Synthesis and Antimalarial Activities of Fluoroalkyl Derivatives of Dihydroartemisinin

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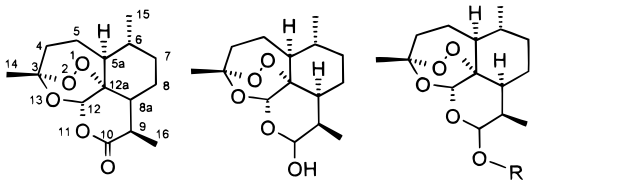
Fluoroalkyl ethers (**4**) of dihydroartemisinin (**2**) have been prepared by reaction of fluoroalkyl alcohols with dihydroartemisinin by different methods (BF_3,Et_2O or TMSCl catalysis or Mitsunobu reaction). Ethers **4a**−**d** derived from primary fluoroalkyl alcohols were obtained in moderate to good yields by these methods. Ethers **4e**−**j** have been prepared from fluoroalkyl secondary and tertiary alcohols and phenol using the Mitsunobu reaction. Although in vitro antimalarial activities of ethers toward *Plasmodium falciparum* W-2 asiatic strain are moderate, in vivo activities against *Plasmodium berghei* (NT 173) are excellent.

Introduction

Artemisinin (**1**) (Chart 1), an unusual sesquiterpene bearing an endoperoxide linkage, isolated from the Chinese medicinal herb *Artemisia annua L.*, is an efficient antimalarial drug for the treatment of multidrug-resistant *Plasmodium falciparum*.[1] However the therapeutic value of **1** is limited to a great extent by its low solubility in both oil and water.[2] In the search for more effective and soluble drugs, a number of ether derivatives of dihydroartemisinin (**2**) (DHA) such as artemether (**3a**) and sodium artesunate (**3b**) have been synthesized.[2−4] The use of ethers of dihydroartemisin and artemisinin itself in the treatment of *P. falciparum* malaria is restricted by their short plasma half-life.[4,5]

In vivo or in liver homogenates, the main pathway of metabolism of ether derivatives of dihydroartemisinin is a rapid hydroxylation by cytochrome P-450 enzymes to generate a hemiketal intermediate. This intermediate decomposes to produce the active compound DHA (**2**) and an aldehyde.[7,8] Plasma half-life of these derivatives depends on the rate of this oxidative dealkylation to give DHA, which itself has a very short plasma half-life[9] (Scheme 1). As a consequence a high rate of recrudescence of parasitemia and a low rate of radical cure are frequently observed after short treatments.[4,6,10] A search for new artemisinin derivatives with a better therapeutic index due to a better solubility and bioavailability has thus become an important target of many laboratories around the world.[11−13] Among these derivatives, DHA ethers have received particular interest.[10,14−17]

Chart 1. Artemisinin Derivatives



Considering the first step of metabolism of DHA ethers (Scheme 1), a feasible approach to prolong the half-life of artemisinin derivatives is to design new ethers that are poorer substrates for cytochrome P-450 than reported DHA ethers or new hemiacetals more stable than DHA. For this purpose we envisaged the introduction of a fluorinated substituent at two specific positions: at the α-methylene carbon of DHA ethers (Chart 2) or at the hemiacetal carbon of DHA (Chart 3). In the first case a slower rate of oxidative dealkylation could be expected, since it has been demonstrated that the protection toward oxidative processes, provided by a fluoroalkyl group, extends to adjacent CH or CH_2 groups.[18,19] Concerning the hemiketal, we already reported that treatment with 10α-(trifluoromethyl)-hydroartemisinin of mice infected with *Plasmodium vinckei petteri* was more efficient that treatment with artemisinin. This result may be accounted for by a longer plasma half-live due to the stabilization of the hemiketal by the electron-withdrawing CF_3 group. It has been reported that the introduction of fluoroalkyl substituents at different sites of the artemisinin skeleton results in good in vitro activity, but their in vivo activity has not been investigated.[12] In this paper, we

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Scheme 1

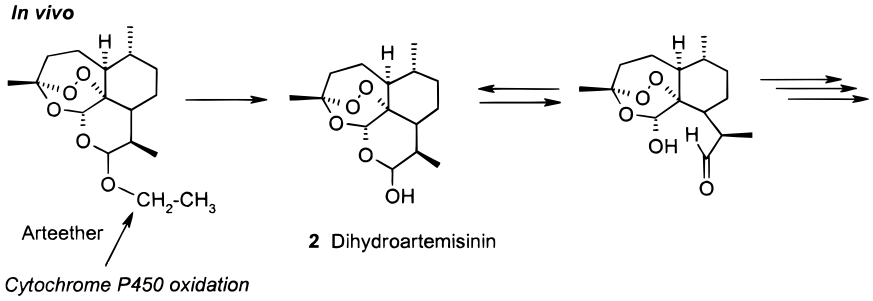

Chart 2. Fluoroalkyl Ether of Dihydroartemisinin

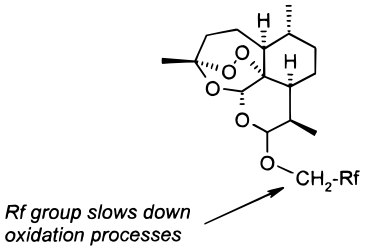

Chart 3. Fluoroalkyl Hemiketal of Artemisinin

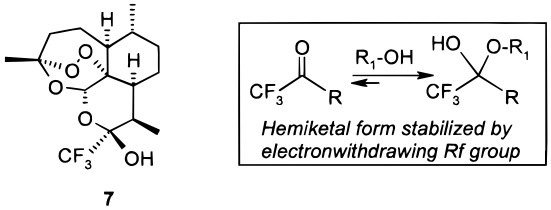

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Table 1. Preparation of Ether **4a**

method	**4a** (%)[a]	β:α	**5** (%)	**6a** (%)
A (BF_3,Et_2O)	67	96:4	20	
B (TMSCl)	86	78:22		8
C (DEAD, PPh_3)	74	93:7		

[a] Isolated yields.

report the preparation and the in vitro and in vivo antimalarial activity of new fluorinated ethers of dihydroartemisin and fluoroalkyl-substituted dihydroartemisinin.

Results and Discussion

Preparation of product **7** from artemisinin and TMS−CF_3 has been reported.[13] Ethers of dihydroartemisinin are generally prepared by treatment of dihydroartemisinin (**2**) with the appropriate alcohol in the presence of boron trifluoride etherate (BF_3,Et_2O) at room temperature.[3a,20] Trifluoroethanol reacted under these conditions (method A) with dihydroartemisin (α:β ~ 50:50) to give the ether **4a** accompanied with 20% of dehydrodeoxoartemisin (**5**). After separation, **4a** could be isolated in good yield (67%) with excellent diastereoselectivity (β:α ~ 96:4) (Table 1, Scheme 2). Dehydrodeoxoartemisin (**5**), which is the result of deprotonation of the intermediate oxonium ion, has previously been reported to be the major product when this reaction is performed with hindered secondary and tertiary alcohols.[3a,20] In our case, partial formation of **5** is a result of the low nucleophilicity of the fluoroalkyl alcohol and not steric hindrance. We have also examined the recently reported procedure using trimethylsilyl chloride (TMSCl) instead of boron trifluoride etherate.[21] Although the yield of ether **4a** was only slightly improved (70%) in the presence of a catalytic amount of TMSCl, when TMSCl was used in large excess (5 equiv) **4a** could be isolated in 86% yield (method B). Under both conditions, the reaction was less stereoselective (β:α ~ 78:22), and a byproduct (8%) which was postulated to be the isomerized ether **6a** was formed. The ^1H and ^{13}C NMR signals of Me-16 are deshielded from 0.95 ppm in **4a** (α or β) to 1.22 ppm in **6a** and from 12.4 ppm (**4a**) to 19.4 ppm (**6a**), respectively, while the H-9 signal in **6a** is shielded from 2.6 ppm (in β-**4a**) or 2.5 ppm (in α-**4a**) to 1.5 ppm, indicating a stereochemical change at this site. Furthermore, the coupling constant J_{H9-H10} is small (4.3 Hz) as in β-**4a** (3.5 Hz), indicating a small dihedral angle which is indicative of a cis relationship between these two protons. This formation of ether **6a**, combined with the higher yield in **4a** with TMSCl, is good evidence that the deprotonation of the oxonium salt leading to dehydrodeoxoartemisin (**5**) is reversible. The protonation at C-9 could occur from the α or the β face of **5** (Scheme 2).

It has been recently reported that a Mitsunobu-type etherification is efficient in the case of fluoroalkyl alcohols.[22,23] We envisaged that chemoselectivity could be improved using this method. Dihydroartemisinin (**2**) readily reacted with trifluoroethanol in the presence of triphenylphosphine (PPh_3) and diethyl azodicarboxylate (DEAD) (method C) to give the ether **4a** in good yield (74%) and with good stereoselectivity (β:α 93:7) (Table 1). The mechanism of Mitsunobu reaction being S_N2 proceeds with inversion of configuration; thus an α:β ~ 50:50 could be expected. The observed stereoselectivity could be explained by a preferential β approach of the alcohol and an equilibrium displacement of nonconsumed β-**2** to α-**2** via the hemiacetal opening.

