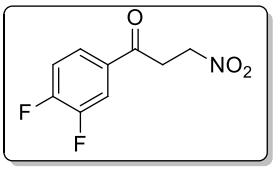
SUPPORTING INFORMATION

Below we describe the synthetic routes and chemical analysis of the starting materials used. Compounds **3** and **4** were synthesised as stated below, while the synthetic routes towards compounds **7**, **8** and **9** are already described elsewhere[1]. Moreover, the conditions for chiral analysis of the products as well as the corresponding HPLC chromatograms are shown.

SYNTHETIC ROUTES AND CHEMICAL ANALYSIS

1-(3,4-difluorophenyl)-3-nitropropan-1-one **3** $C_9H_7F_2NO_3$



A mixture of 3-chloropropanoyl chloride (12.2 g, 96.0 mmol) and 1,2-difluorobenzene (10.0 g, 87.6 mmol) was added dropwise under stirring to a suspension of $AlCl_3$ (12.8 g, 96.0 mmol) in dichloromethane (30 mL), keeping the temperature below 30 °C with external cooling. The mixture was stirred at room temperature for 24 hours (monitoring by TLC hexane/EtOAc 9:1). After cooling to 0 °C, water was slowly added, separated from organic phase and extracted with dichloro methane. The collected organic phases were washed with a saturated solution of $NaHCO_3$ and subsequently dried over Na_2SO_4, filtered and evaporated under vacuum. The residue (brown oil) was used in the next step as a crude to which $NaNO_2$ (4.2 g, 60.8 mmol) was added in a stirred solution (10.0 g, 48.9 mmol) in acetone (400 mL) and maintained at 50 °C for 6 hours. After completion of the reaction (monitored by TLC hexane/EtOAc 7:3) the solvent was evaporated under vacuum and the residue purified by flash chromatography, obtaining **3** (7.5 g, 71%) as a yellow solid

GC-MS (EI) *m/z*: $[M]^+$ calc. for $C_9H_7F_2NO_3^+$: 215.04; found: 215.03

δ_H (400 MHz, $CDCl_3$): 3.61 (2H, t, ^3J 6 Hz, 2-H); 4.83 (2H, t, ^3J 6 Hz, 3-H), 7.31 (1H, ddd, ^3J 9.6 Hz, ^4J 7.6 Hz, ^4J 2 Hz, 2-H'), 7.78 (1H, ddd, ^3J 7.8 Hz, ^4J 4.2 Hz, ^4J 1.4 Hz, 6-H') 7.83 (1H, ddd, ^3J 10.2 Hz, ^3J 7.6 Hz. 5-H').

δ_C (400 MHz, $CDCl_3$): 34.65 (3-C), 68.9 (2-H), 117.5 (dd, ^2J 18 Hz, ^4J 2 Hz, 2-C'), 117.83 (d, ^2J 18 Hz, 5-C'), 125.24 (dd, ^3J 7.6 Hz, ^4J 2.5 Hz, 6- C'), 132.76 (dd, ^3J 4.4 Hz, ^4J 3.7 Hz, 1- C'), 150.62 (dd, ^1J 252 Hz, ^2J 12 Hz, 4- C'), 154.32 (dd, ^1J 258 Hz, ^2J 12.8 Hz, 3- C') 197.4 (1-C).

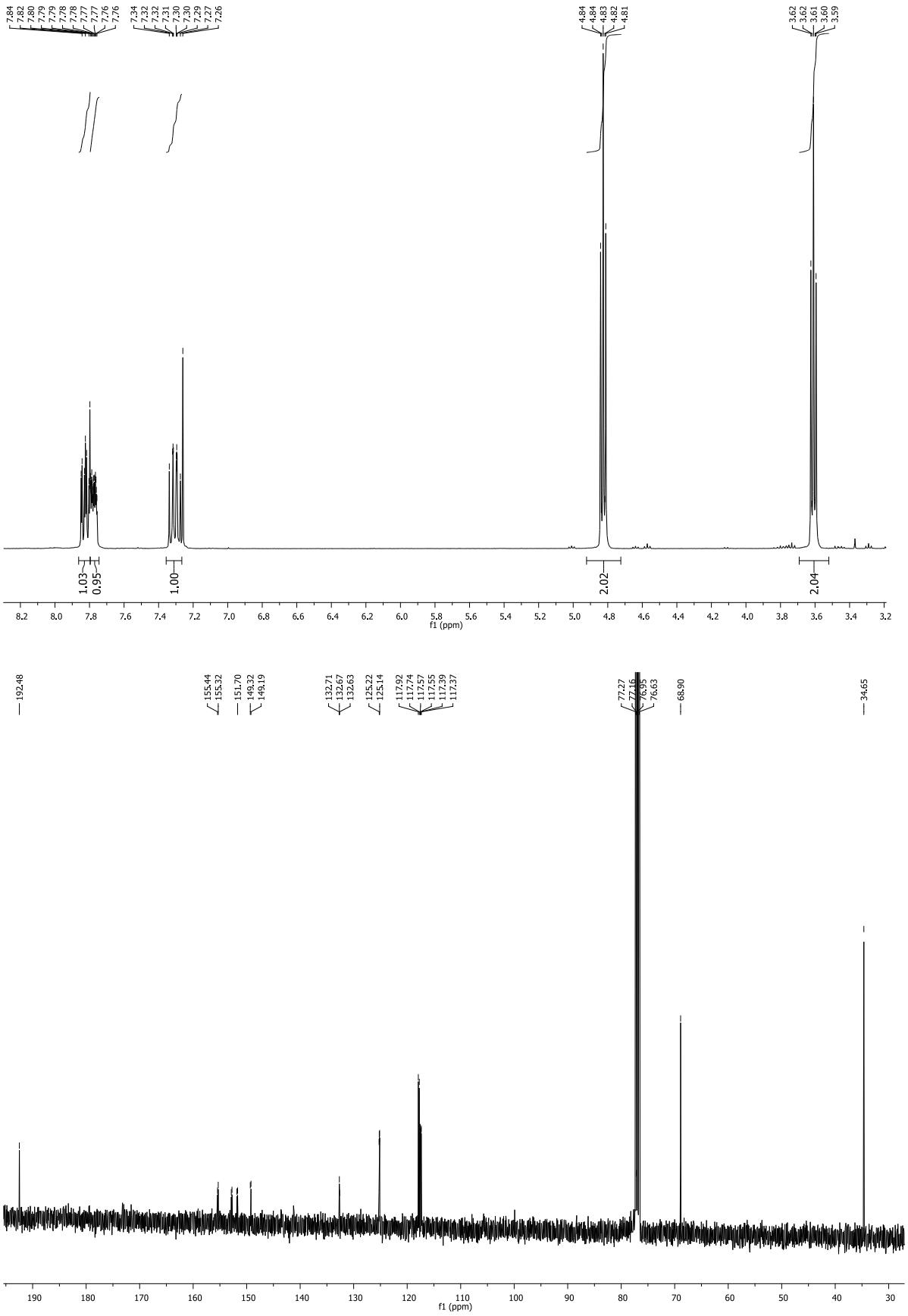
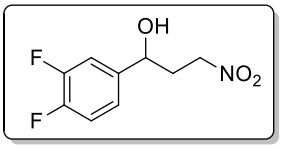


