Articles

Structure−Activity Relationships of the Antimalarial Agent Artemisinin. 5. Analogs of 10-Deoxoartemisinin Substituted at C-3 and C-9

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Novel 3- and 9-substituted analogs (**4**−**19**) of 10-deoxoartemisinin, **3**, were prepared from the corresponding known lactones by one-pot reduction with sodium borohydride and boron trifluoride etherate. Reproducibility problems associated with this heterogeneous reaction were encountered on small reaction scales, and thus alternative methodology was sought for this reduction. Conversion of the lactones to tetrahydropyrans via the corresponding intermediate lactols was made more reproducible using a two-step sequence involving low-temperature reduction with diisobutylaluminum hydride followed by deoxygenation with boron trifluoride etherate in the presence of triethylsilane. In this manner, 10-deoxoartemisinin (**3**) could be obtained from artemisinin (**1**) in greater than 95% overall yield. All analogs were tested *in vitro* against W-2 and D-6 strains of *Plasmodium falciparum*. Several of the analogs were much more active than the natural product (+)-artemisinin (**1**) or 10-deoxoartemisinin (**3**). Conventional structure−activity relationships are discussed in relation to the bioassay data.

(+)-Artemisinin (**1**), a naturally occurring peroxidic cadinane sesquiterpene possessing good antimalarial activity,[1,2] has been the subject of many total syntheses[3] and structure−activity relationship (SAR) studies.[4−6] Much of this intense interest stems from the need for new antimalarial drugs with unconventional structures and novel modes of action to be used for the treatment of pervasive strains of drug-resistant *Plasmodium falciparum*.[7] Simple derivatives obtained by stepwise modification to the lactone carbonyl such as artemether (**2**, R = Me) or sodium artesunate (**2**, R = COCH$_2$CH$_2$-COONa) have provided clinically useful drugs that have been marketed in Southeast Asia. Complete removal of the lactone carbonyl results in 10-deoxoartemisinin (**3**), a compound with excellent potency and chemical stability.[5]

1   **2**   **3**
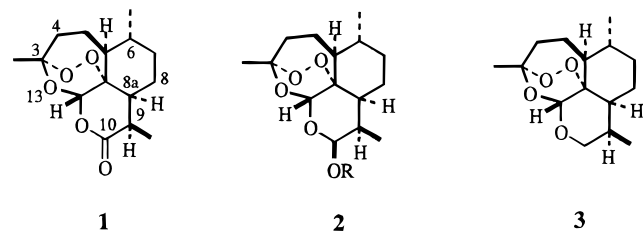
The mechanism of action of these antimalarials has also been the subject of scrutiny as this knowledge is likely to provide the basis for rational drug design efforts.[8−10] While the mode of action of artemisinin and its analogs is not known with absolute certainty, it is generally accepted from *in vitro* studies that scission of the peroxide bond by Fe(II) leads to an intermediate oxyradical that rapidly abstracts a neighboring hydro-
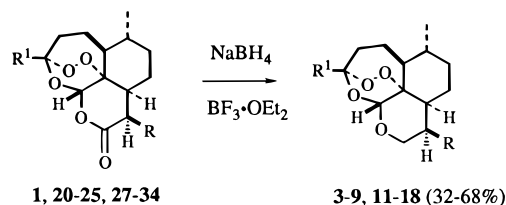
gen atom from the C-4 position resulting in a more stable carbon radical.[11] The fate of this radical intermediate is not understood but is actively under investigation.[12] Activity is improved if groups which stabilize radicals are placed at C-4β but not at C-4α.[13] This behavior is also observed in simple trioxanes which fragment to carbon radicals.[14] Furthermore, total synthesis of 13-carbaartemisinin, in which the nonperoxidic trioxane ring oxygen atom at O-13 is replaced by a methylene, leads to an abrupt loss of activity signaling the mechanistic importance of an intact trioxane ring.[15] While the intermediate carbon radical at C-4 is capable of fragmentation by a deketalization-like process, it would appear that stabilization of the radical at C-4 by the adjacent oxygen atom at O-13 is crucial for antimalarial potency. These studies have proven to be useful in the design of new antimalarials.[13]

In addition to mechanism-based design which focuses upon a single determinant in drug activity, empirical methods, such as quantitative structure−activity relationship (QSAR) studies, are useful in addressing more elusive structure−activity components. Very few reports of a QSAR model for the artemisinin class of antimalarials exist; a classical QSAR study based upon derivatives of dihydroartemisinin was reported a number of years ago[16] and was only recently followed by 3D-QSAR studies from our laboratory.[17,6] In an effort to expand upon our pharmacophore model, we felt that it would be necessary to obtain analogs substituted in as many available positions as possible about the tetracyclic framework of the parent structure **1**. Thus far we have reported comprehensive modifications to C-9[17] and C-3,[18] as well as the heteroatom-modified N-11 analogs.[19] In this paper we focus upon the effect of the 10-deoxomodification of C-3- and C-9-substituted analogs of artemisinin on antimalarial potency. The results are

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Scheme 1

1, 20-25, 27-34 → **3-9, 11-18** (32-68%)

1, 3 R = CH$_3$; R^1 = CH$_3$ **12, 28**, R = H; R^1 = (CH$_2$)$_2$CH$_3$

4, 20, R = H; R^1 = CH$_3$ **13, 29**, R = H; R^1 = (CH$_2$)$_3$CH$_3$

5, 21, R = CH$_2$CH$_3$; R^1 = CH$_3$ **14, 30**, R = H; R^1 = CH$_2$CH(CH$_3$)$_2$

6, 22, R = (CH$_2$)$_2$CH$_3$; R^1 = CH$_3$ **14, 31**, R = H; R^1 = (CH$_2$)$_4$C$_6$H$_5$

7, 23, R = (CH$_2$)$_3$CH$_3$; R^1 = CH$_3$ **16, 32**, R = H; R^1 = (CH$_2$)$_2$C$_6$H$_5$

8, 24, R = (CH$_2$)$_4$CH$_3$; R^1 = CH$_3$ **17, 33**, R = H; R^1 = (CH$_2$)$_3$C$_6$H$_4$Cl

9, 25, R = (CH$_2$)$_3$C$_6$H$_5$; R^1 = CH$_3$ **18, 34**, R = H; R^1 = (CH$_2$)$_2$CO$_2$Et

**11, 27**, R = H; R^1 = CH$_2$CH$_3$

intended for inclusion into a comparative molecular field analysis (CoMFA) which will be reported separately.

