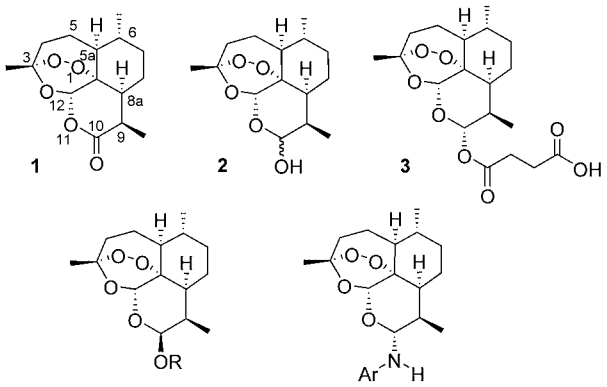
Convenient Access Both to Highly Antimalaria-Active 10-Arylaminoartemisinins, and to 10-Alkyl Ethers Including Artemether, Arteether, and Artelinate

Richard K. Haynes,*[a] Ho-Wai Chan,[a] Wing-Yan Ho,[a] Cliff Ki-Fung Ko,[a] Lucia Gerena,[b] Dennis E. Kyle,[b] Wallace Peters,[c] and Brian L. Robinson[c]

An economical phase-transfer method is used to prepare 10-arylaminoartemisinins from DHA and arylamines, and artemether, arteether, and artelinate from the corresponding alcohols. In vivo sc screens against Plasmodium berghei *and* P. yoelii *in mice reveal that the* p*-fluorophenylamino derivative* ***5g*** *is some 13 and 70 times, respectively, more active than artesunate; this reflects the very high sc activity of 10-alkylaminoartemisinins. However, through the po route, the compounds are less active than the alkylaminoartemisinins, but still approximately equipotent with artesunate.*

Introduction

The search continues apace for new antimalarials based on artemisinin, **1**,[1,2] but with the exception of artelinate (**4c**),[3] no "second generation" candidate has been identified, because



4a: R = Me, artemether
4b: R = Et, arteether
4c: R = $CH_2C_6H_4COOH$-*p*, artelinate

5a: Ar = C_6H_5
5b: Ar = C_6H_4Cl-*p*
5c: Ar = C_6H_4Br-*p*
5d: Ar = C_6H_4I-*p*
5e: Ar = C_6H_4COOH-*p*

the challenges posed by efficacy, economics, and lack of neurotoxicity cannot be met.[4] Unless the derivative possesses chemical robustness, as reflected in a long half-life,[5] and high efficacy coupled with low toxicity, its cost should be comparable to that of artesunate (**3**) (US$ 1.7–2.0 for a box of 12× 50 mg tablets),[6] the most widely used of the current artemisinins. However, this does not apply to derivatives such as those elegantly prepared by Avery and co-workers[2,7,8] required for the evaluation of structure–activity relationships, and which have provided a vital insight into the mechanism of action of the artemisinins.[4,9,10]

Whilst semisyntheses of artemisinins from artemisinic (qinghao) acid[11–16] have been recorded, artemisinic acid is inaccessible, in spite of an assertion to the contrary.[16] This compound is obtained by extraction from *Artemisia annua*,[17] and is converted in two steps into artemisinin itself by a process developed independently by Roth and Acton[11] and by ourselves.[12,13] On the other hand, use of artemisinic acid to prepare artemisinin derivatives can require up to eight steps,[18] and cannot compete with syntheses from artemisinin itself.

Artemisinin is easily extracted from *A. annua* on an industrial scale with hexanes or petroleum.[4] One crystallization of the crude but highly crystalline artemisinin from 95% ethanol suffices to provide pure material. Furthermore, the supply of artemisinin in a particular year is regulated by the need to predict beforehand how much *A. annua* has to be planted, for example in Vietnam, or harvested in the wild, for example in China, and not by agricultural limitations.[19]

Artesunate is made in one step from dihydroartemisinin (DHA, **2**), which is available commercially by reduction of artemisinin.[20] Logically then, any plan to prepare new artemisinin

[a] *Prof. R. K. Haynes, Dr. H.-W. Chan, W.-Y. Ho, C. K.-F. Ko*
Department of Chemistry
The Hong Kong University of Science and Technology
Clear Water Bay, Kowloon, Hong Kong (PR China)
Fax (+852) 2358-1594
E-mail: haynes@ust.hk

[b] *Dr. L. Gerena, Dr. D. E. Kyle*
Division of Experimental Therapeutics
Walter Reed Army Institute of Research
503 Robert Grant Avenue, Silver Spring, MD 20910 (USA)

[c] *Prof. W. Peters, B. L. Robinson*
Centre for Tropical Antiprotozoal Chemotherapy
Northwick Park Institute for Medical Research, Block Y
Watford Road, Harrow, Middlesex, HA1 3UJ (UK)

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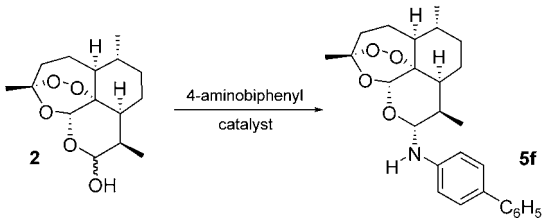
derivatives for the treatment of malaria would best employ artemisinin or DHA as starting material.

As a hemi-ester, artesunate is intrinsically unstable, and is rapidly hydrolyzed under physiological conditions to DHA.[21] The other current derivatives—artemether (**4a**) and arteether (**4b**)—are metabolized to DHA.[22] DHA is neurotoxic,[23] and elicits neurotoxicity in standardized in vitro assays against neuronal cell lines at levels corresponding to its in vitro activity against *P. falciparum*.[24] Therefore, any plan to prepare new artemisinin derivatives should be executed with the "MEAN" paradigm[4] in mind, namely no phase I "metabolism" to DHA, "economy" in production, favorable "adsorption", and "no neurotoxicity". By depressing log *P* through attachment of polar groups, which must also be inert to phase II metabolism, uptake is enhanced, and, at the same time, neurotoxicity is suppressed.[4,25,26] However, the groups must be judiciously chosen so as to keep the economics in check.

