Bioorganic & Medicinal Chemistry 17 (2009) 2236–2275

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Synthetic medicinal chemistry of selected antimalarial natural products

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ARTICLE INFO

Article history:
Received 16 April 2008
Revised 28 July 2008
Accepted 31 October 2008
Available online 5 November 2008

Keywords:
Antimalarial agents
Plasmodium falciparum
Alkaloids
Artemisinin
Quassinoids

ABSTRACT

Natural products remain a rich source of novel molecular scaffolds for novel antimalarial agents in the fight against malaria. This has been well demonstrated in the case of quinine and artemisinin both of which have served as templates for the development of structurally simpler analogues that either served or continue to serve as effective antimalarials. This review will expound on these two natural products as well as other selected natural products that have served either as antimalarial agents or as potential lead compounds in the development of antimalarial drugs.

1. Introduction

Malaria is the most common of the parasitic diseases in tropical and subtropical regions, and it is estimated that about 40% of the world's population lives in malaria endemic areas.[1] It is caused by protozoan parasites of the genus *Plasmodium*, but in humans, it is the four species *P. falciparum*, *vivax*, *malariae* and *ovale* that are responsible for the spread of the disease. The most serious infections among these species are caused by *Plasmodium falciparum*. Because of the widespread and ever increasing resistance against existing antimalarial drugs, there is increasing need for new therapeutic agents against malaria.

Plants have for many years formed the basis of sophisticated traditional medicine systems and lately, natural products are proving to be a good source of lead compounds against various infective diseases. Natural products have made and continue to make an immense contribution to malaria chemotherapy either directly as antimalarial agents or as important lead compounds for the discovery of more potent antimalarials. Isolation of new lead compounds from plants is one of the strategies that can be followed in the search for new drugs.[2]

One of the earliest natural compounds that highlight the value of natural products in the fight against malaria is quinine **1**, isolated from the Cinchona bark. It also served as a template for the development of structurally simpler analogues such as chloroquine **2**, primaquine **3**[3], mepacrine **4**[4] and mefloquine **5** that served as effective antimalarials, Figure 1. It is noteworthy that the absolute configuration in compounds **2**–**5** is not shown as these drugs are used in racemic form. However, the emergence of drug-resistant strains of *Plasmodium falciparum* has spurred renewed efforts in the search for alternative antimalarials to curb the looming threat posed by these resistant strains.

The more recent example among the antimalarial natural products, whose diverse pharmacological potential has captivated the scientific community, is artemisinin **6**.[5] Artemisinin was isolated from the Chinese plant *Artemesia annua* and has been used successfully against chloroquine-resistant malarial parasites. However, the poor solubility of artemisinin, coupled with its short plasma half life led to a high rate of parasite recrudescence. The development of semi-synthetic analogues through the reduced lactone dihydroxyartemisinin **7** gave rise to the oil-soluble derivatives artemether **8** and arteether **9** as well as the water-soluble sodium artesunate **10**.[6] (Fig. 2).

The two antimalarial natural products quinine and artemisinin, briefly highlighted above, clearly demonstrate the enormous potential that natural products hold in providing powerful lead structures for the development of antimalarial agents. This review will expound on these two natural products and highlight the sources, synthesis and medicinal chemistry of these and related synthetic/semi-synthetic derivatives as well as other selected natural products that have served either as antimalarial agents or as lead compounds in the development of antimalarial drugs. For expediency, the coverage on these antiplasmodial natural products will be based on the classes to which the natural products under review belong.

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doi:10.1016/j.bmc.2008.10.072

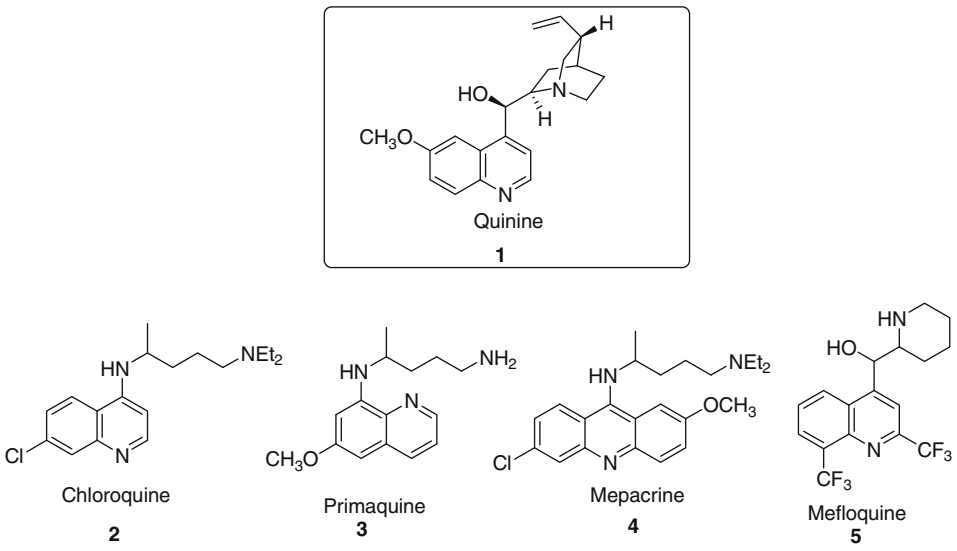


Figure 1. Quinine and its various analogues.

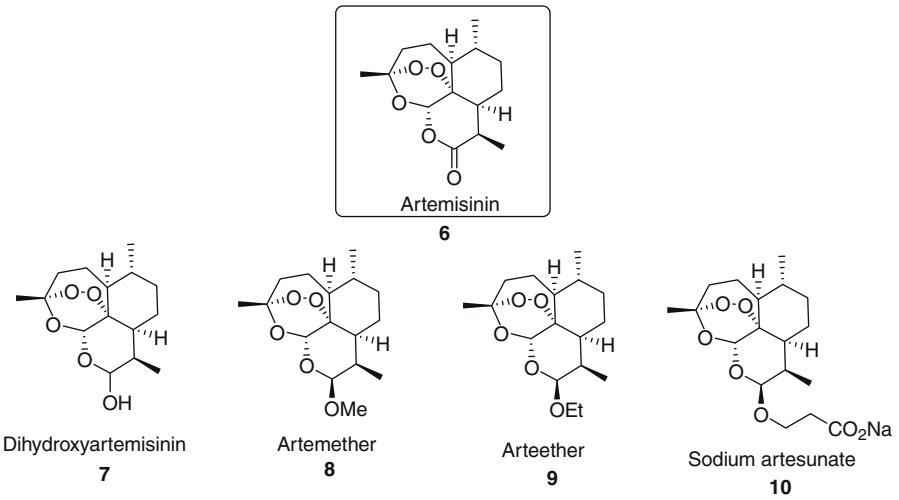


Figure 2. Artemisinin and its synthetic analogues.

2. Alkaloids

2.1. Quinine

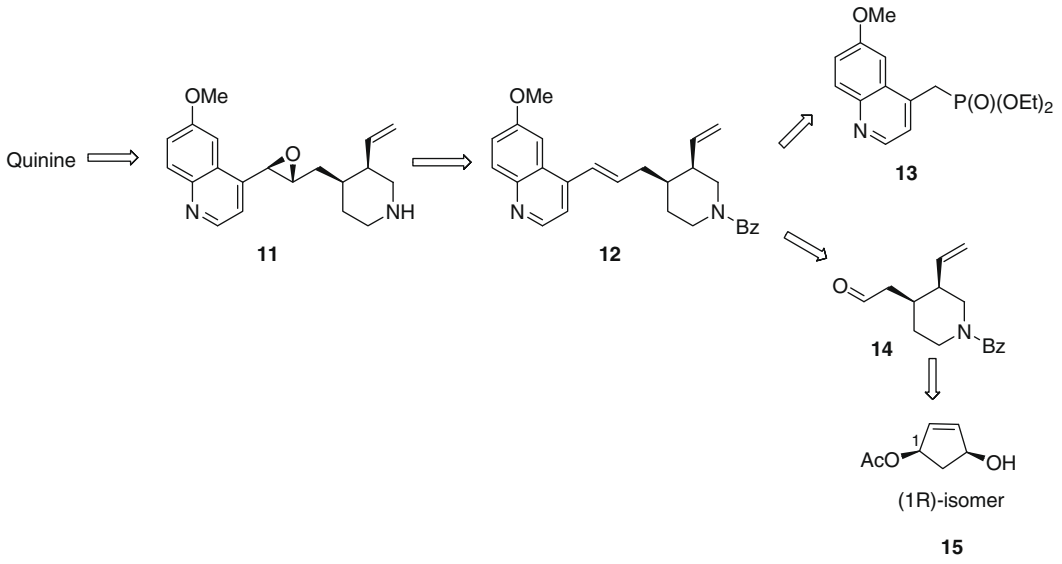
Quinine (**1**), the quintessential naturally occurring antimalarial quinoline alkaloid, has occupied a central place among the plant alkaloids used in medicine.[7] It is a bitter-tasting, crystalline alkaloid with antimalarial properties. It was the first effective treatment for malaria caused by *Plasmodium falciparum*, and for over three centuries, until recently, was the only therapeutic remedy for malaria. Quinine is extracted from the bark of the Cinchona tree found in high altitudes of South America. It was isolated in 1817 by French researchers Pierre Joseph Pelletier and Joseph Bienaime Caventou.

2.1.1. Synthesis of quinine

Although Cinchona trees remain the only practical source of quinine, the synthesis of quinine continues to attract a lot of interest. Rational attempts to synthesize quinine started early in the first half of the twentieth century[8] and a formal chemical synthesis of quinine was accomplished in 1944 by American chemists R.B. Woodward and W.E. Doering.[9] Stork et al. described the first and stereoselective synthesis of quinine.[10] Other elegant stereoselective syntheses of quinine by Jacobsen et al.[11] and Kobayashi et al.[12] are also documented. However, none of these syntheses can compete in economic terms with the isolation of the alkaloid from natural sources.

Highlighted below is Kobayashi et al.'s stereocontrolled synthesis of quinine. The synthesis was executed along the retrosynthetic analysis shown in Scheme 1 from the chiral olefin **11**[13] by using steps consisting of Sharpless asymmetric dihydroxylation[14] of **12** and subsequent epoxide ring formation.[15] The quinoline phosphonate **13** and piperidine aldehyde **14**, derived from the chiral monoacetate **15**, were chosen as precursors to olefin.

The stereocontrolled synthesis began with the conversion of chiral monoacetate **15** into methyl ester **16**, followed by reduction of the ester and selective protection of the primary hydroxyl group resulting in silyl ether **17**. Claisen rearrangement with vinyl ether using $Hg(OAc)_2$ as catalyst afforded an aldehyde, which upon reduction with $NaBH_4$ and subsequent protection of the hydroxyl group as a pivaloate ester provided the key cyclopentene **18**. Ozonolysis of this compound followed by reductive work-up with $NaBH_4$ afforded an alcohol **19**, which was then converted to an iodide. Nucleophilic amino cyclization of with $BnNH_2$ produced *N*-



Scheme 1.

benzyl piperidine **21**. Removal of the benzyl group followed by treatment with ethyl chloroformate delivered carbamate **22**, whose pivaloyl protecting group was removed by treatment with sodium ethoxide. The resulting alcohol underwent elimination by the Grieco et al. protocol[16] to deliver olefin **23**. After a series of protection and deprotection reactions to synthesize intermediate **24**, oxidation of the TBDMS deprotected alcohol with PCC furnished aldehyde **14** (Scheme 2).

Condensation of piperidine aldehyde **14** with the anion derived from quinoline phosphonate **13** using NaH provided olefin **12**, which on asymmetric dihydroxylation using AD-mix-β **25** resulted in the formation of diol **25**. Subsequent conversion of the diol **26** to epoxide **27** under the conditions developed by Sharpless et al.,[17] followed by a deprotection and cyclization step furnished quinine (Scheme 3).

2.1.2. Synthetic analogues of quinine

Following the early success of quinine in combating malaria, quinoline-derived compounds were extensively studied for the development of new synthetic therapeutic agents. The best compound to emerge from these research efforts was chloroquine (highlighted below).

2.2. Chloroquine

Chloroquine,[18] discovered in the 1940s, is a synthetic 4-aminoquinoline antimalarial drug structurally similar to quinine. Indeed, its development was inspired by the earlier success of quinine in combating malaria. It is used in the treatment or prevention of malaria.

2.2.1. Synthesis of chloroquine

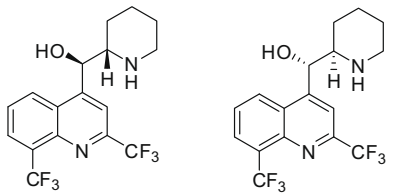
Chloroquine is an important antimalarial drug manufactured on a large scale by the Surrey and Hammer process depicted below.[19] Alternative syntheses of chloroquine are also found in the literature[20] (Scheme 4).

Chloroquine is synthesized starting with the condensation of *m*-chloroaniline **28** with ethyl ethoxalyacetate **29** to provide aniline **30**, followed by a ring closure to generate 4-hydroxyquinoline carboxylate **31**. The hydrolysis of this compound and subsequent decarboxylation of the resulting acid provided 4-hydroxyquinoline **33** whose reaction with $POCl_3$ provided 4-chloroquinoline **34**, which on nucleophilic substitution with 4-diethylamino-1-methylbutylamine **35** provided chloroquine.

For the past six decades, chloroquine and other aminoquinolines have been the frontline antimalarial agents because of their therapeutic efficacy and lower cost.[21] However, the effectiveness of chloroquine and the other existing aminoquinolines has severely declined due to the emergence of resistant strains of the malaria parasite *Plasmodium falciparum* to such an extent that chloroquine has been rendered virtually useless in most endemic areas.

2.3. Mefloquine

Mefloquine **5**, a quinoline methanol derivative and a synthetic analogue of quinine, was developed in 1971 at the Walter Reed Army Institute of Research (USA). Due to its long half life, mefloquine is commonly used in the prevention of malaria (malaria prophylaxis) and treatment of chloroquine-resistant falciparum malaria. However, as mefloquine resistance spreads, its efficacy in the treatment of malaria continues to decline and this is becoming a source of concern in malaria chemotherapy. Highlighted below is Lutz et al. synthesis of mefloquine.[22]



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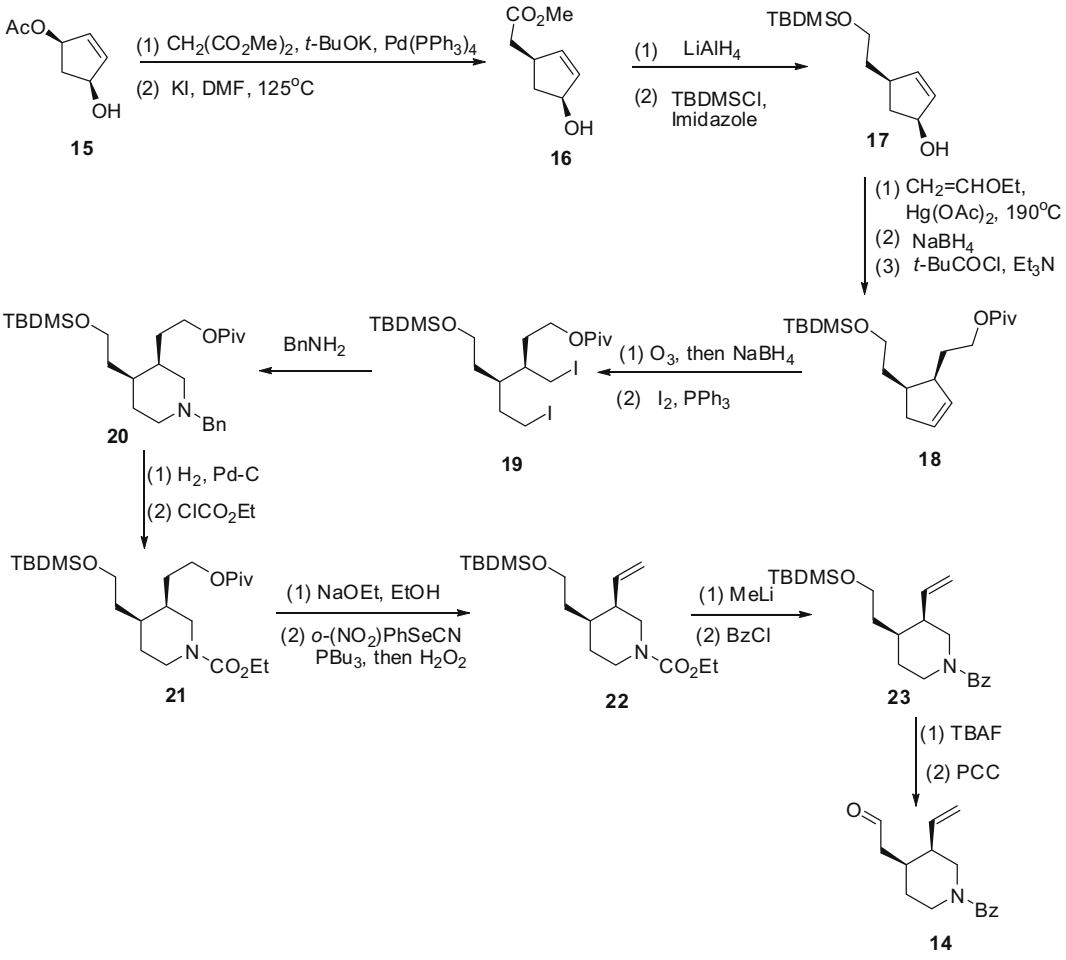
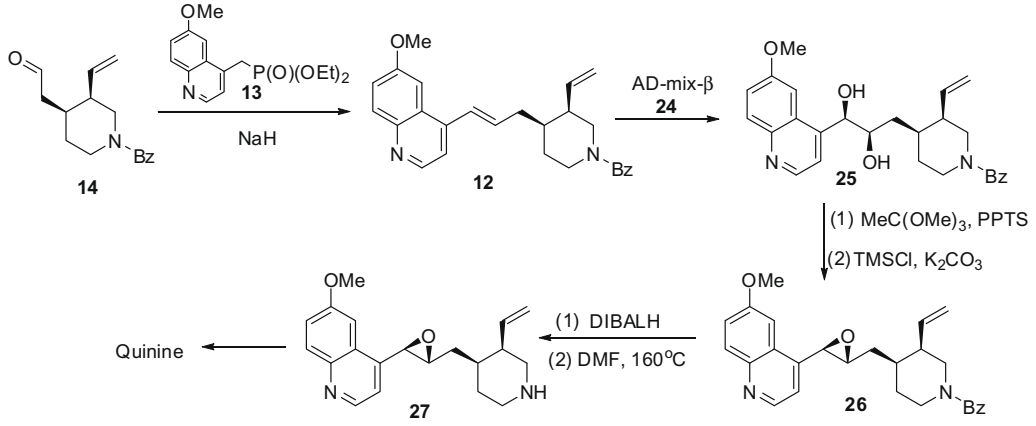
This synthesis of mefloquine begins with the condensation of *p*-trifluoromethylaniline **36** with ethyl 4,4,4-trifluoroacetoacetate **37** using polyphosphoric acid (PPA) in an adaptation of a literature protocol to provide 4-quinolone **38**.[23] Conversion of the quinolone to 4-bromoquinoline **39** using $POBr_3$, followed by CO_2 carboxylation of the 4-lithio derivative of the 4-bromoquinoline furnished cinchonic acid **40**. Addition of 2-pyridyllithium **41** to the cinchonic acid provided pyridyl ketone **42**, which on reduction with H_2/Pt gave mefloquine **5** (Scheme 5).



Scheme 2.



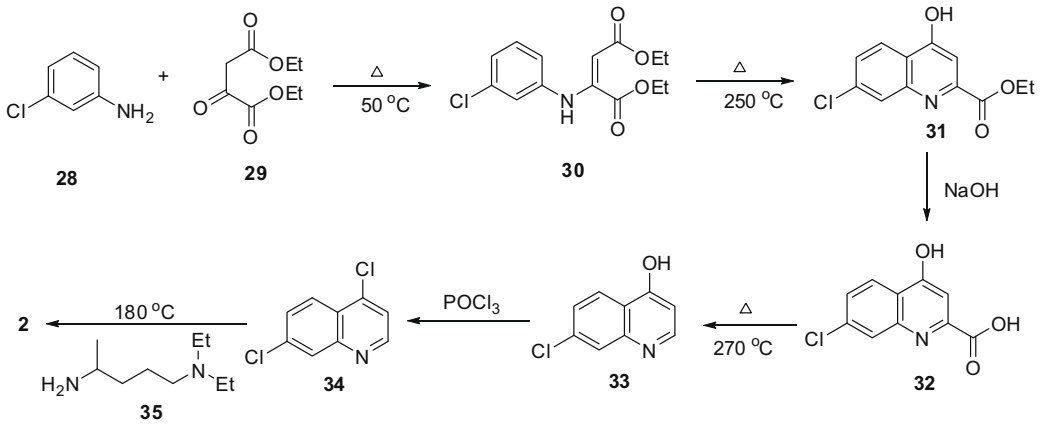
Scheme 3.

2.4. Cryptolepine

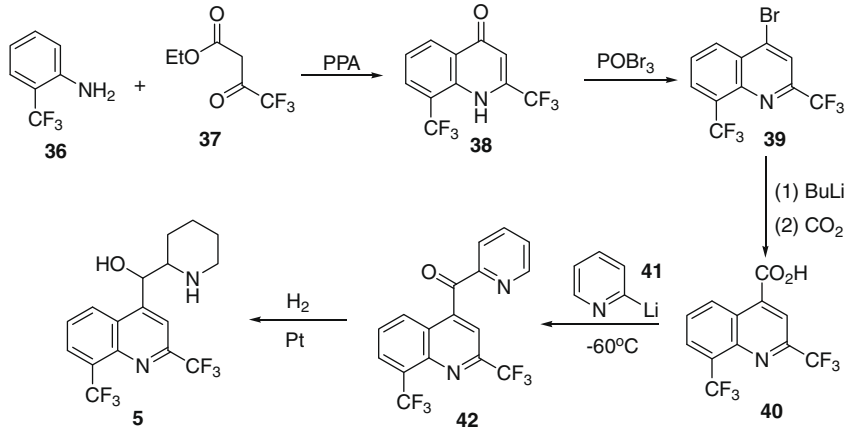
Cryptolepine **43** and its salt form **44** are patent antiplasmodial potent antiplasmodial indoloquinoline alkaloid present as the major constituent of the roots of the climbing shrub *Cryptolepis sanguinolenta*, commonly used in West Africa in the clinical therapy of malaria as well as other diseases.[24] Studies have shown cryptolepine to be active in vitro against both chloroquine-sensitive and chloroquine-resistant *Plasmodium falciparum*.[25] An in vitro IC_{50} value of 0.033 μg/mL for cryptolepine has been reported against the *P. falciparum* strain (K1).[26] An in vivo assay against the same strain also shows a significant reduction in parasitemia when cryptolepine is administered orally at a dose of 50 mg/kg body weight daily for 4 days. Although cryptolepine has a potent in vitro activity, it is cytotoxic on account of its ability to intercalate into DNA, inhibiting DNA replication and transcription[27] (Fig. 3).

2.4.1. Synthesis of cryptolepine

The synthesis of cryptolepine was accomplished well before it was even isolated from nature.[28] Several other syntheses of the



Scheme 4.



Scheme 5.

alkaloid have been reported in the literature.[25,29] However, the most straightforward total synthesis of cryptolepine is based on the synthesis by Holt and Petrow (Scheme 6),[30] which begins with the condensation of isatin **45** with *N*,*O*-diacetylindoxyl **46**, followed by decarboxylation of the resulting quindoline-11-carboxylic acid **47** to provide quindoline **48**. Subsequent methylation of the quindoline with methyl iodide provided the cryptolepine salt **44**.

In 2006 Mohan et al. described the synthesis of indoloquinoline alkaloids using the concept of heteroatom-directed photoannulation.[31] This approach involves an efficient three-step synthesis of indoloquinoline alkaloids via amination of appropriate haloquinolines with anilines. The reaction of 3-bromoquinoline **49** (Scheme 7) with anilines **50** and **51** resulted in intermediates **52** and **53** which on photochemical irradiation followed by oxidative cyclization afforded the corresponding indoloquinolines **54** and **55**. When irradiated, the linear fusion product provided quindoline **55** as a

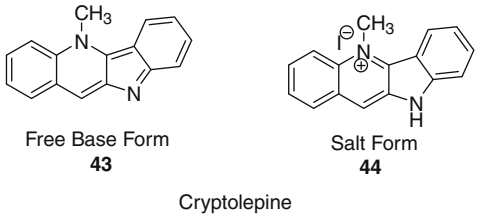
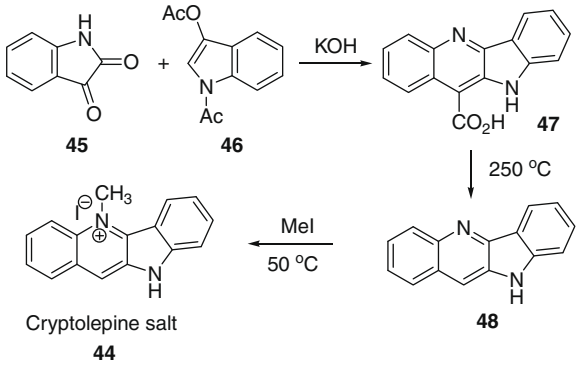


Figure 3. Cryptolepine.

