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An efficient and expeditious synthesis of functionalized trifluoromethyl ketones through lithium-iodine exchange reaction

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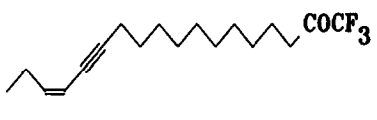
Abstract: A straightforward and very efficient synthesis of unsaturated long-chain trifluoromethyl ketones is achieved by metallation of the corresponding iodides in the presence of an equimolar amount of *tert*-butyllithium, followed by reaction with a fluoroacylating agent. Metallation occurs quantitatively at -78°C and, in contrast to what has been generally recommended, there is no need to add the second equivalent of base, since its presence may be detrimental if other electrophilic functions are present in the molecule.

Trifluoromethyl ketones are an important class of compounds which has received much attention in the last years for their ability to act as potent enzyme inhibitors[1,2]. Their particular properties derive from the unique physical and biological features displayed by the fluorine atom[3], whose steric volume closely mimics that of hydrogen (van der Waals radius of fluorine 1.35Å *vs* 1.20Å of hydrogen). Replacement of hydrogen by fluorine, therefore, results in only a very slight increase in the steric volume of the molecule, allowing the fluorinated compound to interact with sterically-stringent enzyme receptor sites. The high electronegative character of the halogen implies that trifluoromethyl ketones are highly electrophilic compounds, forming stable hydrates or hemiketals in aqueous solutions with a serine residue of the enzyme[4], through tetrahedral adducts similar to the transition state of the water addition to the carbonyl group of a peptide substrate.

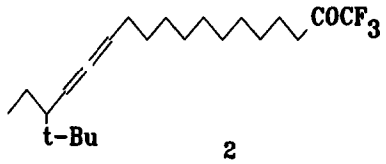
Synthesis of trifluoromethyl ketones has generally involved reaction of a Grignard derivative with a fluorinated electrophilic synthon, but this approach may be limited by the concomitant formation of unwanted secondary or tertiary alcohols[5]. As organometallic reagents, Grignard and organolithium derivatives have often been used but organocadmium[6], organozinc[7] and organomanganous reagents[8] have also been successfully employed. As fluorinated substrates, trifluoroacetic acid derivatives have frequently been utilized, either as metallic salts or as esters, amides, anhydrides, etc[5]. Other recent approaches involve alkylation of ethyl trifluoroacetoacetate[9], condensation of phosphonium ylides with trimethylsilyl trifluoroacetate[10], reaction of trifluoroacetic anhydride with carboxylic acid chlorides in pyridine[11] or arylcopper reagents[12], and fluoroalkyl carbinols oxidation with the Dess-Martin reagent[13], among others. However, in despite of the many methods

available, an easy and efficient method to prepare functionalized long-chain trifluoromethyl ketones is still needed.

In the course of our ongoing program directed to the development of inhibitors of antennal esterases in insects[14], we found that for the preparation of (Z)-1,1,1-trifluoro-15-octadecen-13-yn-2-one (1), a trifluoromethyl ketone analogue of (Z)-13-hexadecen-11-ynyl acetate, the major component of the sex pheromone of the pine processionary moth *Thaumetopoea pityocampa*[15], *trans*-metallation reaction of the required iodide, (Z)-1-iodo-13-hexadecen-11-yne, with 2.2 equivalents of *tert*-BuLi in pentane:ether 3:2 followed by treatment with ethyl trifluoroacetate, led to an inseparable mixture (*ca.* 1:1) of the expected trifluoromethyl ketone 1 and the *tert*-butyl-substituted allene 2. Formation of the allene is obviously the result of the base addition reaction to the enyne function, a fact which has been noticed by other authors to occur not only with alkynes or alkenynes but also with monoalkenes or *bis*-alkenyl derivatives[16].



1



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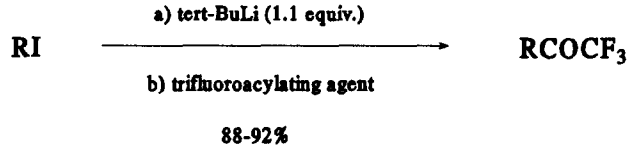
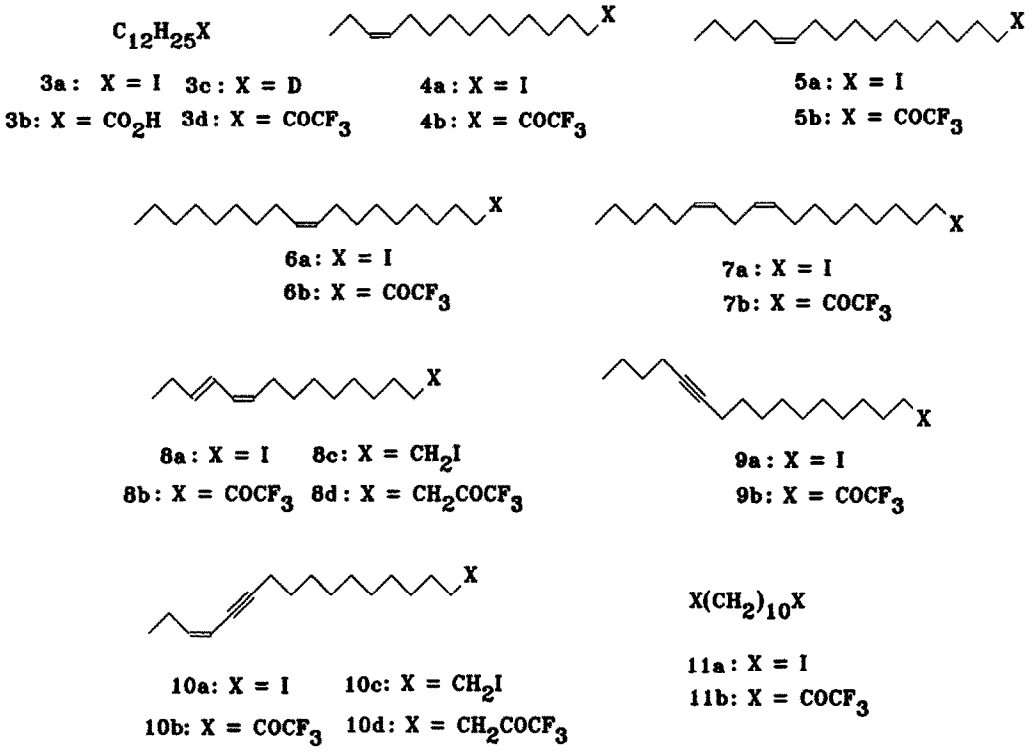
Lithium-halogen exchange reaction[17] has become a very common process to prepare organolithium compounds. The reaction has been so far carried out by using a primary iodide and two-molar equivalents of *tert*-butyllithium[17,18], the second equivalent of base being used to consume the generated *tert*-butyl iodide, thus rendering the interchange irreversible[17c].