Li and co-workers prepared 10-arylamino-artemisinins including **5a**–**5e**[27,28] by treatment of DHA with arylamines in the presence of pyridinium sulfate in pyridine. Antimalarial activities were assessed in vivo against *P. berghei* K173 in mice through subcutaneous (sc) administration in peanut oil. As part of a general drug-development program, we have prepared 10-alkylaminoartemisinins,[29,30] which are both more accessible and more active as antimalarials than derivatives containing amino groups attached via a linker to C-10.[31–33] In order to allow us to select a candidate to replace artesunate, the most active of the current clinically used artemisinins, we required 10-arylaminoartemisinins for direct comparison with the 10-alkylaminoartemisinins. Moreover, arylaminoartemisinins, which are structurally analogous to aryl glycosylamines, should have acceptable stability at pH 4,[34] such as in the intestinal tract or in blood plasma, and thus hydrolysis to DHA should not be as facile as that of artesunate **3.**[21]

Because Li's method for the preparation of arylaminoartemisinins restricts the solvent to pyridine and the catalyst to the conjugate acid, we have developed another method of introducing the arylamine, which is also applicable to preparation of C-10 ethers, including artemether, arteether, and artelinate.

Table 1. *Effects of catalyst and solvents on reaction of DHA* ***2*** *(1 mmol) with 4-aminobiphenyl (1.1 mmol) at 19°C, 24 h.*

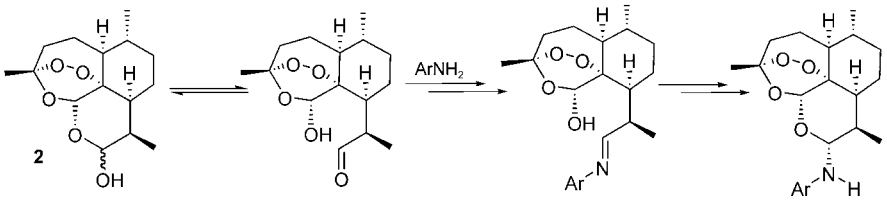


	acid	amount [mol%]	solvent (5 mL)	yield of **5f** [%]
1	$Yb(OTf)_3$	10	THF	29
2	$Yb(OTf)_3$	10	THF/H_2O 10:1	8
3	*p*-TsOH·H_2O	10	CH_2Cl_2/H_2O 1:1	21
4	–	–	CH_3OH[a]	13

[a] At reflux.

and phosphoric acids also catalyzed the reaction, although carboxylic acids, such as acetic or benzoic acids, were ineffective. The preliminary results are given in Table 1.

Glycosylamines are prepared from 1° and 2° amines and reducing sugars by heating in protic solvents.[37] The reaction proceeds through ring opening of the sugar to the aldehyde, which is intercepted by the amine to provide an imine, and closure to the glycosylamine. The structurally analogous DHA was therefore heated with 4-aminobiphenyl in methanol. The desired product **5f** was indeed obtained, albeit in 13% yield (Table 1). The reaction probably proceeds as indicated in Scheme 1. The use of higher-boiling or more polar alcohols (ethylene glycol) or aqueous alcohol solvents in the presence of buffers, according to the Kochetkov method for preparation of primary glycosylamines,[38] did not result in significant improvements in yield of the product.



Scheme 1. *Formation of the 10-arylamino derivative from DHA by ring opening and imine formation.*

Results and Discussion

Exploratory work

The 10-(*p*-biphenyl)amino derivative (**5f**) was obtained in variable yields from DHA (**2**) and 4-aminobiphenyl in THF or THF/water (1:1) in the presence of catalytic amounts of rare earth triflates.[35,36] The best yields (up to 29%) were obtained with $Yb(OTf)_3$ in THF. The acid TfOH, corresponding to the lanthanide counter ion, or, better, *p*-TsOH could be used as catalysts, although the yield was sensitive to the quantities used because of competing protonation of the 4-aminobiphenyl. TFA

Phase-transfer catalysis

As the best preliminary result was obtained with *p*-TsOH in CH_2Cl_2/water (Table 1), formation of **5f** under biphasic conditions was explored with different organic solvents in the presence of aqueous buffer (HCl/KCl) at various pHs with sodium dodecyl sulfate as a cationic phase-transfer (PT) agent. The results are shown in Table 2. The best yield (64%) was obtained at pH 1.2 with CH_2Cl_2 as organic solvent (entry 3).

The PT agent is essential. As seen in Table 3, for reactions with 0.05 M H_2SO_4 (pH ~ 1.2), the yield of **5f** decreases drastically with reduction in the amount of agent.

Table 2. Effect of solvent and pH on the reaction of DHA (1 mmol) with 4-aminobiphenyl (1.1 mmol) under biphasic condition with aqueous buffer and sodium dodecyl sulfate (20 mol%), 19°C, 24 h.

	buffer pH	Yield of **5 f** [%] with solvent (5 mL)			
		CH_2Cl_2	toluene	THF	*t*BuOH
1	~0.2	5	1	2	–[a]
2	1.0	58	5	19	5
3	1.2	64	28	31	9
4	1.4	26	3	3	3
5	2.0	26	–[a]	–[a]	–[a]

[a] Product not detected

Table 3. Effect of varying amounts of sodium dodecyl sulfate on the reaction of DHA (1.0 mmol) with 4-aminobiphenyl (1.10 mmol) under biphasic condition with aqueous H_2SO_4 (0.05 M, 5 mL) in CH_2Cl_2 (5.0 mL) at 19°C, 24 h.

	sodium dodecyl sulfate [mol%]	yield of **5 f** [%]
1	3	9.5
2	5	13
3	10	22
4	20	27

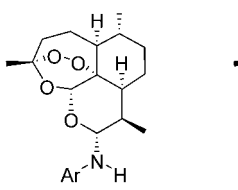
The yield of **5 f** was less than 25% for reactions run with 0.05 M H_2SO_4 in CH_2Cl_2. However, this was markedly improved when the reaction was run at 80°C in toluene, an industrially more desirable solvent (entry 3, Table 4). Addition of NaBr resulted in slightly higher yields (entries 4 and 5). This was finally improved to 74% with dilute HBr (0.1 M) as the aqueous phase (entry 6). Notably, the use of bromide in the biphasic system with CH_2Cl_2 at room temperature, or use of chloride ion or dilute HCl in the biphasic system with toluene was largely ineffective in enhancing yields.

Thus, bromide enhances the conversion of DHA into **5 f** in toluene. The proposed process is given in Scheme 2. The sodium dodecyl sulfate[39] transfers H^+ from the aqueous phase to the organic phase for the protonation of DHA. The protonated DHA reacts, probably though an S_N1 reaction, with Br^- to give bromide **6**,[40] which in turn reacts with the nucleophilic amine to give **5**. The stereochemistry of the amino group is always as depicted; no trace of the other amine epimer or of products differing in configuration of the methyl group at C-9 is observed. This stereochemical outcome is the same as for the reactions of the bromide **6** with alkylamines.[30] Glycal **7** is formed as a side product by the regeneration of HBr in an acid-catalyzed elimination; this by-product is invariably observed in crude reaction mixtures. The protonated DHA may also react with the amine nucleophile, or undergo elimination to the glycal, but these reactions must be slower than the reactions involving formation of the bromide **6**, and its conversion into the arylamino derivative. Evidently in CH_2Cl_2, activities of the putative intermediates—the protonated DHA or the derived chloride—are optimal for nucleophilic displacement, and consequently, the addition of bromide has no observable effect.

