has been suggested, namely, that collapse of the C-4 radical intermediate **3** to a neutral but highly reactive alkoxy epoxide **29** occurs (Scheme 5).[31] Protein alkylation then presumably occurs via **29** and not radical intermediates such as **3**. Unfortunately, epoxide **29** is probably too unstable to be handled or identified. In the case of **19**, however, we were granted the opportunity to test the hypothesis that an intermediate epoxide was responsible for the mode of action. Of the series of three tetracycles, **19** retained nearly two-thirds of the activity of artemisinin. The Fe(II)-induced rearrangement products **42**, a quite stable epoxide, was submitted for antimalarial assay and found to be completely devoid of activity. As **19** is a potent antimalarial but the epoxide **42** is not, it seems reasonable to suggest that the antimalarial activity of **19** is unrelated to epoxy intermediates. Therefore, **19** probably expresses its antimalarial effect via a carbon radical intermediate such as **39** or **40**.

A good deal of importance has been placed on a detailed analysis of the products obtained from the Fe(II)-mediated rearrangement of artemisinin and its analogs. Due to the novelty of our findings in regards to the rearrangement of not only the 13-carba analogs **19** and **21** but also 10-deoxoartemisinin (**43**), some discussion of these results relative to these reports seems warranted.

Typical products from $FeBr_2$ treatment of artemisinin are 4-hydroxy-1-deoxoartemisinin (**30**) (Scheme 5), 1-deoxoartemisinin (**53**), and a ring-contracted product (**52**), occurring in a 1:6:3 ratio, respectively.[31] Exclusive formation of ring-contracted products such as **52** in tricyclic analogs appears to correlate with low antimalarial activity in that secondary C-4 radical formation (e.g., **3**) does not occur on the pathway to **52** but instead radical **51** is formed.[6] How is the rearrangement chemistry of 10-deoxoartemisinin and the 13-carbaartemisinins reconciled with these findings? No products from scissioning of the C3−C4 bond (e.g., **51**) leading to **52**-like products are evidenced in any of these analogs or in 10-deoxoartemisinin (**43**). In fact, novel scissioning to monocyclic cyclohexanones occurs as a major pathway for **43** and **19** but not for **21**.



It could be argued that products from **19** and **43**, the vinyl ether **41** and formate ester **46**, were produced via C-4 radicals but that ensuing intramolecular rearrangement pathways are altered relative to artemisinin and certain tricyclic analogs. The β-fused peroxide **19** would seem to follow two pathways: Radical **37** does not fragment to form a tetrahydrofuran such as **52** but instead undergoes unraveling to produce the cyclohexanone **41**, while **42** is probably formed via the alternate radical **38** via β-scission of **40** with concomitant reoxidation by Fe(IV)=O.[31] 10-Deoxoartemisinin (**43**), like **19**, appears to follow a major decomposition pathway via radicals **44** and **45** (Scheme 8) that furnishes a cyclohexanone (**46**). Finally, for **21** the major product likely occurs from the C-4 radical **31** (Scheme 6).

These rearrangement results indicate that minor modifications to structure can lead to major changes in decomposition pathway and therefore should be viewed from a standpoint of structure−activity relationships with some skepticism.

Tricyclic derivatives of 13-carbaartemisinin, analogs **20** and **23**−**27**, were relatively impotent in the *in vitro* antimalarial screen (Table 2). The best analogs in this series, **26** and **27**, were only a fraction of a percent as active as artemisinin. The olefinic tricyclics **20**, **23**, and **24** were virtually devoid of activity which can perhaps be rationalized by analogy to the facile thermal rearrangement of ascaridole or other endoperoxy olefins.

Summary

A detailed analysis of the products of annihilation of these intermediate radicals does not appear to be of use in the prediction of antimalarial potency. The presence of unraveled products such as **41** and **46** in the Fe(II)-promoted rearrangement of bioactive analogs indicates that a completely unique decomposition pathway is followed after minor structural modification (lactones **1** versus pyrans **43**). Production for the first time of an inactive epoxide intermediate (**42**) in the biomimetic rearrangement of active analog **19** argues against the importance of intermediate epoxides in the mode of action of these non-1,2,4-trioxane endoperoxides. The carba modification, wherein the nonperoxidic trioxane oxygen atom is replaced by carbon, leads to a loss in antimalarial potency in the series of compounds with artemisinin-like stereochemistry. Paradoxically, the abnormal 13-carba analog **19** retains most of the antimalarial activity of artemisinin and is roughly 2 times as potent as the α-peroxides **4** and **21**. Finally, tricyclic derivatives of 13-carbaartemisinin, analogs **20** and **23**−**27**, were likewise relatively impotent in the *in vitro* antimalarial screen. What effect this modification will have on *in vivo* activity is currently under investigation.

Experimental Section

^1H and ^{13}C NMR spectra were recorded on a multinuclear Varian VXR-300, with the former referenced at δ 7.27 and the latter at δ 77.00 in $CDCl_3$, respectively. Two-dimensional NMR spectra were determined on the following 500 MHz NMR instruments: Varian Unity Plus or Bruker DRX. HRMS data were obtained from the University of Minnesota using either EI or chemical ionization. Gas chromatographic data were obtained on a Hewlett-Packard gas chromatograph (5890A) equipped with a fused silica gel capillary column (30 m × 0.32 mm i.d.; DB-1, J&W Scientific). EIMS data were obtained on a Hewlett-Packard 5890A II bench top GC−MS instrument. Elemental analysis data were within 0.4% as determined by Desert Analytics, Tucson, AZ. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Flash chromatography was performed with 230−400 mesh silica gel. IR

spectra were recorded on a Biorad FTS-40 FTIR spectrometer. Singlet oxygenations were conducted with a GE 300 W sunlamp light source.

All reaction solvents were purchased as HPLC grade and, where appropriate, distilled from CaH_2 and then stored over 3 or 4 Å molecular sieves. Most commercial reagents were used without further purification unless otherwise noted in the procedure. Isopulegol (technical grade), rose bengal (90%), rose bengal bis(triethylammonium) salt, CuI (99.999%), Hg-$(OCOCF_3)_2$, $FeBr_2$, bovine hemin, azodicarbonamide, *i*-Pr_3SiCl, vinylmagnesium bromide, *l*-proline, and benzyl bromide were purchased from Aldrich Chemical Co., Inc.

X-ray Crystallographic Data for (1a*S*,3*S*,5a*S*,6*R*,8a*S*,9*R*,-12*S*)-10-Deoxo-13-carbaartemisinin (19). $C_{16}H_{26}O_3$, molecular weight = 266.4, clear colorless needle (0.09 × 0.15 × 0.64 mm), orthorhombic, space group $P2_12_12_1$, a = 9.304(5), b = 14.130(9), and c = 21.876(18) Å, d_{calcd} = 1.230 mg mm^{-3}, 3884 independent relections measured out to $2\theta_{max} = 114°$ with a Siemens P4 diffractometer using Cu Kα radiation (λ = 1.541 78 Å) with a graphite monochromator in the incident beam. The data were collected at room temperature by using the ω scan technique with a variable scan rate of 4.19−29.3°/min. Three standard reflections (800, 040, 206) were collected after every 97 reflections. The crystal decomposed during data collections such that at the end of data collections the standard reflections retained an average of only 74% of their original intensity. To correct for the crystal decomposition, the intensities were normalized with correction factors derived from the standards. The data were also corrected for Lorentz and polarization effects. No absorption correction was applied. The structure was solved by direct methods[40] as implemented by the SHELXTL PLUS system of programs.[41] Full-matrix least-squares refinement was performed on 343 parameters (coordinates and anisotropic thermal parameters for non-hydrogen atoms) using the 2093 reflections for which $|F_o| > 4\sigma(F_o)$. The C−H distances were fixed at 0.96 Å and placed in idealized positions. The final R factors were R = 9.80% and R_w = 9.02%. The goodness of fit parameter was 2.07, and the final difference map was featureless.

X-ray Crystallographic Data for (+)-10-Deoxo-13-carbaartemisinin (21). $C_{16}H_{26}O_3$, molecular weight = 266.4, clear colorless needle (0.26 × 0.40 × 0.40 mm), orthorhombic, space group $P2_12_12_1$, a = 5.833(2), b = 9.485(2), and c = 27.164-(5) Å, d_{calcd} = 1.177 mg mm^{-3}, 1228 independent relections measured out to $2\theta_{max} = 114°$ with a Siemens P4 diffractometer using Cu Kα radiation (λ = 1.541 78 Å) with a graphite monochromator in the incident beam. The data were collected at room temperature by using the 2θ scan technique with a constant scan rate of 14.6°/min. Three standard reflections (200, 040, 008) were collected after every 97 reflections. The crystal decomposed during data collections such that at the end of data collections the standard reflections retained only 24%, 21%, and 17%, respectively, of their original intensity. To correct for the crystal decomposition, the intensities were normalized with correctin factors derived from the standards. The data were also corrected for Lorentz and polarization effects. No absorption correction was applied. The structure was solved by direct methods[40] as implemented by the SHELX-TL PLUS system of programs.[41] Full-matrix least-squares refinement was performed on 172 parameters (coordinates and anisotropic thermal parameters for non-hydrogen atoms) using the 656 reflections for which $|F_o| > 3\sigma(F_o)$. The C−H distances were fixed at 0.96 Å and placed in idealized positions. The final R factors were R = 12.60% and R_w = 11.30%. The goodness of fit parameter was 3.35, and the final difference map was featureless.

