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**Self-Association Based on Orthogonal C=O...C=O Interactions in the
Solid and Liquid State^{†‡}**

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1. X-Ray crystal structure data of (±)-1

Crystal data at 223 K for $C_{29}H_{31}F_2NO_2$: M_r 463.57, monoclinic, space group $P2_1/c$, $D_x = 1.254 \text{ Mg m}^{-3}$, $Z = 4$, $a = 6.1172(2) \text{ \AA}$, $b = 26.1410(10) \text{ \AA}$, $c = 15.5575(6) \text{ \AA}$, $\alpha = 90.00^\circ$, $\beta = 99.276(2)^\circ$, $\gamma = 90.00^\circ$, $V = 2455.3(2) \text{ \AA}^3$. Bruker–Nonius KappaCCD diffractometer, $MoK\alpha$ radiation, $\lambda = 0.71073$, $\mu = 0.088 \text{ mm}^{-1}$. Crystal dimensions $ca.$ 0.36 x 0.2 x 0.08 mm. The numbers of measured and independent reflections were 6501 and 3364, respectively. The structure was solved by direct methods (SIR-97).¹ All non H-atoms with were refined anisotropically (disordered C-atoms of the pentyl chain isotropically at two positions with fixed 50% population) by full-matrix least-squares analysis. Some bond lengths of the disordered pentyl group were restrained. H-positions are based on stereochemical considerations and were included in the structure factor calculation (SHELXL-97).² Final $R(gt) = 0.1065$, $wR(gt) = 0.2838$ for 302 parameters and 3364 reflections with $I > 2s(I)$ and $q_{\max} = 22.98^\circ$.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre: CCDC reference number 736727. For crystallographic data in CIF or other electronic format see [xxx](#).

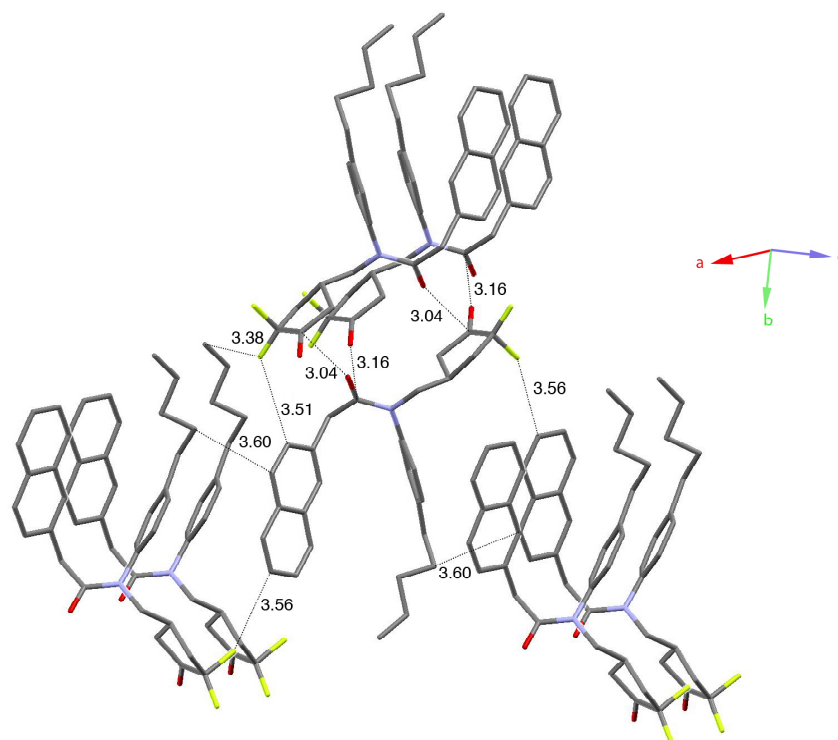


Fig. 1ESI Crystal packing of ($\pm$)-1.

2. Equations

Equation 1: The law of mass for a homodimeric species, solved using the initial concentration $[M]_0$. $[M]$: concentration of monomer; $[D]$: concentration of dimer.

$$K_d = \frac{[M]^2}{[D]} = \frac{([M]_0 - 2[D])^2}{[D]} \quad (1)$$

Equation 2: The observed chemical shift δ_{obs} as weighted average of the chemical shift of the monomeric δ_M and the dimeric δ_D species.

$$\delta_{obs} = \frac{[M]}{2[D] + [M]} \delta_M + \frac{2[D]}{2[D] + [M]} \delta_D \quad (2)$$

Equation 3: Combining equation (1) and (2) yields δ_{obs} as a function of $[M]_0$. This equation was used to determine the K_d by fitting the experimental data.

$$\delta_{obs} = \delta_M + (\delta_D - \delta_M) \frac{4[M]_0 + K_d - \sqrt{8[M]_0 K_d + K_d^2}}{4[M]_0} \quad (3)$$

3. Attempted NMR diffusion measurements

If aggregation is fast on the NMR time scale, an average translational diffusion coefficient D_t for a supramolecular system can be measured by NMR pulsed field gradient spin-echo (PFGSE) experiments. D_t measured at different monomer concentrations can be fitted in a way analogous to the chemical shift in order to determine the diffusion coefficient of the aggregate and hence its size (cf. eqs. 1–3 in the ESI). As for the chemical shift "titration", *i.e.* the dilution study, this procedure requires the stoichiometry of aggregation to be known a priori and can only corroborate an underlying assumption (*i.e.* the composition of the multimer). Furthermore, it relies on the accurate determination of the diffusion coefficient of the solute over a wide range of monomer concentrations under otherwise identical properties of the solution (*e.g.* its viscosity). The diffusion coefficient of the solvent in solutions of ($\pm$)-**1** in C_6D_6 , however, varied from $2.2 \times 10^{-9} \text{ m}^2/\text{s}$ for very dilute samples down to $1.8 \times 10^{-9} \text{ m}^2/\text{s}$ at the highest concentration reached. Based on this finding, we refrained from further characterising these weakly interacting multimers by diffusion NMR spectroscopy.

4. ^1H , ^1H COSY NMR spectrum and additional figures on self-association of ($\pm$)-1

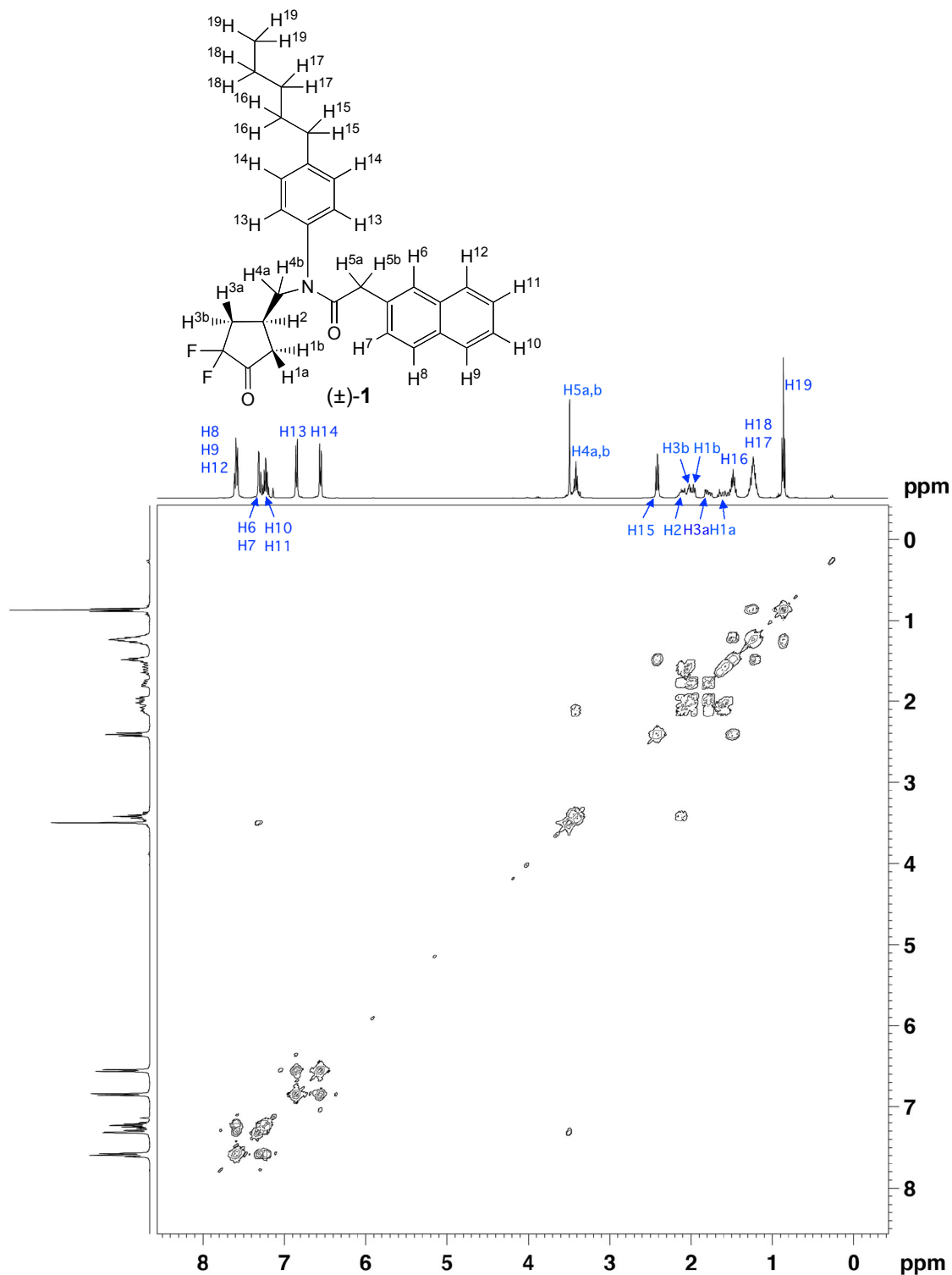


Fig. 2ESI ^1H , ^1H COSY NMR (400 MHz, 300 K) spectrum of ($\pm$)-1 in C_6D_6 . The spectrum was referenced to the solvent signal.

