ELSEVIER

Journal of Fluorine Chemistry 113 (2002) 167–175

JOURNAL OF FLUORINE CHEMISTRY

www.elsevier.com/locate/jfluchem

Synthesis of α-trifluoromethyl unsaturated acids and derivatives

Frédérique Tellier[a,*], Max Audouin[b], Raymond Sauvêtre[c]

[a]*Unité de Phytopharmacie et Médiateurs Chimiques, INRA, Route de Saint-Cyr, 78026 Versailles Cedex, France*
[b]*Laboratoire de Synthèse Organique et Organométallique, Associé au CNRS, Université P. et M. Curie, Boîte 181, 4 Place Jussieu, 75252 Paris Cedex 05, France*
[c]*Laboratoire de Chimie des Organoéléments, Associé au CNRS, Université P. et M. Curie, Boîte 183, 4 Place Jussieu, 75252 Paris Cedex 05, France*

Received 23 July 2001; accepted 18 September 2001

Abstract

A one pot synthesis of α-trifluoromethyl unsaturated acids via a [3,3]-sigmatropic rearrangement of allyl (or propargyl) fluorovinyl ethers is described. By proto- and iodolactonization, these acids lead to the corresponding trifluoromethylated lactones.

Keywords: 1,1,3,3,3-Pentafluoropropene; Addition–elimination; [3,3]-Sigmatropic rearrangement; α-CF_3 unsaturated acids; α-CF_3 furanones; α-CF_3 pyranones

1. Introduction

The replacement of hydrogen atoms by fluorine atoms in biological molecules causes only a relatively small steric perturbation but leads to major changes in hydrophobicity and polarity factors [1,2]. Hence, during the past few years, trifluoromethylated organic molecules have drawn much attention due to their unique biological properties [3–8] and a considerable effort has been devoted to the development of new synthetic routes to these fluorinated compounds [9–11]. The synthesis of intermediates bearing a trifluoromethyl group, such as α-trifluoromethyl unsaturated acids, represents an attractive approach.

Few general and simple synthetic methods are suitable for preparing these acids. Among these, the enzymatic hydrolysis of esters [12,13] (mainly leading to chiral compounds) and the [3,3]-sigmatropic rearrangement [14–20], allow access to the chemical structures described in this paper. In previous studies, we have shown that the [3,3]-sigmatropic rearrangement of allyl fluorovinyl ethers was a useful synthetic method for the stereoselective construction of γ-unsaturated acids. It is the presence of the fluorine atom to the oxygen atom which makes the transposition easier. Thus, with regard to this subject, we have previously reported that allyl chlorodifluoro-, difluoro- and bromofluoro-vinyl ethers rearrange at temperatures far below 0 °C to lead to γ-unsaturated acid fluorides α-chlorinated [21], α-fluorinated [22,23] and α-brominated [24], respectively.

2. Results and discussion

2.1. Synthesis of α-trifluoromethyl unsaturated acids, esters and amides, *4* and *5*

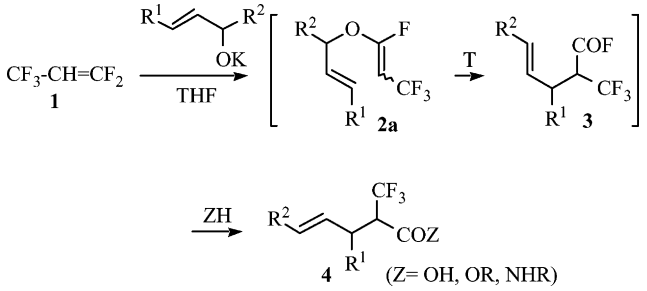
Herein, we show that similarly, allyl (or propargyl) fluorovinyl ethers **2a** (or **2b**), obtained by reaction of the electrophilic 1,1,3,3,3-pentafluoropropene **1** with α-unsaturated alkoxides in an anhydrous medium, lead to α-trifluoromethyl β-substituted γ-ethylenic (or β-allenic) acids and derivatives **4** (Scheme 1) or **5** (Scheme 2) in good yields.

The compounds **4** and **5** are obtained by a one pot synthesis which includes three different steps: reaction between pentafluoropropene **1** and allyl (or propargyl) potassium alkoxide, selective [3,3]-sigmatropic rearrangement, and hydrolysis of acid fluoride. The results are summarized in Tables 1 and 2.

The first step involves a selective fluorine substitution by potassium alkoxide. The alkoxide reacts according to an addition–elimination process [25] (via an intermediate carbanion) to give the vinyl ether **2a** or **2b**. It is the mesomeric effect of fluorine in the difluoromethylene group which determines the orientation of this addition [26] (Scheme 3).

* Corresponding author. Fax: +33-1-30-83-31-19.
E-mail address: ftellier@versailles.inra.fr (F. Tellier).

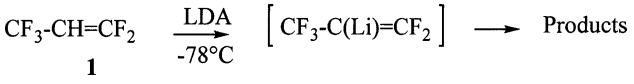
0022-1139/02/$ – see front matter
PII: S0022-1139(01)00542-5



Scheme 1. Synthesis of α-trifluoromethyl γ-ethylenic acids and derivatives **4**.

Potassium alkoxide offers the advantage of reacting in THF with **1** at very low temperature (−90 °C), temperature compatible with our sigmatropic rearrangement which occurs subsequently at about −30 °C.

It is interesting to note that Burton has also used **1**, as starting material to introduce a trifluoromethyl group. But its treatment at −78 °C with either LDA or *t*-BuLi in diethylether and pentane, led to the preparation of CF_3–C(Li)=CF_2, a fluorinated intermediate subsequently involved in additional functionalization reactions [27] (Scheme 4).



Scheme 4. Metallation reaction with LDA in an aprotic medium.

The difference in reactivity between the reagents is explained by the fact that LDA exhibits more basic character in a metallation process, whereas the potassium alkoxide shows more nucleophilic character and reacts accordingly in an addition–elimination process.

The geometry of the vinyl ethers **2** has been shown with a saturated alkoxide (*n*-HeptOK) (Scheme 3). In this case, since the ether (*n*-HeptOCF=$CHCF_3$) cannot undergo the transposition and moreover is stable, it can be isolated and its geometry determined by ^{19}F and ^{1}H NMR spectroscopy ($Z/E \approx 2/1$) [^{1}H NMR: (*E*) isomer $\delta = 3.86$ (t, $J = 6.4$ Hz, 2H), 4.17 (qd, $J = 6.7$ and 2.0 Hz, 1H), (*Z*) isomer $\delta = 4.10$ (t, $J = 6.6$ Hz, 2H), 4.48 (qd, $J = 6.9$ and 3.9 Hz, 1H)].

In a second step, by increasing the temperature of the reaction mixture to about −30 °C, the allyl (or propargyl) fluorovinyl ethers quickly undergo a [3,3]-sigmatropic rearrangement, giving the corresponding acid fluorides **3**. Claisen rearrangement of these ethers offers the advantage that it occurs at very low temperatures. We have already shown that the fluorine atom α to the oxygen atom was responsible for a substantial decrease in the rearrangement reaction temperature [21].

Finally, the hydrolysis of acid fluoride into acid is easy: it occurs in less than 1 h at room temperature for the examples described here. It is interesting to emphasize that the acid fluoride **3** is a reactive intermediary of synthesis, because it can lead to esters or amides if alcohols or amines are added instead of water.

In the case of $R^1 \neq H$, the transposition leads to **4** (**4d**, **4f** and **4h**) as two diastereomers, D^1 and D^2, in a ratio $D^1/D^2 \approx 2/1$. If the allyl potassium alkoxide used is secondary ($R^2 \neq H$), the carbon–carbon double bond formation is stereospecific (**4b**, **4c**, **4e** and **4g**).

Table 1
Claisen rearrangement of allyl fluorovinyl ethers

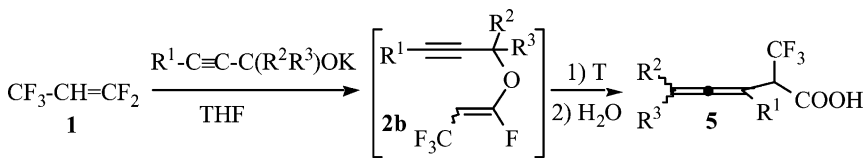
R^1	R^2	ZH	Product	Yield[a] (%)
H	H	H_2O	**4a**	70
H	Me	H_2O	**4b**	82
H	Ph	H_2O	**4c**	21
Me	H	H_2O	**4d**	80[b]
H	Me	EtOH	**4e**	71
–$(CH_2)_3$–		MeOH	**4f**	57[b]
H	Me	*t*-$BuNH_2$	**4g**	64
Ph	H	*t*-$BuNH_2$	**4h**	50[b]

[a] Overall yields based on the starting pentafluoropropene **1**.
[b] dr: $D^1/D^2 \approx 2/1$ (diastereomer ratio determined by ^{19}F NMR).

