Stereoselective Preparation of 10α- and 10β-Aryl Derivatives of Dihydroartemisinin

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Lewis acid-catalysed arylation of the 10β-benzoate and, less effectively, the 10α-benzoate of dihydroartemisinin [DHA] with activated aromatic compounds, including naphthalenes, stereoselectively, provides 10α-aryl derivatives including disubstituted naphthalene derivatives. 2-Methoxynaphthalene provides the 1-, rather than the 3-substituted derivative. In contrast, 10β-aryl derivatives are obtained stereoselectively from the 10β-bromide, generated in situ from trimethylsilyl bromide and the TMS ether of 10α-DHA, and the corresponding aryl Grignard reagents. The 10α-aryl compounds are shown by NMR spectroscopy and X-ray crystallographic analysis to possess a chair pyranose ring with equatorial aryl group, whereas the 10β-aryl derivatives have a twist-boat pyranose ring with equatorial aryl group. The stereochemistry of the Lewis acid-catalysed arylations, which is common to that observed for the Lewis acid-catalysed arylation of pyranosyl glycosides with axial anomeric leaving groups in general, may be rationalized in terms of axial attack from the α or *si* face of the half-chair oxonium ion intermediate. On the other hand, the Grignard reagents activate the axial bromide to elimination through complexation, and thereby the aryl nucleophile attacks the incipient oxonium ion from the β or *re* face.

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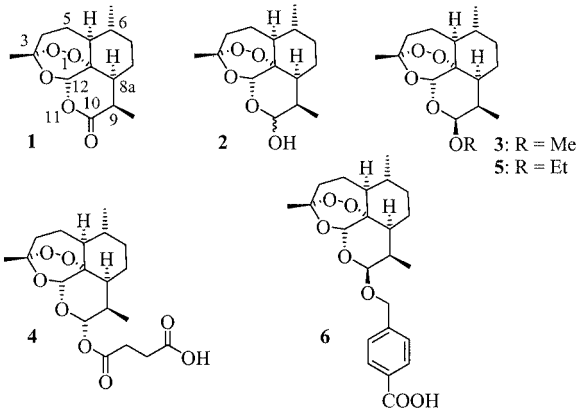
Introduction[1]

Artemisinin (**1,** qinghaosu) and its derivatives artemether (**3**) and artesunate (**4**) represent a distinct, highly effective class of antimalarial drugs developed by Chinese groups.[2−6] Arteether (**5**), first prepared in China, has been developed as an injectable formulation outside China,[7] and artelinate (**6**)[8] is to be developed as a formulation suitable for intravenous administration. Thus, all derivatives currently in use, or to be developed, are either alkyl acetals or an ester acetal derivative of dihydroartemisinin (DHA, **2**).

The problem with such compounds, however, is that they have short pharmacological half-lives, a reflection of their acid lability, and facile metabolism to DHA,[8,9] a highly neurotoxic compound.[10] In particular, artesunate is hydrolytically unstable, even at neutral pH, and has a half-life of just several minutes.[11] Whilst a large amount of work has been carried out with the aim of generating new derivatives,[3,4] so far no putative second-generation artemisinin derivative has been found suitable for carrying forward to development as an antimalarial drug. The work has also



been given added impetus by the demonstrated biological activity of artemisinin and its derivatives against other parasitic[5,12−14] and cellular targets.[15−17] Particularly with regard to the last activity, we were interested in generating more-stable derivatives bearing intercalating groups at C-10.[18] We have described the stereoselective preparation of acetal ester and ether derivatives bearing such groups.[19] Whilst some of these compounds display promising cytotoxic activities,[18] they possess, however, an acetal at C-10, and so the stability problem has not been adequately addressed.

Improved stability is obtained if the acetal at C-10 is converted into an ether through replacement of the exocyclic oxygen atom by a hydrogen atom, or alkyl or aryl groups.

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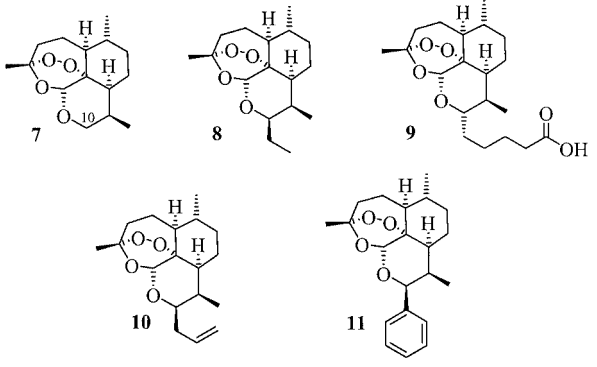
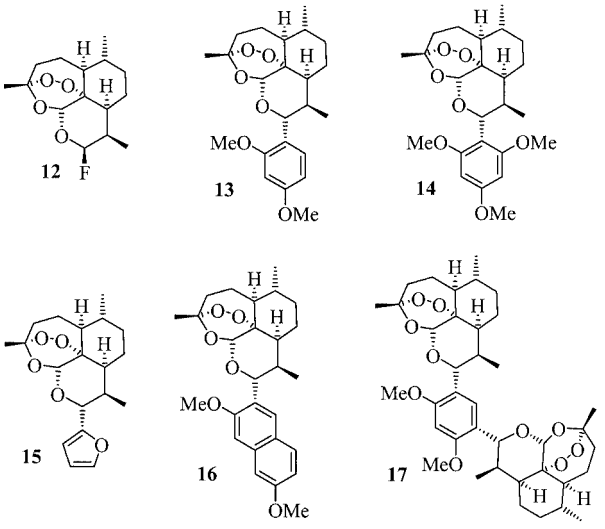
Thus, 10-deoxodihydroartemisinin (**7**) was prepared independently by two groups.[20,21] Derivatives of DHA in which the C-10 hydroxy group is replaced by an alkyl or aryl group were made by indirect semisynthetic routes from qinghao acid.[16,22−26] In this way, our group was the first to prepare the carba analogues **8** and **9** of artemether and artesunate respectively, and the allyl and aryl derivatives **10** and **11**.[24] These procedures, however, typically involved four to five steps, including generation and subsequent elaboration of a hydroperoxide to construct the artemisinin derivative.[27,28]

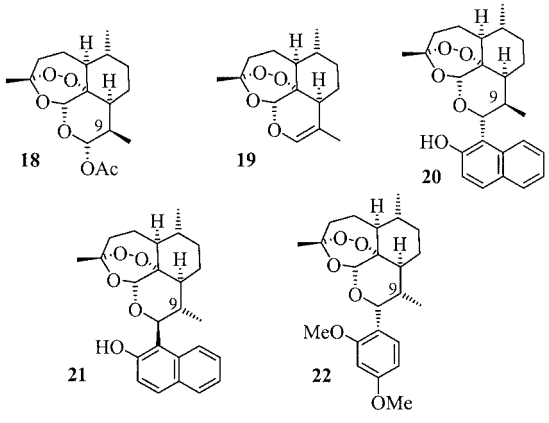
The breakthrough in accessibility came with the demonstration by Pu and Ziffer[29] that *C*-glycosidation methodology may be used to prepare the β-allyl derivative **10** directly from DHA through the use of allyl(trimethyl)silane and boron trifluoride−diethyl ether to activate the hydroxy group to displacement. As only the β derivative was obtained, it appeared that selective activation of α-DHA by the boron trifluoride−diethyl ether and axial displacement from the β or re face[1] by the allyltrimethylsilane was taking place. As shall be seen below, however, this premise is incorrect. Transformation of the allyl group enabled other compounds, including "carba-artemether" (**8**), to be prepared with relative ease. Other groups have subsequently reported similar chemistry.[30,31]



In an extension of the Ziffer method, we turned to activated derivatives of DHA modelled on those used in *C*-glycosidation reactions,[32] and prepared 10β-(fluoro)(deoxo)-dihydroartemisinin (**12**) from DHA and (diethylamino)-sulfur fluoride.[14,18,33] This compound decomposes on storage, however, and this instability, coupled with its expensive preparation, the need to separate it from the less-stable 10α isomer, and the low yield (51%), militate against its usefulness. Nevertheless, the same fluoride was used later by Posner and coworkers to prepare C-10 alkyl, arylalkynyl and aryl derivatives of DHA from electron-rich aromatics, aluminium alkyls and arylalkynyls in the presence of boron trifluoride−diethyl ether.[34,35] Thus, the α-aryl derivatives **13** (71%),[36] **14** (95%), and the furan **15** (72%) were efficiently prepared. The 3-substituted-2,7-(dimethoxy)naphthalene derivative **16** was also claimed, but, as seen below, the actual product is likely to be a different regioisomer. In a noteworthy extension of this work, the disubstituted dimeric arylated derivative **17** was also obtained by treatment of the monomeric arylated artemisinin derivative **13** with the fluoride **12** in the presence of boron trifluoride−diethyl ether.[37]



Other examples of *C*-arylation processes have been reported. Treatment of the α-acetate **18** of DHA with 2-naphthol in the presence of boron trifluoride−diethyl ether gave the derivatives **20** and **21** as a 1:1 mixture in 68% overall yield.[38] Formation of compound **21** involving epimerization at C-9 implied the intermediacy of the glycal **19**,[3] formed by Lewis acid-induced elimination of acetic acid from compound **18**.[38] The overall transformation was therefore held to proceed by an acid-catalysed addition of the naphthol to the glycal followed by O−C rearrangement of an intermediate naphthol ether, a characteristic reaction attending Lewis acid-catalysed *O*-glycosidation reactions of sugars with aromatic alcohols.[32,39] As shall be seen below, this process is not likely to be the case. A reaction commencing with acetate **18** and 1,3-dimethoxybenzene provided products **13** (26%) and **22** (9%).[40] Formation of the latter, but not the former product, was presumed to proceed via glycal **19**. According to analysis of ^{1}H NMR spectroscopic data, compound **21** possesses a twist-boat pyranose ring with an equatorial methyl group at C-9, and an equatorial aromatic group at C-10,[38] whereas compound **22** possesses a chair pyranose ring, with an axial methyl group at C-9 and an equatorial aromatic substituent at C-10.[40,41]



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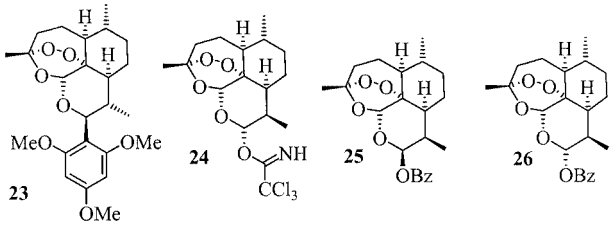
We report here the conversion of DHA into both 10α- and 10β-*C*-arylated compounds by application of *C*-glycosidation methodologies,[32] as part of a larger programme aimed at preparing new artemisinin derivatives tailored for cytotoxic and antiparasitic activities.[13,14,18]

Results and Discussion

α-Aryl Derivatives

Whilst DHA can be converted quantitatively into glycal **19** with boron trifluoride−diethyl ether in ether,[3,42] or with methanesulfonyl chloride in dichloromethane containing triethylamine, reaction of the latter with 1,3,5-trimethoxybenzene in the presence of Lewis acids was not stereoselective in giving mixtures of compounds **14** and **23** in low yields. In attempting to apply the highly effective *C*-aryl glycosidation methodology of Schmidt and coworkers[43] to DHA, we prepared the equatorial α-(trichloro)acetimidate intermediate **24** in situ from DHA and (trichloro)acetonitrile.[19] Activation, however, of this intermediate with a variety of Lewis acids followed by treatment with reactive aromatic nucleophiles did not give satisfactory yields of products. This unsatisfactory outcome may be due to the "wrong" (equatorial) stereochemistry of the (trichloro)acetimidate; in the original work of Schmidt and co-workers, axial (trichloro)acetimidates were used.[43] Therefore, we used the β-benzoate **25** with an axial leaving group, prepared from DHA by the Schmidt procedure,[19] and, for comparative purposes, the α-benzoate[19,44,45] **26** with an equatorial leaving group. Both compounds are indefinitely stable and easily handled.



Structures of arylated products obtained from the reactions of β-benzoate **25** and α-benzoate **26** with a series of activated aromatics in the presence of boron trifluoride−diethyl ether or tin(IV) chloride are depicted in Figure 1, and the reaction conditions and results are summarized in Table 1. The β-benzoate was generally the more effective donor, and in the reaction of the *N*-methylindole (Entries 12, 13), the α-benzoate failed to give the required product at all. In many cases, the glycal **19** was formed as a byproduct, together with varying amounts of the "α,β"-linked dimeric acetal **27**, identified by comparison with an authentic sample prepared from reaction of the β-benzoate **25** and DHA with boron trifluoride−diethyl ether, or more directly, from DHA and *p*-toluenesulfonyl chloride and triethylamine. The compound has been mentioned previously in the literature.[3,15,46] How it is formed in the arylation reactions is not clear. Possibly, it arises by Lewis acid-induced benzoylation of the activated aromatic group by the benzoates **25** or **26**, with concomitant formation of DHA, which undergoes condensation with the benzoate; the putative diaryl ketone, however, was not detected. The stereochemistry of this compound, with one artemisinyl unit linked to the bridging oxygen atom via an equatorial bond and the other via an axial bond, is in agreement with the rule that the equatorial epimer of DHA reacts as a nucleophile.[19] As an oxygen-centred nucleophile, this epimer of DHA undergoes axial addition to the stabilized oxonium cation produced from the benzoate and the Lewis acid, as dictated by the anomeric effect.[19]

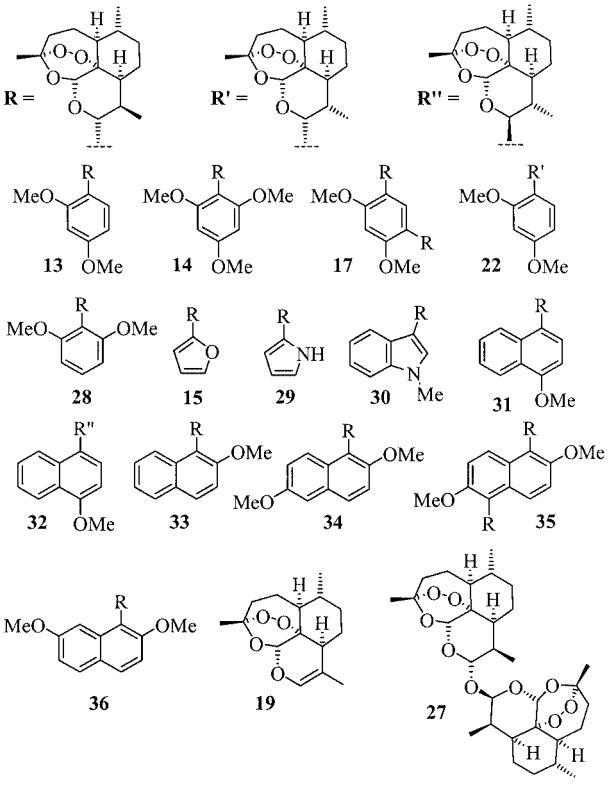


Figure 1. Structures of α-arylated 10-deoxo-10-dihydroartemisinin derivatives and other products obtained fromreactions of DHA β-benzoate **25** and α-benzoate **26** with activated aromatic compounds in presence of $BF_3{\cdot}OEt_2$ and $SnCl_4$

