Locking Out Ants – Synthesis and Biological Evaluation of Some Fluorinated Repellents

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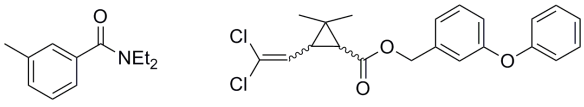
We synthesized a series of fluorinated compounds and tested them in an easy assay for their repellent activity against the ant *Myrmica rubra*. Depending on their chain length and pattern of fluorination these molecules are efficient repellents for this ant. Fluorinated compounds are stronger repellents than their unfluorinated analogs. 1,1,1-Trifluorotridecan-2-one (**4**) is an even better repellent against *M. rubra* than "gold standard" *N*,*N*-diethyl-*m*-toluamide (DEET).

Key words: Fluorination, Trifluoromethyl Ketones, Repellents, Ants

Introduction

Several insects are serious pests since they cause severe damage to crops, livestock and human health in many parts of the world. Addressing the latter problem, the principal approach to prevent vector-borne diseases [1] such as malaria, Dengue fever, yellow fever, Rift valley fever or arboreal encephalitis is avoidance. Repellents may play a significant role in interrupting the insect-target interaction. Thus, to develop new repellents is still of high importance to provide alternatives to established repellents (*N*,*N*-diethyl-*m*-toluamide, DEET (**I**), permethrine (**II**); Fig. 1) that are more efficient, effective for a longer duration and safer in their application to human skin [2]. Although **II** is quite effective against a broad range of pests (acting as a non-systemic insecticide with contact and stomach action), it shows only a slight repellent effect.

Repellent properties of some plants to insects are well-known. Previous studies [3] of long-chain aliphatic methyl ketones showed repellence to arthropods, including bloodsucking insects. Incorporation of one or more fluorine substituents is known to be of advantage both for an improved biological activity, for a higher bioavailability as well as for causing a retarded metabolism of several bioactive compounds [4]. Several reviews [5 – 8] of this extensive subject have been published. Thus, trifluoromethyl ketones [9] are inhibitors of antennal esterases [10]. Recently, the repellency property of long-chain aliphatic methyl ketones against *Anopheles gambiae* has been reported [3]. 2-Dodecanone is a known repellent; it displays repellency against the tick *Rhipicephalus appendiculatus* and the maize weevil (*Sitophilus zeamais*), comparable to that of the commercial arthropod repellent DEET [11, 12].

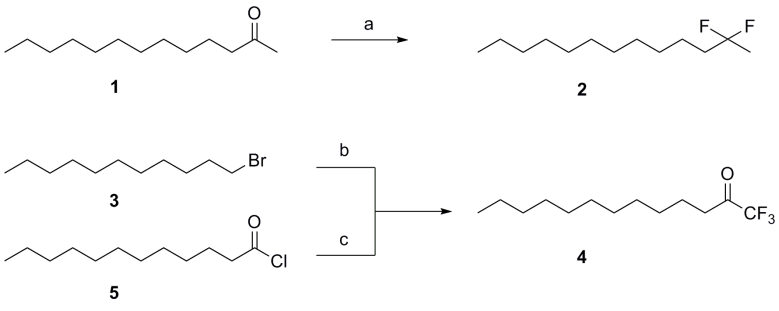


I II

Fig. 1. Structure of established repellents DEET (**I**) and permethrine (**II**).

Results and Discussion

Applying the juice of freshly crushed tomato leaves to the skin is an old household cure against insect bites [13 – 16]. 2-Undecanone and 2-tridecanone being found in tomatoes (*Lycopersicon sp.*) are repellents to mosquitoes [17 – 19]. Thus, we became interested in the synthesis of fluoroanalogs of tridecan-2-one (**1**). In a first approach, the carbonyl group in **1** was replaced by a difluoromethylene substituent (Scheme 1) to afford 2,2-difluorotridecane (**2**) [20]. A convenient way [21] for this replacement is treating **1** with DAST yielding **2**. Compound **2** is characterized in its ^{19}F NMR spectrum by a signal at $\delta = -90.70$ ppm; in the ^{13}C NMR spectrum the CF_2 group is detected

