# Fluoro Artemisinins: Difluoromethylene Ketones

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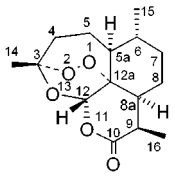
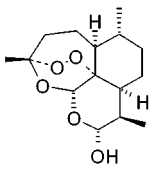
The reactions of the ring-contracted aldehydes, derived from anhydrodihydroartemisinin, with *gem*-difluoroenoxysilanes in the presence of $BF_3{\cdot}Et_2O$ afforded the corresponding difluoromethylene ketol adducts in good yields. Similar Lewis acid catalyzed reactions of dihydroartemisinin acetate with the difluoroenoxysilanes provided the 10-substituted difluoromethylene ketones in good to moderate yields. Interestingly enough, the course and the stereochemistry of these reactions are highly dependent on the nature of the Lewis acids used; the addition reaction was accompanied by epimerization at C-9, and the stereochemistry at C-10 depends on the difluoroenoxysilane used. The best results were obtained using $SnCl_4$ to give the 9α,10*β*-stereoisomer in high stereoselectivity. When 0.4 equiv of $SnCl_4$ was used for the reaction with the α-(4-methoxyphenylenoxysilane)-*β*,*β*-difluoroenoxysilane, however, a rearrangement of the endoperoxide was observed.

*gem*-Difluoroenoxysilanes[1] are excellent building blocks for the synthesis of *gem*-difluorinated compounds. For instance, their use in one-pot reactions with Michael acceptors, allylic alcohol derivatives, and carbonyl compounds provides difluoro-1,5-diketones, the difluoroanalogues of terpenes and disaccharides, and the difluoroaldol compounds, respectively.[2−6] They can also react with glycosyl donors by addition onto the oxonium ion generated by a Lewis acid, giving the difluoro-*C*-glycosides.[7]

Since the discovery of artemisinin, isolated from the plant *Artemisia annua*, a potent antimalarial agent efficient toward drug-resistant *Plasmodium falciparum*,[8] great efforts have been focused on its chemical modifications in order to improve its efficacy and pharmaceutical profile.[8,9] As a part of our research program to design more active and longer lasting antimalarial drugs, we have recently demonstrated that a substitution at C-10 by a fluorinated group greatly improves the in vivo activity of artemisinin derivatives against *P. falciparum*, because of the increased stability toward metabolism processes.[10−12] Along this line, the synthesis of other fluoro analogues of artemisinin derivatives constitutes an interesting aim of further efforts, and addition of difluoroenoxysilanes on artemisinin derivatives could be an interesting approach.



Artemisinin



Dihydroartemisinin (DHA)

Among the numerous reported artemisinin derivatives, Venugopalan et al. have described the aldehyde **1**,[13] a precursor of a variety of novel ring-contracted artemisinin derivatives, and have reported that some of them exhibit high antimalarial activities against chloroquine-sensitive and chloroquine-resistant strains of *Plasmodium*.[13] Considering the great influence of the configuration of the C9-Me in the artemisinin series[14,15] as well as the ring-contracted series[13,16] on the activity on the parasite, we have recently prepared the new stereoisomeric aldehyde **2**,[17,18] where the C9-Me is of *β*-configuration as in arte-

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**Scheme 1. Reactions of Enoxysilanes 3a−c with Aldehydes 1 and 2**

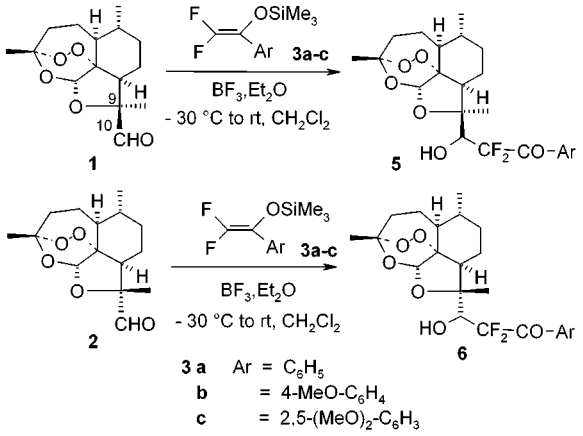


**Table 1. Addition of Difluoroenoxysilanes 3 to Aldehydes 1 and 2**

| aldehyde | enoxy silane | compounds | yield[a] (%) |
|---|---|---|---|
| **1** | **3a** | **5a** | 97 |
| **2** | **3a** | **6a** | 89 |
| **1** | **3b** | **5b** | 74 |
| **2** | **3b** | **6b** | 70 |
| **1** | **3c** | **5c** | 85 |
| **2** | **3c** | **6c** | 98 |

[a] Isolated yields.

misinin series. Thus, we first investigated the reactions of these two aldehydes with difluoro enoxysilanes **3** in order to prepare the corresponding difluoro $\beta$-ketol. In another way, dihydroartemisinin (DHA), a cyclic hemiacetal, can be considered as a *pseudo*-glycoside, able to give a reactive oxonium ion that can react with a nucleophilic entity.[19] Thus, we also investigated the reaction of the hemiketal acetate **4** with difluoroenoxysilanes **3** in order to obtain 10-C-difluoro-substituted derivatives of artemisinin.[20]

Difluoroenoxy silanes were prepared following Uneyama's procedure, based on the $Mg^0$-promoted selective defluorination of trifluoromethyl aryl ketones.[21] The reaction of aldehyde **1** with difluoroenoxy silane **3a** in the presence of 0.5 equiv of $TiCl_4$ or $SnCl_4$ failed (−78 °C to room temperature) and was very slow in the presence of $BF_3{\cdot}Et_2O$ at −78 °C. However, when the reaction was performed with $BF_3{\cdot}Et_2O$ (0.4 equiv) at −30 °C and was then slowly raised to room temperature (3 h), the conversion of aldehyde **1** into difluoro $\beta$-hydroxyketone **5a** was quantitative and stereoselective: only one diastereoisomer was formed (Scheme 1, Table 1). Under the same conditions, the reaction of aldehyde **2** with **3a** provided stereoselectively the corresponding $\beta$-ketol **6a** in an excellent yield (89%). For adducts **5a** and **6a**, the absolute configuration of the carbon bearing the hydroxyl has not been determined yet.

