C-10 Ester and Ether Derivatives of Dihydroartemisinin − 10-α Artesunate, Preparation of Authentic 10-β Artesunate, and of Other Ester and Ether Derivatives Bearing Potential Aromatic Intercalating Groups at C-10

Richard K. Haynes,*[a] Ho-Wai Chan,[a] Man-Ki Cheung,[a] Wai-Lun Lam,[a] May-Kei Soo,[a] Hing-Wo Tsang,[a] Arnd Voerste,[a] and Ian D. Williams[a]

Keywords: Dihydroartemisinin / Esters / Ethers / Intercalations / Natural products

Preparative and stereochemical aspects of reactions providing new C-10 ester and ether derivatives of the antimalarial drug dihydroartemisinin (DHA, **2**) have been examined. β-Artesunate has been prepared for the first time, and has been differentiated from the antimalarial α-artesunate; the latter has been incorrectly designated as the β-epimer in *Chemical Abstracts* and some primary literature. New ester and ether derivatives bearing potential intercalating groups have been synthesised by means of the Schmidt, Mitsunobu and DCC coupling procedures, by acylation in the presence of DMAP, or by hydroxy activation with BF_3 as catalyst. When the hydroxy group of DHA acts as a nucleophile towards activated carboxy groups in acylating agents or the DCC intermediate, α-esters are obtained exclusively. When the hydroxy group is activated for displacement by nucleophiles, as in the Schmidt or Mitsunobu procedures, β-esters and β-ethers are obtained either exclusively or predominantly. An exception is represented by the Mitsunobu procedure involving DHA and 1- and 2-naphthols, in which mixtures of epimers are obtained; however, exclusive formation of β-aryl ethers takes place when the Schmidt procedure is used, with activation of the intermediate trichloracetimidate by $SnCl_2$. The latter method is therefore superior to patented procedures for the preparation of β-aryl ethers from nonbasic aryl alcohols without detectable rearrangement to *C*-aryl compounds. However, the Mitsunobu procedure is better when basic aromatic alcohols are used as nucleophiles. The formation of α-products in which the hydroxy group of DHA acts as a nucleophile is of biological significance in relation to enzyme-mediated Phase II glucuronidation of DHA, in which only the α-DHA glucuronide is formed.

Introduction

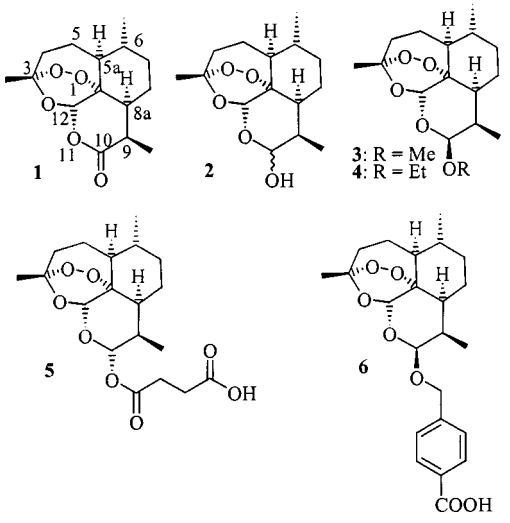
The history of the isolation of artemisinin (qinghaosu, **1**) from *Artemisia annua* (qinghao), and its development as an antimalarial drug by the Chinese is now well known.[1−4] It suffers from poor solubility in both water and oil,[5] and problems of recrudescence,[2,4,6,7] a short pharmacological half-life,[2,8] high first-pass metabolism, and poor oral bioavailability.[4] Chinese scientists, in a remarkable collaborative operation,[5,9,10,11] developed derivatives with better properties. Artemisinin was thus reduced to dihydroartemisinin (DHA, **2**),[5] and then, in an explicit recognition of the formulation problem,[5] the Chinese workers converted this into oil-soluble lactol ethers (commonly referred to in the malaria literature as "ethers"), two of the most important compounds of which are artemether (**3**) and arteether (**4**). Whilst both compounds were first made in China,[9] arteether − rather than artemether − was subsequently developed as an antimalarial drug in the West for the remarkable reason that artemether was presumed to produce the toxic metabolite methanol.[12] The compounds may be given as injections in peanut or sesame oil to comatose malaria patients.[13] However, their pharmacological half lives are not much greater than that of artemisinin, they undergo enzymatic oxidative dealkylation in vivo to dihydroartemisinin, and are hydrolysed under mildly acidic conditions.[14] Furthermore, the ethers, and the product of metabolism, dihydroartemisinin, are profoundly cytotoxic in a validated neuronal cell assay,[15] and are neurotoxic in test animals.[16] This property, whilst apparently not as yet apparent in humans treated with these drugs, imposes a potential hurdle to registration, although it may be noted that arteether has recently been registered in the Netherlands.[17] Dihydroartemisinin (**2**) has also been converted by Chinese workers into the lactol hemiester artesunate (**5**), by esterification with succinic anhydride in chloroform in the presence of amine or bicarbonate bases.[5,18]

This compound is probably the most famous of the artemisinin derivatives. It is by far the most widely used of the derivatives for treatment of malaria, particularly in tablet

[a] Department of Chemistry, The Hong Kong University of Science and Technology,
Clear Water Bay, Kowloon, Hong Kong
Fax: (internat.) + 852/2358-1594
E-mail: haynes@ust.hk
[b] Bayer AG, PF-F/S1, Geb. 6540, Bayer Landwirtschaftszentrum 40789 Monheim, Germany

  1434−193X/02/0101−0113 $ 17.50+.50/0

form, in which it is used orally in combination with a longer half-life quinoline antimalarial.[19] The water-soluble sodium salt, which is generated just prior to intravenous administration, is effective against cerebral malaria.[20] Its utility, however, is impaired by the ease of hydrolysis of the lactol ester linkage in aqueous solution.[21,22] Artelinate (**6**), developed later in high-quality work conducted at the Walter Reed Army Institute of Research in the USA, was designed to overcome the instability of artesunate.[21] As an acetal, it is acid-sensitive, but is relatively stable in aqueous solution at neutral pH. It has high in vivo activity in murine screens when administered orally,[23] but is subject to the same metabolic problems that characterize the other derivatives. It has not yet been used in humans.



In addition to their antiparasitic properties, it is of considerable interest to note that artemisinin derivatives are cytotoxic towards cancer cell lines in vitro.[24] Artemisinin (**1**) and its derivatives are significantly cytotoxic towards murine lymphocytic leukaemia (P-388), human lung carcinoma (A-549), human colon adenocarcinoma (HT-29) and other tumour cell lines.[25] However, the derivatives **3**−**5** appear to be more cytotoxic than artemisinin (**1**) towards Ehrlich ascites tumour (EAT) cells.[26] Exposure of DHA (**2**, 1−200 μM) to molt-4-lymphoblastoid cells (human leukemia) causes rapid cell death.[27]

Overall, then, there is substantial motivation for the development of new artemisinin derivatives with enhanced stability and formulation properties for treatment of malaria. Also, the potential for development as antineoplastic agents should not be overlooked − the very fact that variation in cytotoxic activity exists between known artemisinin derivatives indicates that there is clear opportunity for designing new artemisinin derivatives with enhanced binding properties in relation to selected intracellular targets.

Some time ago, we commenced a comprehensive programme designed to develop new artemisinin derivatives tailored for both antiparasitic and antineoplastic activities.[28] In this and later papers, we will describe the preparation of derivatives bearing ester, ether, aminoalkyl and aminoaryl, and aryl substituents at C-10, including those with groups designed to enhance binding to DNA by intercalation. We have recorded their activities against a range of parasites, and other pathogens, and have examined antineoplastic activities in vitro and in some cases, in vivo; this work will be described elsewhere.

Results and Discussion

Preparation of Esters

The conversion of the lactone carbonyl group of artemisinin into the lactol hydroxy group at C-10 in DHA opened pathways for further derivatisation at C-10 to give ester, carbonate and ether derivatives, largely exploited by the Chinese groups. Whilst in most reports published in China the stereochemistry of the ester and carbonate derivatives was established,[5,9,29,30] it was in some cases left undefined,[31] and there are discrepancies in the reports on the conditions required to deliver either the 10-α or the 10-β esters stereoselectively. Thus, it was reported that acylation of DHA with acid anhydrides in the presence of pyridine delivered the 10-α esters,[9,32] whereas a later report indicated that 10-β esters were stereoselectively obtained with pyridine as base.[29] Therefore, at the outset of our work, conditions that stereoselectively delivered the designated products had not been defined.

There were also inconsistencies in the literature relating to the stereochemistry of ester derivatives. Thus, before 2000, *Chemical Abstracts* (CA) designated artesunate (**5**) as the 10β-isomer, namely compound **8** (see below). Since 2000, three CA entries have appeared for artesunate, either assigning the stereochemistry for the hemisuccinyl residue at C-10 as 10-β (as in compound **8**) *or* as 10-α (as in artesunate **5**), or leaving it undefined.[33] Some reviews and primary publications either have not defined the stereochemistry of artesunate at C-10, or have designated it as 10-β.[34,35] It was nevertheless established through the conversion of artesunate (**5**) into ester derivatives that the hemisuccinyl residue in artesunate (**5**) possesses the α-configuration; this work appeared prior to the foregoing publications.[36] A survey of the literature, including that written in Chinese, and published in China,[37] reveals in fact that the β epimer **8** of artesunate has not been prepared previously.

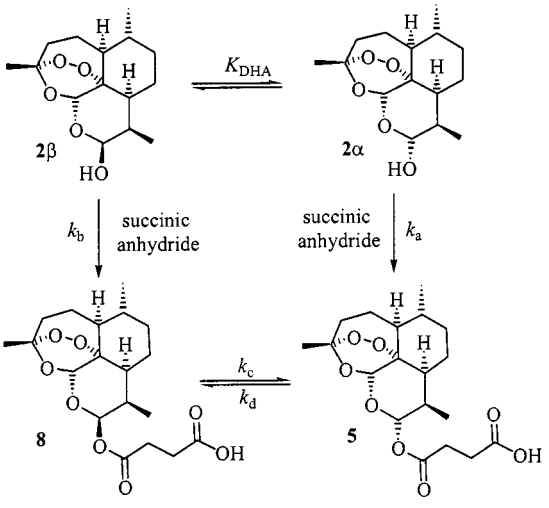
i. *α*- and *β*-Artesunates

Authentic samples of artesunate (**5**), hereinafter designated "α-artesunate", were either obtained from the World Health Organization, Geneva, or from Knoll, AG, Basel.[38] The samples were identical with the compound obtained essentially according to the Chinese procedure[5,18] by treatment of DHA (**2**) with succinic anhydride in dichloromethane in the presence of 1 equiv. of triethylamine or 4-(dimethylamino)pyridine (DMAP), as prisms, m.p. 135.1−135.2 °C, $[\alpha]_D^{21} = +13.3$ ($c = 0.76$, $CHCl_3$). That this is the α-epimer is indicated both by the ^{1}H NMR spectrum

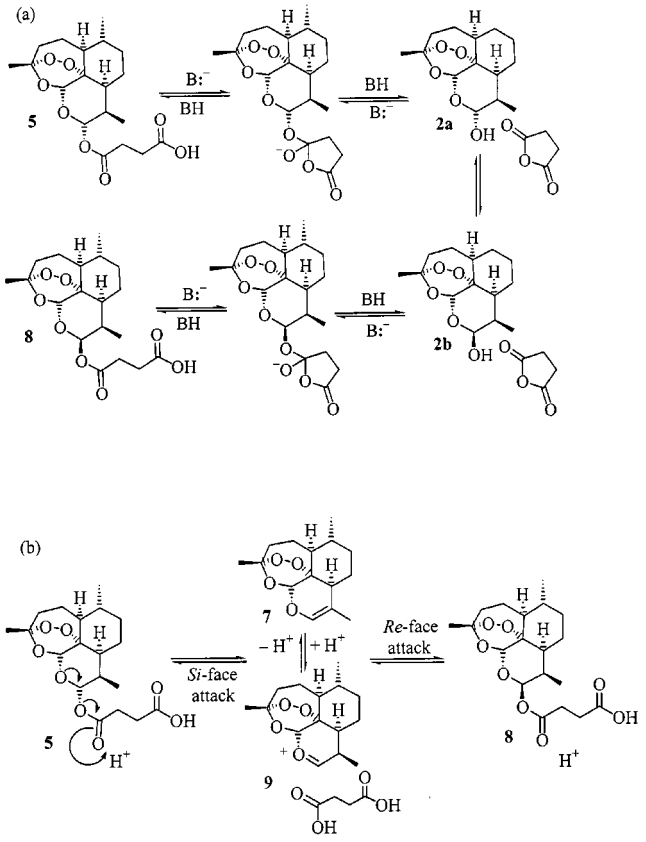
and by an X-ray crystallographic determination, as discussed below. A quantitative ^{1}H NMR spectroscopic determination (at 750 MHz) of impurities in both the commercial and synthetic samples as established by spiking of samples and construction of calibration curves showed no detectable traces ($\leq 0.04\%$) of β-artesunate (**8**), the preparation of which is also described below.

Why does such an acylation reaction give only the α epimer? Bulk solid DHA is likely to be the β epimer **2β**, and an X-ray crystallographic determination has indicated that a crystal of the solid compound is the β epimer.[36] Dissolution of vacuum-dried, bulk solid DHA in $CDCl_3$ provides a solution consisting solely of **2β**, which slowly equilibrates over 10 h to a 1:1 mixture of **2α** and **2β**. This closely parallels the original observation.[36] The rate and extent of equilibration of the epimers in solution is dependent upon the solvent. In CD_2Cl_2, the equilibrium ratio of **2α/2β** is 1:1.35. Addition of 1 equiv. of DMAP or triethylamine (the amount of base used in the preparation of α-artesunate) causes a change in the equilibrium ratio to about 1.2−1.5:1 in favour of **2α**. In methanol[36] and acetone the equilibrium ratio of **2α/2β** is 2:1 and in dimethyl sulfoxide 3:1.[39] In all cases in which bases are added to dichloromethane, or polar solvents are used, equilibrium is established rapidly, usually within 15 min.

Thus, two possibilities for exclusive formation of α-artesunate (**5**) are apparent. Firstly, acylation of *both* epimers of DHA (Scheme 1) takes place with comparable rate constants k_a and k_b for each reaction, but β-artesunate (**8**) is less stable than α-artesunate (**5**); that is, formation of the latter is thermodynamically favoured. Whilst acylation of DHA would normally be expected to be irreversible, in this special case, the product is a lactol hemiester with a free carboxy group, and it is therefore *feasible* that β-artesunate may undergo epimerization through distinct intramolecular processes (i.e., $k_c >> k_d$) (Scheme 1; see also Scheme 2). The second possibility is that interconversion of the artesunate epimers does not take place (i.e., $k_c = k_d \approx 0$); that



Scheme 1. Acylation of DHA epimers and hypothetical equilibration of artesunate epimers



Scheme 2. (a) Putative base-catalysed epimerization of artesunate and (b) putative acid-catalysed epimerization of artesunate

is, acylation of the α epimer **2α** is faster than acylation of the β epimer **2β** for kinetic reasons.

To determine the relative stabilities of both α- and β-artesunate, computational studies were performed with AM1 and PM3 semiempirical methods (PC-Spartan Plus Version 1.5; Wavefunction Inc.). The heats of formation (Table 1) showed that both the epimers of DHA, and of artesunate, had similar thermodynamic stabilities.

Thus, the exclusive formation of α-artesunate cannot be attributed to the relative thermodynamic stability of the epimers. Indeed, it is experimentally demonstrable that no detectable epimerization of α-artesunate takes place under the conditions of the acylation reactions. Therefore, k_c and k_d are insignificant, and the exclusive formation of α-artesunate (**5**) in the acylation is a kinetic phenomenon; that is, $k_a >> k_b$. Thus, in the production of α-artesunate, the α epimer **2α** of DHA is consumed very quickly. Accordingly, K_{eq} (Scheme 1) is shifted towards the right-hand side in favour of **2α**.

Inspection of the modelled 10-α DHA epimer **2α** (Figure 1) reveals that the hydroxy group is equatorial, in line with NMR spectroscopic data on the epimers, in which H-10 in **2α** displays a coupling constant with H-9 of 9.2 Hz, corresponding to a *trans*-diaxial coupling within a chair pyranose ring.[36] In the 10-β epimer **2β**, the hydroxy group is axial (Figure 1); with a 1,3-diaxial interaction with C8−8a, it is in a substantially more crowded environment

Table 1. AM1 and PM3 computational studies on DHA and artesunate epimers **5** and **8**

Compound	Heat of formation (AM1) [kcal mol^{-1}]	Heat of formation (PM3) [kcal mol^{-1}]
α-DHA (**2α**)	−177.709	−170.383
β-DHA (**2β**)	−177.774	−167.698
α-artesunate (**5**)	−302.857	−298.579
β-artesunate (**8**)	−303.793	−296.534

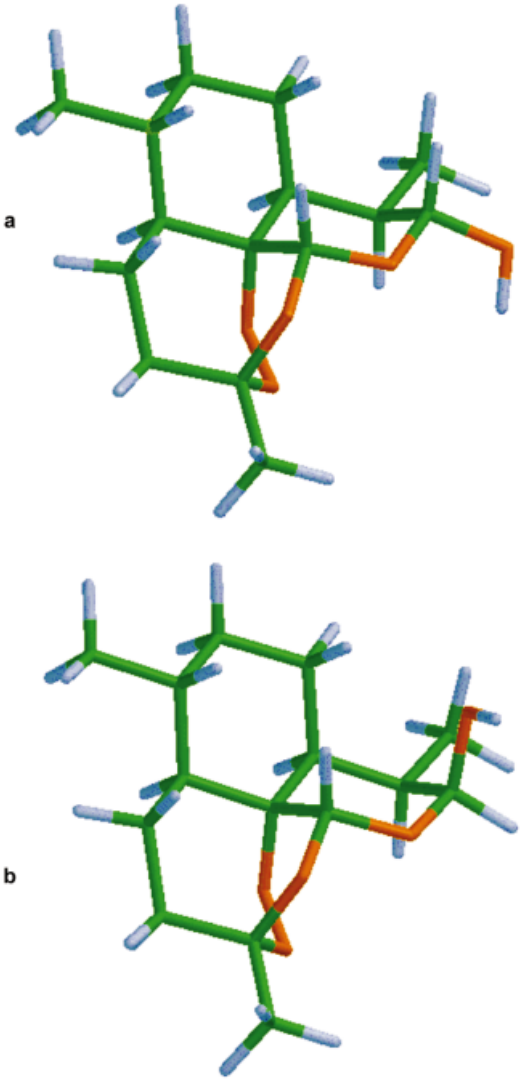


Figure 1. AM1-geometry optimised structures; (a) α-DHA (**2α**) and (b) β-DHA (**2β**)

than is the equatorial hydroxy group in **2α**. Thus, this steric effect raises the energy of the transition state for the acylation reaction producing the β epimer, and acylation of the α epimer of DHA is the preferred reaction.

Because of the favourable thermodynamics, initial attempts to prepare the hitherto unrecorded β-artesunate (**8**) focussed on epimerization of α-artesunate (**5**). Base- or acid-catalysed reactions, proceeding either through DHA as an intermediate, or through oxonium ion **9** and the glycal **7**, as depicted in Scheme 2 can, among others, be envisioned (Scheme 2).

However, treatment of α-artesunate in $CDCl_3$ with DMAP, and analysis by ^{1}H NMR spectroscopy indicated partial, slow decomposition (18%) to a 1:1 mixture of DHA epimers after 11 d. For the attempted acid-catalysed epimerization, α-artesunate and succinic acid in dichloromethane with boron trifluoride−diethyl ether (5 mol%) at 20 °C gave only the glycal **7**. With 30 mol% of the Lewis acid, **7** was the major product, together with minor amounts of DHA, dimeric dihydroartemisininyl ethers and other compounds. Treatment of **7** with succinic acid and catalytic sulfuric acid in dichloromethane (10 mL) at ambient temperature rapidly gave a complex mixture; with succinic acid as the only proton source, the glycal remained intact.

Thus, a method other than the acylation of DHA had to be used to prepare β-artesunate (**8**). It had to rely on hydroxy activation of DHA to provide an adduct bearing the activated hydroxy group with the α configuration, and on the use of succinate as nucleophile to displace the activated hydroxy group by reaction from the β-face. Of a number of possibilities, trichloroacetimidate-mediated glycosylation, introduced by Schmidt and Hoffmann[40] and not hitherto used for the preparation of DHA derivatives, was attractive. It proceeds through a reaction between the hydroxy group and trichloroacetonitrile to provide an intermediate trichloroacetimidate. Lewis acid activation of the trichloroacetimidate may be used, depending upon the type of external nucleophile used to displace the group. For carboxylic acid nucleophiles, activation is brought about by protonation of the trichloroacetimidate. Thus, DHA (**2**) in dichloromethane containing trichloroacetonitrile was treated with a catalytic amount of 1,8-diazabicyclo[5.4.0]undecane (DBU) at 20 °C. The intermediate trichloroacetimidate formed in situ was treated directly with succinic acid to yield β-artesunate (**8**) (45% yield), as transparent plates, m.p. 97.6−98.2 °C, $[\alpha]_D^{19} = +118.5$ (c = 0.92 $CHCl_3$).