Chemistry

Upon treatment of the natural product (+)-artemisinin (**1**) with NaBH$_4$ and BF$_3$ etherate in methanol−THF by Jung's procedure[20] (1−100 g), known product **3** was obtained in 68% yield. When this procedure was applied to **1** or previously reported lactones substituted at C-9 (**20−25**) or C-3 (**27−34**) on small scales (20−100 mg), yields of **3−9** and **11−18** were dramatically variable from run to run. It was found that without suitable modification to the reported procedure, small-scale reactions would frequently result in extensive decomposition. In fact, even with suitable monitoring of the reaction for completion, the deoxo analog **10** could not be prepared by this approach. Thus, it was discovered that this reduction could only be safely achieved on small scales by periodic interruption for TLC monitoring. In this manner, the C-9-substituted analogs (**4−9**) of artemisinin were obtained in yields ranging of 35−58%, while C-3-substituted (C-9 = desmethyl) analogs **11−18** were furnished in 32−64% yield (Scheme 1).

We also found that ester functionality was compatible with this reduction sequence. Thus, treatment of the ester lactone **34** with sodium borohydride and boron trifluoride etherate provided the tetrahydropyran **18** in 55% purified yield. Upon reaction with sodium hydroxide, **18** underwent simple ester hydrolysis to furnish the carboxylic acid **19**.

In order to access the elusive haloaromatic species **10**, alternative approaches were examined. As shown in Scheme 2, alkylation of the synthetic intermediate **35** with 3-(*p*-chlorophenyl)propyl bromide[21] led, as expected, to clean production of the erythro acid **36**. As previously described,[22] low-temperature ozonolysis of **36** followed by *in situ* acidification proceeded, through a series of rearrangements, to the desired lactone **26**. Attempted reduction of **26** using the Jung/McChesney methodology[20] (borohydride/Lewis acid) was unsuccessful in providing **10**. Rather than examine this reaction in detail, the short term goal of rapidly furnishing material for *in vitro* antimalarial bioassay was accomplished by alteration of the oxidation state prior to ozonolysis. Thus, reduction of **36** with LiAlH$_4$ in ether gave alcohol **37** in good yield. Surprisingly, its ozonolysis/cyclization to **10** was accomplished in only 7% yield!
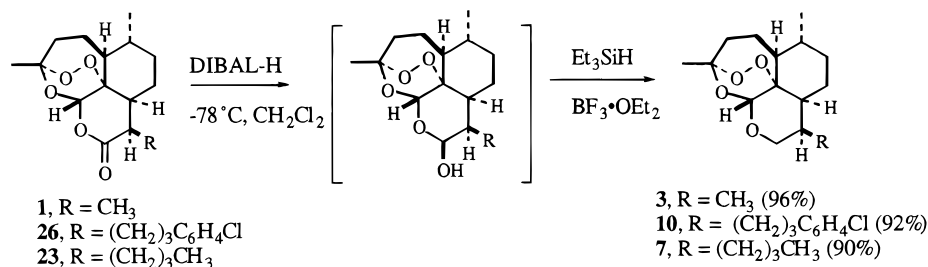
Scheme 2[a]

R = (CH$_2$)$_3$C$_6$H$_4$Cl
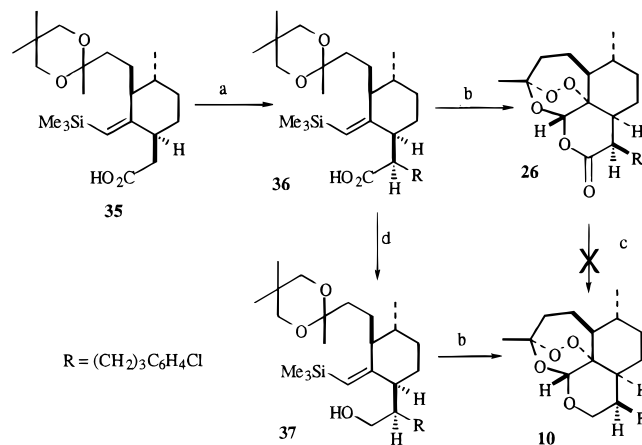
[a] Key: (a) 2 LDA, 50 °C; R-Br, 25 °C; (b) O$_3$, CH$_2$Cl$_2$, −78 °C, then H$_3$O$^+$, SiO$_2$; (c) NaBH$_4$, BF$_3$·OEt$_2$; (d) LiAlH$_4$, Et$_2$O.

While immediate gratification was thus obtained, the overall approach to these compounds seemed less than satisfactory, particularly in light of the enhanced biological activity of analog **10**. Apparently, the problem of reproducibility in these reductions was related to some aggregate involving the heterogeneous nature of the reaction, the inherent difficulties in accurately transferring minute quantities of hygroscopic reductant, and the need to employ refluxing conditions to complete the reduction. Lower reaction temperatures combined with homogeneous conditions could provide a means to reproducibly access 10-deoxo analogs of artemisinin, and we therefore set out to examine this possibility. Based on the precedented reduction of 2*H*-dihydropyrones,[23] the combination of Lewis acid and hydride source exemplified by Et$_3$SiH/BF$_3$ seemed ideally suited to our needs (Scheme 3). While (+)-artemisinin (**1**) could not be reduced directly to 10-deoxoartemisinin (**3**) with Et$_3$-SiH/BF$_3$, dihydroartemisinin (**2**, R = H) was smoothly converted at low temperature to the desired tetrahydropyran **3** in 96% yield. Further, this method was insensitive to scale, being readily accomplished on the gram or milligram level. It was also found that small-scale reductions could be more conveniently conducted utilizing diisobutylaluminum hydride in place of sodium borohydride. As applied to the problematical case, it was found that the lactone **26** could be reduced to lactol and thence **10** as outlined in Scheme 3 in excellent yield. Furthermore, the yield for the conversion of lactone **23** into 9-butyl-10-deoxoartemisinin (**7**) could be similarly improved from 58% to 90%.

