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Configurational assignments in trifluoromethylvinyl compounds using through-space carbon–fluorine coupling constants

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ABSTRACT: Long-range carbon–fluorine coupling constants, ${}^nJ(C,F)$ ($n \geqslant 4$), were observed for up to six-bond separated nuclei in some substituted trifluoromethylvinyl compounds ($CF_3CX{=}CYZ$). When the ${}^nJ(C,F)$ in a *Z*-isomer are compared with those in the corresponding *E*-isomer, the ${}^nJ(C,F)$ in one isomer whose substituent including the coupled carbon is proximate to the trifluoromethyl group are always larger than those in the other isomer. Because the coupling constants are transmitted through space, the ${}^nJ(C,F)$ decrease with increase in the spatial distance of the carbon and the fluorine. This relationship can be used to determine the configurational assignments in the two stereoisomers even in the case where only one isomer is obtained. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: NMR; ${}^1H$ NMR; ${}^{13}C$ NMR; ${}^{19}F$ NMR; $J(C,F)$; configurational assignment; trifluoromethylvinyl compounds

INTRODUCTION

Fluorine is often introduced into biologically active compounds to improve their activity by enhancement of the lipophilicity and the change in both steric and electronic properties.[1–4] During the synthesis of trifluoromethylvinyl compounds, both configurational isomers, *Z* and *E*, are often produced simultaneously.[5–7] Hence their separation and identification are indispensable to the examination of each isomer regarding its biological activities.

The *Z*- and *E*-isomers of 1,2-disubstituted olefinic compounds can be easily distinguished by comparing the size of the ${}^3J(H,H)$[8] for the two olefinic protons or the NOE[9] for the protons near the double bond; the *Z*-isomer shows a smaller ${}^3J(H,H)$ and a larger NOE. In general, an increase in the number of substituents makes the differentiation of the isomers difficult because the ${}^3J(H,H)$ cannot be used in tri- or tetrasubstituted olefins and the NOE sharply decreases with the spatial distance between the nuclei.

The configuration in substituted trifluoromethylvinyl compounds can be assigned by other methods using such features as ${}^4J(H,F)$,[10] ${}^{19}F$ chemical shift,[11] ${}^3J(C,F)$,[12] and heteronuclear NOE between a proton and a fluorine. However, the application of these methods to the configurational assignment is limited by the substitution pattern of the vinyl group and the type of the substituents; the ${}^4J(H,F)$ and ${}^{19}F$ chemical shift can be applied only to the isomers which separately possess a trifluoromethyl group and a proton on the two olefinic carbons, and the ${}^3J(C,F)$ can be applied to trisubstituted olefinic compounds with a trifluoromethyl and an alkoxy or amino group on the same olefinic carbon. Therefore, it is desirable to develop a new method which has a more general applicability to the wide range of trifluoromethylvinyl compounds.

The through-space transmission of a spin–spin coupling between spatially proximate nuclei has been studied both experimentally[13,14] and theoretically.[15,16] Unusually large long-range carbon–fluorine coupling constants, ${}^nJ(C,F)$, have been reported in molecules with rigid chemical structures, e.g. the five-bond ${}^{13}C$–${}^{19}F$ coupling of 24.0 Hz for the C-4 methyl carbon and the fluorine in 1,4,8-trimethyl-5-fluorophenanthrene[13] and the six-bond ${}^{13}C$–${}^{19}F$ coupling of 5.5 Hz for the C-1 carbon and the F-12 fluorine in 9,10,11,12-tetrafluoro-5,6-dihydrobenzo[*b*]naphth[2,1-*f*]oxepin.[17]

We have recently found that smaller but explicit ${}^nJ(C,F)$ are observed even in flexible molecules when the digital resolution in their ${}^{13}C$ NMR spectra is increased sufficiently. In this paper, we report the ${}^nJ(C,F)$ in some trifluoromethylvinyl compounds and demonstrate that the ${}^nJ(C,F)$ can be utilized to determine the *E* and *Z* configuration.

