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Synthesis of Trifluoromethyl Ketones as Inhibitors of Antennal Esterases of Insects

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Abstract—A variety of long chain aliphatic and aromatic trifluoromethyl ketones **I–XIV** has been conveniently prepared, many of them for the first time, from the corresponding Grignard or organolithium derivatives. Two of them, (*Z*)-1,1,1-trifluoro-15-octadecen-13-yn-2-one (**XV**) and (*Z*)-1,1,1-trifluoro-16-nonadecen-14-yn-2-one (**XVI**), structurally-closed analogues of (*Z*)-13-hexadecen-11-ynyl acetate, the sex pheromone of the processionary moth *Thaumetopoea pityocampa*, have been stereospecifically synthesized in excellent yield by a convenient new method. The procedure involves lithiation ot the corresponding iododerivative **XXIX** and **XXX** with *one* equivalent of *tert*-BuLi to obviate addition of the reagent to the enyne system. Some of the compounds have already been tested and found to be good inhibitors of antennal esterases in the Egyptian armyworm *Spodoptera littoralis* and the pheromone action in the processionary moth *Thaumetopoea pityocampa*. β-Thiotrifluoromethyl ketones **XVII–XX**, which are expected to enhance the inhibition activity of the parent ketones due to their higher hydration constants, have also been prepared in good yields.

Introduction

In recent years much attention has been paid to the utilization of trifluoromethyl ketones (TFMKs) as enzyme inhibitors as well as synthons for the preparation of more complex biologically-active fluorinated molecules.[1–3] Their particular features arise from the unique physical and biological properties induced by fluorine, which closely mimics the steric requirement of hydrogen at the enzyme receptor sites. The strong electron-withdrawing effect of the atom causes TFMKs to form stable hydrates or hemiketals in aqueous solutions,[4] whose tetrahedral geometry resembles the transition state of the water addition process to the carbonyl group of a peptide substrate. Consequently, TFMKs are potent inhibitors of a variety of serine esterases, like acetylcholinesterase,[5,6] juvenile hormone esterase[2] or mammalian carboxyl esterases,[7] and have also been tested as inhibitors of antennal esterases in insects.[8–10] In this regard, inhibition of the pheromone degrading enzymes by synthetic chemicals might interfere with the pheromone perception process, which may open new approaches to pest control.[11,12]

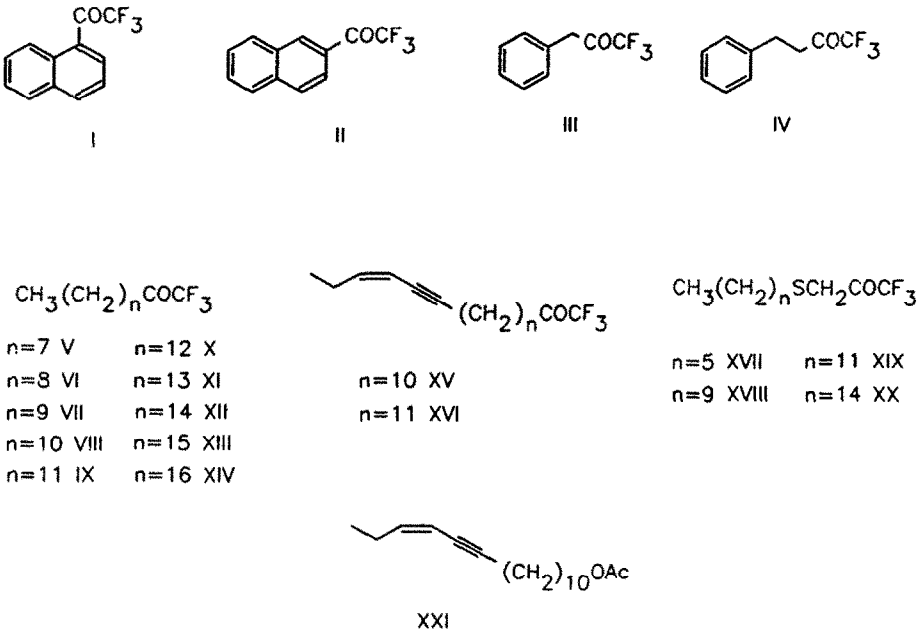
Continuing our efforts in the development of inhibitors of the pheromone perception of the pine processionary moth *Thaumetopoea pityocampa*,[13–15] we now want to report on the synthesis of several long chain aliphatic and aromatic TFMKs **I–XX** (Scheme I), two of them (**XV**, **XVI**) being structurally related to (*Z*)-13-hexadecen-11-ynyl acetate (**XXI**), the only pheromonal component found so far in the sex pheromone gland.[16] In both cases the enyne function and stereochemistry, two key features for attractant activity, have been preserved whereas the acetate group has been replaced by the isosteric trifluoropanone moiety, thus mimicking the putative enzyme-bound intermediate in the pheromone catabolic process. Many of the ketones have been synthesized and fully characterized for the first time, and when required a stereospecific approach has been carried out. Among the TFMKs we have included the β-thiosubstituted ketones **XVII–XX**, since introduction of a sulfur atom in β position to the carbonyl group greatly enhanced the activity of the resulting ketones,[17] probably due to the higher hydration constants in comparison with the parent compounds.[18]

Results and Discussion

Preparation of TFMKs has been generally based on the reaction of an organometallic reagent with a fluorinated carbonyl compound.[1] The reverse process, i.e. reaction of a fluorinated organometallic reagent with a carbonyl compound is of limited value due to the instability and/or lower nucleophilic character of the fluorinated organometallic synthon. The first approach may also be restrained by the concomitant formation of undesired secondary and tertiary alcohols, depending on the factors which govern the stability of the initial adduct between the organometallic reagent and the fluorinated carbonyl derivative, like mode of action, temperature, electronic features of the fluorinating agent, etc.

For the aromatic ketones **II–IV** we found that addition of the fluorinating agent to the Grignard or alkyllithium derivative in ether at low temperature is operationally easier to carry out, without affecting the yield, than the method involving the reverse addition of the reagents.[19] It should be added that in our case activation of magnesium was carried out by ultrasonic irradiation. We have noticed that this is particularly useful for the preparation of Grignard reagents of long chain halides ($n \geq 12$ carbons), whose formation would be sluggish otherwise. Alternatively, ketone **IV** was also prepared by alkylation of ethyl 3-(ethylendioxy)trifluoroacetoacetate (**XXII**)[20] but in lower overall yield (see below).

For the aliphatic ketones **V–XII** reaction of the Grignard derivatives of the corresponding bromides was assayed with



Scheme I. List of compounds prepared.

several fluoroacylating agents, such as methyl trifluoroacetate, ethyl trifluoroacetate and *N*-methoxy-*N*-methyltrifluoroacetamide.[21] The yields of the expected TFMKs were moderate (34–47 %), the major by-products being the self-condensation compounds (Wurtz reaction) (30–40 %) and the secondary trifluoromethyl carbinols (5–10 %). The yields were not improved when in some particular cases bromides were replaced by the corresponding iodides, the Wurtz condensation products being formed exclusively. In any case, compound **XIII** was more conveniently obtained by reaction of 1-iodohexadecane with *tert*-BuLi in a 1:2 molar ratio[22] followed by addition of ethyl trifluoroacetate in 85 % isolated yield. The results of this procedure are therefore markedly superior to the more classical method involving Grignard derivatives. However, as cited below, the method was not suitable for other functionalized structures like TFMKs **XV** and **XVI**.

Compound **XIV** was conveniently prepared through a 3-step sequence starting from the ethylene acetal of ethyl trifluoroacetoacetate (**XXII**). Protection of the carbonyl function of the β-keto ester was required, since direct alkylation of the unprotected ester enolate with unreactive halides leads to mixtures of O- and C-alkylation products. Alkylation of **XXII** with 1-iodohexadecane in the presence of lithium diisopropylamide in THF:HMPA afforded **XXIV** in 90 % yield. Deprotection of the stable dioxolane **XXIV** required a strong Lewis acid catalyst, like boron tribromide, to yield **XXVI** as a mixture of the keto, enol and hydrate forms. Decarboethoxylation of the keto ester under neutral conditions led to ketone **XIV** in 65 % overall yield from **XXII**. In a similar manner, compound **IV** was also obtained but in lower overall yield (41.4 %) (Figure 1).

