Syntheses and Antimalarial Activities of 10-Substituted Deoxoartemisinins

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Two series of 10-substituted deoxoartemisinin derivatives have been synthesized. The first employed the reaction of dihydroartemisinin acetate with several silyl enol ethers in the presence of titanium tetrachloride. The second utilized the reaction of 10-(2-oxoethyl)deoxoartemisinin with several Grignard reagents. The in vitro antimalarial activities of both series were determined against two drug-resistant clones of *P. falciparum*. The activities of **13***β* and **15***β* were 5−7 times greater than that of artemisinin.

Introduction

The spread of drug-resistant strains of malaria threatens to worsen an already difficult situation in Asia, Africa, and parts of South America. A variety of derivatives of the lead compound artemisinin, **1**, have been prepared in the search for a more active drug.[1] Several groups of 10-substituted deoxoartemisinins have been synthesized and shown to be 2−5 times more active than artemisinin, and preliminary data has indicated that several are orally active. Jung et al.[2] have shown that several deoxoartemisinins are more resistant to hydrolyses in simulated mixtures of stomach acid than the dihydroartemisinin derivatives currently in use. The first syntheses of deoxoartemisinin derivatives were lengthy and employed artemisinic acid as their starting material.[3−5] We later demonstrated that this group of compounds could be prepared from dihydroartemisinin by reaction with allyltrimethylsilane in the presence of boron trifluoride etherate.[6] The resulting 10-allyl derivative was converted into several other derivatives. In vitro tests indicated that the 10-*n*-propyl derivative was the most active one, and it was then subjected to in vivo and toxicity tests. The compound proved to be as active and toxic as arteether which was under consideration by the World Health Organization for clinical testing.

Posner et al. have also utilized dihydroartemisinin in their syntheses of new deoxoartemisinin derivatives. They employed a two-step conversion of dihydroartemisinin, via an intermediate 10-fluoro derivative, into a series of aromatic and heterocyclic 10-substituted deoxoartemisinins.[7] Several compounds were up to 8 times more active than artemisinin. Wang et al. prepared two 10-(2-hydroxy-1-naphthyl)deoxoartemisinins by an acid-catalyzed reaction of dihydroartemisinin acetate with 2-naphthol:[8] the 9*β*-methyl derivative was twice as active in vivo as artemether in mice and the 9α-methyl isomer was much less active. O'Neil et al. ozonolyzed 10*β*-allyldeoxoartemisinin, and the resulting aldehyde was then reduced to the alcohol.[9] A series of esters and ethers of the alcohol were prepared. Many of the ethers were several times more active in vitro than artemisinin.[7]

Herein, we describe the syntheses of new deoxoartemisinins from dihydroartemisinin acetate as well as from 10-allyldeoxoartemisinin by modifications of our earlier methodology. The antimalarial activities of these derivatives have been determined and are discussed below.

Chemistry

The enhanced biological activity of deoxoartemisinins compared to artemisinin prompted us to search for new syntheses of this group of compounds from artemisinin. A preliminary report[10] of one promising route involved utilizing methodology developed by Dahanukar and Rychnovsky for the conversion of hemiacetal acetates to C-glycosides by reaction with trimethylsilyl enol ethers in the presence of titanium tetrachloride.

Dihydroartemisinin acetate, **2**, was prepared by DIBAL reduction of artemisinin followed by reaction with acetic anhydride. Reaction of **2** with the silyl enol ethers of acetone, acetophenone, methyl *tert*-butyl ketone, and cyclopentanone in the presence of titanium chloride (Scheme 1) yielded **3**, **5**, **6**, and **7** respectively. The compounds were tested and also employed as intermediates for the reactions described below. Preliminary test data of **3** indicated that it was 1 order of magnitude more active than artemisinin. In an effort to further enhance its activity, we elected to prepare a variety of structural analogues.

The most efficient route appeared to involve preparation of the aldehyde **4** which we had previously prepared by ozonolysis of **1**. However we had employed a reductive workup and it was never isolated. Oxidation of **11** with osmium tetroxide followed by reaction with sodium periodate yielded **4**. The aldehyde **4** was then