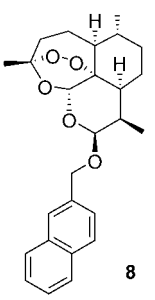
To conclude, the conversion of DHA into 10-arylamino-artemisinins is successful in a two-phase system of an organic solvent and dilute aqueous mineral acid with a phase-transfer catalyst. Bromide ions enhance the rate of conversion in toluene, and dilute HBr is the most convenient source for this purpose.

Preparative aspects and scope

For preparative work, two procedures, A—sodium dodecyl sulfate (20 mol%), aqueous buffer pH 1.2, in CH_2Cl_2 (5.0 mL), 19°C, 24 h—and B—sodium dodecyl sulfate (10 mol%), aqueous HBr (0.1 M, 5.0 mL), toluene, 80°C, 4 h—were used to prepare the arylaminoartemisinins **5 a–c** and **e–k** (Table 5).



5f: Ar = C_6H_4-C_6H_5-*p*
5g: Ar = C_6H_4F-*p*
5h: Ar = $C_6H_4SO_2CH_3$-*m*
5i: Ar = $C_6H_4SO_2CH_3$-*p*
5j: Ar = 2'-CH_3-C_6H_3-4'-NO_2
5k: Ar = $C_6H_4COOCH_3$-*p*



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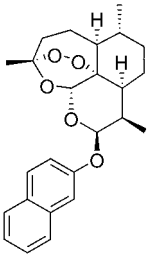

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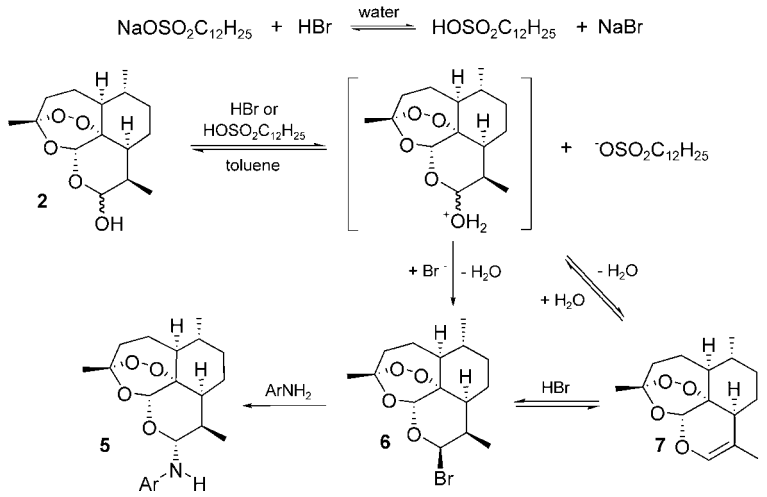
Oxygen nucleophiles also react, and artemether **4 a**, arteether **4 b**, artelinic acid **4 c**, and the ethers **8**[32] and **9**[32] were also prepared (entries 11–15).

Artemether and arteether are normally prepared from DHA by treatment of anhydrous reaction mixtures with either HCl or BF_3 etherate.[41,42] Of the two, artemether is more often used, mainly in a fixed-dose combination with lumifantrine.[43] Thus, the phase-transfer method represents an easier method for their preparation. Artelinic acid has been prepared previously by a more complicated route.[3,44]

The phase-transfer method cannot be applied to zwitterionic amino acids, such as L-cys-

Table 4. Effect of bromide ion on the reaction of DHA (1.0 mmol) with 4-aminobiphenyl (1.10 mmol) under biphasic condition with sodium dodecyl sulfate and aqueous acids.

	sodium dodecyl sulfate [mol%]	NaBr [mol%]	Acid (5 mL)	Solvent (5 mL)	*T* [°C]	reaction time [h]	yield of **5 f** [%]
1	10	0	0.05 M H_2SO_4	CH_2Cl_2	19	24	22
2	10	8.5	–	CH_2Cl_2	19	24	23
3	20	0	–	PhMe	80	4	61
4	10	10	–	PhMe	80	4	63
5	20	10	–	PhMe	80	4	69
6	10	0	0.1 M HBr	PhMe	80	4	74



Scheme 2. *Proposed pathways leading to 10-arylaminoartemisinins from DHA in PT catalysis.*

Table 5. *Reaction of DHA* **2** *(1.0 mmol) with nucleophiles (1.10 mmol) under biphasic conditions. Procedure A: sodium dodecyl sulfate (20 mol%), aqueous buffer, pH 1.2, CH_2Cl_2 (5.0 mL), 19°C, 24 h; Procedure B: sodium dodecyl sulfate (10 mol%), aqueous HBr (0.1 M, 5.0 mL), toluene, 80°C, 4 h.*

	Nucleophile	Product, procedure, isolated yield [%].
1	aniline	**5a**, A 55, B 83
2	*p*-chloroaniline	**5b**, A 40
3	*p*-bromoaniline	**5c**, A 38
4	*p*-aminobenzoic acid	**5e**, A 14, B 50
5	4-aminobiphenyl	**5f**, A 65, B 74
6	*p*-fluoroaniline	**5g**, A 82
7	*m*-(methylsulfonyl)aniline	**5h**, A 37
8	*p*-(methylsulfonyl)aniline	**5i**, A 78
9	2-methyl-4-nitroaniline	**5j**, A 50, B 65
10	methyl *p*-aminobenzoate	**5k**, A 53, B 49
11	methanol	**4a**, A 59
12	ethanol	**4b**, A 44.5
13	4-(hydroxymethyl)benzoic acid	**4c**, A 15, B 50
14	2-naphthalenemethanol	**8**, A 41
15	2-naphthol	**9**, A 17

teine, arylaminosulfonic acids and aromatic thiols and arylsulfinate salts. There also was no reaction at all with primary or secondary alkylamines, probably because these are too basic and are predominantly protonated under the reaction conditions.