However, the presence of an excess of base in the reaction mixture may concomitantly cause its addition to other electrophilic functions eventually present in the molecule. Moreover and although it is recommended to warm to room temperature to consume the excess of base by proton abstraction from the solvent (diethyl ether)[19], the primary organolithium derivative RLi initially formed may give rise under these conditions to an intramolecular cyclization reaction with other suitable functionalities present, a process which has been successfully used for the preparation of polycyclic carbocycles[20]. In this context, we have also noticed that under similar conditions (Z)-4-nonenyllithium readily cyclizes at temperatures above 0°C[21].

We have found that there is really no need to add a second equivalent of base and that lithium-iodine

exchange appears to be complete when primary iodides are treated with *only one equivalent* of *tert*-BuLi, at -78°C for 5 min, as monitored by GC. The procedure was initially tested using 1-iodododecane as substrate and CO_2 and D_2O as electrophilic agents in an anhydrous mixture pentane:ether 3:2 under *oxygen-free* Ar. The resulting carboxylic acid **3b** and deuterated derivative **3c** resulted in 88-91% yields. The use of adequate trifluoroacylating agents, *i.e.* trifluoroacetyl imidazole or ethyl trifluoroacetate, as electrophiles led us to a new and efficient entry for the synthesis of long-chain functionalized trifluoromethyl ketones. The reaction was applied to a variety of aliphatic monoenic iodides (compounds **4a-6a**), unconjugated or conjugated dienic derivatives (compounds **7a, 8a, 8c**) and acetylenic (compound **9a**) and enyne iodides (compounds **10a, 10c**).



Iododerivatives **3a-11a** were obtained in one-step (73-96% yields) from the required alcohols through the intermediate formation of the corresponding trifluoroacetates, followed by reaction with anh. LiI in THF:DMPU or THF:HMPA (1:1), as previously described by us[22]. For iodide **8c**, preparation of the corresponding parent alcohol (*Z,E*)-10,12-pentadecadienol was accomplished by homologation of the commercially available (*Z,E*)-9,11-tetradecadienol. We initially tried the procedure reported by Corey[23], which involved the use of phenylthiomethyllithium as a suitable synthon for extension of the chain, followed by replacement of the phenylthio group by iodo. However, and although the corresponding phenylthio derivative

was obtained in reasonable good yield (61%), trials to substitute iodo for the phenylthio functionality were unsuccessful or afforded the desired iodide in unacceptable yields (10-13%). We then turned to the more classical method of homologation involving the intermediate formation of the nitrile, which resulted more successful. Thus, conversion of (*Z,E*)-9,11-tetradecadienol into the corresponding nitrile was accomplished by nucleophilic substitution of the trifluoroacetate ester with NaCN in THF:HMPA 1:1[24]. The nitrile was subjected to DIBAH reduction in pentane at -70°C to afford the expected aldehyde in quantitative yield. The aldehyde was finally reduced under mild conditions ($NaBH_4$ in THF) to afford (*Z,E*)-10,12-pentadecadienol in 97% isolated yield, which was then transformed into iodide **8c** in 57.2% overall yield. As mentioned above, iodides **3a-10c** were transformed into the corresponding organolithium derivatives, through reaction with one equivalent of *tert*-BuLi, and then allowed to react with trifluoroacetyl imidazole or ethyl trifluoroacetate to yield cleanly trifluoromethyl ketones **3d-10d** in very good to excellent yields (80-92%) (Table 1).

Table 1. Trifluoromethyl ketones **3d-11b** prepared from the corresponding iodides through lithium-iodine exchange reaction.

Entry	Starting iodide	Electrophile	Product	Isolated yield (%)
1	**3a**	CO_2	**3b**	88
2	**3a**	D_2O	**3c**	91
3	**3a**	Trifluoroacetyl imidazole	**3d**	89
4	**4a**	CF_3CO_2Et	**4b**	82
5	**5a**	CF_3CO_2Et	**5b**	84
6	**6a**	CF_3CO_2Et	**6b**	88
7	**7a**	CF_3CO_2Et	**7b**	85
8	**8a**	CF_3CO_2Et	**8b**	84
9	**8c**	CF_3CO_2Et	**8d**	84
10	**9a**	CF_3CO_2Et	**9b**	80
11	**10a**	CF_3CO_2Et	**10b (1)**	92[a]
12	**10c**	CF_3CO_2Et	**10d**	81[a]
13	**11a**	CF_3CO_2Et	**11b**	85

[a]Ref. 14b

It is noteworthy to mention that in no case isomerization of the double(s) bond(s) was noticed and, more

importantly, no addition reaction of the base to the unsaturated system(s) was observed. The reaction was also applied to α,ω-diiododerivatives, *i.e.* 1,10-diiodododecane (**11a**), affording the *bis*-halogenated ketone **11b** in 85% yield. Again, the process was not hampered by possible inter- or intramolecular reactions. The trifluoromethyl ketones were obtained entirely in the keto form and no hydrate was detected by spectroscopic methos (IR, ^{1}H NMR, ^{13}C NMR).

