(1–Naphthyl)(trifluoromethyl) *O*–Carboxy Anhydride as a Chiral Derivatizing Agent: Eclipsed Conformation Enforced by Hydrogen Bonding

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SUPPLEMENTARY INFORMATION

Contents

General experimental conditions

Commercial solvents and reagents were used as received unless stated otherwise. THF was dried over sodium and dichloromethane over P_2O_5.

Ethyl–3,3,3–trifluoro–2–hydroxy–2–(1–naphthyl)propanoate *rac*-**I** and 3,3,3–trifluoro–2–hydroxy–2–(1–naphthyl)propanoic acid *rac*-**II** were prepared according to literature procedures.[1]

NMR spectra were recorded on Bruker Avance 300 MHz, Bruker Avance 400 MHz (TXO probe ^{13}C {^{1}H, ^{19}F}), Bruker Avance 500 MHz (cryoprobe ^{1}H {^{13}C, ^{31}P}) spectrometers.

2D NOESY spectra (pulseprog: noesygpph, mixing time: 1s)

2D HOESY spectra (pulseprog: hoesyph, mixing time: 0.5s)

Spectra were recorded in $CDCl_3$ at room temperature. ^{1}H and ^{13}C chemical shifts are reported in ppm relative to Me_4Si as an external standard. ^{19}F chemical shifts are reported in ppm relative to CF_3COOH as an external standard.

The enantiomeric excess was determined by chiral HPLC with a chiralcel–AD column; eluent isocratic: solvent A: 80% hexane (0.05% TFA), solvent B: 20% 2–propanol; flow rate of 1 mL/min. Detection: UV (278 nm).

Melting points were measured with an Electrothermal digital melting point apparatus and are uncorrected.

Microanalyses were performed by the LCC Microanalysis Service (Toulouse) with a Perkin Elmer 2400.

Mass spectra were recorded on a Hewlett Packard 5989A apparatus.

IR spectra were recorded with a Nexus Thermo Nicolet (DTGS detector) in CCl_4 with a CaF_2 cell.

The naphthyl signals have been assigned according to Figure S1.

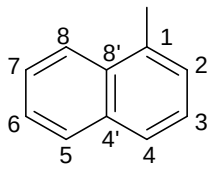
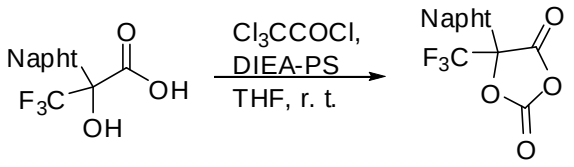


Figure S1. Numbering of the naphthyl group

[1] Blay, G.; Fernández, I.; Marco-Aleixandre, A.; Monje, B.; Pedro, J.R.; Ruiz, R. *Tetrahedron* **2002**, *58*, 8565

Synthesis of *rac*–5–naphthyl– 5–trifluoromethyl–[1,3]–dioxolane–2,4–dione (*rac*–1)

Polystyrene supported diisopropylethylamine, PS–DIEA, (7.00 g, 21.0 mequiv) was added to a cold (0°C) solution of the hydroxyacid *rac*-**II** (2.82 g, 10.44 mmol) in 30 mL dry THF. A solution of diphosgene (1.25 mL, 10.44 mmol) in 10 mL THF was added dropwise over 30 min. After 1 h at this temperature, PS–DIEA was filtered and washed with THF (3x10 mL). The combined organic layers were evaporated under reduced pressure to afford a viscous colourless oil. The crude material was triturated with pentane (20 mL) at -78°C. The solvent was removed from the sticky mass. Pentane (20 mL) was added at room temperature and the clear solution was left at -18°C. The OCA *rac*-**1** precipitated as a white powder (2.10 g, 68%).



rac-**II** *rac*-**1**

$^{19}F\{^{1}H\}$ NMR (δ, $CDCl_3$, 282.4 MHz): -74.8 (s).

^{1}H NMR (*δ*, $CDCl_3$, 300.1 MHz): 8.44 (1H, d, *J* = 8.7 Hz), 8.17 (1H, d, *J* = 7.5 Hz), 8.06 (1H, d, *J* = 8.1 Hz), 7.94 (dd, 1H, *J* = 8.1 and 1.7 Hz), 7.69–7.51 (m, 3H).

$^{13}C\{^{1}H\}$ NMR (*δ*, $CDCl_3$, 75.5 MHz): 160.4 (C=O), 145.1 (C=O), 134.9 (C), 133.6 (CH), 130.2 (C), 129.5 (CH), 128.0 (CH), 127.1 (CH), 126.9 (CH), 125.2 (CH), 124.3 (CH), 120.8 (CF_3, q, $^{1}J_{C–F}$ = 287 Hz), 120.1 (C), 87.6 (C, q, $^{2}J_{C–F}$ = 34 Hz).

IR (CCl_4): 1257, 1825, 1896 cm^{-1}.

M.p.: 50 – 52°C.

Elemental analysis:

Calculated: C% 56.77, H% 2.40

Found: C% 56.27, H% 2.24

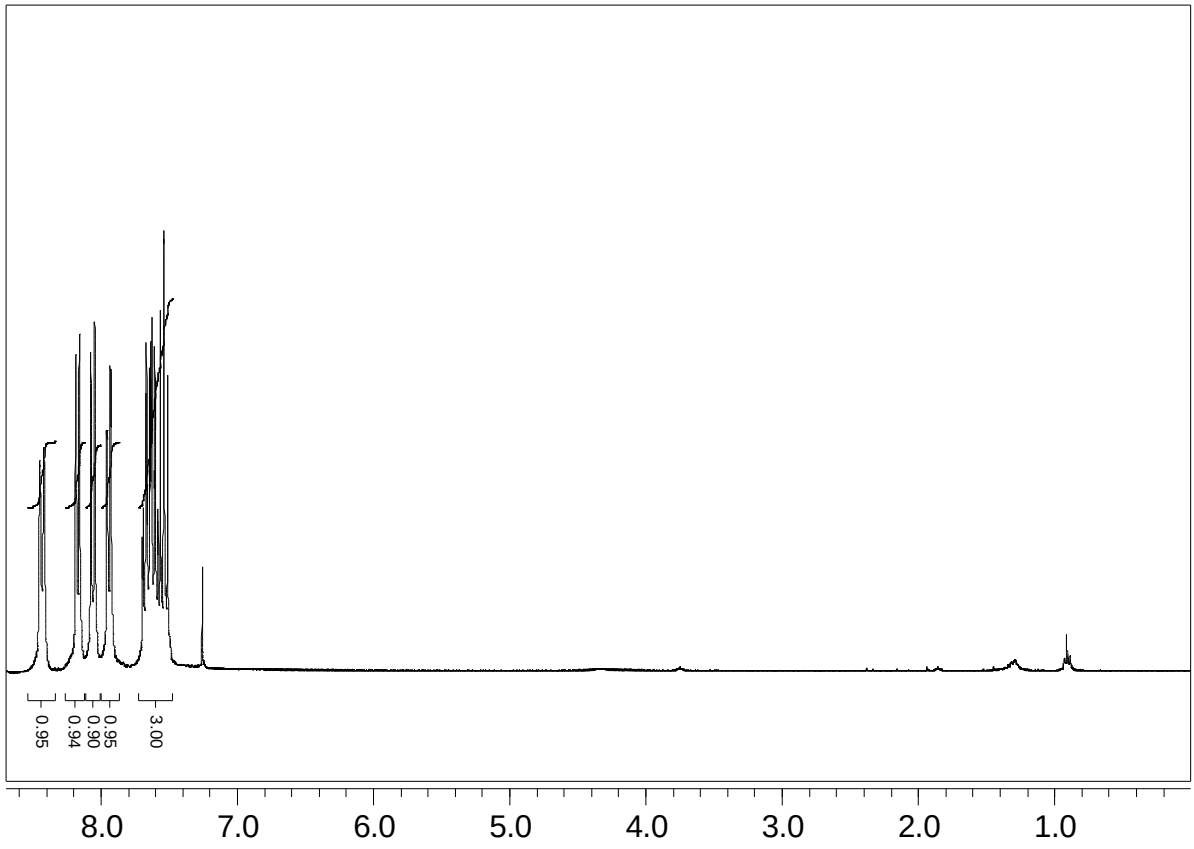
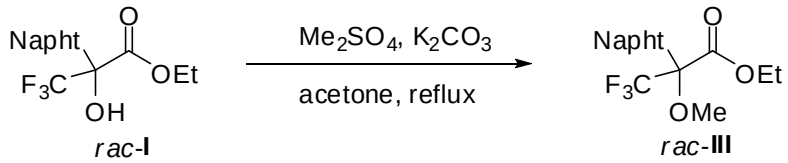


Figure S2. ^{1}H NMR spectrum of *rac*-**1**

Synthesis of *rac*–ethyl 3,3,3–trifluoro–2–methoxy–2–(1–naphthyl)propanoate (*rac*-III)

Dimethyl sulfate (2.0 mL, 21.10 mmol) and potassium carbonate (1.00 g, 6.71 mmol) were added to a solution of the hydroxy ester *rac*-**I** (2.00 g, 6.71 mmol) in acetone (30 mL). The reaction was refluxed for 2 hours. The salts were eliminated by filtration and the solvent evaporated under reduced pressure. Petroleum ether (100 mL) was added and the solution washed with water (3x50 mL), brine and dried with sodium sulfate. The solvent was evaporated to yield a colorless oil (1.74 g, 83%).



$^{19}F\{^{1}H\}$ NMR (δ, $CDCl_3$, 282.4 MHz): -69.1 (s).

^{1}H NMR (δ, $CDCl_3$, 300.1 MHz): 8.26 (1H, m), 7.93 – 7.87 (2H, m), 7.810 (1H, m), 7.52–7.47 (3H, m), 4.43 – 4.15 (2H, m, CH_2), 4.34 (3H, q, J = 1.2 Hz, OCH_3), 1.10 (3H, t, J = 7.1 Hz, CH_3).

$^{13}C\{^{1}H\}$ NMR (δ, $CDCl_3$, 75.5 MHz): 167.1 (C=O), 134.0 (C), 131.2 (C), 130.8 (CH), 129.1 (CH), 127.7 (C), 127.2 (CH, q, J = 11.4 Hz), 126.5 (CH), 126.0, 124.6 (CF_3, q, $^{1}J_{C–F}$ = 311.0 Hz), 124.0 (CH), 85.5 (C, q, $^{2}J_{C–F}$ = 27.0 Hz), 62.8 (CH_2), 54.6 (q, $^{1}J_{C–F}$ = 6.6 Hz, OCH_3), 13.7 (CH_3).

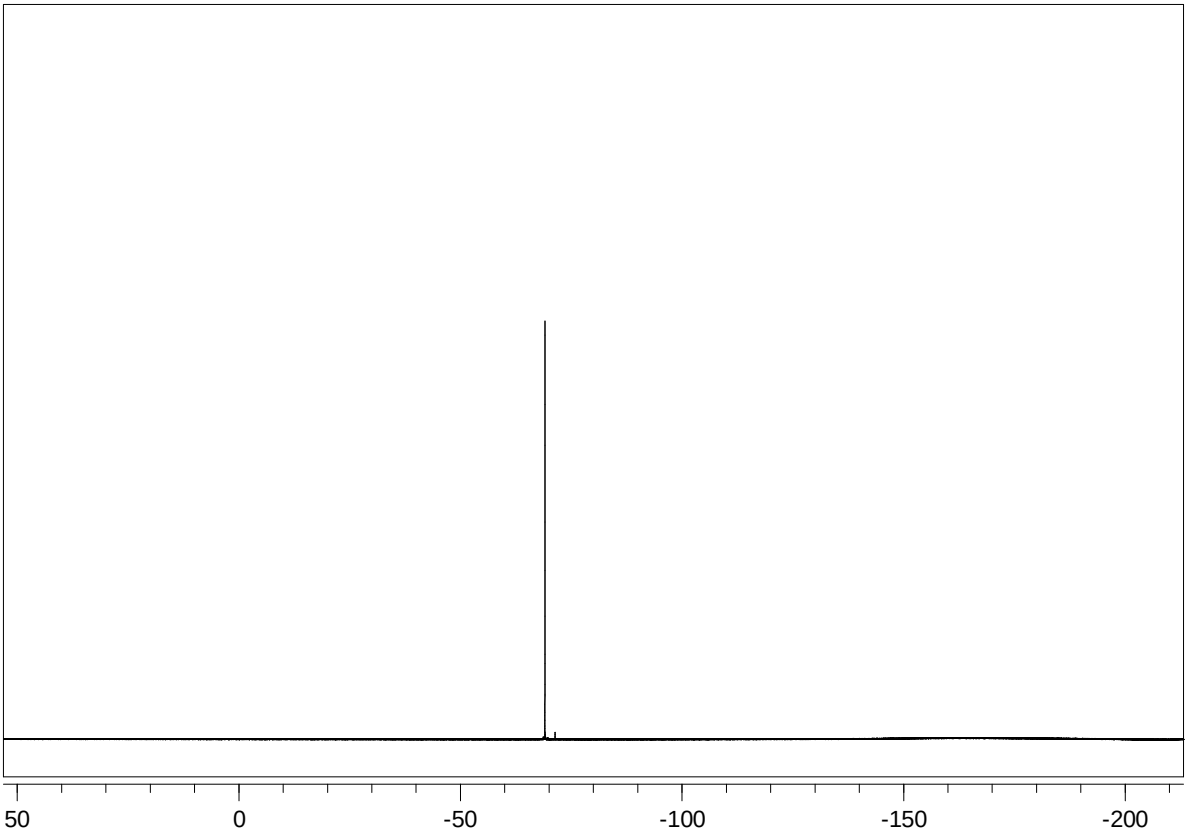


Figure S3. ^{19}F NMR spectrum of *rac*-**III**

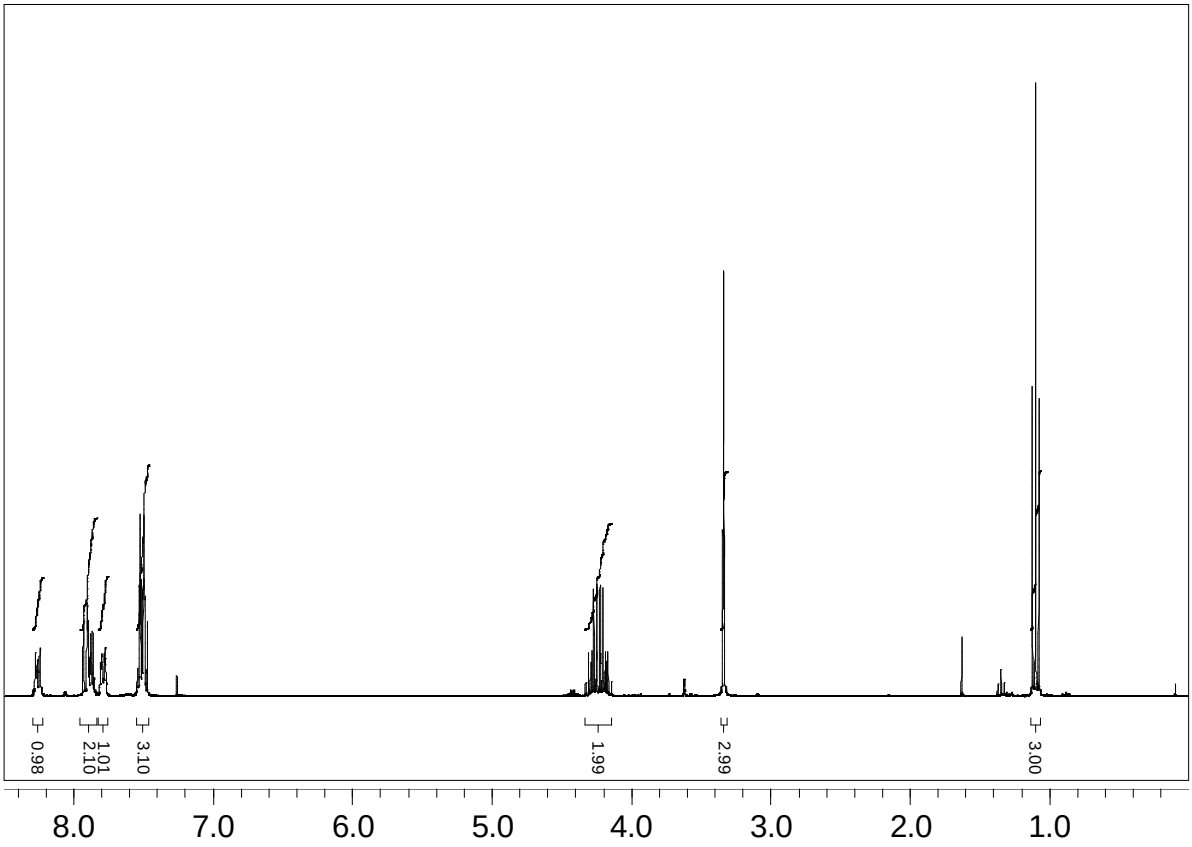


Figure S4. ^{1}H NMR spectrum of *rac*-**III**

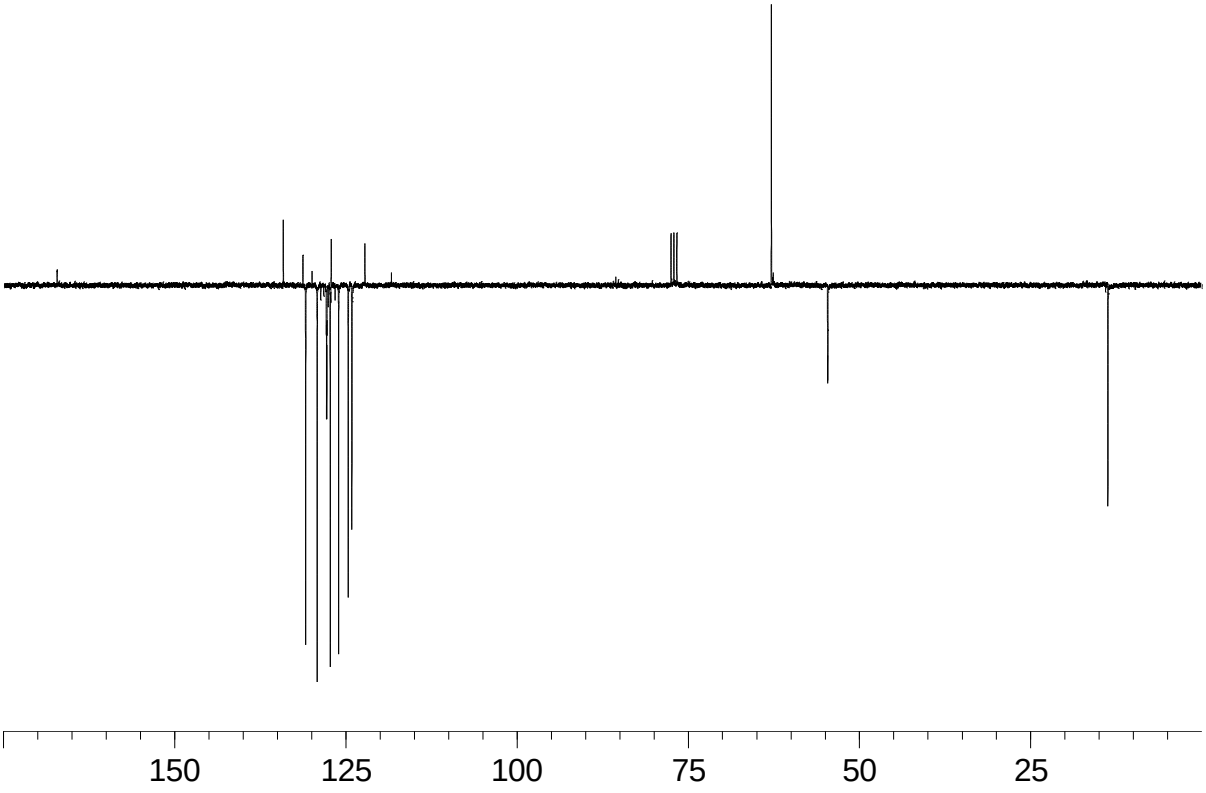
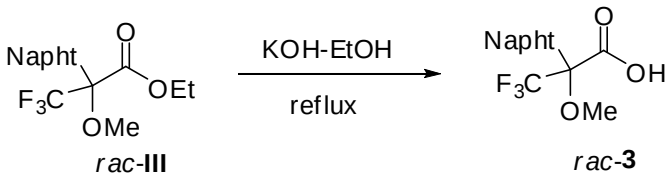


Figure S5. ^{13}C(JMOD) NMR spectrum of *rac*-**III**

Synthesis of *rac*–3,3,3–trifluoro–2–methoxy–2–(1–naphthyl)propanoic acid (*rac*-3)

Compound *rac*-**III** (1.70 g, 5.44 mmol) was dissolved in a 5% ethanolic solution of KOH (20 mL) and heated overnight at 60°C. The reaction mixture was concentrated to 10 mL then poured into water (100 mL) and was extracted with ethyl acetate. The organic phase was discarded and the aqueous phase acidified with cold HCl 2N (20 mL) and extracted with ethyl acetate (3x50 mL). The combined organic layers were washed with brine, dried with sodium sulfate and concentrated under reduced pressure to yield a viscous oil which crystallised after triturating in petroleum ether to give a white powder (1.34 g, 86%).



rac-**III** *rac*-**3**

$^{19}F\{^{1}H\}$ NMR (δ, $CDCl_3$, 282.4 MHz): -68.9 (s).

