Anhydrodihydroartemisinin and Its 10-Trifluoromethyl Analogue: Access to Novel D-Ring-Contracted Artemisinin Trifluoromethyl Ketones

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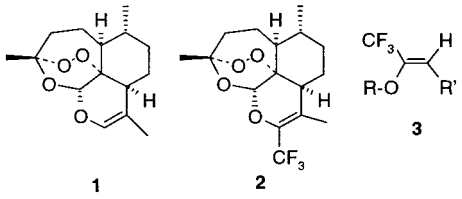
The preparation of the 10-trifluoromethyl hydroartemisinin, followed by dehydration, afforded the trifluoromethyl analogue **2** of anhydrodihydroartemisinin **1**. The reactivity of these two glycals of artemisinin were compared in epoxidation and halogenation reactions. Iodination of glycal **1** in water and the further rearrangement of the produced iodo hemiacetal provided the new D-ring-contracted aldehyde **8**α, where the methyl at C-9 is *β*. Epoxidation of 10-trifluoromethyl anhydrodihydroartemisinin **2** stereoselectively provided the *β*-epoxy ether **11** in high yield. When treated with hexafluoro-2-propanol or trifluoroethanol, **11** readily underwent a rearrangement yielding to the D-ring-contracted trifluoromethyl ketone **9**α with retention of configuration at C-9.

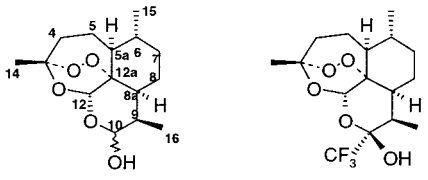
Glycal **1** of artemisinin (anhydrodihydroartemisinin) has recently received great interest because of its specific reactivity compared to that of sugar glycals and its use as a precursor of new derivatives of artemisinin, with the aim of improving its efficacy toward malaria. Glycal **1** can react with bromine and oxidizing reagents to give rise to dibromides,[1] diols,[2] epoxides,[3] bromohydrins.[4] These compounds have been used for various chemical modifications of artemisinin, in particular for the introduction of ionizable functions[1] and for access to novel ring-contracted artemisinin derivatives.[5] Taking in account our previous studies showing that introduction of fluoroalkyl substituents could improve the pharmaceutical profile of artemisinin,[6] we considered that the glycal **2**, a trifluoromethyl analogue of **1**, could be a useful precursor of other fluoro derivatives of artemisinin. Glycal **2** is a peculiar example of CF_3-substituted enol ethers **3**,[7] which we have intensively studied in reactions with electrophiles[8−10] and nucleophiles.[11] It was thus of interest to search for a good access to fluoroglycal **2** and to find out whether it could react similarly to **1** and allow the preparation of new trifluoromethyl analogues of artemisinin.



1 **2** **3**

Results and Discussion

According to the literature procedure, glycal **1** can readily be prepared from dihydroartemisinin **4** (DHA) by reaction with P_2O_5 or $BF_3{\cdot}Et_2O$.[1] Similarly, the 10-trifluoromethyl-hydroartemisinin **5**, an analogue of **4**, that we have recently reported in a preliminary communication[6a] could be, a priori, a precursor of glycal **2**.



4 (DHA) **5**

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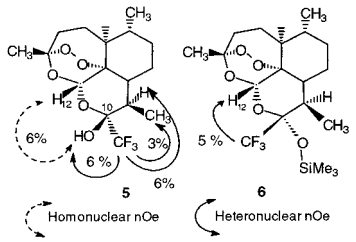
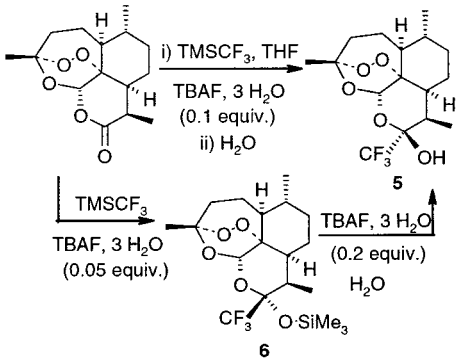


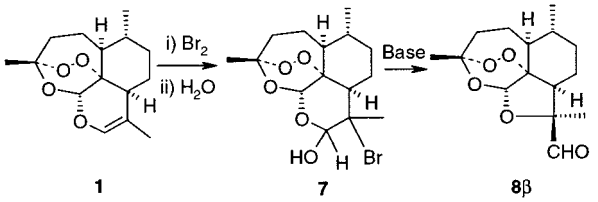
Figure 1. NOE experiments on compounds **5** and **6**.

Scheme 1. Reaction of $TMSCF_3$ with Artemisinin



Hemiketal **5** was prepared from artemisinin by treatment with 2 equiv of trifluoromethyl trimethylsilane ($TMSCF_3$)[12] in the presence of TBAF·$3H_2O$ (0.1 equiv) at room temperature; desilylation occurred after addition of water. The reaction was stereoselective and led to hemiketal **5** in high yield (78%) (Scheme 1). Complete assignment of protons and carbons by NMR and homo and hetero NOE experiments allowed assignment of an α configuration to the CF_3 group (Figure 1). This was very surprising, since the reaction of nucleophiles with dihydroartemisinin is generally favored from the less hindered *β*-face.[4,6,13] The structure of **5** was confirmed by X-ray crystal diffraction.[14] We could show that this stereochemistry is the result not of α attack by the bulky CF_3 group but of a thermodynamic equilibrium of the hemiketal formed. Actually, when the trifluoromethylation reaction was performed using only 0.05 equiv of TBAF, the silyloxy ketal **6** was isolated. In this compound, the configuration of the CF_3 group is *β*, as determined by measurement of hetero NOE (5% with H-12) (Figure 1). Addition of an excess of TBAF and water to the silyloxy ketal **6** afforded the hemiketal **5**, with complete inversion of the configuration at C-10. So the α/*β* equilibrium of **5** is quite different from that of DHA (about 50:50), probably due to the large size of the CF_3 group,[15] which suffers a repulsive interaction with the methyl group at C-9.

Scheme 2. Preparation of Aldehyde 8*β*[5]



Dehydration of **5** was initially attempted under the conditions described for DHA.[1] With P_2O_5 or BF_3·Et_2O, the starting material was recovered. This confirms the great stability of CF_3-substituted hydroxyl compounds in acidic medium.[16] All of our efforts to convert the hydroxyl group into a better leaving group (acetate, mesylate, triflate), to facilitate the elimination, failed. Finally, the glycal **2** was obtained in good yields by treatment of the trifluoromethyl hemiketal **5** with thionyl chloride and pyridine.

With the fluoro glycal **2**, an analogue of **1**, in hand, we investigated its reactivity toward oxidizing agents in order to prepare ring-contracted fluoroartemisinin derivatives. Venugopalan et al. have shown that the addition of bromine onto **1** and further hydrolysis with water afforded 9-bromodihydroartemisinin **7**.[4] This bromohemiacetal readily undergoes a rearrangement under basic conditions, leading to aldehyde **8***β*, isolated as a single isomer (Scheme 2).[5] The aldehyde **8***β* is precursor of a variety of new artemisinin derivatives, some of them exhibiting high antimalarial activities against chloroquine sensitive and chloroquine resistant strains of *Plasmodium falciparum*.[5] Our aim was to study such a rearrangement, starting from fluoroglycal **2**, to have direct access to the trifluoromethyl ketone **9**, an analogue of the aldehyde **8**.

When glycal **2** was reacted with bromine under similar conditions, neither the CF_3-substituted bromo hemiketal nor the precursor dibromoether was detected. We then envisaged preparation of the epoxyether **11**, an analogue of **10** (Schemes 3 and 5),[2] to investigate its rearrangement. Epoxidation of **2** was performed with *m*-chloroperbenzoic acid (*m*-CPBA), as described for the epoxidation of enol ethers **3**,[7] and selectively provided one stereoisomer of epoxy ether **11** in good yield (77%). The presence of the other stereoisomer was not detected at all.