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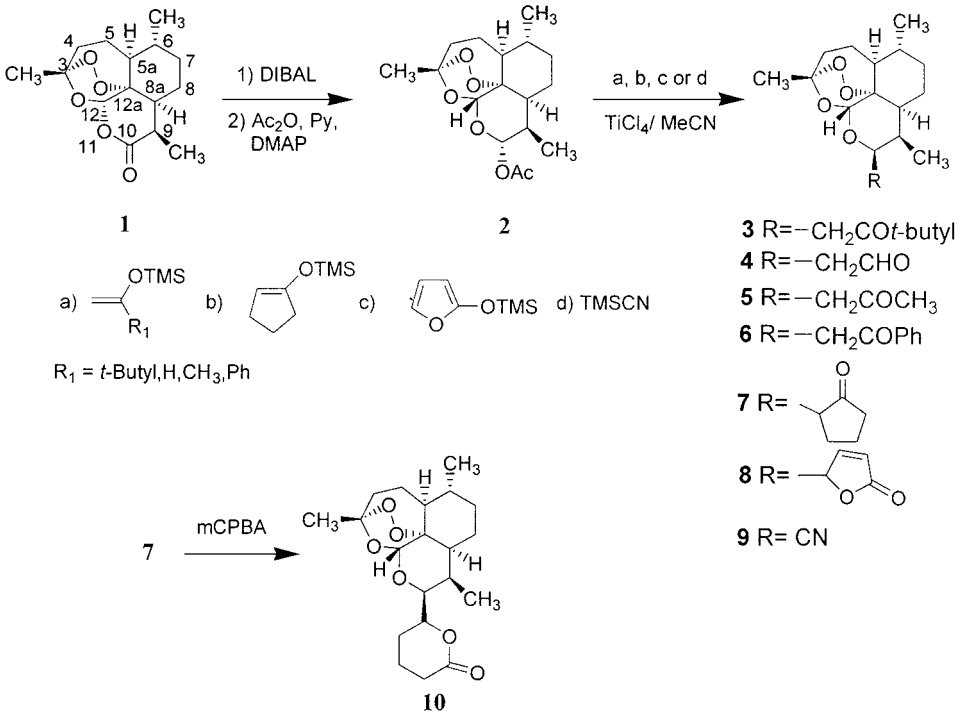
Scheme 1



reacted with a variety of Grignard reagents to produce **12**−**15**.

Oxidation of **7** with *m*-chloroperbenzoic acid yielded **10**. Antimalarial activities of all the deoxoartemisinins were determined against two drug-resistant clones of *Plasmodium falciparum* and are given in Table 1. On retesting, **3** was found to be only twice as active as artemisinin as was also the case for compounds **4**−**7**.

In our attempt to identify the features associated with high activity, a variety of structural analogues of **3** were prepared. Ketone **3** had been synthesized from the reaction of **2** with a silyl enol ether, and a variety of hydroxy analogues were obtained from the reaction of **4** with several Grignard reagents. The alcohols obtained in high yield proved to be approximately 2:1 mixtures of diastereomers which could be separated by flash chromatography. The absolute stereochemistry at the carbinol carbon has not been assigned; we have arbitrarily designated the major less polar isomer as the α-isomer and the minor more polar compound as the *β*-isomer. Compounds **13** and **14** were oxidized to the corresponding ketones **16** and **17**, and their antimalarial activities are given in Table 2. Reaction of **2** with trimethylsilyl cyanide yielded the cyano derivative **9** (see Table 1).

In exploring the use of the aldehyde **4** as an intermediate we also reacted it with a Wittig reagent to produce **18**. The peroxide moiety essential for antimalarial activity was not altered under the reaction conditions of the Wittig or Grignard reactions. The reaction of **4** with trimethyl(trifluoromethyl)silane[11] yielded a pair of isomeric alcohols, **19**α and **19***β*.

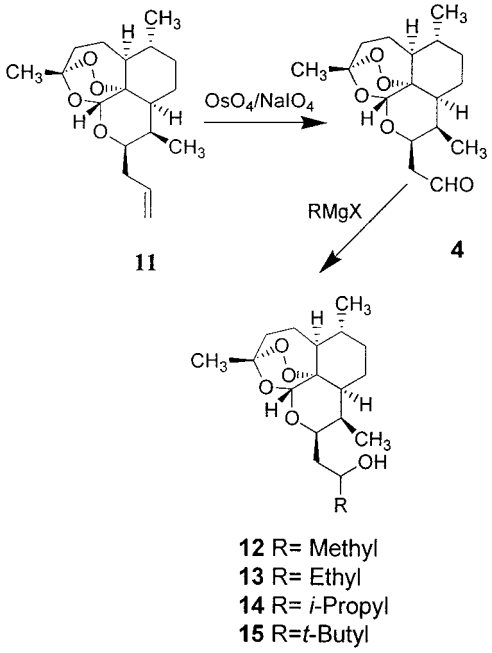
Biological Activity

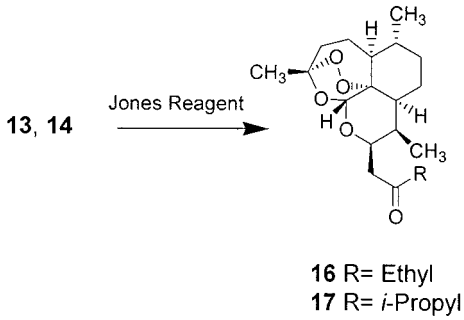
The in vitro antimalarial activities of all the compounds prepared here were determined at the Walter Reed Army Institute of Research using two *P. falciparum* clones designated as Indochina (W-2) and Sierra Leone (D-6).[12] Since the activities were not determined at the same time, they are reported relative to artemisinin (Tables 1 and 2). The W-2 clone is chlorquine-resistant and mefloquine-sensitive, while the D-6 clone is chloroquine-sensitive and mefloquine-resistant. The results from the initial group of compounds are given in Table 1. The first compound tested was **3**, and as mentioned above preliminary testing suggested it was 1 order of magnitude more active than artemisinin. That observation prompted us to prepare **4** and **5**. Final test data indicated that the three compounds were only 2−4 times more active than artemisinin. Although these activities are not exceptional, we elected to continue to examine the effect on their activities of small structural modifications. The activities of compounds **12**−**19** are given in Table 2. The activities of many of the compounds were 2−4 times greater than that of artemisinin, but two compounds, **13***β* and **15***β*, were 5−7 times greater than artemisinin. The use of different drug-resistant clones of *P. falciparum* by different investigators and their ways of reporting activities make it difficult to compare the in vitro activities of **13***β* and **15***β* with literature data. We had previously reported on the in vitro activity of a related derivative, 10-(*n*-propyl)deoxoartemisinin, which was twice as active as artemisinin with the same two *P. falciparum* clones. Its in vivo activity in a mouse model was equal to that of arteether, an artemisinin derivative under consideration for clinical testing at the time.

