



Supporting Information

Enantioselective Organocatalytic Synthesis of Bicyclic Resorcinols *via* an Intramolecular Friedel–Crafts-Type 1,4-Addition: Access to Cannabidiol Analogues

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Supporting Information

Enantioselective Organocatalytic Synthesis of Bicyclic Resorcinols via an Intramolecular Friedel-Crafts-Type 1,4-Addition : Access to Cannabidiol Analogues

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1. General

All reagents were supplied by Sigma Aldrich, Alfa-Aesar, Fisher and VWR and were used as supplied unless otherwise stated. Anhydrous DCM, THF, MeOH were obtained from a dry solvent system.

NMR data: Nuclear Magnetic Resonance spectra (NMR) were recorded in deuterated chloroform (CDCl₃) or methanol (CD₃OH) using a Bruker Ascend 400 (400 MHz) or a Bruker NEO 600 (600 MHz) spectrometer using TMS as internal standard. ¹H NMR splitting patterns are designated as singlet (s), doublet (d), doubledoubledoublet (ddd), doublet of triplets (dt), triplet (t), triplet of doublets (td), quintet (quint), quartet (q), doublet of doublet of triplets (ddt) and triplet of doublets of doublets (tdd). All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplet (m) or broad (br) and the coupling constants *J* are quoted in Hz. All assignments are confirmed by 2D-COSY, 2D-HSQC and HSQC-TOCSY and NOESY measurements where necessary. ¹³C NMR spectra were recorded at 100 MHz on a Bruker Ascend 400 (400 MHz) or a Bruker NEO 600 (150 MHz). NMRs taken on the Bruker NEO 600 (600MHz) were carried out at the NMR Facility of the Centre for Biomolecular Spectroscopy at King's College London. Thank you to Dr R.A. Atkinson for assistance in setting up the experiments.

IR data: IR spectra were recorded on a Shimadzu IRAffinity-1S FTIR Spectrophotometer as a thin film. The selected absorptions are quoted in wavenumbers (cm⁻¹).

MS Data: High-resolution mass spectra were recorded on either Waters LCT Premier (Es-Tof), Thermo Scientific Q-Exactive (APCI) and Micromass Autospec Premier (EI) by Imperial College London, Department of Chemistry Mass Spectrometry Service.

Specific Rotation: Specific rotations were taken using an Anton Parr MCP100 Polarimeter. Specific rotations ($[\alpha]_D^{25}$) were recorded at the sodium D line (589 nm) in methanol or dichloromethane and are quoted in : deg cm² g⁻¹. Solution

concentrations (c) are given in units of 10^{-2} g mL⁻¹. Temperatures are in degrees Celsius (°C). The prefixes (+) and (-) indicate the sign of the optical rotation. Correct units: deg cm² g⁻¹

Melting Point: Melting points were determined on a Stuart SMP30 melting point apparatus and are uncorrected.

HPLC Profiles: HPLC analysis was determined on Agilent Technologies 1200 Series HPLC, using a ratio of HPLC grade hexanes and propan-1-ol as the eluent, using a Chiralpak AD-H, OD or AS column (0.46 cm x 25 cm) and detection by UV at 210 nm.

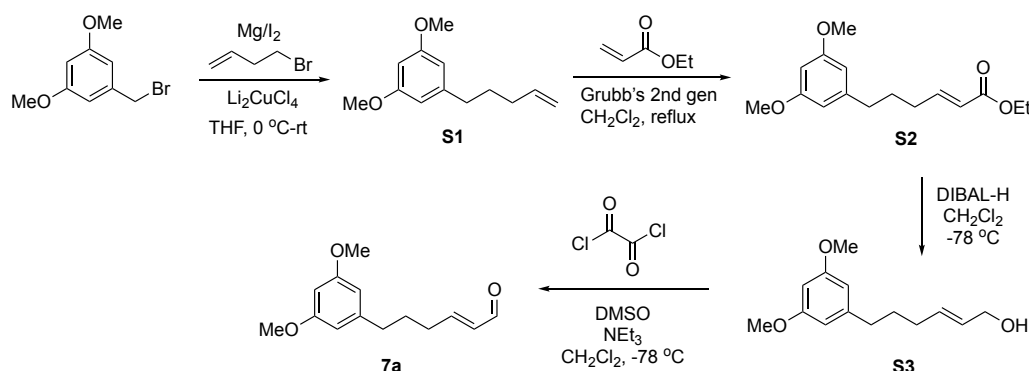
Chromatography: Reactions were monitored by thin layer chromatography on silica gel precoated aluminium sheets (TLC Silica Gel 60 F₂₅₄, Merck). Visualisation was accomplished by irradiation by UV light at 254 nm and/or ninhydrin stain, potassium permanganate stain or *p*-anisaldehyde. Column chromatography was performed on Merck silica gel (60 Å, 230 -400 mesh, 40 - 63 µm).

Catalyst V was purchased from Sigma Aldrich (CAS 1446629-74-4) as well as synthesised according to literature procedure.

2. Synthesis of Substrates

NB: Numbering follows that within the main manuscript, except if preceded by "S"

2.1 Synthesis and Characterisation of 7a



1,3-Dimethoxy-5-(pent-4-en-1-yl)benzene S1 : To a solution of magnesium turnings (1.44 g, 60.00 mmol) and iodine (~5 crystals) in dry THF (22.0 mL) at 0 °C was added bromobutene (5.08 mL, 50.00 mmol) dropwise over 10 min. The solution was warmed to room temperature and stirred for 2 h 20 min. To a separate flask was added lithium chloride (0.17 g, 4.00 mmol), copper (II) chloride (0.27 g, 2.00 mmol) and 3,5-dimethoxybenzyl bromide (4.62 g, 20.00 mmol) in dry THF (200 mL). The Grignard solution was added dropwise at 0 °C to the dilithium tetrachlorocuprate (II) solution over 20 min. A further 18 mL of THF was used to transfer the Grignard solution to the reaction mixture. The reaction was warmed to room temperature and stirred for 2 h 40 min before being quenched with saturated ammonium chloride (aq) (150.0 mL). The layers were separated, and the aqueous layer extracted with Et₂O (x2), the combined organic layers were washed with brine and dried over MgSO₄. The crude material was purified using automated silica column chromatography (gradient, 100% hex-Hex:Et₂O 96.5:3.5) to yield 1,3-dimethoxy-5-(pent-4-en-1-yl)benzene (2.4 g, 59 % yield) as a clear oil.

¹H NMR (400 MHz, CDCl₃) δ 6.36 (d, 2 H, J = 2.1 Hz, b-aromatic), 6.31 (t, 1 H, J = 2.2 Hz, d-aromatic), 5.83 (ddt, 1 H, J = 16.9, 6.7, 10.3 and 6.7 Hz, 2-CH), 5.06-4.97 (m, 2 H, 1-CH₂), 3.78 (s, 6 H, 5-OMe), 2.59-2.55 (m, 2 H, 5-CH₂), 1.76-1.68 (m, 2 H, 3-CH₂), 1.76-1.68 (m, 2 H, 4-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 160.87 (c-aromatic), 145.03 (a-aromatic), 138.72 (2-C), 114.87 (1-C), 106.68 (b-aromatic), 97.83 (d-aromatic), 55.37 (6-OMe), 35.77 (5-CH₂), 33.42 (3-C), 30.51 (4-CH₂) ppm

Ethyl (E)-6-(3,5-dimethoxyphenyl)hex-2-enoate S2 : To a solution of yield 1,3-dimethoxy-5-(pent-4-en-1-yl)benzene (4.87 g, 23.60 mmol) in dry DCM (234.0 mL) was added ethyl acrylate (25.73 mL, 235.96 mmol) and Grubbs 2nd Generation catalyst (0.38 g, 0.45 mmol). The solution was set to reflux for 30 h. Once all of the starting material had been consumed the solvent was removed under reduced pressure and the crude material was purified by automated silica gel chromatography (gradient, 100% hex-8:2 hex/Et₂O) to yield (E)-7-(3,5-dimethoxyphenyl)hept-3-enoate (5.4 g, 82 % yield) as an orange oil.

