Supplementary Information

Allosteric agonists of the calcium receptor (CaR): Fluorine and SF_5 analogues of cinacalcet

Poh Wai Chia [a], Sarah C. Brennan[b], Alexandra M. S. Slawin[a], Daniela Riccardi[b] and David O'Hagan*[a]

GC-MS analysis for determination of enantiopurity of intermediate aldehydes (R)-7 and (S)-7.

Chiral phase GC-MS analysis used a Betadex™ 120 fused silica capillary column (30 m × 0.25 mm i.d., 0.25 μm film thickness). Monitoring of the α-fluoroaldehyde **7** was carried out by extracting an aliquot (0.5 ml) from the reaction at hourly intervals. This aliquot was passed through a 25 mm Whatmann syringe filter. The filtrates were transfered into a GC vial and then make up to 1 ml with DCM. This solution was injected directly onto GCMS with DCM solvent as a control. The oven was held at 80 °C for 20 min, then heated at a gradient of 20 °C/min to 150 °C, 250 °C injector temperature; 100:1 split ratio, 1.0 mL/min flow. The GC-MS chromatogram shown in Figure 1.0 shows a major peak at the retention time of 36.24 min, which corresponds to (*R*)-**7** ($[M]^{+\cdot}$, ***m/z*** = 220, while the minor peak shown at the retention time of 33.16 min was assigned to be the difluorinated compound **8** ($[M]^{+\cdot}$, m/z = 238). The enantiomeric ratio of (*R*)-**7** determined from the chiral phase GC-MS ~ 97%ee. The MS (EI) spectra of the peak at 33.16 (**Figure S1.1**) and 36.2 min (**Figure S1.2**) showed an identical fragment pattern of *m/z* = 159, which corresponds to $[M\text{-}CHFCHO]^{+}$.

Retention time (min)	Area (units)	Ratio
33.16	68530.3	1
36.24	1370606	20

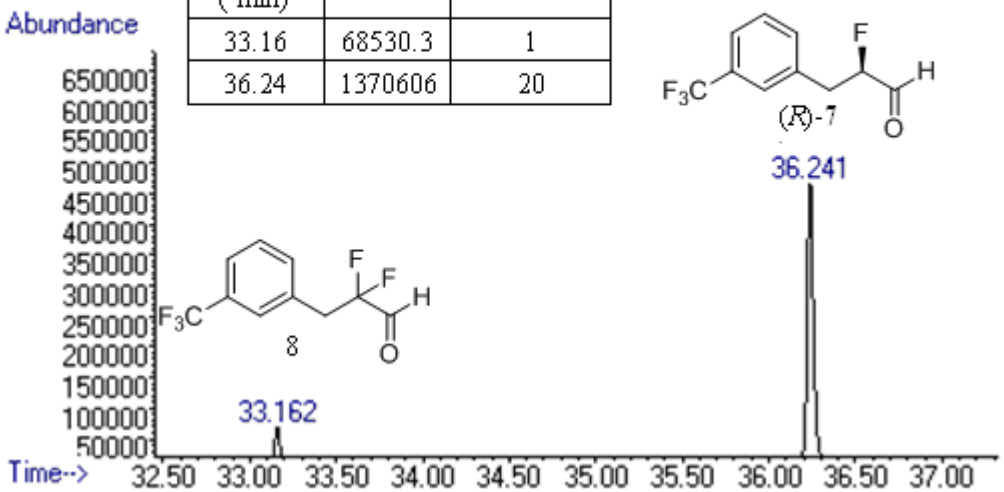


Figure S1.0 The chiral phase GC chromatogram of (*R*)-**7**.: oven started at 80 °C and held for 20 min (gradient at 20 °C/min to 150 °C), 250 °C injector temperature, 100:1 split ratio, 1.0 mL/min flow.

