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An efficient synthesis of (*Z*)-α-fluorochalcones via the palladium-catalyzed cross-coupling reaction of (*Z*)-α-fluorocinnamoyl chloride with boronic acids

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ABSTRACT

An efficient synthesis of α-fluorochalcones (1,3-diphenyl-2-fluoroprop-2-en-1-one) based on the Suzuki–Miyaura palladium-catalyzed cross-coupling reaction of arylboronic acids with α-fluorocinnamoyl chlorides in the presence of Cs_2CO_3 in toluene is described. This approach allows the synthesis of fluorinated analogues of functionalized natural chalcones.

1. Introduction

Chalcones, or 1,3-diphenyl-2-propen-1-ones represent an important group in the polyphenolic family, abundant in fruits, vegetables, and various edible plants.[1] During biosynthesis these compounds are the precursors of flavonoids and isoflavonoids. Chemically, they consist of open-chain flavonoids in which the two aromatic rings are linked by a three carbons-α,β-unsaturated carbonyl system. Chalcones have been reported to possess multiple biological activities, such as antioxidant,[2] antimalarial,[3] antibacterial,[4] antileishmanial,[5] anti-HIV,[6] anti-inflammatory,[7] and antitumoral.[8] The replacement of a hydrogen by a fluorine atom is used in drug development to alter biological functions. Monofluoro analogues of biological active molecules have often proved to have improved properties.[9] Chalcones bearing a fluorine atom or a trifluoromethyl group on either of the aromatic rings have been shown to have many therapeutically activities, such as inhibition of nitric oxide production,[10] inhibition of 5-lipoxygenase, and anti-carcinogenic agent,[11] and anti-vascular pharmacological properties.[12] Lawrence et al. reported that chalcones with a fluorine atom in the α position of the conjugated central double bond have potent cytotoxic and tubulin inhibitory properties.[13] α-Fluorochalcones were obtained from trifluoromethyl ketones via a sequence involving Mg metal-promoted successive double defluorination,[14] by the Wittig reaction via the corresponding α-fluoro substituted ylides,[15] from corresponding propargyl acetates via a gold-catalyzed rearrangement-fluorination,[16] or by nucleophilic fluoromethylation of benzyl halides using α-fluoro-α-(phenylsulfonyl)methane.[17] We previously proposed a general method for the synthesis of chalcones based on the Suzuki–Miyaura reaction either between cinnamoyl chlorides and phenylboronic acids or between benzoyl chlorides and phenylvinylboronic acids.[18] As an extension of this work we herein describe the synthesis of a series of chalcones bearing a fluorine atom in the α-position (1,3-diphenyl-2-fluoroprop-2-en-1-one) by direct palladium-catalyzed cross-coupling reaction of arylboronic acids with α-fluorocinnamoyl chlorides. This method will be useful for the synthesis of a wide variety of naturally occurring chalcones, as this chemistry is compatible with the easily deprotected MOM-protected phenol function as we have shown during the synthesis of fluororesveratrol.[19]

2. Results and discussion

Palladium-catalyzed cross-coupling reactions have a large impact on synthetic organic chemistry and have been applied to the synthesis of various biologically active compounds[20] and complex molecular structures.[21] The palladium-catalyzed coupling of activated carboxylic acid with nucleophiles is a straightforward access to ketones. The reaction can be performed using acid chlorides,[22] acid anhydrides,[23] or thio-esters.[24] The same acyl-palladium