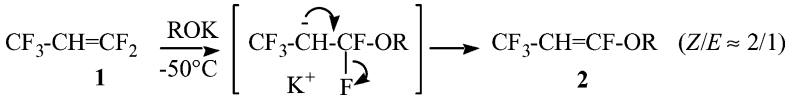
Table 2
Claisen rearrangement of propargyl fluorovinyl ethers

R^1	R^2	R^3	Product	Yield[a] (%)
H	H	H	**5a**	55
Me	H	H	**5b**	58
H	Me	H	**5c**	70[b]
H	Me	Me	**5d**	47

[a] Overall yields based on the starting pentafluoropropene **1**.
[b] dr: $D^1/D^2 = 64/36$ (diastereomer ratio determined by ^{19}F NMR).



Scheme 2. Synthesis of α-trifluoromethyl β-allenic acids **5**.



Scheme 3. Substitution reaction with ROK in THF.

$$CF_3\text{-}CH{=}CF_2 \xrightarrow{PhCH_2OK} CF_3CH_2CF_2OCH_2Ph \xrightarrow{H^+} CF_3CH_2CO_2CH_2Ph$$

Scheme 5. Reaction with a benzyl alkoxide.

Note the case of the benzyl alcohol in which the alkoxide reacts with **1** to give only the addition product and then after hydrolysis the benzyl-3,3,3-trifluoropropionate (Scheme 5).

2.2. Lactonization

Secondly, we are interested in the cyclisation reactions [28–30] of acids **4** and **5** in order to obtain simple cyclic molecules with a CF_3 group α to a carbonyl function.

2.2.1. Protolactonization

The non-fluorinated γ-lactones can show interesting biological properties; for example, a class of butenolides [31] which constitutes the "E" ring of naturally occurring steroids and the eldanolides which are insect sex pheromones [32].

For the four cases studied here, the same procedure is used: the acids **4** and **5** are added at −10 °C in concentrated H_2SO_4 and stirred for 1 h at +20 °C.

*2.2.1.1. Ethylenic acids, **4a** and **4i**.* Acid **4a** easily gives lactone **6** [13,17]. Under our conditions (H_2SO_4, 1 h at +20 °C), **6** is obtained in 70% yield as a mixture of two diastereomers **6a** and **6b** (**6a**/**6b** = 67/33) which are completely separated by silica gel chromatography (Scheme 6).

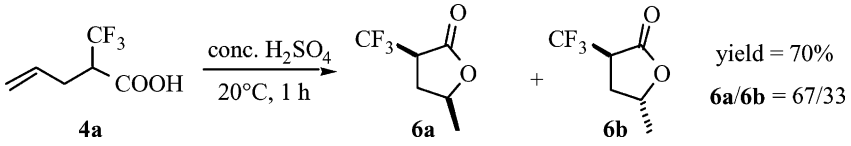
The relative stereochemistry of functional groups, CF_3 and CH_3, in **6a** and **6b** is determined by ^1H (NOE) analysis after irradiation of the protons H^4, $H^{4'}$ or H^5, respectively, at 2.02, 2.68, 4.63 ppm for **6a** and at 2.61, 2.20, 4.80 ppm for **6b** (Scheme 7).

We observe after irradiation of the proton H^5, a significant effect on the H^3 and $H^{4'}$ protons for **6a** and in contrast, no effect for **6b**. These results allow us to conclude that **6a**, the major lactone, is the *cis*-2-trifluoromethyl-4-methyl lactone and **6b**, the *trans*-isomer.

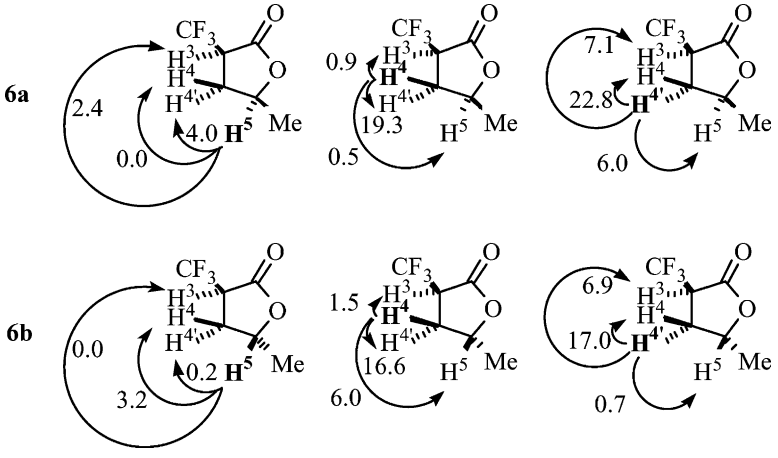
Similarly, the acid **4i** leads in 70% yield to the corresponding bicyclic lactone **7** as a mixture of four diastereomers **7a–d** (**7a**/**7b**/**7c**/**7d** = 41/24/24/11). After their separation by silica gel chromatography, their identification is performed by ^1H (NOE) analysis (Scheme 8).

Thus, after irradiation of the H^4 proton, we note a significant effect on the H^9 proton of **7a** and **7b** and in contrast no effect on that of **7c** and **7d**. This result indicates that the junction of the two rings is *cis* in the lactones **7a** and **7b** (*trans* in **7c** and **7d**). Moreover, the irradiation of the H^4 proton shows that in the lactones **7a** and **7c**, the H^4 and H^3 protons are *trans* (no effect on H^3) and in **7b** and **7d**, *cis* (effect on H^3).

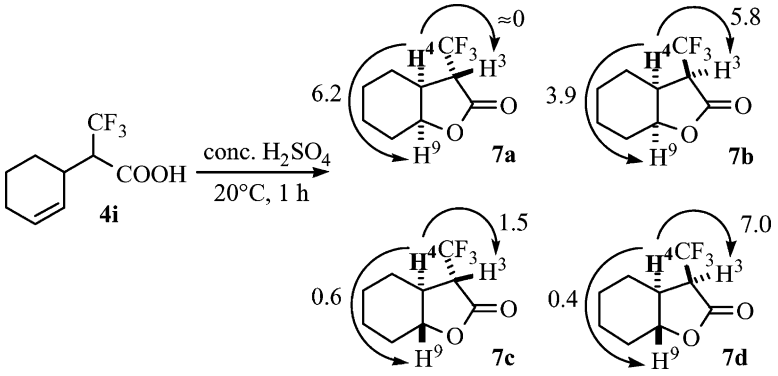
*2.2.1.2. Allenic acids, **5b** and **5d**.* The protolactonization of the acid **5b** leads in 73% yield only to the furanone **8** (Scheme 9). This lactone is very stable in contrast to the iodolactones described in the following section. It is interesting to note that lactone **8** is obtained in the reaction medium as the stable α,β-unsaturated ester form.



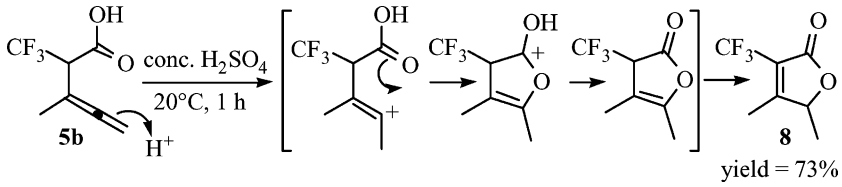
Scheme 6. Protolactonization of the acid **4a**.



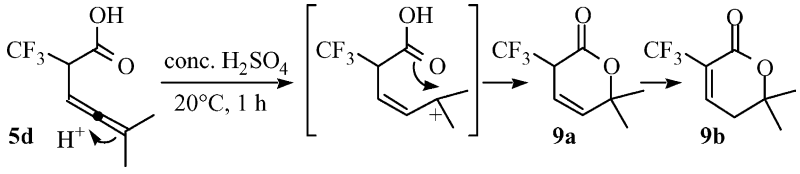
Scheme 7. ^1H NMR NOE intensity changes, given as percent of value.



Scheme 8. Protolactonization of the acid **4i**: ^{1}H NMR NOE intensity changes, given as percent of value.



Scheme 9. Protolactonization reaction of the acid **5b**.



Scheme 10. Protolactonization reaction of the acid **5d**.

For the acid **5d**, in contrast to the previous case, the protolactonization takes place on the central carbon of the allenic system. The tertiary carbocation obtained leads only to the kinetic product, the pyranone **9a** which remains the major product at low temperatures. By increasing in temperature and reaction time, the conjugated pyranone **9b** becomes the main product (Scheme 10 and Table 3).