Synthesis of long chain TFMKs as fluorinated analogues of insect pheromones have scarcely been reported. Only Prestwich and Streinz[8] and Klun *et al.*[10] have described the preparation of (*Z*)-1,1,1-trifluoro-14-nonadecen-2-one and (*Z*)-1,1,1-trifluoro-14-heptadecen-2-one as pheromone analogues of the diamondback moth *Plutella xylostella* and the European corn borer *Ostrinia nubilalis*, respectively, through the Grignard derivatives of the corresponding bromides with *N*-methoxy-*N*-methyltrifluoroacetamide in very modest (28 %) or unreported yields . In our case and for the synthesis of (*Z*)-1,1,1-trifluoro-16-nonadecen-14-yn-2-one (**XVI**), formation of the organomagnesium reagent from (*Z*)-13-hexadecen-11-ynyl bromide was very sluggish, even under ultrasonic irradiation. Again, utilization of iodide **XXIX**, prepared from alcohol **XXVII** in one step by *in situ* formation of the corresponding trifluoroacetate[14] (Figure 2), led only to the Wurtz condensation product. Therefore, a more convenient procedure for the preparation of functionalized long chain TFMKs was needed. We initially tested the synthesis of ketone **XVI** following the same approach (Figure 3) as for compound **XIV**. However, in this case the intermediate ester **XXXI**, which was readily prepared by alkylation of **XXII** with iodide **XXIX**, did not unequivocally deprotect to give **XXXIV** as expected, but concomitantly suffered addition of the Lewis acid catalyst to the enyne function. As an alternative route, alkylation of the *N*,*N*-dimethylhydrazone of ethyl trifluoroacetoacetate (**XXXII**) with **XXIX** led to the dimethylhydrazono derivative **XXXIII** in 80 % yield. Hydrolysis to the corresponding keto ester **XXXIV** was accomplished by treatment with allyl bromide in refluxing ethanol in 80 % yield. However, decarboethoxylation of **XXXIV**, under non-acidic conditions (NaOH/EtOH) to avoid addition to the enyne group, led to the oxidative loss of the $COCF_3$ moiety yielding, unexpectedly, the corresponding carboxylic acid **XXXV**, which was fully characterized by its spectroscopic properties and exact mass measurement. This result may be envisioned by the attack of the base to the highly electrophilic carbonyl of the trifluoroacyl group, followed by loss of trifluoroacetate.

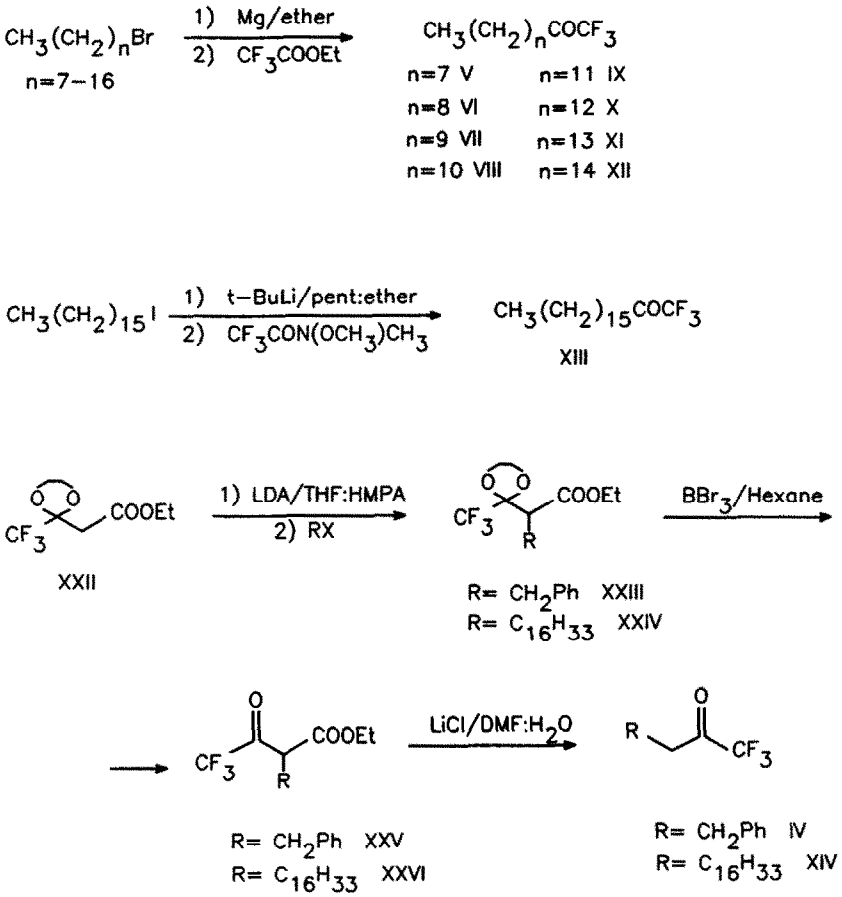


Figure 1. Synthesis of TFMKS **V-XIV**.

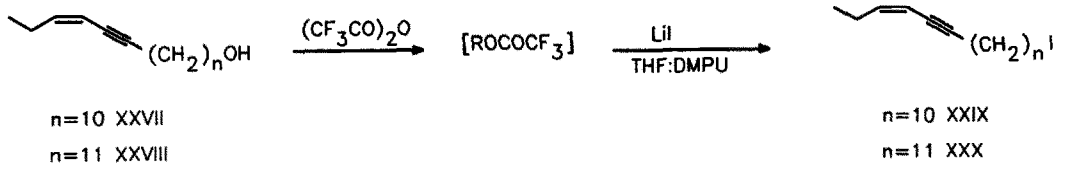


Figure 2. Synthesis of iodides **XXIX** and **XXX**.

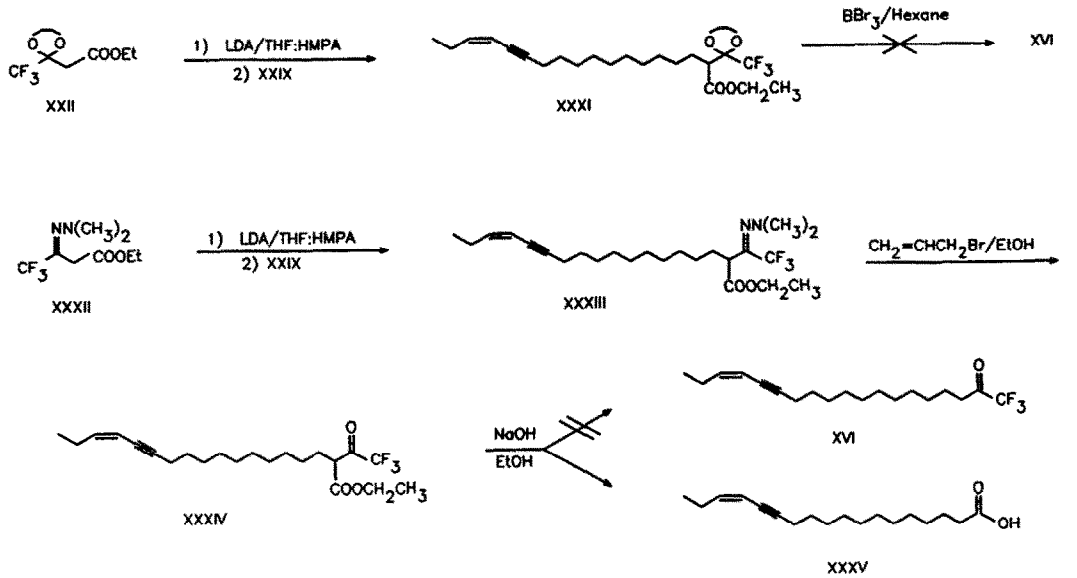


Figure 3. Approaches to the synthesis of ketone **XVI**.

The process may concomitantly occur with saponification of the ester. This assumption may be reinforced taking into account that normal decarboethoxylation process takes place when the parent non-fluorinated analogue affords the expected methyl ketone in good yield, under similar experimental conditions.[23] Therefore, we turned our attention to the direct trifluoroacylation of iodide **XXIX**, through the corresponding lithium salt, as for compound **XIII**. However, reaction of **XXIX** with *tert*-BuLi in a 1:2 molar ratio followed by posterior addition of *N*-methoxy-*N*-methyltrifluoroacetamide afforded an inseparable mixture of two TFMKs, among other minor compounds. One of them was immediately characterized as the expected **XV**, while the other was identified as allene **XXXVI** (n = 10) in base to its spectroscopic features (IR absorptions at ν 1938 and 1764 cm^{-1}; ^1H NMR at δ 5.54 and 5.48 for the allenic protons; ^{13}C NMR at δ 213.6, 98.2 and 97.2 for the central and terminal carbons of the allene). The allene results from the 1,4-addition reaction of *tert*-BuLi to the enyne group, a process which has been reported by other authors to occur both with organolithium[24] and organomagnesium derivatives.[25] To obviate formation of the allene we found that by reducing the molar amount of *tert*-BuLi with regard to the substrate to 1:1 ratio, TFMK **XV** was obtained stereospecifically as a sole product in an excellent 92 % isolated yield. The same procedure was applied for preparation of ketone **XVI**, which was obtained in 81% yield from iodide **XXX** (Figure 4). Our procedure raises the question of why two equivalents of *tert*-BuLi are required for a successful lithium–iodine exchange reaction, as previously described.[22] Under our conditions, metallation appears to be complete avoiding an unnecessary excess of the organolithium derivative, which may be detrimental if other electrophilic moieties are present in the molecule. It should be noted that our method greatly improves the synthesis of functionalized long chain TFMKs, especially in comparison with the procedures involving organomagnesium intermediates.