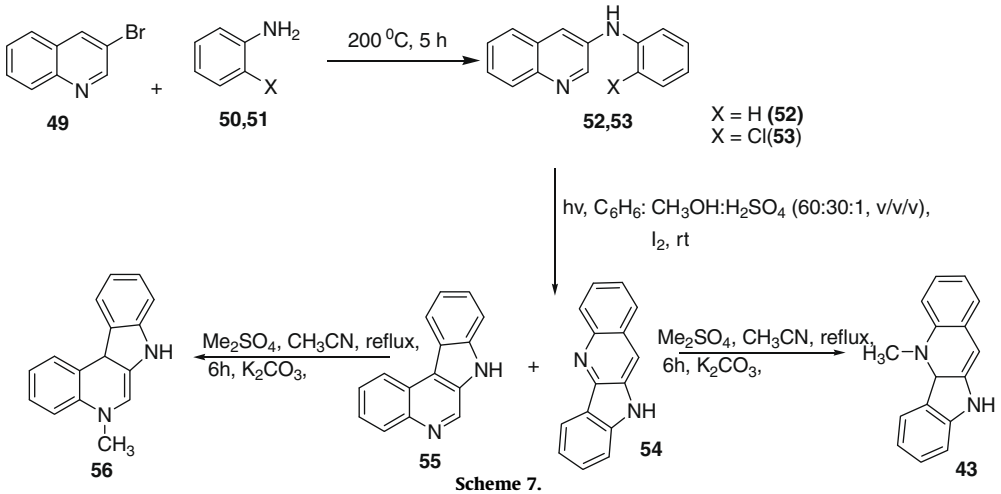


Scheme 6.

minor product. The quindoline **54** on selective methylation on the quinoline nitrogen afforded the alkaloid cryptolepine **43**. The angularly fused indoloquinoline **55** on methylation afforded isoneocrytolepine **56**, which is a synthetic indoquinoline alkaloid.

2.5. Febrifugine and analogues

The alkaloid mixture febrifugine **57** and isofebrifugine **58** originally isolated from the root of *Dichroa febrifuga*[32,33] and extracted from the leaves and buds of *Hydrangea macrophylla* var. *Otaksa*,[34] has been used in Chinese traditional medicine to treat malaria for over 4000 years. Isofebrifugine **58** is an isomer of febrifugine



Scheme 7.

obtained via the mechanism proposed by Berkelhammer et al.[35] Febrifugine is believed to block the proliferation of malarial parasites[36a] and acts by impairing haemazoin formation required for maturation of the parasite at the trophozoite stage.[36b] The purified febrifugine displayed potent antimalarial activity and was found to be 100 times as active as quinine against *P. lophurae* in duck models and 50 times as active as quinine against *P. cynomolgi* infection in rhesus monkeys.[37] Clinical studies of both the crude extract and isolated forms of febrifugine conducted in Yunnan Province and People's Republic of China, from the 1940s through the 1960s showed that it had excellent antipyretic and antiparasitic effects, similar to those of quinine.[32] However, strong liver toxicity has precluded the development of febrifugine as a potential clinical drug candidate.[38,39]

The absolute configurations of **57** and **58** were revised through the asymmetric total synthesis of each stereoisomer of febrifugine.[40,41] It is known that the 4-quinazolinone moiety plays an essential role in the appearance of activity and also the presence of a 1″-amino group and C-2′, C-3″ O-functionalities is crucial in the antimalarial activity of febrifugine.[42–44] In 2005 Jiang et al.[36a] reported the antimalarial activities and therapeutic properties of new febrifugine analogues. These new analogues appear to be promising lead antimalarial compounds that require intensive study for optimization and subsequent development. **WR237645** (halofuginone) **59** was the most active febrifugine analogue against the parasites. Further, febrifugine and the three most potent analogues, including halofuginone, **WR222048** (**60**) and **WR139672** (**61**), Figure 4, were selected for assessment of their in vivo efficacies and toxicities in *P. berghei* infected ICR mice. All these four compounds clearly extended the survival times of the parasite infected mice. Halofuginone was 10 times more efficacious against *P. berghei* than febrifugine.

In 2000, Takeuchi et al.[45] reported the asymmetric synthesis of febrifugine and isofebrifugine from chiral piperidin-3-ol (+)-**63**, which was prepared by the reductive dynamic optical resolution of the 3-piperidone derivatives (±)-**62**) using Baker's yeast.[46] The intramolecular bromoetherification of (+)-**63** using *N*-bromosuccinimide afforded octahydrofuro[3,2-*b*]-pyridine **64**. The 2-methoxy intermediate **65** was prepared as a diastereomeric mixture by dehydrobromination using potassium *tert*-butoxide and bromoetherification using *N*-bromosuccinimide and methanol. Deacetalization of **65** followed by a coupling reaction with 4(3*H*)—quinazolinone resulted in the formation of **66**. The hydrogenolysis of this compound gave isofebrifugine, which upon heating at 80 °C in water resulted in the largest ratio (2:1) of (+)-**57** to (+)-**58** (Scheme 8).

In 2004, Honda et al.[47] reported a novel and stereocontrolled synthetic path to (+)-febrifugine by employing a reductive deamination of an α-amino carbonyl compound and simultaneous recyclization of a proline derivative. In this synthesis, intramolecular Michael addition of the nitrogen to the α,β-unsaturated carbonyl system proceeded stereo-selectively. The silyl ether **67** was oxi-

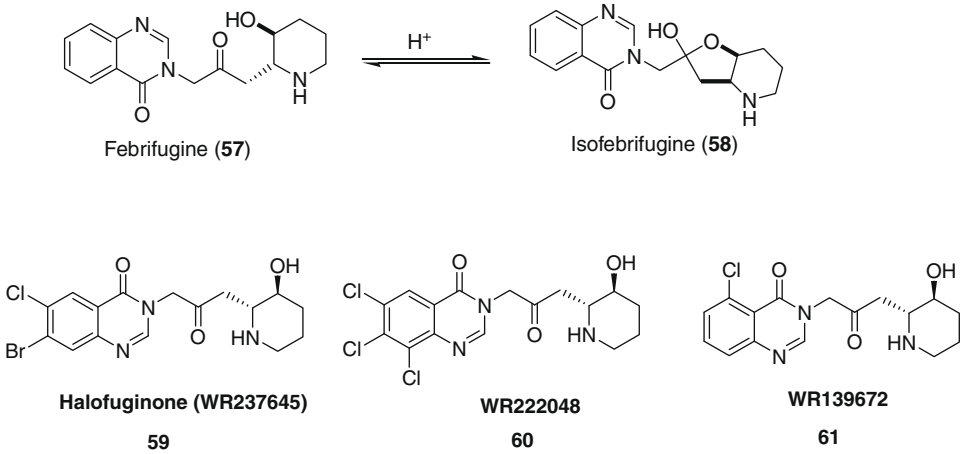
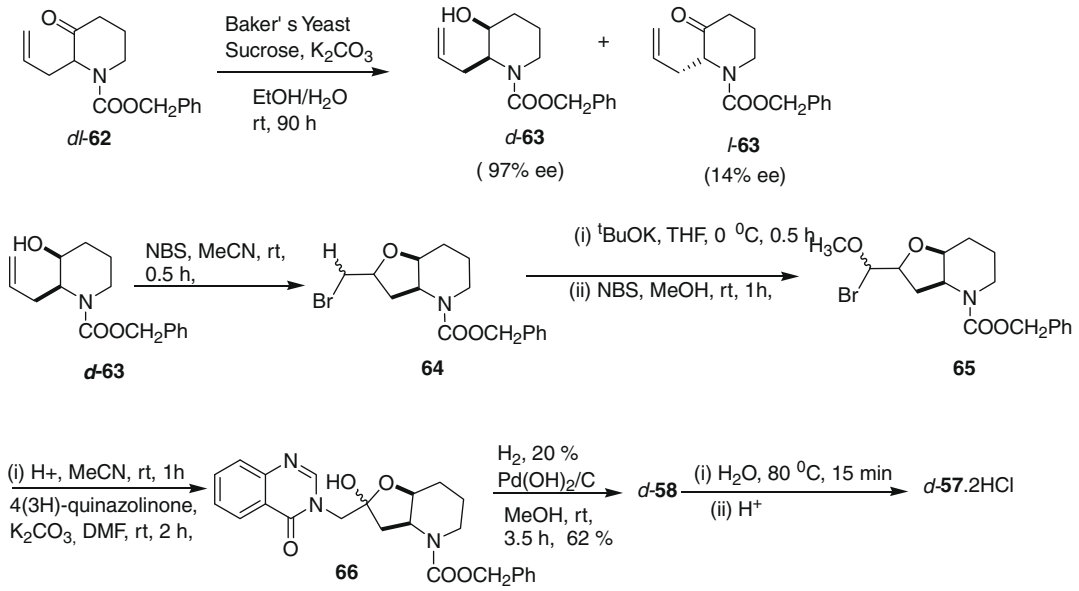


Figure 4. Febrifugine and its analogues.

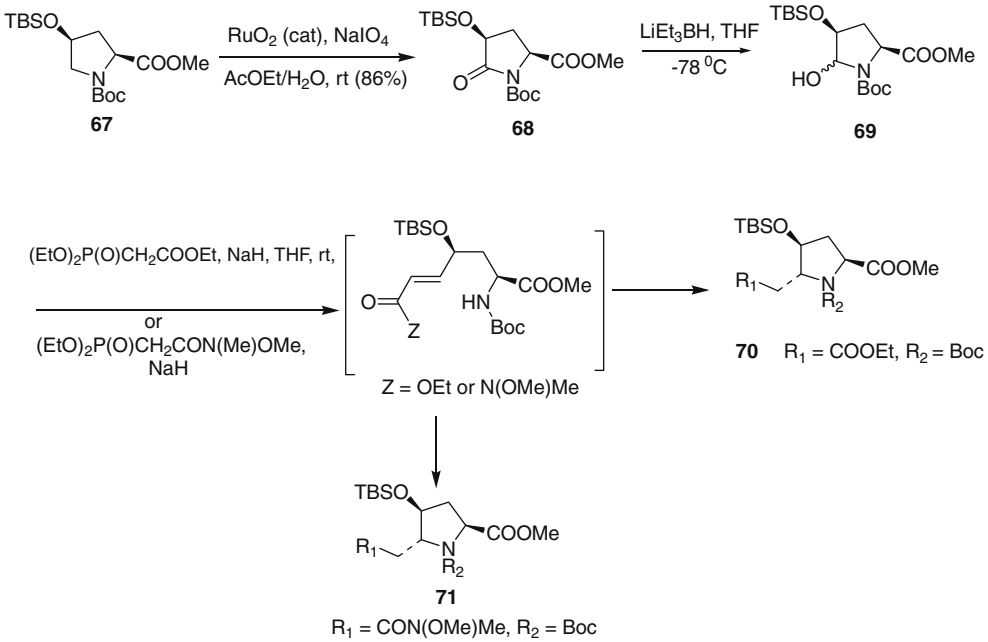


Scheme 8.

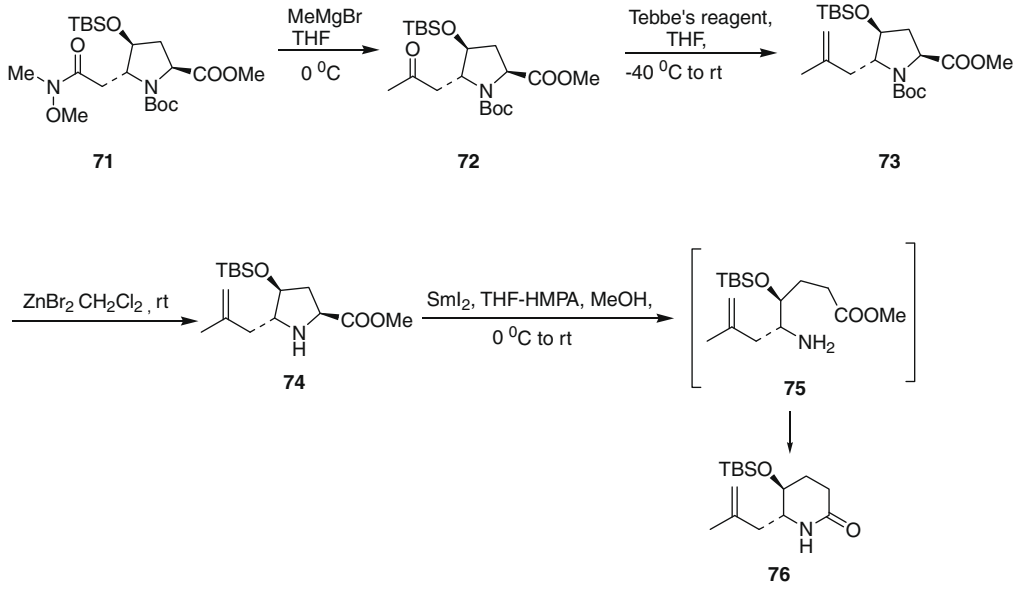
dized with ruthenium tetroxide to yield lactam **68**,[48] which upon reduction with lithium triethylborohydride, followed by treatment of the resulting aminal **69** with triethyl phosphonoacetate or the corresponding amide in the presence of NaH gave the ester **70** and amide **71** stereo-selectively (Scheme 9).

The amide **71** obtained using diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)-phosphate on treatment with methyl magnesium bromide gave the methyl ketone **72**, which on methylenation with Tebbe's reagent gave the olefin **73**. Selective removal of the Boc group of **73** by the use of zinc bromide provided amine **74**, which upon reductive deamination with samarium diiodide furnished amine **75**, which spontaneously cyclized to the δ-lactam **76** (Scheme 10). Reduction of this compound afforded the corresponding hydroxyl-amine **77**, which was transformed into carbamate **78** on treatment with CbzCl. Following protection of the secondary hydroxyl group as its benzyl ether, the resulting product **79** was converted to methyl ketone **80** by ozonolysis, Scheme 11. Finally, bromination of **80** by treatment with trimethylsilyl triflate in the presence of NBS resulted in the formation of α-bromoketone **81** which was further coupled with 4-hydroxyquinazoline in the presence of potassium hydride to furnish the protected febrifugine **82**. Finally treatment with 6 N HCl under reflux conditions delivered febrifugine (Scheme 12).

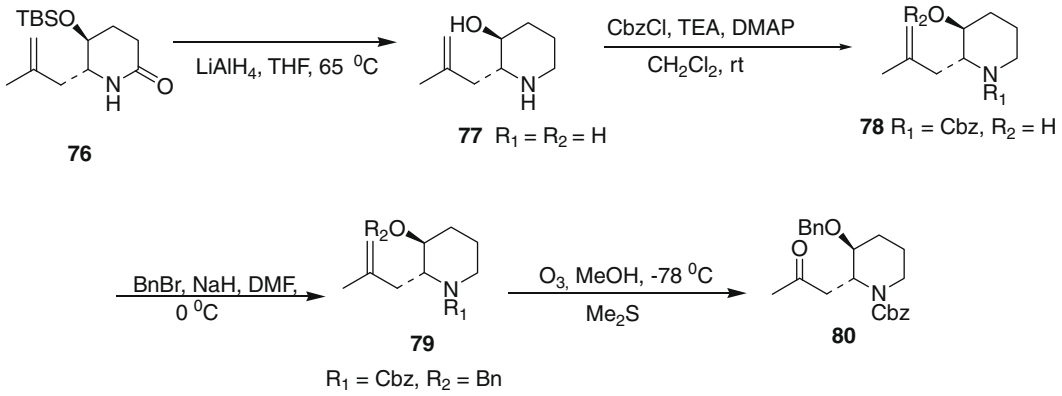
In another approach reported in 1999, Kobayashi et al. proposed the catalytic asymmetric synthesis of febrifugine and isofebrifugine using tin (II)-catalyzed asymmetric aldol and lanthanide catalyzed aqueous three-component reactions.[40] The aldehyde **87** was prepared via a sequential tin (II)-catalyzed asymmetric aldol-lanthanide-catalyzed three-component reaction.[49–51] (Scheme 13). In the presence of a chiral tin (II) Lewis acid (20 mol %), 3-*t*-butyl-



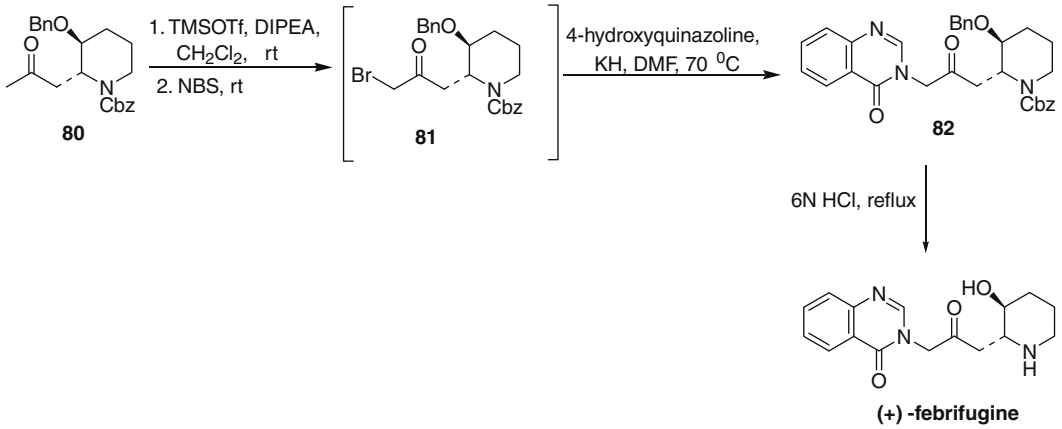
Scheme 9.



Scheme 10.

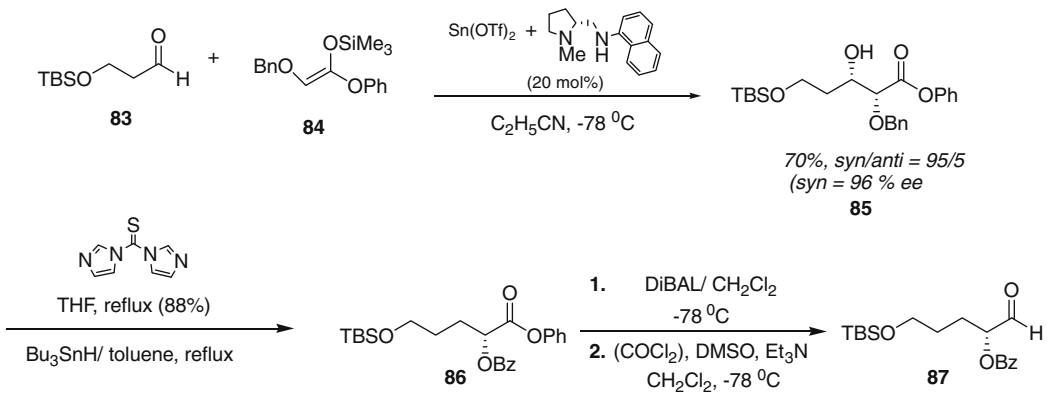


Scheme 11.



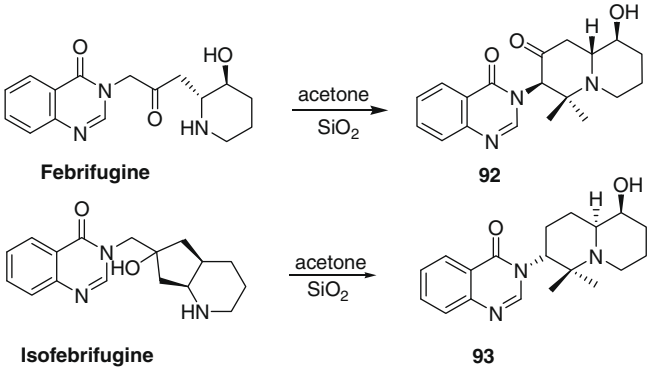
Scheme 12.

dimethylsiloxypropanal **83** was reacted with 2-benzyloxy-1-trimethylsiloxy-1-phenoxyethene **84** in propionitrile at −78 °C to afford the corresponding aldol-type adduct **85** with excellent diastero- and enantioselectivities. The hydroxyl group at position 3 was removed via a 2-step sequence,[52] and the resulting phenyl ester **86** was exhaustively reduced to an alcohol. The phenyl ester **86** was subsequently converted to the aldehyde **87** under the Swern oxidation conditions[53] (Scheme 14). The three-component reaction of aldehyde **87**, 2-methoxyaniline, and 2-methoxypropene was performed in the presence of 10 mol % of ytterbium triflate



Scheme 13.

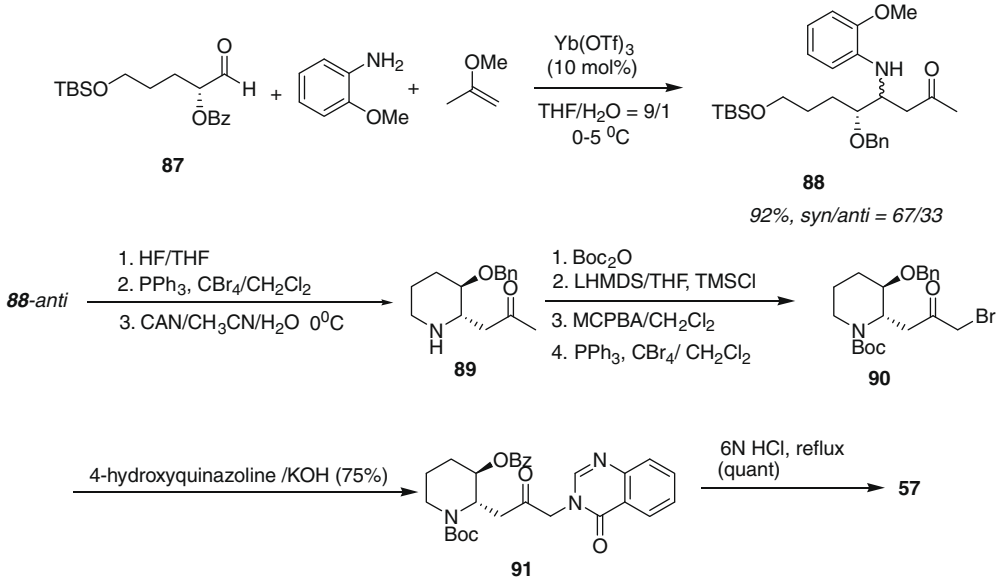
$(Yb(OTf)_3)$[51] to afford the desired Mannich type adduct **88**. These *syn*- and *anti*-diastereomeric adducts were used in the synthesis of isofebrifugine and febrifugine. The *anti*-adduct was then treated with HF to remove the TBS protecting group followed by bromination to give a spontaneously cyclized adduct whose *N*-protected (2-methoxyphenyl) group was removed using cerium ammonium nitrate (CAN)[54,55] to afford piperidine **89**. This compound was then protected as its *N*-Boc and treated first with lithiumhexamethyldisilazide (LHMDS) and then with trimethyl silyl chloride (TMSCl). The resulting silyl enol ether was oxidized and then brominated to give bromoacetone **90**. The coupling reaction of this compound with 4-hydroxyquinazoline was carried out using potassium hydroxide[56] to afford the penultimate compound **91,** whose protecting groups were successfully removed using 6N HCl to afford febrifugine.



Scheme 15.

2.5.1. Transformation of febrifugine and isofebrifugine into their acetone adducts

The cyclization[42] of the nitrogen atom of the piperidine ring and the α-methylene of the keto group of natural febrifugine by the Mannich reaction was undertaken, so as to produce a comparatively rigid conformation with the quinolizidine ring. Febrifugine and isofebrifugine were transformed to their acetone adducts **92** and **93** (Scheme 15). These derivatives showed comparable antimalarial activity to the parent molecules against both the chloroquine-sensitive (FCR-3) and the chloroquine-resistant (K1) strains of *P. falciparum*. In an in vivo study of the antimalarial activity against the mouse malaria parasite *P. berghei*, it was found that compound **92** (ED_{50}: 6.0 μmol/kg) was 24 times more potent than **93** (ED_{50}: 145 μmol/kg), though the effects of both of these highly active compounds against *P. falciparum* in vitro were almost iden-



Scheme 14.

tical. It was found that **92** showed high activity in vivo which was comparable to that of chloroquine.