^{1}H NMR (δ, $CDCl_3$, 300.1 MHz): 8.03 (1H, m), 7.96 (1H, d, J = 8.1 Hz), 7.92 (1H, m), 7.82 (1H, m), 7.56 –7.50 (3H, m), 3.34 (3H, s).

$^{13}C\{^{1}H\}$ NMR (δ, $CDCl_3$, 75.5 MHz): 169.5 (C=O), 134.2 (C), 313.4 (CH), 131.1(C), 129.4 (CH), 128.4 (CH, q, $^{4}J_{C–F}$ = 12 Hz), 128.3 (CH), 127.7 (CH), 126.3 (CH), 125.6 (C), 124.7 (CH), 123.8 (CF_3, q, $^{1}J_{C–F}$ = 292 Hz), 123.5 (CH), 85.0 (C, q, $^{2}J_{C–F}$ = 27 Hz), 54.9 (OCH_3).

MS (EI) : 284 (41), 239 (72), 215 (23), 177 (88), 155 (100), 142 (66).

M.p.: 128 – 131°C.

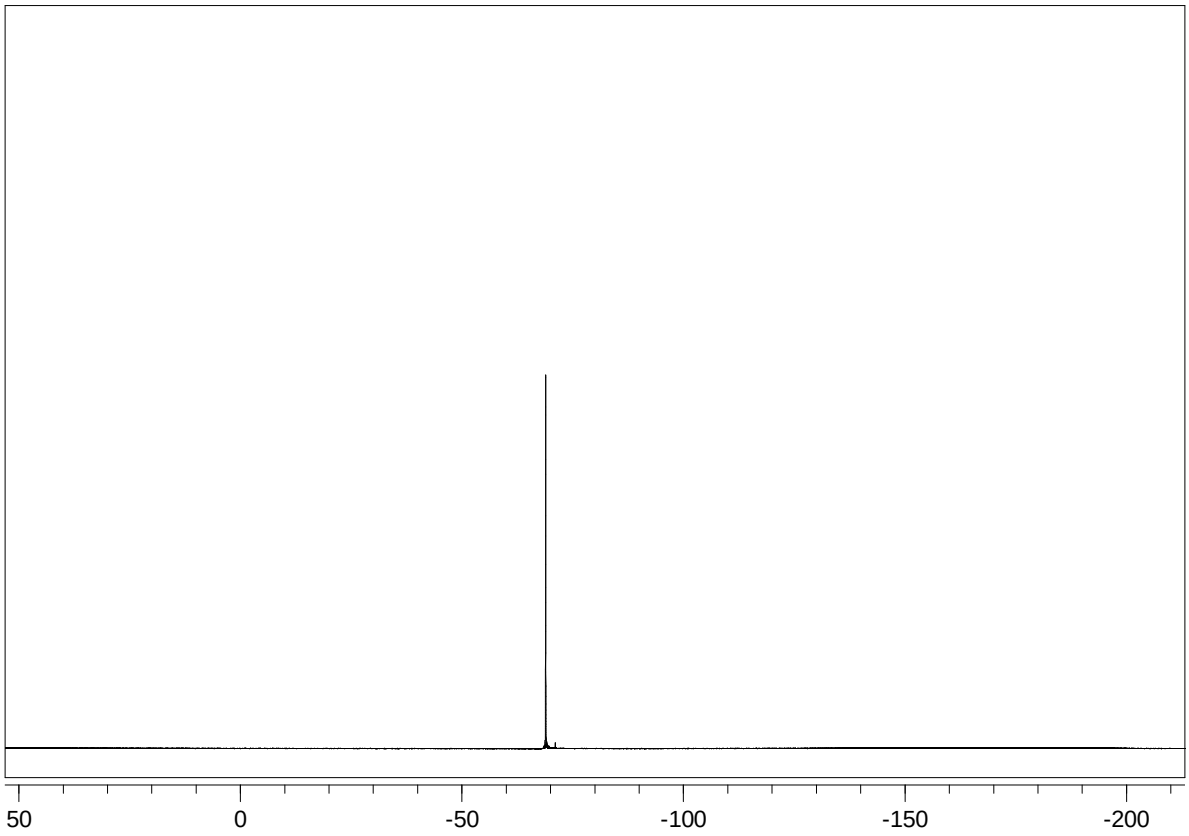


Figure S6. ^{19}F NMR spectrum of *rac*-**3**

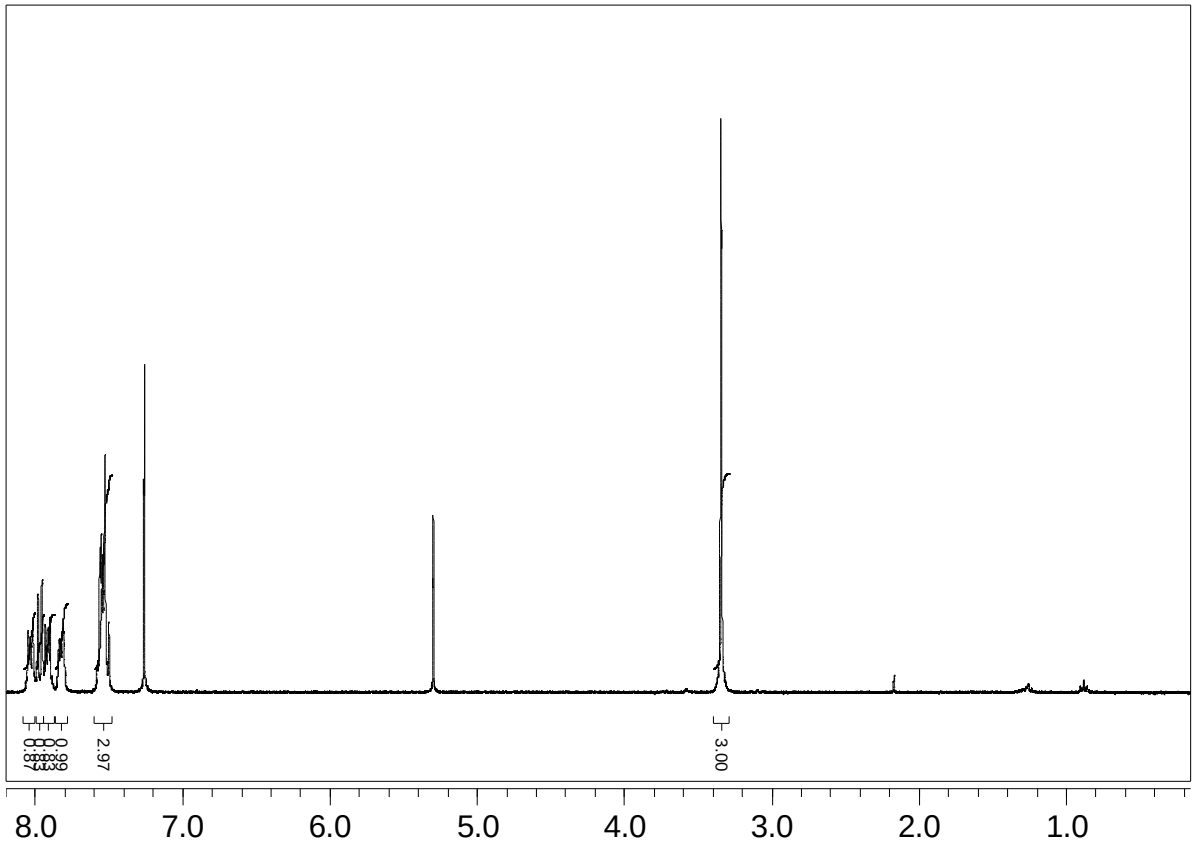


Figure S7. ^{1}H NMR spectrum of *rac*-**3**

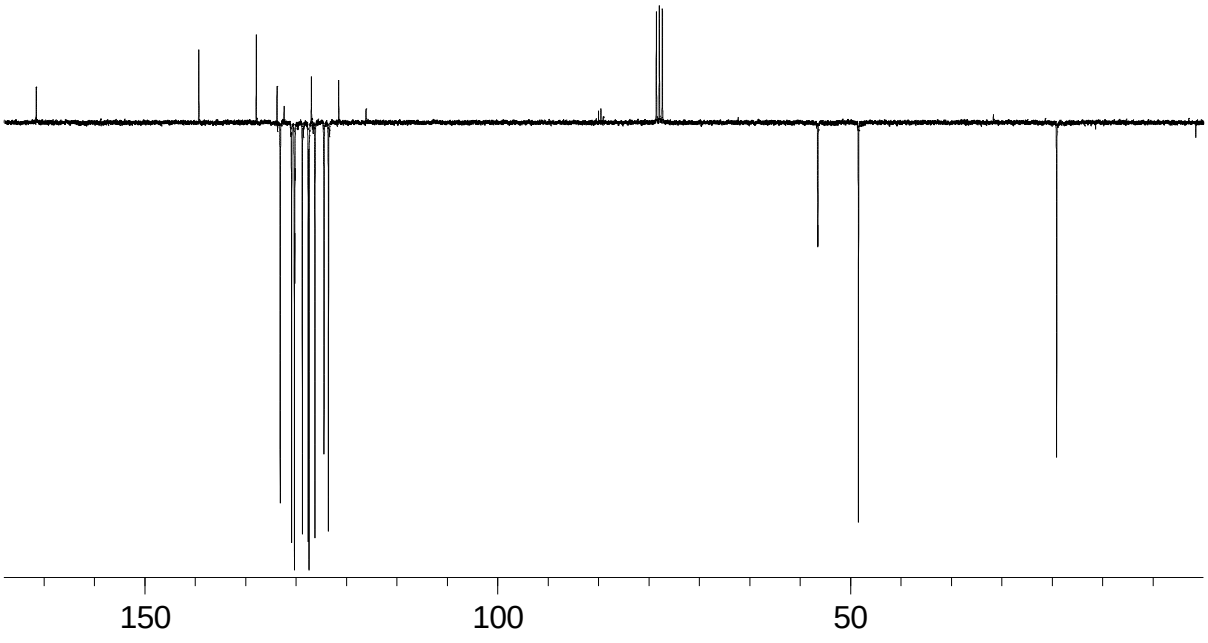


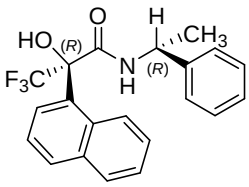
Figure S8. ^{13}C(JMOD) NMR spectrum of *rac*-**3**

Synthesis of 3,3,3–trifluoro–2–hydroxy–2–(1–naphthyl) N–(1–phenyl–ethyl)–propionamides (2)

A dichloromethane solution (2 mL) of the OCA *rac*-**1** (100 mg, 0.34 mmol) was cooled to 0°C and (*R*)–α–methyl benzylamine (87 µL, 0.68 mmol) was added in one portion to the mixture. The reaction mixture was stirred for 30 min, diluted with 10 mL dichloromethane and washed with HCl 2N (2x5 mL), brine and dried with sodium sulfate. The solvent was evaporated and the residue obtained was rapidly purified on silica (eluant: dichloromethane) to give **2** as a white solid (60 mg, 48%) as a 1/1 mixture of diastereomers.

This mixture was further purified on silica gel (95:5 Petroleum Ether:Ethyl Acetate) to yield the two pure diastereomers.

Compound 2a (*R,R*)



RMN $^{19}F\{^{1}H\}$ (δ, $CDCl_3$, 376.5 MHz): -73.2 (s).

RMN ^{1}H (δ, $CDCl_3$, 500.1 MHz): 7.95 (1H, d, J = 9.0 Hz, H_8), 7.92 (1H, d, J = 8.0 Hz, H_4), 7.87 (1H, d, J = 8.5 Hz, H_5), 7.83 (1H, m, H_2), 7.51–7.47 (2H, m, H_3 and H_6), 7.35 (1H, m, H_7), 7.08 (1H, t, J = 7.5 Hz, H_{para} Ph), 6.97 (2H, m, H_{meta} Ph), 6.58 (2H, d, J = 7.5 Hz, H_{ortho} Ph), 5.69 (1H, d br, J = 8.0 Hz, NH), 5.28 (1H, s, OH), 5.09 (1H, dq, J = 7.0 and 8.0 Hz, CH), 1.39 (3H, d, J = 6.9 Hz, CH_3).

RMN $^{13}C\{^{1}H\}$ (δ, $CDCl_3$, 125.7 MHz): 167.8 (C=O), 141.0 (C), 134.5 (C), 131.2 (C), 131.0 (CH), 129.1 (CH), 128.4 (CH), 128.3 (CH), 127.4 (CH), 127.2 (CH), 126.5 (CH, q, $^{4}J_{C–F}$ = 3.8 Hz), 126.2 (CH), 125.9 (CH), 125.6 (CH), 125.2 (CF_3, q, $^{1}J_{C–F}$ = 288.0 Hz), 124.4 (CH), 79.3 (C, q, $^{2}J_{C–F}$ = 25.0 Hz), 50.2 (**C**HCH$_3$), 21.1 (CH**C**H$_3$).

IR (CCl_4): 3421, 1695, 1513 cm^{-1}.

M.p.: 115°C.

Rf = 0.18 (90:10 Petroleum Ether:Ethyl Acetate).

$[\alpha]_D^{23}$ +70.1 (c 0.97 in $CHCl_3$).

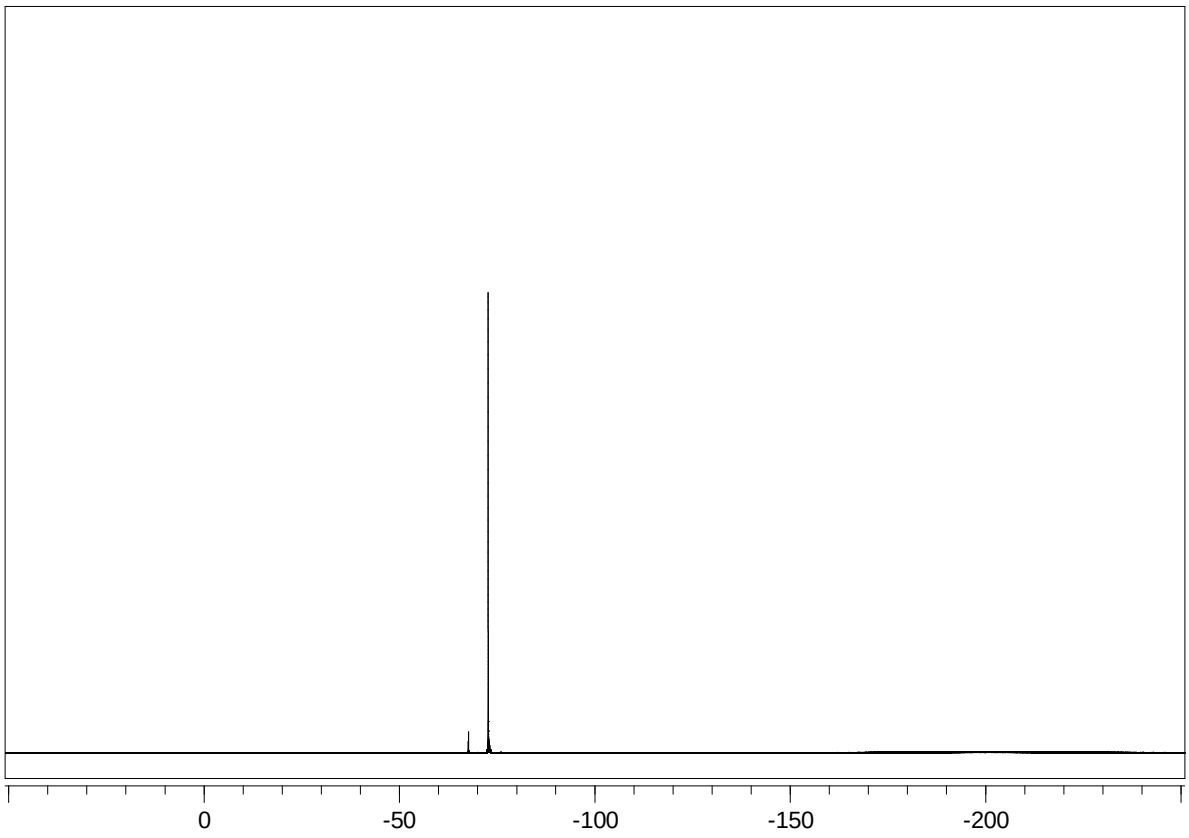


Figure S9. ^{19}F NMR spectrum of **2a**

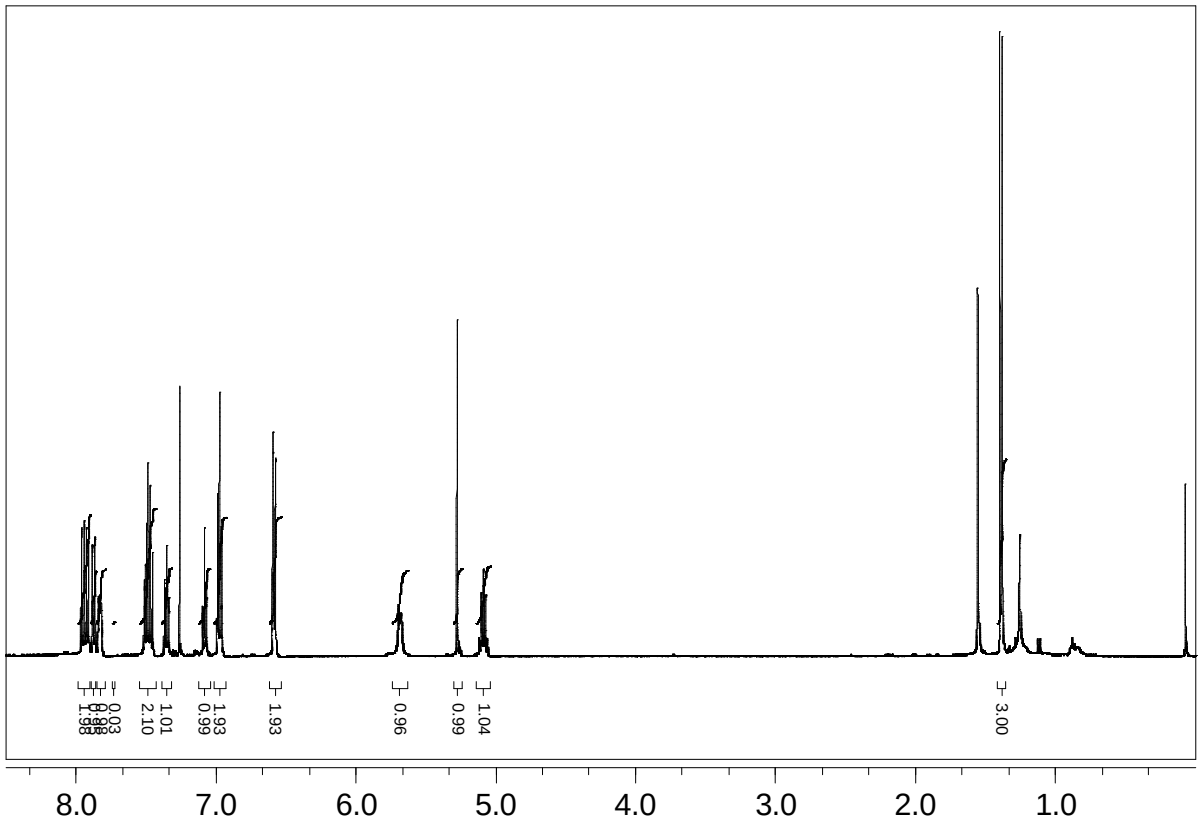


Figure S10. ^{1}H NMR spectrum of **2a**

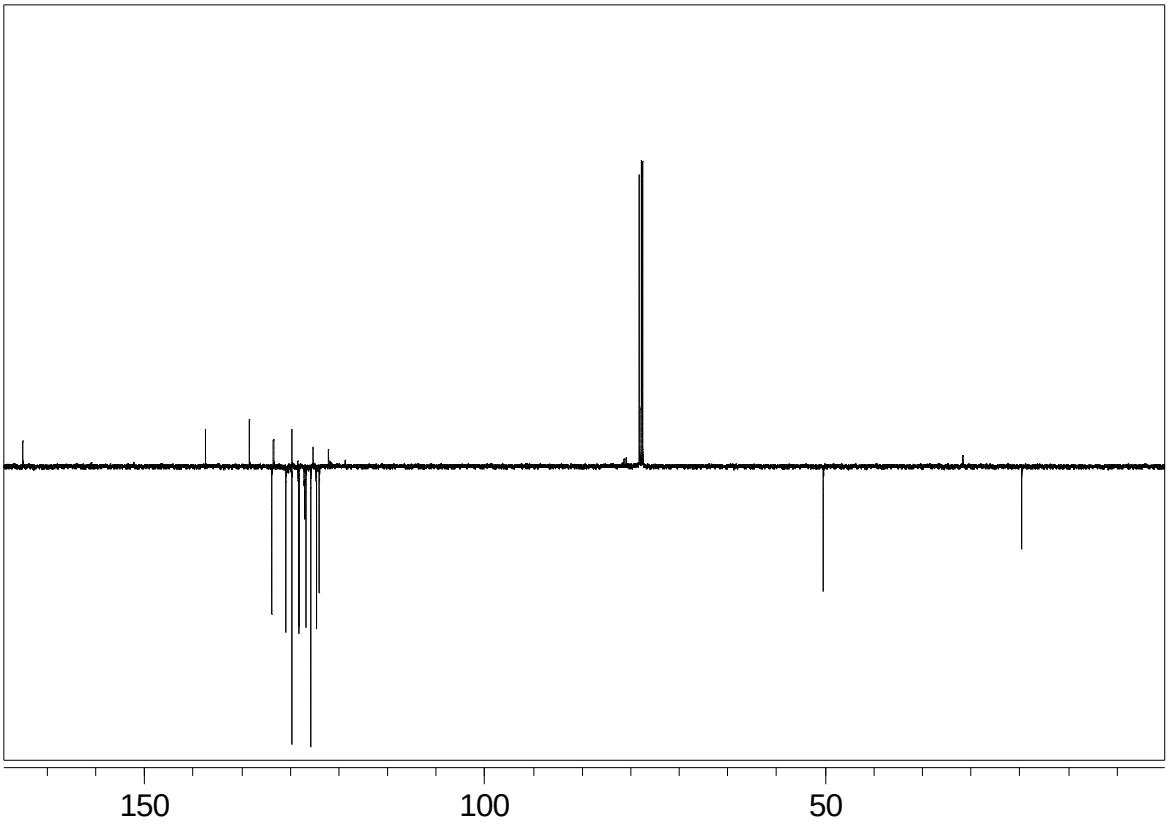
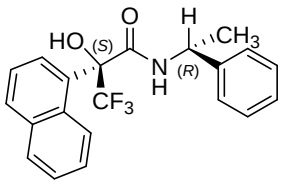


Figure S11. ^{13}C(JMOD) NMR spectrum of **2a**

Compound 2b (*S*,*R*)



RMN $^{19}F\{^1H\}$ (δ, $CDCl_3$, 376.5 MHz): -72.5 (s).

