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C-10-Fluorinated derivatives of dihydroartemisinin: difluoromethylene ketones

Fatima Chorki,[a] Benoît Crousse,[a] Danièle Bonnet-Delpon,[a] Jean-Pierre Bégué,[a,*] Thierry Brigaud[b] and Charles Portella[b]

[a]*BIOCIS, CNRS, Faculté de Pharmacie, Châtenay-Malabry F-92296, France*
[b]*Faculté des Sciences et CNRS, BP 1039, F-51687 Reims Cedex 2, France*

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Abstract—Difluoroenoxysilanes, prepared from aromatic and heterocyclic ketones, reacted with dihydroartemisinin acetate in the presence of Lewis acid to provide in good to moderate yields the 10-substituted difluoromethylene ketones. The introduction of the difluoromethylketone moiety was accompanied by the epimerisation of C-9. Best results were obtained using $SnCl_4$ as Lewis acid. © 2001 Published by Elsevier Science Ltd.

Difluoroenoxysilanes[1] are excellent building blocks for the synthesis of gem-difluorinated compounds. Their in situ generation and their use in a one-pot procedure with Michael acceptors, allylic alcohol derivatives and carbonyl compounds, provides difluoro-1,5-diketones, difluoroanalogues of terpenes and difluoroaldols compounds.[2–6] They can also react with glycosyl donors by addition onto the oxonium ion generated by a Lewis acid giving an access to difluoro *C*-glycosides.[7]

Artemisinin derivatives are potent antimalarial drugs, efficient towards drug-resistant *Plasmodium falciparum*.[8] However, artemisinin derivatives have a very short plasmatic half-live.[9,10] In our search to design more active and longer lasting new drugs, we have previously demonstrated that a substitution at C-10 by a fluorinated substituent strongly improves the in vivo activity of artemisinin derivatives against *P. falciparum*, because of the increased stability towards metabolism processes.[11,12] In this way, the synthesis of 10-difluoro-substituted derivatives of artemisinin constitutes an interesting aim.

Dihydroartemisinin **1** (DHA), which is a cyclic hemiacetal, can be considered as a *pseudo*-glycoside able to give a reactive oxonium ion, which can react with a nucleophilic entity.[13] We have thus investigated the reaction of difluoroenoxysilanes with DHA derivatives and we report our preliminary results.

In our first experiments, we have generated in situ the aromatic difluoroenoxysilane **2a** from benzoyltrimethylsilane and TMS–CF_3.[6] Several Lewis acid have been checked for the activation of the aldol-type condensation reaction with the dihydroartemisinin (DHA). Reaction failed in all cases, excepted in the presence of $SnCl_4$, where the ketone **4a** could be obtained in a very low yield (9%). Starting from the 10α-acetoxydihydroartemisinin[14] (DHA acetate) **3**, instead of DHA, enoxysilane **2a** (1.5 equiv.) and $SnCl_4$ (1.5 equiv.), at −78°C, the difluoroketone **4a** could be isolated in a better yield (23%) as a mixture of two diastereoisomers. However, all our attempts to improve this yield by changes in reaction conditions failed, and with other Lewis acid, such as ytterbium triflate, $BF_3{\cdot}Et_2O$, or trimethylsilyl triflate, DHA acetate **3** did not provide any ketone **4a**.

These disappointing results prompted us to turn towards the use of isolated difluoroenoxysilanes, and we prepared them through the Uneyama's procedure based on the Mg^0-promoted selective defluorination of trifluoromethyl ketones.[15]

For the condensation of isolated enoxysilanes, we chose the best previous conditions, i.e. starting from the DHA acetate **3** and using $SnCl_4$ as catalyst. DHA acetate **3**, placed at −78°C in the presence of 0.2 equiv. of $SnCl_4$ reacted with enoxysilane **2a** for 2 h and after raising the temperature to −20°C, hydrolysis provided the difluoroketone **4a** in a 30% yield. Using 0.4 equivalent of catalyst, after 1 h at −78°C, raising the temperature

* Corresponding author. Fax: 33 1 46 83 57 40; e-mail: jean-pierre.begue@cep.u-psud.fr