Figure 1: NMR spectrum of compound **3**, top ^{1}H-NMR, bottom ^{13}C NMR; $CDCl_3$

rac-1-(3,4-difluorophenyl)-3-nitropropan-1-ol **4** $C_9H_9F_2NO_3$



$NaBH_4$ (1.4 g, 37.0 mmol) was added to a 0 °C cooled solution of the β-nitroketone **3** (6.5 g, 30.2 mmol) in a mixture of THF (70 mL) and H_2O (70 mL). The mixture was stirred for 2 hours at room temperature, monitoring the reaction by TLC (hexane/EtOAc 7:3). At the end of the reaction NH_4Cl was added (until no further evolution of hydrogen is observed), followed by an extraction with diethyl ether. The collected organic phases were dried over Na_2SO_4 filtered and evaporated under reduced pressure. The resulting alcohol **4** contained small amounts of starting material but was no further purified as it was needed for HPLC reference purposes only.

Preparation of (*S*)-1-(3,4-difluorophenyl)-3-nitropropan-1-ol (as HPLC standard):

(*R*)-(+)-2-methyl-CBS-oxaborolidine (2.9 g, 10.5 mmol) was added to a 0 °C cooled solution of the β-nitroketone **3** (10.0 g, 46.5 mmol) in THF (70 mL). The mixture was cooled to -20 °C and a solution (2.0 M) of borane-dimethylsulfide complex in THF (23 mL, 46.0 mmol) was added, maintaining the same temperature under stirring for 12 hours. When the reaction was complete (monitoring by TLC hexane/EtOAc 7:3), the mixture was warmed to 0 °C and MeOH was added until no further evolution of gas was observed. HCl 1N and EtOAc were added, the phases were separated and the aqueous phase was extracted with ethyl acetate. The collected organic phases were dried over Na_2SO_4, filtered and evaporated under vacuum. The residue was purified by flash chromatography, obtaining (*S*)-1-(3,4-difluorophenyl)-3-nitropropan-1-ol (7.6 g, 75%) as a yellow oil with an enantiomeric ratio of 97:3

MS (ES+, m/z) 217 [M^+], 240 [M + Na]

δ_H (400 MHz, $CDCl_3$): 2.30 (1H, dt, ^2J 9 Hz, ^3J 6 Hz 3-H); 2.37 – 2.45 (1H, m, 3-H), 4.47 (1 H dt, ^2J 13.8 Hz, ^3J 6.3 Hz 2-H), 4.61-4.68 (1H, , ^2J 14.2 Hz, ^3J 8.4, ^3J 6.2, 2-H), 4.84 (1H, dd, ^3J 8.7, ^3J 4.4, 1-H), 7.06-7.10 (1H, m, 6-H'), 7.78 (1H, dt, ^3J 10.2 Hz, ^3J 8.1 Hz, 5-H') 7.83 (1H, m, 2-H').

δc (400 MHz, $CDCl_3$): 35.73 (2-C), 69.99 (d, ^4J 1.5 Hz, 1-C), 71.86 (3-C), 114.54 (d, ^2J 17.8), 117.51 (d, ^2J 16.8 Hz, 5- C'), 121.46 (dd, ^3J 6.4 Hz, ^4J 3.7 Hz, 6- C'). 140 (t, ^3J 4.7 Hz, ^4J 4.0 Hz, 1-C'), 149.97 (dd, ^1J 248.77 Hz, ^2J 12.7 Hz, 4- C'), 150.34 (dd, ^1J 250 Hz, ^2J 13 Hz, 3- C').

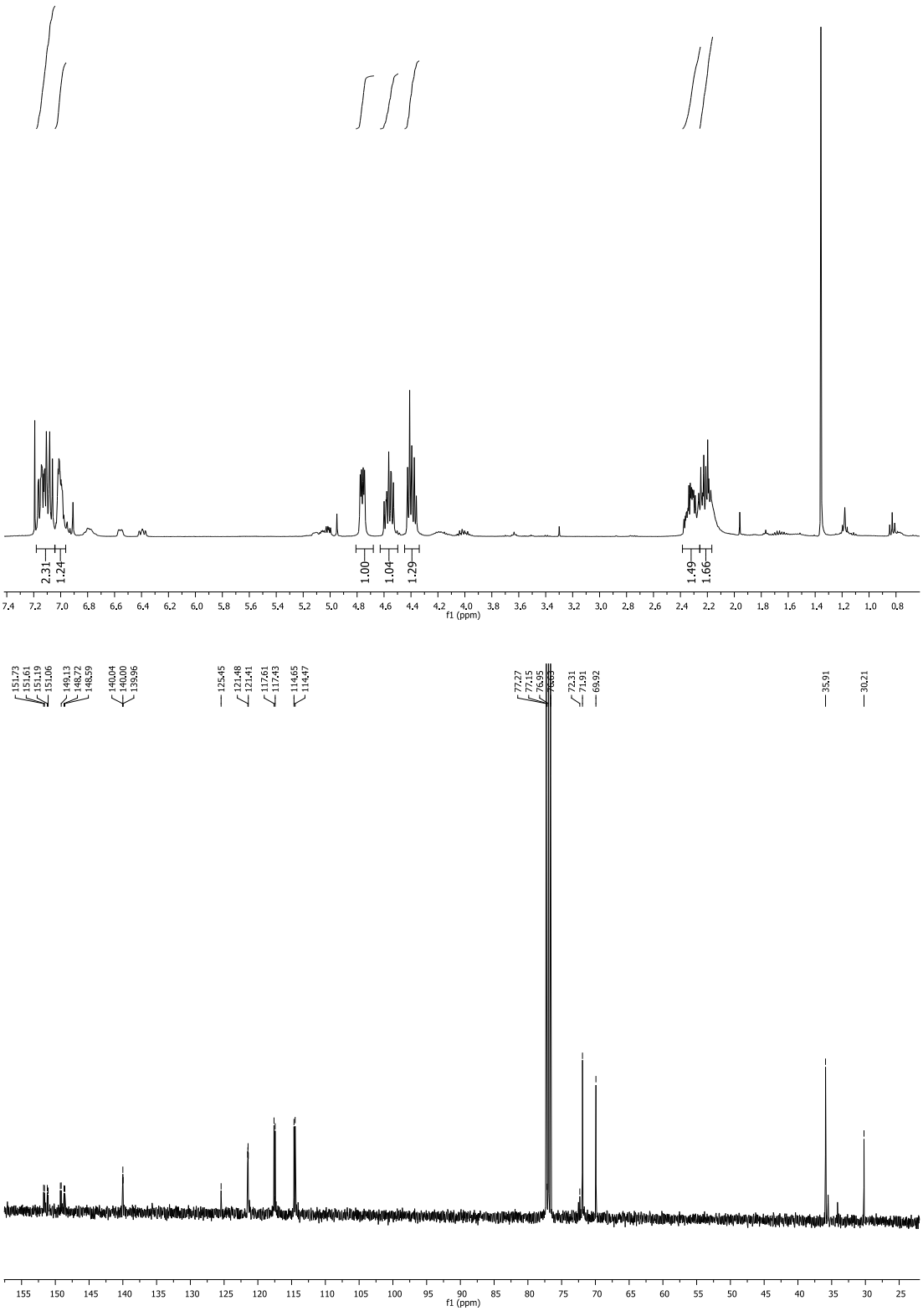
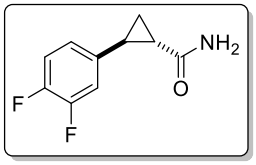