Table 3
Protolactonization of the acid **5d**

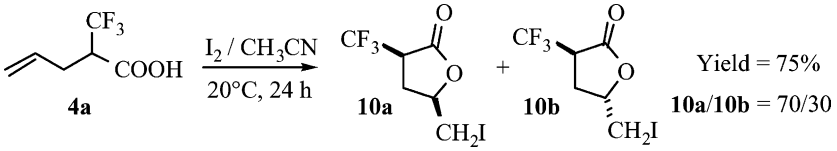
Experimental conditions (°C/h)	Yield (%) **9a** + **9b**	Ratio of **9a**:**9b**
−10/0.5	25	72:28
0/1	35	50:50
20/3	50	10:90
20/24	60	8:92

2.3. Iodolactonization

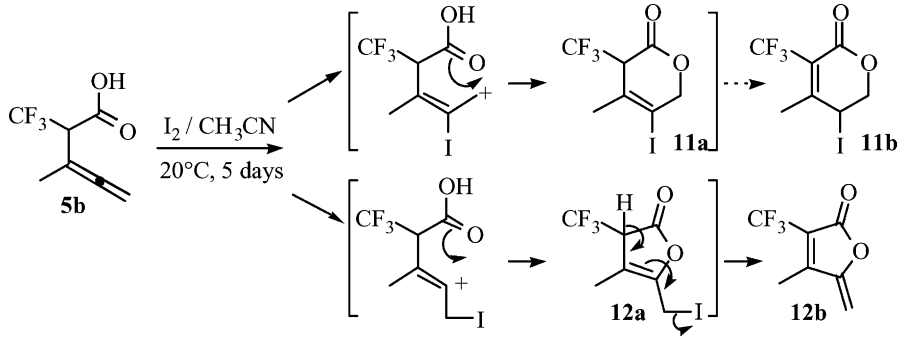
All assays are performed under similar conditions (addition of three equivalents of iodine in acetonitrile, stirring at +20 °C in the dark) except for the reaction time (in the case of the ethylenic acid, the reaction does not proceed further after 24 h but for the allenic acids, it is necessary to maintain the stirring for 5 or 6 days).

2.3.1. Ethylenic acid, *4a*

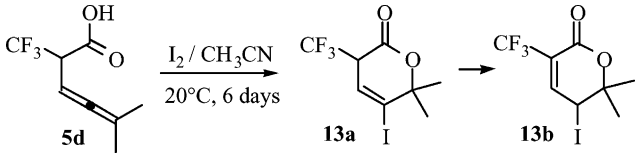
The iodolactonization of **4a** [33] leads to the iodolactones **10a** and **10b** (**10a**/**10b** = 70/30) (Scheme 11). After separation by silica gel chromatography, their geometry is confirmed by reduction with *n*-Bu_3SnH into the *cis*- and *trans*-butyrolactones **6a** and **6b**, respectively. Therefore whether the lactones **6a** and **6b** are obtained by an iodolactonization



Scheme 11. Iodolactonization of the acid **4a**.



Scheme 12. Iodolactonization of the acid **5b**.



Scheme 13. Iodolactonization of the acid **5d**.

followed by a reduction or by a direct prolactonization, the results are similar, giving the same *cis*/*trans* ratio and yield.

2.3.2. Allenic acids, *5b* and *5d*

The iodolactonization of β-allenic acids is characterized by the low reaction rate, the variety of products obtained (five or six membered ring systems, conjugated or non-conjugated ester function) and their instability.

The acid **5b** in the presence of iodine gives several products: the pyranone **11a** (70%), the furanone **12b** (18%) and three non-identified products (12%) (Scheme 12). The pyranone **11a** is obtained in about 45% yield. During the purification, by filtration through a column packed with silica gel, **11a** is partly destroyed. On contact with silica gel, it is probably converted into the conjugated pyranone **11b**, a very unstable lactone which cannot be identified. The percentages of the lactones **11a** and **12b** indicate the ratio of the different intermediate carbocations present in the reaction. Among the three minor products, the most important is probably the remainder of **12a** [^{19}F NMR: $\delta = -65.9$ (dq, $J(F/H^3) = 8.6$ Hz, $J(F/CH_3) = 1.0$ Hz, CF_3)].

In the iodolactonization reaction of **5d**, only the lactone **13a** which comes from the attack of the carbonyl function on the most stable tertiary carbocation intermediate, can be identified with certainty in about 45% yield (Scheme 13). This lactone **13a** is even more unstable than lactone **11a** previously mentioned, and is quickly converted into the unstable conjugated lactone **13b**. Beside this major product, note the presence of one unidentified product characterized by a simple ^{19}F NMR signal (−67.9 ppm, d, $J = 1.0$ Hz).

3. Conclusion

We have shown the very wide-ranging reactivity of unsaturated potassium alkoxides with electrophilic pentafluoropropene. The allyl (or propargyl) fluorovinyl ethers obtained rapidly undergo rearrangement at very low temperatures which makes it possible to synthesize α-trifluoromethyl γ-ethylenic (or β-allenic) acid derivatives in good yields. Moreover, the acids can easily lead by proto- or iodolactonization to α-trifluoromethylated furanones and pyranones.

4. Experimental

^{1}H NMR and ^{13}C NMR spectra ($CDCl_3$: δ (ppm) from TMS) and ^{19}F NMR spectra ($CDCl_3$: δ (ppm) from $CFCl_3$) were recorded on Bruker AC 200 and ARX 400 spectrometers. Infrared spectra were measured on films on a Perkin-Elmer 397 spectrometer. Starting materials were purchased from Aldrich (KH, 35 wt.% dispersion in mineral oil) and PCR-Lancaster (1,1,3,3,3-pentafluoropropene). THF was dried by refluxing and distilling from sodium-benzophenone dianion.

4.1. Preparation of the acids and derivatives, *4a–h* and *5a–d*

Allylic or propargylic alcohol (15 mmol) was added to KH (≈15 mmol) in THF (20 ml). After 30 min at +20 °C, this alkoxide solution was added to a solution of 1,1,3,3,3-pentafluoropropene (10 mmol) in THF (20 ml) at −90 °C. The stirring was continued for 3 h at −50 °C. Then, the mixture was treated at −50 °C either with H_2SO_4 (10%) (**4a–d** and **5a–d**), alcohol (10 equivalents of EtOH or MeOH) (**4e** or **4f**) or amine (10 eq. of *t*-$BuNH_2$) (**4g** and **4h**) and the temperature was allowed to rise to room temperature. After 30 min, the mixture was hydrolyzed with H_2SO_4 (10%) and extracted with Et_2O.

4.1.1. 2-Trifluoromethyl-4-pentenoic acid (*4a*)

IR (neat): $\nu = 3000$ (OH), 1730 (C=O), 1645 (C=C) cm^{-1}. ^{1}H NMR: $\delta = 2.59$ [dddt, $J(H^3/H^{3'}) = 14.7$ Hz, $J(H^3/H^4) = 6.6$ Hz, $J(H^3/H^2) = 5.1$ Hz, $J(H^3/H^5) = J(H^3/H^{5'}) = 1.3$ Hz, H^3], 2.66 [dddt, $J(H^{3'}/H^3) = 14.7$ Hz, $J(H^{3'}/H^2) = 9.7$ Hz, $J(H^{3'}/H^4) = 7.1$ Hz, $J(H^{3'}/H^5) = J(H^{3'}/H^{5'}) = 1.3$ Hz, $H^{3'}$], 3.23 [dqd, $J(H^2/H^{3'}) = 9.7$ Hz,

$J(H^2/F) = 8.1$ Hz, $J(H^2/H^3) = 5.1$ Hz, H^2], 5.15 [dq, $J(H^5/H^4) = 10.2$ Hz, $J(H^5/H^{5'}) = J(H^5/H^3) = J(H^5/H^{3'}) = 1.5$ Hz, H^5], 5.20 [dq, $J(H^{5'}/H^4) = 17.3$ Hz, $J(H^{5'}/H^5) = J(H^{5'}/H^3) = J(H^{5'}/H^{3'}) = 1.5$ Hz, $H^{5'}$], 5.78 [dddd, $J(H^4/H^{5'}) = 17.3$ Hz, $J(H^4/H^5) = 10.2$ Hz, $J(H^4/H^{3'}) = 7.1$ Hz, $J(H^4/H^3) = 6.6$ Hz, H^4], 10.20 (s, H^1). ^{13}C NMR: $\delta = 30.4$ (s, C^3), 50.2 (q, $J = 28.5$ Hz, C^2), 118.9 (s, C^5), 124.4 (q, $J = 278.7$ Hz, CF_3), 132.3 (s, C^4), 171.7 (s, C^1). ^{19}F NMR: $\delta = -68.6$ [d, $J(F/H^2) = 8.1$ Hz] [16].

*4.1.2. (E)-2-trifluoromethyl-4-hexenoic acid (**4b**)*

IR (neat): $\nu = 3000$ (OH), 1725 (C=O) cm^{-1}. ^{1}H NMR: $\delta = 1.67$ [dq, $J(H^6/H^5) = 6.6$ Hz, $J(H^6/H^4) = J(H^6/H^3) = J(H^6/H^{3'}) = 1.5$ Hz, $3H^6$], 2.53 [dddpent, $J(H^3/H^{3'}) = 14.2$ Hz, $J(H^3/H^4) = 6.6$ Hz, $J(H^3/H^2) = 5.1$ Hz, $J(H^3/H^5) = J(H^3/H^6) = 1.3$ Hz, H^3], 2.59 [dddpent, $J(H^{3'}/H^3) = 14.2$ Hz, $J(H^{3'}/H^2) = 9.2$ Hz, $J(H^{3'}/H^4) = 7.1$ Hz, $J(H^{3'}/H^5) = J(H^{3'}/H^6) = 1.2$ Hz, $H^{3'}$], 3.17 [dqd, $J(H^2/H^{3'}) = 9.2$ Hz, $J(H^2/F) = 8.1$ Hz, $J(H^2/H^3) = 5.1$ Hz, H^2], 5.38 [ddd, $J(H^4/H^5) = 15.3$ Hz, $J(H^4/H^{3'}) = 7.6$ Hz, $J(H^4/H^3) = 6.6$ Hz, H^4], 5.63 [dqt, $J(H^5/H^4) = 15.3$ Hz, $J(H^5/H^6) = 6.6$ Hz, $J(H^5/H^3) = J(H^5/H^{3'}) = 1.5$ Hz, H^5], 8.44 (s, H^1). ^{13}C NMR: $\delta = 17.9$ (s, C^6), 29.4 (s, C^3), 50.6 (q, $J = 28.5$ Hz, C^2), 124.4 (q, $J = 280.5$ Hz, CF_3), 124.6 (s, C^4), 129.9 (s, C^5), 172.3 (s, C^1). ^{19}F NMR: $\delta = -68.5$ [d, $J(F/H^2) = 8.1$ Hz] [16].

