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S_N/S_N' Competition: Selective Access to New 10-Fluoro Artemisinins

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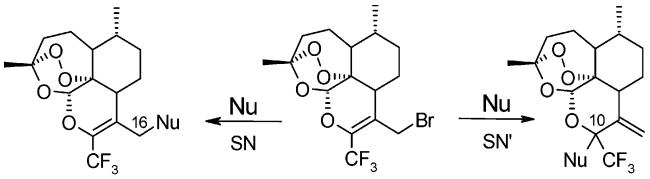


5 **6** **7**

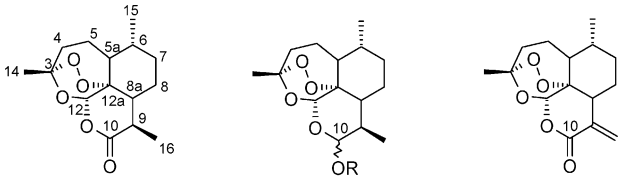
In this paper, we report a simple route to accede to a new family of C-10 fluorinated derivatives of artemisinin **7**. We demonstrated that nucleophilic substitution of the allylic bromide **6** with alcohols can occur at carbon 10 (compounds **7**) under solvolytic conditions (S_N'/S_N ratio, 87:13). Furthermore, using the particular properties of hexafluoroisopropanol (HFIP), we are able to increase the selectivity of the substitution. Primary alcohols are completely selective for allylic substitution. With amines as nucleophiles, selectivity of substitution is dependent on their nucleophilicity, but attack at carbon 16 was always favored. However, the S_N'/S_N ratio could be slightly increased by adding HFIP, which is able to modulate their nucleophilicity through hydrogen bonding. In preliminary in vitro assessments, these new compounds, **7**, exhibited a satisfying activity against malaria.

Introduction

Artemisinin **1** is a natural, efficient, antimalarial drug for the treatment of multidrug-resistant forms of *Plasmodium falciparum*.[1] However, pharmacological issues associated with artemisinin **1**, especially a short plasma half-life with, as a consequence, a possible recrudescence of parasitemia,[2] prompted scientists to search for more metabolically stable derivatives.

The introduction of fluorinated substituents into molecules is known to confer a greater protection to metabolic (oxidative and proteolytic) degradation.[3] In previous works, we showed that introducing a fluoroalkyl group at carbon 10, a crucial position for metabolism (Scheme 1), gave excellent results in vitro and in vivo. Activities by both intraperitoneal and oral routes surpassed those of dihydroartemisinin (DHA **2a)** and its ethers, **2b** and **2c**.[4] A comparison of the plasma half-lives of the C-10 trifluoromethyl-substituted hemiketal **3** ($T_{1/2}$ = 85.9 min) and DHA **2a** ($T_{1/2}$ = 26.3 min), after intravenous administration to rats, demonstrated that the CF_3 group at carbon 10 effectively protects artemisinin derivatives against metabolic degradation. These preclinical assays suggest that CF_3-hemiketal **3** might be a good candidate for further clinical trials.[5]

SCHEME 1



1 artemisinin

2 **2a** R = H : DHA; **2b** R = Me : Artemether; **2c** R = Et : Arteether; **2d** R = $COCH_2CH_2COONa$: Sodium artesunate

artemisitene

(1) Klayman, D. L. *Science* **1985**, *228*, 1049−1055.

(2) (a) Peters, W.; Portus, J. H.; Robinson, B. L. *Trop. Med. Parasitol.* **1994**, *45*, 266−271. (b) De Vries, P. J.; Dien, T. K. *Drugs* **1996**, *52*, 818−836.

(3) (a) Bégué, J. P.; Bonnet-Delpon, D. In *Chimie Bioorganique et Médicinale du Fluor*; CNRS, Eds.; EDP Sciences: Paris, 2005. (b) Irurre, J., Jr.; Casas, J.; Ramos, I.; Messeguer, A. *Bioorg. Med. Chem.* **1993**, *1*, 219−225. (c) Irurre, J., Jr.; Casas, J.; Messeguer, A. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 179−182. (d) Edwards, P. N. In *Organofluorine Chemistry: Principle and commercial application*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Publishing: New York, 1994; pp 501−541.