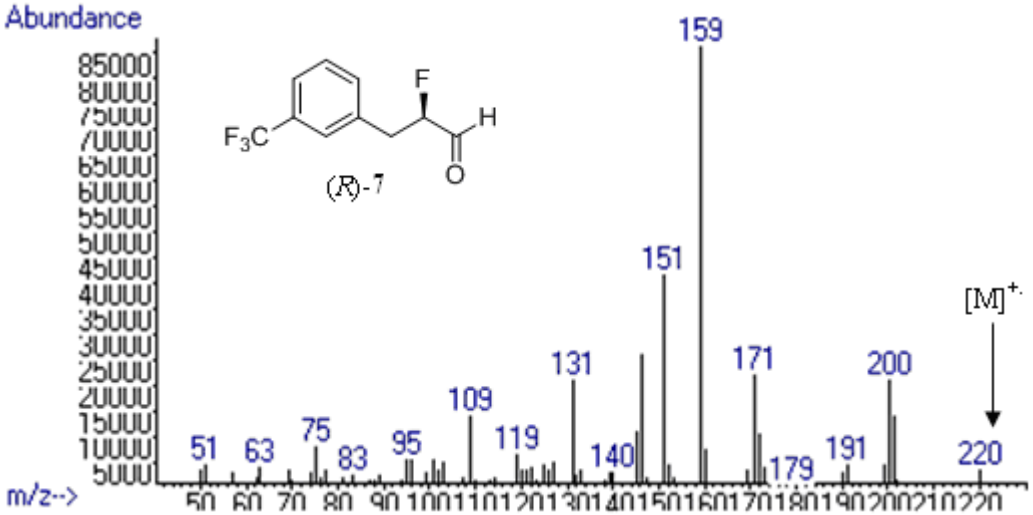


Figure S1.1 Mass spectrum of the GC peak at 36.2 min showing the presence of (*R*)-**7**.

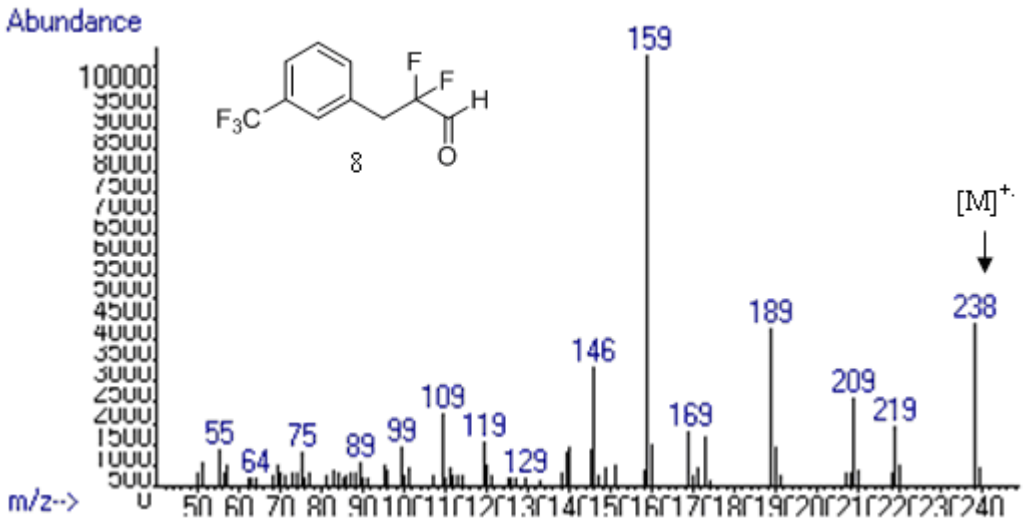


Figure S1.2. Mass spectrum of the GC peak at 33.1 min showing the presence of difluoroaldehyde **8**.

