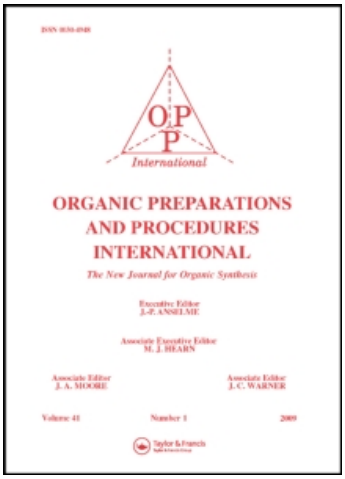

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RECENT PROGRESS IN THE SYNTHESIS OF ARTEMISININ AND ITS DERIVATIVES

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INTRODUCTION

1. Historical Background

In endemic areas, almost all people are exposed to malaria infected *Anopheles* mosquitoes (*Anopheles gambiae,*[1a] *Anopheles funestus,*[1b] *Anopheles stephensi*[1c]) that transmit deadly parasites to a second host, human beings.[1] In the 1960's, the failure of eradication of this infectious disease by global effort (WHO) led to the advent of the drug resistant *Plasmodium falciparum* which is now one of the most serious public health problems in the world.[2] Although significant efforts have been devoted to develop malaria vaccines, none of them has been commercialized yet.[3] Therefore, antimalarial chemotherapy still plays a crucial role in treating this lethal infectious disease.

Chinese scientists have studied biologically active natural products by screening more than 10,000 plants that are cited in Chinese herbal medicine literature, *e. g. Ben Cao Gang Mu.* The literature contains descriptions of a number of natural compounds together with pharmacological and clinical studies.[3] In 1972, a small molecule called Qinghaosu (*artemisinin*) was isolated from a plant Qinghao[4] (*Artemisia annua L.*). The structure of artemisinin was elucidated by X-ray crystallographic analysis in 1979.[4] Since then, it has been discovered that the active ingredient of the herb, artemisinin, can effectively kill malaria parasites, even chloroquine-resistant strains of *Plasmodium.*[5] Artemisinin has a unique pharmacophore, *i. e.*, endoperoxide bridge (1,2,4-trioxane). The endoperoxide group is believed to be responsible for the antimalarial activity of artemisinin, as described below. Artemisinin and its derivatives are of a great benefit to people who live in endemic areas because it can provide a cheap yet quite effective treatment for malaria especially when artemisinin is taken together with other anti-malaria drugs. The only potential concern for their wide-spread use is that some of the artemisinin derivatives have shown neurotoxicity to animals when extremely large doses are given.[38]

In addition to artemisinin, other endoperoxide compounds have been discovered in nature. *Table 1* shows natural products with potent antimalarial activities. All the compounds except quinine in *Table 1* bear the endoperoxide pharmacophore. They all show promising antimalarial and/or antitumor activities. Although artemisinin is probably the most well-studied natural endoperoxide, other endoperoxide compounds could potentially be used to develop useful therapeutic drugs. Natural products play a critical role in medicinal chemistry to identify lead pharmaceuticals by applying the combinatorial technology and conventional synthesis method as well.[6,7] Screening process has been developed to find an active ingredient in the herbal remedies.[6,8]

Table 1. Antimalarial and Antitumor Natural Products

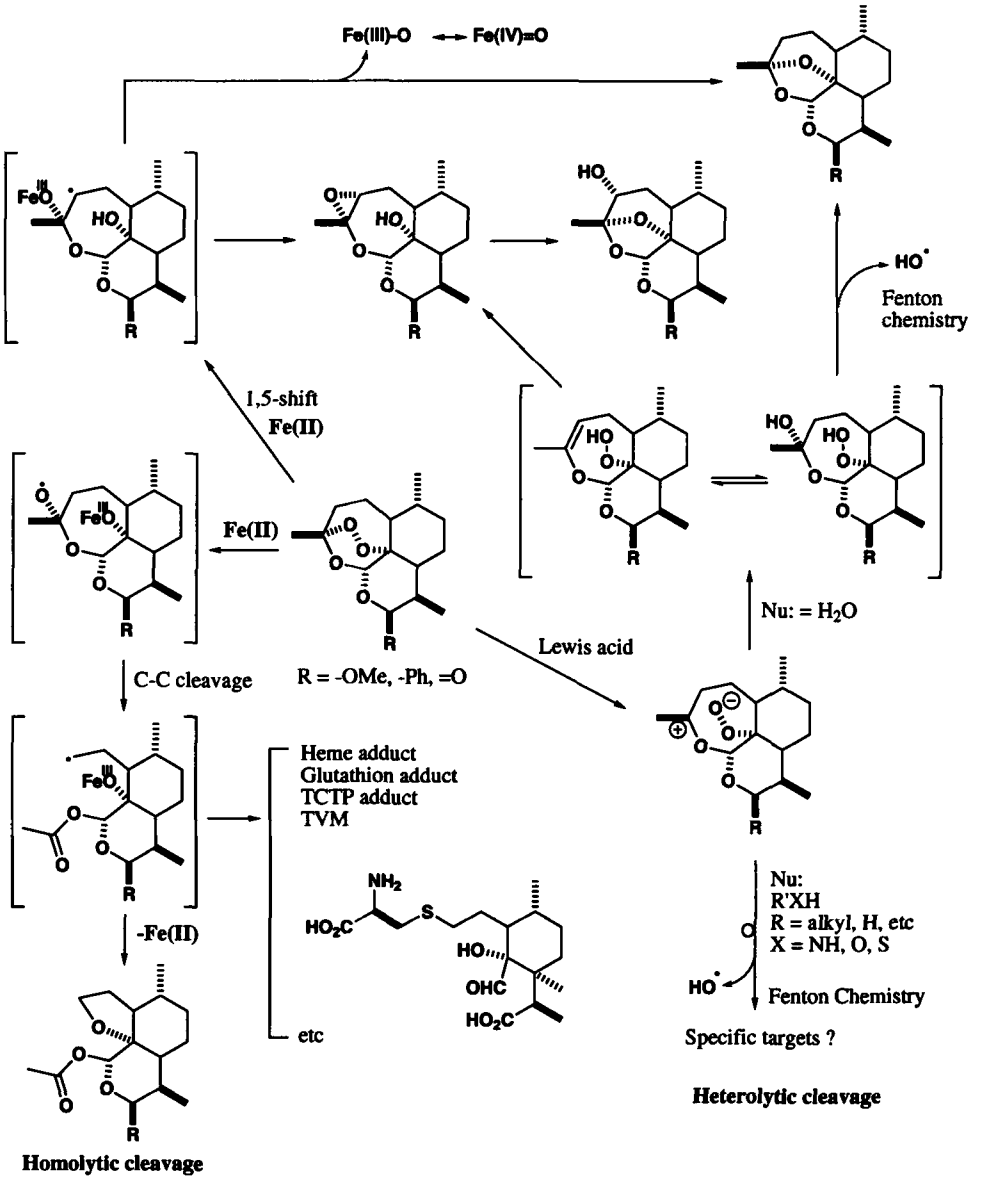
Compound	Type	Source	Remarks
Artemisinin (Qinghaosu)[4] Artemisitene[8]	Terpenoid	Artemisia annua L.	Plant
Yingzhaosu A[9]	Terpenoid	*Artabotrys uncinatus*	
Yingzhaosu C			
Nardoperoxide[11]	Terpenoid Quaiane	*Nardostachys chinensis*	
Zingiberene-3,6-endoperoxide[12]	Terpenoid bisabolane	*Senecio selloi* *Eupatorium rufescens*	
Ergosterol-5,8-endoperoxide[13]	Terpenoid	*Ajuga remota*	
10,12-Peroxy- calamenene[14]	Terpenoid	*Cyperus rotundus*	
Ascaridole[15]	Terpenoid	*Chenopodium anthelminticum L.*	
Quinine[16]	Alkaloid	*Cinchona ledgeriana*	
Plakortides[17]	Terpenoid	*Plakortis halichondrioides*	Marine
Muqubilon[18]	Terpenoid	*Diacarnus erythraeanus*	
Mycaperoixde[19]	Terpenoid	*Mycale sp.*	
Stolonoxide[20]	Terpenoid	*Stolonica socialis*	

In the next section, we discuss proposed modes of action of artemisinin and its cellular targets in malaria parasites. These studies have provided useful insights not only in understanding the antimalaria activity of artemisinin at the molecular level but also in designing more efficient synthetic drugs based on artemisinin.

2. Proposed Modes of Action

Several mechanisms have been proposed to account for the extremely potent and selective cytotoxicity of artemisinin against malaria parasite. All these mechanisms start with an iron-catalyzed (reductive) cleavage of endoperoxide to generate toxic free radicals.[21] Malaria parasites live in red blood cells, digesting hemoglobin as food, and then depositing heme as hemozoin. The parasites therefore, contain higher concentration of iron than other cells in the body, and become

more sensitive to artemisinin. Free radicals are believed to be responsible for the parasite death because they damage important cellular structures and biomolecules in the vicinity. The reaction between artemisinin and intracellular iron would generate the initial *O*-centered radicals that can rearrange to *C*-centered radicals. Also, a Lewis acid-catalyzed rearrangement of the endoperoxide bond followed by Fenton chemistry in the presence of iron could generate a significant amount of the hydroxyl radical. The key question is which radical species are most responsible for the parasite death, and what are the cellular targets, if the reaction is specific (*Scheme 1*).[21,22]



Proposed Mechanisms of Action of Artemisinin and its Analogs

Scheme 1

Below are possible scenarios for the activation of artemisinin by intracellular iron;

(1) Intracellular Fe(II) can coordinate directly to one of the endoperoxide oxygens to cause homolytic cleavage of the -O-O- bond, generating two distinct *O*-centered radicals. Both *O*-centered radicals rearrange to a *C*-centered radical either by 1,5-shift of the radical center or by cleavage of C(3)-C(4) bond. An alternative mechanism for the activation of artemisinin involves the heterolytic cleavage of the O(2)–C(3) bond in the presence of a Lewis acid. The resulting zwitter ion reacts with water to form a hydroperoxide species that then reacts with intracellular Fe(II) *via* Fenton chemistry to generate the hydroxyl radical. These two distinct radical formation reactions can co-exist, depending on the cellular environment surrounding artemisinin.

(2) Under homolytic conditions, the most toxic radical would be *C*-centered radicals which act as an alkylating reagent to heme or specific parasite proteins. Researchers suggested that toxic radicals were responsible for the formation of artemisinin-heme adduct,[23] alkylation of the histidine rich protein,[24] translationally controlled tumor protein (TCTP)[25] or other specific proteins[22,26] of parasite acting as parasite killer (*see the section below*). Recently, the Bachi group has proposed that the *C*-centered radical could be oxidized to the corresponding carbocation. The carbocation can then react with nucleophiles in the parasite.[27] Those reactive species formed under homolytic conditions retain some of the unique molecular structure of artemisinin, and may have specific cellular targets in the parasite.

(3) Under heterolytic conditions, hydroxyl radical would cause an oxidative stress in the infected red blood cell.[28] Unlike *C*- or *O*-centered radicals formed under homolytic condition, hydroxy radical would randomly attack and damage a surrounding cellular structure[28,29] and subcellular components in the parasite.[21,22,27-30]

Although the reactive species and cellular target(s) of artemisinin in malaria parasites still remain a subject of further investigation, intracellular iron appears to play important roles in activating artemisinin inside the cell. Therefore, artemisinin should be able to exert its cytotoxic effect on other cells beside malaria parasite if they contain a high concentration of intracellular Fe(II). Recently, many cancer cells have been shown to be sensitive to artemisinin and its derivatives. Lai and Singh have reported that artemisinin derivatives induce apoptosis of lymphoma and breast cancer cells.[31] Cancer cells need higher iron to support their uncontrolled growth, and become more sensitive to artemisinin compared to the corresponding normal cells. Subsequent reports from other researchers suggest that artemisinin may be effective against many types of cancer cells.[22f] We recently prepared a covalent conjugate of artemisinin and transferrin, an iron-transport protein. The artemisinin-tagged transferrin showed significantly more selective anti-cancer activity compared to artenisinin alone.[52c-d] This is probably because cancer cells take up a large amount of iron *via* the receptor-mediated uptake. Artemisinin-tagged transferrin would concentrate artemisinin in cancer cells. Iron is released from transferrin intracellularly and would react immediately with the tagged artemisinin, causing cell death. Since artemisinin is virtually non-toxic to normal cells, a new type of cancer treatment might be developed based on this natural compound.

3. Cellular Targets of Artemisinins in Malaria Parasites

Since the efficacy of artemisinin toward malaria parasites has been well established, identifying its cellular target(s), if any, would open up a new avenue to design and synthesize artemisinin-like compounds that have similar or even better biological activities.[22,27-32] Artemisinin is known to react with heme, and alkylate the porphyrin ring. The alkylated hemin has been proposed to interfere with the formation of hemozoin, and thus disrupt hemoglobin catabolism and heme detoxification[32] systems of the parasite.

Meshnick first reported that several specific proteins were labeled when a tritium-labeled dihydroartemisinin was incubated with malaria-infected erythrocytes. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) analysis, autoradiography[3b,25] showed that major labeled proteins had molecular weight of 22, 23, 32, 45, 52, 67, 71 and over 200 kDa.[25] Later, the proteins of 22, 45, and 67kDa were identified as monomeric, dimeric, and trimeric Translationally Controlled Tumor Protein (TCTP), respectively, by using immunoblotting techniques.[25c] Although the function of TCTP in parasite is not well-defined, a similar protein has been identified in mammalian cells.[25d] The mammalian TCTP appears to inhibit the apoptosis process, and may be responsible for the anti-anticancer activity of artemisinin. Recently, the second protein, sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), has been identified as a major target of artemisinin in the parasite.[22d] Confocal microscope was used to demonstrate that fluorescence-labeled thapsigargin, a known inhibitor for SERCA, was displaced by adding excess artemisinin.

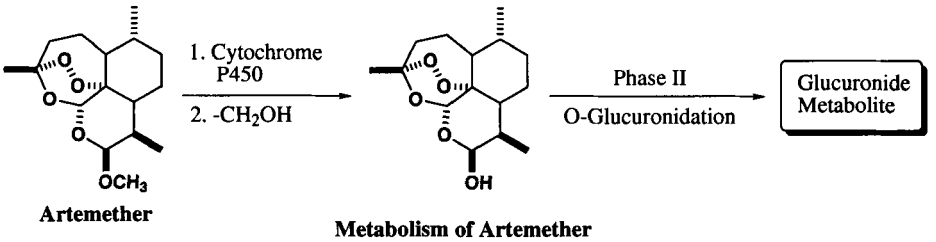
The iron-rich environment of red blood cells during malaria infection might also activate artemisinin, attacking the membrane of the malaria parasite or its infected red blood cell.[29,30] The damaged membrane may interfere with endocytosis,[33] and thus disrupting the uptake of critical nutrients for the growth of parasites inside the red blood cell.

4. Metabolic Stability and Toxicity of Artemisinin Derivatives

After the initial isolation of artemisinin from Qinghao, several researchers have tested its cytotoxicity as well as the antimalarial activity.[21] Artemisinin is essentially non-toxic to normal cells under the conditions where malaria parasites are rapidly killed. However, artemisinin has poor solubility both in water and in oil.[3,5c] In order to improve the poor solubility of artemisinin, artemisinin was converted to give dihydroartemisinin **2** (DHA) in which the lactone group was reduced to the corresponding cyclic hemiacetal. Alkylation or acylation of the OH group at the C-10 position of DHA yielded several useful artemisinin derivatives, artemether and artether as oil soluble compounds, and artesunate and artelinic acid as water soluble compounds.[3,5c,34] These artemisinin derivatives killed malaria parasites more quickly than the parent compound due to their higher solubility, and have been used widely to treat malaria infection. Potential problems with these artemisinin derivatives as a drug include short half-life drug metabolism by mono-chemotherapy,[3,35] degradation by cytochrome P450 oxidation,[22g,36] hydrol-

ysis under acidic condition,[37] and neurotoxicity.[38] The European pharmaceutical companies, *e. g.*, Norvatis and Rhone-Poulenc, has developed a combination therapy by including the longer-acting antimalarial drugs such as benflumetol in the artemisinin treatment to offset the metabolic instability of artemisinin derivatives.[38,39]

Although artemisinin derivatives have been used widely in humans, their neurotoxicities have been a major concern in therapeutic use.[38c] There is no report of neurotoxicity of artemisinin to humans. However, some hydrophobic derivatives of artemisinins including DHA appear to be neurotoxic to animals when an extremely large dose is given to animals intravenously. Serious neurotoxicity of artemisinin, though rare, has been reported in malaria-infected patients in Southeast Asia.[38b] The mechanism for neurotoxicity of artemisinin derivatives has not been well-studied. It has been suggested that the acetal group of artemisinin derivatives such as artemether is readily cleaved under hydrolytic or oxidative conditions to produce neurotoxic dihydroartemisinin (DHA, *Scheme 2*).[40] Karle *et al.* have established the relationship between neurotoxicity of artemisinin derivatives and their structural and electronic properties including dipole moment.[41] According to their studies, lipophilic artemisinin derivatives tend to show higher neurotoxicity. Recently, Gordi and Lepist summarized[38g] literature findings on animal toxicity of artemisinin derivatives, and concluded that the prolonged presence of artemisinins upon slow release from oil-based intramuscular formulations is the main cause of the observed toxicity in laboratory animals.



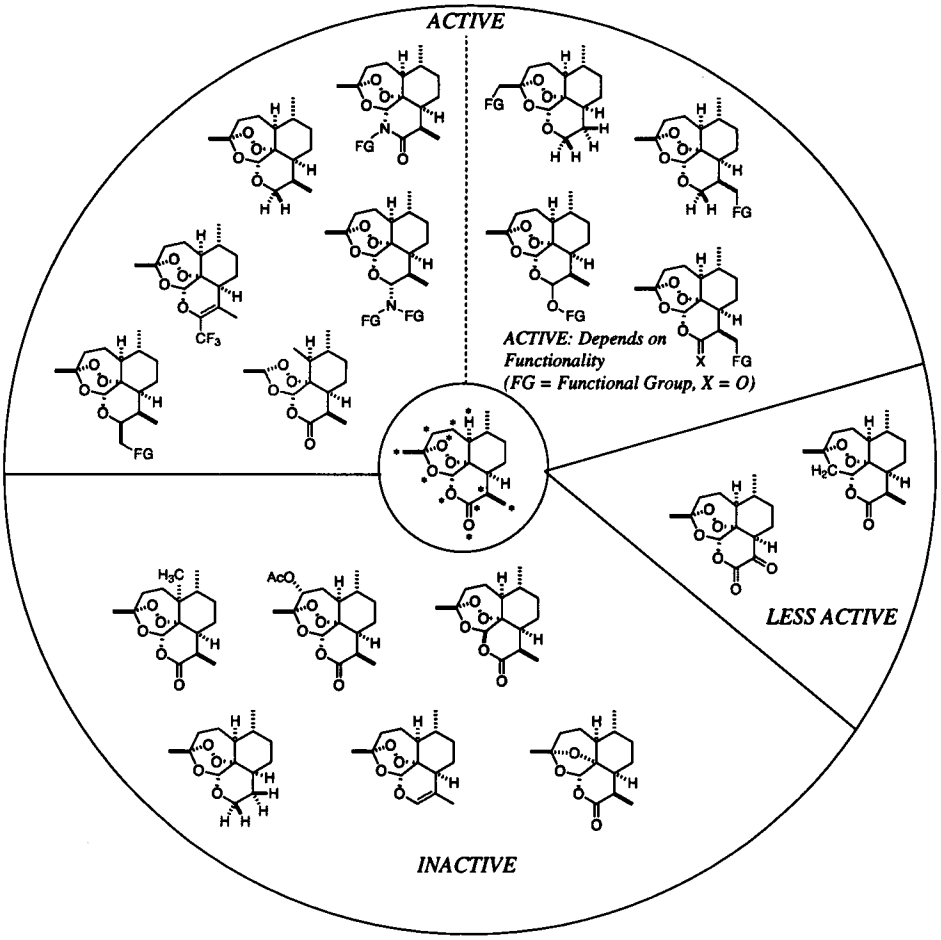
Artemether **Metabolism of Artemether**

Scheme 2

5. Structure-Activity Relationships (SAR)

Since the structure of artemisinin was determined by X-ray crystallography in 1979, artemisinin has attracted much attention of both synthetic and medicinal chemists because of its unique structure and mechanism of action against malaria parasites. A large number of artemisinin analogs have been prepared by various approaches to improve the biological activities. These synthetic approaches will be discussed in more details in later sections. Avery and coworkers carried out a systematic analysis of artemisinin derivatives to identify a possible relationship between structure and activity.[44] They employed computer-aided 3D-quantitative structure-activity relationships (3D-QSAR) with a database of over 200 artemisinin analogs. Both antimalarial and neurotoxicity data were examined. Based on the X-ray structure of artemisinin,

they hypothesized that the endoperoxide bridge must be able to interact with hemin to activate the artemisinin derivatives. To analyze SAR, they used the hemin-docked conformation for comparative molecular field analysis (CoMFA). Although a reasonable correlation between anti-malarial activities and CoMFA data was found, none was determined between structures and neurotoxicity. Representative artemisinin derivatives and their biological activities are illustrated in *Scheme 3*.