2.6. Naphthylisoquinoline (NIQ) Alkaloid

Naphthylisoquinoline (NIQ) alkaloids like dioncophylline A (**94**), dioncophylline B (**95**), dioncophylline C (**96**) and dioncopeltine A (**97**) (Fig. 5) isolated from various species of the tropical plant *Ancistrocladaceae* and *Dioncophyllaceae*, constitute a rapidly growing class of structurally intriguing naturally occurring biaryl compounds with promising antimalarial activity in several African and Asian countries.[57–61] They are active against the asexual erythrocytic stages of *P. falciparum* strains NF-54 and K1 and *P. berghei* in vitro.[62–71] The potential of naphthylisoquinoline alkaloids against exoerythrocytic stages of *P. berghei* in human hepatoma cells has been demonstrated.[71,72] Similar to the antimalarial drug chloroquine,[73,74] these biaryls form complexes with ferriprotoporphyrin[75] thus possibly affecting the hemozoin formation pathway, the essential heme detoxification process in intraerythrocytic stages of *P. falciparum*.[76]

The antiplasmodial activity against chloroquine-resistant strains of *P. faciparum* suggested that either the molecular mechanism of chloroquine-resistance in *P. falciparum* is circumvented by these compounds or that NIQs have a different mode of action, possibly by selective inhibition of one of the essential proteins of the pathogen. The remarkable ability of these naphthylthylisoquinoline derivatives to accumulate exclusively in the pathogen inside infected erythrocytes raised the question as to whether a transport mechanism exists for these biaryl alkaloids or whether they exhibit a high affinity for the pathogen

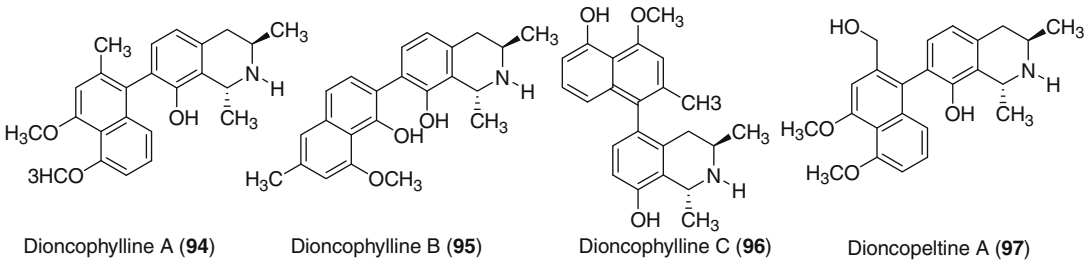
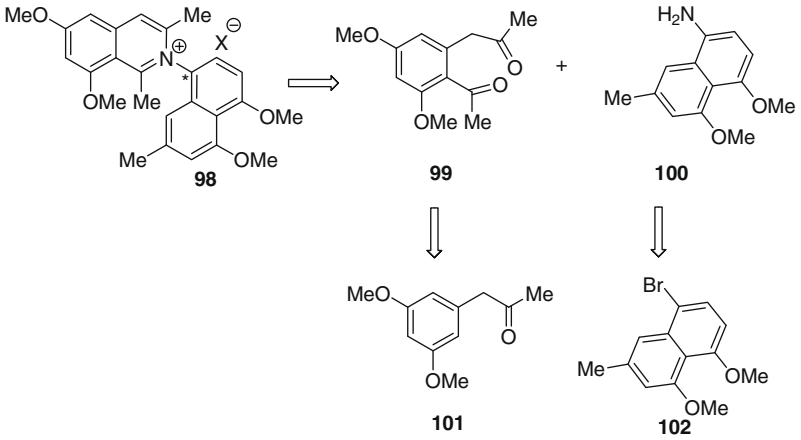
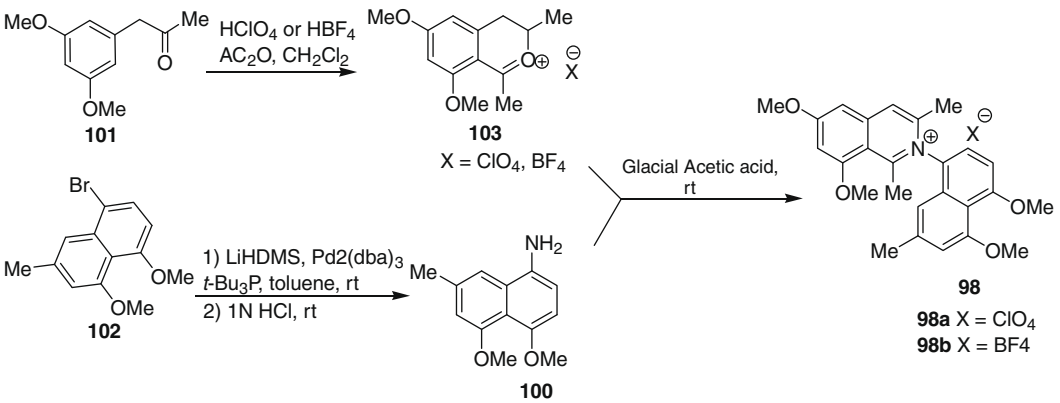


Figure 5. Napthylisoquinoline alkaloids.



Scheme 16.



Scheme 17.

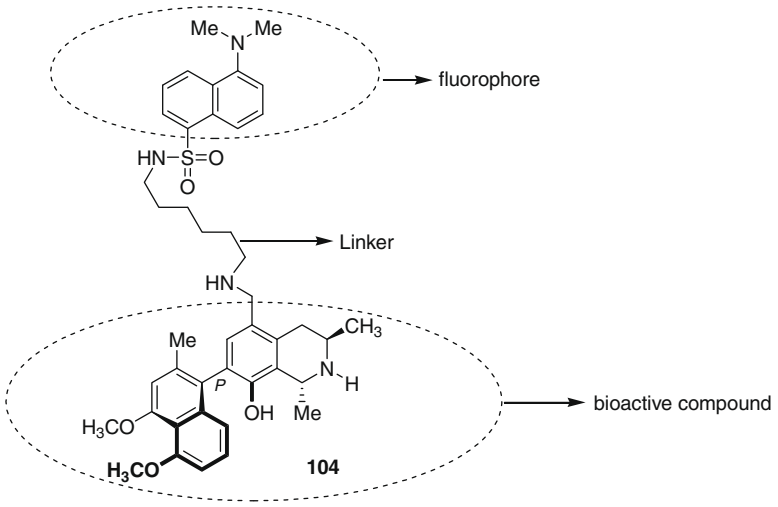
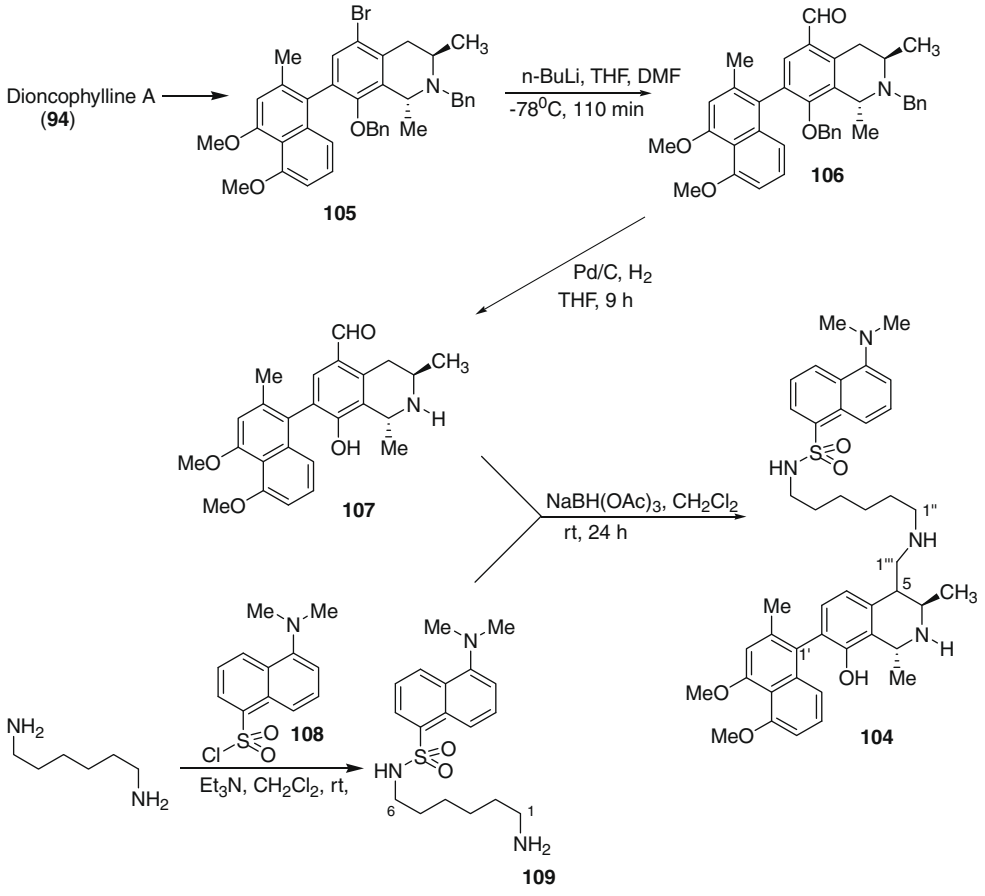


Figure 6. Fluorophore attached to dioncophylline.



Scheme 18.

proteins. The new dioncophylline A analogues constitute a promising basic structure for the development of a malaria—specific diagnosis, for example, for the sensitive fluorescene based detection of parasites in blood samples, even with a low degree of parasitemia.

Most recently Bringmann et al.[77] described the isolation, structure elucidation and bio-testing of six new C–C coupled naphthylisoquinoline alkaloids as well as the synthesis of fluorescence labeled antiplasmodial naphthylisoquinoline analogues in order to investigate their localization in parasite infected cells. The first actual[78] synthetic approach toward the synthesis of N,C-coupled naphthylisoquinoline alkaloid **98** is based on the cyclocondensation of the diketone **99** with the aminonaphthalene **100**. While the diketone **99** is easily prepared from **101**, the amine **100** was obtained by Pd-catalyzed amination of the 1-bromonapthalene **102**.

For the synthesis of the *bis*-methoxylated aminonaphthalene **100**, the bromo compound **102**[79] was transformed into **100** by Buchwald–Hartwig amination (Scheme 16).[80] Due to the instability

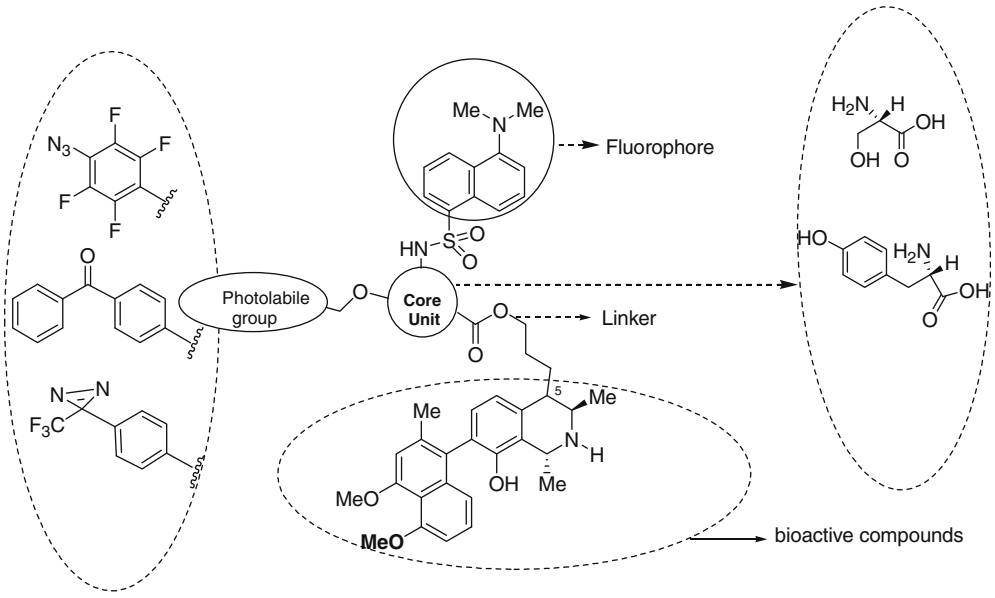
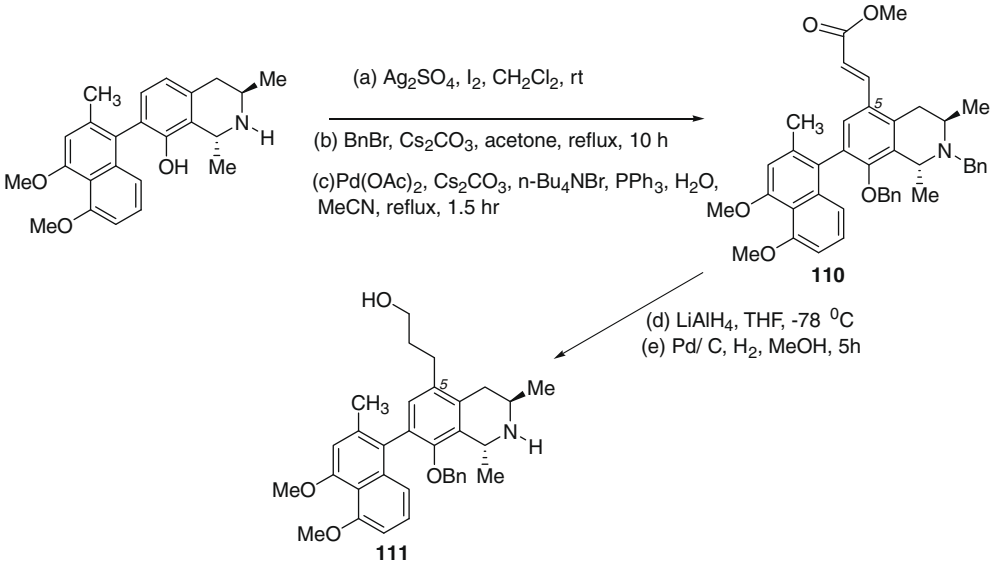


Figure 7. Synthesis of dioncophylline a derivative.



Scheme 19.

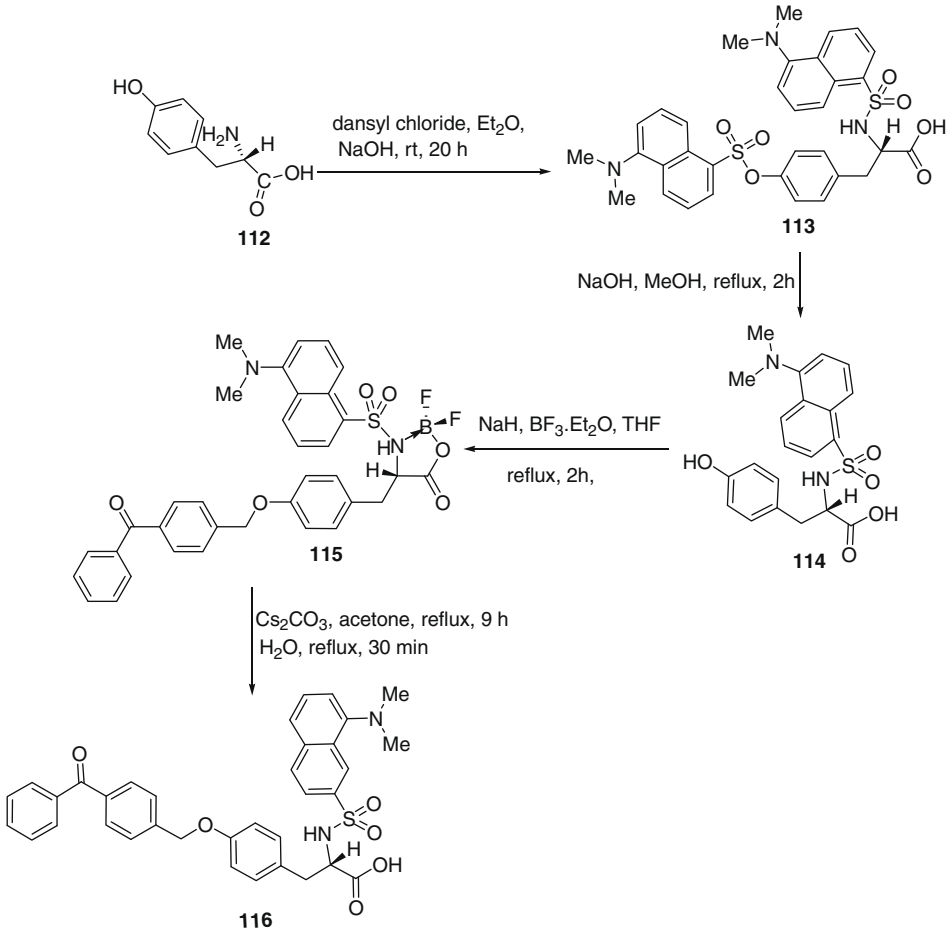
of amine **100**, freshly prepared amine, after neutralization of the reaction mixture with aqueous hydrochloric acid, was added immediately to a solution of the benzopyrilium salt **103** in glacial acetic acid. However, attempted chromatographic purification led to complete decomposition of **98**. To stabilize the ancisheynine **98,** the respective benzopyrylium tetrafluoroborate salt **98** (x = BF_4) was used as a more electron poor anion, with slower decomposition of ancisheynine (Scheme 17).

In a simplified approach,[77] a fluorophore (Fig. 6) was attached to dioncophylline A (**94**) via C-5, using an alkyl chain hexamethylenediamine linker to give the fluorescent analogue **104**. For this purpose dioncophylline A was brominated and O- and N-protected.[65] The resulting *N,8-O*-benzyl-5-bromodioncophylline A **105** was lithiated and formylated with DMF to give the aldehyde **106** followed by debenzylation to give **107**, which was successfully coupled[81] with precursor **109**[82] (prepared from hexamethylenediamine and sulfonyl chloride **108**) via reductive amination to deliver analogue **104** (Scheme 18).

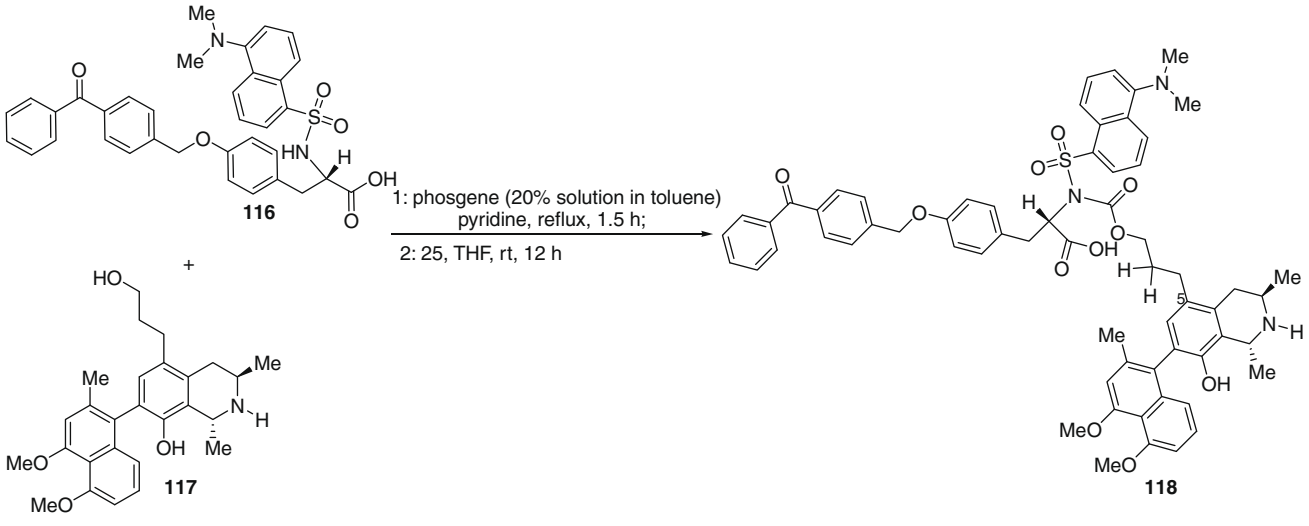
The structural requirements for these compounds according to QSAR studies[83,84] showed that the OH and NH groups in the isoquinoline part of dioncophylline A are crucial for antiplasmodial activity.[84] Position 5 does not belong to the pharmacophore of the molecule, so that functionalization at this position should be possible without any substantial loss of activity. For this reason dioncophylline A was connected at this particular position to a flexible alkyl linker to prevent steric interference of the fluorophore and photo labile groups.

2.6.1. Synthesis of dioncophylline A derivatives

In a second more comprehensive approach,[85] dioncophylline A was equipped with a fluorescent and photo-affinity probe to assemble multifunctional molecules using known strategies. A



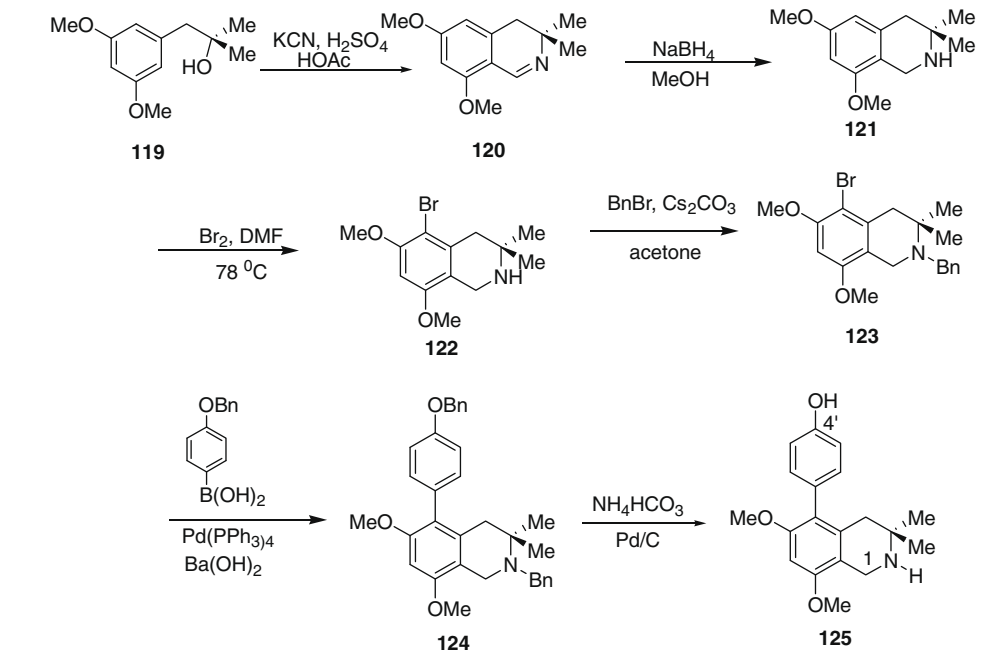
Scheme 20.



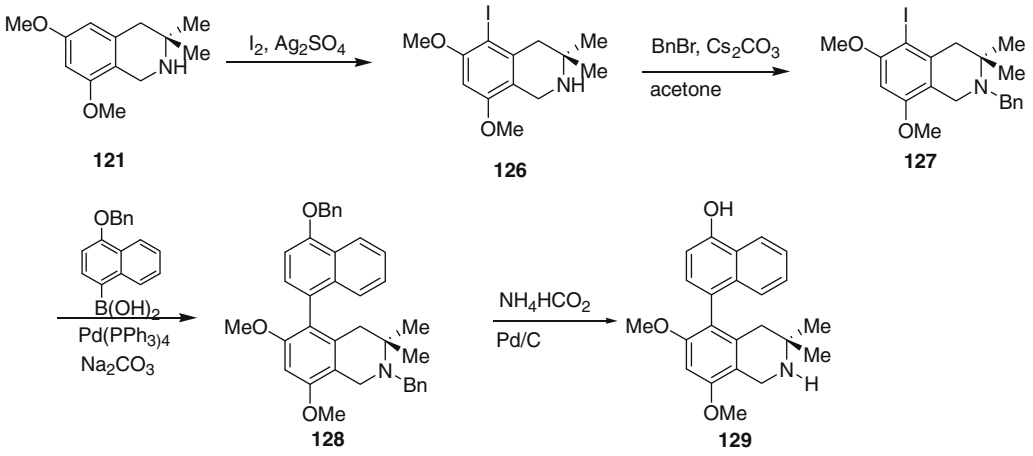
Scheme 21.

three functional core unit served as the central module to connect the required building blocks like hydroxylated aminoacids L-serine and L-tyrosine (Fig. 7).

For the functionalization of dioncophylline A according to the concept presented in Figure 7, the alkaloid was halogenated at C-5 (Scheme 19) using Ag_2SO_4 and I_2 resulting in 5-iododioncophylline A. After standard *O*- and *N*-benzyl protection in acetone/CS_2CO_3, followed by the Heck reaction with methyl acrylate, the cinnamate ester **110** was obtained. Its reduction with $LiAlH_4$ followed by hydrogenation of the exocyclic double bond with simultaneous cleavage of the O-and *N*-protecting groups resulted in intermediate **111**.



Scheme 22.