Biological Activity

The analogs **1** and **3−19** 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[24,25] 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 chloroquine-sensitive but mefloquine-resistant. The relative potency values for these analogs were derived from the IC$_{50}$ value for artemisinin (**1**) divided by their IC$_{50}$ values (Table 1) and then adjusted

Scheme 3

1, R = CH_3
26, R = $(CH_2)_3C_6H_4Cl$
23, R = $(CH_2)_3CH_3$

3, R = CH_3 (96%)
10, R = $(CH_2)_3C_6H_4Cl$ (92%)
7, R = $(CH_2)_3CH_3$ (90%)

Table 1. Relative *in Vitro* Antimalarial Activity of 3- and 9-Substituted Analogs of 10-Deoxoartemisinin against *P. falciparum*

structure	R^1	R	relative activity[a]		anal. (C, H)
			D-6	W-2	
3	CH_3	CH_3	659	567	$C_{15}H_{24}O_4$
4	CH_3	H	237	190	$C_{14}H_{22}O_4$
5	CH_3	CH_3CH_2	914	466	$C_{16}H_{26}O_4$
6	CH_3	$CH_3(CH_2)_2$	473	550	$C_{17}H_{28}O_4$
7	CH_3	$CH_3(CH_2)_3$	5826	2090	$C_{18}H_{30}O_4$
8	CH_3	$CH_3(CH_2)_4$	170	145	$C_{19}H_{32}O_4$
9	CH_3	$C_6H_5(CH_2)_3$	5073	2506	$C_{23}H_{32}O_4$
10	CH_3	p-$ClC_6H_4(CH_2)_3$	6991	3317	$C_{23}H_{31}ClO_4$
11	CH_3CH_2	H	10	10	$C_{15}H_{24}O_4$
12	$CH_3(CH_2)_2$	H	722	685	$C_{16}H_{26}O_4$
13	$CH_3(CH_2)_3$	H	653	556	$C_{17}H_{28}O_4$
14	$(CH_3)_2CHCH_2$	H	183	250	$C_{17}H_{28}O_4$
15	$C_6H_5(CH_2)_4$	H	336	380	$C_{23}H_{32}O_4$
16	$C_6H_5(CH_2)_2$	H	6	2	$C_{21}H_{28}O_4$
17	p-$ClC_6H_4(CH_2)_3$	H	13	28	$C_{22}H_{31}ClO_4$
18	$(CH_2)_2CO_2Et$	H	422	506	$C_{18}H_{28}O_6$
19	$(CH_2)_2CO_2H$	H	0.09	0.09	$C_{16}H_{24}O_6$

[a] Relative activity = $100 \times [IC_{50}(\text{artemisinin, control value})/IC_{50}(\text{analog})]MW(\text{analog})/MW(\text{artemisinin})$, i.e., relative activity of artemisinin = 100.

for molecular weight differences by multiplication of the ratio of the molecular weight of the analog divided by the molecular weight of artemisinin. This approach to reporting activity is based in part on the fact that the analogs were tested on different occasions in which the IC_{50} for the control, artemisinin, had varied anywhere from 0.4 to 9 ng/mL based on parasitemia levels and clone. For example, an IC_{50} value of 0.099 ng/mL was determined for **10** in the W-2 clone, while in parallel artemisinin had an IC_{50} value of 2.28 ng/mL. On another occasion, artemisinin had an IC_{50} value of 0.99 ng/mL.

Structure−Activity Relationships

For the analogs of 10-deoxoartemisinin (**3**) substituted at C-9 (**5**−**10**), or the desmethyl analog **4**, certain qualitative relationships emerge upon examination of Table 1. In the W-2 clone, the homologous series ranging from H to propyl shows a relatively steady potency at 5 times the activity of control (artemisinin, **1**). For butyl, **7**, a dramatic improvement in potency was seen at about 21 times control, while at pentyl, **8**, activity had dropped off somewhat to around 1.5 times the potency of artemisinin. We have found that activity in the W-2 clone is generally paralleled by the more sensitive D-6 clone. Thus, potency ranged from 2 times control for analog **4** up to 58 times control for the butyl

derivative **7** and finally decreased as expected for the pentyl homolog **8**. Profound potency enhancement was observed for the 3-aryl propanes **9** and **10** in both W-2 and D-6 clones, being in the range of 25−70 times more potent than control. *To our knowledge, analogs 7, 9, and 10 are the most potent analogs of artemisinin yet reported in vitro which lack the 10-acetal linkage.*

It is interesting to note that the lactones **20**−**25** corresponding to the above tetrahydropyrans **4**−**9** (with the exception of **26**, the precursor to **10**) showed a similar but attenuated trend in activities. For example, lactones **21** and **22** were the most potent in this series (ethyl and propyl) at about 12 times the activity of artemisinin, but potency dropped significantly with butyl (**23**) and pentyl (**24**). Similarly, the 3-phenylpropyl lactone **25** was reasonably potent at 4−6 times control. It is clear that removal of the lactone carbonyl in the series **3**−**10** provides excellent potency enhancement and that overall trends relative to the lactones **20**−**26** are not radically altered but do seem to be offset somewhat (e.g., ethyl most potent in lactone series and butyl most potent in tetrahydropyran series).

For the C-3 ethyl-substituted analog **11**, a mere one-carbon homologation of compound **4** leads to a significant drop in potency. However, homologation by two carbons (C-3 propyl analog **12**) results in roughly a 70-fold improvement over **11**. For C-3 butyl **13**, activity

Table 2. Calculated Logarithmic Partition Coefficients (log P) for 10-Deoxoartemisinin Analogs

structure	R^1	R	calcd log P CLogP[a]	Tsar[b]
3	CH_3	CH_3	2.58	3.26
4	CH_3	H	2.07	2.86
5	CH_3	CH_3CH_2	3.11	3.65
6	CH_3	$CH_3(CH_2)_2$	3.64	4.05
7	CH_3	$CH_3(CH_2)_3$	4.17	4.45
8	CH_3	$CH_3(CH_2)_4$	4.70	4.84
9	CH_3	$C_6H_5(CH_2)_3$	5.06	5.66
10	CH_3	$p\text{-}ClC_6H_4(CH_2)_3$	5.77	6.18
11	CH_3CH_2	H	2.59	3.42
12	$CH_3(CH_2)_2$	H	3.12	3.82
13	$CH_3(CH_2)_3$	H	3.65	4.22
14	$(CH_3)_2CHCH_2$	H	3.52	4.15
15	$C_6H_5(CH_2)_4$	H	5.07	5.83
16	$C_6H_5(CH_2)_2$	H	4.01	5.04
17	$p\text{-}ClC_6H_4(CH_2)_3$	H	5.25	5.95
18	$(CH_2)_2CO_2Et$	H	2.08	2.96
19	$(CH_2)_2CO_2H$	H	1.14	2.59

[a] Reference 26. [b] Reference 27.

had dropped only slightly. However, the effect of branching (i.e., C-3 isobutyl, **14**) is apparently detrimental toward antimalarial potency. This same effect was noted for C-9-substituted lactones: *n*-Alkanes were usually significantly more active than the homologous isoalkanes. Interestingly, the effect on potency of arylalkyl substitution at C-3 is completely different than noted in the C-9 series. The 3-(*p*-chlorophenyl)propyl-substituted analog **17**, isomeric with highly potent 9-(*p*-chlorophenyl)propyl analog **10**, is practically devoid of antimalarial activity. While the ethylphenyl derivative **16** is impotent, 4-phenylbutyl homolog **15** is about 3 times more active than control. These results support the notion that *antimalarial potency among artemisinin analogs cannot be explained on the sole basis of hydrophobicity.*