(1*R*,3*R*,4*S*,8*R*)-9-[(Triisopropylsilyl)oxy]-*p*-menthol (7). To a 3 L round-bottomed flask at 0 °C containing (−)-isopulegol (124 mL, 800 mmol, technical grade) in THF (900 mL) was slowly added, via cannula, BH_3·THF complex (1150 mL, 1150 mol, 1 M in THF). The reaction mixture was stirred for 6 h at ambient temperature, at which time NaOH (300 mL of a 3 M aqueous solution) was added slowly at 0 °C via syringe. After the addition was complete, H_2O_2 (300 mL, 30% (w/w) in H_2O) was added and the mixture was stirred for 30 min at ambient temperature, poured into saturated aqueous NH_4Cl (500 mL), and extracted with 500 mL of EtOAc. The aqueous layer was washed with 2 × 500 mL of EtOAc, and the combined organic layers were then washed with saturated aqueous NH_4Cl (300 mL) and brine (2 × 300 mL), filtered over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The resultant white semisolid was recrystallized from 5% EtOAc/hexane to afford 55 g of the known diol (1*R*,3*R*,4*S*,8*R*)-9-hydroxy-*p*-menthol as a white crystalline solid (40%). ^{1}H NMR: δ 3.85 (br s, 2H), 3.63 (dd, 1H, J = 5.3, 10.7 Hz), 3.55 (dd, 1H, J = 3.4, 11.0 Hz), 3.42 (ddd, 1H, J = 4.4, 9.9, 9.9 Hz), 1.94 (m, 1H), 1.81 (m, 1H), 1.58 (m, 2H), 1.34 (m, 2H), 1.24 (dd, 1H, J = 4.0, 13.8 Hz), 0.94 (d, 3H, J = 7.3 Hz), 0.91 (d, 3H, J = 6.6 Hz), 0.8−1.0 (m, 2H). ^{13}C NMR: δ 69.68, 66.58, 48.46, 44.25, 38.41, 34.52, 31.33, 29.42, 21.99, 11.95. IR ($CDCl_3$): 3289, 2952, 2920, 2868, 1458, 1377, 1104, 1024 cm^{-1}. EIMS: *m*/*z* (rel intensity) 172 (M, 1.67), 154 (5.), 139 (14), 124 (29), 112 (43), 95 (42), 81 (100), 71 (71), 55 (60).

A mixture of the diol (45.2 g, 263 mmol), *i*-Pr_3SiCl (50.7 g, 263 mmol), NEt_3 (40.3 mL, 290 mmol), and DMAP (3.21 g, 26.3 mmol) in CH_2Cl_2 (1.3 L) was stirred for 3 days at ambient temperature, poured into brine (200 mL), and diluted with 200 mL of CH_2Cl_2. The aqueous layer was extracted with 2 × 150 mL of CH_2Cl_2, and the combined organic layers were then filtered over anhydrous Na_2SO_4. After concentration by rotary evaporation, the crude product was purified by gradient flash chromatography (8−10% EtOAc/hexane) over silica gel to afford alcohol **7** as a clear oil (82.77 g, 96%). ^{1}H NMR: δ 3.98 (br s, 1H), 3.72 (dd, 1H, J = 5.8, 9.84 Hz), 3.62 (dd, 1H, J = 3.2, 9.9 Hz), 3.40 (ddd, 1H, J = 4.2, 10.3, 10.3 Hz), 1.96 (dq, 1H, J = 1.8, 12.7 Hz), 1.87 (m, 1H), 1.60 (m, 1H), 1.52 (dddd, 1H, J = 3.3, 3.3, 3.3, 12.7 Hz), 1.12−1.47 (m, 3H), 1.05 (m, 21H), 0.94 (d, 3H, J = 7.3 Hz), 0.8−1.0 (m, 2H), 0.89 (d, 3H, J = 6.5 Hz). ^{13}C NMR: δ 69.96, 67.77, 49.03, 43.90, 38.20, 34.73, 31.33, 28.69, 22.06, 17.89, 12.73, 11.82 (Si*CH*). IR (neat): 3428, 3363, 2945, 2920, 2865, 1459, 1381, 1374, 1251, 1096, 1066, 1046, 1014, 883, 787, 681 cm^{-1}. EIMS: *m*/*z* (rel intensity) 329.25 (M + 1, 0.024), 285 (2.5), 171 (3.3), 137 (74), 119 (85), 95 (84), 81 (100), 75 (41), 55 (14).

(1*R*,4*S*,8*R*)-9-[(Triisopropylsilyl)oxy]-*p*-menthone (8). To a 2 L round-bottomed flask containing CH_2Cl_2 (1 L) at −78 °C under a N_2 atmosphere was added DMSO (41.56 mL, 586 mmol) followed by $(COCl)_2$ (25.54 mL, 293 mmol). The mixture was stirred for 20 min at 78 °C, and then the alcohol **7** (82 g, 250 mmol) dissolved in 100 mL of CH_2Cl_2 was added. The resultant solution was stirred for 1.5 h at −78 °C, treated with NEt_3 (102 mL, 732 mmol), and allowed to warm to ambient temperature. After 1 h, the mixture was poured into brine (200 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layer was washed with brine (200 mL), filtered over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude product was purified by flash chromatography on silica gel (4% EtOAc/hexane) to afford the ketone **8** as a yellow oil (77.5 g, 95%). ^{1}H NMR: δ 3.68 (dd, 1H, J = 5.1, 9.6 Hz), 3.61 (dd, 1H, J = 5.6, 9.6 Hz), 2.33 (m, 1H), 2.30 (m, 1H), 2.12 (ddd, 1H, J = 3.0, 6.0, 9.0 Hz), 1.95−2.04 (m, 2H), 1.75−1.92 (m, 2H), 1.29−1.51 (m, 2H), 1.04 (m, 21H), 0.99 (d, 3H, J = 6.4 Hz), 0.97 (d, 3H, J = 6.9 Hz). ^{13}C NMR: δ 212.15, 65.70, 52.11, 51.08, 35.68, 35.03, 34.23, 29.83, 22.26, 18.00, 15.27, 11.97. IR (neat): 2943, 2863, 1712 (s, C=O), 1459 (s), 1384, 1365, 1243, 1199, 1103 (s), 1067, 1040, 1011, 992, 883, 794, 682 cm^{-1}. EIMS: *m*/*z* (rel intensity) 325.90 (M, 0.042), 283 (100), 265 (11), 241 (10), 225 (2.7), 197 (2.2), 171 (13), 143 (9), 131 (47), 103 (95), 93 (22), 75 (92), 61 (58).

(1*R*,2*S*,4*S*,8*R*)-2-(3′-Oxobutyl)-9-[(triisopropylsilyl)oxy]-*p*-menthone (9). To an LDA solution [prepared from *n*-BuLi (41.2 mL, 103 mmol, 2.5 M in hexane) and *i*-Pr_2NH (14.43 mL, 103 mmol) in THF (300 mL), −78−0 °C] was added dropwise the ketone **8** (29.2 g, 89.57 mmol). The resulting solution was stirred for 1.5 h at −78 °C, and then 3-(trimethylsilyl)-3-buten-2-one (13.1 g, 92.2 mmol) was added dropwise. The reaction mixture was stirred for 2 h at −78 °C and then for 3.5 h at 0 °C. The pH was then adjusted to 2−3 with 10% HCl, and the mixture was stirred until the TMS group was removed as monitored by GC (ca. 2 h). The reaction mixture was then poured into 5% aqueous $NaHCO_3$ (150 mL) and extracted with

EtOAc (1 L). The organic layer was separated, and the aqueous layer was extracted with 2 × 150 mL of EtOAc. The combined organic layers were washed with brine (2 × 100 mL), filtered over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude product was purified by silica gel gradient flash chromatography (8−12% EtOAc/hexane) to afford diketone **9** as a yellow oil (21.45 g, 60%). ^{1}H NMR: δ 3.66 (dd, 1H, J = 4.9, 9.6 Hz), 3.61 (dd, 1H, J = 5.1, 9.6 Hz), 2.53 (m, 1H), 2.35 (m, 2H), 2.09 (s, 3H), 2.03−2.2 (m, 1H), 1.75 (d, 2H, J = 7.3 Hz), 1.64−2.06 (m, 4H), 1.2−1.6 (m, 3H), 1.03 (m, 23H), 0.94 (d, 3H, J = 6.7 Hz). ^{13}C NMR: δ 213.48, 208.98, 65.53, 57.20, 53.12, 41.45, 40.87, 35.02, 34.95, 31.14, 29.76, 20.52, 20.21, 17.98, 15.58, 11.93. IR (neat): 2946, 2865, 2727, 1738 (sh, C═O), 1711 (s, C═O), 1461, 1364, 1243, 1162, 1103, 1067, 1045, 1013, 996, 883, 799, 683 cm^{-1}. EIMS: *m/z* (rel intensity) 396.10 (M, 0.037), 353 (29), 295 (100), 277 (7), 241 (4), 225 (2), 205 (13), 201 (14), 187 (10), 165 (13), 147 (50), 131 (38), 119 (27), 103 (49), 75 (75), 60 (37).