Biological activities

Efficacy screens against *Plasmodium falciparum* were conducted with the W2 strain, which is resistant to chloroquine, and the D6 strain, which is sensitive to chloroquine but resistant to mefloquine. The assay was conducted by measuring the inhibition of uptake of radiolabeled hypoxanthine by the parasite (Table 6).[45]

With the exception of the arylamino derivatives **5a** and **5f**, and the 2-naphthalenemethanol derivative **8**, activities, as expressed by IC_{50}, are less than 1 ng mL^{-1}. The very poor activity of compound **5f** is anomalous, and might be indicative of a steric effect associated with the *p*-phenyl substituent attached to C-4′ of the phenyl ring in relation to binding in the active site, as discussed below.

In vivo screens were conducted against *P. berghei* in mice according to the Peters four-day test by the sc and oral (po) routes, with values expressed as ED_{90} (Table 7).[46] Here, the sc activities of the arylaminoartemisinins are generally superior to that of artesunate, and, in the case of compound **5g**, the activity is some 13 times greater. However, po activities are relatively quite poor, being approximately equipotent with artesunate. That the compounds have mediocre oral bioavailability relative to the sc route might in part be a reflection of protonation, which blocks uptake and triggers hydrolysis to DHA, which itself has low relative bioavailability, as the compounds pass through the stomach. In contrast, the relative bioavailability of compound **8** is quite good; this might be due to enhanced stability at low pH. The

Table 6. *In vitro antimalarial activity (IC_{50}) of compounds against W2 (chloroquine resistant) and D6 (chloroquine sensitive, mefloquine resistant) strains of* P. falciparum *by tritiated hypoxanthine incorporation assay.*

Compound	W2: IC_{50} [ng mL^{-1}]	D6: IC_{50} [ng mL^{-1}]
5a	0.66	2.14
5c	0.23	0.28
5d	0.33	0.39
5g	0.64	0.61
5f	5.81	9.40
8	1.54	1.24

Table 7. P. berghei *N strain ED_{90}; Peters' four-day test, blood schizontocidal activity; mice treated daily subcutaneously (sc) or orally (po) from day of infection (D0) through D+3; results evaluated from parasite counts in peripheral blood on D+4.*

Compound	ED_{90} [mg kg^{-1}] sc	ED_{90} [mg kg^{-1}] po	ED_{90} po/ ED_{90} sc $= R_{90}$	ED_{90} **3**/ED_{90} compound = Artesunate Index sc	po
Artesunate **3**	4.6	9.3	2.0	1.0	1.0
5b	0.65	14.0	21.5	7.08	0.66
5c	0.75	10.0	13.3	6.13	0.93
5g	0.35	8.2	23.4	13.14	1.13
5h	2.3	25.0	10.87	2	0.37
5i	1.7	7.5	5	2.7	1.24
8	2.3	4.7	2.04	2.00	1.98

arylaminoartemisinins, especially compound **5g**, also possess very good activity by the sc route against chloroquine-resistant *P. yoelii* (Table 8). The (methylsulfonylphenyl)amino compounds **5h** and **5i**, which are the most polar of the arylamino derivatives, unexpectedly are the least active.

Table 8. P. yoelii *NS strain ED_{90}; Peters' four-day test, blood schizontocidal activity; mice treated daily subcutaneously (sc) or orally (po) from day of infection (D0) through D+3; results evaluated from parasite counts in peripheral blood on D+4.*

Compound	ED_{90} [mg kg^{-1}] sc	ED_{90} **3**/ED_{90} compound = Artesunate Index
Artesunate **3**	42.0	1.0
5b	1.7	24.7
5c	1.6	26.3
5g	0.6	70.0
5h	2.3	18.0
5i	3.3	12.7
8	2.3	18.0

Conclusion

The sc activities of the arylaminoartemisinins, especially of compound **5g**, justify further development of this compound class, particularly as the straightforward preparation complies with the economic requirements outlined above. Overall, the sc activities of the arylaminoartemisinins partially reflect the exceptional activities of alkylaminoartemisinins reported earlier.[30] However, po activities are inferior, yet still of the same order of magnitude as artesunate. Thus, on the basis of the sc data, it is apparent that amino groups attached directly to C-10 enhance the activities of artemisinin derivatives in general. This might be due in part to the general resistance of this compound class to competing, and mechanistically irrelevant, decomposition by ferrous iron to C-centered radicals,[30,47] and thereby allow more of the drug to bind to the target.[4,10,30,47,48] A more detailed reasoning for the enhanced antimalarial activities of the 10-aminoartemisinins, as compared to all other artemisinins, will be presented elsewhere.

It is recognized that at low pH, as in the case of glycosylamines, protonation of the basic nitrogen will occur, and hydrolysis to DHA may ensue. However, any instability at low pH encountered on the oral route can be overcome through administration of enteric-coated tablets. Finally, the phase-transfer method described herein is applicable to the preparation of aromatic glycosylamines, and therefore should be of general use.

Experimental Section

Diethyl ether and toluene were dried with sodium wire and distilled from sodium benzophenone ketyl prior to use. Dichloromethane, predried over calcium hydride, was distilled and then stored over 4 Å molecular sieves under nitrogen. DHA was used as supplied by the Kunming Pharmaceutical Corporation. Other chemicals were used without further purification.

^{1}H and ^{13}C NMR spectra were recorded on Bruker ARX-300 and JEOL JNM-EX400 FT-NMR spectrometers operating at 300 or 400 MHz (^{1}H) and at 75 or 100 MHz (^{13}C). Mass spectra were measured on a Finnegan TSQ7000 Mass Spectrometer. Infrared spectra of solid samples were obtained in KBr disks on a Perkin–Elmer Spectrum One. Optical rotations were determined on a Perkin–Elmer Polarimeter Model 241. Melting points were determined in capillary tubes on an electrothermal melting-point apparatus and were uncorrected. Microanalyses were performed by MEDAC Ltd. at the Department of Chemistry, Brunel University, UK. Analytical thin-layer chromatography was performed with pre-coated aluminum plates (Merck Kieselgel 60 F_{254}). Flash chromatography was performed with silica gel (Merck Kieselgel 60 art. 9385 230–400 mesh) under medium pressure.

Standard pH 1.2 buffer solution was prepared according to ref. [49], as follows: an aqueous solution of potassium chloride (0.2 M, 50 mL) was mixed with hydrochloric acid (0.2 M, 85.0 mL) in a 200 mL volumetric flask. The resulting solution was diluted with water to 200 mL to give the standard buffer solution of pH 1.2.

