Synthesis and Antimalarial Activities of Several Fluorinated Artemisinin Derivatives

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The carbonyl groups in several artemisinin derivatives were converted into geminal difluorinated compounds on treatment with diethylaminosulfur trifluoride. A number of other mono- and polyfluorinated artemisinin derivatives were prepared. Their *in vitro* antimalarial activities were all equal to or greater than the nonfluorinated analogs or precursors.

Introduction

The discovery by Chinese investigators that artemisinin, **1** (Chart 1), an active principle of *Artemisia annua*, could be used to treat patients with cerebral malaria (an otherwise fatal condition) as well as those infected with drug-resistant strains of *Plasmodium falciparum* prompted a search for new longer acting derivatives.[1] The overwhelming majority of artemisinin derivatives synthesized to date have been prepared by reducing the lactone in **1** to a hemiacetal, followed by converting the free hydroxyl group into a series of ethers, esters, carbonates, *etc.*[2] These derivatives are believed to be pro-drugs for dihydroartemisinin, **2**, since they are readily converted into **2** by enzymes present in the liver.[3] In a review of the chemistry, pharmacology, and clinical applications of artemisinin derivatives, Luo and Shen[2a] reported that several fluorinated dihydroartemisinin derivatives were 2–3 times more active than artemether, **3**, and arteether, **4**. Posner et al.[2b] reported that a *p*-fluorobenzyl ether of a synthetic 1,2,4-trioxane exhibited twice the antimalarial activity of the corresponding hydrogen analog. Artemether and arteether are approximately 5 times more active than **1**. Although the increased activities of the reported artemisinin derivatives may simply be related to their rates of conversion into **2**, we were interested in following up these observations of increased activity.

A second motive for preparing a variety of fluorinated artemisinin derivatives is to take advantage of progress in the use of fluorinated compounds for *in vivo* imaging, as well as for obtaining subcellular images. Adovelande *et al.*[4a] recently described their use of scanning ion microscopy and mass spectrometry to detect and map the distribution of mefloquine, a fluorinated antimalarial drug, in normal and *P. faliparum* infected red blood cells. Positron emission tomography (PET) techniques[4b] with ^{18}F could be employed to map the *in vivo* distribution of artemisinin derivatives in organs and tissues. Related information previously required an investigator to sacrifice the animal and to measure the quantity of the drug present in each organ. A recent paper[4b] also described progress on the use of ^{19}F NMR spectroscopy for imaging. By combining the data from several imaging techniques, it will be possible to determine the distribution of an antimalarial drug in different organs and cells and possibly to distinguish drugs that bind to macromolecules from those that are free in solution. We report here the preparation and testing of several different fluorinated artemisinin derivatives.

In an effort to prevent some metabolic oxidations, e.g., hydroxylation, we introduced fluorine atoms at positions where hydroxylation was known to occur.[3,5] Several polyfluorinated derivatives were also prepared to effect larger changes in the solubility characteristics of these derivatives than had previously been observed for monofluorinated derivatives. In addition, two carbonyl-containing arteethers and two 12β-alkyldeoxoartemisinin derivatives[6] were reacted with diethylaminosulfur trifluoride (DAST) in order to replace the carbonyl groups by geminal difluoro groups.[7]

Results and Discussion

As part of a study on microbially-mediated oxidation of arteether,[5] we obtained the 9α-hydroxyl and 14-hydroxyl derivatives in sufficient quantities to employ them as intermediates for the preparation of fluorinated compounds. The hydroxyl groups were oxidized to the corresponding aldehyde, **6**, or ketone, **7**, with catalytic quantities of tetra-*n*-propylammonium perruthenate (TPAP) in the presence of excess *N*-methylmorpholine *N*-oxide.[5] Since the peroxide moiety in artemisinin is required for antimalarial activity and is sensitive to acid and base,[2] it was uncertain whether the peroxide would survive under the reaction conditions. On reaction with DAST, **6** and **7** were converted into the corresponding geminal difluoro derivatives, **8** and **9**. In addition to **9**, a monofluoro olefin **10** was obtained from **7** on reaction with DAST. The structural assignments are consistent with their ^{1}H and ^{13}C NMR spectra (a table of the ^{13}C assignments is available as supporting information) and supported by mass spectrometric data. The successful transformations of **6** and **7** into the corresponding geminal difluorinated derivatives demonstrate that the critical peroxide group is unaffected during the reaction and workup. We therefore treated two 12β-alkyldeoxoartemisinin derivatives (**11** and **12**) with DAST. Both compounds had been prepared as part of another study.[6] On reaction with DAST each was converted into the corresponding geminal difluoro derivatives, **13** and **14**, respectively. A fluorinated dihy-

