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DRUG DEVELOPMENT OF THE ANTIMALARIAL AGENT
ARTEMISININ: TOTAL SYNTHESIS, ANALOG SYNTHESIS, AND
STRUCTURE-ACTIVITY RELATIONSHIP STUDIES

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The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.
The enantioselective total synthesis of (+)-artemisinin has been optimized and carried out at multigram scale. An alternate approach to the total synthesis afforded racemic 6,9-desmethylartemisinin (79) and a related analog 80. A synthetic intermediate from the total synthesis, (+)-acid 32, has been alkylated and led to numerous C-9 alkylartemisinin analogs 42 - 62. The acid 22 has also been converted into various N-alkyl amides, which in turn furnished 11-azaartemisinin analogs 64 - 69. Selected various alkylated analogs were converted into the corresponding dihydro-, alkylether derivatives based on arteether-type antimalarials. The total synthesis involved the substitution of a cyclohexyl ring, but at various stages the elaboration of cyclohexanes with less than the total number of requisite substituents resulted in the synthesis of ring cleaved analogs and partial structures of artemisinin: (+)-C/D, (+)-A/B/C, (+)-A/C/D fragments (see 81 - 25). Similarly acyclic analogs 26 and 22 were examined. All of these analogs have been assayed for in vitro antimalarial activity and form a foundation for an ongoing structure-activity relationship (SAR) investigation. At this preliminary stage, a model for improving activity by selecting C-9 substituents has emerged, and the 11-azaartemisinin analogs are comparable to artemisinin in vitro.
Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

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INTRODUCTION

Increasing resistance of the malaria parasite, *Plasmodium falciparum*, toward contemporary antimalarials is cause for concern.\(^1\) Fortunately, the relatively recent isolation and structure determination of the antimalarial constituent of the Chinese medicinal herb Qinghao\(^2\) (*Artemisia annua* L.) yielded the novel natural product (+)-artemisinin (1; qinghaosu, QHS). Subsequently this stable peroxide 1 emerged as a potent antimalarial\(^3\) against resistant strains of *P. falciparum*. The limited availability of the natural product coupled with its modest potency delineated the need for ready synthetic entry to the artemisinin tetracyclic framework. Many valuable contributions to total synthesis\(^4\)-\(^6\) and congener synthesis\(^7\)-\(^9\) have appeared in recent years. In this paper we describe our optimized total synthesis.

![Artether](image)

TOTAL SYNTHESIS OF (+)-ARTEMISININ

From a retrosynthetic standpoint, we felt that the most obvious intermediate in the production of 1 would be the "unraveled" \(\alpha\)-hydroperoxyaldehyde 2 because in a ketalization-like process, simple cyclodehydration of 2 should readily furnish the tetracyclic natural product 1. The inherent synthetic challenge for 1 thus lies in the preparation of the unstable aldehyde 2, and in commendable fashion others have employed an enol ether photo-oxygenation as entry to that functional arrangement.\(^4\)-\(^5\) By contrast, we took advantage of the ozonolysis of a vinyl-silane, a process reported to furnish the desired \(\alpha\)-hydroperoxycarbonyl moiety.\(^10\) Thus, the next retron in our analysis was the 2\(\beta\),6\(\beta\)-disubstituted cyclohexenyl silane 4, which, according to precedent, could afford 2 or the synthetically equivalent dioxetane 3 upon exposure to ozone.
Initially we chose to test elements of this approach to artemisinin in an abbreviated version of 4 that lacked the 2β-(3-oxobutyl) and 3α-methyl groups. Hence, on low-temperature ozonolysis of the vinyl silane 5 in methanol we were rewarded by the transient but stereo-exclusive formation of dioxetane 6 that was observed upon immediate analysis by NMR. On standing, the dioxetane 6 underwent rearrangement and cyclization to furnish the interesting hydroperoxy-lactone 7 in 54% isolated yield on a scale sufficient for X-ray structural study. In a related model system devoid of the propionic acid appendage, 8 was synthesized and examined for its behavior under these conditions. As hoped, the reaction of 8 with ozone proceeded without incident to provide a remarkably stable dioxetane 9. However, as expected, the appended ketone was an incompatible intramolecular cyclization partner: thermal retro-[2+2]cyclization of 9 was observed after several hours at room temperature and, consequently, transformation of 9 as an in situ intermediate was projected. Various attempts to obtain a stable analog of 1 from 9 at low temperature in aprotic solvents with acid to catalyze a rearrangement--akin to the spontaneous 6 to 7 transformation--met with failure. Ultimately dioxetane 9 was successfully intercepted in a methanolic solution containing boron trifluoride etherate and afforded the remarkably stable crystalline aldehyde 10 in 69% isolated yield.
The favorable outcome of these model studies implied that the keto-acid 4 would behave as desired on ozonolysis, initially giving forth a dioxetane, which would then undergo transformation to the natural product 1 on acidification.

A number of approaches to the requisite 2β,6β-disubstituted cyclohexylidenylsilane arrangement (4) were considered but ultimately discarded. For example, an appropriately protected 2,6-disubstituted cyclohexanone could in principle provide the vinylsilane 4 by a Wittig or Peterson olefination. Unfortunately, a well-known reagent for the latter process, bis(trimethylsilyl)methyl lithium, gives vinyl silanes exclusively from non-enolizable ketones.\textsuperscript{11} Furthermore, even in the unlikely event that the sterically bulkier Wittig counterpart, trimethylsilylmethylidene triphenylphosphorane, were to undergo addition, β-elimination would favor silicon over phosphorus.\textsuperscript{12} Although a noteworthy reagent for this transformation, trimethylsilyl(dimethylmethoxysilyl)-methyl lithium,\textsuperscript{13} is now available, we have found that whereas this reagent reacts reasonably well with hindered 2-substituted cyclohexanones,\textsuperscript{7b} its performance is seriously compromised with 2,6-disubstituted cyclohexanones.\textsuperscript{14}

An alternative approach that we examined involved the conceptual joining of the terminal ends of both the 2 and 6 substituents of the requisite cyclohexane 12.\textsuperscript{7e} For example, the known bicyclo[3.2.1]nonenone 13\textsuperscript{15} is incapable of deprotonation by the olefination reagent and, indeed, reaction with bis(trimethylsilyl)methyl lithium\textsuperscript{11} proceeded as desired to furnish the pivotal vinyl silane 14. Selective scission of 14, etc., then afforded access to compounds structurally similar to 4, but with one important drawback--incorporation of the 3α methyl group is not possible because the starting enamine reaction fails when β-alkyl substituents are in the cyclohexyl ring.\textsuperscript{15} Furthermore, the lack of C2 symmetry would introduce regiochemical problems. The use
of bicyclic vinyl silanes such as 14 was therefore restricted to the preparation of a few racemic artemisinin analogs.

Consequently, it was necessary to employ a less direct approach to the construction of the key vinyl silane 4. We recognized that the termini of the carboxyl and vinyl silane moieties were situated in a 1,5 arrangement and that this system might be available by a Claisen ester-enolate rearrangement of 15 as shown:

Indeed, this approach was shown to be viable because the simplified system 5 was prepared by Ireland-Claisen ester-enolate rearrangement of the corresponding α-propionyloxyallylsilane. Thus, on the basis of these results, the possibility of obtaining 4 via Claisen rearrangement of 15 was worth exploring. To complete our retrosynthetic analysis, a plausible route to 15 was proposed, involving straightforward homologation of the 2β,3α-disubstituted cyclohexanone 17 to the cyclohexene-carboxaldehyde 16, which in turn undergoes silylanion addition and subsequent acylation, as envisaged below:

With a reasonable approach outlined, we then set out to synthesize the requisite cyclohexanone 17 in optically active form. The use of the monoterpen R(+)-pulegone as starting material was exploited in this regard as shown in Scheme I. First, R(+)-pulegone 18 was
diisobutylaluminum hydride

-78°C, ether

99%

(+)-artemisinin, 1. R = Me;
20. R = Et; 37. R = n-Pr;
42. R = n-Bu

75% NaBH₄,
MeOH 0°C

36. R = Et
38. R = Pr

EtOH,
BF₃

3. R = Et (arteether)

Scheme I

aKey: a) alkaline HOOH, THF; b) NaSPh, THF; c) m-CPBA, CH₂Cl₂, -78°C; d) 2 LDA, HMPA or DMTP, THF, -35°C; then 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane; e) Al(Hg) amalgam, wet THF; f) p-CH₃PhSO₂NH²H₂, neat, 1 mm Hg; g) 4 BuLi, TMEDA, 0°C; then DMF;
h) DIBAH, Et₂O, -78°C; then TMSCl, pyridine, CH₂Cl₂; i) t-BuLi, THF, -30°C; then HOAc,
-78°C; j) propionic anhydride, DMAP, pyridine, CH₂Cl₂.

44. R = CH₂CH₂CO₂Na,
sodium artesunate

13

Key: a) alkaline HOOH, THF; b) NaSPh, THF; c) m-CPBA, CH₂Cl₂, -78°C; d) 2 LDA, HMPA or DMTP, THF, -35°C; then 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane; e) Al(Hg) amalgam, wet THF; f) p-CH₃PhSO₂NH²H₂, neat, 1 mm Hg; g) 4 BuLi, TMEDA, 0°C; then DMF; h) DIBAH, Et₂O, -78°C; then TMSCl, pyridine, CH₂Cl₂; i) t-BuLi, THF, -30°C; then HOAc, -78°C; j) propionic anhydride, DMAP, pyridine, CH₂Cl₂.
epoxidized with alkaline hydrogen peroxide, providing pulegone expoxide. Thiophenoxide opening of with concomitant retroaldol expulsion of acetone yielded regioisomerically pure thiophenylketone. Customary peracid oxidation of sulfide afforded the sulfoxide in good overall yield.

As outlined by Roush and Walts, the sulfoxide was converted to the corresponding dion with lithium diisopropylamide (LDA) and alkylated with n-butyl iodide to provide a diastereomERICALLY complex mixture that was then converted directly to 2-butyl-3R-methylcyclohex-2-en-1-one (50% yield, 6β:1α mixture at C-2) upon thermolysis. We found that sulfoxide could be alkylated with 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane and that the resultant complex mixture could be desulfurized with aluminum amalgam to furnish the desired ketone in 40-50% yield as a 9:1 (β:α) mixture at C-2. Surprisingly, alkylation of this sulfoxide dion was not improved using 2-(2-iodoethyl)-2,5,5-trimethyl-1,3-dioxane in place of the bromide. The alternate use of the dion of β-ketoester did not afford improvements in the yield of the alkylation step, and saponification of the alkylation product led to epimerization at C-2 (6:4 mixture). Although this approach to via sulfoxide was considered acceptable, it is clear that there remains room for improvement in constructing this functional arrangement.

With the ketone in hand, we then pursued its homologation to the unsaturated aldehyde. We expected that a regioisomerically pure vinyl anion would be accessible from the corresponding hydrazone, and that this anion could be intercepted with dimethylformamide to provide. Upon exposure of the ketone to p-toluenesulfonyl hydrazide in tetrahydrofuran (THF), solvolysis of the ketal group and subsequent hydrazone formation was observed. Under base catalysis with pyridine in THF, epimerization occurred at C-2 prior to hydrazone formation. Fortunately, we found that if the THF and pyridine were simply stripped away and the neat mixture was placed under vacuum, clean hydrazone formation in nearly quantitative yield was obtained. Subsequent treatment of hydrazone in N,N,N'-tetramethylenediamine (TMEDA) with four equivalents of n-butyl lithium afforded a red solution of vinyl anion, which was
quenched with dimethylformamide to afford the regiochemically pure \( \Delta^{1,6} \)-unsaturated aldehyde 16 in 70% yield (Scheme I). At this stage the minor 2\( \alpha \) diastereomer was conveniently removed by chromatography.

Initial efforts to transform the aldehyde 16 to the Claisen precursor 15 involved Brook rearrangement of the corresponding allylic silyl ether 25. The aldehyde 16 underwent smooth 1,2 reduction with diisobutylaluminum hydride in ether and subsequent silylation provided the Brook rearrangement precursor 25. Standard conditions for effecting the deprotonation of an allylic silyl-ether was employed\(^{22}\): treatment of 25 with sec-butyl lithium in the presence of TMEDA furnished the rearranged \( \alpha \)-silyl alcohol 26, but in modest yield with the recovery of the balance of the starting material 25. In an attempt to improve the conversion, the use of tert-butyl lithium promoted rearrangement in a somewhat better, but maximal, yield of 30%. The apparent disparity between the result for 25 and its 2,3-unsubstituted congener (Brook rearrangement yield of 74%)\(^{7a}\) is presumably caused by increased congestion from the large 2-butyl side chain in the transition state for the rearrangement of 25.

Nevertheless, the diastereomeric product 26 was funneled forward to test the validity of the Claisen approach. Thus, esterification of 26 with propionic anhydride offered the needed ester 15 along with the inseparable diastereomer 15a (1:1 ratio). Kinetic deprotonation of the mixture of 15/15a was effected with lithium N-cyclohexyl-N-isopropylamide (LICA) and, upon warming to room temperature, Ireland-Claisen ester enolate rearrangement\(^{23}\) was evident from the production of a diastereomeric mixture of carboxylic acids 27 in moderate yield. Obviously, it was hoped that the acid 4 would constitute part of the mixture and that subsequent deketalization, ozonolysis, and acid treatment would afford artemisinin.
However, after the aforementioned processing, no tetracyclic products were observed. This suggested that the rearrangement had occurred through a "α" (si) face transition state leading to C-6α diastereomers (i.e., 27) that are not capable of ultimate cyclization to tetracyclic products. This result was perhaps not surprising in light of molecular mechanics calculations, which revealed a substantial interaction of the Z-enolate methyl group with the axially disposed C-2 butyl side chain in the "β" face transition state. This interaction was relieved in the "α" face transition state, thus explaining the exclusive formation of undesired "α"-oriented products (i.e., 27).

We examined two alternate approaches that would circumvent these interactions. First, generation of the alternate E-enolate would remove the methyl-butyl axial interaction, making β products possible, but the product(s) would have threo geometry in the acid side chain. One result of this might be the production of 9-epiartemisinin 29, which we originally thought would epimerize to artemisinin under the cyclization conditions. Second, a methyl group could be removed from the transition state by using the acetate rather than the propionate ester, and the resultant product(s) would require a C-methylation to arrive at the requisite substrate. The first approach entailed treatment of the 15/15a mixture with a different amide base, lithium hexamethyldisilazane (LHMDS), which is known to provide enolate geometry ratios in the opposite sense to LDA. The resulting mixture of carboxylic acids 28, produced in modest yield, was deketalized and ozonized to afford an unknown, but chromatographically related, tetracyclic product, which we assumed was 9-epiartemisinin 29. However, this product was not epimerizable to artemisinin and thus we moved on to the next approach. It was later proven that (+)-9-epiartemisinin had indeed been prepared in this sequence, albeit in low overall yield.

Formation of the mixture of acetates 30/31 was straightforward. Subsequent generation of the enolate(s) with LICA as before produced numerous attendant by-products from self-condensation, but it was nevertheless possible to isolate a single carboxylic acid 32 in 29% yield. Upon deketalization with oxalic acid-impregnated silica gel, keto-acid 33 was obtained in 81%
yield. Subsequent ozonolysis in methanol afforded a complex product mixture that could be treated without purification with trifluoroacetic acid in chloroform to furnish (+)-9-desmethylartemisinin 34 in 56% yield. At this stage, it seemed apparent that desired tetracyclic products were being produced. However, to prove our structural assignments unequivocally, the total synthesis was completed before improving the total synthetic route. Hence, as shown in Scheme II, the acid 32 was converted to the corresponding methyl ester under basic conditions, enolized with LDA, and then alkylated with methyl iodide to provide the ester 35 as a 7:3 diastereomeric mixture (83%). Sequential deprotection of ester 37 and ketal functions gave the separable keto-acids 4 (major) and 37 (minor), whose respective stereochemistries were ascertained by conversion (or nonconversion) to natural product. The minor acid 37, upon ozonolysis and acid-catalyzed ring closure, did not afford artemisinin but instead a substance identical with 9-epiartemisinin 29. Control experiments further supported the identity of synthetic 9-epiartemisinin. Enolization of authentic artemisinin with LDA at low temperature followed by kinetic quench gave forth material identical to 29 produced either from 37 or from the propionate Claisen. To finish this preliminary work, the acid tentatively assigned as 4 was submitted to the usual conditions: ozonolysis and acid workup provided material identical in all respects to the natural product (+)-artemisinin (1).

With a workable route in hand, we then set about the task of improving the overall sequence leading to the natural product. Clearly, the route suffered from a lack of stereoselectivity in the Brook rearrangement and later in the side-chain alkylation. We felt that it was likely that only one of the diastereomers produced in the Brook rearrangement was leading to "β" targets. This was evident from the Claisen rearrangement: half of the product was acid 32; the remainder of the acidic component was not transformed to tetracyclic products on ozonolysis/acidification. In fact, examination of possible transition-state geometries for the Claisen rearrangement suggested that a difference might be expected between 30 and 31. With β- and α-face transition states, as well as boat and chair conformers, there are a minimum of eight possible transition states to consider for the mixture of 30/31. Excluding the boat conformers as being energetically unfavorable, there are still at least two possible transition states for each diastereomer. Drawing the four most likely transition states derived via MMP2 (Fig. 1), we can readily see that 30β would be preferred over 30α: a sizeable axial-axial trimethylsilyl-C2-butyl interaction is avoided and the trimethylsilyl group is in a pseudo-equatorial relationship. For 31, the opposite sensibility seems likely: 31α is preferred over 31β, again because of the equatorial disposition of the trimethylsilyl group. If these arguments are valid, then diastereomerically pure 30 should afford only desired erythro acid upon Claisen rearrangement. Unfortunately, it was not possible to
Scheme IIa

Key: a) LICA, THF, -78°C to 23°C; b) 10% aq. oxalic acid, SiO₂, CH₂Cl₂; c) O₃/O₂, MeOH; then TFA, CHCl₃; d) Me₂SO₄, K₂CO₃; e) LDA, THF; MeI; f) KOH, MeOH; g) LDA, THF, -40°C; then HOAc.
Figure 1. Potential transition states in the Claisen Ester-Enolate rearrangement of diastereomers 30 and 31.

separate diastereomers 30/31 chromatographically, and the stereoselective synthesis of 30 was targeted.

Molecular mechanics calculations of the unsaturated aldehyde 16 revealed an interesting possibility. A comparison of the lowest energy conformers of 16 demonstrated a clear preference for diaxially oriented 16a (ΔE_{rel} > 3 Kcal/M). Inspection of this conformer suggested that an incoming nucleophile could approach from one face of the carbonyl to lead to a single product whose relative stereochemistry corresponds to diastereomer 30 (Fig. 1), as depicted in Figure 2.

Thus, if trimethylsilyl anion were used as the nucleophile, then the requisite diastereomer 30 could become available. Of the various counter ions, Li⁺, Na⁺, and K⁺ have been examined by others. None of these species were suitable for direct (1,2) addition to carbonyl compounds. For example, trimethylsilyl lithium (Me₃SiLi) adds nicely 1,4 to enones by a one-electron-transfer process, but does not provide α-silyl alcohols from ketones or aldehydes.³⁰ However, it has been
found that tris(trimethylsilyl)aluminum etherate (TTAE) will undergo unfettered 1,2-addition to benzaldehydes to furnish α-silyl alcohols. In our hands, this reagent reacted with cyclohexene carboxaldehyde (38) at low temperature in ether to afford the corresponding allylic alcohol in nearly quantitative yield. Furthermore, the intermediate aluminate salt 38a was stable to the Brook rearrangement as compared to the lithium analog. As a result, the aluminate salt was captured in situ with acetic anhydride (accelerated by 4-(N,N-dimethylamino)pyridine) to give the desired silyl acetate 39 in 90% yield.

With these encouraging results in hand, we returned to aldehyde 16. Upon reaction with TTAE and subsequent quench with acetic anhydride, 16 was transformed to a single diastereomer 30 in 88% yield. Although it was not determined which diastereomer (30 vs 31) had actually been produced at this stage, the material underwent ester-enolate rearrangement (2.1 LICA, THF, -78°C to 23°C) to a single acid, identical to 32, in 51% yield on the first attempt. The balance of the material from base treatment of 30 corresponded to competing Claisen condensation: β-ketoester 40 and silyl ether 25 (together with desilylated alcohol) were obtained in yields of 12 and 28%, respectively.
With a pure enantiomer of 32 in hand, it was now possible to determine its stereochemistry. Regiochemistry about the vinyl silane moiety in 32 was ascertained by nuclear Overhauser enhancement difference (DNOE) experiments. Decoupling experiments with either downfield methylene proton adjacent to the carboxylic acid (δ 2.62 (dd, 1H, J = 9.5, 15.0 Hz) or δ 2.48 (dd, 1H, J = 5.9, 15.0 Hz)) identified the C-6 proton resonance (δ 2.78 (m, 1H)). Similarly, the C-2 proton resonance was located (δ 2.11 (m, 1H)). Irradiation of the vinylsilane proton singlet at δ 5.38 led to an enhancement of 10% of the C-6 and none at the C-2 proton resonance, thus demonstrating a syn relationship between the vinyl proton and the C-6 proton. The fact that acid 32 was converted to the natural product confirmed that a β-oriented side chain had been produced at C-6 and clinched the stereochemistry of 32 as depicted.

With the desired stereocontrol mastered, the preparation of 32 was optimized. To minimize the unwanted formation of Claisen condensation products, we examined various conditions for the rearrangement. At least two equivalents of base were required and with a single equivalent, only self-condensation was observed. Further, excess base did not improve the yield. Perhaps the by-products formed early during enolization react further with remaining base/enolate in such a manner that two equivalents are needed. In addition, the product distribution was influenced by the amide base employed. With highly hindered lithium bases such as LICA or lithium tetramethylpiperidide (LiTMP), self-condensation products accounted for as much as half of the reaction products. When less bulky amides were used, the rate of deprotonation became more competitive with self-condensation, but instead accompanied by an increased amount of direct displacement by amide anion on the ester carbonyl (low acetoacetate-high silyl ether ratio, with attendant acetamide formation). For example, LDA, lithium diethylamide (LDEA), and lithium pyrrolidineamide (LiNC4H8) each gave 32 in yields of 25, 63, and 20%, respectively. Thus we settled for the optimum reached with LDEA, which gave the desired product 32 in 63% yield.

We next examined the methylation of the clean carboxylic acid 32. Initial efforts at dianion formation failed and therefore the cumbersome route in Scheme II had been employed. A
re-examination of this reaction showed that elevated temperatures were required to form the dianion of acid 32. Thus, warming of a THF solution of 32 with two equivalents of LDA at 50°C for two hours led to an orange solution of dianion. Addition of methyl iodide then gave rise to a single diastereomERICALLY pure homologous acid, 41, in nearly quantitative yield (Scheme III). The stereochemical identity of 41 was determined as erythro by its conversion to the natural product 1. Furthermore, substitution of 14C-methyl iodide in this sequence led eventually to the synthesis of (+)-14C-artemisinin. It has also been found that this alkylation is of general utility in that a wide variety of alkyl halides can be employed, furnishing a myriad of analogs of the natural product.

We have since attempted to understand the outcome of this alkylation, but so far MM2 calculations are insufficient (we have not been able to take into account the counter ions or their interaction with solvent) and actually suggest that the wrong product should predominate. Nevertheless, this fortuitous outcome was gratefully accepted and the final stages of the synthesis were reviewed for improvement. First, if the Claisen rearrangement required excess base, and if the dianion formation could be combined at the terminus of the rearrangement, then it was considered possible that the use of several equivalents of base with the acetate 30 would lead directly to the dianion of 32, which could then be alkylated in situ to provide the homologated acid 41 in one pot. Indeed, treatment of 30 with four equivalents of LDEA (-78°C to 50°C) provided the desired dianion of 32, which upon cooling and admission of methyl iodide, gave the acid 41 in 57% yield.

Finally, the conversion of acid 41 to the natural product 1 was reconsidered. Previously, separate deprotection of the ketal 41 to ketoacid 4 (80% yield) was done prior to ozonolysis. The possibility of a one-pot ozonolysis, deprotection, and cyclization sequence was entertained. Thus, ozonolysis of 41 in dichloromethane, when followed by successive addition of aqueous sulfuric acid and silica gel, led in reasonable yield (33-39%) to (+)-artemisinin 1, identical in all respects to the authentic natural product. Other solvents were examined for this sequence: originally we observed intermediate dioxetane 2 to hydroperoxide 2 rearrangement in methanol, but that solvent is incompatible with the formation of the lactone from 41 to the natural product. Interestingly, other solvents examined for this final sequence (hexane, ethyl acetate, etc.) were poor in comparison to dichloromethane. When a fairly dilute solution of 41 in dichloromethane (0.01M) was subjected to ozone, a higher yield of artemisinin (1) was obtained because of a lower ratio of non-peroxidic desoxyartemisinin. Therefore, additives such as t-butyl hydroperoxide and t-butyl peroxide were used to maintain an oxidative environment during acid treatment after ozone exposure, but they had little effect. In fact, crude products were much cleaner by thin-layer chromatography with the addition of t-butylhydroxytoluene (BHT) subsequent to reaction of 41 with ozone, and a slightly higher yield of artemisinin was obtained.
Scheme III

Key:  a) Tris(trimethylsilyl)aluminum etherate, Et₂O, -78°C; then Ac₂O, DMAP, to 23°C;  
b) 2LiNEt₂, THF, -78°C then 23°C; c) 2LDA, THF, 50°C; then CH₃I, -78°C; d) 4LiNEt₂, THF,  
-78°C to 50°C, then CH₃I, -78°C; e) O₃/O₂, CH₂Cl₂, -78°C; then SiO₂ followed by aq. 3M  
H₂SO₄.

In summary, we have developed a stereoselective 10-step total synthetic route to the  
antimalarial sesquiterpene (+)-artemisinin (1). Crucial elements of the approach include  
diastereoselective trimethylsilylanion addition to the α,β-unsaturated aldehyde 16, and a tandem  
Claisen ester-enolate rearrangement-dianion alkylation to afford the diastereomerically pure erythro  
acid 41. Finally, acid 41 was converted in a one-pot procedure involving sequential treatment with  
ozone followed by wet acidic silica gel to effect a complex process of dioxetane formation, ketal  
deprotection, and multiple cyclizations to the natural product (+)-artemisinin (1). The route was  
designed for the late incorporation of a carbon-14 label and the production of a variety of analogs  
for structure-activity-relationship (SAR) studies. We were successful in preparing 2 mmol of C-14  
I under contract DAMD17-88-C-8047, and analog work directed toward SAR under this contract  
follows.
ANALOG SYNTHESIS

We synthesized a number of analogs, which may be divided into four major groups: (1) optically active, substituted QHS (42-69, Fig. 3) and dihydro-QHS (e.g., arteether, 70-78, Fig. 4), analogs that were produced via branches from our total synthesis; (2) racemic analogs derived from bicyclic synthetic intermediates, 6,9-desmethyl QHS (79) and truncated system 80 (Fig. 5); (3) seco-analogs of racemic nature with lactone substituents (81-84) and optically active substituted cyclohexanes (85-95) (Fig. 6); and (4) highly abbreviated and flexible racemic QHS analogs 96 and 97 (Fig. 6).

![Figure 3. Structures of substituted QHS analogs prepared under DAMD17-88-C-8007.](image-url)
70, \( R = H, R' = H \)
71, \( R = H, R' = Et \)
72, \( R(\beta) = R'(\alpha) = -\text{CH}_2\text{CH}_2\)
73, \( R(\beta) = Et, R' = Et \)
74, \( R(\beta) = Pr, R'(b) = Et \)
75, \( R(\beta) = Me, R'(b) = -\text{O-O-Bu}^t \)
76, \( R(\beta) = Me, R'(b) = \text{CH}_2\text{CH}((\text{OCOC}_{15}\text{H}_{31})\text{CH}_2(\text{OCOC}_{15}\text{H}_{31})) \)
77, \( R(\beta) = Me, R'(a) = -\text{COO-cholestanyl} \)
78, \( R(\beta) = Bu, R' = H \)

Figure 4. Structures of dihydro-QHS analogs prepared under DAMD17-88-C-8007.

Figure 5. Analogs accessed through the bicyclocdecene route

All of these analogs compose our first extensive sample group for a SAR study. The biological results are in progress for a number of these new analogs, and the completed data are discussed in a separate section.
81, $R^1 = R^2 = R^3 = H, R^4 = Me$
82, $R^1 = R^2 = H, R^3 = CH_2CO_2H, R^4 = Me$
83, $R^1 = R^2 = H, R^3 = Bu, R^4 = Me$
84, $R^1 = R^2 = H, R^3 = \text{dimethyl}, R^4 = Me$
85, $R^1 = Me, R^2 = H, R^3 = Me, R^4 = Me$
86, $R^1 = Me, R^2 = H, R^3 = Me, R^4 = H$
87, $R^1 = R^2 = R^3 = R^4 = Me$

88, $R^1 = Me, R^2 = H, R^3 = Me$
89, $R^1 = R^2 = Me, R^3 = H$
90, $R^1 = R^2 = R^3 = Me$

91

92, $R = \text{OCOMe}$
93, $R = \text{OCOEti}$
94, $R = \text{OCO}_2\text{CH}_2\text{Ph}$
95, $R = H$

Figure 6. Various Seco-analogs of artemisinin prepared under DAMD17-88-C-8007.

Substituted QHS and Dihydro-QHS Analogs

From Figure 3, the nor-analog 42, aza-analog 64, and homologue 43 were first prepared via appropriate manipulation of the intermediate ester of acid 32, available from our total synthetic manifold. An account of this effort was detailed in our first publication in Tetrahedron Letters in 1987.\textsuperscript{6} It was further shown that the nor-analog 42 could be obtained upon ozonolysis of the corresponding keto-acid derived from 32. We later showed that the acid 32 could be converted directly in one pot to desmethylartemisinin 42 without prior removal of the ketal.
Furthermore, as described in the first section, dianion alkylation of the acid 32 is most convenient and leads to an array of desirable products. With this new methodology available, the analog 58 was prepared via alkylation of the LDA-generated dianion of 32. In this case, t-butyl bromoacetate was used to provide initially acid-ester 98, which was submitted to successive ozone addition and acidification to give directly the proper tetracyclic peroxide system 99, which was subsequently treated with trifluoroacetic acid to cleave the t-butyl ester to the free acetic acid appendage of target 58 in 20% overall yield from 98.

In a similar, straightforward manner, the homologues 43 through 56 were made on a preparative scale via alkylation of 32 to give the addends 43a through 56a. Subsequent exposure of the resultant alkylation products to ozone, followed by acidification, gave the targets 43-56.
The synthesis of the allyl analog 57 was somewhat more problematic. Direct insertion by
dianion alkylation (as above) would work, but upon ozonolysis, cleavage of the olefin unit would
be anticipated. Thus, a roundabout method was employed wherein the enolate of the nor-analog
42 was generated at low temperature and alkylated to provide an allylated tetracycle, either 57 or
the α-epimer 59. Initially we felt that if the undesired α epimer had been produced, it would be
readily epimerizable to β-57 because 59 is axially substituted. In fact, prolonged treatment of the
product did not result in epimerization, so we assumed the product to be 57. This issue was
passed over for some time; then, when it became desirable to synthesize the crotyl homologue(s)
for SAR (60 and 61), we noticed coupling-constant discrepancies. Indeed, on close examination
of the allyl product, the same thing was seen. When the allyl analog was treated with LDA at low
temperature and quenched with acid, a new product was formed having the correct NMR. Thus,
allylation of 42 gives the α-substituted material 59 initially, which can then be epimerized using
kinetic base.
In addition, it was found that epi-artemisinin 62 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 63.