Figure 2: NMR spectrum of compound **4**, top ^{1}H-NMR, bottom ^{13}C NMR; $CDCl_3$

(±)-trans 2-(3',4'-difluorophenyl)cyclopropanecarboxamide **7** $C_{10}H_9F_2NO$



GC-MS (EI) *m/z*: $[M]^+$ calc. for $C_{10}H_9F_2NO^+$: 197.2, found: 197.1.

δ_H (400 MHz, $CDCl_3$): 1.23 (1H, ddd, ^3J 10.6 Hz, ^3J 6.6 Hz, ^2J 6.6 Hz , 3-H); 1.59-1.65 (2H, m, ^3J 10.6 Hz, ^3J 8.4 Hz, ^3J 4.4 Hz, ^2J 6.8 Hz , 2-H, 3-H), 1.59-1.65 (1H, dt, ^3J 8.7 Hz, ^3J 6.4 Hz, ^3J 4.8 Hz , 1-H), 5.73 (2H broad, NH_2) 6.81-6.84 (1H, m, ^3J 8.2 Hz, ^4J 4.4 Hz, ^4J 2.2 Hz, 5-H'), 6.87 (1H, ddd, ^3J 11.3 Hz, ^4J 7.2 Hz, ^4J 2.2 Hz, 2-H') 7.06 (1H, dt, ^3J 10.4 Hz, ^3J 8.2 Hz. 5-H').

δc (400 MHz, $CDCl_3$): 17.22 (3-C), 25.65 (d, ^4J 18 Hz, 2-C), 26.6 (1-C), 114.8 (d, ^2J 18 Hz, 2-C'), 117.1 (d, ^2J 17 Hz, 5-C'), 122.2 (dd, ^3J 6.2 Hz, ^4J 3.5 Hz, 6-C'), 137.5 (dd, ^3J 6.0 Hz, ^4J 3.6 Hz, 1- C'), 149.2 (dd, ^1J 246 Hz, ^2J 13 Hz, 4-C') 150.32 (dd, ^1J 249 Hz, ^2J 13 Hz, 3-C') 173.8 (carboxamide).

$[\alpha]_D^{20}$ = -321.4 (*c* 1.0 in $CHCl_3$) for (1*R*,2*R*)-7, *ee* = 97%

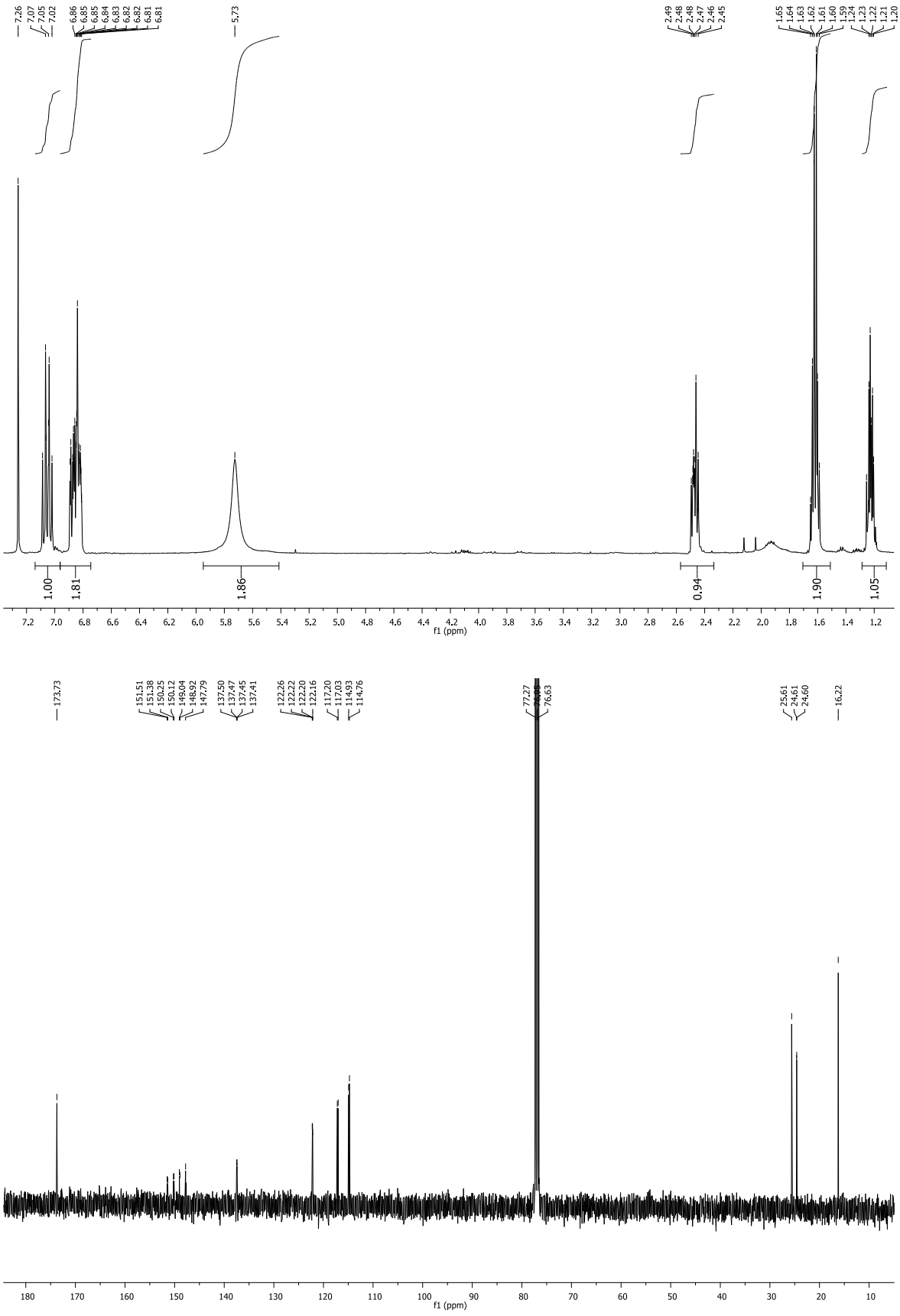
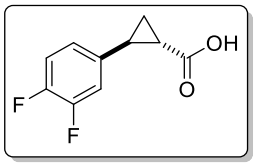


Figure 3: NMR spectrum of compound **7**, top ^{1}H-NMR, bottom ^{13}C NMR; $CDCl_3$

(±)-trans-2-(3,4-difluorophenyl)cyclopropanecarboxylic acid **8** $C_{10}H_8F_2O_2$



GC-MS (EI) *m/z*: $[M]^+$ calc. for $C_{10}H_8F_2O_2^+$: 198.2; found: 198.0.