Each of these three methods was studied and compared with a range of fluoroalkyl alcohols (Table 2, Scheme 3). Their respective efficiency was shown to be highly dependent on the alcohol structure. Clearly, method A (BF_3,Et_2O-catalyzed ether formation) is not suitable with poor nucleophilic fluoroalkyl alcohols. In all cases, the major product was the dihydrodeoxoartemisin (**5**). Method B (TMSCl) was efficient with secondary alcohols; however the presence of the diastereoisomer **6** as sideproduct brought separation problems. In general, method C (Mitsunobu-type reaction) was the most efficient for primary alcohols and for secondary alcohols with the exception of those containing only one CF_3 group (**4e**,**j**), method B being the best in this case. It was possible to form the ethers of tertiary alcohols and pentafluorophenol using method C. Surprisingly

Scheme 2

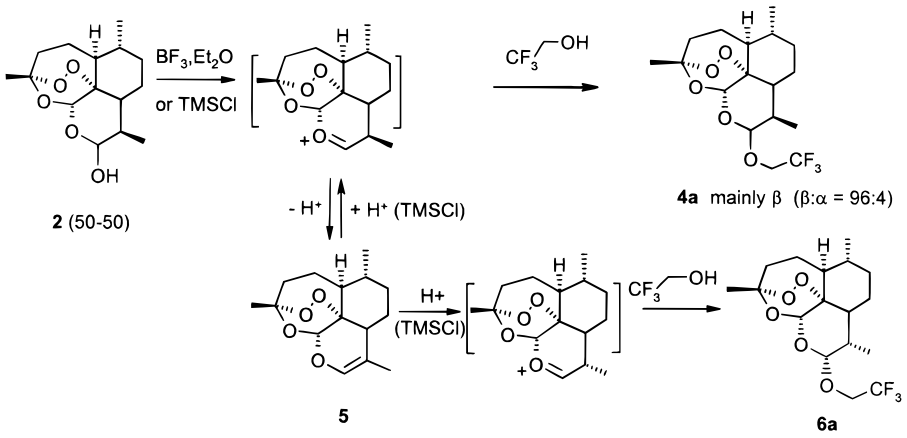


Table 2. Preparation of Ethers **4** from Fluoroalkyl Alcohols

alcohol	**4**	method	yields (%)	β:α	β_1:β_2	**6** (yield, %)
CF_3-CF_2-CH_2OH	**4b**	A	43	97:3		
CF_3-CF_2-CH_2OH	**4b**	B	54	97:3		8
CF_3-CF_2-CH_2OH	**4b**	C	80	93:7		
CF_3-CF_2-CF_2CH_2OH	**4c**	A	30	94:6		
CF_3-CF_2-CF_2CH_2OH	**4c**	B	63	84:16		12
CF_3-CF_2-CF_2CH_2OH	**4c**	C	73	98:2		
CF_3-CHF-CF_2-CH_2OH	**4d**	A	21	100:0	50:50	
CF_3-CHF-CF_2-CH_2OH	**4d**	B	45	95:5	50:50	15
CF_3-CHF-CF_2-CH_2OH	**4d**	C	40	100:0	64:36	
CF_3-CHOH-CH_3	**4e**	A	3			
CF_3-CHOH-CH_3	**4e**	B	53	97:3	52:48	
CF_3-CHOH-CH_3	**4e**	C	20	98:2	100:0	
CF_3-CHOH-C_6H_5	**4f**	A	0			
CF_3-CHOH-C_6H_5	**4f**	B	36	100:0	67:33	8
CF_3-CHOH-C_6H_5	**4f**	C	25	100:0	56:44	
CF_3-CHOH-CF_3	**4g**	A	0			
CF_3-CHOH-CF_3	**4g**	B	26	97:3		4
CF_3-CHOH-CF_3	**4g**	C	60	100:0		
$(CF_3)_2$-COH-C_6H_5	**4h**	B	0			
$(CF_3)_2$-COH-C_6H_5	**4h**	C	30	98:2		
C_6F_5-OH	**4i**	B	7	95:5		
C_6F_5-OH	**4i**	C	50	94:6		
CF_3-CHOH-COOEt	**4j**	A	0			
CF_3-CHOH-COOEt	**4j**	B	25	100:0	55:45	7
CF_3-CHOH-COOEt	**4j**	C	12	100:0		

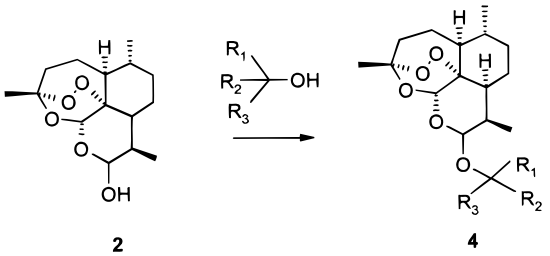
the reaction is not sensitive to steric hindrance. Only a high acidity of the alcohol is required for the reaction to occur. Ethers **4g**,**i** were obtained in good yields with excellent stereoselectivity. Poor results with ethyl trifluorolactate could not be explained.

Biological Assays. The 10α-(trifluoromethyl)hydroartemisinin was more potent (IC_{50} = 2.6 nM) than artemether (IC_{50} = 5.4 nM) against the chloroquine-, cycloguanil-, pyrimithamine-, quinine-, and sulfadoxine-resistant clone of human malaria, *P. falciparum* W-2 (Indochina clone), and on wild isolates of *P. falciparum* from African patients (average value of at least three experiments).[24] The IC_{50} values for the fluoroalkyl ethers were, on the contrary, higher than that of artemether (27 nM < IC_{50} < 72 nM) (Table 3). The structure of the fluorinated chains has only a small influence on in vitro activities.

The in vivo antimalarial activity was assessed in mice infected with *Plasmodium berghei*. A dose of 35.5 μmol/kg of the drugs was administered, 1 day after the infection, over 4 days, by intraperitoneal route.[25] The effect of treatments was measured by life span prolongation of mice and the parasitemia clearance.[25,26]

In the artemisinin-treated group at day 4, the end of the drug administration, and in the untreated control group parasitemia ranged from 20% to 25%. For the artemether-treated group it was 1%, and for the chloroquine-treated group it was 0% (Figure 1). Mice group treated with 10α-(trifluoromethyl)dihydroartemisinin (**7**) (at only 17.5 μmol/kg) had a parasitemia of 2.8% at day 4. This value increased to 25% (as with artemether at 35.5 μmol/kg) and then decreased at day 16. All mice survived at day 42. The fluoroalkyl ethers **4a**,**b**,**g**,**i** provided the best protection, indicated by the low value of residual parasitemia at day 4 (0.6−2%), a complete clearance of parasitemia observed at day 11. All mice were surviving at day 42. The ethers are much more active than artemether which presented an important recrudescence of parasitemia at day 16 (Figure 1).[27] This protection is the result of remaining activity after day 4 and not the result of the clearance of parasitemia at the end of the treatment, as observed for chloroquine.

Scheme 3



a R_1 = CF_3, R_2 = R_3 = H
b R_1 = CF_2-CF_3, R_2 = R_3 = H
c R_1 = CF_2-CF_2-CF_3, R_2 = R_3 = H
d R_1 = CF_2-CHF-CF_3, R_2 = R_3 = H
e R_1 = CF_3, R_2 = CH_3, R_3 = H
f R_1 = CF_3, R_2 = C_6H_5, R_3 = H
g R_1 = R_2 = CF_3, R_3 = H
h R_1 = R_2 = CF_3, R_3 = C_6H_5
i R_1,R_2,R_3 = C_6F_5
j R_1 = CF_3, R_2 = COOEt, R_3 = H

Table 3. In Vitro Antimalarial Activity (IC_{50}) against *P. falciparum* (W-2 Strain)

compd	IC_{50} (nM)	compd	IC_{50} (nM)
3a	7.5	**4e**	35
7	2.6	**4f**	66
4a	31	**4g**	34
4b	27	**4h**	38
4c	36	**4i**	72
4d	34	**4j**	61

