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Electrochemically induced free-radical tandem cyclisation of chlorodifluoromethylated ketones Application to the synthesis of *gem*-difluorinated heterocycles

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Abstract

The synthesis of a series of chlorodifluoromethylated ketones **1–6** is presented and the cyclic voltammetry of the reductive cleavage of these ketones was investigated, in *N*,*N*-dimethylformamide (DMF), at an inert electrode. Indirect electrochemical reduction (by means of an electrogenerated anion radical) in acetonitrile (CH_3CN) or in *N*,*N*-dimethylformamide (DMF), of the naphthalene-derived chlorodifluoroacetylated compounds **1** and **2** in the presence of the olefinic substrates **7–10**, yields new *gem*-difluoro heterocyclic compounds **11–16** after intramolecular cyclisation of a γ,γ-difluoroalkyl radical. Aromatic nucleophilic substitution of α,α-difluoroketones **12** and **13**, in anhydrous dimethylsulfoxide, with several tetramethylammonium salts of imidazole as nucleophiles, proceeds under mild conditions to give the corresponding nitrogen–nitrogen exchanged products **17–23** in moderate to good yields.

Keywords: Free-radical cyclisation; Electrochemistry; α,α-Difluoroketones; *gem*-Difluorinated compounds

1. Introduction

An increasing interest has been paid for several years to the chemistry of various fluorine-containing heterocycles due to their unique physical properties, specific chemical reactivity, and their remarkable potential biological activity [1]. Important efforts have been made toward the synthesis of compounds containing a difluoromethylene group adjacent to a carbonyl group [2], because α,α-difluoroketones have been successfully used as inhibitors of hydrolytic enzymes, and greatly enhanced biological activity has been reported compared with their nonfluorinated analogues [3]. Methods for the preparation of *gem*-difluorocyclic compounds are very limited and have some limitations [2]. Very recently, highly desirable new methodologies for the synthesis of interesting *gem*-difluoromethylene compounds have been published. Among the numerous approaches and systems developed, we can cite the free-radical difluoromethylene radicals including carbon–carbon bond formation via intramolecular cyclisation of α-fluorinated carbon radicals [4–9], as well as nucleophilic difluoromethylene synthons [10]. Chlorodifluoromethylated ketones have been known for a long time [11–14] and have been used in various synthetic applications [3] (the Reformatstky and related reactions being the most common of all the synthetic studies). Such halodifluoromethylated substrates are potentially useful to build new difluorinated materials as it is anticipated that the carbon–halogen bond should be quite reactive in single electron transfer (SET) reactions, both chemically and electrochemically. There are a few reports on the use of these substrates in SET reactions and free-radical cyclisations [15–18], but to the best of our knowledge, their use in *electrochemical* free-radical cyclisation reactions has not been reported in the literature [19].

As part of our ongoing effort in the synthesis of new fluorinated compounds with potential biological and synthetic applications [20–26], we wish to present herein a novel and practical method for the synthesis of α,α-difluoroketones **11–16** involving free-radical electrochemical addition of chlorodifluoroacetylated compounds **1** and **2** in the presence of olefinic substrates **7–10** followed by

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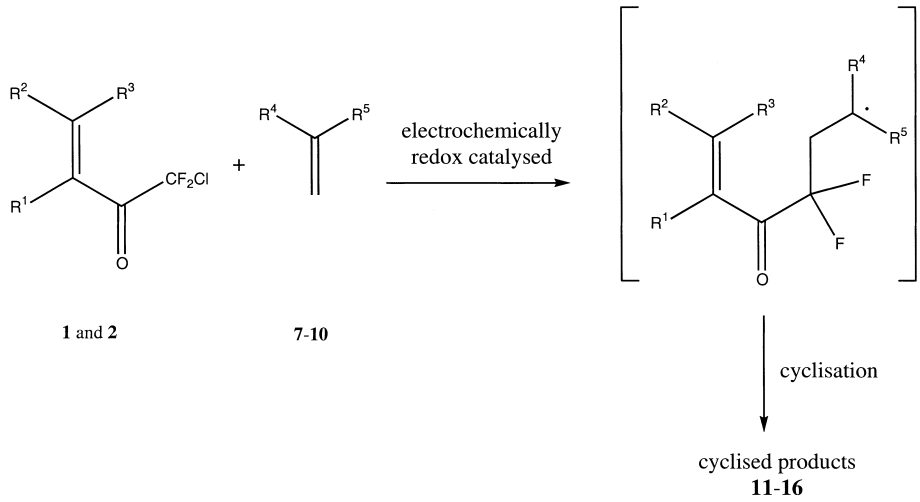


1 and 2 7-10

Scheme 1.

intramolecular cyclisation of the resulting γ,γ-difluoroalkyl radical (Scheme 1).

The α,α-difluoroketones **12** and **13**, prepared by our electrochemical approach, were found to undergo various nitrogen–nitrogen exchange reactions with imidazole nucleophiles such as imidazole, benzimidazole, imidazole 2-carboxaldehyde, 2-(4′-methoxyphenyl)imidazole and 2-methyl-5-nitroimidazole to yield new heterocyclic α,α-difluoroketones **17–23** (Scheme 2).

The structure of compounds is shown in Charts 1 (starting materials), 2 (cyclised products) and 3 (exchanged products). The reduction products ($RCOCF_2H$) of the starting ketones $RCOCF_2Cl$ will be numbered **1A**, **2A** and **2B**, **3A**, **4A**, **5A** and **6A**.

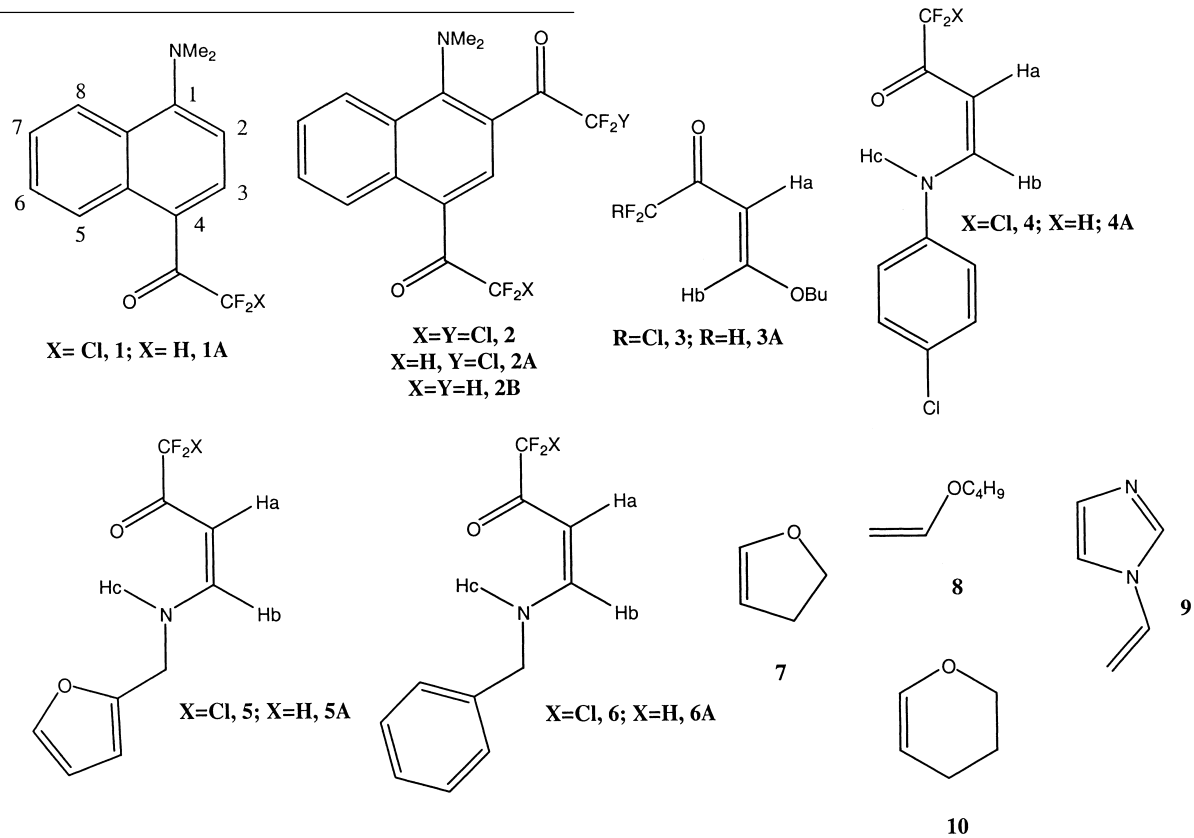
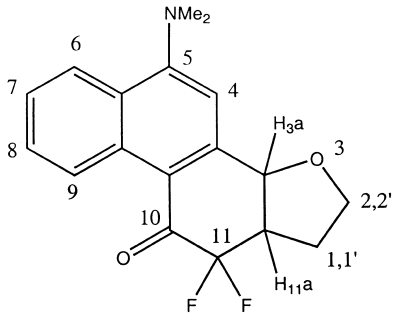


Chart 1.



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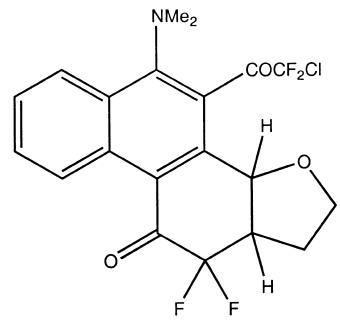

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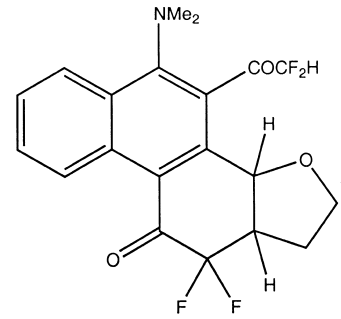

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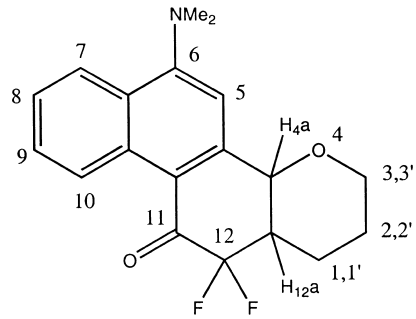

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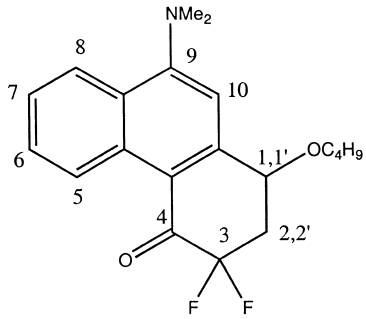

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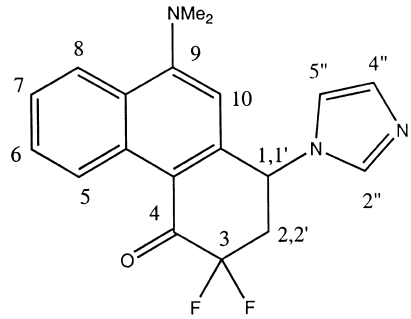

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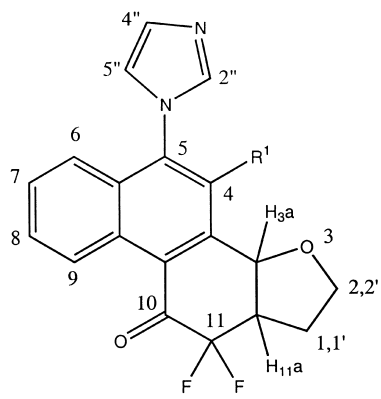
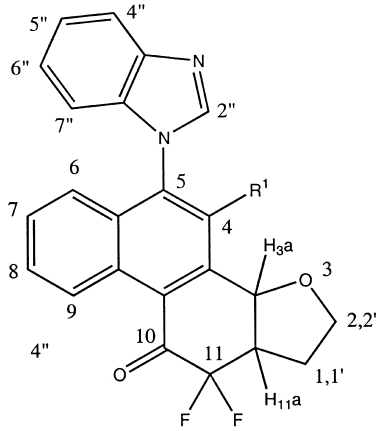
Chart 2.



