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Reduction of 1,1-difluoro-1-alken-3-ols with lithium tetrahydroaluminate. Application to the synthesis of 1,1-difluoro-2-alkenes and 2-alkenals

Frédérique Tellier [a,*], Raymond Sauvêtre [b]

[a] *Unité de Phytopharmacie et Médiateurs Chimiques, INRA, Route de Saint-Cyr, 78026 Versailles, France*

[b] *Laboratoire de Chimie des Organoéléments, associé au CNRS, Université P. et M. Curie, Boîte 183, 4 Place Jussieu, 75252 Paris Cedex, France*

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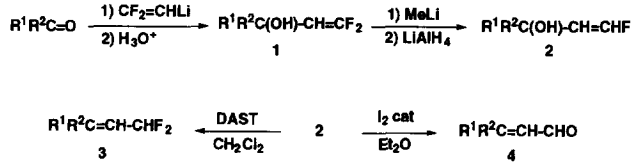
Abstract

The reduction of 1,1-difluoro-1-alken-3-ols with lithium tetrahydroaluminate is described. The 1-fluoro-1-alken-3-ols obtained can be transformed to enals or difluoromethylated allylic derivatives.

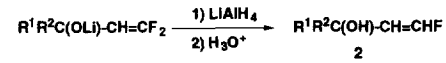
Keywords: Reduction; Difluoro-alkenols; Lithium tetrahydroaluminate; Synthesis; Difluoroalkenes; Alkenals

1. Introduction

Herein we report the nucleophilic replacement of one fluorine atom in 1,1-difluoro-1-alken-3-ols **1** (readily obtained by the addition of difluorovinyl-lithium to carbonyl compounds [1]) by a hydrogen atom to give 1-fluoro-1-alken-3-ols **2**. The monofluorinated alcohols **2** can be used as common intermediates for the synthesis of difluoromethylated alkenes **3** or enals **4** (Scheme 1).



Scheme 1.



2a: R^1=n-Hex, R^2=H

2b: R^1, R^2=$(CH_2)_6$

2c: R^1=Thienyl, R^2=H

2d: R^1=(E)-n-Pent-CH=CH, R^2=H

2e: R^1=(E,E)-Me-$(CH=CH)_2$, R^2=H

Scheme 2.

2. Results and discussion

A systematic study of the reduction of the *free* 1,1,2-trifluoro-1-alken-3-ols with lithium tetrahydroaluminate has shown that two products are formed: 1,2-difluoro-1-alken-3-ols (*E*- and *Z*-isomers) and 1,1,2-trifluoro-2-alkenes (*E*- and *Z*-isomers), obtained respectively via an addition–elimination reaction and S_N2' substitution involving the hydride (the ratio varies according to the solvent) [2].

We have also reported that the reduction of difluoroalkenols **1** with sodium borohydride in diglyme leads to S_N2' substitution products **3** [3].

Here, we show that treatment of *lithium alcoholates* of **1** with $LiAlH_4$ in Et_2O allows the ready preparation at room temperature (4 h) of the pure alcohols **2** (Scheme 2). These are relatively unstable because they can spontaneously undergo a rapid allylic migration to yield a mixture of products; hence, they must be used quickly as the crude materials or stored dilute at −20 °C. The estimated crude yields were about 80%–90%. These alcohols are obtained in all cases with a high stereoselectivity (E/Z=95:5 as evaluated by ^{19}F NMR spectroscopy). Isolation of alcohols **1** and further metallation in lithium alcoholates is necessary (alcoholates obtained by addition of difluorovinyl-lithium to the carbonyl compounds cannot be used directly because of the presence of THF).

The above-mentioned products may be characterized via their spectral properties (IR, NMR) except for **2e** which is too unstable. If R^1 = ^{n}Bu–C≡C and R^2 = H, the reduction reaction does not lead to the desired product; reduction of the triple bond also occurs.

* Corresponding author.

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The replacement of hydrogen atoms by fluorine atoms in biological molecules causes only a small steric perturbation, but leads to major changes in hydrophobicity and polarity of the hydrocarbon chain [4–9]. During the past few years, fluorinated organic molecules have drawn much attention due to their unique biological properties and, in particular, efforts have been devoted to the development of new synthetic routes to introduce a difluorohydrogenomethyl unit which would provide compounds which still retain a hydrogen-bonding potential [10–14].