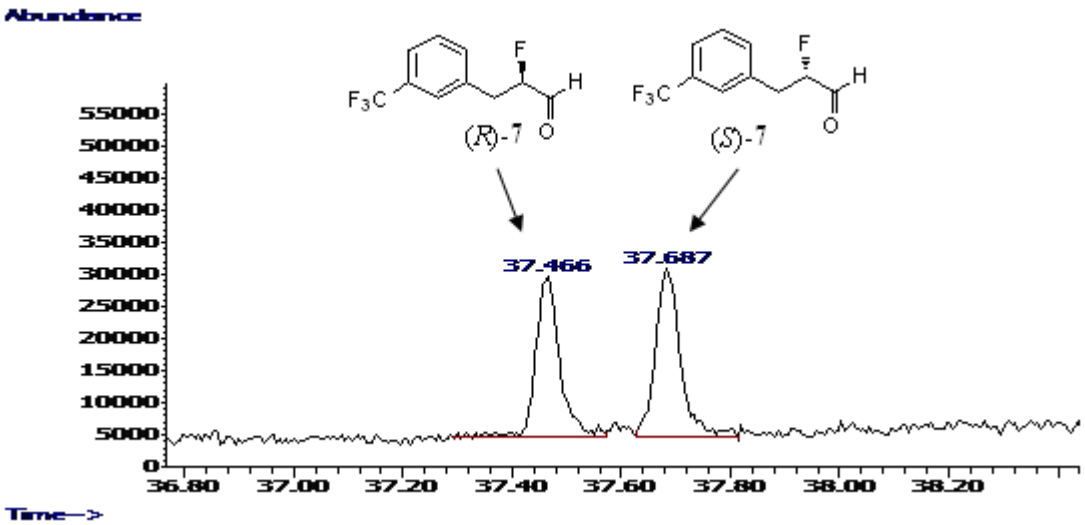
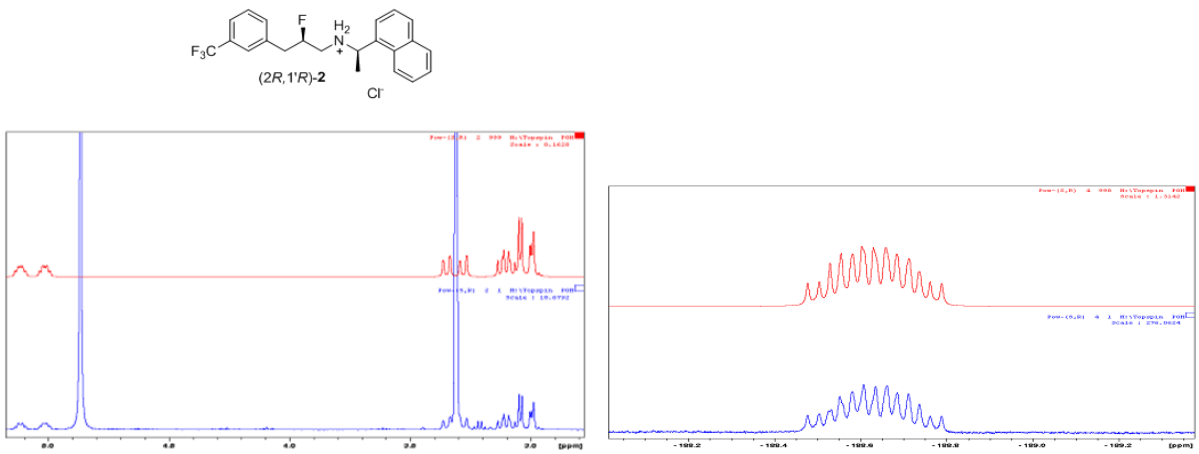
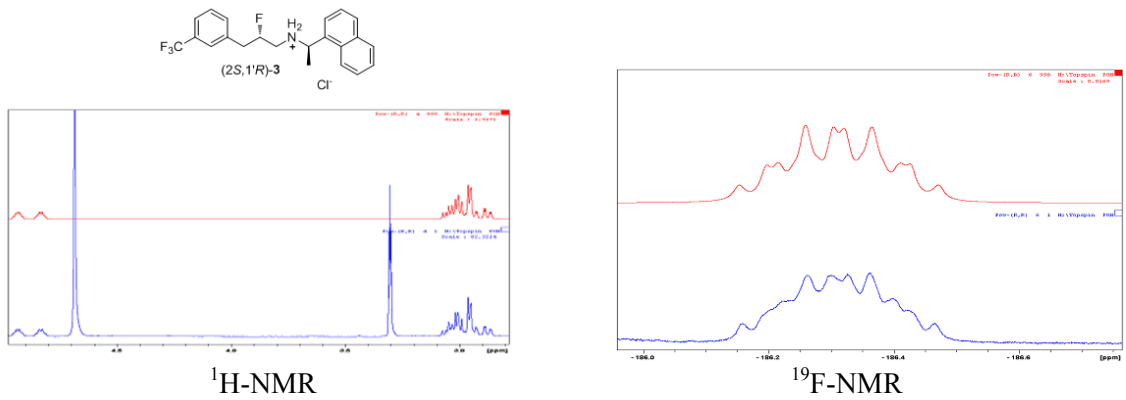