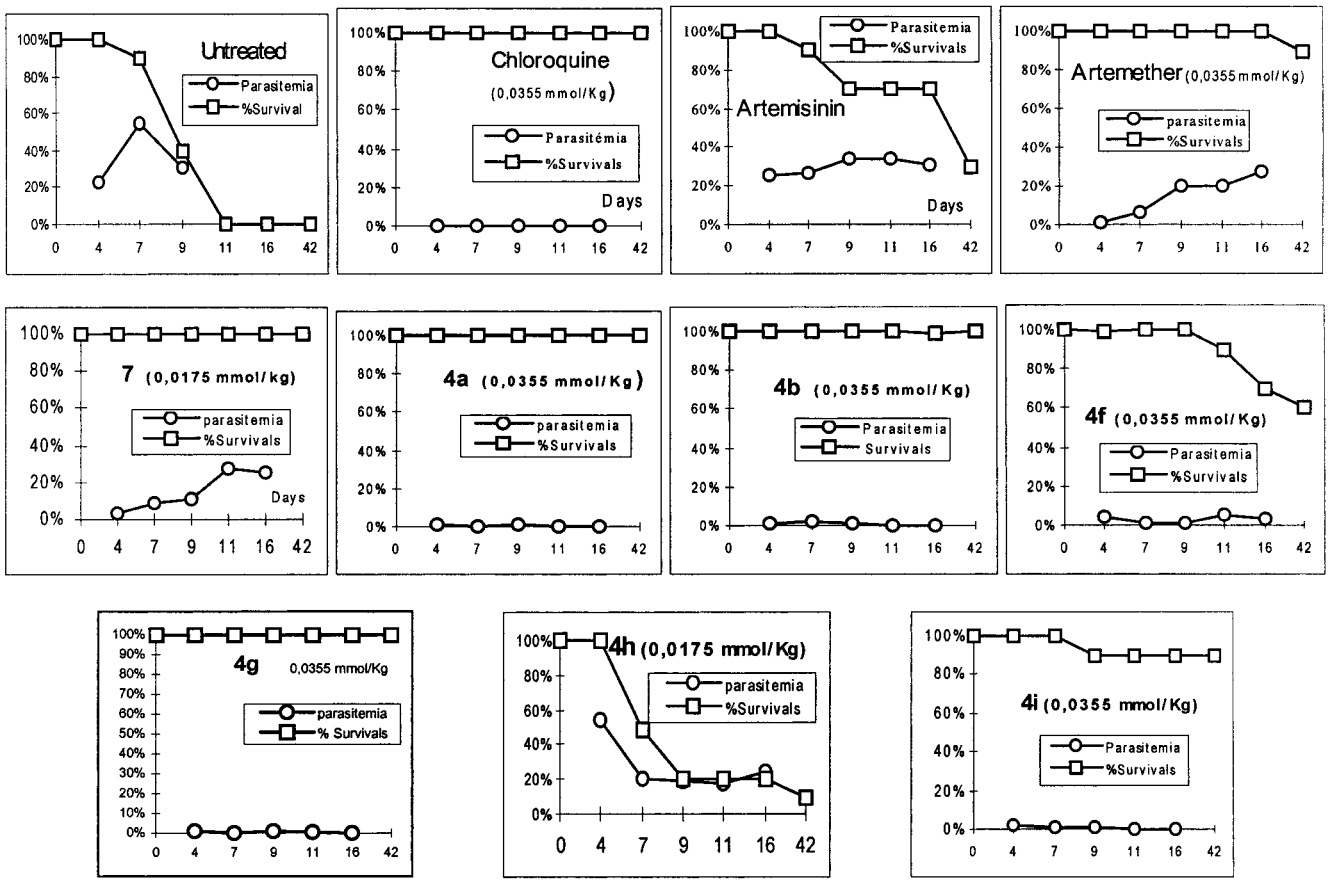


Figure 1. In vivo antimalarial activity of compounds **4** and **7** on mice infected with *P. berghei*.

Protection with ether **4f** is less efficient, with 30% mortality at day 16 (5% of parasitemia at day 11). Mice treated with **4h** at 35.5 μmol/kg presented a parasitemia of 0.2% at day 4. However only 20% survived at day 9 (40% for untreated mice group), and there were no surviving mice at day 13, indicating a toxicity of this compound. When treated at only 17.5 μmol/kg, mice presented an unexpected high parasitemia (54%) at day 4, higher than that of the untreated group, and only 20% of mice survived at day 16. Toxicity of **4h** may inhibit the immunity process. From these data, it seems that the presence of a phenyl group on the fluoroalkyl moiety deeply lowers the efficiency of ethers **4**.

The lack of correlation between in vitro and in vivo activities of the ethers series **4** and the hemiketal **7** probably results from different pharmacokinetic profiles. Additional biological data for these compounds is needed in order to explain the high in vivo activities, in particular of compounds **4a**,**b**,**g**,**i**. Compounds **4** have been designed to decrease the metabolic oxidation leading to DHA. Interestingly, parasitemia ranged from 1% to 2% at the end of treatments, which slowly decreases to 0%, so that the activity of drugs remains many days after the end of treatment. If the activity of ethers **4** is due to their conversion into the active DHA as for artemether, it seems that fluoroalkyl substituents effectively slow this metabolism providing a longer protection. Further studies are required to prove this hypothesis and determine if ethers **4** are directly active on the parasite or through a slow oxidative metabolism to DHA.

Experimental Section

In Vitro Assays. The chloroquine-resistant reference clone of *P. falciparum* W-2 (Indochina) was maintained in continuous culture and twice synchronized with sorbitol before in vitro test. Stock cultures were grown with type A^+ human erythrocytes suspended in RPMI medium (Gibco BRL, Paisley, U.K.) supplemented with 10% human serum (A^+) and buffered with 25 mM HEPES and 25 mM $NaHCO_3$. Cultures were incubated at 37 °C in an atmosphere of 10% O_2, 6% CO_2, and 84% N_2 and a humidity of 95%. Prior to in vitro assay, parasitized erythrocytes were diluted with uninfected, fresh erythrocytes to an initial parasite density of 0.5% and resuspended in culture medium to hematocrit of 1.5%. Artemether was provided by Rhône Poulenc Rorer Doma (Antony, France). Stock solutions of artemether and fluoroalkyl ethers of dihydroartemisinin were prepared in methanol, and 2-fold serial dilutions were prepared in sterile distilled water. Final concentrations ranged from 1.6 to 200 nM and were distributed in triplicate into flat-bottomed, 96-well plates.

For in vitro isotopic microtests, the suspension of parasitized erythrocytes was distributed under 200 μL/well in 96-well plates predosed with antimalarial agents. Parasite growth was assessed by adding 1 μCi of [^{3}H]hypoxanthine with a specific activity of 14.1 Ci/mmol (NEN Products, Dreiech, Germany) to each well. Plates were incubated for 42 h at 37 °C in an atmosphere of 10% O_2, 6% CO_2, and 84% N_2 and a humidity of 95% (optimum conditions in our laboratory). Immediately after incubation the plates were frozen and then thawed to lyse erythrocytes. The contents of each well were collected on standard filter microplates (Unifilter GF/B, Packard Instrument Co., Meriden, CT) and washed using a cell harvester (FilterMate cell harvester, Packard). Filter microplates were dried, and 25 μL of scintillation cocktail (Microscint O, Packard) was placed in each well. Radioactivity incorporated by the parasites was measured using a scintillation counter (Top Count, Packard). The 50% inhibitory concentra-

tion (IC_{50}), i.e., the drug concentration inhibiting 50% of the uptake of [^{3}H]hypoxanthine by the parasites in drug-free control wells, was determined by nonlinear regression analysis of log dose−response curves. Values are the average of at least three experiments.

In Vivo Assays. The antimalarial activity was studied in mice (female CD1, 18−20 g; Charles River Co., France) infected with *P. berghei* (NK 173) (15×10^6 red cells). Each group contained 10 mice. According to the protocol of Peters,[25] treatments with artemisinin, artemether, chloroquine sulfate, and compounds **3a**,**b**,**f**,**g**,**h**,**i** and **7** were performed during 4 days, 1 day after the infection, by intraperitoneal route. The drugs were given once a day at 0.0355 mmol·kg^{-1} or at 0.0175 mmol·kg^{-1} for **3h** and **7**, as a suspension, in an aqueous solution of carboxymethyl cellulose (1%). The untreated group received only carboxymethyl cellulose excipient at 0.1%.

Chemistry. NMR spectra were recorded using Varian EM (90 MHz) FH dual probehead and Bruker AC 200 and ARX 400 (^{1}H, 200 or 400 MHz; ^{19}F, 84, 188, or 376 MHz; ^{13}C, 50 or 100 MHz) spectrometers, in $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to Me_4Si and $CFCl_3$ (for ^{19}F NMR) as internal standards. In the ^{13}C NMR data, reported signal multiplicities are related to C−F coupling. For the determination of fine coupling constants, an acquisition of 16K data points, a Lorentz−Gauss transformation of the FID, and a zero filling to 64K were performed in order to obtain a minimum of resolution of 0.2 Hz/pt (^{1}H) or 0.5 Hz/pt (^{13}C). Complete assignments in NMR result from *J* module, COSY, HMQC, and HMBC experiments performed on a multinuclear probehead equipped with a Z-gradient coil. Optical rotations were measured at 589 nm on a Polartronic E-Schmidt-Haensch apparatus. TLC was performed on Merck Kieselgel 60 F254 silica plates (vanillin−MeOH−H_2SO_4). Column chromatography was carried out on Merck SiO_2 (35−70 mesh).

General Procedures. Method A (using BF_3,Et_2O). BF_3,Et_2O (1.2 equiv) was added to a solution of dihydroartemisinin (DHA) (**2**) (1 equiv) and fluoroalkyl alcohol (2−10 equiv) in Et_2O (30 mL). Reaction mixture was stirred under Ar, at room temperature, for 24 h and then washed with saturated aqueous solution of NaOAc (10 mL) and then with water (10 mL). Organic phase was dried ($MgSO_4$) and evaporated. The crude product was purified on a silica gel column (petroleum ether/AcOEt, 95:5) to give the ether **4**.

