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# Evaluation and Optimization of Synthetic Routes from Dihydroartemisinin to the Alkylamino-artemisinins Artemiside and Artemisone: A Test of *N*-Glycosylation Methodologies on a Lipophilic Peroxide.[†]

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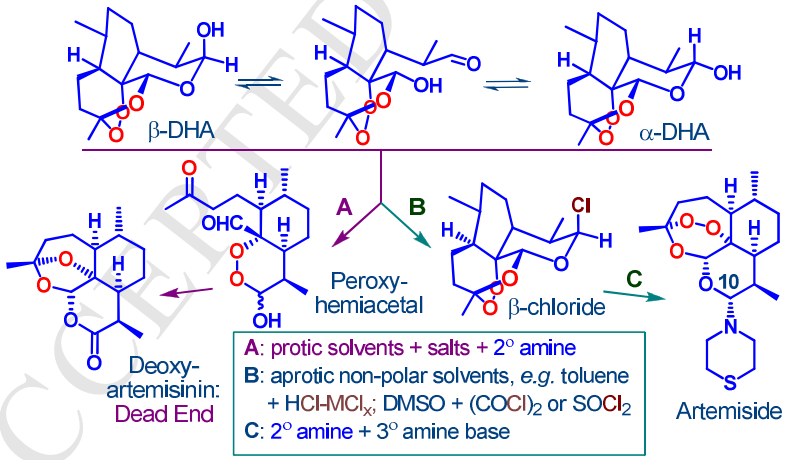
Abstract

10-Alkylamino-artemisinins including artemiside and artemisone display enhanced activities against malaria. Earlier, dihydroartemisinin (DHA) TMS ether was converted by trimethylsilyl bromide into the 10-β-bromide that with amine nucleophiles provided the amino-artemisinins. In an attempt to develop more economic approaches, direct *N*-glycosylation of DHA was examined but 2-deoxyartemisinin was invariably obtained. However, hydroxyl group activation by conversion into the 10β-halide in non-polar solvents with anhydrous HCl and Group I and II metal halides, oxalyl chloride or thionyl chloride with catalytic DMSO, and oxalyl bromide did succeed. The β-halides were converted *in situ* by thiomorpholine into artemiside, and by thiomorpholine-1,1-dioxide into artemisone respectively in scalable reactions. Hydrogen peroxide-acetonitrile or the urea-hydrogen peroxide complex efficiently oxidized the sulfide artemiside to the sulfone artemisone. Overall, a generalized approach to 10-alkylamino-artemisinins is now available.

Graphical Abstract




**Keywords**: Malaria, Antimalarial Drugs, Artemisinins, *N*-Glycosylation, Amino-artemisinins, Artemisone

[†] Dedicated to the memory of Professor Sir Derek Barton, one of the greatest of organic chemists of the 20th Century and a master of all trades within the profession of organic chemistry. He was an inspiring mentor who graciously and enthusiastically shared his knowledge, and he effectively imparted the sense of foresight and introspection required for the conception and successful execution of the varied and potent research projects in which the members of his research groups were engaged. The art and form thereof represented the ideal models upon which to base our activities once we had moved on to become engaged in the complicated tasks of conceiving and then supervising our own research projects. The time at Imperial College was indeed the high point in my early career path.

1. Introduction

The frequency and severity of malaria infections experienced by Vietnamese and Chinese personnel during the US-Vietnam war compounded with restricted access to antimalarial medicines in the 1960s impelled the Chinese leadership to initiate a nation-wide effort to solve the malaria problem. Thereupon, with the involvement of the Chinese National Commission of Science and Technology, the Ministry of Health, the Academy of Science, regional Institutes Materia Medica, and government pharmaceutical agencies, Project 523 was launched on the 23 May 1967 – just over 50 years ago – with the aim of both developing synthetic compounds and surveying herbs used in traditional Chinese medicine for new antimalarial drugs. The Chinese medicinal herb qīng hāo 青蒿 (*Artemisia annua*) that featured in early Chinese pharmacopoeia was selected as a potential source, and through bioassay guided fractionation of extracts in the early 1970s, an antimalarial-active principle was identified. It was at the Shandong Institute Materia Medica and the Yunnan Institute Materia Medica that the active constituent was isolated in sufficient purity so as to actually cure patients with vivax and falciparum malaria respectively. This was the crystalline compound qīng hāo sū 青蒿素, the active principle of qīng hāo. There followed a coordinated effort under the Project 523 umbrella focusing on determining its structure, toxicity, interaction with other drugs, , and efficacy in clinical trials against malaria. With determination of its X-ray crystal structure in 1975 and absolute configuration in 1978, coupled with chemical degradation methods, the compound was shown to be the sesquiterpene lactone peroxide **1** (Fig. 1). Additionally, with a third oxygen atom in the peroxide-containing ring, it was the first example of a 1,2,4-trioxane isolated from a natural source. The English name of artemisinin subsequently appeared, and was later used in the Chinese pharmacopoeia. These notable historical aspects have been carefully reviewed.[1,2,3]

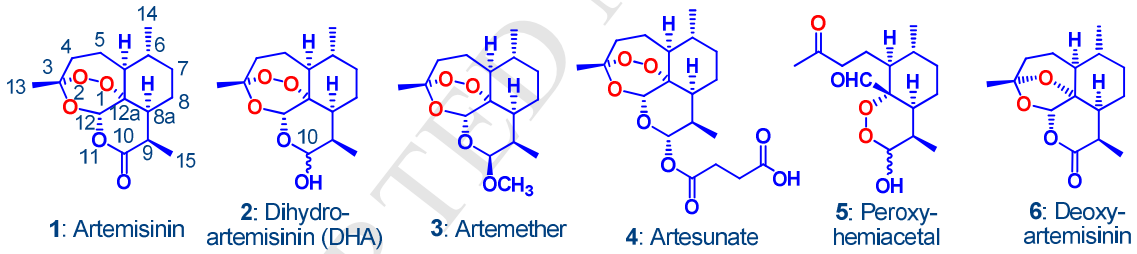



**Fig. 1**. Artemisinin **1** and its current clinical derivatives: the hemiacetal dihydroartemisinin (DHA) **2**, the lactol ether artemether **3**, and the hemiester artesunate **4**. The latter two are rapidly converted into DHA via facile metabolism or hydrolysis respectively. DHA rearranges irreversibly under physiological conditions into the peroxyhemiacetal **5** that in turn rearranges to the inert deoxyartemisinin **6** (ref. 23).

Because of solubility and formulation problems with artemisinin **1** itself, a synthetic chemistry effort involving the Institutes Materia Medica (IMM) in Beijing and Shanghai and the Shanghai Institute of Organic Chemistry and others aimed at preparing more tractable derivatives.[1,2] Thus, artemisinin was reduced to the lactol dihydroartemisinin (DHA) **2** by borohydride-based reagents in methanol, a notable reaction given the general inertness of lactones to reduction with such reagents.[4] At the Shanghai IMM in 1976, DHA was converted into the oil-soluble lactol ether artemether **3** and its α-epimer by reaction of DHA with methanol and an acid catalyst; fractional crystallization was required to isolate the pure β-epimer **3**. At the Guilin Pharmaceutical Factory in 1977 DHA was converted into the hemiester artesunate **4**, produced as the pure α-epimer, by reaction of DHA and succinic anhydride, as part of a drive to generate water soluble derivatives.[5,6] Thereby, the artemisinins were introduced into the armamentarium of drugs for combatting malaria. Indeed, their effectiveness in rapidly clearing parasitaemia was recognized early in Chinese clinical trials, and they rapidly assumed front-line status as

antimalarial drugs on a worldwide basis. Overall, the discovery of the antimalarial activity of artemisinin and its derivatives represents one of the notable developments in medicine in the latter third of the 20th century.[7] Irrespective of the clinical effectiveness of these compounds for the treatment of malaria, their advent has raised fascinating questions on the nature of their intracellular mechanisms,[3,8,9] and raised awareness of the importance of peroxide xenobiotics in modulation of cell physiology. In addition, these compounds and newer derivatives have evinced considerable potential for the therapy of parasitic diseases other than malaria,[10] for non-parasitic infectious diseases[11,12,13] and cancer.[14]

The artemisinins **1**-**4** are used in artemisinin combination therapies (ACTs) with longer half-life drugs for treatment of malaria.[3,15] Their metabolism is facile and subject to marked auto-induction. Thus, time-dependent enhancement of metabolism as observed in malaria patients may result in drug plasma levels falling below the effective therapeutic dosage.[16] Artesunate **4** is hydrolysed *in vitro* at physiological pH (pH 2 or 7.4) and *in vivo*,[17] and artemether **3** is metabolized by oxidative dealkylation,[18] to DHA **2**. The half-life of artesunate is several minutes, whereas artemether **3** is similar to that of DHA at ~1 h.[19] Intriguingly, DHA undergoes a facile and *irreversible* rearrangement under physiological conditions into the peroxyhemiacetal **5** that also possesses antimalarial activity.[20,21] Importantly, this compound has been detected in the plasma of patients treated with artesunate,[22] and is unstable by virtue of a further facile rearrangement into the inert deoxyartemisinin **6**.[23] The neurotoxicity of the artemisinins, in particular of DHA, is well demonstrated.[24] Comparative assays with neuro-toxins such as paraquat suggest that neurotoxicity is due to inhibition of the respiratory chain and rapid induction of oxidative stress in neuronal cells at concentrations >0.001 μg/mL. Additionally, degradation of cytoskeleton elements continues beyond the period of drug administration, a classical indicator of neurotoxicity.[25,26] *In vivo* screens elicit a characteristic neurotoxic behaviour pattern and histopathology reveals a neurodegeneration in the brain stem with impairment of auditory, vestibular, cerebellar, motor and reticular activating systems.[27] Whilst by and large neurotoxicity generally has not been expressed in humans treated with these drugs,[28] there are evident exceptions,[29] and the issue has been debated.[30] However, the perception of a neurotoxic burden is enhanced by the report of a death due to an artesunate overdose.[31] Yet remarkably, in recent times the problem of neurotoxicity has been subsumed by the need to suppress artemisinin resistance by applying more protracted dose regimens of ACTs, where clearly enhanced pharmacovigilance is warranted, particularly in a pediatric situation.[32]