^1H NMR (400 MHz, CDCl_3) δ 6.97 (dt, 1 H, $J = 15.6$ and 6.9 Hz, 3-CH), 6.33-6.30 (m, 3 H, b-CH and d-CH), 5.81 (dt, 1 H, $J = 15.6$ and 1.5 Hz, 2-CH), 4.17 (q, 2 H, $J = 7.1$ Hz, 8- CH_2), 3.78 (s, 6 H, 7-OMe), 2.60-2.56 (m, 2 H, 6- CH_2), 2.26-2.20 (m, 2 H, 4- CH_2), 1.82-1.74 (m, 2 H, 5- CH_2), 1.28 (t, 3 H, $J = 7.2$ Hz, 8- CH_3) ppm; ^{13}C NMR (101 MHz, CDCl_3) δ 166.80 (q, 1-C), 160.90 (q-aromatic), 148.87 (3-C), 144.24 (q-aromatic), 121.80 (2-C), 106.59 (b-aromatic), 97.94 (d-aromatic), 60.30 (8-C), 55.36 (7-OMe), 35.63 (6-C), 31.70 (4-C), 29.50 (5-C), 14.39 (8-C) ppm

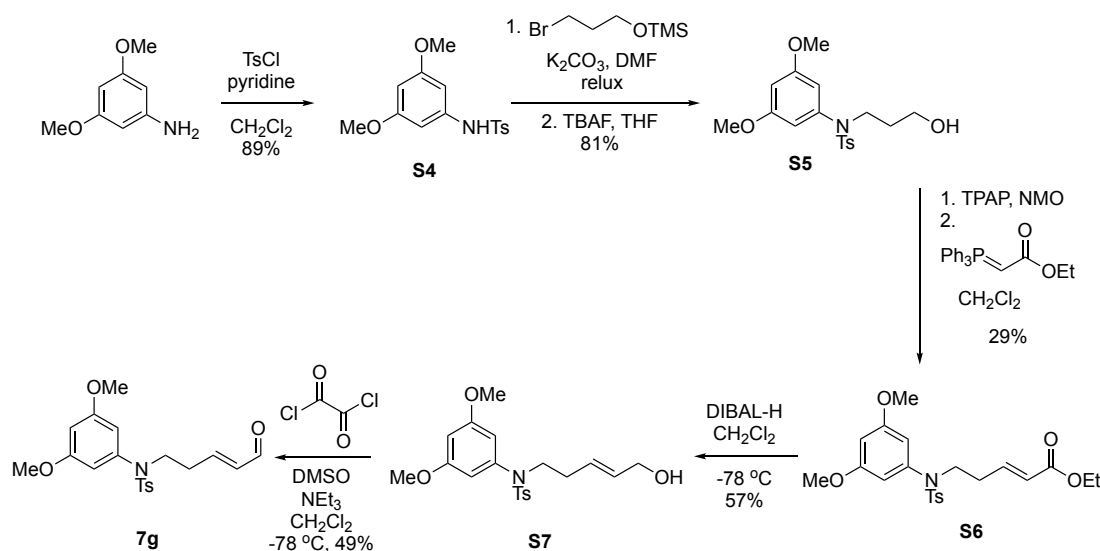
(E)-6-(3,5-dimethoxyphenyl)hex-2-en-1-ol S3 : To a solution of ethyl (E)-7-(3,5-dimethoxyphenyl)hept-3-enoate (3.87 g, 13.91 mmol) in anhydrous DCM (56 mL) at -78 °C was added DIBAL-H (1.0 M in hexanes, 29.2 mL, 29.2 mmol) dropwise. The solution was stirred at -78 °C for 1 h at which point all of the starting material had been consumed. The reaction was quenched with 1 M HCl (40 mL) and left stirring at room temperature for 4 h. The aqueous phase was extracted with DCM (4 x 50 mL). The combined organic layers were dried over MgSO_4 and concentrated under reduced pressure to yield a pale yellow oil (3.2 g, 97% yield). No further purification was required.

^1H NMR (400 MHz, CDCl_3) δ 6.34 (d, 2 H, $J = 2.22$ Hz, b-CH), 6.30 (t, 1 H, $J = 2.2$ Hz, d-CH), 5.70-5.65 (m, 2 H, 2-CH and 3-CH), 4.09 (d, 2 H, $J = 5.2$ Hz, 1- CH_2), 3.78 (s, 6H, 7-OMe), 2.58-2.54 (m, 2 H, 6- CH_2), 2.11-2.06 (m, 2 H, 4- CH_2), 1.74-1.67 (m, 2 H, 5- CH_2), 1.48 (s, 1 H, OH), ppm; ^{13}C NMR (101 MHz, CDCl_3) δ 160.82 (q, aromatic), 144.86 (q, aromatic), 132.89 (3-C), 129.51 (2-C), 106.64 (b-aromatic), 97.78 (aromatic, d), 63.87 (1-C), 55.35 (7-OMe), 35.78 (6-C), 31.84 (4-C), 30.63 (5-C) ppm

(E)-6-(3,5-dimethoxyphenyl)hex-2-enal 7a : To a solution of oxalyl chloride (1.3 mL, 15.46 mmol) in anhydrous DCM (39 mL) at -78 °C was added dropwise a solution of anhydrous DMSO (2.74 mL, 38.64 mmol) in anhydrous DCM (11.5 mL). The mixture was left to stir for 10 min at which point a solution of (E)-6-(3,5-dimethoxyphenyl)hex-2-en-1-ol (2.28 g, 9.66 mmol) in anhydrous DCM (11.5 mL) was added dropwise. The reaction was left stirring at -78 °C for 1.5 h. A solution of anhydrous triethylamine (6.73 mL, 48.30 mmol) in anhydrous DCM (11.5 mL) was added dropwise to the reaction which was then warmed to room temperature. Once warmed, the reaction was quenched with distilled water (80 mL) and extracted with DCM (2 x 50 mL). The organic layers were combined and washed with distilled water (3 x 100 mL). The organic layer was dried over MgSO_4 and solvent was removed under reduced pressure to yield an orange oil (2.3 g, Quantitative yield). No further purification was required.

^1H NMR (400 MHz, CDCl_3) δ 9.51 (d, 1 H, $J = 7.9$ Hz, 1-CH), 6.85 (dt, 1 H, $J = 15.7$ and 6.8 Hz, 3-CH), 6.33-6.31 (m, 3 H, b-CH and d-CH), 6.12 (ddt, 1 H, $J = 15.6$, 7.8 and 1.4 Hz, 2-CH), 3.78 (s, 3 H, 7-OMe), 2.63-2.59 (m, 2 H, 6- CH_2), 2.39-2.33 (m, 2 H, 4- CH_2), 1.88-1.80 (m, 2 H, 5- CH_2) ppm; ^{13}C NMR (101 MHz, CDCl_3) δ 194.16 (1-C), 160.98 (q, aromatic), 158.38 (q, aromatic), 143.88 (3-C), 133.35 (2-C), 106.66 (aromatic), 97.97 (aromatic), 55.39 (7-OMe), 35.63 (6-C), 32.21 (4-C), 29.29 (5-C) ppm; Found 235.1339; IR (diamond) ν 2999, 2938, 2838, 1684, 1636, 1593, 972, 830 cm^{-1} ; HRMS (EI) Exact mass calculated for $\text{C}_{14}\text{H}_{24}\text{O}_3$ $[\text{M}+\text{H}]^+$ 235.1334;

2.2 Synthesis and characterization of 7g



N-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide S4¹ : To a solution of 3,5-dimethoxyaniline (3.83 g, 25.00 mmol) in dry DCM (83 mL) was added anhydrous pyridine (12.13 mL, 150.00 mmol) and tosyl chloride (5.72 g, 30.00 mmol). After stirring for 20h, the reaction was quenched with distilled water (50 mL), washed with brine (50 mL) and dried over Na_2SO_4 . Solvent was removed under vacuum. The crude mixture was diluted with EtOAc (20 mL) and

washed again with 1M HCl (20 mL), distilled water (20 mL) and brine (20 mL) to remove residual pyridine. The organic layer was dried over Na₂SO₄ and solvent removed via reduced vacuum to yield 7.5 g (89% yield) of N-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide as a brown oil which required no further purification.

¹H NMR (400 MHz, CDCl₃) δ 7.74 (d, 2 H, J = 8.1 Hz, b'-aromatic), 7.27 (s, 1 H, 1-NH), 7.23 (d, 2 H, J = 8.1 Hz, c'-aromatic), 6.28 (d, 2 H, J = 2.2 Hz, b-aromatic), 6.16 (t, 1 H, J = 2.2 Hz, d-aromatic), 3.69 (s, 6 H, 2-OMe), 3.36 (s, 3 H, 3-CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 161.26 (c-aromatic), 144.08 (q-aromatic), 138.58 (q-aromatic), 136.03 (q-aromatic), 129.81 (c'-aromatic), 127.45 (b'-aromatic), 99.00 (b-aromatic), 97.18 (d-aromatic), 55.48 (2-OMe), 21.66 (3-C) ppm

N-(3,5-dimethoxyphenyl)-N-(3-hydroxypropyl)-4-methylbenzenesulfonamide S5 : To solution of N-(3,5-dimethoxyphenyl)-4-methylbenzenesulfonamide (6.84 g, 22.24 mmol) in dry DMF (37.00 mL) was added potassium carbonate (6.15 g, 44.48 mmol), and 3-bromopropoxy-trimethylsilane (7.30 mL, 31.51 mmol). The solution was heated to reflux for 18 h. The reaction was quenched with distilled water (30 mL), extracted with diethyl ether (2 x 30 mL), washed with brine and dried over Na₂SO₄. The crude material was dissolved in dry THF (44 mL). To the solution was added TBAF solution (1.0 M, 44.50 mL, 44.50 mmol). The reaction was stirred at room temperature for 4 h and quenched with 1M HCl (40 mL). The aqueous phase was extracted with diethyl ether (2 x 40 mL) and dried over Na₂SO₄. The residue was purified by automated column chromatography on silica gel (gradient 100% hex to 55% EtOAc) to yield 6.5 g (81 % yield) of N-(3,5-dimethoxyphenyl)-N-(3-hydroxypropyl)-4-methylbenzenesulfonamide as a pale yellow oil.