Method B (using TMSCl). TMSCl (3.7 mmol, 5 equiv) was added to the solution of DHA (**2**) (0.7 mmol) and fluoroalkyl alcohol (1.4 mmol) in dichloromethane (6 mL). Reaction mixture was stirred at room temperature, under Ar, for 2−4 h and then washed with saturated sodium acetate solution (10 mL), water (2 × 5 mL), and brine. The organic phase was dried ($MgSO_4$) and the solvent evaporated. The residue was purified by chromatography on silica gel (petroleum ether/AcOEt, 95:5) to give ether **4**.

Method C (using Mitsunobu reaction). To a stirred solution of dihydroartemisin (**3**) and fluoroalkyl alcohol (1.4 mmol, 2 equiv) in toluene (10 mL) was added Ph_3P (257 mg, 2 mmol). After complete dissolution, the solution was treated with DEAD (0.2 mL, 1.4 mmol) and stirred for 2 h at room temperature. The reaction mixture was concentrated in vacuo and the residue purified on silica gel column (petroleum ether/AcOEt, 70:30) and then chromatographed.

10*β*-(Trifluoroethoxy)dihydroartemisinin 4a. Method A: From DHA (100 mg, 0.35 mmol), BF_3,Et_2O (0.05 mL), and trifluoroethanol (0.22 mL, 2.88 mmol), the reaction, workup, and then chromatography provided ether isomer **4a** (*β*:α 96:4) (87 mg, 67%).

Method B: From DHA (100 mg, 0.35 mmol), TMSCl (0.2 mL, 1.6 mmol), and trifluoroethanol (0.22 mL, 2.88 mmol), the reaction, workup, and then chromatography provided ether **4a** (*β*:α 78:22) (110 mg, 86%) and ether **6a** (10 mg, 8%).

Method C: From DHA (300 mg, 1.05 mmol), PPh_3 (550 mg, 2.1 mmol), trifluoroethanol (0.75 mL, 10.3 mmol), and DEAD (0.33 mL, 2.1 mmol), reaction and workup provided crude ether **4a** (*β*:α 93:7). Pure isomer *β*-**4a** (286 mg, 74%) was obtained after SiO_2 chromatography.

10*β*-(Trifluoroethoxy)dihydroartemisinin (4a): mp = 113 °C (AcOEt); $[\alpha]_D = 71°$ (MeOH, $c = 1.75$); ^{19}F NMR δ −74.6 (t, $^3J_{FH} = 8.7$ Hz); ^{1}H NMR δ 0.85 (d, $^3J = 6$ Hz, 3 H, CH_3-15), 0.9 (d, $^3J = 7.5$ Hz, 3 H, CH_3-16), 1.2 (m, 1 H, H-5a), 1.25 (m, 1 H, H_A-5), 1.3 (m, 1 H, H-6) 1.35 (s, 3 H, CH_3-14), 1.45 (m, 1 H, H-8a), 1.65 (m, 2 H, CH_2-7), 1.7−1.9 (m, 3 H), 2.05 (ddd, ^2J = 14.5 Hz, $^3J = 4.7$ Hz, $^3J = 3.2$ Hz, 1 H, H_A-4), 2.3 (ddd, ^2J = 14.5 Hz, $^3J = 13.3$ Hz, $^3J = 3.9$ Hz, 1 H, H_B-4), 2.65 (ddd, ^2J = 7.5 Hz, $^3J = 4.5$ Hz, $^3J = 3.6$, 1 H, H-9), 3.9 (dq, $J_{AB} = 12.3$ Hz, $^3J_{FH} = 8.6$ Hz, 1 H, CH_AH-CF_3), 4.06 (dq, $J_{AB} = 12.3$ Hz, $^3J_{FH} = 8.8$ Hz, 1 H, CHH_B-CF_3), 4.8 (d, $^3J = 3.6$ Hz, 1 H, H-10), 5.34 (s, 1 H, H-12); ^{13}C NMR δ 12.4 (C-16), 20.0 (C-15), 24.0 (C-8), 24.4 (C-5), 25.8 (C-14), 30.4 (C-9), 34.3 (C-7), 36.1 (C-4), 37.1 (C-6), 44.0 (C-8a), 52.3 (C-5a), 64.8 (q, $^2J_{CF} = 34$ Hz, CH_2−CF_3), 80.7 (C-12a), 87.9 (C-12), 102.4 (C-10), 104.0 (C-3), 123.7 (q, $^1J_{CF} = 278$ Hz, CF_3). Anal. ($C_{17}H_{25}F_3O_5$) C, H.

10α-(Trifluoroethyloxy)-13α-methyldihydroartemisinin (6a): $[\alpha]_D = +140°$ (MeOH, $c = 0.7$); ^{19}F NMR δ −74.5 (t, $^3J_{FH} = 8.8$ Hz, CF_3); ^{1}H NMR (C_6D_6/$CDCl_3$) δ 0.75 (d, $^3J = 6$ Hz, 3 H, CH_3-15), 1.1 (m, 1 H), 1.22 (d, $^3J = 7.3$ Hz, 3 H, CH_3-16), 1.28 (m, 3 H), 1.32 (s, 3 H, CH_3-14), 1.4 (m, 2 H), 1.5 (qdd, $^3J = 7.3$ Hz, $^3J = 4.5$ Hz, $^3J = 1.5$ Hz, 1 H, H-9), 1.56 (dd, ^2J = 13.6 Hz, $^3J = 3.6$ Hz, 1 H), 1.65 (dddd, $^2J = 13.6$ Hz, ^3J = 7 Hz, $^3J = 6.3$ Hz, $^3J = 3.3$ Hz, 1 H), 1.8 (m, ddd, $^2J = 14.5$ Hz, $^3J = 4.8$ Hz, $^3J = 3$ Hz, 1-H, H_A-4), 2.2 (ddd, $^2J = 14.5$ Hz, $^3J = 13.3$ Hz, $^3J = 3.9$ Hz, 1 H, H_B-4), 3.7 (dq, $J_{AB} = 12.3$ Hz, $^3J_{HF} = 8.7$ Hz, 1 H, CH_A-CF_2), 4.0 (dq, $J_{AB} = 12.3$ Hz, $^3J_{HF}$ = 8.9 Hz, 1 H, CH_B-CF_2), 4.95 (d, $^3J = 4.5$ Hz, 1 H, H-10), 5.35 (s, 1 H, H-12); ^{13}C NMR δ 14.5 (C-16), 20.1 (C-15), 24.6 (C-5), 25.9 (C-14), 31.4 (C-7), 34.4 (C-4), 36.4 (C-4), 37.2 (C-9), 39.5 (C-6), 46.0 (C-8a), 51.9 (C-5a), 65.2 (t, $^2J_{CF} = 34$ Hz, CH_2−CF_3), 81.4 (C-12a), 89.0 (C-12), 103.4 (C-3), 103.5 (C-10), 123.7 (q, $^1J_{CF} = 278$ Hz, CF_3). Anal. ($C_{17}H_{25}F_3O_5$) C, H.

10*β*-(Pentafluoropropyloxy)dihydroartemisinin (4b). Method A: From DHA (200 mg, 0.7 mmol), BF_3,Et_2O (0.1 mL), and pentafluoropropanol (0.6 mL, 6 mmol), reaction (1 day) and workup provided crude ether **4b** (*β*:α 97:3). Ether **4b** (*β*:α 97:3) (125 mg, 43%) was isolated pure after chromatography.

Method B: From DHA (100 mg, 0.35 mmol), TMSCl (0.2 mL, 1.6 mmol), and pentafluoroethanol (0.3 mL, 3 mmol), reaction (4 h), workup, and then chromatography provided ether **4b** (*β*:α 97:3) (79 mg, 54%) and ether **6b** (11 mg, 8%).

Method C: From DHA (284 mg, 1 mmol), PPh_3 (654 mg, 2.5 mmol), pentafluoropropanol (1 mL, 12 mmol), and DEAD (0.4 mL, 2.5 mmol), reaction and workup provided crude ether **5a** (*β*:α 93:7). Pure isomer *β*-**5a** (336 mg, 80%) was obtained after chromatography.