*4.1.3. (E)-5-phenyl-2-trifluoromethyl-4-pentenoic acid (**4c**)*

IR (neat): $\nu = 1730$ (C=O) cm^{-1}. ^{1}H NMR: $\delta = 2.74$ [dddd, $J(H^3/H^{3'}) = 14.5$ Hz, $J(H^3/H^4) = 7.6$ Hz, $J(H^3/H^2) = 5.3$ Hz, $J(H^3/H^5) = 1.3$ Hz, H^3], 2.81 [dddd, $J(H^{3'}/H^3) = 14.5$ Hz, $J(H^{3'}/H^2) = 9.0$ Hz, $J(H^{3'}/H^4) = 7.6$ Hz, $J(H^{3'}/H^5) = 1.3$ Hz, $H^{3'}$], 3.30 [dqd, $J(H^2/H^{3'}) = 9.0$ Hz, $J(H^2/F) = 8.1$ Hz, $J(H^2/H^3) = 5.3$ Hz, H^2], 6.11 [dt, $J(H^4/H^5) = 15.8$ Hz, $J(H^4/H^3) = J(H^4/H^{3'}) = 7.6$ Hz, H^4], 6.53 [dt, $J(H^5/H^4) = 15.8$ Hz, $J(H^5/H^3) = J(H^5/H^{3'}) = 1.3$ Hz, H^5], 7.3 [m, 5 arom. H], 10.09 (s, H^1). ^{13}C NMR: $\delta = 29.7$ (s, C^3), 50.4 (q, $J = 28.5$ Hz, C^2), 123.3 (s, C^4), 124.3 (q, $J = 280.8$ Hz, CF_3), 126.4, 127.8, 128.7 (s, arom. C), 134.1 (s, C^5), 136.6 (s, C^6), 172.3 (s, C^1). ^{19}F NMR: $\delta = -68.2$ [d, $J(F/H^2) = 8.0$ Hz]. Anal. calcd. for $C_{12}H_{11}F_3O_2$: C, 59.02; H, 4.54. Found: C, 59.57; H, 4.78%.

*4.1.4. 3-Methyl-2-trifluoromethyl-4-pentenoic acid (**4d**)*

$D^1/D^2 = 64/36$. IR (neat): $\nu = 3000$ (OH), 1725 (C=O), 1640 (C=C) cm^{-1}. ^{1}H NMR: $\delta = 1.16$ [d, $J(CH_3/H^3) = 6.7$ Hz, CH_3 (D^1)], 1.22 [d, $J(CH_3/H^3) = 6.8$ Hz, CH_3 (D^2)], 2.87 [hex, $J \approx 7.4$ Hz, H^3], 3.07 [quint, $J(H^2/H^3) = J(H^2/F) = 8.2$ Hz, H^2 (D^2)], 3.10 [quint, $J(H^2/H^3) = J(H^2/F) = 8.2$ Hz, H^2 (D^1)], 5.07 [d, $J(H^5/H^4) = 10.2$ Hz,], 5.14 [d, $J(H^{5'}/H^4) = 16.9$ Hz, $H^{5'}$(D^2)], 5.16 [d, $J(H^{5'}/H^4) = 17.1$ Hz, $H^{5'}$(D^1)], 5.77 [ddd, $J(H^4/H^{5'}) = 17.0$ Hz, $J(H^4/H^5) = 10.0$ Hz, $J(H^4/H^3) = 8.5$ Hz, H^4], 10.90 (s, H^1). ^{13}C NMR: $\delta = 17.9$ [s, CH_3 (D^1)], 18.2 [s, CH_3 (D^2)], 36.6 [s, C^3 (D^1)], 36.8 [s, C^3 (D^2)], 55.8 [q, $J = 26.1$ Hz, C^2 (D^1)], 55.9 [q, $J = 26.4$ Hz, C^2 (D^2)], 115.9 [s, C^5 (D^1)], 116.4 [s, C^5 (D^2)], 124.5 [q, $J = 280.7$ Hz, CF_3 (D^1)], 124.6 [q, $J = 280.8$ Hz, CF_3 (D^2)], 138.7 [s, C^4 (D^2)], 139.1 [s, C^4 (D^1)], 171.2 [q, $J \approx 3$ Hz, C^1 (D^1)], 171.3 [q, $J \approx 3$ Hz, C^1 (D^2)]. ^{19}F NMR: $\delta = -64.9$ [d, $J(F/H^2) = 8.2$ Hz, (D^2)], -65.1 [d, $J(F/H^2) = 8.2$ Hz, (D^1)] [16].

*4.1.5. (E)-ethyl-2-trifluoromethyl-4-hexenoate (**4e**)*

IR (neat): $\nu = 1745$ (C=O) cm^{-1}. ^{1}H NMR: $\delta = 1.28$ [t, $J = 7.1$ Hz, 3H], 1.65 [dq, $J(H^6/H^5) = 6.5$ Hz, $J(H^6/H^4) = J(H^6/H^3) = J(H^6/H^{3'}) = 1.3$ Hz, $3H^6$], 2.47 [dddpent, $J(H^3/H^{3'}) = 14.2$ Hz, $J(H^3/H^4) = 7.8$ Hz, $J(H^3/H^2) = 5.0$ Hz, $J(H^3/H^5) = J(H^3/H^6) = 1.4$ Hz, H^3], 2.58 [dddpent, $J(H^{3'}/H^3) = 14.2$ Hz, $J(H^{3'}/H^2) = 10.2$ Hz, $J(H^{3'}/H^4) = 7.6$ Hz, $J(H^{3'}/H^5) = J(H^{3'}H^6) = 1.1$ Hz, $H^{3'}$], 3.12 [dqd, $J(H^2/H^{3'}) = 10.2$ Hz, $J(H^2/F) = 8.4$ Hz, $J(H^2/H^3) = 4.8$ Hz, H^2], 4.22 [q, $J = 7.1$ Hz, 2H], 5.33 [dtq, $J(H^4/H^5) = 15.3$ Hz, $J(H^4/H^3) = J(H^4/H^{3'}) = 7.6$ Hz, $J(H^4/H^6) = 1.3$ Hz, H^4], 5.58 [dqt, $J(H^5/H^4) = 15.3$ Hz, $J(H^5/H^6) = 6.5$ Hz, $J(H^5/H^3) = J(H^5/H^{3'}) = 1.3$ Hz, H^5]. ^{13}C NMR: $\delta = 14.1$ (s, CH_3), 17.8 (s, C^6), 29.4 (s, C^3), 50.7 (q, $J = 28.5$ Hz, C^2), 61.7 (s, OCH_2), 124.9 (q, $J = 280.8$ Hz, CF_3), 124.9 (s, C^4), 129.4 (s, C^5), 167.1 (s, C^1). ^{19}F NMR: $\delta = -68.7$ [d, $J(F/H^2) = 9.5$ Hz. Anal. calcd. for $C_9H_{13}F_3O_2$: C, 51.43; H, 6.23. Found: C, 51.17; H, 6.05.

*4.1.6. Methyl-2-[2-cyclohexene]-3,3,3-trifluoromethyl propanoate (**4f**)*

$D^1/D^2 = 61/39$. IR (neat): $\nu = 1745$ (C=O) cm^{-1}. ^{1}H NMR: $\delta = 1.37$–1.92 [4 m, $2H^7$ and $2H^8$], 1.98 [m, $2H^6$], 2.80 [m, H^3], 3.02 [quint, $J(H^2/H^3) = J(H^2/F) = 8.5$ Hz, H^2 (D^1)], 3.09 [quint, $J(H^2/H^3) = J(H^2/F) = 8.5$ Hz, H^2 (D^2)], 3.74 [s, 3 H (D^2)], 3.75 [s, 3H (D^1)], 5.43 [dq, $J(H^4/H^5) = 10.2$ Hz, $J(H^4/H^3) = J(H^4/H^6) = 2.5$ Hz, H^4 (D^1)], 5.63 [dm, $J(H^4/H^5) = 10.4$ Hz, H^4 (D^2)], 5.79 [dt, $J(H^5/H^4) = 10.2$ Hz, $J(H^5/H^6) = 3.6$ Hz, H^5 (D^1)], 5.80 [dt, $J(H^5/H^4) = 10.2$ Hz, $J(H^5/H^6) = 3.6$ Hz, H^5 (D^2)]. ^{13}C NMR: $\delta = 20.6$ [s, C^8 (D^2)], 21.0 [s, C^8 (D^1)], 24.7 [s, C^7], 26.1 [s, C^6 (D^2)], 27.1 [s, C^6 (D^1)], 33.5 [s, C^3 (D^2)], 33.9 [s, C^3 (D^1)], 52.4 [s, CH_3], 53.9 [q, $J = 26.5$ Hz, C^2 (D^1)], 55.1 [q, $J = 26.5$ Hz, C^2 (D^2)], 124.7 [q, $J = 280.8$ Hz, CF_3 (D^1)], 124.8 [q, $J \approx 280$ Hz, CF_3 (D^2)], 125.8 [s, C^4 (D^1)], 126.1 [s, C^4 (D^2)], 130.1 [s, C^5 (D^2)], 130.5 [s, C^5 (D^1)], 167.6 [s, C^1]. ^{19}F NMR: $\delta = -64.5$ [d, $J(F/H^2) = 8.5$ Hz, (D^2)], -65.4 [d, $J(F/H^2) = 8.6$ Hz, (D^1)]. Anal. calcd. for $C_{10}H_{13}F_3O_2$: C, 54.05; H, 5.90. Found: C, 53.88; H, 5.72.