¹H NMR (400 MHz, CDCl₃) δ 7.54-7.52 (m, 2 H, b'-aromatic), 7.26-7.24 (m, 2 H, c'-aromatic), 6.38 (t, 1 H, J = 2.2 Hz, d-aromatic), 6.20 (d, 2 H, J = 2.3 Hz, b-aromatic), 3.76-3.74 (m, 2 H, 1-CH₂), 3.70 (s, 6 H, 4-OMe), 3.62-3.58 (t, 2 H, J = 6.3 Hz, 3-CH₂), 2.40 (s, 3 H, 5-CH₃), 2.24 (m, 1 H, 1-OH), 1.61 (m, 2 H, 2-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 160.87 (4-OMe), 143.72 (a-aromatic), 140.85 (d'-aromatic), 135.28 (a'-aromatic), 129.60 (c'-aromatic), 127.84 (b'-aromatic), 107.19 (b-aromatic), 100.30 (d-aromatic), 58.90 (1-C), 55.56 (4-OMe), 47.29 (3-C), 30.66 (2-C), 21.68 (5-C) ppm

Ethyl (E)-5-((N-(3,5-dimethoxyphenyl)-4-methylphenyl)sulfonamido)pent-2-enoate S6 : N-(3,5-dimethoxyphenyl)-N-(3-hydroxypropyl)-4-methylbenzenesulfonamide (0.28 g, 0.75 mmol) was oxidised with TPAP (0.013 g, 0.038 mmol) in the presence of NMO (0.13 g, 1.13 mmol) and homologated with (carbethoxymethylene) triphenylphosphorane (0.37 g, 1.05 mmol) to yield 0.09 g (29 % yield) of ethyl (E)-5-((N-(3,5-dimethoxyphenyl)-4-methylphenyl)sulfonamido)pent-2-enoate as a pale yellow oil after automated column chromatography (gradient, Hex/Et₂O, 100%-1:1).

¹H NMR (400 MHz, CDCl₃) δ 7.53-7.51 (m, 2 H, b'-aromatic), 7.27-7.25 (m, 2 H, c'-aromatic), 6.83 (dt, 1 H, J = 15.7 and 7.1 Hz, 3-CH), 6.39 (t, 1 H, J = 2.3 Hz, d-aromatic), 6.17 (d, 2 H, J = 2.3 Hz, b-aromatic), 5.80 (dt, 1 H, J = 15.6 and 1.4 Hz, 2-CH), 4.17 (q, 2 H, J = 7.1 Hz, 8-CH₃), 3.70 (s, 6 H, 6-OMe), 3.59 (t, 2 H, J = 7.2 Hz, 5-CH₂), 2.42 (s, 3 H, 7-CH₃), 2.39-2.33 (m, 2 H, 4-CH₂), 1.27 (t, 3 H, J = 7.1 Hz, 9-CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 166.23 (1-C), 160.87 (c-aromatic), 144.50 (3-C), 143.74 (q-aromatic), 140.69 (q-aromatic), 135.06 (q-aromatic), 129.55 (c'-aromatic), 127.95 (b'-aromatic), 123.59 (2-C), 107.16 (b-aromatic), 100.54 (d-aromatic), 60.43 (8-C), 55.55 (6-OMe), 49.24 (5-C), 31.39 (4-C), 21.67 (7-C), 14.35 (9-C) ppm;

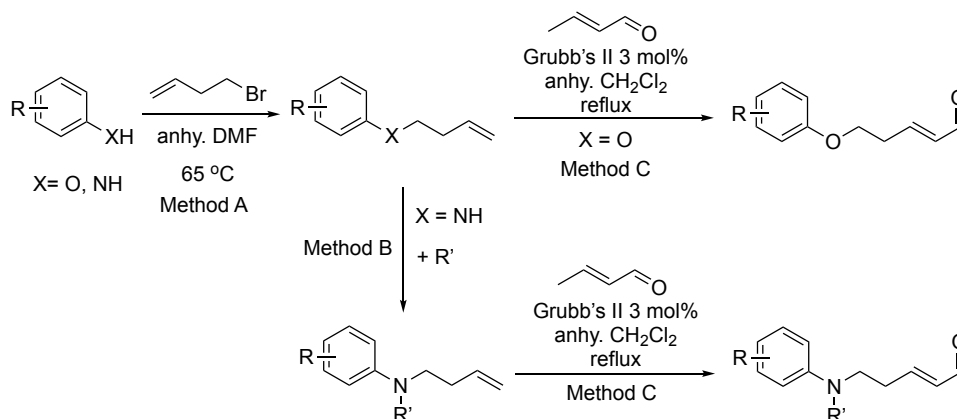
(E)-N-(3,5-Dimethoxyphenyl)-N-(5-hydroxypent-3-en-1-yl)-4-methylbenzenesulfonamide S7 : -(3,5-dimethoxyphenyl)-4-methylphenyl)sulfonamido)pent-2-enoate (1.05 g, 2.41 mmol) was reduced with DIBAL-H (1.0 M in hexanes, 6.51 mL, 6.51 mmol). The crude mixture was purified using silica gel on column chromatography (Et₂O/Hex, 9:1) to yield 0.6 g (57 % yield) of (E)-N-(3,5-dimethoxyphenyl)-N-(5-hydroxypent-3-en-1-yl)-4-methylbenzenesulfonamide as a clear oil.

¹H NMR (400 MHz, CDCl₃) δ 7.53-7.51 (m, 2 H, b'-aromatic), 7.26-7.24 (m, 2 H, c'-aromatic), 6.39 (t, 1 H, J = 2.3 Hz, b-aromatic), 6.19 (d, 1 H, J = 2.3 Hz, d-aromatic), 5.63-5.60 (m, 2 H, 2-CH and 3-CH), 4.05 (m, 2 H, 1-CH₂), 3.71 (s, 6 H, 6-OMe), 3.53 (t, 2 H, J = 7.2 Hz, 5-CH₂), 2.41 (s, 3 H, 7-CH₃), 2.21-2.16 (m, 2 H, 4-CH₂), 1.61 (m, 1 H, 1-OH) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 160.77 (6-OMe), 143.57 (q-aromatic), 140.85 (q-aromatic), 135.36 (q-aromatic), 131.82 (2-C), 129.48 (c'-aromatic), 128.58 (3-C), 127.87 (b'-aromatic), 107.25 (b-aromatic), 100.30 (d-aromatic), 63.54 (1-C), 55.54 (6-OMe), 50.31 (5-C), 31.31 (4-C), 21.65 (7-C) ppm

(E)-N-(3,5-dimethoxyphenyl)-N-(5-hydroxypent-3-en-1-yl)-4-methylbenzenesulfonamide 7g : (E)-N-(3,5-dimethoxyphenyl)-N-(5-hydroxypent-3-en-1-yl)-4-methylbenzenesulfonamide (0.61 g, 1.56 mmol) was oxidised with oxalyl chloride (0.21 mL, 2.50 mmol) and DMSO (0.44 mL, 6.25 mmol). The crude mixture was purified using silica gel on column chromatography (Hex/Et₂O, 3:1) to yield 0.3 g (49 % yield) of (E)-N-(3,5-dimethoxyphenyl)-4-methyl-N-(5-oxopent-3-en-1-yl)benzenesulfonamide as a yellow oil which required no further purification.

m.p: 104.9-106.3 °C ¹H NMR (400 MHz, CDCl₃) δ 9.51 (d, 1 H, J = 7.8 Hz, 1-CH), 7.55-7.53 (m, 2 H, b'-aromatic), 7.30-7.28 (m, 2 H, c'-aromatic), 6.81 (dt, 1 H, J = 6.9 and 15.8 Hz, 3-CH), 6.43 (t, 1 H, J = 2.2 Hz, d-aromatic), 6.19 (d, 2 H, J = 2.2 Hz, b-aromatic), 6.10 (ddt, 1 H, J = 15.8, 7.9 and 1.3 Hz, 2-CH), 3.75-2.68 (m, 8 H, 5-CH₂ and 6-OMe), 2.54-2.49 (m, 2 H, 4-CH₂), 2.45 (s, 3 H, 7-CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 193.76 (1-C), 160.96 (6-OMe), 153.96 (3-C), 143.90 (q-aromatic), 140.47 (q-aromatic), 134.98 (q-aromatic), 134.96 (2-C), 129.62 (b'-aromatic), 127.92 (c'-aromatic), 107.16 (b-aromatic), 100.50 (d-aromatic), 55.59 (6-OMe), 48.97 (5-C), 31.71 (4-C), 21.69 (7-C) ppm; IR (Diamond) ν 3003, 2977, 2936, 2839, 1718, 1678, 1204, 964, 855, 815 cm⁻¹ HRMS (ES-Tof) Exact mass calculated for C₂₀H₂₃NO₅S [M+H]⁺ 390.1375, Found 390.1372

2.3 Synthesis and characterization of remaining substrates



Method A

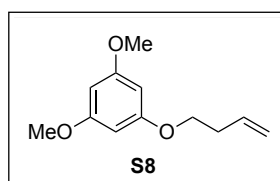
To a solution of phenol/aniline (1 equiv) in dry DMF (0.6 M) was added 4-bromo-1-butene (1.5 equiv) and K₂CO₃ (2 equiv). The reaction was heated to 65 °C for between 17 and 36 h, quenched with distilled water and extracted with Et₂O (x2). The combined organic layers were washed with brine saturated LiCl and dried over MgSO₄. The crude mixture was concentrated under reduced pressure and purified by column chromatography on silica gel.

Method B

To a solution of homologated aniline (1 equiv) in dry DCM (0.5 M) at 0 °C was added dry diisopropylamine (1.5 equiv) and acylating or sulfonylating agent (1.1 equiv). The solution was warmed to room temperature and left stirring overnight. Once all of the starting material had been consumed, the reaction was quenched with saturated NaHCO₃ (aq) and extracted with DCM (x3). The combined organic layers were washed with 1 N HCl (aq) and dried over MgSO₄.

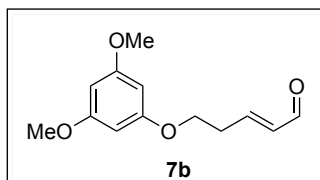
Method C

To a solution of homologated aniline/phenol (1 equiv) in dry DCM (0.1 M) was added crotonaldehyde (10 equiv) and Grubbs 2nd Generation catalyst (3 mol%). The mixture was heated to reflux for 16 h before the solvent was removed by reduced pressure and by N₂. The crude mixture was purified using silica gel on column chromatography (Pentane/Et₂O).



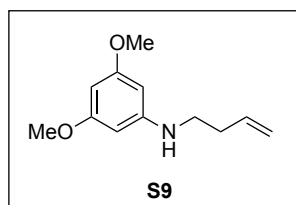
1-(but-3-en-1-yloxy)-3,5-dimethoxybenzene S8 : Following method A, 3,5-dimethoxy phenol (1.00 g, 6.49 mmol) was reacted with 4-bromo-1-butene (0.99 mL, 9.73 mmol). The crude mixture was purified using silica gel on column chromatography (Hex/EtOAc, 9:1) to yield 0.7 g (55 %) of 1-(but-3-en-1-yloxy)-3,5-dimethoxybenzene as a clear oil.

¹H NMR (400 MHz, CDCl₃) δ 6.09 (s, 3 H, 2'-H and 4'-H), 5.90 (ddt, 1 H, J = 17.1, 10.3 and 6.7 Hz, 2-CH), 5.20 (m, 1 H, 1''-H), 5.12 (m, 1 H, 1'-H), 3.98 (t, 2 H, J = 6.7 Hz, 4-CH₂), 3.77 (s, 6 H, 5-OMe), 2.53 (qt, 2 H, J = 6.7 and 1.3 Hz, 3-CH₂), 2.53 (qt, 1 H, J = 6.6 and 1.3 Hz, 3-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 161.59 (q-aromatic), 160.91 (q-aromatic), 134.53 (2-C), 117.13 (3-C), 93.51 (b-aromatic), 93.10 (d-aromatic), 67.30 (4-C), 55.51 (5-OMe), 33.67 (3-C) ppm



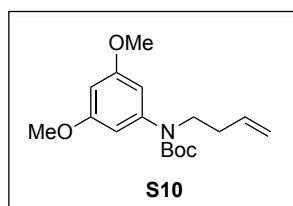
(E)-5-(3,5-dimethoxyphenoxy)pent-2-enal 7b : Following method B, 1-(but-3-en-1-yloxy)-3,5-dimethoxybenzene (0.74 g, 3.54 mmol) was coupled with crotonaldehyde (2.93 mL, 35.36 mmol) using Grubbs 2nd Generation catalyst (0.09 g, 0.11 mmol). The reaction yielded 0.7 g of (E)-5-(3,5-dimethoxyphenoxy)pent-2-enal after column chromatography (pent/Et₂O, 9:1).

m.p: 35.2-36.0 °C ¹H NMR (400 MHz, CDCl₃) δ 9.53 (d, 1 H, J = 7.9 Hz, 1-CH), 6.93 (dt, 1 H, J = 15.7 and 6.7 Hz, 3-CH), 6.26-6.20 (m, 1 H, 2-CH), 6.10-6.06 (m, 3 H, b and d aromatic), 4.08 (t, 2 H, J = 6.1 Hz, 5-CH₂), 3.76 (s, 6 H, 6-OMe), 2.82-2.77 (m, 2 H, 4-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 193.93 (1-C), 161.66 (q-aromatic), 160.41 (q-aromatic), 154.09 (3-C), 134.64 (2-C), 93.48 (b-aromatic), 93.39 (d-aromatic), 65.65 (5-C), 55.45 (6-OMe), 32.51 (4-C) ppm; IR (Diamond) ν 3006, 2968, 2933, 2833, 2751, 1686, 1684, 1594, 1259, 1059, 984, 832 cm⁻¹; HRMS (EI) Exact mass calculated for C₁₃H₁₆O₄ [M+H]⁺ 237.1127



N-(but-3-en-1-yl)-3,5-dimethoxyaniline S9 : Following method A, 3,5-dimethoxyaniline (7.71 g, 50.00 mmol) was reacted with 4-bromo-1-butene (2.03 mL, 20.00 mmol). The crude mixture was purified using automated silica gel on column chromatography (gradient, 100% hex-15% Et₂O) to yield 3.9 g (94 %) of but-3-en-1-yl(3,5-dimethoxyphenyl)-1-azane as a pale yellow oil.

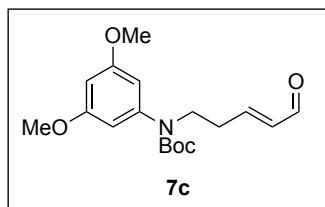
¹H NMR (400 MHz, CDCl₃) δ 5.88 (t, 1 H, J = 2.2 Hz, d-aromatic), 5.87-5.77 (m, 3 H, b-aromatic and 2-CH), 5.18-5.09 (m, 2 H, 1-CH₂), 3.75 (s, 6 H, 5-OMe), 3.70 (s, 1 H, NH), 3.16 (t, 2 H, J = 6.7 Hz, 4-CH₂), 2.37 (qt, 2 H, J = 1.2 and 6.7 Hz, 3-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 161.85 (c-aromatic), 150.30 (a-aromatic), 135.85 (2-C), 117.26 (1-C), 91.81 b-aromatic), 89.86 (d-aromatic), 55.28 (5-OMe), 42.91 (4-C), 33.70 (3-C) ppm; HRMS (ES-Tof) Exact mass calculated for C₁₂H₁₇NO₂ [M+H]⁺ 208.1338, Found 208.1341 IR (Diamond) ν 3405, 2958, 2936, 2839, 1612, 1590, 1201, 1175, 915, 807, 681 cm⁻¹



tert-butyl but-3-en-1-yl(3,5-dimethoxyphenyl)carbamate S10 : Following method B, to a solution of N-(but-3-en-1-yl)-3,5-dimethoxyaniline (0.68 mmol, 3.30 mmol) in dry THF (33 mL) was added anhydrous trimethylamine (1.38 mL, 9.90 mmol) and di-tert-butyl dicarbonate (0.86 g, 3.96 mmol). The reaction was stirred for 24 h and monitored by thin layer chromatography. Due to the lack of complete consumption of starting material, a further 1.2 equiv (0.86 g, 3.96 mmol) of di-tert-butyl dicarbonate was added and the reaction was heated to 45 °C. Solvent was removed after a further 24 h. The crude mixture was partitioned between EtOAc and distilled water and washed with 1N

HCl, water and brine. The organic layer was dried over MgSO₄ and solvent was removed under reduced pressure. The reaction yielded 0.5 g (45 %yield) of tert-butyl but-3-en-1-yl(3,5-dimethoxyphenyl)carbamate as a clear oil after purification using automated column chromatography (100% hex to 9:1 Hex/EtOAc).

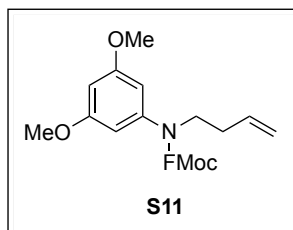
¹H NMR (400 MHz, CDCl₃) δ 6.36 (d, 2 H, J = 2.2 Hz, b-aromatic), 6.33 (t, 1 H, J = 2.2 Hz, d-aromatic), 5.77 (ddt, 1 H, J = 17.2, 6.8 and 10.2 Hz, 2-CH), 5.08-5.00 (m, 2 H, 1-CH₂), 3.77 (s, 6 H, 5-OMe), 5.68-3.64 (m, 2 H, 4-CH₂), 2.33-2.27 (m, 1 H, 3-CH₂), 1.43 (s, 9 H, 8-CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 160.75 (c-aromatic), 154.61 (6-C), 144.26 (q-aromatic), 135.56 (2-C), 116.70 (1-C), 105.92 (b-aromatic), 98.37 (d-aromatic), 80.25 (7-C), 55.50 (5-OMe), 49.55 (4-C), 33.12 (3-C), 28.48 (8-C) ppm; HRMS (ES-Tof) Exact mass calculated for C₁₇H₂₅NO₄ [M+H]⁺ 308.1862, Found 308.1863 IR (Diamond) ν 3005, 2975, 2933, 2842, 1696, 1593, 913, 857, 830, 697 cm⁻¹



tert-butyl (E)-(3,5-dimethoxyphenyl)(5-oxopent-3-en-1-yl)carbamate 7c :

Following method C, tert-butyl but-3-en-1-yl(3,5-dimethoxyphenyl)carbamate (0.46 g, 1.50 mmol) was coupled with crotonaldehyde (1.24 mL, 14.96 mmol) using Grubbs 2nd Generation catalyst (0.038 g, 0.045 mmol). The reaction yielded 0.4 g (70 %) of tert-butyl (E)-(3,5-dimethoxyphenyl)(5-oxopent-3-en-1-yl)carbamate as a pale yellow oil after automated column chromatography (gradient, 100% Pent-65:35 Pent/Et₂O).