The outcome of the reactions of the β-benzoate **25** with 1,3-dimethoxybenzene (Table 1, Entries 1−6) was more complex than that reported for the β-fluoride **12**.[34,35,37] The products were the α-arylated product **13**,[36] the disubstituted aryl product **17**, the glycal **19** and small amounts of an aromatic regioisomer of compound **13**, possibly compound **28**, which could not be separated from compound **13**. Compound **28** was detectable in mixtures by ^1H NMR spectroscopy, and was tentatively identified through the similarities of chemical shifts of the methoxyl groups on the aromatic ring, 10-H, 9-H and the C-15 methyl group with the corresponding protons in compound **14**, as indicated in the Exp. Sect. The use of a larger amount of the Lewis acid

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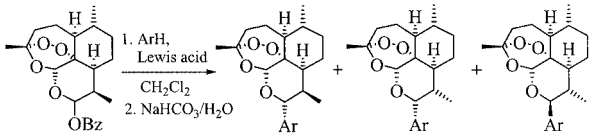
Table 1. Yields of α-arylated derivatives and other products obtained from reactions of DHA β-benzoate **25** and α-benzoate **26** with activated aromatic compounds in presence of $BF_3{\cdot}OEt_2$ and $SnCl_4$



25: 10-β **26:** 10-α | **13-15, 17, 28-31, 33-36** | **22** | **32** + glycal **19** + dimeric acetal **27**

Entry	**25** or **26**	ArH (equiv. with respect to starting benzoate), reaction conditions	Arylated derivative	yield (%)[a]	Other products	yield (%)[a]
1	**25**	1,3-$C_6H_4(OMe)_2$ (1.5 equiv.), $BF_3{\cdot}OEt_2$ (0.2 equiv.), −30 °C, 60 min	**13**	25[b]	**19**	33[c]
			17	3	**27**	10
			28	7[b]		
2	**25**	1,3-$C_6H_4(OMe)_2$ (1.5 equiv.), $BF_3{\cdot}OEt_2$ (0.1 equiv.), −30 °C, 60 min	**13**	19[b]	[d]	
			17	33		
			28	6[b]		
3	**25**	1,3-$C_6H_4(OMe)_2$ (1.5 equiv.), $BF_3{\cdot}OEt_2$ (0.1 equiv.), 0 °C, 60 min	**13**	14[b]	**19**	20[c]
			28	5[b]		
4	**26**	1,3-$C_6H_4(OMe)_2$ (1.5 equiv.), $BF_3{\cdot}OEt_2$ (0.1 equiv.), 0 °C, 60 min	**13**	16[b]	**19**	47[c]
			22	2[e]		
			28	< 1[b]		
5	**25**	1,3-$C_6H_4(OMe)_2$ (0.5 equiv.), $BF_3{\cdot}OEt_2$ (0.2 equiv.), −30 °C, 60 min	**13**	9[b]	**19**	40
			17	6		
			22	1[f]	**27**	7
			28	4[b]		
6	**25**	1,3-$C_6H_4(OMe)_2$ (1.5 equiv.), $SnCl_4$ (0.1 equiv.), −30 °C, 60 min	**13**	20[b]	**19**	17[c]
			17	29		
			28	7[b]		
7	**25**	1,3,5-$C_6H_3(OMe)_3$ (1.5 equiv.), $BF_3{\cdot}OEt_2$ (0.1 equiv.), −30 °C, 60 min	**14**	71	**19**	11
			27	5		
8	**26**	1,3,5-$C_6H_3(OMe)_3$ (1.5 equiv.), $BF_3{\cdot}OEt_2$ (0.1 equiv.), −30 °C, 55 min	**14**	57	**19**	12
					27	3
9	**25**	furan (1.5 equiv.), $BF_3{\cdot}OEt_2$ (0.1 equiv.), −30 °C, 60 min	–		**19**	9
					27	37
10	**25**	furan (15.0 equiv.), $BF_3{\cdot}OEt_2$ (2.0 equiv.), −30 °C, 60 min	**15**	35	[d]	
11	**25**	pyrrole (1.5 equiv.), $BF_3{\cdot}OEt_2$ (2.0 equiv.), −30 °C, 60 min	**29**	82	[d]	
12	**25**	*N*-methylindole (1.5 equiv.), $BF_3{\cdot}OEt_2$ (0.1 equiv.), −30 °C, 80 min	**30**	21[g]	**27**	8[g]
13	**25**	*N*-methylindole (1.5 equiv.) $SnCl_4$ (0.1 equiv.), −30 °C, 65 min	**30**	73	[d]	
14	**25**	1-methoxynaphthalene (1.5 equiv.), $SnCl_4$ (0.1 equiv.), −30 °C, 75 min	**31**	13	**19**	30
			32	5		
15	**25**	2-methoxynaphthalene (1.5 equiv.), $BF_3{\cdot}OEt_2$ (0.1 equiv.), −30 °C, 65 min	**33**	13	[d]	
16	**25**	2-methoxynaphthalene (1.5 equiv.), $SnCl_4$ (0.1 equiv.), −30 °C, 60 min	**33**	44	[d]	
17	**26**	2-methoxynaphthalene (1.5 equiv.), $SnCl_4$ (0.1 equiv.), −30 °C, 60 min	**33**	36	[d]	
18	**25**	2,6-dimethoxynaphthalene (1.5 equiv.), $SnCl_4$ (0.1 equiv.), −30 °C, 60 min	**34**	18	[d]	
			35	19		
19	**26**	2,6-dimethoxynaphthalene (1.5 equiv.), $SnCl_4$ (0.1 equiv.), −30 °C, 60 min	**34**	15	[d]	
			35	38		
20	**25**	2,7-dimethoxynaphthalene (1.5 equiv.), $SnCl_4$ (0.1 equiv.), −30 °C, 60 min	**36**	74	[d]	
21	**26**	2,7-dimethoxynaphthalene (1.5 equiv.), $SnCl_4$ (0.1 equiv.), −30 °C, 60 min	**36**	44	[d]	

[a] Isolated yields, except where indicated. [b] Mixture of **13** and **28**; yield estimated by ^{1}H NMR spectroscopy. [c] Mixture of **13** and 1,3-dimethoxybenzene; yield estimated by ^{1}H NMR spectroscopy. [d] No attempt was made to isolate other products. [e] Mixture of **19** and **22**; yield estimated by ^{1}H NMR spectroscopy. [f] Mixture of **22** and **27**, yield estimated by ^{1}H NMR spectroscopy. [g] Mixture of **27** and **30**; yield estimated by ^{1}H NMR spectroscopy.

had little effect on the yield of **13** and reactions conducted at higher temperatures resulted in overwhelming formation of the glycal **19** (Entries 3 and 4). Attempts to enhance the yield of disubstituted product **17** by using an excess of the β-benzoate at −30 °C also resulted in overwhelming formation of the glycal (Entry 5). The use of tin(IV) chloride as the Lewis acid was also effective in giving the product **17** (Entry 6). With 2-methoxynaphthalene, the only product obtained was the 1-substituted compound **33** (Entries 16 and 17) that was identified unambiguously by X-ray crystallography (Figure 3, Table 2). With 2,7-(dimethoxy)naphthalene, the only arylation product obtained is therefore designated as the 1-substituted product **36** (Entry 20); its spectroscopic data is essentially identical with that reported previously for a compound designated as the 3-substituted regioisomer **16**.[34,35] Other methoxynaphthalenes react quite well with the β-benzoate to give monoadducts,[47] and in one case the diadduct **35** (Entry 18).

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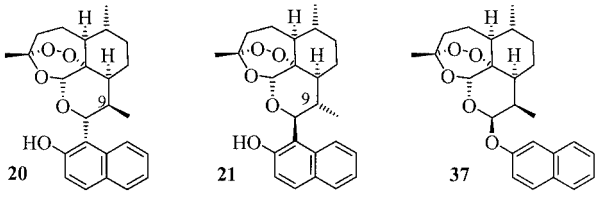
Table 2. Crystallographic details for compounds **33**, **40** and **52**

Compound	**33**	**40**	**52**
CSD deposition number	HING 28	HING 4	WILL 14
Empirical formula	$C_{26}H_{32}O_5$	$C_{21}H_{27}FO_4$	$C_{29}H_{32}NO_4$
Formula mass	424.52	362.43	444.55
Temp. [K], Wavelength [Å]	100(2), 0.71073	295(2), 0.71073	295(2), 0.71073
Crystal system	orthorhombic	orthorhombic	tetragonal
Space group	$P2_12_12_1$	$P2_12_12_1$	$P4_3$
Unit cell *a* [Å]	10.2137(5)	6.0150 (10)	9.3690 (10)
b [Å]	10.6084(6)	14.2590 (10)	9.3690 (10)
c [Å]	40.654(2)	22.075 (3)	26.782 (2)
	90	90	90
V [Å^3], *Z*	4404.9(4), 8	1893.3 (4), 4	2350.9 (4), 4
Density calcd. [g·cm^{-3}]	1.28	1.27	1.26
Abs. coeff. μ [mm^{-1}]		0.093	0.082
$F_{(000)}$	1824	776	952
Description	Colourless plates	Colourless blocks	Colourless prisms
Crystal size, mm	0.3 × 0.2 × 0.08	0.5 × 0.5 × 0.5	0.8 × 0.6 × 0.3
2Θ max.	56.5	55.0	51.0
Reflections	27247	2629	3347
Independent data (R_{int})	10223 (0.069)	2605 (0.027)	2338 (0.082)
Data/restraints/Parameters	10223/0/559	2602/0/235	2335/1/298
GoF on F^2	1.02	1.01	1.01
R indices $I > 2\sigma(I)$	0.0636, 0.1081	0.0444, 0.1015	0.0464, 0.0907
R indices all data	0.1055, 0.1221	0.0694, 0.1160	0.0935, 0.1119
Diff peak and hole (e·Å^{-3})	+0.28/−0.29	+0.20/−0.16	+0.13/−0.17

Reaction of 2-naphthol and the β-benzoate **25** with boron trifluoride−diethyl ether (0.1 equiv.) in dichloromethane at −30 °C with quenching at −30 °C gave only the β-naphthoxy compound **37**[19] in high yield (98%). There was no trace of *C*-arylated products. At a higher temperature (0 °C), a 71:29 mixture of the *C*-arylated products **20** and **21**[38] was obtained almost exclusively, as established by ^{1}H NMR spectroscopic measurements on the crude product mixture. The β-naphthoxy compound **37**, however, did *not* rearrange to the *C*-arylated compounds above 0 °C in the presence of the Lewis acid.[48] The α-benzoate also reacted with 2-naphthol at 0 °C to give the same *C*-arylated products **20** and **21** (71:29) and a trace of glycal **19**. Treatment of glycal **19** and 2-naphthol at 0 °C with the Lewis acid (0.1 equiv.) also gave **20** and **21** (67:33). Thus, the high-temperature conversion of the β-benzoate **25**, and the conversion of the α-benzoate **26** into the latter products, proceeds by way of elimination to glycal **19**, stereorandom protonation at C-9, and *direct* addition of the naphthol nucleophile through C-1′ to the intermediate oxo-stabilized carbocation, as discussed below. This process must also be the case for those reactions commencing with the α-acetate of DHA.[38]



Stereochemical and Mechanistic Aspects

As established unambiguously by analysis of ^{1}H NMR spectra, and X-ray structural data for compound **33**, each α-product possesses a chair pyranose ring with an equatorial β-methyl group at C-9 and an equatorial α-substituent at C-10.[19,49] Thus, the equatorial product is preferentially formed, which is in general accord with the *C*-arylation of glycosides, which have an anomeric axial leaving group, activated by a Lewis acid.[32,43,50−53] This feature also is true for the arylation above of the 10β fluoride **12**.[34,35]

It is likely that the reactions proceed predominantly by addition of the aromatic nucleophile from the si or α face in an S_N1 reaction involving the stabilized half-chair oxonium ion[19] produced by dissociation of the Lewis acid−axial benzoate leaving group ensemble (Scheme 1, a). A kinetic anomeric effect will enhance formation of the oxonium ion from the axial β-benzoate, since stabilization of the developing positive charge by overlap with the axial nonbonding electron pair is possible without major conformational change.[54,55] The addition of the aromatic nucleophile takes place preferentially from the *si* face; this mode of attack may be a reflection of the propensity of large nucleophiles to undergo equatorial approach to sp^2 centres in cyclohexane systems, which will be especially favoured here because of the presence of the axial C8−C8a bond (cf. Scheme 1, a). It is apparent that dissociation of the Lewis acid−equatorial ester leaving group involving the α-benzoate **26** is not as facile; this is due to the inability of the axial

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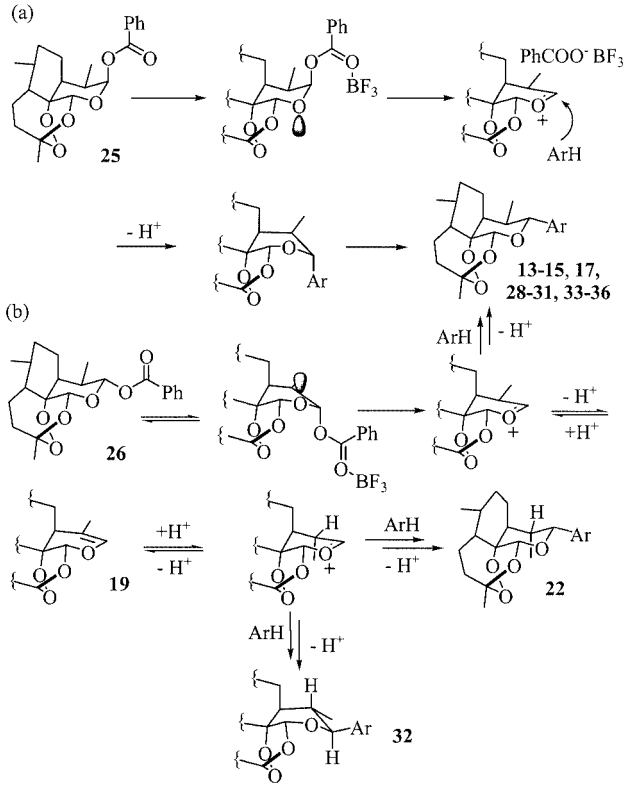
nonbonding electron pair on the oxygen atom in the chair pyranose ring to provide stabilization of the developing cation in the transition state. Therefore, the ring may undergo a conformational change to a twist boat, where participation by the lone pair is now possible; thus, elimination is consequent upon this conformational change (Scheme 1, b). Formation of the oxonium-stabilized cation at the higher temperature results in competing elimination to the glycal **19**, followed by stereorandom protonation of the double bond at C-9, and arylation of the resulting cation at C-10 from either the *re* (β) or *si* (α-) face (Scheme 1, b). In any event, yields of arylated products invariably are lower if the glycal, α-esters, or α-Schmidt trichloroacetimidate is used.



Scheme 1. Arylation of (a) β-benzoate **25** and (b) α-benzoate **26** with activated aromatics in the presence of boron trifluoride−diethyl ether

A parallel in the stereochemical outcome of the current reactions is provided by that of the reactions of axial and equatorial 2-alkoxy-1,3-dioxolanes with Grignard reagents.[54] Those epimers bearing axial alkoxyl groups reacted well, whereas the equatorial epimers failed to react under similar conditions. The major difference to the Lewis acid-catalysed arylations described above, however, is that the Grignard reagents react with retention of configuration, an outcome that is common with that of the reactions described below.