*4.1.7. (E)-N-t-butyl-2-trifluoromethyl-4-hexenamide (**4g**)*

White solid, mp 122 °C. IR (CCl_4): $\nu = 1650$ (C=O) cm^{-1}. ^{1}H NMR: $\delta = 1.35$ (s, 9H), 1.65 [dq, $J(H^6/H^5) = 6.6$ Hz, $J(H^6/H^4) = J(H^6/H^3) = J(H^6/H^{3'}) = 1.3$ Hz, $3H^6$], 2.39 [dddm, $J(H^3/H^{3'}) = 14.0$ Hz, $J(H^3/H^4) = 6.9$ Hz, $J(H^3/H^2) = 4.3$ Hz, $J = 1.3$ Hz, H^3], 2.56 [dddm, $J(H^{3'}/H^3) = 14.0$ Hz, $J(H^{3'}/H^2) = 10.6$ Hz, $J(H^{3'}/H^4) = 7.2$ Hz, $J = 1.1$ Hz, $H^{3'}$], 2.73 [dqd, $J(H^2/H^{3'}) = 10.7$ Hz, $J(H^2/F) = 8.4$ Hz,

$J(H^2/H^3) = 4.3$ Hz, H^2], 5.34 [dtq, $J(H^4/H^5) = 15.3$ Hz, $J(H^4/H^3) = J(H^4/H^{3'}) = 7.1$ Hz, $J(H^4/H^6) = 1.5$ Hz, H^4], 5.45 [s, 1H], 5.59 [dqt, $J(H^5/H^4) = 15.3$ Hz, $J(H^5/H^6) = 6.4$ Hz, $J(H^5/H^3) = J(H^5/H^{3'}) = 1.3$ Hz, H^5]. ^{13}C NMR: $\delta = 17.9$ (s, C^6), 28.6 (s, CH_3), 29.4 (s, C^3), 52.0 (s, quat. C), 52.3 (q, $J = 26.4$ Hz, C^2), 125.1 (q, $J = 280.8$ Hz, CF_3), 123.7 (s, C^4), 129.3 (s, C^5), 165.0 (s, C^1). ^{19}F NMR: $\delta = -68.7$ [d, $J(F/H^2) = 8.6$ Hz]. Anal. calcd. for $C_{11}H_{18}F_3NO$: C, 55.68; H, 7.65; N, 5.90. Found: C, 56.10; H, 8.04; N, 5.63.

4.1.8. N-t-butyl-3-phenyl-2-trifluoromethyl-4-pentenamide (**4h**)

$D^1/D^2 = 62/38$. White solid, mp 180 °C. IR (CCl_4): $\nu = 1650$ (C=O) cm^{-1}. ^{1}H NMR: $\delta = 1.02$ [s, 9H (D^2)], 1.37 [s, 9H (D^1)], 3.72 [dq, $J(H^2/H^3) = 11.4$ Hz, $J(H^2/F) = 8.4$ Hz, H^2 (D^2)], 3.73 [dq, $J(H^2/H^3) = 10.7$ Hz, $J(H^2/F) = 8.1$ Hz, H^2 (D^1)], 3.99 [dd, $J(H^3/H^2) = 10.7$ Hz, $J(H^3/H^4) = 8.6$ Hz, H^3 (D^1)], 4.03 [dd, $J(H^3/H^2) = 11.4$ Hz, $J(H^3/H^4) = 9.4$ Hz, H^3 (D^2)], 5.05 [dd, $J(H^5/H^4) = 10.2$ Hz, $J(H^5/H^{5'}) = 1.8$ Hz, H^5 (D^2)], 5.08 [dd, $J(H^5/H^4) = 10.2$ Hz, $J(H^5/H^{5'}) = 1.8$ Hz, H^5 (D^1)], 5.14 [dt, $J(H^{5'}/H^4) = 17.0$ Hz, $J(H^{5'}/H^5) = J(H^{5'}/H^3) = 1.5$ Hz, $H^{5'}$ (D^1)], 5.20 [dd, $J(H^{5'}/H^4) = 17.0$ Hz, $J(H^{5'}/H^5) = 1.8$ Hz, $H^{5'}$ (D^2)], 6.07 [dtq, $J(H^4/H^{5'}) = 17.0$ Hz, $J(H^4/H^5) = J(H^4/H^3) = 9.7$ Hz, $J(H^4/F) = 1.3$ Hz, H^4 (D^2)], 6.11 [ddd, $J(H^4/H^{5'}) = 17.0$ Hz, $J(H^4/H^5) = 10.2$ Hz, $J(H^4/H^3) = 8.6$ Hz, H^4 (D^1)], 6.92 (s, 1H), 7.20–7.40 (m, 5 arom. H). ^{13}C NMR: $\delta = 29.0$ [s, CH_3 (D^2)], 29.4 [s, CH_3 (D^1)], 50.0 [s, C^3 (D^1)], 50.8 [s, C^3 (D^2)], 52.2 [s, quat. C (D^2)], 52.7 [s, quat. C (D^1)], 56.6 [q, $J = 24.4$ Hz, C^2 (D^1)], 57.1 [q, $J = 24.4$ Hz, C^2 (D^2)], 117.1 [s, C^5 (D^2)], 117.8 [s, C^5 (D^1)], 126.9 [q, $J = 282.8$ Hz, CF_3 (D^1)], 127.0 [q, $J \approx 280$ Hz, CF_3 (D^2)], 128.3–130.0 (arom. C), 139.5 [s, C^4 (D^1)], 140.1 [s, C^4 (D^2)], 142.1 (s, C^6), 165.6 [s, C^1 (D^2)], 166.1 [s, C^1 (D^1)]. ^{19}F NMR: $\delta = -62.7$ [dd, $J(F/H^2) = 8.3$ Hz, $J(F/H^4) = 1.2$ Hz, (D^2)], −62.8 [d, $J(F/H^2) = 8.1$ Hz, (D^1)]. Anal. calcd. for $C_{16}H_{20}F_3NO$: C, 64.20; H, 6.73; N, 4.68. Found: C, 64.05; H, 6.89; N, 4.83.

4.1.9. 2-Trifluoromethyl-3,4-pentadienoic acid (**5a**)

IR (neat): $\nu = 3000$ (OH), 1960 (C=C=C), 1725 (C=O) cm^{-1}. ^{1}H NMR: $\delta = 3.8$ [dqt, $J(H^2/H^3) = 9.2$ Hz, $J(H^2/F) = 8.1$ Hz, $J(H^2/H^5) = 1.0$ Hz, H^2], 5.0 [dd, $J(H^5/H^3) = 6.6$ Hz, $J(H^5/H^2) = 1.0$ Hz, H^5], 5.34 [dt, $J(H^3/H^2) = 9.2$ Hz, $J(H^3/H^5) = 6.6$ Hz, H^3], 8.1 (s, H^1). ^{13}C NMR: $\delta = 50.5$ (q, $J = 28.5$ Hz, C^2), 78.0 (s, C^5), 81.1 (s, C^3), 123.6 (q, $J = 280.8$ Hz, CF_3), 170.5 (s, C^1), 210.8 (s, C^4). ^{19}F NMR: $\delta = -69.2$ [d, $J(F/H^2) = 8.1$ Hz] [17].

4.1.10. 3-Methyl-2-trifluoromethyl-3,4-pentadienoic acid (**5b**)

IR (neat): $\nu = 3000$ (OH), 1960 (C=C=C), 1725 (C=O) cm^{-1}. ^{1}H NMR: $\delta = 1.87$ [t, $J(CH_3/H^5) = 3.1$ Hz, CH_3], 3.75 [q, $J(H^2/F) = 8.3$ Hz, H^2], 4.88 [q, $J(H^5/CH_3) = 3.0$ Hz, $2H^5$], 9.3 (s, H^1). ^{13}C NMR: $\delta = 17.2$ (s, CH_3), 53.6 (q, $J = 28.5$ Hz, C^2), 76.8 (s, C^5), 90.0 (s, C^3), 123.8 (q, $J = 280.8$ Hz, CF_3), 170.6 (s, C^1), 209.0 (s, C^4). ^{19}F NMR: $\delta = -67.1$ [d, $J(F/H^2) = 8.3$ Hz]. Anal. calcd. for $C_7H_7F_3O_2$: C, 46.67; H, 3.92. Found: C, 46.73; H, 4.08.