RESULTS AND DISCUSSION

The ${}^1H$ and ${}^{13}C$ NMR spectra of compounds **1–5** (Fig. 1) were assigned using conventional NMR techniques such as DQF-COSY,[18] DEPT,[19] HETCOR[20] and

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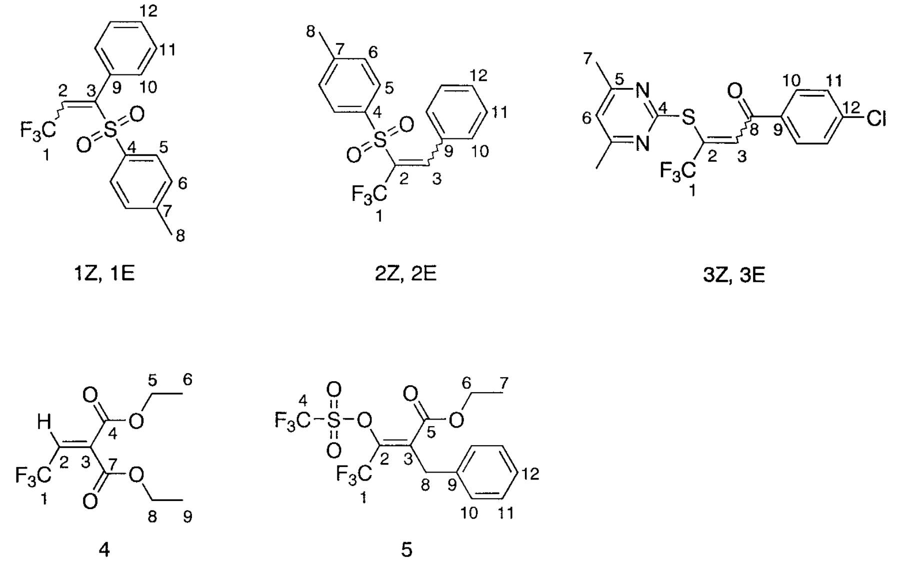

Figure 1. Structures and numbering of the trifluoromethylvinyl compounds investigated.

COLOC.[21] The assignments of *Z*- and *E*-isomers were confirmed based on the several parameters listed in Table 1 as mentioned below. The ^3J(C-9,H-2) of 5.9 Hz in **1Z** is less than that of 8.2 Hz in **1E**,[22] and the NOE between H-2 and H-10 was observed only in **1Z**. In the ^{1}H{^{19}F}-NOE difference spectra shown in Fig. 2, the heteronuclear NOE between F-1 and H-3 at 7.81 ppm was observed only in **2Z** and that between F-1 and H-10 at 7.54 ppm was observed only in **2E**. The smaller ^3J(C-1,H-3), the larger ^4J(H-3,F-1) and the larger $|\delta F|$ in **2Z** than those in **2E** are consistent with the assignment. The configurational assignments of **3Z** and **3E** were confirmed in a way similar to that for **2Z** and **2E**. The two ethoxycarbonyl substituents in **4** were differentiated using the three-bond proton–carbon coupling; ^3J(C-4, H-2) of 6.9 Hz is less than ^3J(C-7,H-2) of 11.4 Hz. The configuration of **5** was determined using the ^{1}H{^{19}F}-NOE difference technique.

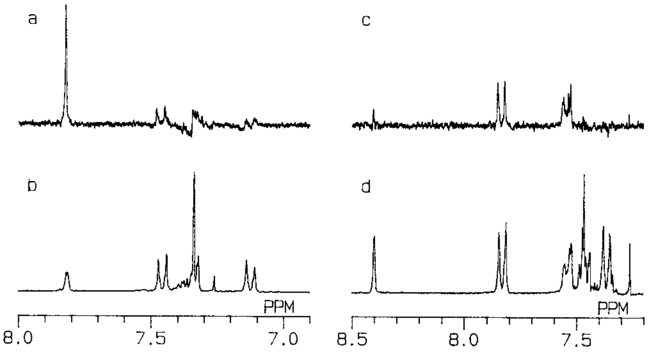

Figure 2. (a) ^{1}H{^{19}F}-NOE difference and (b) ^{1}H NMR spectra of **2Z** and (c, d) the corresponding spectra of **2E**.

The carbon–fluorine coupling constant can be easily obtained in the ^{1}H-decoupled ^{13}C NMR spectra because a distinct quartet is observed when a carbon is coupled to the three equivalent fluorine nuclei. Table 2 shows the absolute value of the carbon–fluorine coupling constants observed in compounds **1**–**5**. No attempt was made to obtain the relative sign of the coupling constants. The ^1J(C,F) are about 275 Hz, the ^2J(C,F) are in the range 30–40 Hz and the ^3J(C,F) are in the range 2–6 Hz. These coupling constants are mainly transmitted through chemical bonds and rapidly decrease with increase in the number of intervening

Table 1. Chemical shifts (ppm), coupling constants (Hz) and NOEs for configurational assignments