β-Aryl Derivatives

Whilst a large number of carbon nucleophiles have been used to convert glycosyl halides into *C*-glycosides, these nucleophiles have been used generally under Lewis acid catalysis.[32,34,50−53] It was reported long ago that aromatic Grignard reagents react with glycosyl halides to form *C*-aryl glycosides;[56,57] the reaction may also be applied to nonaromatic Grignard reagents.[32,52] A potential advantage of glycosyl halides is that they can be prepared in situ. Thus, a fucopyranose TMS ether was converted on treatment with trimethylsilyl iodide into an axial glycosyl iodide, which was treated in situ with alcohols to generate fucopyranosides.[58] We examined, therefore, the conversion of DHA into a glycosyl halide, and treatment with arylmagnesium halides to prepare *C*-aryl glycosides.

The 10α TMS ether **38** of DHA[19,59] is stable and easily handled; it was treated with trimethylsilyl bromide (TMSBr) in dichloromethane at 0 °C to give a solution containing the 10β (axial) bromide **39**. Whilst it was not possible to isolate the compound, its formation was revealed by a ^{1}H NMR spectroscopic examination of a $CDCl_3$ solution of **38** and 1.05 equiv. of TMSBr. The spectrum displayed signals of the glycal **19** at δ = 6.19 ppm (10-H), and a doublet (J = 3.3 Hz) at δ = 6.60 ppm, corresponding to 10-Hα of **39**, which therefore is equatorial and attached to a chair pyranose ring (Figure 2).[19] There was no signal corresponding to an α-bromide, which, on the basis of the anomeric effect, is expected to be unstable. Significantly, exhaustive attempts to prepare the bromide, or other halides, with other halogenating agents on DHA **2** did not succeed, and invariably, the glycal and other products were obtained.

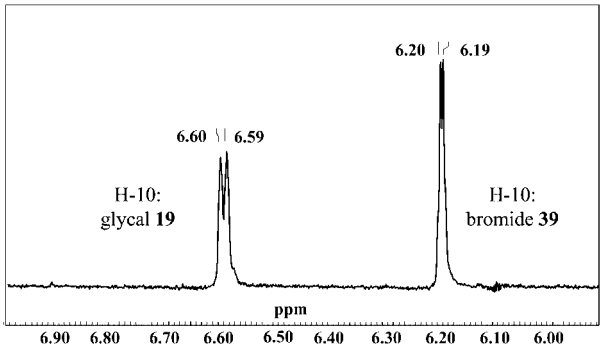


Figure 2. Partial ^{1}H NMR spectrum (300 MHz, CDCl3) in the region δ = 5.9−7.0 ppm of a mixture of the α-TMS ether **38** of DHA (1.0 equiv.) and Me_3SiBr (1.05 equiv.) in $CDCl_3$ at 2 °C, which illustrates the formation after 10 min of glycal **19** and β-bromide **39**

In the event, treatment of the diethyl ether mixture, containing bromide **39** generated in situ, with a variety of aryl Grignard reagents provided the derivatives **11** and **40−54** in acceptable yields. It was not possible to suppress formation of the glycal **19**; when it could not be separated from the arylated products, the crude mixture was treated with *m*-chloroperbenzoic acid to convert it into the more-polar epoxide **55**,[60] which could then be separated from the required product by chromatography. Structures of products

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are depicted in Figure 3 and the yields are summarised in Table 3.

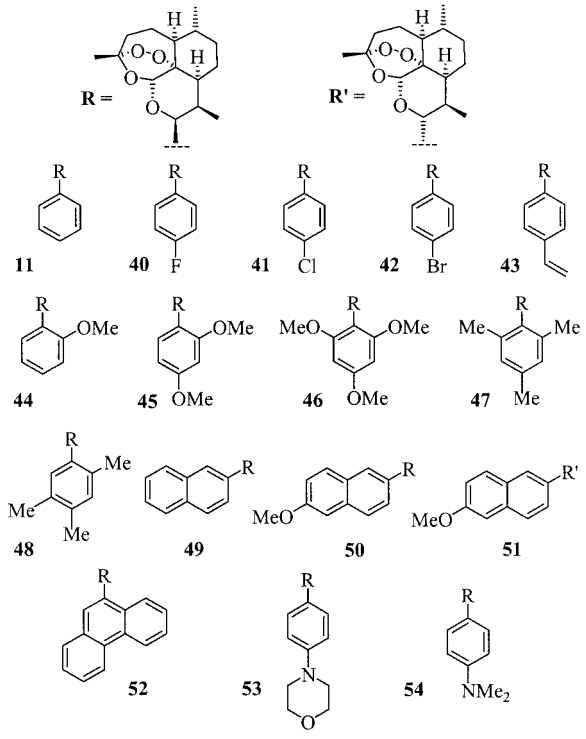


Figure 3. Structures of β- and α-arylated 10-deoxo-10-dihydroartemisinin derivatives obtained from the reactions of β-bromide **39**, generated in situ from the TMS ether of DHA **38**, and aryl Grignard reagents

In the ^{1}H NMR spectra of the β-arylated products, 10-H displays a coupling to 9-H ($J_{10,9}$ = ca. 6.6−7.6 Hz), which is considerably larger than that ($J_{10,9}$ = ca. 3−4 Hz) characteristic of axial β-ethers and esters in a chair pyranose ring.[19] The data is consistent with equatorial aryl groups in a twist-boat pyranose ring, in which the torsion angle between 10-H and 9-H varies between ca. 34−40°.[49] The conformational change from a chair to a twist-boat conformation, with substitution of the halogen atom by an aryl group, arises because the aryl group experiences a 1,3-diaxial interaction with the axial C8−C8a bond in the chair conformer. This interaction is coupled with a loss of anomeric stabilization, normally provided by an electronegative atom attached to C-10 (as in the ethers and esters), which would act to constrain the conformational change from chair to twist-boat.

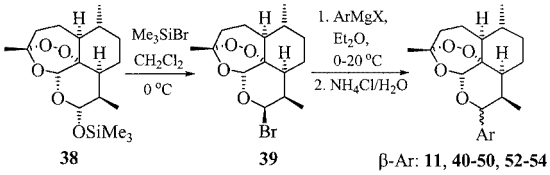
Stereochemical and Mechanistic Aspects

Why is it that the Grignard reagents react with the β-bromide to give β-arylated products, whereas the activated aromatic compounds react with the β-benzoate under Lewis acid catalysis to give the α-arylated products? In general, a clean stereochemical outcome is not observed in the displacement by organometallic reagents of an anomeric axial leaving group in pyranoses where neighbouring group participation may becloud the stereochemistry.[52,53] The relatively clean formation of axial products in our case is common with that recorded for the reaction of axial 2-alkoxy-1,3-dioxanes with aryl Grignard reagents,[54] and is likely to proceed by a similar mechanism, namely formation of an incipient half-chair oxonium ion from the axial β-bromide **39** enhanced by the kinetic anomeric effect indicated above. The key here will be the complexation of the Grignard reagent with the bromide, probably by exchange of an ether ligand, which also induces cleavage of the C−Br bond. Front-side attack on the oxonium ion by the aryl nucleophile from within the complex provides the product (Scheme 2). It was noted previously by Eliel and Nader that activation of the alkoxyl group in the 2-alkoxy-1,3-dioxane by the Grignard reagent is a likely prerequisite for formation of the oxonium ion, a premise validated by the lack of reactivity of organolithium reagents.

X-ray Structural Data

X-ray structural data of compound **33** confirms the α-equatorial stereochemistry and chair conformation of the pyranose ring of the aromatic adducts formed by the Lewis

Table 3. Yields of arylated derivatives from the reactions of β-bromide **39** and aryl Grignard reagents



38 **39** β-Ar: **11**, **40-50**, **52-54** α-Ar: **51**

Product	Ar	Yield (%)	Product	Ar	Yield (%)
11	phenyl	45	**47**	2′,4′,6′-trimethylphenyl	55
40	4′-fluorophenyl	39	**48**	2′,4′,5′-trimethylphenyl	55
41	4′-chlorophenyl	39	**49**	2′-naphthyl	43
42	4′-bromophenyl	64	**50**	6′-methoxynaphthyl	17
43	4′-vinylphenyl	68	**51**	6′-methoxynaphthyl	14
44	2′-methoxyphenyl	59	**52**	9′-phenanthryl	37
45	2′,4′-dimethoxyphenyl	58	**53**	4′-(1′′-morpholino)phenyl	51
46	2′,4′,6′-trimethoxyphenyl	46	**54**	4′-(*N*,*N*-dimethylamino)phenyl	34

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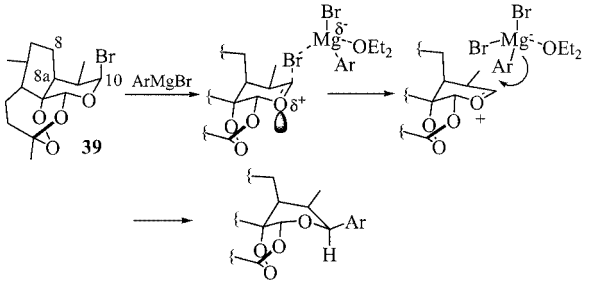

Scheme 2. Reaction of axial bromide **39** with aryl Grignard reagents

acid-catalysed reactions. Similarly, X-ray data for compounds **40** and **52** confirm the β-stereochemistry of the Grignard adducts in which the aromatic substituent is equatorial and the pyranose ring is twist-boat (Figure 4). Key structural parameters are given in Table 4 and Table 5 together with the corresponding data for β-DHA (cf. compound **2**) bearing an axial hydroxy group in a chair pyranose ring.[61]

Artemisinin and its derivatives have a relatively rigid 3-D framework because of the constraints of its polycyclic system that consists of two seven- and three six-membered rings. The peroxy group forms part of both a dioxepane and a trioxane ring. This latter ring is constrained within a twist-boat conformation. The peroxy group has an O(1)−O(2) bond length of ca. 1.47 Å and is asymmetric, with the O(1)−C(1) bond (crystallographic numbering: Figure 3) being significantly longer and weaker than O(2)−C(3), which are typically 1.47 and 1.42 Å, respectively (Table 4). This feature is due to the additional oxygen atom substituent at C(3) that renders it more electrophilic than C(1). The asymmetry of the peroxide unit is also demonstrated in the wider bond angle at O(1) of 113° compared to 109° at O(2). Structural interest in the 10β aromatic derivatives focuses on the ring conformation of the pyranose (oxacyclohexane) ring [C(1)−C(2)−O(4)−C(10)−C(9)−C(12)], which is the only flexible component of the polycyclic system. The crystal structures of compounds **40** and **52** show this ring to be in a twist-boat conformation, which is seen from analysis of both the ring torsion angles and the atomic displacements from the mean plane of the ring (Table 5). The orientation of the phenyl groups is approximately coplanar with the ring oxygen atom O(4). Table 5 also indicates that the H(9)−C(9)−C(10)−H(10) torsion angle for compound **40** is 32.2°, and for **52** it is 40.3°, whilst the H(9)−C(9)−C(12)−H(12) torsion angles are 23.9° and 17.7°, respectively, in the solid state. This feature is in marked contrast to β-DHA in which the ring has a chair conformation and the hydroxy group is axial, which is an arrangement strongly favoured by the anomeric effect; the H(9)−C(9)−C(10)−H(10) torsion angle is −57.2°.

Concluding Comments

The relatively clean stereochemical outcomes of the respective Lewis acid-catalysed reactions on the β-benzoate

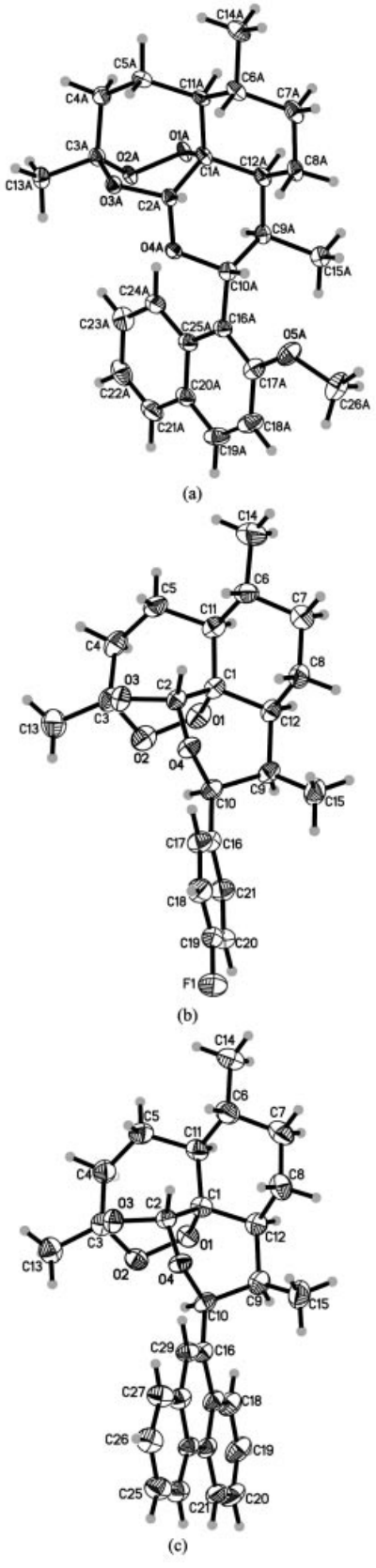

Figure 4. ORTEP plots of (a) 2-methoxynaphthyl derivative **33** formed in the Lewis acid-catalysed reaction; (b) *p*-fluorophenyl (**40**) and (c) phenanthryl (**52**) derivatives formed in the Grignard reactions, indicating stereochemistry of the pyranose ring in each case. Crystallographic numbering is given

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Table 4. Selected bond lengths and angles for compounds **33**, **40**, **52** and β-DHA (**2**)

Compound	**33**	**40**	**52**	β-DHA **2**
Torsion angles [°]				
C(12)−C(1)−C(2)−O(4)	−50.4	−30.1	−32.8	−50.8
C(1)−C(2)−O(4)−C(10)	xf1+53.6	+32.5	+29.9	−54.9
C(2)−O(4)−C(10)−C(9)	xf1−56.9	+67.8	+69.8	−56.1
O(4)−C(10)−C(9)−C(12)	xf1+56.4	+34.9	+41.0	−54.9
C(10)−C(9)−C(12)−C(1)	xf1−55.1	−23.7	−18.0	−53.6
C(9)−C(12)−C(1)−C(2)	xf1−52.1	−57.3	−55.6	−50.6
C(16)−C(10)−C(9)−C(15)	xf1−58.0	+28.2	+34.5	−60.4[a]
H(10)−C(10)−C(9)−H(9)	−179.5	+32.2	+40.3	−57.2
H(9)−C(9)−C(12)−H(12)	xf1−53.9	−23.9	−17.7	−52.8
O(1)−C(1)−C(2)−O(3)	xf1−55.6	−43.3	−44.4	−55.5
O(1)−C(1)−C(2)−O(4)	xf1+63.9	+84.7	+82.4	+63.7
O(2)−O(1)−C(1)−C(2)	xf1+15.7	+13.6	+16.1	+16.0
Ring displacements [Å]				
C(1) C(2) O(4)	+0.21 −0.19 +0.21	+0.38 −0.04 −0.36	+0.39 −0.08 −0.35	+0.21 −0.20 +0.21
C(10) C(9) C(12)	−0.23 +0.25 −0.24	+0.38 −0.02 −0.32	+0.41 −0.07 −0.31	−0.22 +0.23 −0.23
Conformation	chair	twist boat	twist boat	chair

[a] For β-DHA, C(16) is replaced by the oxygen atom of an OH group.

