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Fluoro-artemisinins: When a *gem*-difluoroethylene replaces a carbonyl group

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Abstract

Exo *gem*-difluoromethylene-artemisinins (**8**) has been designed to mimic artemisinin. The classical Wittig olefination reaction applied to artemisinin failed. An alternative reaction involving the generation of an α-CF_3 carbanion, from the corresponding bromide **6**, allowed the access to the target compound **8**, and could also be exemplified in sugar series. The replacement of the carbonyl function by a difluoroethylene moiety resulted in a better antimalarial activity.

Keywords: *gem*-Difluoroolefin; Artemisinin; Malaria; Mimic effect; Carbohydrate lactone

1. Introduction

Artemisinin (**1**), isolated from *Artemisia annua*, is an important antimalarial drug with high activity against chloroquine resistant forms of *Plasmodium falciparum* [1]. However, the clinical use of **1** is limited 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 (Scheme 1) [1].

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, several approaches of structural modulations have been developed [2].

From our part we have developed a novel approach to design more metabolically stable artemisinins, by introducing a fluoroalkyl substituent at C-10. Due to its electron-withdrawing character, this substituent was expected to protect artemisinins from oxidative and hydrolytic cleavage, and from glucuronidation when a hydroxyl is present at C-10. On this statement, the 10-CF_3-analogue of DHA (**3**) has been designed, and prepared [3]. This compound is a potent antimalarial, and furthermore the hypothesis has been clearly validated by kinetic data [4a].

From this hemiketal (**3**), various other trifluoromethyl derivatives of artemisinin have been prepared: CF_3-glycals (**4**) substituted in 16-position [5], and more recently trifluoromethyl analogous of artemether, arteether, artesunate, artelinate (**5**) (Scheme 2) [4].

They exhibited very interesting in vivo antimalarial properties, a better stability under stomach acidic conditions, and a prolonged plasma half-life demonstrated for some of them [3–5].

In this chemistry, bromides **6** and **7** were key intermediates to prepare various fluorinated derivatives by nucleophilic substitution (Scheme 3).

In a similar approach, we also introduced difluoromethylene substituents at C-10. However enoxysilane chemistry involved in the syntheses resulted in rearrangements and changes in stereochemistry, which did not allow to obtain good antimalarials [6].

At this stage the preparation of the difluoroethylene artemisinin derivative **8** could be of a great interest. First an *exo gem*-difluoroethylene moiety is often considered to be sterically and electronically mimic of carbonyl group [7]. Furthermore the reported ionic [8] and radical chemistry [9] of *gem*-difluoroethylenes could give access to various novel *gem*-difluoromethylene artemisinin derivatives. We report here the

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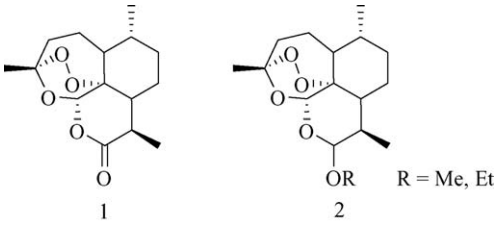
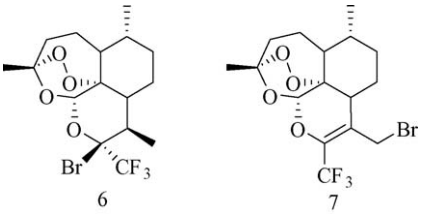


Scheme 1.



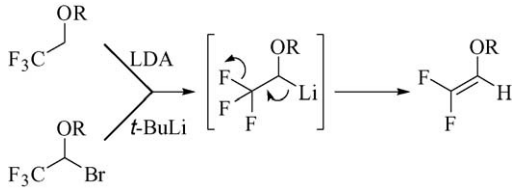
Scheme 3.

preparation of the difluoroethylene artemisinin derivative **8** from the bromide **6**, and its antimalarial activity compared to that of artemisinin.