Figure S1.3 Chiral phase GC chromatogram of a mixture of (*R*)- and (*S*)-**7**.

Figure S1.4 Overlay of the ^{19}F-NMR spectra of (2*R*,1'*R*)-**2** and (2*S*,1'*R*)-**3** and an add mixture of both diastereoisomers, indicating a high diastereomeric ratio.



^{1}H-NMR ^{19}F-NMR



^{1}H-NMR ^{19}F-NMR

Figure S1.5 (a) The simulated (red) and experimental (blue), ^{1}H NMR and ^{19}F-NMR spectra for (2*R*,1'*R*)-**2** and (2*S*,1'*R*)-**3**. Spectra were recorded on a 500MHz Bruker instrument in CD_3OH.

Table 1. Crystal data and structure refinement for (2*R*,1'*R*)-**2.**

Identification code	2	
Empirical formula	C22 H22 Cl F4 N	
Formula weight	411.86	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 7.2710(4) Å	α= 90°.
	b = 13.0197(6) Å	β= 90°.
	c = 22.3322(11) Å	γ = 90°.
Volume	2114.11(18) $Å^3$	
Z	4	
Density (calculated)	1.294 Mg/m^3	
Absorption coefficient	1.967 mm^{-1}	
F(000)	856	
Crystal size	0.12 x 0.05 x 0.05 mm^3	
Theta range for data collection	3.93 to 68.06°.	
Index ranges	-8<=h<=8, -15<=k<=15, -26<=l<=26	
Reflections collected	26693	
Independent reflections	3740 [R(int) = 0.0433]	
Completeness to theta = 67.00°	98.3 %	
Absorption correction	Multiscan	
Max. and min. transmission	1.000 and 0.723	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3740 / 2 / 250	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I)]	R1 = 0.0704, wR2 = 0.1892	
R indices (all data)	R1 = 0.0726, wR2 = 0.1918	
Absolute structure parameter	0.05(3)	
Largest diff. peak and hole	0.972 and -0.609 $e.Å^{-3}$	

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

	x	y	z	U(eq)
Cl(1)	3252(1)	6821(1)	641(1)	36(1)
C(1)	8058(6)	4789(3)	541(2)	31(1)
C(2)	6539(6)	4609(3)	881(2)	37(1)
C(3)	6405(6)	3732(4)	1250(2)	43(1)
C(4)	7793(6)	3046(3)	1265(2)	41(1)
C(5)	9384(6)	3178(3)	920(2)	35(1)
C(6)	10852(8)	2458(4)	931(2)	50(1)
C(7)	12362(7)	2586(4)	600(3)	55(1)
C(8)	12549(8)	3466(4)	225(2)	50(1)
C(9)	11196(6)	4183(4)	205(2)	39(1)
C(10)	9561(6)	4076(3)	549(2)	33(1)
C(11)	8147(7)	5712(3)	119(2)	33(1)
N(12)	7429(5)	6666(2)	409(1)	28(1)
C(13)	8432(6)	6969(3)	969(2)	31(1)
F(14)	7435(4)	8677(2)	825(1)	45(1)
C(14)	7562(6)	7892(3)	1259(2)	31(1)
C(15)	8755(6)	8276(4)	1770(2)	39(1)
C(16)	7929(6)	9105(3)	2159(2)	33(1)
C(17)	6370(7)	9647(3)	2008(2)	39(1)
C(18)	5668(7)	10411(4)	2386(2)	43(1)
C(19)	6536(8)	10626(4)	2923(2)	47(1)
C(20)	8092(8)	10080(4)	3077(2)	53(1)
C(21)	8772(8)	9324(4)	2709(2)	49(1)
C(22)	7079(8)	5515(3)	-449(2)	49(1)
C(23)	3917(12)	10935(5)	2233(2)	84(3)
F(1)	2720(8)	10941(4)	2647(3)	89(2)
F(2)	4237(10)	12002(6)	2245(3)	108(2)
F(3)	2838(12)	10446(6)	1841(4)	125(2)
F(4)	3989(15)	11210(8)	1654(4)	155(3)

