# *RECENT DEVELOPMENTS ON THE CHEMISTRY AND BIOLOGICAL ACTIVITY OF ARTEMISININ AND RELATED ANTIMALARIALS - AN UPDATE*

Asish K. Bhattacharya and Ram P. Sharma*#
Phytochemical Technology Division
Central Institute of Medicinal and Aromatic Plants
P.O. CIMAP, Lucknow-226015, India

**Abstract** - Developments taken place in the field of artemisinin and related anti-malarials during the last seven years have been reviewed.

## CONTENTS

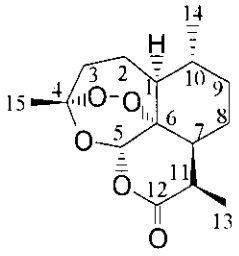


## I. INTRODUCTION

Malaria continues to affect millions of people throughout the world.[1,2] The currently used antimalarial agents are no longer effective against the drug resistant strains of *Plasmodium falciparum*.[3,4] In the recent past artemisinin (**1**) isolated from the Chinese plant *Artemisia annua* has been described as the most effective drug against the multidurg resistant strains of *P. falciparum*. Infact, the derivatives of artemisinin (**1**) are several fold more effective than it and are currently under clinical use in several countries. 1,2,4-Trioxane unit present in artemisinin (**1**) in conjunction with δ-lactone moiety makes it a

#Dedicated to the memory of Prof. Sir Derek Barton for his outstanding contribution to organic chemistry.

unique molecule in terms of its biological activity and chemical synthesis. Therefore, the past decade has witnessed a tremendous research activity on unfolding the mode of action of this unique structural feature, biosynthesis, new biological activities, neurotoxicity and development of new drugs-encompassing the 1,2,4-trioxane moiety. This review article is a supplement of our earlier review published in 1991.[5]



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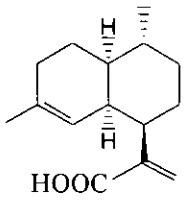

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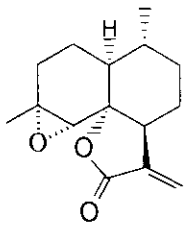

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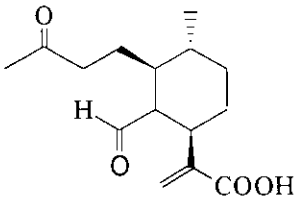
A considerable amount of work has been done on the chemical constituents of *A. annua*. Apart from the three predominant sesquiterpenes- artemisinin (**1**), artemisinic acid (**2**) and arteannuin B (**3**), all the three based on cadinane skeleton, we have reported thirteen compounds belonging to cadinane class in our earlier review.[5] Since then eleven more compounds have been reported from the plant *A. annua*. These are : 4,5-secocadinane (**4**), dihydroxycadinanolide (**5**),[6] artemisinin G (**6**),[7] dihydro-epideoxyarteannuin B



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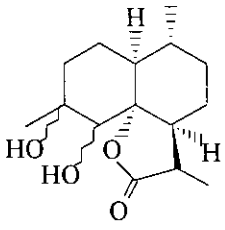

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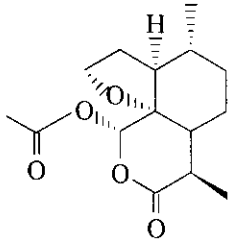

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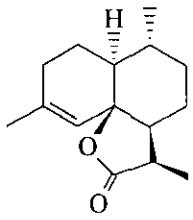
(**7**),[8] annulid (**8**), compound (**9**),[9] compound (**10**),[10] 4-isobutyrylcadin-4-en-11-ol (**11**), cadina-4,7(11)-dien-12-al (**12**), cadina-4(15),11-dien-9-one (**13**)[11] and α-hydroxysantonin (**14**).[12i] While the typing of our manuscript was in progress, Brown *et al.*[12ii] reported the isolation of compounds **A-G** from *A. annua*.

**Biosynthesis**

Through labelling studies Sangwan *et al.*[13] have suggested that artemisinic acid (**2**) might be a common precursor for arteannuin B (**3**) and artemisinin (**1**). Nair *et al.*[14] used the crude and semi cell free extracts of the leaf homogenates of the plant to prove that arteannuin B (**3**) is converted into artemisinin (**1**) and



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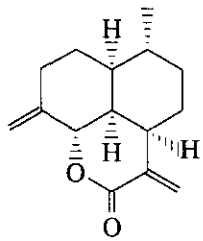

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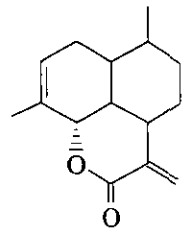

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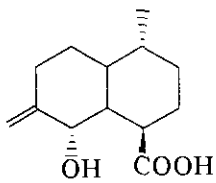

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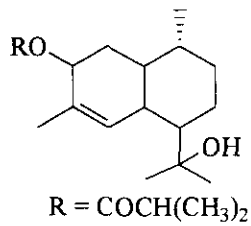

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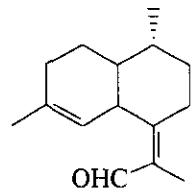

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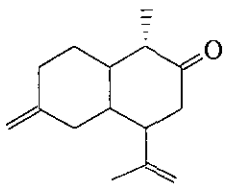

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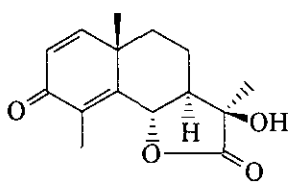

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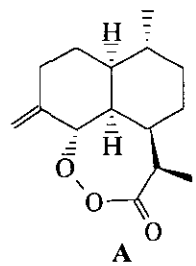

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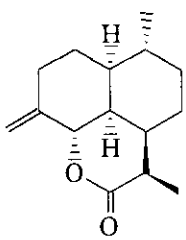

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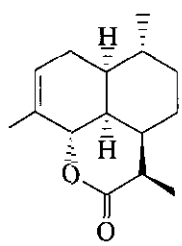

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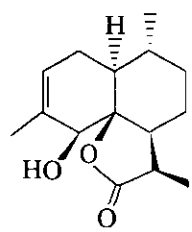

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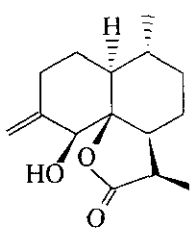

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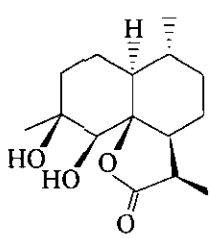

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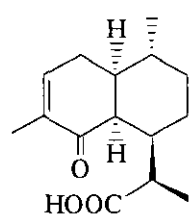
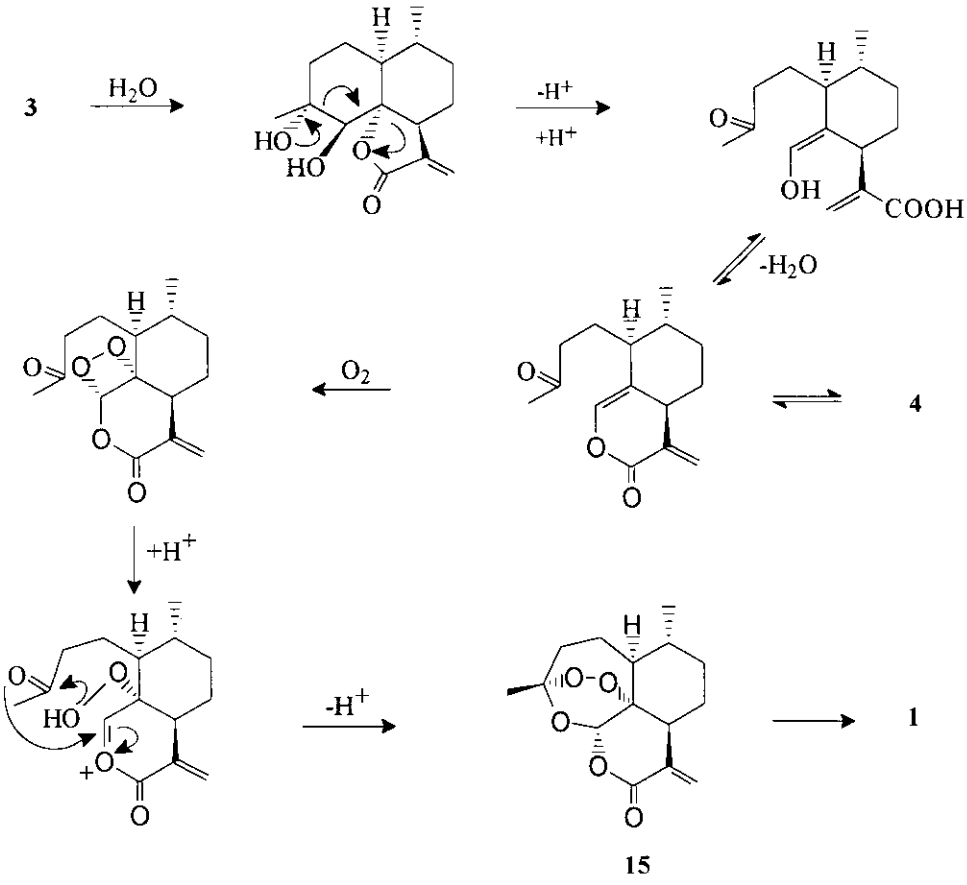


G

hence the former is the biogenetic precursor of the latter. This view has been further corroborated by Brown *et al.*[6] who isolated 4,5-secocadinane (**4**) and dihydroxycadinanolide (**5**) from the plant *A. annua*

and suggested the biosynthetic Scheme 1. Kim *et al.*[15] and Wang *et al.*[16] have also studied the biosynthesis of artemisinin (**1**).

Since artemisinin (**1**) is available in low yields from the plant *A. annua*, there has been a lot of interest in designing new strategies for its total synthesis as well as the partial synthesis from other major secondary metabolites especially artemisinic acid (**2**) and arteannuin B (**3**).

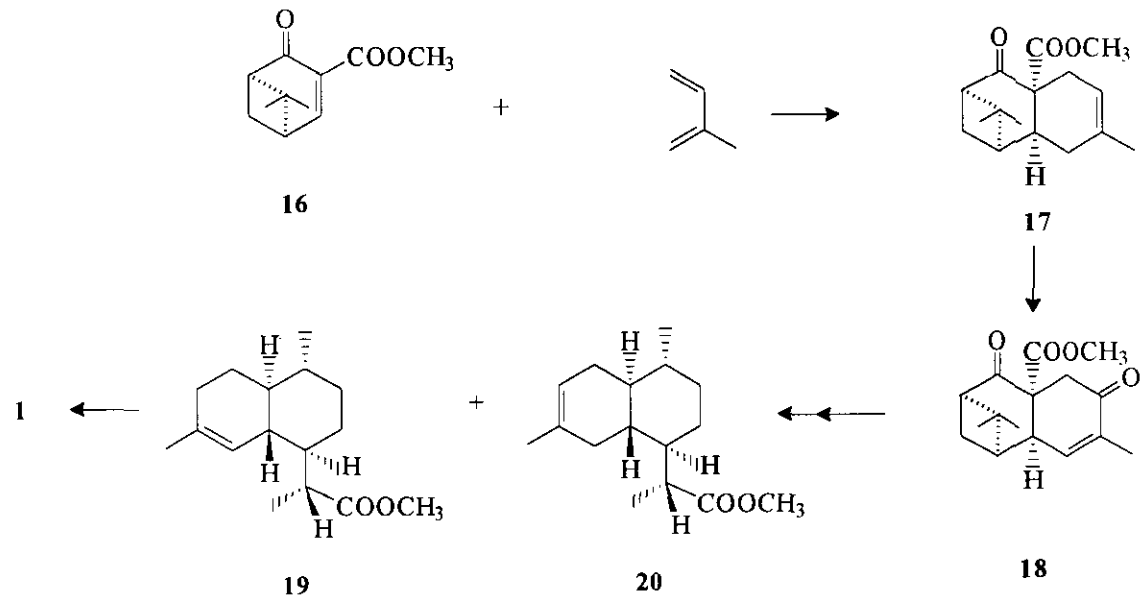



**Scheme 1**

## II. TOTAL SYNTHESIS OF ARTEMISININ

Two types of strategies have been used for the total synthesis of artemisinin (**1**). In the first, total synthesis of artemisinic acid (**2**) has been carried out stereospecifically which was then elaborated to artemisinin (**1**) using the photooxygenation methodology used by Roth and Acton[19] or Jung *et al.*[35] or Haynes *et al.*[44] In the second, the pioneering work of Avery *et al.*[22] describes the total synthesis of artemisinin (**1**) making use of ozonolysis of vinylsilanes as the key step.

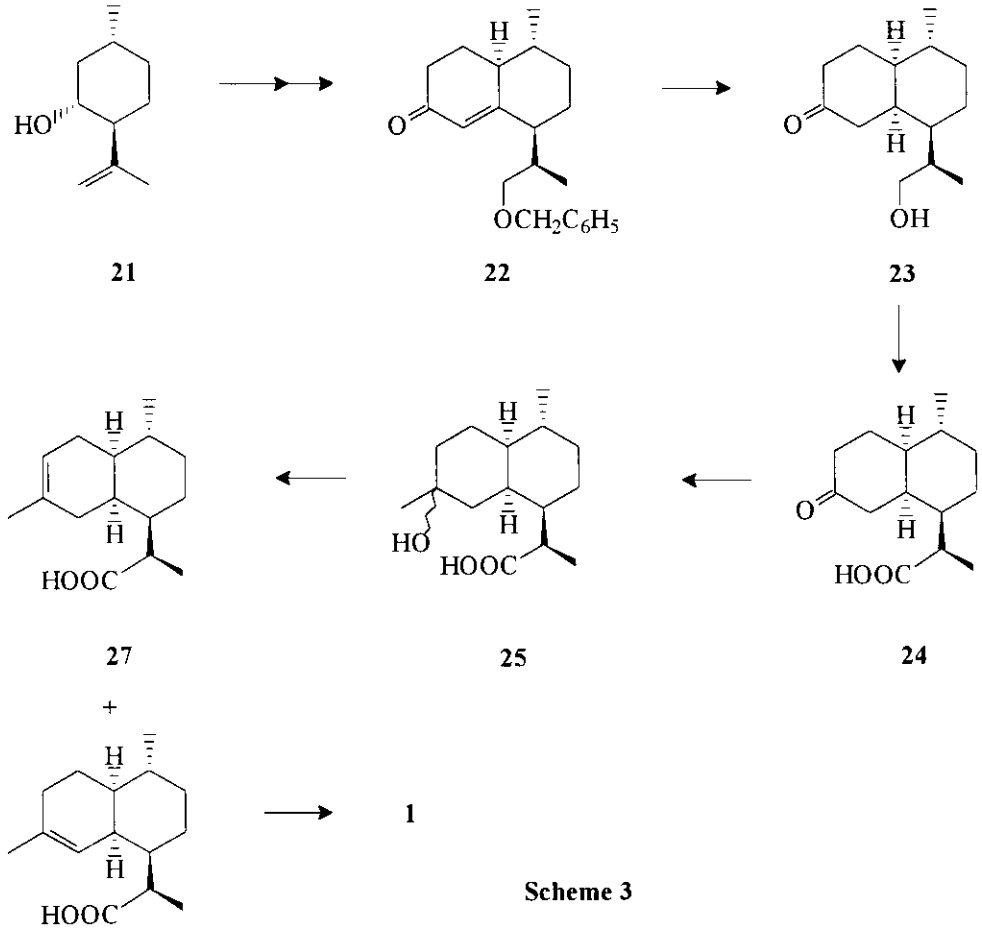
Liu *et al.*[17] in 1993 reported the total synthesis of artemisinin (**1**) using an intermolecular Diels-Alder approach. They began with the zinc chloride catalysed Diels-Alder addition of (+)-enone ester (**16**) readily prepared from (-)-β-pinene in three steps, to isoprene to give compound (**17**). Compound (**17**) on photooxygenation (tungsten lamp) with 5,10,15,20-tetraphenyl-21*H*-23*H*-porphine (TPP) in dichloromethane in the presence of acetic anhydride, pyridine and dimethylaminopyridine effected the migration of the double bond to the strategic position for the eventual incorporation of the peroxy ketal moiety to furnish the enedione (**18**) (90% yield). The key intermediates (**19**) and (**20**) were obtained from **18** in 12 steps in 70% yield and in a ratio of 9:5 with the desired isomer (**19**) predominating. When the mixture of compounds (**19**) and (**20**) was subjected to photooxygenation at room temperature in methylene chloride using methylene blue as a photosensitizer followed by treatment of the crude product with trifluoroacetic acid in petroleum ether in the presence of oxygen, artemisinin (**1**) was produced in 30% yield based on **19** (Scheme 2).




**Scheme 2**

Recently Constantino *et al.*[18] have reported the total synthesis of artemisinin (**1**) from (-)-isopulegol (**21**) (Scheme 3), a cheap and abundantly available monoterpene. They elaborated (-)- isopulegol (**21**) into dihydroartemisinic acid (**26**) after several steps which was transformed into artemisinin (**1**) using Roth and Acton procedure.[19] These authors prepared **22** from (-)-isopulegol (**21**) in five steps (21 % yield) using the procedure reported by Zhou *et al.*[20] The simultaneous reduction of the double bond of **22** and

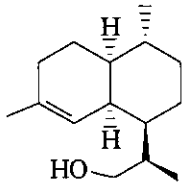
hydrogenolysis of the benzyloxy group were effected by hydrogenating it with 5% Pd-C in ethanol; a mixture of two isomers (**23a**) and (**23b**) was produced, from which the major isomer (**23a**) containing the *cis*-fused ring junction was isolated by column chromatography in 59% yield. Compound (**23a**) on oxidation with pyridinium dichromate furnished the keto acid (**24**) (91% yield). The carbonyl group of the keto acid (**24**) furnished a mixture of epimeric tertiary alcohols (**25a**) and (**25b**) on treatment with methyllithium. Treatment of the mixture of isomers of **25** with *p*-toluenesulfonic acid in benzene gave dihydroartemisinic acid (**26**) in 43% yield together with its regioisomer (**27**). Finally they converted dihydroartemisinic acid (**26**) into artemisnin (**1**) in 11% yield based on **24** by employing the already reported Roth and Acton procedure.[19]




**21** **22** **23** **24** **25** **27** + **26** → **1**

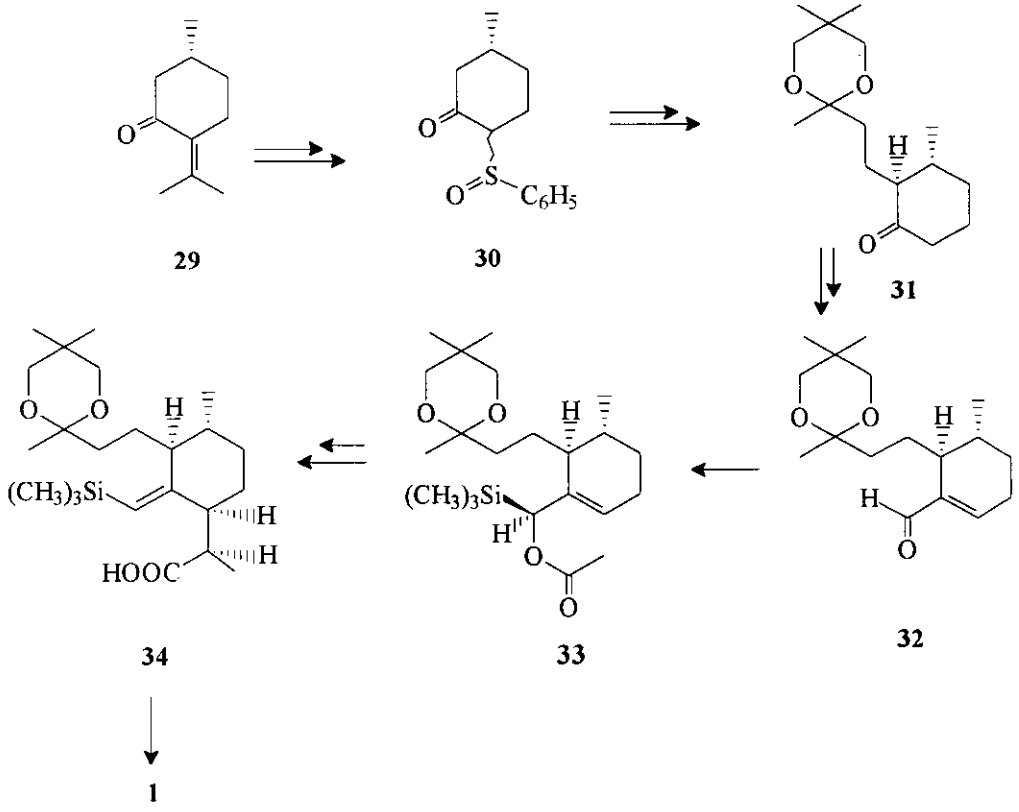
**Scheme 3**

Ravindranathan *et al.*[21] in 1994 reported synthesis of two precursors (**22**) and (**28**) from (-)-menthol which could be elaborated into artemisinin (**1**) using the procedure reported by Zhou *et al.*[20]



**28**

In 1992 Avery *et al.*[22] reported the total synthesis of artemisinin (**1**) starting from (*R*)-(+)-pulegone (Scheme 4). Compound (**29**) was elaborated to the known sulfoxide (**30**) followed by dianion alkylation and desulfurization to provide the *trans*-2,3-substituted cyclohexanone (**31**). Homologation to the cyclohexenecarboxaldehyde (**32**) was followed by a diastereoselective silyl anion addition to afford the silyl acetate (**33**). Tandem Claisen ester-enolate rearrangement and dianion alkylation furnished the fully functionalized vinylsilane (**34**). Finally, acid (**34**) was converted in a one-pot procedure involving sequential treatment with ozone followed by wet acidic silica gel to effect a complex process of dioxetane formation, ketal deprotection, and multiple cyclizations to artemisinin (**1**) in 35% yield.

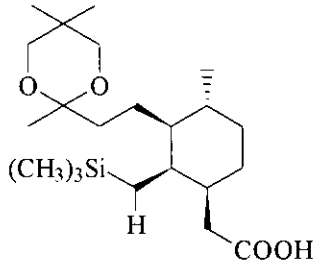


**Scheme 4**

## III. TOTAL SYNTHESIS OF ARTEMISININ ANALOGUES

Pioneering work of Avery *et al.*[23-26] on the total synthesis of artemisinin and its analogues culminated in the Structure Activity Relationship (SAR) directed synthesis and antimalarial activity of several novel artemisinin analogues.

They reported[23] the synthesis and antimalarial activity of tricylic compound (**36**), (-)-5-nor-4,5-seco-artemisinin (**45**), (+)-4,5-secoartemisinin (**46**) and desethanoartemisinin (**47**) with the aim of further defining SAR and improving these antimalarials. On treatment of hydroperoxy lactone[24] (**35**) with an excess of trifluoroacetic acid in acetone, 1,2,4-trioxane (**36**) was obtained in 73% yield. Synthesis of compounds (**45**), (**46**) and (**47**) was accomplished as depicted in Scheme 5. However, antimalarial efficacy of these analogues against the two drug-resistant strains of *P. falciparum* namely, Indochina (W-2) and Sierra Leone (D-6) showed that only analogue (**45**) was as effective as artemisinin (**1**) in D-6 clone and 2/3 as compared to artemisinin (**1**) in W-2 clone where as others showed poor antimalarial activity against both the strains.