2. Results and discussion

An excellent reported access to *gem*-difluoroethylene compounds is the difluoro-Wittig reaction of carbonyl groups well exploited for aldehyde and ketone in particular in carbohydrate series [10]. Glycosyl lactones are also reported to be good substrates for this reaction. However most of described effective lactone difluorination concern furanose series, while it is much less exemplified for pyranose lactones which can be structurally compared to artemisinin [9,10c]. In these reactions, carbonyl compounds are treated with CF_2Br_2, a phosphine (PPh_3 or HMPT) and in some cases in the presence of Zn, to afford the corresponding *gem*-difluoroolefins. When treated under these conditions, the artemisinin provided a mixture of decomposition products. We thus turned to another methodology based on the instability of α-CF_3 carbanion. Indeed, such carbanions, usually prepared with strong bases such as LDA [11], rearrange quickly to afford *gem*-difluoroolefins after loss of a fluoride ion (Scheme 4). There are also some few examples of generation of an α-CF_3 carbanion by halogen–metal exchange [12].

Having in hand the bromide **6**, we attempted the halogen–metal exchange by the use of organolithium reagents. Bromide **6** was thus reacted at −78 °C in THF with 2 equiv. of *n*Buli or *t*BuLi, but no reaction occurred. Surprisingly, when the same conditions were applied to MeLi, bromide **6** was converted into difluoroolefin **8** in 78% yield (Scheme 5) [13]. Some experiments were performed in order to quench the lithium intermediate **A**. Water was added at different times, but the reduced compound could not be detected even when quenching was performed after 2 min at −90 °C. Only the difluoromethylene compound **8** was detected in NMR.

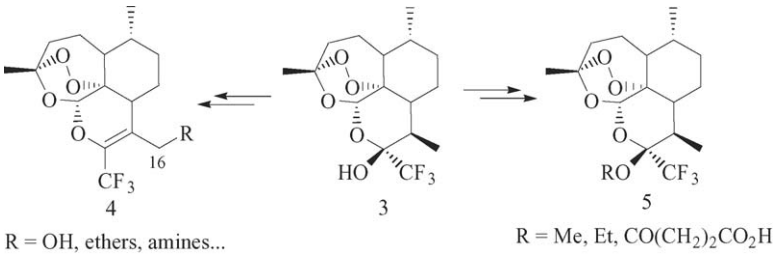


Scheme 4. Synthesis of *gem*-difluoroolefins of TFE derivatives.

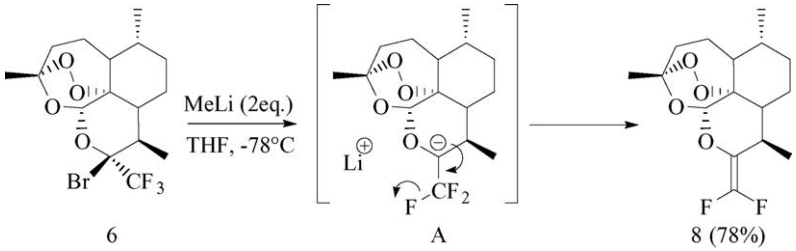
The halogen–lithium exchange could also be achieved from the allyl bromide **7**. When placed in the same reaction conditions (MeLi (2 equiv.), THF at −78 °C), **7** underwent a similar process of exchange and elimination, and was instantaneously converted into *gem*-difluorodiene **9** in 73% yield (Scheme 6). Reactivity of *gem*-difluoro compounds **8**, **9**, and Diels–Alder reaction with **9** are currently investigated.

In order to check the usefulness of this olefination method, it was applied to a 6-member ring lactone carbohydrate. Lactone (**10**) was prepared by the Pfitzner–Moffatt oxidation of the O-protected glucose. The addition of Ruppert's reagent under classical conditions [3a,14] provided the trifluoromethyl glucopyranose (**11**) as a single diastereoisomer which was further treated with $SOBr_2$ to afford the corresponding bromide (**12**) in good yield. NMR HOESY experiments exhibited a correlation between H-2 4.35 ppm and fluorine atoms, indicating their *cis* relationship. No bromide–lithium exchange reaction occurred when bromide (**12**) was placed with 2 equiv. of MeLi . When 5.1 equiv. of MeLi was used at −40 °C, the corresponding *exo*-difluoro glycal (**13**) could be isolated in excellent yield (Scheme 7). A complexation of MeLi with OBn can explain the requirement of the excess of reagent.