* Modified Position

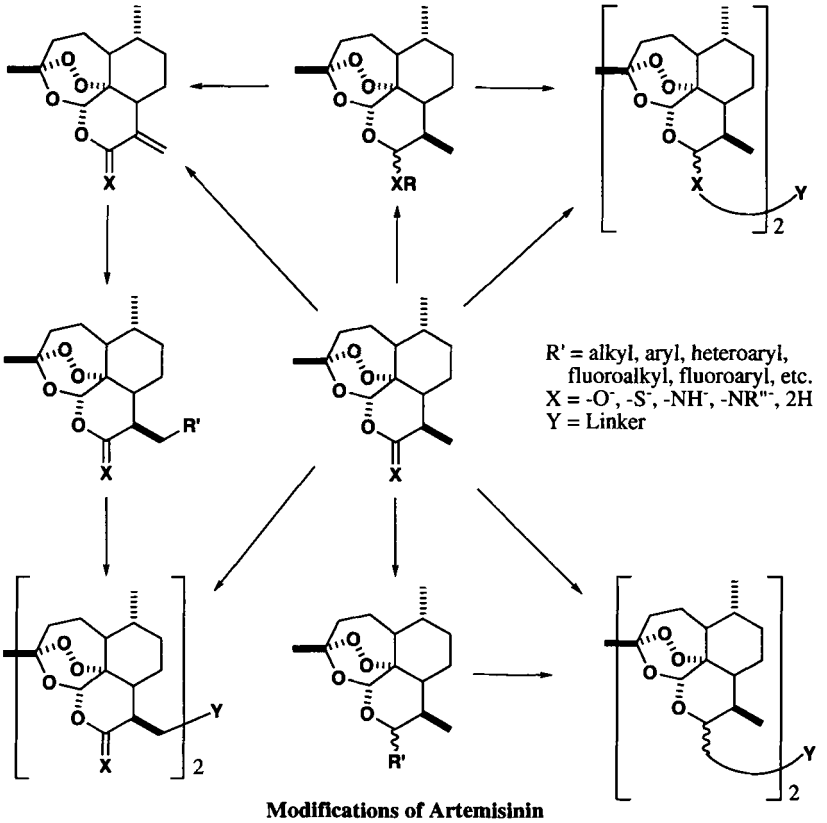
Scheme 3

II. SYNTHETIC APPROACHES TO ARTEMISININ DERIVATIVES

1. General Overview

A number of synthetic analogs have been synthesized to improve the physical and biological properties of artemisinin. A major problem with artemisinin (X = O in *Scheme 4*) was its poor solubility both in water and in oil, resulting in the low bio-availability. Therefore, the

majority of the initial synthetic efforts were directed toward the introduction of suitable side-chains to the artemisinin core. Artemisinin derivatives discussed in this review are shown in *Scheme 4.*



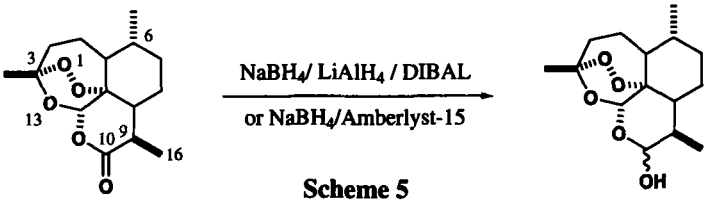
Modifications of Artemisinin

Scheme 4

A group of Chinese scientists and researchers at the US Walter Reed Army Institute initially developed water and oil soluble artemisinin derivatives, *e. g.* artemether, artesunate, artelinic acid. Those artemisinin derivatives showed improved antimalarial activity after administrated both intravenously and orally.[5d,45] They were around ten times more potent than the original natural product **1**. Later, more artemisinin derivatives were synthesized to deal with other problems such as hydrolytic and metabolic stability, even neurotoxicity in some cases. Several useful synthesis routes to modify at the C10 position of artemisinin were successfully developed. The artemisinin derivatives, *e. g. O*-glycoside and *C*-glycoside type, were tested *in vitro* and/or *in vivo* not only for antimalarial activity but also for anticancer activity.[21,22,43] Several groups were able to construct a structure-activity relationship (SAR) for certain classes of artemisinin derivatives. These SAR studies were used to design new artemisinin derivatives, understand the

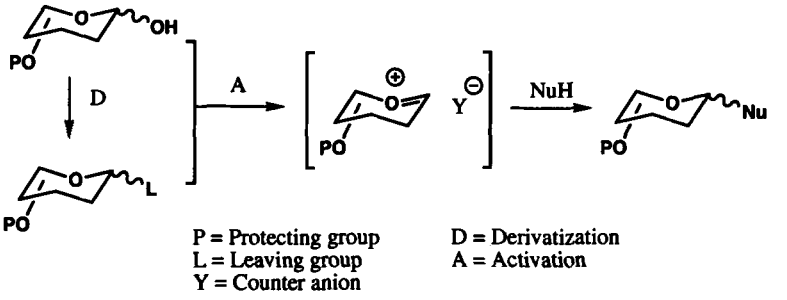
action of artemisinin at the molecular level, and improve artemisinin's bioactivity as well as bioavailability. Recently, new classes of artemisinin analogs such as C10- and C16-modified artemisinin dimers were synthesized. In the following sections, the syntheses of these new artemisinin derivatives are described.

Dihydroartemisinin **2** (DHA) is an important starting material for many artemisinin derivatives. Dihydroartemisinin is easily prepared from artemisinin (**1**) in one step. The lactone group of (**1**) can be readily converted to the lactol of (**2**) by reduction with $NaBH_4$ or other reducing agents shown in *Scheme 5*.[46]



Scheme 5

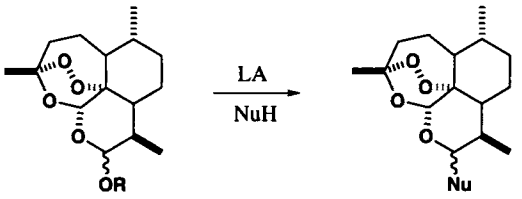
Then, various functional groups can be introduced at the C10 position of artemisinin to improve both biological and physical properties. Glycoside coupling of lactols has been well established in the field of carbohydrate chemistry. Lewis acid mediated glycoside couplings can produce *O*-, *N*-, and *S*-glycosides. In a typical glycoside coupling, a starting glycosidic donor is converted to a derivative with a good leaving group at the anomeric position (process D in *Scheme 6*). The glycoside donor is then activated with a Lewis acid promoter to generate a carbocation interemediate.[47] Finally, nucleophiles attack the activated donor in S_N1 manner to give the corresponding coupled product.



Typical Glycosylation Procedures

Scheme 6

In artemisinin chemistry, dihydroartemisinin (**2**), or DHA, and its derivatives have been used as a donor in the above glycoside coupling chemistry. The Lewis acid-mediated glycoside coupling has been applied to the synthesis of a number of artemisinin derivatives, and is illustrated in *Scheme 7*.



R = -H, -OTMS, -OAc, -F, -COPh

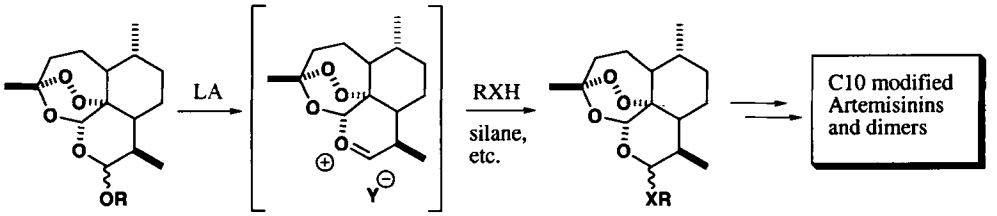
LA = BF_3•OEt_2, TMSCl, TMSBr, TMSOTf, $TiCl_4$, $SnCl_4$, $ZnCl_2$, etc.
NuH = R'OH, R'SH, R'NH_2, R'R"NH, allylsilanes, ArH, etc.
R', R" = alkyl-, aryl-, heteroaryl-, etc.

Scheme 7

2. Dihydroartemisinin (DHA) Derivatives

a) C-X Coupling Reaction via DHA and Acetyl DHA in the Presence of Lewis Acid Catalysis (X=O, N, S)

Lewis acid-catalyzed or mediated coupling provides a convenient method for the synthesis of artemisinin derivatives as shown in *Scheme 8*, but does not always give good results, primarily due to its fragile endoperoxide and/or the formation of side-products, *e. g.*, anhydroartemisinin (AHA).[48]



R = alkyl, aryl, etc
X = O, S, NH, NHR, CH_2R

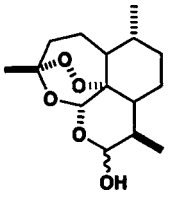
R = -H, -Ac, -COPh , etc; Y- = counter anion

Lewis Acid Catalyzed Coupling Reaction

Scheme 8

The most popular *C-X* coupling method was BF_3 etherate catalyzed reaction between DHA and nucleophiles. The reaction proceeds with dehydration to give C10 modified artemisinin derivatives in good yields.[45,48] Li *et al.* prepared the following artemisinins (**3a-e**) that were shown to target G1 phase of tumor cells cycle.[49a-b] The cytotoxicity of these artemisinins are summarized in *Table a* (Appendix).

Also, Lin *et al.* prepared a series of 4-(*p*-halophenyl)-4'-[10'-dihydroartemisininoxy] butyrate (**4a-f**) as potential antimalarial agents, which were all water soluble with higher efficacy and longer plasma half-life than artelinic acid (**10**, R = -CH_2PhCOOH) (*Table b*, Appendix).[49c] O'Neill and collaborators have developed artemisinin derivatives with a basic substituent to target acidic food vacuole. The same mechanism has been proposed for the accumulation of

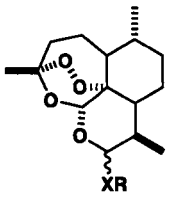


2

BF_3OEt

RXH

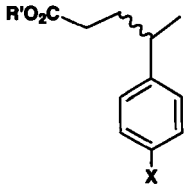
X = O, S



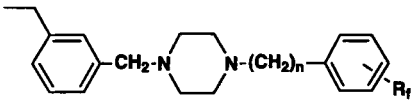
X = O; **3a-3e, 4a-4f, 5a-5h, 6a-6b**

X = S ; **7a-7b**; X = SO_2, **7c**

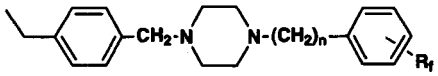
3a, R = -CH_2CN (C10β); **3b**, R = -R-CH(CN)C_6H_5 (C10β); **3c**, R = -S-CH(CN)C_6H_5 (C10β);
3d, R = -R-CH(CN)C_6H_4Br-*p* (C10β, 22%); **3e**, R = -S-CH(CN)C_6H_4Br-p (C10β, 25%);



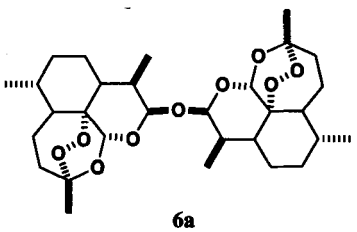
(C10β, *S*): **4a**, R' = Me, X = Cl (30%); **4b**, R' = Me, X= F (30%); **4c**, R' = Me, X = Br (20%);
(C10β, *R*): **4d**, R' = Me, X = Cl (40%); **4e**, R' = Me, X= F (43%); **4f**, R' = Me, X = Br (55%);



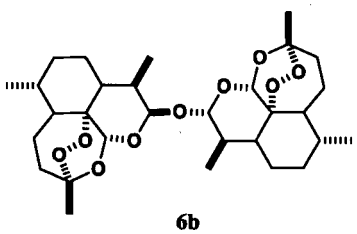
5d, R_f = H; **5e**, R_f = NO_2-*p*; **5f**, R_f = Cl-*p*;
5g, R_f = CF_3-*m*; **5h**, Rf = F-*p*



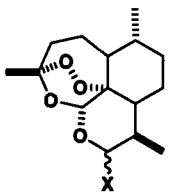
5a, n = 0, R_f = F-*p*; **5b**, n = 0, R_f = CF_3-*p*;
5c, n = 1, R_f = H



6a



6b



7a, R = SH;
7b, R = SPh;
7c, R = SO_2-Ph

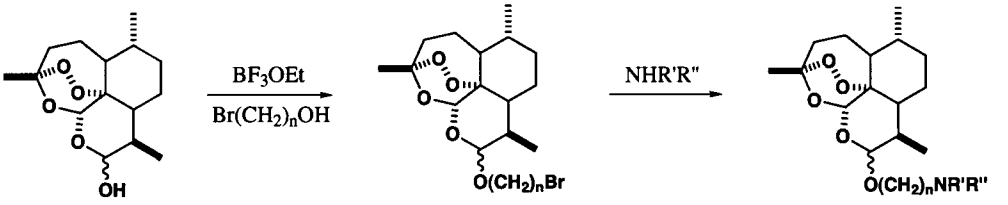
BF_3 Etherate Catalyzed Coupling Reaction

Scheme 9

chloroquine in the food vacuole.[49d] Thus, a piperazine ring was introduced to artemisinin by N-alkylation after *C-O* coupling reaction, with moderate to good yields. The antimalarial activity of the piperazine-linked artemisinins (**5a-h**) is summarized in *Table c* (Appendix). Li and co-workers attempted to improve the antimalarial activity of artemisinin by introducing aromatic amines for metal chelation, but those were actually less potent than non-chelating artemisinins (*Table e*, Appendix).[49f] In 1997, Woerdenbag *et al.* reported the synthesis of artemisinin dimers by the glycoside coupling method. Interestingly, non-symmetrical dimer (**6a**) was more cytotoxic than symmetrical dimer (**6b**) against EN2 tumor cells using the MTT assay (*Table g*,

Appendix).[49h] In 2003, Lee and co-workers synthesized thioacetal artemisinins (**7a-c**) in good yields.[50a-b] These *S*-acetals showed a 2-9 fold better growth inhibition effect than DHA, measured by the MTT assay method.

Li's and O'Neill's groups have prepared other series of water-soluble artemisinin analogs by introducing amine functionality at C10.[49e,51] The analogs were synthesized in moderate yield by a two-step procedure, *i. e.*, *C-O* coupling reaction with bromoalcohols *via* BF_3 catalysis followed by nucleophillic displacement with amine in moderate yields, as shown in *Scheme 10*. Their antimalarial activities are summarized in *Table h* (Appendix).



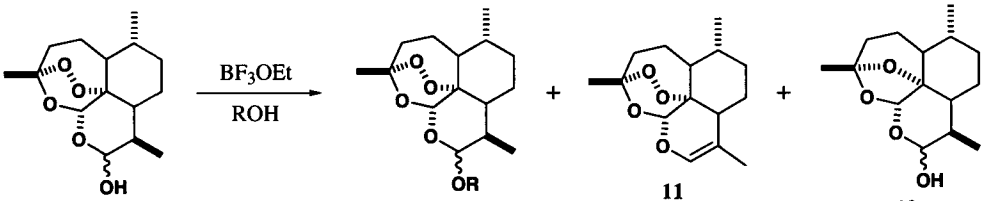
2 **8a**, n = 2; **8b**, n = 3 **9a-g**

9a, n = 2, R' = R" = Me; **9b**, n = 2, R' = R" = Et; **9c**, n = 2, R' = H, R" = -$(CH_2)_2$OH;
9d, n = 2, NR'R" = morpholinyl; **9e**, n = 3, NR'R" = morpholinyl;
9f, n = 2, R' = H, R" = Me; **9g**, n = 2, R' = H, R" = Et;

Synthesis of Amine-containing Artemisinin Derivatives

Scheme 10

The BF_3 catalyzed *C-O* coupling provides a general way to prepare a variety of artemisinin derivatives as described above. The endoperoxide group in artemisinin is remarkably stable under such acidic conditions. However, in many cases, the coupling yields are not very high, primarily due to the formation of anhydroartemisinin (AHA, **11**). The formation of AHA becomes a major problem when phenols[48] and other sterically hindered alcohols are used as a glycosyl acceptor (*Scheme 11*).



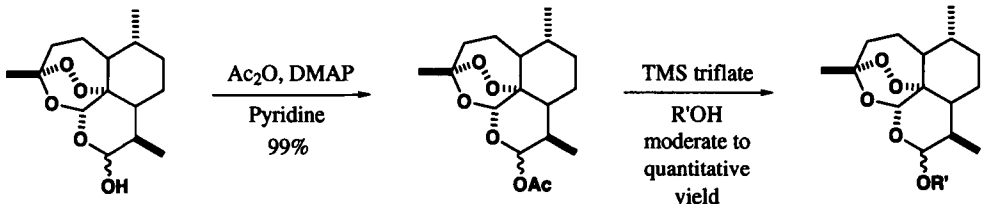
2 **10b-e** minor **11** major **12** trace

Formation of Anhydroartemisinin (AHA) by the C-O Coupling Reaction. See Table 2 for the structure of 10b-e.

Scheme 11

To avoid the formation of AHA, we explored alternative starting materials, including DHA acetate **13**, and different activation methods. We developed the coupling reaction between

O-acetylated DHA **13** and functionalized alcohols (**A** to **I**) in the presence of catalytic amounts of TMS triflate to yield the desired glycosides without the formation of AHA (**11**) and deoxydihydroartemisinin (**12**) (*Scheme 12*).[52]

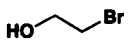
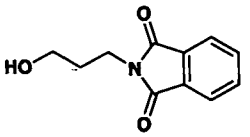
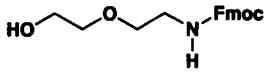
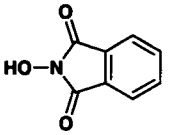
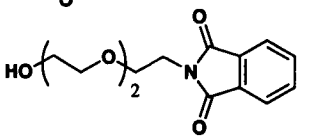
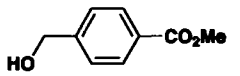
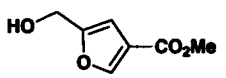
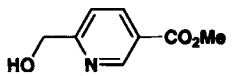


2 (α:β = 1:6) **13** (α:β = 1:4.4) **10a-i**

Scheme 12

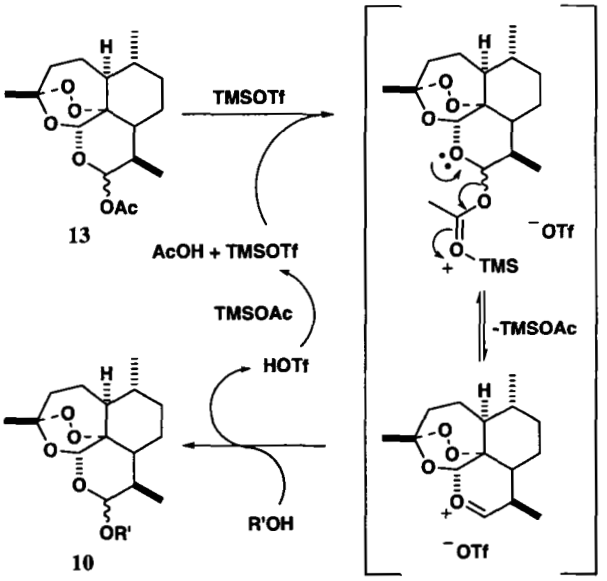
The results for several representative reactions are summarized in *Table 2*. Our new coupling reaction produced the desired glycosides in moderate to quantitative yields, even when

Table 2. TMS-triflate Catalyzed *C-O* Coupling Reactions

Compounds				Results, %		
2, 13		R'OH		BF_3OEt_2	TMSOTf	α:β
2	**A**		**10a**	84		1:10
13					89	1:9
2	**B**		**10b**	32		1:7
13					65	1:9
2	**C**		**10c**	trace		-
13					69	1:9
2	**D**		**10d**	trace		-
13					70	0:>20
2	**E**		**10e**	trace		-
13					87	1:6
13	**F**	CD_3OD	**10f**		99	
13	**G**		**10g**		85	mainly β
13	**H**		**10h**		79	mainly β
13	**I**		**10i**		no reaction	

the catalyst was used 1 mol% (in case of **a**, **b**, **e**, **f**). The coupling reaction was completed within 30 min. Moreover, the reaction could be run at room temperature and was easily scaled up to gram scale. This new coupling method should be useful to bring down the cost of artemisinin derivatives in large scale syntheses.[53]

The new TMSOTf-catalyzed *C-O* coupling reaction is believed to proceed *via* a catalytic cycle of forming the oxonium ion followed by the nucleophillic attack until the reaction is complete (*Scheme 13*). Once DHA acetate **13** is activated by a catalytic amount of TMS triflate (0.01 to 0.1 equiv.) under anhydrous conditions, the oxonium ion is generated. The oxonium ion then reacts directly with alcohols to yield the products. The triflic acid formed in the coupling step may either regenerate TMS triflate or act as the main catalyst.