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Chart 1

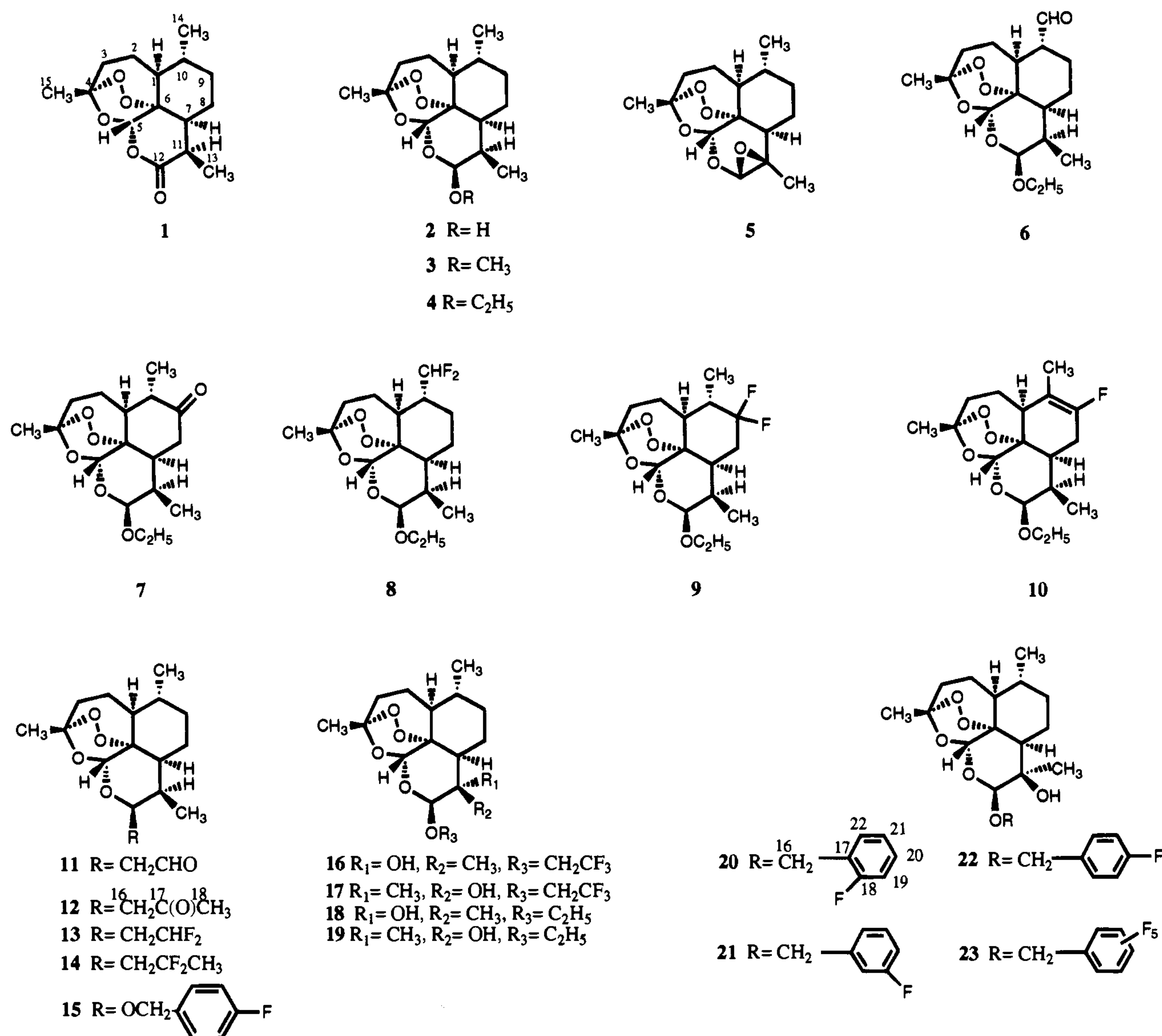

Table 1. *In Vitro* Data for Two Drug-Resistant Strains of *P. falciparum*

	W-2		D-6	
compound	IC_{50} 1/cpd	IC_{50} 4/cpd	IC_{50} 1/cpd	IC_{50} 4/cpd
6	1.4	0.8	1.2	0.1
7	1.2	0.6	0.5	0.05
8	2	1.5	1	0.3
9	1.2	0.8	1.4	0.5
10	0.5	0.3	0.6	0.2
13	1.1	0.73	3.8	1.3
14	0.5	0.3	1.2	0.4
16	1.5		1.8	
17	0.14		0.15	
18	0.3		0.45	
19	0.06		0.08	

Table 2. *In Vitro* Data for a Drug-Resistant Strain of *P. Falciparum* (FCR3)

compound	IC_{50} 1/compound
15	0.04
20	0.11
21	0.11
22	0.10
23	0.10

droartemisinin ether, **15**, was prepared by treating **2** with boron trifluoride etherate and *p*-fluorobenzyl alcohol. The 12β-trifluoroethyl ethers of 11α- (**16**) and 11β-hydroxydihydroartemisinin (**17**) were also prepared and their antimalarial activities compared to those of the corresponding ethyl ethers. Several fluorinated ethers (**20**–**23**) were prepared from the reaction of the 11,12β-oxirane **5** with substituted benzyl alcohols. The ^{13}C spectral assignments are available as supporting information. The antimalarial activities of the compounds are given in Tables 1 and 2.

One purpose of this study was to determine how changes associated with the presence of one or more fluorine atoms on the artemisinin skeleton, as well as on alkyl or aryl groups at C-12, altered the physical and/or chemical characteristics of these sesquiterpene derivatives to affect their antimalarial activities. The antimalarial activities of these derivatives were evaluated in two different laboratories. Since there were differences between the strains of *P. falciparum* employed in each laboratory, we chose to employ a ratio of the activities of each compound relative to that of artemisinin and arteether to evaluate the derivatives. Similar ratios have been employed by others[8] to mini-