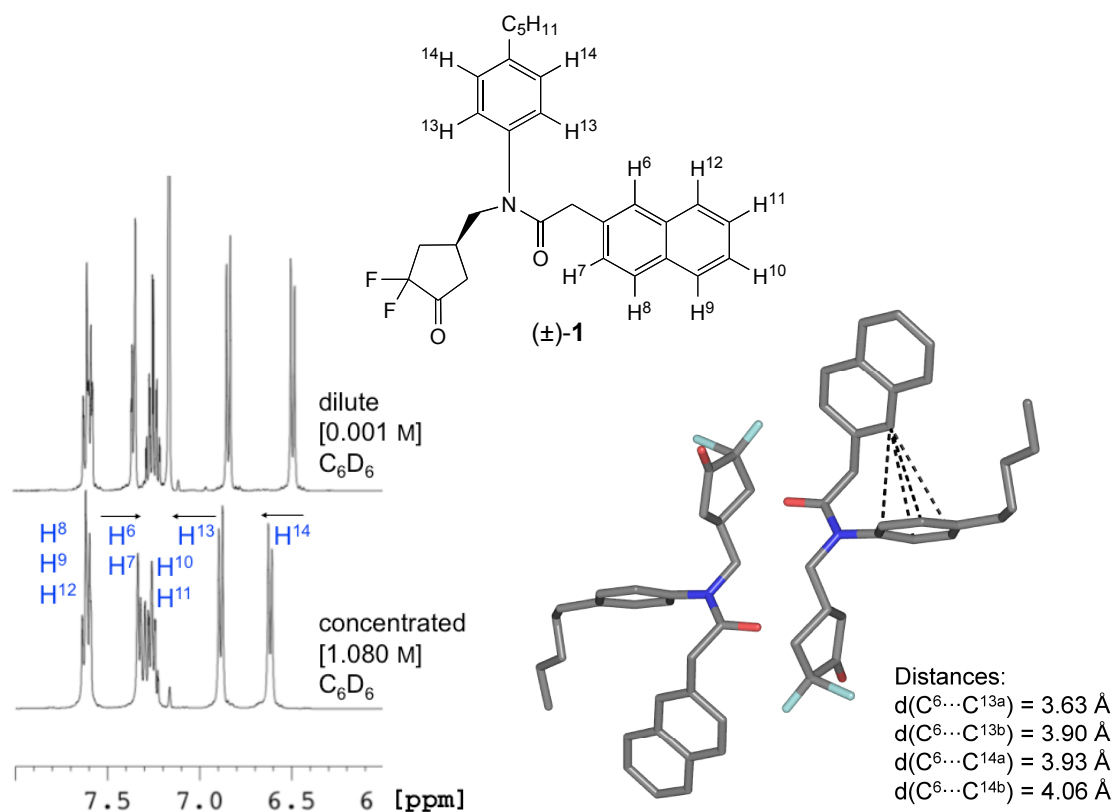


Fig. 3ESI Left: Resonances in the aromatic region for two different concentrations of (±)-**1** in C₆D₆ (400 MHz, 300 K). The spectra were referenced to the solvent signal. Right: The type A dimer based on (R₂N)C=O...C(CF₂)=O interactions, as extracted from the X-ray crystal structure, analysed for possible aromatic contacts. Distances in Å.

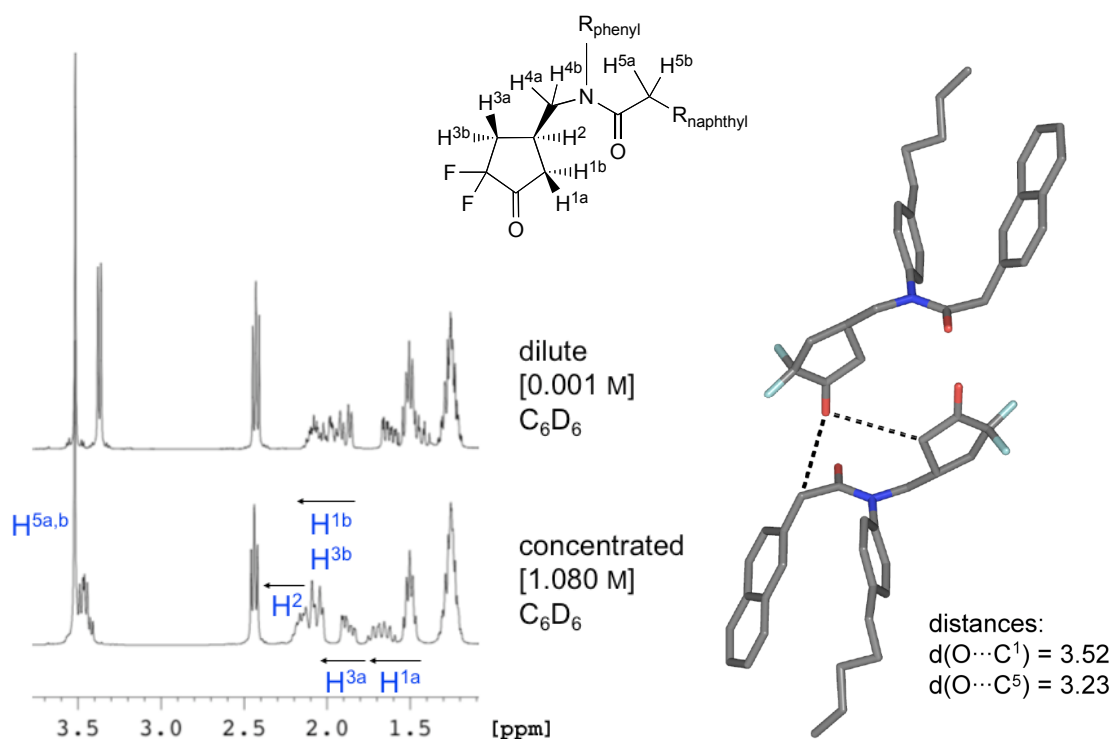


Fig. 4ESI Left: The chemical shifts in the aliphatic region for two different concentrations of (±)-**1** in C₆D₆ (400 MHz, 300 K). The spectra were referenced to the solvent signal. Right: The less probable type B dimer, based on less favourable C(CF₂)=O... (R₂N)C=O interactions, as extracted from the X-ray crystal structure. The influence of the amide carbonyl oxygen on nearby aliphatic protons in the neighbouring molecule is analysed. This self-assembly geometry is not supported by the experimental NMR data. Distances in Å.

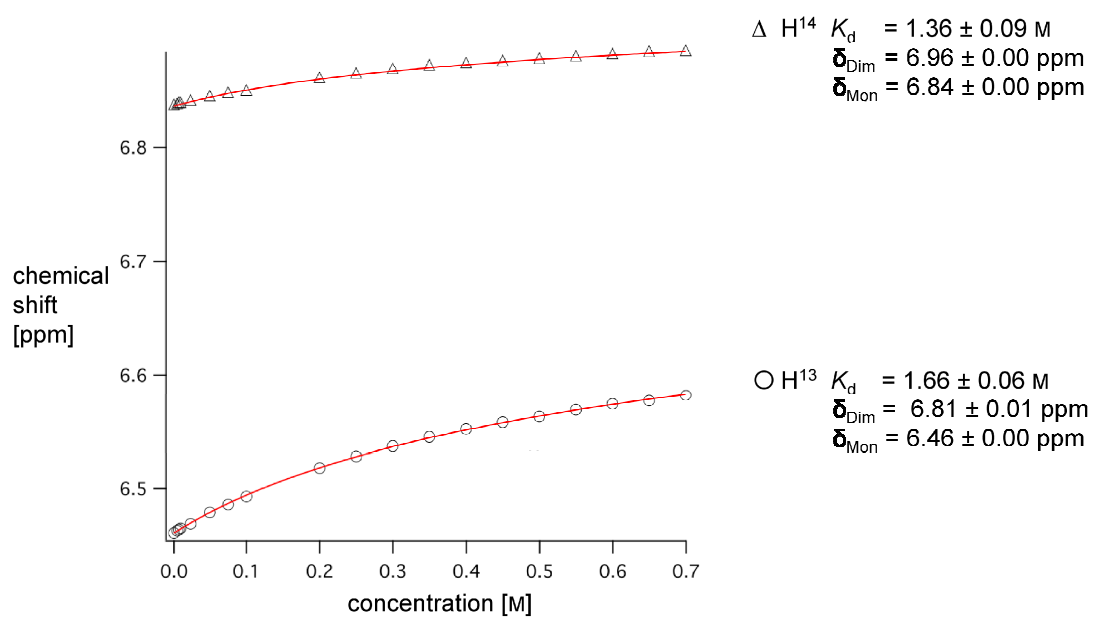


Fig. 5ESI ¹H NMR dilution study in C₆D₆ of (±)-**1** at 300 K (500 MHz) evaluated for the aromatic signals. The spectra were referenced to TMS.

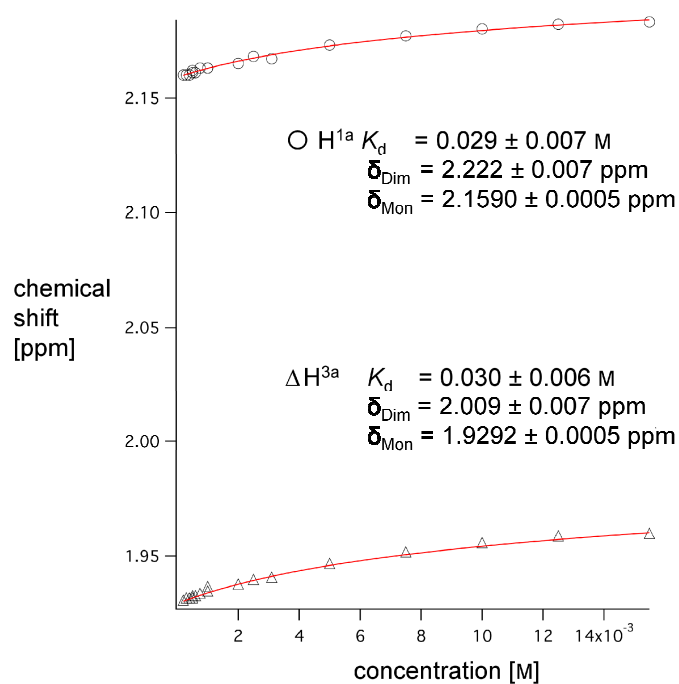


Fig. 6ESI ¹H NMR dilution study in C₆D₁₂ of (±)-**1** at 300 K (500 MHz) evaluated for the aliphatic signals. The spectra were referenced to TMS.