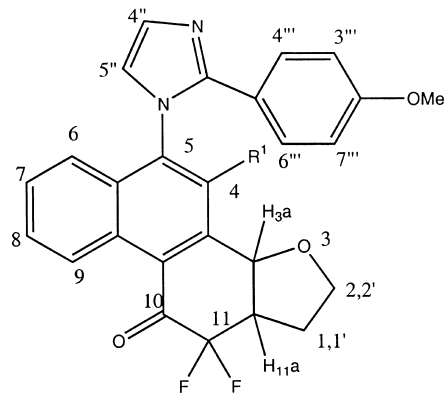
R^1= -$COCF_2Cl$, **17**

R^1= -$COCF_2H$, **18**

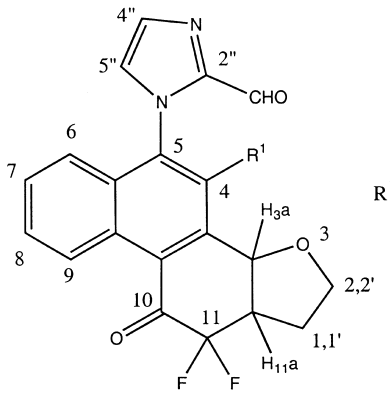


R^1= -$COCF_2Cl$, **19**

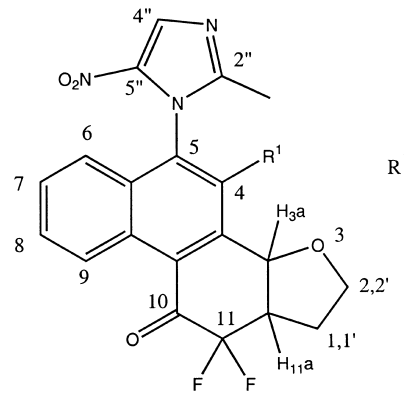
R^1= -$COCF_2H$, **20**



R^1= -$COCF_2Cl$, **21**

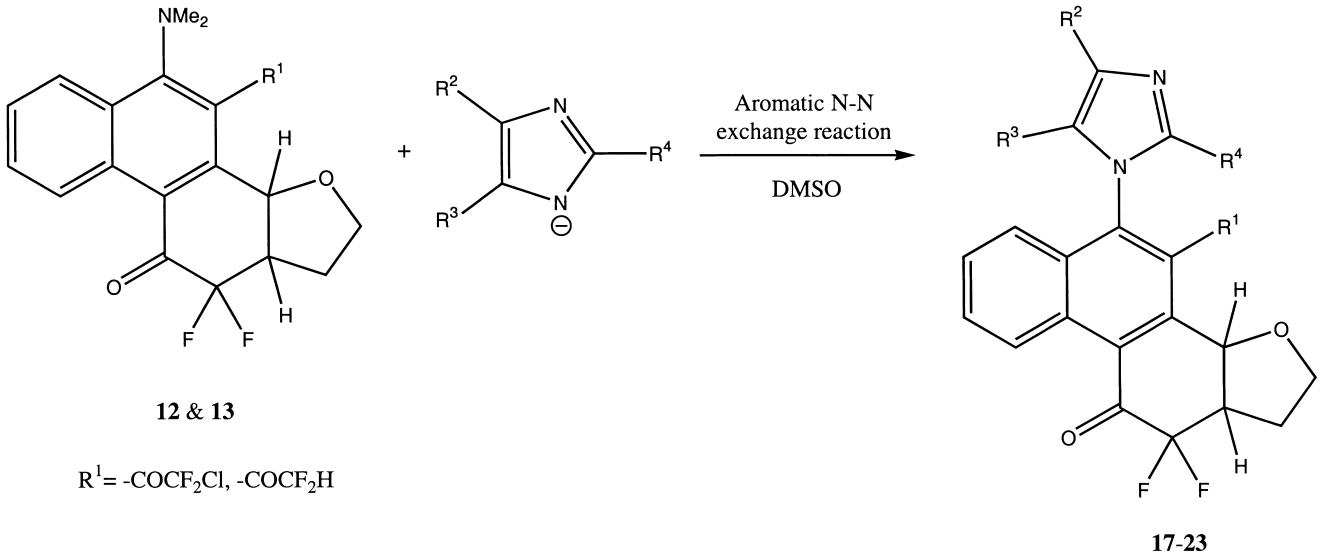


R^1= -$COCF_2Cl$, **22**



R^1= -$COCF_2Cl$, **23**

Chart 3.



12 & 13

R^1= -$COCF_2Cl$, -$COCF_2H$

17-23

Scheme 2.

2. Results and discussion

2.1. Synthesis of the chlorodifluoromethylated ketones 1–6

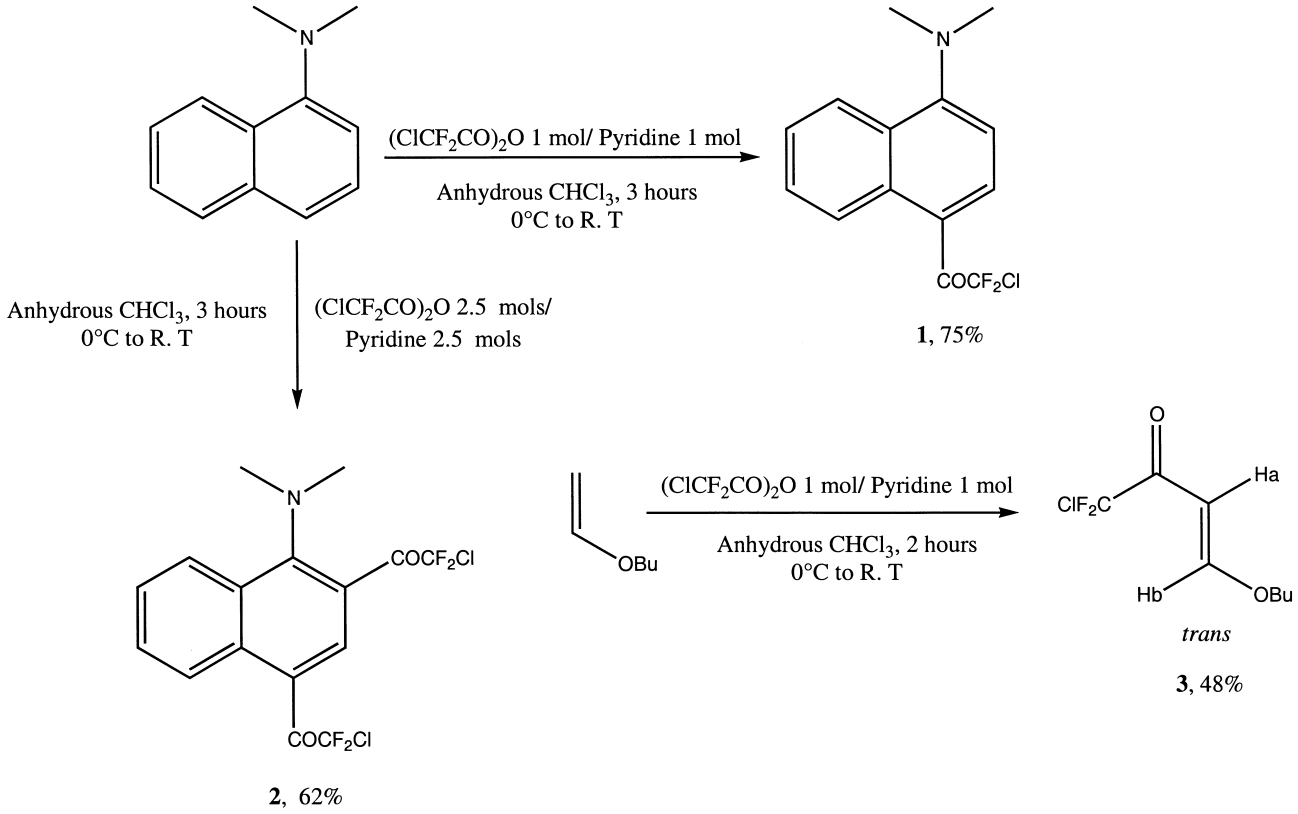
The chlorodifluoromethylated ketones **1–3** were prepared by chlorodifluoroacetylation, with chlorodifluoroacetic anhydride, in anhydrous chloroform (or dichloromethane) of the corresponding electron-rich substrates (*N*,*N*-dimethyl-1-naphthylamine and butylvinylether) in the presence of pyridine as a base. The methodology has been previously presented for similar trifluoroacetylation reactions [27,28]. The reactions can be easily monitored by TLC and are preferably run at 0°C (under nitrogen atmosphere) during the addition of the electron-rich substrate/pyridine (1:1 mol equivalent) solution to the anhydride (1 M equivalent), and then slowly warmed-up to room temperature and maintained at this temperature until complete consumption of the olefinic substrate. The ketone **2** was prepared similarly using 2.5 mol equivalents of the anhydride and pyridine. The ketones **4–6** were prepared by nucleophilic displacement of the $-OC_4H_9$ group in ketone **3** with the appropriate amines [29], in refluxing acetonitrile and the reactions are usually completed in few minutes. Ketone **3** was isolated as the *trans* product as was shown by the large magnitude of the coupling constant $J_{Ha-Hb} = 12.2$ Hz whereas the ketones **4–6** were isolated as *cis* products ($J_{Ha-Hb} = 7.67$ Hz) due to the hydrogen bonding between NH_c and C=O. Yields of the chlorodifluoromethylated ketones are generally good and most of the products were isolated as coloured crystals (**1**, **2** and **6**) or viscous oils (**3–5**) (Schemes 3 and 4). All the ketones are stable compounds except for ketones **3–5** for which storage in the refrigerator is needed to avoid decomposition.

The reduction products ($RCOCF_2H$, **1A–6A**) could be prepared in good yields, under milder conditions, by reductive dechlorination using commercially available sodium formaldehyde sulfoxylate (Rongalite) as the reductant [30,31] (Scheme 5), in refluxing absolute EtOH. The reactions are usually complete in 3 h (as checked by TLC).

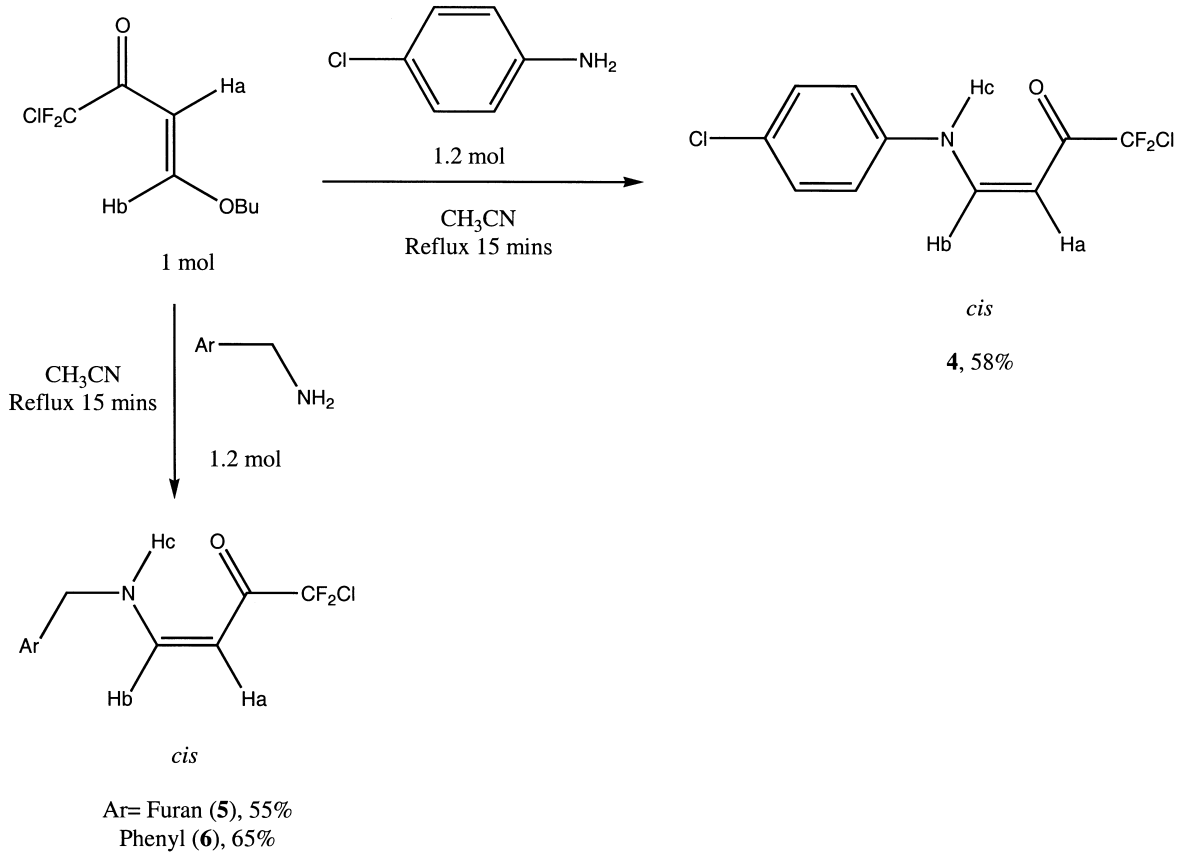
2.2. Electrochemical behaviour of the ketones

Cyclic voltammetry of compound **1**, the 2-chloro-1-(4-dimethylamino-naphthalen-1-yl)-2,2-difluoro-ethanone, shows two successive reduction waves; the first is irreversible (up to 1000 V/s), corresponding to the uptake of two electrons (as compared with the one-electron reversible oxidation wave of ferrocene) and located at −1.16 V versus SCE (peak potential E_p at 0.2 V/s on a glassy carbon electrode; Fig. 1, peak (a)). This reduction step corresponds to the cleavage of the C–Cl bond and to the formation of the (4-dimethylamino-naphthalen-1-yl-)-1-difluoroacetyl (**1A**) as the reduction product. The other wave, partially reversible, located at a more negative potential ($E_p = -1.51$ V versus SCE at 0.2 V/s on a glassy carbon electrode; Fig. 1, peak (b)) is attributed to the reduction of this compound, as was shown by comparison with an authentic sample. Additional reduction steps are observed at more negative potentials and may correspond to the reduction of the C=O bond into the corresponding alcohol (RC**HOH**CF_2H) or dimerisation of the anion radical into the corresponding pinacol [32], or pinacolate as observed for the electrochemical reduction of acetophenone [33].