Another convenient class of analogs was available from the pivotal acid 32. We envisaged conversion into amides and hence to lactams on ozonolytic cleavage/cyclization. Thus, a cold solution of the triethylammonium carboxylate salt of 32 was treated with ethyl chloroformate and the resultant mixed anhydride reacted with various primary amines to give the amides 64a-69a, which proved satisfactory substrates for reaction with ozone and subsequent acidification to afford the lactam analogs 64-69.

In particular examples, further transformations were warranted for deprotection or derivatization: the N-(2-acetic acid) analog 67 was provided upon hydrolysis of ester 67b with trifluoroacetic acid in dichloromethane.

Other workers have described the higher potency of arteether relative to artemisinin (1). This had forecast the selective reduction of the lactone of our novel analogs as a routine method, with the likely potential to increase antimalarial activity. As shown in Figure 4, we prepared six analogs from the corresponding homologous lactones as well as three new analogs from artemisinin itself. These are discussed below.

Reduction of QHS (1) with NaBH₄ by a known method afforded dihydroqinghaosu (DHQHS). Treatment of DHQHS under anhydrous conditions with acid and tert-butylhydroperoxide gave the desired perether 75 in 62% yield. The C-10 ether was shown to be
of the β configuration by NMR ($J_{9,10} = 4.5$ Hz). The perether 75 was tested for antimalarial activity in vitro.

Similarly, we converted our homologues 43/44/45 to their corresponding lactols, which upon treatment of 43/44 with acidic ethanol, afforded β-ethyl ether targets 73 and 74. In this case the C6 ether was also of the β configuration, as determined by NMR ($J_{6,7} = 3.5$ Hz) comparison with the trace accompanying alternate α-isomer3 (also see Experimental Methods). The lactol 45 was submitted unchanged for in vitro assay. Finally, the nor-lactone 42 was transformed into the lactol 70, which was then converted to the ether 71. All were tested for SAR and will be discussed in a later section of this report.

In addition to the per-ether analogs of dihydro-QHS, carbonate analogs have been prepared by acylation of dihydro-QHS. Although numerous analogs derived from DHQHS have appeared in the literature, linkage of DHQHS to cell-membrane components has not been disclosed. Thus, we have synthesized the analogs 76 and 77 where DHQHS is linked to either cholesterol (for 77) or diglycerides such as dipalmitin (for 76). It is expected that much of the damaging action of this class of drugs occurs in the parasite cell membrane; thus, 76/77 would be actively taken to and/or incorporated into the site of action. Also, it was hoped that plasma half-life/metabolism might be extended by this approach (via depot into fatty tissue).
Analogs of Artemisinin Derived from Bicyclo[4.3.1]decenones

We had previously submitted for biological evaluation the analog (±)-6,9-desmethylartemisinin (79), which was prepared according to the synthesis route in Scheme IV. This synthesis is described in U.S. Patent application #108, 145. We have published the preparation of analog 79 with full experimental details.7e Approximately 200 mg of 79 was made. Unfortunately, initial efforts to resolve 79 into its two optical isomers with cellulose triacetate37 have failed.

In the preparation of 79, a Wittig-type reaction of 102 to 103 served to incorporate carbons needed to build the tetracyclic system of artemisinin. As seen in Scheme V, we took a portion of diene 101 and bypassed the introduction of any other carbons. After sequential deprotection of 106 via 107 and 108, closure to a new, more compact tetracyclic peroxide 80 was accomplished with our existing methodology.
Tricyclic (seco) Analogs of Artemisinin

Ring B Seco Analogs

In the past we have synthesized tricyclic analogs of QHS (1), such as 110, from simple materials (109).

The fact that 110 has about 20% of the activity of 1 and is somewhat easier to synthesize has stimulated further efforts in this area.
SAR data indicated that additional alkyl groups in the vicinity of the peroxy group (110 vs. 111) reduced activity substantially. Because we wished, for similar reasons, to examine the lactone ring of 110, we prepared the butyl derivative 83 as shown in Scheme VI.

Acetylation of the alcohol 112 gave the ester 113 in 87% yield after distillation. Claisen rearrangement of 113 using lithium diethylamide as base avoided the usual competing self-condensation side reactions seen with other bases and gave the acid 114 in excellent yield (86%).

We did not know whether alkylation of the dianion derived from 114 would proceed diastereoselectively, as had occurred in the total synthesis 32 → 41. Thus, the dianion of 114 was alkylated with methyl iodide and proceeded, quite unexpectedly, with complete diastereoselection to give 115 in 73% yield. The structure 115 was correlated with the known propionate Claisen product, 119 → 115. We were therefore confident that the alkylation of 114 with butyl iodide would give the desired diastereomer, and so we prepared the acid 116 in 93% yield. On ozonolysis, 116 was transformed to the hydroperoxide 118 (55%) as expected. Finally, 118 was treated in acetone with TFA to give the desired analog 83. The butyl derivative 83 was evaluated for biological activity.

Other racemic analogs 81, 82, and 84 were prepared as shown either in Scheme VI or below, to examine the effects of systematic variation on the lactone ring in some readily made analogs. The alcohol 112 served as starting material for 81, 82, 84 in now-familiar synthesis sequences. For example, the corresponding acetate 113 was made in quantitative yield and underwent Ireland-Claisen rearrangement to acetic acid 114 in 86% yield. The vinylsilane acid 114 was carefully treated with ozone/oxygen to provide the hydroperoxy lactone 117 in 17% yield; subsequent treatment of 117 in acetone with trifluoroacetic acid gave the desired tricyclic analog 81 in 38% yield.
Scheme VI
Access to analogs with a higher degree of substitution was easily obtained. From either the propionate ester 119 or acetic acid 114, we previously made the propionic-acid-appendaged 115, which was in turn alkylated to the gem-dimethyl acid 120 in 76% yield (93% based on recycled starting material). The vinylsilane of 120 underwent addition of ozone to eventually afford hydroperoxide 121, and final ring closure was accomplished with trifluoroacetic acid and acetone to afford gem-dimethyl analog 84 in 19% overall yield from 120.

\[
\text{t-BuMe}_2\text{Si} \quad \overset{2\text{LDA;}}{\longrightarrow} \quad \text{t-BuMe}_2\text{Si} \quad \overset{\text{O}_3}{\longrightarrow} \quad \text{t-BuMe}_2\text{SiO} \quad \overset{\text{acetone, TFA}}{\longrightarrow} \quad \text{84}
\]

Along another parallel synthesis avenue, upon esterification of alcohol 112 the hemisuccinate 122 was obtained in 28% yield (64% based on recyclable starting material). The unprecedented Ireland-Claisen rearrangement of a hemisuccinate was effected by excess LDEA in THF. Upon warming overnight from -78°C, the diacid 123 was produced in 76% yield. The geometry depicted for 123 was expected by analogy and confirmed by DNOE experiments. Treatment of diacid 123 with ozone led to production of a very labile hydroperoxide 124, which was therefore treated immediately with acid and acetone to give carboxyl analog 82 in 6% overall unoptimized yield from 123.
To date we have obtained enough of 81 for biological evaluation. Analogs 82 and 84 await resynthesis to obtain sufficient quantities for testing. However, on inspection of the $^1$H NMR spectra, one sees routine temperature-dependent behavior by 81 and 82. By comparison, gem-dimethyl analog 84 has a sharply resolved $^1$H NMR spectrum at room temperature. The ramifications of the different conformational natures of 81-90 and other similar analogs on biological activity may be a promising area of future exploration.

Within this class of tricyclic analogs of 1, a major area of interest has been the synthesis of an optically active substance, as previously submitted analogs were racemates. Accordingly, we designed a synthesis with a homochiral starting material possessing the correct absolute configuration. Thus, analog 88 was synthesized from 3R-methylcyclohexanone 125 (commercially available) as outlined in Scheme VII.
The hydrazone $126$ was formed quantitatively in THF upon mixing the ketone $125$ with p-toluenesulfonylhydrazide. Evaporation of solvent afforded $126$. Shapiro reaction of $126$ with alkyllithium in TMEDA gave a vinyl anion, which was quenched with dry DMF to afford the isomeric aldehydes $127/128$ in modest yield (1:1 mixture). Attempts to improve this reaction by altering the base were unsuccessful. Silylanion addition to $127/128$ followed by in situ acylation gave the propionate esters $129$ in good yield. At this stage, isomeric contaminant could not be removed and was simply carried through the synthesis. Thus, Claisen ester-enolate rearrangement of $129$ gave a complex mixture of acids $130$. At this point some chromatographic separation was possible, and $130$ had a lower percent of isomeric contamination than did $129$. Ozonolysis of $130$ followed by cyclization in acetone afforded only one discernible product: the isomeric analog $88$. The fact that $88$ and not $85$ had been produced by the sequence in Scheme VII was determined by independent synthesis of $85$, as shown in Scheme VIII.
Scheme VIII
The chiral ketone 131, prepared from isopulegol, was reacted with methoxydimethylsilyltrimethylsilyl-methyl lithium\(^{14}\) to afford 132 as an E/Z mixture. Simple deprotection/oxidation served to convert 132 to the acid 133. Upon ozonolysis of 133 in methanol, removal of solvent, and addition of either acetone or acetaldehyde and acid catalyst, the tricycle 85 and known 86\(^{13}\) were produced. The fact that a known product was produced from a common precursor was sufficient proof of structure 85. The peroxide 85 (Scheme VIII) was slightly different from 88 by NMR, although mp’s and \([\alpha]_D\) were quite similar. To synthesize the methyl homologue, 4,5-secoartemisinin 87, alkylation of the starting ketone 131 was performed, providing 135. Carrying out the synthesis as before, as shown in the scheme, furnished the desired seco analog of artemisinin, 87. As before, we were somewhat worried about the structure assignment to 87 and thus undertook an X-ray crystallographic analysis of 87. We were rewarded with the correct stereochemistry.

The earlier regioisomeric problem upon fragmentation of the tosylhydrazone (i.e., production of mix 127/128') was overcome by increased substitution for increased selectivity. Therefore, 3R-pulegone was used as a starting material for synthesis (Scheme IX). The enolate of pulegone was generated with lithium isopropylcyclohexylamide (LICA) and alkylated with methyl iodide to furnish mainly 2,3-dimethyl-6-isopropylidene cyclohexanone 137 along with by-product 138, which was previously observed by Reusch et al.,\(^{34}\) but 138 did not react in the following conversion of crude material. When the mixture containing the
Scheme IX
isopropylidene 137 was placed in acid and submitted to prolonged heating, acetone distilled prior to the water azeotrope of the epimeric mix of 139:140 (1:1.96, as determined by NMR) in 72% yield. The corresponding tosylhydrazone mix 141 from the mixture of ketones was made as before and underwent n-butyllithium-effected fragmentation in TMEDA to a regioisomerically pure cyclohexenyl anion, which was capped with dimethylformamide to afford isomeric aldehydes 142 in 76% yield. The mixture was treated with tris(trimethylsilyl)aluminum (III) etherate7 and followed by acetylation to provide a mixture of all possible diastereomers of 143. The lack of selectivity was surprising in contrast to the total synthesis of QHS, in which a synthetic intermediate substrate differs in the presence of a 6'-methyl instead of a larger alkyl chain. Regardless, the mixture 143 upon exposure to lithium diethylamide rearranged to a mixture of diastereomeric cyclohexylacetic acids, which upon rigorous chromatographic separation furnished geometric isomers of acid 144 in a 1:1 ratio by NMR, in 28% yield. The acid 144 was submitted to single-pot exposure to ozone and acidification to give trioxane 89 in 22% yield. Alternatively, the acid 144 was methylated via the corresponding LDA-generated dianion to the propionic acid 145, which was subsequently reacted with ozone and acidified to provide trioxane 90. As discussed above, these particular analogs are isomeric about all but the starting 3R chiral center. Close inspection reveals that they are antipodal (except for the 3-methyl) to the materials prepared from Scheme VIII). The two optically active trioxanes 89 and 90 have been assessed for their antimalarial activity. In addition, all optically active trioxanes display temperature-dependent NMR behavior, and we are using these data for a comparison with the low-energy conformers predicted by molecular mechanics. This study is the subject of a manuscript submitted to the Journal of Organic Chemistry (P. Crews, W. Inman, M. A. Avery, and W.K.M. Chong).

**Ring D Seco Analogs**

This novel class of artemisinin (1) analogs is derived conceptually by scission of the 8a, 9 bond of 1:

![Diagram of Ring D Seco Analogs](attachment:image.png)
Such compounds are expected to possess useful antimalarial activity because the crucial peroxy moiety is held in the requisite relative orientation for maximal activity yet the carbonyl group is now capable of rotation into new and novel orientations unavailable to the natural product. Furthermore, the carbonyl substituent is now readily introduced by simple acylation reactions. Other virtues of this class of compounds are: (1) synthetic accessibility (low number of reactions in sequence); (2) wide variety of analogs available (type and position); and (3) optical activity.

As shown in Scheme X, 93 was available from the common, total-synthetic, intermediate 17. Using newly reported methodology for the introduction of vinylsilanes, 14 17 was reacted smoothly with methoxydimethylsilyltrimethylsilyl methyllithium in pentane to afford the E/Z vinylsilane 146 in 54% yield. The main by-product in this reaction was the ketone 17, which could be recycled; thus, based on recovered 17, the yield of 146 was 93%. Hydrolysis of the ketal 146 occurred without protodesilylation upon exposure to aqueous oxalic acid absorbed onto silica gel to give the ketone 147 in 80% yield. Upon low-temperature ozonolysis of 147 in methanol, a remarkably stable dioxetane 149 was produced, as evidenced in the $^1$H NMR spectrum (δ 6.1, s). On prolonged standing, 149 underwent [2 + 2] cycloversion to mainly afford the diketone 150. By contrast, when dioxetane 149 was intercepted with Lewis acid (BF$_3$), a crystalline aldehyde-ketal (91) was produced in good yield (69%).
Scheme X

Key: (a) MeOMe, SbCl₃, MeOH, i-Pr₂Li, pentane; (b) aq. oxalic acid, silica gel, CH₂Cl₂; (c) Cl₂/Cl₂, MeOH, -78°C; (d) O₂/O₂, CH₂Cl₂, -78°C; (e) CCl₄, 25°C; (f) moist CH₂Cl₂, TFA; (g) c followed by BF₃ etherate; (h) NaBH₄, MeOH, 0°C; (i) BF₃ etherate, MeOH, (MeO)₂CO₂H; (j) RCOX, Amberlyst-15, solvent; (k) RCOX, DMAP, CH₂Cl₂; (l) p-TsA, CH₂Cl₂.
The aldehyde 21 was a useful intermediate due to its chemical stability in storage and ready conversion to artemisinin analogs. On treatment of 21 in propionic anhydride with protic acids (HClO₄ or H₂SO₄) or more conveniently with polymer-bound acid (Amberlyst-15), with or without co-solvent (CH₂Cl₂), the 8a,9-seco analog of artemisinin 23 was obtained in 22% yield. It was also possible to treat the dioxetane 149 under the same conditions to arrive at 22 or 22 by substituting acetic anhydride for propionic anhydride, respectively, and in this fashion the analog 92 was obtained in 30% yield.

Hydrolysis of the dioxetane 149, or of the ketal 21, lead to an inseparable mixture of the expected product 151, as well as the bicyclic isomer 152. The mixture was 1:2 (151:152), and underwent standard acylation reactions to give, for example, 22 on treatment with Ac₂O/pyridine/CH₂Cl₂. Carbonates were available from 151, such as 94, on treatment with various chloroformates in pyridine/CH₂Cl₂. In other words, the alcohol 151 could be funneled away from the mixture by reaction with electrophiles, providing the desired tricyclic products.

The bicyclic aldehyde 21 could also be isomerized to the tricyclic ketal 154 under dehydrating conditions in the presence of an alcohol, but this material was not resynthesized on a large-enough scale to permit testing.

Finally, facile reduction of the aldehyde 21 to the alcohol 153 occurred with NaBH₄ in MeOH at 0°C. Exposure of 153 to acid in CH₂Cl₂ led to the expected trans-ketalization product 25 in 79% overall yield. The product 25 is, of course, the A, B, and C rings of artemisinin.

**Flexible, Abbreviated QHS Analogs**

In connection with our quest to identify the minimal structural requirements and the design of increased flexibility for antimalarial activity among the QHS class of compounds, we conceptually cleaved all the rings in QHS (Scheme XI) and targeted the peroxide esters 26 and 27, which were prepared as rapidly as hoped. Commercially available 2-ethylbutene was epoxidized to 155, which was ring-opened in situ upon addition of t-butyl hydroperoxide and p-toluenesulfonic acid. The crude peroxide alcohol 156 was divided into equal portions and acylated to either propionate 26 or butyrate 27, respectively. These esters were tested for antimalarial activity.
BIOLOGICAL RESULTS

The astounding antiparasitic profile exhibited by artemisinin combined with certain drawbacks to its use—such as its limited availability (<0.5% from Artemisia annua L.), relatively low potency in man (0.9-1.2 g/3 days), lack of substantial oral activity, poor oil- or water-solubility, and fetotoxicity—have prompted the search for analogs with more desirable pharmacological properties. Along these lines, certain limited improvements have been made. Some 20 analogs of artemisinin have been reported, and the synthesis of all of them begins with naturally derived 1. Surprisingly, 1 can be selectively reduced with NaBH₄ to afford dihydroartemisinin, which has been shown to be roughly ten times as potent as the parent material 1. Furthermore, the lactol DHQHS has been converted to the various ethers by treatment in ROH with BF₃ (the products arising from acetal formation). Notably, artemether and arteether have been prepared in this manner. These compounds have good oil-solubility and are roughly ten times as active as the natural product. Hence they partially address the issue of improved utility in that they are more potent than 1 and are more readily formulated as injectables (s.c. or i.m. route). Not unexpectedly, DHQHS can be acylated to yield esters or carbonates. Again, the potency of these analogs is generally an order of magnitude higher than that of the natural product 1. Of greatest interest amongst the derivatives is the hemisuccinate derivative commonly referred to as sodium artesunate. This compound enjoys the attributes of enhanced potency and water-solubility (hence its suitability for the i.v. route of administration), but it suffers from problems associated with its intrinsic instability, as evidenced by a short shelf life and decomposition in aqueous medium.
Although the aforementioned analogs provide a very modest contribution to the knowledge of structure-activity relationships (SAR) of 1, the goal of obtaining the ideal analog of artemisinin for the treatment of malaria requires much more SAR information. A few compounds related to 1 are scattered throughout the literature and are of interest in light of our desire to construct an SAR framework on which to build the rational design of analogs of 1.

For example, deoxyartemisinin 1a (which lacks the peroxide linkage of 1) is virtually topologically identical to 1 but is devoid of antimalarial activity. This deoxy analog 1a is a human urinary metabolite of 1, but can also be synthesized from 1 by treatment with Ph3P. Additional urinary metabolites such as dihydrodeoxyartemisinin and the so-called crystal-7 are also devoid of antimalarial activity.

These data strongly suggest that the peroxy group is essential for the antimalarial activity observed in 1. This has raised the obvious question as to whether simple peroxides would be effective against Plasmodia. To test this, various randomly selected peroxides such as ascaridole, tert-butyl hydroperoxide, and hydrogen peroxide have been tested in vitro and in vivo against malaria-infected cell cultures or rodents. In an in vitro test system conducted at the Walter Reed Army Institute of Medical Research (WRAIR), ascaridole had roughly 10% the activity of 1 and, in general, peroxides all show very low antimalarial activity relative to artemisinin (1). In other laboratories using dissimilar in vitro techniques, tert-butyl hydroperoxide was found to be (by extrapolation) roughly 10,000 times less active than 1 and to be similar to hydrogen peroxide H2O2. In in vivo testing, ascaridole was orally inactive, and simple hydroperoxides showed protective effects against malaria infestation when administered i.p. The results presented for a range of peroxides or simple hydroperoxides tend to support the hypothesis that the peroxy group in 1 is essential for activity but, more important, highlights the strong dependence of activity on topology (shape, size, and polar-group arrangement).

Two peroxy-containing unsaturated versions of 1 are known. These are dehydroartemisinin (155) and the olefinic compound 156.
The exomethylenelactone **155** is about one quarter as active as **1**, whereas the olefin **156** is entirely inactive. When the various structures above are compared with **155**, a suspicion arises that the C-9 and C-10 positions of **1** can withstand substantial variation without loss of biological activity. However, this suspicion is difficult to reconcile with the lack of activity displayed by the olefin **156**. Molecular models (MM2) constructed to permit comparison of **1** vs **156** and **1** vs **155** are not particularly illuminating. We believe that the explanation for the difference in activity of **155** vs **156** does not reside in the presence or absence of an oxygen substituent at C-10 or in minor differences in the ring conformations between **155** and **156**. It seems likely that a somewhat more complex rationale is involved in this case. Support for this argument has just been published,\(^7\)\(^d\) 10-desoxyartemisinin is eight times more potent than artemisinin.

More recent additions to artemisinin SAR include a series of ethers of dihydroartemisinin, **157**. These compounds are interesting from a pharmacokinetic standpoint, but are probably activated by cleavage to DHQHS.

![Diagram](image.png)

A single ring-cleaved derivative, called "desethanoartemisinin," \(^8\)\(^6\), has been reported by Lee\(^7\)\(^c\) but was not tested for activity. We have since resynthesized \(^8\)\(^6\) by an alternate route and found only weak activity (3% of **1**). Kepler has synthesized trioxanes of the type \(^{158}\) and found only very poor activity. It was suggested that while the 1,2,4-trioxane ring moiety in artemisinin is a requirement for activity, the trioxane ring in any random lipophilic arrangement of atoms is insufficient for good activity. Finally, a wide range of 1,2,4-trioxanes has been prepared by Jefford. For example, a series of structures \(^{159}\) displayed, as seen by others,\(^8\) only extremely modest activity (5% of artemisinin). The summary of all other investigators' work in this field is that the artemisinin tetracyclic structure is required for potent antimalarial activity. In fact, we would not disagree with this finding. As will be discussed, we have methodically dissected the artemisinin structure and found that the full tetracycle is essential for high potency.
Thus far we have described SAR studies conducted by other workers. Although valuable information comes out of their work, the scope of that work is limited by the necessity either to derivatize the somewhat scarce natural product 1 or to synthesize analogs so far afield from the natural structure that little useful information is gained.

The \textit{in vitro} ED\textsubscript{50} values against \textit{Plasmodium falciparum} of our analogs versus appropriate standards such as artemisinin 1, dihydroartemisinin, and arteether are shown in Tables 1 and 2. These new data have a significant impact on the published body of SAR information discussed previously, and we will address them in as much detail as space permits. One can see that the racemic desmethyl analog of 1 (79) has roughly 50\% the activity of artemisinin. This is a highly significant finding and raises several important issues. First, it could be argued that this loss in activity is because 79 is a racemate and optical activity is a criteria for activity in 1. Alternatively, it may be that the C-15 and/or the C-16 methyl groups contribute to the activity of 1 and that optical activity is not important. Finally, of course, it is possible that some combination of effects is operative in that one enantiomer of 79 is less active than the other and that one or the other (or both) of the methyl groups affects the activity of 1. If it is assumed that only the (+) enantiomer of 1 is active, then a comparison of (+)-9-desmethyartemisinin 42 with (+/-)-6,9-desmethylartemisinin 79 offers some clues regarding SAR at the C-6 position. Because removal of the C-9 methyl leads to a 6-fold enhancement in potency and removal of both C-6 and C-9 methyls (along with a 50\% reduction due to the compound being a racemate) leads to a 50\% reduction, it may be true that the C-6 methyl contributes a 6-fold enhancement to the activity of the basic tetracyclic structure of 1.

To partially address a solution to the SAR information provided by 42 and 79, it would be reasonable to carry out the synthesis of the antipode (mirror image) of artemisinin 1 starting from 3(S)-methylcyclohexanone instead of 3(R)-methylcyclohexanone. The 3R(+)-starting material in Schemes II and III leads to the natural product 1 with the correct absolute configuration. Thus, because stereoselectivity in our total synthesis is achieved by starting with optically pure material, the use of the enantiomeric 3(S)-starting material would clearly lead to the enantiomer of 1.
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<td>(+)</td>
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</tr>
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<tr>
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<tr>
<td>(+/-)</td>
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<tr>
<td>4589</td>
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<td></td>
<td>129.45</td>
<td>2</td>
</tr>
<tr>
<td>(+)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4588</td>
<td>0.18</td>
<td>1226</td>
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<td>0.72</td>
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</table>

Table 1. **In Vitro IC₅₀ Values for Selected Analogs of Artemisinin in Drug-Resistant Strains of *P. falciparum***

*IC₅₀ (ng/ml)*
<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>SRI CODE NUMBER</th>
<th>W-2 CLONE</th>
<th>RELATIVE POTENCY</th>
<th>D-5 CLONE</th>
<th>RELATIVE POTENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)</td>
<td>2800</td>
<td>25.53</td>
<td>0.63</td>
<td>20.89</td>
<td>2.1</td>
</tr>
<tr>
<td>(+)</td>
<td>4598</td>
<td>0.18</td>
<td>272</td>
<td>0.22</td>
<td>550</td>
</tr>
<tr>
<td>(+)</td>
<td>4599</td>
<td>0.04</td>
<td>1225</td>
<td>0.22</td>
<td>550</td>
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<tr>
<td>(+)</td>
<td>4600</td>
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<td>----------------</td>
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<td>------------------</td>
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<tr>
<td>(+)</td>
<td>2810</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>(+)</td>
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<td>NA</td>
<td>NA</td>
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<td>(+)</td>
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<td>(+)</td>
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<td>0.11</td>
<td>445</td>
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Table 1. Continued...
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<th>COMPOUND</th>
<th>SRL CODE NUMBER</th>
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<th>D-6 CLONE</th>
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<td>NA</td>
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<td>(+)</td>
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<td>inactive</td>
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<td>(+)</td>
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<td>67</td>
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<td>(-)</td>
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<tr>
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Table 1. Continued...
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<th>COMPOUND</th>
<th>SRI CODE NUMBER</th>
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<td>20</td>
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<tr>
<td>(+)</td>
<td>2837</td>
<td>0.26</td>
<td>300</td>
<td>&lt;0.16</td>
<td>&gt;137</td>
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<tr>
<td>(+)</td>
<td>2832</td>
<td>1.06</td>
<td>74</td>
<td>0.71</td>
<td>31</td>
</tr>
<tr>
<td>COMPOUND</td>
<td>SRL CODE NUMBER</td>
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<td>RELATIVE POTENCY</td>
<td>D-6 CLONE</td>
<td>RELATIVE POTENCY</td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
<td>-----------</td>
<td>-----------------</td>
<td>-----------</td>
<td>-----------------</td>
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<tr>
<td>(-)</td>
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<td>10.67</td>
<td>7.1</td>
<td>2.45</td>
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Table 2: *In Vitro* IC$_{50}$ Values for Selected Tricyclic Artemisinin Analogs in Drug-Resistant Strains of *P. falciparum*

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>SRI CODE NUMBER</th>
<th>W-2 CLONE</th>
<th>RELATIVE POTENCY</th>
<th>D-6 CLONE</th>
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<tr>
<td>(+/-) t-BuMeSO</td>
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<td>3016.4</td>
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<td>(+/-)</td>
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<td>15</td>
<td>29.72</td>
<td>15</td>
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<tr>
<td>(+/-)</td>
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<td>7</td>
<td>13.95</td>
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<tr>
<td>(-)</td>
<td>113</td>
<td>9.71</td>
<td>8</td>
<td>9.65</td>
<td>8</td>
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</table>

IC$_{50}$ (ng/ml)
<table>
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<tr>
<th>COMPOUND</th>
<th>SRL CODE NUMBER</th>
<th>W-2 CLONE</th>
<th>RELATIVE POTENCY</th>
<th>D-6 CLONE</th>
<th>RELATIVE POTENCY</th>
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<td>NA</td>
<td>1.28</td>
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<tr>
<td>(+)</td>
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<td>(-)</td>
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</tr>
<tr>
<td>(+/-)</td>
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<td>inactive</td>
<td>inactive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+/-)</td>
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### Table 2. Continued...

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<tr>
<th>COMPOUND</th>
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<th>D-6 CLONE</th>
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<tr>
<td>(+)</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td>2806</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>(+)</td>
<td>2808</td>
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<tr>
<td>(+)</td>
<td>2823</td>
<td>---</td>
<td></td>
<td>0.80</td>
<td>37</td>
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</table>
However, time did not permit this undertaking, but we hope to return to this idea in the next three years.

A successful synthesis of the enantiomer of naturally derived artemisinin would accomplish several important goals. First, it would help establish whether the mode of action of $1$ involves binding to a specific receptor or to an optically active site. If the enantiomer of $1$ proved to be totally inactive, then one might safely say that receptor or receptor-like specificity is involved in the mechanism of action of $1$. However, if the enantiomer of $1$ were found to have good activity, it might well be argued that a nonspecific mechanism is involved. This argument would depend to some extent on the degree of activity of the enantiomer of $1$. Second, depending on the outcome of the biological testing of the enantiomer of $1$, further SAR studies would be more directed in focus. For example, one would know whether to carry out syntheses of analogs enantioselectively or merely stereospecifically. Finally, the results of testing of $42$ and $79$ could be more readily explained, and this would provide further valuable insight into SAR in this family of drugs. For example, if it is true that the C-6 methyl is important to activity, then this position of the molecule would be a fruitful area of research.

We have examined the C-9 position of $1$ in some detail because these analogs are readily available by alkylation of the dianion derived from the acid $32$, produced in the total synthesis (Scheme III) of $1$. Of interest is the effect of hydrophobic/hydrophilic groups at C-9. Accordingly, ethyl $43$ through n-hexyl ($44$, $45$, $46$, and $47$, respectively) were examined followed by a jump to n-tetradecyl $48$. An amazing enhancement in potency was gained for ethyl $43$ and n-propyl $44$ (X13). The intermediate n-butyl $45$ and n-pentyl $46$ analogs begin to lose activity and by n-hexyl $47$, activity drops (X7). At n-C14, tetradecyl $48$, activity is almost nil. These data are shown graphically in Figure 7. Thus far, Log P does not seem to explain these findings (we are currently involved in obtaining computer software to aid in interpreting the data presented in the tables, from Tripos and/or Molecular Design). One study has demonstrated a correlation between lipophilicity and antimalarial activity for arteether-like derivatives.

Another possibility here is that as the carbon-chain length increases, the chain begins to fold back on the tetracycle, thus blocking some key binding point. This idea could be tested by introduction of a trans-unsaturation into the hexyl chain (or the longer homologues). We are currently engaged in a consideration of the effects of branching as well. The isopropyl ($53$), isoamyl ($55$), isobutyl ($54$), and isoheptyl ($56$) branched homologues have undergone testing. The results are interesting. Isopropyl $53$ is about equipotent with $1$ whereas n-propyl $44$ is X13! As
can be seen, this is a general trend (Fig. 7). Clearly, branching has a detrimental effect on potency.