4.1.11. 2-Trifluoromethyl-3,4-hexadienoic acid (**5c**)

$D^1/D^2 = 64/36$. IR (neat): $\nu = 3000$ (OH), 1960 (C=C=C), 1725 (C=O) cm^{-1}. ^{1}H NMR: $\delta = 1.69$ [dd, $J(H^6/H^5) = 7.3$ Hz, $J(H^6/H^3) = 3.1$ Hz, $3H^6$], 3.74 [quintd, $J(H^2/F) = 8.4$ Hz, $J(H^2/H^3) = 8.4$ Hz, $J(H^2/H^5) = 1.5$ Hz, H^2], 5.22 [ddq, $J(H^3/H^2) \approx 9.0$ Hz, $J(H^3/H^5) = 6.2$ Hz, $J(H^3/H^6) = 3.1$ Hz, H^3], 5.35 [qdd, $J(H^5/H^6) = 7.1$ Hz, $J(H^5/H^3) = 6.4$ Hz, $J(H^5/H^2) = 1.5$ Hz, H^5], 11.2 (s, H^1). ^{13}C NMR: $\delta = 13.5$ (s, C^6), 51.0 [q, $J = 29.0$ Hz, C^2 (D^1)], 51.1 [q, $J = 29.0$ Hz, C^2 (D^2)], 80.8 (s, C^3), 89.5 (s, C^5), 123.6 (q, $J = 280.8$ Hz, CF_3), 171.7 (s, C^1), 207.7 (s, C^4). ^{19}F NMR: $\delta = -69.8$ [d, $J(F/H^2) = 8.3$ Hz, (D^1)], −69.9 [d, $J(F/H^2) = 8.3$ Hz, (D^2)]. Anal. calcd. for $C_7H_7F_3O_2$: C, 46.67; H, 3.92. Found: C, 47.12; H, 4.41.

4.1.12. 5-Methyl-2-trifluoromethyl-3,4-hexadienoic acid (**5d**)

IR (neat): $\nu = 3000$ (OH), 1970 (C=C=C), 1725 (C=O) cm^{-1}. ^{1}H NMR: $\delta = 1.73$ [d, $J(H^6/H^3) = 2.8$ Hz, $6H^6$], 3.73 [dq, $J(H^2/F) = 8.3$ Hz, $J(H^2/H^3) = 8.3$ Hz, H^2], 5.13 [dhept, $J(H^3/H^2) = 8.3$ Hz, $J(H^3/H^6) = 2.8$ Hz, H^3], 10.5 (s, H^1). ^{13}C NMR: $\delta = 19.8$ (s, $2CH_3$), 51.2 [q, $J = 28.5$ Hz, C^2), 79.2 (s, C^3), 99.6 (s, C^5), 123.7 (q, $J = 278.4$ Hz, CF_3), 171.9 (s, C^1), 205.2 (s, C^4). ^{19}F NMR: $\delta = -69.9$ [d, $J(F/H^2) = 8.2$ Hz]. Anal. calcd. for $C_8H_9F_3O_2$: C, 49.49; H, 4.67. Found: C, 49.71; H, 4.29.

4.2. Preparation of the lactones, **6–9**

10 mmol of the acids **4** or **5** were added to concentrated H_2SO_4 (8 ml) at −10 °C. After 1 h at room temperature, the reaction mixture was poured into ice and extracted with Et_2O. The organic layer was washed successively with saturated aqueous $NaHCO_3$ and NaCl solutions, dried over $MgSO_4$ and concentrated in vacuo to give the corresponding lactones **6**, **7**, **8** or **9**.

4.2.1. Dihydro-5-methyl-3-trifluoromethyl-2(3H)-furanone (**6**)

The lactone **6** was obtained as a mixture of two diastereomers, **6a** and **6b** [**6a/6b** (*cis*/*trans*) = 67/33] which were separated by silica gel chromatography (cyclohexane/AcOEt = 90/10). *cis* **6a** IR (neat): $\nu = 1780$ (C=O) cm^{-1}. ^{1}H NMR: $\delta = 1.49$ [d, $J(CH_3/H^5) = 6.1$ Hz, CH_3], 2.02 [ddd, $J(H^4/H^{4'}) = 12.9$ Hz, $J(H^4/H^3) = 12.2$ Hz, $J(H^4/H^5) = 9.8$ Hz, H^4], 2.68 [ddd, $J(H^{4'}/H^4) = 12.9$ Hz, $J(H^{4'}/H^3) = 9.2$ Hz, $J(H^{4'}/H^5) = 5.8$ Hz, $H^{4'}$], 3.49 [ddq, $J(H^3/H^4) = 11.9$ Hz, $J(H^3/H^{4'}) = 8.9$ Hz, $J(H^3/F) = 8.6$ Hz, H^3], 4.63 [dqd, $J(H^5/H^4) = 9.8$ Hz, $J(H^5/CH_3) = 6.1$ Hz, $J(H^5/H^{4'}) = 6.0$ Hz, H^5]. ^{13}C NMR: $\delta = 20.4$ (s, CH_3), 31.2 (s, C^4), 45.9 (q, $J = 30.5$ Hz, C^3), 75.2 (s, C^5),

123.8 (q, $J = 278.7$ Hz, CF_3), 169.2 (s, C^2). ^{19}F NMR: $\delta = -69.2$ [d, $J(F/H^3) = 8.7$ Hz]. *trans* **6b** IR (neat): $\nu = 1780$ (C=O) cm^{-1}. ^1H NMR: $\delta = 1.45$ [d, $J(CH_3/H^5) = 6.4$ Hz, CH_3], 2.20 [ddd, $J(H^{4'}/H^4) = 13.7$ Hz, $J(H^{4'}/H^3) = 10.0$ Hz, $J(H^{4'}/H^5) = 6.2$ Hz, $H^{4'}$], 2.61 [ddd, $J(H^4/H^{4'}) = 13.7$ Hz, $J(H^4/H^3) = 7.1$ Hz, $J(H^4/H^5) = 6.5$ Hz, H^4], 3.45 [quintd, $J(H^3/H^{4'}) = J(H^3/F) = 9.6$ Hz, $J(H^3/H^4) = 6.2$ Hz, H^3], 4.80 [ddq, $J(H^5/H^4) = 6.6$ Hz, $J(H^5/H^{4'}) = 6.5$ Hz, $J(H^5/CH_3) = 6.4$ Hz, H^5]. ^{13}C NMR: $\delta = 21.0$ (s, CH_3), 30.2 (s, C^4), 44.9 (q, $J = 30.5$ Hz, C^3), 75.8 (s, C^5), 124.2 (q, $J = 278.7$ Hz, CF_3), 169.3 (s, C^2). ^{19}F NMR: $\delta = -69.0$ [d, $J(F/H^3) = 9.5$ Hz] [13,17].

4.2.2. 3-Trifluoromethyl-hexahydro-benzofuran-2-one (7)

The lactone **7** was obtained as a mixture of four diastereomers, **7a–d** [**7a/7b/7c/7d** = 41/24/24/11] which were separated by silica gel chromatography (cyclohexane/AcOEt = 80/20).