A large number of artemisinin derivatives has been made, primarily with the intent of exploring structure-activity relationships and establishing activities against disease targets in addition to malaria, although relatively few have been carried forward for further development.[2,33,34] In our own program, we planned to replace the exocyclic oxygen atom at C-10 in the current derivatives by nitrogen, based on ADME precepts.[35] Thereby, with the aims of preventing metabolism to DHA and countering toxicity, and improving the antimalarial efficacy, we prepared 10-alkylamino- and 10-arylamino-artemisinin and other derivatives.[36] Of the aminoartemisinins, artemisone **8** (BAY 44-9585, also named artemifone), prepared from the thiomorpholine precursor **7** (artemiside, BAY 44-9584) (Fig. 2), emerged as an early clinical development candidate from a collaborative venture involving the Hong Kong University of Science and Technology, Bayer AG and Bayer HealthCare AG, and in part the Medicines for Malaria Venture, Geneva.[37] Like other aminoartemisinins, artemisone is obtained exclusively as the α-epimer (*cf.* artemether **3**, Fig. 1), is highly crystalline with an aqueous solubility at pH 7.2 of 89 mg/L and a Log P (partition coefficient *n*-octanol-water) at pH 7.4 of 2.49 that characterizes it as a relatively non-lipophilic drug. In *in vitro* screens, it elicits no neurotoxicity towards brain stem cell cultures and neurofilaments up to 10 μg/mL, and has no effect on the respiratory chain or on oxidative stress in neuronal cells.[26] Lack of neurotoxicity was also verified in *in vivo* screens and in all other animal screens involved in the preclinical development of artemisone. In particular in pilot tolerability studies involving oral administration in sesame oil to female rats at 50 mg $kg^{-1}$ $d^{-1}$ for 14 days, increase in body weight was as for the controls with no detectable adverse events.[26,38]

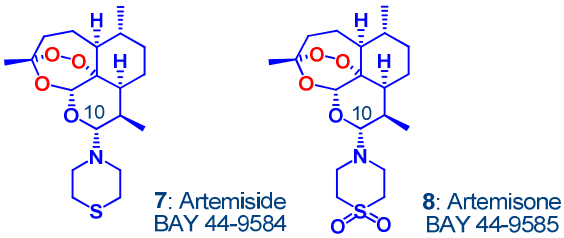



**Fig. 2**. The amino-artemisinins artemiside and artemisone in which the exocyclic oxygen atom at C10 of the current clinical artemisinins (Fig. 1) is replaced by a nitrogen atom. Comparative *in vitro* and *in vivo* assays conducted at the same time under the same conditions with artemisone, other amino artemisinins and one or more of the clinical artemisinins indicate artemisone is the most active, least toxic compound (ref. 37).

Artemisone is up to nine-fold more active than artesunate against the malaria parasite *Plasmodium falciparum in vitro*[37,39,40] and at least three-fold in *in vivo*. It appears to be the most potently active of artemisinins and of synthetic peroxides in general against *P. vivax in vitro*.[41] The enhanced efficacy is reflected in the outcome of a Phase IIa trial on patients with uncomplicated falciparum malaria in Thailand, wherein cure was achieved with an oral administration of 2 mg/kg per day for two days followed by a final dose of 25 mg/kg of mefloquine. This corresponds to a three-fold lower curative dose compared with that of artesunate (4 mg/kg per day for 3 days).[37,42] The feasibility of employing lower dose regimens over a shorter time period is also indicated by the results of primate studies.[37] Artemisone is not metabolized to DHA **2**, but rather to metabolites bearing unsaturation in the thiomorpholine-*S*,*S*-dioxide ring, and/or hydroxyl groups at C-5 or C-7 that are also active antimalarials.[37,43] DHA is not formed upon incubation of artemisone with liver microsomes, hepatocytes and recombinant CYP isoforms, and is not present in the plasma of malaria patients treated with artemisone.[42] Importantly, it displays no clinically-relevant autoinduction of metabolizing enzymes.[37,43] The benefit is that plasma concentrations of artemisone and its active metabolites do not vary significantly over the administration period; this was demonstrated by daily assessment of plasma concentrations in subjects in the Phase I and II studies.[43,44,45] In comparison to DHA,[46] artemisone possesses a longer elimination half-life (~3 h vs ~1 h), lower plasma clearance (~3.5 L/h/kg vs ~5.4 L/h/kg) and a larger volume of distribution (14.5 L/kg vs 7.7 L/kg).[44,45] Overall, artemisone is the only artemisinin derivative developed outside China that has progressed into a clinical trial against malaria.[47] Artemisone has now been registered with the US FDA as an orphan drug planned for use in treatment of severe malaria via intravenous administration.[48]

Artemiside and artemisone are active against the apicomplexan parasite *Toxoplasma gondii*, in particular in a murine model wherein the compounds are significantly more active than artemisinin.[49] Artemisone is active against the veterinary parasite *Neospora caninum* in an animal model[50] and against *N. caninum* tachyzoites *in vitro* with an $IC_{50}$ of 3 nM.[51] For non-parasitic pathogens, artemisone is cytotoxic towards the ulcerogenic bacterium *Helicobacter pylori*, in particular in combination with known antibiotics,[52] and is a potent inhibitor of human cytomegalovirus with an efficacy comparable to that of ganciclovir.[53] Artemisone is among the most potent of all antimalarial peroxides when screened against tumour cell lines,[54] an effect which is enhanced by addition of other cancer drugs.[55] In relation to the mechanism of action, artemisone like other amino-artemisinins[36] does not interact with haemoglobin-Fe(II), and reacts poorly with iron(II) or with heme iron(II) under biomimetic conditions, although partial hydrolysis to DHA is observed.[56] Biological activity is claimed to be associated with alkylation of heme iron(II) based on the outcome of non-biomimetic experiments when heme iron(III) is reduced with sodium dithionite in anhydrous DMSO in an inert gas atmosphere, and then treated with the artemisinin.[57] However, artemisinins retain antimalarial activities *in vitro* against malaria parasites cultured under an atmosphere containing carbon monoxide. CO reacts with heme-Fe(II) to form the stable carboxyheme-Fe(II) complex that does not react

with artemisinins.[56] Significantly, those artemisinins that do react with heme-Fe(II) under biomimetic conditions show improved activities against the malaria parasite under the CO atmosphere, whereas those that do not react with heme-Fe(II), such as artemisone, retain the same activities. Overall, the suppositions on the biological significance of the notably abiotic heme-alkylation experiments have been dealt with, namely the reaction with heme in a biological medium represents a competing degradation which results in attrition of efficacy, and is unrelated to mechanism of action.[9,36,56,58] The ability of the peroxide group to oxidize reduced flavin cofactors important in modulating oxidative stress in the malaria parasite has been demonstrated.[20, 59] That amino-artemisinins are optimum substrates for eliciting parasiticidal action may be rationalized in terms of this oxidant model.[60]

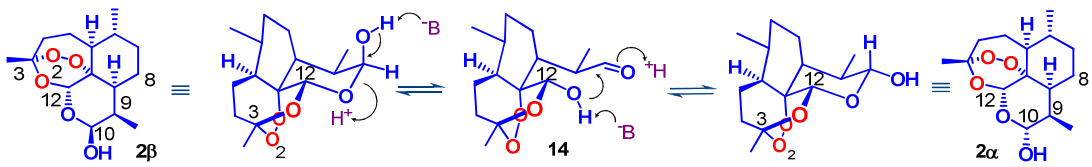
In general, as compared to the relatively facile preparations of the artemisinins of Fig. 1, amino-artemisinins are less accessible - *N*-glycosylation methodologies have to be used on DHA **2** containing a peroxide that confers chemical and thermal instability. However, the considerable promise of clinical use of artemisone **8** against malaria and other parasitic and non-parasitic pathogens impelled us to improve the preparation of amino-artemisinins, and in particular, of artemisone **8** such that this becomes economically accessible on a large scale. Use of reagents and solvents and distinct chemical operations must be minimized, and the product must be isolated without the need for chromatographic purification. We describe here the efforts that eventually led to new scalable processes for preparation of the amino-artemisinins from DHA **2**.

## 2. Discussion

### 2.1. Attempted Direct Preparation from Artemisinin or DHA

As artemisinin **1** is extracted from *Artemisia annua*, its direct conversion into artemisone will confer a cost advantage. Although a lactone, artemisinin reacts like a ketone with hydride and other nucleophiles s to give stable hemiacetal adducts.[4,6,61,62] In addition, artemisinin reacts cleanly with ammonia and primary alkyl amines under protic conditions to give adducts that in a subsequent step are transformed into 11-aza-artemisinins.[63] However, attempted reduction of the putative adducts formed *in situ* from artemisinin and 1° and 2° amines including thiomorpholine with sodium triacetoxyborohydride[64] or borane-amine based reagents[65] was unsuccessful, and mixtures of products arising via reduction of the peroxide were generally obtained.

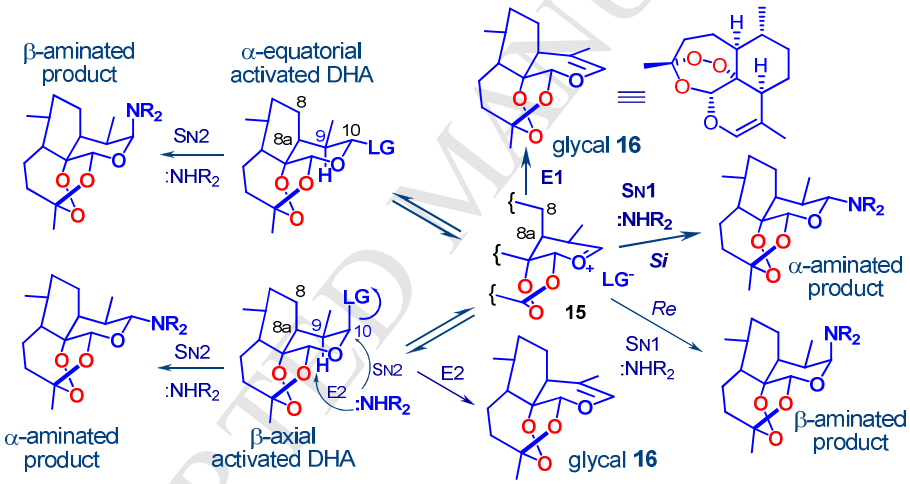
DHA **2** in solution is an equilibrating mixture of the α- and β-epimers (Scheme 1) whose relative amounts depend upon the solvent and the presence of organic bases.[66,67] The pure β-epimer **2β** with axial hydroxyl crystallizes from solution or may be sublimed from solid DHA under high vacuum.[66] Epimerization to the α-epimer in solution likely occurs via the aldehyde **14**. The Kotchetkov aminoglycosylation reaction involves condensation of amines with aldoses in aqueous alcohol containing inorganic salts,[68] and works well for 2° amines such as indoles with glucose[69] and substituted piperazines with glucose or galactose.[70] The reaction proceeds via ring opening of the aldose to the aldehyde, that condenses with the amine to generate the iminium intermediate; this undergoes ring closure to the *N*-glycosylamine. However, under the conditions of the Kotchetkov reaction it was not possible to intercept the aldehyde **14** from DHA with thiomorpholine or other 2° amines, and 2-deoxy-artemisinin **6** (Fig. 1) was obtained as the only identifiable product. Its formation likely proceeds via ring opening of DHA under the protic conditions to an open hydroperoxy keto-aldehyde, reclosure to the peroxyhemiacetal **5** and collapse of the latter by a Kornblum-de la Mare reaction.[23,34] Its appearance under these conditions underscores the labile nature of DHA, and its general unsuitability as a drug for malaria.[23]



**Scheme 1.** Chair pyranose forms of equatorial **2α** and axial epimers **2β** of DHA, and their proposed equilibration via aldehyde **14**.