Sections of 300 MHz ^{1}H NMR spectra of both α-artesunate (**5**) and β-artesunate (**8**), including the signals due to H-10 and H-12, are given in Figure 1. In α-artesunate, H-10 at δ = 5.80 displays J = 9.9 Hz in its coupling with H-9, corresponding to a *trans*-diaxial arrangement of these protons in a chair pyranose ring (Figure 2a and Figure 3). In β-artesunate, H-10 at δ = 6.28 displays J = 3.3 Hz in its

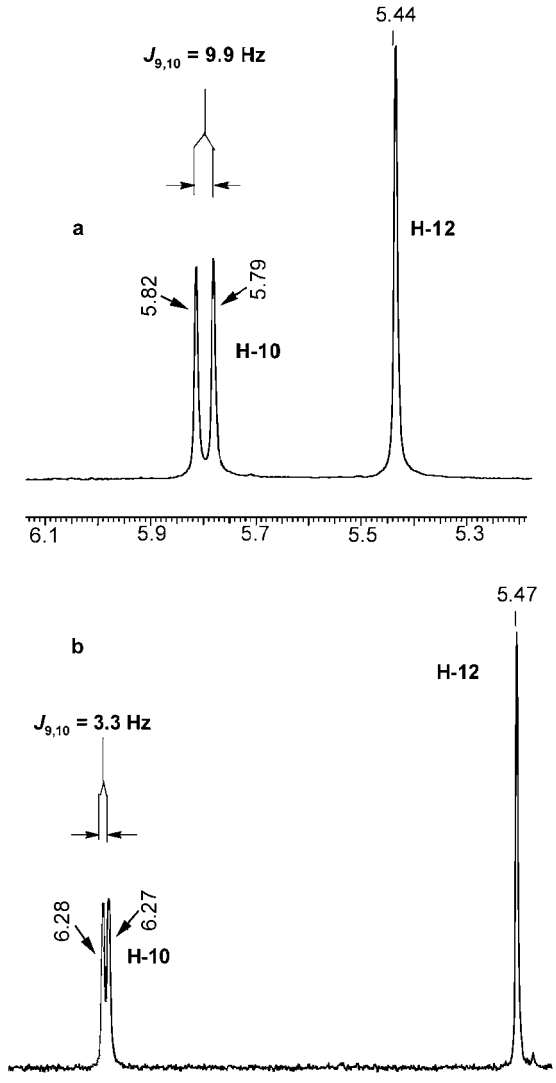


Figure 2. 300 MHz ^{1}H NMR spectrum of (a) α-artesunate (**5**) and (b) β-artesunate (**8**), showing expansion in the region δ = 5.2−6.4 and analysis of the signal due to H-10

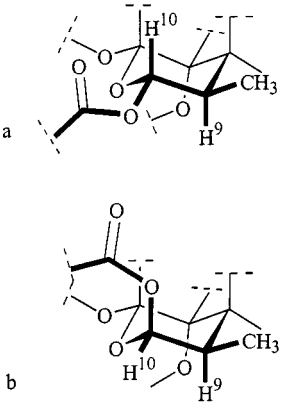


Figure 3. Part structures of (a) α-artesunate (**5**), indicating *trans*-diaxial relationship of H-9 and H-10, and (b) β-artesunate (**8**), indicating *cis*-equatorial-axial relationship between H-9 and H-10

coupling with H-9; this is consistent with a *cis*-equatorial-axial arrangement of these protons in a chair pyranose ring (Figure 2b and Figure 3b). The hemisuccinyl side chain is therefore in the β configuration. This data corresponds well with that used for the assignment of configuration at C-10 in DHA derivatives,[5,29,30,36] *providing that the pyran ring maintains a chair conformation in both epimers.* As will be reported later,[41] certain bulky 10-β substituents cause the pyran ring to adopt a twist-boat conformation, and the coupling constant principle cannot be applied under these conditions.

Structural confirmation was provided by X-ray crystallographic analysis of both the α- and the β-artesunates (Figure 4). In each plot the chair conformation of the pyran ring, and the stereochemistry at C-10, are clearly defined. X-ray structural parameters are summarized in Table 2. In agreement with the precedent provided by *O*-glycosidation chemistry involving the Schmidt reaction,[40] nucleophilic substitution at the anomeric centre proceeds through an S_N2 reaction involving axial displacement from the *Re*- or β-face.

ii. Other Esters

Schmidt and Mitsunobu Procedures

Hydroxy activation of DHA by means of the Mitsunobu reaction,[42] which had not previously been used to prepare esters of DHA, worked well. Thus, treatment of DHA with triphenylphosphane−diethyl azodicarboxylate and aromatic carboxylic acids in THF stereoselectively gave the 10-β derivatives **10**−**22** (Table 3). Here the Schmidt procedure was also superior, as demonstrated by the greater yields of β-benzoate ester **10** from benzoic acid, and the β-naphthoate **11** from 1-naphthoic acid (Table 3).

The β-stereochemistry was again clearly evident from ^{1}H NMR spectroscopic data. For the Mitsunobu process, an S_N1 reaction involving axial attack of the nucleophile on the oxonium cation intermediate **9** may be involved.[43] In the latter case, the pyran ring adopts a twisted half-chair conformation, and C-10 is exposed to a stereoelectronically preferred axial attack from the carboxy group on the *Re*- or β-face. An ion-pair effect operating in the S_N1 reaction may act to inhibit addition from the *Si*-face. The change of stereochemistry with reference to DHA is apparent in Figure 5, in which the minimized-energy conformer (AM1, Titan, Schrödinger Inc.) of the oxonium ion **9** is presented; the cation plane is tilted away from the axial C8−8a bond, and the reaction centre therefore has a very different steric environment than that about the hydroxy group in the β epimer of DHA (cf. Figure 1).

Acylation with Anhydrides and Acid Chlorides

Acylation of DHA (**2**) has been carried out in the presence of base to give esters, the configurations of which were reported to be dependent on the base used.[5,9,29,30,32] It was also reported that the carboxy group activating agent DCC in the presence of DMAP in dichloroethane or dichloromethane gave 10-α esters.[29,30,36] A later report also described

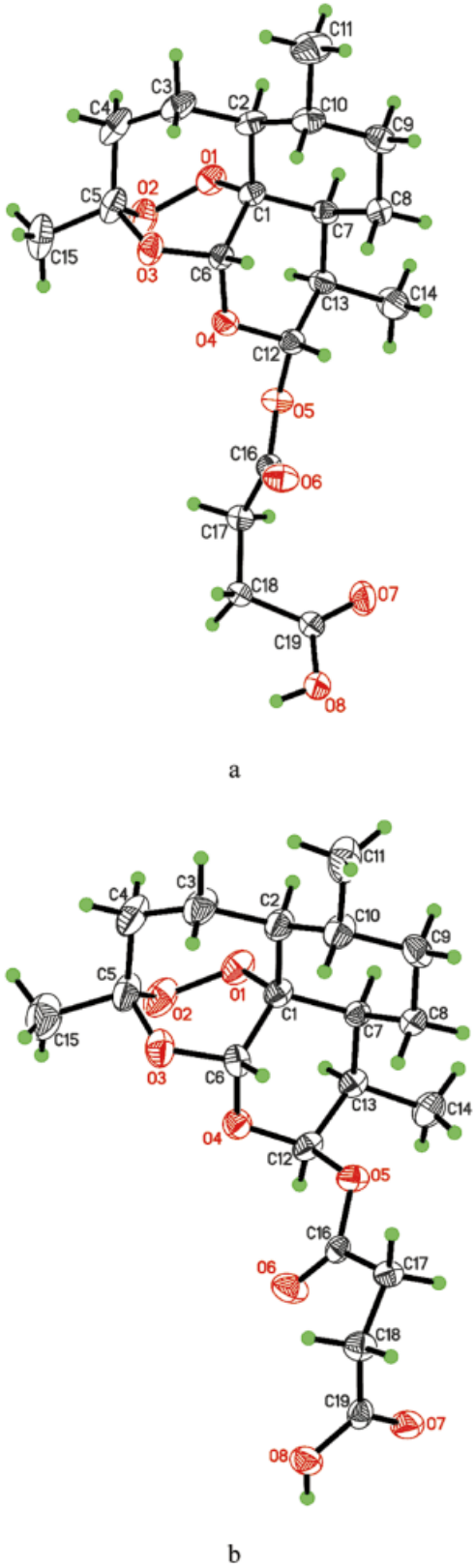


Figure 4. ORTEP plots of (a) α-artesunate (**5**) and (b) β-artesunate (**8**), indicating stereochemistry at C-10 (C-12; crystallographic numbering) and chair conformation of pyran ring; crystallographic numbering is given

the use of DCC/DMAP in dichloromethane to give a 10-α ester, without experimental details.[44]

In the event, DHA (**2**) and anhydrides or acid chlorides in the presence of DMAP, pyridine or triethylamine in dichloromethane gave the 10-α esters **23**−**25** (Table 4); the base thus has no effect on the stereochemistry of acylation. The stereochemistry was apparent from ^{1}H NMR spectroscopic data (H-10, $J_{10,9}$ = 9.8 Hz), which correlated with data for α-artesunate, and literature data.[45] In addition, NOE experiments involving irradiation of the doublet at δ = 5.80 (H-10) in **23** gave no enhancement in the multiplet at δ = 2.55 (H-9). The benzoyl derivative **25** was also synthesised by carboxy activation with DCC. Compounds **23** and **25** have been prepared previously.[9] The β-benzoate ester **10** and the α-benzoate ester **25** are useful compounds for the preparation and examination of mechanistic aspects of formation of C-10-arylated artemisinin derivatives, to be described in a later paper.

In summary, reactions involving hydroxy activation of DHA, as in the Schmidt and Mitsunobu procedures, exclusively provided β-esters; that is, activation of hydroxy groups by these procedures provided α-activated hydroxy intermediates, which underwent S_N2 or S_N1 substitution by carboxylate from the *Re*- or β-face. Direct acylation reactions, in which the hydroxy group of DHA acts as a nucleophile towards activated carboxy groups, as in acyl chlorides or in the activated ester produced in the DCC method, provided the α-esters.

From a biological viewpoint, acylation of DHA is important in Phase II metabolism. It is significant to note that isoforms of glucuronyl uridine diphosphate exclusively generate the α-DHA-β-glucuronide;[46] that is, biological acylation − in line with the laboratory acylation − operates exclusively on the α epimer of DHA. In this context, the α-DHA-α-glucuronide has been prepared from DHA by treatment with acetobromo-α-D-glucuronic acid in the presence of silver carbonate.[47]

Preparation of Ethers

Chinese groups were the first to prepare lactol ethers or acetals by treatment of DHA (**2**) with alcohols in the presence of boron trifluoride−diethyl ether.[5,9,29,32] The reaction has been well exploited by the Walter Reed group in the synthesis of water-soluble ethers such as the sodium salt of artelinate (**6**)[21,48] and alkylbenzylic ethers designed to inhibit oxidative metabolism.[49] Other groups have also used the reaction to prepare functionalized ethers[50,51,52] and thioethers.[53] Mixtures of epimers enriched in the β isomer are formed, as demonstrated by the preparation of artemether, which gave a 78:22 mixture of the β and α epimers.[9] The reaction is under thermodynamic control, and the α epimer may be equilibrated to the mixture enriched in the β epimer by treatment with boron trifluoride−diethyl ether. Operation of the thermodynamic anomeric effect[43] in the enhanced formation of the β-axial ethers is clearly in evidence.

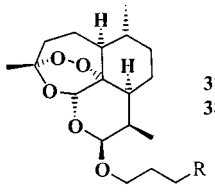
In the current work, the primary emphasis was on the preparation of ethers bearing potential intercalating groups,

Table 2. X-ray parameters for α-artesunate (**5**) and β-artesunate (**8**)

X-ray parameters	α-Artesunate (**5**)	β-Artesunate (**8**)
Empirical formula	$C_{19}H_{28}O_8$	$C_{19}H_{28}O_8$
Molecular mass	384.43	384.41
Temperature [K]	293(2)	293(2)
Wavelength [Å]	0.71073	0.71073
Crystal system	orthorhombic	orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions [Å, °]	a = 9.853(1), α = 90 b = 10.528(1), β = 90 c = 18.783(3), γ = 90	a = 6.858(1), α = 90 b = 7.6810(10), β = 90 c = 36.969(6), γ = 90
Volume [Å^3]	1948.4(4)	1947.4(5)
Z	4	2
Density (calculated) [mg/m^3]	1.310	1.311
Absorption coefficient [mm^{-1}]	0.102	0.102
F(000)	824	824
Crystal size [mm]	1.2 × 1.2 × 1.2	1.6 × 0.8 × 0.8
θ range for data collection	2.33 to 27.47°	1.10 to 24.99°
Index range	$0 \le h \le 12$, $0 \le k \le 13$, $-1 \le l \le 24$	$0 \le h \le 8$, $0 \le k \le 9$, $-1 \le l \le 43$
Reflections collected	2645	2066
Independent reflections	2622 [R_{int} = 0.0154]	2049 [R_{int} = 0.0152]
Completeness to θ [°]	27.47 (98.5%)	24.99 (98.6%)
Refinement method	Full-matrix, least-squares on F^2	Full-matrix, least-squares on F^2
Data/restraints/parameters	2622/0/244	2049/0/244
Goodness-of-fit on F^2	1.010	1.024
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0415, $wR2$ = 0.0989	$R1$ = 0.0675, $wR2$ = 0.1569
R indices (all data)	$R1$ = 0.0574, $wR2$ = 0.1088	$R1$ = 0.1342, $wR2$ = 0.2022
Largest diff. peak and hole [e Å^{-3}]	0.183 and −0.167	0.257 and −0.324

although others bearing lipophilic groups were also targeted for examination of their antiparasitic activity. The 10β ethers **26**−**36** were prepared by treatment of DHA (**2**) with the corresponding alcohol under BF_3 catalysis conditions in ether (Table 5). The stereochemistry was established from ^{1}H NMR spectroscopic data, in which H-10 displayed a coupling of ca. 3.5 Hz to H-9, corresponding to a *cis* arrangement of these protons.[9,12,48,49] No attempt was made to characterize the smaller amounts of α epimer formed in these reactions.

Compound **35** has been prepared previously from DHA under Lewis acid catalysis conditions.[50] Again, the Schmidt reaction worked very well in this case although, in contrast to those reactions involving preparation of esters, a Lewis acid − namely, $SnCl_2$ − was now required to activate the trichloroacetimidate ester intermediately prior to addition of the alcohol, in line with previous experiences with this reaction.[40] The bromo substituent in compound **35** was readily displaced by aniline or morpholine to furnish the amines **37** (54%) and **38** (90%). Compound **38** has been described in the secondary literature without data.[11]

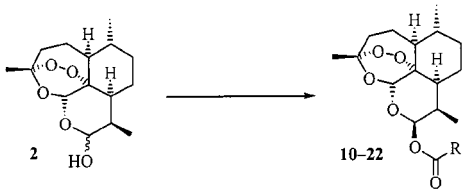


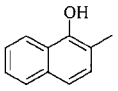
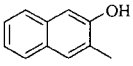
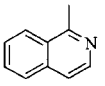
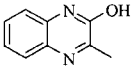
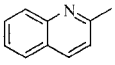
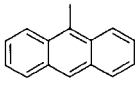
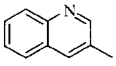
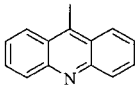
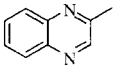
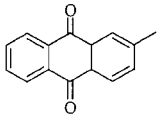
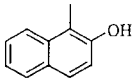
37: R = -NHPh
38: R = 1-morpholino

On the basis of their pronounced biological activities, to be described elsewhere, both epimer pairs **41** and **43**, and **42** and **44**, of the lactol ethers produced from DHA (**2**) and 1- and 2-naphthalenemethanol, respectively, were required. Under standard conditions, consisting of treatment of DHA (**2**) and the alcohol with boron trifluoride−diethyl ether in ether, the ratio was about 2:1 in favour of the less polar 10β epimer (Table 6). DHA (**2**) was converted by treatment with trimethylsilyl chloride in dichloromethane in the presence of triethylamine into the α-TMS ether **40**. Coupling with the TMS ether of 2-naphthalenemethanol in the presence of TMSOTf also gave mixtures of epimers, with a higher temperature favouring the β epimer **43**. The method was based on that reported by the Walter Reed group, in which the β-TMS ether of DHA was coupled with protected sugar derivatives.[54] However, by far the most effective method for preparing the β epimer **43** was through use of the Schmidt reaction; treatment of DHA with trichloroacetonitrile in the presence of catalytic DBU thus provided the intermediate trichloroacetimidate, which gave the product in 77% yield upon activation with catalytic $SnCl_2$ and treatment with 2-naphthalenemethanol; the α epimer was not detectable (Table 6).

It has been found in our laboratory, and elsewhere,[55] that direct coupling of aromatic alcohols with DHA catalysed by boron trifluoride−diethyl ether is complicated by O → C rearrangement of the aromatic ether, a known feature accompanying *O*-glycosidation reactions of sugars with aromatic alcohols in the presence of Lewis acid catalysts.[56]

Table 3. Esters from DHA and aromatic carboxylic acids by Mitsunobu and Schmidt procedures



Product No.	R =	Procedure, Yield (%)	Product No.	R =	Procedure, Yield (%)
10		Mitsunobu 53 Schmidt 80	17		Mitsunobu 17
11		Mitsunobu 38 Schmidt 85	18		Mitsunobu 28
12		Mitsunobu 25	19		Mitsunobu 33[a]
13		Mitsunobu 55	20		Mitsunobu 63
14		Mitsunobu 5	21		Mitsunobu 56
15		Mitsunobu 36	22		Mitsunobu 74
16		Mitsunobu 51			

[a] Unstable compound; characterized by spectroscopic data.

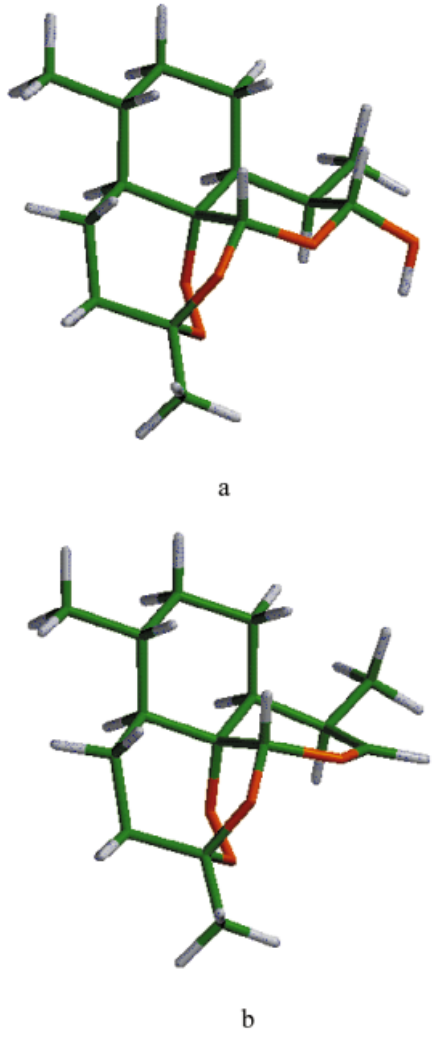
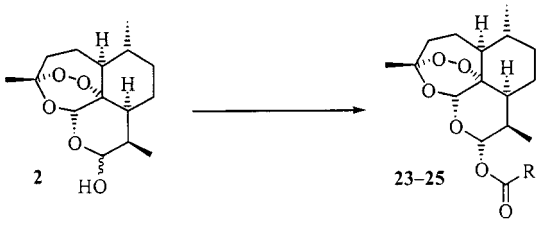


Figure 5. AM1-geometry optimised structures; (a) α-DHA (**2α**) and (b) oxonium ion **9**

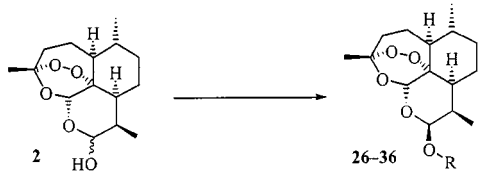
The problem was partially overcome through use of the Mitsunobu[42] procedure, previously applied to *O*-glycosidation of pyranoses, which proceeds with inversion of configuration at the anomeric centre.[56,57] With heteroaromatic alcohols, aromatic ethers **45** and **46** with the 10β configuration were exclusively obtained, albeit in moderate yields (Table 7). However, the limitations of the Mitsunobu method were surprisingly exposed in the coupling of 1- and 2-naphthols, which gave mixtures of α epimers **48** and **50** and β epimers **47** and **49** in low yields. The glycal by-product **7** was also formed in relatively high yield. This compound could only be removed by treating the crude product mixture with *m*-chloroperoxybenzoic acid to convert it into the more polar epoxide **51**,[58,59] which could then be separated from the required products by column chromatography. The problem of accessibility of the naphthyl ethers was again solved through the use of the Schmidt procedure. Thus, treatment of the trichloroacetimidate intermediates, formed from the reaction between the α epimer of DHA with 1- and 2-naphthols in the presence of $SnCl_2$, exclusively gave the β epimers **47** and **49** in yields greater than 70%. Given its simplicity and ease of execution, this method

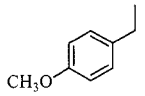
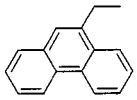
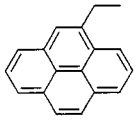
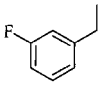
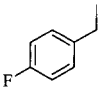
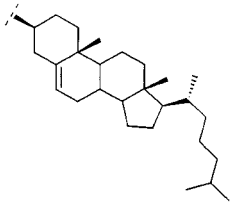
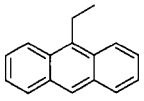
Table 4. Esters from acylation of DHA



DHA in CH_2Cl_2 +	Product No.	R =	Yield (%)
Ac_2O, DMAP	**23**	CH_3	98
4-nitrobenzoyl chloride, NEt_3	**24**	$C_6H_4NO_2$-*p*	82
benzoyl chloride, NEt_3	**25**	C_6H_5	79
benzoic acid, DCC	**25**	C_6H_5	35

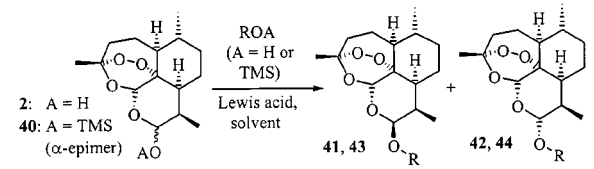
Table 5. Ethers from DHA and alcohols with BF_3–diethyl ether

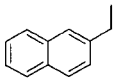
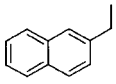
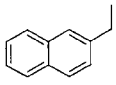


Product No.	R =	Yield (%)	Product No.	R =	Yield (%)
26		96	**32**		83
27		67	**33**		52
28		76	**34**		29
29		83	**35**		52[a]
30		83	**36**		73
31		64			

[a] Obtained in 63% yield by the Schmidt procedure (see text and Exp. Sect.).