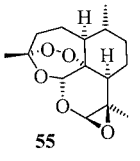
Table 5. Other selected geometric parameters for compounds **33**, **40**, **52** and DHA (**2**)

Compound	**33**	**40**	**52**	β-DHA **2**
O(1)−O(2)	1.472 (2)	1.468 (3)	1.472 (4)	1.471 (3)
O(1)−C(1)	1.462 (3)	1.471 (3)	1.469 (5)	1.462 (3)
O(2)−C(3)	1.417 (3)	1.418 (4)	1.415 (5)	1.414 (4)
O(3)−C(2)	1.408 (3)	1.420 (3)	1.425 (5)	1.405 (3)
O(3)−C(3)	1.432 (3)	1.424 (4)	1.412 (5)	1.427 (4)
O(4)−C(2)	1.417 (3)	1.403 (4)	1.399 (5)	1.430 (3)
O(4)−C(10)	1.440 (3)	1.429 (3)	1.439 (5)	1.432 (3)
C(10)−C(16)	1.517 (4)	1.507 (4)	1.507 (6)	1.396 (3)[a]
Bond angles (°)				
C(1)−O(1)−O(2)	111.2 (2)	113.0 (2)	113.1 (2)	112.1 (2)
O(1)−O(2)−C(3)	108.5 (2)	108.3 (2)	109.8 (3)	108.3 (2)
C(2)−O(3)−C(3)	113.4 (2)	115.5 (2)	116.1 (3)	113.9 (2)
C(2)−O(4)−C(10)	115.0 (2)	115.1 (2)	115.3 (3)	116.1 (2)
O(3)−C(2)−O(4)	105.6 (2)	110.7 (2)	110.0 (3)	105.3 (2)
O(2)−C(3)−O(3)	109.0 (2)	108.3 (2)	108.5 (3)	108.1 (2)
O(4)−C(10)−C(9)	111.5 (2)	109.6 (2)	107.9 (3)	110.1 (2)
O(4)−C(10)−C(16)	106.8 (2)	107.8 (2)	107.1 (3)	111.0 (2)[a]
C(9)−C(10)−C(16)	113.2 (2)	114.4 (2)	117.3 (4)	111.1 (2)[a]

[a] For β-DHA, C(16) is replaced by the oxygen atom of an OH group.

and the Grignard reagents on the β-bromide provide a useful complementarity in the preparation of stereodefined C-10-arylated derivatives of dihydroartemisinin. Whilst in the case of aryl nucleophiles, the stereochemical outcomes may be predicted based on the rationalisations provided above, it must be noted that, as recorded by Ziffer,[29] Lewis acid-catalysed displacement of the hydroxy group in DHA by allylsilane gives the β-product **10**. Whilst this result fits neatly into our previous proposal relating to selective activation, within the equilibrating mixture of epimers, of the α-DHA having an equatorial hydroxy group,[19] the stereochemistry of the allylation is the reverse of that of the Lewis acid-catalysed arylations. We have also found that treatment of either benzoate epimer **25** or **26** with allylsilane in the presence of boron trifluoride−diethyl ether gives only the β-product **10**. Therefore, like the Lewis acid-induced reactions of alkylaluminium nucleophiles with the fluoride **12** reported by Posner,[34,35] and of the silyl enol ethers with the acetate **18** reported by Bégué,[41] these reactions are anomalous, and the exclusive formation of the β-product is unexpectedly reminiscent of operation of the kinetic anomeric effect for these nucleophiles.

Apart from the fact that we have prepared new artemisinin derivatives that bear a series of intercalating groups, as indicated in the Introduction, these compounds are likely to be hydrolytically much more stable than the current derivatives used for treatment of malaria and, therefore, have the potential for development as new drugs for treatment of this disease.[62] Some of these compounds, however, will be too lipophilic to be useful,[5] and will require further functionalisation to enhance their overall polarity. As a preliminary illustration of this concept, compound **43** was converted into the benzoic acid derivative **56** (79%) by using potassium permanganate and potassium hydrogen carbonate in acetone.[63] This transformation thereby provides a potentially more stable analogue of the most widely used of the current artemisinin derivatives, namely artesunate **4**, and further, it possesses a UV chromophore that will greatly facilitate analysis of this compound in pharmacokinetic situations.



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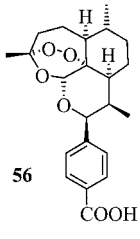

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Experimental Section

General Remarks: The general experimental conditions were as described previously.[19] All reactions were carried out under nitrogen. Grignard reagents were either purchased or prepared in diethyl ether or THF.

Glycal 19: Boron trifluoride−diethyl ether (15.2 mL, 119.72 mmol) was added to a cold (0 °C) stirred mixture of dihydroartemisinin (DHA) **2** (20 g, 70.42 mmol) in diethyl ether (1.5 L). The solution was stirred at room temperature over 18 h. The solution was washed with 5% aqueous $NaHCO_3$ (3 × 200 mL) and water (3 × 200 mL), and then dried ($MgSO_4$). Filtration and evaporation of the filtrate gave a light-yellow solid, which was recrystallised with hexane to give colourless needles (16.82 g, 90%), m.p. 95−97 °C (ref.[42] 96−98 °C). $[\alpha]_D^{22} = +158.69$ (c = 1.22, $CHCl_3$). ^1H NMR: δ = 0.98 (d, J = 5.8 Hz, 3 H, 6-Me), 1.02−1.39 (m, 2 H), 1.42 (m, 3 H, 9-Me), 1.44−1.74 (m, 8 H), 1.86−1.96 (m, 1 H), 2.00−2.10 (m, 2 H), 2.35−2.46 (m, 1 H), 5.54 (s, 1 H, H-12), 6.18 (q, J = 1.33 Hz, 1 H, 10-H) ppm. ^{13}C NMR: δ = 16.8, 20.9, 25.05, 26.5, 30.6, 34.75, 36.9, 38.12, 45.1, 52.1, 79.6, 90.3, 105.2, 108.75, 135.6 ppm. IR (film): $\tilde{\nu}_{max}$ = 812, 828, 850, 858, 870, 880, 904, 938, 954, 972, 992, 1016, 1030, 1054, 1078, 1114, 1142, 1160, 1178, 1200, 1250, 1274, 1306, 1320, 1334, 1338, 1374, 1432, 1686, 2850, 2872, 2924, 2950, 2966, 3082 cm^{-1}. MS (CI, NH_3): m/z (%) = 301 (2) [(MH + 2 NH_4)$^+$], 286 (3) [MNH_4^+, 2 × ^{13}C], 285 (15) [MNH_4^+, ^{13}C], 284 (88) [MNH_4^+], 269 (2) [MH^+, 2 × ^{13}C], 268 (18) [MH^+, ^{13}C], 267 (100) [MH^+], 266 (13) [M^+]. $C_{15}H_{22}O_4$ (266.34): calcd. C 67.65, H 8.33; found C 67.57, H 8.33.

Preparation of Dimeric Acetal 27

Boron trifluoride−diethyl ether (1.95 μL, 2.19 mg, 15.4 μmol, 0.1 equiv.) was added to a cold (0 °C) stirred solution of 10α-dihydroartemisinyl benzoate **26** (60 mg, 0.15 mmol) and DHA **2** (44 mg, 0.15 mmol, 1 equiv.) in dichloromethane (5 mL). After 1 h, the reaction was quenched with water (1 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (1 mL), brine (1 mL) and then dried (Na_2SO_4). Filtration and evaporation of filtrate gave a residue, which on chromatography with ethyl acetate/hexane (18:82) gave the product as a white foamy solid (31.9 mg, 38%). Recrystallisation with dichloromethane/hexane gave colourless rectangular plates, m.p. 140−142 °C. $[\alpha]_D^{20}$ = +163.6 (c = 0.83, $CHCl_3$). ^1H NMR: δ = 0.86 (d, J = 7.1 Hz, 3 H, 9-Me), 0.94 (m, 6 H, 6-Me, 9-Me), 0.95 (d, J = 4.0 Hz, 3 H, 6-Me), 1.17−1.36 (m, 4 H), 1.38 (s, 3 H, 3-Me), 1.43 (s, 3 H, 3-Me), 1.45−1.57 (m, 3 H), 1.63−1.76 (m, 4 H), 1.83−1.90 (m, 2 H), 1.97−2.11 (m, 4 H), 2.17−2.47 (m, 6 H), 2.58−2.66 (m, 1 H), 4.72 (d, J = 9.4 Hz, 1 H, 10-H), 5.01 (d, J = 3.2 Hz, 1 H, 10-H), 5.42 (s, 1 H, H-12), 5.79 (s, 1 H, H-12) ppm. ^{13}C NMR: δ = 13.3, 13.7, 20.95, 21.0, 22.7, 24.9, 25.35, 25.4, 26.55, 26.8, 31.85, 33.6, 34.96, 35.51, 36.9, 37.2, 38.0, 38.1, 45.2, 46.1, 52.2, 53.4, 80.7, 81.8, 89.2, 91.3, 99.6, 102.4, 104.5, 104.55 ppm. IR (film): $\tilde{\nu}_{max}$ = 734, 877, 958, 979, 1012, 1044, 1092, 1376, 1451, 2874, 2926 cm^{-1}. MS (CI, CH_4): m/z (%) = 552 (6), 551 (20) [MH^+]. $C_{30}H_{46}O_9$ (550.7) calcd. C 65.43, H 8.42; found C 65.57, H 8.52. Other products isolated were the glycal **19** (3.7 mg, 9%), an inseparable mixture of 10α-dihydroartemisinyl benzoate **26** and 10β-dihydroartemisinyl benzoate **25** as a white powder (7.5 mg, 13%) in a ratio of 1.0:0.7 in favour of 10α-dihydroartemisinyl benzoate, and an unknown compound (6.5 mg).

A simpler preparation is as follows. A suspension of *p*-toluenesulfonyl chloride (4.36 g, 22.89 mmol, 1.3 equiv.) in dichloromethane (30 mL) was added to a cold (0 °C) stirred mixture of DHA **2**(5.00 g, 17.6 mmol) and triethylamine (3.19 mL, 2.32 g, 22.89 mmol, 1.3 equiv.) in dichloromethane (70 mL). The mixture was warmed to room temperature over 1 d. The reaction was poured into ice-water (ca. 150 mL). The aqueous layer was separated and extracted with dichloromethane (2 × 150 mL). The organic extracts were combined and dried (Na_2SO_4). Filtration and evaporation of filtrate gave an oil, which on chromatography with ethyl acetate/hexane (20:80) gave the dimer as a white powder (2.12 g, 44%).

Lewis Acid-Mediated *C*-Arylation Reactions: Conditions and yields are as given in Table 1. Representative preparations selected from Table 1 are given below.

10α-(2′,4′-Dimethoxyphenyl)-10-deoxo-10-dihydroartemisinin (13): Boron trifluoride−diethyl ether (6.5 μL, 7.3 mg, 0.05 mmol, 0.2 equiv.) was added to a cold (− 30 °C) solution of 10β-dihydroartemisinyl benzoate **25** (100 mg, 0.26 mmol) and 1,3-dimethoxybenzene (53 mg, 51 μL, 0.39 mmol, 1.5 equiv.) in dichloromethane (5 mL) under nitrogen. After 1 h, the reaction was quenched with water (1 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate (1 mL) and brine (1 mL), and then dried (Na_2SO_4). Filtration and evaporation of the filtrate gave an oil, which on chromatography with ethyl acetate/hexane (12:88 then 20:80) gave a mixture of compounds **13** and **28** as an inseparable mixture (33.1 mg, 32%) in a ratio of 1.0:0.32 in favour of **13**. A sample of the compound **13** was obtained as white needles by recrystallisation of the mixture from dichloromethane/hexane, m.p 141−143 °C [ref.[35] (for compound described experimentally as the 2-artemisininyl-substituted 1,3-dimethoxybenzene[36]) 136−138 °C; ref.[40] 138−140 °C]. ^1H NMR: δ = 0.58 (d, J = 7.3 Hz, 3 H, 9-Me), 0.98 (d, J = 6.2 Hz, 3 H, 6-Me), 1.03−1.11 (m, 1 H), 1.42 (s, 3 H, 3-Me), 1.24−1.80 (m, 7 H), 1.84−1.94 (m, 1 H), 1.99−2.07 (m, 1 H), 2.34−2.41 (dt, J = 4.1, 13.5 Hz, 1 H), 2.44−2.59 (m, 1 H), 3.75 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 4.93 (d, J = 10.6 Hz, 1 H, 10-H), 5.39 (s, 1 H, H-12), 6.38 (d, J = 2.3 Hz, 1 H, Ar-H), 6.51−6.55 (dd, J = 2.6, 8.8 Hz, 1 H, Ar-H), 7.52 (d, J = 8.2 Hz, 1 H, Ar-H) ppm. Present in the residue (10 mg) obtained by evaporation of the mother liquors remaining from the crystallisation was an inseparable mixture of compounds **13** and **28**. The latter was tentatively identified as 10α-(2′,6′-dimethoxyphenyl)-10-deoxo-10-dihydroartemisinin on the basis of its ^1H NMR spectrum, which is clearly differentiated from those of the C-9 epimer[40] **22** and the β-arylated compound **45** (see below), but very similar to that of the trimethoxy compound **14**. ^1H NMR: δ = 0.56 (d, J = 7.3 Hz, 3 H, 6-Me), 1.38 (s, 3 H, 3-Me), 0.83−1.90 (m, 12 H), 2.01 (m, 1 H), 2.41 (m, 1 H), 3.37−3.44 (m, 1 H), 3.76 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 5.15 (d, J = 10.9 Hz, 1 H, 10-H), 5.37 (s, 1 H, H-12), 6.47 (d, J = 8.5 Hz, 1 H, Ar-H), 6.56 (d, J = 8.5 Hz, 1 H, Ar-H), 7.14 (t, J = 8.2 Hz, 1 H, Ar-H) ppm. Other products isolated were glycal **19** (22.5 mg, 33%), the dimeric acetal **27** (7.1 mg, 10%) and the disubstituted aryl product **17** as a white powder (3 mg, 3%). The latter compound was obtained in better yield as follows. Tin(IV) chloride (1 M solution in dichloromethane, 25.7 μL, 25.7 μmol, 0.1 equiv.) was added to a cold (− 30 °C) stirred solution of 10β-dihydroartemisinyl benzoate (100 mg, 0.26 mmol) and 1,3-dimethoxybenzene (53 mg, 51 μL, 0.39 mmol, 1.5 equiv.) in dichloromethane (5 mL). After 1 h, the reaction was quenched with water (1 mL). The organic layer was separated and washed with saturated aqueous sodium bicarbonate (1 mL), and brine (1 mL) and then dried (Na_2SO_4). Filtration and evaporation of the filtrate gave an oil, which on chromatography with ethyl acetate/hexane (12:88 then 20:80) gave a 1.0:0.4 mixture of compounds **13** and **22** (30 mg, 27%), the glycal **19** (11.6 mg, 17%), and

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the disubstituted aryl product **17** (25.4 mg, 29%) as a white powder. The latter compound was recrystallised from ethyl acetate/hexane to give colourless plates, m.p. 171−174 °C. [ref.[37] 168−169.2 °C] $[\alpha]_D^{20}$ = +141.0 (*c* = 0.64, $CHCl_3$) [ref.[37] +148.3 (*c* = 0.89, $CHCl_3$)]. ^{1}H NMR: δ = 0.59 (d, *J* = 7.0 Hz, 6 H, 2 × 9-Me), 0.96 (d, *J* = 6.2 Hz, 6 H, 2 × 6-Me), 0.85−1.09 (m, 2 H), 1.44 (s, 6 H, 2 × 3-Me), 1.17−1.90 (m, 14 H), 2.00 (m, 2 H), 2.03 (m, 2 H), 2.31−2.42 (dt, *J* = 3.8, 13.8 Hz, 2 H), 2.57 (m, 2 H), 3.77 (s, 6 H, 2 × OMe), 4.90 (d, *J* = 10.6 Hz, 2 H, 2 × 10-H), 5.39 (s, 2 H, 2 × H-12), 6.31 (s, 1 H, Ar-H), 7.90 (br. s, 1 H, Ar-H) ppm. ^{13}C NMR: δ = 13.9, 20.75, 21.95, 25.3, 26.4, 34.8, 36.8, 37.7, 46.8, 52.4, 56.0, 70.0, 80.5, 92.3, 104.3, 122.6, 127.65, 156.95 ppm. IR (film): $\tilde{\nu}_{max}$ = 845, 881, 904, 932, 1044, 1066, 1134, 1103, 1134, 1206, 1298, 1380, 1457, 1510, 1639, 2920, 2880 cm^{-1}. MS (FAB, NBA): *m*/*z* (%) = 670 (20) [M$^+$], 671 (10) [MH$^+$], 672 (3) [MH$^+$, ^{13}C]. $C_{38}H_{54}O_{10}$ (670.85): calcd. C 68.04, H 8.11; found C 67.85, H 8.15.

