Structure-Activity Relationships of the Antimalarial Agent Artemisinin. 1. Synthesis and Comparative Molecular Field Analysis of C-9 Analogs of Artemisinin and 10-Deoxoartemisinin

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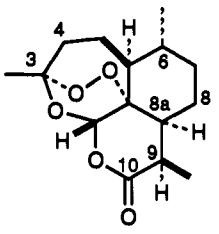
Received July 19, 1993•

A series of C-9 β-substituted artemisinin analogs (**2–21**) were synthesized via dianion alkylation of the total synthetic intermediate **57** followed by subsequent ozonolysis/acidification, or by alkylation of the enolate derived from (+)-9-desmethylartemisinin, **2**. Inactive acyclic analogs **22** and **23** were synthesized by nucleophilic epoxide opening and the ring contracted analog **24** was prepared by an alternate route. 10-Deoxo-9-alkyl derivatives **68** and **70** were synthesized convergently from intermediates in the preparation of 9-alkyl derivatives. *In vitro* bioassay was conducted in W-2 and D-6 clones of drug resistant *Plasmodium falciparum*. Comparative molecular field analysis (CoMFA) of the 9-alkyl lactone derivatives provided a model with a cross-validated $r^2 = 0.793$. Inclusion of inactive 1-deoxyartemisinin analogs **26–42** provided a model with a value of 0.857. The activities of a number of other analogs of divergent structure (**43–56**) were predicted with good accuracy using the CoMFA model.

The serious health threat posed by the increasing resistance of the malaria parasite *Plasmodium falciparum* to single- and multiple-agent drug therapies continues.[1-4] The need for structurally unconventional antimalarials active against resistant strains of *P. falciparum* was provided for a number of years ago with the discovery of (+)-artemisinin (**1**), a unique sesquiterpene isolated from *Artemisia annua* L.[5-7]



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The modest practical utility of the natural product has stimulated the search for congeners with improved properties such as potency, water solubility and oral activity.[8] Accordingly, derivatives of dihydroartemisinin[9] such as artesunate[10] and artemether[11,12] have been fielded, while more recently clinical trials of arteether are planned.[13-15] Numerous approaches to the total synthesis of the natural product[16-18] and analog syntheses[19,20] have not clearly defined structural requirements for biological activity.[21] Although recent mode of action[22-25] and metabolism studies[26,27] shed some light on this class of drugs, it may be some time before these studies can be exploited in drug-design efforts. Only limited efforts have been reported regarding quantitative structure-activity relationships (QSAR) in the artemisinin class of antimalarials, being confined to structure types containing the dihydroartemisinin nucleus.[28]

Early SAR studies in our laboratory focused on simplification of the artemisinin ring system from tetra- to tricyclic. The activity of 4,5-secoartemisinin[29] was unimpressive, as were virtually all other derivatives in this series.[30,31] Crystallography, NMR, and molecular mechanics calculations showed that some of these analogs had a low barrier to conformational inversion.[20] It was felt that a major determinant to potency was positioning of the peroxide bond relative to hydrophobic regions elsewhere in the molecule. Parallel efforts with 8a,9-secoartemisinin and derivatives were conducted by us[20] and others.[32,33] In these cases, alignment of the peroxy moiety was satisfactory but activities were unpredictable, pointing to the importance of the D ring for biological activity.[19] Other minor modifications have been conducted on the intact artemisinin skeleton such as the removal of one[34] or two[35] of the methyl groups at either the C-9 position or both the C-6 and C-9 positions without serious detriment to activity, as well as epimerization at C-9.[36,34]

We felt that the growing array of diverse analogs could guide us in the design of new analogs, and thus approaches to define overall SAR were considered. A comparative molecular field analysis (CoMFA) was particularly useful for relatively rigid molecules[37] and apparently suited to our needs. With the CoMFA approach, groups of molecules are aligned, three-dimensional maps of steric and electrostatic fields are generated, and a statistical correlation and cross-validation[38] are used to create a 3D QSAR model than can be used to predict activities. In this paper we will explore the effects of substitution at C-9 on the antimalarial activities of 26 artemisinin analogs with the CoMFA approach (Table I). Seventeen of the set of 26 analogs **4–21** are homologs of artemisinin, while 9-epiartemisinin (**3**) was included along with 9-desmethylartemisinin (**2**), 6,9-didesmethylartemisinin (**25**), and artemisinin (**1**). Four other related compounds with lower activity, ring contracted **24**, the acyclic peroxides **22** and **23**, and the inactive metabolite **26** (1-deoxyartemisinin),[6] were included to generate the CoMFA. In later iterations, a more accurate CoMFA was obtained by adding the inactive nonperoxidic 1-deoxy analogs **26–42** (Table II). The resultant CoMFA was used to predict the activities

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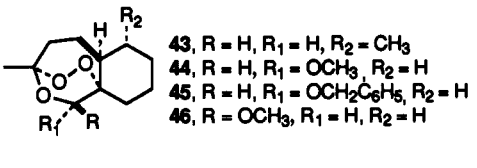
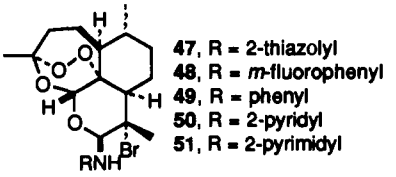
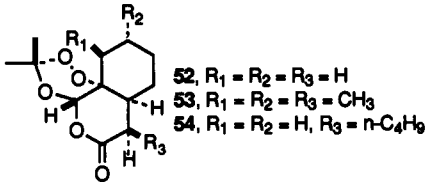
• Abstract published in *Advance ACS Abstracts*, December 1, 1993.

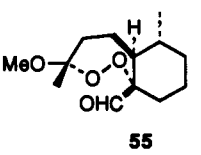
0022-2623/93/1836-4264$04.00/0

Chart I. Structures of Artemisinin Analogs Used for Prediction in the Final CoMFA Field









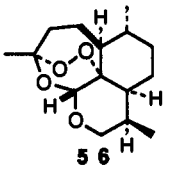
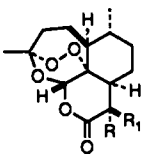
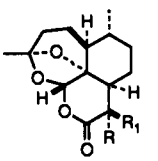


Table I. Relative Activities of Artemisinin Analogs (IC_{50} of Analog/IC_{50} of Artemisinin = Relative Activity)



compd	R	R_1	relative activity W-2 clone	relative activity D-6 clone	anal. C, H
1	H	CH_3	1.00	1.00	
2	H	H	6.50	1.80	ref 34
3	CH_3	H	0.67	0.14	$C_{15}H_{22}O_5$
4	CH_3	CH_3	0.006	0.02	$C_{16}H_{24}O_5$
5	H	C_2H_5	12.26	6.42	$C_{16}H_{24}O_5$
6	H	C_3H_7(n)	12.25	5.50	$C_{17}H_{26}O_5$
7	H	C_3H_7(i)	0.84	2.03	$C_{17}H_{26}O_5$
8	H	C_4H_8(n)	1.28	0.96	$C_{16}H_{28}O_5$
9	H	C_4H_8(i)	0.24	0.20	$C_{16}H_{28}O_5$
10	H	C_5H_{11}(n)	8.67	3.67	$C_{19}H_{30}O_5$
11	H	C_5H_{11}(i)	0.98	1.57	$C_{16}H_{30}O_5$
12	H	C_6H_{13}(n)	5.50	4.67	$C_{20}H_{32}O_5$
13	H	C_6H_{13}(i)	0.74	0.31	$C_{20}H_{32}O_5$
14	H	$(CH_2)_{13}CH_3$	0.001	0.001	$C_{27}H_{46}O_5$
15	H	$C_2H_4C_6H_5$	1.00	1.69	$C_{22}H_{28}O_5$
16	H	$C_3H_6C_6H_5$	4.45	6.11	$C_{23}H_{30}O_5$
17	H	$C_4H_8C_6H_5$	3.00	1.37	$C_{24}H_{32}O_5$
18	H	CH_2COOH	0.003	0.002	$C_{16}H_{22}O_7$
19	H	$CH_2CH{=}CH_2$	0.72	0.31	$C_{17}H_{24}O_5$
20	(*E*)-$CH_3CH{=}CHCH_2$	H	0.22	0.38	$C_{16}H_{26}O_5$
21	(*Z*)-$CH_3CH{=}CHCH_2$	H	0.07	0.09	$C_{16}H_{26}O_5$
22	C_2H_5		0.001	0.001	$C_{13}H_{26}O_4$
23	C_3H_7		0.001	0.001	$C_{14}H_{28}O_4$
24			0.02	0.02	$C_{11}H_{14}O_5$
25			0.96	0.24	ref 35

Table II. Relative Activities of 1-Deoxyartemisinin Analogs (IC_{50} of Analog/IC_{50} of Artemisinin = Relative Activity)



compd	R	R_1	relative activity W-2 clone	relative activity D-6 clone	anal. C, H
26	H	CH_3	0.001	0.001	
27	CH_3	H			
28	CH_3	CH_3			
29	H	H			
30	H	C_2H_5	0.001	0.001	$C_{16}H_{24}O_4$[a]
31	H	C_3H_7(n)	0.07	0.06	$C_{17}H_{26}O_4$[b]
32	H	C_4H_8(n)			
33	H	C_5H_{11}(n)			
34	H	C_6H_{13}(n)	0.02	0.07	$C_{20}H_{32}O_4$[c]
35	H	$CH(CH_3)_2$	0.07	0.02	$C_{17}H_{26}O_4$[b]
36	H	$CH_2CH(CH_3)_2$			
37	H	$(CH_2)_2CH(CH_3)_2$	0.14	0.13	$C_{16}H_{30}O_4$
38	H	$(CH_2)_3CH(CH_3)_2$			
39	H	$C_2H_4C_6H_5$			
40	H	$C_3H_6C_6H_5$	0.15	0.15	$C_{23}H_{30}O_4$
41	H	$C_4H_8C_6H_5$			
42	H	$CH_2CH{=}CH_2$			
71	H	$C_{14}H_{29}$(n)	0.05	0.05	$C_{28}H_{48}O_4$

[a] Exact mass. [b] Hydrate, $^1/_4H_2O$. [c] Hydrate, $^1/_2H_2O$.

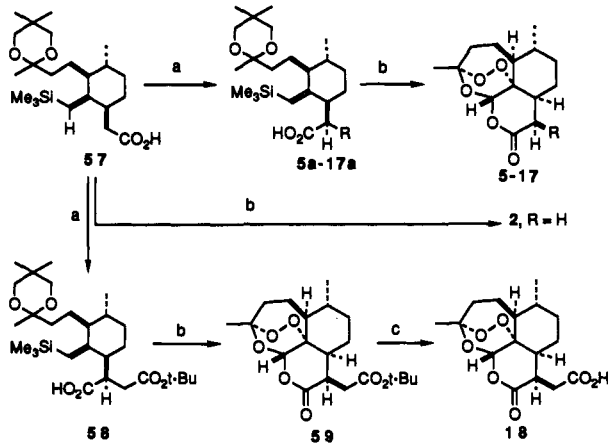
of 11 new analogs **43–56** (Chart I) which were compared to their *in vitro* antimalarial activities in order to test the validity of the model.

Chemistry

The analogs used in this study were prepared by one of four methods. The homologs **5–18** were derived by dianion alkylation of the total synthetic intermediate **57** as shown in Scheme I. Subsequent exposure of the resulting homologated acids **5a–17a** (**58**) to ozone followed by acid-catalyzed cyclization of the resulting dioxetanes provided the expected tetracyclic products.[18] As deduced previously, the dianion alkylation proceeded with complete diastereoselectivity to provide exclusively *erythro* acids as shown in the scheme. The C-9 to C-8a proton NMR coupling constants for the products **5–18** were consistent with β-configured side chains at C-9. For example, $J^{8a,9}$ for **7** is 4.7 Hz, while $J^{8a,9}$ for artemisinin (**1**) is 5.4 Hz and $J^{8a,9}$ for 9-epiartemisinin (**3**) is 1.2 Hz.

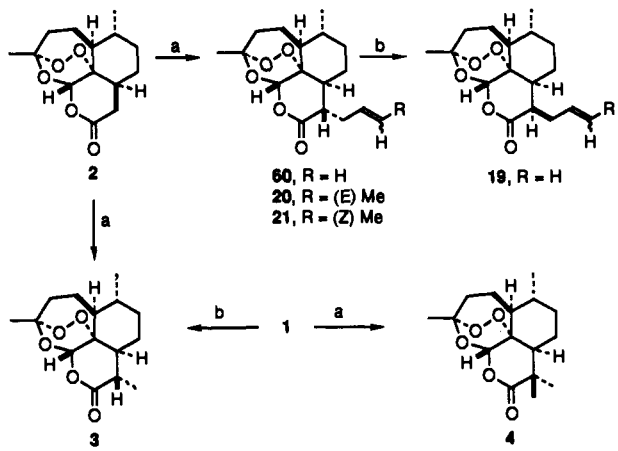
The synthesis of the allyl and crotyl analogs **19–21** was somewhat more problematic. While alkylation of the dianion derived from **57** with allylic halides (as in Scheme I) proceeded smoothly to provide the expected allylated acid(s), the subsequent ozonolysis was not chemoselective. Thus, an alternate route was employed wherein the enolate of the nor analog **2** was generated at low temperature and alkylated to provide α-allylated tetracycles (Scheme II). We hoped initially that the undesired axial α-epimer would readily epimerize to the equatorial β-epimer. Surprisingly, prolonged acid treatment of **60** did not result in epimerization (trifluoroacetic acid, $CHCl_3$). When the allyl analog **60** was treated with LDA at low temperature and quenched with acid, a new product was formed. Consistent assignment of α or β stereochemistry at C-9 could be made, based on NMR data and dihedral angles calculated by MM2.[39] Differences in the proton NMR data between artemisinin

Scheme I[a]



[a] Key: (a) 2 LDA, THF, 50 °C, then RX; (b) O_3/O_2, CH_2Cl_2, −78 °C; then SiO_2 followed by aqueous 3 M H_2SO_4, 23 °C; (c) trifluoroacetic acid, chloroform.