Similar reactions were carried out using other difluoroenoxysilanes such as **3b** and **3c**. In these cases,

**Scheme 2. Reaction of DHA Acetate 4 with Difluoroenoxysilanes 3a−d**

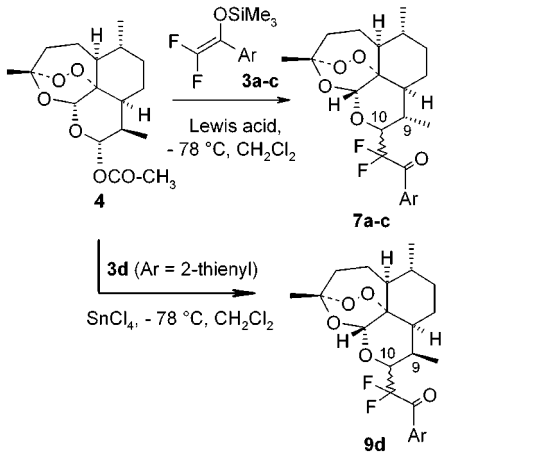


**Table 2. Reactions of Difluoroenoxysilanes 3 with DHA Acetate 4 in the Presence of Lewis Acid**

| runs | enoxy silanes | Lewis acid (equiv) | compounds | isolated yields (%) | $\beta/\alpha$ at C-10 |
|---|---|---|---|---|---|
| 1 | **3a** | $BF_3{\cdot}Et_2O$ (0.2) | *a* | | |
| 2 | **3a** | $SnCl_4$ (0.1) | **7a** (9α-Me)[b] | 30 | 100:0 |
| 3 | **3a** | $SnCl_4$ (0.4) | **7a** (9α-Me) | 66 | 100:0 |
| 4 | **3b** | $SnCl_4$ (0.1) | **7b** (9α-Me)[b] | 33 | 100:0 |
| 5 | **3b** | $BF_3{\cdot}Et_2O$ (0.2) | **7b** (9α-Me) | 73 | 100:0 |
| 6 | **3b** | $SnCl_4$ (0.4) | **8b** (9$\beta$-Me) | 83 | 40:60 |
| 7 | **3c** | $SnCl_4$ (0.4) | **7c** (9α-Me)[b] | 33 | 70:30 |
| 8 | **3d** | $SnCl_4$ (0.4) | **9d** (9$\beta$-Me)[b] | 29 | 65:35 |

[a] Complex mixture. [b] Accompanied by glycal **10**.

complete conversion required 1 equiv of Lewis acid. The $\beta$-hydroxy ketols **5b,c** and **6b,c** were also obtained stereoselectively in good yields (Scheme 1, Table 1).

Next, we examined the reaction of dihydroartemisinin (DHA) with the difluoroenoxy silane **3a**. However the reaction failed in all conditions examined.[20] Since the 10α-acetoxydihydroartemisinin **4**, an activated form of DHA, is more reactive than DHA itself,[15,22] the reaction of **4** with **3a** was attempted using different Lewis acids. The best result was obtained using 0.4 equiv of $SnCl_4$ and 1.5 equiv of **3a**. After 2 h at − 78 °C and raising of the temperature to −20 °C, the difluoroketone **7a** was formed (Scheme 2, Table 2, run 3). Although difluoroketone **7a** was unstable on silica gel and had to be purified on neutral alumina, it was isolated in respectable yield (66%) as a single stereoisomer. Under these conditions, the reaction was highly stereoselective. The stereochemistry of ketone **7a** was determined by NMR. The signal due to the C9-Me is substantially deshielded in $^1H$ ($\delta$ 1.20 ppm) and $^{13}C$ NMR ($\delta$ 21 ppm) compared to the usual range of 0.90−1.0 ppm and 12−13 ppm, respectively, for a $\beta$-$CH_3$ and is typical of the *epi*-artemisinin series, with α-configuration of Me at C-9.[11,22] The large coupling constant ($J$ = 10.5 Hz) observed for $J_{9,10}$ indicates a *trans*-diaxial relationship for these protons and thus a *trans* relationship between Me at C-9 and the difluoromethyl ketone substituent of $\beta$-configuration. These relative configurations were supported both by homo NOE observed between Me at C-9 and both H-8a and H-10 and by hetero NOE $\{^{19}F\}^1H$ effect between the fluorine atoms

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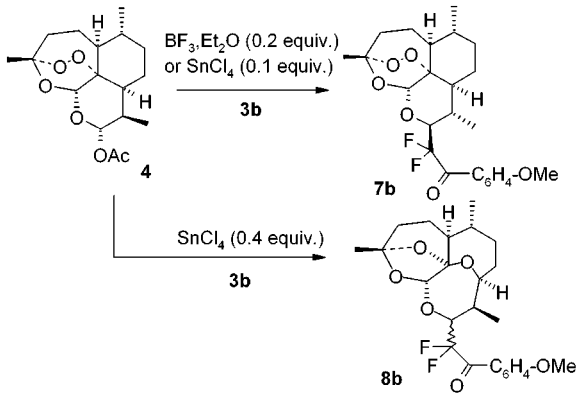
**Scheme 3. Reactions of Enoxysilanes 3b with DHA Acetate 4**




and H-9. These assignments were confirmed by X-ray diffraction.[23]

Similar reactions were investigated using other difluoroenoxysilanes **3b**−**d**. Under the same conditions as described for **3a** (0.4 equiv of $SnCl_4$), the reaction of 4-methoxyphenyl)difluoroenoxysilane **3b** with DHA acetate **4** did not provide the expected compound **7b**, instead leading to the formation of a 10α/*β*-epimeric mixture of the unexpected rearranged difluoroketone **8b** (83% yield) (Table 2, run 6). The structure of this compound was determined by complete assignment of all protons and carbons in NMR and by comparison with the NMR data reported by Ziffer et al. for a similar rearrangement product.[24] The structure of ketone **8b** was confirmed by X-ray diffraction of the 10*β*-minor isomer.[23]

In contrast, however, when only 0.1 equiv of $SnCl_4$ was used, the expected difluoroketone **7b** was obtained stereoselectively, albeit in a poor yield (33%), together with the elimination product, glycal **10** (Table 2, run 4). The best result (73%) was obtained using $BF_3{\cdot}Et_2O$ (0.2 equiv) (Scheme 3, Table 2, run 5). Similar reactions with difluoroenoxysilanes **3c** and **3d** were also examined in the presence of $BF_3{\cdot}Et_2O$ and $SnCl_4$. With $BF_3{\cdot}Et_2O$ no condensation occurred. With $SnCl_4$ (0.1 equiv) the reaction of DHA acetate with **3c** provided **7c** (*β*-isomer) in only 14% yield. The yield was improved up to 33% by using 0.4 equiv of $SnCl_4$, without any formation of the rearranged **8c** (Table 2, run 7). However, **7c** was obtained as a 70:30 mixture of the C-10 *β*/α-epimers. The reaction with **3d** in the presence of 0.4 equiv of $SnCl_4$ afforded ketone **9d** in 29% yield as a 65:35 mixture of the C-10 *β*/α-epimers (Table 2, run 8), in which the C9-Me is of *β*-configuration in contrast with the *epi*-artemisinin (C9-α) configuration observed in the difluoroketones obtained from the reaction with **3a**−**c**. In these experiments, ketones **7c** and **9d** were formed together with an appreciable amount of glycal **10**. In all cases, a high purity of the difluoroenoxysilanes and of the DHA acetate were required for obtaining good reproducibilities; otherwise, the reactions provided complex mixtures or tars.