Compound **7a** ^1H NMR: $\delta = 1.3$–2.0 (m, 8H), 2.74 [quint, $J(H^4/H^3) \approx J(H^4/H^5) \approx J(H^4/H^{5'}) \approx J(H^4/H^9) \approx 6.4$ Hz, H^4], 3.09 [qd, $J(H^3/F) = 9.3$ Hz, $J(H^3/H^4) = 7.1$ Hz, H^3], 4.62 [q, $J(H^9/H^4) \approx J(H^9/H^8) \approx J(H^9/H^{8'}) \approx 6.0$ Hz, H^9]. ^{13}C NMR: $\delta = 20.5, 21.2, 26.1, 28.3$ (s, C^5, C^6, C^7, C^8), 36.1 (s, C^4), 49.6 (q, $J = 28.2$ Hz, C^3), 77.7 (s, C^9), 124.2 (q, $J = 279.2$ Hz, CF_3), 169.5 (s, C^2). ^{19}F NMR: $\delta = -67.7$ [d, $J(F/H^3) = 9.3$ Hz]. Compound **7b** ^1H NMR: $\delta = 1.0$–1.9 (m, 7H), 2.21 [dm, $J(H^5/H^{5'}) = 14.3$ Hz, H^5], 2.65 [dddd, $J(H^4/H^5) = 12.0$ Hz, $J(H^4/H^3) = 6.1$ Hz, $J(H^4/H^{5'}) = 5.4$ Hz, $J(H^4/H^9) = 3.9$ Hz, H^4], 3.47 [qd, $J(H^3/F) = 9.3$ Hz, $J(H^3/H^4) = 6.1$ Hz, H^3], 4.48 [q, $J(H^9/H^4) \approx J(H^9/H^8) \approx J(H^9/H^{8'}) \approx 3.2$ Hz, H^9]. ^{13}C NMR: $\delta = 19.3$, 22.5, 22.8, 27.0 (s, C^5, C^6, C^7, C^8), 37.6 (s, C^4), 52.1 (q, $J = 29.8$ Hz, C^3), 77.5 (s, C^9), 123.5 (q, $J = 277.7$ Hz, CF_3), 169.6 (s, C^2). ^{19}F NMR: $\delta = -63.9$ [d, $J(F/H^3) = 9.3$ Hz]. Compound **7c** ^1H NMR: $\delta = 1.4$–1.9 (m, 6H), 2.0–2.3 (m, 2H), 2.63 [m, H^4], 3.10 [qdd, $J(H^3/F) = 10.3$ Hz, $J(H^3/H^4) = J(H^3/H^9) = 1.0$ Hz, H^3], 4.84 [m, H^9]. ^{13}C NMR: $\delta = 16.1$, 26.8, 27.5, 30.2, 31.1 (s, C^4, C^5, C^6, C^7, C^8), 49.8 (q, $J = 25.9$ Hz, C^3), 76.6 (s, C^9), 124.7 (q, $J = 280.8$ Hz, CF_3), 164.6 (s, C^2). ^{19}F NMR: $\delta = -66.9$ [d, $J(F/H^3) = 10.4$ Hz]. Compound **7d** ^1H NMR: $\delta = 1.5$–1.7 (m, 4H), 1.9–2.2 (m, 4H), 2.58 [m, H^4], 3.31 [qd, $J(H^3/F) = 9.4$ Hz, $J(H^3/H^4) = 5.3$ Hz, H^3], 4.79 [m, H^9]. ^{13}C NMR: $\delta = 15.7$, 26.5, 28.1, 30.9, 31.6 (s, C^4, C^5, C^6, C^7, C^8), 48.8 (q, $J = 26.7$ Hz, C^3), 76.4 (s, C^9), 124.2 (q, $J = 280.0$ Hz, CF_3), 165.5 (s, C^2). ^{19}F NMR: $\delta = -66.2$ [d, $J(F/H^3) = 9.2$ Hz]. Anal. calcd. for $C_9H_{11}F_3O_2$: C, 51.92; H, 5.32. Found: C, 51.49; H, 5.58.

4.2.3. 4,5-Dimethyl-3-trifluoromethyl-2(5H)-furanone (8)

The lactone **8** was obtained after silica gel chromatography (cyclohexane/AcOEt = 80/20). IR (neat): $\nu = 1750$–1780 (C=O), 1680 (C=C) cm^{-1}. ^1H NMR: $\delta = 1.51$ [d, $J(CH_3/H^5) = 6.6$ Hz, CH_3 (C^5)], 2.26 [q, $J(CH_3/F) = 2.0$ Hz, CH_3 (C^4)], 4.98 [qq, $J(H^5/CH_3) = 6.6$ Hz, $J(H^5/F) = 1.5$ Hz, H^5]. ^{13}C NMR: $\delta = 12.8$ [s, CH_3 (C^5)], 17.4 [s, CH_3 (C^4)], 79.9 (s, C^5), 118.0 (q, $J = 34.6$ Hz, C^3), 120.8 (q, $J = 270.6$ Hz, CF_3), 166.8 (s, C^4), 171.9 (s, C^2). ^{19}F NMR: $\delta = -63.2$ [quint, $J(F/H^5) = 2.0$ Hz, $J(F/CH_3\ (C^4)) = 2.0$ Hz]. Anal. calcd. for $C_7H_7F_3O_2$: C, 46.67; H, 3.92. Found: C, 46.62; H, 4.12.

4.2.4. 3,6-Dihydro-6,6-dimethyl-3-trifluoromethyl-2H-pyran-2-one (9a)

^1H NMR: $\delta = 1.43$ (s, CH_3), 1.45 (s, CH_3), 3.70 [qdd, $J(H^3/F) = 8.8$ Hz, $J(H^3/H^5) = 3.5$ Hz, $J(H^3/H^4) = 2.0$ Hz, H^3], 5.70 [dd, $J(H^5/H^4) = 10.2$ Hz, $J(H^5/H^3) = 3.5$ Hz, H^5], 6.10 [ddq, $J(H^4/H^5) = 10.2$ Hz, $J(H^4/H^3) = 2.0$ Hz, $J(H^4/F) = 0.7$ Hz, H^4]. ^{13}C NMR: $\delta = 28.6$ (s, CH_3), 28.8 (s, CH_3), 43.5 (q, $J = 29.0$ Hz, C^3), 84.2 (s, C^6), 114.2 (s, C^5), 123.2 (q, $J = 280.8$ Hz, CF_3), 136.2 (s, C^4), 162.1 (s, C^2). ^{19}F NMR: $\delta = -68.6$ [d, $J(F/H^3) = 8.8$ Hz].

4.2.5. 5,6-Dihydro-6,6-dimethyl-3-trifluoromethyl-2H-pyran-2-one (9b)

The lactone **9b** was purified by silica gel chromatography (cyclohexane/AcOEt = 80/20). IR (neat): $\nu = 1725$ (C=O), 1655 (C=C) cm^{-1}. ^1H NMR: $\delta = 1.44$ (s, $2CH_3$), 2.60 [dq, $J(H^5/H^4) = 4.6$ Hz, $J(H^5/F) = 2.3$ Hz, $2H^5$], 7.33 [tq, $J(H^4/H^5) = 4.4$ Hz, $J(H^4/F) = 1.4$ Hz, H^4]. ^{13}C NMR: $\delta = 27.4$ (s, $2CH_3$), 35.1 (s, C^5), 80.8 (s, C^6), 121.0 (q, $J = 271.6$ Hz, CF_3), 123.1 (q, $J = 32.0$ Hz, C^3), 146.2 (q, $J = 5.3$ Hz, C^4), 158.7 (s, C^2). ^{19}F NMR: $\delta = -66.9$ [td, $J(F/H^5) = 2.3$ Hz, $J(F/H^4) = 1.4$ Hz]. Anal. calcd. for $C_8H_9F_3O_2$: C, 49.49; H, 4.67. Found: C, 49.73; H, 4.95.

4.3. Preparation of the lactones, 10–13

A mixture of **4a**, **5b** or **5d** (5 mmol) and 3.8 g (15 mmol) of solid iodine in 15 ml of acetonitrile was stirred under argon in the dark at room temperature for 24 h (**4a**), 5 days (**5b**) or 6 days (**5d**). After addition of Et_2O, the reaction mixture was washed successively with saturated aqueous $Na_2S_2O_3$, $NaHCO_3$ and NaCl solutions. It was dried over $MgSO_4$, concentrated in vacuo and the products **10**, **11**, **12** or **13** were, respectively, obtained.

4.3.1. Dihydro-5-iodomethyl-3-trifluoromethyl-2(3H)-furanone (10)

The lactone **10** was obtained as a mixture of two diastereomers, **10a** and **10b** [**10a/10b** (*cis/trans*) = 70/30] which were separated by silica gel chromatography (cyclohexane/AcOEt = 90/10).

The lactone **10a** IR (neat): $\nu = 1785$ (C=O) cm^{-1}. ^1H NMR: $\delta = 2.13$ [ddd, $J(H^4/H^{4'}) = 13.2$ Hz, $J(H^4/H^3) = 11.7$ Hz, $J(H^4/H^5) = 9.5$ Hz, H^4], 2.80 [ddd, $J(H^{4'}/H^4) = 13.3$ Hz, $J(H^{4'}/H^3) = 9.5$ Hz, $J(H^{4'}/H^5) = 6.1$ Hz, $H^{4'}$], 3.30 [dd, $J(CHI/CHI) = 10.6$ Hz, $J(CHI/H^5) = 7.4$ Hz, CHI], 3.45 [dd, $J(CHI/CHI) = 10.5$ Hz, $J(CHI/H^5) = 4.6$ Hz, CHI], 3.54 [ddq, $J(H^3/H^4) = 11.7$ Hz, $J(H^3/H^{4'}) = 9.5$ Hz, $J(H^3/F) = 8.6$ Hz, H^3], 4.51 [dddd, $J(H^5/H^4) = 9.5$ Hz, $J(H^5/CHI) = 7.4$ Hz, $J(H^5/H^{4'}) =$

