Enantioselective Synthesis of anti-β-hydroxy-α-amido esters via Transfer Hydrogenation

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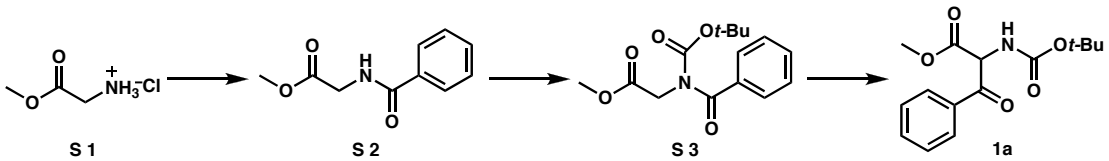
Supporting Information

General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz or 500 MHz spectrometer in $CDCl_3$ using the residual peak of $CHCl_3$ (^{1}H NMR δ 7.26, ^{13}C NMR δ 77.0) as internal standard. Chemical shifts are reported in the δ-scale with multiplicity (b=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants (Hz) and integration. IR-spectra were recorded on an ATI Mattson Infinity Series FTIR and only the strongest/structurally most important peaks (νmax, cm^{-1}) are listed. Optical rotations were determined on a Perkin Elmer Polarimeter 343 using the sodium D line (589 nm) at the indicated temperature. Analytical thin layer chromatography was performed on Merck silica gel 60 F254 plates; the plates were visualized with UV light and phosphomolybdic acid/cerium sulfate staining reagent (purchased from Aldrich as a 20 wt % solution in ethanol and diluted to ca 5 wt % before use) or potassium permanganate stain. Enantioselectivity was determined by HPLC analysis using a Shimadzu DGU-20As instrument (detector UV/VIS, SPD 20A, Column, Chiralcel OD-H, no: ODH0CE-EK017, mobile phase: 3% or 5% 2-propanol in hexanes as indicated, 0.5 mL/min, λ 254 nm). Retention times are given for *S,S* and *R,R* isomers. In the case of the *S,R* and *R,S* isomers an Agilent 1100 series HPLC was used with a Chiracel OJ column, no: OJ00CE-IF050. Air and moisture sensitive reactions were carried out in flame-dried, septum-capped flasks under an atmospheric pressure of nitrogen.



S 1 S 2 S 3 1a

Methyl 2-benzamidoacetate (S2)[1]

After adding a saturated solution of potassium carbonate (19 mL) and benzoyl chloride (4.20 mL, 35.8 mmol) to a solution of glycine methyl ester (**S1**) (3.00 g, 23.9 mmol) in ether (10 mL) the mixture was stirred for 3 hours at 0 °C. The reaction mixture was then transferred to a separatory funnel and the aqueous phase was extracted three times with ether. The organic layer was washed with saturated $NaHCO_3$, water and brine. The aqueous phase was saturated with sodium chloride and then it was extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated. This crude residue could be used directly in the next reaction to form **S3**.

Methyl 2-(N-(tert-butoxycarbonyl)benzamido)acetate (S 3)[2]

S2 (4.00 g, 20.7 mmol) was dissolved in acetonitrile (15 mL). Di-*tert*-butyl dicarbonate (6.90 g, 31.8 mmol) and *N,N*-dimethylaminopyridine (0.30 g, 2.1 mmol) were added successively. The mixture was stirred for 6.5 h and concentrated. Chromatographic purification of the crude residue (Silica, Hept : EtOAc 8:1) gave **S3** (6.08 g, 20.7 mmol) as a colorless oil in 100% yield.

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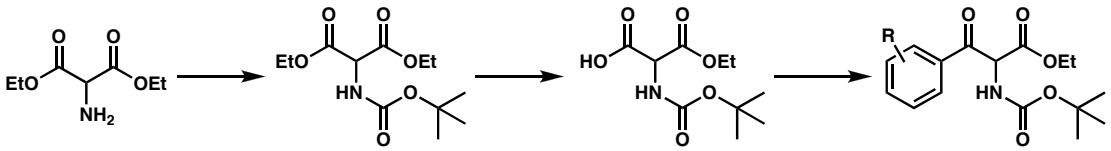
[1] (a) Nemoto, T.; Harada, T.; Matsumoto, T.; Hamada, Y. *Tetrahedron Lett.* **2007**, *48*, 6304-6307. (b) Makino, K.; Okamoto, N.; Hara, O.; Hamada, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1757-1762.

[2] Zeng, L.; Kaoudi, T.; Schiesser, C. H. *Tetrahedron Lett.* **2006**, *47*, 7911-7914.

^{1}H (400 MHz, $CDCl_3$) δ 7.48-7.47 (m, 2H), 7.43-7.42 (m, 1H), 7.41-7.39 (m, 2H), 4.56 (s, 2H), 3.79 (s, 3H), 1.16 (s, 9H). see reference 2 for further characterization.

Methyl 2-(*tert*-butoxycarbonylamino)-3-oxo-3-phenylpropanoate[3] (**1a**)
DMPU (1,3-Dimethyltetrahydropyrimidin-2(1*H*)-one) (2.50 ml, 20.5 mmol) and LiHMDS (Lithium bis(trimethylsilyl)azanide (1M, 25 ml, 25 mmol) were added to a solution of **S3** (3.30 g, 10.2 mmol) in THF (100 ml) at -78 °C. The mixture was stirred for 1.5 h, quenched with saturated NH_4Cl solution and extracted three times with EtOAc. The combined organic phases were washed with water and brine, dried over Na_2SO_4 and concentrated. Chromatographic purification (Silica, Hept : EtOAc 10:1, polarity increased to 3:1 during purification) gave the product **1a** (2.53 g, 8.6 mmol) in 84% yield as a white solid.
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, 2H), 7.65-7.60 (m, 1H), 7.53-7.47 (m, 2H), 5.96 (d, J = 8.1 Hz, 1H), 5.90 (d, J = 8.1 Hz, 1H), 3.71 (s, 3H), 1.44 (s, 9H); ^{13}C (125 MHz, $CDCl_3$) δ 191.8, 167.6, 154.9, 134.3, 134.1, 129.4, 128.7, 80.6, 59.1, 53.0, 28.2.; IR (thin film) 3371, 2978, 1755, 1712, 1693, 1597, 1496, 1450, 1346, 1254, 1165, 1061, 1026 cm^{-1}; HRMS (m/z) calcd for $C_{15}H_{19}NO_5$ $(M+H)^+$ 294.1336, found 294.1339; mp = 96.3-97.2 °C.

General procedure for the preparation of transfer hydrogenation substrates:



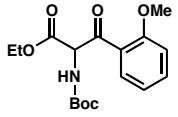
Diethyl 2-(*tert*-butoxycarbonylamino)propandioate (**S5**) was synthesized according to the known procedure from commercially available **diethyl aminopropanedioate** (**S4**).[4]

2-(*tert*-butoxycarbonylamino)-3-ethoxy-3-oxopropanoic acid (**S6**) was synthesized according to known procedure from **S5**.[5]

General procedure for synthesis of the substrates 1b-h:[6]
To a stirred mixture of malonate **S6** (1 equiv or equiv given) and $MgCl_2$ (6 equiv) in THF (15 mL for 0.9 mmol substrate) was added Et_3N (2.5 equiv) at 0 °C. The resulting mixture was stirred at 0 °C for an additional 2 hours. Simultaneously a substituted benzoyl chloride was prepared by heating the corresponding benzoic acid (3 equiv or equiv given) with $SOCl_2$ (2.5 equiv relative to acid) for 2 hours at 80 °C. Evaporation of excess $SOCl_2$ yielded the substituted benzoyl chloride, which was added to the malonate mixture in THF (1 mL) at 0 °C. Then the reaction was brought to rt and stirred over night. After diluting with EtOAc (40 mL), the mixture was

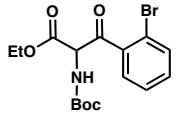
[3] Makino, K.; Hiroki, Y.; Hamada, Y. *J. Am. Chem. Soc.* **2005**, *127*, 5784-5785.
[4](a) Suzuki, N.; Suzuki, T.; Ota, Y.; Nakano, T.; Kurihara, M.; Okuda, H.; Yamori, T.; Tsumoto, H.; Nakagawa, H.; Miyata, N. *J. Med. Chem.* **2009**, *52*, 2909-2922. (b) Denhart, D. J.; Griffith, D. A.; Heathcock, C. H. *J. Org. Chem.* **1998**, *63*, 9616-9617.
[5] Schmidt, U.; Griesser, H.; Lieberknecht, A.; Schmidt, J.; Gr√§ther, T. *Synthesis* **1993**, *1993*, 765-766.
[6] Tao, J.; Hu, S.; Pacholec, M.; Walsh, C. T. *Org. Lett.* **2003**, *5*, 3233-3236.

washed with a saturated NH_4Cl solution (20 mL) and brine (20 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica (10% - 20% EtOAc/Hexanes) to give the product.



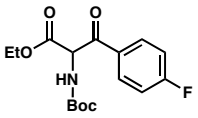
1b

Ethyl 2-(*tert*-butoxycarbonylamino)-3-(2-methoxyphenyl)-3-oxopropanoate (1b)
Prepared from **S6** (1.19 mmol) and *o*-anisic acid (1.14 mmol) yielding the desired product **1b** (271 mg, 0.80 mmol, 70%).
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (m, 1H), 7.48 (m, 1H), 6.99 (m, 1H), 6.94 (m, 1H), 5.91 (d, J = 8.1 Hz, 1H), 5.79 (d, J = 8.1 Hz, 1H), 4.17-4.06 (m, 2H), 3.88 (s, 3H), 1.40 (s, 9H), 1.07 (t, J = 7.1 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 193.2, 167.4, 158.7, 155.0, 134.6, 131.2, 125.0, 120.8, 111.3, 80.1, 63.5, 61.6, 55.3, 28.1, 13.8; IR (thin film) 3429, 3383, 2981, 2939, 1750, 1720, 1689, 1601, 1492, 1255, 1169, 1026, cm^{-1}; HRMS (m/z) calcd for $C_{17}H_{23}NO_6$ $(M+H)^+$ 338.1598, found 338.1602.



1c

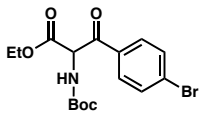
Ethyl 3-(2-bromophenyl)-2-(*tert*-butoxycarbonylamino)-3-oxopropanoate (1c)
Prepared from **S6** (0.87 mmol) and *o*-bromo-benzoic acid (2.62 mmol) yielding product **1c** (174 mg, 0.51 mmol, 59%).
Mixture of rotamers and enol isomers:
1H NMR (500 MHz, Tol) δ 12.93 (s, 1H enol isomer), 7.43 (d, J = 7.2 Hz, 1H enol isomer), 7.38 – 7.32 (m, 1H major), 7.18 (d, J = 8.0 Hz, 1H enol isomer), 7.14 (d, J = 8.0 Hz, 1H major), 6.82 (t, J = 7.5 Hz, 1H enol isomer), 6.75 (t, J = 7.5 Hz, 1H major), 6.67 – 6.55 (m, 1H major and isomer), 5.95 (d, J = 7.6 Hz, 1H major), 5.76 (d, J = 7.7 Hz, 1H major), 5.14 (s, 1H enol isomer), 4.96 (s, 1H enol isomer), 3.93 (q, J = 7.2 Hz, 1H enol), 3.81 (dq, J = 10.7, 7.1 Hz, 1H major), 3.67 (dq, J = 10.8, 7.1 Hz, 1H major), 1.37 (s 9H major), 1.26 (s, 9H isomer), 0.96 (t, J = 7.1 Hz, 3H isomer), 0.70 (t, J = 7.1 Hz, 3H major); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.6, 171.6, 171.1, 168.1, 165.8, 154.9, 154.6, 138.4, 134.8, 134.4, 134.3, 133.7, 133.3, 132.7, 132.5, 132.4, 131.9, 130.8, 123.0, 129.7, 129.5, 129.2, 127.4, 127.3, 127.2, 127.1, 122.0, 120.9, 120.6, 119.7, 102.5, 80.6, 79.8, 64.0, 62.8, 62.5, 61.4, 28.2, 28.0, 27.9, 27.9, 27.8, 27.3, 27.1, 14.1, 13.9, 13.7; IR (thin film) 3394, 2981, 2935, 1719, 1495, 1373, 1343, 1256, 1169, 1053 cm^{-1}. HRMS (m/z) calcd for $C_{16}H_{20}BrNO_5$ $(M+H)^+$ 386.0598, found 386.0588.



1d

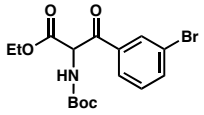
Ethyl 2-(*tert*-butoxycarbonylamino)-3-(4-fluorophenyl)-3-oxopropanoate (1d)
Prepared from **S6** (0.29 mmol) and *p*-fluoro-benzoic acid (0.27 mmol) to yield the product **1d** (60 mg, 0.18 mmol, 66%)

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17-8.09 (m, 2H), 7.19-7.12 (m, 2H), 5.91-5.85 (m, 2H), 4.22-4.10 (m, 2H), 1.43 (bs, 9H), 1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.4 166.9,166.4 (d, J = 257 Hz), 154.9, 132.3 (d, J = 9.6 Hz), 130.7 (d, J = 2.6 Hz), 115.9 (d, J = 22.0 Hz), 80.6, 62.3, 59.3, 28.2, 14.0; δ; IR (CH_2Cl_2) 3429, 3375, 2981, 2935, 1753, 1717, 1697, 1596, 1508, 1369, 1342, 1234, 1060, 1026 cm^{-1}; HRMS (m/z) calcd for $C_{16}H_{20}FNO_5$ $(M+H)^+$ 326.1398, found 326.1399.



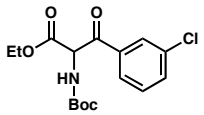
1e

Ethyl 3-(4-bromophenyl)-2-(*tert*-butoxycarbonylamino)-3-oxopropanoate (1e)
Prepared from **S6** (0.58 mmol) and *p*-bromo-benzoic acid (1.17 mmol) to give the product **1e** (186 mg, 0.48 mmol, 82%).
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, J = 8.5 Hz, 2H), 7.64 (d, J = 8.5 Hz, 2H), 5.87 (s, 2H), 4.22-4.07 (m, 2H), 1.44 (s, 9H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 191.1, 166.7, 154.9, 133.0, 132.0, 130.8, 129.7, 80.7, 62.4, 59.3, 28.2, 13.8; IR (thin film) 3379, 2981, 2935, 1751, 1712, 1693, 1585, 1493, 1396, 1369, 1338, 1253, 1223, 1165, 1065, 1026, 887, 837, 775, 482 cm^{-1}; HRMS (m/z) calcd for $C_{16}H_{20}BrNO_5$ $(M+H)^+$ 386.0597, found 386.0591.



1f

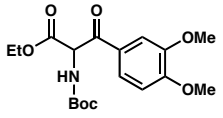
Ethyl 3-(3-bromophenyl)-2-(*tert*-butoxycarbonylamino)-3-oxopropanoate (1f)
Prepared from **S6** (0.63 mmol) and *m*-bromo-benzoic acid (1.89 mmol) yielding **1f** (103 mg, 0.27 mmol, 42%).
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (m, 1H), 8.02 (m, 1H), 7.73 (m, 1H), 7.37 (m, 1H), 5.87 (m, 2H), 4.23-4.10 (m, 2H), 1.43 (bs, 9H), 1.16 (t, J = 6.6 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 190.9, 166.6, 154.9, 137.0, 136.0, 132.3, 130.2, 128.0, 122.9, 80.8, 62.5, 59.5, 28.2, 13.8; IR (CH_2Cl_2) 3379, 2981, 2935, 1751, 1709, 1566, 1496, 1369, 1254, 1219, 1165 cm^{-1}; HRMS (m/z) calcd for $C_{16}H_{20}BrNO_5$ $(M+H)^+$ 386.0598, found 386.0599.



1g

Ethyl 2-(*tert*-butoxycarbonylamino)-3-(3-chlorophenyl)-3-oxopropanoate (1g)
Prepared from **S6** (0.82 mmol) and *m*-chloro-benzoic acid (0.39 mmol) to give **1g** (127 mg, 0.37 mmol, 95%).
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (bs, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 5.92-5.83 (m, 2H), 4.21-4.08 (m, 2H), 1.42 (bs, 9H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 191.0, 166.5, 154.8, 135.8, 134.9, 134.0, 129.9, 129.3, 127.5, 80.6, 62.4, 59.4, 28.1, 13.7; IR (CH_2Cl_2) 3375,

2981, 2935, 1751, 1693, 1496, 1165, 1061 cm^{-1}; HRMS (m/z) calcd for $C_{16}H_{20}ClNO_5$ $(M+H)^+$ 342.1102, found 342.1106.



1h

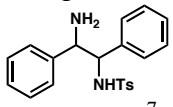
Ethyl 2-(*tert*-butoxycarbonylamino)-3-(3,4-dimethoxyphenyl)-3-oxopropanoate (1h)

Prepared from **S6** (0.55 mmol) and 3,4-dimethoxy benzoic acid (1.11 mmol) to give **1h** (48 mg, 0.13 mmol, 24 %).

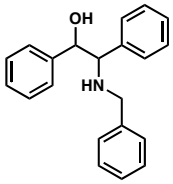
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (dd, J_1 =8.4 Hz, J_2 = 1.6 Hz, 1H), 7.58 (d, J = 1.6 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 5.92 (d, J = 8.1 Hz, 1H), 5.87 (d, J = 8.1 Hz, 1H), 4.20 – 4.04 (m, 2H), 3.94 (s, 3H), 3.91 (s, 3H), 1.43 (bs, 9H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 189.8, 167.3, 154.9, 154.3, 149.0, 127.0, 124.7, 111.1, 110.1, 80.4, 62.1, 59.0, 56.1, 55.9, 28.2, 13.8; IR (thin film) 3417, 3359, 2978, 2939, 1747, 1712, 1681, 1593, 1516, 1269, 1161 cm^{-1}; HRMS (m/z) calcd for $C_{18}H_{25}NO_7$ $(M+H)^+$ 368.1704, found 368.1705.

Ligand Preparation:

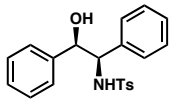
Pseudoephedrine and norephedrine were purchased.



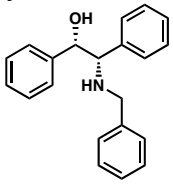
Ts-DPEN was prepared by tosylation of DPEN.[7]



(S,S)- and (*R,S*)-[8] Bn-DPAE were prepared from commercially available 2-amino-1,2-diphenylethanol.



(S,S)-Ts-DPAE[9] was prepared by tosylation of DPAE.[10]



***(1S,2S)*-2-(benzylamino-1,2-diphenylethanol (*(S,S)*-DPAE) (S7)**

[7] Ikariya, T.; Hashiguchi, S.; Murata, K.; Noyori, R. *Org. Syn.* **2005**, *82*, 10-17.

[8] Everaere, K.; Mortreux, A.; Bulliard, M.; Brussee, J.; van der Gen, A.; Nowogrocki, G.; Carpentier, J.-F. *Eur. J. Org. Chem.* **2001**, 275-291., Dinsmore, C. J.; Mercer, S. P. *Org. Lett.* **2004**, *6*, 2885-2888., Zhou, L.; Wang, Z.; Wei, S.; Sun, J. *Chem. Commun.* **2007**, 2977-2979.