Table 3. Bond lengths [Å] and angles [°] for (2*R*,1'*R*)- **2**.

C(1)-C(2)	1.361(6)
C(1)-C(10)	1.434(6)
C(1)-C(11)	1.528(5)
C(2)-C(3)	1.412(6)
C(2)-H(2A)	0.9500
C(3)-C(4)	1.349(6)
C(3)-H(3A)	0.9500
C(4)-C(5)	1.401(6)
C(4)-H(4A)	0.9500
C(5)-C(6)	1.420(6)
C(5)-C(10)	1.439(6)
C(6)-C(7)	1.334(8)
C(6)-H(6A)	0.9500
C(7)-C(8)	1.426(8)
C(7)-H(7A)	0.9500
C(8)-C(9)	1.357(7)
C(8)-H(8A)	0.9500
C(9)-C(10)	1.422(6)
C(9)-H(9A)	0.9500
C(11)-N(12)	1.495(5)
C(11)-C(22)	1.509(6)
C(11)-H(11A)	1.0000
N(12)-C(13)	1.500(5)
N(12)-H(12A)	0.962(19)
N(12)-H(12B)	0.97(2)
C(13)-C(14)	1.505(5)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
F(14)-C(14)	1.411(4)
C(14)-C(15)	1.519(6)
C(14)-H(14A)	1.0000
C(15)-C(16)	1.509(6)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(16)-C(17)	1.377(6)
C(16)-C(21)	1.402(6)
C(17)-C(18)	1.401(6)
C(17)-H(17A)	0.9500
C(18)-C(19)	1.385(7)
C(18)-C(23)	1.484(9)
C(19)-C(20)	1.379(8)
C(19)-H(19A)	0.9500
C(20)-C(21)	1.375(7)
C(20)-H(20A)	0.9500
C(21)-H(21A)	0.9500
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-F(1)	1.270(9)
C(23)-F(3)	1.336(10)
C(23)-F(4)	1.342(11)
C(23)-F(2)	1.409(10)
F(2)-F(4)	1.684(12)
F(3)-F(4)	1.365(11)

