Experimental determination of the conformational free energies (*A* values) of fluorinated substituents in cyclohexane by dynamic ^{19}F NMR spectroscopy. Part 2.† Extension to fluoromethyl, difluoromethyl, pentafluoroethyl, trifluoromethylthio and trifluoromethoxy groups‡

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The synthesis of monosubstituted and 1,4-substituted cyclohexanes bearing one of the title groups is described. The conformational analysis of these compounds was studied by ^{19}F NMR spectroscopy at various temperatures. Chemical shifts for each conformer above the coalescence temperature were obtained by binomial regression from low temperature values, allowing the high precision determination of the equilibrium constants, and the corresponding thermodynamic parameters (ΔG°, ΔH°, ΔS°) of the fluorinated substituents. For *A* values ($-\Delta G^\circ_{298K}$), the following averaged data were obtained: 1.59 (CFH_2), 1.85 (CF_2H), 2.67 (C_2F_5), 0.79 (OCF_3) and 1.18 (SCF_3) [in kcal mol^{-1}].

Introduction

In 1955, Winstein and Holness defined the *A* value of a substituent as the free energy difference between axial and equatorial isomers of monosubstituted cyclohexanes.[1] This parameter has become a very useful resource to assess the steric size of a large variety of substituents. While many *A* values have been determined and compiled,[2,3] very little data concerning fluorinated groups is available. The only studied substituents are the fluorine atom[4] and the trifluoromethyl group.[5,6] Our aim was to extend such data to other fluorinated groups that are receiving a growing interest in the pharmaceutical, agrochemical and material sciences fields: CH_2F, CF_2H, C_2F_5, SCF_3 and OCF_3. To our knowledge, the thermodynamic data of these substituents are not yet reported.

When the steric hindrance of a substituent is important, the axial conformer is extremely minor and the conformational equilibrium is not observable. In such a case, the "counterpoise" method is used by studying *cis*-1,4-disubstituted cyclohexanes.[7] If the bulkinesses of the two groups are close enough with no interaction between both of them, conformational energies are considered to be additive[2] (Scheme 1).

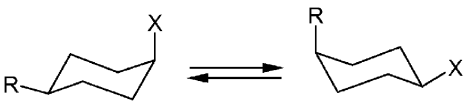
The thermodynamic values of methyl and isopropyl groups are well known[8] (Table 1). The use of these two substituents as counterpoise groups allows the determination of the free energies, enthalpies and entropies of the studied fluorinated cyclohexanes. In the cases of the trifluoromethoxy and trifluoromethylthio groups, we also studied the conformational equilibria of the monosubstituted compounds because we can observe the two conformers without the use of a counterpoise. So we can deduce that the *A* value is smaller than that of an alkyl group in these cases.

In a preceding work on the conformational energy of the trifluoromethyl group (Part 1),[9] we described the efficiency of dynamic ^{19}F NMR spectroscopy for studying conformational equilibria of various trifluoromethyl substituted cyclohexane derivatives. The present paper reports the synthesis of monosubstituted and *cis*-1,4-disubstituted fluorinated cyclohexanes and the study of their conformational equilibria by variable temperature ^{19}F NMR spectroscopy.

Results and discussion

Syntheses of fluorinated cyclohexanes

Pentafluoroethylcyclohexanes **1** were prepared from the corresponding cyclohexanones **6**. The pentafluoroethyl group was introduced by reaction of (pentafluoroethyl)trimethylsilane ($Me_3SiC_2F_5$) with the ketones,[10] in the presence of a catalytic amount of tetrabutylammonium fluoride. The intermediate silyl ethers were desilylated with aqueous hydrochloric acid and the pentafluoroethyl alcohols **7** were isolated as a mixture of diastereoisomers, in high yields (Scheme 2). Dehydration of **7** with thionyl chloride and pyridine in THF[11,12] provided



1 X = C_2F_5
2 X = CH_2F
3 X = CHF_2
4 X = SCF_3
5 X = OCF_3

Scheme 1

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† For Part 1 see ref. 9.

‡ Electronic supplementary information (ESI) available: Variable temperature ^{19}F NMR chemical shifts of *cis*- and *trans*-4-substituted 1-fluorinated cyclohexanes, parameters *a*, *b* and *c* of the temperature dependence of the chemical shifts, equilibrium constants and free energies. See DOI: 10.1039/b516641a

Table 1 Thermodynamic parameters of alkyl counterpoise groups

R	ΔH°/kJ mol^{-1} (ΔH°/kcal mol^{-1})[a]	ΔS°/J mol^{-1} K^{-1} (ΔS°/cal mol^{-1} K^{-1})[b]	A/kcal mol^{-1}
Me	−7.32 (−1.75)	−0.13 (−0.03)	1.74
*i*Pr	−6.36 (−1.52)	9.67 (2.31)	2.21

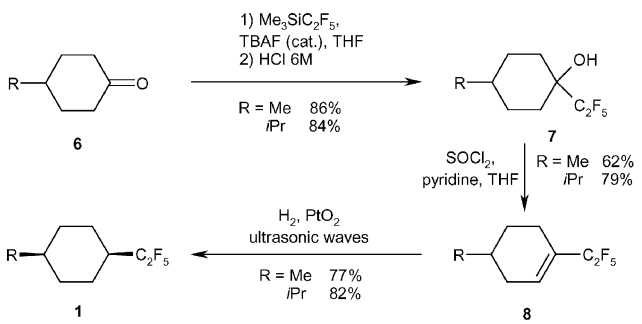
[a] The precision of ΔH° is ±0.25 kJ mol^{-1}. [b] The precision of ΔS° is ±1.5 J mol^{-1} K^{-1}.

pentafluoroethyl alkenes **8**. Hydrogenation of **8** with platinum oxide under ultrasonic waves gave *cis*-4-alkyl-pentafluoroethylcyclohexanes **1** in good yields and with selectivity in favour of the *cis*-isomer (de: 62% for R = Me and 79% when R = *i*Pr), as in the case of the trifluoromethyl analogues.[13]

4-Alkylfluoromethylcyclohexanes **2** and 4-alkyldifluoromethylcyclohexanes **3** were synthesised from *para*-substituted benzoic acids **9**. Catalytic hydrogenation of the aromatic ring provided *cis*-4-alkylcyclohexanecarboxylic acids **10** (Scheme 3).[14,15] The subsequent reduction of the carboxylic acid function with lithium aluminium hydride (LAH)[16] led to the formation of alcohols **11**. A part of these compounds was converted into aldehydes **12** by a traditional Swern procedure.[17] The reaction of (diethylamino)sulfur trifluoride[18,19] (DAST) in dichloromethane (DCM) with alcohols and aldehydes provided, respectively 4-alkyl-1-(fluoromethyl)cyclohexanes **2** and 4-alkyl-1-(difluoromethyl)cyclohexanes **3**. The conversion of the alcohol into the corresponding fluoride leads also to the formation of an alkene by-product, which explains the relatively poor yield for this reaction.

Cyclohexyl trifluoromethyl sulfides **4** were prepared from the corresponding cyclohexanones **6**. The carbonyl group was reduced with LAH, affording *trans*-4-alkylcyclohexanols **13** with good stereoselectivities[20] (Scheme 4). A Mitsunobu nucleophilic substitution[21] led to the formation of thioesters **14**, presenting a *cis*-stereochemistry. Subsequent reduction of these thioesters with LAH[22] gave *cis*-4-alkyl-cyclohexanethiols **15**. Electrophilic trifluoromethylation of these compounds and also of the commercial cyclohexanethiol was then performed, by reaction of Umemoto's reagent **16** with the intermediate thiolates. The cyclohexyl trifluoromethyl sulfides **4** were isolated in moderate yields following the literature method.[23,24]

Trifluoromethyl ethers **5** were also synthesised from various substituted cyclohexanols **17**. The *trans*-4-alkylcyclohexanols **13** were converted into *cis*-isomers **17** by a Mitsunobu reaction[25] (Scheme 5). *cis*-4-Methoxycyclohexanol was obtained by catalytic hydrogenation of *para*-methoxyphenol **18**. Oxidative desulfurisation–fluorination of intermediate dithiocarbonates is a standard procedure to prepare trifluoromethyl ethers from corresponding alcohols.[26,27] So, we converted, with very good yields, those 4-substituted cyclohexanols and also the commercial cyclohexanol into dithiocarbonates **19** by treatment of the alcohols with sodium hydride, carbon disulfide and then with methyl iodide.[28] Reaction of these compounds with 1,3-dibromo-5,5-dimethylhydantoin (DBH) and 50% HF · pyridine complex[29] provided the expected products **5**.