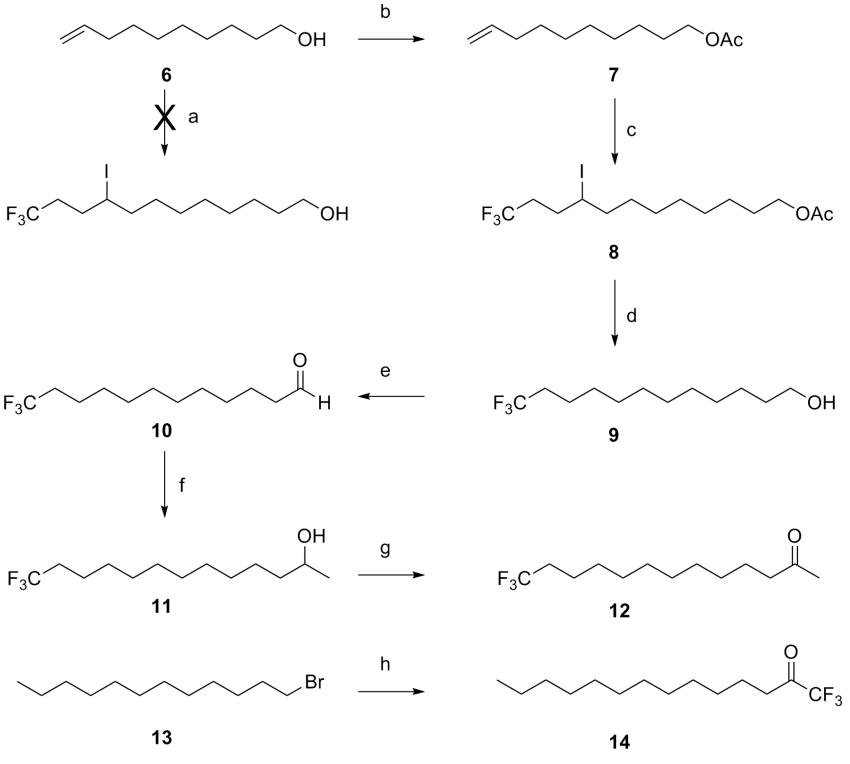


Scheme 1. a) DAST, DCM, 25 °C, 12 d, 64 %; b) Mg, F_3CCO_2Et, −40 °C, 5 h, 55 %; c) $(F_3CCO)_2O$, pyridine, 20 °C, 2 h, 82 %.

at δ = 124.31 ppm showing a $^1J_{C,F}$ coupling constant of 237.0 Hz.

Trifluoromethyl ketones are usually synthesized [10] by elaborating simpler fluorine-containing molecules. Reaction of undecylbromide (**3**) with magnesium under Grignard conditions followed by a reaction with ethyl trifluoroacetate [22] gave 55 % of 1,1,1-trifluorotridecan-2-one (**4**). Previously, **4** has been shown to be an effective inhibitor of several enzymes [23 – 25]. Interestingly enough, no analytical data for this compound have been reported so far. However, yields of this product dropped significantly on scaling up of the reaction. Therefore, as an alternative, dodecanoyl chloride (**5**) was reacted with trifluoroacetic anhydride in pyridine [26], and was isolated in 82 % yield **4**. The reaction advances by a dehydrohalogenation of the acid chloride by pyridine thus producing a ketene that can be captured by trifluoroacetic anhydride; decarboxylation of an intermediary trifluoroacetic 4,4,4-trifluoro-2-alkyl-3-oxobutanoic anhydride finally furnishes the corresponding trifluoromethyl ketone [26, 27]. Compound **4** is characterized in its ^{13}C NMR spectrum by the presence of a CF_3 group at δ = 115.62 ppm ($^1J_{C,F}$ = 292.0 Hz); the adjacent carbonyl group exhibits a quartet signal with $^2J_{C,F}$ = 35 Hz.

The synthesis of 13,13,13-trifluorotridecan-2-one (**12**) started from 9-decen-1-ol (**6**). The reaction of **6**



Scheme 2. a) cat. $Pd(PPh_3)_4$, hexanes [28]; b) Ac_2O, pyridine, Δ, 3 h, 91 %; c) F_3C-CH_2I, DBPO, Δ, Δ*p*, 18 h, 69 %; d) $LiAlH_4$, Et_2O, Δ, 9 h, 63 %; e) PCC, DCM, 25 °C, 2 h, 60 %; f) MeMgBr, Et_2O, Δ, 3 h, 75 %; g) PCC, DMC, 25 °C, 1 h, 72 %; h) F_3CCO_2Et, Mg, −40 °C, 5 h, 75 %.

Compound	**2**	**4**	**12**	**14**	Tridecan-2-one	Tetradecan-2-one	Tetradecan-3-one	DEET
Percentage, %	75	92	85	0	56	0	67	82

Table 1. Percentage of ants *M. rubra* repelled by a 10 % solution of the compound; three experiments each.

with 2,2,2-trifluoroethyl iodide in the presence of $Pd(PPh_3)_4$ [28] failed to give any useful product (Scheme 2). This may be caused by the slow formation of the 2,2,2-trifluoroethyl radical since the trifluoro substitution destabilizes an adjacent radical center.

As an alternative, **6** was acetylated, and acetate **7** [29 – 37] was subjected to a free radical addition reaction. Addition of 2,2,2-trifluoroethyl iodide to terminal alkenes in the presence of a radical initiator followed by a reduction of the resulting secondary iodide provides trifluoroethyl-substituted products [38]. Thus, reaction of **7** with trifluoroethyl iodide using dibenzoylperoxide (DBPO) as an initiator at 95 °C in a steel autoclave gave 69 % of acetate **8**. Reduction of **8** with $LiAlH_4$ gave 63 % of alcohol **9** [39 – 42] whose oxidation with PCC in dichloromethane gave 60 % of aldehyde **10**. Grignard reaction of **10** and Mg/methyl iodide yielded 75 % of alcohol **11** whose PCC oxidation yielded 72 % of **12**.