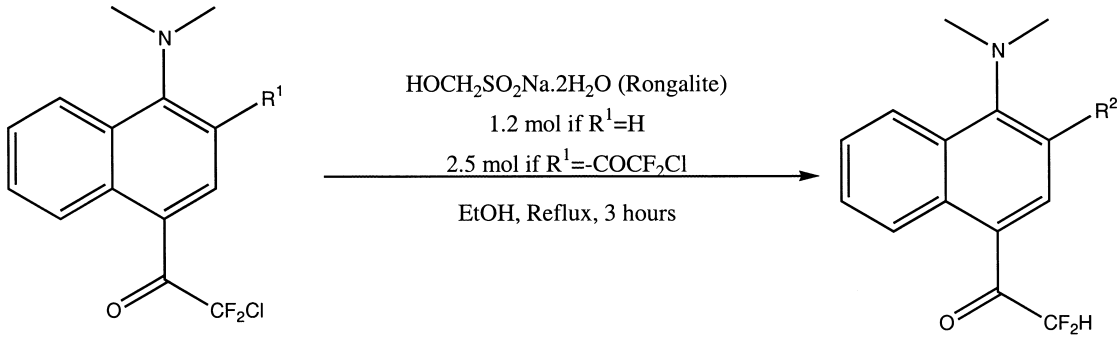
The other ketones **3–6** also present two reduction steps in the same electrochemical medium, usually with reduction potentials ranging from −1.28 to −1.57 V versus SCE (peak potentials E_p at 0.2 V/s on a glassy carbon electrode). The cyclic voltamogramm of ketone **2** is very similar to ketone **1** (despite the presence of the two C–Cl bonds) with a first two-electron reduction, located at a more positive potential, close to −0.97 V versus SCE (peak potential at 0.2 V/s). A second reduction step is located at −1.36 V versus SCE. From the



Scheme 3.



Scheme 4.



$$HOCH_2SO_2^{\ominus} \longrightarrow HSO_2^{\ominus} + HCHO$$

$$RCOCF_2Cl + HSO_2^{\ominus} \xrightarrow{SET} RCOCF_2^{\bullet} + HSO_2^{\bullet} + Cl^{\ominus}$$

Scheme 5.

cyclic voltammetry it is difficult to predict which C–Cl bond is first reduced. Therefore, different electrolyses were conducted, at different potentials, in order to have more information on the reduction process of ketone **2**. If the electrolysis was maintained at a constant potential corresponding roughly to the foot of the reduction wave ($E \sim -0.75$ V versus SCE in DMF + 0.1 M Et_4NBF_4), the reduction of the C–Cl bond occurs predominantly at position 4, and the major product identified by fluorine NMR (65% yield), after 2.1*F*/mol was **2A**. Additional products were the bis-$COCF_2H$ **2B** (15% yield) and unreacted starting material. A constant potential electrolysis in the same electrolytic medium, at a more negative potential, close to −1.25 V versus SCE gave after 2.3*F*/mol, a major compound identified as the bis-$COCF_2H$ reduction product **2B** (62%) from its fluorine NMR spectrum. If the electrolysis was run at a constant potential corresponding to the second reduction step observed in cyclic voltammetry, a complex mixture of fluorinated products including **2A**, **2B** with some alcohols was observed by fluorine NMR. From these experiments we can assume that the reduction of the two C–Cl bonds occur at very close potentials, the C–Cl bond of the –$COCF_2Cl$ moiety at position 4 being slightly easier to reduce.

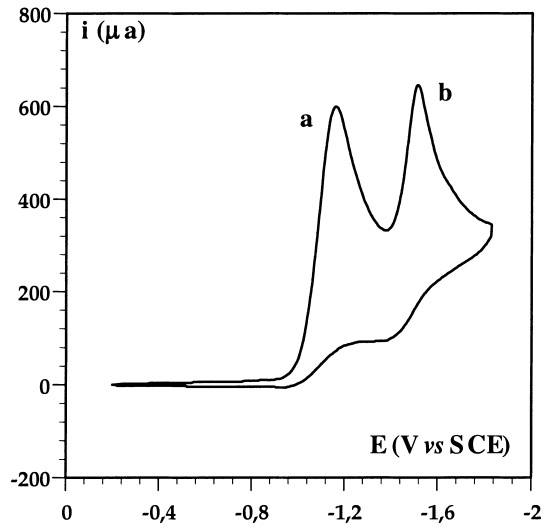


Fig. 1. Cyclic voltammetry of ketone **1** in DMF + 0.01 M Et_4NBF_4. $C = 3.13$ mM. Scan rate: 0.2 V/s. $T = 22$°C. Glassy carbon electrode.

From a mechanistic point of view, we have examined more carefully the first electrochemical reduction of ketone **1**. A linear variation of the peak potential with the scan rate was obtained and a slope of 55 mV/log *v* was measured for scan rates between 1 and 100 V/s. For lower scan rates ($0.1 < v < 1$ V/s) a slope of 47 mV/log *v* was obtained. These results are in agreement with an electrochemical chemical electrochemical (ECE) mechanism [34] (Scheme 6) under mixed kinetic control by the initial electron transfer step generating the anion radical and the following cleavage step (stepwise mechanism).

Comparison of these experimental results with simulated curves [34], allows an estimation of the rate constant of the cleavage of the C–Cl bond in the anion radical, in the range of 10^8–10^9 M^{-1} s^{-1} (assuming the same standard heterogeneous electron transfer rate constant k_s as 4-bromoacetophenone 0.5 cm^{-1} s^{-1}; [35]). The cyclic voltammetry of ketone **2** is comparable to ketone **1** where a slope of 35 mV/log *v* was obtained. For the other ketones **3**–**6**, examination

$$RCOCF_2Cl + 1e \longrightarrow RCOCF_2Cl^{-\bullet} \quad E$$

$$RCOCF_2Cl^{-\bullet} \longrightarrow RCOCF_2^{\bullet} + Cl^{\ominus} \quad C$$

$$RCOCF_2^{\bullet} + 1e \longrightarrow RCOCF_2^{\ominus} \quad E$$

$$RCOCF_2^{\ominus} + H_2O \longrightarrow RCOCF_2H + OH^{\ominus}$$

Scheme 6.

of the first reduction step reveals a value of the transfer coefficient α close to 0.5, derived from the value of the peak width $E_{p/2} - E_p$ [E_p = peak potential; $E_{p/2}$ = half-peak potential: $\alpha = RT/F(1.85/E_{p/2} - E_p)$] showing a similar stepwise mechanism [36]. A more detailed mechanistic study of a series of chlorodifluoromethylated ketones is currently under way.

Quantum mechanical calculations were performed on ketone **1** using semi-empirical AM1 and density functional B3LYP methods. A minimum of energy was found in the optimisation of the geometry for the anion radical which confirms the electrochemical results that the anion radical is indeed a reaction intermediate in the reduction process. Spin density calculations show that the unpaired electron is localised in all the aromatic system which can explain its chemical stability. On the contrary, for the radical produced after the cleavage of the C–Cl bond, the unpaired electron is clearly localised on the –C(O)–CF_2 functionality (0.63 on the C, 0.29 on O; Fig. 2). For ketone **2**, spin densities calculation for the anion radical, shows that almost similar densities of the unpaired electron are present on both carbonyl groups, which does not allow prediction of which of the C–Cl bond will cleave first.

2.3. Cyclisation reactions

Then the question was posed: could we generate a stable and reactive difluoroacetyl electrophilic radical electrochemically, and trap it with olefinic rich substrates? Upon addition of the olefinic substrate **7** (2,3-dihydrofuran) to the DMF (or CH_3CN) solution of **1**, no change in the voltamogramm was observed, even if large excess of the olefin was used. Such behaviour indicates either that the major pathway of the α,α-difluoroalkyl radical is a further reduction to the hydrogenolysis product or that the α,α-difluoroalkyl addition onto the olefinic substrate is too slow to be observed during the time of the cyclic voltammetric experiments. Another possibility could be that the overall electron stoichiometry of the radical addition or the cyclisation process, remains close to 2*F*/mol. To test this possibility, we carried out the constant potential electrolysis ($E = -1.30$ V versus SCE on a carbon felt cathode) of ketone **1** in the presence of 10 mol equivalents of **7**, in anhydrous CH_3CN + 0.1 M Et_4NBF_4; the major product observed by fluorine NMR (82% yield), was the reduction product **1A**. No radical addition product was observed. Evidently the reduction of the α,α-difluoroalkyl is the major pathway upon direct electrochemical reduction, probably due its low reduction potential. Therefore single electron transfer induction by electrochemically generated nitrobenzene anion radical ($E^0 = -1.10$ V versus SCE) for the redox catalysed reduction [37] of substrates **1**, **3**–**7** and by the 4-nitropyridine-*N*-oxide ($E^0 = -0.70$ V versus SCE) for the redox catalysed reduction of substrate **2**, was then employed so as to operate under less reducing conditions. As a typical experiment we carried out a preparative-scale electrolysis

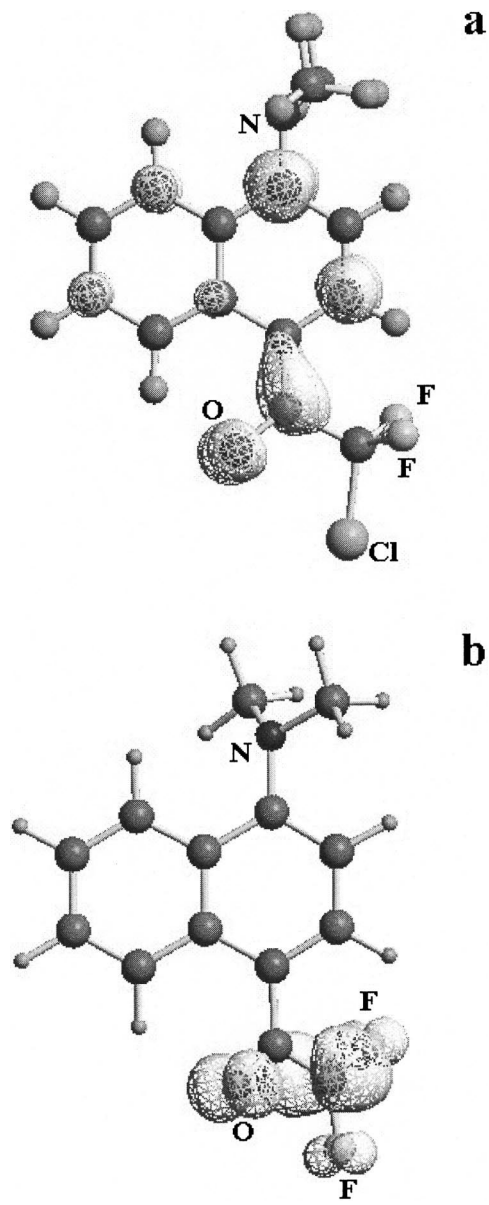


Fig. 2. AM1 optimised conformations and spin densities (calculated at B3LYP/6-31G* level) of the anion radical (a) and of the radical (b) produced after cleavage of C–Cl bond of **1**. Spin densities are drawn for an isodensity of 0.004 a.u.