10α-(2′,4′,6′-Trimethoxyphenyl)-10-deoxo-10-dihydroartemisinin (14): Boron trifluoride−diethyl ether (3.3 μL, 3.6 mg, 0.026 mmol, 0.1 equiv.) was added to a cold (−30 °C) stirred solution of 10β-benzoate **25** (100 mg, 0.26 mmol) and 1,3,5-trimethoxybenzene (65 mg, 0.39 mmol, 1.5 equiv.) in dichloromethane (7 mL). After 1 h at this temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with dichloromethane (3 × 10 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (1 mL) followed by brine (1 mL), and then dried (Na_2SO_4). Filtration and evaporation of filtrate gave an oil that was chromatographed with ethyl acetate/hexane (2:8) to give firstly the glycal **19** (7.2 mg, 11%) and then the product **14** as a white foam, which slowly deposited white microcrystals from hexane (79.8 mg, 71%), m.p. 67−69 °C (ref.[35] 68−71 °C), with other data in agreement with those previously reported.[13,14,18,35] The final product isolated was the dimeric acetal **27** (7.1 mg, 5%).

10α-(2′-Furyl)-10-deoxo-10-dihydroartemisinin (15): This compound was prepared by a method analogous to that for compound **14** above. Thus, from 10β benzoate **25** (193 mg, 0.50 mmol) and furan (542 μL, 7.5 mmol, 15 equiv.) in dichloromethane (5 mL) containing boron trifluoride−diethyl ether (123 μL, 1.0 mmol, 2 equiv.) was obtained a colourless residue, which after chromatography with ethyl acetate/hexane (15:85) gave the product as a white solid (53.7 mg, 32%), m.p. 96−97 °C (ref.[35] 97−98 °C), with other data in agreement with those previously reported.[35]

10α-(Pyrrol-2′-yl)-10-deoxo-10-dihydroartemisinin (29): This compound was prepared by a method analogous to that for compound **14** above. Thus, from 10β-benzoate 25 (700.8 mg, 1.80 mmol) and pyrrole (624 μL, 9.00 mmol, 5 equiv.) in dichloromethane (5 mL) containing boron trifluoride−diethyl ether (332 μL, 2.70 mmol, 3.0 equiv.) was obtained a colourless residue, which after chromatography with ethyl acetate/hexane (30:70) gave the product as a colourless oil (487 mg, 82%). $[\alpha]_D^{20}$ = +198.7 (*c* = 0.105, $CHCl_3$). ^{1}H NMR: δ = 0.93 (d, *J* = 7.0 Hz, 3 H, 6-Me), 0.80−1.15 (m, 4 H), 1.15−1.68 (m, 7 H), 1.68−1.80 (m, 2 H), 1.93 (m, 1 H), 1.95−2.10 (m, 1 H), 2.10−2.50 (m, 2 H), 2.58 (m, 1 H), 4.47 (d, *J* = 10.8 Hz, 1 H, 10-H), 5.39 (s, 1 H, H-12), 6.04 (m, 2 H, 3′-H, 4′-H), 6.71 (m, 1 H, 5′-H), 8.80 (br. s, 1 H, NH) ppm. ^{13}C NMR: δ = 13.9, 14.0, 20.1, 21.2, 24.6, 25.9, 32.9, 34.0, 36.2, 37.2, 45.7, 51.8, 60.2, 71.9, 80.5, 91.9, 104.1, 106.7, 107.2, 117.6, 129.9 ppm. IR (film): $\tilde{\nu}_{max}$ = 722, 1024, 1066, 1376, 1460, 2854, 2924 cm^{-1}. MS (CI, butane): *m*/*z* (%) = 334 (100) [MH$^+$]. $C_{19}H_{27}NO_4$ (309.41): calcd. C 68.44, H 8.16, N 4.20; found C 68.77, H 8.56, N 3.85.

10α-(Indolyl-3′-yl)-10-deoxo-10-dihydroartemisinin (30): Tin(IV) chloride (1.0 M in CH_2Cl_2, 0.026 mmol, 26 μL, 0.1 equiv.) was added to a cold (−30 °C) stirred solution of 10β-benzoate **25** (100 mg, 0.26 mmol) and *N*-methylindole (49 μL, 51 mg, 0.39 mmol, 1.5 equiv.) in dichloromethane (5 mL). After 65 min, the reaction mixture was quenched with water (1 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (1 mL), and brine (1 mL), and then dried (Na_2SO_4). Filtration and evaporation of the filtrate gave a residue, which on chromatography with ethyl acetate/hexane (16:84) gave the product 30 as a pale foamy solid (74.9 mg, 73%), with other data in agreement with those previously reported.[35] Glycal **19** was also isolated as a 1:0.53 mixture with unchanged *N*-methylindole (4.3 mg).

10α-(4′-Methoxynaphthyl)-10-deoxo-10-dihydroartemisinin (31) and 9-epi-10α-(4′-methoxynaphthyl)-10-deoxo-10-dihydroartemisinin (32): Tin(IV) chloride (1.0 M in CH_2Cl_2, 0.26 mmol, 0.26 mL, 0.1 equiv.) was added to a cold (−30 °C) stirred solution of 10β-benzoate **25** (1.0 g, 2.58 mmol) and 1-methoxynaphthalene (0.56 mL, 0.61 g, 3.87 mmol, 1.5 equiv.) in dichloromethane (50 mL). After 75 min, the reaction was quenched with water (10 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL) and dried (Na_2SO_4). Filtration and evaporation of filtrate gave a residue, which on chromatography with ethyl acetate/hexane (8:92) gave first the product **32** as a beige powder (50.1 mg, 5%), recrystallisation of which from ethyl acetate gave colourless plates, m.p. 185−186 °C. $[\alpha]_D^{22}$ = +82.5 (*c* = 0.66, $CHCl_3$). ^{1}H NMR: δ = 0.99 (overlapping dd, *J* = 5.9, 6.7 Hz, 6 H, 6-Me and 9-Me), 1.04−1.64 (m, 10 H), 1.69−1.86 (m, 1 H), 1.96−2.12 (m, 3 H), 2.34−2.44 (m, 1 H), 3.99 (s, 3 H, OMe), 5.58 (s, 1 H, H-12), 5.86 (br. d, *J* = 9.1 Hz,1 H, 10-H), 6.78 (d, *J* = 7.9 Hz, 1 H, Ar-H), 7.41−7.50 (m, 3 H, 3 × Ar-H), 8.25−8.28 (m, 1 H, Ar-H), 8.44 (d, *J* = 8.8 Hz, 1 H, Ar-H) ppm. ^{13}C NMR: δ = 20.3, 20.5, 25.2, 26.3, 32.6, 34.6, 37.1, 37.7, 41.2, 47.9, 52.9, 55.8, 82.8, 91.5, 102.6, 103.3, 122.5, 124.9, 125.1, 126.15, 126.4, 128.6, 155.6 ppm. IR (film): $\tilde{\nu}_{max}$ = 766, 830, 889, 929, 992, 1006, 1052, 1080, 1106, 1158, 1221, 1275, 1375, 1464, 1515, 1588, 2927 cm^{-1}. MS (CI, CH_4): *m*/*z* (%) = 426 (2) [MH$^+$, ^{13}C], 425 (8) [MH$^+$], 424 (5) [M$^+$]. $C_{26}H_{32}O_5$ (424.5): calcd. C 73.56, H 7.60; found C 73.63, H 7.67. The more-polar 10α-(4′-methoxynaphthyl)-10-deoxo-10-dihydroartemisinin **31** was isolated as a colourless gum (142.9 mg, 13%). $[\alpha]_D^{22}$ = +89 (*c* = 0.39, $CHCl_3$). ^{1}H NMR ([D]$_8$toluene, 90 °C): δ = 0.44 (d, *J* = 7.04 Hz, 3 H), 0.82−1.00 (m, 5 H), 1.42 (s, 3 H, 3-Me), 1.02−1.55 (m, 7 H), 1.69−1.76 (m, 1 H), 1.86−1.92 (m, 1 H), 2.41−2.52 (m, 1 H), 3.44 (br. s, 1 H), 3.65 (s, 3 H, OMe), 4.91 (br. d, 1 H, *J* = 10.5 Hz, 10-H), 5.31 (s, 1 H, H-12), 6.53−6.56 (m, 1 H, Ar-H), 7.36−7.52 (m, 2 H, 2 × Ar-H), 8.47 (d, *J* = 8.21 Hz, 1 H, Ar-H) ppm. IR (film): $\tilde{\nu}_{max}$ = 766, 880, 1056, 1095, 1223, 1271, 1376, 1394, 1464, 1514, 1586, 2872, 2936 cm^{-1}. MS (CI, CH_4): *m*/*z* (%) = 424 (16) [M$^+$], 425 (11) [MH$^+$], 426 (4) [MH$^+$, ^{13}C], 427 (1) [MH$^+$, 2 × ^{13}C]. $C_{26}H_{32}O_5$ (424.5): calcd. C 73.56, H 7.60; found C 73.02, H 7.81. The glycal **19** was also isolated as a white powder (208.1 mg, 30%).

10α-(2′-Methoxynaphthyl)-10-deoxo-10-dihydroartemisinin (33): Tin(IV) chloride (1.0 M in CH_2Cl_2, 0.26 mmol, 0.26 mL, 0.1 equiv.) was added to a cold (−30 °C) stirred solution of 10β-benzoate **25** (1.0 g, 2.58 mmol) and 2-methoxynaphthalene (0.61 g, 3.87 mmol, 1.5 equiv.) in dichloromethane (50 mL). After 1 h, the reaction was quenched with water (10 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), and then dried (Na_2SO_4). Filtration and evaporation of filtrate gave a residue, which on chromatography with ethyl acetate/hexane (8:92) gave the product as a white foamy solid (487.8 mg,

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44%). Recrystallisation from ethyl acetate gave colourless plates, m.p. 166−167 °C. $[\alpha]_D^{20}$ = +209.8 (*c* = 1.31, $CHCl_3$). ^1H NMR: δ = 0.51 (d, *J* = 7.3 Hz, 3 H, 6-Me), 1.00 (d, *J* = 6.2 Hz, 3 H, 9-Me), 1.05−1.18 (m, 1 H), 1.43 (s, 3 H, 3-Me), 1.32−1.82 (m, 8 H), 1.89−1.98 (m, 1 H), 2.04−2.12 (m, 1 H), 2.41−2.51 (dt, *J* = 4.1, 13.2 Hz, 1 H), 3.23−3.33 (m, 1 H), 3.89 (s, 3 H, OMe), 5.49 (s, 1 H, H-12), 5.65 (d, *J* = 11.1 Hz, 1 H, 10-H), 7.18 (d, *J* = 9.1 Hz, 1 H, Ar-H), 7.24−7.32 (m, 1 H, Ar-H), 7.41−7.47 (m, 1 H, Ar-H), 7.72 (t, *J* = 2.1 Hz, 1 H, Ar-H), 9.21 (d, *J* = 8.2 Hz, 1 H, Ar-H) ppm. ^{13}C NMR: δ = 13.7, 20.8, 21.6, 25.3, 26.4, 31.5, 34.7, 36.8, 37.85, 46.7, 52.6, 57.2, 70.75, 81.4, 92.6, 104.5, 113.15, 121.1, 123.7, 126.0, 127.4, 128.2, 130.05, 130.3, 132.7, 154.8 ppm. IR (film): $\tilde{\nu}_{max}$ = 732, 752, 809, 845, 879, 918, 933, 1042, 1057, 1084, 1100, 1129, 1249, 1376, 1510, 2871, 2943 cm^{-1}. MS (CI, CH_4): *m/z* (%) = 379 (100) $[M - 3Me]^+$, 424 (24) $[M^+]$, 425 (22) $[MH^+]$, 426 (6) $[MH^+, {}^{13}C]$. $C_{26}H_{32}O_5$ (424.5): calcd. C 73.56, H 7.68; found C 73.34, H 7.63.