Scheme 2

Conformational analyses

In Scheme 6 are gathered all the 4-alkyl-1-fluoroalkylcyclohexanes **1**, **2**, **3**, **4** and **5** which were studied by dynamic ^{19}F NMR spectroscopy.

The method used for the determination of the thermodynamic parameters was previously described and shown to give reliable results.[9] The chemical shift of any fluorine on a molecule in conformational equilibrium is a weighted average of the contributions of each conformer:

$$\delta_{obs} = x_{ax}\delta_{ax} + x_{eq}\delta_{eq} \quad (1)$$

Where x_{ax} and x_{eq} are the molar fractions and δ_{ax} and δ_{eq} the chemical shifts of the axial and equatorial conformers, respectively.

δ_{ax} and δ_{eq} were measured below the coalescence temperature (about 220 K to 168 K). The temperature dependence of the chemical shifts can be described as a binomial function:[30]

$$\delta_{ax} = a + bT + cT^2 \quad (2)$$

$$\delta_{eq} = a' + b'T + c'T^2$$

So, the chemical shifts of the two *cis*-conformers could be calculated at various temperatures from experimental data below the coalescence temperature (the coefficients a, b and c and the experimental and calculated chemical shifts are given in the supporting information‡). Application of eqn (3) to the variable temperature ^{19}F NMR chemical shifts afforded the equilibrium constants K and then the free energies ΔG° (supporting information‡).

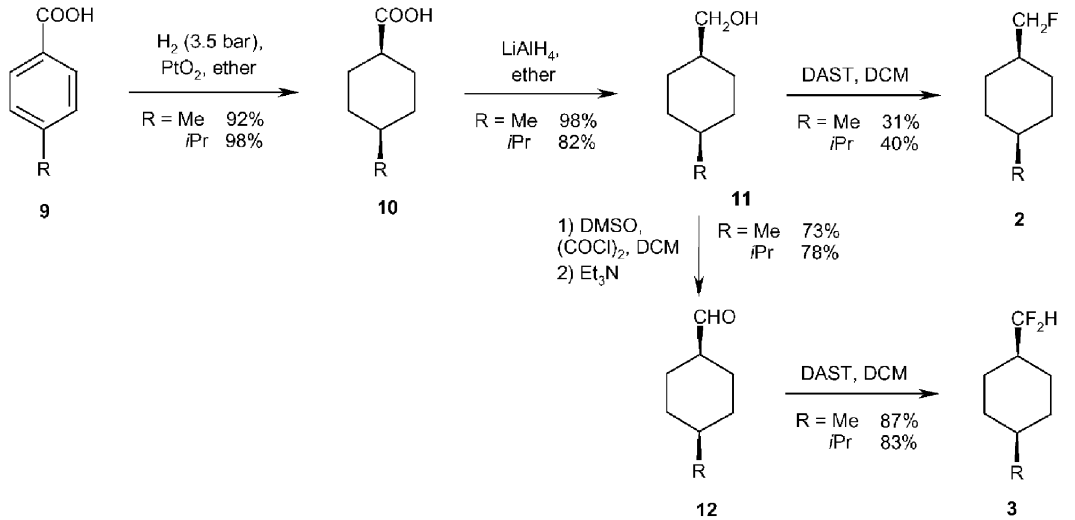
$$K = (\delta_{ax} - \delta_{obs})/(\delta_{obs} - \delta_{eq}) \quad (3)$$

$$\Delta G^\circ = -RT\ln(K) \quad (4)$$

From these values were deduced entropy and enthalpy terms [eqn (5)].

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad (5)$$

In the cases of 4-methyl- and 4-isopropyl-1-(trifluoromethoxy) cyclohexane, equilibria were not observed. It is state of the art that substituents have both a steric and an electronic substituent effect, and in the present discussion this means that there is also a stereoelectronic substituent effect active that shifts the conformational equilibrium to the axial position,[31] and the conformer with the fluorinated group in the equatorial position is extremely minor. When the trifluoromethyl sulfide group of 4-isopropyl-1-(trifluoromethylthio)cyclohexane is in an equatorial position, the ^{19}F NMR signal overlaps with the signal of the *trans*-isomer. Hence it was not possible to obtain precise data from these three particular examples and we

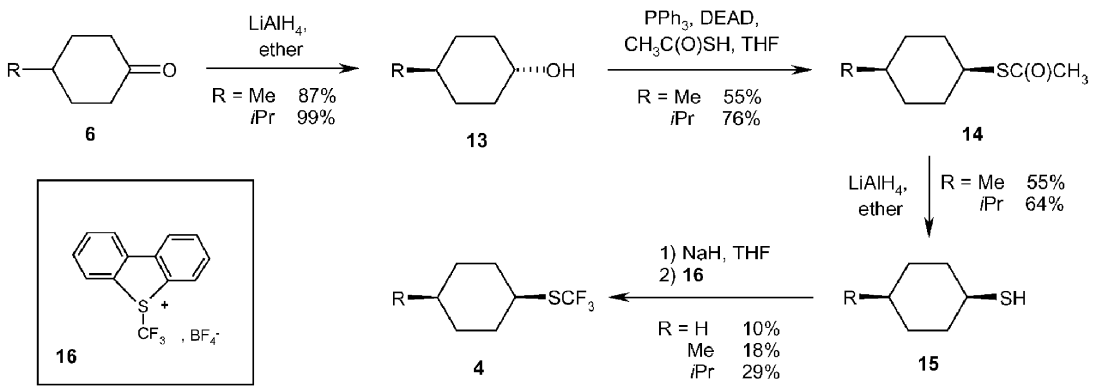


Scheme 3

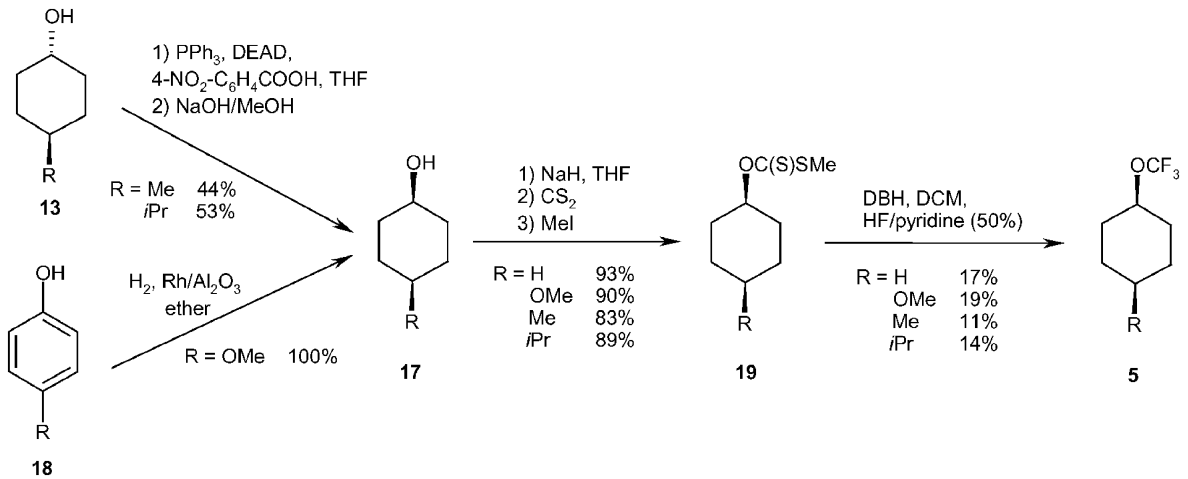
performed the experiments with some new compounds: R = H or OMe (Table 2, entries **4a**, **5a** and **5d**). For the other compounds, the thermodynamic parameters are gathered in Table 2.

Consideration of the entropic and enthalpic contributions of the counterpoise methyl and isopropyl groups (Table 1) and the equation in Scheme 1 ($\Delta G^\circ = \Delta G^\circ_X - \Delta G^\circ_R$), afforded the thermodynamic parameters of the studied fluorinated cyclohexanes. The averaged values are listed in Table 3.