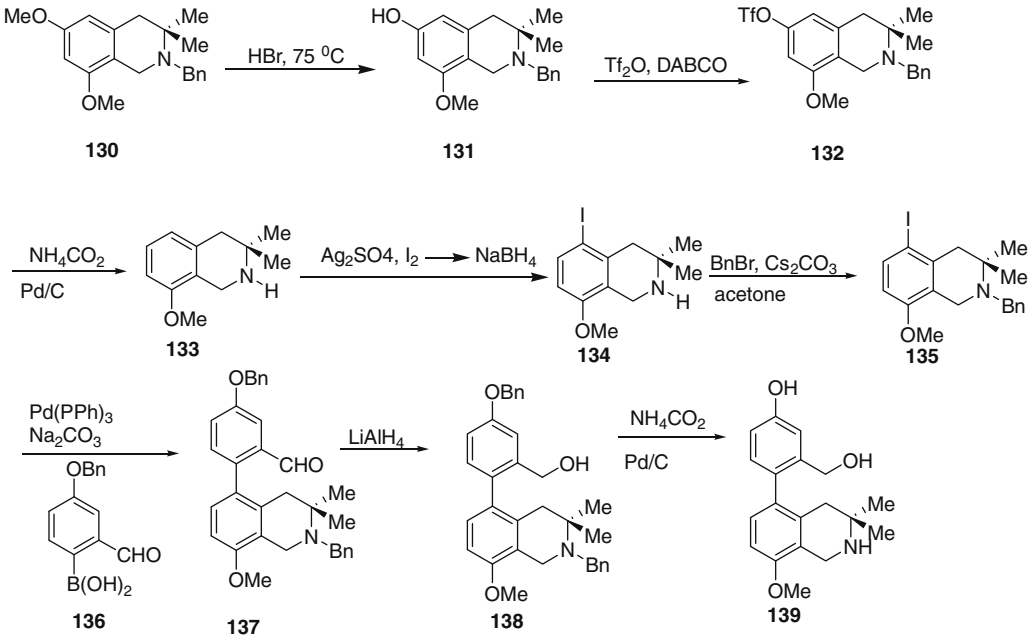


Scheme 23.

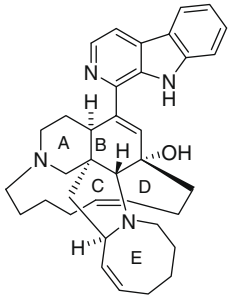
2.6.2. Synthesis of a building block with a tyrosine unit

Another approach for the synthesis of the fluorescent derivatives of napthylisoquinoline was reported by Bringmann et al. involving the initial double dansylation of L-tyrosine **112** in two phase system of $Et_2O/H_2O/NaOH$ resulting in the formation of *N*,*O*-didansyl-L-tyrosine **113** which was easily cleaved back to the desired mono-*N*-dansyl derivative **114** in refluxing NaOH/MeOH, by selective hydrolysis of the sulfone ester. Selective O-alkylation was achieved using protection and deprotection strategies.[86] Thus the reaction of amino acid **114** with BF_3 in the presence of NaH led to the formation of oxazaborolidinone **115** and its hydrolysis resulted in the formation of O-alkylated tyrosine **116** (Scheme 20). The attachment of photoactive and fluorescent amino acid derivative **116** to the alkaloid derivative **117** via an ester-bridge resulted in photoactive fluorescent derivative **118** for the identification of the target proteins for antiplasmodial naphthylisoquinolines (Scheme 21).

There is another group of new NIQ-related biaryls[87] of the type **125** whose isoquinoline portion is significantly simplified by the fact that two methyl groups at the C-1 and C-3 are now both located at C-3, thus avoiding any of the two stereogenic centers present in the natural alkaloids. The target molecule **125** related to the antimalarial alkaloid dioncophylline C, bears a phenyl ring instead of a naphthyl ring with a free OH group in the 4′-position and a tetrahydroisoquinoline moiety with a free NH group. The tetrahydroisoquinoline moiety **120** was synthesized by the Ritter reaction of the tertiary alcohol **119** with potassium cyanide followed by reduction of imine **120** to the corresponding amine **121**. Bromination of this compound gave the bromide **122** and subsequent N-benzylation delivered **123,** which underwent a Suzuki cross coupling reaction with a benzyl-protected boronic acid to give biaryl **124** whose deprotection resulted in achiral 4′-hydroxylphenyl tetrahydroisoquinoline **125** (Scheme 22).



Scheme 24.



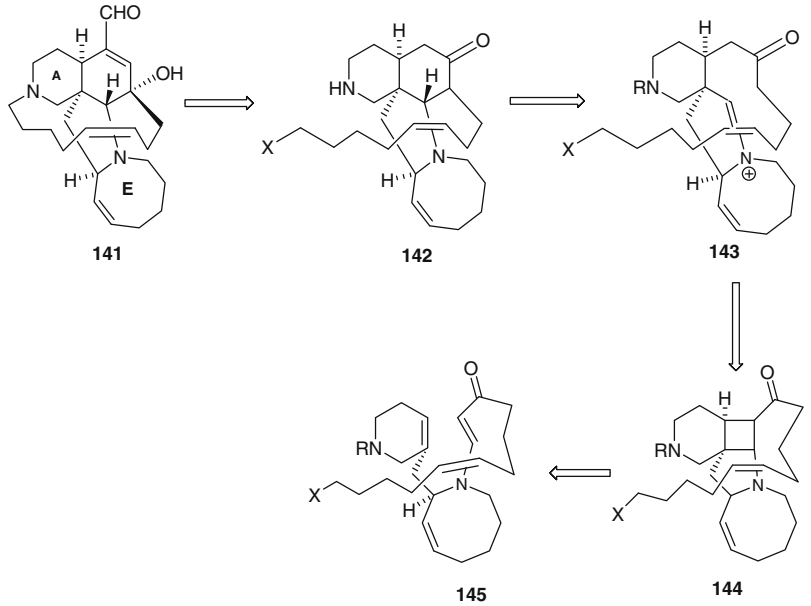
140

Figure 8. Manzamine A.

2.6.3. Synthesis of naphthyl- and biaryl-isoquinolines as simplified analogs of dioncopeltine

One of the most active antiplasmodial NIQ alkaloids, both in vitro and in vivo, is dioncopeltine A.[61] Its most characteristic structural feature is the presence of a hydroxy methyl group on the naphthalene portion. The tetrahydroisoquinoline **121** was activated by iodination leading to **126**, which after N-protection to **127** underwent a Suzuki cross coupling reaction with the appropriate boronic acid resulting in biaryl compound **128**. Hydrogenolytic N- and O-deprotection provided the naphthyl tetrahydroisoquinoline **129**[87] (Scheme 23).

The synthesis of the biaryl analog starts with regioselective O-demethylation at C-6 of the dimethoxy benzyl-protected interme-



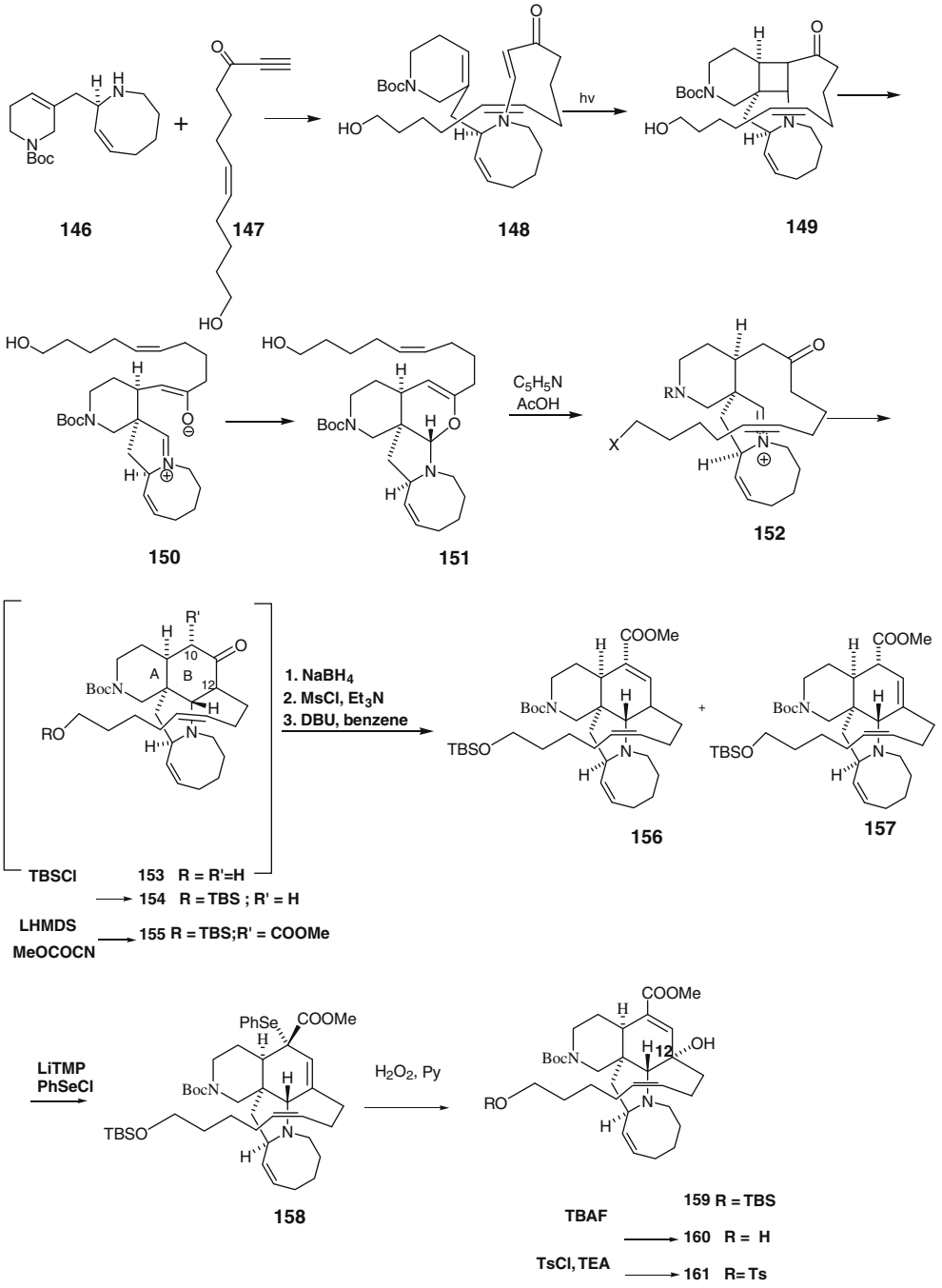
141 142 143 144 145

Scheme 25.

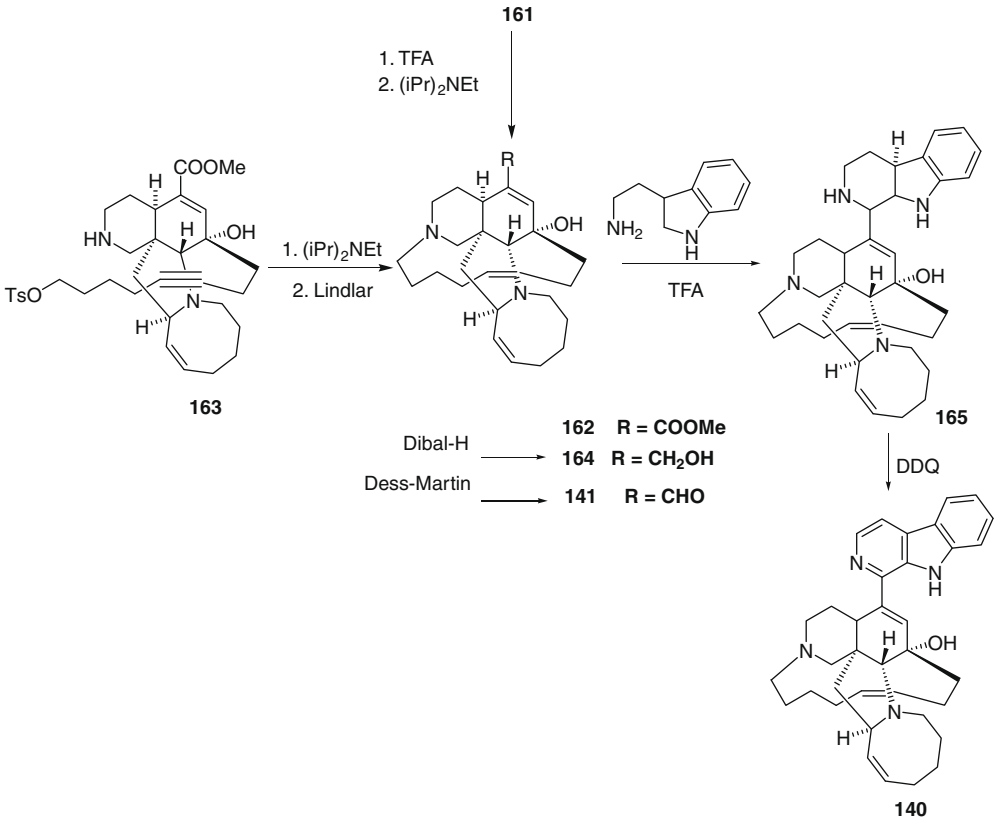
diate **130** to give the phenol **131**, followed by O-triflation to give **132** and hydrogenolytic elimination of the OTf group leading to the tetrahydroisoquinoline **133**.[88] Its iodination under various conditions proved difficult and was accompanied by undesired oxidation to the respective dihydroisoquinoline. The reaction mixture was, therefore, cautiously reduced and submitted to renewed iodination–reduction sequence, finally yielding **134**. A renewed introduction of the *N*-benzyl group completed the synthesis of 6-deoxygenated dioncophyllaceae—like isoquinoline **135**.[60] This new building block was coupled to the commercially available boronic acid aldehyde **136** to give the 5-(2′-formylphenyl)-tetrahydroisoquinoline **137**. Reduction of its aldehyde function to give **138** introduced the desired hydroxyl methyl group. Hydrogenolysis of both *O*-and *N*-benzyl groups generated the dioncopeltine A analog **139** as an unstable compound (Scheme 24).

2.7. Manzamine and analogues

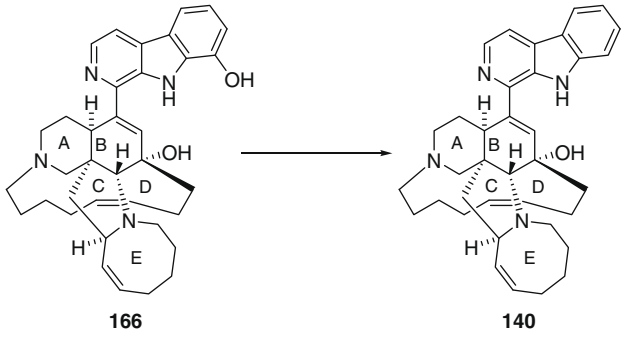
Manzamine A **140** and its precursors are a unique group of β-carboline alkaloids possessing promising antimalarial activity with rapid onset of action and prolonged antiparasitic activity than chloroquine and artemisinin.[89,90] Manzamine A is obtained from several marine sponge species found in the indian and pacific oceans and was initially isolated from the Okinawan sponge *Haliclona* sp.[91] The first total synthesis of manzamine A along with series of its analogues ircinol A was reported by Winkler[92] and Martin,[93] respectively. The unique structure of manzamine A (Fig. 8) comprises a β carboline moiety attached to a novel pentacyclic diamine core containing eight and 13 membered rings on a pyrrolo[2,3-*i*] isoquinoline framework. The *β*-carboline unit is known to impart significant activity.[94]



Scheme 26.



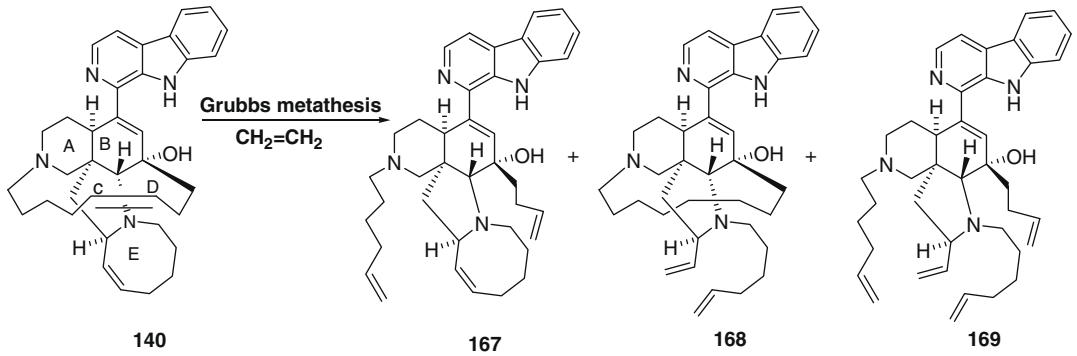
Scheme 27.



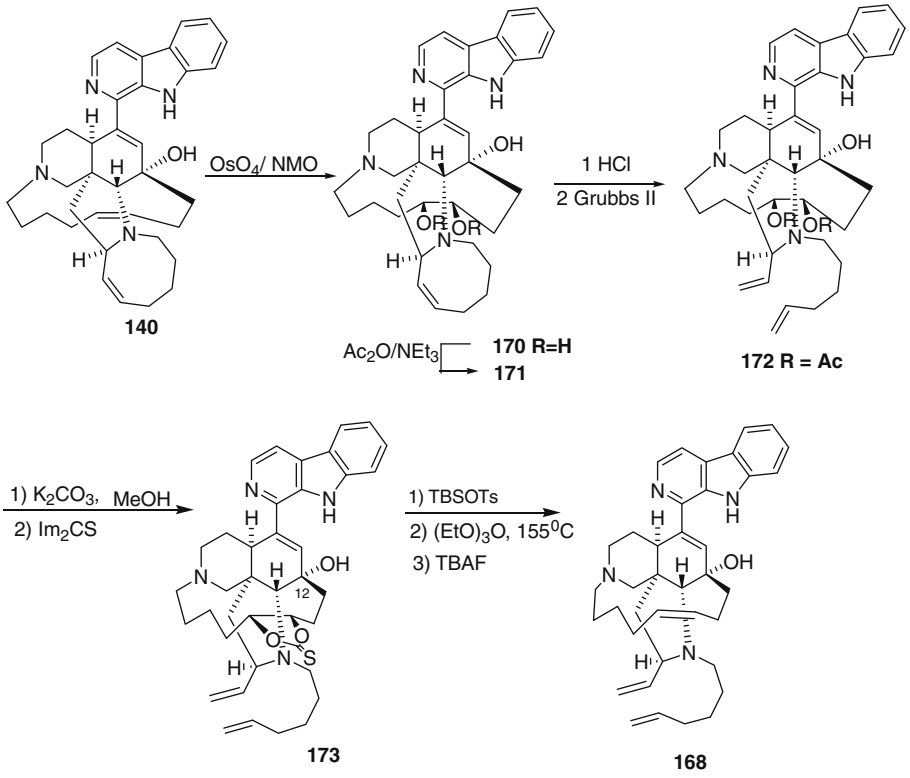
Scheme 28.

The retrosynthetic analysis of manzamine A (Scheme 25) involves disconnection of the β-carboline unit from manzamine A leading to the formation of Ircinal A **141**. Ircinal A could be converted to manzamine A by Pictet-Spengler cyclization via DDQ oxidation.[95] Iricinal A could be obtained by B-ring functionalization and macrocyclization of **142**. The tetracyclic ring system of **143** resulted from the Mannich closure of ketoiminium **144,** which is derived by retro-Mannich fragmentation of **144**, a product of intramolecular cycloaddition of **145**.

The first total synthesis of manzamine A involved a 17-step synthesis from readily available bicyclic precursor **146** and involved the utility of a vinylogous amide photoaddition/fragmentation/Mannich closure sequence. The establishment of the stereochemical relationship in manzamine A from the single stereogenic center in **146** involved the remarkable levels of stereochemical control using this photochemical cascade. The synthesis commenced with the reaction of the secondary amine **146**[92] with acetylenic ketone **147** resulting in vinylogous amide photosubstrate **148**, which underwent photoaddition to **149** and retro-Mannich fragmentation via O-closure of the ketoiminium intermediate **150** to give rise to aminal **151**. Compound **151** in the presence of pyridinium acetate



Scheme 29.



Scheme 30.

isomerises via iminium ion **152** to manzamine tetracycle **153** as a single stereoisomer. The next step involves elaboration of the **B**-ring, which was achieved by carboxylation of the enolate derived from **154**, the silyl ether of **153**, with Mander's reagent to give ketoester **155**. The next steps involved the reduction of the C-11 ketone followed by elimination of the derived mesylate with DBU in refluxing benzene resulting in a mixture of α,β- and β,γ-unsaturated compounds **156** and **157** (Scheme 26).

Selenation of **156** and **157** with LiTMP in the presence of PhSeCl resulted in the formation of α-selenated product **158**. The next step involved the oxidation of selenide **158** resulting in the formation of C-12 α-alcohol **159**. Deprotection and tosylation of the derived alcohol **160** gave **161**. Removal of the Boc group and exposure of secondary amine to Hunigs base led to the formation of methyl ircinate **162.** Cyclization of the acetylinic substrate **163** resulted in the formation of the macrocyclic product which on Lindlar reduction gave **162**. Reaction of α,β-unsaturated ester **162** with DIBAL–H resulted in the first synthesis of ircinol A precursor **164** whose oxidation with Dess Martin reagent gave iricinal A **141**. Using the procedure of Kobayashi,[95] coupling of **141** with tryptamine in the presence of trifluoroacetic acid gave manzamine **D**, **165**, which on oxidation with DDQ provided manzamine A, **140** (Scheme 27).

2.7.1. Biocatalytic conversion of 8-hydroxymanzamine A to manzamine A

Hamann et al.[96] in 2003 described the biocatalytic conversion of 8-hydroxymanzamine A (8-OHMA) to manzamine A by *Fusarium solani* and *Streptomyces seokies*. This biocatalytic reaction is unique as this transformation involved the selective dehydroxlation of the C-8 position of 8-hydroxymanzamine. The antimalarial activity of the manzamine produced by this transformation is more than that of the 8-hydroxymanzamine. This biotransformation involved the addition of 8-hydroxymanzamine A (**166**) into a media inoculated with 1×10^5 conidia of *Fusarium sp*. This biotransformation using *F. solani* resulted in a single metabolite manzamine A (Scheme 28).

A biotransformation using the *Streptomyces seokies* was also successfully performed from 8-hydroxymanzamine A to manzamine A.

2.7.2. Modifications of manzamine A via Grubbs metathesis

In 2007 Winkler et al.[97] described the strategy for the modification of naturally occurring manzamine A to novel structures with enhanced antiprotozoal properties via Grubbs metathesis. The structural modification of manzamine A using olefin metathesis led to highly efficient structures with important antimalarial properties. Selective formation of one of the two possible tetracyclic analogues as well as the tricyclic analogue of Manzamine A was achieved. Exposure of cycloalkene containing manzamine A **140** to the second generation Grubbs catalyst in the presence of ethylene resulted in three new analogues in which both the D and E rings were cleaved by ring opening metathesis to generate compounds **167**, **168** and **169** as new analogues of manzamine A (Scheme 29).

The exposure of the hydrochloride salt of **140** to 15 mol% of the second generation Grubbs catalyst and ethylene led to the formation of a 4:1 mixture of manzamine derived diene **167** and tetraene **169.** The selective formation of **167** in the metathesis ring opening of **140** and failure to observe **168** is presumably due to the rapid ring opening of **168** to generate **169.** Regioselective dihydroxylation of **140** led to the stereoselective formation of the 15, 16-dihydroxy-manzamine **170**. Diacetylation of **170** generated a substrate **171** for Grubbs metathesis opening of the azocine ring. Exposure of **171** to the Grubbs catalyst led to the formation of ring opened product **172**, followed by the hydrolysis of diacetate **172** and its further reaction with thiocarbonyldiimidazole to form **173** (Scheme 30).

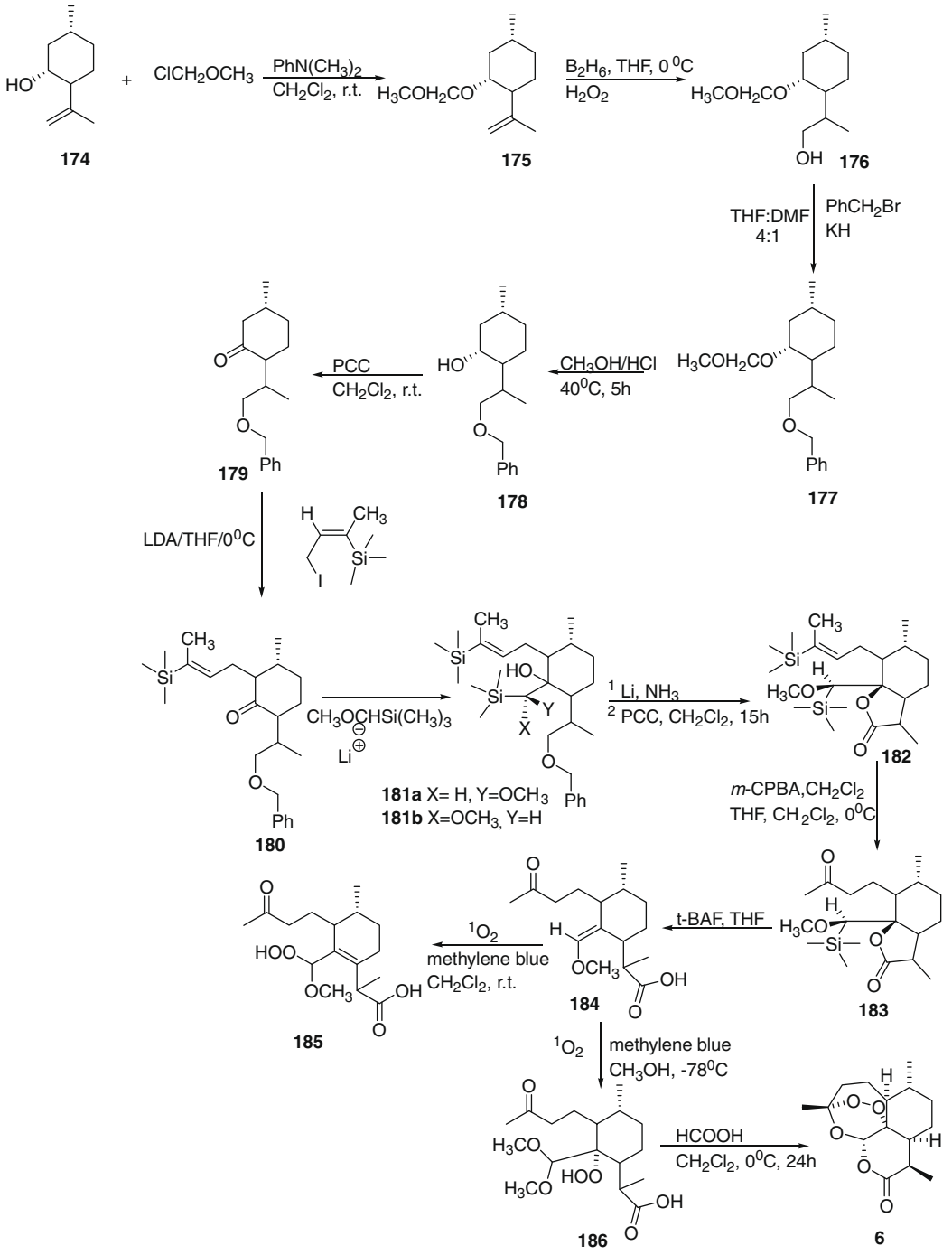
Treatment of the C-12 silyl ether with triethylphosphite led to the regeneration of the alkene moiety, with the retention of the C-12 silyl ether function. Deprotection of the intermediate silyl ether with fluoride afforded **168**. None of the new ana-

logues were more potent than manzamine A against *P. falciparum*, although both of the tetracyclic analogues **167** and **168** are within an order of magnitude of **140** in their antimalarial activity.