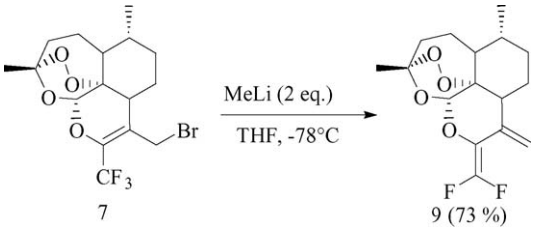
This three steps olefination method thus proceeded in a 60% overall yield which is quite comparable to the direct Wittig-olefination reaction (60–63%) [9a,10b]. It is a good alternative for substrates sensitive to phosphine and/or Zn metal, such as artemisinin.



Scheme 2.



Scheme 5.



Scheme 6.

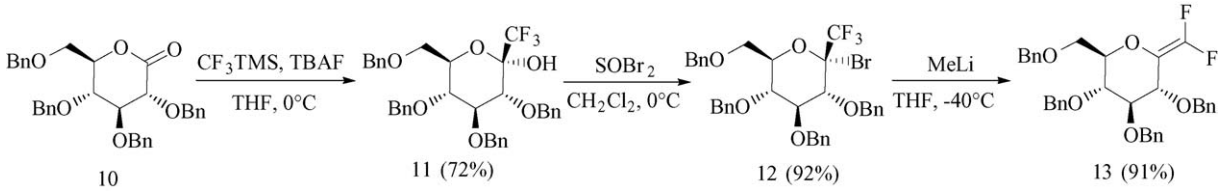
3. Biological evaluation

Fluoroalkanes and fluoroalkenes are isopolar and isosteric analogues of various functionalities (Scheme 8). They have been used for the rational design of bioactive compounds in particular enzyme inhibitors [7]. However, although *gem*-difluoroethylene moiety has been claimed as a bioisostere for carbonyl groups, examples demonstrating this premise are very rare in the literature [15]. The accessibility of the difluoroethylene artemisinin (**8**) gave us a great opportunity to compare its antimalarial activity to that of artemisinin.

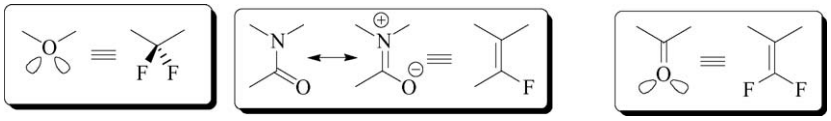
Although the lactone function in artemisinin is not directly involved in the mode of action, it can influence either the generation of reactive radical species or the affinity for the putative receptor [16].

The in vitro antimalarial activity of artemisinin and of compound **8** were determined using the chloroquine resistant FCB1 strain of *P. falciparum*. IC_{50} values are shown in Table 1.