These findings might tempt one to predict that the 3-phenylpropyl analog 51 would be about equipotent with \( \textbf{1} \). Surprisingly, 51 was about 8 times as potent as \( \textbf{1} \). Furthermore, there is also a "length" dependency with phenyl terminators, as shown in Fig. 7. We feel that the sum total of these results suggests that a hydrophobic pocket exists in the putative artemisinin "receptor" and has well-defined dimensions with a (probably) \( \pi \) acceptor (such as a tyrosine, tryptophan, or phenylalanine residue) in some region of the pocket. This idea, although admittedly simplistic, is a useful starting point and is shown in Diagram 1 below:

**Diagram 1.** Putative hydrophobic pocket in the artemisinin "receptor"

Such \( \pi \) stacking would be expected to provide additional binding energy and thus might explain the enhanced potency of 51. Alternatively, or in addition, if the \( \pi \) acceptor were a tryptophan residue, then hydrophobic-hydrophilic repulsion between a branched hydrocarbon chain (e.g., 56) and the indole nitrogen atom might explain the disparity between side chains of similar steric dimensions (51 vs 56). Although these arguments are tentative at this point, incoming test data and new analogs will help to firm up this so-called hydrophobic pocket. We envision studying quantitative structure-activity relationships (QSAR), such as LogP, Es, s*, etc., in an attempt to define a mathematical relationship. In any event, we feel that the Tripos
pharmacophore model, developed by Cramer and recently exemplified for corticosteroids, would be very useful in developing the hydrophobic pocket model (Diagram 1). This approach is particularly useful in examining side-chain modifications of rigid substrate molecules—exactly what we have in this case. From the standpoint of modeling the entire pharmacophore of molecule 1, we envision beginning with the lower "southeast" quadrant of 1 and then proceeding to other rings. We will show as we progress through the tables how more detailed diagrams can be built up, even using our simplistic approach. Ultimately, however, we will use computer-generated images of the putative receptor.

As further support for the model in Diagram 1, we have synthesized the carboxylic acid 58. Originally, we had hoped that this material would serve our purposes of obtaining a chemically stable replacement for sodium artesunate. However, 58 was completely inactive, as would be predicted by the model!

At this point, our approach to defining the dimensions of the pocket in Diagram 1 will be to "fill-in" missing members in n-alkyl and branched alkyl chains. Then we will attempt to find the π acceptor by examining optimum chain length between the tetracycle and the aryl ring. Once optimized, we will then examine substituents on the aromatic ring (e.g., electron-withdrawing/donating, hydrogen-bonding, etc.). In addition, we plan to examine simple homologous olefins, such as the allyl analog 57, as π donators. In this instance, we were somewhat surprised to find that the allyl analog 57 was only 30-70% as potent as artemisinin. Based on what has shown up for aryl analogs and for propyl itself, this is an odd result. Finally, the model derived from the above approach may be useful in designing unanticipated analogs with high potency.

The next group of analogs we have explored are the lactams 64-69. All of these were readily derived, again, from the crucial acid 32 by simple amide formation followed by ozonolysis/cyclization as discussed earlier. Of these amides, test data is available for N-methyl 64, N-CH2CO2H 67, and N-benzyl 66. Interestingly, N-Me 64 is about as active as the natural product. As can be seen, the C-9 methyl is absent (a modification known to enhance potency 6-fold); thus the amide modification alone would probably reduce activity relative to 1. However, N-benzyl 66 is, amazingly, more potent than 64, being roughly twice as active as 1. Curiously, the carboxylic acid 67 was inactive. We are tempted to invoke a modified Diagram 2, which takes into account these results as well as those of Diagram 1. Unfortunately, we have much less information regarding amide derivatives, but we plan to pursue this area vigorously. At the time of writing this report, we had just submitted the longer chain acid 69, which should prove extremely interesting.
Diagram 2. Hydrophobic pockets in artemisinin "receptor" showing hypothetical residues

It should be stated here that these drawings are only an aid to this discussion and clearly suffer from a lack of three-dimensionality. We have minimized (MMP2) the majority of the structures shown in the tables. For the N-benzyl analog 66, we would need the third dimension to adequately describe 66 because the aryl ring is in an unusual position (space/page limitations do not allow for these 3D structures here). For now at least, there is clearly another hydrophobic volume (N-CH$_2$CO$_2$H, 67, is inactive!) possibly containing another $\pi$ acceptor, where N-amide substituents can reside.

As described before for the C-9 substituted analogs of 1, we plan to examine alkyl, branched alkyl, and aryl/alkyl lactam derivatives. We would then more accurately define the "southwest" pocket. Of course, once the C-9 lactone analogs (southeast quadrant) and N-11 lactam analogs (southwest quadrant) are optimized, hybrid structures will be needed to fine-tune the model. Hopefully, however, these separate modifications will combine additively to provide new analogs with greatly enhanced potencies.
Figure 7. Plot of in vitro potency vs chain length of four major classes of artemisinin analogs prepared under USAMRDC Contract No. DAMD17-88-C-8007.

That this additivity cannot be taken for granted with the artemisinin molecule can be gleaned from another study that we carried out. Because we knew that both arteether (ten times more potent than the parent molecule) and our ethyl analog 42 (X13) were separately quite potent, we hoped that by converting 43 to the corresponding ether derivative 73, a substantial enhancement would be gained. In other words, ten times more potent than thirteen times more potent could result in an analog 130 times more potent. As can be seen however, this simple reasoning did not hold and, in fact, 73 was only 3-6 times more potent than 1 and was about half as active as 43! The ether derivative of the propyl analog 74 was equally disappointing. We have modeled these analogs (73 and 74) and found that steric interactions between adjacent bulky alkyl chains force the
groups into new conformations. We guessed that these new conformations are unacceptable and can account for the drop in activity. However, the intermediate lactols should not suffer from these intramolecular interactions and should retain activity. We were very surprised to find that the butyl-substituted lactol 78 (reduction product of 45) was also fairly inactive. Another approach would involve actually joining the two ends of the alkyl substituents to form a ring. Specifically, we synthesized the pentacyclic ether 72:

Again, we were disappointed to find that the pentacycle 72 was less active than are ether.

Another compound of interest is the ring-contracted analog 80. Our primary reason for preparing 80 had to do with the effect of ring-strain on the reactivity of the peroxide group. We hoped that a more reactive peroxide, which shared most of the topological features of the natural product (we have overlapped the minimized structures of 80 with 1 and they are reasonably similar), would be more active. As can be seen, 80 is only poorly active. It is also possible that this idea is valid, but that rapid metabolism of the reactive peroxy group of 80 occurs.

Our next analogs to be considered are the seco derivatives 81 through 95. We were interested in these compounds because geo-economic considerations made their synthetic availability attractive and, of course, for the general SAR information that they afford. There are several points of interest regarding the structural features of these analogs relative to artemisinin 1. Molecular modeling (MMP2) of 1 shows that there is almost no flexibility in the rings, and the minimum energy conformation is the same as the X-ray structure. This is not surprising considering the tetracyclic nature of 1 and the fact that most of the rings in 1 are six-membered. Somewhat surprisingly, however, the seco compounds display a vast array of conformations in solution, as was evidenced by their peculiar NMR behavior. We chose to study two representative examples in detail, 110 and 87. A mixture of conformers of 110 was observed as an overly complex pattern (broad lumps) in the NMR spectra of chromatographically homogeneous samples. In addition, the NMR profile of the mixture changed when examined at -10°C, 3°C, 20°C, and
60°C. An X-ray analysis was performed on 110 and 87 as structure proof and for the conformational information. Detailed energy minimizations of all possible conformers (16 per compound) were undertaken as well as low-temperature 2D NMR experiments (NOESY, ROESY, COSY). Together with the X-ray information, we were able to determine that at -10°C in chloroform solution, there were two conformers (7:3 ratio) of 110. The major conformer corresponded to the all-chair arrangement found in the X-ray structure. The minor conformer was in a chair-chair-boat arrangement. Neither conformer overlapped perfectly with artemisinin 1 and, as can be seen, 110 has only modest potency compared to the natural product. The situation for 87 was quite similar, but trends between conformers were reversed. That is, the X-ray conformer (chair-chair-boat) corresponded to the minor solution isomer of 110 whereas the minor solution isomer of 87 corresponded to the major all-chair conformer of 110. Test data for 82 demonstrated only modest potency (13% of artemisinin). As can also be seen in Table 2, very little change in activity was evidenced with structural changes that were beneficial in the tetracyclic series. Apparently, the lack of good overlap of these seco analogs with 1 has a deleterious effect on activity. We will later speculate in more detail that the absence of the fourth ring may also result in a change in the mode of action of these seco derivatives and thus a loss in potency. For now, however, briefly, once the peroxy group of 1 undergoes scission to a diradical, the ring system would tend to act like a template and hold the diradical in a shape similar to that of the parent tetracycle. However, the seco compound could lose acetone irreversibly to give a radical species that no longer resembles the tetracycle.

Considering these findings, it might be expected that the 8a,9-seco analogs (Table 2, 91-95) would demonstrate better activity than is found for the 4,5-seco analogs discussed above because they more closely resemble the natural product in the crucial peroxy region of the molecule. In other words, 93 overlaps very nicely with all but the lactone ring of 1 (by MMP2). An X-ray analysis of 94 verifies the structural similarities. However, 93 is only poorly active. One likely explanation for this result is that 93 is an unstable oil and probably decomposed somewhat before it was actually tested. This seems likely because the carbonate derivative 94, which is a stable solid, is fairly active (about 30% of artemisinin). We plan to re-synthesize 93 and have the \textit{in vitro} assay conducted in a timely fashion. However, perhaps the activity for these analogs is not surprising. As can be seen for the minimized structures (verified by X-ray) of these analogs, the ester side-chain points in an unusual direction and would not be necessarily expected to occupy the putative hydrophobic pocket (Diagram 1). The analog 95, which lacks the entire lactone ring, is more potent than the carbonate 94. This is an interesting finding in itself because the lack of activity for the dehydro-derivative 156 is misleading. It would seem that the lactone
carbonyl contributes to the potency of the natural material but is not entirely essential for activity. The recent finding that 10-desoxyartemisinin is more active than 1 confuses this issue.

The SAR information that we have presented in the foregoing discussions is quite difficult to explain based on simplistic arguments. Obviously, the interpretation must reside in the mode of action of this class of drugs. Unfortunately, very little is known about the mode of action of artemisinin, and though we have recently submitted 15 mCi of carbon 14-radiolabeled artemisinin as a tool for the study of mode of action, it will nevertheless probably be quite some time before this crucial information is available. Meanwhile, it will be essential to carry out computer-based QSAR to help gain insight into these fascinating results.

EXPERIMENTAL SECTION

All solvents were purchased as HPLC grade and, where appropriate, solvents and reagents were distilled from CaH₂ prior to storage over 4Å molecular sieves. Solvent and reagent transfers were accomplished via dried syringe or cannula, and all reactions were conducted under an atmosphere of argon. 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-micron silica gel thin-layer chromatography plates also purchased from Analtech. NMR analyses were conducted on either a Varian XL-400 or a JEOL FX90Q and were referenced to chloroform at δ 7.27. IR spectra were recorded on a Perkin-Elmer 1310.

**Pulegone oxide (19).**

Pure R(+)-pulegone 18 (Fluka purum grade, 152 g) was converted to the epoxide, according to the procedure of Katsuhara, to give 119 g of 19 (74%). Caution: this reaction is quite exothermic. This material was sufficiently pure by NMR for use in the next reaction. Anal (C₁₀H₁₆O₂): C, H.

**5R-Methyl-2-thiophenylcyclohexanone (20).**

The oxide 19 (119 g) from above was converted to the sulfide 20 by minor modification of a procedure outlined by Caine et al. A 60% oil dispersion of NaH (1.416 mol, 56.64 g) under argon was washed with hexane (3 x 50 mL) to remove the oil. Dry THF (1.5 L) was added followed by a solution of thiophenol (1.416 mole, 146.5 mL) in dry THF (1.5 L). The mixture was stirred at ambient temperature for 30 min and then the epoxide 2 (119 g or 708 mmol) in dry THF (1.0 L) was added. The resulting mixture was heated at reflux for 24 h and allowed to cool. Ice (1 kg) was added and after stirring for 15 min, the mixture was extracted with Et₂O (2 x 500
mL). The combined organic layers were washed with brine and dried over MgSO_4 and the solvent was evaporated in vacuo to give crude 20 (157 g or ca. 100%), which was sufficiently pure (NMR) for the next reaction. An analytical sample was furnished from column chromatography with silica gel and CH_2Cl_2. A yellow solid (mp 67-68°C) was obtained. UV: \( \lambda_{\text{max}} = 250 \text{ nm} \) (log \( \varepsilon \) 3.69). Anal (C_{13}H_{16}O_S): C,H,S.

5R-Methyl-2-phenylsulfinylcyclohexanone (21).

The sulfide 20 was oxidized, as described by Oppolzer and Petrizilka,^18 to the sulfoxide 21. Thus 20 (155.8 g) was converted to crude 21 (241 g). Filtration chromatography on silica gel (723 g of 60-230 mesh) with 35 → 80% EtOAc/hexane gave pure 21 (158 g or 95%). The sulfoxide was stored under argon in the freezer.

More recently, the sulfide 20 was oxidized with the magnesium salt of monoperoxyphthalic acid hexahydrate (MMPP).^33 To a solution of sulfide 20 (63.58 g, 0.289 mol) in 95% ethanol (1 L) at 0°C was added a solution of MMPP (256.86 g of 80%, 0.519 mol) in H_2O (1 L) over 30 min. The resultant mixture was stirred with brine (500 mL), saturated with NaCl, and extracted with ether (5 x 150 mL). The combined ethereal layers were washed with saturated aqueous NaHCO_3 (2 x 200 mL) and brine (2 x 200 mL), dried over MgSO_4, and evaporated to provide 21 as a yellow-orange oil, 62.71 g (91.0%), which was suitable for further use and stored under argon in the freezer. Anal (C_{13}H_{16}O_S): C,H,S.

2.5.5-Trimethvl-2-(2'-1"R-methyl-3"-oxocyclohex-2"-yl)-ethyl)-1.3-dioxane (17).

5R-Methyl-2-phenylsulfinylcyclohexanone (21) (48.4 g, 205 mmol) in dry THF (300 mL) was added to a solution of lithium diisopropylamide (prepared from 63.0 mL or 451 mmol of diisopropylamine and 189 mL of a 2.5 M solution of n-BuLi in hexane) in dry THF (300 mL) at -78°C followed by dry 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMTP) (200 mL). The mixture was stirred at -35°C for 3 h and then 2-(2'-bromoethyl)-2,5,5-trimethyl-1,3-dioxane\(^{20} \) (52.7 mL, 226 mmoles) was added dropwise. The mixture was stirred at -35°C for 1 h and then allowed to warm to room temperature over 1 h. The mixture was poured into ice-cold, saturated ammonium chloride solution (500 mL) and extracted with diethyl ether (2 x 500 mL). The organic layers were washed with water (3 x 500 mL) and brine (500 mL), dried (MgSO_4), and evaporated in vacuo to give 106 g of crude alkylation product, which was dissolved in THF (2.5 L). To the solution was added in succession water (300 mL) and 60 g of aluminum (-45 + 100 mesh) that was activated by sequential washing with 2% aqueous mercuric chloride for 20 sec followed by absolute ethanol and diethyl ether. The mixture was stirred at ambient temperature

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until the temperature reached about 35°C, whereupon ice was gradually added to a cooling bath to control the exotherm. After 2 h the solids were filtered onto celite with the aid of reduced pressure and washed with diethyl ether (1 L). The filtrate was washed with 5% sodium hydroxide solution (2 x 1 L) and brine (1 L). The aqueous phases were extracted with diethyl ether (1 L). The combined organic phases were dried (MgSO₄) and evaporated in vacuo to afford 66.0 g of crude material, which was purified by filtration chromatography on 660 g of silica gel 60 (70-230 mesh) and eluted with EtOAc/hexane (5:95) → (25:75). In this manner 16.7 g of the product 17 and 9.2 g of mixed fractions were obtained. The mixed fractions were purified by flash chromatography on 184 g of silica gel 60 (230-400 mesh) and eluted with EtOAc/hexane (7:93) → (25:75) to give an additional 5.0 g of the product 17. Thus, there was a total yield of 21.7 g (37%) for 17, which at this scale was typically contaminated with approximately 10% of inseparable C-2α isomer as determined by NMR (400MHz), but was suitably pure for further use. When HMPA was substituted for DMTP in this reaction, the yield improved to 50%, with an identical isomeric ratio.

1H NMR: δ 3.53 (2H, dd, J = 2.2, 11.6 Hz), 3.48 (2H, dd, J = 1.4, 11.6 Hz), 2.38 (dddd, 1H, J = 1.1, 4.5, 4.5, 13.1 Hz), 2.27 (dddd, 1H, J = 1.0, 5.6, 11.5, 12.0 Hz), 1.95-2.07 (m, 2H), 1.79-1.92 (m, 2H), 1.58-1.79 (m, 4H), 1.45 (dddd, 1H, J = 3.7, 9.3, 11.2, 11.3 Hz), 1.38 (s, 3H), 1.06 (d, 3H, J = 6.6 Hz), (m, 1H), 0.96 (s, 6H). 13C NMR: δ 213.2, 99.1, 70.5, 70.3, 57.1, 41.6, 41.4, 38.4, 33.5, 33.3, 29.9, 25.6, 22.7, 21.7, 20.8, 20.5. IR: 2960, 2940, 2880 cm⁻¹. EIMS (m/e): 268 (M⁺), 253 (M-Me). Anal. (C16H28O3): C, H.

2,5,5-Trimethyl-2-[2'-("R-methyl-3"-oxocyclohex-2"-yl)-ethyl]-1,3-dioxane p-tosylhydrazone (24).

A mixture of the ketone 17 (41.6 g, 155 mmoles), dry THF (1 L), p-toluenesulfonyl hydrazide (31.8 g, 171 mmol), and dry pyridine (41.6 mL) was rotary-evaporated at 40 mm Hg. After 20 h, the crude material was purified by filtration chromatography on 677 g of silica gel 60 (70-230 mesh) and eluted with EtOAc/hexane (20:80) → (40:60) to give the product 24 (58.0 g, 86%) as a gummy solid that consisted of a 1:1 mix of syn and anti isomers by NMR (400 MHz) and was routinely used without further purification. IR (CHCl₃): 3120, 2955, 2875, 1735, 1635, 1605, 1500 cm⁻¹. EIMS (m/e): 437 (M⁺H), 421 (M-Me). Anal. (C23H36N₂O₄S): C,H,N,S. Careful flash column chromatography provided each of the slowly interconverting geometrical hydrazone isomers in pure form: First eluted isomer: 1H NMR (CDCl₃): δ 7.72 (ddd, 2H, J = 1.8, 1.8, 8.3 Hz), 7.39 (ddd, 2H, J = 0.7, 0.7, 8.3 Hz), 3.78 (d, 1H, J = 11.7 Hz), 3.70 (d, 1H, J = 11.5 Hz), 3.62 (dd, 1H, J = 2.6, 11.6 Hz), 3.49 (dd, 1H, J = 4.4, 11.6 Hz), 3.36 (dd, 1H,
11.4 Hz), 2.95 (dd, 1H, J = 3.8, 12.5 Hz), 2.41 (s, 3H), 2.00-2.10 (m, 1H), 1.98 (dddd, 1H, J = 2.4, 4.2, 12.8, 13.8 Hz), 1.40 (ddd, 1H, J = 2.4, 6.8, 15.0 Hz), 1.20 (s, 3H), 1.13 (s, 3H), 0.90 (d, 3H, J = 7.2 Hz), 0.80 (s, 3H). Last eluted isomer: H NMR (CD$_2$Cl$_2$) $\delta$ 7.81 (ddd, 2H, J = 1.8, 1.8, 8.3 Hz), 7.59 (br s, 1H), 7.30 (ddd, 2H, J = 1.9, 2.6, 8.6 Hz), 3.48 (dd, 1H, J = 4.4, 11.6 Hz), 3.36 (ddd, 1H, J = 1.3, 3.9, 11.4 Hz), 2.40 (s, 3H), 2.20 (ddd, 1H, J = 5.5, 8.5, 14.3 Hz), 2.10 (ddd, 1H, J = 5.0, 7.5, 14.4 Hz), 1.89 (ddd, 1H, J = 5.9, 7.2, 7.2 Hz), 1.78 (ddd, 1H, J = 3.1, 8.2, 17.9 Hz), 1.24 (s, 3H), 0.96 (s, 3H), 0.88 (d, 3H, J = 6.9 Hz), 0.87 (s, 3H).

2.5.5-Trimethyl-2-[2'-((1"S)^3"formyl-6"R-methylcyclohex-2'-enyl)-ethyl]-1.3- dioxane (16).

To a solution of the hydrazone 24 (23.8 g, 54.6 mmol) in dry TMEDA (400 mL) at -78°C under argon was added n-BuLi (136.5 mL of 1.6 M solution in hexane, 218.4 mmol). The mixture was stirred at ambient temperature for 90 min and then cooled to 0°C. After slow addition of dry DMF (54 mL), the mixture was stirred at 0°C for 30 min, poured into ice-cold saturated aqueous ammonium chloride solution (2.0 L), and extracted with ethyl acetate (2 x 1.0 L). The combined organic layers were washed with saturated aqueous ammonium chloride solution (1.0 L), water (1.0 L), and brine (1.0 L), dried (Na$_2$SO$_4$), and evaporated in vacuo to provide 21.5 g of crude material, which was purified by flash chromatography on 215 g silica gel 60 (230-400 mesh) and eluted with EtOAc/hexane (15:85). In this fashion the product 16 (10.7 g, 70%) was isolated as a pale yellow oil. This aldehyde was unstable, could be stored for only brief periods in benzene under argon in freezer (-15°C), and was used as soon as possible. $^1$H NMR: $\delta$ 9.42 (s, 1H), 6.73 (t, 1H, J = 3.8 Hz), 3.51 (dd, 2H, J = 1.9, 11.5 Hz), 3.46 (ddd, 2H, J = 1.3, 4.1, 11.5 Hz), 2.31 (ddd, 2H, J = 1.3, 3.7, 7.9 Hz), 2.24 (br d, 1H, J = 8.5 Hz), 1.94 (ddd, 1H, J = 2.8, 4.0, 8.0, 9.67 Hz), 1.84 (ddd, 1H, J = 4.0, 8.3, 13.6 Hz), 1.34-1.45, 1.31 (3H, s), 0.98 (3H, s), 0.92 (3H, s), 0.89 (3H, d, J = 6.9 Hz). $^{13}$C NMR: $\delta$ 194.7, 151.2, 99.0, 70.3, 41.6, 37.7, 35.0, 29.9, 28.5, 27.5, 26.1, 23.9, 23.0, 22.7, 21.0, 18.6, 14.1. IR (film): 2960, 2870, 2710, 1685, 1635 cm$^{-1}$. UV: $\lambda_{max}$ = 230 nm (log $\varepsilon$ 3.96). EIMS (m/e): (M-Me).

2.5.5-Trimethyl-2-[2'-((1"S)^3"-hydroxymethyl-6"R-methylcyclohex-2'-enyl)-ethyl]-1.3- dioxane.

To a solution of diisobutylaluminum hydride (37.5 mL of 1.0 M in toluene) and THF (200 mL) at -78°C was added dropwise a solution of aldehyde 16 (8.40 g, 30.0 mmol) in THF (50 mL). After 30 min at -78°C, the mixture was allowed to warm to ambient temperature over 30 min, poured into saturated aqueous sodium potassium tartrate (500 mL) at 0°C and extracted with EtOAc (2 x 200 mL). The combined organic layers were washed with saturated aqueous sodium potassium tartrate (2 x 250 mL), dried over MgSO$_4$, and evaporated to give a yellow oil, which
was purified via flash column chromatography with silica gel. Elution with EtOAc/hex led to the isolation of the title alcohol as a colorless oil, 7.0 g (83%). NMR: δ 5.74 (ddd, 1H, J = 1.1, 2.8, 3.7 Hz), 4.09 (dd, 1H, 6.2, 12.5 Hz), 4.01 (d, 1H, J = 12.5 Hz), 3.57 (d, 2H, J = 10.8 Hz), 3.42 (d, 2H, J = 10.8 Hz), 1.93-2.10 (m, 2H), 1.88 (br m, 1H), 1.61-1.79 (m, 7H), 1.51-1.60 (m, 1H), 1.37 (s, 3H), 1.30 (dq, 1H, J = 7.0, 13.0 Hz), 1.04 (s, 3H), 0.96 (d, 3H, J = 6.8 Hz), 0.87 (s, 3H). IR: 3424, 2953, 2922, 2867, 1457, 1375, 1235, 1212, 1129, 1092, 1022, 855 cm⁻¹. MS. m/z (rel int) 267 (M-Me, 7), 178 (13), 157 (12), 129 (100). Anal. (C₁₇H₃₀O₃): C, H.

2,5,5-Trimethyl-2-[2'-(1''S)6''R-methyl-2''-trimethylsilyloxyethylcyclohex-2''-enyl]-ethyl]-1,3-dioxane (25).

To a solution of 2,5,5-trimethyl-2-[2'-(1''S)6''R-methyl-2''-hydroxymethyl-6''R-methylcyclohex-2''-enyl)-ethyl]-1,3- dioxane (2.40 g, 8.51 mmol) in THF (100 mL) and pyridine (1.03 mL, 12.8 mmol) at 0°C was added trimethylsilyl chloride (1.19 mL, 9.36 mmol). The resultant suspension was poured into saturated aqueous NaHCO₃ (75 mL) and ether (50 mL). The separated organic layer was washed with saturated aqueous NaHCO₃ (25 mL), dried over K₂CO₃, and concentrated under reduced pressure; the pyridine was removed via azeotrope with heptane to afford a yellow oil, which was further purified via flash column chromatography with silica gel. Elution with EtOAc/hex furnished silyl ether 25 as a colorless oil, 2.70 g (93%). NMR: δ 5.70 (ddd, 1H, J = 1.4, 2.5, 5.0 Hz), 4.08 (dd, 1H, J = 1.9, 12.9 Hz), 4.01 (dd, 1H, J = 1.4, 12.9 Hz), 3.54 (d, 2H, J = 11.5 Hz), 3.43 (d, 2H, J = 11.5 Hz), 1.90-2.10 (m, 2H), 1.60-1.84 (m, 6H), 1.45-1.55 (m, 1H), 1.36 (s, 3H), 1.31 (heptet, J = 6.8 Hz), 1.02 (s, 3H), 0.96 (d, 3H, J = 6.6 Hz), 0.90 (s, 3H), 0.13 (s, 9H). IR: 2954, 2866, 1251, 1093, 873, 842 cm⁻¹. MS (rel int) 339 (M-Me, 5), 210 (20), 197 (58), 129 (100). Anal. (C₂₀H₃₈O₃Si): C, H.

Tris(trimethylsilyl)aluminum etherate.

A mixture of Fluka aluminum powder (20 g, 100-200 micron), Fluka aluminum granules (5 g, 0.15-1.7 mm), dry diethyl ether (200 mL), and iodine (2.0 g) was magnetically stirred under argon in a 3-neck, 500-mL, r.b. flask until the iodine color disappeared. Mercury (20 g) was added, followed by freshly distilled chlorotrimethylsilane (120 mL, 945 mmol). The mixture was stirred vigorously at room temperature for 3 h and clean lithium wire (3.2-mm diam. ~0.01% Na, 1 mole, 7.0 g, 155 cm) was added in small pieces (0.3-0.5 cm). The well-stirred mixture was rigorously maintained at 35-40°C in an oil bath for 48 h. After allowing to cool and the solids settled, the solution was decanted by cannula (system under argon) carefully transferring solely clear solution. The decantation procedure was repeated with portions of pentane (2 x 200 mL),
and the combined decants were evaporated under vacuum. The residue was dried under high vacuum for 2 h, pentane (50 mL) was added, and the mixture was swirled. After the solid settled, the solution was decanted via cannula and transferred to a new flask under argon. Another portion of pentane (50 mL) was added to the solid material and the procedure was repeated, finishing with the blending of the two pentane solutions. **WARNING:** A pentane solution of tris(trimethylsilyl)aluminum etherate is highly pyrophoric and consequently all operations involving use of this material must be carried out under an inert atmosphere. The solution was indefinitely stable during storage under argon in a freezer. The solution was assayed by reaction with 1-formylcyclohexene that was freshly prepared from 1-hydroxymethylcyclohexene via manganese dioxide oxidation. Typically, the aluminum reagent was added dropwise to 1.0 mmol of 1-formylcyclohexene in dry diethyl ether (2 mL) under argon at -78°C. A transient red color no longer appeared with each drop when the reaction was complete, and when monitored by TLC, the starting material was easily detected in the UV while the product was not, even though the Rf's were similar. For example, with the run following the procedure above, 0.67 mL of the aluminum reagent was required for the assay, indicating a concentration of 1.5N. The titer of tris(trimethylsilyl)aluminum etherate was highly dependent on the brand and lot of aluminum used.

2,5,5-Trimethyl-2-[2'-((1'S)-2'-hydroxymethyl-6'R-methylcyclohex-2'-enyl)-ethyl]-1,3-dioxane Propionate Ester (15).

**A. Via Brook Rearrangement:** To a solution of silyl ether 25 (2.70 g, 7.63 mmol) in THF (40 mL) at -78°C was added t-butyllithium (8.98 mL of 1.70 M in hex, 15.3 mmol). After 2.5 h at -45°C and 1 h at -33 to -35°C, the solution was cooled to -78°C and a degassed solution of acetic acid (5.6 mL) and THF (18 mL) was added dropwise. The cold solution was poured into saturated aqueous NaHCO₃ (300 mL) and extracted with chloroform (200 mL; 2 x 50 mL). The combined organic layers were washed with brine (100mL), dried over MgSO₄ and evaporated to provide a yellow oil, which was purified via flash column chromatography with silica gel. Elution with a EtOAc/hex stepwise gradient led to the separation of recyclable 2,5,5-trimethyl-2-[2'-(1"S)2"-hydroxymethyl-6"R-methylcyclohex-2"-enyl)-ethyl]-1,3-dioxane as a colorless oil, 1.14 g (53%) and desired 2,5,5-trimethyl-2-[2'-(1"S)2"-hydroxy(trimethylsilyl)methyl-6"R-methylcyclohex-2"-enyl)-ethyl]-1,3-dioxane (26) as a yellow oil, 821 mg (30%), which was unstable and typically was used immediately. The NMR spectrum reflected that a mixture of diastereomers were present in a 1:2 ratio with the opposite stereochemical preference to the organoaluminum addition described below. NMR: δ 5.58 (t, 1H, J = 3.8 Hz, minor isomer),

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5.53 (t, 1H, J = 3.8 Hz, major isomer), 3.88 (m, 1H), 3.50-3.62 (m, 2H), 3.35-3.46 (m, 2H),
2.49-2.55 (br m, 1H), 1.37 (s, 3H), 1.03 (s, 3H), 0.89 (s, 3H), 0.088 (s, 9H).

To a solution of alcohol 26 (584 mg, 1.65 mmol) in ether (15 mL), pyridine (0.28 mL),
and 4-(dimethylamino)pyridine (10 mg) was added propionic anhydride (317 μL, 2.48 mmol).
After 12 h at ambient temperature, the solution was stirred with saturated aqueous NH₄Cl: 10%
HCl (35:3 mL). The organic layer was separated, washed with saturated aqueous NH₄Cl (20
mL), saturated aqueous NaHCO₃ (20 mL), and brine (20 mL), dried over Na₂SO₄, and evaporated
to afford a yellow oil, which was purified via flash column chromatography with silica gel.
Elution with EtOAc/hex provided propionate as a yellow oil, 677 mg (100%).