Table 6. Ethers from DHA or DHA α-TMS ether (**40**) and 1- and 2-naphthylmethanol and 2-naphthylmethanol TMS ether



R =	A	DHA or DHA α-TMS ether (**40**) Reaction conditions	β-Epimer Product no.	Yield (%)	α-Epimer Product no.	Yield (%)
	H	**2** $BF_3{\cdot}OEt_2$ (0.2 equiv.), Et_2O, 0–20 °C	**41**[a]	34	**42**	19
	H	**2** $BF_3{\cdot}OEt_2$ (0.2 equiv.), Et_2O, 0–20 °C	**43**	50	**44**	28
	TMS	**40** TMSOTf (0.04 equiv.), CH_2Cl_2, –78 °C	**43**	33	**44**	12
	TMS	**40** TMSOTf (0.04 equiv.), CH_2Cl_2, 0 °C	**43**	84	**44**	11

[a] Obtained as sole product from DHA (**2**) and 1-naphthylmethanol in 78% yield by the Schmidt procedure (see text and Exp. Sect.).

for the preparation of aromatic ethers from DHA and non-basic aromatic alcohols is superior to that employing silver perchlorate–trimethylsilyl triflate, reported after completion of the current work,[60] and which has been presented in a patent application.[61]

It is noteworthy that etherification under Mitsunobu conditions works with heteroaromatic alcohols to give the 10β-ethers, whereas with 1- and 2-naphthols, relatively poor yields of both epimers are obtained, in contrast to the success with the Schmidt procedure (Table 7). The results confirm that a clean S_N2 pathway operates for the Schmidt reaction, and suggest that both S_N2 and S_N1 pathways operate in the Mitsunobu reaction, with the relative amounts of each dependent upon the reactivity of the nucleophile; that is, the S_N1 pathway becomes more important for the less nucleophilic naphthols, as compared to their more nucleophilic heteroaromatic counterparts. In such cases, the

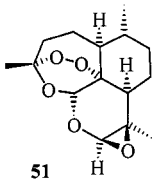
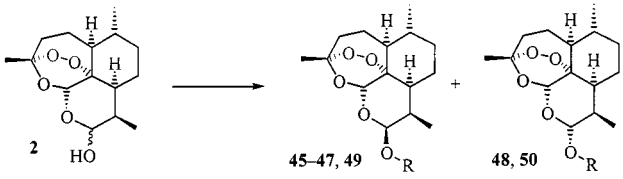
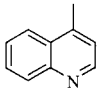
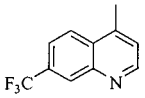
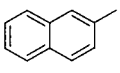
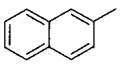


Table 7. Ethers from DHA and aromatic alcohols by Mitsunobu and Schmidt procedures; glycal **7** formed in varying amounts in all cases (see text and Exp. Sect.)



Product No.	R =	Procedure, Yield (%)	Product No.	R =	Procedure, Yield (%)
45 (β)		Mitsunobu 42	**46** (β)		Mitsunobu 66
47 (β)		Mitsunobu 17 Schmidt 73	**48** (α)		Mitsunobu 10 Schmidt 0
49 (β)		Mitsunobu 5 Schmidt 77	**50** (α)		Mitsunobu 11 Schmidt 0

oxonium cation **9** (cf. Scheme 2 above) is an intermediate, and formation of both epimers from the naphthols indicates attack by the naphthol at both the *Si*-(β-) and *Re*-(α-)faces of the cation. The relatively large amounts of the glycal **7**

generated in the Mitsunobu reaction also indicate the operation of a competing E1 process.

Conclusion

The stereochemistry of the conversion of DHA (**2**) into esters and ethers has been clearly defined. α-Esters are exclusively obtained when the hydroxy group of DHA acts as the nucleophile, β-esters when it is activated for displacement, as in the Schmidt and Mitsunobu procedures. Hydroxy activation in this way also provides β-ethers, with the exception of the Mitsunobu procedure with 1- and 2-naphthols, when α-ethers are also obtained. As previously recorded, Lewis acid catalysed ether formation results in formation of mixtures enriched in the β epimer, as is in fact to be anticipated on the basis of the anomeric effect. This is to be discussed in more detail in a later paper.

The biological significance of the α-acylation process lies in the observation that Phase II glucuronidation of DHA exclusively provides the α-DHA epimer. The biological activities of the compounds described here are discussed in detail elsewhere.

Experimental Section

General Remarks: All reactions were carried out under nitrogen. Dihydroartemisinin was obtained either from the Kunming Pharmaceutical Corporation, Kunming, China, or from Haphacen, Hanoi College of Pharmacy, Vietnam, and used without further purification. The following solvents were dried prior to use: ethyl acetate from magnesium sulfate, hexane (calcium chloride), dichloromethane (calcium hydride), triethylamine (calcium hydride and stored over potassium hydroxide pellets), and THF (sodium in benzophenone). TLC was performed with Merck Kieselgel 60 F_{254} plates, with viewing under ultraviolet light (254 nm) and/or by heating after treatment with 5% ammonium molybdate in 10% concentrated sulfuric acid. Column chromatography was performed with Merck 60 silica gel (0.04−0.063 mm). NMR spectroscopic data, unless otherwise stated, were obtained in $CDCl_3$. ^1H, ^{13}C and ^{19}F spectra were obtained with a Bruker ARX 300 spectrometer operating at 300, 75 and 282 MHz, respectively. Melting points were carried out with an Electrothermal 9100 melting point apparatus and are uncorrected. Mass spectroscopic data were obtained with a Finnigan TSQ 7000 Mass Spectrometer. Infrared spectra were recorded either with a Perkin−Elmer PC 16 or a Perkin−Elmer Spectrum One spectrometer. Polarimetry analyses were performed with a Perkin−Elmer model 241 spectrometer. Elemental analyses were obtained from MEDAC Ltd, Surrey, UK.

β-Artesunate (8): Trichloroacetonitrile (1.0 mL, 100 mmol) and 1,8-diazabicyclo[5.4.0]undecane (37 μL, 0.25 mmol) were added to a solution of dihydroartemisinin (DHA, **2**) (1.420 g, 5.0 mmol) in dichloromethane (50 mL). This was then stirred under nitrogen at 20 °C for 2 h. Excess trichloroacetonitrile and solvent were then evaporated in vacuo, and the residue was taken up in dry dichloromethane (50 mL). The resulting solution, containing the trichloroacetimidate of DHA, was cooled in an ice bath, and a suspension of succinic acid (2.95 g, 25.0 mmol) in dichloromethane (125 mL) was added in a single portion. The resulting mixture was warmed gradually to 20 °C over 4 h, and then poured into aqueous H_2SO_4 (2 M, 200 mL). The two-phase mixture was separated, and the aqueous phase was extracted with dichloromethane (2 × 50 mL). The organic phases were combined and then dried with anhydrous sodium sulfate, and the solvents were evaporated to dryness in vacuo. The residue was chromatographed on silica gel (250 g), and the fraction that was eluted with hexane/ethyl acetate/methanol (60:30:5) was crystallized to yield β-artesunate (873 mg, 45%) as a colourless solid. The analytical sample was obtained by recrystallization from ethyl acetate/hexane as colourless, needle-shaped crystals, m.p. 97−98.5 °C. When the mother liquor was exposed to a humid atmosphere, it was noted that co-crystallization of DHA took place together with the desired β-artesunate. To circumvent this, the crude β-artesunate was first taken up in dry dichloromethane and then diluted with anhydrous hexane to the first point of cloudiness. Subsequent crystallization afforded β-artesunate as colourless, rectangular plates, m.p. 97.6−98.2 °C. $[\alpha]_D^{19}$ = +118.5 (c = 0.92 $CHCl_3$). ^1H NMR: δ = 0.87 (d, J = 7.5 Hz, 3 H), 0.9−1.2 (m, 4 H), 1.2−2.0 (m, 12 H), 1.9−2.1 (m, 1 H), 2.3−2.5 (m, 1 H), 2.6−2.7 (m, 5 H), 5.47 (s, 1 H, H-12), 6.28 (d, J = 3.5 Hz, 1 H, H-10). ^{13}C NMR: δ = 12.4, 20.2, 24.1, 24.6, 25.9, 28.7, 29.1, 29.8, 34.4, 36.2, 37.4, 43.8, 52.3, 80.5, 88.7, 95.2, 104.4, 170.7, 174.3. − IR (film): $\tilde{\nu}_{max}$ = 2950, 2876, 1744, 1714, 1450, 1378, 1362, 1252, 1170, 1120, 1104, 1076, 1056, 1034, 1014, 978, 948, 906, 872, 860, 824, 732 cm^{-1}. MS (CI, NH_3): m/z (%) = 402 [MNH_4^+]. $C_{19}H_{28}O_8$ (384.4): calcd. C 59.36, H 7.34; found C 59.44, H 7.38.

10β-Dihydroartemisinyl Benzoate (10). − Procedure 1: Triphenylphosphane (524 mg, 2.0 mmol) and diethyl azodicarboxylate (315 μL, 2.0 mmol) were added to a cold (0 °C), stirred solution of DHA (**2**, 568 mg, 2.0 mmol) and benzoic acid (244 mg, 2.0 mmol) in tetrahydrofuran (15 mL). The reaction mixture was allowed to warm to room temperature overnight with stirring. The solvent was removed under reduced pressure and the residue was submitted to chromatography with ethyl acetate/hexane (10:90) to afford the product as a white powder (419 mg, 53%), m.p. 151−153 °C. $[\alpha]_D^{20}$ = +119 (c = 0.19 $CHCl_3$). ^1H NMR: δ = 0.98 (d, J = 7.4 Hz, 3 H, 9-Me), 1.02 (d, J = 6.1 Hz, 3 H, 6-Me), 1.45 (s, 3 H, 3-Me), 1.33−2.10 (m, 10 H), 2.42 (ddd, J = 17.4, 13.3, 3.9 Hz, 1 H), 2.91−3.01 (m, 1 H, H-9), 5.58 (s, 1 H, H-12), 6.52 (d, 1 H, H-10, J = 3.4), 7.43−8.03 (m, 5 H, Ar-H). ^{13}C NMR: δ = 12.50, 20.14, 24.25, 24.50, 25.78, 29.98, 34.43, 36.10, 37.44, 43.84, 52.27, 80.42, 88.63, 88.66, 95.29, 104.30, 128.39, 129.48, 129.96, 133.03, 165.31. IR (film): $\tilde{\nu}_{max}$ = 2942, 2872, 1724, 1452, 1378, 1268, 1176, 1114, 1064, 1024, 976, 902, 858, 832, 754, 712 cm^{-1}. MS (EI): m/z (%) = 388 [M^+]. $C_{22}H_{28}O_6$ (388.5): calcd. C 68.02, H 7.21; found C 68.02, H 7.41. − **Procedure 2:** Trichloroacetonitrile (0.11 mL, 1.1 mmol) and 1,8-diazabicyclo[5.4.0]undecane (7.5 μL, 0.05 mmol) were added to a stirred solution of DHA (**2**, 284 mg, 1.0 mmol) in dichloromethane (5 mL). After 18 h, the mixture was added to a stirred solution of benzoic acid (340 mg, 3.0 mmol) in dichloromethane (5 mL). After a further 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), and water (10 mL) was added. The organic layer was separated and dried (Na_2SO_4). Filtration and concentration of the filtrate gave a residue, which was purified as described above to give the product (310 mg, 80%).

10β-Dihydroartemisinyl 1′-Naphthoate (11). − Procedure 1: This was as for procedure 1 described for compound **10** above. The product was obtained from DHA (**2**, 568 mg, 2.0 mmol) and 1-naphthoic acid (344 mg, 2.0 mmol, 1 equiv.) as white clusters of fine needles (165 mg, 38%), m.p. 152.4−153.3 °C. $[\alpha]_D^{20}$ = +98.3 (c = 0.041, $CHCl_3$). ^1H NMR: δ = 0.97 (d, J = 6.0 Hz, 3 H, 9-Me), 1.03 (d, J = 7.2 Hz, 3 H, 6-Me), 1.31−1.45 (m, 2 H), 1.46 (s, 3 H, 3-Me), 1.49−1.52 (m, 1 H), 1.62−1.72 (m, 3 H), 1.82−1.93

(m, 3 H), 2.04−2.07 (m, 1 H), 2.36−2.44 (m, 1 H), 2.97−3.01 (m, 1 H), 5.61 (s, 1 H, H-12), 6.63 (d, J = 4.0 Hz, 1 H, H-10), 7.60−7.64 (m, 1 H, Ar-H), 7.89 (d, J = 7.6 Hz, 1 H, Ar-H), 8.03−8.09 (m, 2 H, 2 × Ar-H), 8.95 (d, J = 8.4 Hz, 1 H, Ar-H), − ^{13}C NMR: δ = 12.87, 20.35, 24.32, 24.71, 26.04, 30.29, 34.57, 36.30, 37.54, 44.04, 52.43, 80.57, 88.90, 95.17, 104.39, 124.29, 125.80, 126.30, 127.02, 127.77, 128.32, 129.35, 131.34, 133.39, 133.70, 165.82. IR (film): $\tilde{\nu}_{max}$ = 2924, 1778, 1720, 1574, 1510, 1450, 1378, 1276, 1238, 1194, 1176, 1118, 1102, 1062, 1034, 984, 902, 870, 814, 782 cm^{-1}. MS (CI, NH_3): m/z (%) = 456 (100) $[MNH_4]^+$, 415 (16), 347 (32), 307 (24), 284 (16), 256 (8). $C_{26}H_{36}O_6$ (444.6): calcd. C 71.21, H 6.90; found C 71.51, H 6.93. − **Procedure 2:** Trichloroacetonitrile (0.11 mL, 0.16 g, 1.1 mmol) and 1,8-diazabicyclo[5.4.0]undecane (7.5 μL, 7.6 mg, 0.05 mmol) were added to a stirred mixture of dihydroartemisinin (284 mg, 1.0 mmol) in dichloromethane (5 mL). After 18 h, the mixture was added to a stirred mixture of 1-naphthoic acid (517 mg, 3.0 mmol) in dichloromethane (5 mL). After 2 h, the reaction was quenched with 5% aqueous $NaHCO_3$ (10 mL). The organic layer was separated and dried ($MgSO_4$). Filtration and concentration of the filtrate left a residue, which was purified by column chromatography on silica, with ethyl acetate/hexane (9:91) as eluent, to give the product as clusters of fine white needles (299 mg, 68%).

10β-Dihydroartemisinyl 1′-Isoquinolinecarboxylate (12): This was prepared by procedure 1 as described for compound **10** above, except that the eluent for chromatography was ethyl acetate/hexane (23:77). The product was obtained from DHA (**2**, 568 mg) and 1-isoquinolinecarboxylic acid (346 mg, 2.0 mmol, 1 equiv.) as a white powder (217 mg, 25%), m.p. 167−169 °C. $[\alpha]_D^{20}$ = +142 (c = 0.37, $CHCl_3$). ^{1}H NMR: δ = 0.95 (d, J = 6.1 Hz, 3 H, 9-Me), 1.04 (d, J = 7.3 Hz, 3 H, 6-Me), 1.46 (s, 3 H, 3-Me), 1.29−2.08 (m, 10 H), 2.40 (ddd, J = 13.6, 4.1, 3.9 Hz, 1 H), 2.91−3.01 (m, 1 H, H-9), 5.69 (s, 1 H, H-12), 6.66 (d, J = 3.35 Hz, 1 H, H-10), 7.67−8.71 (m, 6 H, Ar-H). ^{13}C NMR: δ = 12.54, 20.15, 23.68, 24.49, 25.83, 30.22, 34.47, 36.15, 37.18, 43.95, 52.35, 80.63, 88.99, 96.09, 104.25, 123.53, 126.10, 126.40, 126.87, 128.42, 130.32, 136.54, 141.75, 165.01. IR (film): $\tilde{\nu}_{max}$ = 2942, 2870, 1726, 1452, 1376, 1280, 1248, 1226, 1180, 1142, 1102, 1074, 1002, 986, 900, 872, 850, 758 cm^{-1}. MS (EI): m/z (%) = 439 (40) [M$^+$], 394 (34), 380 (44), 354 (64), 336 (100), 322 (44), 309 (46), 299 (80). $C_{25}H_{29}NO_6$ (439.5): calcd. C 68.32, H 6.65, N 3.19; found C 68.03, H 6.90, N 3.13.

10β-Dihydroartemisinyl 2′-Quinolinecarboxylate (13): This was prepared by procedure 1 as for compound **10** above, except that the eluent for chromatography was ethyl acetate/hexane (22:78). The product was obtained from DHA (**2**, 284 mg) and 2-quinolinecarboxylic acid (173 mg, 1.0 mmol, 1 equiv.) as a white microcrystalline powder (242 mg, 55%), m.p. 75−77 °C. $-[\alpha]_D^{20}$ = +138 (c = 0.013, $CHCl_3$). ^{1}H NMR: δ = 1.00−1.05 (m, 6 H, 6-Me, 9-Me), 1.46 (s, 3 H, 3-Me), 0.84−1.72 (m, 4 H), 1.82−2.11 (m, 5 H), 2.28−2.48 (m, 2 H), 2.93−3.03 (m, 1 H), 5.72 (s, 1 H, H-12), 6.62 (d, J = 3.15 Hz, 1 H, H-10), 7.28−8.33 (m, 6 H, Ar-H). ^{13}C NMR: δ = 12.68, 20.37, 24.07, 24.66, 30.34, 34.80, 36.26, 37.56, 44.10, 52.52, 80.74, 89.04, 96.31, 104.41, 120.76, 127.51, 128.58, 129.27, 130.12, 130.93, 137.02, 147.74, 147.86, 164.40. IR (film): $\tilde{\nu}_{max}$ = 2940, 1728, 1462, 1378, 1292.1210, 1140, 1110.1092, 1074, 1034, 986, 902, 874, 854, 778 cm^{-1}. MS (CI, NH_3): m/z (%) = 440 (100) [MH$^+$], 284 (42), 256 (60), 221 (10), 174 (16). $C_{25}H_{29}NO_6$ (439.5): calcd. C 68.32, H 6.65, N 3.19; found C 68.30, H 6.96, N 3.59.

10β-Dihydroartemisinyl 3′-Quinolinecarboxylate (14): This was prepared by procedure 1 as for compound **10** above, except that the eluent for chromatography was ethyl acetate/hexane (22:78). The product was obtained from DHA (**2**, 284 mg) and 3-quinolinecarboxylic acid (173 mg, 1.0 mmol, 1 equiv.) as a white powder (242 mg, 55%), m.p. 88−89 °C. $[\alpha]_D^{22}$ = +81.2 (c = 0.025, $CHCl_3$). ^{1}H NMR: δ = 1.01 (2 × 3 H, d, 6-Me, 9-Me, J = 6.6 Hz), 1.08−0.88 (m, 1 H),1.45 (s, 3 H, 3-Me), 1.23−2.09 (m, 9 H), 2.30−2.46 (m, 1 H), 2.94−3.04 (m, 1 H), 5.61 (s, 1 H, H-12), 6.61 (d, 1 H, J = 3.45 Hz, H-10), 7.63−7.68 (m, 1 H, Ar-H), 7.84−7.89 (m, 1 H, Ar-H), 7.95 (d, J = 8.2 Hz, 1 H, Ar-H), 8.17 (d, J = 8.5 Hz, 1 H, Ar-H), 8.86 (d, J = 1.3 Hz, 1 H, Ar-H), 9.41 (d, J = 1.95 Hz, 1 H, Ar-H). ^{13}C NMR: δ = 164.27, 149.83, 149.51, 139.37, 132.10, 129.39, 129.19, 127.59, 126.86, 122.96, 104.51, 96.03, 88.86, 80.45, 52.31, 43.82, 37.58, 36.14, 34.45, 30.05, 25.84, 24.57, 24.48, 20.17, 12.60. IR (film): $\tilde{\nu}_{max}$ = 2942, 1726, 1620, 1498, 1460, 1376, 1284, 1236, 1196, 1110, 1092, 1072, 1054, 1034, 974, 898, 874, 852, 790, 754 cm^{-1}. MS (CI, NH_3): m/z (%) = 440 (100) [MH$^+$], 284 (26), 256 (90), 239 (10). $C_{25}H_{29}NO_6$ (439.5): calcd. C 68.32, H 6.65, N 3.19; found C 68.30, H 6.96, N 3.59.