It is thus interesting to demonstrate that alcohols **2** can be used as intermediate synthons for synthesizing difluoromethylated products in an allylic position and herein we report an efficient method for the incorporation of a difluorohydrogenomethyl group in various products such as alkenes (**3a, 3b**), styrenes (**3c**), dienes (**3d**) and trienes (**3e**).

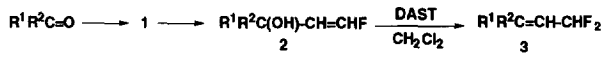
The alcohols **2** react with DAST (diethylaminosulphur trifluoride) by a substitution reaction involving a rearrangement (S_N2'-type) of the hydroxy moiety by a fluoride to afford the corresponding difluorinated compounds **3** (Scheme 3).

The difluorinated alkenes **3** which are S_N2'-like substitution products, are afforded pure, but, in reality, the reaction affords both S_N2' and S_N2 substitution products in variable ratios. Since the S_N2 products are particularly unstable they can only be glimpsed or postulated and hence determination of their ratio is difficult. Nevertheless, for the different cases studied we can make the following comments.

Compound **3a**: ^{19}F NMR of the crude reaction product shows the presence of S_N2' and S_N2 products in the ratio $S_N2'/S_N2 = 95:5$, but the S_N2 product is unstable (allylic and secondary fluorine) and is destroyed when the reaction mixture is filtered through a small column packed with silica. The S_N2' product **3a** can thus be prepared pure with a high stereoselectivity (only the *E*-isomer is obtained).

Compound **3b**: The yield consists of two non-separable products **3b** and **3b'** (**3b/3b'** = 85:15). Product **3b** is the desired S_N2' material and **3b'** must come from the S_N2 product **3b''** which is unstable (allylic and tertiary fluorine) and not observed by NMR spectroscopy (Scheme 4). The 85:15 ratio must correspond to the S_N2'/S_N2 ratio.

Compound **3c**: The relatively low yied (27%) is explained firstly by the high instability of **2c** which is partly decomposed by hydrolysis to the enal **4c**. On the other hand, as in the previous case, the ratio of the S_N2 product (unstable) cannot



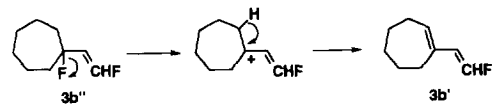
3a: R^1=n-Hex, R^2=H, yield=50% **3d**: R^1=(E)-n-Pent-CH=CH, R^2=H, yield=50%

3b: R^1, R^2=$(CH_2)_6$, yield=59% **3e**: R^1=(E,E)-Me-$(CH=CH)_2$, R^2=H, yield=20%

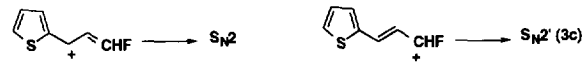
3c: R^1=Thienyl, R^2=H, yield=27%

(overall yields for the three steps based on the starting carbonyl compound)

Scheme 3.



Scheme 4.



Scheme 5.

be evaluated. Nevertheless, we think that the ratio of S_N2 substitution must be high due to the stability of the intermediate leading to the S_N2 product [the latter (allylic and benzylic) must be as stable as the intermediate (fluoroallylic and primary) giving the S_N2' product] (Scheme 5). Only the *E*-isomer of **3c** is obtained.

Compound **3d**: The S_N2 product with a secondary and diallylic fluorine is very unstable and its ratio cannot be determined. As the yield of the S_N2' product is good, this ratio must be low. The S_N2' product **3d** is obtained with a stereoselectivity of 97:3 (*E,E/E,Z*).

Compound **3e**: As in the case of **3c**, the low yield of **3e** (20%) is explained by the high instability of **2e** which involves the synthesis of an important amount of aldehyde **4e** besides the product **3e**. The stability of the intermediates must be similar to that of **3d**, i.e. the ratio of the S_N2 product must be low. The *E,E,E*-isomer is obtained with a stereoselectivity of about 95%.

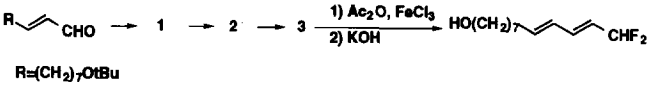
It is interesting to note that we have described previously the attack by DAST on **1** as leading only to S_N2' products, namely to allylic trifluorides [15]. In contrast, it has been shown that attack on the 3-buten-2-ol gave mainly the S_N2 product [16].

The mechanism of fluorination has not been determined, but the results obtained suggest that the fluorination process involves a transition state with a significant carbocation character [16,17].

