Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

A Tripeptide-like Prolinamide-Thiourea as an Aldol Reaction Catalyst

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Supporting Information

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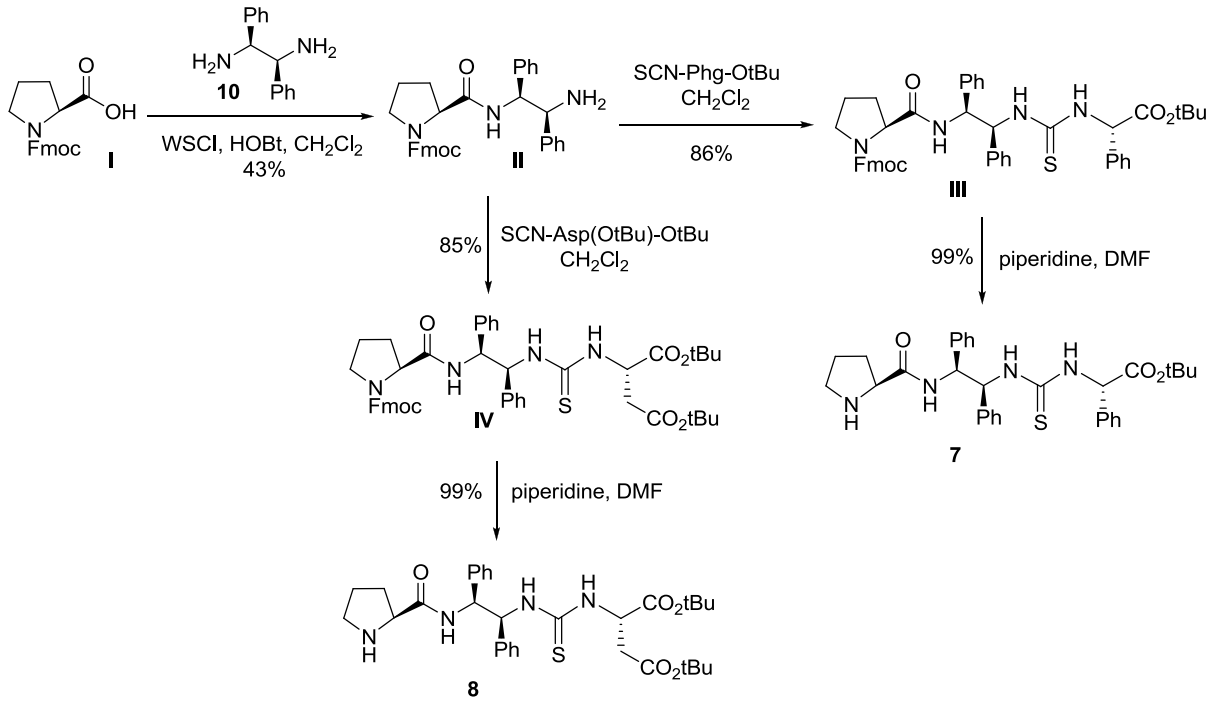
General Remarks

Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on Merck Kieselgel 60 F_{254} 230-400 mesh. Thin-layer chromatography (TLC) was performed on aluminum backed silica plates (0.2 mm, 60 F_{254}). Visualization of the developed chromatogram was performed by fluorescence quenching using phosphomolybdic acid, anisaldehyde or ninhydrin stains. Melting points were determined on a Buchi 530 hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury (200 MHz or 50 MHz) and are internally referenced to residual protio solvent signals ($CDCl_3$, CD_3OD). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, bs = broad signal, bs m = broad signal multiplet), coupling constant and assignment. Wherever rotamers exist, are presented in brankets. Data for ^{13}C NMR are reported in terms of chemical shift (δ ppm). Mass spectra were recorded on a Finnigan Surveyor MSQ Plus, with only molecular ions and major peaks being reported with intensities quoted as percentages of the base peak. IR spectra were recorded on a Nicolet 6700 FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High Performance Liquid Chromatography (HPLC) was used to determine enantiomeric excesses and was performed on a Agilent 1100 Series apparatus using Chiralpak® AD-H, OD-H, AS-H and AD-RH columns. The configuration of the products has been assigned by comparison to literature data. Optical rotations were measured on a Perkin Elmer 343 polarimeter. Catalysts **6** and **6** (*R*,*R*) have been synthesized following our previous protocols.[1]

General Procedure for the Synthesis of the Catalysts 7 and 8



(*S*)-(9*H*-Fluoren-9-yl)methyl 2-[(1*S*,2*S*)-2-amino-1,2-diphenylethylcarbamoyl]pyrrolidine-1-carboxylate (II)

To a stirring solution of Fmoc-proline (0.64 g, 1.88 mmol) in dry CH_2Cl_2 (15 mL) at 0 ^oC, (1*S*,2*S*)-diphenylethylenediamine (0.40 g, 1.88 mmol), 1-hydroxybenzotriazole (HOBt) (0.30 g, 1.88 mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (WSCI) (0.40 g, 2.06 mmol) and Et_3N (0.30 mL, 2.06 mmol), were added consecutively. The reaction mixture was left stirring at 0 ^oC for 1 h, and then warmed to room temperature and left stirring for 18 h. The solvents were evaporated under *vacuo* and the crude product was purified using flash column chromatography eluting with Et_2O:MeOH (90:10). White solid; 0.43 g, 43% yield; mp 71-73 ^oC; $[\alpha]_D$= -57.6 (*c* = 1.0, $CHCl_3$); IR (film) 3303, 3030, 2951, 1700, 1508, 1449, 1352, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.94-7.73 (3H, m, ArH, NH), 7.71-7.50 (2H, m, ArH), 7.52-7.07 (14H, m, ArH), 5.17-5.01 (1H, m, NCH), 4.65-4.00 (5H, m, CHC*H*$_2$O, C*H*CH$_2$O, 2 x NCH), 3.76-3.35 (2H, m, NCH_2), 2.33-1.58 (6H, m, 4 x C*H*H και NH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.1 (171.7) (NHCO), 155.9 (155.1) (OCONH), 143.9 (Ar), 143.8 (Ar), 143.2 (Ar), 141.8

(Ar), 141.2 (Ar), 140.2 (Ar), 128.5 (Ar), 128.3 (Ar), 127.7 (Ar), 127.4 (Ar), 127.2 (Ar), 127.1 (Ar), 126.7 (Ar), 126.4 (Ar), 125.1 (Ar), 119.9 (Ar), 67.8 (O*C*H_2CH), 60.4 (60.9) (NCH), 59.7 (59.3) (NCH), 58.7 (58.5) (NCH), 47.1 (NCH_2), 46.9 (OCH_2*C*H), 28.3 (CH_2), 24.5 (CH_2); MS (ESI) 532 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{34}H_{34}O_3N_3$) requires *m/z* 532.2595, found *m/z* 532.2589.

General Procedure for the coupling of amine II with isothiocyanates

To a stirring solution of amine **II** (0.20 g, 0.38 mmol) in dry CH_2Cl_2 (10 mL), a solution of the corresponding isothiocyanate[2] (0.38 mmol) in dry CH_2Cl_2 (2 mL) was added. The reaction mixture was left stirring at room temperature for 18 h. The solvent was evaporated under *vacuo* and the crude product was purified using flash column chromatography eluting with various mixtures of petroleum ether (40-60 ^oC):EtOAc (40:60).

(*S*)-(9*H*-Fluoren-9-yl)methyl 2-[(1*S*,2*S*)-2-{3-[(*S*)-2-*tert*-butoxy-2-oxo-1-phenylethyl]thioureido}-1,2-diphenylethylcarbamoyl]pyrrolidine-1-carboxylate (III)

White solid; 0.26 g, 86% yield; mp 95-97 ^oC; $[\alpha]_D$= -5.5 (*c* = 1.0, $CHCl_3$); IR (film) 3325, 2954, 2919, 1734, 1707, 1686, 1532, 1452, 1354, 1150, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.26 (1H, br s, NH), 7.86-7.50 (3H, m, ArH), 7.49-6.65 (22H, m, ArH, 2 x NH), 6.16-5.52 (2H, br m, 2 x NCH), 5.25-5.03 (1H, m, NCH), 4.64-3.72 (4H, m, OCH_2, OCH_2C*H*, NCH), 3.68-3.20 (2H, m, NCH_2), 2.14-1.47 (4H, m, 4 x C*H*H), 1.31 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.9 (C=S), 172.9 (CO), 172.8 (CO), 155.7 (OCONH), 144.4 (Ar), 144.0 (Ar), 143.6 (Ar), 141.1 (Ar), 138.6 (Ar), 138.3 (Ar), 137.6 (Ar), 136.4 (Ar), 136.3 (Ar), 128.7 (Ar), 128.6 (Ar), 128.2 (Ar), 128.1 (Ar), 127.4 (Ar), 127.3 (Ar), 127.0 (Ar), 125.4 (Ar), 125.0 (Ar), 119.7 (Ar), 82.3 [*C*$(CH_3)_3$], 67.6 (O*C*H_2CH), 67.3 (NCH), 63.1 (NCH), 62.8 (NCH), 60.6 (NCH), 47.0 (NCH_2), 46.7 (OCH_2*C*H), 29.5 (CH_2), 27.5 [C(*C*$H_3)_3$], 24.3 (CH_2); MS (ESI) 781 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{47}H_{49}O_5N_4S$) requires *m/z* 781.3418, found *m/z* 781.3413.

(*S*)-Di-*tert*-butyl 2-{3-[(1*S*,2*S*)-2-{(*S*)-[((9*H*-fluoren-9-yl)methoxy)carbonyl]pyrrolidine-2-carboxamido}-1,2-diphenylethyl}thioureido}succinate (IV)

White solid; 0.26 g, 85% yield; mp 117-119 ^{o}C; $[\alpha]_D$= +4.5 (*c* = 1.0, $CHCl_3$); IR (film) 3397, 2955, 2918, 1735, 1540, 1465, 1377, 1182 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.09-7.93 (1H, br m, NH), 7.76 (2H, d, *J* = 7.6 Hz, ArH), 7.65-7.29 (7H, m, ArH, NH), 7.26-6.87 (10H, m, ArH), 6.67 (1H, d, *J* = 6.8 Hz, NH), 5.92-5.67 (1H, m, NCH), 5.31-5.07 (2H, m, 2 x NCH), 4.57-3.83 (4H, m, OC*H*$_2$CH, NCH, OCH$_2$C*H*), 3.70-3.27 (2H, m, NCH$_2$), 2.87-2.72 (2H, m, CH$_2$CO), 2.08-1.76 (4H, m, 4 x C*H*H), 1.42 [9H, s, C(CH$_3$)$_3$], 1.35 [9H, s, C(CH$_3$)$_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.0 (C=S), 172.7 (CO), 170.7 (CO), 169.8 (CO), 156.1 (OCONH), 144.4 (Ar), 144.1 (Ar), 143.8 (Ar), 141.2 (Ar), 140.3 (Ar), 140.2 (Ar), 128.4 (Ar), 128.3 (Ar), 127.7 (Ar), 127.6 (Ar), 127.5 (Ar), 127.4 (Ar), 127.0 (Ar), 125.1 (Ar), 119.9 (Ar), 82.3 [*C*(CH$_3$)$_3$], 81.5 [*C*(CH$_3$)$_3$], 67.7 (O*C*H$_2$CH), 63.8 (NCH), 60.5 (NCH), 59.5 (NCH), 54.2 (NCH), 47.1 (NCH$_2$), 46.9 (OCH$_2$*C*H), 37.6 (*C*H$_2$CO), 29.9 (CH$_2$), 28.0 [C(*C*H$_3$)$_3$], 27.9 [C(*C*H$_3$)$_3$], 24.5 (CH$_2$); MS (ESI) 819 (M+H$^+$, 100%); HRMS exact mass calculated for [M+H]$^+$ ($C_{47}H_{55}O_7N_4S$) requires *m/z* 819.3786, found *m/z* 819.3782.

General Procedure for the deprotection of the Fmoc protecting group

To a stirring solution of Fmoc-protected derivative (0.19 mmol) in DMF (1 mL), a solution of piperidine 50% in DMF (2 mL) was added. The reaction mixture was left stirring at room temperature for 1 h. After completion of the reaction, the solvents were removed in *vacuo*. The resulting crude was purified using flash column chromatography eluting with Petroleum ether: EtOAc (40:60) initially, followed by CH_2Cl_2: CH_3OH (70:30).

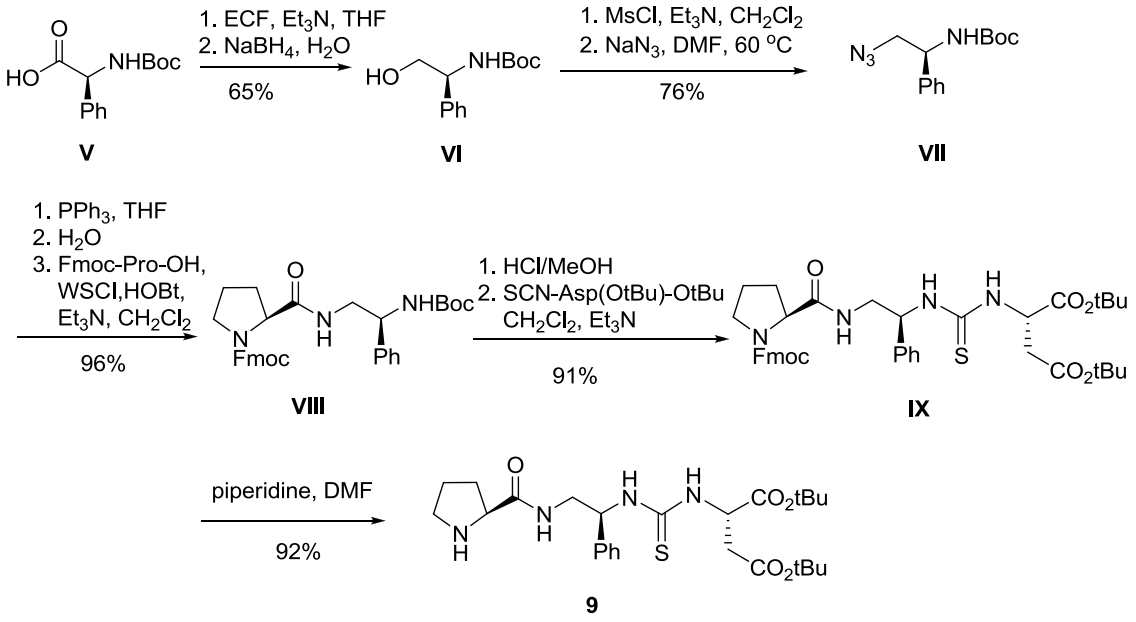
(*S*)-*tert*-Butyl 2-{3-[(1*S*,2*S*)-1,2-diphenyl-2-[(*S*)-pyrrolidine-2-carboxamido]ethyl]thioureido}-2-phenylacetate (7)

Light yellow solid; 0.11 g, 99% yield; mp 79-81 ^{o}C; $[\alpha]_D$= +24.7 (*c* = 1.0, CH_3OH); IR (film) 3289, 2918, 2849, 1734, 1650, 1525, 1465, 1366, 1151, 699 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 7.47-6.98 (15H, m, ArH), 6.03-5.86 (2H, m, 2 x NCH), 5.19 (1H, d, *J* = 10.6 Hz, NCH), 3.79-3.21 (1H, m, NCH), 2.99-2.60 (2H, m, NCH_2), 1.95-1.43 (4H, m, 4 x C*H*H), 1.30 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, CD_3OD) δ 184.2 (184.0) (C=S), 176.2 (176.6) (CO), 171.4 (171.7) (CO), 140.2 (Ar), 139.8 (Ar), 138.0 (Ar), 129.7 (Ar), 129.6 (Ar), 129.4 (Ar), 129.2 (Ar), 128.8 (Ar), 128.7 (Ar), 128.6 (Ar), 128.5 (Ar), 83.2 (82.8) [*C*$(CH_3)_3$], 63.6 (NCH), 62.7 (NCH), 61.4 (NCH), 60.1 (NCH), 46.6 (NCH_2), 31.6 (CH_2), 27.9 (28.1) [C(*C*$H_3)_3$], 26.5 (CH_2); MS (ESI) 559 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{32}H_{39}O_3N_4S$) requires *m/z* 559.2737, found *m/z* 559.2733.

(*S*)-Di-*tert*-butyl 2-{3-[(1*S*,2*S*)-1,2-diphenyl-2-[(*S*)-(pyrrolidine-2-carboxamido]-ethyl]thioureido}succinate (8)

White solid; 0.11 g, 99% yield; mp 89-91 ^{o}C; $[\alpha]_D$= +35.3 (*c* = 0.88, $CHCl_3$); IR (film) 3326, 2955, 2919, 1735, 1654, 1527, 1456, 1367, 1155, 699 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.56 (1H, d, *J* = 8.6 Hz, NH), 8.05-7.87 (1H, br m, NH), 7.46-7.01 (10H, m, ArH), 6.92-6.66 (1H, br m, NH), 5.98-5.65 (1H, m, NCH), 5.33-5.06 (2H, m, 2 x NCH), 3.97-3.68 (1H, m, NCH), 3.09-2.76 (4H, m, CH_2CO and NCH_2), 2.19-2.03 (1H, m, C*H*H), 1.87-1.55 (4H, m, 3 x C*H*H, NH), 1.43 [9H, s, $C(CH_3)_3$], 1.36 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.6 (C=S), 170.4 (CO), 170.1 (CO), 169.9 (CO), 138.7 (Ar), 138.6 (Ar), 128.5 (Ar), 128.3 (Ar), 128.0 (Ar), 127.7 (Ar), 127.5 (Ar), 127.4 (Ar), 82.2 [*C*$(CH_3)_3$], 81.4 [*C*$(CH_3)_3$], 64.2 (NCH), 60.3 (NCH), 58.8 (NCH), 54.0 (NCH), 47.1 (NCH_2), 37.8 (*C*H_2CO), 30.5 (CH_2), 28.0 [C(*C*H_3)], 27.9 [C(*C*H_3)], 25.8 (CH_2); MS (ESI) 597 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{32}H_{45}O_5N_4S$) requires *m/z* 597.3105, found *m/z* 597.3100.

General Procedure for the Synthesis of the Catalyst 9



Compounds **VI** and **VII** were synthesized following literature procedures.[3]

(*S*)-(9*H*-Fluoren-9-yl)methyl 2-[(*S*)-2-(*tert*-butoxycarbonylamino)-2-phenylethylcarbamoyl]pyrrolidine-1-carboxylate (VIII)

To a stirring solution of **VII** (1.00 g, 3.81 mmol) in THF (20 mL), PPh_3 (2.03 g, 7.75 mmol) was added and the mixture was refluxed for 8 h. Water (8 mL) was then added and the mixture was refluxed for another 16 h. The solvents were removed and the crude residue was purified with column chromatography using CH_2Cl_2:CH_3OH (85:15). Colorless oil;[3] 0.89 g, 99% yield; $[\alpha]_D$= +43.8 (*c* = 1.0, $CHCl_3$); IR (film) 3304, 2955, 2924, 1700, 1493, 1455, 1365, 1169, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.36-7.03 (5H, m, ArH), 5.68 (1H, br s, NH), 4.68-4.41 (1H, m, NCH), 3.00-2.86 (2H, m, NCH_2), 1.55-1.03 [11H, m, $C(CH_3)_3$, NH_2]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.6 (OCONH), 140.7 (Ar), 128.4 (Ar), 127.1 (Ar), 126.2 (Ar), 79.2 [$C(CH_3)_3$], 56.4 (NCH), 47.0 (NCH_2), 28.2 [$C(CH_3)$]; MS (ESI) 237 ($M+H^+$, 100%).

To a solution of amine (0.19 g, 0.82 mmol) in CH_2Cl_2 (5 mL), Fmoc-Pro-OH (0.28 g, 0.82 mmol) was added followed by HOBt (0.13 g, 0.82 mmol), WSCI (0.17 g, 0.91 mmol) and Et_3N (0.13 mL, 0.91 mmol). The reaction mixture was left stirring for 24 h,

followed by evaporation of the solvents and purification of the resulting residue with column chromatography using EtOAc. White solid; 0.44 g, 97% yield; mp 178-180 ^{o}C; $[\alpha]_D$= -17.7 (*c* = 1.0, $CHCl_3$); IR (film) 3342, 2955, 2922, 1697, 1524, 1451, 1363, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 6.0 Hz, ArH), 7.66-7.08 (11H, m, ArH), 7.02-6.91 (0.5H, br m, NH), 6.74-6.58 (0.5H, br m, NH), 5.84-5.68 (0.5H, br m, NH), 5.64-5.50 (0.5H, br m, NH), 4.89-4.66 (1H, m, NCH), 4.65-4.52 (4H, m, CHC*H*$_2$O, C*H*CH$_2$O, NCH), 3.75-3.32 (4H, m, 4 x NC*H*H), 2.34-1.70 (4H, m, 4 x C*H*H), 1.38 [9H, s, C(CH$_3$)$_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.7 (CO), 155.7 (OCONH), 155.6 (OCONH), 143.6 (Ar), 141.1 (Ar), 128.5 (Ar), 127.6 (Ar), 127.4 (Ar), 127.3 (Ar), 126.9 (Ar), 126.1 (Ar), 124.9 (Ar), 119.9 (Ar), 79.4 [*C*(CH$_3$)], 67.5 (O*C*H$_2$CH), 60.4 (NCH), 55.2 (NCH), 47.0 (NCH$_2$), 46.8 (OCH$_2$*C*H), 44.5 (NCH$_2$), 30.9 (CH$_2$), 28.1 [C(*C*H$_3$)], 24.3 (CH$_2$); MS (ESI) 573 (M+NH_4^+, 51%), 556 (M+H^+, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{33}H_{38}O_5N_3$) requires *m/z* 556.2806, found *m/z* 556.2800.

(*S*)-Di-*tert*-butyl 2-{3-[(*S*)-1-{[(9*H*-fluoren-9-yl)methoxy)carbonyl]pyrrolidine-2-carboxamido}-1-phenylethyl]thioureido}succinate (IX)

To a stirring solution of **VIII** (0.21 g, 0.38 mmol) in MeOH (5 mL), a 6N HCl/MeOH solution (0.90 mL, 5.40 mmol) was added. The mixture was left stirring for 1 h at room temperature. The volatiles were evaporated in vacuum to give the hydrogen chloride salt quantitatively. Light yellow solid; 0.19 g, 100% yield; mp 91-93 ^{o}C; $[\alpha]_D$= -32.6 (*c* = 1.0, CH_3OH); IR (film) 3333, 2955, 2922, 1735, 1674, 1452, 1378, 700 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 7.92-7.00 (13H, m, ArH), 5.12-5.10 (1H, m, NCH), 4.62-4.39 (1H, m, NCH), 4.37-3.86 (4H, m, CHC*H*$_2$O, C*H*CH$_2$O, NC*H*H), 3.83-3.37 (3H, m, 3 x NC*H*H), 2.19-1.41 (4H, m, 4 x C*H*H); ^{13}C NMR (50 MHz, CD_3OD) δ 175.7 (CO), 156.8 (OCONH), 145.1 (Ar), 142.4 (Ar), 135.8 (Ar), 130.4 (Ar), 130.2 (Ar), 128.8 (Ar), 128.4 (Ar), 128.1 (Ar), 126.1 (Ar), 121.0 (Ar), 68.8 (O*C*H$_2$CH), 62.0 (NCH), 55.8 (NCH), 45.8 (OCH$_2$*C*H), 43.8 (NCH$_2$), 43.0 (NCH$_2$), 31.3 (CH$_2$), 25.3 (CH$_2$); MS (ESI) 456 (M+H^+, 100%).

To a stirring solution of the salt obtained (0.19 g, 0.39 mmol) in CH_2Cl_2 (5 mL), isothiocyanate of Asp(OtBu)-OtBu (0.11 g, 0.39 mmol) was added followed by Et_3N (0.05 mL, 0.39 mmol) at 0 ^{o}C. The mixture was stirred for 24 h at room temperature and

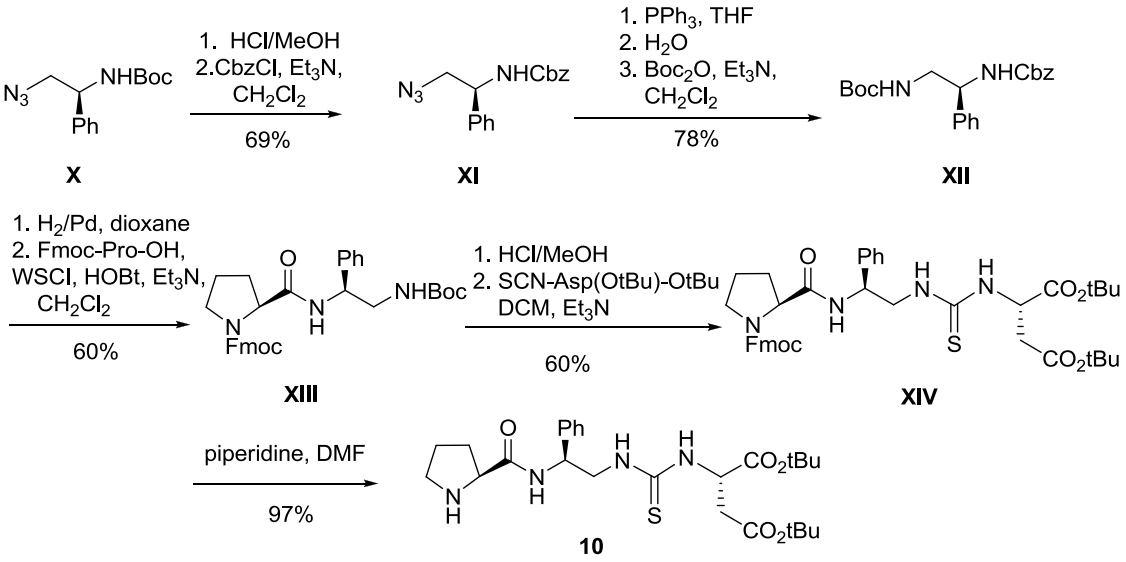
then the solvents were removed to give the crude product that was purified with column chromatography using Petroleum Ether:EtOAc (60:40). White solid; 0.26 g, 91% yield; mp 77-79 ^{o}C; $[\alpha]_D$= -5.5 (*c* = 1.0, $CHCl_3$); IR (film) 3330, 2955, 2918, 1735, 1675, 1531, 1451, 1366, 1156, 699 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86-7.17 (15H, m, ArH, 2 x NH), 6.99 (1H, br s, NH), 5.31-5.07 (1H, m, NCH), 4.56-3.91 (4H, m, NCH, OC*H*$_2$CH, OCH$_2$C*H*), 3.86-3.17 (5H, m, NCH, 4 x NC*H*H), 3.01-2.47 (2H, m, CH_2CO), 2.15-1.57 (4H, m, 4 x C*H*H), 1.37 [9H, s, C(CH$_3$)$_3$], 1.34 [9H, s, C(CH$_3$)$_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.1 (C=S), 172.8 (CO), 170.2 (CO), 169.8 (CO), 155.5 (OCONH), 143.6 (Ar), 141.0 (Ar), 128.5 (Ar), 128.4 (Ar), 127.4 (Ar), 126.8 (Ar), 126.3 (Ar), 126.2 (Ar), 124.8 (Ar), 119.6 (Ar), 81.6 [*C*(CH$_3$)$_3$], 80.8 [*C*(CH$_3$)$_3$], 67.3 (O*C*H$_2$CH), 61.4 (NCH), 60.5 (NCH), 57.8 (NCH), 53.9 (NCH_2), 46.9 (OCH$_2$*C*H), 44.7 (NCH_2), 37.5 (*C*H$_2$CO), 29.6 (CH_2), 27.7 [C(*C*H$_3$)$_3$], 27.6 [C(*C*H$_3$)$_3$], 24.2 (CH_2); MS (ESI) 743 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{41}H_{51}O_7N_4S$) requires *m/z* 743.3473, found *m/z* 743.3468.

(*S*)-Di-*tert*-butyl 2-{3-[(*S*)-1-phenyl-2-[(*S*)-pyrrolidine-2-carboxamido]ethyl]thioureido}succinate (9)

To a stirring solution of **IX** (0.25 g, 0.34 mmol) in DMF (1 mL), piperidine (0.17 mL, 1.68 mmol) was added and the mixture stirred for 1 h at room temperature. DMF was evaporated in vacuum to give the crude product that was purified using flash column chromatography eluting with petroleum ether: EtOAc (40:60) initially, followed by CH_2Cl_2: CH_3OH (70:30). Light yellow solid; 0.16 g, 92% yield; mp 52-54 ^{o}C; $[\alpha]_D$= -8.6 (*c* = 1.0, $CHCl_3$); IR (film) 3309, 2957, 2925, 1734, 1651, 1532, 1367, 1154, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.27-7.99 (2H, m, 2 x NH), 7.43-7.08 (6H, m, ArH, NH), 5.29-5.09 (1H, m, NCH), 4.29-4.11 (1H, m, NCH), 3.93-3.34 (3H, m, NCH, 2 x NC*H*H), 3.00-2.72 (4H, m, CH_2CO and NCH_2), 2.11-1.51 (5H, m, 4 x C*H*H, NH), 1.33 [9H, s, C(CH$_3$)$_3$], 1.30 [9H, s, C(CH$_3$)$_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.7 (C=S), 175.3 (CO), 170.1 (CO), 169.9 (CO), 139.1 (Ar), 128.3 (Ar), 127.3 (Ar), 126.5 (Ar), 81.7 [*C*(CH$_3$)$_3$], 80.9 [*C*(CH$_3$)$_3$], 60.0 (NCH), 58.2 (NCH), 57.9 (NCH), 53.8 (NCH_2), 46.7 (NCH_2), 37.6 (*C*H$_2$CO), 30.3 (CH_2), 27.8 [C(*C*H$_3$)$_3$], 27.7 [C(*C*H$_3$)$_3$], 25.4 (CH_2); MS (ESI) 521

(M+H$^+$, 100%); HRMS exact mass calculated for [M+H]$^+$ ($C_{26}H_{41}O_5N_4S$) requires *m/z* 521.2792, found *m/z* 521.2783.

General Procedure for the Synthesis of the Catalyst 10



Compound **XI** was synthesized following literature procedures.[4]

(*S*)-Benzyl 2-(*tert*-butoxycarbonylamino)-1-phenylethylcarbamate (XII)

To a stirring solution of **XI** (0.31 g, 1.06 mmol) in THF (5 mL), PPh_3 (0.57 g, 2.17 mmol) was added and the mixture was refluxed for 8 h. After this time, water was added (3 mL) and the mixture was refluxed for another 16 h. The solvents were removed and the crude residue was purified with column chromatography using CH_2Cl_2:MeOH (85:15) to afford the corresponding free amine.[4] White solid; 0.25 g, 87% yield; $[\alpha]_D$= +29.5 (*c* = 1.0, CH_3OH); ^{1}H NMR (200 MHz, CD_3OD) δ 7.42-6.96 (10H, m, ArH), 5.13-4.89 (2H, m, CH_2O), 4.81-4.58 (1H, m, NCH), 2.88-2.68 (2H, m, CH_2N); ^{13}C NMR (50 MHz, CD_3OD) δ 158.3 (OCONH), 142.2 (Ar), 137.9 (Ar), 129.5 (Ar), 129.3 (Ar), 128.8 (Ar), 128.7 (Ar), 128.3 (Ar), 127.4 (Ar), 67.4 (CH_2O), 58.9 (NCH), 49.8 (CH_2N); MS (ESI) 271 (M+H$^+$, 100%).

To a stirring solution of the amine obtained (0.24 g, 0.89 mmol) in CH_2Cl_2 (2 mL), Boc_2O (0.29 g, 1.34 mmol) was added followed by Et_3N (0.20 mL, 1.34 mmol). The

reaction mixture was stirred for 24 h at room temperature. The solvent was evaporated and the crude residue was purified with column chromatography using EtOAc. White solid; 0.30 g, 90% yield; mp 103-105 ^{o}C; $[\alpha]_D$= +22.9 (*c* = 1.0, $CHCl_3$); IR (film) 3357, 2956, 2918, 1684, 1533, 1249, 699 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.46-6.86 (10H, m, ArH), 6.23 (1H, d, *J* = 6.0 Hz, NH), 5.18-4.90 (3H, m, CH_2O, NH), 4.87-4.65 (1H, m, NCH), 3.47-3.23 (2H, m, CH_2N), 1.42 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.8 (OCONH), 156.2 (OCONH), 139.8 (Ar), 136.3 (Ar), 128.5 (Ar), 128.3 (Ar), 127.9 (Ar), 127.5 (Ar), 126.2 (Ar), 79.6 [$C(CH_3)_3$], 66.5(CH_2O), 56.6 (NCH), 45.5 (CH_2N), 28.2 [$C(CH_3)_3$]; MS (ESI) 371 ($M+H^+$, 61%); HRMS exact mass calculated for $[M+H]^+$ ($C_{21}H_{27}O_4N_2$) requires *m/z* 371.1965, found *m/z* 371.1964.

(*S*)-(9*H*-Fluoren-9-yl)methyl 2-[(*S*)-2-(*tert*-butoxycarbonylamino)-1-phenylethylcarbamoyl]pyrrolididne-1-carboxylate (XIII)

To a stirring solution of **XII** (0.29 g, 0.77 mmol) in 1,4-dioxane (5 mL), Pd/C (10%, 0.11 g) was added and the mixture was stirred for 24 h under H_2 atmosphere. After filtration over celite, the solvents were removed and the crude residue was purified with column chromatography using initially EtOAc followed by CH_2Cl_2:MeOH (90:10). Colourless oil; 0.11 g, 60% yield; $[\alpha]_D$= -1.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50-7.08 (5H, m, ArH), 5.38-5.14 (1H, m, NH), 4.17-3.91 (1H, m, NCH), 3.45-3.10 (2H, m, CH_2N), 2.65 (2H, br s, NH_2), 1.37 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.0 (OCONH), 142.5 (Ar), 128.5 (Ar), 127.4 (Ar), 126.3 (Ar), 79.1 [$C(CH_3)_3$], 55.4 (NCH), 47.8 (CH_2N), 28.2 [$C(CH_3)_3$]; MS (ESI) 237 ($M+H^+$, 61%).

To a solution of the amine (0.11 g, 0.45 mmol) in CH_2Cl_2 (5 mL), Fmoc-Pro-OH (0.16 g, 0.45 mmol) was added followed by HOBt (0.07 g, 0.45 mmol), WSCI (0.09 g, 0.49 mmol) and Et_3N (0.07 mL, 0.49 mmol). The mixture was left stirring for 24 h followed by evaporation of the solvent and purification of the resulting residue with column chromatography using EtOAc. White solid; 0.25 g, 100% yield; mp 82-84 ^{o}C; $[\alpha]_D$= -21.6 (*c* = 1.0, $CHCl_3$); IR (film) 3306, 2955, 2917, 1735, 1710, 1526, 1465, 1168, 700 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.91 (1H, d, *J* = 6.0 Hz, NH), 7.74 (2H, d, *J* = 7.0 Hz, ArH), 7.58 (2H, d, *J* = 7.0 Hz, ArH), 7.45-7.03 (9H, m, ArH), 5.29-4.90 (2H, m, NH,

NCH), 4.53-3.86 (4H, m, CHC*H*$_2$O, C*H*CH$_2$O, NCH), 3.78-3.09 (4H, m, 2 x NCH$_2$), 2.31-1.65 (4H, m, 4 x C*H*H), 1.38 [9H, s, C(CH$_3$)$_3$]; ^{13}C NMR (50 MHz, CDCl$_3$) δ (172.0) 171.6 (CO), (157.1) 156.7 (OCONH), 155.4 (154.6) (OCONH), 143.7 (Ar), 143.5 (Ar), 141.0 (Ar), 139.3 (Ar), 128.2 (Ar), 127.4 (Ar), 127.0 (Ar), 126.8 (Ar), 126.0 (Ar), 124.9 (Ar), 119.6 (Ar), (79.5) 79.1 [*C*(CH$_3$)], 67.4 (O*C*H$_2$CH), 60.5 (NCH), 54.8 (NCH), 54.5 (54.4) (NCH$_2$), 46.8 (OCH$_2$*C*H), 45.4 (NCH$_2$), 31.1 (CH$_2$), 28.0 [C(*C*H$_3$)], 24.3 (CH$_2$); MS (ESI) 556 (M+H$^+$, 100%); HRMS exact mass calculated for [M+H]$^+$ (C$_{33}$H$_{38}$O$_5$N$_3$) requires *m/z* 556.2806, found *m/z* 556.2809.

