Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

A rapid and efficient one-pot method for the reduction of *N*-protected α-amino acids to chiral α-amino aldehydes using CDI/DIBAL-H

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Supporting Information

General information

All commercially available reagents and solvents were purchased from Sigma-Aldrich, Alfa Aesar, ABCR, Fisher Scientific, Acros Organics, Roth or VWR, and were used without further purification except otherwise stated. When it was required, non-dry solvents were distilled before use. If reactions were performed under inert conditions, e.g. exclusion of water, oxygen or both, all experiments were carried out using established Schlenk techniques. Herein solvents were dried and/or degassed with common methods and afterwards stored under inert gas atmosphere (argon or N_2) over molecular sieves. In some cases, when explicitly mentioned, dry solvents were received from the mentioned suppliers. DCM (EtOH stabilized) was distilled first over P_4O_{10} to remove the stabilizer and then over CaH_2 under argon atmosphere and stored over 4 Å molecular sieves in an amber 1000 mL Schlenk bottle. THF was dried over Na under reflux and argon atmosphere until benzophenone indicated its dryness by turning into deep blue color. The dry THF was stored over 4 Å molecular sieves in an amber 1000 mL Schlenk bottle under argon atmosphere.

In general, when high vacuum was declared in experimental procedures, typically a vacuum of 10^{-2}-10^{-3} mbar was applied. All reactions were stirred with Teflon-coated magnetic stirring bars. Molecular sieves (Sigma Aldrich, beads with 8-12 mesh) were activated in a round-bottom flask with a gas-inlet adapter by heating them carefully in a heating mantle for approximately 12 h under high vacuum until complete dryness was obtained. These activated molecular sieves were stored at room temperature under argon atmosphere.

Temperatures were measured externally if not otherwise stated. When working at a temperature of 0 °C, an ice-water bath served as the cooling medium. Reactions, which were carried out at -78 °C were cooled by keeping the reaction vessel immersed in a properly sized Dewar vessel containing acetone/dry ice.

Analytical thin layer chromatography (TLC) was carried out on Merck TLC silica gel 60 F254 aluminium sheets and spots were visualized by UV light (λ = 254 and/or 366 nm) or by staining with iodide, cerium ammonium molybdate (2.0 g $Ce(SO_4)_2$, 50.0 g $(NH_4)_6Mo_7O_{24}$ and 50 mL conc. H_2SO_4 in 400 mL water) (CAM) or potassium permanganate (0.3 g $KMnO_4$, 20 g K_2CO_3, 5 mL 5 % aqueous NaOH in 300 mL H_2O)

followed by the development of the stains in the heat. Flash column chromatography was performed on silica gel 0.035-0.070 mm, 60 Å (Acros Organics). A 30 to 100 fold excess of silica gel was used with respect to the amount of dry crude product, depending on the separation problem. The dimensions of the column were selected in such a way that the required amount of silica gel formed a pad between 10 cm and 25 cm. The column was equilibrated first with the solvent or solvent mixture, and the crude product diluted with the eluent was applied onto the top of the silica pad. In case when the crude product was insoluble in the eluent, the sample was dissolved in an appropriate solvent (EtOAc or DCM), and the equal amount of diatomaceous earth was added, followed by removal of the solvent under reduced pressure and drying the sample in vacuo, which was then directly loaded onto the top of the silica pad. The mobile phase was forced through the column using a rubber bulb pump.

GC-MS analyses were carried out on an Agilent Technologies 7890A GC system equipped with a 5975C mass selective detector (inert MSD with Triple Axis Detector system, EI, 70 eV). Samples were injected by employing autosampler 7683B in a split mode 20/1 (inlet temperature: 280 °C; injection volume: 0.2 µL) and separated on an Agilent Technologies J&W GC HP-5MS capillary column (30 m x 0.2 mm x 0.25 µm) at a constant helium flow rate (He 5.0 Air Liquide, 1.085 mL/min, average velocity 41.6 cm/sec). A general gradient temperature method was used (initial temperature: 50 °C for 2 min, linear increase to 300 °C (40 °C/min), hold for 5 min, 1 min post-run at 300 °C, detecting range: 50.0-550.0 amu, solvent delay of 2.80 min).

GC-FID analyses for separation of enantiomers or diastereomers were carried out on an Agilent Technologies 6890N GC system equipped with a flame ionization detector (FID). Samples were injected by employing autosampler CTC Analytics CombiPAL in a split mode 5/1 (inlet temperature: 200 °C; injection volume: 1.0 µL) and separated on a Varian CP7503 CP-Chiralsil Dex CP capillary column (25.0 m x 320 µm x 0.25 µm) at a constant nitrogen flow rate (Nitrogen 5.0 Messer, 4.5 mL/min, average velocity 68 cm/sec). Two gradient temperature methods were used: “AMAL_GCPAL.M” (initial temperature: 80 °C for 5 min, linear increase to 150 °C (10 °C/min), hold for 18 min, 1 min post-run at 160 °C) and “AMAL_GCPAL_PHE_4.M” (initial temperature: 80 °C for 5 min, linear increase to 125 °C (10 °C/min), hold for 40 min, 1 min post-run at 160 °C) .

Analytical HPLC-MS analyses were performed on an Agilent Technologies 1200 Series system (G1379 Degasser, G1312 Binary Pump, G1367C HiP ALS SL Autosampler, G1330B FC/ALS Thermostat, G1316B TCC SL column compartment, G1365C MWD SL multiple wavelength detector (deuterium lamp, 190-400 nm)) equipped with a single quadrupole LCMS detector “6120 LC/MS” using electrospray ionization source (ESI in positive and negative mode). The analyses were carried out on an Agilent Poroshell 120 SB-C18 (100 x 3.0 mm, 2.7 µm) column equipped with a Merck LiChroCART® 4-4 pre-column. A general solvent gradient method was used (0-2.00 min: MeCN:H_2O = 10:90 (v/v), 2.00-6.00 min: linear increase to MeCN:H_2O = 40:60 (v/v), 6.00-12.00 min: holding of MeCN:H_2O = 40:60 (v/v), 12.00-16.00 min: linear increase to MeCN:H_2O = 95:5 (v/v), oven temperature: 40 °C, solvent flow: 0.700 mL/min).

Analytical HPLC analyses for separation of enantiomers were performed on an Agilent Technologies 1100 Series system (G1322A Degasser, G1311 Quaternary Pump, G1313A ALS Autosampler, G1316A Column Compartment, G1365B MWD multiple wavelength detector (deuterium lamp, 190-400 nm)). The analyses were carried out on a Daicel Chemical Technologies Chiralpak® AD-H (250 x 4.6 mm, 5.0 µm)

column. An isocratic method was used (0-30.00 min: heptane:2-propanol = 90:10 (v/v), oven temperature: 15 °C, solvent flow: 0.850 mL/min).

^{1}H-, ^{13}C-NMR spectra were recorded on a Bruker AVANCE III 300 spectrometer (^{1}H: 300.36 MHz; ^{13}C: 75.53 MHz). Chemical shifts were referenced to the residual proton and carbon signal of the deuterated solvent, respectively ($CDCl_3$: δ = 7.26 ppm (^{1}H), 77.16 ppm (^{13}C)). Signal multiplicities are abbreviated as s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quadruplet), p (pentet) and m (multiplet). Additionally, quaternary carbon atoms are designated as C_q. Deuterated solvents for nuclear resonance spectroscopy were purchased from Euriso-top®.

Optical rotations were measured in CH_2Cl_2, $CHCl_3$, EtOH and MeOH on a Perkin Elmer 341 polarimeter with a 10 cm cell. Concentration *c* given is in g/100 mL. Each optical rotation measurement was done five times and the mean value is reported.

Melting points were measured on a Mel-Temp® melting point apparatus (Electrothermal) with an integrated microscopical support in open capillary tubes and were not corrected. The temperature was measured with a mercury-in-glass thermometer.

High-resolution mass spectra were recorded using MALDI-TOF on a Micromass® MALDI micro MX™ spectrometer. Dithranol (1,8-dihydroxy-9,10-dihydroanthracen-9-one) or α-cyano-4-hydroxycinnamic acid served as matrix. The stated values are m/z.

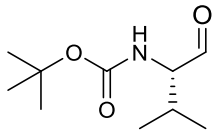
Purification of CDI (1,1´-carbonyldiimidazole)[1]

According to the note 8 in the procedure published by H. A. Staab and K. Wendel [1] an oven dried 250 mL two-neck round-bottom flask with a Schlenk adapter, a reflux condenser, a gas bubbler and a magnetic stirring bar, were purged with N_2. In this flask 25.0 g (154 mmol) CDI were suspended in 40 mL abs. THF and stirred. The mixture was heated to reflux in an oil bath and 20 mL abs. THF were added to facilitate the full dissolution. Stirring was stopped and the pale yellow solution was allowed to cool down to RT for 60 min. Crystallization was completed by cooling in an ice bath for 30 min. Subsequently, under nitrogen counter flow, the reflux condenser was removed and an inert atmosphere frit was mounted together with an additional receiving 250 mL two-neck round-bottom flask at the opposite end of the frit. White crystals were collected by filtration under inert atmosphere, washed with 15 mL of ice-cold abs. THF and dried *in vacuo*. 19.9 g (123 mmol, 80%) white crystalline solid were recovered and stored in a Schlenk flask under nitrogen atmosphere.

General procedure for one-pot conversion of *N*-protected α-amino acids to *N*-protected α-amino aldehydes

A 1000 mL two-neck round-bottom flask with a Schlenk adapter, a glass stopper and a magnetic stirring bar was heated, dried under vacuum and purged with N_2. 50.0 mmol (1.0 eq) protected amino acid were added and dissolved in 333 mL abs. dichloromethane. The solution was cooled to 0 °C (ice bath) and 8.918 g (55.0 mmol, 1.1 eq) 1,1'-carbonyldiimidazole (CDI) were added. A gas bubbler was mounted instead of the glass stopper to maintain a pressure relief. After stirring for 60 min the gas bubbler was removed and the colorless reaction solution was cooled to -78 °C (CO_2/acetone bath) for 15 min. A septum was mounted instead of the glass stopper while maintaining a gentle counter flow of N_2. Subsequently, 105 mL (105 mmol, 2.1 eq) DIBAL-H solution (1.0 M in toluene) were added dropwise with a syringe through the septum throughout 110 min. The reaction mixture was stirred at -78 °C until TLC indicated quantitative conversion (30–60 min). The reaction mixture was quenched by the addition of 335 mL EtOAc. The acetone bath was removed, the gas bubbler was mounted, and 222 mL tartaric acid solution (25 % in H_2O) were added to the mixture under vigorous stirring. The mixture was warmed up by immersing the vessel into a water bath at RT and stirred vigorously for 15 min. The stirring was stopped and the layers were separated. The aqueous phase was extracted with EtOAc (1 x 333 mL) and the combined organic extracts were washed with 1 M HCl (1 x 222 mL), 0.8 M $NaHCO_3$ (1 x 222 mL) and brine (1 x 222 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was frozen in liquid nitrogen and was allowed to reach room temperature under high vacuum. The freeze-thaw procedure was repeated two times. The crude product is used without further purification.

***tert*-Butyl (*S*)-(3-methyl-1-oxobutan-2-yl)carbamate (3a)[2]**



3a

This compound was synthesized according to the general procedure using 10.864 g (50.0 mmol, 1.0 eq) Boc-L-Val-OH. The colorless solution was treated with 8.918 g (55.0 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 105 mL (105 mmol, 2.1 eq) DIBAL-H. The mixture was stirred for 45 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 8.474 g (42.10 mmol, 84 %) of a viscous colorless liquid.

Yield: 8.474 g (42.10 mmol, 84 %), viscous colorless liquid.

$[\alpha]_D^{23}$ = + 78.6 ° (c = 1.07, CH_2Cl_2), lit. $[\alpha]_D^{20}$ = +82.1 ° (c = 1, CH_2Cl_2)[2].

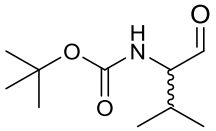
R_f = 0.61 (cyclohexane/ethyl acetate = 2:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.63 (s, 1H, C*H*O), 5.15-4.99 (m, 1H, N*H*), 4.33-4.15 (m, 1H, C*H*CHO), 2.37-2.14 (m, 1H, C*H*$(CH_3)_2$), 1.44 (s, 9H, $(CH_3)_3CO$), 1.02 (d, ^{3}J = 6.9 Hz, 3H, CH(CH_3)(CH_3)), 0.93 (d, ^{3}J = 7.0 Hz, 3H, CH(CH_3)(CH_3)).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 200.5 (s, 1C, *C*HO), 156.0 (s, 1C, C=O), 80.1 (s, 1C, Me_3C), 64.8 (s, 1C), 29.2 (s, 1C), 28.4 (s, 3C), 19.2 (s, 1C), 17.7 (s, 1C).

GC-FID (CP-Chiralsil Dex): t_R (*(S)*-**3a**) = 9.0 min, 100%; t_R (*(R)*-**3a**) = 9.2 min, no abundance detected; ee > 99%.

Racemic *tert*-butyl (3-methyl-1-oxobutan-2-yl)carbamate (rac-3a)



***rac*-3a**

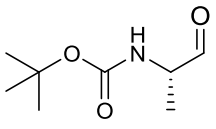
This compound was synthesized according to the general procedure using 43 mg (0.20 mmol, 1.0 eq) Boc-DL-Val-OH. The colorless solution was treated with 36 mg (0.22 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 0.42 mL (0.42 mmol, 2.1 eq) DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 33 mg (0.16 mmol, 80 %) of a colorless liquid.

Yield: 33 mg (0.16 mmol, 80 %), colorless liquid.

R_f = 0.61 (cyclohexane/ethyl acetate = 2:1 (v/v); staining: $KMnO_4$).

GC-FID (CP-Chiralsil Dex CP): t_R (*(S)*-**3a**) = 9.0 min; t_R (*(R)*-**3a**) = 9.2 min.

***tert*-Butyl (*S*)-(1-oxopropan-2-yl)carbamate (3b)[3,4]**



3b

This compound was synthesized according to the general procedure using 9.460 g (50.0 mmol, 1.0 eq) Boc-L-Ala-OH. The colorless solution was treated with 8.918 g (55.0 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 105 mL (105 mmol, 2.1 eq) DIBAL-H. The mixture was stirred for 45 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 7.510 g (43.40 mmol, 87 %) of a white solid.

Yield: 7.510 g (43.40 mmol, 87 %), white solid.

m.p. = 81–84 °C, lit. 90–92 °C [3] and 70 °C. [4]

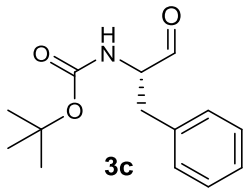
$[\alpha]_D^{23}$ = -39.0 ° (c = 1.0, MeOH), lit. $[\alpha]_D^{20}$ = -40.9 ° (c = 1, MeOH) [3] and $[\alpha]_D^{undisclosed}$ = -39.1 ° (c = 0.69, MeOH).[4]

R_f = 0.38 (cyclohexane/ethyl acetate = 2:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.55 (s, 1H, C*H*O), 5.11-4.99 (m, 1H, N*H*), 4.30-4.12 (m, 1H, C*H*CHO), 1.44 (s, 9H, (CH_3)$_3$CO), 1.32 (d, ^3J = 7.4 Hz, 3H, CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.9 (s, 1C, *C*HO), 155.4 (s, 1C*,* C=O), 80.2 (s, 1C, Me_3C), 55.7 (s, 1C), 28.4 (s, 3C), 15.0 (s, 1C).

tert-Butyl (*S*)-(1-oxo-3-phenylpropan-2-yl)carbamate (3c)[5]



3c

This compound was synthesized according to the general procedure using 53 mg (0.20 mmol, 1.0 eq) Boc-L-Phe-OH. The colorless solution was treated with 36 mg (0.22 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 0.42 mL (0.42 mmol, 2.1 eq) DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 48 mg (0.19 mmol, 96 %) of a white solid.

Yield: 48 mg (0.19 mmol, 96 %), white solid.

m.p. = 80–84 °C, lit. 82 °C. [5]

$[\alpha]_D^{23}$ = +39.3 ° (c = 1.02, CH_2Cl_2), $[\alpha]_D^{undisclosed}$ = +41.6 ° (c = 1.1, CH_2Cl_2). [5]

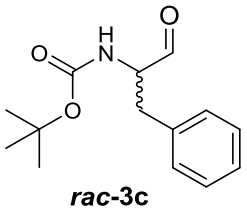
R_f = 0.26 (cyclohexane/ethyl acetate = 4:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.62 (s, 1H, C*H*O), 7.40–7.06 (m, 5H, Ar–*H*), 5.15–4.97 (m, 1H, N*H*), 4.50–4.32 (m, 1H, C*H*CHO), 3.22–2.98 (m, 2H, CH_2), 1.42 (s, 9H, (CH_3)$_3$CO).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.5 (s, 1C, *C*HO), missing carbamate signal (155 ppm), 135.9 (s, 1C, C_q), 129.5 (s, 2C), 128.9 (s, 2C), 127.2 (s, 1C), 80.4 (s, 1C, Me_3C), 60.8 (s, 1C), 35.6 (s, 1C), 28.4 (s, 3C).

GC-FID (CP-Chiralsil Dex): t_R (*(S)*-**3c**) = 38.2 min, 99.51%; t_R (*(R)*-**3c**) = 38.2 min, 0.49%; ee > 99%.

Racemic *tert*-butyl (1-oxo-3-phenylpropan-2-yl)carbamate (*rac*-3c)



***rac*-3c**

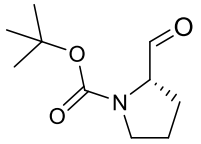
This compound was synthesized according to the general procedure using 53 mg (0.20 mmol, 1.0 eq) Boc-DL-Phe-OH. The colorless solution was treated with 36 mg (0.22 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 0.42 mL (0.42 mmol, 2.1 eq) DIBAL-H. The mixture was stirred for 30 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 46 mg (0.18 mmol, 90 %) of a white amorphous paste.

Yield: 48 mg (0.19 mmol, 96 %), white amorphous paste.

R_f = 0.26 (cyclohexane/ethyl acetate = 4:1 (v/v); staining: $KMnO_4$).

GC-FID (CP-Chiralsil Dex): t_R (*(S)*-**3c**) = 38.3 min; t_R (*(R)*-**3c**) = 39.5 min.

***tert*-Butyl (*S*)-2-formylpyrrolidine-1-carboxylate (3d)[6]**



3d

This compound was synthesized according to the general procedure using 86 mg (0.40 mmol, 1.0 eq) Boc-L-Pro-OH. The colorless solution was treated with 71 mg (0.44 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 0.84 mL (0.84 mmol, 2.1 eq) DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 77 mg (0.39 mmol, 97 %) of a viscous colorless liquid.

Yield: 77 mg (0.39 mmol, 97 %), colorless liquid.

$[\alpha]_D^{23}$ = -97.9 ° (c = 1.02, $CHCl_3$), lit. $[\alpha]_D^{24}$ = -96.1° (c = 0.6, $CHCl_3$).[6]

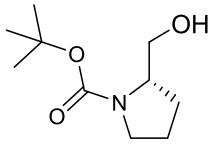
R_f = 0.20 (cyclohexane/ethyl acetate = 4:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$, mixture of two rotamers) δ = 9.54 and 9.44 (s, 1H, C*H*O), 4.24–4.15 and 4.10–3.99 (m, 1H, C*H*CHO), 3.62–3.38 (m, 2H, NCH_2), 2.21–1.73 (m, 4H, CH_2CH_2CH), 1.46 and 1.41 (s, 9H, (CH_3)$_3$CO).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 200.7 and 200.5 (s, 1C, *C*HO), 155.0 and 154.1 (s, 1C, C=O), 80.8 and 80.3 (s, 1C, Me_3C), 65.1 and 65.0 (s, 1C), 47.0 and 46.9 (s, 1C), 28.5 and 28.4 (s, 3C), 28.1 and 26.8 (s, 1C), 24.7 and 24.1 (s, 1C).

Enantiomeric excess was determined indirectly by conversion of freshly isolated material into alcohol **8d**.

tert-Butyl (2*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (8d)[7]



8d

In a 5 mL glass vial equipped with a Teflon®-coated magnetic stirring bar 59 mg (0.27 mmol, 1.0 eq) freshly prepared compound **3d** were dissolved in 4.0 mL of MeOH, stirred and cooled to 0 °C in an ice bath. 17 mg (0.44 mmol, 1.1 eq) $NaBH_4$ were added to the colorless solution at 0 °C, the vial was covered with aluminium foil to facilitate a pressure relief. The mixture was stirred vigorously for 20 min at 0 °C, when TLC indicated full conversion. The reaction was quenched by the addition of 200 µL acetone and stirred for 5 min at RT. The solvents were removed under reduced pressure and the residue was partitioned between 3.0 mL EtOAc and 1.0 mL $NaHCO_3$ (sat). The organic phase was concentrated under reduced pressure and purified by flash chromatography (SiO_2, cyclohexane/EtOAc 2:1) to yield 50 mg (0.25 mmol, 93%) of a white solid.

Yield: 50 mg (0.25 mmol, 93%, 2 steps), white solid.

m.p. = 57–60 °C, lit. 58–59 °C.[7]

$[\alpha]_D^{23}$ = -55.7 ° (c = 0.83, $CHCl_3$), lit. $[\alpha]_D^{26}$ = -52.7 ° (c = 1.05, $CHCl_3$).[7]

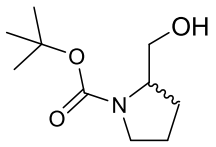
R_f = 0.42 (cyclohexane/ethyl acetate = 1:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.75 (br s, 1H, O*H*), 4.01–3.81 (m, 1H, CH_2CHN), 3.68–3.49 (m, 2H, CH_2O), 3.49–3.36 (m, 1H, NCH*H*), 3.35–3.21 (m, 1H, NC*H*H), 2.07–1.49 (m, 4H, $NCH_2CH_2CH_2$), 1.45 (s, 9H, $((CH_3)_3C$).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.3 (s, 1C, C=O), 80.3 (s, 1C, $(CH_3)_3C$), 67.8 (s, 1C), 60.3 (s, 1C), 47.7 (s, 1C), 28.8 (s, 1C), 28.6 (s, 3C), 24.4 (s, 1C).

HPLC (Daicel Chemical Technologies Chiralpak® AD-H): t_R (*(R)*-**8d**) = 7.2 min, no abundance detected; t_R (*(S)*-**8d**) = 8.4 min, 100%; ee >99%.

Racemic *tert*-butyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (*rac*-8d)



***rac*-8d**

The aldehyde intermediate was synthesized according to the general procedure using 86 mg (0.400 mmol, 1.0 eq) Boc-DL-Pro-OH. The colorless solution was treated with 71 mg (0.440 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 0.84 mL (0.84 mmol, 2.1 eq) 1 M DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying over Na_2SO_4 provided 57 mg (0.29 mmol, 72%) of ***rac*-3d** as colorless oil.

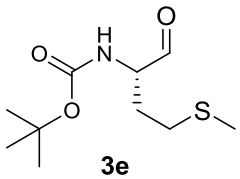
In a 5 mL glass vial equipped with a Teflon-coated magnetic stirring bar 57 mg (0.29 mmol, 1.0 eq) freshly prepared ***rac*-3d** were dissolved in 4.0 mL of MeOH, stirred and cooled to 0 °C in an ice bath. 17 mg (0.44 mmol, 1.1 eq) $NaBH_4$ were added to the colorless solution at 0 °C, the vial was covered with aluminium foil to facilitate a pressure relief. The mixture was stirred vigorously for 20 min at 0 °C, when TLC indicated full conversion. The reaction was quenched by the addition of 200 µL of acetone and stirred for 5 min at RT. Solvents were removed under reduced pressure and the residue was partitioned between 3.0 mL EtOAc and 1.0 mL $NaHCO_3$ (sat). The organic extract was concentrated under reduced pressure and purified via flash chromatography (SiO_2, cyclohexane/EtOAc 2:1) to yield 43 mg (0.21 mmol, 53%, 2 steps) of a colorless oil.

Yield: 43 mg (0.21 mmol, 53%, 2 steps), colorless oil.

R_f = 0.42 (cyclohexane/ethyl acetate = 1:1 (v/v); staining: $KMnO_4$).

HPLC (Daicel Chemical Technologies Chiralpak® AD-H): t_R (*(R)*-**8d**) = 7.2 min; t_R (*(S)*-**8d**) = 8.4 min.

***tert*-Butyl (*S*)-(4-(methylthio)-1-oxobutan-2-yl)carbamate (3e)[8]**



3e

This compound was synthesized according to the general procedure using 100 mg (0.400 mmol, 1.0 eq) Boc-L-Met-OH. The colorless solution was treated with 71 mg (0.44 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 0.84 mL (0.84 mmol, 2.1 eq) 1 M DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 86 mg (0.37 mmol, 96 %) of colorless oil.

Yield: 86 mg (0.37 mmol, 92 %), colorless oil.

$[\alpha]_D^{23}$ = +27.0 ° (c = 1.74, CH_2Cl_2), lit. $[\alpha]_D^{20}$ = +27.8 ° (c = 1, CH_2Cl_2).[8]

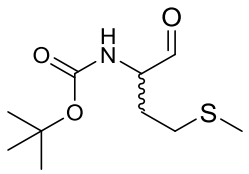
R_f = 0.26 (cyclohexane/ethyl acetate = 4:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.63 (s, 1H, C*H*O), 5.29–5.13 (m, 1H, N*H*), 4.37–4.22 (m, 1H, C*H*CHO), 2.62–2.46 (m, 2H, SCH_2), 2.31–2.13 (m, 1H, NCHC*H*), 2.07 (s, 3H), 2.00–1.84 (m, 1H, NCHC*H*) 1.44 (s, 9H, (CH_3)$_3$CO).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.2 (s, 1C, *C*HO), 155.7 (s, 1C, C=O), 80.4 (s, 1C, Me_3C), 59.2 (s, 1C), 30.0 (s, 1C), 28.9 (s, 1C), 28.4 (s, 3C), 15.5 (s, 1C).

GC-FID (CP-Chiralsil Dex): t_R (*(S)*-**3c**) = 14.2 min, 100%; t_R (*(R)*-**3c**) = 14.4 min, no abundance detected; ee >99%.

Racemic *tert*-butyl (4-(methylthio)-1-oxobutan-2-yl)carbamate (*rac*-3e)



***rac*-3e**

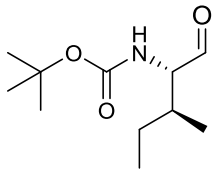
This compound was synthesized by mixing 50 mg (0.20 mmol, 0.5 eq) Boc-L-Met-OH and 50 mg (0.20 mmol, 0.5 eq) Boc-D-Met-OH, and converting the mixture according to the general procedure. The colorless solution was treated with 71 mg (0.44 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 0.84 mL (0.84 mmol, 2.1 eq) DIBAL-H. The mixture was stirred for 30 min at -78 °C until TLC indicated full conversion. Extractive workup and drying over Na_2SO_4 provided 89 mg (0.38 mmol, 95 %) of a colorless oil.

Yield: 89 mg (0.38 mmol, 95 %), colorless oil.

R_f = 0.26 (cyclohexane/ethyl acetate = 4:1 (v/v); staining: $KMnO_4$).

GC-FID (CP-Chiralsil Dex): t_R (*(S)*-**3c**) = 14.2 min; t_R (*(R)*-**3c**) = 14.4 min.

tert-Butyl ((*2S,3S*)-3-methyl-1-oxopentan-2-yl)carbamate (3f)[5]



3f

This compound was synthesized according to the general procedure using 185 mg (0.800 mmol, 1.0 eq) Boc-L-Ile-OH. The colorless solution was treated with 143 mg (0.880 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 1.68 mL (1.68 mmol, 2.1 eq) 1 M DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 156 mg (0.725 mmol, 91 %) of colorless turbid oil.

Yield: 156 mg (0.725 mmol, 91 %), colorless turbid oil.

$[\alpha]_D^{23}$ = +87.1 ° (c = 0.93, CH_2Cl_2), lit. $[\alpha]_D^{undisclosed}$ = +85.0 °.[5]

R_f = 0.39 (cyclohexane/ethyl acetate = 4:1 (v/v); staining: $KMnO_4$).

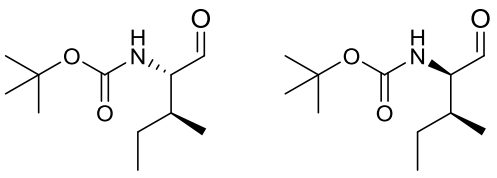
^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.64 (s, 1H, C*H*O), 5.23–4.97 (m, 1H, N*H*), 4.36–4.11 (m, 1H, C*H*CHO), 2.08–1.86 (m, 1H), 1.55–1.33 (m, 10H, (CH_3)$_3$CO and CH_3C*H*H), 1.32–1.12 (m, 1H, CH_3CH*H*), 1.03–0.79 (m, 6H, 2CH_3).

^{13}C APT NMR (75 MHz, $CDCl_3$) δ = 200.8 (s, 1C, *C*HO), 155.9 (s, 1C, C=O), 80.0 (s, 1C, Me_3C), 64.3 (s, 1C), 36.5 (s, 1C), 28.4 (s, 3C), 25.4 (s, 1C), 15.8 (s, 1C), 12.00 (s, 1C).

GC-EI-MS: t_R (*(2S,3S)*-**6**) = 6.09 min; *m/z* = 57 (100%), 69 (9%), 86 (47%), 112 (3%), 130 (29%), 142 (2%), 186 (2%).

GC-FID (CP-Chiralsil Dex): t_R (*(2R,3S)*-**3f**) = 10.0 min, 0.46%; t_R (*(2S,3S)*-**3f**) = 10.1 min, 99.54%; de = >99%.

Partial epimerization of *tert*-butyl ((*2S,3S*)-3-methyl-1-oxopentan-2-yl)carbamate ((*2S,3S*)-3f) to *tert*-butyl ((*2R,3S*)-3-methyl-1-oxopentan-2-yl)carbamate ((*2R,3S*)-3f)



***(2S,3S)*-3f** ***(2R,3S)*-3f**

In a 10 mL Schlenk tube 50 mg (0.23 mmol) crude freshly prepared **3f** were dissolved in 2.0 mL cyclohexane/EtOAc 4:1. The solution was vigorously stirred with a Teflon-coated magnetic stirring bar

and 1.0 g of silica was added. The mixture was immediately purged by three cycles of alternate evacuation to the point of gentle boiling and filling with nitrogen atmosphere. The colorless gel-like mixture was stirred for 45h at 24 °C. Subsequently, the mixture was concentrated and dried under reduced pressure. Filtration through a short pad of silica (SiO_2, cyclohexane/EtOAc 6:1) provided 47 mg (0.22 mmol, 96%) of a colorless oil.

Yield: 47 mg (0.22 mmol, 96%), colorless oil.

$[\alpha]_D^{23}$ = +26.1 ° (c = 1.40, $CHCl_3$).

R_f = 0.39 (cyclohexane/ethyl acetate = 4:1 (v/v); staining: $KMnO_4$).

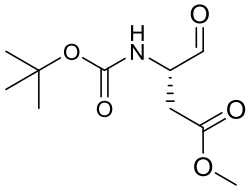
^{1}H NMR (300 MHz, $CDCl_3$, *(2R,3S)*-epimer, based on HSQC) δ = 9.60 (s, 1H, C*H*O), 5.10–4.92 (m, 1H, N*H*), 4.41–4.31 (m, 1H, C*H*CHO), 2.10–1.86 (m, 1H), 1.55–1.36 (m, 10H, (CH_3)$_3$CO and CH_3C*H*H), 1.34–1.14 (m, 1H, CH_3CH*H*), 1.00–0.79 (m, 6H, 2CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, *(2R,3S)*-epimer, based on HSQC) δ = 200.8 (s, 1C, *C*HO), 156.0 (s, 1C, C=O), 80.1 (s, 1C, Me_3C), 63.3 (s, 1C), 35.3 (s, 1C), 28.4 (s, 3C), 26.4 (s, 1C), 14.6 (s, 1C), 12.00 (s, 1C).

GC-EI-MS:
t_R (*(2R,3S)*-**3f**) = 6.04 min, 26.5%, *m/z* = 57 (100%), 69 (10%), 86 (56%), 112 (4%), 130 (36%), 142 (3%), 186 (4%);
t_R (*(2S,3S)*-**3f**) = 6.08 min, 73.5%; *m/z* = 57 (100%), 69 (10%), 86 (57%), 112 (3%), 130 (36%), 142 (3%), 186 (4%).

GC-FID (CP-Chiralsil Dex): t_R (*(2R,3S)*-**3f**) = 10.0 min, 31.58%; t_R (*(2S,3S)*-**3f**) = 10.1 min, 68.42%.

Methyl (*S*)-3-((tert-butoxycarbonyl)amino)-4-oxobutanoate (3g)[8]



3g

This compound was synthesized according to the general procedure using 356 mg (1.44 mmol, 1.0 eq) Boc-L-Asp(OMe)-OH. The colorless solution was treated with 257 mg (1.58 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 3.02 mL (3.02 mmol, 2.1 eq) 1 M DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 295 mg of colorless turbid oil. Purification via flash chromatography (SiO_2, cyclohexane/EtOAc 4:1) furnished 206 mg (0.893 mmol, 62 %) of the desired aldehyde as a colorless oil.

Yield: 206 mg (0.893 mmol, 62 %), colorless oil.

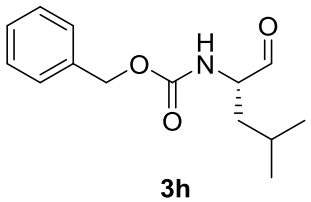
$[\alpha]_D^{23}$ = -16.9 ° (c = 0.92, $CHCl_3$).

R_f = 0.28 (cyclohexane/ethyl acetate = 2:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.64 (s, 1H, C*H*O), 5.72–5.52 (m, 1H, N*H*), 4.44–4.25 (m, 1H, C*H*CHO), 3.69 (s, 3H), 3.08–2.91 (m, 1H, COC*H*H), 2.90–2.74 (m, 1H, COCH*H*), 1.45 (s, 9H, $(CH_3)_3CO$).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.3 (s, 1C, *C*HO), 171.8 (s, 1C, C=O), 155.6 (s, 1C, C=O), 80.7 (s, 1C, Me_3C), 56.1 (s, 1C), 52.3 (s, 1C), 34.5 (s, 1C), 28.4 (s, 3C).

Benzyl (*S*)-(4-methyl-1-oxopentan-2-yl)carbamate (3h)[9]



3h

This compound was synthesized according to the general procedure using 212 mg (0.800 mmol, 1.0 eq) Boc-L-Leu-OH. The colorless solution was treated with 143 mg (0.880 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 1.68 mL (1.68 mmol, 2.1 eq) 1 M DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 174 mg (0.698 mmol, 87 %) of colorless oil.

Yield: 174 mg (0.698 mmol, 87 %), colorless oil.

$[\alpha]_D^{23}$ = -41.7 ° (c = 1.60, MeOH), $[\alpha]_D^{25}$ = -22.8 ° (c = 0.74, MeOH).[9]

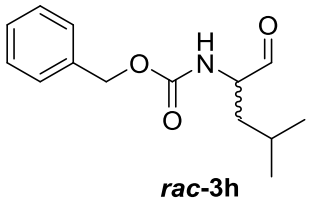
R_f = 0.58 (cyclohexane/ethyl acetate = 1:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$, based on HSQC) δ = 9.59 (s, 1H, C*H*O), 7.47–7.20 (m, 5H, Ar–*H*), 5.30–5.16 (m, 1H, N*H*), 5.12 (s, 2H), 4.41–4.25 (m, 1H, C*H*CHO), 1.87–1.53 (m, 2H, $(CH_3)_2CH$ and NCHC*H*H), 1.51–1.30 (m, 1H, NCHCH*H*), 1.05–0.77 (m, 6H, $2CH_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.8 (s, 1C, *C*HO), 156.3 (s, 1C, C=O), 136.3 (s, 1C, C_q), 128.7 (s, 2C), 128.4 (s, 1C), 128.2 (s, 2C), 67.3 (s, 1C), 59.0 (s, 1C), 38.3 (s, 1C), 24.8 (s, 1C), 23.2 (s, 1C), 22.0 (s, 1C).

GC-FID (CP-Chiralsil Dex): t_R (*(S)*-**3h**) = 24.5 min, 99.24%; t_R (*(R)*-**3h**) = 25.0 min, 0.76%; ee >98%.

Racemic benzyl (4-methyl-1-oxopentan-2-yl)carbamate (*rac*-3h)



***rac*-3h**

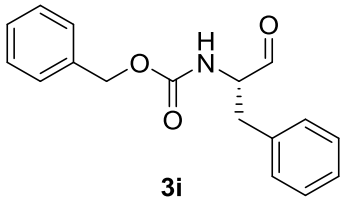
This compound was synthesized according to the general procedure using 53 mg (0.20 mmol, 1.0 eq) Cbz-DL-Leu-OH. The colorless solution was treated with 36 mg (0.22 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 0.42 mL (0.42 mmol, 2.1 eq) 1 M DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 43 mg (0.17 mmol, 85 %) of colorless oil.

Yield: 43 mg (0.17 mmol, 85 %), colorless oil.

R_f = 0.58 (cyclohexane/ethyl acetate = 1:1 (v/v); staining: $KMnO_4$).

GC-FID (CP-Chiralsil Dex): t_R (*(S)*-**3h**) = 24.5 min, t_R (*(R)*-**3h**) = 25.0 min.

Benzyl (*S*)-(1-oxo-3-phenylpropan-2-yl)carbamate (3i)[3]



3i

This compound was synthesized according to the general procedure using 239 mg (0.800 mmol, 1.0 eq) Cbz-L-Phe-OH. The colorless solution was treated with 143 mg (0.880 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 1.68 mL (1.68 mmol, 2.1 eq) of 1 M DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 225 mg (0.794 mmol, 99 %) of white solid.

Yield: 225 mg (0.794 mmol, 99 %), white solid.

m.p. = 76–79 °C, lit. 77–79 °C.[3]

$[\alpha]_D^{23}$ = +43.7 ° (c = 0.56, CH_2Cl_2), lit. $[\alpha]_D^{20}$ = +44.5 ° (c = 1, CH_2Cl_2).[3]

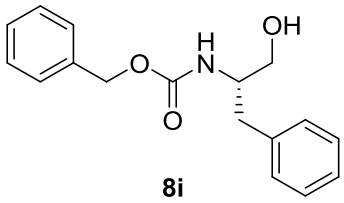
R_f = 0.15 (cyclohexane/ethyl acetate = 4:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.63 (s, 1H, C*H*O), 7.44–7.02 (m, 10H, Ar–*H*), 5.39–5.22 (m, 1H, N*H*), 5.11 (s, 2H, CH_2O), 4.59–4.43 (m, 1H, C*H*CHO), 3.13 (d, ^3J = 6.3 Hz, 2H, CH_2).

^{13}C APT NMR (75 MHz, $CDCl_3$) δ = 199.0 (s, 1C, *C*HO), 156.0 (s, 1C, C=O), 136.2 (s, 1C, C_q), 135.5 (s, 1C, C_q), 129.4 (s, 2C), 129.0 (s, 2C), 128.7 (s, 1C), 128.4 (s, 1C), 128.3 (s, 2C), 127.3 (s, 1C), 67.3 (s, 1C), 61.2 (s, 1C), 35.5 (s, 1C).

Enantiomeric excess was determined indirectly by conversion of freshly isolated material into alcohol **8i**.

Benzyl (*S*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate (8i)[10,11]



8i

In a 5 mL glass vial equipped with a Teflon®-coated magnetic stirring bar 42 mg (0.15 mmol, 1.0 eq) freshly prepared compound **3i** were dissolved in 1.5 mL of MeOH, stirred and cooled to 0 °C in an ice bath. 27 mg (0.17 mmol, 1.1 eq) $NaBH_4$ were added to the colorless solution at 0 °C, the vial was covered with aluminium foil to facilitate a pressure relief. The mixture was stirred vigorously for 20 min at 0 °C, when TLC indicated full conversion. The reaction was quenched by the addition of 200 µL acetone and stirred for 5 min at RT. The solvents were removed under reduced pressure and the residue was partitioned between 3.0 mL EtOAc and 1.0 mL $NaHCO_3$ (sat). The organic phase was concentrated under reduced pressure and purified by flash chromatography (SiO_2, cyclohexane/EtOAc 2:1) to yield 38 mg (0.13 mmol, 86%) of a white solid.

Yield: 38 mg (0.13 mmol, 86%), white solid.

m.p. = 88–90 °C, lit. 90–91 °C. [11]

$[\alpha]_D^{23}$ = -23.2 ° (c = 0.69, $CHCl_3$), lit. $[\alpha]_D^{19}$ = -28.5 ° (c = 1.0, $CHCl_3$). [10]

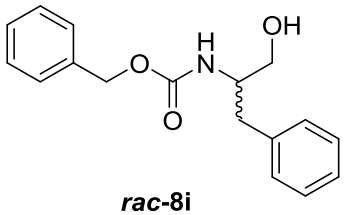
R_f = 0.37 (cyclohexane/ethyl acetate = 1:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.42–7.09 (m, 10H, Ar–*H*), 5.06 (s, 2H, CH_2OCO), 5.06–4.88 (m, 1H, N*H*), 4.02–3.84 (m, 1H, C*H*CH_2O), 3.67 (dd, ^2J = 10.5 Hz, ^3J = 2.7 Hz, 2H, NCHCH*H*), 3.56 (dd, ^2J = 10.5 Hz, ^3J = 4.4 Hz, 2H, NCHC*H*H), 2.85 (d, ^3J = 7.0 Hz, 2H, CH_2OH), 2.08 (s, 1H, O*H*).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 156.6 (s, 1C, C=O), 137.7 (s, 1C, C_q), 136.5 (s, 1C, C_q), 129.4 (s, 2C), 128.8 (s, 2C), 128.7 (s, 2C), 128.3 (s, 1C), 128.2 (s, 2C), 126.8 (s, 1C), 67.0 (s, 1C), 64.1 (s, 1C), 54.3 (s, 1C), 37.5 (s, 1C).

HPLC (Daicel Chemical Technologies Chiralpak® AD-H): t_R (*(S)*-**8i**) = 17.2 min, 98.56%; t_R (*(R)*-**8i**) = 21.0 min, 1.44%; ee > 97%.

Racemic benzyl (1-hydroxy-3-phenylpropan-2-yl)carbamate (*rac*-8i)



***rac*-8i**

The aldehyde intermediate was synthesized according to the general procedure using 60 mg (0.200 mmol, 1.0 eq) Cbz-DL-Phe-OH. The colorless solution was treated with 36 mg (0.220 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 0.42 mL (0.42 mmol, 2.1 eq) 1 M DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 53 mg (0.19 mmol, 94%) of ***rac*-3i** as colorless oil.

In a 5 mL glass vial equipped with a Teflon-coated magnetic stirring bar 42 mg (0.15 mmol, 1.0 eq) freshly prepared ***rac*-3i** were dissolved in 1.5 mL of MeOH, stirred and cooled to 0 °C in an ice bath. 27 mg (0.17 mmol, 1.1 eq) $NaBH_4$ were added to the colorless solution at 0 °C, the vial was covered with aluminium foil to facilitate a pressure relief. The mixture was stirred vigorously for 20 min at 0 °C, when TLC indicated full conversion. The reaction was quenched by the addition of 200 µL of acetone and stirred for 5 min at RT. Solvents were removed under reduced pressure and the residue was partitioned between 3.0 mL EtOAc and 1.0 mL $NaHCO_3$ (sat). The organic extract was concentrated under reduced pressure and purified via flash chromatography (SiO_2, cyclohexane/EtOAc 2:1) to yield 37 mg (0.13 mmol, 81%, 2 steps) of a white solid.

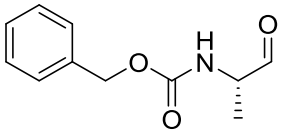
Yield: 37 mg (0.13 mmol, 81%, 2 steps), white solid.

m.p. = 86–89 °C

R_f = 0.37 (cyclohexane/ethyl acetate = 1:1 (v/v); staining: $KMnO_4$).

HPLC (Daicel Chemical Technologies Chiralpak® AD-H): t_R (*(S)*-**8i**) = 17.3 min; t_R (*(R)*-**8i**) = 22.0 min.

Benzyl (*S*)-(1-oxopropan-2-yl)carbamate (3j)[12]



3j

This compound was synthesized according to the general procedure using 179 mg (0.800 mmol, 1.0 eq) Cbz-L-Ala-OH. The colorless solution was treated with 143 mg (0.880 mmol, 1.1 eq) CDI at 0 °C for 60

min, and subsequently, dropwise with 1.68 mL (1.68 mmol, 2.1 eq) 1 M DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 156 mg (0.753 mmol, 94 %) of colorless oil.

Yield: 156 mg (0.753 mmol, 94 %), colorless oil.

$[\alpha]_D^{23}$ = +10.4 ° (c = 1.17, CH_2Cl_2), lit. $[\alpha]_D^{23}$ = +9.9 ° (c = 0.75, CH_2Cl_2). [12]

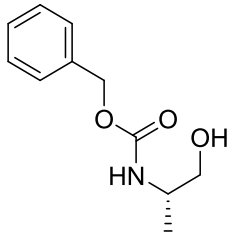
R_f = 0.12 (cyclohexane/ethyl acetate = 4:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.54 (s, 1H, C*H*O), 7.43–7.21 (m, 5H, Ar–*H*), 5.59–5.39 (m, 1H, N*H*), 5.11 (s, 2H, CH_2O), 4.38–4.20 (m, 1H, C*H*CHO), 1.42–1.24 (m, 3H, CH_3).

^{13}C APT NMR (75 MHz, $CDCl_3$) δ = 199.2 (s, 1C, *C*HO), 156.0 (s, 1C, C=O), 136.2 (s, 1C, C_q), 128.7 (s, 2C), 128.4 (s, 1C), 128.2 (s, 2C), 67.2 (s, 1C), 56.0 (s, 1C), 14.9 (s, 1C).

