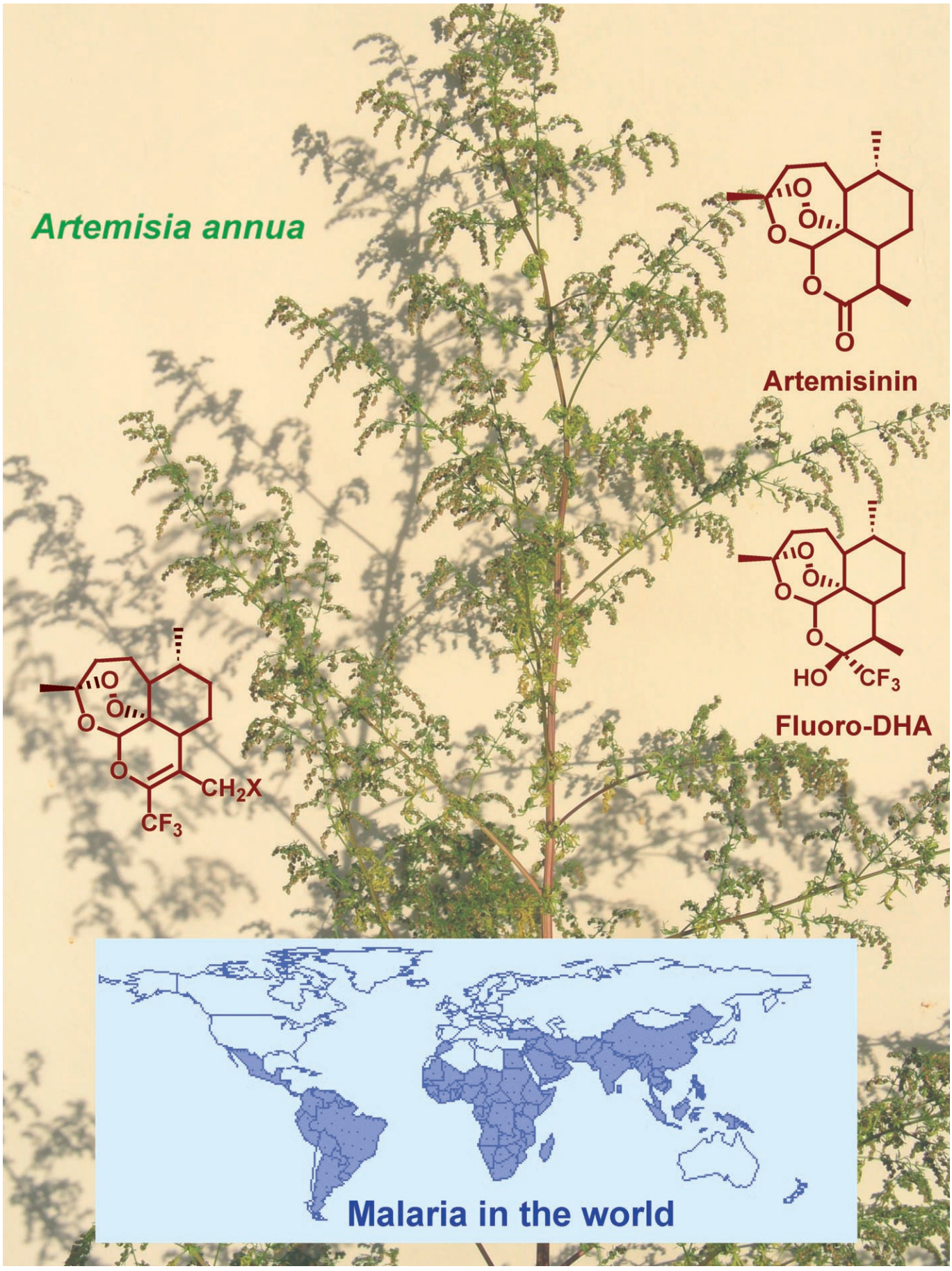

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Fluoroartemisinins: Metabolically More Stable Antimalarial Artemisinin Derivatives

Jean-Pierre Bégué and Danièle Bonnet-Delpon*[a]

This report is an overview on the design, preparation, and evaluation of metabolically stable artemisinins, using fluorine substitution. The chemical challenges encountered for the incorporation of fluorine-containing elements and the preparation of a large range of 10-trifluoromethyl artemisinin derivatives are detailed. Impact of the fluorine substitution on the antimalarial activity is also highlighted. Preclinical data of lead compounds, and evidence for their strong and prolonged antimalarial activity are presented.

Introduction

Malaria continues to be one of the most important infectious diseases in the world.[1] Of the four human malaria parasites, *Plasmodium falciparum* is the overwhelming cause of severe clinical malaria and death. A major cause of malarial morbidity and mortality is certainly the increasing resistance of malaria parasites, in particular *P. falciparum*, to available drugs (chloroquine, pyrimethamine, proguanil, halofantrine, etc.).[2] Moreover this highly worrisome situation is aggravated by the arrival of insecticide-resistant strains of mosquito vectors. The resulting dramatic decline in the efficacy of the most affordable antimalarial drugs leads to a broad consensus on the need to develop new antimalarial drugs.[3] Artemisinin **1** (Figure 1), has emerged as such a chemotherapeutic agent. This naturally-occurring endoperoxide sesquiterpene lactone artemisinin, has been isolated from the plant *Artemisia annua* whose remedial use for high fever extends back over 2000 years in Chinese folk medicine.[4] Artemisinin provides a crucial molecular framework from which medicinal chemists have prepared more efficacious antimalarial drugs (which will be called artemisinins) that retain the uncommon and essential pharmacologically important 1,2,4-trioxane core.[5]

First generation artemisinins have low oral bioavailability, which is fortunately partially countered by their very high intrinsic activities. However, the short half-life of these compounds in the body can lead to recrudescence of parasitemia. Therefore, protracted treatment regimens are required to cure malaria.[6] Their use in combination with longer half-life antimalarial drugs, as recommended by WHO, can not only delay emergence of resistance, but also partially overcome the problem of short plasma half-life.[7] Nevertheless, chemically and metabolically more stable artemisinins would bring improvement in malaria therapy and bitherapy.

According to Scheme 1, the human metabolism of an ether of artemisinin, such as artemether, involves first an oxidation in the liver by cytochrome P450 enzymes that produce dihydroartemisinin (DHA) as the main metabolite, which retains all antimalarial activity.[8] However, DHA is then rapidly eliminated through phase II metabolism by generation of water-soluble conjugates such as α-DHA-β-glucuronides.[9] These two processes are the principal reasons why first generation artemisinins have short half-lives.[5] A second important factor is the low stability of the acetal group under acid conditions, such as those found in the stomach upon oral administration. To overcome these problems and, more importantly, to improve the oral bioavailability of artemisinins, a huge number of compounds have been synthesized from artemisinin.

Artemisinin **1** could be a readily available natural material. The large-scale isolation and purification of artemisinin from wild or cultivated *Artemisia annua* is rather easy (more than 10 tons/year are produced in south-east Asia).[5] Despite current rapidly increasing demand, availability and prices should not be a real handicap for future development of a semisynthetic artemisinin. These semisynthetic artemisinins essentially result from transformation at positions 9, 10, 11, and 16.[5,10–13]

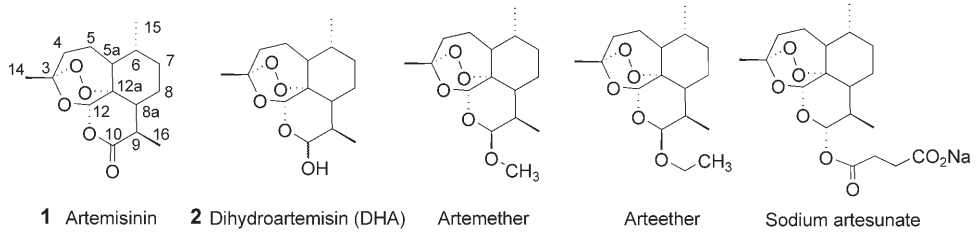

Figure 1. First generation of antimalarial artemisinins.

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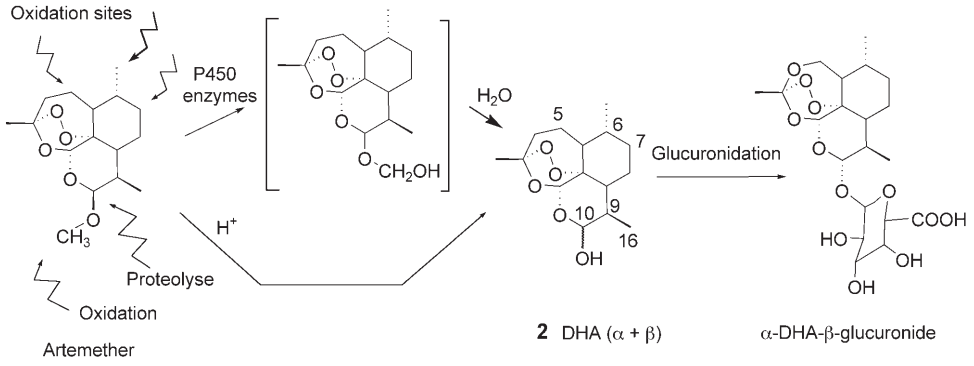

Scheme 1. Metabolism of artemether in humans.

Interestingly, from a chemical point of view, the artemisinin structure tolerates a large variety of chemical reactions without damage, despite the presence of the peroxide bridge. For instance, the endoperoxide bridge is generally stable towards Lewis acids, which allows the generation of an oxonium ion from activated DHA. Further reactions with alcohols, phenols, electron-rich aromatic compounds, silyl enol ethers, functionalized silanes, alkynes, etc. produce sets of *O*, *N*, or *C*-substituted artemisinins at C10.[14–20] Furthermore, nucleophilic additions can also be realized directly on the lactone function of artemisinin.[21] Radical chemistry is also possible without reduction of the endoperoxide bridge.[22] Reactions involving catalytic reductive conditions (Zn, Fe^{2+} etc) are the more critical reactions for the endoperoxide pattern of artemisinin derivatives.

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Danièle Bonnet-Delpon is Director of Research at the CNRS. After her PhD in 1982 on long range functionalizations, she then progressed from the study of CF_3-substituted carbenium ions to synthetic organofluorine chemistry. She developed the synthesis of fluorinated bioactive compounds: ligands of receptors, enzyme inhibitors, and antimalarials. Since 2003, she has in charge the group of Fluorinated Molecules and Medicinal Chemistry at the Faculty of Pharmacy-Paris South.