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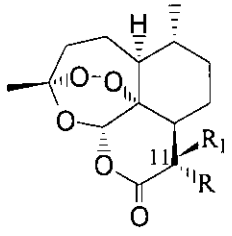
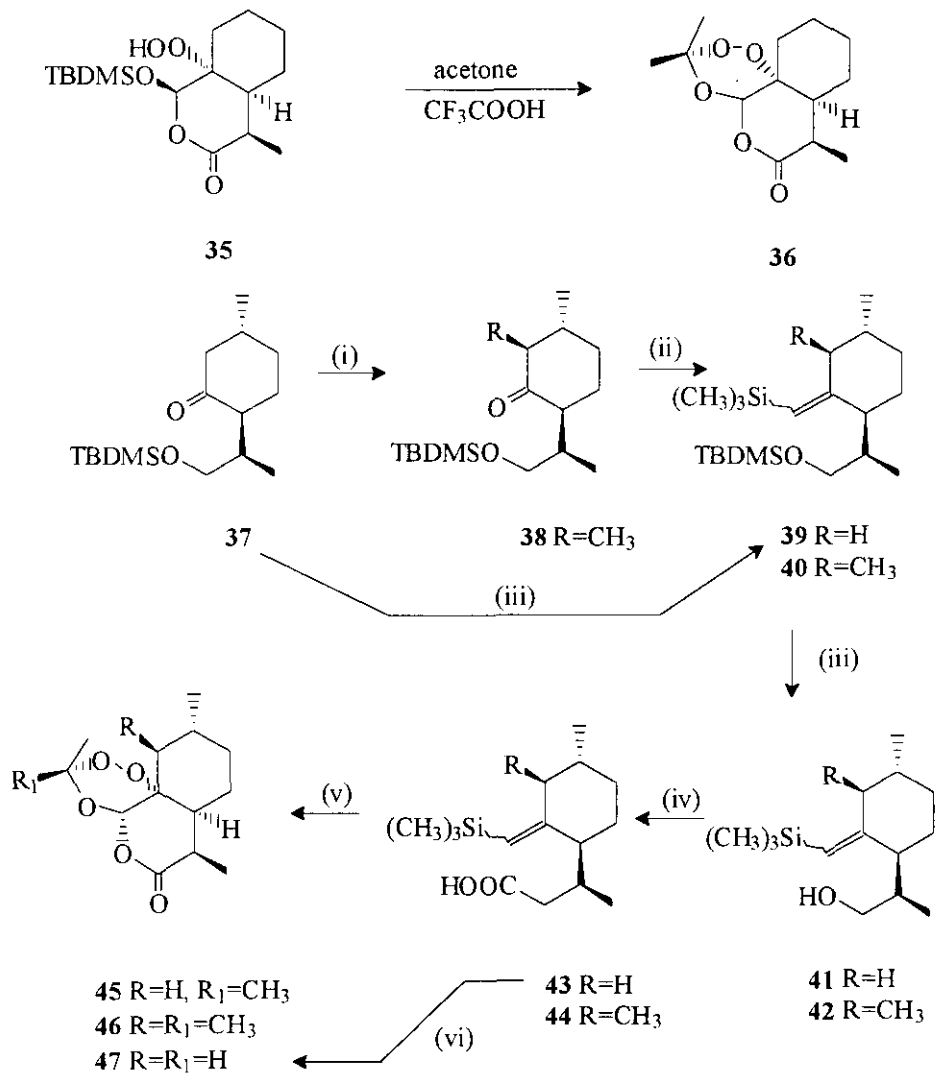



**49a-t**

**49a** R=$R_1$=H; **b** R=$CH_3$, R=H; **c** R=$R_1$=$CH_3$; **d** R=H, $R_1$=$C_2H_5$;
**e** R=H, $R_1$=$C_3H_7$(n); **f** R=H, $R_1$=$C_3H_7$(i); **g** R=H, $R_1$=$C_4H_8$(n);
**h** R=H, $R_1$=$C_4H_8$(i); **i** R=H, $R_1$=$C_5H_{11}$(n); **j** R=H, $R_1$=$C_5H_{11}$(i);
**k** R=H, $R_1$=$C_6H_{13}$(n); **l** R=H, $R_1$=$C_6H_{13}$(i); **m** R=H, $R_1$=$(CH_2)_{13}CH_3$;
**n** R=H, $R_1$=$C_2H_4C_6H_5$; **o** R=H, $R_1$=$C_3H_6C_6H_5$; **p** R=H, $R_1$=$C_4H_8C_6H_5$;
**q** R=H, $R_1$=$CH_2COOH$; **r** R=H, $R_1$=$CH_2CH=CH_2$; **s** R=(*E*)-$CH_3CH=CHCH_2$;
$R_1$=H; **t** R=(*Z*)-$CH_3CH=CHCH_2$, $R_1$=H

The same authors[25] reported the synthesis of C-11 β-substituted analogues (**49a-t**) *via* dianion alkylation of the total synthetic intermediate (**48**) followed by subsequent ozonolysis/acidification or by alkylation of the enolate derived from (+)-11-desmethylartemisinin (**49a**). *In vitro* antimalarial activities of these analogues against W-2 clone of *P. falciparum* showed that analogues (**49d**) and (**49e**) are about 12 times




(i) LDA, THF, 78°C then $CH_3I$; (ii) $CH_3O(CH_3)_2SiCHLiSi(CH_3)_3$, pentane; (iii) $(C_4H_9)_4NF$, THF; (iv) PDC, DMF; (v) $O_3$, $CH_2Cl_2$, -78°C then acetone, Amberlyst-15, 22°C; (vi) $O_3$,$CH_2Cl_2$,-78°C then acetaldehyde, Amberlyst-15 22°C

**Scheme 5**

more active than artemisinin (**1**). The SAR and the comparative molecular field analysis (CoMFA) of these analogues provided a model with a cross-validated $r^2$= 0.793.

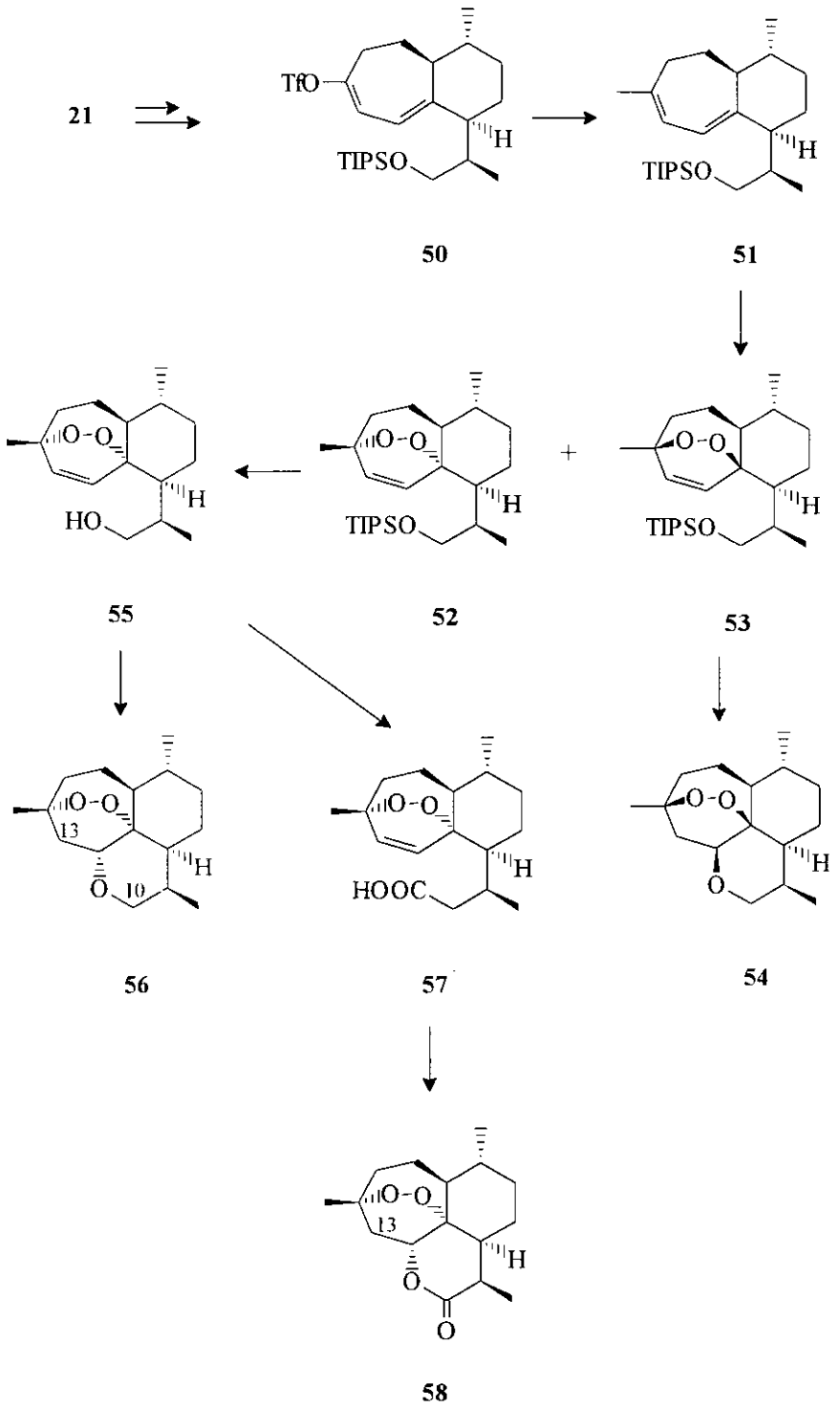
In 1995, Avery *et al.*[26] reported the total synthesis of 13-carba-artemisinins and related structures in which

they replaced the nonperoxidic trioxane oxygen atom of artemisinin (**1**) by carbon and evaluated antimalarial efficacy of these analogues. They synthesised the key intermediate (**50**) from (-)-isopulegol (**21**) in eight steps. Compound (**50**) on treatment with dimethylcopperlithium furnished diene (**51**) in excellent yield. These workers investigated the singlet oxygenation of compound (**51**) with a variety of dyes in different solvents. To their surprise, they found a mixture of diastereomeric peroxides (**52**) and (**53**) in 30% and 54% yields respectively. The unexpected predominant diastereomer (**53**) was then carried through the sequence of silyl group deprotection and Hg(II) cyclization to provide the diastereomeric mixture (**54**). The desired product (**52**) on deprotection with tetrabutylammonium fluoride in THF gave the alcohol (**55**). Intramolecular oxymercuration-demercuration of the alcohol (**55**) furnished (+)-10- deoxy-13-carbaartemisinin (**56**). However, alcohol (**55**) on oxidation with chromium trioxide-acetic acid furnished the acid (**57**). Oxymercuration-demercuration of the acid (**57**) furnished 13-carbaartemisinin (**58**) (Scheme 6). Neither 13-carbaartemisinin (**58**) ($IC_{50}$= 25 ng/mL) nor 10-deoxy-13-carbaartemisinin (**56**) ($IC_{50}$= 5.81 ng/mL) showed substantial antimalarial potency relative to artemisinin (**1**) ($IC_{50}$= 1 ng/mL) *in vitro* against the W-2 clone of *P. falciparum*, a fact that indicated that the inactivity of C-4α substituted artemisinin analogues could be correlated to their inability to undergo C-4 hydrogen atom abstraction.[27] However, the isomeric peroxide (**54**) was found to possess reasonably good antimalarial activity ($IC_{50}$= 1.73 ng/mL).

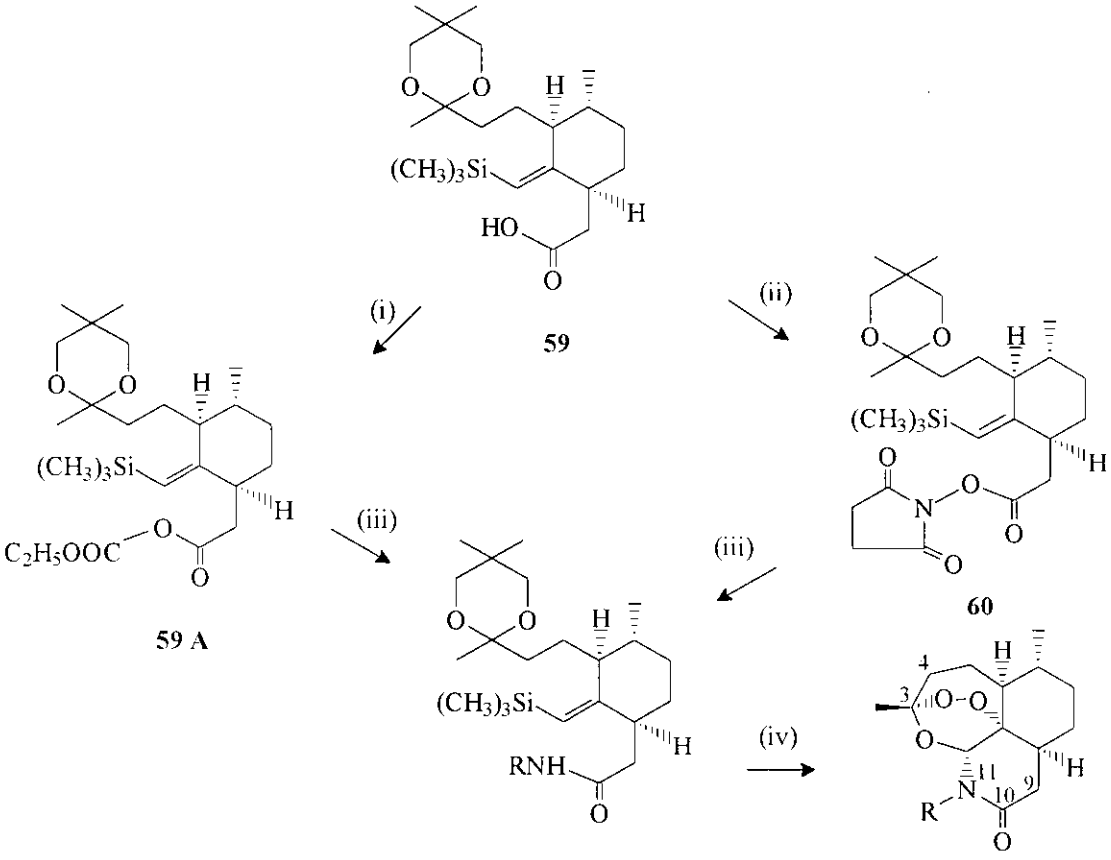
In the same year these authors[28] reported the total synthesis of a novel class of artemisinin analogues, *N*-alkyl-11-aza-9-desmethylartemisinins (**62a-m**) *via* ozonolysis and acid-catalysed cyclization of precursor amides (**61a-l**). They prepared these amides through condensation of an activated ester of the known intermediate acid (**34**) with the corresponding primary amine (Scheme 7). These analogues were tested *in vitro* against both the strains of *P. falciparum viz.* W-2 and D-6. Compound (**62a**) was found to be five times as potent as artemisinin (**1**).

Recently Avery *et al.*[29] reported synthesis of novel antimalarial analogues, 4-alkylartemisinins as well as 4-arylalkyl- and 4-carboxyalkylartemisinins *via* the synthetic intermediate (**63**). Formation of the *N,N*-dimethylhydrazones (**64**) and then regio- and chemoselective deprotonation followed by alkylation provided initially alkylated hydrazones that upon chromatography furnished ketones (**65a-n**). By using their earlier methodology[25,28] they converted these ketones into analogues (**66a-n**) (Scheme 8). They evaluated these analogues *in vitro* against W-2 and D-6 clones of *P. falciparum*. Compound (**66b**) showed 7-21 times activity that of artemisinin (**1**). On the whole, analogues of artemisinin substituted at C-4 were found to be less active than those substituted at C-11.

In 1996, Little *et al.*[30] reported asymmetric total synthesis of (-)-$C_{10}$- desmethylarteannuin B (**67**) from 3-methylcyclohexanone which could be converted to $C_{10}$-desmethylartemisinin (**68**) using Lansbury's methodology.[31]


21
TfO
TIPSO
H
50
51
TIPSO
H
O-O
HO
TIPSO
55
52
53
13
O
10
HOOC
56
57
54
58

Scheme 6



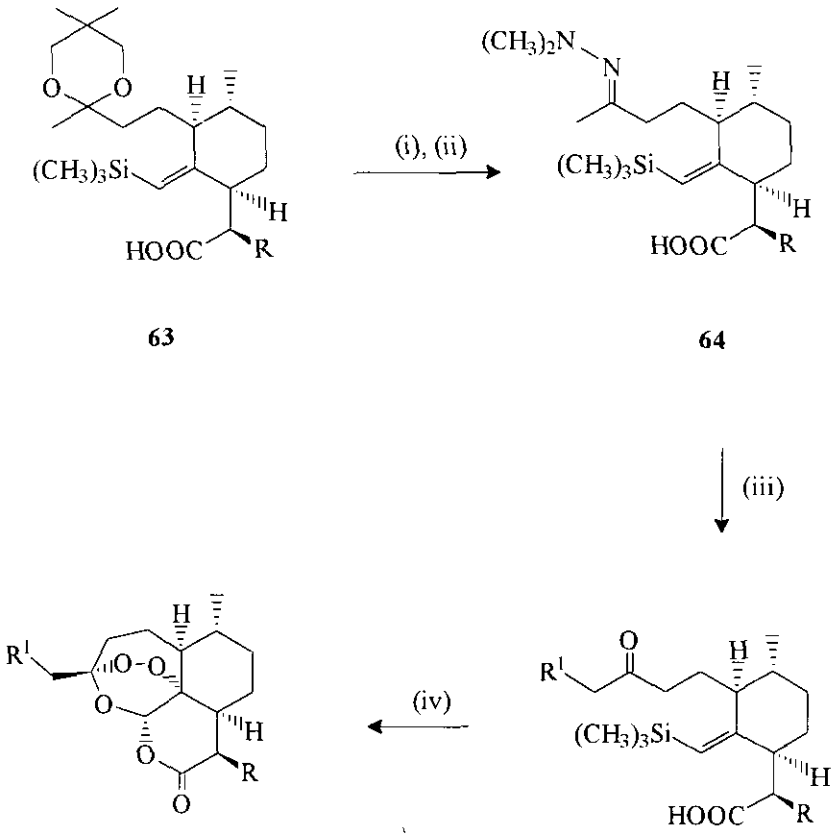

**a** R=$CH_3$, **b** $CH_3(CH)_2$, **c** R=$C_4H_9$(i)
**d** R=$C_5H_{11}$(n), **e** R=$C_5H_{11}$(i),
**f** R=$HOOC(CH_2)_5$, **g** R=$HOOCCH_2$,
**h** R=$HOOC(CH_2)_5$, **i** R=$CH_3CO_2(CH_2)_2$,
**j** R=$C_6H_5CH_2$, **k** R=*p*-$ClC_6H_4CH_2$,
**l** R=$C_6H_5(CH_2)_2$, **m** R=$C_6H_5(CH_2)_3$

(i) $(C_2H_5)_3N$, $ClCO_2C_2H_5$, $CH_2Cl_2$, $0^oC$
(ii) *N*-hydroxysuccinimide, DCC, $CH_2Cl_2$
(iii) $RNH_2$, $CH_2Cl_2$
(v) $O_3$,-78°C then $SiO_2$ followed by 15% $H_2SO_4$

**Scheme 7**

Total synthesis of artemisinin D (**69a**) has been carried out by Liu *et al.*[32] from β-pinene.

Haynes *et al.*[33] in 1994 reported synthesis of a bicyclic analogue of artemisinic acid *via* a Lewis acid catalysed ionic Diels-Alder reaction involving a hydroxy diene and cyclic enone and its facile conversion into (±)-10,11-desdimethylartemisinin (**79**) (Scheme 9). The key intermediate (**73**) on dehydration with $POCl_3$ in pyridine furnished the *trans* analogue (**74**) of desdimethyldihydroartemisinic acid methyl ester as an inseparable 5:2 mixture with its allylic regioisomer (**75**) (86% yield). Compound (**74**) on photooxygenation in presence of Rose Bengal yielded the hydroperoxide (**76**). The hydroperoxide (**76**) was treated



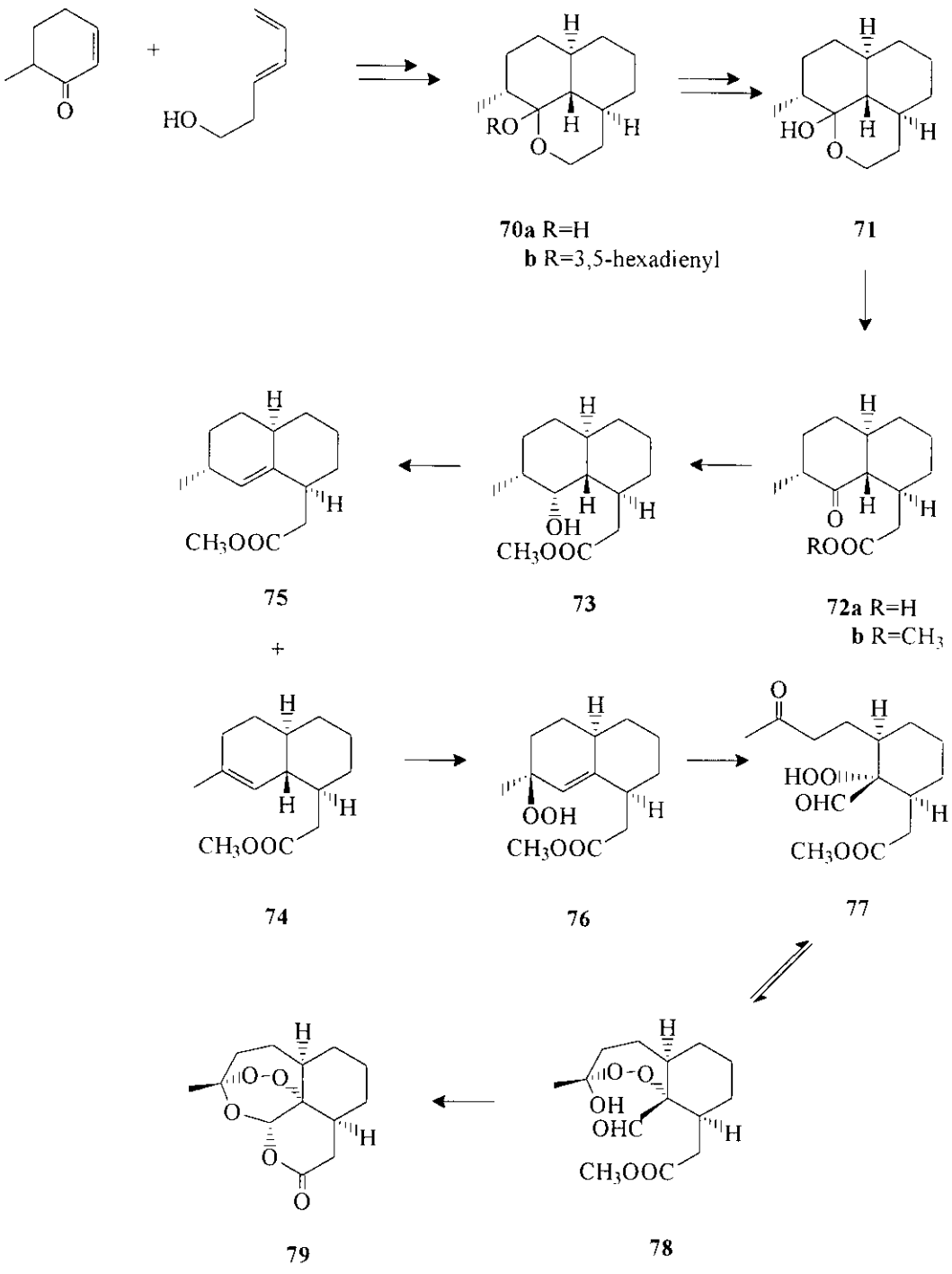

**63** **64**

**66a-n** **65a-n**

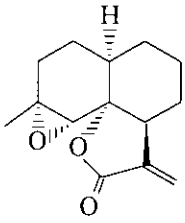
**a** $R^1$=$CH_3$, R=H; **b** $R^1$=$CH_3CH_2$, R=H; **c** $R^1$=$CH_3(CH_2)_2$, R=H;
**d** $R^1$=$(CH_3)_2CH$, R=H; **e** $R^1$=$C_2H_5O_2CCH_2$, R=H; **f** $R^1$=$C_6H_5CH_2$, R=H;
**g** $R^1$=*p*-$ClC_6H_4(CH_2)_2$, R=H; **h** $R^1$=$C_6H_5(CH_2)_3$, R=H; **i** $R^1$=$CH_3$,R=$CH_3(CH_2)_3$;
**j** $R^1$=$CH_3(CH_2)_2$, R=$CH_3(CH_2)_3$; **k** $R^1$=$C_6H_5CH_2$, R=$CH_3(CH_2)_3$;
**l** $R^1$=*p*-$ClC_6H_4(CH_2)_2$, R=$CH_3(CH_2)_3$; **m** $R^1$=$C_6H_5(CH_2)_3$, R=$CH_3(CH_2)_3$;
**n** $R^1$=$C_2H_5O_2CCH_2$, R=$CH_3(CH_2)_3$

(i) aq. oxalic acid, $SiO_2$, $CH_2Cl_2$ (ii) $(CH_3)_2NNH_2$, heat
(iii) 2LDA, THF, HMPA, -78 -20°C then $R^1$-X
(iv) $O_3$, $CH_2Cl_2$, -78°C then aq. $H_2SO_4$, $SiO_2$, $CH_2Cl_2$

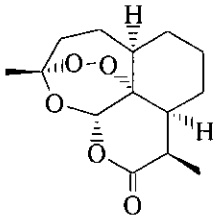
**Scheme 8**



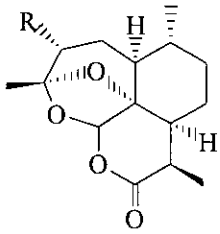

**Scheme 9**



67



68



**69a** R=OH
**69b** R=H

with $Fe(phen)_3(PF)_6$ followed immediately with copper triflate furnished an equilibrium mixture of the hydroxy-keto aldehyde (**77**) and peroxy hemiacetal (**78**) which were treated with *p*-TsOH in dichloromethane to furnish the desired product, desdimethylartemisinin (**79**) in an overall yield of 34% from **74**. The allylic regioisomer (**75**) did not react under these conditions.

