PERKIN 1

Optimisation of the allylsilane approach to C-10 deoxo carba analogues of dihydroartemisinin: synthesis and *in vitro* antimalarial activity of new, metabolically stable C-10 analogues

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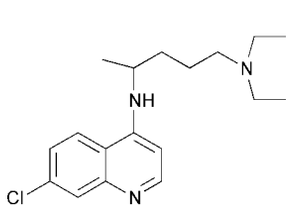
An optimised protocol has been developed for the coupling of dihydroartemisinin benzoate with a range of aromatic allylsilanes to provide a number of new C-10 deoxo derivatives (**11a**–**11g**) in yields ranging from 70 to 94%. These compounds were up to ten times more potent than artemisinin in *in vitro* tests against the chloroquine resistant K1 strain of *Plasmodium falciparum*. Ferrous mediated degradation of these analogues produces as the main product, a dicarbonyl formate **12**, which is not seen when the same reaction is carried out with artemisinin or artemether. This finding may indicate that analogues in this class have a subtly different "antimalarial" mechanism of action.

Introduction

Malaria has a devastating effect throughout the tropics. There are approximately 300 to 500 million clinical cases each year resulting in 1.5 to 2.7 million deaths. Nearly all fatal cases are caused by *Plasmodium falciparum*.[1] The problem is compounded by the spread of drug resistant strains of the parasite. As a result traditional alkaloid drugs such as chloroquine **1** and quinine are now largely ineffective.

In 1979 it was shown that artemisinin (Qinghaosu) **2**, a sesquiterpene 1,2,4-trioxane isolated from the Chinese medicinal herb qinghao (*Artemisia annua* L.), was an effective antimalarial against chloroquine-resistant strains of *Plasmodium falciparum*.[2] Artemisinin has been very impressive in preliminary pharmacological testing; however its poor solubility in both oil and water and hydrolytic instability of the lactone function has led scientists to prepare a series of semi-synthetic first generation analogues such as artemether (**3a**, R = $-CH_3$) and arteether (**3b**, R = $-CH_2CH_3$).[3] Both of these derivatives are readily prepared from dihydroartemisinin (DHA, **3c**), which in turn is produced by borohydride mediated reduction of the D-ring lactone of **2**.[4] Although **3a** and **3b** are potent antimalarials, poor bioavailability and rapid clearance are observed with these derivatives both in man and in animal models.[5] This phenomenon is associated with the inherent chemical and metabolic instability of the acetal functionality. One of the main routes of metabolism of artemether in the rat model involves P450 mediated hydroxylation of the C-10 methyl ether function to an unstable hemiacetal that hydrolyses to dihydroartemisinin.[6] This phase 1 metabolite then undergoes Phase II glucuronidation and is excreted as dihydroartemisinin β-glucuronide.[7]

The increased stability of non acetal-type analogues (*e.g.* **4**) of artemisinin has recently been reported. C-10-Deoxoartemisinins have been shown to be 15–22 times more stable than acetal-type analogues in simulated stomach acid.[8] Such favourable findings have led several groups to develop synthetic and semisynthetic approaches to C-10-deoxoartemisinin derivatives. Early syntheses tended to be lengthy, using artemisinic acid as starting material.[9] Pu and Ziffer[10] successfully used DHA with allyltrimethylsilane in the presence of boron trifluoride–diethyl ether to synthesise a wide range of these compounds and have more recently shown that dihydroartemisinin acetate can be employed as starting material using silyl enol ethers in the presence of titanium tetrachloride.[11] Posner and coworkers have reported a two-step conversion of DHA, *via* an intermediate 10-fluoro derivative, into a series of aromatic and heterocyclic deoxoartemisinin derivatives.[12–13] Wang *et al.*, *via* the acid-catalysed reaction of dihydroartemisinin acetate with 2-naphthol, produced two 10-(2-hydroxy-1-naphthyl)deoxoartemisinins.[14] Previously, we have reported on the synthesis of a range of potent C-10-deoxo carba ether and ester derivatives, some of which were more than fifteen times more potent than the parent drug artemisinin.[15] In this paper, we report on an optimised approach to C-10 carba analogues which is based on the Lewis acid catalysed reaction of a range of allylsilanes with an anomerically activated C-10 benzoate of dihydroartemisinin. We also report on the potent activity of these new derivatives, which, based on biomimetic Fe(II) chemistry, may be different from the parent drug artemisinin.[16]



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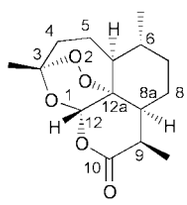

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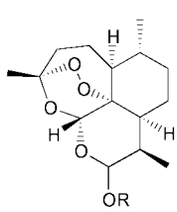
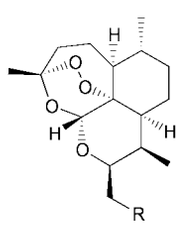


3a, R = Me, β-isomer
3b, R = Et, β-isomer
3c, R = H, mixture of α and β isomers



4, R = Alkyl, Aryl

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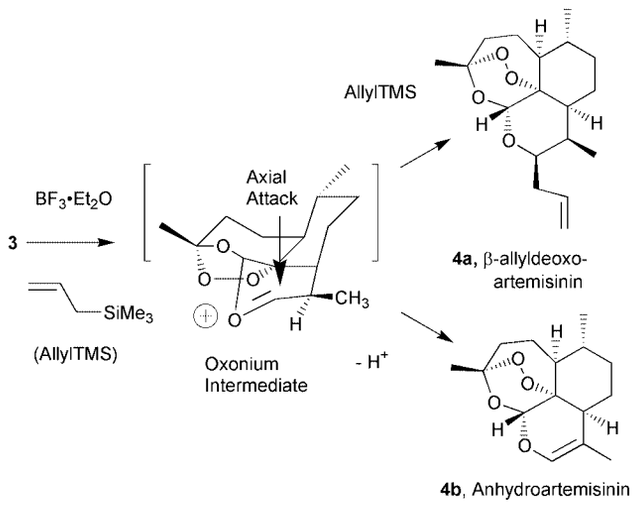
Results and discussion