Enantiomeric excess was determined indirectly by conversion of freshly isolated material into alcohol **8j**.

Benzyl *N*-[(2*S*)-1-hydroxypropan-2-yl]carbamate (8j)[13]



8j

In a 5 mL glass vial equipped with a Teflon®-coated magnetic stirring bar 81 mg (0.39 mmol, 1.0 eq) freshly prepared compound **3j** were dissolved in 4.0 mL of MeOH, stirred and cooled to 0 °C in an ice bath. 17 mg (0.44 mmol, 1.1 eq) $NaBH_4$ were added to the colorless solution at 0 °C, the vial was covered with aluminium foil to facilitate a pressure relief. The mixture was stirred vigorously for 20 min at 0 °C, when TLC indicated full conversion. The reaction was quenched by the addition of 200 µL acetone and stirred for 5 min at RT. The solvents were removed under reduced pressure and the residue was partitioned between 3.0 mL EtOAc and 1.0 mL $NaHCO_3$ (sat). The organic phase was concentrated under reduced pressure and purified via flash chromatography (SiO_2, cyclohexane/EtOAc 2:1) to yield 75 mg (0.36 mmol, 92%) of a colorless oil.

Yield: 50 mg (0.25 mmol, 92%), colorless oil.

$[\alpha]_D^{23}$ = -10.7 ° (c = 0.55, $CHCl_3$), lit. $[\alpha]_D^{22}$ = -6.53 ° (c = 0.95, $CHCl_3$)[13].

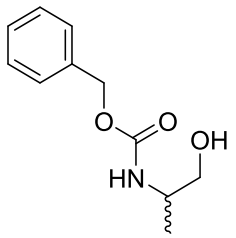
R_f = 0.30 (cyclohexane/ethyl acetate = 1:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$, based on HSQC) δ = 7.44–7.21 (m, 5H, Ar–*H*), 5.09 (s, 2H, CH_2OCO), 5.03–4.89 (m, 1H, N*H*), 3.91–3.75 (m, 1H, C*H*CH_2O), 3.65 (dd, ^{2}J = 10.7 Hz, ^{3}J = 2.8 Hz, 2H, NCHCH*H*), 3.51 (dd, ^{2}J = 10.7 Hz, ^{3}J = 5.7 Hz, 2H, NCHC*H*H), 2.57 (s, 1H, O*H*), 1.16 (d, ^{3}J = 6.8 Hz, 3H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, based on HSQC) δ = 156.7 (s, 1C, C=O), 136.5 (s, 1C, C_q), 128.7 (s, 2C), 128.3 (s, 1C), 128.2 (s, 2C), 67.0 (s, 2C, *C*H_2CO_2 and *C*H_2OH), 49.1 (s, 1C), 17.4 (s, 1C).

HPLC (Daicel Chemical Technologies Chiralpak® AD-H): t_R (*(S)*-**8j**) = 12.3 min, 100%; t_R (*(R)*-**8j**) = 15.6 min, no abundance detected; ee >99%.

Racemic benzyl *N*-[1-hydroxypropan-2-yl]carbamate (*rac*-8j)



***rac*-8j**

The aldehyde intermediate was synthesized according to the general procedure using 45 mg (0.20 mmol, 1.0 eq) Cbz-DL-Ala-OH. The colorless solution was treated with 36 mg (0.22 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 0.42 mL (0.42 mmol, 2.1 eq) 1 M DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 29 mg (0.14 mmol, 70%) of ***rac*-8j** as colorless oil.

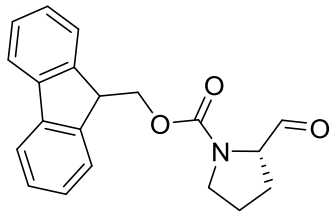
In a 5 mL glass vial equipped with a Teflon-coated magnetic stirring bar 29 mg (0.14 mmol, 1.0 eq) freshly prepared ***rac*-8j** were dissolved in 2.0 mL of MeOH, stirred and cooled to 0 °C in an ice bath. 8 mg (0.2 mmol, 1.1 eq) $NaBH_4$ were added to the colorless solution at 0 °C, the vial was covered with aluminium foil to facilitate a pressure relief. The mixture was stirred vigorously for 20 min at 0 °C, when TLC indicated full conversion. The reaction was quenched by the addition of 200 µL of acetone and stirred for 5 min at RT. Solvents were removed under reduced pressure and the residue was partitioned between 3.0 mL EtOAc and 1.0 mL $NaHCO_3$ (sat). The organic extract was concentrated under reduced pressure and purified via flash chromatography (SiO_2, cyclohexane/EtOAc 2:1) to yield 19 mg (0.091 mmol, 45%, 2 steps) of a colorless oil.

Yield: 19 mg (0.091 mmol, 45%, 2 steps), colorless oil.

R_f = 0.30 (cyclohexane/ethyl acetate = 1:1 (v/v); staining: $KMnO_4$).

HPLC (Daicel Chemical Technologies Chiralpak® AD-H): t_R (*(S)*-**8j**) = 12.3 min; t_R (*(R)*-**8j**) = 15.6 min.

(9*H*-Fluoren-9-yl)methyl (*S*)-2-formylpyrrolidine-1-carboxylate (3k)[14]



3k

This compound was synthesized according to the general procedure using 270 mg (0.800 mmol, 1.0 eq) Fmoc-L-Pro-OH. The colorless solution was treated with 143 mg (0.880 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 2.68 mL (2.68 mmol, 3.1 eq) 1 M DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 272 mg of white amorphous gel. Purification via flash chromatography* (SiO_2, cyclohexane/EtOAc 4:1) provided 184 mg (0.573 mmol, 72 %) of the desired aldehyde as colorless oil.

Yield: 184 mg (0.573 mmol, 72 %), colorless oil.

$[\alpha]_D^{23}$ = -62.7 ° (c = 3.60, $CHCl_3$).

R_f = 0.25 (cyclohexane/ethyl acetate = 2:1 (v/v); staining: $KMnO_4$).

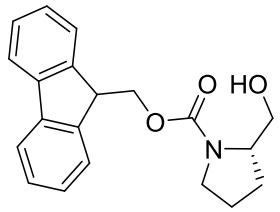
^{1}H NMR (300 MHz, $CDCl_3$, mixture of two conformers, based on HSQC) δ = 9.58 and 9.25 (s, 1H, C*H*O), 7.88–7.20 (m, 8H, Ar–*H*), 4.65–4.37 (m, 2H, CH_2O), 4.37–3.39 (m, 2H, C*H*CHO and C*H*CH_2O), 3.66–3.38 (m, 2H, NCH_2), 2.20–1.69 (m, 4H, NCH_2(CH_2)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$, based on HSQC) δ = 200.0 and 199.8 (s, 1C, *C*HO), 155.4 and 154.6 (s, 1C, C=O), 143.9 and 143.8 (s, 2C, C_q), 141.4 (s, 2C, C_q), 127.8 (s, 2C), 127.1 (s, 2C), 125.2 and 124.9 (s, 2C), 120.0 (s, 2C), 67.6 and 67.3 (s, 1C), 65.3 and 64.8 (s, 1C), 47.3 (s, 1C), 46.7 (s, 1C), 27.8 and 26.6 (s, 1C), 24.6 and 23.6 (s, 1C).

Enantiomeric excess was determined indirectly by conversion of crude, freshly isolated material, not subjected to flash chromatography, into alcohol **8k**.

* Flash chromatography was performed due to somewhat lower purity than in the cases of other aldehydes, to determine the exact abundance of the desired aldehyde. Due to propensity for racemization on silica (demonstrated in epimerization experiment for **3f**), for further synthetic use we recommend the usage of nonchromatographed material, as demonstrated in the examples **8k** and ***rac*-8k**.

9*H*-Fluoren-9-ylmethyl (2*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (8k)[15]



8k

In a 5 mL glass vial equipped with a Teflon®-coated magnetic stirring bar 103 mg (0.320 mmol, 1.0 eq) freshly prepared, nonchromatographed compound **3k** were dissolved in 4.0 mL of MeOH, stirred and cooled to 0 °C in an ice bath. 17 mg (0.44 mmol, 1.4 eq) $NaBH_4$ were added to the colorless solution at 0 °C, the vial was covered with aluminium foil to facilitate a pressure relief. The mixture was stirred vigorously for 20 min at 0 °C, when TLC indicated full conversion. The reaction was quenched by the addition of 200 µL acetone and stirred for 5 min at RT. The solvents were removed under reduced pressure and the residue was partitioned between 3.0 mL EtOAc and 1.0 mL $NaHCO_3$ (sat). The organic phase was concentrated under reduced pressure and purified via flash chromatography (SiO_2, cyclohexane/EtOAc 2:1) to yield 85 mg (0.26 mmol, 81%) of a white solid.

Yield: 85 mg (0.26 mmol, 81%), white solid.

m.p. = 89 °C, lit. 89–90 °C.[15]

$[\alpha]_D^{23}$ = -29.2 ° (c = 0.42, $CHCl_3$), lit. $[\alpha]_D^{24}$ = -30.3 ° (c = 1.02, $CHCl_3$).[15]

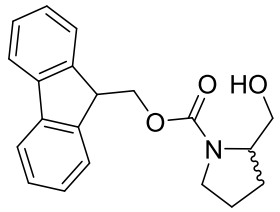
R_f = 0.40 (cyclohexane/ethyl acetate = 1:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$, based on HSQC) δ = 7.78 (d, ^3J = 7.3 Hz, 2H, Ar–*H*), 7.61 (d, ^3J = 7.3 Hz, 2H, Ar–*H*), 7.42 (t, ^3J = 7.3 Hz, 2H, Ar–*H*), 7.33 (t, ^3J = 7.3 Hz, 2H, Ar–*H*), 4.45 (br s, 2H, CH_2OCO), 4.25 (t, ^3J = 6.5 Hz, 1H, benzylic C*H*), 4.10–3.87 (m, 1H, NC*H*CH_2O), 3.78–2.99 (m, 5H, CH_2O*H* and NCH_2CH_2), 2.14–1.53 (m, 4H, $NCH_2CH_2CH_2$).

^{13}C NMR (75 MHz, $CDCl_3$, based on HSQC) δ = 157.3 (s, 1C, C=O), 144.1 (s, 1C, C_q), 141.5 (s, 1C, C_q), 127.8 (s, 2C), 127.2 (s, 2C), 125.1 (s, 2C), 120.1 (s, 2C), 67.6 (s, 1C, *C*H_2CO_2), 67.1 (s, 1C, *C*H_2OH), 60.9 (s, 1C), 47.5 (s, 1C), 47.4 (s, 1C), 28.7 (s, 1C), 24.2 (s, 1C).

HPLC (Daicel Chemical Technologies Chiralpak® AD-H): t_R (*(S)*-**8k**) = 20.5 min, 100%; t_R (*(R)*-**8k**) = 24.3 min, no abundance detected; ee >99%.

Racemic 9*H*-fluoren-9-ylmethyl (2*S*)-2-(hydroxymethyl)pyrrolidine-1-carboxylate (*rac*-8k)



***rac*-8k**

This compound was synthesized by mixing 68 mg (0.20 mmol, 0.5 eq) Fmoc-L-Pro-OH and 68 mg (0.20 mmol, 0.5 eq) Fmoc-D-Pro-OH, and converting the mixture according to the general procedure. The colorless solution was treated with 71 mg (0.44 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 0.84 mL (0.84 mmol, 2.1 eq) 1 M DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 29 mg (0.14 mmol, 70%) of ***rac*-3k** as colorless oil.

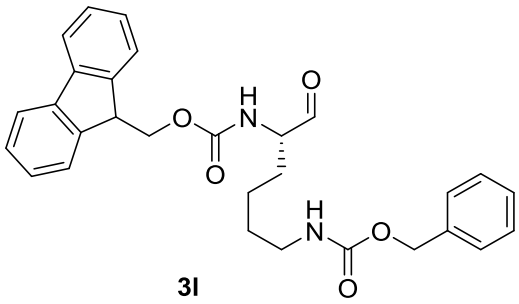
In a 5 mL glass vial equipped with a Teflon-coated magnetic stirring bar 111 mg (0.345 mmol, 1.0 eq) freshly prepared ***rac*-3k** were dissolved in 4.0 mL of MeOH, stirred and cooled to 0 °C in an ice bath. 17 mg (0.44 mmol, 1.1 eq) $NaBH_4$ were added to the colorless solution at 0 °C, the vial was covered with aluminium foil to facilitate a pressure relief. The mixture was stirred vigorously for 20 min at 0 °C, when TLC indicated full conversion. The reaction was quenched by the addition of 200 µL of acetone and stirred for 5 min at RT. Solvents were removed under reduced pressure and the residue was partitioned between 3.0 mL EtOAc and 1.0 mL $NaHCO_3$ (sat). The organic extract was concentrated under reduced pressure and purified via flash chromatography (SiO_2, cyclohexane/EtOAc 2:1) to yield 68 mg (0.21 mmol, 53%, 2 steps) of a colorless oil.

Yield: 68 mg (0.21 mmol, 53%, 2 steps), colorless oil.

R_f = 0.40 (cyclohexane/ethyl acetate = 1:1 (v/v); staining: $KMnO_4$).

HPLC (Daicel Chemical Technologies Chiralpak® AD-H): t_R (*(S)*-**8k**) = 20.5 min; t_R (*(R)*-**8k**) = 24.3 min.

(9*H*-Fluoren-9-yl)methyl benzyl (6-oxohexane-1,5-diyl)(*S*)-dicarbamate (3l)[16]



3l

This compound was synthesized according to the general procedure using 402 mg (0.800 mmol, 1.0 eq) Fmoc-L-Lys(Cbz)-OH. The white colloidal solution was treated with 143 mg (0.880 mmol, 1.1 eq) CDI at 0 °C for 60 min, which resulted in complete dissolution. Subsequently, the reaction solution was treated dropwise with 3.20 mL (3.20 mmol, 4.0 eq) 1 M DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 391 mg of a turbid gel. Purification via flash chromatography[†] (SiO_2, cyclohexane/EtOAc 4:1) furnished 201 mg (0.413 mmol, 52 %) of the desired aldehyde as a viscous colorless oil.

Yield: 201 mg (0.413 mmol, 52 %), viscous colorless oil.

$[\alpha]_D^{23}$ = +10.7 ° (c = 5.30, $CHCl_3$).

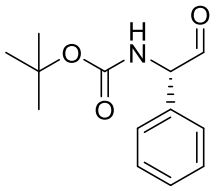
R_f = 0.44 (cyclohexane/ethyl acetate = 1:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.48 (s, 1H, C*H*O), 7.71 (d, ^3J = 7.4 Hz, 2H, Ar–*H*), 7.56 (d, ^3J = 7.0 Hz, 2H, Ar–*H*), 7.40–7.19 (m, 9H, Ar–*H*), 5.65–5.46 (m, 1H, FmocN*H*), 5.04 (s, 2H, PhCH_2O), 4.99–4.82 (m, 1H, CbzN*H*), 4.39 (d, ^3J = 4.7 Hz, 2H, CHCH_2O), 4.27–4.07 (m, 2H, NC*H* and C*H*CH_2O), 3.24–2.96 (m, 2H, NCH_2), 1.94–1.19 (m, 6H, NCH_2(CH_2)$_3$).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 199.5 (s, 1C, *C*HO), 156.7 (s, 1C, C=O), 156.3 (s, 1C, C=O), 143.8 (s, 2C, C_q), 141.4 (s, 2C, C_q), 136.6 (s, 1C, C_q), 128.6 (s, 2C), 128.2 (s, 1C), 128.1 (s, 2C), 127.8 (s, 2C), 127.1 (s, 2C), 125.1 (s, 2C), 67.0 (s, 1C), 66.7 (s, 1C), 60.0 (s, 1C), 47.2 (s, 1C), 40.4 (s, 1C), 29.6 (s, 1C), 28.5 (s, 1C), 22.1 (s, 1C).

HRMS (MALDI-TOF): Calcd. for $C_{29}H_{30}N_2O_5Na$ $[M+Na]^+$: 509.2052; found: 509.2055.

***tert*-Butyl (*S*)-(2-oxo-1-phenylethyl)carbamate (3m)[17]**



3m

This compound was synthesized via a modified procedure using 100 mg (0.400 mmol, 1.0 eq) Boc-L-Phg-OH. The colorless solution was treated with 72 mg (0.44 mmol, 1.2 eq) CDI at 0 °C. After 30 min of stirring 27 mg (0.20 mmol, 0.5 eq) $CuCl_2$ were added and the mixture was stirred at RT for 60 min. Subsequently, 0.84 mL (0.84 mmol, 2.1 eq) 1 M DIBAL-H were added dropwise at the rate of 2.0 mL/min. The mixture was stirred for 30 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 82 mg (0.35 mmol, 88 %) of pale yellow oil.

[†] Flash chromatography was performed due to somewhat lower purity than in the cases of other aldehydes, to determine the exact abundance of the desired aldehyde. Due to propensity for racemization on silica (demonstrated in epimerization experiment for **3f**), for further synthetic use we recommend the usage of nonchromatographed material, as demonstrated in the examples **8k** and ***rac*-8k**.

Yield: 82 mg (0.35 mmol, 88 %), pale yellow oil.

$[\alpha]_D^{23}$ = +213 ° (c = 1.98, CH_2Cl_2), lit. $[\alpha]_D^{20}$ = +272 ° (c = 0.9, CH_2Cl_2).[17]

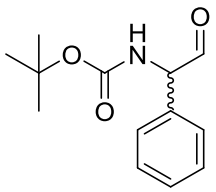
R_f = 0.27 (cyclohexane/ethyl acetate = 4:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.53 (s, 1H, C*H*O), 7.53–7.16 (m, 5H, Ar–*H*), 5.88–5.67 (m, 1H, N*H*), 5.42–5.19 (m, 1H, C*H*CHO), 1.42 (s, 9H, $(CH_3)_3CO$).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 195.2 (s, 1C, *C*HO), 155.1 (s, 1C, C=O), 132.9 (s, 1C, C_q), 129.5 (s, 2C), 128.9 (s, 1C), 127.9 (s, 2C), 80.4 (s, 1C, Me_3C), 65.0 (s, 1C), 28.4 (s, 3C).

GC-FID (CP-Chiralsil Dex): t_R (*(S)*-**3m**) = 14.1 min, 91.51%; t_R (*(R)*-**3m**) = 14.6 min, 8.49%; ee = 83%.

Racemic *tert*-butyl (2-oxo-1-phenylethyl)carbamate (*rac*-3m)



***rac*-3m**

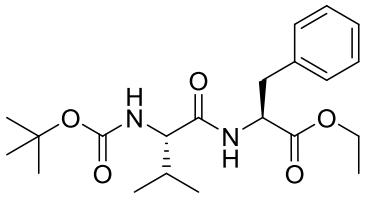
This compound was synthesized according to the general procedure using 75 mg (0.30 mmol, 1.0 eq) Boc-DL-Phg-OH. The colorless solution was treated with 54 mg (0.33 mmol, 1.1 eq) CDI at 0 °C for 60 min, and subsequently, dropwise with 0.63 mL (0.63 mmol, 2.1 eq) of 1 M DIBAL-H. The mixture was stirred for 60 min at -78 °C until TLC indicated full conversion. Extractive workup and drying provided 58 mg (0.25 mmol, 83 %) of pale yellow oil.

Yield: 58 mg (0.25 mmol, 83 %), pale yellow oil.

R_f = 0.27 (cyclohexane/ethyl acetate = 4:1 (v/v); staining: $KMnO_4$).

GC-FID (CP-Chiralsil Dex): t_R (*(S)*-**3m**) = 14.2 min; t_R (*(R)*-**3m**) = 14.6 min.

Ethyl (*tert*-butoxycarbonyl)-L-valyl-L-phenylalaninate (6a)[18]



6a

A 50 mL Schlenk flask with a magnetic stirring bar was dried under vacuum with a heat gun and purged with N_2. 261 mg (1.20 mmol, 1.0 eq) Boc-Val-OH were dissolved in 8 mL abs. DMF and 838 µL (4.80 mmol, 4.0 eq) Hünig's base were added to the stirred solution. After cooling to 0 °C (ice bath), 462 mg (1.44 mmol, 1.2 eq) TBTU were added in one portion. After 5 min of activation time H-Phe-OEt*HCl (304 mg, 1.32 mmol, 1.1 eq) was added, the ice bath removed and the reaction mixture was stirred for 50 min. The mixture was quenched by the addition of 8 mL brine and extracted with EtOAc (32 mL). The layers were separated and the aqueous phase was extracted with 16 mL EtOAc. The combined organic layers were washed with H_2O (2 x 8 mL) and brine (8 mL). The organic phase was dried over Na_2SO_4, concentrated under reduced pressure and purified via flash chromatography (SiO_2; CH_2Cl_2/MeOH = 10:1 v/v).

Yield: 433 mg (1.10 mmol, 92 %), white solid.

m.p. = 112 °C, lit. 117–118 °C.[18]

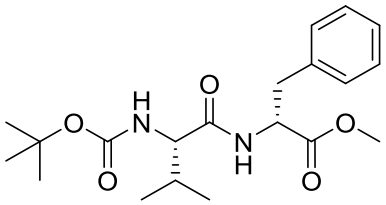
$[\alpha]_D^{23}$ = -24.7° (c = 0.99, EtOH), lit. $[\alpha]_D^{24}$ = -23° (c = 1, EtOH).[18]

R_f = 0.32 (CH_2Cl_2/MeOH = 10:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.33–7.08 (m, 5H, Ar–*H*), 6.39–6.27 (m, 1H, OCN*H*), 5.03 (d, ^3J = 7.3 Hz, 1H, O_2CN*H*), 4.85 (dd, ^3J = 13.6 Hz, 6.1 Hz, 1H, BnC*H*), 4.15 (q, ^3J = 7.1 Hz, 2H, CO_2CH_2), 3.90 (m, 1H, *i*-PrC*H*), 3.12 (d, ^3J = 5.8 Hz, 2H, PhCH_2), 2.16–2.02 (m, 1H, C*H*(CH_3)$_2$), 1.45 (s, 9H, (CH_3)$_3$), 1.22 (t, ^3J = 7.1 Hz, 3H, $CO_2CH_2CH_3$), 0.96–0.82 (m, 6H, CH(CH_3)$_2$).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 171.4 (s, 1C, C=O), 171.3 (s, 1C, C=O), 155.8 (s, 1C, $HNCO_2$), 135.9 (s, 1C, C_q–Ar), 129.5 (s, 2C, C–Ar), 128.7 (s, 2C, C–Ar), 127.3 (s, 1C, C–Ar), 80.0 (s, 1C, Me_3C), 61.6 (s, 1C), 60.0 (s, 1C), 53.3 (s, 1C), 38.2 (s, 1C), 31.0 (s, 1C), 28.4 (s, 3C), 19.3 (s, 1C), 17.8 (s, 1C), 14.2 (s, 1C).

Methyl (*tert*-butoxycarbonyl)-L-valyl-D-phenylalaninate (6b)[19]



6b

A 50 mL Schlenk flask with a magnetic stirring bar was dried under vacuum with a heat gun and purged with N_2. 261 mg (1.20 mmol, 1.0 eq) Boc-Val-OH were dissolved in 8 mL abs. DMF and 838 µL (4.80 mmol, 4.0 eq) Hünig's base were added to the stirred solution. After cooling to 0 °C (ice bath), 462 mg (1.44 mmol, 1.2 eq) TBTU were added in one portion. After 5 min of activation time H-D-Phe-OMe*HCl (285 mg, 1.32 mmol, 1.1 eq) was added, the ice bath removed and the reaction mixture was stirred for 50 min. The mixture was quenched by the addition of 8 mL brine and extracted with EtOAc (32 mL). The layers were separated and the aqueous phase was extracted with 16 mL EtOAc. The combined organic layers were washed with H_2O (2 x 8 mL) and brine (8 mL), was dried over Na_2SO_4, concentrated under reduced pressure and purified via flash chromatography (SiO_2; CH_2Cl_2/MeOH = 10:1 v/v).

Yield: 398 mg (1.05 mmol, 88 %), white solid.

m.p. = 101–103 °C, lit. 104–105 °C.[19]

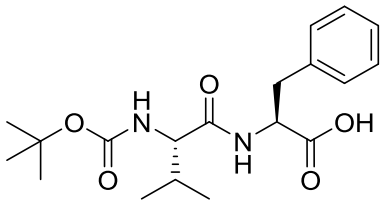
$[\alpha]_D^{23}$ = -35.7° (c = 1.0, $CHCl_3$), lit. $[\alpha]_D^{25}$ = +37.8° (c = 1.0, $CHCl_3$).[19]

R_f = 0.28 (CH_2Cl_2/MeOH = 10:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.35–7.18 (m, 3H, Ar–*H*), 7.17–7.05 (m, 2H, Ar–*H*), 6.44 (d, ^3J = 7.7 Hz, 1H, OCN*H*), 5.05–4.80 (m, 2H, O_2CN*H* and BnC*H*), 3.97 (m, 1H, *i*PrC*H*), 3.71 (s, 3H, CO_2CH_3), 3.19–3.01 (m, 2H, PhCH_2), 2.19–2.03 (m, 1H, C*H*(CH_3)$_2$), 1.43 (s, 9H, (CH_3)$_3$), 0.88 (d, ^3J = 6.7 Hz, 3H, CHCH_3CH$_3$), 0.80 (d, ^3J = 6.8 Hz, 3H, CHCH$_3$CH_3).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.0 (s, 1C, C=O), 171.4 (s, 1C, C=O), 155.9 (s, 1C, $HNCO_2$), 135.9 (s, 1C, C_q–Ar), 129.3 (s, 2C, C–Ar), 128.8 (s, 2C, C–Ar), 127.3 (s, 1C, C–Ar), 80.1 (s, 1C, Me_3C), 59.8 (s, 1C), 53.1 (s, 1C), 52.5 (s, 1C), 38.2 (s, 1C), 30.8 (s, 1C), 28.4 (s, 3C), 19.4 (s, 1C), 17.3 (s, 1C).

(*tert*-Butoxycarbonyl)-L-valyl-L-phenylalanine (7a)[20,21]



7a

In a 50 mL round bottom flask 410 mg (1.04 mmol, 1 eq) **6a** were dissolved in 3.5 mL THF. A solution of 175 mg (4.18 mmol, 4.0 eq) LiOH x H_2O in 5.2 mL H_2O was added under vigorous stirring. After full conversion was indicated by TLC, EtOAc (5 mL) was added and the pH adjusted to 4 with 25 % aqueous citric acid. The mixture was poured into a separation funnel, the layers separated and aqueous layer was extracted with EtOAc (5 mL). The combined organic extracts were washed with H_2O (2.5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified via silica gel filtration (SiO_2; CH_2Cl_2/MeOH = 9:1 (v/v)) to obtain the desired product as a white solid.

Yield: 362 mg (0.99 mmol, 96 %), white solid.

m.p. = 123–128 °C, lit. 114–115 °C.[20]

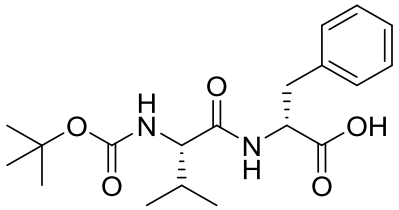
$[\alpha]_D^{23}$ = -15.2° (c = 1.0, MeOH), lit. $[\alpha]_D^{20}$ = +13.7° (c= 1.00, MeOH).[21]

R_f = 0.22 (cyclohexane/EtOAc = 1:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, methanol-d4) δ = 7.30–7.15 (m, 5H, Ar–*H*), 4.68 (dd, ^3J = 7.9 Hz, 5.3 Hz, 1H, BnC*H*), 3.84 (d, ^3J = 7.0 Hz, 1H, *i*-PrC*H*), 3.19 (dd, ^2J = 13.8 Hz, ^3J = 4.9 Hz, 1H, PhCH_2), 2.99 (dd, ^2J = 13.8 Hz, ^3J = 8.5 Hz, 1H, PhCH_2), 2.03–1.86 (m, 1H, C*H*(CH_3)$_2$), 1.43 (s, 9H, (CH_3)$_3$), 0.92–0.80 (m, 6H, CH(CH_3)$_2$).

^{13}C NMR (75 MHz, methanol-d4) δ = 174.3 (s, 1C, C=O), 174.2 (s, 1C, C=O), 157.8 (s, 1C, C=O), 138.3 (s, 1C, C_q–Ar), 130.3 (s, 2C, C–Ar), 129.4 (s, 2C, C–Ar), 127.7 (s, 1C, C–Ar), 80.5 (s, 1C, Me_3C), 61.5 (s, 1C), 54.8 (s, 1C), 38.5 (s, 1C), 32.1 (s, 1C), 28.7 (s, 3C), 19.7 (s, 1C), 18.5 (s, 1C).

(*tert*-Butoxycarbonyl)-L-valyl-D-phenylalanine (7b)



7b

In a 50 mL round bottom flask 363 mg (0.96 mmol, 1 eq) **6b** were dissolved in 3.2 mL THF. A solution of 161 mg (3.84 mmol, 4.0 eq) LiOH x H_2O in 4.8 mL H_2O was added under vigorous stirring. After full

conversion was indicated by TLC, EtOAc (5 mL) was added and the pH adjusted to 4 with 25 % aqueous citric acid. The mixture poured into a separation funnel, the layers separated and aqueous layer was extracted with additional EtOAc (5 mL). The combined organic extracts were washed with H_2O (2.5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified via silica gel filtration (SiO_2; CH_2Cl_2/MeOH = 9:1 (v/v)) to obtain the desired product as a white solid.

Yield: 315 mg (0.84 mmol, 90 %), white solid.

m.p. = 74–78 °C

$[\alpha]_D^{23}$ = -17.2° (c = 1.0, MeOH)

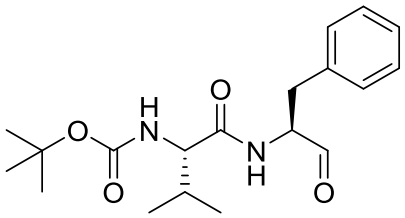
R_f = 0.23 (cyclohexane/EtOAc = 1:1 (v/v); staining: $KMnO_4$).

^{1}H NMR (300 MHz, methanol-d4) δ = 7.32–7.15 (m, 5H, Ar–*H*), 4.68 (dd, ^3J = 8.9 Hz, 4.3 Hz, 1H, BnC*H*), 3.91 (d, ^3J = 5.8 Hz, 1H, *i*-PrC*H*), 3.24 (dd, ^2J = 14.0 Hz, ^3J = 6.7 Hz, PhC*H*H), 2.96 (dd, ^2J = 14.0 Hz, ^3J = 9.6 Hz, PhCH*H*) 1.98–1.74 (m, 1H, C*H*(CH_3)$_2$), 1.43 (s, 9H, (CH_3)$_3$), 0.77 (d, ^3J = 6.8 Hz, 3H, CH(CH_3)$_2$), 0.70 (d, ^3J = 6.8 Hz, 3H, CH(CH_3)$_2$).

^{13}C NMR (75 MHz, methanol-d4) δ = 174.5 (s, 1C, C=O), 174.2 (s, 1C, C=O), 157.9 (s, 1C, $HNCO_2$), 138.4 (s, 1C, C_q–Ar), 130.3 (s, 2C, C–Ar), 129.5 (s, 2C, C–Ar), 127.8 (s, 1C, C–Ar), 80.6 (s, 1C, Me_3C), 61.1 (s, 1C), 54.9 (s, 1C), 38.4 (s, 1C), 32.2 (s, 1C), 28.7 (s, 3C), 19.7 (s, 1C), 17.8 (s, 1C).

HRMS (MALDI-TOF): Calcd. for $C_{19}H_{28}N_2O_5Na$ $[M+Na]^+$: 387.1896; found: 387.1809.

tert-Butyl ((*S*)-3-methyl-1-oxo-1-(((*S*)-1-oxo-3-phenylpropan-2-yl)amino)butan-2-yl)carbamate (4a)[22]



4a

A 50 mL Schlenk flask, equipped with a glass stopper and a magnetic stirring bar was heated, dried under vacuum and purged with N_2. 146 mg (0.400 mmol, 1.0 eq) **7a** were dissolved in 8.0 mL abs. dichloromethane, and the solution was cooled to 0 °C (ice bath). 78 mg (0.480 mmol, 1.2 eq) 1,1'-carbonyldiimidazole (CDI) were added and a gas bubbler was mounted instead of the glass stopper to maintain a pressure relief. After stirring for 60 min the gas bubbler was removed and exchanged by a septum while maintaining a gentle counter flow of N_2. The heterogeneous reaction mixture was cooled to -78 °C (CO_2/acetone bath) for 15 min. Subsequently, 1.24 mL (1.24 mmol, 3.1 eq) DIBAL-H solution (1.0 mol/L in toluene) were added dropwise with a syringe through the septum at a rate of 2.0 mL/h.

Reaction mixture was stirred at -78 °C until TLC indicated quantitative conversion (60 min). The reaction mixture was quenched by addition of 8.0 mL EtOAc. The acetone bath was removed, the gas bubbler was mounted, and 3.0 mL 25% aqueous tartaric acid solution were added to the mixture under vigorous stirring. The mixture was warmed up by immersing the vessel into a water bath at RT and stirred vigorously for 15 min. The stirring was stopped and the layers were separated. The aqueous phase was extracted with EtOAc (1 x 4.0 mL) and the combined organic extracts were washed with 1 M HCl (1 x 3.0 mL), 0.8 M $NaHCO_3$ (1 x 3.0 mL) and brine (1 x 3.0 mL), dried over Na_2SO_4, concentrated under reduced pressure and dried *in vacuo*.

Yield: 124 mg (0.356 µmol, 89 %), white solid.

m.p. = 128–131 °C, lit. 124–125 °C.[22]

$[\alpha]_D^{23}$ = -3.0° (c = 0.69, $CHCl_3$), lit. $[\alpha]_D^{20}$ = -55.4° (c = 1.0, MeOH).[22]

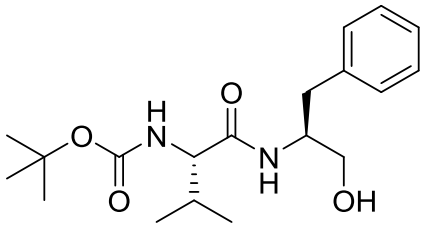
R_f = 0.32 (cyclohexane/EtOAc = 1:1 (v/v); staining: KMnO4).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.61 (s, 1H, C*H*O), 7.39–7.10 (m, 5H, Ar–*H*), 6.52 (br s, 1H, *H*NCO), 5.07–4.90 (m, 1H, *H*NCO_2), 4.71 (d, ^3J = 6.7 Hz, 1H, BnC*H*), 4.01–3.88 (m, 1H, *i*-PrC*H*), 3.15 (d, ^3J = 6.1 Hz, 2H, PhCH_2), 2.20–2.01 (m, 1H, $(CH_3)_2$C*H*), 1.44 (s, 9H, $(CH_3)_3$), 1.00–0.70 (m, 6H, $(CH_3)_2$CH).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 198.6 (s, 1C, HC=O), 172.0 (s, 1C, HNC=O), 155.9 (s, 1C, $HNCO_2$), 135.6 (s, 1C, Ar– C_q), 129.4 (s, 2C, Ar–C), 129.0 (s, 2C, Ar–C), 127.4(s, 1C, Ar–C), 80.2 (s, 1C, Me_3C), 60.1 (s, 1C), 59.8 (s, 1C), 35.4 (s, 1C), 30.7 (s, 1C), 28.4 (s, 3C), 19.4 (s, 1C), 17.7 (s, 1C).

Diastereomeric excess was measured indirectly by reducing the freshly isolated aldehyde **4a** to the alcohol **5a** (*vide infra*).

tert-Butyl ((*S*)-1-(((*S*)-1-hydroxy-3-phenylpropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (5a)[23]



5a

In a 5 mL glass vial 52 mg (0.15 mmol, 1.0 eq) **4a** were dissolved in 1.5 mL MeOH abs, cooled to 0 °C (ice bath) and $NaBH_4$ (27 mg, 0.17 mmol, 1.1 eq) was added in one portion under vigorous stirring. After full conversion was indicated by TLC (20 min), 200 µL acetone were added. The ice bath was removed and

the reaction mixture was stirred for 5 min. The solvents were removed under reduced pressure and the solid residue partitioned between EtOAc (3.0 mL) and 1.0 mL $NaHCO_3$ (0.8 M in H_2O). The organic layer was concentrated and dried under reduced pressure. The product was purified via flash chromatography (SiO_2; cyclohexane/EtOAc = 1:1 (v/v)) to obtain the desired product as a white solid.

Yield: 43 mg (0,12 mmol, 80 %), white solid.

m.p. = 134–138 °C, lit. 145.0–146.0 °C.[23]

$[\alpha]_D^{23}$ = -45.2° (c = 0.8, $CHCl_3$), lit. $[\alpha]_D^{24}$ = -49.4 (c = 1.0, MeOH).[23]

R_f = 0.26 (cyclohexane/EtOAc= 1:1 (v/v); staining: $KMnO_4$).

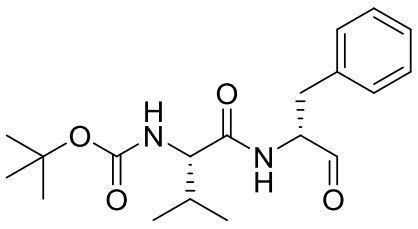
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.37–7.13 (m, 5H, Ar–*H*), 6.47 (d, ^3J = 5.6 Hz, 1H, *H*NCO), 5.04 (d, ^3J = 6.8 Hz, 1H, *H*NCO_2), 4.19 (br s, 1H, BnC*H*), 3.90–3.79 (m, 1H, *i*-PrC*H*), 3.66 (dd, ^3J = 11.1 Hz, 3.5 Hz, 1H, C*H*HOH), 3.57 (dd, ^3J = 11.0 Hz, 4.7 Hz, 1H, CH*H*OH), 2.96–2.79 (m, 2H, PhCH_2), 2.68 (br s, 1H, O*H*), 2.17–2.01 (m, 1H, $(CH_3)_2$C*H*), 1.44 (s, 9H, (CH_3)$_3$), 0.99–0.70 (m, 6H, (CH_3)$_2$CH).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.0 (s, 1C, HNC=O), 156.2 (s, 1C, $HNCO_2$), 137.8 (s, 1C, Ar– C_q), 129.3 (s, 2C, Ar– C), 128.7 (s, 2C, Ar– C), 126.7 (s, 1C, Ar– C), 80.4 (s, 1C, Me_3C), 63.7 (s, 1C), 60.7 (s, 1C), 53.0 (s, 1C), 37.1 (s, 1C), 30.6 (s, 1C), 28.4 (s, 3C), 19.4 (s, 1C), 17.8 (s, 1C).

HPLC-ESI-MS: t_R(**5a**) = 10.66 min, 89.46%; t_R(**5b**) = 11.25 min, 10.54%; de = 78.92%; calc. $[M+Na]^+$ = 373.2, $[M+K]^+$ = 389.2, found $[M+Na]^+$ = 372.9, $[M+K]^+$ = 388.9.

HRMS (MALDI-TOF): Calcd. for $C_{19}H_{30}N_2O_4Na$ $[M+Na]^+$: 373.2103; found: 373.2108.

***tert*-Butyl ((*S*)-3-methyl-1-oxo-1-(((*R*)-1-oxo-3-phenylpropan-2-yl)amino)butan-2-yl)carbamate (4b)**



4b

A 10 mL Schlenk flask, equipped with a glass stopper and a magnetic stirring bar was heated, dried under vacuum and purged with N_2. 31 mg (0.08 mmol, 1.0 eq) **7b** were dissolved in 2.8 mL abs. dichloromethane, and the solution was cooled to 0 °C (ice bath). 13 mg (0.08 mmol, 1.0 eq) HOBt x H_2O were added, immediately by 16 mg (0.10 mmol, 1.1 eq) 1,1'-carbonyldiimidazole (CDI). A gas bubbler was mounted instead of the glass stopper to maintain pressure relief. After stirring for 60 min, the vessel the gas bubbler was replaced with a septum while maintaining a gentle counter flow of N_2. The heterogeneous reaction mixture was cooled to -78 °C (CO_2/acetone bath) for 15 min. Subsequently, 378

µL (0.38 mmol, 4.5 eq) DIBAL-H solution (1.0 M in toluene) were added dropwise with a syringe through the septum at a rate of 2.0 mL/h. Reaction mixture was stirred at -78 °C until TLC indicated quantitative conversion (150 min). The reaction mixture was quenched by addition of 5.6 mL EtOAc. The acetone bath was removed, the gas bubbler was mounted, and 2.8 mL of 25% aqueous tartaric acid solution were added to the mixture under vigorous stirring. The mixture was warmed up by immersing the vessel into a water bath at RT and stirred vigorously for 15 min. The stirring was stopped and the layers were separated. The aqueous phase was extracted with EtOAc (1 x 2.8 mL) and the combined organic extracts were washed with 1 M HCl (1 x 2.8 mL), 0.8 M $NaHCO_3$ (1 x 2.8 mL) and brine (1 x 2.8 mL), dried over Na_2SO_4, concentrated under reduced pressure and dried *in vacuo*.

Yield: 27 mg (78 µmol, 93 %), white solid.

$[\alpha]_D^{23}$ = -3.0° (c = 0.69, $CHCl_3$).

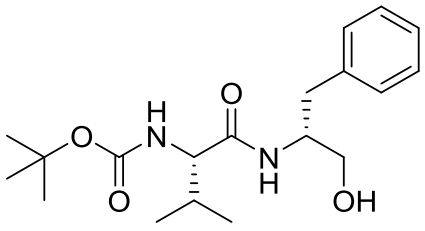
R_f = 0.32 (cyclohexane/EtOAc = 1:1 (v/v); staining: KMnO4).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.61 (s, 1H, C*H*O), 7.38–7.09 (m, 5H, Ar–*H*), 6.49 (br s, 1H, *H*NCO), 5.04–4.89 (m, 1H, *H*NCO_2), 4.74 (dd, ^3J = 13.4 Hz, 6.6 Hz, 1H, BnC*H*), 4.04–3.88 (m, 1H, *i*-PrC*H*), 3.13 (d, ^3J = 6.7 Hz, 2H, PhCH_2), 2.19–2.00 (m, 1H, $(CH_3)_2$C*H*), 1.43 (s, 9H, $(CH_3)_3$), 0.95–0.76 (m, 6H, $(CH_3)_2$CH).

^{13}C NMR (75 MHz, $CDCl_3$, based on HSQC) δ = 198.8 (s, 1C, HC=O), 172.0 (s, 1C, HNC=O), 156.0 (s, 1C, $HNCO_2$), 135.6 (s, 1C, Ar– C_q), 129.4 (s, 2C, Ar–C), 129.0 (s, 2C, Ar–C), 127.4(s, 1C, Ar–C), 80.2 (s, 1C, Me_3C), 60.0 (s, 1C), 59.7 (s, 1C), 35.3 (s, 1C), 30.7 (s, 1C), 28.4 (s, 3C), 19.4 (s, 1C), 17.6 (s, 1C).

Diastereomeric excess was measured indirectly by reducing the freshly isolated aldehyde **4b** to the alcohol **5b** (*vide infra*).

tert-Butyl ((*S*)-1-(((*R*)-1-hydroxy-3-phenylpropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (5b)[23]



5b

In a 5 mL glass vial 27 mg (78 µmol, 1.0 eq) **4b** were dissolved in 0.78 mL MeOH abs, cooled to 0 °C (ice bath) and $NaBH_4$ (14 mg, 86 µmol, 1.1 eq) was added in one portion under vigorous stirring. After full conversion was indicated by TLC (20 min), 200 µL acetone were added. The ice bath was removed and the reaction mixture was stirred for 5 min. The solvents were removed under reduced pressure and the

solid residue partitioned between EtOAc (3.0 mL) and 1.0 mL $NaHCO_3$ (0.8 M in H_2O). The organic layer was concentrated and dried under reduced pressure. The product was purified via flash chromatography (SiO_2; cyclohexane/EtOAc = 1:1 (v/v)) to obtain the desired product as a white solid.

Yield: 17 mg (49 µmol, 62 %), white solid.

m.p. = 125–127 °C, lit. 131–132 °C.[23]

$[\alpha]_D^{23}$ = +1.2° (c = 0.8, $CHCl_3$).

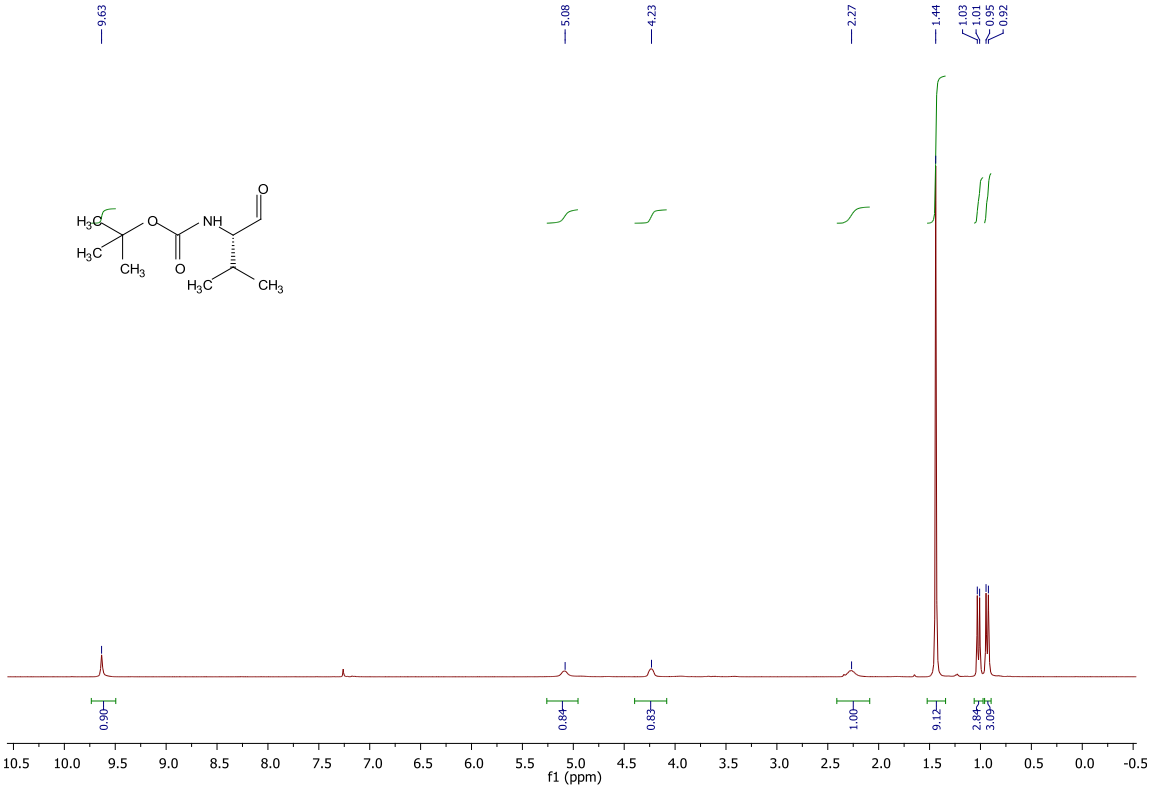
R_f = 0.28 (cyclohexane/EtOAc= 1:1 (v/v); staining: $KMnO_4$).