of the substrate **1** in the presence of large excess of the olefinic acceptor **7** at a potential behind the nitrobenzene ($E = -1.30$ V versus SCE). Using a two-compartment cell with carbon felt as cathode and anode materials, a glass frit as separator, we found that the starting material was consumed after 2.2*F*/mol (as checked by TLC or HPLC) and that two major compounds were produced along with some minor by-products. The major compounds were separated by silica gel chromatography and were identified as **1A** (28%) and as the 5-dimethylamino-11,11-difluoro-1, 2, 11,11a-tetrahydro-3a*H*-phenanthro[1,2-*b*]furan-10-one **11** (60%). The structure of compound **11** was confirmed by

its proton NMR spectrum where the proton at position 4 (see structure in Chart) on the naphthalene ring, appeared as a singlet demonstrating the absence of proton–proton coupling due to the intramolecular cyclisation. A resonance centred at δ −5.3 ppm appeared as a doublet and was assigned to H_{3a} with a ^2J close to 7.15 Hz suggesting a *cis* conformation. The fluorine NMR of compound **11** shows clearly two pairs of doublets of doublets (centred at δ −99.9 and −111.4 ppm/$CFCl_3$) demonstrating that the fluorines are non-equivalent, with F–F and F–H coupling (J_{F-F} = 272 Hz, $^3J_{F-H}$ = 12.5 and 11.5 Hz). It is difficult from the NMR to distinguish between the two possible conformers. The other possible structure (with the same molecular peak at 317) could have been the seven-membered ring cyclised product **11′**. This structure was ruled out since we should have observed in its proton NMR spectrum, the H-3 as a doublet. The simple addition product **11″** was also ruled out since we did obtain a molecular peak of 317 instead of 319 as confirmed by GC/MS as well by microanalysis (Scheme 7).

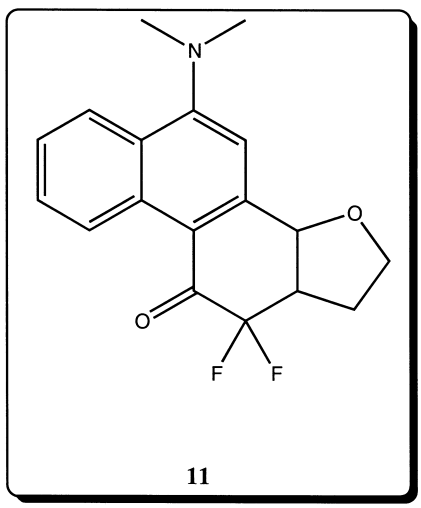
The new *gem*-difluorinated cyclised compounds **11–16** were obtained similarly in moderate yields after separation by silica gel column chromatography (Table 1).

Cyclised product **12** was obtained in 32% isolated yield from the redox catalysed cyclisation of ketone **2** after the consumption of 1.7*F*/mol, at a constant potential close to −0.70 V versus SCE, and compound **13** was obtained in 28% isolated yield after the consumption of 3.2*F*/mol at a more negative potential close to −1.0 V versus SCE, or more conveniently from the reductive dechlorination of **12** with Rongalite (in absolute EtOH for 5 h). Compound **12** can be also synthesised (52%) by direct chlorodifluoroacetylation of **11** in refluxing 1,2-dichloroethane (3 h, no pyridine). We should note that the electrochemical synthesis of **12** and **13** gave also other fluorinated products, usually reduction products in appreciable amounts. Compounds **15** and **16** were obtained as mixture of isomers. Due to overlapping signals in ^{1}H NMR we are not able to determine the ratio of isomers. AM1 optimised geometry calculation suggested that for **15**, the *trans* isomer is more stable by 2.5 kcal/mol. Similar semi-empirical calculations show that the more stable structures for the cyclised product **11**, among the four possible geometries, were the conformations with H_{3a} and H_{11a} being either *axial–axial* or *equatorial–equatorial* (Fig. 3).

Table 1
Synthesis of the cyclised α,α-difluoroketones

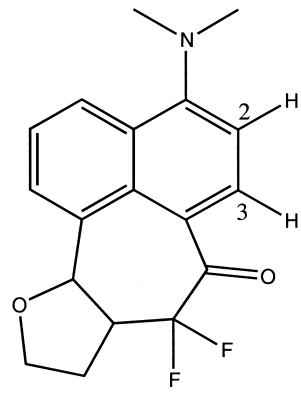
Substrate[a]	Olefinic acceptor	Product (%)[b]
1[c]	2,3-Dihydrofuran **7**	**11** (60)
	n-Butylvinylether **8**	**15** (50)[d]
	1-Vinylimidazole **9**	**16** (30)[e]
	3,4-Dihydropyran **10**	**14** (45)
2[f]	2,3-Dihydrofuran **7**	**12** (32)[g]
		13 (28)[h]

[a] $C_{sub} = 3.53 \times 10^{-3}$ mol + C_{olefin} 35.3×10^{-3} mol in anhydrous DMF + 0.1 M Et_4NBF_4.
[b] Isolated yield; 2.2*F*/mol of starting substrate.
[c] $PhNO_2$ ($C = 0.75 \times 10^{-3}$ mol) was used as redox mediator; electrolysis potential $E = -1.30$ V versus SCE.
[d] Obtained as a *cis*/*trans* mixture.
[e] Fluorine NMR yield.
[f] 4-Nitro pyridine-*N*-oxide ($C = 0.75 \times 10^{-3}$ mol) was used as redox mediator; electrolysis potential $E = -0.70$ V versus SCE.
[g] After 1.7*F*/mol.
[h] After 3.4*F*/mol.



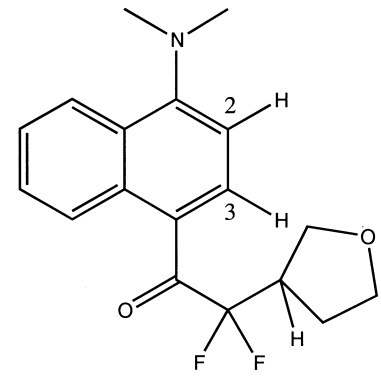
11

$C_{18}H_{17}F_2NO_2$
Exact Mass: 317,1227



11'

$C_{18}H_{17}F_2NO_2$
Exact Mass: 317,1227



11''

$C_{18}H_{19}F_2NO_2$
Exact Mass: 319,1384

Scheme 7.

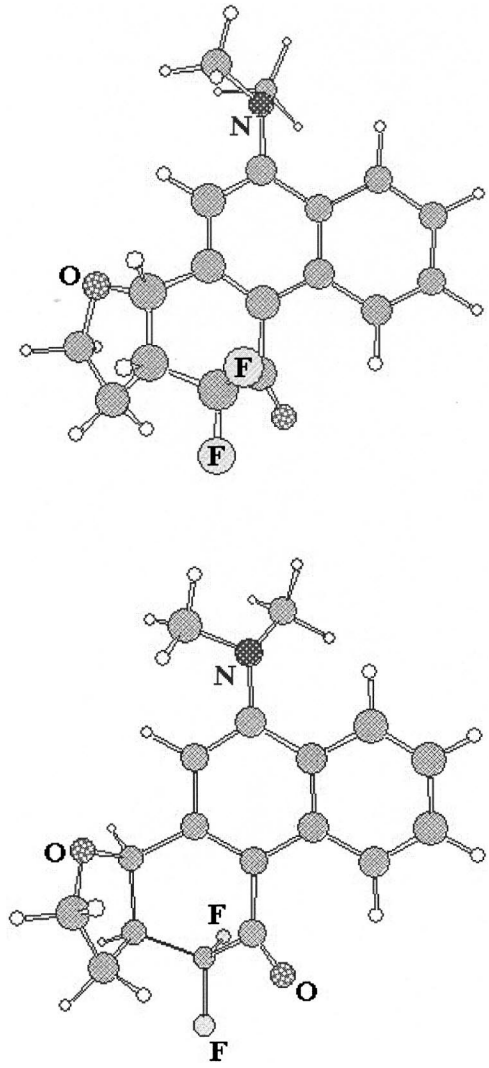
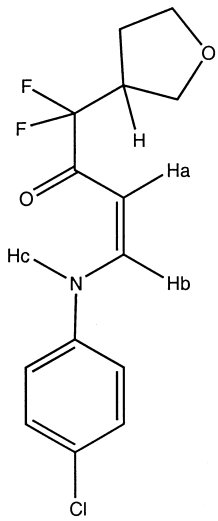


Fig. 3. AM1-optimised geometry of the cyclised product **11**.

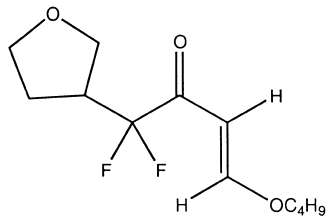
The products which represent the remaining balance material were usually the hydrogenolysis compounds from hydrogen atom transfer to the α,α-difluoroalkyl or from further reduction and protonation. For all the cyclised products, the reduction of the C=O occurs at more negative potentials than the first reduction step of the starting ketones **1** and **2**, close to −1.45 V versus SCE as checked by cyclic voltammetry. For cyclised product **12**, the reductive cleavage of the C–Cl bond seems to occur at −1.38 V versus SCE therefore opening the possibility of further chemical and electrochemical transformations at this site.

Attempts to obtain cyclised products with ketones **3**–**6** and 2,3-dihydrofuran **7** have been thus far less successful; for example the redox catalysed reduction of ketone **3** in the presence of large excess of **7**, in DMF or CH_3CN as solvent, resulted in the formation of the corresponding reduction product **4A** as major component (65%) along with some simple addition product **X** (20%), characterised by its AB pattern in the fluorine spectrum.

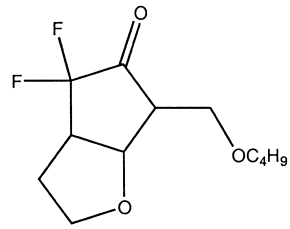


Product X

Reaction of ketone **3** (electrolysis was run at 0°C) with **7** gave at least three fluorinated products where **3A** was the major component; other products were characterised by complicated AB systems and doublet of doublets (cyclised products: 5-*exo* and/or 6-*endo*) in the fluorine spectrum of the crude product. GC/MS could not distinguish between the different possible products since they have the same molecular weight. Work is under progress to find the conditions to obtain the desired cyclised products.

