European Journal of Medicinal Chemistry 45 (2010) 3213–3218

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Short communication

Synthesis and cytotoxic activity of fluorinated analogues of *Goniothalamus* lactones. Impact of fluorine on oxidative processes

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ARTICLE INFO

Article history:
Received 8 January 2010
Received in revised form
18 March 2010
Accepted 20 March 2010
Available online 25 March 2010

Keywords:
Styryl-lactones
Metabolism
Fluorine
Antitumor

ABSTRACT

Novel fluorinated analogues of goniothalamin **1** and howiinol A **2** have been prepared from trifluorocrotonate derivatives. Trifluoromethyl goniothalamin (*R*/*S*) **4** showed a slightly lower activity than **1**, while the trifluoromethyl howiinol A **16** exhibited similar activities on several cell lines in the micromolar range. Unlike (*R*) goniothalamin and howiinol A, trifluoromethyl parent compounds remained unchanged when submitted to biomimetic oxidative systems.

1. Introduction

Naturally occurring styryl-lactones represent a homogeneous group of secondary metabolites isolated from *Goniothalamus*. The first member of this class, the styryl-pyrone goniothalamin **1** can be considered as a biogenetic precursor of other structurally related lactones in particular goniodiol, goniotriol, howiinol A **2** (Fig. 1) [1].

(*R*)-(+)-goniothalamin **1** was isolated for the first time in 1967 [2]. It has shown a wide range of biological activities such as antimicrobial [3], larvicidal [4–6], anti-inflammatory [7,8], and also significant antifungal activities [4–6]. Moreover, goniothalamin exhibited antiproliferative activity against various cancer cell lines: mouse leukemia (P-388; IC_{50} = 3.8 μM) [9], mouse fibro sarcoma (WEHI164; IC_{50} = 8.5 μM) [9], human hepatoma (Hep3B; IC_{50} = 5.4 μM) [10], human hepatocellular carcinoma (HepG2; IC_{50} = 1.6 μM) [10], human breast carcinoma (MCF-7, IC_{50} = 4.5 μM) [10], and estrogen receptor breast cancer (MDA-MB-231, IC_{50} = 5.4 μM) [9]. Recently it has been reported that (*S*)-goniothalamin **1** was also potent against some cancer cells [11].

Although the mechanism of action is not yet elucidated, goniothalamin has been reported to generate the apoptosis process *via* the mitochondrial respiratory chain but also *via* successive activation of caspases [12,13].

The *in vitro* cytotoxicity of the natural (*R*)-goniothalamin **1** has been further confirmed *in vivo* on mice but only in few reports [14]. However, side effects like genotoxicity [15] and embryotoxicity [16] have also been reported. While numerous syntheses of goniothalamin and related lactones have been described [17–24], structure/activity relationship has been much less investigated. It nevertheless appears that the lactone moiety is essential for the activity. The side chain interacts with a hydrophobic domain of the target but the styryl moiety is not always required since the replacement of the phenyl group by a cyclohexyl one also resulted in a good antitumor activity [13]. Although it is difficult, in a general way, to differentiate the antitumor activity from the toxicity, it seems likely that side effects could be imparted to the facile *in vivo* oxidation of the exocyclic double bond into epoxides. The goniothalamin epoxide **3** has been postulated as the biogenetic precursor of other styryl-lactone derivatives [12,25]. Furthermore, it has been isolated, in a non negligible amount, from *Goniothalamus macrophyllus*, a plant traditionally used for its abortive properties [16]. With the aim to limit the oxidative metabolism of the reactive exocyclic double bond, we envisaged to replace the phenyl group in goniothalamin by an appropriate substituent.

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doi:10.1016/j.ejmech.2010.03.032

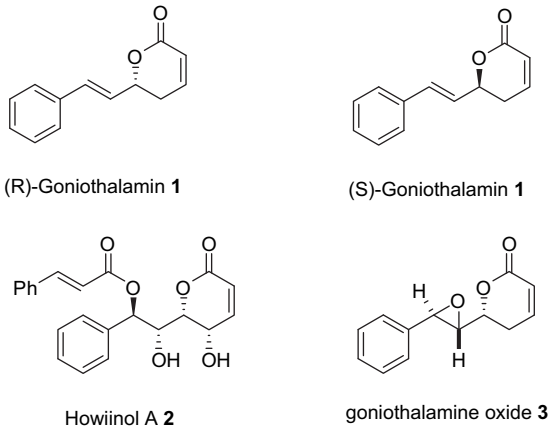


Fig. 1. Structure of styryl-lactones.

The incorporation of fluorine into molecules has become a good tool in medicinal chemistry for improving the pharmacological profile of bioactive compounds, in particular for increasing the metabolic stability [26–31]. Indeed the presence of fluoroalkyl groups slows down the oxidative and hydrolytic processes, therefore avoiding the formation of toxic secondary metabolites. In addition, fluoroalkyl groups, at the same time highly hydrophobic, and sterically demanding, are able to mimic phenyl or benzyl groups with beneficial effects [32,33]. To our knowledge, only one fluorinated analogue of goniothalamin has been reported, where a *gem* difluoro was introduced onto the cyclic lactone part, but no information about its activity was given [34].

Here we report the impact of the replacement of a phenyl group by a trifluoromethyl substituent in two natural styryl-lactone derivatives, goniothalamin and howiinol A.

2. Results and discussion

In the literature cyclic lactones are prepared through two principal ways, intramolecular lactonisation or ring closing metathesis (RCM). This latter was chosen for the synthesis of the (*R*/*S*)-CF_3-goniothalamin **4**, starting from the commercially available ethyl trifluoroacetyl acetate **5** (Scheme 1).

After reduction of **5** [35] and protection of the alcohol with TBDMSCl, the ester **6** was reduced into the aldehyde **7**. This latter reacted under Barbier conditions to afford the allylic alcohol **8** as a 60/40 mixture of diastereomers, which further reacted with acryloyl chloride to provide the di-unsaturated compound **9**. The RCM reaction was performed using the Grubb's second-generation catalyst, and a further deprotection of the alcohol with fluoride anion led to the cyclic lactone **10**. The dehydration of trifluoromethyl alcohols is often difficult and usually requires harsh conditions (P_2O_5 or MsCl/strong base). Under these conditions a complex mixture of products was obtained from the alcohol **10** probably due to the presence of reactive functions.