Synthesis of β-thiotrifluoromethyl ketones **XVII–XX** was accomplished by alkylation of the corresponding thiol with 3-bromo-1,1,1-trifluoropropan-2-one in CH_2Cl_2 using Na_2CO_3 as base (Figure 5). The required ketones were obtained in very good yields as mixtures of the keto and hydrate forms and the hydrates could be transformed into the corresponding ketones by distillation.

Some of the TFMKs reported herein (compounds **I–IV**, **VII**, **IX–XI**, **XIII** and **XIV**) have been tested *in vitro* as inhibitors of crude homogenates of antennal esterases in the Egyptian armyworm *Spodoptera littoralis*, by evaluation of the extent of hydrolysis of the major component of the sex pheromone (*Z,E*)-9,11-tetradecadienyl acetate, labeled with tritium at C-1.[26] The most active compounds, 1,1,1-trifluorotetradecan-2-one (**IX**) (IC_{50} 1.16 μM) and 1,1,1-trifluoropentadecan-2-one (**X**) (IC_{50} 4.4 μM), were found to be tight slow-binding inhibitors, whereas 2-naphthyl trifluoromethyl ketone (**II**) (IC_{50} 7.9 μM) binds to the active site of the enzyme in a time-independent manner. On the other hand in *in vivo* bioassays, compounds **I, II** and **IX** displayed a notable blockage of the pheromone detection by the processionary moth *Thaumetopoea pityocampa* males after pre-exposure to vapors of the chemicals.[27] The activity of **IX** is postulated to be due to the inhibition of the pheromone-degrading esterase. In the field only TFMKs **XV** and **XVI**, two closedly-related structures to the natural pheromone, showed a remarkable disruptant effect of the pheromone action when mixed with the natural attractant in 0.1:1, 1:1 and 10:1 ratios.

In summary, a variety of long chain aliphatic and aromatic TFMKs has been synthesized and fully characterized, many of them for the first time, in a convenient way. A new method for the synthesis of long chain enyne-containing TFMKs, through the corresponding organolithium derivative, has also been developed. The procedure notably improves the previously reported method through the Grignard intermediate.

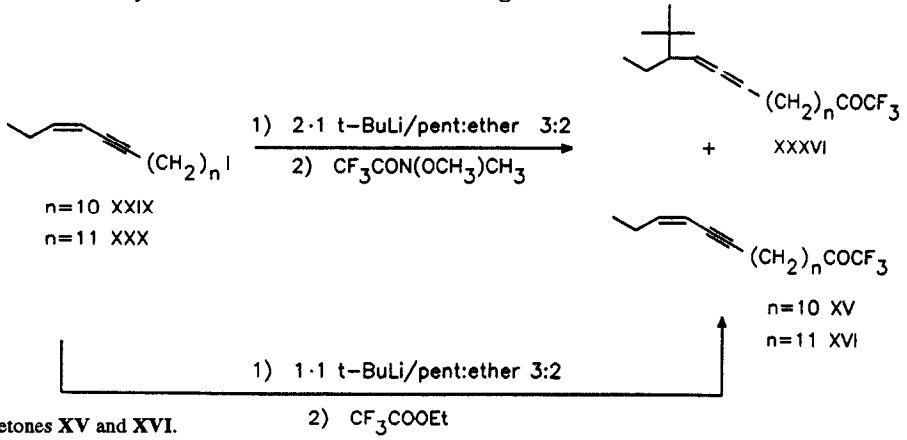


Figure 4. Synthesis of ketones **XV** and **XVI**.

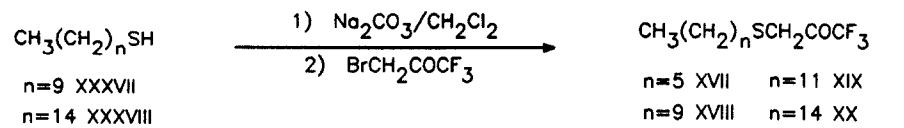


Figure 5. Synthesis of b-thiotrifluoromethyl ketones **XVII-XX**.

Experimental

Boiling points are uncorrected. Elemental analyses were determined on Carlo Erba models 1106 and 1500. IR spectra were recorded on a Perkin Elmer 399B spectrometer or a Bomem MB-120 with Fourier transform instrument. [^{1}H] and [^{13}C]NMR spectra were determined in $CDCl_3$ solutions on a Varian Gemini 200 or Varian Unity 300 spectrometer, operating at 200 and 300 MHz for [^{1}H], respectively, and at 50 and 75 MHz for [^{13}C]. The values are expressed in δ scale relative to TMS. [^{19}F]NMR spectra were recorded on the Varian Unity 300 instrument at 282 MHz and the values are reported in δ scale relative to trifluoroacetic acid. Low resolution mass spectra were run on a HP 5995 mass spectrometer using a SPB-5 30 m x 0.32 μm ID fused silica capillary column. GLC analyses were performed on Carlo Erba models 2350 and 4130, equipped with a FID detector, using a 3 % OV-101 2 m x 3 mm ID glass column on Chromosorb W and nitrogen as carrier gas, or a SE-54 50 m x 0.32 μm ID fused silica capillary column and hydrogen as carrier gas. Exact mass measurements were carried out on a Fisons VG AutospecQ mass spectrometer working at 70 eV ionization energy. Reactions requiring anhydrous conditions were carried out under N_2 or Ar atmosphere. Commercial analytical-grade reagents were from Aldrich Chemie (Steinheim, Germany) and Fluka Chemie AG (Buchs, Switzerland) and were used directly without further purification. Anhydrous solvents were prepared as follows: tetrahydrofuran (THF) and diethyl ether were previously dried with KOH and then distilled from Na/benzophenone under N_2, pentane, hexane and CH_2Cl_2 by distillation from P_2O_5, diisopropylamine from NaOH and benzene and hexamethylphosphoramide (HMPA) from calcium hydride.

1-Naphthyl trifluoromethyl ketone (I)

This compound was prepared as previously described[19] in 51% yield after distillation. bp 147–148 °C/30 mm Hg. IR ν: 3010, 1708, 1510, 1200, 1146, 1067, 919 cm^{-1}. ^{1}H NMR δ: 8.85 (m, 1H, arom. *H*), 8.29 (m, 2H, arom. *H*), 7.95 (m, 1H, arom. *H*), 7.65 (m, 3H, arom. *H*). ^{13}C NMR δ: 182.3 (q, J = 34 Hz, $COCF_3$), 136.2, 133.9, 131.8 (q, J = 3.8 Hz, $CCOCF_3$). 131.2, 129.5, 129.0, 127.2, 126.3, 125.2, 124.2 116.7 (q, J = 292 Hz, $COCF_3$). ^{19}F NMR δ: 5.6 (s). MS m/z (%): 224 (M^+, 29), 155 (M^+-69, 92), 127 (100).

2-Naphthyl trifluoromethyl ketone (II)

Preparation of this compound has been surprisingly unreported in the literature. To a solution of 1.0 g (4.8 mmol) of 2-bromonaphthalene in 5 mL of anh. THF was added dropwise, under Ar and at –78 °C, 2.1 mL (1.1 equiv.) of 2.5 M *n*-BuLi in hexane. The mixture was stirred at this temperature for 2 h and at –30 °C tor 30 min and cooled again at –78 °C. Then a solution of 0.75 g (5.3 mmol) of ethyl trifluoroacetate in 8 mL of anh. THF was added, the mixture allowed to warm to room temperature and stirred for 16 h. The reaction was quenched with NH_4Cl sat. solution and repeatedly extracted with ether. After washing with brine and drying, the solvent was evaporated off to furnish 0.592 g (55 %) of ketone **II**, after purification on neutral alumina (**III**) eluting with hexane:ethyl acetate 92:8. IR ν: 3040, 1720, 1170, 1160, 925 cm^{-1}. ^{1}H NMR δ: 8.63 (s, 1H, arom. *H*), 8.1–7.9 (c, 4H, arom. *H*), 7.73–7.6 (c, 2H, arom. *H*). ^{13}C NMR δ: 180.5 (q, J = 35 Hz, $COCF_3$), 136.5, 133.2 (q, J = 2.6 Hz, $CCOCF_3$), 132.2, 130.2, 130.1, 129.1, 127.9, 127.4, 127.2, 124.2, 116.9 (q, J = 292 Hz, $COCF_3$). ^{19}F NMR δ: 5.02 (s). MS m/z (%): 224 (M^+, 40), 155 (M^+-69, 89), 127 (100). Elemental Analysis: Calcd for $C_{12}H_7OF_3$: C, 64.29; H, 3.15; Found: C, 64.35; H, 3.15.