To favor the rearrangement of epoxy ether **2**, fluorinated alcohols appeared to be excellent candidates for the reaction medium in which to perform this reaction, since they are poor nucleophiles[17] and have been shown to activate oxirane rings.[18−20] Treatment of the epoxy

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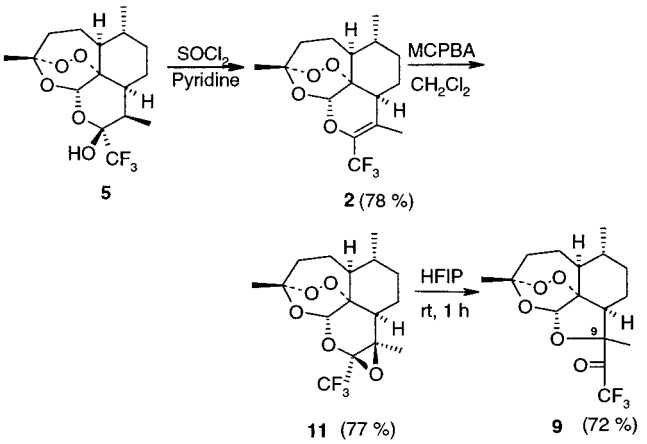
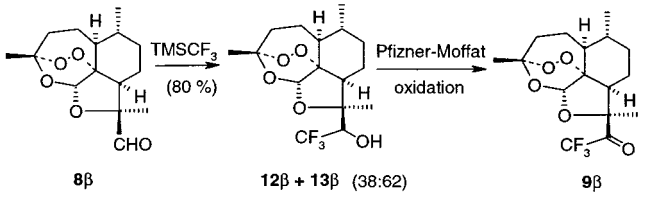
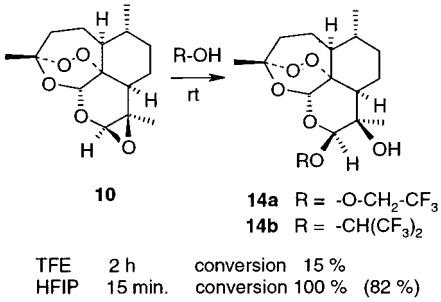
Scheme 3. Epoxidation of Glycal 2 and Rearrangement into Ketone 9



Scheme 4. Preparation of Ketone 9β from Aldehyde 8β



Scheme 5. Solvolysis of Epoxy Ether 10 in Fluoroalkyl Alcohols



ether **11** with hexafluoro-2-propanol (HFIP) or trifluoroethanol (TFE) provided, after 1 h at room temperature, the rearranged trifluoromethyl ketone **9** as a single stereoisomer (72%) (Scheme 3). NMR data of **11** and **9** did not allow the unambiguous determination of the configuration at C-9. A deshielded shift of the methyl substituent at C-9 (^{13}C $\delta = 20$ ppm in both compounds) is generally characteristic of an α-methyl in artemisinin series.[2,6b] However, this criterion cannot be applied to a ring-contracted artemisinin derivative such as **9**, and, in **11**, this deshielding could be an effect of the second substituent at C-9. The α configuration of the methyl at C-9 in the epoxy ether **11** was confirmed by X-ray diffraction,[14] thus indicating that epoxidation of **2** occurs exclusively from the β face. To determine the configuration of ketone **9**, trifluoromethyl ketone **9**β has been prepared from the known aldehyde **8**β,[5] which reacted easily with $TMSCF_3$, leading to a 40/60 mixture of the alcohols **12**β and **13**β, epimers at C-10, in high yield (80%) (Scheme 4). Their oxidation has been performed under Pfizner−Moffat conditions[21] affording the ketone **9**β in 40% yield. NMR data of **9**β are different from those of the ketone resulting from epoxyether **11** rearrangement

Table 1. NMR Data of D-Ring-Contracted Artemisinin Derivatives

		8β	**8**α	**9**β	**9**α	**12**β/**13**β	**12**α/**13**α
^{19}F δ	CF_3			−75.1	−70.3	−71.1/−72.1	−72.3/−71.9
	H-8a	2.20	2.25	2.29	2.70	2.20	2.26/2.52
^{1}H δ	H-10	9.72	9.99			4.06/4.16	4.87/4.49
	H-16	1.58	1.18	1.74	1.41	1.69/1.68	1.29/1.32
	C-8a	52.2	51.8	52.7	49.5	53.2/52.6	48.6/47.8
	C-9	89	89.8	90.3	88.7	84.5/85.2	84.6/83.8
	C-10	204.6	207.4	193.8	192	72.4	73.5/73.8
^{13}C δ	C-12	97.9	96.9	98.1	97	96.9/97.3	95.5/95.9
	C-12a	86	86.3	85.7	86	86.1/86.8	87.1/86.7
	C-16	22.6	17.6	26.4	20.0	21/21.4	16.6/18.8
	CF_3			116	116.2	125/124	124/125

(Table 1), suggesting that the rearrangement of the β epoxy ether **11** provided the ketone epimer **9**α.

These surprising results raised questions about mechanism of these reactions. A plausible mechanism of the rearrangement of bromo hemiacetal **7** should involve the nucleophilic substitution of the bromine by the alkoxide produced by the opening of the hemiacetal, and hence should occur with inversion of the C-9 configuration.[5] This implies that the bromine atom in **7** is β, and that **7** results from the nucleophilic ring opening of a β-bromonium ion. This seems to be consistent with the usual β approach of reagents toward artemisinin derivatives,[4,6,13] as exemplified with the formation of the β epoxy ethers **10** and **11**. Similarly, a concerted rearrangement of the β - epoxy ether **11** should occur with inversion of the C-9 configuration thus leading to ketone **9**β.

To clarify this apparent inconsistency, we searched for conditions which permit the preparation of aldehyde **8**α.[22] At first, although the reactivity of the nonfluorinated epoxy ether **10** was expected to be quite different from that of fluorinated epoxy ether **11**, because of the easier positive charge development at the anomer carbon,[23] the rearrangement of **10** was attempted in fluoro alcohols as solvents. Reaction of epoxy ether **10** with trifluoroethanol was very slow (only 15% of conversion after 2 h), and led to the glycol ether **14a**.[24] With HFIP, after only 15 min at room temperature, the glycol ether **14b** was obtained in 82% yield, with no traces of the rearranged aldehyde **8** (Scheme 5). Despite the very poor nucleophilicity of HFIP, the solvolytic product was obtained. These results reveal the great difference in reactivity between fluorinated and non fluorinated epoxy ethers.[23]

We then revisited the preparation and rearrangement of bromo hemiacetals **7** (Scheme 2), with the aim of determining the structures of intermediates and confirming the postulated mechanism. Bromohemiacetals **7** were prepared from the glycal **1** according to Venugopalan's procedure, by successive additions of bromine and water.[5] A 60/40 mixture of two bromo hemiacetals (out of the four

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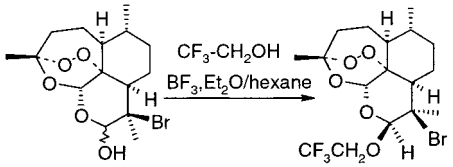
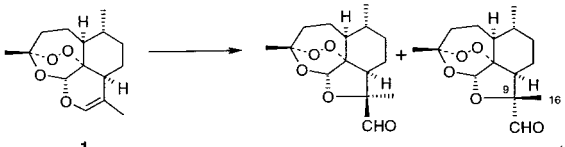
Scheme 6. Preparation of Bromoacetal 15



7 **15**

Scheme 7. Reaction of Glycal 1 with Halogenating Agents



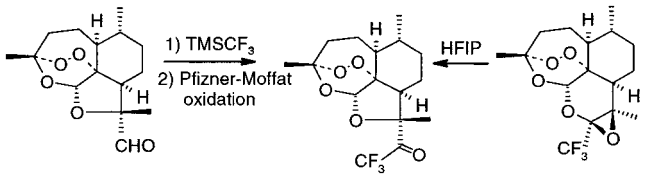
1	**8β**	**8α**	**(8β+8α)**[a,b]
i) Br_2, CCl_4; ii) H_2O; iii) Et_3N	100 %	0 %	(92 %)
i) NBS, H_2O/DME, ii) Et_3N	80 %	20 %	(76 %)
NIS, H_2O, DME	20 %	80 %	(75 %)
I_2, phosphate buffer, H_2O, tBuOH	0 %	100 %	(57 %)

[a] isolated yield
[b] no starting material recovered

possible stereoisomers) was obtained. NMR data did not allow assignment of the configuration at C-9 because the downfield shift of the methyl at this site could be an effect of the gem bromine. Bromohemiacetals **7** could be easily converted into bromo acetals **15** (90/10 mixture, 73%) by reaction of trifluoroethanol, in the presence of $BF_3{\cdot}OEt_2$, in hexane (Scheme 6). Since a 60/40 mixture of **7** provided a 90/10 mixture of **15**, the two isomers should be different in their configuration at C-10. For the major isomer, complete assignment of protons and carbons by NMR, hetero NOE (1.3% with H-12), and homo NOE (10% between H-10 and CH_3-16) experiments suggest a β configuration of Br. This structure was confirmed by X-ray crystal diffraction.[14] We have thus demonstrated that the bromination of glycal **1** leads exclusively to the β bromonium ion, which further provides the β-bromohemicetals **7**.

We next turned to other conditions of halogenation of **1**, and results of this study have recently been reported in a preliminary communication and are summarized in Scheme 7.[22] Interestingly, the stereochemistry of the reaction was found to vary widely with the halogenating agent. While the sequence described in Scheme 2 provided aldehyde **8**β exclusively, treatment of glycal **1** with I_2 in *t*BuOH/H_2O afforded aldehyde **8**α as a single stereoisomer. A similar tendency was observed using *N*-iodosuccinimide in H_2O. With both stereoisomers of **8** in hand, comparison of their NMR data unambiguously allowed the attribution. In NMR data of the previously described aldehyde **8**β, the observation of homo NOE (H-10,H-12 and H-8a,CH_3-16) seemed to confirm the proposed configuration at C-9. However, the correlation between H-8a and CH_3-16 could also be observed between trans equatorial substituents. Since this effect is not observed in the other stereoisomer, when observed, it actually indicates a cis relationship between H-8a and CH_3-16. To explain such a difference in the stereochemical outcome of the reaction, a different rearrangement mechanism could be invoked, for example, involving the intermediate formation of the α-epoxy ether, stereoisomer of **10**. However, considering the ease of the hydrolytic cleavage of the α-epoxy ether,[2] this mechanism is unlikely. A more reasonable explanation would be the change in the steric course of the halogenation reaction. In contrast to the case of the bromohemiacetals **7**, the iodine in the iodo-hemiacetals involved has probably an α configuration. However these intermediates could not be isolated.