C(2)-C(1)-C(10)	120.0(4)
C(2)-C(1)-C(11)	120.9(4)
C(10)-C(1)-C(11)	119.0(4)
C(1)-C(2)-C(3)	121.4(4)
C(1)-C(2)-H(2A)	119.3
C(3)-C(2)-H(2A)	119.3
C(4)-C(3)-C(2)	119.9(4)
C(4)-C(3)-H(3A)	120.0
C(2)-C(3)-H(3A)	120.0
C(3)-C(4)-C(5)	121.5(4)
C(3)-C(4)-H(4A)	119.2
C(5)-C(4)-H(4A)	119.2
C(4)-C(5)-C(6)	122.0(4)
C(4)-C(5)-C(10)	119.4(4)
C(6)-C(5)-C(10)	118.6(4)
C(7)-C(6)-C(5)	121.8(5)
C(7)-C(6)-H(6A)	119.1
C(5)-C(6)-H(6A)	119.1
C(6)-C(7)-C(8)	120.3(4)
C(6)-C(7)-H(7A)	119.9
C(8)-C(7)-H(7A)	119.9
C(9)-C(8)-C(7)	120.1(5)
C(9)-C(8)-H(8A)	119.9
C(7)-C(8)-H(8A)	119.9
C(8)-C(9)-C(10)	121.5(5)
C(8)-C(9)-H(9A)	119.3
C(10)-C(9)-H(9A)	119.3
C(9)-C(10)-C(1)	124.5(4)
C(9)-C(10)-C(5)	117.7(4)
C(1)-C(10)-C(5)	117.8(4)
N(12)-C(11)-C(22)	109.0(4)
N(12)-C(11)-C(1)	111.8(3)
C(22)-C(11)-C(1)	111.2(3)
N(12)-C(11)-H(11A)	108.2
C(22)-C(11)-H(11A)	108.2
C(1)-C(11)-H(11A)	108.2
C(11)-N(12)-C(13)	114.2(3)
C(11)-N(12)-H(12A)	111(2)
C(13)-N(12)-H(12A)	114(2)
C(11)-N(12)-H(12B)	105(4)
C(13)-N(12)-H(12B)	112(4)
H(12A)-N(12)-H(12B)	98(4)
C(14)-C(13)-N(12)	111.4(3)
C(14)-C(13)-H(13A)	109.4
N(12)-C(13)-H(13A)	109.4
C(14)-C(13)-H(13B)	109.4
N(12)-C(13)-H(13B)	109.4
H(13A)-C(13)-H(13B)	108.0
F(14)-C(14)-C(13)	108.1(3)
F(14)-C(14)-C(15)	108.3(3)
C(13)-C(14)-C(15)	110.3(3)
F(14)-C(14)-H(14A)	110.0
C(13)-C(14)-H(14A)	110.0
C(15)-C(14)-H(14A)	110.0
C(16)-C(15)-C(14)	116.1(4)
C(16)-C(15)-H(15A)	108.3
C(14)-C(15)-H(15A)	108.3
C(16)-C(15)-H(15B)	108.2

C(14)-C(15)-H(15B)	108.2
H(15A)-C(15)-H(15B)	107.4
C(17)-C(16)-C(21)	118.0(4)
C(17)-C(16)-C(15)	123.6(4)
C(21)-C(16)-C(15)	118.4(4)
C(16)-C(17)-C(18)	121.1(4)
C(16)-C(17)-H(17A)	119.4
C(18)-C(17)-H(17A)	119.4
C(19)-C(18)-C(17)	119.9(5)
C(19)-C(18)-C(23)	119.9(4)
C(17)-C(18)-C(23)	120.0(4)
C(20)-C(19)-C(18)	119.1(4)
C(20)-C(19)-H(19A)	120.4
C(18)-C(19)-H(19A)	120.4
C(21)-C(20)-C(19)	120.9(4)
C(21)-C(20)-H(20A)	119.5