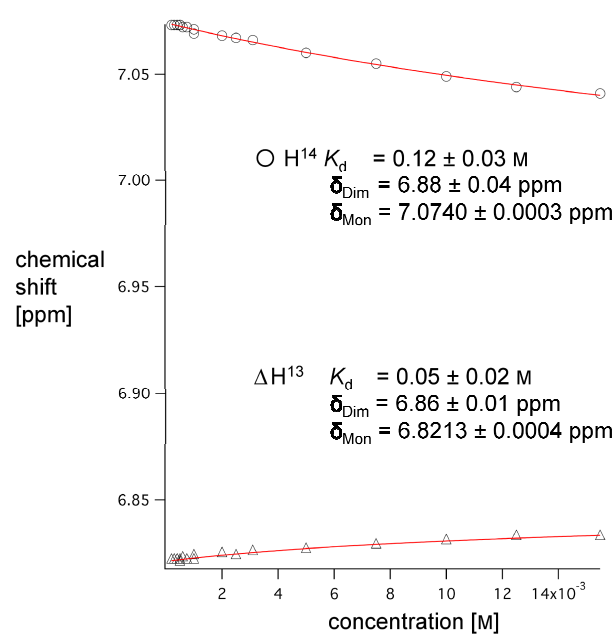


Fig. 7ESI 1H NMR dilution study in C_6D_{12} of $(\pm)$ -**1** at 300 K (500 MHz) evaluated for the aromatic signals. The spectra were referenced to TMS.

5. Self-association of control compounds S1, S2 and (±)-S3

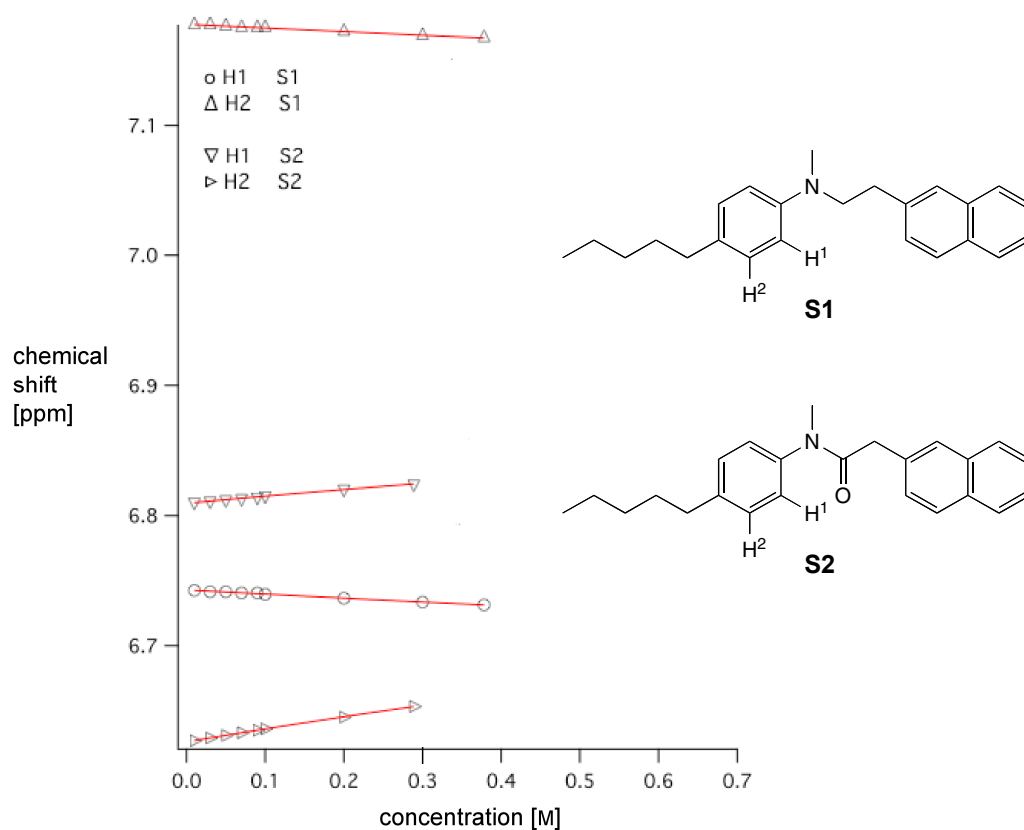


Fig. 8ESI ^1H NMR dilution study in C_6D_6 of test molecules **S1** and **S2** at 300 K (500 MHz). The spectra were referenced to TMS. The difference in the chemical shift (Δ ppm) within the concentration range from 0.1 M to 0.01 M is for **S1**: $\text{H}^1 = 0.003$ ppm, $\text{H}^2 = 0.002$ ppm and for **S2**: $\text{H}^1 = 0.005$ ppm, $\text{H}^2 = 0.009$ ppm.

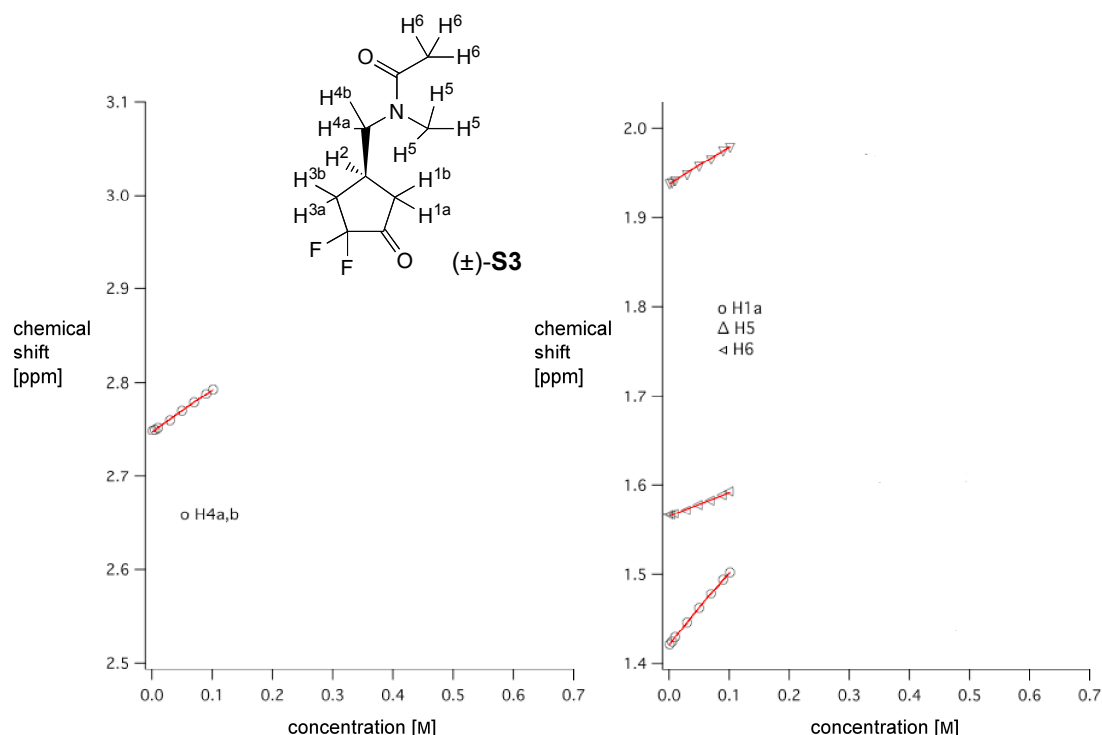


Fig. 9 ESI ^1H NMR dilution study in C_6D_6 of test molecule (±)-**S3** at 300 K (500 MHz). To prevent hydrate formation, one bead of molecular sieves (4 Å) was added for the three lowest concentrations (0.01 M, 0.005 M, 0.001 M). The spectra were referenced to TMS. The difference in the chemical shift (Δ ppm) within the concentration range from 0.1015 M to 0.01 M is for (±)-**S3**: $\text{H}^{4\text{a,b}} = 0.041$ ppm, $\text{H}^5 = 0.038$ ppm, $\text{H}^6 = 0.025$ ppm, $\text{H}^{1\text{a}} = 0.073$ ppm. Due to the low solubility in C_6D_6 , control compound (±)-**S3** was only measured for a limited concentration range. The curves are linear for the measured concentration range, but asymptotic behaviour is assumed for higher concentrations. Two conformations of (±)-**S3** are observed in CDCl_3 and C_6D_6 with a ratio of 5:1 for the favourite conformer. Only protons of the more populated conformer of (±)-**S3** have been analysed with respect to their chemical shift. Slight impurities (10 %) are visible in (±)-**S3**, due to the presumed instability of the molecule under standard HPLC purification conditions.

6. Self-association, CSD data and ^1H , ^1H COSY NMR

spectrum of ($\pm$)-**2**

Modeling of the homodimer of ($\pm$)-**2** is based on a MAB force field (Modeling software MOLOC, Fig 11ESI).³ The torsional angle about the N–C_{cyclohexyl} bond in the computer model is in good accordance with the values found in the CSD (Fig. 11ESI).^{4,5} The increase in association strength, as compared to the dimer of ($\pm$)-**1**, presumably is a result of the higher conformational rigidity of the difluorocyclohexanone ring in ($\pm$)-**2**. Compound ($\pm$)-**2** has some disadvantages: its poor solubility prevented association studies in C₆D₁₂, and the greater ease of hydration of the six-membered ring difluoroketone⁶ required addition of molecular sieves (4 Å) to the NMR solution, which introduces uncertainties in the solute concentration due to adsorption.

