Structure−Activity Relationships of the Antimalarial Agent Artemisinin. 4. Effect of Substitution at C-3

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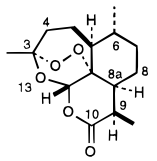
Novel antimalarial artemisinin analogs, 3-alkylartemisinins as well as 3-(arylalkyl)- and 3-(carboxyalkyl)artemisinins, were prepared via the synthetic intermediate **2**. Formation of the *N*,*N*-dimethylhydrazones **5** and **24** and then regio- and chemoselective deprotonation followed by alkylation provided initially alkylated hydrazones that upon chromatography gave ketones **6**−**13** and **25**−**30**. Direct ozonolysis of the ketones followed by *in situ* acidification lead directly to the formation of title compounds **14**−**21** and **31**−**36**. The analogs were tested *in vitro* against W-2 and D-6 strains of *Plasmodium falciparum* and found to be in some cases much more active than the natural product (+)-artemisinin. The results were included in structure−activity relationship (CoMFA) studies for further analog design.

(+)-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]



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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 scissioning of the peroxide bond by Fe(II) leads to an intermediate oxy radical that rapidly abstracts a neighboring hydrogen 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 *in vivo*.[12] Activity is improved if groups which stabilize radicals are placed at C-4β but not 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 modifications to C-9[17] as well as the heteroatom-modified N-11 analogs.[18] In this paper we focus upon the effect of modification to the C-3 position of artemisinin on antimalarial potency.[19] The results are intended for inclusion into a comparative molecular field analysis (3D-QSAR) which will be reported separately.

Chemistry

Both the C-9 and O-11 positions of the artemisinin nucleus have been shown to be available from the ketal acid **2** (Scheme 1), a synthetic intermediate in the total synthesis of (+)-artemisinin (**1**).[20] Because this intermediate could be readily produced in large quantities, investigation into the chemistry of the ketal-bearing side chain seemed a worthwhile goal as it could in principle provide analogs substituted at the C-3, C-4, and C-5 positions. Previously, we had demonstrated that a similar 5,5-dimethyl-1,3-dioxane ketal, differing only in the remote carboxylate side chain, could be selectively deketalized with aqueous oxalic acid-treated silica gel. Similarly, ketal **2** could be readily converted into the keto acid **4**. Yields in this reaction were found to be sensitive to conditions; at higher acid concentrations, protodesilylation led to formation of unwanted exomethylene byproduct **3**. When conducted carefully, yields were typically around 80%. In these circum-

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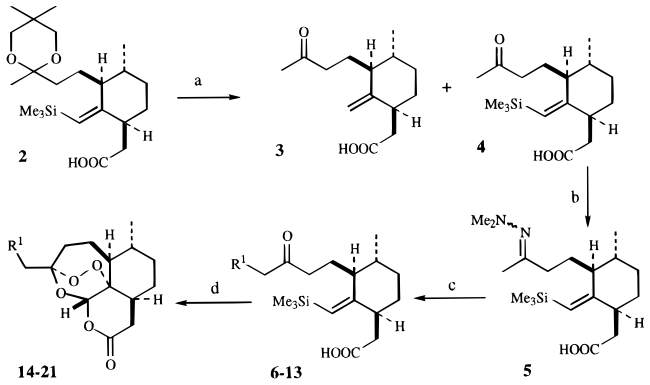
Scheme 1[a]



[a] Key: (a) aq oxalic acid, silica gel, CH_2Cl_2, 82%; (b) Me_2NNH_2, Δ, 92%; (c) 2 LDA, THF, HMPA, −78−20 °C, then R^1-X; (d) O_3, CH_2Cl_2, −78 °C, then aq H_2SO_4, silica gel, CH_2Cl_2.

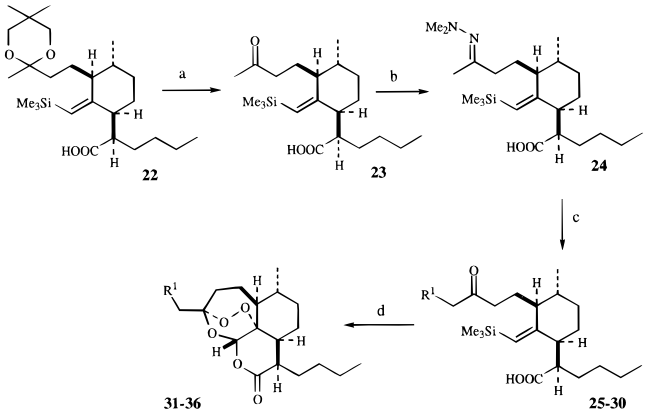
stances there appeared to be very little protodesilylation, the yields being less than theoretical due to facile adsorption of the keto acid **4** onto silica gel.

Initial attempts to alkylate the kinetic enolate of keto acid **4** (generated upon treatment with 2 equiv of LDA) with methyl iodide were unsuccessful due to formation of mono-, di-, and trimethylated ketones. This problem would presumably have worsened with less reactive alkylating agents, and therefore an alternate methodology was sought. Hydrazone chemistry appeared to offer the desired regioselectivity as it has been reported that the less substituted side of *N*,*N*-dimethylhydrazones is preferentially deprotonated, regardless of the hydrazone isomer (*E* or *Z*).[21,22]

The *N*,*N*-dimethylhydrazone **5**, furnished from keto acid **4** upon treatment with *N*,*N*-dimethylhydrazine, was found to be extremely water sensitive. Attempts to form the hydrazone were thwarted by low yields under a number of conditions in which solvents were present. Azeotropic removal of water, with or without molecular sieves, was also unsatisfactory. Eventually, it was found most convenient to simply dissolve the keto acid in neat dimethylhydrazine without dessicant. After heating for a number of hours followed by cooling and removal of excess dimethylhydrazine, formation of the desired hydrazone was apparent by NMR due to loss of the methyl ketone resonance at δ 2.14. This initially formed hydrazone existed as a dimethylhydrazonium carboxylate, but it was found that reversion to the free carboxylic acid **5** occurred *in vacuo*, as evidenced by the proton NMR run in dry $CDCl_3$.

With simple methodology in hand for formation of the requisite hydrazone **5**, we returned to our alkylation studies. Treatment of the hydrazone **5** in tetrahydrofuran (THF) with 2 equiv of LDA at low temperature led to formation of hydrazone enolate as was evidenced by the slow appearance of alkylated products by TLC. However, these reactions were reluctant to go to completion, and it was found that if hexamethylphosphoric triamide (HMPA) were added to the intermediate metalloenamine, alkylation would reach completion in a matter of hours. While the preliminary alkylation product(s) were now relatively stable regioisomeric hydrazones, alkylated exclusively on the methyl group, and could be used crude in the ensuing ozonolysis reaction, products were easier to characterize after silica gel chromatography in which the hydrazone group was cleaved. The products of chromatography, keto acids

Scheme 2[a]



[a] Key: (a) aq oxalic acid, silica gel, CH_2Cl_2, 85%; (b) Me_2NNH_2, Δ, 93%; (c) LDA, THF, HMPA, −78−20 °C, then R^1-X; (d) O_3, CH_2Cl_2, −78 °C, then aq H_2SO_4, silica gel, CH_2Cl_2.

