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Replacing the carbonyl's oxygen with the difluoromethyl group

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ABSTRACT

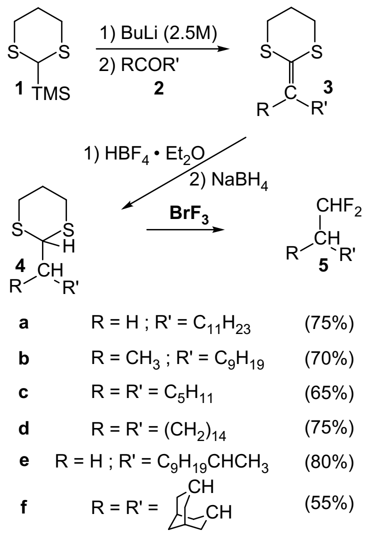
Aldehydes or ketones were reacted with 2-(trimethylsilyl)-1,3-dithiane (**1**) and the products reduced to the corresponding dithianes using tetrafluoroboric acid and sodium borohydride. These sulfur containing compounds were reacted with bromine trifluoride under mild conditions (1–2 min, 0 °C) with a net result of replacing the carbonyls' oxygen with the desired difluoromethyl moiety.

1. Introduction

The difluoromethyl group is extensively sought after in medicinal chemistry,[1] agro-chemistry,[2] anesthetics,[3] sugar chemistry,[4] and more. Similar to the CF_3 group it enjoys high lipophilicity and stability, helping drugs to penetrate lipids and prolong their lifetime in the body. In some respects it can be even better than the trifluoromethyl group since it has reduced steric demands and can form hydrogen bonds.[5] Still, there are not many methods for constructing this group while placing it in specific sites of organic molecules can be an additional challenge. Today the most common route relies on reacting suitable aldehydes with SF_4 or DAST.[6] Adding CF_2Br_2 to double bonds has also been recorded,[7] and in certain cases the use of a source of electrophilic bromine such as NBS or DBH along with a source of nucleophilic fluorine atoms as HF or some of its variations can be employed.[8]

In the past we have used interhalogen reagents such as IF, BrF, and BrF_3 to convert carbonyls to the corresponding CF_2 group via their hydrazone,[9] thioester[10] or dithiane derivatives.[11] A synthesis leading to the CHF_2 moiety from alkyl halides using BrF_3 was also developed.[12] We report here yet another transformation based on aldehydes or ketones resulting in replacing their oxygen atom with both hydrogen and difluoromethyl groups using BrF_3 as a source for the fluorine atoms. The key step of the reaction is treating the carbonyl compounds with 2-(trimethylsilyl)-1,3-dithiane (**1**), reducing the resulting ketene dithioacetals **3** and reacting the dithiane containing product **4** with BrF_3 (Scheme 1).

Bromine trifluoride has been occasionally used in the past. In organic chemistry it has been extensively used for constructing anesthetics,[3] but it was also employed in reactions such as the preparation of hexafluorocyclopentadiene,[13] hypervalent elements in organic derivatives,[14] and more. We have used it as a very potent electrophilic brominating agent,[15] as a tool for transforming nitriles to the corresponding CF_3 moiety,[16] carbonyls to CF_2 moieties,[11,17] and primary alcohols and carboxylic acids into acyl fluorides.[18] This reagent was also instrumental in the synthesis of trifluoromethyl ethers,[19] trifluoromethyl alkanes,[20] OCF_2O moieties,[21] and much more.[22] Since the bromine atom in BrF_3 is a soft acid most of the fluorinations were performed around soft bases such as nitrogen or sulfur atoms, which complex the reagent and place the nucleophilic fluorides in a position for selective substitutions.[23] There are, of course, certain limitations associated with this very reactive agent such as limited choice of solvents (see Experimental section), immediate bromination of activated aromatics,[25] and fast reactions with various double bonds.[24]



Scheme 1. Attachment of difluoromethyl group to the carbonyl carbon.

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2. Results and discussion

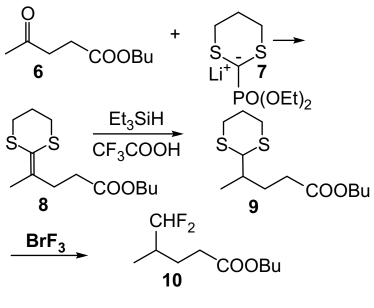
2-(Trimethylsilyl)-1,3-dithiane (**1**) is readily available either commercially or through a simple preparation using 1,3-dithiane and trimethylsilyl chloride.[25] Its lithium salt reacts with aldehydes and ketones (**2**) to form ketene dithioacetals (**3**),[26] which can be reduced with tetrafluoroboric acid and sodium borohydride to the corresponding 2-alkyl-1,3-dithianes (**4**) (Scheme 1).[27]

