ORGANIC LETTERS

2002
Vol. 4, No. 5
757−759

First Synthesis of 10α-(Trifluoromethyl)deoxoartemisinin

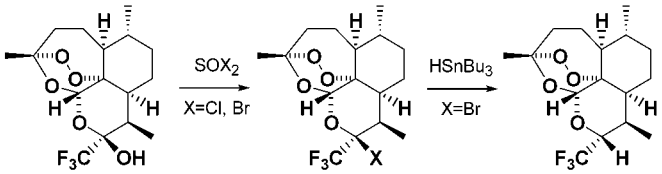
Fatima Chorki,[†] Fabienne Grellepois,[†] Benoit Crousse,[†] Vu Dinh Hoang,[‡] Nguyen Van Hung,[‡] Danièle Bonnet-Delpon,[†] and Jean-Pierre Bégué[†]

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 10α-CF_3-10-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-10[4] 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.

(1) (a) Klayman, D. L. *Science* **1985**, *228*, 1049. (b) Zaman, S. S.; Sharma, R. P. *Heterocycles* **1991**, *32*, 1593. (c) Jefford, C. W. In *Advances in Drug Research*; Academic Press: London, 1997; Vol. 29, p 272. (d) Avery, M. A. *Curr. Pharm. Des.* **1999**, *5*, 101. (e) Bhattacharya, A. K.; Sharma, R. P. *Heterocycles* **1999**, *51*, 1681.

(2) (a) Avery, M. A.; Gao, F.; Chong, W. K. M.; Mehrota, S.; Jenning-White, C. *Trends in Organic Chemistry*; Pergamon Press: Trinandrum, 1993; Vol. 4, p 413. (b) Jung, M. *Curr. Med. Chem.* **1994**, *1*, 35. (c) Wu, Y. L.; Li, Y. *Med. Chem. Res.* **1995**, *5*, 569. (d) Lin, A. J.; Lee, M.; Klayman, D. L. *J. Med. Chem.* **1989**, *32*, 1249 and references therein. (e) Brossi, A.; Venugopalan, B.; Gerpe, L. D.; Yeh, H. J. C.; Flippen-Anderson, J. L.; Buchs, P.; Luo, X. D.; Milhous, W.; Peters, W. *J. Med. Chem.* **1988**, *31*, 645.

(3) (a) Abouabdellah, A.; Bégué, J. P.; Bonnet-Delpon, D.; Gantier, J. C.; Thanh Nga, T. T.; Truong Dinh, T. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 7. (b) Thanh Nga, T. T.; Ménage, C.; Bégué, J. P.; Bonnet-Delpon, D.; Gantier, J. C.; Pradines, B.; Doury, J. C.; Truong Dinh, T. *J. Med. Chem.* **1998**, *41*, 4101.

(4) (a) Jung, M.; Li, X.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D. *Tetrahedron Lett.* **1989**, *30*, 5973. (b) Jung, M.; Li, X.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D.; Milhous, W. K. *J. Med. Chem.* **1990**, *33*, 1516.

(5) (a) Pu, Y.-M.; Yeh, H.; Ziffer, H. *Heterocycles* **1993**, *36*, 2099. (b) Pu, Y.-M.; Ziffer, H. *J. Med. Chem.* **1995**, *38*, 613.

(6) Pu, Y.-M.; Torok, D. S.; Ziffer, H.; Pan, X.-Q.; Meshnick, S. R. *J. Med. Chem.* **1995**, *38*, 4120.

