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First Synthesis of 10 α -(Trifluoromethyl)deoxoartemisinin

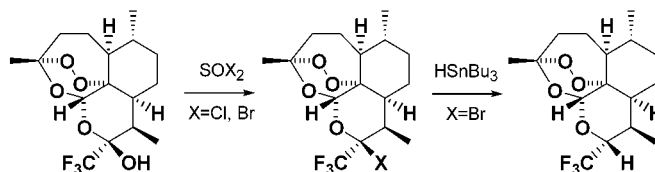
Fatima Chorki,[†] Fabienne Grellepois,[†] Benoit Crousse,[†] Vu Dinh Hoang,[‡]
Nguyen Van Hung,[‡] Danièle Bonnet-Delpon,[†] and Jean-Pierre Bégué[†]

BioCIS, Centre d'Etudes Pharmaceutiques, rue J.B. Clément, Châtenay-Malabry
F-92296 Cedex, France, and Institute of Chemistry, CNST, Hoang Quoc Viet Road,
Hanoi, Vietnam

daniele.bonnet-delpon@cep.u-psud.fr

Received December 13, 2001

ABSTRACT



A novel, nonacetal (trifluoromethyl)deoxoartemisinin was prepared with good stereoselectivity. This compound was obtained by debromination of the 10 α -CF₃-10-bromodeoxoartemisinin in the presence of tributyltin hydride at reflux in toluene without alteration of the endoperoxide bridge. It presented a reasonable antimalarial activity.

Artemisinin **1**, isolated from *Artemisia annua*, is an important antimalarial drug with high activity against multidrug resistant forms of *Plasmodium falciparum*.¹ However, the therapeutic value of **1** is limited to a great extent by its low solubility in both oil and water. Consequently, in the search for more effective and soluble drugs, a number of simple ethers **2** of dihydroartemisinin (DHA) have been prepared by hemisynthesis.^{1,2} Although these derivatives are currently in clinical use against malaria, their limitations are a poor oral bioavailability and a very short plasma half-life as a result of the metabolic instability of the acetal function. To circumvent this instability, two strategies have been reported

in the literature. One involves the introduction of a fluoroalkyl substituent to the hemiacetal center, resulting in a greater stability.³ The second is to eliminate the hemiacetalic structure by removing the hydroxyl at C-10⁴ or replace the C–O bond by a C–C bond at this site.^{5–8} Some of these

[†] Centre d'Etudes Pharmaceutiques.

[‡] Institute of Chemistry, CNST.

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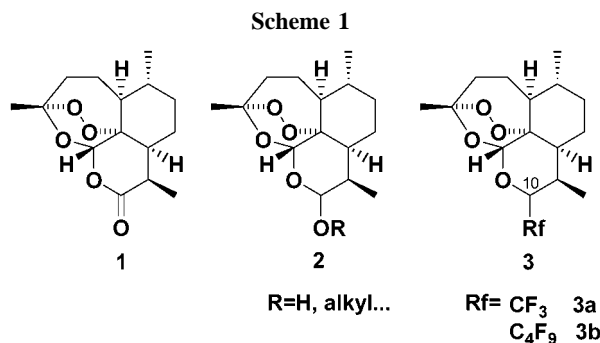
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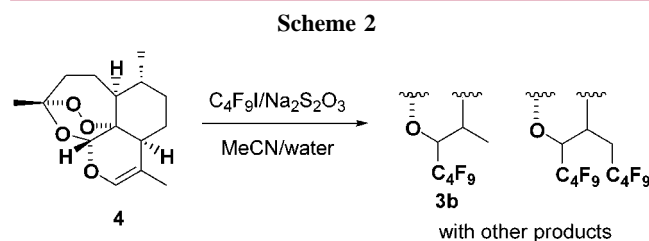
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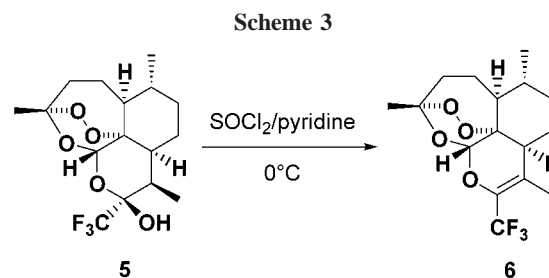
compounds exhibit good in vitro and in vivo antimalarial activity, and simulated stomach acid experiments show that they are more stable than acetal derivatives of artemisinin.⁹ Although some of these nonacetal type analogues contain fluorine atoms,⁶ derivatives with a perfluoro group directly linked to the C-10 site have not been described so far. We recently reported on the introduction of a difluoro moiety at C-10 through the chemistry of enoxysilanes, but this resulted in an epimerization at C-9.¹⁰ Here are reported various strategies that were explored to prepare nonketalic C-10 fluoroalkyl-substituted derivatives **3** of artemisinin (Scheme 1).