RMN ^1H (δ, $CDCl_3$, 500.1 MHz): 8.14 (1H, m, H_8), 7.96 (1H, d, *J* = 8.5 Hz, H_4), 7.93 (1H, m, H_5), 7.89 (1H, m, H_2), 7.59 – 7.53 (2H, m, H_6 and H_7), 7.49 (1H, dd, *J* = 8.8 and 8.5 Hz, H_3), 7.37 –7.29 (3H, m, H_{meta} and H_{para} Ph), 7.19 (2H, d, *J* = 7 Hz, H_{ortho} Ph), 5.97 (1H, d br, *J* = 8.0 Hz, NH), 5.37 (1H, s, OH), 5.15 (1H, dq, *J* = 8.0 and 7.8 Hz, CH), 1.16 (3H, d, *J* = 7.0 Hz, CH_3).

RMN $^{13}C\{^1H\}$ (δ, $CDCl_3$, 125.7 MHz): 165.4 (C=O), 142.2 (C), 134.3 (C), 131.4 (C), 131.3 (CH), 130.8 (CH), 129.4 (CH), 128.7 (CH), 128.5 (C), 127.5 (CH), 126.9 (CH), 126.2 (CH,

$^4J_{C-F}$ = 3.8 Hz), 126.0 (CH), 124.7 (CH), 124.4 (CF_3, q, $^1J_{C-F}$ = 292.0 Hz), 124.0 (CH), 85.6 (C, q, $^2J_{C-F}$ = 26.0 Hz), 54.7 (**C**HCH$_3$), 21.0 (CH**C**H$_3$).

IR (CCl_4): 3421, 1691, 1514.

M.p.: 127 – 128°C.

Rf = 0.13 (90:10 Petroleum Ether:Ethyl Acetate).

$[\alpha]_D^{23}$ -60.0 (c 1.03 in $CHCl_3$).

Elemental analysis:

Calculated: C% 67.56, H% 4.86, N% 3.75

Found: C% 67.47, H% 4.57, N% 3.71

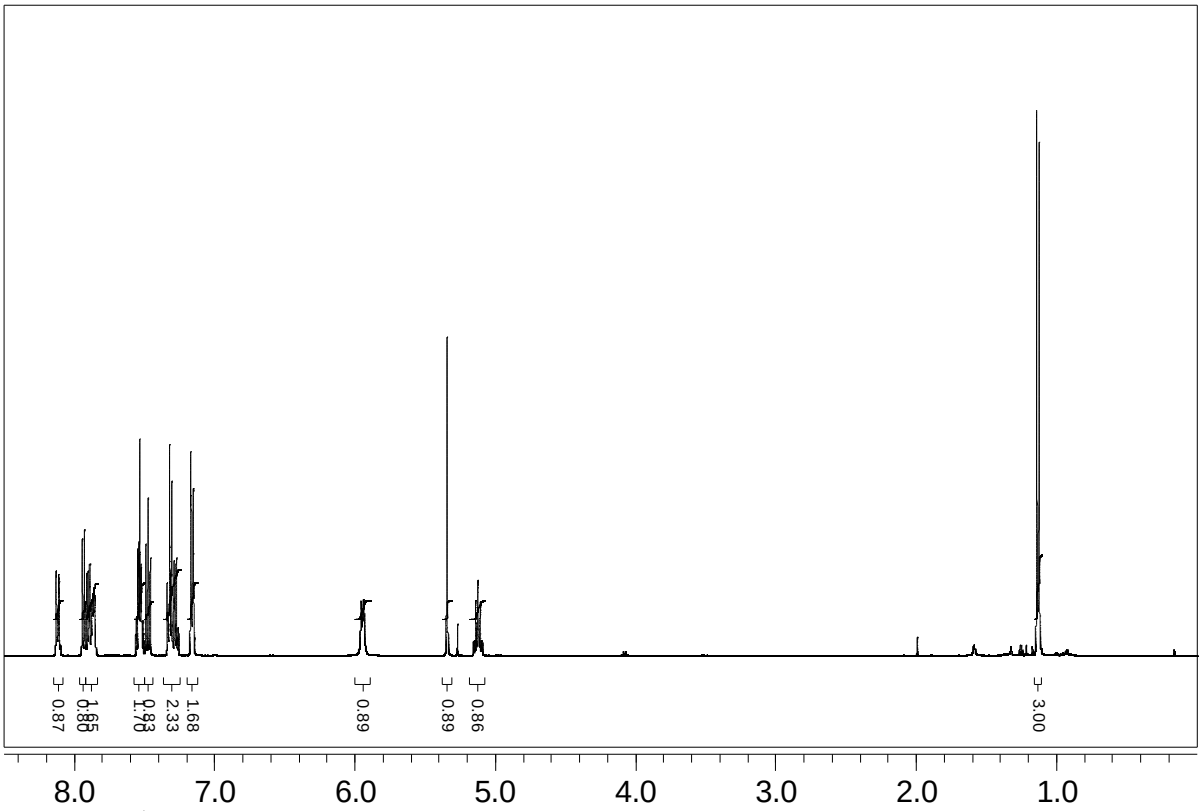


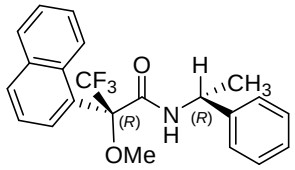
Figure S12. ^{1}H NMR spectrum of **2b**

Synthesis of 3,3,3–trifluoro–2–methoxy–2–(1–naphthyl) N–(1–phenyl–ethyl)–propionamides (4)

A dichloromethane solution (2 mL) of the carboxylic acid *rac*-**3** (140 mg, 0.50 mmol) was added dropwise to a cooled dichloromethane solution (3 mL, 0°C) of DCC (110 mg, 0.55 mmol). The reaction mixture was stirred for 1h30 at this temperature and (*R*)–α–methyl benzylamine (60 µL, 0.50 mmol) was added in one portion. After 2 h at room temperature the reaction mixture was diluted with 10 mL dichloromethane and washed with HCl 2N (2x5 mL), brine and dried with sodium sulfate. The solvent was evaporated and the residue was rapidly purified on silica gel (eluant: dichloromethane) to give a white solid (70 mg, 37%) consisting of a 1/1 mixture of diastereomers.

This mixture was further purified by chromatography on silica gel (eluant: Petroleum Ether:Ethyl Acetate 95:5) to yield the two pure diastereomers as white solids.

Compound 4a (*R,R*)



RMN $^{19}F\{^{1}H\}$ (δ, $CDCl_3$, 282,4 MHz): –68.3 (s).

RMN ^{1}H (δ, $CDCl_3$, 300.13 MHz): 8.25 (1H, m, H_7), 7.92 – 7.87 (2H, m, H_4 and H_8), 7.80 (1H, m, H_2), 7.53 – 7.47 (3H, m, H_3, H_5 and H_9), 7.40 – 7.28 (6H, m, Ph, NH), 5.20 (1H, dq, J = 8.1 and 6.9 Hz, CH), 3.26 (3H, s, OCH_3), 1.60 (3H, d, 6.9Hz, CH_3).

RMN $^{13}C\{^{1}H\}$ (δ, $CDCl_3$, 75.47 MHz): 165.4 (C=O), 142.2 (C), 134.3 (C), 131.4 (C), 130.8 (CH), 129.4 (CH), 128.7 (2 CH), 127.5 (C), 126.9 (CH), 126.2 (CH), 126.0 (CH), 124.7 (CH), 124.4 (CF_3, q, $^{1}J_{C–F}$ = 292.0 Hz), 124.0 (CH), 85.6 (C, q, $^{2}J_{C–F}$ = 25.7 Hz), 54.7 (OCH_3), 49.0 (**C**HCH_3), 21.0 (CH**C**H_3).

M.p.: 110 – 111°C.

Rf = 0.18 (90:10 Petroleum Ether:Ethyl Acetate).

Elemental analysis:

Calculated: C% 68.21, H% 5.21, N% 3.61

Found: C% 68.30, H% 4.83, N% 3.61

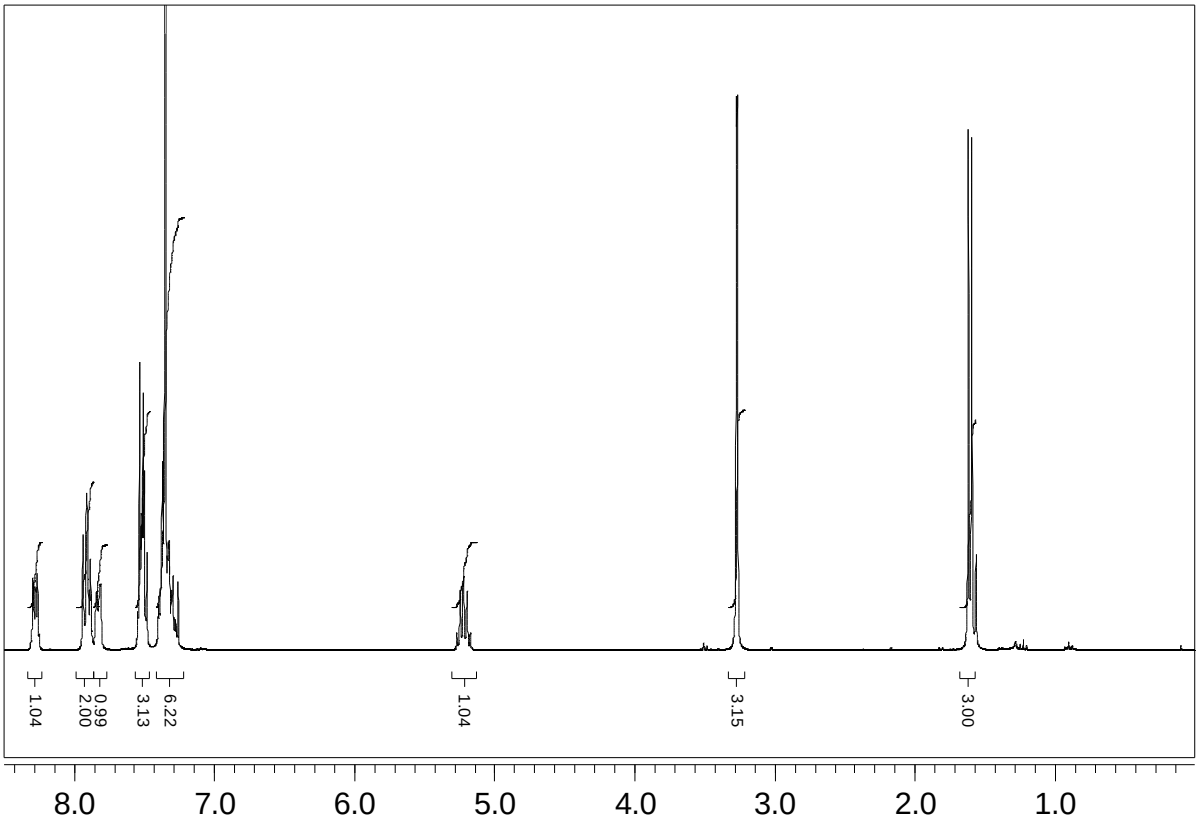
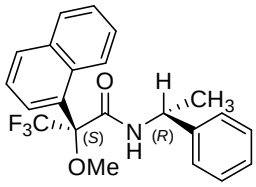


Figure S13. ^{1}H NMR spectrum of **4a**

Compound 4b (*S,R*)



RMN $^{19}F\{^{1}H\}$ (δ, $CDCl_3$, 282.4 MHz): -68.5 (s)

RMN ^{1}H (δ, $CDCl_3$, 300.13 MHz): 7.92 (1H, d, *J* = 8.7, H_8), 7.87 (1H, d, *J* = 8.4, H_4), 7.85 – 7.75 (2H, m, H_2 and H_5), 7.50 – 7.33 (8H, m, Ph, H_3, H_5 and NH), 7.14 (1H, m, H_7), 5.23 (1H, dq, *J* = 8.4 and 6.9 Hz, CH), 3.21(3H, s, OCH_3), 1.59 (3H, d, 6.9 Hz, CH_3).

RMN $^{13}C\{^{1}H\}$ (δ, $CDCl_3$, 75.47 MHz): 165.3 (C=O), 142.3 (C), 134.1 (C), 131.2 (C), 130.7 (CH), 130.2 (C), 129.1 (CH), 128.7 (2 CH), 127.6 (CH), 126.8 (CH), 126.6 (CH), 125.8 (CH), 124.5 (CH), 124.4 (CF_3, q, $^{1}J_{C–F}$ = 292.0 Hz), 124.0 (CH), 85.3 (C, q, $^{2}J_{C–F}$ = 25.0 Hz), 54.6 (OCH_3), 48.8 (**C**HCH_3), 20.7 (CH**C**H_3).

IR(CCl_4): 3422, 1703, 1540.

MS (EI): 387 (3), 344 (3), 239 (100), 155 (21), 142 (22), 84 (86)

M.p.: 104 – 105°C.

Rf = 0.21 (90:10 Petroleum Ether:Ethyl Acetate)