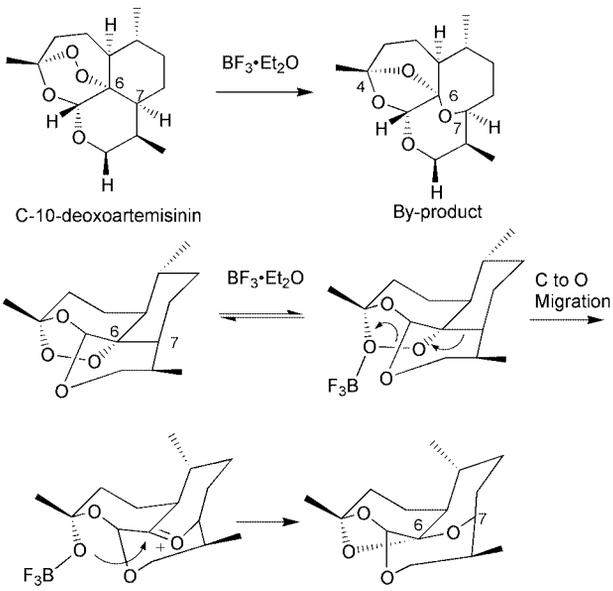
A key intermediate for the preparation of a range of carba analogues of artemisinin, including parasite targeted amine analogues,[17] water soluble sugar analogues,[18] fluorinated benzyl ethers[15] and antitumour dimers,[19] is C-10-allyldeoxoartemisinin **4a**. The original synthesis of **4a** involves Lewis acid mediated (BF_3·Et_2O) reaction of DHA with allyltrimethylsilane as carbon nucleophile. In this reaction, it is proposed that the product is derived by axial attack of allyltrimethylsilane on the intermediate oxonium ion. (Scheme 1).



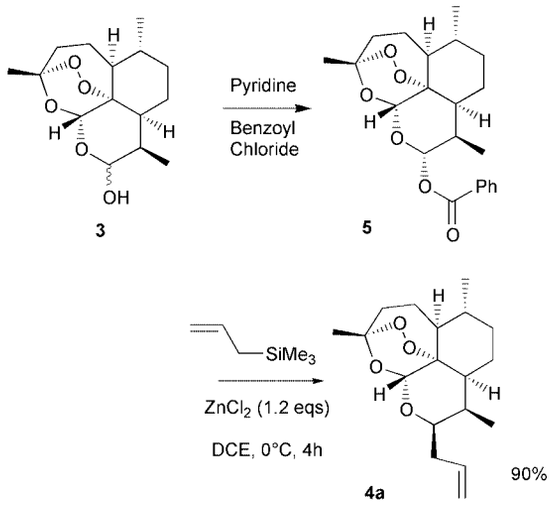
Scheme 1

The drawback in the procedure is the harsh nature of the Lewis acid, which results in the generation of substantial amounts of the dehydration product anhydroartemisinin **4b** (AHA). This makes purification of the desired material extremely difficult on a large scale since **4a** and **4b** have very similar R_fs on silica gel. We reasoned that a milder Lewis acid and a better anomeric leaving group would improve the yield of **4a**. In considering the choice of Lewis acid, we also noted that hard Lewis acids such as BF_3·Et_2O, have the capacity to rearrange target C-10 carba derivatives whereas weaker Lewis acids such as zinc chloride do not. Indeed, in several large-scale runs using BF_3·Et_2O as Lewis acid, several unwanted products were observed including the deoxygenated trioxane by-product shown in Scheme 2.[20] The mechanism for the formation of this product is believed to involve an acid-catalysed C–O migration. With these observations in mind, zinc chloride was chosen as a mild Lewis acid for the coupling reaction with C-10α-benzoate **5**.

The benzoate **5** was prepared in high yield by treatment of DHA with benzoyl chloride in pyridine. NMR studies on the white crystalline solid indicated (α) stereochemistry with respect to the C–O linkage at C-10 (C-10 H appears as a doublet with a J_{9-10} value of 9.9 Hz indicating a dihedral angle of about 180° between itself and C-9 H). After several runs using different temperatures and solvents, optimum conditions were found where the product could be obtained in high yields with only minor quantities of the by-product, **4b**. Thus, reaction of the benzoate with allyltrimethylsilane (5 equivalents) in the presence of $ZnCl_2$ catalyst (1.2 equivalents) at 0 °C for 4 h gave the desired product, **4a**, in 90% yield (Scheme 3). This result suggests that the leaving group and Lewis acid are perfectly tuned for effecting controlled oxonium generation and subsequent reaction with allylsilanes as nucleophiles. Given the dramatic improvement in yield, we reasoned that this approach should be readily applicable to other reactive allylsilanes bearing lipophilic, fluorinated aromatic rings, substituents previously shown to improve the biological activity of peroxide based antimalarials.[21–22] Two approaches were



Scheme 2

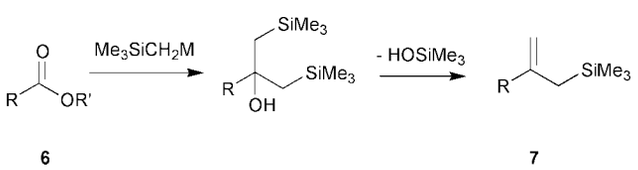


Scheme 3

considered for the preparation of requisite allylsilanes; (i) the cerium mediated conversion of esters to allylsilanes[23] and (ii) $Ni(acac)_2$ cross coupling of silylenol ethers with trimethylsilylmethylmagnesium chloride.[24]

Preparation of allylsilanes

Cerium mediated conversion of esters to allylsilanes.[23] Recent interest has focused on the use of carboxylic acid derivatives as functional precursors for allylsilanes.[23,25,26] The transformation includes twofold addition of a trimethylsilylmetal to the ester yielding the bis(β-silyl) alcohol, which on deoxysilylation leads to the allylsilane **7** (Scheme 4).



Scheme 4

The reaction has been successful, although low yielding, for esters of unbranched carboxylic acids using trimethylsilylmethylmagnesium chloride.[25] The reaction fails completely when using esters of α-branched carboxylic acids[25] where the α-silyl-ketone intermediate resists further addition of Grignard

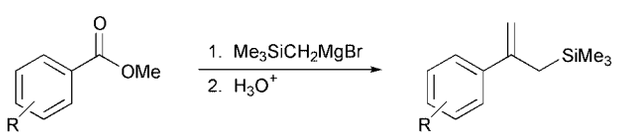
in favour of kinetic enolization. Imamoto, however, has shown that organocerium reagents are especially suited for additions to readily enolized carbonyl systems.[27] The reagent used in our reaction was therefore a preparation of $CeCl_3$ and trimethylsilylmethylmagnesium chloride. Unfortunately this procedure proved very unreliable and frequently, very poor yields of target allylsilanes were obtained (Table 1). The variation in yields prompted us to investigate other methods for synthesising the required allylsilanes.

Nickel-catalyzed cross-coupling of silyl enol ethers with Grignard reagents[24]

In this reaction a silyl enol ether is allowed to react with a Grignard reagent in the presence of nickel acetylacetonate, $Ni(acac)_2$, as catalyst. This gives the cross-coupled product in excellent yield. A range of silyl enol ethers were prepared from commercially available acetophenone derivatives and the resulting enol ethers converted into target allylsilanes. Yields for the synthesis of both silyl enol ethers and allylsilanes are recorded in Table 2.