Data in Table 2 indicate that the more polar alcohols are more active than the corresponding less polar isomers. Furthermore, **13***β* and **15***β* are 2−3 times more active than 10-(*n*-propyl)deoxoartemisinin and therefore warrant the expenses involved with in vivo testing.

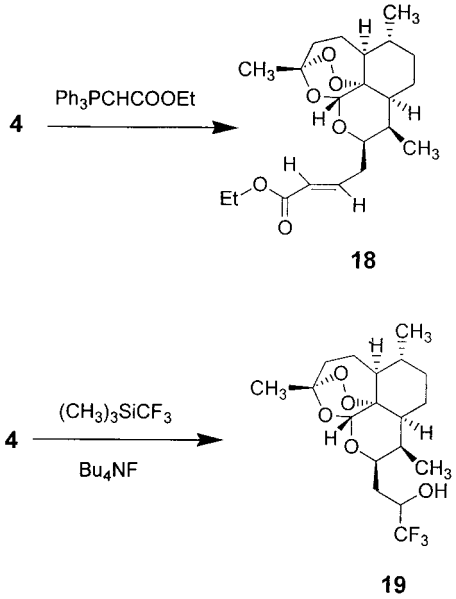
In summary the two synthetic routes described here can be employed for the efficient syntheses of a host of substituted 10-deoxoartemisinin derivatives. The antimalarial activities of the more polar alcohols **12**−**19**

Scheme 2





Scheme 3



were greater than that of the corresponding less polar isomer. The activities of two derivatives, **13**β and **15**β, were significantly greater than those of other compounds in this series to merit in vivo and toxicological testing.

Table 1. Relative Antimalarial Activities against Two *P. falciparum* Clones

	relative activity[a]			relative activity[a]	
compd	W-2	D-6	compd	W-2	D-6
3	2.1	1.6	**7**	1.6	0.91
4	1.8	3.5	**8**	0.18	0.77
5	1.7	2.6	**9**	1.1	1.5
6	2.5	0.16	**10**	2.2	1.4

[a] Relative activity = IC_{50}(artemisinin)/IC_{50}(analogue).

Table 2. Relative Antimalarial Activities against Two *P. falciparum* Clones

	relative activity[a]			relative activity[a]	
compd	W-2	D-6	compd	W-2	D-6
12α	1.0	0.98	**15**α	1.0	1.6
12β	1.7	1.7	**15**β	5.4	6.8
13α	3.6	2.2	**16**	1.3	1.0
13β	4.8	5.8	**17**	2.1	1.8
14α	1.7	2.2	**18**	1.4	1.1
14β	2.3	1.4	**19**α	2.4	3.1
			19β	3.1	2.5

[a] Relative activity = IC_{50}(artemisinin)/IC_{50}(analogue).

Experimental Section

All spectra were recorded in solution in $CDCl_3$ at 300 MHz for ^{1}H, 75 MHz for ^{13}C, and 282 MHz for ^{19}F, on a Varian Gemini-300 NMR spectrometer. Chemical shifts were measured in ppm (δ) relative to $CDCl_3$ (δ, 7.27 ppm) for ^{1}H, relative to $CDCl_3$ (δ, 77.23 ppm) for ^{13}C, and relative to CF_3COOH (δ, 0.00 ppm) for ^{19}F, and coupling constants (J) are in hertz (Hz). The following abbreviations are used to describe the signal multiplicities: s (singlet), d (doublet), t (triplet), q (quadruplet), and m (multiplet). CI-MS were determined on a Finnigan 4600 mass spectrometer. Micro analyses were performed by Atlantic Microlab, Inc., Norcross, GA. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F 254 TLC plates and Merck silica gel 60 (230−400 mesh) was used for flash chromatography.