(4) (a) Abouabdellah, A.; Bégué, J. P.; Bonnet-Delpon, D.; Gantier, J. C.; Thanh Nga, T. T.; Thac, T. D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2717−2720. (b) Thanh Nga, T. T.; Ménage, C.; Bégué, J. P.; Bonnet-Delpon, D.; Gantier, J. C.; Pradines, B.; Doury, J. C.; Thac, T. D. *J. Med. Chem.* **1998**, *41*, 4101−4108.

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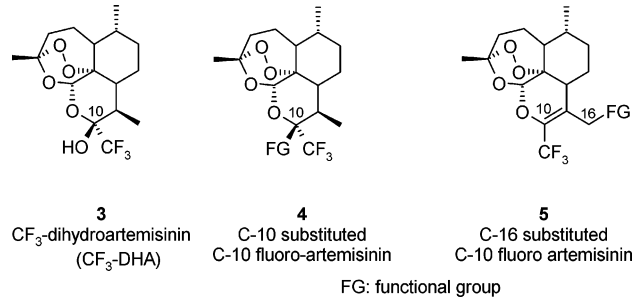
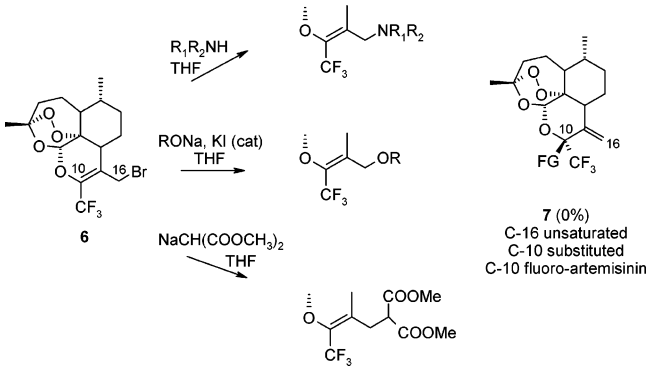
SCHEME 2



SCHEME 3



Other fluorinated functionalized derivatives have been elaborated to increase water solubility while keeping the protective effect of fluorine. Two main families of fluoro-artemisinins have been designed and synthesized: C-10-substituted C-10 CF_3-artemisinins **4**[6] and C-16-substituted C-10 CF_3-artemisinins **5**[7] (Scheme 2). Both families exhibited a very good antimalarial activity and a high stability against degradation.

Compounds **5** were easily prepared from the 10-trifluoromethyl allyl bromide **6** by a substitution reaction with alkylamines, alkoxides, or sodium malonates. (Scheme 3).[7,8] Under the described conditions, the reaction was completely selective at carbon 16, with no trace of allylic rearrangement products, **7**. This was rationalized in terms of the known repulsive effect of the CF_3 group.

With the aim to reverse the regioselectivity of the substitution and to favor the allylic substitution, we revisited the nucleophilic substitution of bromide **6**. We report our study of conditions governing S_N and S_N' substitutions and the subsequent preparation of new artemisinin derivatives, **7**. These compounds, with an unsaturation at carbon 16, are structurally closed to the naturally occurring artemisitene (Scheme 1). Due to its Michael-acceptor structure, artemisitene easily undergoes in vivo degradation. The lack of a Michael-acceptor fragment in our target compounds may increase their stability.

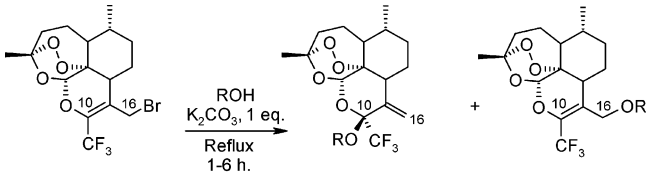
(5) (a) Binh, P. D.; Cong, L. D.; Nhu, T. V.; Tien, N. T.; Nhan, D. H.; Bégué, J. P.; Bonnet-Delpon, D.; Thanh Nga, T. T. *Trans. R. Soc. Trop. Med. Hyg.* **2002**, *96*, 677−683. (b) Nhu, T. V.; Nhan, D. H.; Thu, N. T. M.; Bégué, J. P.; Bonnet-Delpon, D.; Hung, N. V.; Hoang, V. D. *Rev. Pharm.* **2005**, *1*, 12−16.