While the addition of difluoroenoxysilanes on the C-10-contracted aldehydes **1** and **2** is very efficient for the preparation of the corresponding difluoro-aldols, the reactions of DHA acetate **4** with difluoroenoxysilanes **3** are more complicated for at least two reasons: first, careful choices of Lewis acids and of stoichiometry had to be made, and second, surprising changes in the course of reactions were observed, depending critically on the difluoroenoxysilane used. Complications arise not only from this type of reaction with glycosyl donor[7] but also from the peculiar reactivity of artemisinin derivatives.

Such epimerization at C-9 observed herein can result from isomerization of oxonium salts via deprotonation leading to glycal **10** followed by *β*-protonation (Scheme 4). Although partial epimerization has been reported for the Lewis acid catalyzed reactions with DHA or DHA acetate,[20,25] it has never been a major process. In addition, such epimerization has never been observed in the reaction between DHA acetate and non-fluorinated enoxysilanes.[26,27] In our cases, the epimerization seems to be a major pathway, particularly with **3a** and **3b** (Table 2, runs 2 and 4).

The nature of Lewis acid cannot be invoked as a key reason, since epimerization also occurs also with $BF_3{\cdot}Et_2O$ (Table 2, run 5), which is the most often used Lewis acid in the C10-substitution reactions of DHA. Furthermore, we found that the use of $SnCl_4$ instead of $TiCl_4$[26] in the reactions of DHA acetate with a non-fluorinated enoxysilane did not bring about epimerization in an appreciable extent. The rather low reactivity of difluoroenoxysilanes **3** cannot been invoked either, because (i) the reactions occur at low temperature (−78 or −30 °C) to afford ketone **7a,b** in good yields, and (ii) in one case (run 8), non-epimerized compound was obtained, though the yield was low. The exact mechanistic origin of the epimerization observed herein awaits further detailed studies.

The rearrangement observed in the reaction with enoxysilane **3b** leading to ketone **8b** is unexpected in our experimental conditions, since this type of rearrangement has not been observed in numerous reactions of DHA derivatives in the presence of Lewis acid.[25−27] Ziffer has reported a similar rearrangement of dihydro desoxoartemisinin only when a very large excess (20−30 equiv) of Lewis acid was used.[24]

Since the artemisinin derivatives are usually relatively stable in the presence of Lewis acid, the easy cleavages of the endoperoxide bridge and the C12a−C8a bond observed with **3b** and $SnCl_4$ (0.4 equiv) require special events. The reversible interaction between the Lewis acid and the peroxide oxygen might induce the irreversible cleavage of the peroxide bond and then of the C12a−C8a bond.[24,28] Thus, events leading to ketone **8b** could be initiated by participation by the enolic double bond of glycal **10** initially formed (Scheme 5). So, it appears likely

(23) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

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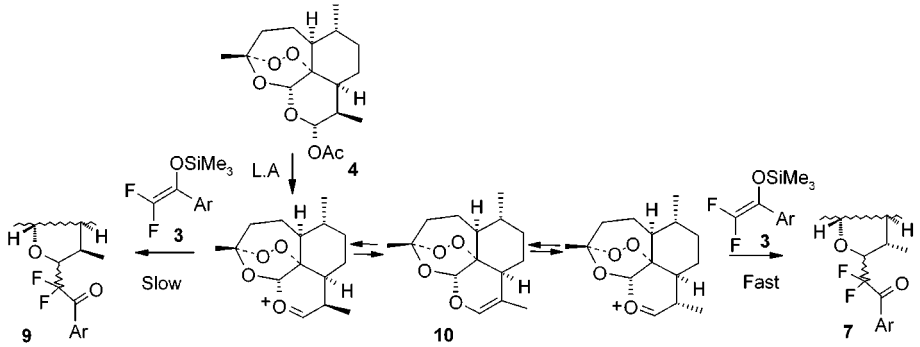
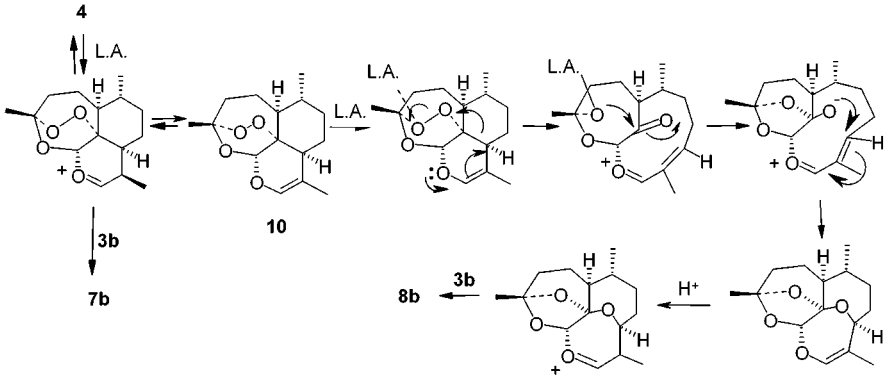
**Scheme 4. Formation of Ketones 7 and 9**




**Scheme 5. Reaction of Enoxysilane 3b with DHA Acetate 4 in Presence of $SnCl_4$ (0.4 equiv)**




that the enolic double bond plays an essential role in facilitating the rearrangement concerned. We verified that, when glycal **10** was treated with enoxysilane **3b** and $SnCl_4$, ketone **8b** was also obtained.

The actual reaction course depends critically on a balance among the rates of addition of the enoxysilanes, deprotonation, and reprotonation. This could explain the significant differences in stereochemical results obtained with different enoxysilanes and hence some reproducibility problems encountered.

In conclusion, we have shown that the reaction of artemisinin-derivated aldehydes and DHA acetate with difluoroenoxysilanes provides new classes of the difluorinated derivatives of D-ring contracted artemisinin and of *epi*-artemisinin without oxygen functionality at C-10. Antimalarial properties of these new difluoro $\beta$-ketols **5** and **6** and ketones **7** and **9** are currently under investigation.