Scheme II[a]

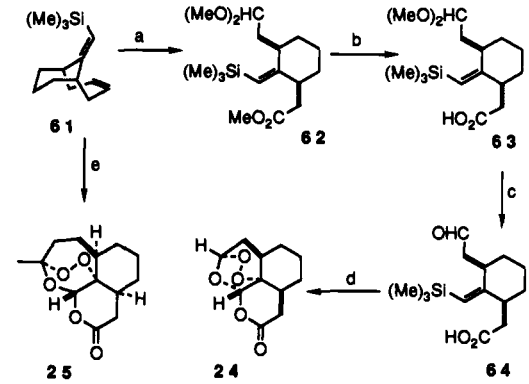


[a] Key: (a) LDA, −40 °C; RCH_2X; (b) LDA, −40 °C; then HOAc.

(1), 9-epiartemisinin (3), and desmethylartemisinin (2) provided useful information for assignments. In general, we have noted that the C-9β proton occurs between 2.2 and 2.4 ppm and the C-9α proton between 3.2 and 3.4 ppm. This effect is no doubt due to the presence of shielding/deshielding regions about the adjacent lactone carbonyl which places the C-9β H in a shielding region while the C-9α H is in the deshielding zone. NMR assignments for norartemisinin (2) are, for the C-9β H, δ 2.26 (dd, J = 1.5, 18.5 Hz) where J^{gem} = 18.5 Hz and $J^{9\beta,8a}$ = 1.5 Hz. The latter small coupling is consistent with the MM2 calculated H^{8a}–$H^{9\beta}$ dihedral angle of 73°. For the C-9α H occurring at δ 3.17 (dd, J 7.1, 18.5 Hz), $J^{9\alpha,8a}$ = 7.1 Hz, which is consistent with the calculated H^{8a}–$H^{9\alpha}$ dihedral angle of −42°. These values are also consistent with the 9α proton of artemisinin (1) (dq, $J^{8a,9\alpha}$ = 5.4 Hz), or the 9β proton of 9-epiartemisinin (3) (dq, $J^{8a,9\beta}$ 1.2). Similar behavior is seen for the α- and β-epimers of 9-allylartemisinin (60 and 19, respectively). The C-9β H for 60 is located at δ 2.20 (ddd, $J^{8a,9\beta}$ = 1.2 Hz), and shifts to δ 3.35 (ddd, $J^{8a,9\alpha}$ = 5.0 Hz) in the β-epimer 19. In addition, it was found that 9-epiartemisinin (3) could be prepared from artemisinin by generation of the enolate as above, or that the enolate could be intercepted with methyl iodide to provide the *gem*-dimethyl analog 4.

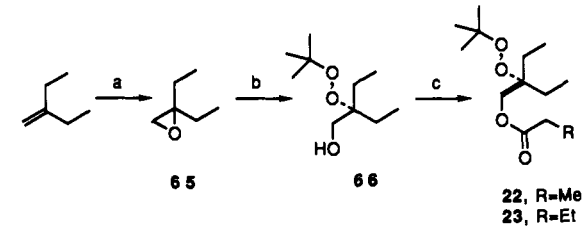
The synthesis of the ring-contracted analog 24 was attractive from the perspective that removal of one of the

Scheme III[a]



[a] Key: (a) O_3, MeOH; H^+; (b) KOH, MeOH; (c) aqueous oxalic acid, SiO_2, CH_2Cl_2; (d) O_3, CH_2Cl_2; then Amberlyst-15; (e) see ref 35.

Scheme IV[a]



[a] Key: (a) *m*-CPBA, CH_2Cl_2; (b) *t*-BuOOH, *p*-TsA, CH_2Cl_2; (c) $(RCO)_2O$, pyridine, DMAP, CH_2Cl_2.

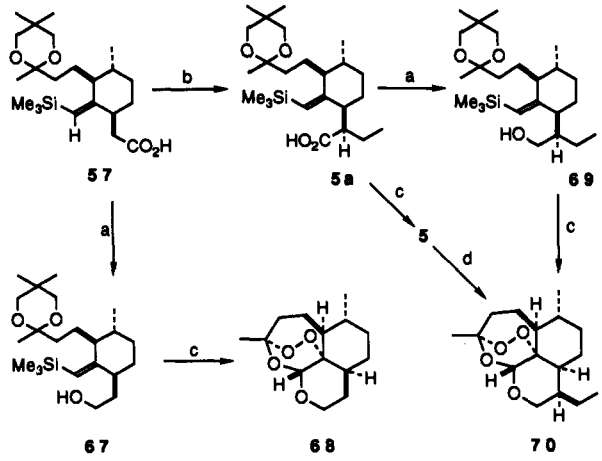
B-ring methylenes would result in a significant alteration of the C-1′, O-1, O-2, O-3 dihedral angle from 49° in artemisinin to −11° in the nor analog 24, while otherwise maintaining a rigid, topologically similar, tetracyclic framework. It was thus expected that SAR's of the 8a,9- and 4,5-seco analogs would be nicely complemented by 24. Modification of our previously employed route to construct 6,9-didesmethylartemisinin 25[35] led to the synthesis of 24 as shown in Scheme III.

Selective scissioning of the disubstituted olefin of 61 with ozone in methanol–dichloromethane gave, after treatment with tosic acid, the expected[40] mixed acetal–ester 62 in modest yield. Simple base hydrolysis afforded acetal–acid 63 which was then carefully deprotected under mild conditions employing oxalic acid impregnated silica gel.[35] Facile aldol or protodesilylation reactions were thus avoided, and the sensitive aldehyde–acid 64 was obtained in 96% yield. Subsequent exposure of 64 to ozone at low temperature, followed by warming and acid-catalyzed cyclization with Amberlyst-15, provided the tetracyclic peroxide 24 in 58% yield. In sharp contrast to artemisinin or the other thermally stable analogs reported in this paper, the peroxide 24 underwent decomposition after prolonged periods at ambient temperature.

The synthesis of the acyclic analogs 22 and 23 was readily accomplished via epoxide 65 as shown in Scheme IV. Treatment of 65 under anhydrous conditions with acid in the presence of *tert*-butyl hydroperoxide provided the vicinal peroxy alcohol 66. Simple esterification of this material with either propionic or butyric anhydride gave the acyclic artemisinin analogs 22 or 23, respectively.

The increases in potency ascribed to the 10-deoxo modification of artemisinin[41] could be readily investigated in the 9-alkyl series using the routes outlined above. Accordingly, analogs in the lactone series showing good activity such as desmethylartemisinin (2) and 9-ethylartemisinin (5) were targeted for the deoxo modification.

Scheme V[a]



[a] Key: (a) $LiAlH_4$, ether; (b) as in Scheme I; (c) O_3, CH_2Cl_2; SiO_2, H^+; (d) $NaBH_4$, BF_3, MeOH.

The corresponding 10-deoxo-9-desmethylartemisinin (**68**) and 10-deoxo-9-ethylartemisinin (**70**) were readily synthesized by the route outlined in Scheme V. Reduction of the intermediate **57** with LAH afforded the alcohol **67** in reasonable yield. Subsequent ozonolysis followed by acid-catalyzed ring closure provided the desmethyl-10-deoxo derivative **68**. Alternatively, the ethyl acid **5a** could be reduced to **69** and cyclized as before to provide **70**. We have also found that the lactone derivatives can be directly reduced to the deoxo series using previously developed methodology.[41] It should be noted that a series of 10-deoxo-9-alkyl derivatives have been synthesized and that bioassay is in progress.

Biological Activity

The analogs (**1–25, 30–31, 34–5, 37, 40**) 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 a modification of the procedure of Desjardins[42,43] involving uptake of tritiated hypoxanthine. Two *P. falciparum* malaria parasite clones, designated as Indochina (W-2) and Sierra Leone (D-6), were utilized in susceptibility testing. The W-2 clone is chloroquine-resistant and mefloquine-sensitive while the D-6 clone is choroquine-sensitive but mefloquine-resistant. The relative potency values for these analogs were derived from their IC_{50} values divided by the IC_{50} for artemisinin **1** (Table 1). For inactive compounds, the relative potency values were set at 0.001 in the QSAR analysis. Four racemic compounds were used in this study, **23**, **23**, **24**, and **25**. Three of these four were virtually inactive, thus chirality was not an issue. For analog **25**, the relative activity was doubled on the assumption that only the (+) enantiomer of artemisinin is biologically active. Very similar CoMFA results were obtained using antimalarial activities for either the D-6 or W-2 clone. In this paper however, only the antimalarial potencies for the D-6 clone have been used to generate the CoMFA.

Structure–Activity Relationships

Comparative Molecular Field Analysis. CoMFA[37] is a module of the Sybyl 5.5 molecular modeling program.[44] Analogous to that described elsewhere,[37] selected analogs were aligned and sampled with various probes over enveloping space at regular 2-Å intervals to generate three-dimensional steric and electrostatic (Gasteiger charge[45]) fields. Partial least-squares (PLS) analysis[38] correlated the resultant fields with antimalarial activity. The correlation was described in traditional QSAR terms and its quality checked accordingly.[46]

Table III. CoMFA of Artemisinin Analogs

no. of compounds	cross-validated r^2	cross-validated optimum component	conventional r^2	conventional S	conventional F
26 (1–26)	0.301	4			
24[a]	0.466	1	0.657	0.742	45.023
23[b]	0.417	2	0.804	0.548	40.912
22[c]	0.793	5	0.985	0.106	208.12
42[d]	0.857	5	0.975	0.261	276.60

[a] Omit 14 and 18 from 1–26. [b] Omit 14, 18, and 4 from 1–26. [c] Omit 14, 18, 4, and 26 from 1–26. [d] 1-Deoxy analogs **27–42** added to **1–26**.

The structures of the analogs for QSAR are shown in Table I. Most analogs had a rigid tetracyclic nucleus and were represented by a single calculated conformer of the 9-alkyl substituent found through systematic conformational search. Likewise, the low-energy conformers of acyclic analogs **22** and **23** were obtained by systematic conformational searching and minimization with the standard Tripos force field.[47]

In this series of molecules, the oxygen atoms (O-1 and O-2) of the peroxide linkage and the lactone ring-oxygen atom (O-11) were selected as atoms pairs between two molecules for alignment in the least-fit protocol ("Field Fit").[37]

We were interested in finding a QSAR model to aid in future target selection and thus needed to demonstrate the quality of predictions made by such a model. In this context, we included and examined with our model: seco analogs of artemisinin **43** and **52–55** (Chart I) from our laboratory,[20] three racemic seco analogs **44–46** prepared by Posner,[32] unusual 9-bromo-10-aminoartemisinin analogs **47–51** reported by Lin,[14] and 10-desoxoartemisinin (**56**) made by McChesney,[41] and these results are discussed herein.

Results and Discussion

The first CoMFA of 26 compounds (**1–26**, see Figure 1) gave a cross-validated r^2 (r^2_{cross}) value of 0.301 (Table III). Graphical analysis showed that four compounds, **4**, **14**, **18**, and **26**, were at least partially responsible for the low r^2_{cross} value. Omission of the tetradecyl analog **14** and the carboxylic acid **18** led to $r^2_{cross} = 0.466$, and residual values for **4** and **26** were −1.66 and −1.61, respectively. Recalculation without **14**, **18**, and **4** gave an $r^2_{cross} = 0.417$ and a residual value for 1-deoxyartemisinin **26** at a high value of −1.53. The next CoMFA without the above four compounds resulted in an r^2_{cross} value = 0.793 (optimum component 5), the conventional correlation coefficient $r^2 = 0.985$, $F = 208$, and a standard error estimate of 0.106. These values indicated a good conventional statistical correlation, and we also found that the resultant CoMFA model had fair predictive ability. However, examination of the steric and electrostatic fields revealed a weak correlation with the peroxy moiety, which was disturbing in light of its known requirement for activity. This merely reflected the exclusion of non-peroxides, such as 1-deoxyartemisinin (**26**) and others.