The yields for the silyl enol ethers ranged from 60 to 80%, with NMR and accurate mass spectrometry establishing the purity of the compounds. In most cases, good yields were achieved for the synthesis of target allylsilanes with one notable exception. No reaction was observed on trying to convert **9c** to the desired allylsilane **10c**. A possible explanation is that the large *p*-trifluoromethyl group is hindering insertion of the catalytically active nickel species into the styryl function of **9c**.

Table 1

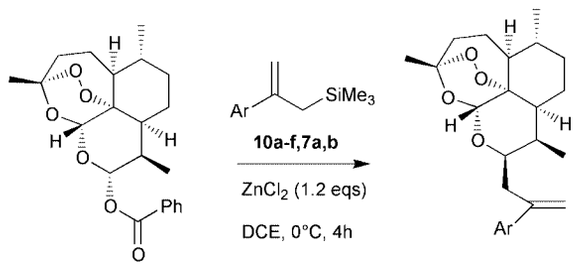


6a **7a**

Starting material	Product	Yield
6a (R = *p*-CF_3)	**7a** (R = *p*-CF_3)	20–67%
6b (R = *m*-F)	**7b** (R = *m*-F)	30–73%

Deoxoartemisinin derivatives

With a range of allylsilanes to hand, we then applied our optimized coupling conditions. C-10 benzoate **5** was allowed to react with a given allylsilane (**7a**, **7b** and **10a**, **b**, **d**, **e**) in the presence of zinc chloride at 0 °C for approximately 4 hours. After extraction into DCM and washing with 5% aqueous citric acid solution, column chromatography furnished the desired compounds as white foams in excellent yield and high purity. A generalised reaction is shown in Scheme 5 and the results are listed in Table 3.



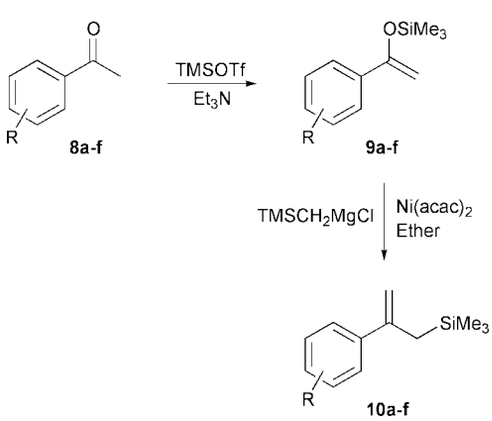
5 **11a-11g**, 70-94%

Scheme 5

The observed stereochemistry in analogues **11a**–**11g** is (β) at the C-10 carbon and this is in line with observations made by Ziffer[10] using a mechanism proposed by Kishi[28], where the nucleophile attacks **5** in an axial manner (Scheme 1). The high yields obtained for target carba analogues compares favourably with other approaches to this type of system. The presence of the C–C linkage should ensure that these compounds have greater metabolic stability than the first generation derivatives artemether and arteether.

Three of the new compounds were tested *in vitro versus* the highly chloroquine resistant K1 strain of *Plasmodium falciparum* (Table 4). Compounds **11f** and **11g** were 10 times more potent than artemisinin and 3 fold more potent than artemether. Table 4 also includes data for chloroquine and allyldeoxoartemisinin **4a**. The data clearly demonstrate that the incorporation of lipophilic fluorinated aryl rings is beneficial to antimalarial activity since **11d**, **11f** and **11g** are more active as antimalarials than **4a**.

Table 2 $Ni(acac)_2$ mediated synthesis of allylsilanes



Starting material	Silyl enol ether	Yield	Allylsilane	Yield
8a, R =–−H	**9a**, R = –H,		**10a**, R = –H	42%
8b, R = –*m*-CF_3	**9b**, R = –*m*-CF_3	75%	**10b**, R = –*m*-CF_3	70%
8c, R–*o*-CF_3	**9c**, R–*o*-CF_3	78%	**10c**, R–*o*-CF_3	No reaction
8d, R = *p*-F	**9d**, R = *p*-F	78%	**10d**, R = *p*-F	81%
8e, R = *o*-F	**9e**, R = *o*-F	80%	**10e**, R = *o*-F	50%
8f, R = *p*-OMe	**9f**, R = *p*-OMe	60%	**10f**, R = *p*-MeO-	40%

Table 3 Yields of C-10 deoxo analogues from allylsilanes

Allylsilane	C-10-deoxoartemisinin	Yield
10a	**11a**, Ar = Ph	91%
10b	**11b**, Ar = *m*-CF_3-Ph	94%
10d	**11d**, Ar = *p*-F-Ph	86%
10e	**11e**, Ar = *o*-F-Ph	70%
7a	**11f**, Ar = *p*-CF_3	81%
7b	**11g**, Ar = *m*-F-Ph	90%

Table 4 *In vitro* antimalarial activity of new analogues *versus* K1 *Plasmodium falciparum*

Analogue	IC50 (nM)	SD±[a]
Artemisinin (**2**)	17.1	4.2
Artemether (**3a**)	9.2	2.1
11d	3.9	0.8
11f	1.8	0.3
11g	2.5	0.8
4a	7.2	1.2

[a] SD± = standard deviation.

The generally accepted mechanism of action of peroxide antimalarials involves the interaction of the peroxide-containing drug with haem, a haemoglobin degradation by-product, derived from proteolysis of haemoglobin.[29] This interaction is believed to result in the formation of a range of potentially toxic oxygen and carbon-centred radicals. In order to gain deeper mechanistic insight into the "actual" radical intermediates or cytotoxic end-products generated, several workers have employed biomimetic Fe(II) mediated decompositions to simulate events in the ferrous rich parasite food vacuole. Surprisingly, ferrous mediated degradation of **11a** provided as the main product, the formate **12** in 60% yield.[30] This type of product is not seen following identical degradation of artemisinin or the first generation compounds artemether or arteether (Scheme 6, A).