10*β*-(Pentafluoropropyloxy)dihydroartemisinin (4b): mp 53 °C (AcOEt); $[\alpha]_D = 90°$ (MeOH, $c = 0.6$); ^{19}F NMR δ −83.7 (br s, CF_3), −123.9 (br t, $^3J_{FH} = 13.4$ Hz, CF_2); ^{1}H NMR δ 0.9 (m, 1 H), 0.92 (d, $^3J = 7.2$ Hz, 3 H, 16-CH_3), 0.95 (d, ^3J = 6 Hz, 3 H, 15-CH_3), 1.2 (m, 2 H), 1.45 (s, 3 H, 14-CH_3), 1.7 (m, 5 H), 1.9 (m, 2 H), 1.7 (m, 5 H), 2.30 (ddd, $^2J = 15$ Hz, ^3J = 13 Hz, $^3J = 4.2$ Hz, 1 H, H_B-4), 3.90 (dtq, $J_{AB} = 13$ Hz, $^3J_{HF}$ = 12.7 Hz, $^4J_{FH} = 0.7$ Hz, 1 H, CH_A-CF_2), and 4.20 (dtq, J_{AB} = 13 Hz, $^3J_{HF} = 12.7$ Hz, $^4J_{FH} = 0.7$ Hz, 1 H, CH_B-CF_2), 4.85 (d, $^3J = 3.5$ Hz, 1 H, H-10), 5.35 (s, 1 H, H-12); ^{13}C NMR δ 12.4 (C-16), 20.0 (C-15), 24.0 (C-8), 24.3 (C-5), 26.0 (C-14), 30.6 (C-9), 34.5 (C-7), 36.2 (C-4), 37.4 (C-6), 44.0 (C-8a), 52.5 (C-5a), 64.4 (t, $^2J_{CF} = 27$ Hz, CH_2−CF_3), 80.9 (C-12a), 88.1 (C-12), 102.8 (C-10), 104.7 (C-3), 119.4 (q, $^1J_{CF} = 229$ Hz, CF_3). Anal. ($C_{18}H_{25}F_5O_5$) C, H.

10α-(Pentafluoropropyloxy)-13α-methyldihydroartemisinin (6b): $[\alpha]_D = +125.6°$ (MeOH, $c = 1.6$); ^{19}F NMR δ −83.7 (br s, CF_3), 123.9 (br t, $^3J_{FH} = 13.4$ Hz, CF_2); ^{1}H NMR δ 0.90 (d, $^3J = 6$ Hz, 3 H, 15-CH_3), 1.0 (m, 1 H), 1.22 (d, ^3J = 7.2 Hz, 3 H, 16-CH_3), 1.3 (m, 3 H), 1.42 (s, 3 H, 14-CH_3), 1.4−1.8 (m, 5 H), 1.8−2.1 (m, 2 H), 2.25 (ddd, $^2J = 14.5$ Hz, ^3J = 13.3 Hz, $^3J = 3.6$ Hz, 1 H, H_B-4), 3.95 (dtq, $J_{AB} = 13.5$ Hz, $^3J_{HF} = 12.5$ Hz, $^4J_{FH} = 1$ Hz, 1 H, CH_A-CF_2), 4.25 (dtq, J_{AB} = 13.5 Hz, $^3J_{HF} = 12.5$ Hz, $^4J_{FH} = 1$ Hz, 1 H, CH_B-CF_2), 5.0 (d, $^3J = 4.2$ Hz, 1 H, H-10), 5.4 (s, 1 H, H-12); ^{13}C NMR δ 19.4 (C-16), 20.1 (C-15), 24.6 (C-5), 25.9 (C-14), 31.3 (C-8), 34.4 (C-7), 36.4 (C-4), 37.3 (C-9), 39.0 (C-6), 46.0 (C-8a), 51.9 (C-5a),

65.0 (t, $^2J_{CF}$ = 30 Hz), 82.0 (C-12a), 88.9 (C-12), 103.1 (C-10), 103.8 (C-3), CF_3 and CF_2 not observed. Anal. ($C_{18}H_{25}F_5O_5$) H; C: calcd, 51.92; found, 51.38.

10β-(2′,2′,3′,3′,4′,4′,4′-Heptafluorobutyloxy)dihydroartemisinin (4c). Method A: From DHA (100 mg, 0.7 mmol), BF_3,Et_2O (0.05 mL), and heptafluorobutanol (0.1 mL, 0.8 mmol), reaction (18 h) and workup provided crude product. Pure ether **4c** (β:α 94:6) (50 mg, 30%) was isolated after chromatography.

Method B: From DHA (100 mg, 0.35 mmol), TMSCl (0. 2 mL, 1.6 mmol), and heptafluorobutanol (0.1 mL, 0.8 mmol), reaction (4 h), workup, and then chromatography provided ether **4c** (β:α 84:16) (103 mg, 63%) and ether **6c** (20 mg, 12%).

Method C: From DHA (200 mg, 0.7 mmol), PPh_3 (258 mg, 1.5 mmol), heptafluorobutanol (0.2 mL, 1.45 mmol), and DEAD (0.24 mL, 1.5 mmol), reaction and then workup provided crude ether **4c** (β:α 98:2). Pure isomer β-**4c** (240 mg, 73%) was obtained after chromatography.

10β-(2′,2′,3′,3′,4′,4′,4′-Heptafluorobutyloxy)dihydroartemisinin (4c): mp 41 °C (CH_2Cl_2); $[\alpha]_D$ = 110° (MeOH, *c* = 5.1); ^{19}F NMR δ −81.2 (t, $^4J_{FF}$ = 8.2 Hz, 3 F, CF_3), −121.0 (m, 2 F, CF_2), −127.6 (br s, 2 F, CF_2); ^{1}H NMR δ 0.86 (d, ^3J = 7.6 Hz, 3 H, 16-CH_3), 0.89 (d, ^3J = 5.6 Hz, 3 H, 15-CH_3), 0.92 (m, 1 H), 1.2 (m, 2 H), 1.2 (m, 2 H), 1.37 (s, 3 H, 14-CH_3), 1.43 (dd, *J* = 12.7 Hz, ^3J = 4.7 Hz, 2 H), 1.5−2.0 (m, 5 H), 2.31 (ddd, ^2J = 14.8, ^3J = 12.7 Hz, ^3J = 3.8 Hz, 1 H, H_B-4), 2.62 (m, 1 H, H-9), 3.92 (dtt, J_{AB} = 13.8 Hz, $^3J_{HF}$ = 12.3 Hz, $^4J_{FH}$ = 1.5 Hz, 1 H, CHH_A-CF_2), 4.24 (dtt, J_{AB} = 13.8 Hz, $^3J_{HF}$ = 12.3 Hz, J_{FH} = 1.5 Hz, 1 H, CHH_B-CF_2), 4.84 (d, ^3J = 3.4 Hz, 1 H, H-10), 5.36 (s, 1 H, H-12); ^{13}C NMR δ 12.5 (C-16), 20.2 (C-15), 24.0 (C-8), 24.6 (C-5), 26.0 (C-14), 30.6 (C-9), 34.5 (C-7), 36.3 (C-4), 37.4 (C-6), 44.1 (C-8a), 52.8 (C-5a), 64.5 (t, $^2J_{CF}$ = 27 Hz), 80.8 (C-12a), 88.0 (C-12), 103.0 (C-10), 104.3 (C-3), 114.8 (q, $^1J_{CF}$ = 256 Hz, CF_3), CF_2 and CF_2 not observed. Anal. ($C_{19}H_{25}F_7O_5$) C, H.

10α-(2′,2′,3′,3′,4′,4′,4′-Heptafluorobutyloxy)-13α-methyldihydroartemisinin (6c): $[\alpha]_D$ = 140° (MeOH, *c* = 0.3); ^{19}F NMR δ −81.1 (t, $^4J_{FF}$ = 9.4 Hz, CF_3), −121.0 (m, 2 F, CF_2), −127.6 (br s, 2 F, CF_2); ^{1}H NMR δ 0.95 (d, ^3J = 5.7 Hz, 3 H, 15-CH_3), 1.1 (m, 1 H), 1.22 (d, ^3J = 7.6 Hz, 3 H, 16-CH_3), 1.3 (br s, 1 H), 1.45 (s, 3 H, 14-CH_3), 1.5−2.1 (m, 7 H), 2.35 (ddd, ^2J = 14.8 Hz, ^3J = 12.8 Hz, ^3J = 4 Hz, 1 H, H_B-4), 3.99 (dt, J_{AB} = 14 Hz, $^3J_{HF}$ = 13.3 Hz, $^4J_{FH}$ = 1 Hz, 1 H, CHH_A-CF_2), and 4.27 (dt, J_{AB} = 14 Hz, $^3J_{HF}$ = 13.3 Hz, $^4J_{FH}$ = 1 Hz, 1 H, CHH_B-CF_2), 5.0 (d, ^3J = 3.8 Hz, 1 H, H-10), 5.4 (s, 1 H, H-12); ^{13}C NMR δ 19.4 (C-16), 20.0 (C-15), 24.6 (C-5), 25.8 (C-14), 31.3 (C-8), 34.4 (C-7), 36.4 (C-4), 37.3 (C-9), 39.0 (C-6), 46.0 (C-8a), 52.0 (C-5a), 64.5 (t, $^2J_{CF}$ = 27 Hz), 81.3 (C-12a), 89.0 (C-12), 103.4 (C-10), 103.9 (C-3), CF_3 and CF_2 not observed. Anal. ($C_{19}H_{25}F_7O_5$) C: calcd, 48.91; found, 48.19. H: calcd, 5.40; found, 6.18.

10β-(2′,2′,3′,4′,4′,4′-Hexafluorobutyloxy)dihydroartemisinin (4d). Method A: From DHA (200 mg, 0.7 mmol), BF_3,Et_2O (0.1 mL), and hexafluorobutanol (0.2 mL, 1.7 mmol), reaction (24 h) and workup provided ether **4d** (β:α 100:0) in a diastereoisomeric mixture β_1:β_2 50:50 (68 mg, 21%).