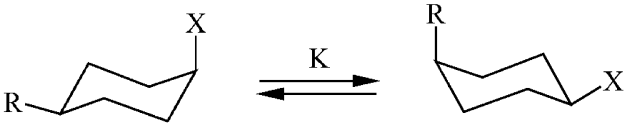
A logical increase in A values is observed in the fluoro, difluoro and trifluoromethyl series (1.59, 1.85 and 2.37, res-



Scheme 4



Scheme 5



	R	X		R	X
1a	Me	C_2F_5	**4a**	H	SCF_3
1b	*i*Pr	C_2F_5	**4b**	Me	SCF_3
2a	Me	CH_2F	**4c**	*i*Pr	SCF_3
2b	*i*Pr	CH_2F	**5a**	H	OCF_3
3a	Me	CF_2H	**5b**	Me	OCF_3
3b	*i*Pr	CF_2H	**5c**	*i*Pr	OCF_3
			5d	OMe	OCF_3

Scheme 6

pectively). *A* values of fluoromethyl and difluoromethyl groups are relatively close to methyl (1.74). That can be explained by the existence of less destabilised conformations when these two substituents are in the axial position, contrary to the case of the trifluoromethyl group where the repulsive interactions cannot be minimised (Scheme 7).

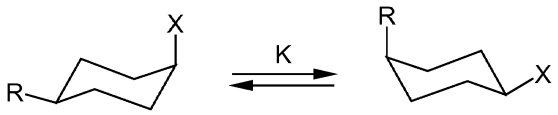
The equatorial preference of the fluoromethyl group is smaller than the methyl one. Similar results were obtained previously with various CH_2X groups; *A* values of CH_2OCH_3 and CH_2OH were reported, respectively as 1.70[32] and 1.40[32] or 1.65.[33] Moreover, Kitching *et al*. studied various substituted methyl groups:[34] conformational energies of CH_2CN and CH_2Br are similar to methyl (1.79 and 1.77). The replacement of a hydrogen by a fluorine induces a decrease of the C–H bond length in fluoromethyl in comparison to methyl, which compensates the increasing van der Waals radius. The introduction of a second fluorine atom leads to a significant increase of the steric effects. The *A* value of the difluoromethyl group is larger than the methyl one (1.85 *versus* 1.74) but much smaller than the isopropyl one (2.21).

The conformational energy of the pentafluoroethyl group is slightly larger than the trifluoromethyl one (2.67 *versus* 2.37), but the difference is much more important than when an ethyl group substitutes a methyl group: by +2.8% for the alkyl groups *versus* +12.6% for the fluorine substituents. The difference remains small because of two stabilised conformations of the axial form (Scheme 8). The *A* value of the pentafluoroethyl group is larger than the isopropyl one (2.67 *versus* 2.21), and smaller than the phenyl one (2.87), but also much smaller than the *tert*-butyl one (4.87).

The comparison between the trifluoromethylthio group and its non-fluorinated analogue does not show any difference (1.18 for SCF_3 and 1.19 for SCH_3). This is in agreement with the assumption that a sulfur lone pair confronts the ring in both these systems[35] (Scheme 9). Moreover, due to the large value of the C–S bond length (0.182 nm *versus* 0.109 for the C–H bond), interactions with the C (3,5) methylenes are poor, whatever the group bonded to the sulfur atom may be.

In the case of the trifluoromethoxy group, the C–O bond length is shorter (0.143 nm) and the CF_3 can interact with the two hydrogens. A difference of 0.3 kcal mol^{-1} is observed between the conformational energies of the trifluoromethoxy and the methoxy groups [0.79 and 0.49, respectively (entries 5 and 6 Table 3)]. This last value was determined using the trifluoromethoxy group as reference. The thermodynamic enthalpy and entropy of the methoxy group were not known in literature. The *A* value was only given at low temperature:[36] 0.55 at 181 K and 0.75 at 190 K. Our value is smaller and shows that it is not valuable to use the data determined at low temperature at 298 K.

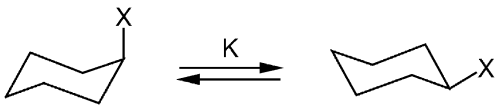
Table 2 Thermodynamic parameters of 4-substituted 1-fluorinated cyclohexanes



	R	X	ΔH°/kJ mol^{-1} (ΔH°/kcal mol^{-1})[a]	ΔS°/J mol^{-1} K^{-1} (ΔS°/cal mol^{-1} K^{-1})[b]	ΔG°_{298K}/kJ mol^{-1} (ΔG°_{298K}/kcal mol^{-1})
1a	Me	C_2F_5	−5.23 (−1.25)	−5.33 (−1.27)	−3.64 (−0.87)
1b	*i*Pr	C_2F_5	−6.59 (−1.58)	−14.86 (−3.55)	−2.17 (−0.52)
2a	Me	CH_2F	2.35 (0.56)	−10.41 (−2.49)	0.76 (0.18)
2b	*i*Pr	CH_2F	2.97 (0.71)	−18.21 (−4.35)	2.49 (0.59)
3a	Me	CF_2H	−1.54 (−0.37)	−4.10 (−0.98)	−0.33 (−0.08)
3b	*i*Pr	CF_2H	−2.07 (−0.50)	−11.51 (−2.75)	1.35 (0.32)
4a	H	SCF_3	2.96 (0.71)	26.30 (6.28)	−4.95 (−1.18)
4b	Me	SCF_3	8.47 (2.02)	20.36 (4.86)	2.39 (0.57)
5a	H	OCF_3	0.87 (0.21)	14.08 (3.36)	−3.32 (−0.79)
5d	OMe	OCF_3	0.23 (0.05)	4.92 (1.18)	−1.24 (−0.30)

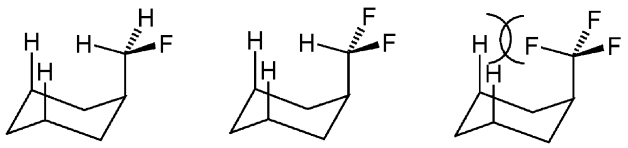
[a] The average precision of ΔH° is 0.07 kJ mol^{-1}. [b] The average precision of ΔS° is 0.26 J mol^{-1} K^{-1}.

Table 3 Thermodynamic parameters of fluorinated and methoxy groups in cyclohexane

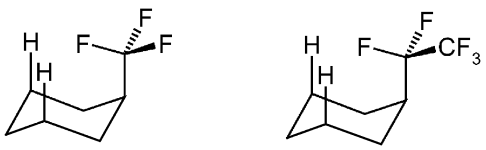


	X	ΔH°/kJ mol^{-1} (ΔH°/kcal mol^{-1})[a]	ΔS°/J mol^{-1} K^{-1} (ΔS°/cal mol^{-1} K^{-1})[b]	A/kcal mol^{-1}
1	C_2F_5	−12.75 (−3.05)	−5.33 (−1.27)	2.67
2	CH_2F	−9.51 (−2.27)	−9.46 (−2.28)	1.59
3	CF_2H	−8.55 (−2.07)	−3.04 (−0.73)	1.85
4	SCF_3	2.06 (0.49)	23.40 (5.59)	1.18
5	OCF_3	0.87 (0.21)	14.08 (3.36)	0.79
6	OMe	0.64 (0.15)	9.16 (2.19)	0.49

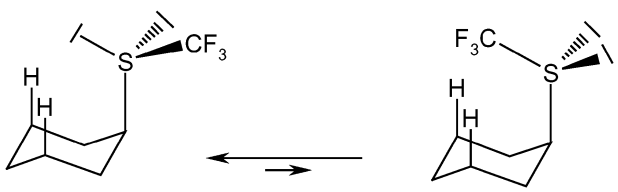
[a] The average precision of ΔH° is 0.08 kJ mol^{-1}. [b] The average precision of ΔS° is 0.82 J mol^{-1} K^{-1}.



Scheme 7



Scheme 8



Scheme 9

Conclusion

Dynamic ^{19}F NMR studies of the conformational equilibrium of several monosubstituted and 1,4-disubstituted cyclohexanes allowed the determination of the thermodynamic parameters of five fluorinated groups. Simulation of the spectra by WYNDIN and calculation of the conformer chemical shifts by regression from low temperature data afforded the results with great accuracy. Thermodynamic parameters of the methoxy group were also determined. These studies led to an order of A values H < OCH_3 < OCF_3 < SCH_3 ~ SCF_3 < CFH_2 ~ CH_3 < CF_2H < $CH(CH_3)_2$ < CF_3 < C_2F_5 < C_6H_5 < $C(CH_3)_3$.