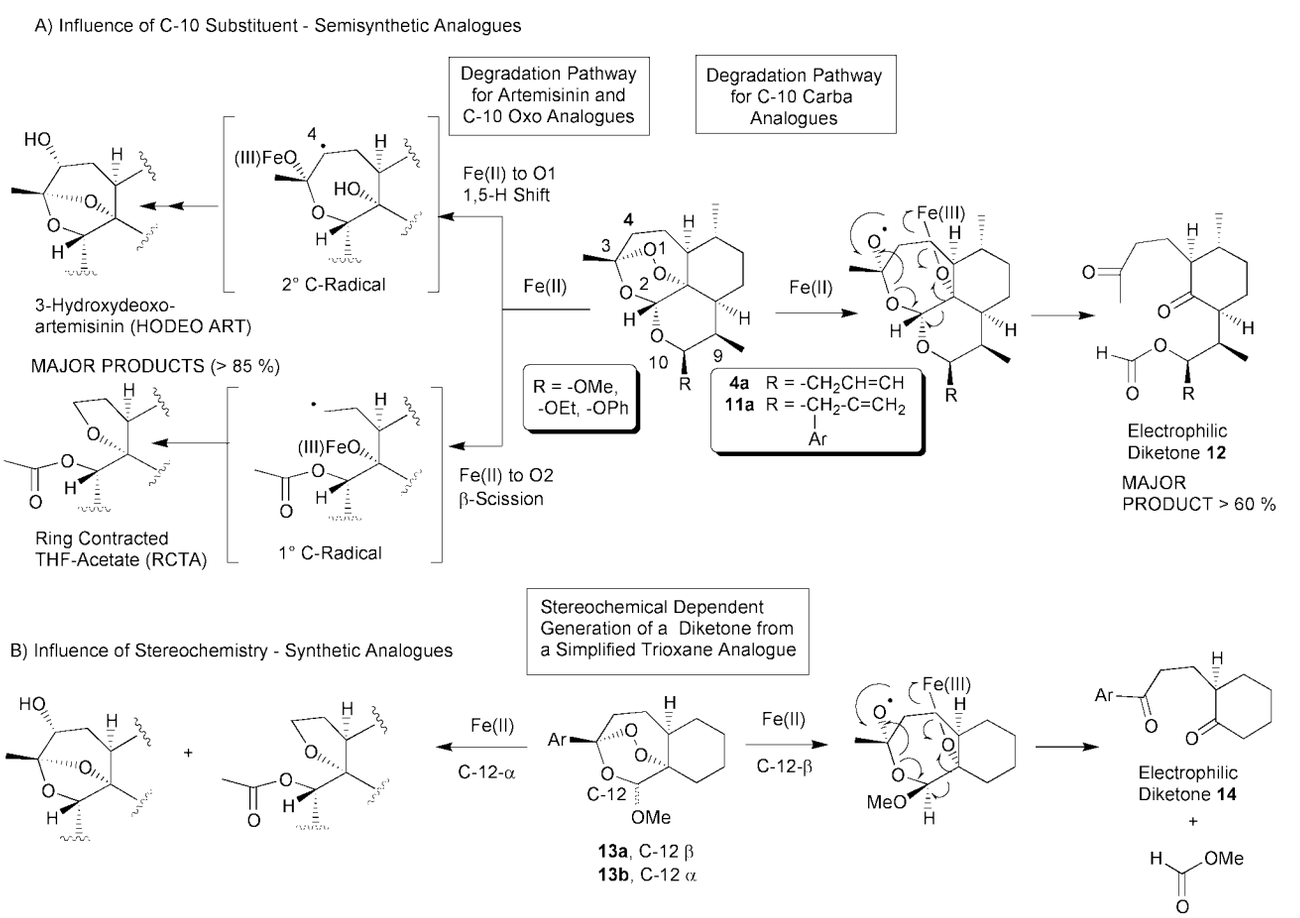
Intraparasitic release of dicarbonyl formate **12**, could in theory be responsible for some of the antimalarial activity of these analogues. Indeed in an earlier study on simplified C-3-aryl trioxanes **13a** and **13b**, Posner and co-workers demonstrated that C-12-β-orientated simplified trioxane **13a** degrades to a dicarbonyl function in a similar manner to that observed in this study.[31] It was proposed that intraparasitic release of this potentially cross-linking dicarbonyl, could be responsible, in part, for the high activity of these analogues. Interestingly, from the mechanistic work of Posner and co-workers, the pathway of ferrous mediated degradation of the trioxane was governed by stereochemistry at the C-12 position, since in contrast to **13a**, C-12-α-orientated trioxane **13b** generated products analogous to those seen with artemether and artemisinin (Scheme 6, B). The explanation as to why stereochemistry at the C-12 position of simplified trioxanes and simply changing carbon for oxygen at the C-10 position of artemisinin or ether derivatives, drives the ferrous mediated cascade toward these dicarbonyl products remains to be clarified.

In summary, we have now developed an optimised approach to C-10-carba analogues which delivers the products in up to 94% yield from the easily prepared C-10 benzoate of dihydroartemisinin. Some of these analogues are more than ten times more potent than artemisinin.

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded on Bruker AC200 and Varian Gemini 300 spectrometers. Mass spectra were recorded



Scheme 6

on VG analytical 7070E and Fisons TRIO 1000 spectrometers using electron ionisation (EI) and chemical ionisation (CI). Infrared spectra were recorded on a Perkin Elmer 1320 and Perkin Elmer FTIR Paragon 1000 spectrometers in the range of 4000–600 cm^{-1}. Analytical TLC was performed on aluminium-backed Merck silica gel 60 F_{254} plates. All liquid chromatography separations were performed using Merck Kieselgel 60 silica. Anhydrous DCM, DCE, diethyl ether, THF were purchased in sure-seal™ bottles from the Aldrich Chemical Company, and used as received. Acetonitrile was distilled from calcium hydride under nitrogen.

General procedure 1: synthesis of silyl enol ethers

To a solution of ketone starting material (1.0 eq.) in anhydrous ether (2 mL $mmol^{-1}$ of ketone) at 0 °C was added Et_3N (1.1 eq.) *via* a syringe. To this mixture, at 0 °C, was slowly added TMSOTf (1.1 eq.) *via* a gas tight syringe. The resulting mixture was stirred at 0 °C for 15 min, warmed to rt, and stirred for 2 hours. Two phases were separated and the ethereal layer was concentrated under reduced pressure. The crude product was purified *via* Kugelrohr distillation to yield silyl enol ether with some starting material.

General procedure 2: synthesis of allylsilanes ($Ni(acac)_2$ catalysed)

To a mixture of trimethylsilylmethylmagnesium chloride in ether (12.5 eq.) and $Ni(acac)_2$ (1.0 eq.) in anhydrous ether (50 mL) was added silyl enol ether starting material (6.3 eq.) at rt under a nitrogen atmosphere. The resulting black solution was heated under reflux for 3–6 hours and monitored by TLC (2% ethyl acetate in hexane). After hydrolysis with dilute hydrochloric acid, and extraction into DCM, the organic phase was washed with sodium bicarbonate and brine, dried with $MgSO_4$ and concentrated under reduced pressure. The product was purified by flash column chromatography with hexane.