Finally, reaction of dodecyl bromide (**13**) with ethyl trifluoroacetate/Mg gave 75 % of 1,1,1-trifluorotetradecan-2-one (**14**). Previously, **14** has been shown to act, *inter alia*, as an inhibitor of antennal esterases of insects [10], of the juvenile hormone esterase [43] and also of other enzymes [44].

Comparative bioassays [45] were performed using colonies of the ant *Myrmica rubra*. *M. rubra* forms tough colonies; they are active and a bit aggressive and prick when they feel under pressure. *M. rubra* is native to the Palearchic regions of Europe and Asia from Ireland to Western Sibiria. There is a concern that the ant is capable of establishing in new areas especially in the USA. Three colonies of *M. rubra* (about 40 individuals each) were reared separately in glass tanks. During the assay the ants were allowed to choose between two pieces of prey (turkey meat with honey) that were placed on a sheet of paper at a distance of *ca.* 50 mm. Each piece was surrounded by a circle soaked either with pure methanol for reference or a 10 % methanolic solution of the compound. The bioassays were evaluated by counting the number of ants feeding at each piece of prey 15 min after starting of the experiment. The results of these experiments are summarized in Table 1.

Evaluation of these data revealed that **4** is a strong repellent and retreats 92 % of the ants looking for prey. The length of the carbon chain seems to be important: elongation for just one methylene group (as exemplified in **14**) destroys the repellent activity. The same was noted for the non-fluorinated analogs: whereas tridecan-2-one is a fair repellent, tetradecan-2-one is lacking any repellent activity. Activity, however, can be restored by shifting the carbonyl group: tetradecan-3-one is a repellent, too. Fluorinated compounds are stronger repellents than their matching non-fluorinated analogs [39, 46]. It seems reasonable that the repellents spread fast on surfaces and in ants (using mainly olfactory sense), and a coating of sensory organs will make them "blind". In addition, it can be expected that the ants get serious problems to evaluate their own trail pheromones.

Experimental Section

General methods

Melting points are uncorrected (Leica hot stage microscope). Optical rotations were obtained using a Perkin-Elmer 341 polarimeter (1 cm micro cell, 20 °C). NMR spectra were recorded using the Varian spectrometers Gemini 200, Gemini 2000 or Unity 500 (δ given in ppm J in Hz, internal Me_4Si or internal CCl_3F), IR spectra (film or KBr pellet) on a Perkin-Elmer FT-IR spectrometer Spectrum 1000. MS spectra were taken on an Intectra GmbH AMD 402 (electron impact, 70 eV) or on a Thermo Electron Finnigan LCQ (electrospray, voltage 4.5 kV, sheath gas nitrogen) instrument. For elemental analysis a Foss-Heraeus Vario EL instrument was used. TLC was performed on silica gel (Merck 5554, detection by UV absorption or by treatment with a solution of 10 % sulfuric acid, ammonium molybdate and cerium(IV) sulfate) followed by gentle heating. The solvents were dried according to usual procedures.

Biological testing

The three colonies of *Myrmica rubra* (obtained from Antstore, Berlin, about 40 individuals each) were reared separately in glass tanks ($25 \times 15 \times 20$ cm^3). The tanks were fitted with a mixture of soil, sand, loam, and stones. All the other internal surfaces were greased with pure Vaseline to prevent the ants escaping from the chambers. Two small containers with 20 % sucrose in water were placed in each tank as a source of food and water. The ants were held at r. t. and in normal laboratory light. Prior to the experiments the ants were put to starving conditions (plenty of water without sucrose for 7 d). During the assay, the ants were allowed to

choose between two pieces of prey (turkey meat with honey water) that were placed on a sheet of paper at a distance of *ca.* 50 mm. Each piece was surrounded by a circle (20 mm radius) soaked (50 mL) either with pure methanol for reference or a solution of the compound (0.5 mL in 50 mL methanol). The bioassays were evaluated by counting the number of ants feeding at each piece of prey 15 min after starting of the experiment. Statistical evaluation of the tests was made using the χ^2 test for pair-wise comparison of the number of ants ($p < 0.05$).