3-Phenyl-1,1,1-trifluoropropan-2-one (III)

This compound was obtained from benzyl chloride in 70 % yield after vacuum distillation, as previously reported.[19] bp 73–74 °C/20 mm Hg. IR ν: 1768, 1278, 1213, 1145, 1018, 709 cm^{-1}. ^{1}H NMR δ: 7.4–7.22 (c, 5H, C_6H_5), 4.02 (s, 2H, CH_2). ^{13}C NMR δ: 188.8 (q, J = 35 Hz, $COCF_3$), 129.6, 128.9, 127.9, 115.8 (q, J = 292.6 Hz, CF_3), 42.9 (CH_2). ^{19}F NMR δ: –2.09 (s). MS m/z (%): 188 (M^+, 91), 119 (M^+-69, 6), 91 (100).

4-Phenyl-1,1,1-trifluorobutan-2-one (IV)

This compound was prepared as for compound **II**, except that the magnesium derivative of 2-phenylethyl chloride was used instead of the corresponding organolithium compound. The ketone **IV** was obtained in 68 % yield after vacuum distillation. bp 79–81°C/10 Torr. IR ν: 1762, 1209, 1170, 1139, 698 cm^{-1}. ^{1}H NMR δ: 7.17 (m, 5H, C_6H_5), 3.03 (m, 4H, CH_2CH_2). ^{13}C NMR δ: 190.7 (q, J = 35.4 Hz, $COCF_3$), 139.2, 128.7, 128.2, 126.7, 115.5 (q, J = 292 Hz, CF_3), 38.1 (CH_2CO), 28.4 ($PhCH_2$). ^{19}F NMR δ: –3.3 (s). MS m/z (%): 202 (M^+, 36), 133 (M^+-69, 45), 105 (38), 91 (100), 77 (17). The compound was alternatively prepared by alkylation of ethyl 3-(ethylendioxy)trifluoroacetoacetate (**XXII**) (see below).

Synthesis of alkyltrifluoromethyl ketones V–XII. General procedure

To an ice-cold solution (0 °C) of the required Grignard reagent (1 equiv.), prepared from the corresponding alkyl bromide (1 equiv.), magnesium turnings (2 equiv.) and a catalytic amount of 1,2-dibromoethane under ultrasonic irradiation tor 30–45 min, was added ethyl trifluoroacetate (2 equiv.), freshly distilled from $NaHCO_3$, in anh. THF under Ar. The mixture was brought to room temperature and stirred for 1–2 h. The reaction was quenched by addition of 5 % HCl solution, extracted with ether and the combined organic phases washed with brine and dried. The solvent was removed under vacuum and the crude purified by column chromatography on silica gel, eluting with hexane:ether 95:5, to afford the expected ketones **V–XII**, in 39, 43, 40, 36, 34, 47, 42 and 39 % yield, respectively. As major by-products the corresponding hydrocarbons (30–40 %) as well as the secondary alcohols (5–10 %) were also obtained.

1,1,1-Trifluorodecan-2-one (V). IR ν: 2956, 2927, 2858, 1764, 1209, 1149 cm^{-1}. ^{1}H NMR δ: 2.7 (t, J = 7.5 Hz,

2H, CH_2COCF_3), 1.66 (m, 2H, $CH_2CH_2COCF_3$), 1.35–1.22 (b, 10H, $5CH_2$), 0.87 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR δ: 191.6 (q, J = 35 Hz, $COCF_3$), 115.6 (q, J = 292 Hz, CF_3), 36.3, 31.8, 29.2, 29.1, 28.8, 22.6, 22.4, 14 (CH_3). ^{19}F NMR δ: –3.7 (s). MS m/z (%): 141 (M^+-69, 100), 71 (42), 70 (40), 69 (49), 57 (63), 56 (49), 55 (53), 43 (66).

1,1,1-Trifluoroundecan-2-one (VI). IR ν: 2924, 2855, 1764, 1207, 1148 cm^{-1}. ^1H NMR δ: 2.7 (t, J = 7.2 Hz, 2H, CH_2COCF_3), 1.66 (m, 2H, $CH_2CH_2COCF_3$), 1.32–1.2 (b, 12H, $6CH_2$), 0.87 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR δ: 191.6 (q, J = 35 Hz, $COCF_3$), 115.6 (q, J = 292 Hz, CF_3), 36.3, 31.9, 29.3–28.7, 22.7, 22.4, 14 (CH_3). ^{19}F NMR δ: –3.7 (s). MS m/z (%): 155 (M^+-69, 100), 139 (28), 85 (26), 84 (31), 83 (42), 71 (47), 70 (58), 69 (48), 55 (53), 43 (87).

1,1,1-Trifluorododecan-2-one (VII). IR ν: 2925, 2856, 1764, 1207, 1147 cm^{-1}. ^1H NMR δ: 2.7 (t, J = 7.2 Hz, 2H, CH_2COCF_3), 1.66 (m, 2H, $CH_2CH_2COCF_3$), 1.35–1.23 (b, 14H, $7CH_2$), 0.87 (t, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR δ: 191.5 (q, J = 35 Hz, $COCF_3$), 115.6 (q, J = 292 Hz, CF_3), 36.3, 31.9, 29.5–29.2, 28.8. 22.7, 22.4, 14 (CH_3). ^{19}F NMR δ: –3.7 (s). MS m/z (%): 169 (M^+-69, 90), 153 (23), 139 (36), 97 (47), 84 (48), 69 (61), 57 (69), 43 (100).

1,1, 1-Trifluorotridecan-2-one (VIII). IR ν: 2925, 2856, 1764, 1207, 1149 cm^{-1}. ^1H NMR δ: 2.7 (t, J = 7.2 Hz, 2H, CH_2COCF_3), 1.67 (m, 2H, $CH_2CH_2COCF_3$), 1.35–1.2 (b, 16H, $8CH_2$), 0.86 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C NMR δ: 191.6 (q, J = 36 Hz, $COCF_3$), 115.6 (q, J = 292 Hz, CF_3), 36.4, 31.9, 29.6–29.2, 28.8, 22.7, 22.4, 14.1 (CH_3). ^{19}F NMR δ: –3.7 (s). MS m/z (%): 183 (M^+-69, 83), 153 (28), 139 (38), 111 (34), 98 (32), 97 (51), 83 (45), 69 (67), 57 (85), 43 (100).

1,1,1-Trifluorotetradecan-2-one (IX). IR ν: 2925, 2856, 1764, 1207, 1149 cm^{-1}. ^1H NMR δ: 2.7 (t, J = 7.2 Hz, 2H, CH_2COCF_3), 1.67 (m, 2H, $CH_2CH_2COCF_3$), 1.36–1.23 (b, 18H, $9CH_2$), 0.88 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR δ: 191.6 (q, J = 35 Hz, $COCF_3$), 115.6 (q, J = 292 Hz, CF_3), 36.4, 31.2, 29.6–28.8, 22.7, 22.4, 14.1 (CH_3). ^{19}F NMR δ: –3.7 (s). MS m/z (%): 266 (M^+, 1), 197 (M^+-69, 28), 97 (29), 84 (29), 83 (35), 71 (32), 70 (44), 69 (50), 57 (83), 56 (40), 55 (53), 43 (100).

1,1,1-Trifluoropentadecan-2-one (X). IR ν: 2923, 2854, 1764, 1207, 1148 cm^{-1}. ^1H NMR δ: 2.7 (t, J = 7.5 Hz, 2H, CH_2COCF_3), 1.67 (m, 2H, $CH_2CH_2COCF_3$), 1.32–1.2 (b, 20H, $10CH_2$), 0.88 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C NMR δ: 191.5 (q, J = 34.6 Hz, $COCF_3$), 115.7 (q, J = 292 Hz, CF_3), 36.3, 32, 29.6–28.8, 22.7, 22.4, 14 (CH_3). ^{19}F NMR δ: –3.7 (s). MS m/z (%): 211 (M^+-69, 15), 97 (31), 84 (27), 83 (39), 71 (36), 70 (38), 69 (51), 57 (78), 56 (38), 55 (56), 43 (100).

1,1,1-Trifluorohexadecan-2-one (XI). IR ν: 2923, 2854, 1764, 1207, 1149 cm^{-1}. ^1H NMR δ: 2.7 (t, J = 7.5 Hz, 2H, CH_2COCF_3), 1.67 (m, 2H, $CH_2CH_2COCF_3$), 1.32–1.2 (b, 22H, $11CH_2$), 0.88 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR δ: 191.6 (q, J = 34.6 Hz, $COCF_3$), 115.6 (q, J = 292 Hz, CF_3), 36.3, 32, 29.7–28.8, 22.7, 22.4, 14.1 (CH_3). ^{19}F NMR δ: –3.7 (s). MS m/z (%): 294 (M^+, 2), 153 (46), 139 (55), 111 (62), 97 (86), 83 (75), 71 (56), 69 (71), 57 (100).