(*S*)-Di-*tert*-butyl 2-{3-[(*S*)-2-[(*S*)-1-[{[(9*H*-fluoren-9-yl)methoxy]carbonyl}pyrrolidine-2-carboxamido]-2-phenylethyl]thioureido}succinate (XIV)

To a stirring solution of **XIII** (0.26 g, 0.47 mmol) in MeOH (2 mL), a 6N HCl/MeOH solution (1.13 mL, 6.77 mmol) was added. The mixture was left stirring for 1 h at room temperature. The volatiles were evaporated in vacuum to give the hydrogen chloride salt quantitatively. Light yellow solid; 0.24 g, 100% yield; mp 116-118 ^{o}C; [α]$_D$= -33.6 (*c* = 1.0, CH$_3$OH); IR (film) 3304, 2954, 2922, 1737, 1674, 1541, 1452, 700 cm^{-1}; ^{1}H NMR (200 MHz, CD$_3$OD) δ 7.90-7.80 (1H, m, ArH), 7.79-7.63 (2H, m, ArH), 7.63-7.47 (2H, m, ArH), 7.46-7.09 (8H, m, ArH), 6.99-6.76 (1H, m, NH), 5.41-5.17 (1H, m, NCH), 4.58-3.69 (4H, m, CHC*H*$_2$O, C*H*CH$_2$O, NCH), 3.66-3.32 (4H, m, 4 x NC*H*H), 2.53-1.48 (4H, m, 4 x C*H*H); ^{13}C NMR (50 MHz, CD$_3$OD) δ 175.2 (CO), 157.1 (156.7) (OCONH), 145.2 (Ar), 144.9 (Ar), 142.4 (Ar), 139.0 (Ar), 130.0 (Ar), 129.9 (Ar), 129.7 (Ar), 129.4 (Ar), 129.2 (Ar), 128.8 (Ar), 128.1 (Ar), 127.8 (Ar), 127.7 (Ar), 126.5 (Ar), 126.1 (Ar), 120.9 (Ar), 68.9 (O*C*H$_2$CH), 62.3 (NCH), 61.7 (61.5) (NCH), (52.9) 52.7 (NCH$_2$), 45.6 (OCH$_2$*C*H), 44.4 (NCH$_2$), (31.2) 31.4 (CH$_2$), 25.4 (CH$_2$); MS (ESI) 456 (M+H$^+$, 100%). To a stirring solution of the salt (0.24 g, 0.47 mmol) in CH$_2$Cl$_2$ (3 mL), isothiocyanate of Asp(OtBu)-OtBu (0.13 g, 0.47 mmol) was added followed by Et$_3$N (0.06 mL, 0.47 mmol) at 0 ^{o}C. The mixture was stirred for 24 h at room temperature, followed by evaporation of the solvent and purification of the resulting residue with column chromatography using Petroleum Ether:EtOAc (60:40). White solid; 0.22 g, 60% yield; mp 98-100 ^{o}C; [α]$_D$=

-4.7 (*c* = 1.0, $CHCl_3$); IR (film) 3330, 2955, 2919, 1736, 1675, 1531, 1452, 1366, 1157, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.00-6.98 (16H, m, ArH, 3 x NH), 5.41-5.13 (1H, m, NCH), 5.09-4.82 (1H, m, NCH), 4.61-3.85 (5H, m, O*CH*$_2$CH, OCH$_2$*CH*, NCH, NC*H*H), 3.82-3.29 (3H, m, 3 x NC*H*H), 3.01-2.70 (2H, m, CH_2CO), 2.23-1.71 (4H, m, 4 x C*H*H), 1.41 [9H, s, C(CH$_3$)$_3$], 1.35 [9H, s, C(CH$_3$)$_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.4 (C=S), 172.4 (CO), (170.8) 170.7 (CO), 170.3 (170.2) (CO), 155.5 (154.7) (OCONH), 144.0 (Ar), 143.7 (Ar), 141.1 (Ar), 139.5 (Ar), 128.4 (Ar), 127.4 (Ar), 127.2 (Ar), 126.9 (Ar), 126.3 (Ar), 125.1 (Ar), 119.7 (Ar), 82.2 [*C*(CH$_3$)$_3$], 81.1 [*C*(CH$_3$)$_3$], 67.4 (O*C*H$_2$CH), 60.8 (NCH), 56.2 (NCH), 55.5 (NCH), 54.1 (NCH_2), 48.5 (NCH_2), 47.0 (OCH$_2$*C*H), 37.5 (*C*H$_2$CO), 29.5 (CH_2), 27.8 [C(*C*H$_3$)$_3$], 27.7 [C(*C*H$_3$)$_3$], 24.3 (CH_2); MS (ESI) 743 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{41}H_{51}O_7N_4S$) requires *m/z* 743.3473, found *m/z* 743.3477.

(*S*)-Di-*tert*-butyl 2-{3-[(*S*)-2-phenyl-2-[(*S*)-pyrrolidine-2-carboxamido]ethyl]thioureido}succinate (10)

To a stirring solution of **XIV** (0.17 g, 0.23 mmol) in DMF (1 mL), piperidine (0.11 mL, 1.13 mmol) was added and the mixture was stirred for 1 h at room temperature. DMF was evaporated in vacuum to give a residue that was purified with column chromatography using initially Petroleum Ether:EtOAc (60:40) followed by CH_2Cl_2: MeOH (90:10). Yellow solid; 0.12 g, 97% yield; mp 73-75 ^oC; $[\alpha]_D$= +19.4 (*c* = 1.0, $CHCl_3$); IR (film) 3303, 2955, 2917, 1735, 1653, 1526, 1456, 1367, 1155, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.46-8.18 (1H, m, NH), 7.69-7.13 (7H, m, ArH, 2 x NH), 5.66-5.34 (1H, m, NCH), 4.49-3.58 (4H, m, NCH_2, 2 x NCH), 3.23-2.52 (4H, m, CH_2CO and NCH_2), 2.29-1.57 (5H, m, 4 x C*H*H, NH), 1.40 [18H, s, 2 x C(CH$_3$)$_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.6 (C=S), 175.2 (CO), 173.6 (CO), 169.2 (CO), 138.5 (Ar), 128.8 (Ar), 127.8 (Ar), 126.3 (Ar), 82.4 [*C*(CH$_3$)$_3$], 82.2 [*C*(CH$_3$)$_3$], 60.4 (NCH), 55.6 (NCH), 51.2 (NCH), 51.0 (NCH_2), 46.9 (NCH_2), 36.2 (*C*H$_2$CO), 30.3 (CH_2), 27.9 [C(*C*H$_3$)$_3$], 27.9 [C(*C*H$_3$)$_3$], 25.9 (CH_2); MS (ESI) 521 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{26}H_{41}O_5N_4S$) requires *m/z* 521.2792, found *m/z* 521.2782.

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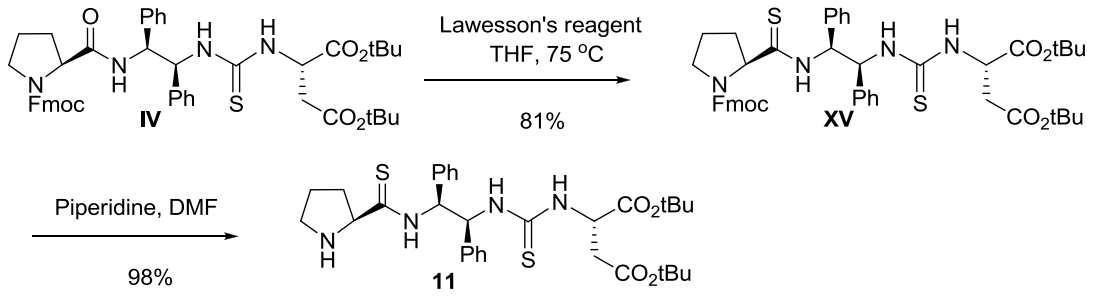


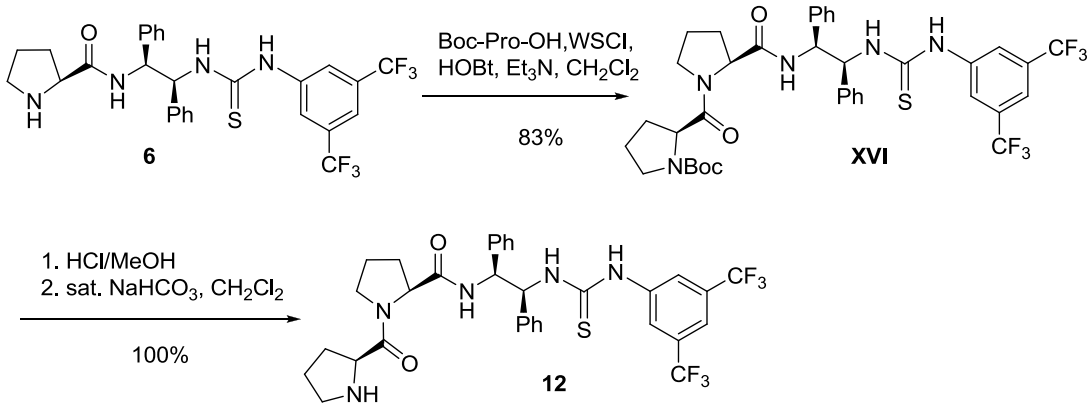
(*S*)-Di-*tert*-butyl 2-{3-[(1*S*,2*S*)-2-{(*S*)-[((9*H*-fluoren-9-yl)methoxy)carbonyl]pyrrolidine-2-carbothioamido}-1,2-diphenylethyl}thioureido}succinate (XV)

To a stirring solution of **IV** (0.17 g, 0.21 mmol) in absolute THF (10 mL), Lawesson's reagent (0.13 g, 0.32 mmol) was added and the mixture was refluxed for 24 h. The solvents were removed and the residue was purified with column chromatography using Petroleum Ether:EtOAc (1:1). Light yellow solid; 0.14 g, 81% yield; mp 96-98 ^{o}C; $[\alpha]_D$= +2.70 (*c* = 1.0, $CHCl_3$); IR (film) 3304, 2955, 2917, 1735, 1674, 1531, 1453, 1365, 1153, 697 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 10.41 (0.6H, br s, NHC=S), 10.05 (0.4H, br s, NHC=S), 8.01-6.88 (20H, m, ArH, 2 x NH), 6.15-5.65 (2H, m, 2 x NCH), 5.40-4.96 (1H, m, NCH), 4.94-4.49 (1H, m, NCH), 4.44-3.41 (5H, m, OC*H*$_2$CH, OCH$_2$C*H*, NCH$_2$), 3.08-2.61 (2H, m, CH_2CO), 2.48-1.87 (4H, m, 4 x C*H*H), 1.41 [9H, s, C(CH$_3$)$_3$], 1.37 [9H, s, C(CH$_3$)$_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 203.9 (C=S), 183.5 (C=S), 170.1 (CO), 170.0 (CO), 155.3 (154.6) (OCONH), 143.9 (Ar), 143.4 (Ar), 140.8 (Ar), 137.6 (Ar), 137.5 (Ar), 137.2 (Ar), 137.1 (Ar), 136.9 (Ar), 136.6 (Ar), 135.3 (Ar), 128.3 (Ar), 128.2 (Ar), 127.8 (Ar), 127.4 (Ar), 127.2 (Ar), 126.7 (Ar), 125.1 (Ar), 119.5 (Ar), 82.2 [*C*(CH$_3$)$_3$], 81.1 [*C*(CH$_3$)$_3$], 67.7 (OCH$_2$CH), 67.3 (NCH), 62.5 (NCH), 60.2 (NCH), 53.9 (NCH), (47.6) 47.5 (NCH$_2$), 46.7 (46.5) (OCH$_2$*C*H), (36.9) 36.7 (*C*H$_2$CO), 29.9 (29.3) (CH_2), 27.6 [C(*C*H$_3$)$_3$], 27.5 [C(*C*H$_3$)$_3$], (23.6) 23.1 (CH_2); MS (ESI) 835 (M+H$^+$, 100%); HRMS exact mass calculated for [M+H]$^+$ ($C_{47}H_{55}O_6N_4S_2$) requires *m/z* 835.3558, found *m/z* 835.3563.

(*S*)-Di-*tert*-butyl 2-{3-[(1*S*,2*S*)-1,2-diphenyl-2-[(*S*)-(pyrrolidine-2-carbothioamido]-ethyl]thioureido}succinate (11)

To a stirring solution of **XV** (0.06 g, 0.07 mmol) in DMF (0.5 mL), piperidine (0.04 mL, 0.36 mmol) was added and the mixture was stirred for 1 h at room temperature. DMF was evaporated in vacuum to give a residue that was purified with column chromatography using initially Petroleum Ether:EtOAc (60:40) followed by CH_2Cl_2: MeOH (90:10). White solid; 0.04 g, 98% yield; mp 82-84 ^oC; $[\alpha]_D$= +21.4 (*c* = 1.0, $CHCl_3$); IR (film) 3355, 2955, 2918, 1733, 1526, 1456, 1367, 1153, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.86 (1H, br s, NHC=S), 7.73-7.07 (12H, m, ArH, 2 x NH), 6.89-6.38 (1H, m, NCH), 6.21-5.84 (1H, m, NCH), 5.25-4.93 (1H, m, NCH), 4.32-4.01 (1H, m, NCH), 3.28-2.67 (4H, m, CH_2CO, NCH_2), 2.47-1.65 (5H, m, 4 x C*H*H, NH), 1.43 [9H, s, $C(CH_3)_3$], 1.39 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.7 (C=S), 181.5 (NHC=SNH), 170.2 (CO), 169.8 (CO), 137.9 (Ar), 136.9 (Ar), 128.7 (Ar), 128.5 (Ar), 128.1 (Ar), 127.8 (Ar), 82.5 [*C*$(CH_3)_3$], 81.9 [*C*$(CH_3)_3$], 67.9 (NCH), 63.2 (NCH), 62.8 (NCH), 54.1 (NCH), 47.2 (NCH_2), 38.0 (*C*H_2CO), 29.7 (CH_2), 28.0 [C(*C*$H_3)_3$], 27.9 [C(*C*$H_3)_3$], 25.8 (CH_2); MS (ESI) 623 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{32}H_{45}O_4N_4S_2$) requires *m/z* 613.2877, found *m/z* 613.2874.

General Procedure for the Synthesis of the Catalyst 12



(*S*)-*tert*-Butyl 2-{(*S*)-2-[(1*S*,2*S*)-2-{3-[3,5-bis(trifluoromethyl)phenyl]thioureido}-1,2-diphenylethylcarbamoyl]pyrrolidine-1-carbonyl}pyrrolidine-1-carboxylate (XVI)

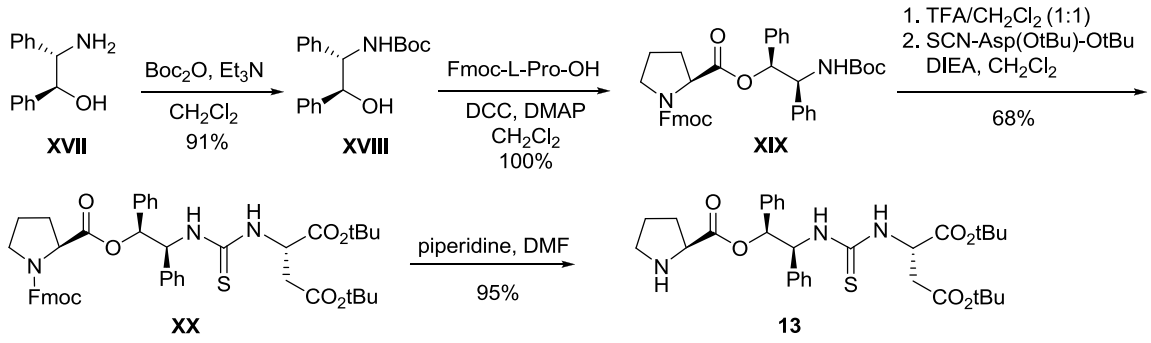
To a solution of the amine **6** (0.10 g, 0.17 mmol) in CH_2Cl_2 (2 mL), Boc-Pro-OH (0.04 g, 0.17 mmol) was added followed by HOBt (0.03 g, 0.17 mmol), WSCI (0.04 g, 0.19 mmol) and Et_3N (0.03 mL, 0.19 mmol). The mixture was left stirring for 24 h followed by evaporation of the solvent and purification of the resulting residue with column chromatography using Petroleum Ether:EtOAc (40:60). White solid; 0.11 g, 83% yield; mp 141-143 ^oC; $[\alpha]_D$= -9.3 (*c* = 1.0, $CHCl_3$); IR (film) 3304, 2918, 2850, 1736, 1670, 1536, 1380, 1277, 1136, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.46-9.33 (0.5H, br m, NH), 8.83-8.67 (0.5H, br m, NH), 8.51 (1H, d, *J* = 7.4 Hz, NH), 8.29-8.03 (2H, m, 2 x ArH), 7.68-7.47 (1H, m, ArH), 7.45-6.96 (11H, m, ArH, NH), 6.19-5.97 (1H, m, NCH), 5.73-5.36 (1H, m, NCH), 5.35-4.82 (1H, m, NCH), 4.52-4.22 (1H, m, NCH), 3.75-3.23 (4H, m, 2 x NCH_2), 2.47-1.68 (8H, m, 8 x C*H*H), 1.52 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.7 (180.8) (C=S), 172.7 (173.9) (CO), 172.0 (171.6) (CO), 155.4 (154.6 (OCONH), 141.3 (Ar), 140.8 (Ar), 138.2 (138.8) (Ar), 131.6 (q, *J* = 33.6 Hz, Ar), 128.5 (Ar), 128.4 (Ar), 128.2 (Ar), 128.0 (Ar), 127.7 (Ar), 127.5 (Ar), 123.7 (Ar), 123.2 (q, *J* = 272.7 Hz, CF_3), 121.9 (Ar), 80.7 (79.6) [$C(CH_3)_3$], 63.0 (62.7) (NCH), 61.8 (61.7) (NCH), 58.9 (60.0) (NCH), 58.7 (57.4) (NCH), 47.4 (46.9) (NCH_2), 47.1 (46.5) (NCH_2), 31.5 (29.7) (CH_2), 29.3 (29.0) (CH_2), 28.5 (28.4) [$C(CH_3)$], 24.1 (25.6) (CH_2), 22.8 (22.6) (CH_2); MS (ESI) 776 ($M-H^-$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{38}H_{42}F_6O_4N_5S$) requires *m/z* 778.2856, found *m/z* 778.2861.

(*S*)-*N*-[(1*S*,2*S*)-2-{3-[3,5-Bis(trifluoromethyl)phenyl]thioureido}-1,2-diphenylethyl]-1-[(*S*)-pyrrolidine-2-carbonyl]pyrrolidine-2-carboxamide (12)

To a stirring solution of **XVI** (0.08 g, 0.10 mmol) in MeOH (1 mL), a 6N HCl/MeOH solution (0.24 mL, 1.42 mmol) was added. The mixture was left stirring for 1 h at room temperature. The volatiles were evaporated in *vacuo* and the resulting hydrochloride salt was suspended in CH_2Cl_2 (4 mL) and a sat. aq. $NaHCO_3$ solution (4 mL) was added. The biphasic system was stirred vigorously for 10 min and then transferred to a separating

funnel. The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (3 x 3mL). The combined organics were washed with brine (1 x 2 mL), dried over Na_2SO_4 and the solvents were removed to afford the desired compound quantitatively. Light yellow solid; 0.07 g, 100% yield; mp 149-151 ^oC; $[\alpha]_D$= -45.1 (*c* = 1.0, CH_3OH); IR (film) 3253, 2923, 2852, 1734, 1627, 1572, 1384, 1276, 1134, 699 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 8.24-8.13 (2H, m, 2 x ArH), 7.66-7.59 (1H, m, ArH), 7.36-7.08 (10H, m, ArH), 6.16 (1H, d, *J* = 9.6 Hz, NCH), 5.40 (1H, d, *J* = 9.6 Hz, NCH), 4.56-4.41 (1H, m, NCH), 4.00-3.84 (1H, m, NCH), 3.65-3.44 (2H, m, NCH_2), 3.14-2.63 (2H, m, NCH_2), 2.33-1.53 (8H, m, 8 x C*H*H); ^{13}C NMR (50 MHz, CD_3OD) δ 182.6 (C=S), 174.1 (173.9) (CO), 172.9 (172.8) (CO), 143.0 (Ar), 140.0 (Ar), 139.7 (Ar), 132.7 (q, *J* = 33.1 Hz, Ar), 129.6 (Ar), 129.5 (Ar), 129.1 (Ar), 128.9 (Ar), 128.7 (Ar), 128.6 (Ar), 124.7 (q, *J* = 272.3 Hz, CF_3), 123.5 (Ar), 117.9 (Ar), 63.9 (NCH), 61.7 (NCH), 60.0 (NCH), 59.8 (NCH), 48.2 (NCH_2), 48.0 (NCH_2), 30.7 (CH_2), 30.4 (CH_2), 26.7 (CH_2), 25.8 (CH_2); MS (ESI) 678 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{33}H_{34}F_6O_2N_5S$) requires *m/z* 678.2332, found *m/z* 678.2322.

General Procedure for the Synthesis of the Catalyst 13



(*S*)-1-(9H-Fluoren-9-yl)methyl 2-((1*S*,2*S*)-2-(tert-butoxycarbonylamino)-1,2-diphenylethyl) pyrrolidine-1,2-dicarboxylate (XIX)

A stirring solution of (1*S*,2*S*)-2-amino-1,2-diphenylethanol (**XVII**) (0.20 g, 0.94 mmol) in CH_2Cl_2 (8 mL) was cooled at 0 ^oC and Et_3N (14 μL, 1.04 mmol) was added, followed by addition of a solution of Boc_2O (0.23 g, 1.04 mmol, 1.1 equiv.) in CH_2Cl_2 (2 mL). The

reaction mixture was stirred at 0 ^{o}C for 1 h and then warmed at room temperature and left stirring for 24 h. The solvent was evaporated and the residue was purified using flash column chromatography eluting with petroleum ether: EtOAc (80:20) initially, followed by CH_2Cl_2: CH_3OH (90:10). White solid; 0.27 g, 91% yield; mp: 118-120 ^{o}C; $[\alpha]_D$= -10.2 (*c* = 1.0, $CHCl_3$); IR (film) 2914, 2361, 1683, 1492, 1365, 1163, 697 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.63-6.85 (10H, m, ArH), 5.64 (1H, s, NH), 4.84 (2H, m, NCH and OCH), 3.39 (1H, s, OH), 1.33 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.7 (OCONH), 140.6 (Ar), 139.8 (Ar), 128.0 (Ar), 127.8 (Ar), 127.2 (Ar), 127.0 (Ar), 126.6 (Ar), 125.9 (Ar), 79.4 [$C(CH_3)_3$], 76.7 (OCH), 60.3 (NCH), 27.9 [$C(CH_3)_3$]; MS (ESI) 314 ($M+H^+$, 100%).

To a stirring solution of Fmoc-L-Pro-OH (0.15 g, 0.42 mmol) in CH_2Cl_2 (10 mL) at 0 ^{o}C, compound **XVIII** (0.13 g, 0.42 mmol) was added followed by dicyclohexylcarbodiimide (DCC) (0.096 g, 0.47 mmol) and 4-dimethylaminopyridine (DMAP) (0.005 g, 0.04 mmol). The mixture was left stirring at 0 ^{o}C for 1 h and then warmed at room temperature and left stirring for 24 h. Dicyclohexylurea (DCU) was filtered and the solvent was evaporated. The residue was purified using flash column chromatography eluting with petroleum ether: EtOAc (70:30). Colourless oil; 0.27 g, 100% yield; $[\alpha]_D$= -23.7 (*c* = 1.0, $CHCl_3$); IR (film) 3348, 2956, 2917, 1736, 1710, 1465, 1377, 1164, 698 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03-7.59 (3H, m, ArH), 7.58-7.08 (14H, m, ArH), 7.08-6.73 (1H, m, ArH), 6.18-6.05 (1H, m, NH), 5.60 (0.5H, d, *J* = 9.1 Hz, OCH), 5.37 (0.5H, d, *J* = 9.1 Hz, OCH), 5.29-5.03 (1H, m, NCH), 4.59-4.37 (2H, m, OC*H*$_2$CH), 4.34-4.08 (1.5H, m, 0.5 x NCH and OCH_2CH), 3.88 (0.5H, t, *J* = 18.6 Hz, NCH), 3.74-3.34 (2H, m, NCH_2), 2.31-1.73 (4H, m, 4 x C*H*H), 1.34 [9H, d, *J* = 18.6 Hz, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.8 (171.3) (CO), (155.0) 154.9 (154.8) (OCONH), 154.1 (OCONH), 144.0 (143.8) (Ar), 143.4 (141.1) (Ar), 140.9 (Ar), 138.8 (Ar), 138.3 (Ar), 136.5 (136.3) (Ar), 128.2 (Ar), 128.1 (Ar), 128.0 (Ar), 127.9 (Ar), 127.5 (Ar), 127.4 (Ar), 127.3 (Ar), 126.8 (Ar), 126.7 (Ar), 126.4 (Ar), 124.9 (Ar), (119.8) 119.6 (Ar), (79.7) 79.5 [*C*$(CH_3)_3$], (78.0) 77.2 (OCH), 67.5 (67.4) (O*C*H_2CH), 59.0 (NCH), 58.7 (NCH), 47.0 (46.9) (NCH_2), (46.8) 46.2 (OCH_2*C*H), (30.7) 29.3 (CH_2), 28.0 [$C(CH_3)_3$], (28.1) 27.9 [$C(CH_3)_3$], 23.9 (23.2) (CH_2); MS (ESI) 633 ($M+H^+$, 34%); HRMS exact mass calculated for $[M+H]^+$ ($C_{39}H_{41}O_6N_2$) requires *m/z* 633.2959, found *m/z* 633.2951.

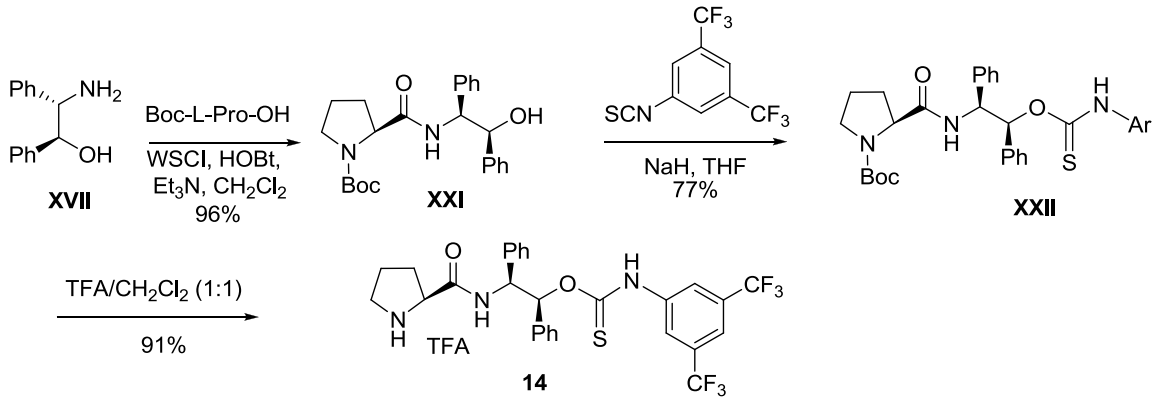
(*S*)-1-(9H-Fluoren-9-yl) methyl 2-((1*S*,2*S*)-2-(3-((*S*)-1,4-di-tert-butoxy-1,4-dioxobutan-2-yl) thioureido)-1,2-diphenyl ethyl) pyrrolidine-1,2-dicarboxylate (XX)

To a stirring solution of compound **XIX** (0.14 g, 0.22 mmol) in CH_2Cl_2 (6 mL), a 1:1 TFA/ CH_2Cl_2 solution (10.75 mmol, 1.65 mL) was added and the mixture was left stirring for 1 h. The volatiles removed in *vacuo* followed by addition of CH_2Cl_2 (6 mL) and evaporation. This process was repeated three times in order to remove the excess of TFA. The resulting solid residue was dried to afford the TFA salt quantitatively (0.14 g, 0.22 mmol, 100%). To a stirring suspension of the salt in CH_2Cl_2 (6 mL) at 0 ^oC, a solution of SCN-Asp(OtBu)-OtBu (0.06 g, 0.22 mmol) in CH_2Cl_2 was added, followed by N,N-diisopropylethylamine (DIPEA) (0.04 mL, 0.22 mmol). The mixture was stirred at 0 ^oC for 30 min., warmed to room temperature and left stirring for 24 h. The solvent was removed and the residue was purified using flash column chromatography eluting with petroleum ether: EtOAc (1:1). White solid; 0.12 g, 68% yield; mp 102-104 ^oC; $[\alpha]_D$= -4.2 (*c* = 1.0, $CHCl_3$); IR (film) 3356, 2955, 2917, 2849, 1736, 1526, 1465, 1418, 1376, 1162, 758 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.83-7.57 (3H, m, ArH), 7.56-7.01 (15H, m, 13 x ArH, 2 x NH), 6.99-6.81 (2H, m, ArH), 6.29-6.03 (1H, m, NCH), 5.25-4.98 (1H, m, OCH), 4.62-4.39 (2H, m, OC*H*$_2$CH), 4.34-4.20 (1H, m, NCH), 4.19-4.03 (1H, m, NCH), 3.85-3.27 (3H, m, NCH_2, OCH_2CH), 2.97-2.68 (2H, m, CH_2CO), 2.37-1.71 (4H, m, 4 x C*H*H), 1.43 [9H, m, C(CH_3)$_3$], 1.35 [9H, m, C(CH_3)$_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.1 (C=S), 171.8 (171.2) (CO), 170.5 (CO), 169.8 (CO), 155.1 (154.3) (OCONH), 144.2 (144.0) (Ar), 143.8 (143.5) (Ar), 141.2 (Ar), 141.0 (140.9) (Ar), 136.4 (Ar), 136.3 (135.8) (Ar), 128.5 (Ar), 128.3 (Ar), 128.1 (Ar), 127.7 (Ar), 127.5 (Ar), 127.4 (Ar), 127.1 (Ar), 126.9 (Ar), 126.6 (Ar), 126.5 (Ar), 125.2 (Ar), 125.0 (Ar), 119.8 (119.7) (Ar), 82.4 (82.2) [*C*(CH_3)$_3$], 81.4 (81.2) [*C*(CH_3)$_3$], (78.2) 77.2 (OCH), (67.6) 67.5 (O*C*H_2CH), 62.3 (NCH), 59.2 (58.8) (NCH), (54.4) 54.2 (NCH), 47.1 (46.9) (NCH_2), 46.4 (OCH_2*C*H), 37.4 (*C*H_2CO), 29.6 (29.3) (CH_2), 27.9 [C(*C*H_3)$_3$], 27.8 [C(*C*H_3)$_3$], 24.1 (23.3) (CH_2); MS (ESI) 820 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{47}H_{54}O_8N_3S$) requires *m/z* 821.0114, found *m/z* 821.0107.

(*S*)-Di-tert-butyl 2-(3-((1*S*,2*S*)-1,2-diphenyl-2-((*S*)-pyrrolidine-2-carbonyloxy) ethyl)thioureido)succinate (13)

Compound **XX** (0.10 g, 0.12 mmol) was deprotected following the general procedure for the removal of Fmoc. The crude product was purified using flash column chromatography eluting with petroleum ether: EtOAc (40:60) initially, followed by CH_2Cl_2: CH_3OH (70:30). White solid; 0.07 g, 95% yield; mp 60-62 ^oC; $[\alpha]_D$= +16.4 (*c* = 1.0, $CHCl_3$); IR (film) 3347, 2955, 2916, 1732, 1539, 1455, 1374, 1152, 686 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.43-6.88 (12H, m, ArH, 2 x NH), 6.19-6.01 (1H, m, NCH), 5.26-5.04 (1H, m, OCH), 3.88-3.68 (1H, m, NCH), 3.18-2.74 (5H, m, CH_2CO, NCH_2 and NCH), 2.25-2.01 (1H, m, C*H*H), 1.99-1.57 (4H, m, 3 x C*H*H and NH), 1.40 [9H, s, C(*C*H_3)$_3$], 1.35 [9H, s, C(*C*H_3)$_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.2 (C=S), 174.8 (174.5) (CO), 170.6 (CO), 170.0 (169.7) (CO), 137.6 (Ar), 136.4 (Ar), 128.3 (Ar), 128.2 (Ar), 127.7 (Ar), 127.4 (Ar), 127.2 (Ar), 126.9 (Ar), 82.2 [*C*(CH$_3$)$_3$], 81.2 [*C*(CH$_3$)$_3$], 78.1 (77.2) (OCH), 62.3 (NCH), 59.7 (NCH), 54.2 (NCH), 46.7 (NCH_2), 37.6 (*C*H_2CO), 30.0 (CH_2), 28.0 [C(*C*H_3)$_3$], 27.8 [C(*C*H_3)$_3$], 25.2 (CH_2); MS (ESI) 598 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{32}H_{44}O_6N_3S$) requires *m/z* 598.2945, found *m/z* 598.2927.

General Procedure for the Synthesis of the Catalyst 14



(*S*)-tert-Butyl 2-((1*S*,2*S*)-2-hydroxy-1,2-diphenylethylcarbamoyl)pyrrolidine-1-carboxylate (XXI)

To a stirring solution of Boc-L-proline (0.20 g, 0.94 mmol) in dry CH_2Cl_2 (10 mL) at 0 ^oC, (1*S*,2*S*)-2-amino-1,2-diphenylethanol (**XVII**) (0.20 g, 0.94 mmol)], 1-hydroxybenzotriazole (HOBt) (0.14 g, 0.94 mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (WSCI) (0.20 g, 1.03 mmol) and Et_3N (0.15 mL, 1.03 mmol) were added consecutively. The reaction mixture was left stirring at 0 ^{o} C for 1 h, and then warmed to room temperature and left stirring for 18 h. The solvents were evaporated under *vacuo* and the crude product was purified using flash column chromatography eluting with EtOAc. White solid; 0.37 g, 96% yield; mp: 169-171 ^oC; $[\alpha]_D$= -75.6 (*c* = 1.0, $CHCl_3$); IR (film) 3345, 2953, 2917, 1675, 1521, 1427, 1366, 1169, 697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.92 (1H, d, *J* = 7.2 Hz, NH), 7.43-6.95 (10 H, m, ArH), 5.17-5.01 (1H, m, OCH), 4.94-4.76 (1H, m, NCH), 4.39-3.97 (2H, m, NCH and OH), 3.45-3.07 (2H, m, NCH_2), 2.19-1.57 (4H, m, 4 x C*H*H), 1.35 [9H, m, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.5 (171.8) (CO), 155.4 (154.3) (OCONH), 141.0 (Ar), 139.4 (Ar), 128.0 (Ar), 127.8 (Ar), 127.2 (Ar), 127.0 (Ar), 126.9 (Ar), 126.1 (Ar), 80.1 [$C(CH_3)_3$], 77.2 (76.8) (OCH), 60.4 (NCH), 59.5 (59.3) (NCH), 46.7 (NCH_2), 30.5 (CH_2), 28.0 (27.7) [$C(CH_3)_3$], 24.3 (23.2) (CH_2); MS (ESI) 411 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{24}H_{31}O_4N_2$) requires *m/z* 411.2278, found *m/z* 411.2272.

(*S*)-tert-Butyl 2-((1*S*,2*S*)- 2-(3,5-bis (trifluoromethyl) phenyl carbamo thioyloxy)-1,2-diphenylethylcarbamoyl) pyrrolidine-1-carboxylate (XXII)

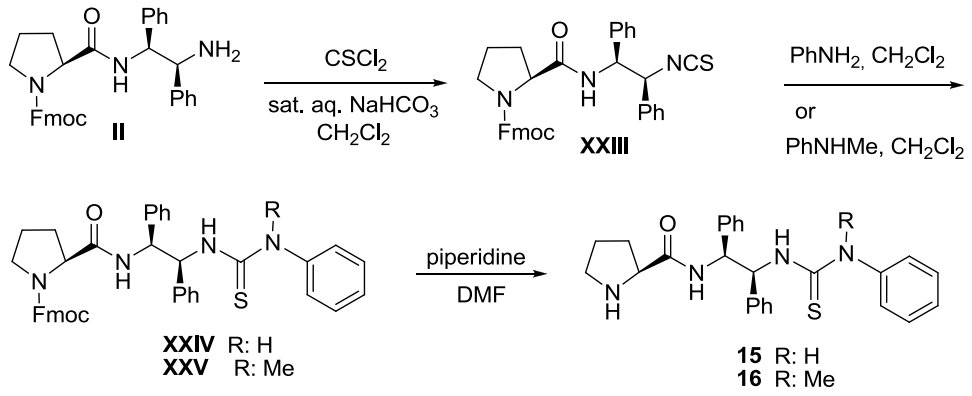
To a stirring solution of compound **XXI** (0.18 g, 0.45 mmol) in dry THF (5 mL) at room temperature under argon, 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (0.09 mL, 0.50 mmol) was added, followed by a suspension of NaH (0.01 g, 0.50 mmol) in dry THF (5 mL). The mixture was left stirring for 24 h, followed by solvent evaporation and purification with flash column chromatography eluting with petroleum ether: EtOAc (60:40). White solid; 0.24 g, 77% yield; mp 99-101 ^oC; $[\alpha]_D$= -54.5 (*c* = 1.0, $CHCl_3$); IR (film) 3291, 2955, 2918, 2850, 1735, 1668, 1540, 1472, 1379, 1278, 1176, 1138, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 10.55-9.92 (1H, m, NH), 8.49-7.95 (2H, m, ArH), 7.64

(1H, s, ArH), 7.49-6.62 (12H, m, 10 x ArH, NH and NCH), 5.67 (1H, s, OCH), 4.58 (1H, s, NCH), 3.51-3.02 (2H, m, NCH_2), 2.30-1.63 (4H, m, 4 x C*H*H), 1.38 [9H, s, $C(CH_3)_3$]; ^{13}C NMR (50 MHz, $CDCl_3$) δ 187.1 (C=S), 171.8 (CO), 156.0 (154.8) (OCONH), 139.2 (Ar), 137.4 (Ar), 136.1 (Ar), 131.8 (q, *J* =33.4 Hz, Ar), 128.3 (Ar), 127.5 (Ar), 127.3 (Ar), 125.7 (Ar), 122.2 (q, *J* = 272.8 Hz, CF3), 120.2 (Ar), 118.2 (Ar), 114.8 (Ar), 80.5 [$C(CH_3)_3$], 77.2 (OCH), 59.6 (59.9) (NCH), 57.3 (57.5) (NCH), 47.0 (NCH_2), 29.6 (CH_2), 28.1 [$C(CH_3)_3$], 24.3 (23.9) (CH_2); MS (ESI) 682 ($M+H^+$, 30%); HRMS exact mass calculated for $[M+H]^+$ ($C_{33}H_{34}F_6O_4N_3S$) requires *m/z* 682.2169, found *m/z* 682.2161.