C(19)-C(20)-H(20A)	119.5
C(20)-C(21)-C(16)	120.9(5)
C(20)-C(21)-H(21A)	119.6
C(16)-C(21)-H(21A)	119.6
C(11)-C(22)-H(22A)	109.5
C(11)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(11)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
F(1)-C(23)-F(3)	94.5(8)
F(1)-C(23)-F(4)	136.6(8)
F(3)-C(23)-F(4)	61.3(5)
F(1)-C(23)-F(2)	95.3(5)
F(3)-C(23)-F(2)	125.4(6)
F(4)-C(23)-F(2)	75.4(7)
F(1)-C(23)-C(18)	115.0(5)
F(3)-C(23)-C(18)	115.8(5)
F(4)-C(23)-C(18)	108.1(7)
F(2)-C(23)-C(18)	107.9(7)
C(23)-F(2)-F(4)	50.5(5)
F(4)-F(3)-C(23)	59.6(6)
F(3)-F(4)-C(23)	59.1(6)
F(3)-F(4)-F(2)	105.8(7)
C(23)-F(4)-F(2)	54.1(5)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for (2*R*,1'*R*)- **2**. 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}
Cl(1)	26(1)	44(1)	36(1)	13(1)	2(1)	5(1)
C(1)	34(2)	25(2)	34(2)	-3(2)	-3(2)	2(2)
C(2)	32(2)	32(2)	46(2)	5(2)	0(2)	1(2)
C(3)	38(3)	41(2)	50(2)	12(2)	3(2)	-3(2)
C(4)	42(3)	31(2)	50(2)	6(2)	-7(2)	-1(2)
C(5)	35(2)	27(2)	43(2)	-6(2)	-11(2)	3(2)
C(6)	58(3)	32(2)	60(3)	-2(2)	-16(3)	9(2)
C(7)	45(3)	44(2)	78(4)	-14(3)	-9(3)	20(2)
C(8)	39(2)	48(3)	64(3)	-15(2)	-1(2)	11(2)
C(9)	37(2)	38(2)	42(2)	-11(2)	1(2)	4(2)
C(10)	35(2)	29(2)	34(2)	-9(2)	-5(2)	3(2)
C(11)	38(2)	30(2)	32(2)	-1(2)	12(2)	6(2)
N(12)	27(2)	26(2)	31(2)	5(1)	2(1)	2(1)
C(13)	29(2)	33(2)	33(2)	-1(2)	2(2)	2(2)
F(14)	68(2)	32(1)	35(1)	2(1)	1(1)	10(1)
C(14)	32(2)	30(2)	31(2)	2(2)	-1(2)	0(2)
C(15)	36(2)	41(2)	38(2)	-4(2)	-4(2)	-2(2)
C(16)	37(2)	31(2)	29(2)	1(2)	-3(2)	-5(2)
C(17)	49(3)	41(2)	27(2)	-3(2)	-4(2)	4(2)
C(18)	56(3)	43(2)	30(2)	-3(2)	3(2)	8(2)
C(19)	67(3)	41(2)	33(2)	-8(2)	1(2)	2(2)
C(20)	62(3)	59(3)	38(2)	-13(2)	-11(2)	-10(3)
C(21)	53(3)	57(3)	37(2)	0(2)	-11(2)	-1(2)
C(22)	75(4)	36(2)	36(2)	-1(2)	-1(2)	1(2)
C(23)	153(7)	72(4)	26(2)	-24(2)	-22(3)	61(5)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for (2*R*,1'*R*)- **2**.