10β-Dihydroartemisinyl 2′-Quinoxalinecarboxylate (15): This was prepared by procedure 1 as for compound **10** above, except that the eluent for chromatography was ethyl acetate/hexane (22:78). The product was obtained from DHA (**2**, 284 mg) and 2-quinoxalinecarboxylic acid (173 mg, 1.0 mmol, 1 equiv.) as a white powder (160 mg, 36%), m.p. 72−73 °C. $[\alpha]_D^{22}$ = +71.7 (c = 0.017, $CHCl_3$). ^{1}H NMR: δ = 1.01−1.04 (m, 6 H, 6-Me, 9-Me), 1.46 (s, 3 H, 3-Me), 0.89−2.48 (m, 11 H), 2.96−3.06 (m, 1 H), 5.69 (s, 1 H, H-12), 6.66 (d, J = 3.0 Hz, 1 H, H-10), 7.86−7.97 (m, 2 H, Ar-H), 8.19−8.26 (m, 2 H, Ar-H), 9.50 (s, 1 H, Ar-H). ^{13}C NMR: δ = 12.61, 20.28, 24.14, 24.62, 25.86, 30.22, 34.64, 36.19, 37.57, 43.92, 52.41, 80.58, 89.06, 96.84, 104.51, 129.29, 130.81, 130.93, 132.40, 141.80, 142.52, 143.63, 144.75, 163.09. −IR (film): $\tilde{\nu}_{max}$ = 2938, 1728, 1494, 1466, 1364, 1304, 1280, 1230, 1156, 1112, 1096, 1074, 1054, 1034, 1014, 978, 900, 874, 852, 804, 778, 752 cm^{-1}. MS (CI, NH_3): m/z (%) = 458 (40) [MNH_4^+], 441 (8) [MH$^+$], 301 (20), 284 (100), 256 (70), 221 (10). $C_{24}H_{28}N_2O_6$ (440.5): calcd. C 65.44, H 6.41, N 6.36; found C 65.23, H 6.40, N 6.48.

10β-Dihydroartemisinyl 2′-Hydroxy-1′-naphthoate (16): This was prepared by procedure 1 as for compound **10** above, except that the eluent for chromatography was ethyl acetate/hexane (7:93). The product was obtained from DHA (**2**, 284 mg) and 2-hydroxy-1-naphthoic acid (188 mg, 1.0 mmol, 1 equiv.) as a viscous gum (231 mg, 51%), $[\alpha]_D^{20}$ = +146 (c = 0.024, $CHCl_3$). ^{1}H NMR: δ = 1.09 (d, 3 H, 9-Me, J = 7.35 Hz), 0.97−1.17 (m, 4 H), 1.54 (s, 3 H, 3-Me), 1.34−1.78 (m, 3 H), 1.88−2.16 (m, 6 H), 2.39−2.54 (m, 1 H), 3.02−3.12 (m, 1 H), 5.68 (s, 1 H, H-12), 6.64 (d, J = 3.5 Hz, 1 H, H-10), 7.39 (d, J = 8.8 Hz, 1 H, Ar-H), 7.53−7.73 (m, 4 H, Ar-H), 7.86 (d, J = 8.0 Hz, 1 H, Ar-H), 8.52 (d, J = 8.20 Hz, 1 H, Ar-H), 12.12 (s, 1 H, OH). ^{13}C NMR: δ = 12.61, 20.23, 24.40, 24.58, 25.88, 30.12, 34.51, 36.17, 37.54, 43.84, 52.34, 80.46, 88.85, 95.92, 104.52, 118.72, 123.56, 123.88, 124.01, 124.83, 125.89, 127.38, 129.61, 137.16, 161.74, 170.28. IR (film): $\tilde{\nu}_{max}$ = 2942, 1660, 1636, 1600, 1578, 1462, 1412, 1390, 1336, 1272, 1252, 1208, 1160, 1104, 1088, 1072, 1054, 1032, 1014, 976, 964, 926, 894, 874, 850, 796, 772, 716 cm^{-1}. MS (EI): m/z (%) = 455 (4) [MH$^+$], 454 (4) [M$^+$], 286 (24), 284 (50), 256 (20), 224 (14), 221 (8). $C_{26}H_{30}O_7$ (454.5): calcd. C 68.71, H 6.65; found C 68.64, H 6.78.

10β-Dihydroartemisinyl 1′-Hydroxy-2′-naphthoate (17): This was prepared by procedure 1 as for compound **10** above, except that the eluent for chromatography was ethyl acetate/hexane (7:93). The product was obtained from DHA (**2**, 284 mg) and 1-hydroxy-2-naphthoic acid (188 mg, 1.0 mmol, 1 equiv.) as needles (76 mg, 17%), m.p 139−140 °C. $[\alpha]_D^{20}$ = +124 (c = 0.019, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2940, 1660, 1634, 1580, 1462, 1390, 1272, 1254, 1160, 1104, 1072, 1032, 976, 894, 850, 796, 772, 716. ^{1}H NMR: δ = 1.04

(d, J = 5.7 Hz, 3 H, 9-Me), 1.15 (d, J = 7.4 Hz, 3 H, 6-Me), 1.56 (s, 3 H, 3-Me), 0.97−2.05 (m, 9 H), 2.13−2.19 (m, 1 H), 2.44−2.53 (m, 1 H), 3.08−3.18 (m, 1 H), 5.70 (s, 1 H, H-12), 6.87 (d, J = 3.65 Hz, 1 H, H-10), 7.27 (d, J = 8.95 Hz, 1 H, Ar-H), 7.35−7.59 (m, 2 H, Ar-H), 7.86 (dd, J = 7.9, 1.1 Hz, 1 H, Ar-H), 7.99 (d, J = 9.0 Hz, 1 H, Ar-H), 8.70 (d, J = 9.0 Hz, 1 H, Ar-H), 11.95 (s, 1 H, OH). ^{13}C NMR: δ = 12.84, 20.21, 24.18, 24.59, 25.90, 30.21, 34.30, 36.19, 37.47, 43.60, 52.30, 80.47, 89.34, 96.76, 104.61, 119.48, 123.72, 125.31, 127.62, 128.58, 129.01, 131.41, 136.64, 172.00. MS (CI, CH_4): m/z (%) = 455 (4) [MH^+], 454 (4), 437 (6), 409 (34), 267 (80), 249 (70), 221 (100), 189 (54), 163 (50). $C_{26}H_{30}O_7$ (454.5): calcd. C 68.71, H 6.65; found C 68.93, H 6.81.

10β-Dihydroartemisinyl 3′-Hydroxy-2′-naphthoate (18): This was prepared by procedure 1 as for compound **10** above, except that the eluent for chromatography was ethyl acetate/hexane (12:88). The product was obtained from DHA (**2**, 284 mg) and 3-hydroxy-2-naphthoic acid (188 mg, 1.0 mmol, 1 equiv.) as a white powder (127 mg, 28%), m.p. 138−139 °C. $[\alpha]_D^{20}$ = +63.7 (c = 0.019, $CHCl_3$). ^{1}H NMR: δ = 1.03−1.05 (m, 6 H, 6-Me, 9-Me), 1.47 (s, 3 H, 3-Me), 1.03−1.62 (m, 4 H), 2.49−2.38 (m, 1 H), 1.69−2.15 (m, 6 H), 2.98−3.03 (m, 1 H), 5.63 (s, 1 H, H-12), 6.58 (d, J = 3.4 Hz, 1 H, H-10), 7.33−7.80 (m, 5 H, Ar-H), 8.35 (s, 1 H, Ar-H), 10.44 (s, 1 H, OH). ^{13}C NMR: δ = 12.62; 20.24, 24.25, 24.59, 25.86, 30.04, 34.55, 36.16, 37.62, 43.83, 52.33, 80.40, 88.90, 96.39, 104.59, 112.08, 114.09, 123.98, 126.39, 126.79, 129.18, 129.31, 131.86, 138.01, 156.63, 169.12. IR (film): $\tilde{\nu}_{max}$ = 3232, 2938, 2880, 1682, 1634, 1514, 1462, 1414, 1380, 1326, 1280, 1212, 1176, 1146, 1106, 1030, 850, 792, 744 cm^{-1}. MS (CI, CH_4): m/z (%) = 472 (56) [MNH_4^+], 301 (10), 284 (100), 267 (16), 256 (10), 221 (22), 206 (32). $C_{26}H_{30}O_7$ (454.5): calcd. C 68.71, H 6.65; found C 68.57, H 6.69.

10β-Dihydroartemisinyl 3′-Hydroxy-2′-quinoxalinecarboxylate (19): This unstable compound, identified by NMR spectroscopy, was prepared by procedure 1 as for compound **10** above, except that the eluent for chromatography was ethyl acetate/hexane (25:75). The product was obtained from DHA (**2**, 284 mg) and 3-hydroxy-2-quinoxalinecarboxylic acid (190 mg, 1.0 mmol, 1 equiv.) as a yellow gum, which could not be further purified (149 mg, 33%). ^{1}H NMR: δ = 0.86 (d, J = 6.0 Hz, 3 H, 9-Me), 0.90−0.97 (m, 1 H), 1.04 (d, 3 H, 6-Me, J = 7.35 Hz), 1.48 (s, 3 H, 3-Me), 1.24−2.14 (m, 9 H), 2.35−2.46 (m, 1 H), 2.89−2.96 (m, 1 H), 5.82 (s, 1 H, H-12), 6.58 (d, J = 3.0 Hz, 1 H, H-10), 7.40−7.94 (m, 4 H, Ar-H), 12.92 (1 H, brs, OH). ^{13}C NMR: δ = 12.49, 14.14, 20.11, 23.83, 24.57, 25.94, 30.97, 34.50, 36.22, 37.37, 43.92, 52.37, 80.66, 89.13, 96.92, 104.40, 116.34, 124.99, 130.33, 132.10, 132.17, 132.89, 148.25, 154.57, 162.36. A correct microanalysis could not be obtained for this compound.

10β-Dihydroartemisinyl 9′-Anthracenecarboxylate (20): This was prepared by procedure 1 as for compound **10** above, except that the eluent for chromatography was ethyl acetate/hexane (17:83). The product was obtained from DHA (**2**, 568 mg) and 9-anthracenecarboxylic acid (444 mg, 2.0 mmol, 1 equiv.) as a white powder (618 mg, 63%), m.p. 130−132 °C. $[\alpha]_D^{20}$ = +49.2 (c = 0.73, $CHCl_3$). ^{1}H NMR: δ = 0.84 (d, J = 6.0 Hz, 3 H, 6-Me), 1.13 (d, J = 7.0 Hz, 3 H, 9-Me), 1.54 (s, 3 H, 3-Me), 0.76−1.56 (m, 8 H), 1.83−1.92 (m, 1 H), 2.08 (ddd, J = 15.3, 4.8, 2.95 Hz, 1 H), 2.42 (ddd, J = 17.5, 13.0, 4.0 Hz, 1 H), 3.00−3.10 (m, 1 H, H-9), 5.59 (s, 1 H, H-12), 6.91 (d, J = 3.45 Hz, 1 H, H-10), 7.52−7.61 (m, 4 H, Ar-H), 8.04−8.15 (m, 4 H, Ar-H), 8.55 (s, 1 H, Ar-H). ^{13}C NMR: δ = 12.63, 19.93, 23.58, 24.42, 25.87, 29.91, 34.00, 36.14, 37.01, 43.69, 52.19, 80.40, 89.05, 89.08, 96.14, 104.34, 124.75, 125.40, 126.92, 128.09, 128.44, 129.03, 130.83, 168.32. IR (film): $\tilde{\nu}_{max}$ = 2922, 1732, 1448, 1376, 1196, 1152, 1102, 1076, 984, 896, 876, 844, 738 cm^{-1}. MS (CI, NH_3): m/z (%) = 506 (24) [MNH_4^+], 488 (2) [M^+], 396 (48), 379 (100), 284 (44), 267 (24), 205 (6). $C_{30}H_{32}O_6$ (488.6): calcd. C 73.75, H 6.60; found C 73.96, H 6.84.

10β-Dihydroartemisinyl 9′-Acridinecarboxlate (21): This was prepared by procedure 1 as for compound **10** above, except that the eluent for chromatography was ethyl acetate/hexane (25:75). The product was obtained from DHA (**2**, 568 mg) and 9-acridinecarboxylic acid (446 mg, 2.0 mmol, 1 equiv.) as a fine short needles (548 mg, 56%), 150−151 °C. $[\alpha]_D^{20}$ = +125 (c = 0.15, $CHCl_3$). ^{1}H NMR: δ = 0.84 (d, J = 6.0 Hz, 3 H, 6-Me); 1.12 (d, J = 7.0 Hz, 3 H, 9-Me), 1.53 (s, 3 H, 3-Me), 1.24−1.59 (m, 8 H), 1.83−1.92 (m, 1 H), 2.08 (ddd, J = 14.5, 4.5, 3.0 Hz, 1 H), 2.41 (ddd, J = 17.0, 13.5, 4.0 Hz, 1 H), 3.00−3.10 (m, 1 H, H-9), 5.54 (s, 1 H, H-12), 6.91 (d, J = 3.5 Hz, 1 H, H-10), 7.59−8.31 (m, 8 H, Ar-H), − ^{13}C NMR: δ = 12.59, 19.89, 23.58, 24.38, 25.81, 29.82, 33.90, 36.06, 37.02, 43.50, 52.10, 80.27, 89.13, 96.93, 104.45, 121.97, 124.75, 127.16, 129.80, 130.28, 136.90, 148.55, 168.35, − IR (film): $\tilde{\nu}_{max}$ = 2948, 1738, 1518, 1462, 1378, 1208, 1104, 986, 892, 876, 848, 764 cm^{-1}. MS (EI): m/z (%) = 489 (6) [M^+], 266 (24), 223 (100), 167 (42), 195 (18). $C_{29}H_{31}NO_6$: (489.6): calcd. C 71.15, H 6.38; N 2.86; found C 70.87, H 6.46, N 2.83.

10β-Dihydroartemisinyl 2′-Anthraquinonecarboxylate (22): This was prepared by procedure 1 for compound **10** above, except that the eluent for chromatography was ethyl acetate/hexane (18:82). The product was obtained from DHA (**2**, 568 mg) and anthraquinone-2-carboxylic acid (505 mg, 2.0 mmol, 1 equiv.) as a white powder (808 mg, 74%), m.p. 114−115 °C. $[\alpha]_D^{20}$ = +35.8 (c = 0.052, $CHCl_3$). ^{1}H NMR: δ = 1.01 (d, J = 7.0 Hz, 3 H, 9-Me); 1.03 (d, 3 H, 6-Me, J = 5.65 Hz), 1.44 (s, 3 H, 3-Me), 0.96−2.10(m, 10 H), 2.35−2.45 (m, 1 H), 2.93−3.03 (m, 1 H, H-9), 5.62 (s, 1 H, H-12), 6.56 (d, J = 3.5 Hz, 1 H, H-10), 7.81−8.88 (m, 7 H, Ar-H). ^{13}C NMR: δ = 12.59, 14.13, 20.23, 24.43, 24.49, 24.57, 25.80, 30.05, 36.14, 37.54, 43.84, 52.32, 80.44, 88.86, 96.43, 104.48, 127.32, 127.36, 127.68, 128.40, 133.26, 133.29, 133.54, 134.40, 134.46, 135.00, 136.12, 163.94, 181.99, 182.33. IR (film): $\tilde{\nu}_{max}$ = 2942, 1732, 1678, 1594, 1452, 1378, 1326, 1296, 1266, 1242, 1172, 1102, 1070, 1054, 1032, 1014, 978, 932, 898, 876, 856, 798, 754 cm^{-1}. MS (EI): m/z (%) = 519 (66) [M^+], 436 (100), 256 (66), 221 (26), 203 (18). $C_{30}H_{30}O_8$ (518.6): calcd. C 69.49, H 5.83; found C 69.85, H 6.07.

10α-Dihydroartemisinyl Acetate (23): 4-(Dimethylamino)pyridine (20 mg, 0.16 mmol) and acetic anhydride (330 μL, 3.00 mmol) were added to a cold (0 °C), stirred solution of DHA (**2**, 284 mg, 1.0 mmol) in dichloromethane (15 mL). The reaction mixture was allowed to warm to room temperature with stirring overnight. The solvent was removed under reduced pressure and the residue was purified by chromatography with ethyl acetate/hexane (20:80) to give the product as a white solid (321 mg, 98%), recrystallisation of which from ethyl acetate/hexane gave needles, m.p. 128−129 °C (ref.[9] 130−132 °C). $[\alpha]_D^{20}$ = +76.2 (c = 0.93, $CHCl_3$). ^{1}H NMR: δ = 0.86 (d, J = 7.0 Hz, 3 H, 9-Me), 0.97 (d, 3 H, 6-Me, J = 5.95 Hz), 1.45 (s, 3 H, 3-Me), 1.94−1.23 (m, 9 H), 2.04 (ddd, J = 14.5, 5.0, 3.0 Hz, 1 H), 2.14 (s, 3 H, MeCO), 2.39 (ddd, J = 17.5, 13.5, 4.0 Hz, 1 H), 2.55 (m, 1 H, H-9), 5.45 (s, 1 H, H-12), 5.80 (d, 1 H, H-10, J = 10.0 Hz). IR (film): $\tilde{\nu}_{max}$ = 2926, 2870, 1752, 1448, 1376, 1228, 1132, 1102, 1028, 876, 848, 826, 754 cm^{-1}. MS (EI): m/z (%) = 326 [M^+]. $C_{17}H_{26}O_6$ (326.4): calcd. C 62.56, H 8.03; found C 62.87, H 8.36.

10α-Dihydroartemisinyl *p*-Nitrobenzoate (24): This was prepared by the method used for compound **23**, except that *p*-nitrobenzoyl chloride (0.39 g, 2.11 mmol, 1.2 equiv.) and triethylamine (0.29 mL,

0.21 g, 1.2 equiv.) were used rather than acetic anhydride and DMAP. The eluent for chromatography was ethyl acetate/hexane (12:88). The product was obtained from DHA (**2**, 500 mg) as a white foam (627 mg, 82%), m.p. 63−66 °C. $[\alpha]_D^{20}$ = +20.26 (*c* = 1.16, $CHCl_3$). ^1H NMR: δ = 0.94 (d, *J* = 7.0 Hz, 3 H, 9-Me), 1.00 (d, *J* = 6.0 Hz, 3 H, 6-Me), 1.21−1.40 (m, 2 H), 1.43 (s, 3 H, 3-Me), 1.58−1.49 (m, 1 H), 1.64−1.97 (m, 5 H), 2.02−2.09 (m, 1 H), 2.22−2.45 (m, 2 H), 2.74−2.81 (m, 1 H), 5.54 (s, 1 H, H-12), 6.02 (d, 1 H, H-10, *J* = 10.0 Hz), 8.30 (s, 4 H, Ph-H). ^{13}C NMR: δ = 12.90, 20.89, 22.71, 25.24, 26.58, 32.58, 34.74, 36.88, 37.96, 45.94, 52.25, 80.79, 92.37, 94.06, 105.24, 124.18, 131.89, 135.70, 151.43, 164.18. IR (film): $\tilde{\nu}_{max}$ = 2926, 2870, 1736, 1608, 1528, 1348, 1266, 1132, 1090, 1036, 1010, 878, 854, 720 cm^{-1}. MS (CI positive, CH_4): *m*/*z* (%) = 462 (4) [MH^+, 2 × CH_4], 435 (6) [MH^+, ^{13}C], , 434 (51) [MH^+], 433 (3.7) [M^+]. $C_{22}H_{27}NO_8$ (433.5): calcd. C 60.96, H 6.28, N 3.23; found C 61.37, H 6.66, N 3.11.