Dihydroartemisinin Acetate, 2. Artemisinin (565 mg, 2 mmol) was added to a 50-mL flame-dried three-necked flask equipped with a thermometer and N_2 inlet followed by 15 mL of dry CH_2Cl_2. DIBAL (1.5 M in toluene, 1.6 mL, 2.4 mmol) was added dropwise at −78 °C under N_2. TLC showed no starting material after 2 h. Pyridine (0.5 mL, 6 mmol), DMAP (292 mg, 2.4 mmol) and finally Ac_2O (0.76 mL, 8 mmol) were added. The reaction was stirred at −78 °C for 3 h and slowly warmed to room temperature overnight. The reaction was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was dried, concentrated and the residue was purified by flash chromatography on silica gel to give 620 mg of white solid: yield 96%; ^{1}H NMR 5.79 (1H, d, J = 9.9 Hz), 5.44 (1H, s), 2.62−2.5 (1H, m), 2.43−2.3 (1H, m), 2.13 (3H, s), 2.1−1.1 (9H, m), 1.44 (3H, s), 1.13 (9H, s), 1.1−0.9 (1H, m), 0.96 (3H, d, J = 6 Hz), 0.85 (3H, d, J = 6.9 Hz); ^{13}C NMR 170.24, 104.73, 92.11, 91.74, 80.33, 51.73, 45.42, 37.4, 36.37, 34.24, 31.88, 26.11, 24.71, 22.10, 21.25, 20.34, 12.14; CI-MS (NH_3) 344 (M + NH_4^+).

General Procedure for Acid-Catalyzed Additions of Silyl Enol Ethers to 2. To a solution of **2** in acetonitrile was added the silyl enol ether followed by titanium tetrachloride at −40 °C under N_2. The solution was stirred for several hours and quenched with dilute aqueous HCl. The mixture was extracted with CH_2Cl_2. The organic layer was washed with aqueous sodium bicarbonate and brine, dried over $NaSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel.

10-(3,3-Dimethyl-2-oxobutyl)deoxoartemisinin, 3. This compound was obtained in 67% yield from the above reaction as a white solid: ^{1}H NMR 5.25 (1H, s), 4.88 (1H, dt, J = 5.7, 6.6 Hz), 2.89 (1H, dd, J = 6.6, 17.4 Hz), 2.72 (1H, m), 2.5 (1H,

dd, J = 5.7, 17.4 Hz), 2.29 (1H, dt, J = 3.9, 13.8 Hz), 2.04−1.85 (2H, m), 1.82−1.72 (1H, m), 1.7−1.56 (2H, m), 1.5−1.1 (4H, m), 1.38 (3H, s), 1.13 (9H, s), 1.0−0.86 (1H, m), 0.93 (3H, d, J = 5.7 Hz), 0.78 (3H, d, J = 7.8 Hz); ^{13}C NMR 219.53, 108.8, 95.07, 86.34, 75.71, 57.46, 49.56, 49.5,42.81, 41.81, 39.67, 34.88, 34.76, 31.64, 31.12, 29.93, 29.87, 25.26, 18.0; CI-MS (NH_3) 384 (M + NH_4^+). Anal. ($C_{21}H_{34}O_5$) C, H.

10-(2-Oxoethyl)deoxoartemisinin, **4.** This compound was prepared in 30% yield using the above general procedure: ^{1}H NMR 9.8 (1H, s), 5.32 (1H, s), 4.97 (1H, m), 2.8−2.6 (2H, m), 2.5−2.3 (2H, m), 2.14−1.9 (2H, m), 1.9−1.6 (3H, m), 1.44−1.2 (4H, m), 1.41 (3H, s), 1−0.8 (1H, m), 0.97 (3H, d, J = 6.3 Hz), 0.87 (3H, d, J = 7.2 Hz); ^{13}C NMR 202.3, 103.45, 89.56, 81.12, 69.58, 52.28, 46.02, 44.57, 44.01, 37.58, 36.61, 34.49, 29.87, 26.05, 24.83, 20.16, 13.06; CI-MS (NH_3) 328 (M + NH_4^+); HRMS (EI) calcd for $C_{17}H_{26}O_5$ m/z 310.1780, found 310.1784.

10-(2-Oxopropyl)deoxoartemisinin, **5.** This material was prepared in 55% yield by the above general procedure: ^{1}H NMR 5.291 (1H, s), 4.87 (1H, ddd, J = 3.9, 6, 9.9 Hz), 2.71 (1H, dd, J = 9.9, 15.6 Hz), 2.67 (1H, m), 2.43 (1H, dd, J = 3.9, 15.6 Hz), 2.3 (1H, dt, J = 3.9, 13.5 Hz), 2.23 (3H, s), 2.05−1.86 (2H, m), 1.81−1.59 (3H, m), 1.38 (3H, s), 1.46−1.18 (4H, m), 1−0.8 (1H, m), 0.95 (3H, d, J = 6 Hz), 0.83 (3H, t, J = 7.8 Hz); ^{13}C NMR 208.31, 103.70, 90.22, 81.60, 70.73, 52.64, 45.84, 44.51, 38.07, 37.10, 34.91, 33.48, 30.36, 26.41, 25.32, 25.20, 20.58, 13.30; CI-MS (NH_3) 342 (M + NH_4^+). Anal. ($C_{18}H_{28}O_5$) C, H.