(*S*)-2-[(1*S*,2*S*)-2-3,5-Bis(trifluoromethyl)phenylcarbamothioyloxy]-1,2-diphenylethylcarbamoyl) pyrrolidinium 2,2,2-trifluoroacetate (14)

To a stirring solution of compound **XXII** (0.12 g, 0.17 mmol) in CH_2Cl_2 (6 mL), a 1:1 TFA/CH_2Cl_2 solution (8.65 mmol, 1.33 mL) was added and the mixture was left stirring for 1 h. The volatiles removed in *vacuo* and a three times repeated addition of CH_2Cl_2 (6 mL) and evaporation was followed, in order to remove the excess of TFA. A twice repeated addition of $CHCl_3$ (6 mL) and evaporation, afforded a light yellow solid that was further suspended in a small volume of $CHCl_3$ (0.5 mL) and precipitated with petroleum ether (8 mL). The resulting white solid was filtered, washed three times with petroleum ether (8 mL) and dried to afford the trifluoroacetate salt **14**. White solid; 0.11 g, 91% yield; mp 97-99 ^oC; $[\alpha]_D$= -9.3 (*c* = 1.0, $CHCl_3$); IR (film) 3239, 2955, 2918, 2850, 1735, 1672, 1563, 1468, 1379, 1278, 1180, 1136, 700 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 8.18-8.01 (2H, m, ArH), 7.74-6.96 (13H, m, 11 x ArH, 2 x NH), 6.32 (0.6H, d, *J* = 12 Hz, OCH), 6.14 (0.4H, dd, *J* = 7.2 Hz and 4.0 Hz, OCH), 4.58-4.46 (0.5H, m, NCH), 4.44-4.26 (0.5H, m, NCH), 4.21-3.98 (1H, m, NCH), 3.31-3.06 (2H, m, NCH_2), 2.57-1.63 (6H, m, 4 x C*H*H, 2 x NH); ^{13}C NMR (50 MHz, CD_3OD) δ 188.5 (C=S), 168.4 (q, *J*= 15.9 Hz, $CF_3CO_2^-$) 168.7 (168.2) (CO), 142.8 (143.5) (Ar), 142.2 (142.5) (Ar), 141.7 (141.8) (Ar), 133.2 (q, *J* =33.2 Hz, Ar), 130.2 (Ar), 129.6 (Ar), 129.2 (Ar), 129.1 (Ar), 128.1(Ar), 127.4 (Ar), 124.5 (q, *J* = 272.1 Hz, CF_3), 119.8 (Ar), 117.4 (Ar), 114.9 (q, *J* = 243.9 Hz, CF_3), 76.9 (80.7) (OCH), 60.7 (m, NCH), 57.9 (58.6) (m, NCH), 47.2 (m, NCH_2), 30.6 (m, CH_2), 24.5 (m, CH_2); MS (ESI) 582 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{28}H_{26}F_6O_2N_3S$) requires *m/z* 582.1644, found *m/z* 582.1626.

General Procedure for the Synthesis of the Catalysts 15 and 16



(*S*)-(9H-Fluoren-9-yl)methyl 2-[(1*S*,2*S*)-2-isothiocyanato-1,2-diphenylethylcarbamoyl]pyrrolidine-1-carboxylate (XXIII)

To a stirring solution of compound **II** (0.27 g, 0.51 mmol) in CH_2Cl_2 (5 mL), a saturated aqueous solution of $NaHCO_3$ (5 mL) was added at 0 ^oC and left stirring vigorously for 10 min. The stirring was stopped and thiophosgene (0.043 mL, 0.57 mmol) was added to the organic layer *via* syringe. The mixture was stirred vigorously at room temperature for 1 h. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4 and the solvent was evaporated to afford the isothiocyanate compound **XXIII** quantitatively. It was used immediately to the next step without purification.

General procedure for the coupling of compound XXIII with aromatic amines

To a stirring solution of freshly prepared isothiocyanate **XXIII** (0.10 g, 0.17 mmol) in CH_2Cl_2 (5 mL), a solution of the appropriate amine (0.17 mmol) in CH_2Cl_2 (2 mL) was added and the mixture was left stirring for 24 h. The solvent was evaporated in *vacuo* and the residue was purified by column chromatography using petroleum ether: EtOAc=40:60.

(*S*)-(9H-Fluoren-9-yl)methyl 2-((1*S*,2*S*)-1,2-diphenyl-2-(3-phenylthioureido) ethylcarbamoyl)pyrrolidine-1-carboxylate (XXIV)

White solid; 0.08 g, 70% yield; mp 119-121 ^{o}C; $[\alpha]_D$= -76.2 (*c* = 1.0, $CHCl_3$); IR (film) 3296, 3061, 2952, 1680, 1530, 1496, 1450, 1353, 1120, 759, 699 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.56 (1H, s, NH), 8.19 (1H, d, *J* = 7.4 Hz, NH), 8.15-8.01 (1H, br m, ArH), 7.73-7.56 (2H, m, ArH), 7.44 (2H, m, ArH), 7.36-6.75 (19H, m, 18 x ArH and NH), 6.11-5.79 (1H, m, NCH), 5.23-5.01 (1H, m, NCH), 4.38-3.73 (4H, m, OC*H*$_2$CH, NCH, OCH$_2$C*H*), 3.63-3.45 (1H, m, NCH*H*), 3.42-3.21 (1H, m, NC*H*H), 2.03-1.58 (4H, m, 4 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.7 (C=S), 172.4 (CO), 155.6 (154.9) (OCONH), 143.7 (Ar), 143.4 (Ar), 140.9 (Ar), 138.6 (Ar), 137.6 (Ar), 137.3 (Ar), 136.4 (Ar), 136.2 (Ar), 129.4 (Ar), 128.4 (Ar), 128.3 (Ar), 128.1 (Ar), 127.7 (Ar), 127.6 (Ar), 127.4 (Ar), 127.3 (Ar), 127.2 (Ar), 126.8 (Ar), 126.7 (Ar), 126.5 (Ar), 126.0 (Ar), 125.1 (Ar), 125.0 (Ar), 124.6 (Ar), 123.6 (Ar), 119.7 (Ar), (67.6) 67.4 (O*C*H$_2$CH), 63.1 (62.7) (NCH), 60.8 (NCH), (60.1) 59.7 (NCH), 47.2 (NCH$_2$), 46.8 (OCH$_2$*C*H), (29.5) 29.2 (CH$_2$), (23.4) 24.2 (CH$_2$); MS (ESI) 667 (M+H$^+$, 100%); HRMS exact mass calculated for [M+H]$^+$ ($C_{41}H_{39}O_3N_4S$) requires *m/z* 667.8378, found *m/z* 667.8372.

(*S*)-(9H-Fluoren-9-yl)methyl 2-((1*S*,2*S*)-2-(3-methyl-3-phenylthioureido)-1,2-diphenylethylcarbamoyl)pyrrolidine-1-carboxylate (XXV)

White solid; 0.09 g, 78% yield; mp 105-107 ^{o}C; $[\alpha]_D$= -86.3 (*c* = 1.0, $CHCl_3$); IR (film) 3378, 2955, 2917, 2849, 1736, 1518, 1466, 1377, 1117, 699 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.29-8.18 (1H, m, NH), 7.78 (2H, d, *J* = 7.0 Hz, ArH), 7.63 (2H, m, ArH), 7.56-7.18 (9H, m, ArH), 7.17-6.91 (7H, m, ArH), 6.90-6.57 (3H, m, ArH), 6.17 (1H, d, *J* = 8.4 Hz, NH), 6.01 (1H, dd, *J* = 8.4 Hz and *J* = 8.6 Hz, NCH), 5.00 (1H, dd, *J* = 7.2 Hz and *J* = 8.0 Hz, NCH), 4.64-4.21 (3H, m, OC*H*$_2$CH, NCH), 4.18-3.92 (1H, m, OCH$_2$C*H*), 3.85-3.31 (5H, m, NCH$_2$, NCH$_3$), 2.38-1.65 (4H, m, 4 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ (181.9) 181.6 (C=S), (172.2) 171.8 (CO), 155.7 (154.5) (OCONH), 143.9 (Ar), 143.6 (Ar), 142.1 (Ar), 141.7 (Ar), 141.0 (Ar), 138.8 (Ar), 138.2 (Ar), 130.4 (Ar), 130.2 (Ar), 128.5 (Ar), 128.3 (Ar), 128.1 (Ar), 128.0 (Ar), 127.6 (Ar), 127.5 (Ar), 127.4 (Ar), 127.1 (Ar), 126.9 (Ar), 126.8 (Ar), 126.2 (Ar), 125.3 (Ar), 125.1 (Ar), 124.9 (Ar), 119.7

(Ar), (67.5) 67.4 (O*C*H_2CH), 63.2 (NCH), 60.8 (60.3) (NCH), 59.6 (NCH), 47.3 (NCH_2), (46.9) 46.8 (OCH_2*C*H), 43.2 (NCH_3), (29.5) 29.2 (CH_2), (23.4) 24.1 (CH_2); MS (ESI) 681 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{42}H_{41}O_3N_4S$) requires *m/z* 681.2894, found *m/z* 681.2888.

General procedure for the deprotection of the Fmoc group

Compounds **XXIV** (0.08 g, 0.12 mmol) or **XXV** (0.08 g, 0.12 mmol) were deprotected following the general procedure for the removal of Fmoc. The crude product was purified using flash column chromatography eluting with petroleum ether: EtOAc (40:60) initially, followed by CH_2Cl_2: CH_3OH (70:30).

(*S*)-*N*-((1*S*,2*S*)-1,2-Diphenyl-2-(3-phenylthioureido) ethyl) pyrrolidine-2-carboxamide (15)

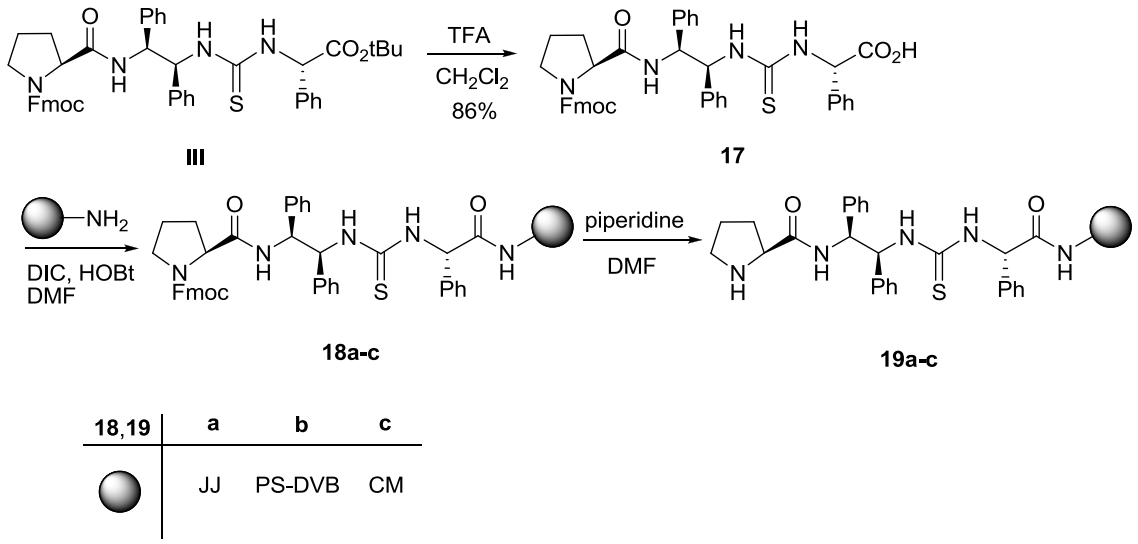
White solid; 0.05 g, 100% yield; mp 85-88 ^oC; $[\alpha]_D$= -25.8 (*c* = 1.0, $CHCl_3$); IR (film) 3304, 2955, 2917, 2849, 1736, 1656, 1540, 1466, 1377, 1116, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.04 (1H, s, NH), 8.63 (1H, d, *J* = 9.4 Hz, NH), 7.86 (1H, d, *J* = 8.8 Hz, ArH), 7.56-6.15 (15H, m, 14 x ArH and NH), 6.07 (1H, t, *J* = 9.0 Hz, NCH), 5.29 (1H, t, *J* = 9.8 Hz, NCH), 3.67 (1H, dd, *J* = 4.2 Hz, *J* = 6.2 Hz, NCH), 3.15-2.63 (3H, m, NCH_2, NH), 2.16-1.35 (4H, m, 4 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.8 (C=S), 175.0 (CO), 137.9 (Ar), 137.4 (Ar), 129.1 (Ar), 128.4 (Ar), 128.2 (Ar), 127.5 (Ar), 127.4 (Ar), 127.3 (Ar), 125.9 (Ar), 124.3 (Ar), 63.3 (NCH), 60.2 (NCH), 58.8 (NCH), 46.6 (NCH_2), 29.9 (CH_2), 25.4 (CH_2); MS (ESI) 445 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{26}H_{29}ON_4S$) requires *m/z* 445.2057, found *m/z* 445.2038.

(*S*)-*N*-((1S,2*S*)-2-(3-Methyl-3-phenylthioureido)-1,2-diphenylethyl)pyrrolidine-2-carboxamide (16)

White solid; 0.06 g, 100% yield; mp 55-57 ^oC; $[\alpha]_D$= -112.5 (*c* = 1.0, $CHCl_3$); IR (film) 3249, 2955, 2917, 2849, 1735, 1651, 1519, 1466, 1376, 1105, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.38 (1H, d, *J* = 9.0 Hz, NH), 7.62-7.39 (3H, m, ArH), 7.38-6.89 (9H, m, ArH), 6.88-6.69 (3H, m, ArH), 6.48 (1H, d, *J* = 8.0 Hz, NH), 5.87 (1H, t, *J* = 8.8 Hz,

NCH), 4.99 (1H, t, *J* = 9.2 Hz, NCH), 3.83-3.35 (4H, m, NCH_3, NCH), 3.02-2.57 (3H, m, NCH_2, NH), 2.16-1.91 (1H, m, C*H*H), 1.79-1.38 (3H, m, 3 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.5 (C=S), 174.8 (CO), 142.6 (Ar), 138.7 (Ar), 138.2 (Ar), 130.4 (Ar), 128.5 (Ar), 128.3 (Ar), 128.2 (Ar), 128.0 (Ar), 127.4 (Ar), 127.3 (Ar), 126.9 (Ar), 64.3 (NCH), 60.3 (NCH), 58.0 (NCH), 47.0 (NCH_2), 43.2 (NCH_3), 30.3 (CH_2), 25.8 (CH_2); MS (ESI) 459 ($M+H^+$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{27}H_{31}ON_4S$) requires *m/z* 459.2213, found *m/z* 459.2196.

General Procedure for the Synthesis of the Catalyst 19a-c



(*S*)-2-{3-[(1*S*,2*S*)-[(*S*)-1-{[(9*H*-Fluoren-9-yl)methoxy]carbonyl}pyrrolidine-2-carboxamido]-1,2-diphenylethyl]thioureido}-2-phenylacetic acid (17)

To a stirring solution of **III** (0.23 g, 0.30 mmol) in CH_2Cl_2 (2 mL), a 1:1 TFA/CH_2Cl_2 solution (0.64 mL, 4.20 mmol) was added and the mixture left stirring for 24 h at room temperature. The volatiles were evaporated in *vacuo* and the residue was purified by column chromatography using initially Petroleum Ether:EtOAc (30:370) followed by CH_2Cl_2:MeOH (90:10). White solid; 0.19 g, 86% yield; mp 185-187 ^{o}C; $[\alpha]_D$= -21.7 (*c* = 1.0, CH_3OH); ^{1}H NMR (200 MHz, CD_3OD) δ 7.85-6.52 (23H, m, ArH), 5.29-4.90 (3H, m, 3 x NCH), 4.41-3.73 (4H, m, NCH, O*C*H_2CH, OCH_2C*H*), 3.58-3.34 (2H, m, NCH_2), 2.29-1.50 (4H, m, 4 x C*H*H); ^{13}C NMR (50 MHz, CD_3OD) δ 182.6 (C=S), 175.0 (CO),

174.9 (CO), 156.7 (OCONH), 145.6 (Ar), 145.5 (Ar), 145.1 (Ar), 144.8 (Ar), 142.8 (Ar), 142.6 (Ar), 142.4 (Ar), 131.1 (Ar), 129.9 (Ar), 129.8 (Ar), 129.7 (Ar), 129.4 (Ar), 129.3 (Ar), 129.2 (Ar), 129.0 (Ar), 128.9 (Ar), 128.4 (Ar), 128.3 (Ar), 128.2 (Ar), 126.4 (Ar), 126.3 (Ar), 121.0 (Ar), 69.2 (NCH), 68.9 (O*C*H_2CH), 61.9 (NCH), 60.9 (NCH), 60.1 (NCH), 47.1 (NCH_2), 46.8 (OCH_2*C*H), 32.3 (CH_2), 25.3 (CH_2); MS (ESI) 723 ($M-H^-$, 100%); HRMS exact mass calculated for $[M+H]^+$ ($C_{43}H_{41}O_5N_4S$) requires *m/z* 725.2792, found *m/z* 725.2783.

General procedure for the synthesis of resins 18a-c

Aminomethylated resin (JandaJel, PS-DVB or CM) (0.015 mmol) was placed in a vessel for solid phase synthesis and swelled with DMF (1 mL) for 20 min. In the meantime, a small excess of **17** (0.02 g, 0.03 mmol) and HOBt (0.004 g, 0.03 mmol), was placed in an eppendorf and the solid mixture was dissolved in DMF (0.1 mL). The solution was cooled at 0 ^oC for 10 min and at room temperature for a few minutes before the addition of an equimolar amount of DIC (N,N-diisopropylcarbodiimide) (0.005 ml, 0.03 mmol). The mixture was left for 10 min at room temperature to complete the generation of the reactive ester and then aspirated to the resin with prior removal of the solvent used for swelling. The heterogeneous mixture was stirred for 24 h at room temperature, filtered and the resin was washed with DMF (4 x 1 mL). Quantitative immobilization indicated by chloranil test. The resin was washed with CH_2Cl_2 (2 x 1 mL), Et_2O (2 x 2 mL) and dried in vacuum.

General procedure for the synthesis of resins 19a-c

The resin **18a-c** were swelled initially with DMF (1 mL) followed by Fmoc cleavage using a 20% piperidine/DMF solution for 20 min (1 mL). The resin was filtered and the procedure was repeated. The resin was washed with DMF (4 x 1 mL), CH_2Cl_2 (2 x 1 mL), Et_2O (2 x 2 mL) and dried in vacuum.

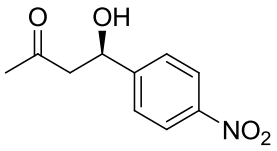
General Procedure for the Aldol Reaction

To a stirring solution of catalyst **8** (8 mg, 0.014 mmol) in toluene (1.0 mL), 4-nitrobenzoic acid (2.5 mg, 0.014 mmol) was added. Aldehyde (0.14 mmol) followed by ketone (1.40 mmol) were added at –20 ^{o}C. The reaction mixture was left stirring at –20 ^{o}C until the reaction was complete (by TLC). The solvent was evaporated and the crude product was purified using flash column chromatography eluting with various mixtures of petroleum ether (40-60 ^{o}C): EtOAc. All characterazation data for the aldol products are in accordance with the literature.

General Procedure for the aldol reaction in the presence of catalyst 14

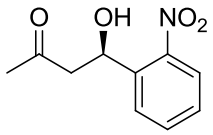
To a stirring solution of catalyst (0.014 mmol) in toluene (0.5 mL), N,N-diisopropylethylamine (DIPEA) (2.5 μL, 0.014 mmol) was added at room temperature. The stirring was continued vigorously for 10 min. Acetone (1.40 mmol) was added and the reaction mixture was cooled down at - 20 ^{o}C. A solution of aldehyde (0.14 mmol) and 4-nitrobenzoic acid (2.5 mg, 0.014 mmol) in toluene (0.5 mL) was added to the mixture. The reaction mixture was left stirring at –20 ^{o}C until the reaction was complete (by TLC). The solvent was evaporated and the crude product was purified using flash column chromatography eluting with various mixtures of petroleum ether (40-60 ^{o}C): EtOAc.

(*R*)-4-Hydroxy-4-(4-nitrophenyl)-butan-2-one[1] (Table 4, entry 1)



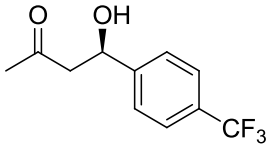
100% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 7.0 Hz, ArH), 7.52 (2H, d, *J* = 7.0 Hz, ArH), 5.25 (1H, m, OCH), 3.56 (1H, br s, OH), 3.01-2.71 (2H, m, CHHCO), 2.21 (3H, s, CH_3CO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.6 (C=O), 149.9 (Ar), 147.4 (Ar), 126.4 (Ar), 123.8 (Ar), 68.9 (OCH), 51.5 (CH_2), 30.7 (CH_3); HPLC analysis: Diacel Chiralpak AD-RH, MeCN:H_2O 30:70, flow rate 0.5 mL/min, retention time: 22.14 (major) and 27.98 (minor).

(*R*)-4-Hydroxy-4-(2-nitrophenyl)-butan-2-one[1] (Table 4, entry 2)



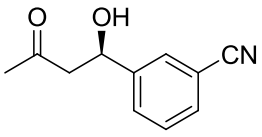
100% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05-7.85 (2H, m, ArH), 7.72-7.61 (1H, m, ArH), 7.49-7.38 (1H, m, ArH), 5.68 (1H, d, *J* = 9.3 Hz, OCH), 3.76 (1H, br s, OH), 3.15 (1H, dd, *J* = 17.8 Hz, C*H*HCO), 2.73 (1H, dd, *J* = 17.8 and 9.3 Hz, C*H*HCO), 2.25 (3H, s, CH_3CO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.7 (C=O), 148.1 (Ar), 144.6 (Ar), 131.8 (Ar), 129.4 (Ar), 122.5 (Ar), 120. 6 (Ar), 68.6 (OCH), 51.4 (CH_2), 30.7 (CH_3); HPLC analysis: Diacel Chiralpak AS-H, hexane:^{i}PrOH 80:20, flow rate 0.8 mL/min, retention time: 18.23 (major) and 30.34 (minor).

(*R*)-4-Hydroxy-4-[4-(trifluoromethyl)phenyl]-butan-2-one[1] (Table 4, entry 3)



100% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62-7.52 (2H, m, ArH), 7.48-7.38 (2H, m, ArH), 5.17 (1H, t, *J* = 5.9 Hz, OCH), 3.62 (1H, br s, OH), 2.85-2.77 (2H, m, CHHCO), 2.17 (3H, s, CH_3CO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.8 (C=O), 146.6 (Ar), 129.6 (q, *J* = 31.0 Hz, Ar), 125.8 (Ar), 125.3 (Ar), 123.9 (q, *J* = 271.0 Hz, Ar), 69.0 (OCH), 51.6 (CH_2), 30.6 (CH_3); HPLC analysis: Diacel Chiralpak AS-H, hexane:^{i}PrOH 80:20, flow rate 0.5 mL/min, retention time: 11.18 (major) and 12.85 (minor).

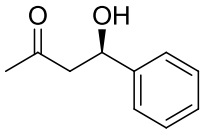
(*R*)-3-(1-Hydroxy-3-oxonutyl)benzonitrile[1] (Table 4, entry 4)



Pale yellow oil, 82% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74-7.68 (1H, m, ArH), 7.65-7.54 (2H, m, ArH), 7.52-7.40 (1H, m, ArH), 5.19 (1H, t, *J* = 6.4 Hz, OCH), 3.61 (1H, br

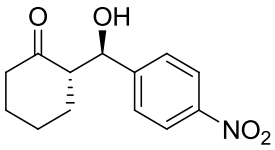
s, OH), 2.84 (2H, d, *J* = 6.4 Hz, CHHCO), 2.22 (3H, s, CH_3CO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.5 (C=O), 144.3 (Ar), 131.1 (Ar), 130.1 (Ar), 129.2 (Ar), 129.1 (Ar), 118.6 (CN), 112.3 (Ar), 68.6 (OCH), 51.5 (CH_2), 30.6 (CH_3); HPLC analysis: Diacel Chiralpak AD-RH, MeCN:H_2O 40:60, flow rate 1.0 mL/min, retention time: 7.58 (major) and 9.04 (minor).

(*R*)-4-Hydroxy-4-phenyl-butan-2-one[1] (Table 4, entry 5)



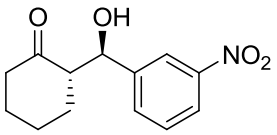
40% yield; ^1H NMR (200 MHz, $CDCl_3$) δ 7.37-7.21 (5H, m, ArH), 5.21-5.07 (1H, m, OCH), 3.27 (1H, br s, OH), 2.88-2.77 (2H, m, CHHCO), 2.15 (3H, s, CH_3CO); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.0 (C=O), 142.5 (Ar), 128.3 (Ar), 127.6 (Ar), 125.5 (Ar), 69.6 (OCH), 51.9 (CH_2), 30.6 (CH_3); HPLC analysis: Diacel Chiralpak AS-H, hexane:^{i}PrOH 90:10, flow rate 0.8 mL/min, retention time: 15.33 (major) and 17.77 (minor).

(*S*)-2-[(*R*)-Hydroxy-(4-(nitrophenyl)methyl]-cyclohexanone[1] (Table 4, entry 6)



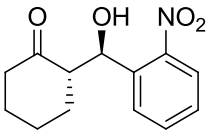
100% yield; ^1H NMR (200 MHz, $CDCl_3$) *anti* δ 8.20 (2H, d, *J* = 8.8 Hz, ArH), 7.51 (2H, d, *J* = 8.8 Hz, ArH), 4.87 (1H, d, *J* = 8.4 Hz, OCH), 4.09 (1H, br s, OH), 2.64-2.26 (3H, m, CH and CHH), 2.17-1.29 (6H, m, 6 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.6 (C=O), 148.4 (Ar), 127.9 (Ar), 127.8 (Ar), 123.4 (Ar), 73.8 (OCH), 57.0 (CH), 42.5 (CH_2), 30.6 (CH_2), 27.5 (CH_2), 24.5 (CH_2); HPLC analysis: Diacel Chiralpak AS-H, hexane:^{i}PrOH 80:20, flow rate 0.5 mL/min, retention time: 24.72 (minor) and 31.71 (major).

(*S*)-2-[(*R*)-Hydroxy-(3-(nitrophenyl)methyl]-cyclohexanone[5] (Table 4, entry 7)



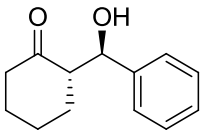
95% yield; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.23-8.14 (2H, m, ArH), 7.67 (1H, d, *J* = 7.3 Hz, ArH), 7.55 (1H, d, *J* = 7.6 Hz, ArH), 4.90 (1H, d, *J* = 8.4 Hz, OCH), 4.11 (1H, br s, OH), 2.68-2.31 (3H, m, COCH and CHH), 2.17-1.32 (6H, m, 6 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.6, 148.2, 143.1, 133.1, 129.2, 122.7, 121.9, 74.0, 57.0, 42.6, 30.6, 27.6, 24.6; HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 92:8, flow rate 1.0 mL/min, retention time: 25.15 (major) and 31.99 (minor).

(*S*)-2-[(*R*)-Hydroxy-(2-(nitrophenyl)methyl]-cyclohexanone[5] (Table 4, entry 8)



92% yield; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.91-7.72 (2H, m, ArH), 7.63 (1H, t, *J* = 6.5 Hz, ArH), 7.42 (1H, t, *J* = 6.6 Hz, ArH), 5.43 (1H, d, *J* = 7.1 Hz, OCH), 4.16 (1H, br s, OH), 2.85-2.01 (3H, m, COCH, CHH), 1.90-1.52 (6H, m, 6 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.9, 136.5, 133.0, 128.9, 128.3, 124.0, 69.7, 57.2, 42.8, 31.1, 27.7, 24.9; HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 95:5, flow rate 0.8 mL/min, retention time: 40.77 (major) and 42.92 (minor).

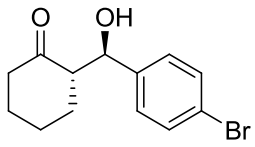
(*S*)-2-[(*R*)-Hydroxy-(phenyl)methyl]-cyclohexanone[6] (Table 4, entry 9)



57% yield; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.51-7.21 (5H, m, ArH), 4.78 (1H, d, *J* = 8.8 Hz, OCH), 3.84 (1H, br s, OH), 2.70-2.31 (3H, m, COCH and CHH), 2.15-1.24 (6H, m, 6 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.5, 140.8, 128.3, 127.8, 125.7, 74.7, 57.4,

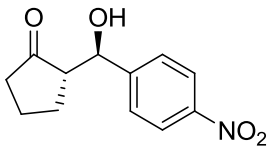
42.6, 30.8, 27.8, 24.7; HPLC analysis: Diacel Chiralpak OD-H, hexane:^{i}PrOH 90:10, flow rate 0.5 mL/min, retention time: 17.73 (major) and 24.49 (minor).

(*S*)-2-[(*R*)-Hydroxy-(4-(bromophenyl)methyl]-cyclohexanone[1] (Table 4, entry 10)



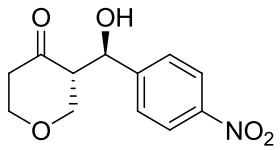
49% yield; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 7.46 (2H, d, *J* = 8.4 Hz, ArH), 7.19 (2H, d, *J* = 8.4 Hz, ArH), 4.74 (1H, d, *J* = 8.7 Hz, OCH), 3.98 (1H, br s, OH), 2.61-2.11 (3H, m, CH and CHH), 2.13-2.07 (1H, m, C*H*H), 1.81-1.43 (5H, m, 5 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 215.2 (C=O), 140.0 (Ar), 131.5 (Ar), 128.7 (Ar), 121.7 (Ar), 74.2 (OCH), 57.3 (CH), 42.7 (CH_2), 30.7 (CH_2), 27.7 (CH_2), 24.7 (CH_2); HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 90:10, flow rate 0.5 mL/min, retention time: 30.19 (minor) and 35.08 (major).

(*S*)-2-[(*R*)-Hydroxy-(4-(nitrophenyl)methyl]-cyclopentanone[1] (Table 4, entry 11)



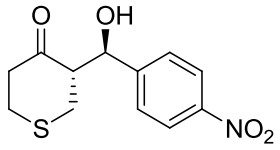
100% yield; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.20 (2H, d, *J* = 8.8 Hz, ArH), 7.15 (2H, d, *J* = 8.8 Hz, ArH), 5.41 (1H, s, OCH *syn*), 4.83 (1H, d, *J* = 9.2 Hz, OCH *anti*), 4.76 (1H, br s, OH *anti*), 2.69 (1H, br s, OH *syn*), 2.52-2.18 (3H, m, CH and CHH), 2.15-1.83 (2H, m, 2 x C*H*H), 1.78-1.55 (2H, m, 2 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.6 (C=O), 213.4 (C=O), 149.2 (Ar), 147.9 (Ar), 147.4 (Ar), 147.3 (Ar), 127.2 (Ar), 126.5 (Ar), 123.0 (Ar), 122.9 (Ar), 73.5 (OCH), 69.8 (OCH), 57.0 (CH), 56.3 (CH), 42.5 (CH_2), 30.2 (CH_2), 27.7 (CH_2), 25.5 (CH_2), 24.6 (CH_2), 24.3 (CH_2); HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 95:5, flow rate 1 mL/min, retention time: 26.80 (*syn* major) and 36.35 (*syn* minor), 45.29 (*anti* minor) and 46.83 (*anti* major).

(*S*)-3-[(*R*)-Hydroxy-[4-(nitrophenyl)methyl]dihydro-2*H*-pyran-4(3*H*)-one[1] **(Table 4, entry 12)**



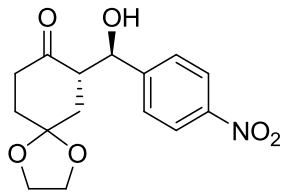
98% yield; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.21 (2H, d, *J* = 8.8 Hz, ArH), 7.50 (2H, d, *J* = 8.8 Hz, ArH), 4.97 (1H, d, *J* = 8.2 Hz, OCH), 4.28-4.09 (1H, m, OC*H*H), 3.90-3.64 (3H, m, 2 x OC*H*H and OH), 3.44 (1H, dd, *J* = 11.4 and 9.8 Hz, OC*H*H), 3.02-2.41 (3H, m, 3 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.2 (C=O), 147.7 (Ar), 147.4 (Ar), 127.4 (Ar), 123.8 (Ar), 71.2 (OCH), 69.7 (OCH_2), 68.2 (OCH_2), 57.5 (CH), 42.7 (CH_2); HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 80:20, flow rate 1 mL/min, retention time: 19.91 (minor) and 23.04 (major).

(*S*)-3-[(*R*)-Hydroxy-[4-(nitrophenyl)methyl]dihydro-2*H*-thiopyran-4(3*H*)-one[1]
(Table 4, entry 13)



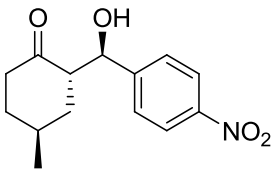
86% yield; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.21 (2H, d, *J* = 8.3 Hz, ArH), 7.53 (2H, d, *J* = 8.3 Hz, ArH), 5.04 (1H, d, *J* = 7.9 Hz, OCH), 3.65 (1H, br s, OH), 3.13-2.91 (3H, m, CH and CHH), 2.87-2.70 (2H, m, 2 x C*H*H), 2.68-2.42 (2H, m, 2 x C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.2 (C=O), 147.7 (Ar), 147.6 (Ar), 127.7 (Ar), 123.8 (Ar), 73.1 (OCH), 59.4 (CH), 44.7 (CH_2), 32.8 (CH_2), 30.7 (CH_2); HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 90:10, flow rate 1 mL/min, retention time: 57.28 (minor) and 65.65 (major).

(*S*)-7-[(*R*)-Hydroxy-4-(nitrophenyl)methyl]-1,4-dioxospiro[4.5]decan-8-one[1] (Table 4, entry 14)



66% yield; ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.20 (2H, d, *J* = 8.8 Hz, ArH), 7.49 (2H, d, *J* = 8.8 Hz, ArH), 4.83 (1H, d, *J* = 7.5 Hz, OCH), 4.04 (1H, br s, OH), 3.98-3.68 (4H, m, 4 x OC*H*H), 2.91-2.74 (1H, m, CH), 2.66-2.54 (1H, m, C*H*H), 2.51-2.42 (1H, m, C*H*H), 2.07-1.55 (3H, m, 3 x C*H*H), 1.54-1.44 (1H, m, C*H*H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 213.1 (C=O), 147.9 (Ar), 127.8 (Ar), 126.5 (Ar), 123.6 (Ar), 106.7 [$\underline{C}(OCH_2)_2$], 73.8 (OCH), 64.6 (OCH_2), 64.5 (OCH_2), 52.9 (CH), 38.8 (CH_2), 37.8 (CH_2), 34.3 (CH_2); HPLC analysis: Diacel Chiralpak AS-H, hexane:^{i}PrOH 70:30, flow rate 1 mL/min, retention time: 11.96 (minor) and 18.97 (major).