10α-Dihydroartemisinyl Benzoate (25). − Procedure 1: Dicyclohexylcarbodiimide (217 mg, 1.05 mmol) was added to a cold (0 °C), stirred solution of DHA (**2**, 284 mg, 1.0 mmol) and benzoic acid (122 mg, 1.0 mmol) in dichloromethane (15 mL). The mixture was stirred at 0 °C for 4 h and then washed with water (3 × 15 mL) and dried ($MgSO_4$). Filtration and concentration of the filtrate gave a residue, which on chromatography with ethyl acetate/hexane (15:85) gave the product as a white powder (137 mg, 35%), m.p. 62−63 °C (ref.[9] m.p. 127−129 °C). $[\alpha]_D^{20}$ = +15 (*c* = 0.017, $CHCl_3$). ^1H NMR: δ = 0.94 (d, *J* = 7.0 Hz, 3 H, 9-Me), 0.99 (d, *J* = 6.0 Hz, 3 H, 6-Me), 0.89−1.07 (m, 1 H), 1.44 (s, 3 H, 3-Me), 1.26−1.54 (m, 4 H), 1.66−1.89 (m, 4 H), 2.03−2.08 (m, 1 H), 2.35−2.44 (m, 1 H), 2.75−2.79 (m, 1 H, H-9), 5.54 (s, 1 H, H-12), 6.02 (d, 1 H, H-10, *J* = 10.0), 7.28−7.60 (m, 3 H, Ar-H), 8.11−8.14 (m, 2 H, Ar-H). ^{13}C NMR: δ = 12.17, 20.18, 21.99, 24.52, 25.89, 31.93, 34.06, 36.19, 37.21, 45.28, 51.58, 80.12, 91.52, 92.46, 104.36, 128.23, 129.55, 130.05, 133.24, 165.22. IR (film): $\tilde{\nu}_{max}$ = 2926, 1732, 1452, 1376, 1266, 1208, 1132, 1088, 1038, 1018, 926, 880, 832, 756, 714, 672 cm^{-1}. MS (CI, NH_3): *m*/*z* (%) = 406 (100) [MNH_4^+], 284 (30), 256 (20). $C_{22}H_{28}O_6$ (388.5): calcd. C 68.02, H 7.21; found C 68.09, H 7.31. − **Procedure 2:** The procedure for the preparation of compound **23** was used, except that benzoyl chloride (0.98 mL, 1.19 g, 8.45 mmol, 1.2 equiv.) and triethylamine (1.18 mL, 0.86 g, 8.45 mmol, 1.2 equiv.) were used in place of acetic anhydride and DMAP. The eluent for chromatography was ethyl acetate/hexane (10:90). DHA (**2**, 2 g) provided **25** (2.17 g, 79%).

10β-[(4′-Methoxyphenyl)methoxy]dihydroartemisinin (26): Boron trifluoride−diethyl ether (3 drops) was added to a stirred solution of DHA (**2**, 284 mg, 1.0 mmol) and 4-methoxybenzyl alcohol (248 mg, 2.0 mmol, 2 equiv.) in diethyl ether (20 mL). After 6 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and dried ($MgSO_4$). Filtration and concentration of the filtrate gave a residue which on chromatography with ethyl acetate/hexane (5:95 to 10:90) gave the product as a white microcrystalline powder (262 mg, 67%), m.p. 100−101 °C. ^1H NMR: δ = 0.98 (d, *J* = 6.0 Hz, 3 H, 9-Me), 1.04 (d, *J* = 7.5 Hz, 3 H, 6-Me), 1.45 (s, 3 H, 3-Me), 0.97−1.05 (m, 1 H), 1.28−1.73 (m, 5 H), 1.87−2.09 (m, 4 H), 2.35−2.45 (m, 1 H), 2.74−2.84 (m, 1 H), 3.78 (s, 3 H, OMe), 5.39 (d, *J* = 3.5 Hz, 1 H, H-10), 5.55 (s, 1 H, H-12), 6.80−7.09 (m, 4 H, Ar-H). ^{13}C NMR: δ = 13.00, 20.31, 24.43, 24.63, 26.07, 31.03, 34.63, 36.37, 37.39, 44.44, 52.54, 55.65, 81.03, 88.16, 101.58, 104.13, 114.56, 118.08, 151.68, 154.73. MS (CI, CH_4): *m*/*z* (%) = 391 (60)[MH^+]. $C_{22}H_{30}O_6$ (390.5): calcd. C 67.67, H 7.74; found C 67.60, H 7.75.

10β-(Phenylmethoxy)dihydroartemisinin (27): This was prepared by the method used for the preparation of compound **26**, except that the eluent for chromatography was ethyl acetate/hexane (10:90). The product was obtained from DHA (**2**, 1 g, 3.5 mmol) and benzyl alcohol (730 μL, 7.0 mmol, 2 equiv.) as a colourless oil (1.26 g, 96%). $[\alpha]_D^{20}$ = +129 (*c* = 0.077, $CHCl_3$). ^1H NMR: δ = 0.96 (d, *J* = 6.0 Hz, 3 H, 9-Me), 0.97 (d, *J* = 7.5 Hz, 3 H, 6-Me), 1.48 (s, 3 H, 3-Me), 0.87−1.97 (m, 9 H), 2.07 (ddd, *J* = 14.5, 5.0, 3.0 Hz, 1 H), 2.41 (ddd, *J* = 17.5, 10.0, 4.0 Hz, 1 H), 2.65−2.75 (m, 1 H, H-9), 4.55 (d, 1 H, H-1, *J* = 12.5 Hz), 4.94 (d, 1 H, H-1′, *J* = 12.5 Hz), 4.95 (d, *J* = 3.5 Hz, 1 H, H-10), 7.28−7.39 (m, 5 H, Ar-H), 5.49 (s, 1 H, H-12). IR (neat): $\tilde{\nu}_{max}$ = 2922, 2874, 1454, 1374, 1100, 1024, 1012, 876, 826, 734, 698 cm^{-1}. MS (CI, NH_3): *m*/*z* = 392 (%): (26) [MNH_4^+], 329 (64), 284 (100), 267 (72), 221 (16). $C_{22}H_{30}O_5$ (374.5): calcd. C 70.56, H 8.07; found C 70.89, H 8.25.

10β-(2′-Fluorophenylmethoxy)dihydroartemisinin (28): This was prepared by the method used for the preparation of compound **26**, except that the eluent for chromatography was ethyl acetate/hexane (10:90). The product was obtained from DHA (**2**, 426 mg, 1.5 mmol) and 2-fluorobenzyl alcohol (330 μL, 3.0 mmol, 2 equiv.) as a white powder (445 mg, 76%), m.p. 81−82 °C. $[\alpha]_D^{20}$ = +121 (*c* = 0.37, $CHCl_3$). ^1H NMR: δ = 0.94 (d, *J* = 7.5 Hz, 3 H, 6-Me), 0.96 (d, *J* = 6.0 Hz, 3 H, 9-Me), 1.48 (s, 3 H, 3-Me), 1.21−1.67 (m, 6 H), 1.77−1.94 (m, 3 H), 2.06 (ddd, *J* = 14.5, 5.0, 3.0 Hz, 1 H), 2.40 (ddd, *J* = 17.5, 13.5, 4.0 Hz, 1 H), 2.68−2.71 (m, 1 H, H-9), 4.54 (d, 1 H, H-1′, *J* = 12.5 Hz), 4.96 (d, *J* = 3.5 Hz, 1 H, H-10), 5.01 (d, 1 H, H-1′, *J* = 12.5 Hz), 5.50 (s, 1 H, H-12), 7.02−7.42 (m, 4 H, Ar-H). ^{13}C NMR: δ = 12.82; 20.20, 24.30, 24.53, 26.04, 30.77, 34.48, 36.28, 37.24, 44.27, 52.44, 64.03 (d, *J* = 4.0 Hz), 80.97, 87.87 (d, *J* = 2.5 Hz), 101.59 (d, *J* = 2.0 Hz), 103.97, 115.03 (d, *J* = 21.0 Hz), 123.74 (d, *J* = 3.5 Hz), 125.36 (d, *J* = 14.5 Hz), 129.01 (d, *J* = 8.0 Hz), 129.46 (d, *J* = 4.5 Hz). IR (film): $\tilde{\nu}_{max}$ = 2950, 2874, 1586, 1492, 1456, 1376, 1228, 1194, 1158, 1140, 1124, 1098, 1012, 978, 958, 938, 876, 756 cm^{-1}. MS (CI, NH_3): *m*/*z* (%) = 410 (MNH_4^+, 16), 393 (MH^+, 2), 347 (28), 284 (100), 267 (64), 126 (4). $C_{22}H_{29}FO_5$ (392.5): calcd. C 67.33, H 7.45; found C 67.23, H 7.48.

10β-(3′-Fluorophenylmethoxy)dihydroartemisnin (29): This was prepared by the method used for the preparation of compound **26**, except that the eluent for chromatography was ethyl acetate/hexane (10:90). The product was obtained from DHA (**2**, 426 mg, 1.5 mmol) and 3-fluorobenzyl alcohol (330 μL, 3.0 mmol, 2 equiv.) as a white powder (489 mg, 83%), m.p. 83−85 °C (ref.[29] m.p. 87−89 °C). $[\alpha]_D^{20}$ = +111 (*c* = 0.77, $CHCl_3$). ^1H NMR: δ = 0.97 (d, *J* = 6.0 Hz, 3 H, 6-Me), 0.98 (d, *J* = 7.5 Hz, 3 H, 9-Me), 1.48 (s, 3 H, 3-Me), 1.22−1.70 (m, 6 H), 1.81−1.95 (m, 3 H), 2.06 (ddd, *J* = 14.5, 5.0, 3.0 Hz, 1 H), 2.40 (ddd, *J* = 17.5, 13.5, 4.0 Hz, 1 H), 2.66−2.76 (m, 1 H, H-9), 4.54 (d, 1 H, H-1′, *J* = 12.5 Hz), 4.92 (d, 1 H, H-1′, *J* = 12.5 Hz), 4.93 (d, *J* = 5.0 Hz, 1 H, H-10), 5.47 (s, 1 H, H-12), 6.95−7.35 (m, 4 H, Ar-H). ^{13}C NMR: δ = 12.93, 20.18, 24.36, 24.52, 26.03, 30.75, 34.44, 36.26, 37.27, 44.20, 52.41, 68.85, 80.94, 87.88 (d, *J* = 2.5 Hz), 101.36, 104.03, 113.60, 114.02 (d, *J* = 21.0 Hz), 122.37 (d, *J* = 2.5 Hz), 129.63 (d, *J* = 8.5 Hz), 140.85. IR (film): $\tilde{\nu}_{max}$ = 2922, 2874, 1618, 1592, 1488, 1450, 1376, 1360, 1254, 1194, 1136, 1102, 1032, 1012, 940, 876, 826, 874 cm^{-1}. MS (CI, NH_3): *m*/*z* (%) = 410 (16) [MNH_4^+], 393 (2) [MH^+], 347 (32), 284 (100), 267 (66), 126 (4). $C_{22}H_{29}FO_5$ (392.5): calcd. C 67.33, H 7.45; found C 67.07, H 7.48.

10β-(4′-Fluorophenylmethoxy)dihydroartemisinin (30): This was prepared by the method used for the preparation of compound **26**, except that the eluent for chromatography was ethyl acetate/hexane (10:90). The product was obtained from DHA (**2**, 426 mg, 1.5 mmol) and 4-fluorobenzyl alcohol (330 μL, 3.0 mmol, 2 equiv.) as a white powder (487 mg, 83%), m.p. 71−72 °C. $[\alpha]_D^{20}$ = +126

(c = 0.34, $CHCl_3$). ^1H NMR: δ = 0.95 (d, 3 H, 6-Me, J = 7.35 Hz), 0.97 (d, J = 6.0 Hz, 3 H, 9-Me), 1.48 (s, 3 H, 3-Me), 1.26−1.69 (m, 6 H), 1.76−1.95 (m, 3 H), 2.07 (ddd, 1 H, J = 14.5, 4.75, 3.0 Hz), 2.41 (ddd, J = 17.5, 13.5, 4.0 Hz, 1 H), 2.64−2.74 (m, 1 H, H-9), 4.51 (d, 1 H, H-1′, J = 12.0 Hz), 4.87 (d, 1 H, H-1′, J = 12.0 Hz), 4.91 (d, J = 3.5 Hz, 1 H, H-10), 5.47 (s, 1 H, H-12), 7.00−7.08 (m, 2 H, H-3′, H-7′), 7.28−7.34 (m, 2 H, H-4′, H-6′). ^{13}C NMR: δ = 12.91, 20.18, 24.35, 24.53, 26.05, 30.72, 34.45, 36.28, 37.28, 44.23, 52.42, 68.91, 80.97, 87.88 (d, J = 2.5 Hz), 101.12, 104.01, 114.99 (d, J = 21.5 Hz), 128.83 (d, J = 8.0 Hz), 133.93 (d, J = 3.0 Hz). IR (film): $\tilde{\nu}_{max}$ = 2920, 1604, 1510, 1450, 1376, 1224, 1156, 1100, 1028, 1012, 956, 938, 876, 826 cm^{-1}. MS (CI, NH_3): m/z (%) = 410 (12) [MNH_4^+], 347 (32), 284 (100), 267 (70), 126 (4). $C_{22}H_{29}FO_5$ (392.5): calcd. C 67.33, H 7.45; found C 67.17, H 7.43.

10β-(9′-Anthrylmethoxy)dihydroartemisinin (31): This was prepared by the method used for the preparation of compound **26**, except that the eluent for chromatography was ethyl acetate/hexane (10:90). The product was obtained from DHA (**2**, 1.0 g, 3.5 mmol) and 9-anthrylmethanol (1.63 g, 7.0 mmol, 2 equiv.) as a pale yellow powder (1.07 g, 64%), m.p. 97−99 °C. $[\alpha]_D^{20}$ = +112.5 (c = 0.63, $CHCl_3$). ^1H NMR: δ = 0.77 (d, J = 7.5 Hz, 3 H, 6-Me), 0.92 (d, J = 6.0 Hz, 3 H, 9-Me), 1.57 (s, 3 H, 3-Me), 1.23−2.70 (m, 12 H), 5.14 (d, J = 3.5 Hz, 1 H, H-10), 5.51 (d, 1 H, H-1′, J = 11.5 Hz), 5.69 (s, 1 H, H-12), 5.86 (d, 1 H, H-1′, J = 11.5 Hz), 7.50−7.58 (m, 3 H, Ar-H), 8.02−8.05 (m, 2 H, Ar-H), 8.41−8.48 (m, 3 H, Ar-H). IR (film): $\tilde{\nu}_{max}$ = 2920, 1448, 1374, 1194, 1098, 1010, 938, 874, 846, 826, 754 cm^{-1}. MS (CI, NH_3): m/z (%) = 492 (18) [MNH_4^+], 474 (8), 446 (6), 284 (32), 267 (18), 207 (10), 191 (100). $C_{30}H_{34}O_5$ (474.6): calcd. C 75.92, H 7.22; found C 75.78, H 6.84.

10β-(9′-Phenanthrylmethoxy)dihydroartemisinin (32): This was prepared by the method used for the preparation of compound **26**, except that the eluent for chromatography was ethyl acetate/hexane (15:85). The product was obtained from DHA (**2**, 1.0 g, 3.5 mmol) and 9-phenanthrylmethanol (1.46 g, 7.0 mmol, 2 equiv.) as a yellow powder (1.38 g, 83%), m.p. 93−94 °C. $[\alpha]_D^{20}$ = +99.2 (c = 0.26, $CHCl_3$). ^1H NMR: δ = 0.89 (d, J = 7.5 Hz, 3 H, 6-Me), 0.96 (d, J = 6.0 Hz, 3 H, 9-Me), 1.52 (s, 3 H, 3-Me), 1.26−2.12 (m, 9 H), 2.43 (ddd, J = 18.5, 13.5, 4.0 Hz, 1 H), 2.69−2.75 (m, 1 H, H-9), 5.00 (d, 1 H, H-1′, J = 12.5 Hz), 5.10 (d, J = 3.5 Hz, 1 H, H-10), 5.43 (d, 1 H, H-1′, J = 12.5 Hz), 5.60 (s, 1 H, H-12), 7.59−8.77 (m, 9 H, Ar-H). IR (film): $\tilde{\nu}_{max}$ = 2920, 1450, 1376, 1248, 1194, 1098, 1042, 1006, 956, 938, 874, 826, 748, 724. MS (CI, NH_3): m/z (%) = 492 (32) [MNH_4^+], 446 (22), 429 (100), 267 (58), 208 (60), 191 (34). $C_{30}H_{34}O_5$ (474.6): C 75.92, H 7.22; found C 75.94, H 7.54.

10β-(5′-Pyrenylmethoxy)dihydroartemisinin (33): This was prepared by the method used for the preparation of compound **26**, except that the eluent for chromatography was ethyl acetate/hexane (10:90). The product was obtained from DHA (**2**, 1.0 g, 3.5 mmol) and 1-pyrylmethanol (1.63 g, 7.0 mmol, 2 equiv.) as a yellow powder (909 mg, 52%), m.p. 90−92 °C. $[\alpha]_D^{22}$ = +84.3 (c = 0.019, $CHCl_3$). ^1H NMR: δ = 0.91 (d, J = 7.5 Hz, 3 H, 6-Me), 0.95 (d, J = 6.0 Hz, 3 H, 9-Me), 8.01−8.35 (m, 9 H, Ar-H), 1.54 (s, 3 H, 3-Me), 0.86−1.61 (m, 6 H), 1.70−1.98 (m, 3 H), 2.11 (ddd, J = 14.5, 4.5, 2.95 Hz, 1 H), 2.43 (ddd, J = 17.5, 13.5, 4.0 Hz, 1 H), 2.69−2.79 (m, 1 H, H-9), 55.13 (d, J = 3.4 Hz, 1 H, H-10), 5.22 (d, 1 H, H-1′, J = 12.0 Hz), 5.63 (s, 1 H, H-12), 5.67 (d, 1 H, H-1′, J = 12.0 Hz). ^{13}C NMR: δ = 13.07, 20.30, 24.47, 24.67, 26.24, 30.99, 34.54, 36.43, 37.37, 44.40, 52.55, 68.48, 81.19, 88.20, 101.48, 104.17, 123.48, 124.48, 124.70, 124.80, 125.16, 125.89, 126.57, 127.29, 127.42, 127.47, 129.03, 130.77, 131.08, 131.23, 131.40. IR (film): $\tilde{\nu}_{max}$ = 2920, 1456, 1374, 1192, 1138, 1098, 1010, 938, 874, 846, 826, 754, 710 cm^{-1}. MS (CI, NH_3): m/z (%) = 516 (6) [MNH_4^+], 470 (8), 329 (8), 284 (28), 215 (100). $C_{32}H_{34}O_5$ (498.6): calcd. C 77.08, H 6.87; found C 76.81, H 7.13.

10β-(2′,2′,2′-Trifluoroethoxy)dihydroartemisinin (34): This was prepared by the method used for the preparation of compound **26**, except that the eluent for chromatography was ethyl acetate/hexane (8:92). The product was obtained from DHA (**2**, 426 mg, 1.5 mmol) and 2,2,2-trifluoroethanol (220 μL, 3.0 mmol, 2 equiv.) as a white powder (157 mg, 29%), m.p. 113−114 °C. $[\alpha]_D^{20}$ = +133 (c = 0.30, $CHCl_3$). ^1H NMR: δ = 0.97 (d, J = 7.5 Hz, 3 H, 6-Me), 0.98 (d, J = 6.0 Hz, 3 H, 9-Me), 1.46 (s, 3 H, 3-Me), 1.22−1.58 (m, 4 H), 1.64−1.96 (m, 5 H), 2.07 (ddd, J = 14.5, 5.0, 3.0 Hz, 1 H), 2.40 (ddd, J = 17.5, 13.5, 4.0 Hz, 1 H), 2.65−2.75 (m, 1 H, H-9), 3.89 (dq, 1 H, H-1′, J = 12.0, 8.5 Hz), 4.15 (dq, 1 H, H-1′, J = 12.0, 9.0 Hz), 4.90 (d, J = 3.5 Hz, 1 H, H-10), 5.43 (s, 1 H, H-12). ^{13}C NMR: δ = 12.47, 20.13, 24.11, 24.47, 25.90, 30.44, 34.39, 36.17, 37.29, 43.99, 52.32, 64.91 (d, J = 34.0 Hz), 80.73, 87.93, 102.41, 104.13. IR (film): $\tilde{\nu}_{max}$ = 2984, 2960, 2928, 2870, 1454, 1414, 1378, 1308, 1278, 1174, 1150, 1110, 1052, 1036, 990, 972, 918, 874, 824 cm^{-1}. MS (CI, NH_3): m/z (%) = 384 (16) [MNH_4^+], 367 (2) [MH^+], 284 (100), 267 (72). $C_{17}H_{25}F_3O_5$ (366.4): calcd. C 55.73, H 6.88; found C 55.79, H 6.81.