It seemed that if a number of the corresponding 1-deoxy congeners of the 9-alkyl analogs were included in the analysis, a better correlation with the peroxy bridge would result. Although 1-deoxy-9-alkylartemisinin analogs could

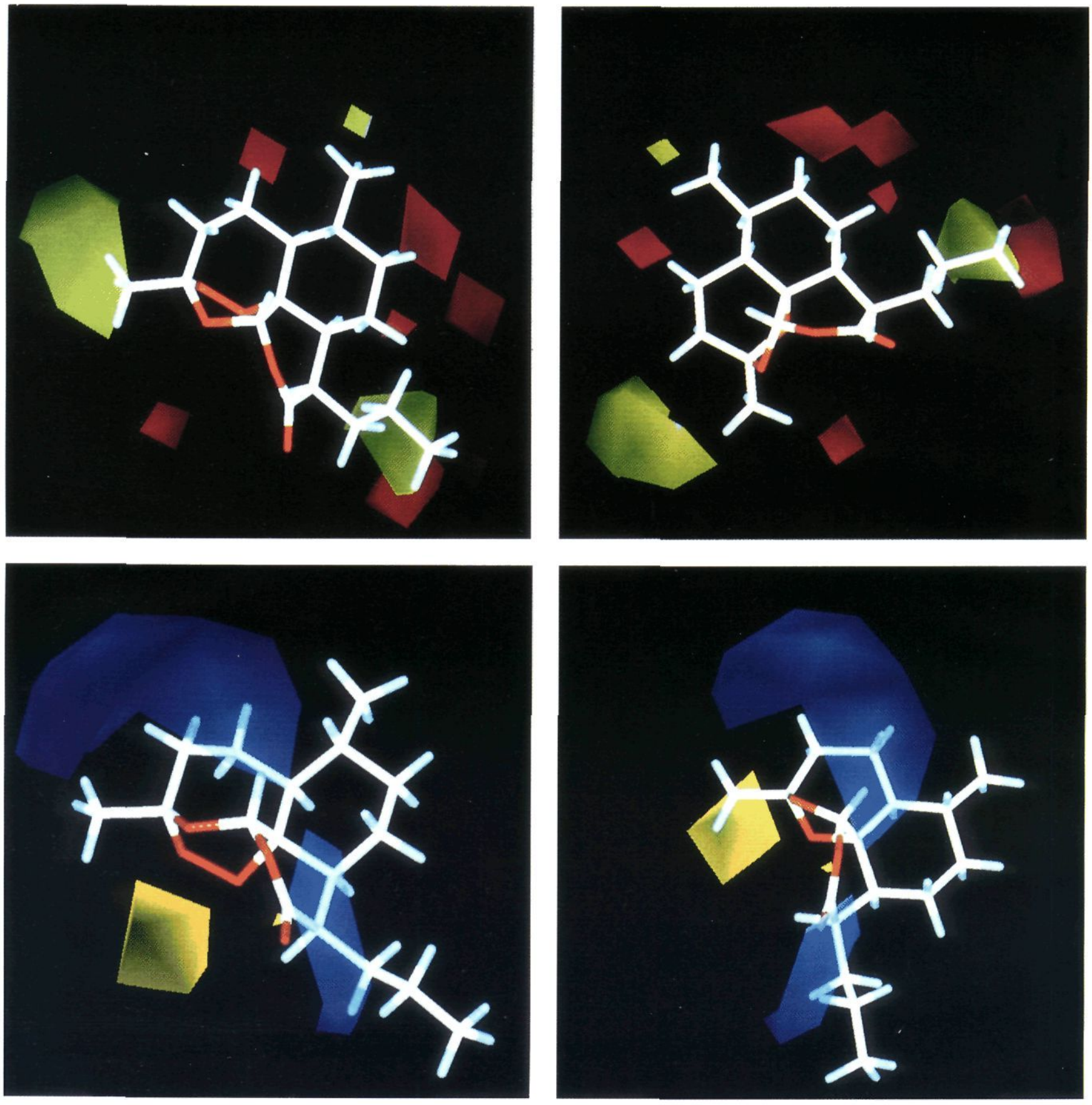


Figure 1. Steric and electrostatic contour maps of the *in vitro* artemisinin CoMFA model (Table IV, r^2 cross = 0.857): (a) steric contour map, upper left, showing the active 9-propyl homologue of artemisinin, **6**; (b) steric contour map, upper right, showing the inactive 1-deoxy-9-propyl homologue of artemisinin, **31**; (c) electrostatic contour map, lower left, showing the active 9-propyl homologue of artemisinin, **6**; (d) electrostatic contour map, lower right, showing the inactive 1-deoxy-9-propyl homologue of artemisinin, **31**.

be assumed to be inactive antimalarials on the basis of the lack of activity of **26**, we measured the activities of a number of 1-deoxy-9-alkylartemisinin analogs (Table II) to be certain. For example, 1-deoxy-9-ethylartemisinin (**30**) was completely inactive, and the corresponding peroxide, 9-ethylartemisinin (**5**), was about 12 times more active than artemisinin (**1**).

The addition of just a few 1-deoxy analogs led to a better electrostatic field correlation to the peroxy moiety, but the best results were obtained when 16 inactive 1-deoxy analogs (**26–42**, Table II) were added to generate the CoMFA. In this case, it was not necessary to omit any of the analogs, and the resulting final CoMFA with 42 compounds gave an r^2_{cross} = 0.857 (optimum component 5), conventional r^2 = 0.975, F = 276, and the standard error of estimate of 0.261.

A comparison of the final CoMFA (42 analogs) with the earlier run that omitted four of the 21 analogs (17 analogs) revealed similar steric contours. However, the final model correctly correlated with electrostatic contours about the peroxide bridge and had significantly better predictive ability.

CoMFA Coefficient Contour Maps. The QSAR produced by CoMFA, with its hundreds or thousands of terms, is usually represented as a three-dimensional "coefficient contour" map. Figure 1, part a or c, and Figure 1 part b or d, show stereo- and electrostatic color views of such maps, respectively. To aid in visualization, one of two molecules, either the potent 9-propyl analog of artemisinin (**6**) or the corresponding inactive 1-deoxy-9-propyl analog of artemisinin (**31**) are displayed in the maps (Figure 1a–d). In general, the colored polyhedra in each

Table IV. Comparison of CoMFA Predicted and Actual *in Vitro* Relative Antimalarial Potencies (D-Clone) of Artemisinin Analogs

	relative activity			relative activity	
compd	predicted	actual	compd	predicted	actual
43	0.25	0.37	**50**	0.17	0.02
44	0.34	0.13	**51**	0.01	0.01
45	0.02	0.03	**52**	0.01	0.01
46	0.10	0.11	**53**	0.12	0.40
47	0.78	0.62	**54**	0.03	0.10
48	0.81	3.50	**55**	0.006	0.001
49	0.14	0.16	**56**	1.05	4.02

map surround all lattice points where the QSAR strongly associates changes in the analogs field values with changes in antimalarial potency.

Color is also used to code the direction and magnitude of those differential interactions. In these steric maps (Figure 1a,c), green polyhedra surround regions where more bulk is "good" for increasing potency while red polyhedra surround regions where less bulk is "good". In Figure 1a, the green polyhedra surround the region in the vicinity of the C-3 methyl group and suggest that increases in steric bulk at this position would be associated with enhanced antimalarial potency. In the region surrounding the C-9 methyl group of artemisinin, there are green and red polyhedra which are consistent with the dependence on activity of chain length and branching. The greatest enhancements in potency are seen with the C-9 ethyl and propyl analogs (Table I), and potency is only poor to average for the C-9 branched alkyl analogs. It should be noted that for these side chains, minimization was conducted on the fully staggered arrangements (lowest E_{rel}) of the side chains and compared to other conformers. The best r^2_{cross} values were obtained for the fully staggered conformers.

In the electrostatic maps shown in Figure 1b,d, blue and yellow contours show regions of desirable positive and negative electrostatic interaction, respectively. In Figure 1b, the yellow polyhedra surround the region of the peroxide bridge with contact points directed toward specific lone electron pairs on each oxygen atom. Analogs which cannot simultaneously fill steric regions and place the peroxide grouping within this electostatic contour would not be predicted to have good antimalarial potency. For example, the weakly active seco analog **53** has been shown to exist primarily in an all chair conformation in solution by a combination of crystallography, NMR, and MM2 calculations.[20] Overlap of **53** with artemisinin, using the cyclohexyl ring as a template, demonstrates that one of the two peroxide atoms of **53** are misplaced relative to the parent molecule. It is clear that a peroxide grouping is required for activity in this class of antimalarials but furthermore, that analog potency is highly dependent on the relative orientation of the peroxy moiety within the hydrocarbon framework.

The most significant evidence for the utility of this CoMFA model is its predictive ability, even for apparently different structural types. Relative antimalarial activities were predicted for compounds **43–56** (Chart I). Compounds chosen for comparison were taken from literature sources as well as from a pool of derivatives from our own lab whose activities were not published before. As seen in Table IV, the differences are small between the predicted *in vitro* antimalarial potencies and the values obtained by *in vitro* bioassay for a variety of artemisinin analogs. For example, the antimalarial activities of the 8a,9-secoartemisinin analogs **43–46**, prepared by Posner[32] and us, were found to correlate well with activities predicted by the CoMFA model.

This finding is surprising in that these structure types are significantly different from the structures used to build the CoMFA model. The QSAR coefficients produced by the relative contributions of steric and electrostatic terms are 0.657 and 0.343, suggesting that steric parameters in the region of the lactone ring of artemisinin analogs are more important than electrostatic considerations. This finding also seems consistent with the observation of enhanced potency in 10-deoxoartemisinin (**56**). However, the predicted potency of **56** using the current model was 1.05 vs the reported relative activity of approximately 4.

To better assess the contribution to activity of the lactone carbonyl in our CoMFA model, compound **56** as well as incoming test results for other 10-deoxo-9-alkyl analogs of artemisinin will be added to the model which is constantly being refined and used to predict the activities of new members in this series of analogs. It may be also be suggested that differences in activity between lactone-containing artemisinin analogs and the 10-deoxo-modified analogs is due to altered phamracokinetics. If this is the case, then a separate CoMFA model will need to be derived.

The syntheses and testing of analogs predicted to have high potency are underway and will be reported in forthcoming papers.

Experimental Section

All solvents were purchased as HPLC grade, and where appropriate, solvents and reagents were distilled from CaH_2 prior to storage over 4-Å molecular sieves. Solvent and reagent transfers were accomplished via dried syringe or cannula, and all reactions were routinely conducted under an inert atmosphere, unless otherwise indicated. Flash chromatography was accomplished using silica gel (Kieselgel 60, 230–400 mesh), preparative thin-layer chromatography utilized 1-, 1.5-, or 2-mm-thick Analtech Uniplates with F-256, and 250-μm silica gel thin-layer chromatography plates were also purchased from Analtech. Unless otherwise noted, NMR analyses were conducted in $CDCl_3$ on a Varian XL-400 or VXR-300 and were referenced to chloroform at δ 7.27. IR spectra were recorded on a Perkin-Elmer 1310 or 1610. UV spectra were recorded on a Perkin-Elmer 552. MS were obtained with a Reibermag R-10-10-C (CIMS) or LKB 9000 (EIMS). Elemental analyses were within ±0.4% as determined by Desert Analytics, Tucson, AZ.

Preparation of 9-Alkylartemisinin Analogs. Method A. Dianion Alkylation of Cyclohexylacetic Acid 57. To a solution of 2.2 equiv of lithium diisopropylamide (~0.5 M in THF) at 0 °C was added a solution of acid **57** (~0.5 M in THF). The resultant solution was allowed to warm to ambient temperature, heated at 50 °C for 2 h, allowed to cool to ambient temperature, and then cooled to −78 °C and treated with alkylating agent (1.2 equiv). After 1–6 h (monitor by TLC) at ambient temperature, the solution was stirred with a mixture containing about 5 equiv of 10% aqueous HCl and excess saturated aqueous NH_4Cl and extracted with $CHCl_3$ (×3). The combined organic layer was washed with saturated aqueous NH_4Cl, dried over Na_2SO_4, and evaporated to afford crude acids, which were routinely purified via flash column chromatography with silica gel and EtOAc/hexane, or EtOAc(1% HOAc)/hexane.

Method B. Alkylation of 9-Desmethylartimisinin. Generation of the α-Epimers. To a solution of 1.25 equiv of lithium diisopropylamide (~0.5 M in THF) at −78 °C was added dropwise, over a 10-min period, a solution of (+)-9-desmethylartemisinin[9] (~0.5 M in THF). After 1 h at −40 °C, alkylating agent (1.25 equiv) was added. The resultant mixture was kept at −40 °C for 90 min and then allowed to warm to −25 °C. After 1 h, the mixture was poured into a mixture of saturated aqueous NH_4Cl containing

5 equiv of aqueous 5 N HCl and was then extracted with Et_2O (3×). The combined ether layer was washed with saturated aqueous NH_4Cl (2×), dried over Na_2SO_4, and evaporated to provide the crude product which was routinely purified via flash column chromatography with silica gel and EtOAc/hex to provide the α-substituted analogs.

Isomerization to β-Epimers. To a solution of 2.5 equiv of LDA in THF (~0.25 M) at −25 °C to −30 °C was added a solution of the α-epimer (1 equiv in THF, ~0.25 M). After 1h, the vessel was packed in solid CO_2 and stored for 16 h and was then rewarmed to −30 °C and treated with glacial acetic acid (10 equiv). The mixture was then poured into saturated aqueous NH_4Cl containing aqueous 5 N HCl (10 equiv) and extracted with ether (3×). The combined ether layer was washed with saturated NH_4Cl (2×), dried over Na_2SO_4, and evaporated to provide the crude product which was routinely purified via flash column chromatography with silica gel and EtOAc/hex to provide the β-substituted analogs.

Method C. Ozonolysis and Cyclization of Acids To Produce Artemisinin Analogs. A solution of vinylsilane–carboxylic acid **5a–17a** in CH_2Cl_2 (100 mL/mmol) was cooled to −78 °C and treated with a stream of ozone (7 psi, 0.4 L/min, 70 V) until a faint blue color was seen. A solution of BHT (30 mg/mmol) in a small volume of CH_2Cl_2 was added, followed by the addition of 70–230-mesh silica gel 60 (10 g/mmol) at −78 °C. The resulting well-stirred mixture was treated with 3 M H_2SO_4 (1 mL/mmol), brought to ambient temperature, and stirred for up to 1 week. The mixture was treated with solid $NaHCO_3$ and stirred for 20 min at room temperature. The product was isolated by filtration, rinsing with 20% EtOAc/hexane. The solvent was removed *in vacuo*, leaving crude product which was purified by flash column chromatography with silica gel and EtOAc/hexane. The resulting white solids were purified by crystallization from hexane, or EtOAc/hexane, and then placed under high vacuum overnight to provide analytically pure materials which could be stored indefinitely at −20 °C under Ar in sealed amber vials.

(1″*S*,1‴*S*,3″*S*,6″*R*)-(2″*E*)-2-[2′-[3″-(1‴-Carboxypropyl)-6″-methyl-2″-[(trimethylsilyl)methylene]cyclohexyl]ethyl]-2,5,5-trimethyl-1,3-dioxane (5a): prepared according to method A from the acid **57** (840 mg, 2.12 mmol) and ethyl iodide (424 μL, 5.3 mmol). The crude product was applied to a column of 25 g of silica gel (230–400 mesh), eluting with (1% HOAc/EtOAc)/hexane (20/80), to give the product **5a** (677 mg, 75%) as a colorless gum. ^{1}H NMR: δ 0.09 (s, 9H), 0.82–0.96 (m, 12H), 1.00 (s, 3H), 1.50–1.90 (bm, 1H), 1.22–1.95 (m, 10H), 2.05–2.15 (m, 1H), 2.32–2.41 (m, 1H), 2.64 (ddd, 1H, *J* = 3.1, 11.7, 11.7 Hz), 3.39 (ddd, 2H, *J* = 1.5, 11.2, 11.2 Hz), 3.53 (d, 2H, *J* = 11.7 Hz), 5.29 (s, 1H). EIMS: *m/z* (rel int) 424 (5), 194 (28), 180 (26), 161 (25), 160 (25), 129 (100).