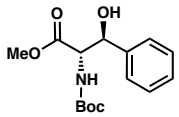
[9] Li, G.; Chang, H. T.; Sharpless, K. B. *Angew. Chem.* **1996**, *108*, 449-452.

[10] Hirayama, L. C.; Gamsey, S.; Knueppel, D.; Steiner, D.; DeLaTorre, K.; Singaram, B. *Tetrahedron Lett.* **2005**, *46*, 2315-2318.

To a solution of (1*S,*2*S)*-2-amino-1,2-diphenylethanol (105 mg, 0.49 mmol) in ethanol (3 mL) was added benzaldehyde (50 uL, 0.49 mmol). The mixture was stirred for 3h at ambient temperature and after which $NaBH_4$ (30 mg, 0.74 mmol) was added as a solid. The reaction was stirred for an additional hour and then cooled to 0 °C. 2 mL of 1M HCl was added to the solution and then the solution was concentrated under reduced pressure. The residue was taken up in 1M NaOH and the aqueous phase was extracted three times with DCM. The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated. The residue was subjected to flash chromatography to yield the product (112 mg, 75 %) as a white solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.45 7.40 (m, 2H), 7.39 – 7.29 (m, 6H), 7.26 7.25(m, 3H), 7.18 – 7.10 (m, 4H), 4.68 (d, *J* = 8.5, 1H), 3.81 (d, *J* = 13.0, 1H), 3.77 (d, *J* = 8.5, 1H), 3.66 (d, *J* = 13.0, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 141.1, 139.8, 128.4, 128.3, 128.2, 127.9, 127.9, 127.8, 127.5, 127.4, 127.1, 126.8, 77.8, 69.63, 51.29; HRMS (m/z) calcd for $C_{21}H_{21}NO_5$ $(M+H)^+$ 304.1696, found 304.1694. mp = 76.1- 76.8 °C. $[\alpha]^{20}_D$ -1.8° (*c* 1.0, CH_2Cl_2). IR (thin film) 3413, 3027, 2931, 1639, 1450 cm^{-1}

General procedure for Ru(II)-catalysed transfer hydrogenation:

First the catalyst was prepared by stirring $[RuCl_2(benzene)]_2$ (0.1 equiv) and the ligand (*S,S*-Bn-DPAE) (0.2 equiv) in *i*-PrOH (200 uL for 0.17 mmol substrate) at +80 °C for 1 h. After letting the catalyst mixture to cool to ambient temperature over 1 h, the catalyst was transferred to a vial containing the transfer-hydrogenation substrate (1 equiv) using HCOOH-Et_3N complex 5:2 (800 uL for 0.17 mmol substrate) and stirred at rt for 7 days (No other solvent is used). Then the mixture was purified by flash chromatography on silica (10% - 20% EtOAc/Hexanes) to give the product.
For the synthesis of the racemic amino alcohols for the ee assay, the TsDPEN ligand (0.2 equiv) and $[RuCl_2(p\text{-cymene})]_2$ (0.1 equiv) were used as the catalyst precursors and the reaction was run at 45 °C following the procedure outlined above.

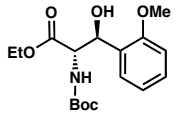


2a

(2*S*,3*S*)-methyl 2-(*tert*-butoxycarbonylamino)-3-hydroxy-3-phenylpropanoate (2a)
Prepared from **1a** (55 mg, 0.19 mmol) to give the product **2a** (54 mg, 0.18 mmol, 95%) as a beige oil.
$[\alpha]^{20}_D$ +81.3° (*c* 1.05, $CHCl_3$)[11]; 97:3 er determined by HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexanes, 0.5 mL/min, λ=254 nm, *R* isomer 20.4 min, *S* isomer 21.3 min); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.22 (m, 5H), 5.27 (m, 1H), 5.19 (m, 1H), 4.72 (m, 1H), 3.70 (bs, 3H), 1.43 (bs, 9H); ^{13}C (125 MHz, $CDCl_3$): δ 170.3, 156.4, 139.1, 128.2, 128.0, 126.0, 80.7, 75.2, 59.6, 52.4, 28.2; IR (thinfilm) 3433,

[11] a) Crich, D.; Banerjee, A. *The Journal of Organic Chemistry* **2006**, *71*, 7106-7109. b) Lago, M. A.; Samanen, J.; Elliott, J. D. *J. Org. Chem.* **1992**, *57*, 3493-3496; c) Kobayashi, J.; Nakamura, M.; Mori, Y.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 9192-9193.

2978, 2931, 1714, 1504, 1454, 1365, 1253, 1169, cm^{-1}; HRMS (m/z) calcd for $C_{15}H_{21}NO_5$ $(M+H)^+$ 296.1493, found 296.1495.

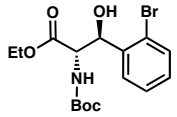


2b

(2*S*,3*S*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-hydroxy-3-(2-methoxyphenyl)propanoate (2b)

Amino alcohol (45 mg, 0.13 mmol, 83%) was obtained as a beige oil from **1b** (53 mg, 0.16 mmol).

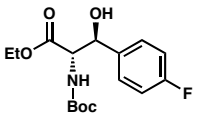
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (m, 1H), 7.26 (m, 1H), 6.95 (m, 1H), 6.84 (m, 1H), 5.36 (m, 1H), 5.27 (m, 1H), 4.67 (m, 1H), 4.18-4.03 (m, 2H), 4.00 (m, 1H), 3.81 (bs, 3H), 1.40 (s, 9H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$): δ 170.6, 156.2, 155.8, 128.9, 127.4, 120.5, 110.1, 80.0, 71.8, 61.2, 58.6, 55.2, 28.2, 13.9; 99:1 er determined by HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexanes, 0.5 mL/min, λ=254 nm, *R* isomer 23.0 min, *S* isomer 29.4 min); IR (CH_2Cl_2) 3433, 2978, 2935, 1719, 1601, 1505, 1373, 1246, 1169, 1053cm^{-1}; HRMS (m/z) calcd for $C_{17}H_{25}NO_6$ $(M+H)^+$340.1754, found 340.1755.



2c

(2*S*, 3*S*)-ethyl 3-(2-bromophenyl)-2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoate (2c)

Amino alcohol (33 mg, 76%) was obtained as a beige oil from **1c** (43 mg, 0.11 mmol), ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 7.9 Hz, 1H), 7.48 (dd, J_1 = 7.9 Hz, J_2 = 1.4 Hz, 1H), 7.31 (t, J = 7.5 Hz, 1H), 7.15 (dt, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H), 5.45 (d, J = 7.3 Hz, 1H), 5.39 (bs, 1H), 4.72 (m, 1H), 4.13 – 3.94 (m, 2H), 1.41 (bs, 9H,), 1.08 (t, J = 6.9 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 170.2, 155.5, 138.7, 132.6, 129.4, 128.3, 127.2, 122.2, 80.4, 73.7, 61.5, 57.8, 28.2, 13.7; 99:1 er determined by HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexanes, 0.5 mL/min, λ=254 nm, *R* isomer 14.9 min, *S* isomer 15.5 min); IR (CH_2Cl_2) 3429, 2978, 2931, 1724, 1694, 1504, 1369, 1169, 1053 cm^{-1}; HRMS (m/z) calcd for $C_{16}H_{22}BrNO_5$ $(M+H)^+$ 388.0754, found 388.0756.

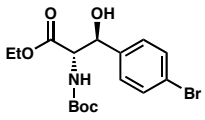


2d

(2*S*,3*S*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(4-fluorophenyl)-3-hydroxypropanoate (2d)

Amino alcohol **2d** (52 mg, 89%) was obtained as a beige oil from **1d** (59 mg, 0.18 mmol) ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (m, 2H), 7.01 (m, 2H), 5.31 (m, 1H), 5.17 (m, 1H), 4.65 (m, 1H), 4.20-4.10 (m, 3H), 1.43 (bs, 9H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ = 169.6, 162.5 (d, J = 246 Hz), 156.5, 135.1 (d, J = 2.8), 127.8 (d, J = 8.1), 115.1 (d, J = 21.5), 80.8, 74.7, 61.8, 59.7, 28.2, 14.0; 98:2 er determined by HPLC analysis (Chiralcel OD-H, 3% 2-propanol in hexanes, 0.5 mL/min, λ=254 nm, *R* isomer 20.4 min, *S* isomer 22.1 min). IR (CH_2Cl_2) 3437, 2981,

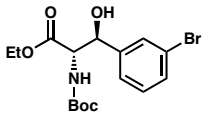
2935, 1709, 1604, 1512, 1369, 1223, 1165 cm^{-1}; HRMS (m/z) calcd for $C_{16}H_{22}FNO_5$ $(M+H)^+$ 328.1554, found 328.1557.



2e

(2*S*,3*S*)-ethyl 3-(4-bromophenyl)-2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoate (**2e**)

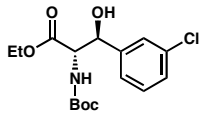
Amino alcohol **2e** (32 mg, 81%) was obtained as a beige oil from **1e** (41 mg, 0.11 mmol) ^1H NMR (500 MHz, $CDCl_3$): δ 7.45 (m, 2H), 7.14 (m, 2H), 5.31 (m, 1H), 5.16 (m, 1H), 4.65 (m, 1H), 4.22 (m, 1H), 4.16 (m, 2H), 1.43 (bs, 9H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C (125 MHz, $CDCl_3$) δ 169.3, 156.5, 138.3, 131.2, 127.8, 121.8, 80.8, 74.7, 61.9, 59.7, 28.2, 14.0; 98:2 er determined by HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexanes, 0.5 mL/min, λ=254 nm, *R* isomer 16.7 min, *S* isomer 17.5 min); IR (neat) 3422, 3377, 2981, 2935, 1693, 1508, 1392, 1369, 1254, , cm^{-1}; HRMS (m/z) calcd for $C_{16}H_{22}BrNO_5$ $(M+H)^+$ 388.0754, found 388.0756.



2f

(2*S*, 3*S*)-ethyl 3-(3-bromophenyl)-2-(*tert*-butoxycarbonylamino)-3-hydroxypropanoate (**2f**)

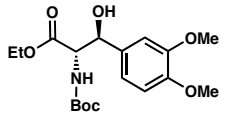
Amino alcohol **2f** (16 mg, 94%) was prepared from **1f** (17 mg, 0.044 mmol). ^1H NMR (500 MHz, $CDCl_3$): δ 7.44 (bs, 1H), 7.40 (m, 1H), 7.22-7.15 (m, 2H), 5.34 (m, 1H), 5.18 (m, 1H,), 4.65 (m, 1H), 4.30 (m, 1H), 4.23-4.11 (m, 2H), 1.45 (bs, 9H,), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 169.2, 156.5, 141.7, 130.9, 129.7, 129.3, 124.6, 122.4, 80.9, 74.7, 62.0, 59.8, 28.2, 14.0; 96:4 er determined by HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexanes, 0.5 mL/min, λ=254 nm, *R* isomer 13.9 min, *S* isomer 14.8 min); IR (CH_2Cl_2) 3421, 2978, 2927, 1712, 1504, 1373, 1250 cm^{-1}; HRMS (m/z) calcd for $C_{16}H_{22}BrNO_5$ $(M+H)^+$ 388.0754 found 388.0747.



2g

(2*S*, 3*S*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(3-chlorophenyl)-3-hydroxypropanoate (**2g**)

Amino alcohol **2g** (43 mg, 69%) was prepared from **1g** (63 mg, 0.18 mmol) ^1H NMR (500 MHz, $CDCl_3$): δ 7.28 (m, 1H), 7.26-7.21 (m, 2H), 7.13 (m, 1H), 5.36 (m, 1H), 5.18 (m, 1H), 4.65 (m, 1H), 4.34 (m, 1H), 4.25-4.07 (m, 2H), 1.44 (bs, 9H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 169.3, 156.5, 141.5, 134.2, 129.4, 128.0, 126.4, 124.2, 80.9, 74.7, 61.9, 59.8, 28.2, 13.9; 66:34 er determined by HPLC analysis (Chiralcel OD-H, 3% 2-propanol in hexanes, 0.5 mL/min, λ=254 nm, *R* isomer 18.9 min, *S* isomer 20.7 min); IR (CH_2Cl_2) 3436, 2981, 2931, 1728, 1512, 1161, cm^{-1}; HRMS (m/z) calcd for $C_{16}H_{22}ClNO_5$ $(M+H)^+$ 344.1259, found 344.1261.

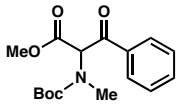


2h

(2*S*,3*S*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(3,4-dimethoxyphenyl)-3-hydroxypropanoate (**1h**)

Amino alcohol (25 mg, 95%) was prepared from **1h** (25 mg, 0.070 mmol) and obtained as a beige oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.85 – 6.74 (m, 3H), 5.26 (d, J = 7.4 Hz, 1H), 5.14 (bs, 1H), 4.65 (q, J = 3.5 Hz, 1H), 4.21 – 4.10 (qd, J_1 = 7.1 Hz, J_2 = 2.0 Hz, 2H), 3.86 (bs, 3H), 3.86 (bs, 3H), 1.42 (bs, 9H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$) δ 169.8, 156.3, 148.8, 148.7, 131.7, 118.3, 110.7, 109.2, 80.58, 74.8, 61.7, 59.6, 55.8, 55.7, 28.2, 14.0; 97:3 er determined by HPLC analysis (Chiralcel OD-H, 5% 2-propanol in hexanes, 0.5 mL/min, λ=254 nm, *R* isomer 39.1 min, *S* isomer 41.2 min); IR (CH_2Cl_2) 3433, 2962, 2927, 2850, 1712, 1516, 1466, 1369, cm^{-1}. HRMS (m/z) calcd for $C_{18}H_{27}NO_7$ $(M+H)^+$ 370.1860, found 370.1860.

Double protected α-amido-β-ketoester

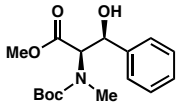


3

Methyl 2-(*tert*-butoxycarbonyl(methyl)amino)-3-oxo-3-phenylpropanoate (**3**)

To a solution of methyl 2-(benzyl(*tert*-butoxycarbonyl)amino)ethanoate[12] (234 mg, 1.15 mmol) in THF (10 mL) was added a freshly prepared LDA solution (10 mL, 1.27 mmol) at 0 °C and stirred for an additional 2 h. Then the mixture was added dropwise to a benzoyl chloride (147 μL, 1.27 mmol) solution in THF (15 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. After quenching with H_2O (50 mL), the mixture was extracted with EtOAc (3x30 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (EtOAc in hexanes), the product was obtained as a clear oil (141.9 mg, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers: δ 12.4 (s, 1H minor), 8.00 (m, 1H, minor) 7.97 (d, 2H major and minor), 7.58 (m, 2H major and minor), 7.47-7.40 (m, 3H major and minor), 7.40-7.32 (m, 1H major), 6.43 (s, 1H major) 5.92 (s, 1H, minor), 3.82 (bs, 3H minor), 3.79 (bs, 3H minor), 3.76 (bs, 3H major), 2.85 (bs, 3H minor), 2.80 (bs, 3H major), 2.79 (bs, 3H minor), 1.45 (s, 9H, major) 1.44 (s, 9H, minor). ^{13}C (125 MHz, $CDCl_3$) mixture of rotamers δ 193.4, 192.2, 172.0, 168.8, 168.7, 168.2, 155.6, 154.3, 134.7, 134.5, 134.0, 133.0, 130.5, 128.7,128.6, 128.4, 128.2, 128.0, 127.5, 108.0, 81.5, 81.0, 80.0, 79.8, 65.0, 64.7, 62.6, 52.4, 52.2, 52.0, 36.2, 35.4, 32.3, 31.7, 28.1, 28.0, 28.0, 18.9. IR (thin film) 3066, 2981, 1743, 1685, 1454, 1423, 1323, 1292, 1149cm^{-1}. HRMS (m/z) calcd for $C_{16}H_{21}NO_5$ $(M+H)^+$ 30.1493, found 308. 1496.

[12] Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1988**, *53*, 487-499.

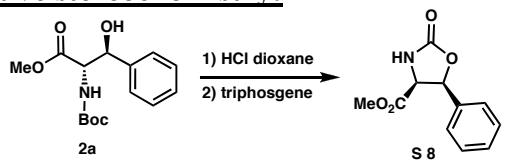


4

(2*R*,3*S*)-methyl 2-(*tert*-butoxycarbonyl(methyl)amino)-3-hydroxy-3-phenylpropanoate (4)

Amino alcohol (44 mg, 82%) was obtained as a yellow oil following the general protocol from **3** (53 mg, 0.17 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) mixture of rotamers: δ 7.39-7.30 (m, 5H), 4.42 (m, 1H), 4.58 (bs, 1H), 4.45 (m, 1H), 3.75 (bs, 3H), 2.72 (bs, 3H), 1.37 (bs, 9H). ^{13}C (125 MHz, $CDCl_3$) δ 169.9, 157.2, 140.6, 128.1, 127.4, 125.9, 80.7, 73.5, 66.4, 52.3, 35.7, 28.1. 97:3 er determined by HPLC analysis (Chiralcel OJ, 15% 2-propanol in hexanes, 0.5 mL/min, λ=210 nm, *S,R* isomer (absolute configuration not determined) 25.1 min, *R,S* isomer 30 min). IR (neat) 3437, 2978, 2936, 1743, 1684, 1481, 1450, 1392, 1369, 1335, 1254, 1159 cm^{-1}. HRMS (m/z) calcd for $C_{16}H_{23}NO_5$ $(M+H)^+$ 310.1649, found 310.1651.

Determination of relative stereochemistry:



2a S 8

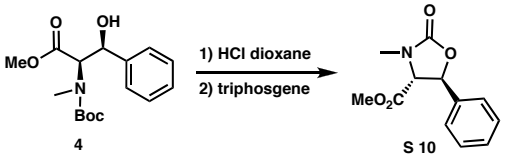
(4S, 5S)-methyl 2-oxo-5-phenyloxazolidine-4-carboxylate (S8)

To a solution of HCl in dioxane (4M, 3.4 mL) at 0°C was added 2a (50 mg, 0.17 mmol). The solution was warmed to ambient temperature and stirred until the reaction was judged complete (TLC). At this point the reaction mixture was concentrated under reduced pressure and the crude residue was taken up in saturated $NaHCO_3$ solution. The aqueous phase was extracted four times with EtOAc, dried over Na_2SO_4, filtered and concentrated. The product was carried on to the next reaction without further purification.

To a solution of the above product and triphosgene (79 mg, 0.27 mmol) in DCM (1mL) at 0°C was added iPr_2NEt (46 uL, 0.27 mmol). The reaction was stirred 30 min at 0°C and then stirred an additional 1 h at ambient temperature. The reaction was quenched with saturated $NaHCO_3$ and the aqueous phase was extracted two times with DCM. The organic layers were dried over Na_2SO_4, filtered and concentrated and then subjected to flash chromatography (1:1 Hexanes: EtOAc) to yield the desired product **S8**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, 3H), 7.34 – 7.30 (m, 2H), 5.84 (d, J = 9.0 Hz, 1H), 5.42 (s, 1H), 4.67 (d, J = 9.0 Hz, 1H), 3.24 (s, 3H).[13]

Evaluation of the relevant *J*-coupling constants indicated the *cis* oxazolidine corresponding to the *anti* amino alcohol.