Compound	δ(F-1)	^4J(H-3, F-1)	^3J(C,H)	NOE[a]
1Z	−53.7		5.9 (C-9, H-2)	H-10{H-2}
1E	−57.9		8.2 (C-9, H-2)	n.o.
2Z	−60.3	1.5	7.6 (C-1, H-3)	H-3{F-1}
2E	−54.6	n.o.[b]	13.0 (C-1, H-3)	H-10{F-1}
3Z	−65.9	1.2	6.3 (C-1, H-3)	H-3{F-1}
3E	−62.6	n.o.	12.7 (C-1, H-3)	n.o. H{F}
4	−62.1		6.9 (C-4, H-2), 11.4 (C-7, H-2)	n.o. H{F}
5	−61.8			H-8{F-1}

[a] Observed NOEs are listed; the irradiated nuclei are shown in braces and the observed nucleus precedes the braces.
[b] Not observed.

Table 2. Carbon–fluorine coupling constants (Hz)[a]

Compound	C-1	C-2	C-3	C-4	C-5	C-7	C-8	C-9	C-10
1Z	272.3	39.7	5.9	0.4	0.5				0.8
1E	273.3	35.8	5.1	n.o.[b]	n.o.			n.o.	1.4
2Z	275.2	30.2	5.7		0.4			n.o.	0.8
2E	275.7	33.5	2.8	0.9	0.7			0.4	2.6
3Z	275.2	34.9	3.9					n.o.	
3E	275.5	35.7	2.8				n.o.	1.1	
4	271.4	36.4	5.1	0.4		1.1			
5	276.1	39.4	1.9				2.4	0.7	0.5

[a] Absolute value is shown.

[b] Not observed.

chemical bonds. For further separated nuclei, smaller ^{n}J(C,F) can be detected. The ^{5}J(C-4,F) and the ^{6}J(C-5,F) in **1Z** are 0.4 and 0.5 Hz, respectively, while those in **1E** were not observed. On the other hand, the ^{5}J(C-10,F) in **1Z** is 0.8 Hz and that in **1E** is 1.4 Hz. Larger ^{n}J(C,F) were observed in the configurational isomer in which the phenyl or 4-methylphenylsulfonyl substituent containing the coupled carbons is spatially proximate to the trifluoromethyl group. A similar tendency was found in the pair **2Z** and **2E**. The ^{4}J(C-9,F) and ^{5}J(C-10,F) in **2Z** were less than the corresponding coupling constants in **2E**. Further, the ^{5}J(C-9,F) in **3Z** was not observed whereas that in **3E** was 1.1 Hz. Because the linewidths at half-height of the protonated carbons such as C-6, C-7 and C-11 in **3Z** and **3E** are less than 0.5 Hz and the linewidth of C-10 in **3E** probably becomes broader owing to the unresolved long-range carbon–fluorine coupling, the fact that the linewidths of C-10 in **3Z** and **3E** are 0.5 and 0.9 Hz, respectively, are well explained. The ^{4}J(C-7,F) of 1.1 Hz is larger than the ^{4}J(C-4,F) of 0.4 Hz in **4**. All of the observed ^{n}J(C,F) and the linewidths have derived the rule that when the ^{n}J(C, F) are compared between *Z*- and *E*-isomers, the more spatially proximate carbon–fluorine assumes larger values. Therefore, ^{n}J(C,F) can be used as a criterion for the determination of the configurational isomers.

Compounds **1**–**4** are all trisubstituted olefinic compounds and the remaining olefinic proton can play a key role in determining the configuration through the measurement of ^{3}J(C,H), ^{4}J(F,H) and $^{1}\mathrm{H}\{^{1}\mathrm{H}\}$-NOE. Compound **5** is a tetrasubstituted olefinic compound, and only one isomer is obtained as a major product. In this compound, ^{4}J(C-8,F-1), ^{5}J(C-9,F-1) and ^{6}J(C-10,F-1) are 2.4, 0.7 and 0.5 Hz, respectively, and ^{4}J(C-5,F-1), ^{6}J(C-6,F-1) and ^{7}J(C-7,F-1) were not observed. Because the six-bond arrangement from F-1 to C-10 is not rigid and also unconjugated, there must be a contribution of the through-space transmission of the coupling. Accordingly, the *Z* configuration can be determined for **5** even though only one isomer is obtained. The ^{5}J(H-8,F-1) of 1.1 Hz is also ascribed to the through-space transmission of the coupling.