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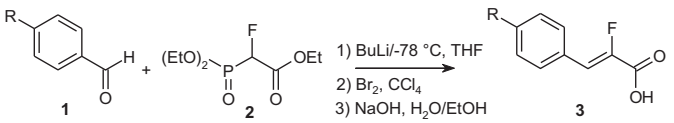
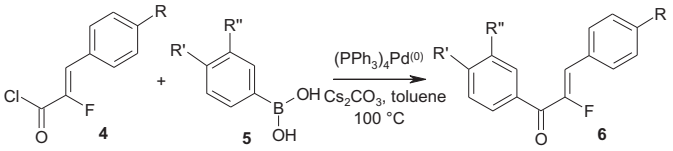
intermediates may be obtained by the carbonylation of a halide with carbon monoxide, leading to a one-pot synthesis of ketones from an organic halide, CO, and a nucleophile.[25] To the best of our knowledge only a few examples of the palladium-catalyzed synthesis of α-fluoro-α,β-unsaturated ketones have been described in literature. The first example, which has been described is the preparation of α-fluoro-α,β-unsaturated ketones by palladium-Cu(I) co-catalyzed cross-coupling reaction of fluorovinylstannanes using an acid chloride as the substrate.[26] The second example consists in the synthesis of α-fluoro-α,β-unsaturated ketones via cross-coupling of 1-fluorovinylstannanes with iodobenzene under a carbon monoxide atmosphere co-catalyzed by palladium(0) and copper (I).[27] Recently Pannecoucke's group developed a synthesis of α-fluoro-α,β-unsaturated ketones, via a Negishi palladium-catalyzed coupling reaction between bromofluoroolefins and alkoxyvinylzinc species.[28]

In our previously work,[18] we described the synthesis of chalcones in good yields by the Suzuki–Miyaura coupling reaction between benzoyl chloride and phenylvinylboronic acid catalyzed by $(PPh_3)_4Pd$. We first planned to extend this method to the synthesis of α-fluorochalcone. Unfortunately, no access to α-fluoro-2-phenylvinylboronic acid is described in the literature. Phenylvinylboronic acid is either commercially available or readily obtained by the reaction of a phenylvinyl anion equivalent with a trialkoxyboron derivative. It is well known that α-fluorovinyl anions are highly unstable.[29] To the best of our knowledge, the direct access to α-fluoro-vinylboronic by reacting an α-fluorovinyl anion with a trialkoxyboron derivative has never been described. This instability is limited to non-stabilized α-fluorovinyl anion and recently lithium trimethoxy(trifluorovinyl)borate has been obtained by this strategy.[30] The second approach to vinylboronic acid is based on the reaction of a vinyl halide with a diboron derivative.[31] However, the reactivity of gemvinyl dihalides including a fluorine atom is very often different from the one of simple monovinyl halides.[32] Therefore, when we reacted (*Z*)-2-bromo-2-fluoroethenylbenzene with bis(pinacolato)diboron we obtained in majority the symmetrical duplication product (1*E*,3*E*)-2,3-difluoro-1,4-diphenyl-buta-1,3-dienes as the major product and only traces (ca. 10%) of the expected (*E*)-fluoro-2-phenylvinylboronic ester and we could not improve this yield.[33] Fortunately, the reaction of phenylboronic acid with cinnamoyl chloride also afforded the expected chalcones but with a lower yield.[18] So we decided to explore this synthetic approach to the synthesis of α-fluorinated analogues of chalcones as the two partners α-fluorocinnamoyl chlorides and phenylboronic acids are readily available. (*Z*)-α-Fluorocinnamic acids were obtained by the Wittig–Horner reaction of 2-(diethoxyphosphinyl)-2-fluoro-acetic acid, ethyl ester **2** with the corresponding aldehydes (Scheme 1). The condensation between benzaldehyde **1a**–**d** and compound **2** in THF in the presence of *n*-butyllithium at −78 °C in THF gave the corresponding (*E*)-α-fluorocinnamic esters as the major product.[34] The isomerization of (*E*)-α-fluorocinnamic esters into (*Z*)-α-fluorocinnamic esters was performed by heating for 1 h in CCl_4 the isomer mixture in the presence of 10% of bromine at 50 °C.[35] Then, the saponification of (*Z*)-α-fluorocinnamic esters was achieved using sodium hydroxide in ethanol/water mixture, which led the desired (*Z*)-α-fluorocinnamic acids.[36] From the corresponding benzaldehydes, pure (*Z*)-2-fluoro-3-phenyl-2-propenoic acids are obtained in fair yields without regards of the substituent. For example, pure (*Z*)-2-fluoro-3-phenyl-2-propenoic acid, and (*Z*)-2-fluoro-3-(4-methoxyphenyl)-2-propenoic acid were obtained in 63% and 59% isolated yield, respectively.



Scheme 1. Synthesis of fluorocinnamic acids.