General procedure 3: synthesis of allylsilanes ($CeCl_3$ method)

Powdered $CeCl_3 \cdot 7H_2O$ (5.4 eq.) was dried in a vacuum oven (30 mmHg, 160 °C) overnight. The cooled flask was vented with nitrogen and anhydrous THF was added. The suspension was stirred at rt for 2 h before being cooled to −70 °C. Trimethylsilylmethylmagnesium chloride (5 eq.) was added *via* a syringe and the suspension left stirring for 1 h, at which time the ester (1 eq.) was added over 2–3 min. Stirring was continued for 2 h at −70 °C upon which time the reaction was allowed to warm to rt overnight. After quenching with hydrochloric acid (1 M), the crude product was isolated by extraction into DCM, drying over $MgSO_4$ and solvent removal under reduced pressure. The product was purified by flash chromatography with hexane.

General procedure 4: synthesis of deoxoartemisinin derivatives

To a solution of allylsilane (4.8 eq.) in anhydrous DCE (5 mL) was added $ZnCl_2$ (1.2 eq.) and 4 Å molecular sieves under an inert nitrogen atmosphere. The mixture was cooled to 0 °C before adding a solution of benzoate (1 eq. in DCE (5 mL)) and leaving to stir at 0 °C for 4 h. After quenching with 5% aq. citric acid solution and separating the organic phase, the crude product was extracted from the aqueous layer into ethyl acetate. The combined organic extracts were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The product was purified by flash chromatography with hexane and ethyl acetate (10 : 1) as eluent.

Dihydroartemisinin 10α-benzoate 5

To a solution of DHA (5.0 g, 1.76 mol) in anhydrous DCM (54 mL) under an inert nitrogen atmosphere was added anhydrous pyridine (9 mL). The mixture was cooled to 0 °C before adding benzoyl chloride (3.17 mL 2.73 mol). After stirring at 0 °C for 15 min, the reaction mixture was allowed to warm to rt and was left for 16 h. The reaction was quenched with 7% aq. citric acid solution and the aqueous phase extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with 7% aq. citric acid solution followed by saturated $NaHCO_3$ and finally dried over $MgSO_4$. The crude mixture was recrystallised from diethyl ether and hexane (1 : 1) at 0 °C to yield white crystals (4.14 g, 61% yield). ν_{max} (Nujol mull)/cm^{-1} 2927, 1737, 1492, 1453, 1113, 876; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14–8.11 (2H, m, Ar), 7.57 (1H, m, Ar), 7.47–7.42 (2H, m, Ar), 6.02 (1H, d, J = 9.9 Hz, 10-H), 5.53 (1H, s, 12-H), 2.76 (1H, m, 9-H), 2.40 (1H, dt, J = 12.9, 4.0 Hz), 2.04 (1H, m), 1.94–1.20 (9H, m), 1.43 (3H, s, CH_3 at C3), 0.98 (3H, d, J = 6.0 Hz, CH_3), 0.93 (3H, J = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.45, 133.38, 130.21, 129.79, 128.39, 104.46, 92.60, 91.64, 80.19, 51.66, 45.34, 37.22, 36.23, 34.09, 31.94, 25.86, 24.52, 21.98, 20.13, 12.11; MS *m*/*z* (CI, NH_3) 284.3 (35%), 267.3 (55), 249.2 (15), 238.3 (18), 221.2 (100), 207.2 (80), 162.2 (31), 149.1 (7), 105.1 (16); Found 406.22436. $C_{22}H_{32}NO_6$ $[M + NH_4]^+$ requires 406.2296, found: C, 68.03; H, 7.25; requires C, 68.02; H, 7.26%.

Trimethyl[2-(4-trifluoromethylphenyl)allyl]silane 7a

This was synthesised in accordance to general procedure 3 using 4-trifluoromethylbenzoic acid methyl ester (0.16 mL, 1.0 mmol). Purification of the product resulted in a clear oil (0.17 g, 67% yield). ν_{max} (neat)/cm^{-1} 3092.0, 1618.0, 1280.0, 1015.0, 846.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57–7.48 (4H, m, Ar), 5.18 (1H, d, J = 1.5 Hz), 4.96 (1H, d, J = 0.9 Hz), 2.02 (2H, d, J = 1.2 Hz), −0.10 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.03, 147.17, 130.61, 128.13, 127.64, 126.64 (1C, d, J_{C-F} = 3.8 Hz), 113.53, 27.51, 0.00; MS *m*/*z* (EI) 243 (6.25%), 203 (7.11), 166 (32.57), 165 (19.14), 164 (6.07), 146 (5.89), 145 (9.43), 116 (9.43), 115 (14.71), 75 (7.50), 74 (8.21), 73 (100.00), 45 (12.71), 43 (11.00); Found 258.10512. $C_{13}H_{17}SiF_3$ requires 258.10516.

[2-(3-Fluorophenyl)allyl]trimethylsilane 7b

This was synthesised in accordance to general procedure 3 using ethyl 3-fluorobenzoate (0.15 mL, 1.0 mmol). Purification of the product resulted in a clear oil (0.15 g, 73% yield). ν_{max} (neat)/cm^{-1} 3090.0, 1611.0, 1265.0, 1159.0, 875.0, 851.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–6.99 (4H, m, Ar), 5.24 (1H, d, J = 1.5 Hz), 4.99 (1H, d, J = 1.2 Hz), 2.07 (2H, s), 0.00 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.86 (1C, d, J_{C-F} = 243.5 Hz), 145.60, 145.28 (1C, d, J_{C-F} = 7.1 Hz), 129.50 (1C, d, J_{C-F} = 8.1 Hz), 122.02, 113.95 (1C, d, J_{C-F} = 21.3 Hz), 113.25 (1C, d, J_{C-F} = 21.8 Hz), 111.00, 26.02, 1.53; MS *m*/*z* (EI) 193 (15.30%), 177 (6.09), 153 (18.66), 115 (24.00), 77 (7.65), 75 (6.25), 74 (7.65), 73 (100.00), 45 (8.46), 43 (6.90); Found 208.10834. $C_{12}H_{17}SiF$ requires 208.10835; found: C, 69.12; H, 8.25; requires C, 69.18; H, 8.22%.

Trimethyl[1-(3-trifluoromethylphenyl)vinyloxy]silane 9b

This was synthesised in accordance to general procedure 1 using 3-(trifluoromethyl)acetophenone (1.83 mL, 12 mmol). Purification of the product by Kugelrohr distillation (70 °C, 0.1 mmHg) resulted in a clear oil in 75% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15–7.20 (4H, m, Ar), 4.91 (1H, d, J = 2.1 Hz), 4.49 (1H, d, J = 2.1 Hz), 0.00 (9H, s); MS *m*/*z* (EI) 245 (31.8%), 191 (16.64), 188 (12.92), 173 (100.00), 169 (13.48), 151 (15.73), 145 (66.57), 103 (17.98), 75 (30.34), 73 (12.50), 47 (10.39), 43 (14.40); Found 260.08330. $C_{12}H_{15}F_3OSi$ requires 260.08441.