2.2. Preparation of artemiside **7**

Activation of the anomeric hydroxyl group in pyranose sugars followed by displacement with nucleophiles leads to glycosides.[71] However, the reactivity of the peroxide in DHA restricts the range of *N*-glycosylation reactions that can be used.In addition, the C-10 (anomeric) hydroxyl in DHA is attached to a chair pyranose ring buttressed against a cis-fused cyclohexano system (Scheme 2). Thus, for an amine nucleophile, an SN2 reaction with the α-equatorial activated DHA leading to the β-axial product is inhibited by the steric hindrance due to the axial C8-C8a bond; similarly an SN1 process involving *Re*-face attack on the oxonium ion **15** is also disfavoured (Scheme 2). The β-axial-activated DHA will be prone to E2 elimination because of the trans-diaxial arrangement of H-9 and leaving group at C-10. However, the predominant pathways for both activated epimers are likely to be E1 and SN1 reactions involving the oxonium ion **15**, with steric or stereoelectronic (anomeric) effects determining the outcome of the latter reactions. In this respect, the α-equatorial trichloroacetimidate obtained via the Schmidt procedure on DHA provides β-axial esters according to the anomeric effect.[67] As amines are not subject to such an effect, α-aminated products are expected to form.

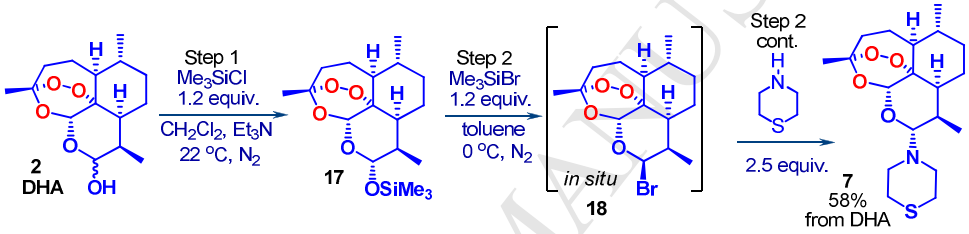



**Scheme 2**. Axial and equatorial activated intermediates from DHA **2** that via SN2 and SN1 reactions involving oxonium ion **15** may provide α- and β-aminated products with amine nucleophiles. The axial 8-8a bond in the α-equatorial activated DHA will inhibit SN2 reactions. *Si*-face addition of the nucleophile leading to the α-aminated product is also favoured for SN1 reactions because of the axial 8-8a bond in **15**. E2 and especially E1 reactions leading to anhydrodihydroartemisinin (glycal) **16** will compete when basic amine nucleophiles are used. The cases below involve the β-axial activated DHA where LG = Br or Cl to provide the α-aminated products.

Thus, conversion of the hydroxyl into halide in aprotic solvents under the mildest possible conditions was required. We originally converted DHA by treatment with diethylaminosulfur fluoride into the 10β-fluoride,[72,73] but the expense of the reagent and the low yield and instability of the product excluded this activation method. According to the conversion of fucopyranose trimethylsilyl ether into the axial iodide by treatment with trimethylsilyl iodide,[74] DHA was converted into the crystalline α-trimethylsilyl ether **17** that with trimethylsilyl bromide (TMSBr) in dichloromethane cleanly provided *in situ* the axial β-bromide **18** (Scheme 3). Exclusive formation of the β-product as favoured by the anomeric effect was revealed by $^{1}$H NMR analyses of reaction mixtures.[73] The bromide was converted by treatment *in situ* with 1° and 2° alkylamines and 1° arylamines into 10-α-amino-artemisinins accompanied by the glycal **16**.[36] The amino derivatives were formed exclusively as the α-epimers. 10-

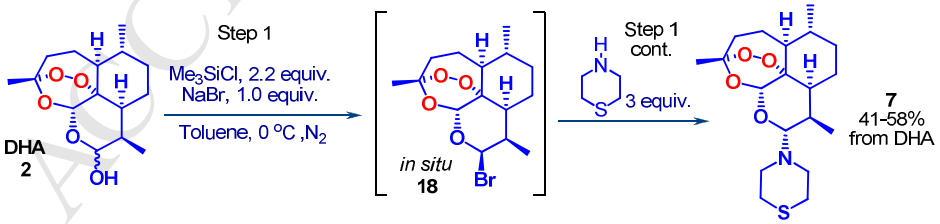
Arylamino-artemisinins have been made by other methods,[75] but our method is the first for making 10-alkylamino-artemisinins. In turning to artemisone **8**, we now describe optimization of the preparation of artemiside **7** from DHA and thiomorpholine that is converted in a separate step into artemisone, and the direct preparation of artemisone from DHA and thiomorpholine-1,1-dioxide.

2.2.1. *DHA trimethylsilyl ether and trimethylsilyl bromide*: We originally reported that treatment of β-bromide **18** generated *in situ* from DHA TMS ether **17** and TMSBr with thiomorpholine (2.5 equiv.) provided artemiside **7** in 58% yield.[37] In seeking to augment the amount of thiomorpholine by using amine bases triethylamine and hexa-methyldisilazane or inorganic bases, yields were not significantly improved. Larger scale preparations (to 10 mmole DHA) concluding with a direct recrystallization of the crude product mixture gave lower isolated yields (30-35%) of artemiside. The non-polar glycal **16** invariably formed as a by-product interfered with the crystal-lization of artemiside, and normally had to be separated by chromatography. The preparation of artemiside according to this process, in which discrete isolation of a product is labelled as a 'step', is summarized in Scheme 3. Disadvantages include the use of TMSBr and excess thiomorpholine, and eventual chromatography of mother liquors to separate residual artemiside **7** from the glycal **16**.




**Scheme 3**. First process for the preparation of artemiside.

2.2.2. *Trimethylsilyl bromide* in situ: Although generation of TMSBr *in situ* requires polar solvents,[76] we found that the β-bromide **18** was readily generated by the treatment of DHA and sodium bromide with trimethylsilyl chloride (TMSCl) in toluene.[37] Next, addition of thiomorpholine to the mixture gave **7** in 58% isolated yield for a reaction conducted on a 1 mmole scale (Scheme 4). Again, use of amine or inorganic bases did not significantly affect yields, and the glycal **16** was always formed. At a 2-3 mole scale, for which a direct crystallization was employed, the isolated yields decreased to ~41%. Thus, the process is scalable, but although it required fewer steps and cheaper reagents, the use of an excess of thiomorpholine, and lower yields at large scale detract from its utility.




**Scheme 4**: Second process for the preparation of artemiside

As noted above (Scheme 2), SN1/SN2 and E1/E2 processes convert the β-activated DHA derivative, namely bromide **18**, into artemiside **7** and glycal **16** respectively. Thus, effect of solvents on the artemiside:glycal ratios required evaluation. An NMR method was used to assess relative amounts of unreacted DHA, artemiside and glycal in the product mixtures by comparing signal integrals with those of the aromatic protons of the internal standard 1,3,5-trimethoxybenzene. The chemical shifts of the signals due to DHA and the products in the downfield region are well separated (Table 1), and assessment of ratios was straightforward.

**Table 1:** $^{1}$H-NMR chemical shifts of characteristic signals.[a]

| Compounds | Chemical Shifts $\delta_H$ (ppm) and Coupling Constants $J$ (Hz) | |
|---|---|---|
| DHA **2** | α-epimer: 4.73, d, $J_{10,9}$ = 8.7 Hz, H-10 | α-epimer: 5.38, s, H12 |
| | β-epimer: 5.31, d, $J_{10,9}$ = 3.6 Hz, H-10 | β-epimer: 5.61, s, H12 |
| Glycal **16** | 6.13, q, $J_{9\text{-Me},10}$ = 1.33 Hz, H-10 | 5.53, s, H-12 |
| Artemiside **7** | 3.93, d, $J_{9,10}$ = 10.2 Hz, H-10 | 5.23, s, H-12 |
| Artemisone **8** | 4.21, d, $J_{9,10}$ = 10.3 Hz, H-10 | 5.28, s, H-12 |
| 1,3,5-Trimethoxybenzene[b] | 3.75, s | 6.08, s |

[a]300 MHz, $CDCl_3$; [b]internal standard.

Lewis basic solvents (Table 2, entries 1-3) generally enhanced formation of the glycal **16** whereas non-polar solvents enhanced formation of artemiside **7**. The bromide **18** decomposes to the glycal via E1 or E2 processes where the basic solvent or thiomorpholine abstracts α-axial H-9 (Scheme 2). Thus, substitution is favoured in non-polar solvents. The best artemiside:glycal ratios were obtained with toluene, cyclohexane and dichloromethane, and best product yields with toluene. The lower solubility of DHA in cyclohexane resulted in a poorer conversion. Use of longer reaction times did not improve the yield. In contrast, the crude product mixture from reactions in toluene contained very little DHA. Thus, focus turned to use of halogenated solvents and toluene.

**Table 2:** Results of Reactions in Various Solvents [a]

| Entry | Solvent | Artemiside **8**:Glycal **16** | % Artemiside **7** formed |
|---|---|---|---|
| 1 | $(CH_3)_2C{=}O$ | 29:71 | 22 |
| 2 | $CH_3CN$ | 33:67 | 11 |
| 3 | $CH_3CO_2CH_2CH_3$ | 38:62 | 13 |
| 4[b] | $(CH_3CH_2)_2O$ | 65:35 | 53 |
| 5 | $CH_2Cl_2$ | 61:39 | 54 |
| 6 | $PhCH_3$ | 73:27 | 58 |
| 7 | *n*-hexane | 63:37 | 27 |
| 8 | cyclohexane | 74:26 | 36 |

[a]All reactions performed with 1 mmol of DHA **2**, 1.1 mmol of sodium bromide and 2.2 mmol of trimethylsilyl chloride in 1 mL of solvent stirred for 15 min and then treated with 2.5 mmol of thiomorpholine, except for entry 4; [b]the mixture in diethyl ether was stirred overnight before addition of thiomorpholine.