6−**13**, could then be stored indefinitely or used directly for the final stage of the synthetic sequence.

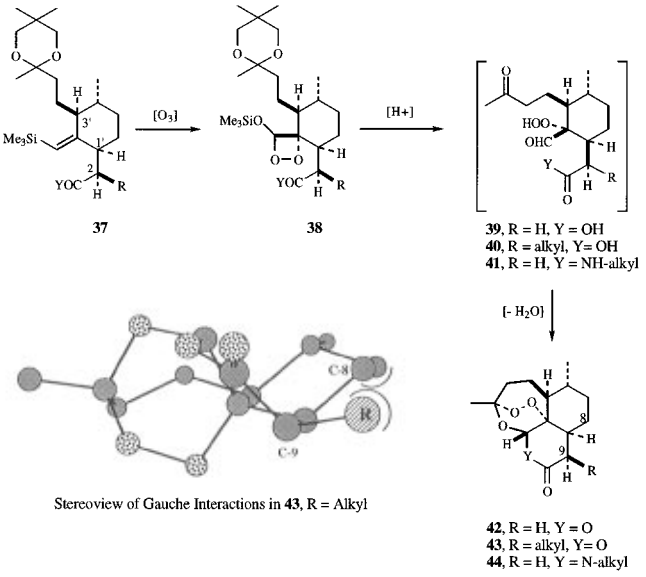
It was anticipated that ozonolysis of the keto acids **6**−**13** would be uncomplicated leading to an intermediate dioxetane or hydroperoxy lactol and that *in situ* acidification would then result in multiple cyclizations to afford desired tetracyclic artemisinin analogs modified at the C-3 position.[17,23−25] In fact, exposure of the keto acids to ozone at low temperature followed by purging of excess ozone and addition of silica gel and aqueous sulfuric acid led, over several days at room temperature, to clean formation of desired targets **14**−**21**. Yields were generally quite good for production of the target analogs, being in the range of 55−66% with one notable exception, the ethyl ester **18** for which the yield was substantially lower at 26%.

We were also interested in the possibility of synthesizing derivatives modified in both the carboxylic acid side chain and ketone-bearing side chain; the resulting tetracyclic analogs of artemisinin would then be modified at both C-3 and C-9. As the requisite ketal(s) were available,[17] their deketalization, hydrazone formation, alkylation, and subsequent ozonolysis and cyclization were explored as shown in Scheme 2.

Starting with known "butylated" ketal acid **22**, readily synthesized in high yield directly from ketal acid **2**, deketalization as before with oxalic acid-treated silica gel gave comparable results to before, with keto acid **23** being produced in 85% yield. Derivatization of this ketone as the hydrazone provided, in high yield, the expected hydrazone **24**, once again as an apparently pure regioisomer as inferred by the appearance in the NMR spectra of **24** of a singlet for the vinylsilane proton at δ 5.30. Alkylation of **24** by treatment first with 2 equiv of LDA followed by addition of HMPA and the alkylating agent gave intermediate hydrazones which upon chromatography underwent hydrolysis and afforded the penultimate intermediate keto acids **25**−**30** in reasonable yields ranging from 42% to 66%. Finally, low-temperature ozonolysis followed by admission of silica gel and aqueous acid furnished the target tetracyclic analogs **31**−**36** substituted at both C-9 and C-3. Unfortunately, yields for targets **31**−**36** were roughly one-half of those obtained for tetracycles not substituted at C-9 (**14**−**21**).

It is noteworthy (Scheme 3) that cyclization of intermediate hydroperoxy aldehyde equivalents such as **40**,

Scheme 3



Stereoview of Gauche Interactions in **43**, R = Alkyl

whether from total synthetic studies,[5] analog work,[6,17] or this work, bearing a substituent in the carboxylate side chain at C-1′ (e.g., **40**, R = alkyl) typically occur in a range of 15−35%. On the other hand, those lacking a substituent (e.g., **39** or **41**, R = H) are more efficiently converted to tetracycles with yields roughly from 50% to 65%. We have noted that this effect is unrelated to the efficiency with which initial oxidative addition occurs providing oxetanes **38**. Molecular modeling studies[26] indicate that increased torsional strain from the C-9 R substituent to the C-8 methylene in product **43** is reflected in less rapid cyclization of intermediate **40**, resulting in an increase in competing decomposition of **40** and thus lower yields of desired products such as **43**. When the R substituent is H, as in **39**, the energetically unfavorable C-9/C-8 interaction in the product **42** is relieved, and thus the reaction is more efficient.

Biological Activity

The analogs **14**−**21** and **31**−**36** 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[27,28] 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 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 was 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 2 ng/mL based on parasitemia levels.

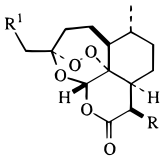
Structure−Activity Relationships

Substitution solely at C-3 and the effect of dual substitution at C-3 and C-9 were examined for their influence on antimalarial potency *in vitro*. Addition of another carbon at C-3 giving the ethyl analog **14** (R^1 = Et, but lacking the C-9 methyl group, R = H) results in little effect on activity, while the next homolog **15** (R^1 = propyl) is quite potent compared to artemisinin. Interestingly, 3-butyl homolog **16** and its branched counterpart **17** have diminished antimalarial activity relative to control. The overall trend for this series is qualitatively similar to that observed for C-9 substitution: A peak and trough in activity is seen upon substitution of *n*-alkyl groups at C-9 of two to six carbons in chain length. For C-9, maximal activity was achieved at ethyl and propyl (12 × activity of artemisinin) but had dropped by hexyl to around 5 times the potency of artemisinin. In this C-3-substituted series, the activity profile is attenuated with a peak occurring at propyl **15** (7−21 times activity of artemisinin) but with lower activity on either side such as ethyl **14** and butyl **16**. Interestingly, placement of an ester group at C-3 as in the propionate ethyl ester **18** results in an analog with better activity than artemisinin (2 × artemisinin), while the closest homolog to **18** is the relatively inactive isobutyl derivative **17**.