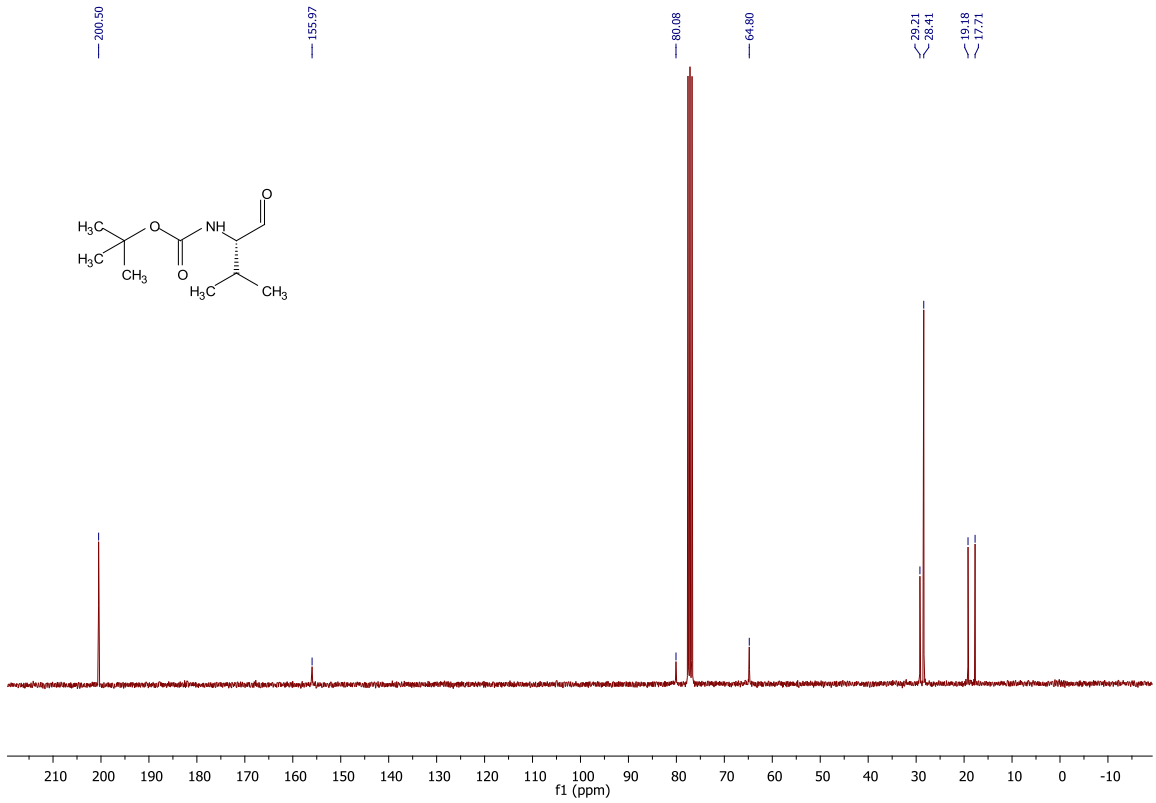
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.34–7.12 (m, 5H, Ar–*H*), 6.36 (d, ^3J = 7.7 Hz, 1H, *H*NCO), 5.21 (d, ^3J = 7.9 Hz, 1H, *H*NCO_2), 4.25 (br s, 1H, BnC*H*), 3.81–3.62 (m, 2H, *i*-PrC*H* and C*H*HOH), 3.54 (dd, ^3J = 11.2 Hz, 4.9 Hz, 1H, CH*H*OH), 2.97–2.74 (m, 2H, PhCH_2), 2.02–1.81 (m, 1H, $(CH_3)_2$C*H*), 1.43 (s, 9H, (CH_3)$_3$), 0.87–0.71 (m, 6H, (CH_3)$_2$CH).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.3 (s, 1C, HNC=O), 156.4 (s, 1C, $HNCO_2$), 137.8 (s, 1C, Ar– C_q), 129.3 (s, 2C, Ar– C), 128.7 (s, 2C, Ar– C), 126.7 (s, 1C, Ar– C), 80.3 (s, 1C, Me_3C), 64.0 (s, 1C), 60.9 (s, 1C), 52.9 (s, 1C), 37.2 (s, 1C), 30.8 (s, 1C), 28.5 (s, 3C), 19.2 (s, 1C), 18.1 (s, 1C).

HPLC-ESI-MS: t_R(**5a**) = 10.43 min, 5.34%; t_R(**5b**) = 10.98 min, 94.66%; de = 89.32%; calc. $[M+Na]^+$ = 373.2, $[M+K]^+$ = 389.2, found $[M+Na]^+$ = 372.9, $[M+K]^+$ = 388.9.

^{1}H- and ^{13}C- NMR spectra and GC-FID chromatograms (enantiopure and racemic) of *tert*-butyl *(S)*-(3-methyl-1-oxobutan-2-yl)carbamate (3a)





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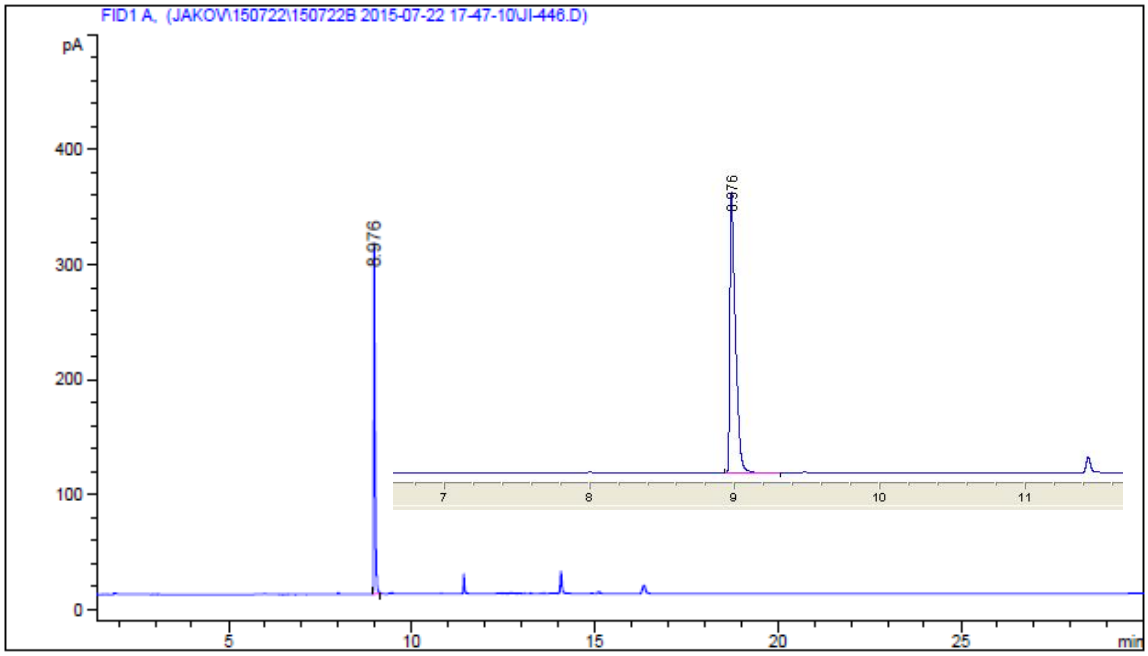


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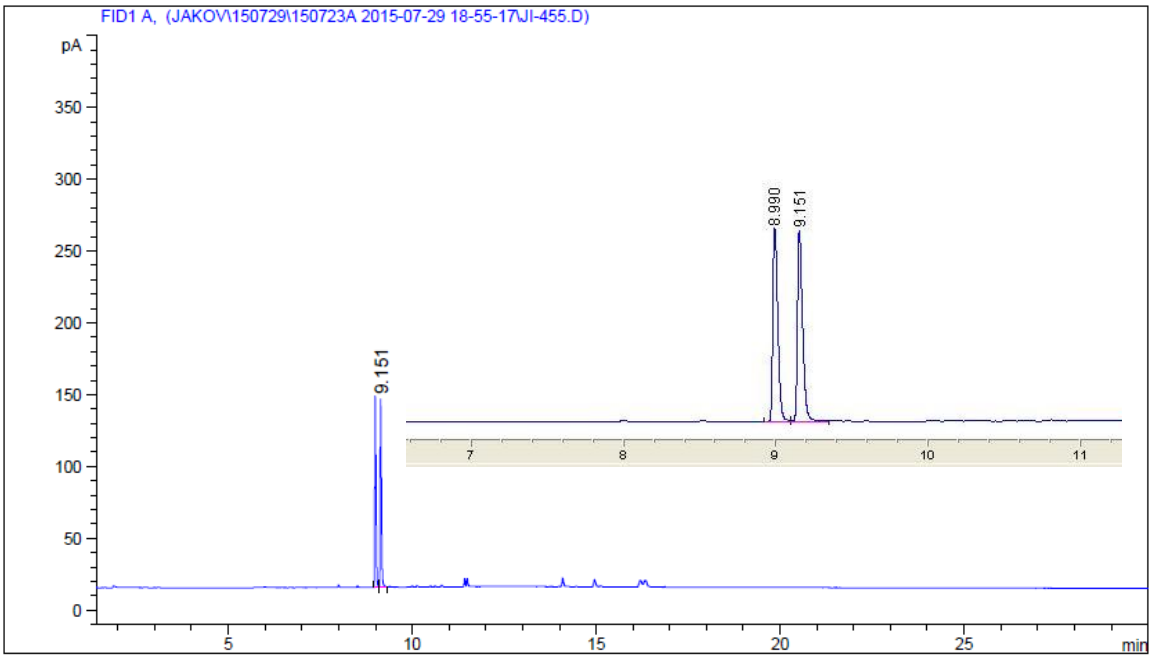
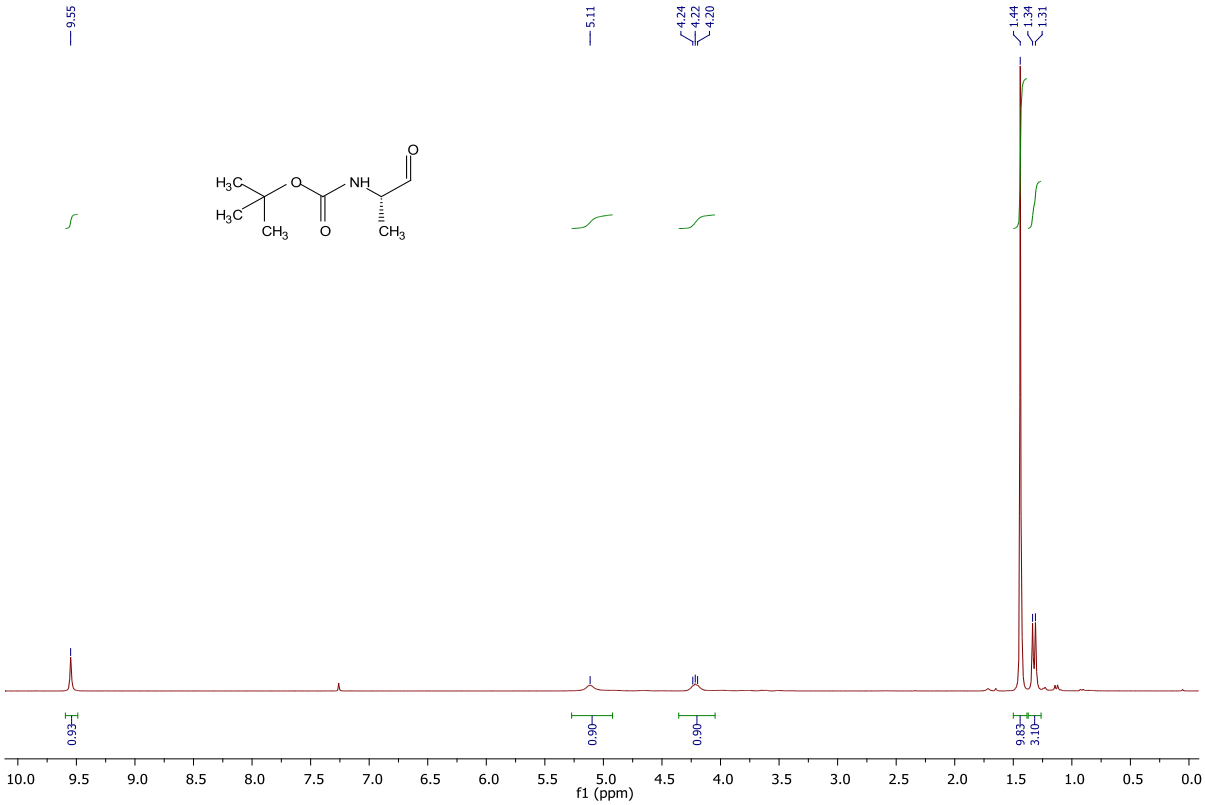
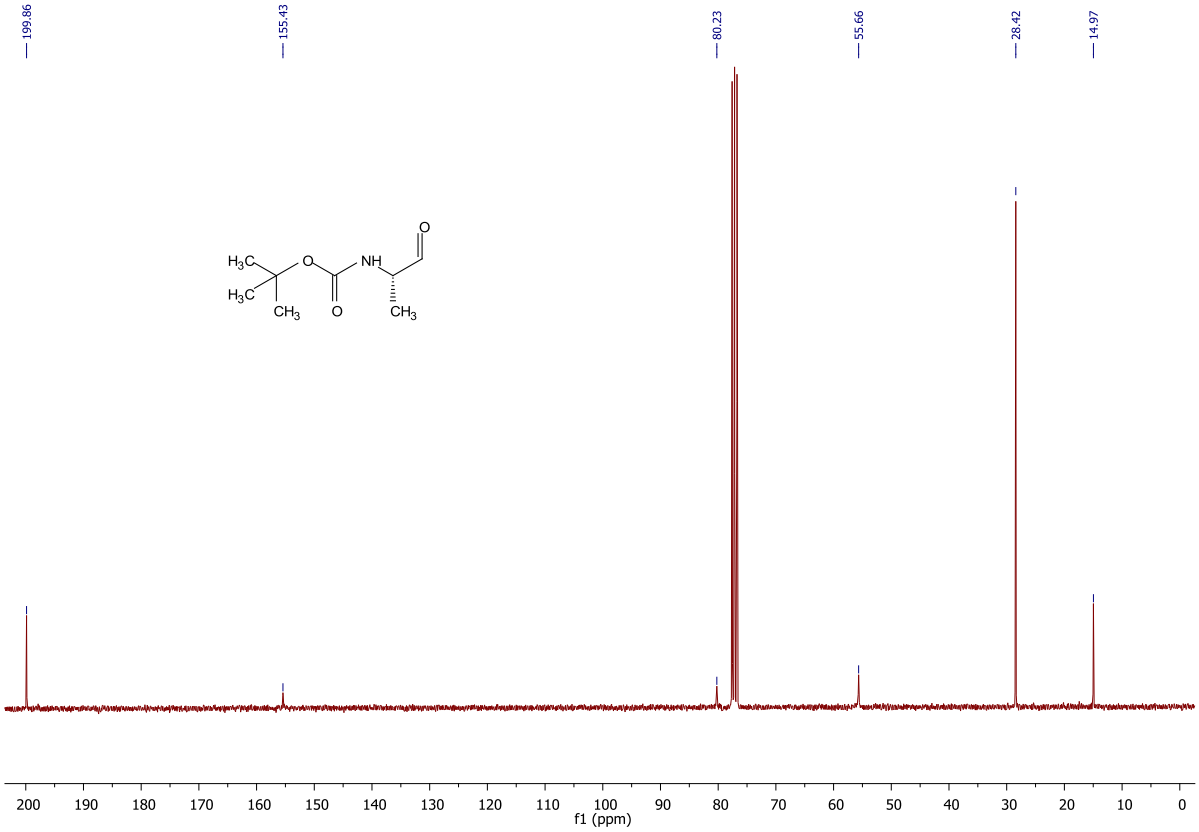


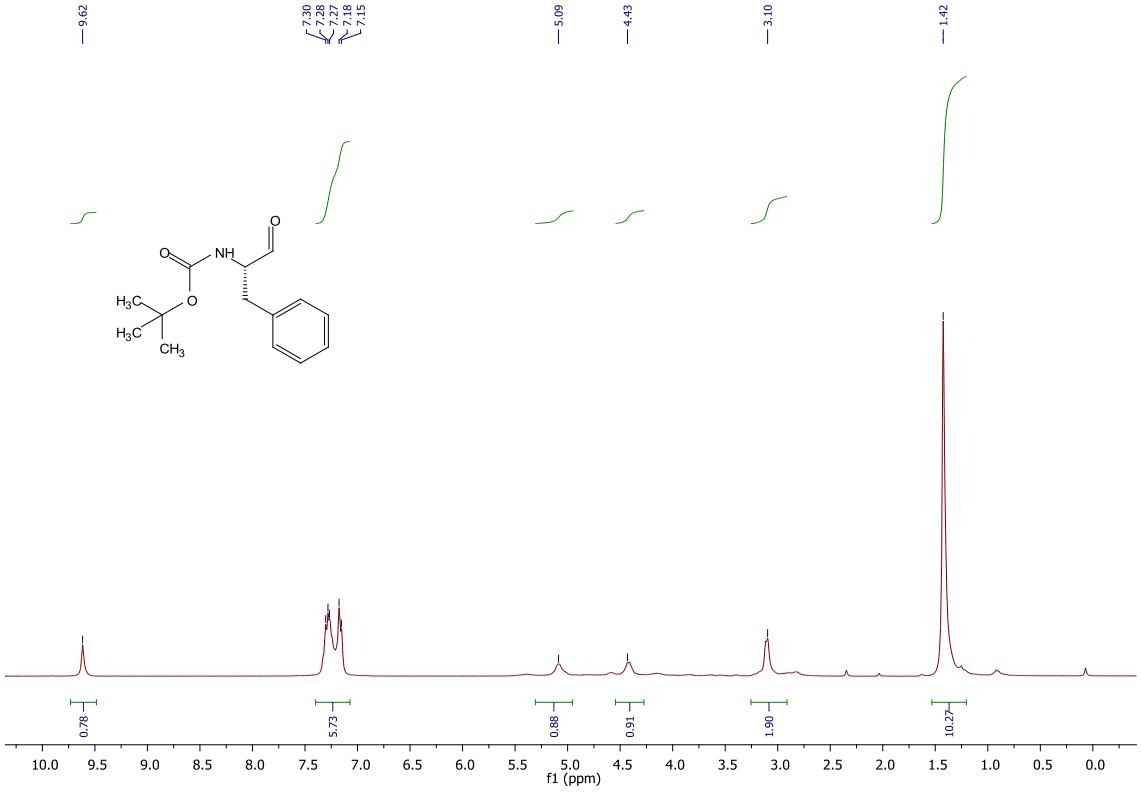

```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   8.990 BV    0.0381  302.95770  131.51054 49.91814
   2   9.151 VB    0.0368  303.95135  130.36398 50.08186

Totals :                   606.90906  261.87453
```

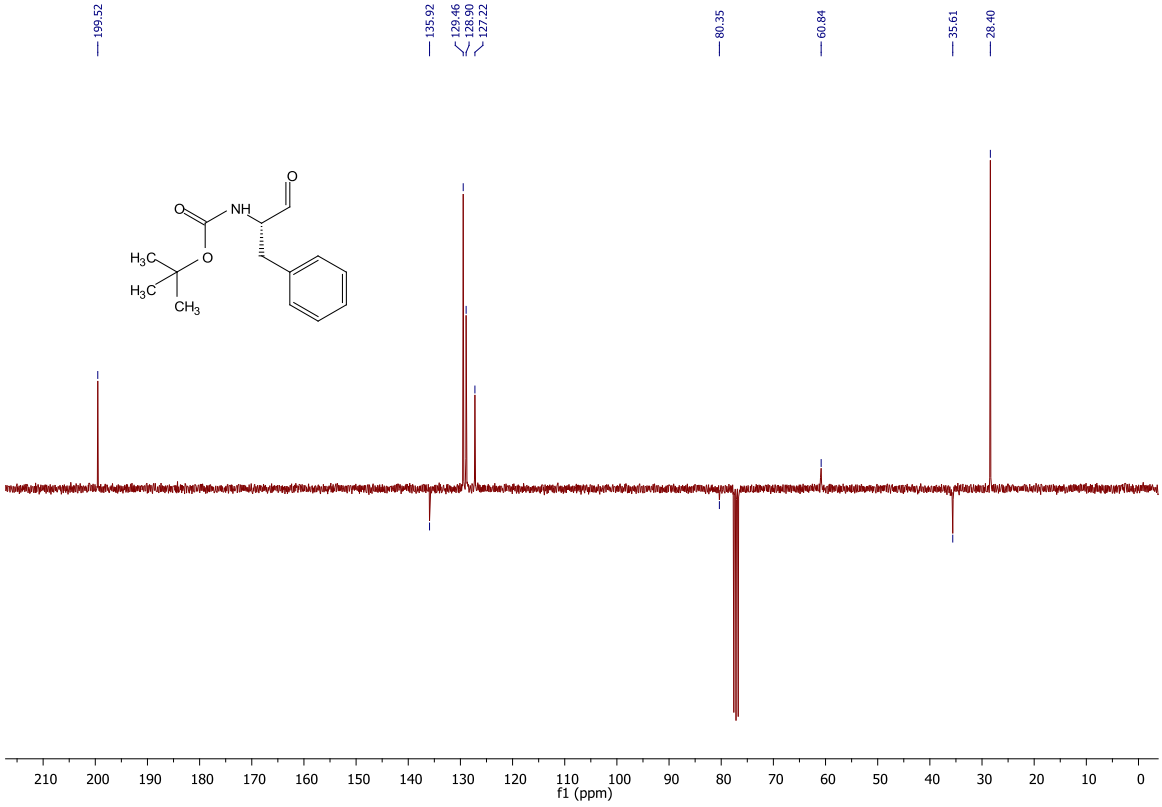
^{1}H- and ^{13}C- NMR spectra of *tert*-butyl *(S)*-(1-oxopropan-2-yl)carbamate (3b)





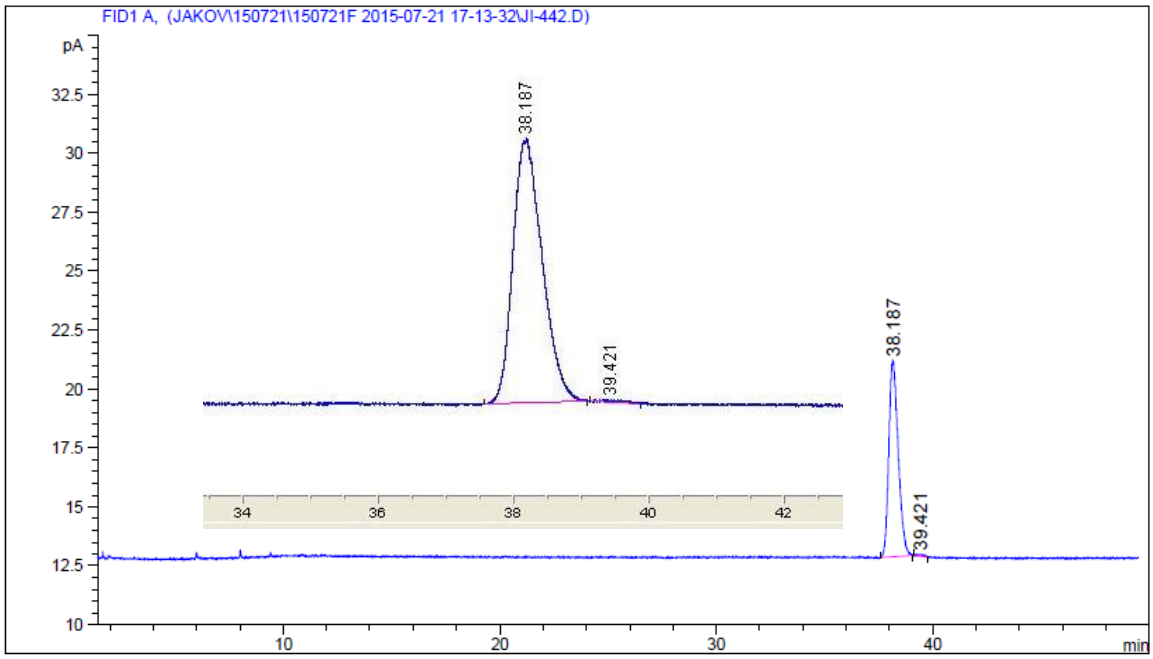
^{1}H- and ^{13}C- NMR spectra and GC-FID chromatograms (enantiopure and racemic) of *tert*-butyl *(S)*-(1-oxo-3-phenylpropan-2-yl)carbamate (3c)





Data File D:\GC\1\DATA\JAKOV\150721\150721F 2015-07-21 17-13-32\JI-442.D
Sample Name: JI-442

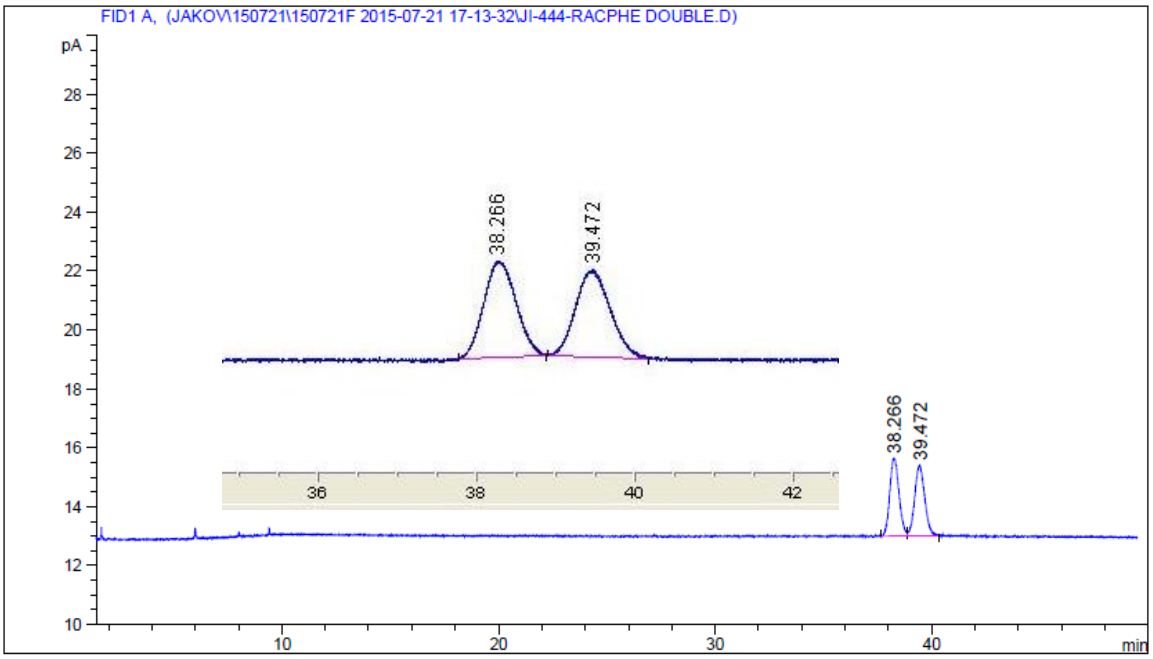
```
==========================================================================
Acq. Operator   : jkv                          Seq. Line :   2
Acq. Instrument : GC Pal                        Location : P1-B-02
Injection Date  : 21.07.2015 18:08:56               Inj :   1
                                               Inj Volume : External
Acq. Method     : D:\GC\1\DATA\JAKOV\150721\150721F 2015-07-21 17-13-32\AMAL_GCPAL_PHE_4.M
Last changed    : 21.07.2015 16:05:38 by jkv
Analysis Method : D:\GC\1\DATA\JAKOV\METHOD\INT.M
Last changed    : 20.08.2015 19:35:49 by jkv
                  (modified after loading)
```




```
==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  38.187 BBA   0.3686  249.81647    8.26684 99.51072
   2  39.421 BBA   0.2664    1.22832 5.58140e-2  0.48928

Totals :                   251.04479    8.32266
```

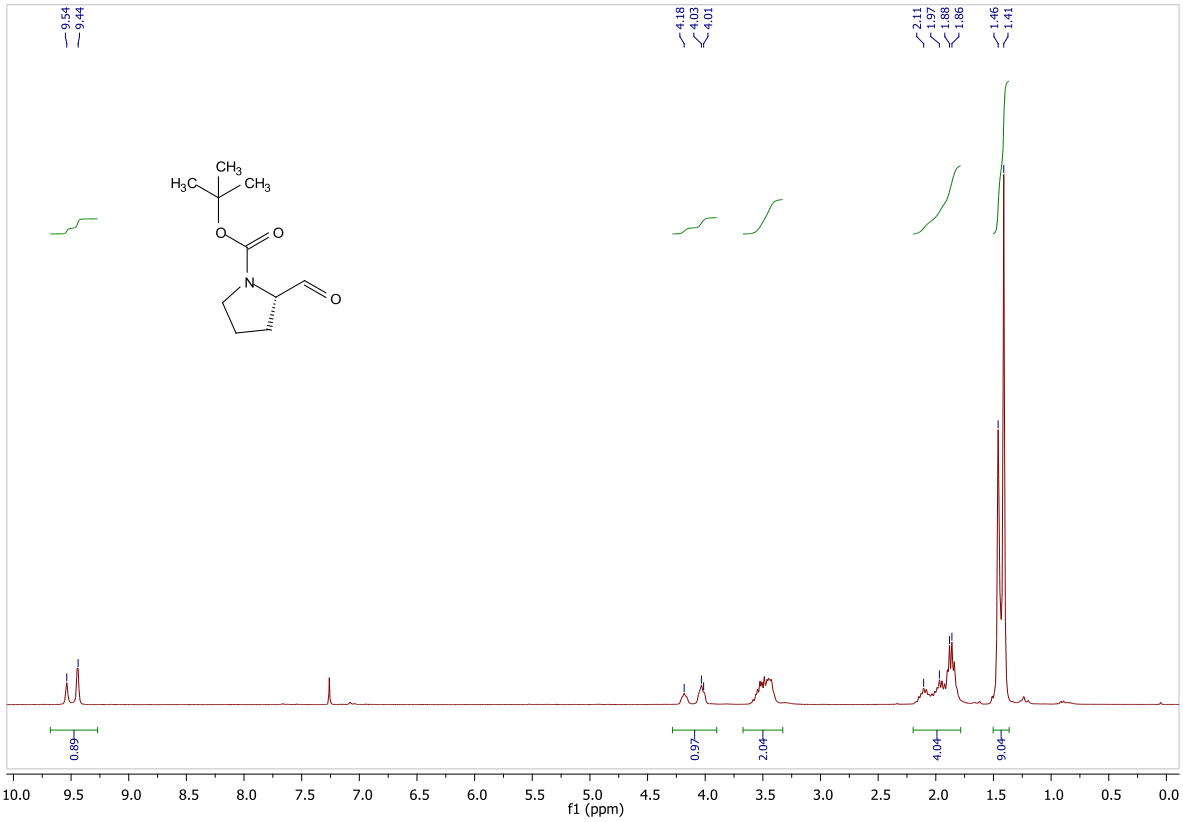
Data File D:\GC\1\DATA\JAKOV\150721\150721F 2015-07-21 17-13-32\JI-444-RACPHE DOUBLE.D
Sample Name: JI-444-racPhe double

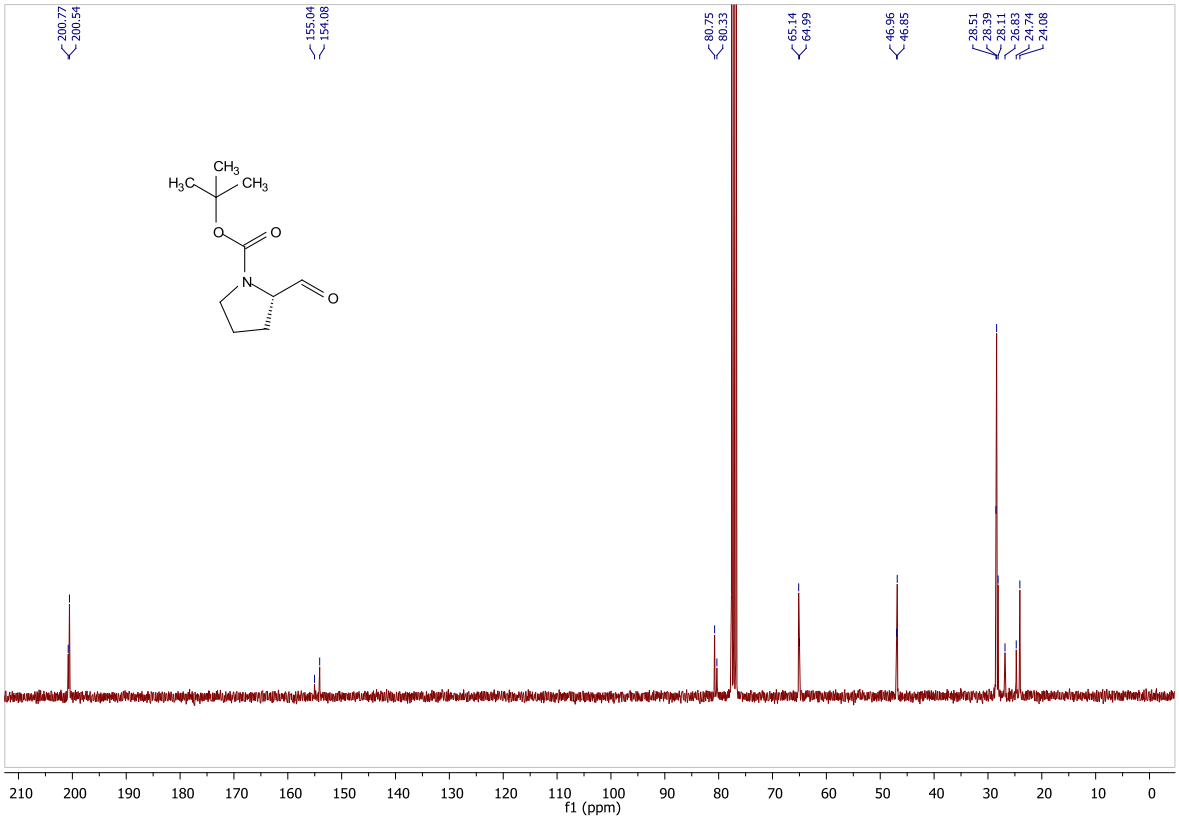
```
======================================================================
Acq. Operator   : jkv                          Seq. Line :   1
Acq. Instrument : GC Pal                        Location : P1-B-01
Injection Date  : 21.07.2015 17:15:01              Inj :   1
                                               Inj Volume : External
Acq. Method     : D:\GC\1\DATA\JAKOV\150721\150721F 2015-07-21 17-13-32\AMAL_GCPAL_PHE_4.M
Last changed    : 21.07.2015 16:05:38 by jkv
Analysis Method : D:\GC\1\DATA\JAKOV\METHOD\INT.M
Last changed    : 20.08.2015 19:25:06 by jkv
                  (modified after loading)
```



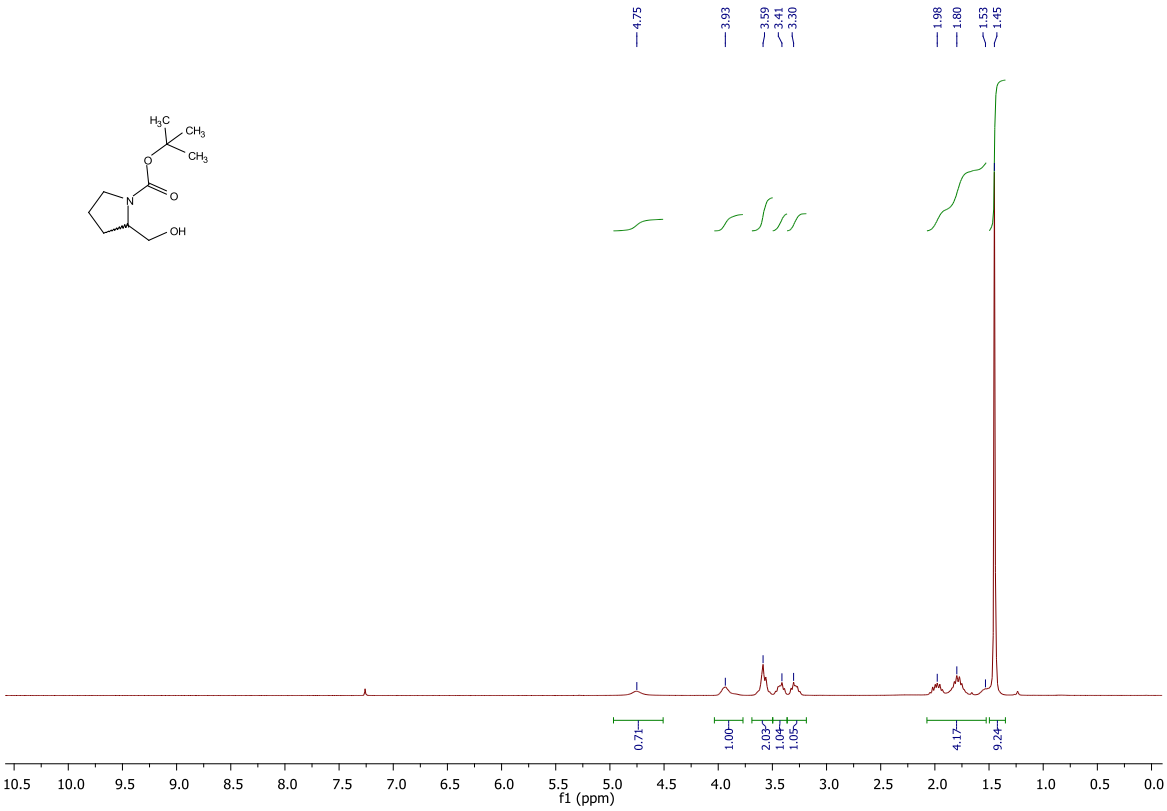

```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  38.266 BV    0.3541   78.59856    2.64965 50.74378
   2  39.472 VB    0.3843   76.29445    2.39575 49.25622

Totals :                   154.89301    5.04540
```

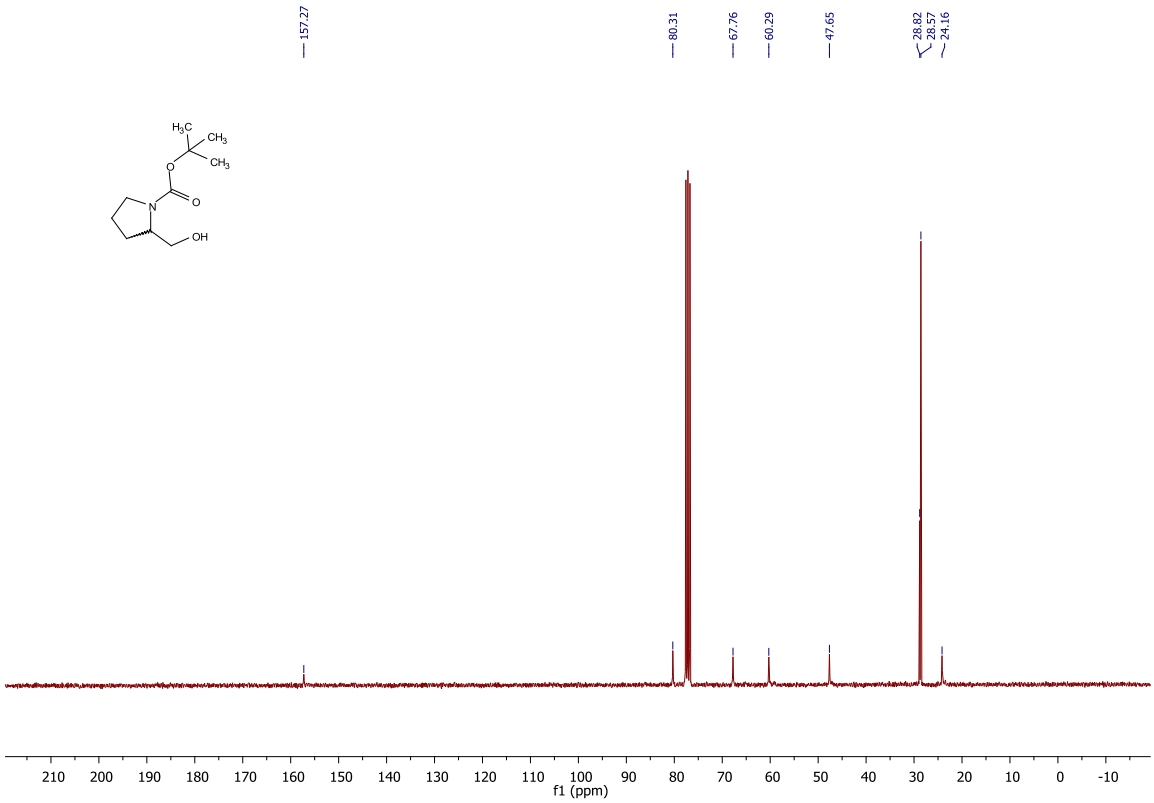
^{1}H- and ^{13}C- NMR spectra of *tert*-butyl *(S)*-2-formylpyrrolidine-1-carboxylate (3d)





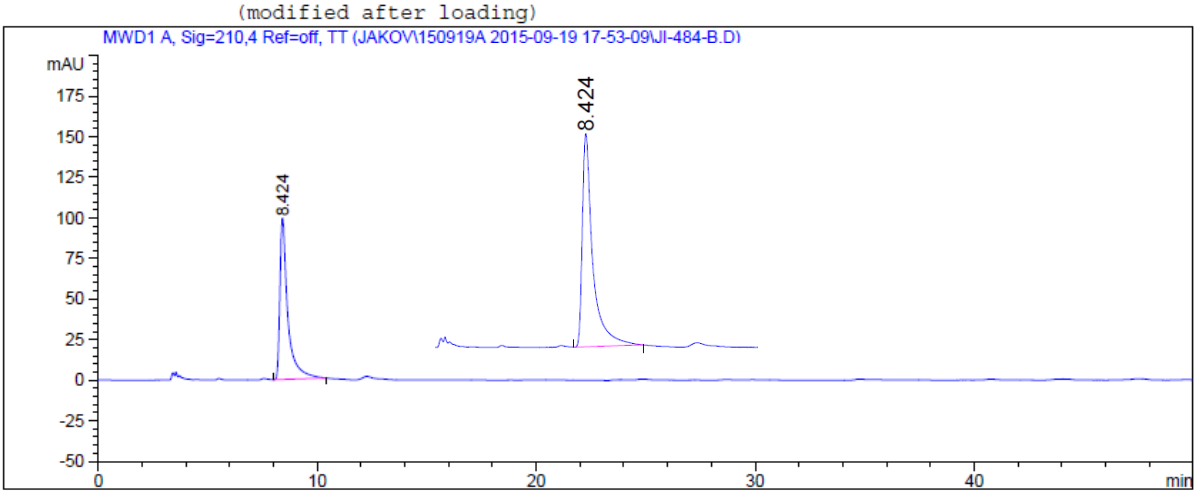
^{1}H- and ^{13}C- NMR spectra, and chiral HPLC chromatograms (enantiopure and racemic) of benzyl (*S*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate (8d)





Data File D:\CHEMSTATION\HPLC LINKS\DATA\JAKOV\150919A 2015-09-19 17-53-09\JI-484-B.D
Sample Name: JI-484-B

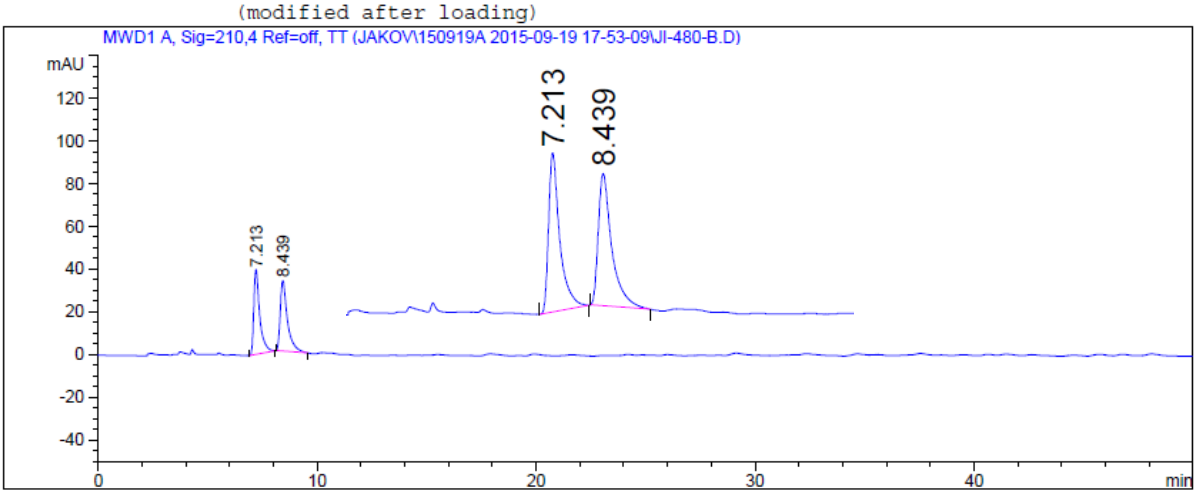
```
=====================================================================
Acq. Operator   : jakov                        Seq. Line :   5
Acq. Instrument : HPLC links                    Location : Vial 52
Injection Date  : 19.09.2015 21:26:48               Inj :   1
                                               Inj Volume : 3.0 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 2.0 µl
Acq. Method     : D:\CHEMSTATION\HPLC LINKS\DATA\JAKOV\150919A 2015-09-19 17-53-09\ADH_
                  HEPTIPROH_90_10.M
Last changed    : 19.09.2015 17:41:23 by jakov
Analysis Method : D:\CHEMSTATION\HPLC LINKS\METHODS\JAKOV\INT.M
Last changed    : 20.09.2015 13:14:06 by jakov
                  (modified after loading)
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 A, Sig=210,4 Ref=off, TT

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   8.424 VBA   0.3625 2495.16821   97.51218 100.0000

Totals :                  2495.16821   97.51218
```