10α-(2′,6′-Dimethoxynaphthyl)-10-deoxo-10-dihydroartemisinin (34) and Bis(1,5-[10α-(10-deoxo-10-dihydroartemisininyl)])-2,6-dimethoxynaphthalene (35): Tin(IV) chloride (1.0 M in CH_2Cl_2, 0.26 mmol, 0.26 mL, 0.1 equiv.) was added to a cold (0 °C) stirred solution of 10β-benzoate **25** (1 g, 2.58 mmol) and 2,6-dimethoxynaphthalene (0.73 g, 3.87 mmol, 1.5 equiv.) in dichloromethane (50 mL). After 1 h, the reaction was quenched with water (10 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), and then dried (Na_2SO_4). Filtration and evaporation of filtrate gave a residue, which on chromatography with ethyl acetate/hexane (14:86 followed by 20:80) gave the product **34** as a white powder (203.9 mg, 18%). Recrystallisation from dichloromethane/hexane gave clusters of colourless needles, m.p. 171−173 °C. $[\alpha]_D^{20}$ = +197 (*c* = 0.84, $CHCl_3$). ^1H NMR: δ = 0.51 (d, *J* = 7.04 Hz, 3 H, 9-Me), 1.00 (d, *J* = 6.14 Hz, 3 H, 6-Me), 0.90−1.15 (m, 2 H), 1.42 (s, 3 H, 3-Me), 1.23−1.81 (m, 8 H), 1.89−1.98 (m, 1 H), 2.03−2.12 (m, 1 H), 2.40−2.51 (dt, *J* = 4.11, 14.07 Hz, 1 H), 3.20−3.27 (m, 1 H), 3.86 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 7.03 (d, *J* = 2.93 Hz, 1 H, Ar-H), 7.11−7.16 (m, 2 H, 2 × Ar-H), 7.62 (d, *J* = 9.09 Hz, 1 H, Ar-H), 9.14 (d, *J* = 9.38 Hz, 1 H, Ar-H) ppm. ^{13}C NMR: δ = 13.7, 20.8, 21.6, 25.3, 26.4, 31.7, 34.7, 36.8, 37.85, 46.7, 52.55, 55.5, 57.4, 70.8, 81.4, 92.5, 104.5, 106.3, 113.95, 118.5, 121.7, 128.1, 128.6, 129.05, 131.5, 153.4, 155.9 ppm. IR (film): $\tilde{\nu}_{max}$ = 737, 828, 850, 880, 920, 1042, 1129, 1152, 1196, 1248, 1375, 1452, 1509, 1661, 1629, 2873, 2937 cm^{-1}. MS (CI, CH_4): *m/z* (%) = 455 (53) $[MH + CH_4]^+$, 454 (38) $[M + CH_4]^+$, 440 (5) $[MH^+, {}^{13}C]$, 439 (17) $[MH^+]$, 438 (13) $[M^+]$, 409 (100) $[MH - 3\ Me]^+$. $C_{27}H_{34}O_6$ (454.6): calcd. C 71.34, H 7.54; found C 70.99, H 7.55. The more-polar disubstituted naphthalene **35** was isolated as a white powder (175.2 mg, 19%). Recrystallisation from methanol gave colourless rods, m.p. 153−154 °C. $[\alpha]_D^{20}$ = +240 (*c* = 0.57, $CHCl_3$). ^1H NMR: δ = 0.48 (d, *J* = 7.0 Hz, 6 H, 2 × 6-Me), 1.02 (d, *J* = 6.16 Hz, 6 H, 2 × 9-Me), 0.82−1.17 (m, 4 H), 1.42 (s, 6 H, 2 × 3-Me), 1.19−1.80 (m, 12 H), 1.86−1.97 (m, 2 H), 2.02−2.33 (m, 2 H), 2.40−2.50 (dt, *J* = 3.8, 13.5 Hz, 2 H), 3.17−3.27 (m, 2 H), 3.86 (s, 6 H, 2 × OMe), 5.47 (s, 2 H, 2 × H-12), 5.62 (d, *J* = 11.0 Hz, 2 H, 2 × 10-H), 7.18 (d, *J* = 9.7 Hz, 2 H, 2 × Ar-H), 9.20 (d, *J* = 9.7 Hz, 2 H, 2 × Ar-H) ppm. ^{13}C NMR: δ = 13.8, 20.8, 21.6, 25.3, 26.4, 31.7, 34.7, 36.8, 37.8, 46.8, 52.6, 57.1, 70.6, 81.5, 92.5, 104.4, 113.0, 120.5, 129.1, 129.4, 153.0 ppm. IR (film): $\tilde{\nu}_{max}$ = 1041, 1057, 1129, 1256, 1318, 1376, 1454, 1514, 1596, 1716, 2873, 2936 cm^{-1}. MS (CI, CH_4): *m/z* (%) = 676 (28) $[MH - 3Me]^+$, 675 (67) $[M - 3Me]^+$, 722 (1) $[MH^+, {}^{13}C]$, 721 (3) $[MH^+]$, 720 (9) $[M^+]$. $C_{42}H_{56}O_{10}$ (720.9): calcd. C 69.98, H 7.83; found C 69.37, H 7.98.

10α-(2′,7′-Dimethoxynaphthyl)-10-deoxo-10-dihydroartemisinin (36): Tin(IV) chloride (1.0 M in CH_2Cl_2, 0.26 mmol, 0.26 mL, 0.1 equiv.) was added to a cold (−30 °C) stirred solution of 10β-benzoate **25** (1.0 g, 2.58 mmol) and 2,7-dimethoxynaphthalene (0.73 g, 3.87 mmol, 1.5 equiv.) in dichloromethane (50 mL). After 1 h, the reaction was quenched with water (10 mL). The organic layer was separated and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), and then dried (Na_2SO_4). Filtration and evaporation of filtrate gave a residue, which on chromatography with ethyl acetate/hexane (12:88 followed by 20:80) gave the product **36** as a white powder (840.6 mg, 74%). Recrystallisation from dichloromethane/hexane gave long colourless needles, m.p. 156−158 °C [ref.[34,35] (for compound described as the 3′-substituted regioisomer) 149−151 °C]. $[\alpha]_D^{22}$ = +242.6 (*c* = 0.77, $CHCl_3$) {ref.[34,35] $[\alpha]_D^{25}$ = +246.4 (*c* = 1.29, $CHCl_3$)} ^1H NMR: δ = 0.46 (d, *J* = 7.33 Hz, 3 H, 6-Me), 1.00 (d, *J* = 6.45 Hz, 3 H, 9-Me), 1.43 (s, 3 H, 3-Me), 1.21−1.82 (m, 7 H), 1.88−1.97 (m, 1 H), 2.04−2.11 (m, 1 H), 2.37−2.47 (dt, *J* = 4.11, 13.49 Hz, 1 H), 3.30−3.42 (m, 1 H), 3.88 (s, 3 H, OMe), 3.99 (s, 3 H, OMe), 5.48 (s, 1 H, H-12), 5.67 (d, *J* = 10.85 Hz, 1 H, 10-H), 6.95 (dd, *J* = 2.64, 9.10 Hz, 1 H, Ar-H), 7.02 (d, *J* = 8.80 Hz, 1 H, Ar-H), 7.59 (d, *J* = 8.80 Hz, 1 H, Ar-H), 7.59 (d, *J* = 8.8 Hz, 1 H, Ar-H), 7.65 (d, *J* = 8.80 Hz, 1 H, Ar-H), 8.36 (d, *J* = 2.34 Hz, 1 H, Ar-H) ppm. ^{13}C NMR: δ = 13.65, 20.8, 21.75, 25.2, 26.6, 30.8, 34.7, 36.8, 37.8, 46.7, 52.8, 56.5, 57.1, 70.5, 81.7, 93.4, 104.4, 105.0, 110.5, 117.2, 119.7, 125.7, 129.7, 129.8, 134.25, 155.6, 158.1 ppm. IR (film): $\tilde{\nu}_{max}$ = 828, 1044, 1061, 1247, 1376, 1427, 1466, 1515, 1626, 2873, 2940 cm^{-1}.

C-Arylations with Grignard Reagents

10β-Phenyl-10-deoxo-10-dihydroartemisinin (11): Trimethylsilyl bromide (140 μL, 1.06 mmol) was added to a cold (0 °C) stirred solution of the DHA 10α-TMS ether **38**[19] (372 mg, 1.04 mmol) in dichloromethane (5 mL). After 0.5 h, the solvent was removed by careful evaporation under reduced pressure to leave a solid residue that was cooled to 0 °C and treated with diethyl ether (5 mL) followed by phenylmagnesium bromide (1.7 M in diethyl ether, 1.40 mL, 2.38 mmol). The resulting mixture was warmed to room temperature overnight, and then treated with saturated aqueous NH_4Cl. The aqueous layer was extracted with ether and the combined ether layers were dried ($MgSO_4$). Filtration and evaporation of the filtrate left an oily residue, which after chromatography with ethyl acetate/hexane (8:92) gave the product as a white solid (159 mg, 45%). Recrystallisation from ether/hexane gave colourless rectangular plates, m.p. 122−123 °C. $[\alpha]_D^{20}$ = −36.0 (*c* = 0.47, $CHCl_3$). ^1H NMR: δ = 0.54 (d, *J* = 7.68 Hz, 3 H, 9-Me), 1.01 (d, *J* = 5.77 Hz, 3 H, 6-Me), 1.41 (s, 3 H, 3-Me), 1.28−1.60 (m, 5 H), 1.65−2.12 (m, 5 H), 2.31−2.42 (m, 1 H), 2.71−2.84 (m, 1 H, 9-H), 5.60 (s, 1 H, H-12), 5.75 (d, *J* = 6.70 Hz, 1 H, 10-H), 7.19−7.34 (m, 5 H, Ph-H) ppm. ^{13}C NMR: δ = 13.6, 19.85, 24.7, 24.9, 25.7, 32.1, 34.2, 36.6, 37.5, 43.45, 51.5, 73.0, 81.1, 90.8, 102.2, 126.1, 126.2, 127.7, 141.0 ppm. IR (film): $\tilde{\nu}_{max}$ = 700, 740, 820, 852, 882, 904, 944, 954, 1010, 1038, 1058, 1076, 1112, 1208, 1376, 1452, 1494, 2874, 2938 cm^{-1}. MS (CI, CH_4): *m/z* (%) = 345 (14) $[MH^+]$, 327 (14), 299 (100). $C_{21}H_{28}O_4$ (344.45): calcd. C 73.26, H 8.14; found C 73.58; H 8.32.

10β-(4′-Fluorophenyl)-10-deoxo-10-dihydroartemisinin (40): According to the method above, from DHA 10α-TMS ether **38** (0.8 g, 2.25 mmol), trimethylsilyl bromide (0.30 mL, 2.29 mmol), and then (4-fluorophenyl)magnesium bromide (2.0 M in ether, 2.25 mL, 4.49 mmol, 2.0 equiv.), followed by chromatography with ethyl acetate/hexane (3:97), a white solid was obtained (314.8 mg, 39%). Recrystallisation from dichloromethane/hexane gave colourless rec-

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tangular crystals, m.p. 134−135 °C. $[\alpha]_D^{20}$ = −35.78 (*c* = 0.83, $CHCl_3$) ppm. ^{19}F NMR: δ = −118 ppm. ^1H NMR: δ = 0.48 (d, *J* = 7.7 Hz, 3 H, 9-Me), 0.99 (d, *J* = 5.8 Hz, 3 H, 6-Me), 1.17−1.49 (m, 8 H), 1.64−1.78 (m, 2 H), 1.82−1.90 (m, 1 H), 1.97−2.10 (m, 2 H), 2.28−2.39 (m, 1 H), 2.65−2.77 (m, 1 H), 5.55 (s, 1 H, H-12), 5.70 (d, *J* = 6.7 Hz, 1 H, 10-H), 6.97−7.04 (m, 2 H, 2 × Ph-H), 7.24−7.29 (m, 2 H, 2 × Ph-H) ppm. ^{13}C NMR: δ = 14.3, 20.5, 25.4, 25.6, 26.35, 32.8, 34.8, 37.3, 38.1, 44.05, 52.1, 73.15, 81.75, 91.55, 102.9, 115.2 (d, $J_{C,F}$ = 21.3 Hz, Ph), 128.3 (d, $J_{C,F}$ = 7.8 Hz, Ph), 137.4 (d, $J_{C,F}$ = 3.09 Hz, Ph), 162.1 (d, $J_{C,F}$ = 244.0 Hz, Ph) ppm. IR (film): $\tilde{\nu}_{max}$ = 782, 838, 882, 906, 944, 1010, 1040, 1110, 1222, 1376, 1452, 1510, 1604, 2873, 2952 cm^{-1}. MS (CI, NH_3): *m/z* (%) = 382 (4) [MNH^+, 2 × ^{13}C], 381 (25) [MNH_4^+, ^{13}C], 380 (100) [MNH_4^+], 363 (6) [MH^+]. $C_{21}H_{27}FO_4$ (362.45): calcd. C 69.59, H 7.51; found C 69.51, H 7.62.

10β-(4′-Chlorophenyl)-10-deoxo-10-dihydroartemisinin (41): According to the method above, from DHA 10α-TMS ether **38** (1.2 g, 3.37 mmol), trimethylsilyl bromide (0.44 mL, 3.37 mmol), and (4-chlorophenyl)magnesium bromide (1.0 M in ether, 5.1 mL, 5.1 mmol, 1.5 equiv.), followed by chromatography with ethyl acetate/hexane (3:97), a white solid was obtained (497 mg, 39%). Recrystallisation from dichloromethane/hexane gave colourless rectangular crystals, m.p. 159−160 °C. $[\alpha]_D^{22}$ = +10.82 (*c* = 0.098, $CHCl_3$). ^1H NMR: δ = 0.49 (d, *J* = 7.7 Hz, 3 H, 9-Me), 0.99 (d, *J* = 5.6 Hz, 3 H, 6-Me), 1.17−1.49 (m, 8 H), 1.65−1.78 (m, 2 H), 1.81−1.90 (m, 1 H), 1.99−2.09 (m, 2 H), 2.28−2.39 (m, 1 H), 2.65−2.78 (m, 1 H), 5.55 (s, 1 H, H-12), 5.69 (d, *J* = 6.7 Hz, 1 H, 10-H), 7.23−7.30 (m, 4 H, 4 × Ph-H) ppm. ^{13}C NMR: δ = 14.4, 20.6, 25.5, 25.7, 26.5, 32.8, 34.9, 37.4, 38.3, 44.2, 52.2, 73.3, 81.9, 91.6, 103.1, 128.3, 128.7, 132.75, 140.4 ppm. IR (Nujol): $\tilde{\nu}_{max}$ = 782, 840, 902, 942, 1008, 1114, 1374, 1456, 1494, 2924 cm^{-1}. MS (CI, NH_3): *m/z* (%) = 399 (8) [MNH_4^+, ^{13}C, ^{37}Cl], 398 (36) (MNH_4^+, ^{37}Cl], 397 (25) [MNH_4^+, ^{13}C], 396 (100) [MNH_4^+]. $C_{21}H_{27}ClO_4$ (378.90): calcd. C 66.57, H 7.18; found C 66.42, H 7.05.

10β-(4′-Bromophenyl)-10-deoxo-10-dihydroartemisinin (42): According to the method above, from DHA 10α-TMS ether **38** (100 mg, 0.28 mmol), trimethylsilyl bromide (37 μL, 0.28 mmol), and (4-bromophenyl)magnesium bromide (1.0 M in ether, 0.56 mL, 0.56 mmol, 2 equiv.). followed by chromatography with ethyl acetate/hexane (2:98 to 3:97), a white solid was obtained (75 mg, 64%). Recrystallisation from dichloromethane/hexane gave colourless rectangular crystals, m.p. 156−159 °C. $[\alpha]_D^{25}$ = −45.14 (*c* = 0.0216, $CHCl_3$). ^1H NMR: δ = 0.48 (d, *J* = 7.8 Hz, 3 H, 6-Me), 0.98 (d, *J* = 5.7 Hz, 3 H, 9-Me), 1.40 (s, 3 H, 3-Me), 1.19−2.10 (m, 10 H), 2.33 (m, 1 H), 2.72 (m, 1 H, 9-H), 5.55 (s, 1 H, H-12), 5.70 (d, *J* = 6.6 Hz, 1 H, 10-H), 7.19 (d, *J* = 8.4 Hz, 2 H, 2 × Ph-H), 7.43 (d, *J* = 8.4 Hz, 2 H, 2 × Ph-H) ppm. IR (Nujol): $\tilde{\nu}_{max}$ = 780, 840, 882, 902, 942, 1008, 1112, 1374, 1454, 1492, 2924 cm^{-1}. MS (CI, CH_4): *m/z* (%) = 453 (18) [$M(Br^{81}) + 2CH_4]^+$, 451 (20) [$M(Br^{79}) + 2CH_4]^+$, 425 (51) [$M(Br^{81}) + 1]^+$, 423 (53) [$M(Br^{79}) + 1]^+$, 407 (40), 405 (32), 392 (35), 390 (48), 379 (100), 377 (88), 335 (20), 333 (28), 267 (32), 221 (41), 209 (78), 191 (78), 191 (26), 163 (59).