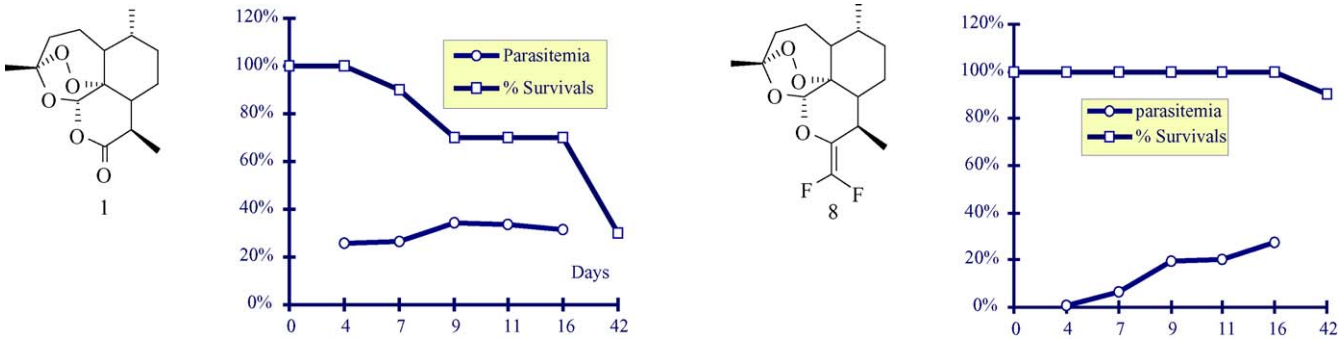
CF_2-artemisinin (**8**) exhibited a good in vitro activity slightly higher than artemisinin one. This result indicates that the



Scheme 7. Difluoromethylenation of D-gluconolactone.



Scheme 8. Fluorinated isosteres of some functionalities.



Scheme 9. Comparative in vivo activity on mice.

Table 1
In vitro activities (*P. falciparum* FCB1 strain)

Compound	IC_{50} (nM)	σ (±)	IC_{90} (nM)	σ (±)
Artemisinin	8.9	0.4	14.5	0.3
CF_2-artemisinin (**8**)	4.6	0.5	7.3	0.5

replacement of a carbonyl function by a *gem*-difluoroolefin group did not affect the recognition process of the drug by the target. Then artemisinin and product **8** were evaluated in vivo on mice, according to the Peters protocol (*Plasmodium berghei* NK 173 infected mice, intraperitoneal administration for 4 days at 35.5 μmol kg^{-1}) [17]. In preliminary experiments, parasitemia at day 4, in control mice and mice treated with artemisinin and *gem*-difluoro artemisinin, was found to be 50%, 25% and 0%, respectively (Scheme 9).

These biological experiments highlighted that the replacement of C=O by a $C{=}CF_2$ resulted in a better in vitro activity. Moreover the difluoroethylene moiety may protect the drug against metabolic processes occurring with artemisinins, as shown by the prolongation of the in vivo antimalarial activity.

4. Conclusion

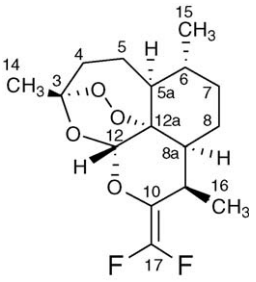
New *exo*-difluoroethylene artemisinin derivatives were easily obtained in a three-step process from artemisinin. This methodology, based on the low stability of an α-CF_3 carbanion, was developed to afford difluoro analogs of artemisinin, and was also successfully applied to carbohydrates. This process is a useful alternative to the difluoro-Wittig reaction, in particular in the case of low reactive compounds such as artemisinin. The synthesis of the *exo*-difluoroethylene artemisinin (**8**) gave the opportunity to evaluate the incidence of the replacement of a carbonyl by the isopolar *gem*-difluoroethylene, on the biological activity. The in vitro antimalarial evaluations indicated that this replacement did not affect the recognition process of the drug by the organism, and resulted in an even better activity. In vivo results highlighted a prolonged antimalarial activity of the CF_2-artemisinin.

5. Experimental

5.1. General experimental procedures

5.1.1. Chemistry

NMR spectra were recorded using Bruker AC 200 (^{1}H, 200 MHz; ^{19}F, 188 MHz; ^{13}C, 50 MHz) spectrometer in $CDCl_3$ solutions. Chemical shifts are reported in ppm relative to Me_4Si and $CFCl_3$ (for ^{19}F NMR) as internal standards. In the ^{13}C NMR data, reported signal multiplicities are related to C–F coupling. Optical rotations were measured at 589 nm on a Polartronic E-Schmidt-Haensch apparatus. TLC was performed on Merck 60 F_{254} silica plates (UV or vanilin-MeOH–H_2SO_4 for artemisinin derivatives). Column chromatography was carried out on Merck SiO_2 (70–230 mesh). Numbering of artemisinin skeleton is as indicated on the following formula:



5.1.2. In vitro assays

Chloroquine-resistant *P. falciparum* strain FCB1 (Colombia) was maintained in a continuous culture of human erythrocytes as described by Trager and Jensen [18]. In vitro antiplasmodial activity of our compounds was determined using a modification of the semi-automated microdilution technique of Desjardins et al. [19]. Stock solutions of tested compounds were prepared in methanol or DMSO. Drug solutions were serially diluted with the culture medium and added to parasite cultures synchronized at the ring stage (1% parasitemia and 1% final hematocrit) in 96-well plates. Parasite growth was assessed by adding 0.5 μCi of [^{3}H]hypoxanthine (10–30 Ci/mmol, Amersham Biosciences Europe GmbH) to each well. Plates were incubated for 48 h at 37 °C in appropriate atmosphere. Immediately after incubation, the plates were frozen and thawed to lyse erythrocytes. The contents of each well were collected on filter microplates, washed, using a cell harvester, and dried. Scintillation cocktail was added to each filter and radioactivity incorporated by the parasites was measured using a scintillation counter. The growth inhibition for each drug concentration was determined by comparison to the radioactivity incorporated in the treated culture with that in the control culture (without drug). The drug concentration causing 50% inhibition (IC_{50}) was determined by nonlinear regression analysis of log dose–response curves. Values are the average of three experiments. DMSO and methanol introduced into the cultures never exceeded 0.1% and did not affect parasite growth.

5.1.3. In vivo assays

The antimalarial activity was studied in mice (female ICR (CD-1), 18–20 g; Harlan, Gannat, France) infected with *P. berghei* (NK 173 strain) (15 to 10^6 red cells) according to the protocol of Peters [17]. Each group contained four to five mice. Treatments with drugs were performed during 4 days, beginning the day of infection, by intraperitoneal route. The drugs were given once a day at 0.0355 mmol kg^{-1} as a suspension, in an aqueous solution of carboxymethyl cellulose (1%). The untreated group received the same amount of DMSO in 1% carboxymethyl cellulose. Efficient doses to inhibit 50% and 90% of parasite growth (ED_{50}, ED_{90}) were determined according to Peters by counting parasitemia at day 4 for drug concentrations ranging from 0.5 to 10 mg/kg. Percentage of inhibition was calculated by comparison to the parasitemia determined in control infected mice.

5.2. Difluoromethylenation: general procedure

Methyllithium (1.6 M (Et_2O), 2.0 mmol) was slowly added to a −78 °C solution of bromide (1.0 mmol) in THF (7 mL). After 5 min stirring at this temperature, the mixture was quenched with aqueous NH_4Cl, extracted with AcOEt, dried over $MgSO_4$ and concentrated under vacuum. The crude was then purified on silica gel (90/10 cyclohexane/AcOEt) to afford the corresponding *gem*-difluoroolefin.

5.3. 10,10-Difluoromethylene-deoxoartemisinin (**8**)

Yield 78%, a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.93 (3H, d, J = 5.7 Hz, H-15), 1.06 (3H, t, J = 7.0 Hz, H-16), 1.41 (3H, s, H-14), 0.79–2.10 (10H, m), 2.35 (1H, m, H-4), 3.23 (1H, m, H-9), 5.3 (1H, s, H-12). ^{13}C NMR ($CDCl_3$): δ 12.9 (d, J = 9.4 Hz, C-16), 19.9 (C-15), 21.9 (C-8), 24.6 (C-5), 25.5 (C-14), 28.5 (d, J = 3.9 Hz, C-9), 33.6 (C-7), 35.8 (C-4), 37.1 (C-6), 46.2 (C-8a), 51.3 (C-5a), 80.7 (C-12a), 93.6 (C-12), 104.4 (C-3), 114.5 (dd, J = 35 and 14 Hz, C-10), 154.9 (dd, J = 286 and 282 Hz, CF_2). ^{19}F NMR ($CDCl_3$): δ −117.0 (dm, J = 80 Hz, 1F, CF_2), −98.9 (dm, J = 80 Hz, 1F, CF_2). Anal. Calcd. for $C_{16}H_{22}F_2O_4$: C, 60.7; H, 7.0. Found: C, 60.1; H, 7.1. α_D = +81 (c = 0.84, MeOH).