10α-((5′-Phenyl)phenyl)amino-10-deoxo-10-dihydroartemisinin (5f): *Procedure A*: 4-Aminobiphenyl (186 mg, 1.10 mmol), DHA (284 mg, 1.0 mmol), and sodium dodecyl sulfate (57 mg, 0.20 mmol) were added to a vigorously stirred mixture of dichloromethane (5 mL) and pH 1.2 buffer solution (5 mL). After 24 h, the mixture was quenched with saturated aqueous sodium bicarbonate solution (5 mL). After effervescence was complete, the mixture was poured into a mixture of brine (30 mL) and dichloromethane (10 mL). This solution was separated, the aqueous layer was extracted with dichloromethane (2×10 mL), and the organic layers were combined and dried (Na_2SO_4). After filtration, the filtrate was concentrated under reduced pressure, and the residue was purified by chromatography (ethyl acetate/hexane 20:80) to give compound **5f** as silky white needles (283 mg, 65%). m.p. 157–159 °C; $[\alpha]_D^{20} = -76.5$ ($c = 0.51$, $CHCl_3$); ^{1}H NMR: $\delta = 0.98$ (d, $J = 7.2$ Hz, 3H; H-15), 1.02 (d, $J = 6.1$ Hz, 3H; H-16), 1.44 (s, 3H; H-14), 1.07–2.09 (m, 10H), 2.36–2.62 (m, 2H), 4.50 (d, $J = 9.85$ Hz, 1H; NH), 4.90 (dd, $J = 9.85$, 9.85 Hz, 1H; H-10), 5.49 (s, 1H; H-12), 6.82–6.87 (m, 2H; Ar-H), 7.25–7.58 (m, 7H; Ar-H); ^{13}C NMR: $\delta = 13.81$, 20.19, 21.68, 21.81, 24.62, 25.98, 34.04, 36.27, 37.30, 45.76, 51.72, 80.42, 80.67, 91.14, 104.14, 114.30, 125.98, 126.29, 127.71, 128.45, 131.53, 141.16, 145.22; IR (film): $\nu_{max} = 698$, 760, 826, 878, 926, 992, 1012, 1040, 1128, 1152, 1196, 1268, 1268, 1378, 1446, 1488, 1528, 1614, 2872, 2924, 3348 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 170 (2), 267 (2), 284 (2), 379 (8), 395 (42), 412 (100), 436 (2) [M^++1]; elemental analysis calcd (%) for $C_{27}H_{33}NO_4$ (435.57): C 74.45, H 7.64, N 3.22; found C 74.18, H 7.60, N 3.16.

Procedure B: 4-Aminobiphenyl (186 mg, 1.10 mmol), DHA (284 mg, 1.0 mmol), and sodium dodecyl sulfate (29 mg, 10 mol%) were added to a vigorously stirred mixture of toluene (5.0 mL) and aqueous hydrobromic acid solution (0.10 M, 5.0 mL) in a round-bottom flask. This was then immersed in an oil bath preheated to 80 °C and kept at that temperature for 4 h, with vigorous stirring of the reaction mixture throughout. After cooling down to ambient temperature, the mixture was quenched by addition of saturated aqueous sodium bicarbonate solution (5 mL). After effervescence was complete, the solution was poured into a mixture of brine (30 mL) and dichloromethane (10 mL), and further processed as described above to give the product **5f** (323 mg, 74%).

10α-(Phenylamino)-10-deoxo-10-dihydroartemisinin (5a): This was obtained according to procedure A or B from aniline (102.4 mg, 1.1 mmol) and other reagents, as described above.

Chromatography (ethyl acetate/hexanes 28:72) gave a white crystalline solid, recrystallization of which from dichloromethane/hexane gave thread like crystals (procedure A: 217 mg, 55%; procedure B: 328 mg, 83%). m.p. 159–160 °C (lit.[27] 121.5–122 °C); $[\alpha]_D^{20} = -51.4$ ($c = 0.35$, $CHCl_3$); ^{1}H NMR: $\delta = 0.95$ (d, $J = 7.18$ Hz, 3H; 6-Me), 1.01 (d, $J = 6.18$ Hz, 3H; 9-Me), 1.05–1.10 (m, 1H), 1.42 (s, 3H; 3-Me), 1.26–1.65 (m, 7H), 1.74–1.92 (m, 4H), 2.00–2.08 (m, 1H), 2.35–2.45 (m, 1H), 2.49–2.61 (m, 1H; H-9), 4.32 (d, $J = 9.81$ Hz, 1H; NH), 4.85 (dd, $J = 9.86$, 9.81 Hz, 1H; H-10), 5.45 (s, 1H; H-12), 6.75–6.87 (m, 3H; Ar-H), 7.17–7.22 (m, 2H; Ar-H); ^{13}C NMR: $\delta = 13.80$, 20.17, 21.79, 24.60, 25.97, 32.71, 34.03, 36.26, 37.18, 45.76, 51.71, 80.39, 80.70, 91.08, 114.02, 118.56, 128.99; IR (film): $\nu_{max} = 690$, 748, 826, 856, 878, 926, 944, 994, 1012, 1040, 1098, 1116, 1152, 1196, 1270, 1314, 1376, 1444, 1502, 1604, 2872, 2924, 3348 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 94 (38), 133 (100), 163 (40), 221 (80), 249 (22), 267 (50), 296 (98), 314 (100), 324 (20), 342 (98), 359 (56) [M^+], 360 (56) [M^++1]; elemental analysis calcd (%) for $C_{21}H_{29}NO_4$ (359.47): C 70.17, H 8.13, N 3.90; found C 70.25, H 8.24, N 3.73.

10α-(4′-Chlorophenylamino)-10-deoxo-10-dihydroartemisinin (5b): This was obtained according to procedure A from *p*-chloroaniline (140.3 mg, 1.1 mmol) and other reagents, as described above. Chromatography (ethyl acetate/hexanes 15:85) gave a white solid, recrystallization of which from dichloromethane/hexane gave thread-like crystals (173.3 mg, 40%). m.p. 179.0 °C (lit.[27] 144.5–145 °C); $[\alpha]_D^{20} = -63.5$ ($c = 0.20$, $CHCl_3$); ^{1}H NMR: $\delta =$ 0.94 (d, $J = 7.18$ Hz, 3H; 6-Me), 1.00 (d, $J = 6.12$ Hz, 3H; 9-Me), 1.41 (s, 3H; 3-Me), 1.05–1.97 (m, 9H), 2.05 (ddd, $J = 14.6$, 4.78, 3.12 Hz, 1H), 2.40 (ddd, $J = 17.4$, 13.5, 3.98 Hz, 1H), 2.49–2.61 (m, 1H; H-9), 4.42 (br s, 1H; NH), 4.78 (br s, 1H; H-10), 5.44 (s, 1H; H-12), 6.66–6.71 (m, 2H; Ar-H), 7.09–7.14 (m, 2H; Ar-H); ^{13}C NMR: $\delta = 13.73$, 20.16, 21.78, 24.59, 25.93, 32.56, 33.99, 36.23, 37.28, 45.67, 51.66, 80.38, 80.76, 91.09, 104.15, 115.28, 123.20, 128.76,144.31; IR (film): $\nu_{max} = 756$, 818, 878, 926, 944, 992, 1012, 1040, 1094, 1152, 1196, 1268, 1378, 1454, 1494, 1514, 1604, 2874, 2926, 3346 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 127 (8), 167 (100), 221 (16), 267 (10), 330 (16), 347 (20), 376 (8), 393 (16) [M^++1]; elemental analysis calcd (%) for $C_{21}H_{28}ClNO_4$ (393.91): C 64.03, H 7.16, N 3.55; found C 64.16, H 7.40, N 3.45.