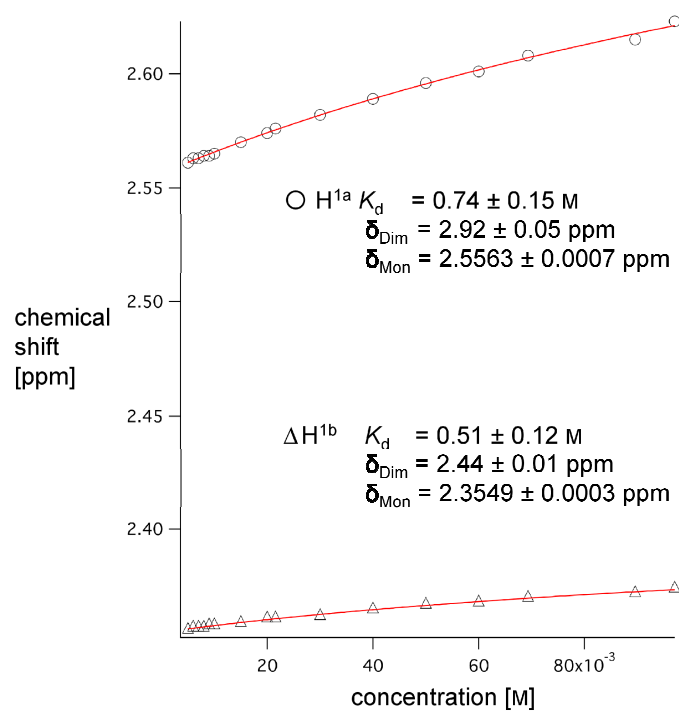


Fig. 10ESI ¹H NMR dilution study in C₆D₆ of (±)-**2** at 300 K (500 MHz, presence of 4Å molecular sieve to prevent hydration) evaluated for the aliphatic signals. The spectra were referenced to TMS. Constitution and relative configuration are confirmed by the ¹H,¹H COSY NMR spectrum of (±)-**2** (Fig. 12ESI).

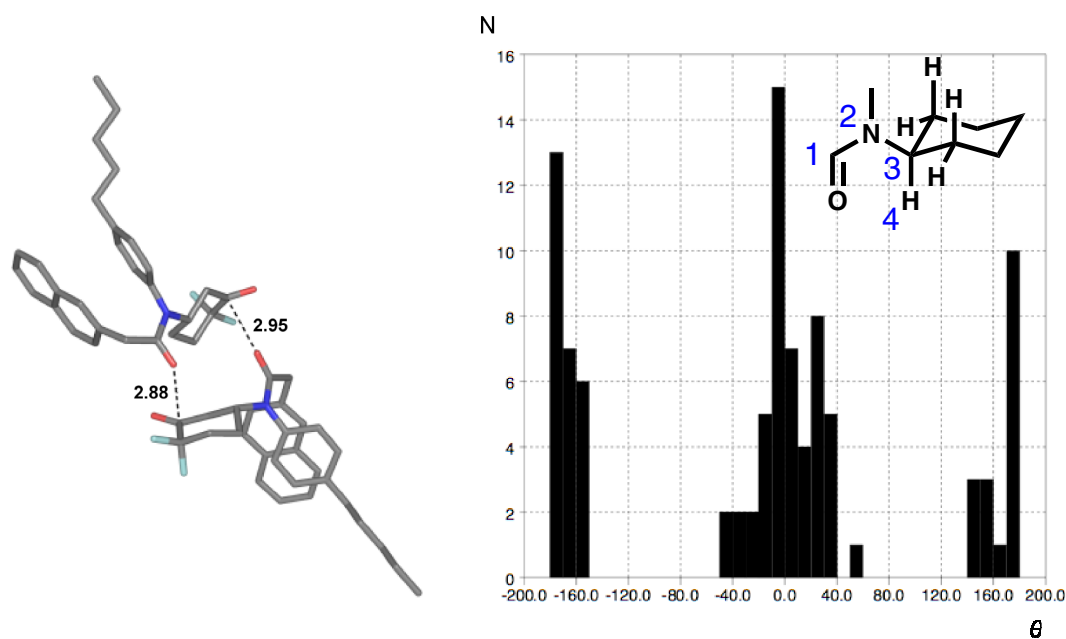


Fig. 11 ESI The cyclohexyl-based α,α -difluoroketone ($\pm$)-**2** (top) and its modeled (MOLOC) homodimer based on orthogonal $\text{C}=\text{O} \cdots \text{C}=\text{O}$ -interactions (left). All distances are given in Å. A search in the CSD⁴ reveals for the given search conditions a number of 94 occurrences. θ = torsional angle $\text{C}_{\text{C}=\text{O}}-\text{N}-\text{C}_{\text{cyclohex}}-\text{H}$ (right). All bonds, which are not included in the cyclohexane ring, were chosen to be acyclic. The search was performed on structures with an R factor ≤ 0.1 (no errors, no partially disordered structures), excluding polymeric, metal organic and powder structures.

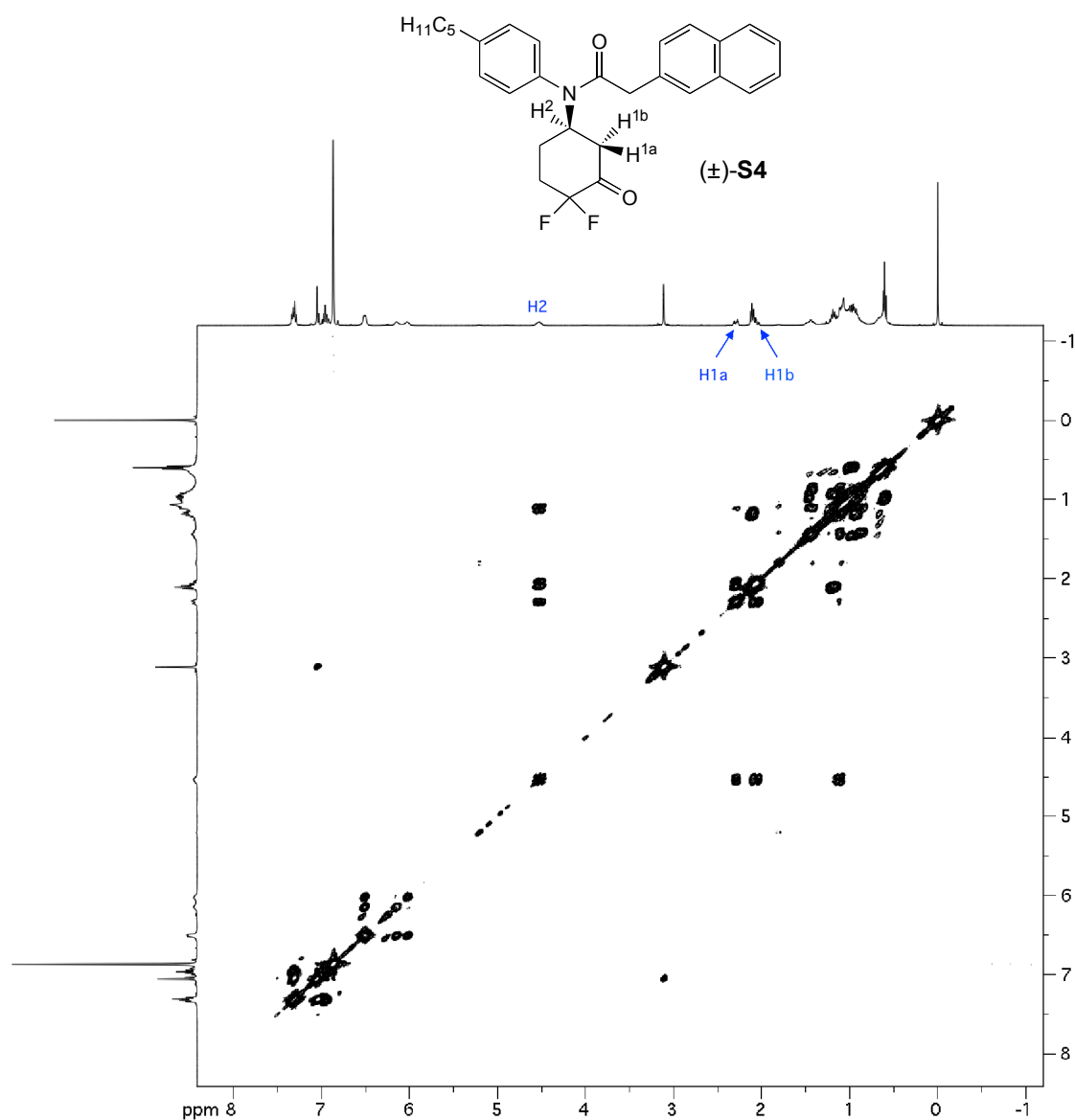


Fig. 12ESI ^1H , ^1H COSY NMR (400 MHz, 300 K) spectrum of $(\pm)$ -2 in C_6D_6 . The spectrum was referenced to TMS.

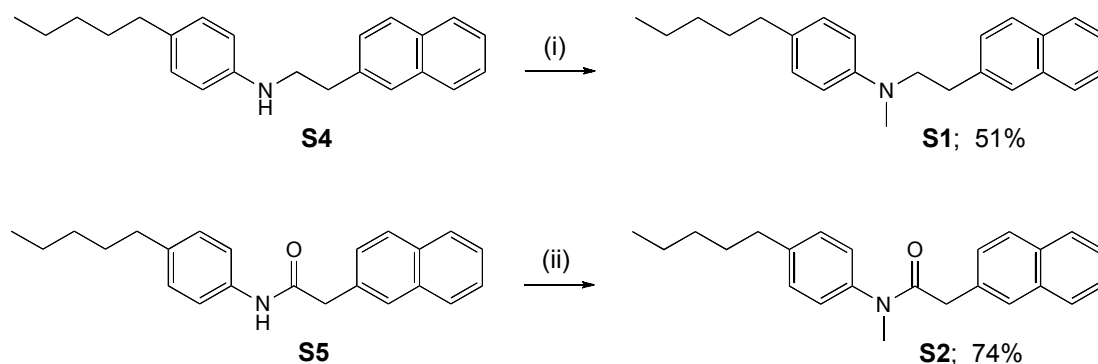
7. Experimental part for S1, S2, and (±)-S3

General details

Solvents and reagents were reagent-grade, purchased from commercial suppliers, and used without further purification unless otherwise stated. THF was freshly distilled from sodium/benzophenone. If not mentioned otherwise, all products were dried under high vacuum (10^{-2} Torr) before analytical characterisation. Column chromatography (CC) was conducted on silica gel (230–400 mesh, 0.040–0.063 mm) from Fluka. Analytical thin layer chromatography (TLC) was conducted on silica gel 60-F₂₅₄ nm (on glass, Merck). Plates were visualised by UV light at 245 nm and staining with a solution of KMnO₄ (1.5 g), K₂CO₃ (10 g), 5% NaOH (2.5 cm³) in H₂O (150 cm³). Melting points (mp) were determined using a Büchi-B540 capillary melting point apparatus and are uncorrected. IR Spectra: Perkin Elmer Spectrum BX FTIR System spectrometer (ATR-unit, Attenuated Total Reflection, Golden Gate). NMR spectra (¹H, ¹³C, ¹⁹F): Varian Mercury-300; spectra were recorded at 25 °C using the solvent peak as an internal reference. Coupling constants (*J*) are given in Hz. The resonance multiplicity is described as s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Mass spectra were recorded on a Bruker Daltonics UltraFlex II (MALDI-TOF, with 2,5-dihydroxybenzoic acid as the Matrix) or Bruker maXis ESI-Q-TOF. HPLC was run on a Merck-Hitachi system with a Merck LiChrospher Si60 (5 µm, 4x250 mm, analytical) and a Kromasil spherical Si60 (100 Å, 5 µm, 20x250 mm, preparative) column; the system was equipped with a L-6250 pump, a L-5200 autosampler, and a Merck Hitachi RI-71 refractive index detector. Compounds were named with the computer program ACD-Name (ACD/Labs).