2.2.3. *Hydrogen chloride*: In accord with the chemistry of anhydro sugars,[77] glycal **16** is rapidly converted into the β-chloride **19** by gaseous HCl in dichloromethane. The reaction was used to prepare isotopically labelled artemisone from labelled glycal.[37] However, attempts to convert DHA in dichloromethane into **19** with gaseous HCl, or by HCl generated *in situ*, *e.g.* from acetyl chloride,[78] were unsuccessful. In contrast, when anhydrous lithium, magnesium or calcium chlorides (1.2-1.6 equiv.) were added, DHA was now rapidly converted into chloride **19**. This was assessed for reactions in $CD_2Cl_2$ or $CDCl_3$ where after filtration to remove the salts, the $^{1}$H NMR spectrum cleanly revealed the presence of the β-chloride **19** (Fig. 3).

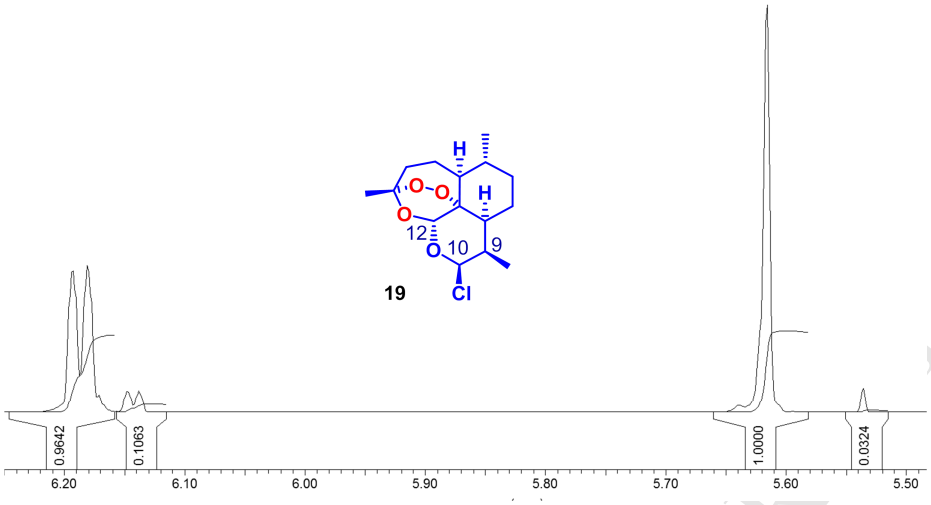


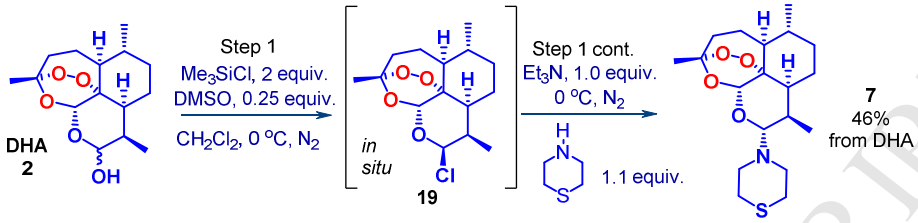

**Figure 3.** $^{1}$H NMR spectrum of the β-chloride **19** (300 MHz, $CD_2Cl_2$). The signal due to H-12 is at δ 5.62 ppm, and H-10 is at δ 6.19 ppm; with $J_{10,9}$ = 3.3 Hz, H-10 is axial with a cis axial-equatorial coupling to H-9. Signals at δ 5.53 and 6.19 ppm are due the glycal **16**.

Treatment of the β-chloride **19** *in situ* with thiomorpholine-triethylamine gave artemisinide in 54-57% isolated yields (Scheme 5). The salts may assist in activating the hydroxyl group to displacement by chloride, and/or by scavenging water, suppress hydrolysis of the β-chloride to DHA. Use of anhydrous sodium chloride or Lewis acids such as zinc or tin(II) chlorides resulted in lower yields of artemisinide, usually at the expense of the glycal. Reaction mixtures obtained from preparative scale experiments with 18 mmole (*ca.* 5 g) or more of DHA were quenched with brine, followed by separation of the organic layer, direct evaporation, and recrystallization of the residue. No drying was used. However, a simple filtration of the reaction mixture, especially at larger scale, to remove the insoluble metal halide and amine hydrochloride salts formed in the reaction, followed by direct evaporation of the filtrate sufficed to provide crude product that was crystallized directly. Successive crops of the product were obtained from the mother liquors. However, dilute solutions of DHA had to be used for optimum yields – at an 18 mmole scale, 0.2 M solutions of DHA were required. Overall, the HCl process is readily scalable, but from an industrial aspect dichloromethane is not regarded as a suitable solvent. However, with toluene containing anhydrous magnesium chloride, the isolated yield of artemisinide decreased to 17%. With magnesium bromide that should generate the more reactive HBr *in situ* from the gaseous HCl in toluene, DHA provided artemisinide in 50% isolated yield, but the solution was difficult to handle once the thiomorpholine had been added, and in order to isolate artemisinide, the mixture had to be diluted with dichloromethane.

**Scheme 5**. Third process for the preparation of artemisinide.

2.2.4. *Trimethylsilyl chloride-dimethyl sulfoxide*: TMSCl and catalytic DMSO in dichloromethane convert alcohols into alkyl chlorides.[79] The reaction proceeds via a siloxysulfonium chloride formed from the DMSO and TMSCl followed by activation of the alcohol via a sulfurane intermediate and displacement by chloride. Because of the cheapness of the reagents, the reaction was examined here. DHA **2** in $CD_2Cl_2$ treated with TMSCl (2 equiv.) and

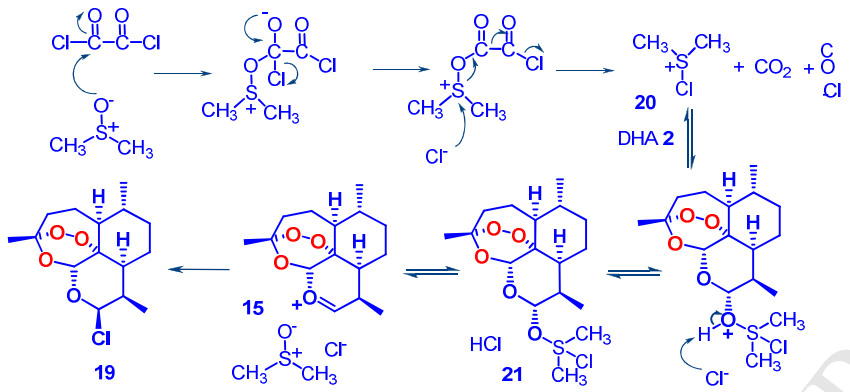
$d_6$-DMSO (0.25 equiv.) gave cleanly the 10β-chloride **19** as verified by $^1$H NMR spectroscopy. At a 1 mmole scale, artemiside was obtained in 60% yield, but more of the glycal **16** was now formed. Use of preparative scale experiments to 18 millimole resulted in lower isolated yields (46%) (Scheme 6); this is ascribed to difficulty of inducing crystallization of artemiside in the presence of large amounts of the glycal, as noted above. The reaction did not succeed in toluene.




**Scheme 6**. Fourth process for the preparation of artemiside

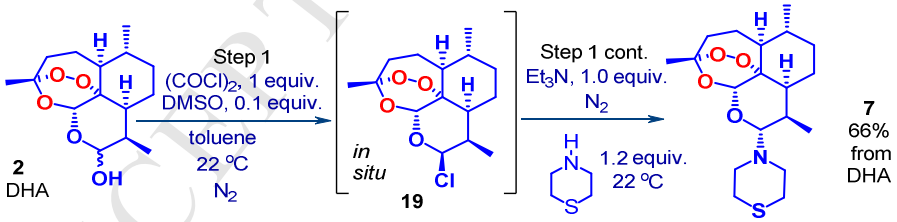
2.2.5. *Oxalyl chloride*: Oxalyl chloride has long been used to convert alcohols into alkyl halides.[80] It reacts by various pathways depending upon the amount of the reagent and the conditions.[81] In the presence of pyridine, an oxalate hemiester is formed from an alcohol that on heating decomposes to the alkyl chloride.[82] In the absence of a base, the reaction with a 3° alcohol directly provides the alkyl halide, assisted by the generation of HCl during the course of the reaction.[80] Treatment of DHA and triethylamine with oxalyl chloride (0.5 equiv.) in $CD_2Cl_2$ gave a product presumed to be the bis-oxalate ester, whose formation was indicated by the appearance of a signal in the $^1$H NMR spectrum at δ 5.83 ppm (H-10, $J_{10,9}$ 9.9 Hz) characteristic of α-esters of DHA in which H-10 displays a trans-diaxial coupling with H-9.[67] Attempts to isolate the ester by crystallization from the reaction mixture resulted in its decomposition to the glycal **16**. Treatment of the bis-oxalate ester with thiomorpholine *in situ* did not give significant amounts of artemiside. The reaction was therefore repeated in the absence of triethylamine. Although clean formation of the β-chloride **19** from DHA and oxalyl chloride in $CD_2Cl_2$ was confirmed by $^1$H NMR spectroscopy, the reaction was surprisingly slower than the DHA-HCl-salt reactions (*cf.* Scheme 5) in this solvent. At a 1.76 mmole scale at 0 °C, 10 minutes were required for the latter reaction, whereas the DHA-oxalyl chloride reaction required 4 hours. Treatment of the reaction mixtures with thiomorpholine-triethylamine gave artemiside **7** in 45-50% isolated yields. Concentrated solutions of DHA ranging from 0.45-0.9M DHA could now be used without diminution in yields. In contrast, for the HCl reactions at an 18 millimole scale, limiting concentrations of approximately 0.3M DHA had to be used for optimum yields. However, the best isolated yields of artemiside obtained for the oxalyl chloride reactions, irrespective of the scale of the reaction, did not exceed 50%. In contrast to the HCl reactions, toluene could now be used as solvent, although isolated yields of artemiside were inferior to those from reactions in dichloromethane.

2.2.6. *Oxalyl chloride-dimethyl sulfoxide and other promoters*: DMSO is paired with oxalyl chloride in the Swern oxidation that proceeds via the chlorosulfonium intermediate **20**. Formation of the chlorosulfurane adduct from the alcohol is followed by its conversion into the carbonyl product and dimethyl sulfide in the presence of a 3° amine base. In the absence of base, the sulfurane of an SN1-reactive alcohol is anticipated to decompose to the alkyl chloride. The idea is illustrated in Scheme 7 for DHA wherein the DHA-sulfurane adduct **21** may equilibrate with the oxonium-stabilized cation **15**, chloride ion and DMSO, the last which will thus cycle in a catalytic fashion.