(6*S*,7*R*,10*S*,2′*S*)-7α-Methyl-10*β*-[1′-[(triisopropylsilyl)oxy]prop-2′-yl]bicyclo[4.4.0]decen-3-one (10). A solution of diketone **9** (12.17 g, 30.73 mmol) and *l*-proline (5.31 g, 30.73 mmol) in MeOH (300 mL) was stirred for 20 h at ambient temperature under N_2, poured into brine (150 mL), and diluted with EtOAc. The organic layer was separated, and the aqueous layer was extracted with 2 × 300 mL of EtOAc. The combined organic layer was washed with 2 × 50 mL of brine, filtered over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude product was then purified by flash chromatography over silica gel (11% EtOAc/hexane) to afford **10** as a viscous, colorless oil. The recovered starting material **9** was recycled twice to give **10** (5.5 g, 47%). ^{1}H NMR: δ 5.81 (s, 1H), 3.66 (d, 2H, J = 4.4 Hz), 2.28 (m, 2H), 2.08 (m, 3H), 1.84 (m, 4H), 1.57 (m, 1H), 0.94−1.28 (m, 27H). ^{13}C NMR: δ 199.80, 170.33, 121.32, 65.33, 48.49, 46.15, 38.89, 35.28, 34.97, 34.08, 31.55, 24.60, 20.16, 17.94, 16.47, 12.00. IR (neat): 3049, 2943, 2866, 2726, 1676 (s, C═O), 1617, 1462, 1380, 1254, 1205, 1101, 884, 788, 682 cm^{-1}. EIMS: *m/z* (rel intensity) 378.30 (M, 2.0), 347 (0.24), 335 (100), 277 (7), 249 (2.8), 211 (4), 187 (5), 165 (1.3) 135 (47), 103 (16), 75 (45), 61 (22).

(6*S*,7*R*,10*S*,2′*S*)-7α-Methyl-10*β*-[2′*β*-[1′-[(triisopropylsilyl)oxy]propyl]]-3-methylenebicyclo[4.4.0]decene (16). To a stirred solution of enone **10** (470 mg, 1.24 mmol) in THF (8 mL) at 0 °C was added dropwise 0.5 M Tebbe reagent (3.75 mL, 1.86 mmol or 1.50 equiv). After 30 min the reaction mixture was diluted with 50 mL of hexane, the reaction was quenched dropwise with 20 mL of saturated aqueous sodium potassium tartrate solution, and then the mixture was stirred for 15 min, warmed to ambient temperature, and finally poured into 200 mL of hexane. The organic layer was washed with 2 × 100 mL of saturated aqueous sodium potassium tartrate solution and 1 × 200 mL of H_2O, dried over anhydrous $MgSO_4$, filtered through a pad of Celite, and concentrated *in vacuo*. The crude oil was purified by silica gel flash chromatography (hexane) to give **16** (443 mg or 95%) as a colorless, viscous oil. ^{1}H NMR: δ 5.95 (s, 1H), 4.70 (br s, 1H), 4.67 (br s, 1H), 3.79 (dd, 1H, J = 3.4, 9.5 Hz), 3.51 (dd, 1H, J = 7.3, 9.5 Hz), 1.21−2.37 (m, 10H), 0.98−1.19 (m, 25H), 0.93 (d, 3H, J = 6.3 Hz), 0.85 (m, 1H). ^{13}C NMR: δ 147.0, 144.4, 120.3, 108.4, 65.8, 47.3, 45.3, 38.9, 35.9, 35.5, 29.8, 28.3, 26.8, 20.2, 18.1, 17.0, 12.0. IR (neat): 3075, 2942, 2865, 1637, 1604, 1463, 1382, 1103, 883, 682 cm^{-1}. DCIMS (NH_3): *m/z* 377 (M + H$^+$), 333, 219, 203, 187, 75.

(3*R*,6*S*,7*R*,10*S*,2′*S*)-3*β*-(Dibromomethyl)-7α-methyl-10*β*-[1′-[(triisopropylsilyl)oxy]prop-2′-yl]bicyclo[4.4.0]decen-3α-ol (12). The following operations were conducted with room lights turned off. To a 250 mL round-bottomed flask at −95 °C containing the enone **10** (6.1 g, 16.14 mmol) and CH_2Br_2 (2.38 mL, 33.9 mmol) in THF (100 mL) was added LDA [prepared from *n*-BuLi (13.56 mL, 33.9 mmol, 2.5 M solution in hexane) and *i*-Pr_2NH (4.75 mL, 33.9 mmol), −78−0 °C] via syringe over 40 min. The mixture was stirred for an additional 1.75 h at −95 °C, and then ice-cold saturated aqueous NH_4Cl (50 mL) was added to the above reaction mixture. The mixture was extracted with EtOAc (700 mL), and the organic layer was washed with saturated aqueous NH_4Cl (100 mL) followed by brine (2 × 50 mL), filtered over anhydrous Na_2SO_4, and concentrated by rotary evaporation (bath temperature <25 °C). The crude mixture was purified by gradient silica gel flash chromatography (6−8% EtOAc/hexane) to afford a pale yellow oil as a 1:1 mixture of **11** and **12** (7.84 g, 88%) that was stored at −20 °C. ^{1}H NMR (1:1): δ 5.71 (d, 1H, J = 4.5 Hz), 5.58 (s, 1H), 5.38 (s, 1H), 3.78 (m, 1H), 3.59 (m, 1H), 1.7−2.2 (m, 6H), 1.60 (m, 2H), 1.27 (m, 5H), 1.06 (m, 21H), 0.83−1.00 (m, 6H). ^{13}C NMR (1:1): 150.31, 149.89, 118.11, 117.42, 73.49, 73.17, 65.63, 65.48, 58.63, 58.42, 47.91, 47.02, 45.43, 44.90, 40.22, 37.80, 35.95, 35.70, 35.53, 35.38, 31.57, 30.74, 30.49, 29.24, 29.00, 24.10, 22.62, 21.86, 20.23, 19.93, 18.05, 16.98, 14.07, 12.01. IR: 3587 (sh), 3553 (sh), 3443 (s, br), 2952, 2864, 2724, 1654, 1463, 1380, 1334, 1247, 1148, 1100, 1070, 1029, 1015, 995, 910, 886, 786, 736, 682 cm^{-1}.

(7*S*,8*R*,11*S*,2′*S*)-8α-Methyl-11*β*-[1′-[(triisopropylsilyl)oxy]prop-2′-yl]bicyclo[5.4.0]undecen-4-one (13). From the dibromomethyl alcohols 11/12: In the dark and to a solution of the dibromomethyl alcohols **11**/**12** (6.16 g, 11.16 mmol) in 60 mL of THF at −95 °C was added over 1 h, *n*-BuLi (9.37 mL, 23.44 mmol, 2.5 M solution in hexane). The mixture was stirred at −95 °C for 1 h, warmed to 0 °C, and stirred for 7 min at 0 °C. The reaction was then quenched with saturated aqueous NH_4Cl (80 mL) and the mixture extracted with EtOAc (500 mL). The organic layer was separated, washed with brine (2 × 50 mL), filtered over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude product was then purified by silica gel flash chromatography (10% EtOAc/hexane) to give 2.33 g of **13** as a viscous oil (53% yield). ^{1}H NMR: δ 5.19 (t, 1H, J = 6.3 Hz), 3.71 (dd, 1H, J = 2.9, 9.6 Hz), 3.57 (dd, 1H, J = 5.7, 9.6 Hz), 3.21 (d, 1H, J = 2.2 Hz), 3.19 (s, 1H), 2.48 (m, 2H), 2.14 (m, 2H), 1.7−2.0 (m, 6H), 1.44 (m, 1H), 1.08−1.3 (m, 1H), 1.04 (m, 21H), 0.97 (d, 3H, J = 6.2 Hz), 0.90 (d, 3H, J = 6.4 Hz). ^{13}C NMR: δ 210.28, 147.25, 109.34, 65.92, 51.32, 49.36, 41.20, 39.50, 38.15, 36.11, 31.40, 24.08, 19.08, 17.98, 16.92, 14.02, 11.95. IR (neat): 3151, 3061, 2919, 2727, 1717, 1650, 1462, 1381, 1246, 1104, 1046, 1014, 997, 883, 797, 684, 660 cm^{-1}. EIMS: *m/z* (rel intensity) 349 (M − C_3H_7, 100), 281 (0.7), 251 (0.9), 227 (2), 214 (6), 201 (12), 171 (12), 171 (12), 159 (18), 133 (33), 119 (36), 105 (26), 93 (30), 75 (73), 61 (41). The conjugated enone **14** was obtained in 13% yield but not used further in this sequence.