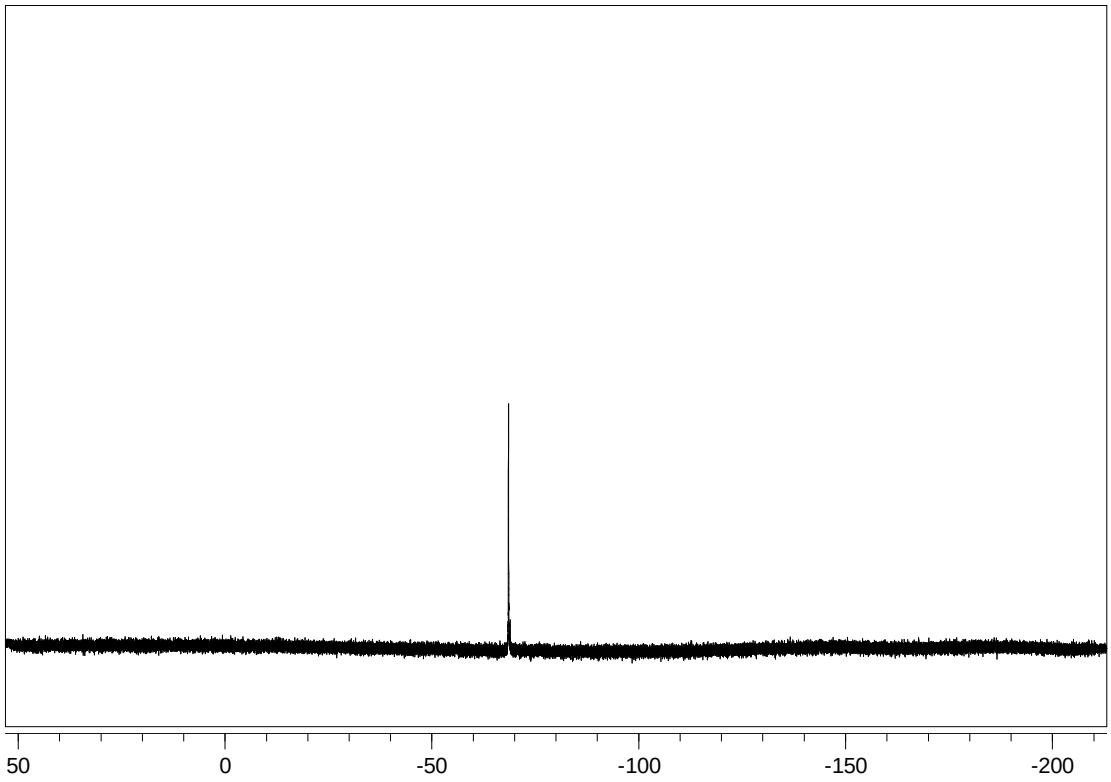


Figure S14. ^{19}F NMR spectrum of **4b**

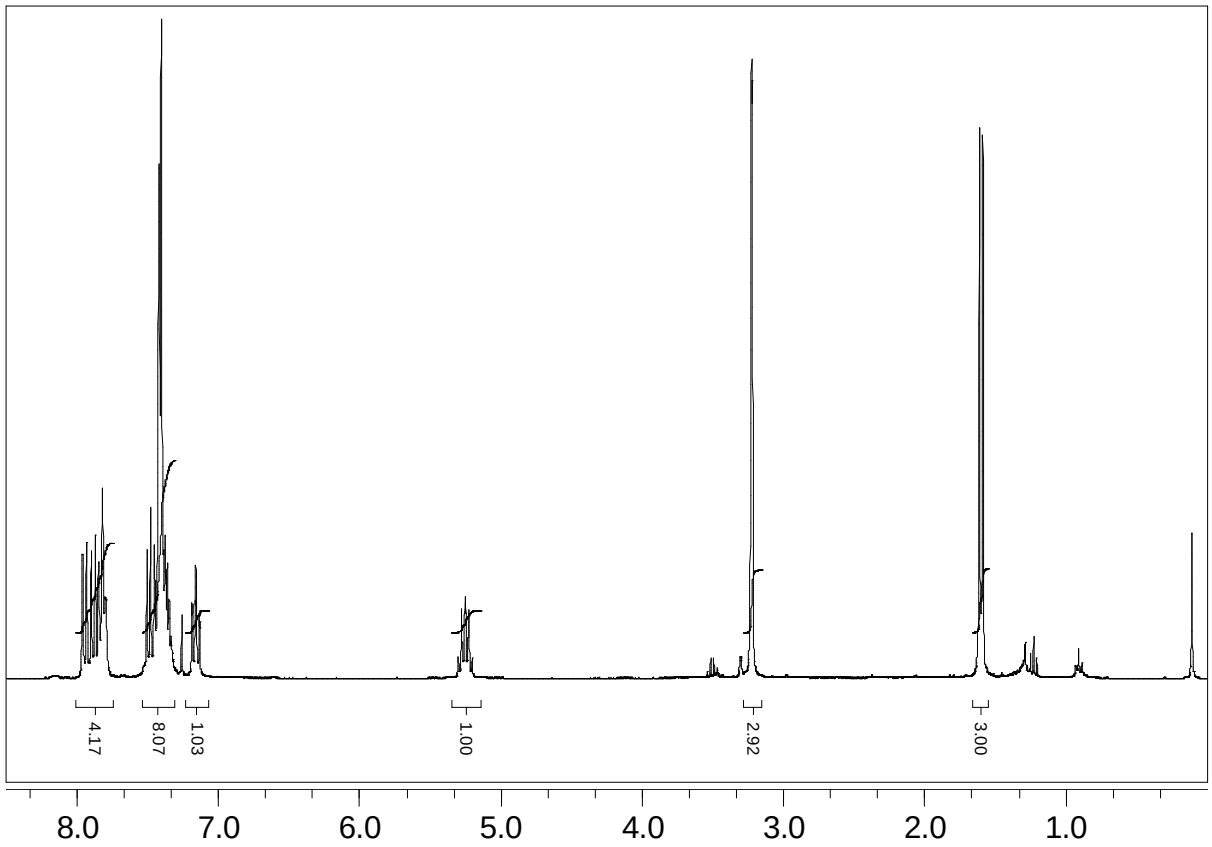


Figure S15. ^{1}H NMR spectrum of **4b**

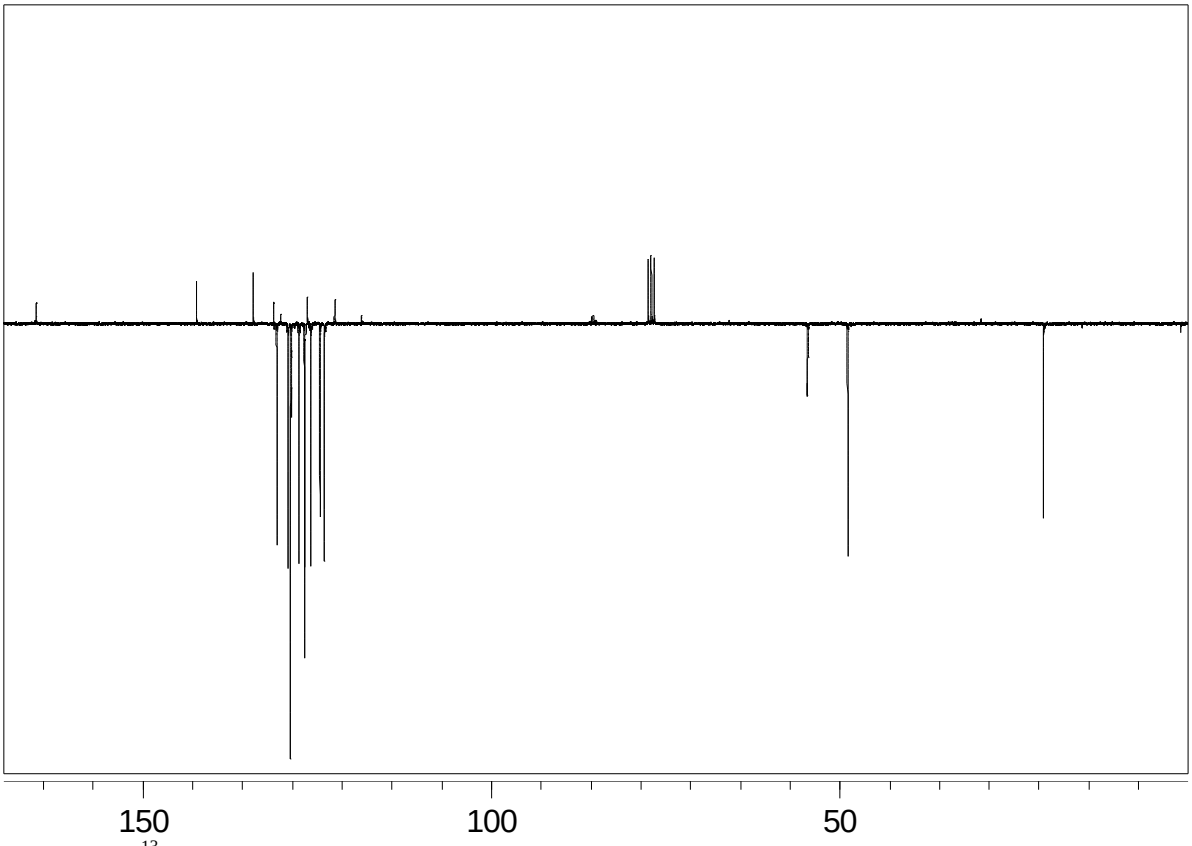


Figure S16. ^{13}C (JMOD) NMR spectrum of **4b**

Resolution of *rac*–3,3,3–trifluoro–2–hydroxy–2–(1–naphthyl)propanoic acid (II)

To a solution of the racemic hydroxyacid **II** (6.00 g, 22.2 mmol) in 2–propanol (60 mL) was added (*S*)–α–methylbenzylamine (2.86 mL, 22.2 mmol). The corresponding ammonium salt crystallizes rapidly and the mixture was left overnight at room temperature. The crystals were filtered–off, washed with cold 2–propanol and dried under vacuum to yield 2.10 g of a white powder (ee = 50.2%; HPLC: 24.9/75.1; Fig. S17–C2). The latter was recrystallized in 2–propanol (20 mL) to yield 1.70 g of salt (ee = 99.4%; HPLC: 0.3/99.7; Fig. S17–C3). A third recrystallization yielded 1.35 g of salt with ee ≥ 99.9%; Fig. S17–C4.

M.p.: 198°C.

The free hydroxyacid **II** was recovered after aqueous HCl work–up and diethyl ether extraction. The solvent was eliminated under reduced pressure and the resultant sticky solid was triturated with pentane to afford a white solid (0.93 g, 15.5 % from racemic hydroxy acid **II**).

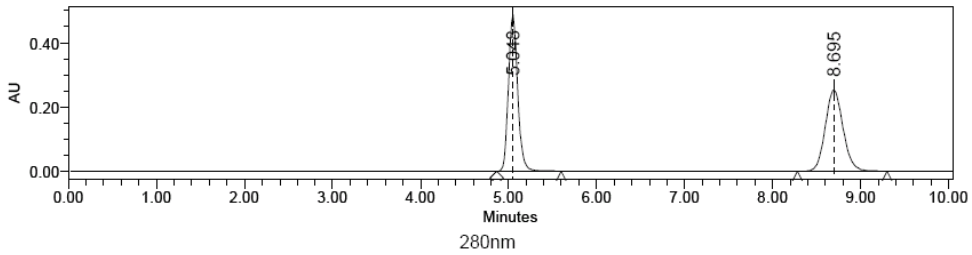
Enantiomeric excess: 99.9%; Fig. S17–C5.

M.p.: 110 – 111°C.

NMR spectroscopic data are in agreement with those reported for the racemic hydroxyacid **II**.

$[\alpha]_D^{23}$ -27.8° (c 1.05 in $CHCl_3$).

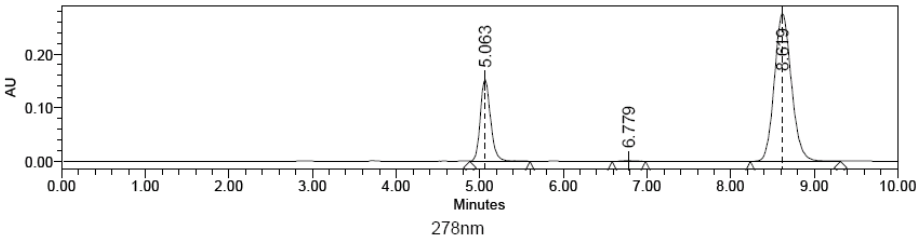
Chromatogram C1: *rac*-II



Pureté et comparaison avec la librairie

	RT	Area	% Area	Purity1 Angle	Purity1 Threshold
1	5.048	3528754	49.98	7.344	4.050
2	8.695	3531831	50.02	2.070	1.652

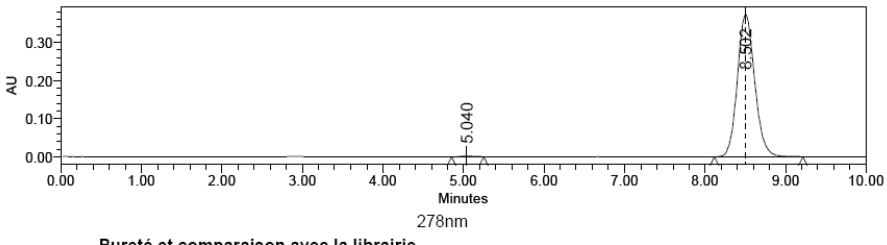
Chromatogram C2



Pureté et comparaison avec la librairie

	RT	Area	% Area	Purity1 Angle	Purity1 Threshold
1	5.063	1290988	24.78	0.496	0.512
2	6.779	10973	0.21	3.950	4.898
3	8.619	3907941	75.01	2.546	1.823

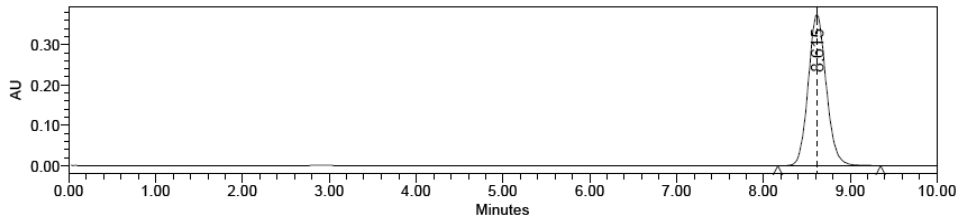
Chromatogram C3



Pureté et comparaison avec la librairie

	RT	Area	% Area	Purity1 Angle	Purity1 Threshold
1	5.040	18959	0.34	3.406	3.256
2	8.502	5575735	99.66	4.938	2.490

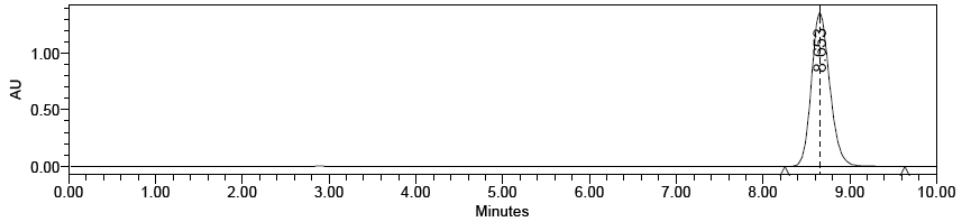
Chromatogram C4



Pureté et comparaison avec la librairie

	RT	Area	% Area	Purity1 Angle	Purity1 Threshold
1	8.615	5413928	100.00	5.144	2.367

Chromatogram C5



Pureté et comparaison avec la librairie

	RT	Area	% Area	Purity1 Angle	Purity1 Threshold
1	8.653	19992448	100.00	15.716	4.138

Figure S17. HPLC chromatograms obtained for (–)–**II**

The mother liquor of the first crystallization was concentrated to dryness and the free hydroxyacid was recovered after HCl work–upt and diethyl ether extraction to yield 4.81 g of enantiomeric enriched hydroxyacid **II**. The solid was dissolved in 2–propanol (50 mL) and 1 equivalent of (*R*)–α–methylbenzylamine (2.30 mL) was added. The mixture was kept cold overnight. The resultant salt was filtered off, washed with cold 2–propanol and dried under vacuum to yield 2.69 g of white crystals (ee = 92.0%; HPLC : 96.0/4.0; Fig. S18–C6). The latter was recrystallized in 2–propanol (30 mL) to yield 2.10 g of salt (ee = 98.8%; HPLC: 99.4/0.6; Fig. S18–C7).

M.p.: 198°C

The free hydroxyacid was recovered following the procedure described for the (–) enantiomer to afford a white solid (1.48 g; 31 % from enantiomeric enriched hydroxyacid).

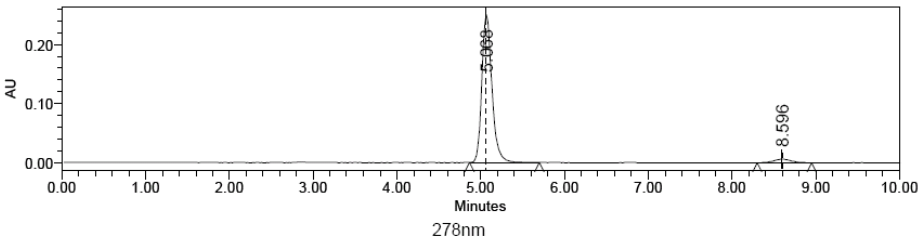
M.p.: 110–111°C

$[\alpha]_D^{23}$ + 27,4° (c 1.16 in $CHCl_3$)

NMR spectroscopic data are in agreement with those reported for the racemic hydroxyacid **II**.

Enantiomeric excess: 99.6%; Fig. S18–C8

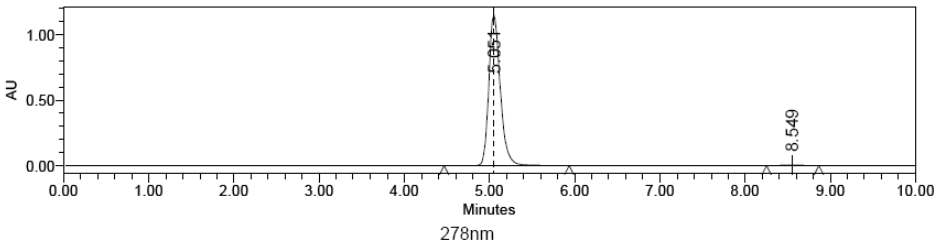
Chromatogram C6



Pureté et comparaison avec la librairie

	RT	Area	% Area	Purity1 Angle	Purity1 Threshold
1	5.068	2099844	95.98	1.420	1.524
2	8.596	88036	4.02	0.619	0.862

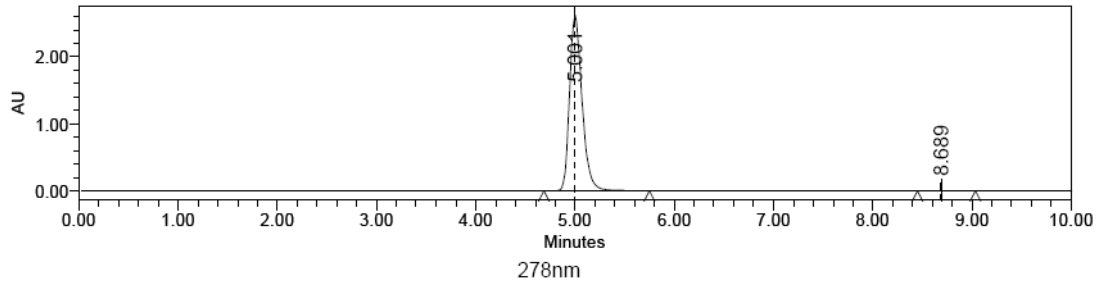
Chromatogram C7



Pureté et comparaison avec la librairie

	RT	Area	% Area	Purity1 Angle	Purity1 Threshold
1	5.051	10690276	99.43	14.863	3.950
2	8.549	61655	0.57	1.481	1.920

Chromatogram C8



Pureté et comparaison avec la librairie

	RT	Area	% Area	Purity1 Angle	Purity1 Threshold
1	5.001	22854644	99.79	18.408	11.670
2	8.689	48596	0.21	1.104	1.402

Figure S18. HPLC chromatograms obtained for (+)–**II**

Synthesis of the *(S)* and *(R)*–5–naphthyl– 5–trifluoromethyl–[1,3]–dioxolane–2,4–diones

Diphosgene (1 mmol, 120 µl) was added dropwise to a cooled solution (-10°C) of (-) or (+) hydroxy acid (1 mmol, 270 mg) and polystyrene supported DIEA (2 mmol, 700 mg) in THF (5 mL). The suspension was stirred 1 hour at 0°C. The solvent was removed under reduced pressure then pentane (4 mL) was added and the mixture cooled to -78°C. A white solid precipitated. The solvent was removed carefully and the residue was dried under vacuum to yield the expected OCA as a colourless oil (175 mg, 59%).

RMN ^{19}F (δ, $CDCl_3$, 282 MHz): -74,3 ppm.

RMN ^{1}H (δ, $CDCl_3$, 300 MHz): 8.41 (1H, d, *J* = 8.7 Hz), 8.15 (1H, d, *J* = 7.5 Hz), 8.07 (1H, d, *J* = 8.1 Hz), 7.94 (1H, dd, *J* = 1.8 and 7.8 Hz), 7.63 (2H, m), 7.54 (1H, t, *J* = 8.1Hz).

$[\alpha]_D^{23}$ +96.1° (c 1.65 in $CHCl_3$) for the *(S)*–5–naphthyl–5–trifluoromethyl–[1,3]–dioxolane–2,4–dione.

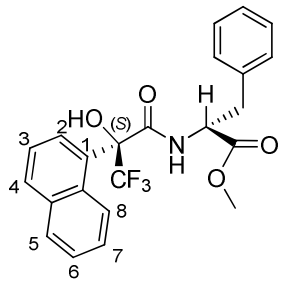
General procedure for the derivatisation of α-chiral primary amines

A dichloromethane solution (1 mL) of (*S*)–**1** [(*R*)–**1** in the case of indane amine] (100 mg, 0.34 mmol) was cooled to 0°C and the amine (0.68 mmol) was added in one portion to the mixture. The reaction media was stirred 30 min, diluted with 10 mL dichloromethane and washed with HCl 2N (2x5 mL), brine and dried with sodium sulphate. The solvent was evaporated and the residue obtained was rapidly purified on silica (dichloromethane 100%) to yield the expected product.

The same protocol has been followed with *S*, *R* or *rac*–**1**.

$\Delta\delta^{RS}$ ($\delta^R - \delta^S$) were determined comparing the ^{1}H NMR spectra of the adducts obtained reacting the amine with *rac*–**1** and *S*–**1** (or *R*–**1**).

(*S*)-3,3,3-trifluoro-2-hydroxy-2-(1-naphthyl) N-(*R*-phenylalanine methyl ester)-propionamide (5)



RMN ^{19}F (δ, $CDCl_3$, 282.4 MHz): -72.7 (s).

RMN ^{1}H (δ, $CDCl_3$, 500.1 MHz): 8.13 (1H, m, H_8), 7.99 – 7.95 (2H, m, H_4 and H_5), 7.78 (1H, m, H_2), 7.56 – 7.53 (2H, m, H_6 and H_7), 7.47 (1H, t, *J* = 7.8 Hz, H_3), 6.99 – 6.95 (1H, td, *J* = 1.1 and 7.5 Hz, H_{para}), 6.77 – 6.74 (2H, t, *J* = 7.7 Hz, H_{meta}), 6.02 (1H, br d, *J* = 8.2 Hz, NH), 5.99 (2H, d, *J* = 7.0 Hz, H_{ortho}), 5.15 (1H, s, OH), 4.96 (1H, m, CH), 3.67 (3H, s, CH_3), 2.97 (1H, dd, *J* = 5.1 and 13.8 Hz, CH_2), 2.63 (1H, dd, *J* = 5.1 and 13.8 Hz, CH_2).

RMN $^{13}C\{^{1}H\}$ (δ, $CDCl_3$, 125.7 MHz): 170.1 (C=O), 168.0 (C=O), 134.8 (C), 134.0 (C), 131.2 (C), 131.1 (CH), 129.4 (CH), 128.5 (CH), 128.3 (CH), 128.2 (C), 127.4 (CH), 127.0 (CH), 126.5 (2 CH), 124.7 (2 CH), 123.7 (CF_3, q, $^{1}J_{C-F}$ = 288.0 Hz), 80 (C, q, $^{2}J_{C-F}$ = 28.1 Hz), 53.7 (CH), 52.5 (CH_3), 37.5 (CH_2).

HRMS (ESI) calculated for $C_{23}H_{20}F_3NO_4$ $[M+Na]^+$, 454.1290; found 454.1242.

$[\alpha]_D^{23}$ -61.5 (c 0.94 in $CHCl_3$).

M.p.: 118 – 119°C.

Rf = 0.44 (CH_2Cl_2).