Direct conversion of (*Z*)-α-fluorocinnamic acids **3** into (*Z*) α-fluorocinnamoyl chlorides **4** was achieved by the treatment of fluorocinnamic acids with thionyl chloride in dichloromethane.[37] Crude acid chloride **4** was used without further purification for this step due to partial decomposition during distillation. The next step of this work is the Suzuki–Miyaura reaction of the acids chloride **4a**–**d** with phenylboronic acids **5a**–**d**. In our previous synthesis of chalcones we used the protocol described by Haddach et al.[38] for the palladium-catalyzed cross-coupling of acid chlorides with arylboronic acids based on using tetrakis(triphenylphosphine)palladium(0) as the catalyst in toluene and cesium carbonate (Cs_2CO_3) as a base. We used the very same conditions for the coupling of arylboronic acids and (*Z*)-α-fluorocinnamoyl chlorides (Scheme 2).



Scheme 2. Synthesis of α-fluorochalcones.

The reaction was performed with various arylboronic acids, which afforded the A ring of the chalcones and (*Z*) α-fluorocinnamic acids, which bring the B ring. The reaction was not affected by substituents located either on the acyl chloride **4a**–**d** or on the boronic acid **5a**–**d** (Table 1, entries 1–7). In all cases the α-fluorinated analogues of chalcones **6a**–**g** were obtained in fair yields (50–58%).

Table 1
Synthesis of (*Z*)-α-fluorochalcones by Suzuki–Miyaura coupling between (*Z*)-α-fluorocinnamoyl chloride **4a**–**d** and phenylboronic acids **5a**–**d**

Entry	4	5	6	R	R′	R″	Isolated yield (%)
1	**a**	**a**	**a**	OMe	H	H	53
2	**b**	**a**	**b**	CH_3	H	H	55
3	**b**	**b**	**c**	CH_3	CHO	H	50
4	**b**	**c**	**d**	CH_3	$N(CH_3)_2$	H	56
6	**b**	**d**	**e**	CH_3	OMe	OMe	52
5	**c**	**d**	**f**	H	OMe	OMe	58
7	**d**	**d**	**g**	F	OMe	OMe	51

We demonstrated that phenyl bearing a phenol function protected by methoxymethyl (MOM) ether group behave similarly to methoxy groups and may be deprotected without loss of a fluorine atom in the vinylic position in the resveratrol series.[19] Therefore, this synthesis paves the way to α-fluorinated analogues of bioactive chalcones. For example, alkoxylated and hydroxylated chalcones on ring A or B are found in antimalarial compounds and inhibitors of Mycobacterium tuberculosis protein tyrosine phosphatase.[39] The alkoxy substituents also serve to link the chalcone moiety to another active molecule, such as dihydroartemisinin.[40] Chalcones bearing amino and fluorine groups on the phenyl rings like **6d** and **6g** have been described as positron emission tomography probes.[41] Chalcones bearing fluorine groups on either rings, such as **6g** or methoxy groups, such as **6a**, **e**–**g** are more efficient against melanoma cell lines.[11a]

3. Conclusion

In conclusion, the cross-coupling reaction of arylboronic acids with (*Z*)-α-fluorocinnamic acid chlorides was achieved using tetrakis(triphenylphosphine)palladium(0) as the catalyst in toluene

and cesium carbonate as a base to afford (*Z*)-α-fluorochalcones in fair yields. The method was applied to a variety of α-fluorocinnamic acid chlorides and boronic acids, which opens the route to a general synthesis of (*Z*)-α-fluoro-α,β-unsaturated ketones bearing reactive substituents like phenol groups. By transforming the ketone group of a chalcone in an imine, several families of potential drugs may be obtained, such as chalcones thiosemicarbazide derivatives, which have been proved to be anticancer agents.[42] Therefore, this general synthesis of (*Z*)-α-fluoro-α,β-unsaturated ketones paves the way to access new families of potentially active compounds.

4. Experimental

4.1. General

All commercially available products were purchased from Aldrich (Saint-Quentin Fallavier, France) and used as received. Deuterated solvents (99.9% or better) were purchased from Eurisо-Top (Saint-Aubin, France). For flash chromatography, Merck silica-gel 60 (230–400 mesh ASTM) was used. The melting points were measured on an Electrothermal (Dubuque, Iowa USA) 9100 apparatus and were not corrected. NMR spectra were recorded on a Bruker (Wissembourg, France) AM 300 spectrometer (300, 282, and 75 MHz, for ^{1}H, ^{19}F, and ^{13}C, respectively) using $CDCl_3$ as solvent and TMS as internal standard; chemical shifts and *J* values are given in parts per million and Hertz, respectively. GC/MS were recorded on a Thermo Fisher Polaris ion trap mass spectrometer fitted with a 60 m 0.32 mm apolar CPSil5 column using electron ionization (EI) at 70 eV. Fast atom bombardment (FAB) mass spectra were measured on a JEOL Mass Station 700 spectrometer at the École Normale Supérieure (Paris, France).