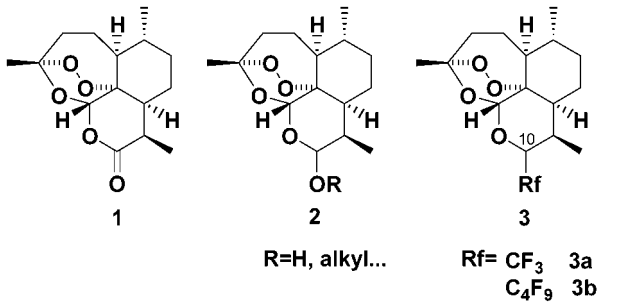
(7) (a) Ma, J.; Katz, E.; Kyle, D. E.; Ziffer, H. *J. Med. Chem.* **2000**, *43*, 4228. (b) Jung, M.; Bae, J. *Heterocycles* **2000**, *52*, 261. (c) Ma, J.; Katz, E.; Ziffer, H. *Tetrahedron Lett.* **1999**, *40*, 8543. (d) O'Neill, P. M.; Searle, L.; Kan, K.-W.; Storr, R. C.; Maggs, J. L.; Ward, S. A.; Raynes, K.; Park, K. *J. Med. Chem.* **1999**, *42*, 5487.

(8) (a) Jung, M.; Lee, S. *Heterocycles* **1997**, *47*, 1055. (b) Jung, M.; Freitas, A. C. C.; McChesney, J. D.; ElSohly, H. N. *Heterocycles* **1994**, *39*, 23. (c) Haynes, R. K.; Vonwiller, S. C. *Synlett* **1992**, 481. (d) Jung, M.; Bustos, D. A.; ElSohly, H. N.; McChesney, J. D. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 741. (e) Posner, G. H.; Parker, M. H.; Northrop, J.; Elias, J. S.; Ploypradith, P.; Xie, S.; Shapiro, T. A. *J. Med. Chem.* **1999**, *42*, 300. (f) Junf, M.; Lee, K.; Jung, H. *Tetrahedron Lett.* **2001**, *42*, 3997.

10.1021/ol017227z CCC: $22.00
Published on Web 02/07/2002

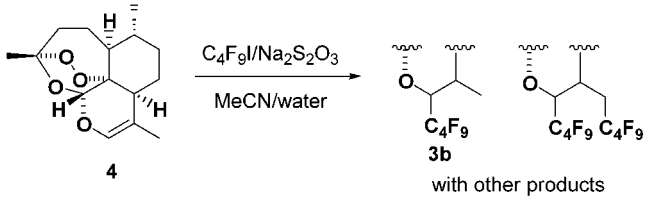
compounds exhibit good in vitro and in vivo antimalarial activity, and simulated stomach acid experiments show that they are more stable than acetal derivatives of artemisinin.[9] Although some of these nonacetal type analogues contain fluorine atoms,[6] derivatives with a perfluoro group directly linked 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).

Scheme 1



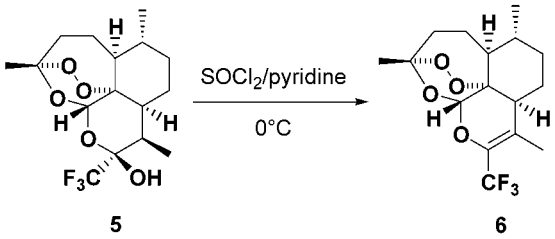
In spite of the possible chemical sensitivity of the endoperoxide bridge, we first investigated the radical addition of 1-iodoperfluoroalkanes to the nonfluorinated glycal of artemisinin **4**.[2e] Perfluoroalkylation of **4** was performed using C_4F_9I and sodium dithionite as initiator under the usual conditions (excess of C_4F_9I, $Na_2S_2O_4$ 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).

Scheme 2



Since the CF_3-glycal **6** could 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.

Scheme 3

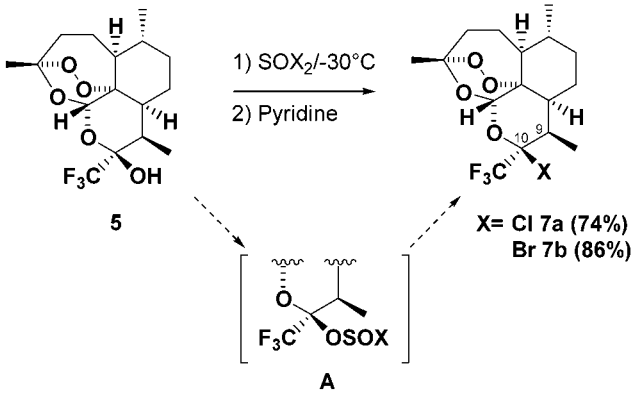


However, reaction of **5** with H_2/Pd/C resulted in reduction of the endoperoxide bridge.[13]

In a similar approach, deoxygenation of the hemiketal **5** was investigated. The classical method described from artemisinin, using $NaBH_4$ and $BF_3{\cdot}Et_2O$,[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

Scheme 4



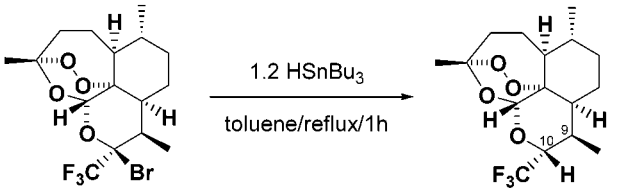
first to **5**, at −30 °C instead of 0 °C, and after addition of 1.5 equiv of pyridine, chloride **7a** could be obtained in 74% yield. When this chloride was placed in the presence of

(9) Jung, M.; Lee, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1003.
(10) Chorki, F.; Grellepois, F.; Crousse, B.; Ourévitch, M.; Bonnet-Delpon, D.; Bégué, J. P. *J. Org. Chem.* **2001**, *66*, 7858.
(11) (a) Brace, N. O. *J. Fluorine Chem.* **1995**, *93*, 1. (b) Furin, G. G. *Russ. Chem. Rev.* **2000**, *69*, 491.
(12) Grellepois, F.; Chorki, F.; Crousse, B.; Ourévitch, M.; Bonnet-Delpon, D.; Bégué, J. P. *J. Org. Chem.* **2002**, *67*, 1253.
(13) Wu, W.-M.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 4279.
(14) Venugopalan, B.; Karnik, P. J.; Bapat, C. P.; Chatterjee, D. K.; Iyer, N.; Lepcha, D. *Eur. J. Med. Chem.* **1995**, *30*, 697.
(15) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (b) Boussaguet, P.; Delmond, B.; Dumartin, G.; Pereyre, M. *Tetrahedron Lett.* **2000**, *41*, 3377.

pyridine, it did not provide the CF_3-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-CF_3-10-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 CF_3 group with both H (6.4%) and CH_3 (3%) at C-9, indicating its α equatorial position and hence the β axial configuration of the halogen. The CF_3 group is in an α position as in the starting material. Consequently, the nucleophilic substitution proceeds with retention of configuration corresponding to an SNi mechanism.

Having in hand the halogenoartemisinin derivatives **7a**,**b**, we could investigate their radical reduction using $HSnBu_3$, at reflux in toluene. The 10α-CF_3-10-chlorodeoxoartemisinin **7a** did not react after 1 h under these conditions. Only starting material was recovered. However, the more reactive 10α-CF_3-10-bromodeoxoartemisinin **7b** could be completely converted into the 10α-(trifluoromethyl)deoxoartemisinin **3a** after 1 h of reaction. The compound was obtained in 75% yield after purification and recrystallization (Scheme 5). The

Scheme 5



7b **3a**

α configuration of the CF_3 group was determined by measurement of heteroNOE between CF_3/H-10 (6%), CF_3/H-9 (3.5%), and CF_3/CH_3-9 (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 CF_3 substituent is anti to the Me at C-9 is thermodynamically more stable.[12]

The in vitro antimalarial activity of the 10α-CF_3-deoxoartemisinin **3a** was determined using the chloroquine-resistant *P. falciparum* W2 strain. Its activity (IC_{50} = 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 μM/kg) showed that **3a** ensured a good protection, but to a lesser extent that **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 CF_3 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.

OL017227Z

(16) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296.

(17) Grellier, P.; et al. Unpublished results.