An effective approach to improve the pharmacological profile concerns the design of oxidation-resistant ethers of dihydroartemisinin, such as the interesting ethers **3a** and **3b**, compounds developed by O'Neill (Figure 2).[23] The replacement of the (*O*,*O*)-acetal function at C10 by an (*N*,*O*)-acetal, as in compounds **4** or **5** is also very fruitful,[24,25] as shown by the current clinical development of artemisone, a 10-amino artemisinin of structure **5a**, by Bayer and MMV (Figure 2).[26] Use of another strategy involving the suppression of the acetal function at C10, led to preparation of 10-carba derivatives;[5,10–13] and they are of course, more robust towards the acidic conditions found in the stomach (Figure 3).

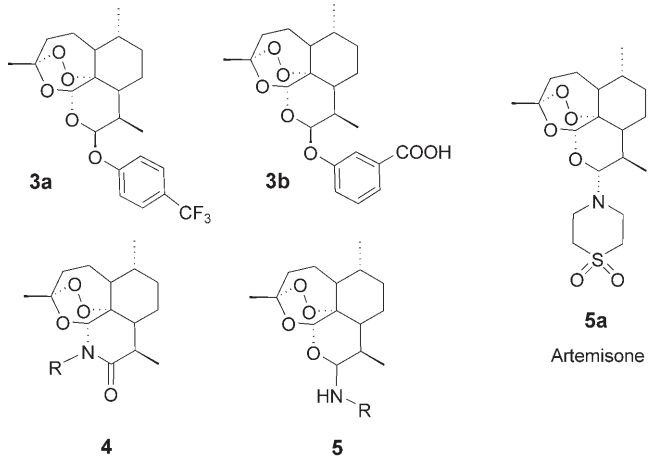


Figure 2. Second generation DHA ethers and nitrogen derivatives.

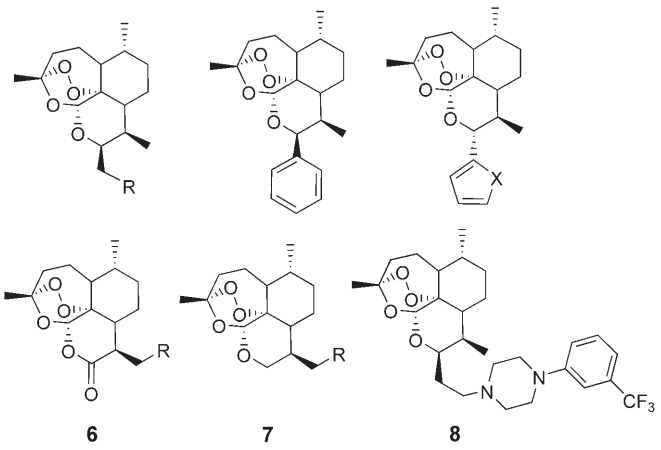


Figure 3. Main structural variations of artemisinin at C10 and C16 for antimalarial drug discovery.

Efforts to prepare 16-functionalized derivatives have also been performed using artemisitene, which is available from artemisinin.[27] Lactones **6**, prepared by a Michael addition onto artemisitene,[28] could be precursors of various analogues of DHA ethers. The resulting derivatives are still acetal-type, and hence not very robust towards an acidic medium. Artemisinic acid is a precursor of 16-functionalized derivatives **7**, nonsubstituted at C10.[29] However this starting material is less readily available from *Artemisia annua* than artemisinin itself.[30]

From these various "robust" artemisinins, current efforts have focused on incorporating or converting functional groups to increase water solubility and to decrease log *P*, as exemplified by artemisone **5a**[26] and compound **8**.[5,31]

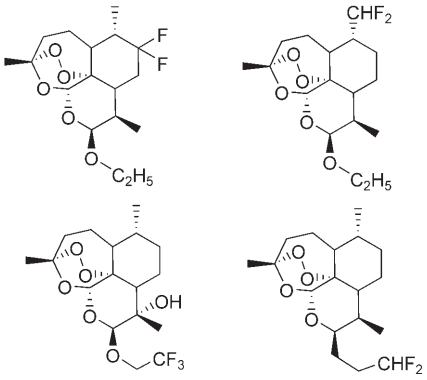


Figure 4. Fluorinated derivatives of artemisinin.[35]

Fluoroartemisinins

Our approach, initiated ten years ago, was to design a metabolically more stable artemisinin using fluorine substitution. This approach is well known in medicinal chemistry and has been used many times to prevent oxidative metabolism and/or to increase hydrolytic stability.[32a,33] The slowing down of metabolism induced by fluorine substitution is a consequence of the intrinsic properties of the fluorine atom. Its electronic structure and strong electronegativity provide a great chemical inertia to the C–F bond, in particular towards oxidation. Furthermore, the electronegativity of the fluorine atom confers a strong electron-withdrawing character to fluoroalkyl substituents. This disfavors a positive charge development on the α-carbon, and consequently the generation of cationic species involved in hydrolytic processes.[32b,33,34]

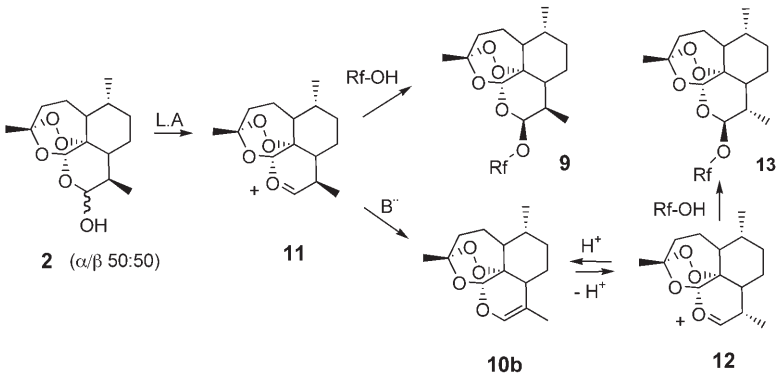
At the time we started this project, Ziffer et al. reported some fluorinated artemisinins, prepared by fluorination of ketone or aldehyde resulting from chemical or metabolic oxidation of artemisinin derivatives (Figure 4).[35] These compounds presented interesting in vitro IC_{50} values. However, probably because of the difficulty in preparing sufficient quantities of these precursors, no information about in vivo investigations was reported.[35,36] The preparation of fluoroartemisinins at adequate scale, specifically designed to slow down metabolism and validate our hypothesis, was our primary objective.

In this review we give an overview of the results of our studies devoted to new potent antimalarial fluoroartemisinins. The effects of fluorine on chemical reactivity render the synthesis of fluoroartemisinins not always straightforward. These specific chemical challenges will be highlighted.

1. Fluoroalkyl ethers of dihydroartemisinin

As indicated in Figure 2, ethers of DHA undergo a rapid hydroxylation by cytochrome P450 enzymes to generate a hemiacetal, which decomposes to produce DHA **2** and an aldehyde (shown in vivo and in liver homogenates).[37] A feasible approach to prolong the half-life of DHA ethers is to design poorer substrates for cytochrome P450 by introduction of a fluorinated substituent at the α-methylene carbon of the alkoxy group. A slower rate of oxidative dealkylation would be expected, as it has been demonstrated that the protection against oxidative processes provided by a fluoroalkyl group is often extended to adjacent CH or CH_2 groups.[32a,38,39]

Ethers of DHA are usually prepared by treatment of DHA **2** (α:β ~ 50:50) with the appropriate alcohol in the presence of BF_3, Et_2O. The stereochemistry of this reaction has been intensively investigated and discussed,[40] in particular by Haynes et al.[18,25,30] This process is less efficient with fluoroalcohols (RfOH), because they are poor nucleophiles. For instance, the reaction of trifluoroethanol with DHA, in the presence of BF_3,Et_2O, yielded the ether **9a** (67%), and dehydrodeoxoartemisinin **10** (20%) resulting from the competing deprotonation of the intermediate oxonium ion **11** (Scheme 2).[31,40a] From pentafluoropropanol, yield in ether **9b** was only 43%, and

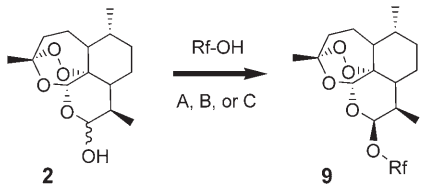


Scheme 2. Etherification reaction of dihydroartemisinin.

more than 50% of dehydrodeoxoartemisinin **10** was isolated.[41] Reactions are highly stereoselective, with the predominant formation of the β isomers **9a** and **9b** (β/α:97/3).[42] Interestingly, the elimination process could be limited by the replacement of the usual solvent (Et_2O) by a less basic one (hexane), where the yield of ether **9b** was strongly increased (97%).[43] Under these conditions the ether **9b** could be prepared in high purity and at a scale greater than 100 g. However, hindered secondary or higher fluoroalcohols did not react

well, even under these improved conditions. Furthermore, in some cases, detection of ethers **13** epimerized at C9 (1–8%) indicated an isomerization of oxonium ion **11** into **12** (Scheme 2).

The Mitsunobu procedure was reported to be efficient in the case of fluoroalkyl alcohols.[44] Unlike nonfluorinated alcohols, the acidic fluoroalcohols[45] are efficiently deprotonated by the PPh_3-DEAD adduct. This facilitates the displacement of the oxyphosphonium leaving group by the alkoxide. By this reaction, a range of ethers **9** were provided from fluoroalcohols in good (from primary alcohols) to moderate yields (secondary alcohols) and always with a high β-stereoselectivity (Scheme 3,



Rf-OH : -CH_2CF_3, -$CH_2CF_2CF_3$, -$CH_2CF_2CFHCF_3$, $CH(CF_3)C_6H_5$, $CH(CF_3)_2$, $C(CF_3)_2C_6H_5$, C_6F_5

Scheme 3. Preparation of DHA fluoroalkyl ethers **9**. A: BF_3, Et_2O, Et_2O; B: BF_3, Et_2O, hexanes; C: DEAD, PPh_3.

Table 1). According to the postulated SN2 mechanism of the Mitsunobu reaction, an α:β ~ 50:50 mixture of isomers was expected from the starting 50:50 α:β mixture of DHA. According to literature work on stereochemistry and reactions of DHA[18,25,30] various pathways can explain such a β-stereoselectivity, for example: 1) a favored reaction of the α-DHA to form the alkoxyphosphonium intermediate, followed by the SN2 displacement by the fluoroalkoxide, and the equilibrium of nonconsumed β-DHA into α-DHA; 2) the formation of both α and β alkoxyphosphonium intermediates followed by a preferential β attack by the alkoxide through the formation of the oxonium ion.