From the diene 16: To a stirred, ambient temperature solution of **16** (200 mg, 0.53 mmol) in MeOH/$CHCl_3$ (10 mL of a 55:45 mixture) was added thallium(III) nitrate trihydrate (230 mg, 0.52 mmol). After 2 min, the solid was removed and washed with 2 × 10 mL of $CHCl_3$. The combined organic layer was diluted with $CHCl_3$ (150 mL) and H_2O (20 mL); the mixture was swirled for a moment and then washed with 1 × 100 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with 1 × 100 mL of $CHCl_3$, and the combined organic layer was then dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resultant oil was purified by preparative silica gel TLC (10:90 EtOAc/hexane) to give the product **13** (136 mg or 65%). Also isolated was the dimethoxy ketal of **13** (16 mg or 7%).

(7*S*,8*R*,11*S*,2′*S*)-8α-Methyl-11*β*-[1′-[(triisopropylsilyl)oxy]prop-2′-yl]bicyclo[5.4.0]undeca-1,4-dienyl 4-Trifluoromethanesulfonate (15). To a stirred suspension of KH (0.545 g, 35% (w/w) in mineral oil, 4.77 mmol, washed three times with hexane) in 12 mL of DME at −20 °C was added the ketone **13** (1.44 g, 3.67 mmol, in 2 mL of DME) dropwise via syringe. The mixture was stirred for 25 min at −20 °C, by which time gas evolution had ceased. $PhNTf_2$ (1.44 g, 4.77 mmol, in 3 mL of THF, recrystallized from hexane) was then added dropwise to the above enolate solution. After stirring for 2.5 h at −20 °C, the mixture was diluted with dry ether (50 mL), filtered through Celite, and rinsed with 300 mL of dry ether. The filtrate was concentrated by rotary evaporation and purified by rapid flash chromatography on silica gel (2% EtOAc/hexane). Triflate **15** was obtained as a yellow oil in 89% yield (1.715 g). The product turned dark quickly at room temperature and was therefore used immediately for the next reaction. ^{1}H NMR: δ 5.91 (dd, 1H, J = 2.4, 9.0 Hz), 5.36 (d, 1H, J = 9.0 Hz), 3.75 (dd, 1H, J = 3.4, 9.6 Hz), 3.69 (dd, 1H, J = 5.4, 9.6 Hz), 2.73 (m, 1H), 2.46 (m, 1H), 2.06 (m, 4H), 1.68−1.72 (m, 2H), 1.56 (m, 1H), 1.28 (m, 3H), 1.07 (m, 21H), 1.02

(d, 3H, J = 6.6 Hz), 0.87 (d, 3H, J = 6.6 Hz). ^{13}C NMR: δ 156.17, 151.30, 117.29, 108.88, 65.96, 51.40, 50.64, 38.43, 35.92, 33.00, 31.61, 29.13, 23.42, 22.86, 18.03, 16.61, 14.07, 12.04. IR (neat): 2943, 2865, 2729, 1670, 1625, 1463, 1419, 1326, 1240, 1209, 1145, 1099, 1025, 914, 866, 826, 810, 791, 684 cm^{-1}.

(7*S*,8*R*,11*S*,2′*S*)-4,8α-Dimethyl-11*β*-[1′-[(triisopropylsilyl)oxy]prop-2′-yl]bicyclo[5.4.0]undeca-1,4-diene (5). To a slurry of CuI (2.49 g, 13.1 mmol) in 20 mL of THF at −5 °C was added MeLi (20.65 mL, 19.6 mmol, 0.95 M solution in ether). The triflate **15** (1.715 g, 3.27 mmol, in 2 mL of THF) was then added to the above solution at −20 °C, and the mixture was allowed to warm to −5 °C and stirred for 3 h. The reaction mixture was then poured into saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (400 mL). The organic layer was washed with 5 × 20 mL of saturated aqueous NH_4Cl and 2 × 20 mL of brine, filtered over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude product was purified by silica gel flash chromatography (1% EtOAc/hexane) to afford the diene **5** as a clear oil (1.2 g, 94%). ^{1}H NMR: δ 5.58 (dt, 1H, J = 1.6, 7.8 Hz), 5.41 (d, 1H, J = 7.8 Hz), 3.79 (dd, 1H, J = 3.3, 9.6 Hz), 3.63 (dd, 1H, J = 6.2, 9.5 Hz), 2.30 (m, 1H), 1.84 (s, 3H), 1.72−2.1 (m, 7H), 1.54 (m, 1H), 1.14−1.32 (m, 3H), 1.09 (m, 21H), 1.05 (d, 3H, J = 6.4 Hz), 0.87 (d, 3H, J = 6.4 Hz). ^{13}C NMR: δ 149.23, 141.35, 120.48, 115.02, 66.27, 52.35, 49.98, 38.89, 36.32, 36.25, 32.49, 30.74, 27.15, 26.61, 18.52, 18.06, 16.88, 12.07. IR (neat): 3150, 3050, 2920, 2862, 2726, 1653, 1624, 1462, 1386, 1369, 1327, 1249, 1095, 1068, 1030, 994, 883, 825, 792, 682 cm^{-1}. EIMS: *m*/*z* (rel intensity) 390.35 (M, 0.98), 347 (6), 289 (0.5), 261 (0.7), 216 (55), 201 (37), 187 (17), 176 (100), 159 (27), 145 (24), 131 (40), 119 (26), 105 (43), 91 (30), 75 (45), 61 (24).

(1*R*,2*S*,2′*S*,5*R*,6*S*,9*R*)-5α-9-Dimethyl-2*β*-[1′-[(triisopropylsilyl)oxy]prop-2′-yl]-10,11-dioxatricyclo[7.2.2.0^{1,6}]tridec-12-ene (17). To a 100 mL 2-necked round-bottomed flask equipped with a reflux condenser were added rose bengal bis(triethylammonium) salt (0.7 g), EtOAc (80 mL), and the diene **5** (2.1 g, 5.38 mmol). Oxygen was bubbled through the above solution during irradiation with a GE 300 W desk lamp. After 7 h, the reaction mixture was filtered through silica gel, the column was rinsed with 30% EtOAc/hexane (400 mL), and the product was concentrated by rotary evaporation. Flash chromatography on silica gel (3% EtOAc/hexane) afforded two products. The more polar fraction was the desired α-peroxide **17** (0.70 g, 30%), and the less polar fraction was the *β*-peroxide (1*S*,2*S*,2′*S*,5*R*,6*S*,9*S*)-5α,9-dimethyl-2*β*-[1′-[(triisopropylsilyl)oxy]prop-2′-yl]-10,11-dioxatricyclo[7.2.2.0^{1,6}]tridec-12-ene (**18**), 1.22 g (54%). ^{1}H NMR (**17**): δ 6.28 (d, 1H, J = 9.3 Hz), 6.13 (d, 1H, J = 9.7 Hz), 3.70 (dd, 1H, J = 4.7, 9.7 Hz), 3.58 (dd, 1H, J = 6.5, 9.7 Hz), 2.05 (dddd, 1H, J = 1.1, 4.0, 13.2, 13.2 Hz), 1.88 (m, 2H), 1.52−1.82 (m, 4H), 1.35−1.47 (m, 2H), 1.25 (s, 3H), 1.14−1.3 (m, 2H), 1.05 (m, 25H), 0.85 (m, 3H). ^{13}C NMR (**17**): δ 134.97, 125.74, 86.23, 79.39, 66.87, 52.21, 47.90, 38.29, 36.61, 35.17, 34.72, 26.53, 25.89, 19.96, 18.18, 18.09, 12.02. IR (**17**, neat): 3046, 2941, 2863, 2724, 1462, 1370, 1249, 1158, 1095, 1065, 1013, 995, 920, 885, 799, 685 cm^{-1}.

^{1}H NMR (**18**): δ 6.21 (d, 1H, J = 9.5 Hz), 6.01 (d, 1H, J = 9.5 Hz), 4.13 (dd, 1H, J = 4.3, 9.7 Hz), 3.34 (dd, 1H, J = 9.9, 9.9 Hz), 2.05 (m, 2H), 1.90 (m, 1H), 1.75 (m, 1H), 1.60 (m, 3H), 1.45 (m, 3H), 1.25 (s, 3H), 1.25 (m, 1H), 1.04 (m, 24H), 0.90 (m, 1H), 0.89 (d, 3H, J = 6.5 Hz). ^{13}C NMR (**18**): δ 134.50, 129.82, 82.89, 79.06, 65.15, 49.97, 48.58, 37.29, 35.80, 34.01, 28.41, 23.85, 22.40, 21.31, 20.92, 18.12, 17.13, 11.96. IR (**18**, $CDCl_3$): 3049, 2943, 2864, 1465, 1375, 1250, 1165, 1092, 1067 cm^{-1}. DCIMS (NH_3): *m*/*z* 423 (M + H), 381, 379, 273, 249, 229.