10β-(3′-Bromopropoxy)dihydroartemisinin (35). − Procedure 1: The compound **35** was prepared by a method analogous to that used for compound **26** above, except that the eluent for chromatography was ethyl acetate/hexane (10:90). The product was thus obtained from DHA (**2**, 1.0 g, 2.0 mmol) and 3-bromopropan-1-ol (182 μL, 2.0 mmol, 1 equiv.) as a fine white microcrystalline powder (419 mg, 52%), m.p. 90−92 °C (ref.[50] m.p. 85−86.5 °C). $[\alpha]_D^{20}$ = +103 (c = 0.013, $CHCl_3$). ^1H NMR: δ = 0.91 (d, J = 7.5 Hz, 3 H, 6-Me), 0.96 (d, J = 6.0 Hz, 3 H, 9-Me), 0.85−0.99 (m, 1 H), 1.45 (s, 3 H, 3-Me), 1.14−1.79 (m, 7 H), 1.87−1.89 (m, 1 H), 2.00−2.13 (m, 3 H), 2.32−2.42 (m, 1 H), 2.63−2.66 (m, 1 H), 3.44−3.58 (m, 3 H, H-1′, 2 × H-3′), 3.97−4.04 (m, 1 H, H-1′), 4.81 (d, J = 3.5 Hz, 1 H, H-10), 5.43 (s, 1 H, H-12). ^{13}C NMR: δ = 12.79, 20.18, 24.33, 24.48, 26.00, 30.40, 30.71, 32.36, 34.45, 36.24, 37.27, 44.21, 52.40, 65.52, 87.74, 101.92. −IR (film): $\tilde{\nu}_{max}$ = 2922, 2874, 1450, 1376, 1194, 1124, 1104, 1024, 984, 874, 826 cm^{-1}. MS(CI, NH_3): m/z (%) = 424 (50) [M − ^{81}Br + NH_4^+], 422 (50) [M − ^{79}Br + NH_4^+], 284 (100). − **Procedure 2:** Trichloroacetonitrile (0.11 mL, 0.16 g, 1.1 mmol) and 1,8-diazabicyclo[5.4.0]undecane (7.5 μL, 7.6 mg, 0.05 mmol) were added to a stirred mixture of dihydroartemisinin (284 mg, 1.0 mmol) in dichloromethane (5 mL). After 18.5 h, the mixture was added to a stirred solution of 3-bromopropan-1-ol (0.26 mL, 417 mg, 3.0 mmol) in dichloromethane. Tin(II) chloride (9.5 mg, 0.05 mmol) was then added. After 2.5 h, the reaction was quenched with 5% aqueous $NaHCO_3$ (10 mL). The organic layer was separated and dried ($MgSO_4$). Filtration and concentration of the filtrate gave a pale yellow oil, which was purified by column chromatography on silica with ethyl acetate/hexane (8:92) to give compound **35** as a white powder (253 mg, 63%).

10β-(3′-Phenylaminopropoxy)dihydroartemisinin (37) and 10β-(3′-Morpholinopropoxy)dihydroartemisinin (38): Compound **35** was converted into the amine **37** as follows. Aniline (0.54 mL, 5.94 mmol) was added to a stirred solution of compound **35** in DMF (20 mL) and the resulting mixture was heated at 60 °C. After 4 h, the dark brown solution was washed with water (5 × 10 mL) and extracted with diethyl ether (2 × 10 mL), and the combined extracts were dried ($MgSO_4$). Filtration and concentration of the filtrate gave a residue that, on chromatography with ethyl acetate/

hexane (30:70), gave the product **37** as a pale straw-coloured oil (62 mg, 54%), $[\alpha]_D^{21}$ = +126 (*c* = 0.51, CH_2Cl_2). ^1H NMR: δ = 0.92 (d, *J* = 6.0 Hz, 3 H, 9-Me), 0.94 (d, *J* = 7.5 Hz, 3 H, 6-Me), 1.44 (s, 3 H, 3-Me), 2.31−2.42 (dt, 1 H, H-5a, *J* = 4.0, 14.0 Hz), 2.60−2.70 (m, 1 H, H-9), 3.23 (t, 2 H, H-2′, *J* = 6.5 Hz), 3.45−3.52 (m, 1 H, H-1′), 3.99−4.06 (m, 1 H, H-1′), 4.82 (d, *J* = 3.45 Hz, 1 H, H-10), 5.39 (s, 1 H, H-12), 6.60 (d, 2 H, H-3′, *J* = 7.5 Hz), 6.70 (t, 1 H, H-5′, *J* = 7.5 Hz), 7.14−7.20 (m, 2 H, H-4′). ^{13}C NMR: δ = 13.08, 20.30, 24.60, 26.16, 29.33, 30.85, 34.57, 36.40, 37.33, 41.63, 44.37, 52.51, 66.46, 81.04, 87.87, 102.02, 104.09, 112.65, 117.24, 129.21, 148.25. IR (film): $\tilde{\nu}_{max}$ = 3405, 3055, 2953, 2921, 2875 cm^{-1}. MS (EI): *m/z* (%) = 417 (4) [M^+]. $C_{24}H_{35}NO_5$ (417.6): calcd. C 68.63, H 8.01, N 3.48; found C 68.22, H 8.25, N 3.36. The amine **38** was obtained as follows. Morpholine (1.05 mL, 12.04 mmol) was added to a stirred solution of compound **35** (239 mg, 0.589 mmol) in 1,4-dioxane (10 mL) and the mixture was heated at 50 °C overnight. Upon cooling, the solvent was removed under reduced pressure to give a residue that, on chromatography with methanol/ethyl acetate (2:98), gave the product **38** as a colourless oil (219 mg, 90%), $[\alpha]_D^{20}$ = +91.9 (*c* = 0.02, $CHCl_3$). ^1H NMR: δ = 0.91 (d, *J* = 7.5 Hz, 3 H, 9-Me), 0.96 (d, *J* = 6.0 Hz, 3 H, 6-Me), 0.87−0.99 (m, 1 H), 1.45 (s, 3 H, 3-Me), 1.21−1.66 (m, 4 H), 1.72−1.89 (m, 5 H), 2.02−2.07 (m, 1 H), 2.38−2.47 (m, 3 H), 2.62−2.64 (m, 1 H), 3.39−3.46 (m, 1 H), 3.71−3.75 (m, 3 H), 3.87−3.94 (m, 1 H), 4.79 (d, *J* = 3.5 Hz, 1 H, H-10), 5.41 (s, 1 H, H-12). ^{13}C NMR: δ = 13.02, 20.35, 24.46, 24.68, 26.19, 26.75, 30.89, 34.63, 36.41, 37.50, 44.42, 52.55, 53.74, 55.92, 66.35, 66.97, 81.09, 87.87, 101.95, 104.04. IR (film): $\tilde{\nu}_{max}$ = 2950, 2872, 2808, 1446, 1376, 1142, 1118, 1104, 1028, 1012, 990, 876, 864, 826 cm^{-1}. MS (CI, NH_3): *m/z* (%) = 412 (100) [MH^+], 366 (90). $C_{22}H_{37}NO_6$ (411.5): calcd. C 64.21, H 9.06, N 3.40; found C 63.66, H 8.75, N 3.13.

10β-[(Cholest-5′-en-3′-yl)oxy]dihydroartemisinin (36): This was prepared by a method analogous to that used for compound **26** above, except that the eluent for chromatography was ethyl acetate/hexane (50:50). The product was thus obtained from DHA (**2**, 426 mg, 1.5 mmol) and cholesterol (1.16 g, 3.0 mmol, 2 equiv.) as a white powder (714 mg, 73%), m.p. 168.3−168.8 °C. $[\alpha]_D^{20}$ = +82.5 (*c* = 0.16, $CHCl_3$). ^1H NMR: δ = 0.70 (s, 3 H), 0.87−2.44 (m, 60 H), 2.60−2.65 (m, 1 H, H-9), 3.57−3.62 (m, 1 H, H-3′), 4.95 (d, *J* = 3.35 Hz, 1 H, H-10), 5.36 (d, 1 H, H-6′, *J* = 5.0 Hz), 5.48 (s, 1 H, H-12). ^{13}C NMR: δ = 11.84, 13.07, 18.70, 19.44, 20.36, 21.06, 22.55, 22.80, 23.81, 24.27, 24.49, 24.68, 26.21, 27.63, 27.99, 28.23, 30.75, 31.87, 34.71, 35.78, 36.17, 36.48, 36.69, 36.97, 37.45, 39.50, 39.75, 40.29, 42.30, 44.53, 50.10, 52.62, 56.13, 56.70, 76.32, 81.21, 88.03, 99.50, 103.98, 121.63, 140.67. IR (film): $\tilde{\nu}_{max}$ = 2936, 1462, 1376, 1100, 1012, 878, 826, 754 cm^{-1}. $C_{42}H_{68}O_5$ (653.0): calcd. C 77.25, H 10.50; found C 77.02, H 10.73.

10β-(Trimethylsilyloxy)dihydroartemisinin (39): Trimethylsilyl chloride (5.22 mL, 4.47 g, 41.17 mmol, 7.74 equiv.) was added to a cold (0 °C), stirred solution of DHA (**2**, 1.51 g, 5.32 mmol) in pyridine (20 mL). After 1.25 h, the mixture was poured into ice/water (50 mL). The solution was extracted with diethyl ether (3 × 30 mL), and the extracts were dried ($MgSO_4$) and filtered. The filtrate was coevaporated with toluene (3 × 30 mL) to give an oil, which was purified by chromatography with ethyl acetate/hexane (5:95) to give the product as white needles (1.43 g, 76%), m.p. 54−55 °C. $[\alpha]_D^{22}$ = +141.77 (*c* = 0.96, $CHCl_3$). ^1H NMR: δ = 0.15 (s, 9 H, Me_3), 0.84 (d, *J* = 7.5 Hz, 3 H, 9-Me), 0.95 (d, 3 H, *J* = 6.15 Hz, 6-Me), 1.17−1.36 (m, 2 H), 1.42 (s, 3 H, 3-Me), 1.45−1.53 (m, 2 H), 1.56−1.65 (m, 1 H), 1.67−1.80 (m, 2 H), 1.84−1.90 (m, 2 H), 1.98−2.04 (m, 1 H), 2.31−2.42 (m, 1 H), 2.41−2.60 (m, 1 H), 5.46 (s, 1 H, H-12), 5.16 (d, *J* = 2.75 Hz, 1 H, H-10). ^{13}C NMR: δ = 0.61, 14.02, 21.05, 25.08, 25.37, 26.88, 32.16, 35.52, 37.18, 38.18, 45.20, 53.32, 81.87, 88.42, 97.09, 104.62. IR (film): $\tilde{\nu}_{max}$ = 2954, 2921, 2873, 1450, 1374, 1250, 1226, 1194, 1160, 1122, 1102, 1036, 992, 942, 890, 842 cm^{-1}. MS (CI, CH_4): *m/z* (%) = 359 (1) [MH^+, 2 × ^{13}C], 358 (4) [MH^+, ^{13}C], 357 (16) [MH^+]. $C_{18}H_{32}O_5Si$ (356.5): calcd. C 60.64, H 9.05; found C 60.42, H 8.89.

10α-(Trimethylsilyloxy)dihydroartemisinin (40): Triethylamine (12.27 mL, 8.91 g, 88.03 mmol, 1.25 equiv.) and trimethylsilyl chloride (11.17 mL, 9.56 g, 88.03 mmol, 1.25 equiv.) were successively added to a cold (0 °C), stirred solution of DHA (**2**, 20.0 g, 70.42 mmol) in dichloromethane (400 mL). After 1.5 h, the reaction mixture was poured into ice/water (400 mL). The aqueous layer was separated and extracted with dichloromethane (3 × 200 mL). The combined organic layers were dried ($MgSO_4$). Filtration and concentration of the filtrate under reduced pressure gave a light brown solid that, on chromatography with ethyl acetate/hexane (5:95), gave the product as a white, microcrystalline solid (20.87 g, 83%), m.p. 88−89 °C. $[\alpha]_D^{22}$ = +26.07 (*c* = 1.35, $CHCl_3$). ^1H NMR: δ = 0.18 (s, 9 H, CMe_3), 0.85 (d, 3 H, 9-Me, *J* = 7.0 Hz,), 0.94 (d, 3 H, 6-Me, *J* = 6.0 Hz,), 1.19−1.35 (m, 1 H), 1.41 (s, 3 H, 3-Me), 1.44−1.87 (m, 8 H), 2.04 (m, 1 H), 2.30−2.40 (m, 2 H), 4.75 (d, 1 H, *J* = 9.03 Hz, H-10), 5.31 (s, 1 H, H-12). ^{13}C NMR: δ = 0.58, 12.71, 20.21, 22.02, 24.68, 25.86, 34.25, 34.52, 36.23, 37.26, 45.23, 51.56, 80.18, 90.85, 94.93, 103.95. IR (film): $\tilde{\nu}_{max}$ = 2957, 2875, 2847, 1454, 1376, 1246, 1207, 1159, 1131, 1087, 1039, 899, 876, 757 cm^{-1}. MS (FAB, NBA): *m/z* (%) = 359 (3) [MH^+, 2 × ^{13}C], 358 (12) [MH^+, ^{13}C], 357 (51) [MH^+], 356 (18) [M^+]. $C_{18}H_{32}O_5Si$ (356.5): calcd. C 60.64, H 9.05; found C 60.55, H 8.74.

10β- and 10α-(1′-Naphthylmethoxy)dihydroartemisinin (41 and 42). − Procedure 1: The first method was analogous to that used for compound **26** above, except that boron trifluoride−diethyl ether (0.18 mg, 160 μL, 1.27 mmol, 0.2 equiv.) was used and the eluent for chromatography was ethyl acetate/hexane (10:90). The less polar 10β-isomer **41** was thus obtained from DHA (**2**, 2.0 g, 7.04 mmol) and 1-naphthylmethanol (1.0 g, 6.33 mmol) as a white foam (904 mg, 34%), m.p. 49−51 °C. $[\alpha]_D^{22}$ = +124 (*c* = 4.56, CH_2Cl_2). ^1H NMR: δ = 0.85 (d, 3 H, 6 or 9-Me, *J* = 7.5 Hz), 0.90 (d, 3 H, 6 or 9-Me, *J* = 8.0 Hz), 0.94−0.97 (m, 1 H), 1.16−1.31 (m, 2 H), 1.38−1.45 (m, 2 H), 1.48 (s, 3 H, 3-Me), 1.51−1.58 (m, 1 H), 1.68−1.92 (m, 3 H), 1.98−1.92 (m, 1 H), 2.32−2.42 (m, 1 H), 2.63−2.71 (m, 1 H), 4.92 (d, 1 H, OCH_2, *J* = 12.5 Hz), 5.15 (d, *J* = 3.5 Hz, 1 H, H-10), 5.37 (d, 1 H, OCH_2, *J* = 12.5 Hz), 5.52 (s, 1 H, H-12), 7.38−7.55 (m, 4 H, 4 × Ar-H), 7.75−7.84 (m, 2 H, 2 × Ar-H), 8.00−8.04 (m, 1 H, Ar-H). ^{13}C NMR: δ = 12.92, 20.19, 24.32, 24.54, 26.09, 30.82, 34.43, 36.29, 37.22, 44.25, 52.40, 68.16, 80.99, 87.98, 101.27, 103.98, 123.81, 125.11, 125.55, 125.60, 125.81, 128.15, 128.37, 131.28, 133.45, 133.61. IR (film): $\tilde{\nu}_{max}$ = 3055, 2954, 2923, 2876 cm^{-1}. MS (CI, NH_3): *m/z* (%) = 444 (3) [MNH_4^+, 2 × ^{13}C] 443 (12) [MNH_4^+, ^{13}C] 442 (43) [MNH_4^+]. $C_{26}H_{32}O_5$ (424.5): calcd. C 73.56, H 7.60; found C 73.66, H 7.59. The more polar component was the 10-α isomer **42**, also obtained as a white foam (515 mg, 19%), m.p. 49−53 °C. $[\alpha]_D^{22}$ = −95.53 (*c* = 0.94, $CHCl_3$). ^1H NMR: δ = 0.76 (d, *J* = 7.0 Hz, 3 H, 9-Me), 0.90 (d, *J* = 5.5 Hz, 3 H, 6-Me), 0.94−0.97 (m, 1 H), 1.04−1.14 (m, 1 H), 1.17−1.30 (m, 3 H), 1.40−1.48 (m, 1 H,), 1.49 (s, 3 H, 3-Me), 1.52−1.62 (m, 2 H), 1.82−1.89 (m, 1 H), 1.98−2.06 (m, 1 H), 2.32−2.39 (m, 1 H), 2.42−2.54 (m, 1 H), 4.56 (d, *J* = 9.0 Hz, 1 H, H-10), 5.03 (d, 1 H, OCH_2, *J* = 12.5 Hz), 5.34 (s, 1 H, H-12), 5.45 (d, 1 H, OCH_2, *J* = 12.5 Hz), 7.38−7.55 (m, 4 H, 4 × Ar-H), 7.76−7.84 (m, 2 H, 2 × Ar-H), 8.14−8.17 (m, 1 H, Ar-H). ^{13}C

NMR: δ = 12.56, 20.11, 21.99, 24.58, 25.97, 32.46, 34.01, 36.19, 37.12, 45.23, 51.45, 68.07, 80.21, 91.12, 98.44, 104.14, 124.27, 125.00, 125.55, 125.86, 126.36, 128.26, 128.33, 131.60, 133.39, 133.53. IR (film): $\tilde{\nu}_{max}$ = 3048, 2924, 1452, 1376, 1168, 1146, 1132, 1052, 1030, 926, 878, 848, 826, 792, 778 cm^{-1}. MS (CI, NH_3): *m/z* (%) = 445 (1) [MNH_4^+, 3 × ^{13}C] 444 (6) [MNH_4^+, 2 × ^{13}C], 443 (6) [MNH_4^+, ^{13}C] 442 (58) [MNH_4^+]. $C_{26}H_{32}O_5$ (424.5): calcd. C 73.56, H 7.60; found C 73.77, H 7.60. − **Procedure 2:** A solution of DHA (284 mg, 1.0 mmol) in anhydrous dichloromethane (5 mL) was treated with trichloroacetonitrile (0.11 mL, 1.1 mmol) and 1,8-diazabicyclo[5.4.0]undecane (7.5 μL, 0.05 mmol), and stirred at ambient temperature (ca. 20 °C) for 18 h. It was then added to a solution of 1-naphthylmethanol (474 mg, 3.0 mmol) in dichloromethane (5 mL), and the resulting mixture was treated with anhydrous $SnCl_2$ (9.5 mg, 0.05 mmol) in one portion. After another 2 h, the reaction mixture was quenched with 5% aqueous $NaHCO_3$ (10 mL). The organic layer was separated and dried (Na_2SO_4). After filtration, it was concentrated under reduced pressure to leave a residue, which was purified by chromatography with ethyl acetate/hexane (5:95) to give solely the 10-β epimer **41** (333 mg, 78%).

10β- and 10α-(2′-Naphthylmethoxy)dihydroartemisinin (43 and 44). − Procedure 1: These were prepared by a method analogous to that used for compound **26** above, except that boron trifluoride−diethyl ether (0.2 equiv.) was used and the eluent for chromatography was ethyl acetate/hexane (10:90). The less polar 10-β isomer **43** was thus obtained from DHA (**2**, 1.0 g, 3.52 mmol) and 2-naphthylmethanol (0.45 g, 2.82 mmol) as a white foam (603 mg, 50%), m.p. 48−49 °C. $[\alpha]_D^{22}$ = +100 (*c* = 1.65, CH_2Cl_2). ^1H NMR: δ = 0.88−0.82 (m, 1 H), 0.91 (d, *J* = 6.0 Hz, 3 H, 9-Me), 0.97 (d, *J* = 7.5 Hz, 3 H, 6-Me), 1.18−1.39 (m, 3 H), 1.47 (s, 3 H, 3-Me), 1.49−1.55 (m, 1 H), 1.56−1.63 (m, 1 H), 1.75−1.92 (m, 3 H), 1.99−2.06 (m, 1 H), 2.32−2.43 (m, 1 H), 2.66−2.73 (m, 1 H), 4.68 (d, 1 H, OCH_2, *J* = 12.5 Hz), 4.96 (d, *J* = 3.5 Hz, 1 H, H-10), 5.04 (d, 1 H, OCH_2, *J* = 12.5 Hz), 5.51 (s, 1 H, H-12), 7.41−7.49 (m, 3 H, Ar-H), 7.76−7.82 (m, 4 H, 4 × Ar-H). ^{13}C NMR: δ = 13.04, 20.23, 24.42, 24.57, 26.11, 30.84, 34.50, 36.32, 37.27, 44.31, 52.45, 69.73, 81.03, 87.95, 101.18, 104.02, 125.48, 125.69, 125.96, 126.00, 127.57, 127.76, 127.93, 132.74, 133.10, 135.64. IR (film): $\tilde{\nu}_{max}$ = 3057, 2924, 2874 cm^{-1}. MS (CI, NH_3): *m/z* (%) = 444 (2) [MNH_4^+, 2 × ^{13}C], 443 (9) [MNH_4^+, ^{13}C], 442 (29) [MNH_4^+] 425 (1) [MH^+], 424 (6) [M^+]. $C_{26}H_{32}O_5$ (424.5): calcd. C 73.56, H 7.60; found C 73.27, H 7.60. The more polar 10-α isomer **44** was also obtained as a white foam (341 mg, 28%), m.p. 43−45 °C. $[\alpha]_D^{22}$ = −82.29 (*c* = 0.7, $CHCl_3$). ^1H NMR: δ = 0.83−0.88 (m, 1 H), 0.93 (6 H, overlapping triplet, 6- and 9-Me, *J* = 5.5 Hz), 1.12−1.27 (m, 2 H), 1.30−1.36 (m, 1 H), 1.38−1.45 (m, 1 H), 1.48 (s, 3 H, 3-Me), 1.51−1.71 (m, 2 H), 1.79−1.92 (m, 2 H), 1.99−2.07 (m, 1 H), 2.34−2.40 (m, 1 H), 2.43−2.60 (m, 1 H), 4.54 (d, *J* = 9.0 Hz, 1 H, H-10), 4.81 (d, 1 H, OCH_2, *J* = 12.5 Hz), 5.12 (d, 1 H, OCH_2, *J* = 12.5 Hz), 5.33 (s, 1 H, H-12), 7.42−7.50 (m, 3 H, 3 × Ar-H), 7.80−7.83 (m, 4 H, 4 × Ar-H). ^{13}C NMR: δ = 12.73, 20.17, 22.10, 24.63, 26.02, 32.63, 34.08, 36.26, 37.21, 45.29, 51.54, 69.76, 80.32, 91.21, 98.62, 104.25, 125.67, 125.78, 125.91, 126.34, 127.60, 127.82, 127.90, 132.82, 133.14, 135. 61. IR (film): $\tilde{\nu}_{max}$ = 3057, 2928, 2874 cm^{-1}. MS (CI, NH_3): *m/z* (%) = 445 (1) [MNH_4^+, 3 × ^{13}C], 444 (6) [MNH_4^+, 2 × ^{13}C], 443 (21) [MNH_4^+, ^{13}C], 442 (76) [MNH_4^+], 425 (1) [MH^+], 424 (2) [M^+]. $C_{26}H_{32}O_5$ (424.5): calcd. C 73.56, H 7.60; found C 73.66, H 7.59. − **Procedure 2:** Trimethylsilyl triflate (50 μL, 0.28 μmol) in dichloromethane (1 mL) was added to a cold (−78 °C), stirred solution of 10α-(trimethylsiloxy)dihydroartemisinin (**40**) (238 mg, 0.67 mmol) and 2-naphthylmethanol TMS ether (170 mg, 0.74 mmol) in dichloromethane (8 mL). The reaction mixture was stirred at this temperature for 18 h and then diluted with dichloromethane (20 mL), washed with aqueous 10% $NaHCO_3$ (2 × 10 mL) and dried ($MgSO_4$). Filtration and concentration of the filtrate gave a residue, which was purified by chromatography with ether/hexane (1:3 to 3:7) to give the10-β epimer **43** (93 mg, 33%) and the 10-α epimer **44** (35 mg, 12%). − **Procedure 3:** This was as for procedure 2 above, except the temperature was kept at 0 °C and stirring at this temperature was for 2 h. Thus, the 10-β epimer **43** (237 mg, 84%) and the 10-α epimer **44** (30 mg, 11%) were isolated from DHA (**2**, 238 mg).