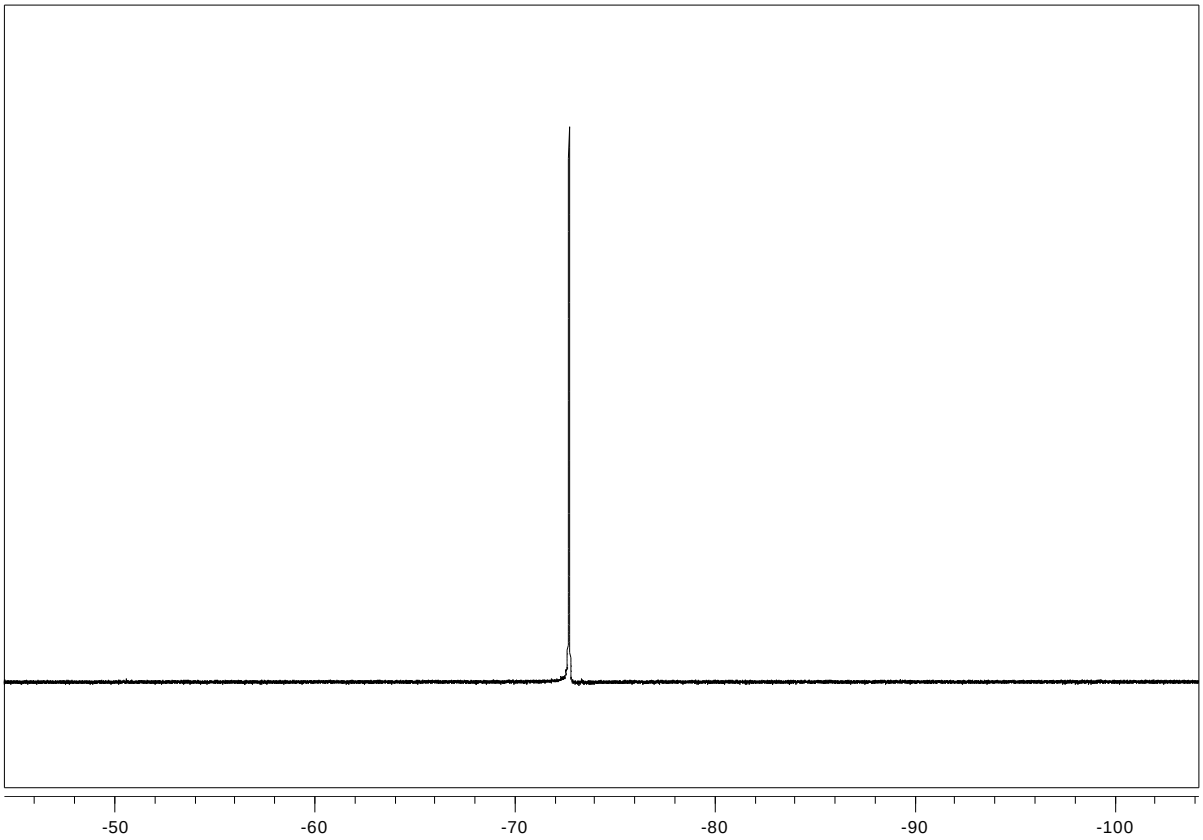
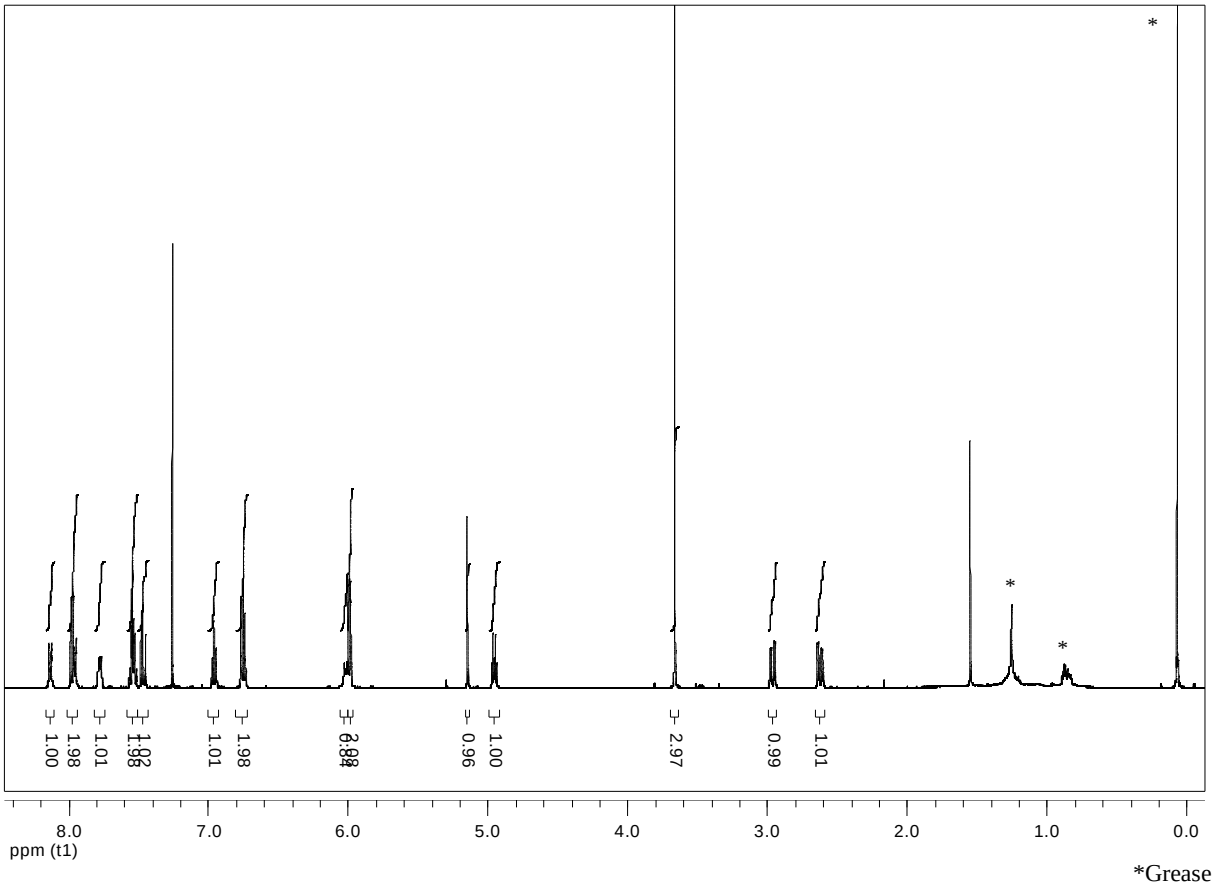


Figure S19. ^{19}F NMR spectrum of **5**



*Grease

Figure S20. ^{1}H NMR spectrum of **5**

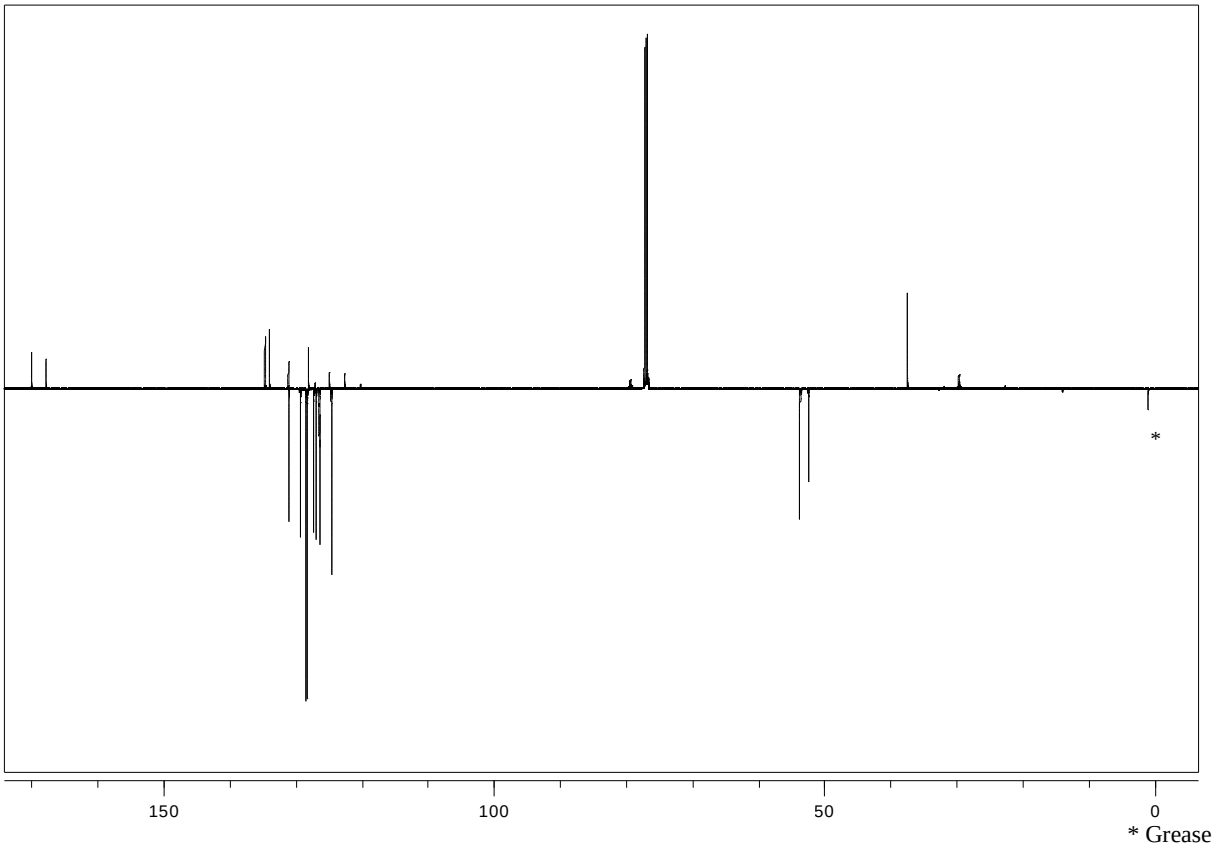
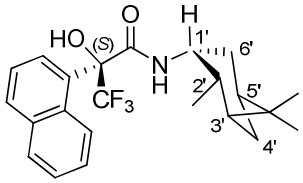


Figure S21. ^{13}C NMR spectrum of **5**

(*S*)-3,3,3-trifluoro-2-hydroxy-2-(1-naphthyl) N-((1'*R*,2'*R*,3'*R*,5'*S*)isopinocampheyl)-propionamide (6)



RMN ^{19}F (δ, $CDCl_3$, 282.4 MHz): -72.9 (s)

RMN ^{1}H (δ, $CDCl_3$, 300.2 MHz): 8.05 (1H, m, H_8), 7.93 (1H, d, *J* = 8.3 Hz, H_4), 7.89 – 7.82 (2H, m, H_5 and H_2), 7.51 – 7.46 (3H, m, H_6, H_7 and H_3), 5.37 (1H, br d, *J* = 8.7 Hz, NH), 5.33 (1H, s, OH), 4.27 (1H, m, CH), 2.31 (1H, m, $H_{6'a}$), 2.22 (1H, m, $H_{4'a}$), 1.75 (1H, s, $H_{3'}$), 1.71 (1H, s, $H_{5'}$), 1.62 (1H, m, $H_{2'}$), 1.14 (3H, s, CH_3), 1.04 (3H, d, *J* = 7.2 Hz, CH_3), 0.99 (3H, s, CH_3), 0.86 (1H, m, $H_{6'b}$), 0.45 (1H, d, *J* = 9.8 Hz, $H_{4'b}$).

RMN $^{13}C\{^{1}H\}$ (δ, $CDCl_3$, 75 MHz): 166.0 (C=O), 134.6 (C), 131.2 (CH), 131.0 (C), 129.2 (CH), 128.6 (C), 127.1 (CH), 126.6 (CH, q, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 126.3 (CH), 124.7 (CH), 124.3 (CH), 124.1 (CF_3, q, $^{1}J_{C–F}$ = 288.0 Hz), 78.9 (C, q, $^{2}J_{C–F}$ = 27.8 Hz), 50.0 (CH), 47.5 (CH), 45.5 (CH), 41.2 (CH), 38.4 (C), 35.5 (CH_2), 35.2 (CH_2), 28.0 (CH_3), 23.3 (CH_3), 20.5 (CH_3).

HRMS (ESI) calculated for $C_{23}H_{26}F_3NO_2$ $[M+Na]^+$, 428.1850; found 428.1813.

$[\alpha]_D^{23}$ -24.7 (c 0.9 in $CHCl_3$).

M.p.: 154 – 155°C.

Rf = 0.58 (CH_2Cl_2).

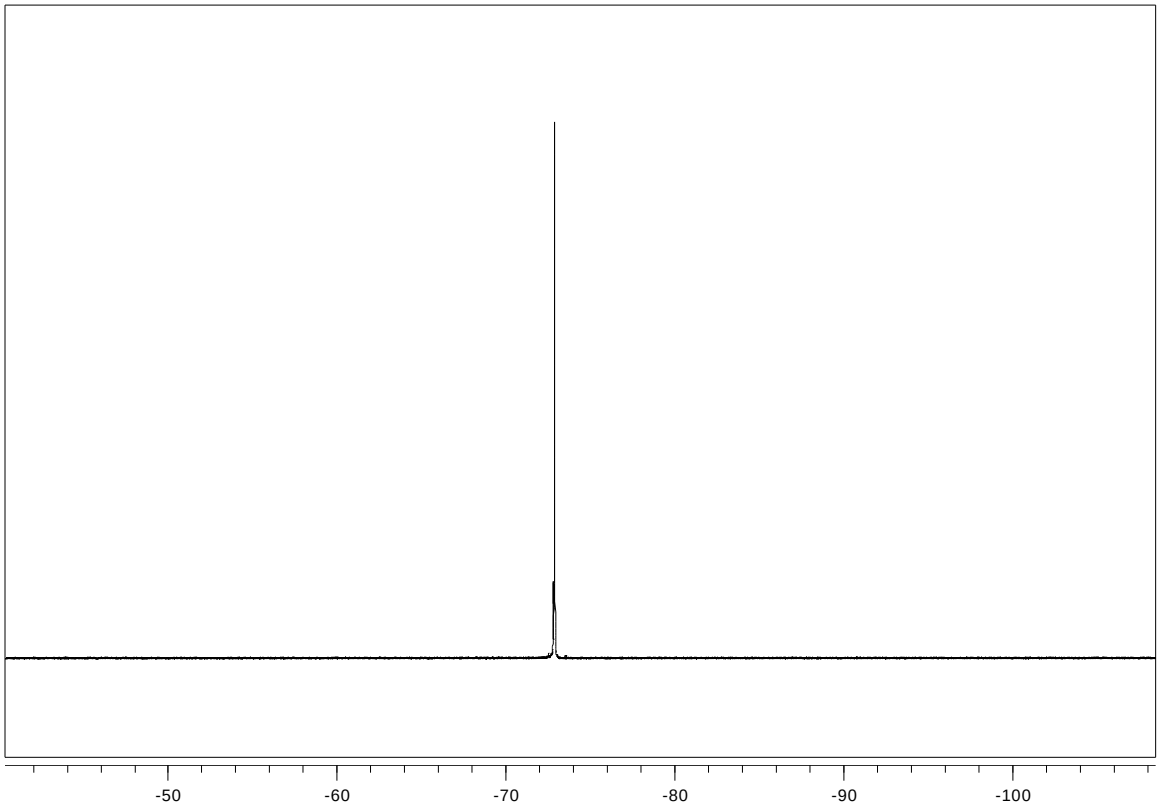
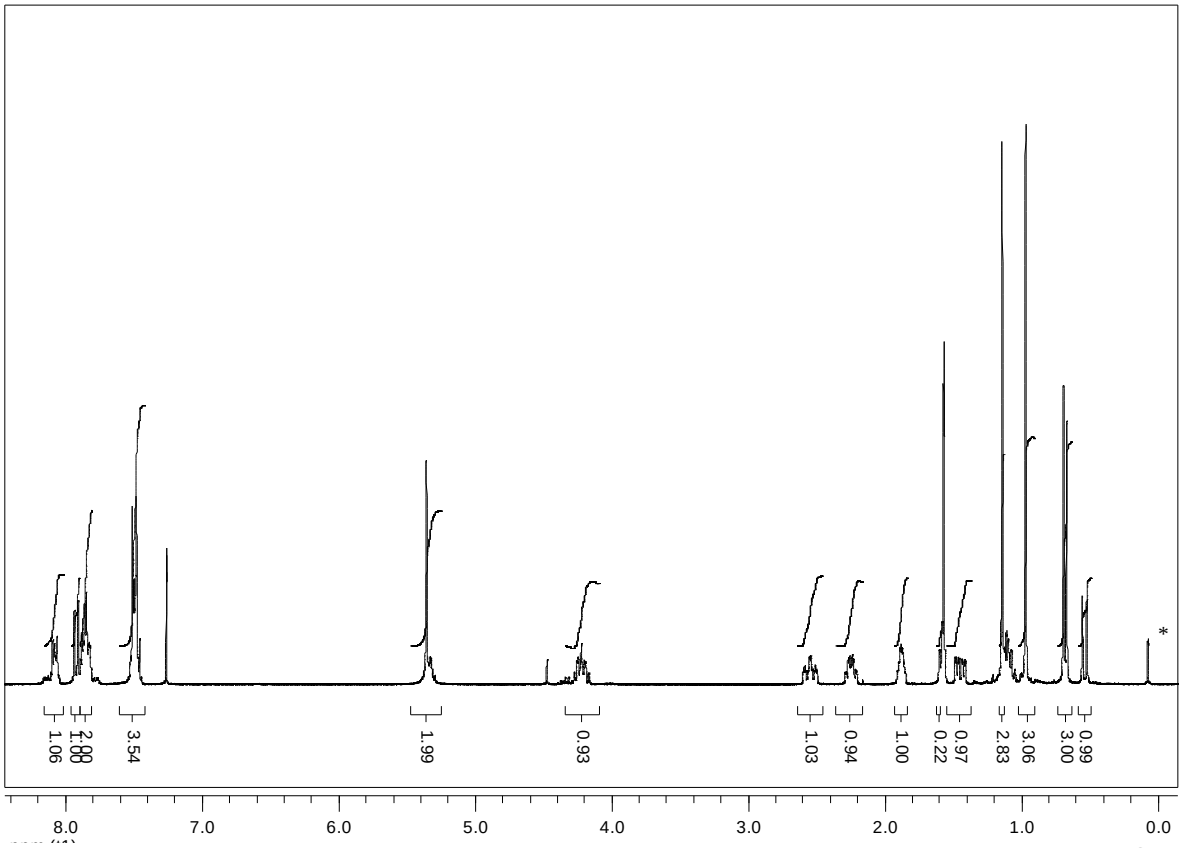


Figure S22. ^{19}F NMR spectrum of **6**



* Grease

Figure S23. ^{1}H NMR spectrum of **6**

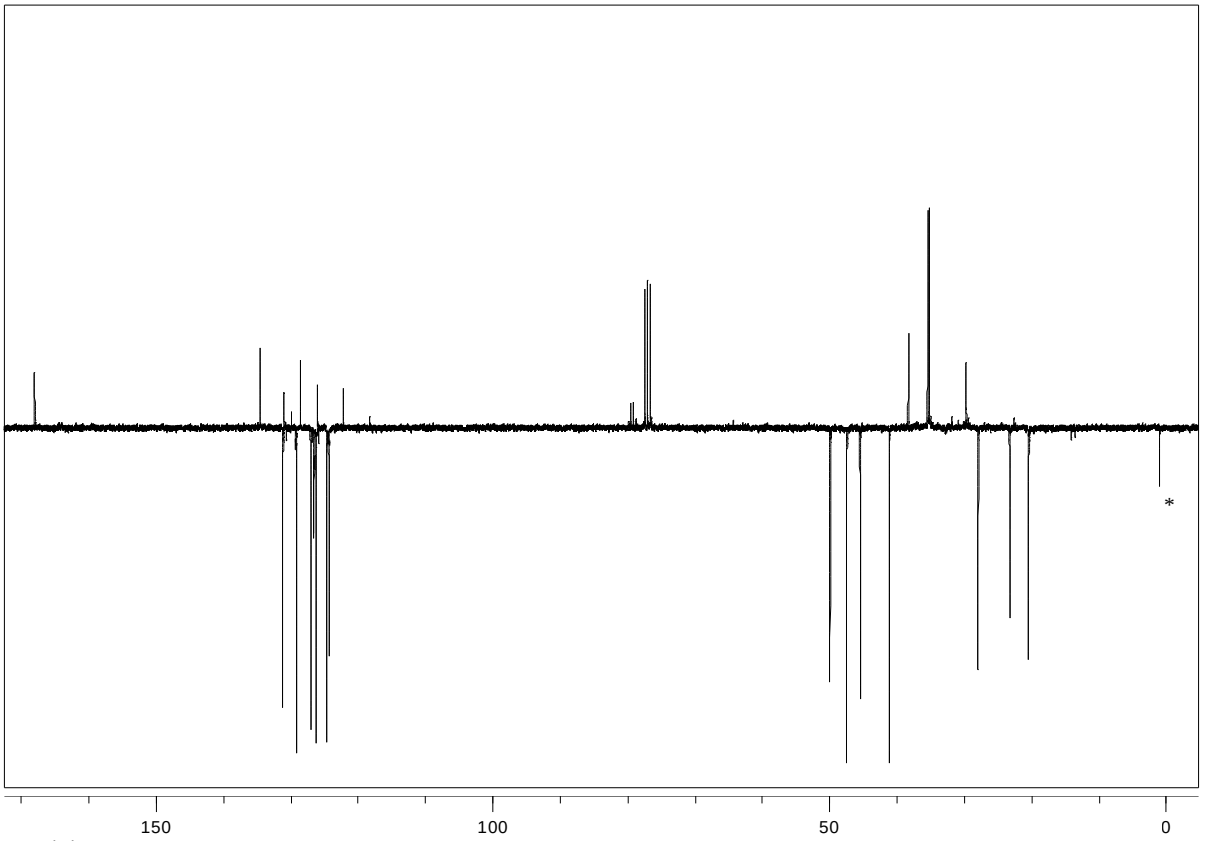
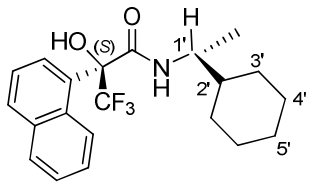


Figure S24. ^{13}C NMR spectrum of **6**

(*S*)-3,3,3-trifluoro-2-hydroxy-2-(1-naphthyl) N-((*R*)-1'-cyclohexyl-ethyl)-propionamide (7).



RMN ^{19}F (δ, $CDCl_3$, 282.4 MHz): -72.6 (s).

RMN ^{1}H (δ, $CDCl_3$, 300.2 MHz): 8.05 (1H, m, H_8), 7.93 (1H, d, *J* = 8.3 Hz, H_4), 7.85 (2H, m, H_5 and H_2), 7.51 – 7.46 (3H, m, H_6, H_7 and H_3), 5.36 (1H, s, OH), 5.27 (1H, br d, *J* = 8.4 Hz, NH), 3.83 (1H, m, CH), 1.70 (2H, m, CH_2), 1.58 (2H, m, CH_2), 1.17 – 1.09 (4H, m, CH and CH_2), 0.90 – 0.80 (3H, m, CH_2), 0.63 (3H, d, *J* = 6.8 Hz, CH_3).