10α-(4′-Bromophenylamino)-10-deoxo-10-dihydroartemisinin (5c): This was obtained according to procedure B from *p*-bromoaniline (189.2 mg, 1.1 mmol) and other reagents as described above. Chromatography (ethyl acetate/hexanes 13:87) gave a white solid, recrystallization of which from dichloromethane/hexane gave thread-like crystals. m.p. 183–183.5 °C (lit.[27] 152–153 °C); $[\alpha]_D^{20} = -60.0$ ($c = 0.23$, $CHCl_3$); ^{1}H NMR: $\delta = 0.94$ (d, $J =$ 7.15 Hz, 3H; 6-Me), 1.00 (d, $J = 6.07$ Hz, 3H; 9-Me), 1.41 (s, 3H; 3-Me), 1.05–2.08 (m, 10H), 2.40 (ddd, $J = 14.0$, 13.7, 3.87 Hz, 1H), 2.49–2.61 (m, 1H; H-9), 4.48 (d, $J = 10.0$ Hz, 1H; NH), 4.78 (dd, $J =$ 10.0, 9.95 Hz, 1H; H-10), 5.44 (s, 1H; H-12), 6.61–6.66 (m, 2H; Ar-H), 7.20–7.25 (m, 2H; Ar-H); ^{13}C NMR: $\delta = 13.71$, 20.17, 21.78, 24.60, 25.92, 32.54, 33.99, 36.24, 37.29, 45.67, 51.67, 80.39, 80.65, 91.09, 104.17, 110.32, 115.76, 131.61, 144.79; IR (film): $\nu_{max} = 756$, 816, 878, 926, 992, 1012, 1040, 1094, 1122, 1152, 1196, 1268, 1378, 1452, 1492, 1514, 1598, 2872, 2924, 3346 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 154 (34), 221 (50), 267 (14), 376 (36), 392 (100), 422 (14), 439 (12) [M^++1]; elemental analysis calcd (%) for ($C_{21}H_{28}BrNO_4$)): C 57.54, H 6.44, N 3.19; found C 57.81, H 6.64, N 3.14.

10α-(4′-Carboxyphenyl)amino-10-deoxo-10-dihydroartemisinin (5e): This was Prepared according to procedure B with 4-aminobenzoic acid (151 mg, 1.10 mmol) and DHA (284 mg, 1.0 mmol). Following chromatography (ethyl acetate/hexane 1:1), the product **5e** was obtained as white needle-shaped crystals (201.6 mg, 50%). m.p. 155–157 °C (lit.[27] 155–157 °C). All other data were in agreement with those previously recorded.[27]

10α-(4′-Fluorophenyl)amino-10-deoxo-10-dihydroartemisinin (5g): This was prepared according to procedure B with 4-fluoroaniline (122 mg, 1.1 mmol) and other reagents as described above. Following chromatography (ethyl acetate/hexanes 13:87), the product was obtained as fine hair-like crystals (310 mg, 82%). m.p. 170–171 °C, from dichloromethane/hexanes; $[\alpha]_D^{20} = -51.5$ ($c = 1.3$, $CHCl_3$); ^{1}H NMR: $\delta = 0.95$ (d, $J = 7.18$ Hz, 3H; 6-Me), 1.00 (d, $J =$ 6.11 Hz, 3H; 9-Me), 1.42 (s, 3H; 3-Me), 1.05–1.97 (m, 9H), 2.05 (ddd, $J = 14.6$, 4.79, 3.07 Hz, 1H), 2.40 (ddd, $J = 17.3$, 13.4, 3.93 Hz, 1H), 2.49–2.61 (m, 1H; H-9), 4.32 (d, $J = 10.0$ Hz, 1H; NH), 4.76 (dd, $J =$ 10.0, 10.0 Hz, 1H; H-10), 5.44 (s, 1H; H-12), 6.66–6.92 (m, 4H; Ar-H); ^{13}C NMR: $\delta = 13.81$, 20.17, 21.79, 24.60, 25.94, 32.60, 34.01, 36.25, 37.29, 45.73, 51.69, 80.41, 81.41, 91.10 (d, $J = 2.22$ Hz), 104.13, 115.15 (d, $J = 2.69$ Hz), 115.34 (d, $J = 17.7$ Hz), 141.95; IR (Nujol): $\nu_{max} = 780$, 810, 832, 846, 880, 924, 942, 1022, 1046, 1099, 1116, 1194, 1216, 1264, 1378, 1460, 1512, 2854, 2924, 3358 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 111 (6), 151 (42), 163 (34), 221 (18), 267 (26), 314 (14), 358 (70), 377 (100) [M^+], 378 (44) [M^++1]; elemental analysis calcd (%) for $C_{21}H_{28}FNO_4$ (377.46): C 66.82, H 7.48, N 3.71; found C 67.06, H 7.60, N 3.51.