Calculated log P data (CLogP)[26] for artemisinin analogs, previously shown to correlate reasonably well with measured log P,[19] has been obtained for these analogs as shown in Table 2. For the 3-(*p*-chlorophenyl)propyl-substituted analogs **17** and **10** illustrated above, log P data show that **17** is roughly as lipophilic as **10**. Subtraction of the fragment constant π for a methyl group of about 0.56 brings the calculated log P for **10** of 5.21 (derived by 5.77−0.56) into parity with the calculated log P of **17** of 5.25. Furthermore, using the entire dataset and attempting simple regression analysis in Tsar[27] with bulk independent variables such as log P or molar refractivity was fruitless, yielding r^2 values approaching zero. Polynomial regression analysis after deletion of **16** provided the "best" statistical correlation with $r^2 = 0.348$, where log RA = −8.68 + 3.93 log P − 0.396 (log $P)^2$. Verloop B_1 (length) parameters and log P were correlated loosely with log relative activity (log RA), giving log RA = 0.65(CLogP) − 0.16B_1 − 0.14; $r^2 = 0.366$. More extensive multiple regression analyses in Tsar combining other parameters such as moment of inertia, dipole, total dipole, bond dipole, charges, topological, connectivity, and shape indices were likewise without statistical significance.

At a glance, the removal of the lactone carbonyl might not be expected to alter the postulated primary mode of antimalarial action put forth by Posner and Meshnick. While it is true that 10-deoxoartemisinin (**3**) undergoes Fe(II)-promoted rearrangement to give dif-

ferent products than those provided by artemisinin (**1**), the biochemical significance is not clear.[15] The existence of a nontrivial structure−activity correlation for these analogs suggests the possibility of selective transport-mediated phenomena. Some evidence for this thesis is provided by the observation of enhanced uptake of dihydroartemisinin into parasitized, over nonparasitized, red blood cells.[28] Along these lines, we found it interesting to note that while the ester **18** demonstrated activity comparable to 10-deoxoartemisinin (**3**), the carboxylic acid **19** was virtually devoid of antimalarial activity. Further, free carboxylic acids attached at either C-9 or N-11 positions demonstrated a thorough lack of activity.[17−19]

Experimental Section

All solvents were purchased as reagent grade and, where appropriate, were distilled from CaH_2 and stored over dry 4 Å sieves for at least 1 day prior to use. Solvent and reagent transfers were accomplished via dried syringe, and all reactions were routinely conducted under an inert atmosphere unless otherwise indicated. Flash chromatography was accomplished using silica gel (Whatman 60, 230−400 mesh). Preparative thin-layer chromatography utilized 1, 1.5, or 2 mm thick Analtech Uniplates with F-256. Silica gel thin-layer chromatography plates (250−μm) were also purchased from Analtech. Unless otherwise noted, all NMR analyses were conducted in $CDCl_3$, on a Varian VXR-300 spectrometer, and referenced to chloroform at δ 7.27. IR spectra were recorded on a Digilab FTS-40 FT-IR and performed neat unless otherwise noted. Mass spectral data were obtained on a VG 7070E-HF instrument. Elemental analyses were within 0.4% as determined by Desert Analytics, Tucson, AZ.

Procedure for Reduction of Artemisinin Analogs to 10-Deoxoartemisinin Analogs Using NaBH$_4$/BF$_3$. Under an inert atmosphere, a 0 °C solution of the artemisinin analog (0.1 mmol) and BF$_3$/Et$_2$O (360 μL) in dry THF (0.6 mL) was added dropwise via cannula to an ice-cold stirred solution of NaBH$_4$ (8 mg) in dry THF (0.6 mL). The reaction mixture was stirred cold for 1 h and then heated at 60 °C in 5 min intervals, monitoring for reaction progress by TLC. Total reaction times varied but were commonly 10−30 min. After cooling again to 0 °C, the reaction mixture was poured over an ice−water slurry and extracted three times with ether. The combined organic layer was dried over anhydrous MgSO$_4$, filtered, and evaporated *in vacuo* to give the crude product. Purification was accomplished on 1.5 mm silica gel preparative TLC plates eluting with 20% EtOAc/hexane. Crystallization was usually accomplished from cold hexane or pentane. Pure products were stored in the freezer.

Octahydro-3,6-dimethyl-3,12-epoxy-12H-pyrano[4,3-*j*]-1,2-benzodioxepin (4). From 9-desmethylartemisinin (**20**) (0.06 g, 0.22 mmol) was obtained 31 mg (55%) of pure **4** as a white solid (mp 87 °C). ^{1}H NMR: δ 5.21 (s, 1H), 3.97 (dd, 1H, J = 4.7, 11.9 Hz), 3.79 (ddd, 1H, J = 2.05, 12.0, 13.0 Hz), 2.41−2.52 (m, 1H), 2.34−2.45 (ddd, 1H, J = 3.9, 13.4, 14.5 Hz), 2.01−2.09 (ddd, 2H, J = 3.06, 4.77, 14.6 Hz), 1.85−1.94 (m, 1H), 1.67−1.79 (m, 2H), 1.46 (s, 3H), 1.25−1.31 (dd, 1H, J = 6.48, 11.4 Hz), 1.11−1.19 (m, 2H), 0.98 (d, 3H, J = 6.3 Hz). IR: 2949, 2921, 2865, 1467, 1370, 1255, 1090, 1052, cm^{-1}. CIMS: m/z 272 (M + NH$_4$), 255 (M + H), 237 (M + H − H$_2$O), 151.

Octahydro-3,6-dimethyl-9-ethyl-3,12-epoxy-12H-pyrano[4,3-*j*]-1,2-benzodioxepin (5). From 9-ethylartemisinin (**21**) (0.03 g, 0.10 mmol) was obtained 10 mg (35%) of pure **5**. ^{1}H NMR: δ 5.21 (s, 1H), 3.83 (ddd, 1H, J = 1.1, 4.3, 11.6 Hz), 3.44 (dd, 1H, J = 11.7, 11.7 Hz), 2.33−2.42 (m, 1H), 2.3 (ddd, 1H, J = 4.0, 13.5, 14.5 Hz), 2.02 (ddd, 1H, J = 3.1, 4.9, 14.5 Hz), 1.85−1.94 (m, 1H), 1.70 (dq, 1H, J = 3.2, 13.1 Hz), 1.43 (s, 3H), 1.15 (dq, 2H, J = 7.0, 14.9 Hz), 0.97 (d, 3H, J = 6.2 Hz), 0.90 (t, 3H, J = 7.3 Hz). IR: 2958, 2928, 2871, 1460, 1374, 1093, 1061 cm^{-1}. CIMS: m/z 300 (M + NH$_4$), 283 (M + H), 265 (M + H − H$_2$O), 251, 237, 179.