Trimethyl[1-(2-trifluoromethylphenyl)vinyloxy]silane 9c

This was synthesised in accordance to general procedure 1 using 2-(trifluoromethyl)acetophenone (1.83 mL, 12 mmol).

Purification of the product by Kugelrohr distillation (50–55 °C, 0.1 mmHg) resulted in a clear oil (2.42 g, 78% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63–7.19 (4H, m, Ar), 4.43 (1H, d, J = 1.6 Hz), 4.37 (1H, d, J = 1.6 Hz), 0.17 (9H, s); MS *m*/*z* (CI, NH_3) 245.0 (10%), 206.1 (50), 191.1 (15), 173.0 (60), 149.0 (24), 90.0 (100.0); Found 261.09329. $C_{12}H_{16}OF_3Si$ $[M + H]^+$ requires 261.09225.

[1-(4-Fluorophenyl)vinyloxy]trimethylsilane 9d

This was synthesised in accordance to general procedure 1 using 4-fluoroacetophenone (1.46 mL, 12 mmol). Purification of the product by Kugelrohr distillation (70–75 °C, 0.1 mmHg) resulted in a clear oil (1.71 g, 68% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.24–6.93 (4H, m, Ar), 4.81 (1H, d, J = 1.9 Hz), 4.37 (1H, d, J = 1.4 Hz), 0.24 (9H, s).

[1-(2-Fluorophenyl)vinyloxy]trimethylsilane 9e

This was synthesised in accordance to general procedure 1 using 2-fluoroacetophenone (1.48 mL, 12 mmol). Purification of the product by Kugelrohr distillation (60–65 °C, 0.1 mmHg) resulted in a clear oil (2.01 g, 80% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.23 (1H, m, Ar), 7.03–6.75 (3H, m, Ar), 4.97 (1H, s), 4.63 (1H, d, J = 1.5 Hz), 0.20 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.19 (1C, d, J_{C-F} = 249.5 Hz), 150.50, 129.41 (1C, d, J_{C-F} = 8.7 Hz), 128.88, 123.74 (1C, d, J_{C-F} = 3.3 Hz), 115.98 (1C, d, J_{C-F} = 23.5 Hz), 97.2 (1C, d, J_{C-F} = 11.0 Hz), 30.83, 0.00; MS *m*/*z* (EI) 209 (36.44%), 195 (59.48), 173 (23.69), 77 (100.00), 73 (22.71); Found 210.08710. $C_{11}H_{15}OFSi$ requires 210.08762.

[1-(4-Methoxyphenyl)vinyloxy]trimethylsilane 9f

This was synthesised in accordance to general procedure 1 using 4-methoxyacetophenone (1.80 g, 12 mmol). Purification of the product by Kugelrohr distillation resulted in a orange oil (1.66 g, 59% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95–6.82 (4H, m, Ar), 4.79 (1H, s), 4.32 (1H, s), 3.79 (3H, s), 0.25 (9H, s).

Trimethyl(2-phenylallyl)silane 10a

This was synthesised in accordance to general procedure 2 using 1-phenyl-1-(trimethylsiloxy)ethylene **9a** (0.96 g, 5.0 mmol). Purification of the product resulted in a clear oil (0.40 g, 42% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.21 (5H, m, Ar), 5.12 (1H, br s), 4.86 (1H, br s), 2.21 (2H, br s), 0.18 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.78, 128.17, 127.36, 126.41, 125.56, 110.10, 20.91, 0.00; found: C, 74.83; H, 9.41; requires C, 75.72; H, 9.53%.

Trimethyl[2-(3-trifluoromethylphenyl)allyl]silane 10b

This was synthesised in accordance to general procedure 2 using **9b** (1.30 g, 5.0 mmol). Purification of the product resulted in a yellow liquid (0.70 g, 50% yield). ν_{max} (neat)/cm^{-1} 2960.0, 1620.0, 1281.0, 1128.0, 854.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54–7.27 (4H, m, Ar), 5.26 (1H, br s), 4.97 (1H, br s), 2.04 (2H, br s), 0.08 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.45, 143.61, 129.58, 128.61, 123.88, 123.11, 111.60, 26.04, −1.52; MS *m*/*z* (EI) 243 (12.22%), 167 (5.05), 166 (47.41), 165 (20.19), 164 (5.56), 146 (9.58), 116 (11.81), 115 (17.78), 77 (11.85), 75 (5.00), 74 (7.41), 73 (100.00), 45 (11.62), 43 (7.87); Found 258.10487. $C_{13}H_{17}F_3Si$ requires 258.10516.

[2-(4-Fluorophenyl)allyl]trimethylsilane 10d

This was synthesised in accordance to general procedure 2 using **9d** (1.05 g, 5.0 mmol). Purification of the product resulted in a yellow liquid (0.84 g, 81% yield). ν_{max} (neat)/cm^{-1} 2958.0, 1603.0, 1248.0, 1160.0, 838.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–6.95 (2H, m, Ar), 7.20–6.95 (2H, m, Ar), 5.07 (1H, d, J = 1.5 Hz), 4.85 (1H, d, J = 0.9 Hz), 1.99 (2H, d, J = 1.2 Hz), 0.09 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.69, 127.95, 115.01, 114.73, 110.03, 26.33, −1.51; MS *m*/*z* (EI) 193 (5.51%), 153 (10.53), 115 (9.46), 75 (6.58), 74 (6.83), 73 (100.00), 45 (10.28); Found 208.10854. $C_{12}H_{17}FSi$ requires 208.10835; found: C, 69.33; H, 8.28; requires C, 69.18; H, 8.22%.

[2-(2-Fluorophenyl)allyl]trimethylsilane 10e

This was synthesised in accordance to general procedure 2 using **9e** (1.05 g, 5.0 mmol). Purification of the product resulted in a yellow liquid (0.57 g, 50% yield). ν_{max} (Nujol mull)/cm^{-1} 2958.0, 1622.0, 1249.0, 1164.0, 880.0, 851.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–6.99 (4H, m, Ar), 5.02 (2H, br s), 2.05 (2H, br s), 0.11 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.68, 130.06, 128.65, 123.84, 115.88, 115.58, 113.79, 30.84, 27.43, −1.71; MS *m*/*z* (EI) 116 (9.85%), 115 (30.61), 77 (17.27), 74 (7.69), 73 (100.00), 45 (7.58); Found 208.10875. $C_{12}H_{17}FSi$ requires 208.10835; found: C, 68.46; H, 8.53; requires C, 69.18; H, 8.22%.