Table 1. Preparation of DHA fluoroalkyl ethers **9**.

Alcohol R_f-OH	Method	**9** Yields [%]	β/α
	A	67	94:4
a CF_3CH_2OH	B	97	96:4
	D	74	93:7
	A	43	97:3
b $CF_3CF_2CH_2OH$	B	54	97:3
	D	80	93:3
c $CF_3CHFCF_2CH_2OH$	A	21	100:0
	D	40	100:0
	A	0	
d $CF_3CHOHC_6H_5$	D	25	100:0
	A	0	
e $CF_3CHOHCF_3$	D	60	100:0
f $(CF_3)_2C(C_6H_5)OH$	A	0	
	D	30	98:2
g C_6F_5OH	A	0	
	D	50	94:6

This preparation of fluoroalkyl ethers has been extended to fluoroalkyl glycosides, which were not available by convenient synthetic methods.[46] The Mitsunobu protocol proceeded well with primary, secondary, tertiary fluorinated alcohols or phenols, and diversely protected mono- and disaccharides, leading to the corresponding fluoroalkyl and fluoroaryl glycosides.[47]

The IC_{50} values for the fluoroalkyl ethers **9**, evaluated on *P. falciparum* (W2 strain) (27 nM < IC_{50} < 72 nM), are higher than that of artemether, with only a small influence of the structure of fluorinated chains. In vivo (Peters' test, *P. berghei,* i.p. administration), ethers **9** were very active, ethers **9b** and **9e** being the best. All animals were cured until day 42 (D-42). Compound **9b** has been investigated more thoroughly. High activity was also found after subcutaneous (ED_{50} = 1 mg kg^{-1}, ED_{90} = 1.5 mg kg^{-1}) and oral administrations (ED_{50} = 2.8 mg kg^{-1}, ED_{90} = 4.3 mg kg^{-1}). However, its water solubility is very low (log *P* = 6.1, water solubility at pH 7.4 < 5 mg mL^{-1}),[48] and a formulation was required.

2. Fluorinated analogues of dihydroartemisinin, artemether, and artesunate

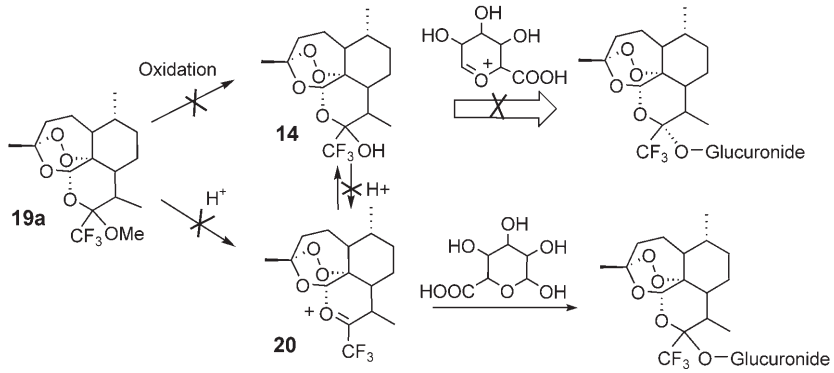
A great effect on both stability and metabolism might be expected from the presence of a trifluoromethyl substituent at C10 in DHA and its ethers. The following effects were anticipated:

- the glucuronidation of CF_3-DHA **14** should be greatly slowed relative to DHA, because the electron withdrawing character of the trifluoromethyl group can affect the two possible glucuronidation processes. The nucleophilicity of the hydroxyl in CF_3-DHA **14** is strongly decreased and, consequently, **14** is expected to be a poorer glycosyl acceptor, independent of its configuration at C10. Alternatively, an intermediate oxonium ion at C10, which is a potential glycosyl acceptor, should be generated from **14** only with a high activation energy (Scheme 4).
- the in vivo stability of the trifluoromethyl analogue **19a** of artemether is anticipated to be increased in two ways: first, the trifluoromethyl group could prevent oxidation of the methoxy group;[32a,38,39] second, the intermediate oxonium ion should be much more difficult to generate in acidic medium.[32a]

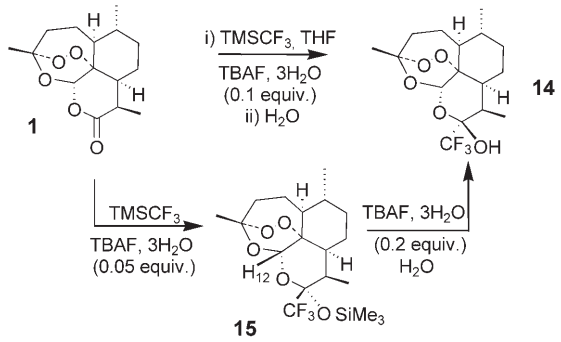
To validate these hypotheses, the synthesis of trifluoromethyl analogues of DHA and artemether was investigated.

Chemistry

The hemiketal **14** was very easily prepared in high yield (78%) from artemisinin by treatment with trifluoromethyl trimethylsilane ($TMSCF_3$) in the presence of tetrabutylammonium fluoride trihydrate (TBAF, $3H_2O$). Complete desilylation occurred after addition of water (Scheme 5). The reaction was stereoselective, and the α configuration of the CF_3-group was unambiguously determined (β-**14**).[41,49] However this configuration at C10 is not the result of an α approach of the CF_3 but of a thermody-



Scheme 4. Expected effect of CF_3-substitution on the stability of artemether and DHA.

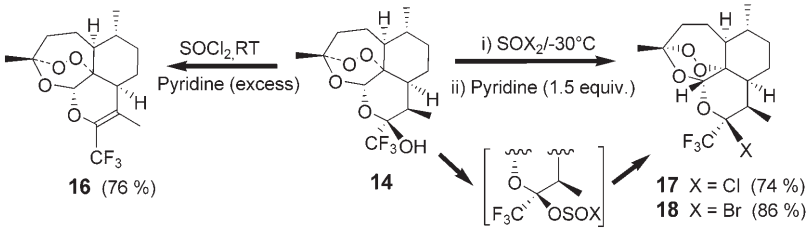


Scheme 5. Reaction of $TMSCF_3$ with artemisinin.

namic equilibrium of the kinetic (β-CF_3, α-hydroxy) product into β-**14**. Actually, when the reaction was performed using only 0.05 equivalents of TBAF, the silyloxy ketal α-**15** was isolated. This indicates that, from artemisinin, there is a kinetic preference for β-addition, such as in reactions from activated DHA involving an oxonium ion.[30] Desilylation with an excess of TBAF and water produced the β-hemiketal **14** (Scheme 5). The axial CF_3 group, which is a bulky substituent (compared to an isopropyl group),[50] probably suffers from a repulsive interaction with both the C8a–C8 axial bond and the methyl substituent, and thus favors this displacement, whereas in DHA **2**, the α/β equilibrium ratio is about 50:50.

We then investigated routes to CF_3-analogues of DHA ethers. All attempts for etherification or acylation of the hydroxyl moiety of hemiketal **14**, failed. Starting hemiketal **14** was recovered under the various conditions generally used for the functionalization of DHA.[51] This can be related to the lack of reactivity of the β-epimer of DHA where the axial hydroxyl experiences a 1,3-diaxial interaction with the C8–C8a bond. The steric effect of the crowded environment coupled with the low nucleophilicity of a tertiary trifluoromethyl hydroxyl, raises the energy activation for alkylation or acylation. Neither were effective alternative routes for a substitution reaction with displacement of the hydroxyl of **14**. Generally, the substitution of α-trifluoromethyl hydroxyl groups is as difficult through SN1 as through SN2 processes. The high electron withdrawing effect of the CF_3 group strengthens the C–O bond and destabilizes the intermediary carbocation in the SN1 process.[52] Despite the presence of an alkoxy substituent at C10, the hemiketal **14** remained unchanged when it was placed under SN1-type conditions (BF_3·Et_2O/MeOH). In an SN2 process, the combination of steric and electronic repulsive effects of fluorine atoms on the incoming nucleophile decreases the reaction rate.[52a,b] Indeed, the Mitsunobu reaction, a typical SN2 process, failed with compound **14** and benzoic acid.

Finally, the chloride **17** and the bromide **18** could be prepared from **14** in good yields by reaction, at −30 °C, with thionyl chloride or thionyl bromide using 1.5 equivalent of pyridine (Scheme 6). It is worth noting that, when performed using pyridine as solvent at room temperature, this reaction provided the glycal **16** in good yield. The formation of halides **17** and **18** was stereoselective, with the same α configuration of the

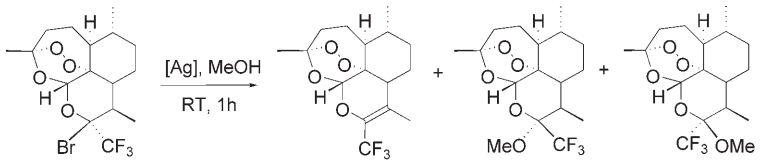


Scheme 6. Preparation of 10-halogeno-10-deoxoartemisinins.

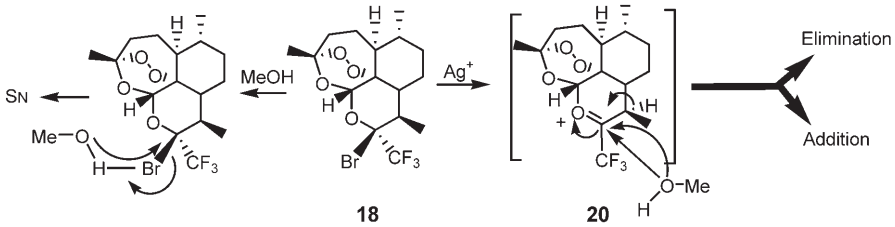
CF_3 group as in the starting material. The nucleophilic substitution proceeds with configuration retention, corresponding to an SNi mechanism.[22] The 10-halogeno compounds **17** and **18** are, a priori, better substrates than the hydroxyl one (CF_3-DHA) for further substitution reactions.

The substitution of bromide **18** was first investigated under conditions of electrophilic assistance, in the presence of Ag_2CO_3 or AgOTf. With methanol used as solvent, the ether **19a** was obtained as a mixture of 2 diastereoisomers, accompanied by a large amount of glycal **16**. Ratios **19a**/**16** and α/β stereoisomers of **19a** are dependent on the counter ion of the silver salt (Scheme 7).[51]

Considering the lack of chemo- and stereoselectivity of these silver-mediated reactions, it is reasonable to postulate a SN1 mechanism type process leading to the oxonium ion **20**, despite the destabilizing effect of the CF_3 group (Scheme 8). Whereas it was anticipated that the basicity of the counter ion



Scheme 7. Substitution of bromide **18** with MeOH, mediated by silver salts.