B. From Addition of Tris(trimethylsilyl)aluminum Etherate: To the aldehyde 16 (10.6
g, 37.9 mmol) in dry diethyl ether (100 mL) under argon at -78°C was added
tris(trimethylsilyl)aluminum etherate (40.0 mmol, 100 mL of 0.4 M solution in pentane). After
stirring at -78°C for 10 min, in succession were added propionic anhydride (18.9 mL, 200 mmol)
and 4-dimethylaminopyridine (200 mg). The mixture was stirred at ambient temperature for 16 h,
poured into ice-cold saturated aqueous sodium potassium tartrate solution (300 mL), and extracted
with diethyl ether (2 x 300 mL). The combined ethereal layers were washed with saturated sodium
potassium tartrate solution (300 mL) and brine (300 mL), dried (MgSO₄), and evaporated in vacuo
to give 22.2 g of crude material, which was purified by flash chromatography on 222 g of silica
gel 60 (230-400 mesh). Elution with EtOAc/hexane (5:95) → (10:90) gave 13.2 g (88%) of the
product 15 as a colorless oil. IR (CHCl₃): 3000, 2960, 2930, 2875, 1725, 1645 cm⁻¹. ¹H
NMR: δ 5.55 (t, 1H, J = 3.6 Hz), 5.25 (d, 1H, J = 0.8 Hz), 3.54 (dd, 2H, J = 1.7, 11.0 Hz),
3.44 (dd, 1H, J = 1.4, 2.7 Hz), 3.42 (dd, 1H, J = 1.1, 2.7 Hz), 2.03 (s, 3H), 1.35 (s, 3H), 0.98
(s, 3H), 0.89 (d, 3H, J = 7.0 Hz), 0.87 (s, 3H), 0.02 (s, 9H). EIMS (m/e): 396 (M+), 395 (M-

2.5.5-Trimethyl-2-2'-["R-methyl-3"-trimethylsilylhydroxymethylcyclohex-3'-en-2'-yl]-ethyl-
1.3-dioxane Acetate Ester (30).

A. Via Brook Rearrangement: The mixture of diastereomeric alcohols 26 was prepared
as in procedure A for acetate 30.

To a solution of silyl alcohol 26 (254 mg, 0.719 mmol) in ether (5 mL), pyridine (0.12
mL), and 4-(dimethylamino)pyridine (10 mg) was added acetic anhydride (96 μL). After 12 h, the
solution was washed with saturated aqueous NH₄Cl: 10% HCl (25:2 mL), saturated aqueous
NH₄Cl (10 mL), saturated aqueous NaHCO₃ (10 mL), and brine (10 mL), dried over Na₂SO₄,
and evaporated to give a colorless oil, which was purified via flash column chromatography with silica gel. Elution with EtOAc/hex led to the obtention of acetates 30/31 as a colorless oil, 285 mg (100%).

B. From Addition of Tris(trimethylsilyl)aluminum Etherate: To the aldehyde 16 (10.6 g, 37.9 mmol) in dry diethyl ether (100 mL) under argon at -78°C was added tris(trimethylsilyl)-aluminum etherate (40.0 mmol, 100 mL of 0.4 M solution in pentane). After stirring at -78°C for 10 min, in succession were added acetic anhydride (18.9 mL, 200 mmoles) and 4-dimethylamino-pyridine (200 mg). The mixture was stirred at ambient temperature for 16 h, poured into ice-cold saturated aqueous sodium potassium tartrate solution (300 mL), and extracted with diethyl ether (2 x 300 mL). The combined ethereal layers were washed with saturated sodium potassium tartrate solution (300 mL) and brine (300 mL), dried (MgSO4), and evaporated in vacuo to give 22.2 g of crude material, which was purified by flash chromatography on 222 g of silica gel 60 (230-400 mesh). Elution with EtOAc/hexane (5:95) → (10:90) gave 13.2 g (88%) of the product 30 as a colorless oil. IR (CHCl3): 3000, 2960, 2930, 2875, 1725, 1645 cm⁻¹. ¹H NMR: δ 5.55 (t, 1H, J = 3.6 Hz), 5.25 (d, 1H, J = 0.8 Hz), 3.54 (dd, 2H, J = 1.7, 11.0 Hz), 3.44 (dd, 1H, J = 1.4, 2.7 Hz), 3.42 (dd, 1H, J = 1.1, 2.7 Hz), 2.03 (s, 3H), 1.35 (s, 3H), 0.98 (s, 3H), 0.89 (d, 3H, J = 7.0 Hz), 0.87 (s, 3H), 0.02 (s, 9H). EIMS (m/e): 396 (M+), 395 (M-H). Anal. (C22H40SiO4): C, H.

2.5.5-Trimethyl-2,5,6,7,8-pentamethyl-2-(4"-(2"-acetic acid)-1"R-methyl-3"-trimethylsilylmethylene cyclohex-2"-yl)ethyll-1,3-dioxane (32).

To freshly distilled dry diethylamine (10.3 mL, 100 mmol) in dry distilled THF (300 mL) at 0°C under argon was added n-BuLi (63 mL or 100 mmol of a 1.6 M solution in hexane). The mixture was stirred at 0°C for 10 min and then was cooled to -78°C. The ester 20 (19.8 g, 50 mmole) in dry distilled THF (50 mL) was added dropwise over 20 min. The mixture was stirred at -78°C for 4 h, allowed to warm gradually to ambient temperature, and stirred for 4 days. The resultant mixture was poured into an ice-cold solution of saturated aqueous ammonium chloride (1 L) and 5N hydrochloric acid (25 mL), and extracted with chloroform (3 x 300 mL). The organic extracts were washed with brine (1 L), dried (MgSO4), and evaporated in vacuo to give 29.8 g of crude material, which was purified by flash chromatography on 400 g of silica gel 60 (230-400 mesh). Elution with (1% HOAc/EtOAc)/hexane (10:90) → (25:75) provided the product 32 (12.47 g, 63%). IR (CHCl3): 3575, 3030, 2955, 2870, 1710, 1610 cm⁻¹. ¹H NMR: δ 5.38 (s, 1H), 3.56 (d, 2H, J = 11.4 Hz), 3.44 (ddd, 2H, J = 1.4, 5.7, 11.4 Hz), 2.78 (m, 1H), 2.62 (dd, 1H, J = 9.5, 15.0 Hz), 2.48 (dd, 1H, J = 5.9, 15.0 Hz), 2.11 (m, 1H), 1.76-1.94 (m, 4H), 1.50-
1.73 (m, 4H), 1.40-1.47 (m, 1H), 1.37 (s, 3H), 1.10-1.20 (m, 1H), 1.03 (s, 3H), 0.94 (d, 3H, J = 7.1 Hz), 0.90 (s, 3H), 0.097 (s, 9H). EIMS (m/e): 396 (M⁺), 381 (M-Me). HRMS. Calcd for C₂₂H₄₀SiO₄: 396.269. Found: 396.270. Anal (C₂₂H₄₀SiO₄): OH.

2.5.5-Trimethyl-2-[(4'-2''-propionic acid)-1''R-methyl-3''-trimethylsilylmethylene]cyclohex-2''-yl)-ethyl-1.3-dioxane (41).

To a solution of diisopropylamine (413 mL, 2.96 mmol) in dry THF (5 mL) under argon at 0°C was added n-butyllithium (2.96 mmol, 1.91 mL of 1.55 M solution in hexane). The mixture was stirred at 0°C for 15 min and then cooled to -78°C. The acid (32) (532 mg, 1.34 mmol) in dry THF (2 mL) was added via syringe and the mixture was allowed to warm to ambient temperature over 30 min, then heated at 50°C for 2 h and recooled to 0°C. Methyl iodide (210 µL, 3.36 mmoles) was added via syringe; then the mixture was stirred at room temperature for 1 h, poured into ice-cold, saturated aqueous ammonium chloride solution (20 mL), and extracted with chloroform (2 x 20 mL). The organic layers were washed with brine (20 mL), dried (MgSO₄), and evaporated in vacuo to give 640 mg of crude material. This was purified by flash chromatography on 64 g of silica gel 60 (230-400 mesh) and eluted with (1% HOAc/EtOAc)/hexane (20:30) to afford the product (41) (535 mg, 97%) as a colorless gum. IR (CHCl₃): 3600, 3500, 3000, 2950, 2870, 2650, 1705, 1605 cm⁻¹. ¹H NMR: δ 5.31 (s, 1H), 3.52 (d, 2H, J = 11.5 Hz), 3.39-3.45 (m, 2H), 2.79 (dq, 1H, J = 6.7, 11.9 Hz), 2.34-2.41 (m, 1H), 2.12 (dd, 1H, J = 3.1, 10.4 Hz), 1.82 (m, 4H), 1.64 (m, 1H), 1.56 (m, 2H), 1.45 (m, 1H), 1.39 (m, 1H), 1.33 (s, 3H), 1.10 (d, 3H, J = 7.0 Hz), 0.98 (s, 3H), 0.92 (d, 3H, J = 7.0 Hz), 0.86 (s, 3H), 0.09 (s, 9H). EIMS (m/e): 410 (M⁺), 395 (M-Me). HRMS. Calcd for C₂₃H₄₂SiO₄: 410.285. Found: 410.286.

3S-(3'-Oxobutyl)-2-trimethylsilylmethylene-1R,4R,7S-menthanoic Acid (4).

To a vigorously stirring suspension of silica gel 60 (70-230 mesh, 500 mg) in CH₂Cl₂ (7 mL) under argon was added 10% aqueous oxalic acid (175 µL). After 15 min, a solution of the ketal 41 (145 mg, 0.350 mmol) in CH₂Cl₂ (3 mL) was added. After 20 h, MgSO₄ (1 g) was added, and the suspended solids were filtered off and washed with EtOAc (3 x 10 mL). The filtrate was evaporated to an oil, which was purified via preparative TLC with silica gel. After development in HOAc/MeOH/CHCl₃, pure ketoacid 4 was obtained as a clear glass, 93 mg (81%). NMR: δ 5.35 (s, 1H), 2.73 (dq, 1H, J = 6.8, 12.0 Hz), 2.67-2.80 (br s, 1H), 2.30-2.58 (br m, 3H), 2.13 (s, 3H), 2.10 (d, 3H, J = 7.2 Hz), 0.92 (d, 3H, J = 6.8 Hz), 0.087 (s, 9H). IR(CHCl₃): 2925, 1695, 1240 cm⁻¹. CIMS (NH₄⁺): m/e (rel int) 328 (M+NH₄⁺, 100), 325 (M+H⁺, 48), 307 (36), 235 (68). Anal (C₁₈H₃₂SiO₃): C, H.
The following reactions were carried out in a hood with its lights off. Into a solution of the ketal-acid 41 (170 mg or 0.426 mmol) in CH₂Cl₂ (40 mL) at -78°C was bubbled a stream of O₃/O₂ (7 p.s.i., 0.4 L/min, 70 v) for 2 min. The mixture was analyzed by TLC (3:7 EtOAc/hexane) to ensure the absence of any starting material, whereupon the mixture was purged with argon. To the mixture was added in succession BHT (20 mg), silica gel (2 g), 15% aqueous H₂SO₄ (0.20 mL) and silica gel (70-230 mesh, 2.03 g). The mixture was allowed to warm to 22°C and stirred efficiently overnight. The suspended solids were filtered and thoroughly rinsed with CH₂Cl₂ (3 x 15 mL) and EtOAc (2 x 10 mL). The filtrate was washed with saturated aqueous NaHCO₃ (35 mL), dried over Na₂SO₄, and evaporated to give a yellow oil, 124 mg, which was purified via flash chromatography with silica gel (10 g). Elution with EtOAc/hexane (3:7) afforded pure 1 as a white solid, 42 mg (35%), that crystallized from hexane. The spectroscopic (NMR, IR, MS), physical (mixed m.p., rotation), and chromatographic (TLC) properties of this product were identical with an authentic sample of (+)-artemisinin. In addition to 1, the above chromatography provided a slightly less polar, white crystalline substance, 7 mg (6%), which was identified as (+)-deoxyartemisinin 1a by spectroscopic comparison to an authentic sample.

2,5,5-Trimethyl-2-[2'-(5''(2''-N-methylacetamide)-1''R-methyl-6''E-trimethylsilylmethylene-cyclohexyl)-ethyl]-1,3-dioxane (64a)

To a solution of the methyl ester derived from 32 (394 mg or 0.96 mmol) in methanol (15 mL) was added aq. methylamine (40%, 6 mL). The mixture was refluxed under argon for 10 h, then stirred overnight at room temperature. The reaction mixture was poured into sat. aq. NH₄Cl (150 mL) and extracted with EtOAc (3 x 70 mL). The combined organic layer was washed with sat. aq. NH₄Cl (1 x 100 mL), dried over MgSO₄, and filtered; the solvent was evaporated. PTLC chromatography on four plates (SiO₂, 1.5 mm) with 1:1 EtOAc/hexane afforded the pure amide 64a as a glass, 150 mg (38% yield).

NMR (400 MHz): δ 0.05 (s, 9H), 0.81 (s, 3H), 0.90 (d, J = 7.0 Hz, 3H), 1.08 (s, 3H), 1.36 (s, 3H), 2.12 (m, 1H), 2.24 (dd, J = 6.8, 13.4 Hz, 1H), 2.40 (dd, J = 9.1, 13.4 Hz, 1H), 2.70 (d, J = 4.8 Hz, 3H), 2.85 (m, 1H), 3.38 (dq, J = 2.2, 3.3, 11.2 Hz, 2H), 3.61 (dd, J = 8.8, 11.2 Hz, 2H), 5.38 (s, 1H), 6.10 (bs, 1H). IR (neat oil): 3300, 2980, 1640, 1550, 1250, 1120, 1090, and 840 cm⁻¹. EIMS: m/e 409 (M+), 394, 324, 308, 305, 265, 253.
(1S,3R,4R)-4-Methyl-N-methyl-(3'-oxobutyl)-2E-trimethylsilyl-methylene cyclohexylacetamide (64b).

To a slurry of 230-400 mesh silica gel 60 (400 mg) and CH₂Cl₂ (4 mL) was added 10% aq. oxalic acid (160 µL). The mixture was stirred under argon until complete mixing was evident, then the ketal 22 (150 mg or 0.367 mmol) in CH₂Cl₂ (4 mL) was added. The mixture was stirred for 20 h, filtered, and washed with EtOAc (3 x 15 mL). The combined organic layer was dried over MgSO₄ and filtered; the solvent was removed to give crude 64b. Chromatography on one PTLC plate (SiO₂, 1.5 mm) with 93:7 CHCl₃/MeOH afforded the pure keto-amide 64b as a white solid, 104 mg (88%).

NMR (400 MHz, CDCl₃): δ 0.06 (s, 9H), 0.92 (d, J = 7.1 Hz, 3H), 2.15 (s, 3H), 2.29 (dq, J = 7.1, 13.9 Hz, 2H), 2.36 (dq, J = 5.0, 11.5, 16.5 Hz, 1H), 2.51 (dq, J = 5.0, 11.5, 16.5, Hz, 1H), 2.75 (d, J = 4.8 Hz, 3H), 2.85 (q, J = 7, 14 Hz, 1H), 5.43 (s, 1H). IR (CDCl₃): 3470, 2960, 1710, 1660, 1600, 1520, 1410, 1360, 1250, 850, 840 cm⁻¹. EIMS: m/e 323 (M+), 308, 280, 266, 253, 238, 234.

(-)-Octahydro-3,6,11-trimethyl-3,12-epoxy-12H-pyrindino[4,3-j]-1,2-benzodioxepin-10(3H)-one (64).

Ozonized oxygen (0.4 L/min, 7 psi., 70 V) was bubbled through a solution of the keto-amide 64b (74 mg or 0.229 mmol) in MeOH (15 mL) at -78°C until a blue color remained (about 2 min). After 5 min, argon was passed through the solution (15 min), and then the solvent was removed by rotary evaporation (bath temperature ca. 20°C). The residual oil was placed under high vacuum for 2 h, dissolved in CHCl₃ (3 mL), and then treated with CF₃CO₂H (30 µL). After 4 h at ambient temperature, solid NaHCO₃ (500 mg) was added. The mixture was stirred for 15 min, then filtered, and the solvent was evaporated. Chromatography on one PTLC plate (SiO₂, 1.0 mm) with 6:4 EtOAc/hexane gave 64 as an oil (35 mg or 54% yield). Crystallization from pet. ether gave pure 64, mp 78-80°C. [α]D²² = -12.2° (c = 1.17, CHCl₃).

¹H NMR (400 MHz): δ 0.97 (d, J = 6.2 Hz, 3H), 1.34 (s, 3H), 1.76 (dt, J = 4.8, 13.6 Hz, 1H), 1.95 (dq, J = 2.9, 6.0, 9.5 Hz, 1H), 2.00 (dq, J = 2.9, 4.4, 15.2 Hz, 1H), 2.10, (d, J = 17.5 Hz, 1H), 2.39 (m, 1H), 2.96 (s, 3H), 3.10 (dd, J = 5.4, 17.5 Hz, 1H), 5.18 (s, 1H).

¹³C NMR: δ 19.79, 25.06, 25.35, 28.96, 29.00, 33.50, 33.96, 37.88, 39.15, 51.34, 79.52, 79.90, 104.69, 168.67. IR (CHCl₃): 3005, 2940, 2880, 1640, 1455, 1410, 1385, 1370, 1330, 1295, 1260, 1160, 1150, 1095, 1035, 950, 895, 870 cm⁻¹. CIMS: m/e 299 (M + NH₄⁺), 282
(M + H\(^+\)), 264, 240, 222. Anal. Calcd. for C\(_{15}\)H\(_{23}\)NO\(_4\): C, 64.06; H, 8.18. Found: C, 64.05; H, 8.11.

\((1'S,2'R,5'S,3'R)2-[2'-(5''-(3''-(t-Butyl-3''''-carboxypropionate)))-2'''-methyl-6''''E-\end{equation}
trimethylsilylmethylene cyclohexyl)ethyl]-2,5,5-trimethyl-1,3-dioxane (58).

To a solution of diisopropylamine (308 \(\mu\)L, 2.2 mmol) in dry THF (4 mL) under argon at 0°C was added \(\eta\)-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 32 (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, t-butyl bromoacetate (323 \(\mu\)L, 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 aq. NH\(_4\)Cl (10 mL), extracted with EtOAc (3 \(\times\) 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%).

NMR (400 MHz): 6 0.098 (s, 9H), 0.82 (s, 3H), 0.91 (d, \(J = 6.8\) Hz, 3H), 0.99 (s, 3H), 1.30 (s, 3H), 1.39 (s, 9H), 2.10 (m, 1H), 2.30 (m, 1H), 2.48 (d, \(J = 3.5\) Hz, 1H), 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/e 510 (M\(^+\)), 495, 476, 474, 454, 439, 437. Exact mass. calcd. for C\(_{28}\)H\(_{50}\)SiO\(_6\): 510.338. Found: 510.340.

Preparation of 9-Alkylartemisinin Analogs

Method A: Alkylation to cyclohexylacetic acids 43a-56a and subsequent ozone addition/acid closure

To a solution of two equivalents of lithium diisopropylamide (~0.5M in THF) at 0°C was added a solution of acid 1Q (~0.5M in THF). The resultant solution was allowed to warm to ambient temperature, then warmed to 65°C for 2 h, allowed to cool to ambient temperature, and treated with alkylating agent (1.2 equiv.). After 1 h, the solution was stirred with 10% aq. HCl and sat. aq. NH\(_4\)Cl and extracted with CHCl\(_3\). The separated organic layer was washed with sat. aq. NH\(_4\)Cl, dried over Na\(_2\)SO\(_4\), and evaporated to afford crude acids, which were routinely purified via flash column chromatography with silica gel and EtOAc/hex. These acids were each submitted to the previously described general method conditions for ozone addition and subsequent acid-catalyzed formation of tetracycles 43-56.
Method B: Alkylation of 9-Desmethylartemisinin, preparation of 59-63 and 57.

To a solution of 1.1 equivalents of lithium diisopropylamide (−0.5M in THF) at −78°C was added dropwise a solution of 9-desmethylartemisinin (−0.5M in THF) over 10 min. After 1 h at −78°C, alkylation agent (1.1 equivalents) was added. The resultant mixture was allowed to warm to 0°C slowly, and then poured into sat aq NH₄Cl and Et₂O. The ethereal layer was separated, washed with sat. aq. NH₄Cl, dried over Na₂SO₄, and evaporated to provide crude solid, which was routinely purified via flash column chromatography with silica gel and EtOAc/hex to provide the α-substituted analogs 59-63. Isomerization of 59 led to the β-product 57.

\[1'"S.2"R.5"S.3"R1-2'-2"-Methyl-5"-(2"-(3"-phenylpropionic acid))-6"E-trimethylsilylmethylene cyclohexyl)ethyl]-2.5.5-trimethyl-1,3-dioxane (49a)\]

According to Method A, from acid 32 (341 mg, 0.863 mmol) was obtained acid 49a as a white foam, 306 mg (73%, 78% based on recovered starting material). NMR (400 MHz, CDCl₃): δ 0.15 (s, 9H), 0.89 (s, 3H), 0.98 (d, 3H, J = 7.0 Hz), 1.02 (s, 3H), 1.23-1.36 (m, 2H), 1.40 (s, 3H), 1.61-1.74 (m, 3H), 1.80-2.02 (m, 5H), 2.19 (bd, 1H, J = 10.8 Hz), 2.47-2.54 (m, 1H), 2.62 (dd, 1H, J = 12.1, 13.6 Hz), 2.98 (dd, 1H, J = 3.3, 13.6 Hz), 3.04 (ddd, 1H, J = 3.3, 7.1, 11.9 Hz), 3.40-3.49 (m, 2H), 3.59 (dd, 1H, J = 1.5, 11.6 Hz), 7.14-7.28 (m, 5H). IR: 3670-2260 (broad), 2960, 2875, 1700, 1250, 870-840 (broad) cm⁻¹. EIMS: m/e (rel int) 486 (1), 194 (46), 129 (100).

\[1'"S.2"R.5"S.3"R1-2'-2"-Methyl-5"-(2"-octanoic acid))-6"E-trimethylsilylmethylene cyclohexyl)ethyl]-2.5.5-trimethyl-1,3-dioxane (47a)\]

Prepared according to Method A from acid 32 (0.57 g or 1.44 mmol) and hexyl bromide (0.5 mL). The acid 47a was obtained as a clear glass, 568 mg or 82% yield. ¹H-NMR (400 MHz, CDCl₃): 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 dd, 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: 3600-2500, 1700, 1600, 1450, 1380, 1250, 1220, 1130, 1100, 850 cm⁻¹. DCIMS-NH₃ (m/e): 498 (M + NH₄), 481 (M + H), 394, 377, 305. Anal. Calcd for C₂₈H₅₂SiO₄: C, 69.95; H, 10.90. Found: C, 70.16; H, 10.91.
Prepared according to Method A from acid 22 (0.5 g or 1.26 mmol) and tetradeeyl bromide (0.90 mL, 3 mmol). The acid 48a was obtained as a white foam, 491 mg or 66% yield. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 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: 3500-2500, 1700, 1600, 1450, 1380, 1130, 1100, 850 cm$^{-1}$. DCIMS-NH$_3$ (m/e): 610 (M + NH$_4$), 593 (M + H), 524, 506, 489, 417. Anal. Calcd for C$_{36}$H$_{68}$SiO$_4$: C, 72.91; H, 11.56. Found: C, 72.89, H, 11.70.

Prepared according to Method A from acid 22 (0.55 g or 1.39 mmol) and l-bromo-3-phenylpropane (0.5 mL). The acid 51a was obtained as a foam, 394 mg or 55% yield. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.098 (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: 3600-2400, 1700, 1600, 1450, 1380, 1250, 1220, 1130, 1100, 850, 750 cm$^{-1}$. DCIMS-NH$_3$ (m/e): 73
587 (M + TMS), 515 (M + H), 446, 428, 411, 359, 339. Anal. Calcd for C_{31}H_{50}SiO_{4}: C, 72.32; H, 9.79. Found: C, 72.68; H, 9.77.

[1']S.2''R.5''S.3''R1-2'-[2''-(2''-Methyl-5''-(5''-methylhexanoic acid))-6''E-trimethylsilyl-methylene-cyclo-hexyl]ethyll-2.5.5-trimethyl-1.3-dioxane (55a)

Prepared according to Method A from acid 32 (0.55 g or 1.39 mmol) and isoamyl bromide (0.4 mL). The acid 55a was obtained as a clear glass, 578 mg or 89% yield. ¹H NMR (400 MHz, CDCl₃): δ 0.124 (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: 3500-2400, 1700, 1600, 1460, 1380, 1270, 1250, 1220, 1130, 1100, 850, 750 cm⁻¹. DCIMS-NH₃ (m/e): 539 (M + TMS), 467 (M + H), 380, 363, 291. Anal. Calcd for C_{27}H_{50}SiO_{4}: C, 69.48; H, 10.80. Found: C, 69.91; H, 10.81.

(+)-Octahydro-3,6-dimethyl-3,12-epoxy-9-hexyl-12H-pyrano[4,3-i]-1,2-benzodioxepin-10(3H)-one (47)

Prepared according to Method A from acid 47a (0.54 g or 1.12 mmol). The peroxide 47, 84.5 mg or 22% yield, was obtained as a white solid, which was recrystallized from cold hexane, m.p. 80.5-82°C. [α]D^21 = + 44.5 (c = 0.40, CDCl₃). ¹H NMR (400 MHz, CDCl₃): 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 (CHCl₃): 1740, 1380, 1190, 1120, 1040, 1010, 890, 840 cm⁻¹. DCIMS-NH₃ (m/e): 370 (M + NH₄), 353 (M + H), 335, 317, 307, 289, 279. Anal. Calcd for C_{20}H_{32}O_{5}: C, 68.15; H, 9.15. Found: C, 68.30; H, 9.31.

(+)-Octahydro-3,6-dimethyl-3,12-epoxy-9-tetradecyl-12H-pyrano[4,3-i]-1,2-benzodioxepin-10(3H)-one (48)

Prepared according to Method A from acid 48a (480 mg or 0.809 mmol). The peroxide 48, 113 mg or 30% yield, was obtained as white platelets, which were recrystallized from hexane, m.p. 65-66°C. [α]D^22 = + 45.7 (c = 0.56, CDCl₃). ¹H NMR (400 MHz, CDCl₃): 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 (CHCl₃): 1735, 1380, 1185, 1120, 1040, 1010, 890, 840 cm⁻¹. DCIMS-NH₃ (m/e): 482 (M +...
Prepared according to Method A from acid 53a (250 mg or 0.57 mmol). The peroxide 53, 30 mg or 17% yield, was obtained as a white crystalline solid which was recrystallized from hexane, m.p. 113-114°C. \([\alpha]^D_{22} = +85.0^\circ (c = 0.20, \text{CH}_2\text{Cl}_2)\). \(^1H\) NMR (400 MHz, CDCl\(_3\)): 0.95 (d, 3H, \(J = 6.8 \text{ Hz}\)), 1.01 (d, 3H, \(J = 5.9 \text{ Hz}\)), 1.10-1.20 (m, 2H), 1.21 (d, 3H, \(J = 6.5 \text{ Hz}\)), 1.35-1.52 (m, 2H), 1.46 (s, 3H), 1.75 (ddd, 1H, \(J = 3.3, 6.4, 13.2 \text{ Hz}\)), 1.84 (ddd, 1H, \(J = 3.6, 6.6, 13.5 \text{ Hz}\)), 1.92 (ddd, 1H, \(J = 4.4, 4.4, 13.1 \text{ Hz}\)), 2.04 (m, 3H), 2.43 (ddd, 1H, \(J = 4.0, 14.4, 16.0 \text{ Hz}\)), 2.97 (dd, 1H, \(J = 4.7, 8.8 \text{ Hz}\)), 5.84 (s, 1H). IR (CHCl\(_3\)): 1740, 1385, 1185, 1015, 975, 890, 845 cm\(^{-1}\). DCIMS-NH\(_3\) (m/e): 328 (M + NH\(_3\)), 311 (M + H), 293, 275, 265, 247, 237, 219. Anal. Calcd for C\(_{17}\)H\(_{26}\)O\(_5\): C, 65.78; H, 8.44. Found: C, 65.63; H, 8.47.

Prepared according to Method A from acid 51a (380 mg or 0.74 mmol). The peroxide 51 was obtained as a white solid, 101 mg or 35% yield, which was recrystallized from ether/hexane, m.p. 137-138°C. \([\alpha]^D_{22} = +34.8^\circ (c = 0.617, \text{CDCl}_3)\). \(^1H\) NMR (400 MHz, CDCl\(_3\)): 0.99 (d, 3H, \(J = 5.9 \text{ Hz}\)), 1.05 (m, 1H), 1.20-1.50 (m, 4H), 1.45 (s, 3H), 1.50-1.20 (m, 10H), 2.43 (m, 1H), 2.60 (m, 1H), 2.70 (m, 1H), 3.23 (m, 1H), 5.85 (s, 1H), 7.10-7.35 (m, 5H). IR (CH\(_2\)Cl\(_2\)): 1740, 1200, 1120, 1040, 1010, 890, 840 cm\(^{-1}\). DCIMS-NH\(_3\) (m/e): 404 (M + NH\(_4\)), 387 (M + H), 369, 351, 341, 323, 313. Anal. Calcd for C\(_{23}\)H\(_{30}\)O\(_5\): C, 71.48; H, 7.82. Found: C, 71.47; H, 7.78.

According to the general method, acid 49a (146 mg, 0.300 mmol) was converted to desired tetracycle and purified via flash column chromatography with silica gel and EtOAc/hex to give 28 mg (26%) of 49 as white crystals, mp 63-64°C. \([\alpha]^D_{22} = +29.5^\circ (c = 0.880, \text{CHCl}_3)\). NMR (400 MHz, CDCl\(_3\)): 0.84-0.93 (m, 1H), 0.95 (d, 3H, \(J = 6.3 \text{ Hz}\)), 1.16 (ddd, 1H, \(J = 3.3, 13.4, 13.4 \text{ Hz}\)), 1.23-1.32 (m, 2H), 1.35-1.51 (m, 5H), 1.53-1.62 (m, 6H), 1.73 (dq, 1H, \(J = 3.6, 13.7 \text{ Hz}\)), 1.91-2.01 (m, 2H), 2.04 (ddd, 1H, \(J = 2.9, 4.8, 14.6 \text{ Hz}\)), 2.39 (ddd, 1H, \(J =
4.0, 13.2, 14.7 Hz), 2.61 (dd, 1H, J = 11.3, 14.7 Hz), 3.57 (dd, 1H, J = 4.8, 14.5 Hz), 3.65 (dt, 1H, J = 4.8, 11.3 Hz), 5.88, (s, 1H), 7.18-7.34 (m, 5H). IR (CHCl3): 1737, 1118, 1040, 1005 cm⁻¹. CIMS (NH4⁺): m/e (rel int) 376 (M⁺ + NH4⁺, 35), 359 (M⁺ + H⁺, 40), 343 (42), 323 (51), 313 (50), 285 (100). Anal. Calcd for C21H26O5: C, 70.37; H, 7.31. Found: C, 70.52; H, 7.21.

(+-)Octahydro-3.6-dimethyl-3.12-epoxy-9-(3-methylbutyl)-12H-pyrano[4.3-ij]-1.2-benzodioxepin-10(3H)-one (55).