5.4. 10,10-Difluoromethylene-deoxoartemisitene (**9**)

Yield 73%, a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.97 (3H, d, J = 5.8 Hz, H-15), 1.41 (3H, s, H-14), 0.80–2.09 (10H, m), 2.33 (1H, m, H-4), 5.18 (1H, dm, J = 2.2 Hz, H-16), 5.26 (1H, dm, J = 2.2 Hz, H-16), 5.57 (1H, d, J = 1.1 Hz, H-12). ^{13}C NMR ($CDCl_3$): δ 19.8 (C-15), 24.6 (C-5), 25.5 (C-14), 30.9 (C-8), 33.8 (C-7), 35.9 (C-4), 37.5 (C-6), 48.1 (C-8a), 50.7 (C-5a), 80.2 (C-12a), 92.3 (dd, J = 2.9 and 1.2 Hz, C-12), 104.0 (C-3), 114.5 (dd, J = 10.6 and 3.1 Hz, C-9), 135.4 (d, J = 6.3 Hz, C-16), 153.9 (dd, J = 291 and 284 Hz, CF_2), C-10 not observed. ^{19}F NMR ($CDCl_3$): δ −110.1 (d, J = 58 Hz, 1F, CF_2), −99.6 (dd, J = 58 and 2.6 Hz, 1F, CF_2). Anal. Calcd. for $C_{16}H_{20}F_2O_4$: C, 61.1; H, 6.4. Found: C, 60.4; H, 6.9.

5.5. 2,3,4,6-Tetrakis-O-benzyl-1-trifluoromethyl-D-glucopyranose (**11**)

CF_3TMS (1.2 mmol, 170 mg) and TBAF (0.1 mmol, 20 mg) were successively added at 0 °C to a solution of lactone 10 (1.0 mmol, 548 mg) in THF (7 mL). When the reaction was finished (TLC), the mixture was quenched with aqueous NaCl (10 mL), extracted with AcOEt (5 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude was then purified on silica gel (80/20 cyclohexane/AcOEt) to afford the trifluoromethylated sugar (**11**) (72%, 444 mg).

Colorless oil. ^{1}H NMR ($CDCl_3$): δ 3.68–4.12 (7H, m), 4.42–5.00 (8H, m), 7.17–7.54 (20H, m, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 68.0 (CH_2), 72.8 (CH), 73.4 (CH_2), 75.0 (CH_2), 75.9 (CH_2), 76.2 (CH_2), 77.4 (CH), 78.6 (CH), 83.4 (CH), 94.4 (q, J = 31 Hz, $\underline{C}$-CF_3), 122.6 (q, J = 288 Hz, CF_3), 127.7–128.5 (C_{Ar}), 138.1 (C_{Ar}), 138.2 (C_{Ar}), 138.4 (C_{Ar}). ^{19}F NMR ($CDCl_3$): δ −83.4 (s, 3F, CF_3).

5.6. 2,3,4,6-Tetrakis-O-benzyl-1-bromo-1-deoxy-1-trifluoromethyl-D-glucopyranose (**12**)

Thionyl bromide (1.5 mmol, 310 mg) and pyridine (1.5 mmol, 79 mg) were successively added at 0 °C to a solution of compound **11** (1.0 mmol, 618 mg) in CH_2Cl_2 (10 mL). When the reaction was finished (TLC), the mixture was quenched with aqueous $NaHCO_3$ (10 mL), extracted with AcOEt (5 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude was then purified on silica gel (90/10 cyclohexane/AcOEt) to afford the corresponding trifluoromethylated bromide (**12**) (92%, 626 mg).