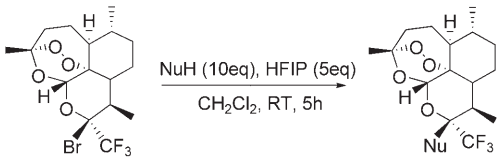
Scheme 8. Both activation pathways of substitution reaction of bromide **18**.

could have an influence on the elimination process, it is more surprising that the stereoselectivity of the substitution reaction also depends on the silver salt used. Indeed, the stereochemical outcome should result from the steric or electronic preference of methanol addition for each face of the trifluoromethyl oxonium ion **20**, the interactions being probably different from those in nonfluorinated DHA derivatives. To disfavor the formation of the oxonium **20**, the reaction was performed without silver salt in MeOH. Whereas the reaction rate did not significantly decrease (2 h), only 23% of glycal **16** was obtained. Furthermore, the substitution leading to **19a** occurred with more than 80% retention of the configuration (α/β:17/83). These results can be rationalized by an electrophilic activation of bromide of **18** by methanol, through a hydrogen bond (α_{MeOH} = 0.98).[53] The main pathway could be a concerted process where, for instance, a molecule of methanol activates bromide and delivers the alkoxide, similar to a SNi process (see below).

A required improvement was to decrease the amount of alcohol used for the substitution. Reaction of bromide **18** in CH_2Cl_2 at RT with MeOH (10 equiv) was very slow (72% conversion after 15 h), but highly diastereoselective (α/β = 8/92) and chemoselective (only 3% of glycal **16**). For a further optimization, 1,1,1,3,3,3-hexafluoro isopropanol (HFIP) was used as additive. HFIP possesses a low nucleophilicity, a high ionizing power, a high hydrogen bond donor ability (α = 1.96), and a strong ability to solvate anions.[45b,54,55] These properties have been exploited in solvolysis reactions[46b,54] and various other reactions.[45b,56]

Under optimized experimental conditions (CH_2Cl_2, MeOH (10 equiv), HFIP (5 equiv)) the reaction was complete at room temperature in less than 5 h. Moreover, the reaction was still chemoselective (less than 5% of the elimination product **16**), and completely stereoselective (the α stereoisomer was not detected, Scheme 9, Table 2).

These conditions were effective with other nucleophiles. Alcohols provided the corresponding 10β-alkoxy-10α-trifluoromethyl desoxoartemisinin in good yields (73–89%), accompanied by only a small amount of glycal **16** (2–6%, Scheme 9). In all cases, the nucleophile reacted with retention of the configuration from the β face of the artemisinin skeleton. With the poorly nucleophilic trifluoroethanol (TFE), β-**19f** was obtained in lower yield (46%). Hydrogen peroxide could also act as a nucleophile in this reaction. To avoid competition between water and hydrogen peroxide substitution, H_2O_2 was delivered through the urea–hydrogen peroxide complex (UHP), a safe source of anhydrous hydrogen peroxide. The reaction of **18** with UHP in a mixture of CH_2Cl_2/HFIP was selective and gave the diperoxide **19g** (β-OOH) in 83% yield. Carboxylic acids could also be used in the substitution reaction: the carboxylate generated in situ from succinic acid and triethyl amine, produced, in the presence of HFIP as a cosolvent (1:1), the trifluoromethyl analogue **19i** of β-artesunate in 68% yield (Scheme 9, Table 2).



Scheme 9. Substitution of bromide **19** with various nucleophiles.

Table 2. Substitution of bromide **18** with various nucleophiles.

Nucleophiles	Compounds	Yields[a] [%]	Glycal **16** [%]
H_2O	**14**	87	12
MeOH	**19a**	79	5
EtOH	**19b**	76	6
4-(MeO_2C)-C_6H_4-CH_2OH	**19c**	76	6
CH_2=CH-CH_2OH	**19d**	73	5
$HOCH_2$-CH_2OH	**19e**	89	2
CF_3-CH_2OH[b]	**19f**	46	12
H_2O_2 (UHP)[c]	**19g**	83	0
4-MeO-C_6H_4-NH_2	**19h**	25	62
HO_2C-$(CH_2)_2$-CO_2H[c]	**19i**	68	5

[a] Isolated yield. [b] Used as solvent. [c] In a mixture 1:1 CH_2Cl_2:HFIP.

As expected, the reaction failed with aliphatic amines, because of their strong complexation with HFIP.[57] Less basic amines, such as *p*-anisidine, provided the substitution product **19h** (β-NHAr) but only in poor yield (25%). It is worth noting that this process is effective for the substitution of DHA itself with amines, as recently reported for the preparation of an analogue of artemisone with an improved yield.[58]

In all cases, the nucleophile is delivered on the same β-face as the leaving group. In similar results from DHA glycosyl donor, it has been rationalized by the formation of the half-chair oxonium ion, and a stereoelectronically preferred axial addition with reactive nucleophiles.[30] Compared to the reaction of **18** with the stronger Ag^+ electrophilic assistance (Schemes 7 and 8), the low ratio of elimination product **16** and the high β-diastereoselectivity suggest a mechanism different from an addition on the oxonium ion **20**. It is also clear that in **18** the side opposite to the bromide is very hindered: the bulky trifluoromethyl moiety and the cyclic oxygen lone pairs offer a more repulsive face than C8–C8a and C–H12 bonds. However such substitution reactions with retention of configuration have been previously observed only when the nucleophile is delivered by the activating agent. That is the case, for instance, for a bromide substitution with a Grignard reagent species in artemisinin series,[12] or for oxirane ring opening with a Lewis acid.[59] In the absence of a good explanation, we suggest a similar mechanism involving ion pairs. In addition to the activation of the C–Br bond of **18** by HFIP, through strong hydrogen bonding, there also exists an association between HFIP and the nucleophile (Figure 5). In such a solvation shell, HFIP assists the departure of the bromide with a strong elongation of the C–Br bond, delivers methanol which can trap the cation as it forms, and the configuration is retained. Current studies in the laboratory show that associations of HFIP with nucleophiles can induce specific reactivity,[57a] and form three-dimensional networks.[57b]

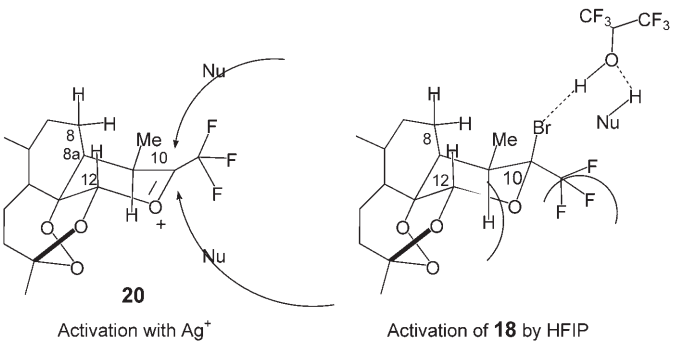


Figure 5. Substitution reaction of bromide **18** in different activation methods.

Biological properties

a) Trifluoromethyl dihydroartemisinin

The 10-*R*-(trifluoromethyl)dihydroartemisinin **14** is more potent than artemether and artesunate against D6 and W2 drug-resistant strains of *P. falciparum* (D6: IC_{50} = 2.6 nM and W2: IC_{50} = 0.9 nM). Moreover, it is active against wild isolates from African patients (with Senegalese isolates, IC50 = 3.3 nM).[41] Compound **14** is also more active in vivo (i.p, subcutaneous, or oral administration) than sodium artesunate in mice infected with murine *P. berghei* (Table 3).[41,60] All mice survived until day 42 in the Peters test.[60] Compound **14** possesses a high oral bioavailability (28%), compared to that of artemether (1.4%), probably because of a good compromise between a convenient log *P* (4.36) and a fairly good solubility.[48] The plasma half-life ($T_{1/2}$ = 86 min), after intravenous (i.v) or oral administration to rats is also higher than that of DHA (23 min.) or artemether (52 min.) (Figure 6).[60,61]

Table 3. Antimalarial activities and pharmacokinetic profile of compound **14**.

	In vitro:IC_{50} [nM]		Subcutaneous		Oral [mg kg^{-1}]	
	D6	W2	ED_{50}	ED_{90}	ED_{50}	ED_{90}
14	2.6	0.9	0.7	1.8	4.3	13.0
Na Artesunate	–	5.4	2.8	10.4	5.4	15.3

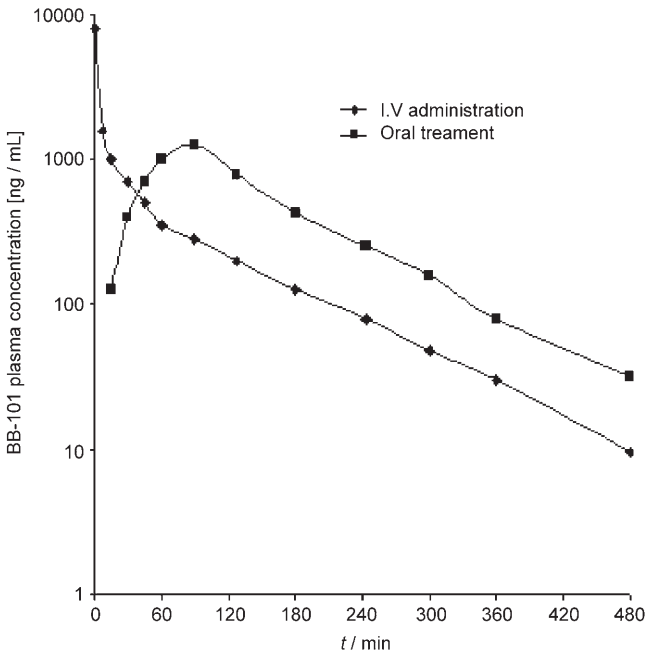


Figure 6. Plasma concentration versus time profiles for **14** after i.v. and oral administration to rats (10 mg kg^{-1} and 50 mg kg^{-1}, respectively).