10β-(4′-Quinolyloxy)dihydroartemisinin (45): Triphenylphosphane (262 mg, 1.0 mmol) and diethyl azodicarboxylate (165 μL, 1.0 mmol) were added to a cold (0 °C), stirred solution of DHA (**2**, 284 mg, 1.0 mmol) and 4-hydroxyquinoline (145 mg, 1.0 mmol) in THF (5 mL). The reaction mixture was stirred overnight. The solvent was removed under reduced pressure and the residue, on chromatography with ethyl acetate/hexane (40:60), gave a crystalline solid (171 mg, 42%), recrystallization of which from ethyl acetate/hexane gave the product as white needles, m.p. 131−134 °C. $[\alpha]_D^{22}$ = + 45.93 (*c* = 0.028, $CHCl_3$). ^1H NMR: δ = 0.99 (d, *J* = 6.0 Hz, 3 H, 9-Me), 1.15 (d, *J* = 7.5 Hz, 3 H, 6-Me), 1.49 (s, 3 H, 3-Me), 1.10−2.18 (m, 10 H), 2.42 (ddd, *J* = 17.0, 13.0, 4.0 Hz, 1 H), 2.95−3.05 (m, 1 H, H-9), 5.49 (s, 1 H H-12), 5.82 (d, *J* = 3.4 Hz, 1 H, H-10), 7.28−8.22 (m, 6 H, Ar-H). IR (film): $\tilde{\nu}_{max}$ = 3252, 2990, 1592, 1532, 1506, 1308, 1244, 1098, 1068, 928, 874, 768 cm^{-1}. MS (CI, CH_4): *m/z* (%) = 412 (48) [MH^+], 284 (36), 267 (24), 221 (12), 191 (100), 146 (84). Correct microanalysis data could not be obtained for this compound.

10β-[4′-(7′-Trifluoromethylquinolyoxy)]dihydroartemisinin (46): This was prepared by a method analogous to that used for compound **45**. The product was thus obtained from DHA (**2**, 284 mg, 1.0 mmol) and 7-trifluoromethyl-4-quinolinol (213 mg, 1.0 mmol) as long needles (315 mg, 66%), m.p. 270−272 °C. $[\alpha]_D^{22}$ = +73.30 (*c* = 0.0179, $CHCl_3$). ^{19}F NMR: δ = 61.09. ^1H NMR: δ = 0.99 (d, *J* = 5.5 Hz, 3 H, 9-Me), 1.15 (d, 3 H, 6-Me, *J* = 7.35 Hz), 1.35−1.48 (m, 3 H), 1.49 (s, 3 H, 3-Me), 1.69−2.23 (m, 7 H), 2.38−2.48 (m, 1 H), 2.99−3.07 (m, 1 H, H-9), 5.47 (s, 1 H, H-12), 5.84 (d, *J* = 3.35 Hz, 1 H, H-10), 7.39−8.91 (m, 5 H, Ar-H). IR (Nujol): $\tilde{\nu}_{max}$ = 2922, 1596, 1570, 1510, 1456, 1378, 1332, 1302, 1194, 1162, 1132, 1098, 1064, 1040, 1014, 984, 950, 930, 898, 874, 828, 738, 684 cm^{-1}. MS (CI, CH_4): *m/z* (%) = 480 (12) [MH^+], 460 (28), 267 (80), 221 (100), 214 (72), 163 (60). $C_{25}H_{28}F_3NO_5$ (479.5): calcd. C 62.62, H 5.89, N 2.92; found C 62.43, H 6.16, N 2.63.

10β- and 10α-(1′-Naphthyloxy)dihydroartemisinins (47 and 48). − Procedure 1: This was analogous to that employed for compound **45**, except that DHA (**2**, 0.8 g, 2.82 mmol), triphenylphosphane (0.78 g, 2.96 mmol, 1.05 equiv.) and 1-naphthol (0.45 g, 3.10 mmol, 1.1 equiv.) were used, and the eluent for chromatography was ethyl acetate/hexane (10:90). Two major fractions were obtained. The less polar fraction consisted of an inseparable mixture of glycal **7** and the 10β-isomer **47** (333 mg overall). A cold (0 °C) solution of the mixture in dichloromethane (15 mL) was treated with *m*-chloroperoxybenzoic acid (0.28 g) in dichloromethane (15 mL). After 5 h, cyclohexene (5 mL) was added and the mixture was diluted with saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted further with dichloromethane (2 × 15 mL). The combined organic layers were dried ($MgSO_4$). Filtration and concentration of the filtrate gave a residue that, after chromatography with ethyl acetate/hexane (5:95), gave the 10-β isomer **47** as a white foam (120 mg, 10%), m.p. 139−141 °C. $[\alpha]_D^{22}$ = +99.90 (*c* = 0.98, $CHCl_3$). ^1H NMR: δ = 0.94 (d, *J* = 6.0 Hz, 3 H, 9-Me), 0.97−1.09 (m, 1 H), 1.12 (d, *J* = 7.5 Hz, 3 H, 6-Me), 1.25−1.32

(m, 2 H), 1.35−1.44 (m, 1 H), 1.46 (s, 3 H, 3-Me), 1.63−1.79 (m, 2 H), 1.83−1.91 (m, 1 H), 1.98−2.05 (m, 1 H), 2.10−2.35 (m, 2 H), 2.38−2.44 (m, 1 H), 2.91−2.97 (m, 1 H), 5.54 (s, 1 H, H-12), 5.71 (d, J = 3.5 Hz, 1 H, H-10), 7.36−7.43 (m, 2 H, 2 × Ar-H), 7.44−7.49 (m, 3 H, 3 × Ar-H). 7.77−7.82 (m, 1 H, Ar-H), 8.11−8.17 (m, 1 H, Ar-H). ^{13}C NMR: δ = 13.25, 20.25, 24.57, 24.62, 26.05, 31.34, 34.65, 36.32, 37.35, 44.40, 52.49, 80.96, 88.31, 100.82, 104.19, 108.49, 121.19, 121.76, 125.27, 125.73, 126.04, 126.33, 127.68, 134.41, 153.41. IR (film): $\tilde{\nu}_{max}$ = 3052, 2922, 2874, 1596, 1578, 1508, 1464, 1400, 1376, 1348, 1264, 1238, 1194, 1176, 1160, 1122, 1102, 1088, 1036, 1014, 990, 978, 954, 936, 874, 854, 794, 772, 738 cm^{-1}. MS (CI, CH_4): m/z (%) = 411 (3) [MH^+], 410 (6) [M^+]. $C_{25}H_{30}O_5$ (410.5): calcd. C 73.15, H 7.37; found C 73.00, H 7.47. The more polar fraction was the 10α-isomer **48**, also obtained as a white foam (192 mg, 17%); m.p. 153−155 °C. $[\alpha]_D^{22}$ = −86.75 (c = 0.8, $CHCl_3$). ^{1}H NMR: δ = 0.87 (d, J = 5.5 Hz, 3 H, 9-Me), 0.94−0.93 (m, 1 H), 0.99 (d, J = 7.0 Hz, 3 H, 6-Me), 1.13−1.29 (m, 3 H), 1.35 (s, 3 H, 3-Me), 1.39−1.49 (m, 1 H), 1.56−1.61 (m, 2 H), 1.63−1.72 (m, 1 H), 1.79−1.84 (m, 1 H), 1.92−1.99 (m, 1 H), 2.27−2.38 (m, 1 H), 2.79−2.91 (m, 1 H), 5.15 (d, 1 H, H-10, J = 10.0 Hz), 5.45 (s, 1 H, H-12), 7.15−7.18 (m, 1 H, Ar-H), 7.26−7.32 (m, 1 H, Ar-H), 7.34−7.41 (m, 3 H, 3 × Ar-H), 7.66−7.72 (m, 1 H, Ar-H), 8.20−8.24 (m, 1 H, Ar-H). ^{13}C NMR: δ = 12.85, 20.19, 22.09, 24.63, 25.93, 32.71, 34.06, 36.24, 37.26, 45.26, 51.55, 80.13, 91.05, 99.30, 104.39, 108.63, 121.57, 122.21, 125.15, 125.84, 126.13, 127.32, 134.34, 153.66. IR (film): $\tilde{\nu}_{max}$ = 3052, 2926, 2874, 1596, 1578, 1506, 1462, 1396, 1378, 1262, 1236, 1180, 1132, 1112, 1088, 1036, 1020, 928, 874, 852, 826, 794, 772, 736 cm^{-1}. MS (CI, NH_3): m/z (%) = 429 (17) [MNH_4^+, ^{13}C], 428 (55) [MNH_4^+]. $C_{25}H_{30}O_5$ (410.5): calcd. C 73.15, H 7.37; found C 72.77, H 7.45. − **Procedure 2:** A solution of DHA (**2**, 284 mg, 1.0 mmol), trichloroacetonitrile (0.11 mL, 1.1 mmol) and 1,8-diazabicyclo[5.4.0]undecane (7.5 μL, 0.05 mmol) in dichloromethane (5 mL) was stirred at ambient temperature (ca. 20 °C). After 18 h, the mixture was added to a solution of 1-naphthol (433 mg, 3.0 mmol) in dichloromethane (5 mL), and anhydrous $SnCl_2$ (9.5 mg, 0.05 mmol) was then added. After another 2 h, the reaction was quenched with 5% aqueous sodium bicarbonate (10 mL). The organic layer was separated and dried (Na_2SO_4), and then concentrated in vacuo. The residue was submitted to chromatography with ethyl acetate/hexane (5:95) to give 10-β epimer **47** (300 mg, 73%) and the glycal **7** (38 mg, 14%).

10α- and 10β-(2′-Naphthoxy)dihydroartemisinin (49 and 50). − Procedure 1: This was analogous to that used for the preparation of compound **45** above, except that DHA (**2**, 0.8 g, 2.82 mmol), triphenylphosphane (0.78 g, 2.96 mmol, 1.05 equiv.) and 2-naphthol (0.45 g, 3.10 mmol, 1.1. equiv.) were used, and the eluent for chromatography was ethyl acetate/hexane (10:90). Two fractions were obtained. The less polar 10β-isomer **49** was obtained as a white foam (111 mg, 10.9%), m.p. 129−131 °C. $[\alpha]_D^{22}$ = +226.98 (c = 0.63, $CHCl_3$). ^{1}H NMR: δ = 0.83−0.93 (m, 1 H), 0.96 (d, J = 6.0 Hz, 3 H, 9-Me), 1.05 (d, J = 7.5 Hz, 3 H, 6-Me), 1.24−1.44 (m, 2 H), 1.46 (s, 3 H, 3-Me), 1.48−1.54 (m, 1 H), 1.57−1.65 (m, 1 H), 1.69−1.74 (m, 1 H), 1.83−2.12 (m, 4 H), 2.34−2.44 (m, 1 H), 2.81−2.91 (m, 1 H), 5.54 (s, 1 H, H-12), 5.65 (d, J = 3.5 Hz, 1 H, H-10), 7.21−7.26 (m, 1 H, Ar-H), 7.30−7.36 (m, 1 H, Ar-H), 7.39−7.46 (m, 1 H, Ar-H), 7.55 (d, J = 2.5 Hz, 1 H, Ar-H), 7.73−7.76 (m, 3 H, 3 × Ar-H). ^{13}C NMR: δ = 12.98, 20.30, 24.45, 24.60, 26.06, 31.04, 34.63, 52.52, 81.02, 88.30, 100.64, 104.20, 110.88, 119.01, 123.94, 126.18, 127.15, 127.48, 129.21, 129.49, 134.46, 155.25. IR (film): $\tilde{\nu}_{max}$ = 2922, 2872, 1628, 1600, 1510, 1466, 1376, 1252, 1214, 1178, 1120, 1094, 1064, 1036, 980, 970, 938, 874, 846 cm^{-1}. MS (CI, CH_4): m/z (%) = 410 (3) [M^+], 267 (56) [M − $ONap^+$]. $C_{25}H_{30}O_5$ (410.5): calcd. C 73.15, H 7.37; found C 73.19, H 7.31. The more polar 10-α isomer **50** was also obtained as a white foam (56 mg, 5%), m.p. 43−45 °C. $[\alpha]_D^{22}$ = −82.29 (c = 0.7, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 3051, 2940, 2928. ^{1}H NMR: δ = 0.98 (d, J = 6.0 Hz, 3 H, 9-Me), 1.01 (d, J = 7.0 Hz, 3 H, 6-Me), 1.04−1.10 (m, 1 H), 1.21−1.40 (m, 3 H), 1.45 (s, 3 H, 3-Me), 1.48−1.59 (m, 2 H), 1.63−1.74 (m, 1 H), 1.77−1.83 (m, 1 H), 1.84−2.01 (m, 1 H), 2.06−2.08 (m, 1 H), 2.36−2.46 (m, 1 H), 2.76−2.82 (m, 1 H), 5.19 (d, J = 9.5 Hz, 1 H, H-10), 5.57 (s, 1 H, H-12), 7.25−7.36 (m, 2 H, 2 × Ar-H), 7.40−7.47 (m, 2 H, 2 × Ar-H), 7.72−7.77 (m, 3 H, 3 × Ar-H). ^{13}C NMR: δ = 12.53, 20.22, 22.15, 24.69, 25.97, 32.53, 34.14, 36.27, 37.34, 45.22, 51.58, 80.16, 91.11, 98.97, 104.46, 110.73, 119.38, 123.97, 126.15, 127.07, 127.55, 129.16, 129. 65, 134.31, 155.64 cm^{-1}. MS (CI, NH_3): m/z (%) = 430 (4) [MNH_4^+, 2 × ^{13}C], 429 (18) [MNH_4^+, ^{13}C], 428 (63) [MNH_4^+], 412 (6) [MH^+, ^{13}C], 411 (8) [MH^+], 410 (16) [M^+]. $C_{25}H_{30}O_5$ (410.5): calcd. C 73.15, H 7.37; found C 73.12, H 7.39. − **Procedure 2:** A solution of dihydroartemisinin (284 mg, 1.0 mmol), trichloroacetonitrile (0.11 mL, 1.1 mmol) and 1,8-diazabicyclo[5.4.0]undecane (7.5 μL, 0.05 mmol) in anhydrous dichloromethane (5 mL) was stirred at ambient temperature (ca. 20 °C) for 18 h. This was then added to a stirred solution of 2-naphthol (433 mg, 3.0 mmol) in dichloromethane (5 mL), and the resulting solution was treated with anhydrous $SnCl_2$ (13.3 mg, 0.07 mmol). After another 2 h, the reaction mixture was quenched with 5% aqueous $NaHCO_3$ (10 mL), and was submitted to workup and chromatography as described above for the 1-naphthol case to give the 10-β epimer **49** (327 mg, 77%). The glycal **7** was detected, and its amount in the crude reaction mixture was estimated to be 8% by means of ^{1}H NMR spectroscopy.

X-ray Crystallographic Study: The diffractometer used was a Siemens P4-RA machine operating at 10.5 kW. Determinations were carried out at ambient temperature. Computations were carried out using the SHELX suite of X-ray programs, either Version 5, or SHELX-97 (G. Sheldrick, University of Göttingen, **1997**). The structures were solved by direct methods, and refined using full-matrix least squares, based on F^2. − **α-Artesunate (5):** As it was possible to map all atoms by this technique, the constitution and relative stereostructure are unambiguously indicated. The reference standard was recrystallized from ethyl acetate solution by layer diffusion with hexane. Crystals grew as large transparent blocks of up to 2 mm max. dimension. Some discoloration was noticed after an extended time. Nevertheless, it is stressed that the purity of the reference standard as assayed by ^{1}H NMR spectroscopy at 750 MHz is 99.95% ± 0.025%. Thus, the crystal was selected from the recrystallized reference standard. The crystals belong to the orthorhombic system with cell parameters a = 9.853(1), b = 10.528(1) and c = 18.783(3) Å. The axial systematic absences (h00, 0k0, 00l = odd) uniquely indicated the space group to be $P2_12_12_1$, consistent with an enantiomerically pure material. A specimen approximately 1.2 × 1.2 × 1.0 mm in dimensions was used for data collection, which was carried out using a custom-built 1.5 mm X-ray collimator designed for use with larger crystal specimens. Intensity data were collected to $2\Theta_{max}$ = 55°, (Mo-K_α radiation) using a variable scan speed between 4.0 and 60° min^{-1}. Of a total of 2645 reflection intensities, 2622 were unique by symmetry and were used for structure refinement. The quality of symmetry equivalents could be gauged by R_{int} = 0.015 for 33 equivalent reflections. The quality of the structure determination was quite good, with all atoms including hydrogen atoms located. Non-hydrogen atoms were refined with anisotropic thermal parameters, hydrogen atoms were placed in geometrically idealized locations based on their experimentally determined ones, and refined with riding constraints

and isotropic thermal parameters linked to the U_{eq} of their parent C or O atom. Final discrepancy indices of $R1 = 0.0415$ and $wR2 = 0.0989$ and GOOF = 1.01 for observed data with $I > 2\sigma(I)$. The final difference electron density was +0.18 and −0.17 eÅ^{-3}. Insufficient anomalous scattering was present to determine the absolute configuration. However, the absolute configuration of the carbon skeleton in this class of compound has previously been determined by anomalous dispersion studies on the parent compound artemisinin by Chinese workers. In addition, the X-ray crystal structure determination has been carried out for a single crystal of dihydroartemisinin.[36] The thermal ellipsoid plot from the current determination is given in Figure 4, and crystal data and structure refinement are summarized in Table 2. The current data therefore provides proof of absolute configuration at all chiral centres. In particular, the absolute configuration at C-10 (C-12, crystallographic numbering, Figure 4) is confirmed as (*S*), corresponding to the α epimer of artesunate. Thus, the pendant side chain is effectively *trans* to the framework atom C(7) (crystallographic numbering, Figure 4). This is shown by the following torsional information: O(5)−C(12)−C(13)−C(14) −65.4°; O(5)−C12)−C(13)−C(7) 168.6°. The molecular structure also includes the key peroxy linkage O(1)−O(2) = 1.474(3) Å, which straddles the C(1−6) ring. The values for the C−O bond lengths involving peroxide oxygen atoms are C(1)−O(1) = 1.457(3) Å (longest), C(5)−O(2) = 1.411(4) Å, and the acetal oxygen atoms are C(5)−O(3) = 1.447(3), C(6)−O(3) = 1.393(3) (shortest) and C(6)−O(4) = 1.435(3) Å. − **β-Artesunate (8):** As it was possible to map all atoms by this technique, the constitution and relative stereostructure are unambiguously indicated. Crystals grew as transparent rods with glassy lustre, of up to 2 mm max. dimension. A tendency to twinning was shown by optical microscopy and X-ray rotation photographs. The crystals fragmented badly upon attempted cleavage across the rod axis. After numerous unsuccessful attempts, a unit cell was obtained on a single specimen (1.6 × 0.8 × 0.8 mm), which was used for single-crystal analysis. The crystals belonged to the orthorhombic system and axial systematic absences ($h00$, $0k0$, $00l$ = odd) uniquely indicated the space group to be $P2_12_12_1$, consistent with an enantiomerically pure material. Intensity data were collected to $2\Theta_{max} = 50°$, (Mo-K_α radiation) using a variable scan speed between 4.0 and 60°/min. The peaks were relatively broad and data were collected using the ω-scan method with scan widths of 1.4°. Of a total of 2066 reflection intensities, 2049 were unique by symmetry and used for structure refinement. The quality of the structure determination suffered slightly from the inherent poor quality of the diffraction profiles, but was unambiguous, with all atoms including hydrogen atoms located. Non-hydrogen atoms were refined with anisotropic thermal parameters, hydrogen atoms were placed in geometrically idealized locations based on their experimentally determined ones, and refined with riding constraints and isotropic thermal parameters linked to the U_{eq} of their parent C or O atom. The final $R = 0.067$, $wR2 = 0.157$ and GOOF = 1.02. Residual electron density was +0.26/−0.32 eÅ^{-3}. Insufficient anomalous scattering to determine the absolute configuration was present. However, the absolute configuration of the carbon skeleton in this class of compounds has previously been determined through anomalous dispersion studies on artemisinin by the Chinese workers. In addition, the X-ray crystal structure determination has been carried out for a single crystal of dihydroartemisinin.[36] The thermal ellipsoid plot from the current determination is given in Figure 4. Crystal data and structure refinement are summarized in Table 2. The current data therefore does provide proof of absolute configuration at all chiral centres, when the data is considered together with the manner of synthesis of β-artesunate from dihydroartemisinin. In particular, the absolute configuration at C-10 (C-12, crystallographic numbering, Figure 4) is confirmed as (*R*), corresponding to the β epimer of artesunate. Thus, the pendant side chain is effectively *cis* to the framework atom C(14) (crystallographic numbering, Figure 4). This is connected through the ester linkage and has a terminal carboxylic acid functionality, which is found to be present in protonated form. The molecular structure also includes the key peroxy linkage O(1)−O(2) = 1.469(8) Å, which straddles the C(1−6) ring. − Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-172514 (**5**) and -172513 (**8**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