(6) Unpublished experiments performed by Charman, University of Monash. For a summary, see: Magueur, G.; Crousse, B.; Charneau, S.; Grellier, P.; Bégué, J. P.; Bonnet-Delpon, D. *J. Med. Chem.* **2004**, *47*, 2694−2699.

(7) Grellepois, F.; Chorki, F.; Ourévitch, M.; Charneau, S.; Grellier, P.; McIntosh, K. A.; Charman, W. N.; Pradines, B.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J. P. *J. Med. Chem.* **2004**, *47*, 1423−1433.

(8) Grellepois, F.; Chorki, F.; Ourévitch, M.; Crousse, B.; Bonnet-Delpon, D.; Bégué, J. P. *Tetrahedron Lett.* **2002**, *43*, 7837−7840.

TABLE 1. Solvolytic Conditions to Favor Allylic Substitution



solvent	S_N' (at C-10)	S_N (at C-16)	ratio S_N'/S_N	yield[a] (%)
MeOH	**7a** (β)	**5a**	87:13	92
EtOH	**7b** (β)	**5b**	85:15	86
CH_2═CH−CH_2−OH	**7c** (β)	**5c**	85:15	80
HC≡C−CH_2OH	**7d** (β)	**5d**	88:12	97
$(CH_3)_2$CH−OH	**7e** (β)	**5e**	70:30	91
CF_3−CH_2−OH[b]	**7f** (β)	**5f**	80:20	52
$(CH_3)_3$C−OH	−	−	−	−
H_2O	**8** ($\beta + \alpha$)	−	100:0	70

[a] The yield of **5** + **7**. [b] The reaction was performed at room temperature.

Results and Discussion

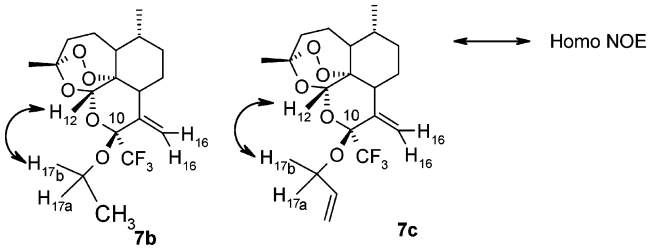
The high electron density around carbon 10 is expected to disfavor the approach of electron-rich nucleophiles such as alkylamines or sodium alkoxides. Thus, we anticipated that solvolytic conditions involving soft or uncharged nucleophiles could allow an S_N' process to occur at carbon 10.

When the CF_3 allyl bromide **6** was placed in methanol at room temperature, the reaction proceeded very slowly (disappearance of starting material occurred after 20 h with apparition of degradation products). In refluxing methanol, starting material **6** was totally converted after 2 h; the S_N' product, **7a**, was obtained as the major product (87%) along with 13% of the product, **5a**, resulting from nucleophilic substitution at carbon 16 (S_N; Table 1). The formation of **7a** was totally diastereoselective (see below). However, the reaction was found to be cleaner when K_2CO_3 or molecular sieves were added, probably as a result of the neutralization (or trapping) of the HBr generated during the reaction. Potassium carbonate gave the best results with a 92% yield of the mixture **7a**:**5a**. When the reaction was performed in THF with 5 equiv of MeOH, the reaction was very slow and incomplete after 3 days without any change in the S_N'/S_N ratio (85% of conversion observed by ^{19}F NMR).