Dodecanal (**2a**) was thus converted to 2-dodecyl-1,3-dithiane (**4a**),[28] which in its turn was reacted for 1 min with 2.5 mol equiv of BrF_3 at 0 °C forming 1,1-difluorotridecane (**5a**) in 75% yield.[29] The reaction is not limited to aldehydes. The ketones 2- and 6-undecanone (**2b** and **2c**) were reacted with the anion of **1** forming the dithianes **4b** and **4c**. These sulfur containing derivatives were reacted with BrF_3 to form the previously unknown 1,1-difluoro-2-methylundecane (**5b**) and 1,1-difluoro-2-pentylheptane (**5c**) in 70% and 65% yield, respectively (Scheme 1).

Macrocyclic molecules could also serve as substrates for this process as demonstrated by cyclopentadecanone (**2d**). Its dithiane derivative (**4d**) was successfully converted to difluoromethyl cyclopentadecane (**5d**) in 75% yield.

Although mainly a source for powerful naked nucleophilic fluorides, in certain cases bromine trifluoride can change the role of its fluorine atoms to act as electrophiles. This is especially true when tertiary hydrogen atoms are present[13,30] in reactions resembling the ones with F_2.[31] However, when the dithiane moiety is at hand, the nucleophilic character dominates the reaction. The branched 2-methyl undecanal (**2e**) and 2-adamantanone (**2f**), both possessing tertiary hydrogens, were converted to their dithiane derivatives **4e** and **4f**[32] that when reacted with BrF_3 gave 1,1-difluoro-3-methyldodecane (**5e**) and 2-difluoromethyladamantane (**5f**) in 80% and 55% yields, respectively.

It was of interest to see if it is possible to accomplish selectively this transformation when additional ester's carbonyl is present. Butyl 3-oxopentanoate (**6**) served us as a model compound. For the preparation of the appropriate ketene dithioacetal (**8**), we used the lithium salt of diethyl (1,3-dithiane-2-yl) phosphonate (**7**) in order to avoid reactions at the α-position of the carboxylic acid.[33] The ketene **8** was then reduced to the desired dithiane **9** using triethylsilane and trifluoroacetic acid, a procedure which did not affect the ester moiety.[34] Reacting **9** with BrF_3 afforded the desired difluoromethyl moiety **10** in 80% yield (Scheme 2).



Scheme 2. Replacing the carbonyl's oxygen with CHF_2 group in compounds that possess an ester moiety.

In conclusion, the above reactions offer a general method for reductive conversion of the carbonyl's oxygen of either aldehydes or ketones to the difluoromethyl group in a fast reaction conducted under mild conditions.

3. Experimental section

3.1. General

^1H NMR spectra were recorded using a 200 MHz spectrometer with $CDCl_3$ as a solvent and Me_4Si as an internal standard. The ^{19}F NMR spectra were measured at 188.1 MHz using $CFCl_3$ as an internal standard. The proton broadband decoupled ^{13}C NMR spectra were recorded at 100.5 MHz. Here too, $CDCl_3$ served as a solvent and Me_4Si as an internal standard. IR spectra were recorded either neat or in chloroform solution on a FTIR spectrophotometer. Since the molecular ion of the final difluoromethyl products could not be detected by any standard MS machine we used Amirav's supersonic GC–MS, which revealed the molecular ion without any difficulties.[35]

3.2. Preparation and handling of BrF_3

Although commercially available, we usually prepare BrF_3 by passing 0.6 mol fluorine through 0.2 mol of bromine placed in a copper reactor and held at temperatures between 0 and +10 °C. Under these conditions pure bromine trifluoride is obtained (can be checked either by its melting point or boiling point) and the higher oxidation state of bromine, BrF_5, will not be formed in any appreciable amount.[36] The reagent can be stored in Teflon® containers indefinitely. *BrF_3 is a strong oxidizer and tends to react very exothermically with water and oxygenated organic solvents such as acetone or THF. Alkanes, like petrol ether, cannot serve as solvents either since they also react quickly with BrF_3. Solvents such as $CHCl_3$, CH_2Cl_2, $CFCl_3$ or, if solubility is not an issue, any perfluoroalkane or perfluoroether can be used. Any work using BrF_3 should be conducted in a well ventilated area and caution and common sense should be exercised.*

3.3. General procedure for the synthesis of ketene dithioacetals (3a–f)

2-Trimethylsilyl-1,3-dithiane (4.81 g, 25 mmol) was dissolved in dry THF (50 mL) under nitrogen. The solution was cooled to −78 °C and BuLi (12 mL, 30 mmol) was added. The reaction mixture was allowed to warm up to 0 °C over 5 h. It was then recooled to −78 °C and the carbonyl derivative (30 mmol) was added. The solution was stirred overnight allowed to warm up to room temperature, poured into water (50 mL), and extracted with CH_2Cl_2 (50 mL). The combined organic phases were dried over $MgSO_4$, the solvent evaporated, and the crude residue was subjected to flash chromatography (using petroleum ether as eluent). We have not attempted to obtain analytically pure samples, but the above procedure provided samples clean enough for the next reductive step.