Moreover, **14** displays low toxicity in rodents. The LD_{50} in mice orally treated was 820 mg kg^{-1} whereas the oral ED_{90} is only 13 mg kg^{-1}. Subacute toxicity testing was performed in rabbits (orally at 20 mg kg^{-1} once daily for 28 days), with no effect on the body weight of animals. The electrocardiogram index was the same in treated and nontreated groups. Haematological, biochemical (SGOT, SGPT, etc.) parameters, and histo-

pathological examinations showed that liver and kidney microstructure were normal in the treated group.[62] In vitro neurotoxicity evaluated on neuroblastoma cultures, in the presence of liver microsomes, showed that the neurotoxicity of **14** is half that of artemether.[63] In vivo tests including speed of establishing the reflex, speed of extinguishing the reflex for searching for food in a maze (mice), and conditional reflex (rats) were only slightly different from the nontreated group.[62] Toxicity studies are now currently being performed on monkeys.[62b]

The CF_3-dihydroartemisinin **14** is chemically stable and large scale preparation is easy, in one reaction step with purification by crystallization.[43,61] It is therefore considered to be a good candidate for future development.

b) Trifluoromethyl (O,O)- and (O,N)-ketals.

Quantitative evaluation of the hydrolytic stability brought to the ketal function by the introduction of a trifluoromethyl group at C10 showed that the trifluoromethyl analogue of artemether was 40 times more stable under acidic conditions (pH 2) than DHA, and 60 times more stable than artemether itself (Table 4). This confirms the hypothesis regarding the effect of the fluorine substitution on proteolytic protection, which occurs by disfavoring the formation of the oxocarbenium ion **20**.[51,60] This higher stability under acidic conditions should increase their half-lives in the stomach and consequently improve oral bioavailability.

Table 4. Stability under acidic conditions (half live at pH 2, 37 °C).

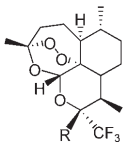
	$t_{1/2}$ [h]		$t_{1/2}$ [h]
DHA	17	Artesunate	<10
CF_3-DHA **14**	760	CF_3-artesunate **19i**	30
Artemether	11	Artelinate	13
CF_3-Artemether **19a**	660	CF_3-Artelinate **19j**	680
Arteether	11		
CF_3-Arteether **19b**	500		

In vitro activities on *P. falciparum* (FCB1 strain) of the trifluoromethyl analogues of (*O*,*O*) and (*O*,*N*) acetals are comparable to, or higher than the parent compounds (for example, 0.8 nM for CF_3-artemether) (Table 5). Comparison of in vivo ED_{50} shows that the CF_3-analogue **19a** of artemether is about twice as active as artemether (Table 6). More important, i.p. administration of the 10-CF_3 analogues of artemether and arteether to mice infected with *P. berghei* (NK173) completely cleared parasitemia from the end of treatment to day 25. This clearance had never previously been observed with artemether itself

Table 6. In vivo antimalarial activity against *P. berghei* NK 173.

	ED_{50} [mg kg^{-1}]	ED_{90} [mg kg^{-1}]
Artemether	2.5	8.5
CF_3-Artemether **19a**	1.25	6.4

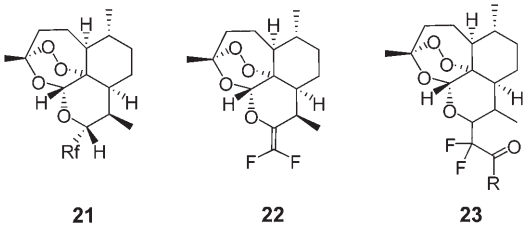
Table 5. In vitro antimalarial activity against *P. falciparum* FCB1 strain.

	R	Compounds	IC_{50} [nM]
Artemether	OMe		3.5
	OMe	**19a**	0.8
	OEt	**19b**	3.3
	OCH_2CF_3	**19f**	8.3
	OBn		8.5
	OH	**14**	9.40.
	OCH_2CH_2OH	**19e**	0.9
	$OCHOHCH_2OH$		0.9
	OOH	**19g**	13.2
	NH_2		18.3
	NH-C_6H_4-4-OCH_3	**19h**	12.3
	OCO-$CH_2CH_2CO_2H$	**19i**	4.1
	$OCH_2C_6H_4$-4-CO_2H	**19j**	10.6

when used at the same concentration (35.5 μmol kg^{-1}). Interestingly, we observed that the β-OMe isomer is more active than that the α one: in a treatment with only 10% of the dose (3.4 μmol kg^{-1}), all mice treated with β-CF_3-artemether survived to day 6; whereas only 50% of mice survived after treatment with a 50:50 mixture of β and α isomers.[60] Polar compounds, such as alcohols and acids, were slightly less effective in this test, with an activity comparable to that of hemiketal **14**. However the amine **19h** (R = NH-C_6H_4-OMe) exhibited an excellent activity (IC_{50} = 12 nM, all mice cured until day 25). Experiments for oral administration are currently in progress.

3. C-10-fluoroalkyl-10-deoxyartemisinin

Because of their potential interest, we also investigated access to nonketalic fluoroartemisinins of structures **21**, **22**, and **23** (Figure 7).



21 **22** **23**

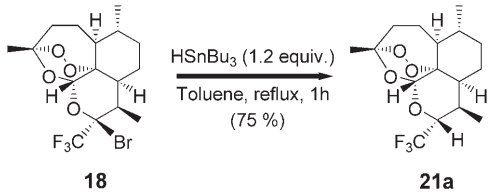
Figure 7. Nonketalic fluoroartemisinins

a) 10-Trifluoromethyl-10-deoxyartemisinin

A first challenge was to prepare compound **21** with a perfluoroalkyl group linked to the C10 carbon, without any other functionality on this site. The radical addition of C_4F_9I to the dehydrodeoxoartemisinin **10**, using sodium dithionite as initiator under the usual conditions, failed,[65] but interestingly the endoperoxide group remained intact.[22]

Various deoxygenation conditions ($NaBH_4/BF_3{\cdot}Et_2O$,[66,40d] Barton-McCombie deoxygenation[67,68]) failed with the hemiketal **14**.[22] Finally, the reductive radical cleavage using $HSnBu_3$, which was known to be compatible with the endoperoxide

bridge,[69] produced the 10-α-trifluoromethyl-deoxoartemisinin **21a** in good yield (75%) when applied to 10-bromo-10-CF_3-artemisinin **18** (Scheme 10). The reaction occurred with complete



Scheme 10. Radical reduction of bromide **18.**

conservation of the α configuration of the CF_3 group at C10.[22] The in vitro (IC_{50} = 6.2 nM) and in vivo antimalarial activities are comparable to that of artemether.[22]

b) 10-Difluoromethylendeoxoartemisinin

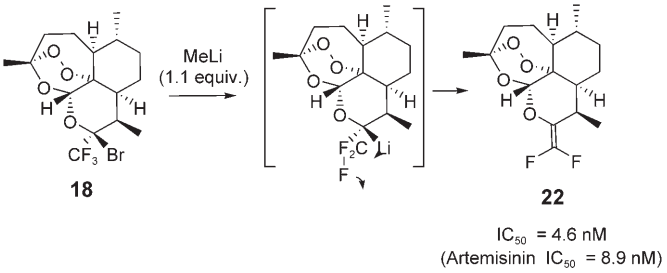
The *gem*-difluoromethylene compound **22** was an attractive target as a potential precursor of difluoro-*C*-10-functionalized artemisinins, using the nice radical chemistry developed by Motherwell et al. for access to difluoro-*C*-glycosides, disaccharides, or glycopeptides.[70] This would allow testing of the validity of the frequently claimed, but as yet unevaluated concept, that a *gem*-difluoromethylene moiety stereoelectronically mimics a carbonyl group in a biological substrate.[32c]

The most typical way to introduce a *gem*-difluoromethylene moiety into a molecule is through the addition of the phosphorus ylide, generated from CF_2CBr_2 and hexamethylphosphorous triamide, onto aldehydes, ketones, or lactones.[71] This reaction has been applied with success to introduce the difluoromethylene moiety on the anomeric position in the carbohydrate series.[72] However, this reaction was not successful in the artemisinin series, probably because of the sensitivity of the endoperoxide to the reductive character of the phosphorous ylide. As an alternative, we investigated the halogen-metal exchange reaction from bromide **18**. Activated zinc in Barbier conditions was not effective. With *n*BuLi and *t*BuLi, no reaction occurred, and the bromide **18** was recovered. However, surprisingly, with MeLi, at −78 °C, the bromide **18** reacted cleanly, providing the 10-difluorovinylidendeoxoartemisinin **22** in good yield (78%) (Scheme 11).[73] The intermediate anionic species could not be trapped by an electrophile, the elimination of a fluoride anion probably being so fast that the reaction with an electrophile could not occur.

Compound **22** exhibits good in vitro antimalarial activity, better than artemisinin. In vivo, it displays a profile (parasitemia and survival) comparable to that of artemether.[73]

c) Reaction of difluoroenoxysilanes with artemisinin derivatives.

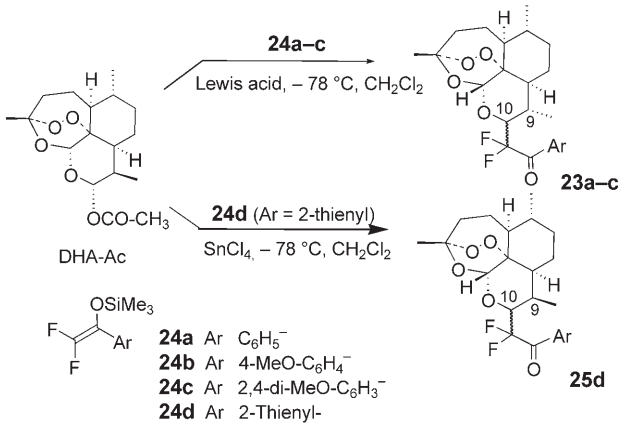
With the objective being preparation of difluoro ketones **23**, we investigated the chemistry of difluoroenoxysilanes, another approach to difluoro-C-glycosides.[74] Ziffer previously reported



Scheme 11. Preparation of 10-difluoromethylendeoxoartemisinin.

that DHA easily reacts with enoxysilanes under Lewis acid catalysis.[15]

Aryl difluoroenoxysilanes **24** were prepared by Mg^0-promoted defluorination of trifluoromethyl ketones, according to the Uneyama procedure.[75] Their reaction with DHA acetate appeared to be much more critical than any other Lewis acid-catalyzed reactions. Each difluoroenoxysilane required different Lewis acids, reaction conditions, and rate of addition; the set up was very troublesome and yields were often low (Scheme 12, Table 7).[17,76] For instance, the best result for the



Scheme 12. Reaction of DHA acetate with enoxysilanes **24a**–**d** in the presence of Lewis acid.[17]