(2*S*,4*R*)-2-[(*R*)-Hydroxy-(4-(nitrophenyl)methyl]-4-methylcyclohexanone[6,7] (Table 4, entry 15)



99% yield; $[\alpha]_D$= -6.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) *anti* δ 8.22 (2H, d, *J* = 8.8 Hz, ArH), 7.51 (2H, d, *J* = 8.8 Hz, ArH), 4.92 (1H, d, *J* = 8.6 Hz, OCH), 3.99-3.87 (1H, br s, OH), 2.81-2.29 (3H, m, CH and CHH), 2.15-1.29 (5H, m, 4 x C*H*H, CH); 1.07 (3H, d, *J* = 7.1 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 214.8 (C=O), 148.4 (Ar), 147.5 (Ar), 127.8 (Ar), 123.7 (Ar), 73.9 (OCH), 52.9 (CH), 38.3 (CH_2), 36.1 (CH_2), 33.0 (CH), 26.5 (CH_2), 18.2 (CH_3); HPLC analysis: Diacel Chiralpak AD-H, hexane:^{i}PrOH 90:10, flow rate 1.0 mL/min, retention time: 28.87 (major) and 31.23 (minor).

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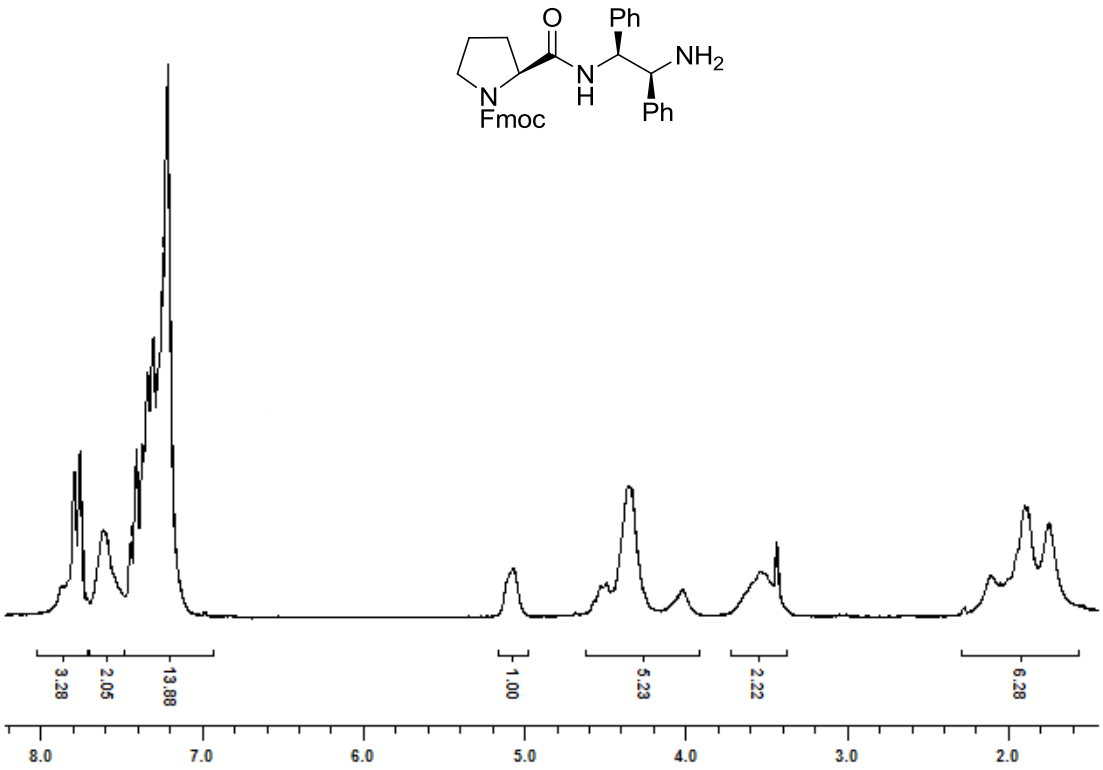
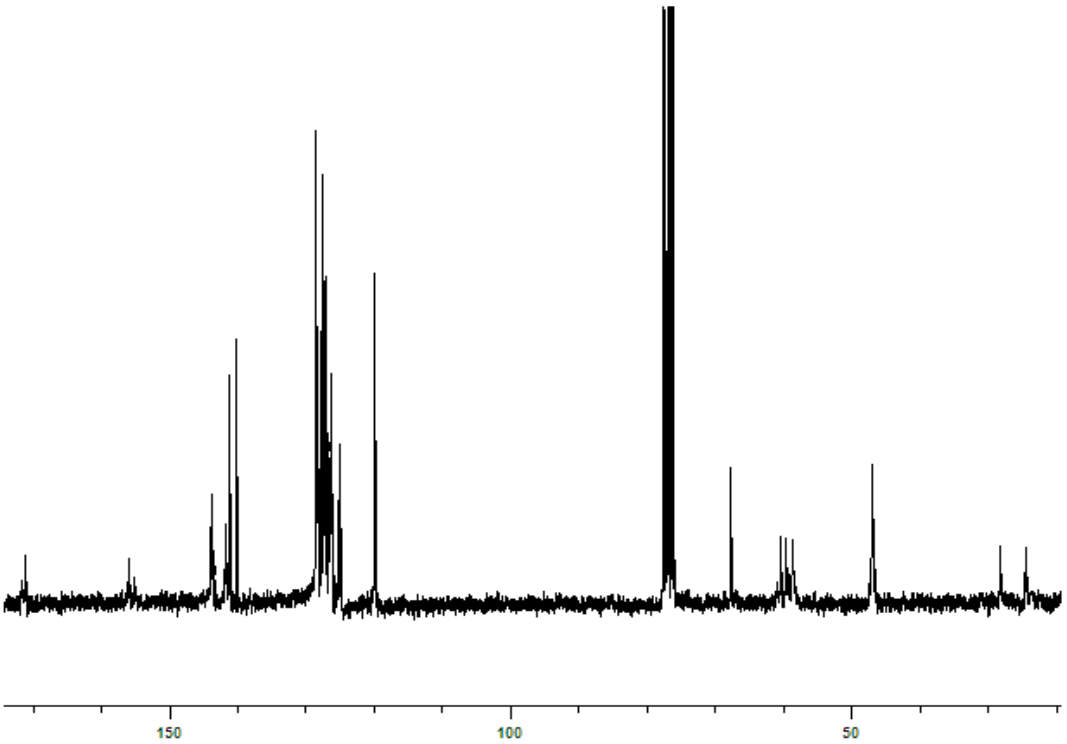
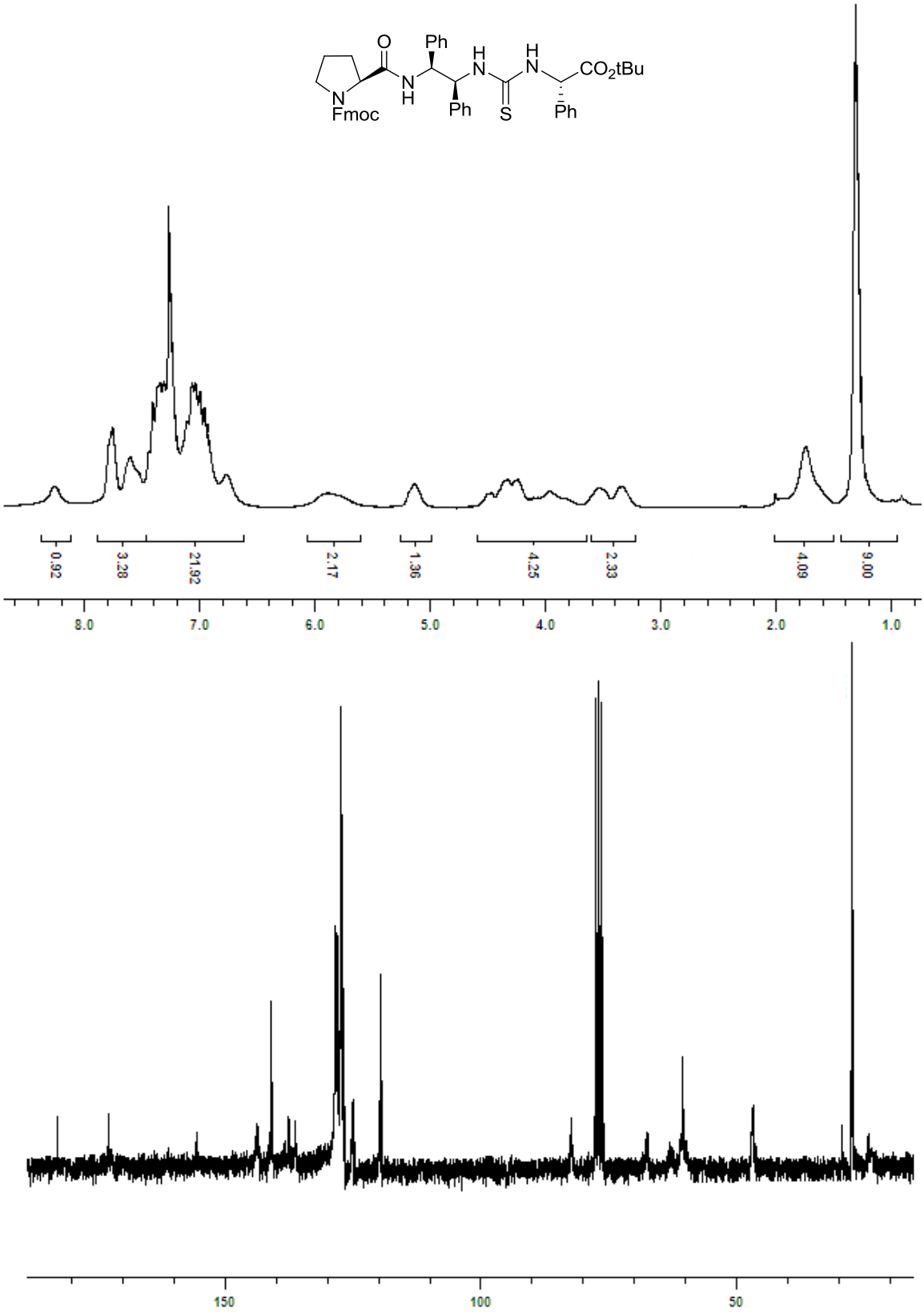
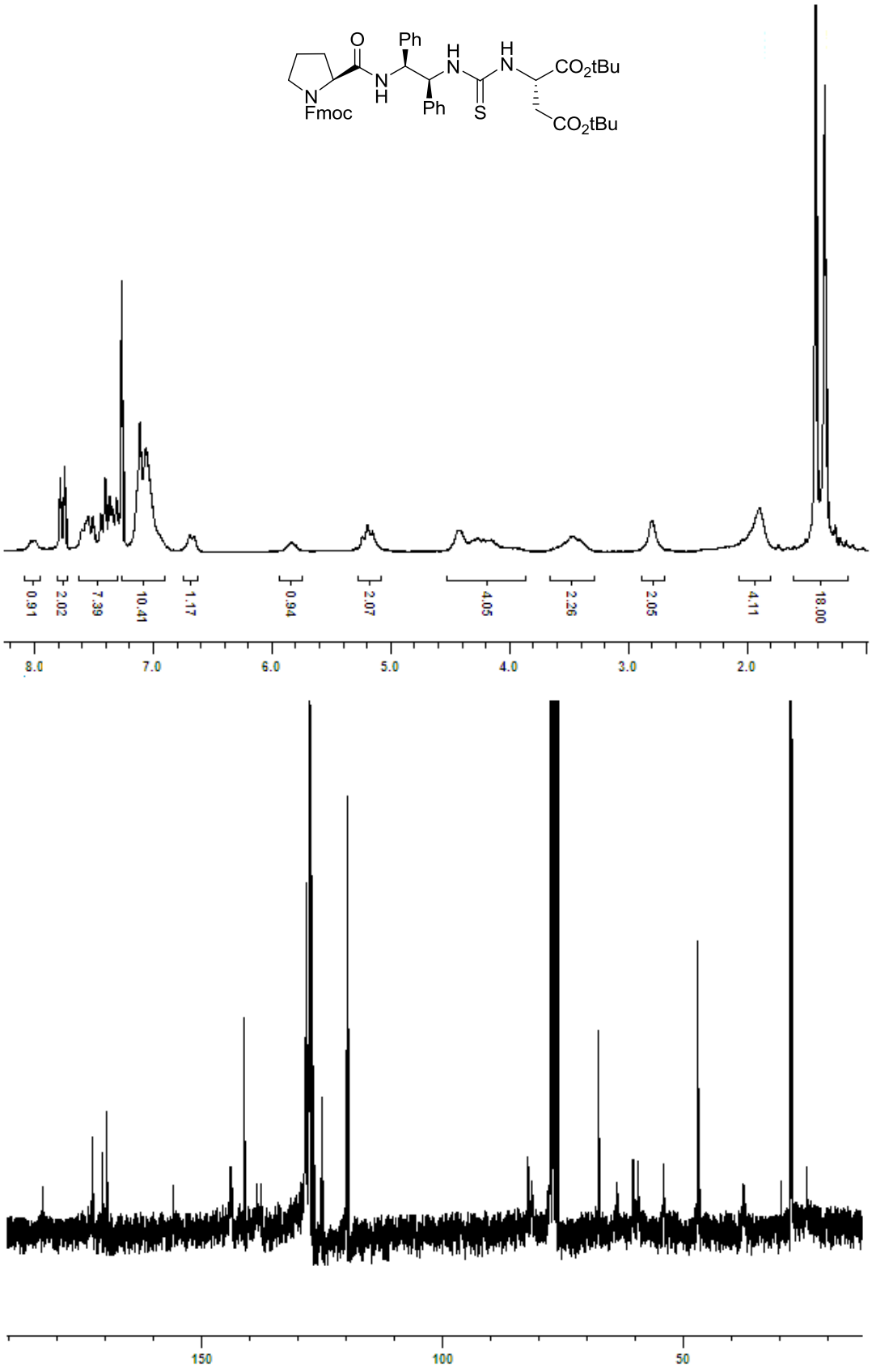
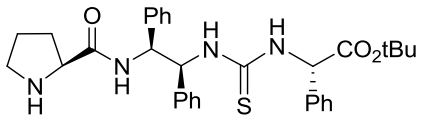
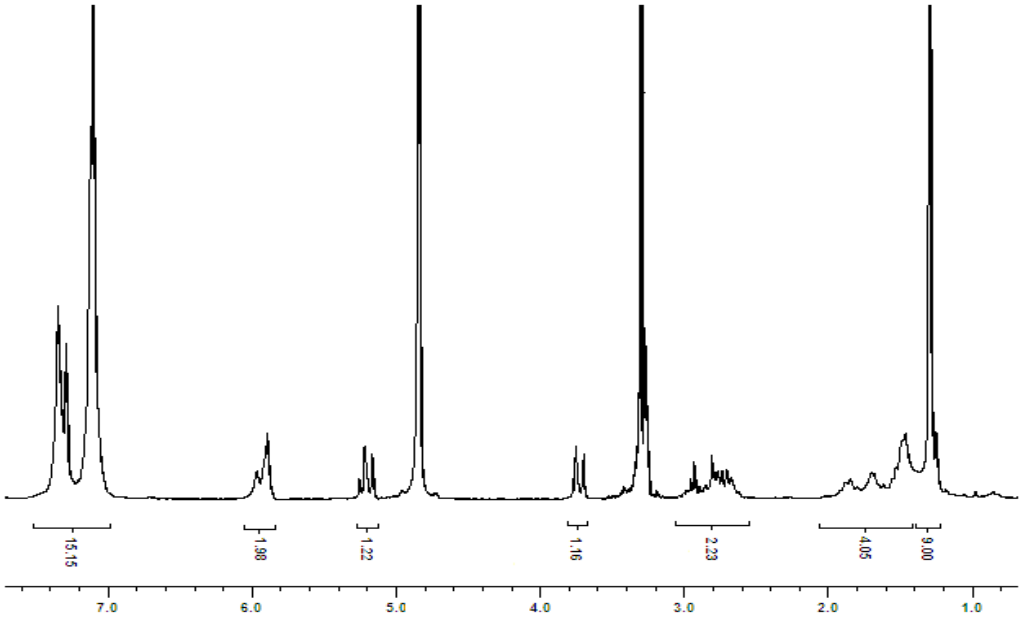