Method B: From DHA (200 mg, 0.7 mmol), TMSCl (0.4 mL, 3.2 mmol), and hexafluorobutanol (0.2 mL, 1.7 mmol), reaction (4 h), workup, and then chromatography provided ether **4d** (β:α 95:5) (β_1:β_2 50:50) (141 mg, 45%) and ether **6d** (α_1:α_2 50: 50) (48 mg, 15%).

Method C: From DHA (142 mg, 0.5 mmol), PPh_3 (196 mg, 0.75 mmol), hexafluorobutanol (0.12 mL, 1.25 mmol), and DEAD (0.2 mL, 1.25 mmol), reaction, then workup, and chromatography provided ether **4d** (β:α 98:2) (β_1:β_2 36:64) (89 mg, 40%).

10β-(2′,2′,3′,4′,4′,4′-Hexafluorobutyloxy)dihydroartemisinin (4d): gum; ^{19}F NMR δ −74.3 and −74.4 (m, 3 F, CF_3), −118.8 (δ_B −116.5, δ_A −121.1) and −118.5 (δ_A −116.9, δ_B −120.2) ($^2J_{FF}$ = 277 Hz, 2 F, CF_2), −213.5 and −214.2 (br d, $^2J_{FH}$ = 44 Hz, 1 F, CFH); ^{1}H NMR δ 0.85 (d, ^3J = 6.7 Hz, 3 H, 16-CH_3) and 0.90 (d, *J* = 5.4 Hz, 3 H, 15-CH_3), 1.25 (m, 4 H), 1.40 (s, 3 H, 15-CH_3), 1.5−2.05 (m, 6 H), 2.35 (ddd, ^2J = 13.3 Hz, ^3J = 12.8 Hz, ^3J = 4.1 Hz, 1 H, H_B-4), 2.70 (m, 1 H, H-9), 3.80 (d, J_{AB} = 11 Hz, 1 H, CH_AHCF$_2$), 4.2 (d, J_{AB} = 11 Hz, 1 H, CHH_BCF$_2$), 4.78 and 4.85 (d, 1H, $^3J_{H/H}$ = 3.3 Hz, H-10), 4.88 (br d, $^2J_{FH}$ = 44 Hz, 1 H, CHF), 5.35 (s, 1H, H-12); ^{13}C NMR δ 12.6 (C-16), 20.1 (C-15), 24.2 (C-8), 24.5 (C-5), 25.9 (C-14), 30.4 (C-9), 34.4 (C-7), 36.2 (C-4), 37.4 (C-6), 44.0 (C-8a), 44.3 (m, CHF), 52.4 (C-5a), 65.7 (t, $^2J_{CF}$ = 31 Hz, *C*H_2−CF_2-), 80.6 (C-12a), 89.0 and 80.2 (C-12), 102.6 and 102.7 (C-10), 104.2 (C-3), 118.0 (m, CF_2), 128.0 (m, CFH). Anal. ($C_{19}H_{26}F_6O_5$) C, H.

10α-(2′,2′,3′,4′,4′,4′-Hexafluorobutyloxy)-13α-methyldihydroartemisinin (6d): ^{19}F NMR δ −74.3 (t, $^3J_{FF}$ = 10.3 Hz, CF_3), −119.1 (q, δ_A −116.5, δ_B −121.4, $^2J_{FF}$ = 273 Hz, 2 F, CF_AF_B) and −119.5 (q, δ_A −117.5, δ_B −121.4, $^2J_{FF}$ = 273 Hz, 2 F, CF_AF_B), −213.7 and −214.0 (br d, $^2J_{FH}$ = 43 Hz, 1 F, CFH); ^{1}H NMR δ 0.85 (m, 1 H), 0.90 and 0.92 (d, ^3J = 5.7 Hz, 3 H, 15-CH_3), 1.18 and 1.20 (d, ^3J = 7 Hz, 3 H, 16-CH_3), 1.23 (br s, 1 H), 1.45 (s, 3 H, 14-CH_3), 1.5−1.7 (m, 5 H), 1.8−2.1 (m, 2 H), 2.35 (ddd, ^2J = 14 Hz, ^3J = 13.5 Hz, ^3J = 4 Hz, 1 H, H_B-4), 3.80 (dt, J_{AB} = 14 Hz, $^3J_{HF}$ = 13.3 Hz, $^4J_{FH}$ = 1 Hz, 1 H, CHH_A-CF_2) and 4.20 (dt, J_{AB} = 14 Hz, $^3J_{HF}$ = 13.3 Hz, J_{FH} = 1 Hz, 1 H, CHH_B-CF_2), 4.98 and 5.03 (d, ^3J = 4.5 Hz, 1 H, H-10), 5.0 (br d, $^2J_{FH}$ = 43 Hz, 1 H, CHF), 5.4 (s, 1 H, H-12); ^{13}C NMR δ 19.2 and 19.3 (C-16), 20.2 (C-15), 24.6 (C-5), 25.7 (C-14), 31.4 and 31.5 (C-8), 34.2 (C-7), 36.3 (C-4), 37.2 (C-9), 39.4 and 39.6 (C-6), 46.1 and 46.3 (C-8a), 51.6 and 51.8 (C-5a), 66.1 and 66.2 (t, $^2J_{CF}$ = 29 Hz, O-*C*$H_2$$CF_2$-), 81.3 and 81.4 (C-12a), 89.0 and 89.2 (C-12), 103.1 and 103.3 (C-3), 103.5 and 103.7 (C-10), CF_3 and CF_2 not observed. Anal. ($C_{19}H_{26}O_5F_6$) C, H.

10β-(Trifluoroisopropyloxy)dihydroartemisinin (4e). Method A: From DHA (200 mg, 0.7 mmol), BF_3,Et_2O (0.1 mL), and trifluoro-2-propanol (0.16 mL, 1.4 mmol), reaction (24 h) and workup provided ether **4e** (β:α 100:0) (8 mg, 3%).

Method B: From DHA (100 mg, 0.35 mmol), TMSCl (0.2 mL, 1.6 mmol), and trifluoro-2-propanol (0.08 mL, 0.7 mmol), reaction (5 h), workup, and then chromatography provided ether **4e** (β:α 97:3) (β_1:β_2 52:48) (68 mg, 53%). Ether β_1-**4e** (35 mg, 27%) and ether β_2-**4e** (33 mg, 26%) were separated by chromatography.

Method C: From DHA (300 mg, 1.05 mmol), PPh_3 (687 mg, 2.62 mmol), trifluoro-2-propanol (0.34 mL, 3 mmol), and DEAD (0.41 mL, 2.62 mmol), reaction, then workup, and chromatography provided ether **4e** (α:β 98:2) (β_1:β_2 100:0) (80 mg, 20%).

10β-(Trifluoroisopropyloxy)dihydroartemisinin (4e). Isomer β_1: mp 68 °C (AcOEt); $[\alpha]_D$ = 150° (MeOH, *c* = 2); ^{19}F NMR δ −79.1 (d, $^3J_{H/F}$ = 6.7 Hz); ^{1}H NMR δ 0.87 (d, ^3J = 7.5 Hz, 3 H, 16-CH_3), 0.9 (m, 2 H), 0.92 (d, ^3J = 6.5 Hz, 3 H, 15-CH_3), 1.24 (m, 1 H), 1.26 (d, ^3J = 6.5 Hz, 3 H, CF_3−C*H*-CH_3), 1.42 (s, 3H, 14-CH_3), 1.45 (dd, ^3J = 9.8 Hz, ^3J = 2.9 Hz, 2 H), 1.6 (br s, 1 H), 1.7 (br t, ^3J = 9.8 Hz, 2 H), 1.8 to 2.1 (m, 2 H), 2.32 (ddd, ^2J = 14.4 Hz, ^3J = 13.2 Hz, ^3J = 3.8 Hz, 1 H, H_B-4), 2.65 (m, 1 H, H-9), 4.29 (m, ^3J = 6.6 Hz, $^3J_{FH}$ = 6.7 Hz, 1 H, C*H*CF_3), 5.0 (d, ^3J = 3.3 Hz, 1 H, H-10), 5.4 (s, 1 H, H-12); ^{13}C NMR δ 12.5 (C-16), 12.8 (*C*H_3−CO), 20.4 (C-15), 24.2 (C-8), 24.7 (C-5), 26.2 (C-14), 30.4 (C-9), 34.7 (C-7), 36.5 (C-4), 37.5 (C-6), 44.3 (C-8a), 52.7 (C-5a), 69.2 (q, $^2J_{CF}$ = 31 Hz, CH−O), 81.0 (C-12a), 88.2 (C-12), 99.1 (C-10), 104.3 (C-3), 125 (q, $^1J_{CF}$ = 270 Hz, CF_3). Anal. ($C_{18}H_{27}F_3O_5$) C, H.