In spite of the possible chemical sensitivity of the endoperoxide bridge, we first investigated the radical addition of 1-iodoperfluoroalkanes to the nonfluorinated glycol of artemisinin **4**.^{2c} Perfluoroalkylation of **4** was performed using $\text{C}_4\text{F}_9\text{I}$ and sodium dithionite as initiator under the usual conditions (excess of $\text{C}_4\text{F}_9\text{I}$, $\text{Na}_2\text{S}_2\text{O}_4$ in acetonitrile/water).¹¹ Although the reaction led to a complex mixture where monoperfluoroalkylated (minor) and diperfluoroalkylated (major) compounds could be detected (NMR), it is interesting to note that these radical conditions did not affect the endoperoxide group (Scheme 2).



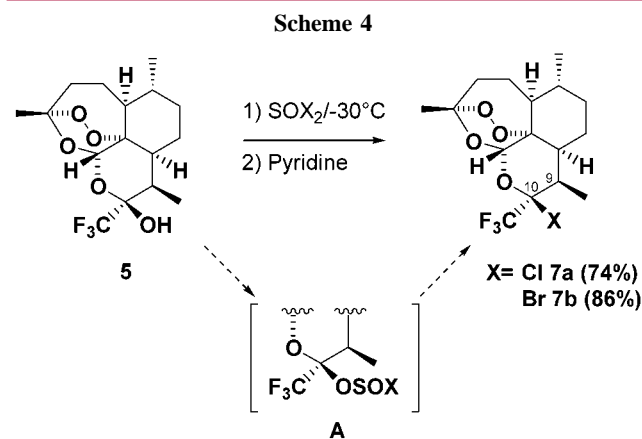
Since the CF_3 -glycal **6** could be prepared by reaction of the CF_3 -substituted dihydroartemisinin **5** with thionyl chloride and pyridine (Scheme 3),¹² a second approach to obtain **3a** would be the hydrogenation of the unsaturated bond.



However, reaction of **5** with $\text{H}_2/\text{Pd/C}$ resulted in reduction of the endoperoxide bridge.¹³

In a similar approach, deoxygenation of the hemiketal **5** was investigated. The classical method described from artemisinin, using NaBH_4 and $\text{BF}_3 \cdot \text{Et}_2\text{O}$,^{4b} cannot be used since **5** does not provide an oxonium intermediate under acidic conditions.¹² We thus turned to conditions involving the radical cleavage of a leaving group at C-10, followed by reduction with HSnBu_3 , which is known to be compatible with the endoperoxide bridge.¹⁴ First, we explored Barton–McCombie deoxygenation involving a thionocarbonate or a xanthate.¹⁵ Unfortunately, our efforts to prepare the intermediate xanthate or thionocarbonate from **5** failed, probably due to the low reactivity of the hydroxyl group deactivated by CF_3 .