In the case of the trifluoromethylthio substituent, due to the length of the C–S bond, the A value does not reflect the bulkiness of this group.

Experimental

General

Each reaction was carried out under an argon atmosphere in a freshly distilled solvent, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium–benzophenone. Dichloromethane was distilled from calcium hydride. Pyridine was distilled and stored under argon. NBS was purified by recrystallisation from hot water. Reactions were monitored by thin-layer chromatography on silica gel 60 F_{254}, or by ^{19}F NMR spectroscopy. Unless otherwise noted, yields refer to materials purified by column chromatography or distillation under reduced pressure.

^{1}H, ^{19}F and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Bruker AC-200 spectrometer operating at 200, 188 or 50 MHz, or on a Bruker AC-300 spectrometer operating at 300, 282 or 75 MHz, respectively. Melting points were measured with a Mettler FP 61 apparatus. IR spectra were recorded on a Nicolet Impact 400D. Mass spectra were recorded on an HP MS 5989B spectrometer. High resolution mass spectra were performed at the Ecole Normale Supérieure (Paris). Elemental analyses were carried out at ICSN (Gif-sur-Yvette). Silica gel from Merck (Kieselgel 60 ACC, 35–70 or 70–200 mesh) was used for column chromatography.

For the assignment of the NMR spectra of the synthesised compounds, we used in ^{19}F NMR spectroscopy the broadness of the signal. The *cis*-isomer was in equilibrium contrary to the *trans*-isomer. In ^{1}H NMR spectroscopy, it is well known that the equatorial proton geminate to an axial substituent is less shielded than the corresponding one on the second diastereoisomer. The assignment of the proton geminate to the fluorine group gave us the stereochemistry of cyclohexanes. Finally the assignment of the ^{13}C NMR signal proceeded from the C–F coupling constants, DEPT, HCOR and JMOD experiments.

Variable temperature ^{19}F NMR spectra were recorded on a Bruker AC-300 spectrometer. Chemical shifts are quoted relative to $CFCl_3$. The studies were performed in THF-d_8, using diluted solutions (~0.1 mol L^{-1}). A 5.7 μs pulse width (90° pulse angle) was used, with a recycle delay of 1 s. The spectra were proton-decoupled and were obtained using 64 K of points. The spectral widths are 16.9 kHz for **1a**–**b**, 11.4 kHz

for **4a**–**4c**, 8.5 kHz for **2a**–**b**, 5.6 kHz for **3a** and **5a**, **5b**, and **5d** and 2.8 kHz for **3b** and **5c**. The spectra were recorded every 5 K between 298 K and 168 K. Before each record a ten minute delay was applied in order to stabilise the temperature. A calibration with methanol was made in the same conditions and allowed the estimation of the temperature accuracy to 0.2 K.

Syntheses

Preparation of pentafluoroethylcyclohexanols 7: general procedure. A mixture of carbonyl compound **6** (50 mmol) and (pentafluoroethyl)trimethylsilane (60 mmol) in THF (50 mL) at room temperature was treated with a catalytic amount (*ca.* 0.5 mL) of TBAF (1.1 M in THF). The reaction mixture was stirred for 1 h. The resulting silyloxy compounds were then hydrolysed with aqueous HCl (6 M). After the reaction, the mixture was extracted with ether (3 × 50 mL) and the combined organic phases were washed with a solution of sodium hydrogen carbonate (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane–ether, 9 : 1). Isolated yields and spectral data for the prepared compounds are given below.

1-Pentafluoroethyl-4-methylcyclohexan-1-ol (**7a**). 86% yield; mixture (69 : 31) of *trans*- and *cis*-isomers; white solid; mp 55 °C (mixture); spectral data for major isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −78.7 (s, 3F), −126.2 (s, 2F); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (d, 3H, $^3J_{H-H}$ = 6.8 Hz), 1.2–1.5 (m, 2H), 1.5–2.0 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.1, 25.8, 26.3, 28.7, 73.4 (t, $^2J_{C-F}$ = 22.7 Hz), 115.1 (tq, $^1J_{C-F}$ = 260 Hz, $^2J_{C-F}$ = 34.8 Hz), 119.6 (qt, $^1J_{C-F}$ = 288 Hz, $^2J_{C-F}$ = 36.9 Hz); spectral data for minor isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −78.7 (s, 3F), −127.3 (s, 2F); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (d, 3H, $^3J_{H-H}$ = 6.9 Hz), 1.2–1.5 (m, 3H), 1.5–2.0 (m, 7H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.0, 26.5, 29.8, 31.6, 73.3 (t, $^2J_{C-F}$ = 22.7 Hz), 115.1 (tq, $^1J_{C-F}$ = 260 Hz, $^2J_{C-F}$ = 34.8 Hz), 119.6 (qt, $^1J_{C-F}$ = 288 Hz, $^2J_{C-F}$ = 36.9 Hz); IR (KBr) 3416, 2976, 2884 cm^{-1}; MS (CI CH_4) *m*/*z* 249 (4), 215 (100), 195 (38); anal. calc. for $C_9H_{13}F_5O$: C, 46.55; H, 5.65. Found: C, 46.7; H, 5.7%.

1-Pentafluoroethyl-4-isopropylcyclohexan-1-ol (**7b**). 84% yield; mixture (70 : 30) of *trans*- and *cis*-isomers; white solid; mp 47 °C (mixture); spectral data for major isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.8 (s, 3F), −125.3 (s, 2F); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, 6H, $^3J_{H-H}$ = 6.6 Hz), 1.0–2.0 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.8, 22.9, 26.7, 27.6, 39.8, 73.3 (t, $^2J_{C-F}$ = 23.3 Hz), 115.3 (tq, $^1J_{C-F}$ = 260 Hz, $^2J_{C-F}$ = 34.5 Hz), 119.6 (qt, $^1J_{C-F}$ = 288 Hz, $^2J_{C-F}$ = 36.9 Hz); spectral data for minor isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −78.7 (s, 3F), −127.3 (s, 2F); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 6H, $^3J_{H-H}$ = 6.6 Hz), 1.0–2.0 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7, 23.5, 30.0, 32.5, 42.9, 73.5 (t, $^2J_{C-F}$ = 22.3 Hz), 115.0 (tq, $^1J_{C-F}$ = 260 Hz, $^2J_{C-F}$ = 34.5 Hz), 119.6 (qt, $^1J_{C-F}$ = 288 Hz, $^2J_{C-F}$ = 36.9 Hz); IR (KBr) 3416, 2955, 2873 cm^{-1}; MS (CI CH_4) *m*/*z* 259 (6), 243 (100), 201 (26), 141 (10); anal. calc. for $C_{11}H_{17}F_5O$: C, 50.8; H, 6.6. Found: C, 50.95; H, 6.6%.

Dehydration of pentafluoroethylcyclohexanols 7: general procedure. Pyridine (30 mmol) and $SOCl_2$ (30 mmol) were added successively at 0 °C to a solution of **7** (10 mmol) in THF (10 mL) with 50 mg of DMAP. The reaction mixture was warmed to 50 °C and stirred between 16 and 48 h (the reaction was followed by ^{19}F NMR spectroscopy). The mixture was then cooled to 0 °C and carefully poured onto saturated aqueous $CuSO_4$ at 0 °C. After extractions with ether (3 × 50 mL), the combined organic phases were washed with 1 M HCl (100 mL), saturated aqueous $NaHCO_3$ (100 mL), water (100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$ and concentrated. The residue was purified by flash chromatography with pentane as eluant.

1-Pentafluoroethyl-4-methylcyclohexene (**8a**). 62% yield; colourless oil; ^{19}F NMR (188 MHz, $CDCl_3$) δ −84.4 (s, 3F), −116.1 (d, 1F, $^2J_{F-F}$ = 265 Hz), −119.1 (d, 1F, $^2J_{F-F}$ = 265 Hz); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (d, 3H, $^3J_{H-H}$ = 6.1 Hz), 1.2–2.2 (m, 7H), 6.32 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3, 22.6, 27.3, 29.9, 33.2, 113.4 (tq, $^1J_{C-F}$ = 252 Hz, $^2J_{C-F}$ = 37.6 Hz), 119.3 (qt, $^1J_{C-F}$ = 287 Hz, $^2J_{C-F}$ = 39.4 Hz), 126.8 (t, $^2J_{C-F}$ = 21.3 Hz), 133.0 (q, $^3J_{C-F}$ = 8.9 Hz); IR (neat) 2950, 2873, 1670 cm^{-1}.