3.3.1. *2-Dodecylidene-1,3-dithiane (**3a**)*

Compound **3a** was prepared from dodecanal (5.53 g) as described above in 80% yield as a waxy solid. R_f (petroleum ether) 0.24; δ_H 5.96 (1H, t, J=7 Hz), 2.92–2.78 (4H, m), 2.29–2.07 (4H, m), 1.48–1.08 (18H, br s), 0.88 (3H, t, J=7 Hz) ppm; δ_C 135.8, 125.9, 32.7, 31.2, 30.5, 30.4, 30.3, 30.2, 30.1, 30.0, 29.9, 29.7, 26.1, 23.4, 14.9 ppm; IR 2923, 2852, 1691, 1464, 1377, 1263, 1126, 1031 cm^{-1}; HRMS (CI): $(M+1)^+$, found 287.1898. $C_{16}H_{31}S_2$ requires 287.1867.

3.3.2. *2-(1-Methyl-decylidene)-1,3-dithiane (**3b**)*

Compound **3b** was prepared from 2-undecanone (5.11 g) as described above in 80% yield as a colorless oil. R_f (petroleum ether) 0.35; δ_H 2.90–2.80 (4H, m), 2.37–2.30 (2H, m), 2.16–2.07 (2H, m), 1.90 (3H, s), 1.43–1.15 (14H, m), 0.88 (3H, t, J=7 Hz) ppm; δ_C 141.3, 118.6, 35.9, 31.8, 30.2, 30.1, 29.5, 29.3, 29.2, 27.8, 25.0, 22.6, 20.1, 14.0 ppm; IR 2924, 2853, 1457, 1275 cm^{-1}; HRMS (CI): $(M-1)^+$, found 271.1550. $C_{15}H_{27}S_2$ requires 271.1554.

3.3.3. *2-(1-Pentyl-hexylidene)-1,3-dithiane (**3c**)*

Compound **3c** was prepared from 6-undecanone (5.11 g) as described above in 60% yield as a colorless oil. R_f (petroleum ether) 0.24; δ_H 2.91–2.78 (4H, m), 2.42–2.22 (4H, m), 2.19–2.03 (2H, m), 1.48–1.15 (12H, m), 0.89 (6H, t, J=7 Hz) ppm; δ_C 146.3, 119.2, 33.8, 31.7, 30.4, 27.9, 25.1, 22.4, 14.0 ppm; IR 2927, 2855, 1457, 1274 cm^{-1}; HRMS (CI): (M)$^+$, found 272.1641. $C_{15}H_{28}S_2$ requires 272.1632.

3.3.4. *2-Cyclopentadecylidene-1,3-dithiane (**3d**)*

Compound **3d** was prepared from cyclopentadecanone (6.73 g) as described above in 60% yield as a waxy solid. R_f (petroleum ether) 0.25; δ_H 2.88–2.81 (4H, m), 2.39–2.28 (4H, m), 2.16–2.07 (2H, m), 1.50–1.24 (24H, m) ppm; δ_C 147.3, 120.2, 35.2, 31.2, 28.5, 27.4, 27.3, 27.2, 27.0, 26.0 ppm; IR 2935, 2855, 1688, 1459, 1349, 1260 cm^{-1}; HRMS (CI): (M−1)$^+$, found 325.2002. $C_{19}H_{33}S_2$ requires 325.2024.

3.3.5. *2-(2-Methyl-undecylidene)-1,3-dithiane (**3e**)*

Compound **3e** was prepared from 2-methyl undecanal (5.53 g) as described above in 65% yield as a colorless oil. R_f (petroleum ether) 0.24; δ_H 5.76 (1H, d, J=10 Hz), 2.92–2.78 (4H, m), 2.78–2.58 (1H, m), 2.25–2.08 (2H, m), 1.36–1.17 (16H, br s), 0.95 (3H, d, J=7 Hz), 0.88 (3H, t, J=7 Hz) ppm; δ_C 141.4, 123.8, 36.9, 34.0, 31.8, 30.5, 29.8, 29.6, 29.5, 29.2, 27.2, 25.4, 22.6, 20.3, 14.0 ppm; IR 2924, 2853, 1684, 1457, 1276 cm^{-1}; HRMS (CI): (M)$^+$, found 286.1785. $C_{16}H_{30}S_2$ requires 286.1789.