Propsosed Mechanism of TMS-triflate Catalyzed C-O coupling Reaction

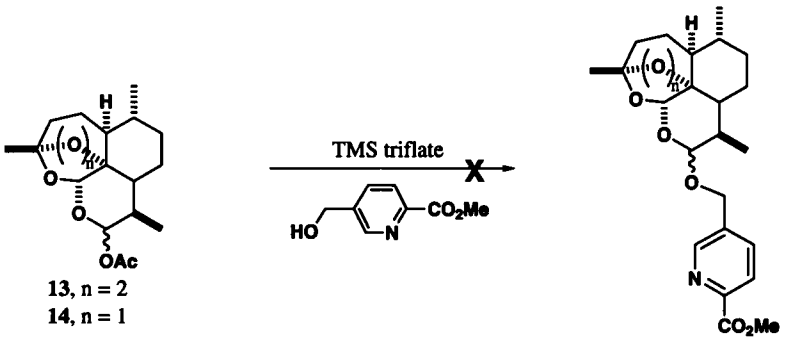
Scheme 13

Artelinic acid methyl ester (**10g**) and its analogs (**10h-i**) (R-$COOCH_3$) readily react with excess hydrazine in methanol to give the corresponding acyl hydrazides (R-CONH-NH_2). These artemisinin hydrazides can be conjugated to a carrier molecule to specifically deliver artemisinin to cancer cells, malaria parasites or other targets. We have conjugated these artemisinin hydrazides to periodate-oxidized transferrin, iron transport protein.[52c] Periodate oxidizes the carbohydrate residues on the protein surface to generate reactive carbonyl groups for conjugation. The resulting artemisinin-tagged transferrin showed a higher cytotoxicity against Molt-4 leukemia cells and a significantly lower toxicity against normal lymphocytes, compared to artelinic acid or DHA (**2**).[52d]

b) C-X Coupling Reaction via Artemisinin Halide (X = O, N)

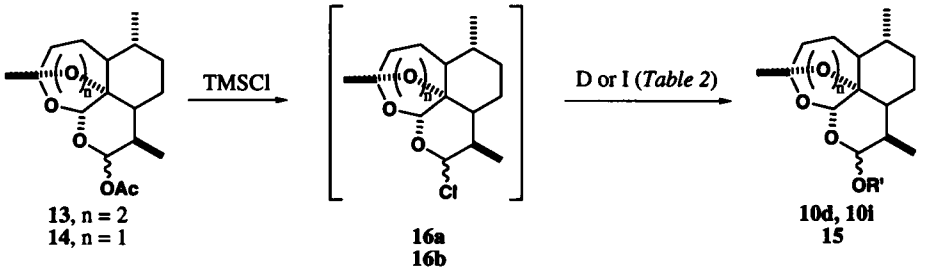
i) Artemisinin Chloride

The new TMS triflate catalyzed reaction described above does not work well when alcohol donors are less reactive or the donor concentration is low. In the coupling reactions of DHA acetate with furan or phenyl based alcohol (*Table 2*), the desired products were obtained in good yields (up to 85%). However, no product was obtained when the same reaction was carried out with the pyridine-based alcohol, which was poorly soluble in chloroform. (*Scheme 14*).[52b]



Scheme 14

To solve the problem, we employed *in situ* conversion of *O*-acyl DHA (**13**) to the corresponding chloride. The same chloride could be prepared from the deoxy compound (**14**) by the addition of a stoichiometric amount of TMSCl. The artemisinin chloride reacted readily with alcohols. The yields were 92% (**10d**), 85% (**10i**), and 67% (**15**) respectively (*Scheme 15*).



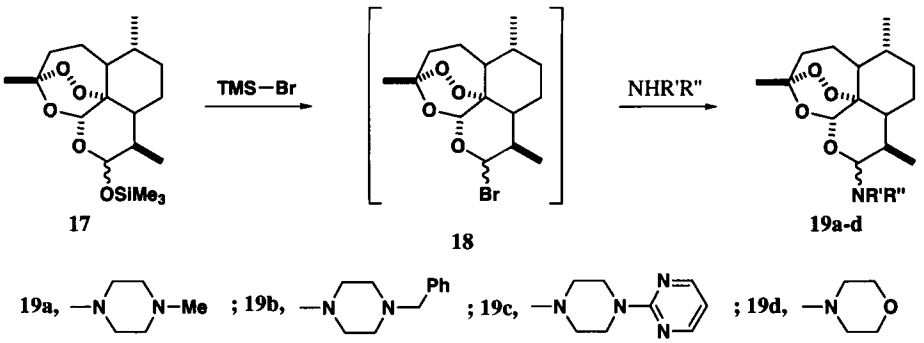
Coupling Reaction *via* Artemisinin Chloride

Scheme 15

ii) Artemisinin Bromide

Haynes *et al.* synthesized (alkyl)aminoartemisinins by the nucleophillic displacement of bromoartemisinins. Artemisinin bromide was prepared *in situ* by treating silylated DHA (**17**) and TMSBr, followed by reaction with alkylamines in dichloromethane at 0°C for 45 min.[22i] Sixteen artemisinin derivatives were synthesized in moderate yields (up to 60%). The structures of these

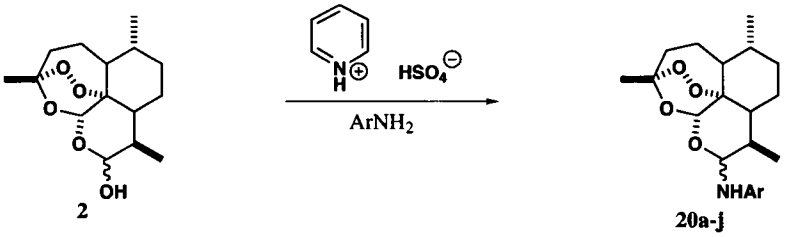
artemisinin derivatives are shown in *Scheme 16*. These compounds are typically 3 to 7 times more potent against *P. yoelii* than artesunate, as shown in *Table i* (Appendix).



Preparation of Aminoartemisinins *via* Artemisinin Bromide (See *Table i* (Appendix))

Scheme 16

Li and coworkers prepared similar aminoartemisinins by reacting DHA with aryl-amines in the presence of catalytic amount of pyridinium sulfonate in pyridine at room temperature. The reaction afforded arylaminoartemisinins in good yields (up to 93%), but could not be applied for the preparation of alkylaminoartemisinins, probably due to their differences in basicity (*Scheme 17*).[54] The arylaminoartemisinins were 4 times more effective against *P. berghei* (K173 strain) in mice than artemisinin.



20a, Ar = -C_6H_5 (93%); **20b**, Ar = -C_6H_4Cl-*m* (62%); **20c**, Ar = -C_6H_4Cl-*p* (72%);
20d, Ar = -C_6H_4Br-*m* (51%); **20e**, Ar = -C_6H_4Br-*p* (75%); **20f**, Ar = -C_6H_4I-*p* (51%);
20g, Ar = -$C_6H_4CH_3$-*p* (69%); **20h**, Ar = -$C_6H_4OCH_3$-*m* (85%);
20i, Ar = -C_6H_4COOH-*p* (62%); **20j**, Ar = -C_6H_4COOH-*m* (77%)

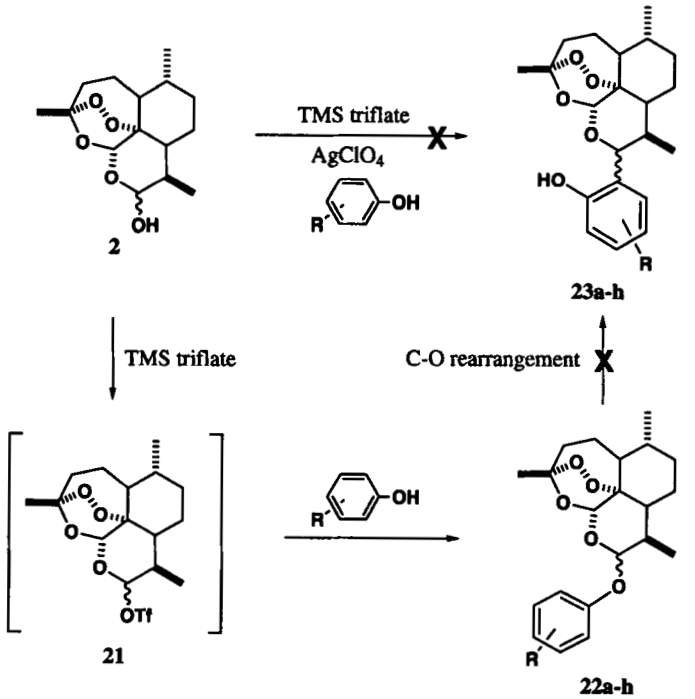
Synthesis of Arylaminoartemisinins

Scheme 17

c) C-O Coupling Reaction via Artemisinin Sulfonate

In the TMS-triflate catalyzed reaction (*Scheme 13*), the real catalyst may be triflic acid after complete consumption of TMS triflate. O'Neill *et al.* attempted to obtain carba-artemisinins bearing 2'-hydroxyphenyl derivatives by changing the acid catalyst from BF_3 etherate to $AgClO_4$-TMS triflate.[48a-b] The coupling reaction proceeds *via* artemisinin sulfonate intermediate. Unfortunately, only *C-O* coupled products (**22a-h**) were obtained, instead of carba-artemisinins (**23a-h**). The *C-O* rearrangement thus appears to be very slow under the experimental conditions

(*Scheme 18* and *Table j* (Appendix)). Interestingly, a similar reaction between the acetyl DHA (**3**) and naphthol in the presence of BF_3 etherate gives the desired carba-artemisinin as discussed in the later section.[56]

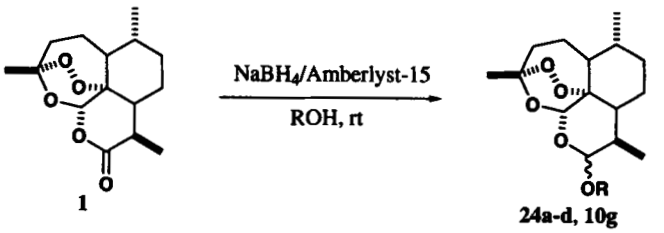


22a, R = H (C10β); **22b**, R = H (C10α): **22a+22b** = 68% (α/β = 1:4);
22c, R = OMe-*p* (C10β); **22d**, R = OMe-*p* (C10α): **22c+22d** = 73% (α/β = 1:4)
22e, R = CF_3-*p* (C10β); **22f**, R = CF_3-*p* (C10α): **22e+22f** = 68% (α/β = 1:8);
22g, R = F-*p* (C10β); **22h**, R = F-*p* (C10α): **22g+22h** = 60% (α/β = 1:3)

Scheme 18

d) C-O Coupling Reaction via Polymer Supported Acid Catalysis

The reduction of artemisinin with $NaBH_4$/Amberlyst-15 in the presence of an alcohol in methylene chloride at room temperature gives a mixture of α- and β-isomers of *C-O* coupled products. (*Scheme 19*) This provides a convenient one-pot conversion of artemisinin to some



24a, R = -Me (77%); **24b**, R = -Et (55%); **24c**, R = $-CH_2CH_2OH$ (70%);
24d, R = $-CH_2CH_2{=}CH_2$ (65%); **10g**, R = $-CH_2C_6H_4COOCH_3$-*p* (49%)

Scheme 19

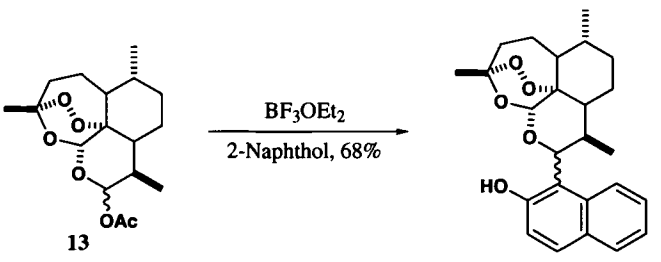
useful derivatives. For example, in the one-pot reaction with methanol, artemether was obtained with the α:β ratio of 1:3.[55]

3. Carba-artemisinin Derivatives

A promising approach to improve the poor hydrolytic and metabolic stability of *O*-glycoside derivatives of DHA is to replace the *C-O* linkage at C10 position with a *C-C* linkage. Many such artemisinin derivatives, carba-artemisinins, showed better bio-availability as well as lower toxicity compared to the corresponding *C-O* derivatives.[37] Some of carba-artemisinins displayed 15 to 22 times higher stability than acetal type of artemisinins in simulated stomach acid.[37] Therefore, carba-artemisinins appear to be more suitable as oral antimalarial or anticancer drugs due to their stability to acids. In the following sections, recent advances in the preparation of carba-artemisinins are discussed.

a) C-C Coupling Reaction via Lewis Acid Catalysis

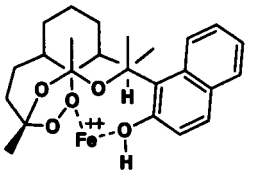
Carba-artemisinins have been prepared by the BF_3 etherate catalyzed coupling reaction (*Scheme 7*). In 1999, Wu *et al.* reported the preparation of 10-(2-hydroxy-1-naphthyl)-deoxoartemisinin (**26**, α:β = 1:1 mixture) by the Friedel-Crafts alkylation of DHA acetate (**13**) with 2-naphthol in the presence of a catalytic amount of BF_3•OEt_2 in moderate yield (68%).[56] Once the oxonium ion is formed under these conditions, *C-O* coupling product is initially formed, and then it undergoes an acid-catalyzed rearrangement to the carba-artemisinin **26**. Alternatively, the initial product may be anhydro-artemisinin, AHA, that undergoes the acid-catalyzed Friedel-Crafts reaction with 2-naphthol to give the corresponding product (**26**).



13 **Scheme 20** **26**

When tested for antimalarial activity against *P. berghei* (K173 strain), the α-isomer of **26** showed higher activity than the β-isomer. The difference in antimalarial activity between the two stereoisomers was explained by the ability of the α-isomer to coordinate with Fe^{2+} as shown in *Scheme 21*. The Fe complex of α-isomer has been suggested to initiate the *O*-2 radical route more readily to result in the higher cytotoxic effect. The hypothesis was supported by the observation in which α-isomer of **26** reacted faster than the other isomer with $FeSO_4$ in aq. acetonitrile.

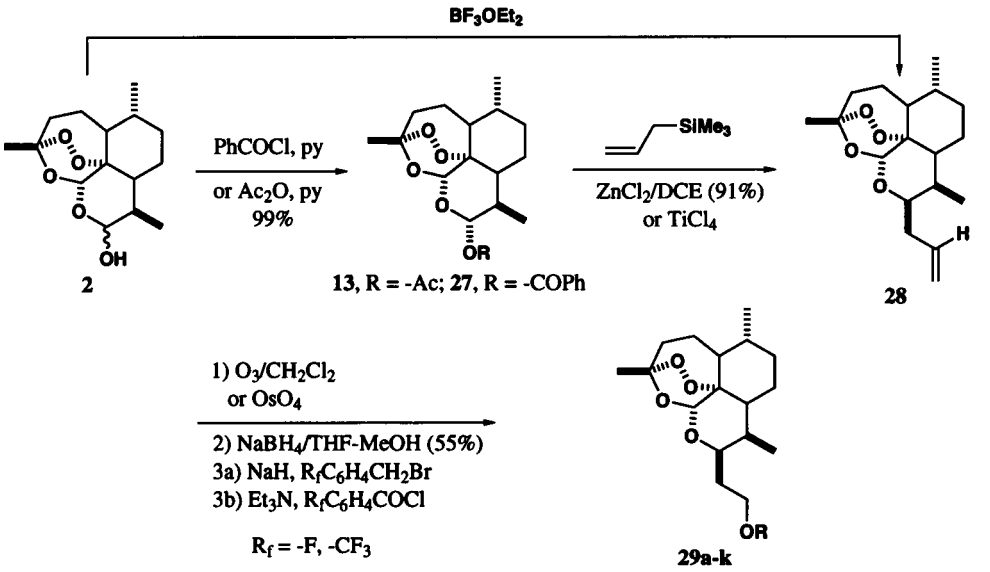
Several groups prepared carba-artemisinins by the reaction of DHA (**2**) or DHA derivatives (**13**, **27**) with silanes in the presence of Lewis acid such as BF_3•OEt_2, $TiCl_4$, $SnCl_4$ and



Proposed Coordination Structure of 26 with Fe2+.

Scheme 21

$ZnCl_2$. Typical examples are shown in *Scheme 22*. In 1999, O'Neill's group prepared C10-propenyl-artemisinin (**28**) from **2** by the reaction with allyltrimethylsilane in the presence of BF_3•OEt_2.[57a] The olefinic product **28** was subsequently converted to the corresponding alcohol **29a** by ozonolysis, followed by $NaBH_4$ reduction. Further reaction with fluorinated benzyl bromide or benzoyl chloride gave **29b-k**. Two compounds, **29b** and **29k**, showed antimalaria activities comparable to that of artemisinin (*Table k* (Appendix)). The antimalarial activity was stereochemistry dependent, *i. e.* the β-isomers were over 5 times more potent than α-isomers against drug-resistant *P. falciparum*.



2

13, R = -Ac; **27**, R = -COPh

28

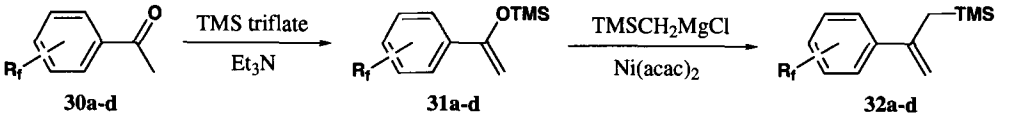
29a-k

29a, R = H; **29b**, R = -$CH_2C_6H_4F$-*o*; **29c**, R = -$CH_2C_6H_4F$-*m*; **29d**, R = -$CH_2C_6H_4F$-*p*; **29e**, R = -$CH_2C_6H_4CF_3$-*o*; **29f**, R = -$CH_2C_6H_4CF_3$-*p*; **29g**, R = -COC_6H_4F-*o*; **29h**, R = -COC_6H_4F-*m*; **29i**, R = -COC_6H_4F-*p*; **29j**, R = -$COC_6H_4CF_3$-*o*; **29k**, R = -$COC_6H_4CF_3$-*p*

Scheme 22

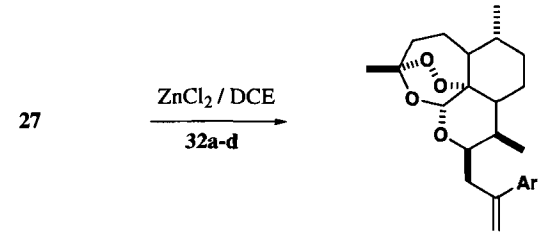
O'Neill's group utilized 2-hydroxyethyl-carba-artemisinin (**29a**) to prepare fluorinated ether and ester derivatives of carba-artemisinins (**29g**, R = -COC_6H_4F-2; **29i**, R = -COC_6H_4F-4). These carba-artemisinins showed good antimalarial activities against K1 and HB3 *P. falciparum* strains in *in vitro* experiments, but in *in vivo* experiments, the bioactivities were less potent than

artemisinin or DHA. For further investigation of the antimalarial activity of carba-artemisinins, the same authors synthesized a series of carba-artemisinins (**28a-d**) by zinc mediated *C-C* coupling reaction of **27** with allylsilanes (**32a-d**). The allylsilanes were prepared by $Ni(acac)_2$ catalyzed cross-coupling of silyl enol ethers (**31a-d**) with $TMSCH_2MgCl$ in moderate yields (*Scheme 23* and *Table l* (Appendix)).[57b]



30a-d **31a-d** **32a-d**

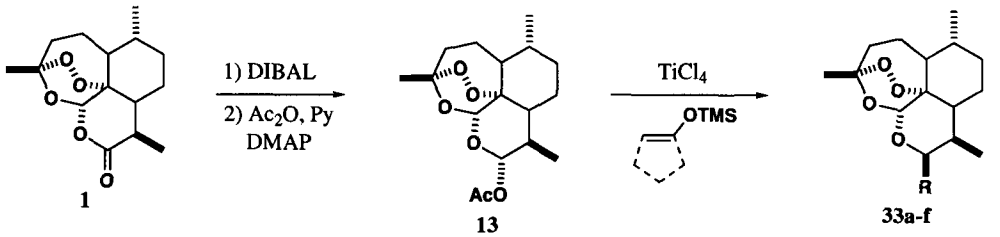
a, R_f = H (<42%); **b**, R_f = CF_3-*m* (53%); **c**, R_f = F-*p* (63%); **d**, R_f = F-*o* (40%)



28a (91%), **28b** (94%), **28c** (86%), **28d** (70%)

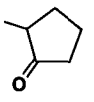
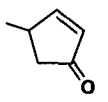
Scheme 23

Ziffer's group improved the Lewis acid mediated *C-C* coupling reaction by changing a combination of glycosyl donor and Lewis acid, *i. e.*, from [DHA]-[BF_3•OEt_2] to [DHA acetate **13**]-[$TiCl_4$]. To gain some mechanistic insights, pure α and β isomers of **13** were prepared separately, and then activated by $TiCl_4$ in acetonitrile. In both cases, the product was predominantly the β isomers, suggesting that a common intermediate, an oxonium ion, was formed during the coupling reaction. The yield was up to 60% (*Scheme 24*).[58] Antimalarial activity of carba-artemisinins (**33a-c**) was 2 fold better than artemisinin against drug-resistance *P. falciparum* strains (*Table m* (Appendix)).