## Experimental Section.

NMR spectra were performed with $CDCl_3$ solutions. Chemicals 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 Lorenz-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 ($^1H$) 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 are 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).

**Addition of Enoxysilanes 3a−c on Aldehydes 1 and 2. General Procedure.** $BF_3{\cdot}Et_2O$ was added dropwise, at − 30 °C and under Ar, to a solution of aldehyde **1** or **2** (150 mg, 0.53 mmol) and of difluoroenoxysilane **3a−c** (0.8 mmol, 1.5 equiv) in $CH_2Cl_2$ distilled on $CaH_2$ (3 mL). The temperature was raised slowly. After complete disappearance of starting material **1** or **2** (TLC), the reaction was diluted with $Et_2O$ and hydrolyzed with aqueous $NaHCO_3$. The organic phase was extracted, washed with brine, and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure provided a residue that was purified on a $SiO_2$ column (petroleum ether/ ethyl acetate containing 0.1% of $Et_3N$) to give the pure compounds **5a−c** or **6a−c**.

**2,2-Difluoro-3-hydroxy-1-phenyl-3-[1*S*,4*R*,5*S*,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-propanone (5a).** $BF_3{\cdot}Et_2O$ (30 $\mu$L, 0.21 mmol, 0.4 equiv) was added dropwise, at −30 °C and under Ar, to a solution of aldehyde **1** (150 mg, 0.53 mmol) and difluoroenoxysilane **3a** (182 mg, 0.80 mmol, 1.5 equiv) in $CH_2Cl_2$ (3 mL). After 5 h of stirring and workup, the residue was purified on an $SiO_2$ column (petroleum ether/ethyl acetate/ $Et_3N$ 6:1:0.1%) to lead to the pure compound **5a** as a white solid (224 mg, 97%): mp 142 °C ($Et_2O$/petroleum ether); $[\alpha]^{26}_D$ +86 (*c* 0.85, MeOH); IR $\nu_{CO}$ 1703 cm$^{-1}$, $\nu_{OH}$ 3610 cm$^{-1}$; NMR $^{19}F$ $\delta$ −102.2 (d, $^2J$ = 267 Hz, 1 F), −119.7 (d, $^2J$ = 264 Hz, 1 F); NMR $^1H$ $\delta$ 0.95 (d, $^3J_{H15-H6}$ = 6.5 Hz, 3 H, $CH_3$-15), 1.02 (qd, $^3J_{H7ax-H8eq}$ = 2.5 Hz, $^2J$ = $^3J_{H7ax-H6}$ = $^3J_{H7ax-H8ax}$ = 13 Hz, 1 H, H-7ax), 1.18 (m, 1 H, H-6), 1.27 (s, 3 H, $CH_3$-14), 1.28 (m, 1 H, H-5ax), 1.38 (qd, $^3J_{H8ax-H7eq}$ = 3 Hz, $^2J$ = $^3J_{H8ax-H7ax}$ = $^3J_{H8ax-H8a}$ = 13 Hz, 1 H, H-8ax), 1.48 (td, $^3J_{H5a-H5eq}$ = 5.5 Hz, $^3J_{H5a-H6}$ = $^3J_{H5a-H5ax}$ = 11.5 Hz, 1 H, H-5a), 1.62 (tdd, $^2J$ = 13 Hz, $^3J_{H7eq-H8eq}$ = 3.5 Hz, $^3J_{H7eq-H8ax}$ = $^3J_{H7eq-H6}$ = 3 Hz, 1 H, H-7eq), 1.7 (t, $^5J_{H16-Fa}$ = $^5J_{H16-Fb}$ = 1.5 Hz, 3 H, $CH_3$-16), 1.89 (tdd, $^2J$ = 13.5 Hz, $^3J_{H5eq-H5a}$ = 5.5 Hz, $^3J_{H5eq-H4ax}$ = $^3J_{H5eq-H4eq}$ = 4 Hz, 1 H, H-5eq), 1.96 (td, $^2J$ = 15 Hz, $^3J_{H4eq-H5eq}$ = $^3J_{H4eq-H5ax}$ = 4 Hz, 1 H, H-4eq), 2.01 (dddd, $^2J$ = 13 Hz, $^3J_{H8eq-H8a}$ = 6 Hz, $^3J_{H8eq-H7ax}$ = 2.5 Hz, $^3J_{H8eq-H7eq}$ = 4 Hz, 1 H, H-8eq), 2.1 (dd, $^3J_{H8a-H8ax}$ = 13 Hz, $^3J_{H8a-H8eq}$ = 6 Hz, 1 H, H-8a), 2.2 (ddd, $^2J$ = 15 Hz, $^3J_{H4ax-H5ax}$ = 13 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 2.4 (bs, 1 H, OH), 4.75 (dd, $^3J_{H10-Fa}$ = 7 Hz, $^3J_{H10-Fb}$ = 22 Hz, 1 H, H-10), 5.1 (s, 1 H, H-12), 7.44 to 7.96 (m, 5 H, $C_6H_5$); NMR $^{13}C$ $\delta$ 20 (C-15), 22.1 (C-16), 24.3 (C-5), 25.2 (C-14), 26 (C-8), 32.6 (C-7), 37 (C-6), 37.3 (C-4), 49.4 (C-

5a), 53.3 (C-8a), 72.3 (C-10), 84.3 (C-9), 86.5 (C-12a), 96.2 (C-12), 103.5 (C-3), 128.3, 129.9, 133.1, 134.2 (C=O and $CF_2$ not observed). Anal. Calcd for $C_{23}H_{28}F_2O_6$: C, 63.00; H, 6.44. Found: C, 62.89; H, 6.72.