Next, the effect of aryl substitution was considered. The series substituted at C-3: 2-phenylethyl **19**, 3-(*p*-chlorophenyl)propyl **20**, and 4-phenylbutyl **21**, displayed roughly 1%, 100%, and 300% the activity of artemisinin, respectively. Compared to the analogous series at C-9 (2-phenylethyl, 100%; 3-phenylpropyl, 500%; 4-phenylbutyl, 300%), these results are only substantially at variance for the phenylethyl analog **19**. Furthermore, as was the case for C-9-substituted arylalkyls, the steric bulk typified by a aryl ring did not adversely effect activity, but branched hydrocarbons did lower potency appreciably.

On the whole, analogs of artemisinin substituted at C-3 were found to be less active than those substituted at C-9. Because it was a simple matter to combine methodologies for synthesis of analogs at both C-3 and

Table 1. Relative *in Vitro* Antimalarial Activity of 3-Substituted Analogs of Artemisinin against *P. falciparum*



structure	R^1	R	relative activity[a] D-6	W-2	anal. (C,H)
1	H	CH_3	100	100	$C_{15}H_{22}O_5$
14	CH_3	H	88	112	$C_{15}H_{22}O_5$
15	CH_3CH_2	H	2102	673	$C_{16}H_{24}O_5$
16	$CH_3(CH_2)_2$	H	20	18	$C_{17}H_{26}O_5$
17	$(CH_3)_2CH$	H	53	45	$C_{17}H_{26}O_5$
18	EtO_2CCH_2	H	232	232	$C_{18}H_{26}O_7$
19	$C_6H_5CH_2$	H	3	1	$C_{21}H_{26}O_5$
20	*p*-$ClC_6H_4(CH_2)_2$	H	114	127	$C_{22}H_{27}ClO_5$
21	$C_6H_5(CH_2)_3$	H	220	281	$C_{23}H_{32}O_5$
31	CH_3	$CH_3(CH_2)_3$	184	257	$C_{19}H_{30}O_5$
32	$CH_3(CH_2)_2$	$CH_3(CH_2)_3$	28	33	$C_{21}H_{34}O_5$
33	$C_6H_5CH_2$	$CH_3(CH_2)_3$	1	1	$C_{25}H_{34}O_5$
34	*p*-$ClC_6H_4(CH_2)_2$	$CH_3(CH_2)_3$	43	53	$C_{26}H_{35}ClO_5$
35	$C_6H_5(CH_2)_3$	$CH_3(CH_2)_3$	39	48	$C_{27}H_{38}O_5$
36	EtO_2CCH_2	$CH_3(CH_2)_3$	1382	2285	$C_{22}H_{34}O_7$

[a] Relative activity = 100 × [IC_{50}(artemisinin, control value)/IC_{50}(analog)]MW(analog)/MW(artemisinin).

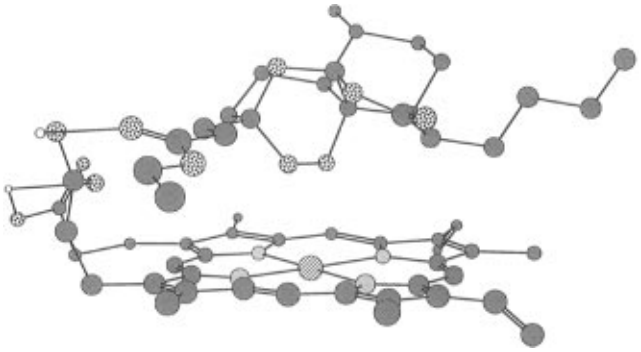


Figure 1. Docking interaction of hemin with artemisinin analog **37** in Sybyl showing hydrogen bonding between hemin side chains and the C-3 ester group of analog **37**.

C-9, we thought that dual substitution would provide additional interesting SAR information. The activities of analogs **32**−**35** were unimpressive, while the activity of **31** and **36** were good to excellent. The following trends were observed. For increasing alkyl bulk at C-3 a drop in antimalarial efficacy was noted (**14**, relative activity of 1.1; **16**, relative activity of 0.2). Upon butyl substitution at C-9, the corresponding dual substituted analogs (3-alkyl, 9-butyl) showed a doubling of activity (**31**, relative activity of 2.6; **32**, relative activity of 0.33). For the C-3 arylalkyl-substituted analogs alone, an increase in activity was observed with increasing chain length between ring system and the aryl ring (two carbons for **19**, relative activity of 0.01; three carbons for **20**, relative activity of 1.3; four carbons for **21**, relative activity of 2.8). Dual substituted arylalkyl analogs (3-arylalkyl, 9-butyl) were generally less active than 3-substituted arylalkyl analogs alone (e.g., **20**, relative activity of 1.3; **34**, relative activity of 0.53). Thus, a number of opposing trends were evident.

The high potency of the dual substituted analog **36**, on the other hand, is somewhat of a surprise in light of the foregoing discussion. By comparison to **18** (ester side chain), **36** should be roughly no better than 2-fold more potent than artemisinin. However, one is faced with a 14−23-fold *enhancement* in activity for **36** relative to artemisinin.

These findings suggest the following qualitative statements: (a) a binding site or acceptor for artemisinin and analogs exists with limited dimensions at both C-9 and C-3, more tolerant of aryl and ester substitution on *n*-alkyl chains than of branched alkanes of any length; b) dual substitution at C-3 and C-9, explored for only 9-butyl analogs, was on the whole detrimental to activity with one interesting exception, **36**. As it happens, **36** would be predicted to dock with hemin better than other members of this series. Perhaps the efficacy of hydrogen bonding of **36** to hemin (putative mechanistic bottleneck in the mode of action of these antimalarials) is reflected in the enhanced activity of this analog. The interaction energies of artemisinin and dihydroartemisinin with hemin have been calculated in Sybyl using the dock routine.[29] We have applied this technique to the interaction of **36** with hemin in the Fe(II) oxidation state. The lowest *E* alignment of **36** with hemin places the ester group in the vicinity of the carboxyl groups of hemin, as shown in Figure 1, and allows for hydrogen bonding between hemin and **36**. If this hypothesis is true, then other hydrogen bond acceptors with appropriate tethers at the C-3 position of artemisinin might be expected to have enhanced activity.

The results of these studies have been incorporated into an evolving QSAR model and will be reported when additional data has been collected for the remaining unexplored positions about the artemisinin framework.