δ_H (400 MHz, $CDCl_3$): 1.36 (1H, dt, ^3J 9.3 Hz, ^3J 5.0 Hz, ^2J 4.9 Hz , 3-H); 1.67 (2H, m, ^3J 8.5 Hz, ^3J 6.5 Hz, ^2J 4.9 Hz, 3-H), 1.86 (1H, ddd, ^3J 8.5 Hz, ^3J 5.2 Hz, ^3J 4.1 Hz , 2-H), 2.55 (1H, ddd, ^3J 9.3 Hz, ^3J 6.5 Hz, ^3J 4.1 Hz , 1-H), 6.83 (1H, m, ^3J 8.5 Hz, ^4J 4.5 Hz, ^4J 2.2 Hz, 6-C'), 6.90 (1H, ddd, ^3J 11.3 Hz, ^4J 7.4 Hz, ^4J 2.2 Hz, 2-H') 7.07 (1H, dt, ^3J 10.4 Hz, ^3J 8.3 Hz. 5-H').
δc (400 MHz, $CDCl_3$): 17.29 (3-C) 23.84 (1-C), 25.21 (d, ^4J 1.4, 2-C), 115.31 (d, ^2J 18 Hz, 2-C'), 117.1 (d, ^2J 17.31 Hz, 5-C'), 122.45 (dd, ^3J 6.0 Hz, ^4J 3.6 Hz, 6-C'), 136.48 (dd, ^3J 6.0 Hz, ^4J 4.0 Hz, 1- C'), 149.2 (dd, ^1J 247.4 Hz, ^2J 11.4 Hz, 4-C') 149.6 (dd, ^1J 247.4 Hz, ^2J 11.4 Hz, 3-C') 179.21 ($C_{carbonyl}$).

$[\alpha]_D^{20}$ = +323.2 (*c 0.*44 in $CHCl_3$) for (1*S*,2*S*)-8, *ee* = 94%

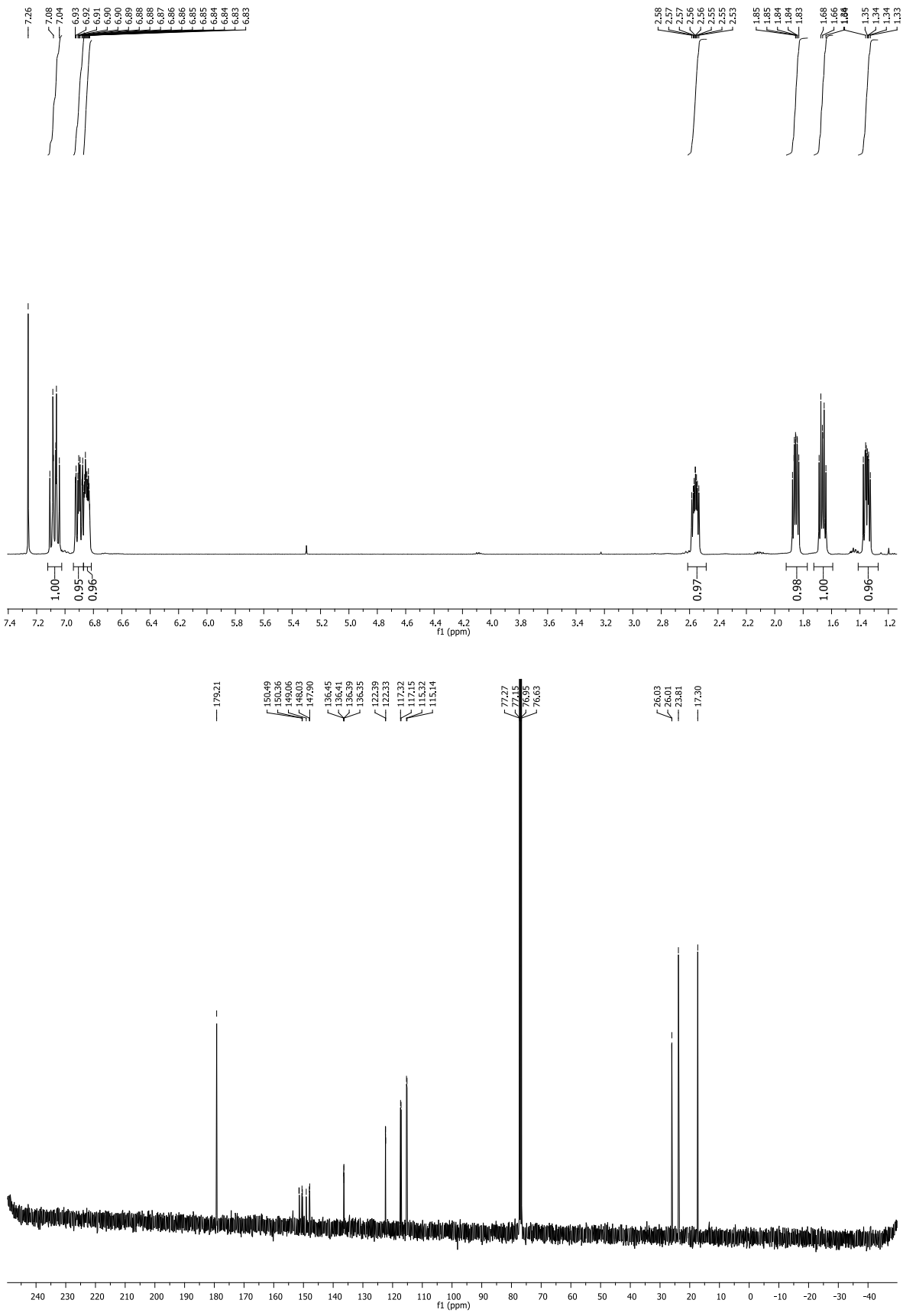
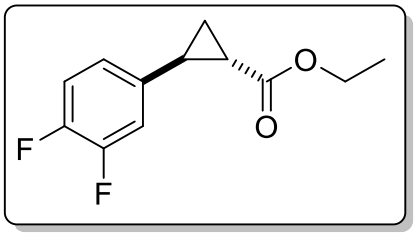


Figure 4: NMR spectrum of compound **8**, top ^{1}H-NMR, bottom ^{13}C NMR; $CDCl_3$

(±)-trans-ethyl 2-(3,4-difluorophenyl)Cyclopropanecarboxylate **9** $C_{12}H_{12}F_2O_2$



GC-MS (EI) *m/z*: $[M]^+$ calc. for $C_{12}H_{12}F_2O_2^+$: 226.08; found: 226.08.

δ_H (400 MHz, $CDCl_3$): 1.25 (1H, ddd, ^3J 8.4 Hz, ^3J 6.4 Hz, ^2J 4.5 Hz , 3-H); 1.28 (3H, t ^3J 6.4 Hz CH_{3Ethyl}) 1.57-1.62 (2H, m, ^3J 9.2 Hz, ^3J 5.2 Hz, ^2J 4.5 Hz, 3-H + H_2O), 1.84 (1H, ddd, ^3J 8.5 Hz, ^3J 5.3 Hz, ^3J 4.3 Hz , 2-H), 2.47 (1H, ddd, ^3J 9.5 Hz, ^3J 6.4 Hz, ^3J 4.2 Hz , 1-H), 4.17 (2H, q, ^3J 6.3 Hz, CH_{2Ethyl}) 6.81-6.87 (1H, m, ^3J 8.5 Hz, ^4J 7.6 Hz, ^4J 2.4 Hz, 6-H'), 6.88 (1H, ddd, ^3J 11.5 Hz, ^4J 7.6 Hz, ^4J 2.2 Hz, 2-H') 7.06 (1H, dt, ^3J 10.3 Hz, ^3J 8.2 Hz. 5-H').

δc (400 MHz, $CDCl_3$): 14.27 (CH_{3Ethyl}), 16.84 (3-C) 24.04 (1-C), 25.14 (d, ^4J 1.4, 2-C), 60.71 (CH_{2Ethyl}), 114.74 (d, ^2J 19 Hz, 2-C'), 117.09 (d, ^2J 18 Hz, 5-C'), 122.25 (dd, ^3J 6.1 Hz, ^4J 3.4 Hz, 6-C'), 137.06 (dd, ^3J 6.1 Hz, ^4J 3.4 Hz, 1- C'), 149.2 (dd, ^1J 248 Hz, ^2J 13 Hz, 4-C') 151.32 (dd, ^1J 249 Hz, ^2J 12.5 Hz, 3-C') 172.87 ($C_{carbonyl}$).

$[\alpha]_D^{20}$ = -381.9 (*c* 1.0 in EtOH) for (1*R*,2*R*)-9, *ee* = 95%

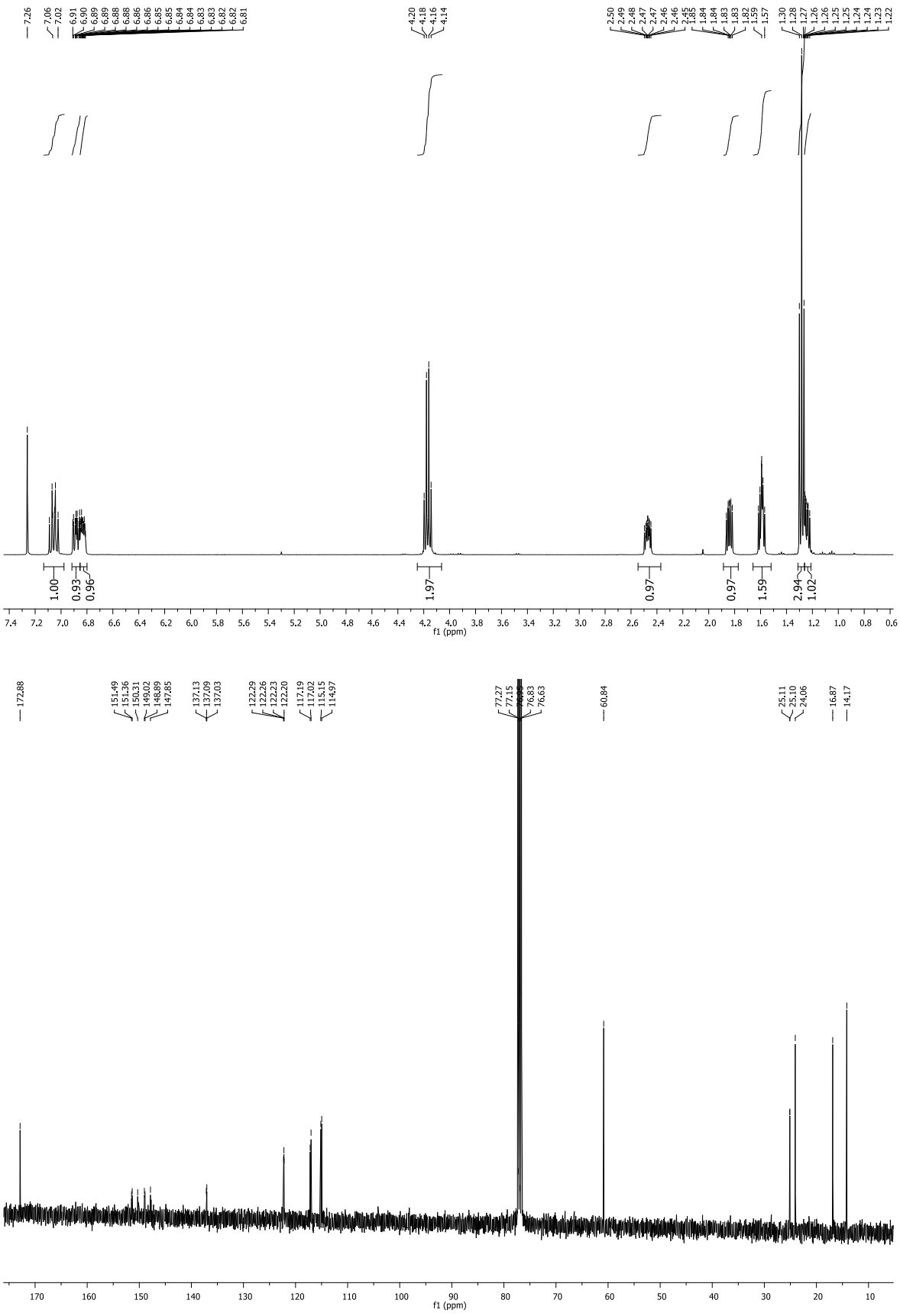


Figure 5: NMR spectrum of compound **9**, top ^{1}H-NMR, bottom ^{13}C NMR; $CDCl_3$

ANALYSIS OF CONVERSION AND ENANTIOMERIC EXCESS.

In case of the KRED-mediated reactions conversions had to be determined by NMR analysis of the reaction crude mixture due to the low UV absorption of the ketone in chiral HPLC, which interfered with its accurate quantification.

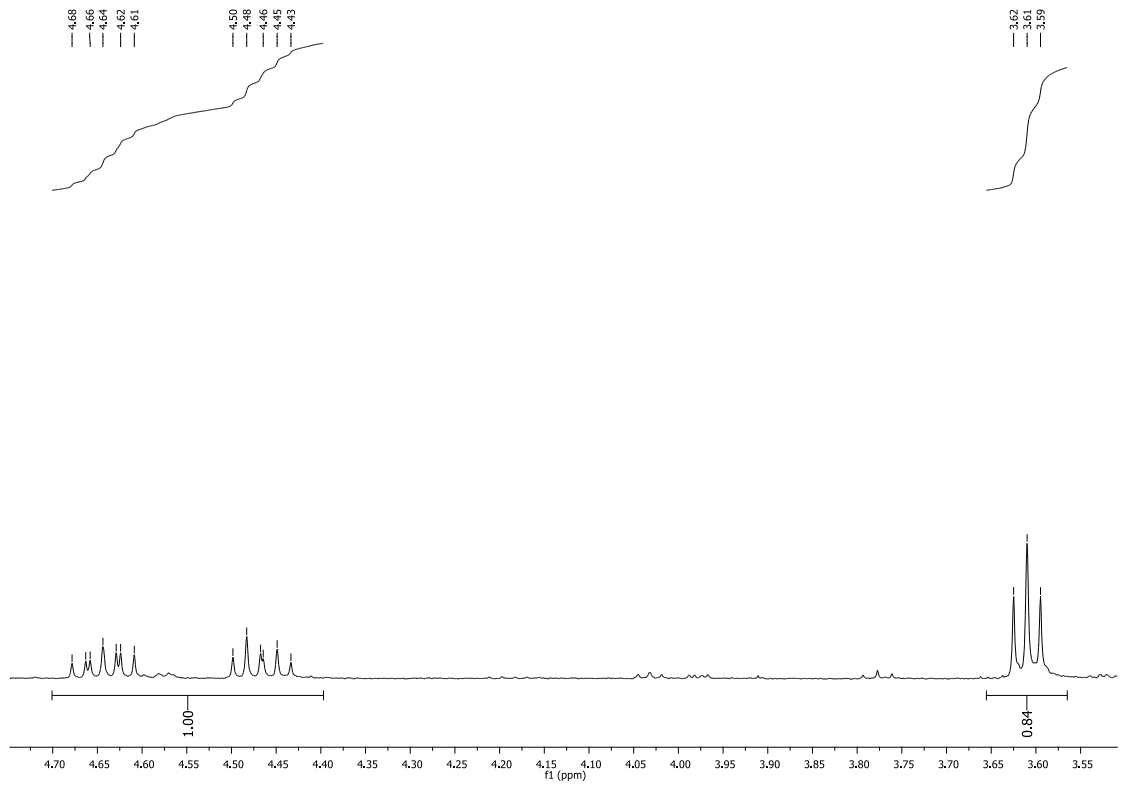


Figure 1: Exemplary NMR-analysis (crude of the reaction mixture) of conversion rates. The region shown is the region of the CH_2 adjacent to the nitrogroup in the alcohol (4.4 – 4.7 ppm) and the α -CH_2 in the ketone (3.55-3.65 ppm) which were chosen for comparison because there is no overlapping of the integrals of alcohol and ketone.

Enantiomeric excesses of all products were determined via chiral HPLC (reference chromatograms see below). Conversions and enantioselectivities were calculated from the HPLC data[2]. The conditions for chiral HPLC analysis are summarised in table 1. Absolute configurations were determined by comparison to enantioenriched samples.

Table 1: HPLC conditions and retention times of compounds 4,7,8 and 9

Entry	Compound	Column	Mobile phase	Flow rate [mL / min]	T [ºC]	Pressure [bar]	t_R [min(Config)]	Reference chromatogram

1	Alcohol 4	Chiralcel OJ-H	H:IPA 9:1	1	20	43	21.0 (*S*) / 22.8 (*R*)	Figure 6
2	Amide 7	Chiralcel OJ-H	H:IPA 95:5	0.8	20	43	42.5 (R) / 47.2 (S)	Figure 7A
3	Acid 8	Chiralcel OJ-H	H:IPA 95:5 + 0.1% TFA	1	20	43	9.7 (R) / 12.3 (S) (retention times vary slightly between runs)	Figure 7B / 8
4	Ester 9	Chiralcel OJ-H	H:IPA 95:5 + 0.1% TFA	1	20	43	6.5 (R) / 7.2 (S)	Figure 9