**2,2-Difluoro-3-hydroxy-1-phenyl-3-[1*S*,4*R*,5*S*,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-propanone (6a).** $BF_3{\cdot}Et_2O$ (30 $\mu$L, 0.21 mmol, 0.4 equiv) was added dropwise, at −30 °C and under Ar, to a solution of aldehyde **2** (150 mg, 0.53 mmol) and difluoroenoxysilane **3a** (182 mg, 0.80 mmol, 1.5 equiv) in $CH_2Cl_2$ (3 mL). After 5 h of stirring and workup, the residue was purified on an $SiO_2$ column (petroleum ether/ethyl acetate/$Et_3N$ 6:1:0.1%) to lead to pure compound **6a**, as a white solid (206 mg, 89%): mp 160 °C (AcOEt/petroleum ether); $[\alpha]^{26}_D$ +49 (*c* 0.80, MeOH); IR $\nu_{CO}$ 1697 cm$^{-1}$, $\nu_{OH}$ 3505 cm$^{-1}$; NMR $^{19}$F $\delta$ −104.3 (dd, $^2J$ = 261 Hz, $^3J_{Fa-H10}$ = 19.5 Hz, 1 F), − 113.9 (bd, $^2J$ = 265 Hz, 1 F); NMR $^1$H $\delta$ 0.99 (d, $^3J_{H15-H6}$ = 6.5 Hz, 3 H, $CH_3$-15), 1.08 (qd, $^3J_{H7ax-H8eq}$ = 2.5 Hz, $^2J$ = $^3J_{H7ax-H6}$ = $^3J_{H7ax-H8ax}$ = 13 Hz, 1 H, H-7ax), 1.17 (s, 3 H, $CH_3$-14), 1.2 (m, 1 H, H-6), 1.4 (m, 2 H, H-5ax, H-8ax), 1.44 (s, 3 H, $CH_3$-16), 1.57 (ddd, $^3J_{H5a-H5eq}$ = 5.5 Hz, $^3J_{H5a-H5ax}$ or $^3J_{H5a-H6}$ = 11 and 12 Hz, 1 H, H-5a), 1.64 (qd, $^2J$ = 13 Hz, $^3J_{H7eq-H8ax}$ = $^3J_{H7eq-H6}$ = $^3J_{H7eq-H8eq}$ = 3.5 Hz, 1 H, H-7eq), 1.8 (ddd, $^2J$ = 13.5 Hz, $^3J_{H8eq-H8a}$ = 7 Hz, $^3J_{H8eq-H7ax}$ = 3 Hz, $^3J_{H8eq-H7eq}$ = 4 Hz, 1 H, H-8eq), 1.92 (tdd, $^2J$ = 14 Hz, $^3J_{H5eq-H5a}$ = 5.5 Hz, $^3J_{H5eq-H4ax}$ = $^3J_{H5eq-H4eq}$ = 4 Hz, 1 H, H-5eq), 2.03 (td, $^2J$ = 15 Hz, $^3J_{H4eq-H5eq}$ = $^3J_{H4eq-H5ax}$ = 4 Hz, 1 H, H-4eq), 2.21 (ddd, $^2J$ = 15 Hz, $^3J_{H4ax-H5ax}$ = 13 Hz, $^3J_{H4ax-H5eq}$ = 4 Hz, 1 H, H-4ax), 2.62 (dd, $^3J_{H8a-H8ax}$ = 13 Hz, $^3J_{H8a-H8eq}$ = 7 Hz, 1 H, H-8a), 3.75 (bs, 1 H, OH), 4.75 (dd, $^3J_{H10-Fa}$ = 20 Hz, $^3J_{H10-Fb}$ = 9.5 Hz, 1 H, H-10), 5.45 (s, 1 H, H-12), 7.46 to 8.1 (m, 5 H, $C_6H_5$); NMR $^{13}$C $\delta$ 19.4 (C-16), 20 (C-15), 23.9 (C-5), 25.1 (C-14), 25.9 (C-8), 32.8 (C-7), 36.8 (C-6), 37.4 (C-4), 47.7 (C-8a), 49.9 (C-5a), 76.1 (C-10), 84.3 (C-9), 87 (C-12a), 95.6 (C-12), 103.4 (C-3), 128.5, 130.4, 133.3, 133.8 (C=O and $CF_2$ not observed). Anal. Calcd for $C_{23}H_{28}F_2O_6$: C, 63.00; H, 6.44. Found: C, 62.68; H, 6.46.

**2,2-Difluoro-1-phenyl-2-[(1*S*,4*R*,5*S*,8*R*,9*R*,10*S*,12*R*,13*S*)-1,5,9-trimethyl-11,14,15,16-tetraoxatetracyclo[10.3.1.0$^{4,13}$.0$^{8,13}$]hexadec-10-yl]-1-ethanone (7a).** $SnCl_4$ (3.1 mL, 0.84 mmol, 0.4 equiv) was added at − 78 °C, under Ar, to a solution of dihydroartemisinin acetate **4** (700 mg, 2.1 mmol) in $CH_2Cl_2$ (15 mL). Difluoroenoxysilane **3a** (710 mg, 3.1 mmol, 1.5 equiv) was then added very slowly at −78 °C. After complete disappearance of the starting DHA acetate **4** (1 h, and raising the temperature to −20 °C), a saturated solution of sodium hydrogenocarbonate was added. After extraction ($CH_2Cl_2$), the organic layer was washed (brine) and dried ($MgSO_4$). Evaporation of the solvent provided a residue that was purified on neutral alumina column (petroleum ether/AcOEt 90:10), leading to the pure compound **7a**, as white crystals (596 mg, 66%): mp 94.5 °C (AcOEt); $[\alpha]^{26}_D$ −60 (*c* 0.57, MeOH); NMR $^{19}$F $\delta$ −103 (d, $^2J$ = 262 Hz, 1 F), −121 (dd, $^2J$ = 261 Hz, $^3J_{Fb-H10}$ = 19 Hz, 1 F); NMR $^1$H $\delta$ 0.85 (s, 3 H, $CH_3$-14), 0.91 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, $CH_3$-15), 1.05 (m, 1 H, H-7), 1.2 (m, 3 H, H-8a, H-5a, H-6), 1.28 (dd, $^3J_{H16-H9}$ = 7 Hz, $^5J_{H16-F}$ = 2 Hz, 3 H, $CH_3$-16), 1.38 (m, 1 H, H-8), 1.45 (m, 1 H, H-4), 1.60 (m, 1 H, H-7), 1.75 (m, 1 H, H-8), 1.85 (m, 1 H, H-5), 1.95 (m, 1 H, H-4), 2.03 (ddq, $^3J_{H9-H10}$ = 10.5 Hz, $^3J_{H9-H8a}$ = 1.5 Hz, $^3J_{H9-H16}$ = 7 Hz, H-9), 2.2 (m, 1H, H-5), 4.9 (ddd, $^3J_{H9-H10}$ = 10.5 Hz, $^3J_{H10-Fa}$ = 5 Hz, $^3J_{H10-Fb}$ = 18.5 Hz, 1 H, H-10), 5.29 (d, $^5J_{H12-F}$=2 Hz, 1 H, H-12), 7.5 (dd, $^2J$ = 8 Hz, $^3J$ = 7.5 Hz, 2 H), 7.6 (d, $^3J$ = 7.5 Hz, 1 H), 8.1 (d, $^3J$ = 8 Hz, 2H); NMR $^{13}$C $\delta$ 19.9 (C-15), 20.1 (C-16), 25.0 (C-14), 25.1 (C-5), 31.5 (C-8), 34.4 (C-7), 34.6 (C-9), 35.3 (C-4), 37.4 (C-6), 48.1 (C-8a), 51.2 (C-5a), 75.2 (C-10), 82.1 (C-12a), 90.1 (C-12), 102.2 (C-3), 128.6, 130.1, 133.5, 188.5 (C=O), ($CF_2$ not observed). Anal. Calcd for $C_{23}H_{28}O_5F_2$: C, 65.39; H, 6.68; Found: C, 65.45; H, 6.74.