(1*R*,2*S*,2′*S*,5*R*,6*S*,9*R*)-5α,9-Dimethyl-2*β*-(1′-hydroxyprop-2′-yl)-10,11-dioxatricyclo[7.2.2.0^{1,6}]tridec-12-ene (20). A solution of **17** (0.78 g, 1.848 mmol), tetrabutylammonium fluoride (2.03 mL, 2.03 mmol, 1 M solution in THF), and THF (15 mL) was stirred for 12 h at ambient temperature. The mixture was then poured into saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (300 mL). The organic layer was separated, washed with brine (2 × 20 mL), filtered over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude product was purified by flash chromatography on silica gel (40% EtOAc/hexane) to afford **20** (0.437 g, 89%) which could be recrystallized from hexane to afford a white crystalline solid. Mp: 84.2−85.8 °C. ^{1}H NMR: δ 6.30 (d, 1H, J = 9.8 Hz), 6.12 (d, 1H, J = 9.8 Hz), 3.66 (dd, 1H, J = 6.7, 11.0 Hz), 3.50 (dd, 1H, J = 5.9, 11.0 Hz), 2.05 (m, 2H), 1.89 (m, 1H), 1.59−1.83 (m, 6H), 1.50 (m, 1H), 1.26 (s, 3H), 0.87−1.24 (m, 3H), 1.00 (d, 3H, J = 7.2 Hz), 0.85 (d, 3H, J = 5.9 Hz). ^{13}C NMR: δ 134.63, 125.31, 86.61, 79.76, 66.60, 52.31, 46.27, 38.54, 38.28, 35.08, 34.55, 26.90, 26.32, 23.76, 19.91, 15.51. IR (neat): 3412 (br, s), 3050, 2935, 2863, 2727, 1650 (w), 1459, 1374, 1342, 1236, 1168, 1121, 1032, 983, 918, 887, 846, 827 cm^{-1}. DCIMS (NH_3): *m*/*z* 267 (M + H), 249 (M − HO), 233, 175.

(1a*S*,3*S*,5a*S*,6*R*,8a*S*,9*R*,12*S*)-10-Deoxo-13-carbaartemisinin (19). A solution of **18** (0.101 g, 0.240 mmol), TBAF (0.240 mL, 0.240 mmol, 1 M solution in THF), and THF (4 mL) was stirred for 10 h at ambient temperature. The mixture was then poured into saturated aqueous (NH_4Cl (20 mL) and extracted with EtOAc (150 mL). The organic layer was separated, washed with brine (2 × 20 mL), filtered over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude product was purified by flash chromatography over silica gel (40% EtOAc/hexane) to afford the alcohol (1*R*,2*S*,2′*S*,5*R*,6*S*,9*R*)-5α,9-dimethyl-2*β*-(1′-hydroxyprop-2′-yl)-10,-11-dioxatricyclo[7.2.2.0^{1,6}]tridec-12-ene as a white solid (0.045 g, 70%). ^{1}H NMR: δ 6.25 (d, 1H, J = 9.6 Hz), 6.04 (d, 1H, J = 9.6 Hz), 3.63 (dd, 1H, J = 9.2, 9.2 Hz), 3.42 (d, 1H, J = 9.9 Hz), 3.27 (ddd, 1H, J = 3.4, 10.9, 10.9 Hz), 2.16 (m, 1H), 1.98 (m, 1H), 1.83 (m, 1H), 1.65 (m, 3H), 1.35−1.6 (m, 3H), 1.28 (s, 3H), 0.85−1.34 (m, 3H), 0.92 (d, 3H, J = 7.1 Hz), 0.89 (d, 3H, J = 7.3 Hz). ^{13}C NMR: δ 134.60, 129.42, 83.25, 79.95, 64.55, 51.28, 48.75, 36.54, 35.59, 34.06, 28.28, 24.00, 22.19, 20.86, 20.31, 18.52. IR ($CDCl_3$): 3531, 3459, 3049, 2951, 2870, 2848, 1459, 1447, 1374, 1251, 1162, 1094, 1036 cm^{-1}.

To an ambient temperature solution of the above alcohol (40 mg, 0.15 mmol) in THF (2 mL) under N_2 was added $Hg(OCOCF_3)_2$ (0.120 g, 0.281 mmol). After 22 h, the reaction mixture was cooled to 0 °C and a mixture of $NaBH_4$ (10 mg) and NaOH (3 M/H_2O, 100 μL) was added. The mixture was stirred for 5 min at 0 °C, poured into saturated aqueous NH_4Cl (20 mL), and then extracted with EtOAc (100 mL). The organic layer was separated, washed with brine (2 × 10 mL), filtered over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude product was purified by flash chromatography over silica gel (20% EtOAc/hexane) to afford **19** as a white solid (31 mg, 78%). ^{1}H NMR: δ 3.86 (dd, 1H, J = 1.1, 11.1 Hz), 3.60 (dd, 1H, J = 1.1, 1.1 Hz), 3.56 (d, 1H, J = 1.1 Hz), 2.32 (dd, 1H, J = 9.2, 14.5 Hz), 2.08 (ddd, 1H, J = 2.7, 14.5, 14.5 Hz), 1.91 (m, 1H), 1.75 (m, 5H), 1.54 (m, 5H), 1.0−1.3 (m, 4H), 1.20 (s, 3H), 0.87 (d, 3H, J = 6.5 Hz). ^{13}C NMR: δ 78.48, 78.31, 74.41, 74.02, 50.09, 46.57, 38.37, 35.59, 35.19, 33.01, 29.63, 27.18, 25.39, 22.34, 20.19, 13.50. IR ($CDCl_3$): 2952, 2926, 2867, 2850, 1458, 1387, 1375, 1364, 1331, 1306, 1248, 1197, 1180, 1160, 1122, 1109, 1094, 1048, 1007, 971 cm^{-1}. DCIMS (NH_3): *m*/*z* 267 (M + H), 266 (M), 251, 249, 233, 223, 204, 195, 165.

(+)-10-Deoxo-13-carbaartemisinin (21). A mixture of alcohol **20** (25 mg, 0.094 mmol), $Hg(OCOCF_3)_2$ (0.130 g, 0.304 mmol), and 1 mL of THF under a N_2 atmosphere was stirred for 20 h at ambient temperature. $NaBH_4$ (0.012 g) and NaOH (aqueous, 3 M, 100 μL) were premixed at 0 °C and added to the above reaction mixture via syringe at 0 °C. After 5 min, the reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the mixture extracted with EtOAc (100 mL). The organic layer was separated, washed with brine (2 × 10 mL), filtered over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude product was purified by flash chromatography over silica gel (20% EtOAc/hexane) to afford 19 mg of a white solid (76%) which could be recrystallized from hexane to afford **21**. Mp: 137−138 °C. ^{1}H NMR: δ 4.00 (d, 1H, J = 8.3 Hz), 3.60 (dd, 1H, J = 4.2, 11.3 Hz), 3.32 (dd, 1H, J = 11.5, 11.5 Hz), 2.59 (m, 1H), 2.18 (d, 2H, J = 8.3, 14.6 Hz), 1.92 (m, 1H), 1.6−1.78 (m, 4H), 1.4−1.6 (m, 2H), 1.21 (s, 3H), 1.22 (m, 3H), 1.05 (m, 1H), 0.91 (d, 3H, J = 5.8 Hz), 0.74 (d, 3H, J = 7.3 Hz). ^{13}C NMR: δ 80.73, 78.09, 67.19, 67.06, 53.41, 44.08, 37.27, 37.10, 36.77, 34.51, 28.16, 27.36, 26.76,

20.85, 20.41, 13.65. $[\alpha]_D^{25} = +94.5°$ ($c = 0.152$, $CHCl_3$). IR ($CDCl_3$): 2959, 2935, 2873, 1462, 1374, 1345, 1297, 1238, 1171, 1146, 1095, 1006 cm^{-1}. DCIMS (NH_3): *m/z* 267 (M + H), 266 (M), 251, 250, 249, 248, 235, 234, 233, 232, 223, 204, 195, 179, 165.