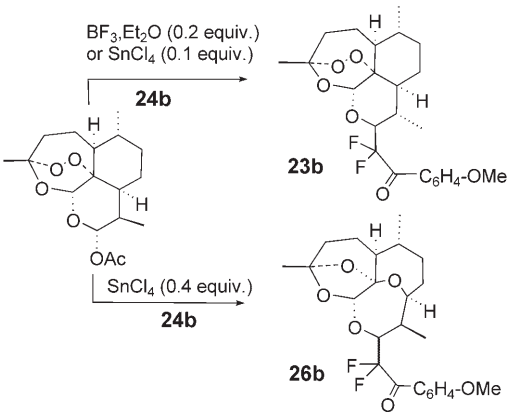
reaction of DHA acetate was obtained at low temperature using $SnCl_4$ (0.4 equiv) with enoxysilane **24a**, and using $BF_3{\cdot}Et_2O$ (0.2 equiv) with enoxysilane **24b**. This latter reacted in the presence of $SnCl_4$ to provide a 10-α/β epimeric mixture of the unexpected rearranged difluoroketone **26b** (83% yield, Scheme 13). Furthermore the stereochemical outcome of reactions is unusual: difluoroketones **23a**–**c** all possess the *epi*-artemisinin configuration at C9 (9α-Me)

The mechanism of this epimerization at C9 is not fully understood, but probably involves a deprotonation-reprotonation of glycal **10** and oxonium ions (**11**↔**12**) (Scheme 2). Interestingly, partial epimerization has been reported as a minor process in rare cases, for other Lewis acid-catalyzed reactions with DHA or DHA acetate.[41,77] The rather low reactivity of difluoroenoxysilanes **24** cannot be invoked as the reaction occurred at low temperature. The nature of the Lewis acid ($SnCl_4$) also

Table 7. Reaction of DHA acetate with enoxysilanes **24a–d** in presence of Lewis acid.[17]

Enoxy silane	Lewis acid	(equiv)	Compound	Isolated yields	(β/α at C-10)
24a	$BF_3{\cdot}Et_2O$	(0.2)	[a]	–	–
24a	$SnCl_4$	(0.4)	**23a** (9α-Me)	66%	100:0
24b	$SnCl_4$	(0.1)	**23b** (9α-Me)[b]	33%	100:0
24b	$BF_3{\cdot}Et_2O$	(0.2)	**23b** (9α-Me)	73%	100:0
24b	$SnCl_4$	(0.4)	**26b** (9β-Me)	83%	40:60
24c	$SnCl_4$	(0.4)	**23c** (9α-Me)[b]	33%	70:30
24d	$SnCl_4$	(0.4)	**25d** (9β-Me)[b]	29%	65:35

[a] complex mixture. [b] accompanied by glycal **16**.



Scheme 13. Reactions of enoxysilane **24b** with DHA acetate.[17]

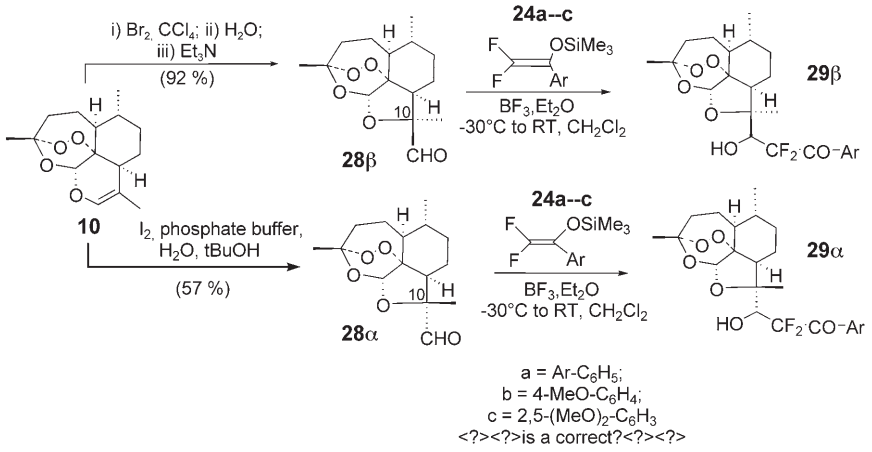
cannot be invoked, as epimerization also occurred with $BF_3{\cdot}Et_2O$, the most frequently used Lewis acid in the chemistry of DHA.

The rearrangement providing compound **26b** results from the cleavage of the O–O bond of the endoperoxide bridge, activated by the Lewis acid. It was not anticipated in our conditions, as it had been previously reported only once, when deoxoartemisinin **10** was placed in the presence of a very large excess (20–30 equiv) of Lewis acid, for instance $BF_3{\cdot}Et_2O$.[78,79] Furthermore, the reason why it occurs only with the *para*-methoxy derivative **24b**, which is more reactive than **24a**, is not clear. A specific role of difluoroenoxysilanes and/or of the reaction medium is more likely as glycal **10** is usually stable, even in reactions of DHA with poor nucleophiles. The previously reported complexity of fluoroenoxysilane with glycosyl donor reactions [74] is greatly aggravated by the peculiar reactivity of dihydroartemisinin derivatives.

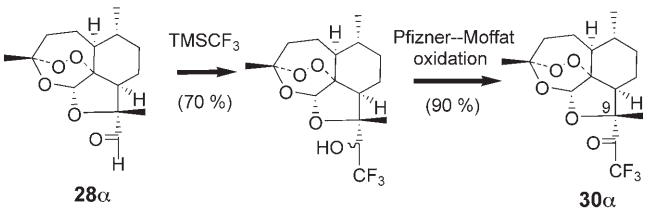
Such difficulties were not encountered in the similar reaction of difluoroenoxysilanes **24** with D-ring contracted aldehydes **28α** and **28β**, stereoselectively obtained by the formation of bromhydrines from glycal **16**, followed by rearrangement. [49,80] Reactions were very efficient with any of difluoroenoxysilanes **24** and produced the difluoro β-hydroxyketones **29α** and **29β** in excellent yields. Only one diastereoisomer at C10 was formed (Scheme 14, Table 8). Aldehydes **28** were also used to provide trifluoromethyl alcohols, by addition of the Ruppert reagent. Corresponding trifluoromethylketones **30α** and **30β** have been prepared from oxidation of these alcohols (Scheme 17).(Scheme 15)

Table 8. Reactions of enoxysilanes **24a–c** with aldehydes **28**.

Aldehyde	Enoxy silane	Compounds	Isolated yields
28β	**24a**	**29βa**	97%
28α	**24a**	**29αa**	89%
28β	**24b**	**29βb**	74%
28α	**24b**	**29αb**	70%
28β	**24c**	**29βc**	85%
28α	**24c**	**29αc**	98%



Scheme 14. Reactions of enoxysilanes **24a–c** with aldehydes **28**.



Scheme 15. Preparation of D-ring contracted ketone **30α**.

Difluoroketones **23**, **25**, and **29α,β** were possible precursors of corresponding acids. Unfortunately, all our attempts (Baeyer–Villiger reaction, oxidation of the aryl moiety) failed. Antimalarial activities of all these compounds have been also evaluated. They are less active in vitro and in vivo than artemether; only the hydroxyketone **29βa** was slightly more active in vitro. The subtle chemistry of difluoroenoxysilanes has not been fruitful in our search for new antimalarial drug candidates. Nevertheless, this study yielded information on the influence of the C9 configuration in the 5 member-D ring artemisinins on antimalarial activity: it is less critical than in 6 member-D ring series.

4. 16 functionalized-10-trifluoromethyl-anhydroartemisinin

With a view of gaining access to C10-trifluoromethylartemisinins bearing a functionality at C16, we investigated the reactivity of glycal **16**. The standard methods of preparing the non-fluorinated parent compound **10** by dehydration of DHA (P_2O_5 or $BF_3{\cdot}Et_2O$),[40,81] failed from the hemiketal **14**, because of the great stability of CF_3-substituted hydroxyl compounds under acidic conditions.[32b,82] However, the glycal **16** could be selectively prepared in good yields by treatment of acetal **14** with thionyl chloride and pyridine in large excess (see Scheme 6).[49]

We first evaluated the effect of the D-ring unsaturation on antimalarial activity before starting any structural modulation and ascertained that the presence of a trifluoromethyl group at C10 could disfavor the protonation leading to oxonium **20**, and hence the further glucuronidation (see above). The antimalarial activity of glycals **10** and **16** have been evaluated and compared: whereas their in vitro activities (IC_{50}) on *P. falciparum* are similar, their in vivo activities are remarkably different. With glycal **10**, there is no clearance of parasitemia at the end of the i.p. treatment of mice infected with *P. berghei* NK 173 (35.5 μmol kg^{-1} according to the Peters' test); there is no survival at day 10. With **16**, all mice survived until day 20 (Figure 8). This validates the effect of the CF_3 substituent at C10 on metabolic stability, and encouraged us in using compound **16** as the precursor for the preparation of functionalized derivatives at C16.

Reactivity of glycal **10** towards brominating agents has been well documented. Dibromides[49,80] and bromohydrins[83,84] have been used for the introduction of ionizable functions in artemisinin,[49,80] and for the access to novel D-ring-contracted artemisinin derivatives.[17,85] However, surprisingly, the allylic radical bromination has not been reported, although

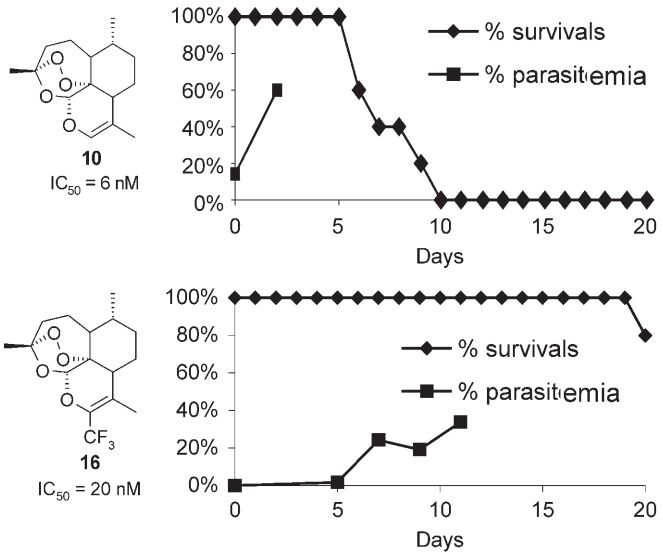
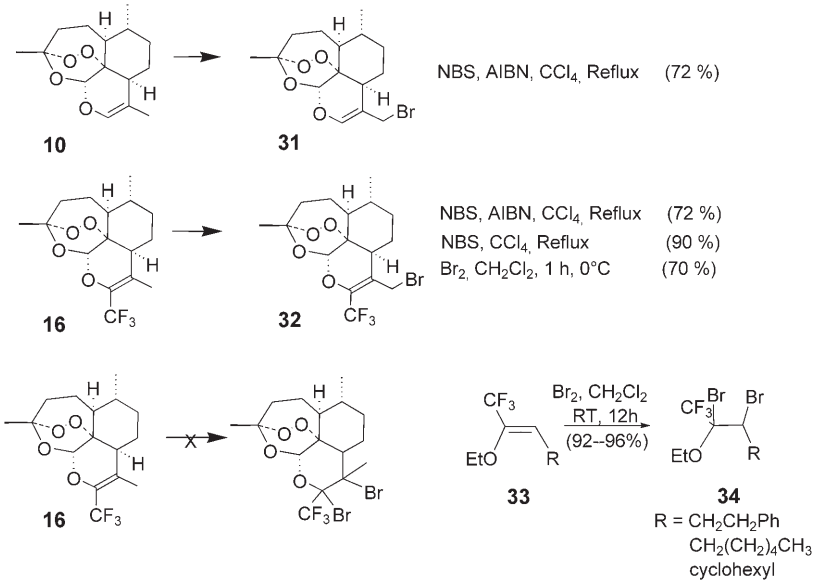