Prepared according to Method A. From acid 55a (566 mg, 1.21 mmol) was obtained 150 mg (37%) of white crystals, which recrystallized from EtOAc/hex in successive crops to provide analytically pure white, fluffy crystals, mp 117-118°C. [α]D²⁰ = + 56.4 (c = 0.525, CHCl3). NMR (400 MHz, CDCl₃): δ 0.91 (ABt, 6H, J = 11.8 Hz, CH(CH₃)₂), 1.01 (d, 3H, J = 5.9 Hz, 6-CH₃), 1.04-1.18 (m, 3H), 1.23-1.44 (m, 4H), 1.45 (s, 3H, 3-CH₃), 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, H12). IR (CH₂Cl₂): 2960, 2882, 1740, 1385, 1190, 1120, 1045 cm⁻¹. CIMS (NH₃): m/e (rel int) 356 (M⁺ + NH₄⁺, 32), 339 (M⁺ + H⁺, 63), 321 (60), 293 (50), 265 (100). Anal. Calcd. for C₁₉H₂₄O₅: C, 67.43; H, 8.93. Found: C, 67.49; H, 8.85.

(+-)Octahydro-9α-allyl-3.6-dimethyl-3.12-epoxy-12H-pyrano[4.3-ij]-1.2-benzodioxepin-10(3H)-one (59, 16-Vinylartemisinin).

According to Method B, from 9-desmethylermestin (100 mg, 0.37 mmol) and allyl bromide (1.5 equiv) was obtained desired material 59 as white hexagonal plates, 57 mg (50%), mp 132.5-133°C, along with recovered starting material (24%). [α]D²² = + 81.2° (c = 0.505, CHCl₃). NMR (400 MHz, CDCl₃); 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), 2.36-2.55 (m, 2H), 2.90 (ddd, 1H, J = 1.5, 1.5, 4.2, 11.2 Hz), 5.10-5.17 (m, 2H), 5.78 (ddd, 1H, J = 5.5, 8.2, 8.8, 10.1 Hz), 5.94 (s, 1H). IR (CH₂Cl₂): 1735, 1115, 1040, 1003 cm⁻¹. DCIMS (NH₃): m/e (rel int) 326 (M⁺ + NH₄⁺, 100), 309 (M⁺ + H⁺, 77), 291 (45), 235 (33). Anal. Calcd for C₁₇H₂₄O₅: C, 66.21; H, 7.84. Found: C, 66.06; H, 7.89.

General Procedure for the Preparation of Amides 65a-69a

To a solution of acid 32 (~0.05 M in CH₂Cl₂) was added triethylamine (2.2 equiv.). After cooling to 0°C, ethyl chloroformate (1.1 equiv.) was added dropwise. After 15 min at 0°C, amine
(1.5 equiv.) was added and the resultant mixture was allowed to warm to ambient temperature. After 1 h, the solution was stirred with 10% HCl: sat. aq. NH₄Cl (1:15, v:v), separated, dried over K₂CO₃, and concentrated under reduced pressure to provide crude amides.

[1S,3S,5R]-2'-[3''-(N-Propyl-2''-acetamide)-6''-methyl-2''Z-trimethylsilylmethylene-cyclohexyl]-ethyl-2,5,5-trimethyl-1,3-dioxane (65a).

Obtained from acid 32 (209 mg, 0.583 mmol) and n-propylamine (freshly distilled, 72 μL, 1.5 equiv.) according to the general procedure as a yellow oil, 206 mg (81%), which was used without further purification. An analytical sample was prepared via flash column chromatography with silica gel and EtOAc/hex. [α]D²₂ = +39.9 (c = 5.17, CH₂Cl₂). NMR (400 MHz, CDCl₃): 0.08 (s, 9H), 0.86 (s, 3H), 0.88-0.98 (m, 6H), 1.09 (s, 3H), 1.39 (s, 3H), 1.40-1.51 (m, 3H), 1.60-1.75 (m, 8H), 2.11-2.17 (br m, 1H), 2.26 (dd, 1H, J = 6.4, 13.6 Hz), 2.44 (dd, 1H, J = 9.2, 13.6 Hz), 2.83-2.91 (br m, 1H), 3.09-3.25 (m, 2H), 3.41 (dt, 2H, J = 1.9, 11.4 Hz), 3.62 (dd, 2H, J = 5.0, 11.4 Hz), 5.42 (s, 1H), 6.06 (br s, 1H, NH). IR: 3300, 2980, 2965, 2880, 1655, 1255, 860, 750 cm⁻¹. EIMS: m/e (rel int) 437(10), 422(21), 281(78), 129(83), 73(100). Anal. Calcd for C₂₅H₄₇NO₃Si: C, 68.60; H, 10.82; N, 3.20. Found: C, 68.86; H, 11.11; N, 3.02.

[1S,3S,5R]-2'-[3''-(N-Benzyl-2''-acetamide)-6''-methyl-2''Z-trimethylsilylmethylene-cyclohexyl]-ethyl-2,5,5-trimethyl-1,3-dioxane (66a).

Obtained from acid 32 (663 mg, 1.85 mmol) and benzylamine (304 μL, 1.5 equiv.) according to the general procedure as a pale yellow oil, 854 mg (95%). [α]D²₂ = +73.9 (c = 2.90, CH₂Cl₂). NMR (400 MHz, CDCl₃): δ 0.09 (s, 9H), 0.78 (s, 3H), 0.94 (d, 3H, J = 6.9 Hz), 1.05 (s, 3H), 1.09-1.23 (m, 4H), 1.44 (br d, 1H, J = 13.3 Hz), 1.56-2.01 (m, 7H), 2.12-2.18 (m, 1H), 2.31 (dd, 1H, J = 6.0, 13.7 Hz), 2.50-2.64 (m, 1H), 2.90-2.98 (br m, 1H), 3.23 (dd, 1H, J = 1.8, 11.2 Hz), 3.34 (dd, 1H, J = 1.7, 11.4 Hz), 3.40 (d, 1H, J = 11.4 Hz), 3.54 (d, 1H, J = 11.4 Hz), 4.37 (dd, 1H, J = 5.3, 14.6, 14.6 Hz), 4.42 (dd, 1H, J = 5.3, 14.6, 14.6 Hz), 5.47 (s, 1H), 6.52 (br m, 1H), 7.22-7.36 (m, 5H). IR (CH₂Cl₂): 3450, 3330, 2960, 2875, 1660, 1510, 1460, 1380, 1218, 1117, 1088, 933, 860 cm⁻¹. EIMS: m/e (rel int) 485(13), 470(20), 329(88), 91(100). Anal. Calcd for C₂₉H₄₇NO₃Si: C, 71.71; H, 9.75; N, 2.88. Found: C, 71.58; H, 9.85; N, 2.72.
Obtained from acid 22 (889 mg, 2.48 mmol) and glycine t-butyl ester (0.560 g, 4.27 mmol) according to the general procedure. Flash column chromatography with silica gel and EtOAc/hex provided the desired amide as a white foam, 857 mg (68%). [α]D^22 = +40.3 (c = 16.2, CH2Cl2). NMR (400 MHz, CDCl3): δ 0.08 (s, 9H), 0.87 (s, 3H), 0.93 (d, J = 7.0 Hz), 1.07 (s, 3H), 1.12-1.20 (br m, 1H), 1.37 (s, 3H), 1.47 (s, 9H), 1.56-1.94 (m, 8H), 2.15 (br t, 1H, J = 6.9 Hz), 2.39 (dd, 1H, J = 8.1, 13.9 Hz), 2.46 (dd, 1H, J = 8.1, 13.9 Hz), 2.82-2.90 (br m, 1H), 3.44 (ddd, 2H, J = 1.6, 6.3, 11.5 Hz), 3.60 (d, 2H, J = 11.5 Hz), 3.79 (dd, 1H, J = 4.7, 18.3 Hz), 4.01 (ddd, 2H, J = 4.7, 18.3 Hz), 5.42 (s, 1H), 6.33 (br m, 1H). IR: 3310, 2950, 2870, 1745, 1655, 1605, 1525, 1455, 1370, 1250, 1165, 1120, 1090, 1043, 917, 855, 735 cm⁻¹. EIMS: m/e (rel int) 509(7), 494(10), 438(11), 366(10), 353(42), 297(42), 129(100). Anal. Calcd for C_{28}H_{51}NO_{5}Si: C, 65.97; H, 10.08; N, 2.75. Found: C, 65.57; H, 10.31; N, 2.76.

Obtained from acid 22 (977 mg, 2.73 mmol) and N,N-dimethylethylenediamine (0.33 mL, 300 mmol) according to the general procedure, except with final alkaline workup (sat. aq. NaHCO3). Flash chromatography with silica gel and 0.5% (58% NH₄OH)/5% MeOH/CH₂Cl₂ afforded a colorless oil, 900 mg (71%). NMR (400 MHz, CDCl₃): δ 0.09 (s, 9H), 0.88 (s, 3H), 0.89-1.05 (m, 6H), 1.06 (s, 3H), 1.45-1.95 (m, 7H), 2.00-2.17 (m, 1H), 2.23 (s, 6H), 2.36 (m, 3H), 3.31 (ddd, 2H, J = 5.9, 5.9, 13.0 Hz), 3.43 (d, 2H, J = 10.8 Hz), 3.58 (d, 2H, J = 10.8 Hz), 5.41 (s, 1H), 6.19 (br m, 1H). IR: 3300, 2960, 2860, 2820, 2770, 1645, 1605, 1550, 1465, 1380, 1253, 1220, 1200, 1120, 1100, 1045, 855 cm⁻¹. EIMS: m/e (rel int) 466(1), 396(6), 129(10), 71(70), 58(100). Anal. Calcd for C_{26}H_{50}O_{3}N_{2}Si: C, 66.90; H, 10.80; N, 6.00. Found: C, 66.59; H, 11.00; N, 5.78.

General procedure for the preparation of 11-Azaartemisinin Analogs 65-69

Through a solution of amide in CH₂Cl₂ (0.04-0.05 M) at -78° was passed a stream of O₃/O₂ until a blue color appeared. Careful monitoring by TLC was routine to gauge the conversion of starting material and minimize overexposure to O₃. The resultant mixture was then treated in succession with a solution of BHT (10 mg) in CH₂Cl₂ (1 mL), silica gel 60 (0.5 wt.: vol. CH₂Cl₂) and 3M H₂SO₄ (0.5 vol.: wt. silica gel 60) and allowed to warm to ambient...
temperature. After 2 days or more, the solid was filtered off and rinsed with CH$_2$Cl$_2$ (2x) and EtOAc (1x). The filtrate was washed with sat. aq. NaHCO$_3$ (2x) and brine (1x), dried over MgSO$_4$, and evaporated under reduced pressure to afford crude product.

(-)-Octahydro-3.6-dimethyl-3,12-epoxy-11-propyl-12H-pyridinol4.3-1j-1.2-benzodioxepin-10(3H)-one (65)

Prepared according to the general procedure from amide 65a (206 mg, 0.471 mmol). Purification via flash column chromatography with silica gel and EtOAc/hex and recrystallization from EtOAc/hex afforded white needles, 52 mg (24%), mp 125.0-125.5°C. [α]$_D^{22}$ = -15.7 (c = 0.890, CHCl$_3$). $^1$H NMR (400 MHz, CDC$_3$): δ 0.93 (t, 3H, J = 7.4 Hz), 1.01 (d, 3H, J = 6.2 Hz), 1.04-1.16 (m, 1H), 1.20-1.37 (m, 2H), 1.39 (s, 3H), 1.40-1.79 (m, 7H), 1.95-2.07 (m, 2H), 2.12 (dd, 1H, J = 1.3, 17.4 Hz), 2.37-2.47 (m, 1H), 3.14 (dd, 1H, J = 6.0, 17.5 Hz), 3.41 (ddd, 1H, J = 5.3, 10.0, 13.2 Hz), 3.58 (ddd, 1H, J = 6.1, 10.0, 13.2 Hz), IR (CH$_2$Cl$_2$): 2940, 1640, 1135, 1080, 1027, 917 cm$^{-1}$. CIMS (NH$_3$): m/e (rel int) 327 (M + NH$_4^+$, 12), 310 (M + H$^+$, 100). Anal. Calcd for C$_{17}$H$_{27}$NO$_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 65.72; H, 8.83; N, 4.32.

(-)-Octahydro-11-benzyl-3.6-dimethyl-3,12-epoxy-12H-pyridinol4.3-1j-1.2-benzodioxepin-10(3H)-one (66)

Prepared according to the general procedure from amide 66a (130 mg, 0.268 mmol). Flash column chromatography with silica gel and EtOAc/hex afforded 24 mg (25%) of white crystals, which recrystallized from EtOAc/hex, mp 177-179°C. [α]$_D^{22}$ = -3.0 (c = 0.500, CH$_2$Cl$_2$). NMR (400 MHz, CDC$_3$): δ 0.94 (s, 3H, 6.2 Hz), 0.97-1.12 (m, 1H), 1.15 (s, 3H), 1.17-1.47 (m, 4H), 1.57-1.69 (m, 3H), 1.75-1.82 (m, 1H), 1.89-2.01 (m, 2H), 2.22 (dd, 1H, J = 1.4, 17.6 Hz), 2.33-2.42 (m, 1H), 4.60 (d, 1H, J = 14.6 Hz), 5.06 (d, 1H, J = 14.6 Hz), 5.14 (s, 1H), 7.19-7.39 (m, 5H). IR (CH$_2$Cl$_2$): 2940, 1643, 1135, 1080, 1027, 917 cm$^{-1}$. CIMS (NH$_3$): m/e (rel int) 375 (M + NH$_4^+$, 5), 358 (M + H$^+$, 100). Anal. Calcd for C$_{21}$H$_{27}$NO$_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.87; H, 7.56; N, 3.81.

(-)-Octahydro-11-(2'-(t-butylacetate))-3.6-dimethyl-3,12-epoxy-12H-pyridinol4.3-1j-1.2-benzodioxepin-10(3H)-one (67)

Prepared according to the general procedure from amide 67a (725 mg, 1.51 mmol). Successive flash column chromatography with silica gel and EtOAc/hex and EtOAc/CH$_2$Cl$_2$, respectively, yielded 202 mg (35%) of yellow solid, which was recrystallized from EtOAc/hex to provide pale yellow hexagonal plates, mp 116-117°C. [α]$_D^{22}$ = -13.3 (c = 9.55, CH$_2$Cl$_2$). NMR
(400 MHz, CDCl₃): δ 1.00 (d, 3H, J = 6.3 Hz), 1.02-1.16 (m, 1H), 1.30-1.42 (m, 4H), 1.43-1.56 (m, 15H), 1.63-1.84 (m, 4H), 1.94-2.07 (m, 2H), 2.18 (dd, 1H, J = 1.3, 17.4 Hz), 2.38-2.48 (m, 1H), 3.16 (dd, 1H, J = 5.9, 17.4 Hz), 3.94 (d, 1H, J = 17.4 Hz), 4.52 (d, 1H, J = 17.4 Hz), 5.43 (s, 1H). IR (CH₂Cl₂): 2930, 1735, 1650, 1367, 1227, 1160, 1135, 1035 cm⁻¹.

CIMS (NH₄⁺): m/e (rel int) 399 (M + NH₄⁺, 7), 382 (M + H⁺, 30), 326 (100). Anal. Calcd for C₂₀H₃₁NO₆: C, 62.97; H, 8.19; N, 3.67. Found: C, 63.23; H, 8.19; N, 3.63.

(-)-Octahydro-11-(2'-aceticacid)-3,6-dimethyl-3,12-epoxy-12H-pyridino[4,3-j]-1,2-benzodioxepin-10(3H)-one (67)

To a solution of t-butyl ester 6jb (135 mg, 0.354 mmol) in CH₂Cl₂ (10 mL) was added TFA (0.50 mL). After 3 h at ambient temperature, the resultant solution was washed with H₂O (4 x 20 mL) and brine (25 mL), dried over Na₂SO₄, and concentrated under reduced pressure to a white solid, which recrystallized from EtOAc/hex to provide 47 mg (41%) of white cubic prisms, mp 169-172°C (d), in successive crops. [a]D²² = -26 (c = 0.730, CHCl₃). NMR (400 MHz, CDCl₃): δ 1.05 (d, 3H, J = 6.2 Hz), 1.07 (dd, 1H, J = 3.7, 12.8 Hz), 1.14 (dd, 1H, J = 3.7, 12.8 Hz), 1.38 (s, 3H), 1.39-1.61 (m, 3H), 1.68 (ddd, 1H, J = 3.1, 6.9, 13.6 Hz), 1.72 (ddd, 1H, J = 3.1, 6.9, 13.6 Hz), 1.83 (br dt, 1H, J = 4.5, 13.7 Hz), 1.95-2.08 (m, 2H), 2.21 (dd, 1H, J = 1.2, 17.6 Hz), 2.43 (ddd, 1H, J = 3.6, 14.3, 14.6 Hz), 3.19 (dd, 1H, J = 6.2, 17.5 Hz), 4.21 (d, 1H, J = 17.4 Hz), 4.52 (d, 1H, J = 17.4 Hz), 5.39 (s, 1H). IR (CHCl₃): 3500-2150 (br, O-H), 2945, 1725, 1648, 1265-1165, 1138, 1038 cm⁻¹. CIMS (NH₃): m/e (rel int) 343 (M + NH₄⁺, 5), 326 (M + H⁺, 100), 240 (50). Anal. Calcd for C₁₆H₂₃NO₆: C, 59.07; H, 7.13; N, 4.30. Found: C, 59.42; H, 7.32; N, 4.33.

(-)-Octahydro-3,16-dimethyl-11-(2'-dimethylaminoethyl-3,12-epoxy-12H-pyridino[4,3-j]-1,2-benzodioxepin-10(3H)-one (68)

To a solution of amine 68a (600 mg, 1.29 mmol) in MeOH (40 mL) was added 10% aq. HCl (1 mL). The MeOH was removed via rotary evaporation under reduced pressure in the cold, and the resultant residue was shaken with sat. aq. NaHCO₃ (15 mL) and CH₂Cl₂ (35 mL). The separated organic layer was washed with sat. aq NaHCO₃, dried over K₂CO₃, and evaporated to a colorless oil, which was placed in MeOH (40 mL) and cooled to -78°C, and a stream of O₃/O₂ was bubbled through. When TLC monitor indicated no starting material remaining, the resultant mixture was concentrated under reduced pressure at below ambient temperature. Final traces of H₂O were removed azeotropically with CH₂Cl₂ (50 mL) and the resultant residue was placed in CH₂Cl₂ (40 mL) and TFA (1 mL). After 3 days at ambient temperature, the mixture was washed with sat. aq. NaHCO₃(2 x 30 mL), dried over K₂CO₃, and evaporated to afford a yellow oil,
which was purified via flash column chromatography with SiO2. After elution with 0.5% (58% NH4OH)/5% MeOH/CH2Cl2, 222 mg (51%) of the title compound was obtained as a yellow oil. \([\alpha]_D^{22} = -16.4^\circ \) (c = 5.54, CH2Cl2).

\[^1H\text{NMR} (400 \text{ MHz, CDCl}_3): \delta 1.00 \text{ (d, 3H, } J = 6.2 \text{ Hz), 1.03-1.18 (m, 1H), 1.30-1.54 (m, 7H), 1.60-1.79 (m, 3H), 1.94-2.06 (m, 2H), 2.11 (dd, 1H, } J = 1.4, 17.4 \text{ Hz), 2.28 (s, 6H), 2.35-2.51 (m, 2H), 2.61-2.70 (m, 1H), 3.13 (dd, 1H, } J = 6.0, 17.4 \text{ Hz), 3.56 (quintet, 1H, } J = 6.8 \text{ Hz), 3.77 (dd, 1H, } J = 5.1, 7.7, 13.5 \text{ Hz), 5.45 (s, 1H).} \]

\[^13C\text{NMR:} \text{ 167.2, 119.2, 103.3, 91.9, 78.5, 77.5, 55.6, 50.1, 44.2, 38.1, 37.6, 36.6, 35.3, 32.7, 32.4, 27.2, 23.7, 18.5.} \]

\[\text{IR: 2980, 2930, 1708, 1465, 1260, 1160, 1039 cm}^{-1}. \]

\[\text{CIMS (NH}_4^+\text{): m/e (rel int) 339 (M}^+ + \text{NH}_4^+, 100) 323 (M}^+ + \text{H}^+, 15), 307(18), 281(20), 240(17), 117(29). \]

\[\text{Anal. Calcd for C}_{18}\text{H}_{30}\text{N}_2\text{O}_3: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.95; H, 9.07; N, 8.13.} \]

**Hydrochloride Monohydrate Salt (68)**

To a solution of the amine \(68\) (68 mg, 0.211 mmol) in 95% EtOH (10 mL) was added 38% HCl (50 }\mu\text{L). The solvent was removed in vacuo to provide a hygroscopic tan foam, which was shown to be the monohydrate by analysis. \([\alpha]_D^{22} = -24.5^\circ \) (c = 2.69, CHCl3). NMR (400 MHz): \(\delta 1.00 \text{ (d, 3H, } J = 6.2 \text{ Hz), 1.03-1.17 (m, 1H), 1.21-1.53 (m, 10H), 1.60-1.84 (br m, 2H), 1.95-2.19 (m, 2H), 2.39 (br ddd, 1H, } J = 3.5, 9.7, 13.6 \text{ Hz), 2.77-3.00 (br m, 7H), 3.11 (dd, 1H, } J = 6.2, 17.7 \text{ Hz), 3.18-3.36 (m, 2H), 3.74 (ddd, 1H, } J = 6.3, 9.5, 13.2 \text{ Hz), 4.09-4.17 (m, 1H), 5.38 (s, 1H).} \]

\[\text{IR (CHCl3): 2970, 2340 (broad, NH), 1645, 1465 cm}^{-1}. \]

\[\text{Anal. Calcd for C}_{18}\text{H}_{30}\text{N}_2\text{O}_4: C, 55.02; H, 8.47; N, 7.13. Found: C, 54.88; H, 8.24; N, 7.15.} \]

\[\text{(+)-Octahydro-3,6-dimethyl-9\beta-carboxymethyl-3,12-epoxy-12H-pyrano[4,3-ij]-1,2-benzo-dioxepin-10(3H)-one (58)} \]

A solution of \(98\) (270 mg, 0.529 mmol) in CH2Cl2 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 CH2Cl2 (1 mL) was added, followed by silica gel (7.5 g) and 3M H2SO4 (3 mL). The resulting mixture was brought to ambient temperature and stirred for 18 h. The silica gel was removed by filtration, rinsing with EtOAc (50 mL). The filtrate was concentrated in vacuo to afford the butyl ester \(99\), which was placed in CH2Cl2 (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, leaving 300 mg of crude product. This was 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% deoxy by NMR. This was taken into EtOAc (1 mL) and crystallized to provide 35 mg (20%) of pure product 5, mp 155-157°C.

NMR (400 MHz): 8 0.98 (d, J = 5.9 Hz, 3H), 1.43 (s, 3H), 2.36 (dd, J = 7.0, 16.7 Hz, 1H), 2.42 (m, 1H), 2.98 (dd, J = 7.0, 16.7 Hz), 3.85 (ddd, J = 5.1, 7.0, 7.0 Hz), 5.87 (s, 1H).


(1'S, 3'S, 5'R, 2''R)-2''Z-2'-3',2''-Butyric acid)-6''-methyl-2'-trimethylsilylmethylene-
cyclohexyllethyl-2.5.5-trimethyl-1.3-dioxane (43a)

To a solution of diisopropylamine (635 µL, 4.24 mmol) in dry THF (8 mL) at 0°C was added n-butyllithium (4.24 mmol, 3.01 mL of 1.55 M in hexane). The resulting solution was stirred at 0°C for 15 min and then cooled to -78°C. The acid 32 (840 mg, 2.12 mmol) in dry THF (4 mL) was added via syringe, and the solution was allowed to warm to ambient temperature over 30 min. The solution was heated to 50°C for 2 h and recooled to 0°C. Ethyl iodide (424 µL, 5.3 mmol) was added and the resulting solution stirred at ambient temperature for 1 h. The solution was treated with aq. NH4Cl (10 mL) and extracted with EtOAc (3 x 20 mL). The organic layers were dried (MgSO4) and evaporated in vacuo to give 1.3 g of crude product, which 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 43a (677 mg, 75%) as a colorless gum.

NMR (400 MHz): 8 0.09 (s, 9H, SiCH3), 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, =CH). EIMS: m/e (rel int) 424 (5), 194 (28), 180 (26), 161 (25), 160 (25), 129 (100). Exact mass calcd. for C24H44O4Si: 424.301. Found 424.300.

A solution of 43a (677 mg, 1.59 mmol) in CH2Cl2 (100 mL) 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 (about 8 min). A solution of BHT (50 mg) in CH2Cl2 (1 mL) was added, followed by the addition of 70-230 mesh silica gel 60 (16 g) at -78°C. The resulting mixture was treated with 3 M H2SO4 (6 mL) and brought to ambient temperature and stirred overnight. The mixture was treated with NaHCO3 (6 g) and stirred for 20 min at room temperature. The product was isolated by filtration, rinsing with EtOAc (100 mL). The solvent was removed in vacuo, leaving 630 mg of crude product. This was adsorbed onto 230-400 mesh silica gel 60 (2 g) and applied to a column of 30 g of silica.
gel 60 (230-400 mesh) eluting with hexane/EtOAc (90/10) to give the product 43 (152 mg, 32%) as a white solid, which was crystallized from hexane to provide white crystals, mp 125-125.5°C. \[\alpha\]D = +70.0 (c = 0.10, EtOH).

NMR (400 MHz): \(\delta\) 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 (CHCl₃): 3030, 2970, 2930, 2880, 1740, 1385, 1190, 1120, 1040, 1000, 890 cm⁻¹. CIMS (NH₄⁺): m/e 314 (M + NH₄⁺), 297 (M + H⁺), 279, 268, 251, 233, 223. Anal. Calcd. for C₁₆H₂₄O₅: C, 64.84; H, 8.16. Found: C, 64.80; H, 8.21.

t-Butylarteperether (75)

To a solution of dihydroqinghaosu (100 mg, 0.32 mmol) in CH₂Cl₂ (7 mL) under argon were added dry 4Å molecular sieves (2.2 g), 3.0 M t-BuOOH in isooctane (200 mL), and p-toluenesulfonic acid (20 μg). The mixture was stirred at 23°C for 30 min and solid NaHCO₃ (ca. 1 g) was added. After 15 min, the mixture was filtered and evaporated. PTLC on 2 x 1.0-mm silica gel plates, eluting with 15% EtOAc/hexane, gave pure 25. (85 mg or 68% yield), which was crystallized from cold pentane or hexane to give cubic crystals, mp 94-95°C. \[\alpha\]D = +157 (c = 0.25, CHCl₃).

400 MHz ¹H NMR (CDCl₃): \(\delta\) 0.93 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 7.5 Hz, 3H), 1.24 (s, 9H), 1.42 (s, 3H), 1.64 (dq, J = 3.1, 6.5, 13.2 Hz, 1H), 1.75 (dq, J = 3.5, 7.3, 13.5 Hz, 1H), 1.85 (ddq, J = 3.1, 4.0, 6.8, 13.5 Hz, 1H), 2.01 (dq, J = 2.9, 4.8, 14.5 Hz, 1H), 2.77 (ddq, J = 4.4, 7.5, 15.2 Hz, 1H), 5.30 (d, J = 4.5 Hz, 1H), 5.51 (s, 1H). IR (CDCl₃): 1380, 1370, 1100, 1050, 980, 960, 940 cm⁻¹. CIMS (NH₃): m/e 374 (M + NH₄), 311, 284, 267, 249, 239, 221. Anal. Calcd. for C₁₉H₂₃O₆: C, 64.02; H, 9.05. Found: C, 64.33; H, 9.35.

(+)-Octahydro-3,6-dimethyl-3,12-epoxy-6β-ethoxy-7β-ethyl-12H-pyranof[4,3-i]-1,2-benzodioxepin-10(3H)-one (73)

A solution of 43 (132 mg, 0.445 mmol) in methanol (6 mL) at 0°C was treated with NaBH₄ (132 mg, 3.49 mmol). The resulting mixture was stirred at 0°C for 1 h. The mixture was treated with glacial acetic acid (200 μL) and water (6 mL). The resulting mixture was extracted with CH₂Cl₂ (3 x 30 mL) and dried (MgSO₄). Evaporation left lactol (129 mg, 97%) as a white solid, which was used without further purification.

A solution of lactol (129 mg, 0.432 mmol) in ethanol (1.5 mL) and benzene (4.5 mL) was treated with BF₃·Et₂O (20 μL) and then heated to 80°C for 1 h. After cooling to room temperature, saturated aqueous NaOAc (1.5 mL) and water (1.5 mL) were added with stirring.
The phases were separated and the aqueous phase was extracted with benzene (2 x 6 mL). The combined organic phases were dried (MgSO₄) and evaporated, leaving 130 mg of crude product. This was applied to a column of silica gel 60 (230-400 mesh), eluting with hexane/EtOAc (90/10) to give 73 (89 mg, 63%) and its C6 epimer (17 mg, 12%). Recrystallization of the 89 mg of 73 along with 11 mg from an earlier run from hexane gave 67 mg of material, mp 97-98°C. [α]D²² = +220 (c = 0.18, CHCl₃).

1H NMR (400 MHz): δ 0.89 (t, 3H, J = 7.4 Hz, CH₂CH₃), 0.96 (d, 3H, J = 6.2 Hz, 10-CH₃), 1.18 (t, 3H, J = 7.0 Hz, OCH₂CH₃), 1.21-1.43 (m, 3H), 1.45 (s, 3H, 3-CH₃), 1.47-1.59 (m, 2H), 1.63 (ddd, 1H, J = 3.4, 7.0, 13.0 Hz), 1.69 (ddd, 1H, J = 3.7, 7.7, 13.0 Hz), 1.78-1.93 (m, 2H), 2.04 (ddd, 1H, J = 3.1, 4.8, 14.5 Hz), 2.30-2.43 (m, 2H), 3.48 (ddd, 1H, J = 7.0, 7.0, 11.0 Hz, OCH₂), 3.87 (ddd, 1H, J = 7.0, 7.0, 11.0 Hz), 4.92 (d, 1H, J = 3.5 Hz, H₆), 5.43 (s, 1H, H₄a).


C6 Epimer: Octahydro-3,6-dimethyl-10β-ethoxy-3,12-epoxy-7β-propyl-12H-pyranof[4.3-j]-1,2-benzodioexepin-10(3H)-one

NMR (400 MHz): δ 0.89 (t, 3H, J = 7.3 Hz, CH₂CH₃), 0.97 (d, 3H, J = 6.0 Hz, 10-CH₃), 0.99-1.22 (m, 2H), 1.22 (t, 3H, J = 7.0 Hz, OCH₂CH₃), 1.25-1.38 (m, 2H), 1.45 (s, 3H, 3-CH₃), 1.48-1.74 (m, 4H), 1.89 (ddd, 1H, J = 3.3, 6.4, 16.8 Hz), 2.03 (ddd, 1H, J = 3.1, 4.4, 14.8 Hz), 2.16 (ddd, 1H, J = 4.1, 9.6, 14.9 Hz), 2.39 (ddd, 1H, J = 4.0, 13.5, 15.2 Hz), 3.49 (ddd, 1H, J = 7.0, 9.6, 15.2 Hz, OCH₇), 4.02 (ddd, 1H, J = 7.0, 9.6, 15.2 Hz, OCH₂), 4.48 (d, 1H, J = 9.3 Hz, H₆), 5.35 (s, 1H, H₄a).