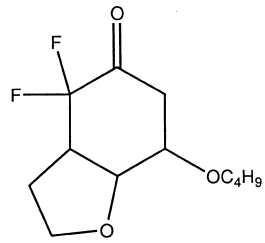


Simple addition product



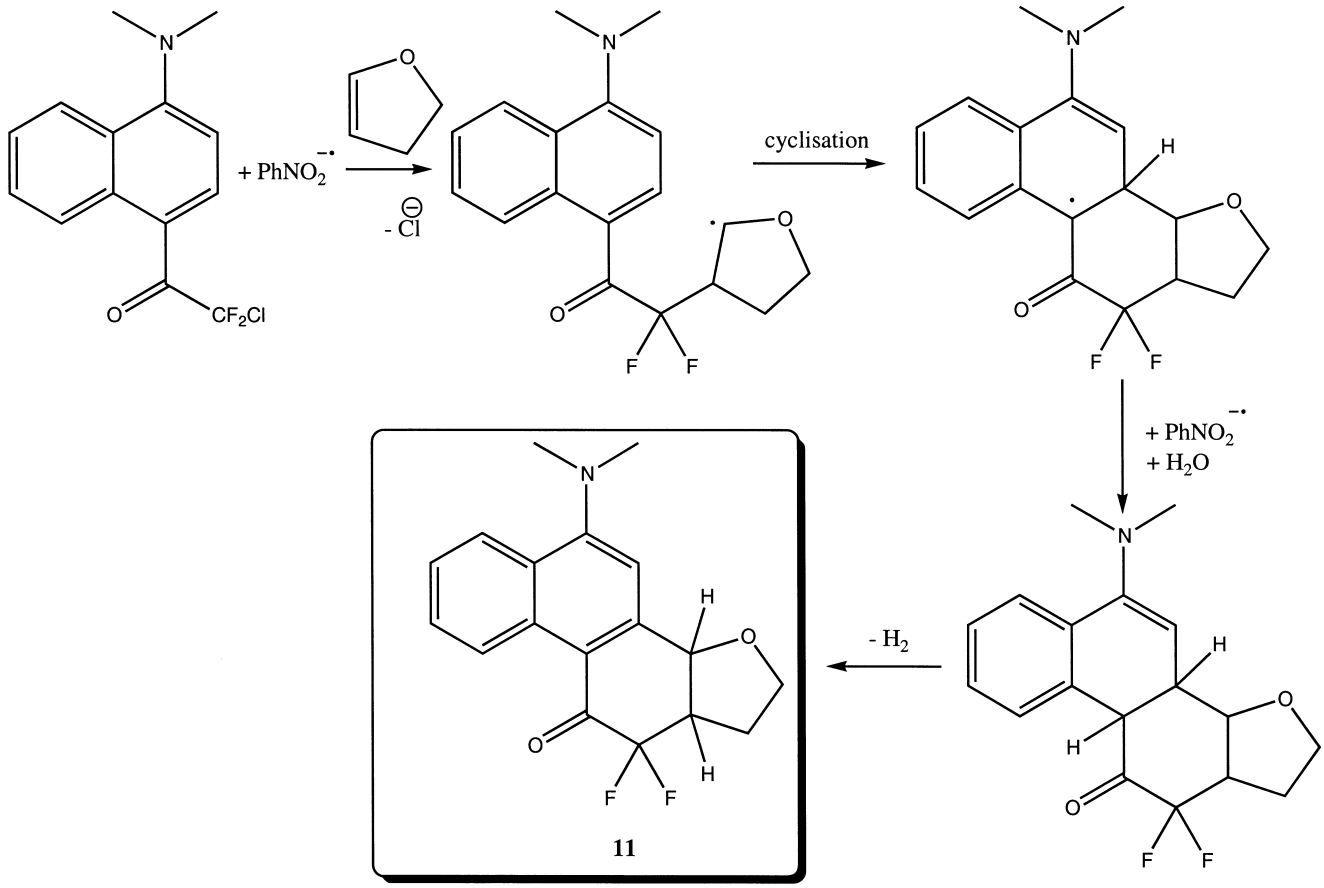
5-*exo* product

3+7 reaction



6-*endo* product

The rather low yield obtained in the reaction of substrate **1** and vinyl imidazole **9** may be related to some partial polymerisation of the olefinic substrate and/or steric hindrance of the imidazole heterocycle unit. The yield of the product was 30% (isomeric mixture) by fluorine NMR; attempts to purify the product by silica gel chromatography resulted in significant loss of product.



Scheme 8.

The mechanism of formation of the cyclised products involves the intramolecular cyclisation of the γ,γ-difluoroalkyl radical obtained after the addition of the α,α-difluoroalkyl radical on the double-bond. The observed consumption of electricity (as measured by cyclic voltammetry and coulometry) is close to 2*F*/mol. This can be due either to the further reduction of the cyclised radical in solution by the anion radical of the catalyst or to an hydrogen atom abstraction from the solvent [38] to give the final product after rearomatisation (Scheme 8). A dismutation of the 'cyclised radical' cannot explain the consumption of electricity (2*F*/mol) since it should have been close to 1*F*/mol.

2.4. Aromatic N–N exchanged reactions

N,*N*-dimethyl-2,4-bis(trifluoroacetyl)-1-naphthylamine was found to undergo various nitrogen–nitrogen, nitrogen–sulfur and nitrogen–oxygen exchange reactions to give interesting trifluoromethylated heterocycles [39]. We have found that the heterocyclic α,α-difluoroketones **12** and **13** could also undergo *N–N* exchange reactions with several tetramethylammonium salts of imidazoles to give the exchanged products **17–23** in moderate to good yields. The *N*,*N*-dimethylamino group of the heterocyclic α,α-difluoroketones **12** and **13** was successfully displaced by the dried tetramethylammonium salt of imidazole ([$NuNMe_4$/[substrate] = 3) in anhydrous DMSO, at 50°C for 10 h, to give the exchanged products **17** (65%) and **18** (55%). Imidazole-2-carboxaldehyde and 2-methyl-5-nitroimidazole anions, less reactive nucleophiles, gave exchanged products in moderate yields with increasing the concentration of the nucleophiles ([$NuNMe_4$/[substrate] = 10). 2-(4′-Methoxyphenyl)imidazole, despite the increasing electron density on the imidazole ring, reacts poorly as compared to the imidazole anion. This unsatisfactory result may be explained by a repulsive effect between the chloro or difluoroacetyl group and the methoxyphenyl ring. The products which represent the remaining balance material were the unreacted starting material (major compound) and other yet unidentified products (as observed by HPLC and ^{19}F NMR of the raw solution). The nucleophilic substitution reaction was found to be regiospecific as the –N(1) isomer was isolated as the sole product. Formation of the substituted products was monitored by HPLC and the yields are moderate to good. The structures of compounds **17–23** obtained after column chromatography, were confirmed by their spectroscopic and analytical data (Table 2).

Table 2
Synthesis of the 5-imidazol-1-yl α,α-difluoroketones

Substrate[a]	Nucleophile[b]	Product (%)[c]
12	Imidazole	**17** (65)
	Benzimidazole	**19** (71)
	2-(4′-Methoxphenyl) imidazole	**16** (32)
	Imidazole-2-carboxaldehyde[d]	**22** (45)
	2-Methyl-5-nitro imidazole[d]	**23** (40)
13	Imidazole	**18** (55)
	Benzimidazole	**20** (48)

[a] $C_{sub} = 1.58 \times 10^{-3}$ mol + $C_{NuNMe_4} = 4.74 \times 10^{-3}$ mol in anhydrous DMSO at 50°C for 10 h.
[b] Used as the tetramethylammonium salt.
[c] Isolated yield.
[d] $C_{sub} = 1.58 \times 10^{-3}$ mol + $C_{NuNMe_4} = 15.8 \times 10^{-3}$ mol in anhydrous DMSO at 50°C for 10 h.

3. Conclusions

These results represent the first example of a free-radical electrochemical intramolecular synthesis of some interesting *gem*-difluoro heterocyclic compounds that could be difficult to obtain from other types of reactions. None of the yields has been optimised and room for improvement certainly exists. The *N–N* exchange reaction is a facile and convenient synthetic method to obtain fluorine-containing naphthalene-fused heterocycles which are difficulty accessible by other methods. This reaction is now being extended to bifunctional nucleophiles and other nitrogen nucleophiles. Work is under progress to find the best conditions to obtain the bicyclic *gem*-difluorinated products with ketones **3–6** as starting materials. The successful cyclisation reaction with the naphthalene ketones **1** and **2**, will be extended to more sophisticated starting chlorodifluoromethylated ketones. Evaluation of the biological activities of all the compounds will be done in a due course.

4. Experimental

The electrochemical equipment has been described in [40]. All the olefinic acceptors are from commercial origins. Benzimidazole, imidazole, 2-methyl-5-nitro imidazole were purchased from Aldrich. Rongalite was purchased from Fluka. Imidazole-2-carboxaldehyde was prepared as in [41] and 2-(4′-methoxyphenyl)imidazole was prepared as in [42]. Anhydrous DMF, CH_3CN (Fluka Puriss dried over molecular sieve) and DMSO (Gold label from Aldrich) were used as received. Silica gel (MN Kieselgel 60, 70–230 mesh, Macherey–Nagel) was employed for column chromatography. Analytical TLC was performed with 0.25 mm coated commercial plates (Macherey–Nagel, Polygram SIL G/UV_{254}). All the reactions with air-sensitive compounds were carried out under nitrogen atmosphere.

NMR spectra (400 MHz Bruker spectrometer) were taken in DMSO-d_6 and $CDCl_3$ using TMS as the internal standard for ^{1}H (250.133 and 400.132 Hz). ^{19}F NMR (235.323 and 376.498 Hz) used CCl_3F as internal standard. Melting points are uncorrected.

All calculations were carried out with the Gaussian 94 package [43]. Geometries of the anions radical and radical were calculated by full optimisation of the conformations using semi-empirical method AM1 [44]. Spin densities were calculated using the B3LYP density functional theory [45] with a 6-31G* basis set [46] on the previously optimised AM1 conformations.

4.1. 2-Chloro-1-(4-dimethylamino-naphthalen-1-yl)-2,2-difluoro-ethanone (**1**)

A representative procedure for the synthesis of the 2-chloro-1-(4-dimethylamino-naphthalen-1-yl)-2,2-difluoroethanone (**1**) is described. Into a three-necked flask equipped with a dropping funnel, a reflux condenser (with a silica gel drying tube) and a nitrogen inlet, were added under nitrogen at 0°C, 25 ml of anhydrous $CHCl_3$ followed by $(ClCF_2CO)_2O$ (14.1 g, 58 mmol) via a syringe. The solution was stirred and maintained at this temperature for 30 min and then was added dropwise a solution containing the *N*,*N*-dimethyl-1-naphthylamine (10 g, 58.4 mmol) and pyridine (4.7 g, 59.4 mmol). When the addition was finished, the solution was stirred at 0°C for 30 min and warmed-up slowly to room temperature over 3 h. After this time, TLC analysis indicated that the *N*,*N*-dimethyl-1-naphthylamine was totally consumed. The yellow solution was diluted with $CHCl_3$, washed with 1N HCl aqueous solution (4×) and dried over $MgSO_4$. Evaporation of the solvent left a viscous orange oil which was recrystallised (two crops) from cold absolute EtOH to give **1** (75%): mp 74°C (yellow crystals). ^{1}H NMR ($CDCl_3$): δ_H 3.11 (6H, s, NMe_2), 6.91 (1H, d, H-2, $J = 8.42$ Hz), 7.52–7.66 (2H, m, H-6 and H-7), 8.16–8.28 (2H, m, H-3 and H-8), 9.01 (1H, dd, H-5, $J = 7.69$, 0.65 Hz). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −58.03 (2F, s). GC/MS: $M^+ = 283$, $M^+ - CF_2Cl = 198$. Anal. Calcd. for $C_{14}H_{12}ClF_2NO$: C 59.27%, H 4.26%, N 4.94%. Found C 59.10%, H 4.43%, N 4.76%.

4.2. 2-Chloro-1-[3-(chloro-difluoro-acetyl)-(4-dimethylamino-naphthalen-1-yl)-2,2-difluoro-ethanone (**2**)

Mp 84°C (orange crystals). ^{1}H NMR ($CDCl_3$): δ_H 3.16 (6H, s, NMe_2), 7.58–7.62 (1H, m, H-7), 7.73–7.77 (1H, m, H-6), 8.22–8.24 (1H, dd, H-8, $J = 7.71$, 0.88 Hz), 8.64 (1H, s, H-3), 8.9 (1H, d, H-5, $J = 8.55$ Hz). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −60.17 (2F, s), −59.18 (2F, s). GC/MS: $M^+ = 395$, $M^+ - CF_2Cl = 310$. Anal. Calcd. for $C_{16}H_{11}ClF_4NO_2$: C 48.51%, H 2.80%, N 3.54%. Found C 48.38%, H 2.63%, N 3.76%.

4.3. 4-Butoxy-1-chloro-1,1-difluoro-but-3-en-2-one (**3**)

Yellowish oil. ^{1}H NMR ($CDCl_3$): δ_H 0.92 (3H, m, CH_3), 1.47 (2H, m, CH_2), 1.69 (2H, m, CH_2), 4.02 (2H, t, CH_2,

$J = 6.49$ Hz), 5.85 (1H, d, H_a, $J = 12.21$ Hz),), 7.87 (1H, d, H_b, $J = 12.22$ Hz). ^{19}F NMR ($CDCl_3/CFCl_3$): δ_F −71.65 (2F, s). GC/MS: $M^+ = 213$, $M^+ - CF_2Cl = 127$. Anal. Calcd. for $C_8H_{11}ClF_2O_2$: C 45.19%, H 5.21%. Found C 45.28%, H 5.43%.