4.2. General procedure for the preparation of α-fluorochalcones

(1.0 mmol) of α-fluorocinnamoyl chloride (0.5 mmol) of arylboronic acid, and (2.5 mmol) of anhydrous cesium carbonate were dissolved in 5 mL of anhydrous toluene. The mixture was treated with 5% of tetrakis(triphenylphosphine) palladium. The solution was heated at 100 °C for 12 h, diluted with ethyl acetate, and washed successively with water, a saturated solution of sodium bicarbonate, and brine. The solvent was evaporated and the residue was purified by flash column chromatography using a mixture of ethyl acetate/pentane 10/90 as eluent, to give the desired product.

*4.2.1. (Z)-2-Fluoro-3-(4-methoxyphenyl)-1-phenyl-2-propen-1-one (**6a**).* ^{1}H NMR ($CDCl_3$): δ=3.85 (s, 3H), 6.82 (d, $^{3}J_{H-F}$=36.3 Hz, 1H), 6.93 (d, $^{3}J_{H-H}$=8.6 Hz, 2H), 7.50 (m, 3H), 7.65 (d, $^{3}J_{H-H}$=8.6 Hz, 2H), 7.85 (d, $^{3}J_{H-H}$=7.7 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ=55.9, 118.6, 119.4 (d, J_{C-F}=5.0 Hz), 127.8, 128.1 (d, J_{C-F}=4.3 Hz), 129.2, 129.5, 130.1, 130.5, 132.4, 153.6 (d, J_{C-F}=271.4 Hz), 161.4, 186.7 (d, J_{C-F}=28.3 Hz) ppm. ^{19}F NMR ($CDCl_3$): −125.2 (d, $^{3}J_{H-F}$=36.4 Hz, 1F) ppm. MS (EI): *m*/*z* (%)=257 (20.5), 256 (100, M^+), 255 (39.4), 237 (19.0), 236 (75.3), 225 (19.5), 208 (20.6), 193 (21.0), 193 (22.5), 165 (18.7), 105 (15.0), 77 (30.4). HRMS: calcd for $C_{16}H_{14}O_2F$ $[M+H]^+$ 257.0972; found 257.0979.

*4.2.2. (Z)-2-Fluoro-3-(4-methylphenyl)-1-phenyl-2-propen-1-one (**6b**).* ^{1}H NMR ($CDCl_3$): δ=2.37 (s, 3H), 6.83 (d, $^{3}J_{H-F}$=36.6 Hz, 1H), 7.23 (d, $^{3}J_{H-H}$=8.2 Hz, 2H), 7.50 (m, 2H), 7.60 (d, $^{3}J_{H-H}$=8.2 Hz, 2H), 7.87 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$): δ=21.5, 120.5 (d, J_{C-F}=5.9 Hz), 128.4, 128.6 (d, J_{C-F}=4.0 Hz), 129.3, 129.4, 129.7, 130.6, 130.7, 132.7, 136.4, 154.2 (d, J_{C-F}=270.8 Hz), 188.0 (d, J_{C-F}=28.3 Hz) ppm. ^{19}F NMR ($CDCl_3$): δ=−124.92 (d, $^{3}J_{H-F}$=36.5 Hz, 1F) ppm. MS (EI): *m*/*z* (%)=240 (45, M^+), 239 (32.5), 226 (15.3), 225 (100), 220 (15.0), 205 (9.5), 105 (12.4), 77 (25.0). HRMS: calcd for $C_{16}H_{14}OF$ $[M+H]^+$ 241.1023; found 241.1027.