mize differences in the conditions of the parasite that are difficult to control during testing. A comparison of the activities of the carbonyl derivatives **6** and **7** with the corresponding geminal difluoro derivatives (Table 1) shows that the latter compounds are slightly more active. This increase in activity is consistent with earlier observations[9] that lipophilic derivatives are more active than their more polar counterparts; *i.e.*, esters and ethers are more active than the corresponding alcohols or acids.

A comparison of the relative activities of **16** and **17** (Table 1) shows that derivatives with an 11α-hydroxyl group are more active than those with an 11β-substituted group. Pu et al.[10] reported that 11β-hydroxyarteether (**19**) was approximately 5 times less active than the 11α-isomer (**18**). An estimate of the consequences of introducing fluorine atoms into these molecules can also be made from a comparison of the activities of **16** and **18**, as well as **17** and **19**. Those comparisons show that there is a 2–5-fold increase in activity upon introduction of fluorine into these molecules. The magnitude of the effect is similar to that observed from an analysis of the data given by Luo and Shen[2a] and Posner et al.[2b]

An examination of the differences between mono- and polyfluorinated aromatic or heterocyclic derivatives given in Table 2 indicates that other structural differences are more important than the number of fluorine atoms in the molecule. The compounds in Table 2 were screened against *P. falciparum* strain FCR3 using a previously published[11] modification of the method of Desjardins et al.[12] In general, the ratios of the activities of **1** to the different fluorinated compounds were less than 1.0; *i.e.*, the compounds were less active than artemisinin or arteether. The ratio was greater than 1 for several compounds, *i.e.*, **8**, **9**, **13**, and **16**. However, the increase was not large enough to warrant preparing the quantities of each compound required for *in vivo* testing.