4 S 10

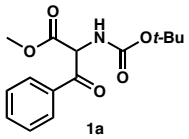
(4*S*,5*R*)-methyl 3-methyl-2-oxo-5-phenyloxazolidine-4-carboxylate (**S10**)

[13] Tomasini, C.; Vecchione, A. *Org. Lett.* **1999**, *1*, 2153-2156., Lago, M. A.; Samanen, J.; Elliott, J. D. *J. Org. Chem.* **1992**, *57*, 3493-3496.

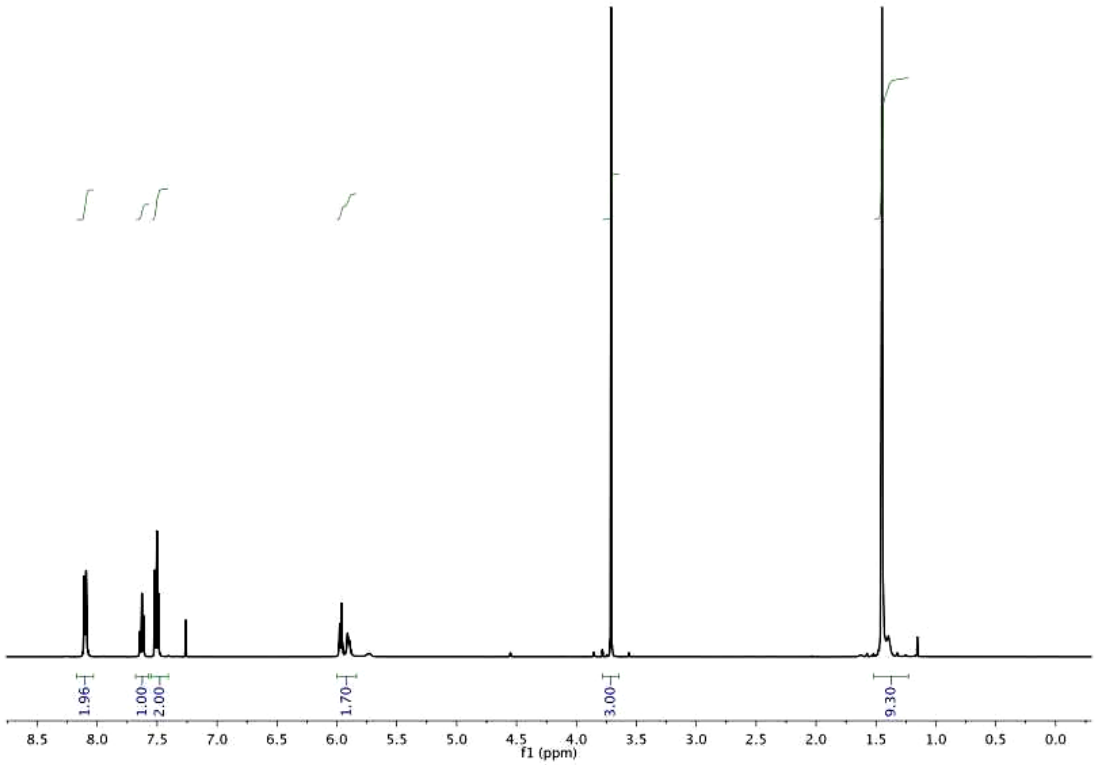
To a solution of HCl in dioxane (4M, 9.38 mL) stirring at 0°C was added **4** (144 mg, 0.47 mmol). The reaction was warmed to room temperature and stirred for an additional 30 minutes. Upon completion of the reaction the solution was concentrated under reduced pressure and the residue was then taken up in saturated $NaHCO_3$. The aqueous layer was extracted five times with DCM and the combined organic layers were dried over Na_2SO_4. The crude residue was subjected to flash chromatography (2:1 → 1:1 hexanes: EtOAc) to yield the product **S9** (82 mg, 84 % yield)
Syn diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 3H), 7.29 (m, 2H), 4.60 (d, J = 7.6 Hz, 1H), 3.55 (s, 3H), 3.22 (d, J = 7.6 Hz, 1H), 2.38 (s, 3H).[14]

To a solution of **S9** (82 mg, 0.39 mmol) and triphosgene (290 mg, 0.98 mmol) in DCM (3.6 mL) at 0°C was added iPr_2NEt (170 uL, 0.98 mmol). The reaction was stirred 30 min at 0°C and then stirred an additional 1 h at ambient temperature. The reaction was quenched with saturated $NaHCO_3$ and the aqueous phase was extracted two times with DCM. The organic layers were dried over Na_2SO_4, filtered and concentrated and then subjected to flash chromatography (1:1 Hexanes: EtOAc) to yield the desired product **S10**.
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 – 7.36 (m, 5H), 5.46 (d, J = 4.9 Hz, 1H), 4.14 (d, J = 4.9 Hz, 1H), 3.88 (bs, 3H), 2.98 (bs, 3H). ^{13}C (125 MHz, $CDCl_3$) δ 169.6, 157.2, 138.1, 129.1, 129.0, 125.1, 76.5, 66.7, 53.0, 30.4. IR (CH_2Cl_2) 2981, 2924, 1743, 1439, 1396, 1311, 1230 cm^{-1}. HRMS (m/z) calcd for $C_{12}H_{13}NO_4$ (M+H) $^+$236.0917, found 236.0917.
Evaluation of the relevant *J*-coupling constants indicated the *trans* oxazolidine corresponding to the *syn* amino alcohol.

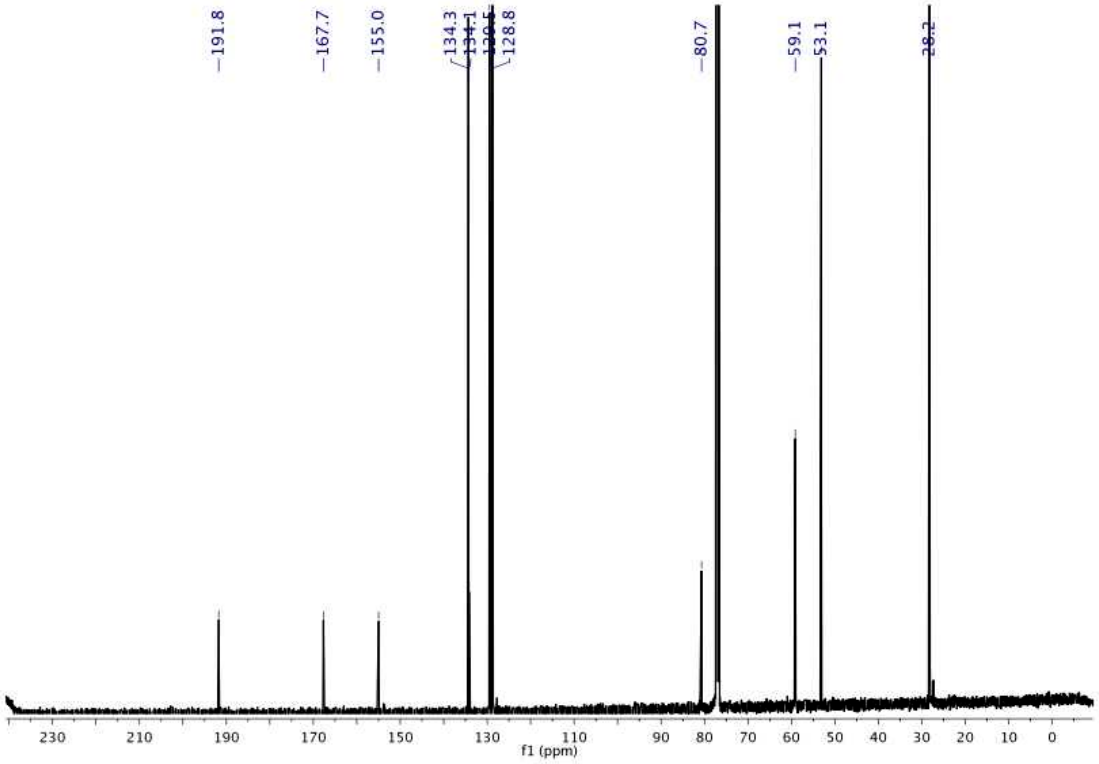
[14] Seashore-Ludlow, B.; Torssell, S.; Somfai, P. *Eur. J. Org. Chem.* **2010**, *2010*, 3927-3933.