An alternative route to **4** was to start from the ethyl trifluorocrotonate **11**, previously described by dehydration with P_2O_5 [35]. Then the CF_3-goniothalamin **4** was prepared as outlined in Scheme 2. The only difference with the previous sequence is the generation of the aldehyde **13** for which a two step oxidation/reduction reaction has been proved to be more efficient.

Due to the volatility of the aldehyde **13**, the allylation reaction under Barbier conditions was directly achieved from the crude product. The CF_3-goniothalamin **4** was obtained successfully by ring closing metathesis with 10 mol% of Grubb's II catalyst in refluxing dichloromethane for 16 h.

3. Biological results

Cytotoxicity activities of the (*R*/*S*)-CF_3-goniothalamin **4** were evaluated against the following cancer cell lines: KB (human oral epidermoid carcinoma), MCF-7, HT29 (human colon cancer cells), HepG2, A549 (human lung carcinoma) (Table 1).

Assays performed at 0.1, 1 and 10 μM with CF_3-goniothalamin **4** showed an $IC_{50} > 10$ μM. We next studied the inhibition of the considered cancer cell lines at 50 μM, and percentage ranged from 73% to 97%. These values let suppose an IC_{50} between 10 and 50 μM.

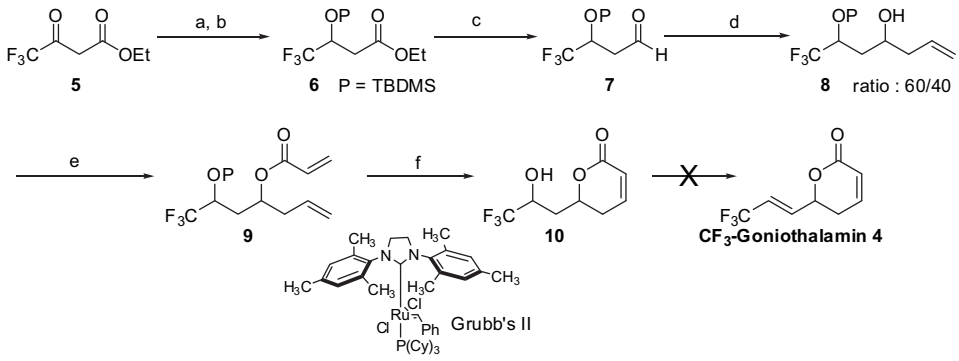
For comparison we also prepared and evaluated the CF_3-analogue **16** of howiinol A **2**, where the CF_3 group also replaces a phenyl in a styryl chain. Howiinol A **2** is described as a potent *in vitro* inhibitor of a variety of cancer cells, with IC_{50} ranging from 1 to 5 μg/mL (around 3–15 μM) [36,37]. To our knowledge its *in vivo* activity is poorly reported with no mention on its toxicity [38].

The CF_3-howiinol **16** was synthesized as shown in Scheme 3. The intermediate **17** was previously described from D-*glycero*-D-*gulo*-heptano-γ-lactone for the synthesis of howiinol A **2** [39]. CF_3-howiinol **16** was obtained from **17** by esterification with trifluorocrotonic acid followed by a deprotection in acidic medium.

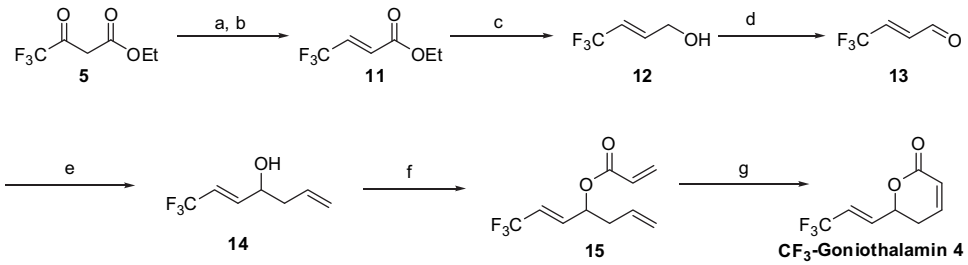
This compound was evaluated against the same cancer cell lines as for goniothalamin derivatives (Table 2).

Interestingly, the CF_3-howiinol **16** exhibited cytotoxicity against all cancer cell lines in the same range than that of the natural compound **2**.

For a preliminary evaluation of the compared metabolic stability of natural compounds **1** and **2**, and their CF_3-analogues **4** and **16**,



Scheme 1. Reagents and conditions: (a) $NaBH_4$, (0.3 eq) Et_2O, 0 °C to rt; (b) TBDMSCl (1.2 eq), imidazole (2.5 eq), 0 °C to rt 75% (2 steps); (c) DIBAL-H (1.5 eq), toluene, −78 °C to rt, 94%; (d) allyl bromide (1.2 eq), Zn (1.3 eq)/TMSCl cat, DMF, rt, 94%; (e) acryloyl chloride (2 eq), DMAP cat., TEA, DCM, −78 °C to rt, 60%; (f) 1) Grubb's II 10 mol%, DCM, reflux, 2) TBAF (2.5 eq), THF, 70%.