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, and 250-μm silica gel thin-layer chromatography plates 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 instrument and run neat unless otherwise indicated. Mass spectral data was obtained on a VG 7070E-HF instrument. Elemental analyses were within 0.4% as determined by Desert Analytics, Tucson, AZ.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(3″-oxobutyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]ethanoic Acid (4). To a vigorously stirring suspension of silica gel 60 (230−400 mesh, 2.33 g) in CH_2Cl_2 (40 mL) was added 10% aqueous oxalic acid (820 μL). After 15 min, a solution of ketal acid **2** (0.65 g, 1.64 mmol) in CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred for 24 h, filtered, and washed with CH_2Cl_2 (10 mL) and then EtOAc (10 mL). The organic layer was washed with water, dried ($MgSO_4$), and evaporated to give 0.414 g (82%) of pure keto acid **4**. ^{1}H NMR: δ 5.42 (s, 1H), 2.74 (br s, 1H), 2.52−2.64 (m, 1H), 2.38−2.48 (m, 1H), 2.14 (s, 3H), 0.91 (d, 3H, J = 6.8 Hz), 0.078 (s, 9H). IR: 2949, 1703, 1601, 1408, 1246, 1163, 834, 747, 689 cm^{-1}. DCIMS (NH_3): *m*/*z* 311 (M + NH_4), 293, 277, 250, 221, 203, 161, 143, 129, 108.

If 1.5 mL of acid was used, small amounts of byproduct **3** were also formed (isolated by flash chromatography, 10:90 MeOH/$CHCl_3$). ^{1}H NMR: δ 4.67 (br s, 1H), 4.61 (br s, 1H), 2.62 (m, 2H), 2.39 (m, 3H), 2.23 (m, 1H), 2.13 (s, 3H), 1.53−2.07 (m, 5H), 1.01−1.31 (m, 3H), 0.97 (d, 3H, J = 5.8 Hz). ^{13}C (75 MHz): δ 209.3, 178.8, 152.5, 103.1, 50.1, 41.4, 40.9, 39.2, 38.0, 34.9, 34.4, 30.0, 22.0, 20.4. IR ($CHCl_3$): 3480, 3089, 2921, 2871, 1708, 1641, 1409, 1288, 1172, 896 cm^{-1}. DCIMS (NH_3): *m*/*z* 256 (M + NH_4), 238 (M^+), 221, 119.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(3″-oxobutyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]ethanoic Acid Dimethylhydrazone (5). To keto acid **4** (0.9 g, 2.9 mmol) was added 1,1-dimethylhydrazine (4 mL). The reaction mixture was refluxed for 5 h and cooled, and the excess dimethylhydrazine was evaporated. The reaction mixture was then dissolved in dry benzene, dried over anhydrous $MgSO_4$, filtered, evaporated, and dried overnight *in vacuo* to give 0.938 g (92%) of pure **5** as a white crystalline solid, mp 98−99 °C. ^{1}H NMR: δ 5.51 (s, 1H), 2.92 (br s, 1H), 2.41−2.50 (m, 8H), 2.24 (m, 4H), 2.00 (s, 3H), 1.84 (m, 4H), 1.60 (m, 1H), 1.42 (m, 1H), 1.12 (m, 1H), 0.94 (d, 3H, J = 7.0 Hz), 0.08 (s, 9H). IR: 2949, 2861, 2813, 1631, 1600, 1414, 1245, 846 cm^{-1}. DCIMS (isobutane): *m*/*z* 353 (M + H), 295, 221, 161.

General Procedure for Alkylation of the Dimethylhydrazones 5 and 24: Synthesis of Ketones 6−13 and 25−30. To an ice-cold solution of diisopropylamine (2.25 mmol) in dry THF (4 mL/mmol) was added *n*-butyllithium (2.25 equiv of a 2.5 M solution). The mixture was stirred at 0 °C for 15 min and then cooled to −78 °C. The hydrazone **5** or **24** (1 mmol) in dry THF (4 mL/mmol) was added via cannula, and the mixture was stirred at −78 °C for 10 min. Dry HMPA (0.5 mL/mmol) was then added to the reaction mixture via syringe, and the mixture was stirred at −78 °C for 15 min. After warming to 0 °C, alkylating agent (2.5 mmol) was added

to the reaction mixture which was then stirred at ambient temperature for 6 h, poured onto ice-cold saturated aqueous NH_4Cl, extracted with EtOAc, dried ($MgSO_4$), and evaporated *in vacuo* to give a crude product which was purified by flash chromatography. Elution with EtOAc/hexane containing 1% HOAc gave pure alkylated products **6**−**13** and **25**−**30**.