In summary, a clean and expeditious synthesis of unsaturated long-chain trifluoromethyl ketones has been developed from the corresponding iodides. The procedure clearly improves other synthetic methods of the halogenated ketones, particularly those involving Grignard reagents, and can also be applied to the preparation of primary isotopically-labelled (^{2}H or ^{3}H) compounds.

Experimental Section

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 30m x 0,32μm 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 2m x 3mm ID glass column on Chromosorb W and nitrogen as carrier gas, or a SE-54 50m 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), Fluka Chemie AG (Buchs, Switzerland) or Sigma Chem. Co. (St. Louis, USA) 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.

Preparation of iodides 4a-11a. The compounds were prepared according to a general method already described by us[22].

(Z)-1-Iodo-11-tetradecene (4a).

Yield 89%. IR ν 3000, 2923, 2852, 1670, 1461, 719 cm^{-1}. ^{1}H NMR δ: 5.34 (m, 2H, C<u>H</u>=C<u>H</u>), 3.18 (t J=7 Hz, 2H, C<u>H</u>$_2$I), 2.0 (m, 4H, C<u>H</u>$_2$CH=CHC<u>H</u>$_2$), 1.8 (m, 2H, C<u>H</u>$_2$CH$_2$I), 1.35 (m, 2H, C<u>H</u>$_2$CH$_2$CH$_2$I), 1.27 (b, 12H, 6C<u>H</u>$_2$), 0.95 (t J=7.5 Hz, 3H, C<u>H</u>$_3$). ^{13}C NMR δ: 131.5 (C-12), 129.3 (C-11), 33.6, 30.5, 29.8-29.2, 28.5, 27.1, 20.5, 14.4 (C-14), 7.3 (C-1). MS m/z (%): 322 (M^+, 2), 252 (2), 127 (3), 125 (3), 111 (11), 97

(31), 83 (49), 69 (78), 67 (25), 57 (21), 55 (100), 43 (25), 41 (86). Elemental Analysis: Calculated for $C_{14}H_{27}I$: C, 52.16; H, 8.45. Found: C, 52.11; H, 8.55.

(*Z*)-1-Iodo-11-hexadecene (5a).

Yield 89%. IR ν 3002, 2923, 2852, 1670, 1464, 1370, 1170, 966, 719 cm^{-1}. ^1H NMR δ: 5.35 (m, 2H, C<u>H</u>=C<u>H</u>), 3.19 (t J=7 Hz, 2H, C<u>H</u>$_2$I), 2.0 (m, 4H, C<u>H</u>$_2$CH=CHC<u>H</u>$_2$), 1.82 (qt J=7.2 Hz, 2H, C<u>H</u>$_2$CH$_2$I), 1.32 (m, 2H, CH$_2$C<u>H</u>$_2$CH$_2$I), 1.27 (b, 16H, 8C<u>H</u>$_2$), 0.89 (t J=7 Hz, 3H, C<u>H</u>$_3$). ^{13}C NMR δ: 129.8 (C-11, C-12), 33.5, 31.9, 30.5, 29.7-29.3, 28.5, 27.2, 26.9, 22.3, 14.0 (C-16), 7.4 (C-1). MS m/z (%): 350 (M^+, 2), 252 (2), 127 (2), 111 (10), 97 (25), 83 (39), 81 (12), 69 (69), 67 (22), 57 (26), 55 (100), 43 (22), 41 (48). Exact Mass: Calculated for $C_{16}H_{31}I$: 350.147053. Found: 350.150155.

(*Z*)-1-Iodo-9-octadecene (6a).

Yield 73%. IR ν 3002, 2952, 2923, 2852, 1653, 1463, 1180, 721 cm^{-1}. ^1H NMR δ: 5.35 (m, 2H, C<u>H</u>=C<u>H</u>), 3.19 (t J=7 Hz, 2H, C<u>H</u>$_2$I), 2.0 (dt J=6.6 Hz, J'=5.8 Hz, 4H, C<u>H</u>$_2$CH=CHC<u>H</u>$_2$), 1.82 (qt J=7.2 Hz, 2H, C<u>H</u>$_2$CH$_2$I), 1.36 (m, 2H, CH$_2$C<u>H</u>$_2$CH$_2$I), 1.27 (b, 20H, 10C<u>H</u>$_2$), 0.88 (t J=6.7 Hz, 3H, C<u>H</u>$_3$). ^{13}C NMR δ: 129.99 (C-10), 129.74 (C-9), 33.5, 31.9, 30.5, 29.8, 29.7-29.2, 28.5, 27.2, 27.1, 22.7, 14.1 (C-18), 7.3 (C-1). MS m/z (%): 378 (M^+, 1), 250 (M^+-128, 2), 127 (5), 111 (10), 97 (34), 95 (25), 83 (53), 82 (35), 81 (44), 69 (67), 68 (33), 67 (51), 57 (32), 55 (100), 54 (30), 43 (47), 41 (83). Elemental Analysis: Calculated for $C_{18}H_{35}I$: C, 57.12; H, 9.33. Found: C, 57.08; H, 9.38.

(*Z,Z*)-1-Iodo-9,12-octadecadiene (7a).