1,1,1-Trifluoroheptadecan-2-one (XII). IR ν: 2925, 2856, 1764, 1206, 1149 cm^{-1}. ^1H NMR δ: 2.7 (t, J = 7.5 Hz, 2H, CH_2COCF_3), 1.67 (m, 2H, $CH_2CH_2COCF_3$), 1.35–1.23 (b, 24H, $12CH_2$), 0.87 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR δ: 191.6 (q, J = 35 Hz, $COCF_3$), 115.6 (q, J = 292 Hz, CF_3), 36.4, 32, 29.7–28.8, 22.7, 22.4, 14.1 (CH_3). ^{19}F NMR δ: –3.7 (s). MS m/z (%): 239 (M^+-69, 7), 153 (5), 139 (8), 111 (13), 97 (23), 83 (26), 71 (34), 69 (38), 57 (98), 56 (35), 55 (67), 43 (100), 41 (65).

1,1,1-Trifluorooctadecan-2-one (XIII). In a 3-round bottomed flask were placed 0.52 g (1.48 mmol) of 1-iodohexadecane in 14 mL of an anh. mixture pentane:ether 3:2 under *oxygen-free* Ar. The solution was cooled to –78 °C and, under vigorous stirring, was added dropwise 2.17 mL (3.25 mmol) of a 1.5 M *tert*-BuLi in hexane. The reaction mixture was stirred at –78 °C for 5 min, left to warm to rt for 1 h and cooled again to –78 °C. Then, 0.487 g (3.1 mmol) of *N*-methoxy-*N*-methyltrifluoroacetamide[21] was added. the reaction further stirred tor 15 min and warmed to rt for 1 h. The reaction mixture was quenched with NH_4Cl sat. solution and extracted with ether. The organic phases were combined, washed with brine and dried to leave a residue, which was purified by column chromatography on silica gel to yield 0.477 g (85 %) of ketone **XIII**. IR ν: 2925, 2854, 1764, 1465, 1209, 1151 cm^{-1}. ^1H NMR δ: 2.7 (t, J = 7.5 Hz, 2H, CH_2COCF_3), 1.67 (m, 2H, $CH_2CH_2COCF_3$), 1.35–1.26 (b, 26H, $13CH_2$), 0.88 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR δ: 191.7 (q, J = 35 Hz, $COCF_3$), 115.6 (q, J = 292 Hz, CF_3), 36.4, 32, 29.7–29.2, 28.7, 22.7, 22.4, 14.1 (CH_3). ^{19}F NMR δ: –3.7 (s). MS m/z (%): 322 (M^+, 2), 253 (M^+-69, 32), 111 (38), 97 (64), 85 (33), 83 (61), 71 (59), 70 (42), 69 (66), 57 (98), 56 (47), 55 (89), 43 (100).

4-Phenyl-1,1,1-trifluorobutan-2-one (IV) and 1,1,1-trifluorononadecan-2-one (XIV)

A three-step sequence from ethyl 3-(ethylendioxy)trifluoroacetoacetate (**XXII**) was applied.

Ethyl 3-(ethylendioxy)trifluoroacetoacetate (XXII)

This compound was prepared as previously reported.[20] To a suspension of 10 g (70 mmol) of ethyl trifluoroacetoacetate and 1.7 g (70 mmol) of sodium hydride in 30 mL of anh. benzene was added 12 g (0.15 mmol) of 2-chloroethanol. The mixture was heated to reflux for 44 h and poured into crushed ice containing 20 % HCl solution The organic phase was extracted with ether, washed with $NaHCO_3$ solution and brine and dried. After evaporation of the solvent, the compound was purified by vacuum distillation (8.4 g, 76 %). ^1H NMR δ: 4.20 (s,

4H, OCH_2CH_2O), 4.15 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 2.9 (s, 2H, CH_2COOEt), 1.27 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR δ: 167.0 (*C*O), 122.7 (q, J = 291 Hz, *C*F_3), 104.0 (q, J = 32 Hz, *C*CF_3), 67.2 (OCH_2CH_2O), 60.9 (OCH_2CH_3), 36.9 (CH_2CO), 13.9 (CH_3). ^{19}F NMR δ: –6.96 (s).

Alkylation of ethyl 3-(ethylendioxy)trifluoroacetoacetate (XXII). General procedure

Synthesis of dioxolanes XXIII and XXIV. To a solution of 1.05 g (4.6 mmol) of ester **XXII** in 100 mL of anh. THF was added 4.6 mL of a 1 M LDA solution in THF at –78 °C under Ar. After stirring for 40 min, 2.47 g (13.8 mmol) of anh. HMPA was added, the reaction stirred for 10 min and the electrophile (benzyl bromide or 1-iodohexadecane) (4.2 mmol) subsequently added. The mixture was stirred at –78 °C for 30 min and at rt for 4 h. The reaction was quenched with 10 % HCl solution and extracted with ether. The combined organic phases were washed with sodium bisulfite sat. solution and water and dried. The solvent was stripped off and the residue chromatographed by column chromatography on neutral alumina for purification of **XXIII** (83 % yield) and silica gel for isolation of **XXIV** (90 % yield). **XXIII**: IR ν: 2993, 1739, 1170, 1043, 945, 700 cm^{-1}. ^1H NMR δ: 7.3–7.1 (c, 5H, C_6H_5), 4.28–4.16 (c, 4H, $2CH_2O$), 3.97 (q, J = 6.9 Hz, 2H, OCH_2CH_3), 3.3 (dd, J = 8.7 Hz, J' = 6.6 Hz, 1H, C*H*), 3.08 (d, J = 9.0 Hz, 1H, $PhCH_ACH$), 3.07 (d, J = 6.3 Hz, 1H, $PhCH_BCH$), 1.01 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR δ: 169.8 (*C*O), 137.8–126.6 (aromat. *C*), 123.1 (q, J = 291 Hz, *C*F_3), 105.3 (q, J = 31 Hz, *C*CF_3), 67.5 (OCH_2), 67.1 (OCH_2), 60.7 (OCH_2CH_3), 50.9 ($PhCH_2$), 32.6 (*C*H), 13.8 (CH_3). ^{19}F NMR δ: –4.98 (s). MS m/z (%): 318 (M^+, 3), 177 (100), 141 (70), 131 (94), 91 (49). **XXIV**: IR ν: 3010, 2930, 1738, 1172 cm^{-1}. ^1H NMR δ: 4.18 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 4.17 (s, 4H, OCH_2CH_2O), 2.97 (dd, J = 11.7 Hz, J' = 3.3 Hz, 1H, C*H*), 1.9–1.6 (c, 2H, CH_2CH), 1.3–1.2 (b, 31H, $14CH_2$ + OCH_2CH_3), 0.88 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR δ: 170.9 (*C*O), 123.1 (q, J = 291 Hz, *C*F_3), 105.5 (q, J = 31 Hz, *C*CF_3), 67.5 (OCH_2), 67.0 (OCH_2), 60.8 (OCH_2CH_3), 49.0 (*C*-2), 31.9 (*C*-16), 29.7–26.4 (*C*-3 to *C*-15), 22.7 (*C*-17), 14.2 ($2CH_3$). ^{19}F NMR δ: –4.96 (s). Elemental Analysis: Calcd for $C_{24}H_{43}O_4F_3$: C, 63.69; H, 9.58; Found: C, 63.68; H, 9.82.