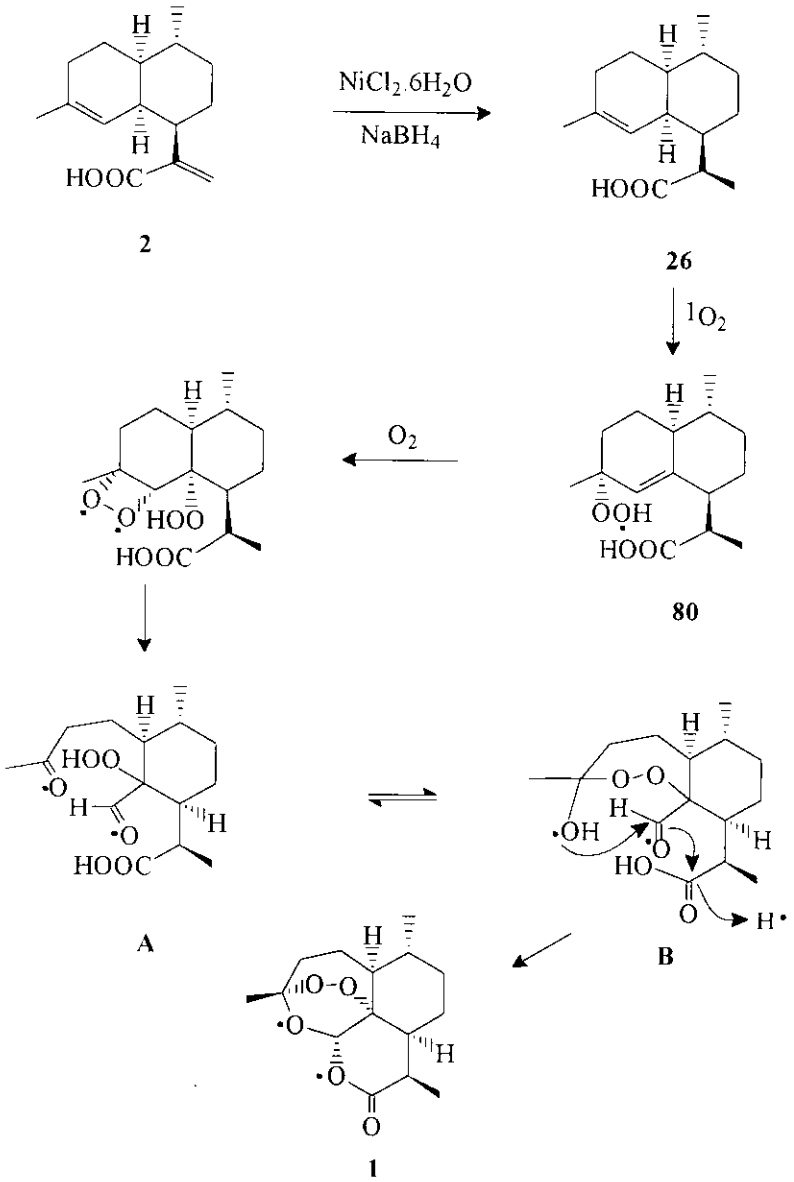
## IV. PARTIAL SYNTHESIS OF ARTEMISININ AND ITS ANALOGUES FROM ARTEMISINIC ACID AND ARTEANNUIN B

*A. annua* has been found to contain approximately 8-10 times more artemisinic acid (**2**) and 2-4 times more arteannuin B (**3**) than artemisinin (**1**).[14,34] Hence, several workers have attempted the conversion of artemisinic acid (**2**) and arteannuin B (**3**) into artemisinin (**1**) and related compounds.

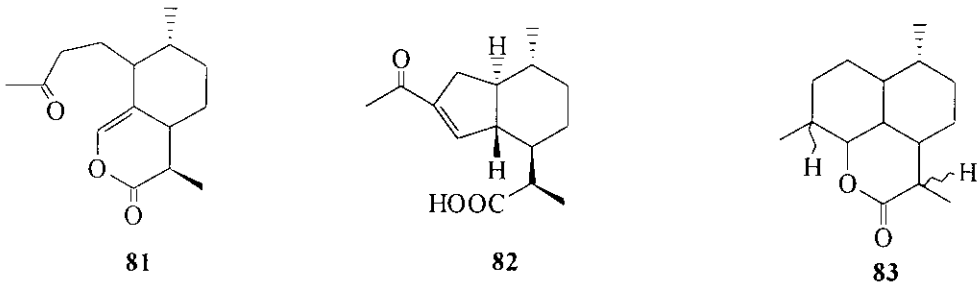
Acton *et al.*[19] using their earlier methodology converted dihydroartemisinic acid (**26**) into artemisinin (**1**) in 17-32% isolated yield. They prepared dihydroartemisinic acid (**26**) by reducing the α,β-unsaturated double bond of the artemisinic acid (**2**) with $Ni_2B$ generated from $NaBH_4$ and $NiCl_2.6H_2O$ in methanol. Photooxidation of dihydroartemisinic acid (**26**) at -78° C in dichloromethane or at 0° C in acetone followed by air oxidation in petroleum ether furnished artemisinin (**1**). By using oxygen-18 in the triplet oxygen oxidation in the transformation of **26** to radio-labelled **1**, they have shown that using $^{18}O_2$ in the photooxidative conversion of **26** into **80** and then air oxidizing resulted in artemisinin (**1**) labelled at two of the nonperoxide positions (Scheme 10). During the course of this two step reaction they have also isolated several minor products (7, **81** to **85**).

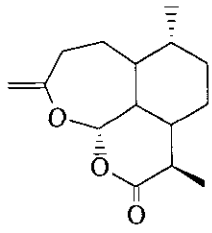
Mainly two strategies have been employed for the synthesis of analogues of artemisinin. Manipulation of the acid group of the artemisinic acid (**2**) or the Michael addition to its α,β-unsaturated double bond moiety has yielded new analogues which have been elaborated to artemisinin analogues by the reported procedures.

Jung *et al.*[35] in 1991 reported the synthesis of 12-(3'-hydroxy-n-propyl)deoxoartemisinin (**91**) from artemisinic acid (**2**) *via* photooxidative cyclization as a key step (Scheme 11). They prepared dihydroarte-

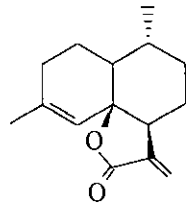

NiCl2.6H2O
NaBH4
1O2
O2
HOOC
HOO
OOH
OH
H
O
2
26
80
A
B
1

**Scheme 10**


O
H
HOOC
81
82
83

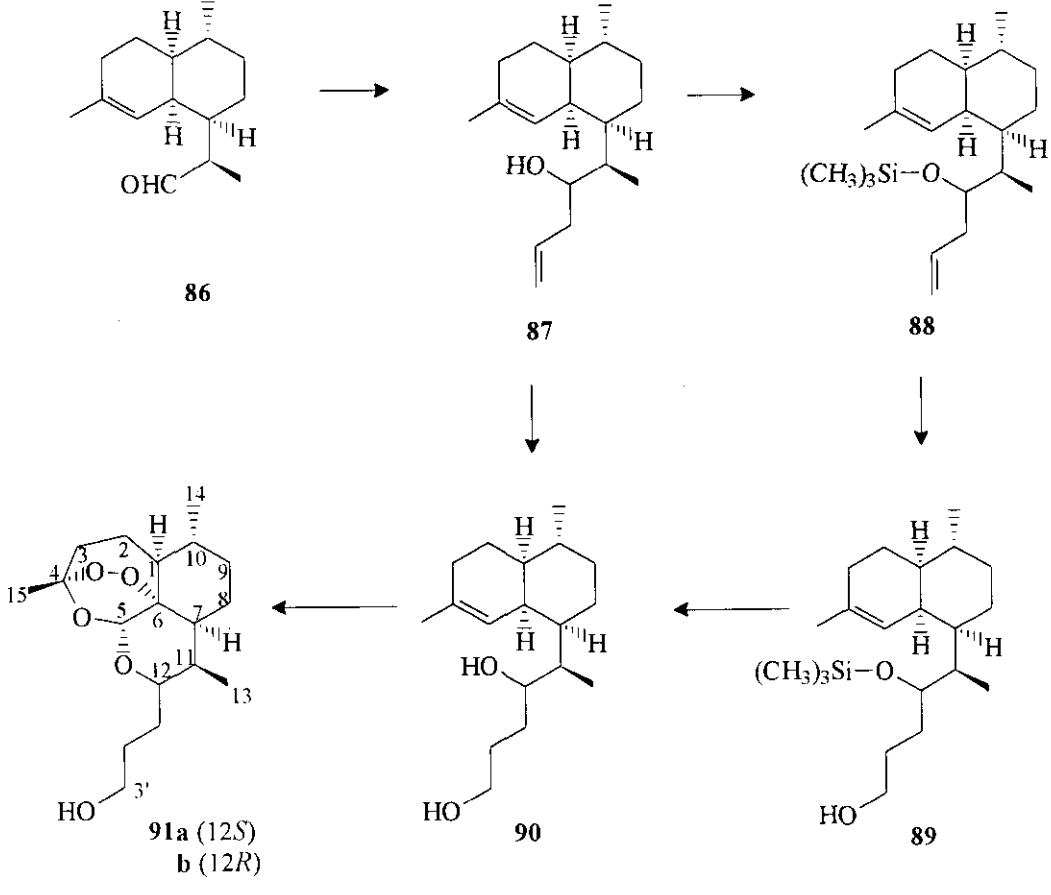


**84**



**85**

misinylaldehyde (**86**) from artemisinic acid (**2**) by following the previously reported procedure.[36] The Grignard addition to **86** with allylmagnesium bromide in anhydrous ether afforded **87** (12*S*/12*R*= 1:1) in 62% yield. Treatment of **87** with *t*-butyldimethylsilyl chloride in DMF at room temperature furnished **88** (93%) and hydroboration of **88** with 9-BBN in anhydrous THF and subsequent oxidation with $H_2O_2$/2N-NaOH afforded **89** (71%) with high regioselectivity. The key intermediate (**90**) was prepared

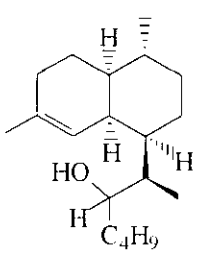


**Scheme 11**

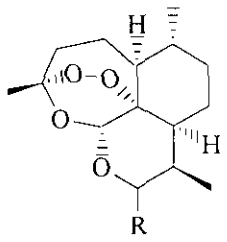
from **89** by cleanly deprotecting the silyl group of the secondary hydroxy function of **89** by treating it with tetrabutylammonium fluoride in high yield (90%). They also prepared **90** from **87** with 9-BBN and subsequent oxidation as described above in 80% yield. The final step involved the chiral photooxidation of **90** with oxygen and irradiation with 450 W medium pressure mercury arc lamp at -78° C in di-chloromethane, followed by acidic Dowex-resin catalysed cyclization of the oxygenation intermediates furnished **91a** (12*S*) and **91**b (12*R*) of natural configuration in 12% and 11% yields respectively. Compound (**91a**) was found to show five times the antimalarial activity of artemisinin (**1**) *in vitro* against chloroquine-resistant malaria.

Synthesis of compounds (**94a-c**) has remained elusive for a long time because their direct synthesis from artemisinin (**1**) is very difficult due to the chemically sensitive functional groups within the molecule. Keeping in mind, the novelty of these antimalarial agents which contain an external C-C bond and carboxyalkyl side chains at C-12 and difficulty in preparing these from **1**, the same authors[37] in 1994 reported the synthesis of compounds (**94a-c**) from artemisinic acid (**2**) as depicted in Scheme 12. Dye-sensitized photooxygenation of olefinic alcohols of dihydroartemisinates (**92a-c**) and direct oxidations of olefinic deoxoartemisinins (**93a-c**) led to the preparation of carboxyalkyldeoxoartemisinins (**94a-c**) as water soluble (sodium salts) and chemically more stable antimalarial agents. The predominant 12*R*-isomers in **93a-c** were easily separated from their 12*S*-isomers by silica gel column chromatography. Compounds (**94b**) and (**94c**) were found to exhibit approximately equal *in vitro* antimalarial activity ($IC_{50}$= 1.30 and <1.28 ng/mL, respectively) as artemisinin (**1**) against chloroquine-resistant malaria.

Jung *et al.*[38] reported the synthesis of (+)-deoxoartemisinin analogues from artemisinic acid (**2**). They prepared **86** from artemisinic acid (**2**) as discussed earlier which on condensation with the Grignard reagent prepared from $C_4H_9Br$ yielded **95**. Compound (**95**) on photooxygenation in $CH_2Cl_2$ in presence of methylene blue furnished deoxoartemisinin analogues (**96a-d**). No antimalarial activity of these analogues has been mentioned.

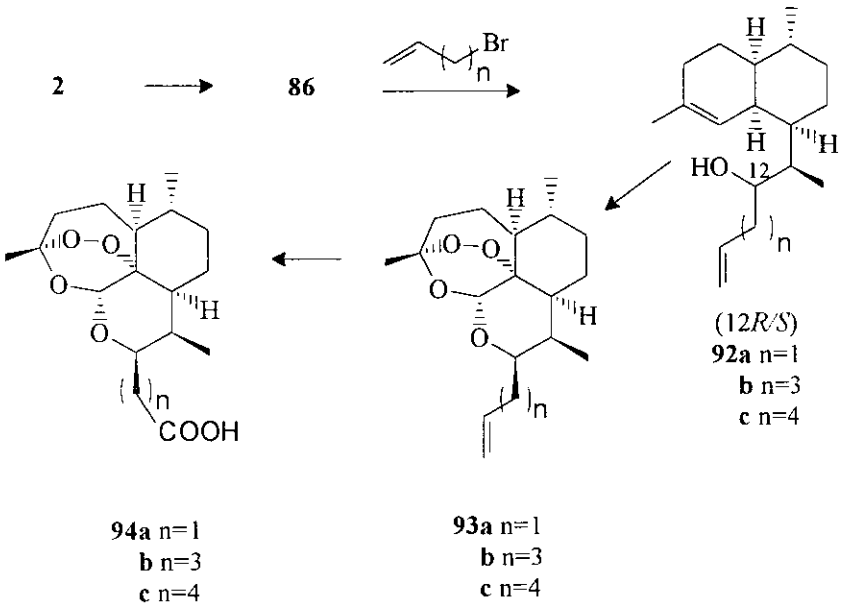



**95**




**96a** R=H
**96b** R=cycloalkyl
**96c** R=hydroxyalkyl
**96d** R=aryl

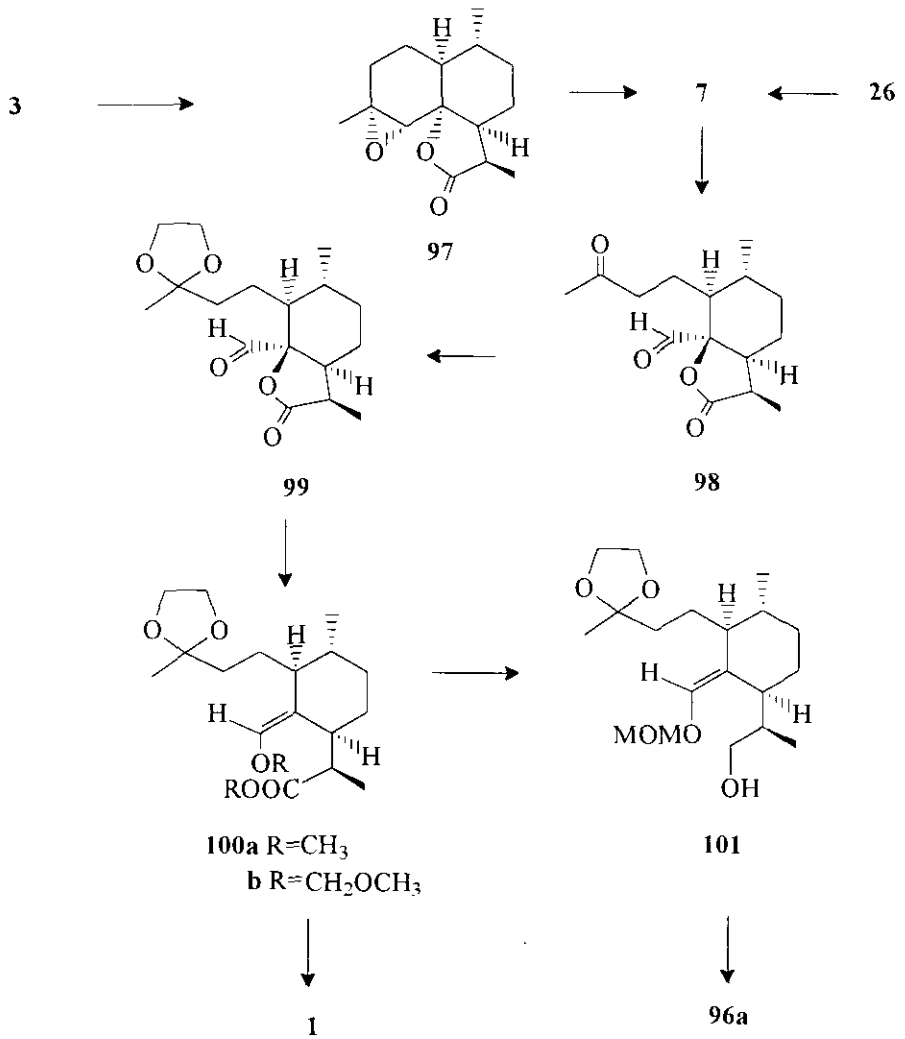
In 1992, Lansbury *et al.*[31] reported the synthesis of (+)-artemisinin (**1**) and (+)-deoxoartemisinin (**96a**).




**Scheme 12**

They converted artemisinic acid (**2**) and arteannuin B (**3**) to **1** and **96a** *via* a common novel pathway that excludes unwanted epimerizations at C-1 or C-7 (Scheme 13). They prepared 11-*R*-dihydroarteannuin B (**97**) in 73% yield from arteannuin B (**3**) by hydrogenating it with pre-reduced Wilkinson's catalyst. Interestingly, dihydroarteannuin B (**97**) on deepoxidation using Sharpless procedure[39] furnished the C-6 epimerized lactone (**7**) in 60% yield presumably by Lewis-acid mediated isomerization of the more strained α-lactone.[40] The novel discovery[20] that allylic oxidation of 11-*R*-dihydroartemisinic acid (**26**) with $Cr_2O_3$-3,5-dimethylpyrazole in $CH_2Cl_2$ proceeded rapidly at -20° C to the carboxyl trapped γ-lactone provided a plentiful source of the key intermediate (**7**). Compound (**7**) on ozonolysis furnished keto aldehyde (**98**) in quantitative yield. The ketone carbonyl group in keto aldehyde (**98**) was selectively protected in the presence of the more hindered aldehyde by using 1 eq. of 1,2-bis(trimethylsilyloxy)-ethane and TMS triflate in $CH_2Cl_2$ to furnish **99** (94% yield). Compound (**99**) on reductive cleavage with 2 eq. of sodium napthalenide in THF at -30° C followed by *in situ* reaction with several alkylating agents *viz.* $CH_3I$, $CH_3OCH_2Cl$ produced enol ether esters (**100a**) and (**100b**) in 70% and 82% yields respectively. Surprisingly the hindered aldehyde enolates underwent only *O*-alkylation even in the absence of dimethyl sulfoxide typically used to solvate the sodium counter ions. Photooxidation of **100a** and **100b** in $CD_3OD$ at -78° C with Rose Bengal as photosensitizer without prior hydrolysis of the ethylene ketal furnished the dioxetane intermediate. The gradual warming of this dioxetane intermediate to room

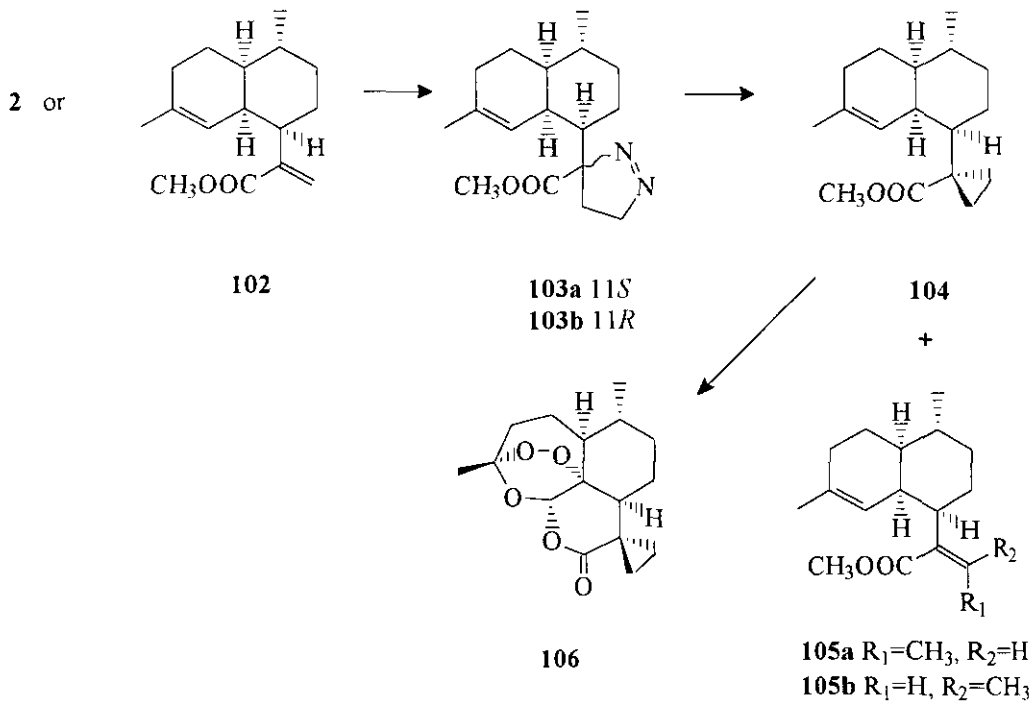
temperature in the presence of camphorsulfonic acid followed by solvent removal and silica gel chromatography afforded **1** in 30-35% isolated yields. The reduction of **100b** with $LiAlH_4$ in ether furnished carbinol (**101**) in 90% yield which upon photooxidation furnished deoxoartemisinin (**96a**) in 65% yield.




**Scheme 13**

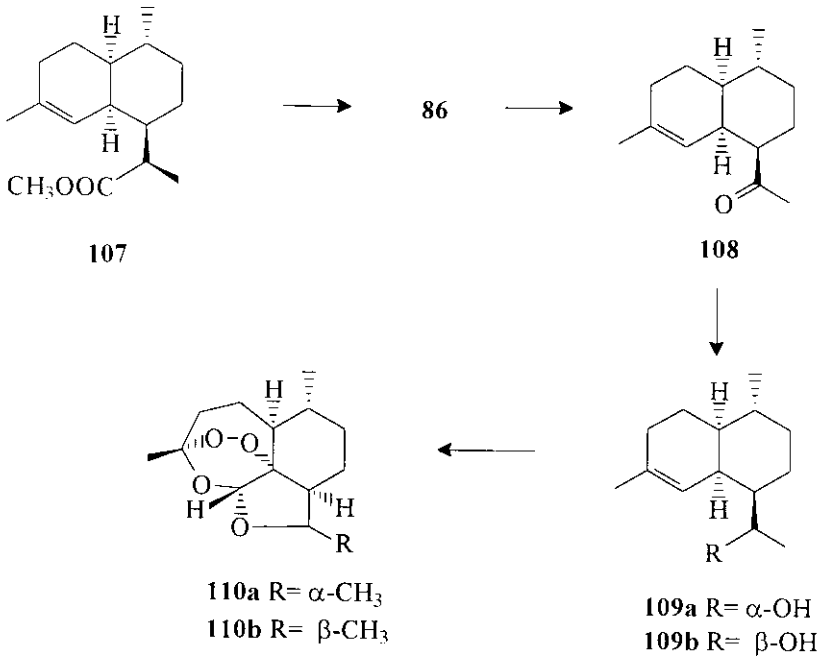
In 1993, Kim *et al.*[41] reported a facile method for the synthesis of alkyl homologues of artemisinic acid, which in turn could serve as precursors for alkyl homologues of artemisinin using the procedure described by Haynes *et al.*[42] Artemisinic acid (**2**) or methyl artemisinate (**102**) when treated with excess of $CH_2N_2$ furnished **103** in 95% yield. The thermal or photochemical denitrogenation of **103a** furnished **104** as the major product (**105a**) and (**105b**) as the minor products. The cyclopropane containing analogue (**104**) on

photochemical oxygenation provided the artemisinin analogue (**106**) (Scheme 14). No pharmacological activity of analogue (**106**) has been reported.