RMN ^{13}C{^{1}H} (δ, $CDCl_3$, 75 MHz): 167.8 (C=O), 134.5 (C), 131.1 (CH), 131.0 (C), 129.1 (CH), 128.7 (C), 127.0 (CH), 126.5 (CH, q, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 126.2 (CH), 124.6 (CH), 124.3 (CH), 124.1 (CF_3, q, $^{1}J_{C–F}$ = 288.0 Hz), 78.9 (C, q, $^{2}J_{C–F}$ = 27.9 Hz), 51.7 (CH), 42.6 (CH), 29.2 (CH_2), 28.4 (CH_2), 26.2 (CH_2), 25.9 (CH_2), 25.8 (CH_2), 17.2 (CH_3).

HRMS (ESI) calculated for $C_{21}H_{24}F_3NO_2$ $[M+Na]^+$, 402.1687; found 428.1657.

$[\alpha]_D^{23}$ -55.2 (c 0.46 in $CHCl_3$).

M.p.: 111 – 112°C.

Rf = 0.52 (CH_2Cl_2).

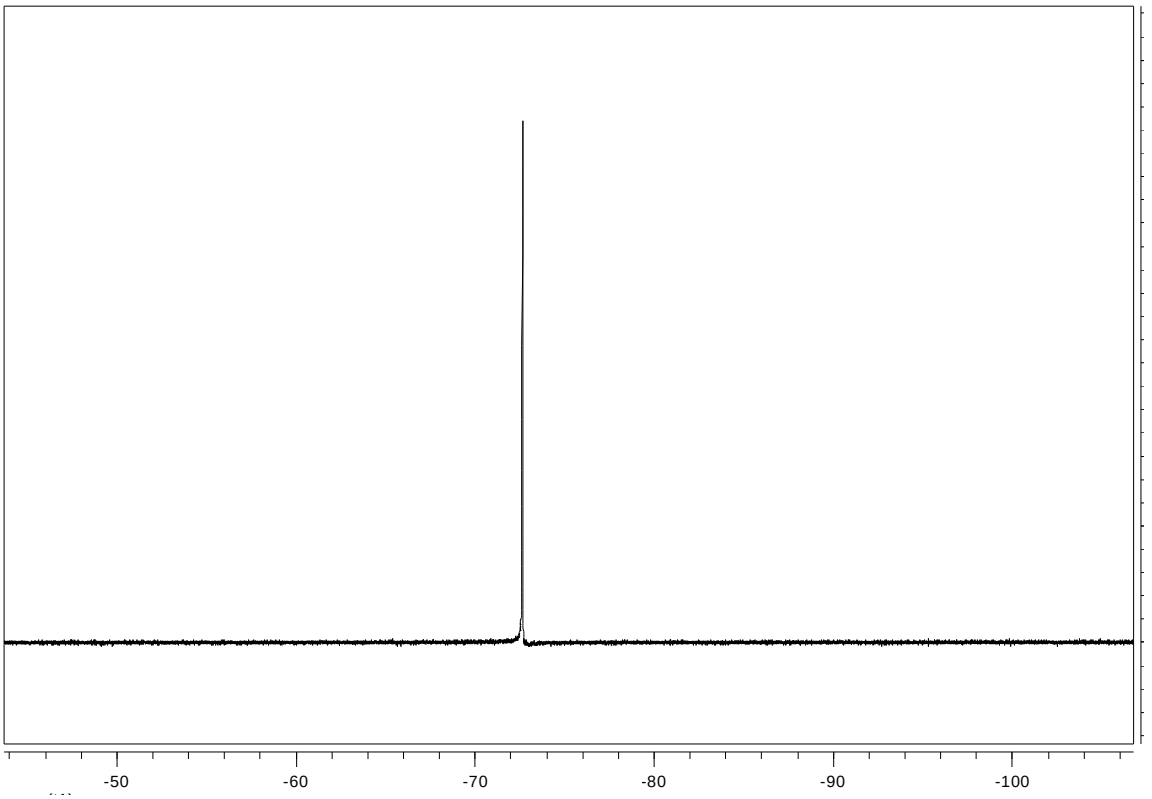


Figure S25. ^{19}F NMR spectrum of **7**

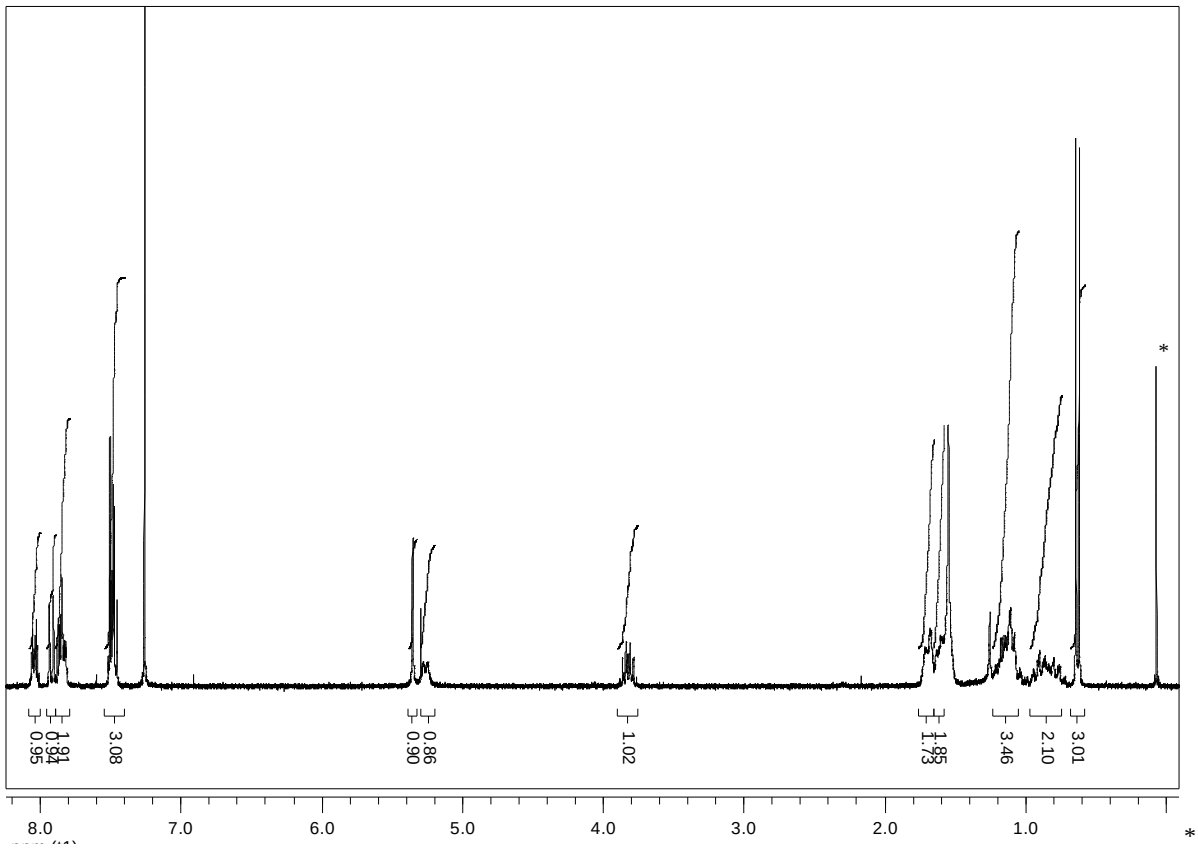


Figure S26. ^{1}H NMR spectrum of **7**

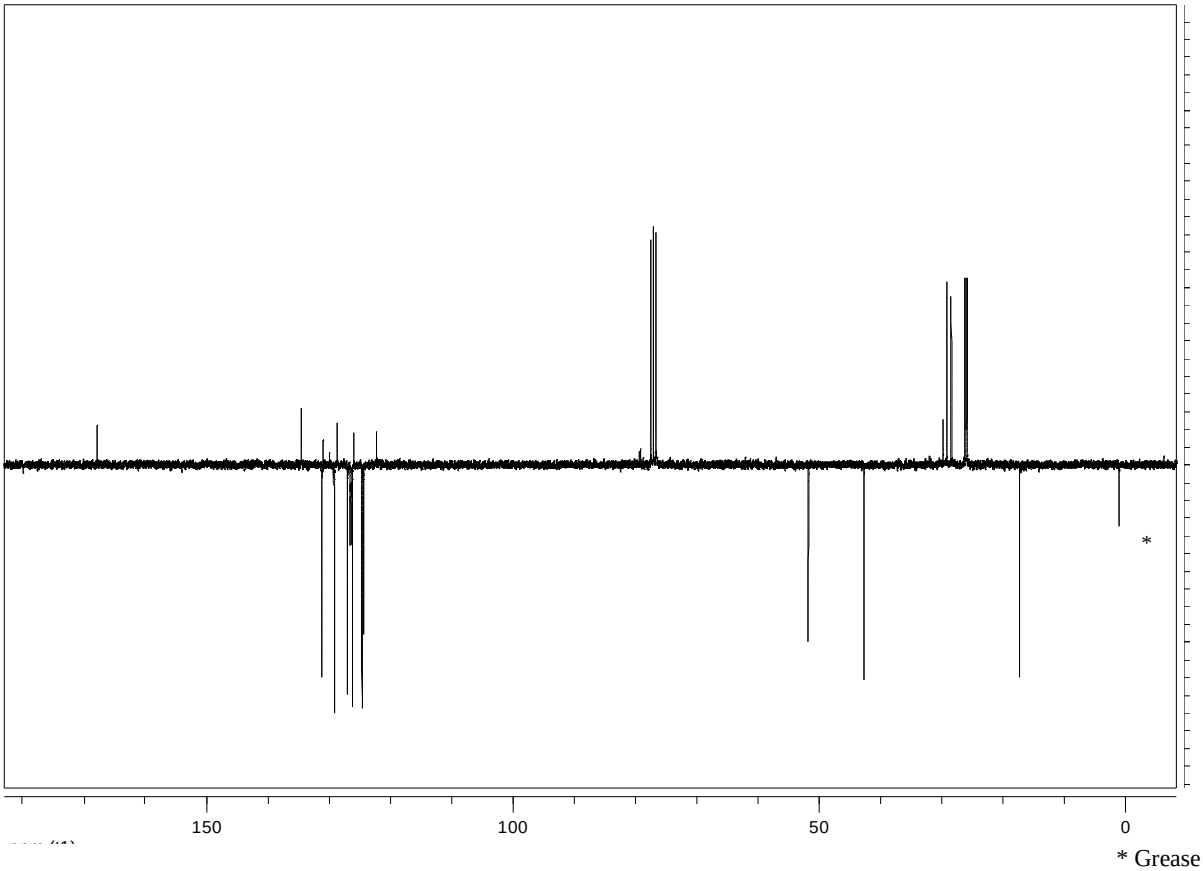
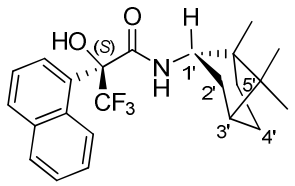


Figure S27. ^{13}C NMR spectrum of **7**

(*S*)-3,3,3-trifluoro-2-hydroxy-2-(1-naphthyl) N-((*R*)-bornyl)-propionamide (8)



RMN ^{19}F (δ, $CDCl_3$, 282.4 MHz): -72.8 (s).

RMN ^{1}H (δ, $CDCl_3$, 300.2 MHz): 8.14 (1H, m, H_8), 7.93 (1H, d, J = 8.3 Hz, H_4), 7.86 (2H, m, H_5 and H_2), 7.49 (3H, m, H_6, H_7 and H_3), 5.45 (1H, br d, J = 8.8 Hz, NH), 5.29 (1H, s, OH), 4.13 (1H, m, CH), 2.30 (2H, m, $H_{2'a}$), 1.59 – 1.53 (3H, m, $H_{3'}$ and $H_{4'}$), 0.84 (3H, s, CH_3), 0.77 (1H, m, $H_{2'b}$), 0.68 (3H, s, CH_3), 0.64 (1H, dd, J = 4.3 and 13.6 Hz, $H_{5'a}$), 0.36 (3H, s, $CH_3\gamma_{NH}$), 0.07 (1H, m, $H_{5'b}$).

RMN $^{13}C\{^{1}H\}$ (δ, $CDCl_3$, 75 MHz): 168.4 (C=O), 134.5 (C), 131.2 (CH), 131.1 (C), 129.2 (CH), 128.8 (C), 127.2 (CH), 126.3 (CH), 126.2 (CH, q, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 125.1 (CH), 124.4 (CH), 124.2 (CF_3, q, $^{1}J_{C–F}$ = 288.1 Hz), 79.5 (C, q, $^{2}J_{C–F}$ = 27.8 Hz), 55.6 (CH), 49.6 (C), 48.1 (C), 44.6 (CH), 37.3 (CH_2), 27.9 (CH_2), 26.8 (CH_2), 19.5 (CH_3), 18.5 (CH_3), 13.2 (CH_3).

HRMS (ESI) calculated for $C_{23}H_{26}F_3NO_2$ $[M+Na]^+$, 428.1798; found 428.1813.

$[\alpha]_D^{23}$ -20.3 (c 0.74 in $CHCl_3$).

M.p.: 145 – 146°C.

Rf = 0.56 (CH_2Cl_2).

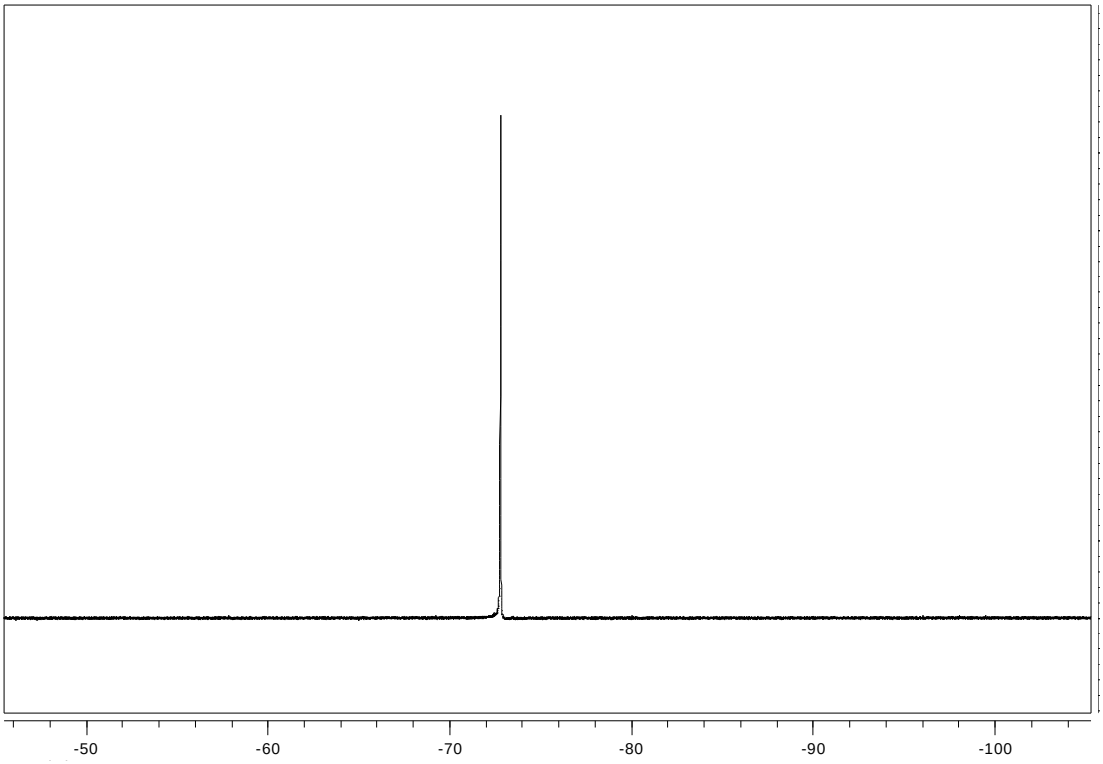


Figure S28. ^{19}F NMR spectrum of **8**

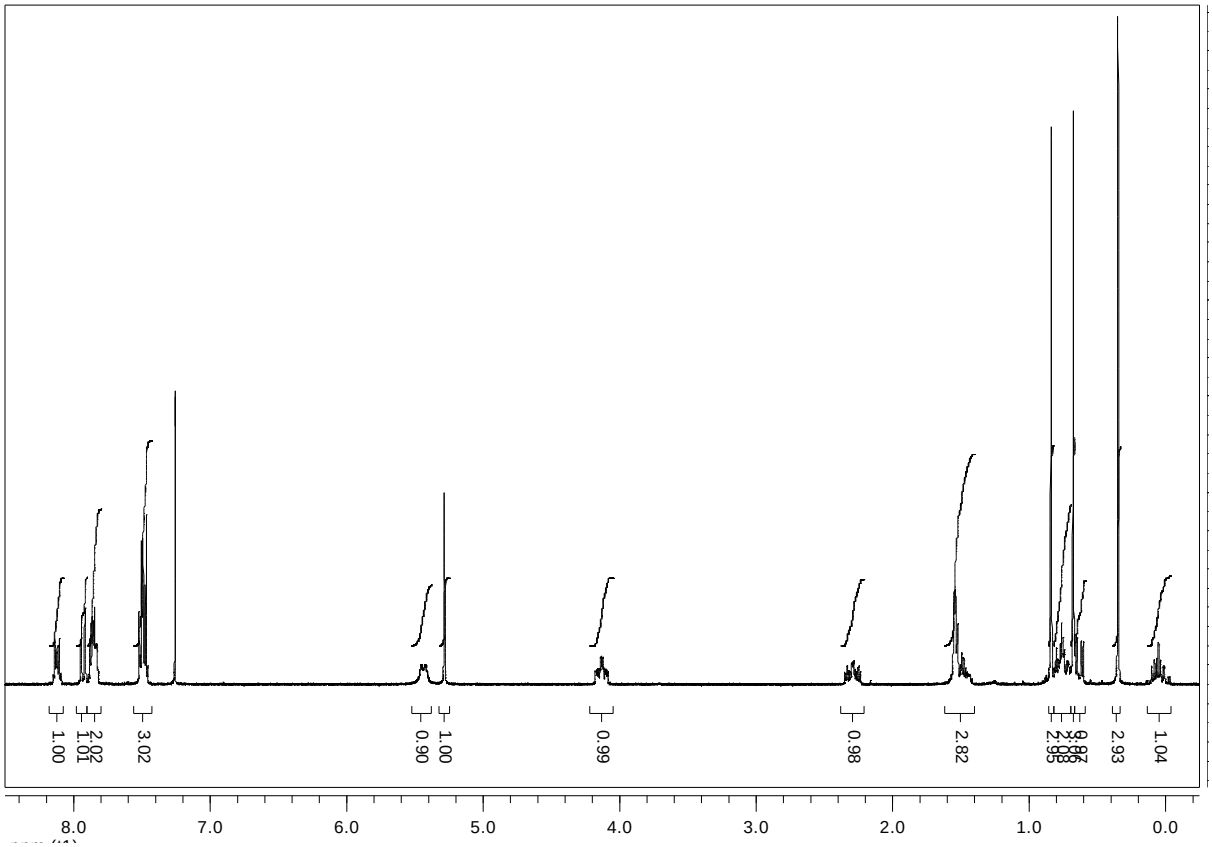


Figure S29. ^{1}H NMR spectrum of **8**

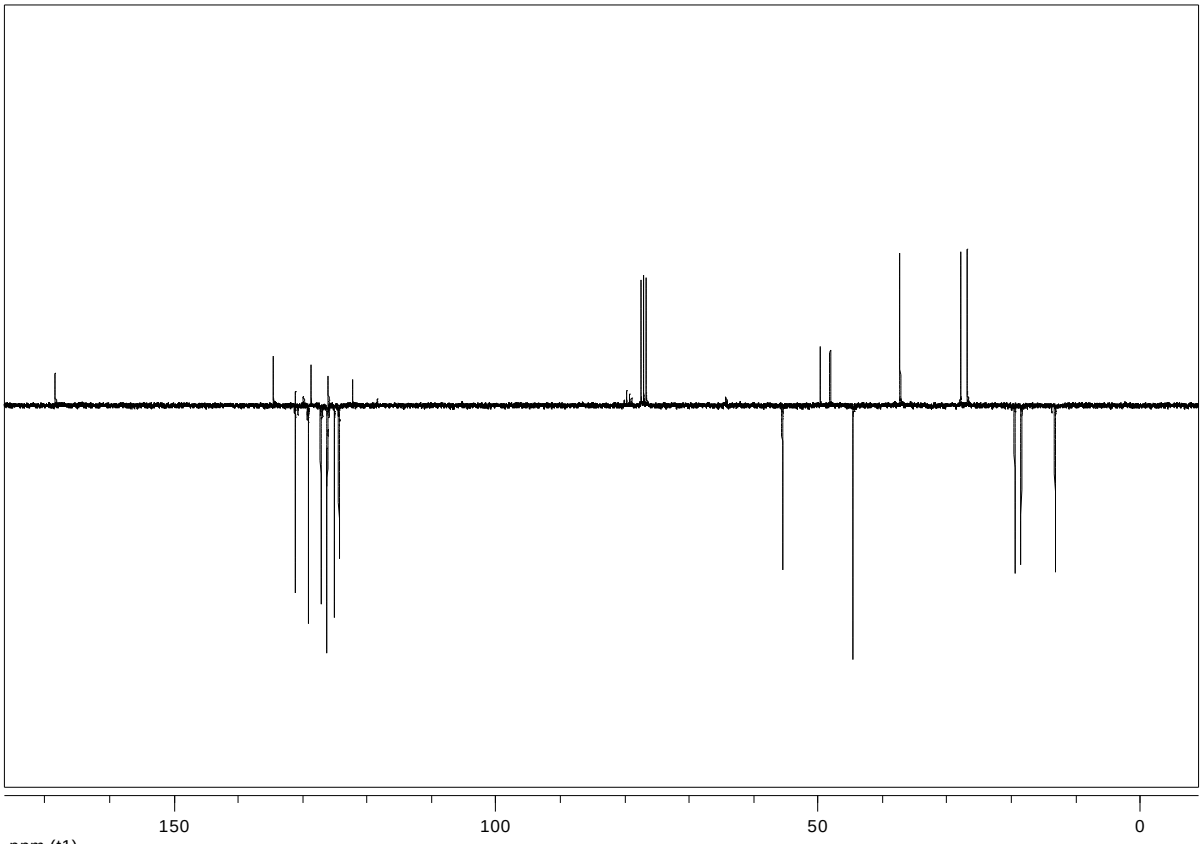
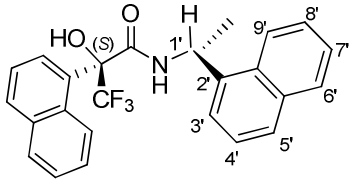


Figure S30. ^{13}C NMR spectrum of **8**

(*S*)-3,3,3-trifluoro-2-hydroxy-2-(1-naphthyl) N-((*R*)-1'-naphtyl-ethyl)-propionamide (9)



RMN ^{19}F (δ, $CDCl_3$, 282.4 MHz): -72.5 (s).