General Procedure for Preparation of Target Artemisinin Analogs: Ozonolysis and Acid-Catalyzed Cyclization of Keto Acids 6−13 and 25−30. Into a solution of keto acid (1 mmol) in dry CH_2Cl_2 (125 mL) at −78 °C was bubbled a stream of O_3/O_2 (4 PSI, 0.04 L/min, 80 V) until the reaction mixture had turned faint blue. After the reaction mixture was purged with O_2 followed by N_2, silica gel (750 mg) and 15% aqueous H_2SO_4 (75 μL) were added. The mixture was allowed to come to ambient temperature and stirred overnight, the solids were filtered and washed with CH_2Cl_2 (2 × 10 mL) and then EtOAc (2 × 10 mL). The resulting filtrate was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated *in vacuo* to give crude products which were easily purified by preparative thin-layer chromatography (PTLC) on silica gel.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(3″-oxopentyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]ethanoic Acid (6). Chromatography of the crude material with 20% EtOAc/hexane provided the pure product **6** in 93% yield. ^{1}H NMR: δ 5.42 (s, 1H), 2.80 (br s, 1H), 2.60 (dd, 1H, J = 9.5, 14.8 Hz), 2.38−2.46 (m, 6H), 2.14 (m, 1H), 1.76−1.90 (m, 4H), 1.68 (m, 1H), 1.42 (m, 1H), 1.04 (dd, 3H, J = 7.3, 7.3 Hz), 0.92 (d, 3H, J = 6.9 Hz), 0.08 (s, 9H). IR: 3280−2810, 1734, 1710, 1601, 1453, 1410, 1291, 1247, 848 cm^{-1}. DCIMS (NH_3): m/z 342 (M + NH_4), 325 (M + H), 307, 235, 175.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(3″-oxohexyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]ethanoic Acid (7). Chromatography of the crude material with 20% EtOAc/hexane provided the pure product **7** in 83% yield. ^{1}H NMR: δ 5.42 (s, 1H), 2.82 (br s, 1H), 2.60 (dd, 1H, J = 9.4, 14.7 Hz), 2.36−2.44 (m, 6H), 2.20 (m, 1H), 1.84 (m, 4H), 1.54−1.68 (m, 3H), 1.42 (m, 1H), 1.14 (m, 1H), 0.91 (dd, 3H, J = 7.4, 7.4 Hz), 0.93 (d, 3H, J = 6.9 Hz), 0.08 (s, 9H), IR: 3300−2800, 1731, 1709, 1601, 1454, 1409, 1247, 867, 837 cm^{-1}. DCIMS (NH_3): m/z 338 (M$^+$), 174, 189, 129, 108, 73.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(3″-oxoheptyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]ethanoic Acid (8). Chromatography of the crude material with 20% EtOAc/hexane provided the pure product **8** in 58% yield. ^{1}H NMR: δ 5.42 (s, 1H), 2.82 (br s, 1H), 2.56−2.64 (m, 1H), 2.37−2.42 (m, 6H), 2.16 (m, 1H), 1.82 (m, 1H), 1.66 (m, 1H), 1.52 (m, 1H), 1.42 (m, 1H), 1.22−1.30 (m, 4H), 0.87−0.94 (m, 6H), 0.09 (s, 9H). IR: 3380−2600, 1712, 1601, 1461, 1409, 1289, 1247, 863, 849 cm^{-1}. DCIMS (NH_3): m/z 370 (M + NH_4), 353 (M + H), 335, 292, 263, 195.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(5″-methyl-3″-oxohexyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]ethanoic Acid (9). Chromatography of the crude material with 20% EtOAc/hexane provided the pure product **9** in 63% yield. ^{1}H NMR: δ 5.42 (s, 1H), 2.82 (br s, 1H), 2.59 (dd, 1H, J = 9.5, 14.8 Hz), 2.34−2.48 (m, 2H), 2.28 (d, 1H, J = 6.6 Hz), 2.10−2.15 (m, 2H), 1.82 (m, 4H), 1.64 (m, 1H), 1.42 (m, 1H), 1.24 (m, 1H), 0.93 (d, 3H, J = 5.6 Hz), 0.92 (d, 6H, J = 6.6 Hz), 0.08 (s, 9H). IR: 3380−2520, 1731, 1708, 1601, 1463, 1452, 1409, 1249, 849 cm^{-1}. DCIMS (NH_3): m/z 370 (M + NH_4), 353 (M + H), 335, 295, 263, 195.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(5″-carbethoxy-3″-oxopentyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]ethanoic Acid (10). Chromatography of the crude material with 20% EtOAc/hexane provided the pure product **10** in 63% yield. ^{1}H NMR: δ 5.43 (s, 1H), 4.11 (dd, 2H, J = 7.1, 14.2 Hz), 2.70−2.84 (m, 2H), 2.52−2.62 (m, 3H), 2.40−2.56 (m, 2H), 2.12−2.20 (m, 1H), 1.78−1.88 (m, 4H), 1.25 (dd, 3H, J = 7.1, 7.1 Hz), 0.93 (d, 3H, J = 7.0 Hz), 0.08 (s, 9H). IR: 3200−2800, 1737, 1712, 1601, 1461, 1411, 1247, 1097, 867, 849 cm^{-1}. DCIMS (NH_3): m/z 414 (M + NH_4), 397 (M + H), 379, 307, 289, 261.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(5″-phenyl-3″-oxopentyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]ethanoic Acid (11). Chromatography of the crude material with 20% EtOAc/hexane provided the pure product **11** in 62% yield. ^{1}H NMR: δ 7.18−7.26 (m, 5H), 5.41 (s, 1H), 2.88 (dd, 2H, J = 7.5, 7.5 Hz), 2.76 (dd, 2H, J = 7.8, 7.8 Hz), 2.57 (dd, 1H, J = 9.5, 14.9 Hz), 2.32−2.42 (m, 3H), 2.12 (m, 1H), 1.72−1.88 (m, 4H), 1.62 (m, 1H), 1.40 (m, 1H), 1.14 (m, 1H) 0.91 (d, 3H, J = 6.8 Hz), 0.07 (s, 9H). IR: 3400−2500, 1715, 1708, 1603, 1495, 1452, 1400, 1247, 873, 839 cm^{-1}. DCIMS (NH_3): m/z 418 (M + NH_4), 401 (M + H), 383, 311, 195.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-[6″-(*p*-chlorophenyl)-3″-oxohexyl]-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]ethanoic Acid (12). Chromatography of the crude material with 20% EtOAc/hexane provided the pure product **12** in 59% yield. ^{1}H NMR: δ 7.24 (d, 2H, J = 8.5 Hz), 7.09 (d, 2H, J = 8.6 Hz), 5.42 (s, 1H), 2.8 (br s, 1H), 2.54−2.62 (m, 3H), 2.34−2.42 (m, 4H), 2.12 (m, 1H), 1.72−1.92 (m, 6H), 1.54−1.68 (m, 2H), 1.42 (m, 1H), 1.12 (m, 1H), 0.92 (d, 3H, J = 6.9 Hz), 0.07 (s, 9H). IR: 3380−2600, 1708, 1601, 1491, 1452, 1407, 1368, 1246, 1092, 867, 847 cm^{-1}. DCIMS (NH_3): m/z 449 (M + H), 448 (M$^+$), 388, 373, 359, 229, 252.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(7″-phenyl-3″-oxoheptyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]ethanoic Acid (13). Chromatography of the crude material with 20% EtOAc/hexane provided the pure product **13** in 62% yield. ^{1}H NMR: δ 7.12−7.28 (m, 5H), 5.42 (s, 1H), 2.80 (br s, 1H), 2.54−2.66 (m, 3H), 2.36−2.48 (m, 4H), 2.12 (m, 1H), 1.74−1.90 (m, 3H), 1.58−1.64 (m, 4H), 1.42 (m, 1H), 1.14 (m, 1H), 0.92 (d, 3H, J = 7.0 Hz), 0.09 (s, 9H). IR: 3400−2500, 1735, 1710, 1602, 1496, 1453, 1294, 1247, 1157, 868, 850 cm^{-1}. DCIMS (NH_3): m/z 446 (M + NH_4), 429 (M + H), 411, 339, 278, 261.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(3″-oxobutyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]hexanoic Acid (23). To a vigorously stirred suspension of silica gel (14.25 g) in dry CH_2Cl_2 (180 mL) was added 10% aqueous oxalic acid (6.8 mL). After 15 min, a solution of the ketal acid **22** (3.2 g, 7.0 mmol) in CH_2Cl_2 was added. The reaction mixture was stirred at ambient temperature for 40 h and then heated at 40 °C for 8 h, filtered, and washed successively with CH_2Cl_2 and then EtOAc. The organic layer was washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to give 2.2 g (85% yield) of pure keto acid **23** as a viscous liquid. ^{1}H NMR: δ 5.35 (s, 1H), 2.65 (m, 1H), 2.35−2.52 (m, 3H), 2.14 (s, 3H), 1.82 (m, 4H), 1.12−1.62 (m, 10H), 0.93 (d, 3H, J = 5.0 Hz), 0.89 (dd, 3H, J = 6.7, 6.7 Hz), 0.09 (s, 9H). IR: 3420−2400, 1730, 1693, 1598, 1461, 1408, 1361, 1246, 1165, 1099, 952, 822 cm^{-1}. DCIMS (NH_3): m/z 384 (M + NH_4), 367 (M + H), 349, 231, 143.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(3″-oxobutyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]hexanoic Acid Dimethylhydrazone (24). To the keto acid **23** (2.20 g, 6.0 mmol) under N_2 was added *N*,*N*-dimethylhydrazine (7.0 mL). The reaction mixture was refluxed for 4 h, excess dimethylhydrazine was evaporated, and the reaction mixture was dissolved in dry benzene, dried over $MgSO_4$, filtered, evaporated, and dried overnight *in vacuo* to give 2.28 g (93%) of the pure hydrazone **24** as a viscous liquid. ^{1}H NMR: δ 5.30 (s, 1H), 2.30−2.46 (m, 9H), 2.02−2.20 (m, 2H), 1.90 (m, 4H), 1.75 (m, 2H), 1.08−1.52 (m, 10H), 0.92 (d, 3H, J = 8.3 Hz), 0.82 (dd, 3H, J = 7.0, 7.0 Hz), 0.10 (s, 9H). IR: 2953, 2947, 2896, 1704, 1600, 1452, 1359, 1246, 1164, 854, 846 cm^{-1}. DCIMS (isobutane): m/z 409 (M + H), 366, 319, 256, 221, 164.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(3″-oxopentyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]hexanoic Acid (25). Flash chromatography of the crude product was accomplished eluting with 20% EtOAc/hexane and gave pure **25** (56%) as a yellow viscous liquid. ^{1}H NMR: δ 5.34 (s, 1H), 2.68 (m, 1H), 2.30−2.50 (m, 6H), 2.14 (m, 1H), 1.86 (m, 4H), 1.42−1.68 (m, 2H), 1.12−1.66 (m, 6H), 1.06 (dd, 3H, J = 7.3, 7.3 Hz), 0.93 (d, 3H, J = 7.1 Hz), 0.89 (dd, 3H, J = 6.8, 6.8 Hz), 0.10 (s, 9H). IR: 3400−2400, 1735, 1697, 1599, 1453, 1414, 1290, 1246, 1160, 1108, 861 cm^{-1}. DCIMS (isobutane): m/z 381 (M + H), 363 (M − H_2O), 291, 264, 157.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(3″-oxoheptyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]hexanoic Acid (26). Flash chromatography over silica gel with 20% EtOAc/hexane gave pure **26** (82%) as a thick oil. ^{1}H NMR: δ 5.34 (s, 1H), 2.68 (m, 1H), 2.30−2.52 (m, 6H), 2.12 (m, 1H), 1.82 (m, 4H), 1.52−1.60 (m, 4H), 1.12−1.42 (m, 8H), 0.90 (dd, 3H, J = 7.3,