*4.2.3. 4-[(Z)-2-Fluoro-3-(4-methylphenyl)-3-oxo-1-propenyl] benzaldehyde (**6c**).* ^{1}H NMR ($CDCl_3$): δ=2.20 (s, 3H), 6.86 (d, $^{3}J_{H-F}$=36.5 Hz, 1H), 7.23 (d, $^{3}J_{H-H}$=7.6 Hz, 2H), 7.62 (d, $^{3}J_{H-H}$=7.6 Hz, 2H), 7.80 (d, $^{3}J_{H-H}$=7.8 Hz, 2H), 8.05 (d, $^{3}J_{H-H}$=7.8 Hz, 2H), 10.12 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=21.7, 110.9, 118.3 (d, J_{C-F}=6.4 Hz), 124.2 (d, J_{C-F}=2.0 Hz), 123.1 (d, J_{C-F}=3.7 Hz), 129.8, 130.8, 130.6, 132.5, 132.8, 139.8 (d, J_{C-F}=2.8 Hz), 156.2 (d, J_{C-F}=274.6 Hz), 188.4 (d, J_{C-F}=28.2 Hz), 191.7 ppm. ^{19}F NMR ($CDCl_3$): δ=−125.3 (d, $^{3}J_{H-F}$=36.5 Hz, 1F) ppm. MS (EI): *m*/*z* (%)=268 (25.5, M^+), 267 (18.5), 254 (19.5), 253 (100), 239 (17.4), 239 (14.2), 219 (9.5), 191 (9.0), 133 (13.5), 105 (11.0), 77 (12.3). HRMS: calcd for $C_{17}H_{14}O_2F$ $[M+H]^+$ 269.0972; found 269.0980.

*4.2.4. (Z)-1-(4-Dimethylaminophenyl)-2-fluoro-3-(4-methylphenyl)-2-propen-1-one (**6d**).* ^{1}H NMR ($CDCl_3$): δ=2.37 (s, 3H), 3.07 (s, 6H), 6.67 (d, $^{3}J_{H-H}$=9.0 Hz, 2H), 6.81 (d, $^{3}J_{H-F}$=37.5 Hz, 1H), 7.21 (d, $^{3}J_{H-H}$=8.1 Hz, 2H), 7.59 (d, $^{3}J_{H-H}$=9.0 Hz, 2H), 7.74 (d, $^{3}J_{H-H}$=8.0 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ=21.5, 40.0, 110.6, 117.5 (d, J_{C-F}=6.1 Hz), 123.55 (d, J_{C-F}=2.2 Hz), 129.2 (d, J_{C-F}=3.7), 129.5, 130.3, 130.4, 132.1, 132.2, 139.6 (d, J_{C-F}=2.8 Hz), 155.4 (d, J_{C-F}=274.3 Hz), 185.0 (d, J_{C-F}=28.0 Hz) ppm. ^{19}F NMR ($CDCl_3$): δ=−121.9 (d, $^{3}J_{H-F}$=37.5 Hz, 1F), MS (EI): *m*/*z* (%)=284 (15.3, M^++1), 283 (100, M^+), 263 (65.0), 262 (20.0), 235 (12.5), 148 (45.0), 134 (21.5), 77 (9.5) ppm. HRMS: calcd for $C_{18}H_{19}OFN$ $[M+H]^+$ 284.1451; found 284.1455.

*4.2.5. (Z)-1-(3,4-Dimethoxyphenyl)-2-fluoro-3-(4-methylphenyl)-2-propen-1-one (**6e**).* ^{1}H NMR ($CDCl_3$): δ=2.37 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H), 6.86 (d, $^{3}J_{H-F}$=36.9 Hz, 1H), 6.90 (d, $^{3}J_{H-H}$=8.4 Hz, 1H), 7.22 (d, $^{3}J_{H-H}$=8.0 Hz, 2H), 7.48 (s, 1H), 7.59 (d, $^{3}J_{H-H}$=8.0 Hz, 2H), 7.62 (d, $^{3}J_{H-H}$=8.4 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=21.5, 56.0, 56.1, 110.1, 111.9 (d, J_{C-F}=5.0 Hz), 119.2 (d, J_{C-F}=6.0 Hz), 124.3 (d, J_{C-F}=7.5 Hz), 129.7, 130.5, 130.6, 140.2 (d, J_{C-F}=2.9 Hz), 149.0, 153.5, 154.6 (d, J_{C-F}=272.5 Hz), 186.0 (d, J_{C-F}=28.4 Hz) ppm. ^{19}F NMR ($CDCl_3$): δ=−123.30 (d, $^{3}J_{H-F}$=36.8 Hz, 1F) ppm. MS (EI): *m*/*z* (%)=301 (20.0), 300 (100, M^+), 285 (70.0), 280 (68.5), 269 (42.3), 237 (12.0), 181 (9.5), 209 (14.5), 166 (15.0), 165 (48.0), 137 (13.5), 121 (9.0), 77 (9.5). HRMS: calcd for $C_{18}H_{18}O_3F$ $[M+H]^+$ 301.1240; found 301.1244.