1-Pentafluoroethyl-4-isopropylcyclohexene (**8b**). 79% yield; colourless oil; ^{19}F NMR (282 MHz, $CDCl_3$) δ −84.4 (s, 3F), −115.8 (d, 1F, $^2J_{F-F}$ = 264 Hz), −119.2 (d, 1F, $^2J_{F-F}$ = 264 Hz); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, 3H, $^3J_{H-H}$ = 6.8 Hz), 0.93 (d, 3H, $^3J_{H-H}$ = 6.8 Hz), 1.2–1.4 (m, 2H), 1.53 (m, 1H), 1.8–2.3 (m, 5H), 6.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.4, 19.7, 23.4, 25.4, 28.6, 32.0, 39.1, 113.4 (tq, $^1J_{C-F}$ = 252 Hz, $^2J_{C-F}$ = 37.7 Hz), 119.4 (qt, $^1J_{C-F}$ = 287 Hz, $^2J_{C-F}$ = 39.7 Hz), 127.0 (t, $^2J_{C-F}$ = 21.5 Hz), 133.4 (q, $^3J_{C-F}$ = 8.5 Hz); IR (neat) 2960, 2868, 1665 cm^{-1}; MS (CI CH_4) *m*/*z* 243 (34), 223 (100), 203 (86); anal. calc. for $C_{11}H_{15}F_5$: C, 54.55; H, 6.25. Found: C, 54.6; H, 6.2%.

Synthesis of pentafluoroethylcyclohexanes 1: general procedure. In a Schlenk tube PtO_2 (5 mol%) in ether (10 mL) was sonicated under hydrogen 30 min prior to the addition of a solution of alkene **8** (2 mmol) in ether (10 mL). The mixture was reduced at room temperature for 6 h under an atmospheric pressure of hydrogen, under ultrasound. The solution was then filtered and concentrated under reduced pressure.

1-Pentafluoroethyl-4-methylcyclohexane (**1a**). The substrate was purified by flash chromatography with pentane as eluant; 77% yield; mixture (88 : 12) of *cis*- and *trans*-isomers; colourless oil; spectral data for major isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −82.3 (s, 3F), −121.1 (d, 2F, $^3J_{F-H}$ = 15.3 Hz); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (d, 3H, $^3J_{H-H}$ = 7.1 Hz), 1.2–2.2 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.7, 19.3 (td, $^3J_{C-F}$ = 4.1 Hz, $^4J_{C-F}$ = 1.4 Hz), 27.0, 30.5, 39.3 (t, $^2J_{C-F}$ = 20.6 Hz), 116.7 (tq, $^1J_{C-F}$ = 254 Hz, $^2J_{C-F}$ = 36.0 Hz), 119.6 (qt , $^1J_{C-F}$ = 287 Hz, $^2J_{C-F}$ = 37.3 Hz); spectral data for minor isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −82.2 (s, 3F), −122.0 (d, 2F, $^3J_{F-H}$ = 14.5 Hz); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (d, 3H, $^3J_{H-H}$ = 7.1 Hz), 1.2–2.2 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.3, 24.4 (td, $^3J_{C-F}$ = 4.2 Hz, $^4J_{C-F}$ = 1.4 Hz), 31.9, 33.9, 39.8 (t, $^2J_{C-F}$ = 20.6 Hz), 116.5 (tq, $^1J_{C-F}$ =

253 Hz, $^2J_{C-F}$ = 36.1 Hz), 119.6 (qt , $^1J_{C-F}$ = 287 Hz, $^2J_{C-F}$ = 37.3 Hz); MS (EI) *m*/*z* 216 (100); MS HR calc. for $C_9H_{13}F_5$: 216.0937. Found: 216.0937.

1-Pentafluoroethyl-4-isopropylcyclohexane (**1b**). The substrate was purified by distillation under reduced pressure (65 °C, 20 mmHg); 82% yield; mixture (78 : 22) of *cis*- and *trans*-isomers; colourless oil; spectral data for major isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −82.5 (s, 3F), −120.4 (d, 2F, $^3J_{F-H}$ = 16.5 Hz); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 6H, $^3J_{H-H}$ = 6.6 Hz), 1.2–2.2 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4 (td, $^3J_{C-F}$ = 3.8 Hz, $^4J_{C-F}$ = 1.4 Hz), 20.7, 26.6, 27.1, 38.6 (t, $^2J_{C-F}$ = 20.6 Hz), 40.5, 116.9 (tq, $^1J_{C-F}$ = 254 Hz, $^2J_{C-F}$ = 36.1 Hz), 119.6 (qt, $^1J_{C-F}$ = 287 Hz, $^2J_{C-F}$ = 37.3 Hz); spectral data for minor isomer: ^{19}F NMR (282 MHz, $CDCl_3$) δ −82.2 (s, 3F), −122.1 (d, 2F, $^3J_{F-H}$ = 15.2 Hz); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 6H, $^3J_{H-H}$ = 6.6 Hz), 1.2–2.2 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6, 24.6 (td, $^3J_{C-F}$ = 4.2 Hz, $^4J_{C-F}$ = 1.4 Hz), 28.5, 32.7, 40.2 (t, $^2J_{C-F}$ = 20.7 Hz), 43.3, 116.5 (tq, $^1J_{C-F}$ = 253 Hz, $^2J_{C-F}$ = 36.1 Hz), 119.6 (qt, $^1J_{C-F}$ = 287 Hz, $^2J_{C-F}$ = 37.3 Hz); MS (CI CH_4) *m*/*z* 243 (83), 225 (77), 205 (100), 183 (68), 163 (20), 159 (20); anal. calc. for $C_{11}H_{17}F_5$: C, 54.1; H, 7.0. Found: C, 54.05; H, 6.9%.

Catalytic hydrogenation of *para*-substituted benzoic acids 9: general procedure. A mixture of **9** (100 mmol) and platinum oxide (0.3 g) in ether (100 mL) was placed in a 250 mL Parr bomb and hydrogenated overnight under 3.5 bar of hydrogen. The solution was then filtered and concentrated under reduced pressure.

4-Methylcyclohexanecarboxylic acid (**10a**) *[934-67-8]*. 92% yield; mixture (82 : 18) of *cis*- and *trans*-isomers; colourless oil.

4-Isopropylcyclohexanecarboxylic acid (**10b**) *[7077-05-6]*. 98% yield; mixture (80 : 20) of *cis*- and *trans*-isomers; colourless oil.

Synthesis of (4-alkylcyclohexyl)methanols 11: general procedure. A solution of **10** (50 mmol) in dry ether (100 mL) was added dropwise to a suspension of $LiAlH_4$ (100 mmol) in dry ether (100 mL) at 0 °C. The resulting mixture was then warmed to room temperature and stirred overnight. The mixture was cooled to 0 °C and iced water (50 mL) and aqueous sulfuric acid (10%, 100 mL) were carefully added. The organic phase was separated. The aqueous phase was extracted with ether two times. The combined organic phase was washed with sat. $NaHCO_3$ solution and then with brine, dried over magnesium sulfate and concentrated under reduced pressure.

(4-Methylcyclohexyl)methanol (**11a**) *[3937-48-2]*. 98% yield; mixture (82 : 18) of *cis*- and *trans*-isomers; colourless oil.

(4-Isopropylcyclohexyl)methanol (**11b**) *[5502-75-0]*. 82% yield; mixture (77 : 23) of *cis*- and *trans*-isomers; colourless oil.

Synthesis of (4-alkylcyclohexyl)methanals 12: general procedure. A mixture of oxalyl chloride (35 mmol) and dichloromethane (75 mL) was cooled to −78 °C. Dimethyl sulfoxide (70 mmol) was added dropwise and the resulting mixture was stirred for 2 min. A solution of alcohol **11** (25 mmol) in dichloromethane (25 mL) was added slowly over 5 min. The resulting mixture was stirred 15 min before triethylamine (125 mmol) was added. The mixture was warmed to room temperature and water (50 mL) was added. The organic phase was separated. The aqueous phase was extracted with dichloromethane three times. The combined organic phase was washed with aqueous hydrochloric acid (1%), with an aqueous $NaHCO_3$ solution and with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane–ether, 9 : 1).