4.4. 1-Chloro-4-(4-chloro-phenylamino)-1,1-difluoro-but-3-en-2-one (**4**)

A representative procedure for the synthesis of the 1-chloro-4-(4-chloro-phenylamino)-1,1-difluoro-but-3-en-2-one (**4**) is described. Into a three-necked flask equipped with a reflux condenser (with a silica gel drying tube) and a nitrogen inlet, were added under nitrogen 15 ml of an anhydrous CH_3CN solution containing **3** (2.1 g, 9.85 mmol). The solution was stirred at room temperature for 30 min and then were added 1.2 g (10 mmol) of 4-chloroaniline. When the addition was finished, the solution was heated to reflux for 30 min. After this time, TLC indicated that the amine was totally consumed. Evaporation of the solvent left a viscous orange oil which was recrystallised (two crops) from hexane to give **4** (58%): mp 84°C (yellowish needles). ^1H NMR ($CDCl_3$): δ_H 5.68 (1H, d, H_a, $J = 7.62$ Hz), 7.03–7.09 (2H, m, H-arom), 7.32–7.37 (2H, m, H-arom), 7.61 (1H, dd, H_b, $J = 13.0$, 7.62 Hz), 11.62 (1H, br s, H_c). ^{19}F NMR ($CDCl_3/CFCl_3$): δ_F −65.75 (2F, s). GC/MS: $M^+ = 265$, $M^+ - CF_2Cl = 180$. Anal. Calcd. for $C_{10}H_7Cl_2F_2NO$: C 45.14%, H 2.65%, N 5.26%. Found C 45.10%, H 2.53%, N 5.46%.

4.5. 1-Chloro-1,1-difluoro-4-[(furan-2-ylmethyl)-amino]-but-3-en-2-one (**5**)

The product was purified by silica gel chromatography (Et_2O/hexane, 60:40) and obtained as a yellowish oil. ^1H NMR ($CDCl_3$): δ_H 4.46 (2H, d, $J = 5.75$ Hz), 5.39 (1H, d, H_a, $J = 7.27$ Hz), 6.27–6.34 (2H, m, H-furan), 7.17 (1H, dd, H_b, $J = 13.4$, 7.3 Hz), 7.36 (1H, d, H-furan, $J = 1.0$ Hz), 10.16 (1H, br s, H_c). ^{19}F NMR ($CDCl_3/CFCl_3$): δ_F −68.81 (2F, s). GC/MS: $M^+ = 235$, $M^+ - CF_2Cl = 150$. Anal. Calcd. for $C_9H_8ClF_2NO_2$: C 45.88%, H 3.42%, N 5.94%. Found C 45.62%, H 3.52%, N 6.03%.

4.6. 4-Benzylamino-1-chloro-1,1-difluoro-but-3-en-2-one (**6**)

The product was purified by silica gel chromatography (hexane/EtOAc, 70:30) and obtained as a yellowish oil. ^1H NMR ($CDCl_3$): δ_H 4.71 (2H, br s, CH_2), 5.58 (1H, d, H_a, $J = 7.54$ Hz), 7.17 (1H, dd, H_b, $J = 13.2$, 7.1 Hz), 7.37–7.58 (5H, m, arom-H), 10.26 (1H, br s, H_c). ^{19}F NMR ($CDCl_3/CFCl_3$): δ_F −68.32 (2F, s). GC/MS: $M^+ = 245$, $M^+ - CF_2Cl = 160$. Anal. Calcd. for $C_{11}H_{10}ClF_2NO$: C 53.78%, H 4.10%, N 5.70%. Found C 53.82%, H 4.32%, N 5.53%.

4.7. 4-Dimethylamino-naphthalen-1-yl-1-difluoroacetyl (**1A**)

A representative procedure for the synthesis of the 4-dimethylamino-naphthalen-1-yl-1-difluoroacetyl (**1A**) is described. Into a three-necked flask equipped with a reflux condenser (with a silica gel drying tube) and a nitrogen inlet, were added under nitrogen, 25 ml of absolute EtOH followed by **1** (0.5 g, 1.76 mmol). The solution was stirred until complete dissolution and then Rongalite (0.32 g, 2.12 mmol) was added. The whole mixture was then heated at reflux until complete consumption of starting material (2 h). The solution was filtered, and evaporated to dryness. The crude product was filtered through a short column of silica gel eluting with hexane/EtOAc (70:30) and recrystallised from hexane to give **1A** (68%); mp = 70–72°C (yellow powder). ^1H NMR ($CDCl_3$): δ_H 3.07 (6H, s, $-NMe_2$), 6.44 (1H, t, $-CF_2H$, $^2J_{H-F} = 57$ Hz), 6.92 (1H, d, H-2, $J = 8.36$ Hz), 7.50–7.68 (2H, m, H-6 and H-7), 8.13–8.20 (2H, m, H-3 and H-8), 9.2 (1H, d, H-5, $J = 8.38$ Hz). ^{19}F NMR ($CDCl_3/CFCl_3$): δ_F −119.31 (2F, d, $^2J_{H-F} = 54$ Hz). GC/MS: $M^+ = 249$, $M^+ - CF_2H = 198$. Anal. Calcd. for $C_{14}H_{13}F_2NO$: C 67.46%, H 5.22%, N 5.62%. Found C 67.68%, H 5.43%, N 5.87%.

4.8. 1-[3-(2,2-Difluoro-acetyl)-4-dimethylamino-naphthalen-1-yl]2,2-difluoro-ethanone (**2B**)

Yellowish viscous oil. ^1H NMR ($CDCl_3$): δ_H 3.12 (6H, s, $-NMe_2$), 6.44 (1H, t, $-CF_2H$, $^2J_{H-F} = 57$ Hz), 6.58 (1H, t, $-CF_2H$, $^2J_{H-F} = 52$ Hz), 7.68–8.01 (2H, m, H-6 and H-7), 8.22–8.24 (1H, dd, H-8, $J = 7.71$, 0.88 Hz), 8.64 (1H, s, H-3), 8.9 (1H, d, H-5, $J = 8.55$ Hz). ^{19}F NMR ($CDCl_3/CFCl_3$): δ_F −119.31 (2F, d, $^2J_{H-F} = 57$ Hz), −123.2 (2F, d, $^2J_{H-F} = 52$ Hz). GC/MS: $M^+ = 327$, $M^+ - CF_2H = 276$. Anal. Calcd. for $C_{16}H_{13}F_4NO_2$: C 58.72%, H 4.00%, N 4.28%. Found C 58.68%, H 4.33%, N 4.53%.

4.9. 4-Butoxy-1,1-difluoro-but-3-en-2-one (**3A**)

The product was obtained as a yellowish oil after purification by silica gel chromatography (hexane/EtOAc, 80:20). ^1H NMR ($CDCl_3$): δ_H 0.96 (3H, m, CH_3), 1.34 (2H, m, CH_2), 1.66 (2H, m, CH_2), 4.02 (2H, t, CH_2, $J = 6.49$ Hz), 5.85 (1H, d, H_a, $J = 12.21$ Hz),), 6.68 (2H, t, $-CF_2H$, $^2J_{H-F} = 51$ Hz), 7.87 (1H, d, H_b, $J = 12.22$ Hz). ^{19}F NMR ($CDCl_3/CFCl_3$): δ_F −122.2 (2F, t, $^2J_{H-F} = 51$ Hz). GC/MS: $M^+ = 178$, $M^+ - CF_2H = 127$ Anal. Calcd. for $C_8H_{12}F_2O_2$: C 53.93%, H 6.79%. Found C 54.04%, H 6.43%.

4.10. 4-(4-Chloro-phenylamino)-1,1-difluoro-but-3-en-2-one (**4A**)

The product was obtained as a yellowish viscous oil after purification by silica gel chromatography (hexane/EtOAc,

80:20). ^{1}H NMR ($CDCl_3$): δ_H 5.45 (1H, d, H_a, $J = 7.62$ Hz), 6.05 (1H, t, $-CF_2H$, $^2J_{H-F} = 56$ Hz), 7.03–7.09 (2H, m, H-arom), 7.32–7.37 (2H, m, H-arom), 7.61 (1H, dd, H_b, $J = 13.0$, 7.62 Hz), 11.42 (1H, br s, H_c). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −125.2 (2F, t, $^2J_{H-F} = 57$ Hz). GC/MS: $M^+ = 231$, $M^+ - CF_2Cl = 180$. Anal. Calcd. for $C_{10}H_8ClF_2NO$: C 51.85%, H 3.48%, N 6.05%. Found C 51.68%, H 3.53%, N 6.26%.

4.11. 1,1-Difluoro-4-[(furan-2-yl-methyl)-amino]-but-3-en-2-one (**5A**)

The product was purified by silica gel chromatography (Et_2O/hexane, 60:40) and obtained as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ_H 4.26 (2H, d, $J = 5.75$ Hz), 5.29 (1H, d, H_a, $J = 7.27$ Hz), 6.15 (1H, t, $-CF_2H$, $^2J_{H-F} = 52$ Hz), 6.57–6.84 (2H, m, H-furan), 7.37 (1H, dd, H_b, $J = 13.4$, 7.3 Hz), 7.56 (1H, d, H-furan, $J = 1.0$ Hz), 10.26 (1H, br s, H_c). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −124.5 (2F, t, $^2J_{H-F} = 53$ Hz). GC/MS: $M^+ = 201$, $M^+ - CF_2Cl = 150$. Anal. Calcd. for $C_9H_9F_2NO_2$: C 53.73%, H 4.51%, N 6.96%. Found C 53.62%, H 4.52%, N 6.93%.

4.12. 4-Benzylamino-1,1-difluoro-but-3-en-2-one (**6A**)

The product was purified by silica gel chromatography (hexane/EtOAc, 70:30) and obtained as a yellowish oil. ^{1}H NMR ($CDCl_3$): δ_H 4.71 (2H, CH_2, br s), 5.78 (1H, d, H_a, $J = 7.54$ Hz),), 6.15 (1H, t, $-CF_2H$, $^2J_{H-F} = 52$ Hz), 7.37 (1H, dd, H_b, $J = 13.2$, 7.1 Hz), 7.67–7.98 (5H, m, arom-H), 10.16 (1H, br s, H_c). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −126.5 (2F, t, $^2J_{H-F} = 55$ Hz). GC/MS: $M^+ = 211$, $M^+ - CF_2Cl = 160$. Anal. Calcd. for $C_{11}H_{11}F_2NO$: C 62.55%, H 5.25%, N 6.63%. Found C 62.62%, H 5.32%, N 6.73%.

4.13. 5-Dimethylamino-11,11-difluoro-1,2,11,11a-tetrahydro-3aH-phenanthro[1,2-b]furan-10-one (**11**)

A representative procedure for the synthesis of the cyclised product 5-dimethylamino-11,11-difluoro-1,2,11,11a-tetrahydro-3a*H*-phenanthro[1,2-b]furan-10-one (**11**) is described. A solution of nitrobenzene (0.15 g, 1.2 mmol), 2-chloro-1-(4-dimethylamino-naphthalen-1-yl)-2,2-difluoro-ethanone **1** (1 g, 3.53 mmol), 2,3-dihydrofuran **7** (2.5 g, 35.3 mmol) and NEt_4BF_4 (2.17 g, 10 mmol) in DMF (80 ml) was reduced at −1.30 V versus SCE in a cylindrical Pyrex cell with carbon felt (15 cm^2) as cathode, separated from the anolyte compartment (carbon felt anode 10 cm^2) with a glass frit (porosity 4), until almost all the starting material was consumed (as checked by TLC; 2.2*F*/mol). The red solution was evaporated to dryness and the crude product was extracted with $CHCl_3$ (3×); the combined organic extracts were washed with brine (3×), water (3×), dried over $MgSO_4$ and filtered. Evaporation of the solvent left an orange-red viscous solid as crude product. Silica gel chromatography using EtOAc/hexane (50/50) gave first the 4-dimethylamino-naphthalen-1-yl-1-difluoroacetyl **1A** (0.24 g, 0.98 mmol, 28%) and then **11** in 60% yield: mp = 108−110°C (greenish powder). ^{1}H NMR ($CDCl_3$): δ_H 2.06–2.13 (1H, m, H_1 or $H_{1'}$), 2.28–2.35 (1H, m, $H_{1'}$ or H_1), 3.08 (6H, s, $-NMe_2$), 3.41–3.44 (1H, m, H_{11a}), 3.85–4.00 (2H, m, H_2 and $H_{2'}$), 5.32–5.35 (1H, d, H_{3a}, $J_{H_{3a}-H_{11a}} = 7$ Hz), 7.05 (1H, s, H-4), 7.49–7.69 (2H, m, H-7 and H-8), 8.11–8.15 (1H, d, H-6), 9.29–9.34 (1H, d, H-9). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −99.22 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 12.5$ Hz), −111.40 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 11.5$ Hz). MS (CI/NH_3): $M+H^+ = 318$, $M + NH_4^+ = 335$. Anal. Calcd. for $C_{18}H_{17}F_2NO_2$: C 68.13%, H 5.40%, N 4.41%. Found C 68.32%, H 5.32%, N 4.73%.

4.14. 4-(2-Chloro-2,2-difluoro-acetyl)-5-dimethylamino-11,11-difluoro-1,2,11,11a-tetrahydro-3aH-phenanthro[1,2-b]furan-10-one (**12**)

Mp = 127°C (yellowish powder). ^{1}H NMR ($CDCl_3$): δ_H 2.06–2.13 (1H, m, H_1 or $H_{1'}$), 2.28–2.35 (1H, m, $H_{1'}$ or H_1), 3.08 (6H, s, $-NMe_2$), 3.41–3.44 (1H, m, H_{11a}), 3.85–4.00 (2H, m, H_2 and $H_{2'}$), 5.32–5.35 (1H, d, H_{3a}, $J_{H3a-H11a} = 7.2$ Hz), 7.42–7.58 (2H, m, H-7 and H-8), 8.22–8.26 (1H, d, H-6), 9.32–9.37 (1H, d, H-9). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −61.4 (s, 2F), −99.22 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 12.5$ Hz), −111.40 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 11.5$ Hz). MS (CI/NH_3): $M + H^+ = 430$, $M + NH_4^+ = 447$. Anal. Calcd. for $C_{20}H_{16}F_4NO_3$: C 55.89%, H 3.75%, N 3.26%. Found C 55.72%, H 3.82%, N 3.43%.

4.15. 4-(2,2-Difluoro-acetyl)-5-dimethylamino-11,11-difluoro-1,2,11,11a-tetrahydro-3aH-phenanthro[1,2-b]furan-10-one (**13**)

Mp = 119°C (yellowish powder). ^{1}H NMR ($CDCl_3$): δ_H 2.06–2.13 (1H, m, H_1 or $H_{1'}$), 2.28–2.35 (1H, m, $H_{1'}$ or H_1), 3.08 (6H, s, $-NMe_2$), 3.41–3.44 (1H, m, H_{11a}), 3.85–4.00 (2H, m, H_2 and $H_{2'}$), 5.32–5.35 (1H, d, H_{3a}, $J_{H_{3a}-H_{11a}} = 7$ Hz), 6.58 (1H, t, $-CF_2H$, $^2H_{H-F} = 54$ Hz), 7.42–7.58 (2H, m, H-7 and H-8), 8.22–8.26 (1H, d, H-6), 9.32–9.37 (1H, d, H-9). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −99.22 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 12.5$ Hz), −111.40 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 11.5$ Hz), −122.4 (2F, d, $^2J_{H-F} = 54$ Hz). MS (CI/NH_3): $M + H^+ = 396$, $M + NH_4^+ = 413$. Anal. Calcd. for $C_{20}H_{17}F_4NO_3$: C 60.76%, H 4.33%, N 3.54%. Found C 60.72%, H 4.42%, N 3.43%.

4.16. 6-Dimethylamino-12,12-difluoro-2,3,12,12a-tetrahydro-1H-4aH-4-oxa-chrysen-11-one (**14**)

Mp = 105°C (yellowish powder). ^{1}H NMR ($CDCl_3$): δ_H 1.56–2.13 (4H, m, H_1 and $H_{1'}$ and H_2 and $H_{2'}$), 3.08 (6H, s, $-NMe_2$), 3.41–3.44 (1H, m, H_{12a}), 3.85–4.00 (2H, m, H_3 and $H_{3'}$), 5.32–5.35 (1H, d, H_{4a}, $J_{H_{4a}-H_{12a}} = 7$ Hz), 7.12 (1H, s,

H-5), 7.42–7.58 (2H, m, H-8 and H-9), 8.22–8.26 (1H, d, H-7), 9.32–9.37 (1H, d, H-10). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −101.22 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{12a}} = 12.5$ Hz), −114.40 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{12a}} = 11.5$ Hz). MS (CI/NH_3): $M + H^+ = 332$, $M + NH_4^+ = 349$. Anal. Calcd. for $C_{19}H_{19}F_2NO_2$: C 68.87%, H 5.78%, N 4.23%. Found C 68.72%, H 5.82%, N 4.13%.

*4.17. 1-Butoxy-9-dimethylamino-3,3-difluoro-2,3-dihydro-1H-phenanthren-4-one (**15**)*

Viscous yellowish oil. ^{1}H NMR ($CDCl_3$): δ_H 0.92 (3H, m, CH_3), 1.47 (2H, m, CH_2), 1.69 (2H, m, CH_2), 2.28–2.35 (1H, m, H_2 and $H_{2'}$), 2.85 (6H, s, –NMe_2), 3.47 (2H, t, CH_2, $J = 6.49$ Hz), 3.85–4.00 (1H, m, H_1 and $H_{1'}$), 7.05 (1H, s, H-10), 7.49–7.69 (2H, m, H-6 and H-7), 8.11–8.15 (1H, d, H-8), 9.29–9.34 (1H, d, H-5). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −99.22 (1F, ddd, $J_{F-F} = 272$ Hz, $^3J_{F-H} = 23.2$, 11.5 Hz), −102.4 (1F, ddd, $J_{F-F} = 272$ Hz, $^3J_{F-H} = 23.2$, 11.5 Hz). MS (CI/NH_3): $M + H^+ = 348$, $M + NH_4^+ = 365$. Anal. Calcd. for $C_{20}H_{23}F_2NO_2$: C 69.15%, H 6.67%, N 4.03%. Found C 69.42%, H 6.72%, N 4.33%.

*4.18. 9-Dimethylamino-3,3-difluoro-1-imidazol-1-yl-2,3-dihydro-1H-phenanthren-4-one (**16**)*

Viscous yellowish oil. ^{1}H NMR ($CDCl_3$): δ_H 2.85 (6H, s, –NMe_2), 2.28–2.45 (1H, m, H_2 and $H_{2'}$), 3.85–4.00 (1H, m, H_1 and $H_{1'}$), 7.15 (1H, s, H-10), 7.22 (2H, m, H-4″ and H-5″), 7.49–7.69 (2H, m, H-6 and H-7), 8.11–8.15 (2H, m, H-8 and H-2″), 9.29–9.34 (1H, d, H-5). ^{19}F NMR ($CDCl_3$/$CFCl_3$): $\delta_F\delta_F$ −101.2 (1F, ddd, $J_{F-F} = 272$ Hz, $^3J_{F-H} = 25.2$, 12.5 Hz), −103.5 (1F, ddd, $J_{F-F} = 272$ Hz, $^3J_{F-H} = 22.3$, 11.5 Hz). MS (CI/NH_3): $M + H^+ = 342$, $M + NH_4^+ = 359$. Anal. Calcd. for $C_{19}H_{17}F_2N_3O$: C 66.85%, H 5.02%, N 12.31%. Found C 66.61%, H 5.42%, N 12.54%.

*4.19. 4-(2-Chloro-2,2-difluoro-acetyl)-11,11-difluoro-5-imidazolyl-1-yl-1,2,11,11a-tetrahydro-3aH-phenanthro[1,2-b]furan-10-one (**17**)*

A typical procedure for the reaction between α,α-difluoroketone **12** and the anion of imidazole is as follows: into a three-necked flask equipped with a reflux condenser, a dropping funnel and a nitrogen inlet were added 0.5 g (1.58 mmol) of the α,α-difluoroketone **12** in 20 ml of anhydrous DMSO. The solution was stirred vigorously until complete dissolution. Then a 20 ml DMSO solution of 0.66 g (4.73 mmol) of the tetramethylammonium salt of imidazole (carefully dried under high vacuum) was added dropwise over 20 min. When the addition was complete, the solution was heated at 50°C for 10 h when the yield of the exchanged product remains constant (as checked by HPLC). The solution was diluted with brine (100 ml) and extracted with EtOAc (3 × 100 ml); the combined organic solutions were washed with brine (2 × 100 ml), water (2 × 100 ml) and dried over $MgSO_4$. Filtration and evaporation of the solvent under reduced pressure gave a yellow solid as crude product which was purified by silica gel chromatography (hexane/EtOAc 70:30); evaporation of the appropriate fractions and recrystallisation from $CHCl_3$/hexane gave 0.35 g (1.03 mmol, 65%) of the 4-(2-chloro-2,2-difluoro-acetyl)-11, 11-difluoro-5-imidazolyl-1-yl-1, 2, 11, 11a-tetrahydro-3a*H*-phenanthro[1,2-b]furan-10-one (**17**); mp = 122–124°C (yellowish powder). ^{1}H NMR (DMSO-d_6): δ_H 2.03–2.12 (1H, m, H_1 or $H_{1'}$), 2.30–2.38 (1H, m, $H_{1'}$ or H_1), 3.46–3.48 (1H, m, H_{11a}), 3.85–4.00 (2H, m, H_2 and $H_{2'}$), 5.32–5.35 (1H, d, H_{3a}, $J_{H3a\text{-}H11a} = 6.87$ Hz Hz), 7.28 (1H, s, H-2″), 7.49–7.69 (2H, m, H-7 and H-8), 7.72 (1H, s, H-4″ or H-5″), 8.11–8.15 (1H, d, H-6), 9.29–9.34 (d, 1H, H-9). ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −56.7 (2F, s), −101.2 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 13.5$ Hz), −112.40 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 12.5$ Hz) Mass (CI/CH_4): $m/e = 341$ ($M + H^+$). Anal. Calcd. for $C_{21}H_{13}ClF_4N_2O_3$: C 55.71%, H 2.89%, N 6.19%. Found C 55.42%, H 2.72%, N 6.33%.

*4.20. 4-(2,2-Difluoro-acetyl)-11,11-difluoro-5-imidazol-1-yl-1,2,11,11a-tetrahydro-3aH-phenanthro[1,2-b]furan-10-one (**18**)*

The compound can be prepared as described for the synthesis of **17** or by reductive dechlorination of **17** with Rongalite (1.5 equivalents) in refluxing absolute EtOH (3 h); mp = 101–104°C (yellowish powder). ^{1}H NMR (DMSO-d_6): δ_H 2.03–2.12 (1H, m, H_1 or $H_{1'}$), 2.30–2.38 (1H, m, $H_{1'}$ or H_1), 3.46–3.48 (1H, m, H_{11a}), 3.85–4.00 (2H, m, H_2 and $H_{2'}$), 5.32–5.35 (1H, d, H_{3a}, $J_{H_{3a}-H_{11a}} = 6.87$ Hz), 6.51 (1H, t, –CF_2H, $^2J_{F-F} = 58$ Hz), 7.28 (1H, s, H-2″), 7.49–7.69 (2H, m, H-7 and H-8), 7.72 (1H, s, H-4″ or H-5″), 8.11–8.15 (1H, d, H-6), 9.29–9.34 (d, 1H, H-9). ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −101.2 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 13.5$ Hz), −112.40 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 12.5$ Hz), −122.4 (2F, d, $^2J_{H-F} = 58$ Hz). Mass (CI/CH_4): $m/e = 419$ ($M + H^+$). Anal. Calcd. for $C_{21}H_{14}F_4N_2O_3$: C 60.29%, H 3.37%, N 6.70%. Found C 60.42%, H 3.52%, N 6.83%.

*4.21. 5-Benzoimidazol-1-yl-4-(2-chloro-2,2-difluoro-acetyl)-11,11-difluoro-1,2,11,11a-tetrahydro-3aH-phenanthro[1,2-b]furan-10-one (**19**)*

Mp = 141°C (off-white powder). ^{1}H NMR (DMSO-d_6): δ_H 2.03–2.12 (1H, m, H_1 or $H_{1'}$), 2.30–2.38 (1H, m, $H_{1'}$ or H_1), 3.46–3.48 (1H, m, H_{11a}), 3.85–4.00 (2H, m, H_2 and $H_{2'}$), 5.32–5.35 (1H, d, H_{3a}, $J_{H_{3a}-H_{11a}} = 6.87$ Hz), 7.28 (2H, m, H-5″ and H-6″), 7.49–7.69 (2H, m, H-7 and H-8), 7.72–7.88 (3H, m, H-4″ and H-7″ and H-6), 8.11 (1H, s, H-2″), 9.29–9.34 (d, 1H, H-9). ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −61.2 (2F, s), −101.2 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 13.5$ Hz), −112.40 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 12.5$ Hz). Mass (CI/CH_4): $m/e = 503$ ($M + H^+$). Anal.

Calcd. for $C_{25}H_{15}ClF_4N_2O_3$: C 59.71%, H 3.01%, N 5.57%. Found C 59.62%, H 3.22%, N 5.63%.

*4.22. 5-Benzoimimidazol-1-yl-4-(2,2-difluoro-acetyl)-11,11-difluoro-1,2,11,11a-tetrahydro-3aH-phenanthro[1,2-b]furan-10-one (**20**)*

The compound can be prepared as described for the synthesis of **17** or by reductive dechlorination of **19** with Rongalite (1.5 equivalents) in refluxing absolute EtOH (4.5 h); mp = 132°C (off-white powder). ^{1}H NMR (DMSO-d_6): δ_H 2.03–2.12 (1H, m, H_1 or $H_{1'}$), 2.30–2.38 (1H, m, $H_{1'}$ or H_1), 3.46–3.48 (1H, m, H_{11a}), 3.85–4.00 (2H, m, H_2 and $H_{2'}$), 5.32–5.35 (1H, d, H_{3a}, $J_{H_{3a}-H_{11a}} = 6.87$ Hz), 6.51 (1H, t, –CF_2H, $^2J_{H-F} = 58$ Hz), 7.28 (2H, m, H-5″ and H-6″), 7.49–7.69 (2H, m, H-7 and H-8), 7.72–7.88 (3H, m, H-4″ and H-7″ and H-6), 8.11 (1H, s, H-2″), 9.29–9.34 (d, 1H, H-9). ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −101.2 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 13.5$ Hz), −112.40 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 12.5$ Hz), −122.4 (2F, d, $^2J_{H-F} = 58$ Hz). Mass (CI/CH_4): $m/e = 469$ ($M + H^+$). Anal. Calcd. for $C_{25}H_{16}F_4N_2O_3$: C 64.10%, H 3.44%, N 5.98%. Found C 64.32%, H 3.62%, N 5.83%.

*4.23. 4-(2-Chloro-2,2-difluoro-acetyl)-11,11-difluoro-5-[2-(4-methoxy-phenyl)-imidazol-1-yl]-1,2,11,11a-tetrahydro-3aH-phenanthro[1,2-b]furan-10-one (**21**)*

Mp = 122–124°C (yellowish powder). ^{1}H NMR (DMSO-d_6): δ_H 2.03–2.12 (1H, m, H_1 or $H_{1'}$), 2.30–2.38 (1H, m, $H_{1'}$ or H_1), 3.46–3.48 (1H, m, H_{11a}), 3.85–4.00 (5H, m, H_2 and $H_{2'}$ and –OCH_3), 5.32–5.35 (1H, d, H_{3a}, $J_{H_{3a}-H_{11a}} = 6.87$ Hz), 7.10–7.22 (2H, m, H-3‴ and H-7‴), 7.49–7.69 (4H, m, H-4‴ and H-6‴ and H-7 and H-8), 7.82 (2H, m, H-4″ and H-5″), 8.11–8.15 (1H, d, H-6), 9.29–9.34 (d, 1H, H-9). ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −56.7 (2F, s), −101.2 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 13.5$ Hz), −112.40 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 12.5$ Hz) Mass (CI/CH_4): $m/e = 559$ ($M + H^+$). Anal. Calcd. for $C_{28}H_{19}ClF_4N_2O_4$: C 60.17%, H 3.43%, N 5.01%. Found C 60.32%, H 3.57%, N 5.33%.

*4.24. 1-[4-(Chloro-difluoro-acetyl)-11,11-difluoro-10-oxo-1,2,3a,10,11,11a-hexahydro-phenanthro[1,2-b]furan-5-yl]-1H-imidazole-2-carbaldehyde (**22**)*

Mp = 132°C (yellowish powder). ^{1}H NMR (DMSO-d_6): δ_H 2.03–2.12 (1H, m, H_1 or $H_{1'}$), 2.30–2.38 (1H, m, $H_{1'}$ or H_1), 3.46–3.48 (1H, m, H_{11a}), 3.85–4.00 (2H, m, H_2 and $H_{2'}$), 5.32–5.35 (1H, d, H_{3a}, $J_{H_{3a}-H_{11a}} = 6.87$ Hz), 7.28 (1H, s, H-2″), 7.49–7.69 (2H, m, H-7 and H-8), 7.72 (1H, s, H-4″ or H-5″), 8.11–8.15 (1H, d, H-6), 9.29–9.34 (d, 1H, H-9). ^{19}F NMR (DMSO-d_6/$CFCl_3$): δ_F −56.7 (2F, s), −101.2 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 13.5$ Hz), −112.40 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 12.5$ Hz) Mass (CI/CH_4): $m/e = 481$ ($M + H^+$). Anal. Calcd. for $C_{22}H_{13}ClF_4N_2O_4$: C 54.96%, H 2.73%, N 5.83%. Found C 55.02%, H 2.72%, N 5.63%.

*4.25. 4-(2-Chloro-2,2-difluoro-acetyl)-11,11-difluoro-5-(2-methyl-5-nitro-imidazol-1-yl)-1,2,11,11a-tetrahydro-3aH-phenanthro[1,2-b]furan-10-one (**23**)*

At mp = 152°C (yellowish powder). ^{1}H NMR ($CDCl_3$): δ_H 2.03–2.12 (1H, m, H_1 or $H_{1'}$), 2.30–2.38 (1H, m, $H_{1'}$ or H_1), 3.46–3.48 (1H, m, H_{11a}), 3.85–4.00 (2H, m, H_2 and $H_{2'}$), 5.32–5.35 (1H, d, H_{3a}, $J_{H_{3a}-H_{11a}} = 6.87$ Hz), 7.49–7.69 (2H, m, H-7 and H-8), 7.72 (1H, s, H-4″), 8.11–8.15 (1H, d, H-6), 9.29–9.34 (d, 1H, H-9). ^{19}F NMR ($CDCl_3$/$CFCl_3$): δ_F −56.7 (2F, s), −101.2 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 13.5$ Hz), −112.40 (1F, dd, $J_{F-F} = 272$ Hz, $^3J_{F-H_{11a}} = 12.5$ Hz) Mass (CI/CH_4): $m/e = 512$ ($M + H^+$). Anal. Calcd. for $C_{22}H_{14}ClF_4N_3O_5$: C 51.63%, H 2.76%, N 6.93%. Found C 51.42%, H 2.72%, N 6.73%.

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References

[1] K. Burger, U. Wucherpfennig, E. Brunner, Adv. Heterocyclic Chem. 60 (1994) 1.
[2] M.J. Tozer, T.F. Herpin, Tetrahedron 52 (1996) 8619.
[3] J.T. Welch, S. Eswarakrishnan, Fluorine in Bioorganic Chemistry, Wiley, New York, 1991.
[4] F. Barth, C. O-Yang, Tetrahedron Lett. 42 (1991) 5873.
[5] T. Taguchi, Y. Kodama, M. Kanazawa, Carbohydr. Res. 249 (1993) 243.
[6] L.A. Buttle, W.B. Motherwell, Tetrahedron Lett. 35 (1994) 3995.
[7] K. Uneyama, T. Yanagiguchi, H. Asai, Tetrahedron Lett. 38 (1997) 7763.
[8] T. Itoh, K. Sakabe, K. Kudo, P. Zagatti, M. Renou, Tetrahedron Lett. 39 (1998) 4071.
[9] T. Itoh, K. Sakabe, K. Kudo, P. Zagatti, M. Renou, J. Org. Chem. 64 (1999) 252.
[10] J.M. Percy, M.E. Prime, M.J. Broadhurst, J. Org. Chem. 63 (1998) 8049 and references cited therein.
[11] T. Ishihara, T. Yamanaka, T. Ando, Chem. Lett. (1984) 1165.
[12] M. Kuroboshi, T. Ishihara, Tetrahedron Lett. 28 (1987) 6481.
[13] M. Kuroboshi, T. Ishihara, Bull. Chem. Soc. Jpn. 63 (1990) 428.
[14] R.W. Lang, B. Schaub, Tetrahedron Lett. 29 (1988) 2943.
[15] O. Kitagawa, A. Miura, Y. Kobayashi, T. Taguchi, Chem. Lett. (1990) 1011.
[16] Z.-M. Qiu, D.J. Burton, J. Org. Chem. 60 (1995) 5570.
[17] D.J. Burton, J. Fluorine Chem. 100 (1999) 177.
[18] T. Yamamoto, S. Ishibuchi, T. Ishizuka, M. Haratake, T. Kunieda, J. Org. Chem. 58 (1993) 1997.

[19] M. Médebielle, Tetrahedron Lett. 36 (1995) 2071.
[20] S. Fujii, K. Kato, M. Médebielle, Tetrahedron 56 (2000) 2655.
[21] C.R. Burkholder, W.R. Dolbier Jr., M. Médebielle, J. Fluorine Chem. 102 (2000) 369.
[22] C.R. Burkholder, W.R. Dolbier Jr., M. Médebielle, J. Fluorine Chem. 95 (1999) 127.
[23] C.R. Burkholder, W.R. Dolbier Jr., M. Médebielle, J. Org. Chem. 63 (1998) 5385.
[24] C.R. Burkholder, W.R. Dolbier Jr., M. Médebielle, A. Ndedi, Tetrahedron Lett. 39 (1998) 8853.
[25] M. Médebielle, M.A. Oturan, J. Pinson, J.-M. Savéant, J. Org. Chem. 61 (1996) 1331.
[26] M. Médebielle, Tetrahedron Lett. 37 (1996) 5119.
[27] M. Hojo, R. Masuda, E. Okada, Tetrahedron Lett. 28 (1987) 6199.
[28] M. Hojo, R. Masuda, S. Sakaguchi, M. Takagawa, Synthesis (1986) 1016.
[29] M. Hojo, R. Masuda, E. Okada, S. Sakaguchi, H. Narumiya, K. Morimoto, Tetrahedron Lett. 30 (1989) 6173.
[30] V. Kumar, P. McCloskey, M.R. Bell, Tetrahedron Lett. 35 (1994) 833.
[31] A.R. Harris, Synth. Commun. 17 (1987) 1587.
[32] C.P. Andrieux, J.-M. Savéant, Bull. Soc. Chim. Fr. (1972) 3281.
[33] L. Nadjo, J.-M. Savéant, J. Electroanal. Chem. 33 (1971) 419.
[34] L. Nadjo, J.-M. Savéant, J. Electroanal. Chem. 48 (1973) 113.
[35] C.P. Andrieux, P. Hapiot, J.-M. Savéant, J. Phys. Chem. 92 (1988) 5987.
[36] C.P. Andrieux, J.-M. Savéant, A. Tallec, R. Tardivel, C. Tardy, J. Am. Chem. Soc. 119 (1997) 2420.
[37] C.P. Andrieux, J.-M. Savéant, Electrochemical Reactions, in: C.F. Bernasconi (Ed.), Investigation of Rates and Mechanisms of Reactions, Techniques of Chemistry, Vol. VI/4E, Part 2, Wiley, New York, 1986, pp. 305–390.
[38] C.P. Andrieux, J. Badoz-Lambling, C. Combellas, D. Lacombe, J.-M. Savéant, A. Thiébault, D. Zann, J. Am. Chem. Soc. 109 (1987) 1518.
[39] E. Okada, N. Tsukushi, Y. Otsuki, S. Nishiyama, T. Fukuda, Synlett (1999) 126 and references cited therein.
[40] M. Médebielle, J. Pinson, J.-M. Savéant, J. Am. Chem. Soc. 113 (1990) 6872.
[41] K.L. Kirk, J. Org. Chem. 43 (1978) 4381.
[42] H. Kimoto, S. Fujii, L.A. Cohen, J. Org. Chem. 49 (1984) 1060.
[43] M. J. Frisch, G.W. Trucks, H.B. Schlegel, P.M.W. Gill, B.G. Johnson, M.A. Robb, J.R. Cheeseman, T. Keith, G.A. Petersson, J.A. Montgomery, K. Raghavachari, M.A. Al-Laham, V.G. Zakrzewski, J.V. Ortiz, J.B. Foresman, J. Cioslowski, B.B. Stefanov, A. Nanayakkara, M. Challacombe, C.Y. Peng, P.Y. Ayala, W. Chen, M.W. Wong, J.L. Andres, A.S. Replogle, R. Gomperts, R.L. Martin, D.J. Fox, J.S. Binkley, D.J. Defrees, J. Baker, J.P. Stewart, M. Head-Gordon, C. Gonzalez, J.A. Pople, Gaussian 94, Revision E.1 Gaussian, Inc., Pittsburgh, PA, 1995.
[44] M. Dewar, W. Thiel, J. Am. Chem. Soc. 99 (1977) 4499.
[45] A.D. Becke, J. Chem. Phys. 98 (1993) 5648.
[46] J.A. Pople, R.K. Nesbet, J. Chem. Phys. 22 (1974) 571.