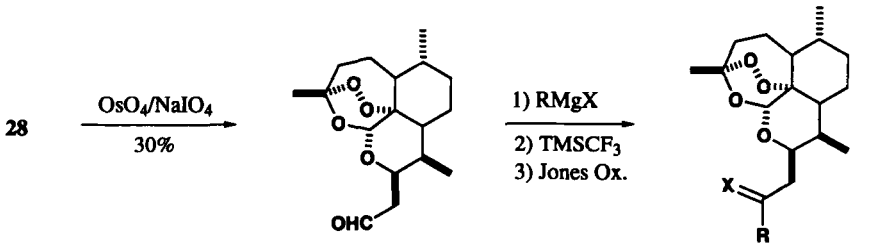
1 **13** **33a-f**

33a, R = CHO; **33b**, R= (C=O)Me;
33c, R = (C=O)Bu^t; **33d**, R = Ph; **33e**, R = CN;

33f, R =  ; **33g**, R = 

Scheme 24

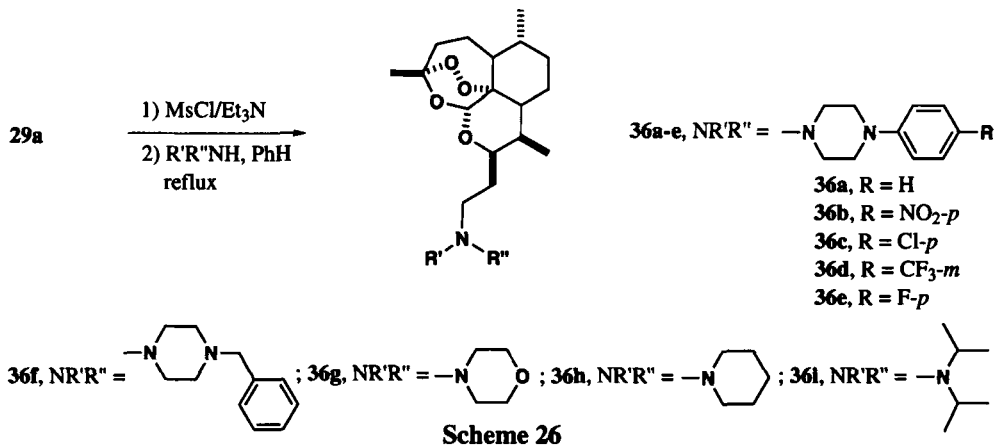
As shown in *Scheme 22*, the carba-artemisinin **28a** was prepared by the $TiCl_4$ mediated C-C coupling reaction between **13** and allylsilane in a good yield. Oxidation of **28** with OsO_4 followed by reaction with $NaIO_4$ afforded the corresponding aldehyde **34**. The aldehyde **34** was treated with Grignard reagents to yield **35a-d** (*Scheme 25* and *Table m* (Appendix)).



35a, R = Me, X = H, OH (α:β = 1.7:1; 98%); **35b**, R = Et, X = H, OH (α:β = 1.7:1; 79%);
35c, R = Pri, X = H, OH (α:β = 2:1; 44%); **35d**, R = Bu^t, X = H, OH (α:β = 2:1; 33%);
35e, R = CF_3, X = H, OH (α:β = 1.4:1; 91%); **35f**, R = Et, X = O (86%); **35g**, R = -Pr^i, X = O (86%)

Scheme 25

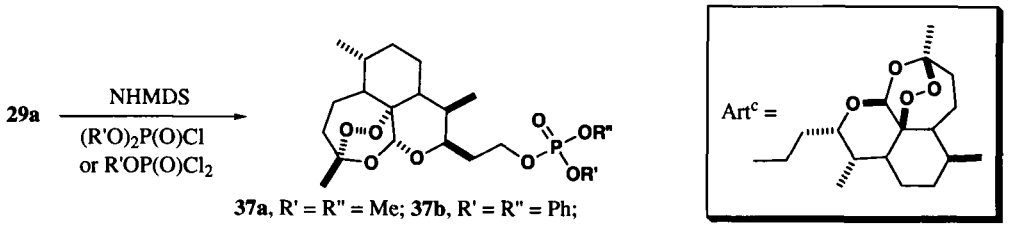
O'Neill *et al.* have also prepared several types of carba-artemisinins which have shown better bioactivity and bio-availability than the *C-O* type of artemisinin derivatives (**5a-h**).[49d] These compounds were prepared in good yield by nucleophillic displacement of mesylated **29a** with amines in benzene, and showed good bio-availability as well as good antimalarial activity (*Scheme 26* and *Table n* (Appendix)).



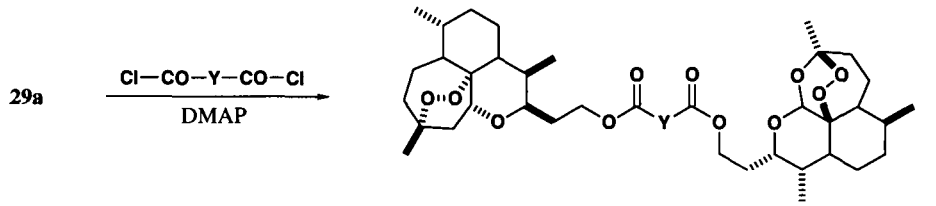
Scheme 26

Artemisinin dimers have shown good antimalarial and antitumor activities both *in vitro* and *in vivo*. Carba-artemisinin dimers especially are more attractive than glycoside dimers due to their hydrolytic stability as well as bioactivity. O'Neill and co-workers synthesized a series of C10 carba-artemisinin dimers (**36a-d, 37a-h**) that showed potent antimalarial activities. Phosphate monomers (**37a, 37b**) and dimers (**37c, 37d**) were prepared by deprotonation of carba-artemisinin alcohol (**29a**) with sodium hexamethyldisilazide (NHMDS) followed by the addition

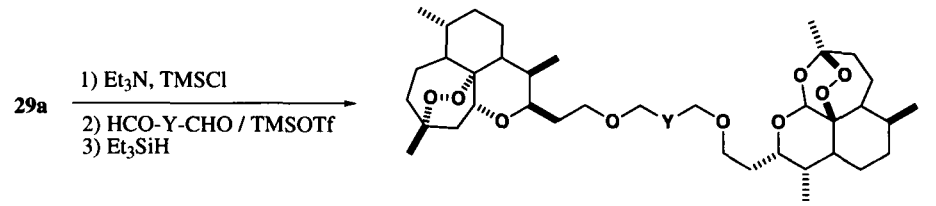
of the appropriate phosphate (di)chloride to give the desired dimer in a moderate yield (*Scheme 27* and *Table o* (Appendix)).[59] The phosphate ester dimers have shown nanomolar growth inhibitory (GI_{50}) values against various cancer cell lines, but monomers were inactive even though they have shown a better antimalarial activity compared to artemisinin. Another class of trioxane dimers (**38a-h**) was prepared by treating 2 equiv. of **29a** and 1 equiv. of acid chlorides with catalytic amount of 4-(dimethylamino)pyridine (DMAP). (*Table p* (Appendix)). Unfortunately, these compounds showed poor anticancer activity against the NCI (National Cancer Institute) 60 human cancer cell lines.



37a, R' = R" = Me; **37b**, R' = R" = Ph;
37c, R' = Me, R" = Art^c; **37d**, R' = -Ph, R" = -Art^c



38a, Y = -C_6H_4-*p* (75%); **38b**, Y = -C_6H_4-*m* (58%); **38c**, Y = -C_6H_4-*p* (61%)
38g, Y = -CH_2- (66%); **39h**, Y = -CH_2CH_2- (60%)

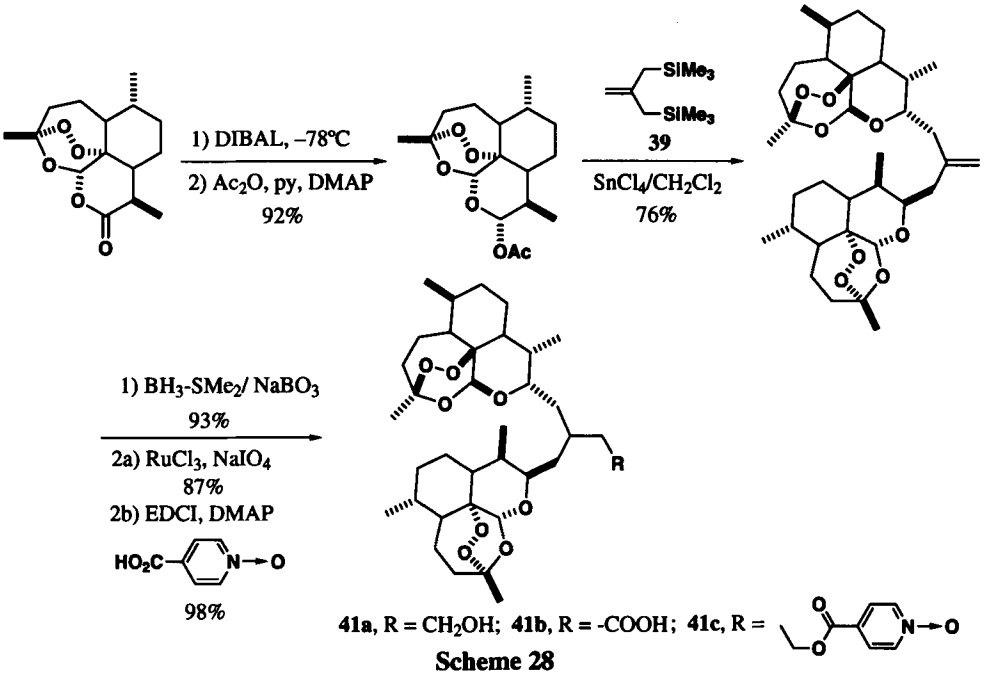


38d, Y = -C_6H_4-*p* (75%); **38e**, Y = -C_6H_4-*m* (58%); **38f**, Y = -C_6H_4-*p* (75%)

Scheme 27

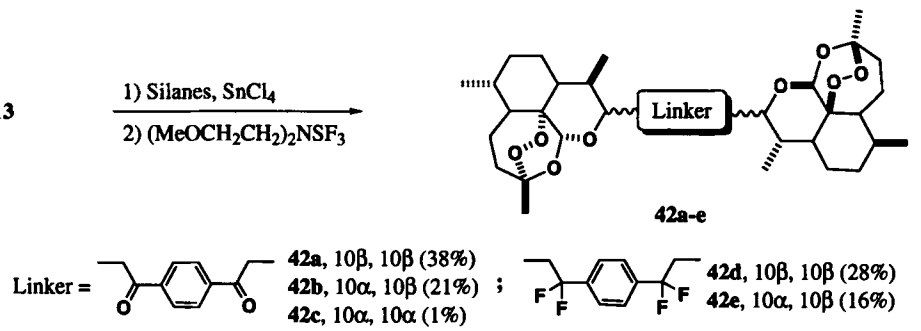
The titanium promoted condensation between artemether (**24a**) and trimethylsilyl enol ethers has been used to prepare carba-artemisinins, but the coupling yield is generally low. Posner and co-workers improved the *C-C* coupling method by developing $SnCl_4$ catalyzed coupling reaction between DHA acetate and silanes. Recently, the same group prepared carba-artemisinin dimers by the $SnCl_4$ catalyzed nucleophillic displacement of the acetate **13** with allylsilane **39**, then subsequent reduction with borane followed by further oxidation and esterification reaction, as shown in *Scheme 28*. The antimalarial activity of these dimers is summarized in *Table q* (Appendix).[60] Trioxane dimers showed excellent dual activities in both malaria parasite

(*P. falciparium* NF54) and prostate cancer (transgenic adenocarcinoma of mouse prostate [TRAMP] clonal cell lines). Anti-cancer activities of dimers **41a** and **41c** were comparable to that of *gemzar* or *adriamycin*. Esterification of **41a** with succinic anhydride and isonicotinic acid has shown 5 times better antimalarial activity than artemisinin.



Scheme 28

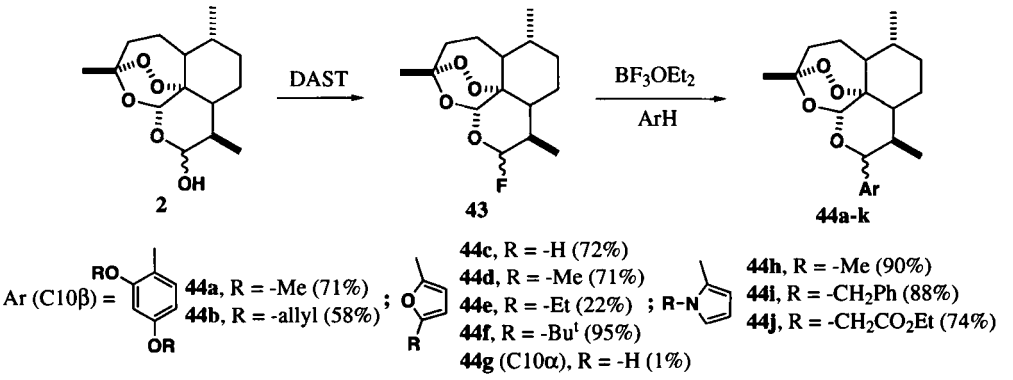
To improve pharmacological properties of the carba-artemisinin dimers **42a** and **42b**, tetrafluorinated dimers **42d** and **42e** were prepared by replacing carbonyl oxygen by a fluorinated linker. The ketone dimers (**42a-c**) were, however, more potent anti-cancer agents than the fluorinated dimers (**42d-e**). The stereochemistry of C10 position of the fluorinated carba-artemisinins does not appear to correlate with biological activities. All these carba-artemisinin dimers showed higher bioactivities than that of artemisinin (*Scheme 29* and *Table r* (Appendix)).[61]



Scheme 29

b) C-C coupling reaction via artemisinin fluoride

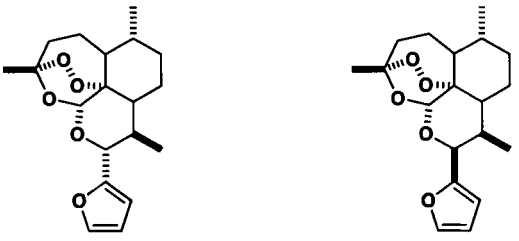
In 1998, Posner and his group reported the synthesis of electrophilic artemisinin fluoride (fluoro-deoxyartemisinin) in quantitative yield by treatment of DHA with a stoichiometric amount of diethylamino sulfur trifluoride (DAST) at –78°C (*Scheme 30*).[62] 10-Fluoro-10-deoxoartemisinin (**43**) is much more stable than other deoxoartemisinin halides (**16**, **18**). The fluoride **43** can be kept in freezer for 1 week without decomposition or hydrolysis. The artemisinin fluoride reacts with various nucleophillic aromatics or heteroaromatics by BF_3 etherate mediated Friedel-Crafts alkylation to afford C10-carba-artemisinins in moderate to good yields. The preferred stereochemistry of C10 in the Friedel-Crafts reaction is β-isomer. Interestingly, the coupling reaction of fluoroartemisinin **43** with aluminum-acetylides as nucleophiles in the presence of BF_3 etherate gives the opposite stereochemistry at C10. The mechanism for the change in stereochemical preference in these reactions is not clear.



Friedel-Craft Alkylation *via* Fluoro-deoxyartemisinin

Scheme 30

The aryl and heteroaryl analogues of carba-artemisinin derivatives (**44a-k**) showed high *in vitro* antimalarial activity. In case of the furan derivatives **44c** and **44g**, their biological activities were strongly dependent on the stereochemistry at C-10 position as shown in *Scheme 28*. In *in vitro* experiment, the biological activity of **44c** was 67-fold higher than **44g** against chloroquine sensitive NF54 strain of *P. falciparum* (*Table s* (Appendix)).

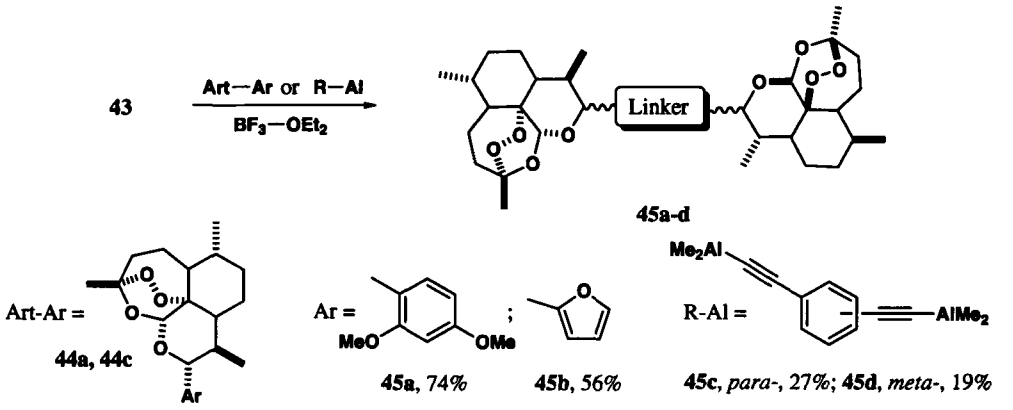


44c
IC_{50} = 1.4 nM

44g
48 nM

Scheme 31

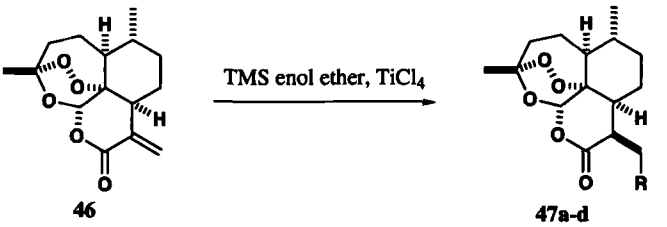
Friedel-Crafts condensation between **44a** or **44c** and 10-fluoro-deoxoartemisinin (**43**) provided the β-linked dimers in moderate yields. On the other hand, aluminum acetylide condensation yielded the α-linked dimers. It is unclear why different stereo isomers are obtained in these two seemingly similar coupling reactions. All dimers were particularly inhibitory to leukemia cells of NCI human cancer cell lines although those dimers are less effective than calcitriol. They show anti-proliferative activities at nanomolar concentrations, much more potent than artemisinin (*Scheme 32*).[62c]



Scheme 32

c) Artemisinins Modified at C-16

In 2000, Ziffer *et al.* reported $TiCl_4$ catalyzed Michael additions of trimethylsilyl enol ethers to artemisiten, *i. e.*, the Mukaiyama-Baba procedure, to afford C-16 substituted artemisinins.[63] The reaction between artemisitene and silyl enol ethers in the presence of $TiCl_4$ yielded a mixture of α- and β-isomer whose antimalarial activity increased several folds (*Scheme 33* and *Table t* (Appendix)).