7.3 Hz), 0.87 (dd, 3H, J = 6.8, 6.8 Hz), 0.93 (d, 3H, J = 7.0 Hz), 0.10 (s, 9H). IR: 3400−2400, 1735, 1704, 1599, 1463, 1454, 1290, 1246, 1161, 1102, 859 cm^{-1}. DCIMS (isobutane): m/z 409 (M + H), 391 (M − H_2O), 319, 292, 273, 203.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(5″-phenyl-3″-oxopentyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]hexanoic Acid (27). Chromatography of the crude material with 20% EtOAc/hexane provided the pure product **26** in 42% yield. ^{1}H NMR: δ 7.18−7.30 (m, 5H), 5.34 (s, 1H), 2.90 (dd, 1H, J = 7.6, 7.6 Hz), 2.62−2.74 (m, 3H), 2.26−2.52 (m, 6H), 2.12 (m, 1H), 1.72−1.88 (m, 4H), 1.12−1.74 (m, 8H), 0.92 (d, 3H, J = 7.1 Hz), 0.87 (dd, 3H, J = 6.8, 6.8 Hz), 0.09 (s, 9H). IR: 3380−2500, 1729, 1703, 1600, 1452, 1408, 1290, 1246, 857, 835 cm^{-1}. DCIMS (isobutane): m/z 457 (M + H), 439, 367, 340, 251, 233.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′Methyl-3′-[6″-(*p*-chlorophenyl)-3″-oxohexyl]-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]-hexanoic Acid (28). Chromatography of the crude material with 20% EtOAc/hexane provided the pure product **28** in 60% yield. ^{1}H NMR: δ 7.26 (d, 2H, J = 8.5 Hz), 7.08 (d, 2H, J = 8.6 Hz), 5.34 (s, 1H), 2.54−2.68 (m, 2H), 2.32−2.48 (m, 4H), 2.08−2.14 (m, 1H), 1.74−1.92 (m, 6H), 1.42−1.72 (m, 2H), 1.12−1.40 (m, 9H), 0.92 (d, 3H, J = 7.0 Hz), 0.85 (dd, 3H, J = 6.8, 6.8 Hz), 0.09 (s, 9H). IR: 3400−2329, 1712, 1703, 1598, 1491, 1454, 1406, 1365, 1290, 1246, 1216, 1091, 858, 834 cm^{-1}. DCIMS (isobutane): m/z 505 (M + H), 487, 415, 369, 299, 281.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(6″-phenyl-3″-oxoheptyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]hexanoic Acid (29). Chromatography of the crude material with 20% EtOAc/hexane provided the pure product **29** in 66% yield. ^{1}H NMR: δ 7.16−7.28 (m, 5H), 5.34 (s, 1H), 2.62 (m, 3H), 2.28−2.52 (m, 4H), 2.12 (m, 1H), 1.82 (m, 4H), 1.61 (m, 6H), 1.12−1.15 (m, 8H), 0.93 (d, 3H, J = 7.0 Hz), 0.92 (dd, 3H, J = 6.9, 6.9 Hz), 0.10 (s, 9H). IR: 3400−2480, 1730, 1703, 1600, 1494, 1452, 1408, 1373, 1291, 1246, 1216, 1104, 962, 858, 835 cm^{-1}. DCIMS (isobutane): m/z 485 (M + H), 467 (M − H_2O), 395, 368, 349, 279, 261.

(2*R*,1′*S*,3′*S*,4′*S*)-2-[4′-Methyl-3′-(5″-carbethoxy-3″-oxopentyl)-2′(*E*)-[(trimethylsilyl)methylene]cyclohexyl]-hexanoic Acid (30). Chromatography of the crude material with 20% EtOAc/hexane provided the pure product **30** in 40% yield. ^{1}H NMR: δ 5.34 (s, 1H), 4.12 (dd, 2H, J = 7.1, 14.2 Hz), 2.44−2.72 (m, 4H), 2.40 (m, 3H), 2.14 (m, 3H), 1.82−1.92 (m, 4H), 1.12−1.64 (m, 13H), 0.93 (d, 3H, J = 7.0 Hz), 0.89 (dd, 3H, J = 6.9, 6.9 Hz), 0.10 (s, 9H). IR: 3400−2400, 1738, 1707, 1599, 1463, 1452, 1411, 1367, 1247, 1099, 1029, 858, 835 cm^{-1}. DCIMS (isobutane): m/z 453 (M + H), 435, 336, 317, 229, 194.