Yield 81%. IR ν 3008, 2954, 2925, 2854, 1650, 1460, 1401, 910, 721 cm^{-1}. ^1H NMR δ: 5.35 (m, 4H, C<u>H</u>=C<u>H</u>CH$_2$C<u>H</u>=C<u>H</u>), 3.19 (t J=7.1 Hz, 2H, C<u>H</u>$_2$I), 2.77 (d J=5.9 Hz, 2H, CH=CHC<u>H</u>$_2$CH=CH), 2.04 (dt J=6.7 Hz, J'=6.6 Hz, 4H, C<u>H</u>$_2$CH=CHCH$_2$CH=CHC<u>H</u>$_2$), 1.82 (m, 2H, C<u>H</u>$_2$CH$_2$I), 1.35 (m, 2H, CH$_2$C<u>H</u>$_2$CH$_2$I), 1.3 (b, 14H, 7C<u>H</u>$_2$), 0.89 (t J=6.8 Hz, 3H, C<u>H</u>$_3$). ^{13}C NMR δ: 130.2, 130.0, 128.0, 127.9 (C-9, C-10, C-12, C-13), 33.5, 31.5, 30.5, 29.6-29.2, 28.5, 27.2, 25.6, 22.6, 14.1 (C-18), 7.3 (C-1). MS m/z (%): 376 (M^+, 4), 248 (M^+-128, 1), 127 (4), 123 (10), 109 (22), 96 (28), 95 (50), 82 (31), 81 (64), 79 (36), 69 (27), 68 (31), 67 (100), 55 (74), 54 (40), 41 (72).

(*Z,E*)-1-Iodo-9,11-tetradecadiene (8a).

Yield 81%. IR ν 3013, 2925, 2852, 1650, 1459, 1189, 981, 946, 726 cm^{-1}. ^1H NMR δ: 6.26 (dd J=15 Hz, J'=10.9 Hz, 1H, CH=C<u>H</u>CH=CH), 5.92 (dd J=J'=10.9 Hz, 1H, CH=CHC<u>H</u>=CH), 5.67 (dt J=15 Hz, J'=6.6 Hz, 1H, C<u>H</u>=CHCH=CH), 5.26 (dt J=10.8 Hz, J'=7.5 Hz, 1H, CH=CHCH=C<u>H</u>), 3.18 (t J=7.1 Hz, 2H, C<u>H</u>$_2$I), 2.1 (m, 4H, C<u>H</u>$_2$CH=CHC<u>H</u>$_2$), 1.8 (m, 2H, C<u>H</u>$_2$CH$_2$I), 1.3 (b, 10H, 5C<u>H</u>$_2$), 1.0 (t J=7.5 Hz, 3H, C<u>H</u>$_3$). ^{13}C NMR δ: 136.2 (C-12), 130 (C-9), 128.6 (C-10), 124.6 (C-11), 33.5, 30.5, 29.6-28.5, 27.6, 25.9, 13.7 (C-14), 7.3 (C-1). MS m/z (%): 320 (M^+, 15), 127 (1), 123 (3), 109 (8), 97 (3), 95 (57), 93 (11), 82 (67), 81 (66), 79 (33), 68 (41), 67 (100), 55 (36), 53 (11), 41 (33). Elemental Analysis: Calculated for $C_{14}H_{25}I$: C, 52.48; H, 7.87. Found: C, 52.14; H, 7.81.

(*Z,E*)-10,12-pentadecadienonitrile. To a solution of 154 mg (0.732 mmole) of (*Z,E*)-9,11-tetradecadienol in 1ml of anh. THF was added, under inert atmosphere, 205 mg (0.978 mmole) of trifluoroacetic anhydride,

freshly distilled over $NaHCO_3$. The mixture was stirred for 15 min at room temperature and the volatile material stripped off. The residue was diluted with 2.2 ml of an anh. mixture THF:HMPA 1:1 and then 180 mg (3.663 mmole) of NaCN, previously dried at 100-120°C/0.1.mm for 5 h, was added. The reaction mixture was heated to reflux for 3 h, cooled to room temperature and the THF removed under vacuum. The residue was diluted with hexane, washed with brine and dried ($MgSO_4$). After filtration and removal of the solvent, the nitrile was purified by column chromatography on silica gel eluting with hexane:ether 100:12 to afford 112 mg (70%) of pure product.

IR ν 3013, 2975, 2929, 2854, 2250, 1650, 1458, 1426, 981, 948, 726 cm^{-1}. ^1H NMR δ: 6.25 (dd J=15 Hz, J'=10.9 Hz, 1H, CH=C<u>H</u>CH=CH), 5.91 (dd J=J'=10.9 Hz, 1H, CH=CHC<u>H</u>=CH), 5.66 (dt J=15 Hz, J'=6.7 Hz, 1H, C<u>H</u>=CHCH=CH), 5.25 (dt J=10.8 Hz, J'=7.5 Hz, 1H, CH=CHCH=C<u>H</u>), 2.3 (t J=7.1 Hz, 2H, C<u>H</u>$_2$CN), 2.1 (m, 4H, C<u>H</u>$_2$CH=CHC<u>H</u>$_2$), 1.65 (m, 2H, C<u>H</u>$_2$CH$_2$CN), 1.41 (m, 2H, C<u>H</u>$_2$CH$_2$CH$_2$CN), 1.29 (b, 8H, 4C<u>H</u>$_2$), 0.99 (t J=7.4 Hz, 3H, C<u>H</u>$_3$). ^{13}C NMR δ: 136.1 (C-13), 129.8 (C-10), 128.6 (C-11), 124.5 (C-12), 119.8 (C-1), 29.5-29.0, 28.6, 28.5, 27.5, 25.8, 25.2, 17.0, 13.6 (C-15). MS m/z (%): 219 (M^+, 9), 95 (51), 82 (43), 81 (57), 79 (32), 77 (16), 68 (44), 67 (100), 55 (39), 54 (16), 41 (54). Elemental Analysis: Calculated for $C_{15}H_{25}N$: C, 82.13; H, 11.49; N, 6.38. Found: C, 82.11; H, 11.46, N, 6.35.