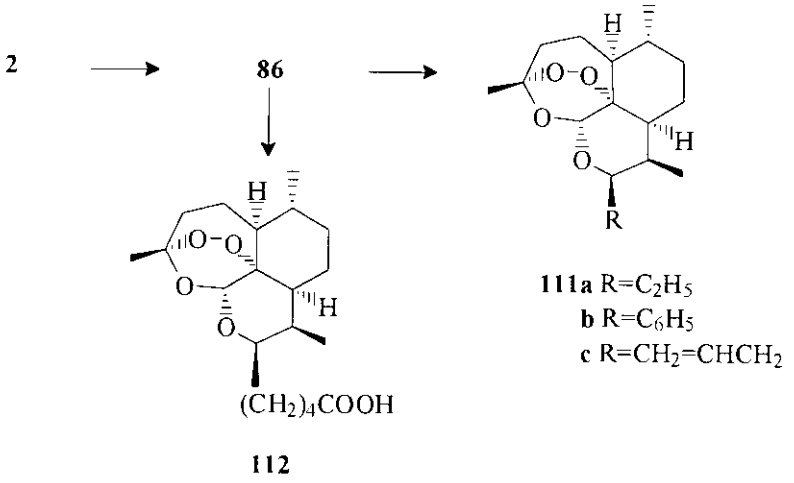

**Scheme 14**

Haynes *et al.*[43] in 1995 reported D-ring-contracted analogues of artemisinin. They prepared aldehyde (**86**) from methyl ester of dihydroartemisinic acid (**107**) or directly from artemisinic acid (**2**). The aldehyde (**86**) on oxidative deformylation with $Cu(OAc)_2.H_2O$/DABCO/2,2'-bipyridyl in DMF at 70-75° C furnished the ketone (**108**) in 70% yield. $NaBH_4$ reduction of **108** gave the key inermediates (**109a**) and (**109b**) in 80% and 12% yield respectively. They converted these alcohols into the ring contracted analogues of artemisinin (**110a**) (25% yield) and **110b** (39% yield) by using their earlier methodology[42] of photooxygenation with copper triflate as catalyst (Scheme 15). *In vitro* activity against *P. falciparum* showed that **110a** was almost ten times more active than **110b** and as active as β-artemether (**116c**) having an $IC_{50}$ values of 0.36 ng/mL and 0.67 ng/mL against W-2 and D-6 clones of *P. falciparum* respectively. They attributed this dramatic influence by the methyl substituent to the increased rigidity of the five-membered D-ring which should enhance the effects brought about by changes in substitution at C-11.



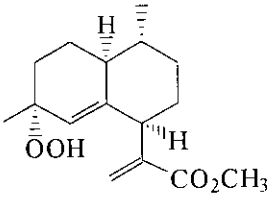

**Scheme 15**

The same authors[44] converted artemisinic acid (**2**) *via* dihydroartemisinic aldehyde (**86**) into different secondary alcohols which upon photooxygenation using copper triflate as catalyst furnished the deoxoartemisinin analogues (**111a-c**) and 5-carba-4-deoxoartesunic acid (**112**).

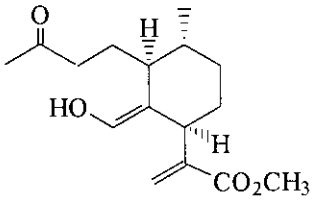



The semi-synthesis of artemisinin derivatives from artemisinic acid (**2**) and related compounds is gaining increasing importance despite the fact that the key step in the transformation *i.e.* the cleavage oxygenation

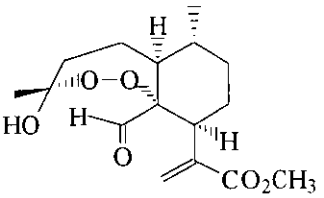
of the intermediate allylic hydroperoxides to form peroxy hemiacetals, is not well understood. Bearing this notion in mind, Haynes *et al.*[45] in 1995 showed that the allylic hydroperoxides (**113**) derived from the methyl ester of artemisinic acid under catalysis by trifluoromethane sulfonic acid (TfOH) in $CH_2Cl_2$ or copper(II)-trifluoromethane sulfonate [$Cu(OTf)_2$] in $CH_3CN$ forms a thermally labile intermediate. Chromatographic isolation of the intermediate at low temperature and analysis by low temperature $^1H$ and $^{13}C$ NMR spectroscopies showed it to be the simple enol (**114**), a compound possessing unexpected stability. The enol (**114**) undergoes autooxidation at room temperature or facile oxygenation at -20° C in the presence of Cu(II) and oxygen to give the peroxy hemiacetal (**115**). Thus, they established that the catalysed cleavage of cyclic allylic hydroperoxides proceeds *via* enol intermediates and it would seem that the propensity for subsequent oxygenation is related to the stability of the enol.



**113**

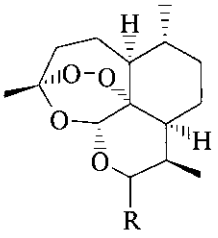


**114**

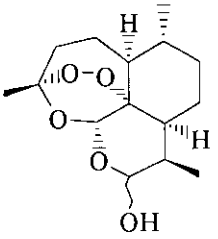


**115**

However, more recently it has been shown that β-arteether (**116a**) and β-artemether (**116c**) can cause fatal neurotoxicity in animals.[46,47] It has been observed that these drugs are rapidly and extensively metabolized and a major metabolite of 12-ether derivatives of artemisinin (**1**) was found to be highly

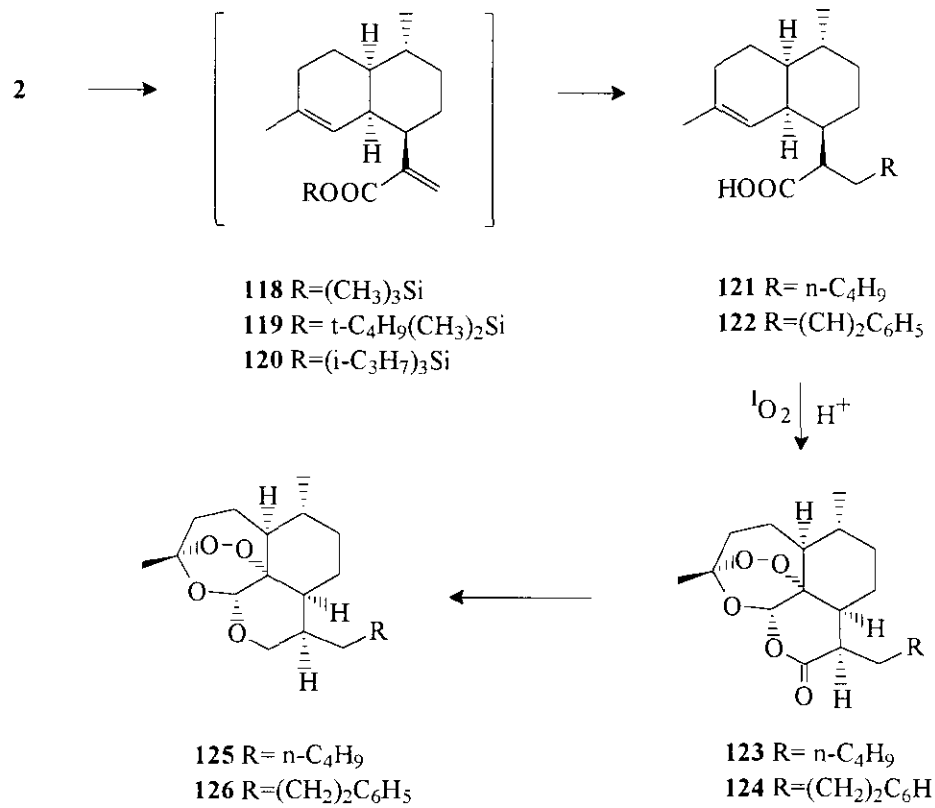


**116a** R=β-$OC_2H_5$
**b** R=α-$OC_2H_5$
**c** R=β-$OCH_3$
**d** R=α-$OCH_3$



**117**

neurotoxic (both *in vivo* and *in vitro*) dihydroartemisinin (**117**). Based upon this rationale, Avery *et al.*[48] in 1997 devised a novel methodology for the synthesis of 11-alkyl-12-deoxoartemisinin analogues (**125** and **126**) reported to be highly potent antimalarials lacking the neurotoxic 12-lactol moiety,[49] by employing




**118** R=$(CH_3)_3Si$
**119** R= t-$C_4H_9(CH_3)_2Si$
**120** R=(i-$C_3H_7)_3Si$

**121** R= n-$C_4H_9$
**122** R=$(CH)_2C_6H_5$

**125** R= n-$C_4H_9$
**126** R=$(CH_2)_2C_6H_5$

**123** R= n-$C_4H_9$
**124** R=$(CH_2)_2C_6H$

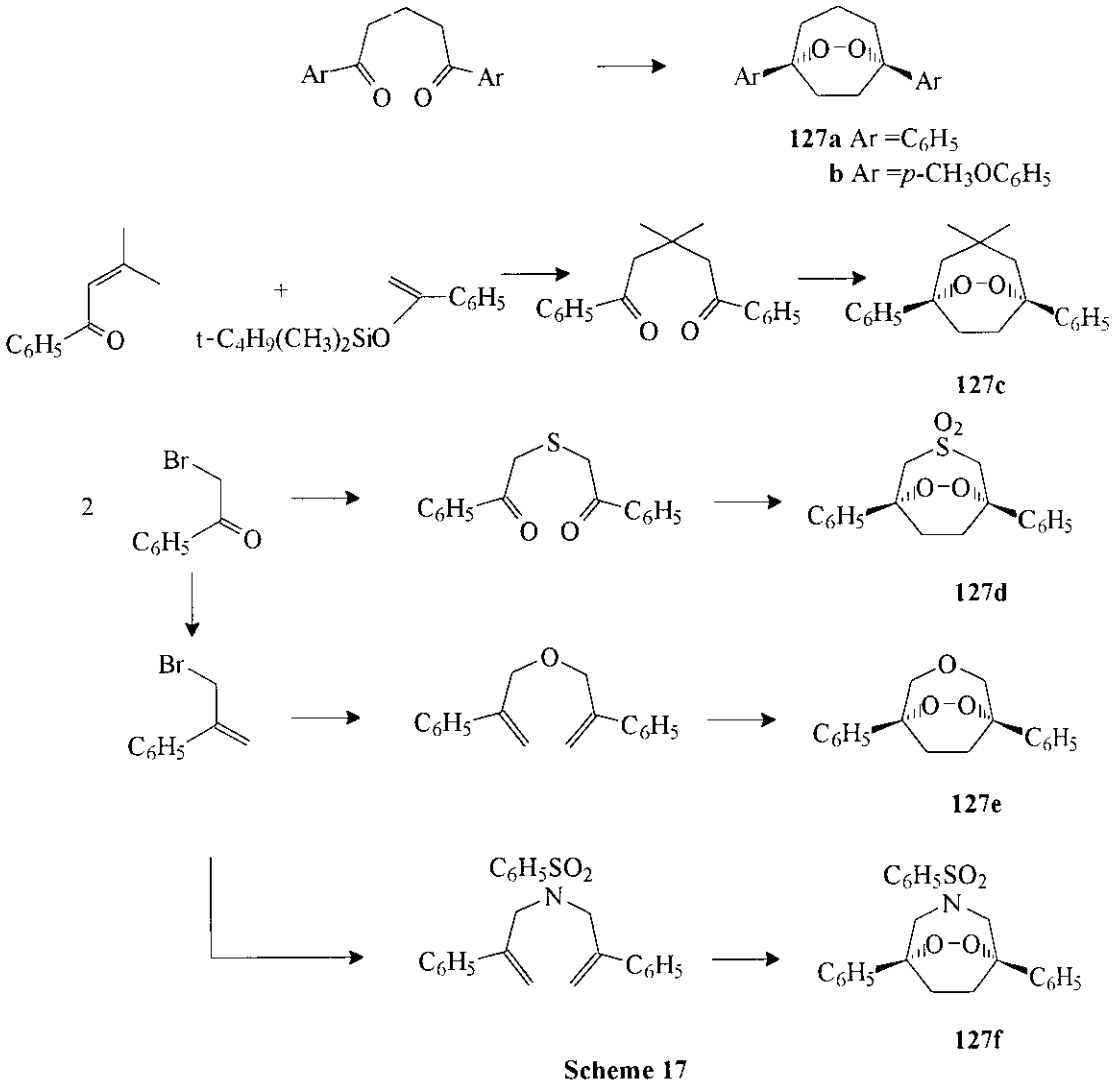
**Scheme 16**

photoxygenation of homologated derivatives of artemisinic acid (**121** and **122**). Artemisinic acid (**2**) was deprotonated with $C_4H_9Li$ and *in situ* protected as a silyl ester with trialkyl silyl chloride at 0°C immediately followed by copper(I) iodide catalysed 1,4-addition of Grignard reagent and deprotection to furnish **121** and **122** (Scheme 16). The key intermediates (**121**) and (**122**) on singlet oxygenation followed by acid treatment with Amberlyst-15 afforded 11-alkylartemisinins (**123**) and (**124**) in 40% and 38% yields respectively. Avery *et al.*[49] using their recently devised methodology converted **123** and **124** to 11-alkyl-12-deoxoartemisinins (**125**) (in 33% overall yield) and (**126**). In their preliminary *in vitro* bioassay of pyrans (**125**) and (**126**), Avery *et al.* observed that these analogues demonstrated weak neurotoxicity relative to dihydroartemisinin (**117**) suggesting that metabolism to lactols does not occur *in vitro*.

## V. SYNTHESIS OF PEROXIDES AND TRIOXANES

Posner *et al.*[50] while carrying out pioneering work on the mode of action of the 1,2,4-trioxanes reported the mechanism based design of simple, symmetrical and easily preparable endoperoxides with antimalarial

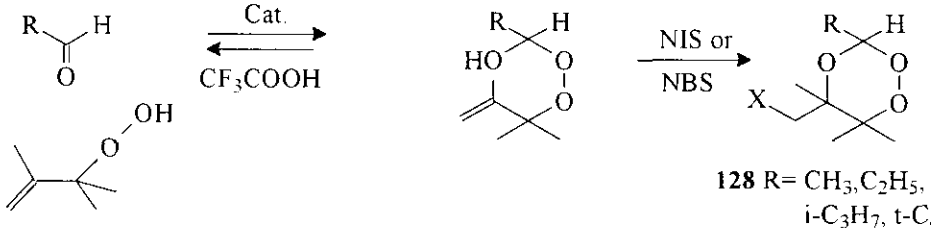
efficacy. They prepared bicyclo[3.2.2]nonane endoperoxides (**127a**) (41% yield), (**127b**) (40% yield) and (**127c**) according to literature[51] by photosensitised oxygenative cyclization of the corresponding 1,6-dienes (Scheme 17). Tebbe methylenation[52] of α-bromoacetophenone and reaction of the resultant allylic bromide with either bis(tributyltin) oxide or with benzene sulfonamide produced hetero-atom-containing 1,6-dienes that underwent smooth photooxidative cyclization to form ether endo peroxide (**127e**) and sulfonamide endo peroxide (**127f**). *In vitro* antimalarial activity of these endo peroxides against chloroquine-sensitive *P. falciparum* (NF 54) showed that bicyclic endo peroxides (**127a**) and




**Scheme 17**

(**127b**) both have high antimalarial activity, about 1/7 that of artemisinin (**1**) on a nanomolar basis; gem-dimethyl bicyclic endo peroxide (**127c**) was found to be almost inactive. None of the endo peroxide (**127d-f**) containing sulfur, oxygen or nitrogen atoms showed any significant antimalarial activity.

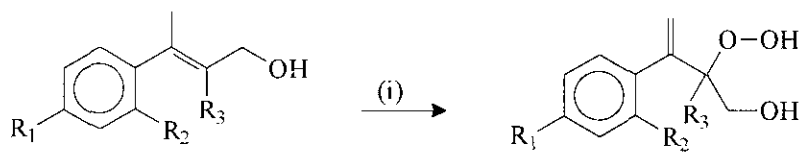
In 1993, Bloodworth and Shah[53] reported synthesis of 3-alkyl-5-halomethyl-5,6,6-trimethyl-1,2,4-trioxanes (**128**). Hemiperoxy acetals derived from 2,3-dimethylbut-4-en-2-hydroperoxide and aliphatic aldehydes underwent cyclisation with NIS or NBS to furnish the corresponding 1,2,4-trioxanes (**128**) in yields of 20-65% (Scheme 18). However, in their report, no antimalarial efficacy of these trioxanes has been mentioned.



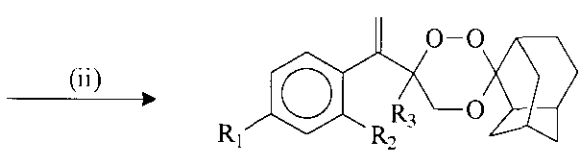

**128** R= $CH_3$,$C_2H_5$, $C_6H_{13}$, i-$C_3H_7$, t-$C_4H_9$
X= I, Br

**Scheme 18**

Singh *et al.*[54] have prepared a series of 1,2,4-trioxanes from allylic alcohols (**129a-h**) which on photooxygenation furnished β-hydroxy hydroperoxides (**130a-h**). Compounds (**130a-h**) on acid-catalysed condensation with 2-adamantone furnished spiro trioxanes (**131a-h**) (Scheme 19). The *in vivo* antimalarial activity against *P. berghei* showed that trioxanes (**131a-f**) were active at 90 mg/kg while only **131c** and **131e** were active at 30 mg/kg.




**129a-h** **130a-h**



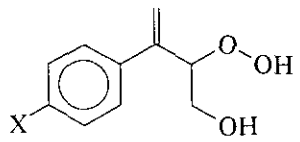

**131 a** $R_1$=$R_2$=$R_3$=H, **b** $R_1$=$CH_3$, $R_2$=$R_3$=H,
**c** $R_1$=$OCH_3$, $R_2$=$R_3$=H, **d** $R_1$=F, $R_2$=$R_3$=H,
**e** $R_1$=Cl, $R_2$=$R_3$=H, **f** $R_1$=$R_2$=$CH_3$, $R_3$=H,
**g** $R_1$=$R_2$=H, $R_3$=$CH_3$, **h** $R_1$=Cl, $R_2$=H, $R_3$=$CH_3$

(i) $^1O_2$, $C_2H_5OH$, Methylene Blue, 0-10°C, 10-16 h

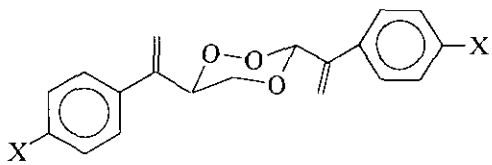
(ii) 2-Adamantone, $H^+/CH_2Cl_2$, 0-5°C, overnight

**Scheme 19**

In 1993, the same authors[55] reported the synthesis of 3,6-bis-(α-arylvinyl)-1,2,4-trioxanes (**133a-d**) from 3-aryl-1-hydroxybut-3-ene-2-hydroperoxides (**132a-d**) which underwent an acid catalysed tandem fragmentation-condensation reaction. However, no antimalarial activity of these 1,2,4-trioxanes has been mentioned.



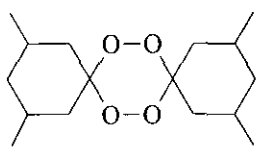
**132a-d**



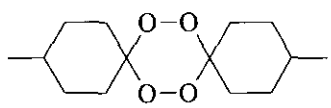
**133a-d**

**a** X=H; **b** X=$CH_3$; **c** X=F; **d** X=Cl

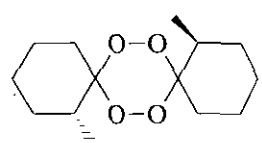
Vennerstorm *et al.*[56] reported the synthesis and antimalarial activity of a new class of peroxides, dispiro-1,2,4,5-tetraoxanes (**134a-c**). They synthesised **134a-c** by the acid-catalysed peroxyketalization between a 1:1 mole ratio of the substituted cyclohexanone and hydrogen peroxide. These compounds showed curative activity against *P. berghei in vivo* at single dose of 320 and 640 mg/kg. *In vivo* antimalarial activity against the *P. falciparum* indicates that **134a** and **134b** are 2 to 26-fold less potent than artemisinin (**1**); curiously **134b**, in contrast to **1**, **134a** and **134c**, has a high resistance index. Dispiro-1,2,4,5-tetraoxane (**134c**) is only 1.5 fold less potent than **1** against both the clones (D-6 and



**134a**



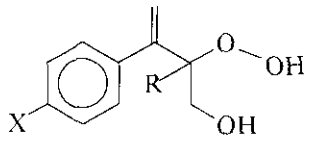
**134b**



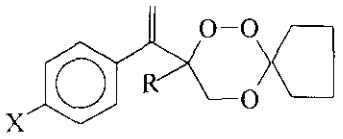
**134c**

W-2) of *P. falciparum*. The excellent activity of **134c** against *P. falciparum in vitro* is consistent with its superior single dose *in vivo* activity in comparison to **134a** and **134b**.

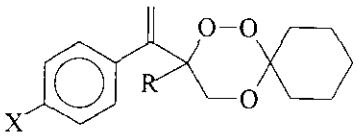
Recently, Singh *et al.*[57] prepared a series of new trioxanes belonging to 6,7,10-trioxaspiro[4.5]decane and 1,2,5-trioxaspiro[5.5]undecane series and assayed in an *in vivo* system for antimalarial activity against strain of *P. berghei*. They synthesised **136a-g** by the acid catalysed condensation of hydroperoxides (**135a-g**) with cyclopentanone in 42-61% yields. Similarly, the reaction of **135a-g** with cyclohexanone furnished trioxanes (**137a-g**) is 45-73% yields. The trioxanes (**136a-e**) and (**137b-c**) were found to be active at 90 mg/kg. Compounds (**136f-g**), (**137a**) and (**137d-g**) were inactive at this dose. At 30 mg/kg



**135a-g**



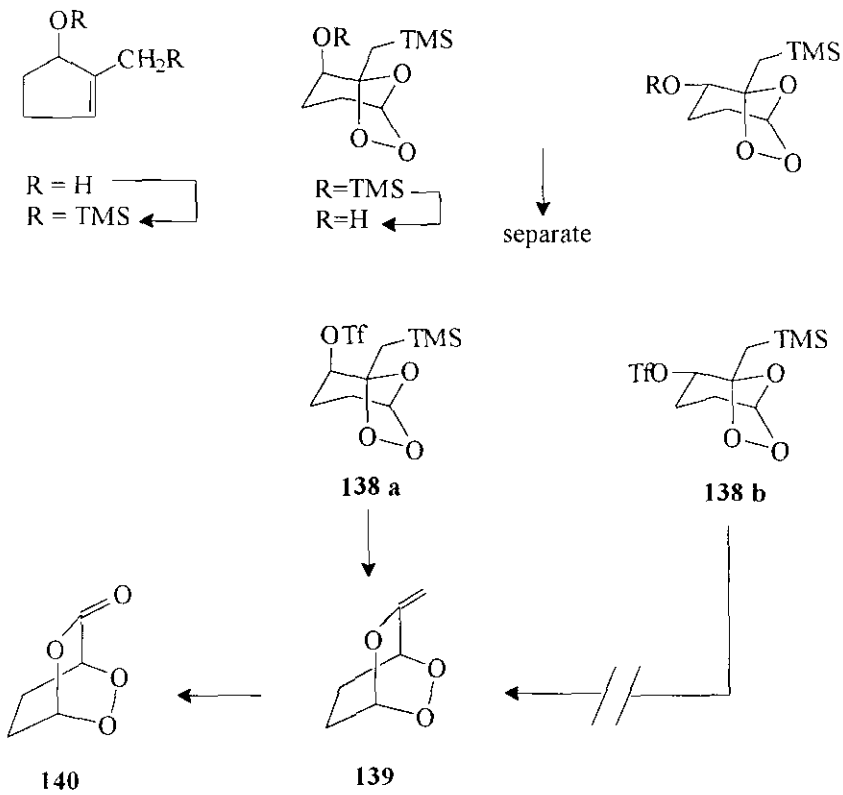
**136a-g**



**137a-g**

**a** X=R=H, **b** X=F, R=H, **c** X=Cl, R=H, **d** X=$OCH_3$, R=H, **e** X=$CH_3$, R=H, **f** X=H, R=$CH_3$, **g** X=Cl, R=$CH_3$

dose, trioxanes (**136a**) and (**136c**) showed more than 90% suppression of parasitaemia on the 6th day which eventually cleared completely and all the animals survived beyond 30 days; however, all other trioxanes were inactive at this dose. From the above mentioned pharmacological data, it is clear that 6,7,10-trioxaspiro[4.5]decanes are more active than 1,2,5-trioxaspiro[5.5]undecanes; introduction of methyl group at carbon carrying the α-arylvinyl group leads to abolition of activity and introduction of an electronegative atom in benzene ring in 1,2,5-trioxaspiro[5.5]undecane series enhances the antimalarial activity.