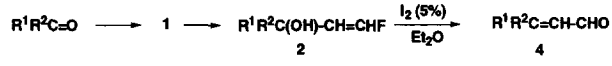
In summary, in the case of saturated aldehydes and α-enals as starting compounds, this reaction allows the ready preparation of products **3** in good overall yield. In the case of ketones, the desired difluoroalkenes are also obtained in good yield but the decomposition of S_N2 product affords an undesirable stable compound besides **3**. In other cases (polyunsaturated or aromatic systems), the yields are low because of two reaction intermediates: one stabilized by the fluorine atom (leading to product **3**) and the other by the unsaturated system.

This methodology has been applied to the preparation of an analogue of *E,E*-8,10-dodecadienol (codlemone), a sex pheromone component of *Cydia pomonella* (Scheme 6).

Finally, we describe in this respect a new simple route to enals from the intermediate alcohols **2**. Conjugated polyenals are well recognized as useful building blocks in organic synthesis [18].



Scheme 6.



4a: R^1=n-Hex, R^2=H

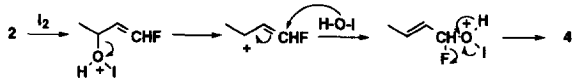
4b: R^1, R^2=$(CH_2)_6$

4c: R^1=Thienyl, R^2=H

4d: R^1=(E)-n-Pent-CH=CH, R^2=H

4e: R^1=(E,E)-Me-$(CH=CH)_2$, R^2=H

Scheme 7.



Scheme 8.

We have found that the reaction of monofluorinated alcohols **2** with a catalytic amount of I_2 (5%) in Et_2O after 15 h at room temperature leads to enals **4** with good yield (50%–60%, based on the starting carbonyl compounds) and high stereoselectivities (if R^2=H, only the *E*-isomer) (Scheme 7).

A plausible reaction mechanism is outlined below (Scheme 8):

3. Experimental details

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL GSX 400 spectrometer [$CDCl_3$; δ(ppm) from TMS, *J*(Hz)] and ^{19}F NMR spectra on a JEOL FX 90 spectrometer [$CDCl_3$; δ(ppm) from $CFCl_3$, *J*(Hz)]. Infrared spectra were measured on a Perkin-Elmer 397 spectrometer (neat, cm^{-1}).

3.1. Preparation of the intermediate difluorinated alcohols 1

The experimental procedure has been described previously [15c]. Alcohols **1** (and especially **2**) are unstable in the pure state but can be stored without any problem in Et_2O solution (with a small amount of $NaHCO_3$) at −20 °C.

3.2. Preparation of the intermediate monofluorinated alcohols 2

A solution of MeLi (20 mmol) was added to a stirred solution of difluorovinyl alcohol **1** (prepared from 20 mmol of carbonyl derivative) in Et_2O (50 ml) at −30 °C. The resultant mixture was stirred at 0 °C for 15 min and powdered lithium tetrahydroaluminate (13 mmol) added. The temperature was increased to 20 °C and after 4 h the reaction was complete. Ethyl acetate (5 ml) was added to the mixture followed by H_2SO_4 solution (1 N) and extraction with Et_2O. The organic layer was washed successively with saturated aqueous solutions of $NaHCO_3$ and NaCl, and dried over $MgSO_4$. The solvents were evaporated ($\leqslant$20 °C) when the crude alcohol **2** was obtained. This was stored diluted in 50 ml of Et_2O.

1-Fluoro-1-nonen-3-ol (**2a**): steric purity, *E*/*Z*=95:5. IR (cm^{-1}): 3340; 2920; 2850; 1670; 1460; 1100; 915. ^{19}F NMR δ: −128.2 (dd, *J*=84, 43 Hz, *Z*-isomer); −130.2 (dd, *J*=84, 18 Hz, *E*-isomer) ppm. ^{1}H NMR δ: 0.9 (t, 3H); 1.3 (m, 8H); 1.5 (m, 2H); *E*-isomer: 4.1 (dt, H^3); 5.4 (ddd, H^2); 6.7 (dd, H^1) ppm. [$J(H^1/F)$=83.3 Hz, $J(H^2/F)$=18.1 Hz, $J(H^1/H^2)$=11.0 Hz, $J(H^2/H^3)$=8.2 Hz, $J(H^3/H^4)$=6.6 Hz]; *Z*-isomer: 4.65 (dt, H^3); 4.9 (ddd, H^2); 6.5 (dd, H^1) ppm. [$J(H^1/F)$=84.1 Hz, $J(H^2/F)$=42.3 Hz, $J(H^2/H^3)$=8.8 Hz, $J(H^3/H^4)$=7 Hz, $J(H^1/H^2)$=4.1 Hz]. ^{13}C NMR δ: *E*-isomer: 14.1, 22.6, 25.3, 29.1, 31.8, 37.6, 68.0 (d, C^3, *J*=11.0 Hz); 115.2 (d, C^2, *J*=7.4 Hz); 150.6 (d, C^1, *J*=259.2 Hz) ppm.