(1*R*,2*S*,2′*S*,5*R*,6*S*,9*R*)-5α,9-Dimethyl-2*β*-(1′-carboxyprop-2′yl)-10,11-dioxatricyclo[7.2.2.0^{1,6}]tridec-12-ene (22). To a 5 mL round-bottomed flask were added alcohol **20** (40 mg, 0.150 mmol), glacial acetic acid (1 mL), H_2O (0.2 mL), and CrO_3 (0.090 g, 0.902 mmol). The flask was sealed and stirred for 10 h at ambient temperature. The reaction mixture was then chromatographed over silica gel with hexane/EtOAc/MeOH (70:25:5). The acid **22** was obtained as a yellow oil (30 mg, 71%). ^{1}H NMR: δ 6.36 (d, 1H, $J = 9.8$ Hz), 6.07 (d, 1H, $J = 9.8$ Hz), 2.65 (m, 1H), 2.05 (m, 2H), 1.55−1.85 (m, 5H), 1.44 (m, 1H), 1.24 (s, 3H), 1.25 (m, 3H), 0.75−1.2 (m, 6H). ^{13}C NMR: δ 182.00, 136.35, 124.21, 85.66, 79.66, 51.95, 46.90, 38.05, 34.56, 34.43, 27.04, 26.40, 23.88, 23.82, 19.83, 17.53. IR (neat): 2937 (br, s), 2627, 1706 (s), 1460, 1415, 1377, 1293, 1217, 914, 825 cm^{-1}.

(+)-13-Carbaartemisinin (4). To a solution of the carboxylic acid **22** (25 mg, 0.089 mmol) under N_2 in THF (1 mL) was added $Hg(OCOCF_3)_2$ (0.057 g, 0.134 mmol). After stirring at ambient temperature for 18 h, the reaction mixture was cooled to 0 °C and a mixture of $NaBH_4$ (9 mg) and NaOH (aqueous 3 M solution, 100 μL) was added. After 5 min at 0 °C, the reaction mixture was poured into saturated aqeous NH_4Cl (20 mL) and extracted with EtOAc (100 mL). The organic layer was separated, washed with brine (2 × 10 mL), filtered over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude product was purified by flash chromatography on silica gel eluting with hexane/EtOAc/MeOH (70:25:5) to afford a white solid (15 mg, 60%) which was recrystallized from hexane to afford **4**. Mp: 160−162 °C. ^{1}H NMR: δ 4.92 (dd, 1H, $J = 1.5$, 9.8 Hz), 3.40 (ddd, 1H, $J = 5.1$, 7.3, 14.4 Hz), 2.17−2.31 (m, 2H), 2.10 (m, 1H), 1.90 (m, 2H), 1.75 (m, 3H), 1.0−1.4 (m, 5H), 1.23 (s, 3H), 1.18 (d, 3H, $J = 7.2$ Hz), 0.96 (d, 3H, $J = 6.0$ Hz). ^{13}C NMR: δ 173.40, 77.10, 79.75, 78.75, 71.50, 51.64, 45.73, 37.52, 37.28, 36.34, 33.79, 33.15, 26.60, 23.77, 19.95, 12.55. $[\alpha]_D^{25} = +69.3°$ ($c = 0.138$, $CHCl_3$). IR ($CDCl_3$): 2976, 2949, 2934, 2879, 1729 (s), 1458, 1381, 1203, 1170, 1113, 1029 cm^{-1}. DCIMS (NH_3): *m/z* 281 (M + H), 263 (M − HO), 247, 235, 219, 209, 179.

(1*R*,2*S*,2′*S*,5*R*,6*S*,9*R*)-5α,9-Dimethyl-2*β*-(1′-hydroxyprop-2′-yl)-10,11-dioxatricyclo[7.2.2.0^{1,6}]tridecane (25). To a 25 mL round-bottomed flask containing alcohol **20** (30 mg, 0.113 mmol) and potassium azodicarboxylate (0.656 g, 3.38 mmol) in 10 mL of CH_2Cl_2 at 0 °C was added dropwise over 15 min HOAc (0.291 mL, 5.08 mmol, in 0.4 mL of CH_2Cl_2). The reaction mixture was then stirred for 10 min at 0 °C. The mixture was then allowed to warm to ambient temperature and stirred for 72 h, during which period of time two portions of equal amounts of PADA and HOAc were added when the yellow color had faded. The reaction mixture was carefully poured into ice−water (50 mL) and extracted with EtOAc (200 mL). The organic layer was washed with brine (20 mL), filtered over Na_2SO_4, and concentrated by rotary evaporation. The crude product was purified by flash chromatography over silica gel (35% EtOAc/hexane) to give **25** as a white solid (19 mg or 63%) that was recrystallized from hexane to afford **25** as a white crystalline material. Mp: 120−121 °C. ^{1}H NMR: δ 3.74 (dd, 1H, $J = 4.9$, 10.0 Hz), 3.38 (dd, 1H, $J = 7.7$, 10.9 Hz), 2.21 (m, 1H), 2.08 (m, 2H), 1.91 (m, 2H), 1.55−1.83 (m, 6H), 0.9−1.4 (m, 6H), 1.15 (s, 3H), 1.05 (d, 3H, $J = 7.0$ Hz), 0.90 (d, 3H, $J = 6.1$ Hz). ^{13}C NMR: δ 85.74, 79.10, 66.48, 55.33, 49.72, 37.47, 37.34, 35.69, 35.39, 27.53, 27.39, 27.05, 25.04, 19.97, 19.08, 17.97. IR ($CDCl_3$): 3620, 3474 (s, br), 2969, 2929, 2869, 1458, 1375, 1267, 1232, 1199, 1119, 1025 cm^{-1}. DCIMS (NH_3): *m/z* 269 (M + H), 251 (M − HO), 235, 233, 215, 177, 175.

(1*R*,2*S*,2′*S*,5*R*,6*S*,9*R*)-5α,9-Dimethyl-2*β*-(1′-methoxyprop-2′-yl)-10,11-dioxatricyclo[7.2.2.0^{1,6}]tridec-12-ene (23). To a 5 mL round-bottomed flask were added the alcohol **20** (25 mg, 0.094 mmol), DMF (1.3 mL), and MeI (70.2 μL, 1.128 mmol). The mixture was cooled to 0 °C, and NaH (15 mg, 0.376 mmol, in 60% (w/w) mineral oil) was added in one portion. The reaction was stirred for 10 min at 0 °C and then for 4 h at ambient temperature. The reaction mixture was then poured into saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (100 mL). The organic layer was separated, washed with brine (2 × 10 mL), filtered over anhydrous Na_2SO_4, and concentrated by rotary evaporation. The crude product was purified by silica gel flash chromatography (15% EtOAc/hexane) to afford the methyl ether **23** as a yellow oil which solidified upon storage in the refrigerator (23 mg, 87%). ^{1}H NMR: δ 6.30 (d, 1H, $J = 9.8$ Hz), 6.12 (d, 1H, $J = 9.7$ Hz), 3.38 (dd, 1H, $J = 5.4$, 9.4 Hz), 3.30 (s, 3H), 3.24 (dd, 1H, $J = 6.7$, 9.4 Hz), 1.96−2.11 (m, 2H), 1.56−1.84 (m, 5H), 1.44 (m, 2H), 0.85−1.3 (m, 3H), 1.25 (s, 3H), 1.02 (d, 3H, $J = 7.1$ Hz), 0.85 (d, 3H, $J = 5.9$ Hz). ^{13}C NMR: δ 135.06, 125.58, 86.30, 79.48, 76.89, 58.60, 52.18, 48.16, 38.22, 35.09, 34.65, 34.19, 26.50, 25.58, 23.89, 19.94, 18.30. IR ($CDCl_3$): 3048, 2974, 2931, 2872, 2812, 1653 (w), 1459, 1449, 1392, 1375, 1199, 1163, 1111, 982 cm^{-1}.

(1*R*,2*S*,2′*S*,5*R*,6*S*,9*R*)-5α,9-Dimethyl-2*β*-[1′-(benzyloxy)-prop-2′-yl]-10,11-dioxatricyclo[7.2.2.0^{1,6}]tridec-12-ene (24). **24** was prepared according to the procedure for the preparation of **23** starting with alcohol **20** (25 mg, 0.094 mmol), $PhCH_2Br$ (56 μL, 0.47 mmol), and NaH (15 mg, 0.376 mmol, in 60% (w/w) mineral oil) in DMF (1.3 mL). The product was chromatographed over silica gel (13% EtOAc/hexane) to afford the benzyl ether **24** as a light yellow solid (25 mg, 80%) that was recrystallized from hexane to afford a white crystalline material. Mp: 86−88 °C. ^{1}H NMR: δ 7.33 (m, 5H), 6.26 (d, 1H, $J = 9.8$ Hz), 6.10 (d, 1H, $J = 9.7$ Hz), 4.49 (d, 2H, $J = 2.4$ Hz), 3.50 (dd, 1H, $J = 5.2$, 9.4 Hz), 3.36 (dd, 1H, $J = 6.8$, 9.4 Hz), 2.06 (m, 2H), 1.55−1.85 (m, 6H), 1.37−1.49 (m, 2H), 0.82−1.32 (m, 2H), 1.26 (s, 3H), 1.07 (d, 3H, $J = 7.0$ Hz), 0.84 (d, 3H, $J = 5.6$ Hz). ^{13}C NMR: δ 138.97, 135.06, 128.22, 127.45, 127.26, 125.61, 86.30, 79.48, 77.20, 77.12, 74.30, 72.77, 52.21, 48.22, 38.25, 35.13, 34.69, 34.15, 26.51, 25.58, 23.92, 19.93, 18.50. IR (neat): 3085, 3062, 3030, 2970, 2932, 2869, 2796, 2000−1600 (w), 1499, 1455, 1370, 1102, 1073, 736, 699 cm^{-1}. DCIMS (NH_3): *m/z* 249 (M − benzyloxy), 247, 233, 217, 216, 201, 175, 173.