H = Hexane / IPA = 2-Propanol / TFA = Trifluoroacetic acid

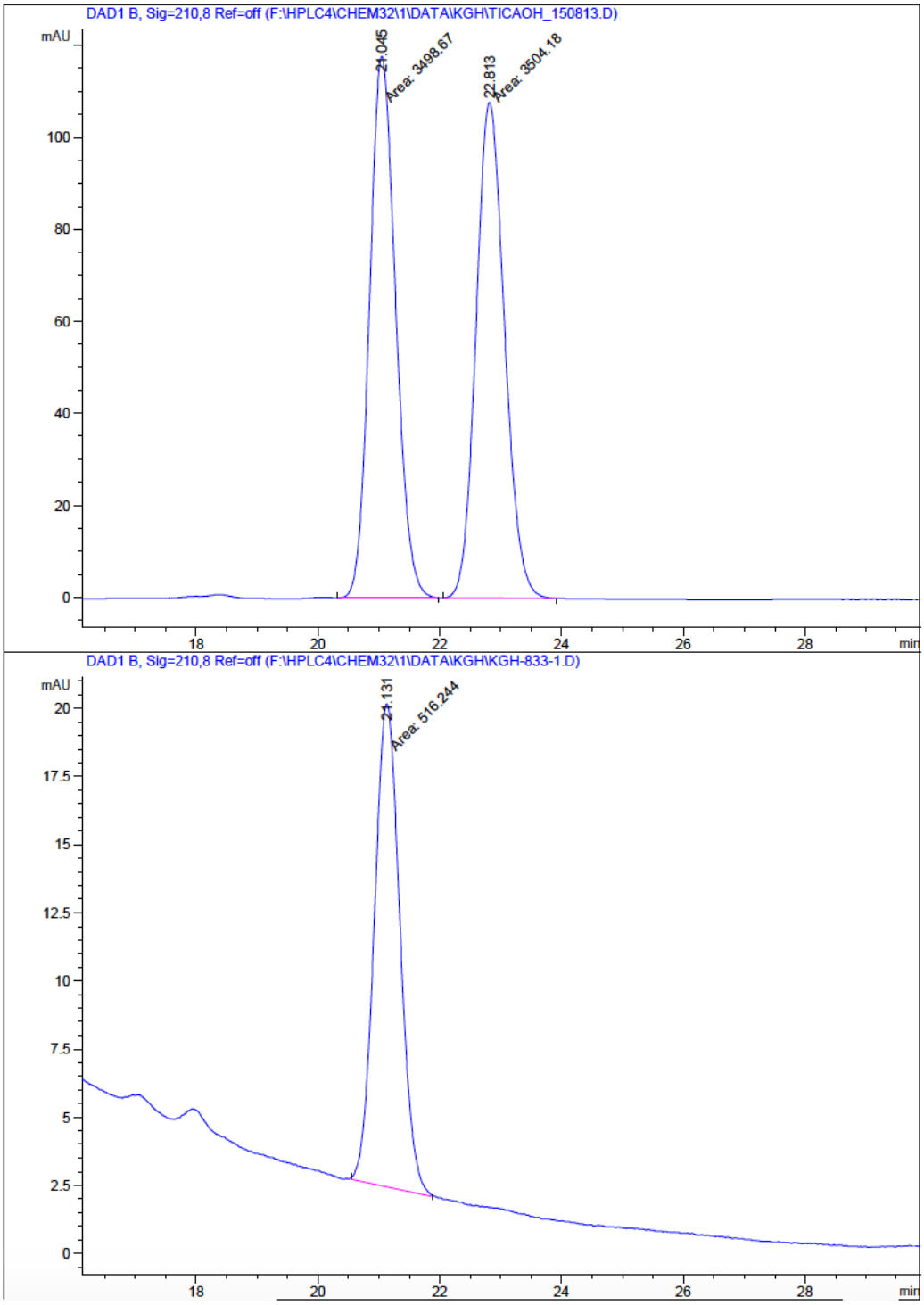
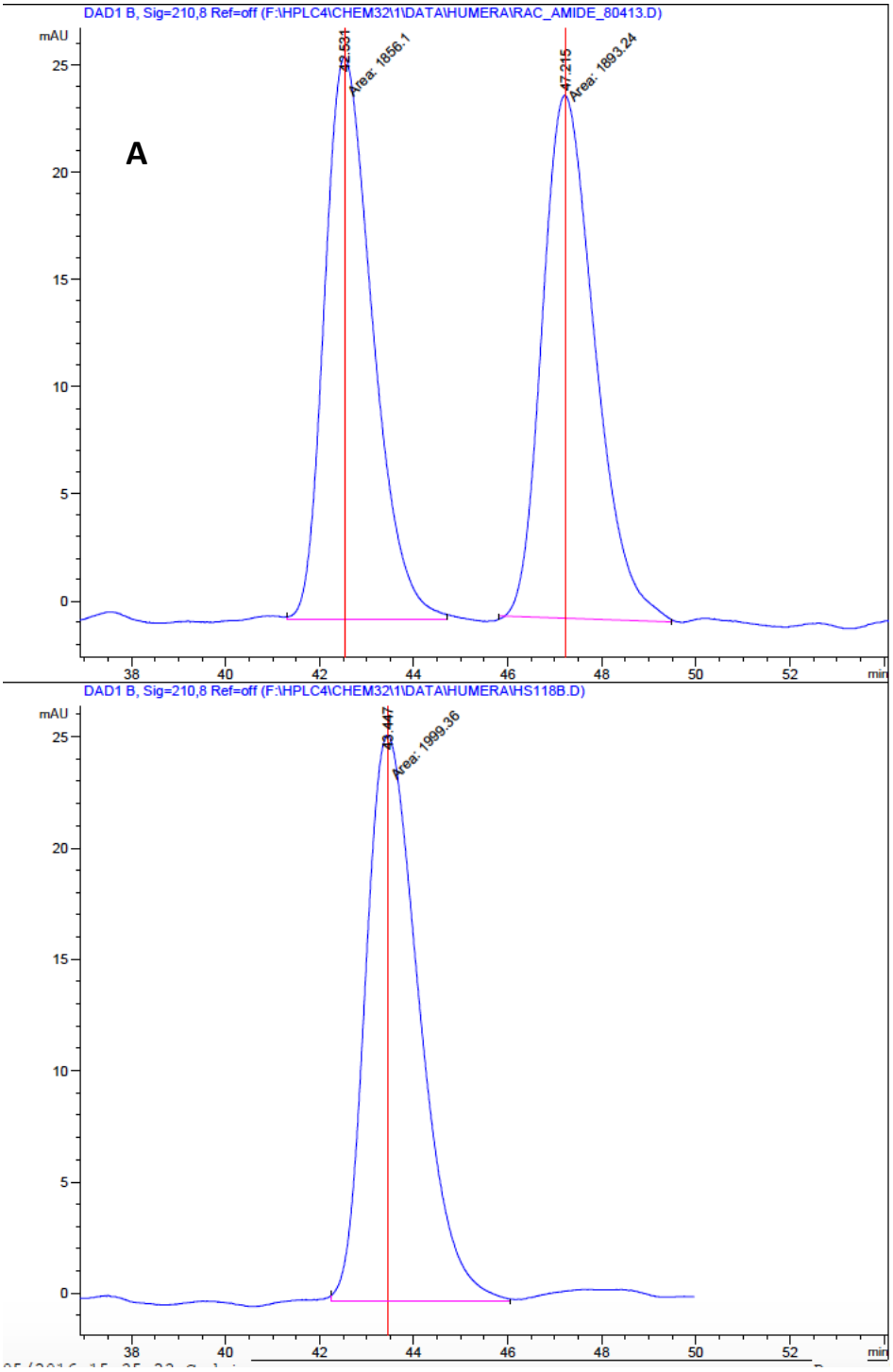


Figure 6: Chromatogram for KRED-mediated conversion of ketone **3** to alcohol **4**. Top racemic alcohol, bottom product.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Area: 1856.1
47.215
Area: 1893.24
min
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mAU
43.447
Area: 1999.36
min