(4-Methylcyclohexyl)methanal (**8a**) *[7133-04-2]*. 73% yield; mixture (80 : 20) of *cis*- and *trans*-isomers; colourless oil.

(4-Isopropylcyclohexyl)methanal (**8b**) *[32533-97-4]*. 78% yield; mixture (78 : 22) of *cis*- and *trans*-isomers; colourless oil.

Fluorination of (4-alkylcyclohexyl)methanols (11) and (4-alkylcyclohexyl)methanals (12): general procedure. A solution of 10 mmol of substrate (**11** or **12**) in dichloromethane (10 mL) was added dropwise to a mixture of (diethylamino)sulfur trifluoride (20 mmol) in dichloromethane (10 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred overnight. Iced water (20 mL) was then added slowly. The organic phase was separated. The aqueous phase was extracted with dichloromethane three times. The combined organic phase was washed with water and dried over magnesium sulfate. The solvent was removed by distillation under atmospheric pressure. The substrate was purified by distillation "bulb to bulb" (less than 20 mmHg).

4-Methyl-1-fluoromethylcyclohexane (**2a**). 31% yield; mixture (55 : 45) of *cis*- and *trans*-isomers; colourless oil; spectral data for major isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −222.6 (td, $^2J_{F-H}$ = 48.3 Hz, $^3J_{F-H}$ = 16.1 Hz); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.92 (d, 3H, $^3J_{H-H}$ = 6.5 Hz), 1.0–2.0 (m, 10H), 4.34 (dd, 2H, $^2J_{H-F}$ = 47.7 Hz, $^3J_{H-H}$ = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.5, 24.3 (d, $^3J_{C-F}$ = 6.4 Hz), 30.2, 31.0, 36.1 (d, $^2J_{C-F}$ = 18.0 Hz), 85.9 (d, $^1J_{C-F}$ = 166.8 Hz); spectral data for minor isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ 222.9 (td, $^2J_{F-H}$ = 48.3 Hz, $^3J_{F-H}$ = 16.9 Hz); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, 3H, $^3J_{H-H}$ = 6.0 Hz), 1.0–2.0 (m, 10H), 4.23 (dd, 2H, $^2J_{H-F}$ = 47.9 Hz, $^3J_{H-H}$ = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.6, 28.5 (d, $^3J_{C-F}$ = 5.7 Hz), 32.6, 34.4, 38.4 (d, $^2J_{C-F}$ = 17.7 Hz), 88.7 (d, $^1J_{C-F}$ = 167.5 Hz); MS (EI) *m*/*z* 130 (100); HR MS calc. for $C_8H_{15}F$: 130.1158. Found: 130.1156.

4-Isopropyl-1-fluoromethylcyclohexane (**2b**). 40% yield; mixture (62 : 38) of *cis*- and *trans*-isomers; colourless oil; spectral data for major isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −222.6 (td, $^2J_{F-H}$ = 47.3 Hz, $^3J_{F-H}$ = 16.5 Hz); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (d, 6H, $^3J_{H-H}$ = 6.5 Hz), 1.0–2.0 (m, 11H), 4.37 (dd, 2H, $^2J_{H-F}$ = 47.6 Hz, $^3J_{H-H}$ = 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.2, 25.2 (d, $^3J_{C-F}$ = 6.5 Hz), 25.6, 30.2, 35.3 (d, $^2J_{C-F}$ = 17.8 Hz), 42.7, 86.4 (d, $^1J_{C-F}$ = 166.4 Hz); spectral data for minor isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ 222.8 (td, $^2J_{F-H}$ = 47.7 Hz, $^3J_{F-H}$ = 16.5 Hz); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (d, 6H, $^3J_{H-H}$ = 6.7 Hz), 1.0–2.0 (m, 11H), 4.23 (dd, 2H, $^2J_{H-F}$ = 47.8 Hz, $^3J_{H-H}$ = 6.1

Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.8, 28.7 (d, $^3J_{C-F}$ = 5.7 Hz), 28.9, 32.9, 38.8 (d, $^2J_{C-F}$ = 17.8 Hz), 44.0, 88.8 (d, $^1J_{C-F}$ = 167.3 Hz); MS (EI) *m*/*z* 158 (100); HR MS calc. for $C_{10}H_{19}F$: 158.1472. Found: 158.1474.

4-Methyl-1-difluoromethylcyclohexane (**3a**). 87% yield; mixture (78 : 22) of *cis*- and *trans*-isomers; colourless oil; spectral data for major isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −123.0 (dd, $^2J_{F-H}$ = 57.2 Hz, $^3J_{F-H}$ = 14.7 Hz); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.96 (d, 3H, $^3J_{H-H}$ = 6.9 Hz), 1.0–2.0 (m, 10H), 5.68 (td, 1H, $^2J_{H-F}$ = 57.2 Hz, $^3J_{H-H}$ = 5.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.2, 21.5 (t, $^3J_{C-F}$ = 5.0 Hz), 28.8, 30.5, 39.8 (t, $^2J_{C-F}$ = 19.3 Hz), 118.9 (t, $^1J_{C-F}$ = 240 Hz); spectral data for minor isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −123.3 (dd, $^2J_{F-H}$ = 57.2 Hz, $^3J_{F-H}$ = 14.7 Hz); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, 3H, $^3J_{H-H}$ = 6.7 Hz), 1.0–2.0 (m, 10H), 5.53 (td, 1H, $^2J_{H-F}$ = 56.9 Hz, $^3J_{H-H}$ = 4.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.4, 25.3 (t, $^3J_{C-F}$ = 4.6 Hz), 32.3, 33.8, 41.4 (t, $^2J_{C-F}$ = 19.3 Hz), 119.3 (t, $^1J_{C-F}$ = 241 Hz); MS (EI) *m*/*z* 148 (100); HR MS calc. for $C_8H_{14}F_2$: 148.1064. Found: 148.1065.

4-Isopropyl-1-difluoromethylcyclohexane (**3b**). 83% yield; mixture (89 : 11) of *cis*- and *trans*-isomers; colourless oil; spectral data for major isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −122.8 (dd, $^2J_{F-H}$ = 57.2 Hz, $^3J_{F-H}$ = 13.7 Hz); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (d, 6H, $^3J_{H-H}$ = 6.7 Hz), 1.0–2.0 (m, 11H), 5.73 (td, 1H, $^2J_{H-F}$ = 57.2 Hz, $^3J_{H-H}$ = 5.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.3, 22.8 (t, $^3J_{C-F}$ = 5.0 Hz), 25.9, 29.5, 39.1 (t, $^2J_{C-F}$ = 19.2 Hz), 41.9, 118.8 (t, $^1J_{C-F}$ = 241 Hz); spectral data for minor isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −123.3 (dd, $^2J_{F-H}$ = 56.5 Hz, $^3J_{F-H}$ = 13.0 Hz); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (d, 6H, $^3J_{H-H}$ = 6.7 Hz), 1.0–2.0 (m, 11H), 5.53 (td, 1H, $^2J_{H-F}$ = 57.1 Hz, $^3J_{H-H}$ = 5.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.7, 25.5 (t, $^3J_{C-F}$ = 4.6 Hz), 28.4, 32.8, 41.8 (t, $^2J_{C-F}$ = 19.2 Hz), 43.7, 119.3 (t, $^1J_{C-F}$ = 241 Hz); MS (EI) *m*/*z* 176 (100); HR MS calc. for $C_{10}H_{18}F_2$: 176.1377. Found: 176.1381.

Synthesis of *trans*-4-substituted cyclohexanols 13: general procedure. A solution of 4-substituted cyclohexanone **6** (100 mmol) in dry ether (250 mL) was added dropwise to a suspension of $LiAlH_4$ (200 mmol) in dry ether (250 mL) at 0 °C. The resulting mixture was then warmed to room temperature and stirred for 2 h. The mixture was cooled to 0 °C and iced water (50 mL) and aqueous sulfuric acid (10%, 100 mL) were added carefully. The organic phase was separated. The aqueous phase was extracted with ether two times. The combined organic phase was washed with sat. $NaHCO_3$ solution and then with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane–ether, 9 : 1).

4-Methylcyclohexanol (**13a**) *[7731-29-5]*. 87% yield; mixture (86 : 14) of *trans*- and *cis*-isomers; colourless oil.