**1-(2,5-Dimethoxyphenyl)-2,2-difluoro-2-[(1*S*,4*R*,5*S*,8*R*,9*R*,10*S*,12*R*,13*S*)-1,5,9-trimethyl-11,14,15,16-tetraoxatetracyclo[10.3.1.0$^{4,13}$.0$^{8,13}$]hexadec-10-yl]-1-ethanone (7c).** $SnCl_4$ (0.12 mL, 0.2 mmol, 0.4 equiv) was added at −78 °C, under Ar, to a solution of dihydroartemisinin acetate **4** (200 mg, 0.6 mmol) in $CH_2Cl_2$ (6 mL). Difluoroenoxysilane **3c** (264 mg, 0.9 mmol, 1.5 equiv) was then added very slowly at −78 °C. After complete disappearance of the starting DHA acetate 4 (2 h, and raising the temperature to −20 °C), a saturated solution of sodium hydrogenocarbonate was added. After extraction ($CH_2Cl_2$), the organic layer was washed (brine) and dried ($MgSO_4$). Evaporation of the solvent provided a residue that was purified on neutral alumina column (petroleum ether/AcOEt 90:10), leading to the pure compound **7c**, mixture of two isomers $\beta$ and $\alpha$ ($\beta$:$\alpha$ 70:30), as an oil (80 mg, 33%). Anal. Calcd for $C_{25}H_{32}O_7F_2$: C, 62.23; H, 6.68. Found: C, 62.67; H, 7.19.

**Major $\beta$-isomer 7c**: NMR $^{19}$F $\delta$ −112.5 (d, $^2J$ = 259 Hz, 1 F), −129.4 (dd, $^2J$ = 259 Hz, $^3J_{Fb-H10}$ = 19 Hz, 1 F); NMR $^1$H $\delta$ 0.93 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, $CH_3$-15), 1.0 (m, 1H, H-7), 1.2 (m, 1 H, H-8), 1.22 (s, 3 H, $CH_3$-14), 1.23 (m, $^3J_{H16-H9}$= 7 Hz, $^5J_{H16-F}$ = 2 Hz, 3 H, $CH_3$-16), 1.25 (m, 2 H, H-6, H-5a), 1.38 (m, 1H, H-8a), 1.4 (m, 1 H, H-8), 1.6 (m, 1H, H-7), 1.95 (m, 3 H, H-4, H-5, H-5′), 2.0 (m, 1H, H-9), 2.25 (m, 1H, H-4), 3.75 (s, 3 H, $OCH_3$), 3.85 (s, 3 H, $OCH_3$), 4.9 (ddd, $^3J_{H9-H10}$ = 10.5 Hz, $^3J_{H10-Fa}$ = 4 Hz, $^3J_{H10-Fb}$ = 19 Hz, 1 H, H-10), 5.35 (d, $^5J_{H12-F}$= 2.5 Hz, 1 H, H-12), 6.9 (d, $^3J$ = 9 Hz, 1 H), 7.0 (dd, $^3J$ = 9 Hz, $^4J$ = 3 Hz, 1 H), 7.16 (d, $^4J$ = 3 Hz, 1 H); NMR $^{13}$C $\delta$ 19.5 (C-15), 20.0 (C-16), 25.0 (C-14), 25.1 (C-5), 25.5 (C-8), 34.0 (C-9), 34.5 (C-7), 36.0 (C-4), 37.0 (C-6), 48.0 (C-8a), 51.5 (C-5a), 55.5 ($OCH_3$), 57.5 ($OCH_3$), 75.0 (C-10), 81.5 (C-12a), 90.0 (C-12), 102.3 (C-3), 112.5, 115.0, 119.0, 126.0, 152.5, 154.0, (C=O and $CF_2$ not observed).

**Minor α-isomer 7c:** NMR $^{19}$F $\delta$ −115.0 (d, $^2J$ = 269 Hz, 1 F), −124.3 (dd, $^2J$ = 269 Hz, $^3J_{Fb-H10}$ = 26.5 Hz, 1 F); NMR $^1$H $\delta$ 0.95 (d, $^3J_{H15-H6}$ = 6 Hz, 3 H, $CH_3$-15), 1.09 (ddd, $^3J_{H16-H9}$ = 8 Hz, $^5J_{H16-Fa}$ = 3 Hz, $^5J_{H16-Fb}$ = 2 Hz, 3 H, $CH_3$-16), 1.33 (s, 3 H, $CH_3$-14), 2.0 (m, 1 H, H-9), 3.74 (s, 3 H, $OCH_3$), 3.83 (s, 3 H, $OCH_3$), 5.3 (ddd, $^3J_{H9-H10}$ = 7 Hz, $^3J_{H10-Fb}$ = 21.5 Hz, $^3J_{H10-Fa}$ = 2.5 Hz, 1 H, H-10), 5.36 (d, $^5J_{H12-F}$ =2 Hz, 1 H, H-12), 6.89 (d, $^3J$ = 9 Hz, 1 H), 7.0 (m, 1 H), 7.1 (d, $^4J$ = 3 Hz, 1 H); NMR $^{13}$C $\delta$ 20.0 (C-15 and C-16), 34.0 (C-9), 34.5, 36.0, 37.0, 43.5 (C-8a), 51.5, 55.5, 57.5, 70.5 (C-10), 81.5, 90.0 (C-12), 102.3, 112.5, 115.0, 119.0, 151.5, 152.5, 154.0, (C=O and $CF_2$ not observed).