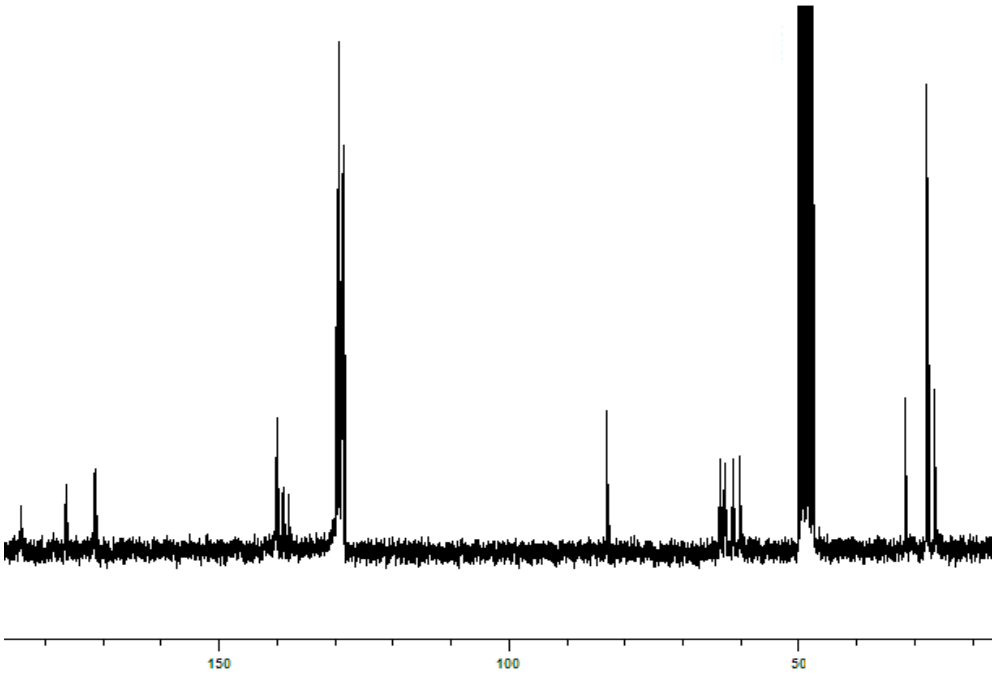


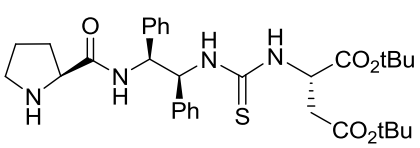


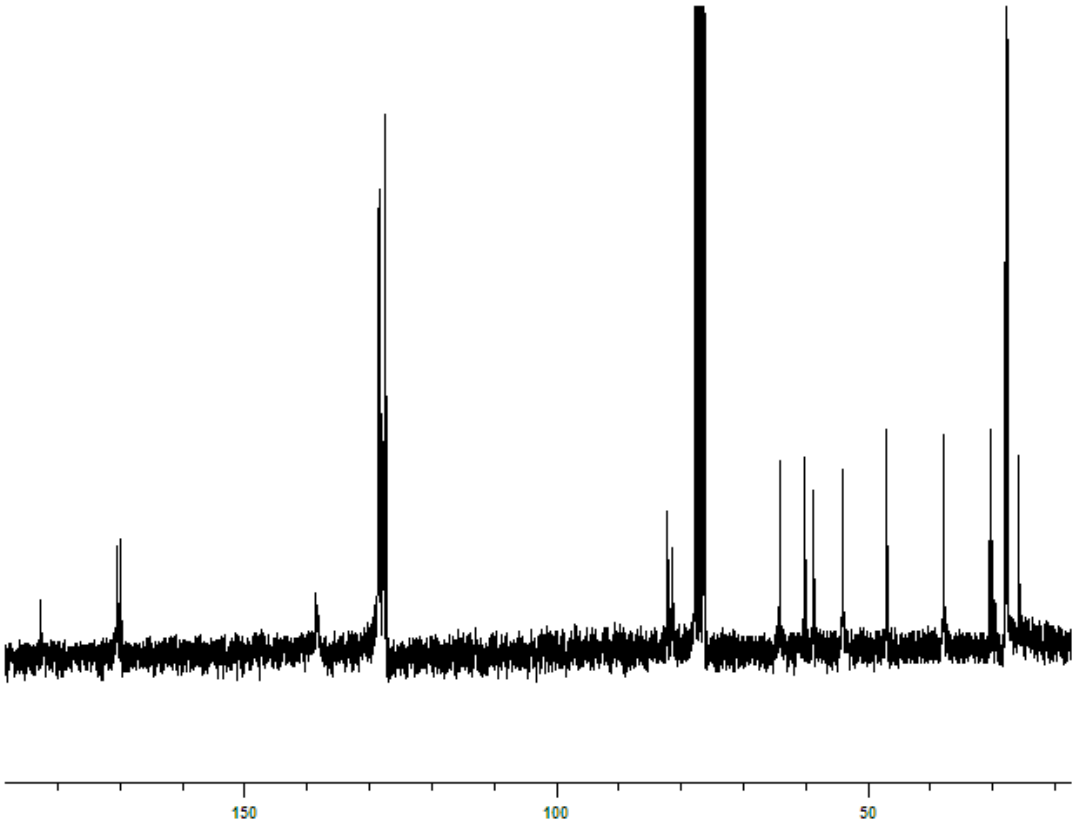


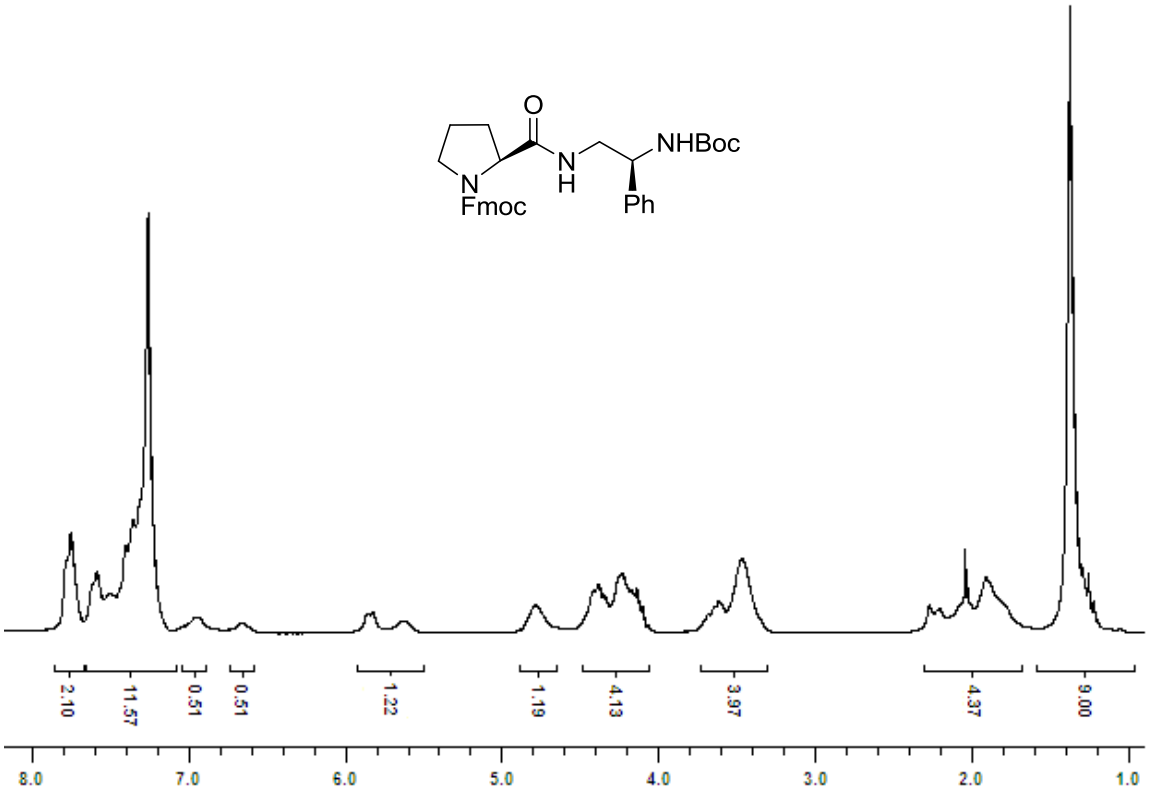


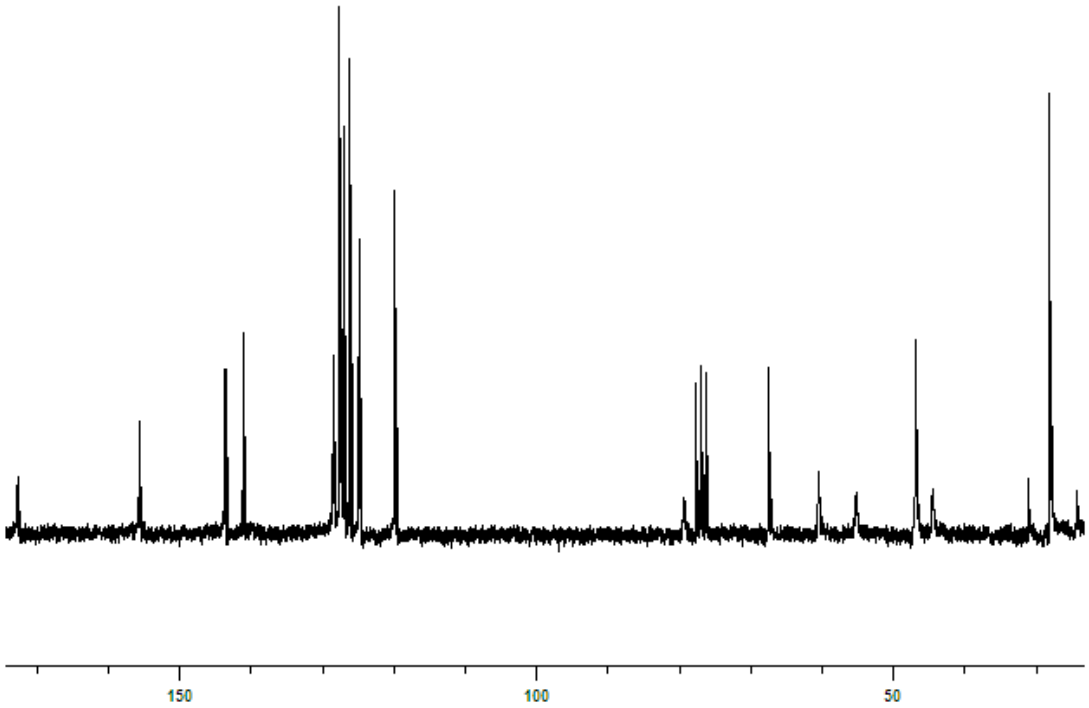


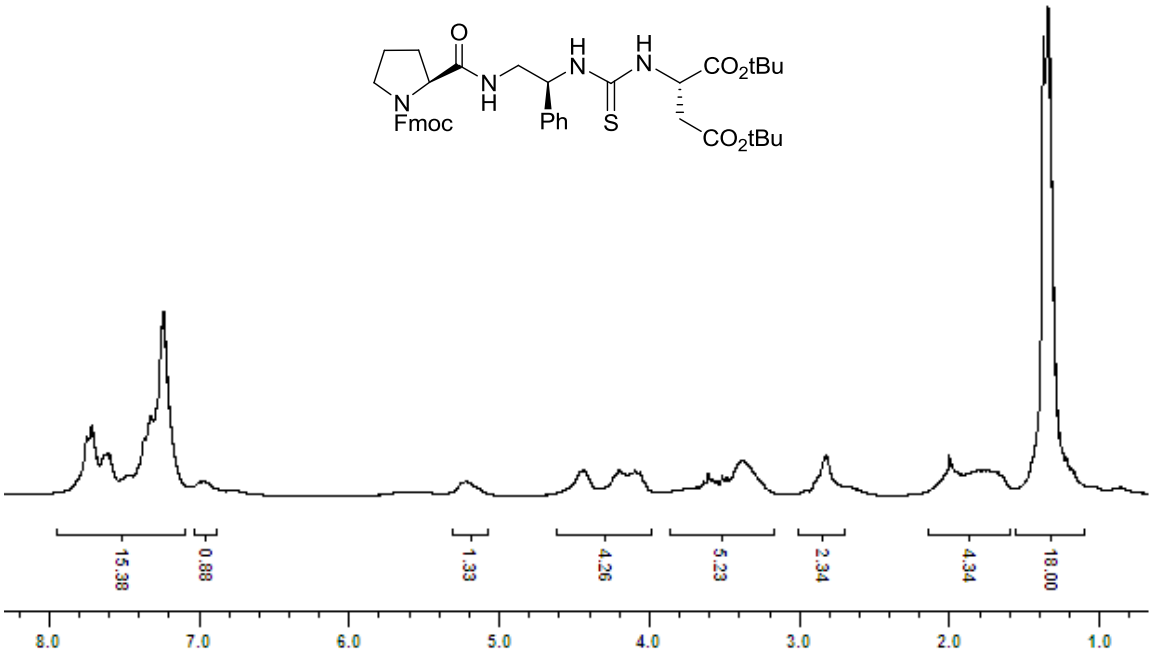


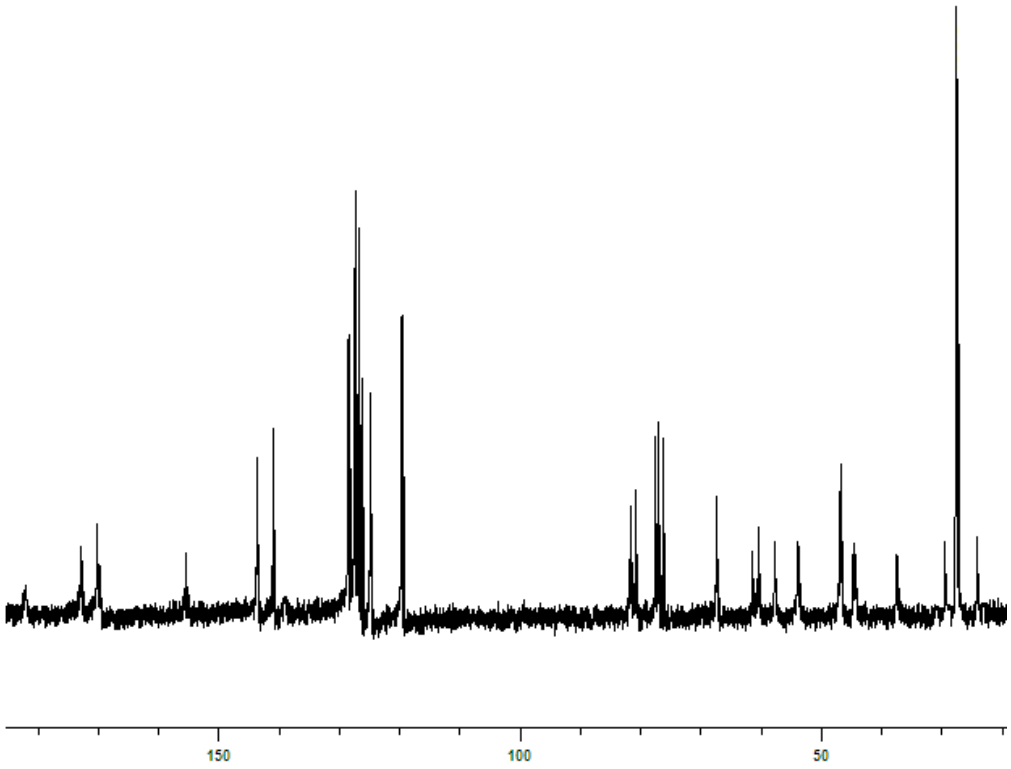


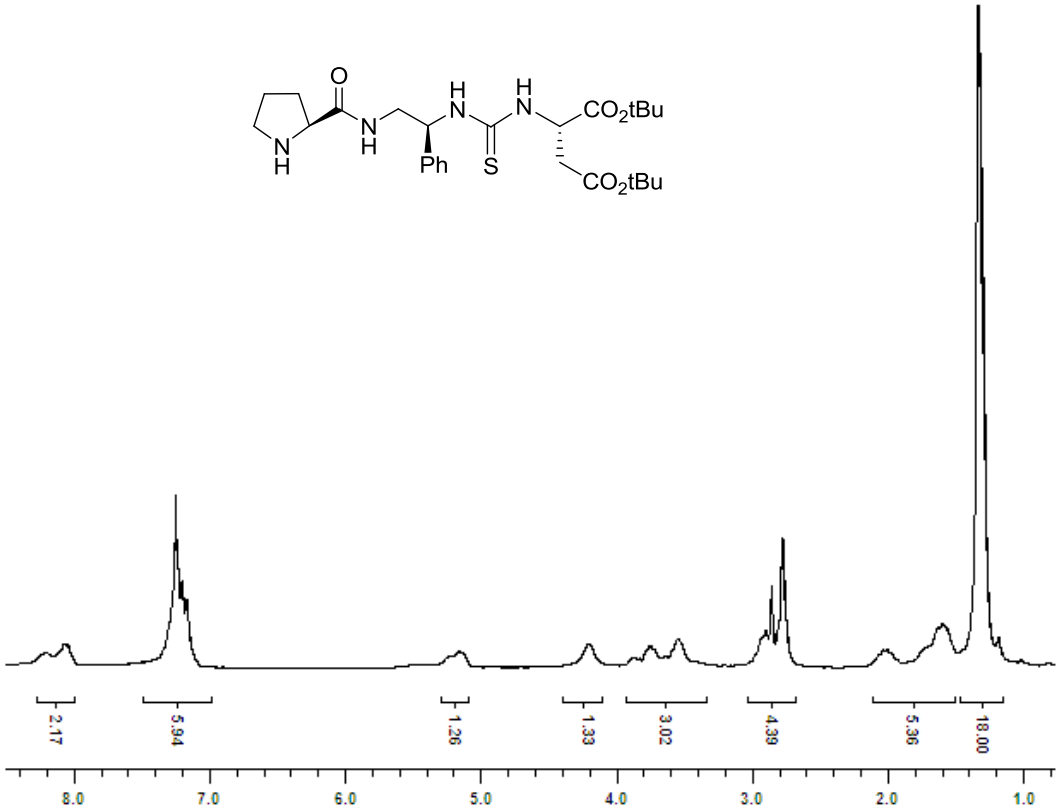


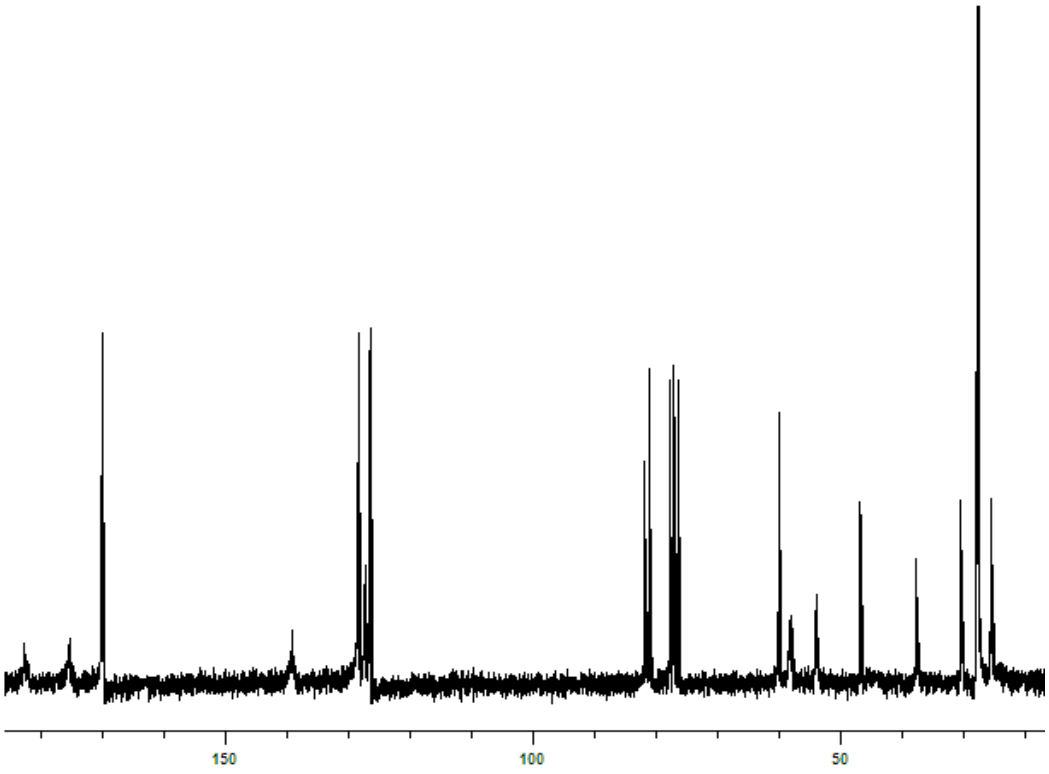


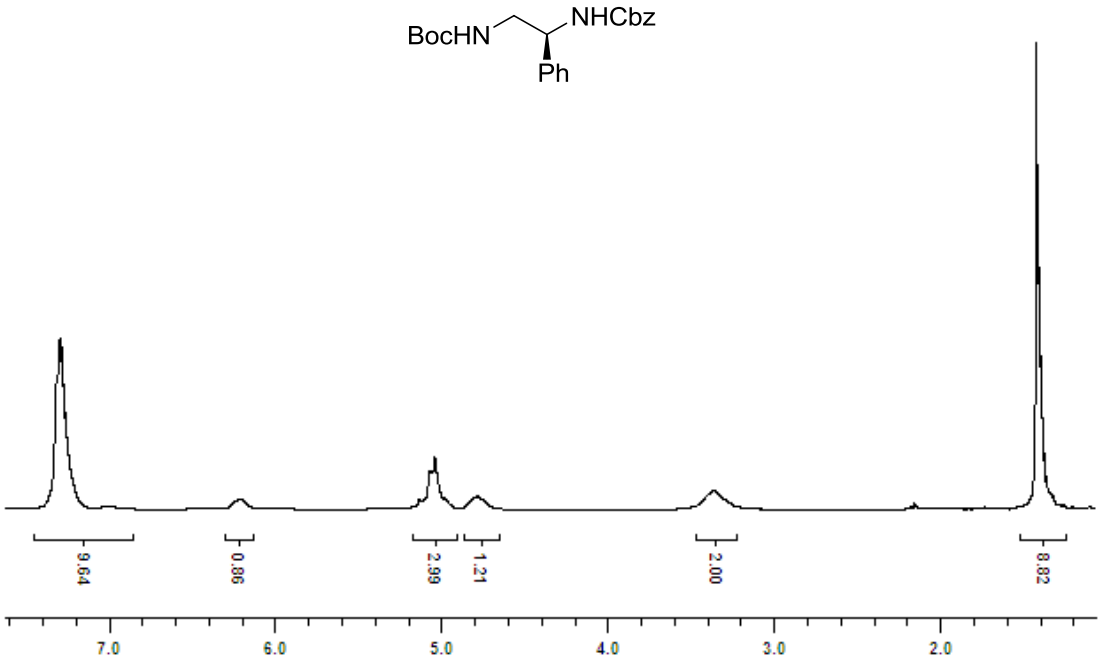


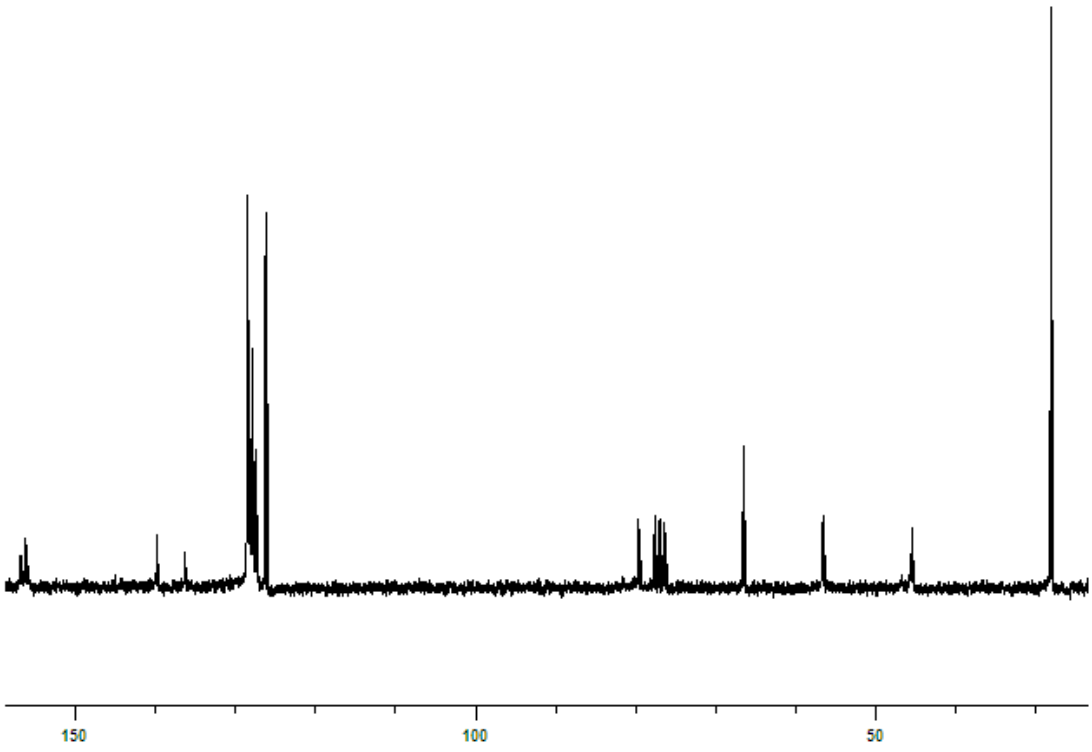


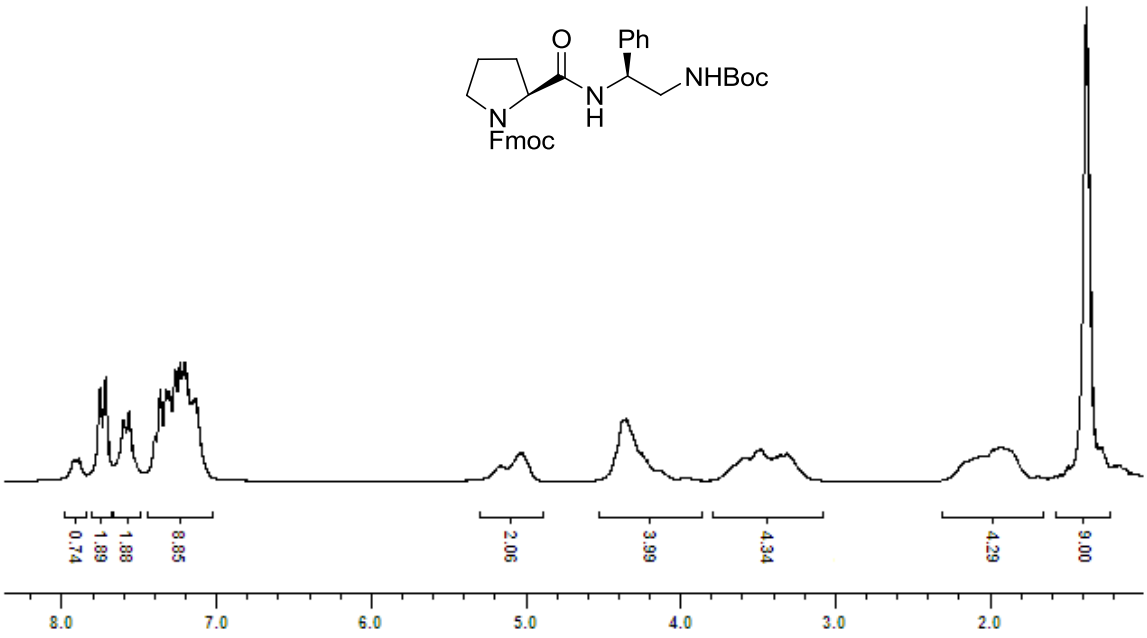


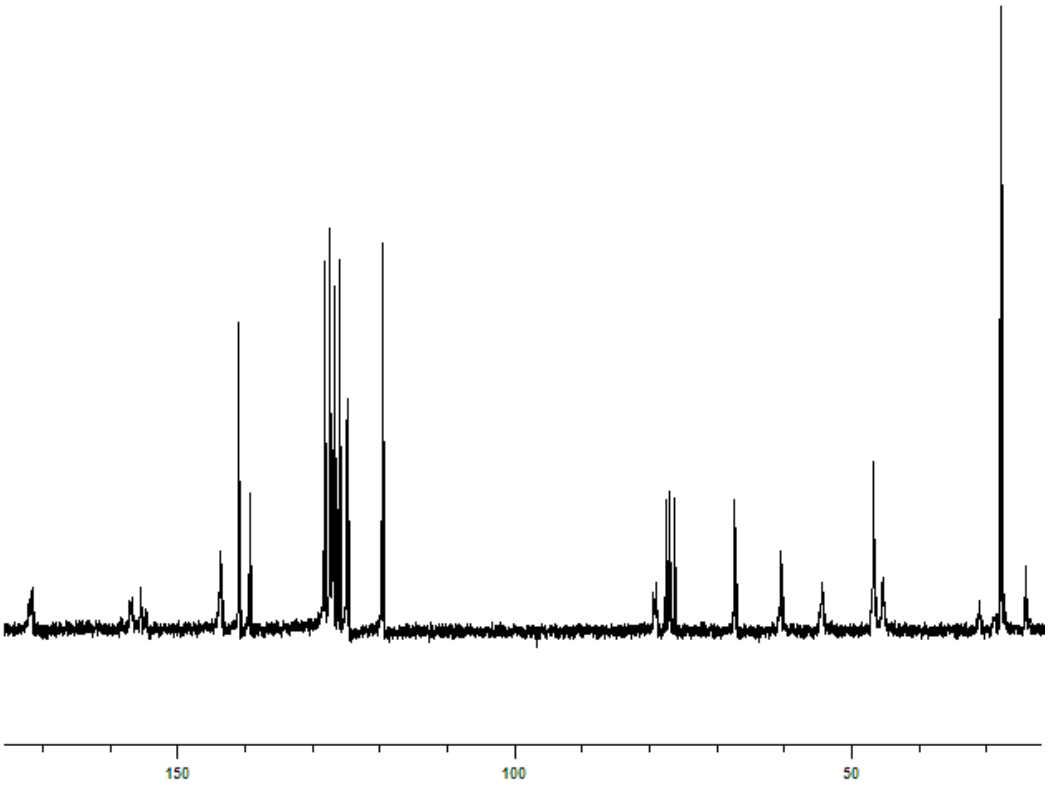


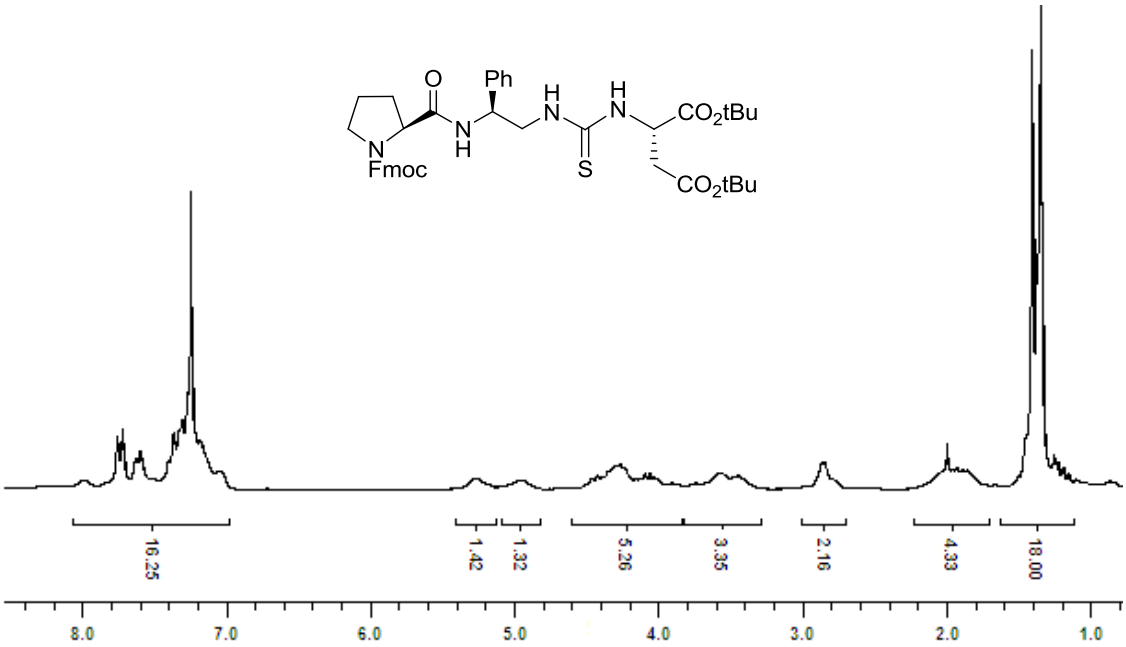


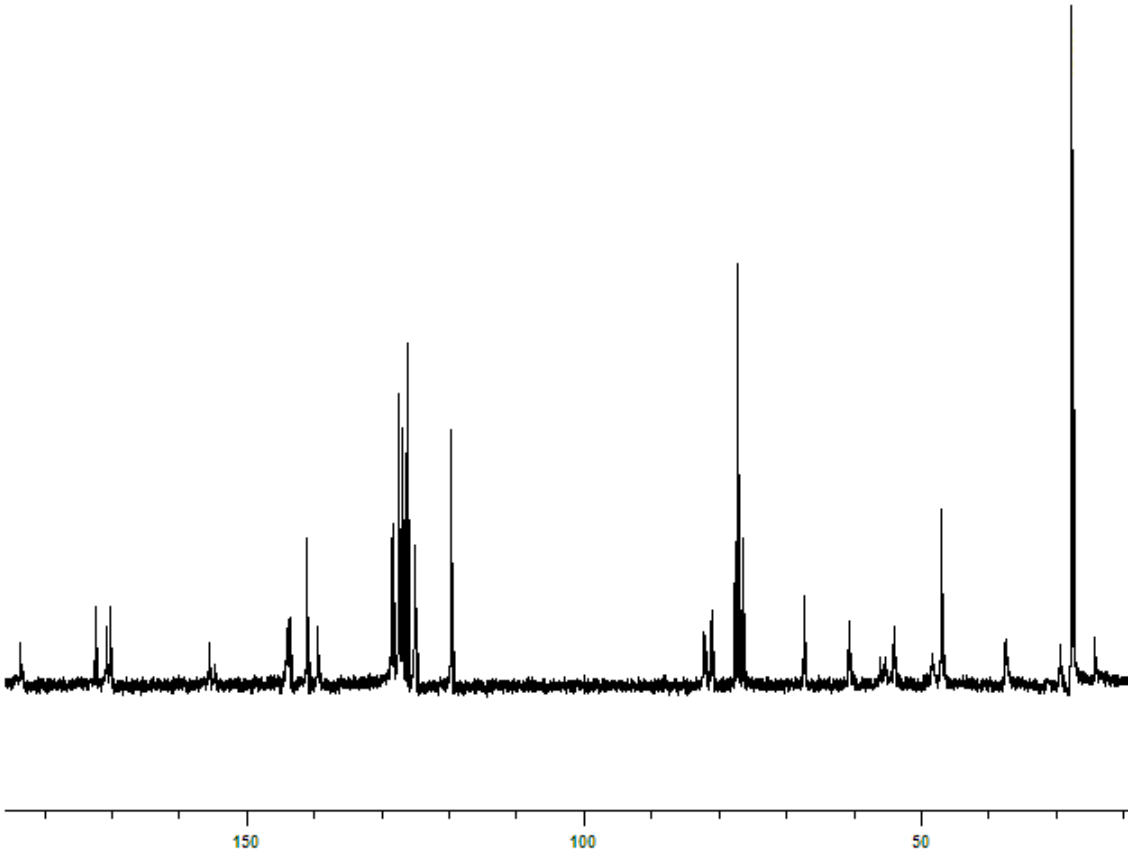


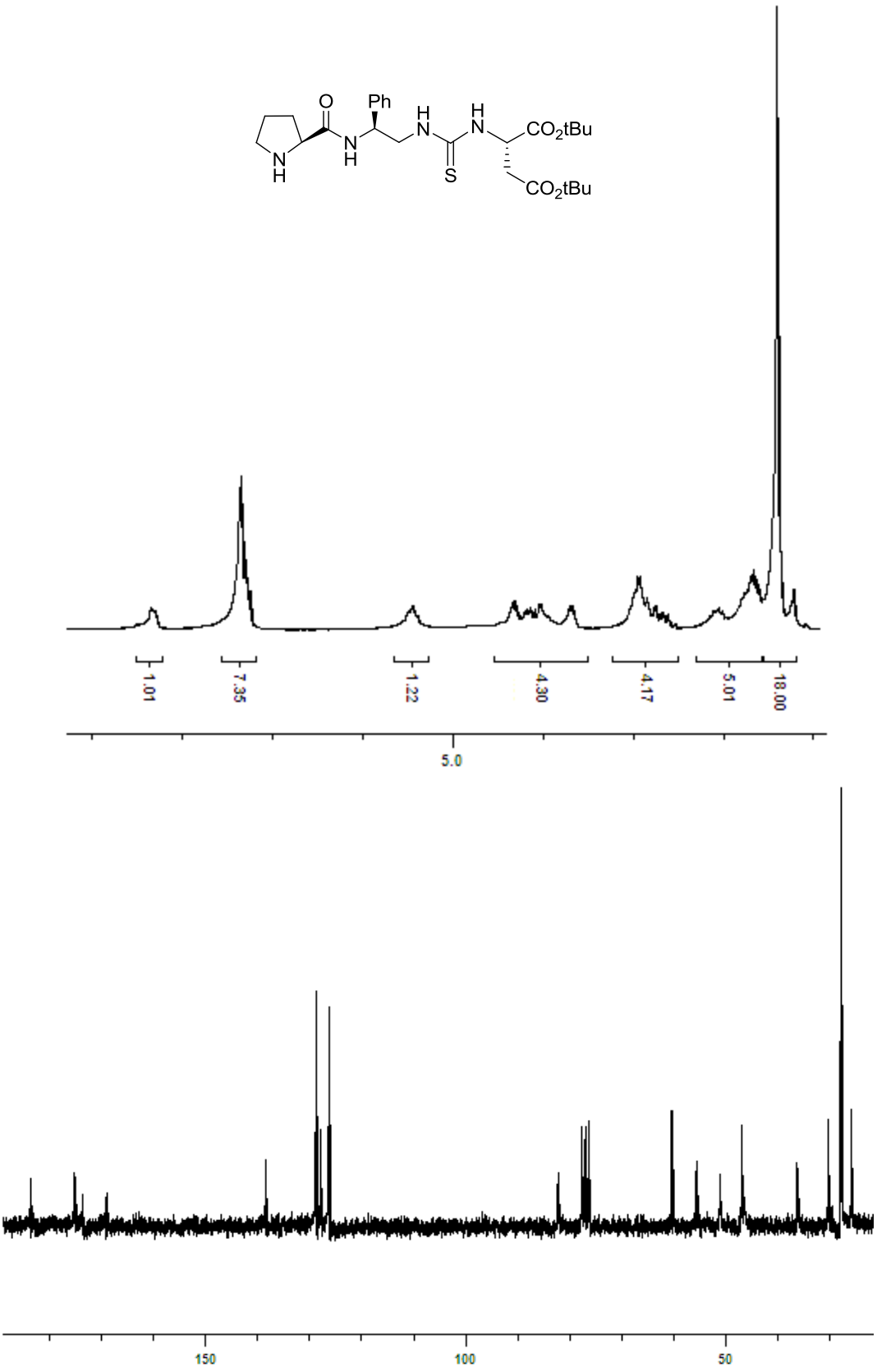


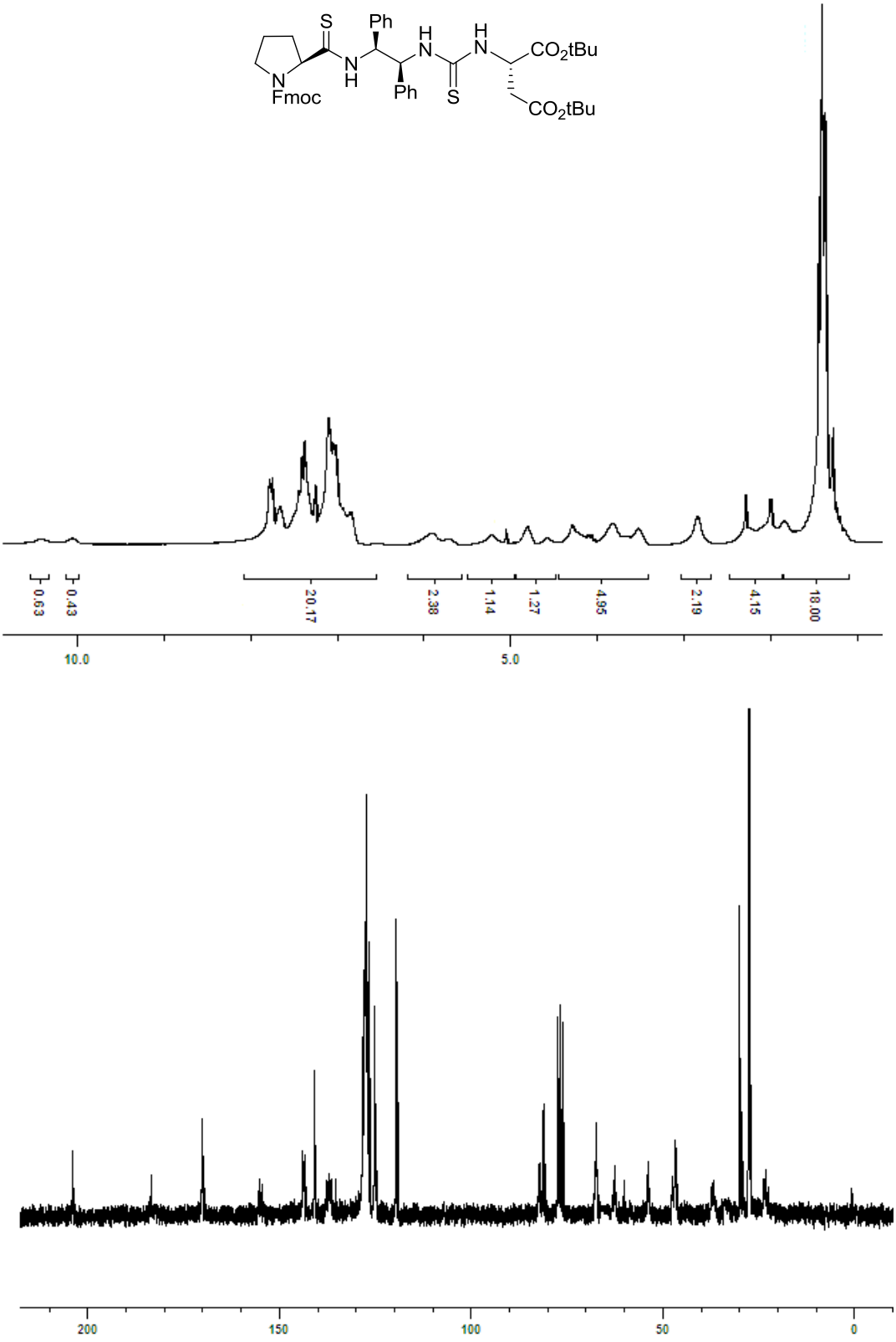


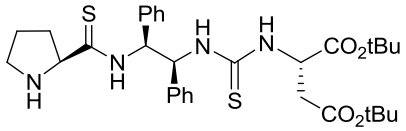


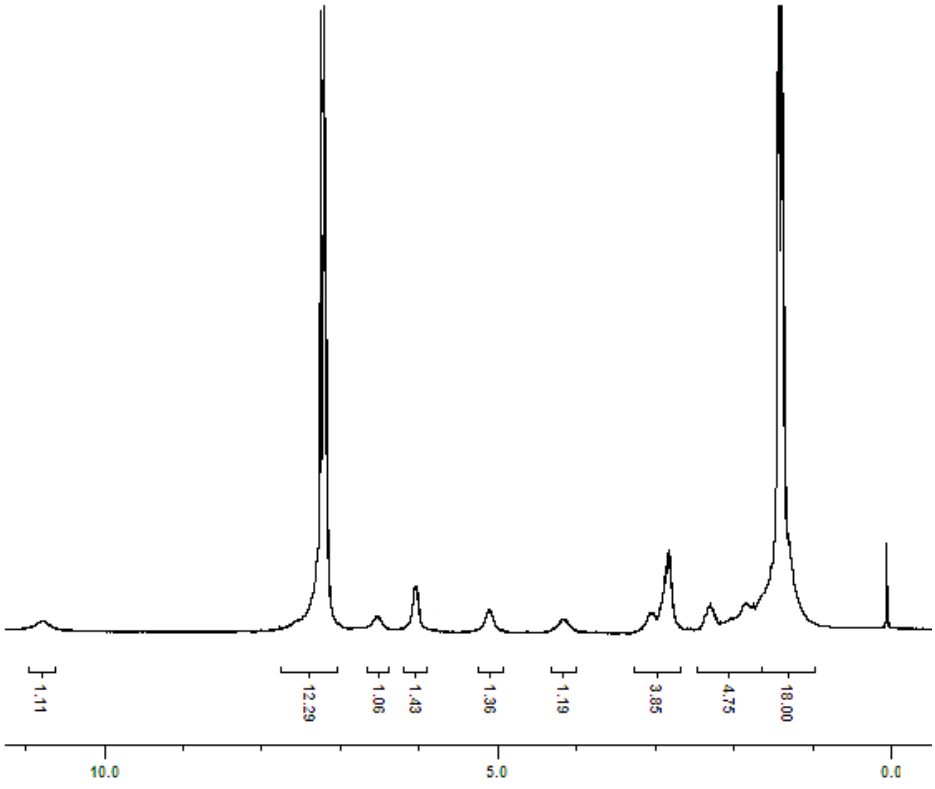


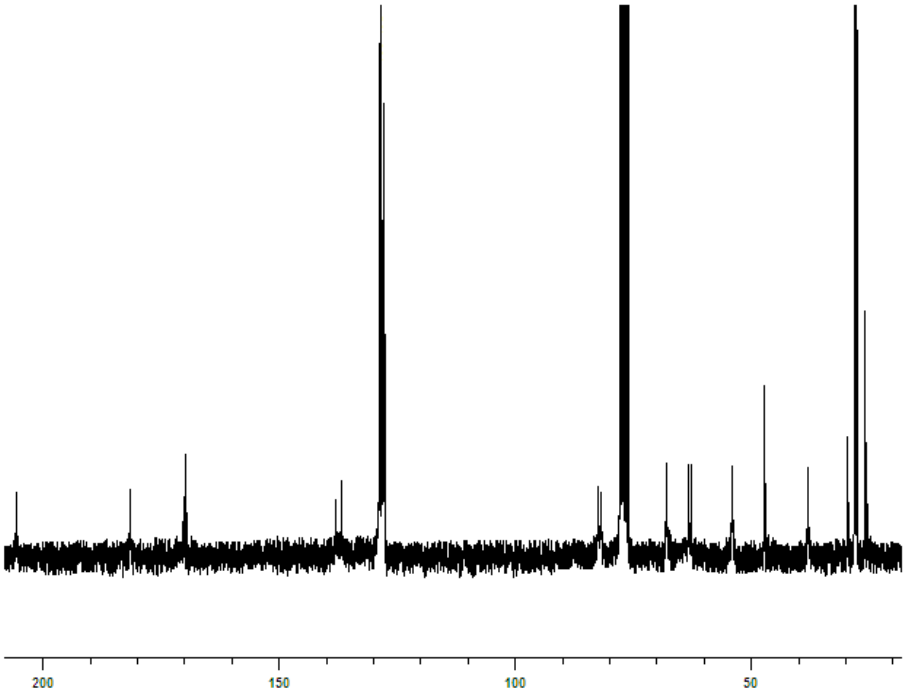


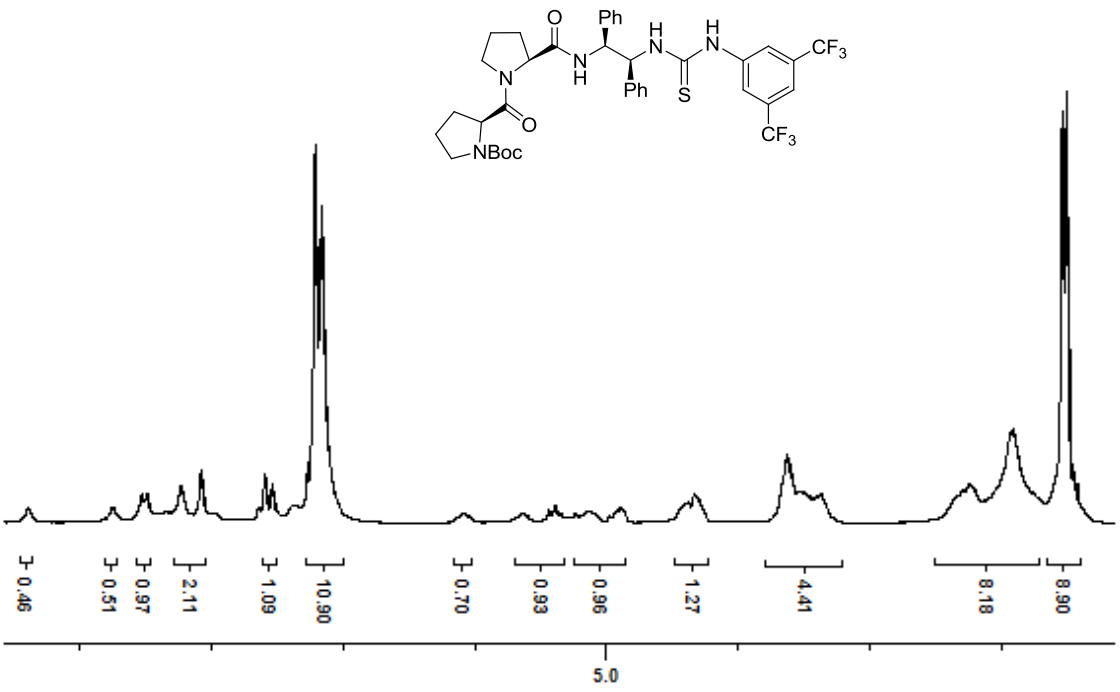


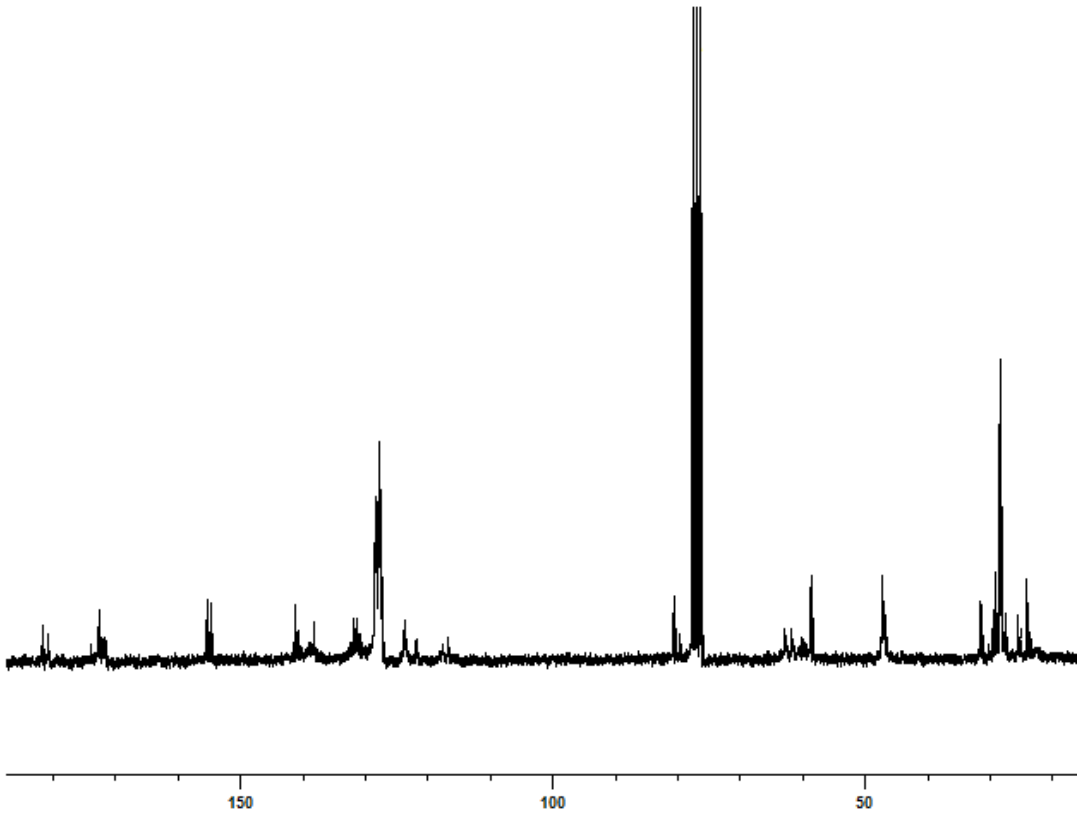


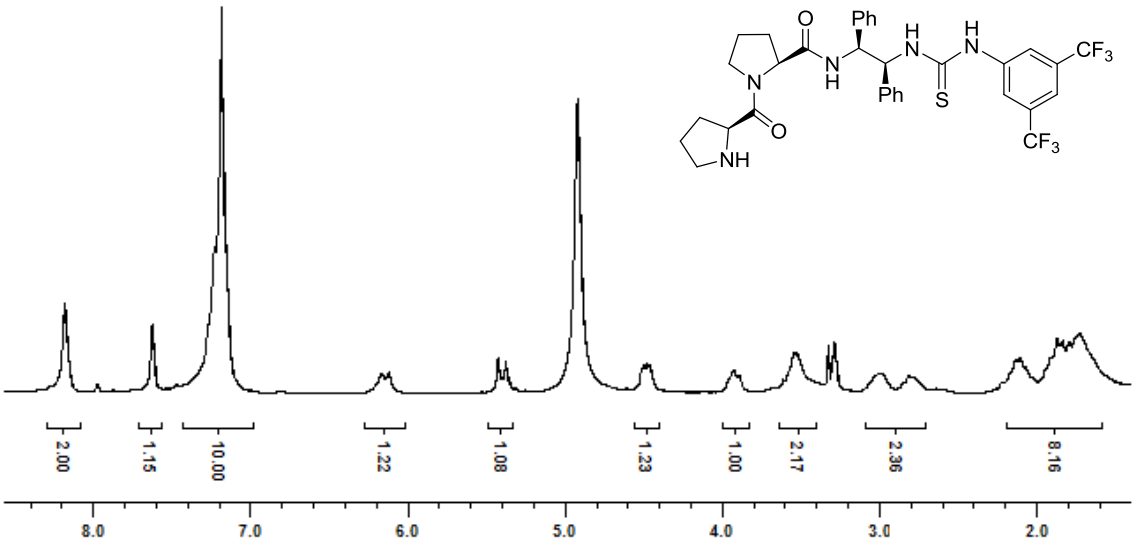


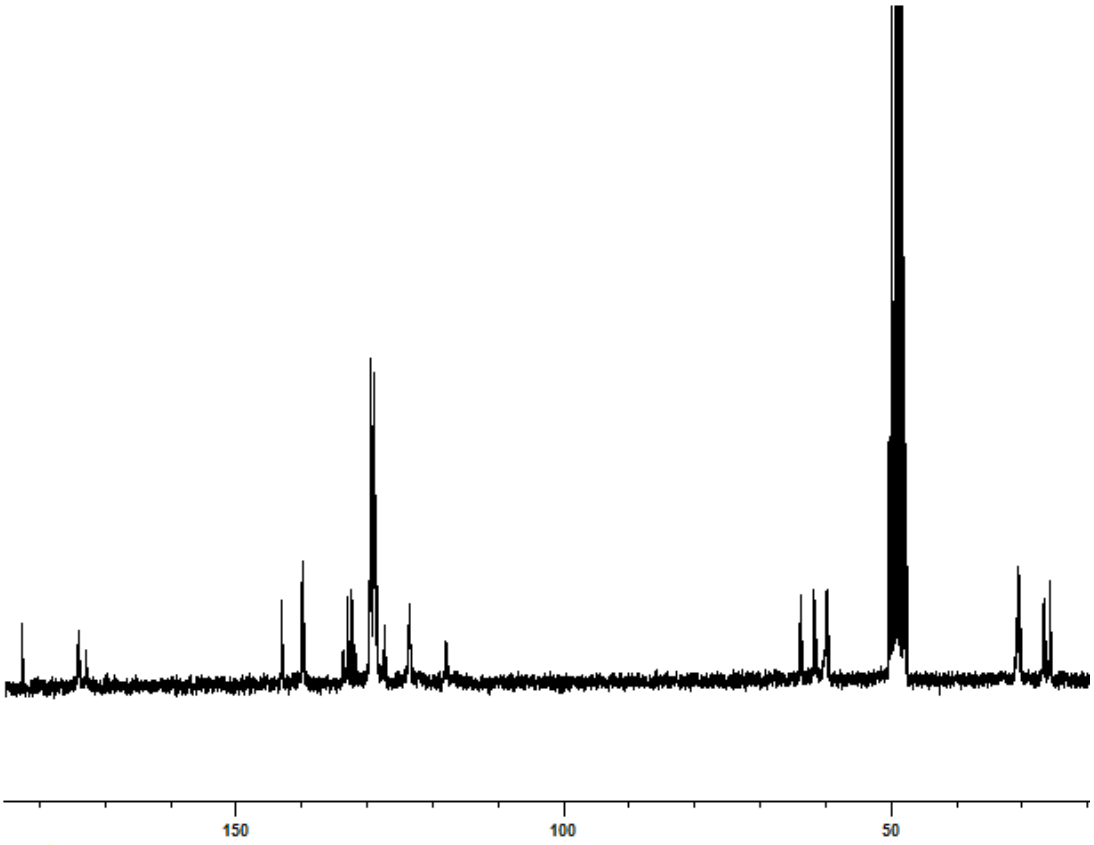


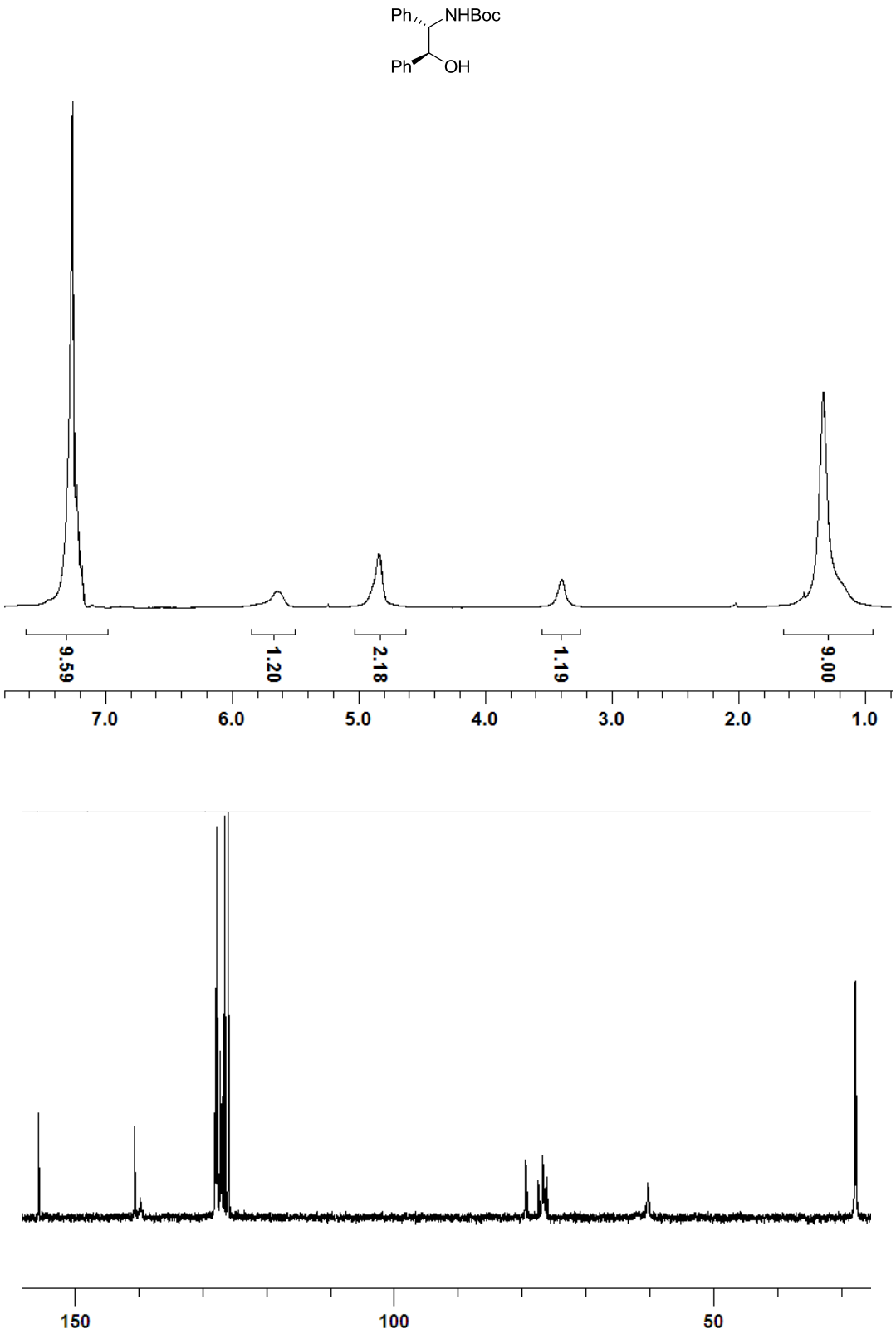


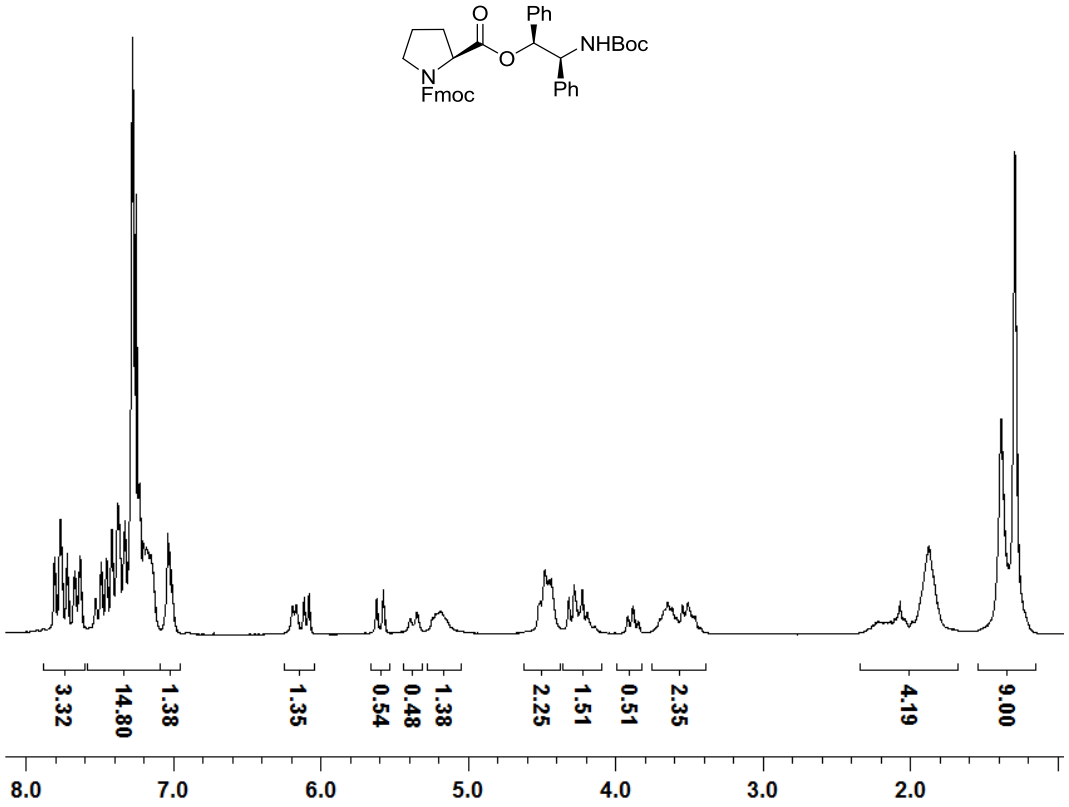


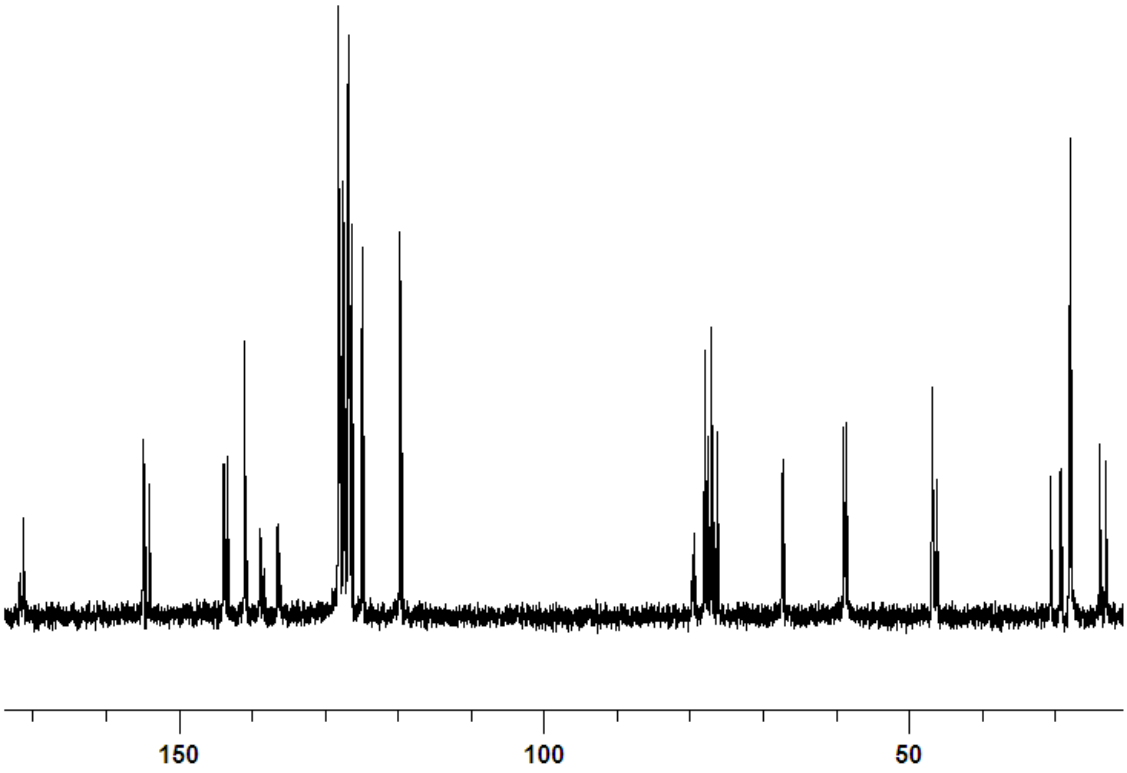