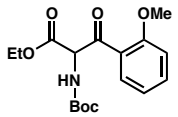


500 MHz, $CDCl_3$



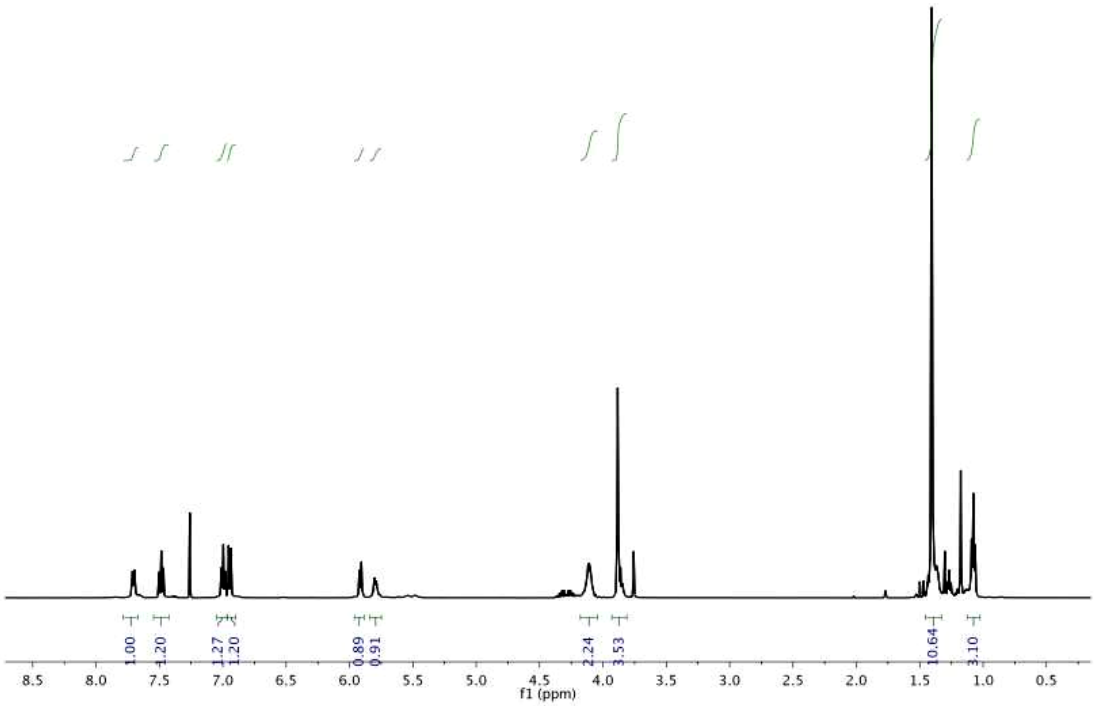
125 MHz, $CDCl_3$



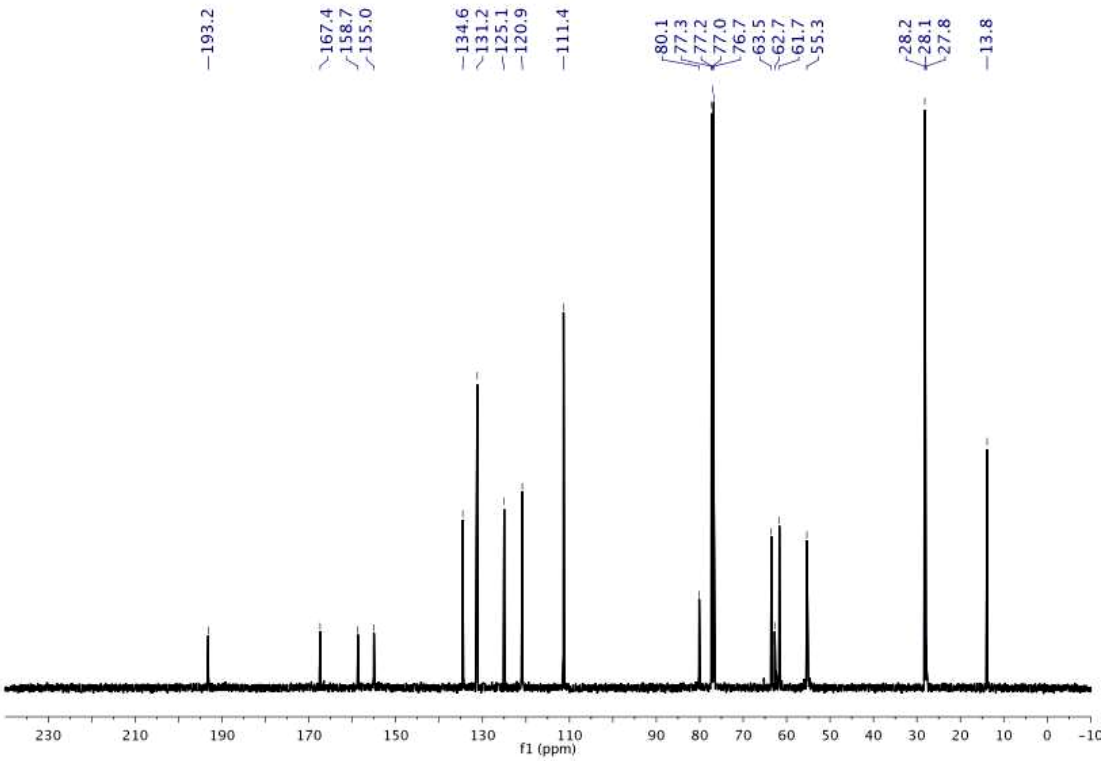


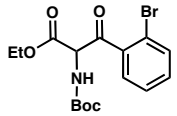
1b

500 MHz, $CDCl_3$



125 MHz, $CDCl_3$

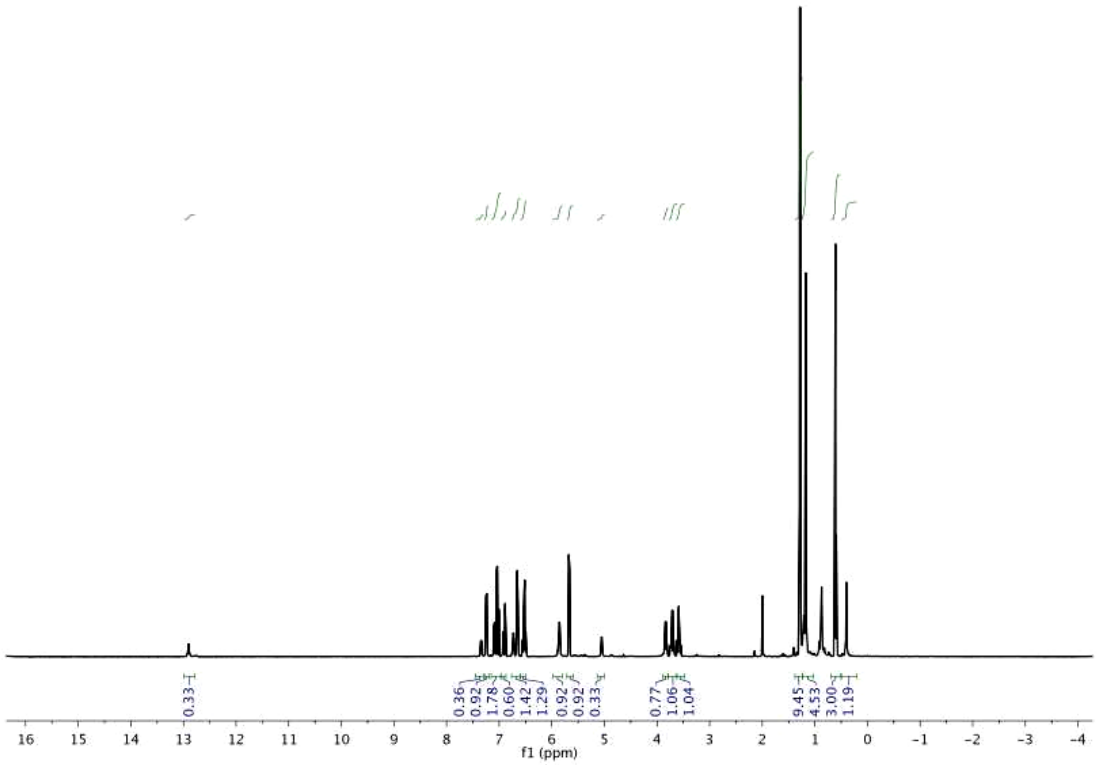




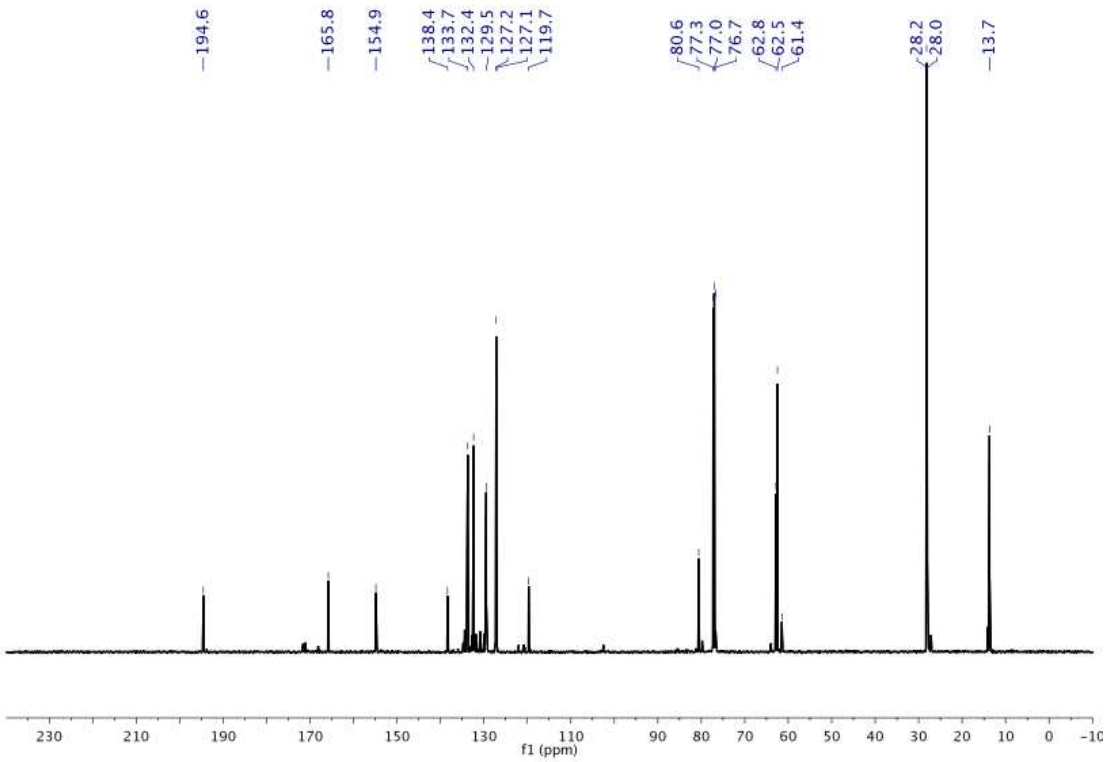
1c

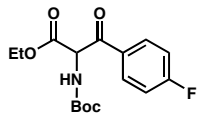
mixture of rotamers/enol isomer

500 MHz, Toluene-D6



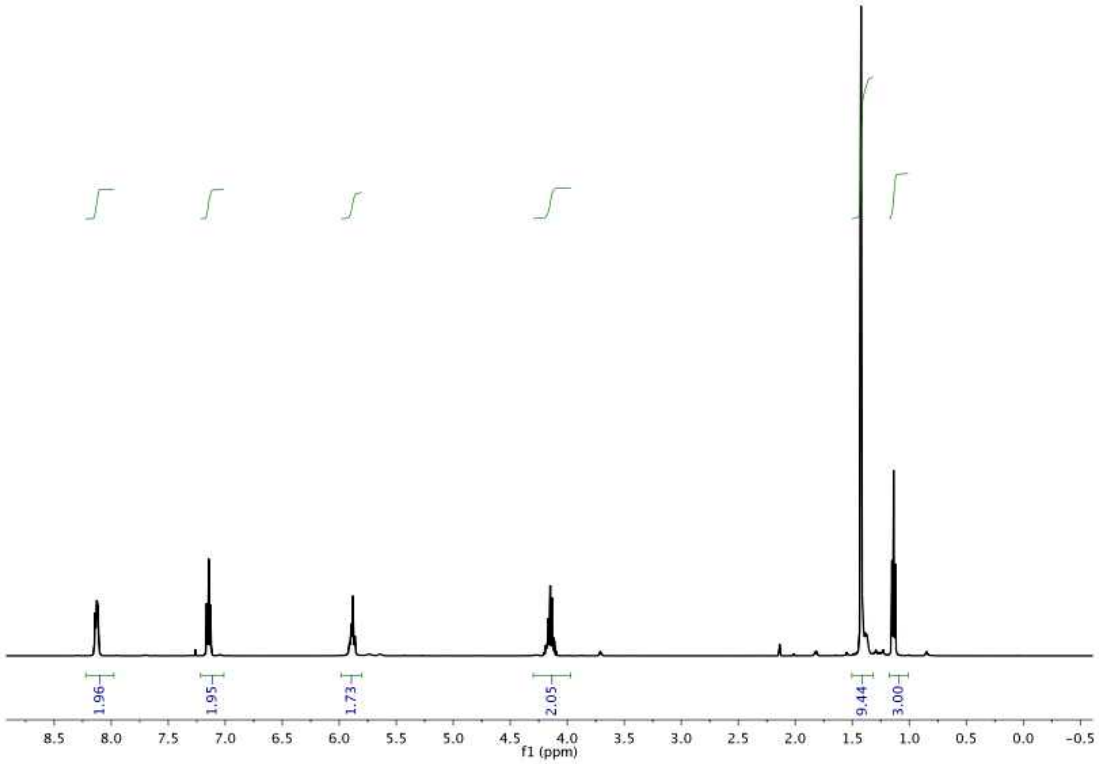
125 MHz, $CDCl_3$



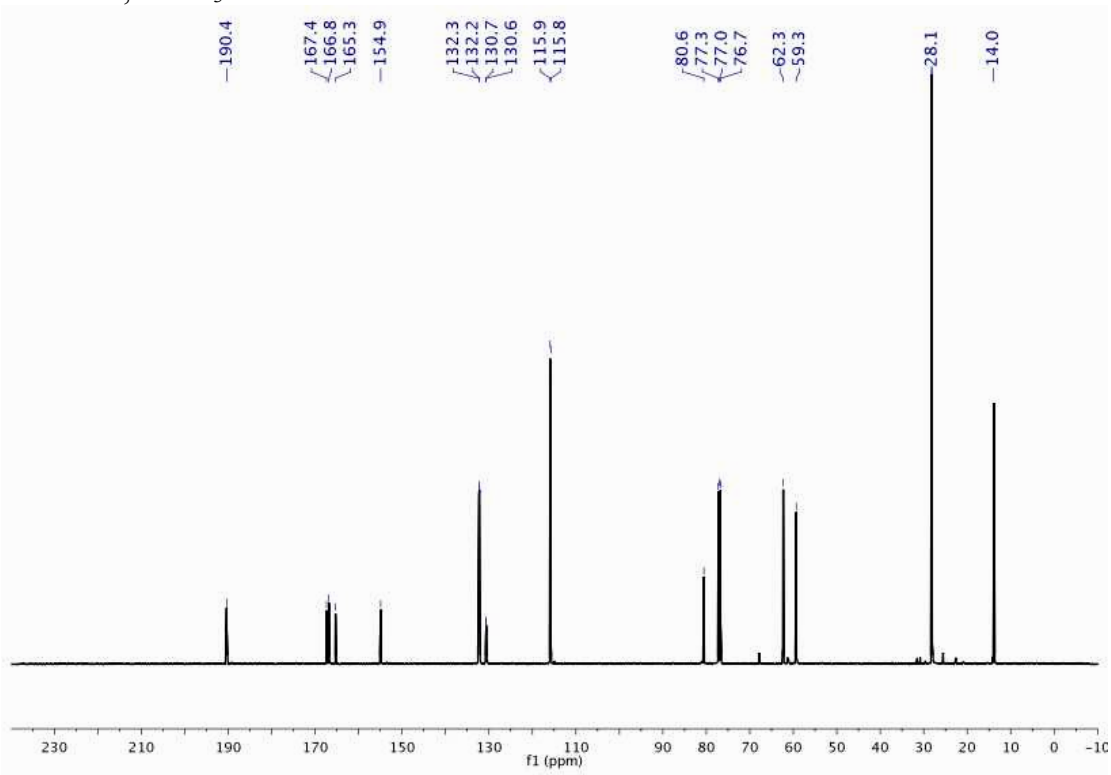


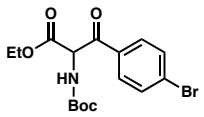
1d

500 MHz, $CDCl_3$



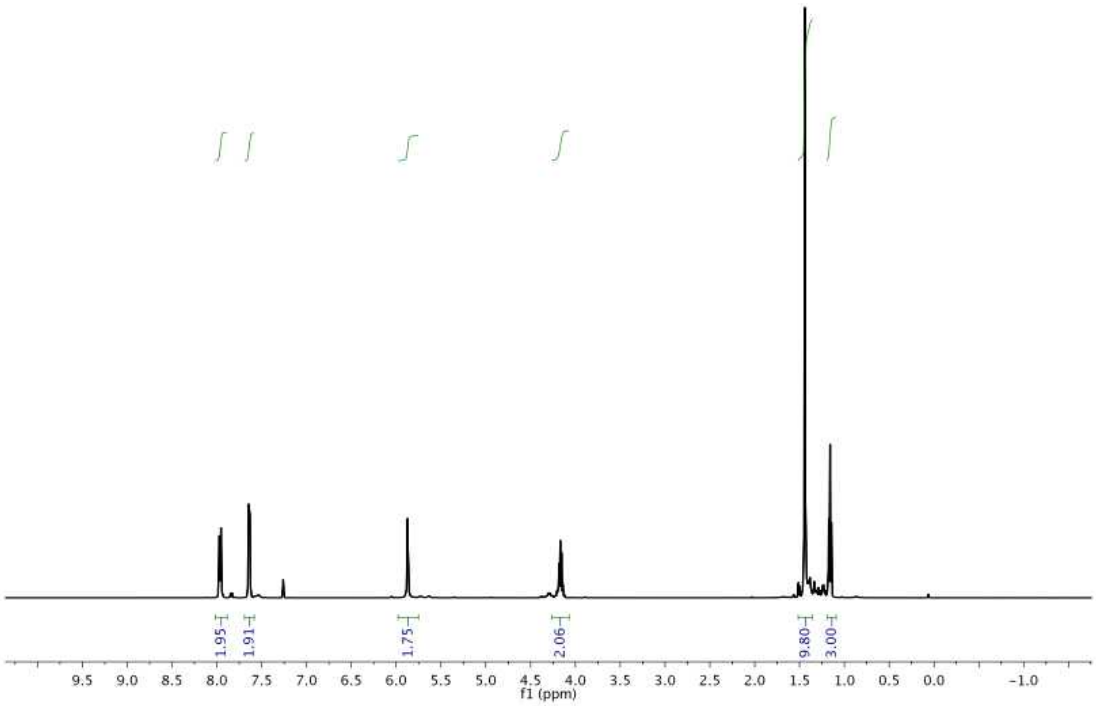
125 MHz, $CDCl_3$



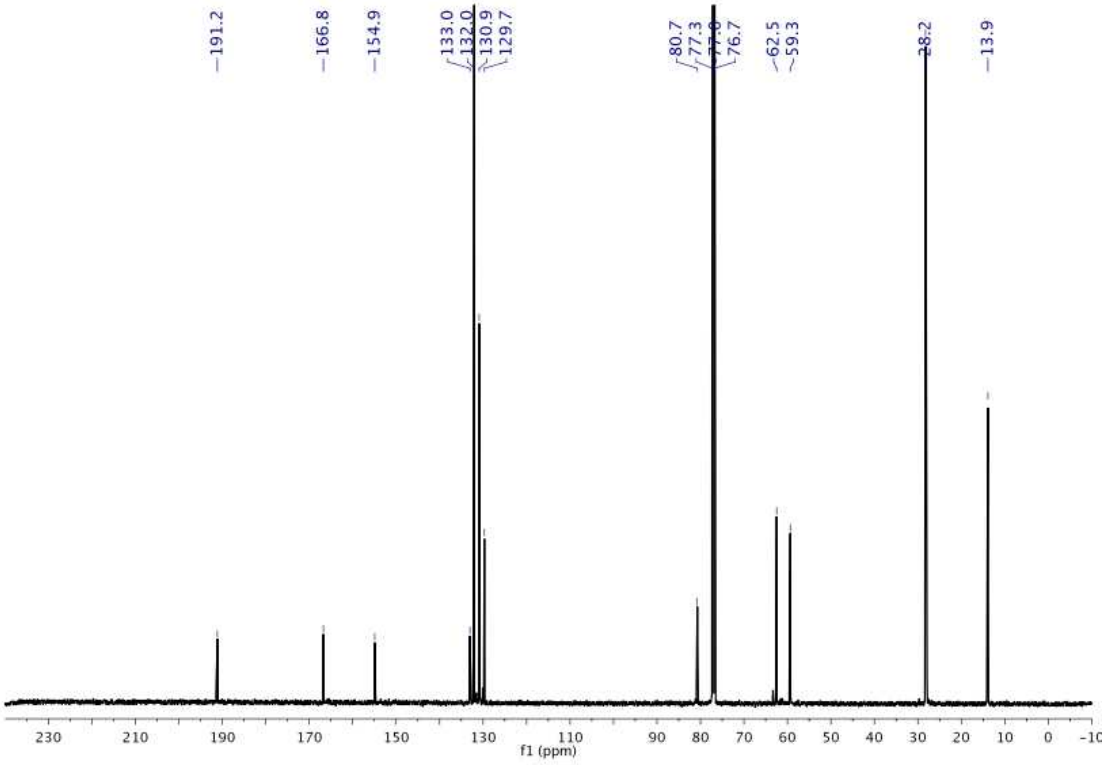