Scheme 8. Preparation of Ketone 9α



8α **9α** **11**

So, taking advantage of this remarkable difference in the stereochemical outcome of reactions of the glycal **1** of artemisinin using brominating and iodinating agents, we could selectively obtain the hitherto unknown aldehyde **8**α in good yield. The reaction of $TMSCF_3$ with **8**α provided a 90/10 mixture of alcohols **12**α and **13**α (70%), which were further oxidized into ketone **9**α (88%) as described for **12**β and **13**β. NMR data of ketone **9**α are identical to those of the ketone **9** obtained by epoxy ether **11** rearrangement (Table 1, Scheme 8). The mechanism of this rearrangement is very surprising: it seems to involve the unusual cleavage of the C−O bond β to CF_3,[23] thus suggesting a favored development of positive charge on the C-9 tertiary carbon rather than on the C-10 carbon substituted by both CF_3 and alkoxyl groups. This may be due to the dissymmetric structure of the oxirane in **11**, where the C10−O bond length is 1.367 Å, while the C9−O bond is 1.473 Å.[14] Furthermore, this rearrangement occurs with retention of configuration at C-9, which is unexpected in a concerted process. A rearrangement involving the C10−O bond cleavage thus cannot be ruled out.

It is worth noting that, with ^{13}C and ^{1}H NMR data of the α/β pair of aldehydes **8**, ketones **9**, and alcohols **12** and **13** (Table 1) taken into account, a deshielded shift of C-16 and H-16 in D-ring-contracted artemisinin derivatives seems to be characteristic of an α methyl such as in artemisinin derivatives.[2,6b]

In conclusion, we have performed comparative studies on the reactivity of glycal **1** of artemisinin and its 10-trifluoromethyl analogue **2**. Both compounds have been used to prepare novel D-ring-contracted artemisinin derivatives with a trifluoromethyl ketone at C-9, through the rearrangement of the corresponding iodohemiacetal for the former and the rearrangement of the corresponding epoxy ether, in hexafluoro-2-propanol, for the latter. Although its mechanism is not yet elucidated, this easy rearrangement of CF_3-substituted epoxyether in HFIP, with retention of configuration at the substitution site, is of synthetical interest.

These reactions have allowed access to a new family of fluorinated artemisinin derivatives with a rearranged skeleton. Antimalarials properties of trifluoromethyl ketones and parent alcohols are under evaluation.

Experimental Section

NMR spectra were performed with $CDCl_3$ solution. Chemical shifts are reported in parts per million 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 cou-

pling. For the determination of fine coupling constants, an acquisition of 16K data points, a Lorenz-Gauss transformation of the FID, and a zero filling to 64K were performed to obtain a minimum of resolution of 0.2 Hz/pt (^{1}H) or 0.5 Hz/pt (^{13}C). When indicated, assignments of signals resulted from a complete assignment of the spectrum through HMQC, HMBC experiments performed on a multinuclear probehead equipped with a *Z*-gradient coil. In NMR data, numbering of atoms is presented according to the usual numbering in artemisinin as indicated in the text.

Artemisinin is extracted and purified at the Institute of Natural Products (CNST, Hanoi, Vietnam).

(1*S*,4*R*,5*R*,8*R*,9*R*,10*R*,12*R*,13*R*)-1,5,9-Trimethyl-10-(trifluoromethyl)-11,14,15,16-tetracyclo[10.3.1.0.^{4,13}0^{8,13}]hexadecan-10-ol (5). $TMSCF_3$ (4.2 mL, 28 mmol, 2 equiv) was added to a stirred solution of artemisinin (4 g, 14 mmol) and TBAF·3H_2O (442 mg, 1.4 mmol, 0.1 equiv) in THF (24 mL) at 0 °C. After 2 h, the reaction medium was warmed to room temperature, and 0.5 mL of water was added; the mixture was stirred for 30 min at room temperature. Complete disappearance of the silyloxy ketal was checked by TLC. The reaction medium was poured into brine and extracted (Et_2O). The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The crude product was dissolved in petroleum ether and filtered on silica gel (90:10 petroleum ether/AcOEt). After evaporation of solvents, petroleum ether was added to the already crystalline product for complete crystallization to give pure hemiketal **5** (3.84 g, 77%): mp 156 °C (petroleum ether/AcOEt); $[\alpha]^{25}_D$ +107 (*c* 0.5, MeOH); ^{19}F NMR δ −84.5 (q, $^4J_{F-H}$ = 1.5 Hz, CF_3); ^{1}H NMR δ 0.94 (m, 1 H, H-7ax), 0.97 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.07 (d, $^3J_{H16-H9}$ = 7 Hz, 3 H, CH_3-16), 1.3 (m, 1 H, H-6), 1.32 (m, 1 H, H-5a), 1.42 (s, 3 H, CH_3-14), 1.49 (dddd, ^2J = 14 Hz, $^3J_{H5ax-H4ax}$ = 13.5 Hz, $^3J_{H5ax-H5a}$ = 11.5 Hz, $^3J_{H5ax-H4eq}$ = 5 Hz, 1 H, H-5ax), 1.55 (dt, $^3J_{H8a-H8ax}$ = 12.5 Hz, $^3J_{H8a-H8eq}$ = $^3J_{H8a-H9}$ = 5.5 Hz, 1 H, H-8a), 1.7 (dq, ^2J = 13.5 Hz, $^3J_{H7eq-H8ax}$ = $^3J_{H7eq-H8eq}$ = $^3J_{H7eq-H6}$ = 3.5 Hz, 1 H, H-7eq), 1.81 (dddd, ^2J = 14 Hz, $^3J_{H8ax-H7ax}$ = 13.5 Hz, $^3J_{H8ax-H8a}$ = 13 Hz, $^3J_{H8ax-H7eq}$ = 3.5 Hz, 1 H, H-8ax), 1.85 (m, 1 H, H-8eq), 1.91 (dddd, ^2J = 14 Hz, $^3J_{H5eq-H5a}$ = 6.5 Hz, $^3J_{H5eq-H4ax}$ = 4 Hz, $^3J_{H5eq-H4eq}$ = 3 Hz, 1 H, H-5eq), 2.05 (ddd, ^2J = 14.5 Hz, $^3J_{H4eq-H5eq}$ = 5 Hz, $^3J_{H4eq-H5ax}$ = 3 Hz, 1 H, H-4eq), 2.4 (ddd, ^2J = 14.5 Hz, $^3J_{H4ax-H5ax}$ = 13.5 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 2.77 (d, $^4J_{OH-H9}$ = 2 Hz, 1 H, OH), 2.84 (qdd, $^3J_{H9ax-H16}$ = 7 Hz, $^3J_{H9ax-H8a}$ = 5.5 Hz, $^4J_{H9-OH}$ = 2 Hz, 1 H, H-9ax), 5.55 (s, 1 H, H-12); ^{13}C NMR δ 12.4 (C-16), 20.1 (C-15), 23.1 (C-8), 24.6 (C-5), 25.5 (C-14), 28.2 (C-9), 34.4 (C-7), 36.1 (C-4), 37.4 (C-6), 45.8 (C-8a), 51.7 (C-5a), 79.9 (C-12a), 88.8 (C-12), 96.9 (q, $^2J_{C-F}$ = 31 Hz, C-10), 104.4 (C-3), 122.6 (q, $^1J_{C-F}$ = 282 Hz, CF_3). Anal. Calcd for $C_{16}H_{23}F_3O_5$: C, 54.54; H, 6.58. Found: C, 54.55; H, 6.59.