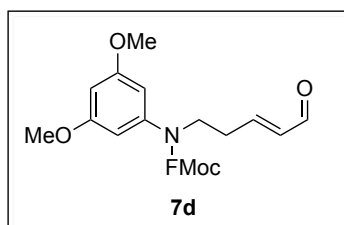
¹H NMR (400 MHz, CDCl₃) δ 9.47 (d, 1 H, J = 7.8 Hz, 1-CH), 6.81 (dt, 1 H, J = 15.6 and 6.9 Hz, 3-CH), 6.34-6.30 (m, 3 H, b and d-aromatic), 6.15-6.09 (m, 1 H, 2-CH), 3.81 (t, 2 H, J = 6.9 Hz, 5-CH₂), 3.79 (s, 6 H, 6-OMe), 2.56 (m, 2 H, 4-CH₂), 1.41 (s, 9 H, 9-CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 193.84 (1-C), 160.91 (q-aromatic), 155.11 (3-C), 154.51 (q-aromatic), 143.63 (q-aromatic), 134.39 (2-C), 105.88 (b-aromatic), 98.51 (d-aromatic), 80.75 (8-C), 55.52 (6-OMe), 48.24 (5-C), 32.20 (4-C), 28.42 (9-C) ppm; HRMS (ES-Tof) Exact mass calculated for C₁₈H₂₇NO₅ [M+H]⁺ 336.1811, Found 336.1819 IR (Diamond) ν 2982, 2969, 2929, 2866, 2827, 1690, 1205, 987, 847 cm⁻¹



(9H-fluoren-9-yl)methyl but-3-en-1-yl(3,5-dimethoxyphenyl)carbamate S11 : To a solution of but-3-en-1-yl(3,5-dimethoxyphenyl)-l2-azane (0.64 g, 3.10 mmol) and 10% NaHCO₃ (aq) (34 mL) in dioxane (34.00 mL) at 0 °C was slowly added a solution of fluorenylmethoxycarbonyl chloride (2.01 g, 7.75 mmol) in dioxane (17.00 mL). The temperature of the reaction was maintained at 0 °C for 30 min before being raised to room temperature and stirred overnight. Once all of the starting material had been consumed, the reaction was quenched with distilled water and extracted with diethyl ether. The combined organic layers were washed with brine and dried over MgSO₄. The

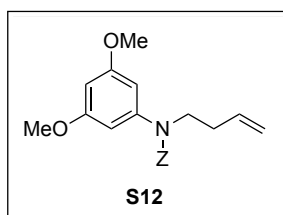
crude mixture was purified using automated column chromatography (9:1, hex/Et₂O) to yield (9H-fluoren-9-yl)methyl but-3-en-1-yl(3,5-dimethoxyphenyl)carbamate as a clear oil in 87 % yield (1.16 g).

¹H NMR (400 MHz, CDCl₃) δ 7.22 (d, 2 H, J = 7.56 Hz, f'-aromatic), 7.38-7.21 (m, 6 H, c', d' and e'-aromatic), 6.46 (s, 1 H, d-aromatic), 6.39 (d, 2 H, J = 2.3 Hz, b-aromatic), 5.73 (s, 1 H, a'-aromatic), 5.08-5.03 (m, 2 H, 7-CH₂), 4.36 (s, 2 H, 1-CH₂), 4.13 (s, 1 H, 2-CH), 3.80 (s, 6 H, 5-OMe), 3.68 (s, 2 H, 4-CH₂), 2.29 (s, 2 H, 3-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 161.18 (c-aromatic), 155.45 (6-C), 144.02 (g'-aromatic), 143.36 (a-aromatic), 141.41 (b'-aromatic), 135.30 (a'-aromatic), 127.71 (e'-aromatic), 127.02 (d'-aromatic), 125.34 (c'-aromatic), 119.99 (f'-aromatic), 116.97 (7-C), 106.55 (b-aromatic), 99.42 (d-aromatic), 67.63 (1-C), 55.61 (5-OMe), 49.79 (4-C), 47.23 (2-C), 32.82 (3-C) ppm; HRMS (EI) Exact mass calculated for C₂₇H₂₇NO₄ [M+H]⁺ 430.2018, Found 430.2009 IR (Diamond) ν 3067, 2938, 2843, 1702, 1605, 1594, 926, 758 cm⁻¹



(9H-Fluoren-9-yl)methyl (E)-(3,5-dimethoxyphenyl)(5-oxopent-3-en-1-yl)carbamate 7d : Following method C, (9H-fluoren-9-yl)methyl but-3-en-1-yl(3,5-dimethoxyphenyl)carbamate (1.12 g, 2.61 mmol) was coupled with crotonaldehyde (2.16 mL, 26.07 mmol) using Grubbs 2nd Generation catalyst (0.066 g, 0.078 mmol). The reaction yielded 1.1 g (89 %) of (9H-fluoren-9-yl)methyl (E)-(3,5-dimethoxyphenyl)(5-oxopent-3-en-1-yl)carbamate as viscous brown oil after automated column chromatography (gradient, 100% Pent-55:45 Pent/Et₂O).

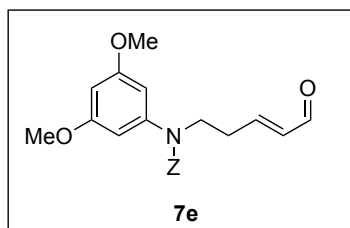
¹H NMR (400 MHz, CDCl₃) δ 9.48 (d, 1 H, J = 8.1 Hz, 1-CH), 7.72 (d, 2 H, J = 7.7 Hz, f'-aromatic), 7.38-7.21 (m, 6 H, c', d', e'-aromatic), 6.73 (s, 1 H, 3-CH), 6.45 (s, 1 H, d-aromatic), 6.31 (d, 2 H, J = 2.0 Hz, b-aromatic), 6.10 (s, 1 H, 2-CH), 4.39 (s, 2 H, 8-CH₂), 3.96 (s, 1 H, a'-aromatic), 3.79 (s, 8 H, 5-CH₂ and 6-OMe), 2.53 (s, 2 H, 4-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 193.79 (1-C), 161.34 (c-aromatic), 155.40 (), 154.51 (), 143.85 (g'-aromatic), 142.85 (a-aromatic), 141.43 (b'-aromatic), 134.53 (2-C), 127.78 (d'-aromatic), 127.06 (e'-aromatic), 125.21 (c'-aromatic), 120.03 (f'-aromatic), 106.32 (b-aromatic), 99.51 (d-aromatic), 67.71 (8-C), 55.63 (6-OMe), 48.61 (5-C), 47.16 (a'-aromatic), 31.87 (4-C) ppm; HRMS (EI) Exact mass calculated for C₂₈H₂₇NO₅ [M+H]⁺ 458.1967, Found 458.1978 IR (Diamond) ν 3017, 3004, 2971, 2839, 1740, 1684, 1592, 993, 758 cm⁻¹



Benzyl but-3-en-1-yl(3,5-dimethoxyphenyl)carbamate S12 : To a solution of N-(but-3-en-1-yl)-3,5-dimethoxyaniline (0.68 mmol, 3.30 mmol) in dry THF (8 mL) at 0 °C was added sodium bicarbonate (0.31 g, 3.63 mmol) and benzyl chloroformate (0.51 mL, 3.63 mmol). After 15 min, the reaction was warmed to rt and left stirring overnight. Once all of the starting material had been consumed the reaction was quenched with distilled water and the layers separated. The aqueous phase was extracted with EtOAc (x2) and dried over MgSO₄. The crude mixture was purified by column chromatography on silica gel (Hex/EtOAc, 8:2) to yield benzyl but-3-en-1-yl(3,5-dimethoxyphenyl)carbamate as a

clear oil (1.0 g, 88 % yield).

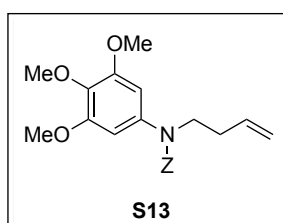
¹H NMR (400 MHz, CDCl₃) δ 7.37-7.28 (m, 5 H, b', c' and d'-aromatic), 6.40 (s, 3 H, b and d-aromatic), 5.78 (ddt, 1 H, J = 7.0, 10.1 and 17.1 Hz, 2-CH), 5.18 (s, 2 H, 7-CH₂), 5.10-5.03 (m, 2 H, 1-CH₂), 3.78-3.74 (m, 8 H, 5-OMe and 4-CH₂), 2.37-2.31 (m, 2 H, 3-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 160.91 (q-aromatic), 155.33 (q-aromatic), 143.43 (q-aromatic), 136.85 (q-aromatic), 135.26 (2-C), 128.50 (d'-aromatic), 127.77 (c'-aromatic), 127.96 (b'-aromatic), 116.95 (1-C), 105.97 (b-aromatic), 99.13 (d-aromatic), 67.22 (7-C), 55.50 (5-OMe), 49.90 (4-C), 32.89 (3-C) ppm; HRMS (ES-Tof) Exact mass calculated for C₂₀H₂₃NO₄ [M+H]⁺ 342.1705, Found 342.1720 IR (Diamond) ν 3074, 2006, 2944, 2842, 1701, 1592, 1204, 832, 694 cm⁻¹



Benzyl (E)-(3,5-dimethoxyphenyl)(5-oxopent-3-en-1-yl)carbamate 7e :

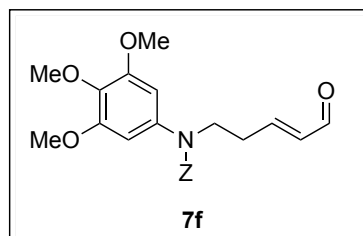
Following method C, benzyl but-3-en-1-yl(3,5-dimethoxyphenyl)carbamate (1.00 g, 2.92 mmol) was coupled with crotonaldehyde (2.42 mL, 29.15 mmol) using Grubbs 2nd Generation catalyst (0.074 g, 0.087 mmol). The reaction yielded 1.0 g (79 %) of benzyl (E)-(3,5-dimethoxyphenyl)(5-oxopent-3-en-1-yl)carbamate as a pale brown solid after automated column chromatography (gradient, 100% Pent-6:4 Pent/Et₂O).