Isomer β_2: mp 64 °C (CH_2Cl_2); $[\alpha]_D$ = 130° (MeOH, *c* = 2.2); ^{19}F NMR δ −79.3 (d, $^3J_{H/F}$ = 6.5 Hz); ^{1}H NMR δ 0.92 (d, ^3J = 7.3 Hz, 3 H, 16-CH_3), 0.95 (m, 2 H), 0.96 (d, ^3J = 5.4 Hz, 3 H, 15-CH_3), 1.26 (m, 1 H), 1.34 (d, ^3J = 6.6 Hz, CF_3−C*H*-CH_3), 1.42 (s, 3 H, 14-CH_3), 1.47 (br dd, ^3J = 10.5 Hz, ^3J = 4.5 Hz, 2 H), 1.6−2.1 (m, 5 H), 2.35 (ddd, ^3J = 14.5 Hz, ^3J = 13 Hz, ^3J = 4 Hz, 1 H, H_B-4), 2.63 (m, 1 H, H-9), 4.16 (m, ^3J = 6.6 Hz, $^3J_{FH}$ = 6.7 Hz, 1 H, C*H*CF_3), 5.0 (d, ^3J = 3.3 Hz, 1 H, H-10), 5.4 (s, 1 H, H-12); ^{13}C NMR δ 12.5 (C-16), 15.5 (*C*H_3−CHOH), 20.3 (C-15), 24.3 (C-8), 24.6 (C-5), 26.0 (C-14), 30.7 (C-9), 34.5 (C-7), 36.3 (C-4), 37.5 (C-6), 44.2 (C-8a), 52.5 (C-5a), 71.7 (q, $^2J_{CF}$ = 30 Hz, *C*H−CF_3), 80.9 (C-12a), 88.2 (C-12), 103.1 (C-3), 104.3 (C-10), 126.0 (q, $^1J_{CF}$ = 274 Hz, CF_3). Anal. ($C_{18}H_{27}F_3O_5$) C, H.

10β-(1′,1′,1′-Trifluoro-2-phenylethoxy)dihydroartemisinin (4f). Method A: From DHA (100 mg, 0.35 mmol), BF_3,-

Et_2O (0.05 mL), and 1,1,1-trifluoro-2-phenylethanol (0.16 mL, 1.1 mmol), reaction (24 h) and workup did not provide ether **4f**.

Method B: From DHA (100 mg, 0.35 mmol), TMSCl (0.2 mL, 1.6 mmol), and trifluoro-2-propanol (0.16 mL, 1.1 mmol), reaction (5 h), workup, and then chromatography provided ether β-**4f** (β_1:β_2 67:33) (57 mg, 36%) and ether **6f** (13 mg, 8%), isolated by chromatography.

Method C: From DHA (284 mg, 1 mmol), PPh_3 (524 mg, 2 mmol), 1,1,1-trifluoro-2-phenylethanol (528 mg, 3 mmol), and DEAD (0.32 mL, 2 mmol), reaction, then workup, and chromatography provided ether **4f** (β_1:β_2 56:44) (108 mg, 25%).

10β-(1′,1′,1′-Trifluoro-2-phenylethoxy)dihydroartemisinin (4f): ^{19}F NMR δ −76.5 (d, ^3J = 7 Hz, CF_3) (β major) and −76.55 (d, ^3J = 7 Hz, CF_3) (β major); ^{1}H NMR δ 0.85 (d, ^3J = 7.3 Hz, 3 H, CH_3-1), 0.9 (m, 2 H), 0.92 (d, ^3J = 6 Hz, 3 H, CH_3-15),1.25 (m, 2 H), 1.35 (s, 3 H, CH_3-14), 1.45 (m, 1 H), 1.65 (br d, ^3J = 13.5 Hz, 2 H, 7-CH_2), 1.75 to 2.1 (m, 3 H), 2.25 and 2.35 (ddd, ^2J = 14.2 Hz, ^3J = 13.5 Hz, ^3J = 4 Hz, 1 H, H_B-4), 2.55 (m, 1 H, H-9), 4.62 (d, ^3J = 3.5 Hz, 1 H, H-10) (β major) and 5.12 (d, ^3J = 4.6 Hz, 1 H, H-10) (β minor), 4.9 (β minor) and 5.0 (β major) (s, 1 H, H-5), 4.95 (β minor) and 5.16 (β major) (q, 1 H, $^3J_{FH}$ = 7 Hz, 1 H, CF_3−C*H*-C_6H_5), 7.3 (m, 5 H); ^{13}C NMR δ 12.4 and 12.8 (C-16), 16.0 and 20.1 (C-15), 24.2 and 24.5 (C-8), 24.2 and 24 (C-5), 25.7 and 25.8 (C-14), 29.8 and 30.2 (C-9), 33.9 and 34.4 (C-7), 36.0 and 36.2 (C-4), 37.2 and 37.3 (C-6), 43.9 and 44 (C-8a), 51.3 and 52.4 (C-5a), 74.3 (q, $^2J_{CF}$ = 32 Hz, *C*H−CF_3), 80 and 80.8 (C-12a), 87.9 and 88 (C-12), 102.8 and 103.0 (C-10), 103.9 and 104.1 (C-3), 124 (q, $^1J_{CF}$ = 300 Hz, CF_3) and 124.3 (q, $^1J_{CF}$ = 300 Hz, CF_3), 127.7, 128.3, 128.3, 128.6, 129.0, 129.5, 131.8, 133.4. Anal. Calcd for $C_{23}O_5F_3H_{29}$: C, 62.44; H, 6.56. Found: C, 61.80; H, 7.18.

10β-(Hexafluoroisopropyloxy)dihydroartemisinin (4g). Method A: From DHA (200 mg, 0.7 mmol), BF_3,Et_2O (0.1 mL), and hexafluoro-2-propanol (0.15 mL, 1.4 mmol), reaction (24 h) and workup did not provide ether **4g**.

Method B: From DHA (150 mg, 0.53 mmol), TMSCl (0.2 mL, 1.6 mmol), and hexafluoro-2-propanol (0.1 mL, 1 mmol), reaction (5 h), workup, and then chromatography provided ether **4e** (β:α 97:3) (58 mg, 25%) and ether **6g** (9 mg, 4%).

Method C: From DHA (300 mg, 1.05 mmol), PPh_3 (687 mg, 2.62 mmol), hexafluoro-2-propanol (0.22 mL, 2.1 mmol), and DEAD (0.41 mL, 2.62 mmol), reaction and then workup provided a crude product (400 mg). To purified **4g** from dehydrodesoxyartemisin (**6**) in the crude product, the residue was treated with osmium tetroxide (0.8 mL of a 2.5% solution in *t*-BuOH) in the presence of *N*-methylmorpholine *N*-oxide (120 mg, 0.88 mmol) in a solution in a mixture of H_2O/*t*-BuOH (17 mL, 16:1) for 2 h. After usual workup, the ether β-**4g** (139 mg, 60%) was easily obtained pure by chromatography.

10β-(Hexafluoroisopropyloxy)dihydroartemisinin (4g): $[\alpha]_D$ = 163° (MeOH, *c* = 0.4); ^{19}F NMR δ −73.7 (d, ^3J = 6 Hz, CF_3); ^{1}H NMR δ 0.84 (m, 2 H), 0.9 (d, ^3J = 5.9 Hz, 3 H, 15-CH_3), 0.92 (d, ^3J = 7 Hz, 3 H, 16-CH_3), 1.2 (m, 2 H), 1.35 (s, 3 H, 14-CH_3), 1.4−1.7 (m, 3 H), 1.75 (dd, *J* = 12.3 Hz, *J* = 2.4 Hz, 1 H), 1.9 (m, 2 H), 2.3 (ddd, ^2J = 14.5 Hz, ^3J = 13 Hz, ^3J = 3.9 Hz, 1 H, H_B-4), 2.6 (m, 1 H, H-9), 4.56 (heptuplet, $^3J_{FH}$ = 6 Hz, 1 H, C*H*-$(CF_3)_2$), 5.0 (d, ^3J = 3.5 Hz, 1 H, H-10), 5.36 (s, 1 H, H-5); ^{13}C NMR δ 12.2 (16-CH_3), 20.1 (15-CH_3), 24.0 (C-8), 24.4 (C-5), 25.8 (CH_3-14), 30.2 (C-9), 34.4 (C-7), 36.2 (C-4), 37.4 (C-6), 43.8 (C-8a), 53.2 (C-5a), 71.8 (m, $^2J_{CF}$ = 32 Hz, *C*H−$(CF_3)_2$), 80.5 (C-12a), 88.2 (C-12), 103.4 (C-10), 104.3 (C-3), 121.1 (q, $^1J_{CF}$ = 283 Hz, *C*F_3), 122.2 (q, $^1J_{CF}$ = 280 Hz, *C*F_3). Anal. ($C_{18}H_{24}F_6O_5$) C, H.

10β-(1′,1′,1′,3′,3′,3′-Hexafluoro-2′-phenyl-2′-propyloxy)-dihydroartemisinin (4h). Method B: From DHA (100 mg, 0.35 mmol), TMSCl (0.2 mL, 1.6 mmol), and hexafluoro-2-phenyl-2-propanol (0.24 mL, 1.4 mmol), reaction (1 day) and workup provided dehydrodesoxyartemsinin (**5**) and starting alcohol.