(1*R*,2*S*,2′*S*,5*R*,6*S*,9*R*)-5α,9-Dimethyl-2*β*-(1′-methoxyprop-2′-yl)-10,11-dioxatricyclo[7.2.2.0^{1,6}]tridecane (26). **26** was prepared according to the procedure for the preparation of **23** starting with alcohol **25** (23 mg, 0.0858 mmol), MeI (64 μL, 1.03 mmol), and NaH (14 mg, 0.344 mmol, in 60% (w/w) mineral oil) in DMF (1.2 mL). The crude product was chromatographed over silica gel with 15% EtOAc/hexane to afford the methyl ether **26** as a light yellow solid (23 mg, 95%). ^{1}H NMR: δ 3.39 (dd, 1H, $J = 4.3$, 9.2 Hz), 3.30 (s, 3H), 3.08 (dd, 1H, $J = 8.1$, 9.2 Hz), 12.0−2.3 (m, 3H), 1.52−2.3 (m, 8H), 0.82−1.37 (m, 5H), 1.14 (s, 3H), 1.03 (d, 3H, $J = 7.0$ Hz), 0.90 (d, 3H, $J = 6.1$ Hz). ^{13}C NMR: δ 85.29, 78.86, 76.84, 58.75, 55.27, 50.85, 37.51, 37.34, 35.44, 31.92, 27.56, 27.45, 27.10, 24.19, 19.99, 19.68, 18.81. IR ($CDCl_3$): 2972, 2928, 2872, 2812, 1459, 1373, 1265, 1200, 1103 cm^{-1}.

(1*R*,2*S*,2′*S*,5*R*,6*S*,9*R*)-5α,9-Dimethyl-2*β*-[1′-(benzyloxy)-prop-2′-yl]-10,11-dioxatricyclo[7.2.2.0^{1,6}]tridecane (27). **27** was prepared according to the procedure for the preparation of **23** starting with alcohol **25** (23 mg, 0.0858 mmol), $PhCH_2$-Br (51 μL, 0.43 mmol), and NaH (14 mg, 0.344 mmol, in 60% (w/w) mineral oil) in DMF (1.4 mL). The product was chromatographed over silica gel with 13% EtOAc/hexane to afford the benzyl ether **27** as a light yellow solid (21 mg, 70%) that was recrystallized from hexane to afford a white crystalline material. Mp: 98−99 °C. ^{1}H NMR: δ 7.33 (m, 5H), 4.49 (d, 2H, $J = 4.5$ Hz), 3.49 (dd, 1H, $J = 4.4$, 9.2 Hz), 3.21 (dd, 1H, $J = 8.1$, 9.3 Hz), 2.0−2.33 (m, 2H), 1.32−1.96 (m, 6H), 0.8−1.4 (m, 8H), 1.15 (s, 3H), 1.08 (d, 3H, $J = 7.0$ Hz), 0.90 (d, 3H, $J = 5.2$ Hz). ^{13}C NMR: δ 128.23, 127.44, 127.28, 85.32, 78.88, 74.16, 72.82, 55.30, 50.89, 37.36, 31.95, 27.59, 27.48, 27.13, 24.23, 22.33, 20.00, 19.85, 18.85, 14.05. IR ($CDCl_3$): 3088, 3065, 3032, 2929, 2869, 2000−1600 (w), 1496, 1455, 1361, 1268, 1204, 1096, 1071, 1027, 995 cm^{-1}.

Rearrangement of 10-Deoxo-13-carbaartemisinin (21) with $FeBr_2$: Synthesis of 5,8,12-Trimethyl-2,14-dioxatetracyclo[7.4.2.^{5,11}0.^{1,15}0^{9,15}]pentadecan-12-ol (35). To a 5 mL round-bottom flask were added **21** (19 mg, 0.0714 mmol),

THF (1.2 mL), and $FeBr_2$ (0.0308 g, 0.143 mmol). The mixture was stirred at ambient temperature under a N_2 atmosphere for 8 h and then directly chromatographed over silica gel (60% EtOAc/hexane). The product **35** was isolated in 79% yield (15 mg). ^{1}H NMR: δ 4.00 (dt, 1H, J = 1.5, 7.9 Hz), 3.89 (s, 1H), 3.65 (m, 2H), 3.25 (t, 1H, J = 11.7 Hz), 2.43 (m, 1H), 2.10 (dddd, 1H, J = 2.4, 7.8, 7.8, 7.8 Hz), 1.78 (dd, 1H, J = 4.7, 15.3 Hz), 1.5−1.86 (m, 5H), 1.2−1.5 (m, 4H), 1.04 (s, 3H), 0.93 (d, 3H, J = 5.8 Hz), 0.75 (d, 3H, J = 7.1 Hz). ^{13}C NMR: 83.48, 79.28, 70.47, 70.19, 68.70, 55.50, 44.26, 35.80, 35.50, 31.41, 30.04, 29.69, 28.90, 22.84, 20.52, 13.02. IR ($CDCl_3$): 3532 (br), 2954, 2934, 2877, 2850, 1457, 1402, 1378, 1322, 1301, 1263, 1247, 1216, 1137, 1092, 1002 cm^{-1}. EIMS: *m/z* (rel intensity) 266.15 (M, 8.5), 195 (39), 178 (8), 165 (100), 138 (15), 121 (2.7), 109 (3.5), 95 (5.8), 79 (5.5), 67 (6.3), 55 (9).

Rearrangement of Diastereomeric 10-Deoxo-13-carbaartemisinin (19) with $FeBr_2$: Synthesis of 2-[1′-(Ethenyloxy)prop-2′-yl]-5-methyl-6-(3″-oxobutyl)cyclohexanone (41) and 4,8,13-Trimethyl-2,12-dioxatetracyclo-[7.5.1.^{1,9}0.^{5,15}0^{11,13}]pentadecan-15-ol (42). To a 25 mL round-bottom flask were added **19** (0.352 g, 1.323 mmol), THF (12 mL), and $FeBr_2$ (0.571 g, 2.65 mmol). The mixture was stirred at ambient temperature under a N_2 atmosphere for 8 h and then directly chromatographed over silica gel using gradient elution (20−30% EtOAc/hexane). The least polar fraction gave **41** as an oil (0.138 g, 39%). ^{1}H NMR (**41**): δ 6.47 (dd, 1H, J = 6.8, 14.4 Hz), 4.17 (dd, 1H, J = 1.9, 14.4 Hz), 3.97 (dd, 1H, J = 1.9, 6.8 Hz), 3.68 (dd, 1H, J = 4.7, 9.7 Hz), 3.60 (dd, 1H, J = 5.6, 9.7 Hz), 2.56 (m, 1H0, 2.29−2.44 (m, 2H), 2.20 (m, 1H), 2.13 (s, 3H), 2.05 (m, 2H), 1.7−1.9 (m, 3H), 1.3−1.57 (m, 3H), 1.07 (d, 3H, J = 6.1 Hz), 1.00 (d, 3H, J = 6.9 Hz). ^{13}C NMR (**41**): δ 212.98, 209.08, 152.00, 86.20, 70.32, 57.06, 53.38, 41.39, 40.59, 34.79, 32.07, 30.51, 29.89, 20.58, 20.24, 15.75. IR (**41**) ($CDCl_3$): 2959, 2928, 2875, 2853, 1708 (s), 1635, 1615, 1456, 1380, 1364, 1321, 1203, 1167 cm^{-1}. EIMS (**41**): *m/z* (rel intensity) 266.15 (M, 0.074), 223 (23), 207 (1.5), 182 (5.6), 165 (100), 149 (4.3), 137 (7), 124 (23), 109 (11), 95 (12), 69 (25), 55 (19).