Conclusion

The finding that a variety of carbonyl derivatives can be converted into the corresponding geminal difluoro derivatives without destroying the critical peroxide grouping is important and should assist investigators that wish to prepare fluorinated artemisinin derivatives. Although we did not encounter an exceptionally large increase in antimalarial activity by introducing one or more fluorine atoms into these compounds, a several fold increase in antimalarial activity was observed. These results should be considered in optimizing the antimalarial activity of new derivatives.

Experimental Section

Melting points were determined on a Reichert melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Varian Gemini 300 spectrometer, in $CDCl_3$ solutions. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane used as an internal standard for ^{1}H NMR or hexafluorobenzene (δ = 0) for ^{19}F NMR. CI-MS analyses were performed on a Finnigan 4600 mass spectrometer. IR spectra were obtained from neat films on a Perkin-Elmer BIO-Rad FTS-45 spectrophotometer. Optical rotations were measured at 589 nm on a Perkin-Elmer 241 MC polarimeter. Thin-layer analyses were performed on EM silica gel 60 F-254 plates. Radial dispersion chromatography (RDC) was performed on a Chromatotron (Harrison Research, Palo Alto, CA) using 1- or 2-mm silica gel coated plates, and TLC-grade silica gel (cat. no. 10050) was purchased from Analtech, Neward, DE 19713. All reagents were purchased from the Aldrich Chemical Co., Milwaukee, WI, and used without further purification, unless otherwise noted. Dichloromethane was dried over P_2O_5 and distilled prior to use.

Only milligram quantities of most of the starting materials were available for these studies. They and their fluorinated derivatives were purified by chromatography. Their identities and purities were established by CI-MS under conditions where the presence of other artemisinin derivatives would have been detected. Their ^{1}H and ^{13}C NMR did not show the presence of impurities.

14,14-Difluoroartheether (8). 14-Hydroxyartheether[5] (30 mg, 0.091 mmol) was converted to aldehyde **6**[5] (14 mg) in 45% yield. The aldehyde was dissolved in dry dichloromethane (2 mL), cooled to 0 °C and treated with DAST (40 μL). The solution was stirred for 1 h at 0 °C and added to water (2 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated. The reaction mixture was purified by preparative TLC on four 5 × 10 cm silica gel plates (0.25 mm) using hexane/$CHCl_3$/ether (50:50:1) to yield **8** (9.3 mg, 63%) as a white solid: mp 94–96 °C; $[\alpha]^{25}_D$ +110° (c 0.25, $CHCl_3$), +105° (c 0.25, EtOH); ^{1}H NMR δ 0.93 (3H, d, *J* = 7.3 Hz, H-13), 1.19 (3H, t, *J* = 7.1 Hz, H-17), 1.46 (3H, s, H-15), 1.2–1.9 (9H, m), 2.08 (1H, m), 2.38 (1H, m), 2.64 (1H, m, H-11), 3.48 (1H, dq, *J* = 9.7, 7.1 Hz, H-16a), 3.86 (1H, dq, *J* = 9.7, 7.1 Hz, H-16b), 4.80 (1H, d, *J* = 3.2 Hz, H-12), 5.39 (1H, s, H-5), 5.90 (1H, dt, *J* = 56.0, 1.9 Hz, H-14); ^{19}F NMR ($CDCl_3$) δ −112.1 (1F, ddd, *J* = 7.6, 56.1, 282 Hz), −116.5 (1F, ddd, *J* = 22, 57, 282 Hz); ^{13}C NMR data are available as supporting information; CI-MS (NH_3) 366 (29%, M + NH_4^+), 320 (100%), 303 (49%).