Octahydro-3-ethyl-6-methyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (14). The crude product was purified by PTLC eluting with 20% EtOAc/hexane to give **14** (62%) as an oil. ^{1}H NMR: δ 5.92 (s, 1H), 3.17 (dd, 1H, J = 6.9, 18.2 Hz), 2.27−2.38 (m, 1H), 2.27 (dd, 1H, J = 1.2, 8.2 Hz), 1.94−2.08 (m, 2H), 1.84−1.94 (m, 1H), 1.68−1.80 (m, 4H), 1.38−1.52 (m, 4H), 0.99 (d, 3H, J = 5.8 Hz), 0.95 (dd, 3H, J = 7.5, 7.5 Hz). IR: 2978, 2920, 2862, 1744, 1460, 1208, 1031, 998, 895 cm^{-1}. DCIMS (isobutane): m/z 283 (M + H), 282 (M$^+$), 247.

Octahydro-3-propyl-6-methyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin-(3*H*)-one (15). Flash chromatography over silica gel with 20% EtOAc/hexane gave **15** (58%) as an oil. ^{1}H NMR: δ 5.91 (s, 1H), 3.17 (dd, 1H, J = 6.9, 18.2 Hz), 2.33−2.40 (m, 1H), 2.27 (dd, 1H, J = 1.1, 18.2 Hz), 1.94−2.10 (m, 2H), 1.62−1.78 (m, 4H), 1.36−1.52 (m, 6H), 0.99 (d, 3H, J = 6.9 Hz), 0.89 (dd, 3H, J = 7.3, 7.3 Hz). IR: 2959, 2926, 2871, 1747, 1208, 1031, 994, 949 cm^{-1}. FABMS: m/z 297 (M + H), 289, 279, 251.

Octahydro-3-butyl-6-methyl-3,12-epoxy-12*H*-pyrano-[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (16). PTLC on silica gel, eluting with 20% EtOAc/hexane, gave **16** (55%) as an oil. ^{1}H NMR: δ 5.91 (s, 1H), 3.19 (dd, 1H, J = 6.8, 18.2 Hz), 2.33−2.40 (m, 1H), 2.28 (dd, 1H, J = 1.1, 18.2 Hz), 1.94−2.10 (m, 2H), 1.82−1.94 (m, 1H), 1.64−1.78 (m, 4H), 1.24−1.48 (m, 6H), 0.99 (d, 3H, J = 5.7 Hz), 0.88 (dd, 3H, J = 7.1, 7.1 Hz). IR: 2954, 2937, 2914, 2872, 1743, 1458, 1210, 1106, 1032, 1002, 993 cm^{-1}. FABMS: m/z 311 (M + H), 297, 265, 237, 165, 154, 137.

Octahydro-3-(2-methylpropyl)-6-methyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (17). PTLC of the crude product on silica gel, eluting with 20% EtOAc/hexane, gave **17** (49%) as an oil. ^{1}H NMR: δ 5.92 (s, 1H), 3.19 (dd, 1H, J = 6.9, 8.3 Hz), 2.33−2.42 (m, 1H), 2.27 (dd, 1H J = 1.1, 8.2 Hz), 1.82−2.08 (m, 4H), 1.66−1.76 (m, 2H), 1.54−1.64 (m, 6H), 1.82−1.98 (m, 2H), 0.99 (d, 3H, J = 5.9 Hz), 0.93 (dd, 3H, J = 6.7, 8.4 Hz). IR: 2959, 2926, 2895, 1749, 1465, 1365, 1208, 1106, 1032, 994, 948 cm^{-1}. DCIMS (isobutane): m/z 310 (M$^+$), 296, 294, 281, 212, 197.

Octahydro-3-(3′-carbethoxyethyl)-6-methyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (18). The crude product was purified on a silica gel PTLC plate using 50% EtOAc/hexane to give pure **18** (26%) as an oil. ^{1}H NMR: δ 5.91 (s, 1H), 4.11 (dd, 2H, J = 7.1, 14.2 Hz), 3.17 (dd, 1H, J = 6.9, 18.2 Hz), 2.30−2.52 (m, 4H), 2.26 (dd, 1H, J = 1.1, 18.2 Hz), 1.96−2.09 (m, 4H), 1.84−1.94 (m, 1H), 1.70−1.78 (m, 2H), 1.38−1.48 (m, 4H), 1.23 (dd, 3H, J = 7.1, 7.1 Hz), 0.99 (d, 1H, J = 5.9 Hz). IR: 2952, 2926, 1744, 1209, 1191, 1091, 1001, 940, 895 cm^{-1}. FABMS: m/z 355 (M + H), 337, 307, 237, 154, 136.

Octahydro-3-(2-phenylethyl)-6-methyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (19). The crude product was purified by flash chromatography eluting with 20% EtOAc/hexane to give pure **19** as a white crystalline solid, mp 114 °C. ^{1}H NMR: δ 7.14−7.28 (m, 5H), 5.96 (s, 1H), 3.21 (dd, 1H, J = 6.2, 18.9 Hz), 2.65−2.84 (m, 2H), 2.35−2.48 (m, 1H), 2.30 (dd, 1H, J = 1.1, 18.2 Hz), 1.98−2.12 (m, 4H), 1.88−1.98 (m, 1H), 1.72−1.80 (m, 2H), 1.39−1.58 (m, 5H), 1.01 (d, 3H, J = 5.7 Hz). IR: 2967, 2926, 2852, 1741, 1453, 1208, 1030, 995 cm^{-1}. FABMS: m/z 359 (M + H), 313, 307, 289, 279.

Octahydro-3-[3-(4-chlorophenyl)propyl]-6-methyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (20). The crude product was purified by flash chromatography eluting with 20% EtOAc/hexane to give **20** (63%) as an oil. ^{1}H NMR: δ 7.24 (d, 2H, J = 8.5 Hz), 7.08 (d, 2H, J = 8.6 Hz), 5.91 (s, 1H), 3.18 (dd, 1H, J = 6.9, 18.2 Hz), 2.52 (m, 2H), 2.26−2.38 (m, 1H), 2.27 (dd, 1H, J = 1.1, 18.2 Hz), 1.96−2.02 (m, 2H), 1.84−1.94 (m, 1H), 1.69−1.78 (m, 6H), 1.40 (m, 4H), 0.98 (d, 3H, J = 5.8 Hz). IR: 2955, 2924, 2848, 1743, 1491, 1209, 1089, 999 cm^{-1}. DCIMS (NH_3): m/z 407, (M + H), 406 (M$^+$), 392, 377, 362, 358.