Octahydro-3,6-dimethyl-9-propyl-3,12-epoxy-12H-pyrano[4,3-*j*]-1,2-benzodioxepin (6). From 9-propylartemisinin

(**22**) (0.05 g, 0.16 mmol) was obtained 14 mg (29%, 37% based on recovered starting material) of pure **6**. ¹H NMR: δ 5.20 (s, 1H), 3.80 (ddd, 1H, J = 1.0, 4.3, 11.7 Hz), 3.42 (dd, 1H, J = 11.7, 11.7 Hz), 2.43–2.52 (m, 1H), 2.38 (ddd, 1H, J = 4.3, 13.4, 14.6 Hz), 2.01 (ddd, 1H, J = 3.0, 4.7, 14.7 Hz), 1.83–1.92 (m, 1H), 1.69 (ddd, 1H, J = 3.0, 4.7, 14.7 Hz), 1.47–1.62 (m, 3H), 1.43 (s, 3H), 1.22–1.34 (m, 4H), 1.01–1.10 (m, 2H), 0.95 (d, 3H, J = 6.3 Hz), 0.89 (t, 3H, J = 7.3 Hz). IR: 2958, 2924, 2873, 2852, 1461, 1373, 1193, 1133, 1099, 1064 cm⁻¹. DCIMS (NH₃): 315 (M + NH₄), 297 (M + H), 296 (M⁺), 294, 279. FABMS: m/z 297 (M + H), 295, 279, 264, 251.

Octahydro-3,6-dimethyl-9-butyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin (7). From 9-butylartemisinin (**23**) (0.06 g, 0.18 mmol) was obtained 0.03 g (58%) of pure **7**. ¹H NMR: δ 5.22 (s, 1H), 3.80 (ddd, 1H, J = 1.2, 4.1, 11.5 Hz), 3.46 (dd, 1H, J = 11.8, 11.8 Hz), 2.40–2.50 (m, 1H), 2.40 (ddd, 1H, J = 4.0, 13.5, 14.6 Hz), 2.03 (ddd, 1H, J = 3.1, 4.9, 14.4 Hz), 1.85–1.94 (m, 1H), 1.71 (dq, 1H, J = 3.3, 12.9 Hz), 1.50–1.62 (m, 4H), 1.45 (s, 3H), 1.21–1.38 (m, 5H), 0.98 (d, 3H, J = 6.2 Hz), 0.90 (t, 3H, J = 7.0 Hz). IR: 2945, 2925, 2858, 1461, 1373, 1098, 1064, 877 cm⁻¹. CIMS: m/z 328 (M + NH₄), 311 (M + H), 293, 275, 265, 207.

Octahydro-3,6-dimethyl-9-pentyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin (8). From 9-pentylartemisinin (**24**) (105 mg, 0.3 mmol) was obtained 0.04 g (40%) of pure **8**. ¹H NMR: δ 5.21 (s, 1H), 3.81 (ddd, 1H, J = 1.1, 4.2, 11.8 Hz), 3.46 (dd, 1H, J = 11.7, 11.7 Hz), 2.42–2.52 (m, 1H), 2.39 (ddd, 1H, J = 4.0, 13.5, 14.9 Hz), 2.04 (ddd, 1H, J = 3.1, 5.0, 14.5 Hz), 1.88–1.96 (m, 1H), 1.71 (dq, 1H, J = 3.4, 13.1 Hz), 1.44 (s, 3H), 1.24–1.28 (m, 5H), 0.96 (d, 3H, J = 6.2 Hz), 0.87 (t, 3H, J = 7.0 Hz). IR: 2952, 2924, 2869, 2856, 1465, 1130, 1097, 1066, 877 cm⁻¹. CIMS: m/z 342 (M + NH₄), 325 (M + H), 307, 289, 279, 265, 221.

Octahydro-3,6-dimethyl-9-(3-phenylpropyl)-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin (9). From 9-(3-phenylpropyl)artemisinin (**25**) (20 mg, 0.051 mmol) was obtained 10 mg (50%) of pure **9**. ¹H NMR: δ 7.15–7.34 (m, 5H), 5.21 (s, 1H), 3.80 (ddd, 1H, J = 1.1, 4.2, 11.5 Hz), 3.45 (dd, 1H, J = 11.7, 11.7 Hz), 2.57–2.70 (m, 2H), 2.50 (dddd, 1H, J = 4.0, 7.6, 11.6, 11.6 Hz), 2.39 (ddd, 1H, J = 4.0, 13.4, 14.5 Hz), 2.03 (ddd, 1H, J = 3.0, 4.8, 14.7 Hz), 1.89 (dddd, 1H, J = 2.9, 3.8, 6.7, 13.6 Hz), 1.63 (t, 2H, J = 7.7 Hz), 1.44 (s, 3H), 1.27 (dd, 2H, J = 6.4, 11.3 Hz), 0.96 (d, 3H, J = 6.2 Hz). IR: 2927, 2867, 1452, 1097, 1067, 877 cm⁻¹. CIMS: m/z 390 (M + NH₄), 373 (M + H), 355, 337, 327, 269.