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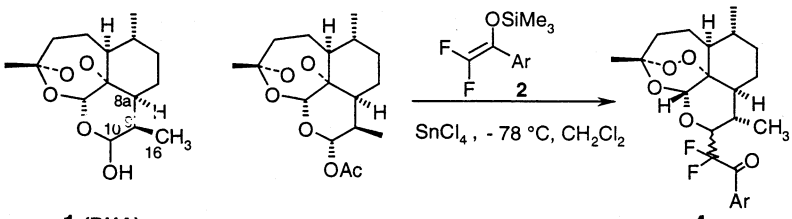


		β:α	Yields
a	R = $-C_6H_5$	100:0	(66 %)
b	= $4\text{-}C_6H_4\text{-}OCH_3$	100:0	(73 %)
c	= $2,5\text{-}C_6H_3\text{-}(OCH_3)_2$	70:30	(33 %)
d	= 2-Thiophenyl	70:30	(29 %)

to −20°C, the difluoroketone **4a** was isolated after chromatography on a neutral alumina column[16] in a 66% yield.[17,18] Under these conditions, the reaction was stereoselective. The structure of ketone **4a** with its surprising stereochemistry was determined by NMR: signals of the methyl 16 at C-9 are strongly deshielded in ^1H and ^{13}C NMR (δ 1.20 ppm and 21 ppm instead of 0.90–1.0 ppm and 12–13 ppm), and are typical of the *epi*-artemisinin series (configuration α of Me-16).[12,19,20] The large coupling constant ($J=10.6$ Hz) observed for $J_{H\text{-}9\text{–}H\text{-}10}$ indicates a *trans–trans* diaxial relationship for these protons, and thus a *trans* relationship between Me-16 and the difluoromethyl ketone substituent, which is in β-configuration. These relative configurations are confirmed by homo NOE observed between Me-16 and both H-8a and H-10, and by hetero NOE $\{^{19}F\}^1H$ effect between fluorinated atoms and H-9.

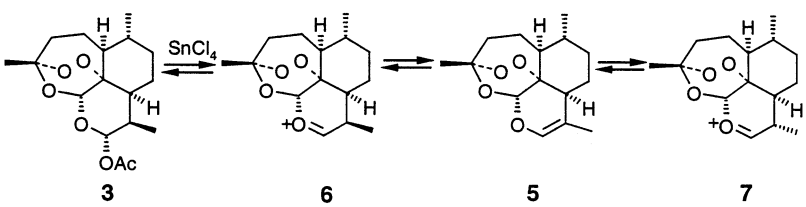
The reaction failed with $TiCl_4$, scandium or ytterbium triflates used in catalytical amounts (0.2 equiv.) at room temperature, and with TMSOTf, or $BF_3{\cdot}Et_2O$ at −78°C, only small amounts of difluoromethylene ketone **4a** could be detected.

The reaction has then been investigated with other enoxysilanes. Under the same conditions (0.4 equiv. of $SnCl_4$) reaction of 4-methoxyphenyl difluoroenoxysilane **2b** with DHA acetate **3** led to a mixture of rearranged compounds.[21] Using only 0.1 equivalents of $SnCl_4$, the difluoroketone **4b** could be obtained stereoselectively in 30% yield. The best results were finally obtained using $BF_3{\cdot}Et_2O$ (0.2 equiv.) with a yield in **4b** of 73%. Reactions with enoxysilanes **2c** and **2d** have been checked in the presence of $BF_3{\cdot}Et_2O$ and $SnCl_4$. With $BF_3{\cdot}Et_2O$, no condensation occurred. With $SnCl_4$ (0.1 equiv.) reaction of **3** and **2c** provided **4c** (β-isomer) in only 14% yield. It could be improved to 33% by using 0.4 equiv. of $SnCl_4$. However, **4c** was obtained as a 70:30 mixture of β/α diastereoisomers. From **2d**, the best results were obtained with 0.4 equiv. of $SnCl_4$ and ketone **4d** was obtained in 29% yield as a 70:30 mixture of diastereoisomers. In these two latter experiments, ketones **4** were accompanied with a non-negligible amount of elimination product **5**.

In these reactions, it has been observed that each kind of electrophile needed a careful choice of the Lewis acids and its stoechiometry. $SnCl_4$ provided the best results.

The epimerisation of the C-9 centre probably results from a rapid equilibrium between oxonium ions **6** and **7**, through the glycal **5** which can be reprotonated, as expected, by the β-face, before the addition of enoxysilane. Surprisingly, such epimerisation did not occur in the $TiCl_4$-catalyzed reaction of non-fluorinated enoxysilanes with DHA acetate.[22] In order to check if the epimerisation was due to the nature of Lewis acid, we have performed the $SnCl_4$-catalyzed reaction of non-fluorinated enoxysilane with DHA acetate. No epimerisation occurred suggesting peculiar behaviour of the difluoroenoxysilanes.

Also surprising is the striking difference of reactivity of enoxy silanes **2a–d**: the presence of *p*-methoxy substituent in **2b** seems to facilitate the reaction. Conversely **3b** appeared to be less reactive and formation of glycal **5** is predominant.



In conclusion, the addition of difluoroenoxysilanes provides a new generation of fluorinated derivatives of *epi*-artemisinin, without oxygen fonctionality at C-10. Antimalarial properties of difluoroketones **4** are currently under investigation.

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16. Compounds **4** are unstable on SiO_2 chromatography column.
17. Typical procedure for compound **4a**: $SnCl_4$ (3.1 mL, 0.84 mml, 0.4 equiv.) was added at −78°C, under Ar, to a solution of dihydroartemisinin acetate **3** (700 mg, 2.1 mmol) in CH_2Cl_2 (15 mL). Difluoroenoxysilane **2a** (710 mg, 3.1 mmol, 1.5 equiv.) was then added very slowly at −78°C. After complete disappearance of the starting **3** (1 h, and rising the temperature to −20°C), a saturated solution of sodium hydrogenocarbonate was added. After extraction (CH_2Cl_2), the organic layer was washed (brine) and dried ($MgSO_4$). Evaporation of the solvent provided a residue which was purified on neutral alumina column[16] (petroleum ether/AcOEt 90:10), leading to the pure compound **4a** (596 mg, 66%).
18. **3a**: mp 94.5°C (AcOEt); $[\alpha]_D$ = −60 (c = 5.7 g/L); ^{19}F NMR: δ −103 (d, J = 262 Hz, 1 F), 121.0 (dd, J = 261 Hz, J = 19 Hz, 1 F); ^1H NMR: δ 0.85 (s, 3 H, CH_3-14), 0.91 (d, J = 6 Hz, 3 H, CH_3-15), 1.05 (m, 1 H, H-7a), 1.2 (m, 3 H, H-8a, H-5a, H-6), 1.28 (m, J = 7 Hz, J_{HF} = 2 Hz, 3 H, CH_3-16), 1.38 (m, 1 H, H-8a), 1.45 (m, 1 H, H-4a), 1.60 (m, 1 H, H-7a), 1.75 (m, 1 H, H-8 equiv.), 1.85 (m, 1 H, H-5b), 1.95 (m, 1 H, H-4 equiv.), 2.03 (ddq, $J_{H\text{-}9,H\text{-}10}$ = 10.5 Hz, $J_{H\text{-}9,H\text{-}8a}$ = 1.5 Hz, $J_{H\text{-}9,CH3\text{-}16}$ = 7 Hz, H-9), 2.2 (m, 1 H, H-5 equiv.), 4.9 (ddd, $J_{H\text{-}9,H\text{-}10}$ = 10.5 Hz, $J_{H\text{-}10,Fa}$ = 5 Hz, $J_{H\text{-}10,Fb}$ = 18.5 Hz, 1 H, H-10), 7.47-8.1 (m, 5 H, C_6H_5); ^{13}C NMR: δ 19.9, 20.1, 25.0, 25.1, 31.5, 34.4, 34.6, 35.3, 37.4, 48.1, 51.2, 82.1, 75.2, 90.1, 102.2, 128.6, 130.1, 133.5, 188.5. Anal. calcd for $C_{23}H_{28}F_2O_5$: C, 65.39; H, 6.68; Found: C, 65.45; H, 6.74.
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21. With more than 0.1 equiv. of $SnCl_4$, a rearrangement of the *endo* peroxide bridge occurs leading to an original new compound.[20]
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