10-(2-Oxo-2-phenylethyl)deoxoartemisinin, **6.** This compound was obtained in 72% yield using the general procedure: ^{1}H NMR 8−7.95 (2H, m), 7.6−7.42 (3H, m), 5.35 (1H, s), 5.1 (1H, dt, J = 6, 8.1 Hz), 3.3 (1H, dd, J = 8.1, 15.6 Hz), 3.12 (1H, dd, J = 6, 15.6 Hz), 2.81 (1H, m), 2.31 (1H, m), 2.08−1.6 (5H, m), 1.46−1.2 (4H, m), 1.31 (3H, s), 0.9−0.8 (1H, m), 0.97 (3H, d, J = 5.7 Hz), 0.9(3H, d, J = 7.8 Hz); ^{13}C NMR 198.54, 137.34, 133.27, 128.84, 128.59, 103.22, 89.8, 81.06, 70.43, 52.22, 44.26, 40.32, 37.64, 36.67, 34.55, 29.99, 25.87, 20.22, 13.06; CI-MS (NH_3) 404 (M + NH_4^+). Anal. ($C_{23}H_{30}O_5$) C, H.

10-(2-Oxocyclopentyl)deoxoartemisinin, **7.** This compound was obtained in 79% yield using the general procedure: ^{1}H NMR 5.27 (1H, s), 4.73 (1H, t, J = 7 Hz), 2.61 (1H, m), 2.4−2.12 (5H, m), 2.1−1.9 (4H, m), 1.82−1.6 (5H, m), 1.4−1.1 (3H, m), 1.38 (3H, s), 1−0.85 (1H, m), 0.94 (3H, d, J = 6 Hz), 0.93 (3H, d, J = 8 Hz); ^{13}C NMR 219.42, 102.37, 90.95, 81.18, 70.86, 51.57,50.39, 43.47, 38.62, 37.71, 36.73, 34.43, 30.6, 26.84, 25.08, 24.96, 20.83, 13.3; CI-MS (NH_3) 368 (M + NH_4^+). Anal. ($C_{20}H_{30}O_5$) C, H.

10-(5-Oxo-2,5-dihydrofuran-2-yl)deoxoartemisinin, **8.** This compound was obtained in 60% yield employing the general procedure: ^{1}H NMR 7.81 (1H, d, J = 6 Hz), 6.16 (1H, dd, J = 2.4, 6 Hz), 5.34 (1H, s), 5.02 (1H, dd, J = 2.4, 9.9 Hz), 4.30 (1H, dd, J = 6, 9.9 Hz), 2.66 (1H, m), 2.82 (1H, m), 2.06−1.92 (2H, m), 1.9−1.78 (2H, m), 1.74−1.64 (1H, m), 1.4−1.16 (4H, m), 1.33 (3H, s), 1.11 (3H, d, J = 7.8 Hz), 1−0.8 (1H, m), 0.97 (3H, d, J = 5.7 Hz); ^{13}C NMR 173.46, 157.56, 121.79, 102.61, 90.95, 81.78, 81.18, 73.16, 51.61, 43.11, 37.64, 36.49, 34.31, 29.75, 25.81, 25.01, 25.01, 19.98, 11.90; CI-MS (NH_3) 368 (M + NH_4^+). Anal. ($C_{19}H_{25}O_6$) C, H.

10-Cyanodeoxoartemisinin, 9. To a solution of **2** (220 mg, 0.67 mmol) in acetonitrile, was added trimethylsilyl cyanide (200 mg, 2 mmol) followed by the solution of titanium tetrachloride in CH_2Cl_2 (1.3 mL, 1.3 mmol) at −40 °C under N_2. The reaction mixture was stirred for 3 h, then 10% HCl was added. The mixture was extracted with CH_2Cl_2; the organic phase was washed with water and saturated $NaHCO_3$ solution, dried and concentrated. The residue was purified by chromatography on silica gel to give 150 mg of white solid: 76% yield; ^{1}H NMR 5.53 (1H, s), 4.77 (1H, d, J = 6 Hz), 2.89 (1H, m), 2.38 (1H, dt, J = 3.9, 13.5 Hz), 2.1−1.2 (9H, m), 1.43 (3H, s), 1.07 (3H, d, J = 6.6 Hz), 1.05−0.85 (1H, m), 0.98 (3H, d, J = 6 Hz); ^{13}C NMR 118.7, 105.4, 91.07, 80.87, 66.42, 52.94, 45.05, 37.71, 36.55, 34.73, 29.51, 26.35, 25.02, 22.47, 20.71, 13.6; CI-MS (NH_3) 311 (M + NH_4^+). Anal. ($C_{16}H_{23}NO_4$) C, H, N.

10-(6-Oxotetrahydropyran-2-yl)deoxoartemisinin, **10.** To a 25-mL flask were added 35 mg of compound **7** (0.1 mmol) and 5 mL CH_2Cl_2, followed by $NaHCO_3$ (25 mg, 0.3 mmol). The mixture was cooled to 0 °C and mCPBA (67 mg, 0.3 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 3 h. Water was added to the mixture which was then extracted with CH_2Cl_2. The organic layer was separated and washed with brine, dried and concentrated. The residue was purified by flash chromatography on silica gel to afford 28 mg (77% yield) of **10** as a white solid: ^{1}H NMR 5.32 (1H, s), 4.53 (1H, dd, J = 5.7, 8.7 Hz), 4.4 (1H, dt, J = 3.9, 8.7 Hz), 2.7−2.46 (3H, m), 2.35−2.15 (2H, m), 2.1−1.5 (8H, m), 1.4−1.1 (4H, m), 1.39 (3H, s), 1.0−0.8 (1H, m), 1.02 (3H, d, J = 7.8 Hz), 0.97 (3H, d, J = 5.1 Hz); ^{13}C NMR 171.52, 102.30, 91.13, 81.42, 78.50, 72.01, 51.61, 42.86, 37.64, 36.55, 34.30, 29.99, 28.96, 25.93, 25.26, 25.14, 24.95, 19.98, 17.67, 11.35; CI-MS (NH_3) 3874 (M + NH_4)$^+$. Anal. ($C_{20}H_{30}O_6$) C, H.