Octahydro-3-(4-phenylbutyl)-6-methyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (21). The crude product was purified by flash chromatography eluting with 20% EtOAc/hexane to give **21** (44%) as an oil. ^{1}H NMR: δ 7.10−7.28 (m, 5H), 5.91 (s, 1H), 3.18 (dd, 1H, J = 6.9, 18.2 Hz), 2.59 (m, 2H), 2.33−2.40 (m, 1H), 2.27 (d, 1H, J = 18.2 Hz), 1.81−2.19 (m, 3H), 1.70−1.80 (m, 3H), 0.99 (d, 3H, J = 5.8 Hz). IR: 2959, 2917, 2857, 1744, 1210, 1031, 995 cm^{-1}. FABMS: m/z 387 (M + H), 386, 341, 313, 154, 136, 117.

Octahydro-3-ethyl-6-methyl-9-butyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (31). The crude product was purified by silica gel PTLC eluting with 20% hexane/$CHCl_3$ to give **31** (26%) as the pure product. Crystallization from hexane gave white crystals, mp 86−88 °C. ^{1}H NMR: δ 5.83 (s, 1H), 3.18 (m, 1H), 2.28−2.40 (m, 1H), 1.96−2.08 (m, 3H), 1.68−1.82 (m, 6H), 1.20−1.48 (m, 8H), 1.12 (m, 1H), 1.00 (d, 3H, J = 5.6 Hz), 0.93 (dd, 3H, J = 7.5, 7.5 Hz), 0.88−0.92 (m, 3H). IR: 2954, 2928, 2869, 1741, 1461, 1392, 1346, 1286, 1216, 1182, 1113, 1035, 1002, 946, 895 cm^{-1}. DCIMS (NH_3): m/z 356 (M + NH_4), 339 (M + H), 323, 293, 275, 265.

Octahydro-3-butyl-6-methyl-9-butyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (32). The crude product was purified by silica gel PTLC eluting with 20% hexane/$CHCl_3$ to give pure **32** (29%) as an oil. ^{1}H NMR: δ 5.84 (s, 1H), 3.20 (m, 1H), 2.30−2.40 (m, 1H), 1.96−2.08 (m, 3H), 1.64−1.84 (m, 6H), 1.20−1.48 (m, 12H), 1.12 (m, 1H), 1.00 (d, 3H, J = 5.9 Hz), 0.85−0.95 (m, 6H). IR: 2953, 2926, 2870, 1747, 1456, 1392, 1344, 1270, 1178, 1112, 1033, 1004, 953 cm^{-1}. FABMS: m/z 367 (M + H), 349 (M − H_2O), 293, 221, 193.

Octahydro-3-(2-phenylethyl)-6-methyl-9-butyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (33). The crude product was purified by silica gel PTLC eluting with

20% hexane/$CHCl_3$ to give pure **33** (25%) as a white solid, mp 103−105 °C. ^{1}H NMR: δ 7.22−7.36 (m, 5H), 5.92 (s, 1H), 3.30 (dddd, 1H, J = 2.5, 5.0, 5.0, 8.0, Hz), 2.72−2.92 (m, 2H), 2.44−2.58 (m, 1H), 2.02−2.22 (m, 5H), 1.82−1.96 (m, 3H), 1.34−1.64 (m, 9H), 1.14 (m, 1H), 1.10 (d, 3H, J = 5.7 Hz), 0.99 (dd, 3H, J = 6.7, 6.7 Hz). IR: 2951, 2869, 1739, 1453, 1217, 1195, 1183, 1112, 1033, 1002, 898 cm^{-1}. DCIMS (NH_3): m/z 432 (M + NH_4), 415 (M + H), 414 (M^+), 397, 386, 369, 341, 105, 91.

Octahydro-3-[2-(4-chlorophenyl)ethyl]-6-methyl-9-butyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10-(3*H*)-one (34). The crude product was purified by silica gel PTLC eluting with 20% hexane/$CHCl_3$ to give pure **34** (27%) as an oil. ^{1}H NMR: δ 7.24 (d, 2H, J = 8.5 Hz), 7.08 (d, 2H, J = 8.6 Hz), 5.8 (s, 1H), 3.14 (m, 1H), 2.54 (m, 2H), 2.28−2.38 (m, 1H), 1.92−2.08 (m, 2H), 1.62−1.84 (m, 6H), 1.22−1.44 (m, 9H), 1.02 (m, 2H), 0.98 (d, 3H, J = 5.7 Hz), 0.90 (dd, 3H, J = 6.7, 6.7 Hz). IR: 2960, 2955, 2920, 2868, 1743, 1492, 1456, 1405, 1272, 1217, 1189, 1112, 1035, 1003, 901, 833 cm^{-1}. FABMS: m/z 463 (M + H), 445, 417, 389, 309, 251, 221.

Octahydro-3-(4-phenylbutyl)-6-methyl-9-butyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (35). The crude product was purified by silica gel PTLC eluting with 20% hexane/$CHCl_3$ to give pure **35** (27%) as an oil. ^{1}H NMR: δ 7.14−7.26 (m, 5H), 5.85 (s, 1H), 3.28 (m, 1H), 2.60 (m, 2H), 2.32 (m, 1H), 1.94−2.08 (m, 3H), 1.65−2.84 (m, 4H), 1.56−1.62 (m, 3H), 1.20−1.50 (m, 9H), 1.02−1.12 (m, 2H), 0.99 (d, 3H, J = 5.7 Hz), 0.91 (dd, 3H, J = 6.8, 6.8 Hz). IR: 2950, 2926, 2867, 1741, 1494, 1453, 1392, 1350, 1193, 1111, 1033, 999, 954 cm^{-1}. FABMS: m/z 443 (M + H), 425 (M − H_2O), 397, 369, 221, 193.

Octahydro-3-(3-ethoxypropionyl)-6-methyl-9-butyl-3,-12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10(3*H*)-one (36). The crude product was purified by silica gel PTLC eluting with 20% hexane/$CHCl_3$ to give pure **36** (21%) as an oil. ^{1}H NMR: δ 5.84 (s, 1H), 4.11 (dd, 2H, J = 7.1, 14.2 Hz), 3.12 (m, 1H), 2.34−2.60 (m, 4H), 1.96−2.12 (m, 5H), 1.80 (m, 3H), 1.20−1.42 (m, 1H), 1.10 (m, 1H), 1.00 (d, 3H, J = 5.9 Hz), 0.91 (dd, 3H, J = 6.8, 6.8 Hz). IR: 2959, 2921, 2869, 2851, 1737, 1459, 1376, 1262, 1103, 1033, 895, 796 cm^{-1}. DCIMS (isobutane): m/z 411 (M + H), 395, 377, 378, 301, 221, 129.

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