(1″*S*,1‴*S*,3″*S*,6″*R*)-(2″*E*)-2-[2′-[3″-(1‴-Carboxybutyl)-6″-methyl-2″-[(trimethylsilyl)methylene]cyclohexyl]ethyl]-2,5,5-trimethyl-1,3-dioxane (6a): prepared according to method A from the acid **57** (550 mg, 1.38 mmol) and propyl iodide (338 μL, 3.46 mmol). The crude product was applied to a column of 25 g of silica gel 60 (230–400 mesh), eluting with (1% HOAc/EtOAc)/hexane (20/80), to give the product **6a** (483 mg, 80%) as a colorless gum. ^{1}H NMR: δ 0.11 (s, 9H), 0.88 (t, 3H, *J* = 7.1 Hz), 0.89 (s, 3H), 0.92 (d, 3H, *J* = 6.9 Hz), 1.00 (s, 3H), 1.34 (s, 3H), 2.10 (br d, 1H, *J* = 12 Hz), 2.39 (br dd, 1H, *J* = 4, 11.5 Hz), 2.71 (ddd, 1H, *J* = 3.9, 11.2, 11.2 Hz), 3.42 (dt, 2H, *J* = 1, 12 Hz), 3.54 (d, 2H, *J* = 12 Hz), 5.30 (s, 1H). IR (film): 3600–2500, 1737, 1708, 1599, 1451, 1395, 1247, 1210, 1127, 1084, 853 cm^{-1}. DCIMS-NH_3: *m/z* 439 (M + H), 352, 335, 293, 263.

(1″*S*,1‴*S*,3″*S*,6″*R*)-(2″*E*)-2-[2′-[3″-(1‴-Carboxy-2‴-methylpropyl)-6″-methyl-2″-[(trimethylsilyl)methylene]-cyclohexyl]ethyl]-2,5,5-trimethyl-1,3-dioxane (7a): prepared according to method A from acid **57** (579 mg or 1.46 mmol) and isopropyl iodide (0.5 mL, 5 mmol). The acid **7a** was obtained as a white foam, 346 mg or 54% yield. ^{1}H NMR: δ 0.12 (s, 9H), 0.89 (s, 3H), 0.95 (t, 6H, *J* = 6.8 Hz), 1.00 (d, 3H, *J* = 7.1 Hz), 1.03 (s, 3H), 1.38 (s, 3H), 1.49 (m, 1H), 1.60 (m, 1H), 1.68 (m, 1H), 1.88 (m, 6H), 2.09 (br dd, 1H, *J* = 2.7, 10.6 Hz), 2.65 (br d, 1H, *J* = 12.0 Hz), 2.79 (br dd, 1H, *J* = 2.7, 10.6 Hz), 3.43 (m, 2H), 3.56 (d, 2H, *J* = 11.0 Hz), 5.41 (s, 1H). IR (Nujol): 3500–2500, 1700, 1600, 1460, 1380, 1250, 1220, 1100, 850, 750 cm^{-1}. DCIMS-NH_3: *m/z* 511 (M + TMS), 456 (M + NH_4), 439 (M + H), 370, 352, 335.

(1″*S*,1‴*S*,3″*S*,6″*R*)-(2″*E*)-2-[2′-[3″-1‴-Carboxypentyl)-6″-methyl-2″-[(trimethylsilyl)methylene]cyclohexyl]ethyl]-2,5,5-trimethyl-1,3-dioxane (8a): prepared according to method A from acid **57** (0.6 g or 1.51 mmol) and butyl iodide (0.8 mL). The acid **8a** was obtained as a clear glass, 515 mg or 75% yield. ^{1}H-NMR: δ 0.13 (s, 9H), 0.88 (t, 3H, *J* = 7.2 Hz), 0.89 (s, 3H), 0.94 (d, 3H, *J* = 7.1 Hz), 1.03 (s, 3H), 1.36 (s, 3H), 2.11 (br dd, 1H, *J* = 1.9, 10.5 Hz), 2.40 (br dd, 1H, *J* = 5.0, 11 .9 Hz), 2.72 (br t, 1H, *J* = 11.2 Hz), 3.44 (dt, 2H, *J* = 1.4, 11.5 Hz), 3.55 (dd, 2H, *J* = 1.4, 11.5 Hz), 5.32 (s, 1H). IR (CH_2Cl_2): 3600–2500, 1734, 1703, 1600, 1456, 1395, 1374, 1246, 1212, 1164, 1091, 845 cm^{-1}. EIMS: *m/z* 452 (M$^+$), 437 (M − Me), 348, 338, 296.

(1″*S*,1‴*S*,3″*S*,6″*R*)-(2″*E*)-2-[2′-[3″-(1‴-Carboxy-3‴-methylbutyl)-6″-methyl-2″-[(trimethylsilyl)methylene]cyclohexyl]ethyl]-2,5,5-trimethyl-1,3-dioxane (9a): prepared according to method A from acid **57** (1100 mg or 2.79 mmol) and isobutyl bromide (0.78 mL, 6.97 mmol). The acid **9a** was obtained as a pale yellow glass, 660 mg or 52% yield. ^{1}H NMR: δ 0.12 (s, 9H), 0.89 (d, 3H, *J* = 6.5 Hz), 0.90 (d, 3H, *J* = 6.5 Hz), 0.91 (s, 3H), 0.94 (d, 3H, *J* = 7.0 Hz), 1.00 (s, 3H), 1.18 (br dt, 1H, *J* = 3.3, 11.0 Hz), 1.29 (m, 2H), 1.34 (s, 3H), 1.62 (dq, 1H, *J* = 3.5, 12.5 Hz), 1.68 (dq, 1H, *J* = 3.3, 12.3 Hz), 1.8–2.0 (m, 4H), 2.11 (br d, 1H, *J* = 10.2 Hz), 2.36 (br dd, 1H, *J* = 4.4, 10.2 Hz), 2.82 (ddd, 1H, *J* = 3.1, 11.7, 11.7 Hz), 3.30 (dd, 1H, *J* = 1.1, 11.7 Hz), 3.43 (dd, 1H, *J* = 1.1, 11.7 Hz), 3.54 (br d, 2H, *J* = 11.7 Hz), 5.30 (s, 1H). IR (Nujol): 3500–2500, 1704, 1601, 1467, 1248, 1094, 849 cm^{-1}. EIMS: *m/z* 452 (M$^+$), 437 (M − Me), 389, 367, 361, 351, 348, 338.

(1″*S*,1‴*S*,3″*S*,6″*R*)-(2″*E*)-2-[2′-[3″-(1‴-Carboxyhexyl)-6″-methyl-2″-[(trimethylsilyl)methylene]cyclohexyl]ethyl]-2,5,5-trimethyl-1,3-dioxane (10a): prepared according to method A from acid **57** (0.6 g or 1.51 mmol) and pentyl iodide (0.8 mL). The acid **10a** was obtained as a clear glass, 491 mg or 70% yield. ^{1}H NMR: δ 0.12 (s, 9H), 0.86 (t, 3H, *J* = 7.2 Hz), 0.88 (s, 3H), 0.94 (d, 3H, *J* = 7.1 Hz), 1.03 (s, 3H), 1.35 (s, 3H), 1.84 (m, 1H), 1.92 (m, 1H), 2.11 (br dd, 1H), 2.40 (br dd, 1H, *J* = 3.9, 11.9 Hz), 2.72 (br t, 1H, *J* = 11 Hz), 3.42 (dt, 2H, *J* = 1.4, 11.5 Hz), 3.57 (dd, 2H, *J* = 1.4, 11.5 Hz), 5.32 (s, 1H). IR (CH_2Cl_2): 3600–2500, 1734, 1703, 1600, 1455, 1374, 1247, 1213, 1092, 848 cm^{-1}. EIMS: *m/z* 466 (M$^+$), 451 (M − Me), 425, 381, 362, 338.

(1″*S*,1‴*S*,3″*S*,6″*R*)-(2″*E*)-2-[2′-[3″-(1‴-Carboxy-4‴-methylpentyl)-6″-methyl-2″-[(trimethylsilyl)methylene]cyclohexyl]ethyl]-2,5,5-trimethyl-1,3-dioxane (11a): prepared according to method A from acid **57** (0.55 g or 1.39 mmol) and isoamyl bromide (0.4 mL). The acid **11a** was obtained as a clear glass, 578 mg or 89% yield. ^{1}H NMR: δ 0.12 (s, 9H), 0.85 (dd, 6H, *J* = 2.8, 6.6 Hz), 0.89 (s, 3H), 0.94 (d, 3H, *J* = 7.0 Hz), 1.03 (s, 3H), 1.05–1.30 (m, 5H), 1.35 (s, 3H), 1.38–2.00 (m, 9H), 2.12 (br dd, 1H, *J* = 2.5, 10.5 Hz), 2.41 (br dd, 1H, *J* = 4.0, 11.7 Hz), 2.67 (ddd, 1H, *J* = 3.0, 11.7, 11.7 Hz), 3.43 (br dt, 2H, *J* = 1.5, 9.7 Hz), 3.55 (br d, 2H, *J* = 11.5 Hz), 5.33 (s, 1H). IR (Nujol): 3500–2400, 1700, 1600, 1460, 1380, 1270, 1250, 1220, 1130, 1100, 850, 750 cm^{-1}. DCIMS-NH_3: *m/z* 539 (M + TMS), 467 (M + H), 380, 363, 291.

(1″*S*,1‴*S*,3″*S*,6″*R*)-(2″*E*)-2-[2′-[3″-(1‴-Carboxyheptyl)-6″-methyl-2″-[(trimethylsilyl)methylene]cyclohexyl]ethyl]-2,5,5-trimethyl-1,3-dioxane (12a): prepared according to method A from acid **57** (0.57 g or 1.44 mmol) and hexyl bromide (0.5 mL). The acid **12a** was obtained as a clear glass, 568 mg or 82% yield. ^{1}H NMR: δ 0.12 (s, 9H), 0.87 (t, 3H, *J* = 7.1 Hz), 0.88 (s, 3H), 0.94 (d, 3H, *J* = 7.1 Hz), 1.03 (s, 3H), 1.10–1.30 (m, 10H), 1.35 (s, 3H), 1.38–1.50 (m, 3H), 1.56 (br dt, 1H, *J* = 4.2, 12.8 Hz), 1.68 (dq, 1H, *J* = 3.5, 12.0 Hz), 1.84 (m, 1H), 1.92 (m, 1H), 2.11 (br dd, 1H, *J* = 2.5, 10.8 Hz), 2.40 (br dd, 1H, *J* = 3.8, 11.9 Hz), 2.72 (br ddd, 1H, *J* = 3.0, 11.5, 11.5 Hz), 3.43 (dt, 2H, *J* = 1.4, 11.5 Hz), 3.56 (dd, 2H, *J* = 1.4, 11 .5 Hz), 5.32 (s, 1H). IR (Nujol): 3600–2500, 1700, 1600, 1450, 1380, 1250, 1220, 1130, 1100, 850 cm^{-1}. DCIMS-NH_3: *m/z* 498 (M + NH_4), 481 (M + H), 394, 377, 305.

(1″*S*,1‴*S*,3″*S*,6″*R*)-(2″*E*)-2-[2′-[3″-(1‴-Carboxy-5‴-methylhexyl)-6″-methyl-2″-[(trimethylsilyl)methylene]cyclohexyl]ethyl]-2,5,5-trimethyl-1,3-dioxane (13a): prepared according to method A from acid **57** (0.49 g or 1.23 mmol) and 4-methylpentyl bromide (0.7 g). The acid **13a** was obtained as a clear glass, 429 mg or 52% yield. ^{1}H NMR: δ 0.12 (s, 9H), 0.85 (dd, 6H, *J* = 0.7, 6.4 Hz), 0.87 (s, 3H), 0.94 (d, 3H, *J* = 6.0 Hz),

1.04 (s, 3H), 1.05–1.30 (m, 6H), 1.35 (s, 3H), 1.37–1.62 (m, 14H), 1.69 (dq, J = 4.2, 11.3 Hz, 1H), 1.83 (dd, J = 3.6, 13.0 Hz, 1H), 1.9 (m, 5H), 2.11 (br dd, 1H, J = 2.0, 10.2 Hz), 2.40 (br dd, 1H, J = 3.8, 11.2 Hz), 2.74 (ddd, 1H, J = 3.1, 11.2, 11.2 Hz), 3.41 (dd, 1H, J = 1.6, 11.4 Hz), 3.43 (dd, J = 1.6, 11.4 Hz, 1H), 3.55 (d, 1H, J = 11.4 Hz), 3.56 (d, J = 11.4 Hz, 1H), 5.31 (s, 1H). IR (Nujol): 3500–2400, 1704, 1600, 1248, 848, 787 cm^{-1}. EIMS: m/z 480 (M^+), 465 (M – Me), 394, 375, 360, 337, 323, 305.

(1″*S*,1‴*S*,3″*S*,6″*R*)-(2″*E*)-2-[2′-[3″-(1‴-Carboxypentadecyl)-6″-methyl-2″-[(trimethylsilyl)methylene]cyclohexyl]ethyl]-2,5,5-trimethyl-1,3-dioxane (14a): prepared according to method A from acid **57** (0.5 g or 1.26 mmol) and tetradecyl bromide (0.90 mL, 3 mmol). The acid **14a** was obtained as a white foam, 491 mg or 66% yield. ^{1}H NMR: δ 0.12 (s, 9H), 0.88 (s, 3H), 0.88 (overlapped t, 3H), 0.94 (d, 3H, J = 7.1 Hz), 1.03 (s, 3H), 1.10–1.33 (m, 23H), 1.35 (s, 3H), 1.38–1.50 (m, 3H), 1.56 (br ddd, 1H, J = 3.8, 12.9, 12.9 Hz), 1.69 (dq, 1H, J = 3.5, 11.4 Hz), 1.80–2.00 (m, 3H), 2.11 (br dd, 1H, J = 2.5, 10.5 Hz), 2.40 (br dd, 1H, J = 4.3, 11.5 Hz), 2.71 (br t, 1H, J = 11.5 Hz), 3.43 (dt, 2H, J = 1.2, 11.5 Hz), 3.56 (dd, 2H, J = 1.2, 11.5 Hz), 5.31 (s, 1H). IR (Nujol): 3500–2500, 1700, 1600, 1450, 1380, 1250, 1130, 1100, 850 cm^{-1}. DCIMS-NH_3: m/z 610 (M + NH_4), 593 (M + H), 524, 506, 489, 417.