3.3.6. *2-(2-Adamantanylidene)-1,3-dithiane (**3f**)*

Compound **3f** was prepared from 2-adamantanone (4.51 g) as described above in 80% yield as a colorless solid. Its physical properties fully matched the ones in the literature.[37]

3.4. General procedure for the reduction of ketene dithioacetals to dithianes (4a–f)

Tetrafluoroboric acid (3 mL, 54% in ether, 22 mmol) was added at room temperature to a stirred solution, or suspension, of a respective ketene dithioacetal (10 mmol) in dry acetonitrile (25 mL). A brown solution was obtained and after 30 min the solution was cooled to 0 °C and powdered sodium borohydride (0.7 g, 18.5 mmol) was gradually added. The resulting suspension was stirred overnight at room temperature, poured into an aqueous ammonium chloride solution (10%, 100 mL), and extracted with ether (100 mL). The combined organic phases were washed with water (50 mL), dried over Na_2SO_4, and filtered. Evaporation of the solvent followed by flash chromatography (using petroleum ether as eluent) gave the desired dithiane pure enough for the final fluorination step.

3.4.1. *2-Dodecyl-1,3-dithiane (**4a**)*

Compound **4a** was prepared from **3a** (2.87 g) as described above in 60% yield as a colorless oil. Its physical properties fully matched the ones in the literature.[28]

3.4.2. *2-(1-Methyl-decyl)-1,3-dithiane (**4b**)*

Compound **4b** was prepared from **3b** (2.73 g) as described above in 90% yield as a colorless oil. R_f (petroleum ether) 0.13; δ_H 4.14 (1H, d, J=4 Hz), 3.00–2.76 (4H, m), 2.19–2.02 (1H, m), 1.98–1.71 (2H, m), 1.42–1.13 (16H, br s), 1.07 (3H, d, J=7 Hz), 0.88 (3H, t, J=7 Hz) ppm; δ_C 55.5, 48.5, 33.9, 31.8, 31.1, 30.8, 29.6, 29.5, 29.2, 27.2, 26.3, 22.6, 16.9, 14.0 ppm; IR 2924, 2853, 1458, 1421, 1378, 1275, 1185 cm^{-1}; HRMS (CI): (M−1)$^+$, found 273.1692. $C_{15}H_{29}S_2$ requires 273.1711.

3.4.3. *2-(1-Pentyl-hexyl)-1,3-dithiane (**4c**)*

Compound **4c** was prepared from **3c** (2.73 g) as described above in 85% yield as a colorless oil. R_f (petroleum ether) 0.18; δ_H 4.23 (1H, d, J=4 Hz), 2.95–2.78 (4H, m), 2.14–2.06 (1H, m), 1.90–1.76 (1H, m), 1.69–1.50 (3H, m), 1.39–1.21 (14H, m), 0.89 (6H, t, J=7 Hz) ppm; δ_C 54.0, 43.7, 31.9, 31.1, 27.1, 26.4, 22.5, 14.0 ppm; IR 2927, 2856, 1457, 1275 cm^{-1}; HRMS (CI): (M)$^+$, found 274.1813. $C_{15}H_{30}S_2$ requires 274.1789.

3.4.4. *2-Cyclopentadecyl-1,3-dithiane (**4d**)*

Compound **4d** was prepared from **3d** (3.27 g) as described above in 85% yield as colorless oil. R_f (petroleum ether) 0.20; δ_H 4.16 (1H, d, J=4 Hz), 2.93–2.79 (4H, m), 2.14–2.05 (1H, m), 1.90–1.76 (1H, m), 1.74–1.54 (3H, m), 1.48–1.20 (26H, m) ppm; δ_C 54.7, 42.2, 31.0, 30.7, 27.2, 26.9, 26.6, 26.5, 26.4, 26.3, 25.8 ppm; IR 2927, 2855, 1459, 1421, 1350, 1275, 1183 cm^{-1}; HRMS (CI): (M)$^+$, found 328.2253. $C_{19}H_{36}S_2$ requires 328.2258.