9,9-Difluoroarteether (9). To a solution of **7**[5] (12 mg) in CH_2Cl_2 (2.0 mL) was added DAST (0.2 mL), and the solution was stirred for 24 h at room temperature. Water (2 mL) was added and the organic layer separated, dried (Na_2SO_4), and concentrated. The crude product was purified by preparative TLC on silica gel with hexane/ethyl acetate (9:1) to yield the less polar **10** (3.0 mg, 25%) and the more polar **9** (5.5 mg, 42%): mp 137–138 °C; $[\alpha]^{25}_D$ +125° (c 0.5, $CHCl_3$), +120° (c 0.55, EtOH); ^{1}H NMR δ 0.92 (3H, d, *J* = 7.4 Hz, H-13), 1.09 (3H, d, *J* = 6.1 Hz, H-14), 1.19 (3H, t, *J* = 7.1 Hz, H-17), 1.45 (3H, s, H-15), 1.5–2.5 (9H, m), 2.63 (1H, m, H-11), 3.48 (1H, dt, *J* = 9.7, 7.1 Hz, H-16a), 3.89 (1H, dt, *J* = 9.7, 7.1 Hz, H-16b), 4.82 (1H, d, *J* = 3.2 Hz, H-12), 5.46 (1H, s, H-5); ^{19}F NMR δ −88.1 (1F, d, *J* = 239 Hz), −104.4 (1F, dm, *J* = 239 Hz); ^{13}C NMR data are available as supporting information; CI-MS (NH_3) 366 (M + NH_4^+, 50%), 337 (6%), 320 (100%).

12β-17,17-Difluoroethyldeoxoartemisinin (13). To a solution of **11**[6] (14 mg) in CH_2Cl_2 (1.5 mL) was added DAST (30 μL) at 0 °C, and the solution was stirred for 1 h. Water (2.0 mL) was added and the organic layer separated, dried (Na_2SO_4), and concentrated. The crude product was purified by chromatography on four 5 × 10 cm silica gel plates (0.25 mm) with hexane/$CHCl_3$/ether (50:50:1) to yield **13** (8.0 mg, 53%) as a white solid: mp 122–123 °C; $[\alpha]^{25}_D$ +70° (c 0.23, $CHCl_3$) +52° (c 0.23, EtOH); ^{1}H NMR δ 0.87 (3H, d, *J* = 7.6 Hz, H-13), 0.97 (3H, d, *J* = 5.6 Hz, H-14), 1.40 (3H, s, H-15), 1.0–2.2 (12H, m), 2.33 (1H, m, H-3), 2.68 (1H, m, H-11), 4.50 (1H, m, H-12), 5.31 (1H, s, H-5), 6.03 (1H, ddt, *J* = 56.0, 7.6, 2.0 Hz, H-17); ^{19}F NMR δ −104.2 (1F, ddt, *J* = 282, 56.8, 9.7 Hz), −106.7 (1F, dm, *J* = 282 Hz); ^{13}C NMR data are available as supporting information; CI-MS (NH_3) 350 (M + NH_4^+, 100%).

12β-17,17-Difluoropropyldeoxoartemisinin (14). A sample of 12β-allyldeoxoartemisinin[6] was epoxidized with *m*-chloroperoxybenzoic acid (MCPBA) and the resulting epoxide reduced with $LiAlH_4$. The resulting alcohol was oxidized with catalytic quantities of TPAP as previously described[5] for 14-hydroxyarteether and 9α-hydroxyarteether to yield **12** in 45% yield. A solution of **12** (13.0 mg, 0.04 mmol) in dichloromethane (2.0 mL) was treated with DAST (0.25 mL) and the solution refluxed for 36 h. The reaction mixture was cooled to 0 °C and water added (2 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated. The product was