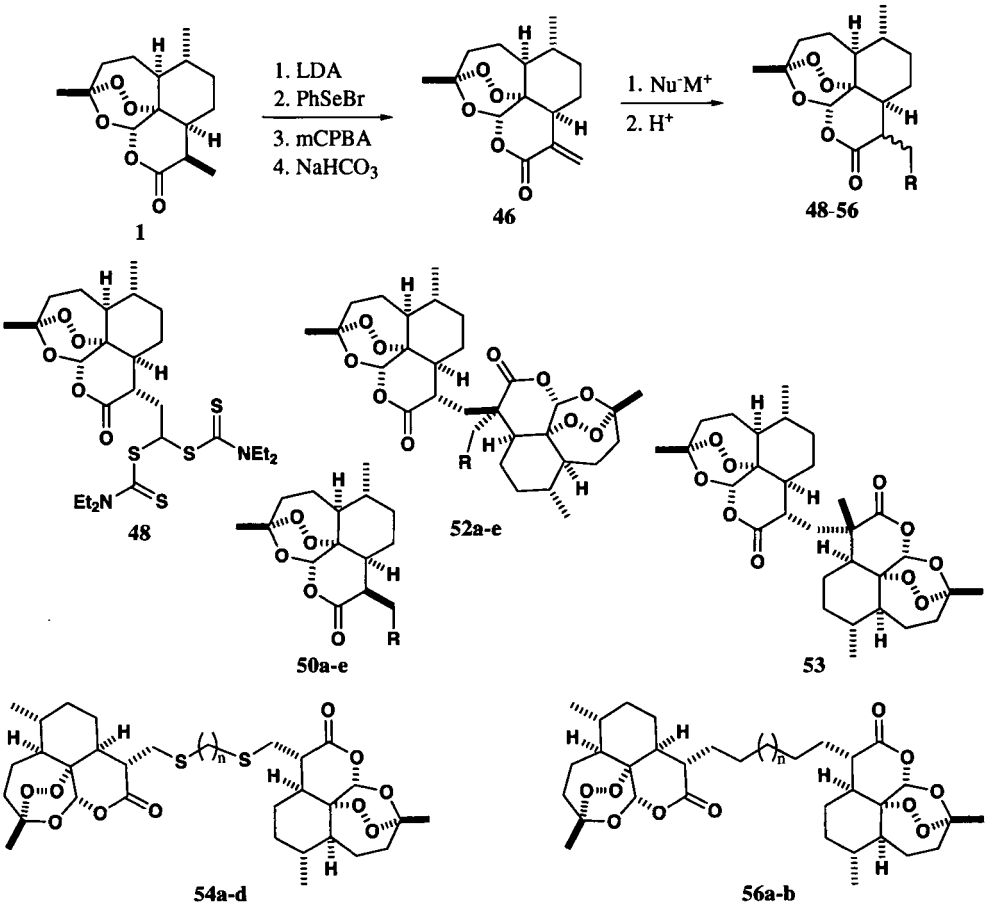


47a, R = -CN; **47b**, R = $-CH_2CH{=}CH_2$; **47c**, R = $-CH_2COBu^t$; **47d**, R = 2'-cyclopentanone

Scheme 33

Thebtaranonth *et al.* have also demonstrated that C-16 modified artemisinins are pharmacologically useful by *in vitro* experiments.[64] Artemisinin was regiospecifically converted to

artemisitene by treatment with LDA and PhSeBr at –78°C followed by oxidation and elimination reactions. The yield was 73%. Artemisitene reacts with various nucleophiles such as organo-lithiums and Grignard reagents by conjugate addition to give the corresponding products in good yield (*Scheme 34*). The biological activities with structures for these compounds are summarized in *Table u* (Appendix).

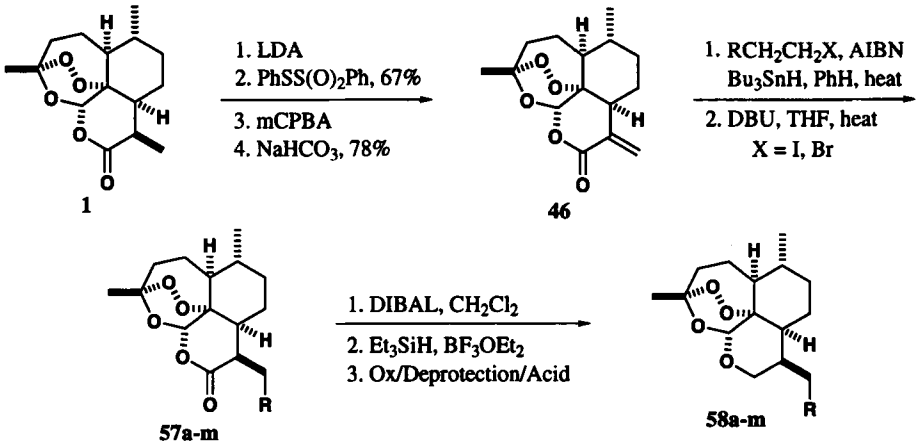


50a, R = -Et; **50b**, R = -Pr; **50c**, R = -Bu; **50d**, R = -$(CH_2)_3$Ph; **50e**, R = -C_6H_4F-*p*
52a, R = -Et; **52b**, R = -Pr; **52c**, R = -Bu; **52d**, R = -$(CH_2)_3$Ph; **52e**, R = -C_6H_4F-*p*
54a, n = 2; **54b**, n = 3; **54c**, n = 4; **54d**, n = 5
56a, n = 2; **56b**, n = 3

Scheme 34

4. Deoxoartemisinins

Avery[65a-b] and Acton[65c] groups developed a useful approach to prepare C10-deoxo-C16-substituted artemisinin from artemisitene. In these approaches, artemisitene was transformed to several artemisinin derivatives by either radical or nucleophillic conjugate addition.



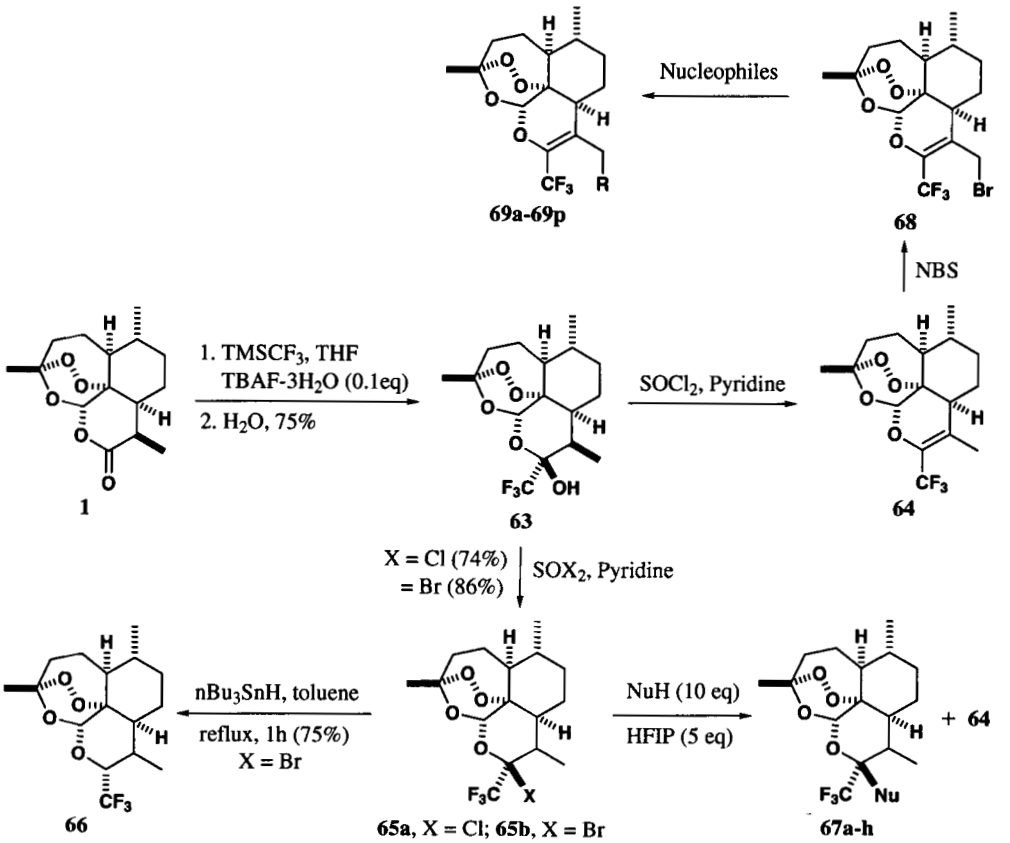
a, R = -$(CH_2)_3$OTMS; **b**, R = -$(CH_2)_2CF_3$; **c**, R = -$(CH_2)_2C_6H_4$Cl-*m*; **d**, R = -$(CH_2)_2C_6H_4$Cl-*p*;
e, R = -$(CH_2)_2C_6H_4$F-*m*; **f**, R = -$(CH_2)_2C_6H_4CF_3$-*m*; **g**, R = -$(CH_2)_2C_6H_4CF_3$-*p*;
h, R = -$(CH_2)_2C_6H_3(CF_3)_2$-3,5; **i**, R = -$(CH_2)_2C_6H_3F_2$-3,5; **j**, R = -$(CH_2)_2$Ph;
k, R = -$(CH_2)_2C_6H_4SO_2$Me-*p*; **l**, R = -$(CH_2)_2C_6H_4$OH-*p*; **m**, R = -$(CH_2)_2C_6H_4NMe_2$-*p*·HCl

Scheme 35

Avery *et al.* developed radical induced Michael addition of artemisitene with appropriate alkyl- or aryl halides. The reaction was initiated by 2,2'-azobisisobutyronitrile (AIBN) followed by the addition of Bu_3SnH.[65a-b] The addition reaction resulted in an almost equal mixture of α- and β-isomers. The α-isomer was readily converted β-isomer by refluxing with 7,11-diazabicyclo[5.4.0]undec-11-ene (DBU) in THF for 12 h, which worked better than deprotonation of α-epimer with a base then subsequent kinetic quench. The other approach to obtain deoxoartemisinins was a conjugate addition of Grignard reagent in the presence of Cu(I) catalyst. This synthetic route was adapted to solve the limitation of the radical addition. Also, the Acton group has developed another coupling chemistry of artemisitene by employing the El-Feraly method.[65c] Biological activities of these artemisinin derivatives are shown in *Table v, w* and *z* (Appendix).[65, 71]

5. Fluorocarba-artemisinins

Introduction of fluoro-functionality to artemisinin backbone could provide a promising way to improve both physical and biological activities of artemisinin. Bonnet-Delpon and coworkers initially reported the ring contraction of artemisinin to give the corresponding aldehyde, which could be converted to several furanosyl types of artemisinins.[66] Later, these authors reported the preparation of fluorocarba-artemisinin derivatives. These fluorinated carba-artemisinins showed higher metabolic stabilities and bioactivities than non-fluorinated analogs (*Scheme 36*).[67a-e]

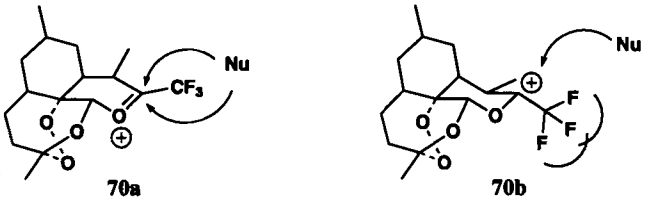


67a, Nu = OMe; **67b**, Nu = OEt; **67c**, Nu = OCH_2CH_2OH; **67d**, Nu = OCH_2CF_3; **67e**, Nu = OOH
69a, R = -morpholinyl; **69b**, R = -NHMe; **69c**, R = $-NHCH_2CH_2NH_2$; **69d**, R = $-N_3$; **69e**, R = $-NH_2$;
69f, R = $-NHSO_2CH_3$; **69g**, R = -NHEt; **69h**, R = -OBn; **69i**, R = $-OCH_2CH_2OMe$;
69j, R = $-OCH_2CH{=}CH_2$; **69k**, R = $-OCH_2CH_2OH$; **69l**, R = $-OCOCH_3$; **69m**, R = -OH;
69n, R = $-OCH_2CHOHCH_2OH$; **69o**, R = -OEt; **69p**, R = $-CH_2(CO_2Me)_2$

Scheme 36

10α-Trifluoromethyl-dihydroartemisinin (**63**) was prepared by treatment of **1** with trifluoromethyl trimethylsilane ($TMSCF_3$) in the presence of tetrabutylammonium fluoride hydrate ($TBAF{\bullet}3H_2O$) at room temperature, followed by hydrolysis of O-Si bond. The reaction selectively yielded α-isomer of **63** in 78% yield.[67a] The preference of α-CF_3 configuration of C10 is probably due to the large size of the CF_3 group compared to the OH group, which repels the methyl group at C9. The elimination of OH group of **63** by treatment with $SOCl_2$ in pyridine at 0°C readily yielded **64**, but conventional dehydrations failed because of the low reactivity of OH group, which is deactivated by the electron-withdrawing CF_3 group. Unlike DHA, the reaction between **63** and SOX_2 (X = Cl, Br) at low temperature produced 10α-trifluoromethyl-10-halodeoxoartemisinin (**65a**, **65b**) stereoselectively in excellent yields. The bromodeoxoartemisinin **65b** converted to 10α-(trifluoromethyl)deoxoartemisinin (**66**) by the radical

reduction with *n*-Bu_3SnH in toluene under reflux conditions for 1 h in 75% yield; moreover, the radical reaction led to complete retention of the configuration of CF_3. However, the chlorodeoxoartemisinin **65a** was unreactive under the same radical reaction conditions. The *in vitro* antimalarial activity (IC_{50}) of **66** (6.2 nM) is similar to that of artemether (7 nM) against chloroquine-resistant W2 strain of *P. falciparum* (*Table x* (Appendix)). In replacement reactions with nucleophiles, **65b** was activated by the addition of stronger hydrogen bond donor but with less nucleophilicity such as 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). The intermediate carbocation is not planar. The stereoselectivity of the reaction was rationalized in terms of the fact that the β-approach of the nucleophile into an intermediate alkoxy carbenium ion (**70b**) is more favorable electronically and that the α-approach is sterically disfavored. (*Scheme 37*).[67c]



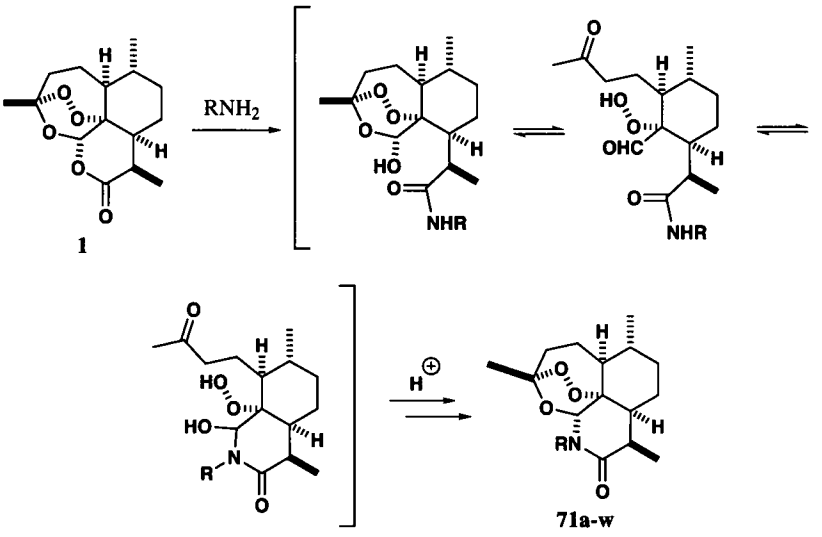
70a **70b**

Scheme 37

The optimized ratio of nucleophile and HFIP was found to be 2:1 in dichloromethane. When the nucleophile is MeOH, the yield of the HFIP-mediated coupling reaction was higher than that for a simple silver-assisted solvolysis reaction.[67c-d] Trifluoromethyl-substituted **67a-h** were prepared by the optimized condition in yields up to 89%. Under the simulated stomach acid conditions, half-life of these CF_3 substituted artemisinins is 12 to 40 times longer than DHA (half life time = 17h), which was measured by ^{19}F NMR spectroscopy.[67d] The biological activities of these fluorinated compounds *in vitro* are summarized in *Table x* (Appendix). In addition, CF_3 substituted glycal **64** is an interesting class of artemisinin derivatives because the glycal type of artemisinin derivatives showed generally higher biological activity than artemisinin.[67b,67e] The glycal **64** obtained from **63** were converted to **68** through allylic bromination with NBS in 90% yield. The allylic bromide **68** is stabilized by the electron-withdrawing CF_3 group. The reaction of **68** with nucleophiles provided C16 substituted glycals **69a-p** as shown in *Scheme 36*. In the SAR study of C16 substituted CF_3 glycals, a carboxylic ester group at C16 decreased the biological activities (*Table y* (Appendix)).

6. Aza-artemisinins

Aza-artemisinins are derivatives of artemisinin in which the lactone ring is replaced by the corresponding lactam. They can be easily prepared by the treatment of artemisinin with amines in methanol at room temperature, followed by the sulfuric acid/ silica gel treatment. Their biological activities are listed in *Table aa* and *Table bb* (Appendix).[68]



Synthesis of Aza-artemisinins from Artemisinin

Scheme 38

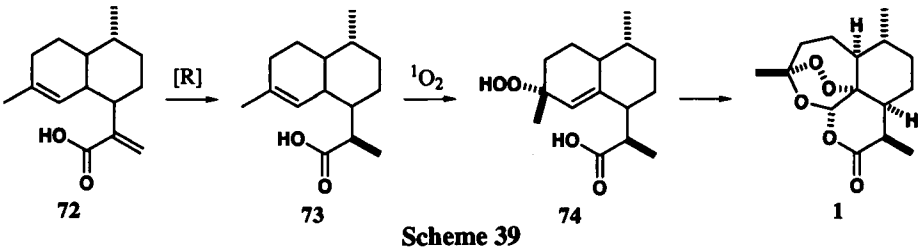
7. Artemisinin Derivatives from Artemisinic Acid

a) Artemisinin and Hydroxylated Artemisinins

Chemical modification of artemisinin currently provides cheap and convenient routes to prepare artemisinin derivatives as shown in the previous sections. A major problem is the limited supply of artemisinin which must be extracted from the dried herb. Alternative approaches would involve the total synthesis and semi-synthesis from biosynthetic precursors such as artemisinic acid (**72**).[9a,69] The total chemical synthesis of artemisinin and its derivatives has been reviewed by Xu.[9a] Although the total synthesis of artemisinin is a significant academic achievement, it will not be practical in the pharmaceutical industry. On the other hand, semi-synthetic routes may become more practical, if appropriate synthetic precursors are easily available in a large quantity. Recently, bacteria have been genetically engineered to produce artemisinic acid. Artemisinin can be prepared from artemisinic acid in only a few steps.[70] This new source of artemisinic acid would attract more organic chemists to engage in artemisinin research in order to develop new artemisinin derivatives.

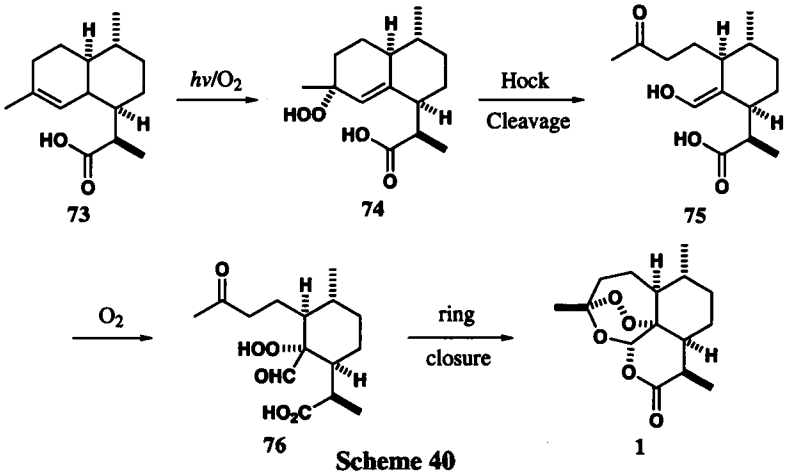
Several groups have reported the conversion of artemisinic acid to artemisinin and its derivatives. The synthetic route of artemisinin involves the reduction of artemisinic acid (**72**) to dihydroartemisinic acid (**73**), followed by the treatment with singlet oxygen and additional air oxidation to afford artemisinin (**1**). (*Scheme 39*)

Brown and co-workers proposed that artemisinin is naturally produced from dihydroartemisinic acid (**73**) by spontaneous auto-oxidation.[71] According to the proposed pathway, the



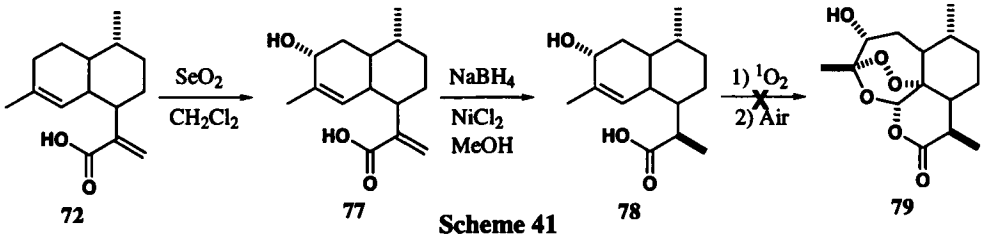
Scheme 39

transformation of artemisinic acid to artemisinin involves initial oxygenation of the C4,5 double bond in dihydroartemisinic acid **73** to yield the tertiary allylic hydroperoxide which then undergoes Hock cleavage leading to the enolic intermediate **75**. This enol **75** is highly susceptible to auto oxidation by oxygen resulting in the presumed vicinal hydroperoxy aldehyde intermediate **76** which then finally undergoes cyclization to the 1,2,4-trioxane ring of artemisinin (*Scheme 40*).