**Scheme 7.** Proposal for conversion of DHA **2** into the β-chloride **19** with oxalyl chloride and DMSO; the reaction is catalytic with respect to DMSO. The sulfurane **21** will be generated as the α-epimer as it is formed by nucleophilic attack by the α-epimer of DHA with equatorial hydroxyl on the sulfonium salt, as is discussed elsewhere for reaction of DHA with other electrophiles (ref. 67).

The reaction was examined by $^{1}$H NMR spectroscopy with oxalyl chloride, $d_6$-DMSO and DHA in $d_8$-toluene. Whilst DHA is partially soluble in toluene, a colourless solution corresponding to formation of the β-chloride **19** formed as soon as the oxalyl chloride was added. At a 1.76 mmole scale, formation of **19** in toluene was complete in 30 minutes. Treatment with thiomorpholine-triethylamine gave artemiside **7** in 55% isolated yield. At larger scale, the best conditions involved treating DHA in toluene containing DMSO (0.1 equiv.) with oxalyl chloride (1 equiv.), then adding thiomorpholine and triethylamine and allowing the reactions to run for 2 h. Composition of the crude product mixtures isolated from several experiments was assessed by $^{1}$H NMR spectroscopy with 1,3,5-trimethoxybenzene as standard (*cf.* Table 1); yields ranged from 76-79%. Concentrated solutions could now be used: DHA (17.7 mmole, 5 g) in 15 mL of toluene, corresponding to a 1.2 M solution, gave artemiside in 66% isolated yield (Scheme 8). This method is facile, but the industrial scalability needs to be assessed.

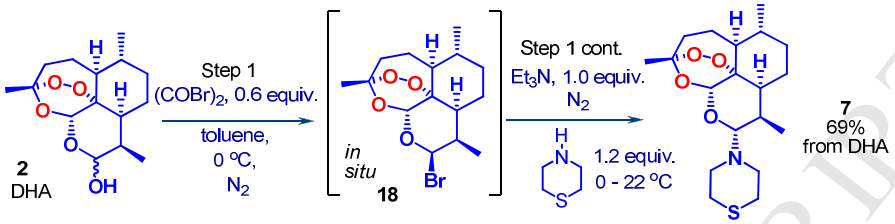



**Scheme 8**: Fifth process for the preparation of artemiside

Although Swern oxidation of DHA to artemisinin **1** did not take place, there was a slight odour of dimethyl sulfide associated with the reaction work-up. However, use of the non-volatile *p*-chlorophenyl sulfoxide as the activator resulted in a slower reaction, and yields of product were not significantly improved. Dimethyl formamide may be activated by oxalyl chloride as the Vilsmeier reagent to chlorinate alcohols, but its use here instead of DMSO did not give any product.

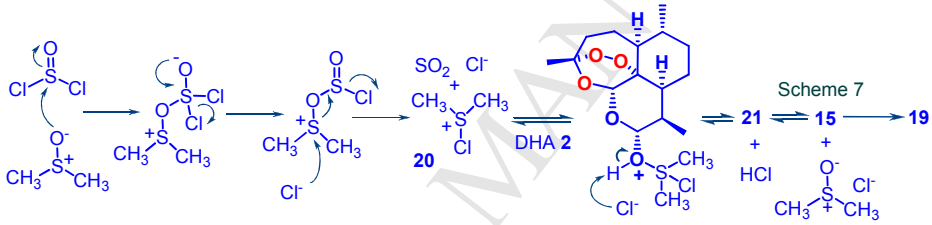
2.2.7. *Oxalyl bromide*: Although oxalyl bromide is more expensive than oxalyl chloride, it is more reactive; it also will provide a more economic route to artemiside than the use of TMSBr (*cf.* Scheme 3). The enhanced reactivity of oxalyl bromide also means that DMSO may not be required as a promoter in toluene solvent. In the event, at a 1.78 mmole scale, DHA was converted by oxalyl bromide (0.6 equiv.) and thiomorpholine-triethylamine into

artemiside in 69% isolated yield. Clearly, HBr formed in the reaction of DHA with oxalyl bromide is also able to convert DHA into the β-bromide. This was verified by treating DHA in $d_8$-toluene with HBr gas, and examining the reaction mixture by $^1$H NMR spectroscopy. Thus HBr in contrast to HCl works without any metal halide promoters in toluene. The reaction succeeded well with a concentration of DHA of approximately 0.4 M (Scheme 9).



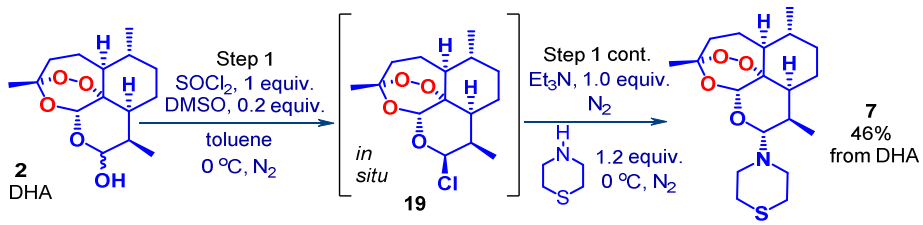

**Scheme 9**: Sixth process for the preparation of artemiside

2.2.8. *Thionyl chloride-dimethyl sulfoxide*: Thionyl chloride efficiently converts DMSO into the chlorosulfonium intermediate **20** wherein it is a more effective activator of DMSO than is oxalyl chloride in the Swern oxidation (Scheme 10).[83] Although the caveat is the production of sulfur dioxide, the reaction is more atom-economical than with oxalyl chloride.




**Scheme 10**. Proposal for thionyl chloride activation by DMSO (*cf.* Scheme 7). As in the case of oxalyl chloride, the reaction is catalytic with respect to DMSO, but here $SO_2$ rather than carbon oxides are the gaseous by-products.

DHA **2** at a 1.76 mmol scale and DMSO (0.2 equiv.) in toluene was treated with thionyl chloride (1 equiv.) and after 60 min, with thiomorpholine-triethylamine according to the foregoing conditions. Examination of the product mixture by $^1$H NMR spectroscopy indicated the presence of artemiside (54-75%) and variable amounts of glycal (15-27%). For larger scale experiments (to 14.1 mmole or 4 g of DHA), the best conditions involved treating DHA in toluene containing DMSO (0.2 equiv.) with thionyl chloride (1 equiv.), then adding thiomorpholine and triethylamine and allowing the reactions to run for 3 h. Direct recrystallization of the product mixture from methanol provided artemiside (46%), although additional material was able to be recovered by fractional crystallization of mother liquors. As in the TMSCl-DMSO reaction above (Scheme 6), the glycal **16** interfered with isolation of the artemiside. It is of note that a control reaction using thionyl chloride in toluene in the absence of DMSO over 2 h returned unchanged DHA (92%). Although product yields of the thionyl chloride-DMSO reactions as determined by $^1$H NMR spectroscopy and by direct isolation are currently lower than those from the oxalyl chloride-DMSO reactions, the reactions are easily carried out.

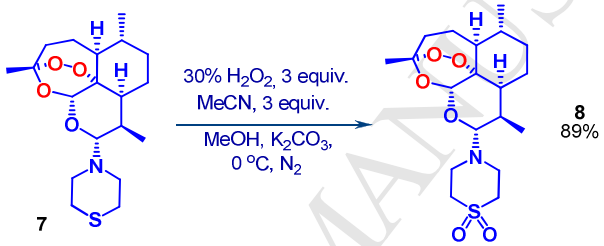


**Scheme 11**: Seventh process for the preparation of artemiside

The process as encapsulated in Scheme 11 potentially represents the most economical approach to artemiside. It is clear here and in the above cases that there is a need to suppress formation of the glycal in order to enhance yields and facilitate isolation of the artemiside.

2.3. Conversion of artemiside to artemisone

We previously used tetrapropylammonium perruthenate-*N*-methylmorpholine-*N*-oxide (TPAP) for conversion of artemiside **7** into artemisone **8**.[37] However, metal-free oxidation is preferable from a drug development viewpoint. At a 1.36 mmol scale (500 mg artemiside), use of the Payne system,[84] namely 30% aqueous $H_2O_2$-acetonitrile in a mixed methanol-ether or methanol-dichloromethane solvent system containing potassium carbonate at 0 °C was highly effective in providing artemisone in 89% yield (Scheme 12). Use of other alcohols as co-solvents – ethanol, isopropanol – resulted in lower yields. The $H_2O_2$-urea complex, a convenient solid source of $H_2O_2$ that efficiently oxidizes sulfides to sulfones,[85] under the foregoing conditions also provided comparable yields of artemisone from artemiside.

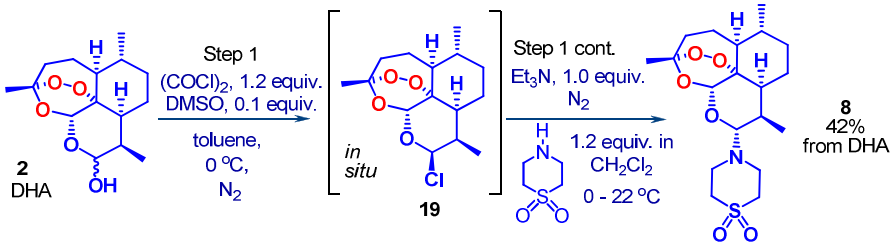



**Scheme 12**: Oxidation of artemiside to artemisone.

The latter reagent was used to treat crude product mixtures obtained from the DHA-oxalyl bromide-thiomorpholine reactions described above (Scheme 9), whence at a 35 mmole scale (10 g DHA), crystalline artemisone was obtained in 48% yield from DHA.