Figure 8. Effect of fluorine substitution at C10 on antimalarial activity of glycals **10** and **16**.

the bromide **31** could obviously provide a shorter route to 16-substituted derivatives than the previously described approaches from artemisitene[16,28,86,87] or from artemisinic acid.[88]

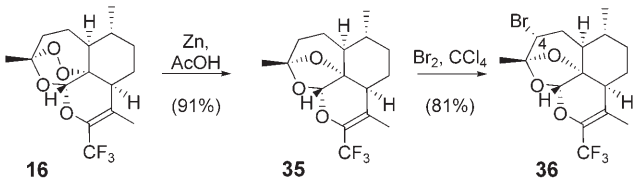
Allylic bromination of glycals **10** and **16** was investigated under the usual Wohl–Ziegler conditions (NBS/CCl_4/reflux) in the presence of an initiator (AIBN).[89] Accurate conditions had to be found for the preparation of the allyl bromide **31**. Although yield was high (>70%), **31** had to be used without isolation because of its instability.[90] The parent 10-CF_3-16-bromo derivative **32** was also obtained in good yield (72%) from the trifluoromethyl glycal **16** and is much more stable than bromide **31** (Scheme 16). The compound could be purified by crystallization and stored for several weeks at 0 °C. Clearly, the



Scheme 16. Bromination reactions of glycal **10** and **16** and enol ethers **33** with bromine.

electron withdrawing character of the CF_3 group makes the allyl bromide less labile.

The presence of an initiator (AIBN) was not necessary in this bromination reaction of glycal **16** and even yield was improved to 90% when the reaction was performed without AIBN. Similar results were obtained with Br_2 without initiator. Unlike the reaction performed from the nonfluorinated glycal **10**,[49,80] the dibromo adduct resulting from an electrophilic addition of Br_2 on the double bond, was not observed. This result was quite unexpected as stable dibromoadducts **34** were also obtained by treatment with bromine of the trifluoromethyl substituted parent enol ethers **33**, albeit with long reaction times because of the poor reactivity of the CF_3-substituted enol bond.[91] The ease of the allylic bromination of **16** has been attributed to the presence of the endoperoxide which can initiate the radical reaction. Additional experiments performed in the absence of light and from the nonperoxidic trifluoromethyl deoxyglycal **35** supported this hypothesis (Scheme 17).[49]

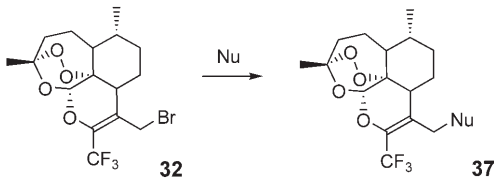


Scheme 17. Reaction of CF_3-deoxy glycal **16** with bromine.

The allyl bromide **32** is a very successful and useful intermediate for access to a large range of **16**-functionalized compounds whose solubility properties might improve oral antimalarial treatment (see below).

Reactions of the allyl bromide 32 with nucleophiles

Trifluoromethyl allyl bromide **32** reacted selectively with amines and alcoholates, leading to 16-substituted compounds **37** (SN2-type products), with no trace of the allylic rearrangement product (SN′2-type products) **38**. Excellent yields were obtained with secondary amines. With primary amines, polyalkylation could be avoided by using dilute conditions. Preparation of the primary amine at C16 was more problematic, as none of the reductive conditions used to convert the azide **37 f** into the primary amine **37 g** are compatible with the endoperoxide bridge.[92] The primary amine at C16 was prepared using NH_3 as nucleophile, in a very large excess (Scheme 18, Table 9). Sodium alkoxides, generated in situ using sodium hydride, also reacted well to generate corresponding ethers in good to excellent yields, but addition of a catalytic amount of KI was required (Scheme 18, Table 10). The substitution of **32** with sodium acetate, followed by treatment of the resulting 16-acetoxy **37 m** with MeOH/NaOMe (69% overall yield) was more efficient to prepare the alcohol **37 n** than the direct hydrolysis of bromide **32** with KOH/DMSO/H_2O. As the substitution of bromide **32** with glycerol was troublesome, diol **37 p** was prepared (77% yield) by dihydroxylation of the allylic ether **37 k** with OsO_4 and NMO, as previously described in an artemisinin series (Scheme 19).[93] Dimethyl sodium malonate reacted with bromide **32** leading to the diester **37 q** in excellent yield (90%) (Scheme 18, Table 10).



Nu = Amines, Alcoholates, Malonate, etc...

Scheme 18. Reactions of bromide **32** with *N*-, *O*-, and *C*-nucleophiles.

Table 9. Reactions of bromide **32** with *N*-nucleophiles.

N-Nucleophile[a]	Equiv	*t* [h]	**37**	Yield[b]
Morpholine	4	6	**a**	90%
Piperazine ethanol	4	6	**b**	87%
$EtNH_2$	10	4	**c**	85%
$MeNH_2$	10	3	**d**	98%
$NH_2CH_2CH_2NH_2$	10	3	**e**	95%
NaN_3[c]	1.5	1	**f**	95%
NH_3[d]				77%

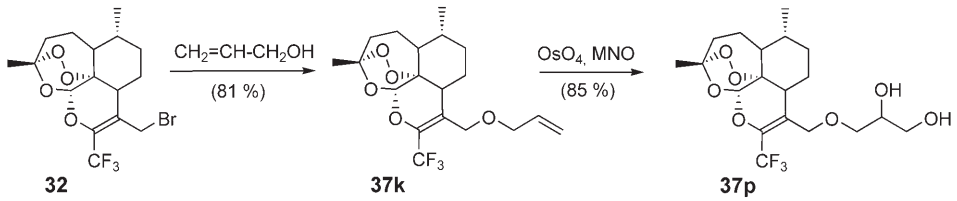
[a] Reactions performed in THF. [b] Isolated yield. [c] Reaction performed in DMSO. [d] Reaction performed at −15 °C, large excess of NH_3 in a mixture NH_3/THF 1:1.

We also sought to reverse the regioselectivity of the substitution of bromide **32** and thereby gain access to SN′ products (10-trifluoromethyl artemisitene-like derivatives **38**). In connection to this, we anticipated that with a strong nucleophile, in a second order substitution, the delivery of nucleophiles should be easier to the primary C16 site of bromide **32** than to the crowdy CF_3-substituted C10 carbon atom. Conversely, with weaker nucleophiles, under solvolytic conditions, the process

Table 10. Reactions of bromide **32** with *O*-and *C*-nucleophiles.

Nucleophile[a]	equiv	NaH (equiv)	Solvent	Time (h)	**37**	Yield[b]
EtOH	20	3	THF			98%
BnOH	1.5	3	THF	18	**i**	97%
$MeOCH_2CH_2OH$	3	2	DMSO	1	**j**	96%
$CH_2=CH\text{-}CH_2OH$	3	2.5	DMSO	2	**k**	81%
$HOCH_2CH_2OH$	4	1.5	DMSO			69%
NaOAc[c]	1.5		DMF			82%
$CH_2(COOMe)_2$	1.5	1.8	THF	5	**q**	90%

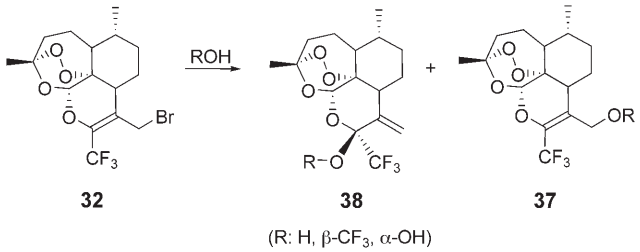
[a] in presence of KI (0.1 equiv). [b] Isolated yield. [c] 0.2 equiv of KI were used.



Scheme 19. Preparation of diol **37p**.

should be mostly determined by properties of the electrophile. The regioselectivity would be thus governed by the distribution of positive charge on different sites of the allyl system, induced by the C–Br bond breaking. It is likely that, despite of the presence of the CF_3 substituent, a development of positive charge is easier at the alkoxy-substituted C10 carbon atom than at the primary C16 carbon.

With this in mind, we investigated the solvolysis of bromide **32** in MeOH.[94] The reaction required reflux (2 h) for complete conversion (92% yield), and generated the SN′ product **38a** as the major product (ratio SN′/SN: **38a**/**37a**: 85:15). The reaction



Scheme 20. Substitution of bromide **32.**

Table 11. Substitution of bromide **32.**

ROH		Ratio **38/37**	Yields % (**38** + **37**)
MeOH	**a**	87:13	92
EtOH	**b**	85:15	86
CH_2=CH-CH_2OH	**c**	85:15	80
HC≡C-CH_2OH	**d**	88:12	97
CH_3-CHOH-CH_3	**e**	70:30	91
$(CH_3)_3$-C-OH	**f**		No reaction
CF_3-CH_2OH	**g**	80:20	52%
H_2O	**n**	100:0	90%

was extended to other alcohols (Scheme 20, Table 11). In all cases the SN′ products **38** were obtained as major products, even with the hindered isopropanol, albeit in a lower ratio (70:30). Reactions are stereoselective: only the β-alkoxy isomer was detected. Bromide **32** was selectively hydrolyzed, with water alone, into the hemiketal **38n**, with no trace of alcohol **37n**. In this case, both α and β hemiketals were kinetically formed. However, the β-hydroxy ketal slowly isomerized to give the more thermodynamically stable α-hydroxy isomer. It is interesting to note that in the saturated series, the more stable isomer is the β-hydroxy compound **14**. This clearly indicates that the relative steric hindrance of each face of the artemisinin skeleton is different when the D-ring is saturated than when a sp^2 carbon atom is present. This also underscores the influence of Me16.