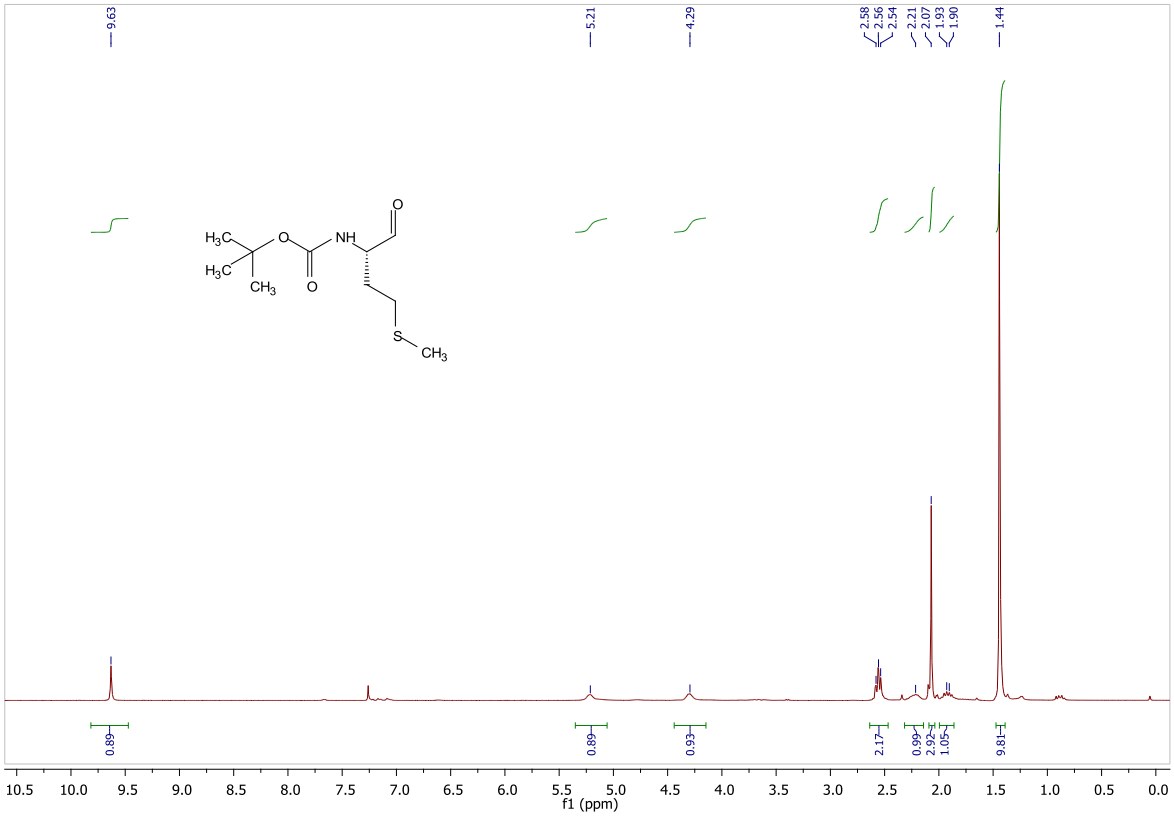
Data File D:\CHEMSTATION\HPLC LINKS\DATA\JAKOV\150919A 2015-09-19 17-53-09\JI-480-B.D
Sample Name: JI-480-B

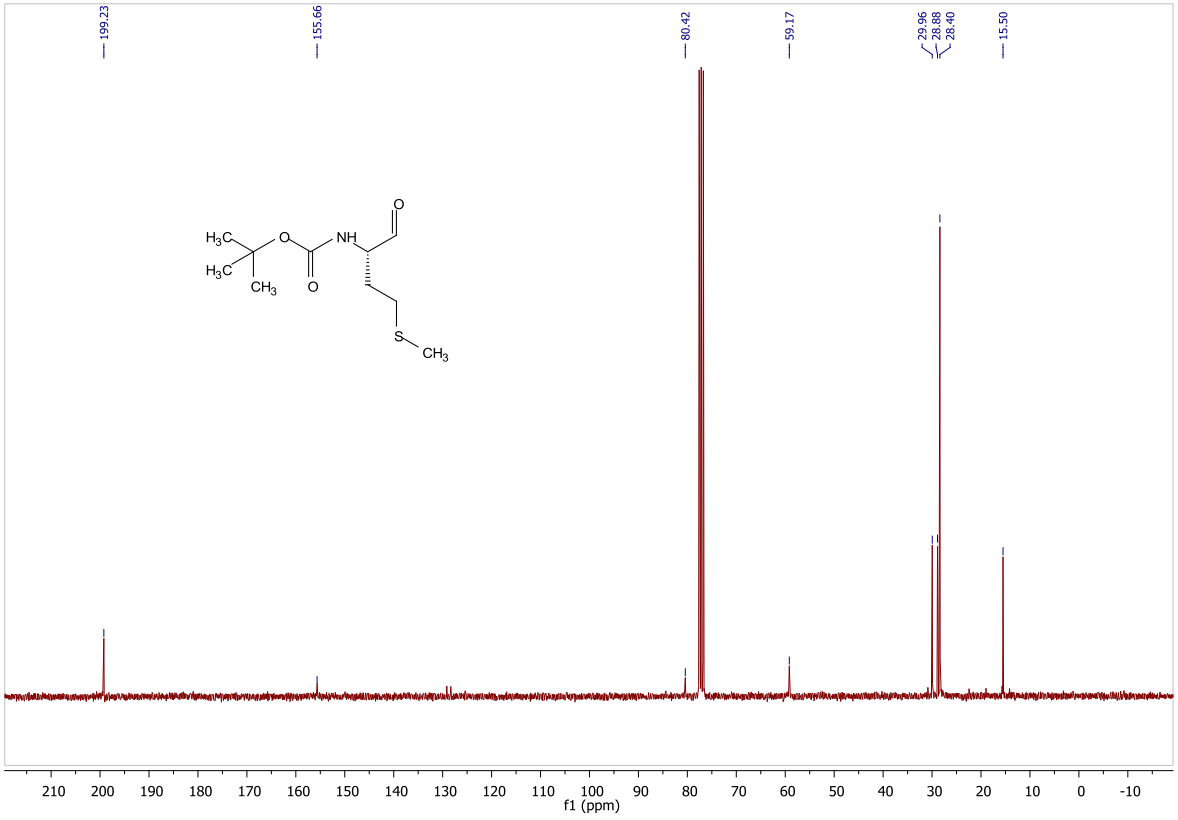
```
=====================================================================
Acq. Operator   : jakov                          Seq. Line :   8
Acq. Instrument : HPLC links                     Location : Vial 42
Injection Date  : 20.09.2015 00:01:53                 Inj :   1
                                                 Inj Volume : 3.0 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 2.0 µl
Acq. Method     : D:\CHEMSTATION\HPLC LINKS\DATA\JAKOV\150919A 2015-09-19 17-53-09\ADH_
                  HEPTIPROH_90_10.M
Last changed    : 19.09.2015 17:41:23 by jakov
Analysis Method : D:\CHEMSTATION\HPLC LINKS\METHODS\JAKOV\INT.M
Last changed    : 20.09.2015 13:02:47 by jakov
                  (modified after loading)
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 A, Sig=210,4 Ref=off, TT

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.213 BBA   0.2889  749.21967   38.85792  50.0228
   2   8.439 BBA   0.3490  748.53644   32.46803  49.9772

Totals :                  1497.75610   71.32595
```

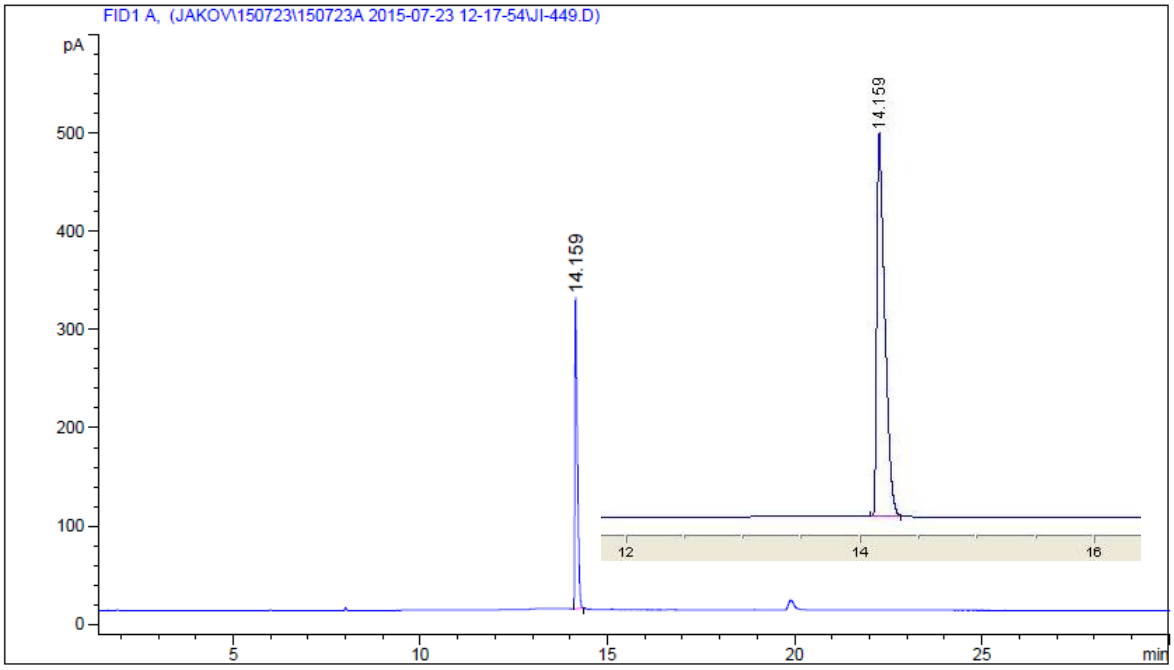
^{1}H- and ^{13}C- NMR spectra and chiral GC-FID chromatograms (enantiopure and racemic) of *tert*-butyl *(S)*-(4-(methylthio)-1-oxobutan-2-yl)carbamate (3e)




199.23
155.66
80.42
59.17
29.96
28.88
28.40
15.50
O
NH
O
O
S
CH3
H3C
H3C
CH3
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Data File D:\GC\1\DATA\JAKOV\150723\150723A 2015-07-23 12-17-54\JI-449.D
Sample Name: JI-449

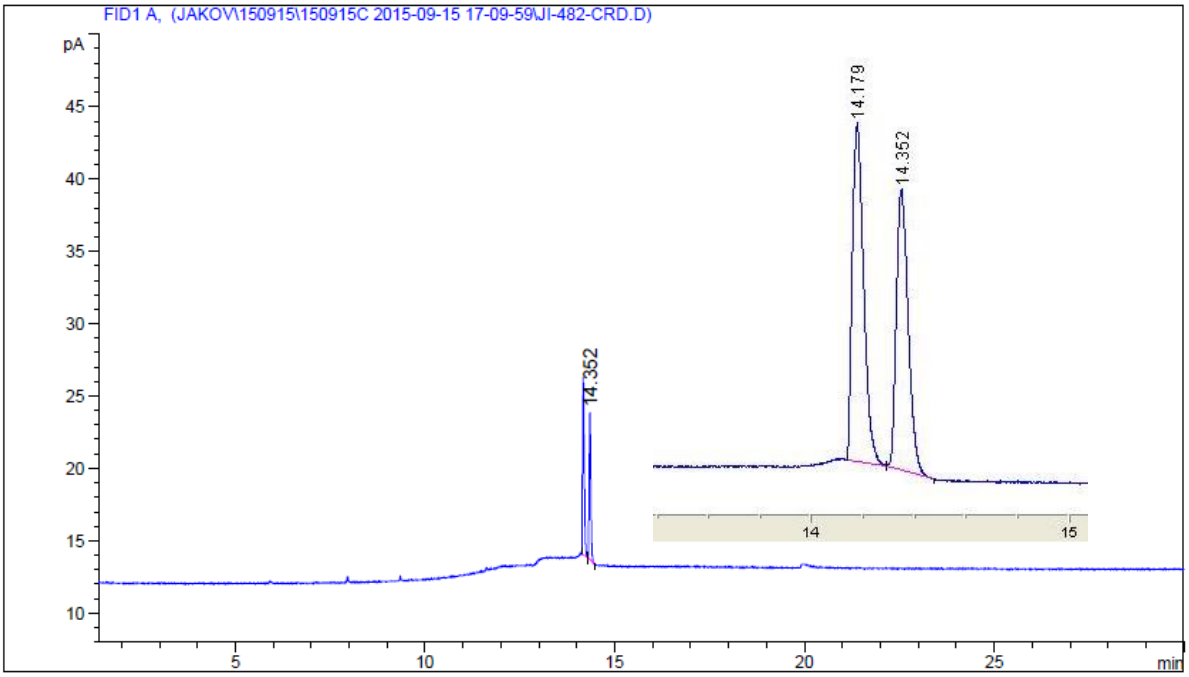
```
==========================================================================
Acq. Operator    : jkv                          Seq. Line :   2
Acq. Instrument : GC Pal                         Location : P1-C-04
Injection Date  : 23.07.2015 12:59:09                Inj :   1
                                               Inj Volume : External
Acq. Method     : D:\GC\1\DATA\JAKOV\150723\150723A 2015-07-23 12-17-54\AMAL_GCPAL.M
Last changed    : 22.05.2015 15:01:11 by jkv
Analysis Method : D:\GC\1\DATA\JAKOV\METHOD\INT.M
Last changed    : 20.09.2015 14:54:09 by jkv
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  14.159 BBA   0.0709 1485.10144  315.67136 1.000e2

Totals :                  1485.10144  315.67136
```

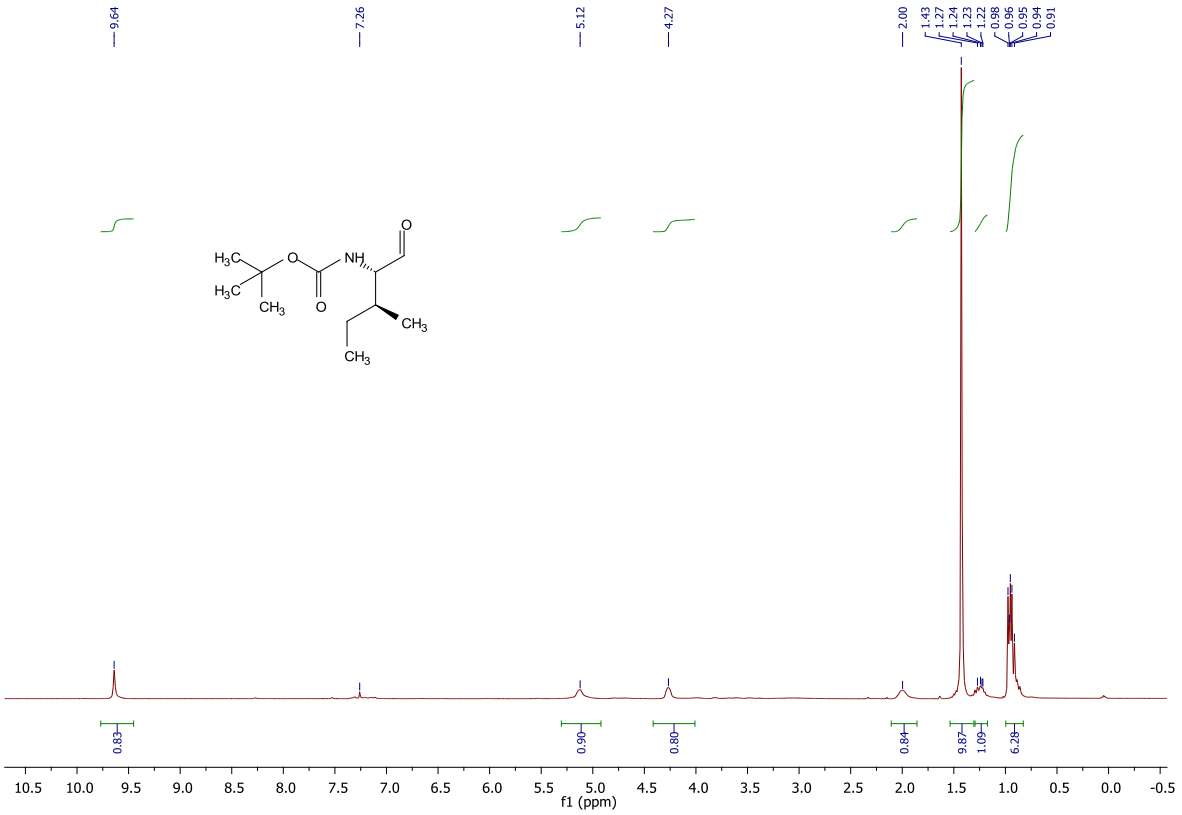
Data File D:\GC\1\DATA\JAKOV\150915\150915C 2015-09-15 17-09-59\JI-482-CRD.D
Sample Name: JI-482-CRD

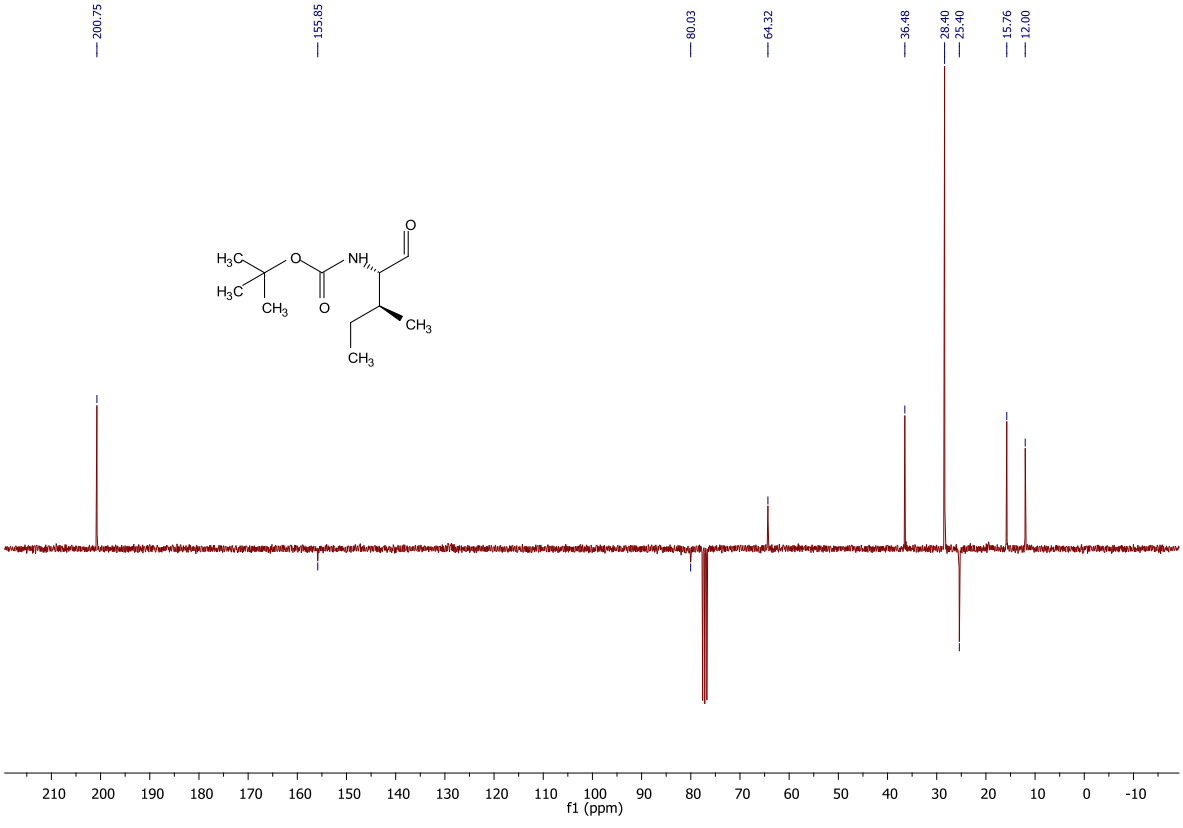
```
======================================================================
Acq. Operator    : jkv                              Seq. Line :   1
Acq. Instrument : GC Pal                             Location : P1-E-04
Injection Date   : 15.09.2015 17:11:11                    Inj :   1
                                                   Inj Volume : External
Acq. Method      : D:\GC\1\DATA\JAKOV\150915\150915C 2015-09-15 17-09-59\AMAL_GCPAL.M
Last changed     : 29.07.2015 18:50:33 by jkv
Analysis Method : D:\GC\1\DATA\JAKOV\METHOD\INT.M
Last changed     : 20.09.2015 14:42:58 by jkv
                   (modified after loading)
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [pA*s]     [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  14.179 BB    0.0486   37.50543   12.23780 53.56450
   2  14.352 BBA   0.0501   32.51377   10.16623 46.43550

Totals :                    70.01920   22.40403
```

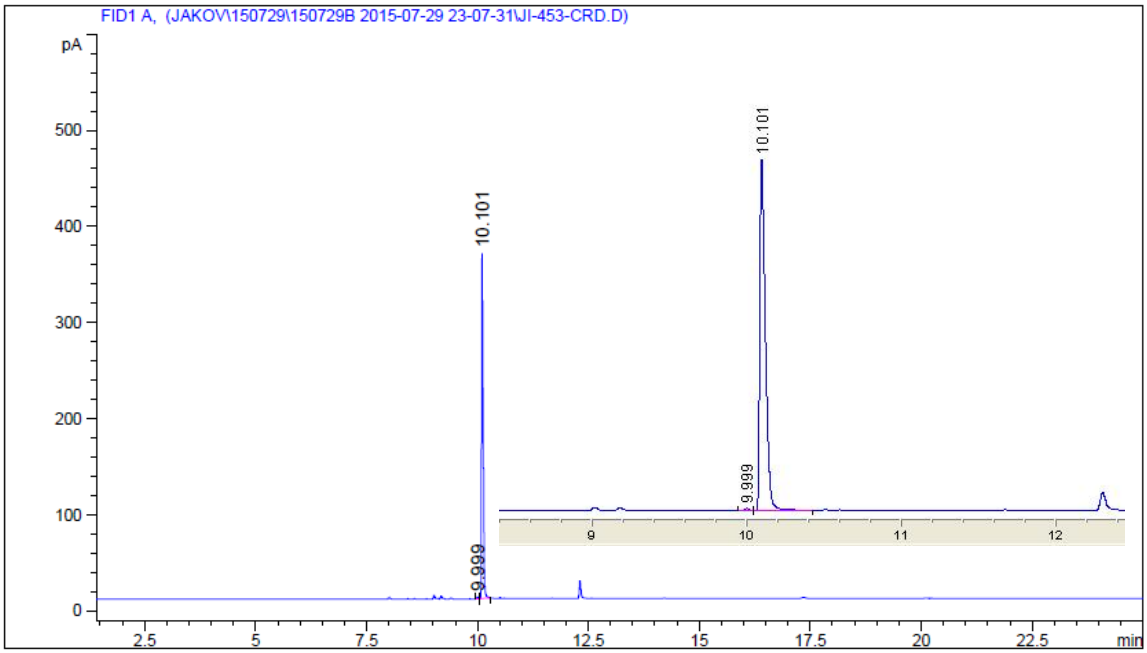
^{1}H- and ^{13}C- NMR spectra, GC-FID chromatogram (enantiopure) and GCMS spectrum of *tert*-butyl ((*2S,3S)*-3-methyl-1-oxopentan-2-yl)carbamate (3f)





Data File D:\GC\1\DATA\JAKOV\150729\150729B 2015-07-29 23-07-31\JI-453-CRD.D
Sample Name: JI-453-crd

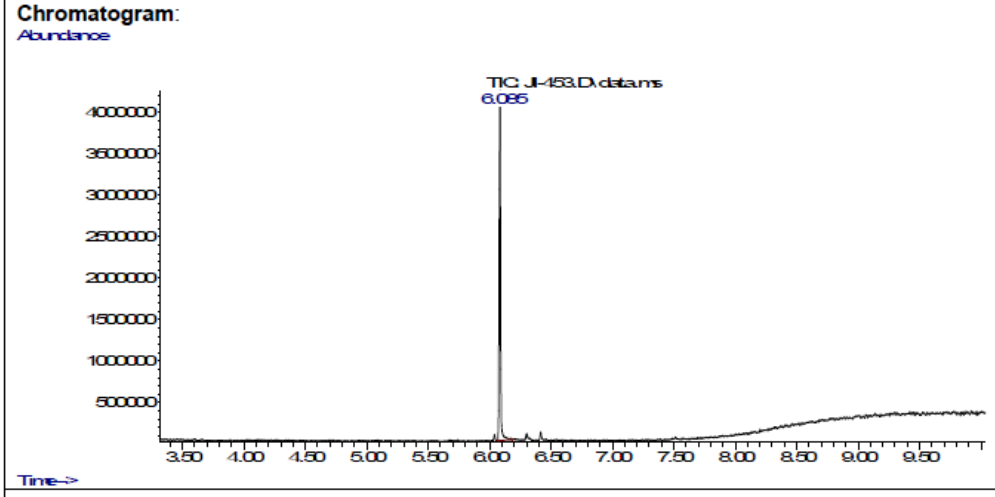
```
======================================================================
Acq. Operator   : jkv                          Seq. Line :   1
Acq. Instrument : GC Pal                        Location : P1-D-04
Injection Date  : 29.07.2015 23:09:02               Inj :   1
                                               Inj Volume : External
Acq. Method     : D:\GC\1\DATA\JAKOV\150729\150729B 2015-07-29 23-07-31\AMAL_GCPAL.M
Last changed    : 29.07.2015 18:50:33 by jkv
Analysis Method : D:\GC\1\DATA\JAKOV\METHOD\INT.M
Last changed    : 20.08.2015 19:21:48 by jkv
                  (modified after loading)
Additional Info : Peak(s) manually integrated
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   9.999 BV    0.0324    4.08141    2.08409  0.45230
   2  10.101 VB    0.0387  898.28186  359.77570 99.54770

Totals :                   902.36327  361.85978
```

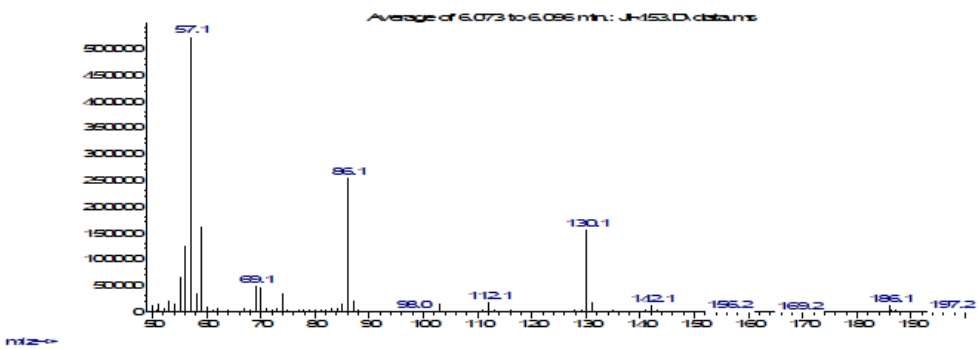
JI-453
Method: JI_M300_S 29.07.2015

Chromatogram:



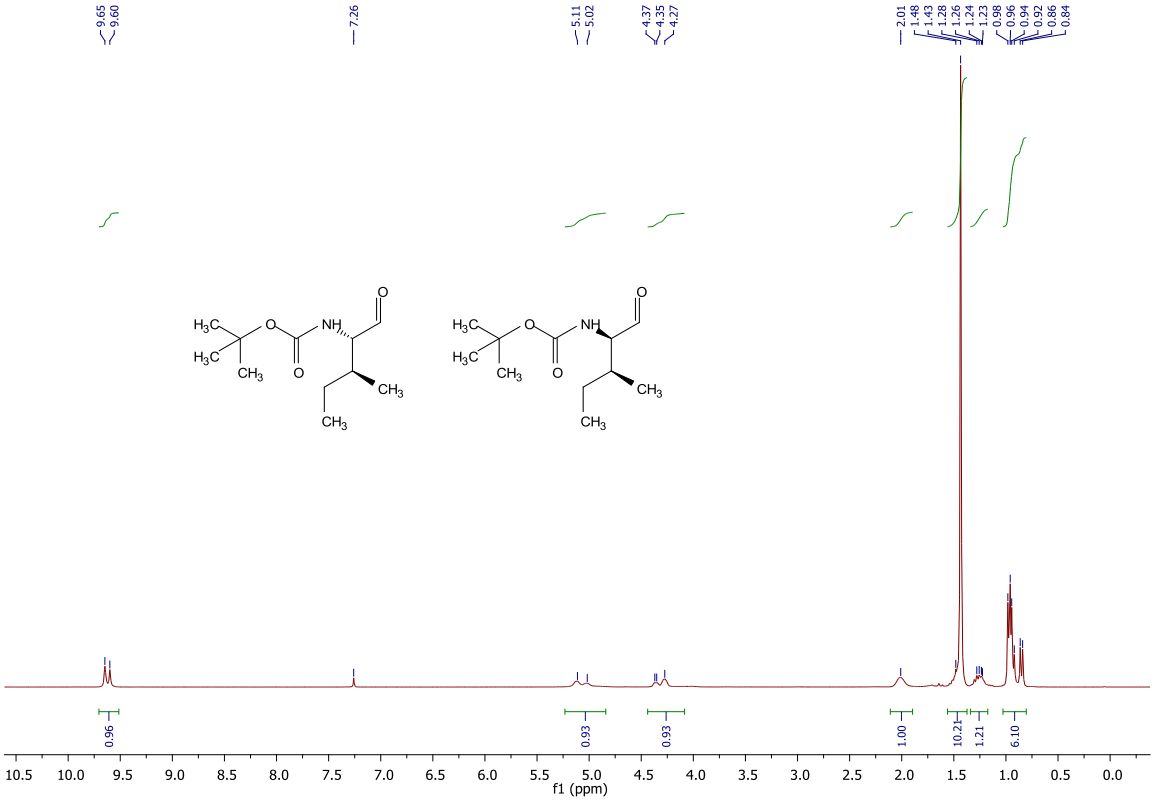
t_R [min]	A [%]:	A
6.085	100.0%	31301873

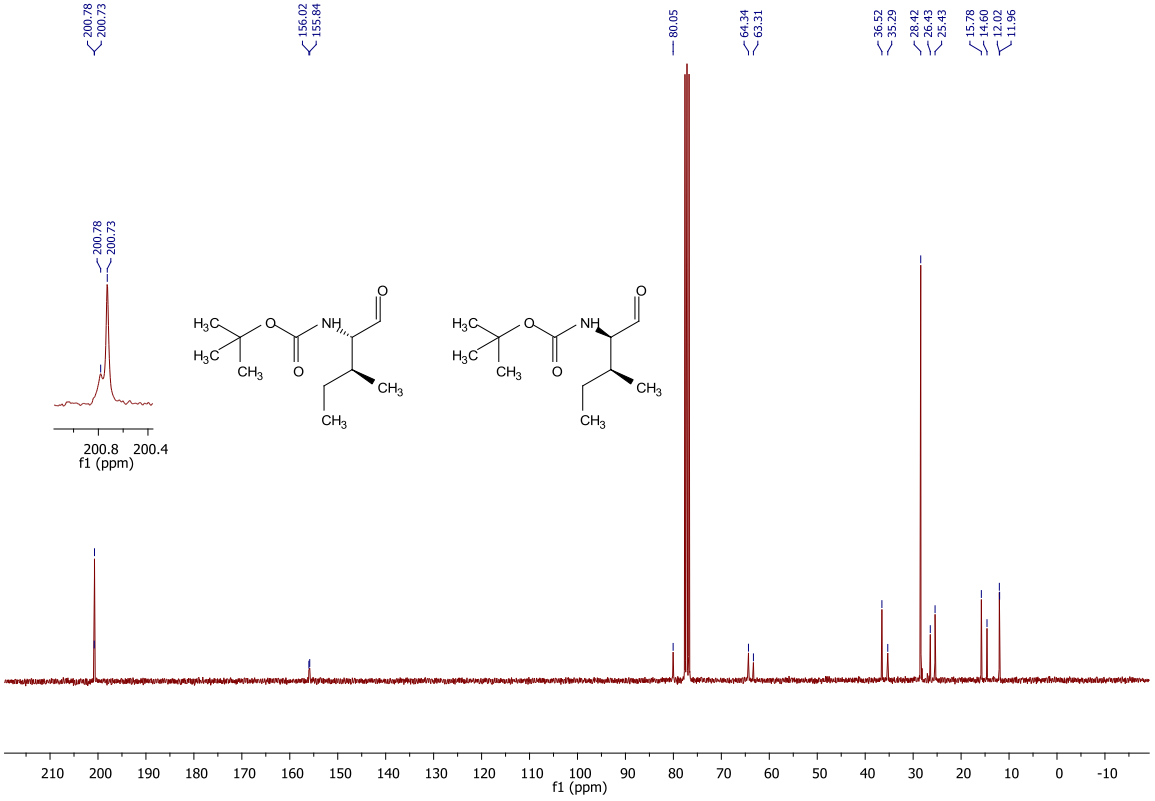
MS Spectra:

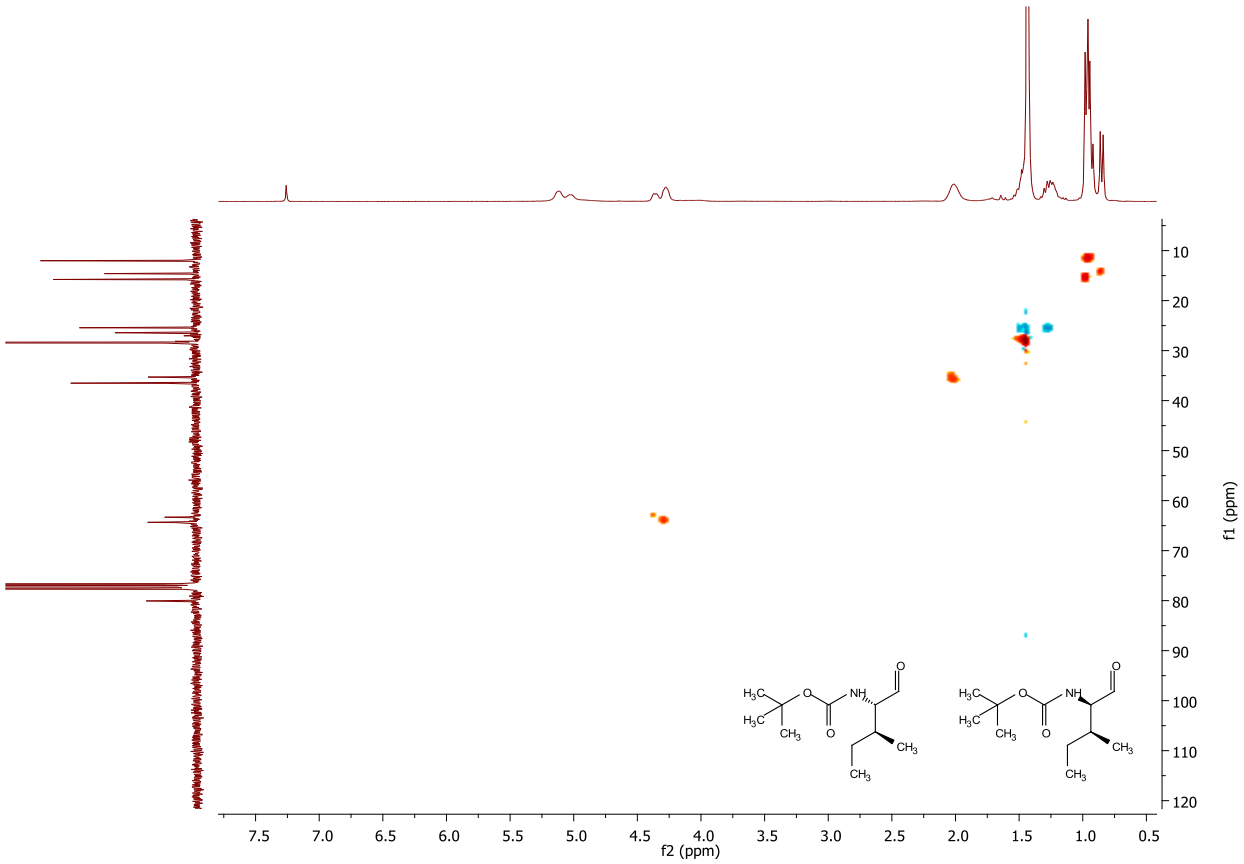


57 (100), 69 (9), 86 (47), 112 (3), 130 (29), 142 (2), 186 (2)

^{1}H-, ^{13}C- and HSQC NMR spectra, GC-FID chromatogram and GCMS spectra of mixture of epimers: *tert*-butyl (*(2S,3S)*-3-methyl-1-oxopentan-2-yl)carbamate (*(2S,3S)*-3f) and *tert*-butyl (*(2R,3S)*-3-methyl-1-oxopentan-2-yl)carbamate (*(2R,3S)*-3f)

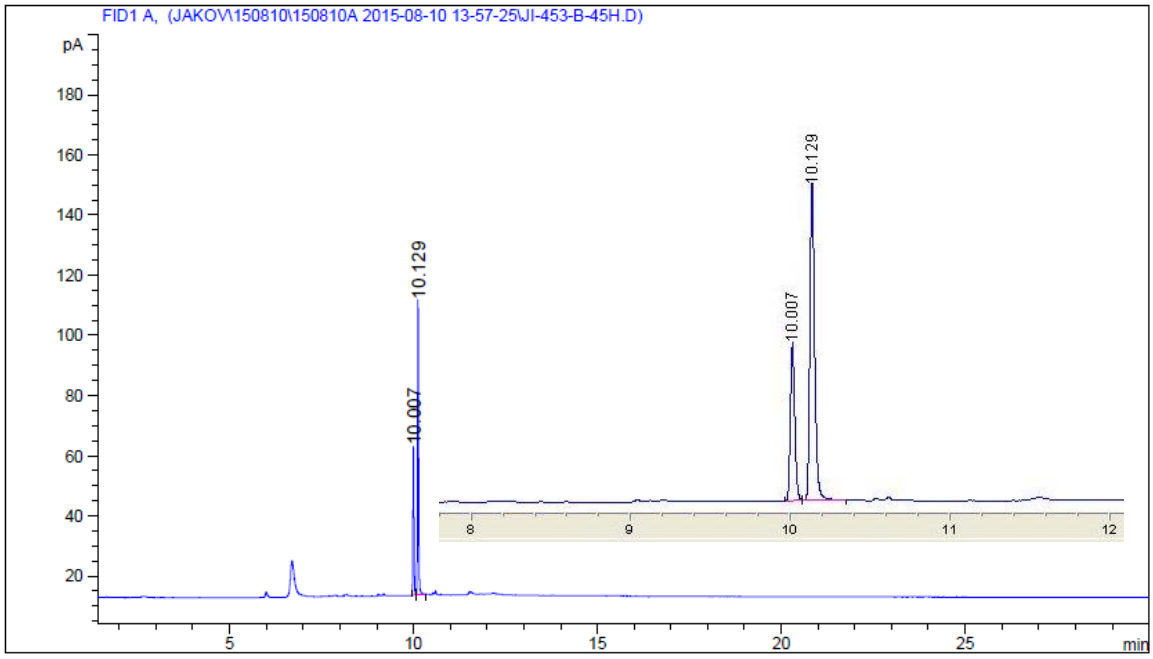





7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
10
20
30
40
50
60
70
80
90
100
110
120
f1 (ppm)
H3C
CH3
O
NH
CH3

Data File D:\GC\1\DATA\JAKOV\150810\150810A 2015-08-10 13-57-25\JI-453-B-45H.D
Sample Name: JI-453-B-45h

```
======================================================================
Acq. Operator    : jkv                          Seq. Line :   1
Acq. Instrument : GC Pal                         Location : P1-D-06
Injection Date   : 10.08.2015 14:01:32               Inj :   1
                                                Inj Volume : External
Acq. Method      : D:\GC\1\DATA\JAKOV\150810\150810A 2015-08-10 13-57-25\AMAL_GCPAL.M
Last changed     : 29.07.2015 18:50:33 by jkv
Analysis Method : D:\GC\1\DATA\JAKOV\METHOD\INT.M
Last changed     : 13.08.2015 14:12:57 by jkv
                   (modified after loading)
```

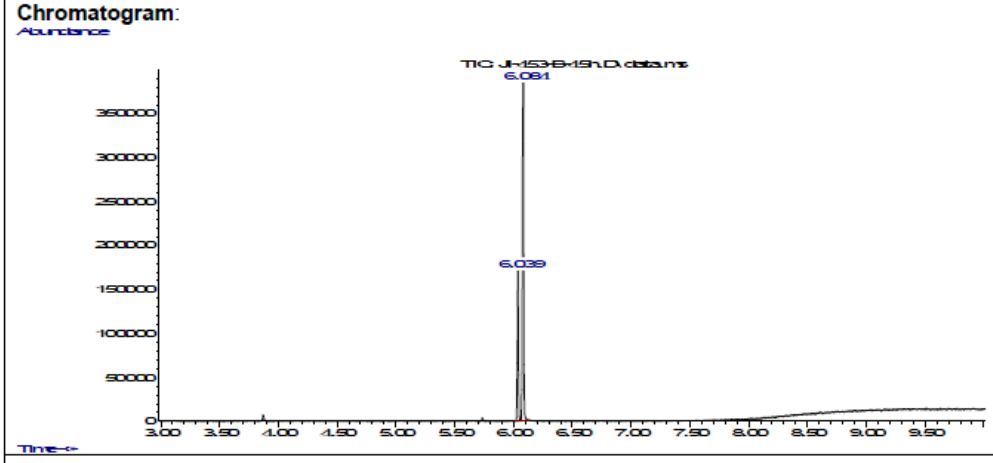



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  10.007 BB    0.0323   93.81950   48.11873 31.57841
   2  10.129 BB    0.0342  203.28065   96.49541 68.42159