2.4. Preparation of Artemisone from DHA

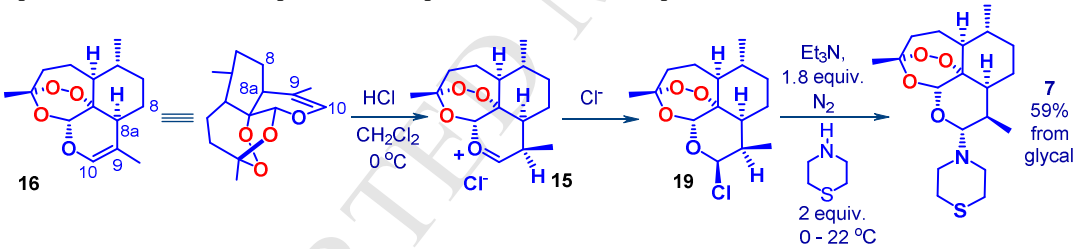
Reaction of activated DHA **2** with thiomorpholine-1,1-dioxide was now examined. The latter, in contrast to thiomorpholine, is a solid whose poor solubility in non-polar solvents requires adjustment of the above procedures. Two solvents were used to dissolve the dioxide – dichloromethane and acetone. The preparative methods focussed on oxalyl chloride and oxalyl bromide, as each reagent can be used in relatively concentrated reaction mixtures containing DHA. At a 17.7 mmole scale (5 g), DHA on treatment with oxalyl chloride-DMSO (0.1 equiv.) in toluene followed by treatment with thiomorpholine-1,1-dioxide and triethylamine in dichloromethane gave artemisone (42% isolated yield) (Scheme 13). As above, product yields were also estimated by the $^1$H NMR method with 1,3,5-trimethoxybenzene as standard; at a 1.77 mmole scale, yields of artemisone ranged from 64-70%. Reactions using acetone to dissolve the 1,1-dioxide provided artemisone in similar yields; however, the formation of a minor amount of an unidentified by-product derived from the DHA was evident. Surprisingly, when oxalyl bromide (0.6 equiv.) in dichloromethane or toluene was used to activate DHA followed by treatment with the 1,1-dioxide and triethylamine in dichloromethane, the yields from reactions conducted at a 1.77 mmole scale were lower (to 50%).




**Scheme 13**: Direct preparation of artemisone from DHA with oxalyl chloride-DMSO.

2.5. Preparation of Artemiside from Anhydrodihydroartemisinin (glycal)

The crystalline glycal **16** that is readily obtained from DHA **2** by treating with $BF_3$ etherate or other dehydrating agent[467] inevitably appears among the reaction products here; thus by converting this by-product into artemiside or artemisone on an industrial scale, the effective overall consumption of DHA will be enhanced. Acid-catalysed methods can be used to add nucleophiles to the C10 position via protonation of the double bond at C9 to produce the oxonium ion intermediate **15**.[86] *Si*-face addition of the proton at C9 is favoured because of the steric hindrance of the adjacent pseudoaxial C8-C8a bond on the *Re*-face (Schemes 2, 14). We have already converted isotopically-labelled glycal via addition of HCl and treatment with thiomorpholine into labelled artemiside, and thence, the corresponding labelled artemisone wherein the β-chloride is detected as the intermediate by $^1$H NMR spectroscopy.[37] However, we re-evaluated the procedure here by using the HCl conditions described above. In the event, treatment of glycal **16** with gaseous HCl followed by thiomorpholine-triethylamine provided artemiside (59% isolated yield). Notably, use of thiomorpholine-1,1-dioxide under the foregoing conditions gave a comparatively much lower yield (21%) of artemisone as estimated by $^1$H NMR spectroscopy, indicating that thiomorpholine *S*,*S*-dioxide is a poorer nucleophile than the thiomorpholine.




**Scheme 14:** Addition of HCl to glycal **16** to provide β-chloride **19** and conversion into artemiside **7**.

3. Conclusion

We have evaluated various processes for *N*-glycosylation of DHA **2** involving conversion into artemiside **7** and thence into the lead compound artemisone **8**. The use of gaseous HCl coupled with anhydrous Group I or II metal halide salts in toluene represent a particularly economical approach for converting DHA via the β-chloride into artemiside **7**, although relatively dilute solutions of DHA (to 0.3M) are required for optimum yields. The oxalyl chloride process involving DMSO as promoter in toluene appears to be the best at this stage. Although DHA is a lactol, it could in principle be oxidized to artemisinin via the Swern reaction under these conditions; however such a process does not compete. The benefit also is that more concentrated solutions (to 0.9M DHA) can now be used without diminution in yields. Whilst oxalyl bromide works well for preparation of artemiside **7** from DHA in toluene in the absence of promoter, use of the reagent in conjunction with thiomorpholine-1,1-dioxide for direct preparation of artemisone **8** is not as successful. Although the dioxide is insoluble in toluene, it could be added to the toluene reaction mixtures as a solution in dichloromethane or acetone. However, in a direct comparison, it is noted to react less efficiently with the β-chloride **19** in dichloromethane than does thiomorpholine itself. The process for obtaining artemisone using oxalyl bromide-thiomorpholine, and then oxidation of the crude product

mixture with urea-hydrogen peroxide directly provides artemisone in 48% yield at a multigram scale from DHA. The reagents used, oxalyl bromide and urea-hydrogen peroxide, are easy to handle and no halogenated solvent is used through the whole process. Extractive work up and chromatography are not required, and the product is easily crystallized from isopropanol.

## 4. Experimental Section

### 4.1. General

DHA was obtained from the Kunming Pharmaceutical Corporation, Kunming, Yunnan Province, China, or from the Dang Quang Trading Company, Hanoi, Vietnam. Dichloromethane was distilled from and stored over calcium hydride, triethylamine and thiomorpholine were distilled from calcium hydride and stored over potassium hydroxide, toluene was dried over sodium wire and distilled from sodium benzophenone ketyl immediately prior to use. Dichloromethane was distilled from calcium hydride immediately prior to use. Thiomorpholine-1,1-dioxide was provided by Bayer AG Zentralforschung, and used as such. Acetone, AR grade (Lab-Scan), oxalyl chloride (98%) and oxalyl bromide (97%), and urea-hydrogen peroxide (98%) (Sigma-Aldrich) were used as received. Dimethyl sulfoxide (BDH) was dried and fractionally distilled from calcium hydride, and stored over 4 Å molecular sieves under nitrogen. TLC was performed with Merck Kieselgel 60 $F_{254}$ plates and visualised with ultra violet light (254 nm) and/or heating after treatment with 5% ammonium molybdate in 10% concentrated sulfuric acid. Column chromatography was performed with Merck silica gel 60 (0.04-0.063 mm).

$^1$H spectra were recorded on a Varian Mercury-300 spectrometer. Chemical shifts are in ppm relative to tetramethylsilane (0.03% v/v) as 0.0 ppm for proton and $CHCl_3$ in $CDCl_3$ as 7.26 ppm. Melting points were carried out on a Leica Hot Stage DME E microscope and are corrected. Mass spectral data were obtained on Finnigan TSQ 7000 mass spectrometer (CI) and on an API QSTAR high performance triple quadrupole time-of-flight mass spectrometer with electrospray ionization. Infrared spectra were recorded either on a Perkin Elmer PC 16 or a Perkin Elmer Spectrum One spectrometer. Yield readouts from $^1$H NMR spectra were determined by adding the internal standard crystalline 1,3,5-trimethoxybenzene (0.33 equiv. with respect to DHA) to the crude product mixture. This has a singlet signal from the three aromatic protons at 6.08 ppm. The yields of product were obtained by comparing the integral of this signal with the integral of the signal due to H-12 in the products (*cf.* Table 1).

Hydrogen chloride gas was generated by dropwise addition of concentrated $H_2SO_4$ onto $NH_4Cl$ powder at a rate of 1 drop per 5 s with a flow rate of *ca*. 5.5 mmol per min. The cannulas used for transfer of reaction mixtures were 30.5 cm (12") long with ID 0.8 mm, OD 1.0 mm for reactions with 500 mg DHA, and 43.2 cm (17") long with ID 1.2 mm, OD 1.5 mm for 5 g or larger scale reactions. Magnetic stirrer bars were 2 x 1 cm for 500 mg reactions and 2.5 x 1.3 cm for 5 g reactions of DHA. The stirring velocity was from 650 to 750 $min^{-1}$. Nitrogen flushing required in the first step to assist in removal of excess of hydrogen chloride was effected by passing dry nitrogen gas over the reaction mixture.

### 4.2. Preparation of Artemiside **7**

Data for artemiside and procedures for its preparation via the first process with DHA TMS ether and TMSBr (Scheme 4), and the second process involving generation of TMSBr *in situ* (Scheme 5) are given in the Supporting Information 1 associated with ref. 37**.**

*Attempted preparation from DHA by the Kotchetkov Reaction*: A solution of thiomorpholine (0.12 mL, 1.2 mmol) and dihydroartemisinin (DHA, 285.6 mg, 1.01 mmol) in ethanol (20 mL) under nitrogen was heated under reflux for 20 h. Half of the ethanol was then evaporated, and saturated aqueous ammonium chloride (5 mL) was added

followed by evaporation of remaining solvent under reduced pressure. The residue was triturated with dichloromethane, filtered and the filtrate was washed with brine (5 mL). The organic layer was separated and dried ($MgSO_4$), and after filtration, the solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography (25:75 ethyl acetate-hexane) to give deoxyartemisinin **6** (179 mg, 67%). This was recrystallized from ethyl acetate–hexane to give **6** as colourless rectangular plates, m.p. 114–115.8 °C, $\delta_H$ 0.95-0.97 (3H, d, J = 5.0 Hz, 6 Me), 1.20-1.23 (3H, d, J = 2.4 Hz, 9 Me), 1.27-1.29 (2H, m), 1.54-1.65 (7H, m), 1.76-2.06 (5H, m), 3.18-3.24 (1H, m), 5.70 (1H, s, H-12); m/z (%) 151.2 (13) 164.2 (30), 193.2 (16), 203.2 (34), 222.3 (21), 267.2 (100); HRMS (ESI) calcd. 267.1596 [$M^+$+1], found 267.1605. This sample was identical with that of deoxyartemisinin obtained by catalytic hydrogenation of artemisinin.[4] Repetition of the procedure with each of methanol, ammonium chloride (0.16 g 3 mmol) in 4:1 ethanol-water, and $MgCl_2$ (0.1 equiv) in ethylene glycol at 40 °C provided 2-deoxyartemisinin **6** as the only identifiable product in varying yields.

4.2.1. From DHA, HCl and Group I and II metal halides

*Dichloromethane*: HCl gas was passed over a stirred mixture of DHA **2** (5.0 g, 17.6 mmol) and anhydrous LiCl (1.2 g, 28.3 mmol) in dichloromethane (80 mL) at 0 °C. The colour of the reaction mixture changed from colourless to pale purple. The system was gently flushed by passage of nitrogen gas over the reaction mixture for 5 min. After gentle degassing further under reduced pressure with alternate nitrogen flushing, dichloromethane (20 mL) was added. Then, the mixture was treated dropwise with a neat mixture of thiomorpholine (2.0 mL, 2.1 g, 19.9 mmol) and triethylamine (2.5 mL, 1.8 g, 18.0 mmol). The colour of the reaction mixture changed to pale yellow. After 45 min., the reaction mixture was quenched with brine (50 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$). Filtration and evaporation of the filtrate gave a pale yellow solid, which was recrystallized directly from methanol to give artemiside **7** as a fine white needles (3.58 g, 55%), mp 147.0-147.6 °C (lit.[37] 152.5-153 °C). Further material was able to be recovered by fractional crystallization from the mother liquors.