It is interesting to compare $^{1}\mathrm{H}\{^{19}\mathrm{F}\}$-NOE with ^{n}J(C, F) as the methods to identify the configurational isomers. The two ethoxycarbonyl groups in **4** could be distinguished using the ^{3}J(C,H) and also the ^{4}J(C,F) in the way described before. However, the $^{1}\mathrm{H}\{^{19}\mathrm{F}\}$-NOE difference spectrum could not distinguish the two ethoxycarbonyl groups because the methylene protons, H-8, are very far from the trifluoromethyl group and the protons are expected to relax predominantly due to the dipole–dipole interaction within the methylene and the methyl protons. This example demonstrates the superiority of the ^{n}J(C,F) method to the $^{1}\mathrm{H}\{^{19}\mathrm{F}\}$-NOE method in distinguishing the configurational isomers.

The ^{n}J(C,F) basically decrease with the increase in the spatial distance of the two nuclei;[14] therefore, the conformation of a compound considerably influences the size of ^{n}J(C,F) through the change in the internuclear distance. However, the ^{n}J(C,F) are not only dependent on the spatial distance of the two nuclei. The quaternary carbons C-9 in **1E** and C-8 in **3E** did not show any recognizable ^{4}J(C,F), whereas ^{4}J(C-8,F-1) in **5** is 2.4 Hz even though the spatial distances between the carbon and the fluorine are supposed to be the same for the three compounds. This result can be ascribed to the lack of an intermediate proton for the quaternary carbons; the proton plays an important role in transmitting the spin information.[16]

Besides the configurational assignments in trifluoromethylvinyl compounds described in this paper, the through-space carbon–fluorine coupling constant may be utilized for other purposes, e.g. the assignment of the stereoisomers for fluorine-containing cyclic compounds, the ^{13}C NMR assignment for the carbon which is spatially proximate to a fluorine nucleus in a flourine-containing compound and even the investigation of a conformational preference in a favorable situation.

EXPERIMENTAL

Synthesis of compounds

4-Methylphenyl(3,3,3-trifluoro-1-phenyl-1-propenyl)sulfone (1*Z*, 1*E*) and 4-methylphenyl[2-phenyl-1-(trifluoromethyl)-1-ethenyl]sulfone (2*Z*, 2*E*). To a suspension of NaH (60%, 0.72 g, 0.018 mol) in DMF (4 ml) was added a DMF (4 ml) solution of *p*-toluenethiol (2.24 g, 0.018 mol) dropwise at room temperature. After stirring for 30 min, this solution was added to a DMF (6 ml) solution of 2-chloro-1-phenyl-3,3,3-trifluoropropene[6] (3.10 g, 0.015 mol) at 60°C and stirred for 30 min at the same temperature. The reaction mixture was poured into ice–water, extracted with diethyl ether and the ether layer was washed with 1 M NaOH solution and brine. The extract was dried with magnesium sulfate and concentrated. The crude material was dissolved in acetic acid (20 ml) and treated with hydrogen peroxide (30%, 10 ml) at 70°C and stirred at 100°C for 3 h. After saturated aqueous Na_2SO_3 had been cautiously added to the solution, the mixture was poured into ice–water. The precipitates were filtered off and dried to give the product. Each isomer was isolated by preparative HPLC (LC-20, Japan Analytical Industry) on an octadecylsilylated gel column (YMC-Pack ODS/D, YMC) using acetonitrile–water (65:35, v/v) as the mobile phase at a flow-rate of 9.5 ml min^{-1}. The UV detector was set at 220 nm. **1Z**: ^{1}H NMR, δ = 2.38 (s, 3H, H-8), 6.10 [q, 1H, *J*(H,F) = 8.8 Hz, H-2], 7.19 (d, 2H, *J* = 8.4 Hz, H-6), 7.22 (d, 2H, H-10), 7.27 (t, 2H, *J* = 7.3 Hz, H-11), 7.36 (tt, 1H, *J* = 7.2, 2.2 Hz, H-12), 7.50 (d, 2H, *J* = 8.4 Hz, H-5); ^{13}C NMR, δ = 21.7 (C-8), 120.2 (C-1), 127.4 (C-2), 128.3 (C-11), 129.0 (C-5), 129.5 (C-10), 129.7 (C-6), 130.0 (C-12), 133.2 (C-9), 135.2 (C-4), 145.5 (C-7), 153.3 (C-3). **1E**: ^{1}H NMR, δ = 2.41 (s, 3H, H-8), 7.00 (d, 2H, H-10), 7.13 [q, 1H, *J*(H,F) = 7.3 Hz, H-2], 7.22 (d, 2H, *J* = 8.2 Hz, H-6), 7.27 (t, 2H, *J* = 7.6 Hz, H-11), 7.38 (tt, 1H, *J* = 7.4, 2.0 Hz, H-12), 7.43 (d, 2H, *J* = 8.4 Hz, H-5); ^{13}C NMR, δ = 21.7 (C-8), 121.5 (C-1), 124.9 (C-2), 128.0 (C-9), 128.0 (C-11), 129.2 (C-5), 129.6 (C-10), 129.7 (C-6), 129.9 (C-12), 133.2 (C-4), 145.6 (C-7), 153.3 (C-3). **2Z**: ^{1}H NMR, δ = 2.36 (s, 3H, H-8), 7.13 (d, 2H, *J* = 8.6 Hz, H-6), 7.33 (d, 2H, H-10), 7.33 (m, 2H, H-11), 7.38 (m, 1H, H-12), 7.46 (d, 2H, *J* = 8.4 Hz, H-5), 7.81 [q, 1H, *J*(H,F) = 1.5 Hz, H-3]; ^{13}C NMR, δ = 21.6 (C-8), 121.4 (C-1), 128.0 (C-11), 128.2 (C-5), 129.2 (C-10), 129.3 (C-6), 130.3 (C-12), 130.8 (C-9), 134.9 (C-2), 137.2 (C-4), 145.1 (C-7), 145.8 (C-3). **2E**: ^{1}H NMR, δ = 2.45 (s, 3H, H-8), 7.36 (d, 2H, *J* = 8.6 Hz, H-6), 7.45 (m, 2H, H-11), 7.47 (m, 1H, H-12), 7.54 (d, 2H, *J* = 8.0 Hz, H-10), 7.83 (d, 2H, *J* = 8.4 Hz, H-5), 8.40 (s, 1H, H-3); ^{13}C NMR, δ = 21.7 (C-8), 121.0 (C-1), 128.4 (C-5), 128.8 (C-11), 130.0 (C-6), 130.3 (C-10), 130.7 (C-9), 131.6 (C-12), 131.7 (C-2), 136.7 (C-4), 145.2 (C-7), 148.3 (C-3).