Scheme 40

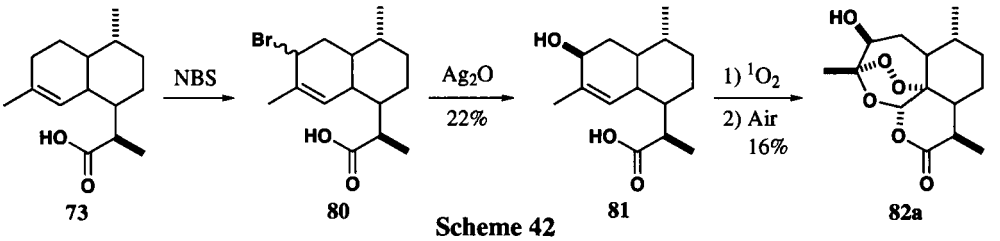
Acton group synthesized 3-hydroxy-artemisinin to investigate the biological activities of hydroxylated metabolites of artemisinin.[70] Initial attempts to prepare 3α-hydroxyartemisinin (**79**) failed in the final step of air oxidation and cyclization (*Scheme 41*), but 3β-hydroxyartemisinin (**82**)



Scheme 41

was successfully synthesized through the route shown in *Scheme 42*. Dihyroartemisinic acid (**73**) was converted to 2-bromo-dihydroartemisinic acid (**80**) as a mixture (α:β = 1:2) by the treatment with NBS. After hydrolysis with Ag_2O, 2-hydroxydihydroartemisinic acid (**81**) was treated with

singlet oxygen, followed by subsequent air oxidation to transform to **82a** in a very low yield. A similar approach was applied to synthesize artemisinin derivatives with a substitutent at C13 position, starting from substituted artemisinic acid.[72]



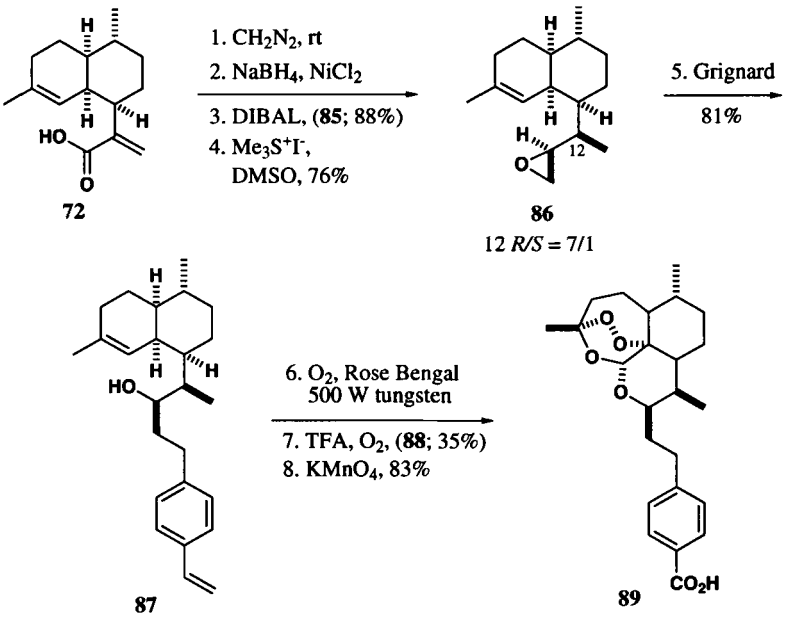
73 80 81 82a

Scheme 42

Table z (Appendix) shows biological activities of acetylated **82a** (**82b**) and artemisinin derivatives with a substituent at C13 (**83a-f**) together with related artemisinin derivatives (**84a-f**) that are prepared from artemisinin.[65c,72]

b) Carba-artemisinins from Artemisinic Acid

Jung *et al.* reported the synthesis of carba-artemisinin derivatives from artemisinic acid. Water soluble (+)-deoxoartelinic acid (**89**) was synthesized as a possible substitute for artelinic acid (**10**, R = -CH_2-Ph-COOH) (*Scheme 43).* The carba-artelinic acid **89** showed a strong antimalarial activity comparable to that of artelinic acid (*Table cc* (Appendix)).[73a]



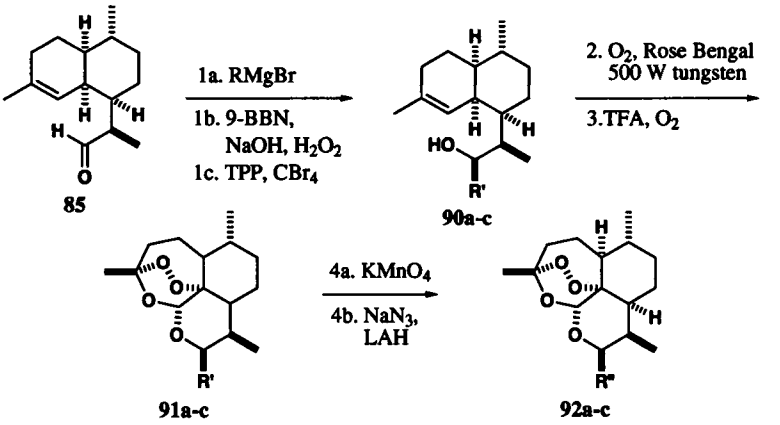
72 86 87 89

12 *R/S* = 7/1

Preparation of C10-Deoxoartelinic Acid

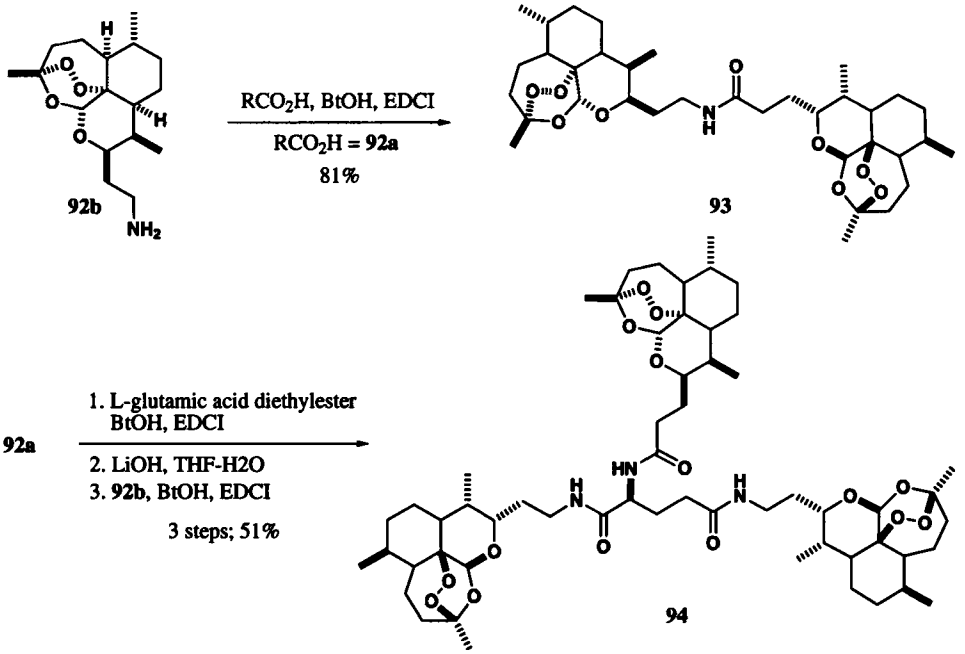
Scheme 43

In the synthesis of **89**, artemisinic acid (**72**) was converted in good yields to the epoxide **86** through a four-step procedure that involved methylation of the acid, reduction of the olefin with $NiCl_2 \cdot 6H_2O$, treatment with DIBAL, then reaction with trimethylsulfonium iodide. The *R/S* ratio of C12 was 7:1. The ring opening of **86** with 4'-vinylbenzylmagnesium chloride yielded the alcohol **87** (81%). Ring closure of **87** under photo-oxidation conditions afforded the corresponding 4'-vinylhomobenzyl-C10-deoxoartemisinin (**88**) with β-configuration of C10. Oxidation with $KMnO_4$ gave carba-artelinic acid **89** in 83% yield. In 2003, Jung and collaborators also synthesized various types of carba-artemisinin monomers, dimers and trimers, starting from artemisinic acid. These compounds have shown promising anti-tumor activities.[73b]



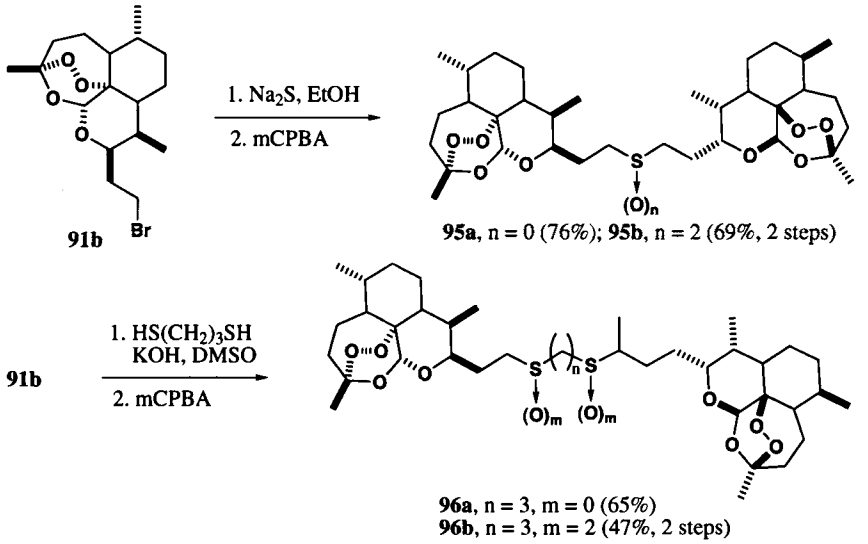
85 **90a-c** **91a-c** **92a-c**

a, R = -CH=CH$_2$; **b**, R = -CH$_2$CH=CH$_2$; **c**, R = -(CH$_2$)$_2$CH=CH$_2$;
90a, **91a**, R' = -(CH$_2$)$_2$CH=CH$_2$; **90b**, **91b**, R' = -(CH$_2$)$_2$Br; **90c**, **91c**, R' = -(CH$_2$)$_4$Br;
92a, R" = -(CH$_2$)$_2$CO$_2$H; **92b**, R" = -(CH$_2$)$_2$NH$_2$; **92c**, R" = -(CH$_2$)$_4$NH$_2$



Scheme 44-1

Scheme 44 shows the synthesis of various deoxo- and carba-artemisinins reported by Jung *et al.* The aldehyde **85** is a good precursor for homologated alcohols (**90a-c**) by the reaction with Grignard reagents with appropriate functional group conversions. The reaction proceeded with moderate yield. Photo-oxygenative cyclization of the intermediate alcohols yielded carba-artemisinins (**91a-c**) in 25-40%. Oxidation of **91a** with $KMnO_4$ provided the corresponding acid **92a** in 73% yield. **91b** and **91c** were treated with NaN_3 followed by the reduction with $LiAlH_4$ to give the corresponding amines **92b** (78%) and **92c** (79%), respectively. The coupling reaction between the acid **92a** and the amine **92b** in the presence of ethyl dimethylaminoethylcarbodiimide (EDCI) and *n*-hydroxybenzotriazole (BtOH) provided the dimer **93** (81%). The coupling reaction with glutamic acid yielded the trimer **94** through a 3 steps procedure (51%). Carba-artemisinin dimers linking with alkyl sulfide or sulfone (**95a-b, 96a-b**) were obtained *via* two successive nucleophillic displacements in good yield (*Scheme 44*).[73b]

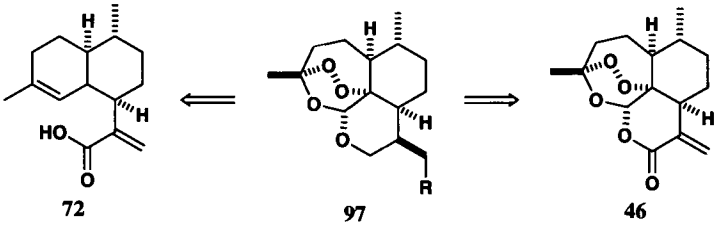


Synthesis of Carba-artemisinin Monomers, Dimers and Trimers from Artemisinic Acid.

Scheme 44-2

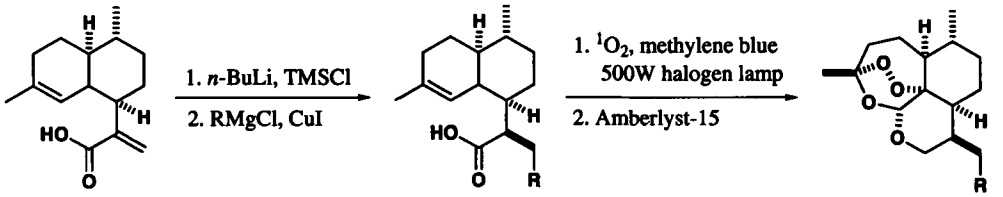
c) Deoxo-artemisinins from Artemisinin Acid

Derivatives of C10-deoxoartemisinin, where oxygen functionality at C10 is removed, can be synthesized from either artemisitene (**46**) or artemisinic acid (**72**) as shown in *Scheme 45*.



Scheme 45

Avery's synthesis of deoxoartemisinins *via* artemisitene shown in *Scheme 35* has already been discussed in the previous section. Jung *et al.* developed a new synthetic route for the production of C10-deoxo-C16-substituted artemisinins, starting from artemisinic acid (*Scheme 46*).[74a] Artemisinic acid (**72**) was converted to 13-substituted dihydroartemisinic acid (**98a-b**) by nucleophillic addition with Grignard reagent, followed by photo-oxygenative cyclization, to give the corresponding deoxoartemisinins **97a** and **97b** in moderate yields.



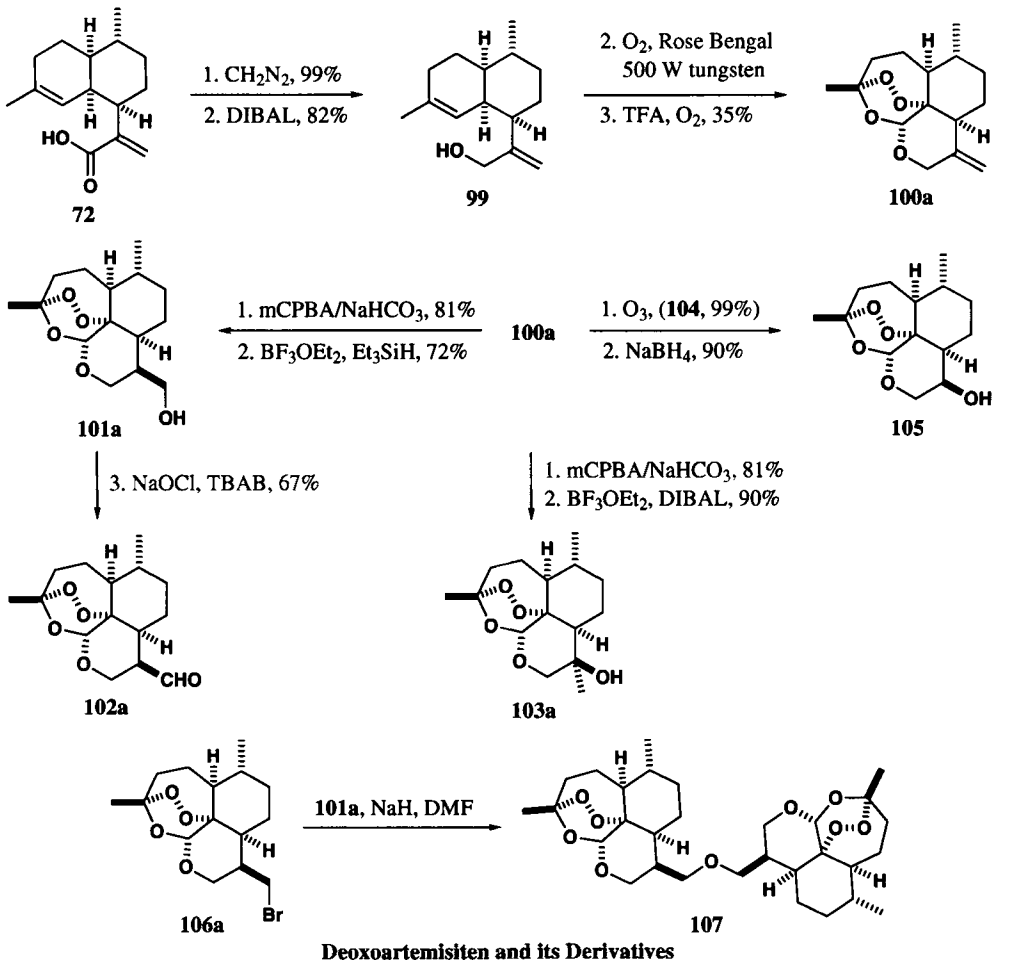
72 **98a-b** **97a-b**

a, R = -CH_2CH_2Ph; **b**, R = -$(CH_2)_2C_6H_4Cl$-*p*

Scheme 46

The same group applied the same strategy to prepare a number of deoxo-artemisinin derivatives.[74b] The alcohol **99** was obtained by esterification of acid **72** with diazomethane, followed by reduction with DIBAL (81%). The photo-oxidative cyclization provides a 35% yield of deoxoartemisitene (**100a**), which is a good synthon for modification at C16 of artemisinin. Ozonolysis of **100a** with 60% ozone yielded deoxoartemisitone (**104**) through spontaneous cleavage of ozonide intermediate without a reducing agent. Alternatively, the reduction of ozonide with $NaBH_4$ gave the corresponding 9-β alcohol **105** as the predominant product. However, attempts to prepare **101a** by hydroboration of **104** using 9-BBN or catecholborane failed. An alternative route to **101a** *via* a two-step procedure involved the epoxidation and BF_3•OEt catalyzed ring opening. Further modification of **101a** and **100a**, or coupling with **106a** provided deoxoartemisinins with a functionality of C16 such as **102**, **103a**, and **107**, in good yield (*Scheme 47*).[74b]

Deoxoartemisitene and its derivatives shown in *Scheme 47* have shown a good correlation between the structure and antimalarial activity (SAR). If the compound has electron-withdrawing group at C16 position, the antimalarial activity decreased. Deoxoartemisitene derivatives with β-configuration at C16 showed strong biological activities while the corresponding α-isomers showed only poor activities. C16-Hydroxy- or bromo-C10-deoxoartemisinins showed strong antimalarial activities, comparable to artether, against chloroquinin sensitive as well as to chloroquinin resistant *Plasmodium* (*Table ee*, Appendix)).



Deoxoartemisiten and its Derivatives

Scheme 47

II. CONCLUSION

Artemisinin, isolated from a traditional Chinese herb, *Artemisia annua L*, has been used as a folk medicine for centuries. Traditional medicines or folk medicines are difficult to study scientifically because they are generally a complex mixture of biologically active components. Artemisinin represents a rare example where rigorous scientific tools and methodologies can be applied to understand and possibly improve the biological activity of a folk medicine. Since the discovery of artemisinin, an increasing number of natural endoperoxides are being discovered in various plants, mushrooms and other sources.[75] Some of them show promising anti-cancer and other biological activities. Mechanistic studies of artemisinin suggest that these natural endoperoxides may constitute a new class of bioactive molecules that are activated by intracellular redox active ions such as iron.