Scheme 2. Reagents and conditions: (a) $NaBH_4$, (0.3 eq) Et_2O, 0 °C to rt; (b) P_2O_5 (2.0 eq) 66% (2 steps); (c) $LiAlH_4$ (1.5 eq)/$AlCl_3$ (1.5 eq), Et_2O, 82%; (d) PCC (1.0 eq), DCM; (e) allyl bromide (1.2 eq), Zn (1.3 eq)/TMSCl cat., DMF, rt, 60% (2 steps); (f) acryloyl chloride (2 eq), DMAP cat., TEA, DCM, −78 °C to rt, 6 h, 60%; (g) Grubb's II 10 mol%, DCM, reflux, 16 h, 70%.

these compounds have been submitted to biomimetic oxidation systems. Experiments were performed with H_2O_2/imidazole or mCPBA as oxidants, by using three metalloporphyrin catalytic systems, developed for mimicking the activity of cytochromes P450 [40,41]. Among them, one allowed a complete disappearance of goniothalamin **1** after 24 h, and GC/MS analyses showed the generation of three main oxidized products (M + 16) obtained in similar proportions. Two of them are the epoxide **3** and its diastereomer, as determined by comparison with authentic samples prepared according to literature [16]. In MS spectra they exhibit the same important transannular fragments of aryl epoxides (m/z = 216, 105, 97, 91, 82, 69). The third one is obviously oxidized at a different site but its structure could not be unambiguously determined. Under the same conditions, the CF_3-goniothalamin **4** was completely recovered unchanged. As postulated, CF_3-goniothalamin epoxides, analogues of **3**, were not formed, but surprisingly, the replacement of the phenyl group of the side chain by a CF_3 group seems to protect other sites from oxidation.

Submitted to the same oxidative systems, howiinol A **2** was proved to be much more resistant with a 15% conversion into oxidized products (M + 16) after 24 h. No oxidation at all was observed with CF_3-howiinol **16**.

4. Conclusion

The replacement of a phenyl group by a trifluoromethyl group in goniothalamin and howiinol A resulted in a slightly lower or similar cytotoxicity against various cancer cell lines. In contrast a great impact of the CF_3 substituent was exhibited in a biomimetic oxidative metabolism experiment. All sites of molecules were protected from oxidation. *In vivo* assays are currently under investigation in order to confirm the beneficial impact of the fluoroalkyl substituent.

5. Experimental section

5.1. Chemistry

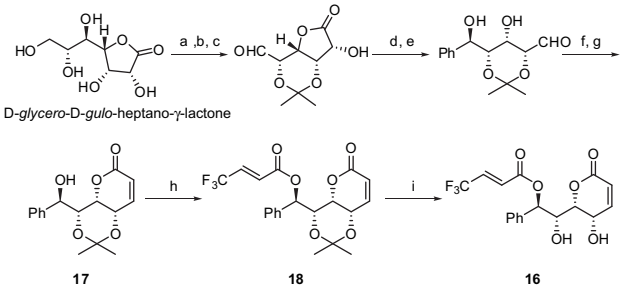
General chemical techniques: usual solvents were purchased from commercial sources and dried and distilled by standard procedures. Pure products were obtained after flash chromatography using Merck silica gel 60 (40–63 μm). TLC analyses were performed with 0.25 mm 60 F254 silica plates (Merck). Element analyses (C, H, N) were performed on a Perkin–Elmer CHN, Analyser 2400. IR spectra were recorded on a Bruker Vector 22 FT-IR spectrometer. Melting points were determined on a Kofler melting point apparatus. NMR spectra were recorded on a Bruker AMX 200, (^{1}H, 200 MHz, ^{19}F: 188 MHz ^{13}C, 50 MHz). Chemical shift δ are in ppm and the following abbreviations are used: singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet (m), broad singlet (brs).

5.1.1. Ethyl 3-(tert-butyldimethylsilyloxy)-4,4,4-trifluorobutanoate (**6**)

To a solution of ethyl 4,4,4-trifluoro-3-hydroxybutanoate (5.0 g, 26.8 mmol) in dry dimethylformamide (10 mL), at 0 °C, imidazole (4.6 g, 67.0 mmol) was added followed by *tert*-butyldimethylsilyl chloride (4.9 g, 32.2 mmol). Then, the reaction mixture was warmed to room temperature and stirred for 28 h. Dichloromethane (50 mL) was added, and the resulting mixture was successively washed with an aqueous hydrochloric acid solution (0.1 M, 10 mL), a saturated aqueous solution of $NaHCO_3$ (15 mL), and with brine (10 mL). The organic layer was dried over anhydrous $MgSO_4$. Filtration and removal of the solvent provided the product **6** (7.0 g, 87%) as an yellow oil which can be used without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.08 (s, 3H); 0.13 (s, 3H); 0.87 (s, 9H); 1.27 (t, J = 7.2 Hz, 3H); 2.58 (dd, J = 15.9, 7.9 Hz, 1H); 2.68 (dd, J = 15.9, 4.3 Hz, 1H); 4.16 (q, J = 7.2 Hz, 2H); 4.51 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −3.2; −3.1; 13.8; 17.7; 25.2; 36.9; 60.8; 68.3 (q, J = 31.7 Hz, **C**HCF$_3$); 124.4 (q, J = 282.2 Hz, **C**F$_3$); 169.5. ^{19}F NMR (188 MHz, $CDCl_3$): δ −79.6 (d, J = 6.9 Hz, CF_3). IR (cm^{-1}): 2941; 1710.

5.1.2. 3-(tert-Butyldimethylsilyloxy)-4,4,4-trifluorobutanal (**7**)

Diisobutylaluminium hydride (35.0 mL, 1.0 M in hexane, 35.0 mmol) was added drop by drop for 1h at −78 °C to a solution of



Scheme 3. (a) $ZnCl_2$, H_3PO_4, acetone, rt, 24 h, 87%; (b) CH_3COOH, H_2O, rt, 48 h, 70%; (c) $NaIO_4$, MeOH, H_2O, rt, 30 min; (d) PhMgBr, THF, 0 °C, 2 h, 56%; (e) $NaIO_4$, MeOH, H_2O, rt, 30 min; (f) Ph_3P = CHCOOMe, MeOH, t.a., 2 h, 79%; (g) DBU cat., THF, reflux, 70%; (h) trifluorocrotonic acid, EDC/DMAP cat., DCM, 0 °C to rt, 94%; (i) CH_3COOH aq. 50%, 80 °C, 60%.

Table 1
IC_{50} (μM) of (*R*/*S*) goniothalamin **1**, (*R*/*S*)-CF_3-goniothalamin **4**, against cancer cell lines. IC_{50} means the concentration that elicits cell growth inhibition by 50%.

Compounds	KB	MCF-7	HT29	HepG2	A549
1[a]	3.0	3.5	10.1	2.4	9.1
4[b]	>10	>10	>10	>10	>10

[a] *R*/*S* goniothalamin has been prepared according to ref. [18,19].
[b] % inhibition at 50 μM was found to be around 90%.