(+)-Octahydro-3,6-dimethyl-10β-ethoxy-3,12-epoxy-7β-propyl-12H-pyranof[4.3-j]-1,2-benzodioexpine (90)

To a solution of (+)-octahydro-3,6-dimethyl-3,12-epoxy-7β-propyl-12H-pyranof[4.3-j]-1,2-benzodioexepin-10(3H)-one (44, 80 mg, 0.26 mmol) in MeOH (4 mL) at 0°C were added NaBH₄ (80 mg, 2.1 mmol). After 1 h at 0°C, glacial acetic acid (120 µL) and H₂O (4 mL) were added and the mixture was extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over MgSO₄ and evaporated to provide 61 mg (75%) of lactol as a white solid, which was used without further purification.
To a solution of lactol (61 mg, 0.20 mmol) in benzene (4.5 mL) and ethanol (1.5 mL) was added boron trifluoride etherate (10 uL). The resultant solution was heated at 80°C for 1 h, allowed to cool to ambient temperature, treated with saturated aqueous sodium acetate (1.5 mL) and H2O (1.5 mL), and extracted with benzene (2 x 10 mL). The combined organic layers were dried over MgSO4 and evaporated to give 61 mg (90% crude) of white crystalline solid, which upon recrystallization afforded pure title compound as analytically pure white crystals, mp 109-111°C. [α]D20 = +79.3 (c = 0.440, CHCl3). 1H NMR (400 MHz): δ 0.90 (t, 3H, J = 7.1 Hz), 0.96 (d, 3H, J = 6.3 Hz), 1.19 (t, 3H, J = 7.1 Hz), 1.22-1.42 (m, 6H), 1.45 (s, 3H), 1.48-1.59 (m, 3H), 1.62 (ddd, 1H, J = 3.3, 6.6, 13.2 Hz), 1.69 (ddd, 1H, J = 4.1, 8.2, 14.1 Hz), 1.79-1.93 (m, 2H), 2.04 (ddd, 1H, J = 2.9, 4.8, 14.7 Hz), 2.38 (ddd, 1H, J = 4.0, 14.5, 14.6 Hz), 2.39-2.48 (brm, 1H), 3.58 (dq, 1H, J = 7.0, 11.3 Hz), 3.87 (dq, 1H, J = 7.1, 11.3 Hz), 4.88 (d, 1H, J = 3.5 Hz, H10ω), 5.43 (s, 1H). 13C NMR: 14.3, 15.2, 19.8, 20.4, 24.5, 24.8, 26.3, 29.8, 34.8, 35.6, 36.5, 37.5, 42.9, 52.7, 63.7, 81.0, 88.2, 100.7, 104.0. CIMS (NH4+): m/e (rel int) 358 (M + NH4+, 13), 312 (27), 295 (100), 277 (35), 249 (68).

Also, some of the alternate 10α epimer was isolated:

Octahydrop-3.6-dimethyl-10α-ethoxy-3.12-epoxy-9β-propyl-12H-pyrano[4.3-j]-1.2-benzo-dioxepine

NMR (400 MHz) 0.90 (t, 3H, J = 7.3 Hz), 0.96 (d, 3H, J = 7.1 Hz), 1.00-1.11 (m, 3H), 1.22 (t, 3H, J = 7.0 Hz), 1.45 (s, 3H), 1.47-1.73 (m, 7H), 1.89 (brm, 1H), 2.03 (ddd, 1H, J = 2.9, 4.8, 14.6 Hz), 2.26 (ddd, 1H, J = 5.0, 9.8, 18.4 Hz), 2.38 (ddd, 1H, J = 4.0, 13.5, 14.6 Hz), 3.50 (dq, 1H, J = 7.0, 9.6 Hz), 4.02 (dq, 1H, J = 7.1, 9.5 Hz), 4.48 (d, 1H, J = 9.2 Hz, H10b), 5.34 (s, 1H).

(-)-10α-(3-O-Cholesteroloxycarbonyloxy)dihydroartemisinin (77)

To a solution of dihydroartemisinin (100 mg or 0.352 mmol) in CH2Cl2 (8 mL) under argon was added DMAP (60 mg or 0.5 mmol) followed by cholesteroylchloroformate (190 mg or 0.42 mmol). After 100 min the bulk of the solvent was evaporated and the residue was applied to two 20 x -20 cm, 1.5-mm SiO2 PTLC plates. The plates were eluted with 10% EtOAc/hexane to give 77 (210 mg or 86% yield) as a glass. Crystallization from hexane afforded a white powder, m.p. 123-125°C. [α]D22 = -27.9 (c = 2.85, CDCl3). 1H NMR (400 MHz, CDCl3): δ 0.68 (s, 3H), 0.87 (dd, 6H, J = 1.8, 6.6 Hz), 0.91 (d, 3H, J = 7.1 Hz), 0.92 (d, 3H, J = 6.4 Hz), 0.97 (d, 3H, J = 6.0 Hz), 1.01 (s, 3H), 1.43 (s, 3H), 2.39 (m, 2H), 2.59 (ddq, 1H, J = 4.5, 7.0, 9.9 Hz), 4.52 (ddddd, 1H, J = 1.3, 5.5, 10.2, 15.7 Hz), 5.40 (br d, 1H, J = 6.3 Hz), 5.44 (s, 1H), 85
5.59 (d, 1H, J = 9.9 Hz). IR (CDCl₃): 2950, 2880, 1745, 1450, 1375, 1270, 1260, 1140, 1040, 1000, 900 (br) cm⁻¹. DCIMS (NH₃): m/e 714 (M + NH₄), 386, 369, 284, 267, 249, 239. Anal. Calcd for C₄₃H₆₈O₇: C, 74.10; H, 9.83. Found: C, 74.29; H, 9.96.

(+)-Octahydro-10b-[2'S,3'-bis(hexadecanoyloxy)prop-1'-yloxy]-3,6,9-trimethyl-3,12-epoxy-12H-pyrano-[4,3-j]-1,2-benzodioxepin (76)

To a solution of triphosgene (127 mg or 0.426 mmol) in CH₂Cl₂ (8 mL) under argon at 22°C was added 1,2-dipalmitoyl-sn-glycerol [Sigma Chemical Co., [α]D²² = -3.8° (c = 1.3, CHCl₃); 600 mg or 1.05 mmol] followed by pyridine (85 µL or 83 mg or 1.05 mmol). The mixture was stirred at 22°C for 60 min whereupon dihydroartemisinin (270 mg or 0.95 mmol) was added at once. Pyridine (95 µL) was added, vigorous gas evolution was noted, and the mixture was stirred 16 h at 22°C, and poured into sat. aq. NaHCO₃ (100 mL). The mixture was extracted with EtOAc (1 x 75 mL). The organic layer was washed with sat. aq. NH₄Cl (3 x 50 mL), dried over MgSO₄ and filtered; the solvent was evaporated to give 873 mg of crude product. Flash chromatography on 75 g of silica gel with 10% EtOAc/hexane afforded (at Rf ~0.3) the product 26 (125 mg, 15%) as an oil. Crystallization from cold hexane gave 26 as a white waxy solid (100 mg), m.p. 49-50.5°C. [α]D²² = +64.5 (c = 0.44, CHCl₃). ¹H NMR (400 MHz, CDCl₃) shows a 9:1 ratio of isomers at C10b:a, respectively: 8 0.88 (t, 6H, J = 7.0 Hz), 0.89 (d, 3H, J = 7.0 Hz), 0.96 (d, 3H, J = 6.2 Hz), 1.26 (br m, 62H), 1.43 (s, 3H), 1.45-1.68 (m, 10H), 1.74 (br ddd, 2H, J = 3.3, 8.2, 12.7 Hz), 1.90 (dddd, 1H, J = 1.0, 2.6, 6.0, 13.7 Hz), 2.04 (ddd, 1H, J = 2.9, 4.5, 14.5 Hz), 2.32 (m, 6H), 2.64 (ddq, 1H, J = 3.3, 4.9, 7.0 Hz), 3.54 (dd, 1H, J = 5.8, 10.6 Hz), 3.99 (dd, 1H, J = 4.5, 10.6 Hz), 4.13 (dd, 1H, J = 6.1, 11.9 Hz), 4.31 (dd, 1H, J = 3.8, 11.9 Hz), 4.79 (d, 1H, J = 3.3 Hz), 5.25 (dddd, 1H, J = 3.8, 4.5, 5.8, 6.1 Hz), 5.39 (s, 1H). IR (CHCl₃): 2930(s), 2860(s), 1735, 1460, 1380, 1220(br, 1165(br), 1115, 1030, 990, 960, 940, 880, 830 cm⁻¹. DCIMS (NH₃): m/e 852 (M + NH₄), 806, 789, 614, 586, 551. Anal. Calcd for C₅₁H₉₀O₁₁: C, 71.90; H, 10.86. Found: C, 71.93; H, 10.72.

(+)-Octahydro-3,12-epoxy-3,6,9,9-tetramethyl-12H-pyrano[4,3-j]-1,2-benzodioxepin-10(3H)-one (63)

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 (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 NH₄Cl (15 mL) and 10% HCl (1 mL) were added, and the resultant mixture was
extracted with ether (3 x 15 mL). The combined ethereal layers were washed with saturated aqueous NH₄Cl (15 mL), H₂O (3 x 50 mL), and brine (2 x 25 mL), dried over Na₂SO₄ and evaporated to provide 94 mg of yellow, semicrystalline solid, which was purified via flash column chromatography with SiO₂. Elution with EtOAc/benzene afforded 39 mg (37%) of white crystals, which recrystallized from hexane to furnish analytically pure white needles, mp 117-118°C. 

[α]D²² = +73.2 (c = 0.645, CHCl₃). NMR (400 MHz): δ 0.99 (d, 3H, J = 6.0 Hz), 1.06 (dd, 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 (CH₂Cl₂): 1720, 1095, 1020, 985 cm⁻¹. CIMS (NH₄⁺): m/e (rel int) 314 (M + NH₄⁺, 90), 297 (M + H⁺, 40), 279 (92), 251 (50), 233 (45), 233 (100). Anal. calcd for C₁₆H₂₄O₅: C, 64.84; H, 8.16. Found: C, 64.70; H, 8.03.

**Methyl syn-2[(3-(2,2-Dimethoxyethyl)-2E,Z-trimethylsilylmethylene)cyclohexylacetate (106)**

As per Schreiber’s procedure, through a solution of 10-trimethylsilylmethylene bicyclo[4.3.1]-dec-3-ene (101, 1.78 g, 7.99 mmol) in dry CH₂Cl₂ (25 mL) and absolute MeOH (5 mL) at -78°C was passed a stream of O₃/O₂. The disappearance of starting material was monitored by periodic TLC (SiO₂ in EtOAc/hex) before the mixture was purged with inert gas, treated with pTsOH·H₂O (0.13 g, 0.68 mmol) and allowed to warm to ambient temperature over 2 h. The resultant solution was neutralized with NaHCO₃ (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 Et₃N (1.67 mL) and ACO₂ (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 0.1N HCl (3 x 35 mL) and 10% aq NaOH (3 x 30 mL), dried over Na₂SO₄, 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 106 (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.

NMR (400 MHz): δ 0.079, 0.096 (2s, 9H, -Si(CH₃)₃), 0.72-1.70 (m, 5.5H), 1.77 (bd, 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, -CH₂CH (OMe)₂), 2.46 (ddd, 1.5H, J = 26.4, 14.5, 9.0 Hz, -CH₂CO₂Me), 2.68 (dd, 1H, J = 15.4, 12.3 Hz, -CH₂CO₂Me), 2.81 (bm, 0.5H), 3.12 (bm, 0.5H), 3.27 (s, 1.5H, -CH(OCH₃)₂), 3.29 (s, 1.5H, -CH(OCH₃)₂), 3.32 (s, 1.5H, -CH(OCH₃)₂), 3.63 (s, 1.5H, -CO₂CH₃), 3.66 (s, 1.5H, -CO₂CH₃), 4.29 (t, 0.5H, J = 7.3 Hz, -CH(OMe)₂), 4.35 (dd, 0.5H, J = 7.3, 4.9 Hz, -CH(OMe)₂), 5.23 (bs, 1H, =CH(SiMe₃)). IR (neat): 2960, 2940, 2870, 2840,
1742, 1608, 1440, 1370, 1293, 1250, 1195, 1175, 1150, 1130, 1083, 1060, 870, 845 cm⁻¹.
CIMS: (NH₄⁺) m/e (rel int): 328, (28), 327, (100) for each of two components observed by GC.

syn-2-[3-(2,2-Dimethoxyethyl)-2E,2Z-trimethylsilylmethylene]cyclohexylacetic Acid (107)

To a solution of methyl ester 106 (516 mg, 1.63 mmol) in absolute MeOH (15 mL) was added freshly prepared 6N KOH (4 mL). The resultant yellow solution was degassed with argon, refluxed for 90 min, allowed to cool to ambient temperature, stirred with sat. aq. NH₄Cl (15 mL), and extracted with Et₂O (4 x 15 mL). The combined ethereal layers were washed with sat. aq. NH₄Cl (2 x 35 mL), dried over Na₂SO₄, 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 CCl₄, 338 mg (68.7% yield) of acid 107 was obtained as a colorless oil. NMR (400 MHz) showed a mixture of diastereomers present.

NMR (400 MHz): δ 0.084, 0.099 (2s, 9H, -Si(CH₃)₃), 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, -CH=CH=), 2.42-2.50 (m, 1H, -CH=CH=), 2.55 (dd, 0.5H, J = 8.0, 14.5 Hz, -CH=CH=), 2.72 (dd, 1H, J = 11.6, 15.3 Hz, -CH₂CO₂H), 2.82 (bm, 0.5H, -CH₂CO₂H), 3.12 (bm, 0.5H, -CH₂CO₂H), 3.27 (s, 1.5H, -CH(OCH₃)₂), 3.29 (s, 1.5H, -CH(OCH₃)₂), 3.30 (s, 1.5H -CH(OCH₃)₂), 3.32 (s, 1.5H, -CH(OCH₃)₂), 3.34 (s, 1.5H, -CH(OCH₃)₂), 4.31 (t, 0.5H, J = 6.5 Hz, -CH(OMe)₂), 4.37 (dd, 0.5H, J = 6.5, 7.3 Hz, -CH(OMe)₂), 5.25 (s, 0.5H, =CH(SiMe₂)), 5.27 (s, 0.5H, =CH(SiMe₃)). IR (neat): 3000, 2950, 2875, 2840, 1710, 1610, 1250, 1130, 1090, 1060, 870, 845 cm⁻¹. CIMS: of TMS esters, m/e (rel int) 385 (M + NH₄⁺; 3), 308 (35), 290 (100) for each of two components observed by GC.

Octahydro-3,11-epoxy-11H-pyrano[4,3-j]-1,2-benzodioxan-9(3H)-one (80)

To a stirring suspension of dimethyl acetal 107 (330 mg, 0.915 mmol) and 230-400 mesh silica gel 60 (0.85 g) in CH₂Cl₂ (10 mL) was added a freshly prepared solution of 10% aq. oxalic acid (0.20 mL). After 18 h, the silica gel was filtered off and rinsed with CH₂Cl₂ (35 mL). The filtrate was concentrated in vacuo to 287 mg of yellow oil, which was further purified via flash-column chromatography with silica gel. After elution with HOAc/EtOAc/hexane, 258 mg of aldehyde-acid 108 as a yellow oil was obtained and used immediately. NMR (400 MHz) showed that a 1:1 mixture of vinylsilane geometrical isomers was present.

NMR (400 MHz): δ 0.099, 0.096 (2s, 9H, -Si(CH₃)₃), 0.83-1.81 (m, 6H), 2.29 (dd, 0.5H, J = 2.2, 16.7 Hz, -CH=CH=), 2.41-2.62 (m, 2.5H, -CH₂CHO, -CH=CH=), 2.69 (dd, 1H, J = 11.6, 15.3 Hz, -CH₂CO₂H), 2.75-2.90 (m, 1H, -CH₂CO₂H, -CH₂CHO), 2.97 (bm, 0.5H,
Through a solution of aldehyde-acid 108 in dry CH$_2$Cl$_2$ (30 mL) at -78°C was passed a stream of O$_3$/O$_2$ from a Welsbach generator (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 ethyl acetate/hexane. In this fashion 119 mg (58% yield) of lactone 80 as a pale yellow oil was obtained. Crystallization from ethyl acetate/hexane provided analytically pure microprisms, mp 97.5-98.0°C.

NMR (400 MHz): $\delta$ 1.23-1.48 (3H, m), 1.63 (1H, ddd, J = 2.1, 5.5, 13.6 Hz, H$_4$), 1.73-1.97 (4H, bm), 2.21 (1H, dd, J = 1.0, 18.7 Hz, H$_8$), 2.33 (1H, m, H$_4$), 2.48 (1H, ddd, J = 2.6, 10.6, 13.6 Hz, H$_4$), 2.94 (1H, dd, J = 8.0, 18.7 Hz, H$_8$), 5.44 (AB system, 1H, J = 2.1, 6 Hz, H$_3$), 6.06 (s, 1H, H$_1$). IR (KBr): 2950, 1740, 1205, 1080, 1038 an' 1. CIMS: m/e (rel int) 243 (100)(M + NH$_4^+$), 228, (11), 181 (10). Anal. Calcd. for C$_{11}$H$_{14}$O$_5$: C, 58.40; H, 6.24. Found: C, 58.18; H, 6.33.

$t$-Butyldimethylsilylcyclohexenylmethyl Acetate (113)

To a solution of the alcohol 112 (2.5 g, 11.1 mmol) in dry ether (25 mL) at 22°C under argon was added pyridine (1.8 mL), followed by acetic anhydride (1.3 mL or 1.2 eq) and DMAP (100 mg). The mixture was stirred overnight and poured into sat. aq. NH$_4$Cl. The resulting mixture was extracted with ether (3 x 75 mL) and sat. aq. NH$_4$Cl (2 x 250 mL). The combined organic layer was dried over MgSO$_4$, filtered, and evaporated to give crude 54. Distillation at 120°C (0.6 mmHg) gave 2.57 g of 112 (87%) as a colorless oil.

NMR (400 MHz): $\delta$ 0.034 (s, 3H), 0.052 (s, 3H), 0.88 (s, 9H), 2.01 (s, 3H), 5.07 (s, 1H), 5.49 (bs, 1H). IR (neat): 1740, 1470, 1370, 1230, 1020, 835, 780 cm$^{-1}$. GC-EIMS: m/e 268 (M+), 225, 211. Anal. Calcd. for C$_{15}$H$_{28}$SiO$_2$: C, 67.11; H, 10.51. Found: C, 67.29; H, 10.71.

2',Z'-t-Butyldimethylsilylmethyldenecyclohexylacetic Acid (114)

To a 0°C solution of dry diethylamine (1.45 mL, 14 mmol) in THF (30 mL) was added 1.55 M n-butyllithium (9 mL, 14 mmol). After 15 min, the reaction was cooled to -78°C and a solution of the ester 113 (2.5 g, 9.33 mmol) in THF (7 mL) was added dropwise (15 min). The
reaction mixture was then allowed to warm slowly to 22°C over 4 h and stirred for 72 h. The mixture was then heated at 50°C for 4 h, cooled to 22°C, and poured into sat. aq. NH₄Cl. The resultant mixture was extracted with CHCl₃ (3 x 50 mL). The organic layers were dried (MgSO₄), filtered, and evaporated to give crude 114. Flash chromatography on silica gel (180 g) with 20% EtOAc (1% HOAc)/hexane gave 114 (21.5 g, 86%) as a colorless glass.

NMR (400 MHz): δ 0.035 (s, 3H), 0.042 (s, 3H), 0.85 (s, 9H), 2.05 (m, 1H), 2.31 (m, 1H), 2.40 (m, 1H), 2.58 (m, 2H), 5.04 (s, 1H). IR (neat): 1710, 1615, 1460, 1450, 1410, 1300, 1250, and 840 cm⁻¹. EIMS: m/e 253 (M - Me), 211 (M-tertbutyl). CIMS(NH₃): m/e 286 (M+ NH₄), 269 (M +H). Exact mass for C₁₅H₂₈SiO₂-CH₃: Calcd., 253.162. Found, 253.162. For C₁₅H₂₈SiO₂-tertbutyl: Calcd., 211.115. Found, 211.117.

1'R-Butyl-2Z-tertbutyldimethylsilylmethylenecyclohexylacetic Acid (116)

To a solution of dry diisopropylamine (0.59 mL, 4.21 mmol) in THF (15 mL) at 0°C under argon was added 2.8 M n-Buli (1.55 mL, 4.21 mmol). After 15 min, the reaction mixture was cooled to -78°C, and the acid 114 (500 mg, 1.87 mmol) in THF (5 mL) was added dropwise. The reaction mixture was warmed to 22°C, then heated at 50°C for 2 h and cooled to -78°C, at which point purified n-butyl iodide (0.5 mL) was added. After 2 h at 22°C, the reaction mixture was poured into sat. aq. NH₄Cl and extracted with EtOAc. The organic layers were dried over MgSO₄, filtered, and the solvent was removed to afford crude 116 (650 mg). Flash chromatography on silica gel (75 g) with 20% EtOAc (1% HOAc)/hexane gave pure 116 as a waxy solid (563 g, 93%).

NMR (400 MHz): δ 0.042 (s, 3H), 0.054 (s, 3H), 0.86 (s, 9H), 1.74 (m, 1H), 1.94 (ddd, J = 4, 4, 13 Hz, 1H), 2.27 (dt, J = 3, 13 Hz, 1H), 2.37 (broad dt, J = 3, 11 Hz, 1H), 2.67 (ddd, J = 4, 4, 11 Hz, 1H), 5.18 (s, 1H). EIMS: m/e 309 (M-Me), 267 (M-tertbutyl). CIMS(NH₃): m/e 342 (M + NH₄), 325 (M + H), 211. Exact mass for C₁₈H₃₀O₂Si-Me: Calcd., 309.225. Found, 309.226. For C₁₈H₃₀O₂ Si-tertbutyl: Calcd., 267.178. Found, 267.179.

18-tert-Butyldimethylsilyloxy-4B-butyl-8aa-hydroperoxy-4aa-hexahydroisochroman-3-one (118)

A solution of the acid 116 (560 mg, 1.73 mmol) in MeOH (20 mL) at -78°C was treated with a stream of O₃/O₂ (7 psi, 0.5 L/min, 70 V) for 8 min. The TLC was examined (20% EtOAc/hexane-SiO₂) for 116 (absent), then argon was passed through the solution. The solvent was evaporated (bath temp. below 10°C), and the residue was placed under high vacuum for 24 h. After another 48 h at 5°C, the residue was flash-chromatographed on silica gel (50 g) with 10% EtOAc/hexane to give pure 118 (355 mg, 55%) as an oil.
NMR (90 MHz): δ 0.16 (s, 3H), 0.20 (s, 3H), 0.93 (s, 9H), 2.70 (m, 1H), 5.70 (s, 1H). IR (neat): 1750 cm⁻¹. CIMS(NH₃): m/e 390 (M + NH₄), 373 (M + H), 357, 346, 339, 327, 313, 242, 226. Exact mass for C₁₉H₃₅O₃Si-OOH: Calcd., 339.235. Found, 339.237. For C₁₉H₃₅O₃Si-tertbutyl: Calcd., 315.163. Found, 315.164.

7-Butyl-3,3-dimethyl-4aH,6H-hexahydro-1,2,4-trioxino[6,5-i] benzopyran-6-one (83)

To a solution of the hydroperoxide 118 (330 mg) in acetone (20 mL) under argon at 22°C was added TFA (2.5 mL). After 24 h the mixture was poured into water (100 mL) and extracted with hexane (100 mL). The hexane layer was washed with sat. aq. NaHCO₃ (3 x 75 mL), dried over MgSO₄, filtered, and evaporated to give crude 26 (250 mg). PTLC on silica gel (3 x 1.5-mm plates) with 10% EtOAc/hexane gave pure 83 (141 mg, 52%). Crystallization from cold pentane gave crystals, mp 60-62°C.

¹H NMR (400 MHz, DMSO-d₆, 100°C): δ 0.89 (t, J = 6.8 Hz, 3H), 1.40 (bs, 3H), 1.48 (bs, 3H), 1.93 (dt, J = 4.5, 13 Hz, 1H), 2.32 (bs, 1H), 2.92 (m, 1H), 3.00 (m, 0.5 H), 5.74 (s, 1H). ¹³C NMR (DMSO-δ₆, at 100°C): δ 12.9, 21.2, 21.3, 22.5, 23.3, 24.1, 25.4, 28.2, 30.4, 37.9, 40.6, 77.5, 93.3, 102.1, 170.4. IR (CHCl₃): 1740, 1390, 1180, 1110, 1090, 1000 cm⁻¹. CIMS(NH₃) m/e: 316 (M + NH₄⁺), 300, 299, (M + H⁺), 257, 240, 223, 212. Anal. Calcd. for C₁₆H₂₆O₅: C, 64.41; H, 8.78. Found: C, 64.67; H, 9.06.

(±)-Hexahydro-3,3-dimethyl-4aH,6H-1,2,4-trioxino-[6,5-i][2] benzopyran-6-one (81)

Through a solution of 2Z-t-butyldimethylsilylmethylenecyclohexylacetic acid (114, 1.00 g, 3.73 mmol) in absolute MeOH (100 mL) at -78°C was passed O₃/O₂ for 10 min, whereupon starting material was absent by TLC (SiO₂ in HOAc/EtOAc/hex). The reaction mix was purged with argon, allowed to warm to 10°C, and concentrated in vacuo to a yellow oil, which was allowed to sit at 1 mmHg for 15 h at ambient temperature prior to purification via flash-column chromatography with SiO₂. Elution with HOAc/EtOAc/hex allowed isolation of 18-t-butyldimethylosiloxyl-8α-hydroperoxy-5α,7,8α-hexahydroisochroman-3-one (117) as a yellow, semicrystalline oil, 186 mg (17%), which was routinely used without further purification.

The hydroperoxide 117 (140 mg, 0.486 mmol) was placed in acetone (5 mL) and treated with TFA (1.0 mL). More TFA (0.25 mL) was added after 6 h. After 30 h, the reaction was quenched with sat. aq. NaHCO₃ (30 mL) and extracted into EtOAc (4 x 15 mL). The combined EtOAc layers were washed with sat. aq. NaHCO₃ (25 mL) and brine (50 mL), dried over Na₂SO₄, and evaporated to yellow oil, which was purified via successive flash-column and thin-layer
chromatography with SiO₂. Elution with EtOAc/hex afforded 30 mg of 8J as colorless oil, which crystallized from hex, mp 106-107°C.

1H NMR (400 MHz, DMSO-d₆, 90°C): δ 1.17-1.42 (m, 2H), 1.42-1.57 (m, 7H), 1.57-1.73 (m, 3H), 2.00-2.47 (bm, 2H), 2.75 (dd, 1H, J = 5.8, 17 Hz), 5.65 (s, 1H). IR (CH₂Cl₂): 2945, 1748, 1380, 1210, 1120, 1050, 1000 cm⁻¹. CIMS (NH₄⁺): m/e (rel int) 260 (M + NH₄⁺, 28), 243 (M + H⁺, 7), 186 (22), 174 (19), 157 (20), 156 (100), 139 (93). Anal. Calcd. for C₁₂H₁₈O₅: C, 59.49; H, 7.49. Found: C, 59.64; H, 7.64.

2-(2'E-t-Butyldimethylsilylmethylidene)cyclohexyl)-2-methylpropionic Acid (120)

To a solution of diisopropylamine (1.24 mL, 8.89 mmol) in dry THF (25 mL) at 0°C was added dropwise n-BuLi (5.56 mL of 1.60 M in hexane). After 10 min at 0°C, a solution of monomethyl acid 115 (1.14 g, 4.04 mmol) in THF (5 mL) was added via cannula. The resultant orange solution was allowed to warm to ambient temperature, then heated in an oil bath to 60°C. After 20 h, the resultant red solution was treated with MeI (0.90 mL), whereupon a yellow solution was obtained. A yellow suspension formed after cooling to ambient temperature over 30 min. The suspension was stirred with 10% aq. HCl (15 mL). The organic layer was reserved, and the aqueous layer was further extracted with CHCl₃ (4 x 15 mL). The combined organic layers were washed with 10% aq. HCl (15 mL) and freshly prepared 20% aq. NaHSO₃ (2 x 25 mL), dried over Na₂SO₄, and evaporated to provide 1.35 g of a yellow semicrystalline solid, which was further purified upon flash chromatography with silica gel. After elution with HOAc/EtOAc/hex, 905 mg (76%) of desired gem-dimethyl acid 120 as pale yellow crystals, mp 113-114°C, was obtained along with 121 mg (10% recovery) of starting material.

NMR (400 MHz): δ 0.02 (s, 3H, Si(CH₃)₃), 0.03 (s, 3H, Si(CH₃)), 0.83 (s, 9H, (H₃C)₃Si), 1.21 (s, 6H, CH₃), 1.32-1.83 (m, 6H, CH₂), 2.04 (ddd, 1H, J = 5.0, 9.8, 12.8 Hz, =C=CH₂), 2.36 (dt, 1H, J = 5.0, 12.8 Hz, =C=CH₂), 2.42 (dd, 1, J = 4.4, 8.8 Hz, =C=CH), 5.10 (s, 1H, =CH). IR (CH₂Cl₂): 3300-2100, 1700 cm⁻¹. EIMS: m/e (rel int): 281 (2, M-,CH₃), 239 (78), 147 (23), 75 (100), 73 (25). Anal. Calcd. for C₁₇H₃₂O₂Si: C, 68.86; H, 10.88. Found: C, 69.14; H, 11.06.