Organic peroxides are generally unstable, and have not been considered important in medicine until recently. Artemisinin is a remarkably stable endoperoxide compound, and can be stored on shelf for many years without noticeable decomposition. Nevertheless, the endoperoxide group in artemisinin provides a unique challenge for synthetic organic chemists. Many redox active metals, for example, cannot be used in the transformation of artemisinin derivatives. However, a surprising array of reactions have been found to be compatible with the endoperoxide group as shown in this review. Organometallic reagents, Lewis acid catalysts and strong bases are all routinely used for the synthesis of artemisinin derivatives. Some of the synthetic methodologies developed for artemisinin derivatives could be applied to other natural endoperoxides. Synthetic derivatives of these natural endoperoxides would further advance our knowledge on the mechanism of action of this class of molecules, and facilitate the development of new pharmaceutical products based on the endoperoxide group.

Acknowledgments.- This work was supported by the Akibene Foundation. We thank Profs Henry Lai and Narendra Singh for valuable discussions on the biological activities of artemisinin derivatives.

III. APPENDIX

Tables a-ee. Antimalarial Activity and Cytotoxicity of Artemisinin Derivatives

Table a. *Cytotoxicity of Artemisinin analogs*

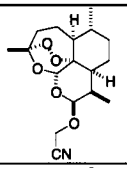
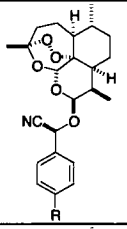
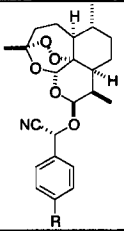
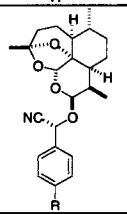
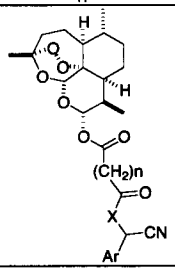
No.	Structure	Activity, IC_{50}, nM		*References*
		P388	A549	
3a		1,855	79,432	*48a, 48b*
3b, R = -H **3d**, R = -Br		238 12	1,227 47	
3c, R = -H **3e**, R = -Br		48 11	662 39	
3f, R = -Br		24,200	41,900	
n = 2, 4, 5, 7; X = -O, -NH, -NMe; Ar = aryl-		Essentially non-toxic		

Table b. *Antimalarial Activity of Artemisinin analogs*

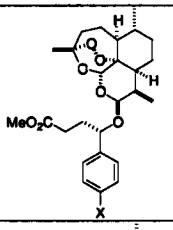
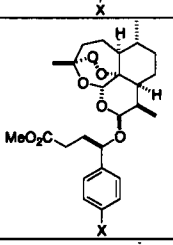
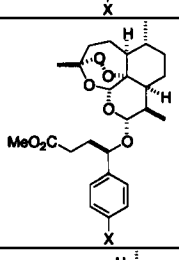
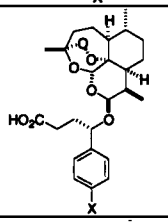
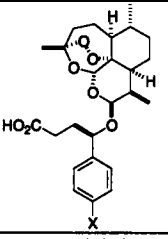
No.	Structure	Activity, IC_{50}, ng/mL		*References*
		D6	W2	
4a, X = -Cl **4b**, X = -F **4c**, X = -Br		0.90 0.62 1.01	0.79 0.49 0.62	
4d, X = -Cl **4e**, X = -F **4f**, X = -Br **4g**, X = -OMe		0.73 0.43 0.67 0.83	0.63 0.40 0.54 0.65	
4h, X = -Cl		0.39	0.66	*49c*
4i, X = -Cl **4j**, X = -F **4k**, X = -Br		2.40 2.33 1.36	1.26 0.83 0.42	
4l, X = -Cl **4m**, X = -F **4n**, X = -Br **4o**, X = -OMe		0.38 2.20 0.41 3.83	0.36 1.34 0.42 3.45	
Control	Artemisinin Artelinic acid	3.91 4.07	2.14 1.38	

Table c. *Antimalarial Activity of Artemisinin analogs*

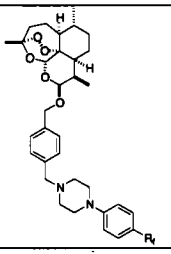
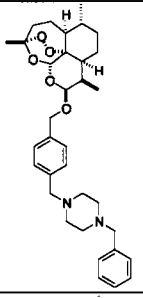
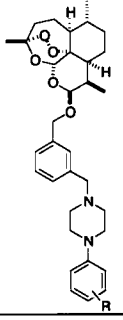
No.	Structure	Activity, IC_{50}, nM		*References*
		HB3	K1	
5a, R_f = -F **5b**, R_f = $-CF_3$		2.3 8.1	6.3 12.5	*49d*
5c		1.8	3.8	
5d, R = -H **5e**, R = $-NO_2$-*p* **5f**, R = -Cl-*p* **5g**, R = $-CF_3$-*p* **5h**, R = -F-*p*		3.4 4.3 - - 12.6	6.6 4.3 13.3 22.5 12.5	
control	Artemisinin Artemether	- 9.2	12.5 6.5	

Table d. *Antimalarial Activity of Artemisinin analogs*

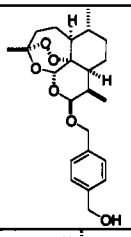
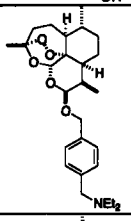
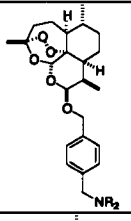
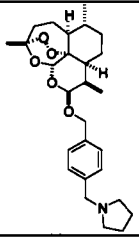
No.	Structure	Activity, IC_{50}, nM		*References*
		HB3	K1	
5i		4.2	4.4	*49e*
5j		3.1	1.4	
5k, NR_2 = morphorinyl **5l**, NR_2 = piperidinyl		50 12.2	35 45	
5m		2.3	2.3	
Control	Artemisinin	7.3	6.4	

Table e. Antimalarial Activity of Artemisinin analogs

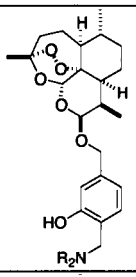
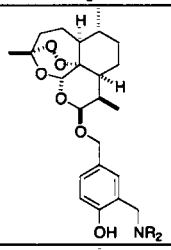
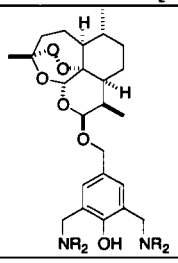
No.	Structure	Activity, IC_{50}, ng/mL		*References*
		NF54	K1	
5n, R = -Me		NA	NA	
5o, NR_2 = pyrrolidinyl		NA	NA	
5p, NR_2 = morphorinyl		NA	Na	
5q, R = -Et		0.36	0.18	
5r, R = -Bu^t, -H		0.17	0.25	
5s, R = -Me		NA	NA	*49f*
5t, R = -Et		0.29	0.26	
5u, NR_2 = pyrrolidinyl		NA	NA	
5v, NR_2 = morphorinyl		NA	NA	
Control	Artesunate	1.2	1.2	

Table f. Antimalarial Activity of Artemisinin analogs

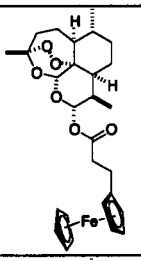
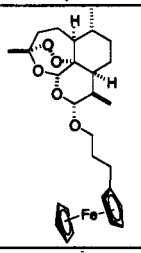
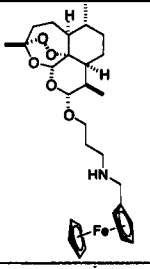
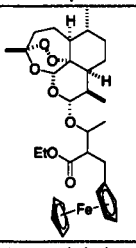
No.	Structure	Activity, IC_{50}, nM		*References*
		HB3	Dd2	
5w		10	32	*49g*
5x		36	86	
5y		12	14	
5z		21	45	
Control	Artemisinin DHA	7 5	13 5	

Table g. *Cytotoxicity of Artemisinin analogs*

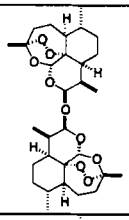
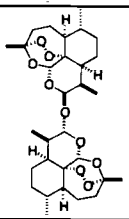
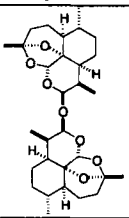
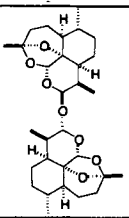
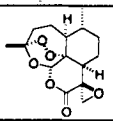
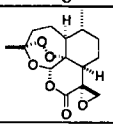
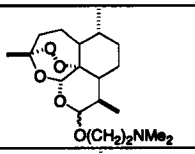
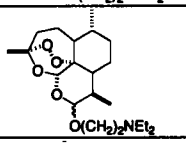
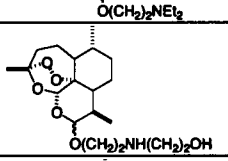
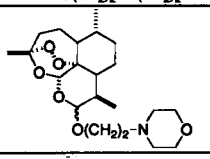
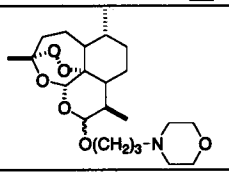
No.	Structure	Activity, IC_{50}, μM HeLa tumor cells	*References*
6a		0.11	*49h*
6b		2.0	
6c		8.9	
6d		99.8	
6e		12.7	
6f		100	
Control	Artemisinin deoxoartemisinin	0.98 111	

Table h. *Antimalarial Activity of Artemisinin analogs*

No.	Structure	Activity, SD_{50}, mg/Kg/day *P. berhei*, K137	*References*
9a		1.61	*51a*
9b		1.74	
9c		1.67	
9d		1.61	
9e		1.82	
Control	Artesunate	6.33	

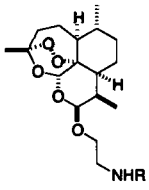
No.	Structure	Activity, IC_{50}, nM		*References*
		HB3	K1	
9f, R = -Me **9g**, R = -Et		2.7 4.1	2.4 4.1	*51b*
Control	Artemisinin	7.3	6.4	

Table i. *Antimalarial Activity of Artemisinin analogs*

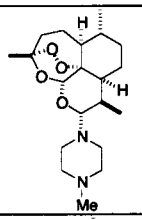
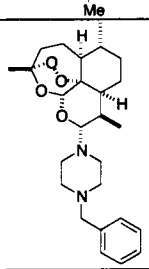
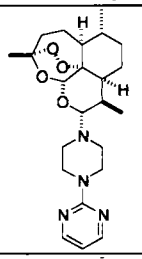
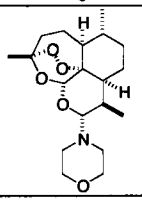
No.	Structure	Activity, EC_{50}, sc, mg/Kg		*References*
		P. berghei	P. yoelii	
19a		1.45	22.0	*22i*
19b		0.78	0.85	
19c		0.45	0.52	
19d		0.18	1.25	
Control	Artesunate	4.6	42	

Table j. *Antimalarial Activity of Artemisinin analogs*

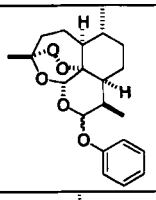
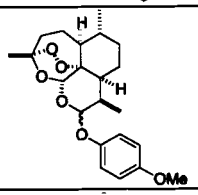
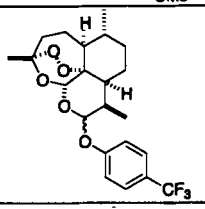
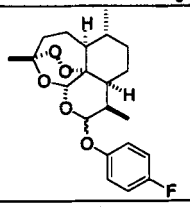
No.	Structure	Activity, IC_{50}, nM		*References*
		HB3	K1	
22a, C10-β **22b**, C10-α		3.24 2.61	3.66 2.97	*48a-b*
22c, C10-β **22d**, C10-α		- 3.32	4.58 3.86	
22e, C10-β **22f**, C10-α		3.90 3.42	5.29 4.62	
22g, C10-β **22h**, C10-α		2.88 4.04	4.58 5.70	
Control	Artemisinin Artemether Artether	9.67 3.42 0.2	11.15 4.55 0.9	

Table k. *Antimalarial Activity of Artemisinin analogs*

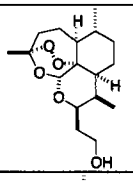
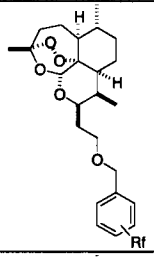
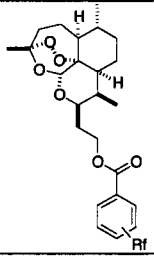
No.	Structure	Activity, IC_{50}, nM		*References*
		HB3	K1	
29a		3.51	6.67	*57a*
29b, Rf = -F-2 **29c**, Rf = -F-3 **29d**, Rf = -F-4 **29e**, Rf = -CF_3-2 **29f**, Rf = -CF_3-4		0.22 0.32 0.73 1.64 4.24	1.02 6.43 6.08 3.60 3.75	
29g, Rf = -F-2 **29h**, Rf = -F-3 **29i**, Rf = -F-4 **29j**, Rf = -CF_3-2 **29k**, Rf = -CF_3-4		0.53 0.35 0.69 0.64 0.59	1.12 3.78 1.92 4.70 14.24	
Control	Artemisinin DHA	3.04 1.04	3.60 2.20	

Table I. Antimalarial Activity of Artemisinin analogs

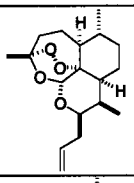
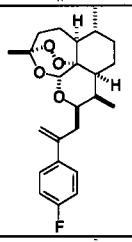
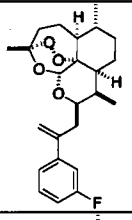
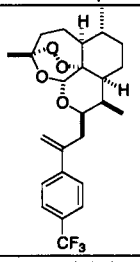
No.	Structure	Activity, IC_{50}, nM K1	*References*
28		7.2	*57b*
28c		3.9	
28e		2.5	
28f		1.8	
Control	Artemisinin Artmether	17.1 9.2	

Table m. *Antimalarial Activity of Artemisinin analogs*

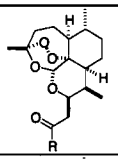
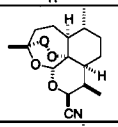
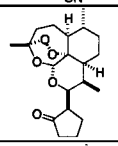
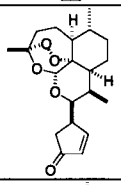
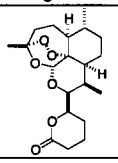
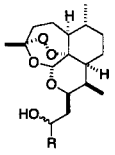
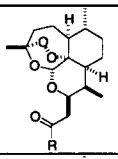
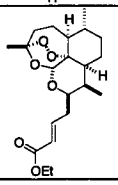
No.	Structure	Relative Activity		*References*
		D6	W2	
33a, R = -H **33b**, R = -Me **33c**, R = -Bu^t **33d**, R = -Ph		3.5 2.6 1.6 0.16	1.8 1.7 2.1 2.5	*58*
33e		1.1	1.5	
33f		0.91	1.6	
33g		0.77	0.18	
33h		2.2	1.4	
α: β **35a**, R = -Me **35b**, R = -Et **35c**, R = -Pr^i **35d**, R = -Bu^t **35e**, R = -CF_3		α: β 0.98:1.7 2.2:5.8 2.2:1.4 1.6:6.8 3.1:2.5	α: β 1.0:1.7 3.6:4.8 1.7:2.3 1.0:5.4 2.4:3.1	
35f, R = -Et **35g**, R = -Pr^i		1.0 1.8	1.3 2.1	
35h		1.1	1.4	
Control	Artemisinin	1	1	

Table n. *Antimalarial Activity of Artemisinin analogs*

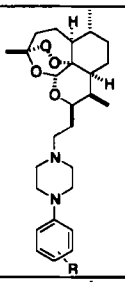
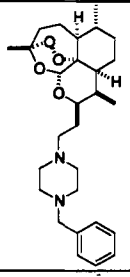
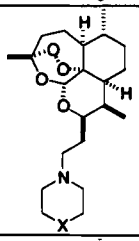
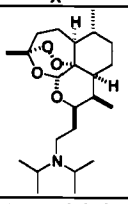
No.	Structure	Activity, IC_{50}, nM K1	*References*
36a, R = -H **36b**, R = -NO_2-*p* **36c**, R = -Cl-*p* **36d**, R = -CF_3-*m* **36e**, R = -F-*p*		3.15 4.29 8.16 6.19 5.96	*49d*
36f		4.22	
36g, X = O **36h**, X = CH_2		4.22 4.83	
36i		7.51	
Control	Artemisinin	12.5	

Table o. *Antimalarial Activity and Cytotoxicity of Artemisinin analogs*

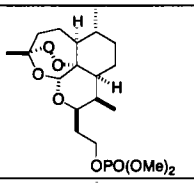
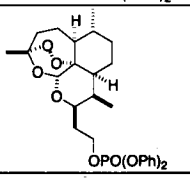
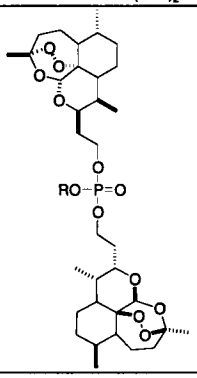
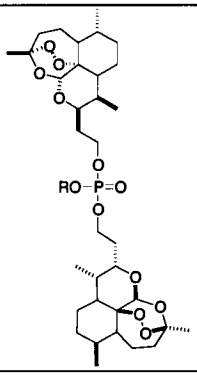
No.	Structure	Anticancer activity, IC_{50}, μM HL60	Activity, IC_{50}, nM HB3/K1	*References*
37a			-/2.2	
37b			-/3.1	
37c, R = Me **37d**, R = Ph		0.143 0.241	0.09/0.2 0.18/0.5	*59*
Control	Artemisinin DHA Doxorubicin	- 1.21 0.51	/14.512.3	
		Cytotoxicity, LC_{50}, μM Molt-4/MCF7		
37c, R = Me **37d**, R = Ph		33.5/72.2 >100/>100		

Table p. *Antimalarial Activity of Artemisinin analogs*

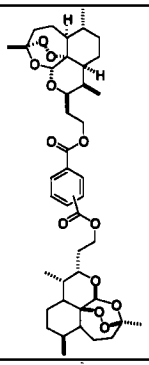
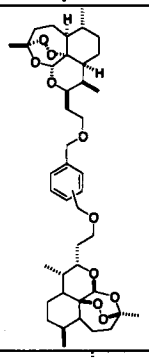
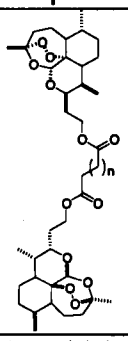
No.	Structure	Activity, IC_{50}, nM		*References*
		HB3	K1	
38a, para **38b**, meta **38c**, ortho		- - 1.6	4.6 42.2 2.6	*59*
38d, para **38e**, meta **38f**, ortho		- 2.1 1.3	2.4 2.7 2.9	
38g, n = 1 **38h**, n = 2		1.4 1.1	1.8 2.4	
control	Artemisinin	14.5	12.3	

***Table q**. Antimalarial Activity of Artemisinin analogs*

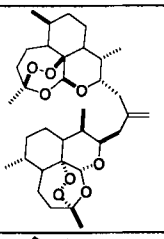
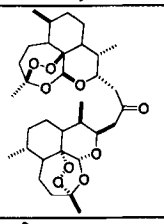
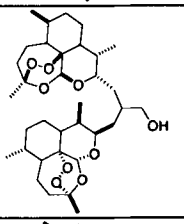
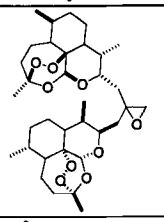
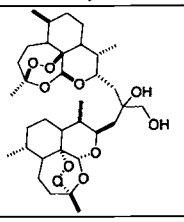
No.	Structure	Activity, IC_{50}, ng/mL	*References*
		NF54	
40a		24	*60*
40b		0.91	
40c		0.87	
40d		2.8	
40e		0.59	
Others		Near artemisinin	
Control	Artemisinin	9.0	