1-(4-Chlorophenyl)-3-[(4,6-dimethyl-2-pyrimidinyl)thio]-4,4,4-trifluoro-2-buten-1-one (3*Z*, 3*E*). 1-(4-Chlorobenzoyl)-3,3,3-trifluoroacetone (**3a**) was prepared by Claisen condensation between ethyl trifluoroacetate and *p*-chloroacetophenone according to the method given in the literature.[23] 1-(4-Chlorobenzoyl)-3,3,3-trifluoro-2-trifluoromethylsulfonyloxypropene (**3b**) was prepared from **3a** and trifluoromethanesulfonic anhydride in the presence of NaH. A DMF (25 ml) solution of 4,6-dimethyl-2-mercaptopyrimidine (1.7 g, 0.012 mol) was gradually added to a suspension of NaH (60%, 0.48 g, 0.012 mol) in DMF (15 ml) under ice cooling and stirred at room temperature for 30 min followed by adding a DMF (12 ml) solution of **3b** (3.8 g, 0.010 mol) and stirring the resulting mixture at room temperature for several hours. The reacted mixture was poured into water and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried with magnesium sulfate and concentrated. The mixture was chromatographed on a silica gel column [hexane–ethyl acetate (4:1)] to afford **3Z** (2.0 g, 53%) and **3E** (0.39 g, 11%). **3Z**: ^{1}H NMR, δ = 2.26 (s, 6H, H-7), 6.70 (s, 1H, H-6), 7.30 (d, 2H, *J* = 8.6 Hz, H-11), 7.66 [q, 1H, *J*(H,F) = 1.2 Hz, H-3], 7.90 (d, 2H, *J* = 8.6 Hz, H-10); ^{13}C NMR, δ = 23.4 (C-7), 117.1 (C-6), 121.9 (C-1), 128.7 (C-11), 129.6 (C-2), 130.4 (C-10), 133.9 (C-9), 139.7 (C-3), 140.5 (C-12), 167.1 (C-4), 167.5 (C-5), 188.9 (C-8). **3E**: ^{1}H NMR, δ = 2.47 (s, 6H, H-7), 6.85 (s, 1H, H-6), 7.49 (d, 2H, *J* = 8.8 Hz, H-11), 7.32 (s, 1H, H-3), 8.23 (d, 2H, *J* = 8.8 Hz, H-10); ^{13}C NMR, δ = 23.7 (C-7), 117.2 (C-6), 121.5 (C-1), 126.0 (C-2), 129.0 (C-11), 130.9 (C-10), 133.4 (C-9), 140.9 (C-12), 146.7 (C-3), 167.8 (C-5), 168.8 (C-4), 189.5 (C-8).