*2,2-Difluorotridecane (**2**)*

To a solution of **1** (6.0 g, 3.0 mmol) in dry dichloromethane (20 mL) a solution of DAST (5.0 g, 3.1 mmol) in dichloromethane (10 mL) was added at 25 °C. Stirring at 25 °C was continued for another 12 d (reaction monitored by TLC, silica gel, hexane-ethyl acetate 9 : 1). The reaction was then stopped by the slow addition of ice water (25 mL). The layers were separated, and the organic layer was dried over $MgSO_4$. The solvent was removed, and the crude product was distilled and purified by chromatography (silica gel, hexane-ethyl acetate, 20 : 1) to yield **2** (4.3 g, 64 %) as a colorless liquid. – B. p. 113 – 115 °C/4 torr. – IR (film): ν = 3003m, 2926s, 2885s, 1467m, 1391s, 1317w, 1241m, 1183m, 1141m, 1115m, 1055w cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, ^3J = 6.99 Hz, 3 H, CH_3), 1.24 – 1.30 (m, 16 H, 8× CH_2), 1.41 – 1.45 (m, 2 H, CH_2), 1.56 (t, $^3J_{H,F}$ = 18.79 Hz, 3 H, CH_3), 1.75 – 1.85 (m, 2 H, CH_2). – ^{13}C NMR (500 MHz, $CDCl_3$): δ = 14.13 (CH_3), 22.76 (CH_2), 22.84 (t, $^3J_{C,F}$ = 4.81 Hz, $CH_2CH_2CF_2$), 23.21 (t, $^2J_{C\text{-}F}$ = 28.0 Hz, CF_2CH_3), 29.42 (CH_2), 29.44 (CH_2), 29.48 (CH_2), 29.56 (CH_2), 29.69 (CH_2), 29.70 (CH_2), 31.99 (CH_2), 38.06 (t, $^2J_{C,F}$ = 25.3 Hz,CH_2CF_2), 124.31 (t, $^1J_{C,F}$ = 237.0 Hz, CF_2). – ^{19}F NMR (470 MHz, $CDCl_3$): δ = −90.70 (sext, $^3J_{H,F}$ = 18.00 Hz). – MS (EI, 70 eV): m/z (%) = 43 (100), 57 (73), 65 (51), 69 (32), 82 (56), 85 (12), 96 (42), 110 (18), 111 (11), 124 (17), 138 (19), 151 (4), 163 (1), 180 (6), 201 (2), 220 (1). – $C_{13}H_{26}F_2$ (220.35): calcd. C 70.86, H 11.89; found C 70.65, H 12.07.

*1,1,1-Trifluorotridecan-2-one (**4**)*

From dodecanoyl chloride and trifluoroacetic anhydride

To a solution of trifluoroacetic anhydride (10 mL, 71.0 mmol) in dry diethyl ether (110 mL), at 0 °C dodecanoyl chloride (5) (62.8 mL, 12.0 mmol) and pyridine (8 mL, 95.0 mmol) were added. The reaction mixture was stirred at 20 °C for 2 h (TLC monitoring, silica gel, hexane-ethyl acetate 9 : 1), water (40 mL) was added, and stirring was continued until the evolution of carbon dioxide had ceased. The reaction mixture was then poured into water (550 mL) and extracted with diethyl ether (4 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ solution (100 mL), water (50 mL), brine (50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was distilled to yield 4 (2.5 g, 82 %) as a colorless liquid. – B. p. 103 – 104 °C/5 torr. – IR (film): ν = 2927s, 2856s, 1765s, 1468w, 1405w, 1378w, 1293w, 1209m, 1150m, 1030w cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.87 (t, ^{3}J = 6.92 Hz, 3 H, CH_3), 1.25 (m, 16 H, 8× CH_2), 1.66 (quint., ^{3}J = 7.21 Hz, 2 H, CH_2), 2.69 (t, ^{3}J = 7.30 Hz, 2 H, CH_2). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.01 (CH_3), 22.41 (CH_2), 22.68 (CH_2), 28.76 (CH_2), 29.20 (CH_2), 29.33 (CH_2), 29.37 (CH_2), 29.56 (CH_2), 29.59 (CH_2), 31.92 (CH_2), 36.35 (CH_2), 115.62 (q, $^1J_{C,F}$ = 292.0 Hz, CF_3), 191.56 (q, $^2J_{C,F}$ = 35.0 Hz, C=O). – ^{19}F NMR (470 MHz, $CDCl_3$): δ = −79.93 (s). – MS (EI, 70 eV): m/z (%) = 57 (100), 70 (50), 84 (36), 97 (30), 111 (12), 139 (9), 153 (8), 183 (22), 209 (3), 223 (3), 252 (3). – $C_{13}H_{23}F_3O$ (252.32): calcd. C 61.88, H 9.19; found C 61.51, H 9.32.

From ethyl trifluoroacetate and undecyl bromide

To a solution of ethyl trifluoroacetate (14.0 g, 10.0 mmol) in diethyl ether (110 mL) kept at −78 °C, undecyl magnesium bromide [prepared from undecyl bromide (**3**), 24 g, 10.0 mmol) and magnesium (2.4 g, 10.0 mmol) in diethyl ether (200 mL)] was slowly added. The reaction was stirred for an additional 5 h at −40 °C. The mixture was quenched with 1 N HCl, the organic layer was separated, washed with brine (50 mL) and dried over $MgSO_4$. The solvent was removed, and the crude product was purified by distillation followed by chromatography (silica gel, hexane-ethyl acetate, 9 : 1) to afford **4** (13.6 g, 55 %) as a colorless liquid. – $C_{13}H_{23}F_3O$ (252.32): calcd. C 61.88, H 9.19; found C 61.76, H 9.28.