Manzamine A and its selected derivatives have shown potential as novel antimalarial agents with rapid onset of action and prolonged antiparasitic activity. However, manzamine A is reportedly lethal to mice at a dose of 500 mmol/kg, which is only 10 times higher than the dose (50 mmol/kg) that suppresses parasitemia. Despite the narrow therapeutic index of manzamine A, its synthesis has provided a platform for the structure–activity evaluation and synthesis of effective and safer manzamine related antimalarial compounds in future. It is particularly noteworthy that compound **167** is almost four times less toxic than manzamine A, thus revealing the potential of these analogs as antimalarial agents.

2.8. Artemisinin and analogues

Artemisinin was first isolated by Chinese researchers in 1972, as part of a program launched by Chinese government to discover new antimalarial drugs.[98–101] Although the extraction and purification procedures for artemisinin are reasonably straightforward,[102] the maximum yield obtained is 0.1%. The unusual chemical structure of artemisinin coupled with its proven antimalarial efficacy, low toxicity and low yields from natural sources prompted scientists to search for new synthetic routes for artemisinin and related compounds.[103]

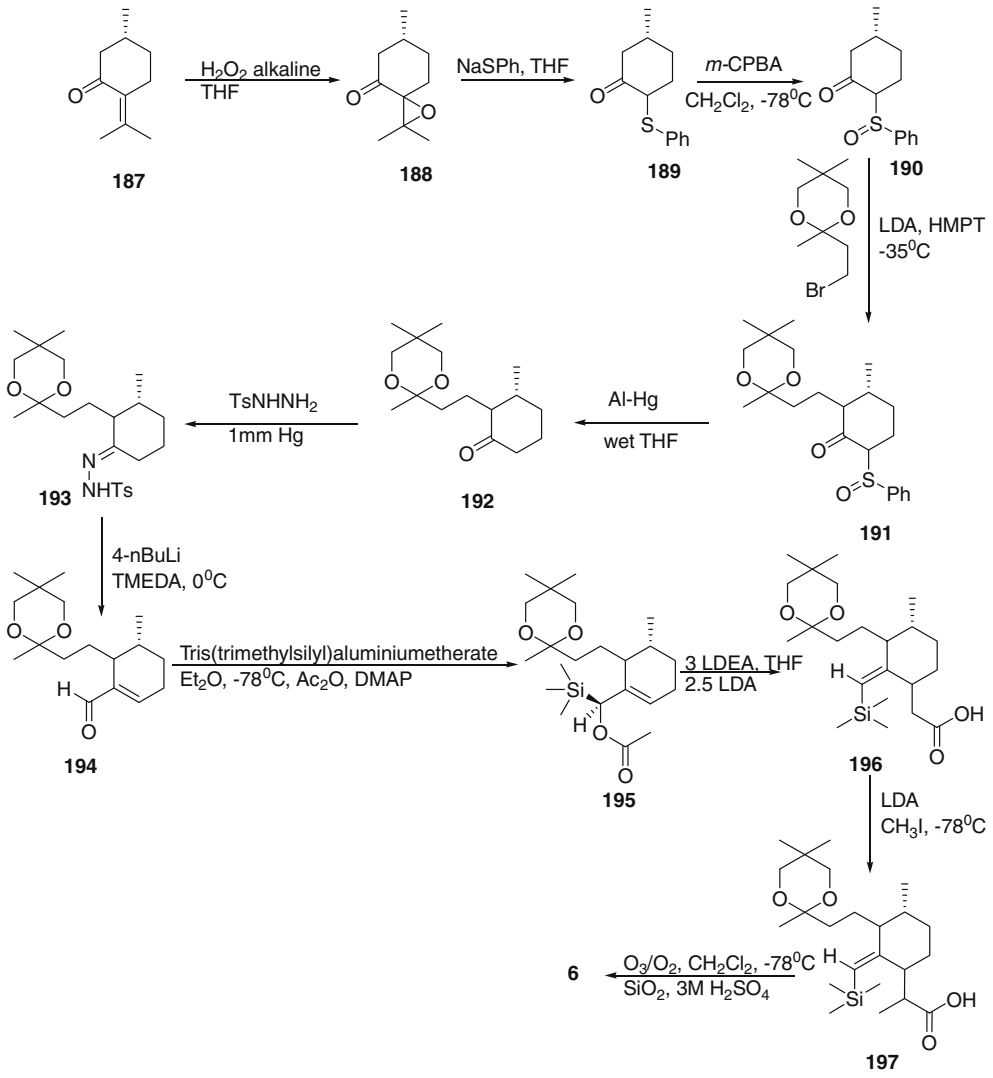


Scheme 31.

The unique 1,2,4-trioxane structure of artemisinin is entirely incompatible with the traditional antimalarial structure–activity theory. It was proposed[98] from the beginning, that these types of agents have a mode of action entirely different from those of traditional alkaloid antimalarial agents. Amongst several proposed mechanisms,[104,105] artemisinin is believed not to directly exert its lethal effects on the malarial parasite through the whole intact molecule but rather through transient free radical species generated by the reaction of endoperoxide bridge with iron content of the parasite.[104] Recent studies also suggest that artemisinin is effective at treating various forms of cancer such as leukaemia and breast cancer presumably through a similar mechanism.[106]

The first total synthesis of artemisinin was reported by Schmidt and Hofeinz.[107] Their methodology involved the conversion of (−) isopulegol **174** into methoxymethyl ether **175** which upon hydroboration–oxidation led to the formation of the corresponding alcohol **176** in 80% yield. Benzylation of **176** followed by cleavage of the resulting methoxymethyl ether **177** using hydrochloric acid resulted in the formation of alcohol **178**. This compound was then oxidized using PCC to yield the corresponding menthone **179**, which was then treated with (3-iodo-l-methyl-l-propenyl)-trimethylsilane in the presence of LDA to deliver a 6:1 mixture of epimeric alkylated products **180**. The addition of 1 equiv. of lithium methoxy(trimethylsilyl) methylide in THF at −78 °C resulted in a 1:1 ratio of diasteromeric alcohols **181a** and **181b** in quantitative yield. Compound **181a** was debenzylated using Li/NH_3 and the resulting alcohol was oxidized using PCC to the corresponding lactone **182**. This compound was then treated with *m*-CPBA in dichloromethane to achieve the conversion of the vinylsilane to the corresponding ketone **183** which was desilylated with TBAF to vinyl ether **184** with concomitant opening of the lactone ring. Ene reaction of **184** with singlet oxygen/methylene blue in dichloromethane led to the formation of hydroperoxide **185**. However, changing the solvent system to methanol resulted in the formation of **186** which on treatment with HCOOH at 0 °C resulted in the formation of crystalline artemisinin (Scheme 31).

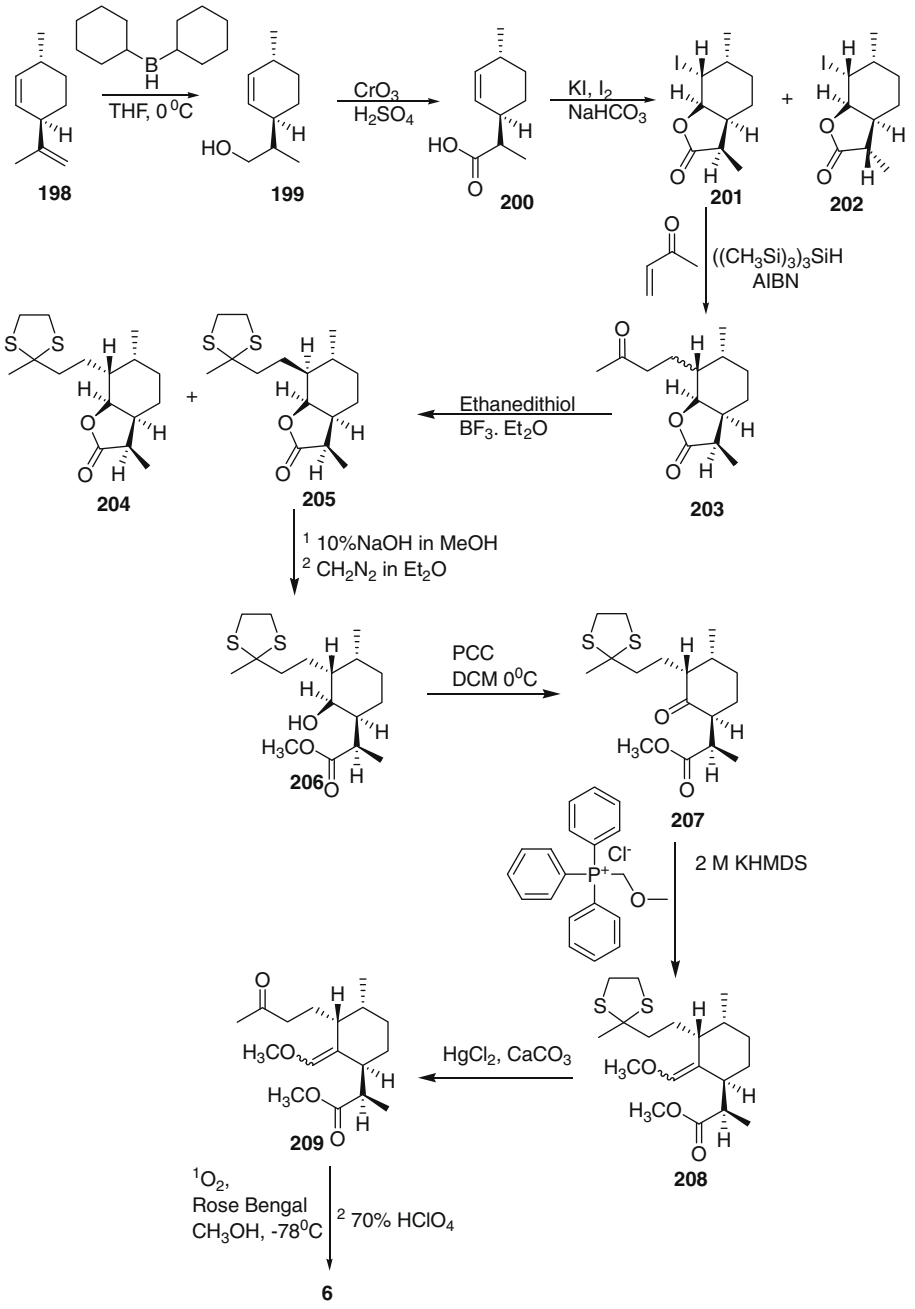
Avery and co-workers[108] have described a 10-step stereoselective total synthesis of (+)-artemisinin starting with R-(+)-pulegone **187**. Epoxidation of this compound with alkaline H_2O_2 led to pulegon epoxide **188**. Thiophenoxide ring opening of this compound and loss of acetone afforded the thiophenyl ketone **189** in a regiospecific fashion. Oxidation of **189** with *m*-CPBA furnished sulfoxide **190**, which was then alkylated using LDA and 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane to provide intermediate **191** that was desulfurized with aluminium amalgam to afford the desired ketone **192**. The reaction of ketone **192** with *p*-toluenesulfonohydrazide provided the corresponding hydrazone **193**, which was subsequently treated with 4 eq of *n*-BuLi in *N*,*N*,*N*′,*N*′-tetramethyl-



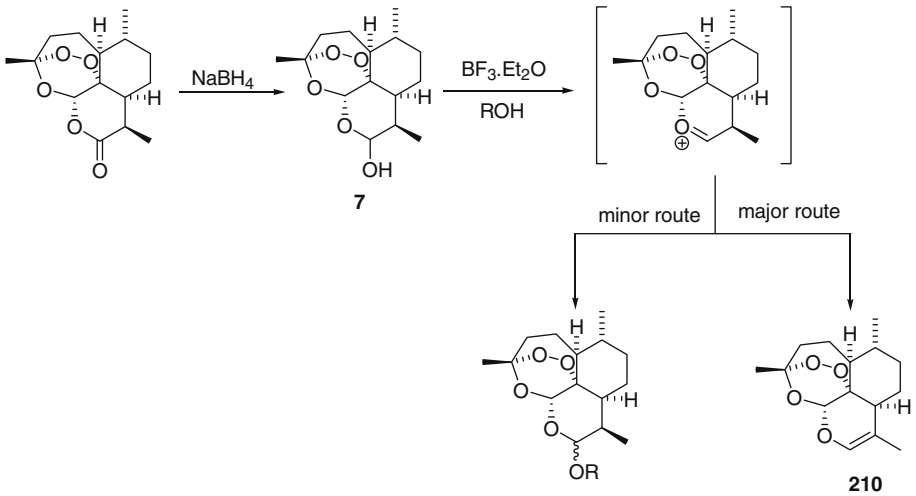
Scheme 32.

enediamine (TMEDA) providing regiochemically pure unsaturated aldehyde **194**. Diastereomer **195** was furnished by the reaction of aldehyde **194** with *tris*(trimethylsilyl)aluminium etherate in 88% yield. A convenient one pot approach to vinylsilane **196** was developed by reacting **195** with 3 equiv of LDEA followed by 2.5 equiv of LDA. The resulting dianion was quenched with CH_3I to afford acid **197**, which upon ozonolysis in dichloromethane at −78 °C followed by addition of aqueous H_2SO_4 and silica gel furnished (+)-artemisinin **6** in 33–39% yield, Scheme 32.

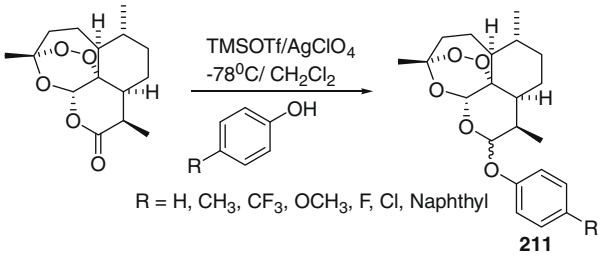
Yadav et al.[109] have reported another approach for the stereoselective synthesis of (+)-artemisinin starting with the regioselective hydroboration–oxidation of (+)-isolimonene **198** using dicyclohexylborane to yield the required alcohol **199** in 82% yield. The alcohol was converted to the corresponding acid **200** using Jones' oxidation and in turn subjected to iodolactonization using KI, I_2 in aq $NaHCO_3$ to afford the corresponding iodolactones **201** and **202** as a separable diastereomeric mixture. The iodolactone **201** was then subjected to an intermolecular radical reaction with methyl vinyl ketone using *tris*(trimethylsilyl)silane and AIBN in toluene resulting in the formation of the corresponding alkylated lactone **203**. The keto group of **203** was transformed into the dithioketal moiety to give diastereomeric lactones **204** and **205** by treatment with ethanedithiol in the presence of $BF_3{\cdot}Et_2O$ in dichloromethane at 0 °C. Lactone **205** was isolated and subjected to hydrolysis and esterification using diazomethane providing hydroxyl ester **206** in good yield. Transformation of compound **206** into keto ester **207** was achieved using PCC at room temperature. The Wittig reaction of **207** with methoxymethyl triphenylphosphonium chloride furnished the corresponding methyl vinyl ether **208** whose deprotection using $HgCl_2{\cdot}CaCO_3$ resulted in the key intermediate **209** in 80% yield. Photo-oxidation of **209** and subsequent acid hydrolysis led to the formation of **6** (Scheme 33).



Scheme 33.

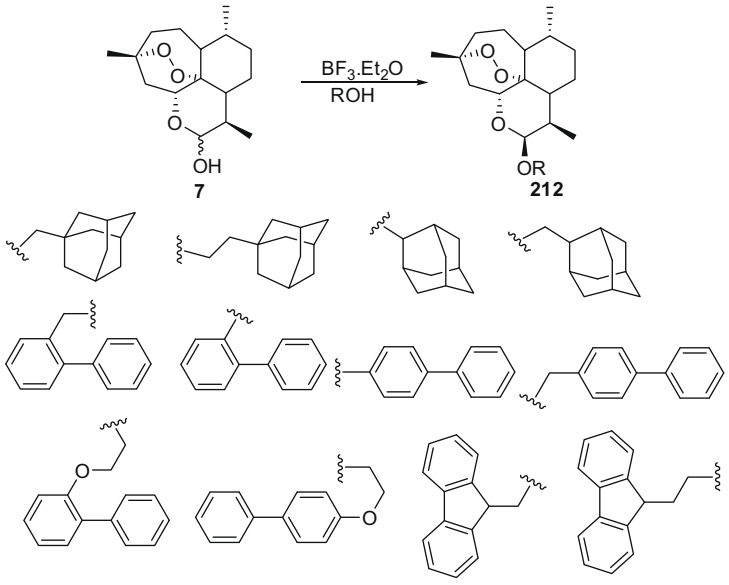


Scheme 34.



Scheme 35.

Although artemisinin has been used clinically in China for the treatment of multidrug resistant *P. falciparum* malaria, the therapeutic value of this drug is limited to a great extent by the following factors: (i) its low solubility either in oil or water,[110] (ii) high rate of parasite recrudescence after treatment,[111] (iii) its short plasma half life[112] and (iv) its poor oral activity.[111] Consequently in the search for more effective and soluble drugs, a number of derivatives of the present drug have been prepared. Reduction of artemisinin to the lactone dihydroartemisinin (DHA) **7** has in turn led to the preparation of a series of semi-synthetic first generation analogues which include artemether **8**,[113] arteether **9**[113] and water-soluble sodium artesunate **10**.[114,115] Artemether and arteether are more potent than artemisinin but have short plasma half-lives and produce fatal CNS toxicity in chronically dosed rats and dogs.[116–118] Although neurotoxicity is an issue in animal models, recent studies have shown a lack of neuronal death in patients who had received high doses of artemether by intramuscular injection.[119] Despite these observations, there is no comparative data on oral dosing with first generation alkyl ether prodrugs of the neurotoxic dihydroartemisinin. The initial approach for the preparation of these derivatives was to couple DHA **7** with various alcohols in the presence of boron trifluoride diethyl ether as catalyst. Many researchers have used this method to synthesize first generation endoperoxides.[120] The method involves the reaction of 1 equiv. of DHA with 4 equiv of alcohol in anhyd. ether at room temperature in the presence of $BF_3{\cdot}Et_2O$.[121] The formation of anhydroartemisinin **210** (AHA) in high yield in these reactions suggests the involvement of an oxonium ion intermediate, which being a chem-



Scheme 36.

ically reactive intermediate either reacts with an alcohol to give the corresponding ether or loses a proton to give the by product AHA **210** (Scheme 34).

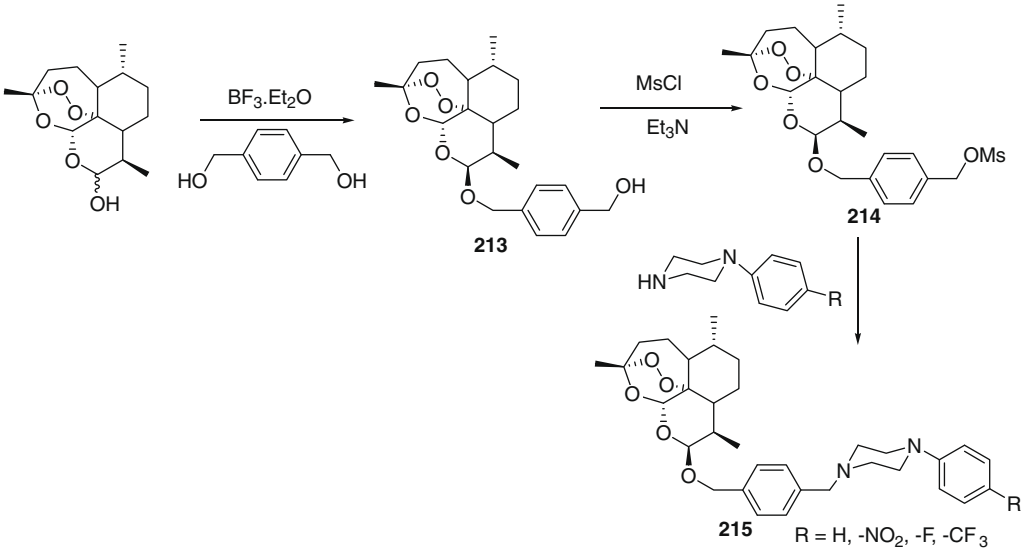
Although these derivatives are potent antimalarial agents in vitro, they have poor bioavailability principally as a result of the metabolic instability of the acetal function. An approach for increasing the metabolic stability of artemisinin derivatives involves the incorporation of a phenyl group in place of an alkyl group. O'Neill and co-workers have synthesized a series of C-10 *o*-aryl substituted artemisinin derivatives using the TMSOTf-$AgClO_4$ system as catalyst.[122] The approach involved dissolving 1 equiv of DHA, 2 equiv of desired phenol and 0.2 equiv of $AgClO_4$ in anhydrous dichloromethane, under a N_2 atmosphere at −78 °C followed by the addition of 1 equiv of TMSOTf. The reaction resulted in excellent yields of corresponding products **211** with only minor quantities of AHA (Scheme 35).

Singh et al.[123] have recently reported the synthesis of new orally active derivatives of artemisinin with high efficacy against multidrug-resistant malaria parasites in mice. Dihydroartemisinin **7** was prepared by standard reduction protocol followed by its $BF_3{\cdot}Et_2O$-catalyzed reaction with alcohols at sub-zero temperature furnishing the corresponding ether derivatives **212** in 65–99% yields as diastereomeric mixtures of α and β-isomers (Scheme 36).

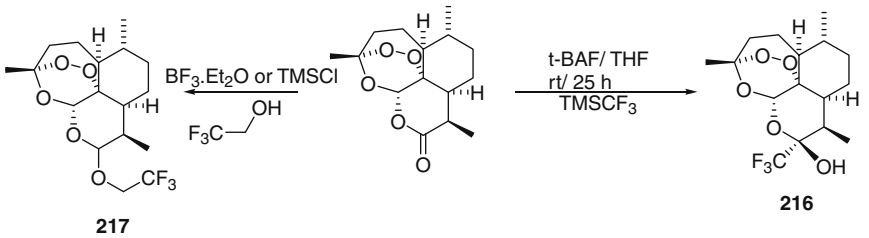
Since one of the mechanisms of action of artemisinin is believed to involve its interaction with ferriprotoporphyrin IX (heme) or ferrous ions in the acidic parasite food vacuole, any chemical modification that would increase the cellular accumulation of the drug would enhance drug activity. On this basis, O'Neill and co-workers[124] have reported the synthesis of artemisinin derivatives with two basic amino groups that would be expected to increase the cellular accumulation of drug in the ferrous rich parasite food vacuole. One of their approaches involved the synthesis of C-10 ether linked diamino analogues. DHA was coupled with 1,4-/1,3-dibenzen methanol to give the corresponding alcohol **213**. The alcohol was then converted into mesylate **214** by treatment with mesyl chloride in the presence of triethylamine. The mesylate was then allowed to react with a range of diamino nucleophiles to yield the desired compounds **215**, Scheme 37.

In vivo, the main pathway of metabolism of ether derivatives of dihydroartemisinin is a rapid hydroxylation by cytochrome P-450 enzymes to generate a hemiketal intermediate and subsequently DHA which has a very short plasma half life. Considering this, Begué et al.[125] envisaged a feasible approach to prolong the half life of artemisinin derivatives involving the design of new ethers that are not the proper substrates for cytochrome P-450. Their approach was based on the introduction of a flourine substituent at two specific positions: at the α-methylene carbon of DHA ethers (by either following the conventional route involving the reaction of fluorinated alcohols in the presence of $BF_3{\cdot}Et_2O$ or trimethylsilylchloride) or at the hemiacetal carbon of DHA. The methodology for the synthesis of **216** involved treatment of artemisinin with 1.1 equiv of $TMSCF_3$ in the presence of 1.1 equiv of trihydrate tetra butyl ammonium fluoride (*t*-BAF·$3H_2O$) at room temperature for 25 h. The triflouromethylation reaction proceeded with high selectivity with the formation of only one stereoisomer **217**, Scheme 38.