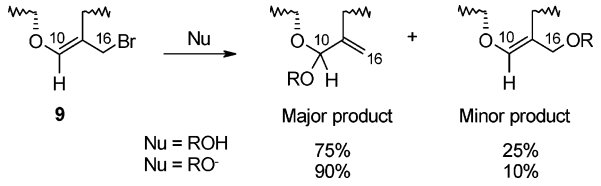
The same reaction was then performed with other primary alcohols used as the solvents: ethanol, allyl alcohol, and propargyl alcohol (Table 1). In all cases, the allylic rearrangement was the main process (around 85%). Compounds **7b**−**d** were obtained, accompanied with 12−15% of the S_N product **5b**−**d**. As expected, the substitution at carbon 16 increased with the steric hindrance of the alcohol; with a secondary alcohol, such as 2-propanol, the amount of S_N product was increased to 30%. When *tert*-butanol was used as solvent, only degradation of the starting material was observed.

With all alcohols, the S_N' reaction was stereoselective, leading only to the β-OR diastereoisomer. This selectivity is not surprising; due to the globular structure of the artemisinin skeleton, the β face is the less-hindered one, and the β selectivity is usually observed in nucleophilic additions to artemisinin derivatives.[4,9] The configuration at carbon 10 was assigned by NMR with NOESY experiments for compounds **7b** and **7c**.

SCHEME 4



SCHEME 5



From homo-NOE experiments, the observed correlation between the H-12 and H-17b protons indicates their proximity, which is only possible if the ethoxy or allyloxy groups are β (pseudoaxial; Scheme 4).[10]

The reaction was then performed in water (H_2O/THF, 1:2, 40 °C, overnight) without K_2CO_3 (because of the sensitivity of the expected hemiketal ring to traces of base). Hydrolysis of the allylic bromide **6** was totally regioselective; no substitution was observed at carbon 16 (Table 1). Surprisingly, in this case, ^{19}F NMR indicated the presence of two products, both identified as diastereoisomers **8α** and **8*β***. When hydrolysis was monitored by ^{19}F NMR, a progressive conversion of **8*β*** to **8α** was observed. As with alcohols, the reaction proceeded stereoselectively with an attack onto the β face, and the kinetic product **8*β*** gradually isomerized to **8α** by an opening/closing process of the hemiketal ring. This phenomena was also observed in the series saturated at carbon 9 (i.e., bearing a methyl instead of a methylene).[9,11] However, the configuration of the thermodynamic compound **8α** (α-OH, β-CF_3) is opposite to that of the thermodynamic saturated CF_3-hemiketal **3** (β-OH, α-CF_3). In compound **3**, the repulsion between β-CF_3 and β-Me-9 favors its isomerization to the α-CF_3 product. For structure **8**, where this repulsion is weak and not discriminant, the β-CF_3 compound is thermodynamically favored.

By comparison, the nonfluorinated bromide **9**[8] always provided the S_N' product as a major product. Whatever the nucleophile used (alcohol or alcoholate, ratio S_N'/S_N, 90:10, Scheme 5), the C-10 site is always electronically favored.

The different behavior of bromide **6** highlights the strong effect of CF_3 on the course of the substitution. In a second-order substitution, the delivery of nucleophiles to the C-10 fluorinated site of bromide **6** should be disfavored by the steric and electronic hindrance of CF_3. This repulsion is stronger in the case of charged and strong nucleophiles, which more easily provide an S_N2-type substitution at carbon 16. Conversely, with weak nucleophiles, the process should be mostly determined by the properties of the electrophile; the regioselectivity is thus governed by the less energetically demanding development of positive charge. Regardless of the presence of the CF_3 substituent, development of positive charge is probably easier at the alkoxy-substituted C-10 carbon than at the primary C-16 carbon.[12]

Surprisingly, when the CF_3-allyl bromide **6** was placed in methanol in the presence of silver salts (triflate or acetate) known to favor push/pull reactions or the formation of cationic intermediates, the **7a**:**5a** ratio remained unchanged (85:15). The **7a**:**5a** ratio slightly decreased (80:20) when the same reaction was performed in CH_2Cl_2 with 5, 10, or 20 equiv of methanol.