[2-(4-Methoxyphenyl)allyl]trimethylsilane 10f

This was synthesised in accordance to general procedure 2 using **9f** (1.11 g, 5.0 mmol). Purification of the product resulted in a orange liquid (0.41 g, 35% yield). ν_{max} (Nujol mull)/cm^{-1} 2957.0, 2850.0, 1608.0, 1248.0, 833.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.41 (2H, m, Ar), 6.89–6.84 (2H, m), 5.28 (1H, br s), 5.00 (1H, brs), 3.82 (3H, s), 2.14 (2H, br s), 0.19 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.66, 113.63, 110.69, 55.30, 21.88, 0.05; MS *m*/*z* (EI) 205 (29.36%), 165 (100.00), 73 (37.77); Found 220.12852. $C_{13}H_{20}SiO$ requires 220.12834.

10β-Allyldeoxoartemisinin 4a

This was synthesised in accordance to general procedure 4 using allyltrimethylsilane to give the product as a white solid (90%, mp 77–79 °C). The physical properties were identical to those reported in ref. 8.

Anhydroartemisinin 4b

ν_{max} (Nujol mull)/cm^{-1} 2923.9, 2852.4, 1685.9, 1459.9, 1112.8, 880.2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (1H, s, 10-H), 5.42 (1H, s, 12-H), 2.41 (1H, dt, J = 13.9, 4.8 Hz), 2.04 (2H, m), 1.92 (1H, m), 1.74–1.36 (5H, m), 1.59 (3H, d, J = 1.2, CH_3), 1.42 (3H, s, CH_3 at C3), 1.14 (2H, m), 0.98 (3H, d, J = 6.0 Hz, CH_3); ^{13}C (75 MHz, $CDCl_3$) δ 135.12, 108.11, 104.56, 89.74 (C10), 78.99, 51.50, 44.50, 37.50, 36.27, 34.14, 30.00, 25.89, 24.42, 20.25, 16.14.

10β-(2-Phenylallyl)deoxoartemisinin 11a

This was synthesised in accordance to general procedure 4 using **10a** (0.39 g, 2.0 mmol). Purification of the product resulted in a white glue (0.14 g, 91% yield). ν_{max} (Nujol mull)/cm^{-1} 2927.0, 1463.0, 1104.0, 895.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.24 (5H, m, Ar), 5.36 (2H, br s), 5.27 (1H, d, J = 1.4 Hz), 4.52 (1H, m, 10-H), 2.72–1.20 (17H, m), 0.97–0.92 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.26, 127.30, 126.47, 114.36, 102.80 (C12), 89.65 (C10), 71.70, 52.18, 44.24, 37.53, 36.69, 35.85, 34.49, 30.48, 25.75, 24.93, 20.09, 12.73; MS *m*/*z* (EI) 338 (23.84%), 165 (20.93), 163 (44.19), 162 (100.00), 157 (24.61), 145 (28.49), 138 (21.12), 129 (24.42), 124 (21.32), 118 (36.82), 117 (31.20), 115 (35.85), 105 (43.02), 103 (31.98), 95 (32.56), 93 (22.29), 91 (58.14), 81 (32.56), 79 (23.06), 77 (31.78), 71 (23.84), 69 (36.24), 67 (23.84), 55 (51.94), 45 (88.37), 41 (35.66); Found 384.22957. $C_{24}H_{32}O_4$ requires 384.23004; found: C, 73.89; H, 8.31; requires C, 74.97; H, 8.39%.

10β-[2-(3-Trifluoromethylphenyl)allyl]deoxoartemisinin 11b

This was synthesised in accordance to general procedure 4 using **10b** (0.56 g, 2.2 mmol). Purification of the product

resulted in a white glue (0.24 g, 94% yield). ν_{max} (Nujol mull)/cm^{-1} 2923.1, 1456.6, 1376.9, 1123.1, 880.7; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.42 (4H, m, Ar), 5.42 (1H, s), 5.37 (1H, s, 12-H), 5.35 (1H, s), 4.52 (1H, m, 10-H), 2.62 (1H, m, 9-H), 2.28 (1H, dt, J = 13.9, 4.0 Hz), 2.06–1.20 (12H, m), 1.25 (3H, s, CH_3 at C3), 0.98 (3H, d, J = 5.7 Hz, CH_3), 0.96 (3H, d, J = 7.8 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.02, 142.38, 129.74, 128.72, 123.99, 123.35, 116.03, 102.79 (C12), 89.72 (C10), 81.02, 71.42, 52.10, 44.11, 37.54, 36.64, 35.88, 34.44, 30.48, 25.67, 24.92, 24.79, 20.06, 12.59; MS *m*/*z* (EI) 163 (25.00%), 162 (53.19), 124 (23.01), 109 (20.74), 95 (28.46), 93 (23.54), 81 (27.79), 79 (21.68), 71 (20.61), 69 (31.38), 67 (24.20), 55 (59.04), 43 (100.00), 41 (36.17); Found 452.21724. $C_{25}H_{31}O_4F_3$ requires 452.21744.

10β-[2-(4-Fluorophenyl)allyl]deoxoartemisinin 11d

This was synthesised in accordance to general procedure 4 using **10d** (0.66 g, 3.2 mmol). Purification of the product resulted in a clear glue (0.26 g, 86% yield). ν_{max} (Nujol mull)/cm^{-1} 2922.7, 1455.9, 1375.8, 1125.9, 879.8; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–6.96 (4H, m, Ar), 5.34 (1H, s, 12-H), 5.30 (1H, s), 5.25 (1H, d, J = 1.2 Hz), 4.50 (1H, m, 10-H), 2.60 (1H, m, 9-H), 2.28 (1H, dt, J = 13.8, 3.7 Hz), 2.01–1.19 (12H, m), 1.26 (3H, s, CH_3 at C3), 0.96 (3H, d, J = 6.1 Hz, CH_3), 0.92 (3H, d, J = 7.6 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.09, 137.56, 128.04 (1C, d, J_{C-F} = 8.2 Hz), 115.18, 114.90, 114.40, 102.80 (C12), 89.72 (C10), 81.04, 71.50, 52.13, 44.16, 37.54, 36.67, 36.12, 34.46, 30.48, 25.74, 24.92, 24.79, 20.07, 12.65; MS *m*/*z* (CI, NH_3) 373.2 (9%), 357.2 (100), 343.2 (19), 267.2 (8), 221.2 (9), 162.1 (7); Found 420.25622. $C_{24}H_{35}NO_4F$ $[M + NH_4]^+$ requires 420.25501.