Further, in order to enhance the water solubility and antimalarial activity, Lin and co-workers[126] have synthesized DHA analogues containing an α-sugar moiety. The methodology involved the condensation of 10-*O*-(trimethylsilyl)dihydroartemisinin **218** (prepared by treatment of DHA with chlorotrimethylsilane in

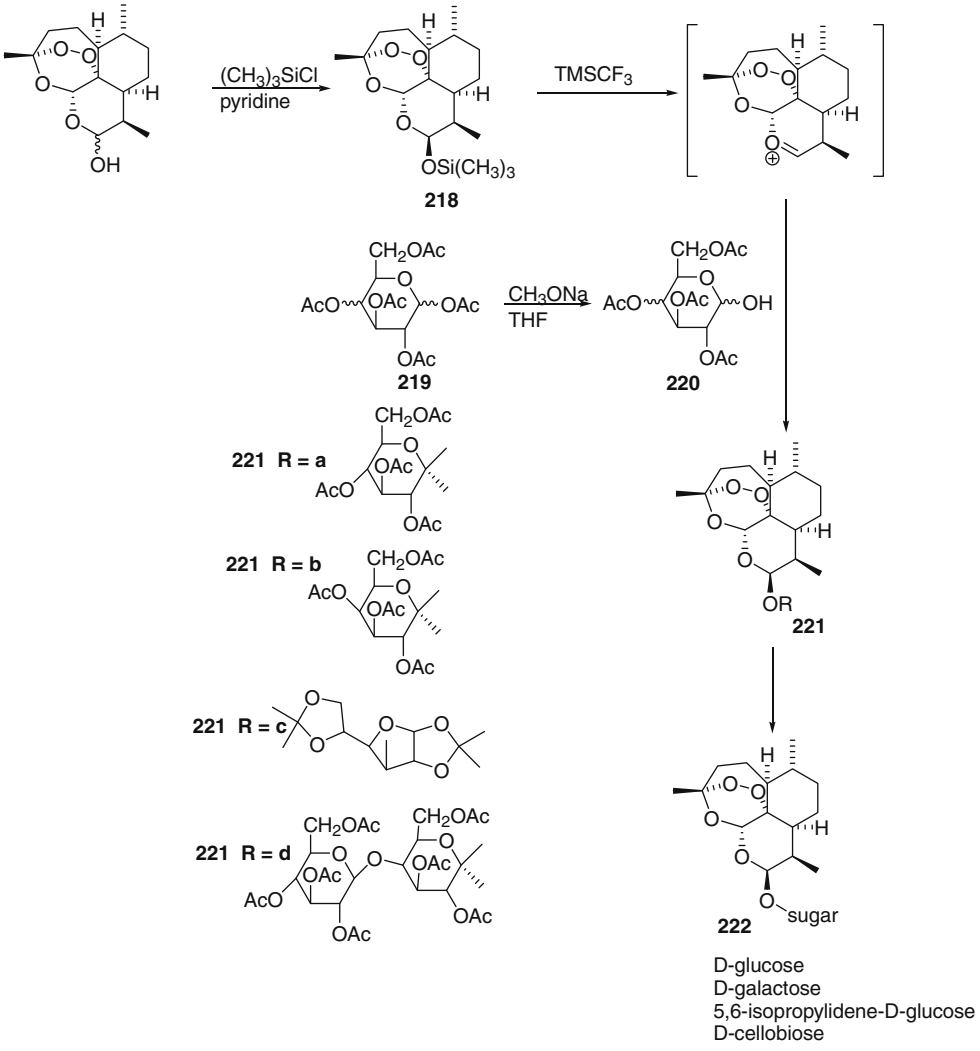


Scheme 37.

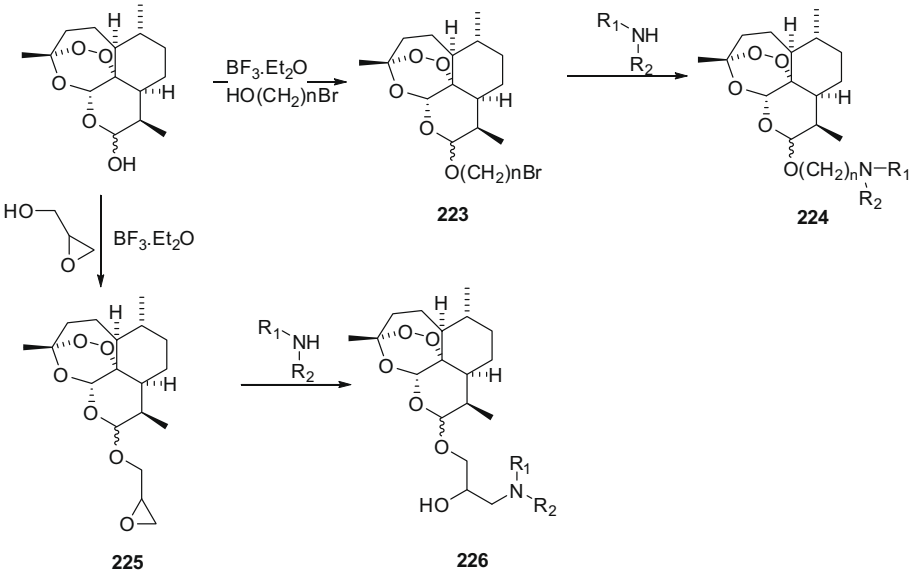


Scheme 38.

pyridine at −10 °C) with another intermediate **220** (prepared by regioselective 1-O-deacylation of the fully acetylated sugars **219** with sodium methoxide in THF) in the presence of a catalytic amount of trimethylsilyltrifluoromethane sulfonate in dichloro-



Scheme 39.



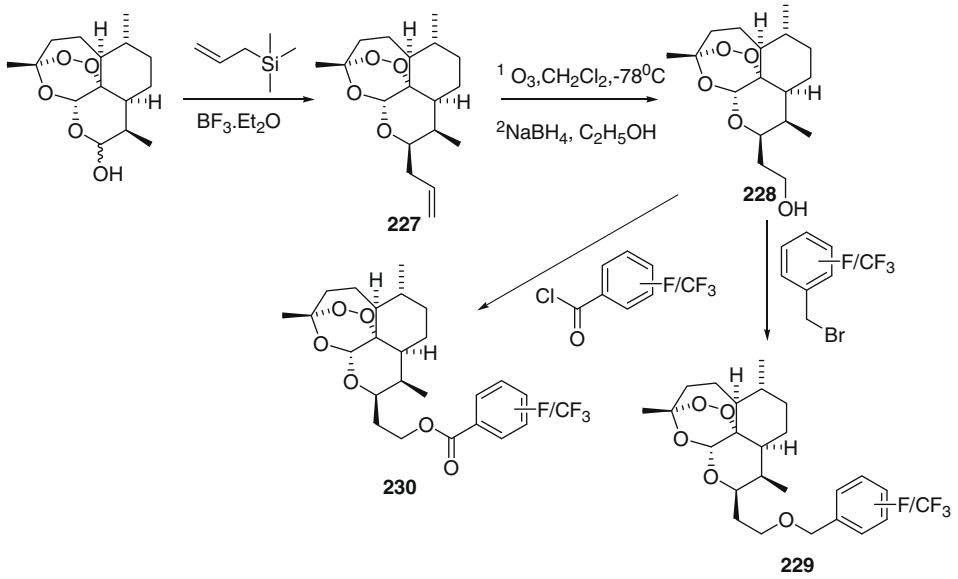
Scheme 40.

methane at −78 °C. The acetylated sugar-artemisinin derivatives **221** were then deacetylated using BaO/CH_3OH to yield the desired dihydroartemisinin-sugar derivatives **222**, Scheme 39.

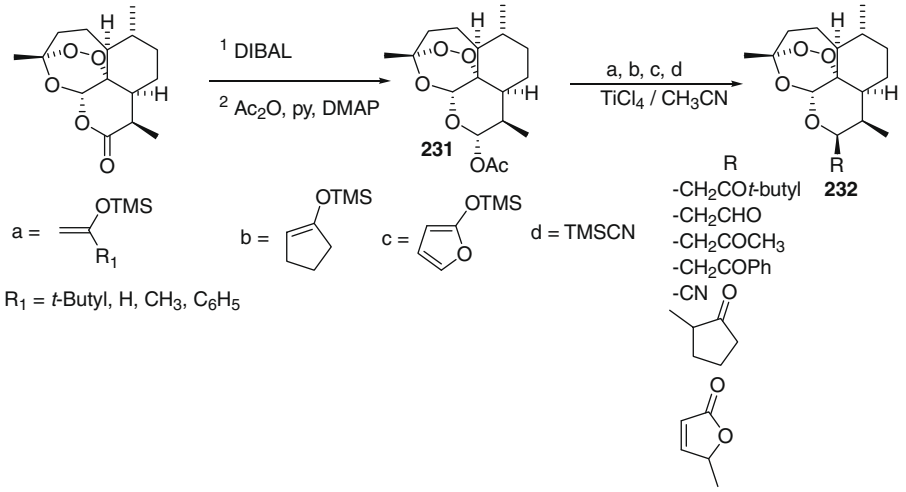
These derivatives were tested for inhibitory properties *in vitro* against two clones of human malaria *P. falciparum* D-6 (Sierra Leone clone), which is resistant to mefloquine and W-2 (Indochina clone), which is resistant to chloroquine, pyrimethamine, sulfadoxine, and quinine. The results indicated that these derivatives were not cross-resistant with any of the existing antimalarial agents. The compounds were, in general, more effective against the W-2 than the D-6 strain. It is interesting to note that the intermediate, trimethylsilylated compound **218**, is more effective than the derivatives **221 a–d.** The new compounds were also tested against *P. berghei* in mice. While the acetylated compounds **221 a–d** showed moderate in vivo activity, the deacetylated compounds **222** were inactive. The antimalarial results indicated that the in vitro activity of the compounds parallel those observed in vivo in that the increase in polarity or water solubility tends to decrease antimalarial activity.

In search for water-soluble derivatives Li et al.[127] have also reported the synthesis and antimalarial activity of artemisinin derivatives containing an amino group. The introduction of an amino group was based on the reasoning that most of the antimalarial agents such as chloroquine and quinine contain an amino group and are used as their salts. On similar grounds, the introduction of amino groups into artemisinin may lead to water-soluble derivatives. Reaction of DHA with bromoalcohol in the presence of $BF_3{\cdot}Et_2O$ yielded bromides **223** which were converted to **224** by reacting with appropriate amines. A similar strategy was employed in the synthesis of **226** from **225** (Scheme 40).

As discussed earlier, the poor bioavailability and rapid clearance observed with first generation analogues of DHA is due to the acetal function present in these derivatives. Replacement of the oxygen atom at the C-10 position with carbon would be expected to produce compounds not only with greater hydrolytic stability but also with longer half-lives and potentially lower toxicity. Consequently several groups have developed synthetic and semi-synthetic approaches to C-10 carba-analogues. O'Neill and coworkers[128] have reported the synthesis of a range of carba-analogues of artemisinin having fluorine containing aromatic groups attached either through an ether or ester linkage. The key intermediate required for the synthesis of the targets was allyldeoxoarte-

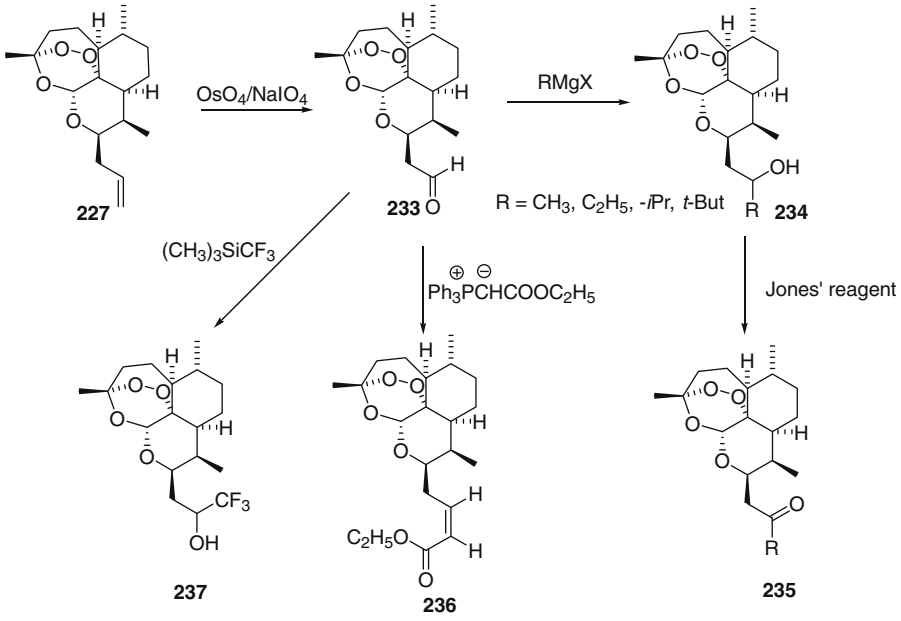


Scheme 41.

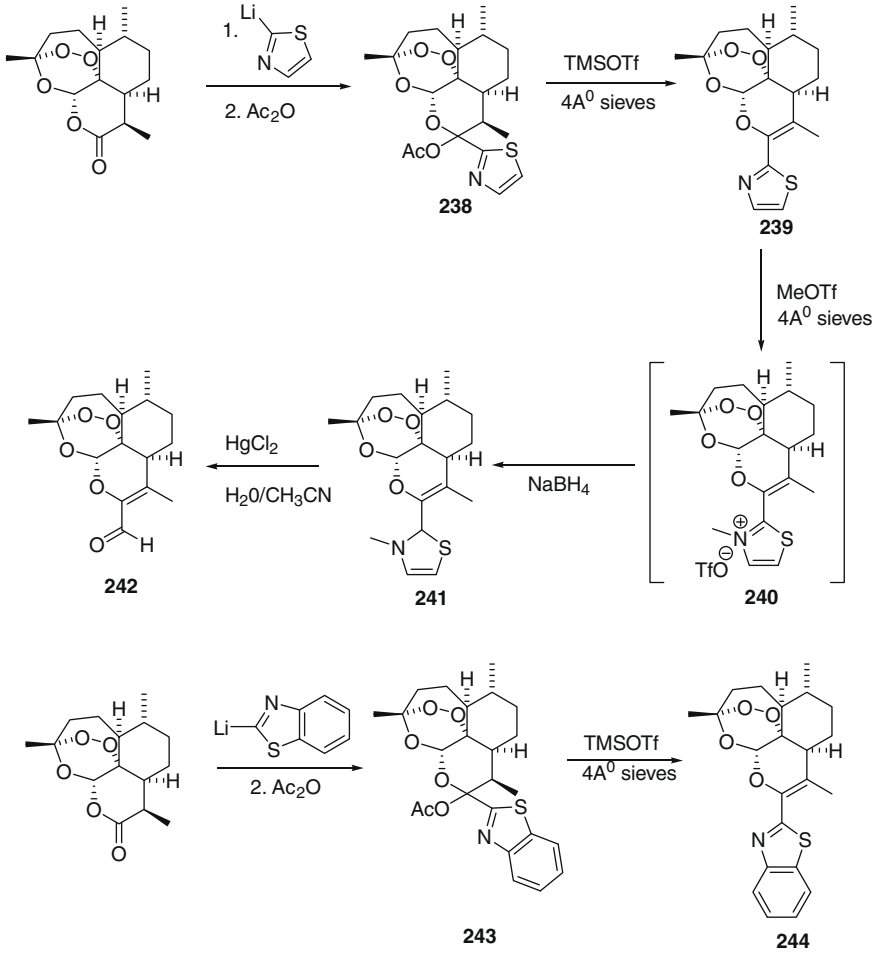


Scheme 42.

misinin **227** which was prepared by the coupling of DHA with allyl trimethylsilane in the presence of $BF_3{\cdot}Et_2O$. The resulting alkene was then subjected to ozonolysis followed by its subsequent reduction with $NaBH_4$ in THF/methanol to yield the corresponding alcohol **228**. The alcohol was then deprotonated and reacted with a range of benzyl bromides to give the desired products **229**. Synthe-



Scheme 43.

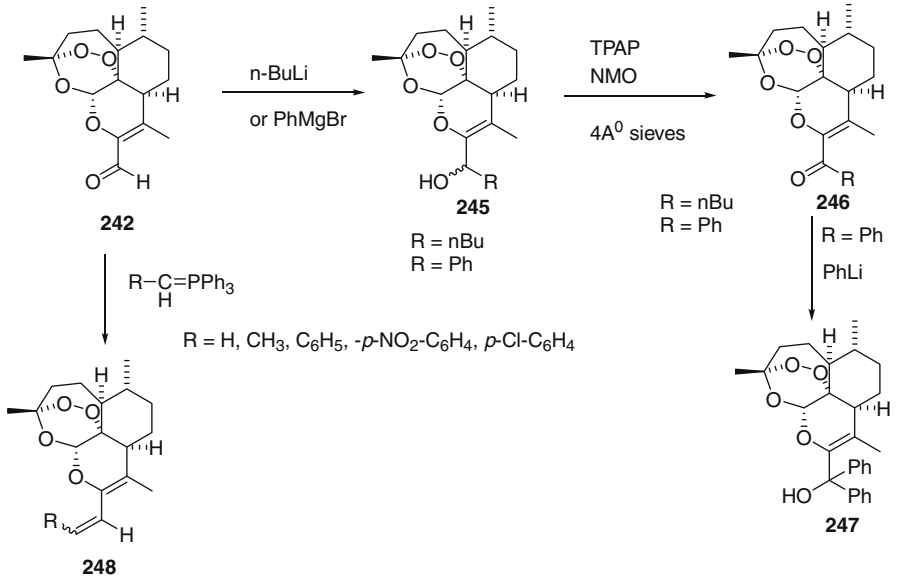


Scheme 44.

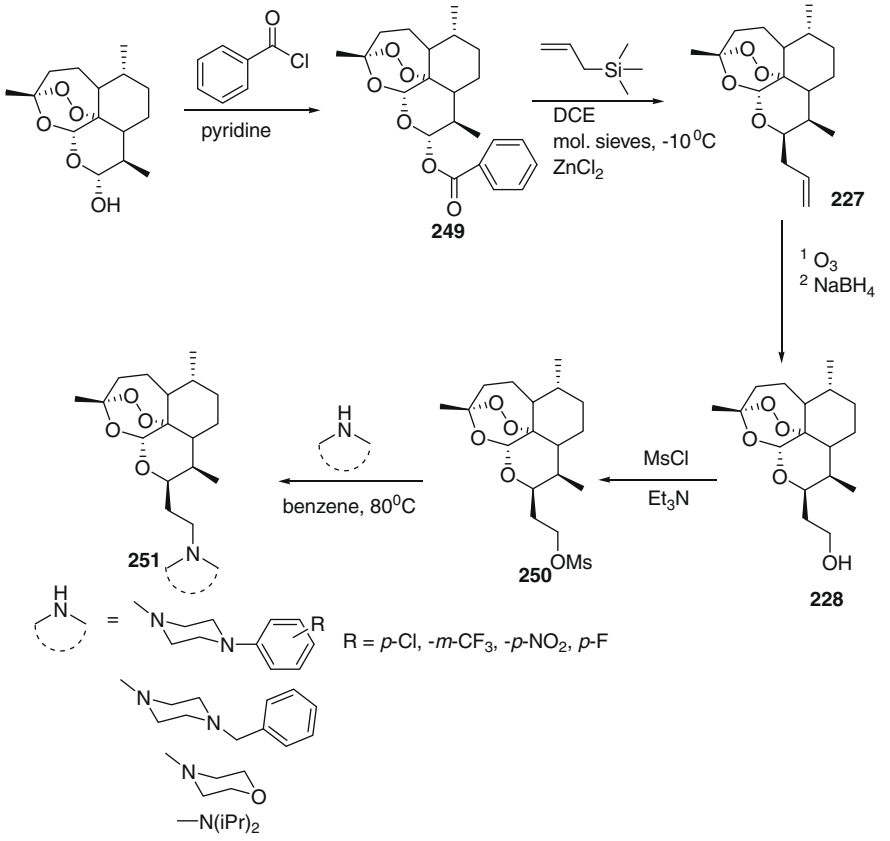
sis of ester derivatives **230** was accomplished by standard esterification procedures (Scheme 41).

Ziffer et al.[129] have reported a synthetic strategy toward the synthesis of the carba-analogues starting with key intermediate DHA acetate **231** prepared by DIBAL reduction of artemisinin followed by its reaction with acetic anhydride. Reaction of this compound with silyl enol ethers of acetone, acetophenone, methyl *tert*-butylketone and cyclopentanone in the presence of titanium (IV) chloride yielded the desired products **232** (Scheme 42).

Further, allylartemisinin **227** was converted to the corresponding aldehyde **233** by its reaction with osmium tetraoxide/sodium periodate. The aldehyde obtained was then reacted with a range of Grignard reagents to yield the corresponding alcohols **234**, which were then subjected to Jones' oxidation to yield the corre-



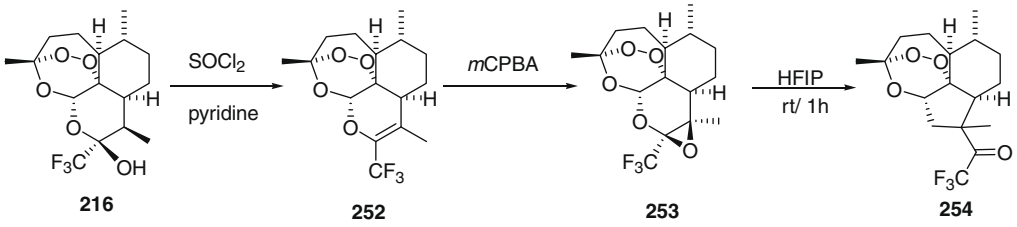
Scheme 45.



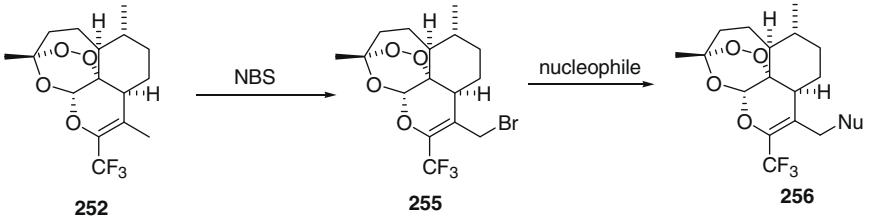
Scheme 46.

sponding ketones **235**. They also carried out the reaction of the aldehyde **233** with a Wittig reagent to produce the Michael acceptor **236**. The reaction of **233** with trimethyl (triflouromethyl) silane yielded the corresponding trifluoromethyl substituted alcohol **237**[130] (Scheme 43).

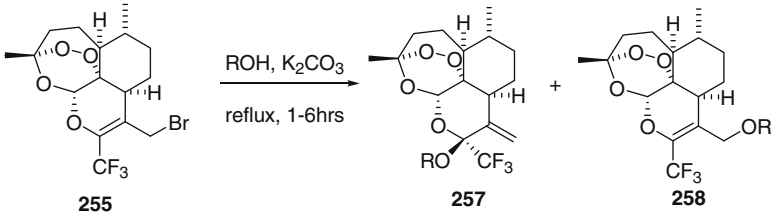
Another route toward the synthesis of C-10 carba-analogues of artemisinin was reported by Posner and co-workers.[131] Their approach involved the addition of 2-lithio-thiazole to the carbonyl group of artemisinin followed by in situ O-acetylation with acetic anhydride to form **238**. The artemisinin thiazole acetate thus formed was treated with TMSOTf resulting in the formation of the elimination product **239**. Treatment of this with methyltriflate generated intermediate **240**, which upon reaction with sodium borohydride resulted in reduction product **241**, whose hydrolysis using mer cury chloride delivered aldehyde **242**. A similar chemoselective result was obtained when the reaction was carried out with lithiobenzothiazole as nucleophile to generate compounds **243** and **244**. The synthesis of 9,10-unsaturated C-10 aldehyde



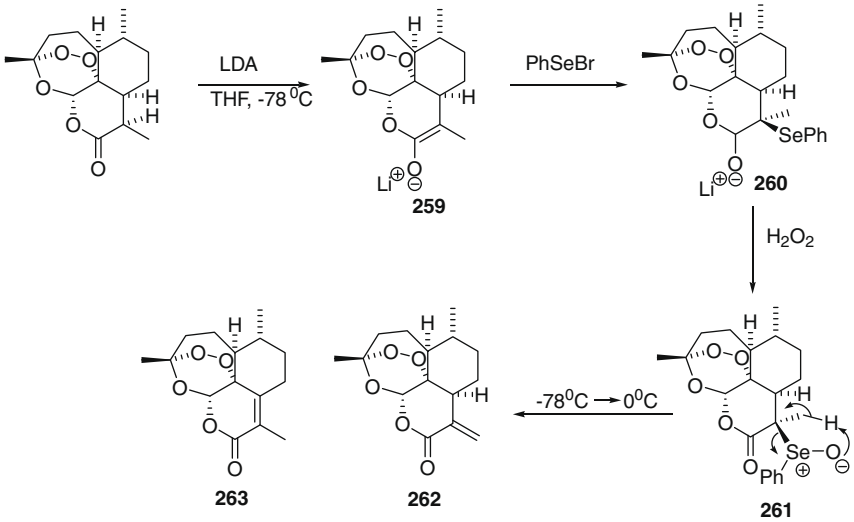
Scheme 47.