10α-(3′-Methylsulfonylphenyl)amino-10-deoxo-10-dihydroartemisinin (5h): 3-Methylsulfonylaniline hydrochloride (684 mg, 3.30 mmol), DHA (852 mg, 3.0 mmol), and sodium dodecyl sulfate (173 mg, 0.6 mmol) were added to a vigorously stirred mixture of dichloromethane (15 mL) and buffer solution at pH 1.2 (15 mL) according to procedure A. After 24 h, the reaction was quenched by addition of saturated aqueous sodium bicarbonate solution (15 mL). The usual workup, followed by chromatography (ethyl acetate/hexanes 30:70) gave compound **5h** as white needles (490 mg, 37%). m.p. 116–117 °C; $[\alpha]_D^{20} = -51.6°$ ($c = 0.655$, $CHCl_3$); ^{1}H NMR: $\delta = 0.93$ (d, $J = 6.9$ Hz, 3H; 9-Me), 0.99 (d, $J = 6.3$ Hz, 3H; 6-Me), 1.05–1.30 (m, 2H), 1.39 (s, 3H; 3-Me), 1.42–1.95 (m, 7H), 1.95–2.10 (m, 1H), 2.30–2.50 (m, 1H), 2.50–2.65 (m, 1H), 3.04 (s, 3H; SO_2CH_3), 4.75 (d, $J = 10.0$ Hz, 1H; NH), 4.87 (t, $J = 9.9$ Hz, 1H; H-10), 5.46 (s, 1H; H-12), 6.96 (dt, $J = 2.0$, 7.3 Hz, 1H; ArH), 7.23–7.28 (3H; m, ArH); ^{13}C NMR: $\delta = 13.8$, 20.3, 21.9, 24.7, 25.9, 32.5, 34.0, 36.4, 37.3, 44.2, 45.7, 51.7, 80.2, 80.5, 91.3, 104.3, 111.3, 116.1, 119.1, 129.4, 140.5, 146.6; IR (KBr): $\nu_{max} = 763$, 826, 877, 926, 1011, 1038, 1144 ($\nu_{S=O}$), 1196, 1269, 1299 ($\nu_{S=O}$), 1378, 1431, 1452, 1483, 1527, 1603, 2875, 2927, 3340 cm^{-1} (ν_{N-H}); MS (CI, CH_4): *m/z* = 438 [M^++1]; elemental analysis calcd (%) for $C_{22}H_{31}NO_6S$ (437.56): C 60.39, H 7.14, N 3.20; found C 60.40, H 6.99, N 3.20.

10α-(4′-Methylsulfonylphenyl)amino-10-deoxo-10-dihydroartemisinin (5i): This was prepared from 4-methylsulfonylaniline hydrochloride (228 mg, 1.10 mmol), DHA (284 mg, 1.00 mmol), and sodium dodecyl sulfate (59 mg, 0.20 mmol) in dichloromethane (15 mL) and buffer solution (15 mL) at pH 1.2 according to procedure A. Following chromatography (ethyl acetate/hexanes 30:70), **5i** was obtained as needles (341 mg, 78%). m.p. 152.2–153.8 °C; $[\alpha]_D^{20} = 91.6°$ ($c = 0.518$, $CHCl_3$); ^{1}H NMR: $\delta = 0.94$ (d, $J = 7.1$ Hz, 3H; 9-Me), 1.00 (d, $J = 6.1$ Hz, 3H; 6-Me), 1.05–1.30 (m, 2H), 1.37 (s, 3H; 3-Me), 1.40–2.15 (m, 8H), 2.30–2.50 (m, 1H), 2.50–2.70 (m, 1H), 2.96 (s, 3H; SO_2CH_3), 4.90 (t, $J = 10.0$ Hz, 1H; H-10), 5.50 (d, $J = 9.9$ Hz, 1H; NH), 5.51 (s, 1H; H-12), 6.82 (dd, $J = 2.6$, 11.4 Hz, 2H; ArH), 7.56 (dd, $J = 2.6$, 11.4 Hz, 2H; ArH); ^{13}C NMR: $\delta = 13.6$, 14.1, 20.2, 20.9, 21.8, 24.6, 25.9, 32.3, 34.0, 36.3, 37.3, 45.0, 45.6, 51.7, 60.3, 79.9, 80.5, 91.3, 104.4, 113.4, 128.6, 150.5; IR (KBr): $\nu_{max} = 767$, 827, 878, 926, 957, 1012, 1038, 1092, 1144 ($\nu_{S=O}$), 1297 ($\nu_{S=O}$), 1326, 1416, 1454, 1524, 1599, 2874, 2926, 3348 (ν_{N-H}) cm^{-1}; MS (CI, NH_3): *m/z* = 438 [M^++H], 455 [M^++NH_4]; elemental analysis calcd (%) for

$C_{22}H_{31}NO_6S$ (437.56): C 60.39, H 7.14, N 3.20; found C 60.43, H 7.23, N 3.08.

10α-(2′-Methyl-4′-nitrophenyl)amino-10-deoxo-10-dihydroartemisinin (5j): This was prepared from 2-methyl-4-nitroaniline (167 mg, 1.10 mmol), DHA (284 mg, 1.0 mmol), and sodium dodecyl sulfate (29 mg, 10 mol%) in toluene (5 mL) and dilute HBr (0.1 M, 5 mL) according to procedure B. Following chromatography (ethyl acetate/hexanes 30:70), **5j** was obtained as needles (270 mg, 65%). m.p. 152–153 °C; $[\alpha]_D^{28} = 198.63°$ ($c = 0.945$, CH_2Cl_2); ^{1}H NMR: $\delta = 4.78$ (d, $J = 8.8$ Hz, 1H; NH), 4.90 (dd, $J = 9.6$, 9.2 Hz, 1H; H-10), 5.49 (s, 1H; H-12), 6.90 (d, $J = 8.8$ Hz, 1H; Ar-H), 7.99–8.05 (m, 2H; Ar-H); ^{13}C NMR: $\delta = 14.0$, 17.5, 20.4, 22.0, 24.8, 26.1, 32.7, 34.1, 36.3, 37.5, 45.7, 51.8, 80.2, 80.4, 91.2, 104.4, 110.5, 122.3, 124.1, 126.0, 149.6; IR (film) ν_{max} 737, 752, 830, 879, 926, 1017, 1039, 1111, 1134, 1293, 1330, 1379, 1500, 1530, 1591, 2873, 2928, 3407 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 136 (18), 154 (100), 192 (16), 221 (25), 231 (7), 267 (3), 325 (5), 343 (16), 355 (17), 373, (24), 401 (10), 419 (3.5) [M^++1]; elemental analysis calcd (%) for $C_{22}H_{29}N_2O_6$: C 63.87, H 7.46, N 6.48; found: C 63.88, H 7.55, N 6.60.