(1″*S*,1‴*S*,3″*S*,6″*R*)-(2″*E*)-2-[2′-[3″-(1‴-Carboxy-3‴-phenylpropyl)-6″-methyl-2″-[(trimethylsilyl)methylene]cyclohexyl]ethyl]-2,5,5-trimethyl-1,3-dioxane (15a): prepared according to method A from acid **57** (0.60 g or 1.52 mmol) and 1-bromo-2-phenylethane (0.45 mL). The acid **15a** was obtained as a foam, 619 mg or 81% yield. ^{1}H NMR: δ 0.10 (s, 9H), 0.87 (s, 3H), 0.95 (d, 3H, J = 7.1 Hz), 1.04 (s, 3H), 1.18 (br d, J = 9.7 Hz), 1.34 (s, 3H), 1.40–2.00 (m, 12H), 2.08 (br dd, 1H, J = 2.7, 10.2 Hz), 2.46 (br dd, 1H, J = 4.5, 12.1 Hz), 2.5–2.7 (m, 2H), 2.84 (ddd, 1H, J = 3.3, 11.3, 11.3 Hz), 3.41 (dd, 1H, J = 1.7, 11.3 Hz), 3.44 (dd, 1H, J = 1.7, 11.3 Hz), 3.58 (dd, J = 2.2, 11.3 Hz, 2H), 5.33 (s, 1H), 7.20–7.40 (m, 5H). IR (Nujol): 3600–2400, 1700, 1600, 1450, 1380, 1250, 1220, 1130, 1100, 850 750, 710 cm^{-1}. EIMS: m/z 500 (M^+), 485 (M – Me), 456, 415, 396, 365, 356, 344.

(1″*S*,1‴*S*,3″*S*,6″*R*)-(2″*E*)-2-[2′-[3″-(1‴-Carboxy-4‴-phenylbutyl)-6″-methyl-2″-[(trimethylsilyl)methylene]cyclohexyl]ethyl]-2,5,5-trimethyl-1,3-dioxane (16a): prepared according to method A from acid **57** (0.55 g or 1.39 mmol) and 1-bromo-3-phenylpropane (0.5 mL). The acid **16a** was obtained as a foam, 394 mg or 55% yield. ^{1}H NMR: δ 0.10 (s, 9H), 0.87 (s, 3H), 0.93 (d, 3H, J = 7.1 Hz), 1.02 (s, 3H), 1.37 (m, 2H), 1.40–2.00 (m, 12H), 2.08 (br dd, 1H, J = 2.8, 11.5 Hz), 2.39 (br dd, 1H, J = 4.8, 12.0 Hz), 2.59 (br t, 2H, J = 6.8 Hz), 2.74 (br t, 1H, J = 11.5 Hz), 3.41 (br dt, 2H, J = 1.4, 11.0 Hz), 3.55 (dd, 2H, J = 3.1, 11.5 Hz), 5.29 (s, 1H), 7.10–7.30 (m, 5H). IR (Nujol): 3600–2400, 1700, 1600, 1450, 1380, 1250, 1220, 1130, 1100, 850, 750, 710 cm^{-1}. DCIMS-NH_3: m/z 587 (M + TMS), 515 (M + H), 446, 428, 411, 359, 339.

(1″*S*,1‴*S*,3″*S*,6″*R*)-(2″*E*)-2-[2′-[3″-(1‴-Carboxy-5‴-phenylpentyl)-6″-methyl-2″-[(trimethylsilyl)methylene]cyclohexyl]ethyl]-2,5,5-trimethyl-1,3-dioxane (17a): prepared according to method A from acid **57** (0.70 g or 1.77 mmol) and 1-bromo-4-phenylbutane (0.91 mL). The acid **71a** was obtained as a foam, 643 mg or 69% yield. ^{1}H NMR: δ 0.12 (s, 9H), 0.86 (s, 3H), 0.89 (t, 3H, J = 7.1 Hz), 0.94 (d, 3H, J = 6.9 Hz), 1.00 (s, 3H), 1.09 (br dt, 1H, J = 3.4, 10.4 Hz), 1.31 (s, 3H), 1.83 (br dt, 2H, J = 3.8, 12.5 Hz), 1.92 (br t, 2H, J = 10.4 Hz), 2.17 (br dd, 1H, J = 2.5, 10.4 Hz), 2.41 (br dd, 1H, J = 4.6, 13.7 Hz), 2.57 (br t, 2H, J = 7.7 Hz), 2.74 (br dt, 1H, J = 3.8, 13.7 Hz), 3.37 (ddd, 2H, J = 1.3, 11.3, 14.1 Hz), 3.52 (dd, 2H, J = 6.7, 11.3 Hz), 5.32 (s, 1H), 7.10–7.30 (m, 5H). IR (neat film): 3600–2400, 1704, 1601, 1454, 1374, 1247, 1213, 1091, 1021, 848, 747, 697 cm^{-1}. EIMS: m/z 528 (M^+), 513 (M – Me), 443, 424.

(1″*S*,1‴*S*,3″*S*,6″*R*)-(2″*E*)-2-[2′-[3″-(1‴-Carboxy-3‴-oxo-3‴-*tert*-butoxypropyl)-6″-methyl-2″-[(trimethylsilyl)methylene]cyclohexyl]ethyl]-2,5,5-trimethyl-1,3-dioxane (58). To a solution of diisopropylamine (308 μL, 2.2 mmol) in dry THF (4 mL) under argon at 0 °C was added n-butyllithium (2.2 mmol, 1.42 mL of 1.55 M solution in hexane). The resulting solution was stirred at 0 °C for 15 min and then cooled to –78 °C. The acid **57** (396 mg, 1.00 mmol) in dry THF (2 mL) was added via syringe, and the resulting solution was allowed to warm to ambient temperature over a 30-min period. The solution was heated to 50 °C for 2 h and then cooled to –78 °C. Next, *tert*-butyl bromoacetate (323 μL, 2 mmol) was added and the resulting solution stirred at 0 °C for 1 h and at ambient temperature for 30 min. The solution was treated with aqueous NH_4Cl (10 mL), extracted with EtOAc (3 × 200 mL), dried over $MgSO_4$, and evaporated to furnish 711 mg of crude product. This was applied to a column of 80 g of silica gel 60 (230–400 mesh), eluting with (1% HOAc/EtOAc)/hexane (20:80) to give product **58** (388 mg, 76%). ^{1}H NMR: δ 0.10 (s, 9H), 0.82 (s, 3H), 0.91 (d, 3H, J = 6.8 Hz), 0.99 (s, 3H), 1.30 (s, 3H), 1.39 (s, 9H), 2.10 (m, 1H), 2.30 (m, 1H), 2.48 (d, 1H, J = 3.5 Hz), 2.50 (s, 1H), 3.36 (m, 2H), 3.51 (m, 2H), 5.28 (s, 1H). IR ($CDCl_3$): 1725, 1710 cm^{-1}. EIMS: m/z 510 (M^+), 495, 476, 474, 454, 439, 437.

(+)-Octahydro-3,6α,9α-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (3). (+)-9-Epiartemisinin has been reported previously[9,22] and can also be prepared according to method B. Recrystallization from EtOAc/hexane gave **3**, mp 161–162 °C, $[\alpha]_D^{22}$ = +76.0° (c = 0.955, $CHCl_3$). ^{1}H NMR: δ 1.00 (d, 3H, J = 6.0 Hz), 1.12 (ddq, 1H, J = 1.8, 3.8, 13.3 Hz), 1.38–1.52 (m, 2H), 1.46 (s, 3H), 1.48 (d, 3H, J = 7.4 Hz), 1.66 (ddd, 1H, J = 1.1, 4.4, 13.5 Hz), 1.92 (dq, 1H, J = 3.3, 13.3 Hz), 1.80 (br dq, 1H, J = 4.0, 13.5 Hz), 2.07 (ddd, 1H, J = 3.8, 4.4, 14.8 Hz), 2.28 (dq, 1H, J = 1.2, 7.4 Hz), 2.40 (ddd, 1H, J = 4.0, 13.0, 14.8 Hz), 5.93 (s, 1H). IR (Nujol): 2930, 2850, 1738, 1460, 1380, 1215, 1160, 1110, 1040, 1000, 885, 835 cm^{-1}. DCIMS-NH_3: m/z (rel int) 300 (M + NH_4, 100), 283 (M + H, 25), 265 (32), 254 (10), 247 (10), 240 (17), 237 (22), 219 (10), 209 (33).

(+)-Octahydro-3,12-epoxy-3,6α,9,9-tetramethyl-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (4). To a solution of diisopropylamine (60 μL, 0.426 mmol) in THF (1 mL) at 0 °C was added n-butyllithium (266 μL of 1.60 M in hexane). After 10 min at 0 °C, the resultant solution was cooled to –78 °C, and a solution of (+)-artemisinin **1** (100 mg, 0.355 mmol) in THF (3 mL) was added dropwise over 30 min. After 1 h at –78 °C, methyl iodide (55 μL) was added and the resultant mixture was placed in a –40 °C bath. After 90 min between –40 °C and –30 °C, saturated aqueous NH_4Cl (15 mL) and 10% HCl (1 mL) were added, and the resultant mixture was extracted with ether (3 × 15 mL). The combined etheral layers were washed with saturated aqueous NH_4Cl (15 mL), H_2O (3 × 50 mL), and brine (2 × 25 mL), dried over Na_2SO_4, and evaporated to provide 94 mg of yellow, semicrystalline solid which was purified via flash column chromatography with SiO_2. Elution with EtOAc/benzene afforded 39 mg (37%) of white crystals, which recrystallized from hexane to furnish analytically pure **4** as white needles, mp 117–118 °C, $[\alpha]_D^{22}$ = +73.2° (c = 0.645, $CHCl_3$). ^{1}H NMR: δ 0.99 (d, 3H, J = 6.0 Hz), 1.06 (dddd, 1H, J = 3.6, 11.7, 12.0, 12.0 Hz), 1.19–1.31 (m, 1H), 1.26 (s, 3H), 1.33–1.53 (m, 3H), 1.48 (s, 3H), 1.56 (s, 3H), 1.69 (dd, 1H, J = 4.4, 13.7 Hz), 1.76 (ddd, 1H, J = 3.3, 6.7, 13.5 Hz), 1.91–2.01 (m, 2H), 2.02–2.09 (m, 1H), 2.37–2.47 (m, 1H), 5.89 (s, 1H). IR (CH_2Cl_2): 1720, 1095, 1020, 985 cm^{-1}. DCIMS-NH_3: m/z (rel int) 314 (M + NH_4, 90), 297 (M + H, 40), 279 (92), 251 (50), 233 (45), 233 (100).

(+)-Octahydro-3,6α-dimethyl-3,12-epoxy-9β-ethyl-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (5): prepared according to method C from acid **5a** (677 mg, 1.59 mmol). The peroxide **5** was obtained (152 mg, 32%) as a white solid after flash chromatography on silica gel. Crystallization from hexane provided white crystals, mp 125–125.5 °C, $[\alpha]_D^{22}$ = +70.0° (c = 0.10, EtOH). ^{1}H NMR: δ 0.95 (t, 3H, J = 7.5 Hz), 0.98 (d, 3H, J = 5.9 Hz), 1.43 (s, 3H), 2.04 (m, 3H), 2.40 (m, 1H), 3.09 (dt, 1H, J = 5.5, 9.3 Hz), 5.83 (s, 1H). IR ($CHCl_3$): 3030, 2970, 2930, 2880, 1740, 1385, 1190, 1120, 1040, 1000, 890 cm^{-1}. DCIMS-NH_3: m/z 314 (M + NH_4), 297 (M + H), 279, 268, 251, 233, 223. A less polar fraction from the chromatography afforded (–)-1-deoxy-16-methylartemisinin (**30**) (49 mg or 11%), mp 50–53 °C, $[\alpha]_D^{22}$ = –40.0° (c = 0.10, $CHCl_3$). ^{1}H NMR: δ 0.92 (d, 3H, J = 6.0 Hz), 0.96 (t, 3H, J = 7.6 Hz), 1.05 (m, 2H), 1.25 (m, 4H), 1.34 (ddq, 1H, J = 7.6, 9.2, 16.0 Hz), 1.51 (s, 3H), 1.53–1.66 (m, 3H), 1.72–1.84 (m, 3H), 1.89 (m, 1H), 2.05 (ddq, 1H, J = 7.6, 9.2, 16.0 Hz), 2.09 (ddd, 1H, J = 4.0, 4.0, 13.2 Hz), 2.86 (ddd, 1H, J = 5.0, 9.2, 9.2 Hz), 5.65 (s, 1H). IR ($CHCl_3$): 3040, 2980, 2950, 1750, 1150, 1120, 1030, 930 cm^{-1}. DCIMS-NH_3: m/z 298 (M + NH_4), 281 (M + H), 258, 251, 236, 223.