10β-(4′-Vinylphenyl)-10-deoxo-10-dihydroartemisinin (43): According to the method above, from DHA 10α-TMS ether **38** (356 mg, 1.0 mmol), trimethylsilyl bromide (0.2 mL, 1.5 mmol), and (4-vinylphenyl)magnesium bromide (0.5 M in ether, 4.0 mL, 2.0 mmol, 2 equiv.), followed by chromatography with ethyl acetate/hexane (5:95), a white solid was obtained (251 mg, 68%), m.p. 109−110 °C. $[\alpha]_D^{22}$ = −64.6 (*c* = 0.028, $CHCl_3$). ^1H NMR: δ = 0.54 (d, *J* = 7.7 Hz, 3 H, 9-Me), 0.98 (d, *J* = 5.7 Hz, 3 H, 6-Me), 7.37 (d, *J* = 8.3 Hz, 2 H, 2 × Ph-H), 0.83−0.99 (m, 1 H), 1.38 (s, 3 H, 3-Me), 1.17−2.09 (m, 9 H), 2.28−2.38 (m, 1 H), 2.71−2.78 (m, 1 H), 5.20 (d, *J* = 10.9 Hz, 1 H, vinyl-H), 5.57 (s, 1 H, H-12), 5.69−5.76 (m, 2 H, vinyl−H, 10-H), 6.71 (dd, *J* = 17.6, 10.9 Hz, 1 H, vinyl-H), 7.27 (d, *J* = 8.3 Hz, 2 H, 2 × Ph-H) ppm. IR (film): $\tilde{\nu}_{max}$ = 756, 788, 844, 882, 904, 944, 1010, 1074, 1116, 1200, 1376, 1406, 1452, 1512, 1630, 2876, 2948 cm^{-1} ppm. ^{13}C NMR: δ = 13.75, 19.97, 24.80, 24.98, 25.80, 32.19, 34.26, 36.73, 37.58, 43.58, 51.58, 73.07, 81.24, 90.89, 102.40, 113.09, 125.72, 126.36, 135.74, 136.75, 140.91 ppm. MS (CI, NH_3): *m/z* (%) = 388 (100) MNH_4^+], 325 (20). $C_{23}H_{30}O_4$ (370.49): calcd. C 74.56, H 8.16; found C 74.58, H 8.26.

10β-(2′-Methoxyphenyl)-10-deoxo-10-dihydroartemisinin (44): According to the method above, from DHA 10α-TMS ether **38** (214 mg, 0.68 mmol), trimethylsilyl bromide (90 μL, 0.68 mmol), and (2-methoxyphenyl)magnesium bromide (1.0 M in ether, 1.2 mL, 1.2 mmol, 2 equiv.), followed by chromatography with ethyl acetate/hexane (8:92), a white solid was obtained (133 mg, 59%), m.p. 59−61 °C. $[\alpha]_D^{20}$ = −41.4 (*c* = 0.049, $CHCl_3$). ^1H NMR: δ = 0.43 (d, *J* = 7.6 Hz, 1 H, 9-Me), 1.01 (d, *J* = 5.8 Hz, 3 H, 6-Me), 1.39 (s, 3 H, 3-Me), 1.19−2.11 (m, 10 H), 2.30−2.40 (m, 1 H), 2.86−2.99 (m, 1 H, 9-H), 3.84 (s, 3 H, OMe), 5.58 (s, 1 H, H-12), 5.94 (d, *J* = 6.7 Hz, 1 H, 10-H), 6.83−7.50 (m, 4 H, 4 × Ph-H) ppm. ^{13}C NMR: δ = 13.45, 19.8, 24.75, 25.0, 25.7, 29.9, 34.2, 36.7, 37.5, 43.4, 51.3, 55.2, 68.6, 90.9, 109.2, 120.0, 126.4, 127.0, 134.85 ppm. IR (film): $\tilde{\nu}_{max}$ = 754, 854, 882, 944, 1010, 1052, 1102, 1110, 1178, 1240, 1284, 1374, 1462, 1492, 1590, 2874, 2938 cm^{-1}. MS (CI, CH_4): *m/z* (%) = 375 (12) [MH^+], 374(16) [M^+], 342 (100), 329 (48), 311 (14), 284 (28), 182 (56), 148 (76), 137 (60), 121 (48). $C_{22}H_{30}O_5$ (374.48): calcd. C 70.56, H 8.07; found C 70.78, H 8.28.

10β-(2′,4′-Dimethoxyphenyl)-10-deoxo-10-dihydroartemisinin (45): According to the method above, from DHA 10α-TMS ether **38** (100 mg, 0.28 mmol), trimethylsilyl bromide (37 μL, 0.28 mmol), and (2,4-dimethoxyphenyl)magnesium bromide (1.0 M in ether, 0.56 mL, 0.56 mmol, 2 equiv.), followed by chromatography with ethyl acetate/hexane (20:80 to 40:60), a white solid was obtained (64 mg, 58%), m.p. 62−63 °C. $[\alpha]_D^{25}$ = −64.21 (*c* = 0.0114, $CHCl_3$). ^1H NMR: δ = 0.40 (d, *J* = 7.5 Hz, 3 H, 5-Me), 1.00 (d, *J* = 5.7 Hz, 3 H, 6-Me), 1.20−2.10 (m, 13 H), 2.32 (m, 1 H), 2.84 (m, 1 H, 9-H), 3.79, 3.80 (2 × s, 6 H, 2 × OMe), 5.54 (s, 1 H, H-12), 5.84 (d, *J* = 6.6 Hz, 1 H, 10-H), 6.42 (d, *J* = 2.4 Hz, 1 H, Ph-H), 6.47 (dd, *J* = 8.4, 2.4 Hz, 1 H, Ph-H), 7.33 (d, *J* = 8.4 Hz, 1 H, Ph-H) ppm. IR (Nujol): $\tilde{\nu}_{max}$ = 726, 780, 832, 880, 946, 1010, 1040, 1120, 1156, 1208, 1286, 1258, 1376, 1464, 1506, 1590, 1614, 2920 cm^{-1}. MS (CI, CH_4): *m/z* (%) = 405 (15) [MH^+], 359 (100) [$M - 3CH_3]^+$, 317 (6), 275 (28), 221(8), 154 (22). $C_{23}H_{32}O_6$ (404.51): calcd. C 68.29, H 7.97; found C 68.55, H 8.14.

10β-(2′,4′,6′-Trimethoxyphenyl)-10-deoxo-10-dihydroartemisinin (46): According to the method above, from DHA 10α-TMS ether **38** (356 mg, 1.0 mmol), trimethylsilyl bromide (0.2 mL,1.5 mmol), and (2,4,6-trimethoxyphenyl)magnesium bromide (0.25 M in ether, 1.7 mL, 0.42 mmol, 1.5 equiv.), followed by chromatography with ethyl acetate/hexane (25:75), a white solid was obtained (202 mg, 46%), m.p. 58−60 °C. $[\alpha]_D^{22}$ = +10.6 (*c* = 0.016, $CHCl_3$). ^1H NMR: δ = 0.72 (d, *J* = 7.7 Hz, 3 H, 9-Me), 1.00 (d, *J* = 5.7 Hz, 3 H, 6-Me), 0.84−1.11 (m, 1 H), 1.40 (s, 3 H, 3-Me), 1.20−1.57 (m, 3 H), 1.68−1.84 (m, 4 H), 1.97−2.08 (m, 2 H), 2.29−2.38 (m, 1 H), 2.64−2.72 (m, 1 H), 3.78 (s, 6 H, 2 × OMe), 3.81 (s, 3 H, OMe), 5.52 (s, 1 H, H-12), 6.13 (s, 1 H, Ph-H), 6.16 (d, *J* = 8.1 Hz, 1 H, 10-H) ppm. IR (film): $\tilde{\nu}_{max}$ = 954, 1006, 1126, 1154, 1204, 1456, 1608, 2938 cm^{-1}. MS (CI, CH_4): *m/z* (%) = 435 (10) [MH^{+1}], 417 (8), 389 (100), 371 (6), 347 (10), 329 (16), 221 (8): $C_{24}H_{34}O_7$ (422.52): calcd. C 66.34, H 7.89; found C 66.57, H 8.04.

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10β-(2′,4′,6′-Trimethylphenyl)-10-deoxo-10-dihydroartemisinin (47): According to the method above, from DHA 10α-TMS ether **38** (356 mg, 1.0 mmol), trimethylsilyl bromide (0.2 mL, 1.5 mmol), and (2,4,6-trimethylphenyl)magnesium bromide (0.5 M in ether, 0.85 mL, 0.42 mmol, 1.5 equiv.), followed by chromatography with ethyl acetate/hexane (5:95), a colourless oil was obtained (213 mg, 55%), which was recrystalllized from ethyl acetate to give the product as a fine microcrystalline powder, m.p. 64−66 °C. $[\alpha]_D^{22} = +13.7$ ($c = 0.019$, $CHCl_3$). ^1H NMR: δ = 0.64 (d, $J = 7.8$ Hz, 3 H, 9-Me), 1.03 (d, $J = 5.9$ Hz, 3 H, 6-Me), 0.84−1.04 (m, 1 H), 1.29−1.50 (m, 6 H), 1.64−1.90 (m, 4 H), 2.05−2.11 (m, 2 H), 2.27 (s, 3 H, Me), 2.32 (s, 3 H, Me), 2.26−2.40 (m, 1 H), 2.48 (s, 3 H, Me), 2.74−2.85 (m, 1 H), 5.55 (s, 1 H, H-12), 6.05 (d, $J = 7.6$ Hz, 1 H, 10-H), 6.81 (s, 2 H, 2 × Ph-H) ppm. ^{13}C NMR: δ = 13.2, 19.9, 20.6, 20.7, 22.3, 24.5, 25.0, 25.7, 30.4, 34.2, 36.8, 37.6, 43.9, 51.3, 71.82, 80.9, 90.7, 102.3, 128.4, 130.8, 133.5, 135.2, 135.6, 137.2 ppm. IR (Neat): $\tilde{\nu}_{max}$ = 724, 756, 780, 848, 880, 896, 942, 958, 1008, 1076, 1106, 1208, 1376, 1452, 2874, 2938 cm^{-1}. MS (CI, CH_4): *m*/*z* (%) = 387 (6) [MH^+], 386 (8), 385 (10), 341 (100), 327 (8), 299 (8), 267 (14), 221 (10), 209 (4), 163 (8), 133 (8): $C_{24}H_{34}O_4$ (374.53): calcd. C 74.58, H 8.87; found C 74.48, H 8.98.

10β-(2′,4′,5′-Trimethylphenyl)-10-deoxo-10-dihydroartemisinin (48): According to the method above, from DHA 10α-TMS ether **38** (356 mg, 1.0 mmol), trimethylsilyl bromide (135 μL, 1.0 mmol), and (2,4,5-trimethylphenyl)magnesium bromide (0.25 M in ether, 4.4 mL, 1.10 mmol, 1.1 equiv.), followed by chromatography with ethyl acetate/hexane (5:95), a colourless oil was obtained (212 mg, 55%), which was recrystallized from ethyl acetate to give the product as a fine microcrystalline powder, m.p. 140−141 °C. $[\alpha]_D^{20} = -55.6$ ($c = 0.068$, $CHCl_3$). ^1H NMR: δ = 0.55 (d, $J = 7.7$ Hz, 3 H, 9-Me), 1.11 (d, $J = 5.8$ Hz, 3 H, 6-Me), 0.97−1.11 (m, 1 H), 1.40−1.55 (m, 7 H), 1.78−2.00 (m, 3 H), 2.10−2.19 (m, 2 H), 2.31 (s, 3 H, Me), 2.33 (s, 6 H, 2 × Me), 2.38−2.48 (m, 1 H), 2.80−2.90 (m, 1 H), 5.67 (s, 1 H, H-12), 5.94 (d, $J = 6.7$ Hz, 1 H, 10-H), 6.99 (s, 1 H, Ph), 7.32 (s, 1 H, Ph) ppm. ^{13}C NMR: δ = 13.65, 18.7, 19.2, 19.9, 24.8, 25.0, 25.6, 29.9, 34.2, 36.8, 37.6, 43.5, 51.3, 70.0, 81.1, 91.0, 102.1, 127.1, 130.8, 131.0, 134.0, 136.6, 133.1 ppm. IR (Neat): $\tilde{\nu}_{max}$ = 754, 820, 880, 896, 934, 954, 978, 1040, 1000, 1056, 1100, 1120, 1180, 1202, 1220, 1374, 1278, 1452, 1502, 2874, 2922 cm^{-1}. MS (CI, CH_4): *m*/*z* (%) = 387 (10) [MH^+], 386 (44) [M^+, 44], 354 (60), 341 (84), 296 (6), 282 (18), 109 (20), 182 (28), 160 (100), 149 (56), 133 (38), 121 (30). $C_{24}H_{34}O_4$ (374.53): calcd. C 74.58, H 8.87; found C 74.63, H 8.73.

10β-(2′-Naphthyl)-10-deoxo-10-dihydroartemisinin (49): According to the method above, from DHA 10α-TMS ether **38** (1.2 g, 3.37 mmol), trimethylsilyl bromide (0.47 mL, 3.54 mmol), and (2-naphthyl)magnesium bromide (0.48 M in THF, 14.0 mL, 6.75 mmol, 2.0 equiv.), followed by chromatography with ethyl acetate/hexane (5:95), an inseparable mixture of **49** and glycal **19** (1.01 g) was obtained. Potassium carbonate (0.53 g, 3.58 mmol) and *m*-chloroperbenzoic acid (0.88 g, 5.13 mmol) were added to a cold (0 °C) stirred solution of this mixture in dichloromethane (10 mL). After 21 h, the mixture was filtered and the filtrate was removed to give a residue that was submitted to chromatography with ethyl acetate/hexane (5:95) to afford the product **49** as a white powder (565 mg, 43%), m.p. 145−146 °C. $[\alpha]_D^{20} = -67.8$ ($c = 0.027$, $CHCl_3$). ^1H NMR: δ = 0.55 (d, $J = 7.7$ Hz, 1 H, 9-Me), 1.02 (d, $J = 6.1$ Hz, 1 H, 6-Me), 1.42 (s, 3 H, 3-Me), 0.86−2.13 (m, 10 H), 2.33−2.48 (m, 1 H), 2.81−2.94 (m, 1 H, 9-H), 5.67 (s, 1 H, H-12), 5.93 (d, $J = 6.6$ Hz, 1 H, 10-H), 7.42−7.51 (m, 3 H, 3 × Ar-H), 7.80−7.85 (m, 4 H, 4 × Ar-H) ppm. ^{13}C NMR: δ = 13.65, 19.85, 24.8, 24.9, 25.7, 32.1, 34.15, 36.6, 37.5, 43.4, 51.5, 73.0, 90.9, 124.3, 124.8, 125.2, 125.65, 127.1, 127.4, 127.8, 134.85 ppm. IR (film): $\tilde{\nu}_{max}$ = 750, 786, 824, 854, 886, 936, 954, 1010, 1040, 1074, 1106, 1208, 1376, 1452, 1510, 2874, 2950 cm^{-1}. MS (CI, CH_4): *m*/*z* (%) = 395 (16) [MH^+], 394 (32) [M^+, 32], 362 (44), 349 (84), 331 (16), 304 (20), 291 (26), 182 (100), 168 (60). $C_{25}H_{30}O_4$ (370.49): calcd. C 76.11, H 7.66; found C 76.24, H 7.69.