Table 2
IC_{50} (μM) of howiinol A **2** and CF_3-howiinol **16** against cancer cell lines.

Compounds	KB	MCF-7	HT29	HepG2	A549
2[a]	0.9	1.1	2.6	1.6	1.5
16	1.4	1.6	4.5	1.8	3.0

[a] Howiinol A **2** was prepared according to ref. [39].

ester **6** (7.0 g, 23.3 mmol) in dry toluene (10 mL). After stirring for 2 h under an inert atmosphere, the reaction was carefully quenched at −78 °C with methanol (40 mL). Citric acid (10% aqueous solution, 30 mL) was then added, and the mixture was allowed to warm to room temperature for 30 min. The resulting residue was removed by filtration, and the aqueous phase was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduce pressure to give the crude aldehyde **7** (5.6 g, 94%) as an yellow oil, which was used on the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.19 (s, 3H); 0.24 (s, 3H); 0.96 (s, 9H); 2.80 (ddd, J = 17.5, 3.8, 0.9 Hz, 1H); 2.90 (ddd, J = 17.5, 10.0, 1.7 Hz, 1H); 4.65 (dqd, J = 10.4, 6.6, 3.8 Hz, 1H); 9.86 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −3.1; −3.0; 18.0; 25.5; 45.3; 66.8 (q, J = 32.5 Hz, **C**HCF$_3$); 124.7 (q, J = 282.2 Hz, **C**F$_3$); 197.7. ^{19}F NMR (188 MHz, $CDCl_3$): δ −79.4 (d, J = 6.2 Hz, CF_3). IR (cm^{-1}): 2933; 1720.

5.1.3. 6-(tert-Butyldimethylsilyloxy)-7,7,7-trifluorohept-1-en-4-ol (*8*)

To a solution of **7** (2.0 g, 7.9 mmol) in anhydrous dimethylformamide (6 mL) were added allyl bromide (1.1 g, 9.4 mmol), granular zinc (670.0 mg, 10.2 mmol) and two drops of TMSCl. After being stirred at room temperature for 3 h, the reaction mixture was quenched with a saturated solution of NH_4Cl (15 mL) and extracted with ethyl acetate (3 × 15 mL). The organic layers were washed with brine (15 mL), dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel (cyclohexane/EtOAc : 80/20) to afford **8** (2.2 g, 94%) as a yellow oil (mixture of two diastereoisomers : 60/40). Major diastereoisomer ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.125 (s, 3H); 0.133 (s, 3H); 0.905 (s, 9H); 1.72 (m, 2H); 2.27 (m, 2H); 3.84 (m, 1H); 4.23 (m, 1H); 5.12 (m, 1H); 5.19 (m, 1H); 5.83 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −3.3; −3.1; 18.1; 25.6; 37.4; 42.5; 65.5; 68.3 (q, J = 30.9 Hz, **C**HCF$_3$); 118.8; 125.3 (q, J = 282.3 Hz, **C**F$_3$); 134.0. ^{19}F (188 MHz, $CDCl_3$): δ −78.9 (d, J = 6.9 Hz, CF_3). Minor diastereoisomer ^{13}C NMR (75 MHz, $CDCl_3$) − δ −3.2; −3.0; 18.0; 25.5; 38.2; 41.9; 67.5; 69.4 (q, J = 30.9 Hz, **C**HCF$_3$); 118.6; 125.2 (q, J = 282.3 Hz, **C**F$_3$); 134.0. ^{19}F NMR (188 MHz, $CDCl_3$) − δ −78.6 (d, J = 6.2 Hz, CF_3). IR (cm^{-1}): 3650; 2982; 1952.

5.1.4. 6-(tert-Butyldimethylsilyloxy)-7,7,7-trifluorohept-1-en-4-yl acrylate (*9*)

Triethylamine (1.5 g, 15.0 mmol) and a catalytic amount of DMAP (18.0 mg, 0.2 mmol, 3 mol%) were added to a solution of **8** (1.5 g, 5.0 mmol) in anhydrous dichloromethane (10 mL) at −78 °C under an inert atmosphere. Acryloyl chloride (mL, 10.0 mmol) was then added drop by drop for 10 min. After being stirred for 6 h, the mixture was hydrolyzed by a saturated aqueous solution of $NaHCO_3$ (15 mL), and extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduce pressure. The crude product was purified with chromatography on silica gel (cyclohexane/CH_2Cl_2: 80/20) to afford **9** (1.1 g, 60%) as a yellow oil (mixture of two diastereoisomers : 60/40). Major diastereoisomer ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 3H); 0.07 (s, 3H); 0.90 (s, 9H); 1.92 (m, 2H); 2.4 (ddd, J = 7.2, 2.6, 1.1 Hz, 1H); 2.46 (ddd, J = 7.2, 2.9, 1.1 Hz, 1H); 4.0 (m, 1H); 5.07 (m, 1H); 5.14 (m, 2H); 5.71 (m, 1H); 5.82 (dd, J = 12.0, 2.6 Hz, 1H); 6.08 (dd, J = 17.2, 5.3 Hz, 1H); 6.36 (dd, J = 17.3, 1.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.1; −5.0; 18.1; 25.6; 35.2; 38.8; 68.0 (q, J = 31.3 Hz, **C**HCF$_3$); 69.7; 118.6; 129.7 (q, J = 282.3 Hz, **C**F$_3$); 128.4; 131.0; 132.4; 165.5. ^{19}F NMR (188 MHz, $CDCl_3$): δ −79.0 (d, J = 6.9 Hz, CF_3). IR (cm^{-1}): 2980; 1722; 1637; 1188; 1043. Minor diastereoisomer ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.103 (s, 3H); 0.115 (s, 3H); 0.91 (s, 9H); 1.92 (m, 2H); 2.36 (m, 2H); 4.01 (m, 1H); 4.0 (m, 1H); 5.07 (m, 1H); 5.14 (m, 2H); 5.71 (m, 1H); 5.81 (dd, J = 8.6, 2.5 Hz, 1H); 6.13 (dd, J = 17.3, 5.3 Hz, 1H); 6.45 (dd, J = 17.3, 1.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.1; −5.0; 18.0; 25.5; 35.9; 38.4; 68.4 (q, J = 31.3 Hz, **C**HCF$_3$); 69.6; 118.5; 129.6 (q, J = 282.3 Hz, **C**F$_3$); 128.5; 130.9; 132.5; 165.3. ^{19}F NMR (188 MHz, $CDCl_3$): −78.7 (d, J = 6.2 Hz, CF_3). IR (cm^{-1}): 2980; 1722; 1637; 1188; 1043.