(+)-Octahydro-3,6α-dimethyl-3,12-epoxy-9β-propyl-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (6): prepared

according to method C from acid **6a** (580 mg, 1.32 mmol). The peroxide **6** was obtained (103 mg, 25%) as a white solid after flash chromatgraphy on silica gel. Crystallization from hexane provided white crystals, mp 149–150 °C, $[\alpha]^{22}_D$ = +64.9° (*c* = 0.892, $CHCl_3$). ^1H NMR: δ 0.94 (t, 3H, *J* = 7.4 Hz), 1.02 (d, 3H, *J* = 6.0 Hz), 1.08 (m, 2H), 1.3–1.5 (m, 6H), 1.45 (s, 3H), 1.79 (m, 3H), 2.03 (m, 3H), 2.43 (ddd, 1H, *J* = 3.5, 13.0, 14.6 Hz), 3.22 (ddd, 1H, *J* = 5.2, 5.2, 8.6 Hz), 5.85 (s, 1H). IR (KBr): 3030, 2970, 2930, 2880, 1740, 1385, 1190, 1120, 1040, 1000, 890 cm^{-1}. DCIMS-NH_3: *m/z* 328 (M + NH_4), 311 (M + H). A less polar fraction from the chromatography afforded 1-deoxy-16-ethylartemisinin (**31**). ^1H NMR (300 MHz, $CDCl_3$): δ 5.67 (s, 1H), 2.98 (ddd, 1H, *J* = 4.6, 5.8, 10.4 Hz), 2.07 (ddd, *J* = 4.3, 8.6, 12.9 Hz), 1.84–2.01 (m, 2H), 1.67–1.83 (m, 3H), 1.52 (s, 3H), 1.2–1.4 (m, 6H), 0.89–0.96 (m, 5H). IR (KBr): 2959, 2951, 2869, 1747, 1460, 1389, 1139, 1020 cm^{-1}. DCIMS-NH_3: *m/z* 312 (M + NH_4^+), 295 (M + H^+).

(+)-Octahydro-3,6α-dimethyl-3,12-epoxy-9β-(1′-methylethyl)-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (7): prepared according to method C from acid **7a** (250 mg or 0.57 mmol). The peroxide **7**, 30 mg or 17% yield, was obtained as a white crystalline solid which was recrystallized from hexane, mp 113–114 °C, $[\alpha]^{22}_D$ = +85.0° (*c* = 0.20, CH_2Cl_2). ^1H NMR: δ 0.95 (d, 3H, *J* = 6.8 Hz), 1.01 (d, 3H, *J* = 5.9 Hz), 1.10–1.20 (m, 2H), 1.21 (d, 3H, *J* = 6.5 Hz), 1.35–1.52 (m, 2H), 1.46 (s, 3H), 1.75 (ddd, 1H, *J* = 3.3, 6.4, 13.2 Hz), 1.84 (ddd, 1H, *J* = 3.6, 6.6, 13.5 Hz), 1.92 (ddd, 1H, *J* = 4.4, 4.4, 13.1 Hz), 2.04 (m, 3H), 2.43 (ddd, 1H, *J* = 4.0, 14.4, 16.0 Hz), 2.97 (dd, 1H, *J* = 4.7, 8.8 Hz), 5.84 (s, 1H). IR ($CHCl_3$): 1740, 1385, 1185, 1115, 1040, 1015, 975, 890, 845 cm^{-1}. DCIMS-NH_3: *m/z* 328 (M + NH_4), 311 (M + H), 293, 275, 265, 247, 237, 219. A less polar fraction from the chromatography gave 1-deoxy-16,16-dimethylartemisinin (**35**). ^1H NMR (300 MHz, $CDCl_3$): δ 5.65 (s, 1H), 2.68 (dd, 1H, *J* = 4.0, 9.2 Hz), 2.20 (ddd, 1H, *J* = 4.2, 8.3, 12.8 Hz), 1.98–2.10 (m, 1H), 1.54 (s, 3H), 1.18 (d, 3H, *J* = 6.4 Hz), 0.91 (d, 3H, *J* = 5.3 Hz), 0.93 (d, 3H, *J* = 5.3 Hz). IR (KBr): 2960, 2925, 2869, 1747, 1389, 1105, 1019 cm^{-1}. EIMS: *m/z* 295 (M + H^+), 294 (M^+), 266, 252, 238, 207, 165, 151.

(+)-Octahydro-9β-butyl-3,6α-dimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (8): prepared according to method C, acid **8a** (480 mg, 1.06 mmol) gave the peroxide **8** (116 mg, 34%) as a white solid, which was crystallized from EtOAc/hexane to provide white crystals, mp 129–130 °C, $[\alpha]^{21}_D$ = +61.3° (*c* = 0.375, $CHCl_3$). ^1H NMR: δ 0.92 (t, 3H, *J* = 7.1 Hz), 1.01 (d, 3H, *J* = 6.0 Hz), 1.09 (m, 2H), 1.46 (s, 3H), 1.2–1.6 (m, 8H), 1.80 (m, 3H), 2.04 (m, 3H), 2.43 (ddd, *J* = 3.9, 13.0, 14.5 Hz, 1H), 3.20 (ddd, 1H, *J* = 5.7, 5.7, 8.2 Hz), 5.86 (s, 1H). IR (CH_2Cl_2): 3054, 2958, 1736, 1421, 1274, 1264, 1254, 1114, 1001, 895, 740 cm^{-1}. DCIMS-NH_3: *m/z* (rel int) 342 (M + NH_4, 31), 325 (M + H, 25), 307 (60), 289 (22), 274 (41), 261 (22), 251 (100).

(+)-Octahydro-3,6α-dimethyl-3,12-epoxy-9β-(2′-methylpropyl)-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (9): prepared according to method C from acid **9a** (860 mg or 1.90 mmol). The peroxide **9**, 108 mg or 17% yield, was obtained as a white crystalline solid which was recrystallized from hexane, mp 185–186 °C, $[\alpha]^{22}_D$ = +79.0° (*c* = 0.520, CH_2Cl_2). ^1H NMR: δ 0.90 (d, 3H, *J* = 6.5 Hz), 0.94 (d, 3H, *J* = 6.5 Hz), 1.01 (d, *J* = 6.0 Hz, 3H), 1.09 (m, 2H), 1.32 (ddd, 1H, *J* = 5.0, 9.7, 14.3 Hz), 1.37–1.56 (m, 4H), 1.46 (s, 3H), 1.62 (m, 1H), 1.78 (m, 2H), 1.85 (ddd, 1H, *J* = 5.5, 9.7, 15.0 Hz), 2.01 (m, 1H), 2.06 (m, 3H), 2.44 (ddd, 1H, *J* = 4.0, 13.0, 14.7 Hz), 3.32 (ddd, 1H, *J* = 5.5, 5.5, 9.7 Hz), 5.86 (s, 1H). IR (CH_2Cl_2): 3057, 2958, 1736, 1457, 1380, 1260, 1186, 1114, 1000, 888, 756 cm^{-1}. DCIMS-NH_3: *m/z* 342 (M + NH_4), 325 (M + H), 307, 289, 279, 261, 251, 233.

(+)-Octahydro-3,6α-dimethyl-3,12-epoxy-9β-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (10): prepared according to method C, acid **10a** (450 mg, 0.966 mmol) gave the peroxide **10** (118 mg, 36%) as a white solid, which was crystallized from EtOAc/hexane to provide white crystals, mp 122.5–123.5 °C, $[\alpha]^{21}_D$ = +55.0° (*c* = 0.583, $CHCl_3$). ^1H NMR: δ 0.90 (t, 3H, *J* = 6.7 Hz), 1.01 (d, 3H, *J* = 5.9 Hz), 1.09 (m, 2H), 1.45 (s, 3H), 1.2–1.6 (m, 10H), 1.80 (m, 3H), 2.04 (m, 3H), 2.44 (ddd, 1H, *J* = 4.0, 13.0, 14.4 Hz), 3.21 (ddd, 1H, *J* = 5.3, 5.3, 8.2 Hz), 5.86 (s, 1H). IR (CH_2Cl_2): 3054, 2986, 1735, 1421, 1273, 1263, 1253, 895 cm^{-1}. DCIMS-NH_3: *m/z* (rel int) 356 (M + NH_4, 34), 339 (M + H, 28), 321 (56), 303 (22), 293 (48), 275 (18), 265 (100).

(+)-Octahydro-3,6α-dimethyl-3,12-epoxy-9β-(3′-methylbutyl)-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (11): prepared according to method C from acid **11a** (566 mg, 1.21 mmol). The peroxide **11** was obtained as crystals, 150 mg or 37%, which was recrystallized from EtOAc/hex in successive crops to provide analytically pure white, fluffy crystals, mp 117–118 °C, $[\alpha]^{20}_D$ = +56.4° (*c* = 0.525, $CHCl_3$). ^1H NMR: δ 0.91 (ABt, 6H, *J* = 11.8 Hz), 1.01 (d, 3H, *J* = 5.9 Hz), 1.04–1.18 (m, 3H), 1.23–1.44 (m, 4H), 1.45 (s, 3H), 1.48–1.63 (m, 2H), 1.75–1.86 (m, 3H), 1.97–2.12 (m, 3H), 2.44 (ddd, 1H, *J* = 4.3, 13.3, 14.6 Hz), 3.17 (dt, 1H, *J* = 5.2, 9.0 Hz), 5.86 (s, 1H). IR (CH_2Cl_2): 2960, 2882, 1740, 1385, 1190, 1120, 1045, 1010 cm^{-1}. DCIMS-NH_3: *m/z* (rel int) 356 (M + NH_4, 32), 339 (M + H, 63), 321 (60), 293 (50), 265 (100).

(+)-Octahydro-3,6α-dimethyl-3,12-epoxy-9β-hexyl-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (12): prepared according to method C from acid **12a** (0.54 g or 1.12 mmol). The peroxide **12**, 84.5 mg or 22% yield, was obtained as a white solid, which was recrystallized from cold hexane, mp 80.5–82 °C, $[\alpha]^{21}_D$ = +44.5° (*c* = 0.40, $CDCl_3$). ^1H NMR: δ 0.89 (br t, 3H, *J* = 6.9 Hz), 1.00 (d, 3H, *J* = 5.9 Hz), 1.08 (m, 1H), 1.25–1.44 (m, 9H), 1.45 (s, 3H), 1.80 (m, 3H), 2.04 (m, 3H), 2.43 (ddd, 1H, *J* = 3.7, 13.1, 14.6 Hz), 3.20 (m, 1H), 5.86 (s, 1H). IR ($CHCl_3$): 1740, 1380, 1190, 1120, 1040, 1010, 890, 840, cm^{-1}. DCIMS-NH_3: *m/z* 370 (M + NH_4), 353 (M + H), 335, 317, 307, 289, 279. A less polar fraction from the chromatography gave 1-deoxy-16-pentylartemisinin (**34**). ^1H NMR (300 MHz, $CDCl_3$): δ 5.66 (s, 1H), 2.95 (ddd, 1H, *J* = 4.6, 8.86, 9.5 Hz), 2.08 (ddd, 1H, *J* = 4.3, 8.6, 12.6 Hz), 1.88–2.02 (m, 2H), 1.52 (s, 3H), 0.93 (d, 3H, *J* = 5.6 Hz), 0.87 (t, 3H, *J* = 7.0 Hz). IR (KBr): 2959, 2926, 2857, 1748, 1457, 1387, 1137, 1019 cm^{-1}. EIMS: *m/z* 337 (M + H^+), 294, 276, 250, 234, 182, 165.

(+)-Octahydro-3,6α-dimethyl-3,12-epoxy-9β-(4′-methylpentyl)-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (13): prepared according to method C. From acid **13a** (145 mg, 0.302 mmol) was obtained 36 mg (34%) of crystalline **13** which recrystallized from hexane in successive crops to provide analytically pure white, fluffy crystals, mp 104–105 °C, $[\alpha]^{22}_D$ = +75° (*c* = 0.06, CH_2Cl_2). ^1H NMR: δ 0.88 (d, 3H, *J* = 6.6 Hz), 0.89 (d, 3H, *J* = 6.6 Hz), 1.01 (d, 3H, *J* = 5.9 Hz), 1.09 (m, 2H), 1.21 (m, 2H), 1.26–1.44 (m, 4H), 1.45 (s, 3H), 1.47–1.61 (m, 3H), 1.81 (m, 3H), 2.20 (m, 3H), 2.44 (ddd, 1H, *J* = 4.1, 13.1, 14.8 Hz), 3.17 (dt, 1H, *J* = 5.3, 8.6 Hz), 5.86 (s, 1H). IR (CH_2Cl_2): 3054, 2957, 1734, 1421, 1268, 1115, 1004, 896, 754 cm^{-1}. DCIMS-NH_3: *m/z* (rel int) 370 (M + NH_4, 73), 353 (M + H, 67), 335 (72), 317 (28), 307 (67), 279 (100). A less polar fraction from the chromatography gave 1-deoxy-16-isobutylartemisinin (**37**). ^1H NMR (300 MHz, $CDCl_3$): δ 5.66 (s, 1H), 2.92 (ddd, 1H, *J* = 4.8, 9.4, 13.8 Hz), 2.10 (ddd, 2H, *J* = 4.3, 8.6, 12.8), 1.72–1.84 (m, 3H), 1.52 (s, 3H), 1.24 (m, 4H), 0.90 (d, 3H, *J* = 5.4 Hz), 0.88 (d, 3H, *J* = 5.4 Hz), 0.91 (d, 3H, *J* = 5.4 Hz). IR (KBr): 2961, 2929, 2860, 1747, 1390, 1138, 1020 cm^{-1}. EIMS: *m/z* 323 (M + H^+), 280, 262, 251, 236, 220, 182, 165.

(+)-Octahydro-3,6α-dimethyl-3,12-epoxy-9β-tetradecyl-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (14): prepared according to method C from acid **14a** (480 mg, 0.809 mmol). The peroxide **14**, 113 mg or 30% yield, was obtained as white platelets, which were recrystallized from hexane, mp 65–66 °C, $[\alpha]^{22}_D$ = +45.7° (*c* = 0.56, $CDCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, 3H, *J* = 7.0 Hz), 1.00 (d, 3H, *J* = 6.0 Hz), 1.08 (m, 1H), 1.20–1.43 (m, 23H), 1.45 (s, 3H), 1.80 (m, 3H), 2.04 (m, 3H), 2.43 (ddd, 1H, *J* = 3.8, 13.0, 14.7 Hz), 3.19 (m, 1H), 5.85 (s, 1H). IR ($CHCl_3$): 1735, 1380, 1185, 1120, 1040, 1010, 890, 840 cm^{-1}. DCIMS-NH_3: *m/z* 482 (M + NH_4), 465 (M + H), 447, 436, 419, 391. A less polar fraction from the chromatography gave 1-deoxy-16-tridecylartemisinin (**71**). ^1H NMR (300 MHz, $CDCl_3$): δ 5.67 (s, 1H), 2.94 (ddd, 1H, *J* = 5.3, 8.0, 12.7 Hz), 2.08 (ddd, 1H, *J* = 4.2, 8.7, 12.9 Hz), 1.86–2.02 (m, 2H), 1.72–1.84 (m, 3H), 1.52 (s, 3H), 0.93 (d, 3H, *J* = 5.7 Hz), 0.88 (t, 3H, *J* = 6.7 Hz). IR (KBr): 2918, 2848, 1757, 1740, 1458, 1140, 1018 cm^{-1}. EIMS: *m/z* 449 (M + H^+), 448 (M^+), 430, 419, 406, 388, 362, 346, 265.