*4.2.6. (Z)-1-(3,4-Dimethoxyphenyl)-2-fluoro-3-phenyl-2-propen-1-one (**6f**).* ^{1}H NMR ($CDCl_3$): δ=3.95 (s, 3H), 3.97 (s, 3H), 6.87 (d, $^{3}J_{H-F}$=36.8 Hz, 1H), 6.93 (d, $^{3}J_{H-H}$=8.4 Hz, 1H), 7.22 (m, 2H), 7.40 (m, 3H), 7.50 (s, 1H), 7.70 (d, $^{3}J_{H-H}$=8.4 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=56.0, 56.1, 110.4, 112.3 (d, J_{C-F}=4.5 Hz), 119.6 (d, J_{C-F}=6.0 Hz), 124.7 (d, J_{C-F}=7.0 Hz), 129.7, 130.8, 130.9, 140.4 (d, J_{C-F}=2.5 Hz), 149.7, 153.6, 154.6 (d, J_{C-F}=273.4 Hz), 185.9 (d, J_{C-F}=28.4 Hz) ppm. ^{19}F NMR ($CDCl_3$): δ=−123.8 (d, $^{3}J_{H-F}$=36.8 Hz 1F) ppm. MS (EI): *m*/*z* (%)=287 (18.5), 286 (100, M^+), 285 (75.0), 266 (40.3), 255 (24.5), 183 (14.6), 165 (74.5), 137 (18.5), 121 (10.5), 77 (11.0). HRMS: calcd for $C_{17}H_{16}O_3F$ $[M+H]^+$ 287.1078; found 287.1080. (**6a**).

*4.2.7. (Z)-1-(3,4-Dimethoxyphenyl)-2-fluoro-3-(4-fluorophenyl)-2-propen-1-one (**6g**).* ^{1}H NMR ($CDCl_3$): δ=3.93 (s, 3H), 3.95 (s, 3H), 6.83 (d, $^{3}J_{H-F}$=36.9 Hz, 1H), 6.91 (d, $^{3}J_{H-H}$=8.5 Hz, 1H), 7.15 (d, $^{3}J_{H-H}$=8.0 Hz, 2H), 7.48 (s, 1H), 7.63 (d, $^{3}J_{H-H}$=8.5 Hz, 1H), 7.68 (dd, $^{3}J_{H-H}$=8.6 Hz, $^{3}J_{H-F}$=5.5, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ=56.0, 56.1, 110.1, 110.4, 111.5, 111.9 (d, J_{C-F}=3.6 Hz), 115.9, 116.2, 117.6 (d, J_{C-F}=5.9 Hz), 119.1, 124.4 (d, J_{C-F}=7.9 Hz), 128 (d, J_{C-F}=2.0 Hz), 132.4, 132.5, 132.6, 134.2, 149.1, 153.6, 154.7 (d, J_{C-F}=274.1 Hz), 163.3 (d, J_{C-F}=251.7 Hz), 185.5 (d, J_{C-F}=28.6 Hz) ppm. ^{19}F NMR ($CDCl_3$): δ=−125.6 (d, $^{3}J_{H-F}$=36.8 Hz 1F), −112.4 (m, 1F) ppm. MS (EI): *m*/*z* (%)=305 (20.0), 304 (100, M^+), 284 (67.5), 273 (46.0), 241 (10.5), 213

(14.6), 201 (9.5), 165 (63.5), 137 (16.3), 79 (9.5), 77 (9.0). HRMS: calcd for $C_{17}H_{15}O_3F_2$ $[M+H]^+$ 305.0984; found 305.0982.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2012.12.025. These data include MOL files and InChiKeys of the most important compounds described in this article.

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