Diethyl 2-(2,2,2-trifluoroethylidene)malonate (4). Compound 4 was prepared according to the method given in the literature.[24] ^{1}H NMR, δ = 1.33 (t, 3H, H-6), 1.34 (t, 3H, H-9), 4.32 (q, 2H, H-5), 4.36 (q, 2H, H-8), 6.76 [q, 1H, *J*(H,F) = 7.7 Hz, H-2]; ^{13}C NMR, δ = 12.9 (C-6), 12.9 (C-9), 61.7 (C-8), 62.2 (C-5), 121.1 (C-1), 126.7 (C-2), 135.7 (C-3), 160.9 (C-4), 161.9 (C-7).

Ethyl (*Z*)-2-benzyl-4,4,4-trifluoro-3-trifluoromethylsulfonyloxy-2-butenoate (5). To a suspension of NaH (60%, 2.64 g, 0.066 mol) in pentane (120 ml) at room temperature was added ethyl 2-benzyl-4,4,4-trifluoroacetoacetate[25] (16.44 g, 0.060 mol) dropwise. After stirring for 30 min, trifluoromethanesulfonic anhydride (18.62 g, 0.066 mol) was added dropwise at 0°C. The reaction mixture was stirred for 30 min at room temperature, then filtered and the filtrate was concentrated. Compound **5** (14.9 g, 61%) was isolated by column chromatography (hexane–ethyl acetate). ^{1}H NMR, δ = 1.15 (t, 3H, H-7), 3.97 [q, 2H, ^{5}J(H,F) = 1.1 Hz, H-8], 4.18 (q, 2H, H-6), 7.19 (d, 2H, H-10), 7.29 (t, 2H, H-11), 7.31 (t, 1H, H-12); ^{13}C NMR, δ = 13.5 (C-7), 34.2 (C-8), 62.7 (C-6), 118.3 (C-4), 119.2 (C-1), 127.6 (C-12), 128.3 (C-10), 128.8 (C-11), 134.1 (C-9), 134.9 (C-2), 136.0 (C-3), 163.1 (C-5).

NMR experiments

NMR spectra were recorded at 297 K on a JEOL JNM-GSX400 spectrometer operating at 399.8 and 100.5 MHz for ^{1}H and ^{13}C, respectively, and a Varian Gemini 300 spectrometer operating at 282.3 MHz for ^{19}F. The NMR sample was prepared by dissolving 5–50 mg of each compound in 0.6 ml of $CDCl_3$ in a 5 mm NMR tube. The chemical shifts are reported in parts per million *vs.* internal tetramethylsilane for ^{1}H and ^{13}C and external trichlorofluoromethane for ^{19}F. The conditions for ^{1}H NMR were a 40° pulse angle, a 10 s delay between pulses, a 4.0 kHz spectral width, 32K data points and 32 scans. The conditions for survey ^{13}C NMR spectra were a 60° pulse angle, a 3 s delay between pulses, a 22.0 kHz spectral width, 32K data points and more than 512 scans. For the measurement of ^{n}J(C,F), the spectral width was narrowed and the number of data points was increased to give a digital resolution of better than 0.14 Hz and no window function before Fourier transformation was employed. The ^{3}J(C,H) were obtained from ^{1}H-coupled ^{13}C NMR spectra. The conditions for ^{19}F NMR were a 40° pulse angle, a 10 s delay between pulses, a 65.4 kHz spectral width, 64K data points and 32 scans. For the assignment of ^{1}H and ^{13}C NMR spectra, DQF-COSY, DEPT, HETCOR and COLOC were carried out using standard pulse sequences. ^{1}H{^{19}F}-NOE difference spectra with a 30 s saturation time were obtained on a JEOL JNM-GSX270 spectrometer equipped with a ^{1}H (270.2 MHz) and ^{19}F (254.2 MHz) dual probe. The dissolved oxygen was removed by repeating a freeze–thaw cycle five times before the measurement.

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