We express our thanks to Dr. Melba Gomes, Manager, Task Force on Severe Malaria, Special Programme for Research and Training in Tropical Diseases (TDR), WHO, Geneva, and to Dr. Robert Carter, Head, Chemical Development and Product Management, Knoll AG, Liestal, for samples of Chinese and Vietnamese artesunate and DHA, and for their constructive advice and assistance in the artesunate programme. Financial support from UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) Grant No. 981123, WHO98/99.SC01 for the artesunate programme is gratefully acknowledged. Financial and material support from Bayer AG (Leverkusen, Germany), Grant Nos. HKUST/BAY 95/96, 97/98 and 99/00 for the preparation of new derivatives are gratefully acknowledged. Financial support from The Government of the HKSAR University Grants Council, Grant No. HKUST 6184/99P is also gratefully acknowledged.

[1] China Co-operative Research Group on Qinghaosu, *Kexue Tongbao* **1977**, *22*, 142; Qinghaosu Antimalarial Coordinating Research Group, *Chin. Med. J.* **1979**, *92*, 811−816; Qinghaosu Research Group, *Sci. Sin.* **1980**, *23*, 380−396.
[2] L. J. Bruce-Chwatt, *Brit. Med. J.* **1982**, *284*, 767−768; D. L. Klayman, A. J. Lin, N. Acton, J. P. Scovill, J. M. Hoch, W. K. Milhous, A. D. Theoharides, A. S. DoBek, *J. Nat. Prod.* **1984**, *47*, 715−717; C.-C. Shen, L.-G. Zhuang, *Med. Res. Rev.* **1984**, *4*, 47−86; T. T. Hien, N. J. White, *Lancet* **1993**, *341*, 603−608; Y. Li, Y.-L. Wu, *Med. Trop.* **1998**, *58*, suppl. 3, 9−12; M. A. van Agtmael, T. A. Eggelte, C. J. van Boxtel, *Trends Pharmacol. Sci.* **1999**, *20*, 199−205.
[3] D. L. Klayman, *Science* **1985**, *228*, 1049−1055.
[4] China Co-operative Research Group on Qinghaosu and its Derivatives as Antimalarials, *J. Tradit. Chin. Med.* **1982**, *2*, 45−50.
[5] China Co-operative Research Group on Qinghaosu and its Derivatives as Antimalarials, *J. Tradit. Chin. Med.* **1982**, *2*, 9−16.
[6] X. Lusha, *China Reconstructs* **1979**, 48−49.
[7] H. A. C. Titulaer, J. Zuidema, C. B. Lugt, *Int. J. Pharm.* **1991**, *69*, 83−92.
[8] China Co-operative Research Group on Qinghaosu and Its Derivatives as Antimalarials, *J. Tradit. Chin. Med.* **1982**, *2*, 25−30.
[9] Y. Li, P.-L. Yu, Y.-X. Chen, L.-Q. Li, Y.-Z. Gai, D. -S Wang, Y.-P. Zheng, *Acta Pharm. Sin.* **1981**, *16*, 429−439.
[10] P. I. Trigg, *Econ. Med. Plant Res.* **1989**, *3*, 20−55.
[11] Y.-L. Wu, Y. Li, *Med. Chem. Rev.* **1995**, *5*, 569−586.
[12] A. Brossi, B. Venugopalan, L. Dominguez Gerpe, H. J. C. Yeh, J. L. Flippen-Anderson, P. Buchs, X. D. Luo, W. Milhous, W. Peters, *J. Med. Chem.* **1988**, *31*, 645−650.
[13] M. J. Schmuklarsky, D. L. Klayman, W. K. Milhous, D. E.

Kyle, R. N. Rossan, A. L. Ager, D. B. Tang, M. H. Heiffer, C. J. Canfield, B. G. Schuster, *Am. J. Trop. Med. Hyg.* **1993**, *48*, 377−384.
[14] V. Leskovac, A. D. Theoharides, *Comp. Biochem. Physiol.* **1991**, *99*, 383−390; V. Leskovac, A. D. Theoharides, *Comp. Biochem. Physiol.* **1991**, *99*, 391−396; J. K. Baker, J. D. McChesney, H-T. Chi, *Pharm. Res.* **1993**, *10*, 662−666.
[15] G. Schmuck, R. K. Haynes, *Neurotoxic. Res.* **2000**, *2*, 37−49.
[16] T. G. Brewer, J. O. Peggins, S. J. Grate, J. M. Petras, B. S. Levine, P. J. Weina, J. Swearengen, M. H. Heiffer, B. G. Schuster, *Trans. R. Soc. Trop. Med. Hyg.* **1994**, *88*, 33−36; T. G. Brewer, S. J. Grate, J. O. Peggins, P. J. Weina, J. M. Petras, B. S. Levine, M. H. Heiffer, B. G. Schuster, *Am. J. Trop. Med. Hyg.* **1994**, *51*, 251−259.
[17] Registered as Artemotil: TDR News, June **2000**, no. 62.
[18] X. Liú, *Yao Hue Tong Bao* **1980**, *15*, 183; X. Liu, *Chem. Abstr.* **1987**, *107*, 78111j.
[19] *The Use of Artemisinin and Its Derivatives as Anti-Malarial Drugs' Report of a Joint CTD/DMP/TDR Informal Consultation*, Malaria Unit, Division of Control of Tropical Diseases, World Health Organization, Geneva, 10−12 June **1998**;.
[20] Q. Yang, W. Shi, R. Li, J. Gan, *J. Tradit. Chin. Med.* **1982**, *2*, 99−103; G. Li, X. Guo, R. Jin, Z. Wang, H. Jian, Z. Li, *J. Tradit. Chin. Med.* **1982**, *2*, 125−130.
[21] A. J. Lin, D. L. Klayman, W. K. Milhous, *J. Med. Chem.* **1987**, *30*, 2147−2150.
[22] K. T. Batty, K. F. Ilett, T. Davis, M. E. Davis, *J. Pharm. Pharmacol.* **1996**, *48*, 22−26.
[23] P. H. van Vianen, D. L. Klayman, A. J. Lin, C. B. Lugt, A. L. van Engen, H. J. van der Kaay, B. Mons, *Exp. Parasitol.* **1990**, *70*, 115−123.
[24] A. C. Beekman, A. R. W. Barentsen, H. J. Woerdenbag, W. van Uden, N. Pras, A. W. T. Konings, F. S. El-Feraly, A. M. Galal, H. V. Wikström, *J. Nat. Prod.* **1997**, *60*, 325−330; A. C. Beekman, H. J. Woerdenbag, H. H. Kampinga, A. W. T. Konings, *Phytother. Res.* **1996**, *10*, 140−144.
[25] G.-Q. Zheng, *Planta Med.* **1994**, *60*, 54−57; M. Jung, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1091−1094; G. H. Posner, P. Ploypradith, W. Hapangama, D. Wang, J. N. Cumming, P. Dolan, T. W. Kensler, D. Klinedinst, T. A. Shapiro, Y. Q. Zheng, C. K. Murray, L. G. Pilkington, L. R. Jayasinghe, J. F. Bray, R. Daughenbaugh, *Bioorg. Med. Chem.* **1997**, *5*, 1257−1265.
[26] H. J. Woerdenbag, T. A. Moskal, N. Pras, T. M. Malingré, F. El-Feraly, H. H. Kampinga, A. W. T. Konings, *J. Nat. Prod.* **1993**, *56*, 849−856.
[27] H. Lai, N. P. Singh, *Cancer Lett.* **1995**, *91*, 41−46.
[28] R. K. Haynes, W. L. Lam, A. Voerste, G. Schmuck, G. Greif, *C-11 Aza derivatives of Artemisinin for Treatment of Malaria, Coccidiosis, and Neosporosis*, 98305592.2, Europe, 14 July **1998**; Europe, 14 July **1999**; R. K. Haynes, W. L. Lam, H. W. Chan, M. K. Cheung, H. W. Tsang, G. Greif, *C-10 Ester Derivatives of Artemisinin for Treatment of Malaria, Coccidiosis, and Neosporosis*, 98305595.5, 14 July **1998**; Europe; July **1999**; R. K. Haynes, W. L. Lam, H. W. Chan, M. K. Cheung, H. W. Tsang, G. Greif, *C-9 Sulfur-, Nitrogen-, and Carbon Linked Derivatives of Artemisinin for Treatment of Malaria, Coccidiosis, and Neosporosis*, 98305628.4, Europe, 14 July **1998**; International (PCT) PCT/GB99/02272, July **1999**; R. K. Haynes, W. L. Lam, H. W. Chan, M. K. Cheung, H. W. Tsang, G. Greif, *C-10 Ether Derivatives of Artemisinin for Treatment of Malaria, Coccidiosis, and Neosporosis*, 98305594.8, Europe, 14 July **1998**; Europe, July **1999**; R. K. Haynes, W. L. Lam, H. W. Chan, M. K. Cheung, H. W. Tsang, Greif, G; G. Schmuck, *C-10 halogen, Amino- and Carbon-Substituted Derivatives of Artemisinin for Treatment of Malaria, Coccidiosis, and Neosporosis*, 98305596.3, Europe, 14 July **1998**; International (PCT) PCT/GB99/02267, July **1999**; R. K. Haynes, W. L. Lam, W. W. L. Hsiao, H. W. Chan, M. K. Cheung, H. W. Tsang, G. Greif, G. Schmuck, H. G. Lerchen, *Artemisinin Derivatives Bearing DNA Intercalating and Binding Groups Displaying Anticancer Activity*, 98305593.0, Europe, 14 July, **1998**; International (PCT) PCT/GB99/02276, July **1999**.
[29] P.-L. Yu, Y.-X. Chen, L. Ying, R.-Y. Ji, *Acta Pharm. Sin.* **1985**, *20*, 357−365.
[30] L. Ying, P. L. Yu, Y.-X. Chen, R.-Y. Ji, *Acta Chim. Sin.* **1982**, *40*, 557−561.
[31] M.-Z. Cao, S.-C. Hu, M.-H. Li, S. Zhang, *J. Nanjing College Pharm.* **1982**, *3*, 53−54.
[32] Y. Li, P.-L. Yu, Y.-X. Chen, L-Q. Li, Y.-Z. Gai, D.-S. Wang, Y.-P. Zheng, *Kexue Tongbao* **1979**, *24*, 667−669.
[33] For artesunate, MF $C_{19}H_{28}O_8$, the CAS RN 88495−63−0 and index name butanedioic acid, mono[(3*R*,5a*S*,-6*R*,8a*S*,9*R*,10*R*,12*R*,12a*R*)-decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10-yl] ester, or butanedioic acid, mono(decahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10-yl) ester, [3*R*-(3α,5aβ,6β,8aβ,9α,10α,12β,12a*R**)] or for the sodium salt, the CAS RN 82864−68−4, butanedioic acid, mono(decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10-yl) ester, sodium salt, [3*R*-(3α,5aβ,6β,8aβ,9α,10α,12β,12a*R**)] appeared in *Chemical Abstracts* until **1999**, with the hemisuccinate residue defined as 10*R* or "10-β". From **1999**, the "correct" name appeared after the abstracting of primary literature published by Chinese groups in Western journals, and in response to personal correspondence to CA in **1999** from R. K. H. through Dr. Melba Gomes and Dr. Mark Demesmaeker, Quality Assurance and Safety: Medicines, World Health Organization, Geneva, with *Chemical Abstracts*. The RN 182824−33−5, and CA index name butanedioic acid, mono[(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*S*,12*R*,12a*R*)-decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10-yl] ester was assigned; the hemisuccinyl residue is "10-α", corresponding to the correct absolute configuration for the Chinese artesunate, namely compound **5**, prepared from dihydroartemisinin and succinic anhydride. However, another substance designated artesunate also appears in *Chemical Abstracts*, with the RN 252637−87−9, and the CA index name butanedioic acid, mono[(3*R*,5a*S*,6*R*,8a*S*,9*R*,12*R*,12a*R*)-decahydro-3,6,9-trimethyl-3,12-epoxy-12*H*-pyrano[4,3-*j*]-1,2-benzodioxepin-10-yl] ester, MF $C_{19}H_{28}O_8$; in this case, the stereochemistry at C-10 is undefined. With the preparation of authentic β-epimer **8** as described in the current paper, a new CAS RN has to be assigned.
[34] H. Ziffer, R. J. Highet, D. L. Klayman, *Prog. Chem. Org. Nat. Prod.* **1997**, *72*, 121−214 (p. 142); J. A. Vroman, Alvimm. Gaston, M. A. Avery, *Curr. Pharm. Design* **1999**, *5*, 101−138 (p. 123).
[35] H. O. Chang, D. Wang, J. N. Cumming, G. H. Posner, *Spectrosc. Lett.* **1997**, *30*, 241−255; G. H. Posner, J. N. Cumming, H. S.Woo, P. Ploypradith, S. Xie, T. A. Shapiro, *J. Med. Chem.* **1998**, *41*, 940−951; J. N. Cumming, D. Wang, S. B. Park, T. A. Shapiro, G. H. Posner, *J. Med. Chem.* **1998**, *41*, 952−964.
[36] X. D. Luo, H. J. C. Yeh, A. Brossi, J. L. Flippen-Anderson, R. Gilardi, *Helv. Chim. Acta* **1984**, *67*, 1515−1522.
[37] We express our gratitude to Dr. Ho-Wai Chan for his careful written translations of the Chinese literature sources quoted in this paper.
[38] Samples were supplied by Dr. Melba Gomes, TDR/WHO, Geneva, and Dr. Robert Carter, Knoll AG, Liestal, included dual injection pack from Guilin Pharmaceutical Factory, China B/N 920615, commercial artesunate tables, Guilin Pharmaceutical Factory (from which artesunate was extracted), and from Knoll AG, Liestal, Switzerland, B/N 120995.
[39] R. K. Haynes, A. Voerste, unpublished work; A. Voerste, *The Preparation and Evaluation of Known and New Derivatives of Artemisinin and Totally Synthetic Trioxanes as Antimalarials*, Bayer AG, Leverkusen, **1996**.
[40] R. R. Schmidt, M. Hoffman, *Tetrahedron Lett.* **1982**, *23*, 409−412; R. R. Schmidt, "New Aspects of Glycosylation Re-

actions" in *Carbohydrates: Synthetic Methods and Applications in Medicinal Chemist'* (Eds.: H. Ogura, A. Hasegawa, T. Tsumi), Kodansha-VCH, Tokyo, Weinheim, **1992**, pp. 66−88.
[41] R. K. Haynes, H. W. Chan, M. K. Cheung, W.-L. Lam, H.-W. Tsang, unpublished work.
[42] O. Mitsunobu, *Synthesis* **1981**, 1−28.
[43] See, inter alia: P. Deslongchamps, "Intramolecular Strategies and Stereoelectronic Effects: Glycosides and Orthoesters Hydrolysis Revisited" in *The Anomeric Effect and Associated Stereoelectronic Effects* (Ed: G. R. J. Thatcher), Am. Chem. Soc., Washington D. C., **1993**, ACS Symp. Ser. 539, chapter 3; N. Pothier, S. Goldstein, P. Deslongchamps, *Helv. Chim. Acta* **1992**, *75*, 604; A. J. Bennett, M. L. Sinnot, *J. Am. Chem. Soc.* **1986**, *108*, 7287.
[44] M. Jung, S. Lee, *Heterocycles* **1997**, *45*, 1055−1058.
[45] X. D. Luo, C. C. Shen, *Med. Res. Rev.* **1987**, *7*, 29−52.
[46] J. L. Maggs, S. Madden, L. P. Bishop, P. M. O'Neill, K. B. Park, *Drug Metab. Dispos.* **1997**, *25*, 200−1204.
[47] K. Ramu, J. K. Baker, *J. Med. Chem.* **1995**, *38* 1911−1921.
[48] A. J. Lin, M. Lee, D. L. Klayman, *J. Med. Chem.* **1989**, *32*, 1249−1252.
[49] A. J. Lin, R. E. Miller, *J. Med. Chem.* **1995**, *38*, 764−770.
[50] S. Kamchonwongpaison, S. Paitayatat, Y. Thebtaranonth, P. Wilairat, Y. Yuthavong, *J. Med. Chem.* **1995**, *38*, 2311−2316.
[51] T. D. Quan, T. V. Sung, H. Ripperger, G. Adam, *J. Prakt. Chem.* **1997**, *339*, 642−645.
[52] G. H. Posner, P. Ploypradith, W. Hapangama, D. Wang, J. N. Cumming, P. Dolan, T. W. Kensler, D. Klinedinst, T. Shapiro, Q.-Y. Zheng, C. K. Murray, L. G. Pilkington, L. R. Jayasinghe, J. F. Bray, R. Daughenbaugh, *Biorg. Med. Chem.* **1997**, *5*, 1257−1265.
[53] B. Venugopalan, P. J. Karnik, C. P. Bapat, D. K. Chatterjee, N. Iyer, D. Lepcha, *Eur. J. Med. Chem.* **1995**, *30*, 697−706.
[54] A. J. Lin, L.-Q. Li, S. L. Andersen, D. L. Klayman, *J. Med. Chem.* **1992**, *35*, 1639−1642.
[55] D.-Y. Wang, K. Y. Wu, Y.-L. Wu, Y. Li, F. Shan, *J. Chem. Soc., Perkin Trans. 1* **1999**, 1827−1831.
[56] M. H. D. Postema, *Tetrahedron* **1992**, *48*, 8545−8599, and references therein.
[57] T. Kometani, H. Kondo, Y. C. Fujimori, *J. Chem. Soc., Chem. Commun.* **1987**, 1245−1246; T. Kometani, H. Kondo, Y. Fujimori, *Synthesis* **1988**, 1005−1007; A. B. Smith, K. J. Hale, H. A. Vaccaro, *J. Am. Chem. Soc.* **1991**, *113*, 2092.
[58] C. D. Hufford, S. I. Khalifa, A. T. McPhail, F. S. El-Feraly, M. S. Ahmad, *J. Nat. Prod.* **1993**, *56*, 62−66.
[59] O. Petrov, I. Ogynyanov, *Coll. Czech. Chem. Commun.* **1991**, *56*, 1037−1041.
[60] P. M. O′Neill, A. Miller, S. A. Ward, B. K. Park, F. Scheinmann, A. V. Stachulski, *Tetrahedron Lett.* **1999**, *40*, 9129−9132; P. M. O'Neill, A. Miller, L. P. D. Bishop, S. Hindley, J. L. Maggs, S. A. Ward, S. M. Roberts, F. Scheinmann, A. V. Stachulski, G. H. Posner, B. K. Park, *J. Med. Chem.* **2001**, *44*, 58−68.
[61] P. M. O'Neill, S. A. Ward, *Synthesis and Antimalarial Activity of Phenoxy Derivatives of Dihydroartemisinin*, PCT Int. Appl. WO 2001004123, 18 January **2001**.

Received August 2, 2001
[O01385]