Trimethylsilyl(1*S*,4*R*,5*R*,8*R*,9*R*,10*R*,12*S*,13*R*)-1,5,9-trimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0.^{4,13}0^{8,13}]hexadec-10-yl Ether (6). $TMSCF_3$ (0.53 mL, 3.4 mmol, 2 equiv) was added to a stirred solution of artemisinin (500 mg, 1.7 mmol) and TBAF·3 H_2O (27 mg, 0.09 mmol, 0.05 equiv) in THF (15 mL) at 0 °C, and the reaction medium was warmed to room temperature for 7 h. Complete disappearance of artemisinin was checked by TLC. The reaction medium was poured into brine and extracted (Et_2O). The organic phase was dried ($MgSO_4$) and concentrated. The crude product was purified by filtration on a SiO_2 column (95:5 petroleum ether/AcOEt) to give pure silyloxyketal **6** (593 mg, 79%): mp 97 °C (petroleum ether/AcOEt); $[\alpha]^{25}_D$ + 35 (*c* = 0.54, MeOH); ^{19}F NMR δ −75.2 (s, 3 F, CF_3); ^{1}H NMR δ 0.25 (s, 9 H, $Si(CH_3)_3$), 0.95 (m, 1H, H-7ax), 0.95 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.06 (dq, $^3J_{H16-H9}$ = 8 Hz, $^4J_{F-H16}$ = 2 Hz, 3 H, CH_3-16), 1.25 (m, 1 H, H-5a), 1.28 (m, 1 H, H-6), 1.42 (s, 3 H, CH_3-14), 1.45 (m, 1 H, H-5ax), 1.5 (m, 1 H, H-8ax), 1.55 (m, 1 H, H-8a), 1.65 (dq, ^2J = 13.5 Hz, $^3J_{H7eq-H6}$ = $^3J_{H7eq-H8eq}$ = $^3J_{H7eq-H8ax}$ = 3 Hz, 1 H, H-7eq), 1.75 (dq, ^2J = 13 Hz, $^3J_{H8eq-H7eq}$ = $^3J_{H8eq-H8a}$ = $^3J_{H8eq-H7ax}$ = 3 Hz, 1 H, H-8eq), 1.88 (m, 1 H, H-5eq), 2.05 (m, 1 H, H-4eq), 2.3 (m, 1 H, H-4ax), 2.75 (qdq, $^3J_{H9-H16}$ = 7.5 Hz, $^3J_{H9ax-H8a}$ = 5.5 Hz, $^4J_{H9ax-F}$ = 2 Hz, 1 H, H-9ax), 5.5 (s,1 H, H-12); ^{13}C NMR δ 2 ($Si(CH_3)_3$), 12 (C-16), 20 (C-15), 22 (C-8), 24 (C-5), 26 (C-14), 34.2 (C-7), 35.5 (C-4), 37 (C-6), 37.2 (C-9), 45 (C-8a), 52.5 (C-5a), 80 (C-12a), 91.5 (C-12), 98 (C-10), 104 (C-3), 123.5 (CF_3). Anal. Calcd for $C_{19}H_{31}F_3O_5Si$: C, 53.75; H, 7.36. Found: C, 53.41; H, 7.31.

(1*S*,4*R*,5*R*,8*R*,12*R*,13*R*)-1,5,9-Trimethyl-10-(trifluoromethyl)-11,14,15,16-tetraoxatetracyclo[10.3.1.0.^{4,13}0^{8,13}]-hexadec-2-ene (2). $SOCl_2$ (32 μL, 0.42 mmol, 1.5 equiv) was added, under Ar, at 0 °C to a solution of hemiketal **6** (100 mg, 0.28 mmol) in pyridine (1 mL, distilled on KOH). After 1 h, aqueous 3 M HCl solution (5 mL) was added. After extraction (CH_2Cl_2), the organic phase was washed (brine), dried ($MgSO_4$), and concentrated. The crude glycal, accompanied by 10% of the corresponding chloride, was purified on a SiO_2 column (95:5 petroleum ether/AcOEt) to give the pure glycal **2** as white crystals (82 mg, 78%): mp 115 °C (petroleum ether/AcOEt); $[\alpha]^{25}_D$ − 43 (*c* 0.54, MeOH); ^{19}F NMR δ − 65.2 (qd, $^5J_{F-H16}$ = 2.5 Hz, $^5J_{F-H12}$ = 1.5 Hz, 3 F, CF_3); ^{1}H NMR δ 1.01 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.18 (m, 1 H, H-7ax), 1.24 (qd, ^2J = $^3J_{H8ax-H7ax}$ = $^3J_{H8ax-H8a}$ = 13 Hz, $^3J_{H8ax-H7eq}$ = 3 Hz, 1 H, H-8ax), 1.43 (s, 3 H, CH_3-14), 1.45 (m, 2 H, H-5a and H-5), 1.46 (m, 1 H, H-6), 1.73 (dq, ^2J = 13 Hz, $^3J_{H7eq-H6ax}$ = $^3J_{H7eq-H8eq}$ = $^3J_{H7eq-H8ax}$ = 3 Hz, 1 H, H-7eq), 1.82 (m, 1 H, H-8a), 1.83 (q, $^5J_{H16-F}$ = 2.5 Hz, 3 H, CH_3-16), 1.95 (m, 1 H, H-5), 2.03 (m, 1 H, H-8eq), 2.05 (ddd, ^2J = 14.5 Hz, $^3J_{H4eq-H5eq}$ = 4.5 Hz, $^3J_{H4eq-H5ax}$ = 3 Hz, 1 H, H-4eq), 2.41 (ddd, ^2J = 14.5 Hz, $^3J_{H4ax-H5ax}$ = 13 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 5.7 (s, 1 H, H-12); ^{13}C NMR δ 15.5 (C-16), 20.2 (C-15), 24.5 (C-5), 25.7 (C-14), 28.9 (C-8), 34.2 (C-7), 36.2 (C-4), 37.7 (C-6), 47.5 (C-8a), 50.8 (C-5a), 78.5 (C-12a), 90.5 (C-12), 105 (C-3), 112 (C-9), 135 (m, C-10). Anal. Calcd for $C_{16}H_{23}F_3O_4$: C, 57.14; H, 6.89. Found: C, 57.46; H, 6.33.

(1*R*,3*R*,5*R*,6*R*,9*R*,10*R*,13*S*,16*R*)-5,9,13-Trimethyl-3-(trifluoromethyl)-2,4,14,15,17-pentaoxapentacyclo-[11.3.1.0.^{3,5}0.^{6,16}0^{10,16}]heptadecane (11). MCPBA (60%) (630 mg, 3 mmol, 2 equiv) was added to a solution of glycal **2** (500 mg, 1.5 mmol), in solution in dichloromethane (15 mL). After 15 h at room temperature, an aqueous saturated solution of $NaHCO_3$ (30 mL X 3) was added, and the reaction medium was extracted (CH_2Cl_2). Organic phases were washed to neutrality (brine), dried ($MgSO_4$), and concentrated. The crude product was purified on a SiO_2 column (90:10 petroleum ether/AcOEt) to lead to the pure epoxy ether **11** (400 mg, 77%) as white crystals: mp 123 °C (petroleum ether/AcOEt); $[\alpha]^{25}_D$ +118 (c 0.5, MeOH); ^{19}F NMR δ − 74.3 (s, 3 F, CF_3); ^{1}H NMR δ 0.97 (d, $^3J_{H15-H6}$ = 7 Hz, 3 H, CH_3-15), 1.09 (tdd, ^2J = $^3J_{H7ax-H8ax}$ = 11.5 Hz, $^3J_{H7ax-H6ax}$ = 15.5 Hz, $^3J_{H7ax-H8eq}$ = 3.5 Hz, 1 H, H-7ax), 1.35 (m, 2 H, H-5a and H-6), 1.43 (s, 3 H, CH_3-14), 1.47 (dq, ^2J = 13.5 Hz, $^3J_{H5eq-H4ax}$ = $^3J_{H5eq-H4eq}$ = $^3J_{H5eq-H5a}$ = 3.5 Hz, 1 H, H-5eq), 1.53 (s, 3 H, CH_3-16), 1.72 (dq, ^2J = 13 Hz, $^3J_{H7eq-H8ax}$ = $^3J_{H7eq-H8eq}$ = $^3J_{H7eq-H6}$ = 3.5 Hz, 1 H, H-7eq), 1.8 (m, 1 H, H-8), 1.87 (m, 1 H, H-8a), 1.9 (m, 1 H, H-5ax), 2.04 (ddd, ^2J = 14.5 Hz, $^3J_{H4eq-H5ax}$ = 5 Hz, $^3J_{H4eq-H5eq}$ = 3 Hz, 1 H, H-4eq), 2.33 (ddd, ^2J = $^3J_{H4ax-H5ax}$ = 13 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 5.37 (s, 1 H, H-12); ^{13}C NMR δ 20.5 (C-16, C-15), 23 (C-8), 24 (C-5), 26 (C-14), 62 (C-9), 33.5 (C-7), 36.2 (C-4), 37.2 (C-6), 47.5 (C-8a), 51.5 (C-5a), 78 (C-12a), 91.5 (C-12), 84.2 (C-10), 104.5 (C-3), CF_3 not observed. Anal. Calcd for $C_{16}H_{21}F_3O_5$: C, 54.85; H, 6.04. Found: C, 54.68; H, 5.90.