5.1.5. 6-(3,3,3-Trifluoro-2-hydroxypropyl)-5,6-dihydro-2H-pyran-2-one (*10*)

Grubb's II catalyst (99.3 mg, 0.1 mmol, 10 mol%) was added to a solution of **9** (820.0 mg, 2.3 mmol) in dry dichloromethane (6 mL). The reaction was heated 16 h under reflux. The reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The crude product was purified with column chromatography (cyclohexane/EtOAc: 80/20) to afford the corresponding lactone (521.5 mg, 70%) as a pale yellow oil (mixture of two diastereoisomers : 60/40). Major diastereoisomer ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.13 (s, 3H); 0.14 (s, 3H); 0.90 (s, 9H); 2.12 (m, 2H); 2.35 (m, 1H); 2.41 (m, 2H); 4.60 (m, 1H); 6.06 (br dt, J = 9.6, 1.9 Hz, 1H); 6.87 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.2; −5.0; 18.1; 25.6; 29.7; 36.0; 66.8 (q, J = 30.9 Hz, **C**HCF$_3$); 72.6; 121.4; 124.9 (q, J = 282.2 Hz, **C**F$_3$); 145.1; 163.4. ^{19}F NMR (188 MHz, $CDCl_3$): δ −78.28 (d, J = 6.2 Hz, CF_3). Minor diastereoisomer ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.11 (s, 3H); 0.15 (s, 3H); 0.89 (s, 9H); 1.85 (ddd, J = 14.1, 10.7, 2.5 Hz, 1H); 2.08 (m, 1H); 2.38 (m, 2H); 4.39 (m, 1H); 4.60 (m, 1H); 6.05 (br td, J = 9.7, 1.8 Hz, 1H); 6.91 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.1; −4.9; 18.3; 25.7; 29.8; 36.2; 66.9 (q, J = 30.9 Hz, **C**HCF$_3$); 72.5; 121.1; 125.2 (q, J = 282.2 Hz, **C**F$_3$); 145.4; 163.6. ^{19}F NMR (188 MHz, $CDCl_3$): δ −79.237 (d, J = 6.2 Hz, CF_3). IR (cm^{-1}): 2932; 1722; 1264; 1135.

To a solution of lactone (*6-(2-(tert-butyldimethylsilyloxy)-3,3,3-trifluoropropyl)-5,6-dihydro-2H-pyran-2-one)* (260.0 mg, 0.8 mmol) in dry tetrahydrofuran (4 mL), *tert*-butylammonium fluoride (0.6 mL, 1.0 M in THF, 2.0 mmol) was added at room temperature. The reaction mixture was stirred for 24 h, then hydrolyzed with a saturated aqueous solution of $NaHCO_3$ (10 mL), and extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduce pressure. The crude product was purified by chromatography on silica gel (cyclohexane/EtOAc: 30/70) to give **10** (129.4 mg, 77%) as a colorless oil. Major diastereoisomer ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.88 (ddd, J = 14.0, 8.4, 2.4 Hz, 1H); 2.06 (ddd, J = 13.9, 10.6, 2.4 Hz, 1H); 2.38 (ddd, J = 7.2, 3.3, 2.2 Hz, 1H); 2.41 (ddd, J = 7.2, 4.4, 1.8 Hz, 1H); 4.43 (m, 2H); 4.76 (dqd, J = 10.3, 8.3, 2.5, 1H); 6.00 (br dt, J = 9.8, 1.8 Hz, 1H); 6.92 (ddd, J = 9.8, 4.5, 3.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.6; 34.7; 66.1 (q, J = 31.7 Hz **C**HCF$_3$); 73.2; 121.3; 125.1 (q, J = 283.0 Hz, **C**F$_3$); 145.4; 164.1. ^{19}F NMR (188 MHz, $CDCl_3$): δ −80.7 (d, J = 6.2 Hz, CF_3). IR (cm^{-1}): 3651; 2948; 1716; 1266; 1132. Anal. for $C_8H_9F_3O_3$: calcd. C, 45.72; H, 4.32; found C, 45.47; H, 4.33.

5.1.6. 4,4,4-Trifluoro-but-2-enoic acid ethyl ester (*11*)

To a suspension of $NaBH_4$ (1.23 g, 32.6 mmol) in anhydrous diethyl ether (10 mL) at 0 °C under an inert atmosphere was slowly added a solution of 4,4,4-trifluoro-3-oxo-butyric acid ethyl ester **5**

(20.0 g, 108 mmol) in anhydrous diethyl ether (10 mL). The mixture was stirred at 0 °C for 5 h. Then, a 1 M aqueous hydrochloric acid solution (15 mL) was carefully added to the media, stirred for 30 min, and the resulting residue was removed by filtration. The aqueous layer was extracted with diethyl ether (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduce pressure to give crude ethyl 4,4,4-trifluoro-3-hydroxybutanoate (17.5 g, 87%) as an yellow oil, which was used on the next step without purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 3H); 2.68 (d, J = 4Hz, 2H); 3.72 (brs, 1H); 4.20 (q, J = 7.2 Hz, 2H); 4.43 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8; 34.9; 61.5; 67.0 (q, J = 32.5 Hz, **C**HCF$_3$); 124.5 (q, J = 280.7 Hz, **C**F$_3$); 170.8. ^{19}F NMR (188 MHz, $CDCl_3$): δ −80.3 (d, J = 6.2 Hz, CF_3).