Yield 92%, a yellow oil. ^{1}H NMR ($CDCl_3$): δ 3.76–3.84 (2H, m), 3.95 (1H, dd, J = 7.6 and 4.6 Hz), 4.35 (1H, d, J = 4.3 Hz H-2), 4.43 (1H, dd, J = 10.5 and 4.3 Hz), 4.52–4.91 (9H, m), 7.22–7.44 (20H, m, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 67.8 (CH_2), 73.39 (CH_2), 73.40 (CH_2), 74.2 (CH_2), 74.6 (CH_2), 75.4 (CH), 77.7 (CH), 83.1 (CH), 83.3 (CH), 92.1 (q, J = 32 Hz, $\underline{C}$-CF_3), 121.9 (q, J = 286 Hz, CF_3), 127.5–128.5 (C_{Ar}), 136.8 (C_{Ar}), 137.7 (C_{Ar}), 137.8 (C_{Ar}), 138.0 (C_{Ar}). ^{19}F NMR ($CDCl_3$): δ −71.9 (s, 3F, CF_3).

5.7. 2,6-Anhydro-1-deoxy-1,1-difluoro-3,4,5,7-tetrakis-O-benzyl-D-gluco-hept-1-enitol (**13**)

Reaction of bromide **12** (184 mg, 0.3 mmol) with methyllithium (5.1 equiv., 1.6N) at −40 °C gave compound **13** as a colorless oil (142 mg, 91%) after purification on silica gel. Spectral data of this compound are the same than those reported in the literature [10b].

^{13}C NMR ($CDCl_3$): δ 68.7 (CH_2), 71.0 (CH_2), 72.8 (CH_2), 73.0 (t, J = 2.7 Hz, CH), 73.4 (CH_2), 73.6 (CH_2), 76.8 (CH), 77.1 (CH), 82.3 (CH), 112.3 (dd, J = 39 and 13 Hz, $\underline{C}$=CF_2), 127.5–128.5 (C_{Ar}), 137.4 (C_{Ar}), 137.7 (C_{Ar}), 137.9 (C_{Ar}), 138.1 (C_{Ar}), 153.6 (dd, J = 290 and 278 Hz, CF_2). ^{19}F NMR ($CDCl_3$): δ −116.8 (dd, J = 74 and 3.3 Hz, 1F, CF_2), −99.9 (dd, J = 74 and 1.1 Hz, 1F, CF_2).

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References

[1] D.L. Klayman, Science 228 (1985) 1049–1055.
[2] J.-P. Bégué, D. Bonnet-Delpon, Drugs Future 30 (2005) 509–518, and references cited therein.
[3] (a) A. Abouabdellah, J.P. Bégué, D. Bonnet-Delpon, J.C. Gantier, N. Truong Thi Thanh, T. Truong Dinh, Bioorg. Biomed. Chem. Lett. 6 (1996) 2717–2720;
(b) T.T. Nga, C. Ménage, J.P. Bégué, D. Bonnet-Delpon, J.C. Gantier, B. Pradines, J.C. Doury, T.D. Thac, J. Med. Chem. 21 (1998) 4101–4108;

(c) P.D. Binh, L.D. Cong, D.H. Nhan, T.V. Nhu, N.T. Tien, J.P. Bégué, D. Bonnet-Delpon, T.T.T. Nga, Trans. Roy. Soc. Trop. Med. Hyg. 96 (2002) 677–683.

[4] (a) G. Magueur, B. Crousse, S. Charneau, P. Grellier, J.P. Bégué, D. Bonnet-Delpon, J. Med. Chem. 47 (2004) 2694–2699;
(b) G. Magueur, B. Crousse, M. Ourévitch, J.P. Bégué, D. Bonnet-Delpon, J. Org. Chem. 68 (2003) 9763–9766.

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

[6] F. Chorki, F. Grellepois, B. Crousse, M. Ourévitch, J.P. Bégué, D. Bonnet-Delpon, J. Org. Chem. 66 (2001) 7858–7863.