(1*S*,4*R*,5*S*,8*R*,9*S*,11*S*,12*S*)-1,5,9-Trimethyl-10,13,14,15-tetraoxatetracyclo[9.3.1.0.^{4,12}0^{8,12}]pentadecane-9-carbaldehyde (8*β*).[5] A solution of glycal **1** (2.0 g, 7.5 mmol) in CCl_4 (40 mL) was cooled to 0 °C, and Br_2 (1 M in CCl_4, 11.3 mL, 11.3 mmol, 1.5 equiv) was added dropwise. After 30 min of stirring at this temperature, distilled water (10 mL) was added and the mixture was stirred for an additional 1 h. The reaction was diluted with Et_2O, washed with sodium thiosulfate aqueous solution, aqueous $NaHCO_3$, and brine, and then dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded the 9*β*-bromodihydroartemisinin **7** (2.6 g, 96%) as a white solid (mixture of two isomers determined by ^{1}H NMR).[4] The crude product **7** (2.6 g, 7.2 mmol) was dissolved in CH_2Cl_2 (60 mL), and Et_3N (1.5 mL, 10.8 mmol, 1.5 equiv) was added. After 30 min of stirring, the reaction medium was concentrated and the residue was purified on a SiO_2 column (CH_2Cl_2) to provide aldehyde **8*β*** (1.9 g, 89% from **1**) as a white

solid: mp 148 °C (ether/petroleum ether); $[\alpha]_D^{25}$ + 42 (*c* 0.51, MeOH); IR ν_{CO} 1734 cm^{-1}; ^{1}H NMR δ 0.95 (d, $^3J_{H15-H6}$ = 6.5 Hz, 3 H, CH_3-15), 0.98 (m, 1 H, H-7ax), 1.13 (qd, ^2J = $^3J_{H8ax-H7ax}$ = $^3J_{H8ax-H8a}$ = 13.5 Hz, $^3J_{H8ax-H7eq}$ = 3 Hz, 1 H, H-8ax), 1.22 (m, 1 H, H-6), 1.39 (m, 1 H, H-5ax), 1.44 (s, 3 H, CH_3-14), 1.5 (m, 1 H, H-5a), 1.57 (qd, ^2J = 13.5 Hz, $^3J_{H7eq-H6}$ = $^3J_{H7eq-H8eq}$ = $^3J_{H7eq-H8ax}$ = 3 Hz, 1 H, H-7eq), 1.58 (s, 3 H, CH_3-16), 1.72 (tdd, ^2J = 13 Hz, $^3J_{H8eq-H7ax}$ = $^3J_{H8eq-H7eq}$ = 3.5 Hz, $^3J_{H8eq,H8a}$ = 6.5 Hz, 1 H, H-8eq), 1.97 (tdd, ^2J = 14 Hz, $^3J_{H5eq-H4ax}$ = $^3J_{H5eq-H4eq}$ = 4 Hz, $^3J_{H5eq-H5a}$ = 5.5 Hz, 1 H, H-5eq), 2.08 (td, ^2J = 14.5 Hz, $^3J_{H4eq-H5ax}$ = $^3J_{H4eq-H5eq}$ = 3.5 Hz, 1 H, H-4eq), 2.2 (dd, $^3J_{H8a-H8ax}$ = 13.5 Hz, $^3J_{H8a-H8eq}$ = 6.5 Hz, 1 H, H-8a), 2.31 (ddd, ^2J = 13 Hz, $^3J_{H4ax-H5ax}$ = 15 Hz, $^3J_{H4ax-H5eq}$ = 5 Hz, 1 H, H-4ax), 5.82 (s, 1 H, H-12), 9.72 (s, 1 H, H-10); ^{13}C NMR δ 19.6 (C-15), 22.6 (C-16), 24.2 (C-5), 25.1 (C-14), 25.8 (C-8), 32.3 (C-7), 36.6 (C-6), 36.9 (C-4), 48.2 (C-5a), 52.2 (C-8a), 86 (C-12a), 89 (C-9), 97.9 (C-12), 103.7 (C-3), 204.6 (C-10). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.23; H, 7.59.

(1*S*,4*R*,5*S*,8*R*,9*R*,11*S*,12*S*)-1,5,9-Trimethyl-10,13,14,15-tetraoxatetracyclo[9.3.1.0^{4,12}.0^{8,12}]pentadecane-9-carbaldehyde (8α). To a suspension of glycal **1** (200 mg, 0.8 mmol) maintained in the dark in *t*-BuOH (8 mL) were added distilled water (1 mL) and a phosphate buffer solution (20 mL, pH 7.2). I_2 (508 mg, 2 mmol, 2.5 equiv) was then added to the vigorously stirred reaction medium. After the mixture was stirred for 24 h, water was poured, and the mixture was extracted with Et_2O. Organic phases were washed with sodium thiosulfate aqueous solution, aqueous $NaHCO_3$, and brine and then dried ($MgSO_4$). After evaporation of the solvent under reduced pressure, the crude product was purified on a SiO_2 column (CH_2Cl_2) to give aldehyde **8**α (126 mg, 57%) as a white solid: mp 105 °C (AcOEt/petroleum ether); $[\alpha]_D^{25}$ +131 (*c* 0.51, MeOH); IR ν_{CO} 1722 cm^{-1}; ^{1}H NMR δ 0.99 (d, $^3J_{H15-H6}$ = 6.5 Hz, 3 H, CH_3-15), 1.05 (ddd, ^2J = 13.5 Hz, $^3J_{H7ax-H8ax}$ = 12 Hz, $^3J_{H7ax-H6}$ = 3 Hz, 1 H, H-7ax), 1.18 (s, 3 H, CH_3-16), 1.25 (m, 1 H, H-6), 1.3 (qd, ^2J = $^3J_{H8ax-H7ax}$ = $^3J_{H8ax-H8a}$ = 13.5 Hz, $^3J_{H8ax-H7eq}$ = 3 Hz, 1 H, H-8ax), 1.39 (m, 1 H, H-5ax), 1.43 (s, 3 H, CH_3-14), 1.51 (td, $^3J_{H5a-H5ax}$ = $^3J_{H5a-H6}$ = 11.5 Hz, $^3J_{H5a-H5eq}$ = 6 Hz, 1 H, H-5a), 1.68 (qd, ^2J = 13.5 Hz, $^3J_{H7eq-H6}$ = $^3J_{H7eq-H8ax}$ = $^3J_{H7eq-H8eq}$ = 3.5 Hz, 1 H, H-7eq), 1.78 (td, ^2J = 13.5 Hz, $^3J_{H8eq-H7eq}$ = $^3J_{H8eq-H8a}$ = 3 Hz, 1 H, H-8eq), 1.98 (dddd, ^2J = 14 Hz, $^3J_{H5eq-H4ax}$ = 4 Hz, $^3J_{H5eq-H4eq}$ = 3.5 Hz, $^3J_{H5eq-H6a}$ = 5.5 Hz, 1 H, H-5eq), 2.07 (td, ^2J = 14.5 Hz, $^3J_{H4eq-H5ax}$ = $^3J_{H4eq-H5eq}$ = 4 Hz, 1 H, H-4eq), 2.25 (dd, $^3J_{H8a-H8ax}$ = 13.5 Hz, $^3J_{H8a-H8eq}$ = 4 Hz, 1 H, H-8a), 2.29 (dd, ^2J = 13 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 5.77 (s, 1 H, H-12), 9.99 (s, 1 H, H-10); ^{13}C NMR δ 17.6 (C-16), 19.5 (C-15), 24.5 (C-5), 24.6 (C-8), 25.2 (C-14), 32.2 (C-7), 36.8 (C-6), 37 (C-4), 47.5 (C-5a), 51.8 (C-8a), 86.3 (C-12a), 89.8 (C-9), 96.9 (C-12), 103.5 (C-3), 207.4 (C-10). Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.68; H, 7.91.

(1*S*,4*R*,5*S*,8*R*,9,11*S*,12*S*)-1,5,9-Trimethyl-10,13,14,15-tetraoxatetracyclo[9.3.1.0^{4,12}.0^{8,12}]pentadecane-9-carbaldehyde (8β and 8α). *Using NBS:* To a solution of **1** (1.0 g, 3.8 mmol) in DME-distilled water (2:1, 30 mL) was added NBS (1.0 g, 5 mmol, 1.5 equiv) at 0 °C. After the mixture was stirred for 45 min, from 0 °C to room temperature, water was poured, and the mixture was extracted with Et_2O. Organic phases were washed with sodium thiosulfate aqueous solution and brine and then dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded the 9-bromo-dihydroartemisinin **7** (1.3 g, 95%) as a white solid (mixture of four isomers determined by ^{1}H NMR).[4] The crude product **7** (1.3 g, 3.6 mmol) was dissolved in CH_2Cl_2 (50 mL), and Et_3N (0.75 mL, 5.4 mmol, 1.5 equiv) was added. After the mixture was stirred for 30 min, the reaction medium was concentrated and the residue was purified on a SiO_2 column (CH_2Cl_2) to provide **8** (772 mg, 76% from **1**, mixture of **8**β:**8**α = 80:20 determined by ^{1}H NMR) as a white solid. *Using NIS:* To a solution of **1** (800 mg, 3.0 mmol) in DME-distilled water (2:1, 22.5 mL) was added NIS (1.02 g, 4.5 mmol, 1.5 equiv) at −20 °C. After the mixture was stirred for 24 h , from −20 °C to room temperature, water was poured, and the mixture was extracted with Et_2O. Organic phases were washed with sodium thiosulfate aqueous solution and brine and then dried ($MgSO_4$). Evaporation of the solvent under reduced pressure and purification of the residue on a SiO_2 column (CH_2Cl_2) give **8** (650 mg, 75%, mixture of **8**β:**8**α = 20:80 determined by ^{1}H NMR) as a white solid.