Hydrolysis of dioxolanes XXIII and XXIV. General method

To a solution of dioxolanes **XXIII** or **XXIV** (0.88 mmol) in 10 mL of hexane was slowly added, at –10 °C under Ar, 1.32 mL of a 1 M boron tribromide solution in hexane. After stirring for 1 h, water was added, the organic material extracted with ether and washed with brine. After drying, the organic phase was freed trom solvent and the crude purified by column chromatography on silica gel eluting with CH_2Cl_2, to obtain the expected keto esters **XXV** (83 % yield) or **XXVI** (88 % yield), as mixture of keto, enol and hydrate forms. **XXV**: IR ν: 3442, 2985, 1768, 1743, 1731, 1708, 1666, 1265, 1178, 700 cm^{-1}. ^1H NMR δ: 13.06 (q, J = 2.1 Hz, 1H. O*H* enol), 7.27–7.17 (c, 15H, $3C_6H_5$ keto + enol + hydrate forms), 4.24–3.84 (c, 8H, $3OCH_2$ keto + enol + hydrate + $PhCH_2C$ = enol), 3.7 (s, 2H, 2O*H* hydrate) 3.3–2.8 (c, 6H, $2PhCH_2$ keto + hydrate + 2C*H*CO keto + hydrate), 1.28–0.87 (c, 9H, $3CH_3$ keto + enol + hydrate). ^{13}C NMR (keto form) δ: 186.4 (q, J = 36.3 Hz, *C*OCF_3), 166.5 (*C*OO), 136.0–126.2 (aromat. *C*), 115.5 (q, J = 292 Hz, *C*F_3), 62.4 (OCH_2CH_3), 55 ($PhCH_2$), 33.7 (*C*H), 13.8 (CH_3); hydrate form: 174.3 (*C*OO), 136.8–126.9 (aromat. *C*), 122.6 (q, J = 288 Hz, *C*F_3), 93.7 (q, J = 32.2 Hz, *C*CF_3), 61.6 (OCH_2CH_3), 49.6 ($PhCH_2$), 33.1 (*C*H), 13.5 (CH_3); enol form: 174.7 (*C*OO), 172.9 (*C*=C(OH)CF_3), 157.2 (q, J = 37.5 Hz, C=*C*(OH)CF_3), 136–126.2 (aromat. *C*), 13.7 (CH_3). ^{19}F NMR δ: –2.01 (keto form), –4.6 (enol form), –7.6 (hydrate form). MS m/z (%) (keto form): 274 (M^+, 2), 201 (25), 183 (16), 177 (39), 131 (100), 91 (69). **XXVI**: IR ν: 3550, 2900, 2840, 1760, 1730, 1700, 1650, 1460, 1260, 1150 cm^{-1}. ^1H NMR δ: 12.8 (q, J = 2.1 Hz, 1H, O*H* enol), 4.35–4.17 (c, 6H, $3OCH_2$ keto + enol + hydrate forms), 3.79 (t, J = 6.0 Hz, C*H* keto), 1.94 (m, 2H, CH_2C=C enol), 1.38–1.19 (b, 88H, $44CH_2$ keto + enol + hydrate), 0.88 (t, J = 6.9 Hz, 9H, $3CH_3$ keto + enol + hydrate). ^{13}C NMR δ: 187.1 (q, J = 35.8 Hz, *C*OCF_3), 175.5 (q, J = 34.5 Hz, *C*=C(OH)CF_3) 175.2 (*C*O O hydrate), 173.2 (*C*OO enol), 167.2 (*C*OO keto), 156.1 (q, J = 34.5 Hz, C=*C*(OH)CF_3), 123.6 (q, J = 290.5 Hz, *C*F_3 enol) 115.6 (q, J = 290.5 Hz, *C*F_3 keto), 115.3 (q, J = 290.5 Hz, *C*F_3 hydrate). (Assignments corresponding to very close absorptions may be interchanged). ^{19}F NMR δ: –2.1 (keto form), –3.7 (enol form), –7.9 (hydrate form). Elemental Analysis (keto form): Calcd for $C_{22}H_{39}O_3F_3$: C, 64.68; H, 9.62; Found: C, 64.71; H, 9.84.

Decarboethoxylation of keto esters XXV and XXVI: 4-phenyl-1,1,1-trifluorobutan-2-one (IV) and 1,1,1-trifluorononadecan-2-one (XIV)

A solution of keto esters **XXV** or **XXVI** (2.55 mmol) in 7 mL of DMF was heated to reflux for 2 h in the presence of 216 mg (5.1 mmol) of LiCl and 46 mg (2.56 mmol) of water. The reaction mixture was diluted with water and the organic material repeatedly extracted with hexane. The combined organic phases were thoroughly washed with water and dried. The solvent was removed and the crude purified by column chromatography to afford pure TFMKs **IV** (59 % yield) or **XIV** (82 % yield). **XIV**: IR ν: 2920, 2840, 1760, 1460, 1150 cm^{-1}. ^1H NMR δ: 2.7 (t, J = 7.5 Hz, 2H, CH_2COCF_3), 1.67 (m, 2H, $CH_2CH_2COCF_3$), 1.4–1.2 (b, 28H, $14CH_2$), 0.88 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C NMR δ: 191.7 (q, J = 35 Hz, *C*OCF_3), 115.6 (q, J = 292 Hz, *C*F_3), 36.4 (CH_2CO), 32, 29.7–29.2, 28.7, 22.7, 22.4, 14.1 (CH_3). ^{19}F NMR δ: –3.7 (s). MS m/z (%): 267 (M^+-69, 7), 111 (22), 97 (30), 83 (29), 71 (37), 69 (32), 57 (83), 55 (49), 43 (100)

(Z)-13-Hexadecen-11-yn-1-ol (XXVII)

This compound was prepared as previously reported by us[28] and the stereochemical purity was higher than 95 % *Z*.

(Z)-14-Heptadecen-12-yn-1-ol (XXVIII)

This compound was prepared in 70.1 % overall yield from (*Z*)-1-bromo-1-butene and 2-(12-tridecynyloxy)-tetrahydropyran, in an analogous manner to alcohol **XXVII**. The stereochemical purity of **XXVIII** was higher than 95 % *Z*. IR ν: 3600–3100, 3020, 2920, 2850, 1620, 1460, 1050, 726 cm^{-1}. ^1H NMR δ: 5.8 (dt, J = 10.5 Hz, J' = 7 Hz, 1H, CH_2CH=CH), 5.35 (dm, J = 10.5 Hz, 1H, CH=C*H*C≡C), 3.6 (t, J = 6 Hz, 2H, CH_2OH), 2.6 (s, 1H, O*H*), 2.45–2.2 (c, 4H, CH_2CH=CHC≡CCH_2), 1.5 (m, 2H, CH_2CH_2OH), 1.39–1.2 (b, 16H, 8CH_2), 0.95 (t, J = 7 Hz, 3H, CH_3). ^{13}C NMR δ: 143.9 (*C*-15), 108.8 (*C*-14), 94.5 (*C*-12), 77.2 (*C*-13), 63.0 (*C*-1), 32.8 (*C*-2), 29.5–28.8 (*C*-4 to *C*-10), 25.7 (*C*-3), 23.4 (*C*-16), 19.5 (*C*-11), 13.4 (*C*-17).

(Z)-1-Iodo-13-hexadecen-11-yne (XXIX)

This compound was previously described by us.[14]

(Z)-1-Iodo-14-heptadecen-12-yne (XXX)

This enyne was prepared in 79 % overall yield from alcohol **XXVIII** according to a method previously developed by us.[29] IR ν: 3020, 2920, 1460 cm^{-1}. ^1H NMR δ: 5.85 (dt, J = 10.8 Hz, J' = 7 Hz, 1H, CH_2CH=CH), 5.45 (dm, J = 10.8 Hz, 1H, CH=C*H*C≡C), 3.18 (t, J = 6.5 Hz, 2H, CH_2I), 2.35–2.2 (c, 4H, CH_2CH=CHC≡CCH_2), 1.8 (m, 2H, CH_2CH_2I), 1.55 (m, 2H, $CH_2CH_2CH_2I$), 1.4–1.2 (b, 14H, 7CH_2), 1.0 (t, J = 7 Hz, 3H, CH_3). ^{13}C NMR δ: 143.9 (*C*-15), 108.8 (*C*-14), 94.4 (*C*-12), 77.4 (*C*-13), 33.5–28.4 (*C*-2 to *C*-10), 23.4 (*C*-16), 19.5 (*C*-11), 13.4 (*C*-17), 7.0 (*C*-1). MS m/z (%): 360 (M^+, 5), 135 (56), 107 (44), 95 (69), 93 (77), 91 (49), 79 (100), 67 (46), 55 (44). Elemental Analysis: Calcd for $C_{17}H_{29}I$: C, 56.51; H, 8.03; Found: C, 56.45; H, 7.92.

Ethyl (Z)-12-(1-ethylendioxy-2-trifluoromethyl)]-13-hexadecen-11-ynoate (XXXI)

Following the same procedure as for compound **XXIV**, alkylation of **XXII** with iodide **XXIX** in the presence of LDA in THF:HMPA 1:1, furnished compound **XXXI** in 92 % yield, after column chromatography on silica gel eluting with hexane:ether 93:7. ^1H NMR δ: 5.8 (dt, J = 10.5 Hz, J' = 7 Hz, 1H, CH_2CH=CH), 5.3 (dm, J = 10.5 Hz, 1H, CH=C*H*C≡C), 4.18 (q, J = 7 Hz, 2H, CH_2CH_3), 4.15 (s, 4H, OCH_2CH_2O), 2.9 (m, 1H, C*H*), 2.3 (m, 4H, CH_2CH=CHC≡CCH_2), 1.4–1.1 (b, 21H, 9CH_2 + CH_3), 1.0 (t, J = 7 Hz, 3H, CH_3).

Hydrolysis of XXXI

The same procedure followed for hydrolysis of ester **XXIV** was applied. However, the expected keto ester **XXXIV** was not obtained satisfactorily, since concomitant addition of the catalyst to the enyne system was mainly observed.