The dilution in a solvent (THF), and hence a lower concentration of MeOH did not change the ratio of **38**/**37**, although reaction rates were greatly slowed. The presence of silver salt (triflate or acetate) did not significantly change the 85:15 ratio of **38**/**37**. Finally, using an activation with HFIP with the conditions optimized for the solvolysis of the bromide **18** (see above),[51] we succeeded in improving the regioselectivity of the SN′ product (ratio 95:5).

As anticipated and according to all our results, it seems the weaker the nucleophile is, the more likely the attack occurs at C10. Experiments in the presence of HFIP in which the SN2 process was almost suppressed, confirm our explanations. From a general point of view, the high ionization power of HFIP and the high hydrogen bonding facilitate the positive charge development in the reaction.[45b,54,55] In addition, HFIP decreases the nucleophilicity of a nucleophile through the reversible formation of complexes.[57] Despite an evident influence of HFIP in the competive SN/SN′ processes, regioselectivity could not be reversed with amine, and substitution at C16 was always the major process.

Biological activity

Most of the 16-functionalized fluoroartemisinins exhibited strong antimalarial activity in vitro (Table 12) and in vivo (Tables 13 and 14). At the present time, the more promising candidates for an oral treatment are the amines **36a**–**c**, which are more active than sodium artesunate, as shown by the ED_{50} and ED_{90} values (Table 14).

Pharmacokinetic studies performed on compound **37b** exhibited a significantly better bioavailability in rats than artemether (Tables 15 and 16).[61] C_{max} and T_{max} values for **37b**, determined from the oral dosing studies, were 607.9 ng/mL and 60 min, respectively, compared to 168.4 ± 50.2 ng mL^{-1} and 20.4 ± 7.6 min, respectively, for artemether. At a 50 mg kg^{-1} oral dose, oral bioavailability was 34.6%, a significant improvement over the 1.4% observed for artemether. This oral bioavailability may reflect the enhanced metabolic stability imparted by the presence of the trifluoroalkyl group and/or its better aqueous solubility. Solubility is likely to be even higher upon ionization in the acidic medium of the stomach. However, the intravenous and oral plasma profiles for the piperazino ethanol derivative **37b** exhibit a faster metabolic clearance, induced by the P450 enzyme, than the hemiketal **14** (Figure 9). Current experiments are in progress to exploit this new series by optimization of the polar substituent at C16.

Table 12. In vitro activities of compounds **37** and artemether on the chloroquine-resistant *Plasmodium falciparum* FcB1 and W2 clones and Clog *P* values.[[a]]

-Nu		IC_{50} [nM][b]	Clog *P*[a]	Clog *P*[c]
Artemether **1b**		3.5 ± 1.2[d]	2.92	
37a	-Morpholino-	3.1 ± 0.5[d]	3.89	2.62
37b	-Piperazinoethanol	15.2 ± 6.7[e]	2.43	1.15
37c	-NHEt	13.4 ± 4.5[e]	3.40	2.12
37d	-NHMe	9.2 ± 2.4[d]	2.87	1.59
37e	$-NHCH_2CH_2NH_2$	1.2 ± 0.7[d]	2.50	1.22
37f	$-N_3$	10.0 ± 7.6[d]	4.97	3.69
37g	$-NH_2$	4.4 ± 0.4[d]	3.13	1.86
37h	$-NHSO_2CH_3$	20.0 ± 6.3[d]	3.07	1.80
37i	$-NHSO_2C_6H_4CH_3$	19.1 ± 3.5[d]	5.25	3.97
37h	-OEt	25.0 ± 7[e]	3.73	2.45
37i	-OBn	20 ± 5[e]	5.72	4.44
37j	$-OCH_2CH_2OMe$	2.7 ± 0.4[d]	3.26	1.99
37k	$-OCH_2CH{=}CH_2$	6.0 ± 1.7[d]	4.43	3.15
37l	$-OCH_2CH_2OH$	2.4 ± 0.4[d]	3.09	1.82
37m	$-OCOCH_3$	1.7 ± 0.5[d]	3.97	2.69
37n	-OH	7.5 ± 0.8[d]	3.05	1.77
37p	$-OCH_2CHOHCH_2OH$	3.7 ± 0.5[d]	2.27	0.99
37q	$-CH(COOMe)_2$	> 1000[e]	3.79	2.51
37r	$-CH(COOH)_2$	> 1000[e]	3.00	1.73

[a] Calc. log *P* values were calculated using the http://www.daylight.com/cgi-bin/contrib/pcmodels.cgi program. [b] Mean ± standard deviation was calculated for $n = 3$ experiments. [c] Clog *P* of the analogue without CF_3 at C10. [d] Assays performed on *P. falciparum* FcB1 strain. [e] Assays performed on *P. falciparum* W2 strain.

Table 13. Antimalarial activity of C-16 substituted artemisinin derivatives on *P. berghei* NK 173 in mice.[a]

	parasitemia [%] at day 4[a]	parasitemia [%] at day 11	survival[b,c]
Artemether	0	32	5/5
37a	18	45	4/5
37b	0.5[c]	37	5/5
37c	5[c]	66	5/5
37e	0	25[d]	4/5
37g	0.7	nd[e]	4/5
37h	0.4	30	4/5
37j	6	nd	4/5
37l	2	nd	5/5
37n	40	nd	1/5

[a] drug administered by intraperitoneal route at the concentration of 35.5 μmol kg^{-1} for four days. [b] 20 days post-infection. [c] determined at day 5. [d] determined at day 10. [e] nd = not determined.

Table 14. In vivo data for amines **37a–c**, ether **37h** and Na artesunate (*P. berghei* N) s.c. and p.o. administration.

	route	ED_{50}	ED_{90}	Reduction of parasitemia [%][a]
Na artesunate	sc	2.8	10.5	90
Na artesunate	po	5.4	15.3	–
37a	sc	< 10	< 10	98.1
37a	po	< 10	< 10	93.3
37b	sc	< 10	< 10	100
37b	po	< 10	< 10	100
37c	sc	< 10	< 10	98.1
37c	po	< 10	< 10	96
37h	sc	< 10	< 10	100
37h	po	> 10	nd	15.6

[a] at D4 with 10 mg kg^{-1}.

Table 15. Log *P/D* values and equilibrium solubilities of **37b** and artemether.[a]

	artemether	**37b**
Log*P*	3.36	3.52
Log*D* (pH 7.4)	–	3.46
pK_a	–	6.59
Solubility i.v. formulation (μg mL^{-1})[b]	4700	> 3000
Oral formulation (μg mL^{-1})[c]	256	675.9
PBS (pH 7.4) (μg mL^{-1})	63.4	234.5

[a] incubation at 25 °C for 72 h. [b] IV formulation is 0.1 M Captisol in water for artemether and 10% ethanol/0.1 M Captisol, pH 3 for **37b**. [c] Oral formulation contains 0.5% *w/v* carboxymethyl cellulose, 0.5% v/v benzyl alcohol, 0.4% *v/v* Tween 80 in 0.9% *w/v* NaCl for artemether, and 0.5% *w/v* Hydroxypropylmethyl cellulose, 0.5% *v/v* benzyl alcohol, 0.4% *v/v* Tween 80 in 0.9% *w/v* NaCl for **37b**.

Table 16. Pharmacokinetic data for artemether and **37b**.

	artemether[a]	**37b**
C_{max} (ng mL^{-1})	168.4 ± 50.2	607.9
T_{max} (min.)	20.4 ± 7.6	60
$T_{1/2}$ (min)[b]	52.2 ± 5.8	55.3
Plasma clearance (mL min^{-1} Kg^{-1})	114.1 ± 20.6	148.7
Volume of distribution (L Kg^{-1})[b]	8.4 ± 1.7	11.8
Oral bioavailability (%)	1.4 ± 0.6	34.6

[a] Artemether pharmacokinetic parameters from previous studies (unpublished, Charman et al.). [b] after 10 mg kg^{-1} (iv administration).

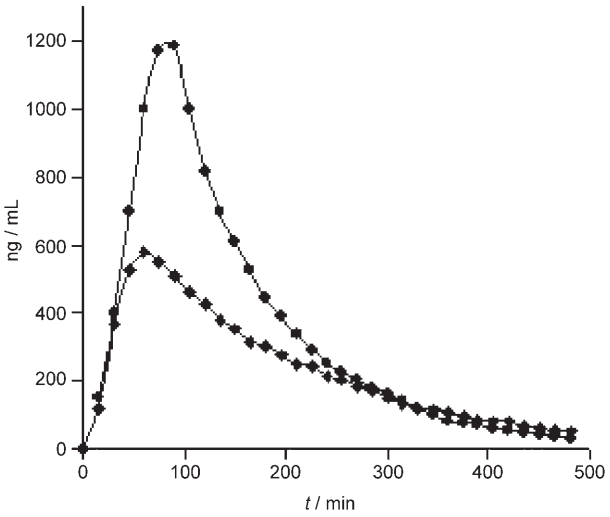


Figure 9. Plasma concentration versus time for compounds **14** (upper line) and **37b** after oral administration to rats at a dose of 50 mg kg^{-1}.

Conclusions

Considering the increasing resistance of *Plasmodium falciparum* towards most of available antimalarial drugs, artemisinin derivatives constitute the greatest hope in the fight against malaria. Drawbacks stemmed by their instability and short plasma half-life prompted medicinal chemists to design and prepare more efficacious derivatives, but retaining the 1,2,4-tri-

oxane pharmacophore. With this aim, the concept of fluorine substitution appeared to be appropriate for an improved pharmacological profile. By taking in consideration main sites of oxidative and hydrolytic sites of degradation, we have prepared new series of fluorinated derivatives of artemisinin.

The uncommon structural artemisinin framework, in addition to the well-known difficulty to selectively introduce a fluorinated motif in a molecule, led us to face numerous chemical challenges. This exploration was worth reporting in detail with both synthetic problems we had to overcome, and the evaluation of fluorine effect on physicochemical and antimalarial properties. These data, and preclinical data of lead compounds, provide evidence for the strong and prolonged antimalarial activity of fluoroartemisinins.

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Keywords: artemisinin · drug metabolism · fluorine · malaria

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