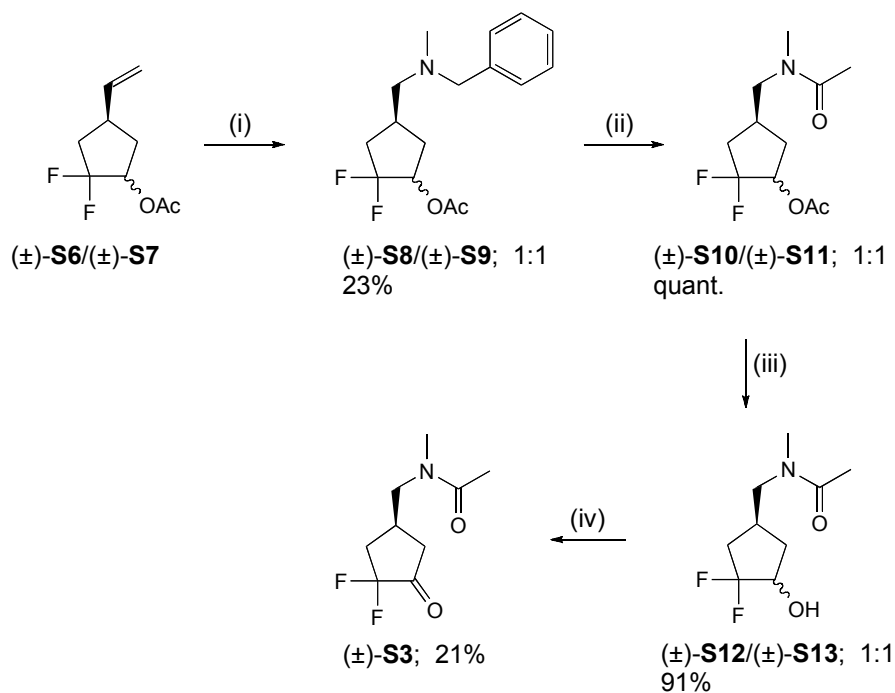
Synthesis of reference compounds **S1**, **S2**, and ($\pm$)-**S3**

Reference compound **S1** was synthesised from the previously described aniline⁶ **S4** by methylation under basic conditions (Scheme 1ESI). In an analogous procedure, the known amide⁶ **S5** was transformed into the tertiary amide **S2**.



Scheme 1ESI (i) NaH, MeI, THF, 22 °C, 22 h, 51%; (ii) NaH, MeI, THF, 22 °C, 26h, 74%.

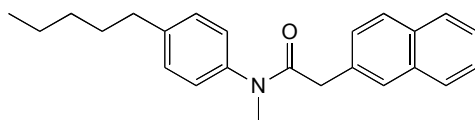
Reference compound ($\pm$)-**S3** was synthesised starting from an already described diastereoisomeric mixture of the difluorides⁶ ($\pm$)-**S6**/ $\pm$)-**S7** (Scheme 2ESI). Compounds ($\pm$)-**S6**/ $\pm$)-**S7** were transformed into the diastereoisomeric mixture of the tertiary amines ($\pm$)-**S8**/ $\pm$)-**S9** by a reductive amination with *N*-benzylamine. Reductive removal of the protecting group in ($\pm$)-**S8**/ $\pm$)-**S9** and subsequent acetylation of the secondary amine yielded the diastereoisomeric mixture of the amides ($\pm$)-**S10**/ $\pm$)-**S11**. Saponification of the ester group of ($\pm$)-**S10**/ $\pm$)-**S11** under basic conditions gave the free alcohols ($\pm$)-**S12**/ $\pm$)-**S13**, which were oxidised to the reference compound ($\pm$)-**S3**.



Scheme 2ESI (i) OsO₄, NaIO₄, dioxane/H₂O, 22 °C, 16 h; *N*-benzylamine, NaBH(OAc)₃, 1,2-dichloroethane, 22 °C, 3 h; (ii) Pd/C, H₂, CH₂Cl₂, 22 °C, 34 h; AcCl, DIPEA, CH₂Cl₂, 43 h, 22 °C; (iii) K₂CO₃ in MeOH, H₂O, CH₂Cl₂, 22 °C, 4.5 h; (iv) *Dess-Martin*-Periodinane, CH₂Cl₂, 22 °C, 32.5 h
DIPEA: Diisopropylethylamine, AcCl: Acetyl chloride.

Procedures

N-methyl-2-(2-naphthyl)-*N*-(4-pentylphenyl)acetamide (**S1**)

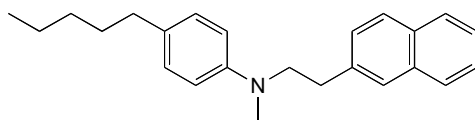


S1

To a solution of 2-(2-naphthyl)-*N*-(4-pentylphenyl)acetamide⁶ **S4** (129 mg, 0.39 mmol, 1.0 eq) in THF (2.5 cm³) under Ar at 22 °C, NaH (60 % in paraffin oil; 19 mg, 0.47

mmol 1.2 eq) was added. After 5 min, MeI (0.034 cm³, 77 mg, 0.55 mmol, 1.4 eq) was added and the mixture stirred for 26 h. Saturated aqueous NH₄Cl (30 cm³) was added and the aqueous layer extracted with EtOAc (3x30 cm³). The combined organic phases were dried over MgSO₄. Purification of the crude product (SiO₂; EtOAc:heptane 1:5, then 1:4) afforded **S1** as a brown oil (97 mg, 72%). ν_{max} (solid)/cm⁻¹ 3053, 2954, 2926, 2855, 1654, 1508, 1416, 1375, 1304, 1115, 1018, 855, 792, 739; δ_{H} (300 MHz; CDCl₃) 0.95 (3 H, t, *J* 6.9), 1.34-1.40 (4 H, m), 1.64-1.69 (2 H, m), 2.65 (2 H, t, *J* 7.8), 3.29 (3 H, s), 3.65 (2 H, s), 7.03, 7.19 (4 H, AA'BB', *J* 8.2), 7.25 (1 H, dd, *J* 1.7, 8.2), 7.42-7.47 (3 H, m), 7.70-7.75 (2 H, m), 7.78-7.81 (1 H, m); δ_{C} (75 MHz; CDCl₃) 13.98, 22.45, 31.02, 31.38, 35.40, 37.53, 41.09, 125.35, 125.73, 127.28, 127.36, 127.47, 127.51, 127.72, 129.47, 132.17, 132.98, 133.30, 141.38, 142.82, 170.99 (one signal not visible due to overlap); *m/z* (ESI-MS) 346.2158 (100%, [M+H]⁺. C₂₄H₂₈NO⁺ requires 346.2165), 368.1979 (4, [M+Na]⁺. C₂₄H₂₇NONa⁺ requires 368.1985).

Methyl[2-(2-naphthyl)ethyl](4-pentylphenyl)amine (**S2**)

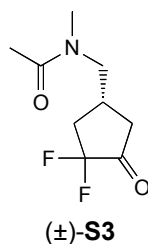


S2

To a solution of [2-(2-naphthyl)ethyl](4-pentylphenyl)amine⁶ **S5** (200 mg, 0.63 mmol, 1.0 eq) in THF (4 cm³) under Ar at 22 °C, NaH (60 % in paraffin oil; 30 mg, 0.76 mmol 1.2 eq) was added. After 10 min, MeI (0.055 cm³, 125 mg, 0.88 mmol, 1.4 eq) was added and the mixture stirred for 22 h. Saturated aqueous NH₄Cl (50 cm³) was added and the aqueous layer extracted with EtOAc (3x50 cm³) and the combined organic

phases dried over MgSO_4 . Purification of the crude product (SiO_2 ; EtOAc:heptane 1:19) afforded amine **S2** as a brown solid (107 mg, 51%). mp 41–43 °C; ν_{max} (solid)/ cm^{-1} 2923, 2853, 1612, 1517, 1464, 1348, 1279, 1206, 1179, 1101, 959, 859, 818, 800, 753, 740; δ_{H} (300 MHz; CDCl_3) 1.01 (3 H, t, J 6.9), 1.37-1.48 (4 H, m), 1.65-1.73 (2 H, m), 2.63 (2 H, t, J 7.6), 2.97 (3 H, s), 3.09 (2 H, t, J 7.6), 3.71 (2 H, t, J 7.6), 6.82, 7.19 (4 H, AA'BB', J 8.6), 7.44 (1 H, dd, J 1.6, 8.4), 7.51-7.57 (2 H, m), 7.73 (1 H, s), 7.85-7.91 (3 H, m); δ_{C} (75 MHz; CDCl_3) 14.33, 22.82, 31.73, 31.76, 33.22, 35.05, 38.81, 55.11, 112.43, 125.25, 125.96, 126.95, 127.38, 127.42, 127.61, 128.02, 129.14, 130.72, 132.04, 133.60, 137.44, 146.89; m/z (MALDI-HRMS) 332.2367 (100%, $[M+H]^+$. $\text{C}_{24}\text{H}_{30}\text{N}^+$ requires 332.2373).