RMN ^{1}H (δ, $CDCl_3$, 300.2 MHz): 8.04 (1H, m, H_8), 7.96 – 7.87 (4H, m, H_4, H_5, H and H), 7.68 (1H, d, J = 8.2 Hz, $H_{5'}$), 7.63 (1H, m, H_2), 7.43 (4H, m, H_6, H_7, H, and H), 7.29 (2H, m, H_3 and $H_{4'}$), 7.15 (1H, m, $H_{3'}$), 5.79 (1H, m, CH), 5.70 (1H, br d, J = 8.1 Hz, NH), 5.21 (1H, s, OH), 1.22 (1H, d, J = 6.6 Hz, CH_3).

RMN $^{13}C\{^{1}H\}$ (δ, $CDCl_3$, 75 MHz): 167.6 (C=O), 135.6 (C), 133.8 (C), 131.2 (CH), 131.0 (C), 130.8 (C), 129.2 (CH), 128.9 (CH), 128.8 (CH), 128.3 (C), 127.1 (CH), 126.7 (CH), 126.6 (CH, q, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 126.3 (CH), 126.1 (CH), 125.6 (C), 124.9 (CH), 124.6 (CH), 124.4 (CH), 123.9 (CF_3, q, $^{1}J_{C–F}$ = 288.3 Hz), 123.0 (CH), 122.7 (CH), 79.5 (C, q, $^{2}J_{C–F}$ = 28.0 Hz), 46.8 (CH), 19.2 (CH_3).

HRMS (ESI) calculated for $C_{25}H_{20}F_3NO_2$ $[M+Na]^+$, 446.1361; found 446.1344.

$[\alpha]_D^{23}$ -123.8 (c 0.53 in $CHCl_3$).

M.p.: 150 – 151°C.

Rf = 0.55 (CH_2Cl_2).

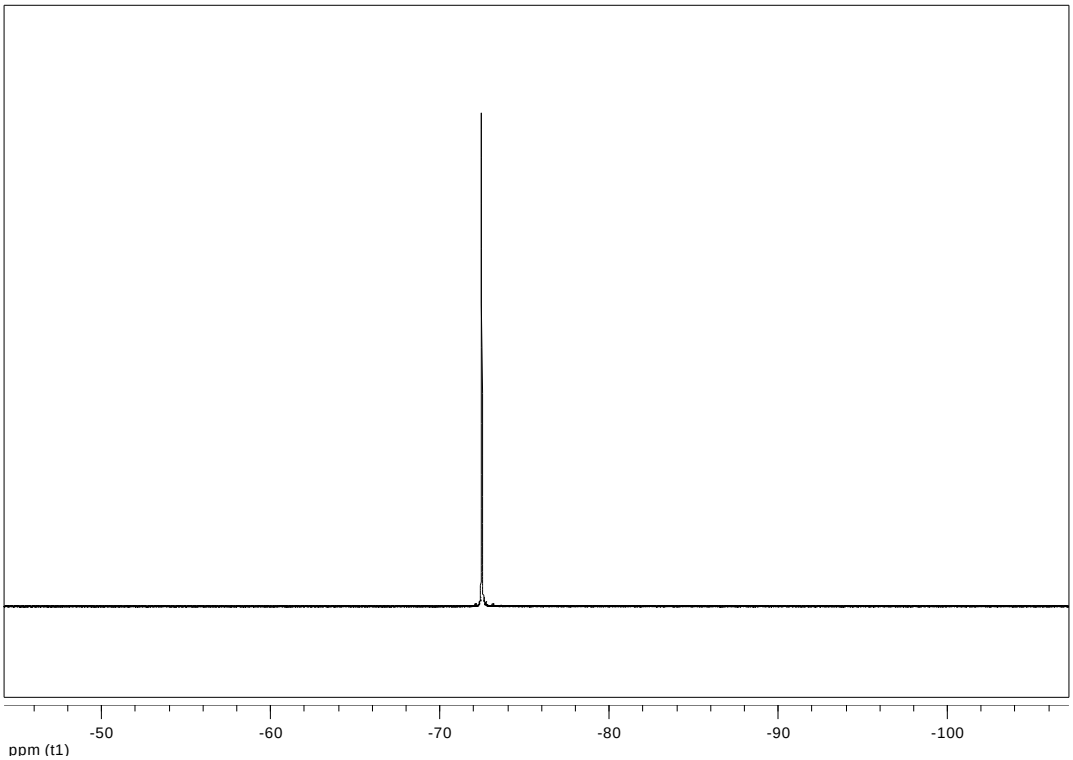


Figure S31. ^{19}F NMR spectrum of **9**

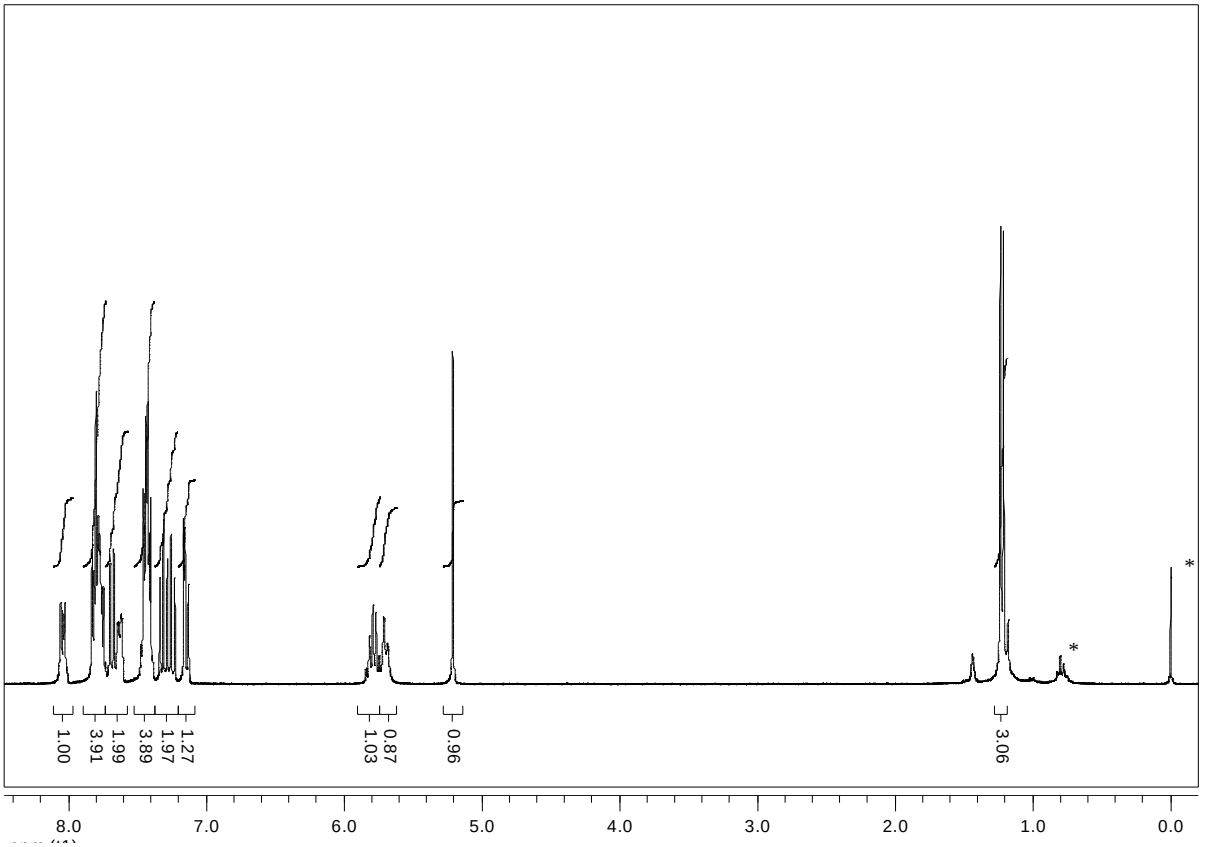


Figure S32. ^{1}H NMR spectrum of **9**

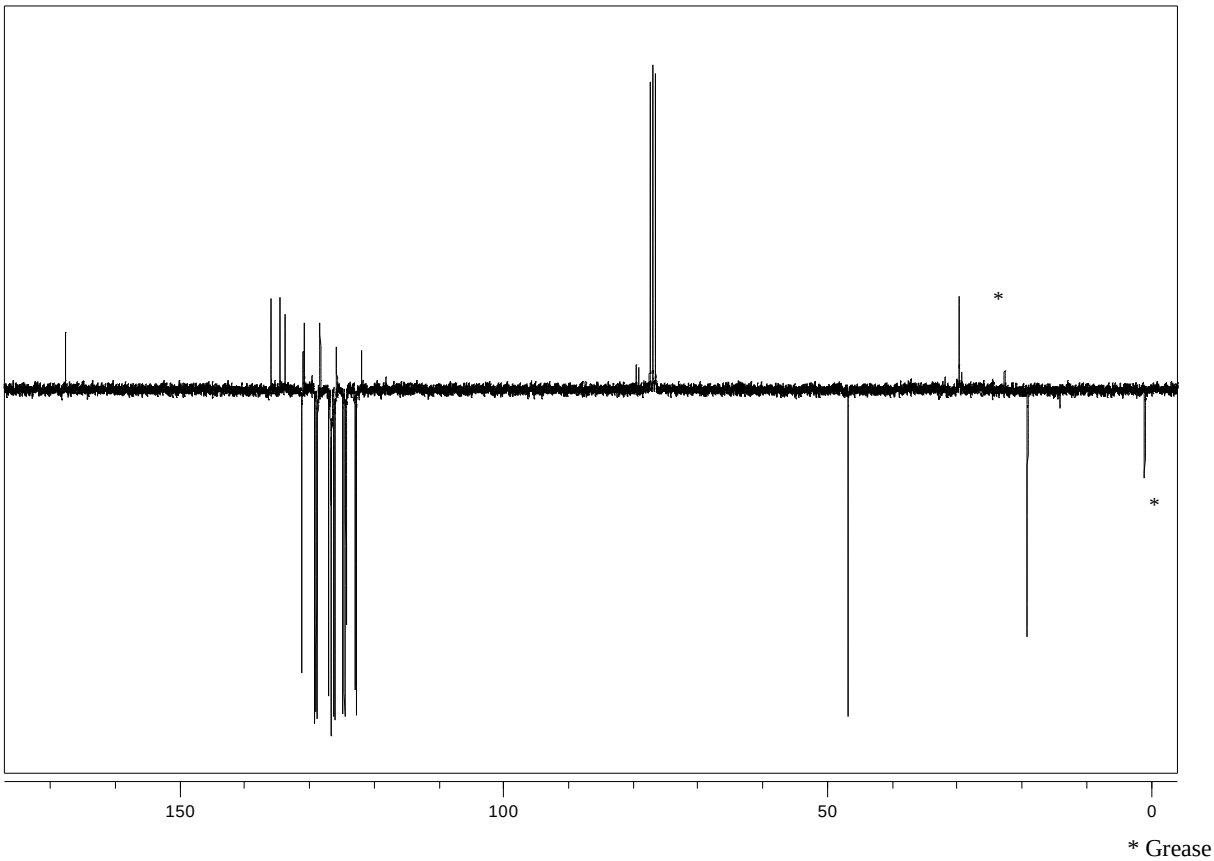
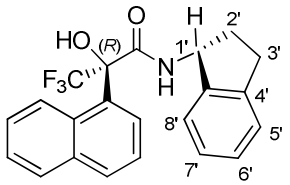


Figure S33. ^{13}C NMR spectrum of **9**

(*R*)-3,3,3-trifluoro-2-hydroxy-2-(1-naphthyl) N-((*R*)-2',3'-dihydro-1H-inden-1-yl)-propionamide (10)



RMN ^{19}F (δ, $CDCl_3$, 282.4 MHz): -72.6 (s).

RMN ^{1}H (δ, $CDCl_3$, 300.2 MHz): 8.22 (1H, m, H_8), 7.90 (2H, m, H_4 and H_5), 7.80 (1H, m, H_2), 7.60 (2H, m, H_3 and H_6), 7.43 (1H, t, J = 7.7 Hz, H_7), 7.08 (2H, m, $H_{6'}$ and $H_{5'}$), 6.77 (1H, m, $H_{7'}$), 5.99 (1H, d, J = 7.6 Hz, $H_{8'}$), 5.69 (1H, br d, J = 8.3 Hz, NH), 5.47 (1H, m, CH), 5.34 (1H, s, OH), 2.82 (2H, m, $H_{3'}$), 2.60 (1H, m, $H_{2'a}$), 1.69 (1H, ddq, J = 0.8 and 8.9 and 13.0 Hz, $H_{2'b}$).

RMN $^{13}C\{^{1}H\}$ (δ, $CDCl_3$, 75 MHz): 168.4 (C=O), 143.1 (C), 141.3 (C), 134.6 (C), 131.3 (CH), 131.2 (C), 129.4 (CH), 128.3 (C), 128.1 (CH), 127.3 (CH), 126.7 (CH), 126.6 (CH, q, $^{4}J_{C\text{-}F}$ = 3.7 Hz), 126.3 (CH), 124.8 (CH), 124.7 (CH), 124.4 (CH), 124.0 (CF_3, q, $^{1}J_{C–F}$ = 288.2 Hz), 123.8 (CH), 79.5 (C, q, $^{2}J_{C–F}$ = 27.9 Hz), 56.1 (CH), 33.5 (CH_2), 30.1 (CH_2).

HRMS (ESI) calculated for $C_{22}H_{18}F_3NO_2$ $[M+Na]^+$, 408.1204; found 408.1187.

$[\alpha]_D^{24}$ +79.8 (c 0.62 in $CHCl_3$).

Rf = 0.51 (CH_2Cl_2).

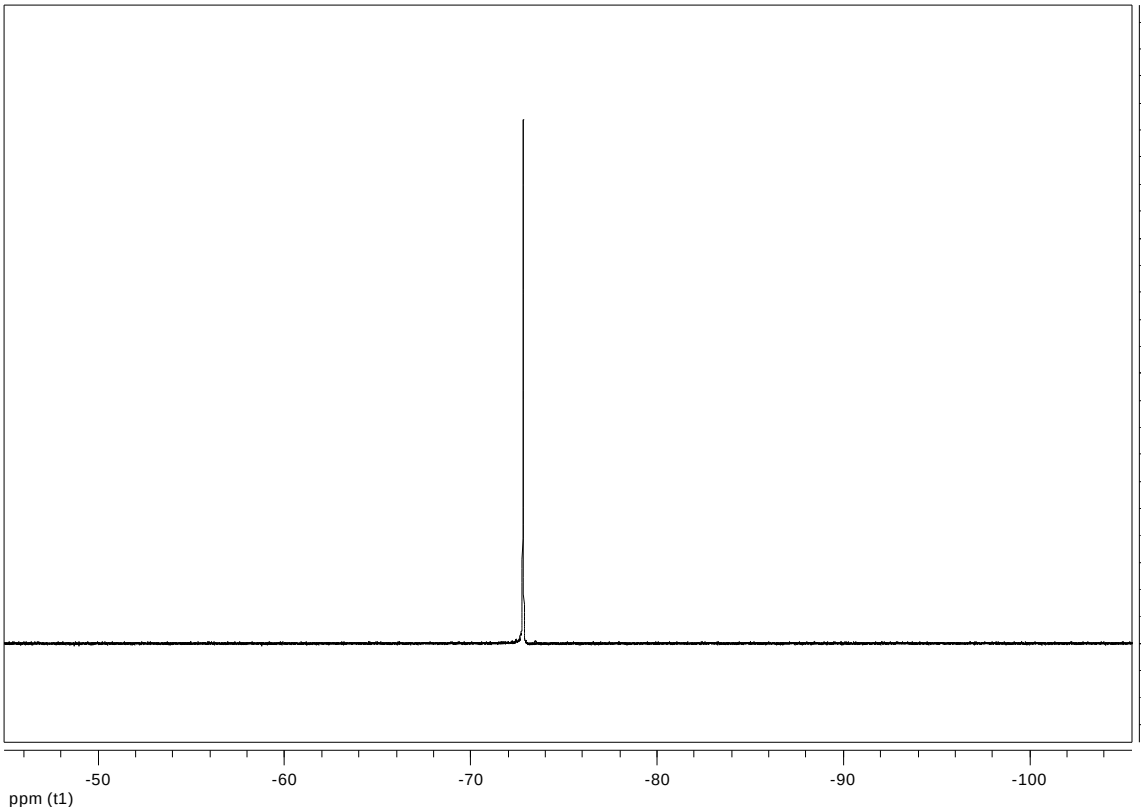
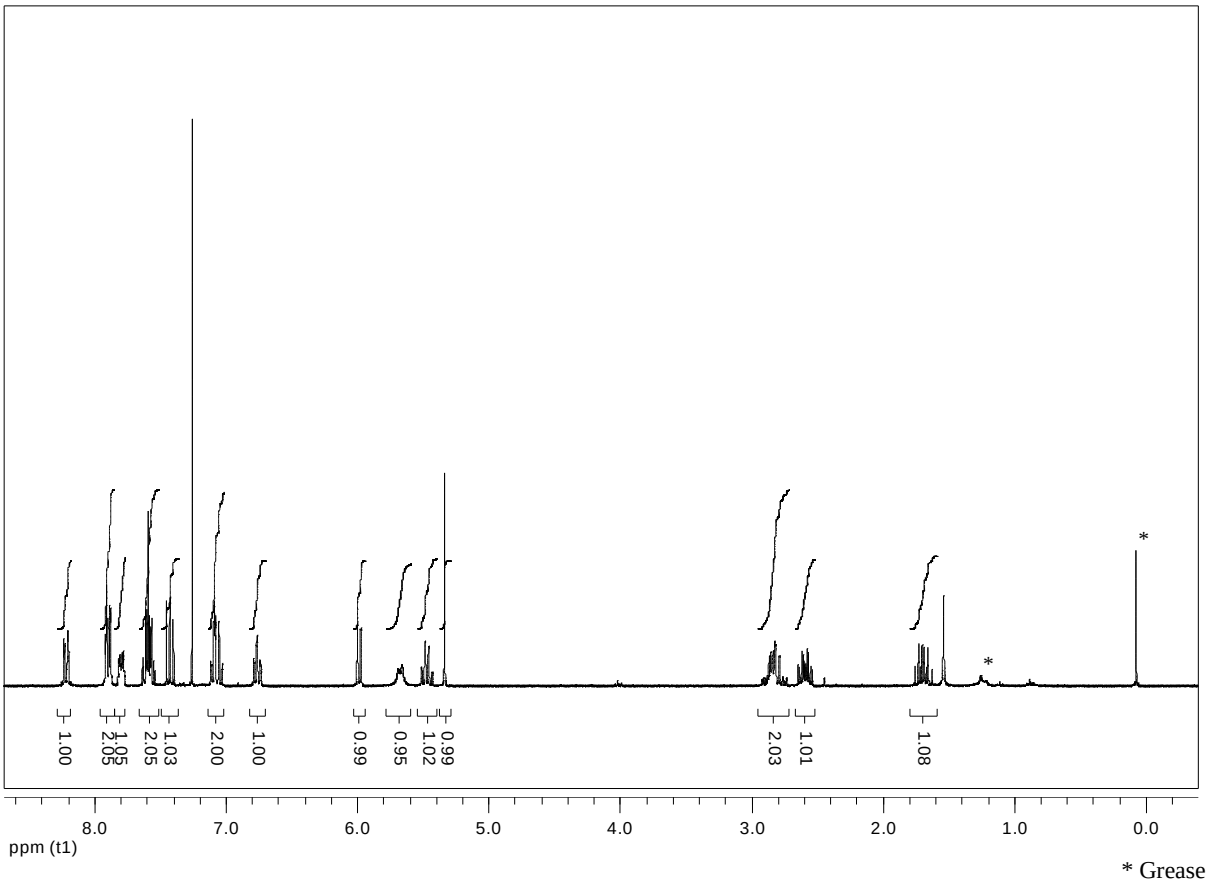