The reaction of **5** was then revisited with thionyl chloride in order to favor an intramolecular substitution by a chlorine atom toward an elimination process, from the postulated intermediate **A** (Scheme 4). When thionyl chloride was added



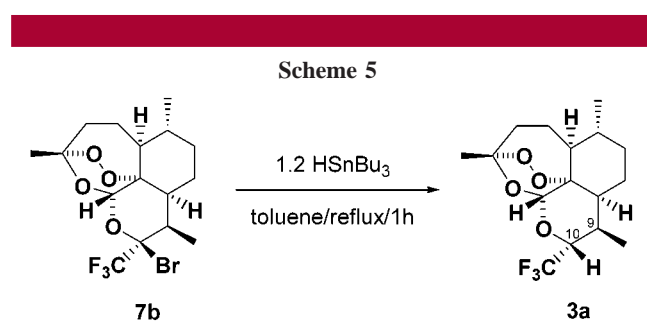
first to **5**, at $-30\text{ }^\circ\text{C}$ instead of $0\text{ }^\circ\text{C}$, and after addition of 1.5 equiv of pyridine, chloride **7a** could be obtained in 74% yield. When this chloride was placed in the presence of

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pyridine, it did not provide the CF₃-glycal **6**, confirming that the latter is obtained by an elimination reaction from the intermediate **A**. An energetic pathway leading to glycal **6** or chloride **7a** should be very close since slight modifications of reaction conditions allow for control of the outcome of the reaction. A similar reaction using thionyl bromide provided the corresponding 10-CF₃-10-bromodeoxoartemisinin **7b** in good yield (86%). In both cases, the reaction is stereoselective. The configuration of compounds **7a,b** was determined by hetero NOE between the CF₃ group with both H (6.4%) and CH₃ (3%) at C-9, indicating its α equatorial position and hence the β axial configuration of the halogen. The CF₃ group is in an α position as in the starting material. Consequently, the nucleophilic substitution proceeds with retention of configuration corresponding to an S_Ni mechanism.

Having in hand the halogenoartemisinin derivatives **7a,b**, we could investigate their radical reduction using HSnBu₃, at reflux in toluene. The 10 α -CF₃-10-chlorodeoxoartemisinin **7a** did not react after 1 h under these conditions. Only starting material was recovered. However, the more reactive 10 α -CF₃-10-bromodeoxoartemisinin **7b** could be completely converted into the 10 α -(trifluoromethyl)deoxoartemisinin **3a** after 1 h of reaction. The compound was obtained in 75% yield after purification and recrystallization (Scheme 5). The



α configuration of the CF₃ group was determined by measurement of heteroNOE between CF₃/H-10 (6%), CF₃/

H-9 (3.5%), and CF₃/CH₃-9 (2%). This radical reaction occurred with complete conservation of the configuration at C-10. Stereocontrol in free radical reactions is often observed.¹⁶ In our case, two effects can explain this control. The steric hindrance of the α face of the artemisinin usually favor β attacks. Furthermore, even if the radical at C-10 is stable enough to undergo a change in conformation, it is likely that the conformer where the CF₃ substituent is anti to the Me at C-9 is thermodynamically more stable.¹²

The in vitro antimalarial activity of the 10 α -CF₃-deoxoartemisinin **3a** was determined using the chloroquine-resistant *P. falciparum* W2 strain. Its activity (IC₅₀ = 6.2 nM) is similar to that of artemether (7 nM) but is slightly weaker than that of the hemiketal **5** (2.6 nM). Preliminary in vivo experiments performed with a single dose of **3a** (35.3 μ M/kg) showed that **3a** ensured a good protection, but to a lesser extent than **5**.¹⁷

In conclusion, we have prepared a new perfluorinated nonacetal artemisinin derivative. This compound was prepared by a radical dehalogenation reaction and possessed the CF₃ group at position-10 with the configuration α . The stereoselectivity was conserved during each of the reactions. It possessed a reasonable antimalarial activity.

Acknowledgment. We thank the MENRT program for financial support (F.G.); the program PAL+; Philippe Grellier for the in vivo antiparasitaire tests (Museum National d'Histoire Naturelle); Daniel Parzy for the tests in vitro (Unité de Parasitologie de l'Institut de Médecine Tropicale; and the GDR Etude des protozoaires pathogènes: cibles thérapeutiques et vaccinales.

Supporting Information Available: Experimental procedures and full characterization for compounds **3a** and **7a,b**. The antimalarial testing protocol is described. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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