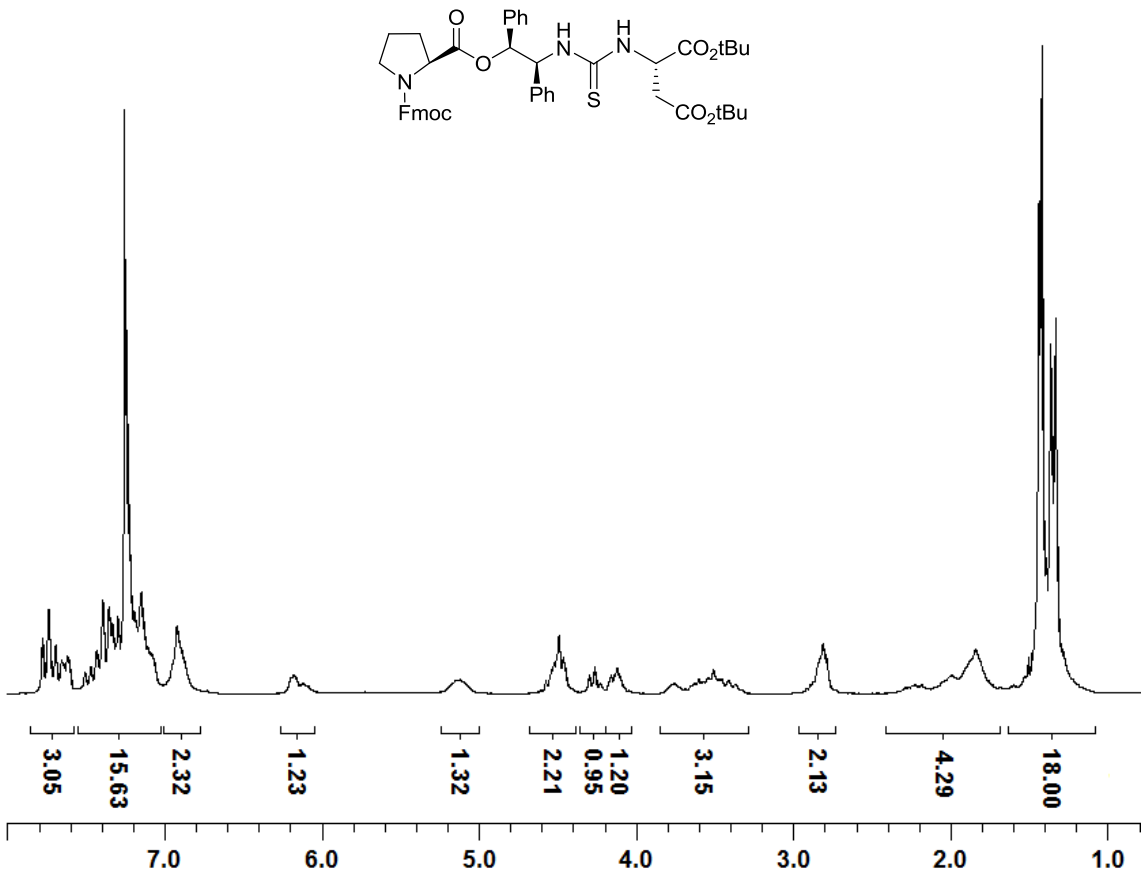


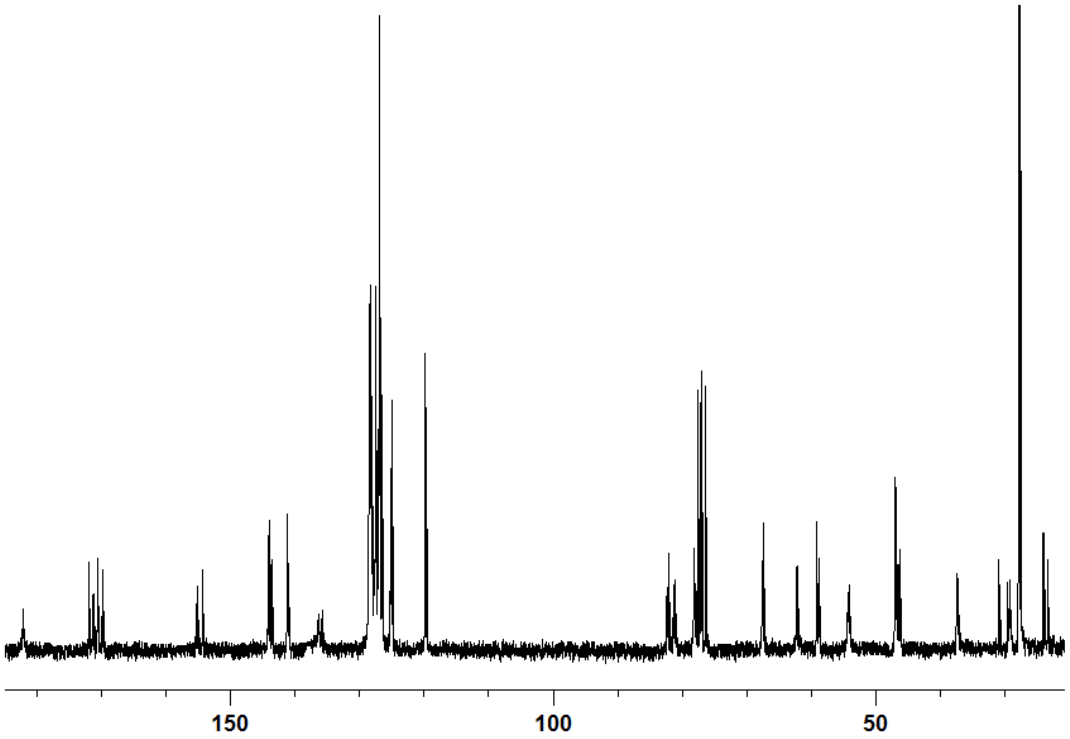


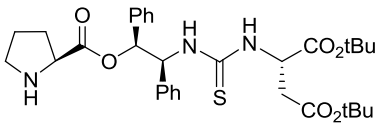


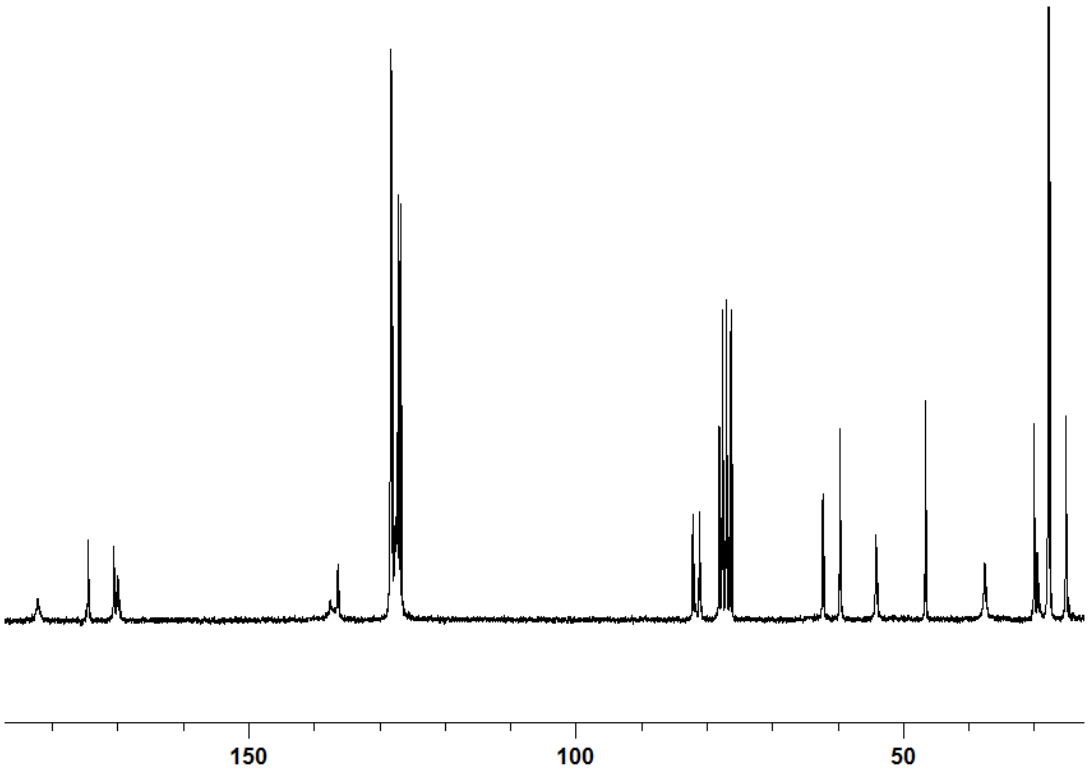


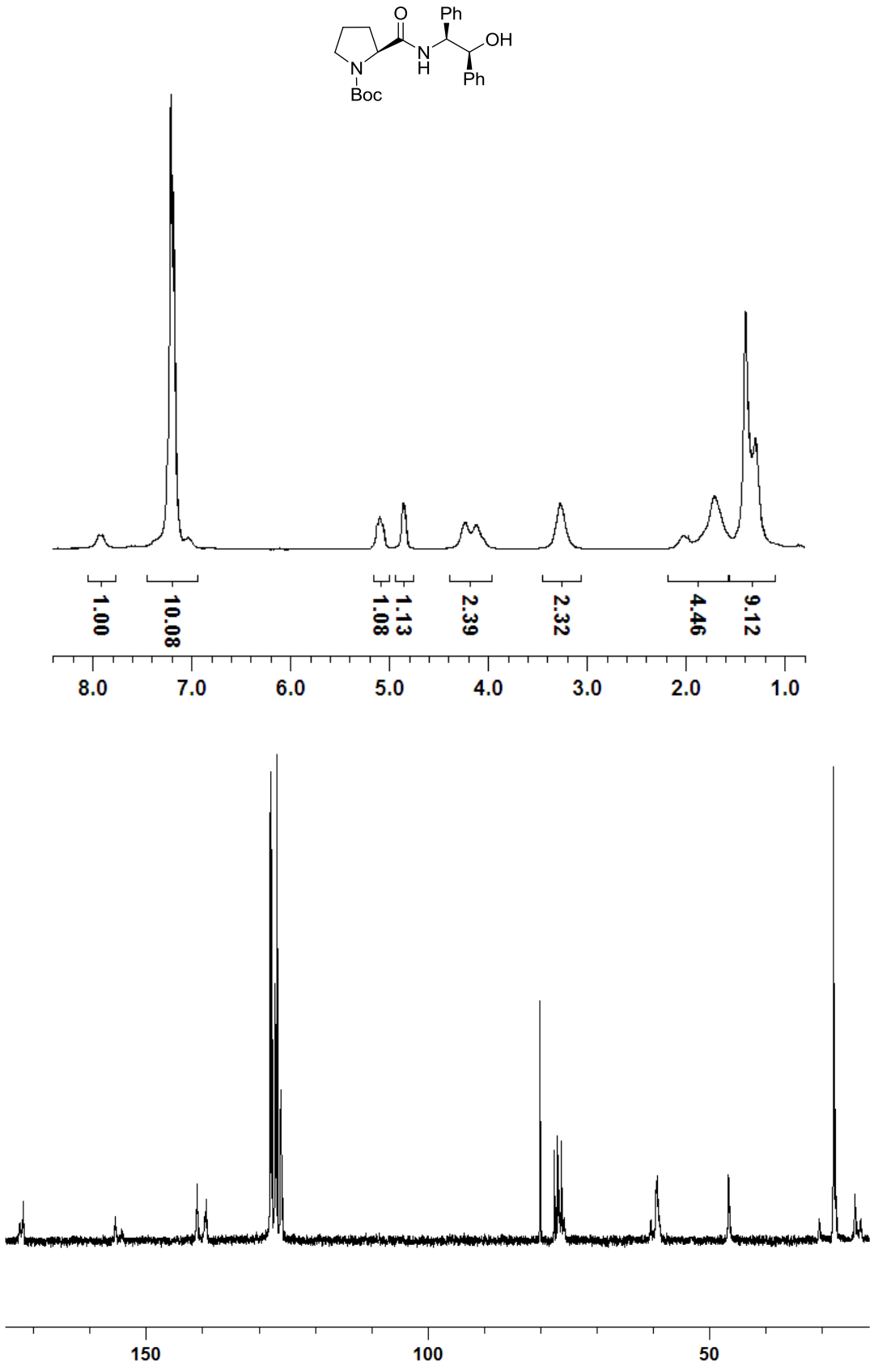


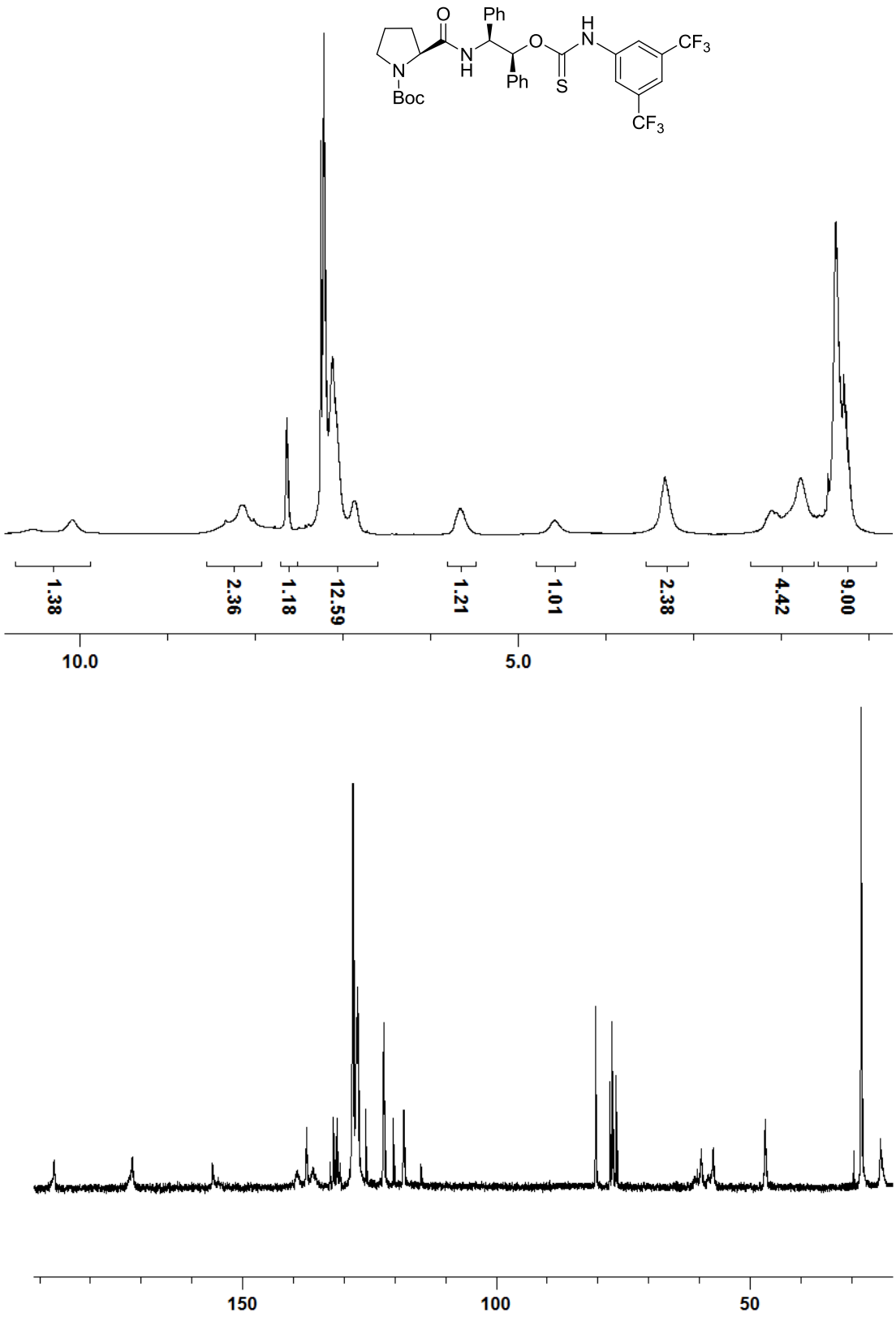


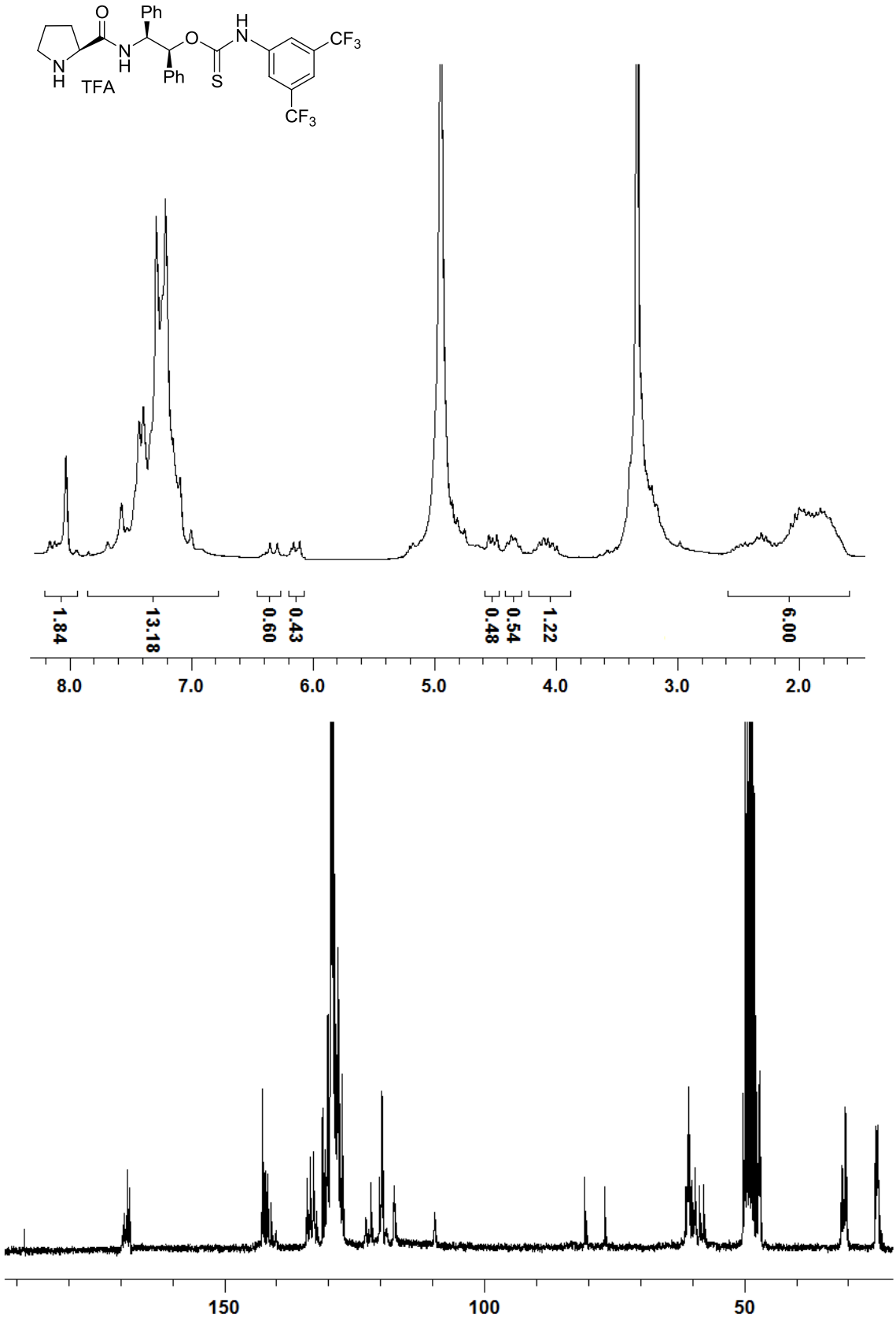


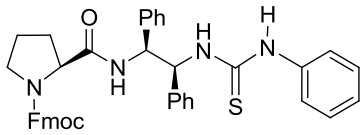


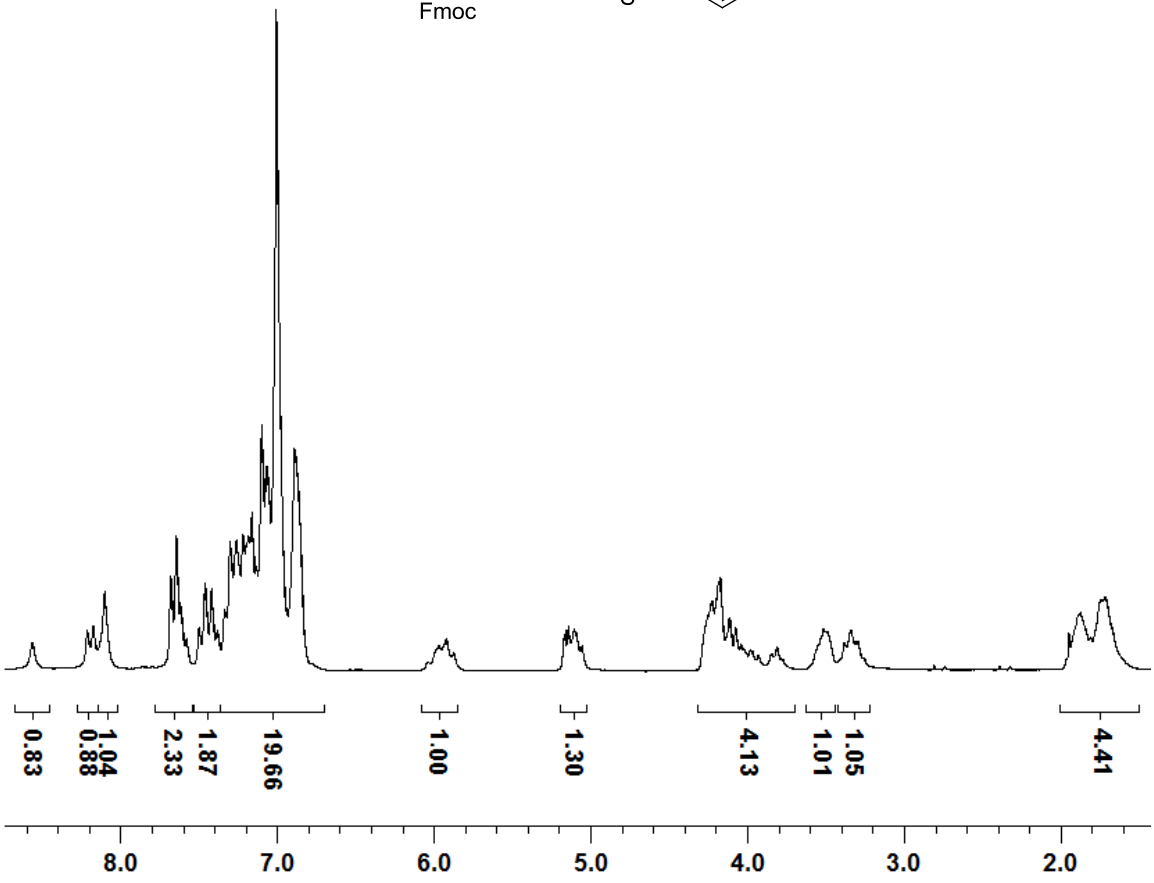


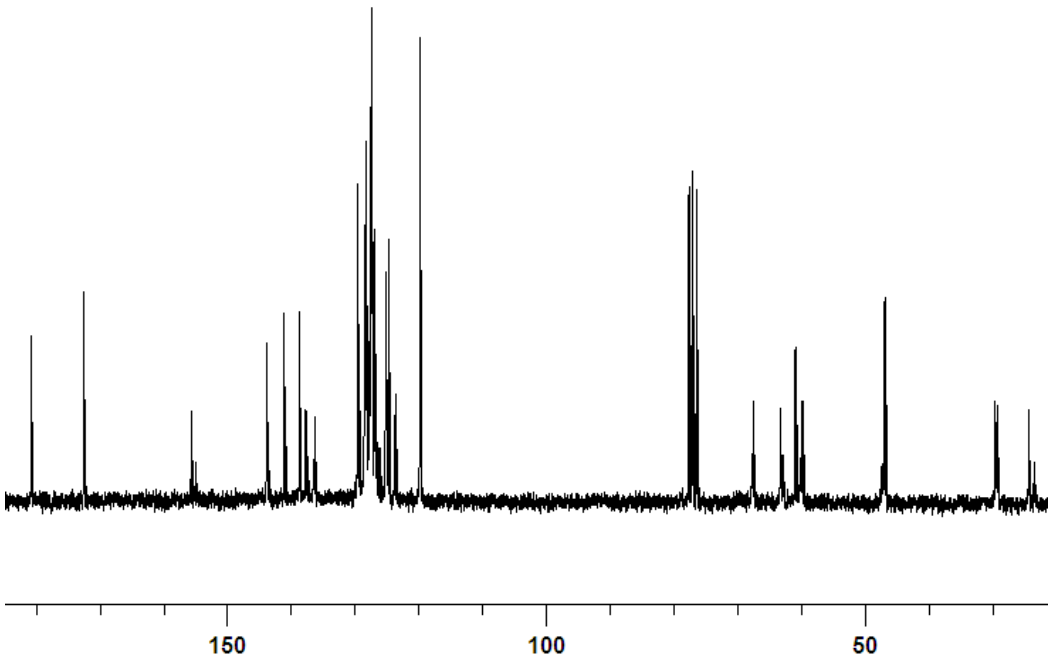


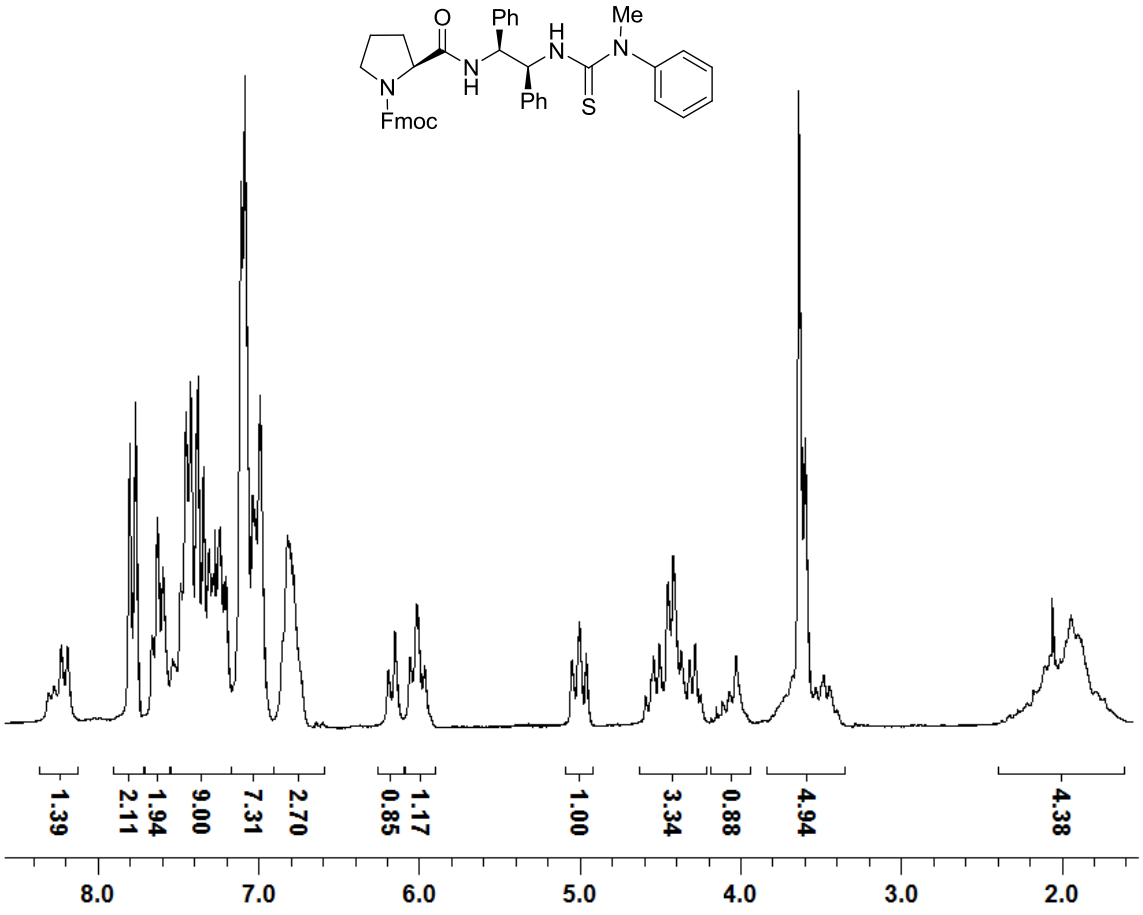


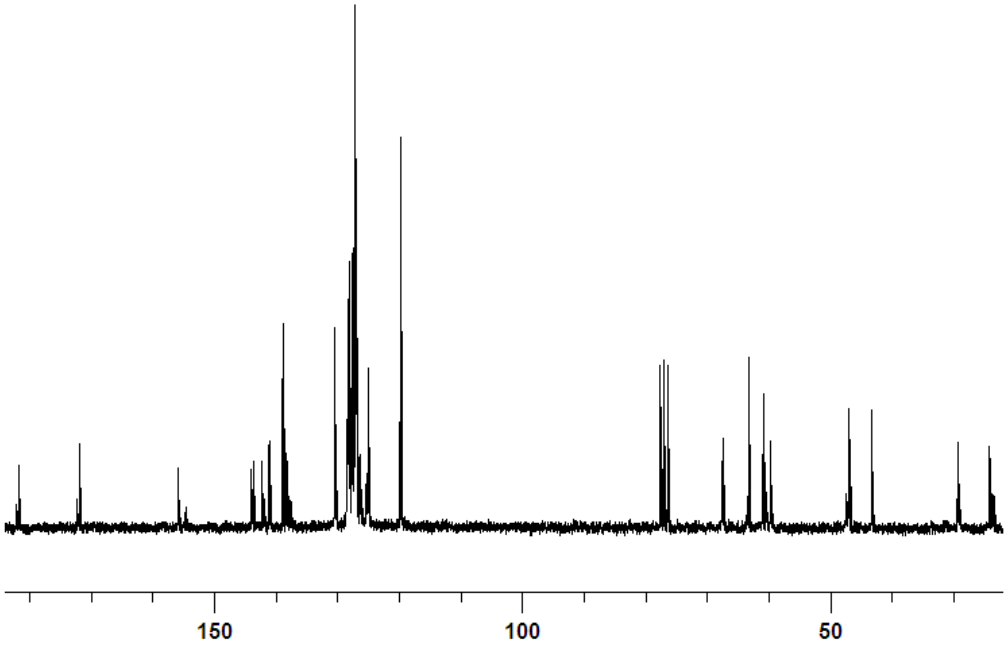


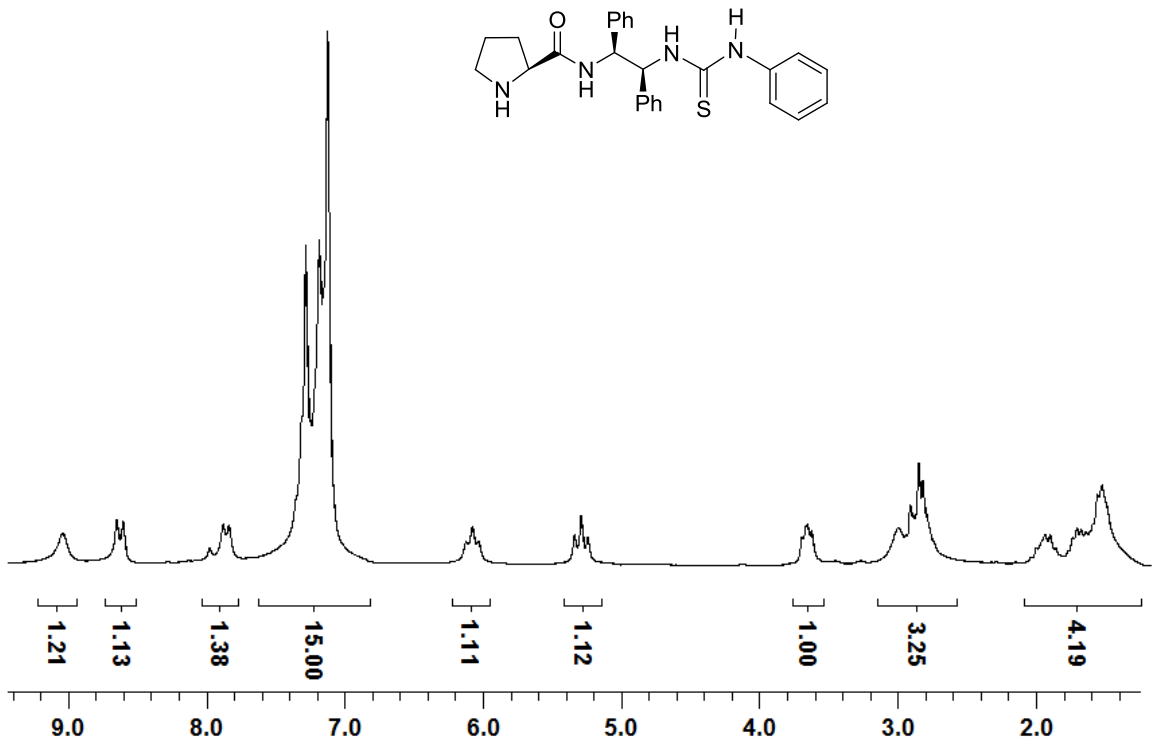


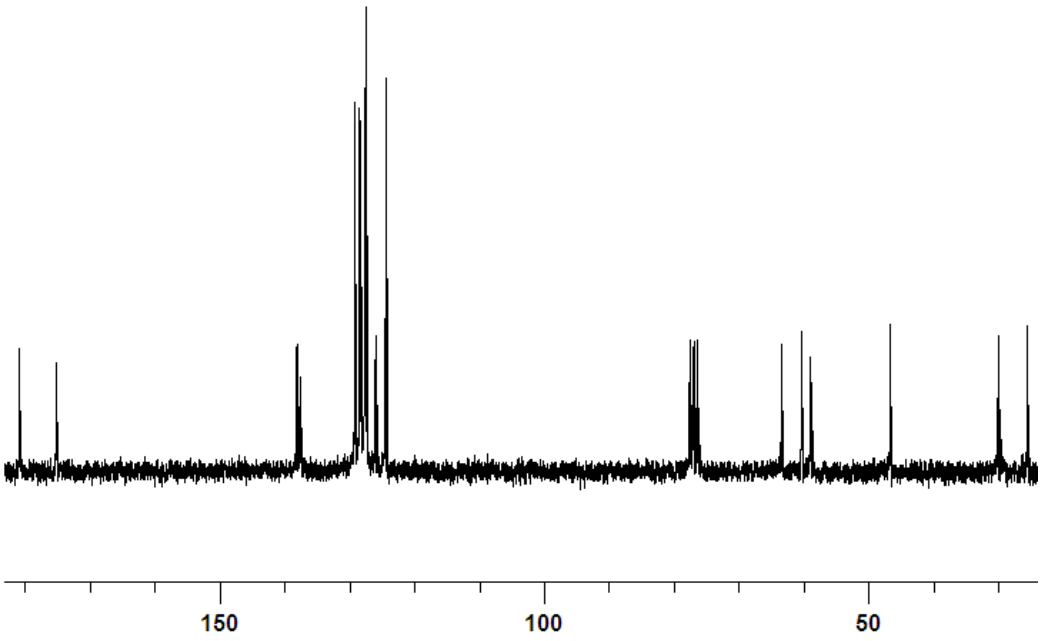


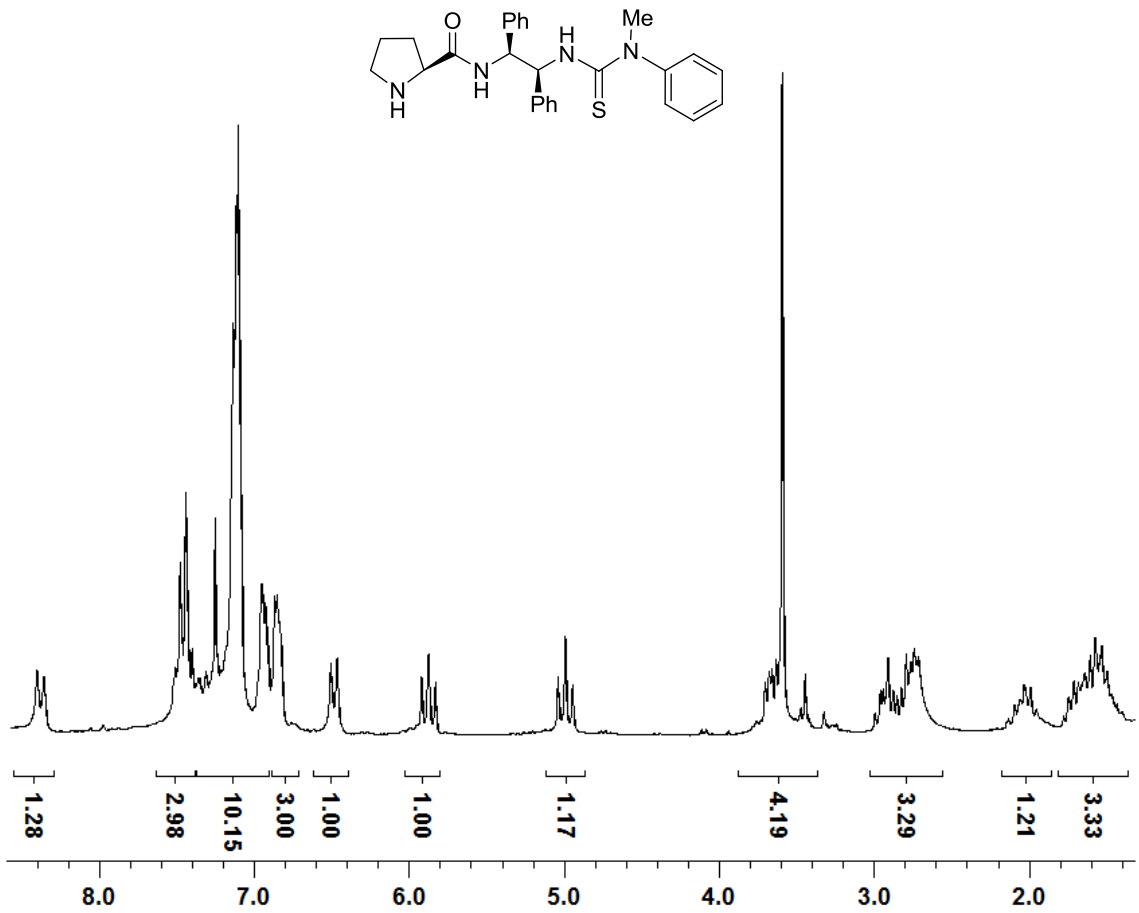


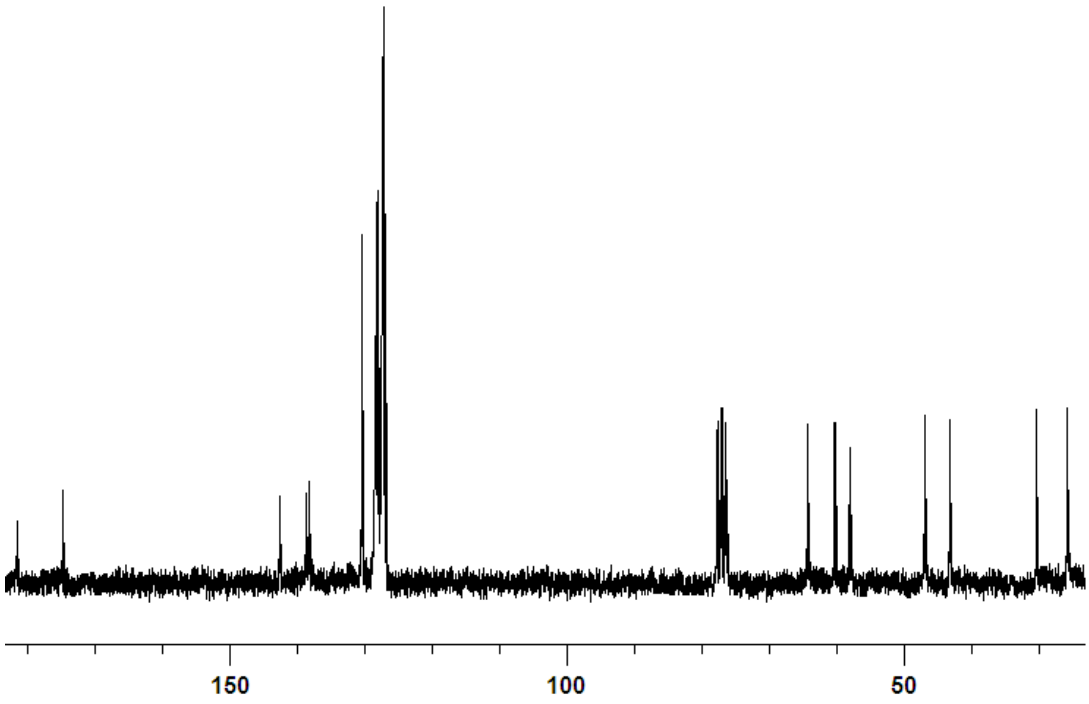


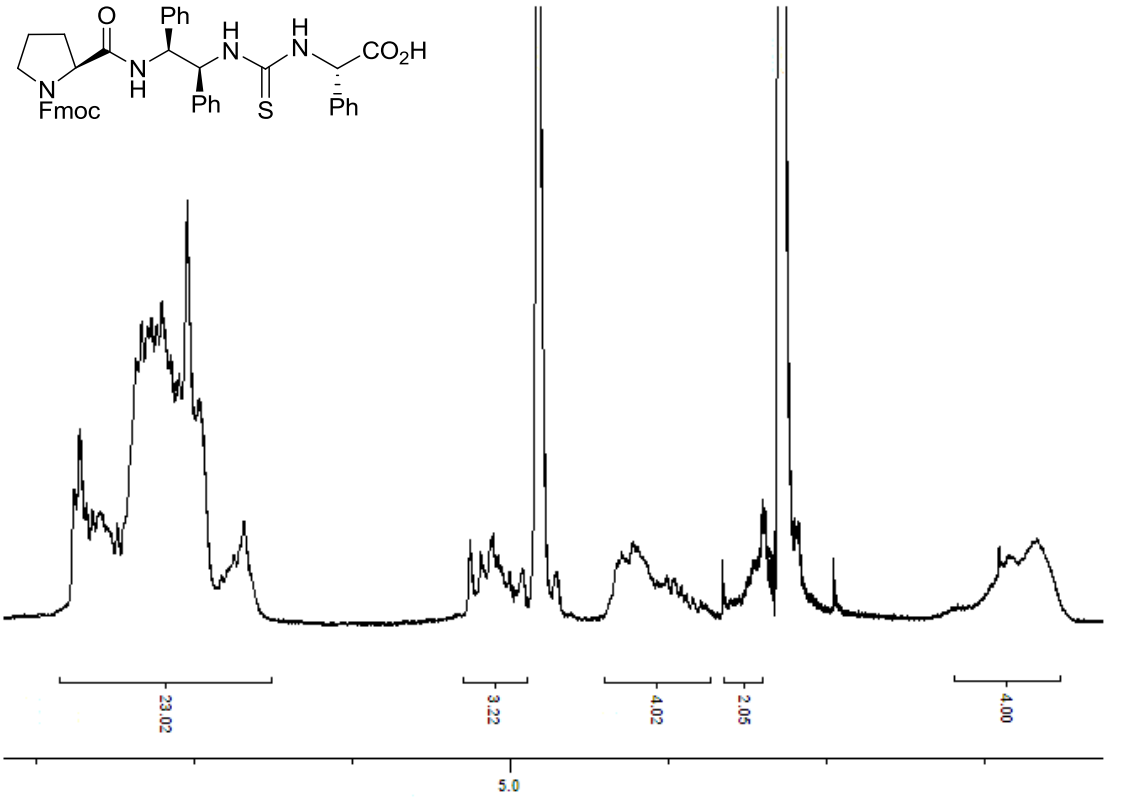


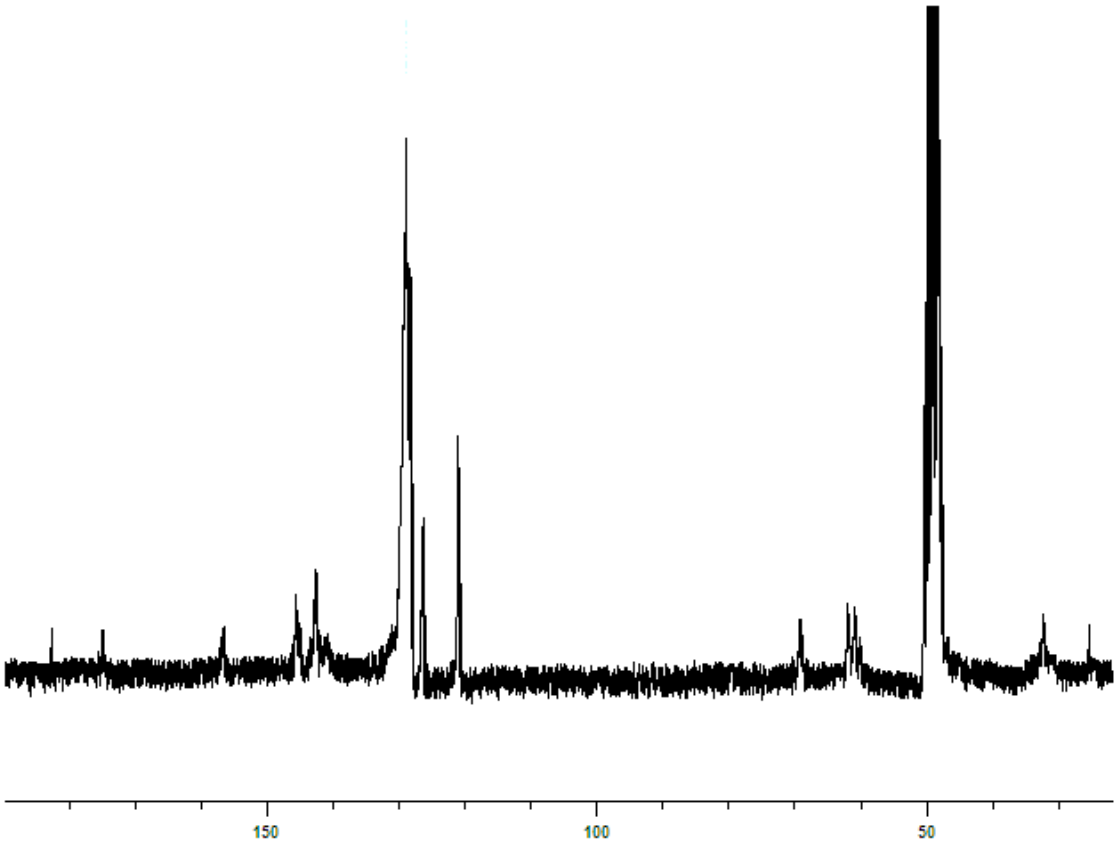


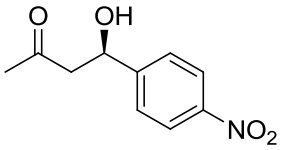


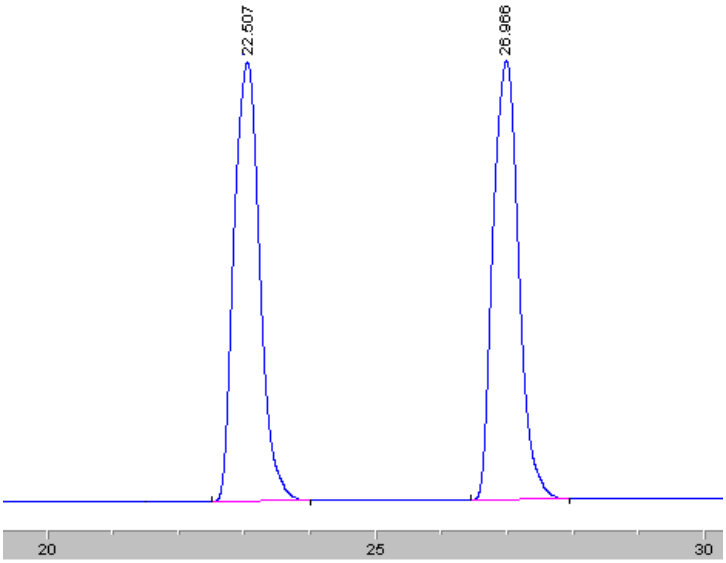




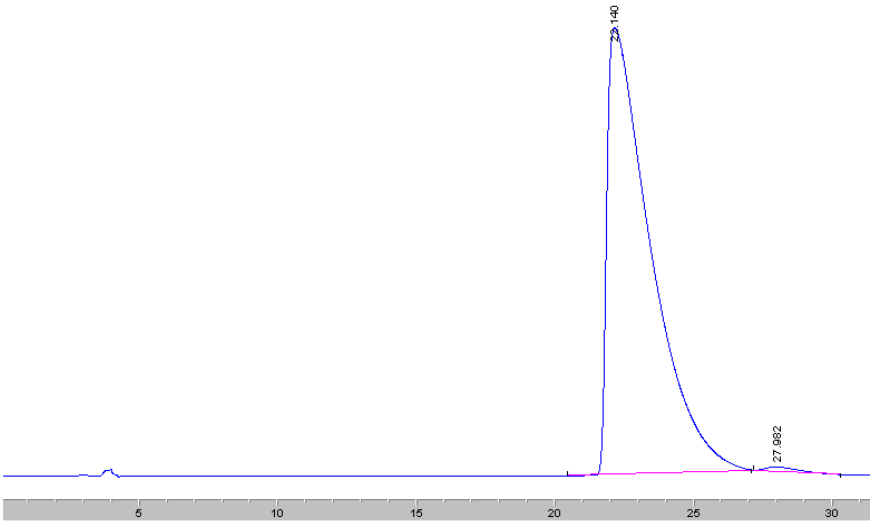




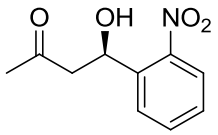


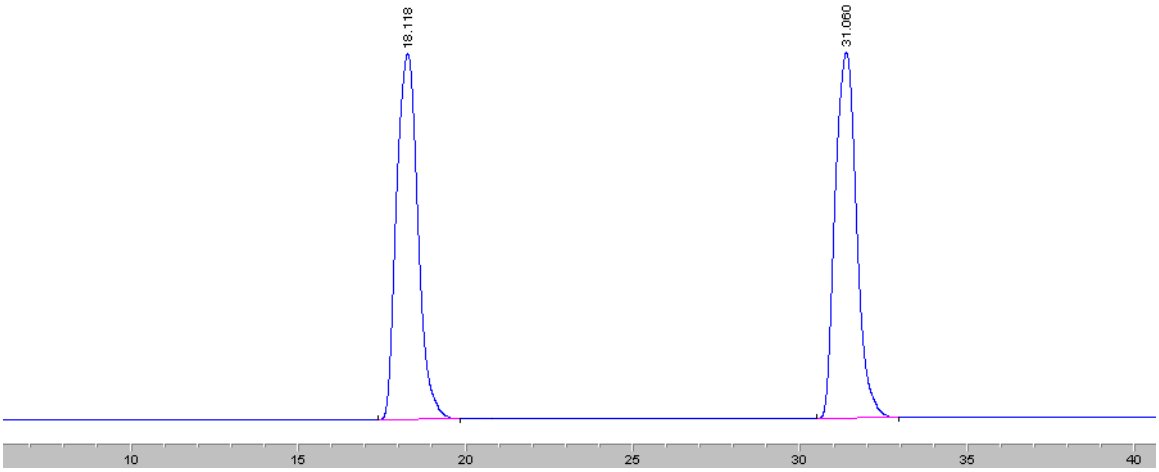


#	Time	Area	Height	Width	Area%
1	22.507	1684.6	45.7	0.47	52.071
2	26.966	1550.6	30.5	0.5997	47.929

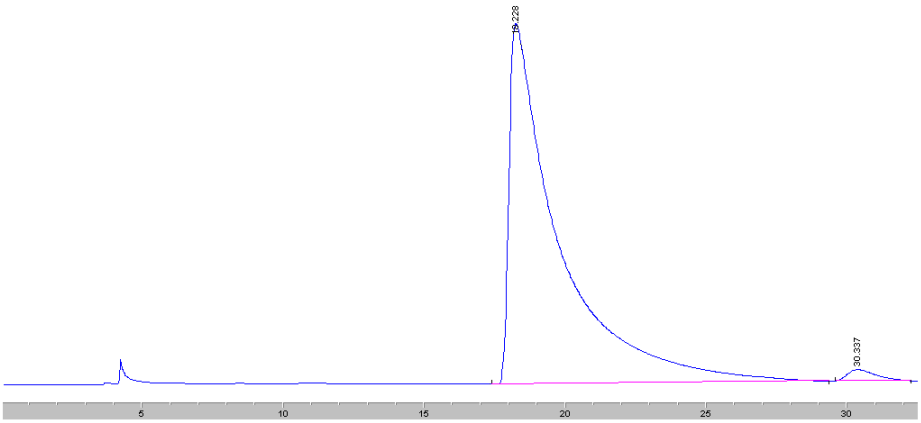


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.140	MM	1.8109	2.03895e5	1876.58374	99.4995