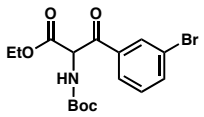
1e

500 MHz, $CDCl_3$



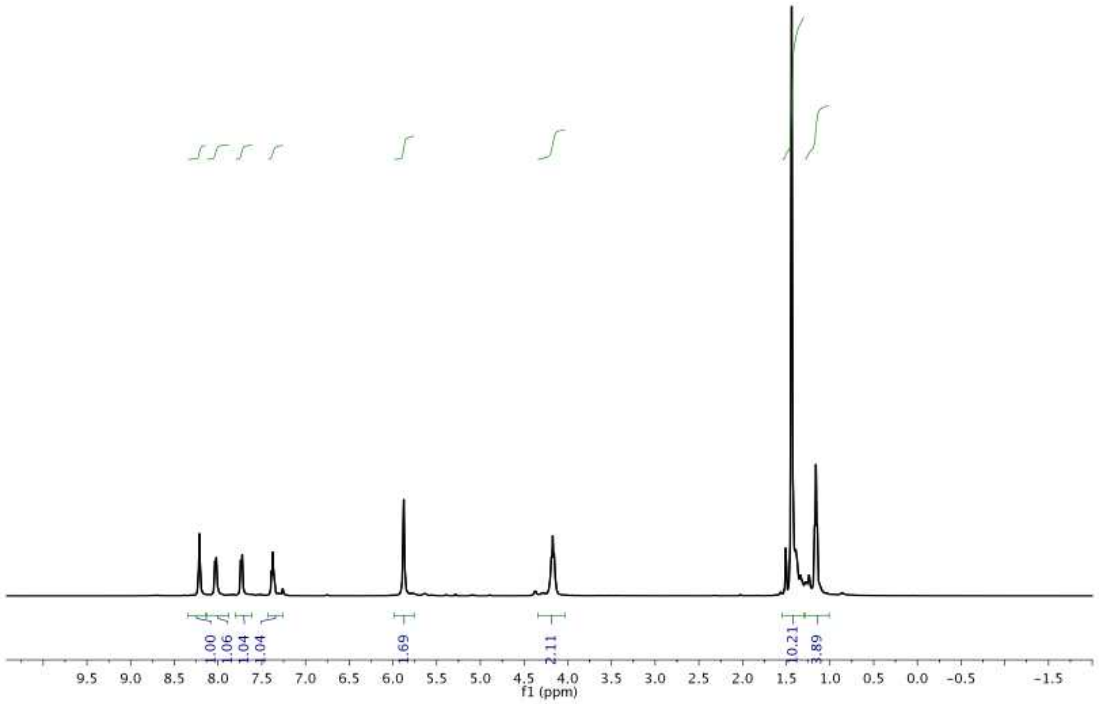
125 MHz, $CDCl_3$



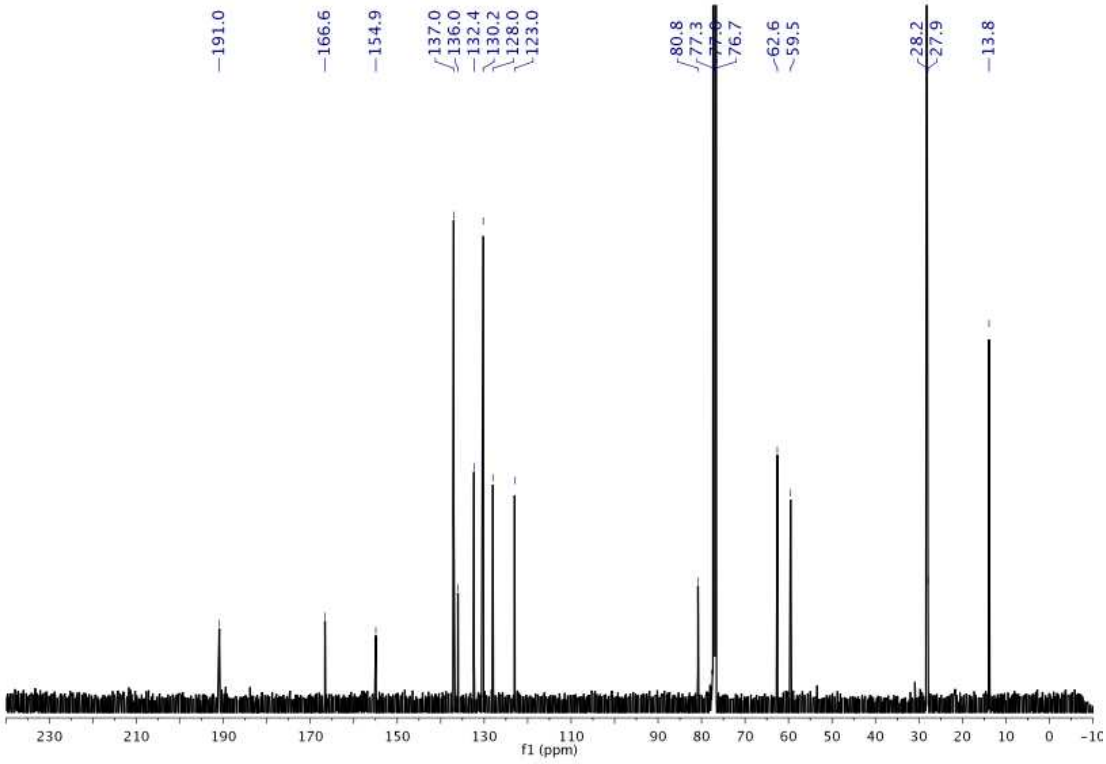


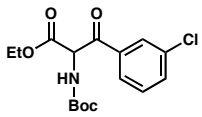
1f

500 MHz, $CDCl_3$



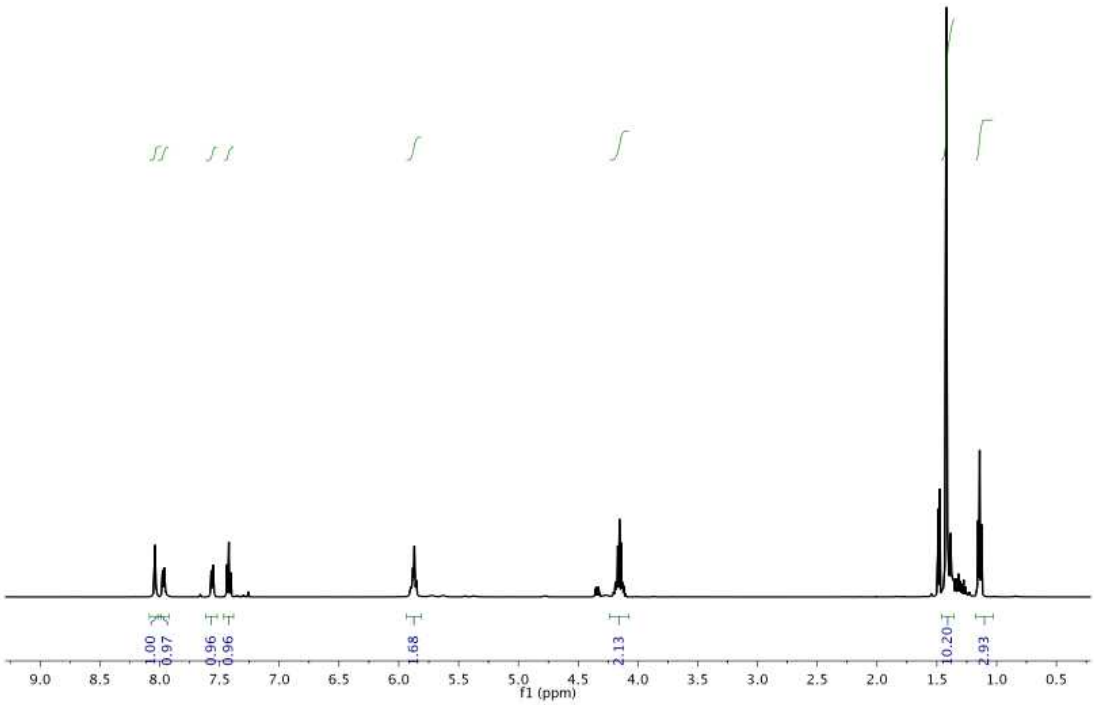
125 MHz, $CDCl_3$



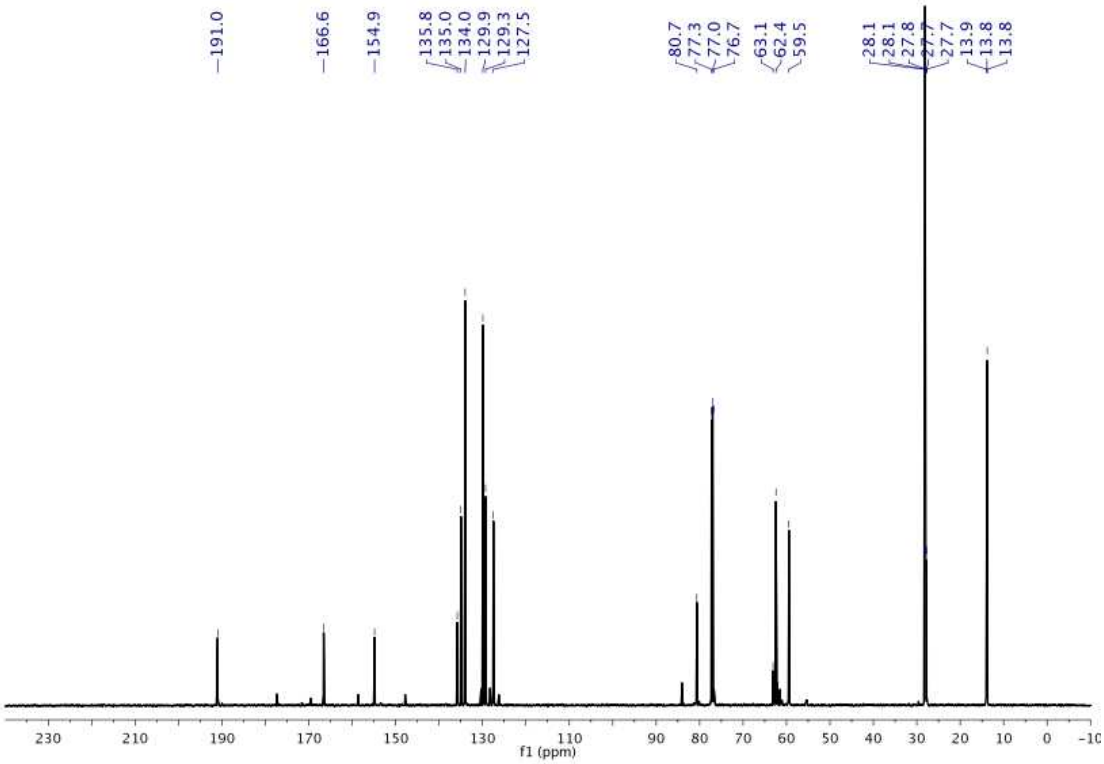


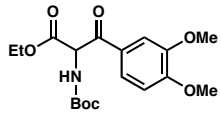
1g

500 MHz, $CDCl_3$



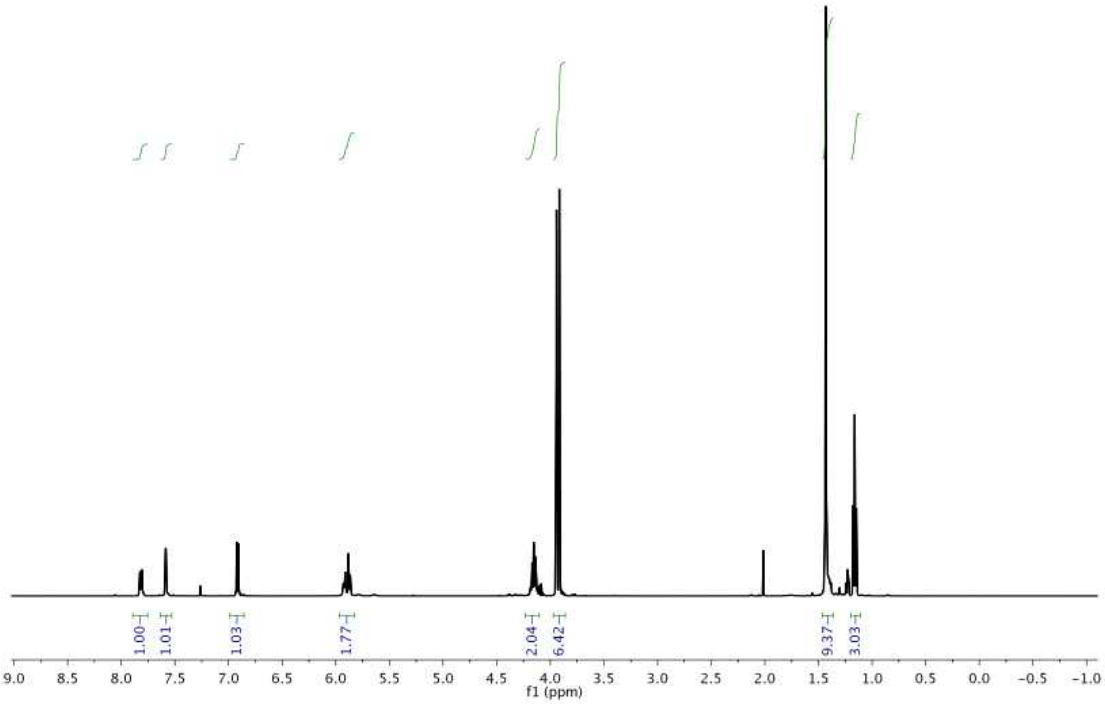
125 MHz, $CDCl_3$



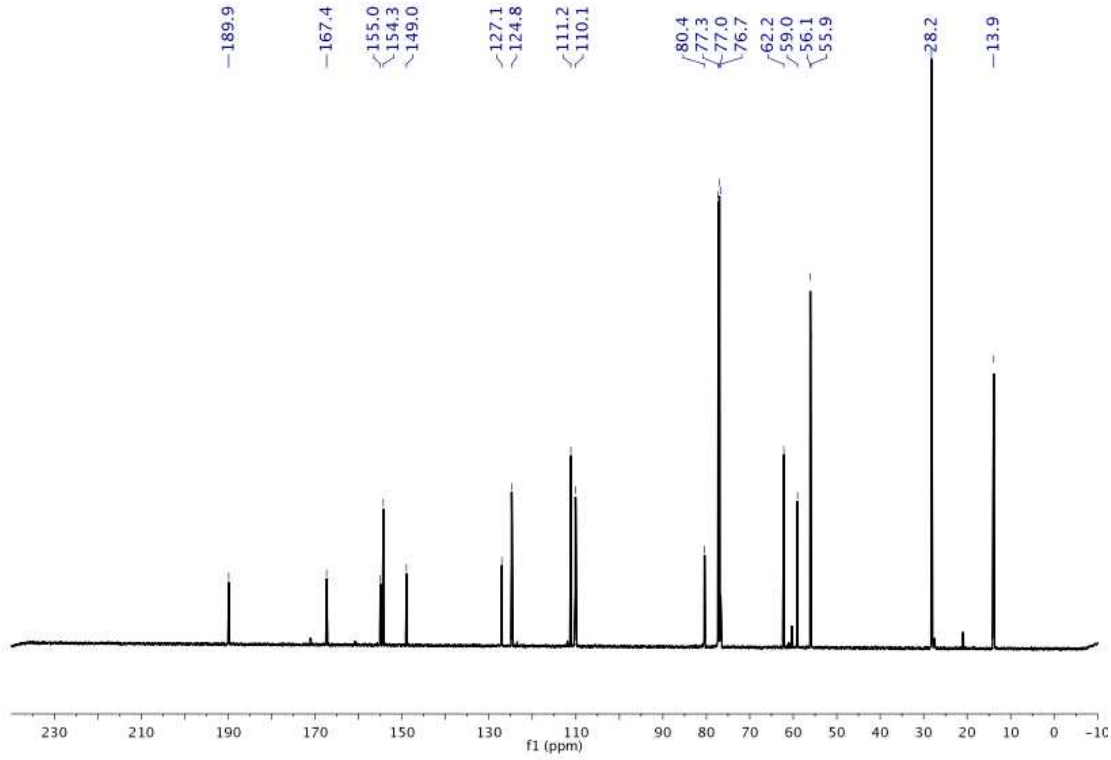


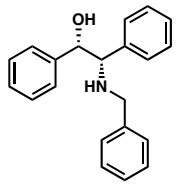
1h

500 MHz, $CDCl_3$



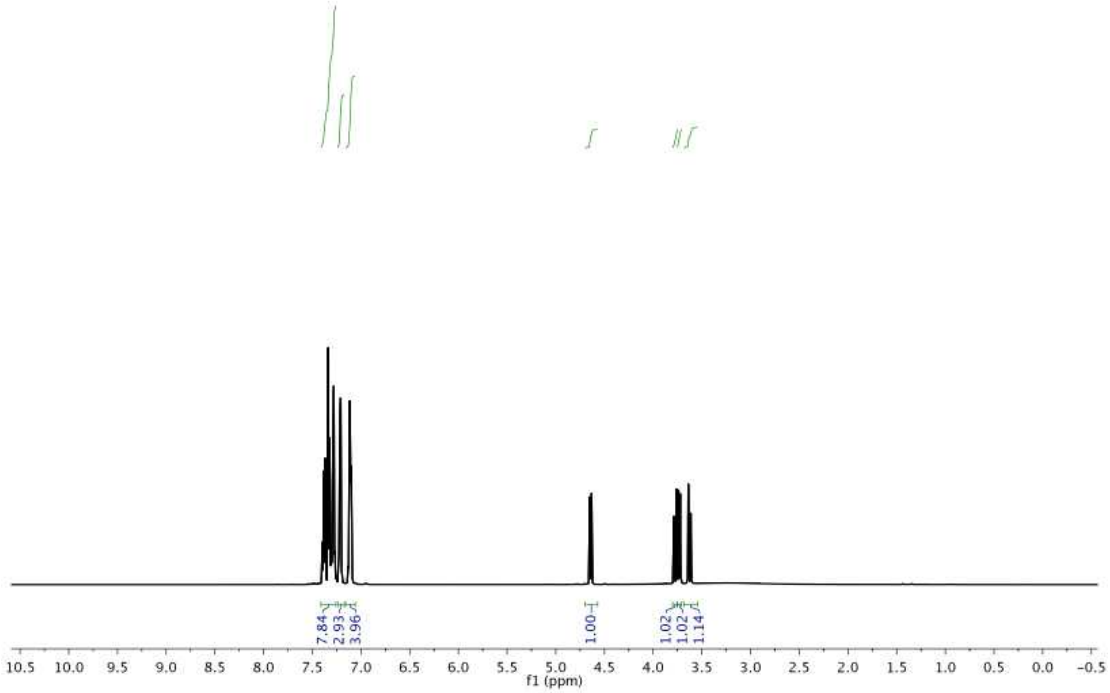
125 MHz, $CDCl_3$



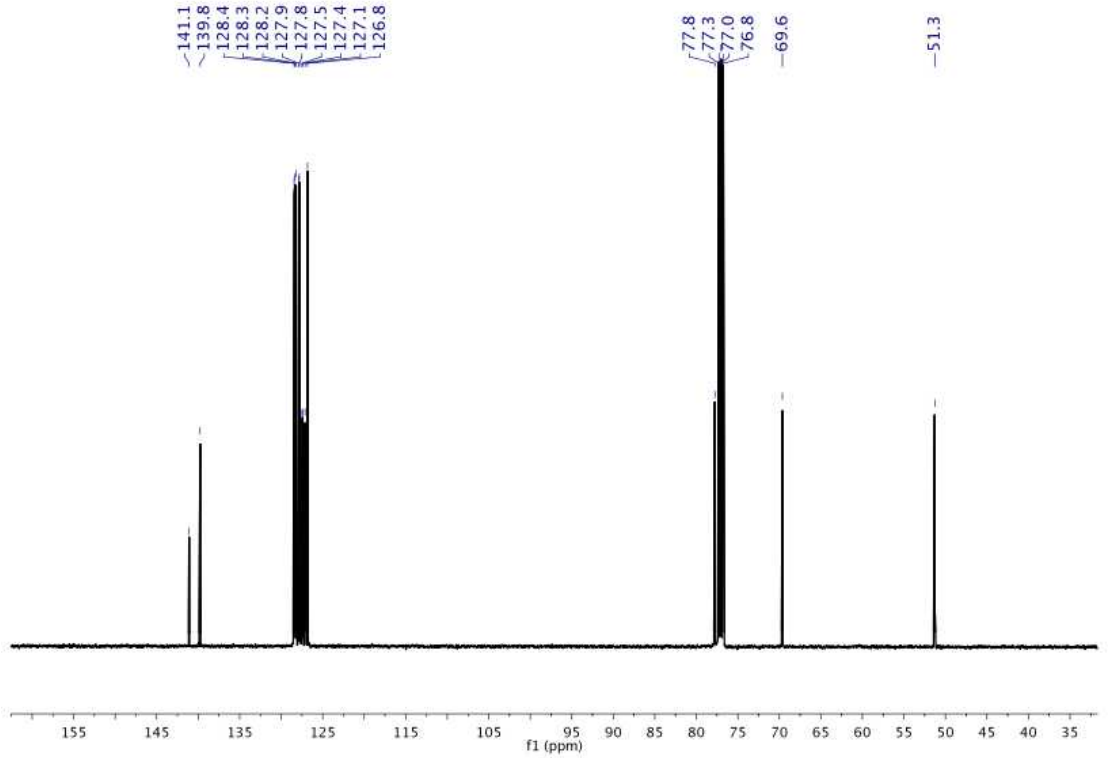