1-(2-Fluoroethene)cycloheptanol (**2b**): steric purity, *E*/*Z*=96:4. IR (cm^{-1}): 3380; 2920; 2850; 1665; 1455; 1095; 1020; 915. ^{19}F NMR δ: −126,4 (dd, *J*=85, 47 Hz, *Z*-isomer); −138.0 (dd, *J*=85, 21 Hz, *E*-isomer) ppm. ^{1}H NMR δ: 1.4–1.8 (m, 12H); *E*-isomer: 5.6 (dd, H^2); 6.75 (dd, H^1) ppm [$J(H^1/F)$=85.5 Hz, $J(H^2/F)$=20.9 Hz, $J(H^1/H^2)$=11.0 Hz]; *Z*-isomer: 4.9 (dd, H^2); 6.35 (dd, H^1) ppm [$J(H^1/F)$=84.7 Hz, $J(H^2/F)$=47.3 Hz, $J(H^1/H^2)$=5.5 Hz]. ^{13}C NMR δ: *E*-isomer: 22.2, 29.5, 42.3, 73.9 (d, C^3, *J*=11.0 Hz); 121.0 (d, C^2, *J*=7.3 Hz); 149.6 (d, C^1, *J*=253.7 Hz) ppm.

1-Fluoro-3-thienyl-1-propen-3-ol (**2c**): steric purity, *E*/*Z*=95:5. IR (cm^{-1}): 3340; 2850–2950; 1670; 1100; 1000; 910; 830; 700. ^{19}F NMR δ: −127.6 (dd, *J*=83, 41 Hz, *Z*-isomer); −129.4 (dd, *J*=83, 17 Hz, *E*-isomer) ppm. ^{1}H NMR δ: *E*-isomer: 5.45 (d, H^3); 5.7 (ddd, H^2); 6.85 (dd, H^1); 7.0 (m, 2H); 7.3 (dd, 1H, *J*=4.95, 1.65 Hz) ppm [$J(H^1/F)$=83.0 Hz, $J(H^2/F)$=17.0 Hz, $J(H^1/H^2)$=11.0 Hz, $J(H^2/H^3)$=7.7 Hz]; *Z*-isomer: 5.2 (ddd, H^2); 6.0 (d, H^3); 6.6 (dd, H^1) ppm [$J(H^1/F)$=83 Hz, $J(H^2/F)$=41 Hz, $J(H^2/H^3)$=9 Hz, $J(H^1/H^2)$=5 Hz]. ^{13}C NMR δ: *E*-isomer: 65.3 (d, C^3, *J*=9.2 Hz); 114.7 (d, C^2, *J*=11.0 Hz); 123.0, 124.1, 125.8, 147.4 (d, C^4, *J*=3.7 Hz); 150.4 (d, C^1, *J*=261.0 Hz) ppm.

1-Fluoro-1,4-decadien-3-ol (**2d**): steric purity, *E*/*Z*=96:4. IR (cm^{-1}): 3340; 2910; 2850; 1670; 1460; 965; 910; 730. ^{19}F NMR δ: −128.1 (dd, *J*=83, 40 Hz, *Z*-isomer); −130.4 (dd, *J*=84, 18 Hz, *E*-isomer) ppm. ^{1}H NMR δ: 0.9 (t, 3H); 1.3 (m, 4H); 1.4 (m, 2H); 2.05 (q, 2H); 4.55 (t, H^3); *E*-isomer: 5.45 (ddd, H^2); 5.5 (dd, H^4); 5.7 (dt, H^5); 6.7 (dd, H^1) ppm [$J(H^1/F)$=84.1 Hz, $J(H^2/F)$=18.1 Hz, $J(H^4/H^5)$=15.4 Hz, $J(H^1/H^2)$=11.0 Hz, $J(H^2/H^3)$=7.1 Hz, $J(H^3/H^4)$=7.1 Hz, $J(H^5/H^6)$=6.6 Hz]. ^{13}C NMR δ: *E*-isomer: 14.1, 22.6, 28.8, 31.5, 32.2, 68.4 (d, C^3, *J*=12.9 Hz); 114.7 (d, C^2, *J*=9.2 Hz); 131.2 (s); 132.8 (s); 150.6 (d, C^1, *J*=259.2 Hz) ppm.