General Procedure for the Reaction of 4 with Grignard Reagent. To a solution of **4** in THF was added the appropriate Grignard reagent (2 equiv) at 0 °C under N_2. The solution was kept at 0 °C and monitored by TLC. After the starting material disappeared, the reaction was quenched with saturated aqueous NH_4Cl. The mixture was extracted with ether, and the organic layer was washed with brine, dried over $NaSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel.

The reaction of **4** with methylmagnesium bromide yielded the less polar isomer **12**α: 62% yield; ^{1}H NMR 5.38 (1H, s), 4.52 (1H, dd, J = 6.3, 8.4 Hz), 4.1−3.9 (1H, m), 3.64 (1H, br), 2.6−2,58 (1H, m), 2.4−2.2 (1H, m), 2.1−1.6 (6H, m), 1.5−1.1 (5H, m), 1.40 (3H, s), 1.21 (3H, d, J = 6 Hz), 1.0−0.8 (1H, m), 0.97 (3H, d, J = 5.7 Hz), 0.86 (3H, d, J = 7.5 Hz); ^{13}C NMR 103.27, 89.43, 81.12, 75.89, 69.37, 52.22, 43.96, 38.13, 37.5, 36.56, 34.43, 30.61, 25.99, 24.81, 23.39, 20.16, 12.76; CI-MS (NH_3) 344 (M + NH_4)$^+$. Anal. ($C_{18}H_{30}O_5$) C, H.

The more polar isomer, **12**β, was also isolated: 36% yield; ^{1}H NMR 5.29 (1H, s), 4.57 (1H, ddd, J = 2.1, 6.3, 11.4 Hz), 4.06 (1H), 2.66−2.56 (1H, m), 2.48 (1H, br), 2.30 (1H, dt, J = 3.3, 13.8 Hz), 2.1−1.1 (11H, m), 1.39 (3H, s), 1.24 (3H, d, J = 6.6 Hz), 1−0.8 (1H, m), 0.94 (3H, d, J = 5.4 Hz), 0.84 (3H, d, J = 7.8 Hz); ^{13}C NMR 103.26, 89.55, 81.21, 71.24, 65.67, 52.32, 42.30, 37.76, 37.65, 36.72, 34.55, 30.31, 26.18, 24.96, 24.91, 20.29, 12.99; CI-MS (NH_3) 344 (M + NH_4)$^+$. Anal. ($C_{18}H_{30}O_5$) C, H.

Reaction of **4** with ethylmagnesium bromide yielded **13**α: 50% yield; ^{1}H NMR 5.38 (1H, s), 4.52 (1H, ddd, J = 4.8, 6.3, 11.4 Hz), 3.74 (2H, m), 2.62 (1H, m), 2.32 (1H, dt, J = 3.6, 13.5 Hz), 2.1−1.1 (13H, m), 1.40 (3H, s), 1.0−0.8 (1H, m), 0.97 (3H, d, J = 6 Hz), 0.96 (3H, t, J = 7.5 Hz), 0.87 (3H, d, J = 7.8 Hz); ^{13}C NMR 103.24, 89.40, 81.12, 76.11, 74.62, 52.22, 43.99, 37.50, 36.53, 35.78, 34.43, 30.67, 30.15, 25.99, 24.78, 20.16, 12.76, 9.87; CI-MS (NH_3) 358 (M + NH_4)$^+$. Anal. ($C_{19}H_{32}O_5$) C, H.

The more polar **13**β was also obtained: 29% yield; ^{1}H NMR 5.32 (1H, s), 4.61 (1H, ddd, J = 2.4, 6.3, 11.7 Hz), 3.83−3.75 (1H, m), 2.63 (1H, m), 2.32 (1H, dt, J = 3.9, 14.4 Hz), 2.4−2.2 (1H, br), 2.1−1.1 (13H, m), 1.40 (3H, s), 1.0−0.8 (1H, m), 0.97 (3H, d, J = 6 Hz), 0.958 (3H, t, J = 7.5 Hz), 0.957 (3H, d, J = 5.4 hz), 0.86 (3H, d, J = 7.8 Hz); ^{13}C NMR 103.40, 89.71, 81.30, 71.25, 70.92, 52.37, 44.12, 37.63, 36.77, 35.65, 34.53, 33.34, 30.46, 26.04, 25.07, 24.89, 20.44, 14.39, 12.84; CI-MS (NH_3) 358 (M + NH_4)$^+$. Anal. ($C_{19}H_{32}O_5$) C, H.