[7] (a) Biomedical Frontiers of Fluorine Chemistry, I. Ojima, J.R. McCarthy, J.T. Welch (Eds.), ACS Symposium Series 639, American Chemical Society, Washington, DC, 1996;
(b) J.P. Bégué, D. Bonnet-Delpon, Chimie Bioorganique et Médicinale du Fluor, Interéditions/CNRS, Paris, 2005.

[8] (a) X.-H. Huang, P.-Y. He, G.-Q. Shi, J. Org. Chem. 65 (2000) 627–629;
(b) S. Hayashi, T. Nakai, N. Ishikawa, D.J. Burton, D.G. Naae, H.S. Kesling, Chem. Lett. (1979) 983–986.

[9] (a) W.B. Motherwell, M.J. Tozer, B.C. Ross, J. Chem. Soc., Chem. Commun. (1989) 1437–1439;
(b) T.F. Herpin, W.B. Motherwell, M.J. Tozer, Tetrahedron Asymm. 5 (1994) 2269–2282;
(c) T.M. Herpin, J.S. Houlton, W.B. Motherwell, B.P. Roberts, J.M. Weibel, Chem. Commun. (1996) 613–614.

[10] (a) D.J. Burton, Z.Y. Yang, W. Qiu, Chem. Rev. 96 (1996) 1641–1715;
(b) J.S. Houlton, W.B. Motherwell, B.C. Ross, M.J. Tozer, D.J. Williams, A.M.Z. Slawin, Tetrahedron 49 (1993) 8087–8106;
(c) C. Taillefumier, Y. Chapleur, Chem. Rev. 104 (2004) 263–292.

[11] (a) K. Tanaka, T. Nakai, N. Ishikawa, Tetrahedron Lett. 48 (1978) 4809–4810;
(b) S.T. Patel, J.M. Percy, R.D. Wilkes, Tetrahedron 51 (1995) 9201–9216;
(c) G.Q. Shi, W.L. Cai, Synlett (1996) 371–372.

[12] (a) H. Gilman, R.G. Jones, J. Am. Chem. Soc. 65 (1943) 2037–2038;
(b) B.W. Metcalf, E.T. Jarvi, J.P. Burkhart, Tetrahedron Lett. 26 (1985) 2861–2864;
(c) T. Okano, K. Ito, T. Ueda, H. Muramatsu, J. Fluor. Chem. 32 (1986) 377–388;
(d) G.Q. Shi, W.L. Cai, J. Org. Chem. 60 (1995) 6289–6295.

[13] While the commercially Et_2O solution of MeLi is claimed to be free of LiBr, the presence of lithium salts cannot be excluded to explain this different reactivity.

[14] G.K.S. Prakash, A.K. Yudin, Chem. Rev. 97 (1997) 757–786.

[15] (a) C. Leriche, X. He, C.-W.T. Chang, H.-W. Liu, J. Am. Chem. Soc. 125 (2003) 6348–6349;
(b) Z. Zhao, H.-W. Liu, J. Org. Chem. 66 (2001) 6810–6815.

[16] (a) U. Eckstein-Ludwig, R.J. Webb, I.D.A. van Goethem, J.M. East, A.G. Lee, P.M.O. Neill, P.G. Bray, S.A. Ward, S. Krishna, Nature 424 (2003) 957–961;
(b) R.K. Haynes, S. Krishna, Microbes Infect. 6 (2004) 1339–1346.

[17] W. Peters, Techniques of drug evaluation. I. Primary screening, in: W. Peters (Ed.), Chemotherapy and Drug Resistance in Malaria, vol. 1, Academic Press, London, 1987, pp. 100–123.

[18] W. Trager, J.B. Jensen, Science 193 (1976) 673–677.

[19] R.E. Desjardins, C.J. Canfield, J.D. Haynes, D.J. Chulay, Antimicrob. Agents Chemother. 16 (1979) 710–718.