Phosphorus pentoxide (15.3 g, 107.5 mmol) was added to the crude ethyl 4,4,4-trifluoro-3-hydroxybutanoate (10.0 g, 53.7 mmol) and the mixture was distillated to afford **11** (6.8 g, 76%) as an yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, J = 7.2 Hz, 3H); 4.27 (q, J = 7.2 Hz, 2H); 6.48 (dq, J = 15.8, 1.9 Hz, 1H); 6.77 (dq, J = 15.8, 6.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0; 61.7; 122.0 (q, J = 270.6 Hz, CF_3); 128.9 (q, J = 6.0 Hz); 131.3 (q, J = 35.7 Hz, $CHCF_3$); 160.9. ^{19}F NMR (188 MHz, $CDCl_3$): δ −66.2 (dd, J = 6.2, 1.4 Hz, CF_3).

5.1.7. 4,4,4-Trifluoro-but-2-en-1-ol (**12**)

A solution of $AlCl_3$ (1.67 g, 12.5 mmol) in anhydrous diethyl ether (5 mL) was added at 0 °C, under an atmosphere of argon, to a suspension of $LiAlH_4$ (1.01 g, 26.7 mmol) in diethyl ether (10 mL). After 15 min a solution of 4,4,4-trifluoro-but-2-enoic acid ethyl ester **11** (3.0 g, 17.8 mmol) in diethyl ether (10 mL) was dropped at 0 °C. After 2 h of stirring, the reaction mixture was carefully quenched by a saturated aqueous solution of Na_2SO_4 (40 mL), then extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by distillation (96 °C, 760 mmHg) to give **12** (2.0 g, 88%) as an yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.19 (brs, 2H); 5.88 (m, 1H); 6.42 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 60.5; 117.5 (q, J = 34.0 Hz, **C**HCF$_3$); 123.20 (q, J = 269.0 Hz, **C**F$_3$); 139.2 (q, J = 6.0 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ −64.7 (dd, J = 6.2, 2.8 Hz, CF_3).

5.1.8. 7,7,7-Trifluoro-hepta-1,5-dien-4-ol (**14**)

To a solution of **12** (2.0 g, 16.8 mmol) in anhydrous CH_2Cl_2 (8 mL) was added pyridinium chlorochromate (3.4 g, 16.8 mmol). The mixture was stirred until complete disappearance of the starting material (monitored by ^{19}F NMR). After 2.5 h of stirring at room temperature, the reaction mixture was filtered through a short pad of Celite and Fluorisil. Due to its high volatility, the compound was kept on dichloromethane. ^{1}H NMR showed a peak at 9.6 and ^{19}F NMR showed only one doublet at −66.2 ppm corresponding to the aldehyde **13**.

A solution of allyl bromide (1.7 g, 14.4 mmol) in anhydrous DMF (10 mL) was then introduced at room temperature to the solution of the aldehyde followed by granular zinc (1.0 g, 15.7 mmol) and 2 drops of TMSCl. After being stirred under an inert atmosphere for 4 h, the reaction mixture was quenched by a saturated aqueous solution of NH_4Cl (20 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by chromatography on silica gel (cyclohexane/EtOAc: 60/40) to afford **14** (2.1 g, 75%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (ddd, J = 13.9, 7.3, 0.9 Hz, 1H); 2.41 (ddd, J = 13.9, 6.4, 1.1 Hz, 1H); 4.33 (brs, 1H); 5.20 (m, 2H); 5.84 (m, 2H); 6.41 (ddq, J = 15.6, 4.1, 2.07 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.1; 69.0; 118.1 (q, J = 34.0 Hz, **C**HCF$_3$); 119.6; 126.8 (q, J = 271.7 Hz, **C**F$_3$); 132.8; 141.3 (q, J = 6.6 Hz). ^{19}F NMR (188 MHz, $CDCl_3$): δ −64.5 (dt, J = 6.2, 2.1 Hz, CF_3). IR (cm^{-1}): 3356; 2956; 2933; 1641; 1462; 1144; 1036. Anal. for $C_7H_9F_3O_3$: calcd. C, 50.60; H, 5.46; found C, 50.72; H, 5.58.

5.1.9. Acrylic acid 1-allyl-4,4,4-trifluoro-but-2-enyl ester (**15**)

To a solution of **14** (2.1 g, 12.6 mmol) in dry dichloromethane (10 mL), under an argon atmosphere, were added triethylamine (3.2 g, 31.6 mmol) and a catalytic amount of DMAP (46.3 mg, 0.4 mmol, 3 mol%). The solution was then cooled to −78 °C, and acryloyl chloride (2.1 mL, 25.3 mmol) was added drop by drop. The reaction mixture was stirred at −78 °C for 6 h, then a saturated aqueous solution of $NaHCO_3$ (20 mL) was added. The aqueous layer was extracted by dichloromethane (3 × 15 mL). The combined organic layers were dried over anhydrous $MgSO_4$, and filtered. The solvent was removed under reduced pressure and the crude product was purified by chromatography on silica gel (cyclohexane/CH_2Cl_2: 50/50) to give **15** (1.7 g, 60%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.48 (m, 2H); 5.15 (m, 2H); 5.52 (m, 1H); 5.79 (m, 2H); 5.90 (dd, J = 10.5, 1.3 Hz, 1H); 6.15 (dd, J = 17.3, 10.3 Hz, 1H); 6.37 (m, 1H); 6.46 (dd, J = 17.3, 1.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 38.2; 70.8; 119.2; 119.3 (q, J = 34.0 Hz, **C**HCF$_3$); 122.7 (q, J = 269.5 Hz, **C**F$_3$); 127.9; 131.7; 131.8; 137.5 (q, J = 6.6 Hz); 164.9. ^{19}F NMR (188 MHz, $CDCl_3$): δ −64.8 (dt, J = 6.2, 2.1 Hz, CF_3). IR (cm^{-1}): 2979; 2939; 1722; 1637; 1188; 1043. Anal. for $C_{10}H_{11}F_3O_2$: calcd. C, 54.55; H, 5.04; found C, 54.68; H, 5.14.