3.4.5. *2-(2-Methyl-undecyl)-1,3-dithiane (**4e**)*

Compound **4e** was prepared from **3e** (2.87 g) as described above in 80% yield as colorless oil. R_f (petroleum ether) 0.12; δ_H 4.10 (1H, dd, J=8, 6 Hz), 3.01–2.72 (4H, m), 2.22–2.04 (1H, m), 1.99–1.63 (3H, m), 1.61–1.40 (2H, m), 1.38–1.08 (17H, br s), 0.96–0.82 (6H, m) ppm; δ_C 45.5, 42.5, 36.7, 31.8, 30.5, 30.3, 29.8, 29.5, 29.3, 26.7, 26.0, 22.6, 19.3, 14.0 ppm; IR 2924, 2853, 1458, 1377, 1274 cm^{-1}; HRMS (CI): (M−1)$^+$, found 287.1852. $C_{16}H_{31}S_2$ requires 287.1867.

3.4.6. *2-(2-Adamantanyl)-1,3-dithiane (**4f**)*

Compound **4f** was prepared from **3f** (2.53 g) as described above in 60% yield as a white solid. Its physical properties fully matched the ones in the literature.[32]

3.5. Experimental procedure for the synthesis of butyl 4-(1,3-dithian-2-ylidene)pentanoate (8)

Diisopropyl amine (8.50 mL, 60 mmol) in dry THF (70 mL) was cooled to −78 °C and BuLi (24 mL, 60 mmol) was added. After 30 min 1,3-dithiane (3.6 g, 30 mmol) in dry THF (10 mL) was added slowly at the same temperature and stirred for another 30 min followed by addition of diethyl chlorophosphate (4.4 mL, 30 mmol) in dry THF (10 mL). The reaction mixture was stirred for 1 h at −78 °C. Butyl 3-oxopentanoate (5.3 mL, 30 mmol) in dry THF (10 mL) was then added in one portion. The solution was allowed to warm up to room temperature and stirred overnight. Brine (50 mL) was added and the aqueous layer extracted with ether. The combined organic phases were dried over $MgSO_4$, the solvent evaporated, and the residue subjected to flash chromatography (using 2.5% ethyl acetate in petroleum ether as eluent). The desired product was obtained in 65% yield as a colorless oil. R_f (2.5% ethyl acetate/petroleum ether) 0.09; δ_H 4.08 (2H, t, J=7 Hz), 2.93–2.78 (4H, m), 2.73–2.59 (2H, m), 2.45–2.31 (2H, m), 2.19–2.02 (2H, m), 1.90 (3H, s), 1.70–1.52 (2H, m), 1.49–1.27 (2H, m), 0.93 (3H, t, J=7 Hz) ppm; δ_C 173.8, 138.1, 122.0, 65.1, 33.2, 31.9, 31.4, 30.8, 30.7, 25.5, 20.7, 19.9, 14.4 ppm; IR 2958, 1733, 1420, 1360, 1275, 1173, 1064 cm^{-1}; HRMS (CI): (M)$^+$, found 274.1089. $C_{13}H_{22}O_2S_2$ requires 274.1061.

3.6. Experimental procedure for the synthesis of butyl 4-(1,3-dithian-2-yl)pentanoate (9)

Triethylsilane (3.0 mL, 18.75 mmol), trifluoroacetic acid (7.5 mL, 100 mmol), and **8** (4.115 g, 15 mmol) were dissolved in CH_2Cl_2 (50 mL) at room temperature. The solution was stirred for 3 days. Saturated $NaHCO_3$ (100 mL) solution was added gradually, the aqueous phase extracted with CH_2Cl_2 (100 mL), and the combined organic phases dried over $MgSO_4$. Evaporation of the solvent followed by flash chromatography (using 5% ethyl acetate in petroleum ether as eluent) gave the desired product in 85% yield as a colorless oil. R_f (5% ethyl acetate/petroleum ether) 0.25; δ_H 4.13 (1H, d, J=4 Hz), 4.07 (2H, t, J=7 Hz), 2.93–2.80 (4H, m), 2.43–2.27 (2H, m), 2.15–2.06 (1H, m), 2.02–1.77 (3H, m), 1.73–1.55 (3H, m), 1.38 (2H, sextet, J=7 Hz), 1.10 (3H, d, J=7 Hz), 0.94 (3H, t, J=7 Hz) ppm; δ_C 173.3, 64.2, 54.8, 37.8, 32.0, 31.0, 30.7, 30.6, 29.1, 26.2, 19.0, 16.6, 13.6 ppm; IR 2959, 1733, 1457, 1421, 1275, 1177 cm^{-1}; HRMS (CI): (M)$^+$, found 276.1271. $C_{13}H_{24}O_2S_2$ requires 276.1218.