Ethyl 3-(dimethylhydrazono)trifluoroacetoacetate (XXXII)

This compound was prepared as previously described.[20] A mixture of 10 g (54 mmol) of ethyl trifluoroacetoacetate and 6.5 g (108 mmol) of *N,N*-dimethylhydrazine in 50 mL of absolute ethanol was heated to reflux for 18 h. The excess of hydrazine and the solvent were evaporated under vacuum (100 mm Hg) and the residue fractionally distilled to afford 9.1 g (74%) of hydrazone **XXXII**. IR ν: 2985, 2880, 1730, 1630, 1360, 1290, 1020 cm^{-1}. ^1H NMR δ: 4.2 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 3.52 (s, 2H, CH_2COOEt), 2.82 (s, 6H, $N(CH_3)_2$), 1.27 (t, J = 7 Hz, 3H, CH_3). ^{13}C NMR δ: 168.2 (*C*OO), 136.0 (q, J = 33 Hz, *C*N), 121.5 (q, J = 275 Hz, *C*F_3), 61.7 (OCH_2), 46.8 ($N(CH_3)_2$), 37.3 (CH_2CO), 14.1 (CH_2CH_3). ^{19}F NMR δ: 6.8 (s).

Ethyl (Z)-12-(1-dimethylhydrazono-2-trifluoromethyl)]-15-octadecen-13-ynoate (XXXIII)

To a flask containing 1.15 mL (1.21 mmol) of a 1.05 M LDA solution was added, at 0 °C under Ar, a solution of 260 mg (1.15 mmol) of **XXXII** in 2.5 mL of anh. THF. After stirring for 2 h, the mixture was cooled to –78 °C and 200 mg (0.578 mmol) of iodide **XXIX** in 1.5 mL of anh. HMPA subsequently added. The reaction mixture was further stirred for 2 h, left warming to rt and stirred for 16 h more. After hydrolysis with 10 % HCl solution, the organic material was extracted with ether, washed with brine and dried to afford a crude, which was purified by column chromatography on alumina(III) eluting with hexane:ether 96:4, to yield 205 mg (80 %) of pure **XXXIII**. IR ν: 2910, 2840, 1735, 1460, 1340, 1180, 1140 cm^{-1}. ^1H NMR δ: 5.84 (dt, J = 10.5 Hz, J' = 7 Hz, 1H, CH_2CH=CH), 5.3 (dm, J = 10.5 Hz, 1H, CH=C*H*C≡C), 4.3 (m, 1H, C*H*), 4.15 (q, J = 7.2 Hz, 2H, OCH_2CH_3), 2.6 (s, 6H, $N(CH_3)_2$), 2.5–2.1 (c, 4H, CH_2CH=CHC≡CCH_2), 1.7–1.2 (b, 21H, 9CH_2 + CH_3), 1.0 (t, J = 7.2 Hz, 3H, CH_3). Exact Mass: Calcd for $C_{24}H_{39}O_2N_2F_3$ m/z 444.296364; Found 444.294375.

Hydrolysis of hydrazone XXXIII

A mixture of 344 mg (775 mmol) of hydrazone **XXXIII** in 4 mL of 90 % ethanol and 1.4 g (15 mmol) of allyl bromide was heated to reflux for 2.5 h. Then, the volatile material was stripped off under vacuum, the residue taken up in ether, washed with water and dried. The solvent was removed and the expected compound **XXXIV** obtained in 80 % yield as mixture of the keto and hydrate forms. IR ν: 3560, 3390, 2920, 2850, 1740, 1700, 1460, 1250, 1170, 1020 cm^{-1}. ^{19}F NMR δ: –2.0 (keto form), –7.8 (hydrate form). Exact Mass (keto form): Calcd for $C_{22}H_{33}O_3F_3$ m/z 402.238180; Found 402.237965.

Decarboethoxylation of XXXIV

To a solution of 300 mg (0.74 mmol) of keto ester **XXXIV** in 11 mL of ethanol was added 298 mg (7.4 mmol) of NaOH and the mixture heated to reflux for 15 h. The solvent was removed under vacuum, the residue treated with NH_4Cl sat. solution and extracted with ether. The organic phases were washed with brine and dried to yield a crude (80 %), which was characterized as carboxylic acid **XXXV**. The expected TFMK **XVI** was not detected. IR ν: 3200, 2920, 2850, 1700, 1455 cm^{-1}. ^1H NMR δ: 5.85

(dt, J = 10.8 Hz, J' = 7 Hz, 1H, CH_2CH=CH), 5.45 (dm, J = 10.8 Hz, 1H, CH=CHC≡C), 2.4–2.2 (c, 4H, CH_2CH=CHC≡CCH_2), 1.65 (m, 2H, CH_2CH_2CO), 1.5 (m, 2H, $CH_2CH_2CH_2$CO), 1.4–1.2 (b, 14H, 7CH_2), 1.0 (t, J = 7 Hz, 3H, CH_3). Exact Mass: Calcd for $C_{18}H_{30}O_2$ m/z 278.224580; Found 278.224556.

(Z)-1,1,1-Trifluoro-15-octadecen-13-yn-2-one (XV)

A solution of 415 mg (1.20 mmol) of iodide **XXIX** in 13 mL of an anh. mixture pentane:ether 3:2 was placed in a previously flamed 2-neck round-bottomed flask. The solution was cooled to –78 °C and 1.18 mL (1.24 mmol) of 1.05 M *tert*-BuLi in hexane was added dropwise under *oxygen-free* Ar. The solution was stirred for 5 min and then 351 mg (2.47 mmol) of freshly distilled ethyl trifluoroacetate was added. The reaction was stirred for 10 min at –78 °C and at rt for 1 h, quenched with water, extracted with ether and washed with brine. After drying, the solvent was evaporated off, and the crude purified by column chromatography on silica gel, eluting with hexane:ether 95:5, to obtain 364 mg (92 %) of the expected ketone **XV**. IR ν: 2929, 2856, 1764, 1461, 1207, 1151, 736 cm^{-1}. ^{1}H NMR δ: 5.85 (dt, J = 10.8 Hz, J' = 7 Hz, 1H, CH_2CH=CH), 5.45 (dm, J = 10.8 Hz, 1H, CH=CHC≡C), 2.7 (t, J = 7.2 Hz, 2H, CH_2CO), 2.4–2.2 (c, 4H, CH_2CH=CHC≡CCH_2), 1.65 (m, 2H, CH_2CH_2CO), 1.5 (m, 2H, $CH_2CH_2CH_2$CO), 1.4–1.2 (b, 12H, 6CH_2), 1.0 (t, J = 7 Hz, 3H, CH_3). ^{13}C NMR δ: 191.5 (q, J = 35 Hz, COCF$_3$), 144 (*C*-16), 115.6 (q, J = 292 Hz, CF$_3$), 108.7 (*C*-15), 94.4 (*C*-13), 77.2 (*C*-14), 36.3 (*C*-3), 29.4–22.3 (*C*-4 to *C*-11 and *C*-17), 19.5 (*C*-12), 13.4 (*C*-18). ^{19}F NMR δ: –3.7 (s). MS m/z (%): 316 (M$^+$, 4), 247 (M$^+$-69, 4), 135 (31), 95 (50), 93 (67), 91 (41), 79 (100), 77 (33), 67 (35), 55 (33). Exact Mass: Calcd for $C_{18}H_{27}OF_3$ m/z 316.201400; Found 316.200058.

(Z)-1,1,1-Trifluoro-16-nonadecen-14-yn-2-one(XVI)

Following the same procedure as for compound **XV**, TFMK **XVI** was obtained in 81 % isolated yield from iodide **XXX**. IR ν: 2929, 2855, 1764, 1461, 1207, 1151, 735 cm^{-1}. ^{1}H NMR δ: 5.85 (dt, J = 10.8 Hz, J' = 7 Hz, 1H, CH_2CH=CH), 5.45 (dm, J = 10.8 Hz, 1H, CH=CHC≡C), 2.7 (t, J = 7.2 Hz, 2H, CH_2CO), 2.4–2.2 (c, 4H, CH_2CH=CHC≡CCH_2), 1.66 (m, 2H, CH_2CH_2CO), 1.51 (m, 2H, $CH_2CH_2CH_2$CO), 1.4–1.2 (b, 14H, 7CH_2), 1.0 (t, J = 7 Hz, 3H, CH_3). ^{13}C NMR δ: 191.7 (q, J = 35 Hz, COCF$_3$), 144 (*C*-17), 115.6 (q, J = 292 Hz, CF$_3$), 108.7 (*C*-16), 94.4 (*C*-14), 77.2 (*C*-15), 36.3 (*C*-3), 29.5–22.4 (*C*-4 to *C*-12 and *C*-18), 19.5 (*C*-13), 13.4 (*C*-19). ^{19}F NMR δ: –3.7 (s). MS m/z (%): 330 (M$^+$, 4), 261 (M$^+$-69, 6), 233 (1), 135 (42), 95 (57), 93 (70), 91 (40), 79 (100), 67 (38), 55 (41). Exact Mass: Calcd for $C_{19}H_{29}OF_3$ m/z 330.217051. Found 330.216934.