2	27.982	MM	1.0241	1025.61145	16.69159	0.5005
Totals :				2.04921e5	1893.27533	

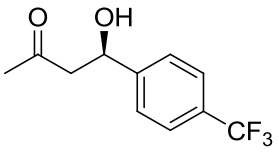


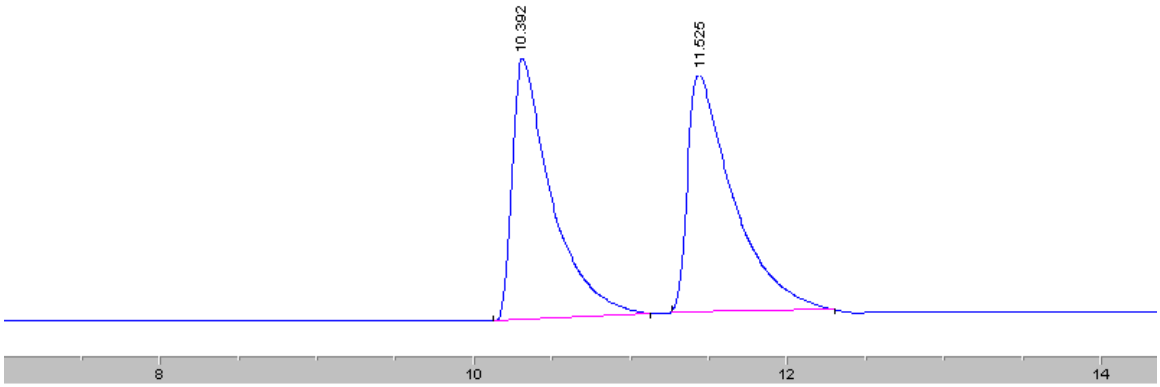


#	Time	Area	Height	Width	Area%
1	18.118	660.2	8.5	0.918	50.975
2	31.06	635	22.7	0.4656	49.025

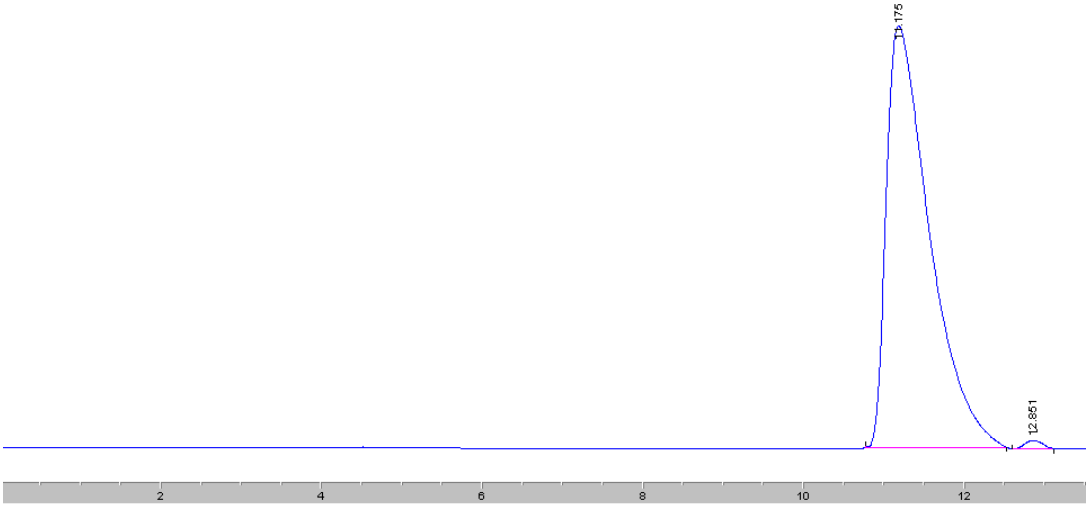


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.228	MM	2.0324	1.32561e5	1087.07886	98.1137
2	30.337	MM	1.2145	2548.53540	34.97424	1.8863
Totals :				1.35109e5	1122.05309	

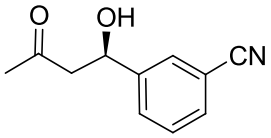


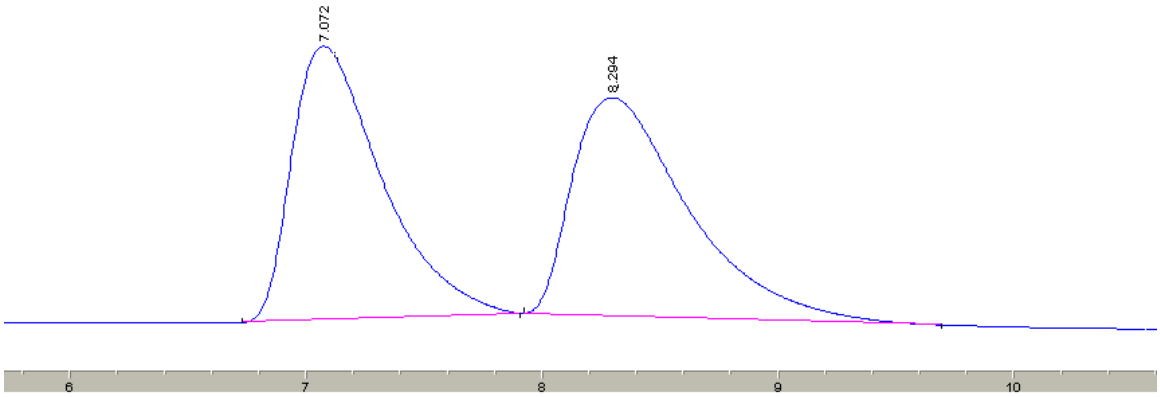


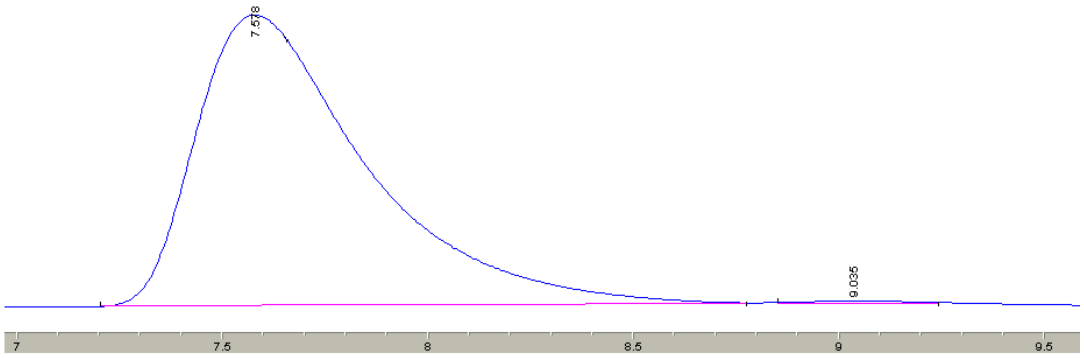
#	Time	Area	Height	Width	Area%
1	10.392	29	1.6	0.2939	49.108
2	11.525	30	5	0.0998	50.892



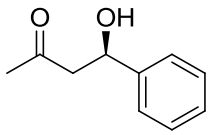
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.175	MM	0.6240	4794.53467	128.06207	99.4063
2	12.851	MM	0.2232	28.63451	2.13799	0.5937
Totals :				4823.16918	130.20006	

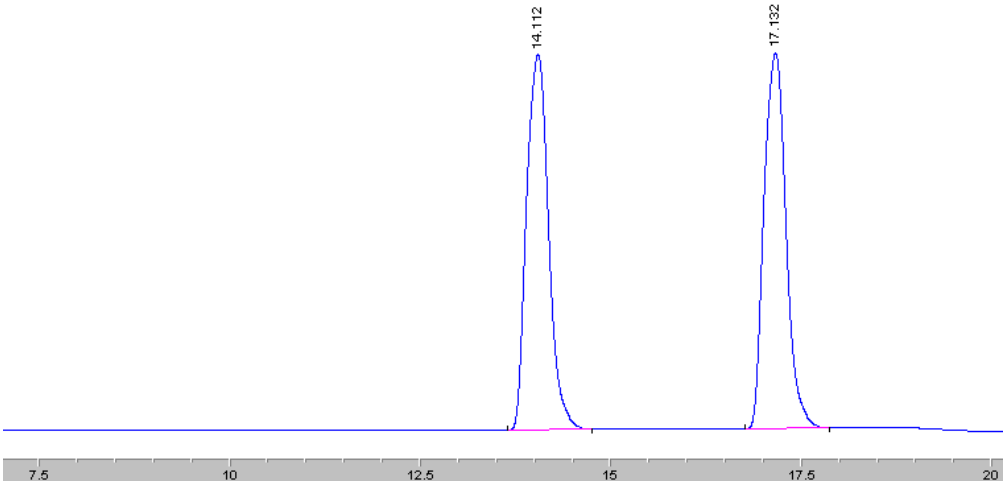




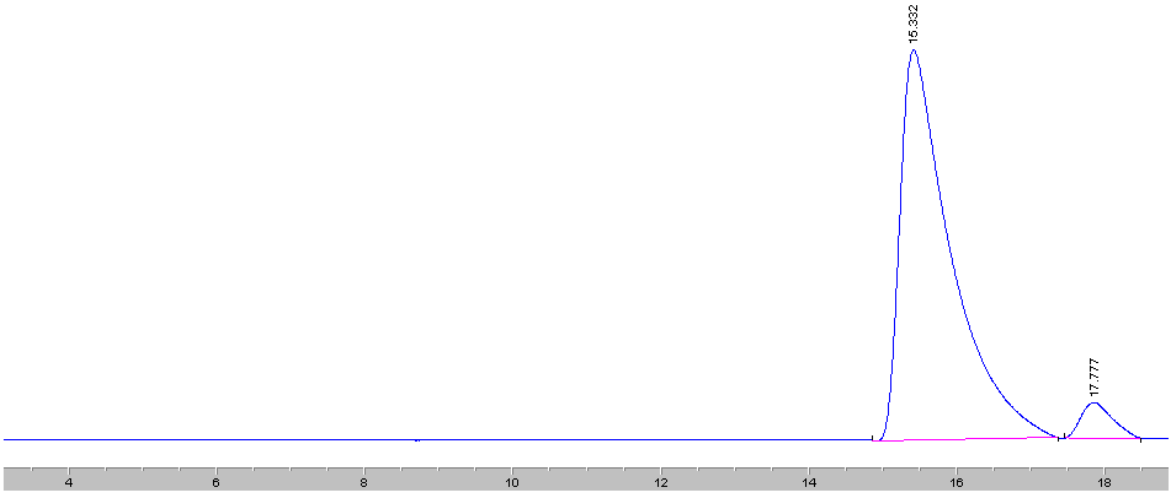


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.578	MM	0.4818	2519.35937	87.15219	99.3181
2	9.035	MM	0.3225	17.29844	8.94104e-1	0.6819