(+)-Octahydro-3,6α-dimethyl-3,12-epoxy-9β-(2′-phenylethyl)-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (15): prepared according to method C from acid **15a** (380 mg or

0.74 mmol). The peroxide **15** was obtained as an oil, 66 mg or 22% yield, which was recrystallized from EtOAc/hexane, mp 120.5–122 °C, $[\alpha]^{22}_D$ = +81.8° (*c* = 0.235, CH_2Cl_2). ^1H NMR: δ 1.01 (d, 3H, *J* = 5.9 Hz), 1.10 (m, 2H), 1.35–1.54 (m, 3H), 1.45 (s, 3H), 1.62 (dddd, 1H, *J* = 2.2, 5.5, 10.0, 13.5 Hz), 1.75–1.95 (m, 3H), 2.02 (m, 1H), 2.06 (ddd, 1H, *J* = 2.9, 4.6, 14.3 Hz), 2.36 (dddd, 1H, *J* = 6.4, 6.4, 10.3, 14.0 Hz), 2.44 (ddd, 1H, *J* = 3.9, 13.0, 14.6 Hz), 2.67 (ddd, 1H, *J* = 5.7, 10.3, 13.8 Hz), 2.81 (ddd, 1H, *J* = 6.4, 10.3, 13.8 Hz), 3.26 (ddd, 1H, *J* = 5.2, 6.4, 7.8 Hz), 5.87 (s, 1H), 7.18–7.34 (m, 5H). IR (CH_2Cl_2): 3055, 2931, 1737, 1454, 1380, 1202, 1112, 1004, 1010, 890, 840 cm^{-1}. DCIMS-NH_3: *m/z* 390 (M + NH_4), 373 (M + H), 355, 337, 327, 309, 299.

(+)-Octahydro-3,6α-dimethyl-3,12-epoxy-9β-(3′-phenylpropyl)-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (16): prepared according to method C from acid **16a** (380 mg or 0.74 mmol). The peroxide **16** was obtained as a white solid, 101 mg or 35% yield, which was recrystallized from ether/hexane, mp 137–138 °C, $[\alpha]^{22}_D$ = +34.8° (*c* = 0.617, $CDCl_3$). ^1H NMR: δ 0.99 (d, 3H, *J* = 5.9 Hz), 1.05 (m, 1H), 1.20–1.50 (m, 4H), 1.45 (s, 3H), 1.50–2.20 (m, 10H), 2.44 (ddd, 1H, *J* = 4.4, 13.5, 5.1 Hz), 2.61 (ddd, 1H, *J* = 7.2, 8.4, 13.8 Hz), 2.71 (ddd, 1H, *J* = 5.6, 8.4, 13.8 Hz), 3.25 (ddd, 1H, *J* = 5.8, 5.8, 8.8 Hz), 5.85 (s, 1H), 7.10–7.35 (m, 5H). IR (CH_2Cl_2): 1740, 1200, 1120, 1040, 1010, 890, 840 cm^{-1}. DCIMS-NH_3: *m/z* 404 (M + NH_4), 387 (M + H), 369, 351, 341, 323, 313. A less polar fraction from the chromatography gave 1-deoxy-16-(2-phenylethyl)artemisinin (**40**). ^1H NMR (300 MHz, $CDCl_3$): δ 7.14–7.32 (m, 5H), 5.66 (s, 1H), 2.98 (ddd, 1H, *J* = 6.0, 8.6, 13.3 Hz), 2.56–2.76 (m, 2H), 2.02 (m, 3H), 1.90 (m, 1H), 1.52 (s, 3H), 0.92 (d, 3H, *J* = 5.6 Hz). IR (KBr): 2947, 2927, 1745, 1138, 1107, 1018 cm^{-1}. EIMS: *m/z* 371 (M + H^+), 370 (M^+), 352, 328, 310, 299, 282.

(+)-Octahydro-3,6α-dimethyl-3,12-epoxy-9β-(4′-phenylbutyl)-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (17): prepared according to method C from acid **17a** (780 mg or 1.48 mmol). The peroxide **17** was obtained as a colorless oil, 152 mg or 26% yield, $[\alpha]^{22}_D$ = +63.2° (*c* = 3.11, CH_2Cl_2). ^1H NMR: δ 1.02 (d, 3H, *J* = 5.6 Hz), 1.06 (m, 2H), 1.20–1.50 (m, 6H), 1.47 (s, 3H), 1.60–1.85 (m, 5H), 2.04 (m, 3H), 2.44 (ddd, 1H, *J* = 3.5, 13.5, 14.7 Hz), 2.64 (ddd, 1H, *J* = 7.9, 13.0, 15.1 Hz), 2.67 (ddd, 1H, *J* = 7.9 13.0, 15.1 Hz), 3.21 (ddd, 1H, *J* = 4.8, 5.5, 8.8 Hz), 5.85 (s, 1H), 7.10–7.35 (m, 5H). IR (neat film): 2928, 1740, 1453, 1378, 1183, 1111, 1032, 1003, 885, 833 cm^{-1}. DCIMS-NH_3: *m/z* 418 (M + NH_4), 401 (M + H), 383, 365, 355, 337, 327.

(+)-Octahydro-9β-(carboxymethyl)-3,6α-dimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one, *tert*-Butyl Ester (59). A solution of **58** (270 mg, 0.529 mmol) in CH_2Cl_2 was cooled to −78 °C and treated with ozone (7 psi, 0.4 L/min, 70 V) until a faint blue color was seen (about 4 min). A solution of BHT (30 mg) in CH_2Cl_2 (1 mL) was added, followed by silica gel (7.5 g) and 3 M H_2SO_4 (3 mL). The resulting mixture was brought to ambient temperature and stirred for 18 h and then treated with solid sodium bicarbonate. The silica gel was removed by filtration, rinsing with EtOAc (50 mL). The filtrate was concentrated *in vacuo* to afford the crude *tert*-butyl ester **59** which was used directly for the following reaction. A small sample was purified by PTLC on a 2-mm silica gel plate eluting with 30% EtOAc/hexane. ^1H NMR: δ 0.96 (d, 3H, *J* = 5.9 Hz), 1.05 (m, 1H), 1.42 (s, 3H), 1.43 (s, 9H), 1.76 (m, 2H), 1.90 (br dt, 1H, *J* = 5.1, 13.5 Hz), 2.00 (m, 2H), 2.22 (dd, 1H, *J* = 8.4, 15.9 Hz), 2.42 (m, 1H), 2.88 (dd, 1H, *J* = 6.6, 15.9 Hz), 3.79 (ddd, 1H, *J* = 5.5, 6.6, 8.4), 5.84 (s, 1H).

(+)-Octahydro-9β-(carboxymethyl)-3,6α-dimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (18). The above sample of crude **59** was placed in CH_2Cl_2 (25 mL) and treated with trifluoroacetic acid (0.60 mL). The resultant solution was stirred at room temperature for 2 h. The solution was filtered through silica gel (15 g), rinsing with EtOAc (75 mL). The solvent was removed *in vacuo*, adsorbed onto 2 g of silica gel, and placed on top of a column of 30 g of silica gel 60 (230–400 mesh), eluting via stepwise gradient of hexane/(1% HOAc/EtOAc) from 90/10 to 60/40. After elution with 50 mL of 90/10, 100 mL of 80/20, 100 mL of 70/30, and 92 mL of 60/40, the product was collected from the next 115 mL of 60/40. Evaporation left 64 mg of product containing ~20% 16-carboxydeoxyartemisinin by NMR. This was taken into EtOAc (1 mL) and crystallized to provide 35 mg (20% overall from **57**) of pure product **18**, mp 155–157 °C. IR ($CHCl_3$): 2980, 2940, 2880, 1740, 1720, 1450, 1385, 1120, 1045, 1010 cm^{-1}. ^1H NMR: δ 0.98 (d, 3H, *J* = 5.9 Hz), 1.43 (s, 3H), 2.36 (dd, 1H, *J* = 7.0, 16.7 Hz), 2.42 (m, 1H), 2.98 (dd, 1H, *J* = 7.0, 16.7 Hz), 3.85 (ddd, 1H, *J* = 5.1, 7.0, 7.0 Hz), 5.87 (s, 1H). ^{13}C NMR: δ 175.2, 170.5, 105.6, 93.9, 79.1, 49.9, 43.0, 37.5, 35.8, 35.5, 33.4, 32.1, 25.1, 24.8, 23.8, 19.7. DCIMS-NH_3: *m/z* 344 (M + NH_4), 327 (M + H), 311, 298, 284, 263, 253.

(+)-Octahydro-3,6α-dimethyl-3,12-epoxy-9α-(2-propenyl)-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (60). According to method B, from 9-desmethylartemisinin (100 mg, 0.37 mmol) and allyl bromide (1.5 equiv), was obtained the α-epimer **60** as white hexagonal plates, 57 mg (50%), mp 132.5–133 °C, along with recovered starting material (24%), $[\alpha]^{22}_D$ = +81.2° (*c* = 0.505, $CHCl_3$). ^1H NMR: δ 1.00 (d, 3H, *J* = 5.1 Hz), 1.05–1.19 (m, 1H), 1.36–1.51 (m, 5H), 1.51–1.59 (m, 2H), 1.63–1.73 (m, 2H), 1.82 (ddd, 1H, *J* = 0.91, 4.2, 14.5 Hz), 1.91–2.01 (m, 1H), 2.08 (ddd, 1H, *J* = 2.8, 4.4, 14.6 Hz), 2.20 (ddd, 1H, *J* = 1.2, 4.2, 10.6 Hz), 2.40 (m, 1H), 2.50 (ddddd, 1H, *J* = 0.6, 0.6, 8.9, 10.5, 14.2 Hz), 2.90 (ddddd, 1H, *J* = 1.5, 1.5, 4.2, 10.6, 14.2 Hz), 5.10–5.17 (m, 2H), 5.78 (dddd, 1H, *J* = 5.4, 8.8, 10.1, 17.0 Hz), 5.94 (s, 1H). IR (CH_2Cl_2): 1735, 1115, 1040, 1003 cm^{-1}. DCIMS-NH_3: *m/z* (rel int) 326 (M + NH_4, 100), 309 (M + H, 77), 291 (45), 235 (33).

(+)-Octahydro-3,6α-dimethyl-3,12-epoxy-9β-(2-propenyl)-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (19). The α-epimer **60** (165 mg or 0.615 mmol) was isomerized according to method B. The crude product (105 mg) was purified by PTLC on a 1.5-mm silica gel plate eluting with 30% EtOAc/hexane to provide recovered starting material (31 mg) along with the desired product **19** as a white solid (39 mg or 29%). Recrystallization afforded 32 mg of white crystals, mp 86–87 °C, $[\alpha]^{22}_D$ = +90.5° (*c* = 0.158, $CHCl_3$). ^1H NMR: δ 1.0 (d, 3H, *J* = 6.0 Hz), 1.08 (m, 2H), 1.45 (s, 3H), 1.8 (m, 3H), 2.2 (m, 3H), 2.43 (m, 1H), 2.90 (ddddd, 1H, *J* = 1.9, 1.9, 5.0, 10.1, 13.2 Hz), 3.35 (ddd, 1H, *J* = 5.0, 5.0, 10.6 Hz), 5.11 (m, 2H), 5.76 (dddd, 1H, *J* = 5.1, 8.8, 10.1, 17.0 Hz), 5.87 (s, 1H). IR (CH_2Cl_2): 2927, 2873, 1739, 1642, 1450, 1378, 1189, 1113, 1036, 1000, 974, 923, 886, 834, 777 cm^{-1}. DCIMS-NH_3: *m/z* (rel int) 326 (M + NH_4, 50), 309 (M + H, 25), 291 (35), 273 (33), 263 (28), 245 (22), 235 (100).

Octahydro-9α-(2(*E*)-butenyl)-3,6α-dimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (20) and Octahydro-9α-(2(*Z*)-butenyl)-3,6α-dimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (21): according to method B, from 9-desmethylartemisinin (**2**) (300 mg or 0.746 mmol) and freshly distilled Aldrich crotyl bromide (*E*/*Z* mixture, 0.6 mL). The crude product was first purified by 1.5-mm silica gel PTLC to give 161 mg of a mixture of **20** and **21** in a 6:4 ratio by NMR along with recovered starting material (60 mg). Repeated fractional crystallizations from cold hexane gave the *E* regioisomer **20** (9:1 *E*:*Z*, 46.5 mg or 16%) as long needles, mp 90–90.5 °C. ^1H NMR: δ 1.0 (d, 3H, *J* = 6.0 Hz), 1.14 (m, 1H), 1.46 (s, 3H), 1.69 (dd, 3H, *J* = 3.3, 6.2 Hz), 1.81 (m, 1H), 1.96 (m, 1H), 2.08 (m, 1H), 2.15 (m, 1H), 2.41 (m, 2H), 2.81 (m, 1H), 5.38 (dddq, 1H, *J* = 3.3, 5.5, 8.7, 15.1 Hz), 5.56 (dddq, 1H, *J* = 0.8, 1.6, 6.2, 15.1 Hz), 5.92 (s, 1H). IR (Nujol): 2921, 2854, 1725, 1460, 1376, 1220, 1152, 1126, 1102, 1064, 1034, 990, 948, 887, 861, 833, 775, 721 cm^{-1}. DCIMS-NH_3 of the 6:4 *E*/*Z* mixture: *m/z* (rel int) 340 (M + NH_4, 8), 323 (M + H, 7), 305 (25), 287 (28), 263 (43), 259 (33), 249 (100), 231 (26), 219 (29). Repeated fractional crystallization of the mother liquors from ether/hexane provided the *Z* regioisomer **21** (2:8 *E*:*Z*, 55 mg or 19%) as white fluffy crystals, mp 120–123 °C. ^1H NMR: δ 1.00 (d, 3H, *J* = 6.0 Hz), 1.13 (m, 1H), 1.47 (s, 3H), 1.67 (complex dd, 3H), 1.75 (m, 1H), 1.96 (m, 1H), 2.06 (m, 1H), 2.17 (m, 1H), 2.41 (m, 2H), 2.70 (m, 2H), 5.38 (br dddq, 1H), 5.62 (br dddq, 1H), 5.93 (s, 1H). IR (Nujol): 2923, 2854, 1722, 1455, 1376, 1221, 1151, 1124, 1102, 1067, 1033, 992, 947, 886, 864, 834, 764, 731 cm^{-1}.