3.3. Preparation of the difluorinated alkenes 3

DAST (2.5 ml, 20 mmol) was added (over 5 min) at −70 °C to a solution of the crude alcohol **2** (prepared in two steps from 20 mmol of the carbonyl derivative) in CH_2Cl_2 (50 ml). After 15 min at −70 °C, the temperature is allowed to warm up to 0 °C (15 min). The reaction mixture was hydrolyzed by means of H_2O (30 ml) at 0 °C and extracted with Et_2O. The organic phase was successively washed with saturated aq. solus. of $NaHCO_3$ and NaCl. It was then dried over $MgSO_4$ and concentrated in vacuo. The crude residue was filtered through a small column packed with silica (eluting with cyclohexane, except for **3d**: cyclohexane/AcOEt = 90:10). The solvent was evaporated and the residue distilled to give the difluorinated product **3**.

E-1,1-Difluoro-2-nonene (**3a**): yield, 50%; b.p. 55 °C/10 Torr. Steric purity, $E \geqslant 99\%$. IR (cm^{-1}); 2920; 2850; 1675; 1460; 1385; 1125; 1020; 960; 915. ^{19}F NMR δ: −110.0 (ddtd, J = 56, 8, 4, 3 Hz) ppm. ^1H NMR δ: 0.9 (t, 3H); 1.3 (m, 6H); 1.4 (m, 2H); 2.1 (m, 2H); 5.6 (dtdt, H^2); 6.02 (td, H^1); 6.06 (dtt, H^3) ppm [$J(H^1/F)$ = 56.1 Hz, $J(H^2/H^3)$ = 16.0 Hz, $J(H^2/F)$ = 7.7 Hz, $J(H^3/H^4)$ = 6.6 Hz, $J(H^1/H^2)$ = 6.0 Hz, $J(H^3/F)$ = 3.3 Hz, $J(H^2/H^4)$ = 1.6 Hz]. ^{13}C NMR δ: 14.1, 22.6, 28.2, 28.8, 31.6, 31.8, 115.6 (t, C^1, J = 232.6 Hz); 123.2 (t, C^2, J = 23.9 Hz); 140.3 (t, C^3, J = 11.0 Hz) ppm. Analysis: Calc. for $C_9H_{16}F_2$: C, 66.63; H, 9.94%. Found: C, 66.41; H, 9.82%.

Z-1,1-Difluoro-2-nonene: the alcohol **2a** treated by $LiAlH_4$ in diglyme (1 h at 80 °C) afforded this *Z*-alkene mixed with the *E*-isomer (*E*/*Z* = 2:1). ^{19}F NMR δ: −111.4 (ddt, J = 56.8, 3 Hz) ppm. ^1H NMR δ: 0.9 (t, 3H); 1.3 (m, 6H); 1.4 (m, 2H); 5.6 (m, H^2); 5.9 (m, H^3); 6.4 (tdd, H^1) ppm [$J(H^1/F)$ = 56.1 Hz, $J(H^1/H^2)$ = 7.7 Hz, $J(H^1/H^3$ = 1.1 Hz].

2-Cycloheptylidene-1,1-difluoroethane (**3b**): yield, 59%. IR (cm^{-1}) 2920; 2840; 1660; 1440; 1390; 1120; 1060; 1000; 915. ^{19}F NMR δ: −110.2 (dm, J = 56 Hz) ppm. ^1H NMR δ: 1.5–1.7 (m, 8H); 2.35 (m, $2H^{4'}$); 2.4 (m, $2H^4$); 5.4 (tdt, H^2); 6.35 (td, H^1) ppm [$J(H^1/F)$ = 56.4 Hz, $J(H^2/F)$ = 8.8 Hz, $H(H^1/H^2)$ = 6.8 Hz, $J(H^2/H^4)$ = 1.1 Hz]. ^{13}C NMR δ: 27.1, 28.0, 28.8, 29.4, 30.2, 37.5, 112.8 (t, C^1, J = 229.8 Hz); 118.7 (t, C^2, J = 25.7 Hz); 153.6 (t, C^3, J = 11.9 Hz) ppm.