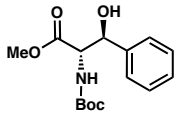
S7

500 MHz, $CDCl_3$



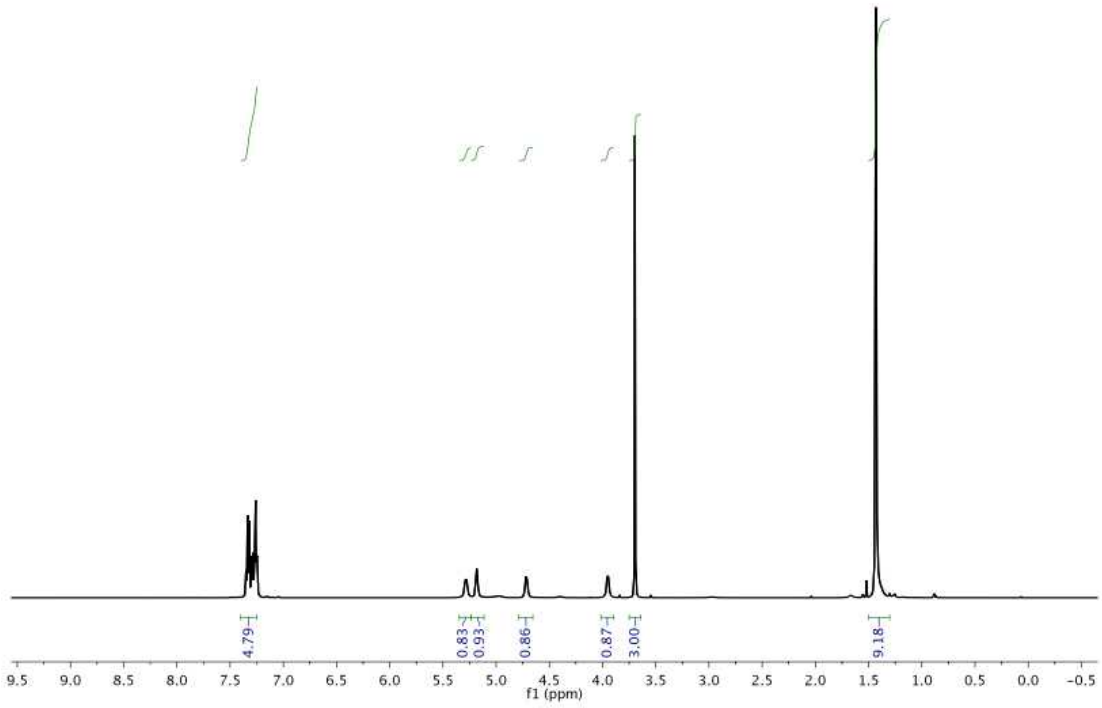
125 MHz, $CDCl_3$



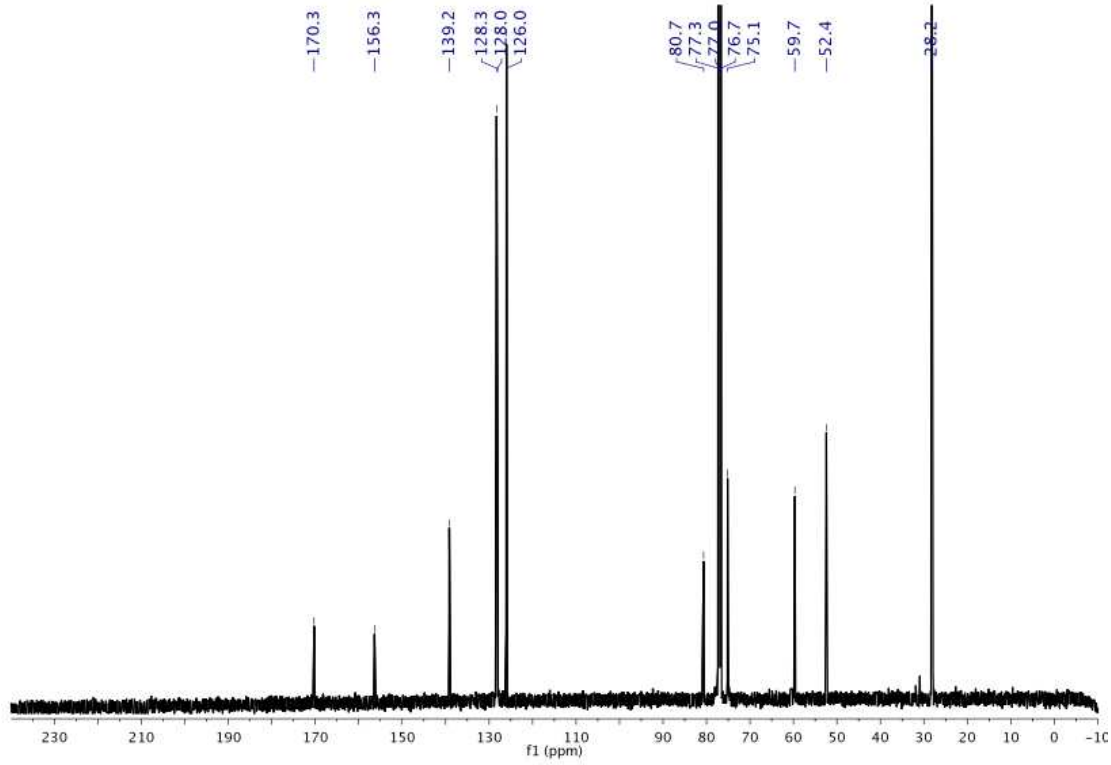


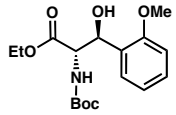
2a

500 MHz, $CDCl_3$



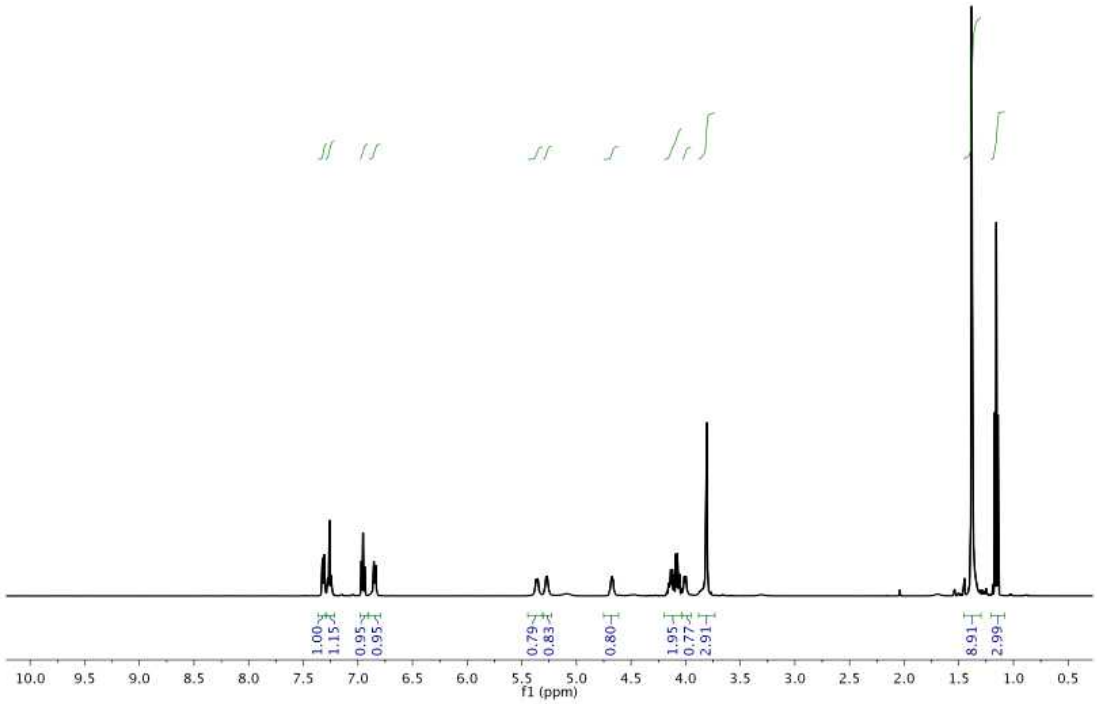
125 MHz, $CDCl_3$



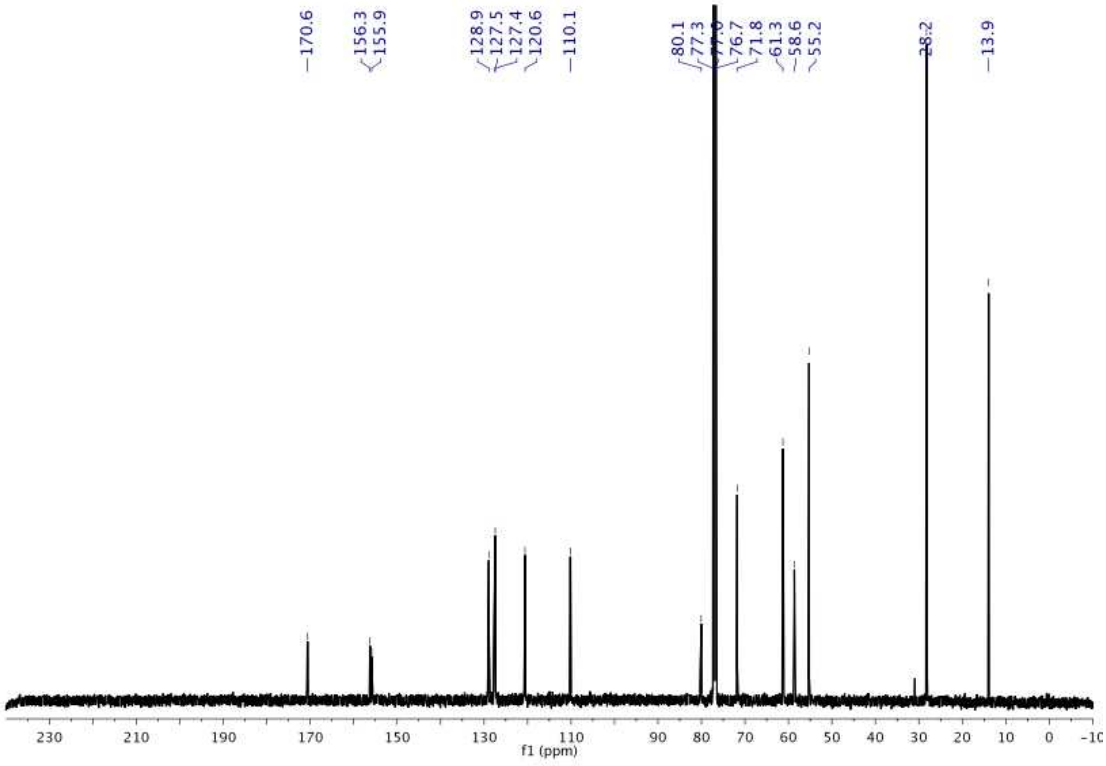


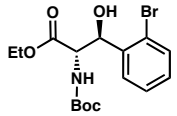
2b

500 MHz, $CDCl_3$



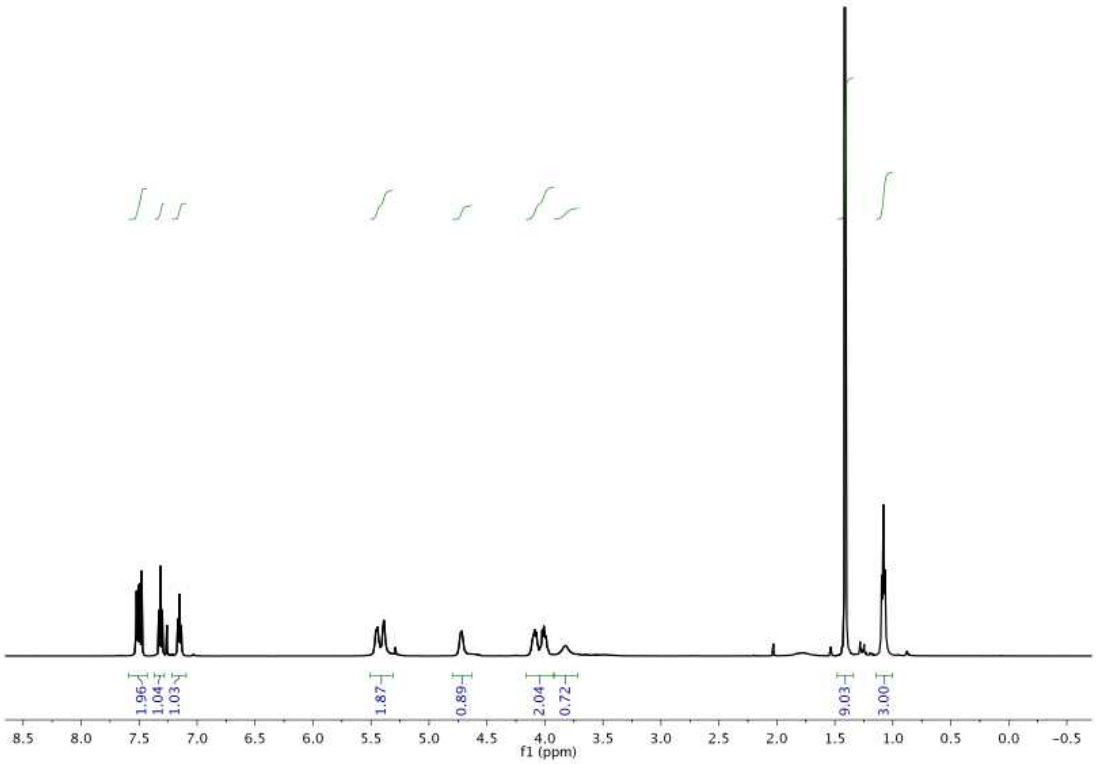
125 MHz, $CDCl_3$



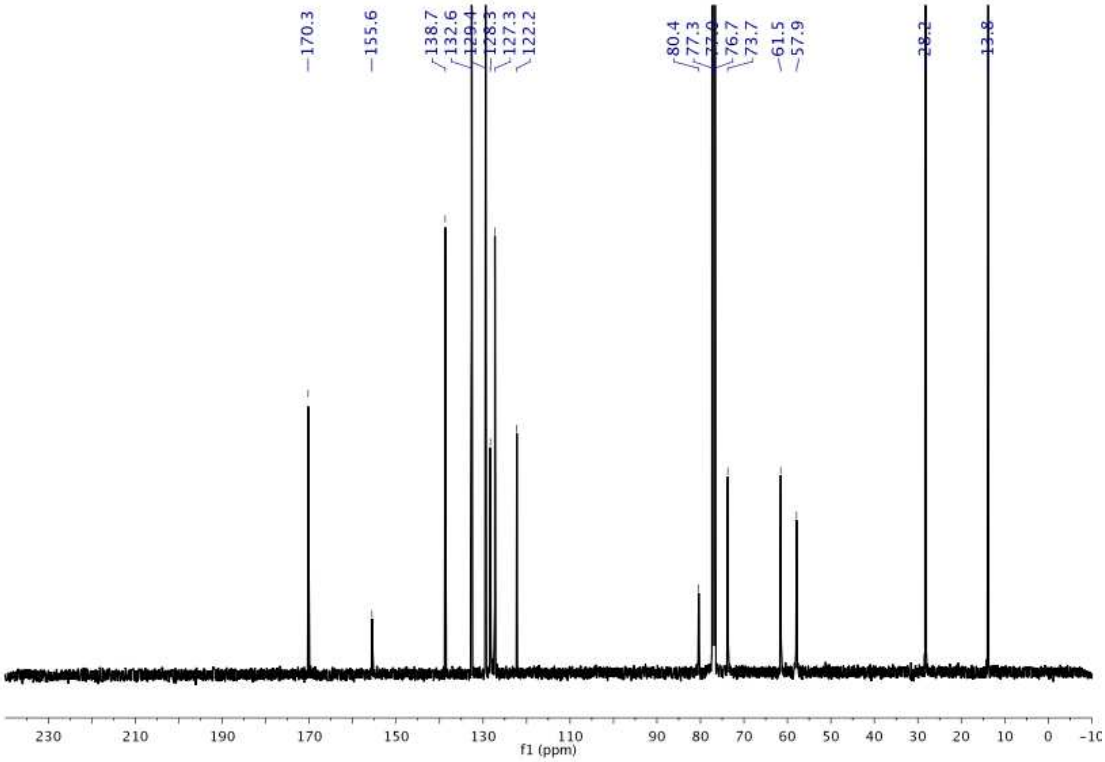


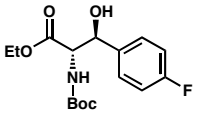
2c

500 MHz, $CDCl_3$



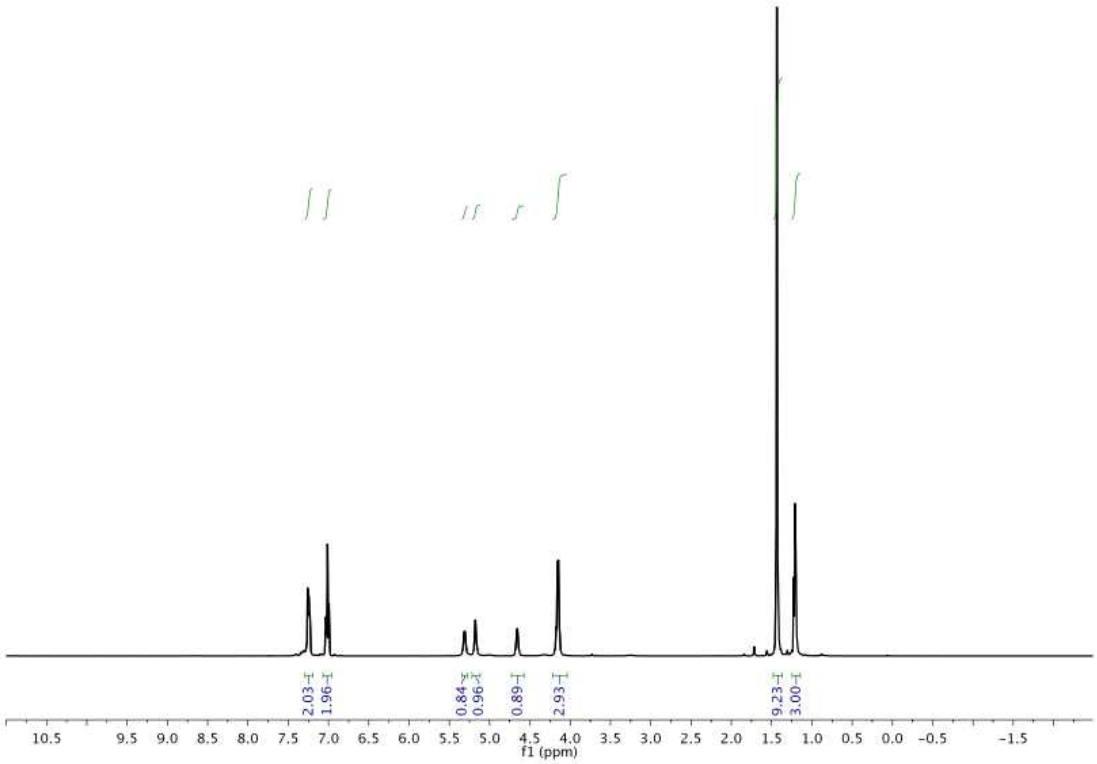
125 MHz, $CDCl_3$



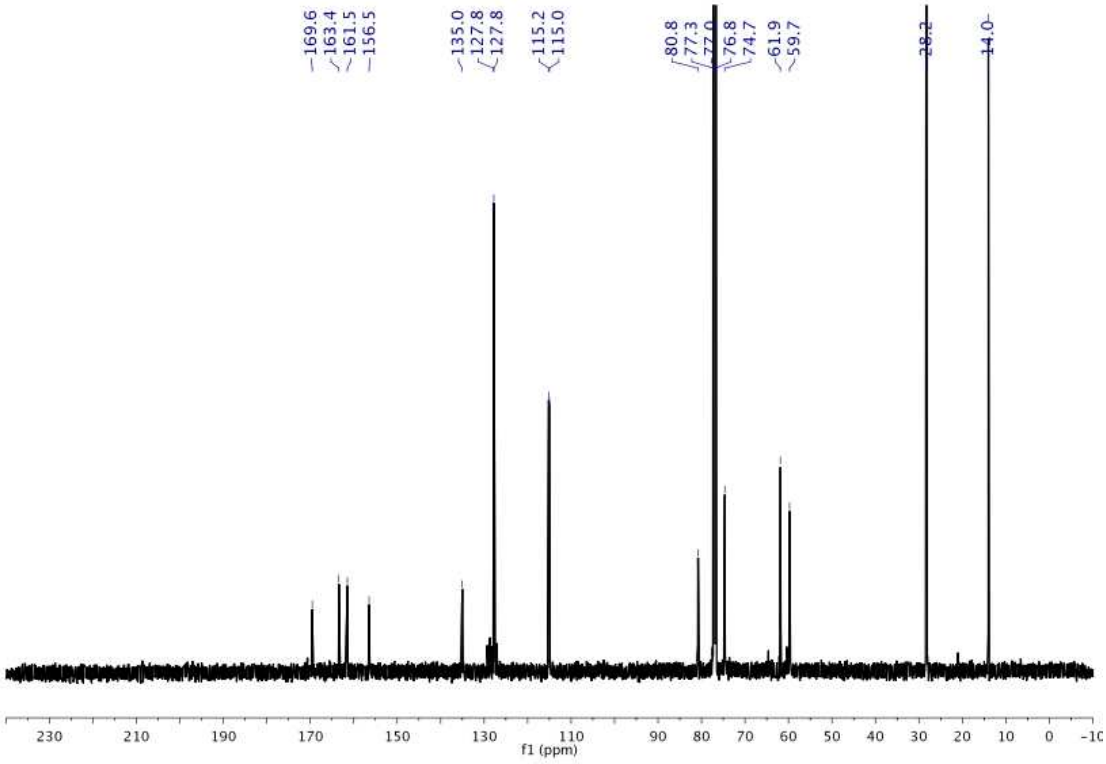


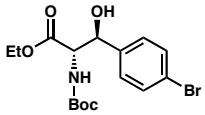