***N*-(3,3-difluoro-4-oxocyclopentyl)methyl]-*N*-methylacetamide ((±)-**S3**)**



To a solution of the two diastereoisomers⁶ (±)-**S6** and (±)-**S7** (800 mg, 4.21 mmol, 1.0 eq) in a mixture of dioxane/water (10:1, 33 cm^3) under Ar at 0 °C, a 0.025 M solution of OsO_4 in $t\text{BuOH}$ (5.032 cm^3 , 107 mg, 0.42 mmol 0.1 eq) was added. After 30 min, the mixture was allowed to warm up to 22 °C and after another 30 min, NaIO_4 (2699 mg, 12.62 mmol, 3.0 eq) was added and the mixture stirred for 16 h. The mixture was then filtrated over Celite and concentrated *in vacuo*. To a solution of the crude aldehyde (827 mg, 4.30 mmol, 1.0 eq) in 1,2-dichloroethane (25 cm^3), *N*-benzylmethylamine

(0.555 cm³, 522 mg, 4.30 mmol, 1.0 eq) was added under Ar at 22 °C. After 30 min, NaBH(OAc)₃ (1003 mg, 4.73 mmol, 1.1 eq) was added and the mixture stirred for 3 h. A saturated aqueous solution of NaHCO₃ (30 cm³) was then added and the aqueous phase extracted with CH₂Cl₂ (3x40 cm³). The combined organic phases were dried over MgSO₄. Purification of the crude product (SiO₂; EtOAc:heptane 1:4 + 1% Et₃N) afforded a 1:1 mixture of two diastereoisomers (±)-**S8** and (±)-**S9** (290 mg, 23%) as a colourless oil.

To a solution of the diastereomeric amines (±)-**S8** and (±)-**S9** (290 mg, 0.98 mmol, 1.0 eq) in CH₂Cl₂ (8 cm³) under Ar at 22 °C, Pd/C catalyst (60 mg) was added. The Schlenk flask was then carefully evacuated and refilled with H₂. After 29 h, additional Pd/C (25 mg) was added as a suspension in CH₂Cl₂ (2 cm³). After 5 h, the mixture was filtered over Celite and concentration *in vacuo* yielded the crude amines.

To a solution of the crude amines in CH₂Cl₂ (8 cm³) under Ar at 22 °C, DIPEA (0.366 cm³, 277 mg, 2.15 mmol, 2.2 eq) and AcCl (0.076 cm³, 84 mg, 1.07 mmol, 1.1 eq) were added. The resulting mixture was stirred for 43 h. After 21.5 h and 36.5 h, additional AcCl (0.076 cm³, 84 mg, 1.07 mmol, 1.1 eq) was added. A saturated aqueous solution of NaHCO₃ (20 cm³) was then added and the aqueous phase extracted with EtOAc (3x20 cm³). The combined organic phases were dried over MgSO₄. Purification of the crude product (SiO₂; MeOH:CH₂Cl₂ 1:99) afforded the 1:1 mixture of the two diastereoisomers (±)-**S10** and (±)-**S11** (243 mg, quant) as a brown oil.

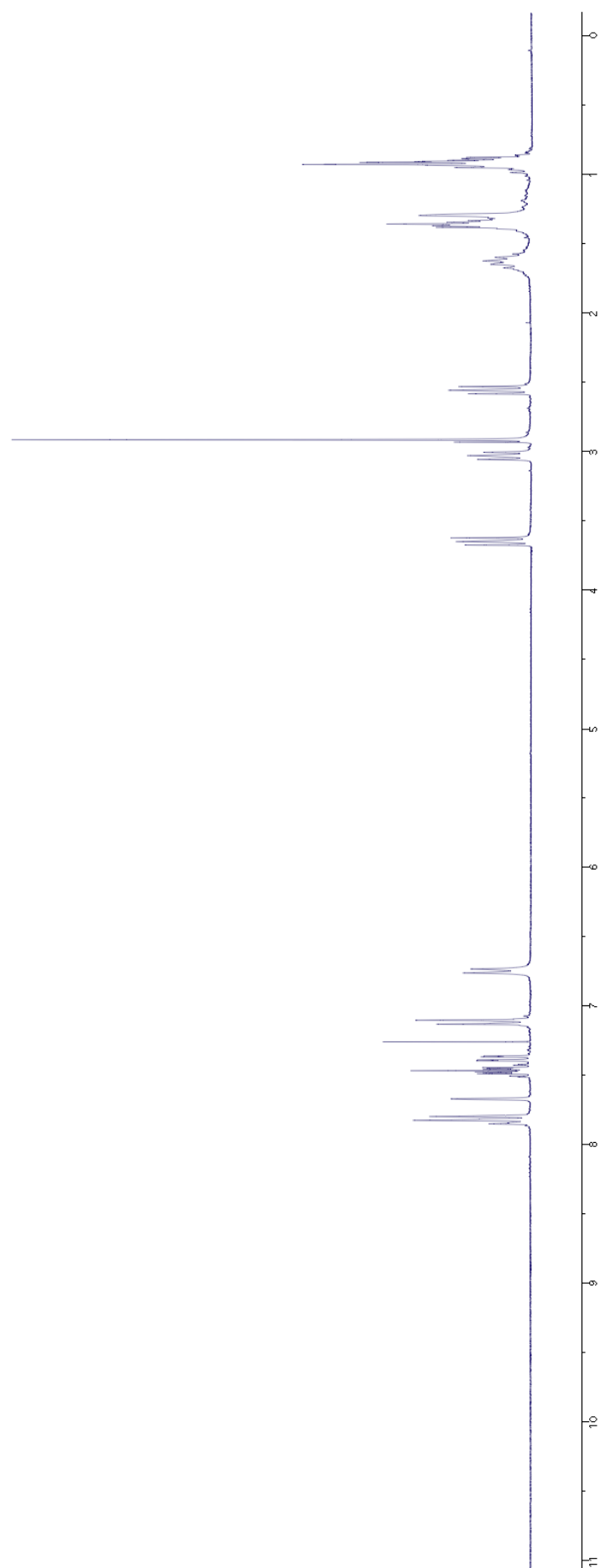
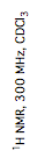
To a solution of amides (±)-**S10** and (±)-**S11** (211 mg, 0.85 mmol, 1.0 eq) in CH₂Cl₂ (5 cm³), a solution of K₂CO₃ (5 cm³; 1.0 g, K₂CO₃ dissolved in 30 cm³ H₂O and 115 cm³ MeOH) was added under Ar at 0 °C. The mixture was allowed warm up to 22 °C. After 4.5 h, a saturated aqueous solution of NH₄Cl (20 cm³) was added and the aqueous phase extracted with EtOAc (3x40 cm³). The combined organic phases were dried over

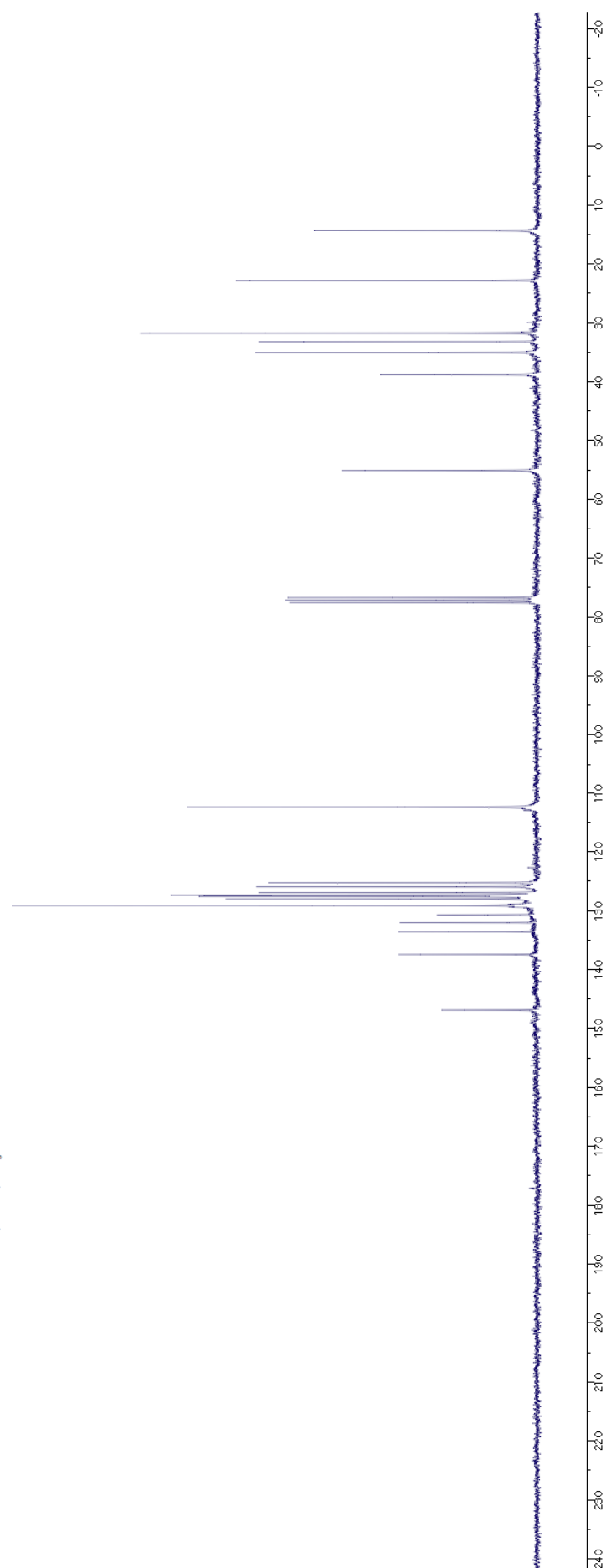
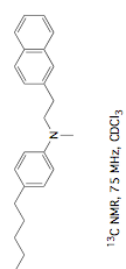
MgSO₄. Purification of the crude product (SiO₂; MeOH:EtOAc 2:98) afforded a 1:1 mixture of two diastereoisomers (±)-**S12** and (±)-**S13** (160 mg, 91%) as a yellow oil.