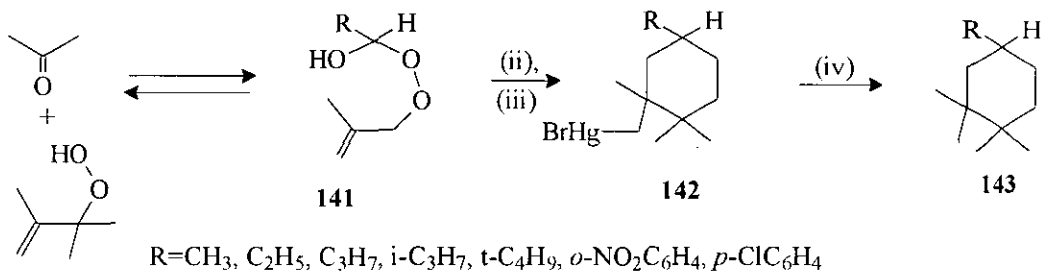


**138 a** **138 b** **140** **139**

**Scheme 20**

Bunnelle *et al.*[58] reported synthesis of 1,2,4-trioxane (**140**) envisaging a cationic ring expansion of the ozonide, involving 1,2-migration of the peroxide triggered by ionization of the leaving group. They prepared ozonide (**138**) as depicted in Scheme 20. The triflate (**138a**) on stirring at room temperature in $CH_3CN$ buffered with $NaHCO_3$ furnished compound (**139**) in 90% yield. Compound (**139**) was converted into lactone endo peroxide (**140**) with ozone. However, no antimalarial activity has been reported.

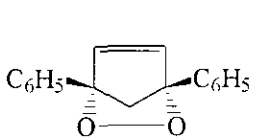
Bloodworth and Shah[59] reported synthesis of 1,2,4-trioxanes *via* intramolecular oxymercuriation. They prepared 3-alkyl- and 3-aryl-5,5,6,6-tetramethyl-1,2,4-trioxanes (**143**) by the reduction of the corresponding 5-bromomercuriomethyl compounds (**142**) obtained after anion exchange, by intramolecular oxymercuriation of the hemiperacetals (**141**) formed from aldehydes and 2,3-dimethylbut-1-en-3-yl hydroperoxide (Scheme 21). No pharmacological activity of these trioxanes has been reported.



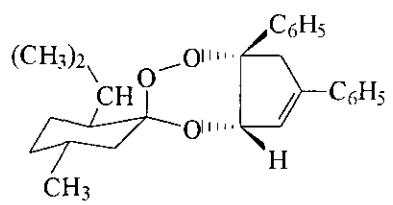

R=$CH_3$, $C_2H_5$, $C_3H_7$, i-$C_3H_7$, t-$C_4H_9$, *o*-$NO_2C_6H_4$, *p*-$ClC_6H_4$
(i) Cat. $CF_3COOH$; (ii) $Hg(OAc)_2$, 6 mol% $HClO_4$; (iii) KBr; (iv) $NaBH_4$, NaOH

**Scheme 21**

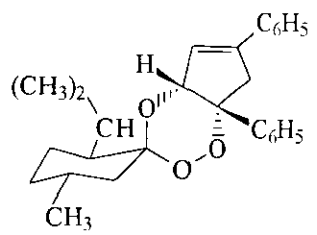
Jefford *et al.*[60] in continuation of their pioneering work on the synthesis of 1,2,4-trioxanes having better antimalarial efficacy than artemisinin (**1**) but of simple structures, reported that 1,4-diphenylcyclopent-2-



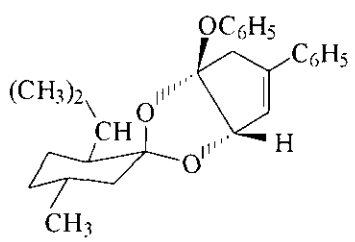

**144**




**145**




**146**

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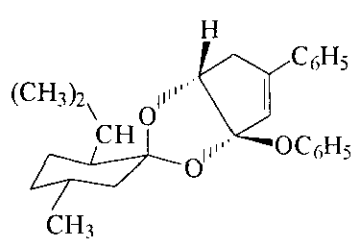
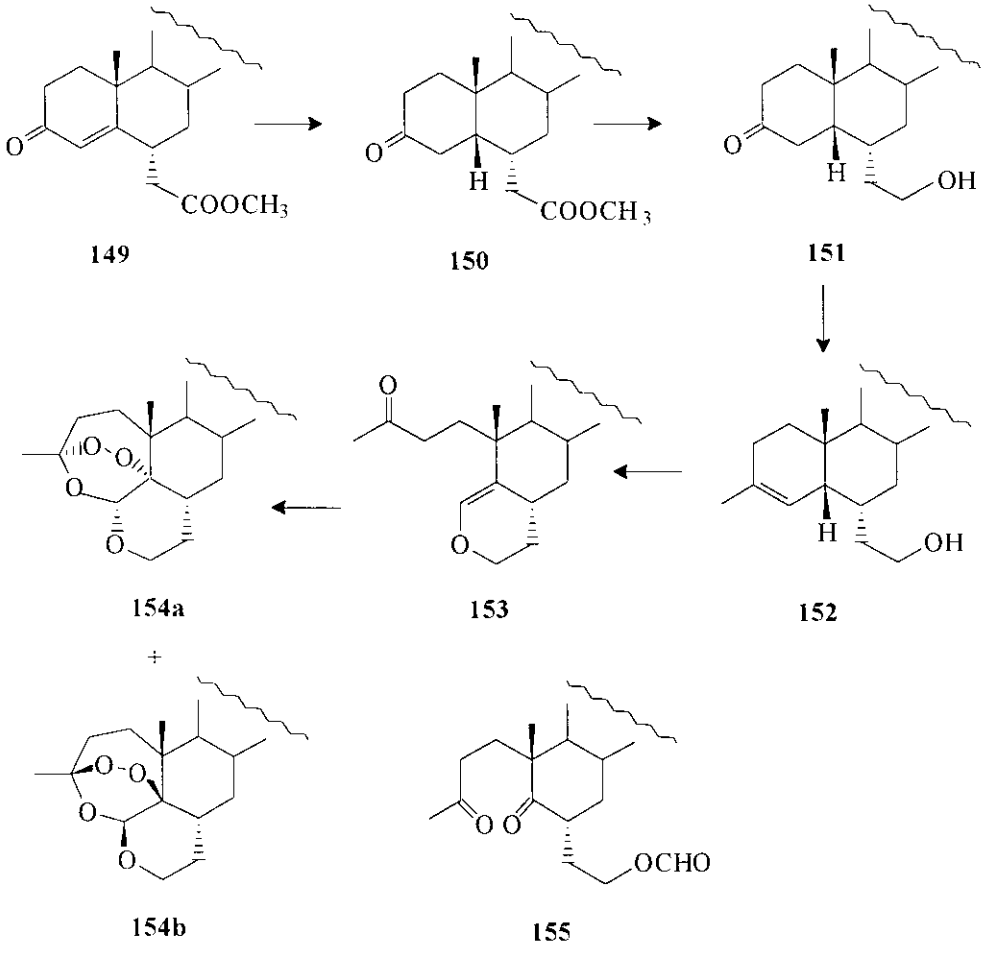



**148**

ene-1,4-endoperioxide (**144**) on catalysis with trimethylsilyl trifluoromethanesulfonate reacted with (-)-menthone in a doubly diastereoselective manner to yield two tricyclic 1,2,4-trioxanes (**145**) and (**146**) and also the corresponding pair of 1,3-dioxolanes (**147**) and (**148**) arising by Baeyer-Villiger type rearrangement. They have not reported antimalarial activity associated with any of these trioxanes.

Bloodworth *et al.*[61] reported preparation of several cyclic peroxides by cycloperoxymercuriation of unsaturated hydroperoxides. However, in their report, no antimalarial activity of these peroxides has been mentioned.

It has been proposed that artemisinin (**1**) acts primarily on membrane integrity and that its high affinity for plasmodial membranes may be because of its similarity to cholesterol, a compound of which these membranes contain little.[62] On the basis of above reasoning, Wu *et al.*[63] in 1993 decided to combine in one compound the crucial 1,2,4-trioxane structure with that of cholesterol in order to see how the




**149** **150** **151**

**154a** **153** **152**

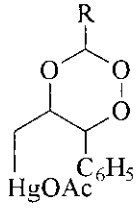
+

**154b** **155**

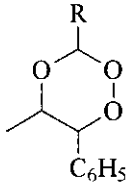
**Scheme 22**

introduction of the lipophilic steroidal moiety would affect the antimalarial activity. They expected that the presence of the cholesterol structure would increase the affinity of the compound for plasmodial membranes. Since 1,2,4-trioxane structure is accessible by photooxidation of a suitable cyclic enol ether. they chose methyl 3-oxocholest-4-en-6β-yl acetate (**149**) as the starting material (Scheme 22). Hydrogenation of **149** in pyridine with palladium catalyst furnished **150** in 80% yield. Ketalization of **150** with $CH(OMe)_3$-TsOH followed by reduction afforded **151** (82% yield). They treated **151** with methylmagnesium iodide to furnish a mixture of 3α- and 3β-alcohols which were dehydrated in acetonitrile by $CuSO_4$-$SiO_2$ to afford **152** in 89% yield. Ozonolysis of **152** at -78° C followed by treatment with *p*-TsOH-toluene yielded the key intermediate (**153**) (36% yield). The enol ether (**153**) on photooxygenation in a solution of $CH_2Cl_2$ in the presence of methylene blue at -78° C under a bubbling stream of oxygen furnished two isomers (**154a**) (16% yield) and (**154b**) (20% yield) and also a by-product (**155**). Compounds (**154a**) and (**154b**) were found to be more effective than artemisinin (**1**) *in vivo* against *P. berghei*.

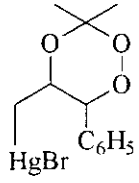
Bloodworth *et al.*[64] reported synthesis of 3,5,6-trisubstituted 1,2,4-trioxanes (**156a-c**) by treating hemiperoxy acetals, derived from 1-phenyl-prop-2-enyl hydroperoxide with mercury(II) acetate and perchloric acid catalyst.




**156a**

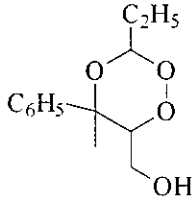



**156b**

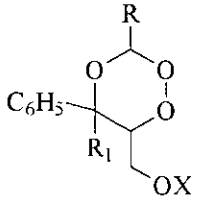



**156c**

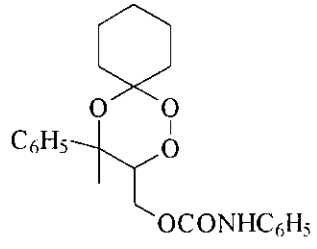
R=$CH_3$, i-$C_3H_7$, $C_2H_5CH(CH_3)$, $CCl_3$




**157a**




**157** **b** R=$R_1$=$C_2H_5$, X=$CONHC_6H_5$
**c** R=$C_3H_7$, $R_1$=$CH_3$, X=$CONHC_6H_5$
**d** R=$C_2H_5$, $R_1$=$CH_3$, X=$COOCH_3$

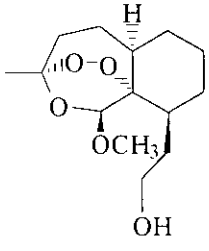



**157e**

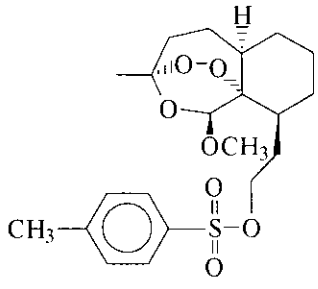
The same authors[65] reported another route for the synthesis of 6-hydroxymethyl-1,2,4-trioxanes and derivatives from β',γ'-unsaturated β-hydroxy peroxides. They observed that allylic hydroperoxides $CH_2$:$C(C_6H_5)CH(OOH)CH_2OX$ (X=H, $CONHC_6H_5$, Ac) from regiospecific photooxygenation of allylic alcohols $CH_3C(C_6H_5)$:$CHCH_2OX$ form hemiperoxy acetals with aldehydes or ketones which upon cyclisation with mercury(II) trifluoroacetate followed by reduction with sodium borohydride diastereoselectively afforded 1,2,4-trioxanes (**157a-e**).

**Synthesis of 1,2,4-trioxanes related to artemisinin**

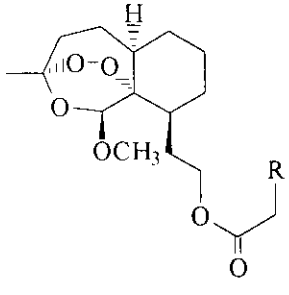
Posner *et al.*[66] in 1992 reported the synthesis of a new racemic tricyclic trioxane alcohol (**158**) from commercially available cyclohexanone in 9 steps as a structurally simple analogue of clinically useful artemisinin (**1**). Further, they prepared a series of twenty ester and ether derivatives of alcohol (**158**) without disturbing the crucial trioxane system. Chemical structure-antimalarial activity for each derivative was evaluated *in vitro* against chloroquine resistant and chloroquine-sensitive *P. falciparum* parasites. Many of these derivatives showed high efficacy; carboxylate ester (**160c**), carbamate ester (**160d**) and sulfonate ester (**159**) showed antimalarial potency similar to that of artemisinin (**1**) and carboxylate esters (**160a**) and (**160b**), carbamate esters (**160e**) and (**160f**) and phosphate esters (**161a-c**) showed antimalarial



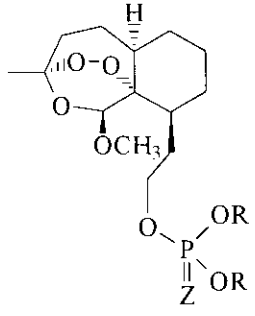
**158**



**159**



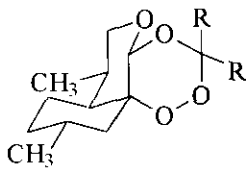
| R | |
|---|---|
| **160a** | $CH_3OOCC_6H_4(CH_3)$-*p* |
| **b** | $(C_2H_5)NCOC_6H_4(CH_3)$-*p* |
| **c** | $CH_3(CH_3)_2CHOOCNHCH_2$- |
| **d** | $(CH_3)_2N$-; **e** $(C_2H_5)_2N$- |
| **f** | $(C_6H_5)_2N$- |



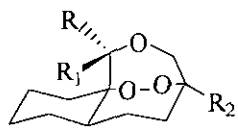
| | R | Z |
|---|---|---|
| **161 a** | $C_6H_5$ | O |
| **b** | $C_2H_5$ | O |
| **c** | $C_2H_5$ | S |

potency upto seven times higher than that of artemisinin (**1**). Several of these most active analogues e.g. (**160a**), (**160d**) and (**160f**) were found to be stable, crystalline solids, a feature of considerable practical value for any new drug candidate.

Jefford *et al.*[67] in 1993 reported synthesis and antimalarial activity of tricyclic 1,2,4-trioxanes contain ing the ABC (**162a** and **b**) and ACD ring portions (**163a-f**) of artemisinin (**1**) which were synthesised by successive photooxygenation of appropriate enol ether precursors to 1,2-dioxanes and inter and intramolecular reaction with a carbonyl compound or oxo-substituted side chain. *In vitro* antimalarial activity of these trioxanes against chloroquine sensitive and chloroquine-resistant *P. falciparum* parasites showed that trioxanes (**162b**) and (**163a**) were as active as artemisinin (**1**). The structure-activity relationship (SAR) demonstrated that neither the lactone function nor rings B and D of artemisinin (1) were essential for antimalarial activity.



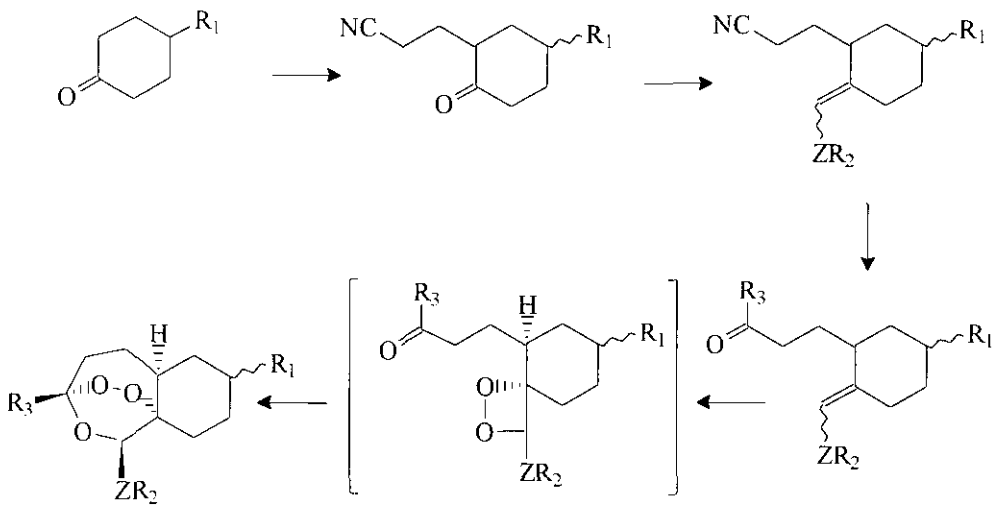
**162a** R = $CH_3$
**b** R= -$(CH_2)_4$



**163a** R=H, $R_1$=$OCH_3$, $R_2$=$CH_3$
**b** R=$OCH_3$, $R_1$=H, $R_2$=$CH_3$
**c** R=H, $R_1$=$OCH_3$, $R_2$=$C_6H_5$
**d** R=$OCH_3$, $R_1$=H, $R_2$=$C_6H_5$
**e** R=H, $R_1$=$OCH_3$, $R_2$=H
**f** R=$OCH_3$, $R_1$=$R_2$=H

In continuation of their efforts to synthesise novel 1,2,4-trioxanes related to artemisinin (**1**), Posner *et al.*[68] in 1995 reported the synthesis and antimalarial activities of eleven derivatives of tricyclic 1,2,4-trioxanes (**165a-k**). They took cyclohexanone and its 4-substituted derivatives and prepared the key intermediate (**164a-k**) as depicted in Scheme 23. They have demonstrated the usefulness of $(C_2H_5)_3SiOOOH$ as a new dioxetane-forming reagent not involving oxygen as evidenced by the conversion of keto vinyl ethers (**164a-k**) into 1,2,4-trioxanes (**165a-k**) in 3- 61% yields. These trioxanes (**165a-k**) were tested *in vitro* against the African Sierra Leone (D-6) and the Indochina (W-2) clones of *P. falciparum* for their antimalarial activity. Two analogues (**165d**) and (**165g**) showed antimalarial activities similar to that of artemisinin (**1**) having $IC_{50}$ values of 1.74 and 0.86 ng/mL respectively against the W-2 clone. Other analogues showed considerable *in vitro* antimalarial activity against the W-2 clone. On the basis of antimalarial activity data of these analogues, Posner *et al.* observed that qualitative SAR generalizations point to the importance of lipophilicity in increasing the likelihood that a new artemisinin

analogue will have strong antimalarial activity and further observed that structural variations at several different positions of simple 1,2,4-trioxanes like (**165a-k**) could be made without undermining antimalarial activity.

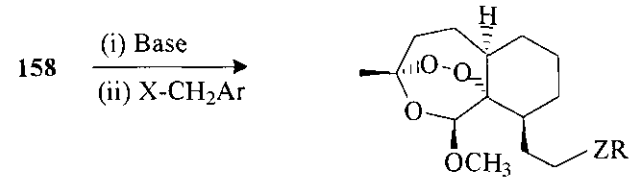


**165a-k** **164a-k**

**a** $R_1$=H, $ZR_2$=$OCH_3$, $R_3$=$CH_3$, **b** $R_1$=$C_2H_5$, $ZR_2$=$OCH_3$, $R_3$=$CH_3$,
**c** $R_1$=$C_6H_5$, $ZR_2$=$OCH_3$, $R_3$=$CH_3$, **d** $R_1$=$CH_3$, $ZR_2$=$OCH_3$, $R_3$=$CH_3$,
**e** $R_1$=H, $ZR_2$=$OC_2H_5$, $R_3$=$CH_3$, **f** $R_1$=H, $ZR_2$=$SCH_3$, $R_3$=$CH_3$,
**g** $R_1$=H, $ZR_2$=$OCH_3$, $R_3$=$CH_3$, **h** $R_1$=H, $ZR_2$=$OCH_3$, $R_3$=$HOCH_2CH_2$,
**i** $R_1$=H, $ZR_2$=$OCH_3$, $R_3$=$C_2H_5$, **j** $R_1$=H, $ZR_2$=$OCH_3$, $R_3$=$C_6H_5$,
**k** $R_1$=H, $ZR_2$=$OCH_3$, $R_3$=$C_6H_5CH_2$

**Scheme 23**

The same authors[69] reported the synthesis and antimalarial activity of several lactone ring-opened analogues of artemisinin by alkylating previously synthesised trioxane alcohol (**158**) with various benzylic halides (Scheme 24). *In vitro* antimalarial activity of these analogues against *P. falciparum* demonstrated that trioxane fluorobenzyl ether (**166b**) stands out as the most active in this series [more active than artemisinin (**1**)] with considerable activity also in mice infected with *P. berghei* and with ten times higher activity than artemisinin (**1**) in killing immature *P. falciparum* gametocytes. Several potentially chelating derivatives *viz.* 2-pyridyl system (**166c**), heteroaromatic carboxylates (**166f** and **g**), quinolene sulfonate (**166h**) and two water soluble quaternary ammonium salts (**166e**) and (**166j**) were not especially active antimalarials *in vitro*. They predicted that these qualitative SAR results may help in designing better trioxane drugs for chemoprevention and chemotherapy of malaria.




**166a-j**

**166a** ZR = -$OCH_2$-$C_6H_4$-$C_6H_5$ **b** ZR = -$OCH_2$-$C_6H_4$-(*p*)-F

**c** ZR = -$OCH_2$-(N-heterocycle)

**d** ZR = -$OCH_2$-(N-heterocycle)

**e** ZR = -$OCH_2$-(N-heterocycle)$^+$-$CH_3$ $I^-$

**f** ZR = -OOC-(N-heterocycle)

**g** ZR = -OOC-(N-heterocycle)

**h** ZR = -$O_3S$-(N-heterocycle)

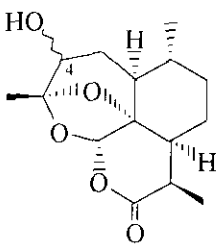
**i** ZR = —N(N)—(C$_6$H$_4$)—F

**j** ZR = —N$^+$(CH$_3$)(N)—(C$_6$H$_4$)—F $I^-$

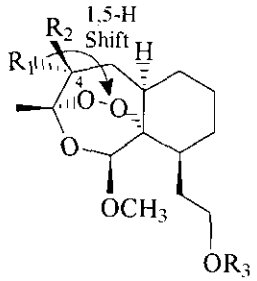
**Scheme 24**

*Posner et al.*[27i] reported synthesis of new 4-methylated trioxanes structurally related to artemisinin (**1**) in order to prove that 1,5-hydrogen atom transfer (specifically $H_{4\alpha}$ ) is a critical step for antimalarial activity and for the formation of the typical microbial metabolite hydroxylated dioxolane (**167**). Preventing such a 1,5-shift by a structural modification of the trioxane skeleton should effectively shut down this mechanistic pathway and thus, also shut down antimalarial activity. They prepared analogues (**168a-c**) and evaluated their antimalarial efficacy *in vitro* against W-2 and D-6 clones of *P. falciparum*. The antimalarial activities of these analogues demonstrated that 4β-methylated trioxane (**168a**) that could undergo the 1,5-hydrogen atom transfer was at least 100 times more potent than 4α-methylated trioxane (**168b**) and (**168c**), those could not undergo such a hydrogen atom transfer. Finally, 4β-methylated trioxane (**168a**) was found to be more potent than artemisinin (**1**). The observations made by Posner *et al.* suggested for the first time that a reaction pathway proceeding *via* a carbon-centered radical is likely to be important for the antimalarial activities of some trioxanes like artemisinin (**1**).