(*Z,E*)-10,12-pentadecadienal. A mixture of 37 mg (0.167 mmole) of (*Z,E*)-10,12-pentadecadienonitrile, 0.2 ml of 1M DIBAH soln. in pentane (0.2 mmole) and 2.6 ml of anh. pentane was stirred at -78°C under nitrogen. After 4 h the reaction was complete by GC analysis. The mixture was warmed to 0°C and then 5 ml of NH_4Cl sat. soln. was added. After stirring for 5 min, the organic phase was decanted and the aqueous layer extracted with ether after acidification. The combined organic phases were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel eluting with hexane:ether 100:12 to afford the expected aldehyde in almost quantitative yield (99%).

IR ν 3013, 2960, 2927, 2854, 2713, 1726, 1650, 1464, 1258, 1095, 1026, 981, 954, 808 cm^{-1}. ^1H NMR δ: 9.76 (t J=1.8 Hz, 1H, C<u>H</u>O), 6.26 (dd J=15 Hz, J'=10.9 Hz, 1H, CH=C<u>H</u>CH=CH), 5.92 (dd J=J'=10.9 Hz, 1H, CH=CHC<u>H</u>=CH), 5.67 (dt J=15 Hz, J'=6.6 Hz, 1H, C<u>H</u>=CHCH=CH), 5.26 (dt J=10.8 Hz, J'=7.5 Hz, 1H, CH=CHCH=C<u>H</u>), 2.42 (t J=7.3 Hz, 2H, C<u>H</u>$_2$CHO), 2.14 (m, 4H, C<u>H</u>$_2$CH=CHC<u>H</u>$_2$), 1.62 (m, 2H, C<u>H</u>$_2$CH$_2$CHO), 1.36 (m, 2H, C<u>H</u>$_2$CH$_2$CH$_2$CHO), 1.29 (b, 8H, 4C<u>H</u>$_2$), 1.01 (t J=7.5 Hz, 3H, C<u>H</u>$_3$). ^{13}C NMR δ: 203.0 (C-1), 136.2 (C-13), 130.1 (C-10), 128.6 (C-11), 124.6 (C-12), 43.9, 29.6-29.1, 27.6, 25.9, 22.0, 13.7 (C-15).

(*Z,E*)-10,12-pentadecadienol. To a solution of the previous aldehyde (34 mg, 0.153 mmole) in 1 ml of THF containing 4 μl of water was added 6 mg (0.159 mmole) of $NaBH_4$. The mixture was stirred at room temperature for 1 h, the solvent evaporated and the crude diluted with pentane. The solution was treated with 0.1N HCl soln., the organic phase decanted and washed with brine and dried. Evaporation of the solvent and purification on column chromatography eluting with hexane:ether 100:40 afforded the dienic alcohol (33 mg, 97%).

IR ν 3338, 3025, 2962, 2925, 2852, 1650, 1459, 1058, 981, 945, 721 cm^{-1}. ^1H NMR δ: 6.25 (dd J=15 Hz,

J'=10.8 Hz, 1H, CH=C<u>H</u>CH=CH), 5.91 (dd J=J'=10.9 Hz, 1H, CH=CHC<u>H</u>=CH), 5.67 (dt J=15 Hz, J'=6.6 Hz, 1H, C<u>H</u>=CHCH=CH), 5.26 (dt J=10.8 Hz, J'=7.5 Hz, 1H, CH=CHCH=C<u>H</u>), 3.64 (t J=6.6 Hz, 2H, C<u>H</u>$_2$OH), 2.14 (m, 4H, C<u>H</u>$_2$CH=CHC<u>H</u>$_2$), 1.56 (m, 2H, C<u>H</u>$_2$CH$_2$OH), 1.36 (m, 2H, C<u>H</u>$_2$CH$_2$CH$_2$OH), 1.29 (b, 10H, 5C<u>H</u>$_2$), 1.01 (t J=7.5 Hz, 3H, C<u>H</u>$_3$). ^{13}C NMR δ: 136.1 (C-13), 130.1 (C-10), 128.5 (C-11), 124.6 (C-12), 63.1 (C-1), 32.8, 29.7-29.2, 27.7, 25.9, 25.7, 13.7 (C-15). MS m/z (%): 207 (M^+-17, 3), 95 (38), 91 (18), 82 (52), 81 (48), 79 (51), 77 (20), 68 (28), 67 (100), 55 (51), 43 (20), 41 (63).

(*Z,E*)-1-Iodo-10,12-pentadecadiene (8c). Following the general procedure, iodide **8c** was obtained in 83% yield, after purification on silica gel eluting with hexane.

IR ν 3013, 2987, 2958, 2923, 2852, 1650, 1461, 1456, 1434, 1180, 985, 954 cm^{-1}.

^{1}H NMR δ: 6.26 (dd J=15.1 Hz, J'=10.9 Hz, 1H, CH=C<u>H</u>CH=CH), 5.92 (dd J=J'=10.9 Hz, 1H, CH=CHC<u>H</u>=CH), 5.67 (dt J=15 Hz, J'=6.6 Hz, 1H, C<u>H</u>=CHCH=CH), 5.26 (dt J=10.8 Hz, J'=7.5 Hz, 1H, CH=CHCH=C<u>H</u>), 3.19 (t J=7.1 Hz, 2H, C<u>H</u>$_2$I), 2.15 (m, 4H, C<u>H</u>$_2$CH=CHC<u>H</u>$_2$), 1.82 (m, 2H, C<u>H</u>$_2$CH$_2$I), 1.37 (m, 2H, C<u>H</u>$_2$CH$_2$CH$_2$I), 1.29 (b, 10H, 5C<u>H</u>$_2$), 1.02 (t J=7.3 Hz, 3H, C<u>H</u>$_3$). ^{13}C NMR δ: 136.1 (C-13), 130.1 (C-10), 128.6 (C-11), 124.6 (C-12), 33.5, 32.5, 30.5, 29.7-29.1, 28.5, 27.6, 25.9, 13.6 (C-15), 7.4 (C-1).

1-Iodo-11-hexadecyne (9a).