m.p: 51.6-52.5 °C ¹H NMR (400 MHz, CDCl₃) δ 9.43 (d, 1 H, J = 7.8 Hz, 1-CH), 7.34-7.26 (m, 5 H, a', b', c' and d'-aromatic), 6.76 (dt, 1 H, J = 15.7 and 7.1 Hz, 3-CH), 6.38 (t, 1 H, J = 2.3 Hz, d-aromatic), 6.31 (s, 2 H, b-aromatic), 6.09 (ddt, 1 H, J = 15.7, 7.8 and 1.3 Hz, 2-CH), 5.15 (s, 2 H, 8-CH₂), 3.88 (t, 2 H, J = 7.1 Hz, 5-CH₂), 3.74 (s, 6 H, 6-OMe), 2.61-2.56 (m, 2 H, 4-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 193.78 (1-C), 161.12 (c-aromatic), 155.32 (7-aromatic), 154.57 (3-C), 142.87 (a-aromatic), 136.57 (a'-aromatic), 134.58 (2-C), 128.62 (c'-aromatic), 128.20 (d'-aromatic), 127.89 (b'-aromatic), 105.92 (b-aromatic), 99.31 (d-aromatic), 67.53 (8-C), 55.56 (6-OMe), 48.70 (5-C), 31.99 (4-C), ppm; HRMS (ES-ToF) Exact mass calculated for C₂₁H₂₃NO₅ [M+H]⁺ 370.1654, Found 370.1655 IR (Diamond) ν 2993, 2944, 2821, 2745, 1696, 1679, 1591, 1231, 1148, 995, 964, 853, 743 cm⁻¹



Benzyl but-3-en-1-yl(3,4,5-trimethoxyphenyl)carbamate S13 : To a solution of N-(but-3-en-1-yl)-3,4,5-trimethoxyaniline (0.69 mmol, 2.89 mmol) in dry THF (7.20 mL) at 0 °C was added sodium bicarbonate (0.27 g, 3.18 mmol) and benzyl chloroformate (0.45 mL, 3.18 mmol). After 15 min, the reaction was warmed to rt and left stirring overnight. Once all of the starting material had been consumed the reaction was quenched with distilled water and the layers separated. The aqueous phase was extracted with EtOAc (x2) and the combined organic phases combined and dried over MgSO₄. The crude pale yellow oil was used in the next step without further purification (1.0 g, 89 % yield).

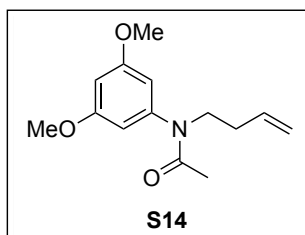
¹H NMR (400 MHz, CDCl₃) δ 7.40-7.31 (m, 5 H, b', c' and d'-aromatic), 6.41 (s, 2 H, b-aromatic), 5.76 (ddt, 1 H, J = 6.9 10.2 and 17.0 Hz, 2-CH), 5.16 (s, 2 H, 8-CH₂), 5.08-5.02 (m, 2 H, 1-CH₂), 3.85 (s, 3 H, 6-OMe), 3.79 (s, 6 H, 5-OMe), 3.74-3.71 (m, 2 H, 4-CH₂), 2.35-2.30 (m, 2 H, 3-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 155.52 (7-C), 153.33 (c-aromatic), 136.95 (a-aromatic), 136.83 (d-aromatic), 135.36 (2-C), 129.49 (d'-aromatic), 128.54 (c'-aromatic), 128.05 (b'-aromatic), 127.85 (a'-aromatic), 117.00 (1-C), 105.24 (b-aromatic), 67.24 (8-C), 61.01(6-C), 56.23 (5-C), 50.09 (4-C), 46.40 (3-C) ppm; HRMS (EI) Exact mass calculated for C₂₁H₂₅NO₅ [M+H]⁺ 372.1811, Found 372.1811 IR (Diamond) ν 3075, 2939, 2832, 1777, 1698, 1641, 1228, 917, 831, 767 cm⁻¹



Benzyl (E)-(5-oxopent-3-en-1-yl)(3,4,5-trimethoxyphenyl)carbamate 7f :

Following method C, benzyl but-3-en-1-yl(3,4,5-trimethoxyphenyl)carbamate (1.02 g, 2.76 mmol) was coupled with crotonaldehyde (2.12 mL, 25.64 mmol) using Grubbs 2nd Generation catalyst (0.065 g, 0.077 mmol). The reaction yielded 0.9 g (77 %) of benzyl (E)-(5-oxopent-3-en-1-yl)(3,4,5-trimethoxyphenyl)carbamate as a dark brown oil after automated column chromatography (gradient, 100% Pent-7:3 Pent/Et₂O).

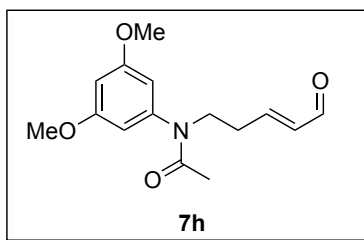
¹H NMR (400 MHz, CDCl₃) δ 9.44 (d, 1 H, J = 7.37 Hz, 1-CH), 7.31-7.26 (m, 5 H, a', b', c' and d'-aromatic), 6.81-6.74 (m, 1 H, 3-CH), 6.35 (s, 2 H, b-aromatic), 6.11 (dd, 1 H, J = 15.7 and 7.82 Hz, 2-CH), 5.15 (s, 2 H, 9-CH₂), 3.89-3.83 (m, 5 H, 5-CH₂ and 7-OMe), 3.78 (s, 6 H, 6-OMe), 2.62-2.57 (m, 2 H, 4-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 193.66 (1-C), 155.45 (8-C), 154.51 (3-C), 153.50 (c-aromatic), 137.21 (d-aromatic), 136.84 (a-aromatic), 136.51 (a'-aromatic), 134.62 (2-C), 128.62 (c'-aromatic), 128.26 (d'-aromatic), 127.93 (d'-aromatic), 105.10 (b-aromatic), 67.52 (9-C), 61.01 (7-OMe), 56.27 (6-OMe), 48.89 (5-C), 32.02 (4-C) ppm; HRMS (EI) Exact mass calculated for C₂₂H₂₅NO₆ [M+H]⁺ 400.1760, Found 400.1777 IR (Diamond) ν 2941, 2829, 1686, 1684, 1229 974, 833 cm⁻¹



N-(but-3-en-1-yl)-N-(3,5-dimethoxyphenyl)acetamide S14 : N-(but-3-en-1-yl)-N-(3,5-dimethoxyphenyl)acetamide was isolated in 86 % yield (0.6 g) as a clear oil from the reaction of N-(but-3-en-1-yl)-3,5-dimethoxyaniline (0.56 g, 2.70 mmol) and acetyl chloride (0.21 mL, 2.97 mmol). The crude material was used without further purification.

¹H NMR (400 MHz, CDCl₃) δ 6.44 (t, 1 H, J = 2.2 Hz, d-aromatic), 6.31 (d, 2 H, J = 2.2 Hz, b-aromatic), 5.77 (ddt, 1 H, J = 10.3, 17.1 and 7.0 Hz, 2-CH), 5.08-5.01 (m, 2 H, 1-CH₂), 3.79-3.72 (m, 8 H, 4-CH₂ and 5-OMe), 2.31-2.25 (m, 2 H, 3-CH₂), 1.87 (s, 3 H, 7-CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 170.30 (6-C), 161.48 (c-aromatic), 144.82 (a-aromatic), 135.82 (2-C), 116.74 (1-C), 106.72 (b-aromatic), 99.72 (d-aromatic), 55.63 (5-OMe), 48.15 (4-C), 32.43 (3-C), 22.77 (7-C) ppm;

HRMS (EI) Exact mass calculated for $C_{14}H_{19}NO_3$ $[M+H]^+$ 250.1443, Found 250.1452 IR (Diamond) ν 2982, 2973, 2924, 2869, 2844, 1651, 1635, 1247, 1153, 985, 833 cm^{-1}

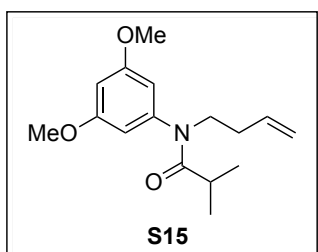


(E)-N-(3,5-dimethoxyphenyl)-N-(5-oxopent-3-en-1-yl)acetamide 7h :

Following method C, N-(but-3-en-1-yl)-N-(3,5-dimethoxyphenyl)acetamide (0.58 g, 2.32 mmol) was coupled with crotonaldehyde (1.48 mL, 23.24 mmol) using Grubbs 2nd Generation catalyst (0.059 g, 0.07 mmol). The reaction yielded 0.5 g (80 %) of (E)-N-(3,5-dimethoxyphenyl)-N-(5-oxopent-3-en-1-yl)acetamide as brown oil after automated column chromatography (gradient, 100% Pent-9:1 Pent/Et₂O).