purified by preparative TLC on a 20 × 20 cm, 0.5 mm silica plate with hexane/ethyl acetate (9:1) to yield **14** (8.5 mg, 60%): mp 110–112 °C; $[\alpha]^{25}_D$ +57° (c 0.6, $CHCl_3$) +54° (c 0.6, EtOH); ^1H NMR δ 0.88 (3H, d, *J* = 7.5 Hz, H-13), 0.97 (3H, d, *J* = 5.7 Hz, H-14), 1.41 (3H, s, H-15), 1.0–2.2 (12H, m), 1.74 (3H, t, *J* = 19.2 Hz, H-3′), 2.33 (1H, ddd, *J* = 4.0, 13.8, 13.8 Hz, H-3), 2.66 (1H, m, H-11), 4.50 (1H, m, H-12), 5.31 (1H, s, H-5); ^{19}F NMR δ −70.50 (1F, dm, *J* = 242 Hz), −77.90 (1F, dm, *J* = 242 Hz); ^{13}C NMR data are available as supporting information; CI-MS (NH_3) 364 (M + NH_4^+, 32%), 347 (39%), 329 (42%), 314 (50%).

12β-[(p-Fluorobenzyl)oxy]dihydroartemisinin (15). To a stirred solution of **2** (142 mg, 0.50 mmol) and *p*-fluorobenzyl alcohol (183 mg, 1.45 mmol) in dry Et_2O (25 mL) at room temperature was added freshly distilled $BF_3 \cdot Et_2O$ (72 μL, 0.58 mmol). After 28 h the solution was washed with 5% $NaHCO_3$ and water, dried (Na_2SO_4), and purified by RDC (1 mm silica gel, 0–30% (v/v) hexane/EtOAc stepwise gradient; 5% steps over 1 h) to yield 120 mg (61%): R_f = 0.83 (EtOAc/hexane, 3:7); ^1H NMR δ 0.93 (3H, d, *J* = 7.1 Hz, H-13), 0.95 (3H, d, *J* = 4.4 Hz, H-14), 1.23–1.44 (3H, m), 1.46 (3H, s, H-15), 1.45–1.57 (2H, m), 1.60–1.91 (4H, m), 2.01–2.07 (1H, m), 2.38 (1H, dt, *J* = 14.0, 3.9 Hz), 2.65–2.70 (1H, m, H-11), 4.49 (1H, d, *J* = 12.2 Hz, H-16a), 4.85 (1H, d, *J* = 12.3 Hz, H-16b), 4.89 (1H, d, *J* = 3.6 Hz, H-12), 5.45 (1H, s, H-5), 7.03 (2H, t, *J* = 8.7 Hz), 7.28 (2H, dd, *J* = 5.7, 15 Hz); ^{13}C NMR spectral data are available as supporting information; CI-MS (NH_3) 410 (M + NH_4^+, 22%), 392 (3%).

11α-Hydroxy-12β-17,17,17-trifluoroarteether (16). To a solution of 11α-hydroxydihydroartemisinin[10] (36 mg, 0.12 mmol) and 2,2,2-trifluoroethanol (0.30 mL) in acetonitrile (3.0 mL) was added $BF_3 \cdot OEt_2$ (25 μL). The solution was stirred at room temperature for 5 min, and then chloroform (5 mL) and water (5 mL) were added. The organic layer was separated, dried (Na_2SO_4), and concentrated. The crude product was purified by TLC (20 × 20 cm, 0.5 mm) with $CHCl_3$/hexane/CH_3OH (50:50:2) to afford **16** (25 mg, 54%) as a white solid: mp 114–115 °C; $[\alpha]^{25}_D$ +116° (c 0.22, $CHCl_3$); ^1H NMR δ 0.96 (3H, d, *J* = 5.8 Hz, H-14), 1.0–2.0 (9H, m), 1.20 (3H, s, H-13), 1.46 (3H, s, H-15), 2.08 (1H, ddd, *J* = 3.9, 3.9, 14.0 Hz, H-3a), 2.37 (1H, ddd, *J* = 3.9, 14.0, 14.0 Hz, H-3b), 3.95 (2H, m, H-1′), 4.25 (1H, m, H-16), 4.76 (2H, s, H-12, O*H*), 5.45 (1H, s, H-5); ^{19}F NMR δ −72.3 (3F, t, *J* = 8.5 Hz); ^{13}C NMR data are available as supporting information; CI-MS (NH_3) 400 (M + NH_4^+, 100%), 300 (45%).