Method C: From DHA (300 mg, 1.5 mmol), PPh_3 (550 mg, 2.1 mmol), 1,1,1-trifluoro-2-phenylethanol (0.35 mL, 2.1 mmol), and DEAD (0.33 mL, 2.1 mmol), reaction and then workup provided ether **4h** (β:α 92:2). Pure ether β-**4h** (154 mg, 30%) was obtained after chromatography.

10β-(1′,1′,1′,3′,3′,3′-Hexafluoro-2′-phenyl-2′-propyloxy)-dihydroartemisinin (4h): mp = 102 °C (AcOEt); $[\alpha]_D$ = 107° (MeOH, *c* = 2); ^{19}FNMR δ −67.8 (q, $^4J_{FF}$ = 11.7 Hz, CF_3), −73.7 (q, $^4J_{FF}$ = 11.7 Hz, CF_3); ^{1}H NMR δ 0.96 (d, ^3J = 6 Hz, 3 H, 15-CH_3), 1.0 (m, 1 H), 1.1 (d, ^3J = 6.7 Hz, 3 H, 16-CH_3), 1.27 (dd, ^3J = 11.5 Hz, ^3J = 6 Hz, 2 H), 1.35 (s, 3 H, 14-CH_3), 1.5 to 1.9 (m 7 H), 2.35 (ddd, ^2J = 14.5 Hz, ^3J = 13.3 Hz, ^3J = 3.6 Hz,1 H, H_B-4), 2.72 (m, 1 H, H-9), 5.2 (d, ^3J = 5 Hz, H-10), 5.6 (s, 1 H, H-12), 7.5 (m, 5 H, C_6H_5); ^{13}C NMR δ 13.9 (C-16), 20.0 (C-15), 24.2 (C-8), 25.0 (C-5), 25.5 (C-14), 31.6 (C-9), 33.8 (C-7), 36.1 (C-4), 37.4 (C-6), 44.5 (C-8a), 52.2 (C-5a), 80.4 (C-12a), 82.9 (m, $^2J_{CF}$ = 28.5 Hz, *C*-$(CF_3)_2$), 88.0 (C-12), 98.1 (C10), 103.8 (C-3), 122.5 (q, $^1J_{CF}$ = 290 Hz, *C*F_3), 122.8 (q, $^1J_{CF}$ = 290 Hz, *C*F_3), 126.8 (m, $^3J_{CF}$ = 1.9 Hz), 128.4, 129.1, 130.4 (Ph). Anal. ($C_{24}H_{28}F_6O_5$) C, H.

10β-(Pentafluorophenoxy)dehydroartemisinin (4i). Method B: From DHA (100 mg, 0.35 mmol), TMSCl (0.2 mL, 1.6 mmol), and pentafluorophenol (129 mg, 0.7 mmol), reaction (1 day) and workup provided dehydrodesoxyartemsinin (**5**) and ether **4i** (β:α 95:5) (7 mg, 7%).

Method C: From DHA (300 mg, 1.5 mmol), PPh_3 (550 mg, 2.1 mmol), 1,1,1-pentafluorophenol (388 mg, 2.1 mmol), and DEAD (0.33 mL, 2.1 mmol), reaction, then workup, and chromatography provided ether **4i** (β:α 94:6) (224 mg, 50%).

10β-(Pentafluorophenoxy)dehydroartemisinin (4i): $[\alpha]_D$ = 126° (MeOH, *c* = 2); ^{19}F NMR δ −156 (dt, $^3J_{FF}$ = 20 Hz, $^4J_{FF}$ = 2 Hz, 2 F), −162.0 (tt, $^3J_{FF}$ = 20 Hz, $^4J_{FF}$ = 2 Hz, 1 F), −163.0 (dd, $^3J_{FF}$ = 22 Hz, $^3J_{FF}$ = 20 Hz, 1 F); ^{1}H NMR δ 0.9 (d, ^3J = 6 Hz, 3 H, 15-CH_3), 0.92 (m, 1 H), 1.05 (d, ^3J = 7.3 Hz, 3 H, 16-CH_3), 1.22 (dd, ^3J = 10.5 Hz, ^3J = 6.3 Hz, 2 H), 1.35 (s, 3 H, 14-CH_3), 1.5 (m, 2 H), 1.65 (dq, ^3J = 13 Hz, ^3J = 3.4 Hz, 1 H), 1.7−2.0 (m, 4 H), 2.3 (ddd, ^2J = 14.4 Hz, ^3J = 13.2 Hz, ^3J = 3.8 Hz, 1 H, H_B-4), 2.75 (m, 1H, H-9), 5.38 (d, ^3J = 3.4 Hz, H-10), 5.6 (s, 1 H, H-12) (α-**4i** 4.94 (d, ^3J = 9.1 Hz, H-10), 5.24 (s, 1 H, H-12)); ^{13}C NMR δ 12.6 (C-16), 20.1 (C-15), 24.2 (C-8), 24.4 (C-5), 25.8 (C-14), 30.8 (C-9), 34.4 (C-7), 36.1 (C-4), 37.4 (C-6), 43.8 (C-8a), 52.3 (C-5a), 80.4 (C-12a), 88.6 (C-12), 104.3 (C-3), 106.0 (C-10), 131.03, 135.5, 140.11, 144.8. Anal. ($C_{21}H_{23}F_5O_5$) C, H.

10β-(2-Carbethoxy-3′,3′,3′-trifluoropropyloxy)dihydroartemisinin (4j). Method A: From DHA (200 mg, 0.35 mmol), BF_3,Et_2O (0.1 mL), and ethyl trifluorolactate[26] (242 mg, 1.48 mmol), reaction (24 h) and workup provided dehydrodesoxyartemisinin (**6**) and starting ethyl trifluorolactate.

Method B: From DHA (500 mg, 1.8 mmol), TMSCl (1.25 mL, 9.8 mmol), and ethyl trifluorolactate (1.2 g, 7 mmol), reaction (5 h), workup, and then chromatography provided ether β-**4j** (β_1:β_2 55:45) (125 mg, 25%) and ether α-**6j** (α_1:α_2 52:48), isolated by chromatography (34 mg, 7%).

Method C: From DHA (300 mg, 1.05 mmol), PPh_3 (549 mg, 2.16 mmol), ethyl trifluorolactate (363 mg, 2.16 mmol), and DEAD (0.18 mL, 2.16 mmol), reaction, then workup, and chromatography provided ether β-**4j** (β_1:β_2 55:45) (58 mg, 12%).

10β-(2-Carbethoxy-3′,3′,3′-trifluoropropyloxy)dihydroartemisinin (4j): ^{19}F NMR δ −73.6 (d, $^3J_{FH}$ = 7 Hz, CF_3, 45%) and −74.1 (d, $^3J_{FH}$ = 7 Hz, CF_3, 55%); ^{1}H NMR δ 0.85 (m, 1H), 0.94 (d, ^3J = 7 Hz, 3 H, 16-CH_3) or (d, ^3J = 6 Hz, 3 H, 15-CH_3), 1.25 (t, ^3J = 7 Hz, 3 H), 1.38 and 1.41 (s, 3 H, 14-CH_3), 1.48 (m, 1 H), 1.65 (dq, ^3J = 13.7 Hz, ^3J = 3.2 Hz, 1 H), 1.7−2.1 (m, 3H), 2.35 (m, 1 H, H_B-4), 2.70 (m, 1 H, H-9), 4.25 (q, ^3J = 7 Hz, 2 H, CH_2−CH_3), 4.52 and 4.80 (q, $^3J_{FH}$ = 7 Hz, C*H*-CF_3), 4.9 (br d, ^3J = 3 Hz, 1 H, H-10), 5.38 and 5.55 (s, 1 H, H-12); ^{13}C NMR δ 12.4 and 12.6 (CH_3-16), 13.9 and 14.2 (OCH_2-*C*H_3), 20.2 (CH_3 15), 23.9 and 24.1 (C-8), 24.6 and 24.7 (C-5), 25.9 (C-14), 30.4 and 30.6 (C-9), 34.6 (C-7), 36.3 (C-4), 37.4 (C-6), 44.1 (C-8a), 52.4 (C-5a), 62.4 (s, OCH_2), 72.1 and 74.9 (q, $^2J_{C/F}$ = 32 Hz, CH−CF_3), 80.9 (C-12a), 88.6 (C-12), 100.9 (C-10), 104.3 (C-3), 122.5 (q, $^1J_{C/F}$ = 270.9 Hz, CF_3), 164.7. Anal. ($C_{20}H_{21}F_3O_7$) C, H.

10α-(2-Carbethoxy-3′,3′,3′-trifluoropropyloxy)-12α-methyldihydroartemisinin (6j): ^{19}F NMR δ −73.6 (d, $^3J_{FH}$ = 7 Hz, CF_3, 10%) and −74.3 (d, $^3J_{FH}$ = 6.8 Hz, CF_3, 11%),

4.54 and 4.83 (q, $^3J_{FH} = 7$ Hz, 1 H, C*H*-CF_3), 4.98 and 5.02 (d, $^3J = 3$ Hz, 1 H, H-10), 5.4 and 5.5 (s, 1 H, H-12).

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