2d

500 MHz, $CDCl_3$



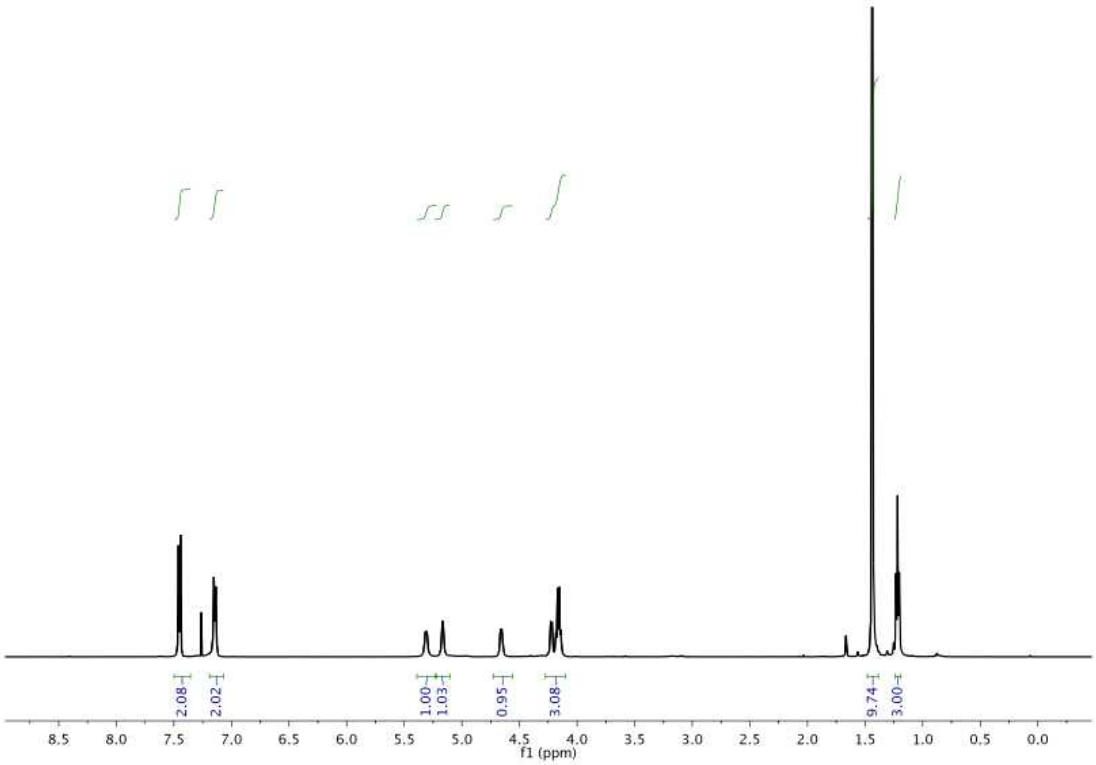
125 MHz, $CDCl_3$



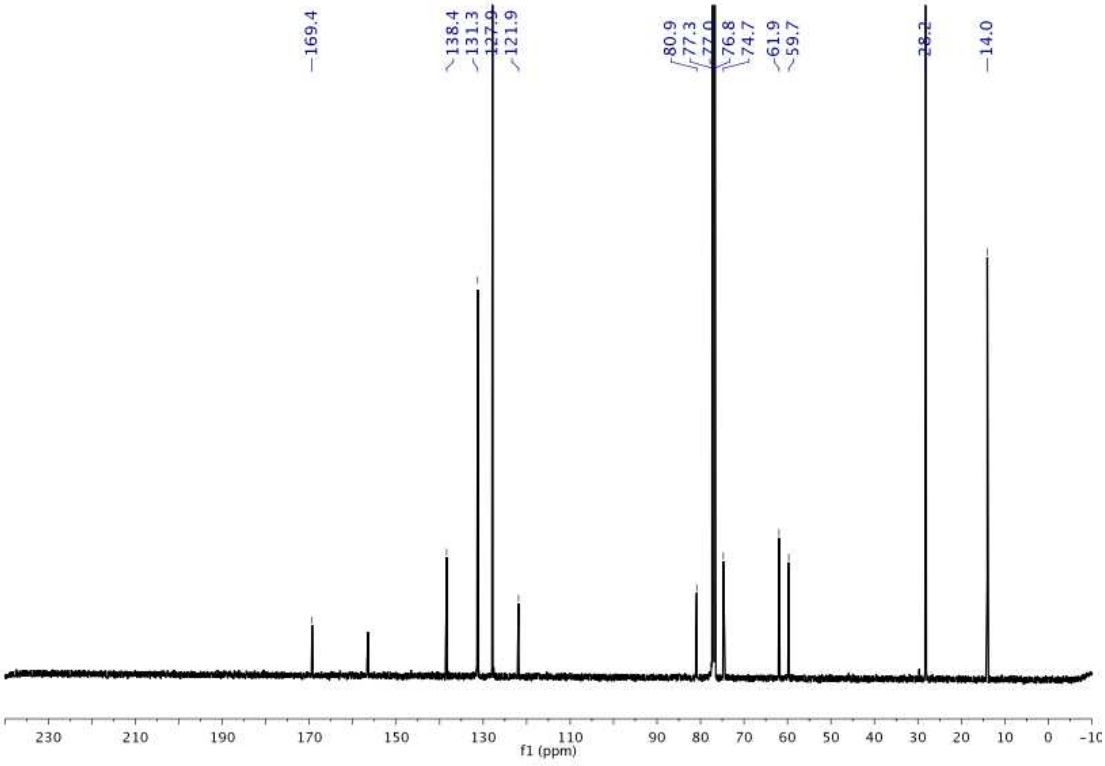


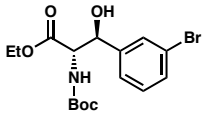
2e

500 MHz, $CDCl_3$



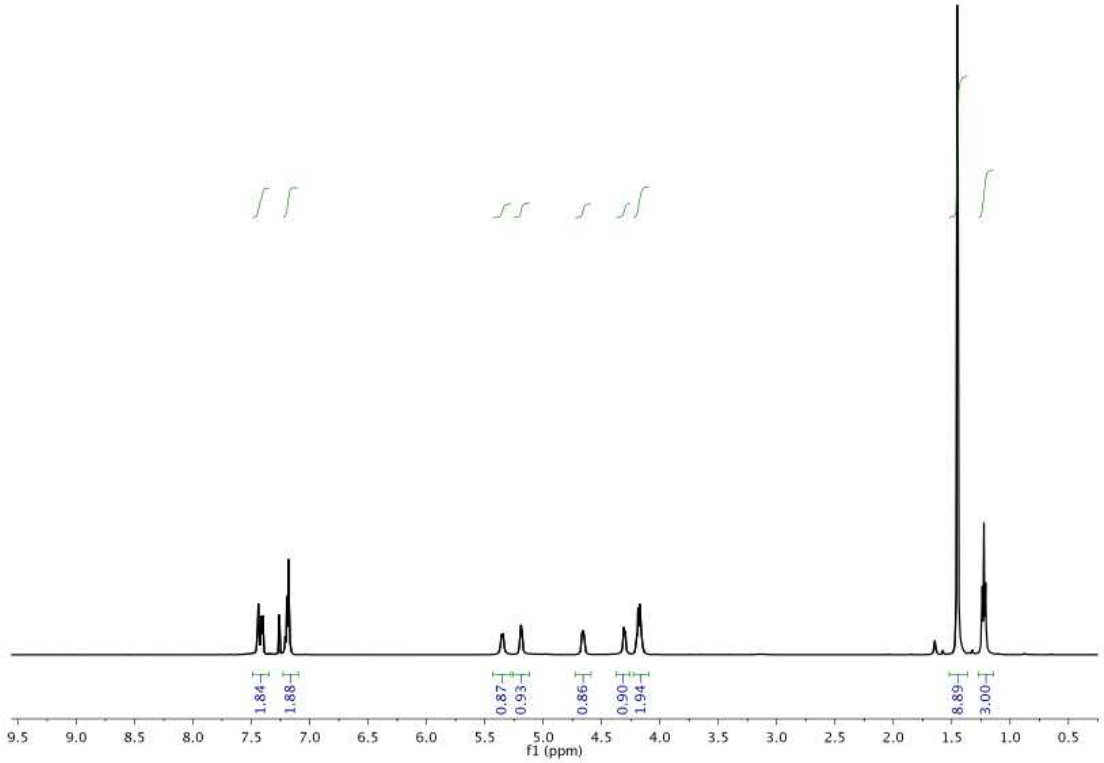
125 MHz, $CDCl_3$



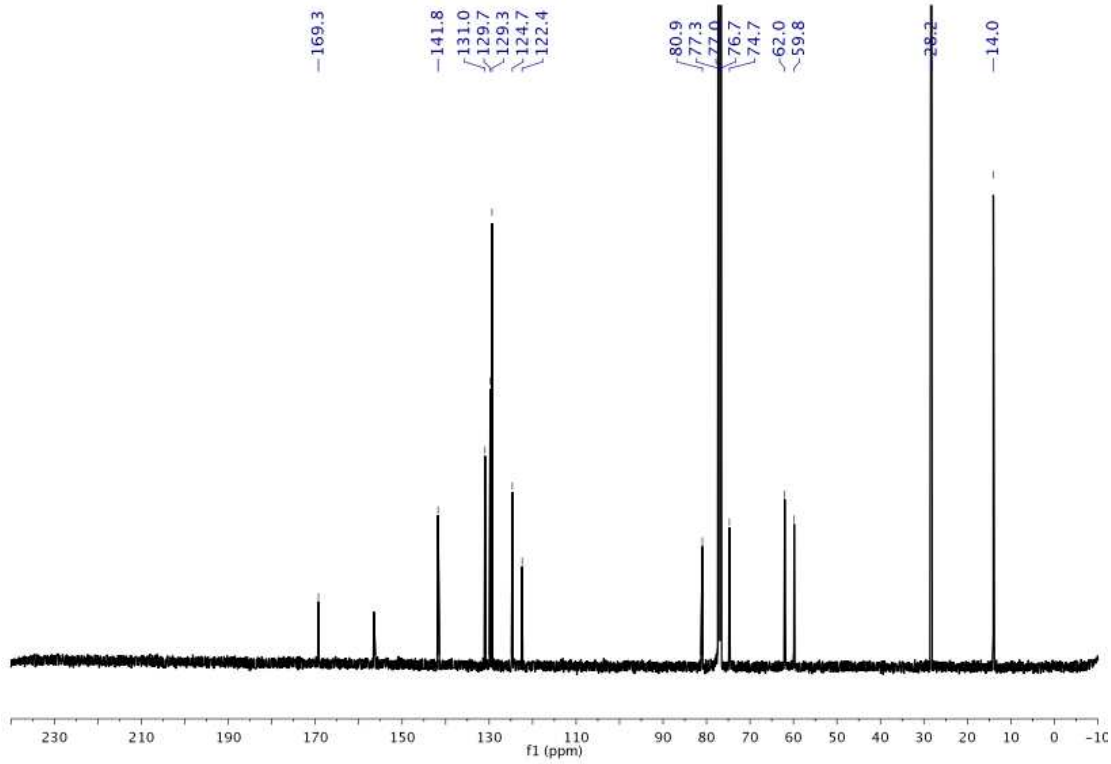


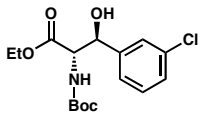
2f

500 MHz, $CDCl_3$



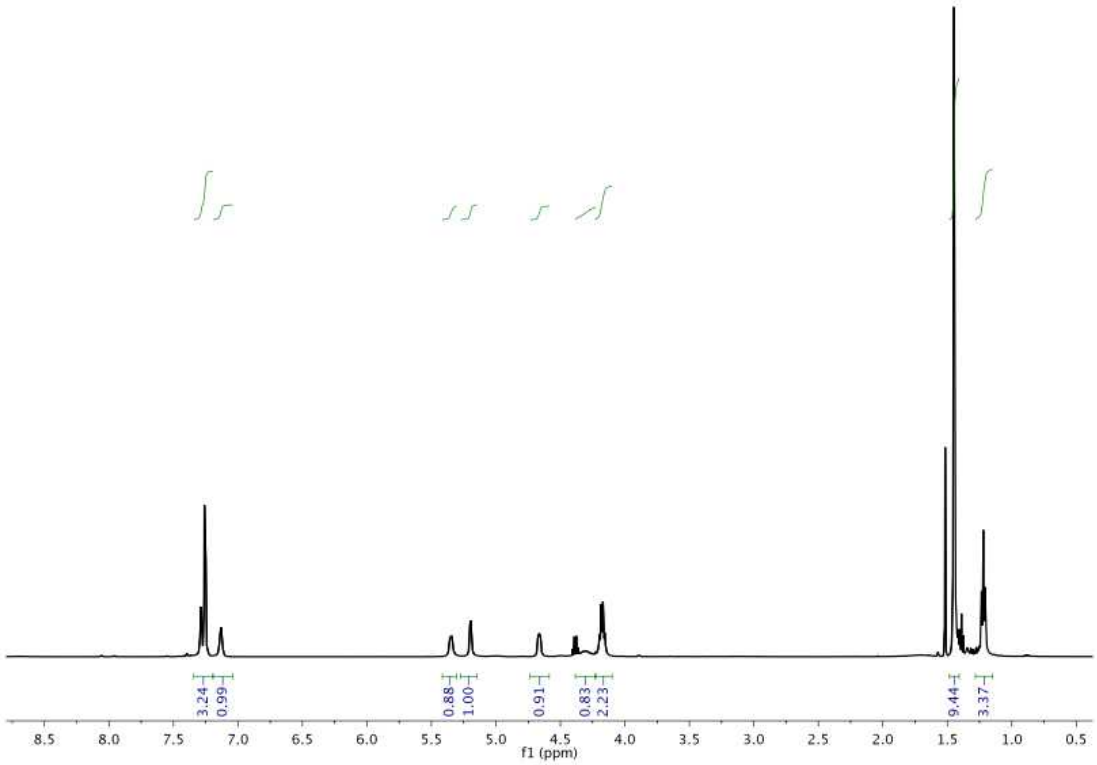
125 MHz, $CDCl_3$



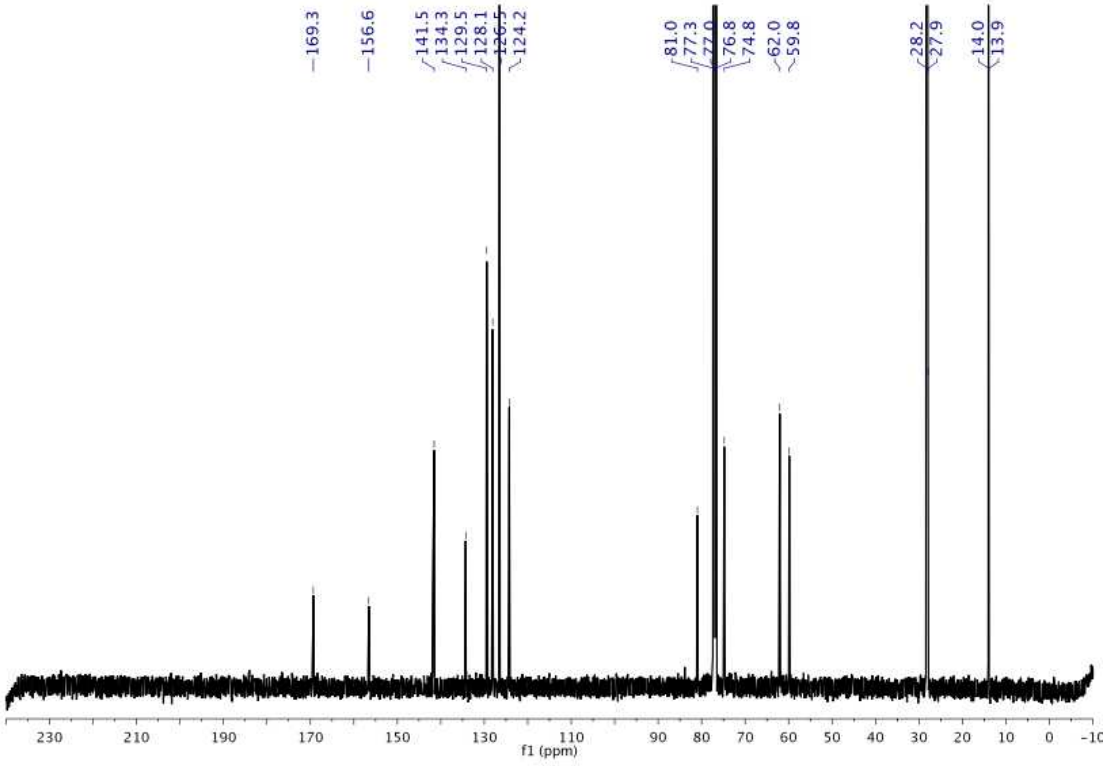


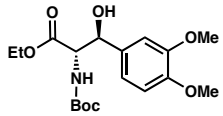
2g

500 MHz, $CDCl_3$



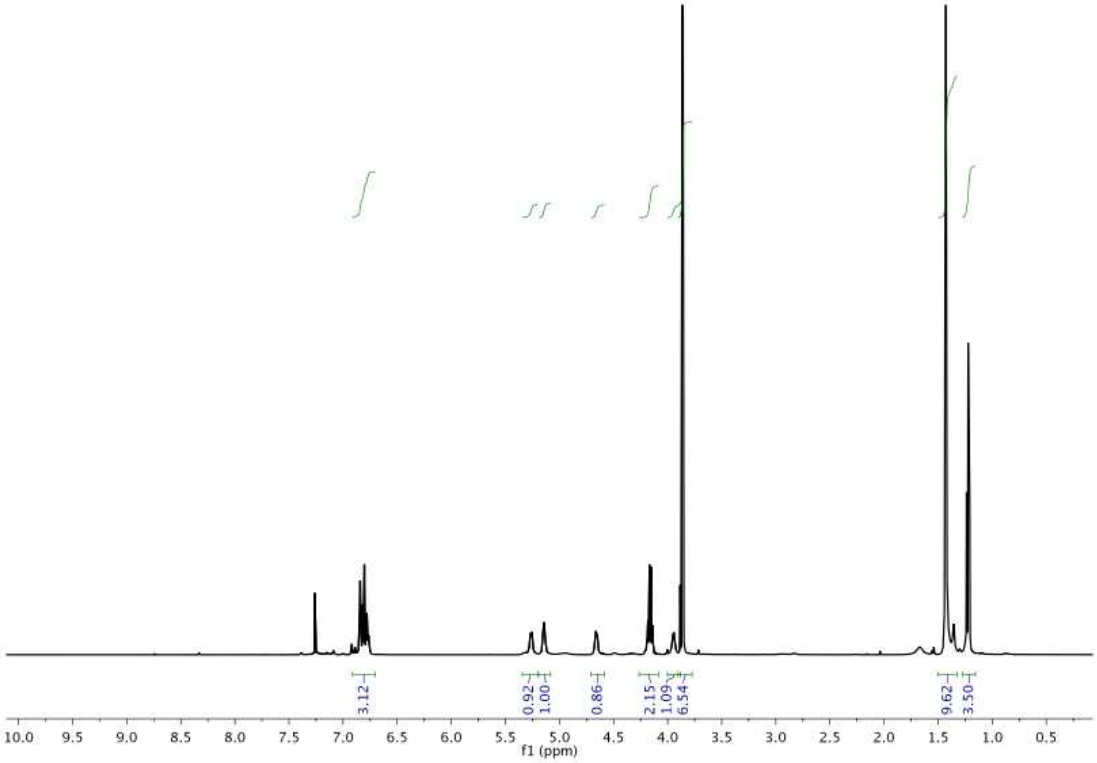
125 MHz, $CDCl_3$



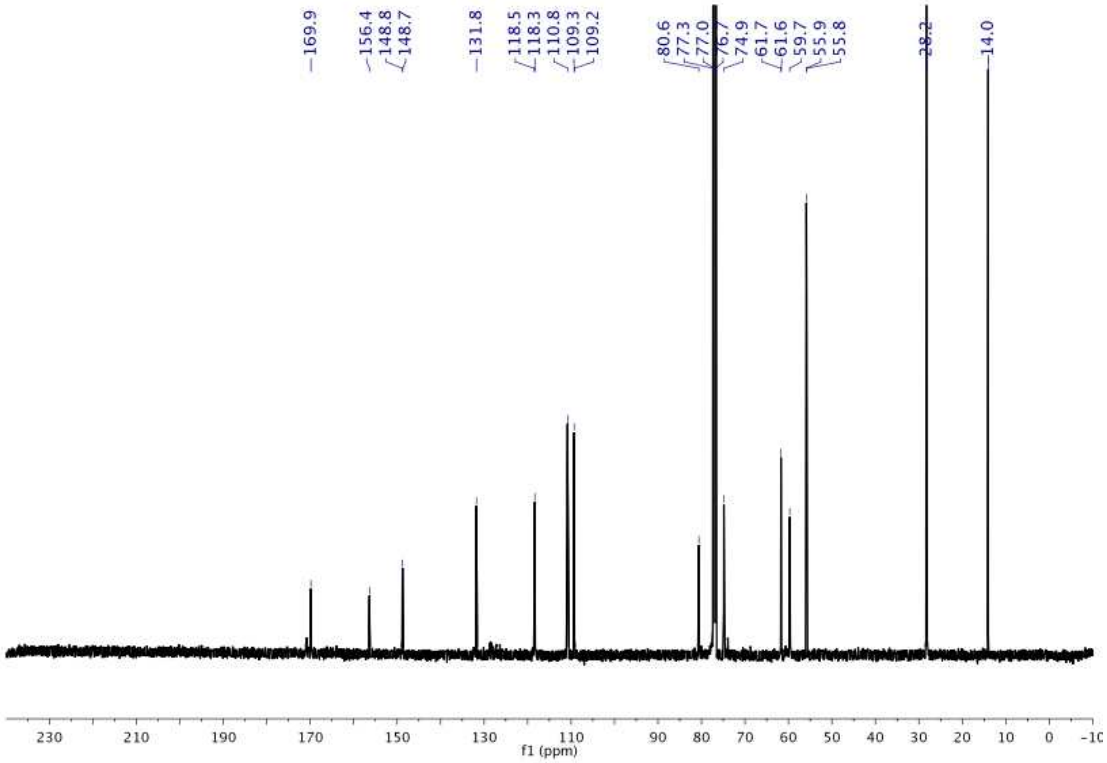


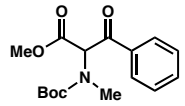
2h