6.1 Hz, $J(H^5/CHI) = 4.6$ Hz, H^5]. ^{13}C NMR: $\delta = 5.1$ (s, CH_2I), 30.1 (s, C^4), 45.9 (q, $J = 30.5$ Hz, C^3), 76.5 (s, C^5), 123.6 (q, $J = 277.7$ Hz, CF_3), 168.1 (s, C^2). ^{19}F NMR: $\delta = -69.4$ [d, $J(F/H^3) = 8.5$ Hz]. Compound **10b** IR (neat): $\nu = 1785$ (C=O) cm^{-1}. ^1H NMR: $\delta = 2.35$ [ddd, $J(H^{4'}/H^4) = 14.3$ Hz, $J(H^{4'}/H^3) = 10.6$ Hz, $J(H^{4'}/H^5) = 5.9$ Hz, $H^{4'}$], 2.64 [ddd, $J(H^4/H^{4'}) = 14.3$ Hz, $J(H^4/H^5) = 7.9$ Hz, $J(H^4/H^3) = 6.4$ Hz, H^4], 3.35 [dd, $J(CHI/CHI) = 10.8$ Hz, $J(CHI/H^5) = 6.1$ Hz, CHI], 3.42 [dd, $J(CHI/CHI) = 10.8$ Hz, $J(CHI/H^5) = 4.2$ Hz, CHI], 3.55 [dqd, $J(H^3/H^{4'}) = 10.6$ Hz, $J(H^3/F) = 9.3$ Hz, $J(H^3/H^4) = 6.4$ Hz, H^2], 4.65 [dddd, $J(H^5/H^4) = 7.9$ Hz, $J(H^5/CHI) = 6.1$ Hz, $J(H^5/H^{4'}) = 5.9$ Hz, $J(H^5/CHI) = 4.2$ Hz, H^5]. ^{13}C NMR: $\delta = 7.4$ (s, CH_2I), 29.0 (s, C^4), 45.1 (q, $J = 30.5$ Hz, C^3), 76.7 (s, C^5), 123.9 (q, $J = 279.2$ Hz, CF_3), 168.5 (s, C^2). ^{19}F NMR: $\delta = -69.6$ [d, $J(F/H^3) = 9.3$ Hz].

4.3.2. 3,6-Dihydro-5-iodo-4-methyl-3-trifluoromethyl-2H-pyran-2-one (**11a**)

^1H NMR: $\delta = 2.10$ (s, CH_3), 3.94 [q, $J(H^3/F) = 8.8$ Hz, H^3], 5.0 [2d, $J(H^6/H^{6'}) \approx 15$ Hz, H^6 and H^6]. ^{13}C NMR: $\delta = 26.4$ (s, CH_3), 52.2 (q, $J = 28.6$ Hz, C^3), 77.7 (s, C^6), 93.7 (s, C^5), 123.3 (q, $J = 283.8$ Hz, CF_3), 130.8 (s, C^4), 161.6 (s, C^2). ^{19}F NMR: $\delta = -66.6$ [dq, $J(F/H^3) = 8.8$ Hz, $J(F/CH_3) = 0.8$ Hz].

4.3.3. 4-Methyl-5-methylene-3-trifluoromethyl-2(5H)-furanone (**12b**)

^1H NMR: $\delta = 2.36$ (q, $J(CH_3/F) = 1.9$ Hz, CH_3), 5.28 (d, $J(H^6/H^{6'}) = 3.3$ Hz, H^6), 5.46 (d, $J(H^{6'}/H^6) = 3.3$ Hz, $H^{6'}$). ^{19}F NMR: $\delta = -62.0$ [q, $J(F/CH_3) = 1.9$ Hz].

4.3.4. 3,6-Dihydro-5-iodo-6,6-dimethyl-3-trifluoromethyl-2H-pyran-2-one (**13a**)

^1H NMR: $\delta = 1.62$ (s, CH_3), 1.65 (s, CH_3), 3.74 [qd, $J(H^3/F) = 8.6$ Hz, $J(H^3/H^4) = 3.9$ Hz, H^3], 6.37 [d, $J(H^4/H^3) = 3.9$ Hz, H^4]. ^{19}F NMR: $\delta = -68.2$ [d, $J(F/H^3) = 8.6$ Hz].

4.3.5. 5,6-Dihydro-5-iodo-6,6-dimethyl-3-trifluoromethyl-2H-pyran-2-one (**13b**)

^1H NMR: $\delta = 1.63$ (s, CH_3), 1.68 (s, CH_3), 4.93 [dq, $J(H^5/H^4) = 6.1$ Hz, $J(H^5/F) = 1.4$ Hz, H^5], 7.48 [dq, $J(H^4/H^5) = 6.1$ Hz, $J(H^4/F) = 1.2$ Hz, H^4].

4.4. Reduction of **10** with tri-n-butyltin hydride

To a mixture of *cis*- and *trans*-lactone **10** (5 mmol, *cis*/*trans* = 70/30) in anhydrous Et_2O (15 ml) was added Bu_3SnH (8 mmol) at 20 °C. This solution was stirred for 30 h at room temperature. Usual work-up followed by a purification gave the lactone **6**, as a colorless liquid (*cis*/*trans* = 70/30 by comparison with an authentic sample) [34].

Acknowledgements

This work was supported by INRA and CNRS.

References

[1] G.D. Prestwich, Pestic. Sci. 37 (1986) 430–440.
[2] G.D. Prestwich, W.C. Sun, M.S. Mayer, J.C. Dickens, J. Chem. Ecol. 16 (1990) 1761–1778.
[3] R.E. Banks (Ed.), Organofluorine Chemicals and their Industrial Applications, Ellis Horwood, Chichester, 1979.
[4] R. Filler, Y. Kobayashi (Eds.), Biomedicinal Aspects of Fluorine Chemistry, Kodansha, Tokyo, 1982.
[5] J.T. Welch, Tetrahedron 43 (1987) 3123–3197.
[6] R. Noyori, Y. Morisawa, T. Maeda, A. Yasuda, K. Uchida, Jpn. Kokai Tokyo Koho JP02256, 462 [9056, 462]; Chem. Abs. 113 (1990) 59620g.
[7] H. Urata, T. Fuchikami, Tetrahedron Lett. 32 (1991) 91–94.
[8] M. Zupan, Z. Bregar, Tetrahedron Lett. 31 (1990) 3357–3358.
[9] D.J. Burton, Z.Y. Yang, Tetrahedron 48 (1992) 189–275.
[10] M.A. Mc Clinton, D.A. Mc Clinton, Tetrahedron 48 (1992) 6555–6666.
[11] D.J. Burton, Z.Y. Yang, P.A. Morken, Tetrahedron 50 (1994) 2993–3063.
[12] S. Watanabe, Y. Shimada, T. Kitazume, T. Yamazaki, J. Fluorine Chem. 59 (2) (1992) 249–256.
[13] S. Watanabe, Y. Sakai, M. Takeda, T. Kitazume, T. Yamazaki, J. Fluorine Chem. 67 (2) (1994) 149–152.
[14] C.G. Krespan, Tetrahedron 23 (1967) 4243–4249.
[15] L.I. Zakharkin, V.N. Lebedev, Zh. Obshei. Khim. 41 (1971) 817–823.
[16] T. Yokozawa, T. Nakai, N. Ishikawa, Tetrahedron Lett. 25 (1984) 3991–3994.
[17] V.G. Andreev, A.F. Kolomiets, A.V. Fokin, Izv. Akad. Nauk. SSSR Ser. Khim. 12 (1991) 2805–2810.
[18] V.G. Andreev, Izv. Akad. Nauk. SSSR Ser. Khim. 7 (1994) 1273–1277.
[19] K.I. Ogu, M. Akazome, K. Ogura, Tetrahedron Lett. 39 (1998) 305–308.
[20] J.A. Cooper, C.M. Olivares, G. Sandford, J. Org. Chem. 66 (2001) 4887–4891.
[21] J.F. Normant, O. Reboul, R. Sauvêtre, H. Deshayes, D. Masure, J. Villieras, Bull. Soc. Chim. Fr. (1974) 2072–2078.
[22] F. Tellier, M. Audouin, M. Baudry, R. Sauvêtre, Tetrahedron Lett. 39 (1998) 5041–5044.
[23] F. Tellier, M. Audouin, M. Baudry, R. Sauvêtre, J. Fluorine Chem. 94 (1999) 27–36.
[24] F. Tellier, M. Audouin, M. Baudry, R. Sauvêtre, Eur. J. Org. Chem. (2000) 1933–1937.
[25] R.D. Chambers, Fluorine in Organic Chemistry, Wiley, New York, 1973, p. 104.
[26] M. Stacey, J.C. Tatlow, A.G. Sharpe (Eds.), Advances in Fluorine Chemistry, Vol. 4, Butterworths, London, 1965, p. 52.
[27] P.A. Morken, H. Lu, A. Nakamura, D.J. Burton, Tetrahedron Lett. 32 (1991) 4271–4274.
[28] J. Grimaldi, C. R. Acad. Sci. Ser. C 286 (1978) 593–594.
[29] P.A. Bartlett, in: J.D. Morrison (Ed.), Asymetric Synthesis, Vol. 3, Academic Press, New York, 1984, pp. 411–454.
[30] G. Cardillo, M. Orena, Tetrahedron 46 (1990) 3321–3408.
[31] Y.S. Rao, Chem. Rev. 64 (1964) 353–388.
[32] T. Itoh, K. Sakabe, K. Kudo, P. Zagatti, M. Renou, Tetrahedron Lett. 39 (1998) 4071–4074.
[33] T. Kitazume, M. Takeda, J. Chem. Soc. Chem. Commun. (1995) 39–40.
[34] Y. Tamaru, M. Mizutani, Y. Furukawa, S.I. Kawamura, Z.I. Yoshida, K. Yanagi, M. Minobe, J. Am. Chem. Soc. 106 (1984) 1079–1085.