5.1.10. (E)-6-(3,3,3-trifluoroprop-1-enyl)-5,6-dihydro-2H-pyran-2-one (**4**)

Grubb's II catalyst (169.8 mg, 0.2 mmol, 10 mol%) was added to a solution of **15** (500.0 mg, 2.3 mmol) in dry dichloromethane (10 mL). The reaction was heated 16 h under reflux. The reaction mixture was filtered through Celite, and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/EtOAc: 60/40) to afford **4** (300.5 mg, 70%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ ppm: 2.51 (m, 2H); 5.07 (m, 1H); 6.04 (m, 1H); 6.10 (m, 1H); 6.36 (ddq, J = 15.8, 6.0, 2.0 Hz, 1H); 6.86 (ddd, J = 9.4, 5.6, 2.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ ppm: 28.9; 74.5; 120.4 (q, J = 34.6 Hz, **C**HCF$_3$); 121.6; 122.6 (q, J = 269.5 Hz, **C**F$_3$); 135.6 (q, J = 6.6 Hz); 144.0; 162.6. ^{19}F NMR (188 MHz, $CDCl_3$): δ −65.1 (dt, J = 6.2, 2.1 Hz, CF_3). IR (cm^{-1}): 2989; 2914; 1729; 1125; 1085. Anal. for $C_8H_7F_3O_2$: calcd. C, 50.01; H, 3.67; found C, 50.19; H, 3.88.

5.1.11. (E)-((R)-((4R,4αR,8αS)-2,2-dimethyl-6-oxo-4,4-α,6,8α-tetrahydropyrano[3,2-d][1,3]dioxin-4-yl)(phenyl)methyl) 4,4,4-trifluorobut-2-enoate (**18**)

To a solution of **17** (50.0 mg, 0.2 mmol) in dichloromethane (10 mL) were added 4,4,4-trifluorocrotonic acid (42.0 mg, 0.3 mmol), EDC (100.0 mg, 0.5 mmol) and DMAP (115.0 mg, 0.9 mmol). The mixture was then stirred at room temperature for 3 h. Water (10 mL) was added and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$. After filtration and removal of the solvent, the resulting residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH: 98/2) to give **18** (74.0 mg, 94%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 3H); 1.36 (s, 3H); 4.33 (brt, J = 1.9 Hz, 1H); 4.36 (dd, J = 9.0, 1.9 Hz, 1H); 4.40 (dd, J = 6.0, 2.1 Hz, 1H); 6.13 (d, J = 9.0 Hz, 1H); 6.26 (d, J = 9.6 Hz, 1H); 6.48 (dq, J = 15.8, 1.9 Hz, 1H); 6.80 (dq, J = 15.8, 6.4 Hz, 1H); 6.90 (dd, J = 9.6, 6.0 Hz, 1H); 7.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.5; 28.9; 60.1; 68.9; 71.3; 73.7; 99.7; 121.8 (q, J = 270.6 Hz, **C**F$_3$); 125.5; 127.4; 128.2 (q, J = 6.0 Hz); 128.4; 128.6; 132.1 (q, J = 31.3 Hz, **C**HCF$_3$); 136.6; 140.4; 161.8; 162.4. ^{19}F NMR (188 MHz, $CDCl_3$): δ −66.0 (dd, J = 6.7, 2.1 Hz, CF_3). IR (cm^{-1}): 3050; 2920; 2912; 1720; 1261; 1131. Anal. for $C_{20}H_{19}F_3O_6$: calcd. C, 58.25; H, 4.64; found C, 58.25; H, 4.59. m.p. (°C): 148 (recrystallization in pentane).

*5.1.12. (E)-((1R,2R)-2-hydroxy-2-((2R,3S)-3-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)-1-phenylethyl) 4,4,4-trifluorobut-2-enoate (**16**)*

18 (50.0 mg, 0.1 mmol) was dissolved in an 80% aqueous acetic acid solution (5 mL) and warmed at 90 °C for 3 h. The solvent was then removed under reduce pressure, and the resulting residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH: 95/5) to give 16 (25.0 mg, 57%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.33 (dd, J = 4.8, 3.2 Hz, 1H); 4.43 (m, 1H); 4.53 (dd, J = 6.2, 4.9 Hz, 1H); 6.00 (d, J = 6.3 Hz, 1H); 6.06 (dd, J = 9.7, 6.5 Hz, 1H); 6.64 (d, J = 15.8 Hz, 1H); 6.99 (m, 2H); 7.36 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 62.0; 72.6; 76.7; 79.6; 122.2; 123.1(q, J = 269.6 Hz, **C**F_3); 128.1; 128.7; 128.9; 129.2; 129.7 (q, J = 6.2 Hz); 132.0 (q, J = 35.1 Hz, **C**HCF_3); 137.4; 141.1; 145.7; 163.4; 164.9. ^{19}F NMR (188 MHz, $CDCl_3$): δ −66.0 (dd, J = 6.3, 1.8 Hz, CF_3). IR (cm^{-1}): 3670; 3050; 2920; 1727; 1257; 1131. Anal. for $C_{17}H_{15}F_3O_6$: calcd. C, 54.84; H, 4.06; found C, 54.78; H, 4.02. m.p. (°C): 123 (recrystallization in pentane).

Acknowledgments

We thank the European Community for the financial support (Marie Curie Early Stage Training Fellowship of the European Community's Sixth Framework Programme: contract BioMedChem (for L.D.), CNRS for a French-Vietnamese joint program (PICS), and Ile de France Region for support. Thierry Cresteil and Geneviève Aubert (Cibliothèque cellulaire de l'ICSN, UPR CNRS 2301, 91190 Gif sur Yvette, France) are acknowledged for the biological tests.