10β-[2-(2-Fluorophenyl)allyl]deoxoartemisinin 11e

This was synthesised in accordance to general procedure 4 using **10e** (0.46 g, 2.2 mmol). Purification of the product resulted in a colourless glue (0.14 g, 70% yield). ν_{max} (Nujol mull)/cm^{-1} 2923.4, 1448.2, 1375.4, 1092.9, 879.7; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–6.98 (4H, m, Ar), 5.40 (1H, s), 5.33 (1H, s, 12-H), 5.24 (1H, s), 4.40 (1H, m, 10-H), 2.61 (1H, m, 9-H), 2.29 (1H, dt, J = 12.8, 3.9 Hz), 2.01–1.17 (12H, m), 1.28 (3H, s, CH_3 at C3), 0.96 (3H, d, J = 6.0 Hz, CH_3), 0.88 (3H, d, J = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.31, 143.06, 130.83, 128.81 (1C, d, J = 8.2 Hz), 124.09, 117.61, 115.56 (1C, d, J = 23.0 Hz), 102.88 (C12), 89.51 (C10), 81.06, 72.09, 52.23, 44.29, 37.53, 36.70, 34.49, 30.37, 25.81, 24.88, 24.79, 20.12, 12.68; MS *m*/*z* (EI) 312 (21.94%), 175 (38.27), 163 (42.18), 162 (44.22), 161 (39.29), 149 (23.30), 147 (20.75), 135 (39.63), 133 (29.08), 123 (40.65), 121 (35.37), 115 (22.62), 109 (78.23), 107 (28.06), 101 (21.09), 95 (43.54), 93 (31.12), 91 (20.58), 81 (39.46), 79 (27.89), 71 (27.72), 69 (40.48), 67 (33.33), 55 (67.35), 43 (100.00), 41 (37.93); Found 402.22001. $C_{24}H_{31}FO_4$ requires 402.22064.

10β-[2-(4-Trifluoromethylphenyl)allyl]deoxoartemisinin 11f

This was synthesised in accordance to general procedure 4 using **7a** (0.08 g, 0.3 mmol). Purification of the product resulted in a white glue (0.04 g, 81% yield). ν_{max} (Nujol mull)/cm^{-1} 2923.5, 1456.5, 1376.1, 1127.4, 879.9; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59–7.50 (4H, m, Ar), 5.42 (1H, s), 5.37 (1H, s, 12-H), 5.33 (1H, s), 4.52 (1H, m, 10-H), 2.64 (1H, m, 9-H), 2.31 (1H, m), 2.09–1.05 (12H, m), 1.21 (3H, s, CH_3 at C3), 0.96 (3H, d, J = 6.3 Hz, CH_3), 0.94 (3H, d, J = 7.8 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.12, 135.12, 126.80, 125.26, 116.30, 102.73 (C12), 89.83 (C10), 81.01, 71.19, 52.05, 44.06, 37.54, 36.27, 35.96, 34.42, 30.49, 25.61, 24.91, 24.80, 20.03, 12.57; MS *m*/*z* (EI) 225 (20.00%), 163 (37.31), 162 (66.92), 159 (27.12), 151 (27.31), 124 (23.46), 123 (25.77), 121 (21.92), 109 (27.69), 107 (25.58), 95 (24.62), 81 (37.88), 79 (26.15), 71 (24.62), 69 (38.08), 55 (64.62), 43 (100.00), 41 (35.38); Found 452.21724. $C_{25}H_{31}F_3O_4$ requires 452.21747.

10β-[2-(3-Fluorophenyl)allyl]deoxoartemisinin 11g

This was synthesised in accordance to general procedure 4 using **7b** (0.28 g, 1.3 mmol). Purification of the product resulted in a white glue (0.14 g, 90% yield). ν_{max} (Nujol mull)/cm^{-1} 2956.0, 1462.0, 1377.0, 1124.0, 872.0; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–6.92 (4H, m, Ar), 5.38 (1H, d, J = 1.0 Hz), 5.34 (1H, s, 12-H), 5.31 (1H, d, J = 1.1 Hz), 4.52 (1H, m, 10-H), 2.62 (1H, m, 9-H), 2.27 (1H, dt, J = 13.7, 3.8 Hz), 2.02–1.18 (12H, m), 1.27 (3H, s, CH_3 at C3), 0.96 (3H, d, J = 7.6 Hz, CH_3), 0.93 (3H, d, J = 7.7 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.95 (1C, d, J_{C-F} = 244.1 Hz), 145.02, 143.97 (1C, d, J_{C-F} = 7.1 Hz), 129.66 (1C, d, J_{C-F} = 8.3 Hz), 122.10, 115.35, 114.07 (1C, d, J_{C-F} = 21.3 Hz), 113.45 (1C, d, J_{C-F} = 21.8 Hz), 102.80 (C12), 89.75 (C10), 81.03, 71.42, 52.11, 44.13, 37.54, 36.68, 35.88, 34.45, 30.48, 25.71, 24.93, 24.80, 20.06, 12.61; MS *m*/*z* (EI) 175 (20.98%), 165 (26.57), 163 (35.31), 162 (54.55), 161 (21.85), 147 (21.50), 138 (30.42), 135 (21.50), 133 (22.20), 124 (26.75), 123 (22.20), 109 (41.08), 95 (21.85), 81 (28.50), 79 (22.38), 69 (24.83), 67 (22.90), 55 (60.14), 43 (100.00), 41 (37.41); Found 402.22040. $C_{24}H_{31}O_4F$ requires 402.22064; found: C, 71.14; H, 7.71; requires C, 71.62; H, 7.76%.

$FeCl_2$-mediated degradation of 10β-(2-phenylallyl)deoxoartemisinin (11a)

To a solution of **11a** (0.14 g, 0.4 mmol) in CH_3CN (13 mL) was added $FeCl_2 \cdot 4H_2O$ (0.1 g, 0.5 mmol) under nitrogen atmosphere. The reaction was left stirring at rt for 30 min before being filtered through Celite and washed with CH_3CN. Concentration under reduced pressure and flash column chromatography using ethyl acetate and hexane (1 : 10) as eluent yielded the product **12** as yellow oil (0.86 g, 60% yield). ν_{max} (Nujol mull)/cm^{-1} 3042.1, 2926.3, 1713.8, 1628.8; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (1H, s, HC=O), 7.43–7.21 (5H, m, Ar), 5.35 (1H, br s, C=CH), 5.14 (2H, m, C=CH & 10-H), 2.96–1.26 (12H, m), 2.11 (3H, s, CH_3), 1.01 (3H, d, J = 6.3 Hz), 0.99 (3H, d, J = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.31, 209.02, 160.66, 144.16, 140.12, 128.47, 127.79, 126.33, 115.85, 72.53, 57.52, 54.42, 41.38, 38.22, 34.60, 34.13, 31.02, 29.81, 20.40, 20.36, 12.26; MS *m*/*z* (CI, NH_3) 355.3 (13%), 339.3 (100), 221.1 (6); Found 402.26497. $C_{24}H_{36}NO_4$ $[M + NH_4]^+$ requires 402.26443.

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