General Procedure for Addition of $TMSCF_3$ to Aldehydes 8α and 8β. $TMSCF_3$ (0.15 mL, 1.0 mmol, 1.9 equiv) and TBAF·3H_2O (50 mg, 0.16 mmol, 0.3 equiv) were added to a solution of aldehyde **8**α or **8**β (150 mg, 0.53 mmol) in anhydrous THF (3 mL) at 0 °C and under Ar. The reaction was monitored by TLC. After the disappearance of starting material **8**α or **8**β and the intermediate silyloxy ether, the mixture was diluted with Et_2O, washed with water and brine, and then dried ($MgSO_4$). Evaporation of the solvent afforded the crude product, which was purified on a SiO_2 column (7:1 petroleum ether/AcOEt containing 0.1% of Et_3N) to afford a mixture of trifluoromethyl carbinols (**12**α and **13**α or **12**β and **13**β).

(1*S*,1*R*)-2,2,2-Trifluoro-1-[(1*S*,4*R*,5*S*,8*R*,9*S*,11*S*,12*S*)-1,5,9-trimethyl-10,13,14,15-tetraoxatetracyclo[9.3.1.0.^{4,12}0^{8,12}]-pentadec-9-yl]-1-ethanol (12β and 13β). Aldehyde **8**β (150 mg, 0.53 mmol) afforded, after 5 h of reaction, workup, and purification, alcohols **12**β and **13**β (150 mg, 80%) as a colorless oil (mixture of two isomers in a ratio of 62:38 determined by ^{19}F NMR): IR ν_{OH} 3424 cm^{-1}. Anal. Calcd for $C_{16}H_{23}F_3O_5$: C, 54.54; H, 6.58. Found: C, 54.76; H, 6.46. *Major Isomer:* ^{19}F NMR δ −72.1 (d, $^3J_{H-F}$ = 7.5 Hz, 3 F, CF_3); ^{1}H NMR δ 0.99 (d, $^3J_{H15-H6}$ = 6.5 Hz, 3 H, CH_3-15), 1.03 (m, 1 H, H-7ax), 1.2 (m, 1 H, H-6), 1.39 (m, 1 H, H-5), 1.45 (s, 3 H, CH_3-14), 1.5 (td, $^3J_{H5a-H6}$ = $^3J_{H5a-H5ax}$ = 13 Hz, $^3J_{H5a-H5eq}$ = 3 Hz, 1 H, H-5a), 1.52 (td, ^2J = $^3J_{H8ax-H7ax}$ = 11 Hz, $^3J_{H8ax-H7eq}$ = 6 Hz, 1 H, H-8ax), 1.63 (m, 1 H, H-7eq), 1.68 (q, $^5J_{H16-F}$ = 2 Hz, 3 H, CH_3-16), 1.87 (m, 1 H, H-8eq), 1.98 (m, 1 H, H-5), 2.2 (dd, $^3J_{H8a-H8ax}$ = 12 Hz, $^3J_{H8a-H8eq}$ = 6 Hz, 1 H, H-8a), 2.31 (ddd, ^2J = 15 Hz, $^3J_{H4ax-H5ax}$ = 13 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 3.75 (bd, 1 H, OH), 4.16 (q, $^3J_{H10-F}$ = 7 Hz, 1 H, H-10), 5.65 (s, 1 H, H-12); ^{13}C NMR δ 19.8 (C-15), 21.4 (q, $^4J_{C-F}$ = 2.5 Hz, C-16), 24.2 (C-5), 25 (C-14), 25.4 (q, $^5J_{C-F}$ = 1.5 Hz, C-8), 36.8 (C-6), 36.9 (C-7), 37.1 (C-4), 48.9 (C-5a), 52.6 (C-8a), 72.4 (q, $^2J_{C-F}$ = 29 Hz, C-10), 85.2 (q, $^3J_{C-F}$ = 1.5 Hz, C-9), 86.8 (C-12a), 97.3 (C-12), 103.8 (C-3), 124 (q, $^1J_{C-F}$ = 277 Hz, CF_3). *Minor Isomer:* ^{19}F NMR δ −71.1 (d, $^3J_{H-F}$ = 6 Hz, 3 F, CF_3); ^{1}H NMR δ 0.98 (d, $^3J_{H15-H6}$ = 6.5 Hz, 3 H, CH_3-15), 1.03 (m, 1 H, H-7ax), 1.2 (m, 1 H, H-6), 1.39 (m, 1 H, H-5), 1.44 (s, 3 H, CH_3-14), 1.5 (td, $^3J_{H5a-H6}$ = $^3J_{H5a-H5ax}$ = 13 Hz, $^3J_{H5a-H5eq}$ = 3 Hz, 1 H, H-5a), 1.52 (td, ^2J = $^3J_{H8ax-H7ax}$ = 11 Hz, $^3J_{H8ax-H7eq}$ = 6 Hz, 1 H, H-8ax), 1.63 (m, 1 H, H-7eq), 1.69 (q, $^5J_{H16-F}$ = 2 Hz, 3 H, CH_3-16), 1.87 (m, 1 H, H-8eq), 1.98 (m, 1 H, H-5), 2.2 (dd, $^3J_{H8a-H8ax}$ = 12 Hz, $^3J_{H8a-H8eq}$ = 6 Hz, 1 H, H-8a), 2.3 (ddd, ^2J = 14.5 Hz, $^3J_{H4ax-H5ax}$ = 13 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 3.15 (bd, 1 H, OH), 4.06 (q, $^3J_{H10-F}$ = 7.5 Hz, 1 H, H-10), 5.66 (s, 1 H, H-12); ^{13}C NMR δ 19.7 (C-15), 21 (C-16), 24.3 (C-5), 24.9 (C-8), 25.1 (C-14), 32.3 (C-7), 37 (C-6), 37.2 (C-4), 49 (C-5a), 53.2 (C-8a), 72.4 (q, $^2J_{C-F}$ = 29 Hz, C-10), 84.5 (C-9), 86.1 (C-12a), 96.9 (C-12), 103.6 (C-3), 125 (q, $^1J_{C-F}$ = 277 Hz, CF_3).

(1*S*,1*R*)-2,2,2-Trifluoro-1-[(1*S*,4*R*,5*S*,8*R*,9*R*,11*S*,12*S*)-1,5,9-trimethyl-10,13,14,15-tetraoxatetracyclo[9.3.1.0.^{4,12}0^{8,12}]-pentadec-9-yl]-1-ethanol (12α and 13α). Aldehyde **8**α (150 mg, 0.53 mmol) afforded, after 6 h of reaction, workup, and purification, alcohols **12**α and **13**α (139 mg, 76%) as a colorless oil (mixture of two isomers in a ratio of 88:12 determined by ^{19}F NMR): IR ν_{OH} 3508 cm^{-1}. Anal. Calcd for $C_{16}H_{23}F_3O_5$: C, 54.54; H, 6.58. Found: C, 54.70; H, 6.43. *Major Isomer:* ^{19}F NMR δ −72.3 (d, $^3J_{F-H}$ = 7.5 Hz, 3 F, CF_3); ^{1}H NMR δ 0.99 (d, $^3J_{H15-H6}$ = 6.5 Hz, 3 H, CH_3-15), 1.06 (td, ^2J = $^3J_{H7ax-H8ax}$ = 13.5 Hz, $^3J_{H7ax-H8eq}$ = 2.5 Hz, 1 H, H-7ax), 1.23 (m, 1 H, H-6), 1.29 (q, $^5J_{H-F}$ = 2 Hz, 3 H, CH_3-16), 1.39 (m, 1 H, H-8ax), 1.4 (m, 1 H, H-5), 1.41 (s, 3 H, CH_3-14), 1.52 (td, $^3J_{H5a-H5ax}$ = $^3J_{H5a-H-6}$ = 11.5 Hz, $^3J_{H5a-H5eq}$ = 5.5 Hz, 1 H, H-5a), 1.65 (qd, ^2J = 13.5 Hz, $^3J_{H7eq-H6}$ = $^3J_{H7eq-H8ax}$ = $^3J_{H7eq-H8eq}$ = 3 Hz, 1 H, H-7eq), 1.78 (m, 1 H, H-8eq), 1.98 (m, 1 H, H-5), 2.06 (ddd, ^2J = 14.5 Hz, $^3J_{H4eq-H5ax}$ = 3.5 Hz, $^3J_{H4eq-H5eq}$ = 4 Hz, 1 H, H-4eq), 2.26 (dd, $^3J_{H8a-H8ax}$ = 13.5 Hz, $^3J_{H8a-H8eq}$ = 6.5 Hz, 1 H, H-8a), 2.29 (ddd, ^2J = 14 Hz, $^3J_{H4ax-H5ax}$ = 9.5 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 3.7 (bd, 1 H, OH), 4.87 (q, $^3J_{H-F}$ = 8 Hz, 1 H, H-10), 5.6 (s, 1 H, H-12); ^{13}C NMR δ 16.6 (q, $^4J_{C-F}$ = 2 Hz,