4-Isopropylcyclohexanol (**13b**) *[15890-36-5]*. 99% yield; mixture (88 : 12) of *trans*- and *cis*-isomers; colourless oil.

Synthesis of 4-substituted cyclohexyl thioacetates 14: general procedure. Diethyl azodicarboxylate (68 mmol) was added to a solution of triphenylphosphine (68 mmol) in THF (140 mL) at 0 °C. The resulting mixture was stirred for 30 min and a solution of **13** (34 mmol) in THF (100 mL) and then thioacetic acid (68 mmol) successively were added dropwise. The resulting mixture was stirred for 1 h at 0 °C and overnight at room temperature. The solvent was removed under reduced pressure and ether was added in order to precipitate phosphine oxide. The solution was then filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane–ether, 9 : 1).

4-Methylcyclohexyl thioacetate (**14a**). 55% yield; mixture (82 : 18) of *cis*- and *trans*-isomers; amber oil; spectral data for major isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (d, 3H, $^3J_{H-H}$ = 6.4 Hz), 1.1–1.3 (m, 2H), 1.39 (m, 1H), 1.5–1.9 (m, 6H), 2.26 (s, 3H), 3.83 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.7, 30.7, 30.8, 31.2, 31.3, 41.3, 195.3; spectral data for minor isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (d, 3H, $^3J_{H-H}$ = 6.4 Hz), 1.0–2.0 (m, 9H), 2.24 (s, 3H), 3.28 (tt, 1H, $^3J_{H_{ax}-H_{ax}}$ = 12.3 Hz, $^3J_{H_{ax}-H_{eq}}$ = 3.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.1, 30.6, 31.6, 32.9, 35.0, 42.1, 195.5; IR (neat) 2925, 2843, 1685 cm^{-1}; MS (CI NH_3) *m*/*z* 190 (100), 173 (37).

4-Isopropylcyclohexyl thioacetate (**14b**). 76% yield; mixture (84 : 16) of *cis*- and *trans*-isomers; amber oil; spectral data for major isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (d, 6H, $^3J_{H-H}$ = 6.8 Hz), 1.1–1.9 (m, 10H), 2.30 (s, 3H), 3.91 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.7, 26.0, 30.9, 31.4, 32.2, 41.8, 43.3, 195.6; IR (neat) 2925, 2858, 1685 cm^{-1}; MS (CI NH_3) *m*/*z* 201 (100), 157 (15), 125 (95).

Synthesis of 4-substituted cyclohexanethiols 15: general procedure. A solution of **14** (25 mmol) in dry ether (35 mL) was added dropwise to a suspension of $LiAlH_4$ (79 mmol) in dry ether (40 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred overnight. The mixture was cooled to 0 °C and iced water (20 mL) and aqueous sulfuric acid (10%, 30 mL) were added carefully. The organic phase was separated. The aqueous phase was extracted with ether two times. The combined organic phase was washed with sat. $NaHCO_3$ solution and then with brine, dried over magnesium sulfate and concentrated under reduced pressure.

4-Methylcyclohexanethiol (**15a**) *[60260-87-9]*. 55% yield; mixture (81 : 19) of *cis*- and *trans*-isomers; colourless oil.

4-Isopropylcyclohexanethiol (**15b**). 64% yield: mixture (83 : 17) of *cis*- and *trans*-isomers; colourless oil; spectral data for major isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (d, 6H, $^3J_{H-H}$ = 6.6 Hz), 1.04 (m, 1H), 1.3–1.6 (m, 6H), 1.6–1.9 (m, 4H), 3.36 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.9, 24.3, 31.6, 33.9, 36.9, 43.3; MS (CI NH_3) *m*/*z* 157 (14), 125 (100).

Trifluoromethylation of cyclohexanethiols 15: general procedure. A solution of thiol **15** (5 mmol) in THF (10 mL) was added dropwise to a suspension of sodium hydride (5.5 mmol) in THF (10 mL). The mixture was stirred for 1 h before Umemoto's reagent **16** (5 mmol) was added. The resulting mixture was stirred for 2 h. Water (20 mL) and ether (20 mL)

were added. The organic phase was separated. The aqueous phase was extracted with ether three times. The combined organic phase was washed with aqueous hydrochloric acid and then with brine, and dried over magnesium sulfate. The solvent was removed by distillation under atmospheric pressure. The substrate was purified by distillation "bulb to bulb" (under 20 mmHg).

Cyclohexyl trifluoromethyl sulfide (**4a**) *[6476-52-4]*. 10% yield; colourless oil.

4-Methylcyclohexyl trifluoromethyl sulfide (**4b**). 18% yield; mixture (80 : 20) of *cis*- and *trans*-isomers; colourless oil; spectral data for major isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −40.4 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.93 (d, 3H, $^3J_{H-H}$ = 6.3 Hz), 1.0–2.2 (m, 9H), 3.63 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.5, 30.2, 31.2, 31.3, 43.1 (q, $^3J_{C-F}$ = 1.1 Hz), 131.5 (t, $^1J_{C-F}$ = 306 Hz); spectral data for minor isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −39.4 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, 3H, $^3J_{H-H}$ = 6.6 Hz), 1.0–2.2 (m, 9H), 3.11 (tt, 1H, $^3J_{H_{ax}-H_{ax}}$ = 12.3 Hz, $^3J_{H_{ax}-H_{eq}}$ = 3.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.1, 31.5, 33.9, 35.0, 43.7 (q, $^3J_{C-F}$ = 1.1 Hz), 131.1 (q, $^1J_{C-F}$ = 307 Hz); MS (CI CH_4) *m*/*z* 197 (28), 179 (52), 129 (100).

4-Isopropylcyclohexyl trifluoromethyl sulfide (**4c**). 29% yield; mixture (73 : 27) of *cis*- and *trans*-isomers; colourless oil; spectral data for major isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −40.4 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (d, 6H, $^3J_{H-H}$ = 6.6 Hz), 1.0–2.1 (m, 10H), 3.68 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.7, 25.0, 29.7, 31.9, 43.2, 43.4, 131.5 (t, $^1J_{C-F}$ = 306 Hz); spectral data for minor isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −39.3 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (d, 6H, $^3J_{H-H}$ = 6.6 Hz), 1.0–2.1 (m, 10H), 3.10 (tt, 1H, $^3J_{H_{ax}-H_{ax}}$ = 12.2 Hz, $^3J_{H_{ax}-H_{eq}}$ = 3.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.9, 32.0, 32.6, 34.1, 42.8, 44.0, 131.5 (q, $^1J_{C-F}$ = 307 Hz); MS (EI) *m*/*z* 226 (8), 157 (100), 125 (53), 81 (91); HR MS calc. for $C_{10}H_{17}SF_3$: 226.1003. Found: 226.0997.

Synthesis of *cis*-4-substituted cyclohexanols 17: general procedure. Diethyl azodicarboxylate (80 mmol) was added dropwise to a solution of *trans*-4-substituted cyclohexanol **13** (40 mmol), triphenylphosphine (80 mmol) and *para*-nitrobenzoic acid (80 mmol) in THF (320 mL) at 0 °C. The resulting mixture was stirred overnight at room temperature and for 3 h at 40 °C. The mixture was cooled to room temperature and ether (300 mL) was added. The organic phase was washed with sat. $NaHCO_3$ solution, dried over magnesium sulfate and concentrated under reduced pressure. Ether (50 mL) was added in order to precipitate phosphine oxide. The solution was then filtered and concentrated under reduced pressure. To the residue was added methanol (120 mL) and aqueous sodium hydroxide (6 mol L^{-1}, 120 mL). The resulting mixture was stirred for 3 h under reflux and overnight at room temperature. The mixture was extracted with ether three times. The combined organic phase was washed brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane–ether, 3 : 2).

4-Methylcyclohexanol (**17a**) *[7731-28-4]*. 44% yield; mixture (92 : 8) of *cis*- and *trans*-isomers; colourless oil.

4-Isopropylcyclohexanol (**17b**) *[22900-08-9]*. 53% yield; mixture (91 : 9) of *cis*- and *trans*-isomers; colourless oil.

Alternative synthesis of 4-methoxylcyclohexanol (17c) [18068-06-9]. A mixture of *para*-methoxyphenol **18** (7.45 g, 60 mmol) and 5% rhodium on alumina (1.53 g) in ethanol (20 mL) was placed in a 100 mL Parr bomb and hydrogenated overnight under 3.5 bar pressure. The solution was then filtered and concentrated under reduced pressure. The compound was isolated in 100% yield as a mixture (71 : 29) of *cis*- and *trans*-isomers.