Yield 91%. IR ν 2954, 2927, 2852, 1463, 1431, 1330, 1211, 1174, 726 cm^{-1}. ^{1}H NMR δ: 3.18 (t J=7.1 Hz, 2H, C<u>H</u>$_2$I), 2.14 (m, 4H, C<u>H</u>$_2$C≡CC<u>H</u>$_2$), 1.81 (qt J=7.1 Hz, 2H, C<u>H</u>$_2$CH$_2$I), 1.4 (m, 4H, C<u>H</u>$_2$CH$_2$C≡CCH$_2$C<u>H</u>$_2$), 1.35 (m, 2H, C<u>H</u>$_2$CH$_2$CH$_2$I), 1.28 (b, 12H, 6C<u>H</u>$_2$), 0.9 (t J=7.1 Hz, 3H, C<u>H</u>$_3$). ^{13}C NMR δ: 80.17, 80.15 (C-12, C-11), 33.5, 31.3, 30.5, 29.4-29.1, 28.8, 28.5, 21.9, 18.7, 18.4, 13.6 (C-16), 7.4 (C-1). MS m/z (%): 348 (M^+, 1), 254 (3), 127 (10), 123 (9), 109 (16), 95 (58), 93 (23), 82 (27), 81 (100), 79 (38), 69 (30), 67 (88), 55 (75), 54 (41), 43 (26), 41 (86). Exact Mass: Calculated for $C_{16}H_{29}I$: 348.131403; Found: 348.134812.

(Z)-1-Iodo-13-hexadecen-11-yne (10a).

This compound was previously described by us[25].

(Z)-1-Iodo-14-heptadecen-12-yne (10c).

This compound was already reported by us[14b].

1,1-Diiodododecane (11a).

Yield 96%. IR ν 3001, 2923, 2850, 1461, 1425, 1249, 1232, 1211, 1197, 1170, 719 cm^{-1}. ^{1}H NMR δ: 3.19 (t J=7 Hz, 4H, 2C<u>H</u>$_2$I), 1.82 (qt J=7.1 Hz, 4H, 2C<u>H</u>$_2$CH$_2$I), 1.39 (m, 4H, 2C<u>H</u>$_2$CH$_2$CH$_2$I), 1.29 (b, 8H, 4C<u>H</u>$_2$). ^{13}C NMR δ: 33.5, 30.4, 29.3, 28.5, 7.4 (C-1, C-10). Exact Mass: Calculated for $C_{10}H_{20}I_2$: 393.965455; Found: 393.965769.

Preparation of trifluoromethyl ketones 3d-11b. General procedure. In a two-neck round bottomed flask was placed a solution of the iodide **3a-11a** (1 mmole) in 11 ml of an anhydrous mixture pentane:diethyl ether 3:2 under *oxygen-free* Ar. The solution was cooled to -78°C and then *tert*-BuLi 1,25M in pentane (1,1 mmole, except for **11a** which requires 2.2 mmole) was dropwise added. The mixture was stirred for 5 min and

then freshly distilled ethyl trifluoroacetate or trifluoroacetyl imidazole (6,0 mmole) was added. The reaction mixture was stirred at -78°C for 10 min and brought to room temperature for 1 h. After quenching with NH_4Cl sat. sol., the aqueous layer was extracted with ether and the combined organic phases washed with brine and dried. The crude material was chromatographed on silica gel eluting with hexane:ether mixtures to afford the expected trifluoromethyl ketone **3d-11b** in the specified yields.

1,1,1-Trifluorotetradecan-2-one (3d).

Yield 89%. IR ν: 2925, 2856, 1764, 1207, 1149 cm^{-1}. ^1H NMR δ: 2.7 (t J=7,2 Hz, 2H, $C\underline{H}_2COCF_3$), 1.67 (m, 2H, $C\underline{H}_2CH_2COCF_3$), 1.3 (b, 18H, $9C\underline{H}_2$), 0,88 (t J=6,9 Hz, 3H, $C\underline{H}_3$). ^{13}C NMR δ: 191.6 (q J=35 Hz, $\underline{C}OCF_3$), 115.6 (q J=292 Hz, CF_3), 36.4, 31.2, 29.6-28.8, 22.7, 22.4, 14.1 (C-14). ^{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).

(Z)-1,1,1-Trifluoro-13-hexadecen-2-one (4b).

Yield 82%. IR ν 3004, 2927, 2854, 1764, 1650, 1464, 1408, 1295, 1207, 1151, 1018, 708 cm^{-1}. ^1H NMR δ: 5.33 (m, 2H, $C\underline{H}=C\underline{H}$), 2.7 (t J=7.3 Hz, 2H, $C\underline{H}_2COCF_3$), 2.0 (m, 4H, $C\underline{H}_2CH=CHC\underline{H}_2$), 1.67 (qt J=7.1 Hz, 2H, $C\underline{H}_2CH_2COCF_3$), 1.27 (b, 14H, $7C\underline{H}_2$), 0.95 (t J=7.5 Hz, 3H, $C\underline{H}_3$). ^{13}C NMR δ: 191.6 (q J=34.5 Hz, $\underline{C}OCF_3$), 131.5 (C-14), 129.3 (C-13), 115.5 (q J=290.5 Hz, $CO\underline{C}F_3$), 36.4, 29.7-29.2, 28.7, 27.1, 22.4, 20.5, 14.4 (C-16). ^{19}F NMR δ: -3.7 (s). MS m/z (%): 292 (M^+, 3), 223 (M^+-69, 4), 207 (2), 97 (16), 83 (23), 82 (18), 70 (22), 69 (58), 67 (24), 56 (36), 55 (100), 43 (29), 41 (88). Exact Mass: Calculated for $C_{16}H_{27}F_3O$: 292.201400; Found: 292.203050.

(Z)-1,1,1-Trifluoro-13-octadecen-2-one (5b).