Taking into account our previous results on the use of 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) to promote substitution reactions, we used it as an additive in the substitution reaction.[13,14] CF_3-allyl bromide **6** was placed in dichloromethane with 10 equiv of methanol and 5 equiv of HFIP. Under these optimized conditions, the reaction was almost completely regioselective, with the formation of 95% of **7a**. The reaction was faster at 65 °C (2 h instead of 24 h at room temperature), and the addition of 1 equiv of K_2CO_3 was essential to avoid the degradation of starting material. In the presence of HFIP, the S_N process was almost suppressed. This nicely supports the hypothesis that the S_N' process is favored when the nucleophile is softer. Indeed, we previously reported that HFIP greatly decreases the nucleophilicity of a nucleophile through strong hydrogen bonds.[15] These H-bonding associations are stronger with alkylamines than with aromatic ones. Accordingly, we compared the substitution of CF_3-allyl bromide **6** with piperidine and anilines, with or without HFIP (Table 2).

When CF_3-allyl bromide **6** was treated with 10 equiv of piperidine in dichloromethane, only S_N substitution at carbon 16 was observed (**5g**, 100%). When HFIP was added (5 equiv), the same result was obtained. Increasing the number of equivalents of HFIP to 20 resulted in a decreased reaction rate (24 h instead of 2.5 h) but the same regioselectivity.

Similar experiments were performed with 10 equiv of aniline (pK_a = 4.58) and 4-chloro-aniline (pK_a = 3.98) in dichloromethane. In both cases, we observed a minor formation of S_N' compounds (**5h**:**7h**, 83:17; **5i**:**7i**, 76:24) that increased when 5 equiv of HFIP were added (**5h**:**7h**, 76:24; **5i**:**7i**, 66:34). Surprisingly, the S_N' reaction was not stereoselective, and both diastereomers were obtained after purification of the crude mixture. Moreover, as already observed with the unsaturated hemiketal **8**, isomerization of the β isomers to the α isomers was also noted.

These results confirm the influence of nucleophilicity on the S_N'/S_N ratio. Despite an evident influence of HFIP in this competitive process, the regioselectivity could not be reversed with amines.

Preliminary antimalarial activity was evaluated in vitro for **8** (IC_{50} = 81.6 nM, on a chloroquine-resistant clone) and **7a** (IC_{50}

(9) Haynes, K. R.; Chan, H.-W.; Cheung, M.-K.; Lam, W.-L.; Soo, M.-K.; Tsang, H.-W.; Voerste, A.; Williams, I. D. *Eur. J. Org. Chem.* **2002**, 113−132.

(10) For compound **4**, where the methoxyl at carbon 10 is α, no correlation is observed between the H-17 and H-12 protons (ref 14).

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(12) As already observed for the ring opening of epoxides, see: (a) Bégué, J. P.; Bonnet-Delpon, D.; Benayoud, F. *J. Org. Chem.* **1995**, *60*, 5029−5036. (b) Iskra, J.; Bonnet-Delpon, D.; Bégué, J. P. *J. Fluorine Chem.* **2005**, *126*, 549−554.

(13) (a) Bégué, J. P.; Bonnet-Delpon, D.; Crousse, B. In *Handbook of Fluorous Chemistry*; Gladysz, J., Horvath, I., Curran, D., Eds; Wiley-VCH: Weinheim, Germany, 2004; pp 341−349. (b) Bégué, J. P.; Bonnet-Delpon, D.; Crousse, B. *Synlett* **2004**, *1*, 18−29.

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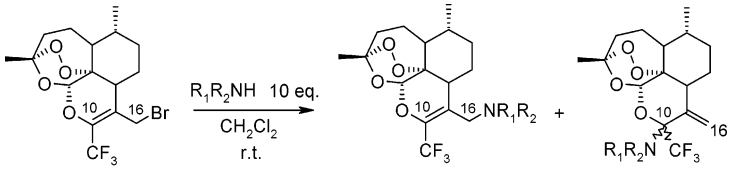
(15) Das, U.; Crousse, B.; Kesavan, V.; Bonnet-Delpon, D.; Bégué, J. P. *J. Org. Chem.* **2000**, *65*, 6749−6751.