Figure S34. ^{19}F NMR spectrum of **10**



* Grease

Figure S35. ^{1}H NMR spectrum of **10**

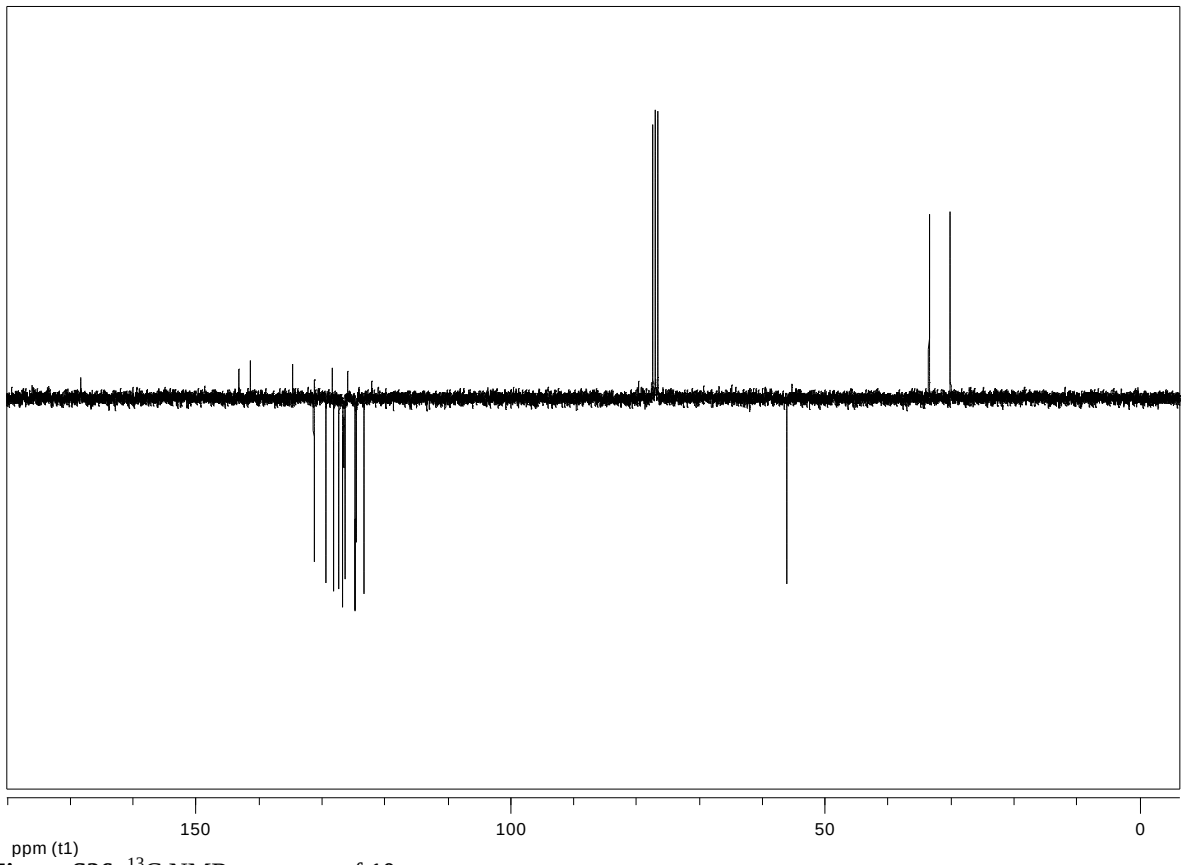
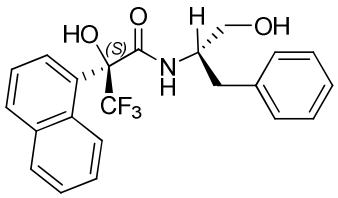


Figure S36. ^{13}C NMR spectrum of **10**

(*S*)-3,3,3-trifluoro-2-hydroxy-2-(1-naphthyl)-N-((*S*)-1'-benzyl-2'-hydroxy-éthyl)-propionamide (11)



RMN ^{19}F (δ, $CDCl_3$, 282.4 MHz): -72.9 (s)

RMN ^{1}H (δ, $CDCl_3$, 300.2 MHz): 8.05 (1H, m, H_8), 7.92 (1H, d, J = 8.3 Hz, H_4), 7.88 (1H, m, H_5), 7.79 (1H, m, H_2), 7.52-7.46 (3H, m, H_3, H_6 and H_7), 7.22 (3H, m, H_{meta} and H_{para}), 7.02 (2H, m, H_{ortho}), 5.74 (1H, br d, J = 8.1 Hz, NH), 5.18 (1H, br s, OH), 4.16 (1H, m, CH), 3.30 (2H, m, CH_2), 2.70 (2H, m, CH_2)

RMN $^{13}C\{^{1}H\}$ (δ, $CDCl_3$, 125.8 MHz): 168.7 (C=O), 136.5 (C), 134.5 (C), 131.2 (CH), 131.0 (C), 129.5 (CH), 128.9 (CH), 128.6 (CH), 128.4 (C), 127.0 (CH), 126.8 (CH), 126.7 (CH, q, $^{4}J_{C\text{-}F}$ = 3.5 Hz), 126.2 (CH), 124.6 (CH), 124.2 (CH), 123.8 (CF_3, q, $^{1}J_{C-F}$ = 288.2 Hz), 79.4 (C, q, $^{2}J_{C-F}$ = 28.0 Hz), 62.4 (CH_2), 53.9 (CH), 36.4 (CH_2)

HRMS (DCI) calculated for $C_{22}H_{20}F_3NO_3$ $[M+H]^+$, 404.1474; found 404.1451

$[\alpha]_D^{23}$ - 15.7 (c 0.35 in $CHCl_3$)

Rf = 0.33 (CH_2Cl_2/MeOH 98/2).

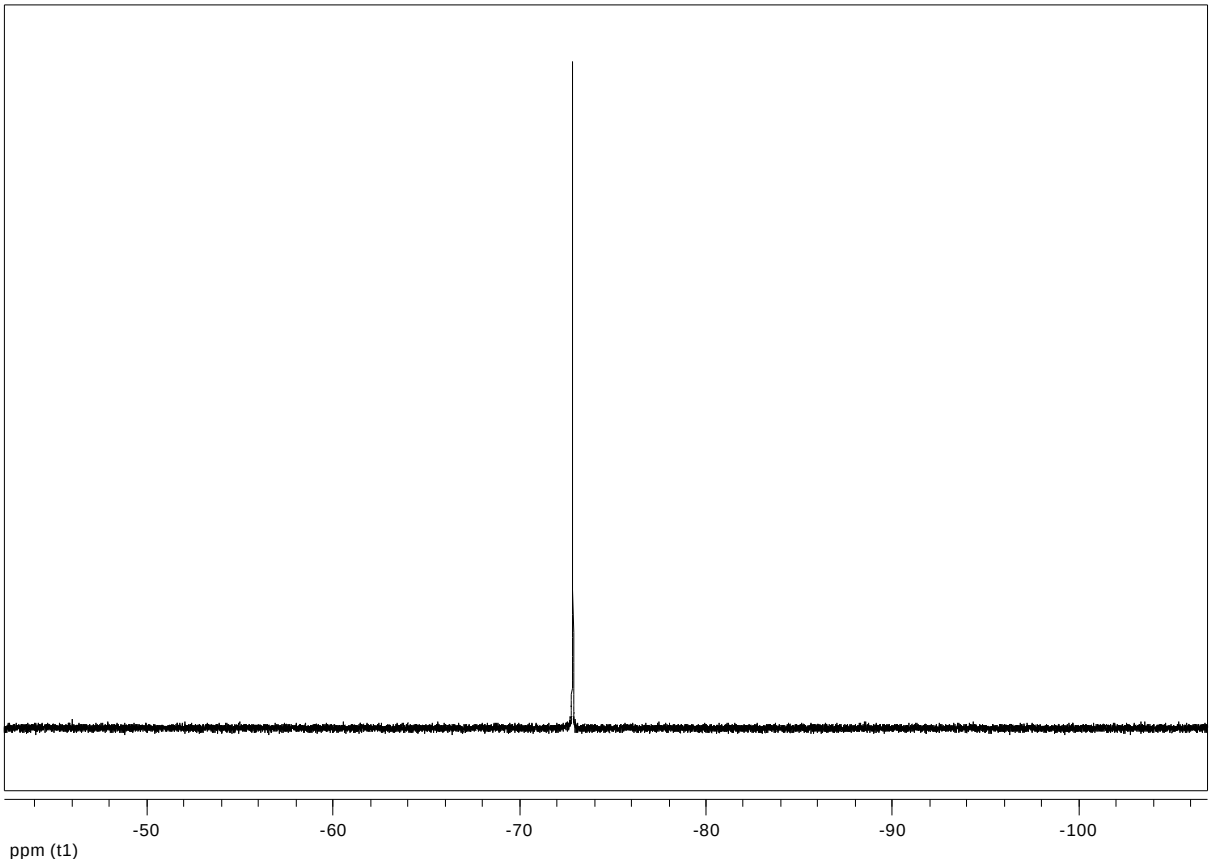


Figure S37. ^{19}F NMR spectrum of **11**

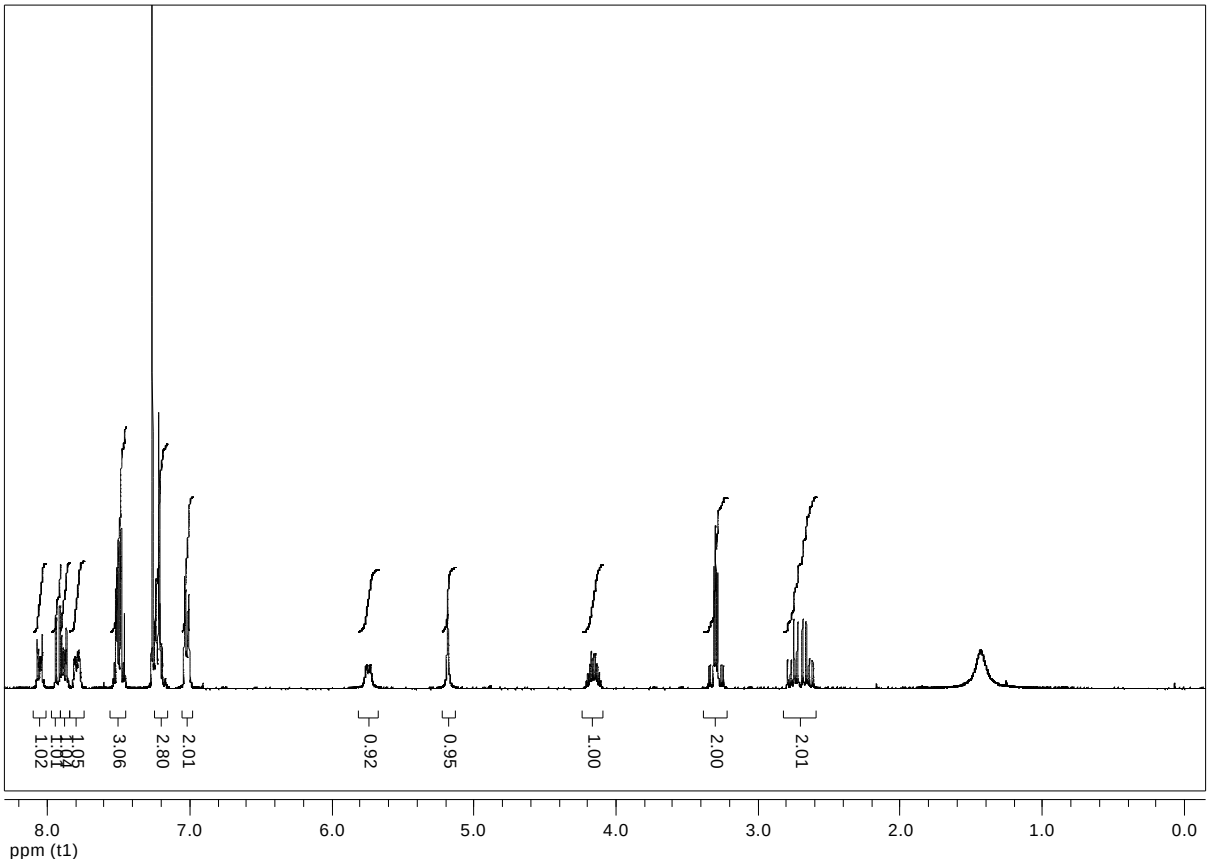


Figure S38. ^{1}H NMR spectrum of **11**

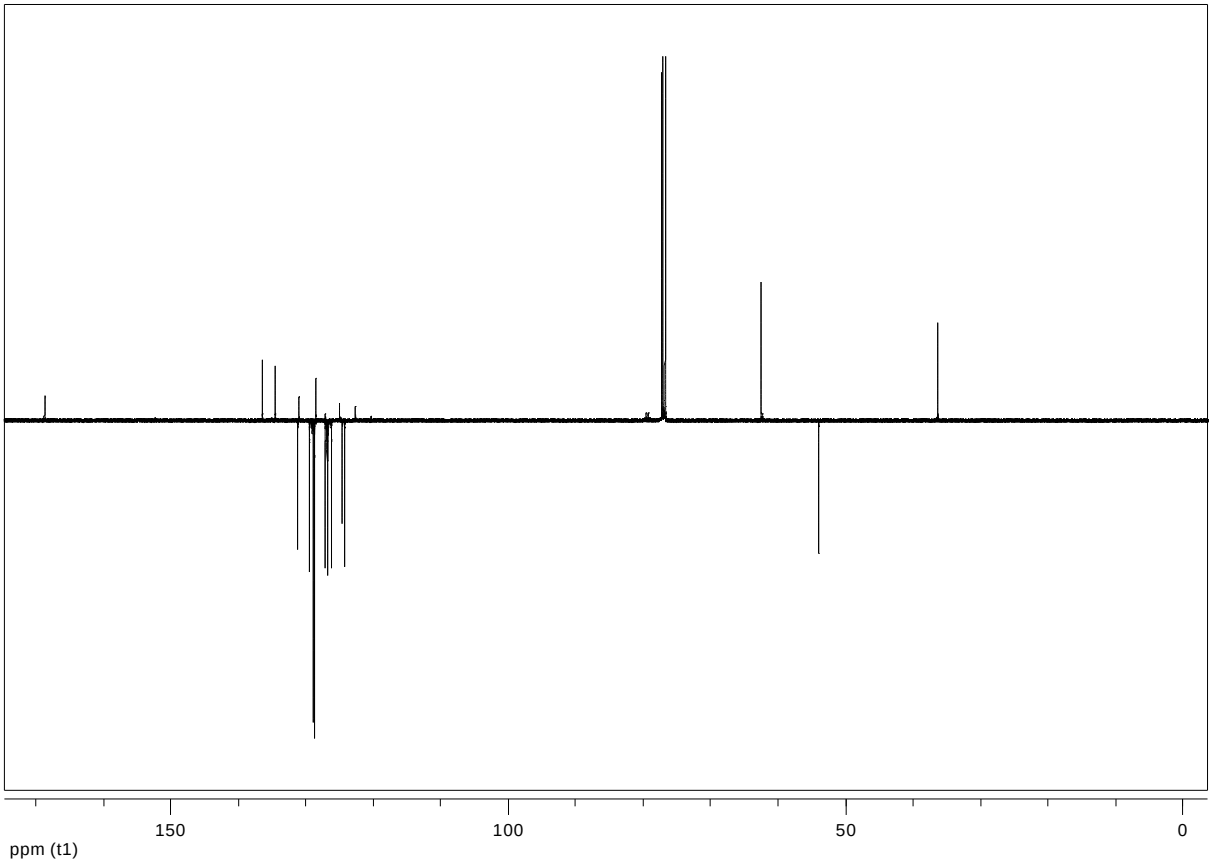
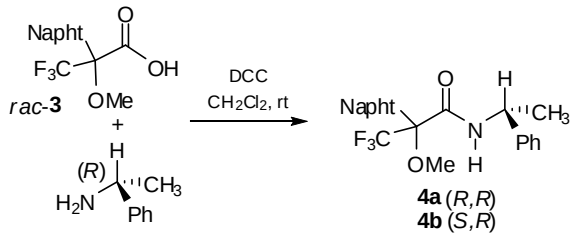


Figure S39. ^{13}C NMR spectrum of **11**

The α–methoxy acid **3** was prepared in two steps (70% overall yield) from ethyltrifluoromethylpyruvate. Condensation with (*R*)–α–methylbenzyl amine was then achieved in dichloromethane at room temperature using DCC (Scheme S1). The resulting equimolar mixture of α–methoxyamides **4a** and **4b** was separated by silica–gel chromatography. In contrast to those observed for **2a**/**2b**, the ^{1}H NMR chemical shifts for the methyl group of **4a**/**4b** are almost identical ($\Delta\delta$ = 0.01 ppm). Once again, a conformational analysis of diastereomers **4a** and **4b** was undertaken in order to rationalize precisely the striking difference between CDAs **1** and **3**.

Scheme S1. Reaction of *rac*-**3** with (*R*)–α–methylbenzylamine



First, an X–ray diffraction analysis identified **4a** as the (*R*,*R*) diastereomer and revealed its conformation in the solid state (Figure S37). The most significant difference compared with **2b** is the antiperiplanar conformation (*ap*) of the O–C–C=O skeleton combined with an intramolecular hydrogen bond between the OMe and NH groups. This results in a staggered arrangement of the CF_3/Ph and Naphthyl/CH_3 groups, respectively.

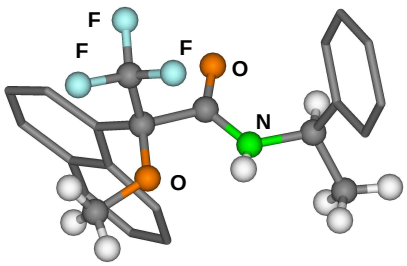


Figure S37. Molecular structure of **4a**.

According to ^{1}H NMR, the same (*ap*) conformation is favored in solution for both diastereomers **4a** and **4b**. Indeed, the chemical shifts for the amide proton of **4a**/**4b** (~ 7.4

ppm) are much higher than those of **2a**/**2b** (5.69 / 5.97 ppm respectively) and diagnostic for the presence of an intramolecular hydrogen bond in such *O*–alkylated amides.[2] As a result, both diastereomers **4a** and **4b** preferentially adopt a staggered conformation in solution, which explain the weaker anisotropic effect of the naphthyl group on the amide substituents (Figure S38).

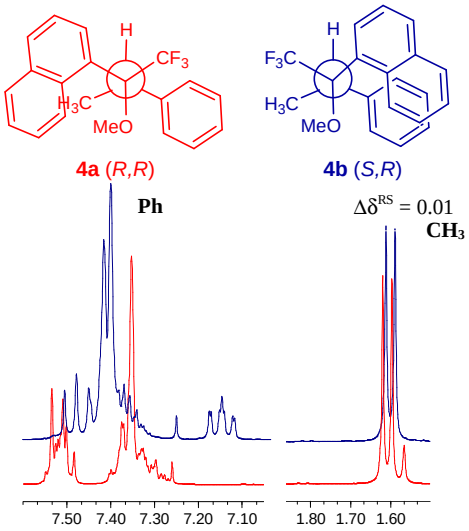


Figure S38. Extended Newman projections of **4a**/**4b** and ^{1}H NMR spectra (aromatic and methyl regions) of **4a**/**4b** illustrating the staggered conformation and the resulting weak anisotropic effect of the naphthyl ring.

[2] A similar situation has already been reported for related amides, in which the NH protons involved in intramolecular hydrogen bonding resonate at $\delta > 6.5$ ppm whereas those not involved resonate at $\delta < 6.5$. See references: a) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202. b) Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1999**, *64*, 4669. c) Chinchilla, R.; Falvello, L.R.; Nájera, C. *J. Org. Chem.* **1996**, *61*, 7285. d) Helmchen, G.; Ott, R.; Sauber, K. *Tetrahedron Lett.* **1972**, *37*, 3873. e) Ahn, H. C.; Choi, K. *Org. Lett.* **2007**, *9*, 3853.

Crystallographic data

Data for all structures were collected at 173(2) K using an oil–coated shock–cooled crystal on a Bruker–AXS CCD 1000 diffractometer (λ = 0.71073 Å). Semi–empirical absorption corrections were employed for **2b**.[3] The structures were solved by direct methods (SHELXS–97),[4] and refined using the least–squares method on F^2.[5]

[3] SADABS, Program for data correction, Bruker-AXS.
[4] G. M. Sheldrick, *Acta Crystallogr.* **1990**, *A46*, 467–473.
[5] SHELXL-97, Program for Crystal Structure Refinement, G. M. Sheldrick, University of Göttingen, **1997**.