500 MHz, $CDCl_3$



125 MHz, $CDCl_3$

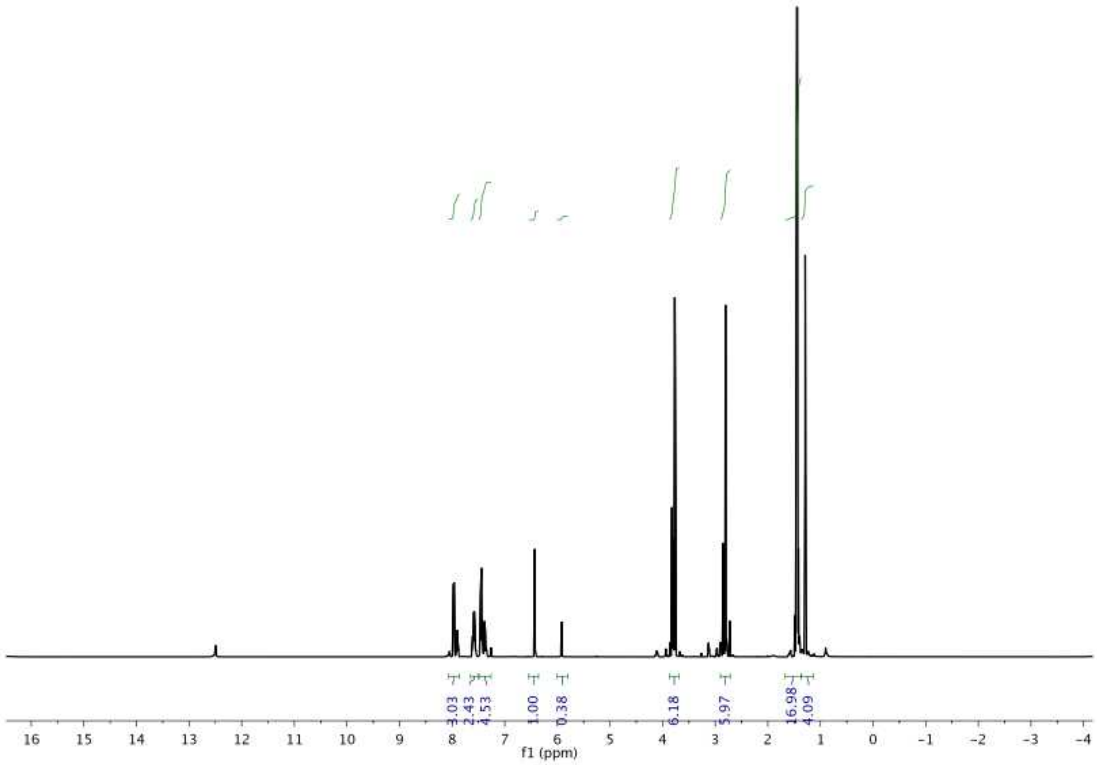




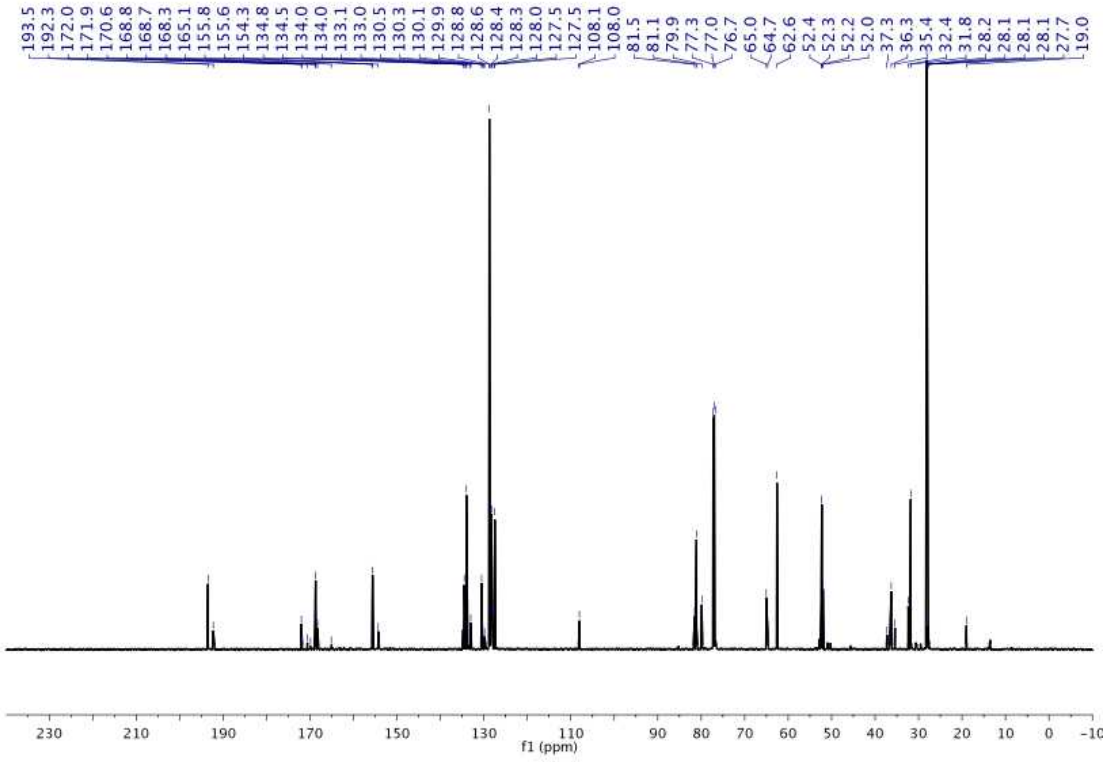
3

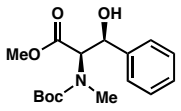
mixture of rotamers

500 MHz, $CDCl_3$



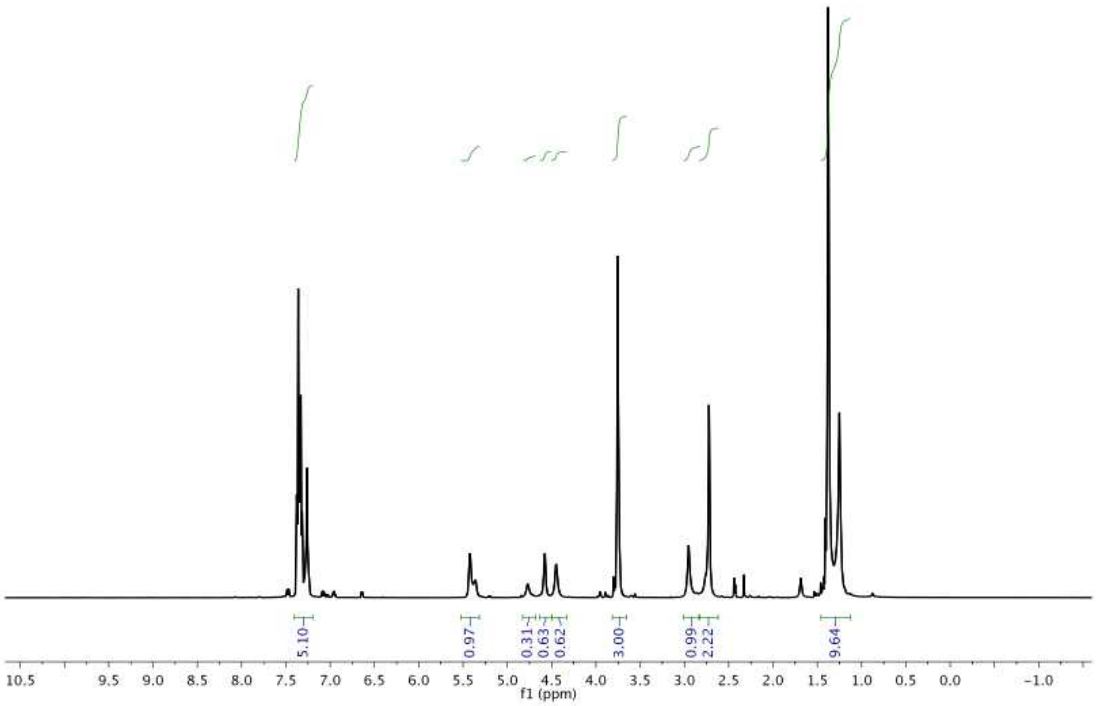
125 MHz, $CDCl_3$



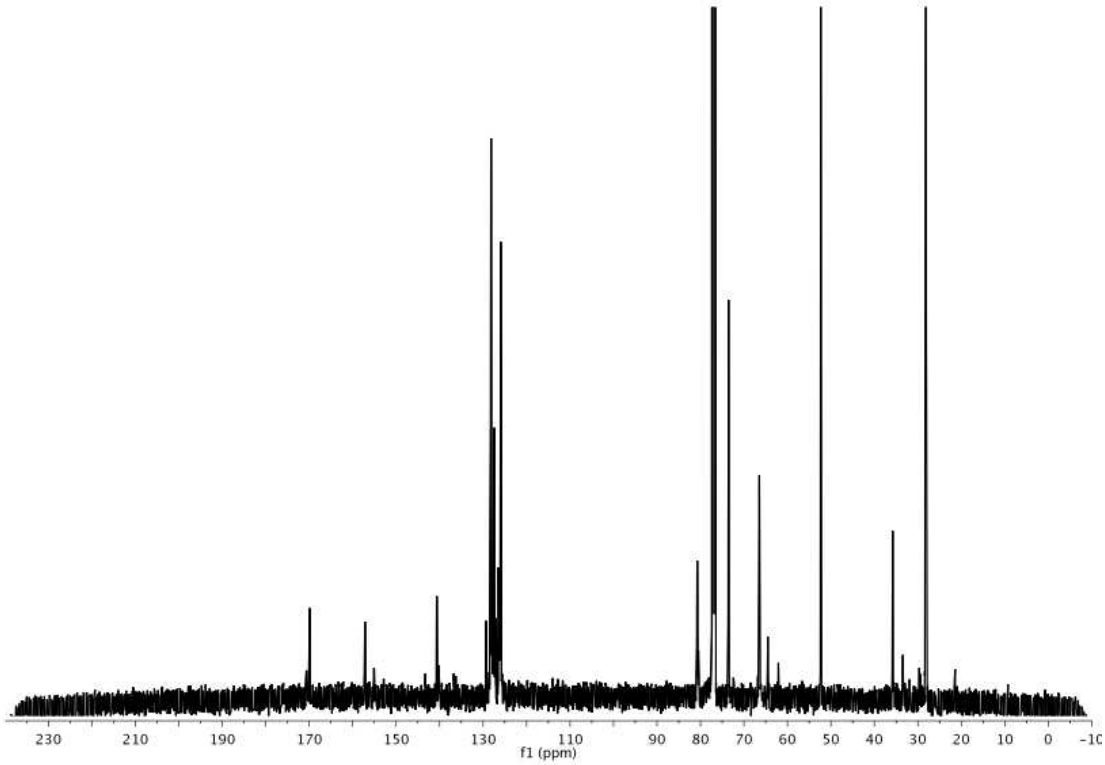


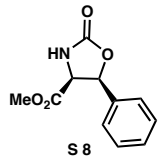
4

500 MHz, $CDCl_3$



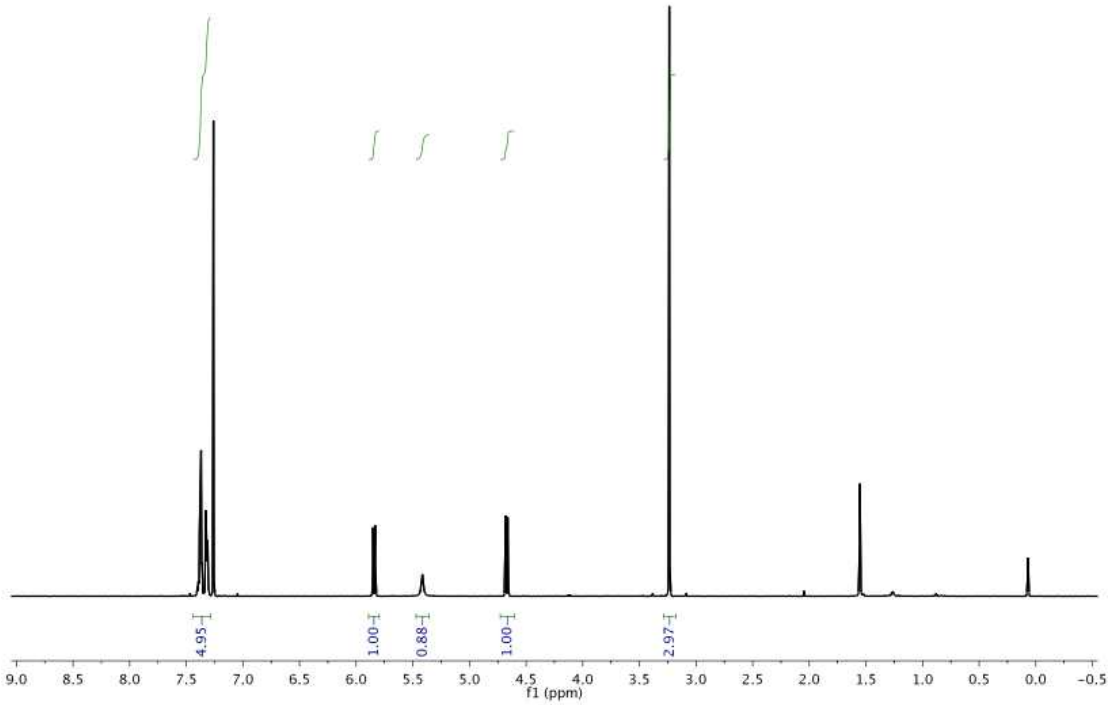
125 MHz, $CDCl_3$

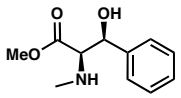




S 8

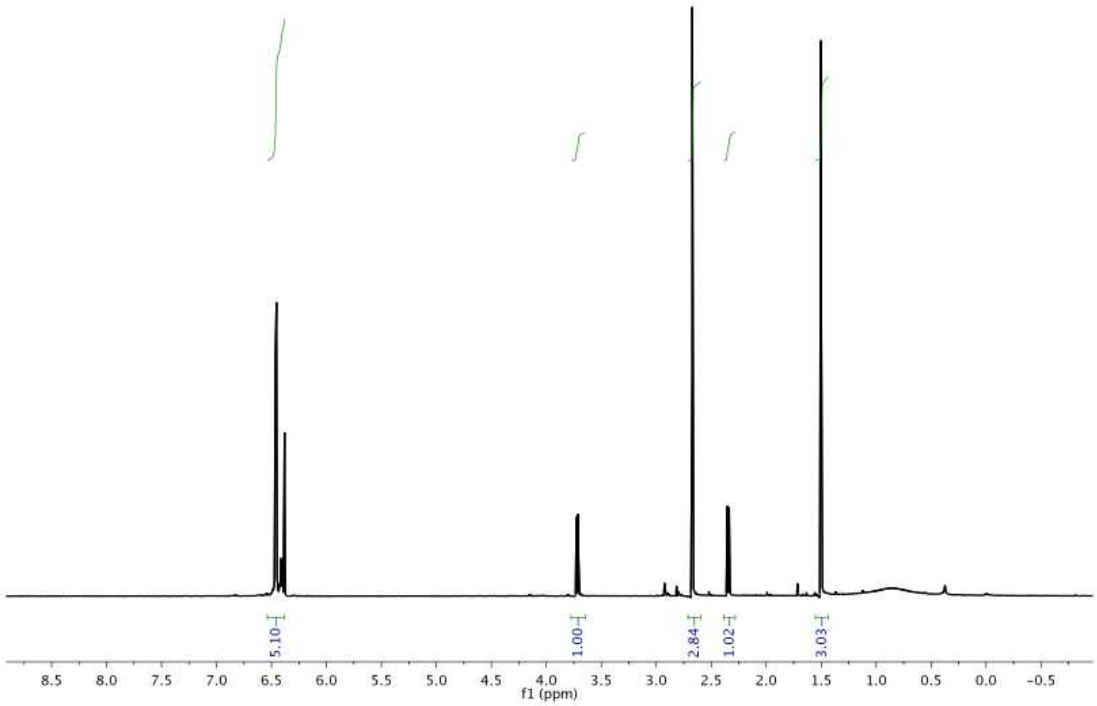
500 MHz, $CDCl_3$

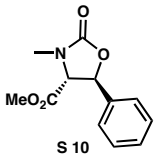




S9

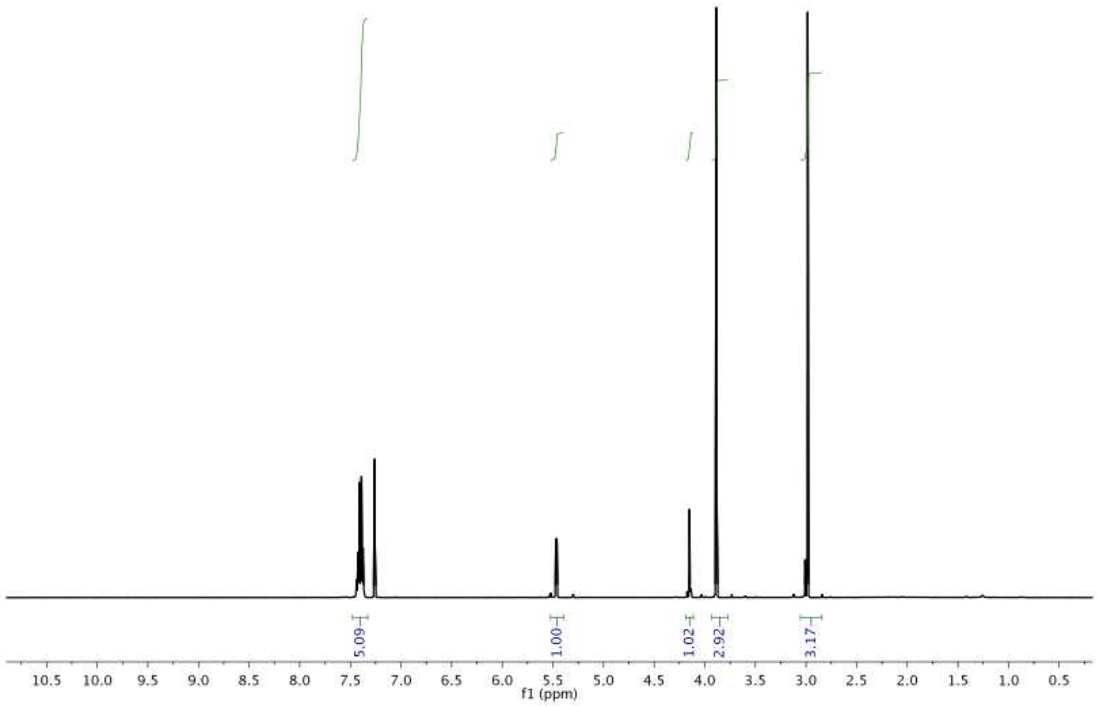
500 MHz, $CDCl_3$





S 10

500 MHz, $CDCl_3$



125 MHz, $CDCl_3$