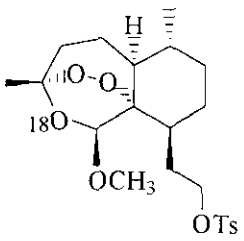
The same authors[27ii] reported synthesis of regiospecifically oxygen-18 labelled 1,2,4-trioxane (**169**), a potent antimalarial compound in order to gain better understanding at the molecular level of antimalarial activity of activated artemisinin (**1**), since the hemin-rich internal environment of malarial parasites is thought to be responsible for the selective toxicity of trioxanes like artemisinin (**1**) toward these parasites. Their study provided firm mechanistic evidence that deoxygenation of a 1,2,4-trioxane into the correspond-



167



**168a** $R_1$=H, $R_2$=$CH_3$
**b** $R_1$=$CH_3$, $R_2$=H
**c** $R_1$=$R_2$=$CH_3$

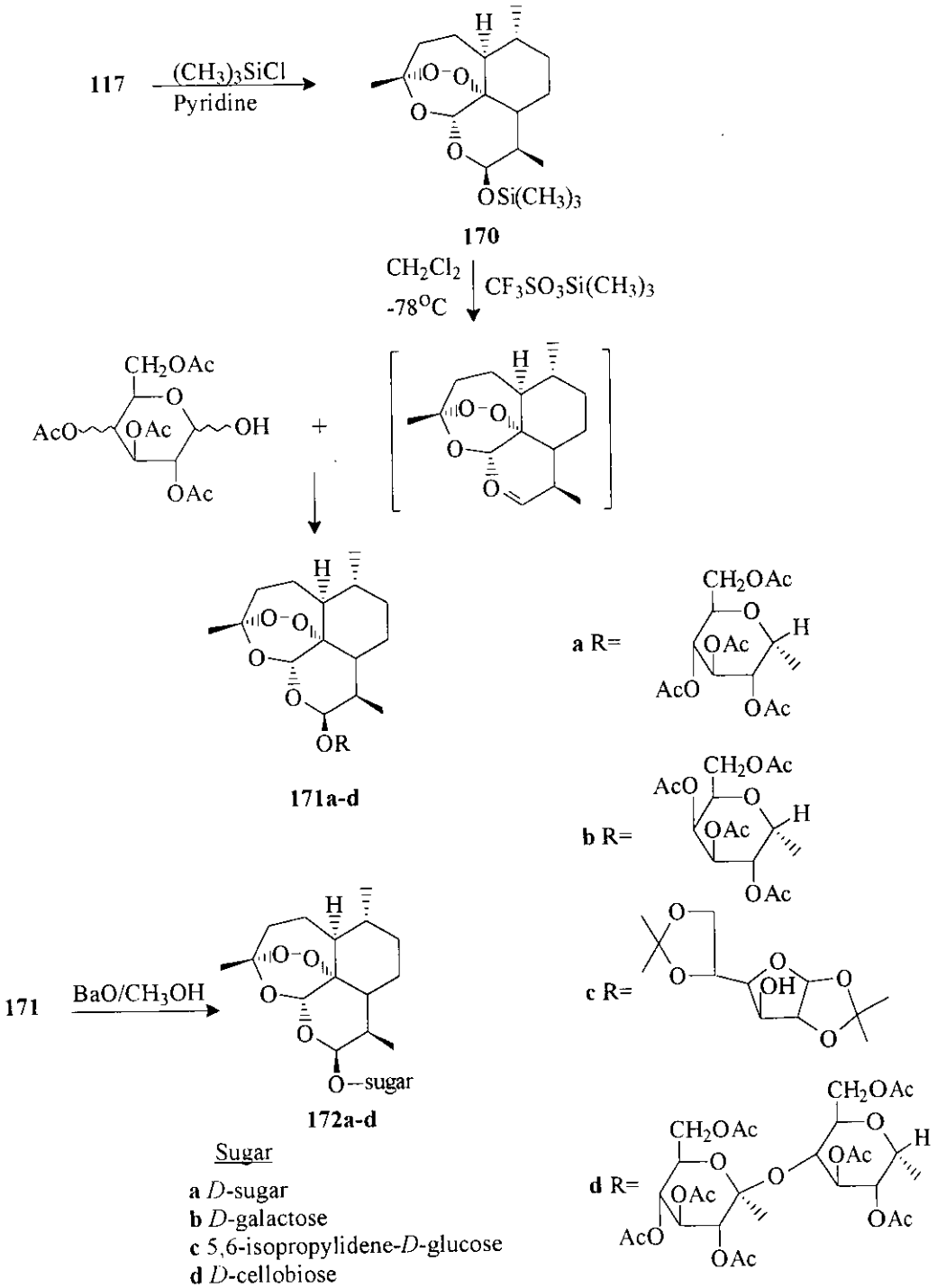


169

ing 1,3-dioxolane occurs *via* a tandem unzipping-zipping process and further showed that trioxane cleavage by ferrous ions follows a different mechanistic course and leads to different products than trioxane cleavage by non ferrous reducing agents.

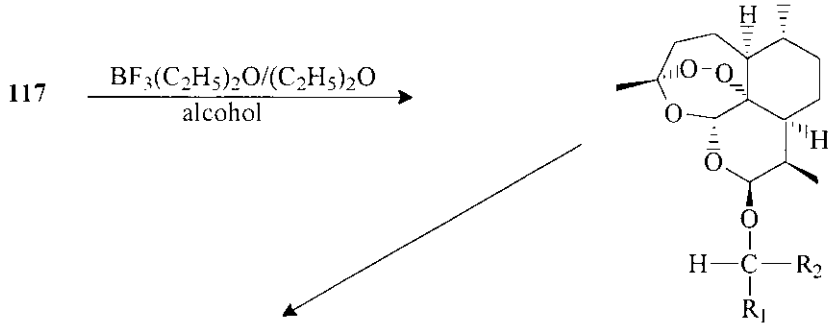
## VI. SYNTHESIS OF ETHERS, ESTERS AND OTHER DERIVATIVES OF DIHYDROARTEMISININ

In continuation of their search for new artemisinin analogues with enhanced water solubility and high antimalarial activity, Lin *et al.*[70] in 1992 reported synthesis and antimalarial activities of new dihydroartemisinin derivatives which contain a sugar moiety. The preparation of new derivatives was achieved by treatment of dihydroartemisinin (**117**), which was prepared according to literature procedure, with chlorotrimethylsilane in pyridine solution at -10° C to furnish 12-*O*-(trimethylsilyl)dihydroartemisinin (**170**) in quantitative yield. Compound (**170**) was then condensed with 1-hydroxy polyacetylated sugars in presence of a catalytic amount of trimethylsilyl trifluoromethane sulfonate in $CH_2Cl_2$ at -78° C to give the acetylated sugar-dihydroartemisinin derivatives (**171a-d**). Deacetylation of intermediates (**171a-d**) furnished the desired sugar derivatives (**172a-d**) in 50-85% yield (Scheme 25). The resulting derivatives when tested *in vitro* against *P. falciparum* were found to be more effective against W-2 and D-6 clones and were not cross-resistant with existing antimalarials. Compound (**170**) was more effective than derivatives (**171a-d**) which possess activity comparable to or better than that of artemisinin (**1**) itself. However, deacetylated compounds (**172a-d**) were found to be substantially less active than **171a-d** in both cell lines. In *P. berghei* infected mice, compounds (**171a-c**) showed 5/5, 2/5 and 3/5 cures respectively at 320 mg/kg per day for 3 days whereas **171d** showed no activity at the same dosage. Compound (**170**) was also the most effective among the derivatives studied with 5/5 cures at 80 mg/kg per day for 3 days. The sugar derivatives (**172a-d**) showed only slight *in vivo* antimalarial activity. The antimalarial activity results suggested that the *in vitro* activity of these new derivatives parallel those observed *in vivo* tests and that the increase in polarity or water solubility tends to decrease antimalarial activity.


117
(CH3)3SiCl
Pyridine
OSi(CH3)3
170
CH2Cl2
-78°C
CF3SO3Si(CH3)3
CH2OAc
AcO
OAc
OH
OAc
+
OR
171a-d
a R=
b R=
c R=
d R=
171
BaO/CH3OH
O--sugar
172a-d
Sugar
a D-sugar
b D-galactose
c 5,6-isopropylidene-D-glucose
d D-cellobiose

**Scheme 25**

The same authors[71] in 1995 reported synthesis of a series of new dihydroartemisinin α-alkyl benzylic ethers (Scheme 26) and assayed their *in vitro* antimalarial activity against W-2 and D-6 clones *P. falciparum*. As was observed with the existing derivatives of this class, these new compounds showed higher inhibitory activity against W-2 and D-6 clones. Compound (**173i**) ($IC_{50}$= 0.0487 ng/mL against W-2 and 0.2463 against D-6) which was found to be the most active of this class, showed inhibitory activity about 10-, 20- and 40- fold better than artemether (**116c**), artemisinin (**1**) and artelinic acid (**197c**) respectively.




**173a-k**

**174a-c**

| | $R_1$ | $R_2$ |
|---|---|---|
| **a** | (*R*) $-CH_3$ | *p*-$COOHC_6H_4$- |
| **b** | (*S*) *p*-$COOHC_6H_4$- | $-CH_3$ |
| **c** | (*R*) $-CH_2COOH$ | *p*-$NO_2C_6H_4$- |

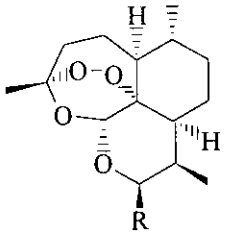
| | $R_1$ | $R_2$ |
|---|---|---|
| **a** | (*R*) $-CH_2CH_2CH_3$ | $-CH_2C_6H_5$ |
| **b** | (*S*) $-CH_2C_6H_5$ | $-CH_2CH_2CH_3$ |
| **c** | (*R*) $-C_6H_5$ | $-COOCH_2CH_3$ |
| **d** | (*S*) $-COOCH_2CH_3$ | $-C_6H_5$ |
| **e** | (*R*) $-CH_3$ | *p*-$CF_3C_6H_4$- |
| **f** | (*R*) $-CH_2COOCH_2CH_3$ | $-C_6H_5$ |
| **g** | (*S*) $-C_6H_5$ | $-CH_2COOCH_2CH_3$ |
| **h** | (*R*) $-CH_2COOCH_2CH_3$ | *p*-$NO_2C_6H_4$- |
| **i** | (*S*) *p*-$NO_2C_6H_4$- | $-CH_2COOCH_2CH_3$ |
| **j** | (*R*) $-CH_3$ | *p*-$COOCH_3C_6H_4$- |
| **k** | (*S*) *p*-$COOCH_3C_6H_4$- | $-CH_3$ |

**Scheme 26**

The fact that compounds (**173e, j** and **k**) which have a small methyl group substituted at the α-methylene carbon showed weaker activity than the compounds with a carbethoxyalkyl substituent *viz.* (**173c,d** and **f-i**) suggested that the lipophilicity and the steric effects of the molecule play an important role in their antimalarial activity. This fact was further corroborated by the significantly weaker antimalarial activity of the carboxylic acids (**174a-c**) than their corresponding esters (**173h,j** and **k**) respectively. Furthermore, since compound (**173i**) with a $NO_2$ substituent was three fold more potent than the unsubstituted **173g**, the electronic effect also contributed significantly to the activity. The *S*-isomers in general are several fold

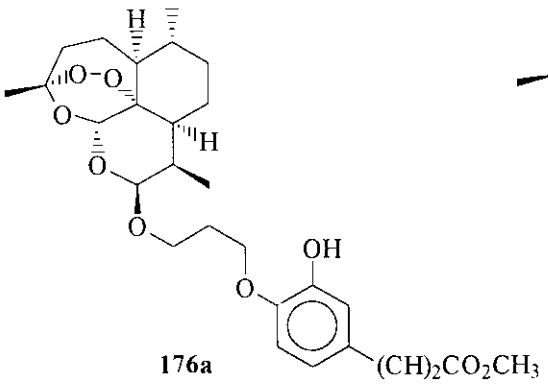
more active than the corresponding *R*-isomers. The differences in antimalarial activity observed with the *R*- and *S*-diastereomers suggested the possibility of the involvement of enzymatic bioactivation as a mode of action.

In the same year, Ziffer *et al.*[72] reported stereoselective synthesis of 12β-allyldeoxoartemisinin (**175a**) from dihydroartemisinin (**117**) and subsequent transformations to other 12β-alkyldeoxoartemisinins (**175b-d**). These analogues were tested for their antimalarial efficacy against W-2 and D-6 clones of *P. falciparum* in order to test the hypothesis that dihydroartemisinin (**117**) was responsible for the toxicity observed[46,73] in dogs given repeated large doses of arteether (**116a**). *In vitro* activity of these analogues indicated that 12β-propyldeoxoartemisinin (**175b**) was almost as active as β-arteether (**116a**). The *in vivo* activity and toxicity of **175b** were comparable to that of arteether (**116a**) although **175b** could not be converted into dihydroartemisinin (**117**).

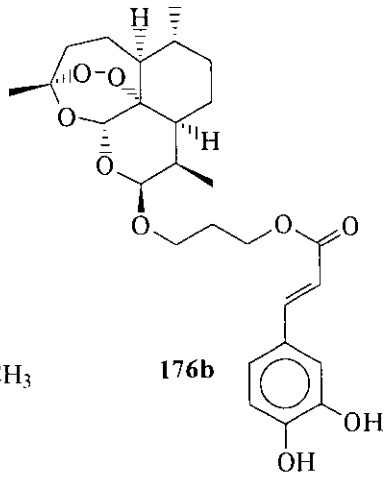


**175a** R= $CH_2CH{=}CH_2$; **b** R= $CH_2CH_2CH_3$
**c** R= $CH_2CH_3$; **d** R= $CH_2CH_2OH$

Yuthavong *et al.*[74] have reported the synthesis of various derivatives of artemisinin (**1**) covalently linked to iron chelators (**176a-d**) and evaluated their antimalarial efficacy against *P. falciparum* malaria. *In vitro*

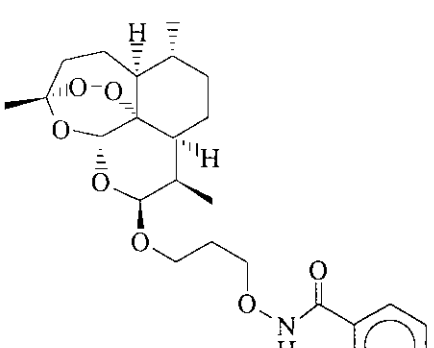


**176a**

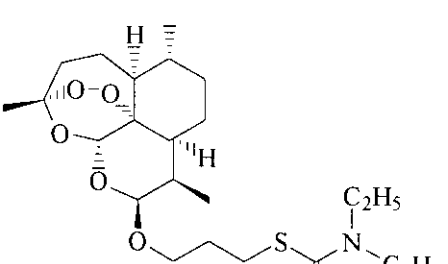


**176b**

antimalarial test data showed no indication that the presence of an iron chelator in the vicinity of artemisinin potentiates its action, the linked compounds synthesised still retained comparable activities



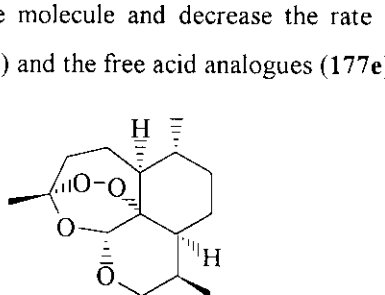
**176c**



**176d**

to that of artemisinin (**1**).

Most recently Lin *et al.*[75] reported the synthesis of a series of new stereoisomers of 4-(*p*-substituted phenyl)-4'(*R* or *S*)-[10(α or β)-dihydroartemisinoxy]butyric acids (**177e-h**) as potential antimalarial agents. These authors have taken two approaches in the designing of these new compounds in their attempt to increase the lipophilicity of the molecule and decrease the rate of oxidative dealkylation of the target compounds. The esters (**177a-d**) and the free acid analogues (**177e**) and (**177g**) with $IC_{50}$ values less than



**177a** $R_1$=Cl, $R_2$=$CH_3$, **b** $R_1$=F, $R_2$=$CH_3$,
**c** $R_1$=Br, $R_2$=$CH_3$, **d** $R_1$=$OCH_3$, $R_2$=$CH_3$
**e** $R_1$=Cl, $R_2$=H, **f** $R_1$=F, $R_2$=H,
**g** $R_1$=Br, $R_2$=H, **h** $R_1$=$OCH_3$, $R_2$=H

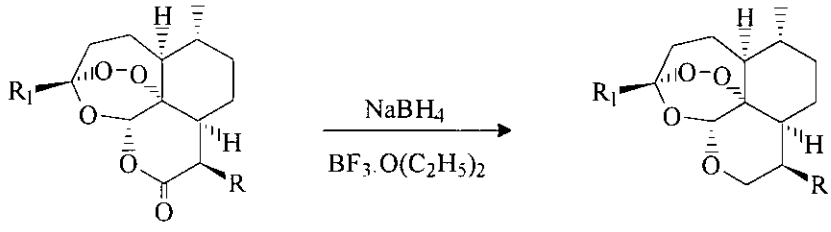
1 ng/mL were found to be as active as the lipophilic arteether (**116a**). In general, the new compounds showed a 2-10 fold increase in *in vitro* antimalarial activity against D-6 and W-2 clones of *P. falciparum* than artemisinin (**1**) or artelinic acid (**197c**).

The same authors[76] have also reported the synthesis of 11-hydroxy esters from dihydroartemisinin (**117**) as the new antimalarial agents.

## VII. CHEMICAL AND BIO-TRANSFORMATION OF ARTEMISININ AND ITS ANALOGUES

### Chemical transformations

Avery *et al.*[49] on the basis of quantitative structure-activity relationship studies reported synthesis of analogues of 12-deoxoartemisinin substituted at C-4 and C-11. They prepared 4- and 11-substituted analogues of 12-deoxoartemisinin (**179a-p**) from the corresponding lactones by one-pot reduction with $NaBH_4$ and $BF_3.(C_2H_5)_2O$ (Scheme 27). They faced reproducibility problems associated with this heterogeneous reaction on small reaction scales and hence they devised an alternative methodology for this

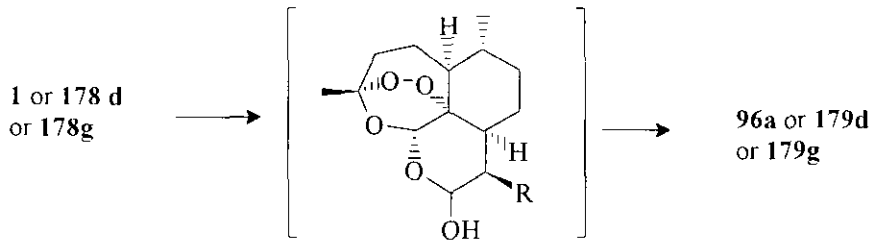



**178a-p** **179a-p**

**a** $R_1$=$CH_3$, R=H; **b** $R_1$=$CH_3$, R=$CH_2CH_3$; **c** $R_1$=$CH_3$, R=$(CH_2)_2CH_3$;
**d** $R_1$=$CH_3$, R=$(CH_2)_3CH_3$; **e** $R_1$=$CH_3$,R=$(CH_2)_4CH_3$; **f** $R_1$=$CH_3$, R=$(CH_2)_3C_6H_5$;
**g** $R_1$=$CH_3$, R=*p*-$ClC_6H_4(CH_2)_3$; **h** $R_1$=$CH_3CH_2$, R=H; **i** $R_1$=$CH_3(CH_2)_2$, R=H;
**j** $R_1$=$CH_3(CH_2)_3$, R=H; **k** $R_1$=$(CH_3)_2CHCH_2$, R=H; **l** $R_1$=$C_6H_5(CH_2)_4$, R=H;
**m** $R_1$=$C_6H_5(CH_2)_2$, R=H; **n** $R_1$=*p*-$ClC_6H_4(CH_2)_3$, R=H; **o** $R_1$=$(CH_2)_2COOC_2H_5$, R=H;
**p** $R_1$=$(CH_2)_2COOH$, R=H

**Scheme 27**

reduction. Based on the novel discovery made by Kraus *et al.*[77] that lactones could be converted into ethers, Avery *et al.*[49] converted lactones to tetrahydropyrans *via* the corresponding intermediate lactols which was made more reproducible using a two-step sequence involving low-temperature reduction with diisobutylaluminium hydride followed by deoxygenation with boron trifluoride etherate in the presence of triethylsilane (Scheme 28). This methodology yielded analogues of 12-deoxoartemisinin(**179a-p**) substituted at C-4 and C-11. The SAR showed that *in vitro* antimalarial activity against the W-2 clone, the homologous series ranging from H to propyl shows a relatively steady potency at five times the activity of artemisinin (**1**). But for butyl (**179d**), a dramatic improvement in potency was observed at about 21 times that of artemisinin (**1**) while for pentyl (**179e**), activity had dropped off somewhat to around 1.5 times the potency of artemisinin (**1**). Since the activity in the W-2 clone is generally paralleled by the more sensitive

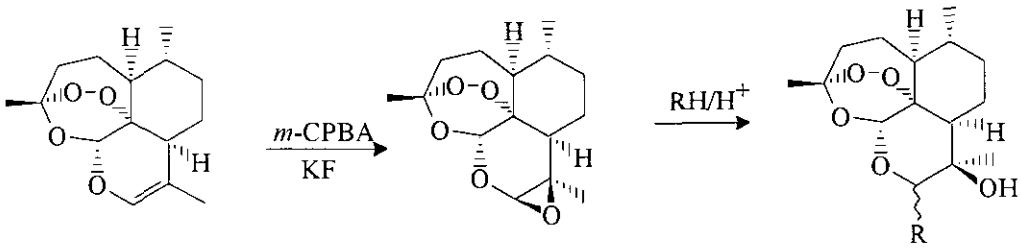



**Scheme 28**

D-6 clone, the potency ranged from two times of **1** for analogue (**179a**) up to 58 times of **1** for the butyl derivative (**179d**) and finally decreased as expected for the pentyl homologue (**179e**). Profound potency enhancement was observed for the 3-arylpropanes (**179f**) and (**179g**) against both W-2 and D-6 clones, being in the range of 25-70 times more potent than artemisinin (**1**). For the C-4 ethyl-substituted analogue (**179h**), a mere one-carbon homologation of compound (**179a**) leads to a significant drop in activity. However, homologation by two carbons, C-4 propyl analogues (**179i**) results in approximately a 70 times enhancement over (**179h**). For C-4 butyl (**179j**), activity dropped only slightly. However, the effect of branching *viz.* C-4 isobutyl (**179k**) is apparently detrimental toward antimalarial activity. The same effect was observed for C-11 substituted lactones e.g. n-alkanes were usually significantly more active than the homologous isoalkanes. It is important to note here that the effect of activity of arylalkyl substitution at C-4 is completely different than observed in the C-11 series. The 4-(*p*-chlorophenyl)propyl substituted analogue (**179n**), isomeric with highly potent 11-(*p*-chlorophenyl)propyl analogue (**179g**) was found to be practically devoid of antimalarial activity. From the above mentioned test data, it is clear that the anti-malarial activity among artemisinin analogues can not be explained solely on the basis of hydrophobicity.