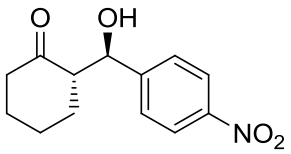


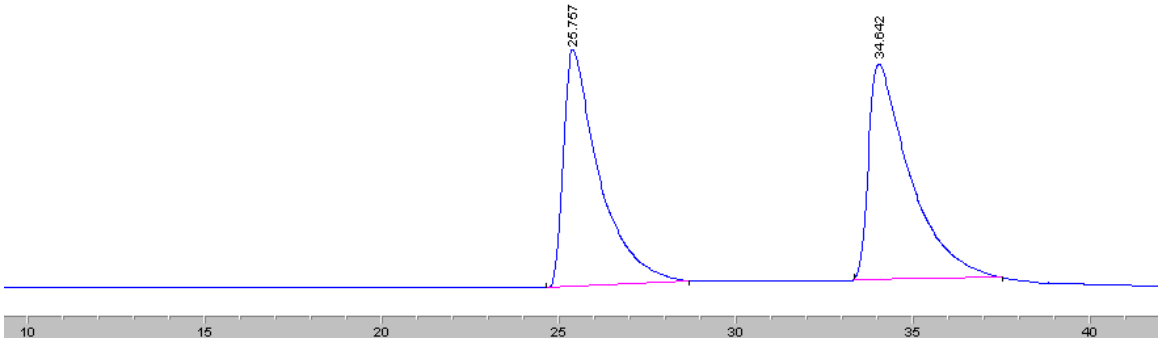


#	Time	Area	Height	Width	Area%
1	14.112	1777.8	43.1	0.6874	51.547
2	17.132	1671.1	61.5	0.4527	48.453

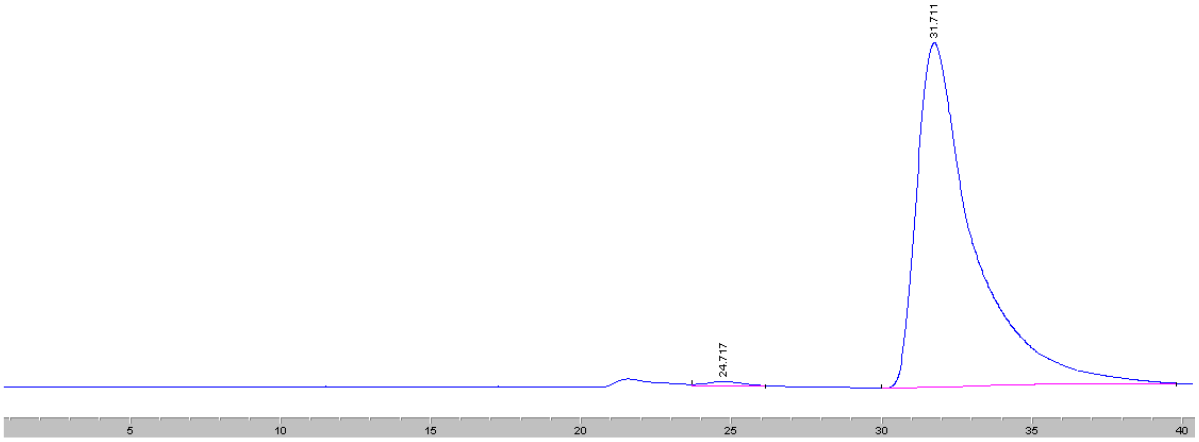


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.332	MM	0.7999	3.76392e4	784.21271	94.9274
2	17.777	MM	0.5047	2011.30298	66.41292	5.0726
Totals :				3.96505e4	850.62563	

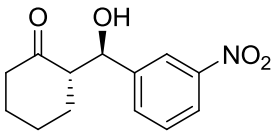


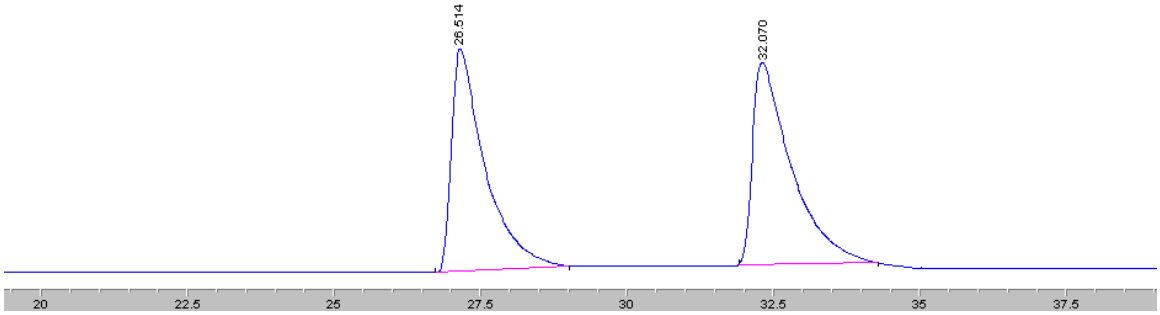


#	Time	Area	Height	Width	Area%
1	25.757	13903.3	282.6	0.7299	47.479
2	34.642	15380	587.5	0.4363	52.521

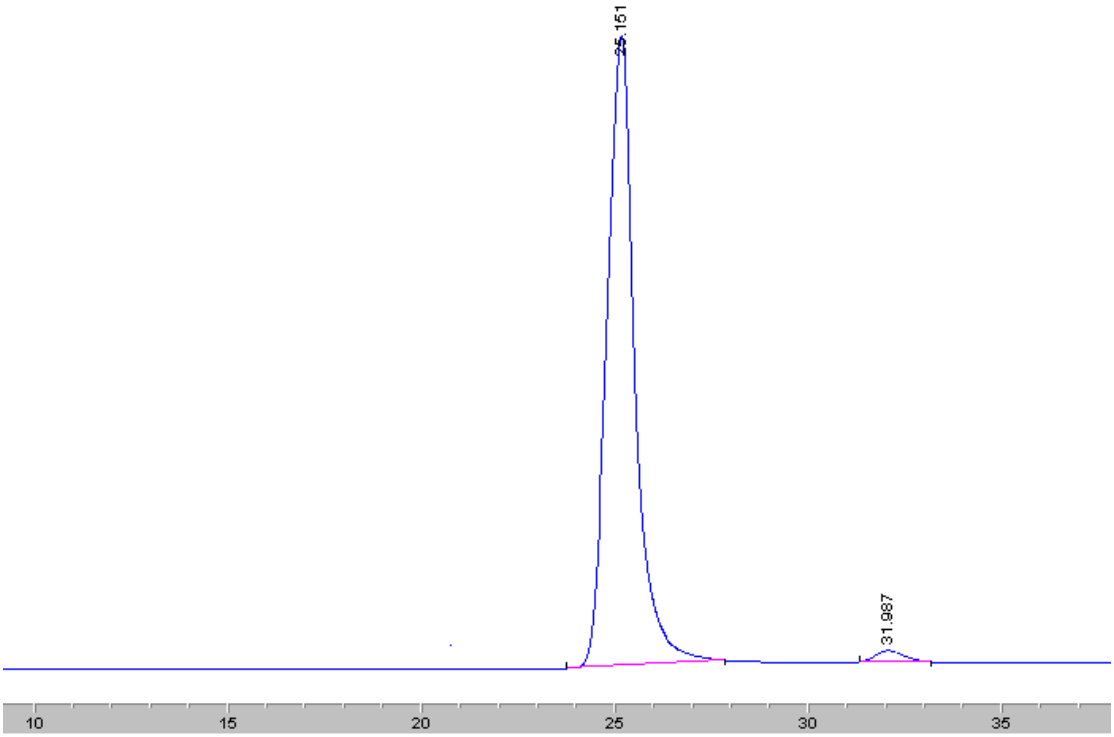


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.717	MM	1.3633	768.16370	9.39069	0.5022
2	31.711	MM	3.5234	1.52186e5	719.88208	99.4978
Totals :				1.52955e5	729.27277	

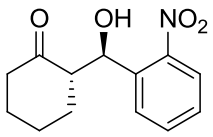


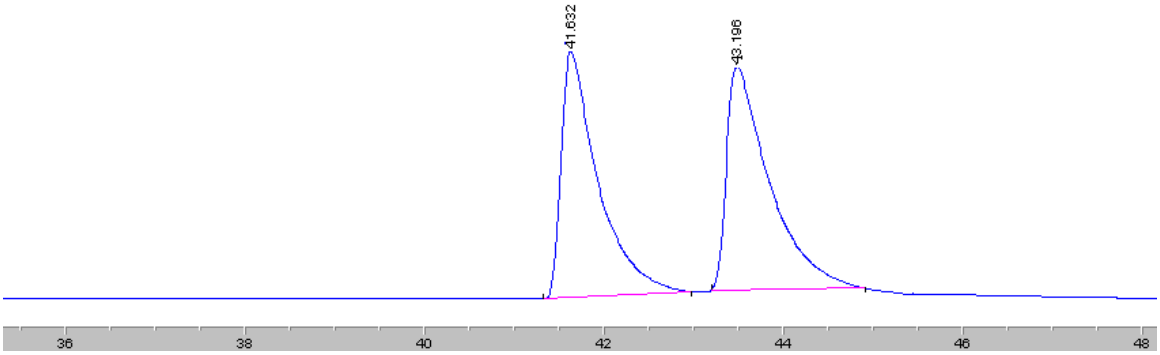


#	Time	Area	Height	Width	Area%
1	26.514	7035	129.9	0.7616	51.004
2	32.07	6758.1	103.3	1.0899	48.996

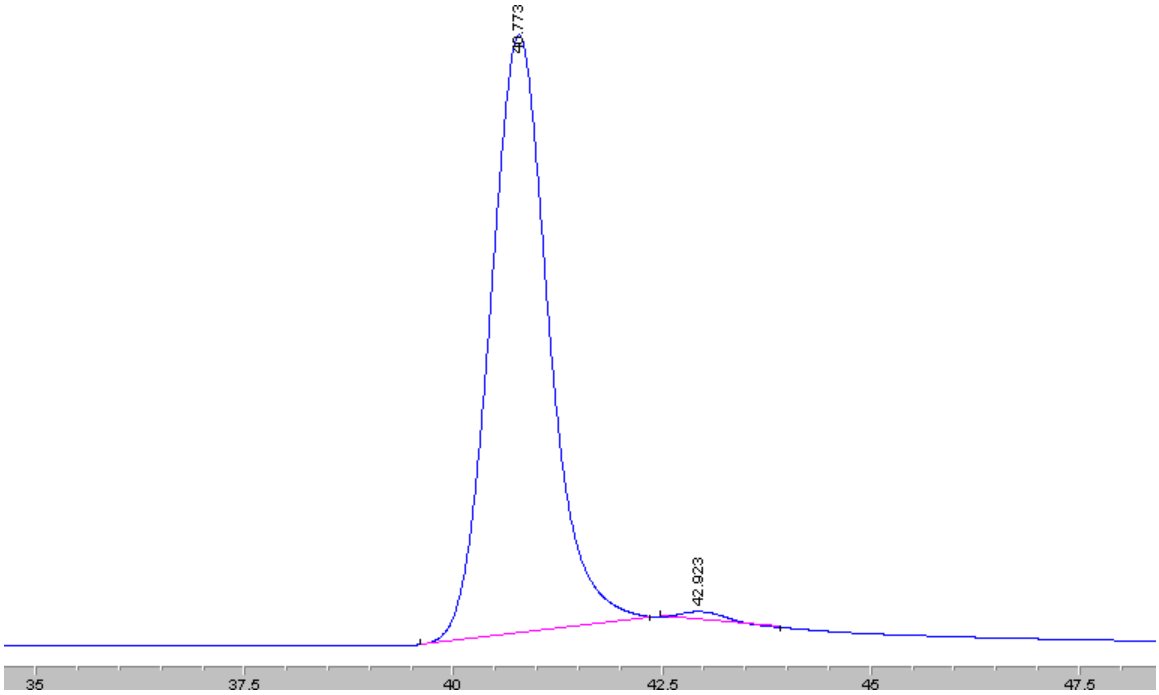


#	Time	Area	Height	Width	Area%	Symmetry
1	25.151	51218.4	1030.5	0.7519	98.229	1.011
2	31.987	923.2	18.5	0.8328	1.771	0.747

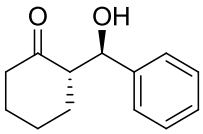


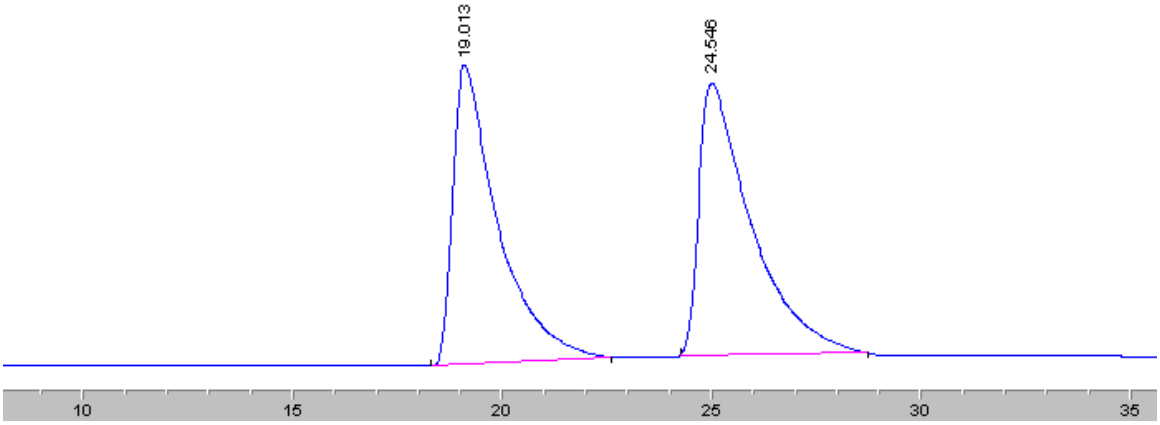


#	Time	Area	Height	Width	Area%
1	41.632	344.7	18.1	0.4063	49.293
2	43.196	354.6	9.2	0.6445	50.707

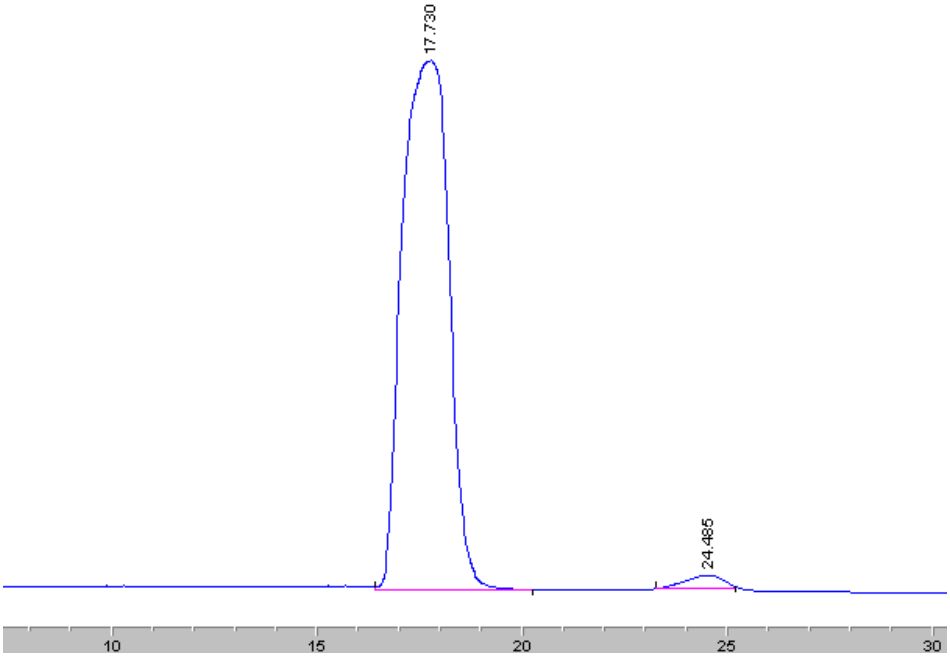


#	Time	Area	Height	Width	Area%	Symmetry
1	40.773	13055.1	267.4	0.7496	98.889	0.913
2	42.923	146.6	3.9	0.5448	1.111	0.575

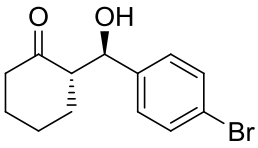


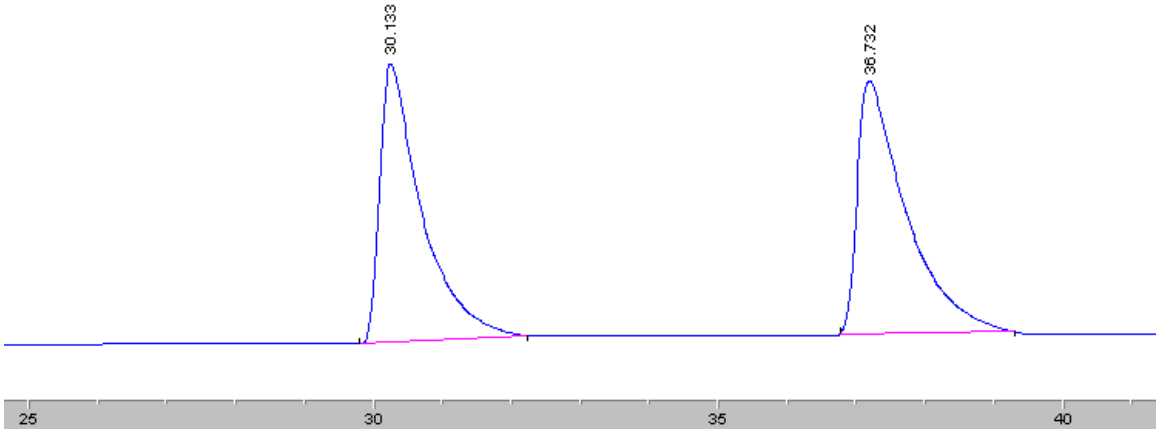


#	Time	Area	Height	Width	Area%
1	19.013	1986.3	42.5	0.6075	47.286
2	24.546	2214.3	54.1	0.6821	52.714

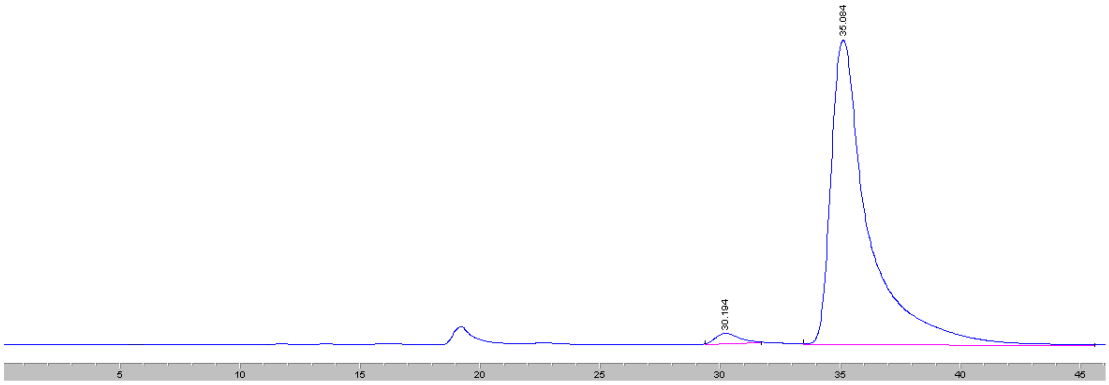


#	Time	Area	Height	Width	Area%	Symmetry
1	17.73	129938.7	1643.5	1.0744	98.076	1.474
2	24.485	2548.8	40.1	1.06	1.924	1.456

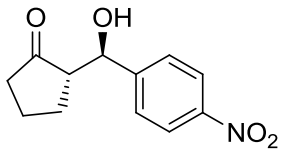


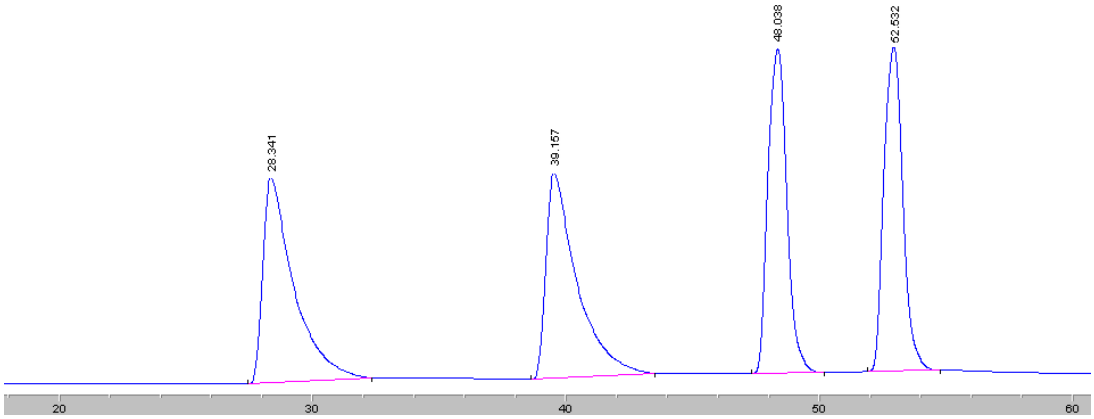


#	Time	Area	Height	Width	Area%
1	30.133	33.8	8E-1	0.7067	48.345
2	36.732	36.1	6.2E-1	0.6847	51.655

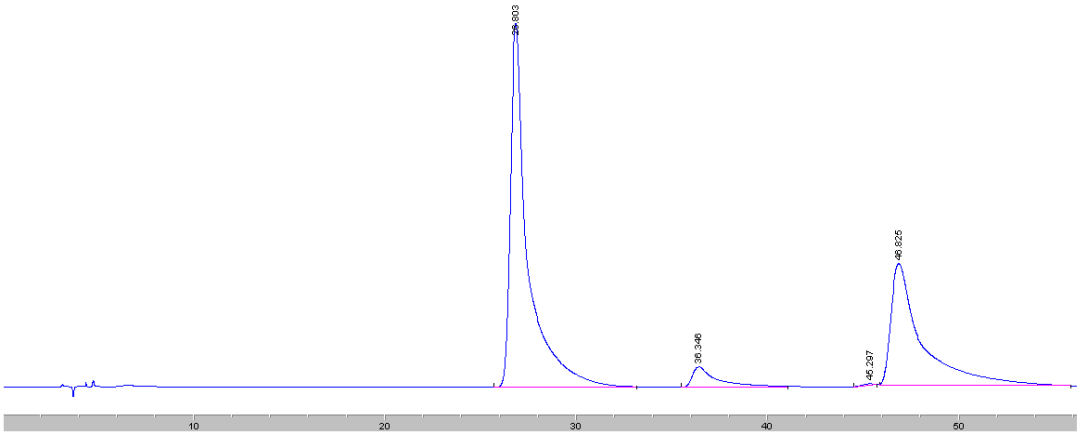


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	30.194	MM	1.1655	2740.69214	39.19107	2.1611
2	35.084	MM	1.8117	1.24077e5	1141.41467	97.8389
Totals :				1.26817e5	1180.60575	

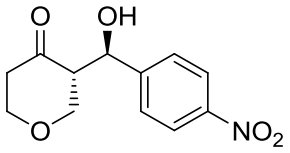


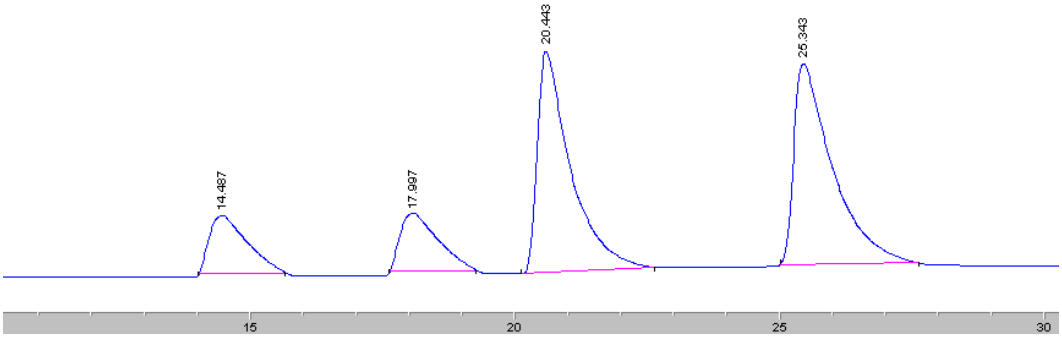


#	Time	Area	Height	Width	Area%
1	28.341	615.4	8.5	1.2048	25.099
2	39.157	653.1	8.5	0.9221	26.639
3	48.038	607.4	22.4	0.4515	24.775
4	52.532	575.8	9.8	0.6905	23.487

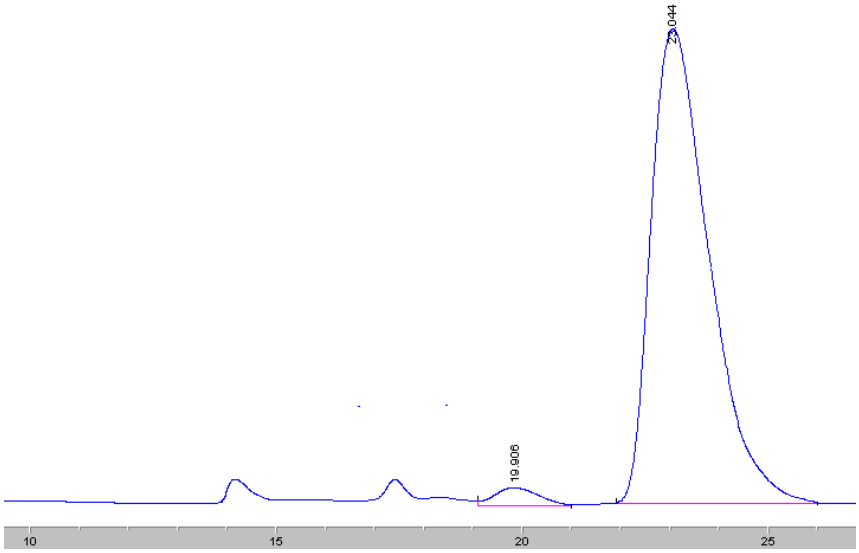


#	RetTime	Area	Height	Width	Area %
1	26.803	86511.1	1361.6	1.0589	59.953
2	36.346	6863.8	75.7	1.5109	4.757
3	45.297	268.1	5.7	0.7819	0.186
4	46.825	50656	455.6	1.8532	35.105

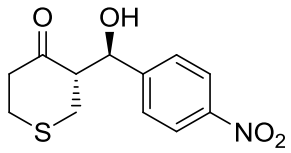


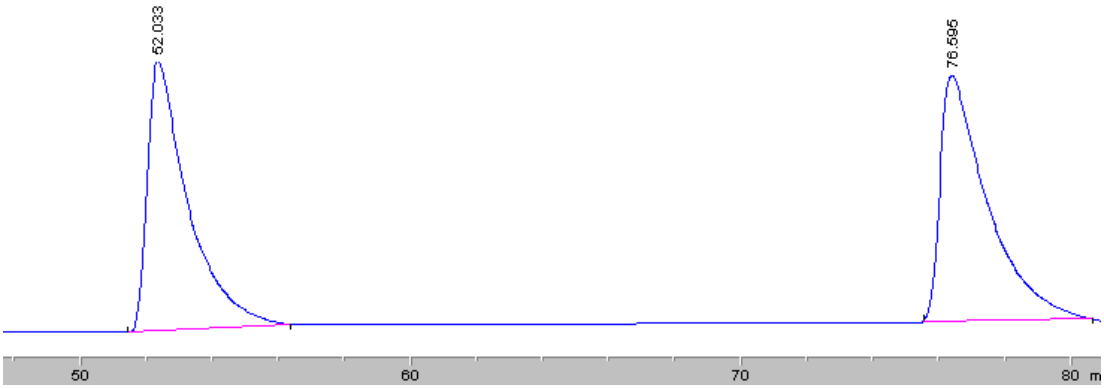


#	Time	Area	Height	Width	Area%
1	14.487	2790.4	203.9	0.2281	16.893
2	17.997	2908.5	53.2	0.912	17.608
3	20.443	5477	241	0.3787	33.158
4	25.343	5342	94.7	0.7158	32.341

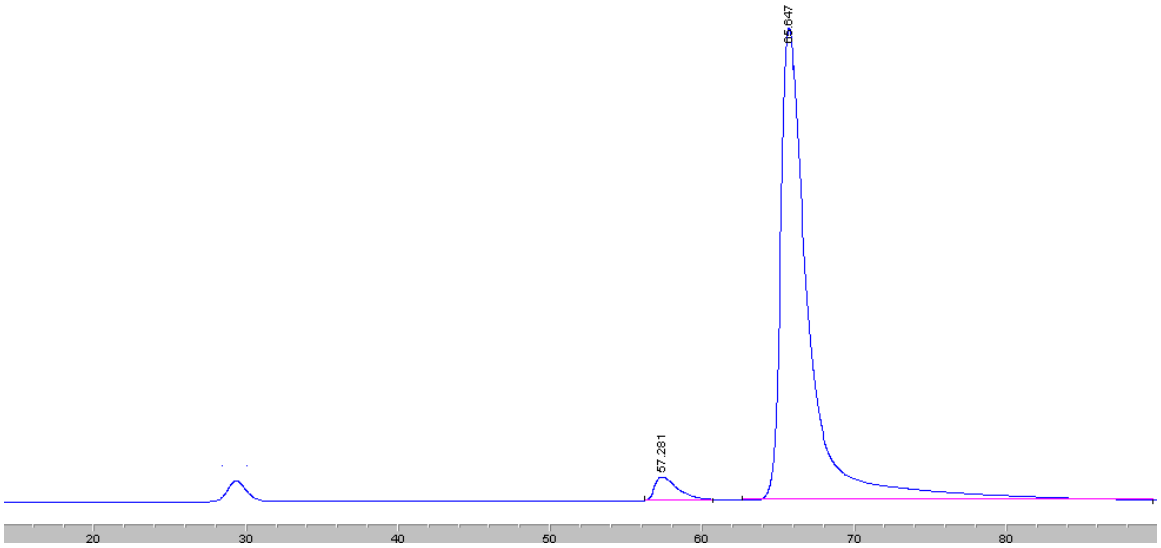


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.906	MM	0.7784	673.63885	14.42324	1.3033
2	23.044	MM	1.5266	5.10141e4	556.96405	98.6967
Totals :				5.16877e4	571.38729	

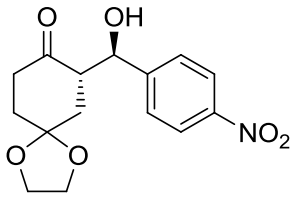


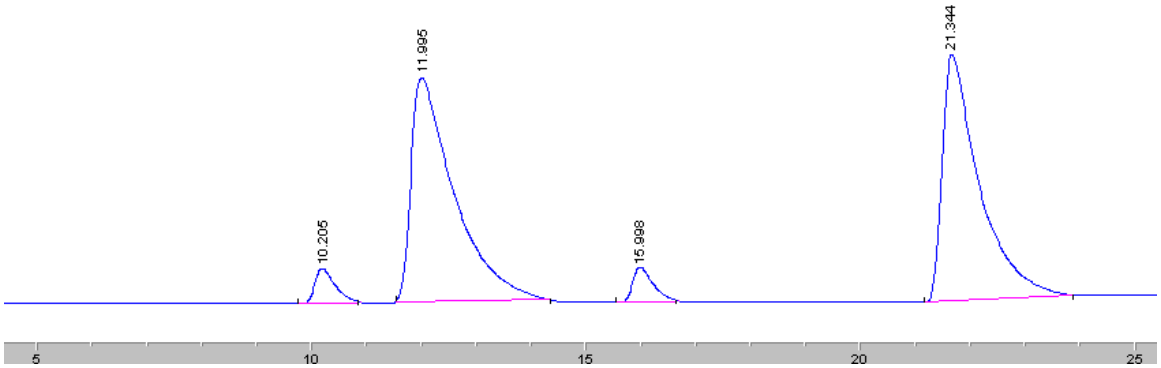


#	Time	Area	Height	Width	Area%
1	33.034	81.9	3.1	0.3105	6.956
2	42.172	86.7	3.4	0.3044	7.364
3	52.033	535.7	4.7	1.3424	45.505
4	76.595	473	6.6	0.8497	40.174

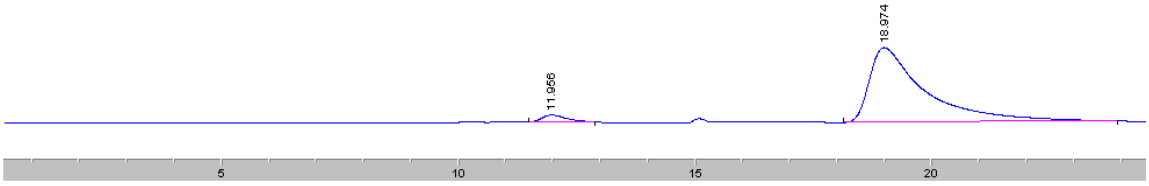


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	57.281	MM	1.7020	1658.82910	16.24372	3.5977
2	65.647	MM	2.2174	4.44490e4	334.09885	96.4023
Totals :				4.61078e4	350.34257	

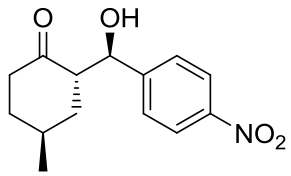


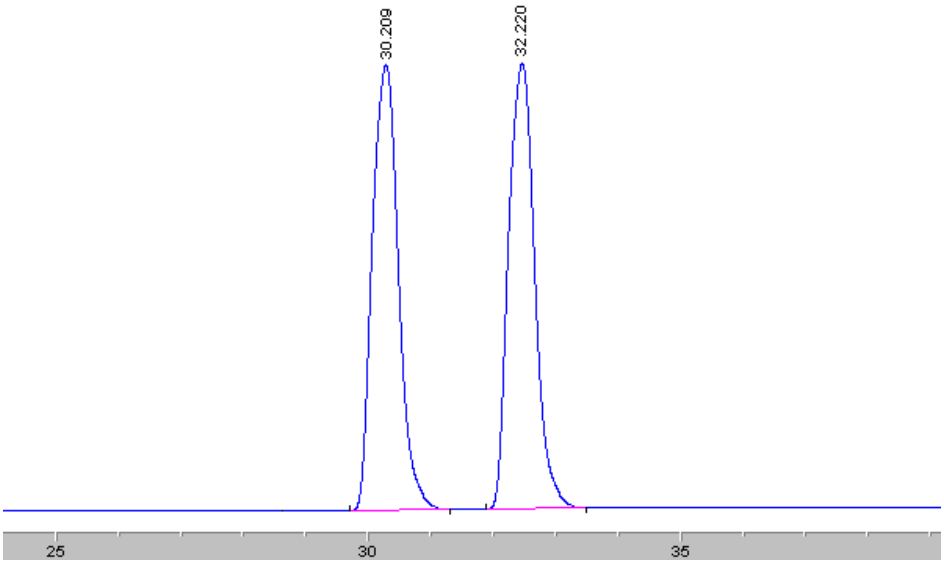


#	Time	Area	Height	Width	Area%
1	10.205	70.8	6.8	0.1725	4.482
2	11.995	653	18.1	0.6019	41.343
3	15.998	95.1	4.8	0.2333	6.024
4	21.344	760.6	11.5	0.772	48.152

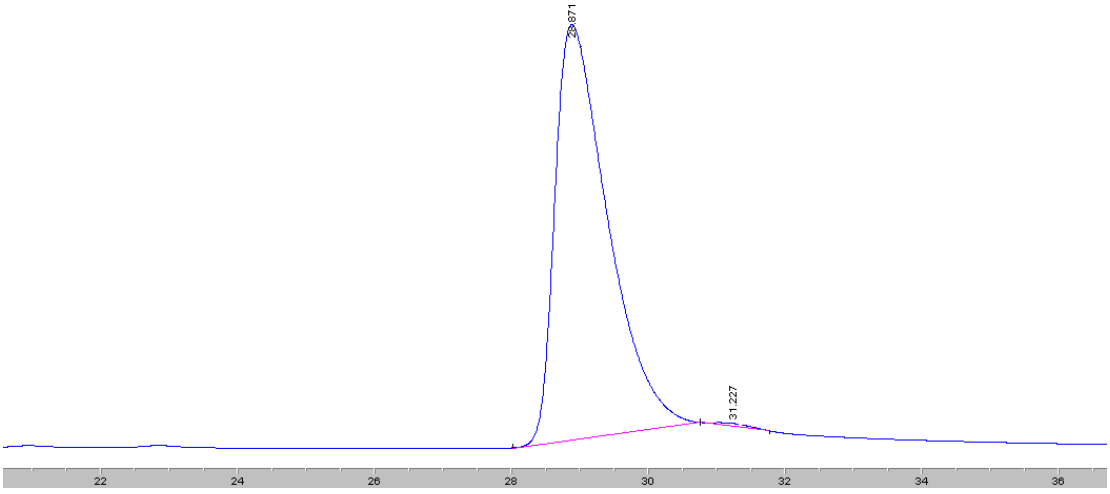


#	RetTime	Area	Height	Width	Area %
1	11.956	702.8	18.7	0.6255	4.093
2	18.974	16466.3	197.5	1.3894	95.907





#	Time	Area	Height	Width	Area%
1	30.209	470.8	46.3	0.1695	49.614
2	32.22	478.1	13.8	0.5776	50.386



#	Time	Area	Height	Width	Area%	Symmetry
1	28.871	78680.6	1459.8	0.8983	99.437	0.461
2	31.227	445.4	12.1	0.6143	0.563	0.197