Totals :                   297.10015  144.61414
```

JI-453-B-45h

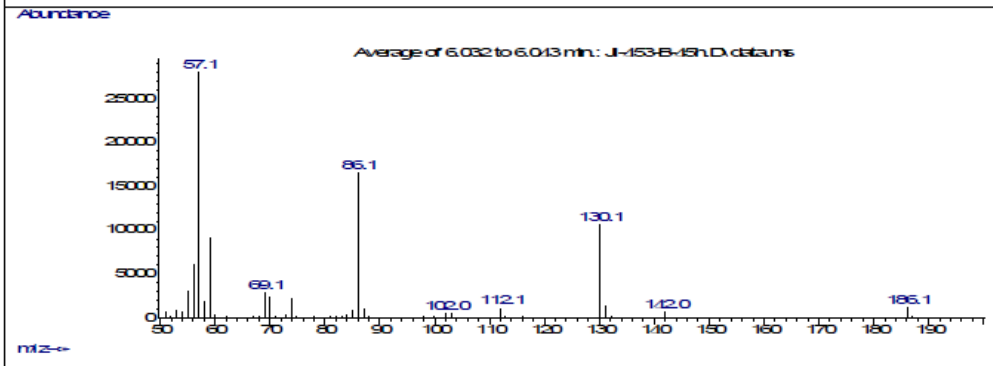
Method: JI_M300_S 10.08.2015

Chromatogram:

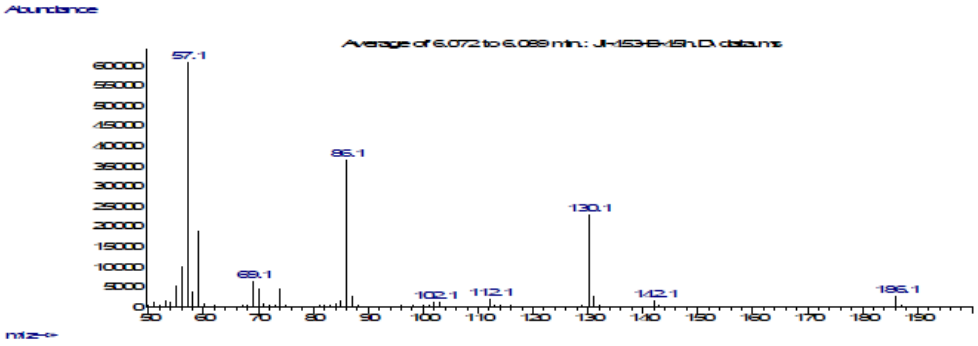


t_R [min]	A [%]:	A
6.039	26.5%	1035332
6.084	73.5%	2864847

MS Spectra:

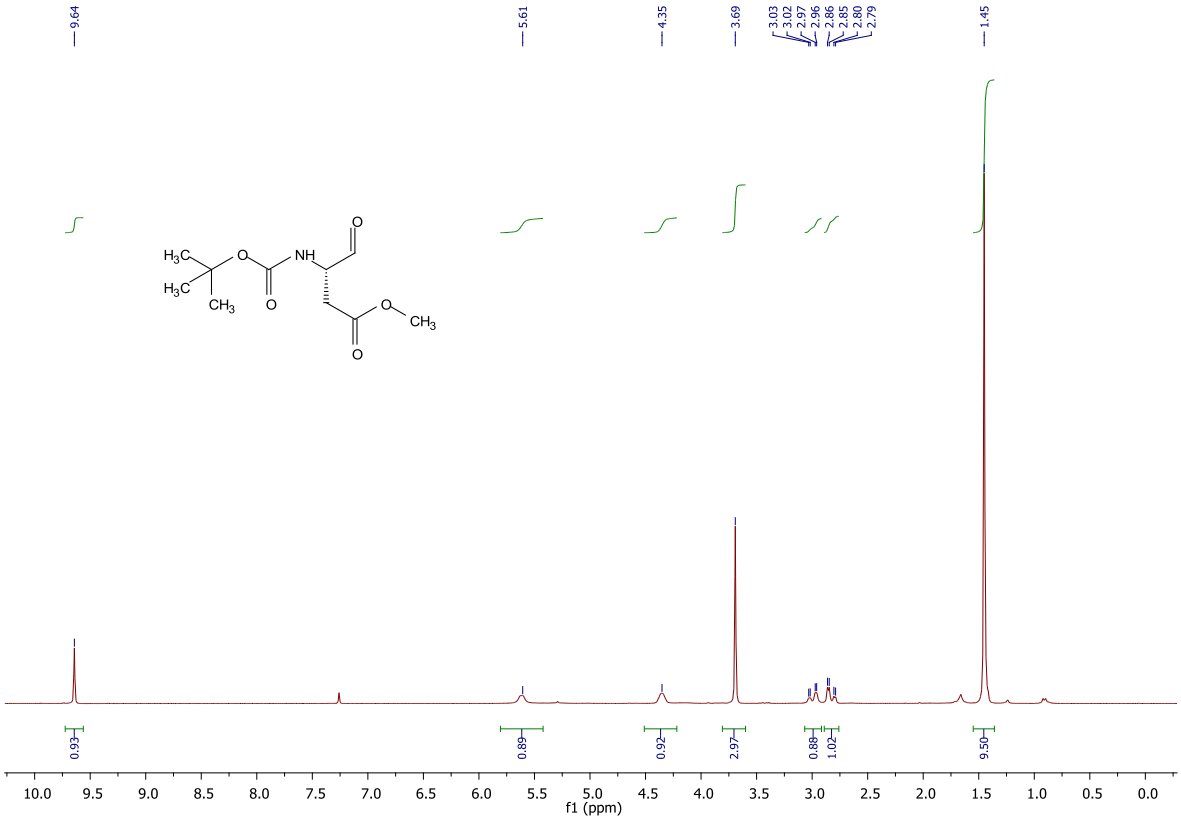


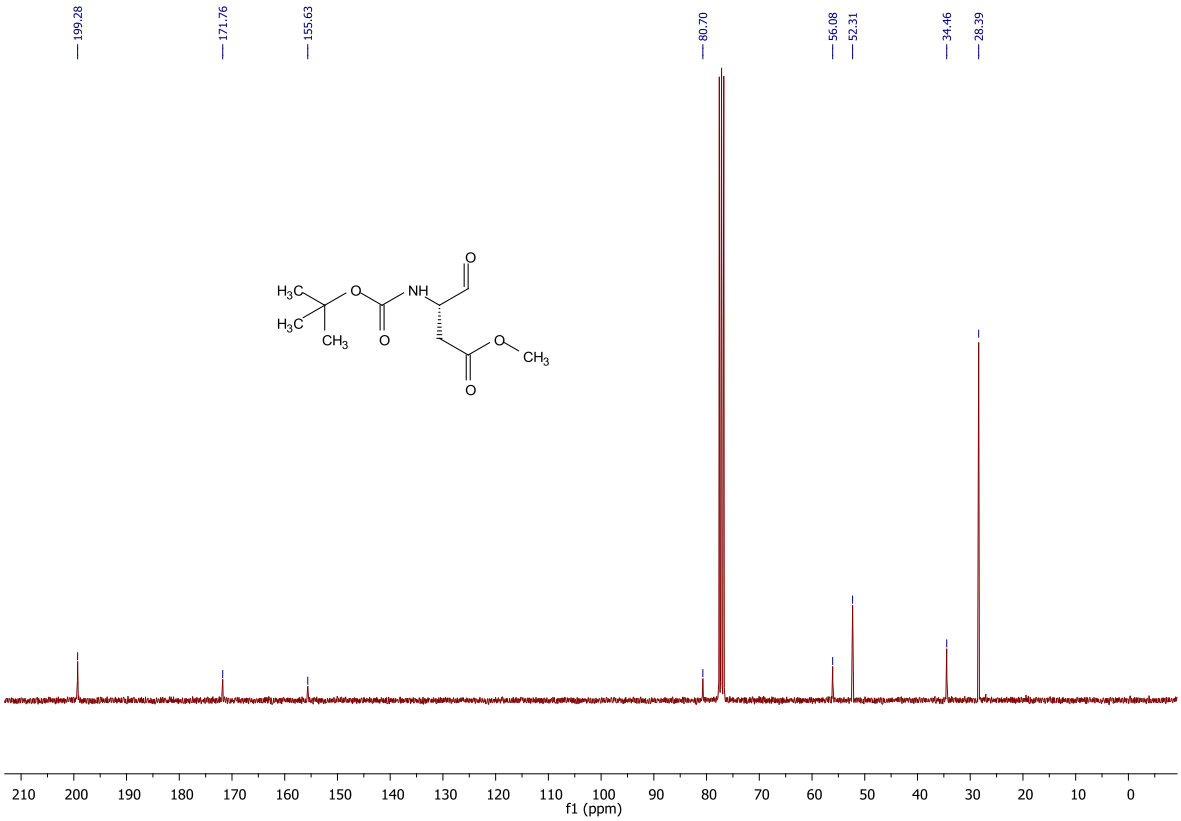
57 (100), 69 (10), 86 (56), 112 (4), 130 (36), 142 (3), 186 (4)



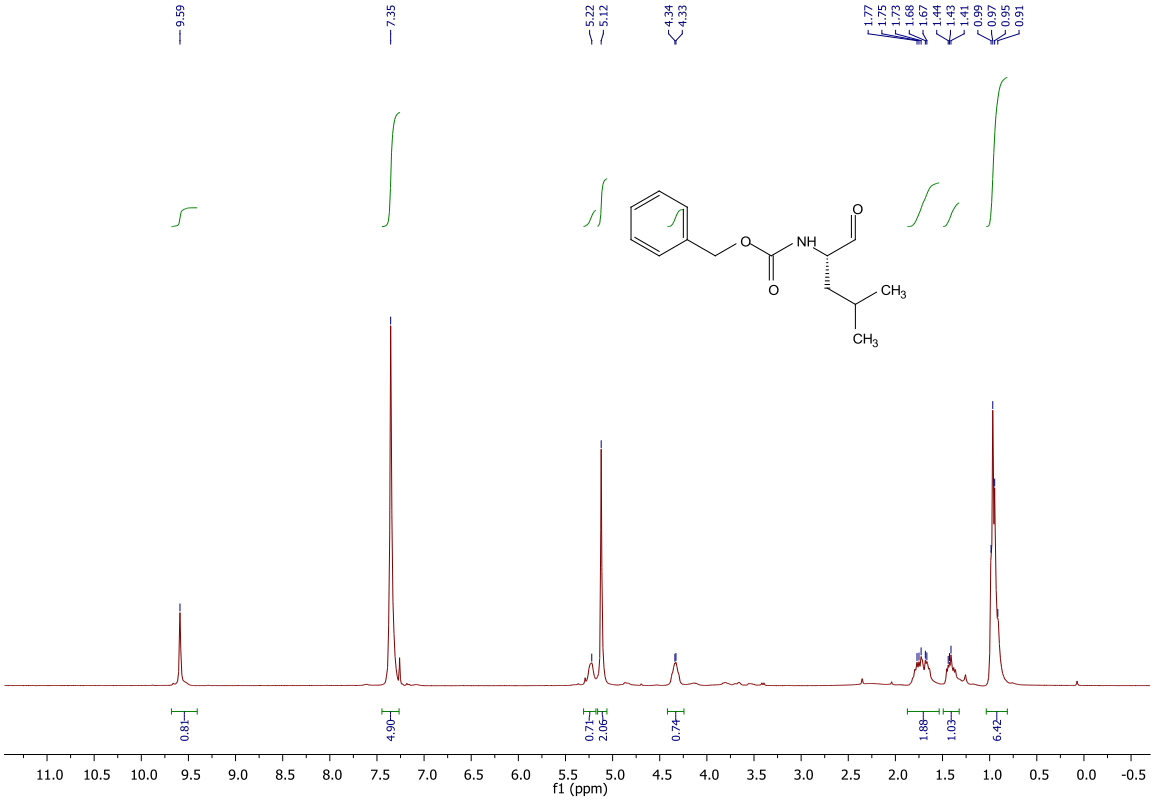
57 (100), 69 (10), 86 (57), 112 (3), 130 (36), 142 (3), 186 (4)

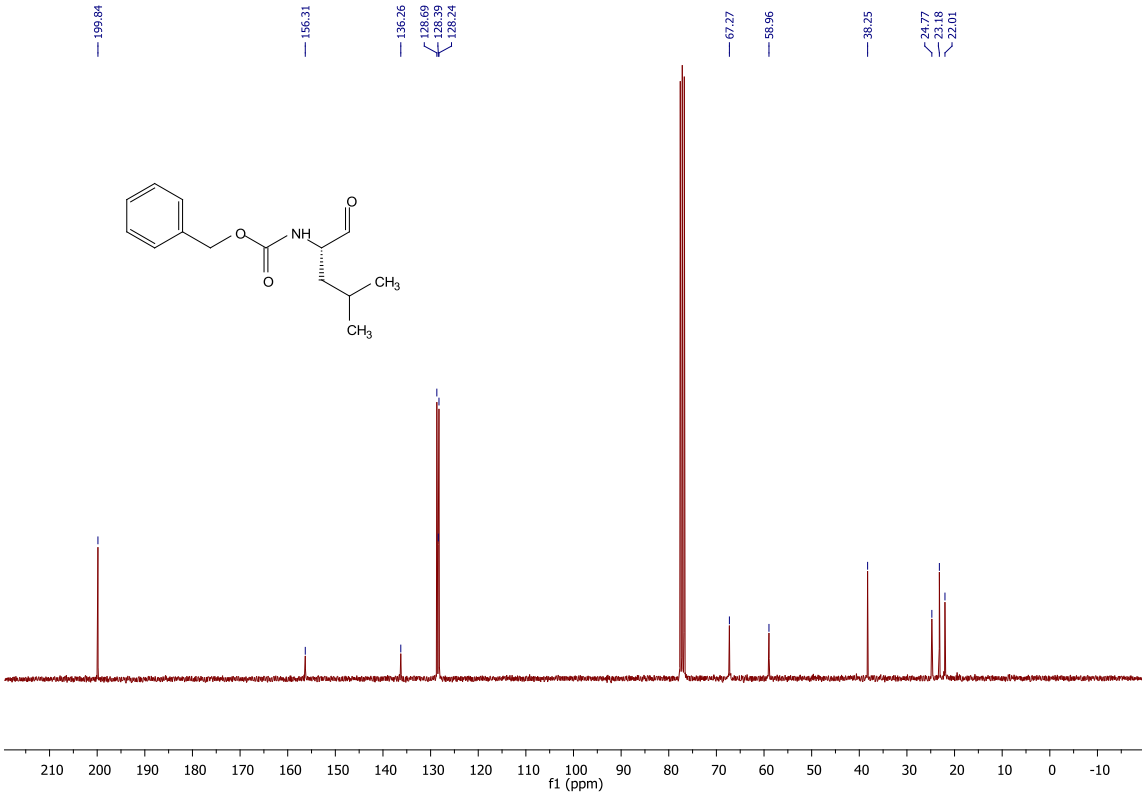
^{1}H- and ^{13}C- NMR spectra of methyl *(S)*-3-((*tert*-butoxycarbonyl)amino)-4-oxobutanoate (3g)

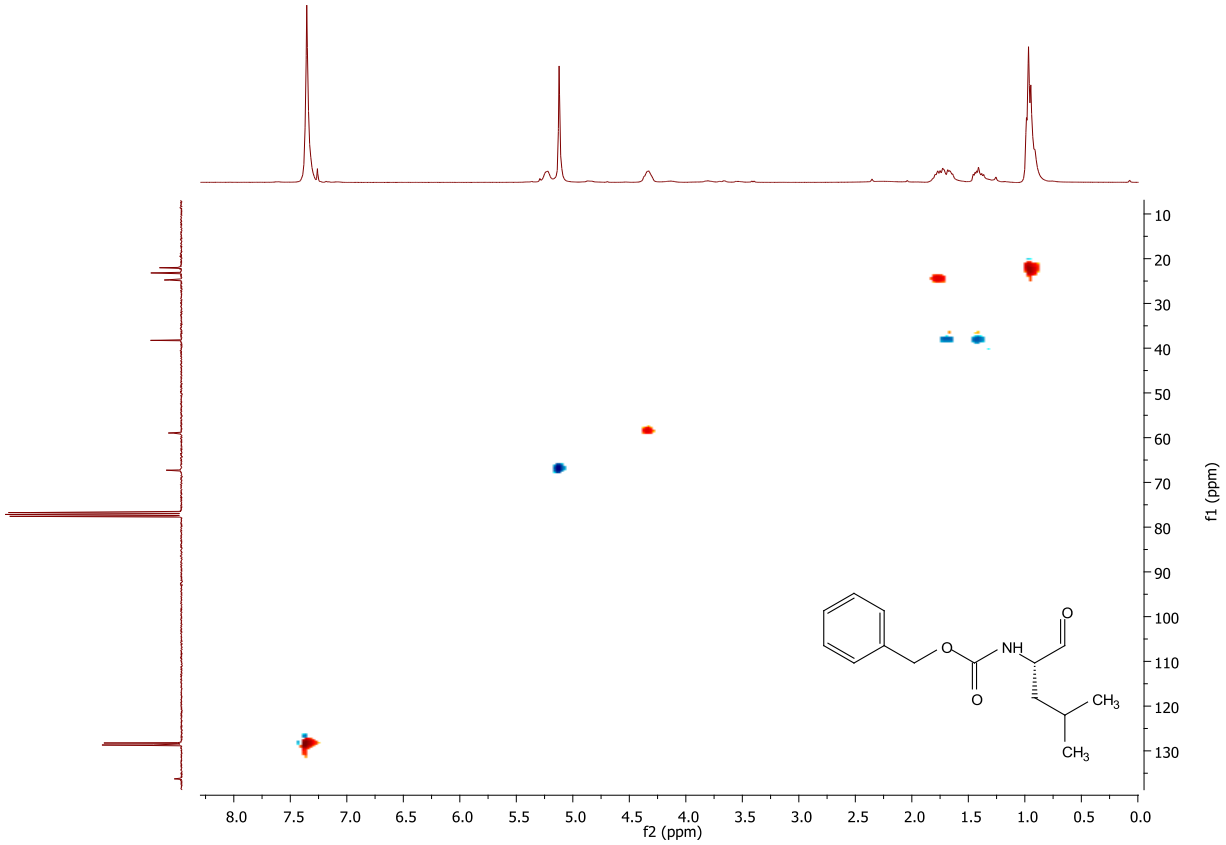




^{1}H-, ^{13}C- NMR and HSQC spectra, and GC-FID chromatograms (enantiopure and racemic) of benzyl (*S*)-(4-methyl-1-oxopentan-2-yl)carbamate (3h)

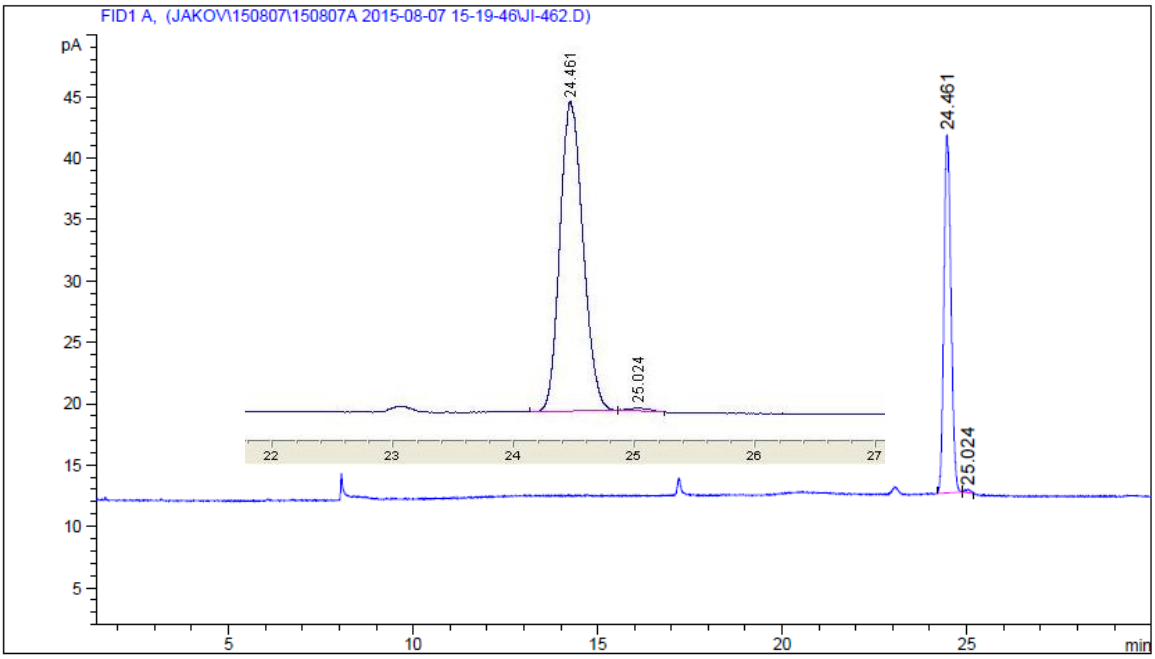





f1 (ppm)
f2 (ppm)
O
NH
O
O
CH3
CH3

Data File D:\GC\1\DATA\JAKOV\150807\150807A 2015-08-07 15-19-46\JI-462.D
Sample Name: JI-462

```
=====================================================================
Acq. Operator    : jkv                          Seq. Line :   2
Acq. Instrument  : GC Pal                        Location : P1-D-02
Injection Date   : 07.08.2015 15:55:37               Inj :   1
                                                Inj Volume : External
Acq. Method      : D:\GC\1\DATA\JAKOV\150807\150807A 2015-08-07 15-19-46\AMAL_GCPAL.M
Last changed     : 29.07.2015 18:50:33 by jkv
Analysis Method  : D:\GC\1\DATA\JAKOV\METHOD\INT.M
Last changed     : 20.08.2015 19:08:53 by jkv
                   (modified after loading)
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  24.461 BB    0.2053  388.27646   29.09629 99.32977
   2  25.024 BBA   0.1590    2.61991 2.34725e-1  0.67023

Totals :                   390.89637   29.33102
```

Data File D:\GC\1\DATA\JAKOV\150807\150807A 2015-08-07 15-19-46\JI-463-RAC.D
Sample Name: JI-463-rac

```
======================================================================
Acq. Operator    : jkv                          Seq. Line :   1
Acq. Instrument : GC Pal                         Location : P1-D-01
Injection Date   : 07.08.2015 15:21:15               Inj :   1
                                                Inj Volume : External
Acq. Method      : D:\GC\1\DATA\JAKOV\150807\150807A 2015-08-07 15-19-46\AMAL_GCPAL.M
Last changed     : 29.07.2015 18:50:33 by jkv
Analysis Method : D:\GC\1\DATA\JAKOV\METHOD\INT.M
Last changed     : 20.08.2015 19:03:50 by jkv
                   (modified after loading)
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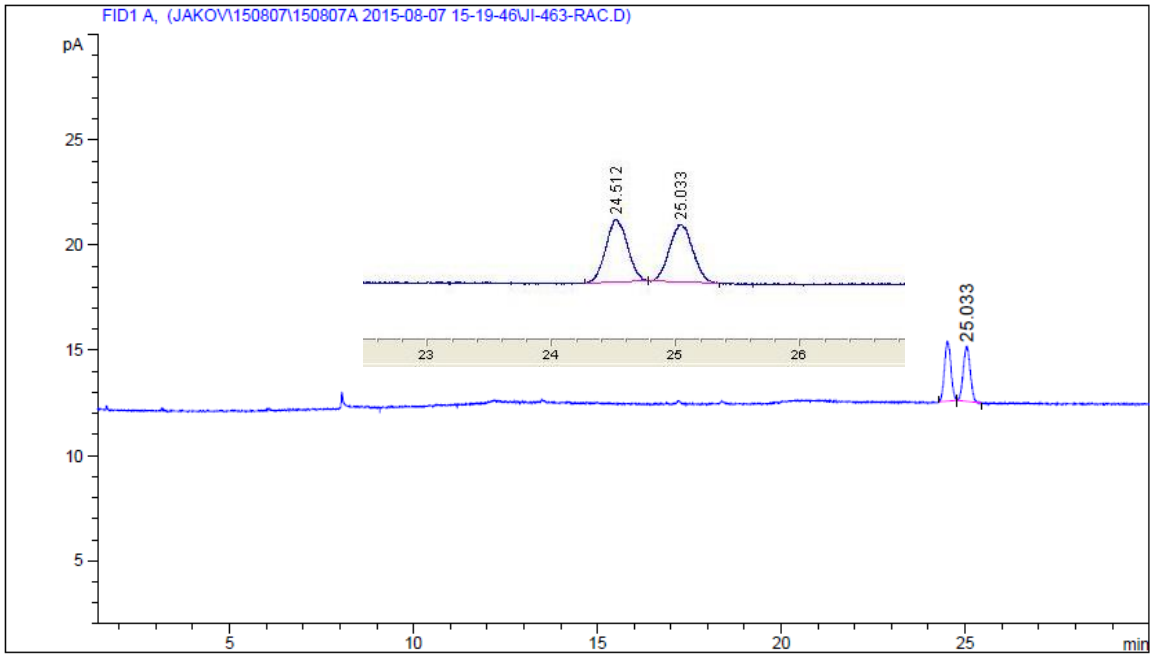



```
======================================================================
                        Area Percent Report
======================================================================

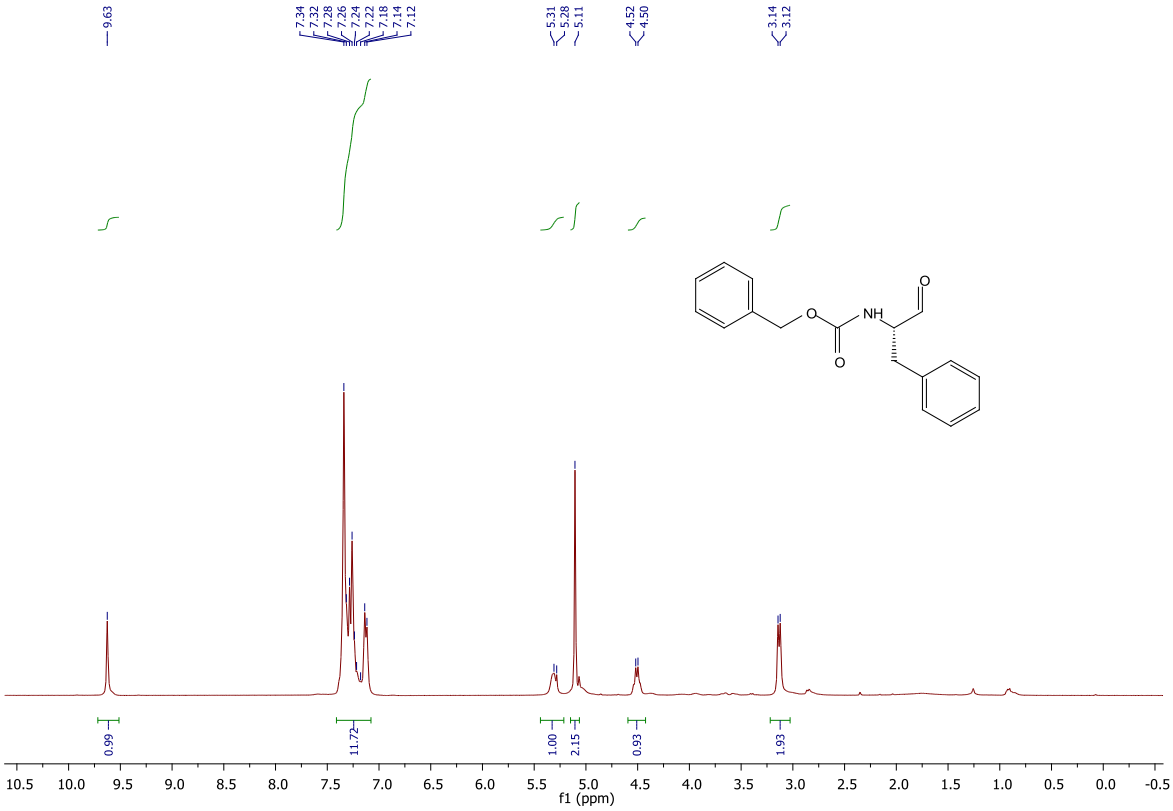
Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

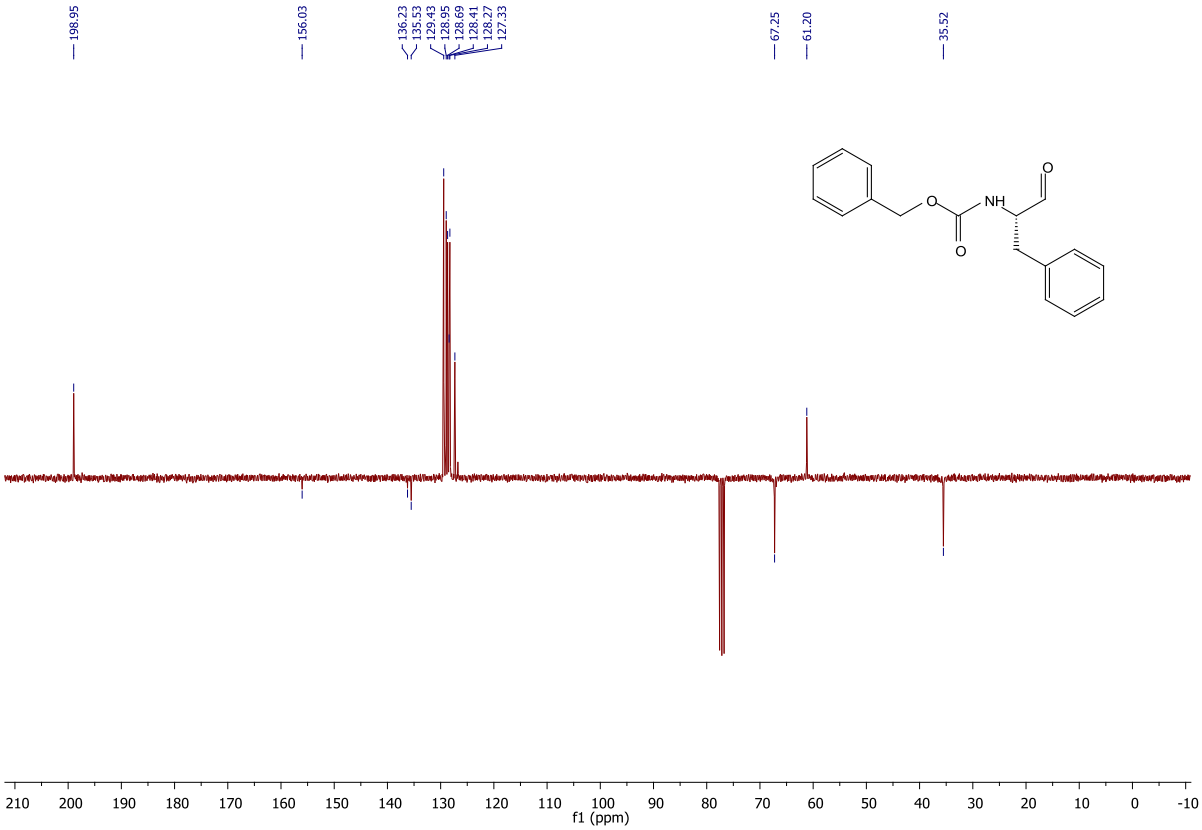

Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  24.512 BB    0.1719   34.82494    2.83855 49.98275
   2  25.033 BB    0.2071   34.84898    2.60788 50.01725

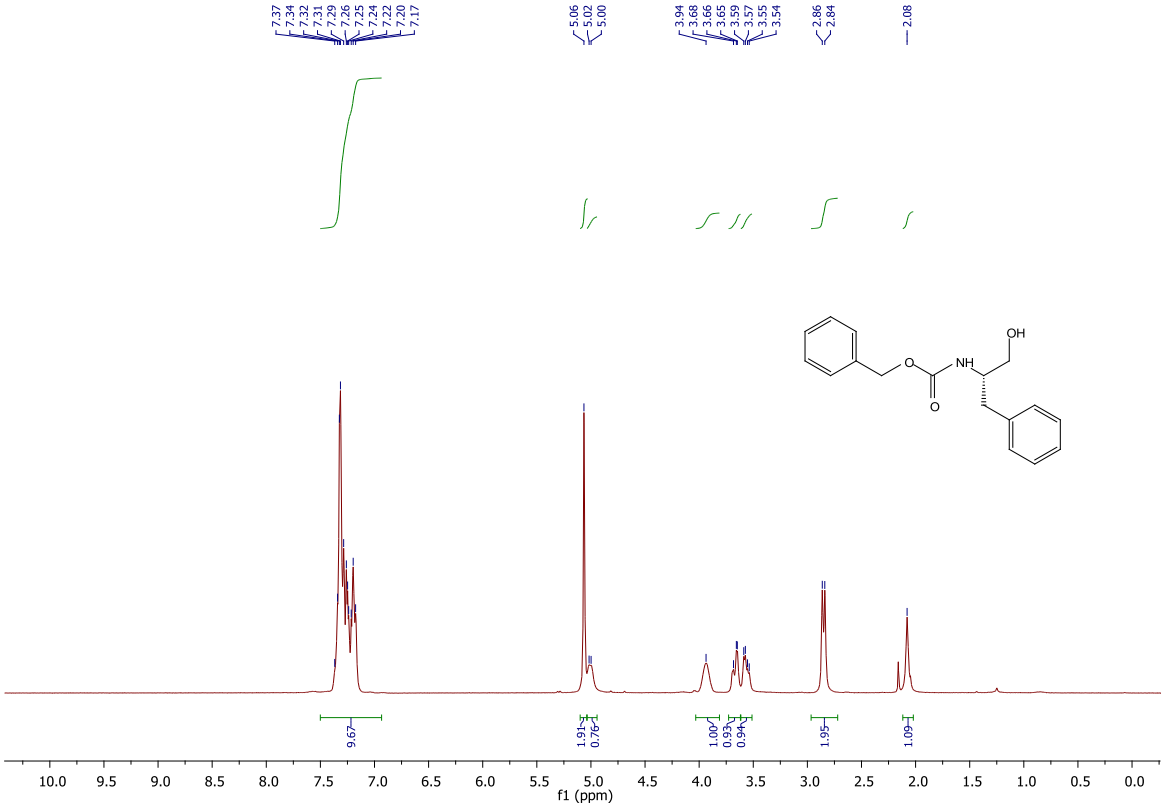
Totals :                    69.67392    5.44643
```

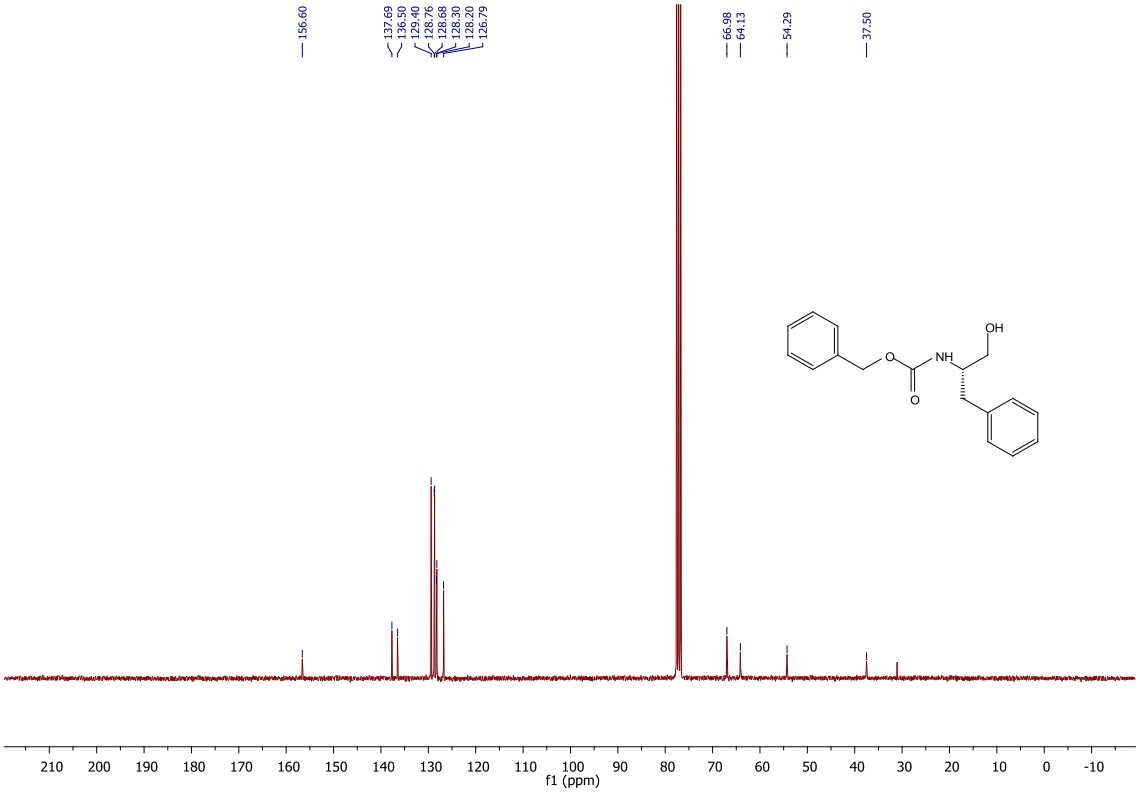
^{1}H- and ^{13}C- NMR spectra benzyl (*S*)-(1-oxo-3-phenylpropan-2-yl)carbamate (3i)





^{1}H- and ^{13}C- NMR spectra, and chiral HPLC chromatograms (enantiopure and racemic) of benzyl (*S*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate (8i)





Data File D:\CHEMSTATION\HPLC LINKS\DATA\JAKOV\150808A 2015-08-08 21-16-11\JI-464-B 2.D
Sample Name: JI-464-B 2

```
=====================================================================
Acq. Operator    : jakov                          Seq. Line :   4
Acq. Instrument : HPLC links                       Location : Vial 22
Injection Date   : 08.08.2015 23:31:25                  Inj :   1
                                                  Inj Volume : 3.0 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 30.0 µl
Acq. Method      : D:\CHEMSTATION\HPLC LINKS\DATA\JAKOV\150808A 2015-08-08 21-16-11\ADH_
                   HEPTPROH_90_10.M
Last changed     : 08.08.2015 22:03:38 by jakov
Analysis Method : D:\CHEMSTATION\HPLC LINKS\METHODS\JAKOV\INT.M
Last changed     : 09.08.2015 11:56:06 by jakov
                   (modified after loading)
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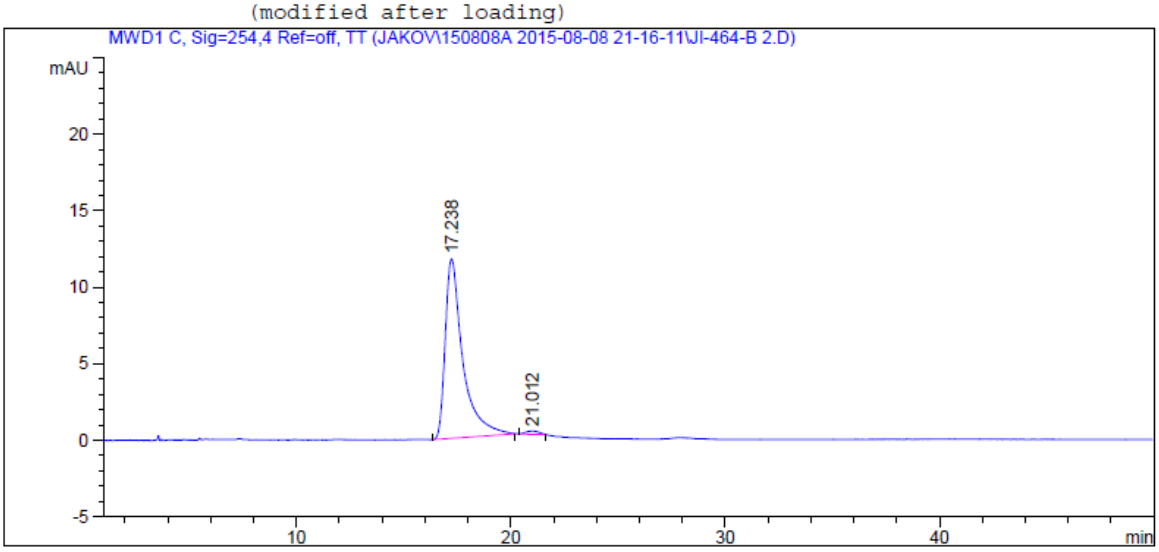
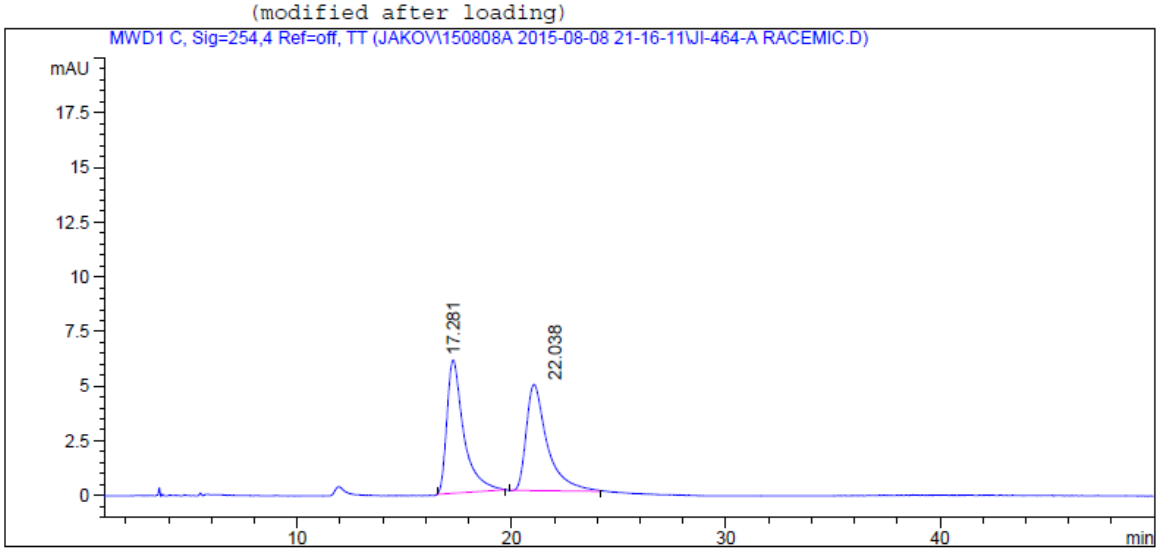



```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 C, Sig=254,4 Ref=off, TT

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  17.238 BB    0.8070  668.83026   11.73473  98.6409
   2  21.012 BBA   0.4980    9.21526 2.21237e-1   1.3591

Totals :                   678.04552   11.95597


=====================================================================
                        *** End of Report ***
```

Data File D:\CHEMSTA...PLC LINKS\DATA\JAKOV\150808A 2015-08-08 21-16-11\JI-464-A RACEMIC.D
Sample Name: JI-464-A rac

```
    ======================================================================
    Acq. Operator    : jakov                          Seq. Line :   6
    Acq. Instrument  : HPLC links                      Location : Vial 21
    Injection Date   : 09.08.2015 01:13:56                  Inj :   1
                                                     Inj Volume : 3.0 µl
    Different Inj Volume from Sequence !     Actual Inj Volume : 30.0 µl
    Acq. Method      : D:\CHEMSTATION\HPLC LINKS\DATA\JAKOV\150808A 2015-08-08 21-16-11\ADH_
                       HEPTPROH_90_10.M
    Last changed     : 08.08.2015 22:03:38 by jakov
    Analysis Method  : D:\CHEMSTATION\HPLC LINKS\METHODS\JAKOV\INT.M
    Last changed     : 09.08.2015 12:04:07 by jakov
                       (modified after loading)
```

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    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier:                   :      1.0000
    Dilution:                     :      1.0000
    Use Multiplier & Dilution Factor with ISTDs

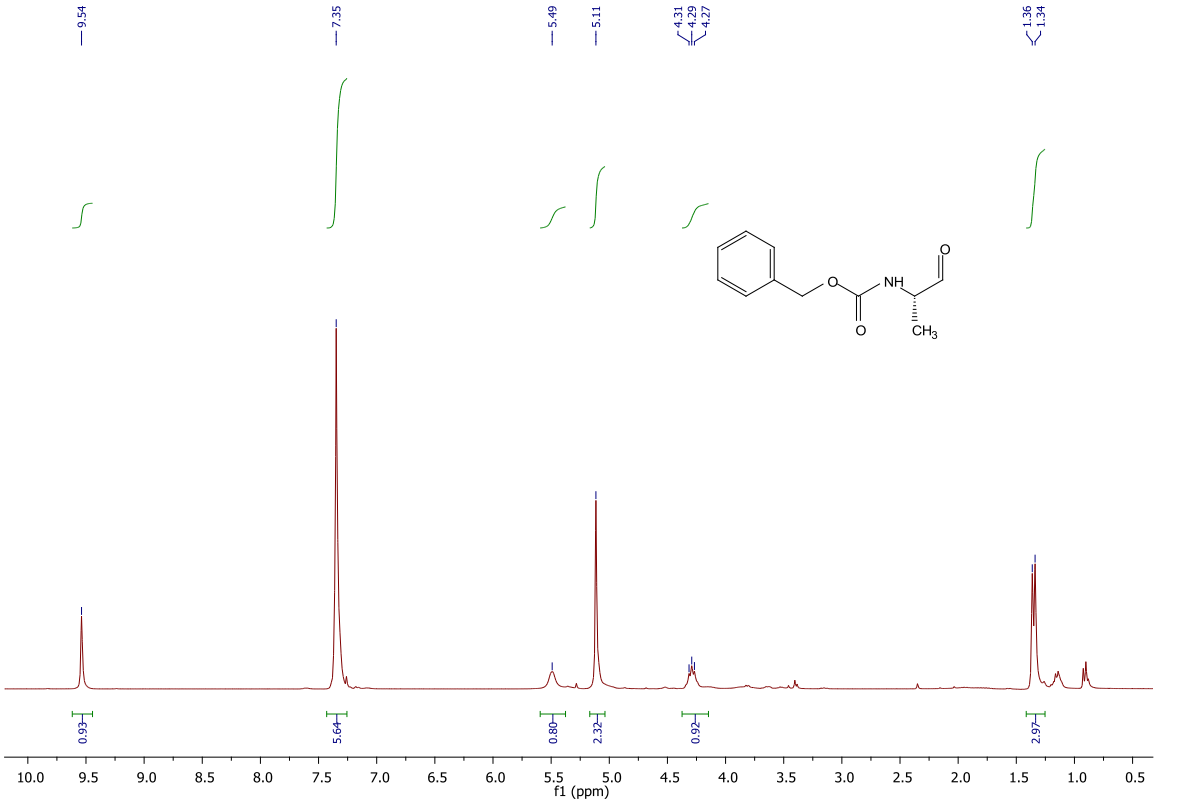

    Signal 1: MWD1 C, Sig=254,4 Ref=off, TT

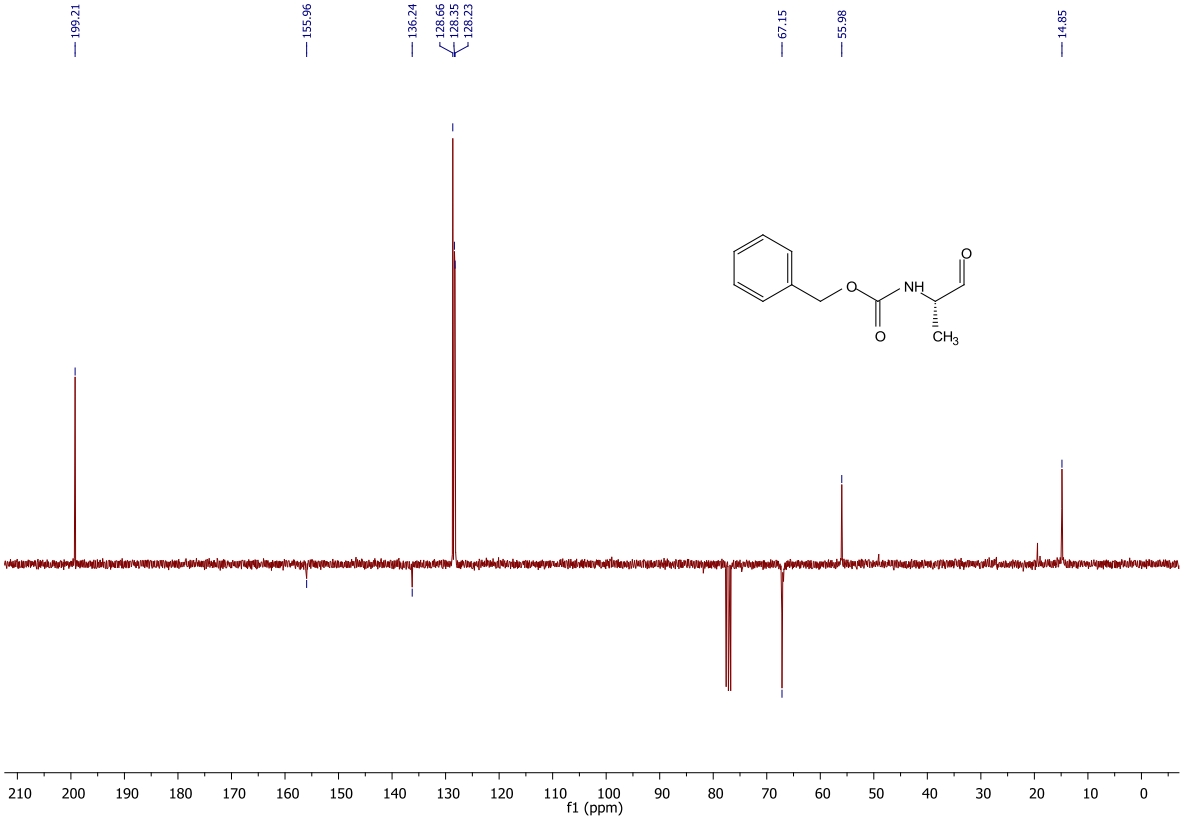
    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  17.281 BB    0.7845  332.86594    6.08177  50.0895
       2  22.038 VVA+  1.1351  331.67657    4.87000  49.9105

    Totals :                   664.54251   10.95177

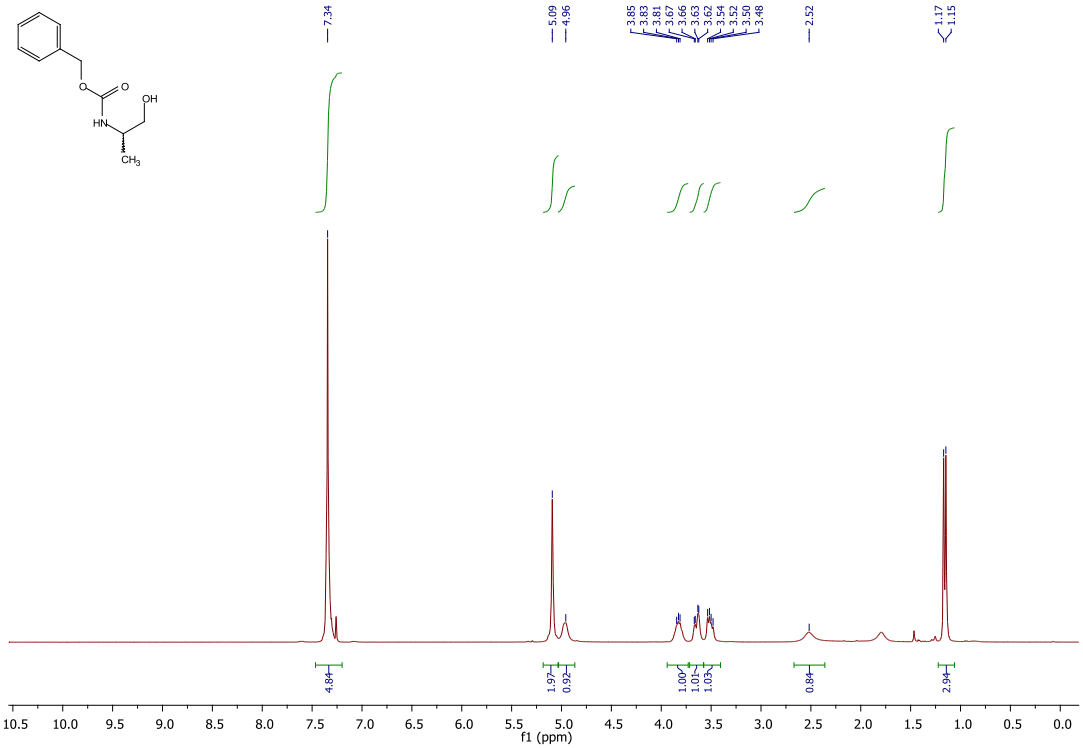

    ======================================================================
                            *** End of Report ***
```