Scheme 48.



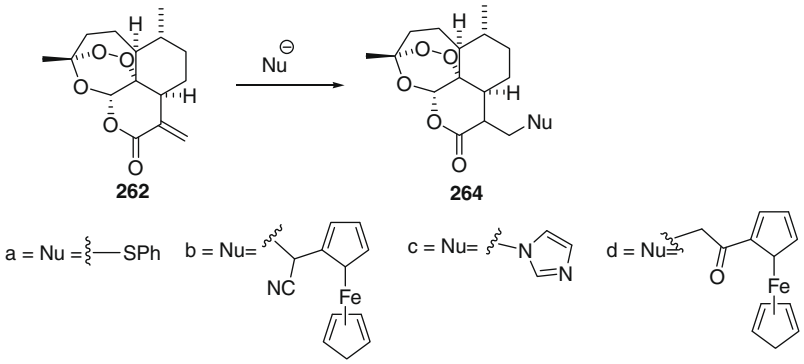
Scheme 49.



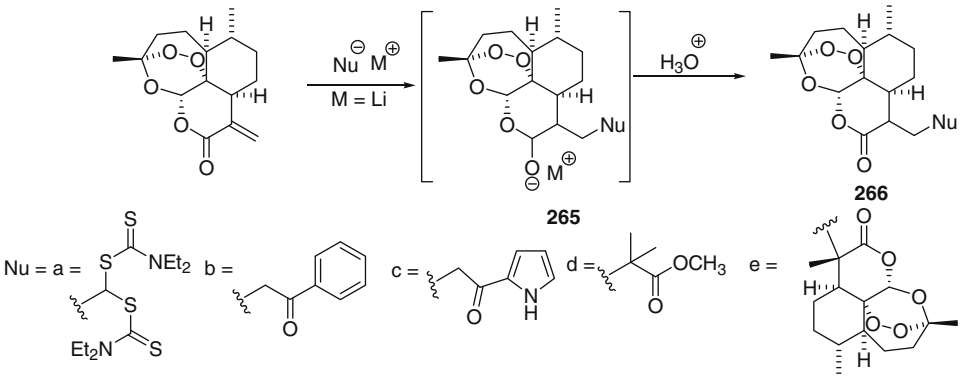
Scheme 50.

242 by N-methylation, reduction and hydrolyzation was also reported (Scheme 44).

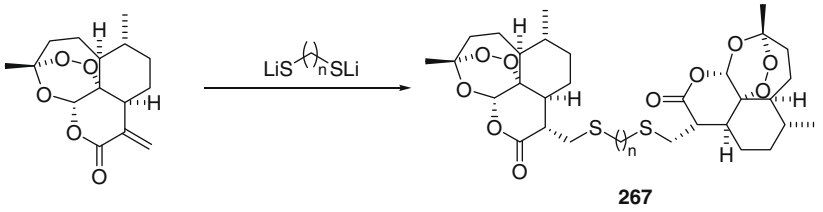
When *n*-butyl lithium was added to **242,** a roughly 2:1 diastereomeric mixture of allylic alcohols **245** was obtained. Addition of



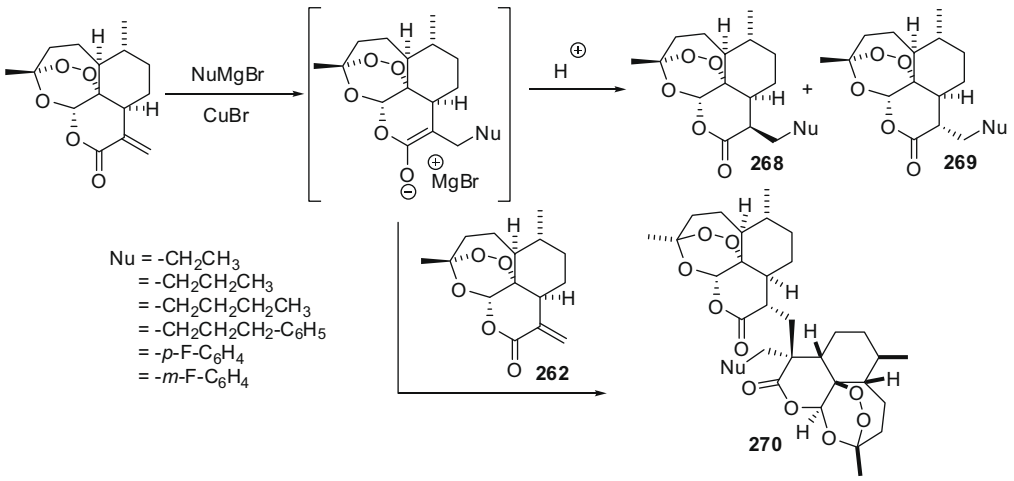
Scheme 51.



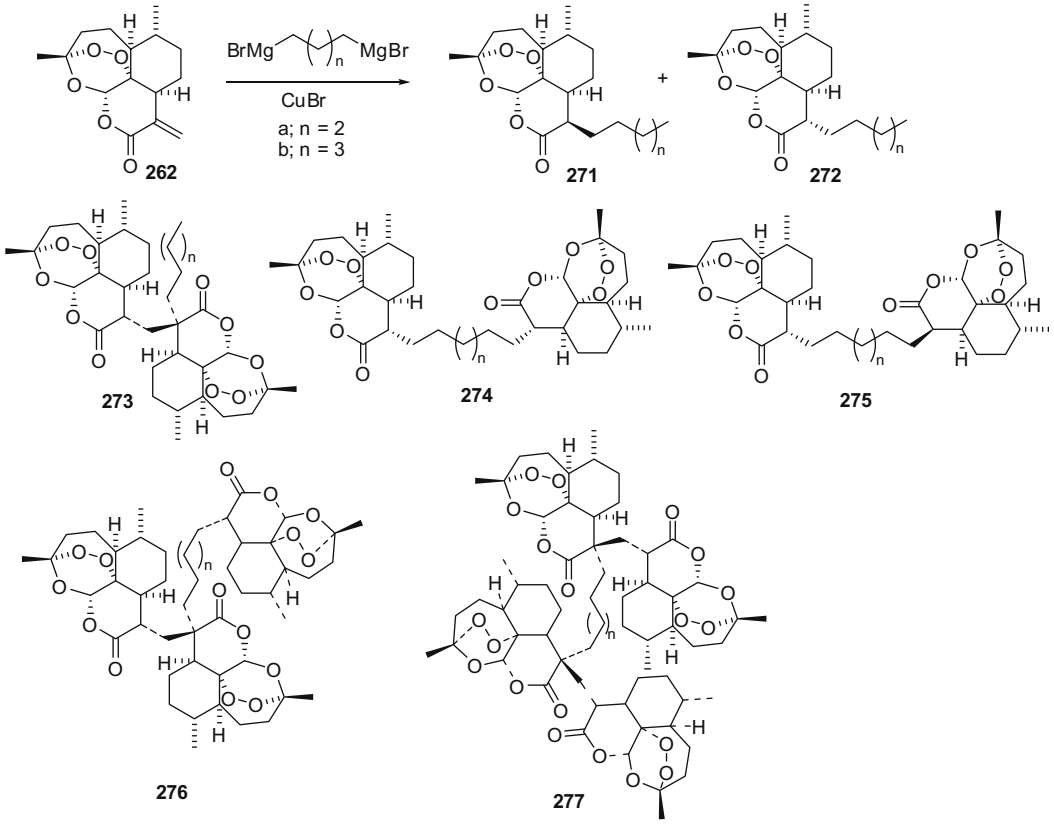
Scheme 52.



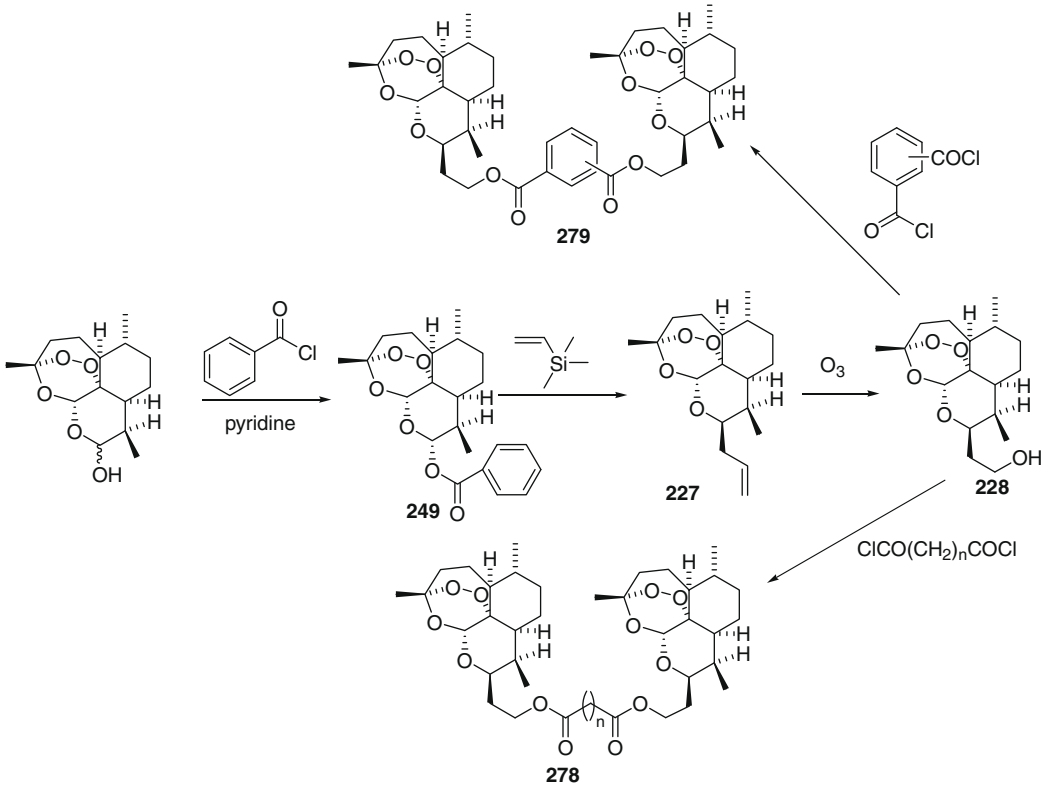
Scheme 53.



Scheme 54.

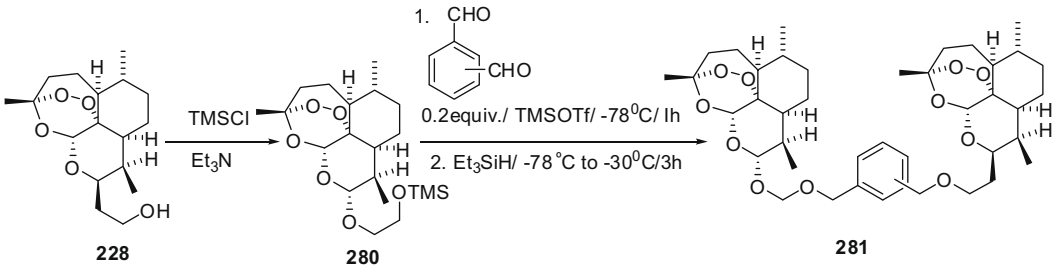


Scheme 55.

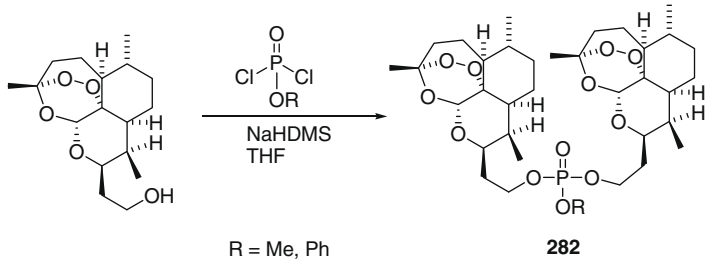


Scheme 56.

phenyl lithium resulted in the formation of a 3.2:1.0 mixtures of diasteromers. However, when excess PhMgBr was used, the peroxide O–O bond in trioxane bridge underwent nucleophilic rupture. Oxidation of **245** with tetra propylammoniumperruthenate (TPAP)



Scheme 57.



Scheme 58.

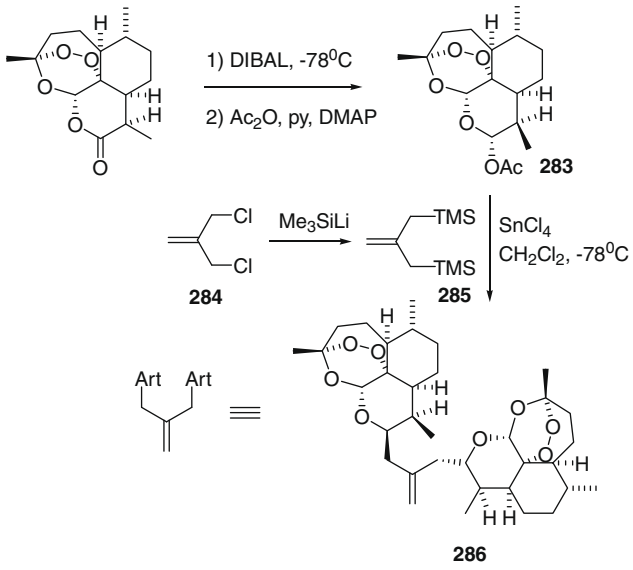
in the presence of *N*-methylmorpholine-*N*-oxide (NMO)[132] produced enone **246**. Phenyl enone (R = Ph) reacted exclusively with phenyllithium giving rise to trioxane tertiary alcohol **247**. Also, nucleophilic phosphonium ylides alkylidenated aldehyde **250** to form a mixture of geometric isomers of exocyclic alkenes **248** (Scheme 45).

An approach for the synthesis of C-10 carba linked amino analogues was reported by O'Neill and co-workers.[133] The methodology involves the reaction of DHA with benzoyl chloride in the presence of pyridine to form the corresponding C-10 benzoate **249**, which was then reacted with allyl trimethylsilane using $ZnCl_2$ as the Lewis acid in the presence of 4 Å molecular sieves and dichloroethane as solvent to yield allyl artemisinin **227**. This compound was first ozonized and reduced to yield the alcohol **228** which was first mesylated to give **250** and then reacted with appropriate amines to produce the desired products **251** (Scheme 46).

Begue and co-workers[134] have further exploited the intermediate as a potentially useful precursor for the synthesis of a variety of novel artemisinin derivatives. Thus, the reaction of **216** with thionyl chloride in the presence of pyridine resulted in the formation of glycal **252** in good yields. This was then epoxidized with *m*-chloroperbenzoic acid resulting in the selective formation of one stereoisomer of epoxy ether **253** in good yields (77%). Compound **253** upon stirring in hexaflouro-2-propanol (HFIP) or trifluoroethanol (TFE) provided after 1 h at room temperature, the rearranged trifluoromethyl ketone **254** as a single isomer (Scheme 47).

The glycal **252** has further been exploited in the synthesis of a range of artemisinin analogues. The allylic bromination of **252** was performed with NBS without any initiator leading to the CF_3-16-bromo derivatives **255**. The 10-trifluoromethyl allylic bromide was then reacted with a range of N-, O-, and C-nucleophiles to give substitution product **256**,[135] Scheme 48.

Recently the selective access to C-10 substituted C-10 CF_3-artemisinins **257** and C-16-substituted C-10 CF_3-artemisinins **258** by examining the above reactions over a range of conditions has been reported.[136] Preferential formation of C-16 substituted C-10 CF_3-artemisinins **258** over their counterparts was rationalised on the basis of presence of high electron density around C-10 which



Scheme 59.

disfavors the approach of electron rich nucleophiles such as alkyl amines or alkoxides. Reactions were accordingly carried out under solvolytic conditions with soft or uncharged nucleophiles. Thus, the reaction of **255** with alcohols in the presence of K_2CO_3 under refluxing conditions resulted in the formation of compounds **258** in a highly selective manner (Scheme 49).

Artemisitene **262**, the oxidized form of artemisinin is reported to be a minor constituent in an American variant of *Artemisinin annua* L.[137] The unique structural feature of artemisitene bearing an exocyclic α,β-unsaturated ketone moiety chemically presents an opportunity for nucleophilic attack via a Michael 1,4-conjugate addition reaction. However, owing to the fact that artemisitene coexists with artemisinin in rather low and variable quantities, and also that its isolation and purification from the crude extract are not straight forward; artemisitene has so far been underutilized. Yuthavong and co-workers[138] have reported a straight for-

ward, regiospecific one pot conversion of artemisinin to artemisitene through selenoxide elimination. The methodology involved the treatment of artemisinin **6** with LDA in THF at −78 °C generated lithium enolate **259**. Sequential addition of phenylselenide bromide and 30% aqueous H_2O_2 yielded **260** and **261**, respectively. The latter rearranged to artemisitene **262** in 73% yield. The origin of reaction regiospecificity, providing only artemisitene without any trace of its double-bond isomer **263**, isoartemisitene, can be explained on the basis of stereospecific reaction of the lithium ester enolate **259** which stereospecifically reacts with phenylselenide bromide on the β-face to provide **260** and finally **261** as shown in Scheme 50.

Artemisitene **262** obtained was then reacted with sulfur, carbon and nitrogen nucleophiles to give the corresponding Michael adducts **264** (Scheme 51).

Furthermore, these workers have reported the nucleophilic additions of a range of nucleophiles to artemisitene.[138] The reaction of artemisitene with alkyllithium and lithium keto and ester enolates at -78 °C in THF gave the corresponding enolate **265** which upon protonation yield the corresponding C-16 derivatives **266** (Scheme 52).

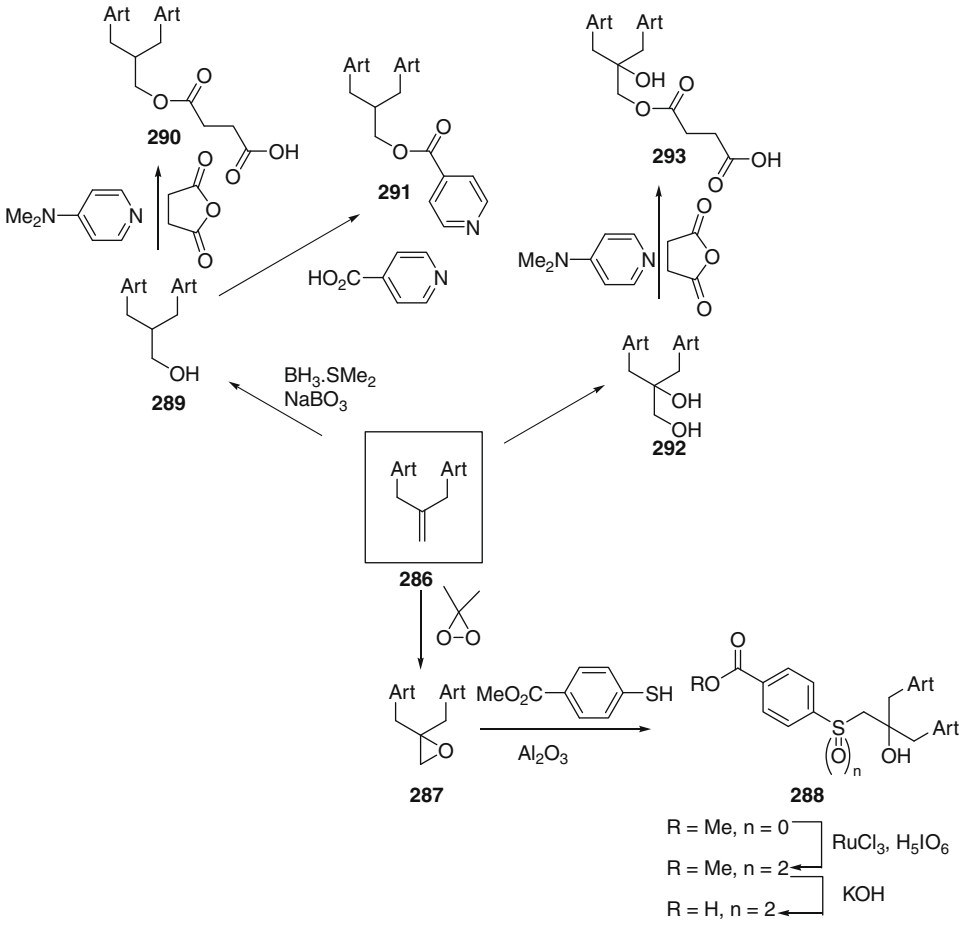
Related nucleophilic addition reactions between artemisitene and dithiolates derived from the corresponding dithiols were also reported resulting in the formation of dimeric artemisinin analogues **267** with linkers –S–$(CH_2)_n$–S– of various lengths and flexibility (Scheme 53).

Likewise Grignard reagents have been employed as alternative Michael donors in the addition reaction to artemisitene. The reactions were conducted in THF at −78 °C in the presence of a Cu (I) salt to afford diastereomeric products **268** and **269** along with dimer **270** resulting from further reaction of an emerging enolate with another molecule of artemisinin (Scheme 54).

The reaction of 2 equiv of artemisitene with 1 equiv of bifunctional Grignard reagent resulted in the synthesis of a mixture of novel artemisinin derivatives. The bifunctional reagent reacted either on one end with the first molecule of **263**, to generate diastereomers **271** and **272** followed by trapping of the emerging enolate with another molecule of **263** (to give **273**) or at both ends with two molecules of **263** (yielding **274** and **275**) followed by the further addition of the *bis* enolate to one or two molecules of **263** to provide the trimer **276** or tetramer **277**, respectively (Scheme 55).

O'Neill and co-workers[139] have reported the synthesis of a range of C-10 non-acetal dimers of artemisinin by the initial benzoylation of DHA in the presence of pyridine. The benzoate **249** thus formed was reacted with 5 equiv of allyltrimethylsilane in the presence of $ZnCl_2$ catalyst (1.2 equiv) to give the desired product **227**. Ozonolysis of this compound and in situ reduction of the ozonide provided the key alcohol **228** required for dimerization. The reaction of 2 equiv of **228** and 1 equiv of acid chloride in the presence of catalytic quantities of 4-(dimethylamino) pyridine resulted in the formation of the corresponding dimers **278** and **279** (Scheme 56).

The ether derivatives were prepared by a mild reductive etherification procedure developed by Hatakeyama and co-workers.[140] The trioxane alcohol was converted into the corresponding TMS ether and then coupled with an aromatic *bis*-aldehyde at −78 °C followed by the addition of Et_3SiH to yield **281** (Scheme 57). Similarly phosphate esters **282** have been prepared from trioxanes alcohol by deprotection with sodium hexamethyldisilazide followed by the addition of the appropriate phosphorus dichloride (Scheme 58).



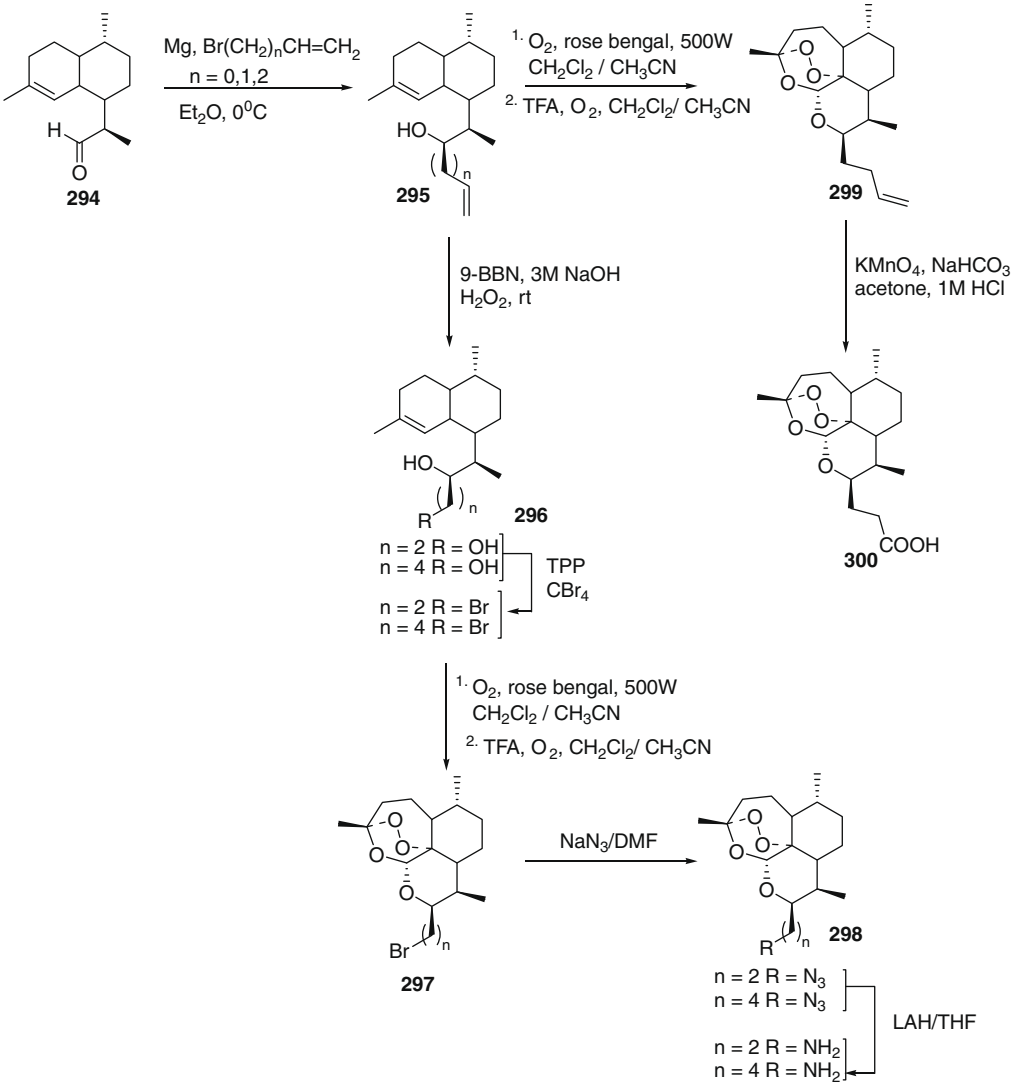
Scheme 60.

The synthesis of symmetric artemisinin dimers has received a great deal of attention mainly due to their cytotoxicity against tumor cells. Posner and co-workers[141] have reported the synthesis of highly stable artemisinin-based C-10 non-acetal trioxane dimers **286** from C-10 acetate **283** by its reaction with allylic *bis* silane **285**, which was conveniently prepared from the commercially available allylic dichlorides **284** followed by its reaction with artemisinin C-10 acetate **283** in the presence of tin tetrachloride in dichloromethane at −78 °C resulting in the formation of the dimer **286** (Scheme 59).

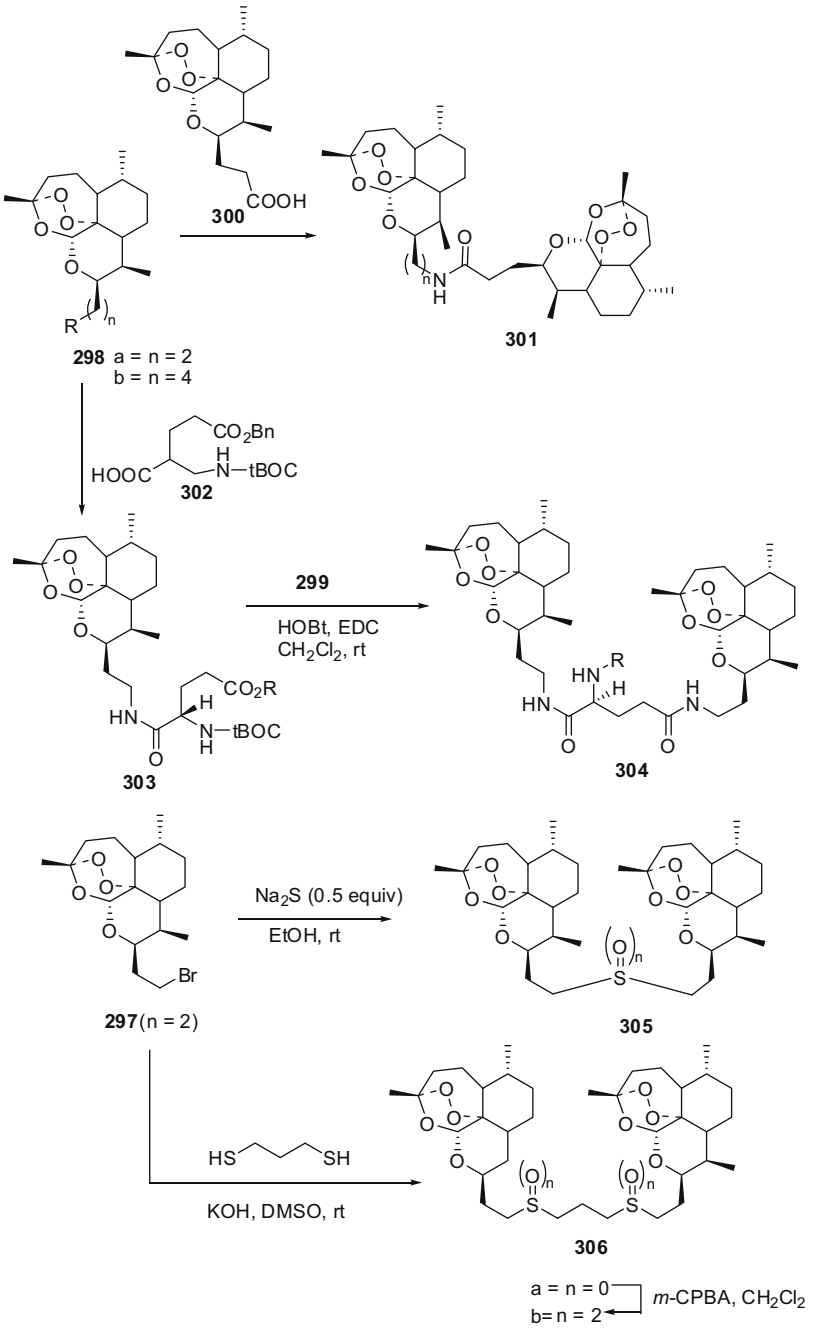
To further illustrate the stability of the trioxane dimer, a number of synthetic transformations have been carried out viz; (i) epoxidation followed by chemospecific substitution of the resulting epoxide with a substituted benzene thiol to give β-hydroxysulfide, which upon oxidation give rise to sulfones **288**. (ii) its conversion to the corresponding primary alcohol **289** with $BH_3{\cdot}SMe_2$ and $NaBO_3$ followed by its reaction with succinic anhydride to form *bis*-artesunate **290**, (iii) esterification of the primary alcohol **289** to give isonicotinate ester **291**, (iii) conversion to diol **292** with OsO_4 which on reaction with succinic anhydride generates the tertiary alcohol primary succinate ester **293** (Scheme 60).

Jung et al.[142] have recently reported the synthesis of novel deoxyartemisinin monomers, dimers and trimers through synthetic transformations of dihydroartemisinyl aldehyde **294** prepared from artemisinic acid by a reported procedure. The reaction of aldehyde **294** with vinyl, 1-propenyl and 1-butenyl magnesium chloride gave homologated alcohols **295**. Photooxygenative cyclization of these alcohols followed by $KMnO_4$-mediated direct oxidation of the terminal olefin **299** yielded the 12-carboxyethyldeoxoartemisinin **300**. Direct hydroborative oxidation (9-BBN followed by $NaOH/H_2O_2$) of terminal olefin **295** afforded the diols **296**. Treatment with CBr_4/PPh_3 in methylene chloride gave the corresponding bromo compounds **297** which were converted to azides (NaN_3 in DMF) and subsequently reduced to novel amino alkyl derivatives **298** (Scheme 61).

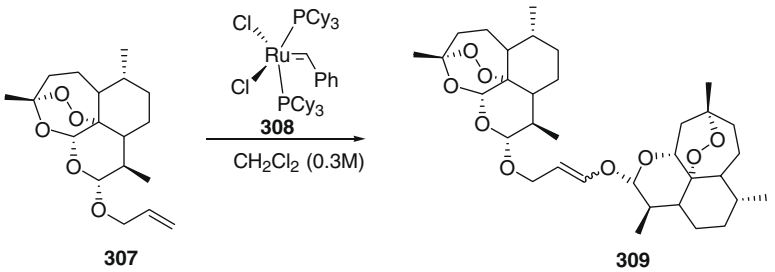
Coupling of **298** (R = NH_2) with **300** in the presence of EDC and HOBt gave the corresponding amides **301** in 81% yields. Direct coupling with protected gluterate **302** afforded **303** in 84% yield. Hydrolysis of the benzyl ester with LiOH, H_2O/THF delivered the corresponding acid whose subsequent coupling with **298** in EDC/HOBt afforded dimers **304**. Dimeric deoxyartemisinin derivatives with alkyl sulfides or sulfone linkers of various lengths and flexibility were obtained via a *bis* nucleophilic coupling reaction. Treatment of **297** ($n = 2$) with sodium sulfide followed by oxidation with *m*-CPBA afforded dimeric sulfone **305**. Similarly, *bis* nucleophilic substitution of 2 mol of **297** ($n = 2$) with 1,3-propane thiol gave **306** in good yields which was further oxidized using *m*-CPBA (Scheme 62).



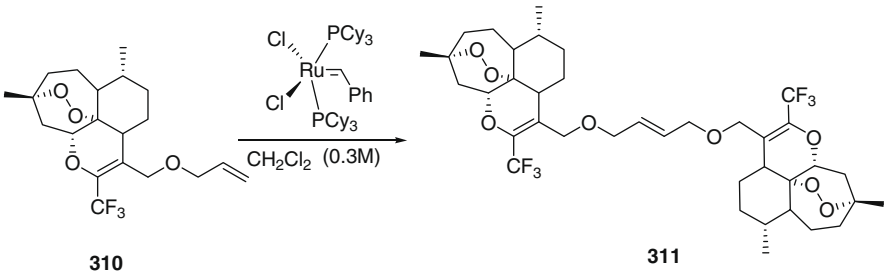
Scheme 61.



Scheme 62.



Scheme 63.



Scheme 64.

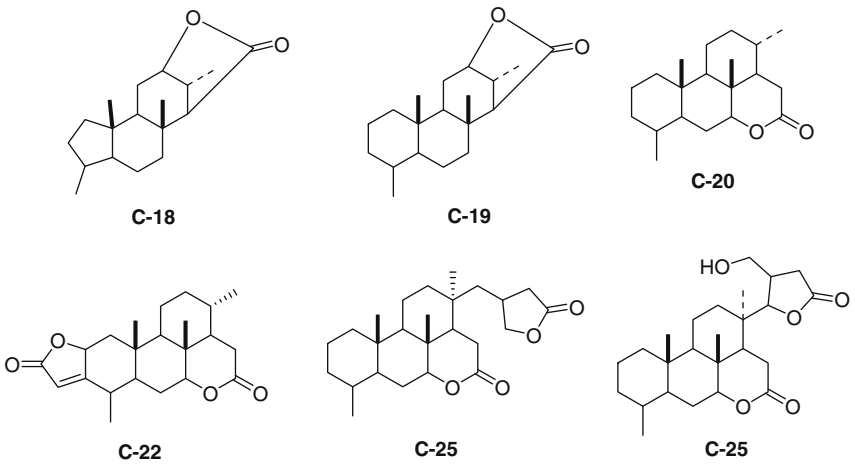


Figure 9. Various quassinoid analogues.

Begué and co-workers[143] have recently reported the synthesis of artemisinin-derived dimers by a self-cross-metathesis reaction. Thus, the reaction of *O*-allyl artemisinin **307** with Grubbs catalyst **308** in dichloromethane at room temperature led to the formation of homodimers **309** with 85% conversion (Scheme 63).

After this successful application of the olefin cross-metathesis reaction to artemisinin derivatives, the approach was extended to allylether **310** for the synthesis of novel C-16 dimers **311** metabolically stabilized by triflouromethyl substituents at C-10 (Scheme 64).

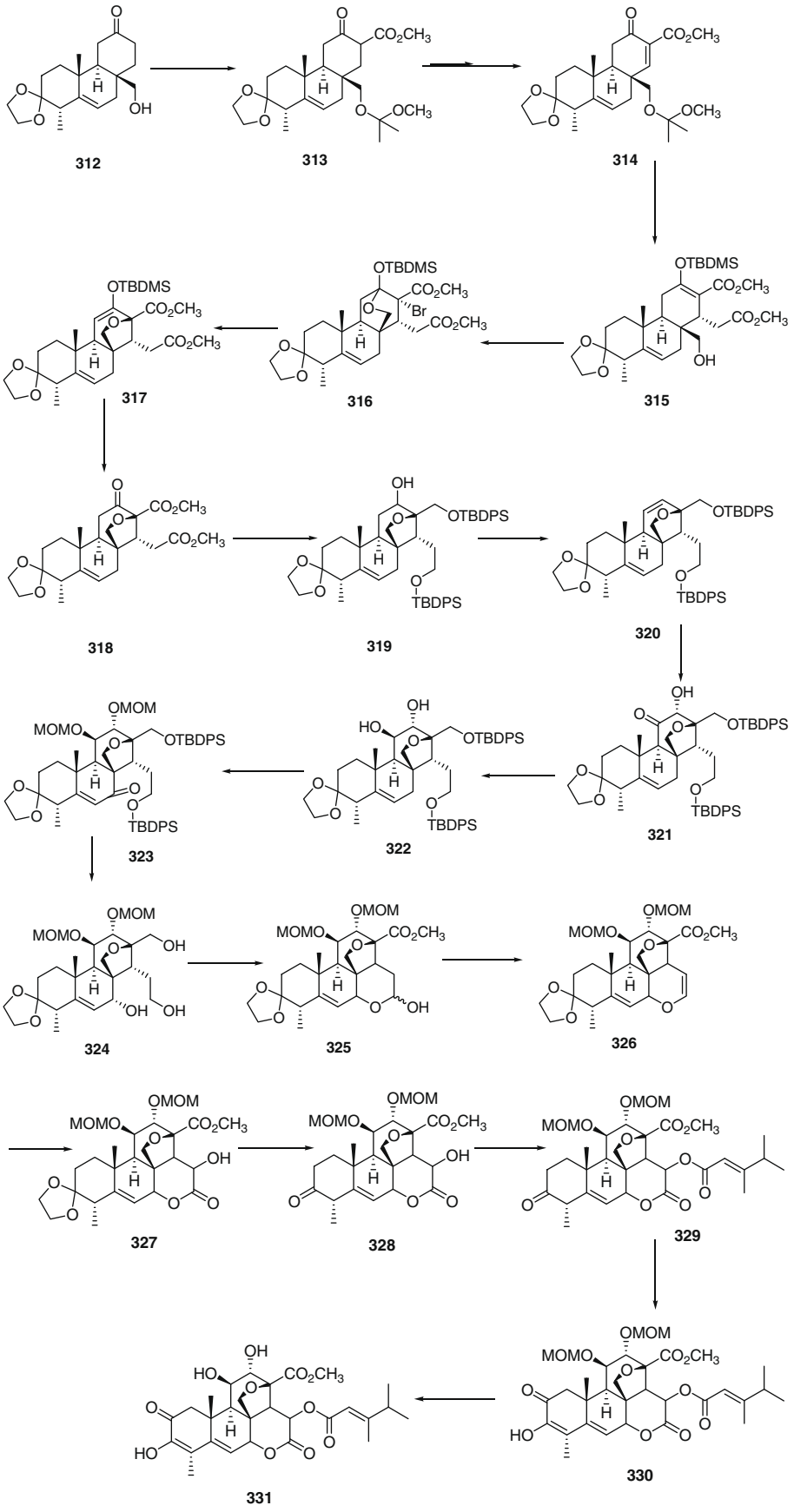
2.9. Quassinoids

Quassinoids refer to the group of compounds, which are the bitter principles of the *Simaroubaceae* family.[144] According to their basic skeleton; quassinoids are categorized into five distinct groups, C-18, C-19, C-20, C-22 and C-25 types as shown in Figure 9[145] (Scheme 65 and 66).

The research and application of quassinoids continued to extend through the 1990's with the isolation and structure elucidation of many new compounds. Today, over 150 quassinoids have been isolated and fully characterized. Many of these quassinoids display a wide range of biological activities in vitro and/or in vivo, including antitumor, antimalarial, antiviral, anti-inflammatory, antifeedant, insecticidal, amoebicidal, antiulcer and herbicidal activities. It has been considered as a great discovery that several quassinoids possess potent antimalarial activity, especially against chloroquine-resistant *Plasmodium falciparum*.[146,147] IC_{50}'s of bruceantin and glaucarubinone are at in the nM range and are superior to those of chloroquine. The mechanism of action is believed to be the inhibition of the protein synthesis.[148] In the malaria parasite, quassinoids are rapid and potent inhibitors of protein synthesis, most likely due to effects upon the ribosome rather than upon nucleic acid metabolism.[148] Studies have shown that the chance of cross-resistance between quassinoids and chloroquine is less, since chloroquine did not affect protein synthesis. Thus quassinoids may be presumed to act upon the malaria parasite through a fundamentally different mechanism to that of chloroquine.[148] Some quassinoids have shown greater selectivity against *P. falciparum* than against KB cells.[149] For instance, the cytotoxic activity of glaucarubinone against KB cells is 285 times its activity against *P. falciparum*. This result suggests that it may be possible to develop more selective quassinoid derivatives.[150] Using the inhibition of incorporation of [3H]-hypoxanthine as an index, Ekong et al.[151] have shown that a chloroquine-sensitive and a chloroquine-resistant strain of *P. falciparum* did not differ in their sensitivities to the quassinoids; therefore, these triterpenoids offer a promising source for the development of new antimalarial drugs against chloroquine-resistant malaria.

The wide spectra of biological activities and the complexity of the structures of quassinoids have challenged synthetic chemists for over two decades. In 1980, Grieco and co-workers completed the first total synthesis of quassin. Since then the list of total syntheses has slowly been increasing to include (±)-amarolide,[152] (±)-klaineanone,[153] (±)-castelanolide,[154] (±)[155] and (−)-chaparrinone,[156] (±)[157] and (−)-bruceantin,[158] (+)-picrasane B,[159] (+)-Δ^2-picrasane B,[158] (±)-shinjulactone C[160] and shinjulactone D,[159] (±)-holocanthone,[161] (±)[160] and (−)-glaucarubolone,[156] (+)-simalikalactone D,[162] (±)-shinjudilactone,[163] (+)-quassimarin,[164] (+)-glucaruinone,[155] (±)-samaderin B,[165] (+)-quassin,[166] (±)-14β, 15β-dihydroxyklaineanone,[167] (−)-peninsularinone[168] and most recently (+)-des-D-chaparrinone.[169]

The synthesis of bruceantin by Grieco's group is a primary example of the total synthesis of quassinoids.[157] The synthesis commences with protection of the hydroxymethyl group of a tri-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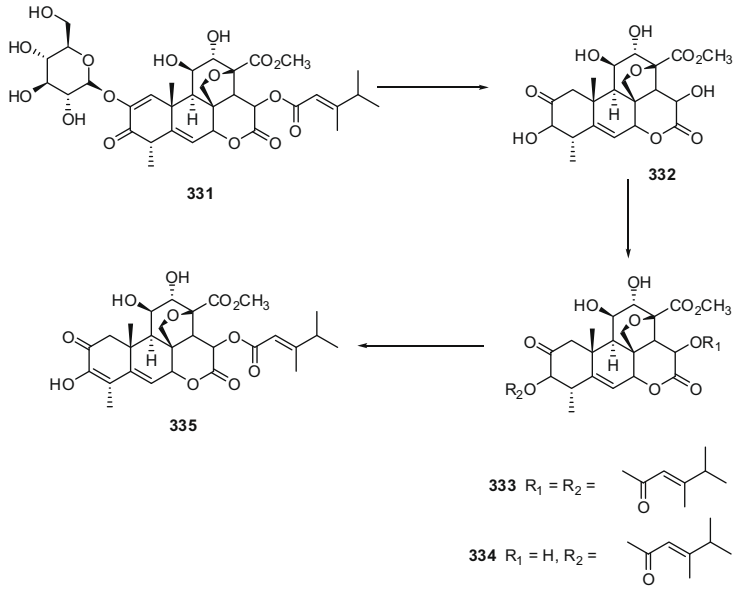
Scheme 65.



Scheme 66.

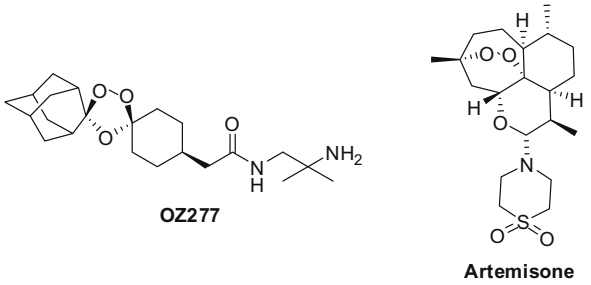


Figure 10. Synthetic antimalarial endoperoxides.

cyclic ketone **312** at C-8, followed by carbomethoxylation to afford compound **313**. The α,β-unstaurated double bond can be introduced by selenylation and elimination of benzeneselenic acid to afford tricyclic enone **314**, which can be converted to compound **315** through the introduction of a two carbon unit and cleavage of the protecting group. Bromination of **315** gave bromide **316** followed by heating with collidine yielding the compound **317,** which can be quantitatively converted to tetracyclic ketone **318**. Introduction of the *trans* diaxial diol unit into the C-ring was achieved via an eight step sequence by way of intermediates **319**-**322** to produce compound **323**, which is appropriately set up to form the D-ring. Upon selective protection, oxidation, reduction and deprotection, triol **324** was obtained, which was then transformed via a four step sequence into a pentacyclic lactol **325** from which ketone **327** was prepared, via intermediate **326**, through elimination, oxidation and hydrolysis. Acylation of compound **328** to **329** followed by oxidation gave compound **330** which upon deprotection of two C-ring MOM ether hydroxyl groups gave crystalline racemic bruceantin **331**.

The most successful example of semisynthesis of quassinoids is the conversion of bruceoside A, a compound easily obtained from *Brucea javanica* Biomass[170] into Bruceantin, a compound difficult to obtain in large quantities for clinical trials. Bruceoside A **332** upon selective hydrolysis gives the compound **333** which can then be re-esterified to afford a mixture of compound **334** and **335**. The compound can be further esterified to get and the subsequent selective hydrolysis of C-3 ester gives bruceantin in a 40% yield.[171]

3. Conclusion

It is quite clear that resistance to classical antimalarial drugs has been on the increase and new antimalarial agents with novel modes of action and structurally unrelated to existing drugs are not being developed fast enough to keep pace with resistance. Although modification of existing drugs to produce new effective analogs has been a viable option as exemplified by aminoquinoline and endoperoxide analogs, this has only provided short term solutions. Novel molecular scaffolds on which to base antimalarial drug discovery campaigns are urgently needed. Natural products are the sources of quinine and artemisinin, two of the most important antimalarial drugs. They remain a rich source of novel molecular scaffolds beyond current imagination. The challenge is to come up with new effective antimalarial natural products, which are easy and cheap to prepare given the prevalence of malaria mostly in poor Third World countries. This will require the development of flexible total syntheses pathways to antimalarial natural products that will lend themselves to the synthesis of libraries of analogues for structure–activity relationship studies. Thus the importance of synthetic organic chemistry cannot be overemphasized in this regard.

Of the natural products discussed in this review, artemisinin has shown the greatest utility in recent years from the perspective of identification of useful semi- and fully-synthetic analogs as well as a combination therapy to control the onset of resistance. Relatively simple chemical modifications of the natural product parent compound in a few steps have led to highly potent antimalarials. Within the context of controlling the onset of resistance, the World Health Organization (WHO) currently recommends the use of fixed-dose combination medications using artemisinin-based compounds (aka artemisinin combination therapy, ACT) in all malaria treatments, to help reduce drug resistance. However, the high cost of ACT is a major drawback particularly in poor endemic countries. The approach of using natural products as sources of new antimalarials must take into account the requirement for very inexpensive and simple to use new therapies.

For natural products, molecular remedies have to be found wherein the natural product is simplified to allow for chemical derivatization around the minimum structural requirement for antimalarial activity in vitro (bioactiphore or pharmacophore sub-

structure). Overall, the envisaged lead development based on antimalarial natural products will likely involve determining the minimum structural requirement for biological activity in vitro (bioactiphore) followed by appendage of substituents/groups that support the pharmacophore or bioactiphore. Re-elaboration into a novel patentable structural series and optimization should then follow. The discovery and development of **OZ277** by Vennerstrom and co-workers, and Artemisone by Haynes and co-workers (Fig. 10) after the initial discovery of artemisinin are excellent examples of this approach.[172,173]

In terms of the pharmacological target(s) of the arteminin and related endoperoxide antimalarials, there has been intense debate regarding the mode of action of these trioxane-based compounds.[174,175] Among the different proposed mechanisms, some authors suggest that the endoperoxide group plays a key role in the antimalarial activity of the artemisinin-like compounds via a ferrous iron-mediated C-centered radical formation and alkylation of heme derivatives.[176,177] This mechanism has been thrown into question following the disclosure that endoperoxides were not activated by heme iron and free radicals are not needed for its toxicity.[178] Specific binding between artemisinin and the *P. falciparum* homologue of the sarco-endoplasmic reticulum Ca^{2+}-ATPase (SERCA) a protein which is not located in the digestive vacuole of the parasite has been reported.[179] Evidence for inhibition of inducible nitric oxide synthase and nuclear factor NF-kB has also been provided.[180] It is conceivable that other (yet unknown) targets for artemisinin will be disclosed in the future.

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