11β-Hydroxy-12β-17,17,17-trifluoroarteether (17). To a solution of **5**[10] (35 mg, 0.12 mmol) and 2,2,2-trifluoroethanol (0.35 mL) in CH_2Cl_2 (10 mL) was added *p*-toluenesulfonic acid (0.175 mL of a 62 mg/mL of CH_2Cl_2 solution), and the solution was stirred at room temperature for 10 min. Water was added and the organic layer separated, dried, and concentrated. The product was purified by preparative TLC on silica gel plates using hexane/ethyl acetate (6:1) to yield **17** (30 mg 63%) as a solid: mp 110–112 °C; $[\alpha]^{25}_D$ +108° (c 0.33, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.96 (3H, d, *J* = 5.8 Hz, H-14), 1.0–2.0 (10H, m), 1.44 (3H, s, H-15), 1.57 (3H, s, H-13), 2.37 (1H, ddd, *J* = 14.0, 14.0, 3.9 Hz, H-3), 2.45 (1H, s, O*H*), 3.97 (1H, m, H-16a), 4.20 (1H, m, H-16b), 4.77 (1H, s, H-12), 5.41 (1H, s, H-5); ^{19}F NMR δ −72.1 (3F, t, *J* = 8.4 Hz); ^{13}C NMR data are available as supporting information; CI-MS (NH_3) 400 (100%), 300 (60%).

Representative Procedure for the Preparation of 11β-Hydroxy-12β-(benzyloxy)dihydroartemisinins. 11β-Hydroxy-12β-[(o-Fluorobenzyl)oxy]dihydroartemisinin (20). To a stirred solution of 11,12β-oxirane **5**[10] (28 mg, 0.10 mmol) and o-fluorobenzyl alcohol (108 μL, 1.0 mmol) in dry CH_2Cl_2 (5 mL), at room temperature, was added *p*-toluenesulfonic acid (PTSA; 9.5 mg, 0.05 mmol). After 1 h the solution was washed with 5% $NaHCO_3$, dried, and purified by RDC (1 mm silica gel, 0–30% (v/v) hexane/EtOAc stepwise gradient; 5% steps over 1 h) to yield 24 mg (59%) of **20** as a clear oil: R_f = 0.67 (acetone/CH_2Cl_2, 3:7); $[\alpha]^{25}_D$ +121.4° (c 0.28, CH_2Cl_2); IR (neat) 3574–3430, 2952, 2923, 2873, 1588 cm^{-1}; ^1H NMR δ 0.84–0.90 (m, 1H), 0.95 (d, *J* = 5.7 Hz, 3H, H-14), 1.23–1.26 (m, 3H), 1.47 (s, 3H, H-15), 1.57 (s, 3H, H-13), 1.47–1.83 (m, 3H), 1.84–1.95 (m, 1H), 1.96–2.10 (m, 2H), 2.36 (dt, *J* = 13.8, 3.8 Hz, 1H), 2.58 (s, 1H, O*H*), 4.60 (d, *J* = 11.7 Hz, 1H, H-16), 4.83 (s, 1H, H-12), 5.02 (d, *J* = 11.7 Hz, 1H, H-16), 5.50 (s, 1H, H-5), 7.08 (t, *J* = 9.8 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.32–7.36 (m, 2H); ^{13}C NMR data are available as supporting information; CI-MS (NH_3) 426 (M + NH_4^+, 45%), 408 (M, 1%).