¹H NMR (400 MHz, CDCl₃) δ 9.48 (d, 2 H, J = 7.7 Hz, 1-CH), 6.80 (dt, 1 H, J = 15.8 and 6.9 Hz, 3-CH), 6.44 (t, 1 H, J = 2.2 Hz, d-aromatic), 6.27 (d, 2 H, J = 2.2

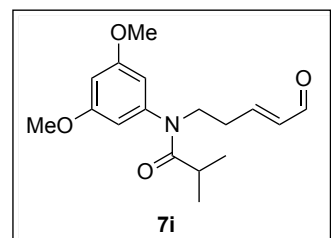
Hz, b-aromatic), 6.11 (ddt, 1 H, J = 15.7, 7.9 and 1.3 Hz, 2-CH), 3.87 (t, 2 H, J = 7.1 Hz, 5-CH₂), 3.79 (s, 3 H, 6-OMe), 2.58 (qd, 2 H, J = 7.1 and 1.4 Hz, 4-CH₂), 1.88 (s, 3 H, 8-CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 193.88 (1-C), 170.58 (7-C), 161.68 (c-aromatic), 154.96 (3-C), 144.27 (a-aromatic), 134.37 (2-C), 106.55 (b-aromatic), 99.79 (d-aromatic), 55.65 (6-OMe), 47.05 (5-C), 31.63 (4-C), 22.64 (8-C) ppm; HRMS (EI) Exact mass calculated for $C_{15}H_{19}NO_4$ $[M+H]^+$ 278.1392, Found 278.1398 IR (Diamond) ν 3101, 3067, 2943, 2810, 2727, 1684, 1639, 1635, 1165, 1138, 980, 961, 847 cm^{-1}



N-(but-3-en-1-yl)-N-(3,5-dimethoxyphenyl)isobutyramide S15 : Following method B, N-(but-3-en-1-yl)-N-(3,5-dimethoxyphenyl)isobutyramide was isolated in 81 % yield (0.6 g) as a clear oil from the reaction of N-(but-3-en-1-yl)-3,5-dimethoxyaniline (0.052 g, 2.50 mmol) and isobutyryl chloride (0.29 mL, 2.75 mmol). The crude material was used purified using silica gel automated column chromatography (gradient, 100 % hex-85:15 hex/EtOAc).

¹H NMR (400 MHz, CDCl₃) δ 6.44 (t, 1 H, J = 2.3 Hz, d-aromatic), 6.31 (d, 2 H, J = 2.3 Hz, b-aromatic), 5.76 (ddt, 1 H, J = 17.2, 10.1 and 6.8 Hz, 2-CH), 5.07-5.00 (m, 2

H, 1-CH₂), 3.79 (s, 6 H, 5-OMe), 3.73-3.69 (m, 2 H, 4-CH₂), 2.55-2.45 (sept, 1 H, J = 6.6 Hz, 7-CH), 2.31-2.25 (m, 2 H, 3-CH₂), 1.02 (d, 6 H, J = 6.7 Hz, 8-CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 171.19 (6-C), 161.45 (c-aromatic), 144.56 (a-aromatic), 135.69 (2-C), 116.60 (1-C), 106.81 (b-aromatic), 99.63 (d-aromatic), 55.62 (5-OMe), 48.31 (4-C), 32.49 (3-C), 31.52 (7-C), 20.04 (8-C) ppm; HRMS (ES-Tof) Exact mass calculated for $C_{16}H_{23}NO_3$ $[M+H]^+$ 278.1756, Found 278.1760 IR (Diamond) ν 3006, 2978, 2939, 2843, 1643, 1591, 1550, 1231, 916, 840 cm^{-1}

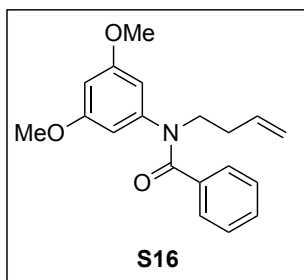


(E)-N-(3,5-dimethoxyphenyl)-N-(5-oxopent-3-en-1-yl)isobutyramide 7i :

Following method C, N-(but-3-en-1-yl)-N-(3,5-dimethoxyphenyl)isobutyramide (0.58 g, 2.01 mmol) was coupled with crotonaldehyde (1.28 mL, 20.01 mmol) using Grubbs 2nd Generation catalyst (0.051 g, 0.06 mmol). The reaction yielded 0.5 g (75 %) of (E)-N-(3,5-dimethoxyphenyl)-N-(5-oxopent-3-en-1-yl)isobutyramide as a dark orange oil after automated column chromatography (gradient, 100% Pent-65:35 Pent/Et₂O).

m.p: 63.2-64.4 °C ¹H NMR (400 MHz, CDCl₃) δ 9.49 (d, 1 H, J = 7.9 Hz, 1-CH), 6.82 (dt, 1 H, J = 15.7 and 6.9 Hz, 3-CH), 6.46 (t, 1 H, J = 2.2 Hz, d-aromatic), 6.28

(d, 2 H, J = 2.3 Hz, b-aromatic), 6.13 (ddt, 1 H, J = 15.7, 7.8 and 1.3 Hz, 2-CH), 3.86 (t, 2 H, J = 7.0 Hz, 5-CH₂), 3.80 (s, 6 H, 6-OMe), 2.62-2.49 (m, 3 H, 4-CH₂ and 8-CH), 1.02 (d, 6 H, J = 6.8 Hz, 9-CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 193.85 (1-C), 177.52 (7-C), 161.63 (c-aromatic), 155.15 (3-C), 143.98 (a-aromatic), 134.28 (2-C), 106.62 (b-aromatic), 99.70 (d-aromatic), 55.62 (6-OMe), 47.19 (5-C), 31.76 (4-C), 31.43 (8-C), 19.97 (9-C) ppm; IR (Diamond) ν 3000, 2983, 2966, 2843, 1686, 1683, 990, 928, 859 cm^{-1} HRMS (Es-Tof) Exact mass calculated for $C_{17}H_{23}NO_4$ $[M+H]^+$ 306.1705, Found 306.1702

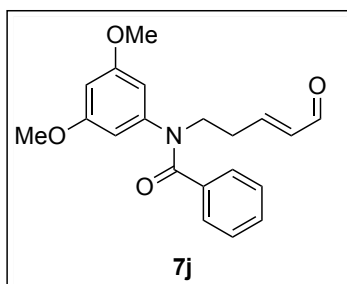


N-(but-3-en-1-yl)-N-(3,5-dimethoxyphenyl)benzamide S16 : Following method B, N-(but-3-en-1-yl)-N-(3,5-dimethoxyphenyl)benzamide was isolated in 84 % yield (0.7 g) as a clear oil from the reaction of N-(but-3-en-1-yl)-3,5-dimethoxyaniline (0.52 g, 2.50 mmol) and benzoyl chloride (0.35 mL, 2.75 mmol). The crude material was used purified using automated column chromatography (gradient, 100 % hex-8:2 hex/EtOAc).

¹H NMR (400 MHz, CDCl₃) δ 7.35-7.33 (m, 2 H, c'-aromatic), 7.27-7.23 (m, 1 H, d'-aromatic), 7.20-7.16 (m, 2 H, b'-aromatic), 6.25 (t, 1 H, J = 2.3 Hz, d-aromatic), 6.18

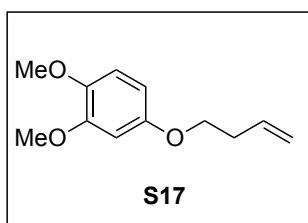
(d, 2 H, J = 2.2 Hz, b-aromatic), 5.86 (ddt, 1 H, J = 17.1, 10.2 and 6.7 Hz, 2-CH), 5.13-5.06 (m, 2 H, 1-CH₂), 4.00-3.96 (m, 2 H, 4-CH₂), 3.64 (s, 6 H, 5-OMe), 2.45-2.40 (m, 2 H, 3-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 170.48 (6-C), 160.92 (c-aromatic), 145.17 (a-aromatic), 136.58 (a'-aromatic), 135.53 (2-C), 129.68 (d'-aromatic), 128.43 (c'-aromatic), 127.86 (b'-aromatic), 116.92 (1-C), 106.54 (b-aromatic), 98.75 (d-aromatic), 55.50 (5-

OMe), 49.67 (4-C), 32.33 (3-C) ppm; HRMS (EI) Exact mass calculated for C₁₉H₂₁NO₃ [M+H]⁺ 312.1600, Found 312.1610 IR (Diamond) ν 3083, 3061, 3013, 2973, 2944, 2842, 1636, 1633, 1593, 1202, 916, 822 cm⁻¹



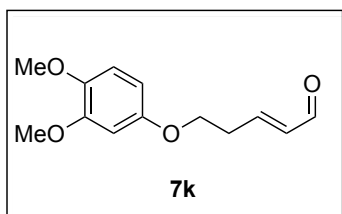
(E)-N-(3,5-dimethoxyphenyl)-N-(5-oxopent-3-en-1-yl)benzamide 7j : Following method C, N-(but-3-en-1-yl)-N-(3,5-dimethoxyphenyl)benzamide (0.65 g, 2.09 mmol) was coupled with crotonaldehyde (1.32 mL, 20.09 mmol) using Grubbs 2nd Generation catalyst (0.053 g, 0.06 mmol). The reaction yielded 0.4 g (63 %) of (E)-N-(3,5-dimethoxyphenyl)-N-(5-oxopent-3-en-1-yl)benzamide as brown oil after automated column chromatography (gradient, 100% Pent-3:2 Pent/Et₂O).