The reaction was repeated according to the conditions above with DHA **2** (5.0 g, 17.6 mmol) and each of anhydrous $MgCl_2$ (1.90 g, 20.0 mmol) and $CaCl_2$ (2.2 g, 19.8 mmol) followed by treatment with the neat mixture of thiomorpholine and triethylamine as above; quenching with brine followed by workup and recrystallization gave artemiside **7** (3.60 g, 55% and 3.49 g, 54%, respectively).

The following procedure omitted the quenching step. HCl gas was passed over a stirred mixture of DHA **2** (5.0 g, 17.6 mmol) and anhydrous $MgCl_2$ (0.6 g, 6.30 mmol) in dichloromethane (80 mL) at 0 °C. The colour of the reaction mixture became pale purple. After 10 min., ingress of HCl was halted, and the reaction vessel was flushed by gentle passage of nitrogen gas over the reaction mixture at 0 °C for 5 min. After gentle degassing further under reduced pressure with alternate nitrogen flushing, dichloromethane (20 mL) was added to dilute the reaction mixture. The mixture was treated with a neat mixture of thiomorpholine (2.0 mL, 2.1 g, 19.9 mmol) and triethylamine (2.5 mL, 1.8 g, 18.0 mmol). The colour of the reaction mixture changed to pale yellow. After 45 min, the reaction mixture was filtered directly through a sintered glass funnel. The residue in the funnel was washed with dichloromethane (2 x10 mL), and the washings and filtrate were combined. The solution was evaporated under reduced pressure to leave a pale yellow solid, which was recrystallized from methanol to give artemiside (3.50 g, 54%). The glycal **16** and additional artemiside **7** were recovered from the mother liquors after chromatography over silica gel, and eluting with ethyl acetate-hexane (8:92).

*Toluene*: HCl gas was passed over a stirred mixture of DHA **2** (5.0 g, 17.6 mmol) and $MgBr_2$ (1.65 g, 8.96 mmol) in toluene (80 mL) at 0 °C. The colour of the reaction mixture became dark blue. After 10 min., ingress of HCl was halted, and the system was flushed by passage of nitrogen gas over the reaction mixture for 15 min. After

gently outgassing under reduced pressure with alternate nitrogen flushing, the reaction mixture was treated with slow dropwise addition of a neat mixture of thiomorpholine (2.0 mL, 2.1 g, 19.9 mmol) and triethylamine (2.5 mL, 1.8 g, 18.0 mmol). The colour of the reaction mixture changed to pale yellow with concomitant formation of a white bulky precipitate. Dichloromethane (20 mL) had to be added to the resulting very thick mixture so as to facilitate stirring. After 45 min., the reaction mixture was quenched with brine (50 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were dried ($Na_2SO_4$). Filtration and evaporation of the filtrate gave a pale yellow solid, which was recrystallized directly from methanol to give artemiside (3.26 g, 50%). More artemiside was recovered from the mother liquors by evaporation and chromatography over silica gel with chromatography (8:92 ethyl acetate-hexane).

4.2.2. From DHA, trimethylsilyl chloride and DMSO

Trimethylsilyl chloride (4.50 mL, 3.85 g, 35.46 mmol) was added to a stirred solution of DHA **2** (5.0 g, 17.6 mmol) in dichloromethane (80 mL) under nitrogen at 0 ºC. After 15 min., DMSO (0.315 mL, 0.345 g, 4.42 mmol) was added. The colour of the reaction mixture changed to pink and then to pale purple after 1.5 h. The mixture was treated by slow dropwise addition of a neat mixture of thiomorpholine (2.0 mL, 2.1 g, 19.9 mmol) and triethylamine (2.5 mL, 1.8 g, 18.0 mmol), whereupon the colour changed to pale yellow. After 45 min., the reaction mixture was quenched with brine (50 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined organic extracts were dried ($Na_2SO_4$). Filtration and evaporation of the filtrate under reduced pressure left a pale yellow solid, which was recrystallized from methanol to give artemiside **7** (3.0 g, 46%). More artemiside was recovered from the mother liquors by evaporation and chromatography over silica gel (8:92 ethyl acetate-hexane).

4.2.3. From DHA and oxalyl chloride

*Dichloromethane*: A solution of DHA **2** (504.3 mg, 1.78 mmol) and oxalyl chloride (0.16 mL, 1.76 mmol) in dichloromethane (8 mL) was stirred under nitrogen at 0 °C for 4 h. Thereafter, a solution of thiomorpholine (0.2 mL, 1.99 mmol) and triethylamine (0.25 mL, 1.8 mmol) in dichloromethane (1 mL) was transferred by cannula into the reaction mixture, and the resulting mixture was stirred at room temperature for another 2 h. This was then quenched with saturated aqueous $NaHCO_3$ (5 mL), the organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layer was washed with water (2 x 5 mL) and brine (2 x 5 mL), and then dried ($MgSO_4$) and filtered, and the filtrate evaporated. The yellow residue was purified by column chromatography (8:92 ethyl acetate-hexane) to give artemiside **7** as a white crystalline solid (310.6 mg, 48%).

*Toluene*: A solution of DHA **2** (497 mg, 1.75 mmol) and oxalyl chloride (0.16 mL, 1.76 mmol) in toluene (8 mL) was stirred under a gentle stream of nitrogen at room temperature for 4 h. Thereafter, a solution of thiomorpholine (0.2 mL, 1.99 mmol) and triethylamine (0.25 mL, 1.8 mmol) in toluene (1 mL) was added and the reaction mixture was stirred for another 1.75 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and processed as described above, to give after column chromatography (8:92 ethyl acetate-hexane) artemiside **7** as a white crystalline solid (247.5 mg, 39%).

*DHA, oxalyl chloride and DMSO in toluene*: Oxalyl chloride (1.6 mL, 18.3 mmol, 1.03 equiv.) was added to a stirred mixture of DHA (5.027 g, 17.7 mmol) and dimethyl sulfoxide (DMSO, 0.13 mL, 1.8 mmol) in toluene (15 mL) in a 100 mL two-necked round bottom flask under gentle nitrogen flush over the reaction mixture at room temperature. After 30 min, triethylamine (2.5 mL, 18.0 mmol) followed by thiomorpholine (2.0 mL, 21.1 mmol)

was added to the reaction mixture that was stirred for another 2 h; the nitrogen flush was continued for the first 15 minutes. The mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water (2 x 50 mL) and then brine (2 x 50 mL) and dried ($MgSO_4$). After filtration and concentration of the filtrate under reduced pressure, direct crystallization from methanol gave artemiside (4.31 g, 66%), with further amounts being recovered from the mother liquors. In general practice, however, it was usually necessary to submit the residue obtained by evaporation of the mother liquors to column chromatography (8:92 ethyl acetate-hexane) to separate the non-polar glycal **16** from artemiside which could then be recovered. A further two experiments were conducted and $^1$H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard to measure amount of **7** in the residue obtained directly after workup indicated the formation of artemiside (72 and 79% respectively, based on reacting DHA), with small amounts of unreacted DHA **2** (3 and 4%) and glycal **16** (22% for each experiment, based on reacting DHA) also present.

4.2.4. From DHA and oxalyl bromide

A solution of oxalyl bromide (0.1 mL, 1.033 mmol, 0.6 equiv.) in toluene (1 mL) was transferred dropwise via cannula under nitrogen into a suspension of DHA **17** (504.2 mg, 1.78 mmol) in toluene (3 mL) at 0 °C under nitrogen. The resulting mixture was stirred at 0 °C with gentle nitrogen flush over the reaction mixture for 30 minutes. A solution of thiomorpholine (0.2 mL, 1.99 mmol) and triethylamine (0.25 mL, 1.8 mmol) in toluene (1 mL) was added to the reaction mixture which was allowed to warm to room temperature and stirred for another 1 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL), the organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layer was washed with water (2 x 5 mL) and brine (2 x 5 mL), and dried ($MgSO_4$). After filtration, the solvent was evaporated and the residue crystallized directly from methanol to give artemiside **7** (452.1 mg, 69%). Repetition of the experiment (x7) and using $^1$H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard to assess product mixtures after workup indicated formation of artemiside **7** (71-75%), glycal **16** (27-29% based on reacting DHA), and DHA (6-8%).

A solution of oxalyl bromide (1 mL, 10.33 mmol, 0.6 equiv.) in toluene (10 mL) was transferred dropwise via cannula under nitrogen into a suspension of DHA **2** (5.044 g, 17.76 mmol) in toluene (30 mL) at 0 °C under nitrogen. The mixture was stirred at 0 °C under nitrogen for 30 minutes with occasional gentle outgassing and then treated via cannula with a solution of thiomorpholine (2 mL, 19.9 mmol) and triethylamine (2.5 mL, 18 mmol) in toluene (10 mL). The mixture was warmed to room temperature and stirred for another 2 hours, and then processed as described above to provide the product mixture, analysis of which by $^1$H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard indicated formation of artemiside **7** (71%).

4.2.5. From DHA and thionyl chloride-DMSO

DMSO (25 µL, 0.2 equiv) was added into a stirred mixture of DHA **2** (500 mg, 1.76 mmol) in toluene (10 mL) under nitrogen. Thionyl chloride (127.7 µL, 1 equiv) was added slowly into the mixture at 0 °C, and the resulting solution was stirred for 1 hour at 0 °C, and then gently flushed by passage of nitrogen over the reaction mixture for 15 minutes. Thereupon, a neat mixture of triethylamine (294.5 µL, 1.2 equiv.) and thiomorpholine (212.5 µL, 1.2 equiv.) was added slowly into the reaction mixture that was then stirred for 2 hours at 0 °C. Before workup, the standard 1,3,5-trimethoxybenzene was added and the reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ (30 mL) and extracted with ethyl acetate (3 x 15 mL). The extracts were combined and the organic layer was washed with brine (30 mL), and then dried ($MgSO_4$) and filtered. The filtrate was evaporated under reduced pressure to give the crude product mixture, analysis of which by $^1$H NMR spectroscopy with the

internal standard 1,3,5-trimethoxybenzene indicated all DHA had been consumed, and that artemiside **7** (75%) and glycal **16 (**16%) were present.