*9-Decenyl acetate (**7**)*

A mixture of freshly distilled acetic anhydride (11.6 g, 115.2 mmol), 9-decen-1-ol (**6**) (18.0 g, 115.2 mmol) and dry pyridine (11.0 g, 138.2 mmol) was boiled under reflux for 3 h. The reaction mixture was poured into ice water (35 mL) and acidified with HCl (10 %) The aq. phase was extracted with diethyl ether (4 × 30 mL). The combined organic phases were washed with HCl (200 mL, 10 %), $NaHCO_3$ solution (100 mL), water (50 mL), and finally dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was distilled to yield **7** (20.7 g, 91 %) as a colorless liquid. – B. p. 102 °C/3 torr (lit.: 50 – 51 °C/0.01 [29], 95 – 97 °C/ 0.9 torr [33]). – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (brs, 10 H, 5× CH_2), 1.60 (t, ^3J = 6.64 Hz, 2 H, CH_2), 1.97 – 2.02 (m, 5 H, CH_2 + CH_3), 4.03 (t, ^3J = 6.64 Hz, 2 H, CH_2) 4.89 – 5.02 (m, 2 H, CH_2), 5.69 – 5.89 (m, 1 H, CH). – ^{13}C NMR (125 MHz, $CDCl_3$):

δ = 20.83 (CH_3), 25.81 (CH_2), 28.52 (CH_2), 28.79 (CH_2), 28.92 (CH_2), 29.10 (CH_2), 29.25 (CH_2), 33.66 (CH_2), 64.43 (O-CH_2), 113.98 (CH=CH_2), 138.81 (CH=CH_2), 170.79 (C=O). – MS (EI, 70 eV): m/z (%) = 55 (100), 68 (87), 82 (69), 96 (50), 109 (24), 138 (14), 198 (2).

*12,12,12-Trifluoro-9-iodododecyl acetate (**8**)*

In a safety steel autoclave (Parr), previously purged with argon, **7** (10.6 g, 53.6 mmol), trifluoroethyl iodide (13.5 g, 60.3 mmol) and dibenzoyl peroxide (DBPO; 0.26 g, 1.1 mmol) were heated in an oil bath to 95 °C. After 3 h at this temperature, the autoclave was cooled and opened. Additional portions of DBPO (0.26 g, 1.1 mmol) and trifluoroethyl iodide (1 g, 4.8 mmol) were added, and the autoclave was heated again for 3 h. This operation was repeated once more for another 3 h, and finally, after a fourth portion of DBPO had been added, for 6 h. The autoclave was then cooled, and the solution was filtered, washed with $NaHCO_3$ solution (100 mL) and water (50 mL), and finally dried over $MgSO_4$. The crude product **8** (15.1 g, 69 %) was used without purification; colorless liquid. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.26 – 1.37 (m, 10 H, 5× CH_2), 1.50 – 1.59 (m, 3 H), 1.93 – 2.01 (m, 6 H), 2.10 – 2.45 (m, 2 H), 3.54 (q, ^3J = 9.68 Hz, 1 H), 4.00 (t, ^3J = 6.64 Hz, 2 H). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.79 (CH_3), 25.86 (CH_2), 28.41 (CH_2), 29.36 (CH_2), 29.37 (CH_2), 29.41 (CH_2), 29.69 (CH_2), 30.04 (q, $J_{C,F}$ = 2.8 Hz, CHI), 31.3 (q, $J_{C,F}$ = 28.0 Hz, CH_2), 35.01 (q, $J_{C,F}$ = 5.6 Hz, CH_2), 126.41 (q, $J_{C,F}$ = 286.1 Hz, CF_3). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −67.13 (t, $^3J_{H,F}$ = 10.71 Hz).

*12,12,12-Trifluorododecan-1-ol (**9**)*

A solution of **8** (15.1 g, 37.0 mmol) in diethyl ether (40 mL) was added dropwise to a suspension of $LiAlH_4$ (4.2 g, 115.0 mmol) in diethyl ether (75 mL). After heating under reflux for 9 h, the reaction was quenched by the successive addition of water (4 mL), NaOH solution (4 mL, 15 %) and water (10 mL). The resulting granular salts were filtered off and washed with diethyl ether (4 × 20 mL). The ether solution was dried over $MgSO_4$, the solvent was removed, and crude **9** was subjected to chromatography (silica gel, hexane-ethyl acetate, 2 : 1) to yield **9** (5.54 g, 63 %) as a solid. – M. p. 39 – 41 °C (lit.: 42 °C [40], 27 °C [41]). – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 – 1.37 (m, 14 H, 7× CH_2), 1.46 – 1.54 (m, 4 H, 2× CH_2), 1.95 – 2.05 (m, 2 H, CH_2), 2.31 (brs, 1 H, OH), 3.57 (t, ^3J = 6.64 Hz, 3 H, CH_3). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.77 (q, $^3J_{C,F}$ = 3.0 Hz, $CF_3CH_2CH_2$), 25.68 (CH_2), 28.61 (CH_2), 29.09 (CH_2), 29.26 (CH_2), 29.35 (CH_2), 29.40 (CH_2), 29.48 (CH_2), 29.50 (CH_2), 33.65 (q, $^2J_{C,F}$ = 28.0 Hz, CF_3CH_2), 62.80 (CH_2OH), 127.00 (q, $^1J_{C,F}$ = 276.0 Hz, CF_3). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −67.11 (t, $^3J_{H,F}$ = 10.73 Hz). – MS (EI, 70 eV): m/z (%) = 55 (100), 69 (64), 83 (41), 97 (18), 111 (5), 124 (3), 138 (9), 152 (12), 166 (9), 180 (5), 194 (17), 222 (6), 240 (1). – $C_{12}H_{23}F_3O$ (240.31): calcd. C 59.98, H 9.64; found C 59.71, H 9.83.