10β- and 10α-[2′-(6′-Methoxynaphthyl)]-10-deoxo-10-dihydroartemisinin (50 and 51): According to the method above, from DHA 10α-TMS ether **38** (200 mg, 0.56 mmol), trimethylsilyl bromide (74 μL, 0.56 mmol), and 6-methoxy-2-(naphthyl)magnesium bromide (0.7 M in THF, 1.6 mL, 1.12 mmol, 2.0 equiv.), followed by chromatography with ethyl acetate/hexane (10:90). The less-polar 10β-isomer **50** was obtained as a white powder (41 mg, 17%), m.p. 165−167 °C. $[\alpha]_D^{20} = -49$ ($c = 0.115$, DMF). ^1H NMR: δ = 0.52 (d, $J = 7.7$ Hz, 3 H, 9-Me), 0.88−0.94 (m, 1 H), 0.99 (d, $J = 5.6$, 3 H, 6-Me), 1.23−1.51 (m, 7 H), 1.58−2.09 (m, 5 H), 2.30−2.40 (m, 1 H), 2.78−2.86 (m, 1 H), 3.91 (s, 3 H, OMe), 5.54 (s, 1 H, H-12), 5.86 (d, $J = 3.7$ Hz, 1 H, 10-H), 7.11−7.14 (m, 2 H, 2 × Ar-H), 7.39−7.35 (m, 1 H, Ar), 7.67−7.74 (m, 3 H, 3 × Ar-H) ppm. ^{13}C NMR: δ = 14.5, 20.7, 25.6, 25.7, 26.5, 33.0, 35.0, 37.45, 38.3, 44.3, 52.3, 55.9, 73.9, 82.0, 91.7, 103.1, 106.3, 119.2, 125.0, 126.2, 126.8, 129.4, 130.1, 134.1, 137.1, 158.0 ppm. MS (CI, CH_4): *m*/*z* (%) = 426 (2) [MH^+, ^{13}C], 425 (8) [MH^+], 424 (7) [M^+]. $C_{26}H_{32}O_5$ (424.54): calcd. C 73.56, H 7.60; found C 73.35, H 7.70. The more-polar component was the 10α-isomer **51**, also obtained as a white powder (32 mg, 14%), m.p. 146−148 °C. $[\alpha]_D^{22} = +129$ ($c = 0.08$, DMF). ^1H NMR: δ = 0.55 (d, $J = 7.2$ Hz, 3 H, 9-Me), 0.99 (d, $J = 6.2$ Hz, 3 H, 6-Me), 1.05−1.13 (m, 1 H), 1.46 (s, 3 H, 3-Me), 1.53−1.68 (m, 4 H), 1.74−1.81 (m, 1 H), 1.87−1.96 (m, 1 H), 2.02−2.10 (m, 1 H), 2.43−2.49 (m, 1 H), 2.65−2.72 (m, 1 H), 3.91 (s, 3 H, OMe), 4.50 (d, $J = 10.7$ Hz, 1 H, 10-H), 7.10−7.13 (m, 2 H, 2 × Ar-H), 7.55−7.59 (m, 2 H, Ar-H), 7.70−7.73 (m, 3 H, 3 × Ar-H) ppm. ^{13}C NMR: δ = 14.8, 21.0, 22.2, 25.5, 26.75, 34.55, 34.9, 37.05, 38.1, 46.8, 52.7, 55.9, 79.15, 81.4, 92.8, 104.9, 106.3, 119.2, 126.5, 127.0, 127.65, 129.3, 130.1, 135.1, 136.7, 158.2 ppm. MS (EI): *m*/*z* (%) = 424 (4) [MH^+]. $C_{26}H_{32}O_5$ (424.54): calcd. C 73.56, H 7.60; found C 73.41, H 7.61.

10β-(9′-Phenanthryl)-10-deoxo-10-dihydroartemisinin (52): According to the method above, from DHA 10α-TMS ether **38** (0.3 g, 0.84 mmol), trimethylsilyl bromide (0.12 mL, 0.88 mmol), and 9-(phenanthryl)magnesium bromide (0.6 M in THF, 4.22 mL, 2.53 mmol, 1.1 equiv.), followed by chromatography with ethyl acetate/hexane (7:93), a white solid was obtained (140 mg, 37%), m.p. 89−91 °C. $[\alpha]_D^{20} = -68.8$ ($c = 0.016$, $CHCl_3$). ^1H NMR: δ = 0.39 (d, $J = 7.6$ Hz, 3 H, 9-Me), 1.06 (d, $J = 5.7$ Hz, 3 H, 6-Me), 1.41 (s, 3 H, 3-Me), 0.86−1.60 (m, 5 H), 1.73−1.84 (m, 2 H), 2.00−2.16 (s, 3 H), 2.37−2.48 (m, 1 H), 3.06−3.19 (m, 1 H), 5.75 (s, 1 H, H-12), 6.50 (d, $J = 6.5$ Hz, 1 H, 10-H), 7.57−7.72 (m, 4 H, 4 × Ph-H), 7.91−8.10 (m, 3 H, 3 × Ph-H), 8.68−8.81 (m, 2 H, 2 × Ph-H) ppm. ^{13}C NMR: δ = 13.2, 20.0, 24.95, 25.1, 25.8, 31.55, 34.3, 36.9, 37.7, 43.8, 51.45, 69.9, 81.4, 91.3, 102.5, 122.3, 123.2, 123.7, 123.8, 126.0, 126.0, 126.5, 126.7, 128.8, 129.6, 130.0, 130.1, 131.7, 135.2 ppm. IR (film): $\tilde{\nu}_{max}$ = 726, 748, 794, 832, 886, 906, 930, 956, 1010, 1040, 1110, 1220, 1246, 1376, 1450, 1498, 2362, 2874, 2922 cm^{-1}. MS (CI, CH_4): *m*/*z* (%) = 445 (22) [MH^+], 444 (100), 398 (40), 384 (16), 352 (16), 328 (44), 267 (6), 218 (84), 203 (48), 178 (60), 163 (44), 138 (70), 107 (62). $C_{29}H_{32}O_4$ (443.57): calcd. C 78.35, H 7.26; found C 78.56, H 7.54.

10β-[4′-(1′′-Morpholino)phenyl]-10-deoxo-10-dihydroartemisinin (53): According to the method above, from DHA 10α-TMS ether **38** (800 mg, 2.25 mmol), trimethylsilyl bromide (0.31 mL, 2.36 mmol), and 4-(morpholino)phenylmagnesium bromide (0.46 M

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in THF, 7.3 mL, 3.37 mmol, 1.5 equiv.), followed by chromatography with ethyl acetate/hexane (20:80), a white solid was obtained (495 mg, 51%), m.p. 121−122 °C. $[\alpha]_D^{22}$ = −39.14 (*c* = 0.51, $CHCl_3$). ^1H NMR: δ = 0.55 (d, *J* = 7.7 Hz, 3 H, 9-Me), 0.88−0.97 (m, 1 H), 0.98 (d, *J* = 5.6 Hz, 3 H, 6-Me), 1.16−1.35 (m, 3 H), 1.38 (s, 3 H, 3-Me), 1.42−1.49 (m, 1 H), 1.56−1.87 (m, 3 H), 1.98−2.08 (m, 2 H), 2.28−2.39 (m, 1 H), 2.66−2.78 (m, 1 H), 3.14 (m, 4 H, 2 × morpholino CH_2), 3.86 (m, 4 H, 2 × morpholino CH_2), 5.56 (s, 1 H, H-12), 5.64 (d, *J* = 6.6 Hz, 1 H, 10-H), 6.87 (d, *J* = 8.7 Hz, 2 H, 2 × Ph-H), 7.22 (d, *J* = 8.7 Hz, 2 H, 2 × Ph-H) ppm. ^{13}C NMR: δ = 13.9, 20.0, 24.8, 25.0, 25.8, 32.35, 34.3, 36.7, 37.56, 43.65, 49.6, 51.6, 66.9, 73.0, 81.2, 90.8, 102.4, 115.2, 127.0, 132.9, 149.8 ppm. MS (CI, CH_4): *m*/*z* (%) = 432 (3) [MH^+, 2 × ^{13}C], 431 (13) [MH^+, ^{13}C], 430 (45) [MH^+], 429 (17) [M^+]. $C_{25}H_{35}NO_5$ (429.56): calcd. C 69.90, H 3.26; found C 69.90, H 3.22.

10β-(4′-*N*,*N*-Dimethylaminophenyl)-10-deoxo-10-dihydroartemisinin (54): According to the method above, from DHA 10α-TMS ether **38** (1.5 g, 4.21 mmol), trimethylsilyl bromide (0.58 mL, 4.42 mmol), and [4-(dimethylamino)phenyl]magnesium bromide (0.4 M in THF, 21 mL, 8.43 mmol, 2 equiv.), followed by chromatography with ethyl acetate/hexane (8:92), a white solid was obtained (551 mg, 34%), m.p. 154−155 °C. $[\alpha]_D^{22}$ = −54.49 (*c* = 0.69, $CHCl_3$). ^1H NMR: δ = 0.73 (d, *J* = 7.8 Hz, 3 H, 9-Me), 1.06 (m, 1 H), 1.12 (d, *J* = 6.1 Hz, 3 H, 6-Me), 1.41−1.49 (m, 2 H), 1.53 (s, 3 H, 3-Me), 1.56−1.58 (m, 1 H), 1.78−1.99 (m, 4 H), 2.12−2.23 (m, 2 H), 2.44−2.52 (m, 1 H), 2.84−2.90 (m, 1 H), 3.07 (s, 6 H, NMe_2), 5.71 (s, 1 H, H-12), 5.76 (d, *J* = 6.6 Hz, 1 H, 10-H), 6.86 (d, *J* = 8.8 Hz, 2 H, 2 × Ph-H), 7.33 (d, *J* = 9.1 Hz, 2 H, 2 × Ph-H) ppm. ^{13}C NMR: δ = 14.1, 20.1, 24.85, 25.1, 25.9, 32.55, 34.4, 36.8, 37.6, 40.9, 43.8, 51.7, 73.2, 81.2, 90.8, 102.3, 112.2, 126.9, 129.3, 149.2 ppm. MS (EI): *m*/*z* (%) = 389 (2) [MH^+, ^{13}C], 388 (9) [MH^+], 387 (64) [M^+], 343 (3) [$M - NMe_2]^+$. $C_{23}H_{33}NO_4$ (387.52): calcd. C 71.29, H 8.58, N 3.61; found C 70.85, H 8.60, N 3.69.

4′-(10β-Dihydroartemisinyl)benzoic acid (56): A suspension of compound 43 (209 mg, 0.565 mmol), $KMnO_4$ (268 mg, 1.70 mmol) and $NaHCO_3$ (24 mg, 0.283 mmol) in acetone (20 mL) was stirred at room temperature. After 5 h, the precipitate was removed by filtration through a pad of Celite. The residue was washed with acetone, water was added, and the filtrate was concentrated. The residue was then extracted with ethyl acetate (3 × 15 mL) and the combined organic extracts were dried ($MgSO_4$). Filtration and evaporation of filtrate gave a residue, which after chromatography with ethyl acetate/hexane (40:60 to 60:40) gave a white solid (173 mg, 79%), m.p. 177−178 °C. $[\alpha]_D^{22}$ = −63.2 (*c* = 0.019, $CHCl_3$). ^1H NMR: δ = 0.51 (d, *J* = 7.6 Hz, 3 H, 9-Me), 1.01 (d, *J* = 5.5 Hz, 3 H, 6-Me), 0.87−1.02 (m, 1 H), 1.41 (s, 3 H, 3-Me), 1.23−2.10 (m, 9 H), 2.31−2.40 (m, 1 H), 2.76−2.83 (m, 1 H), 5.60 (s, 1 H, H-12), 5.82 (d, *J* = 6.6 Hz, 1 H, 10-H), 7.45 (d, *J* = 8.3, 2 H, 2 × Ph-H), 8.09 (d, *J* = 8.3 Hz, 2 H, 2 × Ph-H) ppm. ^{13}C NMR: δ = 13.4, 19.8, 24.7, 25.6, 29.05, 31.9, 34.0, 36.5, 37.4, 43.3, 51.35, 72.7, 81.1, 90.8, 102.3, 126.15, 127.3, 129.7, 147.4, 171.7 ppm. IR (film): $\tilde{\nu}_{max}$ = 732, 766, 802, 824, 854, 882, 908, 944, 954, 968, 980, 1012, 1040, 1056, 1074, 1116, 1178, 1208, 1222, 1286, 1314, 1376, 1424, 1452, 1512, 1578, 1612, 1688, 2252, 2546, 2670, 2878, 2954 cm^{-1}. MS (CI, CH_4): *m*/*z* (%) = 389 (8) [MH^+], 329 (100), 283 (36), 267 (20), 219 (26), 177 (80), 129 (64). $C_{22}H_{28}O_6$ (388.46): calcd. C 68.02, H 7.27; found C 67.77, H 7.31.

X-ray Crystallographic Study: Single-crystal X-ray structure determinations were carried out on five of the new compounds (**33**, **40**, **52**, **53** and **54**). These compounds were recrystallized from CH_2Cl_2/hexane by layer diffusion and, in general, afforded large colourless single crystals. Specimens were mounted on glass fibres and glued with epoxy cement that had nearly set. This precaution was taken to prevent significant crystal decomposition resulting from the peroxide linkage present in the compounds. For compound **33**, X-ray intensity data were collected at 100 K with a Bruker SMART APEX CCD diffractometer. The other compounds were studied at room temperature with a Bruker P4-RA 4-circle diffractometer fitted with molybdenum rotating anode operating at 10 kW. A custom-built 1.2-mm collimator was used with this instrument to allow data collection of the large specimens up to 1 mm dimension. All compounds crystallized in the chiral space groups orthorhombic $P2_12_12_1$, tetragonal $P4_3$ or monoclinic $P2_1$. This observation is consistent with their derivation from the enantiomerically pure chiral natural product artemisinin. The absolute configuration of the five compounds studied here was not directly confirmed from these experiments, but has been unambiguously established by numerous previous structural studies within our group and by others.[61]

The crystal structures were successfully solved and refined using the SHELX suite of X-ray computer programs throughout. A summary of the crystal data and structure determination parameters for compounds **33**, **40** and **52** are given in Table 2. Key geometric features of the artemisinin moiety and the effect of 10-aryl substituents on the pyranose ring are given in Table 4 and 5.

CCDC-208727 and -175439 to -175442 for compounds **33**, **40**, **52**−**54** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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Note Added in Proof (April 19, 2003): Phenyl-, benzyl-, allyl-, vinyl- and *n*-butylzinc reagents are reported to react stereoselectively with either 10α- or 10β-(benzenesulfonyl)-10-deoxo-10-dihydroartemisinin to give exclusively or predominantly 10β-substituted-10-deoxo-10-dihydroartemisinins, for example compounds **10** and **11**; see: S. Lee, S. Oh, *Tetrahedron Lett.* **2002**, *43*, 2891−2894. These excellent results clearly indicate that organometallic nucleophiles are predisposed to attack from the *re* (β) face, regardless of the stereochemistry of the leaving group (cf. Scheme 2).

[1] A note about nomenclature: DHA **2** has a chair-like pyranose ring. The "α"-epimer has an equatorial hydroxy group, the "β"-epimer an axial hydroxy group (see also ref.[19]). Artemether **3** (axial methoxyl) is sometimes referred to as β-artemether, to distinguish this compound from the "α"-epimer with an equatorial methoxyl group, in the malaria literature. This "convention," however, which has grown from the "normal" manner of representing structures of artemisinin and its derivatives in the voluminous literature of artemisinin derivatives (see refs. [2−7]), is the reverse of that normally used for designating the stereochemistry of sugars and their glycosides, in which, for example, α-D-glucopyranose possesses an axial hydroxy group. This inconsistency is unfortunate, but for convenience, here we continue to use the artemisinin stereochemical "convention."

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