According to a recent assumption,[78] the antimalarial effect of dihydroartemisinin (**117**) could be connected with the specific assembly of oxygen atoms in a rigid lipophilic molecule, favouring interactions mainly with the parasite membranes. In the light of this suggestion introduction of an additional oxygen substituent in the polar edge of the molecule may improve the selectivity and increase the antimalarial activity. Based upon this rationale, Ognyanov *et al.*[79] synthesised novel 11-hydroxyartemisinin derivatives using the epoxide (**181**) as a key intermediate. They prepared anhydrodihydroartemisinin (**180**) in 90% yield from artemisinin (**1**) using already reported methods.[80] Epoxidation of **180** with the 1:2 complex of *m*-CPBA/KF in $CH_2Cl_2$ at 0° C proceeded with high stereoselectivity furnishing the key intermediate (**181**) in 60% yield. The peroxide (**181**) was found to be highly sensitive to acids and even in the presence of wet silica gel could easily be transformed to 11-hydroxydihydroartemisinin (**182b**) and similarly to other alkoxysubstituted oxiranes. Compound (**181**) smoothly underwent regioselective oxirane ring opening

when treated with alcohols or carboxylic acids giving the corresponding C-12 derivatives of 11-hydroxydihydroartemisinin (**182a,c-e**) in quantitative yields (Scheme 29). However, in their report, no mention of the antimalarial activity of these compounds has been made.

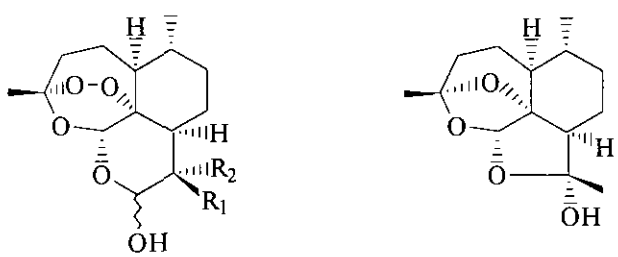



**180** **181**

**182a** R=*m*-$ClC_6H_4COO(\beta)$
**b** R=OH ($\alpha + \beta$)
**c** R=$CH_3COO$ ($\beta$)
**d** R=$CH_3O$ ($\beta$)
**e** R=$CH_3O$ ($\alpha$)

**Scheme 29**

Ziffer *et al.*[81] observed novel silica gel catalysed reactions of dihydroartemisinin (**117**) to deoxy-artemisinin (**69b**) and 11β-hydroxy-12-epidihydroartemisinin (**183**) to compound (**184**) under mild conditions. They demonstrated that the 1,2,4-trioxane system opens and undergoes a series of reactions under very mild acidic conditions on silica gel surfaces. It is pertinent to mention here that the configuration of the hydroxy group at C-11 controls the conversion of peroxide (**183**) into oxide (**184**).

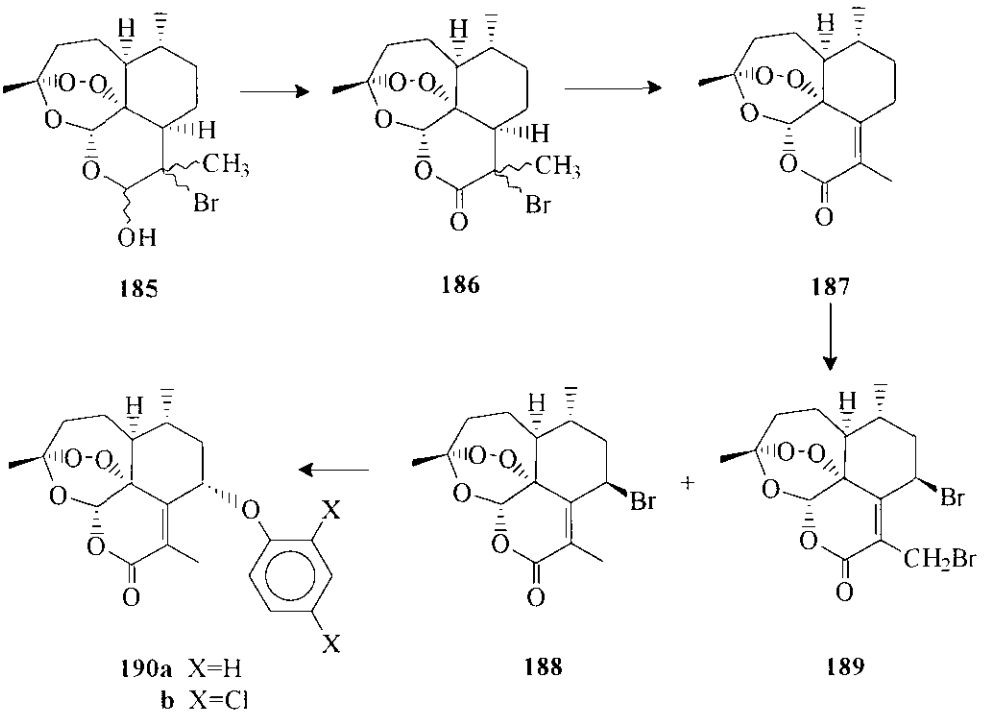


**183** $R_1$ = OH, $R_2$ = $CH_3$ **184**
(**183a** = 12β-OH, **183b** = 12α-OH)

In 1994, Sharma *et al.*[82] observed that when β-arteether (**116a**) is treated with anhydrous ferric chloride in $CH_2Cl_2$ at 0°C, it epimerises to α-arteether (**116b**) in excellent yield. Their observation is noteworthy because in the synthesis of 70:30 mixture of β-/α-arteethers (**116a/b**), which is currently being developed as a new candidate antimalarial drug,[83] α-arteether (**116b**) is formed in low yield.

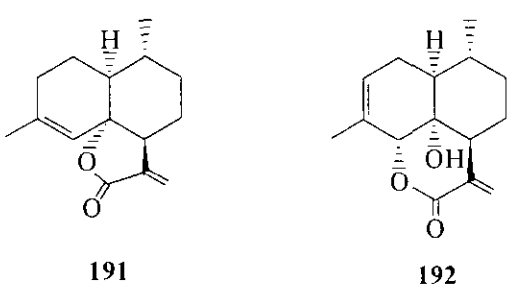
Venugopalan and Bapat[84] reported the synthesis of isoartemisinin (**187**) and its derivatives through functionalisation in order to study the detailed mechanism of action. The oxidation of bromohydrin (**185**)

with pyridinium chlorochromate in $CH_2Cl_2$ furnished the bromo lactone (**186**) in 85% yield which on exposure with DBU provided isoartemisinin (**187**) in 85% yield (Scheme 30). The aryl ether derivatives (**190a**) and (**190b**) were obtained from compound (**188**) by treating it with phenol and substituted phenol in the presence of NaH/DMF. These derivatives showed moderate activity against *P. berghei* in the mice model as compared to arteether (**116a**).

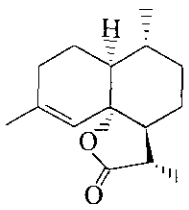



**Scheme 30**

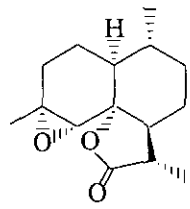
Recently Sharma *et al.*[85] in their effort to synthesise deoxyarteannuin B (**191**) from arteannuin B (**3**), treated the latter with chlorotrimethylsilane and sodium iodide in acetonitrile. They obtained an acid-catalysed rearranged δ-lactone, 6α-hydroxyisoannulide (**192**) which was identified on the basis of 2D NMR studies and chemical transformations.



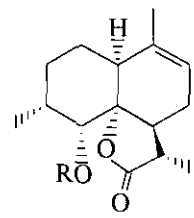
In an attempt to prepare the dihydrodeoxyarteannuin B (**193**), the same authors[86] studied the reaction of dihydroarteannuin B (**194**) with boron trifluoride-acetic anhydride at 0-5°C. The major product obtained was identified as the rearranged product (**195a**) based on its extensive chemical transformations, 2D NMR studies and finally the X-Ray analysis of the single crystals of the alcohol (**195b**). 1,3 or 1,5-Hydride shift has been proposed in the formation of **195a**. Compound (**195b**) opens new vistas for its elaboration to C-9 and C-10 functionalized artemisinin analogues by known methodologies.



**193**



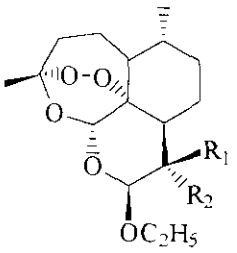
**194**



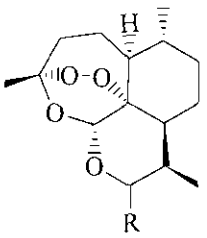
**195a** R=Ac
**b** R=H

El-Feraly *et al.*[87] reported the synthesis of β-arteether (**116a**) and 11-epi-arteether (**196a**) by treating anhydrodihydroartemisinin (**180**), which was prepared according to the previously reported procedures[80ii] with absolute $C_2H_5OH$ in the presence of *p*-toluenesulfonic acid as a catalyst to afford **116a** and **196a** as major and minor products respectively. They have also observed that when $CH_2Cl_2$ is used as a solvent, **196a** is obtained as the major product. They have also shown that this procedure could be used to prepare C-11 deuterated arteether (**196b-c**) which may be utilised for metabolic studies.

Vishwakarma *et al.*[88] reported stereoselective synthesis of α-artelinic acid (**197b**) as the potent, stable and water-soluble antimalarial agent and its blood schizontocidal antimalarial activity against *P. knowlesi*. They treated dihydroartemisinin (**117**), which was prepared by the known procedure with methyl *p*-iodomethylbenzoate in dry dichloromethane using freshly prepared $Ag_2O$ at room temperature to furnish exclusively the α-epimer (**197a**) as methyl *p*-[(12α-dihydroartemisinoxy)-methyl]benzoate. The alkaline hydrolysis of **197a** at room temperature furnished *p*-[12α-dihydroartemisinoxy)methyl]benzoic acid or α-artelinic acid (**197b**). They tested α-artelinic acid (**197b**) dissolved in 5% $NaHCO_3$ solution in rhesus monkeys infected with *P. knowlesi* at a dose of 20 mg/kg for three days and observed parasite clearance from blood circulation within 24 h. This dose was found to be curative and no recrudescence was observed until 50 days. Besides, it was safer as the $LD_{50}$ of **197b** in Swiss mice was found to be 1000 mg/kg, a better therapeutic index than that of β-artelinate (**197c**).



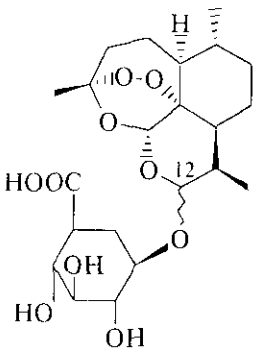
**196a** $R_1$=H, $R_2$=$CH_3$
**b** $R_1$=$CH_3$, $R_2$=D
**c** $R_1$=D, $R_2$=$CH_3$



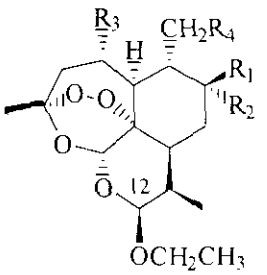
**197a** R=α-$OCH_2C_6H_4$-*p*-$COOCH_3$
**b** R=α-$OCH_2C_6H_4$-*p*-COOH
**c** R=β-$OCH_2C_6H_4$-*p*-COOH

Sharma *et al.*[89] reported a simple and efficient method for the synthesis of ether derivatives (**116a-d**) of dihydroartemisinin (**117**) using chlorotrimethylsilane as a catalyst. The advantage of this method lies in the fact that the candidate antimalarial drug[85] [70:30 mixture of β-/α-arteethers (**116a/b**)] as discussed earlier could be directly obtained from the reaction mixture almost in the same ratio.

Ramu and Baker[90] in 1995 reported synthesis and antimalarial activity of several glucuronid conjugates of β-arteether (**116a**). They synthesised chemically β-glucuronides of α-dihydroartemisinin (**198a**), β-dihydroartemisinin (**198b**), 9β-hydroxyarteether (**199a**), 2α-hydroxyarteether (**199b**), 14-hydroxy-arteether (**199c**) and 9α-hydroxyarteether (**199d**) starting from the hydroxylated metabolites which in turn



**198a** 12α
**b** 12β



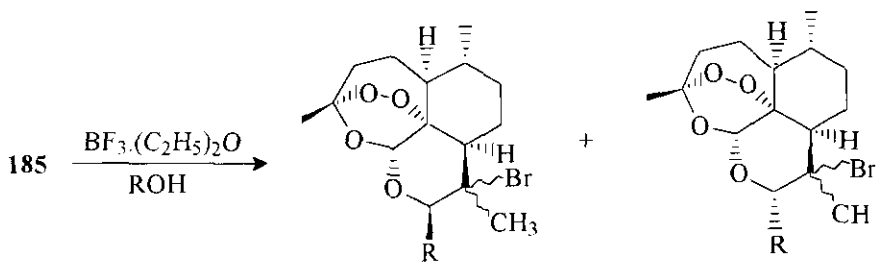
| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| **199a** | G | H | H | H |
| **b** | H | H | G | H |
| **c** | H | H | H | G |
| **d** | H | G | H | H |
| **e** | OH | H | H | H |

were obtained chemically or using fermentation techniques.[91] The *in vitro* antimalarial activity of these glucuronides were determined against *P. falciparum* strain FCR-3. Compound (**198b**) was found to be around 20 times less active than its aglycone dihydroartemisinin (**117**), while the α-isomer (**198a**) was

found to be almost inactive. Among the 9-hydroxyarteether glucuronides, the glucuronide of 9β-hydroxyarteether (**199a**) ($IC_{50}$ = 89.3 ng/mL) was the most potent and most polar (logP=0.61) of all the glucuronide conjugates and around 100 times less active than its aglycone (**199e**) and they predicted that the activity of **199a** was within a range that would have potential therapeutic use.

Considering the pharmacological importance of deoxoartemisinin (**96a**) which is eight times more active than artemisinin (**1**) and its poor availability by synthesis, Wu *et al.*[92] reported an efficient synthesis of **96a** from dihydroartemisinin (**117**) in quantitative yield. When compound (**117**) was mixed with $BH_3N(C_2H_5)_3$ and $(CH_3)_3SiCl$ in DME and stirred at room temperature, deoxoartemisinin (**96a**) was obtained in 81% isolated yield.

In continuation of their synthesis of different artemisinin based ring skeletons for antimalarial activity, Venugopalan *et al.*[93] reported the synthesis of artemisinin based novel ring systems using tin mediated radical cyclisation reactions because of its simplicity and high stereoselectivity. $BF_3.(C_2H_5)_2O$ catalysed reaction of bromohydrin[94] (**185**) with primary alcohols furnished bromo ethers (**200a-f**) (Scheme 31). The propargyl ether (**200c**) on refluxing with n-$(C_4H_9)_3SnH$/AIBn in toluene at 110°C for 18 h provided the single stereoisomer (**201a**) in 82% yield which underwent oxidation in the presence of $OsO_4$ to furnish the keto compound (**202**) (30% yield) (Scheme 31a). Similarly, the other isomer (**200d**) underwent a smooth radical cyclisation reaction under similar condition to give **201b**. The allyl ether (**200e**) underwent cyclisation reaction to furnish exclusively **203** in 75% yield. On the contrary, the radical cyclisation of **200f** gave two products (**204a**) (30% yield) and (**204b**) (21% yield). However, no biological activity of these compounds was mentioned in their report.

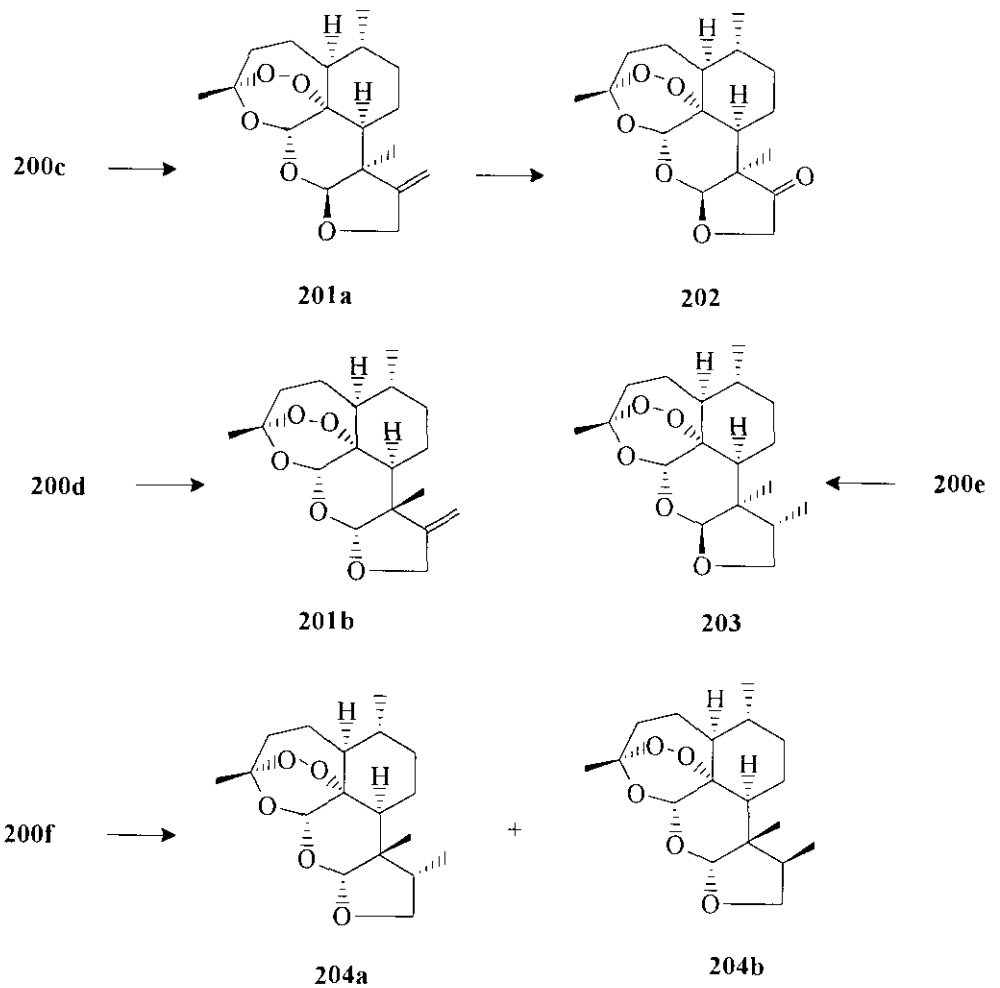



**200 a-f**

**200a,b** R=$OC_2H_5$ ; **c,d** R=$OCH_2C{\equiv}CH$

**e,f** R=$OCH_2CH{=}CH_2$

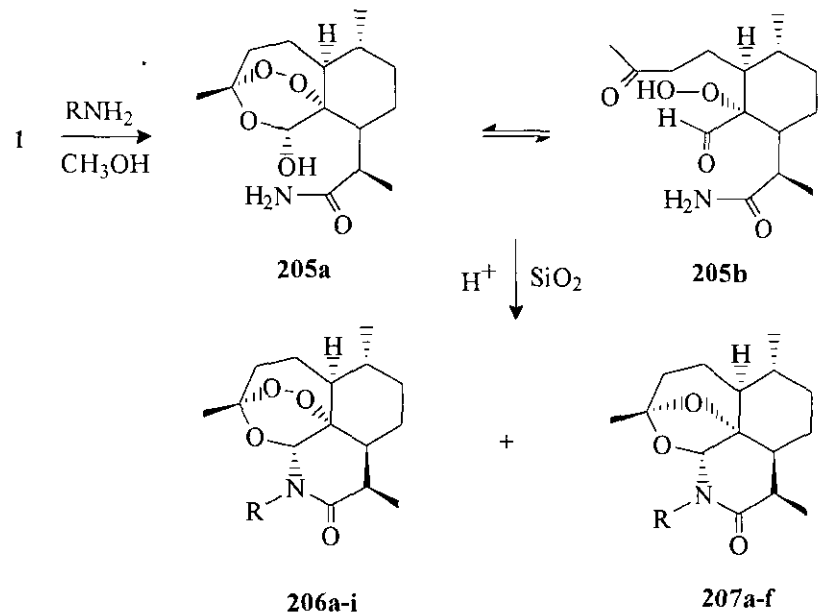
**Scheme 31**




**Scheme 31a**

In 1995, Ziffer *et al.*[95] reported a novel class of artemisinin analogues, *N*-alkylazaartemisinins (**206a-i**) and *N*-alkylaza-deoxyartemisinins (**207a-f**). The syntheses demonstrated that lactone of **1** could be opened to produce an amide and the tetracyclic ring system was reformed in the process of converting the amide into a lactam without disturbing the critical peroxide. They treated artemisinin (**1**) with methanolic ammonia which produced a equilibrium mixture of **205a** and **205b** (Scheme 32). When crude mixture of hydroperoxides was subjected to reaction conditions employed by Avery *et al.*[22] compounds (**206a**) and (**207a**) were obtained in 45% and 9% yields respectively. They have clearly demonstrated that the conversion of lactone moiety of artemisinin (**1**) into a lactam does not reduce its biological activity as shown by the *in vivo* and *in vitro* test data for a number of *N*-substituted azaartemisinins against drug resistant strains of *P. falciparum*. The two most active derivatives (**206i**) and (**206e**) were 26 and 22 times

more active *in vitro* than artemisinin (**1**) respectively. *In vivo* test data showed that the lactam (**206i**) was approximately four times more active than artemisinin (**1**) and as potent as β-arteether (**116a**).




**a** R=H, **b** R= -$CH_2CH(CH_3)_2$, **c** R= -$CH_2CH{=}CH_2$

**d** R= -$CH_3$ **e** R= -$CH_2$—(N-heterocycle)

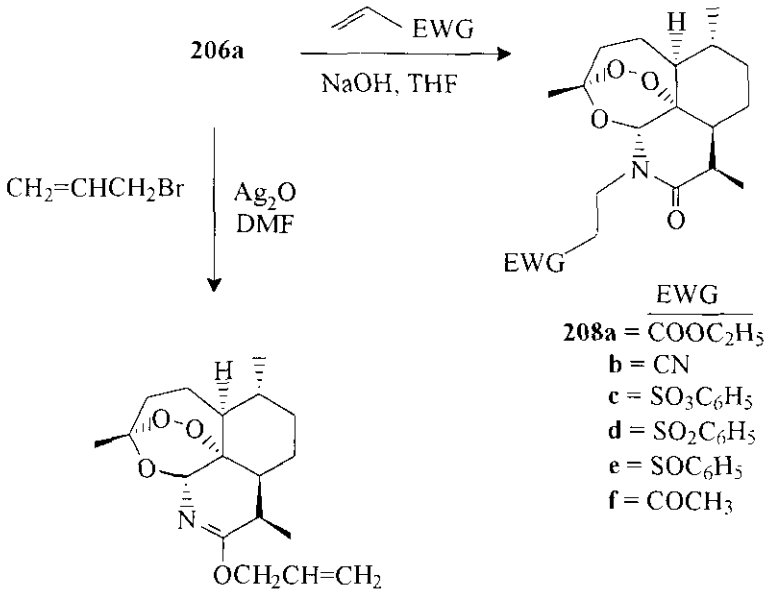
**f** R= -$CH_2$—(O-heterocycle) **g** R= -$CH_2C_6H_5$

**h** R= -$CH_2$—(S-heterocycle) **i** R= -$CH_2CHO$

**Scheme 32**

In continuation of their work on synthesis of *N*-alkylazaartemisinin derivatives, Ziffer *et al.*[96] most recently reported a new route for the synthesis of a series of *N*-substituted azaartemisinins (**208a-f**) in high yield by Michael additions to the amide nitrogen in compound (**206a**). Reaction of compound (**206a**) with catalytic amounts of sodium hydroxide and ethyl acrylate in THF at room temperature yielded the *N*-alkyl derivatives (**208a-f**) in 73-90% yield (Scheme 33). Michael additions to **206a** thus offered a new and high yield route to compounds which were accessible with difficulty by their earlier synthesis[95] of *N*-substituted azaartemisinins. However, no antimalarial activity of these analogues has been reported.