Table r. *Antimalarial Activity of Artemisinin analogs*

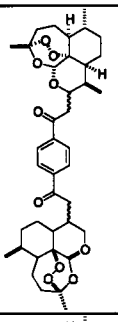
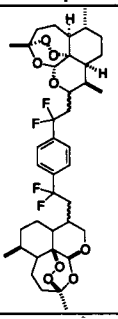
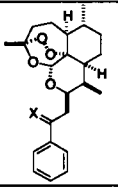
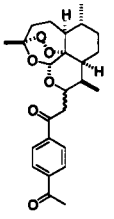
No.	Structure	Activity, IC_{50}, nM NF54	*References*
42a, 10β, 10β **42b**, 10α, 10β **42c**, 10α, 10α		1.9 1.7 3.9	*61*
42d, 10β, 10β **42e**, 10α, 10β		28 15	
42f, X = O **42g**, X = 2F		5.2 5.1	
42h, 10β **42i**, 10α		4.4 3.0	
Control	Artemisinin	7.6	

Table s. *Antimalarial Activity of Artemisinin analogs*

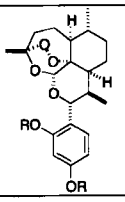
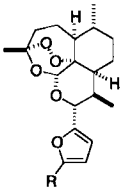
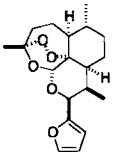
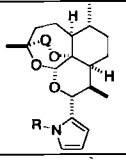
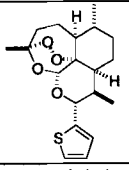
No.	Structure	Activity, IC_{50}, nM K1	*References*
44a, R = -Me **44b**, R = allyl-		4.2 6.6	*62*
44c, R = -H **44d**, R = -Me **44e**, R = -Et **44f**, R = -Bu^t		1.4 5.2 8.6 10	
44g		48	
44h, R = -Me **44i**, R = -CH_2Ph **44j**, R = -CH_2CO_2Et		4.6 16 9.1	
44k		9.2	
Control	Artemisinin	9.9	

Table t. *Antimalarial Activity of Artemisinin analogs*

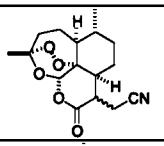
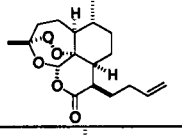
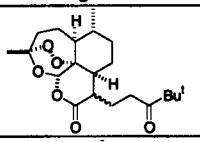
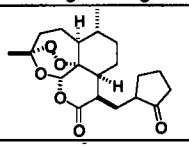
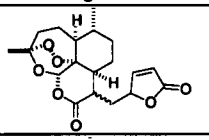
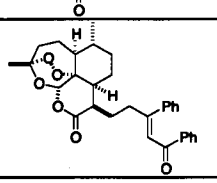
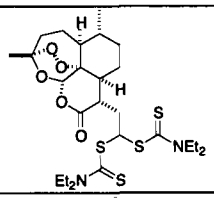
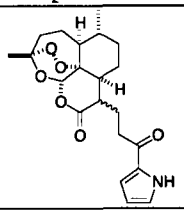
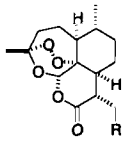
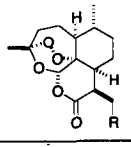
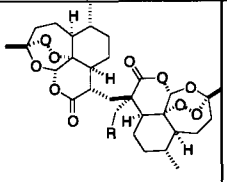
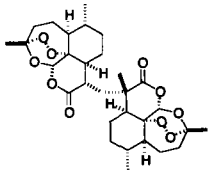
No.	Structure	Relative Activity		
		D6	W2	
47a		0.17	0.04	
47b		2.3	2.9	
47e, 9α **47c, 9β**		7.4 4.5	1.13 0.74	*63*
47d		0.47	0.29	
47f, 9α **47g, 9β**		0.06 0.33	0.03 0.04	
47f		6.2	0.55	
Control	Artemisinin	1	1	

Table u. *Cytotoxicity and Antimalarial Activity of Artemisinin analogs*

No.	Structure	Cytotoxicity, IC_{50}, μM	Activity, EC_{50}, nM	*References*
		KB/BC/Vero	K1	
48		2.5/2.4/6.6	1.9	*64*
49a, 9α **49b**, 9β		-	24.8 8.8	
50a, R = -Et **50b**, R = -Pr^n **50c**, R = -Bu^n **50d**, R = -$(CH_2)_3Ph$ **50e**, R = -C_6H_4F-*p*		 11/11/19 5.2/5.0/13 35/41/120	11.0 13.8 11.7 10.3 12.9	
51a, R = -Et **51b**, R = -Pr^n **51c**, R = -Bu^n **51d**, R = -$(CH_2)_3Ph$ **51e**, R = -C_6H_4F-*p*		 6.2/5.7/16 11/14/16	6.3 11.3 8.9 8.4 6.7	
52a, R = Et **52b**, R = -Pr^n **52c**, R = -Bu^n **52d**, R = -$(CH_2)_3Ph$ **52e**, R = -C_6H_4F-*p*		 23/36/63 5.7/1.2/2.4 7.7/7.4/1.1	4.4 4.3 3.9 3.4 2.3	
53		23/13/89	1.0	

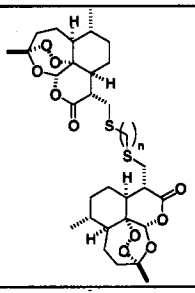
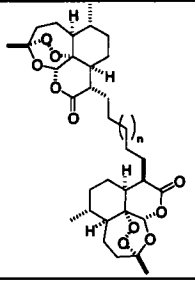
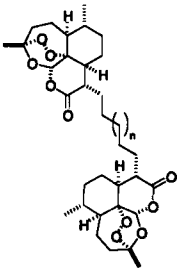
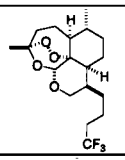
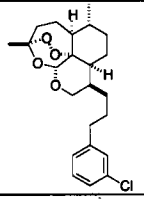
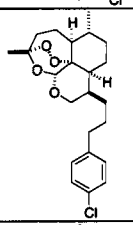
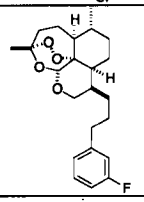
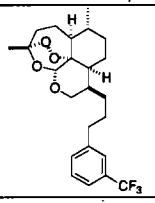
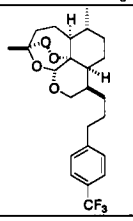
No.	Structure	Cytotoxicity, IC_{50}, μM KB/BC/Vero	Activity, EC_{50}, nM K1	*References*
54a, n = 2 **54b**, n = 3 **54c**, n = 4 **54d**, n = 5		-	7.4 13.0 5.7 12.0	*64*
55a, n = 2 **55b**, n = 3		1.8/1.6/10 0.76/0.36/2.8	10.5 0.91	
56a, n = 2 **56b**, n = 3		2.3/1.6/10 1.1/1.1/4.9	1.4 1.1	

Table v. *Antimalarial Activity of Artemisinin analogs*

No.	Structure	Activity, IC_{50}, ng/mL		*References*
		D6/W2	K1/NF54	
58b		12.46/8.87	-/-	*65a-b*
58c		7.55/21.6	10.07/18.27	
58d		1.9/2.6	-/-	
58e		8.28/26.83	11.56/41.76	
58f		8.48/30.32	12.00/35.60	
58g		28.13/58.01	39.55/101.52	

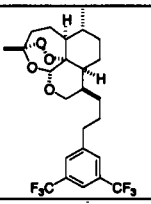
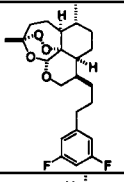
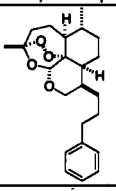
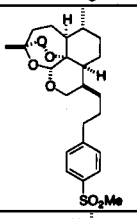
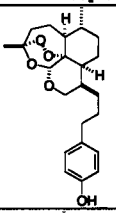
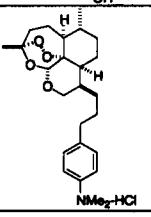
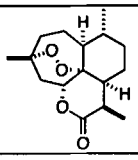
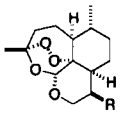
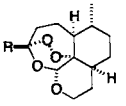
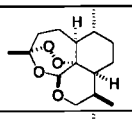
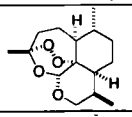
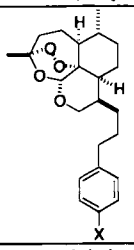
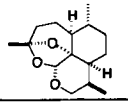
58h		0.78/7.11	4.06/-	
58i		0.82/6.50	3.20/-	
58j		4.7/1.3	-/-	
58k		30.13/20	-/-	
58l		7.9/4.7	-/-	
58m		16.5/14.3	-/-	
Control	Artemisinin	17.0/14.5		

Table w. *Antimalarial Activity of Artemisinin analogs*

No.	Structure	Relative Activity		*References*
		D6	W2	
59		38.8	12.6	*65d-g*
60a, R = -Me		659 (0.15)	567 (0.58)	
60b, R = -H		237	190	
60c, R = -Et		914	466	
60d, R = -Pr^n		473	550	
60e, R = -Bu^n		5826	2090	
60f, R = Pentyl-		170	145	
61a, R = -Et		10	10	
61b, R = -Pr^n		722	685	
61c, R = -Bu^n		653	556	
61d, R = -Bu^i		183	250	
61e, R = -$(CH_2)_4$Ph		336	380	
61f, R = -$(CH_2)_2$Ph		6	2	
61g, R = -$(CH_2)_2CO_2$Et		422	506	
61h, R = -$(CH_2)_2CO_2$H		0.09	0.09	
62		(1.72)	(0.78)	
60a		(2.87)	(2.79)	
58d, X = Cl		6991	3317	
58j, X = H		5073	2506	
Artemisinin		100 (1.21)	100 (2.33)	
DHA		0.04	0.11	
Control		(250)	(250)	

( ) = *In vitro* Antimalarial activity (IC_{50}, ng/mL)

Table x. *Antimalarial Activity of Artemisinin analogs*

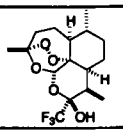
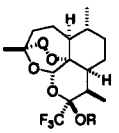
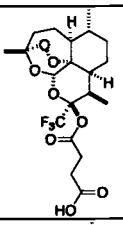
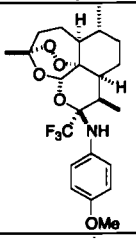
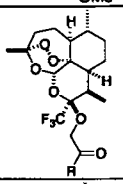
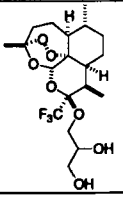
No.	Structure	Activity, IC_{50}, nM FCB1	*References*
63		3.1	*67c*
65a, R = -Me **65b**, R = -Et **65c**, R = -$(CH_2)_2OH$ **65d**, R = -CH_2CF_3 **65e**, R = -OH		0.8 3.3 0.9 8.3 13.2	
65f		4.1	
65g		12.3	
65h, R = -OH **65i**, R = -H		30.4 21.4	
65j		0.9	
Control	Artemether	3.5	

Table y. *Antimalarial Activity of Artemisinin analogs*

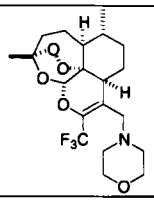
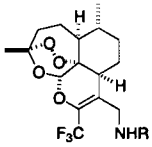
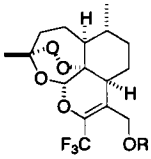
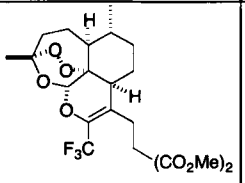
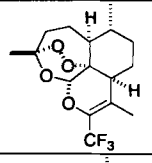
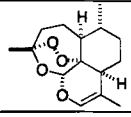
No.	Structure	Activity, IC_{50}, nM FCB1	*References*
69a		3.1	*67e*
69b, R = -Me **69c**, R = $-CH_2CH_2NH_2$ **69d**, R = N_3 **69e**, R = -H **69f**, R = $-NHSO_2CH_3$ **69g**, R = -Et		9.2 1.2 10.0 4.4 20.0	
69h, R = $-CH_2Ph$ **69i**, R = $-CH_2CH_2OMe$ **69j**, R = $-CH_2CH{=}CH_2$ **69k**, R = $-CH_2CH_2OH$ **69l**, R = $-COCH_3$ **69m**, R = -H **69n**, R = $-CH_2CHOHCH_2OH$ **69o**, R = -Et		20.0 2.7 6.0 2.4 1.7 7.5 3.7 25.0	
69p		1000	
64		6	
11		20	
Control	Artemether	3.5	

Table z. Antimalarial Activity of Artemisinin analogs

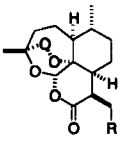
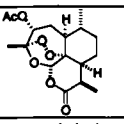
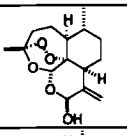
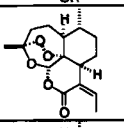
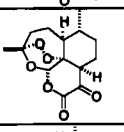
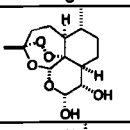
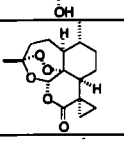
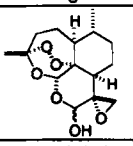
No.	Structure	Activity, IC_{50}, ng/mL		*References*
		D6	W2	
83a, R = -CN		18.4	8.4	*72*
83b, R = $-CO_2Me$		46	33	
83c, R = -OMe		75	59	
83d, R = $-SO_2Et$		500	500	
83e, R = $-CH_2NO_2$		0.68	0.26	
83f, R = $-CH(CH_3)NO_2$		12.8	3.86	
82b		11.1	2.07	
Control	Artemisinin	0.5	0.2	
84a		119	232	*65c*
84b		2.1	2.3	
84c		319	278	
84d		7.3	7.4	
84e		10.0	8.6	
84f		1.8	3.4	
Control	Artemisinin Artemisitene	1.89 5.30	0.95 7.44	

Table aa. *Antimalarial Activity of Artemisinin analogs*

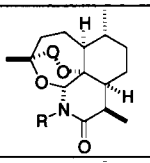
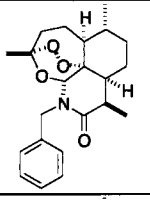
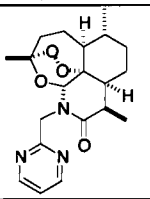
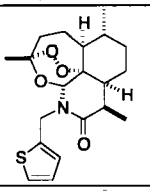
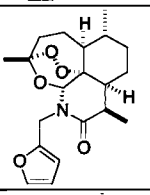
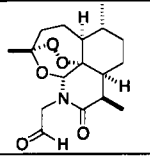
No.	Structure	Relative Activity FCR3	*References*
71a, R = -H **71b**, R = allyl- **71c**, R = -Pr^{i} **71d**, R = -Me		1 0.8 9.0 2.6	*68a*
71e		-	
71f		22	
71g		1.1	
71h		1	
71i		26	
Control	Artemisinin	1	

Table bb. *Antimalarial Activity of Artemisinin analogs*

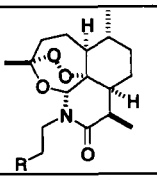
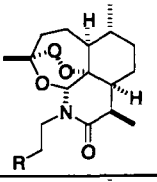
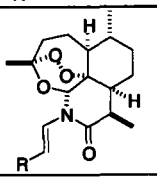
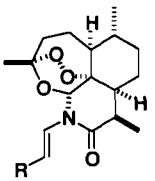
No.	Structure	Activity, IC_{50}, nM		*References*
		D6	W2	
71j, R = $-CO_2CH_3$		1.77	1.0	*68c*
71k, R = $-CO_2Et$		1.5	0.41	
71l, R = $-COCH_3$		3.2	3.0	
71m, R = -COPh		1.8	1.8	
71n, R = -CN		1.3	0.43	
71o, R = $-SO_3Ph$		1.7	0.96	
71p, R = $-SO_2Ph$		1.1	0.32	
71q, R = $-CH_2OH$		1.02	0.64	
71r, R = -CHO		0.49	0.18	
71s, R = $-CO_2Bu^t$		0.03	0.0012	
71t, R = $-CO_2CH_3$		2.0	1.2	
71u, R = $-COCH_3$		2.54	1.25	
71v, R = -(Z)-CN		2.7	1.7	
71w, R = $-CONMe_2$		0.39	0.35	

Table cc. *Antimalarial Activity of Artemisinin analogs*

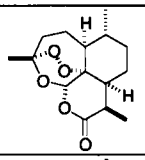
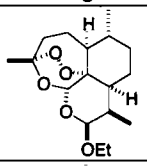
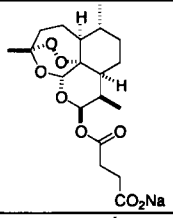
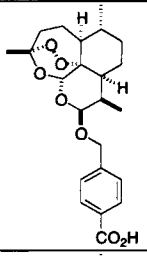
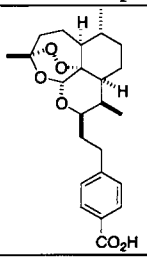
No.	Structure	Activity, ED_{50}, ng/mL		*References*
		3D7	K1	
1		2.9	0.7	*73*
24b		0.2	0.9	
Artesunate		0.2	0.6	
Artelinic acid		4.0	1.4	
88		1.1	0.6	

Table dd. *Cytotoxicity of Artemisinin analogs*

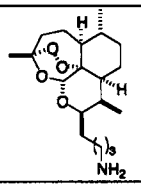
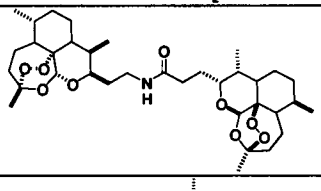
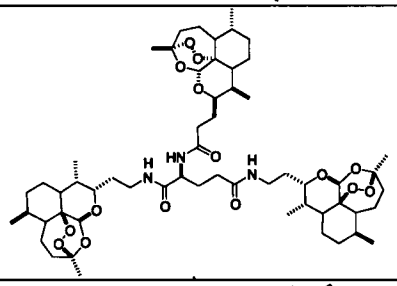
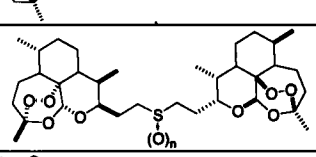
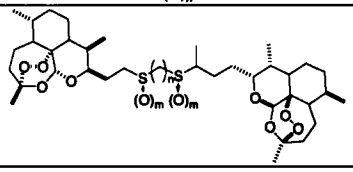
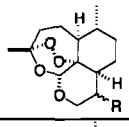
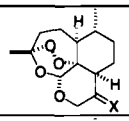
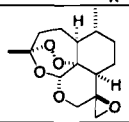
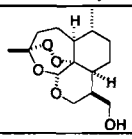
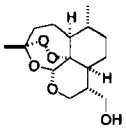
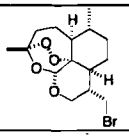
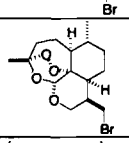
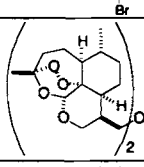
No.	Structure	Activity, IC_{50}, μg/mL P388/HT-29/MCF7	*References*
92c		6.18/2.20/0.02	*73*
93		10.40/0.69/0.005	
94		0.12/0.09/0.017	
95a, n = 0 **95b**, n = 2		0.4/0.24/0.017 5.6/0.38/0.025	
96b, n = 3, m = 2		8.4/0.38/5.6	
Control	Adriamycin Mitomycin Taxol	0.39/0.10/0.12 1.5/0.02/0.93 2.27/0.01/0.0001	

Table ee. *Antimalarial Activity of Artemisinin analogs*

No.	Structure	Activity, ID_{50}, ng/mL		*References*
		3D7	K1	
102a, R = -CHO **102b**, R = -CH_2OMs **102c**, R = -CH_2OTs **102d**, R = -CO_2H		inactive	inactive	*74*
100a, X = CH_2 **100b**, X = O		20	20	
100c		30	10	
101a		0.1	0.6	
101b		60	50	
106b		0.2	0.1	
106a		10	3	
107		40	20	
Control	Artemisinin Artether Artesunate	10 0.1 0.2	2 0.1 0.6	

IV. TERMINOLOGY IN APPENDIX

IC_{50}: The concentration of a drug required for 50% inhibition of cell replication *in vitro*.

EC_{50}: The plasma concentration required for obtaining 50% of the maximum effect *in vivo*.

ED_{50}: Pharmacologically effective for 50% of the population exposed to the drug.

LD_{50}: The drug dose that kills 50% of the animals tested

W2, A4: Chloroquine-resistant *P. falciparum.*

D6, NF54, HB3: Chloroquine-sensitive *P. falciparum.*

FCR3: Mildly chloroquine-resistant *P. falciparum.*

K1: Atovaquone-resistant *P. falciparum.*

Molt-4: Acute lymphoblastic leukemia cells

P388: Lymphocytic leukemia cells

MCF-7: Breast cancer cells

A549: Lung cancer cells

HeLa: Cervical cancer cells

HL60: Acute promyelocytic leukemia.

KB: Epidermoid carcinoma cells (a variant of HeLa)

VERO African green monkey fibroblastoid kidney cells

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