For an example of a larger scale preparative reaction, thionyl chloride (1.022 mL, 1 equiv) was added slowly to a stirred mixture of DHA (4.0 g, 14.085 mmol) in toluene (20 mL) containing DMSO (200 µL, 0.2 equiv) at 0 °C. The resulting solution was stirred for 1.3 hour at 0 °C, and then gently flushed with argon for 20 minutes. A 1:1 mixture of triethylamine (2.356 mL) and thiomorpholine (1.70 mL) (each 1.2 equiv) was added slowly into the reaction mixture that was then stirred for 3 hours at 0 °C. Just before workup, a known amount of the internal standard 1,3,5-trimethoxybenzene was added into the reaction mixture that was quenched by addition of saturated aqueous $NaHCO_3$ (180 mL). The mixture was extracted with ethyl acetate (3 x 30 mL) and the combined organic layer was washed with saturated aqueous $NaHCO_3$ (60 mL), then with brine (60 mL) and dried ($MgSO_4$). The filtrate was evaporated under reduced pressure to give the crude product that was crystallized directly from methanol to give artemiside **7** (2.39 g, 46%). More artemiside was recovered from the first mother liquors by evaporation and fractional crystallization, and then by chromatography of the final residue over silica gel (8:92 ethyl acetate-hexane).

5. Preparation of Artemisone **8**

Data for artemisone and procedures for its preparation via oxidation of artemiside **7** with tetrapropylammonium perruthenate-*N*-methylmorpholine-*N*-oxide are given in the Supporting Information 1 associated with ref. 37**.**

5.1. By oxidation of artemiside

*30% $H_2O_2$-acetonitrile*: Acetonitrile (0.21 mL, 4.07 mmol, 2.3 equiv.), and potassium carbonate (0.272 g, 1.96 mmol, 1.11 equiv.) were added to a stirred solution of artemiside **7** (500.0 mg, 1.36 mmol) in methanol (10 mL) and dichloromethane (2 mL). The resulting mixture was cooled to 0 °C, and aqueous hydrogen peroxide (30%, 0.46 mL, 4.07 mmol, 2.3 equiv.) in methanol (2 mL) was added dropwise. After completion of the addition, the reaction mixture was allowed to warm to room temperature and stirred for 21 hours. It was then filtered through a filter paper. The filter paper was rinsed with dichloromethane (20 mL) with washings passing into the filtrate. The filtrate was treated with brine (10 mL). The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organic layer was dried ($MgSO_4$), filtered and evaporated to dryness to leave a white crystalline residue that was essentially pure artemisone **8** (531.4 mg, 98%). The residue was recrystallized from isopropanol to give artemisone (482.6 mg, 89%), as needles, m.p. 152-153 °C (lit.[37] 152.3-152.7 °C),

*Urea-$H_2O_2$-complex*: Acetonitrile (0.12 µL, 2.3257 mmol, 6.6 equiv.) was added to a stirred solution of artemiside **7** (128.0 mg, 0.355 mmol), 98% urea-hydrogen peroxide (67.6 mg, 0.704 mmol, 2 equiv.) and potassium carbonate (70.3 mg, 0.5069 mmol, 1.44 equiv.) in methanol (2 mL) at 0 °C. The mixture was allowed to warm up to room temperature and stirred for 21 hours. The solvent was evaporated to leave a solid residue that was triturated thoroughly with distilled water. The undissolved solid was collected by filtration and dried under high vacuum; thereby was obtained artemisone **8** (131 mg, 94%).

5.2. By direct oxidation of the crude residue from the DHA-thiomorpholine-oxalyl bromide reaction

A solution of oxalyl bromide (2 mL, 20.66 mmol, 0.6 equiv,) in toluene (20 mL) was added dropwise via cannula to a stirred mixture of DHA **2** (10.002 g, 35.2 mmol) in toluene (60 mL) at 0 °C under nitrogen. The resulting solution was stirred at 0 °C under nitrogen for 30 minutes with gentle outgassing from time to time. Thereafter, a solution of thiomorpholine (4 mL, 39.8 mmol, 1.13 equiv) and triethylamine (1.06 equiv, 5 mL, 36

mmol) in toluene (1 mL) was added, and the reaction mixture was warmed up to room temperature and stirred for another 2 hours. The precipitate was collected by filtration and washed with ethyl acetate into the filtrate. The filtrate was evaporated under reduced pressure to leave a yellow residue that was treated sequentially with methanol (160 mL), acetonitrile (11.8 mL, 232.3 mmol, 6.6 equiv), urea-hydrogen peroxide (6.7577 g, 70.4 mmol, 2 equiv.) and potassium carbonate (7.001 g, 50.69 mmol, 1.44 equiv.) at 0 °C. The resulting mixture was stirred with warming to room temperature for 21 hours. The solvent was evaporated to leave a residue that was treated with water as described above to leave a crystalline solid. This was collected by filtration, dried under vacuum and recrystallized from isopropanol to give artemisone **8** (6.70 g, 48%).

5.3. From DHA and thiomorpholine-1,1-dioxide

*Oxalyl chloride in toluene*: Oxalyl chloride (1.8 mL, 20.6 mmol, 1.16 equiv.) was added to a stirred mixture of DHA (5.027 g, 17.7 mmol) and DMSO (0.13 mL, 1.8 mmol) in toluene (50 mL) under gentle nitrogen flush at room temperature. After 30 min, a solution of triethylamine (2.53 mL, 18.18 mmol, 1.01 equiv.) and thiomorpholine-1,1-dioxide (2.84 mg, 21.1 mmol, 1.19 equiv.) in dichloromethane (5 mL) was transferred dropwise via cannula into the mixture. This was stirred for another 105 min with the gentle nitrogen flush continuing for the first 45 minutes. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL), and the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was washed with water (2 x 50 mL) and then brine (2 x 50 mL) and dried ($MgSO_4$). After filtration and concentration of the filtrate under reduced pressure, analysis of the residue by $^1$H NMR spectroscopy with 1,3,5-trimethoxybenze as internal standard indicated formation of artemisone **8** (70% based on reacting DHA) and the presence of DHA (3%) and glycal **16** (20% based on reacting DHA). Crystallization of the residue from isopropanol provided crystalline artemisone (2.98 g, 42%). Repetition of the reaction by using acetone (5 mL) instead of dichloromethane to dissolve the thiomorpholine-1,1-dioxide provided similar yields of artemisone with the evident formation of a small amount of an additional by-product derived from the DHA.

*Oxalyl bromide in dichloromethane*: A solution of oxalyl bromide (0.1 mL, 1.033 mmol, 0.6 equiv.) in dichloromethane (1 mL) was added via cannula under nitrogen to a solution of DHA **2** (503.4 mg, 1.77 mmol) in dichloromethane (1.5 mL) at 0 °C. The reaction mixture was stirred at 0 °C under nitrogen for 30 minutes with two cycles of gentle outgassing and nitrogen flush over the mixture. Thereupon a solution of thiomorpholine-1,1-dioxide (0.27 g, 1.99 mmol, 1.13 equiv.) and triethylamine (0.25 mL, 1.8 mmol, 1.06 equiv.) in dichloromethane (0.5 mL) was added to the reaction mixture, and the reaction mixture was warmed up to room temperature and stirred for another 4 hours. Saturated aqueous $NaHCO_3$ (5 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layer was washed with water (2 x 5 mL) and brine (2 x 5 mL). The solution was dried ($MgSO_4$) and filtered. The solvent was evaporated. The yield of artemisone **56** (39%) was determined by NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

*Oxalyl bromide in toluene*: A solution of oxalyl bromide (0.1 mL, 1.033 mmol, 0.6 equiv.) in toluene (0.5 mL) was added dropwise via cannula to a stirred suspension of DHA (501.0 mg, 1.76 mmol) in toluene (1.5 mL) at 0 °C under nitrogen. The reaction mixture was stirred at 0 °C under nitrogen for 30 minutes with a cycle of gentle outgassing. Thereupon a solution of thiomorpholine-1,1-dioxide (0.27 g, 1.99 mmol, 1.13 equiv.) and triethylamine (0.25 mL, 1.8 mmol, 1.06 equiv) in dichloromethane (0.5 mL) was added dropwise via cannula into the reaction mixture. The reaction mixture was warmed to room temperature with stirring for another 3 h. Saturated aqueous $NaHCO_3$ (5 mL) was added to quench the reaction. The organic layer was separated and the

aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layer was washed with water (2 x 5 mL) and brine (2 x 5 mL). The solution was dried ($MgSO_4$) and filtered. The solvent was evaporated. The yield of artemisone **56** (50%) was determined by $^1$H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

5.4. Preparation of artemiside **7** from glycal **16**.

HCl gas was passed over a stirred mixture of glycal **16** (241 mg, 0.91 mmol) in dichloromethane (5 mL) at 0 °C. After 10 minutes, the system was flushed with nitrogen for 15 min. Then, under an atmosphere of nitrogen, a mixture of thiomorpholine (0.10 mL, 1.0 mmol) and triethylamine (0.125 mL, 1.0 mmol) in dichloromethane (1.3 mL) was added. After stirring 1 hour at room temperature, the reaction mixture was quenched with brine (5 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layer was dried ($MgSO_4$) and then filtered. The solvent was evaporated to give a pale yellow residue. The yield (74%) of artemiside **7** was determined by $^1$H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard; recrystallization of the residue directly from methanol provided artemiside **7** (197 mg, 59%).

5.5. Preparation of artemisone **8** from glycal **16**.

HCl gas was passed over a stirred mixture of glycal **16** (94.4 mg, 0.355 mmol) in dichloromethane (2 mL) at 0 °C. After 10 minutes, the system was flushed with nitrogen for 15 minutes. Then, under an atmosphere of nitrogen, a solution of thiomorpholine-1,1-dioxide (57.3 mg, 0.398 mmol) and triethylamine (0.05 mL, 0.36 mmol) in dichloromethane (0.5 mL) was added. After stirring 4 hours at room temperature, the reaction mixture was quenched with brine (2 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layer was dried ($MgSO_4$) and then filtered. The solvent was evaporated to give a yellow residue. The yield of artemisone **8** (21%) was determined by NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard; .

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7 Whilst the discovery of artemisinin resulted in the award in 2015 of the Nobel Prize for Physiology or Medicine to Youyou Tu , the award is best seen as recognition of the achievements of all collaborating groups under Project 523. Youyou Tu was associated with the Beijing Institute Materia Medica, and certain descriptions of events in her book (Tu, Y-Y. Qinghao and Qinghaosu Derivative Drugs, Chemical Industry Publication, Beijing, 2009) and in the publication Tu YY. *Southeast Asian J. Trop. Med. Public Health* 2004; 35:250 either do not acknowledge or do not correctly assign the responsibilities for the actual discoveries made by other groups working under the Project 523. The detailed records of those discoveries are presented in the publications of refs. 1-3.

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