The more polar fraction gave **42** as a crystalline solid (70 mg or 20%). ^{1}H NMR (**42**): δ 3.82 (dd, 1H, J = 1.0, 11.3 Hz), 3.71 (dd, 1H, J = 2.9, 11.3 Hz), 3.11 (dd, 1H, J = 1.5, 11.5 Hz), 2.73 (dd, 1H, J = 6.3, 9.3 Hz), 2.15 (dd, 1H, J = 12.9, 12.9 Hz), 1.98 (dd, 1H, J = 6.6, 14.4 Hz), 1.38 (s, 3H), 1.15−1.9 (m, 11H), 1.10 (d, 3H, J = 7.4 Hz), 0.95 (d, 3H, J = 6.4 Hz). ^{13}C NMR (**42**): 82.41, 75.47, 73.77, 61.49, 57.02, 47.02, 46.22, 36.96, 35.68, 33.22, 31.93, 26.45, 26.09, 22.51, 21.35, 15.17. IR (**42**) ($CDCl_3$): 3590 (br, w), 3524 (br, w), 2957, 2928, 2854, 1476, 1458, 1381, 1316, 1242, 1192, 1167, 1115, 1082, 1041, 1027, 1007, 982 cm^{-1}. EIMS (**42**): *m/z* (rel intensity) 266.05 (M, 7.6), 248 (6.7), 233 (11), 219 (11), 205 (32), 165 (100), 151 (35), 137 (61), 123 (33), 107 (45), 95 (59), 81 (44), 69 (50), 55 (70).

Rearrangement of 10-Deoxoartemisinin (43) with $FeBr_2$: Synthesis of 2-[1′-(Formyloxy)prop-2′-yl]-5-methyl-6-(3″-oxobutyl)cyclohexanone (46) and 1,10-Dideoxoartemisinin (49). To a 25 mL round-bottom flask were added **43** (0.32 g, 1.19 mmol), THF (10 mL), and $FeBr_2$ (0.50 g, 2.31 mmol). The mixture was stirred at ambient temperature under a N_2 atmosphere for 15 min and then poured into water (100 mL) and extracted with 3 × 25 mL of EtOAc. The combined organic layer was washed with 3 × 25 mL of saturated aqueous NH_4Cl, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Preparative TLC on silica gel with 95:5 benzene/ether gave two main products. The higher R_f material **49** (25 mg or 8.3%) slowly crystallized on standing and ultimately correlated chromatographically and spectroscopically with 1,10-dideoxoartemisinin prepared by reduction of 10-deoxoartemisinin (**43**). ^{1}H NMR (**49**): δ 5.25 (s, 1H), 3.94 (*AB* dd, 1H, J = 6.8, 11.5 Hz), 3.28 (A*B* dd, 1H, J = 4.6, 11.5 Hz), 2.27 (dq, 1H, J = 4.3, 7.0 Hz), 1.89 (ddd, 1H, J = 4.3, 7.0, 13.5 Hz), 1.53 (s, 3H), 0.92 (d, 3H, J = 7.5 Hz), 0.89 (d, 3H, J = 6.1 Hz). ^{13}C NMR (**49**): δ 107.3, 96.2, 82.6, 64.5, 45.9, 40.0, 35.3, 34.5, 34.4, 26.4, 24.0, 23.9, 22.1, 18.8, 16.6. IR (neat): 2958, 2940, 2922, 2871, 2852, 1458, 1390, 1361, 1207, 1143, 1104, 995, 960, 937 cm^{-1}. FAB-MS: *m/z* 253 (M + H), 252 (M), 251, 235, 220, 205, 193, 187, 177, 165.

The lower R_f material **46** (523 mg or 79%) was crystalline at −20 °C but a liquid at ambient temperature. ^{1}H NMR (**46**): δ 8.06 (d, 1H, J = 0.6 Hz), 4.19 (*AB*, ddd, 1H, J = 0.7, 4.7, 10.8 Hz), 4.05 (A*B*, ddd, 1H, J = 0.7, 6.3, 10.8 Hz), 2.55 (ddd, 1H, J = 5.8, 9.0, 17.5 Hz), 2.35 (ddd, 1H, J = 6.2, 9.0, 9.0 Hz), 2.30 (m, 1H), 2.22 (ddd, 1H, J = 4.9, 6.6, 12.5 Hz), 2.12 (s, 3H), 1.87 (ddd, 1H, J = 2.5, 5.8, 11.6 Hz), 1.78 (dq, 1H, J = 5.8, 9.0 Hz), 1.06 (d, 3H, J = 6 Hz), 0.99 (d, 3H, J = 6.8 Hz). ^{13}C NMR (**46**): δ 212.3, 209.0, 161.1, 66.4, 56.9, 53.2, 41.3, 40.4, 34.6, 31.6, 30.2, 29.9, 20.5, 20.1, 15.5. IR (neat): 2958, 2925, 2875, 1722, 1710 (sh), 1458, 1444, 1376, 1361, 1180 cm^{-1}. FAB-MS: *m/z* 269 (M + H), 267, 251, 223, 207, 193, 182, 165.

1,10-Dideoxoartemisinin (49). To a stirred solution of 10-deoxoartemisinin (**43**) (20 mg or 0.075 mmol) in THF (1 mL) were added Zn dust (10 mg or 0.15 mmol) and glacial acetic acid (50 μL). The mixture was stirred for 16 h, filtered, and concentrated *in vacuo*. The crude low-R_f material was dissolved in $CHCl_3$ (1 mL) and treated with *p*-toluenesulfonic acid monohydrate (2 mg) at ambient temperature. After 1 h, solid $NaHCO_3$ was added, and the mixture was allowed to stand for 1 h. After filtration, the solution was concentrated and the residue chromatographed on a silica gel TLC plate (20% EtOAc/hexane) to give **49** as a white crystalline solid. Mp: 102−104 °C (14 mg or 73%). This synthetic material was identical with **49** obtained in the Fe(II)-promoted rearrangement of 10-deoxoartemisinin.

(1*S*,6*S*,7*R*,10*S*,11*R*)-7α,11*β*-Dimethyl-13-oxatricyclo-[8.3.0.^{1,6}0^{1,10}]tridecan-3-one (50). Cyclization of diketo formate 46: To an ambient temperature solution of the formate ester **46** (30 mg or 0.11 mmol) in reagent grade methanol (moist, 1.25 mL) was added solid $NaHCO_3$ (133 mg or 1.58 mmol). The mixture was stirred at ambient temperature for 16 h, diluted with EtOAc (5 mL), washed with water (3 × 1 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. This intermediate was dissolved in $CHCl_3$ (2 mL), treated with Amberlyst-15 beads (10 mg), and stirred for several hours at ambient temperature, during which time progress was monitored by TLC (35% EtOAc/hexane). The beads were removed by filtration and the mixture concentrated by evaporation. The crude material was purified by chromatography on a silica gel TLC plate to give **50** (13 mg or 52%) as a crystalline solid. Mp: 70−72 °C.

Cyclization of enone 10: To an ambient temperature solution of the enone **10** (25 mg or 0.066 mmol) in THF (1.5 mL) was added tetrabutylammonium fluoride (0.1 mL of a 1 M solution in THF, 0.1 mmol). The mixture was stirred for 14 h, diluted with EtOAc (5 mL), and washed with water (3 × 2 mL). The organic layer was dried over $MgSO_4$ and filtered and the solvent evaporated *in vacuo*. The crude product was purified as above to give **50** (10 mg or 69%) as a white solid. Mp: 69−71 °C.

Cyclization of diketo vinyl ether 41: To an ambient temperature solution of the vinyl ether **41** (15 mg or 0.056 mmol) in moist CH_2Cl_2 (0.5 mL) was added *p*-toluenesulfonic acid (1 mg). The mixture was stirred for 1 h, at which time the mixture was filtered, concentrated by evaporation, and purified on a silica gel TLC plate as above. The product **50** was identical with the ketones prepared from either **10** or **46**. The following spectral data were obtained for all three samples of **50**. ^{1}H NMR: δ 3.98 (AB, dd, 1H, J = 8.5, 8.5 Hz), 3.39 (AB, dd, 1H, J = 8.5, 9.5 Hz), 2.72 (m, 1H), 2.70 (dd, 1H, J = 2.5, 13.8 Hz), 2.45 (dddd, 1H, J = 2.5, 2.5, 5.5, 15.5 Hz), 2.26 (ddd, 1H, J = 10.0, 12.7, 14.9 Hz), 2.17 (d, 1H, J = 13.8 Hz), 2.11 (dddd, 1H, J = 2.5, 3.5, 7.5, 7.5 Hz), 1.72 (m, 3H), 0.96 (d, 3H, J = 6.4 Hz), 0.94 (d, 3H, J = 7.5 Hz). ^{13}C NMR: δ 210.4, 86.6, 71.3, 51.7, 48.7, 45.4, 40.8, 35.3, 34.0, 31.7, 25.1, 23.3, 20.1, 12.0. IR (neat): 2970, 2952, 2931, 2871, 1714, 1456, 1429, 1217, 1022, 983, 958, 908, 737 cm^{-1}. HR-FAB-MS: *m/z* 223 (M + H), 215, 205, 193, 185, 179.

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Supporting Information Available: Tables of atomic coordinates, bond lengths, and angles, anisotropic displacement coefficients, and H atom coordinates for **19** and **21** and NMR spectral data for **23**, **26**, **27**, **35**, **42**, **46**, **49**, and **50** (43 pages). Ordering information is given on any current masthead page. Tables of atomic coordinates and thermal parameters have been deposited with the Crystallographic Data Centre, Cambridge University Chemical Laboratory, Cambridge CB2 1EW, England.

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