C-16), 19.6 (C-15), 24.2 (C-5), 25 (C-14), 25.3 (C-8), 32.4 (C-7), 36.6 (C-6), 36.9 (C-4), 48.6 (q, $^4J_{C-F}$ = 2 Hz, C-8a), 48.6 (C-5a), 73.5 (q, $^2J_{C-F}$ = 28 Hz, C-10), 84.6 (C-9), 87.1 (C-12a), 95.5 (C-12), 103.8 (C-3), 124 (q, $^1J_{C-F}$ = 281 Hz, CF_3). *Minor Isomer:* ^{19}F NMR δ −71.9 (d, $^3J_{F-H}$ = 7.6 Hz, 3 F, CF_3); ^{1}H NMR δ 1.0 (d, $^3J_{H15-H6}$ = 6.5 Hz, 3 H, CH_3-15), 1.1 (qd, ^2J = $^3J_{H7-H8}$ = $^3J_{H7-H6}$= 13 Hz, $^3J_{H7-H8'}$ = 2.5 Hz, 1 H, H-7), 1.23 (m, 1 H, H-6), 1.33 (q, $^5J_{H-F}$ = 1.5 Hz, 3 H, CH_3-16), 1.38 (m, 1 H, H-5), 1.4 (m, 1 H, H-8), 1.42 (s, 3 H, CH_3-14), 1.55 (m, 1 H, H-5a), 1.65 (m, 1 H, H-7′), 1.73 (m, 1 H, H-8′), 1.96 (m, 1 H, H-5′), 2.1 (td, ^2J = 15 Hz, $^3J_{H4'-H5}$ = $^3J_{H4'-H5'}$ = 4 Hz, 1 H, H-4′), 2.28 (ddd, ^2J = 14.5 Hz, $^3J_{H4-H5}$ = 13 Hz, $^3J_{H4-H5'}$ = 4 Hz, 1 H, H-4), 2.52 (dd, $^3J_{H8a-H8ax}$ = 13 Hz, $^3J_{H8a-H8eq}$ = 7 Hz, 1 H, H-8a), 3.5 (bd, 1 H, OH), 4.49 (q, $^3J_{H-F}$ = 8 Hz, 1 H, H-10), 5.53 (s, 1 H, H-12); ^{13}C NMR δ 18.8 (q, $^4J_{C-F}$ = 2 Hz, C-16), 19.9 (C-15), 23.9 (C-5), 25.2 (C-14), 25.9 (C-8), 32.6 (C-7), 36.6 (C-6), 37.2 (C-4), 47.6 (q, $^4J_{C-F}$ = 2 Hz, C-8a), 49.5 (C-5a), 74.2 (q, $^2J_{C-F}$ = 28 Hz, C-10), 83.7 (C-9), 86.8 (C-12a), 95.8 (C-12), 103.6 (C-3), 124 (q, $^1J_{C-F}$ = 281 Hz, CF_3).

2,2,2-Trifluoro-1-[1*S*,4*R*,5*S*,8*R*,9*R*,11*R*,12*S*)-1,5,9-trimethyl-10,13,14,15-tetraoxatetracyclo[9.3.1.0.^{4,12}0 ^{8,12}]pentadec-9-yl]-1-ethanone (9α). *From Rearrangement of Epoxy Ether 11:* A solution of epoxy ether **11** (100 mg, 0.28 mmol) in HFIP (4 mL) was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was purified on a SiO_2 column leading to pure ketone **9**α as white crystals (70 mg, 72%). The same reaction performed in trifluoroethanol provided ketone **9**α (complete conversion in 1 h 30 min). *From Oxidation of Trifluoromethyl Alcohols **12**α and **13**α:* To a solution of alcohols **12**α and **13**α (90 mg, 0.26 mmol) in DMSO/toluene (1:1, 6 mL) were added, at 0 °C and under Ar, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (489 mg, 2.60 mmol, 10 equiv) and dichloroacetic acid (99 mg, 0.77 mmol, 3 equiv). After the mixture was stirred for 15 h at room temperature, the reaction medium was hydrolyzed with water. The organic phase was washed with aqueous $NaHCO_3$ and brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded a light yellow solid, which was purified on a SiO_2 column (4:1 petroleum ether−ethyl acetate) to give the ketone **9**α (81 mg, 89%) as a white solid: mp 133 °C (petroleum ether/Et_2O); $[\alpha]^{25}_D$ +92 (*c* 0.51, MeOH); IR ν_{CO} 1759 cm^{-1}; ^{19}F NMR δ − 70.3 (s, 3 F, CF_3); ^{1}H NMR δ 1.01 (d, $^3J_{H15-H6}$ = 6.5 Hz, 3 H, CH_3-15), 1.11 (tdd, ^2J = $^3J_{H7ax-H8ax}$ = 13 Hz, $^3J_{H7ax-H6ax}$ = 12.5 Hz, $^3J_{H7ax-H8eq}$ = 3 Hz, 1 H, H-7ax), 1.3 (m, 2 H, H-5eq and H-6), 1.39 (s, 3 H, CH_3-14), 1.4 (m, 1 H, H-8ax), 1.41 (s, 3 H, CH_3-16), 1.55 (td, $^3J_{H5a-H5ax}$ = $^3J_{H5a-H6}$ =11 Hz, $^3J_{H5a-H5eq}$ = 5.5 Hz, 1 H, H-5a), 1.72 (dq, ^2J = 13.5 Hz, $^3J_{H7eq-H8ax}$ = $^3J_{H7eq-H8eq}$ = $^3J_{H7eq-H6}$ = 3.5 Hz, 1 H, H-7eq), 1.8 (m, 1 H, H-8eq), 2.02 (m, 1 H, H-5ax), 2.06 (m, 1 H, H-4eq), 2.23 (m, 1 H, H-4ax), 2.7 (dd, $^3J_{H8a-H8ax}$ = 13 Hz, $^3J_{H8a-H8eq}$ = 6 Hz, 1 H, H-8a), 5.73 (s, 1 H, H-12); ^{13}C NMR δ 19.7 (C-15), 20 (C-16), 25 (C-5 and C-8), 25.2 (C-14), 32.5 (C-7), 36.9 (C-4), 37 (C-6), 47.8 (C-5a), 49.5 (C-8a), 86 (C-12a), 88.7 (C-9), 97 (C-12), 103.5 (C-3), 116.2 (q, $^1J_{C-F}$ = 295 Hz, CF_3), 191.3 (d, $^2J_{C-F}$ = 32 Hz, C-10). Anal. Calcd for $C_{16}H_{21}F_3O_5$: C, 54.85; H, 6.04. Found: C, 55.05; H, 6.12.

2,2,2-Trifluoro-1-[(1*S*,4*R*,5*S*,8*R*,9*S*,11*R*,12*S*)-1,5,9-trimethyl-10,13,14,15-tetraoxatetracyclo[9.3.1.0.^{4,12}0 ^{8,12}]pentadec-9-yl]-1-ethanone (9β). To a solution of alcohols **12**β and **13**β (252 mg, 0.72 mmol) in DMSO/toluene (1:1, 20 mL) were added, at 0 °C and under Ar, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.7 g, 14.3 mmol, 20 equiv) and dichloroacetic acid (557 mg, 4.3 mmol, 6 equiv). After the mixture was stirred for 4 h at room temperature, the reaction medium was hydrolyzed with water. The organic phase was washed with aqueous sodium hydrogenocarbonate and brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded a light yellow oil, which was purified on a SiO_2 column (4:1 petroleum ether/AcOEt) to give the ketone **9**β (102 mg, 40%) as a colorless oil and a mixture of starting alcohols **12**β and **13**β (80 mg, 32%) (ratio of 70:30 determined by ^{19}F NMR) as a colorless oil: $[\alpha]^{25}_D$ +46 (*c* 0.64, MeOH); IR ν_{CO} 1752 cm^{-1}; ^{19}F NMR δ −75.2 (s, 3 F, CF_3); ^{1}H NMR δ 0.91 (d, $^3J_{H6-H15}$ = 6.5 Hz, 3 H, CH_3-15), 0.92 (m, 1 H, H-7ax), 1.17 (m, 1 H, H-6), 1.33 (qd, ^2J = $^3J_{H5ax-H4ax}$ = $^3J_{H5ax-H5a}$ = 12 Hz, $^3J_{H5ax-H4eq}$ = 4.5 Hz, 1 H, H-5ax), 1.41 (s, 3 H, CH_3-14), 1.47 (ddd, $^3J_{H5a-H5eq}$ = 5.5 Hz, $^3J_{H5a-H5ax}$ = 12 Hz, $^3J_{H5a-H6}$ = 11 Hz, 1 H, H-5a), 1.53 (qd, ^2J = 11 Hz, $^3J_{H7eq-H6}$ = $^3J_{H7eq-H8eq}$ = $^3J_{H7eq-H8ax}$ = 2.5 Hz, 1 H, H-7eq), 1.68 (m, 1 H, H-8eq), 1.74 (s, 3 H, CH_3-16), 1.91 (m, 1 H, H-8ax), 1.92 (tdd, ^2J = 14 Hz, $^3J_{H5eq-H4eq}$ = $^3J_{H5eq-H4ax}$ = 4 Hz, $^3J_{H5eq-H5a}$ = 5.5 Hz, 1 H, H-5eq), 2.03 (ddd, ^2J = 14.5 Hz, $^3J_{H4eq-H5eq}$ = 3.5 Hz, $^3J_{H4eq-H5ax}$ = 4.5 Hz, 1 H, H-4eq), 2.26 (ddd, ^2J = 14.5 Hz, $^3J_{H4ax-H5ax}$ = 13 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 2.29 (dd, $^3J_{H8a-H8ax}$ = 13 Hz, $^3J_{H8a-H8eq}$ = 6.5 Hz, 1 H, H-8a), 5.69 (s, 1 H, H-12); ^{13}C NMR δ 19.7 (C-15), 24.2 (C-5), 25.2 (C-14), 26.4 (C-16), 26.9 (C-8), 32.3 (C-7), 36.6 (C-4), 48.3 (C-5a), 52.7 (C-8a), 85.7 (C-12a), 90.3 (C-9), 98 (C-12), 103.8 (C-3), 115.3 (q, $^1J_{C-F}$ = 290 Hz, CF_3), 193.7 (d, $^2J_{C-F}$ = 33 Hz, C-10). Anal. Calcd for $C_{16}H_{21}F_3O_5$: C, 54.85; H, 6.04. Found: C, 54.84; H, 6.10.