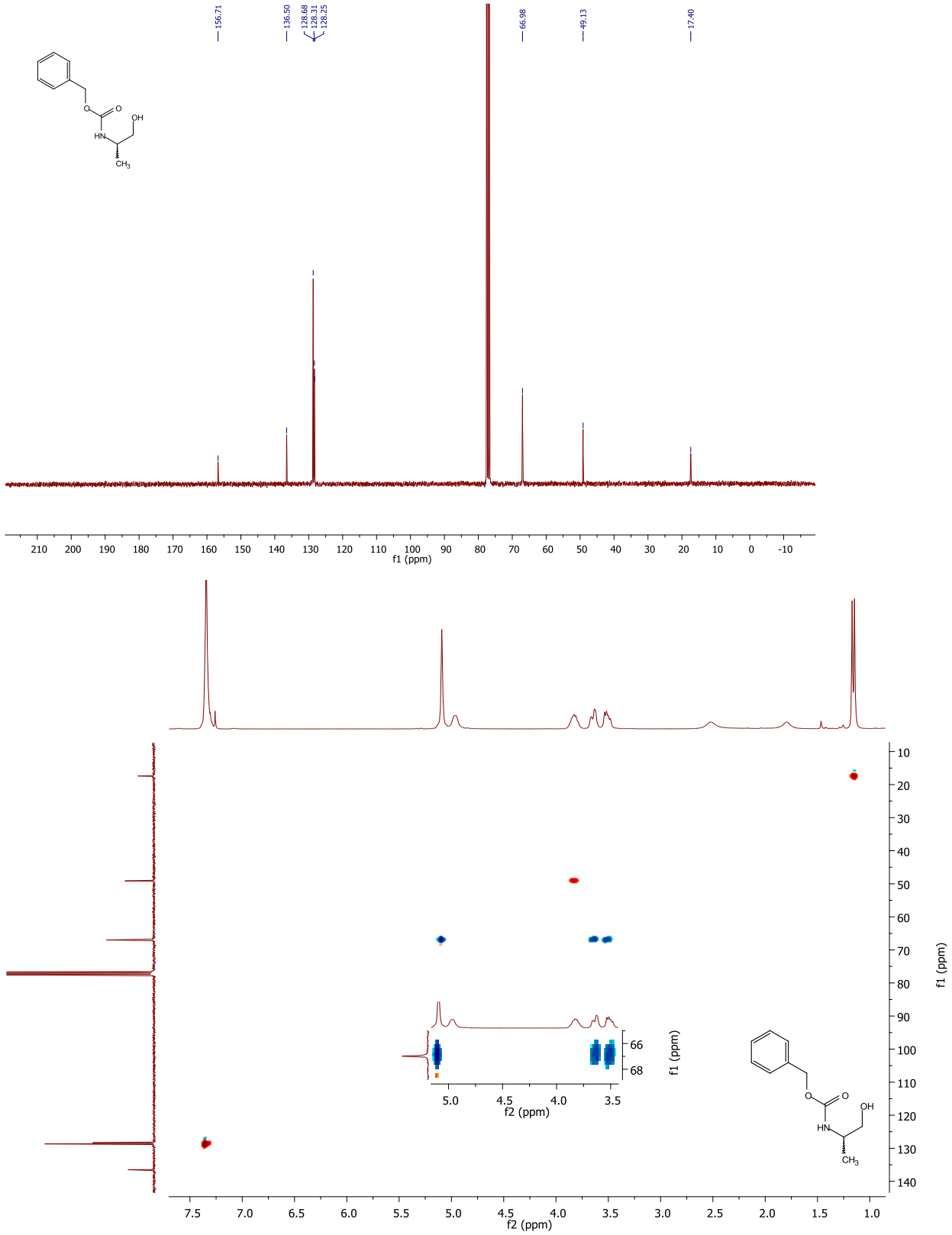
^{1}H- and ^{13}C- NMR spectra of benzyl (*S*)-(1-oxopropan-2-yl)carbamate (3j)





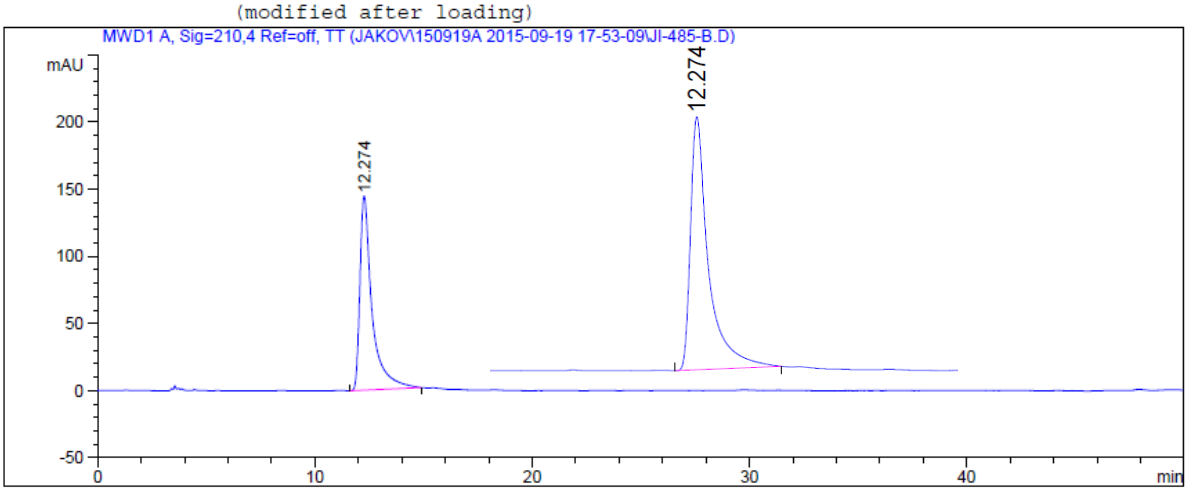
^{1}H-, ^{13}C- and HSQC NMR spectra, and chiral HPLC chromatograms (enantiopure and racemic) of benzyl (*S*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate (8j)




156.71
136.50
128.68
128.31
128.25
66.98
49.13
17.40
f1 (ppm)
f2 (ppm)
f1 (ppm)
66
68
f2 (ppm)
f1 (ppm)
OH
HN
CH3

Data File D:\CHEMSTATION\HPLC LINKS\DATA\JAKOV\150919A 2015-09-19 17-53-09\JI-485-B.D
Sample Name: JI-485-B

```
=====================================================================
Acq. Operator   : jakov                          Seq. Line :   6
Acq. Instrument : HPLC links                     Location : Vial 53
Injection Date  : 19.09.2015 22:18:35                 Inj :   1
                                                 Inj Volume : 3.0 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 2.0 µl
Acq. Method     : D:\CHEMSTATION\HPLC LINKS\DATA\JAKOV\150919A 2015-09-19 17-53-09\ADH_
                  HEPTIPROH_90_10.M
Last changed    : 19.09.2015 17:41:23 by jakov
Analysis Method : D:\CHEMSTATION\HPLC LINKS\METHODS\JAKOV\INT.M
Last changed    : 20.09.2015 13:15:50 by jakov
                  (modified after loading)
```




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs

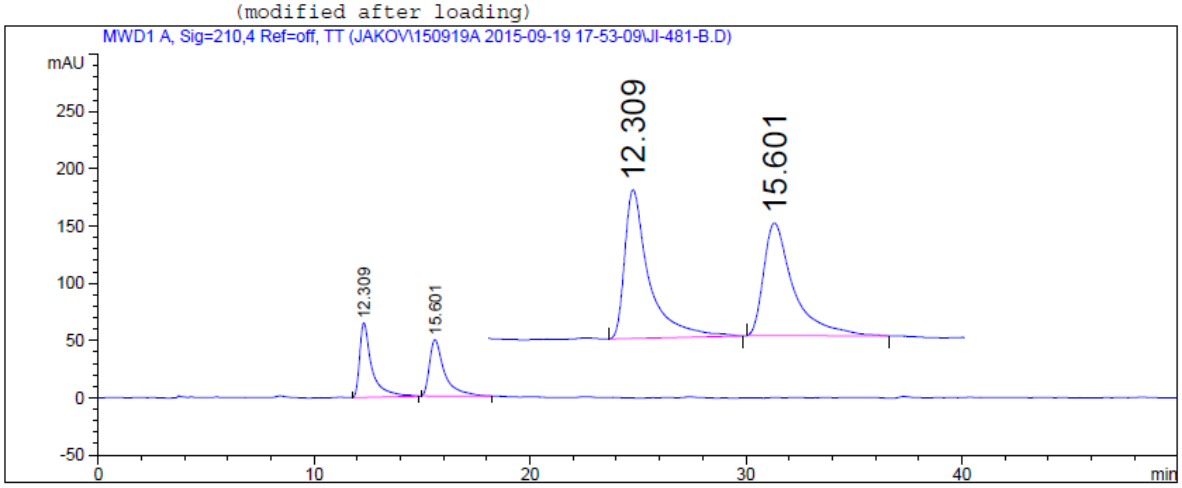

Signal 1: MWD1 A, Sig=210,4 Ref=off, TT

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.274 VBA   0.5836 5630.50195  144.19669 100.0000

Totals :                  5630.50195  144.19669
```

Data File D:\CHEMSTATION\HPLC LINKS\DATA\JAKOV\150919A 2015-09-19 17-53-09\JI-481-B.D
Sample Name: JI-481-B

```
=====================================================================
Acq. Operator   : jakov                          Seq. Line :   9
Acq. Instrument : HPLC links                     Location : Vial 43
Injection Date  : 20.09.2015 00:53:34                 Inj :   1
                                                 Inj Volume : 3.0 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 2.0 µl
Acq. Method     : D:\CHEMSTATION\HPLC LINKS\DATA\JAKOV\150919A 2015-09-19 17-53-09\ADH_
                  HEPTIPROH_90_10.M
Last changed    : 19.09.2015 17:41:23 by jakov
Analysis Method : D:\CHEMSTATION\HPLC LINKS\METHODS\JAKOV\INT.M
Last changed    : 20.09.2015 13:04:33 by jakov
                  (modified after loading)
```




```
=====================================================================
                        Area Percent Report
=====================================================================

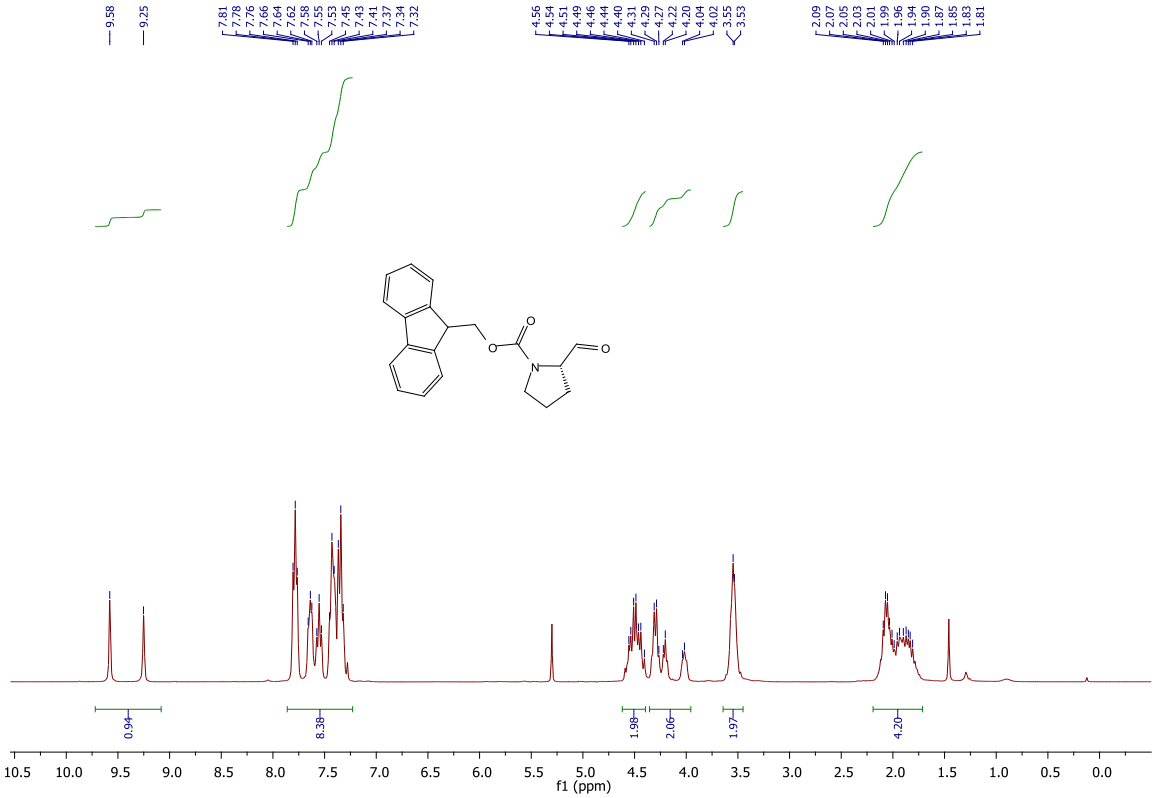
Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs

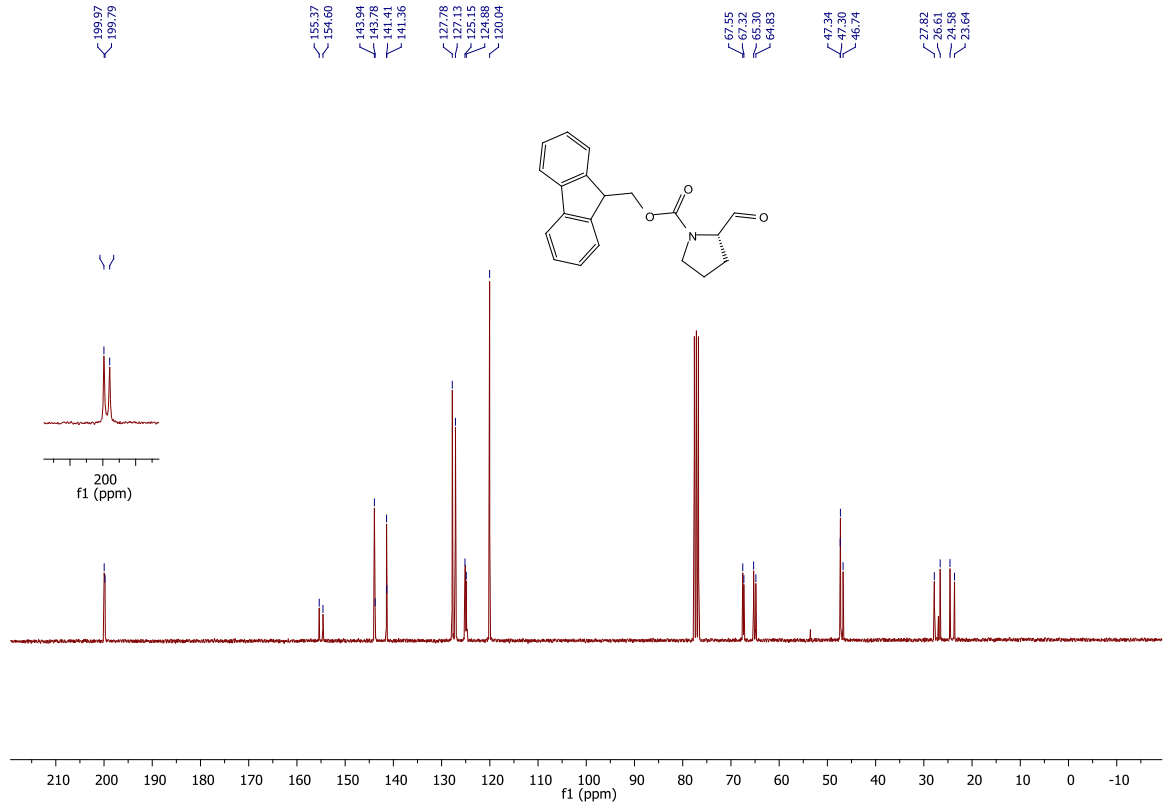

Signal 1: MWD1 A, Sig=210,4 Ref=off, TT

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  12.309 BBA   0.5722 2560.35425   64.91381  51.7055
   2  15.601 BBA   0.7103 2391.44458   49.26488  48.2945

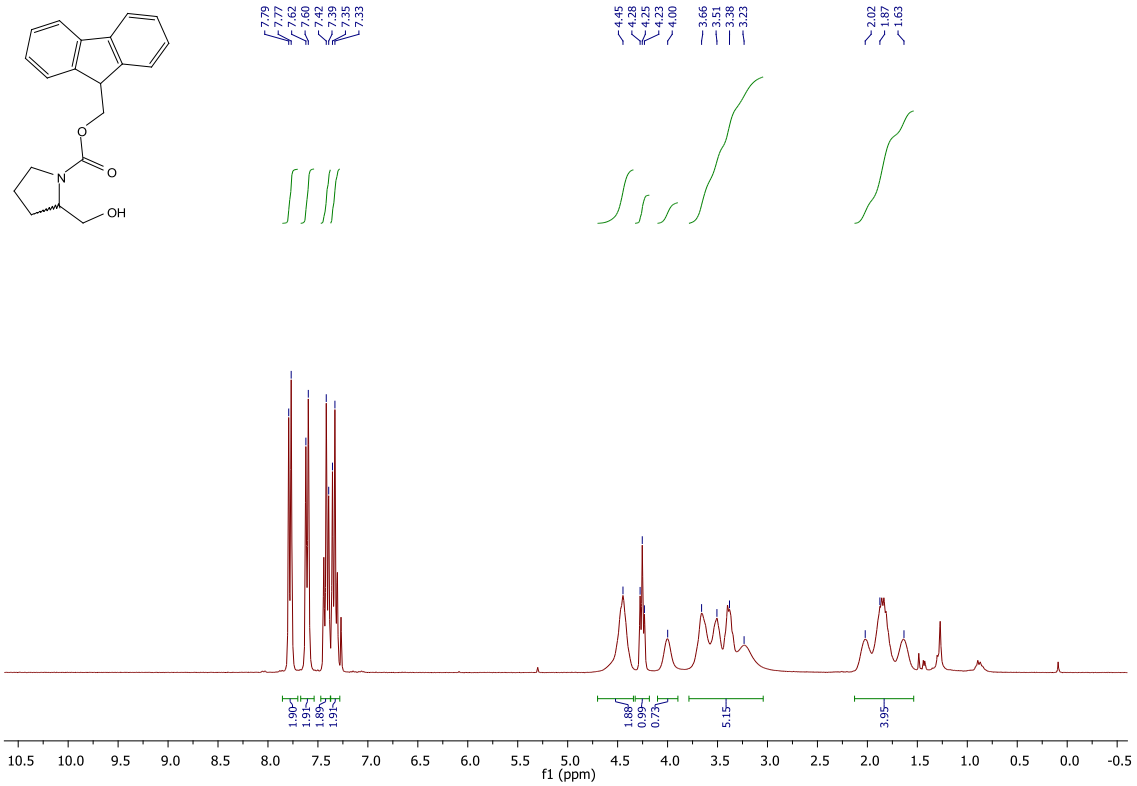
Totals :                  4951.79883  114.17870
```

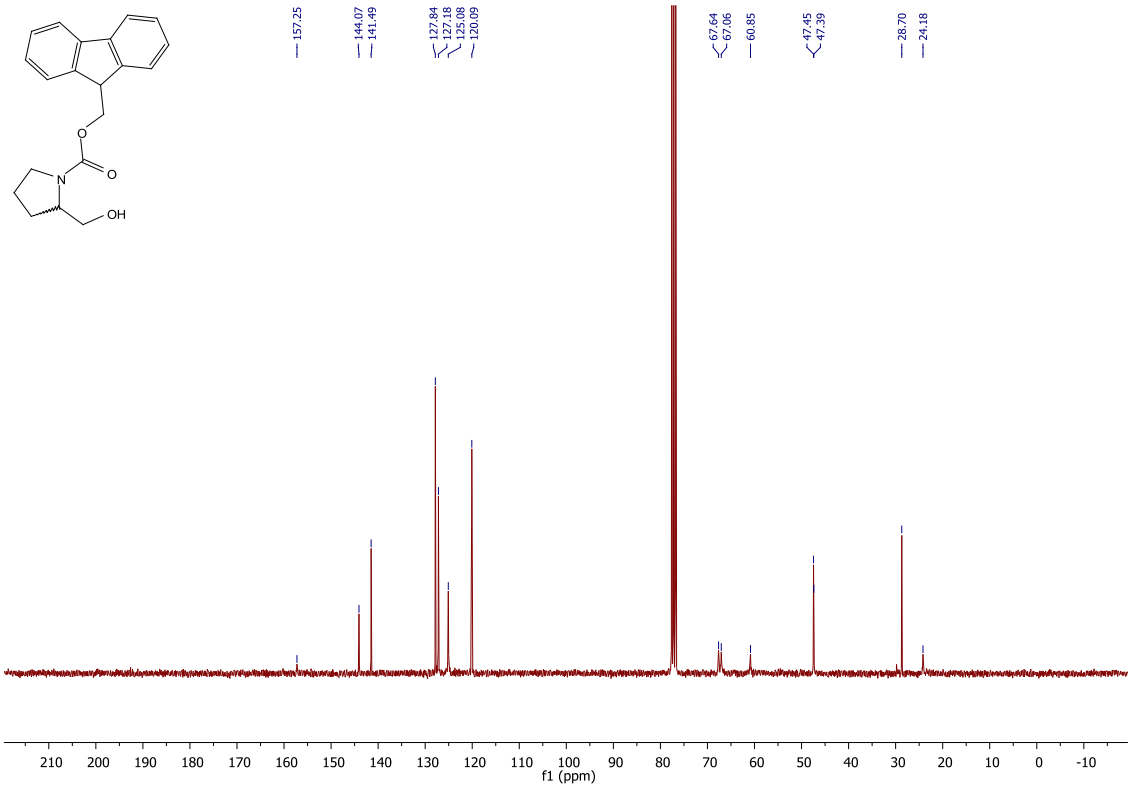
^{1}H- and ^{13}C- NMR spectra of (9*H*-fluoren-9-yl)methyl (*S*)-2-formylpyrrolidine-1-carboxylate (3k)

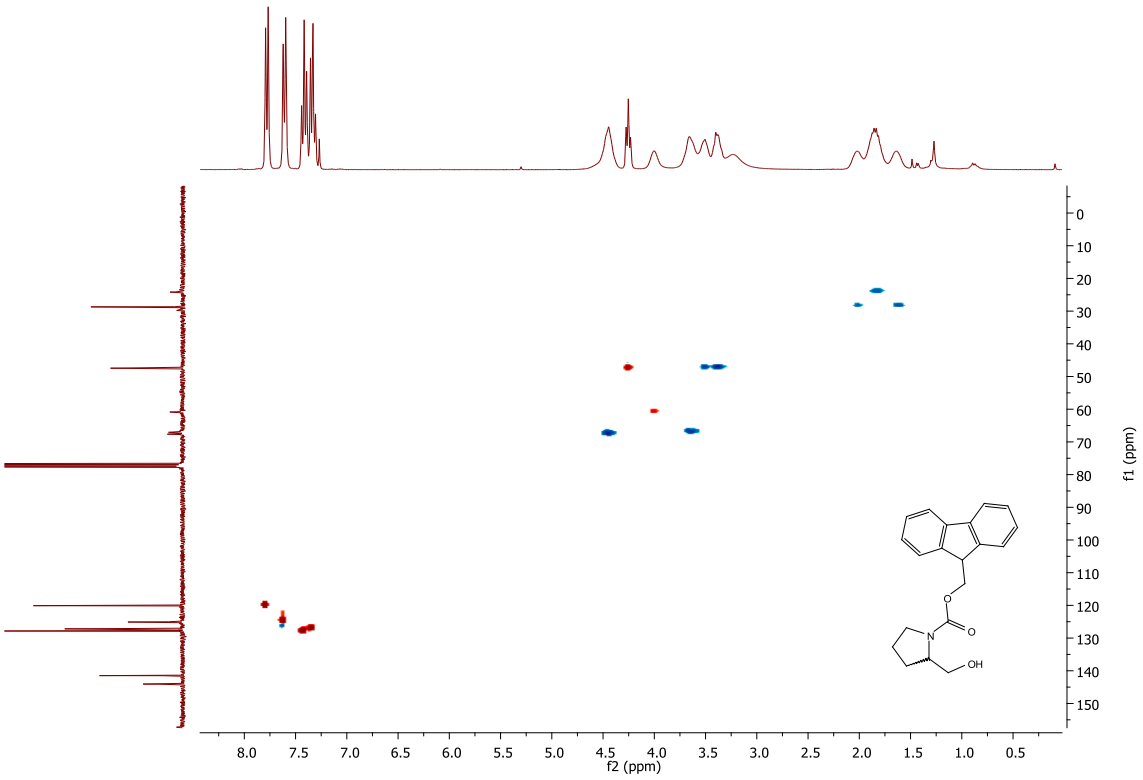




^{1}H-, ^{13}C- and HSQC NMR spectra, and chiral HPLC chromatograms (enantiopure and racemic) of benzyl (*S*)-(1-hydroxy-3-phenylpropan-2-yl)carbamate (8k)

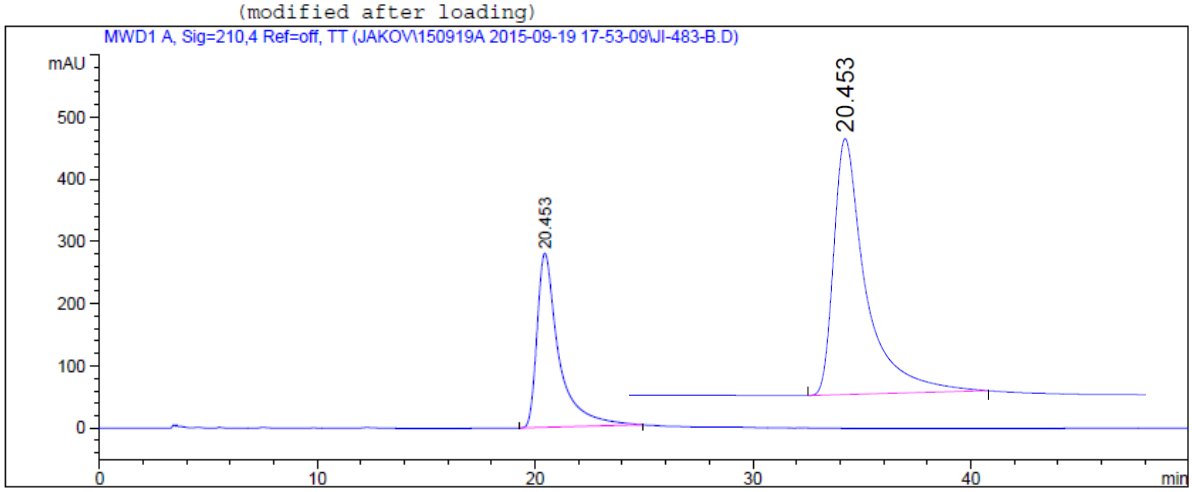



157.25
144.07
141.49
127.84
127.18
125.08
120.09
67.64
67.06
60.85
47.45
47.39
28.70
24.18
O
N
O
OH
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150
f1 (ppm)
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f2 (ppm)
O
N
O
OH

Data File D:\CHEMSTATION\HPLC LINKS\DATA\JAKOV\150919A 2015-09-19 17-53-09\JI-483-B.D
Sample Name: JI-483-B

```
======================================================================
Acq. Operator   : jakov                          Seq. Line :   4
Acq. Instrument : HPLC links                     Location : Vial 51
Injection Date  : 19.09.2015 20:35:01                 Inj :   1
                                                 Inj Volume : 3.0 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 2.0 µl
Acq. Method     : D:\CHEMSTATION\HPLC LINKS\DATA\JAKOV\150919A 2015-09-19 17-53-09\ADH_
                  HEPTIPROH_90_10.M
Last changed    : 19.09.2015 17:41:23 by jakov
Analysis Method : D:\CHEMSTATION\HPLC LINKS\METHODS\JAKOV\INT.M
Last changed    : 20.09.2015 13:08:19 by jakov
                  (modified after loading)
```




```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 A, Sig=210,4 Ref=off, TT

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  20.453 BBA   1.0226 1.95293e4   279.68515 100.0000

Totals :                  1.95293e4   279.68515
```

Data File D:\CHEMSTATION\HPLC LINKS\DATA\JAKOV\150919A 2015-09-19 17-53-09\JI-479-B.D
Sample Name: JI-479-B

```
==========================================================================
Acq. Operator   : jakov                          Seq. Line :   7
Acq. Instrument : HPLC links                     Location : Vial 41
Injection Date  : 19.09.2015 23:10:13                 Inj :   1
                                                 Inj Volume : 3.0 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 2.0 µl
Acq. Method     : D:\CHEMSTATION\HPLC LINKS\DATA\JAKOV\150919A 2015-09-19 17-53-09\ADH_
                  HEPTIPROH_90_10.M
Last changed    : 19.09.2015 17:41:23 by jakov
Analysis Method : D:\CHEMSTATION\HPLC LINKS\METHODS\JAKOV\INT.M
Last changed    : 20.09.2015 12:59:48 by jakov
                  (modified after loading)
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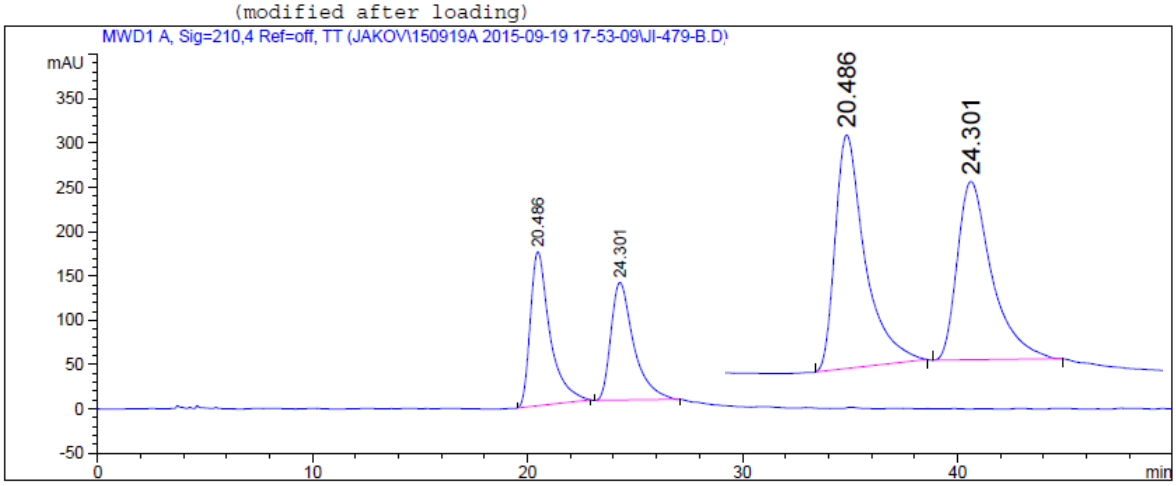


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==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 A, Sig=210,4 Ref=off, TT

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  20.486 BBA   0.9361 1.10681e4   173.52591  53.0224
   2  24.301 BBA   1.1027 9806.33496  132.61919  46.9776

Totals :                  2.08745e4   306.14510
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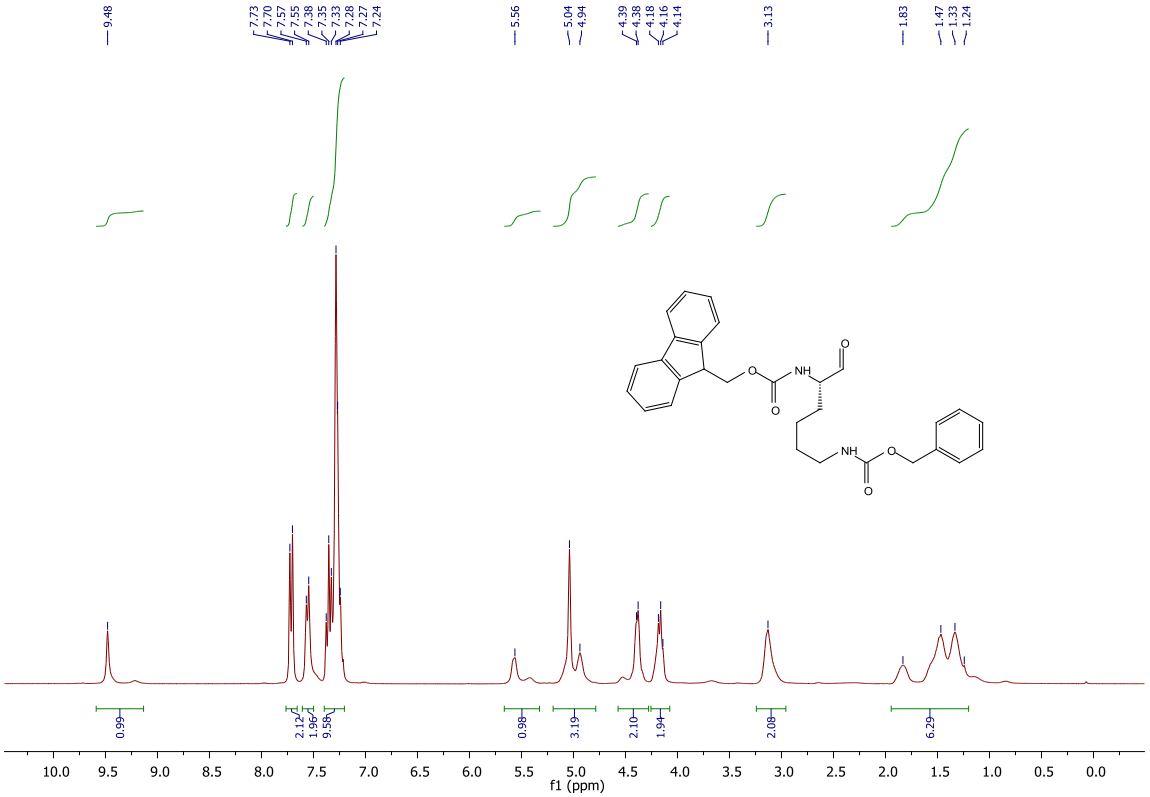
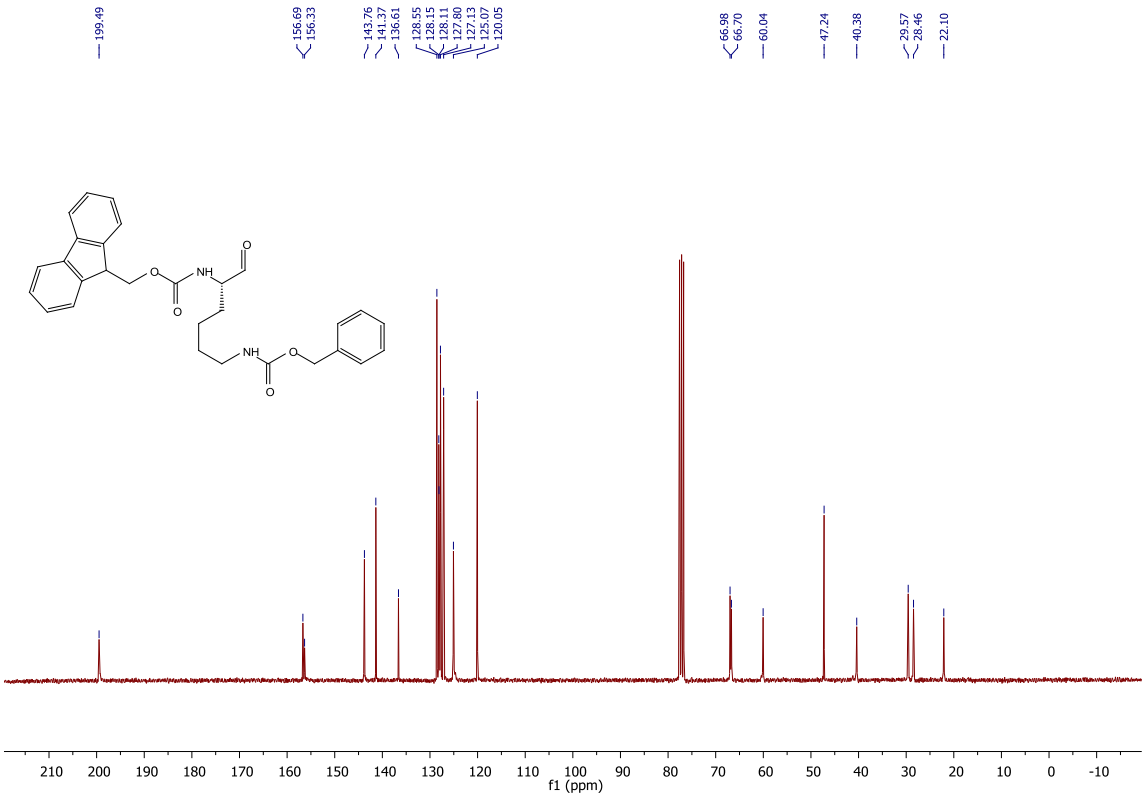
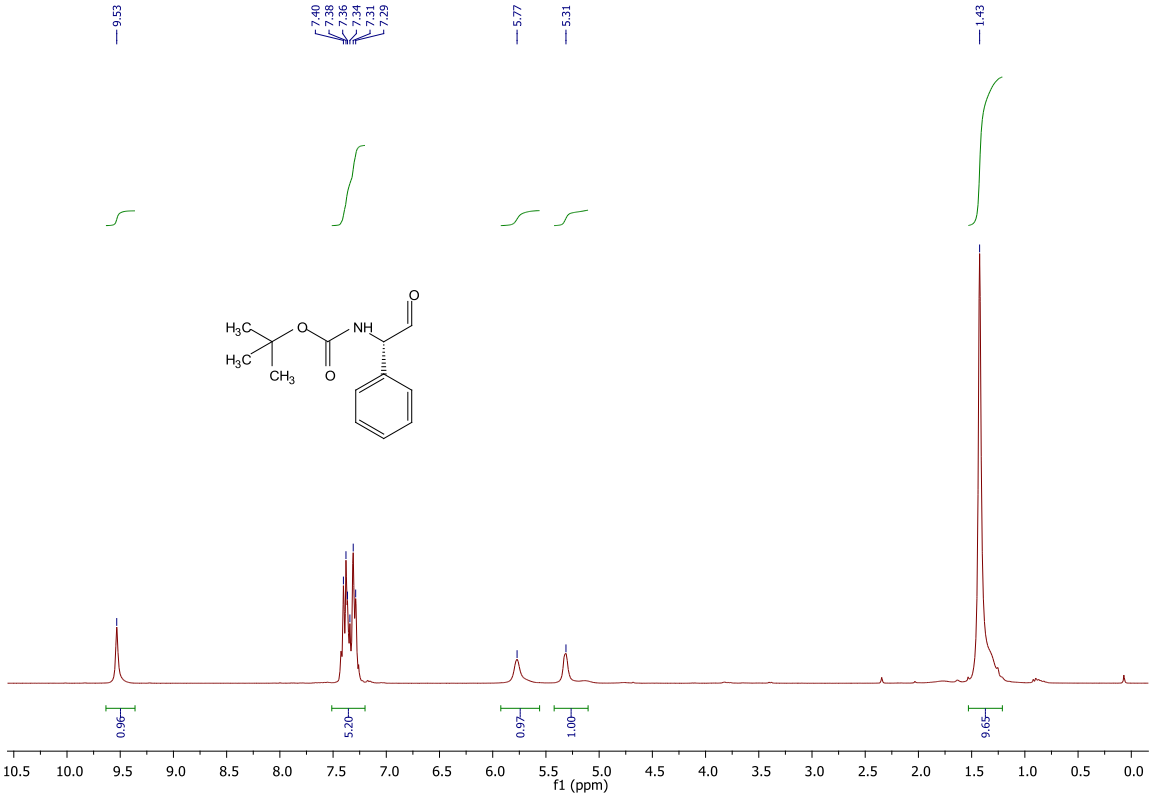
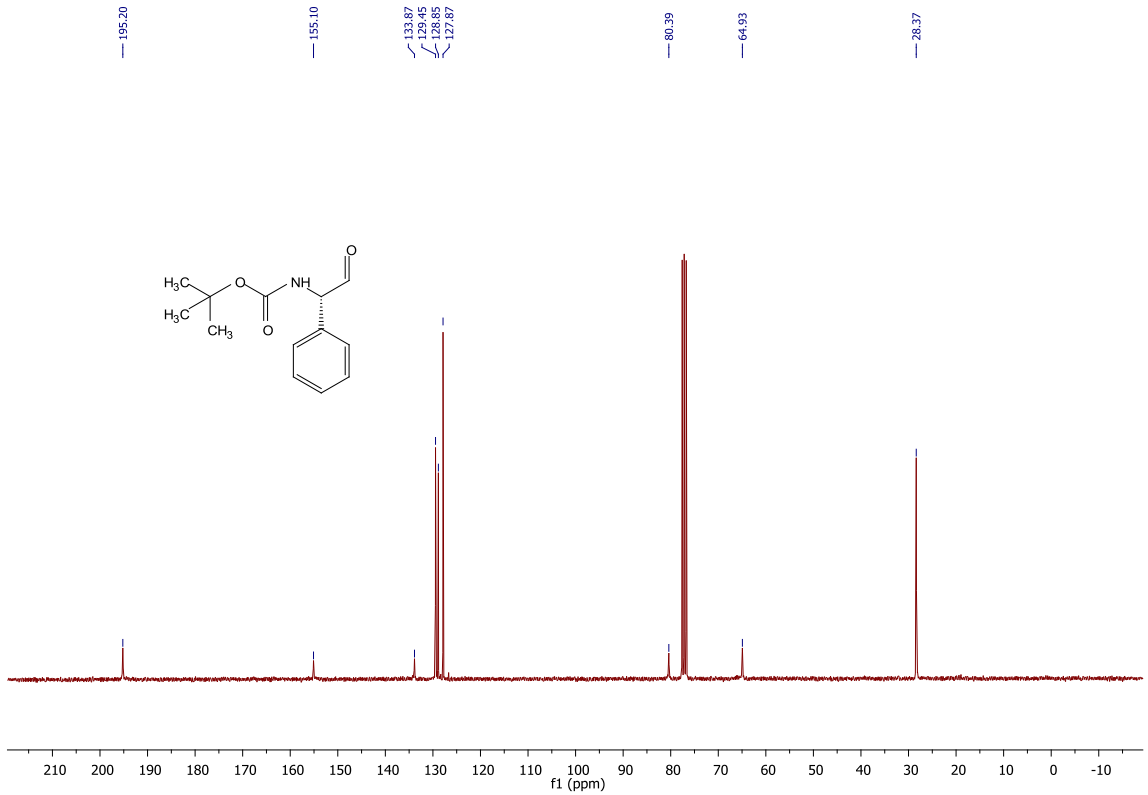
^{1}H- and ^{13}C- NMR spectra of (9*H*-Fluoren-9-yl)methyl benzyl (6-oxohexane-1,5-diyl)(*S*)-dicarbamate (3l)





^{1}H- and ^{13}C- NMR spectra and GC-FID chromatograms (scalemic and racemic) of *tert*-butyl *(S)*-(2-oxo-1-phenylethyl)carbamate (3m)





Data File D:\GC\1\DATA\JAKOV\150813\150813A 2015-08-13 11-38-49\JI-473-B.D
Sample Name: JI-473-B

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                                               Inj Volume : External
Acq. Method     : D:\GC\1\DATA\JAKOV\150813\150813A 2015-08-13 11-38-49\AMAL_GCPAL.M
Last changed    : 29.07.2015 18:50:33 by jkv
Analysis Method : D:\GC\1\DATA\JAKOV\METHOD\INT.M
Last changed    : 13.08.2015 14:22:49 by jkv
                  (modified after loading)
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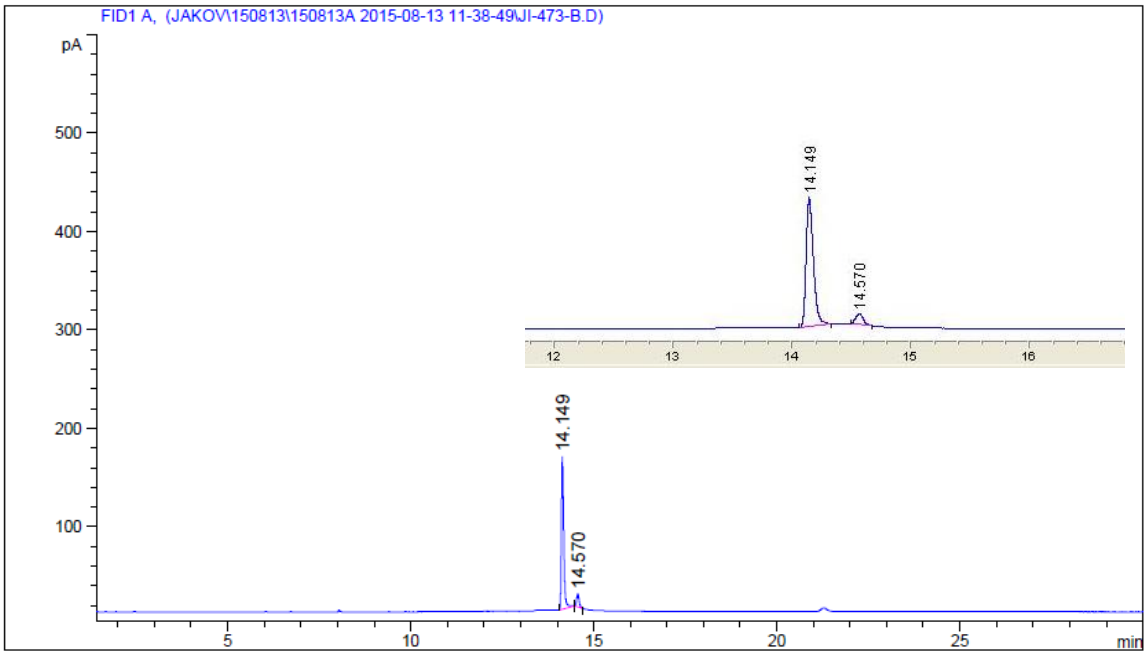


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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

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  #   [min]        [min]   [pA*s]      [pA]       %
----|-------|----|-------|----------|----------|--------|
   1  14.149 BB    0.0663  667.43793  154.75189 91.50501
   2  14.570 BBA   0.0741   61.96250   13.16249  8.49499

Totals :                   729.40042  167.91439
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Data File D:\GC\1\DATA\JAKOV\150327C\150327C 2015-03-29 14-07-47\1AGF0701.D
Sample Name: JI-379-RefRAC

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Injection Date  : 29.03.2015 17:35:52           Inj :   1
                                                Inj Volume : External
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Last changed     : 29.03.2015 14:07:22 by jkv
Analysis Method : D:\GC\1\DATA\JAKOV\METHOD\INT.M
Last changed     : 20.08.2015 18:56:09 by jkv
                   (modified after loading)
Additional Info : Peak(s) manually integrated
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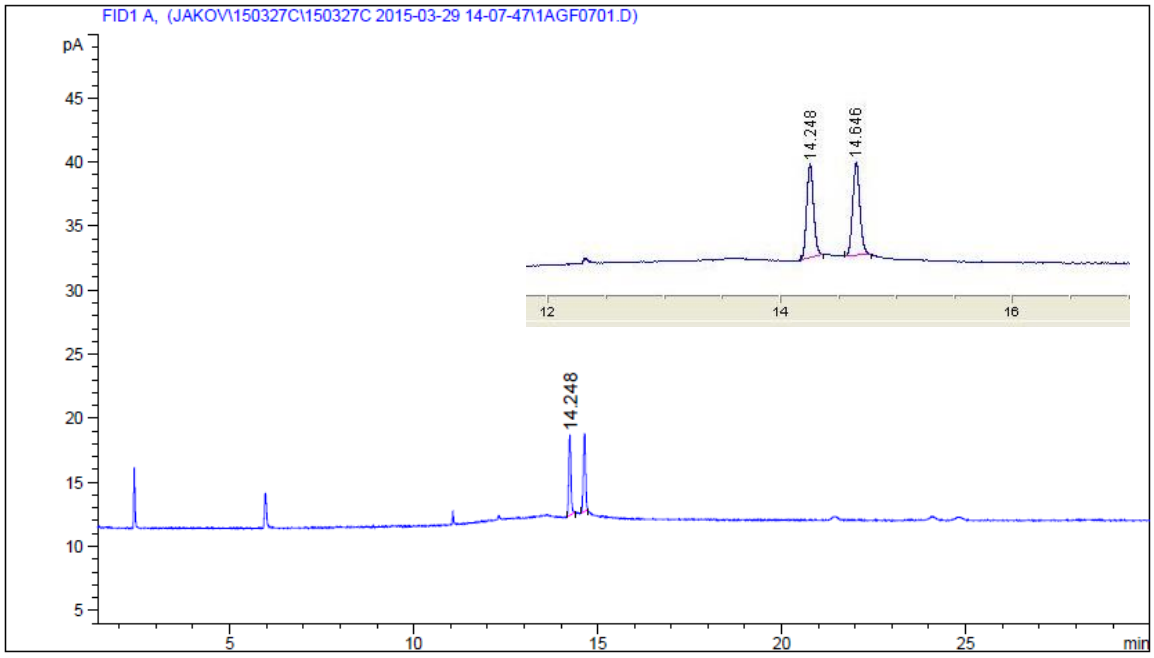


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==========================================================================
                        Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1  14.248 BB    0.0661   25.83864    6.21485 50.59744
   2  14.646 BBA   0.0659   25.22845    6.09536 49.40256

Totals :                   51.06708   12.31021
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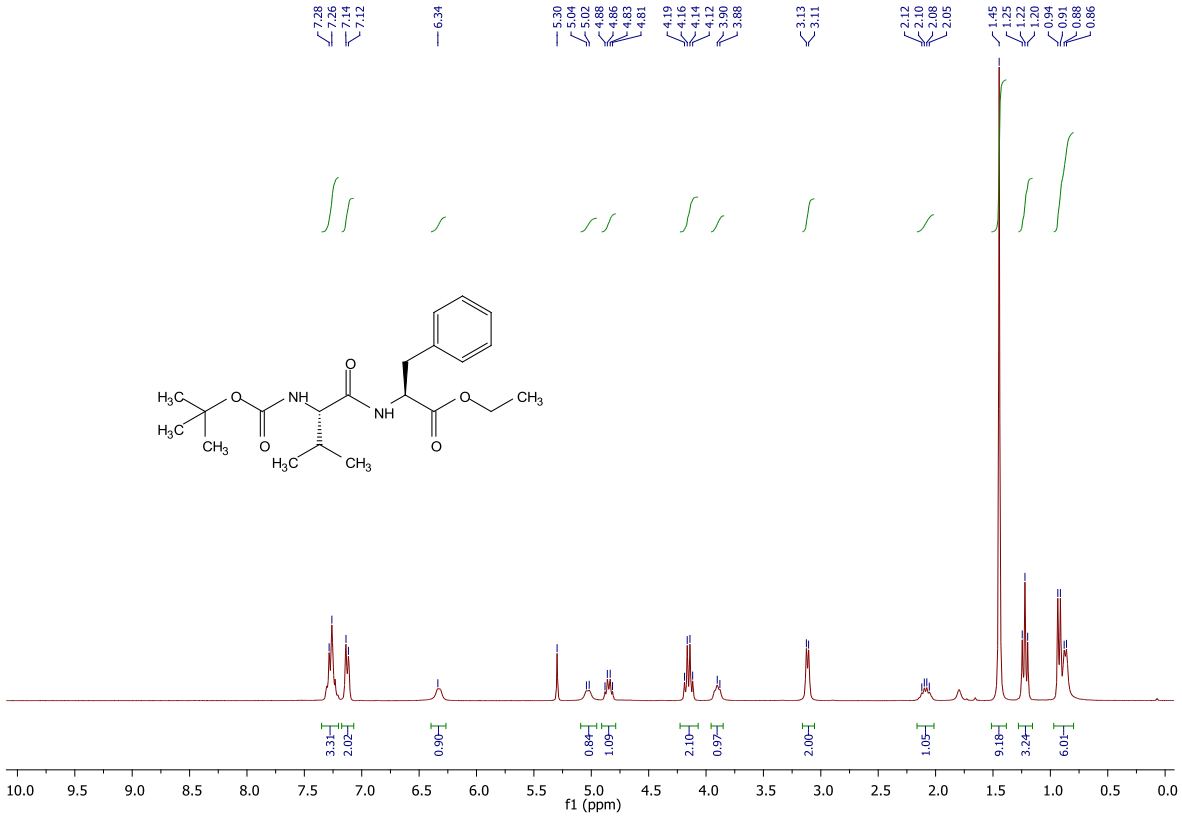
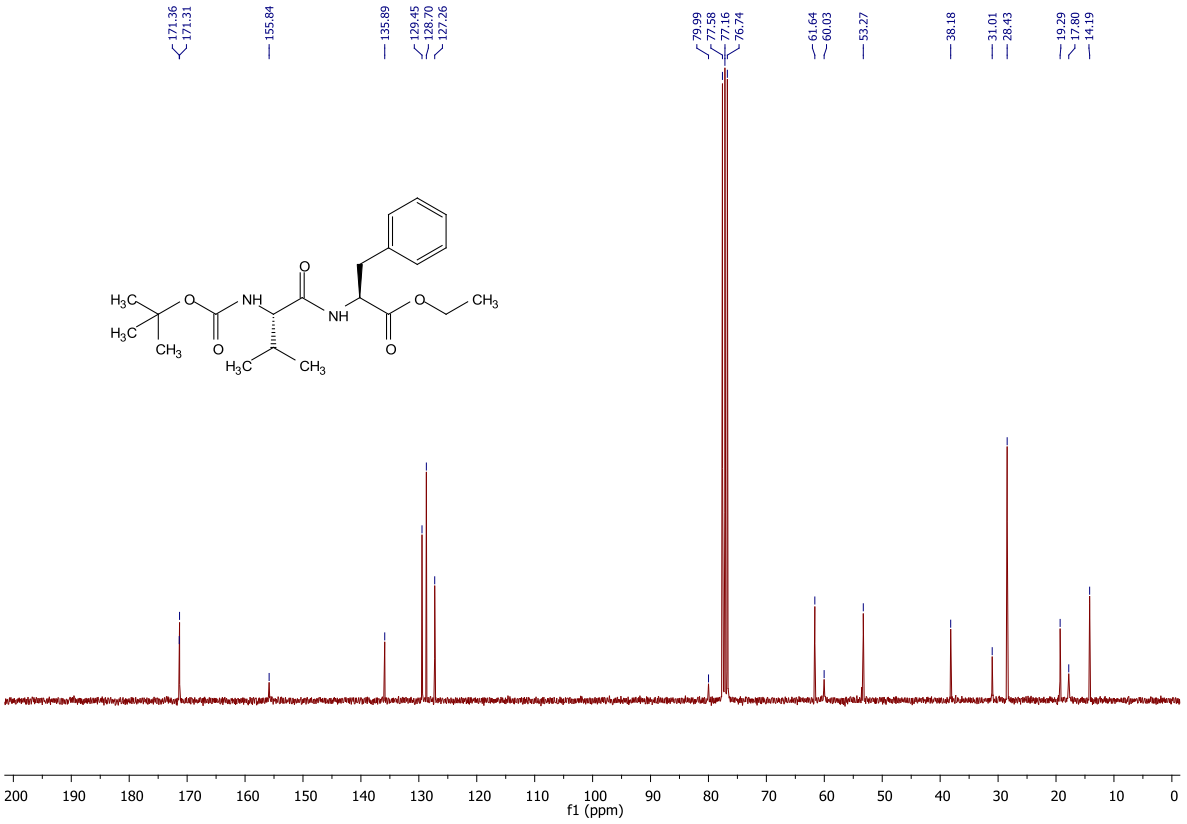
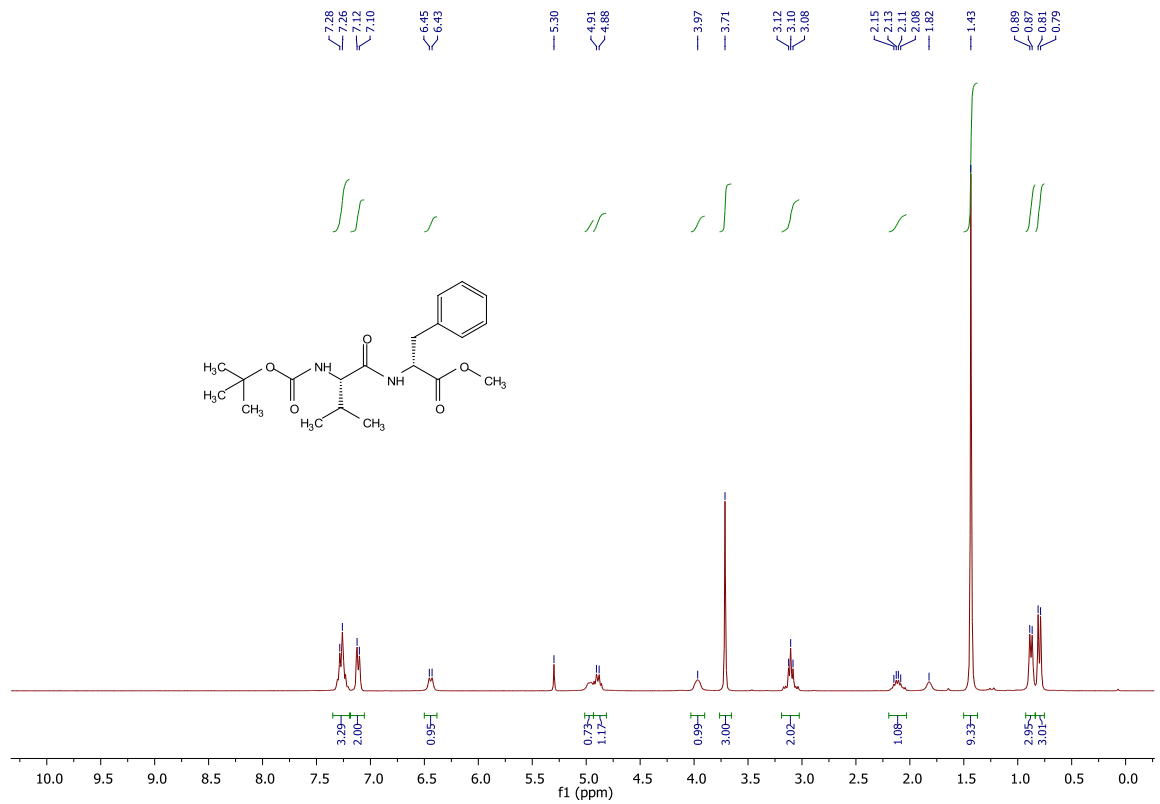
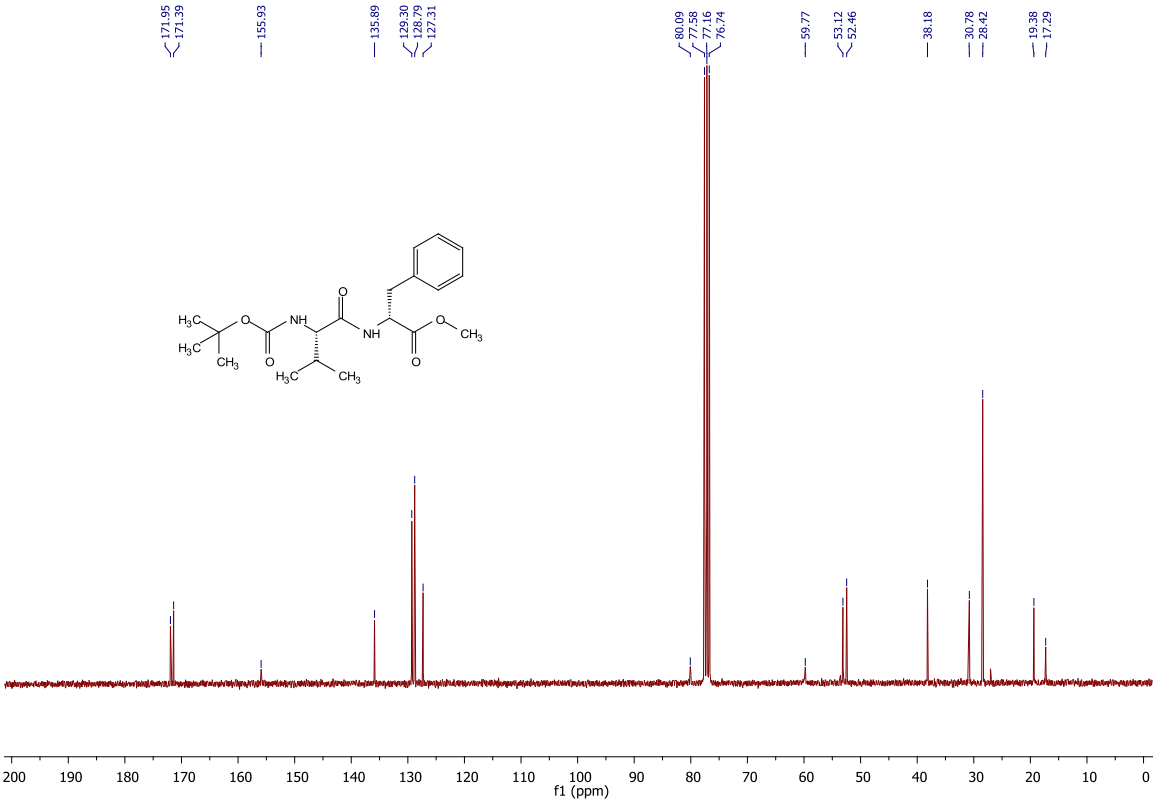
^{1}H- and ^{13}C- NMR spectra of ethyl (*tert*-butoxycarbonyl)-L-valyl-L-phenylalaninate (6a)



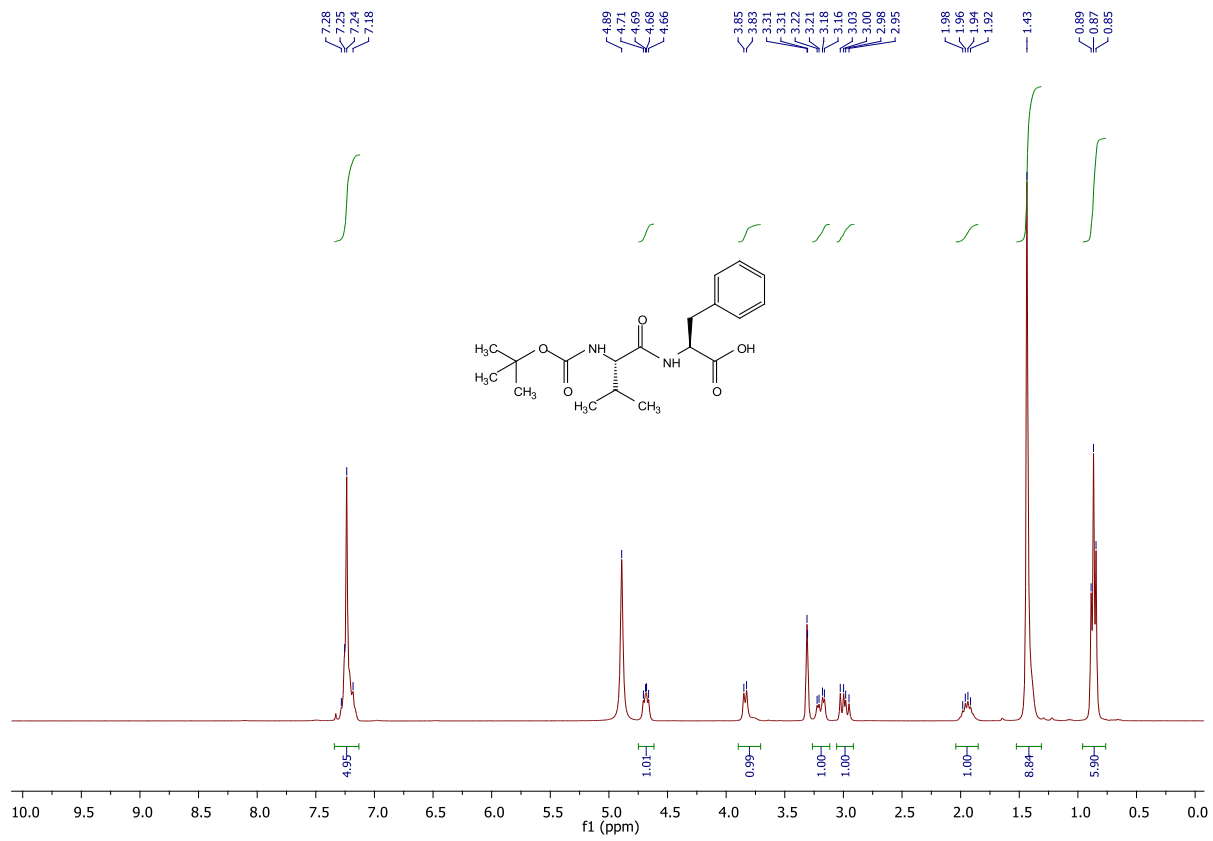


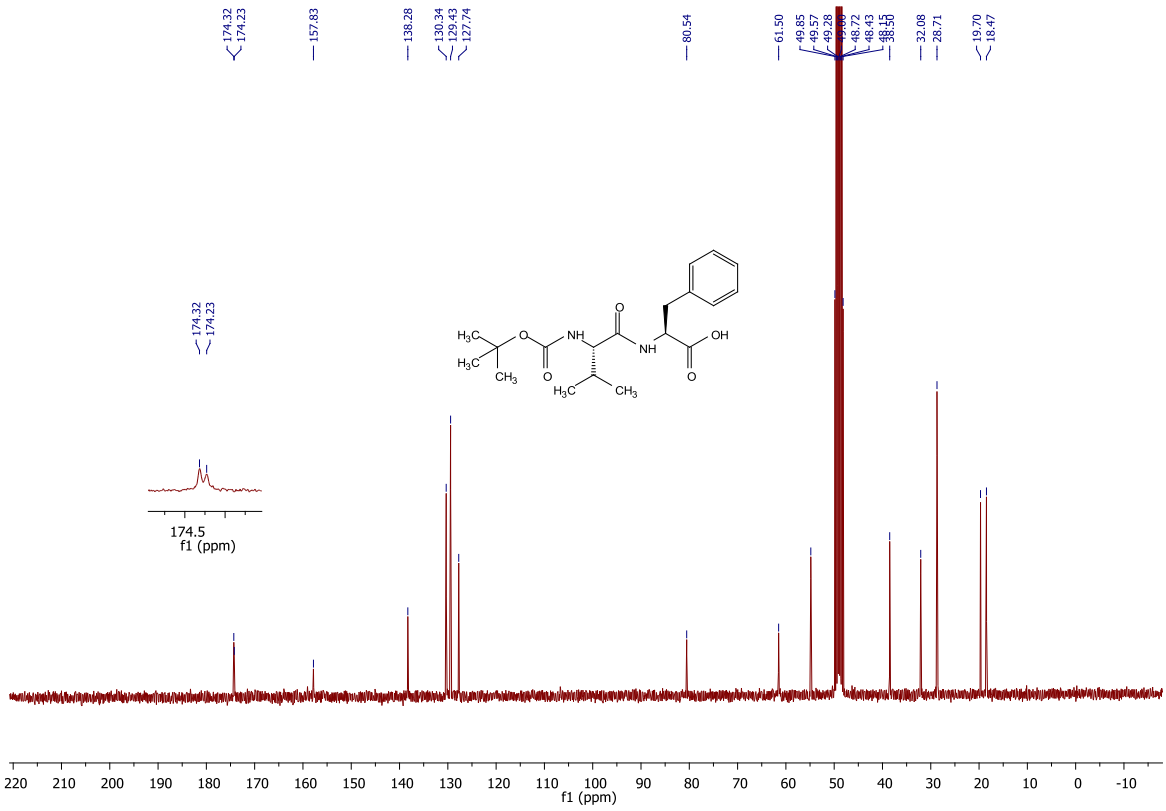
^{1}H- and ^{13}C- NMR spectra of methyl (tert-butoxycarbonyl)-L-valyl-D-phenylalaninate (6b)



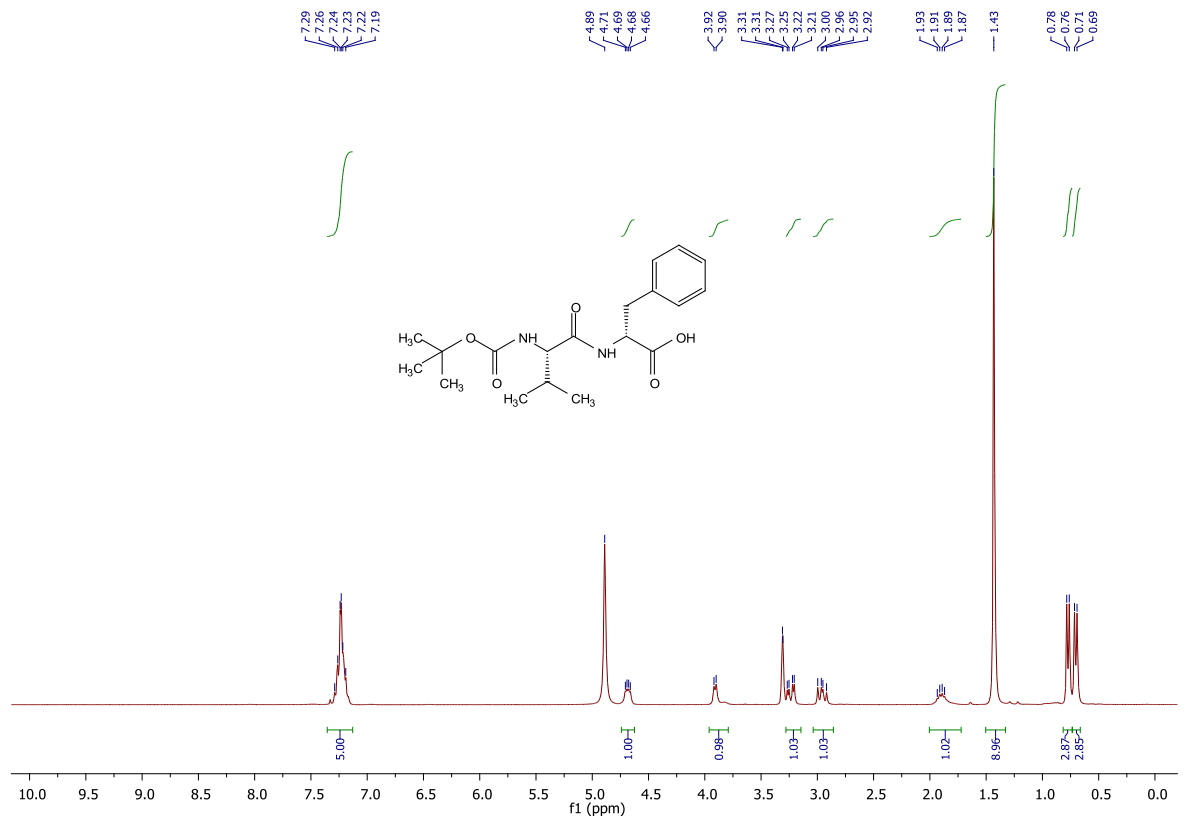


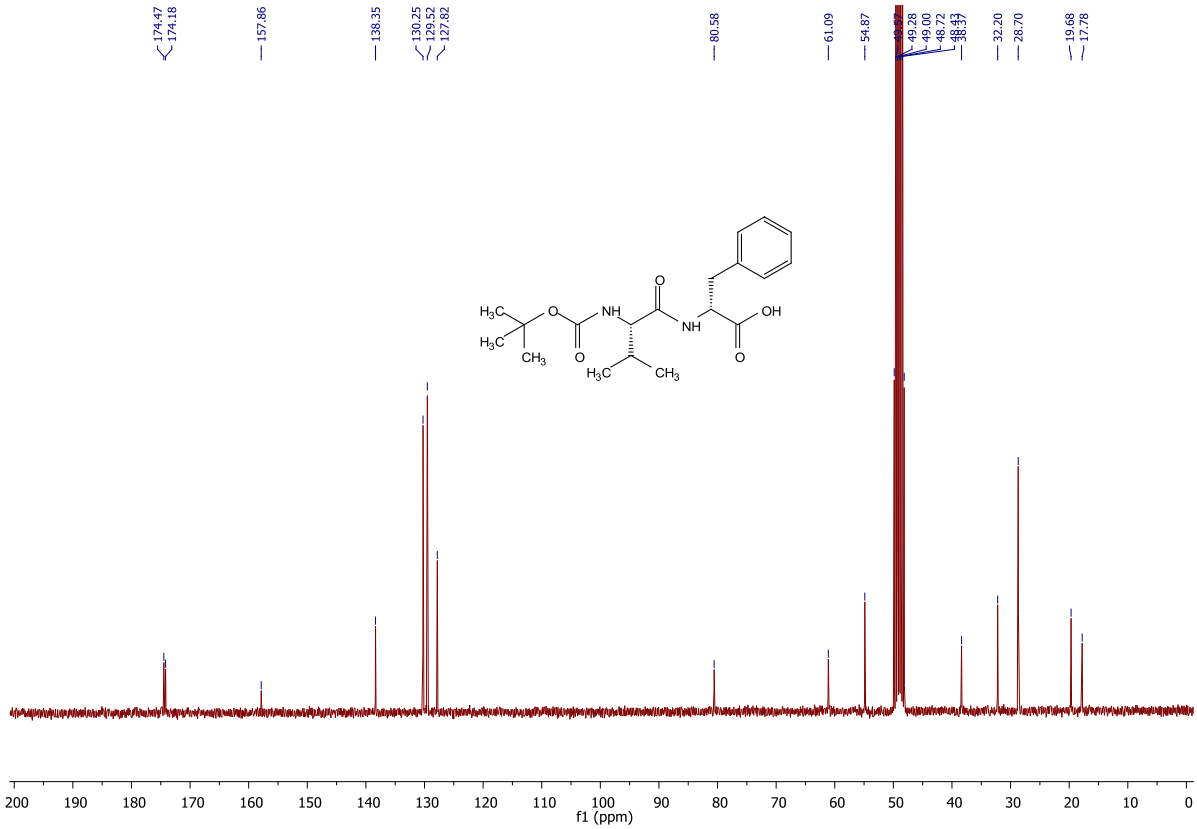
^{1}H- and ^{13}C- NMR spectra of (*tert*-butoxycarbonyl)-L-valyl-L-phenylalanine (7a)



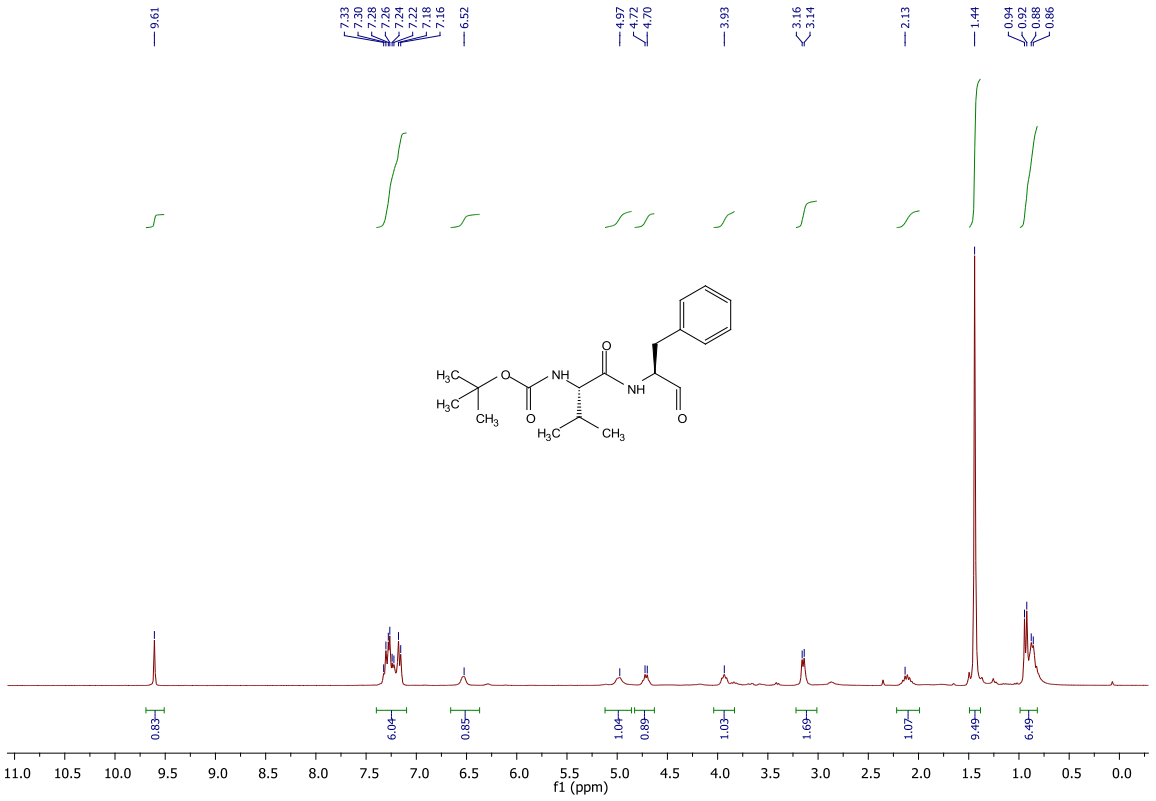


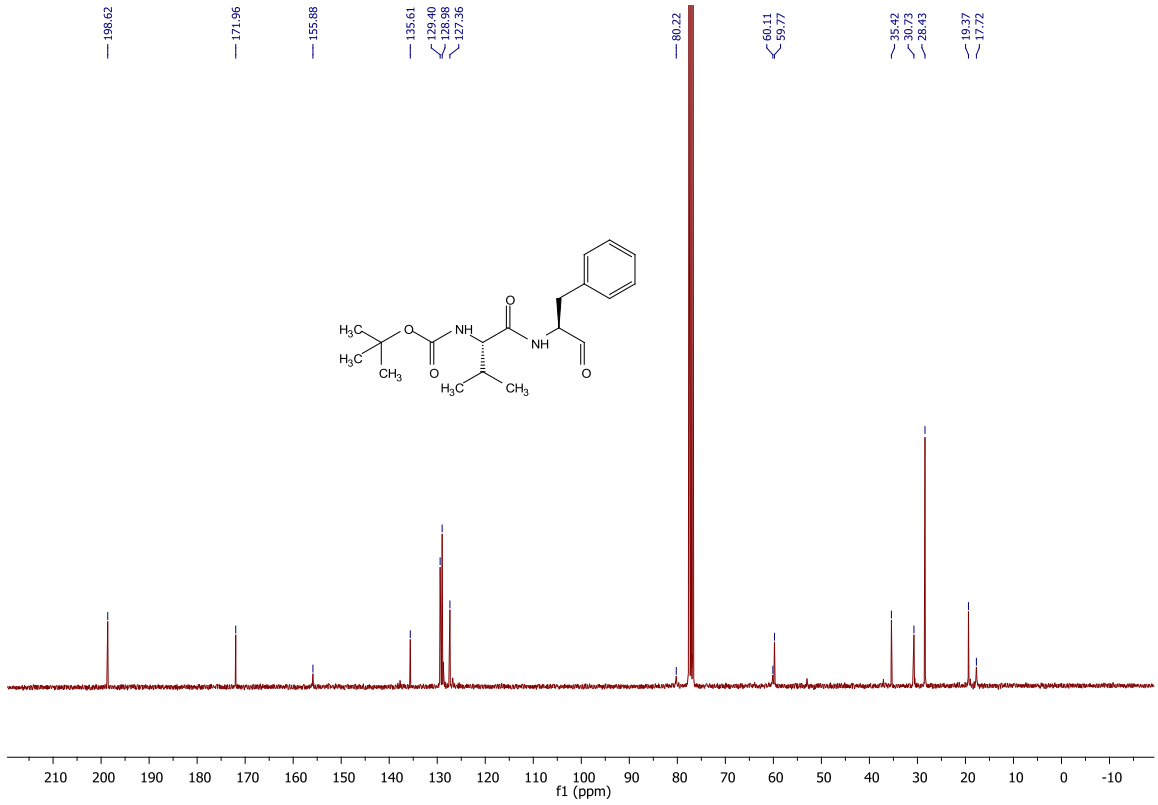
^{1}H- and ^{13}C- NMR spectra of (*tert*-butoxycarbonyl)-L-valyl-D-phenylalanine (7b)



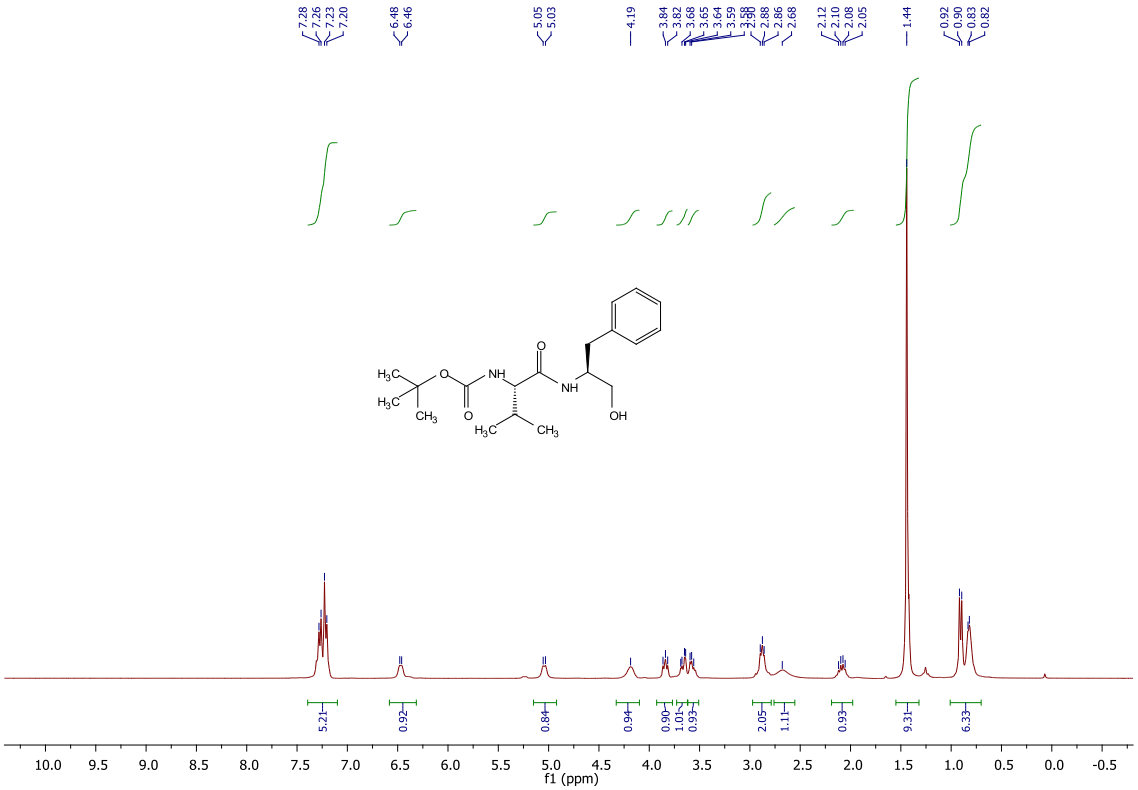


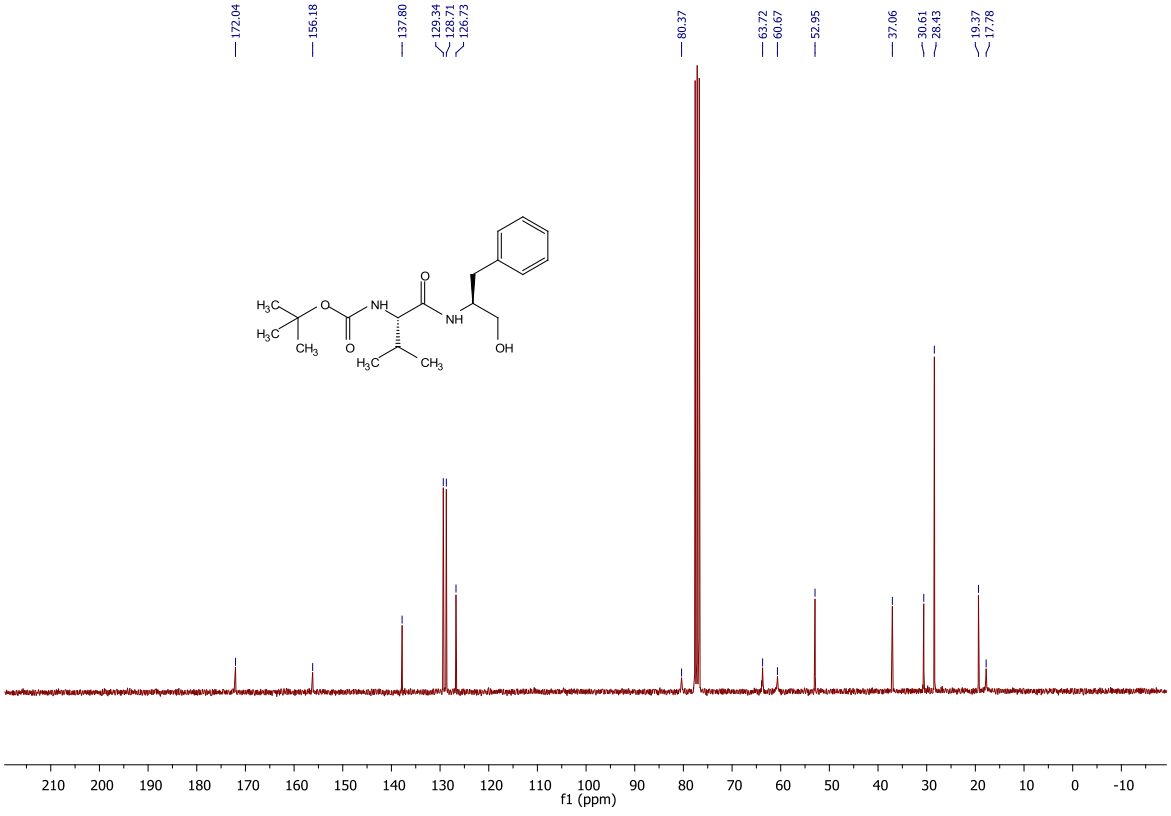
^{1}H- and ^{13}C- NMR spectra of *tert*-butyl ((*S*)-3-methyl-1-oxo-1-(((*S*)-1-oxo-3-phenylpropan-2-yl)amino)butan-2-yl)carbamate (4a)



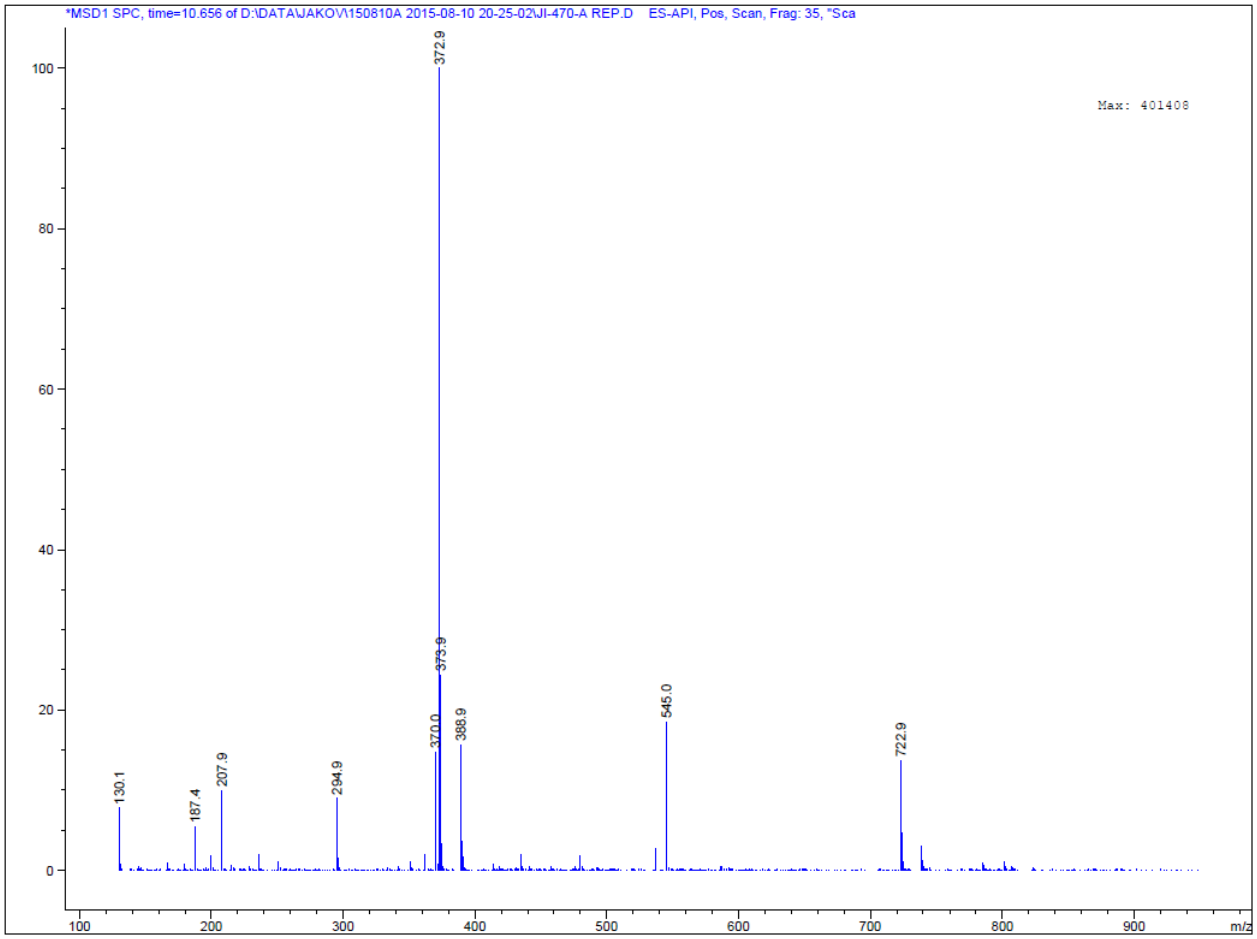


^{1}H-, ^{13}C- NMR spectra, mass spectrum and HPLC chromatogram of *tert*-butyl ((*S*)-1-(((*S*)-1-hydroxy-3-phenylpropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (5a)





MS Spectrum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373.9
370.0
388.9
545.0
722.9
130.1
187.4
207.9
294.9
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80
60
40
20
0
100
200
300
400
500
600
700
800
900
m/z

Data File D:\DATA\JAKOV\150810A 2015-08-10 20-25-02\JI-470-A REP.D
Sample Name: JI-470-A

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Injection Date  : 10.08.15 21:26:07                  Inj :   1
                                              Inj Volume : 2.0 µl
Different Inj Volume from Sequence !     Actual Inj Volume : 5.0 µl
Acq. Method     : D:\DATA\JAKOV\150810A 2015-08-10 20-25-02\LONG_POROSHELL120_001HCOOH_
                  40PCISOCRAT.M
Last changed    : 10.08.15 21:22:06 by Kathrin
Analysis Method : D:\METHODS\JAKOV\1.M
Last changed    : 24.08.15 16:20:45 by christian
                  (modified after loading)
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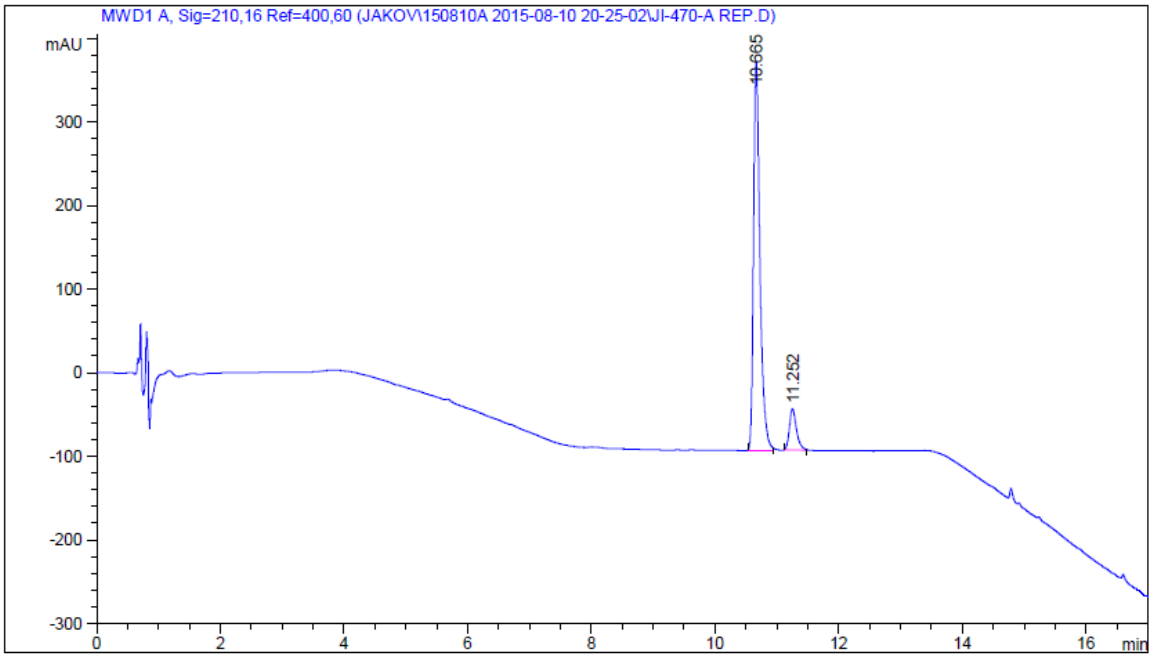


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======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 A, Sig=210,16 Ref=400,60

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  #   [min]        [min]   [mAU*s]     [mAU]       %
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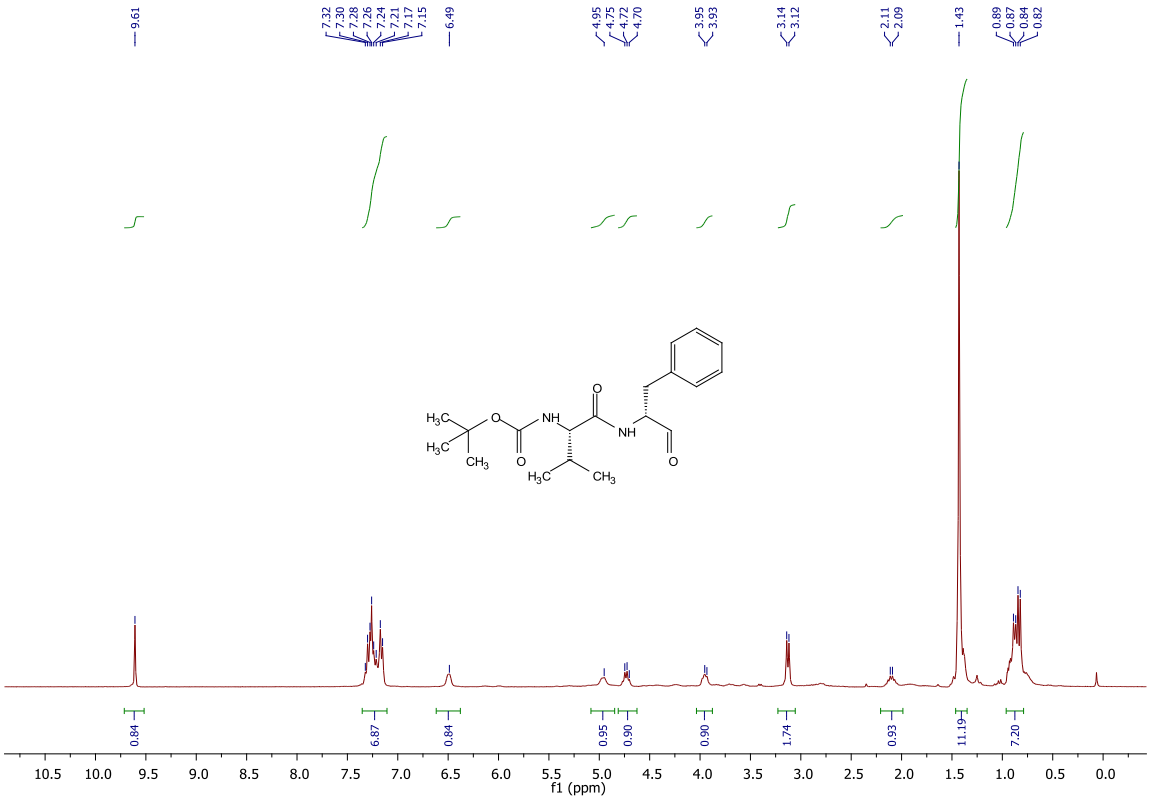
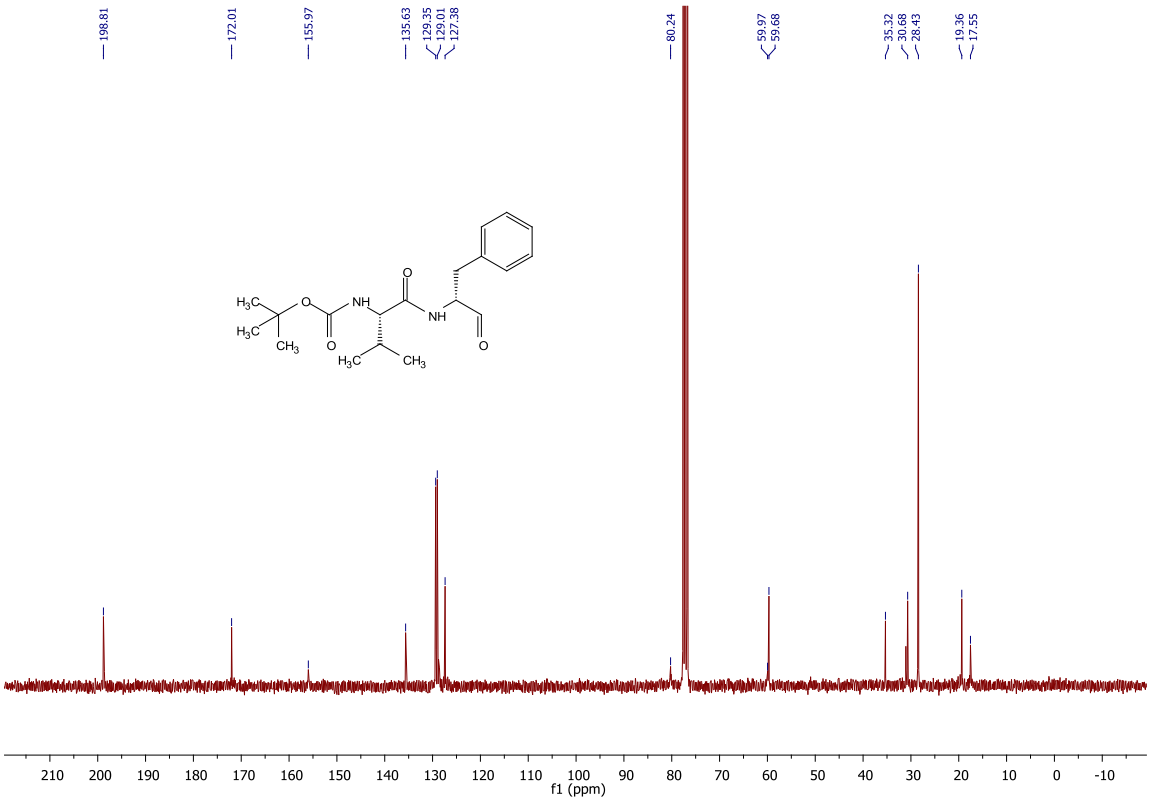
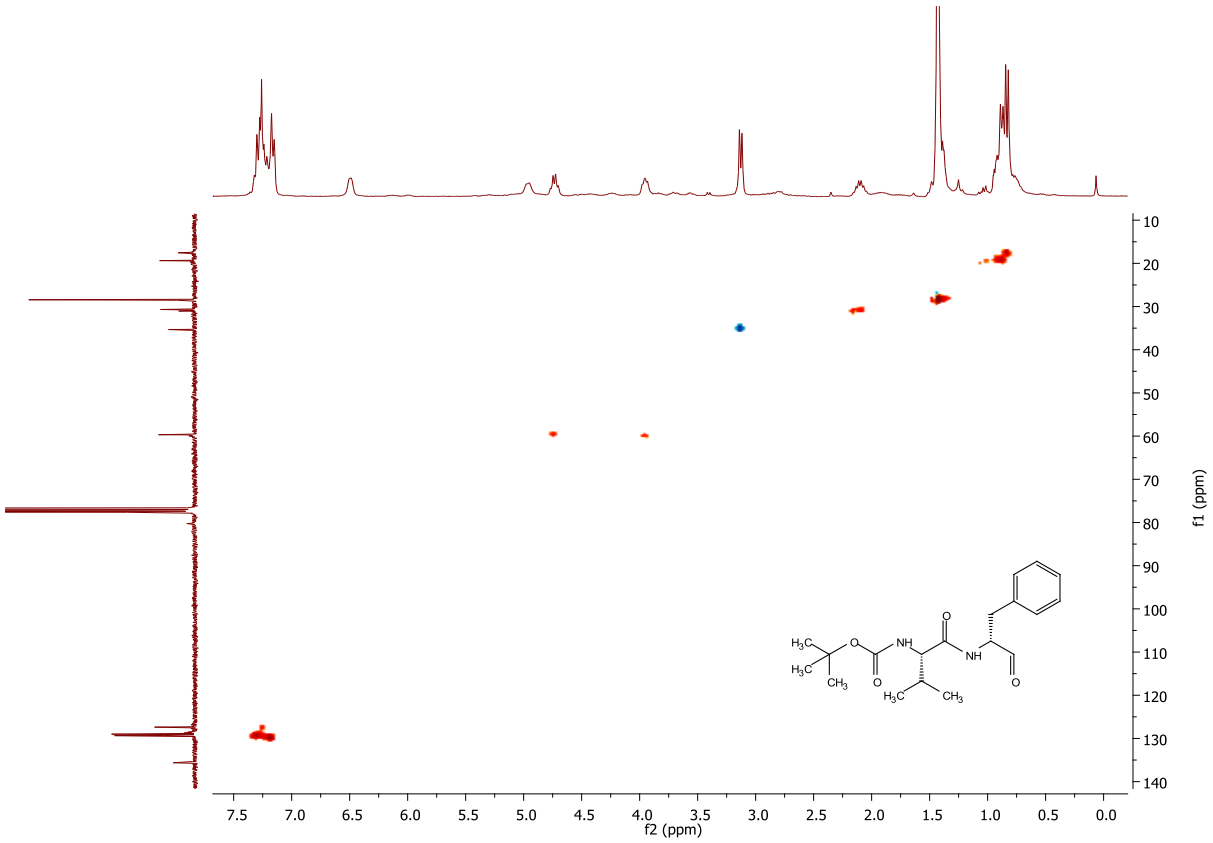
   1  10.665 BB    0.1067 3335.37036  464.84384  89.4637
   2  11.252 BB    0.1180  392.81415   49.78807  10.5363

Totals :                  3728.18451  514.63191
```

^{1}H-, ^{13}C- and HSQC NMR spectra of *tert*-Butyl ((*S*)-3-methyl-1-oxo-1-(((*R*)-1-oxo-3-phenylpropan-2-yl)amino)butan-2-yl)carbamate (4b)






f2 (ppm)
f1 (ppm)
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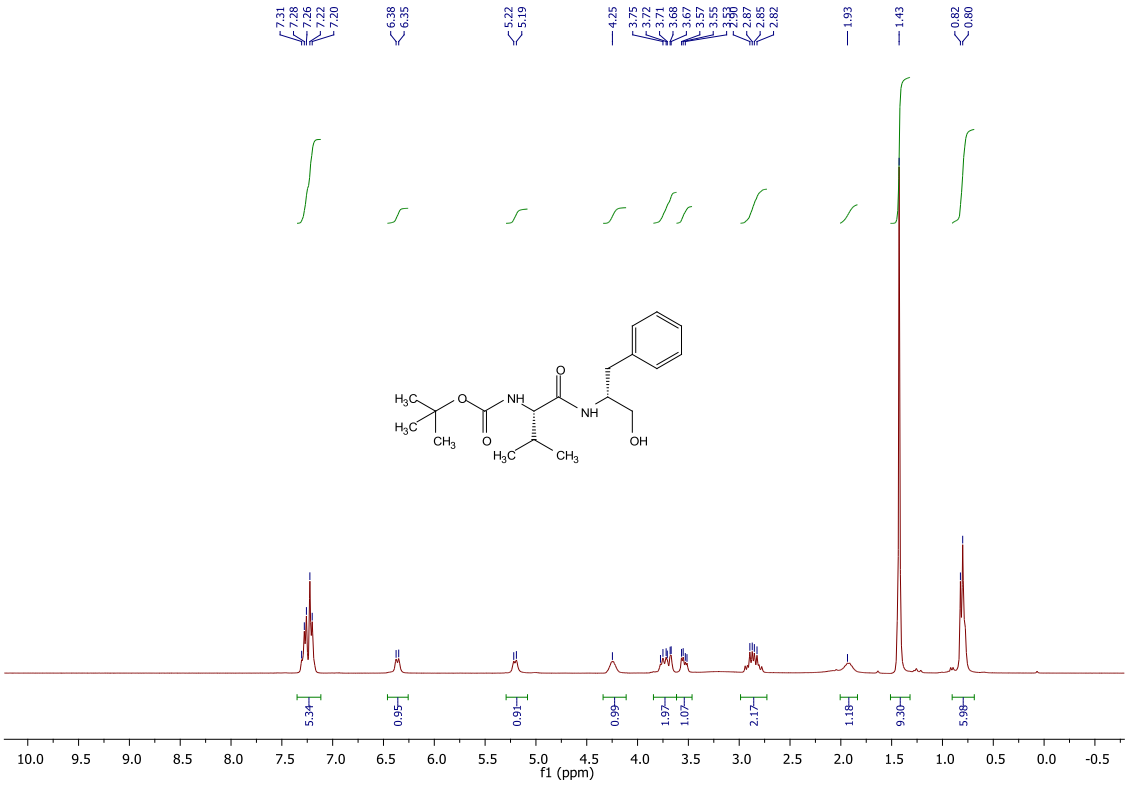
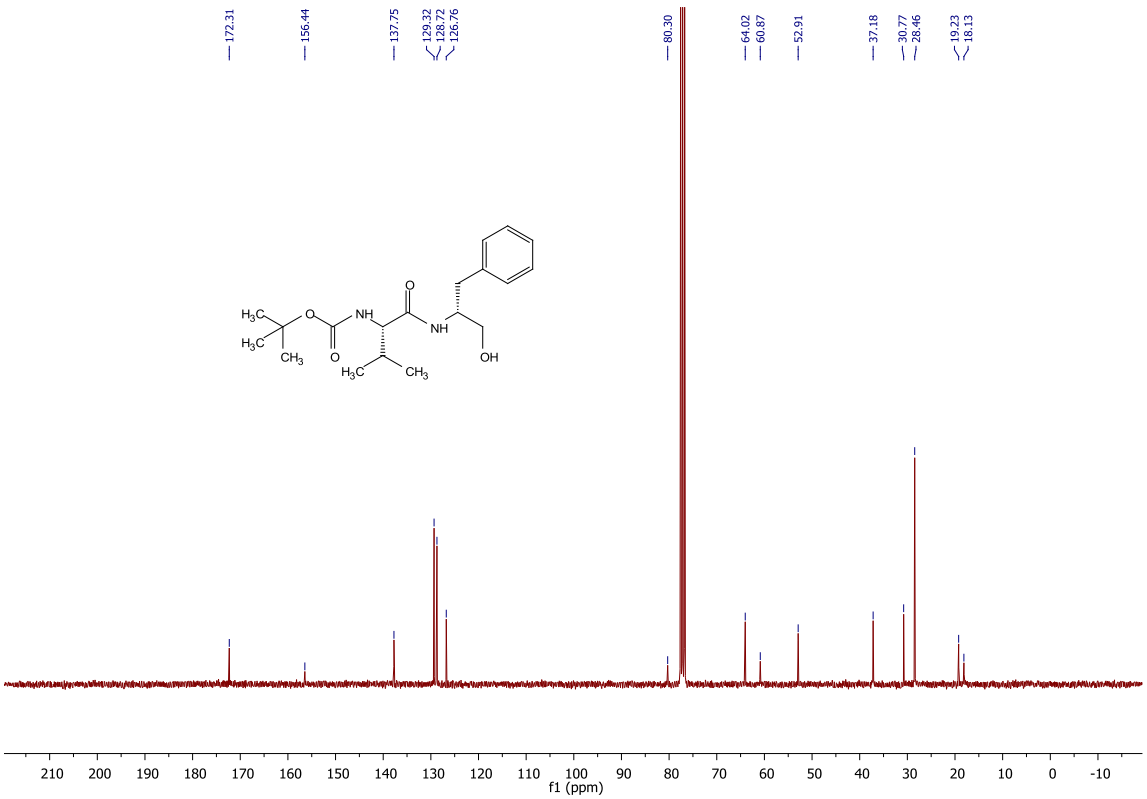
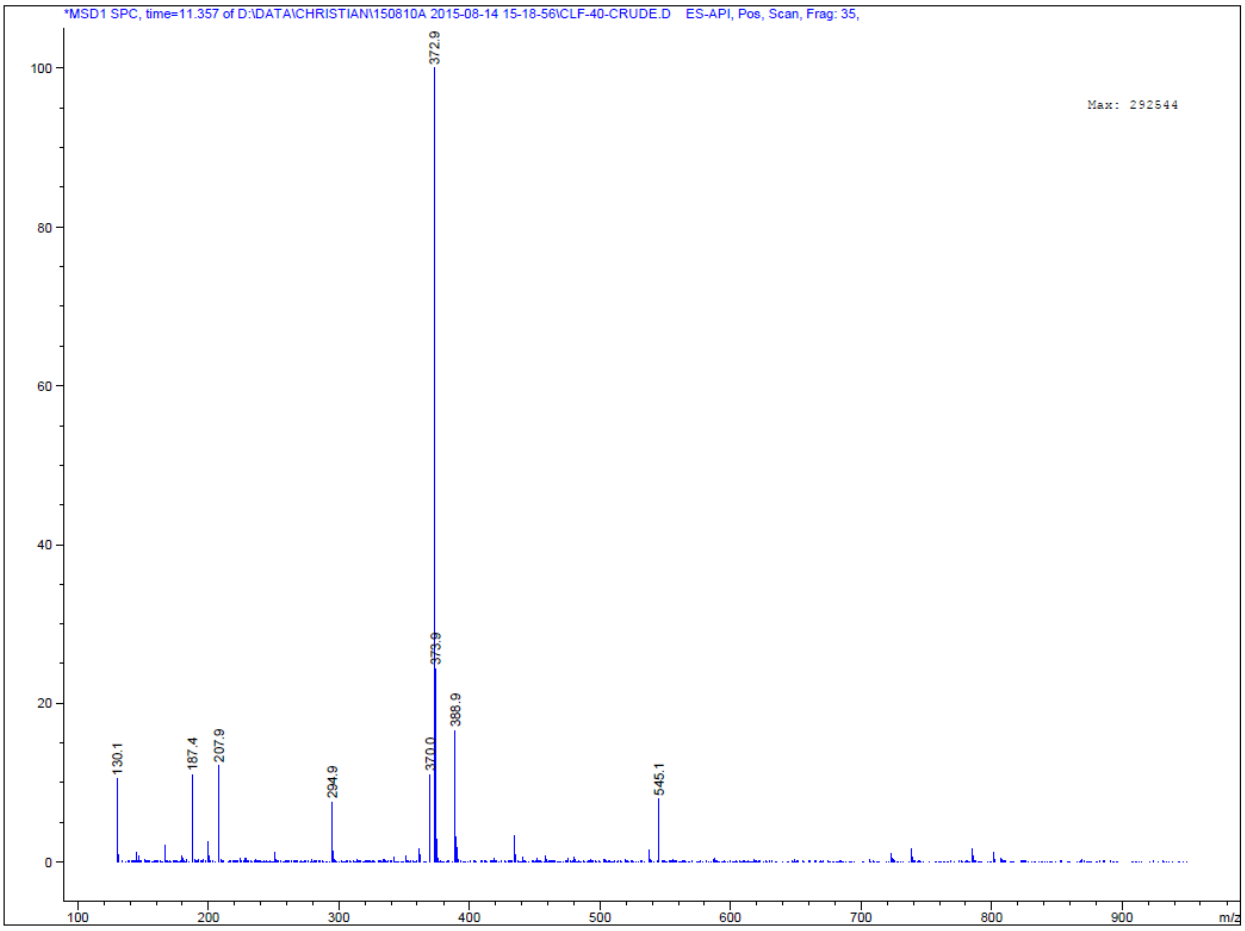
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
H3C
CH3
O
NH
O
O
NH
O
H3C
CH3

^{1}H-, ^{13}C- NMR spectra, mass spectrum and HPLC chromatogram of *tert*-butyl ((*S*)-1-(((*R*)-1-hydroxy-3-phenylpropan-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (5b)





MS Spectrum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Max: 292544
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373.9
388.9
130.1
187.4
207.9
294.9
370.0
545.1
100
80
60
40
20
0
100
200
300
400
500
600
700
800
900
m/z

Data File D:\DATA\CHRISTIAN\CLF-40-F3-6.D
Sample Name: CLF-40-F3-6

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Injection Date  : 20.08.15 15:19:16
                                                  Inj Volume : 4.0 µl
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Last changed    : 20.08.15 15:18:35 by clf
                  (modified after loading)
Analysis Method : D:\METHODS\JAKOV\1.M
Last changed    : 20.08.15 15:51:06 by christian
                  (modified after loading)
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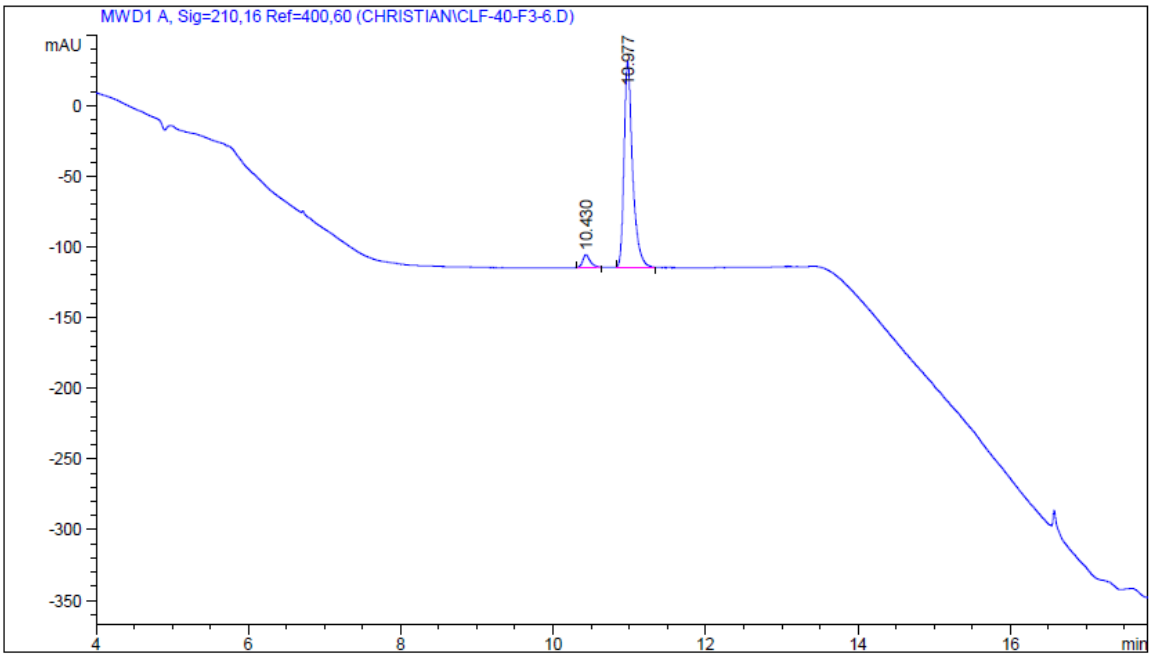


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                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier:                   :      1.0000
Dilution:                     :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: MWD1 A, Sig=210,16 Ref=400,60

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]    [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  10.430 BB    0.1025   63.88106    9.25823   5.3423
   2  10.977 BB    0.1157 1131.88049  145.51410  94.6577

Totals :                  1195.76155  154.77233
```

Dependence of ee of Boc-phenylglycinal on the rate of addition of DIBAL-H

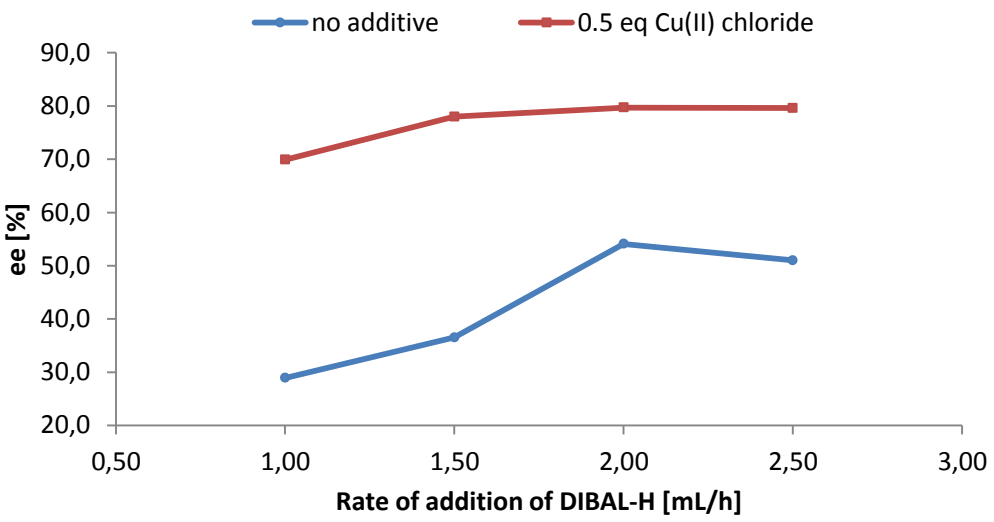


Figure S1 Dependence of ee of Boc-phenylglycinal on the rate of addition of DIBALH. Each reaction instance was performed using 50 mg (0.20 mmol) Boc-L-Phg-OH, 32 mg (0.20 mmol, 1.0 eq) CDI and 0.42 mL (0.42 mmol, 2.1 eq) 1M DIBAL-H in 2.0 mL of absolute CH_2Cl_2, according to the general procedure, with the altered rates of addition, regulated by settings on the syringe pump. A parallel instance was performed for each reaction, differing by having 13 mg (0.10 mmol, 0.5 eq) of $CuCl_2$ added after the activation step and stirred for 60 min more before the DIBAL-H reduction. Enantiopurity was determined by chiral GC-FID.

Table S1 Dependence of ee of Boc-phenylglycinal on the rate of addition of DIBALH.

rate of add. [mL/h]	CDI [eq]	DIBAL-H [eq]	no additive ee [%]	0.5 eq of $CuCl_2$ ee [%]
1,00	1.0	2.1	28,9	**69,9**
1,50	1.0	2.1	36,5	**78,0**
2,00	1.0	2.1	54,1	**79,7**
2,50	1.0	2.1	51,0	**79,6**

Dependence of yield of Boc-phenylglycinal on the temperature maintained during the addition of DIBAL-H

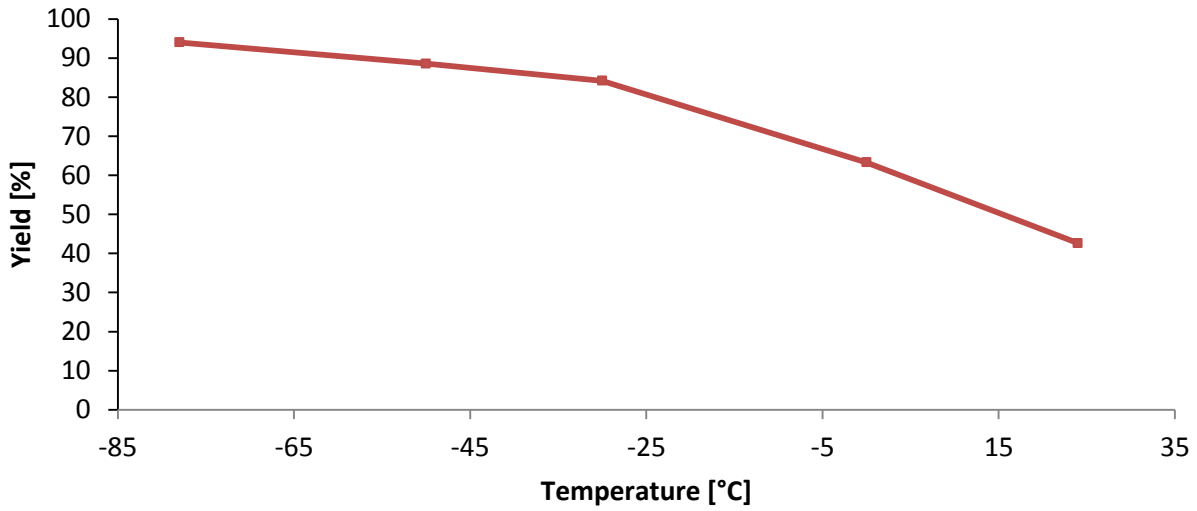


Figure S2 Dependence of yield of Boc-phenylglycinal on the temperature during addition DIBALH. Each reaction instance was performed using a 2.0 mL aliquot of a stock solution of 270 mg (1.07 mmol) of Boc-L-Phg-OH and 135 µL (1.07 mmol) of *p*-xylene (internal standard) in 10.8 mL of absolute CH_2Cl_2, according to the general procedure with altered temperatures used during the reduction step (-78 °C, -50 °C, -30 °C, 0 °C and 24 °C respectively). For other temperatures relative yield was calculated using the determined isolated yield at -78 °C and the integrated GC-based peak areas (*A*), according to the following equation:

$$Yield = \frac{A(aldehyde) / A(xylene)}{A(aldehyde)_{-78°C} / A(xylene)_{-78°C}} * Yield_{-78°C}$$

Table S2 Dependence of yield of Boc-phenylglycinal on the temperature during the addition of DIBALH.

temp. [°C]	A (ald)	A (xyl)	yield [%]
24	673713	2245673	**43**
0	1764540	3959756	**63**
-30	2654574	4478668	**84**
-50	2760001	4425637	**89**
-78	2444543	3694009	**94**

Purity of isolated Boc-phenylglycinal after reductions at different temperatures

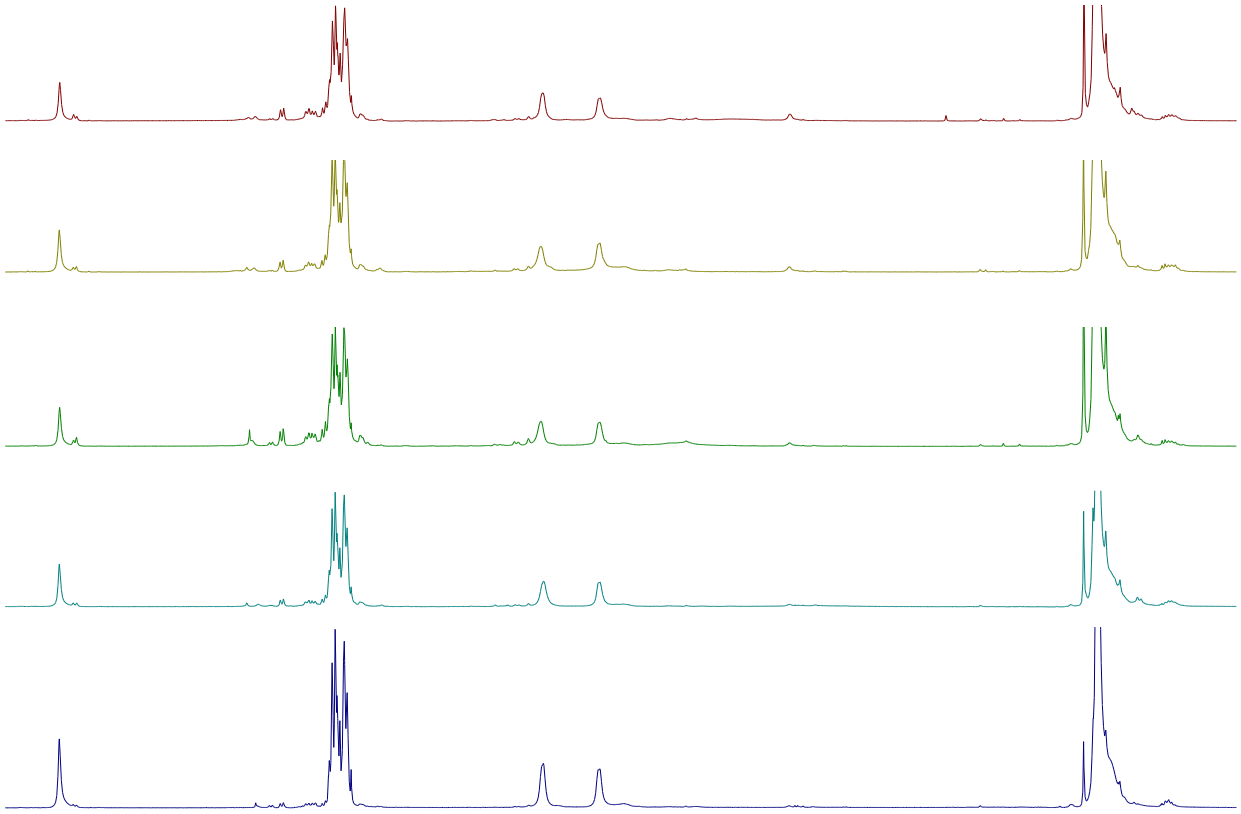


Figure S3 ^{1}H NMR spectra of the crude Boc-phenylglycinal isolated from the reactions at 24 °C, 0 °C, -30 °C, -50 °C and -78 °C, top to bottom, respectively. Interestingly, fairly pure aldehyde was isolated after reduction at each temperature, though optimum seems to be -78 °C.

Dependence of *ee* of Boc-phenylglycinal on the temperature during the addition of DIBAL-H

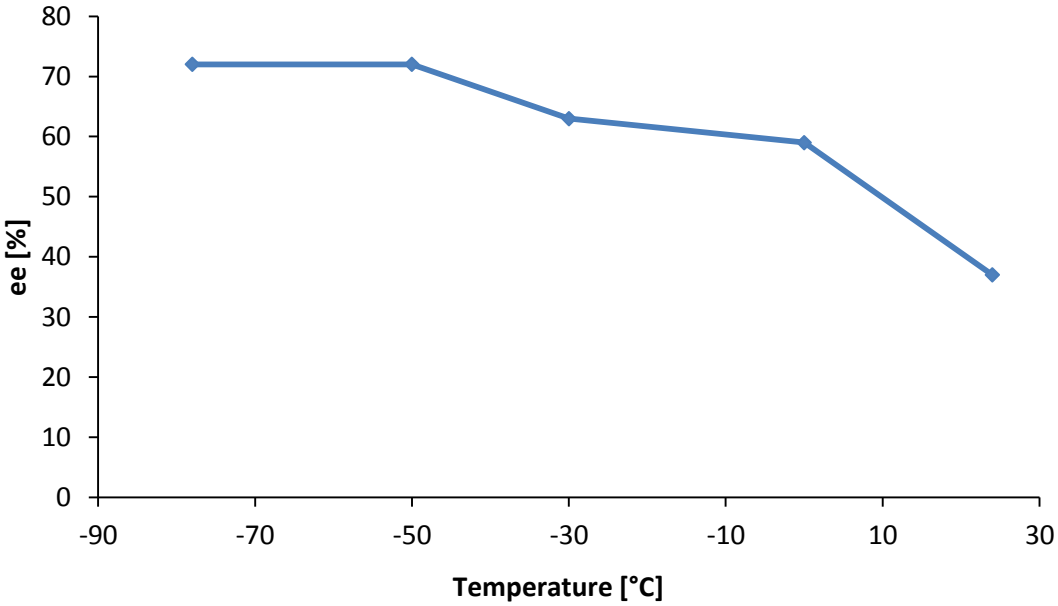
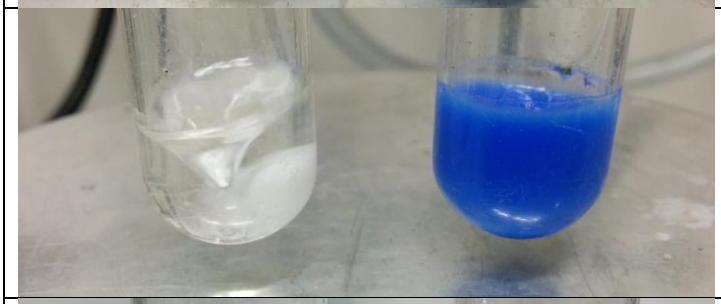


Figure S4 Dependence of yield of Boc-phenylglycinal on the temperature during addition DIBALH. Each reaction instance was performed using 50 mg (0.20 mmol) Boc-L-Phg-OH, 36 mg (0.22 mmol, 1.1 eq) CDI and 0.42 mL (0.42 mmol, 2.1 eq) 1M DIBAL-H in 2.0 mL of absolute CH_2Cl_2, according to the general procedure with altered temperatures used during the reduction step (-78 °C, -50 °C, -30 °C, 0 °C and 24 °C respectively). Enantiopurity was determined by chiral GC-FID.

Table S3 Dependence of *ee* of Boc-phenylglycinal on the temperature during addition of DIBALH.

temp. [°C]	CDI [eq]	DIBAL-H [eq]	*ee* [%]
24	1.1	2.1	**37**
0	1.1	2.1	**59**
-30	1.1	2.1	**63**
-50	1.1	2.1	**72**
-78	1.1	2.1	**72**

Figure S5 Appearance of the reaction solution during the time of activation with CDI and after the treatment with DIBAL-H. Reactions were performed in Schlenk tubes, under N_2 atmosphere.

No additive vs **0.5 eq $CuCl_2$**	**Time after CDI is added**
	5 min
	30 min
	60 min
	15 min after DIBAL-H addition had been completed

References

[1] H. A. Staab and K. Wendel, *Org. Synth.* 1968, **48**, 44.

[2] J. Fehrentz, B. Castro, *Synthesis* **1983**, 676–678.

[3] Y. Hamada, T. Shiori, *Chem. Pharm. Bull*. **1982**, *30*, 1921–1924.

[4] E. A. Jares-Erijman, C. P. Bapat, A. Lithgow-Bertelloni, K. L. Rinehart, R. Sakai, *J. Org. Chem*., **1993**, *58*, 5732–5737.

[5] C. L. Moore, D. D. Leatherwood, T. S. Diehl, D. J. Selkoe, M. S. Wolfe, *J. Med. Chem.* **2000**, *43*, 3434–3442.

[6] M. Uyanik, M. Akakura, K. Ishihara, *J. Am. Chem. Soc*. **2009**, *131*, 251–262.

[7] D. J. Morris, A. S. Partridge, C. V. Manville, D. T. Racys, G. Woodward, G. Docherty, M. Wills, *Tetrahedron Lett.* **2010**, *51*, 209–212.

[8] J. Ahlfors, K. Mekouar, WO 2009140765.

[9] H. Khatri, C. H. Stammer, *J.C.S. Chem. Comm*. **1979**, 79–80.

[10] T. James, I. Simpson, J. A. Grant, V. Sridharan, A. Nelson, *Org. Lett.* **2013**, *15*, 6094–6097.

[11] M. Nakamura, H. Miyashita, M. Yamaguchi, Y. Shirasaki, Y. Nakamura, J. Inoue, *Bioorg. Med. Chem*. **2003**, *11*, 5449–5460.

[12] B. Schmidt, S. Hauke, N. Muehlenberg, *Synthesis* **2014**, *46*, 1648–1658.

[13] R. I. McDonald, G. W. Wong, R. P. Neupane, S. S. Stahl, C. R. Landis, *J. Am. Chem. Soc*. **2010**, *132*, 14027–14029.

[14] J. Bondebjerg, Z. Xiang, R. M. Bauzo, C. Haskell-Luevano, M. Meldal, J. Am. Chem. Soc. **2002**, *124*, 11046–11055.

[15] A. Boeijen, J. van Ameijde, R. M. J. Liskamp, *J. Org. Chem*. **2001**, *66*, 8454–8462.

[16] G. Chennakrishnareddy, B. Vasantha, N. Narendra, Vommina V. Sureshbabu*, International Journal of Peptide Research and Therapeutics* **2011**, *17*, 185–191.

[17] A. E. Wroblewski, D. G. Piotrowska, *Tetrahedron: Asymmetry* **2002**, *13*, 2509–2512.

[18] R. Chinchilla, D. Dodsworth, C. Najera, J. M. Soriano, M. Yus, *ARKIVOC* **2003**, *10*, 41–47.

[19] D. Crich, K. Sana, S. Guo, *Org. Lett.* **2007**, *9*, 4423–4426.

[20] S. Maity, P. Kumar, D. Haldar, *Soft Matter* **2011**,***7***, 5239–5245.

[21] D. Krois, M. Simonetti, E. Wünsch*, Monatsh. Chem.* **1989**, *120*, 1029–1041.

[22] B. Kammermaier, G. Beck, W. Holla, D. Jacobi, B. Napierski, H. Jendralla, *Chem. Eur. J.* **1996**, *2*, 307–315.

[23] A. R. Katritzky, N. E. Abo-Dya, S. R. Tala, K. Gyanda, Z.K. Abdel-Samii, *Org. Biomol. Chem.* **2009**, *7*, 4444–4447.