E-2-(1-Cycloheptenyl)-1-fluoro-1-ethene (**3b'**): yield, 11%. ^{19}F NMR δ: −138.0 (dd, J = 84, 23 Hz) ppm. ^1H NMR δ: 2.2 (m, 4H); 5.8 (t, H^4, J = 6.9 Hz); 6.0 (dd, H^2); 6.75 (dd, H^1) ppm [$J(H^1/F)$ = 84.7 Hz, $J(H^2/F)$ = 22.0 Hz, $J(H^1/H^2)$ = 11.0 Hz]. ^{13}C NMR δ: 26.1, 26.7, 28.3, 28.4, 32.0, 118.2 (d, C^2, J = 14.7 Hz); 132.9 (d, C^4, J = 9.2 Hz); 137.2 (d, C^3, J = 8 Hz); 148.3 (d, C^1, J = 253.7 Hz) ppm.

E-1,1-Difluoro-3-thienyl-2-propene (**3c**): yield, 27%; b.p. 30–40 °C/0.1 Torr. Steric purity, E = 100%. IR (cm^{-1}): 3100, 1650, 1380; 1130; 1010; 950; 850; 810; 700. ^{19}F NMR δ: −110.1 (dd, J = 55, 9 Hz) ppm. ^1H NMR δ: 6.0 (dtd, H^2); 6.15 (td, H^1); 6.92 (dt, H^3); 6.94 (dd, 1H, J = 4.95, 3.3 Hz); 7.05 (d, 1H, J = 3.3 Hz); 7.2 (d, 1H, J = 4.95 Hz) ppm [$J(H^1/F)$ = 55.5 Hz, $J(H^2/H^3)$ = 15.9 Hz, $J(H^2/F)$ = 9.1 Hz, $J(H^1/H^2)$ = 5.5 Hz, $J(H^3/F)$ = 3.3 Hz)]. ^{13}C NMR δ: 114.9 (t, C^1, J = 233.5 Hz); 119.8 (t, C^2, J = 23.9 Hz); 126.8, 127.7, 128.8, 129.8 (t, C^3, J = 12.8 Hz); 139.2 (s, C^4) ppm. Analysis: Calc. for $C_7H_6F_2S$: C, 52.49; H, 3.78%. Found: C, 52.36; H, 3.92%.

1,1-Difluoro-2,4-decadiene (**3d**): yield, 50%. Steric purity, *E*,*E*/*E*,*Z* = 97:3. IR (cm^{-1}): 2920; 2840; 1660; 1625; 1460; 1385; 1130; 1015; 980. ^{19}F NMR δ: −109.8 (dd, J = 55, 9 Hz, *E*,*E*-isomer); −110.6 (dd, J = 56, 11 Hz, *E*,*Z*-isomer) ppm. ^1H NMR δ: *E*-isomer: 0.9 (t, 3H); 1,3 (m, 4H); 1.4 (m, 2H); 2.15 (q, 2H); 5.6 (dtd, H^2); 5.9 (dt, H^5); 6.07 (dd, H^4); 6.09 (td, H^1); 6.45 (ddt, H^3) ppm [$J(H^1/F)$ = 56.1 Hz, $J(H^2/H^3)$ = 15.4 Hz, $J(H^4/H^5)$ = 14.8 Hz, $J(H^3/H^4)$ = 10.7 Hz. $J(H^2/F)$ = 8.8 Hz, $J(H^5/H^6)$ = 7.15 Hz, $J(H^1/H^2)$ = 6.0 Hz, $J(H^3/F)$ = 3.6 Hz]. ^{13}C NMR δ: 14.0, 22.5, 28.4, 31.4, 32.7, 115.5 (t, C^1, J = 232.6 Hz); 121.5 (t, C^2, J = 23.9 Hz); 127.8 (s, C^4); 137.4 (t, C^3, J = 12.9 Hz); 141.2 (s, C^5) ppm. Analysis: Calc. for $C_{10}H_{16}F_2$: C, 68.93; H, 9.26%. Found: C, 68.81; H, 9.34%.