Synthesis of dithiocarbonates 19: general procedure. To a suspension of sodium hydride (60% in oil, 40 mmol) in THF (75 mL) was added dropwise a solution of **17** (20 mmol) in THF (75 mL). Then the resulting mixture was stirred for 1 h under reflux and carbon disulfide (60 mmol) was added slowly at room temperature. The resulting mixture was stirred for 30 min. Methyl iodide (80 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature. Iced water was then added at 0 °C and the mixture was treated with aqueous hydrochloric acid (2 mol L^{-1}, 30 mL). The organic phase was separated. The aqueous phase was extracted with ether three times. The combined organic phase was washed with sat. $NaHCO_3$ solution and then with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (elution with pentane).

O-Cyclohexyl S-methyl dithiocarbonate (**19a**). 93% yield; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2–1.8 (m, 8H), 1.9–2.1 (m, 2H), 2.53 (s, 3H), 5.55 (tt, 1H, $^3J_{H_{ax}-H_{ax}}$ = 8.6 Hz, $^3J_{H_{ax}-H_{eq}}$ = 3.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.6, 23.5, 25.1, 30.8, 82.2, 214.8; IR (neat) 2945, 2853, 1050 cm^{-1}; MS (IC NH_3) *m*/*z* 208 (12), 191 (100), 83 (2).

O-(4-Methylcyclohexyl) S-methyl dithiocarbonate (**19b**). 83% yield; mixture (90 : 10) of *cis*- and *trans*-isomers; yellow oil; spectral data for major isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (d, 3H, $^3J_{H-H}$ = 6.0 Hz), 1.0–1.8 (m, 7H), 2.07 (m, 2H), 2.55 (s, 3H), 5.77 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.6, 22.0, 29.1, 29.7, 32.2, 79.1, 214.7; spectral data for minor isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, 3H, $^3J_{H-H}$ = 6.0 Hz), 1.0–1.8 (m, 7H), 2.07 (m, 2H), 2.55 (s, 3H), 5.48 (tt, 1H, $^3J_{H_{ax}-H_{ax}}$ = 11.1 Hz, $^3J_{H_{ax}-H_{eq}}$ = 4.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.1, 21.7, 30.8, 31.5, 32.8, 83.2, 214.7; IR (neat) 2940, 2842, 1050 cm^{-1}; MS (CI NH_3) *m*/*z* 205 (100), 97 (20).

O-(4-Isopropylcyclohexyl) S-methyl dithiocarbonate (**19c**). 89% yield; mixture (92 : 8) of *cis*- and *trans*-isomers; yellow oil; spectral data for major isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, 6H, $^3J_{H-H}$ = 6.8 Hz), 1.0–1.8 (m, 8H), 2.12 (m, 2H), 2.54 (s, 3H), 5.78 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.5, 19.7, 24.4, 29.5, 32.3, 42.9, 80.0, 214.4; spectral data for minor isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (d, 6H, $^3J_{H-H}$ = 6.7 Hz), 1.0–1.8 (m, 8H), 2.12 (m, 2H), 2.54 (s, 3H), 5.44 (tt, 1H, $^3J_{H_{ax}-H_{ax}}$ = 11.1 Hz, $^3J_{H_{ax}-H_{eq}}$ = 4.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.7, 19.8, 27.5, 31.0, 32.2, 42.8, 83.5, 214.6; IR (neat) 2950, 2863, 1050 cm^{-1}; MS (CI NH_3) *m*/*z* 233 (100), 125 (76).

O-(4-Methoxylcyclohexyl) S-methyl dithiocarbonate (**19d**). 90% yield; mixture (73 : 27) of *cis*- and *trans*-isomers; yellow oil; spectral data for major isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2–2.1 (m, 8H), 2.51 (s, 3H), 3.25 (m, 1H), 3.32 (s, 3H), 5.59 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.5, 26.6, 27.1, 55.5, 75.6, 80.1, 214.7; spectral data for minor isomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2–2.1 (m, 8H), 2.52 (s, 3H), 3.25 (m, 1H), 3.32 (s, 3H), 5.53 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.7, 27.0, 27.5, 55.8, 76.4, 81.0, 214.9; IR (neat) 2940, 2863, 1045 cm^{-1}; MS (CI NH_3) *m*/*z* 221 (100), 113 (86), 81 (48).

Oxidative desulfurisation–fluorination of dithiocarbonates 19: general procedure. To a suspension of 1,3-dibromo-5,5-dimethylhydantoin (75 mmol) in dichloromethane (50 mL) successively were added dropwise at −78 °C pyridine (6.75 mL) and 70% HF · py (15 mL). The mixture was stirred for 10 min at room temperature and cooled to 0 °C. A solution of dithiocarbonate **19** (15 mL) in dichloromethane (50 mL) was added dropwise. The resulting mixture was stirred for 1 h at 0 °C, carefully poured into an iced aqueous $NaHCO_3$ solution, neutralised with aqueous sodium hydroxide and extracted with dichloromethane three times. The combined organic phase was washed successively with aqueous hydrochloric acid (1%), aqueous $NaHSO_3$ and brine, and dried over magnesium sulfate. The solvent was removed by distillation under atmospheric pressure. The residue was then purified by distillation "bulb to bulb" (20 mmHg).

Trifluoromethoxycyclohexane (**5a**). 17% yield, colourless oil, ^{19}F NMR (188 MHz, $CDCl_3$) δ −58.1 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.2–2.0 (m, 10H), 4.21 (t, 1H, $^3J_{H_{ax}-H_{ax}}$ = 9.0 Hz, $^3J_{H_{ax}-H_{eq}}$ = 3.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.4, 25.0, 32.4, 77.6, 121.7 (q, $^1J_{C-F}$ = 253 Hz); MS (CI CH_4) *m*/*z* 167 (44), 125 (100).

4-Methyl-1-trifluoromethoxycyclohexane (**5b**). 11% yield; mixture (68 : 32) of *cis*- and *trans*-isomers; colourless oil; spectral data for major isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −58.2 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.97 (d, 3H, $^3J_{H-H}$ = 6.0 Hz), 1.0–2.0 (m, 9H), 4.35 (m, 1H); spectral data for minor isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −58.0 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (d, 3H, $^3J_{H-H}$ = 6.0 Hz), 1.0–2.0 (m, 9H); MS (CI CH_4) *m*/*z* 132 (97), 113 (100).

4-Isopropyl-1-trifluoromethoxycyclohexane (**5c**). 14% yield; mixture (84 : 16) of *cis*- and *trans*-isomers; colourless oil; spectral data for major isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −58.2 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, 6H, $^3J_{H-H}$ = 6.8 Hz), 1.0–2.0 (m, 10H), 4.34 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.8, 23.6, 30.8, 32.3, 42.9, 75.1, 121.8 (q, $^1J_{C-F}$ = 252 Hz); spectral data for minor isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −58.0 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.87 (d, 3H, $^3J_{H-H}$ = 6.7 Hz), 1.0–2.0 (m, 10H), 3.97 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.8, 27.5, 32.4, 32.6, 42.6, 78.6, 121.8 (q, $^1J_{C-F}$ = 252 Hz); MS (CI CH_4) *m*/*z* 209 (7), 225 (100).

4-Methoxy-1-trifluoromethoxycyclohexane (**5d**). 19% yield; mixture (82 : 12) of *cis*- and *trans*-isomers; colourless oil; spectral data for major isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −58.4 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.4–2.3 (m, 8H), 3.29 (s, 3H), 4.28 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 26.7, 27.9, 55.5, 75.2, 75.6 (q, $^3J_{C-F}$ = 2.1 Hz), 121.7 (q, $^1J_{C-F}$ = 252 Hz); spectral data for minor isomer: ^{19}F NMR (188 MHz, $CDCl_3$) δ −58.3 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.4–2.3 (m, 8H), 3.46 (s, 3H), 4.41 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.2, 28.5, 55.7, 75.8, 76.3, 121.7 (q, $^1J_{C-F}$ = 254 Hz); MS (EI) *m*/*z* 198 (52), 166 (13), 81 (61), 71 (100); HR MS calc. for $C_8H_{13}O_2F_3$: 198.0868. Found: 198.0869.

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