*12,12,12-Trifluorododecanal (**10**)*

A solution of **9** (2.3 g, 9.5 mol) in dichloromethane (2 mL) was added dropwise to a stirred suspension of PCC (3.2 g, 14.6 mmol) in anhydrous dichloromethane (20 mL). After stirring for 2 h, dry diethyl ether (20 mL) was added, and the supernatant liquid was decanted from a black gum. The insoluble residue was washed with dry diethyl ether (3 × 10 mL), and the combined organic solutions were passed through a short pad of silica gel. The solvent was evaporated, and the crude product was distilled to yield **10** (1.4 g, 60 %) as a colorless liquid. – IR (film): ν = 2921s, 2854s, 1699s, 1467s, 1433s, 1412s, 1391m, 1247s, 1144s, 1052m cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (brs, 12 H, 6× CH_2), 1.49 – 1.54 (m, 2 H, CH_2), 1.60 (t, ^3J = 7.22 Hz, 2 H, CH_2), 1.98 – 2.08 (m, 2 H, CH_2), 2.40 (td, $^3J_{H,H}$ = 7.20 Hz, $^4J_{H,H}$ = 1.91 Hz, 2 H, CH_2), 9.74 (t, $^4J_{H,H}$ = 1.91 Hz, 1 H, CHO). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.81 (q, $^3J_{C,F}$ = 2.7 Hz, $CF_3CH_2CH_2$), 28.65 (CH_2), 29.00 (CH_2), 29.12 (CH_2), 29.16 (CH_2), 29.24 (CH_2), 29.28 (CH_2), 29.34 (CH_2), 29.37 (CH_2), 33.71 (q, $^2J_{C,F}$ = 28.1 Hz, CF_3CH_2), 127.29 (q, $^1J_{C,F}$ = 276.2 Hz, CF_3), 200.00 (CHO). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −67.17 (t, $^3J_{H,F}$ = 10.76 Hz). – $C_{12}H_{21}F_3O$ (238.30): calcd. C 60.48, H 8.88; found C 60.31, H 8.93.

*13,13,13-Trifluorotridecan-2-ol (**11**)*

To a solution of **10** (1.4 g, 5.7 mmol) in diethyl ether (2 mL), a solution of methyl magnesium iodide [freshly prepared from methyl iodide (1.2 g, 8.1 mmol) and magnesium turnings (0.3 g, 10.0 mmol) in diethylether (3 mL)] was added, and the mixture was heated under reflux for 3 h. Usual aqueous work-up followed by chromatography (silica gel hexane-ethyl acetate, 7 : 1) afforded **11** (1.12 g, 75 %) as a colorless liquid. – ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.15 (d, $^3J_{H,H}$ = 6.02 Hz, 3 H, CH_3), 1.26 (brs, 16 H, 8× CH_2), 1.34 – 1.55 (m, 2 H, CH_2), 1.90 – 2.15 (m, 2 H, CH_2), 3.76 (dt, ^3J = 6.05 Hz, 1 H, CH). – ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.98 (CH_2), 23.73 (CH_2), 29.00 (CH_2), 29.11 (CH_3), 29.31 (CH_2), 29.42 (CH_2), 29.53 (q, $J_{C,F}$ = 2.1 Hz, CH_2), 29.56 (CH_2), 29.91 (CH_2), 31.10 (q, $J_{C,F}$ = 28.4 Hz, CH_2), 43.73 (CH_2), 125.10 (q, $J_{C,F}$ = 276.2 Hz, CF_3), 208.71 (CHO). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −67.18 (t, $^3J_{H,F}$ = 10.71 Hz). – $C_{13}H_{25}F_3O$ (254.34): calcd. C 61.39, H 9.91; found C 61.22, H 10.03.

*13,13,13-Trifluorotridecan-2-one (**12**)*

Oxidation of **11** (0.9 g, 3.5 mmol) with PCC (0.9 g, 3.5 mmol) in dichloromethane (2 mL) for 1 h as described

above followed by usual work-up and bulb-to-bulb distillation afforded **12** (0.64 g, 72 %) as a colorless liquid. – IR (film): ν = 2929s, 2857s, 1718s, 1465m, 1440m, 1388m, 1361m, 1336w, 1255s, 1135m, 1099m, 1038m cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 1.25 (brs, 14 H, 7× CH_2), 1.45 – 1.56 (m, 2 H, CH_2), 1.97 – 2.08 (m, 2 H, CH_2), 2.11 (s, 3 H, CH_3), 2.39 (t, ^3J = 7.27 Hz, 2 H, CH_2). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.83 ($CF_3CH_2CH_2$), 21.86 (CH_2), 23.86 (CH_2), 28.68 (CH_2), 28.86 (CH_2), 29.15 (CH_2), 29.28 (CH_2), 29.34 (CH_2), 29.80 (CH_3), 33.74 (q, $^2J_{C,F}$ = 28.43 Hz, CF_3CH_2), 43.77 (CH_2-CO), 127.25 (q, $^1J_{C,F}$ = 275.91 Hz, CF_3), 209.06 (C=O). – ^{19}F NMR (188 MHz, $CDCl_3$): δ = −67.11 (t, $^3J_{H,F}$ = 10.75 Hz). – MS (EI, 70 eV): m/z (%) = 58 (100), 69 (5), 71 (46), 77 (4), 85 (9), 91 (3), 99 (2), 113 (2), 127 (2), 139 (1), 153 (2), 165 (2), 192 (7), 209 (2), 237 (3), 252 (10). – $C_{13}H_{23}F_3O$ (252.32): calcd. C 61.88, H 9.19; found C 61.67, H 8.97.

