Electronic Supplementary Material (ESI) for Chemical Communications
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SUPPLEMENTARY INFORMATION

Synthesis and structure of all-*syn*-1,2,3,4-tetrafluorocyclohexane

Alastair J Durie, Alexandra M. Z. Slawin, Tomas Lebl, Peer Kirsch and David O'Hagan.

Synthesis

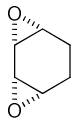
General Experimental

All chemicals were purchased from Acros, Sigma Aldrich, Alfa Aeser, Fisher Scientific, Fluorochem or Merck. Triphenylphosphite was purified by separation between diethyl ether and 5% aq. NaOH, then the organic layer was washed with water and sat. aq. NaCl, dried over Na_2SO_4 and the solvent removed under reduced pressure. All non-aqueous reactions were carried out in oven-dried glassware under an inert argon atmosphere. Anhydrous CH_2Cl_2 was obtained for a MBraun MB SPS-800 solvent purification system dispensed under an atmosphere of argon gas. Thin layer chromatography was carried out on aluminium backed Merck TLC silica gel 60 F_{254} plates. These plates were visualised using UV light at a wavelength of 254 nm, potassium permanganate or phosphomolybdic acid.

All NMR spectra were recorded using either a Bruker Avance II 400, Bruker Avance 300 or 500 spectrometers in deuterated solvents. ^{1}H NMR spectra were recorded at either 300, 400 or 500 MHz. ^{13}C NMR spectra were recorded using the DEPTQ pulse sequence and broadband proton decoupling at either 75, 100 or 126 MHz. ^{19}F NMR spectra were recorded at 282, 376 or 470 MHz. All chemical shifts, δ, are stated in units of parts per million (ppm), relative to a standard reference point, for ^{1}H NMR and ^{13}C NMR the reference point is TMS, where δ_H and δ_C is 0.00 ppm. For ^{19}F NMR the reference point is CCl_3F, where δ_F is 0.00 ppm.

Melting points were determined using a Griffin MPA350 melting point apparatus and are uncorrected. High and low resolution mass spectra were obtained using electrospray, in both negative and positive mode or chemical ionisation. Electospray spectra were run using a micromass LCT spectrometer. Chemical ionisation spectra were run using a Micromass GCT spectrometer.

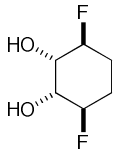
Diepoxide 4 [1,2]



Triphenylphosphite (1.75 mL, 2.07 g, 6.55 mmol, eq 1.05) in CH_2Cl_2 (50 mL) was treated with ozone at -78 °C until the solution went blue. A solution of 1,3-cyclohexadiene **2** (0.60 mL, 0.50 g, 6.24, eq 1) in CH_2Cl_2 (5 mL) was added at -78 °C under argon and the reaction warmed to -25 °C and stirred for 2 h. Solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (20 mL) and added to a solution of $Ru(PPh_3)_3Cl_2$ (60 mg, 0.0624 mmol, eq 0.01) in CH_2Cl_2 (20 mL) at 0 °C under argon. The reaction was left to stir for 1 h at 0 °C and then 1 h at RT. Solvent was removed under reduced pressure and the product purified over silica gel, eluting with ether: hexane (1:4) to give the diepoxide **4** (329 mg, 46%) as a colourless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 3.43 – 3.31 (2H, m, C<u>H</u>O), 3.07 – 3.04 (2H, m, C<u>H</u>O), 1.81 – 1.79 (4H, m, C<u>H</u>$_2$).

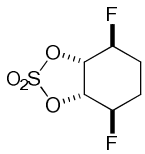
1. R. W. Murray, *J. Am. Chem. Soc.*, 1969, **91**, 5358.
2 M. Suzuki, H. Ohtake, Y. Kameya, N. Hamanaka, R. Noyori, *J. Org. Chem.*, 1989, **54**, 5292.

3,6-Difluorocyclohexane-1,2-diol 5



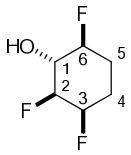
A solution of diepoxide **4** (320 mg, 2.86 mmol, eq 1) in $Et_3N.3HF$ (3.5 mL, 3.5 g, 21.5 mmol, eq 7.5) was heated to 90 °C for 3 h. The reaction was quenched with sat. aq. $NaHCO_3$ (50 mL) and the product extracted into diethyl ether (50 mL × 4). The combined organics were dried and the solvent removed using reduced pressure, to give difuorodiol **5** (466 mg), as a yellow crystalline solid, which was used without further purification. A sample for analysis was purified by recrystallisation from $CHCl_3$. **mp** 110 - 112 °C ($CHCl_3$); **^{1}H {^{19}F} NMR** (400 MHz, $CDCl_3$) δ_H 4.69 – 4.62 (2H, m, C<u>H</u>F), 4.02 – 3.98 (2H, m, C<u>H</u>O), 2.68 (2H, br. S, O<u>H</u>), 1.94 – 1.79 (4H, m, C<u>H</u>$_2$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ_c 90.9 (d, *J* 170.7 Hz, <u>C</u>HF), 71.4 (dd, *J* 24.1, 3.8 Hz, <u>C</u>HO), 24.0 (dd, *J* 19.6, 6.8 Hz, <u>C</u>H$_2$); **^{19}F {^{1}H} NMR:** δ_F(376 MHz, $CDCl_3$) δ_F -193.4 (2F, s); **HRMS** *m/z* (Cl^+) [Found: $(M+H)^+$ 153.0734. $C_6H_{11}O_2F_2^+$ requires *m/z* 153.0727]; **MS** (ES^+) *m/z* 153 ($[M+H]^+$, 8%), 135 ($[M+H-H_2O]^+$, 20%), 133 ($[M+H-HF]^+$, 25%), 115 ($[M+H-H_2O-HF]^+$, 100%).

Cyclic sulfate 6



Pyridine (730 µL, 710 mg, 8.94 mmol, eq 3) and thionyl chloride (430 µL, 710 mg, 5.97 mmol, eq 2) were added to a solution of difluorodiol **5** (460 mg, 2.98 mmol, eq 1) in CH_2Cl_2 (50 mL) at 0 °C under argon. The reaction was stirred, warming slowly to room temperature over 14 h. The reaction was then quenched using sat. aq. $CuSO_2$ (50 mL) and the product extracted into CH_2Cl_2 (50 mL × 3). The combined organics were dried and the solvent removed under reduced pressure. The residue was dissolved in MeCN (60 mL)and then $NaIO_4$ (1.3 mg, 5.96 mmol, eq 2) was added to the solution. This mixture was cooled to 0 °C and $RuCl_3.xH_2O$ (3 mg, 0.015, eq 0.005) was added followed by water (20 mL). The reaction was warmed to RT, stirred for 2 h and then concentrated under reduced pressure. The product was extracted into diethyl ether (50 mL × 3) and the combined organics were dried and the solvent removed under reduced pressure. The resulting oil was purified over silica gel, eluting with ether: hexane (1:9), to give cyclic sulfate **6** (214 mg, 35% from **4**) as a colourless cystaline solid. **mp** 64 - 65 °C (MeCN). **^{1}H {^{19}F} NMR** (400 MHz, $CDCl_3$) δ_H 5.15 – 5.10 (2H, m, C<u>H</u>O), 5.09 – 5.04 (2H, m, C<u>H</u>F), 2.09 – 1.87 (4H, m, C<u>H</u>$_2$); **^{19}F {^{1}H} NMR:** δ_F(376 MHz, $CDCl_3$) δ_F 189.6 (2F, s); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_c 87.0 (d, *J* 177.0 Hz, <u>C</u>HF), 81.8 (dd, *J* 32.7, 3.5 Hz, <u>C</u>HO), 22.8 (dd, *J* 20.4, 6.9 Hz, <u>C</u>H$_2$); **HRMS** *m/z* (Cl$^+$) [Found: (M+H)$^+$ 215.0186. $C_6H_9O_4SF_2^+$ requires *m/z* 215.0190]; **MS** (Cl$^+$) *m/z* 215 ([M+H]$^+$, 10%), 195 ([M+H-HF]$^+$, 10%), 117 (M+H-H_2SO_4, 100 %).

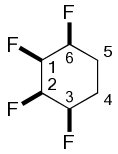
2,3,6-Trifluorocyclohexanol 7



A solution of the cyclic sulfate **6** (260 mg, 1.21 mmol, eq 1) in $Et_3N.3HF$ (3.0 mL, 3.0 g, 18.4 mmol, eq 15) was heated to 120 °C for 20 h. The reaction was quenched with sat. aq. $NaHCO_3$ (50 mL) and extracted into diethyl ether (50 mL × 4). The combined organics were dried and the solvent removed using reduced pressure. The residue was purified over silica gel eluting with ethyl acetate: hexane (3:7), to give the 2,3,6-Trifluorocyclohexanol **7** (130 mg, 70%) as colourless crystalline solid. **mp** 98 - 99 °C (Et_2O); **^{1}H {^{19}F} NMR** (400 MHz, $CDCl_3$) δ_H 4.81 – 4.76 (1H, m, C<u>H</u>F-2), 4.24 – 3.86 (3H, m, C<u>H</u>-1,3 and 6) 2.03 – 1.92 (1H, m, C<u>H</u>H), 1.88 – 1.64 (2H, m, C<u>H</u>H), 1.33 – 1.19 (1H, m, C<u>H</u>H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ_c 92.6 (dd, *J* 179.1, 10.3 Hz, <u>C</u>F-6), 92.5 (ddd, J 186.7, 17.0, 10.6 Hz, <u>C</u>F-2), 88.1 (ddd, *J* 177.3, 16.4, 1.3 Hz, <u>C</u>F-3), 72.7 (ddd, *J* 19.6, 19.6, 2.3 Hz, <u>C</u>HO), 24.3 – 23.6 (m, <u>C</u>H$_2$); **^{19}F {^{1}H} NMR:**

δ_F(376 MHz, $CDCl_3$) δ_F -187.4 (1F, d, *J* 2.7 Hz, F-6), -201.4 (1F, dd, *J* 15.8, 2.7 Hz, F-2), -202.1 (1F, d, *J* 15.8 Hz, F-3); **HRMS** *m/z* (ES^+) [Found: $(M+Na)^+$ 177.0499. $C_6H_9OF_3Na^+$ requires *m/z* 177.0503]; **MS** (ES^+) *m/z* 236, 177 ($[M+Na]^+$, 100%).

1,2,3,4-Tetrafluorocyclohexane 8

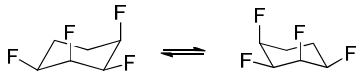


Tf_2O (150 µL, 250 mg, 0.89 mmol, eq 7) was added to a solution of 2,3,6-trifluorocyclohexanol **7** (19 mg, 0.12 mmol, eq 1) in pyridine(0.5 mL) and the reaction left to stir for 2 h. The reaction was quenched using sat. aq. $CuSO_4$ (20 mL) and extracted into diethyl ether (20 mL × 4). The combined organics were dried and the solvent removed under reduced pressure. The residue was dissolved in $Et_3N.3HF$ (0.5 mL, 0.5 g, 3.1 mmol, eq 26) and heated to 120 °C for 16 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and extracted into diethyl ether (20 mL × 4). The combined organics were dried and the solvent removed using reduced pressure. Purification over silica gel, eluting with CH_2Cl_2, gave 1,2,3,4-tetrafluorocyclohexane **8** (6.7 mg, 35%) as a colourless crystalline solid. **mp** 82-83 °C ($CHCl_3$); **^{1}H {^{19}F} NMR** (400 MHz, $CDCl_3$) δ_H 4.74 – 4.56 (4H, m CHF), 2.23 – 2.12 (2H, m, CHH), 1.62 – 1.50 (2H, m, CHH); **^{13}C NMR** (126 MHz, $CDCl_3$) δ_c 87.6 (dddd, *J* 193.0, 17.4, 17.4, 4.7 Hz, CHF-2 and 3), 86.9 (ddd, *J* 186.4, 17.9, 5.0 Hz, CHF-1 and 4), 21.9 – 21.6 (m, CH_2); **^{19}F {^{1}H} NMR:** δ_F(282 MHz, $CDCl_3$) δ_F -195.2 (2F, br. s, F-1 and 4), -209.8 (2F, br. s, F-2 and 3); **HRMS** *m/z* (Cl^+) [Found: $(M+H-HF)^+$ 137.0591. $C_6H_8F_3^+$ requires *m/z* 137.0578]; **MS** (ES^+) *m/z* 137 (M+H-HF, 7%), 117 ($[M+H-2HF]^+$, 100%).

2D EXSY spectroscopy

2D ^{19}F spectra were recorded using Bruker AVANCE 500 MHz spectrometer equipped with 5 mm QNP-probe at 200 K. The spectra were acquired using *noesyph* sequence which was adjusted by adding ^{1}H decoupling for directly detected dimension and the ^{1}H 180° refocusing pulse in the middle of t_1 evolution period to achieve decoupling in the F1 dimension. Each spectrum was digitised using 1024 points in F2 dimension and 128 points in F1 dimension which was later zero-filled to 1024 points. 8 scans were accumulated for each increment with interscan delay 2s.

^{19}F-NMR Data for Eyring Plot analysis for the ring interconversion of 1

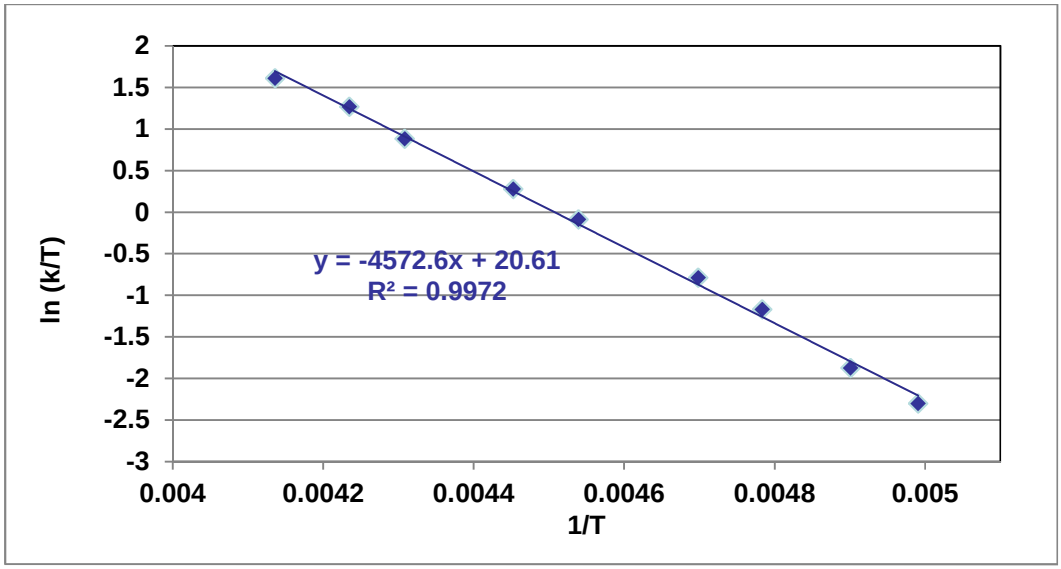


eaea *aeae*

The ^{19}F spectra in CD_2Cl_2 were recorded using Bruker AVANCE 500 MHz spectrometer equipped with 5 mm QNP-probe across the temperature range 200-242 K. Complete lineshape analysis was carried out using Bruker Topspin D-NMR module.

Temperature dependence of the rate constant of the ring interconversion.

T [K]	k [Hz]
200.38	20.0
204.05	31.3
209.06	64.9
212.85	96.8
220.30	201.8
224.59	296.8
232.11	561.7
236.16	837.7
241.79	1208.5



Fitting experimental data to the Eyring equation provides activation parameters of the ring interconversion process $\Delta G^{\#}_{298}$ = 45.8±0.1 kJ.mol^{-1}, $\Delta H^{\#}$ = 38.0 ± 0.8 kJ.mol^{-1} and $\Delta S^{\#}$ = - 26.2±3.5 J.K^{-1}.mol^{-1}

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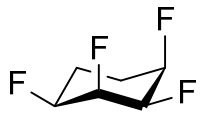
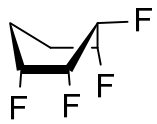
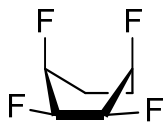
Theory Study MP2/6-311+G(2d,p)//B3LYP/6-311+G(2d,p))

Computational Study on Relative Energies of the Chair and Boat Conformers for Ring Interconversion of 1

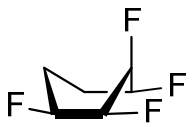
The geometries were optimized on the B3LYP/6-311+G(2d,p) level of theory, and the absence of negative eigenfrequencies was verified. Then, single point energies for these optimized structures were calculated on the MP2/6-311+G(2d,p) level, using the B3LYP zero point energies (ZPE).

Chair - *aeae* 	B3LYP/6-311+G(2d,p)// B3LYP/6-311+G(2d,p)	MP2/6-311+G(2d,p)// B3LYP/6-311+G(2d,p)
E [kcal mol^{-1}]	-397225.30135925	-396340.96372675
ZPE [kcal mol^{-1}]	86.91676000	86.91676000
E + ZPE [kcal mol^{-1}]	-397138.38459925	-396254.04696675
Relative Energy [kcal mol^{-1}]	0.00	0.00
Dipole Moment m [D]	4.91	5.44

Boat - *aaee* 	B3LYP/6-311+G(2d,p)// B3LYP/6-311+G(2d,p)	MP2/6-311+G(2d,p)// B3LYP/6-311+G(2d,p)
E [kcal mol^{-1}]	-397218.01231925	-396333.09450025
ZPE [kcal mol^{-1}]	86.94605000	86.9460500
E + ZPE [kcal mol^{-1}]	-397131.06626925	-396246.14845025
Relative Energy [kcal mol^{-1}]	7.32	7.90
Dipole Moment m [D]	4.77	5.30

Boat - *aeea* 	B3LYP/6-311+G(2d,p)// B3LYP/6-311+G(2d,p)	MP2/6-311+G(2d,p)// B3LYP/6-311+G(2d,p)
E [kcal mol^{-1}]	-397216.38621575	-396331.54325750
ZPE [kcal mol^{-1}]	86.96593000	86.96593000
E + ZPE [kcal mol^{-1}]	-397129.42028575	-396244.57732750
Relative Energy [kcal mol^{-1}]	8.96	9.47
Dipole Moment m [D]	5.82	6.46

Boat - *eaae*	B3LYP/6-311+G(2d,p)// B3LYP/6-311+G(2d,p)	MP2/6-311+G(2d,p)// B3LYP/6-311+G(2d,p)
E [kcal mol^{-1}]	-397218.26400950	-396333.51843925
ZPE [kcal mol^{-1}]	86.99080000	86.99080000
E + ZPE [kcal mol^{-1}]	-397131.27320950	-396246.52793925
Relative Energy [kcal mol^{-1}]	7.11	7.52
Dipole Moment m [D]	3.31	3.72

Boat - *eeae* 	B3LYP/6-311+G(2d,p)// B3LYP/6-311+G(2d,p)	MP2/6-311+G(2d,p)// B3LYP/6-311+G(2d,p)
E [kcal mol^{-1}]	-397218.04476100	-396333.09230400
ZPE [kcal mol^{-1}]	87.00250000	87.00250000
E + ZPE [kcal mol^{-1}]	-397131.04226100	-396246.08980400
Relative Energy [kcal mol^{-1}]	7.34	7.96
Dipole Moment m [D]	4.77	5.30

Crystallographic Data for 1

Table 1. Crystal data and structure refinement for **1**.

Identification code	1	
Empirical formula	C6 H8 F4	
Formula weight	156.12	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/m	
Unit cell dimensions	a = 8.229(6) Å	α= 90°.
	b = 7.736(5) Å	β= 97.507(18)°.
	c = 9.953(8) Å	γ = 90°.
Volume	628.1(8) Å^3	
Z	4	
Density (calculated)	1.651 Mg/m^3	
Absorption coefficient	0.178 mm^{-1}	
F(000)	320	
Crystal size	0.10 x 0.10 x 0.10 mm^3	
Theta range for data collection	3.63 to 25.31°.	
Index ranges	-9<=h<=9, -9<=k<=9, -8<=l<=11	
Reflections collected	1838	
Independent reflections	604 [R(int) = 0.0519]	
Completeness to theta = 25.00°	97.3 %	

Absorption correction	Multiscan
Max. and min. transmission	1.000 and 0.674
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	604 / 1 / 58
Goodness-of-fit on F^2	1.129
Final R indices [I>2sigma(I)]	R1 = 0.0439, wR2 = 0.1173
R indices (all data)	R1 = 0.0477, wR2 = 0.1346
Largest diff. peak and hole	0.286 and -0.333 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for **1**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
F(1)	4859(2)	0	3097(1)	18(1)
C(1)	6513(3)	0	3683(2)	15(1)
F(2)	6487(1)	3063(1)	3594(1)	21(1)
C(2)	7345(2)	1605(2)	3225(2)	15(1)
F(3)	5970(3)	1801(4)	966(2)	19(1)
C(3)	7465(2)	1639(2)	1714(2)	18(1)
C(4)	8306(3)	0	1308(2)	18(1)

Table 3. Bond lengths [Å] and angles [°] for **1**.