Yield 84%. IR ν 3004, 2925, 2854, 1764, 1650, 1465, 1401, 1292, 1207, 1151, 1020, 708 cm^{-1}. ^1H NMR δ: 5.35 (m, 2H, $C\underline{H}=C\underline{H}$), 2.7 (t J=7.2 Hz, 2H, $C\underline{H}_2COCF_3$), 2.01 (m, 4H, $C\underline{H}_2CH=CHC\underline{H}_2$), 1.67 (qt J=7.1 Hz, 2H, $C\underline{H}_2CH_2COCF_3$), 1.27 (b, 18H, $9C\underline{H}_2$), 0.89 (t J=7 Hz, 3H, $C\underline{H}_3$). ^{13}C NMR δ: 191.6 (q J=34.6 Hz, $\underline{C}OCF_3$), 129.86, 129.83 (C-13, C-14), 115.6 (q J=290.6 Hz, $CO\underline{C}F_3$), 36.3, 31.9, 29.7-29.2, 28.7, 27.2, 26.9, 22.4, 22.3, 14 (C-18). ^{19}F NMR δ: -3.7 (s). MS m/z (%): 320 (M^+, 3), 251 (M^+-69, 4), 97 (18), 70 (24), 69 (54), 67 (20), 57 (21), 56 (34), 55 (100), 43 (27), 41 (51). Exact Mass: Calculated for $C_{18}H_{31}F_3O$: 320.232701; Found: 320.235987.

(Z)-1,1,1-Trifluoro-11-eicosen-2-one (6b).

Yield 88%. IR ν 3004, 2925, 2854, 1764, 1660, 1464, 1401, 1258, 1207, 1151, 1026, 808, 708 cm^{-1}. ^1H NMR δ: 5.34 (m, 2H, $C\underline{H}=C\underline{H}$), 2.7 (t J=7.1 Hz, 2H, $C\underline{H}_2COCF_3$), 2.0 (dt J=6.6 Hz, J'=5.8 Hz, 4H, $C\underline{H}_2CH=CHC\underline{H}_2$), 1.67 (qt J=7.2 Hz, 2H, $C\underline{H}_2CH_2COCF_3$), 1.35 (m, 2H, $C\underline{H}_2CH_2CH_2COCF_3$), 1.3 (b, 20H, $10C\underline{H}_2$), 0.88 (t J=6.7 Hz, 3H, $C\underline{H}_3$). ^{13}C NMR δ: 191.6 (q J=34.5 Hz, $\underline{C}OCF_3$), 130.0 (C-12), 129.7 (C-11), 115.5 (q J=291 Hz, $CO\underline{C}F_3$), 36.3, 31.9, 29.8-29.1, 28.7, 27.2, 27.1, 22.7, 22.4, 14.1 (C-20). ^{19}F NMR δ: -3.7 (s). MS m/z (%): 348 (M^+, 3), 207 (2), 111 (14), 97 (33), 83 (43), 82 (20), 70 (28), 69 (57), 57 (45), 56 (43), 55 (100), 54 (28), 43 (55), 41 (70). Exact Mass: Calculated for $C_{20}H_{35}F_3O$: 348.264001; Found: 348.266510.

(*Z,Z*)-1,1,1-Trifluoro-11,14-eicosadien-2-one (7b).

Yield 85%. IR ν 3010, 2954, 2927, 2856, 1764, 1640, 1464, 1401, 1264, 1207, 1151, 1101, 1029, 808, 714 cm^{-1}. ^1H NMR δ: 5.35 (c, 4H, C<u>H</u>=C<u>H</u>CH$_2$C<u>H</u>=C<u>H</u>), 2.77 (t J=5.8 Hz, 2H, CH=CHC<u>H$_2$</u>CH=CH), 2.71 (t J=7.2 Hz, 2H, C<u>H$_2$</u>COCF$_3$), 2.04 (dt J=6.8 Hz, J'=6.6 Hz, 4H, C<u>H$_2$</u>CH=CHCH$_2$CH=CHC<u>H$_2$</u>), 1.65 (qt J=7.1 Hz, 2H, C<u>H$_2$</u>CH$_2$COCF$_3$), 1.35 (m, 2H, C<u>H$_2$</u>CH$_2$CH$_2$COCF$_3$), 1.3 (b, 14H, 7C<u>H$_2$</u>), 0.89 (t J=6.8 Hz, 3H, C<u>H$_3$</u>). ^{13}C NMR δ: 191.6 (q J=34.6 Hz, <u>C</u>OCF$_3$), 130.2, 130.0, 128.0, 127.9 (C-11, C-12, C-14, C-15), 115.6 (q J=290.6 Hz, CO<u>C</u>F$_3$), 36.3, 31.5, 29.6-29.2, 28.7, 27.2, 27.18, 25.6, 22.6, 22.3, 14.1 (C-20). ^{19}F NMR δ: -3.7 (s). MS m/z (%): 346 (M^+, 3), 277 (M^+-69, 2), 96 (29), 95 (40), 82 (38), 81 (64), 79 (29), 69 (27), 68 (35), 67 (100), 55 (58), 54 (52), 43 (19), 41 (55). Exact Mass: Calculated for $C_{20}H_{33}F_3O$: 346.248351; Found: 346.252689.

(*Z,E*)-1,1,1-Trifluoro-11,13-hexadecadien-2-one (8b).