TABLE 2. S_N/S_N' Competititon with Amines



6 **5g-i** **7h-i**

amines	S_N (C-16)	S_N' (C-10)	ratio[a] S_N/S_N' (β:α) R_1R_2NH (10 equiv)	ratio[a] S_N/S_N' (β:α) R_1R_2NH/HFIP (10:5 equiv)	yield (%)
piperidine	**5g**		100:0	100:0	80
aniline	**5h**	**7h**	83:17	76:24	75
p-chloroaniline	**5i**	**7i**	76:24	66:34	75

[a] After purification of the crude mixture.

= 10.4 nM).[16] These compounds are less-active than the corresponding saturated analogues **3** (IC_{50} = 3 nM) and **4a** (IC_{50} = 0.8 nM)[6] and slightly less-active than artemisitene (IC_{50} = 7.44 on a chloroquine-resistant clone).[17]

Conclusion

A very active antimalarial drug family of C-10 fluorinated artemisinins **5**, functionalized at carbon 16, had been previously synthesized from the allyl bromide **6** via an S_N reaction. We found that, under solvolytic conditions, various alcohols could be selectively introduced at carbon 10 (S_N' reaction), giving rise to high yields of new fluorinated artemisinin derivatives **7**. Selectivity was improved by adding HFIP in the reaction medium. Remarkably, regioselectivity could be completely reversed in this allylic substitution, despite the presence of the electronically and sterically repulsive CF_3 group. The original structure of this new family of artemisinin derivatives can allow further functionalization for entry to other CF_3-substituted artemisinins.

Experimental Section

10-Trifluoromethylallyl bromide **6** was synthesized according to the usual procedure.

General Procedure for the Nucleophilic Substitution of 10-Trifluoromethylallyl Bromide 6 with Alcohols: 10-Trifluoromethylallyl bromide **6**[8] (100 mg, 0.24 mmol) and potassium carbonate (33 mg, 0.24 mmol) were dissolved in the alcohol (4 mL). The reaction mixture was then heated and stirred until the disappearance of starting material, cooled to room temperature, and diluted with Et_2O (15 mL). The organic layer was washed with a saturated aqueous solution of sodium hydrogen carbonate (15 mL) and water (15 mL) and then dried over magnesium sulfate. Solvents were removed under reduced pressure to afford a yellow oil. The crude product was purified by chromatography on silica gel (petroleum ether/ethyl acetate, 9:1) to furnish compounds **7** and **5** (nonseparated) as a white powder.

Specific Example of Allylic Substitution of 10-Trifluoromethylallyl Bromide 6 with Methanol and HFIP: To a solution of 10-trifluoromethylallyl bromide **6** (100 mg, 0.24 mmol) in dichloromethane (2 mL) were added MeOH (100 μL, 2.4 mmol), HFIP (250 μL, 1.2 mmol), and Na_2CO_3 (37 mg, 2.6 mmol). The reaction mixture was stirred for 2 h in refluxing dichloromethane until the disappearance of starting material, cooled to room temperature, and diluted with dichloromethane (15 mL). The organic layer was washed successively with a saturated solution of sodium hydrogen carbonate (15 mL) and water (15 mL) and dried over magnesium sulfate. Solvents were evaporated under reduced pressure to obtain a yellow oil. The crude product was purified by chromatography on silica gel (petroleum ether/ethyl acetate, 9:1) to furnish compounds **7a** as a white powder (95%). $[\alpha]^{25}_D = +161$ (*c* 0.33, MeOH).

Acknowledgment. We thank Philippe Grellier at the Muséum National d'Histoire Naturelle (USM 504, Paris) for biological testing. We are grateful to the Institute of Natural Products (CNST, Hanoi, Vietnam) for supplying artemisinin and to Jean-Pierre Bégué for fruitful discussions. We thank Sophie Mairesse-Lebrun at the Microanalysis service of BioCIS for elementary analysis.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060032Q

(16) Performed on the FcB_1 strain by the Philippe Grellier group, Muséum National d'Histoire Naturelle, USM 504, Paris.

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