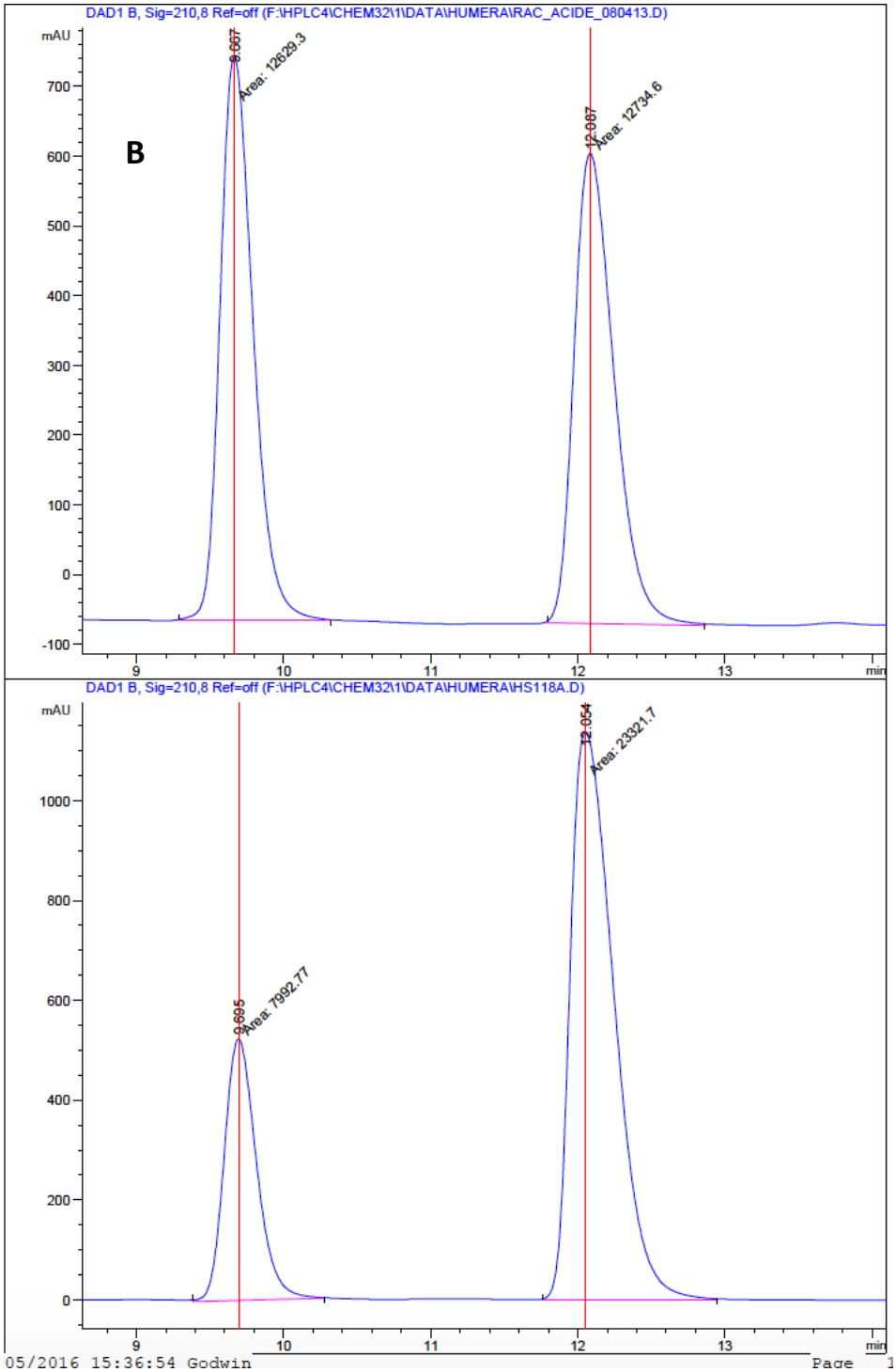

Figure 7: Chromatogram for Amidase-mediated conversion of amide **7** to acid **8**. [A] Top racemic starting material, bottom basic extract (remaining amide). [B] Top racemic acid, bottom acidic extract (product acid).

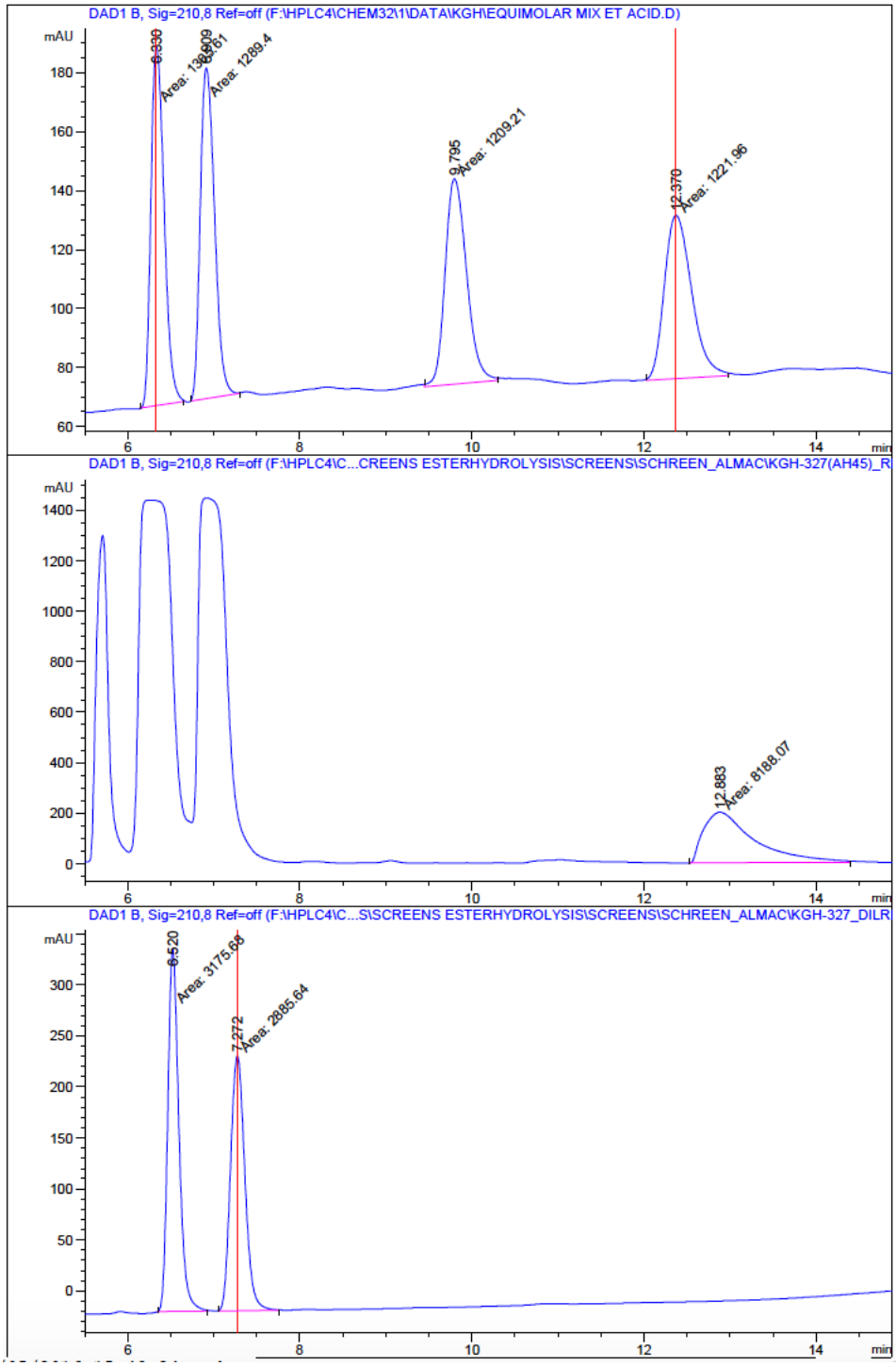

Figure 8: Chromatogram for Lipase-mediated conversion of ester **9** to acid **8**. Top racemic ester and acid, middle and bottom (same sample, diluted) reaction mixture.

1 H. Zhang, J. Liu, L. Zhang, L. Kong, H. Yao and H. Sun, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 3598–602.

2 C. Chen, Y. Fujimoto, G. Girdaukas and C. J. Sih, *J. Am. Chem. Soc*, 1982, **104**, 7294–7299.