References

[1] R.Y. Chen, D.Q. Yu, Acta Pharm. Sinica 33 (1998) 453–460.
[2] J.R. Hlubucek, A.V. Robertson, Aust. J. Chem. 20 (1967) 2199–2206.
[3] S. El-Sharkawi, Z. Yusuf, A.H.L. Pihie, A.M. Ali, Boll. Chim. Farm. 135 (1996) 35–40.
[4] M.A. Mosaddik, M.E. Haque, Phytother. Res. 17 (2003) 1155–1157.
[5] K.E. Kabir, A.R. Khan, M.A. Mosaddik, J. Appl. Ent. 127 (2003) 112–115.
[6] J.R. Jewers, J.B. Davies, J. Dougan, A.H. Manchanda, G. Blunden, A. Kui, S. Wetchaiman, Phytochemistry 11 (1972) 2025.
[7] M.A. Mosaddik, M.E. Hauque, M.A. Rashid, Biochem. Syst. Ecol. 28 (2000) 1039.
[8] S. Tanaka, S. Yoichi, L. Ao, M. Matumoto, K. Morimoto, N. Akimoto, G. Honda, M. Tabata, T. Oshima, T. Masuda, M. Zaini bin Asmawi, Z. Ismail, S.M. Yusof, L. B. Din, I.M. Said, Phytother. Res. 15 (2001) 681–686.
[9] S.-G. Cao, X.-H. Wu, K.-Y. Sim, B.K.H. Tan, J.T. Pereira, S.-H. Goh, Tetrahedron 54 (1998) 2143–2148.
[10] Y.-H. Lan, F.-R. Chang, C.-C. Liaw, C.-C. Wu, M.-Y. Chiang, Y.-C. Wu, Planta Med. 71 (2005) 153–159.
[11] A. De Fatima, L.K. Kohn, J.E. Carvalho, R.A. Pilli, Bioorg. Med. Chem. 14 (2006) 622–631.
[12] M.A. Blasquez, A. Bermejo, M.C. Zafra-Polo, D. Cortes, Phytochem. Anal. 10 (1999) 161–170.
[13] A. De Fátima, L.A. Modolo, L.S. Conegero, R.A. Pilli, C.V. Ferreira, L.K. Kohn, J. E. de Carvalho, Curr. Med. Chem. 13 (2006) 3371–3384.
[14] N. Meenakshii, A. Lee, H.L.P. Azimahtol, S. Hasidah, Malays. Appl. Biol. 29 (2000) 121–126.
[15] N. Umar-Tsafe, M.S. Mohamed-Said, R. Rosli, L.B. Din, L.C. Lai, Mutat. Res. 562 (2004) 91–102.
[16] T.W. Sam, C. Sew-Yeu, S. Matsjeh, E.K. Gan, D. Razak, A.L. Mohamed, Tetrahedron Lett. 28 (1987) 2541–2544.
[17] A. De Fátima, L. Kohn, M.A. Antonio, D.E. Carvalho, R.A. Pilli, Bioorg. Med. Chem. 13 (2005) 2927–2933.
[18] P.V. Ramachandran, M.V.R. Reddy, H.C. Brown, Tetrahedron Lett. 41 (2000) 583–586.
[19] A. De Fatima, A. Pilli, Arkivoc 10 (2003) 118–126.
[20] A. De Fatima, A. Pilli, Tetrahedron Lett. 44 (2003) 8721–8724.
[21] M. Quitschalle, M. Christmann, U. Bhatt, M. Kalesse, Tetrahedron Lett. 42 (2001) 1263–1265.
[22] Z.Y. Liu, J.X. Ji, B.G. Li, J. Chem. Res. 1 (2004) 61–63.
[23] E. Sundby, L. Perk, T. Anthonsen, A.J. Aasen, T.V. Hansen, Tetrahedron 60 (2004) 521–524.
[24] M. Gruttadauria, P. Lo Meo, R. Noto, Tetrahedron Lett. 45 (2004) 83–85.
[25] P. Harsh, G.A. O'Doherty, Tetrahedron 65 (2009) 5051–5055.
[26] J.-P. Bégué, D. Bonnet-Delpon, J. Fluor. Chem. 127 (2006) 992–1012.
[27] W.K. Hagmann, J. Med. Chem. 51 (2008) 4359–4369.
[28] C. Isanbor, D. O'Hagan, J. Fluor. Chem. 127 (2006) 303–319.
[29] F.M.D. Ismail, J. Fluor. Chem. 118 (2002) 27–33.
[30] J.P. Bégué, D. Bonnet-Delpon, Bioorganic and Medicinal Chemistry of Fluorine. Wiley-Hoboken Ltd., 2008.
[31] A. Tressaud, G. Haufe, Fluorine and Health: Molecular Imaging, Biomedical Materials and Pharmaceuticals. Elsevier Science Ltd., 2008.
[32] I. Ojima, J.C. Slater, R.H. Gimi, C.M. Sun, M. Ourévitch, S. D Kuduk, S. Charkravarty, A. Abouabdellah, J.P. Bégué, D. Bonnet-Delpon, J.M. Veith, P. Pera, R.J. Bernacki, in: I. Ojima, J.R. McCarthy, J.T. Welch (Eds.), Biomedical Frontiers of Fluorine Chemistry, ACS Symposium Series, 1996, pp. 228–243 Washington DC (Chapter 17).
[33] M. Molteni, C. Pesenti, M. Sani, A. Volonterio, M. Zanda, J. Fluor. Chem. 125 (2004) 1735–1743.
[34] Z.W. You, Z.X. Jiang, B.L. Wang, F.L. Qing, J. Org. Chem. 71 (2006) 7261–7267.
[35] M. Ratier, M. Pereyre, A.G. Davies, R.J. Sutcliffe, J. Chem. Soc. Perkin Trans. 2 (1984) 1907–1915.
[36] J.-H. He, Y. Ye, C.-X. Xu, Yao Xue Xue Bao 33 (1998) 566–570.
[37] D.-Q. Xu, Pure Appl. Chem. 71 (1999) 1119–1122.
[38] C.-X. Xu, J.-H. He, JANPR 2 (1999) 1–19.
[39] T.K.M. Shing, H.-C. Tsui, Z.-H. Zhou, J. Org. Chem. 60 (1995) 3121–3130.
[40] Systems developed by Alpha Chimica®, Faculté de Pharmacie, 5, rue J.-B. Clément, 92290 Châtenay-Malabry. France mailto: contact@alphachimica.com (French patent: 08–02745; PCT/FR 2009/000573).
[41] B. Akagah, A.-T. Lormier, A. Fournet, B. Figadère, Org. Biomol. Chem. 6 (2008) 4494–4497.