Yield 84%. IR ν 3013, 3006, 2962, 2929, 2856, 1764, 1651, 1458, 1408, 1289, 1207, 1149, 1045, 983, 946, 708 cm^{-1}. ^1H NMR δ: 6.25 (dd J=15 Hz, J'=10.9 Hz, 1H, CH=C<u>H</u>CH=CH), 5.91 (dd J=J'=10.9 Hz, 1H, CH=CHC<u>H</u>=CH), 5.67 (dt J=15 Hz, J'=6.6 Hz, 1H, C<u>H</u>=CHCH=CH), 5.26 (dt J=10.8 Hz, J'=7.5 Hz, 1H, CH=CHCH=C<u>H</u>), 2.7 (t J=7.2 Hz, 2H, C<u>H$_2$</u>COCF$_3$), 2.14 (m, 4H, C<u>H$_2$</u>CH=CHC<u>H$_2$</u>), 1.67 (qt J=7.1 Hz, 2H, C<u>H$_2$</u>CH$_2$COCF$_3$), 1.3 (b, 10H, 5C<u>H$_2$</u>), 1.01 (t J=7.4 Hz, 3H, C<u>H$_3$</u>). ^{13}C NMR δ: 191.6 (q J=34.5 Hz, <u>C</u>OCF$_3$), 136.2 (C-14), 130 (C-11), 128.6 (C-12), 124.6 (C-13), 115.6 (q J=290.6 Hz, CO<u>C</u>F$_3$), 36.3, 29.6-29.1, 28.7, 27.6, 25.9, 22.4, 13.6 (C-16). ^{19}F NMR δ: -3.7 (s). MS m/z (%): 290 (M^+, 9), 221 (M^+-69, 2), 95 (51), 82 (54), 81 (35), 79 (23), 68 (26), 67 (100), 55 (37), 41 (41). Exact Mass: Calculated for $C_{16}H_{25}F_3O$: 290.185750; Found: 290.189282.

(*Z,E*)-1,1,1-Trifluoro-12,14-heptadecadecadien-2-one (8d).

Yield 84%. IR ν 3016, 2980, 2925, 2854, 1764, 1650, 1463, 1458, 1207, 1149, 985, 946, 707 cm^{-1}. ^1H NMR δ: 6.27 (dd J=15 Hz, J'=10.9 Hz, 1H, CH=C<u>H</u>CH=CH), 5.90 (dd J=J'=10.9 Hz, 1H, CH=CHC<u>H</u>=CH), 5.65 (dt J=15 Hz, J'=6.6 Hz, 1H, C<u>H</u>=CHCH=CH), 5.27 (dt J=10.8 Hz, J'=7.5 Hz, 1H, CH=CHCH=C<u>H</u>), 2.7 (t J=7.2 Hz, 2H, C<u>H$_2$</u>COCF$_3$), 2.14 (m, 4H, C<u>H$_2$</u>CH=CHC<u>H$_2$</u>), 1.67 (m, 2H, C<u>H$_2$</u>CH$_2$COCF$_3$), 1.3 (b, 10H, 5C<u>H$_2$</u>), 1.01 (t J=7.2 Hz, 3H, C<u>H$_3$</u>). ^{13}C NMR δ: 191.6 (q J=34 Hz, <u>C</u>OCF$_3$), 136.1 (C-15), 130.1 (C-12), 128.6 (C-13), 124.6 (C-14), 115.5 (q J=290.6 Hz, CO<u>C</u>F$_3$), 36.3, 29.7-29.1, 28.7, 27.6, 25.9, 22.3, 13.6 (C-17). ^{19}F NMR δ: -3.7 (s). Exact Mass: Calculated for $C_{17}H_{27}F_3O$: 304.201400; Found: 304.199308.

1,1,1-Trifluoro-13-octadecyn-2-one (9b).

Yield 80%. IR ν 2929, 2856, 2220, 1764, 1464, 1401, 1289, 1205, 1149, 1105, 1097, 1026 cm^{-1}. ^1H NMR δ: 2.7 (t J=7.2 Hz, 2H, C<u>H$_2$</u>COCF$_3$), 2.14 (m, 4H, C<u>H$_2$</u>C≡C<u>CH$_2$</u>), 1.67 (qt J=7.1 Hz, 2H, C<u>H$_2$</u>CH$_2$COCF$_3$), 1.44 (m, 4H, C<u>H$_2$</u>CH$_2$C≡CCH$_2$<u>CH$_2$</u>), 1.37 (m, 2H, C<u>H$_2$</u>CH$_2$CH$_2$COCF$_3$), 1.28 (b, 12H, 6C<u>H$_2$</u>), 0.9 (t J=7.1 Hz, 3H, C<u>H$_3$</u>). ^{13}C NMR δ: 191.6 (q J=34.7 Hz, <u>C</u>OCF$_3$), 115.5 (q J=290 Hz, CO<u>C</u>F$_3$), 80.19, 80.15 (C-13, C-14), 36.3, 31.2, 29.4-29.1, 28.8, 28.7, 22.3, 21.9, 18.7, 18.4, 13.6 (C-18). ^{19}F NMR δ: -3.7 (s). MS m/z (%): 96 (42), 95 (59), 82 (31), 81 (100), 79 (24), 69 (26), 67 (83), 55 (76), 54 (83), 43 (27), 41 (67). Exact

Mass: Calculated for $C_{18}H_{29}F_3O$: 318.217051; Found: 318.213181.

(Z)-1,1,1-Trifluoro-15-octadecen-13-yn-2-one (10b).

This compound was already reported by us[14b].

(Z)-1,1,1-Trifluoro-16-nonadecen-14-yn-2-one (10d).

This compound was already described by us[14b].

1,1,1,14,14,14-Hexafluoro-2,13-tetradecanedione (11b).

Yield 85%. IR ν 2929, 2858, 1764, 1464, 1404, 1290, 1247, 1207, 1149, 1053, 1010, 714 cm^{-1}. ^1H NMR δ: 2.71 (t J=7.2 Hz, 4H, $2CH_2COCF_3$), 1.67 (m, 4H, $2CH_2CH_2COCF_3$), 1.29 (b, 12H, $6CH_2$). ^{13}C NMR δ: 191.6 (q J=34.6 Hz, $2COCF_3$), 115.5 (q J=291.5 Hz, $2COCF_3$), 36.3, 29.2, 29.1, 28.7, 22.3. ^{19}F NMR δ: -3.7 (s). Exact Mass: Calculated for $C_{14}H_{20}F_6O_2$: 334.136750; Found: 334.135223.

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