Methyl *syn*-2-[3-(2,2-dimethoxyethyl)-2(*E*,*Z*)-[(trimethylsilyl)methylene]cyclohexyl]acetate (62). As per Schreiber's procedure,[35] through a solution of 10-[(trimethylsilyl)methylene]-bicyclo[4.3.1]dec-3-ene (**61**, 1.78 g, 7.99 mmol) in dry CH_2Cl_2 (25 mL) and absolute MeOH (5 mL) at −78 °C was passed a stream of O_3/O_2. The disappearance of starting material was monitored by periodic TLC (SiO_2 in EtOAc/hex) before the mixture was purged with inert gas, treated with *p*-TsOH·H_2O (0.13 g, 0.68 mmol), and allowed to warm to ambient temperature over 2 h. The resultant solution was neutralized with $NaHCO_3$ (230 mg),

filtered, diluted with dry benzene (10 mL), and concentrated under reduced pressure to 5-mL volume, which was cooled to 0 °C and successively treated with Et_3N (1.67 mL) and Ac_2O (2.26 mL). After 15 min at 0 °C, the mixture was allowed to warm to ambient temperature. After 6 h, the resultant solution was washed with 0.1 N HCl (3 × 35 mL) and 10% aqueous NaOH (3 × 30 mL), dried over Na_2SO_4, and evaporated to provide 2.77 g of pale yellow oil, which was further purified via flash-column chromatography with silica gel. After elution with EtOAc/hexane, acetal ester **62** (0.99 g, 39.2% yield) was obtained as a colorless oil, which consisted of a 1:1 mixture of *E*:*Z* isomers by NMR and was used without further purification: ^{1}H NMR (400 MHz): δ 0.079, 0.096 (2 s, 9H), 0.72–1.70 (m, 5.5H), 1.77 (br d, 0.5H, *J* = 11.6 Hz), 1.89 (ddd, 0.5H, *J* = 14.5, 10.9, 6.5 Hz), 2.24 (ddd, 0.5H, *J* = 16.0, 2.8, 0.7 Hz), 2.46 (ddd, 1.5H, *J* = 26.4, 14.5, 9.0 Hz), 2.68 (dd, 1H, *J* = 15.4, 12.3 Hz), 2.81 (br m, 0.5H), 3.12 (br m, 0.5H), 3.27 (s, 1.5H), 3.29 (s, 1.5H), 3.32 (s, 1.5H), 3.63 (s, 1.5H), 3.66 (s, 1.5H), 4.29 (t, 0.5H, *J* = 7.3 Hz), 4.35 (dd, 0.5H, *J* = 7.3, 4.9 Hz), 5.23 (br s, 1H). IR (neat): 2960, 2940, 2870, 2840, 1742, 1608, 1440, 1370, 1293, 1250, 1195, 1175, 1150, 1130, 1083, 1060, 870, 845 cm^{-1}. DCIMS-NH_3: *m*/*z* (rel int) 328 (28), 327 (100) for each of two components observed by GC.

***syn*-2-[3-(2,2-Dimethoxyethyl)-2(*E*,*Z*)-[(trimethylsilyl)methylene]cyclohexyl]acetic Acid (63).** To a solution of methyl ester **62** (516 mg, 1.63 mmol) in absolute MeOH (15 mL) was added freshly prepared 6 N KOH (4 mL). The resultant yellow solution was degassed with argon, refluxed for 90 min, allowed to cool to ambient temperature, stirred with saturated aqueous NH_4Cl (15 mL), and extracted with Et_2O (4 × 15 mL). The combined ethereal layers were washed with saturated aqueous NH_4Cl (2 × 35 mL), dried over Na_2SO_4, and evaporated to give a cloudy oil, 378 mg, which was purified via flash-column chromatography with silica gel. After elution with HOAc/EtOAc/hexane and subsequent azeotropic removal of HOAc with CCl_4, 338 mg (68.7% yield) of acid **63** was obtained as a colorless oil. Proton NMR showed that a mixture of diastereomers was present. ^{1}H NMR: δ 0.084, 0.099 (2 s, 9H), 0.73–1.82 (m, 5.5H), 1.87 (ddd, 0.5H, *J* = 5.1, 12.4, 14.5 Hz), 2.31 (dd, 0.5H, *J* = 2.2, 16.7 Hz), 2.42–2.50 (m, 1H), 2.55 (dd, 0.5H, *J* = 8.0, 14.5 Hz), 2.72 (dd, 1H, *J* = 11.6, 15.3 Hz), 2.82 (br m, 0.5H), 3.12 (br m, 0.5H), 3.27 (s, 1.5H), 3.29 (s, 1.5H), 3.30 (s, 1.5H), 3.32 (s, 1.5H), 4.31 (t, 0.5H, *J* = 6.5 Hz), 4.37 (dd, 0.5H, *J* = 6.5, 7.3 Hz), 5.25 (s, 0.5H), 5.27 (s, 0.5H). IR (neat): 3000, 2950, 2875, 2840, 1710, 1610, 1250, 1130, 1090, 1060, 870, 845 cm^{-1}. DCIMS of TMS esters: *m*/*z* (rel int) 385 (M + NH_4, 3), 308 (35), 290 (100) for each of two components observed by GC.

***syn*-2-[3-(2-ethanalyl)-2(*E*,*Z*)-[(trimethylsilyl)methylene]cyclohexyl]acetic Acid (64).** To a stirring suspension of dimethyl acetal **63** (330 mg, 0.915 mmol) and 230–400-mesh silica gel 60 (0.85 g) in CH_2Cl_2 (10 mL) was added a freshly prepared solution of 10% aqueous oxalic acid (0.20 mL). After 18 h, the silica gel was filtered off and rinsed with CH_2Cl_2 (35 mL). The filtrate was concentrated *in vacuo* to 287 mg of yellow oil, which was further purified by flash-column chromatography with silica gel. After elution with HOAc/EtOAc/hexane, 258 mg of aldehyde–acid **64** as a yellow oil was obtained and used immediately. The ^{1}H NMR showed that a 1:1 mixture of vinylsilane geometrical isomers was present. ^{1}H NMR: δ 0.099, 0.096 (2 s, 9H), 0.83–1.81 (m, 6H), 2.29 (dd, 0.5H, *J* = 2.2, 16.7 Hz), 2.41–2.62 (m, 2.5H), 2.69 (dd, 1H, *J* = 11.6, 15.3 Hz), 2.75–2.90 (m, 1H), 2.97 (br m, 0.5H), 3.12 (br m, 0.5H), 3.25 (br m, 0.5H), 5.31 (s, 0.5H), 5.33 (s, 0.5H), 9.66 (t, 0.5H, *J* = 2.4 Hz), 9.72 (dd, 0.5H, *J* = 2.4, 6.8 Hz).

(±)-Octahydro-3,11-epoxy-11*H*-pyrano[4,3-*f*]-1,2-benzodioxan-9(3*H*)-one (24). Through a solution of aldehyde–acid **64** in dry CH_2Cl_2 (30 mL) at −78 °C was passed a stream of O_3/O_2 (6.0 psi, 70 V, 0.4 L/min) for 2 min. After the resultant solution was purged with argon, Amberlyst 15 (200 mg) was added, and the mixture was allowed to warm to ambient temperature. After 20 h, the resin was filtered off, and the filtrate was concentrated *in vacuo* to 128 mg of yellow oil, which was further purified via flash-column chromatography with silica gel and EtOAc/hexane. In this fashion, 119 mg or 58% yield of lactone **24** as a pale yellow oil was obtained. Crystallization from EtOAc/hexane provided analytically pure microprisms of **24**, mp 97.5–98.0 °C. ^{1}H NMR: δ 1.23–1.48 (m, 3H), 1.63 (ddd, 1H, *J* = 2.1, 5.5, 13.6 Hz), 1.73–1.97 (m, 4H), 2.21 (dd, 1H, *J* = 1.0, 18.7 Hz), 2.33 (m, 1H), 2.48 (ddd, 1H, *J* = 2.6, 10.6, 13.6 Hz), 2.94 (dd, 1H, *J* = 8.0, 18.7 Hz), 5.44 (AB system, 1H, *J* = 2.1, 2.6 Hz), 6.06 (s, 1H). IR (KBr): 2950, 1740, 1205, 1080, 1038 cm^{-1}. DCIMS-NH_3: *m*/*z* (rel int) 243 (M + NH_4^+, 100), 228 (11), 181 (10).

2-(*tert*-Butylperoxy-)-2-ethylbutan-1-ol (66). To a solution of *m*-chloroperbenzoic acid (1.8 g of 80%, 10.5 mmol) in dry CH_2Cl_2 (35 mL) at 0 °C was added 2-ethylbutene (1.0 mL, 8.2 mmol). After 1 h at 0 °C, the solid was filtered off and washed with pentane. To the filtrate containing oxirane **65** was added a solution of *tert*-butyl hydroperoxide (11 mL of 3 M in isopentane). The solution was cooled to 0 °C, and *p*-toluenesulfonic acid (50 mg) was added. After 90 min, the reaction contents were poured into cold 10% aqueous KOH and extracted with Et_2O (100 mL). The ethereal layer was washed with H_2O (2 × 100 mL), dried over $MgSO_4$, and evaporated cold behind an explosion shield to give 2-(*tert*-butylperoxy)-2-ethylbutanol (**66**) as a colorless oil, 1.6 g, (80%), which was used immediately without further purification. ^{1}H NMR (90 MHz): δ 0.70–0.93 (m, 6H), 1.21, 1.22 (2 s, 9H), 1.33–1.75 (m, 4H), 3.56 (m, 2H).

2-(*tert*-Butylperoxy)-2-ethylbutan-1-ol, Propionate Ester (22). To a solution of crude peroxy alcohol **66** (800 mg, 4.2 mmol) and pyridine (0.5 mL) in CH_2Cl_2 (15 mL) was added propionic anhydride (0.58 mL, 4.5 mmol). After 10 min, DMAP (12 mg) was added. After 21 h, the reaction was poured into 5% aqueous NaOH (100 mL) and extracted with hexane (100 mL). The separated hexane layer was washed with 5% aqueous NaOH (100 mL) and saturated NH_4Cl (3 × 50 mL), dried over $MgSO_4$, and evaporated cold behind an explosion shield to give a crude oil, which was purified via flash-column chromatography with SiO_2. After gradient elution with EtOAc/hexane, **22** was obtained as a colorless oil, 594 mg (57%). ^{1}H NMR: δ 0.87 (t, 6H, *J* = 7.6 Hz), 1.15 (t, 3H, *J* = 8.0 Hz), 1.20 (s, 9H), 1.49 (dd, 2H, *J* = 7.4, 14 Hz), 1.53–1.71 (m, 2H), 2.34 (q, 2H, *J* = 7.6 Hz), 4.14 (s, 2H). ^{13}C NMR: δ 7.3 (2), 9.2, 23.8 (2), 26.5 (3), 27.7, 64.6, 78.5, 82.7, 174.3. IR (neat): 2990, 1747, 1200 cm^{-1}.

2-(*tert*-Butylperoxy)-2-ethylbutan-1-ol, Butanoate Ester (23). To a solution of crude **66** (800 mg, 4.2 mmol) and pyridine (0.5 mL) in CH_2Cl_2 (15 mL) was added butyric anhydride (0.73 mL, 4.5 mmol). After 10 min, DMAP (12 mg) was added. After 21 h, the reaction was poured into 5% aqueous NaOH (100 mL) and extracted with hexane. The separated hexane layer was washed with 5% aqueous NaOH (100 mL) and saturated aqueous NH_4Cl (3 × 50 mL), dried over $MgSO_4$, and evaporated cold behind an explosion shield to afford the crude product which was purified via flash-column chromatography with SiO_2. After gradient elution with EtOAc/hexane, **23** was isolated as a colorless oil, 440 mg (40%). ^{1}H NMR: δ 0.87 (t, 6H, *J* = 7.6 Hz), 0.96 (t, 3H, *J* = 7.2 Hz), 1.20 (s, 9H), 1.46–1.73 (m, 8H), 2.31 (t, 2H, *J* = 7.6 Hz), 4.14 (s, 2H). ^{13}C NMR: δ 7.3 (2), 13.7, 18.5, 23.8 (2), 26.5 (3), 36.4, 64.5, 78.5, 82.7, 173.6. IR (neat): 2980, 2940, 1743, 1462, 1365, 1205, 1185 cm^{-1}.

Acknowledgment. We wish to thank the U.S. Army Medical Research and Development Command for support of this work (Contribution No. 1995) under Contract Number DAMD17-88-C-8007 as well as George Detre for NMR spectra, and Dr. Robert Engle of WRAIR for many helpful discussions.

Supplementary Material Available: Figure 2 and Table V containing residual values from the CoMFA study in plotted and tabular format, respectively (2 pages). Ordering information is given on any current masthead page.

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