(1*S*,4*R*,5*S*,8*R*,9*S*,10*R*,12*S*,13*S*)-1,5,9-Trimethyl-10-[2,2,2-trifluoro-1-(trifluoromethyl)ethoxy]-11,14,15,16-tetraoxatetracyclo[10.3.1.0.^{4,13}0^{8,13}]hexadecane-9-ol (14b). A solution of epoxide **10** (200 mg, 0.71 mmol) in HFIP (5 mL) was stirred for 30 min at room temperature. After evaporation of the solvent under reduced pressure, the crude product was purified by chromatography on a SiO_2 column (9:1 petroleum ether/ethyl acetate) to afford **14b** (261 mg, 82%) as a white solid: mp 114 °C (ether/petroleum ether); $[\alpha]_D^{25}$ +133 (*c* 0.53, MeOH); ^{19}F NMR δ −73.5 (qd, $^3J_{H-Fa}$ = 6 Hz, $^4J_{Fa-Fb}$ = 9 Hz, 3F, CF_3-a), −73.7 (qd, $^3J_{H-Fb}$ = 6 Hz, $^4J_{Fb-Fa}$ = 9 Hz, 3 F, CF_3-b); ^{1}H NMR δ 0.95 (m, 1H, H-7ax), 0.96 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.25 (m, 2 H, H-5a and H-6), 1.42 (s, 3 H, CH_3-14), 1.45 (ddd, $^3J_{H5ax-H4ax}$ = 13.5 Hz, $^3J_{H5ax-H4eq}$ = 5 Hz, $^3J_{H5ax-H5a}$ = 11.5 Hz, 1 H, H-5ax), 1.58 (d, $^4J_{H16-OH}$ = 1 Hz, 3 H, CH_3-16), 1.65 (m, 1 H, H-8), 1.69 (qd, ^2J = 13 Hz, $^3J_{H7eq-H6}$ = $^3J_{H7eq-H8ax}$ = $^3J_{H7eq-H8eq}$ = 3 Hz, 1 H, H-7eq), 1.75 (dd, $^3J_{H8a-H8eq}$ = 5.5 Hz, $^3J_{H8a-H8ax}$ = 13.5 Hz, 1 H, H-8a), 1.85 (dddd, ^2J = 13.5 Hz, $^3J_{H5eq-H5a}$ = 9.5 Hz, $^3J_{H5eq-H4eq}$ = 3 Hz, $^3J_{H5eq-H4ax}$ = 4.5 Hz, 1 H, H-5eq), 2.01 (m, 1 H, H-4eq), 2.04 (m, 1 H, H-8), 2.33 (d, $^4J_{OH-H16}$ = 1 Hz, 1 H, OH), 2.35 (ddd, ^2J = 14.5 Hz, $^3J_{H4ax-H5eq}$ = 13.5 Hz, $^3J_{H4ax-H5ax}$ = 4 Hz, 1 H, H-4ax), 4.66 (sept, $^3J_{H\alpha-F}$ = 6 Hz, 1 H, H-α), 4.95 (s, 1 H, H-10), 5.44 (s, 1 H, H-12); ^{13}C NMR δ 20.1 (C-15), 23.2 (C-8), 24.3 (C-5), 25.5 (C-14), 28.2 (C-16), 33.9 (C-7), 36.2 (C-4), 37.5 (C-6), 49.6 (C-8a), 52.5 (C-5a), 69.6 (C-9), 72.2 (t, $^2J_{C\alpha-F}$ = 33 Hz, C-α), 81.5 (C-12a), 88.2 (C-12), 104.4 (C-3), 105.4 (C-10), 121.3 (q, $^1J_{C-F}$ = 288 Hz, CF_3). Anal. Calcd for $C_{18}H_{24}F_6O_6$: C, 48.00; H, 5.37. Found: C, 48.17; H, 5.43.

(1*S*,4*R*,5*S*,8*S*,9*S*,10*R*,12*R*,13*S*)-9-Bromo-1,5,9-trimethyl-10-(2,2,2-trifluoroethoxy)-11,14,15,16-tetraoxatetracyclo-[10.3.1.0.^{4,13}0^{8,13}]hexadecane (15β). To a suspension of 9β-bromo-dihydroartemisinin **7** (100 mg, 0.28 mmol) and 2,2,2-trifluoroethanol (42 mg, 0.42 mmol, 1.5 equiv) in hexane (2 mL) was added $BF_3{\cdot}Et_2O$ (9 μL, 0.07 mmol, 0.25 equiv). After the mixture was stirred for 1 h, the residue was dissolved with Et_2O. The organic phase was washed with aqueous $NaHCO_3$ and brine and then dried. Evaporation of the solvent under reduced pressure provided a residue that was purified on a SiO_2 column (6:1 petroleum ether/ethyl acetate) to give **15** (91 mg, 73%) as a white solid (mixture of two isomers at C-10 in a ratio of 9:91 determined by ^{19}F NMR); ^{19}F NMR δ −73.9 (t, $^3J_{H-F}$ = 9.5 Hz, CF_3) (9%, minor compound), −74.3 (t, $^3J_{H-F}$ = 8.5 Hz, CF_3) (91%, major compound). These compounds were not easily separable. However, small amounts of the major product could be isolated as a pure compound: mp 154 °C (ether/hexane); $[\alpha]_D^{26}$ +103 (*c* 0.99, MeOH); IR ν_{COC} 1275 cm^{-1}; ^{19}F NMR δ −74.3 (t, $^3J_{H-F}$ = 8.5 Hz, 3 F, CF_3); ^{1}H NMR δ 0.90 (m, 1 H, H-7ax), 0,96 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, CH_3-15), 1.24 (td, $^3J_{H5a-H5eq}$ = 6.5 Hz, $^3J_{H5a-H5ax}$ = $^3J_{H5a-H6}$ = 11 Hz, 1 H, H-5a), 1.3 (m, 1 H, H-6), 1.44 (s, 3 H, CH_3-14), 1.5 (dddd, ^2J = 14.5 Hz, $^3J_{H5ax-H4ax}$ = 13.5 Hz, $^3J_{H5ax-H4eq}$ = 6.5 Hz, $^3J_{H5ax-H5a}$ = 11 Hz, 1 H, H-5ax), 1.66 (qd, ^2J = 13.5 Hz, $^3J_{H7eq-H6}$ = $^3J_{H7eq-H8ax}$ = $^3J_{H7eq-H8eq}$ = 3.5 Hz, 1 H, H-7eq), 1.81 (m, 1 H, H-8ax), 1.9 (m, 1 H, H-8a), 2.0 (m, 1 H, H-5eq), 2.05 (ddd, ^2J = 14.5 Hz, $^3J_{H4eq-H5eq}$ = 5 Hz, $^3J_{H4eq-H5ax}$ = 3 Hz, 1 H, H-4eq), 2.3 (s, 3 H, CH_3-16), 2.36 (ddd, ^2J = 14.5 Hz, $^3J_{H4ax-H5ax}$ = 13 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 2.4 (m, 1 H, H-8eq), 4.0 (qd, ^2J = 12 Hz, $^3J_{H\alpha-F}$ = 8.5 Hz, 1 H, H-α), 4.15 (qd, ^2J = 12 Hz, $^3J_{H\beta-F}$ = 8.5 Hz, 1 H, H-β), 4.9 (s, 1 H, H-10), 5.48 (s, 1 H,

H-12); ^{13}C NMR δ 20 (C-15), 25.3 (C-14), 30.2 (C-8), 34.4 (C-16), 34.6 (C-5 and C-7), 36.2 (C-4), 37.2 (C-6), 50.7 (C-8a), 52.8 (C-5a), 65.8 (CH_2), 67.2 (C-9), 82.8 (C-12a), 87.1 (C-12), 104 (C-3), 104.6 (C-10), 123.3 (q, $^1J_{C-F} = 264$ Hz, CF_3). Anal. Calcd for $C_{17}H_{23}BrF_3O_5$: C, 45.96; H, 5.22. Found: C, 46.04; H, 5.34.

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