3.7. General procedure for reacting 2-alkyl-1,3-dithiane with BrF_3

A dithiane (1–3 mmol) was dissolved in 10–20 mL of $CFCl_3$ and cooled to 0 °C. BrF_3 (2.5 mol equiv) was dissolved in 20 mL of the same solvent, cooled to 0 °C, and added dropwise to the reaction mixture during 1–2 min. After the addition was completed, the reaction was washed with $Na_2S_2O_3$ solution till colorless. The aqueous layer was extracted with CH_2Cl_2 (50 mL) and the organic phase dried over $MgSO_4$. Evaporation of the solvent followed by flash chromatography (using petroleum ether as eluent) gave the desired difluoromethyl product.

*3.7.1. 1,1-Difluorotridecane (**5a**)*[25]

Compound **5a** was prepared from **4a** (218 mg, 1 mmol) as described above in 75% yield as a colorless oil. R_f (petroleum ether) 0.78; δ_H 5.79 (1H, tt, J=57, 5 Hz), 1.97–1.66 (2H, m), 1.26 (20H, br s), 0.88 (3H, t, J=7 Hz) ppm; δ_C 117.4 (t, J=239 Hz), 34.0 (t, J=20 Hz), 31.8, 29.5, 29.4, 29.3, 29.1, 29.0, 28.7, 28.6, 22.6, 22.0 (t, J=5 Hz), 14.0 ppm; δ_F −116.2 (dt, J=57, 17 Hz) ppm; IR 2931, 2859, 1412, 1384, 1121, 1042 cm^{-1}; MS (EI) m/z=220 (M)$^+$.

*3.7.2. 1,1-Difluoro-2-methyldodecane (**5b**)*

Compound **5b** was prepared from **4b** (824 mg, 3 mmol) as described above in 70% yield as a colorless oil. R_f (petroleum ether) 0.72; δ_H 5.60 (1H, td, J=57, 4 Hz), 2.00–1.69 (1H, m), 1.27 (16H, br s), 0.98 (3H, d, J=7 Hz), 0.88 (3H, t, J=7 Hz) ppm; δ_C 120.2 (t, J=242 Hz), 38.0 (t, J=19 Hz), 32.6, 30.5 (t, J=5 Hz), 30.4, 30.3, 30.2, 30.1, 27.4, 23.4, 14.9, 13.0 (t, J=5 Hz) ppm; δ_F −122.7 (1F, ddd, J=276, 57, 13 Hz), −125.4 (1F, ddd, J=276, 57, 17 Hz) ppm; IR 2926, 2861, 1464, 1379, 1109, 1038 cm^{-1}; MS (EI) m/z=206 (M)$^+$. Anal. Calcd for $C_{12}H_{24}F_2$: C, 69.86; H, 11.73; F, 18.42. Found: C, 68.52; H, 11.76; F, 18.21.

*3.7.3. 1,1-Difluoro-2-pentylheptane (**5c**)*

Compound **5c** was prepared from **4c** (824 mg, 3 mmol) as described above in 65% yield as a colorless oil. R_f (petroleum ether) 0.75; δ_H 5.70 (1H, td, J=57, 4 Hz), 1.80–1.65 (1H, m), 1.53–1.40 (2H, m), 1.40–1.20 (14H, m), 0.89 (6H, d, J=7 Hz) ppm; δ_C 119.8 (t, J=242 Hz), 42.8 (t, J=19 Hz), 32.8, 28.4 (t, J=4 Hz), 27.3, 23.3, 14.8 ppm; δ_F −123.4 (dd, J=57, 16 Hz) ppm; IR 2933, 2862, 1466, 1380, 1106, 1039 cm^{-1}; MS (EI) m/z=206 (M)$^+$. Anal. Calcd for $C_{12}H_{24}F_2$: C, 69.86; H, 11.73; F, 18.42. Found: C, 68.08; H, 11.78; F, 17.92.

*3.7.4. Difluoromethyl cyclopentadecane (**5d**)*

Compound **5d** was prepared from **4d** (657 mg, 2 mmol) as described above in 75% yield as a colorless oil. R_f (petroleum ether) 0.75; δ_H 5.65 (1H, td, J=57, 4 Hz), 1.85–1.60 (1H, m), 1.33 (28H, br s) ppm; δ_C 120.1 (t, J=242 Hz), 41.8 (t, J=19 Hz), 28.1, 27.6, 27.5, 27.4, 27.3, 27.1, 25.9 ppm; δ_F −122.8 (dd, J=57, 16 Hz) ppm; IR 2930, 2858, 1461, 1390, 1353, 1121, 1032 cm^{-1}; MS (EI) m/z=260 (M)$^+$. Anal. Calcd for $C_{16}H_{30}F_2$: C, 73.80; H, 11.61; F, 14.59. Found: C, 73.52; H, 11.89; F, 14.39.