F(1)-C(1)	1.409(3)
C(1)-C(2)	1.516(2)
C(1)-C(2)#1	1.516(2)
C(1)-H(1A)	1.0000
F(2)-C(2)	1.405(2)
C(2)-C(3)	1.520(3)
C(2)-H(2A)	1.0000
F(3)-C(3)	1.358(3)
F(3)-H(3B)	0.41(3)
C(3)-C(4)	1.524(2)
C(3)-H(3A)	1.0000
C(3)-H(3B)	0.96(2)
C(4)-C(3)#1	1.524(2)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
F(1)-C(1)-C(2)	109.00(12)
F(1)-C(1)-C(2)#1	109.00(12)
C(2)-C(1)-C(2)#1	109.91(19)
F(1)-C(1)-H(1A)	109.6
C(2)-C(1)-H(1A)	109.6
C(2)#1-C(1)-H(1A)	109.6
F(2)-C(2)-C(1)	108.47(14)
F(2)-C(2)-C(3)	110.13(13)
C(1)-C(2)-C(3)	113.67(15)
F(2)-C(2)-H(2A)	108.1
C(1)-C(2)-H(2A)	108.1
C(3)-C(2)-H(2A)	108.1
C(3)-F(3)-H(3B)	13(10)
F(3)-C(3)-C(2)	111.88(18)
F(3)-C(3)-C(4)	109.98(19)
C(2)-C(3)-C(4)	109.78(15)
F(3)-C(3)-H(3A)	108.4
C(2)-C(3)-H(3A)	108.4
C(4)-C(3)-H(3A)	108.4
F(3)-C(3)-H(3B)	6(4)
C(2)-C(3)-H(3B)	107(4)
C(4)-C(3)-H(3B)	115(4)
H(3A)-C(3)-H(3B)	108.5
C(3)#1-C(4)-C(3)	112.6(2)
C(3)#1-C(4)-H(4A)	109.1
C(3)-C(4)-H(4A)	109.1
C(3)#1-C(4)-H(4B)	109.1
C(3)-C(4)-H(4B)	109.1
H(4A)-C(4)-H(4B)	107.8

Symmetry transformations used to generate equivalent atoms:

#1 x,-y,z

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for **1**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F(1)	12(1)	21(1)	21(1)	0	4(1)	0
C(1)	11(1)	21(1)	12(1)	0	1(1)	0
F(2)	24(1)	17(1)	23(1)	-5(1)	4(1)	3(1)
C(2)	13(1)	16(1)	16(1)	-3(1)	3(1)	3(1)
F(3)	18(1)	25(1)	15(1)	0(1)	0(1)	3(1)
C(3)	18(1)	20(1)	15(1)	3(1)	3(1)	-2(1)
C(4)	18(1)	24(2)	13(1)	0	5(1)	0

Table 5. Hydrogen coordinates ($x 10^4$) and isotropic displacement parameters ($Å^2 x 10^3$) for **1**.

	x	y	z	U(eq)
H(1A)	6575	0	4693	18
H(2A)	8482	1652	3722	18
H(3A)	8150	2654	1521	21
H(4A)	8312	0	314	22
H(4B)	9460	0	1742	22
H(3B)	6370(40)	1810(90)	1260(70)	22

Table 6. Torsion angles [°] for **1**.

F(1)-C(1)-C(2)-F(2)	57.16(19)
C(2)#1-C(1)-C(2)-F(2)	176.56(10)
F(1)-C(1)-C(2)-C(3)	-65.70(19)
C(2)#1-C(1)-C(2)-C(3)	53.7(2)
F(2)-C(2)-C(3)-F(3)	-54.2(2)
C(1)-C(2)-C(3)-F(3)	67.7(2)
F(2)-C(2)-C(3)-C(4)	-176.60(14)
C(1)-C(2)-C(3)-C(4)	-54.7(2)
F(3)-C(3)-C(4)-C(3)#1	-68.4(3)
C(2)-C(3)-C(4)-C(3)#1	55.1(2)

Symmetry transformations used to generate equivalent atoms:

#1 x,-y,z