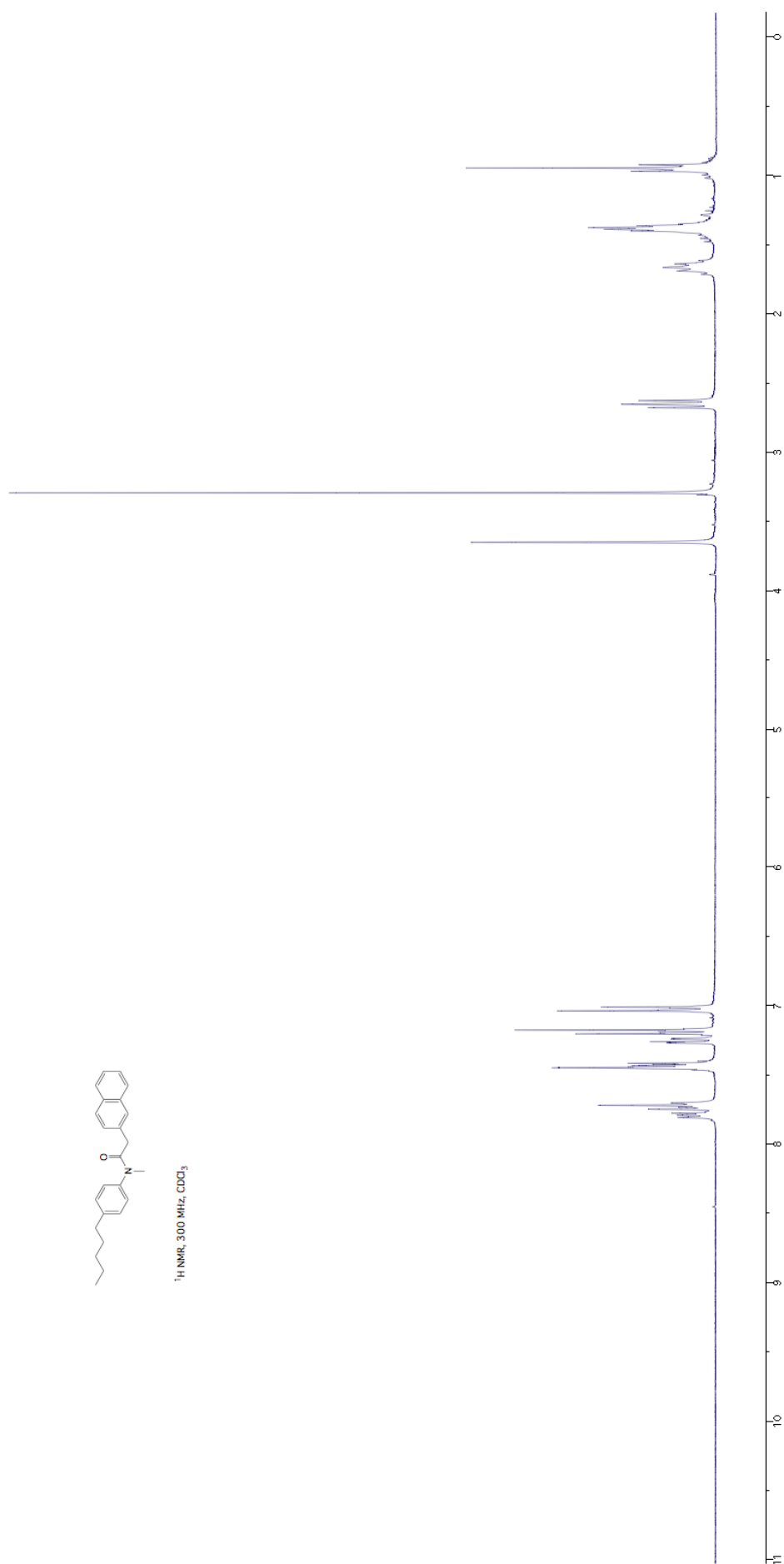
To a solution of the alcohols (±)-**S12** and (±)-**S13** (160 mg, 0.77 mmol, 1.0 eq) in CH₂Cl₂ (4 cm³), *Dess-Martin* periodinane (DMP) (15% in CH₂Cl₂; 3.206 cm³, 655 mg, 1.54 mmol, 2.0 eq) was added under Ar at 0 °C. The mixture was stirred for 32.5 h. After 22 h (0.800 cm³, 164 mg, 0.39 mmol, 0.51 eq) and 26.5 h (0.300 cm³, 66 mg, 0.15 mmol, 0.2 eq) additional DMP was added. A saturated aqueous solution of NaHCO₃ (10 cm³) and a 10% solution of NaS₂O₃ (10 cm³) were then added and the resulting mixture stirred for 30 min. The aqueous phase was extracted with EtOAc (3x40 cm³) and the combined organic phases were dried over MgSO₄.

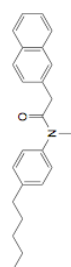
The crude product was dissolved in dry CH₂Cl₂ (10 cm³) and dried with molecular sieves (4 Å). Purification of the crude product (SiO₂; EtOAc) did not afford the pure product. Purification by HPLC (SiO₂; EtOAc), subsequent dissolution in CH₂Cl₂ (10 cm³) and stirring over molecular sieves (4 Å) afforded the title compound in higher purity, but not completely pure. A side product, which was only formed in small amounts by FCC, was now observed. This may have been the reason for the tailing of the peaks observed in the HPLC.⁷ We therefore assume, that the product is not very stable on silica gel. Ketone (±)-**S3** with ca. 10% estimated impurity was obtained as a colourless wax (33 mg, 21%). It exists as two rotamers at 22 °C in a ratio of approximately 5:1 (determined by ¹⁹F NMR; spectrum page 32). $\nu_{\max}$ (solid)/cm⁻¹ 3253, 2925, 1775, 1621, 1491, 1408, 1330, 1253, 1193, 1176, 1104, 1020, 860, 728; δ_{H} (300 MHz; CDCl₃) 1.91-2.09 (1 H, m), 2.11 (3 H, s), 2.12-2.25 (1 H, m), 2.26-2.68 (3 H, m), 2.96, 3.06 (3 H, 2 x s), 3.44 (1 H, dd, *J* 6.9, 13.7), 3.55 (1 H, dd, *J* 6.9, 13.7); δ_{C} (75 MHz; CDCl₃) 21.92, 28.93 (dd, *J* 1.3, 6.3), 36.74 (dd, *J* 19.7, 22.4), 37.14, 38.94 (dd, *J* 1.2, 3.5), 51.52, 116.93 (dd, *J* 251.7, 261.8), 171.18, 202 (t, *J* 25.6); δ_{F} (282 MHz;

CDCl₃) conformer 1 (major) (−113.97)–(−112.93) (1 F, m), (−109.46)–(−108.32) (1 F, m), conformer 2 (minor) (−111.69)–(−110.62) (1 F, m), (−110.05)–(−108.93) (1 F, m); *m/z* (ESI-MS) 206.0986 (41%, [*M*+H]⁺. C₉H₁₄F₂NO₂⁺ requires 206.0987), 200.1082 (38), 238.1249 (100).