*3.7.5. 1,1-Difluoro-3-methyldodecane (**5e**)*

Compound **5e** was prepared from **4e** (866 mg, 3 mmol) as described above in 80% yield as a colorless oil. R_f (petroleum ether) 0.74; δ_H 5.85 (1H, tdd, J=57, 5, 4 Hz), 2.00–1.56 (3H, m), 1.26 (15H, br s), 0.96 (3H, d, J=6 Hz), 0.88 (3H, t, J=7 Hz) ppm; δ_C 117.9 (t, J=239 Hz), 41.7 (t, J=20 Hz), 37.7, 32.7, 30.5, 30.4, 30.3, 30.1, 28.6 (t, J=5 Hz), 27.4, 23.4, 20.4, 14.9 ppm; δ_F −115.1 (dt, J=57, 17 Hz) ppm; IR 2926, 2855, 1466, 1401, 1381, 1120, 1039 cm^{-1}; MS (EI) m/z=220 (M)$^+$. Anal. Calcd for $C_{13}H_{26}F_2$: C, 70.86; H, 11.89; F, 17.24. Found: C, 70.53; H, 12.13; F, 17.54.

*3.7.6. 2-Difluoromethyladamantane (**5f**)*

Compound **5f** was prepared from **4f** (509 mg, 2 mmol) as described above in 55% yield as a white solid. Mp 72.6–73.4 °C; R_f (petroleum ether) 0.88; δ_H 6.01 (1H, td, J=57, 8 Hz), 2.08–1.97 (3H, m), 1.95–1.81 (6H, m), 1.79–1.75 (3H, br s), 1.75–1.71 (1H, br s), 1.68–1.65 (1H, br s), 1.65–1.62 (1H, br s) ppm; δ_C 118.8 (t, J=239 Hz), 48.4 (t, J=19 Hz), 38.9, 38.5, 33.0, 28.3, 28.1 (t, J=5 Hz) ppm; δ_F −123.5 (dd, J=57 Hz, J=12 Hz) ppm; IR 3054, 2917, 1422, 1260, 1030 cm^{-1}; MS (EI) m/z=186 (M)$^+$. Anal. Calcd for $C_{11}H_{16}F_2$: C, 70.94; H, 8.65; F, 20.40. Found: C, 70.92; H, 8.65; F, 19.85.

*3.7.7. Butyl 5,5-difluoro-4-methylpentanoate (**10**)*

Compound **10** was prepared from **9** (830 mg, 3 mmol) as described above and purified by flash chromatography (using 2.5% ethyl acetate in petroleum ether) in 80% yield (the yield was determined using ^{1}H NMR) as a colorless oil. R_f (2.5% ethyl acetate/petroleum ether) 0.25; δ_H 5.64 (1H, td, J=57, 4 Hz), 4.09 (2H, t, J=7 Hz), 2.47–2.30 (2H, m), 2.00–1.85 (2H, m), 1.65–1.54 (3H, m), 1.38 (2H, sextet, J=7 Hz), 1.05 (3H, d, J=7 Hz), 0.94 (1H, t, J=7 Hz) ppm; δ_C 173.1, 118.9 (t, J=239 Hz), 64.3, 36.6 (t, J=19 Hz), 31.4, 30.6, 24.9 (t, J=5 Hz), 19.0, 13.6, 12.2 (t, J=5 Hz) ppm; δ_F −123.2 (1F, ddd, J=278, 56, 13 Hz), −124.2 (1F, ddd, J=278, 56, 14 Hz) ppm; IR 2963, 2876, 1736, 1466, 1396, 1269, 1183, 1137, 1092 cm^{-1}; MS (CI) m/z=209 (M+1)$^+$. Anal. Calcd for $C_{10}H_{18}F_2O_2$: C, 57.68; H, 8.71. Found: C, 57.36; H, 8.69.