1,1-Difluoro-2,4,6-octatriene (**3e**): yield, 20%. Steric purity, *E*,*E*,*E* ≈ 95%. IR (cm^{-1}): 1630; 1590; 1440; 1370; 1120; 980–1040; 925. ^{19}F NMR δ: −109.8 (dd, J = 58, 9 Hz, *E*,*E*,*E*-isomer) ppm. ^1H NMR δ: 1.8 (d, 3H, H^8); 5.7 (H^2, dtd); 5.85 (H^7, dq); 6.10 (H^1, td); 611 (m, H^4 and H^6); 6.35 (H^5, dd); 6.5 (H^3, ddt) ppm [$J(H^1/F)$ = 56.1 Hz, $J(H^2/H^3)$ = 15.4 Hz, $J(H^6/H^7)$ = 15.4 Hz, $J(H^4/H^5)$ = 14.8 Hz, $J(H^3/H^4)$ = 11.0 Hz), $J(H^5/H^6)$ = 11.0 Hz, $J(H^2/F)$ = 9.3 Hz, $J(H^7/H^8)$ = 6.6 Hz, $J(H^1/H^2)$ = 6.0 Hz, $J(H^3/F)$ = 3.8 Hz]. ^{13}C NMR δ: 18.3, 115.3 (t, C^1, J = 232.6 Hz); 122.5 (t, C^2, J = 23.0 Hz); 127.1, 131.0, 133.3, 137.1 (t, C^3, J = 12.8 Hz); 138.0 ppm. Analysis: Calc. for $C_8H_{10}F_2$: C, 66.65; H, 6.99%. Found: C, 66.53; H, 7.15%.

3.4. Preparation of the aldehydes 4

To the crude alcohol **2** (prepared in two steps from 20 mmol of the carbonyl derivatives) in Et_2O (50 ml) was added a catalytic amount of I_2 (5%). After 15 h at room temperature, enal **4** was obtained. The product was then purified by silica gel chromatography (eluting with cyclohexane/AcOEt = 90:10).

E-2-Nonenal (**4a**): yield, 52%; b.p. 40–41 °C/0.05 Torr. Steric purity, E = 100%. ^{13}C NMR δ: 14.1; 22.7; 28.0; 29.0; 31.7; 32.9; 133.6; 159.9; 195.2 ppm.

2-Cycloheptylidene ethanal (**4b**): yield, 63%; b.p. 58–60 °C/0.1 Torr. ^{13}C NMR δ: 27.6; 28.8; 29.5; 30.7; 39.1; 128.3; 171.1; 192.0 ppm.

E-3-Thienyl-2-propenal (**4c**): yield, 74%; b.p. 68–70 °C/0.1 Torr. Steric purity, E = 100%. ^{13}C NMR δ: 127.8; 129.2; 131.1; 132.8; 139.8; 145.1; 193.7 ppm.

E,*E*-2,4-Decadienal (**4d**): yield, 56%. Steric purity, *E*,*E*/*E*,*Z* = 99:1. IR (cm^{-1}): 2940; 2910; 2850; 2720; 1680; 1610; 1440; 1370; 1155; 1110; 1005; 980. ^1H NMR δ: 0.9 (t, 3H); 1.3 (m, 4H); 1.5 (m, 2H); 2.2 (m, 2H); 6.1 (dd, H^2); 6.27 (dt, H^5); 6.33 (dd, H^4); 7.1 (dd, H^3); 9.55 (d, H^1) ppm [$J(H^2/H^3)$ = 15.4 Hz, $J(H^4/H^5)$ = 15.4 Hz, $J(H^3/$

H^4) = 10.0 Hz, $J(H^1/H^2)$ = 7.7 Hz, $J(H^5/H^6)$ = 6.6 Hz]. ^{13}C NMR δ: 14.1; 22.6; 28.4; 31.6; 33.4; 129.3; 130.7; 148.2; 153.7; 194.8 ppm.

E,E,E-2,4,6-Octatrienal (**4e**): yield, 50%. Steric purity, *E,E,E* = 95%. IR (cm^{-1}): 1670; 1610; 1440; 1250; 1160; 1110; 1010; 990; 920; 880; 830. ^1H NMR δ: 1.8 (dd, 3H, H^8); 5.95 (H^7, dq); 6.05 (H^2, dd); 6.1 (H^6, ddq); 6.25 (H^4, dd); 6.6 (H^5, dd); 7.05 (H^3, dd); 9.45 (dd, H^1) ppm [$J(H^2/H^3)$ = 14.8 Hz, $J(H^4/H^5)$ = 14.8 Hz, $J(H^6/H^7)$ = 14.8 Hz, $J(H^3/H^4)$ = 11.3 Hz, $J(H^5/H^6)$ = 10.7 Hz, $J(H^1/H^2)$ = 7.7 Hz, $J(H^7/H^8)$ = 6.6 Hz, $J(H^6/H^8$ = 1.1 Hz]. ^{13}C NMR δ: 18.6, 127.5; 130.6; 131.1; 137.1; 143.1; 152.4; 193.5 ppm.