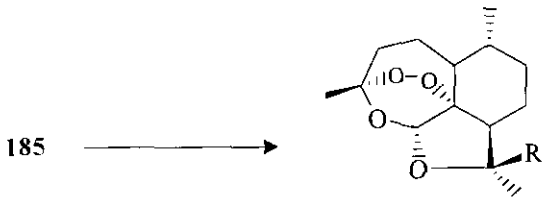
Recently Venugopalan *et al.*[97] reported synthesis and antimalarial activities of ring-contracted artemisinin derivatives. Bromoacetal (**185**) underwent a novel ring-contracted reaction to furnish the aldehyde (**210a**) in the presence of DBU or triethylamine in 85% yield. The aldehyde (**210a**) when reduced with $NaBH_4$,




**Scheme 33**

furnished alcohol (**210b**) (72% yield). Compound (**210b**) on oxidation afforded acid (**210c**) in 76% yield (Scheme 34). They have reported synthesis of 37 derivatives of (**210b**) and (**210c**) out of which only 14 showed antimalarial activity. When dihydroartemisinin (**117**) was treated with alcohol (**210b**) in the presence of $BF_3.(C_2H_5)_2O$, two diastereoisomers (**211a**) and (**211b**) were obtained in a ratio of 2:1 (Scheme 35). Compounds (**210f-h**), (**210l**) and (**210n**) showed moderate activity and 100% activity were shown by compounds (**210a**), (**210d-l**), (**210j-k**) and (**210m**) but were found to be less active than arteether (**116a**) against *P. berghei* (K-173 strain). The thiocarbamate (**210i**) showed 100% activity at 2.5 mg/kg x 5, sc and 45% at 1 mg/kg x 5 sc. Against chloroquine resistant NS strain, it showed 100% activity at a dose of 5 mg/kg x5, sc and 25 mg/kg x5, po. The ether (**211a**) showed an activity of 100% at 1.25 mg/kg x 5, sc and 73% activity at a dose of 0.625 mg/kg x 5, sc. It displayed 100% activity at a dose of 7.5 mg/kg x 5, sc and 78% activity at 2.5 mg/kg x 5, sc against NS strain. The excellent activity was shown by the other diastereoisomer (**211b**). It was found to be 100% active at 0.625 mg/kg x 5, sc and 25 mg/kg x 5, po. It showed 100% activity at 2.5 mg/kg x 5, sc and 25 mg/kg x 5, po against NS strain. From the above test data, it may be concluded that compounds (**210i**), (**211a**) and (**211b**) showed better activity than the other derivatives and the activity is comparable to that of arteether (**116a**).

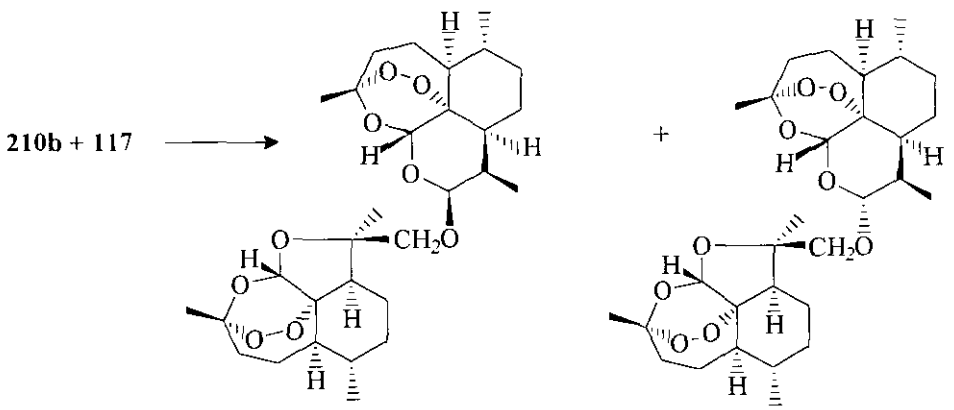
Acton *et al.*[98] reported synthesis and antimalarial activity of several 11-substituted artemisinin derivatives. They carried out synthesis of these derivatives either from artemisitene (**15**), the hydroperoxide (**212a**) which has been found to be the last intermediate in the synthesis of artemisitene (**15**)[81iii] or the alcohol




**210a-n**

**a** R= CHO, **b** R= $CH_2OH$, **c** R= COOH, **d** R= $CH_2OCH_2O_2CCH_2$,
**e** R= $CH_2OCH_2CH{=}CH_2$, **f** R= *p*-$NO_2C_6H_4COOCH_2$,
**g** R= *p*-$CH_3C_6H_4SO_2OCH_2$, **h** R= *p*-$ClC_6H_4NHCOOCH_2$,
**i** R= *p*-$ClC_6H_4NHCSOCH_2$, **j** R= *p*-$FC_6H_4NHCSOCH_2$,
**k** R= $CH_2OCSNHC_6H_5$, **l** R= *p*-$CF_3C_6H_4CS_2NHCO$,
**m** R= *p*-$CF_3C_6H_4CH{=}CH$, **n** R= -CO-$SC_6H_5$

**Scheme 34**

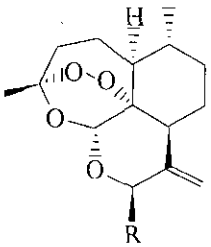



**211a** **211b**

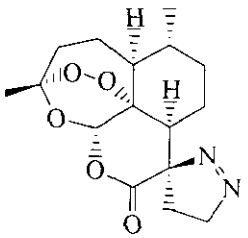
**Scheme 35**

(**212b**) derived from **212a** using literature procedure.[99] These compounds were tested *in vitro* against D-6 and W-2 clones of human malaria, *P. falciparum*. However, only one compound (**214**) was found to be having identical activity to that of artemisinin (**1**), rest of compounds either showed poor activity or none at all.

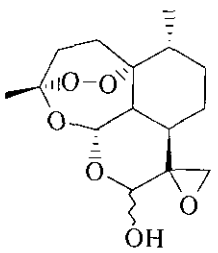
In a review in 1987, Luo *et al.*[100] reported that several fluorinated dihydroartemisinin derivatives were 2-3 times more active than arteether (**116a**) and artemether (**116c**). Posner *et al.*[69] reported that a *p*-fluorobenzyl ether of a synthetic 1,2,4-trioxane showed twice the antimalarial activity of the corresponding hydrogen analogue. Ziffer *et al.*[101] in 1995 synthesised and tested several fluorinated artemisinin derivatives



**212a** R=OOH
**b** R=OH



**213**



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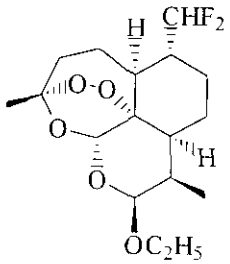
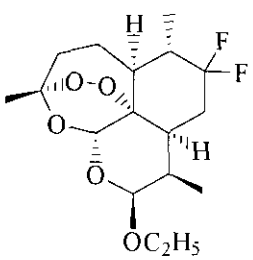
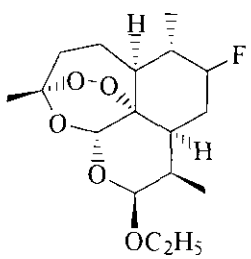


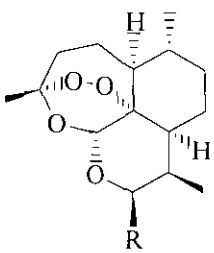
**215**



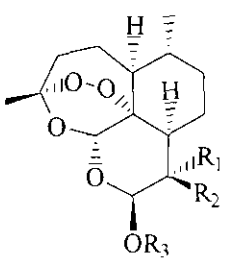
**216**



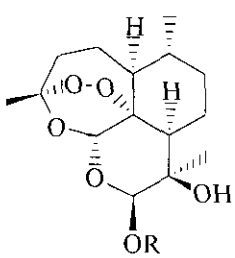
**217**



**218a** R= $CH_2CHF_2$
**b** R= $CH_2CF_2CH_3$
**c** R= *p*-$FC_6H_4CH_2O$



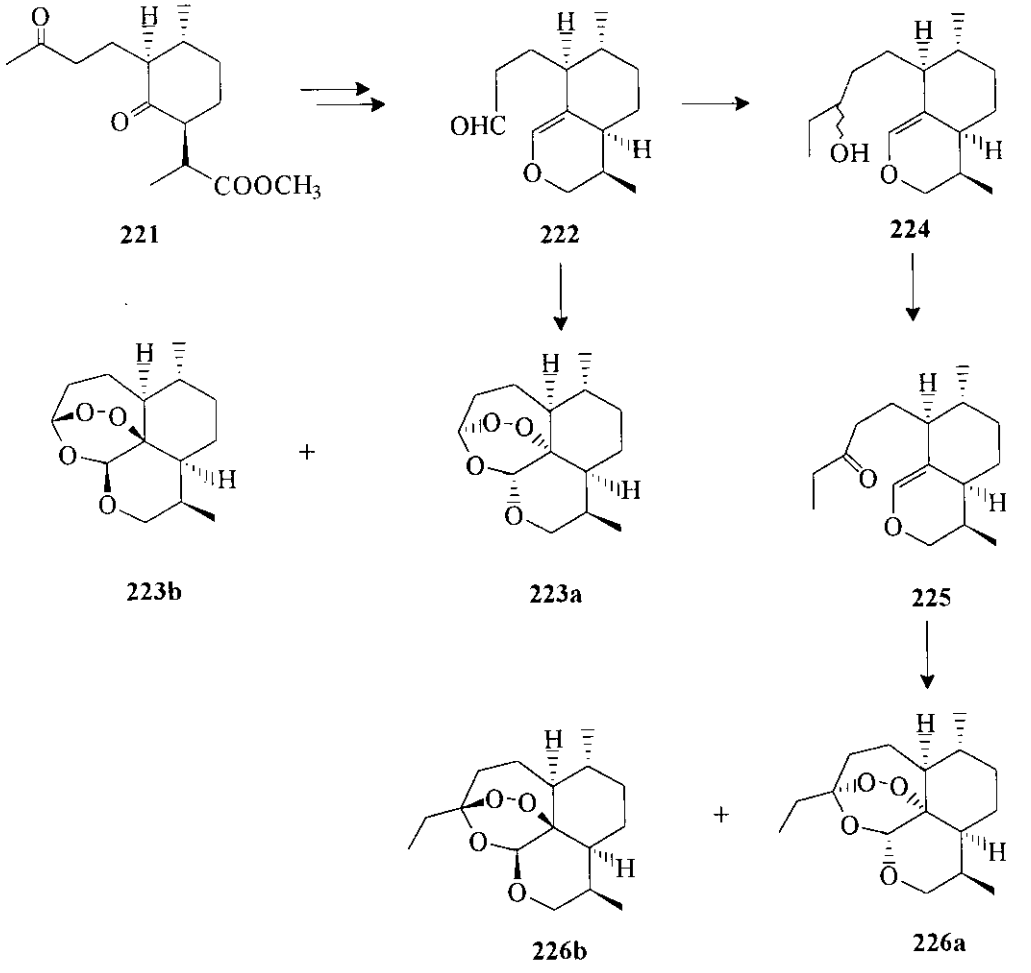
**219a** $R_1$= OH, $R_2$= $CH_3$
$R_3$= $CH_2CF_3$
**b** $R_1$= $CH_3$, $R_2$= OH
$R_3$= $CH_2CF_3$



**220a** R= *o*-$FC_6H_4CH_2$
**b** R= *m*-$FC_6H_4CH_2$
**c** R= *p*-$FC_6H_4CH_2$
**d** R= $CH_2C_6H_4F$

(**215-220**) in order to determine how changes associated with the presence of one or more fluorine atoms on the artemisinin skeleton, as well as on alkyl or aryl groups at C-12, altered the physical and or chemical characteristics of these sesquiterpene derivatives to affect their antimalarial activities. These derivatives were tested for their antimalarial efficacy against the drug-resistant strains of *P. falciparum*. The antimalarial activity of these derivatives showed that fluoro derivatives were slightly more active than their precursors or analogues. In general, the ratios of the activities of artemisinin (**1**) to the different fluorinated compounds were less than 1 i.e. the compounds were less active than artemisinin (**1**) or arteether (**116a**).

The SAR for various artemisinin analogues have proved that the peroxide bridge in artemisinin (**1**) is a crucial feature for the antimalarial activity whereas the carbonyl group at C-12 may be removed as shown by deoxoartemisinin (**96a**) which possess higher activity than artemisinin (**1**). So far, however, nothing was known about the effect of 4-methyl group on antimalarial activity of (**1**). Since the 4-methyl group is that nearest to the crucial 1,2,4-trioxane structure in artemisinin (**1**), Wu *et al.*[102] argued that the synthesis of 4-demethyldeoxoartemisinin (**223a**) and 4-ethyl-4-demethyldeoxoartemisinin (**226a**) will provide useful



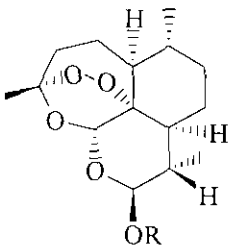

**Scheme 36**

information about the SAR of artemisinin (**1**). They prepared the key intermediate, enol ether (**222**) (34% yield) in 6 steps from diketone (**221**) - the acid degraded[103] product of artemisinin (**1**). The compound (**222**) on photooxidation in the presence of methylene blue at -78°C under a stream of oxygen and subsequent *in situ* treatment with trimethylsilyl trifluoromethanesulfonate (TfOTMS) furnished **223a** (15%

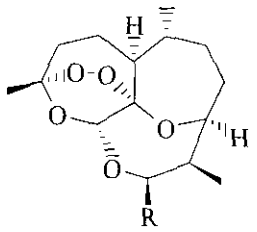
yield) and a by product (**223b**) (11% yield). Treatment of **222** with ethylmagnesium bromide at 0°C in dry ether afforded the alcohol (**224**) in 98% yield. Oxidation of **224** with $(COCl)_2$-DMSO in $CH_2Cl_2$ at -60°C provided **225** in 62% yield. Photooxidation of the enol ether (**225**) as discussed above, followed by cyclization with TfOTMS furnished **226a** (26% yield) and **226b** (9.4% yield) (Scheme 36). However, in their report no antimalarial activity of these compounds has been mentioned.

Ziffer *et al.*[104] used triphenylphosphine hydrobromide catalysed addition of alcohols to anhydro-dihydroartemisinin (**180**) to prepare a series of 11-epidihydroartemisinin β-ethers (**227a-d**). Their *in vitro* antimalarial activities were found to be very similar but less than those of the corresponding isomers with a β-C-11 methyl.

The same authors[105] reported formation of ring enlarged oxides by the Lewis acid-catalysed rearrangement of the peroxide group in two 1,2,4-trioxanes, deoxoartemisinin (**96a**) and 12β-allyl-deoxoartemisinin (**175a**). When they treated compound (**96a**) and (**175a**) in dried acetonitrile with $BF_3.(C_2H_5)_2O$ at 0-5°C, oxides (**228a**) and (**228b**) were obtained in 64% and 57% yields respectively.

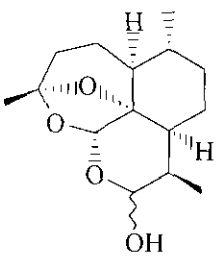


**227a** R= $C_2H_5$; **b** R= $CH_3$
**c** R= n-$C_3H_7$; **d** R= n-$C_4H_9$

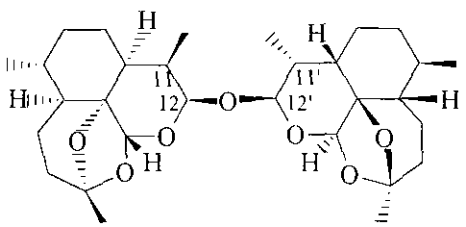


**228a** R= H
**b** R= $CH_2CH{=}CH_2$

Recently El-Feraly *et al.*[106] reported synthesis of a new artemisinin-derived dimer (**230**). Treatment of deoxydihydroartemisinin (**229**) with $BF_3.(C_2H_5)_2O$ in dry ether furnished the dimer (**230**) in 30% yield. They established its structure on the basis of spectral data and by X-Ray crystallographic analysis.



**229**

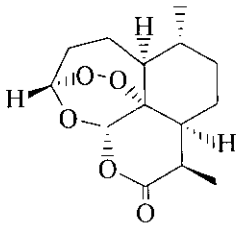


**230**

Wu *et al.*[107] in their effort to synthesise 15-desmethylartemisinin (**231**), prepared olefin (**232**) from diketo ester (**221**), the degradation product of artemisinin after several steps. However, photooxygenation of

compound (**232**) with methylene blue in acetonitrile at room temperature for 10 hours furnished (**233**) and (**234**) in 15% and 52% yield, respectively. Treatment of the mixture with trifluoroacetic acid in dichloromethane for two days afforded peroxide lactone (**235**) and allylic peroxide (**234**) in 12% and 54% yield, respectively.

Most recently, Yuthavong *et al.*[108] reported synthesis of artemisinin derivatives (**236a-d**) and (**237a-e**) with binding affinity with ferroprotoporphyrin IX.



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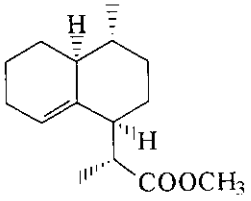
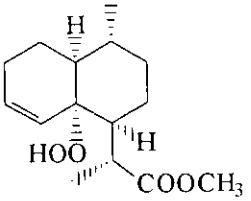


**232**



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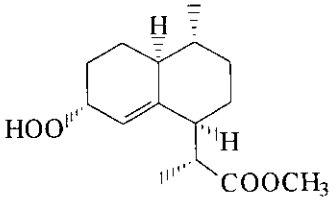
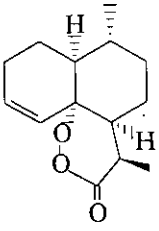
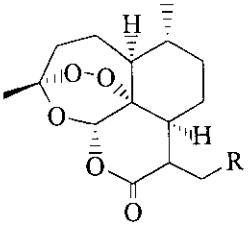


**234**

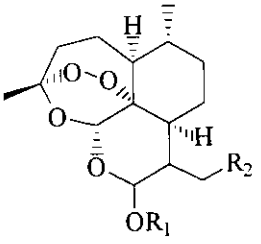


**235**



**236a-d**

**a** R= $SC_6H_5$
**b** R= -$CH(CN)C_5H_3FeC_5H_4$
**c** R= -$CH_2COC_5H_3FeC_5H_4$
**d** R= 



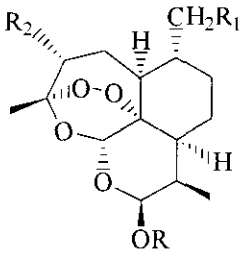
**237a-e**

**a** $R_1$= $R_2$=H
**b** $R_1$= $CH_3$, $R_2$=H
**c** $R_1$= $C_2H_5$, $R_2$=H
**d** $R_1$= $COOCH_2CH_2COONa$, $R_2$=H
**e** $R_1$= H, $R_2$= 

Several workers[109-112] have prepared trideuteroartemisinin, dihydroartemisinin, arteether and $^{14}C$-artemisinin for carrying out metabolic studies, ultimately allowing faster progress toward a more refined and potent antimalarial drug.

## Microbiological transfromations

In recent years, several workers in USA and China have prepared a variety of esters and ethers of dihydroartemisinin (**117**) in their search for more promising antimalarials but metabolic studies have shown that these groups were enzymatically hydrolysed or oxidized to yield dihydroartemisinin (**117**). In order to prepare and investigate new types of derivatives, it was felt necessary to introduce another functional group at various sites in the molecule. Ziffer *et al.*[113] in 1992 investigated the microbial metatabolism of arteether (**116a**) with *Beauveria sulfurescens* and identified three metabolites (**199e**), (**238b**) and (**238c**). They have been able to realize the goal of employing microbially mediated oxidations to introduce functional groups on unactivated methyl and methylene groups for (**116a**) and (**238a**).



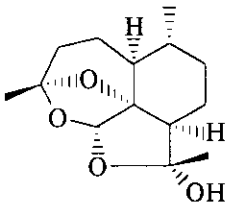
**238a-e**

**a** R= $CONHC_6H_5$, $R_1$=$R_2$= H; **b** R= $C_2H_5$, $R_1$= OH, $R_2$= H;
**c** R= $C_2H_5$, $R_1$= H, $R_2$= OH ; **d** R= $R_1$= H, $R_2$= OH;
**e** R= $CONHC_6H_5$, $R_1$= OH, $R_2$= H

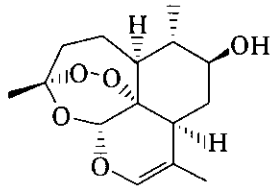
Hufford *et al.*[114] in 1994 reported the microbial metabolism studies of anhydrodihydroartemisinin (**180**) on large scale fermentation with *Streptomyces lavendulae* L-105 and *Rhizopogon* species (ATCC 36060) which resulted in the isolation of four microbial metabolites: compound (**239**), 9β-hydroxyanhydrodihydroartemisinin (**240**), 11-epi-deoxydihydroartemisinin (**241**) and 3α-hydroxydeoxyanhydrodihydroartemisinin (**242**). They also observed that thermospray mass spectroscopy/high-performance liquid chromatographic analysis of plasma from rats used in mammalian metabolism studies of anhydrodihydroartemisinin (**180**) shows microbial metabolite (**240**) to be the major metabolite. *In vitro* antimalarial activity of the metabolite (**240**) had shown that it possesses antimalarial activity but was found to be less active than anhydrodihydroartemisinin (**180**).

Ziffer *et al.*[115] observed that compound (**238a**), a derivative of dihydroartemisinin (**117**) prepared by the procedure of Brossi *et al.*[116] when incubated with *Beauveria sulfurescens*, furnished a hydroxylated derivative (**238e**).

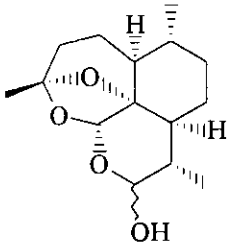
Baker *et al.*[117] have studied the metabolic pathway of arteether (**116a**) in rat liver microsomal homogenates which resulted in the formation of several hydroxylated products such as 9β-hydroxy-



**239**



**240**



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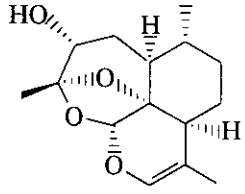
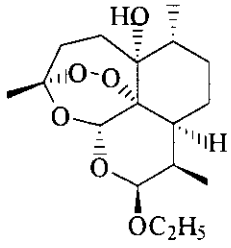


**242**

arteether (**199e**), 9α-hydroxyarteether, 2α-hydroxyarteether and 14-hydroxyarteether in addition to *O*-dealkylation giving dihydroartemisinin (**117**).

Hydroxyarteethers with hydroxy group at 9, 2 and 14 carbon atoms were also prepared using fermentation with *Streptomyces lavendulae*.[90,118] Using *Cunninghamellal elegans*, 9β-hydroxyarteether (**199e**) was obtained.[90,118]

Hufford *et al.*[119] in 1995 reported the microbial transformation of arteether (**116a**) to 1α-hydroxy-arteether (**243**) using *C. elegans* (ATCC 9245).



**243**

## VIII. MODE OF ACTION, NEUROTOXICITY AND OTHER BIOLOGICAL ACTIVITIES

### Mode of Action

In a recent study of the mechanism of the mode of action, Posner *et al.*[27i,120-123] have suggested the intermediacy of high valent iron-oxo species at the molecular level. The molecular mechanism represents

the first report of generation of Fe(IV)=O during ferrous ion activation of a 1,2,4-trioxane rather than, as usual heme protein[124-143] or metalloporphyrin model compounds activating dioxygen or hydrogen peroxide.[144-145] The mode of action has also been studied by other groups of workers.[146-148]

**Neurotoxicity**

In a recent report, it has been shown that arteether (**116a**) and artemether (**116c**) can cause fatal neurotoxicity in animals. It was further observed that the major metabolite of these compounds, dihydroartemisinin (**117**) is most probably responsible for the neurotoxicity problem.[46,47,149-152] Some other side effects have also been reported.[73i,135,153-158]

**Other biological activities**

Two groups of workers[159-161] have studied the cytotoxicity of artemisinin (**1**) and its analogues. Derivatives of dihydroartemisinin (**117**) *viz.* artemether (**116c**), arteether (**116a**), sodium artesunate and sodium artelinate have exhibited some what more cytotoxicity than artemisinin (**1**). Sun *et al.*[162] have reported on the *in vitro* cytotoxic effects of derivatives of artemisinic acid (**2**) and artemisitene (**15**) against the murine leukemia cell line P388, the human hepatoma cell line SMMC-7721, the human embryonic lung cell line WI-38 and the human gastric cancer cell line SGC-7901. Many other biological activities associated with the trioxane nucleus have recently been reported.[100,158,163-172]

**ACKNOWLEDGEMENT**

The authors are grateful to the Director, CIMAP, Lucknow for providing the necessary facilities.

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Received, 29th June, 1998