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References and notes

1. Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013.
2. Goure, W. F.; Leschinsky, K. L.; Wratten, S. J.; Chupp, J. P. *J. Agric. Food Chem.* **1991**, *39*, 981.
3. (a) Rozov, L. A.; Huang, C.; Halpern, D. F.; Vernice, G. G. U.S. Patent 5,283,372, 1994; (b) Halpern, D. F.; Robin, M. L. U.S. Patent 4,996,371, 1991; (c) Ruzicka, J. A.; Hrdy, J. B.; Baker, M. T. *J. Fluorine Chem.* **1995**, *75*, 191.
4. (a) Houlton, S. J.; Motherwell, W. B.; Ross, B. C.; Tozer, M. J.; Williams, D. J.; Slawin, A. M. Z. *Tetrahedron* **1993**, *49*, 8087; (b) Kaneko, S.; Yamazaki, T.; Kitazume, T. *J. Org. Chem.* **1993**, *58*, 2302.
5. Erickson, J. A.; McLoughlin, J. I. *J. Org. Chem.* **1995**, *60*, 1626.
6. Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
7. Gonzales, J.; Foti, C. J.; Elsheimer, S. *J. Org. Chem.* **1991**, *56*, 4322.
8. (a) Ie, Y.; Nitani, M.; Ishikawa, M. i.; Nakayama, K.-I.; Tada, H.; Kaneda, T.; Aso, Y. *Org. Lett.* **2007**, *9*, 2115; (b) Kirsch, P.; Taugerbeck, A. *Eur. J. Org. Chem.* **2002**, 3923.
9. Rozen, S.; Brand, M.; Zamir, D.; Hebel, D. *J. Am. Chem. Soc.* **1987**, *109*, 896.
10. Rozen, S.; Mishani, E. *J. Chem. Soc., Chem. Commun.* **1993**, 1761.
11. Rozen, S.; Mishani, E.; Bar-Haim, A. *J. Org. Chem.* **1994**, *59*, 2918.
12. Sasson, R.; Hagooly, A.; Rozen, S. *Org. Lett.* **2003**, *5*, 769.
13. Soelch, R. R.; Mauer, G. W.; Lemal, D. M. *J. Org. Chem.* **1985**, *50*, 5845.
14. (a) Michalak, R. S.; Wilson, S. R.; Martin, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 7529; (b) Michalak, R. S.; Martin, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 214.
15. Rozen, S.; Lerman, O. *J. Org. Chem.* **1993**, *58*, 239.
16. Rozen, S.; Rechavi, D.; Hagooly, A. *J. Fluorine Chem.* **2001**, *111*, 161.
17. Cohen, O.; Rozen, S. *Tetrahedron* **2008**, *64*, 5362.
18. (a) Rozen, S.; Ben-David, I. *J. Fluorine Chem.* **1996**, *76*, 145; (b) Cohen, O.; Sasson, R.; Rozen, S. *J. Fluorine Chem.* **2006**, *127*, 433.
19. Ben-David, I.; Rechavi, D.; Mishani, E.; Rozen, S. *J. Fluorine Chem.* **1999**, *97*, 75.
20. Hagooly, A.; Ben-David, I.; Rozen, S. *J. Org. Chem.* **2002**, *67*, 8430.
21. Hagooly, Y.; Rozen, S. *J. Org. Chem.* **2008**, *73*, 6780.
22. Rozen, S. *Acc. Chem. Res.* **2005**, *38*, 803.
23. Hagooly, Y.; Sasson, R.; Welch, M. J.; Rozen, S. *Eur. J. Org. Chem.* **2008**, 2875.
24. Sasson, R.; Rozen, S. *J. Fluorine Chem.* **2006**, *127*, 962.
25. Corey, E. J.; Seebach, D.; Freedman, R. *J. Am. Chem. Soc.* **1967**, *89*, 434.
26. Aggarwal, V. K.; Steele, R. M.; Ritmaleni, R.; Barrell, J. K.; Grayson, I. *J. Org. Chem.* **2003**, *68*, 4087.
27. Ceruty, M.; Degani, I.; Fochi, R. *Synthesis* **1987**, *1*, 79.
28. Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901.

29. Martinez, G. A.; Barcina, O. J.; Rys, A. Z.; Subramanian, L. R. *Tetrahedron Lett.* **1992**, *33*, 7787.
30. (a) Boguslavskaya, L. S.; Kartashov, A. V.; Chuvatkin, N. N. *J. Org. Chem. USSR* **1989**, *25*, 1835; *Zh. Org. Khim.* **1989**, *25*, 2029; (b) Boguslavskaya, L. S.; Kartashov, A. V.; Chuvatkin, N. N. *Russ. Chem. Rev.* **1990**, *59*, 501.
31. Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, *52*, 4928.
32. Duddeck, H.; Kaiser, M.; Rosenbaum, D. *Tetrahedron Lett.* **1986**, *27*, 473.
33. Liu, B.; Duan, S.; Sutterer, A. C.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 10101.
34. Carey, F. A.; Court, A. S. *J. Org. Chem.* **1972**, *37*, 1926.
35. Fialkov, A. B.; Amirav, A. *J. Chromatogr., A* **2004**, *1058*, 233.
36. Lehmann, E.; Naumann, D.; Schmeisser, M. *Z. Anorg. Allg. Chem.* **1972**, *388*, 1.
37. Waldemar, A.; Luis, A. A. E. *Chem. Ber.* **1982**, *115*, 2592.