3-Hexylthio-1,1,1-trifluoropropan-2-one (XVII)

To a solution of 1.0 g (8.5 mmol) of hexanethiol in 68 mL of anh. CH_2Cl_2 was added 3.4 g (32 mmol) of anh. Na_2CO_3 and 2.45 g (12.8 mmol) of 3-bromo-1,1,1-trifluoropropan-2-one. The mixture was stirred at rt for 21 h, diluted with CCl_4 and filtered. The solvent was stripped off and the crude purified by column chromatography on silica gel eluting with hexane:ether 100:10, to afford 2.26 g of the expected product **XVII** as mixture of ketone (30 %) and hydrate (70 %). IR ν: 3465, 2958, 2929, 2853, 1745, 1464, 1201, 1182, 1159, 1043, 695 cm^{-1}. ^{1}H NMR δ: 4.0 (s, 2H, OH hydrate), 3.47 (s, 2H, SCH_2COCF$_3$), 2.88 (s, 2H, SCH_2C(OH)$_2$CF$_3$), 2.7 (t, J = 7.4 Hz, 2H, CH_2SCH$_2$C(OH)$_2$CF$_3$), 2.5 (t, J = 7.3 Hz, 2H, CH_2SCH$_2$COCF$_3$), 1.6 (m, 4H, CH_2CH_2SCH$_2$COCF$_3$ and CH_2CH_2SCH$_2$C(OH)$_2$CF$_3$), 1.36 (b, 12H, 6CH_2 ketone + hydrate), 0.87 (t, J = 6.7 Hz, 6H, 2CH_3 ketone + hydrate). ^{13}C NMR δ: 185 (q, J = 34.2 Hz, COCF$_3$), 123 (q, J = 284.6 Hz, C(OH)$_2$$CF_3$), 115.5 (q, J = 290.7 Hz, COCF$_3$), 92.3 (q, J = 32 Hz, C(OH)$_2$CF$_3$), 36.4, 34.8, 33.6, 31.9, 31.3, 31.2, 29.3–28.2, 22.5, 22.4, 13.93, 13.92 (*C*-9 ketone, *C*-9 hydrate). ^{19}F NMR δ: 0.11 (s, COCF_3), –9.72 (s, C(OH)$_2$CF_3). Exact Mass: Calcd for $C_{19}H_{29}OF_3$ m/z 330.217051; Found 330.216934. Distillation of the mixture afforded pure ketone **XVII** in 88 % yield (50 °C/0.07 mm Hg). MS m/z (%) (ketone): 228 (M$^+$, 7), 131 (30), 117 (57), 83 (40), 69 (31), 61 (97), 56 (77), 55 (100), 43 (82), 42 (25), 41 (69). Exact mass (ketone): Calcd for $C_9H_{15}F_3OS$ m/z 228.079572; Found 228.078943.

3-Decylthio-1,1,1-trifluoropropan-2-one (XVIII)

The same procedure as for compound **XVII** was applied. Ketone **XVIII** was obtained in 68 % yield, after column chromatography purification on silica gel, as mixture of ketone (64 %) and hydrate (36 %). IR ν: 3463, 2925, 2838, 1747, 1465, 1184, 1157 cm^{-1}. ^{1}H NMR δ: 4.0 (s, 2H, OH hydrate), 3.48 (s, 2H, SCH_2COCF$_3$), 2.89 (s, 2H, SCH_2C(OH)$_2$CF$_3$), 2.71 (t, J = 7.3 Hz, 2H, CH_2SCH$_2$C(OH)$_2$CF$_3$), 2.51 (t, J = 7.4 Hz, 2H, CH_2SCH$_2$COCF$_3$), 1.6 (m, 4H, CH_2CH_2SCH$_2$COCF$_3$ and CH_2CH_2SCH$_2$C(OH)$_2$CF$_3$), 1.26 (b, 28H, 14CH_2 ketone + hydrate), 0.88 (t, J = 6.5 Hz, 6H, 2CH_3 ketone + hydrate). ^{13}C NMR δ: 185 (q, J = 34 Hz, COCF$_3$), 123 (q, J = 284.5 Hz, C(OH)$_2$$CF_3$), 115 (q, J = 290.7 Hz, COCF$_3$), 92 (q, J = 32 Hz, C(OH)$_2$CF$_3$), 36.4, 34.8, 33.6, 31.9, 31.8, 29.5–28.5, 22.7, 14.1 (*C*-13 ketone, *C*-13 hydrate). ^{19}F NMR δ: 0.04 (s, COCF_3), –9.69 (s, C(OH)$_2$CF_3). MS m/z (%) (ketone): 284 (M$^+$, 2), 187 (19), 173 (70), 97 (20), 83 (40), 70 (26), 69 (56), 61 (54), 57 (43), 56 (32), 55 (100), 43 (69), 41 (78). Exact mass (ketone): Calcd for $C_{13}H_{23}F_3OS$ m/z 284.142172; Found 284.142190.

3-Dodecylthio-1,1,1-trifluoropropan-2-one (XIX)

Following the same procedure, ketone **XIX** was obtained as mixture of keto and hydrate forms in a 1:2 ratio. IR ν: 3413, 2925, 2854, 1745, 1470, 1182, 695 cm^{-1}. ^{1}H NMR δ: 3.9 (s, 2H, OH hydrate), 3.47 (s, 2H, SCH_2COCF$_3$), 2.9 (s, 2H, SCH_2C(OH)$_2$CF$_3$), 2.7 (t, J = 7.4 Hz, 2H, CH_2SCH$_2$C(OH)$_2$CF$_3$), 2.5 (t, J = 7.3 Hz, 2H,

$CH_2SCH_2COCF_3$), 1.6 (m, 4H, $CH_2CH_2SCH_2COCF_3$ and $CH_2CH_2SCH_2C(OH)_2CF_3$), 1.25 (b, 36H, $18CH_2$ ketone + hydrate), 0.87 (t, J = 6.5 Hz, 6H, $2CH_3$ ketone + hydrate). ^{19}F NMR δ: 0.05 (s, $COCF_3$), –9.67 (s, $C(OH)_2CF_3$). By flash distillation pure ketone **XIX** was obtained in 98% yield (bp 150 °C/0.1 mm Hg) . ^{13}C NMR (ketone) δ: 185.0 (q, J = 34.3 Hz, $COCF_3$), 115.6 (q, J = 291 Hz, $COCF_3$), 36.5, 34.8, 33.7, 32.0, 31.9, 29.6–28.6, 22.6, 14.0 (*C*-15). MS m/z (%) (ketone): 312 (M^+, 2), 215 (26), 201 (100), 97 (24), 83 (35), 70 (24), 69 (71), 61 (47), 57 (50), 56 (27), 55 (88), 43 (67), 41 (67). Exact mass (ketone): Calcd for $C_{15}H_{27}F_3OS$ m/z 312.173472; Found 312.173080.

3-Pentadecylthio-1,1,1-trifluoropropan-2-one (XX).

In the same manner, ketone **XX** was obtained in 69 % yield as mixture of ketone and hydrate in 38:62 ratio, after column chromatography purification. IR ν: 3413, 2920, 2850, 1745, 1470, 1176, 1103, 1078, 1068 cm^{-1}. ^1H NMR δ: 3.9 (s, 2H, *OH* hydrate), 3.48 (s, 2H, SCH_2COCF_3), 2.89 (s, 2H, $SCH_2C(OH)_2CF_3$), 2.71 (t, J = 7.3 Hz, 2H, $CH_2SCH_2C(OH)_2CF_3$), 2.5 (t, J = 7.3 Hz, 2H, $CH_2SCH_2COCF_3$), 1.6 (m, 4H, $CH_2CH_2SCOCF_3$ and $CH_2CH_2SCH_2C(OH)_2CF_3$), 1.25 (b, 48H, $24CH_2$ ketone + hydrate), 0.88 (t, J = 6.7 Hz, 6H, $2CH_3$ ketone + hydrate). ^{13}C NMR δ: 185 (q, J = 34 Hz, $COCF_3$), 123 (q, J = 284.5 Hz, $C(OH)_2CF_3$), 115.5 (q, J = 291 Hz, $COCF_3$), 92.4 (q, J = 32 Hz, $C(OH)_2CF_3$), 36.4, 34.8, 33.6, 31.97, 31.93, 29.7–28.5, 22.7, 14.1 (*C*-18 ketone, *C*-18 hydrate). ^{19}F NMR δ: 0.02 (s, $COCF_3$), –9.7 (s, $C(OH)_2CF_3$). MS m/z (%) (ketone): 354 (M^+, 2), 257 (22), 243 (100), 111 (8), 97 (19), 83 (26), 71 (21), 69 (48), 61 (29), 57 (51), 55 (69), 43 (69), 41 (59). Exact mass (ketone): Calcd for $C_{18}H_{33}F_3OS$ m/z 354.220423; Found 354.219309.

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