(+)-1β-t-Butyldimethylsilyloxy-4,4-dimethyl-8αα-hydroperoxy-5aa,7,8αα-hexahydroisochroman-3-one (121)

Through a solution of 2-(2'E-t-butyldimethylsilylmethylidencyclohexyl)-2-methylpropionic acid (120, 900 mg, 3.00 mmol) in absolute MeOH (100 mL) at -78°C was passed O₃/O₂ until a blue color persisted. The resultant solution was carefully concentrated in vacuo to a yellow
oil, which was stored under argon at -15°C for two days before purification via flash-column chromatography with silica gel. Elution with HOAc/EtOAc/hex provided isochroman-3-one \( \text{Hi} \) as white crystals, 0.19 g (50%), mp 116-116.5°C.

\[ ^1\text{H NMR (400 MHz): } \delta 0.15 \text{ (s, 3H, SiCH}_3\text{), 0.16 \text{ (s, 3H, SiCH}_3\text{), 0.89 \text{ (s, 9H, (CH}_3\text{)}_3\text{C), 1.21 \text{ (s, 3H, CH}_3\text{), 1.22 \text{ (s, 3H, CH}_3\text{), 1.33 (dddd, 1H, J = 6.1, 8.0, 8.2, 13.9 Hz), 1.42-1.49 (m, 1H), 1.50-1.64 (bm, 4H), 1.82 (bd, 1H, J = 12.9 Hz), 2.05-2.17 (m, 2H), 5.53 (s, 1H, OCHO), 7.89 (bs, 1H, OOH). IR (CH}_2\text{Cl}_2\text{): 3520, 3300 (broad), 2950, 2870, 1725, 1393, 1185, 1103, 1030, 1008, 850 cm}^{-1}, \text{CIMS: (NH}_4^+\text{: m/e (rel int) 357 (M + NH}_4^+, 2), 345 (M + H^+, 5) 214 (100). Anal. Calcd. for C}17\text{H}_32\text{O}_5\text{Si: C, 59.27; H, 9.36. Found C, 59.68; H, 9.38.} \]

(±)-Hexahydro-3,3,7,7-tetramethyl-4aH,6H-1,2,4-trioxino[6,5-j][2]benzopyran-6-one (84)

To a solution of hydroperoxide 121 (74 mg, 0.22 mmol) in acetone (10 mL) was added TFA (0.50 mL). Additional TFA aliquots (0.25 mL) were added at 24 and 30 h. After 48 h, sat. aq. NaHCO\(_3\) (35 mL) was carefully added and the resultant mix was extracted with EtOAc (4 x 15 mL). The organic layers were combined, washed with sat. aq. NaHCO\(_3\) (35 mL) and brine (2 x 50 mL), dried over Na\(_2\)SO\(_4\), and evaporated to provide 54 mg of yellow oil, which was purified via flash-column chromatography with silica gel. Elution with EtOAc/hex afforded 23 mg (39%) of 84 as white platelets, which were recrystallized from hex to give white prisms, mp 116-117°C.

\[ ^1\text{H NMR (400 MHz): } \delta 1.06-1.93 \text{ (bm, 1H), 1.26 (s, 3H), 1.28 (s, 3H), 1.38 (bs, 3H), 1.49-1.73 (m, 9H), 1.90 (bd, 1H, J = 12.8 Hz), 2.78 (bd, J = 12.5 Hz), 5.22 (s, 1H). IR (CH}_2\text{Cl}_2\text{): 2955, 1733, 1388, 1215, 1170, 1135, 1100, 1055, 1013, 995 cm}^{-1}, \text{CIMS (NH}_4^+\text{: m/e (rel int) 288 (M + NH}_4^+, 6), 271 (M + H^+, 2), 189 (100), 167 (65). Anal. Calcd. for C}14\text{H}_22\text{O}_5\text{Si: C, 62.20; H, 8.20. Found C, 62.52; H, 8.31.} \]

t-Butyldimethylsilylcyclohexylmethyl Hemisuccinate (122)

To a solution of alcohol 112 (2.57 g, 11.4 mmol) in Et\(_2\)O (25 mL) were added in succession DMAP (100 mg), pyridine (1.8 mL), and succinic anhydride (1.37 g). The resultant suspension was diluted with CH\(_2\)Cl\(_2\) (100 mL). After 12 h, more pyridine (1.8 mL) and succinic anhydride (1.37 g) were added. After 3 days, the mix was stirred with 5% HCl (75 mL) and extracted with CHCl\(_3\) (3 x 100 mL). The combined organic layers were washed with 5% aq. HCl (50 mL) and brine (150 mL), dried over Na\(_2\)SO\(_4\), and evaporated to give a pale brown oil, which was purified via flash-column chromatography with SiO\(_2\). Elution with HOAc/EtOAc/hex provided 1.05 g (28%, 64% based on recovery of 112) of hemisuccinate 122 as a colorless oil.
NMR (400 MHz): δ -0.05 (s, 3H, SiCH₃), 0.04 (s, 3H, SiCH₃), 0.87 (s, 9H, C(CH₃)₃), 1.42-1.67 (m, 4H, -CH₂CH₂), 1.80-2.09 (m, 4H, -CH₂CO₂), 2.58-2.73 (m, 4H, =CH-CH₂), 5.10 (s, 1H, CO₂CHSi), 5.48 (s, 1H, =CH). IR (neat): 3500-2200, 2940, 2870, 1740, 1720, 1250, 1160 cm⁻¹. EIMS: m/e (rel int) 326 (3), 225 (23), 131 (25), 75 (37), 73 (100).

(±)-erythro-3-Carboxy-2(2′E-t-butyl)dimethyl-methylenecyclohexylpropionic Acid (123)

To a solution of diethylamine (0.33 mL) in THF (5 mL) at 0°C was added dropwise n-butyllithium (2.0 mL of 1.60 M in hex). After 15 min at 0°C, the solution was cooled to -78°C, and a solution of hemisuccinate 122 (417 mg, 1.28 mmol) in THF (2 mL) was added dropwise via cannula and allowed to slowly warm to ambient temperature overnight. After 15 h, the resultant yellow solution was stirred with sat. aq. NH₄Cl (35 mL) and 10% aq. HCl (10 mL) and extracted with CHCl₃ (3 x 25 mL). The combined layers were washed with brine (35 mL), dried over Na₂SO₄, and evaporated to afford a yellow crystalline solid, which was recrystallized from EtOAc to provide 123 as colorless crystals, mp 179-180°C.

NMR (400 MHz, DMSO-d₆): δ 0.02 (s, 3H, SiCH₃), 0.03 (s, 3H, SiCH₃), 0.84 (s, 9H, C(CH₃)₃), 1.36-1.65 (m, 6H, CH₂CH₂), 2.07-2.15 (m, 1H, HO₂CCH) 2.33-2.52 (m, 4H, HO₂CCH₂, =CH-CH₂), 3.01 (ddd, 1H, J = 10.9, 7.6, 3.7 Hz, =CH-CH), 5.03 (s, 1H, =CH). IR (nujol): 3480-2110, 1710 cm⁻¹. CIMS: m/e (rel int) 344 (M + NH₄⁺, 10), 327 (M + H⁺, 45), 211 (100). Anal. Calcd. for C₁₇H₃₀O₄Si: C, 62.54; H, 9.26. Found: C, 62.66; H, 9.41.

(+)-Hexahydrro-7-(2′-acetic acid)-3,3-dimethyl-4aH, 6H-1,2,4-trioxinol[5,6- j][2]benzopyran-6-one (82)

Through a solution of diacid 123 (595 mg, 1.83 mmol) in absolute MeOH (75 mL) at -78°C was passed O₃/O₂ for 6 min, whereupon starting material was absent by TLC (SiO₂ in HOAc/EtOAc/hex). The resultant solution was purged with argon, allowed to warm to 0°C, and concentrated under reduced pressure to a colorless foam, which was allowed to set for 24 h prior to purification via flash-column chromatography. Elution with HOAc/EtOAc/hex led to the isolation of 185 mg (27%) of hydroperoxyisochromanone 124 as an unstable white foam, which was used immediately without further purification.

NMR (90 MHz): δ 0.19 (s, 6H, SiCH₃), 0.093 (s, 9H, SiC(CH₃)₃), 1.10-2.07 (m, 9H), 2.30-3.05 (m, 3H), 5.66 (s, 1H). IR (CH₂Cl₂): 3500, 3550-2000 (broad), 2937, 1745, 1721, 848 cm⁻¹.
To a solution of the hydroperoxide 124 (160 mg, 0.428 mmol) in acetone (10 mL) was added TFA (0.75 mL). More TFA aliquots (0.25 mL) were added at 1, 19, 23, 27, 30, and 33 h. After 6 days, the resultant brown solution was diluted with brine (30 mL) and H$_2$O (enough to dissolve solids) and extracted with CHCl$_3$. The combined organic layers were washed with brine (4 x 35 mL), dried over Na$_2$SO$_4$, and evaporated to give a brown oil, which was purified via flash-column chromatography with SiO$_2$. Elution with HOAc/EtOA$^e_3$ led to isolation of desired acetonide 82 as a white foam, 29 mg (23%), which crystallized from EtOA$^e_3$/hex, mp 159-160$^\circ$C.

NMR (400 MHz, DMSO-d$_6$, 95$^\circ$C): $\delta$ 1.32-1.59 (m, 10H), 1.60-1.76 (bm, 2H), 1.98 (quintet, 1H, J = 7.2 Hz), 2.59 (dd, J= 4.8, 14.4 Hz), 2.62 (dd, 1H, J = 4.8, 14.4 Hz), 2.90-3.15 (bm, 4H), 5.51 (s, 1H). IR (CH$_2$Cl$_2$): 3260-2280 (broad), 1757, 1722, 1052 cm$^{-1}$. CIMS (NH$_4$+): m/e (rel int) 318 (M + NH$_4$+, 3), 301 (M + H+, 7), 283 (5), 244 (30), 214 (100).

(4aS,7R,7aS,10R,11aS) Hexahydro-3,3,7,10-tetramethyl-4aH,6H-1,2,4-trioxino[6,5-j][2]benzopyran-6-one (29i)

To a solution of N'-3'R-methylcyclohexylimine p-toluenesulfonyl hydrazide 126 (from R-pulegone, 19.0 g, 67.8 mmol) in dry TMEDA (100 mL) at -78$^\circ$C was added n-BuLi (100 mL of 2.7 M in hex). The resultant mix was allowed to warm to ambient temperature. After 90 min, the mix was cooled to 0$^\circ$C and dry DMF (50 mL) was added. After 30 min, the mixture was poured into sat. aq. NaH$_4$Cl and extracted with Et$_2$O (3x). The combined ethereal layers were washed with sat. aq. NH$_4$Cl, sat. aq. NaHCO$_3$ (2x), H$_2$O (2x), and brine, dried over MgSO$_4$, filtered through SiO$_2$, and evaporated at below ambient temperature to provide an oil, which was purified after flash-column chromatography with SiO$_2$ (Et$_2$O/hex) and subsequent distillation at aspirator pressure (~50 mm Hg), bp 120$^\circ$C, to afford 2.9 g (34%) of oil. The TLC and $^1$H NMR (400 MHz) spectrum indicated that a 1:1 mix of double-bond isomeric aldehydes, 5R-methylcyclohexenecarboxaldehyde (127) and 3R-methylcyclohexenecarboxaldehyde (128), had been obtained. This mixture was typically used without further purification, but in some experiments each isomer was enriched via rigorous flash-column chromatography with SiO$_2$ (Et$_2$O/hex) and partially characterized.

3R-Methylcyclohexenecarboxaldehyde (128)

NMR (90 MHz): $\delta$ 0.93-2.64 (m, 10H), 6.61 (m, 1H, =CH), 9.30 (s, 1H, CHO).
5R-Methylcyclohexenecarboxaldehyde (127)

NMR (90MHz): δ 0.93-1.95 (m, 8H), 2.00-2.69 (bm, 2H), 6.75 (m, 1H, =CH), 9.40 (s, 1H, CHO).

To a solution of 5R-methylcyclohexenecarboxaldehyde (127) (380 mg, 3.06 mmol) in Et2O (10 mL) at -78°C was added a solution of tris(trimethylsilyl)aluminum(III) etherate (3 mL of 1.4 M in pentane). After a few minutes, the mixture was treated in succession with DMAP (10 mg) and propionic anhydride (1 mL) and allowed to warm to ambient temperature. After 3 days, the reaction was stirred with aq. sodium potassium tartrate. The separated organic layer was washed with sat. aq. NH4Cl4 and sat. aq. NaHCO3, dried over Na2SO4, and evaporated to provide 650 mg of oil, which was purified via flash-column chromatography. Elution with EtOAc/hex led to the isolation of 450 mg (58%) of diasteromeric 5'R-methylcyclohexenyltrimethylsilylmethyl propionate (129) as an oil.

NMR (400 MHz): δ 0.02 (s, 9H, SiCH3), 0.92, 0.93 (2d, 3H, J = 6.4 Hz, 3'-CH3), 1.12, 1.13 (2t, 3H, J = 7.6 Hz, CH2CH3), 1.44-1.78 (m, 4H), 1.80-2.23 (m, 3H), 2.32, 2.33 (2q, 2H, J = 3.4 Hz), 4.93, 4.96 (2s, 1H, SiCHO2C), 5.38, 5.43 (2bs, 1H, =CH). IR (neat): 2860, 2820, 1743, 1255, 1190, 848 cm⁻¹. EIMS: m/e (rel int) 254 (10), 225 (10), 197 (33), 131 (20), 73 (100). Exact Mass Caled. for C14H26O2Si: 254.170. Found: 254.170.

To a solution of diethylamine (385 mL, 3.7 mmol) in THF (5 mL) at -78°C was added n-BuLi (1.38 mL of 2.7 M in hex). The solution was allowed to warm to 0°C over 15 min, then recooled to -78°C, and a solution of propionate (430 mg, 1.69 mmol) in THF (5 mL) was added. The resultant solution was allowed to warm to ambient temperature overnight. The reaction was stirred with sat. aq. NH4Cl (150 mL) and 5N HCl (1 mL) and extracted with CHCl3 (3x). The combined organic layers were washed with brine, dried over Na2SO4, and evaporated to afford 510 mg of crude product, which was purified after flash-column chromatography with SiO2. Elution with HOAc/EtOAc/hex provided 288 mg (67%) of oil, which was primarily erythro-2(2'E,Z-t-butyldimethylsilylmethylene-3'R-methylcyclohexyl)propionic acid (130) as determined by 400 MHz 1H NMR (approximately 50% desired isomer) and was used without further purification.

Through a solution of vinylsilane acid (275 mg, 0.92 mmol) in absolute MeOH (40 mL) at -78°C was passed O3/O2 for 5 min, whereupon a blue color persisted. The mixture was purged with argon, concentrated in vacuo at 17°C, and stored under high vacuum at ambient temperature overnight. The resultant residue was placed in acetone (10 mL) and treated with TFA
(1.9 mL). After 7 h, the mixture was stirred with H2O and extracted with EtOAc (2x). The combined organic layers were washed with sat. aq. NaHCO3, dried over Na2SO4, and evaporated to give 139 mg of crude material, which was purified via thin-layer chromatography with SiO2. Development with EtOAc/hex provided 23 mg (11%) of trioxane 88 as white crystals from cold pentane, mp 106-108°C. [α]D23 = -112.7 (c = 0.14, CHCl3).

\[ \text{H NMR (DMSO-d}_6, 120°C):} \delta \text{ 0.80 (d, 3H, J = 7.5 Hz, 10-CH}_3\text{), 1.16 (d, 3H, J = 7.1 Hz, 7-CH}_3\text{), 1.41 (bs, 3H, 3-CH}_3\text{), 1.48 (bs, 3H, 3-CH}_3\text{), 1.50-1.65 (m, 5H), 2.37 (bt, 1H, J = 5.8 Hz), 2.21 (bm, 1H), 2.33 (bm, 1H), 3.08 (bm, 1H), 5.67 (s, 1H, H}_4\text{).} \]


2S-(1'-t-Butyldimethylsilyloxy-2'R-propyl)-5R-methyl-1-E/Z-trimethylsilylmethylenecyclohexane (122)

To solution of dry pentane (200 mL) and methoxydimethylsilyltrimethylsilylmethane (4.5 mL or 20 mmol) under argon at -78°C was added 1.7 M t-BuLi (11.8 mL or 20 mmol). The mixture was warmed to 23°C and stirred 120 min, recooled to -78°C, and treated with the ketone 131 (5.6 g or 18 mmol) dissolved in pentane (50 mL). The mixture was allowed to warm slowly to 23°C while stirring overnight. The reaction mixture was poured into sat. aq. NH4Cl (500 mL), washed with additional portions of NH4Cl (2 x 500 mL), dried over MgSO4 and filtered; the solvent was evaporated to give a light yellow oil. Flash chromatography on silica gel (150 g) with 5-20% EtOAc/hexane gave the desired product 132 (1.21 g or 19% yield) as a colorless oil. While the product 132 was most conveniently used as a 60:40 E/Z mixture, the isomers could be separated by SiO2 PTLC, eluting with hexane. In this manner, 380 mg of 132 gave 203 mg of isomer 132a and 127 mg of 132b. For 132a, H NMR (400 MHz, CDC13): \( \delta \) 0.06 (s, 6H), 0.10 (s, 9H), 0.84 (d, 3H, J = 6.8 Hz), 0.91 (s, 9H), 1.22 (br dddd, 1H, J = 2.4, 4.1, 4.5, 13.3 Hz), 1.61 (ddd, 1H, J = 4.1, 4.1, 13.8 Hz), 1.67 (m, 1H), 1.74 (br d, 1H, J = 13.0 Hz), 1.82 (ddd, 1H, J = 4.7, 4.7, 13.7, 13.7 Hz), 1.97 (m, 1H), 2.07 (m, 1H), 2.34 (br d, 1H, J = 10.6 Hz), 2.52 (ddd, 1H, J = 1.3, 5.3, 12.5 Hz), 3.54 (dd, 1H, J = 5.7, 9.9 Hz), 3.65 (dd, 1H, J = 3.2, 9.9 Hz), 5.15 (d, 1H, J = 1.1 Hz). IR: 1615, 1260, 1120, 875, 850, 780 cm\(^{-1}\). EIMS: (m/e) 354 (M\(^+\)), 339 (M-CH3), 297 (M-tBu), 222, 211, 209, 182. Anal. Calcd for C20H42Si2O: C, 67.72; H, 11.93. Found: C, 68.01; H, 12.17. For Isomer 132b, H NMR (400 MHz, CDC13): \( \delta \) 0.047 (s, 6H), 0.10 (s, 9H), 0.9 (s, 9H), 0.91 (d, 3H, J = 6.6 Hz), 0.93 (d, 3H, J = 6.6 Hz), 1.05-1.25 (m, 2H), 1.66 (m, 1H), 1.76 (dd, 1H, J = 8.8, 12.6 Hz), 1.83 (m, 2H), 1.90 (dq, 1H, J = 3.5, 6.6 Hz), 2.41 (ddd, 1H, J = 1.1, 4.2, 12.5 Hz), 3.42 (dd, 1H, J = 6.8, 9.7 Hz), 3.68 (dd, 1H, J = 3.5, 9.7 Hz), 5.14 (s, 1H). IR: 1615, 1250, 1100, 840, 780 cm\(^{-1}\).

**2S-(2'R-Propionyl)-5R-methyl-1E/Z-trimethylsilylmethylenecyclohexane (133)**

Isomer 132a (190 mg or 0.54 mmol) and 132b (110 mg or 0.31 mmol) were each separately dissolved in THF (5 mL) and treated, at 22°C under argon, with 1.1 mL and 0.7 mL, respectively, of 1.0 M Bu₄NF in THF (Aldrich Chemical Co.). After 2.5 h at 22°C, the separate reactions were each poured into water and extracted with Et₂O (3 x 25 mL). The combined organic layers were washed with sat. aq. NaHCO₃ (3 x 50 mL), dried over MgSO₄, filtered, and evaporated to give the crude alcohols, 130 and 75 mg, respectively, which were used without further purification as follows. The alcohols a and b (130 mg and 75 mg) were each dissolved in dry DMF (6 and 4 mL) and treated separately, at 22°C under argon, with pyridinium dichromate (700 mg and 400 mg). The mixtures were stirred for 18 h at 22°C and then poured into water (100 mL) and extracted with ether (3 x 25 mL). The combined organic phases were washed with sat. aq. NH₄Cl:5 N HCl (9:1, 2 x 50 mL), and sat. aq. NaCl (2 x 50 mL), dried over MgSO₄, and filtered; the solvent was evaporated to give the crude acids 133a (125 mg) and 133b (71 mg). PTLC of both acids on 1.5 mm SiC₆ plates with 10% EtOAc/hexane produced each of the pure acids: 122a (114 mg or 84%) as a white crystalline solid, m.p. 75-77°C. ¹H NMR (400 MHz, CDCl₃): δ 0.14 (s, 9H), 0.91 (d, 3H, J = 7.0 Hz), 1.09 (d, 3H, J = 6.9 Hz), 1.29 (br d, 1H, J = 15.3 Hz), 1.52 (br d, 1H, J = 12.5 Hz), 1.73 (ddd, 1H, J = 4.5, 4.5, 10 Hz), 1.77 (br d, 1H, J = 12.8 Hz), 1.90 (ddddd, 1H, J = 4.2, 4.2, 13.7, 13.7 Hz), 2.10 (br m, 1H), 2.43 (ddd, J = 1.5, 5.3, 12.9 Hz, 1H), 2.73 (br dd, 1H, J = 3.0, 10.0 Hz), 2.91 (br dq, 1H, J = 7.0, 12.0 Hz), 5.25 (s, 1H). Anal. Calcd for C₁₄H₂₆Si₂O₂: C, 66.09; H, 10.30. Found: C, 65.80; H, 10.41. PTLC also gave acid 133b (62 mg or 78%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃): 0.11 (s, 9H), 0.93 (d, 3H, J = 6.6 Hz), 1.16 (d, 3H, J = 6.5 Hz), 5.15 (s, 1H). Anal. Calcd for C₁₄H₂₆Si₂O₂: C, 66.09; H, 10.30. Found: C, 65.85; H, 10.32.

(-)-4αβ,7α,7α,10β-Hexahydro-3,3,7β,10α-tetramethyl-4aH,6H-trioxino[6,5-j][2]benzopyran-6-one (85)

The acids 133 were ozonized, either as mixtures or as the separate isomers with identical results, as follows: to a -78°C solution of acid 133 (260 mg, 1.02 mmol) in methanol (8 mL) was bubbled ozonized oxygen from an OREC ozone generator (0.6 L/min, 7 p.s.i, 65 V, 0.7 amps) until a faint blue-grey color was observed (about 4 min). The -78°C solution was purged with argon until the color was gone, the stir bar was removed and the mixture was evaporated to dryness by rotary evaporation (bath temperature < 20°C). The mixture was evaporated to dryness
from hexane (10 mL) twice, and placed under vacuum (0.2 mm Hg) for 30 min. The residual glass was dissolved in CH2Cl2 (3 mL), to which was sequentially added acetone (3 mL) and Amberlyst-15® (275 mg). The mixture was stirred at 22°C under argon for 18 h and then filtered. The filtrate was evaporated to give crude 133 (233 mg). Purification on one SiO2 PTLC plate, eluting with 10% EtOAc/hexane, gave pure 85 (68 mg or 25% yield) as a white solid, which was recrystallized from cold hexane, m.p. 109-110°C. [α]D22 = -94.5° (c = 0.145, CHCl3). 1H NMR (400 MHz, CDCl3) was temperature-dependent. At 23°C, the spectra was broad; at -10°C, a clean 2:1 mixture was observed: δ 0.98 and 1.00 (2d, 3H, J = 6.4 Hz), 1.19 and 1.23 (2d, 3H, J = 7.2 Hz), 1.41 and 1.57 (2s, 3H), 1.64 and 1.65 (s, 3H), 2.02 and 2.68 (ddd, 1H, J = 2.0, 4.0, 13.5 Hz), 3.10 and 3.55 (2dq, 1H, J = 5.0, 7.2 Hz), 5.61 and 5.70 (2s, 1H). IR (Nujol): 1755, 1215, 1180, 1100, 1030, 1010, 880, 840 cm⁻¹. DCIMS-NH3: (m/e) 288 (M + NH4), 271 (M + H), 255, 230, 212, 195, 184, 167. Anal. Calcd for C14H22O5: C, 62.20; H, 8.20. Found: C, 61.90; H, 8.02.

(-)-4α,7α,7αα,10β-Hexahydro-3β,7β,10α-trimethyl-4αH,6H-trioxinox[6.5-j][2]-benzopyran-6-one (86)

The acid 133 was ozonized as described above for 85, and treated identically except that acetaldehyde was substituted for acetone and the ensuing cyclization was complete in a few hours. The purification product 86 was crystallized from hexane, m.p. 102-103°C (lit.7c mp 95-96°C). No rotation was given; we found [α]D22 = -19.3° (c = 0.28, CHCl3). The NMR was in accord with the reported spectra.

(-)-Hexahydro-3,3,10α-tetramethyl-4αH,6H-1,2,4-trioxinox[6,5-j]benzopyran-6-one (89)

To a solution of cyclohexylisopropylamine (15.5 g, 18 mL, 0.11 mol) in THF (150 mL) at 0°C was added n-BuLi (41 mL of 2.7 M in hex). After 15 min, (+)-R-pulegone (16.25 mL, 0.100 mol) was added dropwise. After 30 min at 0°C, MeI (9 mL, 0.144 mol) was added. After 90 min at 0°C, the resultant mixture was stirred with H2O and extracted with pet. ether (30-60). The combined organic layers were washed with sat. aq. NH4Cl (3x) and evaporated to provide crude material, which was purified after distillation at aspirator pressure (~50 mmHg), bp 135-145°C. In this manner, 15.1 g (91%) of an oil was obtained, which was mostly 2-methylpulegone (137) with a small amount of 3,5-dimethyl-2(2-propenyl)cyclohexanone, as determined by NMR (90 MHz) and in agreement with that previously observed by Reusch et al.34 This material was used without further purification.
Crude 2-methylpulegone (137.13 mL, 90 mmol), H₂O (25 mL), and 38% HCl (25 mL) were heated in a distillation apparatus at 130°C. Initially, acetone was collected, and thereafter, over 3 h, the dimethylcyclohexanone azeotrope with water distilled at 105°C. The organic layer of the distillate was separated, dried over K₂CO₃, and distilled (bp 172-178°C) to provide 8.14 g (72%) of colorless oil, which was determined to be a mixture of desired trans-cis-dimethylcyclohexanones 139 and 140 in a ratio of 1.96:1, respectively, by H NMR (400 MHz). This oil was used without further purification.

NMR (400 MHz) of 1: δ 0.00 (d, 3H, J = 6.5 Hz, 3-CH₃), 1.02 (d, 3H, J = 6.1 Hz, 2-CH₃). IR (neat): 2970, 2940, 2880, 1720, 1455 cm⁻¹. EIMS: m/e (rel int) 126 (45), 55 (100). Exact mass Calcd. for C₈H₁₄O: 126.1045. Found: 126.1044.

A solution of (2S,3R)2,3-dimethylcyclohexanone 140 (7.95 g, 63.1 mmol) and p-toluene-sulfonylhydrazide (12 g, 65 mmol) in THF (125 mL) was allowed to stir overnight. When the solvent was removed in vacuo, 18.5 g (100%) of N’-[(2S,3R)2,3-dimethylcyclohexylimine]-p-toluenesulfonylhydrazide (141) was obtained as a crude solid, which was spectrally characterized and used without further purification.

NMR (90 MHz): δ 0.70-2.85 (m, 17H), 7.10-7.52 (m, 2H, ArH), 7.55-7.95 (m, 2H, ArH). IR (melt): 3230 (broad), 2940, 2890, 1605, 1455, 1400, 1340, 1175, 1095, 1010, 930, 825 cm⁻¹. EIMS: m/e (rel int) 294 (7), 139 (100).

To a solution of N’-[(2S,3R)2,3-dimethylcyclohexylimino]-p-toluenesulfonyl hydrazide (141, 6.5 g, 22.1 mmol) in TMEDA (45 mL) at -78°C was added n-BuLi (33 mL of 2.7 M in hex). The resultant mixture was allowed to warm to ambient temperature. After 90 min, the mix was cooled to 0°C and dry DMF (10 mL) was added. After 90 min, the reaction contents were poured into stirring sat. aq. NH₄Cl and extracted with Et₂O (3x). The combined ethereal layers were washed with sat. aq. NH₄Cl (2x) and brine, dried over MgSO₄, and evaporated below ambient temperature to afford an oil, which was initially passed as an ethereal solution through SiO₂ and fractionally distilled at aspirator pressure (~50 mmHg). In this manner, 1.05 g of oil, bp 135°C, was obtained and shown to be a 7:3 mix, respectively, of 6S:6R 5,6-dimethylcyclohexene carboxaldehydes 142 by NMR (400 MHz). This mixture was submitted to further transformation without additional purification.

NMR (400 MHz) of (5R,6S)5,6-dimethylcyclohexene carboxaldehyde: δ 0.89 (d, 3H, J = 6.7 Hz, 3-CH₃), 1.06 (d, 3H, J = 6.9 Hz, 2-CH₃), 1.15-1.90 (m, 4H), 2.15-2.63 (m, 2H),
6.73 (t, 1H, J = 7.1 Hz, =CH), 9.37 (s, 1H, CHO). IR (neat): 2969, 2925, 2885, 1685, 1642, 1378 cm⁻¹.

To a solution of (5R,6S)5,6-dimethylcyclohexene carboxaldehyde (142, 1.0 g, 7.25 mmol) in Et₂O at -78°C was added a solution of tris(trimethylsilyl)aluminum(III) etherate (6 mL of 1.4 M in pentane). After a few minutes, acetic anhydride (1.5 mL, 15.9 mmol) and DMAP (50 mg) were added and the mixture was allowed to warm to ambient temperature overnight. The resultant mix was poured into H₂O. The separated organic layer was washed with aq. sodium potassium tartrate (3x), sat. aq. NH₄Cl, and sat. aq. NaCl, dried over Na₂SO₄, and evaporated to give an oil that was purified via flash-column chromatography with SiO₂. Elution with hexane provided 1.4 g (76%) of oil, which was a mixture of diastereomeric 5,6-dimethylcyclohexenyl(trimethylsilyl)methyl acetates 143, as confirmed by 'H NMR (400 MHz) and GLC analysis. This mixture was used without further purification.

NMR (400 MHz): δ 0.021, 0.028, 0.039, 0.043 (4s, 9H, SiCH₃), 2.01, 2.03, 2.04, 2.05 (4s, 3H, O₂CCH₃). IR (neat): 1742 cm⁻¹. EI MS: m/e (rel int) 254 (2), 117 (100). Exact mass Calcd. for C₁₄H₂₆SiO₂: 254.1702. Found: 254.1703.

To a solution of diethylamine (5.4 mL) in THF (100 mL) at -78°C was added n-BuLi (20 mL of 2.7 M in hex). After 45 min, a solution of a diastereomeric mixture of (5R)5,6-dimethylcyclohexenyl-(trimethylsilyl)methyl acetate (143, 5.88 g, 23.1 mmol) in THF (40 mL) was added dropwise via cannula. The reaction was allowed to warm to 22°C over several hours. After 65 h at ambient temperature, the reaction mix was stirred with sat. aq. NH₄Cl (150 mL) and 5N HCl (1 mL) and extracted with CHCl₃ (3x). The combined organic layers were washed with brine and evaporated to give an oil, which was purified via flash-column chromatography with SiO₂ to provide, after stepwise gradient elution with HOAc/EtOAc/hex, 1.66 g (28%) of (2'E,Z,1'S,3'S,4'R)3',4'-dimethyl-2'(trimethylsilylmethylene)cyclohexylacetic acids 144 as an oil. This material was used without further purification.

NMR (400 MHz): δ 0.062 (s, 9H, SiCH₃), 0.88 (d, 1.5H, J = 6.8 Hz, CH₃), 0.91 (d, 1.5H, J = 7.2 Hz, CH₃), 0.95 (d, 1.5 H, J = 7.4 Hz), 1.14 (d, 1.5H, J = 7.5 Hz, CH₃), 1.22-1.46 (m, 2H), 1.52-1.92 (m, 3H), 2.32-2.64 (m, 4H), 5.22-5.25 (m, 0.5H, =CH), 5.32 (s, 0.54, =CH).

Through a solution of vinylsilane acid 144 (675 mg, 2.66 mmol) in CH₂Cl₂ (30 mL) at -78°C was passed O₃/O₂ for 10 min, whereupon a blue color persisted. The reaction was purged with argon, and the resultant decolorized mixture was diluted with acetone (5 mL) and treated with
The reaction was allowed to warm to 22°C. After 20 h, the mixture was partitioned between EtOAc and H2O. The separate aqueous layer was extracted with more EtOAc (2x). The combined organic layers were evaporated to give a material that was purified via thin-layer chromatography with SiO2. After two developments with EtOAc/hex, the title trioxane 89 was isolated as a colorless oil, 160 mg (22%), which proved to be a hydrate (C14H22O5·1/4 H2O) by analysis. [α]D^22 = -52.8 (c = 0.58, CHCl3).