Octahydro-3,6-dimethyl-9-[3-(*p*-chlorophenyl)propyl]-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin (10). To a solution of alcohol **36** (0.27 g, 0.5 mmol) in dry CH₂Cl₂ (50 mL) at −78 °C was bubbled a stream of O₃/O₂ (4 psi, 0.04 L/min, 80 V) for 5 min until the reaction mixture turned faint blue. The reaction mixture was then purged with O₂ followed by N₂. To the mixture were added silica gel (2.5 g) and 15% aqueous H₂SO₄ (250 μL). The mixture was then allowed to come to ambient temperature and was subsequently stirred for 4 days. The solids were filtered and washed with CH₂Cl₂ (20 mL) and EtOAc (20 mL). The filtrate was washed with aqueous saturated NaHCO₃, dried over anhydrous Na₂SO₄, and evaporated to give crude product which was purified by flash chromatography. Elution with hexane/EtOAc (80:20) gave pure **10**, 15 mg (7%). ¹H NMR: 7.12–7.30 (m, 4H), 5.19 (s, 1H), 3.78 (ddd, 1H, J = 1.3, 4.3, 7.2 Hz), 3.44 (dd, 1H, J = 11.7, 11.7 Hz), 2.60 (ddd, 2H, J = 5.1, 7.4, 7.4 Hz), 2.43–2.53 (m, 1H), 2.37 (ddd, 1H, J = 4.1, 13.4, 14.7 Hz), 2.01 (ddd, 1H, J = 3.0, 4.8, 14.7 Hz), 1.83–1.93 (m, 1H), 1.62 (t, 2H, J = 7.8 Hz), 1.42 (s, 3H), 1.25 (dd, 2H, J = 6.5, 11.1 Hz), 0.95 (d, 3H, J = 6.2 Hz). IR: 2926, 2913, 2866 1494, 1454, 1091, 1067 cm⁻¹. DCIMS (NH₃): m/z 424 (M + NH₄), 407 (M + H).

Octahydro-3-ethyl-6-methyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin (11). From 3-ethyl-9-desmethylartemisinin (**27**) (27 mg, 0.095 mmol) was obtained 11 mg (44%) of pure product **11**. ¹H NMR: δ 5.18 (s, 1H), 3.93 (dd, 1H, J = 4.2, 11.9 Hz), 3.75 (ddd, 1H, J = 1.7, 12.6, 12.6 Hz), 2.39 (dq, 1H, J = 4.8, 13.3 Hz), 2.27 (ddd, 1H, J = 3.9, 13.9, 13.9 Hz), 1.98–2.10 (ddd, 1H, J = 3.0, 4.6, 14.4 Hz), 1.84–1.96 (m, 1H), 1.68–1.78 (m, 3H), 1.22–1.28 (m, 2H), 1.1–1.18 (m, 2H), 0.96 (d, 3H, J = 6.8 Hz), 0.94 (t, 3H, J = 7.8 Hz). IR:

2966, 2924, 2902, 2877, 2850, 1465, 1249, 1092, 1064, 1027 cm⁻¹. FABMS: m/z 269 (M + H), 251, 223.

Octahydro-3-propyl-6-methyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin (12). From 3-propyl-9-desmethylartemisinin (**28**) (34 mg, 0.11 mmol) was obtained 18 mg (64%) of pure product **12** along with 4 mg of recovered starting material. ¹H NMR: δ 5.17 (s, 1H), 3.95 (ddd, 1H, J = 1.1, 4.7, 11.9 Hz), 3.76 (ddd, 1H, J = 2.1, 12.5, 12.5 Hz), 2.43 (dq, 1H, J = 4.8, 13.5 Hz), 2.29 (ddd, 1H, J = 4.0, 13.3, 14.4 Hz), 2.08 (ddd, 1H, J = 3.2, 4.6, 14.5 Hz), 1.82–1.94 (m, 1H), 1.62–1.72 (m, 4H), 1.32–1.56 (m, 4H), 1.24 (dd, 1H, J = 6.5, 11.2 Hz), 1.10–1.18 (m, 2H), 0.95 (d, 3H, J = 6.3 Hz), 0.88 (t, 3H, J = 7.3 Hz). IR: 2965, 2957, 2925, 2874, 2850, 1467, 1436, 1244, 1182, 1092, 1072, 1027, 897 cm⁻¹. FABMS: m/z 283 (M + H), 237, 151.

Octahydro-3-butyl-6-methyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin (13). From 3-butyl-9-desmethylartemisinin (**29**) (47 mg, 0.15 mmol) was obtained 10 mg (32%) of pure **13** along with 14 mg of recovered starting material. ¹H NMR: δ 5.17 (s, 1H), 3.96 (dd, 1H, J = 5.3, 12.4 Hz), 3.75 (ddd, 1H, J = 2.2, 12.5, 12.5 Hz), 2.38–2.52 (m, 1H), 2.29 (ddd, 1H, J = 4.0, 13.8, 13.8 Hz), 2.05 (ddd, 1H, J = 3.3, 4.7, 14.5 Hz), 1.84–1.96 (m, 1H), 1.64–1.82 (m, 4H), 1.22–1.32 (m, 3H), 1.10–1.18 (m, 2H), 0.95 (d, 3H, J = 6.2 Hz), 0.86 (t, 3H, J = 7.7 Hz). IR: 2955, 2933, 2915, 2870, 1467, 1159, 1093, 1074, 1028, 947 cm⁻¹. FABMS: m/z 297 (M + H), 279, 264, 251.

Octahydro-3-(2-methylpropyl)-6-methyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin (14). From 3-isobutyl-9-desmethylartemisinin (**30**) (16 mg, 0.05 mmol) was obtained 9 mg (64%) of the pure product **14**. ¹H NMR: δ 5.17 (s, 1H), 3.95 (dd, 1H, J = 4.6, 12.2 Hz), 3.74 (ddd, 1H, J = 2.3, 12.6, 12.6 Hz), 2.34–2.48 (m, 2H), 2.30 (ddd, 1H, J = 4.0, 13.3, 14.6 Hz), 2.02–2.11 (m, 1H), 1.83–1.94 (m, 2H), 1.50–1.72 (m, 3H), 1.18–1.26 (m, 2H), 1.08–1.17 (m, 1H), 0.95 (dd, 6H, J = 1.9, 8.4 Hz), 0.93 (d, 3H, J = 10.4 Hz). IR: 2953, 2949, 2931, 2924, 2878, 2864, 1467, 1188, 1092, 1075, 1030, 945, 900 cm⁻¹. FABMS: m/z 297 (M + H), 279, 264, 251.

Octahydro-3-(4-phenylbutyl)-6-methyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin (15). From 3-(4-phenylbutyl)-9-desmethylartemisinin (**31**) (36 mg, 0.093 mmol) was obtained 15 mg (44%) of the pure product **15**. ¹H NMR: δ 7.14–7.27 (m, 5H), 5.17 (s, 1H), 3.95 (dd, 1H, J = 4.2, 11.7 Hz), 3.75 (ddd, 1H, J = 2.1, 12.6, 12.6 Hz), 2.59 (t, 2H, J = 7.7 Hz), 2.39 (dq, 1H, J = 4.8, 13.5 Hz), 2.27 (ddd, 1H, J = 3.9, 13.9, 13.9 Hz), 2.00 (ddd, 1H, J = 3.2, 4.8, 14.6 Hz), 1.82–1.92 (m, 1H), 1.42–1.52 (m, 3H), 1.23 (dd, 2H, J = 6.4, 11.4 Hz), 1.09–1.18 (m, 2H), 0.95 (d, 3H, J = 6.2 Hz). IR: 2962, 2950, 2924, 2914, 2867, 2847, 1465, 1452, 1090, 1027, 946 cm⁻¹. FABMS: m/z 373 (M + H), 355, 327, 173.