11β-Hydroxy-12β-[(m-fluorobenzyl)oxy]dihydroartemisinin (21). Oxirane **5**[10] (28 mg, 0.10 mmol) was reacted with *m*-fluorobenzyl alcohol (108 μL, 1.0 mmol) as described for **20** to yield **21** (25 mg, 63%): R_f = 0.66 (EtOAc/hexane, 3:7); $[\alpha]^{25}_D$ +115.8° (c 0.17, CH_2Cl_2); IR (neat) 3577–3471, 2952, 2924, 2874, 1617, 1591 cm^{-1}; ^1H NMR δ 0.86–0.90 (m, 1H), 0.96 (d, *J* = 5.7 Hz, 3H, H-14), 1.24–1.28 (m, 3H), 1.45 (s, 3H, H-15), 1.56 (s, 3H, H-13), 1.45–1.85 (m, 3H), 1.87–1.93 (m, 1H), 2.02–2.10 (m, 2H), 2.36 (dt, *J* = 13.9, 4.0 Hz, 1H), 2.58 (bs, 1H, O*H*), 4.58 (d, *J* = 12.2 Hz, 1H, H-16a), 4.83 (s, 1H, H-12), 4.93 (d, *J* = 12.2 Hz, 1H, H-16b), 5.46 (s, 1H, H-5), 7.00–7.08 (m, 2H), 7.11 (d, *J* = 11.4 Hz, 1H), 7.33 (1H, m); ^{13}C NMR data are available as supporting information; CI-MS (NH_3) 426 (M + NH_4^+, 58%), 408 (M, 3%).

11β-Hydroxy-12β-[(p-fluorobenzyl)oxy]dihydroartemisinin (22). Oxirane **5**[10] (28 mg, 0.10 mmol) was reacted with *p*-fluorobenzyl alcohol (108 μL, 1.0 mmol) as described for **20** to yield 0.025 g (69%) of **22**: R_f = 0.42 (EtOAc/hexane, 2:8); $[\alpha]^{25}_D$ +95.4° (c 0.35, CH_2Cl_2); IR (neat) 3575–3440, 2953, 2924, 2855, 1604 cm^{-1}; ^1H NMR δ 0.86–0.99 (m, 1H), 0.95 (d, *J* = 5.4 Hz, 3H, H-14), 1.23–1.40 (m, 3H), 1.45 (3H, s, H-15), 1.54 (3H, s, H-13), 1.45–1.80 (m, 3H), 1.87–1.93 (1H, m), 2.02–2.09 (2H, m), 2.36 (1H, dt, *J* = 14.0, 3.9 Hz), 2.52 (1H, s, O*H*), 4.55 (1H, d, *J* = 11.7 Hz, H-16), 4.81 (1H, s, H-12), 4.88 (1H, d, *J* = 11.7 Hz, H-16), 5.45 (1H, s, H-5), 7.08 (2H, t, *J* = 8.7 Hz), 7.30 (1H, d, *J* = 8.3 Hz), 7.31 (1H, d, *J* = 8.6 Hz); ^{13}C NMR data are available as supporting information; CI-MS (NH_3) 426 (M + NH_4^+, 94%), 408 (M, 5%).

11β-Hydroxy-12β-[(pentafluorobenzyl)oxy]dihydroartemisinin (23). Oxirane **5**[10] (28 mg, 0.10 mmol) was reacted with pentafluorobenzyl alcohol (108 μL, 1.0 mmol) as described for **20** to yield 32 mg (67%) of **23**: R_f = 0.77 (EtOAc/hexane, 3:7); $[\alpha]^{25}_D$ +180.0° (c 0.017, CH_2Cl_2); IR (neat) 3735–3490, 2925, 2850, 2820 cm^{-1}; ^1H NMR δ 0.84–1.00 (1H, m), 0.95 (3H, d, *J* = 5.5 Hz, H-14), 1.22–1.36 (1H, m), 1.45 (3H, s, H-15), 1.54 (3H, s, H-13), 1.45–1.68 (4H, m), 1.73–2.07 (4H, m), 2.30–2.41 (2H, m), 4.69 (1H, d, *J* = 10.9 Hz, H-16), 4.82 (1H, s, H-12), 4.99 (1H, d, *J* = 10.5 Hz, H-16), 5.44 (1H, s, H-5); ^{13}C NMR data are available as supporting information; CI-MS (NH_3) 498 (M + NH_4^+, 30%), 480 (M, 5%).

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Supporting Information Available: Two tables of the assigned ^{13}C chemical shifts of the compounds synthesized in this paper (2 pages). Ordering information is given on any current masthead page.

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