**2,2-Difluoro-1-(2-thienyl)-2-[(1*S*,4*R*,5*S*,8*R*,9*R*,10*S*,12*R*,-13*S*)-1,5,9-trimethyl-11,14,15,16-tetraoxatetracyclo-[10.3.1.0$^{4,13}$.0$^{8,13}$]hexadec-10-yl]-1-ethanone (9d).** $SnCl_4$ (0.12 mL, 0.2 mmol, 0.4 equiv) was added at −78 °C, under Ar, to a solution of dihydroartemisinin acetate **4** (200 mg, 0.6 mmol) in $CH_2Cl_2$ (10 mL). Difluoroenoxysilane **3a** (200 mg, 0.9 mmol, 1.5 equiv) was then added very slowly at −78 °C. After complete disappearance of the starting acetate **4** (1 h, and raising the temperature to −20 °C), a saturated solution of sodium hydrogenocarbonate was added. After extraction ($CH_2Cl_2$), the organic layer was washed (brine) and dried ($MgSO_4$). Evaporation of the solvent provided a residue that was purified on neutral alumina column (petroleum ether/AcOEt 90:10), leading to the pure compound **9d** as an oil (40 mg, 29%) as a mixture of two isomers $\beta$ and $\alpha$ ($\beta$:$\alpha$ 70:30). Anal. Calcd for $C_{21}H_{26}O_5F_2$: C, 58.87; H, 6.11. Found: C, 58.19; H, 6.35.

**Major $\beta$-isomer 9d:** NMR $^{19}$F $\delta$ −108.8 (d, $^2J$ = 272 Hz, 1 F), −115.4 (dd, $^2J$ = 272 Hz, $^3J_{Fb-H10}$ = 24 Hz, 1 F); NMR $^1$H $\delta$ 0.94 (d, $^3J_{H15-H6}$ = 7 Hz, 3 H, $CH_3$-15), 1.0 (m, 1H, H-7), 1.11 (s, 3 H, $CH_3$-14), 1.12 (ddd, $^3J_{H16-H9}$ = 6.5 Hz, $^5J_{H16-Fa}$ = 2 Hz, $^5J_{H16-Fb}$ = 4.2 Hz, 3 H, $CH_3$-16), 1.25 (m, 2 H, H-6, H-5a), 1.35 (m, 1H, H-8), 1.4 (m, 1 H, H-5), 1.7 (m, 1 H, H-7), 1.75 (m, 1 H, H-8), 1.83 (m, 1 H, H-8a), 1.95 (m, 1 H, H-4), 2.25 (m, 1 H, H-4), 2.82 (m, 1 H, H-9), 5.27 (td, $^3J_{H9-H10}$ = 6.5 Hz, $^3J_{H10-Fa}$ = 6.5 Hz, $^3J_{H10-Fb}$ = 25 Hz, 1 H, H-10), 5.35 (d, $^5J_{H12-F}$ = 2 Hz, 1 H, H-12), 7.16 (dd, $^3J'$ = 5 Hz, $^3J$ = 4 Hz, 1 H), 7.74 (dd, $^3J'$ = 5 Hz, $^4J$ = 1.2 Hz, 1 H), 8.0 (dd, $^3J'$ = 4 Hz, $^4J'$ = 1 Hz, 1 H); NMR $^{13}$C $\delta$ 11.9 (C-16), 20.0 (C-15), 24.0 (C-8), 25.0 (C-14), 26.0 (C-5), 29.1 (C-9), 34.0 (C-7), 37.0 (C-4), 38.0 (C-6), 43.5 (C-8a), 51.5 (C-5a), 70.0 (C-10), 81.5 (C-12a), 91.0 (C-12), 104.0 (C-3), 117.8 (t, $^1J$ = 264 Hz, $CF_2$), 128.0, 135.5, 137.5, 139.0, (C=O not observed).

**Minor α-isomer 9d:** NMR $^{19}$F $\delta$ −103.9 (d, $^2J$ = 256 Hz, 1 F), −118 (dd, $^2J_{Fa-Fb}$ = 256 Hz, $J_{Fb-H10}$ = 16.5 Hz, 1 F); NMR $^1$H $\delta$ 0.92 (d, $^3J_{H15-H6}$ = 7.5 Hz, 3 H, $CH_3$-15), 1.01 (ddd, $^3J_{H16-H9}$ = 7 Hz, $^5J_{H16-Fa}$ = 1 Hz, $^5J_{H16-Fb}$ = 3.5 Hz,3 H, $CH_3$-16), 1.13

(s, 3 H, $CH_3$-14), 2.8 (m, 1 H, H-9), 3.99 (ddd, $^3J_{H9-H10}$ = 11 Hz, $^3J_{H10-Fa}$ = 7 Hz, $^3J_{H10-Fb}$ = 17 Hz, 1 H, H-10), 5.16 (d, $^5J_{H12-Fa}$ = 2 Hz, 1 H, H-12), 7.11 (dd, $^3J$ = 5 Hz, $^3J$ = 5 Hz, 1 H), 7.71 (dd,$^3J'$ = 5 Hz, $^4J$ = 1 Hz, 1 H), 8.07 (m, $^3J'$ = 5 Hz, $^4J'$ = 1 Hz, 1 H); NMR $^{13}$C $\delta$ 13.0 (C-16), 20.0 (C-15), 24, 25.0 (C-14), 25.2, 26.0, 27.5 (C-9), 34.0, 34.6, 36.0, 37.0, 47.1 (C-8a), 51.5, 75.0 (C-10), 81.5, 91.0 (C-12), 102.5 (C-3), 128.0, 136, 137.5, 139.7, ($CF_2$ and C=O not observed).

**2,2-Difluoro-1-(4-methoxyphenyl)-2-[(1*R*,3*S*,6*R*,7*S*,10*R*,-11*S*,12*R*,14*R*)-3,7,11-trimethyl-2,13,15,16-tetraoxatetracyclo[8.4.1.1$^{3,14}$.0$^{1,6}$]hexadec-12-yl]-1-ethanone (8b).** $SnCl_4$ (0.06 mL, 0.12 mmol, 0.4 equiv) was added at − 78 °C, under Ar, to a solution of dihydroartemisinin acetate **4** (100 mg, 0.3 mmol) in $CH_2Cl_2$ (4 mL). Difluoroenoxysilane **3b** (118 mg, 0.46 mmol, 1,5 equiv) was then added very slowly at −78 °C. After complete disappearance of the starting acetate **4** (2 h, and raising the temperature to −20 °C), a saturated solution of sodium hydrogenocarbonate was added. After extraction ($CH_2Cl_2$), the organic layer was washed (brine) and dried ($MgSO_4$). Evaporation of the solvent provided a residue that was purified on neutral alumina column (petroleum ether/AcOEt 90:10), leading to the pure compound **8b** as white crystals (115 mg, 83%), as a 65:35 mixture of the two $\beta$ and α diastereoisomers, which have been separated by chromatography on neutral alumina. Anal. Calcd for $C_{24}H_{30}O_6F_2$: C, 63.70; H, 6.68; Found: C, 61.98; H, 6.63.