Octahydro-3-(2-phenylethyl)-6-methyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin (16). From 3-(2-phenylethyl)-9-desmethylartemisinin (**32**) (89 mg, 0.25 mmol) was obtained 55 mg (64%) of the pure product **16**. ¹H NMR: δ 7.16–7.26 (m, 5H), 5.22 (s, 1H), 3.97 (dd, 1H, J = 4.7, 12.2 Hz), 3.77 (ddd, 1H, J = 1.7, 12.4, 12.4 Hz), 2.72–2.78 (m, 2H), 2.42–2.50 (m, 1H), 2.09 (ddd, 1H, J = 3.2, 4.2, 14.5 Hz), 1.96–2.03 (m, 2H), 1.62–1.80 (m, 2H), 1.25–1.30 (m, 3H), 1.11–1.20 (m, 2H), 0.97 (d, 3H, J = 6.3 Hz). IR: 2963, 2933, 2868, 2847, 1495, 1465, 1453, 1251, 1085, 1047, 1026, 700 cm⁻¹. FABMS: m/z 345 (M + H), 307, 289.

Octahydro-3-[3-(4-chlorophenyl)propyl]-6-methyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin (17). From 3-[3-(4-chlorophenyl)propyl]-9-desmethylartemisinin (**33**) (13 mg, 0.03 mmol) was obtained 7 mg (56%) of the pure product **17**. ¹H NMR: δ 7.06–7.24 (m, 4H), 5.16 (s, 1H), 3.95 (dd, 1H, J = 5.4, 11.3 Hz), 3.76 (ddd, 1H, J = 2.0, 12.5, 12.5 Hz), 2.59–2.50 (m, 2H), 2.36–2.48 (m, 1H), 2.27 (ddd, 1H, J = 3.9, 13.7, 13.7 Hz), 2.00 (ddd, 1H, J = 3.7, 3.7, 14.6 Hz), 1.82–1.92 (m, 1H), 1.63–1.73 (m, 4H), 1.24 (s, 2H), 1.10–1.20 (m, 2H), 0.94 (d, 3H, J = 6.3 Hz). IR: 2953, 2925, 2874, 2854, 1491, 1461, 1251, 1090, 1078, 1050, 1015 cm⁻¹. DCIMS (isobutane): m/z 393 (M + H), 392 (M⁺), 271, 240, 204.

Octahydro-3-(2-carboethoxyethyl)-6-methyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin (18). From 3-(2-carboethoxyethyl)-9-desmethylartemisinin (**34**) (16 mg, 0.16 mmol) was obtained 31 mg (55%) of pure product **18**. ¹H NMR: δ

5.17 (s, 1H), 4.10 (q, 2H, J = 7.1 Hz), 3.91 (dd, 1H, J = 4.5, 11.8 Hz), 3.73 (ddd, 1H, J = 2.1, 12.4, 12.4 Hz), 2.40−2.54 (m, 3H), 2.30 (ddd, 1H, J = 3.9, 13.4, 14.4 Hz), 1.96−2.06 (m, 3H), 1.82−1.95 (m, 1H), 1.62−1.74 (m, 2H), 1.22 (t, 3H, J = 7.1 Hz), 1.08−1.18 (m, 1H), 0.95 (d, 3H, J = 6.3 Hz). IR: 2927, 2916, 2851, 1737, 1730, 1315, 1251, 1191, 1180, 1093, 1037, 951 cm^{-1}. FABMS: m/z 341 (M + H), 323, 307, 289, 249.

Octahydro-3-(2-carboxyethyl)-6-methyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin (19). To a solution of ester **18** (12 mg) in 95% EtOH (0.5 mL) was added 10% NaOH (0.5 mL). The reaction mixture was stirred at ambient temperature for 3 h and then poured onto ice-cold water. The mixture was then neutralized with 10% HCl (0.5 mL) and extracted with EtOAc (3 × 5 mL), and the combined organic layer was washed with water (3 × 5 mL). The organic layer was then dried over MgSO$_4$, filtered, and evaporated to give a crude product which was purified on a 1.5 mm silica gel preparative plate (50% EtOAc/hexane) to give 4 mg (36%) of pure acid **19** as a white solid (mp 144−146 °C). ^{1}H NMR: δ 5.18 (s, 1H), 3.92 (dd, 1H, J = 4.2, 12.0 Hz), 3.75 (ddd, 1H, J = 2.8, 12.1, 12.1 Hz), 2.51−2.62 (m, 1H), 2.40 (dq, 1H, J = 4.5, 13.4 Hz), 2.31 (ddd, 1H, J = 3.9, 13.9, 13.9 Hz), 1.92−2.08 (m, 3H), 1.62−1.76 (m, 3H), 1.30−1.56 (m, 1H), 1.10−1.30 (m, 4H), 0.95 (d, 3H, J = 6.3 Hz). IR: 2979, 2963, 2926, 2852, 1735, 1463, 1457, 1261, 1018, 1101, 748 cm^{-1}. FABMS: m/z 313 (M + H), 308, 273, 257.

2,5,5-Trimethyl-2-[2′-[4″-[(1S)-carboxy-5-(p-chlorophenyl)pent-2-yl]-(1″R)-methyl-3″-[(trimethylsilyl)methylene]cyclohex-2″-yl]ethyl]-1,3-dioxane (36). To an ice-cold solution of diisopropylamine (469 μL, 3.3 mmol) in dry THF (4 mL) under N$_2$ was added butyllithium (1.36 mL of 2.5 M solution in hexane, 3.3 mmol). The mixture was stirred at 0 °C for 15 min and then cooled to −78 °C. The acid **35** (0.602 g, 1.52 mmol) in dry THF (4 mL) was added, and the mixture was allowed to warm to ambient temperature over 30 min and then heated at 50 °C for 2 h and recooled to 0 °C. 3-(p-Chlorophenyl)propyl bromide (0.888 g, 3.81 mmol) was then added via syringe, and the reaction mixture was stirred at room temperature for 5 h, poured into ice-cold saturated aqueous NH$_4$Cl solution (25 mL), and extracted with EtOAc (3 × 30 mL). The organic layer was washed with saturated NaCl (40 mL), dried (MgSO$_4$), filtered, and evaporated *in vacuo* to give 0.721 g (87%) of **36** as a viscous liquid. ^{1}H NMR: δ 7.23 (d, 2H, J = 8.3 Hz), 7.10 (d, 2H, J = 8.4 Hz), 5.26 (s, 1H), 3.54 (dd, 2H, J = 2.3, 11.6 Hz), 3.38−3.48 (m, 2H), 2.71 (br t, 2H, J = 10.5 Hz), 2.56 (m, 1H), 2.06 (br dd, 1H, J = 2.9, 10.7 Hz), 1.72−1.94 (m, 3H), 1.31 (s, 3H), 1.15 (m, 1H), 1.01 (s, 3H), 0.86−0.94 (m, 6H), 0.09 (s, 9H). IR: (KBr) 3400−2500, 1700, 1598, 1491, 1454, 1246, 1091, 861, 748 cm^{-1}. DCIMS (NH$_3$): m/z 566 (M + NH$_4$), 549 (M$^+$).