*1,1,1-Trifluoro-2-tetradecanone (**14**)*

To a solution of ethyl trifluoroacetate (9.7 g, 6.8 mmol) in diethyl ether (75 mL), dodecyl magnesium bromide in diethyl ether (140 mL) [prepared from dodecyl bromide (**13**), 16.1 g, 6.8 mmol) and magnesium (1.7 g, 6.8 mmol)] was slowly added at −78 °C. After stirring at −40 °C for an additional 5 h, the mixture was quenched with 1 N HCl, the organic layer was separated, washed with brine (50 mL), and dried over $MgSO_4$. The solvent was removed, and the crude product was purified by distillation and chromatography (silica gel, hexane-ethyl acetate, 9 : 1) to yield **14** (13.6 g, 75 %) as a colorless liquid. – B. p. 103 – 104 °C/4 torr (lit.: 95 – 96 °C/2 torr [22], 113 – 114 °C/6 torr [47]). – IR (film): ν = 2926s, 2856s, 1766s, 1468m, 1405w, 1379w, 1291m, 1209s, 1150s, 1035m cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, $^3J_{H,H}$ = 6.82 Hz, 3 H, CH_3), 1.25 (m, 18 H, 9× CH_2), 1.65 (m, $^3J_{H,H}$ = 7.20 Hz, 2 H, CH_2), 2.68 (t, $^3J_{H,H}$ = 7.30 Hz, 2 H, CH_2). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.12 (CH_3), 22.49 (CH_2), 22.73 (CH_2), 24.40 (CH_2), 28.82 (CH_2), 29.23 (CH_2), 29.38 (CH_2), 29.40 (CH_2), 29.59 (CH_2), 29.66 (CH_2), 31.97 (CH_2), 36.41 (CH_2), 115.59 (q, $^1J_{C,F}$ = 292.0 Hz, CF_3), 191.47 (q, $^2J_{C,F}$ = 34.7 Hz, C=O). – ^{19}F NMR (200 MHz, $CDCl_3$): δ = −80.02 (s). – MS (EI, 70 eV): m/z (%) = 43 (100), 57 (73), 69 (54), 83 (32), 97 (27), 115 (15), 125 (9), 139 (17), 153 (13), 163 (7), 177 (4), 191 (3), 197 (33), 209 (3), 223 (2), 238 (1), 266 (1). – $C_{14}H_{25}F_3O$ (266.35): calcd. C 63.13, H 9.46; found C 63.39, H 9.53.

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[1] D. J. Gubler, *Rev. Sci. Tech.* **2009**, *28*, 583 – 588.
[2] A. R. Katritzky, Z. Wang, S. Slavov, M. Tsikolia, D. Dobchev, N. G. Akhmedov, C. D. Hall, U. R. Bernier, G. G. Clark, K. J. Linthicum, *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 7359 – 7364.
[3] E. Innocent, N. K. Gikonyo, M. H. Nkunya, *Tanzan. J. Health Res.* **2008**, *10*, 50 – 54.
[4] J. T. Welch, S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, **1991**.
[5] C. Walsh, *Adv. Enzymol.* **1983**, *55*, 197 – 289.
[6] B. Imperiali, *Adv. Biotechnol. Processes* **1988**, *10*, 97 – 129.
[7] R. H. Abeles, T. A. Alston, *J. Biol. Chem.* **1990**, *265*, 16705 – 16708.
[8] M. Chabre, *Trends Biochem.* **1990**, *15*, 6 – 10.
[9] J. -P. Begue, D. Bonnet-Delpon, *Tetrahedron* **1991**, *47*, 3207 – 3258.
[10] A. Parrilla, I. Villuendas, A. Guerrero, *Bioorg. Med. Chem.* **1994**, *2*, 243 – 252.
[11] M. Debboun, S. P. Frances, D. Strickman, *Insect Repellents - Principles, Methods, Uses*, CRC Press, Boca Raton, FL **2006**.
[12] B. W. Bissinger, R. M. Roe, *Pesticide Biochem. Physiol.* **2010**, *96*, 63 – 79.
[13] G. Antonious, J. Snyder, *J. Environ. Sci. Health, Part B* **2006**, *41*, 43 – 55.
[14] G. F. Antonious, *J. Environ. Sci. Health, Part B* **2001**, *B36*, 835 – 848.
[15] G. F. Antonious, D. L. Dahlman, L. M. Hawkins, *Bull. Environ. Contam. Toxicol.* **2003**, *71*, 400 – 407.
[16] G. F. Antonious, J. C. Snyder in *Tomatoes and Tomato Products – Nutritional, Medicinal and Therapeutic Properties*, (Eds.: V. R. Preedy, R. R. Watson), Science Publishers, Enfield, NH **2008**, pp. 269 – 297; *CAPLUS* **2009**, 149343.
[17] R. M. Roe, US 20040242703A1, **2004**; *CAPLUS* **2004**, 1036725.
[18] R. M. Roe, US 6437001B1, **2002**; *CAPLUS* **2002**, 632805.
[19] R. M. Roe, A. L. Jones, Jr., WO 2009002485A2, **2008**; *CAPLUS* **2008**, 1548964.
[20] T. Umemoto, Y. Xu, US 7265247B1, **2007**; *Chem. Abstr.* **2007**, *147*, 322721.
[21] W. J. Middleton, *J. Org. Chem.* **1975**, *40*, 574 – 578.
[22] S. Watanabe, T. Fujita, M. Sakamoto, H. Hamano, T. Kitazume, T. Yamazaki, *J. Fluorine Chem.* **1997**, *83*, 15 – 19.
[23] D. L. Boger, H. Sato, A. E. Lerner, B. J. Austin, J. E. Patterson, M. P. Patricelli, B. F. Cravatt, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 265 – 270.
[24] L. Munoz, E. Rosa, M. P. Bosch, A. Guerrero, *Tetrahedron Lett.* **2005**, *46*, 3311 – 3313.