10α-(4′-Methoxycarbonylphenyl)amino-10-deoxo-10-dihydroartemisinin (5k): This was prepared according to procedure B with methyl 4-aminobenzoate (166 mg, 1.10 mmol) and DHA (284 mg, 1.0 mmol). Following chromatography (ethyl acetate/hexanes 1:1), **5k** was obtained as a fine white solid (204.4 mg, 49%). m.p. 118–119 °C; $[\alpha]_D^{20} = -84.1$ ($c = 0.82$, $CHCl_3$); ^{1}H NMR: $\delta = 0.92$ (d, $J =$ 7.11 Hz, 3H; 6-Me), 0.99 (d, $J = 6.09$ Hz, 3H; 9-Me), 1.39 (s, 3H; 3-Me), 0.85–2.04 (m, 10H), 2.33–2.42 (m, 1H), 2.56–2.60 (m, 1H), 3.83 (s, 3H; OMe), 4.88 (dd, $J = 9.89$, 9.89 Hz, 1H; H-10), 5.06 (d, $J =$ 9.96 Hz, 1H; NH), 5.46 (s, 1H; H-12), 6.66–7.76 (m, 4H; Ar-H); ^{13}C NMR: $\delta = 13.67$, 14.10, 20.22, 20.94, 21.84, 24.66, 25.92, 32.50, 34.04, 36.30, 37.34, 45.67, 51.40, 51.70, 80.02, 80.49, 91.21, 104.30, 113.01, 119.64, 131.04, 149.99, 167.06; IR (film): $\nu_{max} = 768$, 842, 878, 926, 1012, 1040, 1110, 1178, 1270, 1378, 1434, 1528, 1608, 1710, 2948, 3344 cm^{-1}; MS (CI, CH_4): *m/z* (%) = 152 (26), 221 (28), 358 (8), 372 (100), 400 (6), 418 (32) [M^++1]; elemental analysis calcd (%) for $C_{23}H_{31}NO_6$ (417.51): C 66.17, H 7.48, N 3.35; found C 65.57, H 7.57, N 3.36.

Artemether (4a): DHA (284 mg, 1.00 mmol) and sodium dodecyl sulfate (29 mg, 10 mol%) were added to a vigorously stirred mixture of toluene (5.0 mL), methanol (2 mL), and aqueous hydrobromic acid solution (0.10 M, 5.0 mL). The mixture was kept at 80 °C for 4 h, then cooled to ambient temperature, and the reaction was quenched by addition of saturated aqueous sodium bicarbonate (5 mL). After effervescence was complete, the mixture was poured into a mixture of brine (30 mL) and dichloromethane (10 mL). The resulting solution was separated, and the aqueous layer was extracted with more dichloromethane (2×10 mL). The combined extract was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography (ethyl acetate/hexane 10:90) to give crystalline β-artemether (176.9 mg, 59%), m.p. 86.0–87.0 °C (lit.[41] 86–88 °C). This was identical with an authentic sample either obtained from suppliers (Kunming Pharmaceutical Corporation) or prepared according to the literature procedure.[41] On the basis of its ^{1}H NMR spectrum (see below), the second fraction (21 mg, 7.0%), which was not further purified, was assumed to be α-artemether.

Arteether (4b): This was prepared according to the procedure used above from DHA (284 mg, 1.00 mmol) and absolute ethanol (2 mL). Following chromatography (ethyl acetate/hexane 10:90) crystalline β-arteether was obtained (139.0 mg, 45%). m.p. 80.8–81.6 °C (lit.[42] 81–83 °C); ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 3.4$–3.5 (m, 1H; diastereotopic OCH_2CH_3), 3.8–3.9 (m, 1H; diastereotopic OCH_2CH_3), 4.80 (d, $J = 2.4$ Hz, 1H; H-10), 5.41 (s, 1H; H-12). A fraction was also isolated as an oil (18.5 mg, 6%) and identified on the basis of its ^{1}H NMR spectrum as α-arteether: ^{1}H NMR: $\delta = 3.9$–4.1 (m, 1H; diastereotopic OCH_2CH_3), 4.44 (d, $J = 9.2$ Hz, 1H; H-10), 5.392 (s, 1H; H-12).

Artelinate (4c):[50] Procedure B with 4-hydroxymethylbenzoic acid (167 mg, 1.10 mmol) and DHA (284 mg, 1.0 mmol) was modified as follows. The reaction mixture was heated in an oil bath at 80 °C, with vigorous stirring for 4 h, then the mixture was cooled. The toluene layer was separated, and the aqueous layer was extracted with dichloromethane (3×10 mL). The toluene layer and the dichloromethane extracts were combined, and washed once with water (20 mL). After drying, the solvent was evaporated to leave an opaque residue, which was submitted to chromatography (ethyl acetate/hexanes = 1:1) to give the product **4c** as a fine white solid (209 mg, 50%) after crystallization from methanol/water (1:1). m.p. 144–145 °C (lit.[3] 142–145 °C); ^{13}C NMR: $\delta = 13.2$, 20.4, 24.6, 24.7, 26.2, 31.0, 34.6, 36.4, 37.5, 44.4, 52.5, 69.2, 81.1, 88.0, 101.6, 104.1, 126.7, 128.2, 130.1, 144.4, 171.2; MS (CI, CH_4) *m/z* (%) = 123 (2), 135 (11), 163 (14), 180 (6), 221 (100), 267 (8), 315 (2), 331 (8), 355 (5), 373 (7), 401 (47). Other data were in agreement with the literature.[3]

10β-(2′-Naphthalenemethoxy)-10-deoxo-10-dihydroartemisinin (8): According to procedure A, 2-naphthalenemethanol (174 mg, 1.10 mmol), DHA (284 mg, 1.0 mmol), and sodium dodecyl sulfate (58 mg, 0.20 mmol) in dichloromethane (5 mL) and aqueous buffer (5 mL, pH 1.2) gave **8** as a white foam (180.0 mg, 41%) after chromatography (ethyl acetate/hexanes 5:95). m.p. 48–49 °C, identical with an authentic sample.[32]

10β-(2′-Naphthoxy)-10-deoxo-10-dihydroartemisinin (9): According to procedure A, 2-naphthol (159 mg, 1.10 mmol), DHA (284 mg, 1.0 mmol), and sodium dodecyl sulfate (58 mg, 0.20 mmol) in dichloromethane (5 mL) and aqueous buffer (5 mL, pH 1.2) gave **9** (70 mg, 17%) as a white foam after chromatography (ethyl acetate/hexanes 5:95). m.p. 129–131 °C, identical with an authentic sample.[32]

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[46] An initial screening dose of 10 mg kg^{-1} sc and po is used, which provides a preliminary evaluation of relative activity of compounds administered by each route, relative activities between compounds, and activities relative to the artesunate standard. The Peters four-day test for blood schizontocidal activity is then conducted in which mice are treated daily subcutaneously or orally from the day of infection (D0) through D+3. Results are evaluated on the basis of parasite counts in peripheral blood on D+4. For both screening and the four-day test, screens are also carried out with mice infected with the chloroquine-resistant NS species of *P. yoelii*: W. Peters, B. L. Robinson in *Handbook of Animal Models of Infection Section VI: Parasitic Infection Models* (Eds.: O. Zak, M. Sande), Academic Press, London, **1999**, pp. 756–771.
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