Octahydro-3,6-dimethyl-9-[3-(p-chlorophenyl)propyl]-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10(3H)-one (26). To a solution of acid **36** (0.65 g, 1.1 mmol) in dry CH$_2$Cl$_2$ (160 mL) at −78 °C was bubbled a stream of O$_3$/O$_2$ (4 psi, 0.04 L/min, 80 V) for 5 min until the reaction mixture turned faint blue. The reaction mixture was then purged with O$_2$ followed by N$_2$. To the mixture were added silica gel (2.5 g) and 15% aqueous H$_2$SO$_4$ (250 μL). The mixture was then allowed to come to ambient temperature and was subsequently stirred for 4 days. The solids were filtered and washed with CH$_2$Cl$_2$ (30 mL) and EtOAc (20 mL). The filtrate was washed with saturated aqueous NaHCO$_3$, dried over anhydrous Na$_2$SO$_4$, and evaporated to give a crude product which was purified by flash chromatography. Elution with hexane/EtOAc (80:20) gave pure **26**, 0.122 g (25%). ^{1}H NMR: δ 7.23 (d, 2H, J = 8.2 Hz), 7.09 (d, 2H, J = 8.3 Hz), 5.83 (s, 1H), 3.14−3.24 (m, 1H), 2.52−2.72 (m, 2H), 2.34−2.48 (m, 1H), 1.96−2.09 (m, 3H), 1.67−1.82 (m, 4H), 1.44 (s, 3H), 0.98 (d, 3H, J = 5.7 Hz). IR: 2951, 2925, 1740, 1491, 1112, 1031, 1000 cm^{-1}. CIMS: m/z 459 (M + K$^+$), 443 (M + Na$^+$), 409, 347.

2,5,5-Trimethyl-2-[2′-[4″-[1-hydroxy-5-(4-chlorophenyl)pent-2-yl]-(1″R)-methyl-3″-[(trimethylsilyl)methylene]cyclohex-2″-yl]ethyl]-1,3-dioxane (37). To an ice-cold solution of the (chlorophenyl)propyl acid **36** (0.548 g, 1 mmol) dissolved in THF (5 mL) was added LiAlH$_4$ (4 mL of 1 M solution in THF, 4 mmol). The reaction mixture was stirred

overnight at room temperature, cooled to 0 °C, quenched by dropwise addition of 2:1 H$_2$O:AcOH (4 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layer was sequentially washed with saturated NaHCO$_3$ solution (2 × 20 mL) and water (2 × 20 mL), dried over anhydrous MgSO$_4$, filtered, and evaporated *in vacuo* to give a crude product which was purified by flash chromatography to give 0.28 g (53%) of **37** as a viscous liquid. ^{1}H NMR: δ 7.14−7.28 (m, 4H), 5.19 (s, 1H), 3.68 (d, 2H, J = 3.2 Hz), 3.46−3.54 (m, 2H), 3.41 (dd, 2H, J = 9.2, 10.8 Hz), 2.56 (t, 2H, J = 7.4 Hz), 2.04−2.18 (m, 2H), 1.32 (s, 3H), 0.88−0.98 (m, 9H), 0.09 (s, 9H). IR: (KBr) 3600−3200, 2948, 2907, 2864, 1598, 1494, 1454, 1372, 1247, 1095, 825, 742, 694 cm^{-1}. DCIMS (NH$_3$): m/z 535 (M + H).

Procedure for Reduction of Artemisinin Lactone Analogs to 10-Deoxoartemisinin Analogs Using Diisobutylaluminum Hydride followed by Et$_3$SiH/BF$_3$. To a stirred solution of artemisinin (**1**) (90 mg, 0.319 mmol, 1.0 equiv) in 3 mL of dry CH$_2$Cl$_2$ at −78 °C was added DIBAL-H (335 μL, 335 mmol, 1.05 equiv, 1.0 M in hexanes). The dry ice/acetone bath was removed for long enough to allow complete dissolution of the substrate and then replaced (about 1 min). After 1.25 h, the reaction was quenched with 1 mL of saturated NaHCO$_3$, and the mixture was diluted with 3 mL of CH$_2$Cl$_2$ and allowed to warm to ambient temperature with stirring. The mixture was diluted with 25 mL of CH$_2$Cl$_2$ and washed (1 × 10 mL) with 10% HCl/saturated NH$_4$Cl (1:15, v/v). The CH$_2$Cl$_2$ layer was then dried (MgSO$_4$), filtered, and concentrated *in vacuo* to give 90 mg (100%) of a white solid which was pure enough for the next step. The lactol from above was dissolved in 3 mL of dry CH$_2$Cl$_2$ and cooled to −78 °C, whereupon 210 μL of Et$_3$SiH (1.31 mmol, 4.1 equiv) was added. The reaction mixture was stirred for 10 min, at which time 45 μL of BF$_3$·OEt$_2$ (0.366 mmol, 1.15 equiv) was added. The resultant solution was allowed to stir for 3 h at −78 °C, and the reaction was then quenched at −78 °C with 150 μL of pyridine (1.85 mmol, 5.8 equiv). After 5 min, the reaction mixture was poured into 10 mL of aqueous saturated NH$_4$Cl and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with NH$_4$Cl (2 × 15 mL), dried (MgSO$_4$), filtered, and concentrated *in vacuo* to give a white solid which was purified by PTLC (silica gel) eluting with 75:25 Et$_2$O/hexanes to give 82 mg (96%) of pure product **3** as a white crystalline solid. When this procedure was applied to lactones **23** and **26**, purified product tetrahydropyrans **7** and **10** were obtained in overall yields of 90% and 92%, respectively.

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