The reaction of **4** with isopropylmagnesium chloride yielded **14**α**:** 30% yield; ^{1}H NMR 5.37 (1H, s), 4.5 (1H, m), 3.72 (1H, br), 3.59 (1H, m), 2.66−2.58 (1H, m), 2.32 (1H, dt, J = 3.9, 13.2 Hz), 2.1−1.1 (12H, m), 1.40 (3H, s), 1−0.8 (1H, m), 0.96 (3H, d, J = 6.6 Hz), 0.94 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 6.9 Hz), 0.87 (3H, d, J = 7.5 Hz); ^{13}C NMR 103.27, 89.49, 81.18, 78.23, 76.38, 52.25, 43.99, 37.56, 36.59, 34.46, 32.79, 30.85, 26.05, 24.90, 24.84, 20.20, 18.62, 17.74, 12.79; CI-MS (NH_3) 372 (M + NH_4)$^+$. Anal. ($C_{20}H_{34}O_5$) C, H.

The more polar isomer **14**β was also obtained: 14% yield; ^{1}H NMR 5.31 (1H, s), 4.59 (1H, ddd, J = 2.1, 6, 11.4 Hz), 3.7−

3.58 (1H, m), 2.74−2.6 (1H, m), 2.44−1.2 (14H, m), 1.42 (3H, s), 1−0.8 (1H, m), 0.973 (3H, d, J = 6.9 Hz), 0.969 (3H, d, J = 4.8 hz), 0.92 (3H, d, J = 6.9 Hz), 0.88 (3H, d, J = 7.5 Hz); ^{13}C NMR 103.37, 89.61, 81.27, 73.92, 71.46, 52.40, 44.39, 37.65, 36.71, 34.52, 33.55, 33.10, 30.30, 26.17, 24.39, 24.84, 20.23, 19.04, 18.13, 12.97; CI-MS (NH_3) 372 $(M + NH_4)^+$. Anal. ($C_{20}H_{34}O_5$) C, H.

Reaction of **4** with *tert*-butylmagnesium chloride yielded **15**α**:** 20% yield; ^{1}H NMR 5.35 (1H, s), 4.51 (1H, q, J = 6 Hz), 3.81 (1H, s), 3.41(1H, dd, J = 4.5, 6.6 Hz), 2.67−2.55 (1H, m), 2.30 (1H, dt, J = 3.9, 13.8 Hz), 2.1−1.1 (11H, m), 1.38 (3H, s), 1−0.8 (1H, m), 0.95 (3H, d, J = 5.7 Hz), 0.90 (9H, s), 0.86 (3H, d, J = 7.5 Hz); ^{13}C NMR 103.24, 89.46, 81.46, 81.15, 76.81, 52.29, 44.05, 37.66, 36.65, 34.91, 34.55, 31.03, 30.66, 26.15, 26.05, 25.02, 24.92, 20.30, 12.92; CI-MS (NH_3) 386 $(M + NH_4)^+$. Anal. ($C_{21}H_{36}O_5$) C, H.

The more polar isomer was also obtanined: 13% yield; ^{1}H NMR 5.26 (1H, s), 4.52−4.47 (1H, m), 3.59 (1H, d, J = 10.5 Hz), 2.75−2.68 (1H, m), 2.33 (1H, dt, J = 3.6, 14.1 Hz), 2.1−1.1 (12H, m), 1.42 (3H, s), 1−0.8 (1H, m), 0.96 (3H, d, J = 5.1 Hz), 0.91 (9H, s), 0.87 (3H, d, J = 7.2 Hz); ^{13}C NMR 103.46, 89.38, 81.26, 75.61, 71.99, 52.59, 44.68, 37.75, 36.78, 34.84, 34.67, 30.63, 30.25, 26.43, 25.99, 25.21, 24.89, 20.39, 13.34; CI-MS (NH_3) 386 $(M + NH_4)^+$; HRMS (FAB) calcd for $C_{21}H_{37}O_5$ $(M^+ + 1)$ m/z 269.2641, found 269.2649.

10-(2-Oxobutyl)deoxoartemisinin, 16, was afforded in 86% yield by oxidation of **13**α and **13**β in acetone with Jones reagent: ^{1}H NMR 5.28 (1H, s), 4.86 (1H, ddd, J = 3.9, 6, 9.9 Hz), 2.75−2.5 (6H, m), 2.1−1.6 (5H, m), 1.5−0.9 (4H, m), 1.38 (3H, s), 1.04 (3H, d, J = 7.2 Hz), 1−0.8 (1H, m), 0.94 (3H, d, J = 5.7 Hz), 0.84 (3H, d, J = 7.5 Hz); ^{13}C NMR 210.09, 103.21, 89.65, 81.09, 70.43, 52.16, 40.08, 37.59, 36.62, 35.86, 34.46, 30.03, 25.96, 24.84, 24.72, 20.16, 12.88, 7.63; CI-MS (NH_3) 356 $(M + NH_4)^+$. Anal. ($C_{19}H_{30}O_5$) C, H.