NMR (400 MHz): δ 0.89 (d, 3H, J = 7.2 Hz, CH3), 1.05 (d, 3H, J = 8.0 Hz, CH3), 1.30-1.48 (bm, 3H), 1.57 (bs, 3H, 3-CH3) 1.62 (bs, 3H, 3-CH3), 1.63-1.84 (m, 2H), 1.97-2.09 (bm, 1H), 2.58 (quintet, 1H, J = 9.4 Hz), 2.80-2.95 (m, 1H), 5.50 (s, 1H, H4a). IR (CHCl3): 2945, 1758, 1388, 1188, 1060 cm^-1. EIMS: m/e (rel int) 238 (M+ -O2, 1), 180 (M+ -acetone, -O2, 33), 83 (85), 69 (60), 55 (83), 43 (100). CIMS (NH4+): m/e (rel int) 288 (M + NH4+, 22), 271 (M + H+, 6), 167 (100). Anal. Calcd. for C14H22O5·1/4H2O: C, 61.18; H, 8.07. Found: C, 61.31; H, 7.98.

(2'E,Z,1'R,3'S,4'R)-2-[3'-4'-Dimethyl-2'-(trimethylsilylmethylene)cyclohexenylacetic Acid (86)

To a solution of diisopropylamine (0.90 mL, 6.4 mmol) in THF (20 mL) at -78°C was added n-BuLi (2.4 mL of 2.7 M in hex). The solution was allowed to warm to 0°C and, after 15 min at 0°C, recooled to -78°C, whereupon a solution of (2'EZ,1'S,3'S,4'R)3',4'~dimethyl-2-(trimethylsilylmethylene)cyclohexenylacetic acid (144, 743 mg, 2.92 mmol) in THF (7 mL) was added. The reaction was allowed to warm to ambient temperature and then heated at 50°C for 2 h before cooling to -78°C and subsequent treatment with methyl iodide (0.54 mL, 8.5 mmol). The mixture was allowed to warm to ambient temperature and after 90 min was poured into sat. aq. NH4Cl (250 mL) and 5N HCl (5 mL) and extracted with CHCl3 (3 x 75 mL). The combined organic layers were dried over MgSO4 and evaporated to give a crude product, which was purified via flash-column chromatography with SiO2. Elution with EtOAc/hex provided 760 mg (97%) of the title diastereomers 145 as a pale yellow oil.

NMR (400 MHz): δ 0.084, 0.088 (2s, 9H, SiCH3), 0.85-0.97 (m, 5H), 1.01-1.21 (m, 6H), 1.22-1.33 (m, 1H), 1.35-1.47 (m, 1H), 1.48-1.95 (m, 4H), 2.25-2.43 (m, 1.5H), 2.57 (ddd, 0.5H, J = 5.0, 7.1 7.2 Hz), 2.74 (ddd, 0.5H, J = 7.0, 12.9, 13.4 Hz), 2.80 (ddd, 0.5H, J = 7.0, 12.9, 13.4 Hz), 5.20 (s, 0.5H, =CH), 5.29 (s, 0.54, =CH). IR (neat): 3600-2250, 1713, 1610, 1470, 1255, 1225, 900, 850 cm^-1. EIMS: m/e (rel int) 268 (2), 75 (57), 73 (100). Exact mass Calcd. for C15H28SiO2: 268.1859. Found: 268.1860.
Through a solution of vinylsilane acid (145, 700 mg, 2.61 mmol) in CH$_2$Cl$_2$, (30 mL) at 78°C was passed O$_3$/O$_2$ until a blue-gray coloration appeared. The color disappeared upon purging with argon, and acetone (15 mL) and TFA (2 mL) were added. The reaction was allowed to warm to ambient temperature over 40 min and, after 22 h, was stirred with sat aq NaHCO$_3$ and extracted with hexane (3 x 50 mL). The combined organic layers were washed with sat. aq. NaHCO$_3$, dried over MgSO$_4$, and evaporated to a crude material, which was purified via successive (2x) thin-layer chromatography with SiO$_2$. After development in EtOAc/hex, the resultant colorless oil slowly crystallized from cold pentane to afford 45 mg (6%) of 90 as white crystals, mp 67-69°C. $[\alpha]_D^{22} = +18.12$ (c = 0.275, CHCl$_3$).

NMR (400 MHz, DMSO-d$_6$, 90°C): $\delta$ 0.92 (d, 3H, J = 7.2 Hz, CH$_3$), 1.05 (d, 3H, J = 7.2 Hz, CH$_3$), 1.10 (d, 3H, J = 7.2 Hz, CH$_3$), 1.40 (s, 3H, 3 -CH$_3$), 1.47 (s, 3H, 3 -CH$_3$), 1.52-1.75 (m, 3H), 1.82-2.05 (m, 4H), 3.48 (m, 1H, H$_7$), 5.74 (s, 1H, H$_{4a}$). IR (CHCl$_3$): 2960, 2940, 1740, 1385, 1175 cm$^{-1}$. CIMS (NH$_4^+$): m/e (rel int) 302 (M + NH$_4^+$,5), 285 (M + H$^+$, 6), 209 (58), 191 (60), 181 (100). Anal. Calcd. for C$_{15}$H$_{24}$O$_5$: C, 63.36; H, 8.51. Found: C, 63.61; H, 8.59.

3R-Methyl-2R-[(2°,5°,5°)-trimethylcyclohexane-1E/Z-3trimethylsilylmethylenecyclohexane (146)

To a dry 500-mL, 3-necked, round-bottom flask equipped with argon inlet, stopper, septum, and magnetic stirrer were added pentane (200 mL) and methoxydimethylsilyltrimethylsilylmethane (10 mL, 47 mmol). The mixture was cooled to 0°C and a pentane solution of tert-butyl lithium was added (28 mL of 1.7M or 47 mmol) over a 5-min period. The mixture was warmed to 22°C and stirred for 2 h. The resultant yellow solution was cooled to -78°C and a solution of ketone 17 (11.4 g or 42.5 mmol) in pentane (100 mL), was added via cannula over 10 min. The reaction mixture was allowed to warm slowly to 22°C and left overnight. The reaction mixture was poured into sat. aq. NH$_4$Cl (500 mL) and then washed with additional sat. aq. NH$_4$Cl (2 x 500 mL). The pentane was then washed with sat. aq. NaCl (500 mL), dried over MgSO$_4$ and filtered, and the solvent was evaporated to afford 17.6 g of yellow oil. Gradient elution flash chromatography on silica gel (150 g) was carried out with 5→20% EtOAc/hexane. Polar material eluted from the column weighed 1.57 g and appeared to be a tertiary alcohol adduct of t-BuLi with 17. The starting ketone was recovered to provide 6.38 g of 17. The desired olefin 146 (5.23 g or
36.4% yield) was isolated as a light yellow oil. Based on recovered recyclable starting material, the yield of \( \text{146} \) was 83%. \(^1\)H NMR (400 MHz, CDCl\(_3\)) indicates a 3:1 ratio of isomers: \( \delta \) 0.096 and 0.128 (2s, 9H), 0.90 and 0.93 (2d, 3H, \( J = 6.5 \text{ Hz} \)), 0.93 and 0.95 (2s, 3H), 0.96 and 0.98 (2s, 3H), 1.36 and 1.39 (2s, 3H), 3.49 (m, 4H), 5.11 and 5.12 (2s, 1H). IR: 2950, 2860, 1610, 1450, 1370, 1250, 1190, 1090, 1050, 1020, 865, 840, and 690 cm\(^{-1}\). EIMS: (m/e) 338 (M\(^+\)), 323 (M-Me), 234, 219, 194, 179, 162, 141, 129, 107. Exact mass. Calcd for C\(_{20}\)H\(_{38}\)SiO\(_2\): 338.2641. Found 338.2634. Anal. Calcd for C\(_{20}\)H\(_{38}\)SiO\(_2\): C, 70.94; H, 11.31. Found: C, 70.87; H, 11.33.

(\(+\)-3R-Methyl-2R-(3'-oxobutyl)-1Z-trimethylsilylmethylenecyclohexane (147)

To a well-stirred solution of the ketal \( \text{146} \) (4.5 g or 13.31 mmol) in CH\(_2\)Cl\(_2\) (175 mL) at 22°C under argon was added 230-400 mesh silica gel (24 g) followed by 10% aq. oxalic acid (5 mL). The mixture was vigorously stirred until the oxalic acid/H\(_2\)O was absorbed onto the support and then allowed to stir for 18 h. The mixture was filtered and the silica gel was washed with EtOAc (300 mL). The combined organic layers were washed with sat. aq. NaHCO\(_3\) (3 x 100 mL), dried over MgSO\(_4\), filtered, and the solvent was evaporated to give 3.67 g of yellow oil. Gradient elution flash chromatography on silica gel (175 g) with hexane (1 L), 1% EtOAc/hexane (1 L), 2% EtOAc/hexane (1 L), and 3% EtOAc/hexane (1 L), collecting 25 x 50-mL fractions, gave in fractions #4-8: 1.53 g of isomerically pure \( \text{147} \). \([\alpha]_D^{21} = +15.7 \) (c = 1.65, CHCl\(_3\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)):\( \delta \) 0.098 (s, 9H), 0.91 (m, 2H), 0.93 (d, \( J = 7.0 \text{ Hz} \), 3H), 1.27 (m, 2H), 1.52 (m, 1H), 1.6-1.9 (m, 3H), 2.12 (s, 3H), 2.04-2.22 (m, 2H), 2.35 (m, 2H), 5.06 (s, 1H). IR: 2950, 2920, 2860, 1720, 1610, 1450, 1400, 1360, 1250, 1165, 1050, 870, 840, and 690 cm\(^{-1}\). DClIMS-NH\(_3\) (m/e): 253 (M + H), 235, 219, 194, 181, 163, 143. DClIMS-NH\(_3\) exact mass. Calcd for C\(_{15}\)H\(_{29}\)SiO (M + H): 253.1988. Found: 253.1976. Anal. Calcd for C\(_{15}\)H\(_{28}\)SiO: C, 71.36; H, 11.18. Found: C, 71.08; H, 11.31. Fractions #9-15 were an E/Z mixture predominating in \( \text{147} \) (Z), and weighing 1.08 g. The total product was 2.61 g or 78% yield.

(\(+\)-3a,6a-Dimethyl-3\(\alpha\)-methoxyoctahydrobenzo-1,2-dioxepin-9\(\alpha\)-carboxaldehyde (91)

Through a -78°C solution of the vinylsilane \( \text{147} \) (E/Z mixture from above) (0.78 g or 3.1 mmol) in methanol (25 mL) was bubbled ozonized oxygen (0.5 L/min, 7.5 p.s.i., 70 V) until a faint blue-grey color persisted (about 18 min). The solution was purged with a stream of argon and when the color of excess ozone was gone, the mixture was treated with boron trifluoride ethereal complex (200 \( \mu \)L) and warmed to 22°C. After 90 min at 22°C under argon, the reaction mixture was poured into sat. aq. NaHCO\(_3\) (250 mL). The mixture was extracted with EtOAc (3 x
75 mL), dried over MgSO\textsubscript{4} and filtered, and the solvent was evaporated to give 658 mg of a colorless glass. Flash chromatography on silica gel (20 g) with 7% EtOAc/hexane gave 91 (440 mg or 59% yield) as a colorless oil, which slowly solidified and was recrystallized from cold hexane, m.p. 100-102\degree C. \([\alpha]\)\textsubscript{D}\textsuperscript{23} = +317 (c = 1.18, CDCl\textsubscript{3}).

NOESY, DQCOSY, HETCOR, APT, single-frequency decoupling, and Eu(fod)\textsubscript{3} NMR experiments were performed in order to make assignments to the \(\text{H NMR (400 MHz, CDCl}\textsubscript{3}): \delta \) 0.90 (m, 1H, H\textsubscript{9a}), 0.94 (d, 3H, J = 6.4 Hz, 8\textalpha-Me), 1.19 (d, 3H, J = 1.2 Hz, 4\beta-Me), 1.25 (m, 2H, H\textsubscript{10b/10a}), 1.32 (dddd, 1H, J = 3.8, 12.1, 14.0, 14.0 Hz, H\textsubscript{11a}), 1.52 (dddd, 1H, J = 1.3, 11.8, 11.8, 14.5 Hz, H\textsubscript{6b}), 1.68 (m, 2H, H\textsubscript{9b/11b}), 1.85 (dddd, 1H, J = 1.2, 3.0, 7.8, 14.6 Hz, H\textsubscript{5b}), 1.93 (br d, 1H, J = 11.4 Hz, H\textsubscript{10a}), 1.97 (br d, 1H, J = 11.4 Hz, H\textsubscript{6a}), 2.08 (dd, J = 1.3, 7.8, 14.6 Hz, H\textsubscript{5a}), 2.18 (dddq, 1H, J = 4.0, 6.4, 11.4, 11.4 Hz, H\textsubscript{8b}), 3.34 (s, 3H, 4\alpha-OMe), 9.51 (d, 1H, J = 2.8 Hz, long-range W-coupling to 7\alpha). IR: 2940, 2865, 2720, 2700, 1740, 1450, 1375, 1270, 1250, 1210, 1190, 1165, 1110, 1085, 1065, 1000, 900, 880, 835, 770, and 740 cm\textsuperscript{-1}. Anal. Calcd for C\textsubscript{13}H\textsubscript{22}O\textsubscript{4}: C, 64.44; H, 9.14. Found: C, 64.28; H, 9.34. DCIMS-NH\textsubscript{3}: (m/e) weak 260 (M + NH\textsubscript{4}), strong 228 (260-CH\textsubscript{3}OH), 220, 211 (M-O\textsubscript{2} + H), 206, 195, 189, 183, 171, 165.

\((+)-12\text{-Acetoxymethyl}-2,3,13\text{-triaxatritricyclo[5.4.2.1\textsuperscript{4}.1\textsuperscript{7}]tridecane (93)\)

Through a -78\degree C solution of the silane 147 (175 mg or 0.69 mmol) in MeOH (8 mL) was bubbled ozonized oxygen (0.5 L/min, 7.5 p.s.i., 70 v) until a faint blue-grey color appeared. The solution was purged with argon and rotary-evaporated (bath temp. <20\degree C). Hexane (10 mL) was added. After rotary evaporation, the process was repeated and the product was placed under high vacuum (30 min, 0.05 mm H\textsubscript{g}) to provide the dioxetane 5R-(3-oxobutyl)-6R-methyl-3RS-trimethylsilyloxy-1,2-dioxa-4S-spiro[5.3]nonane (149). \(\text{H NMR (400 MHz, CDCl}\textsubscript{3}): \delta 0.20 \text{(s, 9H), 1.00 } \text{(d, 3H, J = 6.4 Hz), 2.17 (s, 3H), 6.08 (s, 1H). IR (film): 2960, 2940, 2880, 1720, 1450, 1410, 1380, 1360, 1260, 1170, 1080, 1000, 960, 880-850 (br), and 760 cm}\textsuperscript{-1}.

The product 149 was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (2 mL) under argon, and acetic anhydride (2 mL) and Amberlyst-15 (200 mg) were added. After 100 min, heptane (75 mL) was added, and the mixture was filtered. The solvent was evaporated and the crude product was placed on a PTLC plate (1.5 mm SiO\textsubscript{2}). Elution with benzene afforded pure 23 (56 mg or 30% yield) as a colorless oil. \([\alpha]\)\textsubscript{D}\textsuperscript{21} = +9.3 (c = 1.5, hexane). \(\text{H NMR (400 MHz, CDCl}\textsubscript{3}): \delta 6.44 \text{(s, 1H, H\textsubscript{12b}), 2.39 (ddd, 1H, J = 4.0, 13.2, 14.5 Hz, H5\alpha), 2.20 (s, 3H), 2.14 (m, 1H, H\textsubscript{11b}), 2.02 (ddd, 1H, J = 3.0, 4.8, 14.5, H\textsubscript{5b}), 1.91 (ddddd, 1H, J = 1.2, 3.5, 6.6, 16.7 Hz, H\textsubscript{6a}), 1.62 (m, 2H, H\textsubscript{9b/10a}), 1.48 (m, 2H, H\textsubscript{6b/8b}), 1.39 (s, 3H, 4-Me), 1.39 (m, 1H, H\textsubscript{7a}), 1.25 (m, 2H,
\begin{align*}
\text{H}^{11}\alpha/108\), 0.98 (m, 1H, H_{9\alpha}), 0.97 (d, J = 6.3 Hz, 8-Me). \text{\textsuperscript{13}C NMR (CDCl}_3\): 170.4 (-OAc), 104.5 (C4), 88.3 (C12), 83.1 (C1), 51.6 (C7), 37.6 (-OAc), 36.1 (C5), 34.6 (C11), 33.9 (C6), 25.9 (Me), 24.9 (C10), 22.1 (C9), 21.4 (C8), 20.1 (Me). \text{IR: 2940, 2880, 1750, 1450, 1360, 1240, 1230, 1210, 1165, 1140, 1100, 1070, 1010, 970, 880, 840 cm}\^{-1}. \text{DCIMS (NH}_3\): m/e 288 (M + NH}_4\), 271 (M + H), 228, 211 (M-OAc), 195, 183, 169, 151, 139. \text{HRDCIMS (NH}_3\). \text{Calcd for C}_{14}H_{22}O_5: 271.1545. \text{Found: 271.1549. Anal. Calcd for C}_{14}H_{22}O_5: C, 62.20; H, 8.20. \text{Found C, 62.53; H, 8.25.}
\end{align*}

4.8-Dimethyl-(-)-12-propionyloxy-2.3.13-trioxatricyclo-[5.4.2.1\textsuperscript{4}0\textsuperscript{1}7]tridecane (8a,9-secoartemisinin, 92)

To a solution of the aldehyde 91 (250 mg or 1.03 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (2 mL) under argon at 22°C was added propionic anhydride (6 mL) and Amberlyst-15 (300 mg). The mixture was stirred overnight, filtered, and poured into \text{aq. NaOH} (100 mL). The mixture was extracted with ether (3 x 50 mL) and the combined organic layers were washed with \text{aq. NaOH} (2 x 50 mL). The organic layer was dried over MgSO\textsubscript{4}, filtered, and the solvent was evaporated to afford crude 92 (186 mg). PTLC on two 1.5-mm-thick SiO\textsubscript{2} plates with 7% ether/pentane gave pure 92 (63 mg or 22% yield) as a colorless oil. [\alpha]_\text{D}{^{22}} = +26.3 (c = 1.90, hexane). \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\): \delta 0.96 (m, 1H), 0.98 (d, 3H, J = 6.2 Hz), 1.20 (t, 3H, J = 7.5 Hz), 1.2-1.6 (m, 7H), 1.38 (s, 3H), 1.90 (dddd, 1H, J = 1.1, 3.0, 7.0, 16.8 Hz), 2.02 (ddd, 1H, J = 3.0, 4.9, 14.6 Hz), 2.14 (m, 1H), 2.39 (ddd, 1H, J = 4.0, 13.4, 14.6 Hz), 2.46 (q, 1H, J = 7.5 Hz), 6.45 (s, 1H). \text{IR: 2940, 2880, 1745, 1450, 1380, 1355, 1270, 1210, 1190, 1130, 1080, 1035, 990, 970, 910, 880, 840, and 810 cm}\^{-1}. \text{DCIMS-NH}_3\): (m/e) 302 (M + NH}_4\), weak 285 (M + H), 260, strong 228, 211, 195, 183, 165, 147. \text{Anal. Calcd for C}_{15}H_{24}O_5: C, 63.36; H, 8.51. \text{Found C, 63.85; H, 8.48.}

4.8-Dimethyl-12-methoxy-2.3.13-trioxatricyclo-[5.4.2.1\textsuperscript{4}0\textsuperscript{1}7]tridecane (154)

To a solution of the aldehyde 91 (129 mg) in benzene (5 mL) and methanol (2 mL) under argon at 22°C was added triethylorthoacetate (1 mL) and BF\textsubscript{3}\cdot OEt\textsubscript{2} (100 \mu L). The orange-red mixture was stirred 18 h, poured into sat. aq. NaHCO\textsubscript{3} (50 mL), and extracted with EtOAc (100 mL). The organic layer was washed with sat. aq. NaHCO\textsubscript{3} (2 x 100 mL), dried over MgSO\textsubscript{4}, filtered, and the solvent was evaporated to give a yellow oil. PTLC (two 1.5-mm-thick SiO\textsubscript{2} plates) with benzene gave recovered 91 (43 mg) and tricyclic 154 (31 mg or 38% yield, based on recovered starting material) as a 3:1 mixture of isomers (12\textalpha:12\beta) as seen in the \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\): \delta 0.92 (d, J = 6.4 Hz, minor isomer), and 0.97 (d, J = 6.08 Hz, major isomer of 3H), 1.40 (s, 3H), 1.89 (m, 1H), 2.0 (m, 1H), 2.39 (m, 2H), 3.51 (s, 3H), 4.91 (s, minor
isomer), 4.95 (s, major isomer of 1H). IR: 2930, 2880, 1450, 1380, 1350, 1100, 1020, 880, 840 cm\(^{-1}\). DCIMS-NH\(_3\): (m/e) 228 (M-O\(_2\) + NH\(_4\)), 211 (M-O\(_2\) + H), 195, 183, 177, 165, 151.

4.8-Dimethyl-12-hydroxy-2,3,13-trioxatricyclo-[5.4.2.1\(^4\)0\(^1\)7]-tridecane (151/152)

To the dioxetane 149, freshly prepared as described above (derived from 1.18 g of 147), was added THF (45 mL) and 1 M aq. HCl (5 mL). The mixture was stirred under argon for 75 min and poured into sat. aq. NaHCO\(_3\) (400 mL). The mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with sat. aq. NaHCO\(_3\) (100 mL), dried over MgSO\(_4\) and filtered, and the solvent was evaporated to give 0.94 g of a colorless oil. Flash chromatography on silica gel (30 g) with 20% EtOAc/hexane gave 151/152 (528 mg or 50% yield) as a colorless oil that was a complex mixture. The ratio from the NMR was 1.2:1, respectively.

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.93 (d, J = 6.6 Hz, Me), 1.28 (s, Me), 1.42 (s, Me), 2.14 (s, Me), 3.38 (d, J = 13.0 Hz), 5.28 (d, J = 13 Hz), 9.48 (d, J = 2.8 Hz), 9.50 (d, J = 2.7 Hz). IR (film): 3400, 2940, 2860, 2700, 1740, 1710, 1450, 1380, 1210, 1170, 1080, 1020, 955, 880, 840 cm\(^{-1}\). DCIMS-NH\(_3\) (m/e): 246 (M + NH\(_4\)), 228 (M), 216, 200, 195, 183 (M-HC\(_2\)O\(_2\)H), 172, 165.

(-)-12-Benzylcarbonyloxy-4.8-dimethyl-2,3,13-trioxatricyclo-[5.4.2.1\(^4\)0\(^1\)7]-tridecane (94)

To a solution of the alcohol 151/152 (200 mg or 0.88 mmol) in CH\(_2\)Cl\(_2\) (5 mL) at 22°C under argon was added benzylchloroformate (150 \(\mu\)L or 1.0 mmol) followed by 4-(N,N-dimethylamino)pyridine (150 mg or 1.2 mmol). The solution turned yellow and gave off gas (CO\(_2\)). After 1 h, the reaction mixture was poured into sat. aq. NH\(_4\)Cl (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with sat. aq. NH\(_4\)Cl (2 x 50 mL) and sat. aq. NaCl (50 mL), dried over MgSO\(_4\), and filtered, then evaporated to give a yellow oil. PTLC on two 1.5-mm-thick SiO\(_2\) plates with 20% EtOAc/hexane gave the product 94 as a colorless oil (69 mg or 22% yield), which contained a minor isomeric contaminant (9:1 ratio by NMR) that was removed by trituration from hexane followed by recrystallization from hexane/CH\(_2\)Cl\(_2\), mp 110°C. [\(\alpha\)]\(_D\)^{22} = -17.5° (c = 0.37, CDCl\(_3\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 0.98 (d, 3H, J = 6.2 Hz), 1.0 (m, 1H), 1.2-1.7 (m, 7H), 1.40 (s, 3H), 1.91 (dddd, 1H, J = 1.0, 3.3, 6.2, 16.3 Hz), 2.03 (dddd, 1H, J = 3.1, 4.9, 14.8 Hz), 2.20 (m, 1H), 2.40 (dddd, 1H, J = 4.0, 13.2, 14.8 Hz), 5.24 (s, 2H), 6.31 (s, 1H), 7.38 (m, 5H). IR (CHCl\(_3\)): 3000, 2940, 2880, 1745, 1455, 1385, 1270, 1225, 1175, 1140, 1100, 1070, 1055, 1035, 955, 940, 910, 880, 840 cm\(^{-1}\). DCIMS-NH\(_3\): (m/e) 380 (M + NH\(_4\)), 363 (M + H), 303, 228, 211, 195, 183, 165, 151. Anal. Caled for C\(_{20}\)H\(_{26}\)O\(_6\): C, 66.28; H, 7.23. Found: C, 66.41; H, 7.14. An X-ray crystallographic analysis of this material supported the structure assignment.
4R,8R-Dimethyl-1S-hydroxymethyl-4b-methoxy-2,3-dioxabicyclo[5.4.0]undecane (153)

To a solution of the aldehyde 91 (352 mg or 1.45 mmol) in MeOH (35 mL) under argon at 0°C was added solid NaBH₄ (350 mg or 9.2 mmol). After about 5 min (the reaction was done by TLC), the mixture was poured into sat. aq. NH₄Cl (200 mL) and extracted with Et₂O (3 x 50 mL). The combined organic layers were washed with sat. aq. NH₄Cl (2 x 75 mL), brine (50 mL), dried over MgSO₄, and filtered, and the solvent was evaporated to afford the alcohol 153 as a colorless oil (335 mg or 95% yield), which was sufficiently pure for direct use.

(+)-4,8-Dimethyl-2,3,13-trioxatricyclo[5.4.2.1.7.10]tridecane (95)

The crude alcohol 153 (305 mg or 1.25 mmol) was dissolved in CH₂Cl₂ (25 mL) and treated with pTsOH·H₂O (30 mg). After brief warming to dissolve the acid, the mixture was stirred at 21°C for 30 min and poured into sat. aq. NaHCO₃. The mixture was extracted with Et₂O (2 x 50 mL). The ether layers were washed with NaHCO₃ (2 x 50 mL), dried over MgSO₄, and filtered, and the solvent was evaporated to give crude 95, which was purified by flash chromatography on SiO₂ (4-cm diam x 6") with 5% EtOAc/hexane to give 95 (246 mg or 79% yield) as an oil, which solidified on standing and could be recrystallized from cold pentane, mp 69-71°C. [α]D²² = +88.8° (c = 1.02, CDCl₃). ¹H NMR (400 MHz, CDCl₃): δ 0.98 (d, 3H, J = 6.1 Hz), 1.33 (s, 3H), 1.80 (m, 1H), 1.88 (ddd, 1H, J = 3.3, 6.1, 16.7 Hz), 2.00 (ddd, 1H, J = 3.3, 4.9, 14.6 Hz), 2.42 (ddd, 1H, J = 3.8, 13.4, 14.6 Hz), 4.03 (dd, 1H, J = 1.5, 11.0 Hz), 4.19 (d, 1H, J = 11.0 Hz). IR: 2910, 2870, 1450, 1370, 1210, 1170, 1150, 1070, 1040, 900, 870, 840 cm⁻¹. DCIMS-NH₃: (m/e) 230 (M + NH₄), 213 (M + H), 200, 195, 183.

2-t-Butylperoxy-2-ethylbutanol (156)

To a solution of m-chloroperbenzoic acid (1.8 g of 80%, 10.5 mmol) in dry CH₂Cl₂ (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 155 was added a solution of t-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% aq. KOH and extracted with Et₂O (100 mL). The ethereal layer was washed with H₂O (2 x 100 mL), dried over MgSO₄, and evaporated below room temperature behind an explosion shield to give 2-(t-butylperoxy)-2-ethylbutanol (156) as a colorless oil, 1.6 g, (80%), which was not stored but was used immediately without further purification. CAUTION: this peroxide should be handled with due caution, although we have not experienced any problems so far.
WARNING: Crazy Englishmen sneaking up behind you while manipulating the material, who yell BOOM!!, should be avoided at all costs.

NMR (90 MHz): δ 0.70-0.93 (m, 6H, CH₃), 1.21, 1.22 (2s, 9H, (CH₃)₃C), 1.33-1.75 (m, 4H, CH₂), 3.56 (bm, 2H, CH₂OH).

**2-t-Butylperoxy-2-ethylbutyl propionate (97)**

To a solution of crude peroxide alcohol 156 (800 mg, 4.2 mmol) and pyridine (0.5 mL) in CH₂Cl₂ (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% aq. NaOH (100 mL) and extracted with hexane (100 mL). The separated hexane layer was washed with 5% aq. NaOH (100 mL) and sat. aq. NH₄Cl (3 x 50 mL), dried over MgSO₄, and evaporated below room temperature behind an explosion shield to give a crude oil, which was purified via flash-column chromatography with SiO₂. After gradient elution with EtOAc/hex, 2-t-butylperoxy-2-ethylbutyl propionate (97) was obtained as a colorless oil, 594 mg (57%).

**1H NMR (400 MHz):** δ 0.87 (t, 6H, J = 7.6 Hz, CH₃), 1.15 (t, 3H, J = 8.0 Hz, O₂CCH₂CH₃), 1.20 (s, 9H, (CH₃)₃C), 1.49 (dd, 2H, J = 7.4, 14 Hz, CH₂), 1.53-1.71 (m, 2H, CH₂), 2.34 (q, 2H, J = 7.6 Hz, O₂CCH₂), 4.14 (s, 2H, CH₂O₂C). **13C 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. Anal Calcd. for C₁₃H₂₆O₄: C, 63.38; H, 10.64. Found: C, 63.15; H, 10.43.

**2-t-Butylperoxy-2-ethylbutyl Butyrate (96)**

To a solution of crude 2-t-butylperoxy-2-ethyl-butanol 156 (800 mg, 4.2 mmol) and pyridine (0.5 mL) in CH₂Cl₂ (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% aq. NaOH (100 mL) and extracted with hexane. The separated hexane layer was washed with 5% aq. NaOH (100 mL) and sat. aq. NH₄Cl (3 x 50 mL), dried over MgSO₄, and evaporated behind an explosion shield below room temperature to afford a crude product, which was purified via flash-column chromatography with SiO₂. After gradient elution with EtOAc/hex, 2-t-butylperoxy-2-ethylbutyl butyrate (96) was isolated as a colorless oil, 440 mg (40%).

**1H NMR (400 MHz):** δ 0.87 (t, 6H, J = 7.6 Hz, CH₃), 0.96 (t, 3H, J = 7.2 Hz, O₂CCH₂CH₃), 1.20 (s, 9H, (CH₃)₃C), 1.46-1.73 (m, 8H), 2.31 (t, 2H, J = 7.6 Hz, O₂CCH₂), 4.14 (s, 2H, CO₂CH₂). **13C 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\(^{-1}\). Anal. Calcd. for C\(_{14}H_{28}O_{4}\)/C\(_{6}H_{14}\): C, 65.24; H, 11.02. Found: C, 65.18; H, 11.06.

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