[25] D. Leung, W. Du, C. Hardouin, H. Cheng, I. Hwang, B. F. Cravatt, D. L. Boger, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1423 – 1428.
[26] J. Boivin, L. Elkaim, S. Z. Zard, *Tetrahedron* **1995**, *51*, 2573 – 2584.
[27] J. Boivin, L. Elkaim, S. Z. Zard, *Tetrahedron* **1995**, *51*, 2585 – 2592.
[28] G. Johansson, V. Percec, G. Ungar, J. P. Zhou, *Macromolecules* **1996**, *29*, 646 – 660.
[29] M. Gardette, A. Alexakis, J. F. Normant, *Tetrahedron* **1985**, *41*, 5887 – 5899.
[30] R. Winter, P. G. Nixon, G. L. Gard, D. H. Radford, N. R. Holcomb, D. W. Grainger, *J. Fluorine Chem.* **2001**, *107*, 23 – 30.
[31] G. Y. Ishmuratov, R. Y. Kharisov, M. P. Yakovleva, O. V. Botsman, R. I. Galeeva, N. M. Ishmuratova, G. A. Tolstikov, *Russ. Chem. Bull.* **1998**, *47*, 1595 – 1597.
[32] S. C. Ats, J. Lehmann, S. Petry, *Carbohydr. Res.* **1992**, *233*, 125 – 139.
[33] H. J. Bestmann, W. Stransky, O. Vostrowsky, P. Range, *Chem. Ber.* **1975**, *108*, 3582 – 3595.
[34] P. Schnurrenberger, M. F. Zueger, D. Seebach, *Helv. Chim. Acta* **1982**, *65*, 1197 – 1201.
[35] K. E. Murphy, A. H. Hoveyda, *J. Am. Chem. Soc.* **2003**, *125*, 4690 – 4691.
[36] B. R. Travis, R. S. Narayan, B. Borhan, *J. Am. Chem. Soc.* **2002**, *124*, 3824 – 3825.
[37] G. Takeuchi, M. Weiss, A. G. Harrison, *Anal. Chem.* **1987**, *59*, 918 – 921.
[38] R. Cloux, E. S. Kovats, *Synthesis* **1992**, 409 – 412.
[39] A. H. Andrieu, H. Blancou, A. Commeyras, Fr. Demande 2613357A1, **1988**; *Chem. Abstr.* **1989**, *111*, 133341.
[40] C. Gu, V. H. Wysocki, A. Harada, H. Takaya, I. Kumadaki, *J. Am. Chem. Soc.* **1999**, *121*, 10554 – 10562.
[41] C. L. Claypool, F. Faglioni, W. A. Goddard, III, H. B. Gray, N. S. Lewis, R. A. Marcus, *J. Phys. Chem. B* **1997**, *101*, 5978 – 5995.
[42] R. J. Koshar, H. A. Brown, US 3359131, **1967**; *CAPLUS* **1968**, 50896.
[43] C. E. Wheelock, Y. Nakagawa, M. Akamatsu, B. D. Hammock, *Bioorg. Med. Chem.* **2003**, *11*, 5101 – 5116.
[44] M. Riba, A. Sans, P. Bau, G. Grolleau, M. Renou, A. Guerrero, *J. Chem. Ecol.* **2001**, *27*, 1879 – 1897.
[45] L. E. Dyer, C. D. Dodson, G. Gentry, *Phytochem. Anal.* **2003**, *14*, 381 – 388.
[46] M. Riba, J. Sole, A. Sans, G. Rosell, E. Rosa, L. Munoz, M. P. Bosch, A. Guerrero, *Chemoecology* **2008**, *18*, 99 – 108.
[47] I. I. Lapkin, E. V. Dormidontova, Y. P. Dormidontov, *Zh. Org. Khim.* **1970**, *6*, 241 – 243.