	x	y	z	U(eq)
H(2A)	5548	5084	869	44
H(3A)	5337	3626	1487	51
H(4A)	7690	2459	1516	49
H(6A)	10755	1870	1180	60
H(7A)	13317	2089	615	67
H(8A)	13624	3550	-12	60
H(9A)	11345	4769	-43	47
H(11A)	9463	5830	9	40
H(12A)	6110(30)	6640(30)	452(18)	21(10)
H(12B)	7490(90)	7190(30)	100(20)	67(18)
H(13A)	8424	6387	1254	38
H(13B)	9729	7127	869	38
H(14A)	6309	7712	1411	37
H(15A)	9068	7684	2029	46
H(15B)	9919	8540	1600	46
H(17A)	5760	9500	1642	47
H(19A)	6068	11142	3182	57
H(20A)	8702	10228	3444	64
H(21A)	9827	8946	2828	59
H(22A)	7159	6118	-710	74
H(22B)	5788	5381	-350	74
H(22C)	7596	4916	-655	74

Table 6. Torsion angles [°] for (2*R*,1'*R*)- **2**.

C(10)-C(1)-C(2)-C(3)	0.5(6)
C(11)-C(1)-C(2)-C(3)	176.9(4)
C(1)-C(2)-C(3)-C(4)	-0.7(7)
C(2)-C(3)-C(4)-C(5)	-0.2(7)
C(3)-C(4)-C(5)-C(6)	-179.7(5)
C(3)-C(4)-C(5)-C(10)	1.2(6)
C(4)-C(5)-C(6)-C(7)	179.8(5)
C(10)-C(5)-C(6)-C(7)	-1.1(7)
C(5)-C(6)-C(7)-C(8)	0.4(8)
C(6)-C(7)-C(8)-C(9)	0.5(8)
C(7)-C(8)-C(9)-C(10)	-0.7(7)
C(8)-C(9)-C(10)-C(1)	-178.5(4)
C(8)-C(9)-C(10)-C(5)	0.0(6)
C(2)-C(1)-C(10)-C(9)	179.1(4)
C(11)-C(1)-C(10)-C(9)	2.7(6)
C(2)-C(1)-C(10)-C(5)	0.6(6)
C(11)-C(1)-C(10)-C(5)	-175.9(3)
C(4)-C(5)-C(10)-C(9)	180.0(4)
C(6)-C(5)-C(10)-C(9)	0.9(6)
C(4)-C(5)-C(10)-C(1)	-1.4(6)
C(6)-C(5)-C(10)-C(1)	179.5(4)
C(2)-C(1)-C(11)-N(12)	44.0(5)
C(10)-C(1)-C(11)-N(12)	-139.6(4)
C(2)-C(1)-C(11)-C(22)	-78.1(5)
C(10)-C(1)-C(11)-C(22)	98.3(5)
C(22)-C(11)-N(12)-C(13)	-177.7(4)
C(1)-C(11)-N(12)-C(13)	58.9(5)
C(11)-N(12)-C(13)-C(14)	-176.2(3)
N(12)-C(13)-C(14)-F(14)	-53.6(4)
N(12)-C(13)-C(14)-C(15)	-171.8(3)
F(14)-C(14)-C(15)-C(16)	70.2(5)
C(13)-C(14)-C(15)-C(16)	-171.7(3)
C(14)-C(15)-C(16)-C(17)	-12.9(6)
C(14)-C(15)-C(16)-C(21)	165.9(4)
C(21)-C(16)-C(17)-C(18)	1.4(7)
C(15)-C(16)-C(17)-C(18)	-179.8(4)
C(16)-C(17)-C(18)-C(19)	-0.5(7)
C(16)-C(17)-C(18)-C(23)	-175.9(5)
C(17)-C(18)-C(19)-C(20)	0.1(8)
C(23)-C(18)-C(19)-C(20)	175.5(6)
C(18)-C(19)-C(20)-C(21)	-0.6(8)
C(19)-C(20)-C(21)-C(16)	1.6(8)
C(17)-C(16)-C(21)-C(20)	-2.0(7)
C(15)-C(16)-C(21)-C(20)	179.2(5)
C(19)-C(18)-C(23)-F(1)	-47.5(9)
C(17)-C(18)-C(23)-F(1)	127.8(6)
C(19)-C(18)-C(23)-F(3)	-156.3(6)
C(17)-C(18)-C(23)-F(3)	19.1(10)
C(19)-C(18)-C(23)-F(4)	137.5(7)
C(17)-C(18)-C(23)-F(4)	-47.1(9)
C(19)-C(18)-C(23)-F(2)	57.4(7)
C(17)-C(18)-C(23)-F(2)	-127.2(5)
F(1)-C(23)-F(2)-F(4)	-136.8(8)
F(3)-C(23)-F(2)-F(4)	-37.5(8)
C(18)-C(23)-F(2)-F(4)	104.7(7)
F(1)-C(23)-F(3)-F(4)	142.0(7)

F(2)-C(23)-F(3)-F(4)	42.2(9)
C(18)-C(23)-F(3)-F(4)	-97.4(8)
C(23)-F(3)-F(4)-F(2)	-28.5(6)
F(1)-C(23)-F(4)-F(3)	-63.3(12)
F(2)-C(23)-F(4)-F(3)	-145.5(7)
C(18)-C(23)-F(4)-F(3)	110.1(7)
F(1)-C(23)-F(4)-F(2)	82.2(10)
F(3)-C(23)-F(4)-F(2)	145.5(7)
C(18)-C(23)-F(4)-F(2)	-104.4(8)
C(23)-F(2)-F(4)-F(3)	30.4(7)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for (2*R*,1'*R*)- **2** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(12)-H(12A)...Cl(1)	0.962(19)	2.14(2)	3.088(4)	170(3)
N(12)-H(12B)...F(14)	0.97(2)	2.52(6)	2.778(4)	95(4)

Symmetry transformations used to generate equivalent atoms: