# SUPPORTING INFORMATION

# Synthesis of Enantiomerically Pure *N*-Acyl Amino Nitriles *via* Catalytic Dehydration of Oximes and Application in a *de novo*-Synthesis of Vildagliptin

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# 1 General information

The *N*-Boc-protected amino aldehydes derived from phenylalanine and proline were purchased from *Sigma-Aldrich* and used without further purification. According to the supplier, the purity of these compounds (*N*-Boc L-prolinal, *N*-Boc D-prolinal, *N*-Boc L-phenylalaninal, *N*-Boc D-phenylalaninal) was 97%. Other reagents were purchased from *Alfa Aesar*, from *fluorochem* and from *Acros Organics* and also used without further purification.

$^{1}$H- and $^{13}$C-NMR spectra were recorded on a Bruker Avance 500 at 500 MHz ($^{1}$H) or 125 MHz ($^{13}$C) in deuterated dichloromethane ($CD_2Cl_2$) or deuterated chloroform ($CDCl_3$) without the usage of an internal standard. Chemical shifts are reported in ppm.

Mass spectra were recorded on an Esquire 3000 using electron spray ionization (ESI).

IR-spectra were recorded on a Thermo Nicolet 380 FT-IR.

GC-chromatograms were recorded on a Shimadzu GC-2010 using the column *Agilent* CP-Chirasil-Dex CB with different temperature programs.

Melting points were determined with a Büchi Melting Point B-540 and are uncorrected.

Optical rotation angles were measured on a Perkin Elmer Polarimeter Model 341.

Column chromatography was performed either manually or using an automatic column chromatography system Isolera One by Biotage.

RP-HPLC-chromatograms were recorded on a JASCO system utilizing a *Macherey-Nagel* Nucleodur $C_{18}$ HTec column with different ratios of water/acetonitrile as mobile phase (listed below).

NP-HPLC-chromatograms were recoreded on a JASCO system utilizing a *Daicel* Chiracel AD-H column with different ratios of supercritical $CO_2$/Isopropanol as mobile phase (listed below).

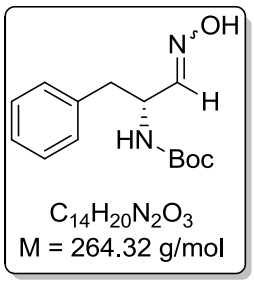
# 2 EXPERIMENTAL PROCEDURES – ENANTIOSELECTIVE NITRILE SYNTHESIS

## 2.1 SYNTHESIS OF ALDOXIMES BY CONDENSATION OF ALDEHYDES WITH HYDROXYLAMINE SALTS

### 2.1.1 GENERAL PROCEDURE (GOP) 1: CONDENSATION OF MONO-ALDEHYDES WITH HYDROXYLAMINE SALTS

Hydroxylamine hydrochloride (1.5 eq.) and sodium carbonate (1.5 eq.) were diluted in a mixture of $H_2O$ and 1-propanol or ethanol at room temperature. Aldehyde was added to this solution and stirred vigorously until complete conversion according to TLC analysis (cyclohexane/ethyl acetate in different volumetric percentages) was achieved. The solution was extracted three times with ethyl acetate (1:1 v/v) and the combined organic phases were washed with $H_2O$ (1:3 v/v). Drying over $MgSO_4$ and evaporation of the solvent gave a crude product, which was purified by silica column chromatography if desired. The *E*/*Z*-ratio of the product was determined by $^1$H-NMR spectroscopy in $CD_2Cl_2$ or in $CDCl_3$.

### 2.1.2 *N*-BOC D-*E/Z*-PHENYLALANINAL OXIME ((*R*)-*E/Z*-**13**)




The synthesis was carried out according to GOP1. Hydroxylamine hydrochloride (146 mg, 2.11 mmol) and sodium carbonate (223 mg, 2.11 mmol) were diluted in 5 mL $H_2O$ and 4 mL 1-propanol at RT. After the addition of *N*-Boc D-phenylalaninal (350 mg, 1.40 mmol) the resulting solution was stirred for 18 hours, upon which complete conversion was achieved according to TLC analysis. The work up yielded a mixture of (*R*)-*E/Z*-**13** as colorless solid. The isomers were separated by column chromatography (cyclohexane:ethyl acetate 3:1, v/v), and obtained as colorless solids after removal of the solvent at room temperature.

<u>*N*-Boc D-*E*-phenylalaninal oxime:</u>

**Yield**: 200 mg, 54%.

**$^1$H-NMR** (500 MHz, $CD_2Cl_2$): δ [ppm] = 10.50 (s, 1H, NO*H*), 7.65 (s, 1H, N*H*), 7.42 (br s, 1H, C*H*NOH), 7.31 (m, 2H, Ar-*H*) 7.23 (m, 1H, Ar-*H*), 7.18 (m, 2H, Ar-*H*), 4.98 (s, 1H, $CH_2CH$NH), 4.52 (m, 1H, $CH_2CH$NH), 2.96 (m, 2H, $CH_2$), 1.38 (s, 9H, Boc *H*).

*N*-Boc D-*Z*-phenylalaninal oxime:

**Yield**: 142 mg, 38%.

**$^1$H-NMR** (500 MHz, $CD_2Cl_2$): δ [ppm] = 7.75 (s, 1H, NO*H*), 7.32 (m, 2H, Ar-*H*), 7.24 (m, 3H, Ar-*H*), 6.68 (d, 1H, $^3J$ = 6.1 Hz, C*H*NOH), 4.93 (m, 1H, $CH_2CHNH$), 4.79 (s, 1H, N*H*), 3.03 (dd, 1H, $^2J$ = 13.9 Hz, $^3J$ = 5.4 Hz, $CH_2$), 2.94 (m, 1H, $CH_2$), 1.38 (s, 9H, Boc *H*).

*N*-Boc D-*E/Z*-phenylalaninal oxime:

**$^{13}$C-NMR** (125 MHz, $CD_2Cl_2$): δ [ppm] = 156.8, 155.8, 155.5, 153.0, 151.0, 149.2, 137.6, 137.3, 130.15, 129.9, 19.0, 127.2, 81.6, 80.2, 51.7, 48.3, 41.8, 39.9, 37.9, 28.6.

**MS** (ESI): *m*/*z* = 265.1 ($[M+H]^+$), 287.2 ($[M+Na]^+$), 551.3 ($[2M+Na]^+$).

**IR** [$cm^{-1}$]: 3349, 1690, 1518, 1245, 1165, 698.

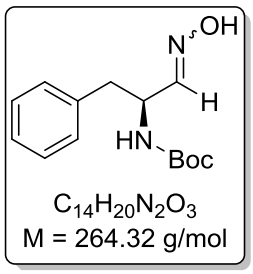
**MP**: 125 °C.

**RP-HPLC**: *Macherey-Nagel* Nucleodur $C_{18}$ HTec, Water/Acetonitrile 50:50, v/v, 1.0 mL/min, 40 °C, 220 nm, $R_t$ = 5.4 min.

**NP-HPLC**: *Daicel* Chiracel AD-H, $CO_2$/Isopropanol 95:5, v/v, 0.75 mL/min, 30 min -> 90:10, 2.00 mL/min, 30 min, 20 °C, 210 nm, $R_{tZ}$ = 40.6 min, $R_{tE}$ = 43.5 min.

The analytical data are in accordance with the corresponding literature data.[1]

## 2.1.3 *N*-BOC L-*E/Z*-PHENYLALANINAL OXIME ((*S*)-*E/Z*-**13**)




The synthesis was carried out according to GOP1. Hydroxylamine hydrochloride (100 mg, 1.43 mmol) and sodium carbonate (152 mg, 1.43 mmol) were diluted in 5 mL $H_2O$ and 4 mL 1-propanol at RT. After the addition of *N*-Boc L-phenylalaninal (238 mg, 955 µmol) the colorless suspension was stirred for 18 hours, upon which complete conversion was achieved according to TLC analysis. The work up yielded a mixture of (*S*)-*E/Z*-**13** as a colorless solid.

**Yield**: 212 mg, 84%.

*N*-Boc L-*E,Z*-phenylalaninal oxime:

**$^1$H-NMR** (500 MHz, $CD_2Cl_2$): δ [ppm] = 10.02 (s, 1H, NO*H*), 7.86 (s, 1H, NO*H*), 7.54 (s, 1H, N*H*), 7.42 (br s, 1H, C*H*NOH), 7.33-7.18 (m, 5H, Ar-*H*), 6.68 (d, 1H, $^3J$ = 6.1 Hz, C*H*NOH), 5.71 (br s, 1H), 4.95 (s, 1H, $CH_2CHNH$), 4.81 (s, 1H, N*H*), 4.52 (m, 1H,

$CH_2CHNH$), 3.03 (dd, 1H, $^2J$ = 13.9 Hz, $^3J$ = 5.4 Hz, $CH_2$), 2.96 (m, 2H, $CH_2$), 1.38 (s, 9H, Boc *H*).

**$^{13}$C-NMR** (125 MHz, $CD_2Cl_2$): δ [ppm] = 156.7, 155.7, 155.4, 153.1, 151.2, 149.4, 137.6, 137.3, 130.2, 129.9, 129.1, 129.0, 127.3, 127.2, 81.5, 80.1, 51.7, 41.7, 39.9, 28.5.

**IR** [$cm^{-1}$]: 3349, 1690, 1518, 1245, 1165, 699.

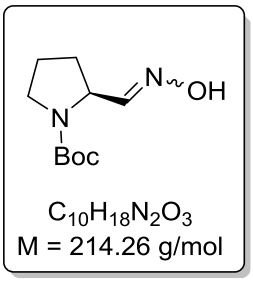
**MP**: 127 °C.

**RP-HPLC**: *Macherey-Nagel* Nucleodur $C_{18}$ HTec, Water/Acetonitrile 50:50, v/v, 1.0 mL/min, 40 °C, 220 nm, $R_t$ = 5.4 min.

**NP-HPLC**: *Daicel* Chiracel AD-H, $CO_2$/Isopropanol 95:5, v/v, 0.75 mL/min, 30 min -> 90:10, 2.00 mL/min, 30 min, 20 °C, 210 nm, $R_{tZ}$ = 43.5 min, $R_{tE}$ = 55.1 min.

The analytical data are in accordance with the corresponding literature data.[1]

## 2.1.4 *N*-Boc L-*E/Z*-Prolinal oxime ((*S*)-*E/Z*-**10**)




$C_{10}H_{18}N_2O_3$
M = 214.26 g/mol

The synthesis was carried out according to GOP1. Hydroxylamine hydrochloride (104 mg, 1.50 mmol) and sodium carbonate (159 mg, 1.50 mmol) were diluted in 3 mL $H_2O$ and 2 mL ethanol at RT. After the addition of *N*-Boc L-prolinal (199 mg, 1.00 mmol) the resulting solution was stirred for 20 hours, upon which complete conversion was achieved according to TLC analysis. The work up yielded a mixture of (*S*)-*E/Z*-**10** as a colorless oil. The product was isolated by column chromatography (cyclohexane:ethyl acetate 3:1, v/v), and obtained as a colorless oil with an *E*/*Z* ratio of 65:35 after removal of the solvent at 40 °C. The *E*- and *Z*-isomers could not be separated.

**Yield**: 143 mg, 67%.

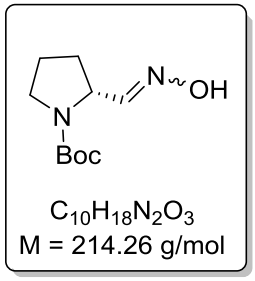
**$^1$H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 8.36 + 8.21 (2 s, 1H, *Z*-NO*H*), 8.01 + 7.90 (2 s, 1H, *E*-NO*H*), 7.40 + 7.31 (2 s, 1H, *E*-C*H*NOH), 6.74 + 6.69 (2 s, 1H, *Z*-C*H*NOH), 4.88 + 4.83 (2 s, 1H, *Z*-BocNC*H*), 4.46 + 4.31 (2 s, 1H, *E*-BocNC*H*), 3.41 (m, 2H, BocNC$H_2$), 2.26 – 1.75 (m, 4H, $BocNCH_2CH_2CH_2$), 1.46 + 1.44 (2 s, 9H, Boc *H*).

**$^{13}$C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 154.5, 151.9, 80.1, 56.2, 52.8, 46.5, 30.7, 28.8, 28.6, 28.5, 28.4, 27.0.

**GC**: *Agilent* CP-Chirasil-Dex CB (0.32 mm ID x 25 m length, 0.25 µm film), 160 °C initial temperature (7 min), 2 °C/min ramp, 180 °C final temperature, $R_t$ = 12.3 min (*E* and *Z* isomers).

The analytical data are in accordance with the corresponding literature data.[1]

### 2.1.5 *N*-Boc D-*E/Z*-Prolinal oxime ((*R*)-*E/Z*-**10**)




The synthesis was carried out according to GOP1. Hydroxylamine hydrochloride (104 mg, 1.50 mmol) and sodium carbonate (159 mg, 1.50 mmol) were diluted in 3 mL $H_2O$ and 2 mL ethanol at RT. After the addition of *N*-Boc D-prolinal (199 mg, 1.00 mmol) the resulting solution was stirred for 24 hours, upon which complete conversion was achieved according to TLC analysis. The work up yielded a mixture of (*R*)-*E/Z*-**10** as a colorless oil. The product was isolated by column chromatography (cyclohexane:ethyl acetate 2:1, v/v), and obtained obtained as a colorless oil with an *E*/*Z* ratio of 72:28 after removal of the solvent at 40 °C. The *E*- and *Z*-isomers could not be separated.

**Yield**: 177 mg, 81%.

**$^1$H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 8.37 + 8.21 (2 s, 1H, *Z*-NO*H*), 8.02 + 7.90 (2 s, 1H, *E*-NO*H*), 7.41 + 7.31 (2 s, 1H, *E*-C*H*NOH), 6.74 + 6.68 (2 s, 1H, *Z*-C*H*NOH), 4.89 + 4.83 (2 s, 1H, *Z*-BocNC*H*), 4.47 + 4.31 (2 s, 1H, *E*-BocNC*H*), 3.41 (m, 2H, BocNC$H_2$), 2.26 – 1.82 (m, 4H, BocNCH$_2$C$H_2$C$H_2$), 1.46 + 1.44 (2 s, 9H, Boc *H*).

**$^{13}$C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 154.5, 151.6, 80.0, 56.3, 52.7, 46.5, 30.7, 28.8, 28.6, 28.5, 28.4, 27.0.

**GC**: *Agilent* CP-Chirasil-Dex CB (0.32 mm ID x 25 m length, 0.25 µm film), 160 °C initial temperature (7 min), 2 °C/min ramp, 180 °C final temperature, $R_t$ = 10.7 min (*E* and *Z* isomers).

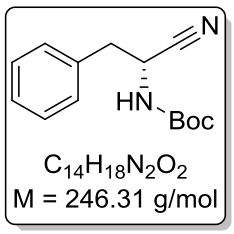
The analytical data are in accordance with the corresponding literature data.[1]

## 2.2 SYNTHESIS OF ENANTIOMERICALLY ENRICHED *α*-AMINO NITRILES BY $CU^{II}$-CATALYZED DEHYDRATION OF ALDOXIMES

### 2.2.1 GENERAL PROCEDURE (GOP) 2: COPPER(II) ACETATE-CATALYZED DEHYDRATION OF *N*-ACYL *α*-AMINO ALDOXIMES

Copper(II) acetate (10 mol-% or 2 mol-%) was dissolved in acetonitrile. Upon addition of the aldoxime, a rapid change in color from cyan to deep green was observed. The resulting suspension was heated to reflux for 60 minutes or 7 hours. After removal of the acetonitrile in vacuum, complete conversion was determined via TLC analysis (cyclohexane/ethyl acetate in different volumetric percentages). The crude product, containing one equivalent of acetamide, was dissolved in cyclohexane/ethyl acetate (2:1, v/v) and filtered over a small silica column (4 cm), effectively removing acetamide and residual copper(II) acetate. Removal of the solvent yielded the desired nitrile. To determine the retention of absolute configuration, the product was analyzed by chiral HPLC or chiral GC. Alternatively to NMR, conversion could be measured via RP-HPLC or GC.

### 2.2.2 *N*-BOC (*R*)-PHENYLALANINE NITRILE ((*R*)-**14**)




The synthesis was carried out according to GOP2. Copper(II) acetate (10.3 mg, 56.7 µmol) was dissolved in 1.5 mL acetonitrile. *N*-Boc D-*E/Z*-Phenylalaninal oxime ((*R*)-*E/Z*-**13**, 150 mg, 567 µmol) was added and the reaction mixture was heated to reflux for 60 min. The work up yielded (*R*)-**14** as a colorless solid.

**Yield**: 116 mg, 83%.

**$^1$H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 7.33 (m, 5H, Ar-*H*), 4.84 (br s, 2H, C*H* and N*H*), 3.09 (m, 2H, PhC$H_2$), 1.44 (s, 9H, Boc *H*).

**MS** (ESI): *m*/*z* = 269.1 ($[M+Na]^+$), 515.2 ($[2M+Na]^+$).

**IR** [$cm^{-1}$]: 3350, 2922, 1688, 1518, 700.

**MP**: 115 °C.

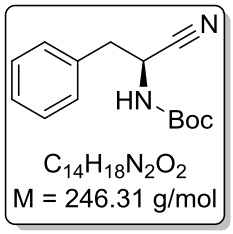
**$[\alpha]^{20}_D$**: + 16 (c 0.98 dioxane).

**RP-HPLC**: *Macherey-Nagel* Nucleodur $C_{18}$ HTec, Water/Acetonitrile 50:50, v/v, 1.0 mL/min, 40 °C, 220 nm, $R_t$ = 9.0 min.

**NP-HPLC**: *Daicel* Chiracel AD-H, $CO_2$/Isopropanol 95:5, v/v, 0.75 mL/min, 30 min -> 90:10, 2.00 mL/min, 30 min, 20 °C, 210 nm, $R_t$ = 23.3 min.

The analytical data are in accordance with the corresponding literature data.[2,3]

### 2.2.3 *N*-Boc (*S*)-Phenylalanine nitrile ((*S*)-**14**)




The synthesis was carried out according to GOP2. Copper(II) acetate (7.3 mg, 40.2 µmol) was dissolved in 1.0 mL acetonitrile. *N*-Boc L-*E/Z*-Phenylalaninal oxime ((*S*)-*E/Z*-**13**, 85.0 mg, 322 µmol) was added and the reaction mixture was heated to reflux for 60 min. The work up yielded (*S*)-**14** as a colorless solid.

**Yield**: 73 mg, 92%.

**$^1$H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 7.33 (m, 5H, Ar-*H*), 4.84 (br s, 2H, C*H* and N*H*), 3.09 (m, 2H, Ph$CH_2$), 1.44 (s, 9H, Boc *H*).

**IR** [$cm^{-1}$]: 3351, 2923, 1688, 1518, 700.

**MP**: 115 °C.

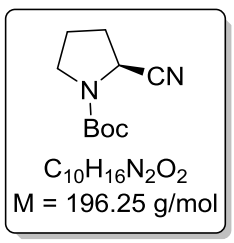
**$[\alpha]^{20}_D$**: - 16 (c 0.98 dioxane).

**RP-HPLC**: *Macherey-Nagel* Nucleodur $C_{18}$ HTec, Water/Acetonitrile 50:50, v/v, 1.0 mL/min, 40 °C, 220 nm, $R_t$ = 9.0 min.

**NP-HPLC**: *Daicel* Chiracel AD-H, $CO_2$/Isopropanol 95:5, v/v, 0.75 mL/min, 30 min -> 90:10, 2.00 mL/min, 30min, 20 °C, 210 nm, $R_t$ = 20.9 min.

The analytical data are in accordance with the corresponding literature data.[2,3]

### 2.2.4 *N*-Boc (*S*)-Pyrrolidine carbonitrile ((*S*)-**11**)




The synthesis was carried out according to GOP2. Copper(II) acetate (2.58 mg, 11.5 µmol) was dissolved in 7 mL acetonitrile. *N*-Boc L-*E/Z*-prolinal oxime ((*S*)-*E/Z*-**10**, 123 mg, 570 µmol) was added and the reaction mixture was heated to reflux for 7 hours and stirred for another 16 hours. The work up yielded (*S*)-**11** as a colorless oil with an enantiomeric excess of 97%.

**Yield**: 97 mg, 86%.

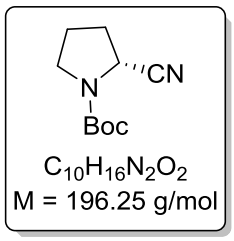
**$^1$H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 4.57 + 4.45 (2 d, 1H, C*H*CN), 3.51 + 3.37 (2 m, 2H, BocNC*H*$_2$), 2.25 – 2.02 (m, 4H, BocNCH$_2$C*H*$_2$C*H*$_2$), 1.51 + 1.48 (2 s, 9H, Boc *H*).

**$^{13}$C-NMR** (125 MHz, $CDCl_3$): δ [ppm] = 153.2, 119.3, 81.6, 81.1, 47.3, 46.1, 45.9, 31.8, 31.0, 28.5, 24.8, 24.0.

**GC**: *Agilent* CP-Chirasil-Dex CB (0.32 mm ID x 25 m length, 0.25 µm film), 160 °C initial temperature (7 min), 2 °C/min ramp, 180 °C final temperature, $R_t$ = 3.9 min.

The analytical data are in accordance with the corresponding literature data.[4]

## 2.2.5 *N*-Boc (*R*)-Pyrrolidine carbonitrile ((*R*)-**11**)




The synthesis was carried out according to GOP2. Copper(II) acetate (2.73 mg, 15.0 µmol) was dissolved in 7 mL acetonitrile. *N*-Boc D-*E/Z*-prolinal oxime ((*R*)-*E/Z*-**10**, 161 mg, 750 µmol) was added and the reaction mixture was heated to reflux for 7 hours and stirred for another 16 hours. The work up yielded (*R*)-**11** as a colorless oil with an enantiomeric excess of 99%.

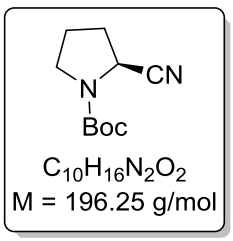
**Yield**: 130 mg, 88%.

**$^1$H-NMR** (500 MHz, $CDCl_3$): δ [ppm] = 4.57 + 4.45 (2 d, 1H, C*H*CN), 3.51 + 3.36 (2 m, 2H, BocNC*H*$_2$), 2.25 – 2.02 (m, 4H, BocNCH$_2$C*H*$_2$C*H*$_2$), 1.51 + 1.48 (2 s, 9H, Boc *H*).

**GC**: *Agilent* CP-Chirasil-Dex CB (0.32 mm ID x 25 m length, 0.25 µm film), 160 °C initial temperature (7 min), 2 °C/min ramp, 180 °C final temperature, $R_t$ = 4.0 min.

The analytical data are in accordance with the corresponding literature data.[5]

## 2.2.6 Influence of the co-solvent on the $Cu^{II}$-catalyzed dehydration




The nitrile synthesis with varying amounts of acetonitrile and varying solvents was carried out in 2 mL glass vials. For each reaction, copper(II) acetate (1.09 mg, 6.0 µmol) and *N*-Boc L-*E/Z*-prolinal oxime (64.3 mg, 300 µmol) were dissolved in 1 mL ethyl acetate. Then, defined amounts of acetonitrile (1 to 20 equivalents, see table 1) were added to the mixture. For comparison, one reaction was also carried out in pure acetonitrile (1 mL, 64 equivalents) without additional solvent. In a further approach, the same amounts of

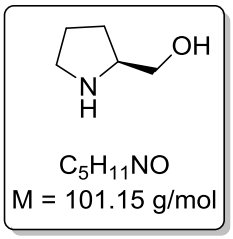
copper(II) acetate and *N*-Boc L-*E/Z*-prolinal oxime were mixed with different solvents (1 mL; for the type of solvents, see Table 1), and acetonitrile (10 equivalents) was added. The reaction mixture was heated to 70 °C and stirred for 5 hours. After removal of the solvents in vacuum, 2 mL water was added to the residual. The mixture was extracted three times with dichloromethane (1:1 v/v) and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent, the residue was analyzed by $^1$H-NMR spectroscopy to determine the conversion *via* comparison of the substrate and product integrals (see Table S1).

**Table S1.** Screening parameters for the optimization of the copper-catalyzed dehydration of *N*-Boc L-*E/Z*-prolinal oxime.

| **entry** | **solvent** | **amount of acetonitrile [eq.]** | **conversion [%]** |
|---|---|---|---|
| 1 | ethyl acetate | 1 | 54 |
| 2 | ethyl acetate | 2 | 57 |
| 3 | ethyl acetate | 4 | 71 |
| 4 | ethyl acetate | 6 | 74 |
| 5 | ethyl acetate | 8 | 78 |
| 6 | ethyl acetate | 10 | 81 |
| 7 | ethyl acetate | 15 | 92 |
| 8 | ethyl acetate | 20 | 92 |
| 9 | acetonitrile | 64 | 92 |
| 10 | cyclohexane | 10 | 88 |
| 11 | toluene | 10 | 89 |
| 12 | water | 10 | 46 |
| 13 | ethanol | 10 | 80 |
| 14 | methanol | 10 | 74 |
| 15 | 2-methyl THF | 10 | 70 |
| 16 | dimethyl carbonate | 10 | 94 |

## 2.3 De novo-Synthesis of Vildagliptin

### 2.3.1 L-Prolinol ((*S*)-**16**)




The reaction was carried out in a stainless steel autoclave. Methyl L-prolinate hydrochloride (2.00 g, 12.0 mmol) was dissolved in 25 mL THF and potassium methoxide (1.68 g, 24.0 mmol) was added. While flushing the autoclave with argon, the catalyst Ru-MACHO (1 mol%) was added and the system was closed airtight afterwards. A hydrogen pressure of 100 bar was applied and the reaction mixture was stirred mechanically for 24 hours at 100 °C. After removing the hydrogen pressure and flushing the system with nitrogen, 15 mL water was added. The phases were separated and the aqueous phase was extracted four times with ethyl acetate (1:1 v/v). After drying the organic phase over $MgSO_4$, the solvent was removed in vacuum. The product (*S*)-**16** was obtained as a yellowish oil and used without further purification in the next step.

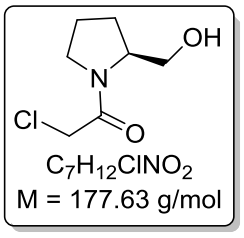
**Yield**: 300 mg, 25%.

**$^1$H-NMR** (500 MHz, $CD_3OD$): δ [ppm] = 3.49 (m, 2H, C**H$_2$**OH), 3.14 (m, 1H, C**H**$^{chiral}$), 2.93 + 2.81 (2m, 2H, CH$^{chiral}$-NH-C**H$_2$**), 1.85 + 1.76 + 1.46 (3m, 4H, C**H$_2$**C**H$_2$**$CH_2$N).

**$^{13}$C-NMR** (125 MHz, $CD_3OD$): δ [ppm] = 65.4, 61.2, 47.0, 28.7, 26.2.

The analytical data are in accordance with the corresponding literature data.[6]

### 2.3.2 *N*-Chloroacetyl L-prolinol ((*S*)-**17**)




L-Prolinol ((*S*)-**16**, 10.0 g, 99.0 mmol) was dissolved in 100 mL dichloromethane. Triethylamine (13.7 mL, 99.0 mmol) was added under vigorous stirring and the reaction mixture was cooled to 0 °C in a bath of water and ice. A solution of chloroacetyl chloride (7.9 mL, 99 mmol) in 50 mL dichloromethane was added dropwise within an hour while stirring the reaction mixture at 0 °C vigorously. After completed addition the ice bath was removed and the reaction mixture was stirred at room temperature for 2 hours. After removal of the solvent in vacuum, the residue was suspended in diethyl ether, filtered through a frit (pore size 4) and washed with further portions of diethyl ether. The combined ethereal phases were evaporated. The product (*S*)-**17** was isolated by column chromatography (dichloromethane / methanol), freed from the solvent in vacuum and obtained as a yellow oil.

**Yield**: 12.5 g, 71%.

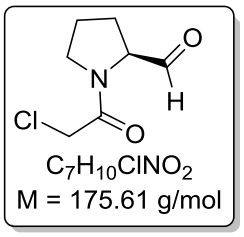
**$^1$H-NMR** (500 MHz, $CD_2Cl_2$): $\delta$ [ppm] = 4.26 (bs, 1H, $CH_2O\mathbf{H}$), 4.14 (m, 1H, $C\mathbf{H}^{chiral}$), 4.08 (s, 2H, $C(O)C\mathbf{H_2}Cl$), 3.63 - 3.48 (m, 4H, $C\mathbf{H_2}OH$, $CH^{chiral}CH_2CH_2C\mathbf{H_2}N$), 2.08 - 1.61 (4m, 4H, $CH^{chiral}C\mathbf{H_2}C\mathbf{H_2}CH_2N$).

**$^{13}$C-NMR** (125 MHz, $CD_2Cl_2$): $\delta$ [ppm] = 167.6, 66.7, 62.6, 48.6, 43.3, 28.6, 25.0.

**MS (ESI)**: $m/z$ = 178 $[M+H]^+$, 200 $[M+Na]^+$.

The analytical data are in accordance with the corresponding literature data.[7]

## 2.3.3 *N*-2-Chloroacetyl (*S*)-pyrrolidine-2-carbaldehyde ((*S*)-**18**)




*N*-Chloroacetyl L-prolinol ((*S*)-**17**, 3.00 g, 16.9 mmol) was dissolved in 8 mL dichloromethane and TEMPO (26 mg, 0.17 mmol) was added. To this mixture a solution of NaBr (174 mg, 1.69 mmol) in 1 mL water was added under stirring. The mixture was cooled to 0 °C in a bath of ice and NaCl. Subsequently, NaOCl (1.96 M in water, pH adjusted to 9.5 by addition of solid $NaHCO_3$, 8.9 mL, 18.6 mmol) was added within 20 min slowly to the reaction mixture under stirring so that the temperature of the mixture remained between 0 and 4 °C. After complete addition, the reaction mixture was stirred for further 20 min at 0 °C. The phases were separated and the aqueous phase was extracted four times with 10 mL dichloromethane. The combined organic layers were washed step-by-step with aqueous solutions of HCl (2 M, including solid KI (0.34 mmol, 56 mg)), $Na_2S_2O_3$ (0.1 M), $NaHCO_3$ (10%) and water, each 10 mL, and dried over $MgSO_4$. After removal of the solvent in vacuum, the product (*S*)-**18** was obtained as an orange oil and used without further purification in the next step.

**Yield**: 1.61 g, 54%.

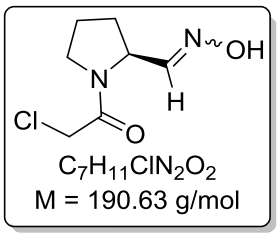
**$^1$H-NMR** (500 MHz, $CDCl_3$): $\delta$ [ppm] = 9.61 + 9.56 (2s, 1H, $C\mathbf{H}O$), 4.53 (m, 1H, $C\mathbf{H}^{chiral}$), 4.10 (m, 2H, $C(O)C\mathbf{H_2}Cl$), 3.66 (m, 2H, $CH^{chiral}CH_2CH_2C\mathbf{H}_2N$), 2.12-1.96 (m, 4H, $CH^{chiral}C\mathbf{H_2}C\mathbf{H_2}CH_2N$).

**$^{13}$C-NMR** (125 MHZ, $CDCl_3$): $\delta$ [ppm] = 198.4, 198.0, 165.8, 65.8, 65.4, 53.6, 47.4, 41.8, 27.9, 25.9, 25.0, 22.3.

**MS (ESI)**: $m/z$ = 176 $[M+H]^+$, 198 $[M+Na]^+$, 239 $[M+CH_3CN+Na]^+$.

**HRMS (ESI):** calcd for $C_7H_{11}ClNO_2$ $[M+H]^+$: 176.0473, found: 176.0470.

### 2.3.4 *N*-2-Chloroacetyl (*S*)-pyrrolidine-2-carbaldehyde oxime ((*S*)-**19**)




The synthesis was carried out according to GOP1. Hydroxylamine hydrochloride (178 mg, 2.6 mmol) and sodium carbonate (272 mg, 2.6 mmol) were dissolved in 3 mL $H_2O$ at RT. After the addition of 1-*N*-2-chloroacetyl (*S*)-pyrrolidine-2-carbaldehyde ((*S*)-**18**, 300 mg, 1.7 mmol) the resulting solution was stirred for 3 hours, upon which complete conversion was achieved according to TLC analysis. The work up yielded (*S*)-**19** (as an *E/Z*-mixture) as a colorless oil. The product was isolated by column chromatography (ethyl acetate), and obtained as a colorless solid with an *E*/*Z* ratio of 72:28 after removal of the solvent in vacuum. The *E*- and *Z*-isomers could not be separated.

**Yield**: 148 mg, 45%.

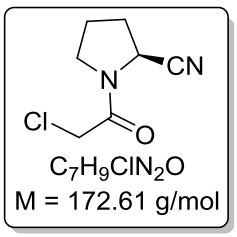
**$^1$H-NMR** (500 MHz, $CDCl_3$): $\delta$ [ppm] = 8.28 (bs, 1H, CNO**H**), 7.45 + 7.34 (2d, 0.72H, *E*-NC**H**), 6.72 (m, 0.28H, *Z*-NC**H**), 5.23 + 5.06 (2m, 0.28H, *Z*-C**H**$^{chiral}$), 4.76 + 4.63 (2m, 0.72H, *E*-C**H**$^{chiral}$), 4.04 (m, 2H, C(O)C**H$_2$**Cl), 3.62 (m, 2H, CH$^{chiral}$CH$_2$CH**$_2$**C**H**$_2$N), 2.11-1.91 (m, 4H, CH$^{chiral}$C**H$_2$**C**H$_2$**CH$_2$N).

**$^{13}$C-NMR** (125 MHz, $CDCl_3$): $\delta$ [ppm] = 166.2, 165.5, 149.8, 149.5, 56.5, 47.0, 42.2, 31.3, 28.46, 24.49, 22.21.

**MS (ESI)**: *m*/*z* = 213 $[M+Na]^+$, 231 $[M+K]^+$, 403 $[2M+Na]^+$, 593 $[3M+Na]^+$.

**HRMS (ESI):** calcd for $C_7H_{12}ClN_2O_2$ $[M+H]^+$: 191.0582, found: 191.0578.

### 2.3.5 *N*-2-Chloroacetyl (*S*)-pyrrolidine-2-carbonitrile ((*S*)-**5**)




The synthesis was carried out according to GOP2. Copper(II) acetate (2.86 mg, 15.7 µmol) was dissolved in 3 mL acetonitrile. *N*-2-Chloroacetyl (*S*)-pyrrolidine-2-carbaldehyde oxime ((*S*)-**19**, 60 mg, 0.31 mmol) was added and the reaction mixture was heated to reflux for 20 hours. The work up yielded (*S*)-**5** as a colorless oil.

**Yield**: 33 mg, 61%.

**specific rotation angle**: $[\alpha]_D^{20}$ = - 147° (c = 1.01, $CH_2Cl_2$).

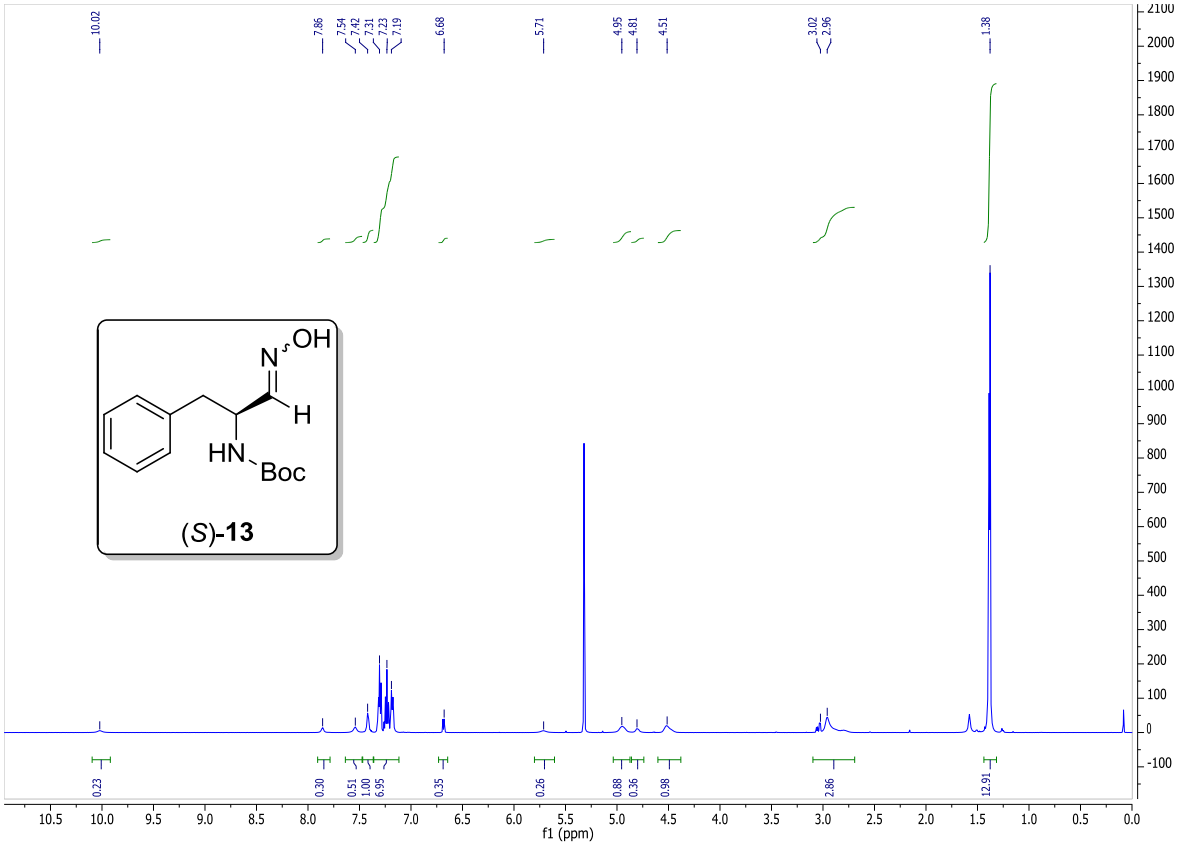
**$^1$H-NMR** (500 MHz, $CDCl_3$): $\delta$ [ppm] = 4.87 + 4.77 (2d, 1H, C**H**$^{chiral}$), 4.10 (m, 2H, C(O)C**H$_2$**Cl), 3.74 – 3.51 (m, 2H, CH$^{chiral}$CH$_2$CH**$_2$**C**H**$_2$N), 2.42 – 2.13 (m, 4H, CH$^{chiral}$C**H$_2$**C**H$_2$**CH$_2$N).

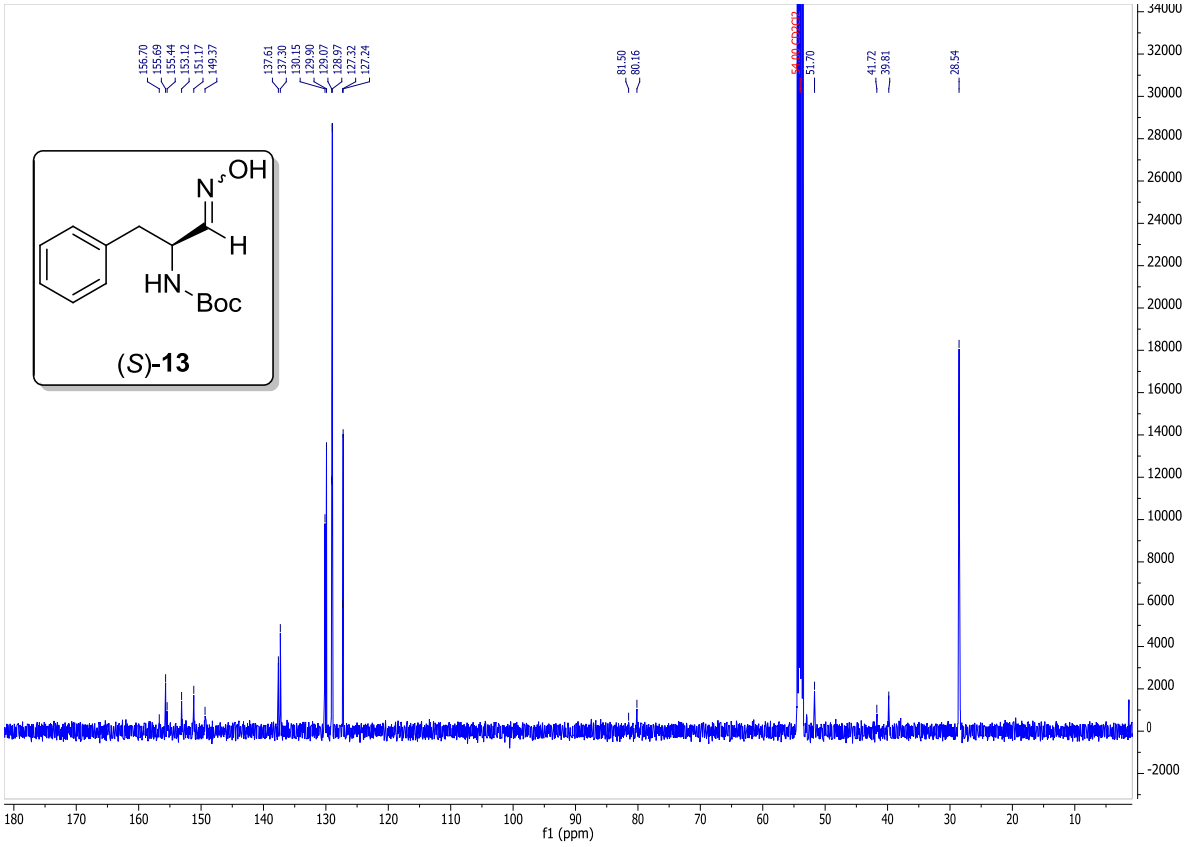
**$^{13}$C-NMR** (125 MHz, $CDCl_3$): $\delta$ [ppm] = 166.4, 117.9, 47.1, 46.7, 41.6, 30.2, 25.4.

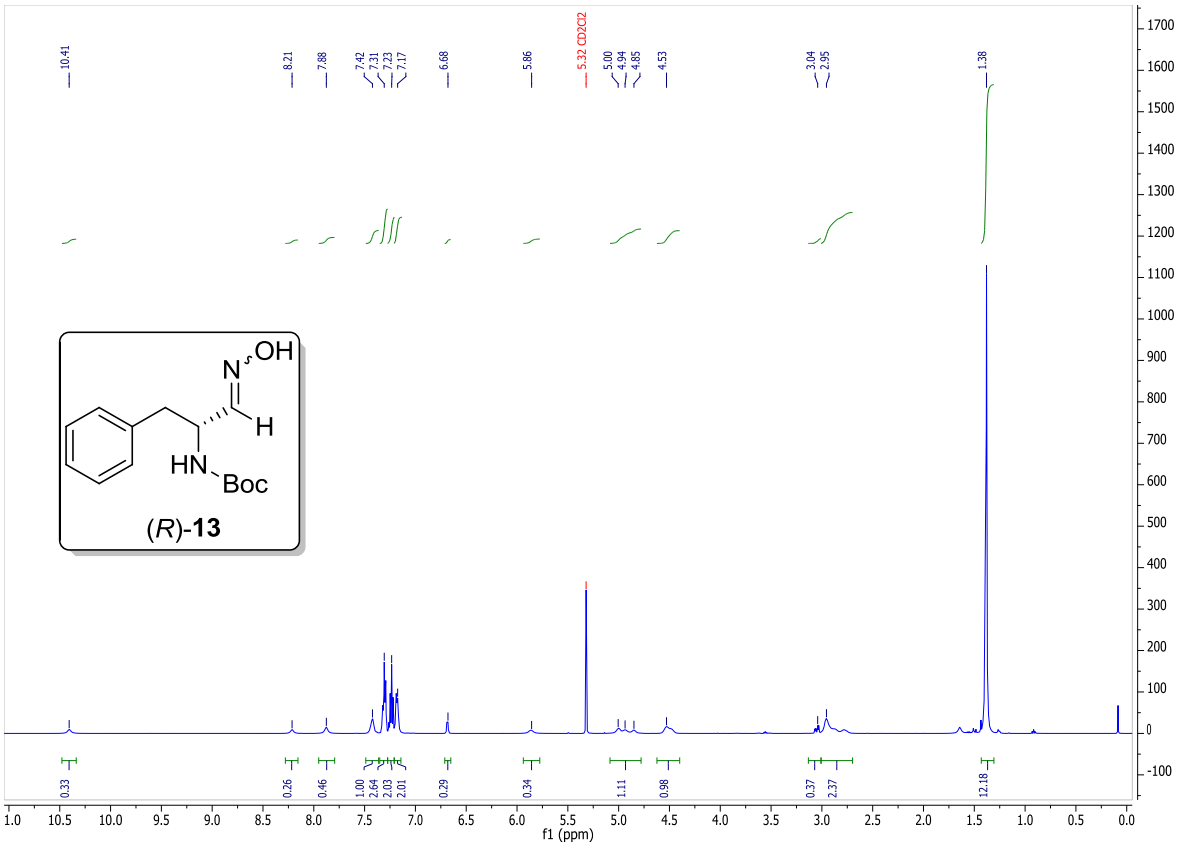
**MS (ESI)**: $m/z$ = 173 $[M+H]^+$, 190 $[M+NH_4]^+$, 195 $[M+Na]^+$, 236 $[M+CH_3CN+Na]^+$, 367 $[2M+Na]^+$.

The analytical data are in accordance with the corresponding literature data.[8]

# 3 $^{1}$H- AND $^{13}$C-NMR SPECTRA

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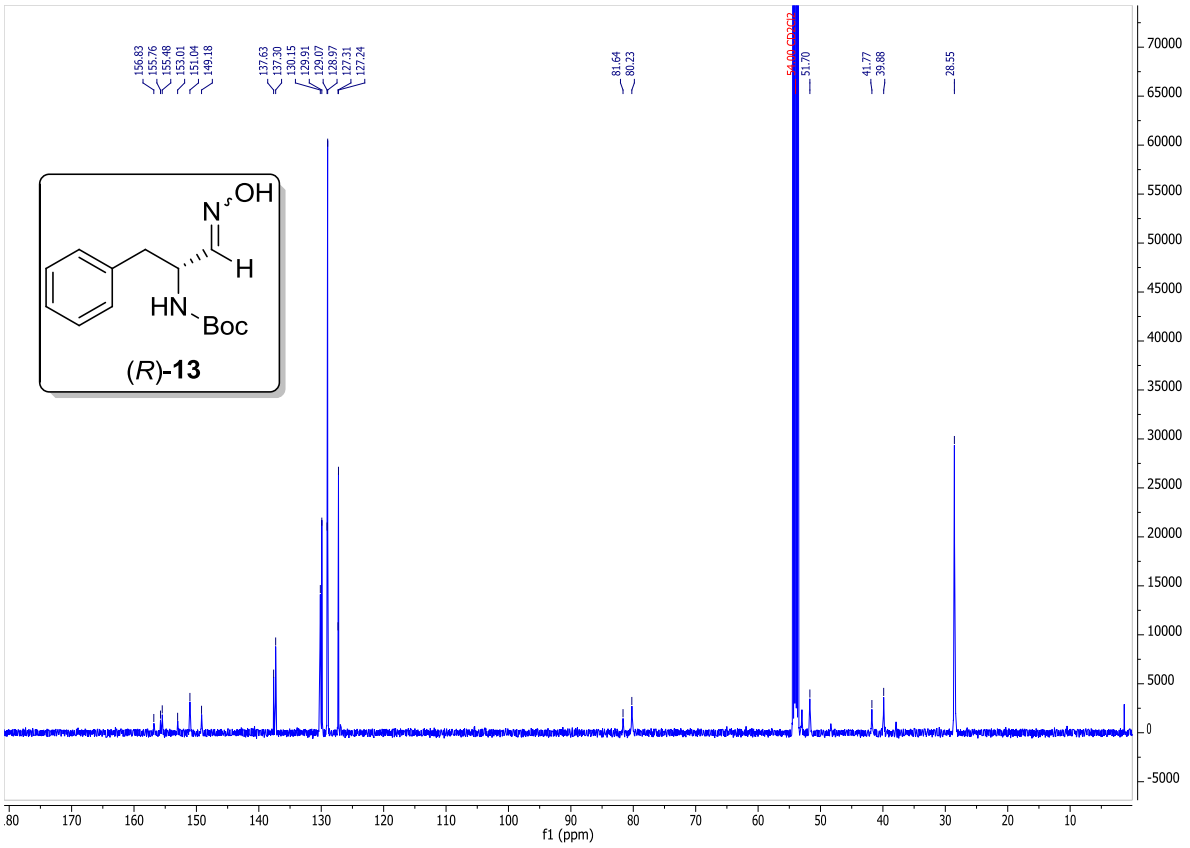
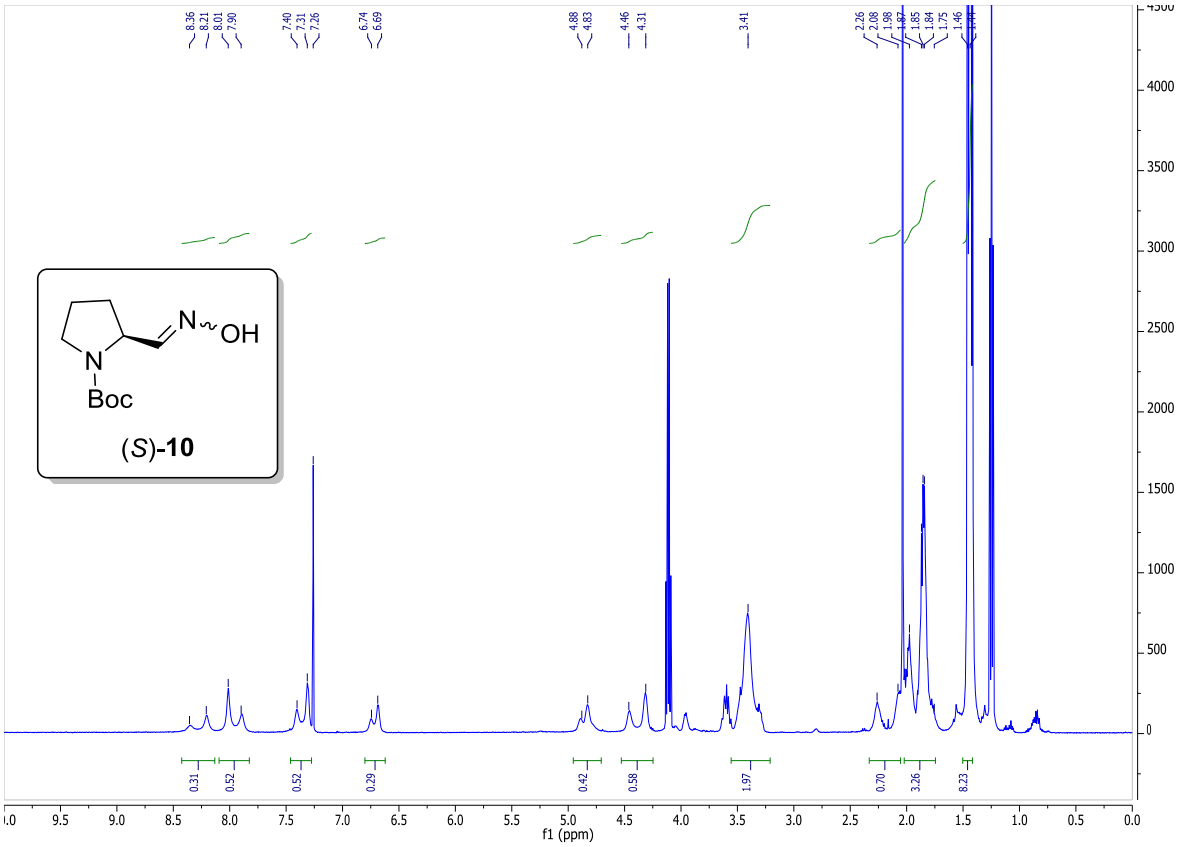
8.21
7.88
7.42
7.31
7.23
7.17
6.68
5.86
5.32 CD2Cl2
5.00
4.94
4.85
4.53
3.04
2.95
1.38
OH
N
H
HN
Boc
(R)-13
0.33
0.26
0.46
1.00
2.64
2.03
2.01
0.29
0.34
1.11
0.98
0.37
2.37
12.18
f1 (ppm)


156.83
155.76
155.48
153.01
151.04
149.18
137.63
137.30
130.15
129.91
129.07
128.97
127.31
127.24
81.64
80.23
54.00 CD2Cl2
51.70
41.77
39.88
28.55
OH
N
H
HN
Boc
(R)-13
f1 (ppm)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8.21
8.01
7.90
7.40
7.31
7.26
6.74
6.69
4.88
4.83
4.46
4.31
3.41
2.26
2.08
1.98
1.87
1.85
1.84
1.75
1.46
N
OH
N
Boc
(S)-10
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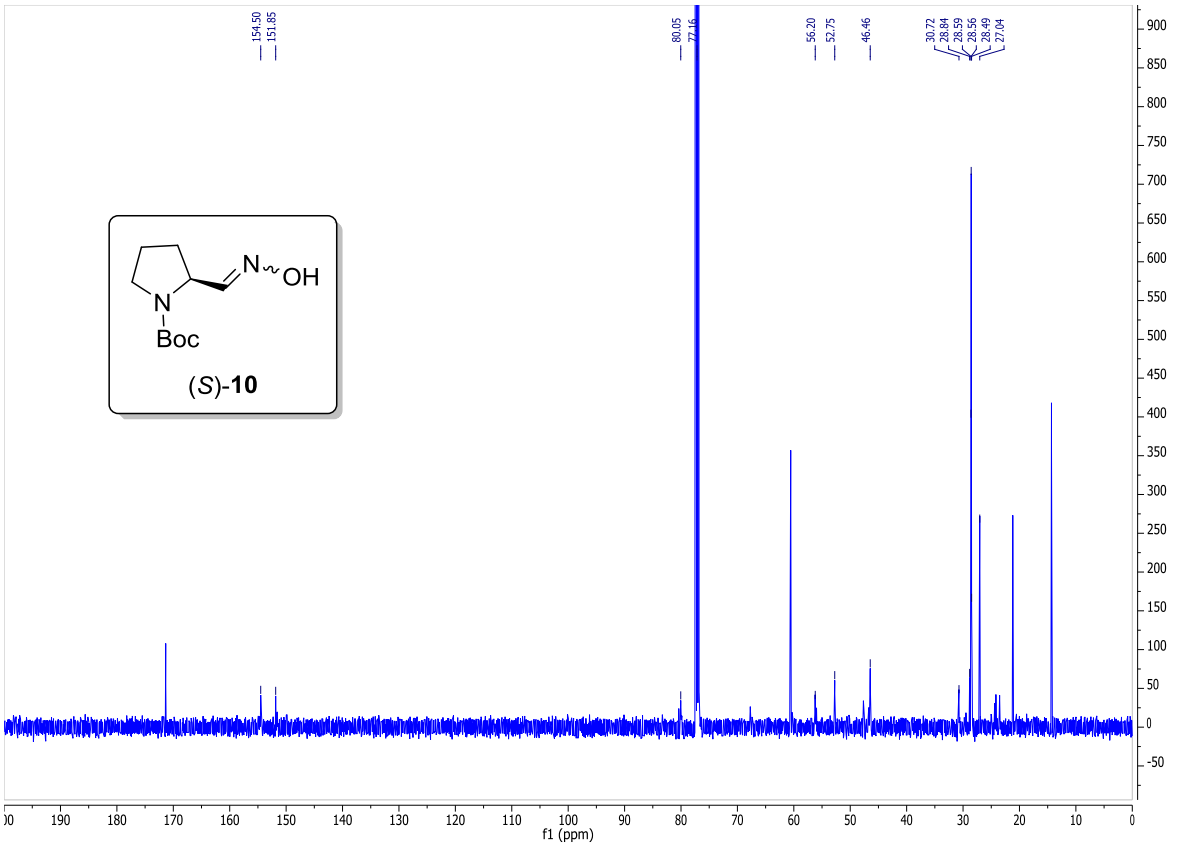
0.52
0.52
0.29
0.42
0.58
1.97
0.70
3.26
8.23
f1 (ppm)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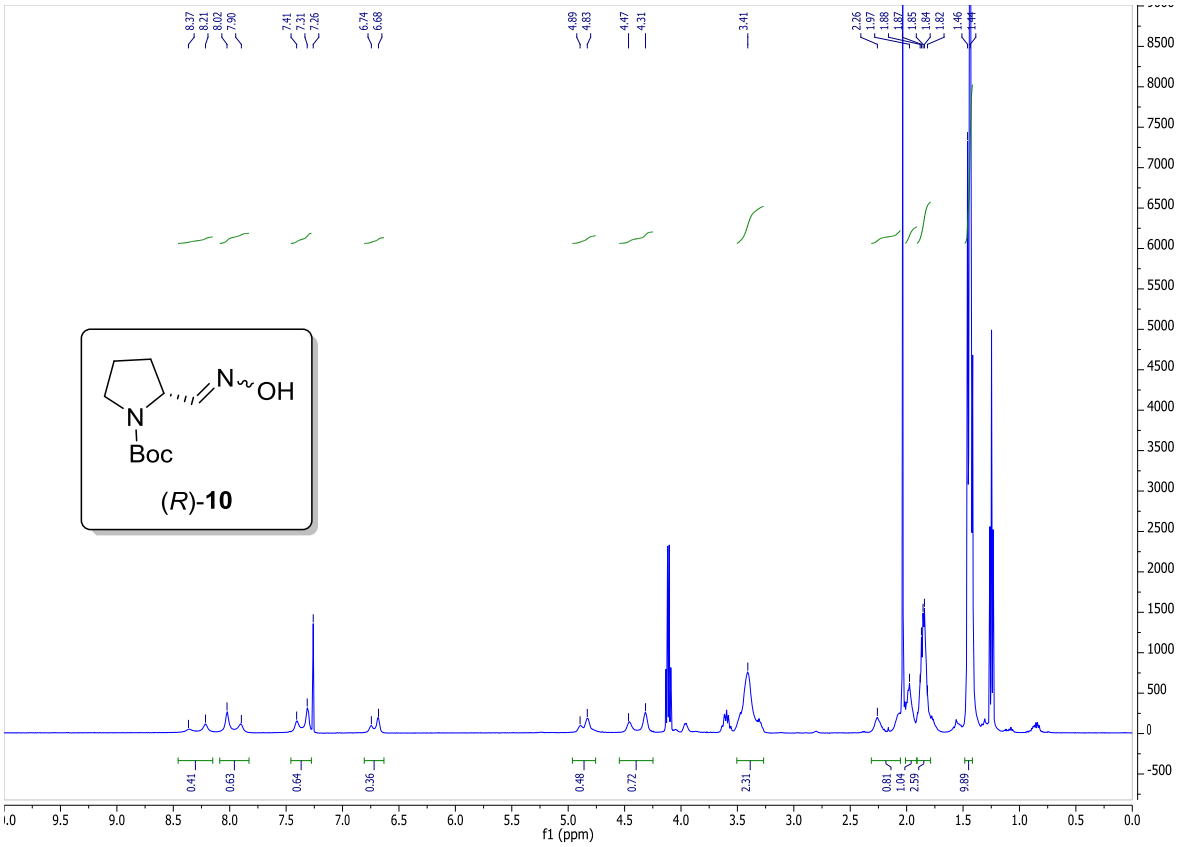
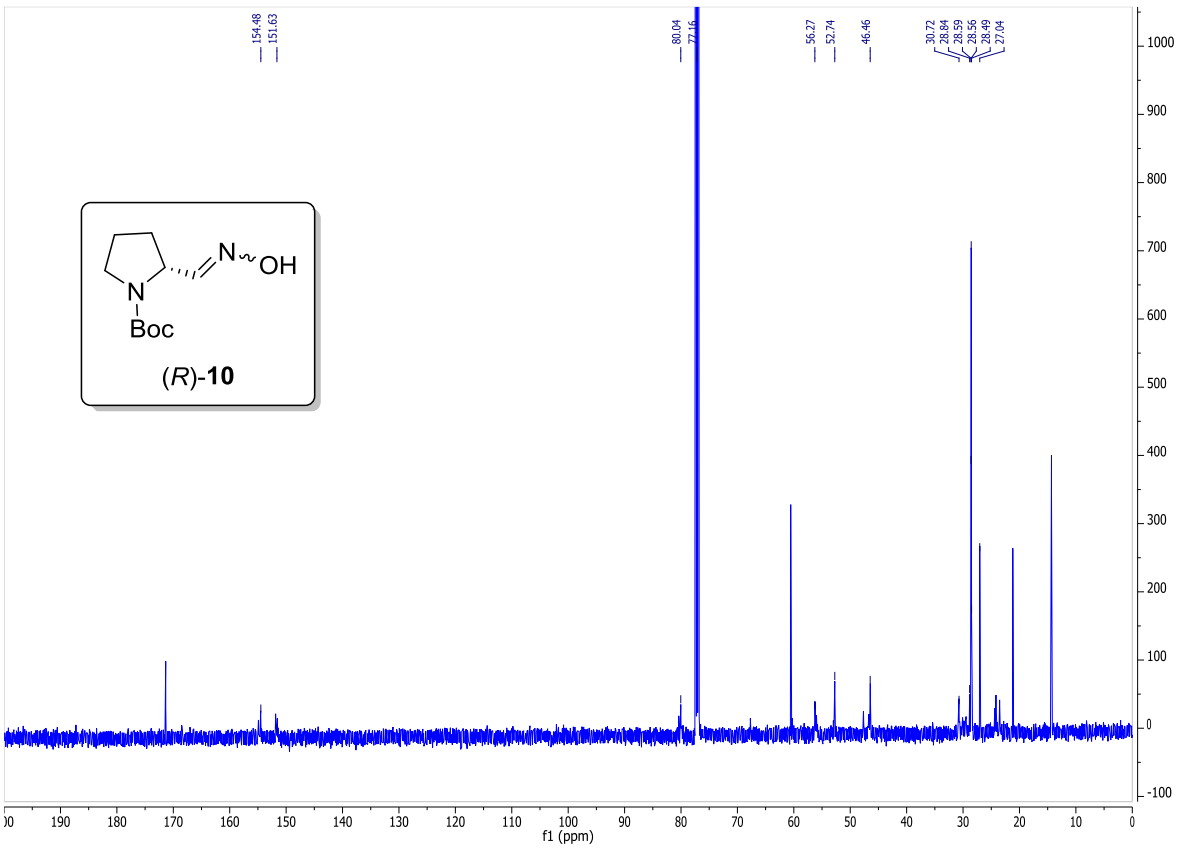
151.85
80.05
77.16
56.20
52.75
46.46
30.72
28.84
28.59
28.56
28.49
27.04
N
OH
N
Boc
(S)-10
f1 (ppm)


8.37
8.21
8.02
7.90
7.41
7.31
7.26
6.74
6.68
4.89
4.83
4.47
4.31
3.41
2.26
1.97
1.88
1.87
1.85
1.84
1.82
1.46
1.44
N
OH
N
Boc
(R)-10
0.41
0.63
0.64
0.36
0.48
0.72
2.31
0.81
1.04
2.59
9.89
f1 (ppm)


154.48
151.63
80.04
77.16
56.27
52.74
46.46
30.72
28.84
28.59
28.56
28.49
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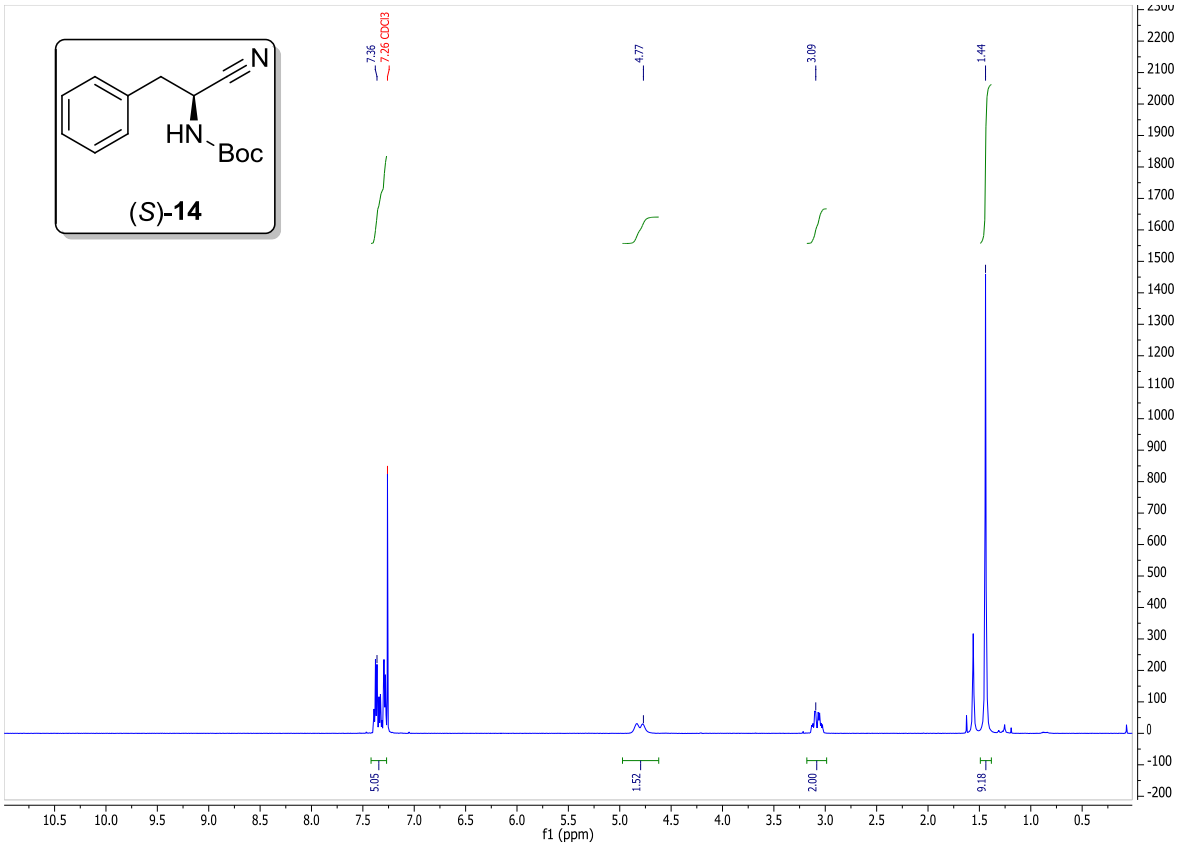
N
OH
N
Boc
(R)-10
f1 (ppm)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HN
Boc
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7.26 CDCl3
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3.09
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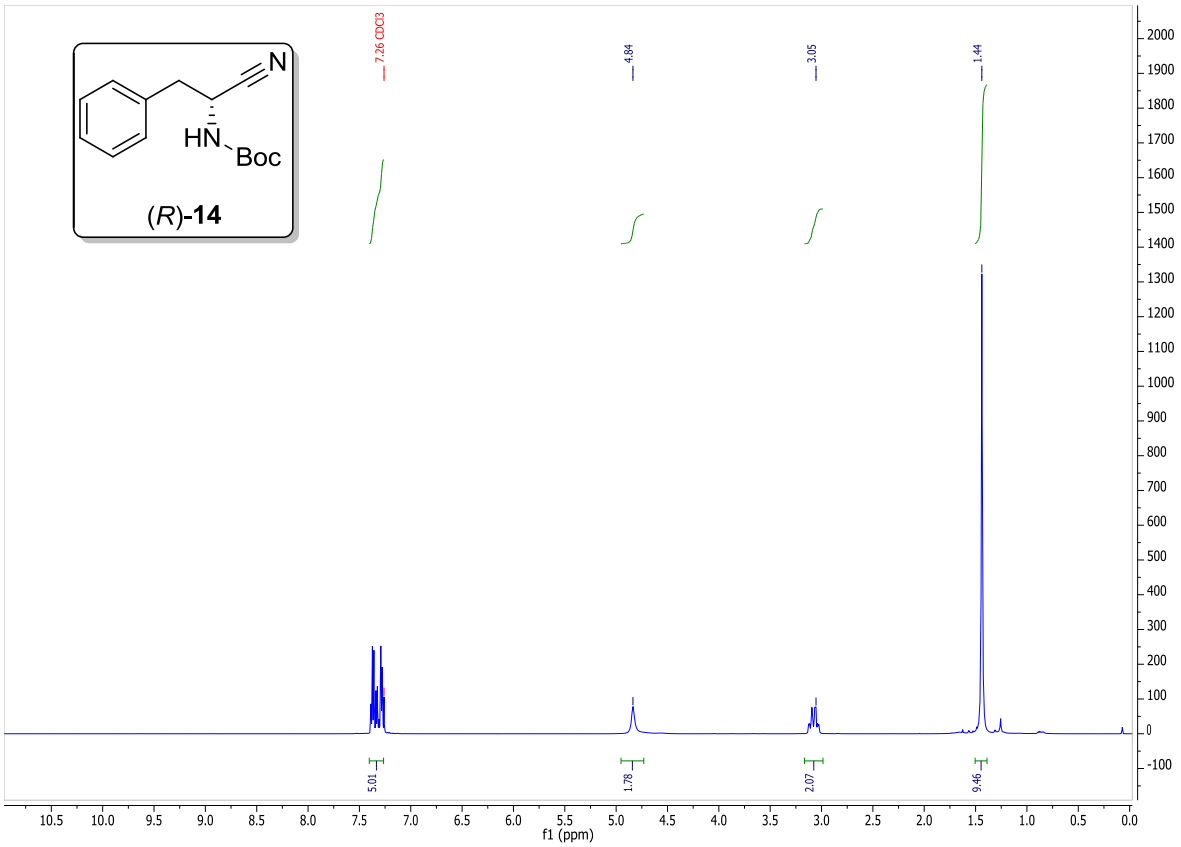
5.05
1.52
2.00
9.18
f1 (ppm)


N
HN
Boc
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7.26 CDCl3
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3.05
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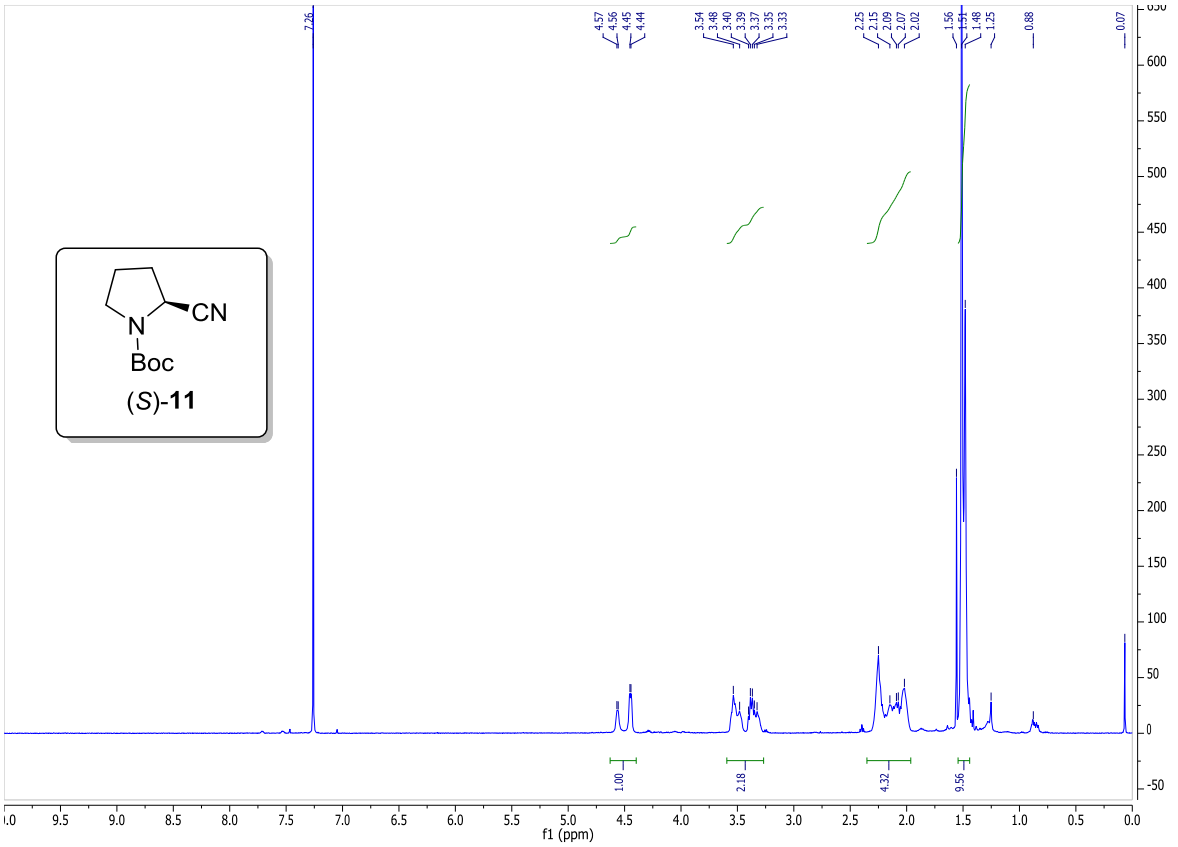
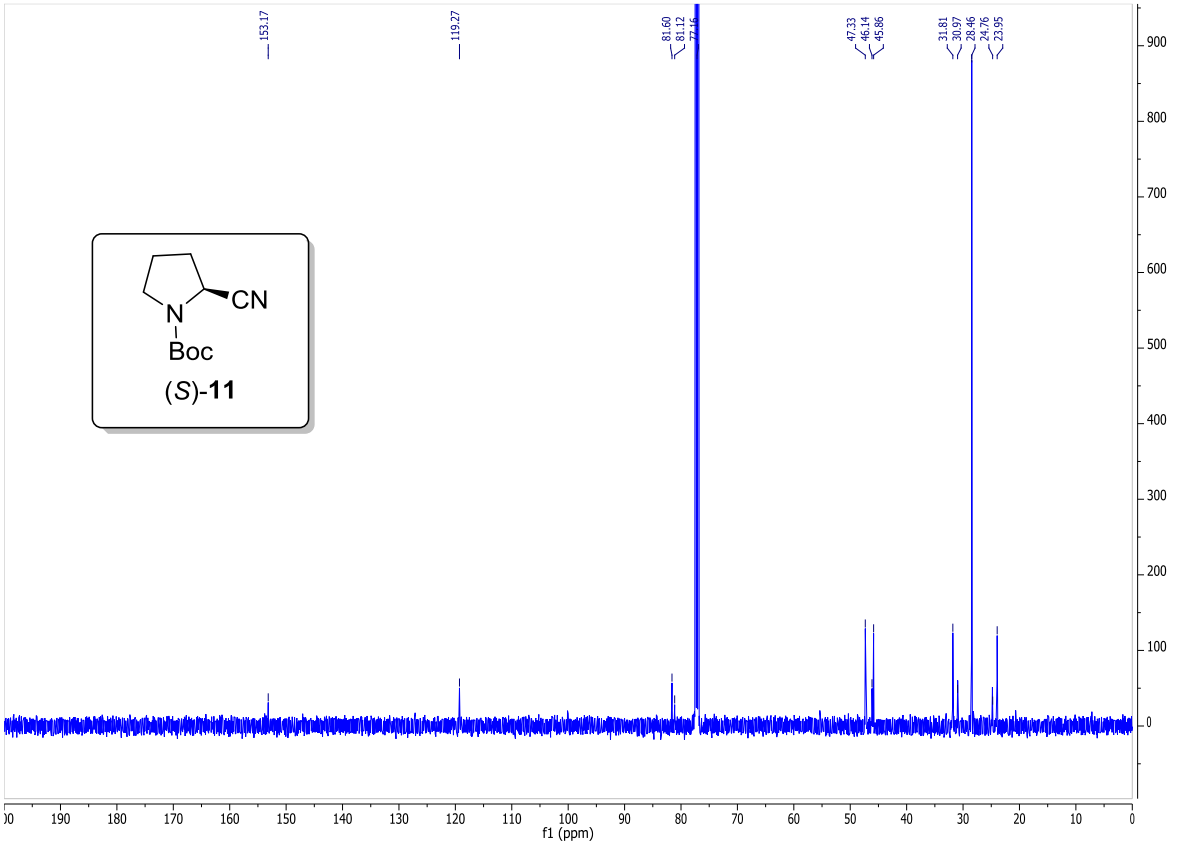
1.78
2.07
9.46
f1 (ppm)


CN
N
Boc
(S)-11
f1 (ppm)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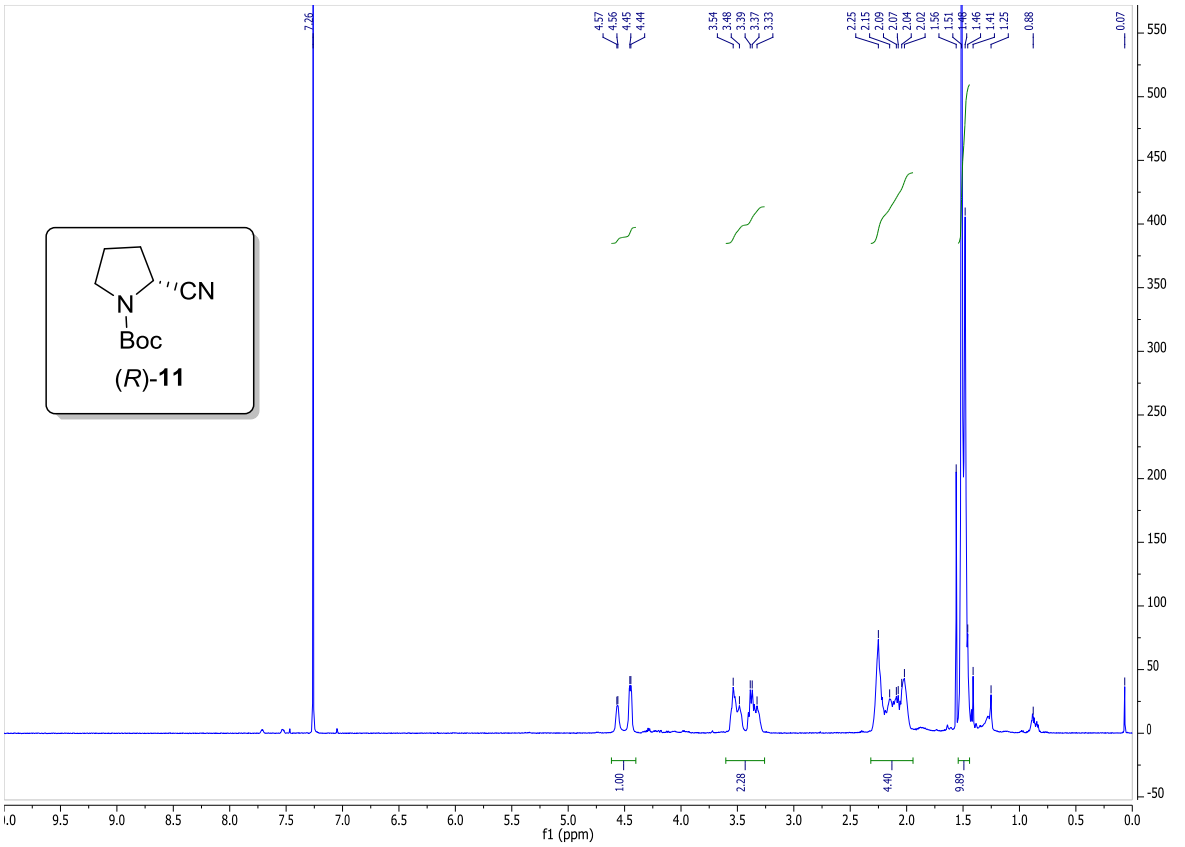
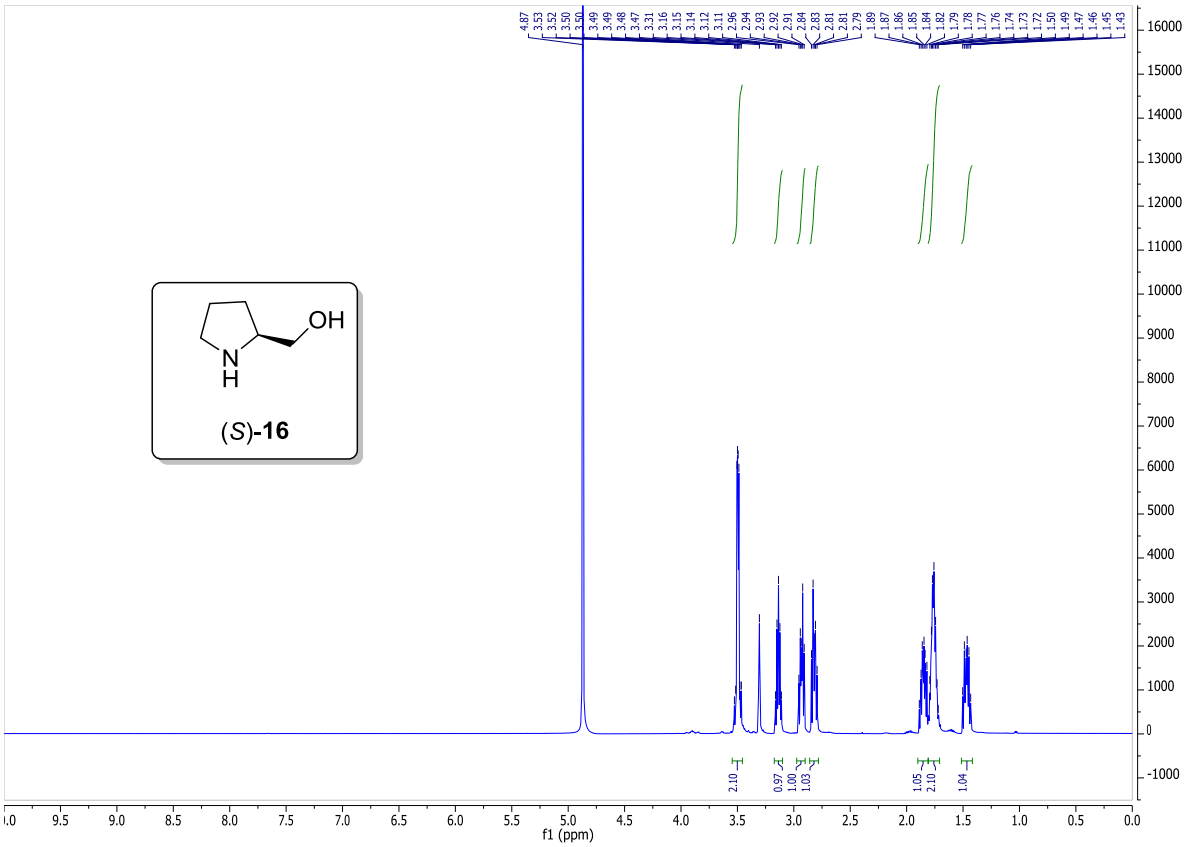
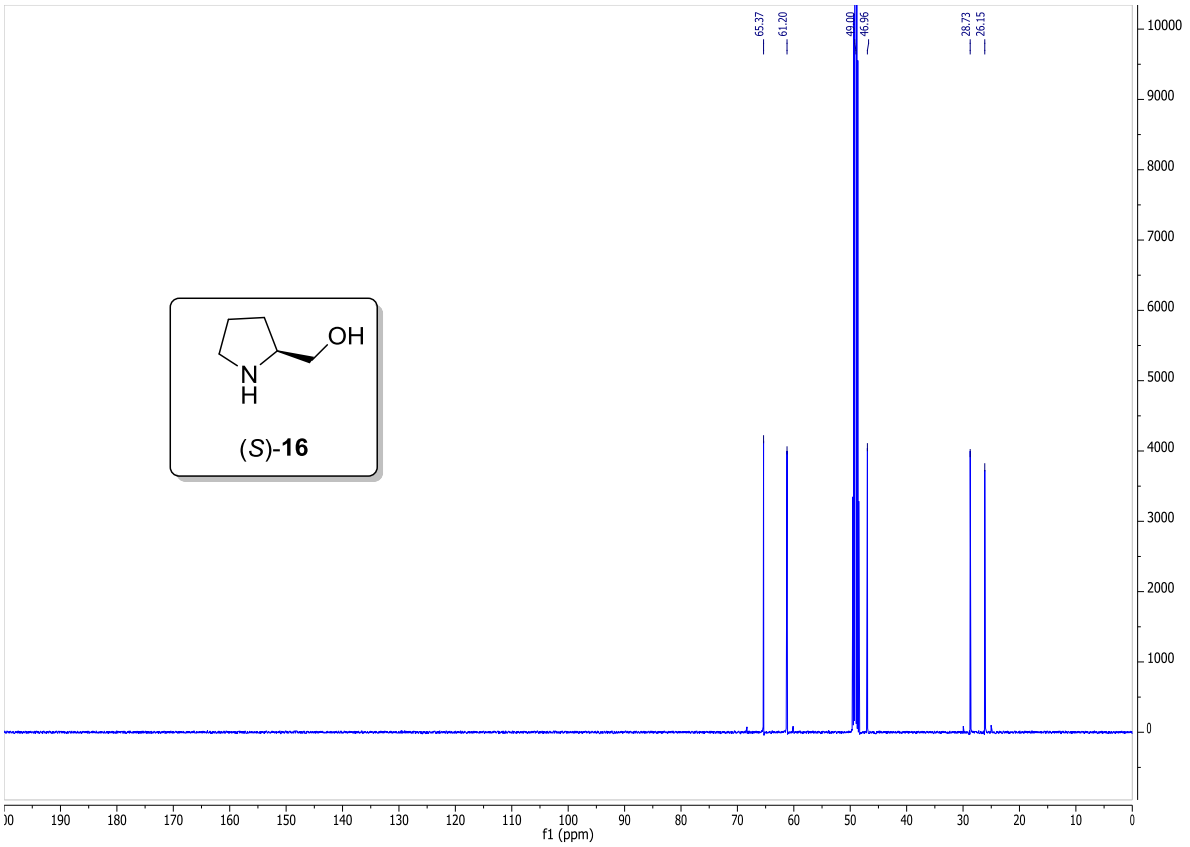
N
Boc
(S)-11
f1 (ppm)


CN
N
Boc
(R)-11
f1 (ppm)


OH
N
H
(S)-16
f1 (ppm)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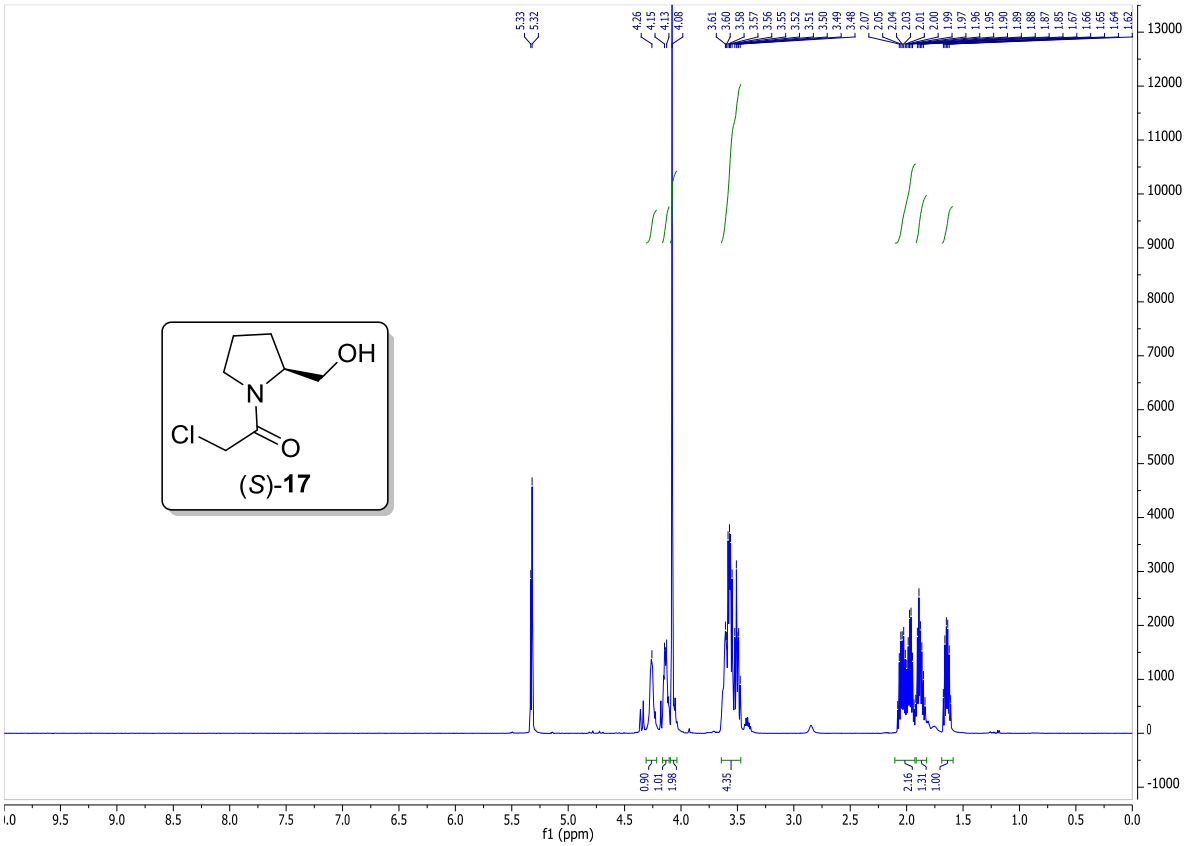
26.15
OH
N
H
(S)-16
f1 (ppm)


5.33
5.32
4.26
4.15
4.13
4.08
3.61
3.60
3.58
3.57
3.56
3.55
3.52
3.51
3.50
3.49
3.48
2.07
2.05
2.04
2.03
2.01
2.00
1.99
1.97
1.96
1.95
1.90
1.89
1.88
1.87
1.85
1.67
1.66
1.65
1.64
1.62
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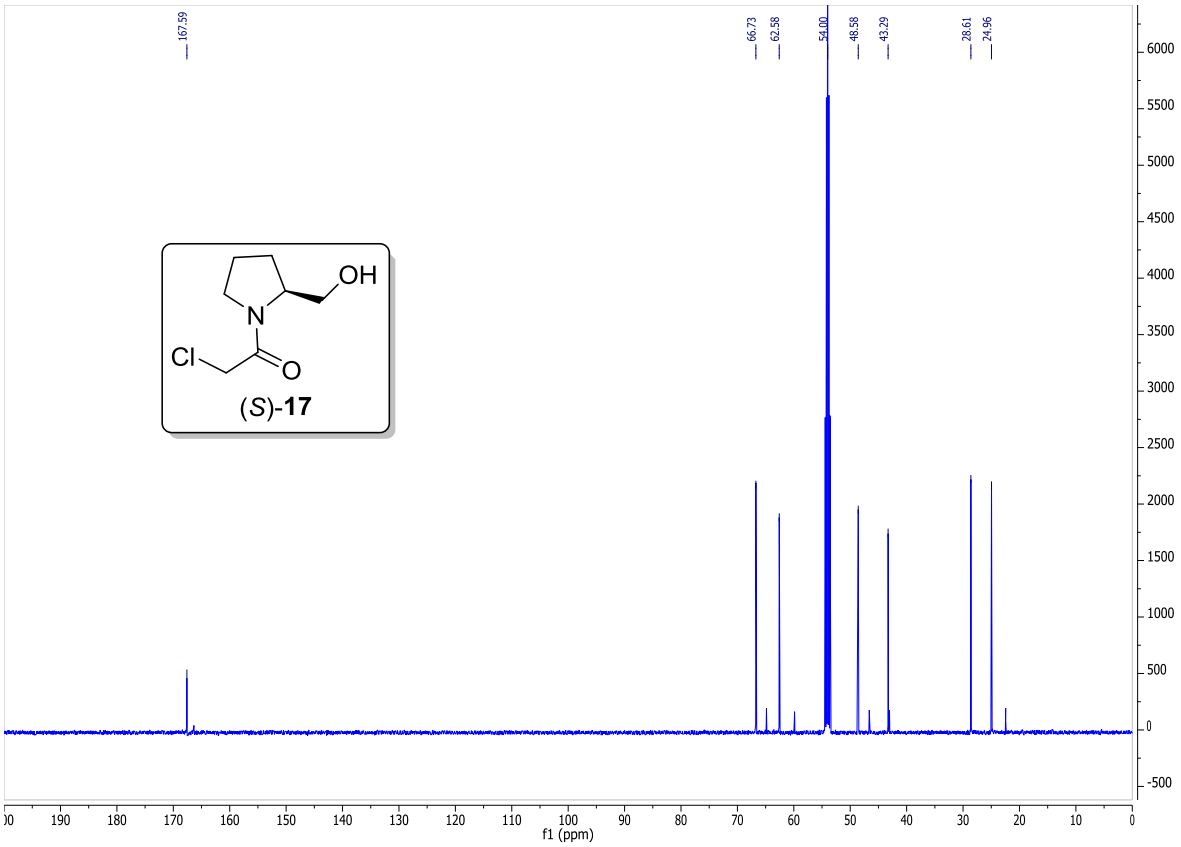
Cl
O
(S)-17
f1 (ppm)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48.58
43.29
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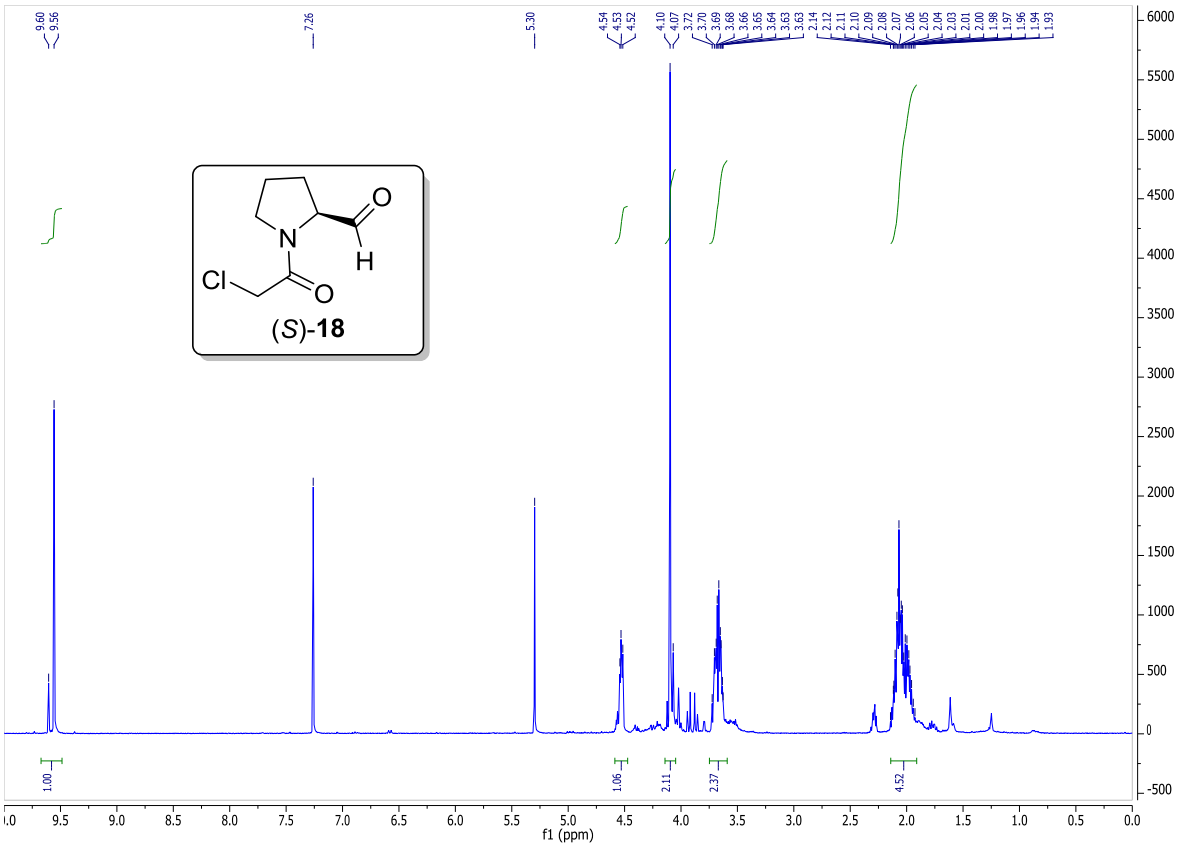
24.96
OH
N
Cl
O
(S)-17
f1 (ppm)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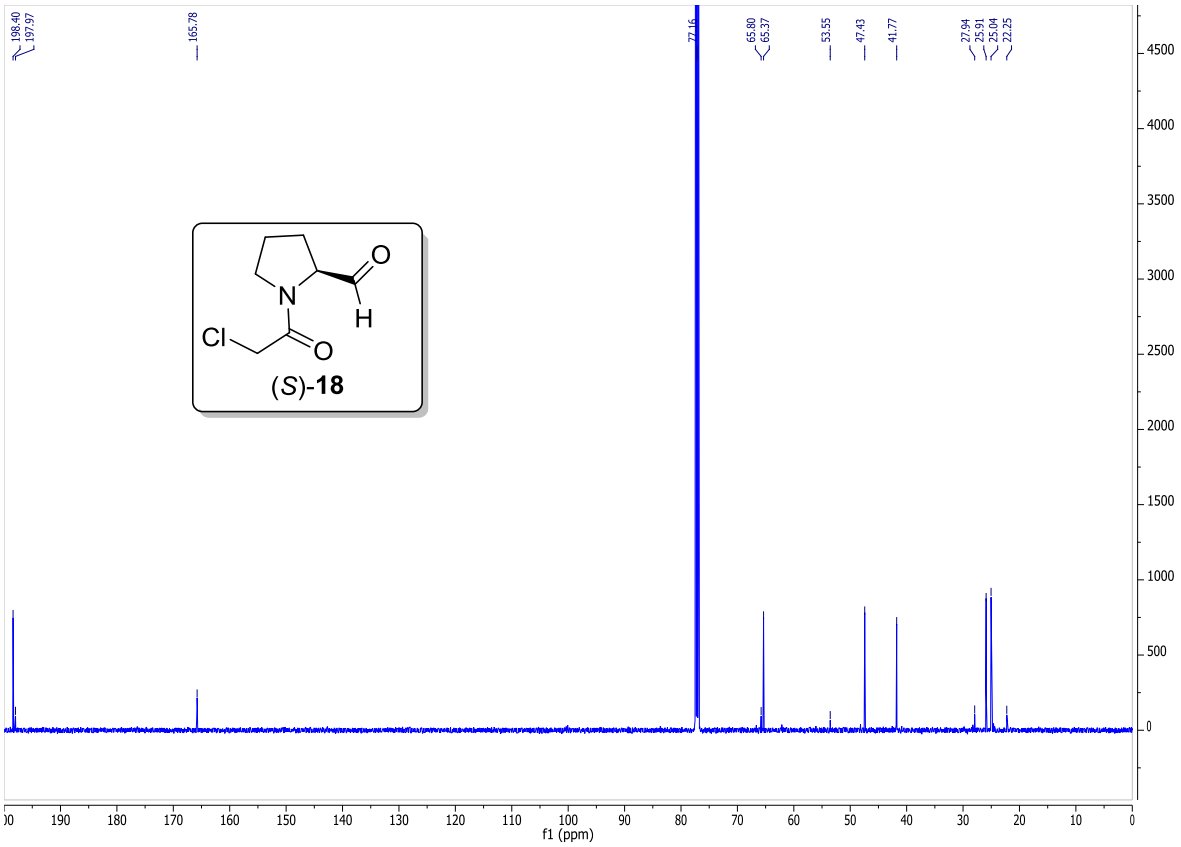
4.53
4.52
4.10
4.07
3.72
3.70
3.69
3.68
3.66
3.65
3.64
3.63
3.63
2.14
2.12
2.11
2.10
2.09
2.08
2.07
2.06
2.05
2.04
2.03
2.01
2.00
1.98
1.97
1.96
1.94
1.93
O
N
H
Cl
O
(S)-18
1.00
1.06
2.11
2.37
4.52
f1 (ppm)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53.55
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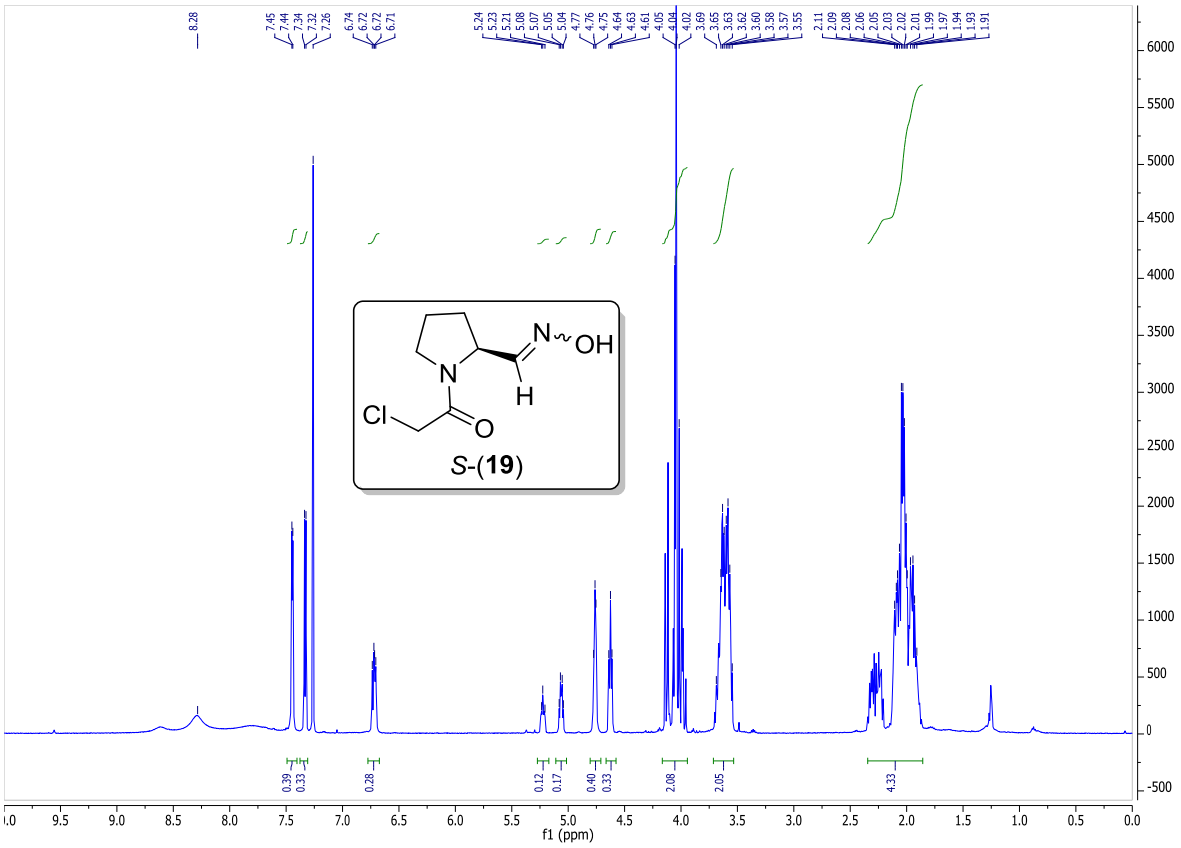
27.94
25.91
25.04
22.25
(S)-18
f1 (ppm)


8.28
7.45
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7.32
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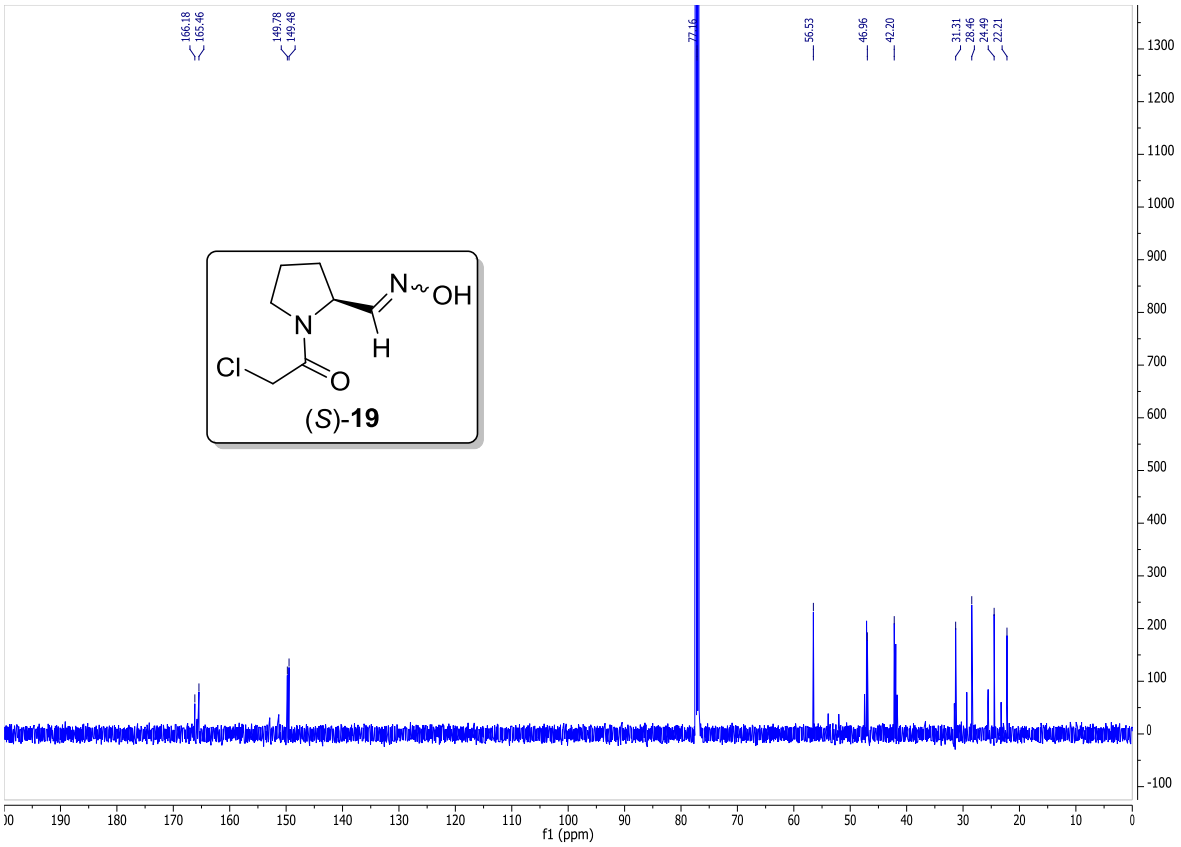
6.74
6.72
6.72
6.71
5.24
5.23
5.21
5.08
5.07
5.05
5.04
4.77
4.76
4.75
4.64
4.63
4.61
4.05
4.04
4.02
3.69
3.65
3.63
3.62
3.60
3.58
3.57
3.55
2.11
2.09
2.08
2.06
2.05
2.03
2.02
2.01
1.99
1.97
1.94
1.93
1.91
0.39
0.33
0.28
0.12
0.17
0.40
0.33
2.08
2.05
4.33
S-(19)
f1 (ppm)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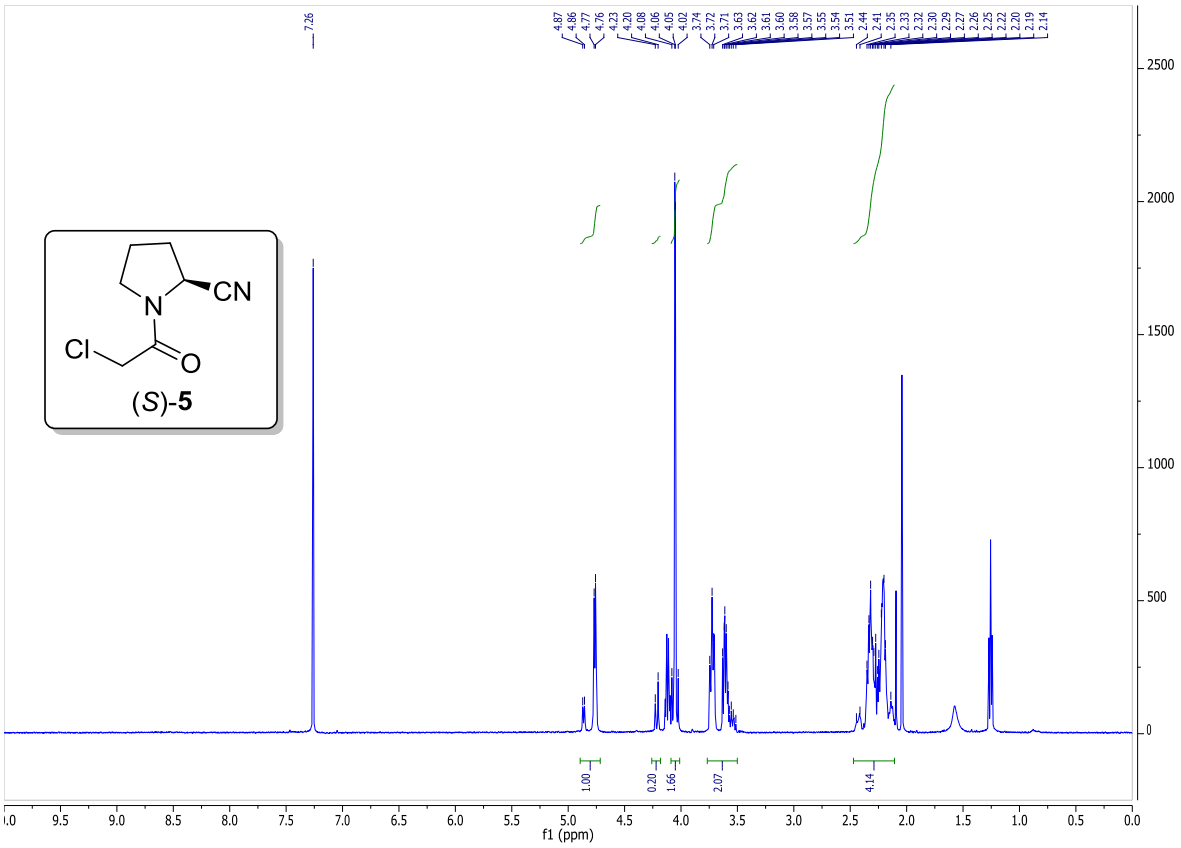
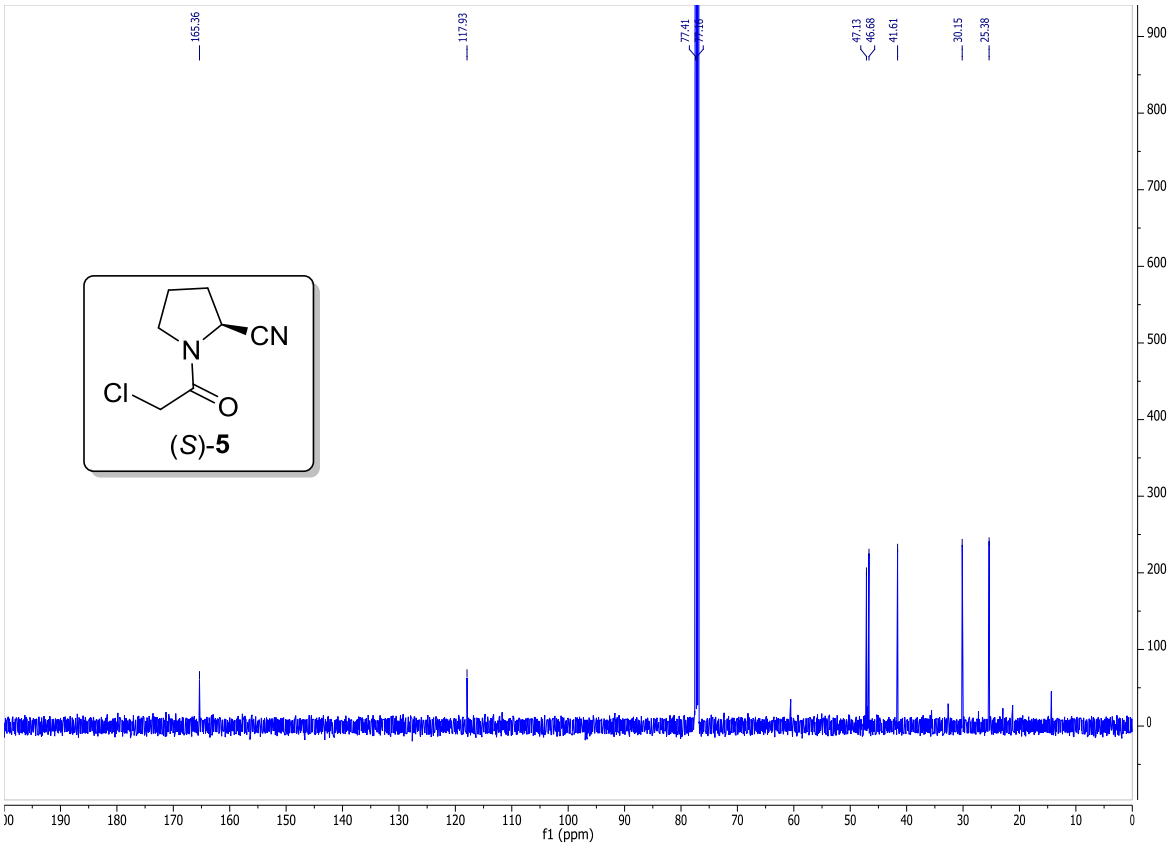
149.48
77.16
56.53
46.96
42.20
31.31
28.46
24.49
22.21
N
OH
H
N
Cl
O
(S)-19
f1 (ppm)


7.26
4.87
4.86
4.77
4.76
4.23
4.20
4.08
4.06
4.05
4.02
3.74
3.72
3.71
3.63
3.62
3.61
3.60
3.58
3.57
3.55
3.54
3.51
2.44
2.41
2.35
2.33
2.32
2.30
2.29
2.27
2.26
2.25
2.22
2.20
2.19
2.14
1.00
0.20
1.66
2.07
4.14
CN
N
Cl
O
(S)-5
f1 (ppm)

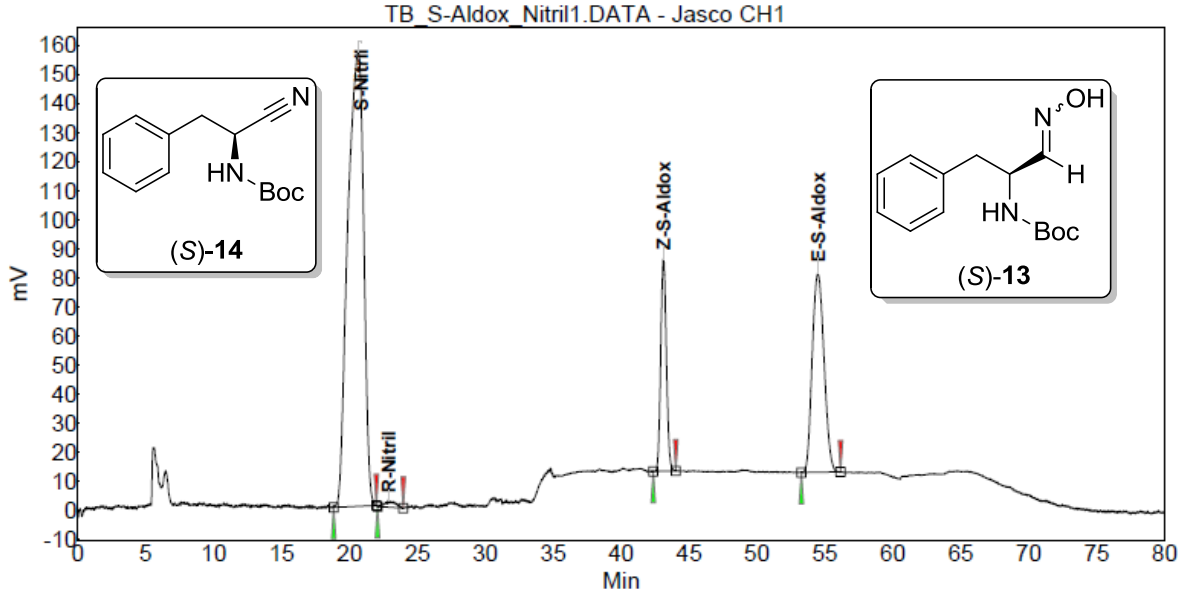

165.36
117.93
77.41
47.13
46.68
41.61
30.15
25.38
CN
N
Cl
O
(S)-5
f1 (ppm)

# 4 HPLC- AND GC-CHROMATOGRAMS

## Chromatogram : TB_S-Aldox_Nitril1

System : Jasco HPLC-SFC
Method : TB_Pos5_95-5_0,75mL mit Spülrampe
User : Tobias Betke

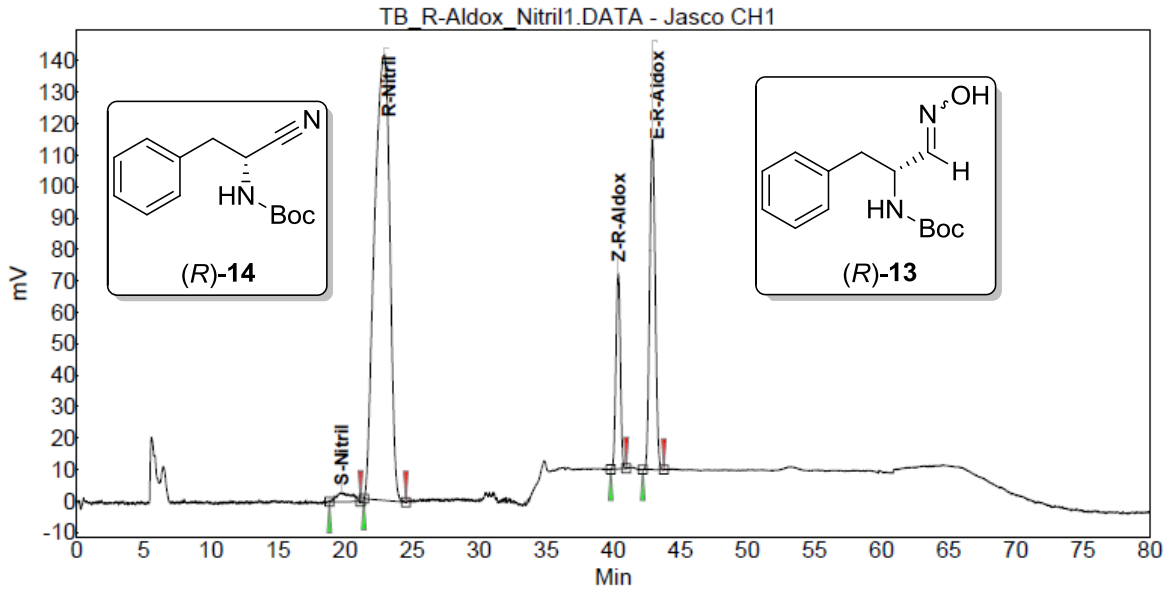
Acquired : 25.08.2015 19:25:28
Processed : 26.08.2015 09:21:34
Printed : 26.08.2015 09:21:53




## Chromatogram : TB_R-Aldox_Nitril1

System : Jasco HPLC-SFC
Method : TB_Pos5_95-5_0,75mL mit Spülrampe
User : Tobias Betke

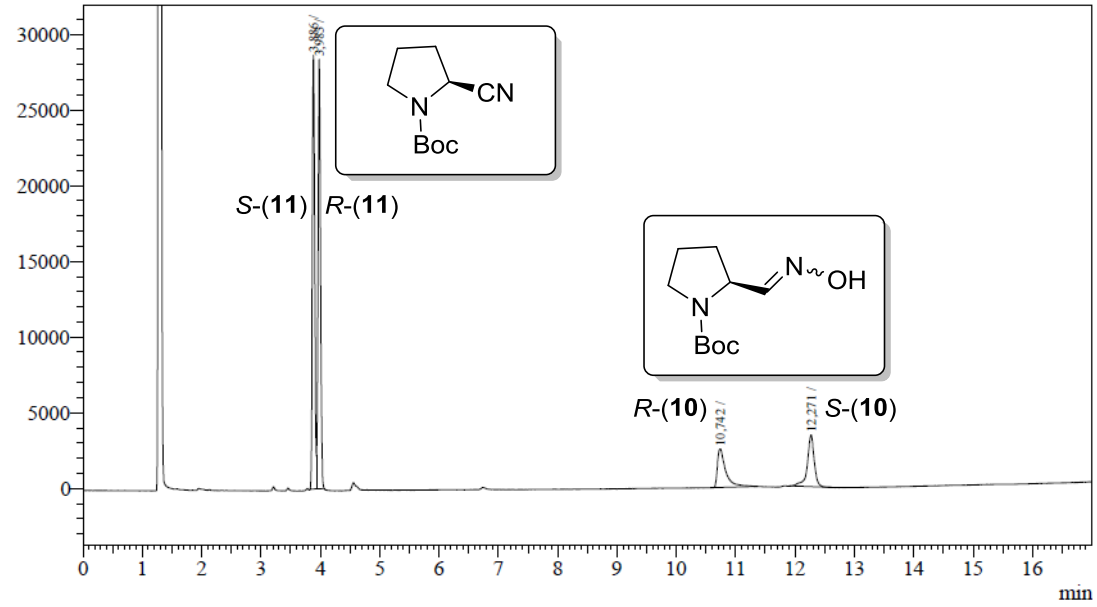
Acquired : 25.08.2015 18:02:57
Processed : 26.08.2015 09:09:53
Printed : 26.08.2015 09:10:32



| | |
|---|---|
| Analysis Date & Time | : 04.08.2015 13:24:28 |
| User Name | : Admin |
| Vial# | : 5 |
| Sample Name | : IW-B-13_3mg/mL-3 |
| Sample ID | : |
| Sample Type | : Unknown |
| Injection Volume | : 8,00 |
| ISTD Amount | : |

| | |
|---|---|
| Data Name | : C:\Programme\GCSolutions\Data\Project1\Daten\2015\OC1\Philipp Rommelmann\IW-B-13_3mg$mL-3_04.( |
| Method Name | : C:\Programme\GCSolutions\Data\Project1\Methoden\Philipp Rommelmann\Prolin-Aldoxim-Nitril.gcm |

Intensity




| Peak# | Ret.Time | Area | Height | Conc. | Unit | Mark | ID# | Cmpd Name |
|---|---|---|---|---|---|---|---|---|
| 1 | 3,886 | 79120 | 28557 | 37,017 | | | | |
| 2 | 3,983 | 82171 | 28270 | 38,445 | | V | | |
| 3 | 10,742 | 24734 | 2554 | 11,572 | | | | |
| 4 | 12,271 | 27713 | 3420 | 12,966 | | | | |
| **Total** | | 213738 | 62801 | | | | | |

# 5 REFERENCES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