10-(3-Methyl-2-oxobutyl)deoxoartemisinin, 17, was obtained in 86% yield by oxidation of **14**α and **14**β in acetone with Jones reagent: ^{1}H NMR 5.30 (1H, s), 4.89 (1H, ddd, J = 4.5, 6.3, 10.8 Hz), 2.8 (1H, dd, J = 9, 15.9 Hz), 2.8−2.68 (2H, m), 2.53 (1H, dd, J = 4.5, 15.9 Hz), 2.33 (1H, m), 2.1−1.6 (5H, m), 1.5−0.9 (4H, m), 1.40 (3H, s), 1.11 (6H, d, J = 7.5 Hz), 1−0.8 (1H, m), 0.97 (3H, d, J = 5.7 Hz), 0.84 (3H, d, J = 7.5 Hz); ^{13}C NMR 213.0, 103.21, 89.65, 81.02, 70.37, 52.19, 44.14, 41.99, 40.50, 37.62, 36.62, 34.49, 29.91, 25.93, 24.84, 24.75, 20.16, 18.29, 18.16, 12.91; CI-MS (NH_3) 370 $(M + NH_4)^+$. Anal. ($C_{20}H_{32}O_5$) C, H.

10-(*trans*-3-Ethyl propenoate)deoxoartemisinin, 18. To a solution of **4** (45 mg, 0.15 mmol) in THF was added (carbethoxymethylene)triphenylphosphorane (110 mg, 0.3 mmol) at room temperature. After stirring for 6 h, no starting material remained. The mixture was concentrated and residue was purified by flash chromatography on silica gel to afford 44 mg (80% yield) of **18** as an oil: ^{1}H NMR 7.04 (1H, td, J = 6.9, 15.6 Hz), 5.98 (1H, d, J = 16.5 Hz), 5.33 (1H, s), 4.48 (1H, ddd, J = 3.9, 6.9, 9.6 Hz), 4.18 (2H, q, J = 7.8 Hz), 2.7−2.3 (4H, m), 2.1−1.6 (5H, m), 1.5−1.2 (4H, m), 1.43 (3H, s), 1.28 (3H, t, J = 7.8 Hz), 1−0.8 (1H, m), 0.97 (3H, d, J = 6 Hz), 0.89 (3H, d, J = 7.8 Hz); ^{13}C NMR (75 Hz, CDCl3) δ 166.78, 146.75, 122.95, 103.22, 89.68, 61.18, 72.98, 60.17, 52.22, 44.02, 37.52, 36.61, 34.43, 32.91, 30.30, 25.93, 24.89, 24.77, 20.16, 14.27, 12.69; CI-MS (NH_3) 398 $(M + NH_4)^+$. Anal. ($C_{21}H_{32}O_6$) C, H.

10-(3,3,3-Trifluoro-2-hydroxypropyl)deoxoartemisinin, 19. To a 50-mL flask were added 217 mg (7 mmol) of **4**, THF (15 mL), a solution of trimethyl(trifluromethyl)silane in THF (0.5 M, 2.8 mL, 1.4 mmol) followed by the solution of tetrabutylammonium fluoride in THF (1 M, 0.035 mL, 0.035 mmol). The mixture was stirred for 1 h at room temperature, dilute HCl was added and the mixture was stirred for another hour. The solution was extracted with ether and the organic layer washed with brine, dried, and concentrated. The residue was purified by flash chromatography on silica gel to afford **19**α, as a white solid: 53% yield; ^{1}H NMR 5.37 (1H, s), 4.72 (1H, ddd, J = 10.8, 6.3, 5.4 Hz), 4.29 (1H, s, OH), 4.2 (1H, m), 2.59 (1H, m), 2.32 (1H, m), 2.1−1.6 (7H, m), 1.5−1.1 (4H, m), 1.40 (3H, s), 1.0−0.8 (1H, m), 0.97 (3H, d, J = 5.7 Hz), 0.89 (3H, d, J = 7.5 Hz); ^{19}F NMR −4.57 (d, J = 6.6 Hz); ^{13}C NMR 124.96 (q, J = 280 Hz), 103.21, 89.98, 81.09, 73.77, 71.95 (q, J = 32 Hz), 51.95, 43.42, 37.59, 36.50, 34.31, 30.76, 29.82, 25.87, 24.84, 20.04, 12.18; CI-MS (NH_3) 398 $(M + NH_4)^+$. Anal. ($C_{18}H_{27}F_3O_5$) C, H.

The more polar **19**β was obtained as a white solid: 38% yield; ^{1}H NMR 5.30 (1H, s), 4.59 (1H, m), 4.28 (1H, m), 3.42 (1H, d, J = 6 Hz), 2.73 (1H, m), 2.33 (1H, m), 2.1−1.6 (7H, m), 1.5−1.1 (4H, m), 1.41 (3H, s), 1.0−0.8 (1H, m), 0.97 (3H, d, J = 5.7 Hz), 0.89 (3H, d, J = 7.5 Hz); ^{19}F NMR −3.62 (d, J = 2.5 Hz); ^{13}C NMR 125.78 (q, J = 280 Hz), 103.70, 89.37, 81.09, 70.28, 67.67 (q, J = 32 Hz), 52.31, 44.23, 37.56, 36.59, 34.43, 29.79, 29.24, 25.93, 24.87, 24.75, 20.16, 12.88; CI-MS (NH_3) 398 $(M + NH_4)^+$. Anal. ($C_{18}H_{27}F_3O_5$) C, H.

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