**Major α-isomer 8b:** 63 mg (45%); mp 218 °C (petroleum ether/AcOEt); $[\alpha]^{26}_D$ +0.5 (*c* 0.59, MeOH); NMR $^{19}$F $\delta$ −99.9 (d, $^2J$ = 263 Hz, 1 F), −118.3 (dd, $^2J$ = 263 Hz, $^3J_{Fb-H10}$ = 19 Hz, 1 F); NMR $^1$H $\delta$ 0.96 (dd, $^3J_{H16-H9}$ = 7 Hz, $^5J_{H16-F}$ = 4 Hz, 3 H, $CH_3$-16), 0.98 (d, $^3J_{H15-H6}$ = 6.5 Hz, 3 H, $CH_3$-15), 1.15 (m, 1 H, H-6), 1.33 (s, 3 H, $CH_3$-14), 1.4 (m, $^3J_{H5a-H6}$ = 11 Hz; $^3J_{H5a-H5eq}$ = 5.5 Hz, $^3J_{H5a-5ax}$ = 12 Hz, 1 H, H-5a), 1.45 (m, 2 H, H 8ax, H-5ax.), 1.5 (m, 2 H, H-7, H-4), 1.75 (m, 1H, H-7), 1.9 (dtd, $^2J_{H5eq-H5ax}$ = 13.5 Hz, $^3J_{H5eq-H4}$ = $^3J_{H5eq-H5a}$ = 5 Hz, $^3J_{H5eq-H4ax}$ = 3 Hz, 1 H, H-5eq), 2.03 (m, $^2J$ =14.5 Hz, $^3J_{H8eq-H8a}$ = 6 Hz, $^3J_{H8eq-H7ax}$= 8 Hz, 1 H, H-8eq), 2.77 (dqd, $^3J_{H9-H8a}$ = 3.5 Hz, $^3J_{H9-H16}$ = 7 Hz, $^3J_{H9-H10}$= 11 Hz, 1 H, H-9), 3.85 (s, 3 H, $OCH_3$), 4.04 (m, $J_{H8a-H8eq}$ = 6 Hz, $^3J_{H8a-H9}$ = 4 Hz, $^3J_{H8a-H8ax}$ = 13 Hz, 1 H, H-8a), 4.08 (ddd, $^3J_{H10-H9}$ = 11 Hz, $^3J_{H10-Fa}$ = 6 Hz, $^3J_{H10-Fb}$ = 18 Hz, 1 H, H-10), 4.88 (s, 1 H, H-12), 6.9 (d, $^3J$ = 9 Hz, 2 H), 8.09 (d, $^5J$ = 1.7 Hz, $^3J$ = 9 Hz, 2 H); NMR $^{13}$C $\delta$ 12.5 (C-16), 21.5 (C-15), 24.5 (C-14, C-5), 27.5 (C-15), 32.0 (C-7), 33.5 (C-4), 39 (C-9), 40.0 (C-6), 47.7 (C-5a), 55.5 ($OCH_3$), 76.0 (C-10), 80.5 (C-8a), 101.0 (C-12), 108.5 (C-3), 109.5 (C-12a), 113.5, 118.5 (t, $^1J$ = 262 Hz, $CF_2$), 127.0, 133.2, 164.1, 190.5 (C=O).

**Minor *β*-isomer 8b:** 47 mg (35%); mp 130 °C (petroleum ether/AcOEt); $[\alpha]^{26}_D$ −3.8 (*c* 0.61, MeOH); NMR $^{19}$F $\delta$ −112.7 (d, $^2J$ = 269 Hz, 1 F), −118.5 (dd, $^2J$ = 269 Hz, $^3J_{Fb-H10}$ = 23 Hz, 1 F); NMR $^1$H $\delta$ 0.96 (d, $^3J_{H15-H6}$ = 6.5 Hz, 3 H, $CH_3$-15), 1.05 (m, 1 H, H-7), 1.06 (dd, $^3J_{H16-H9}$= 7.5 Hz, $^5J_{H16-F}$ = 3 Hz, 3 H, $CH_3$-16), 1.2 (m,1 H, H-6), 1.25 (m, 1 H, H-5a), 1.26 (s, 3 H, $CH_3$-14), 1.45 (1 H, H-7), 1.5 (1 H, H-4), 1.7 (dtd, $^2J$ = 14 Hz, $^3J$ = 8 Hz, $^3J$ = 3 Hz, 1 H, H-5), 1.87 (m, 3 H, H-4, H-5, H-8), 2.80 (m, $^3J_{H9-H8a}$ = $^3J_{H9-H16}$ = 7.5 Hz, $^3J_{H9-H10}$ = 4 Hz, 1 H, H-9), 3.87 (s, 3 H, $OCH_3$), 4.16 (ddd, $^3J_{H8a-H8eq}$ = 6 Hz, $^3J_{H8a-H9}$ = 8.5 Hz, $^3J_{H8a-H8ax}$ = 13 Hz, 1 H, H-8a), 5.2 (d, $^5J_{F-H12}$= 2. Hz, 1 H, H-12), 5.25 (ddd, $^3J_{H10-H9}$ = 4 Hz, $^3J_{H10-Fa}$ = 5 Hz, $^3J_{H10-Fb}$ = 24 Hz, 1 H, H-10), 6.95 (d, $^3J$ = 9 Hz, 2 H), 8.1 (d, $^3J$ = 9 Hz, 2 H); NMR $^{13}$C $\delta$ 10.0 (C-16), 21.0 (C-15), 23.0 (C-14), 25.0 (C-8), 29.1 (C-5), 33.0 (C-4, C-7), 38.0 (C-9), 39.5 (C-6), 48.0 (C-5a), 56 ($OCH_3$), 71.0 (C-10), 78 (C-8a), 98 (C-12), 106 (C-3), 108 (C-12a), 114, 127.0, 132, 164.5, 189.0 (C=O), ($CF_2$ not observed).

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**Supporting Information Available:** Experimental procedures and full characterization (IR, $^1$H, $^{13}$C, $^{19}$F NMR spectra and analysis) for compounds **5b**−**c**, **6b**−**c** and **7b**. X-ray structural information on **7a** and **8b** including ORTEP figures, tables of fractional atomic coordinates, bond lengths and angles. This material is available free of charge via the Internet at http://pubs.acs.org.

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