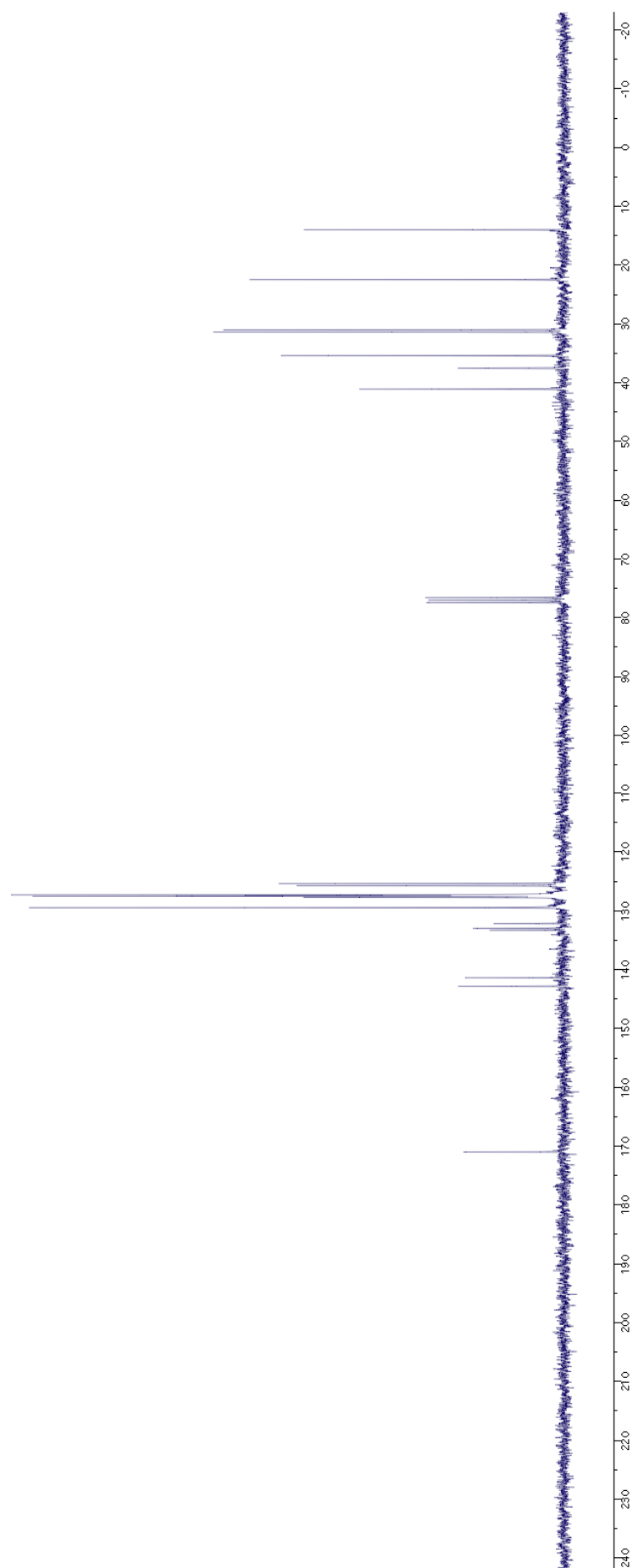


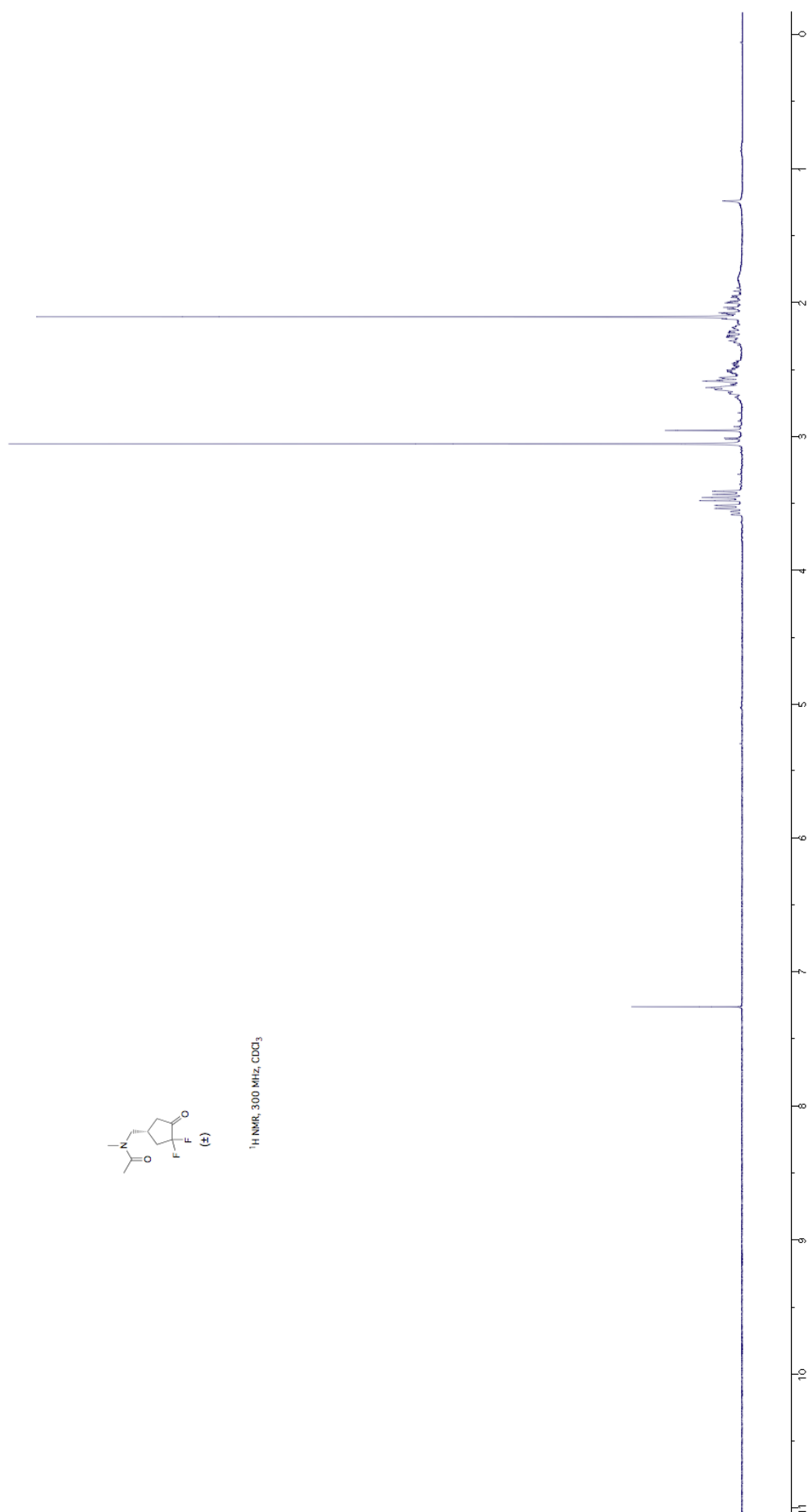


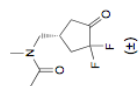




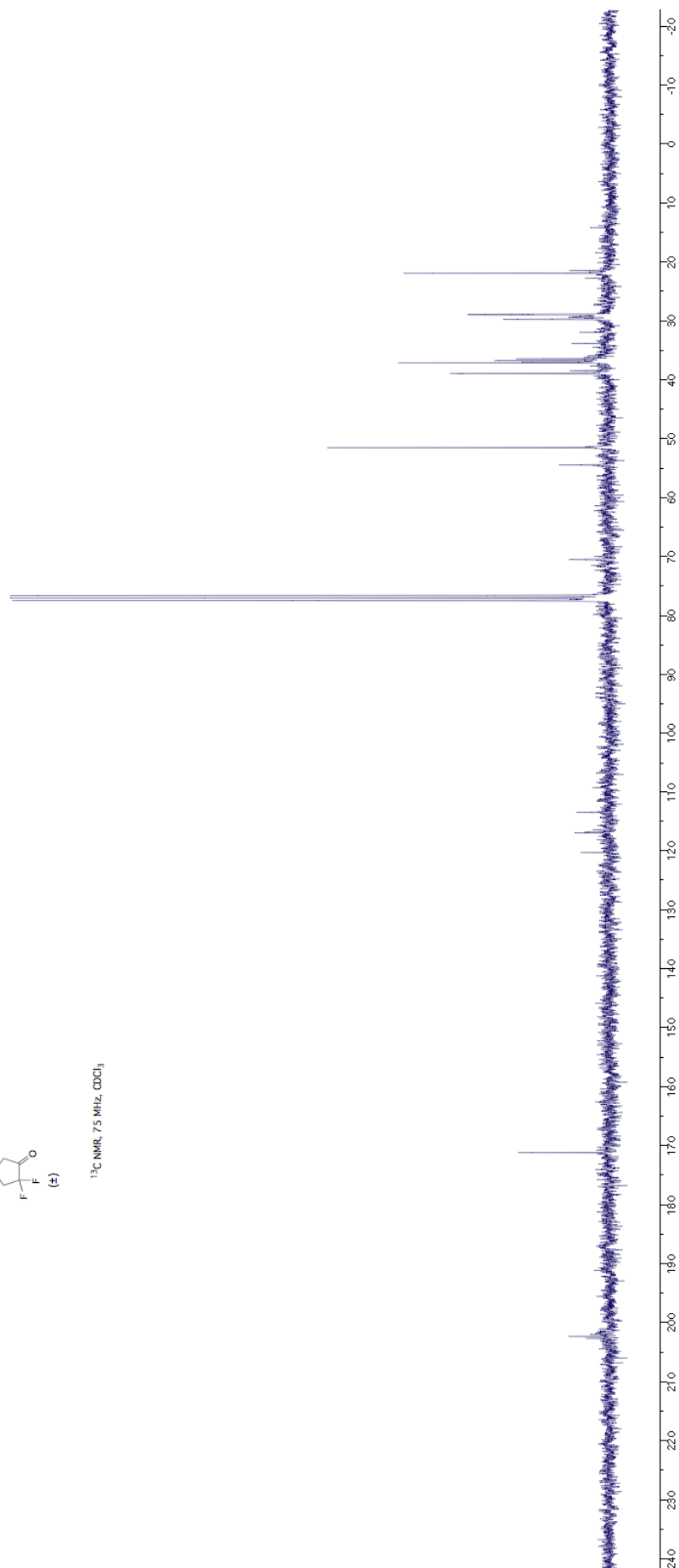
^{13}C NMR, 75 MHz, CDCl_3

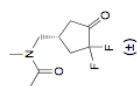




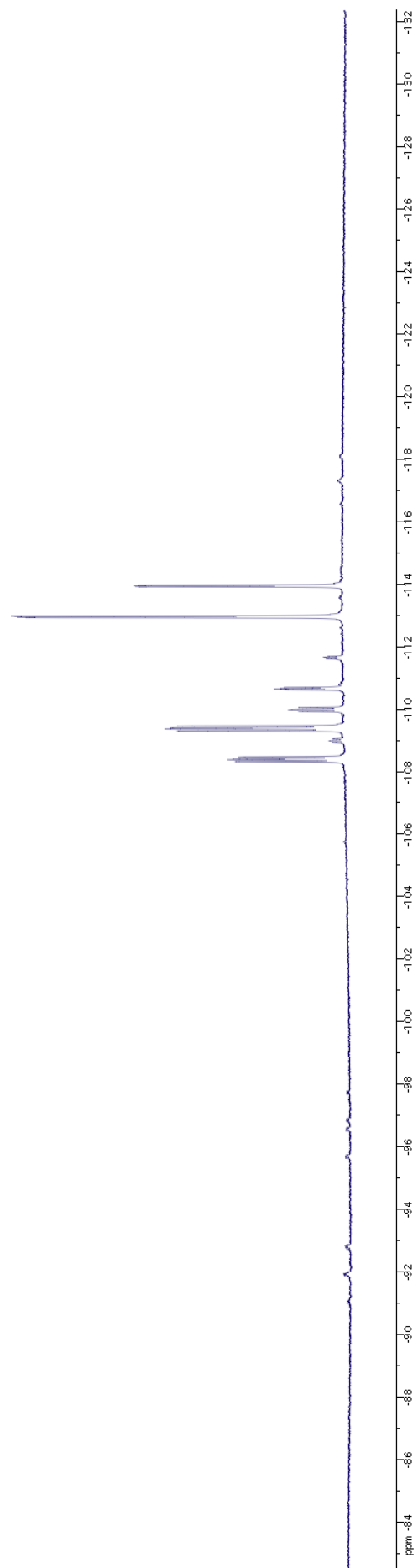


^{13}C NMR, 75 MHz, CDCl_3





^{19}F NMR, 282 MHz, CDCl_3



8. Literature

- 1 A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni and R. Spagna, *J. Appl. Crystallogr.*, 1999, **32**, 115–119.
- 2 G. M. Sheldrick, *SHELXL-97, Program for the Refinement of Crystal Structures*, University of Göttingen, Germany, 1997.
- 3 P. R. Gerber and K. Müller, *J. Comput.-Aided Mol. Design*, 1995, **9**, 251–268.
- 4 Cambridge Structural Database (CSD) Version 5.29, November 2007 (update January 2008), containing about 440000 entries.
- 5 The torsional angle $C_{C=O}-N-C_{\text{cyclohexyl}}-H = 35^\circ$ is in an acceptable range as revealed by a search in the Cambridge Structural Database (CSD) Version 5.29, November 2007 (update January 2008), containing about 440000 entries
- 6 C. Fäh, L. A. Hardegger, L. Baitsch, W. B. Schweizer, S. Meyer, D. Bur and F. Diederich, *Org. Biomol. Chem.*, 2009, **7**, 3947–3957.
7. We thank Dr. Thomas Mäder for help with the HPLC purification.