3.5. Preparation of a difluorinated analogue of codlemone

3.5.1. E,E-12-t-Butoxy-1,1-difluoro-2,4-dodecadiene

This product was prepared from the appropriate aldehyde, i.e. *E*-10-t-butoxy-2-decenal [15b]. The experimental procedure was the same as that described previously. Yield, 50%. Steric purity, *E,E/E,Z* = 97:3. IR (cm^{-1}): 1660; 1625. ^1H NMR δ: 1.2 (s, 9H); 1.3 (m, 6H); 1.4 (m, 2H); 1.5 (m, 2H); 2.1 (q, 2H); 3.3 (t, 2H); 5.6 (dtd, H^2); 5.9 (dt, H^5); 6.07 (dd, H^4); 6.09 (td, H^1); 6.45 (ddt, H^3) ppm [$J(H^1/F)$ = 56.1 Hz, $J(H^2/H^3)$ = 15.4 Hz, $J(H^4/H^5)$ = 14.8 Hz, $J(H^3/H^4)$ = 10.4 Hz, $J(H^2/F)$ = 8.8 Hz, $J(H^5/H^6)$ = 6.6 Hz, $J(H^1/H^2)$ = 6.0 Hz, $J(H^3/F)$ = 3.6 Hz]. ^{13}C NMR δ: 26.1; 27.5; 28.7; 29.0; 29.2; 30.5; 32.6; 61.6; 72.6; 115.4 (t, C^1, J = 232.6 Hz); 121.5 (t, C^2, J = 23.9 Hz); 127.7 (s, C^4); 137.3 (t, C^3, J = 12.0 Hz); 141.0 (s, C^5) ppm.

3.5.2. E,E-12-Acetoxy-1,1-difluoro-2,4-dodecadiene

This acetate was obtained from the previous ether according to a described method ($FeCl_3$, Ac_2O in Et_2O) [19]. Yield, 50%. Steric purity, *E,E/E,Z* = 96:4. IR (cm^{-1}): 1735; 1660; 1625; ^1H NMR δ: 1.3 (m, 6H); 1.4 (m, 2H); 1.5 (m, 2H); 2.05 (s, 3H); 2.1 (q, 2H); 4.05 (q, 2H) ppm, data for the double-bond system the same as for the t-butoxydiene. ^{13}C NMR δ: 21.0; 25.8; 28.5; 28.7; 28.96; 28.99; 32.6; 64.5; 115.4 (t, C^1, J = 232.6 Hz); 121.6 (t, C^2, J = 23.9 Hz); 127.8 (s, C^4); 137.3 (t, C^3, J = 12.9 Hz); 140.8 (s, C^5); 171.2 ppm.

3.5.3. E,E-1,1-Difluoro-2,4-dodecadien-12-ol

This alcohol was afforded by saponification of the previous acetate with 2 N KOH in MeOH [19]. Yield: 95%. Steric purity: *E,E/E,Z* = 96:4. IR (cm^{-1}): 3370; 2920; 2840; 1660; 1625; 1385; 1130; 1010; 980. ^{19}F NMR δ: −109.2 (dd, J = 56, 9 Hz, *E,E*-isomer) ppm. ^1H NMR δ: 1.3 (m, 6H); 1.4 (m, 2H); 1.55 (m, 2H); 2.1 (q, 2H); 3.65 (t, 2H) ppm, data for the double-bond system the same as for the t-butoxydiene. ^{13}C NMR δ: 25.7, 28.8, 29.1, 29.2, 32.66, 32.74, 62.9, 115.5 (t, C^1, J = 233.5 Hz); 121.6 (t, C^2, J = 23.9 Hz); 127.8 (s, C^4); 137.4 (t, C^3, J = 12.9 Hz); 141.0 (s, C^5) ppm. Analysis: Calc. for $C_{12}H_{20}F_2O$: C, 66.03; H, 9.23%. Found: C, 66.15; H, 9.34%.

4. Conclusion

We have shown that 1-fluoro-1-alken-3-ols can be obtained from a large variety of carbonyl compounds and that the latter could be interesting synthesis precursors allowing the introduction of a difluoromethylene group or aldehydic function in the allylic position with a high regio- and stereoselectivity.

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