¹H NMR (400 MHz, CDCl₃) δ 9.51 (d, 1 H, J = 7.9 Hz, 1-CH), 7.33-7.31 (m, 2 H, b'-aromatic), 7.28-7.25 (m, 2 H, d'-aromatic), 7.21-7.17 (m, 2 H, c'-aromatic), 6.89 (dt, 1 H, J = 15.7 and 7.0 Hz, 3-CH), 6.26 (t, 1 H, J = 2.2 Hz, d-aromatic), 6.17-6.11 (m, 3 H, 2-CH and b-aromatic), 4.12 (t, 2 H, J = 7.0 Hz, 5-CH₂), 3.63 (s, 6 H, 6-OMe), 2.70 (qd, 2 H, J = 7.1 and 1.2 Hz, 4-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 193.82 (1-C), 170.63 (7-C), 161.10 (c-aromatic), 154.88 (3-C), 144.57 (a-aromatic), 135.93 (a'-aromatic), 134.93 (2-C), 130.00 (d'-aromatic), 128.45 (b'-aromatic), 127.94 (c'-aromatic), 106.40 (b-aromatic), 98.85 (d-aromatic), 55.51 (6-OMe), 48.38 (5-C), 31.48 (4-C) ppm; HRMS (Es-Tof) Exact mass calculated for C₂₀H₂₁NO₄ [M+H]⁺ 340.1549, Found 340.1559 IR (Diamond) ν 3060, 2943, 2845, 1686, 1684, 975, 832 cm⁻¹



4-(but-3-en-1-yloxy)-1,2-dimethoxybenzene S17 : Following method A, 3,4-dimethoxyphenol (1.54 g, 10.00 mmol) was reacted with 4-bromo-1-butene (1.52 mL, 15.00 mmol). The crude mixture was purified using silica gel on column chromatography (Hex/Et₂O, 8:2) to yield 0.64 g (31 %) of 4-(but-3-en-1-yloxy)-1,2-dimethoxybenzene as a clear oil.

¹H NMR (400 MHz, CDCl₃) δ 6.78 (d, 1 H, J = 8.8 Hz, c-aromatic), 6.53 (d, 1 H, J = 2.7 Hz, f-aromatic), 6.39 (dd, 1 H, J = 8.8 and 2.7 Hz, b-aromatic), 5.90 (ddt, 1 H, J = 17.1, 10.1 and 6.7 Hz, 2-CH), 5.20-5.14 (m, 1 H, 1''-CH), 5.12-5.09 (m, 1 H, 1'-CH), 3.97 (t, 2 H, J = 6.6 Hz, 4-CH₂), 3.85 (s, 3 H, 6-OMe), 3.83 (5-OMe), 2.55-2.50 (m, 2 H, 3-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 153.6 (e-aromatic), 149.9 (d-aromatic), 143.6 (a-aromatic), 134.7 (2-C), 117.1 (1-C), 111.9 (c-aromatic), 103.9 (b-aromatic), 101.1 (f-aromatic), 67.8 (4-C), 56.5 (5-OMe), 55.9 (6-OMe), 33.9 (3-C) ppm.



(E)-5-(3,4-dimethoxyphenoxy)pent-2-enal 7k : Following method C, 4-(but-3-en-1-yloxy)-1,2-dimethoxybenzene (0.64 g, 3.07 mmol) was coupled with crotonaldehyde (2.54 mL, 30.71 mmol) using Grubbs 2nd Generation catalyst (0.078 g, 0.092 mmol). The reaction yielded 0.60 g (83 %) of benzyl (E)-(3,5-dimethoxyphenyl)(5-oxopent-3-en-1-yl)carbamate as a pale brown oil after automated column chromatography (gradient, 100% Pent-6:4 Pent/Et₂O).

¹H NMR (400 MHz, CDCl₃) δ 9.55 (d, 1 H, J = 7.9 Hz, 1-CH), 6.95 (dt, 1 H, J = 15.7 and 6.7 Hz, 3-CH), 6.77 (d, 1 H, J = 8.6 Hz, c-aromatic), 6.51 (d, 1 H, J = 2.8 Hz, f-aromatic), 6.39 (dd, 1 H, J = 8.9 and 2.9 Hz, b-aromatic), 6.24 (ddt, 1 H, J = 15.7, 7.8 and 1.5 Hz, 2-CH), 4.09 (t, 2 H, J = 6.6 Hz, 5-CH₂), 3.85 (s, 3 H, 7-OMe), 3.83 (s, 3 H, 6-OMe), 2.80 (m, 2 H, 4-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 193.9 (1-C), 154.2 (3-C), 153.1 (a-aromatic), 150.0 (e-aromatic), 144.0 (d-aromatic), 134.6 (2-C), 111.8 (c-aromatic), 103.8 (b-aromatic), 101.1 (f-aromatic), 66.2 (5-C), 56.5 (7-OMe), 56.0 (6-OMe), 32.7 (4-C) ppm; IR (Diamond) ν 3006, 2983, 2958, 2866, 2844, 1740, 1684, 1596, 1509, 1507, 1261, 1226, 1034, 994, 991, 832 cm⁻¹ HRMS (ES-Tof) Exact mass calculated for C₁₃H₁₆O₄ [M+H]⁺ 237.1127, Found 237.1133

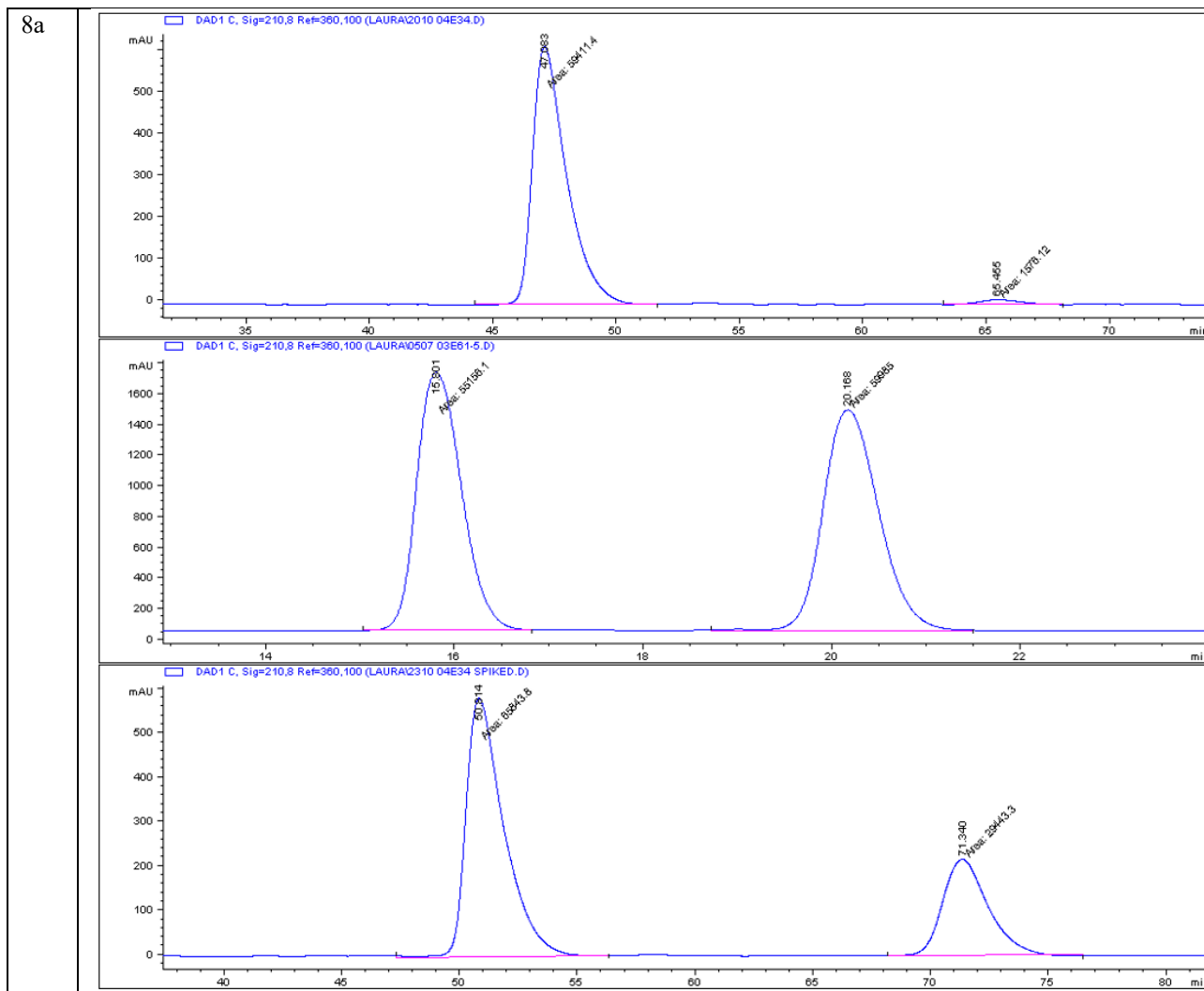
3. General method for the generation of racemic products

To a solution of α,β -unsaturated aldehyde (1 equiv) in THF (0.2 M) was added *p*-TSA (0.5 equiv). The mixture was stirred at room temperature until consumption of starting material. Once the reaction was complete, the reaction was diluted with ethyl acetate and washed with sodium bicarbonate (aq) (x2). The solution was cooled to 0 °C and diluted with methanol (0.2 M). Sodium borohydride (1.5 equiv) was added to the reaction and the reaction stirred for 1 h at 0 °C. Once all of the cyclized starting material had been consumed, the reaction was quenched with saturated ammonium chloride (aq). The layers were separated and the aqueous extracted with ethyl acetate. The organic layers were combined, washed with brine and dried over MgSO₄.

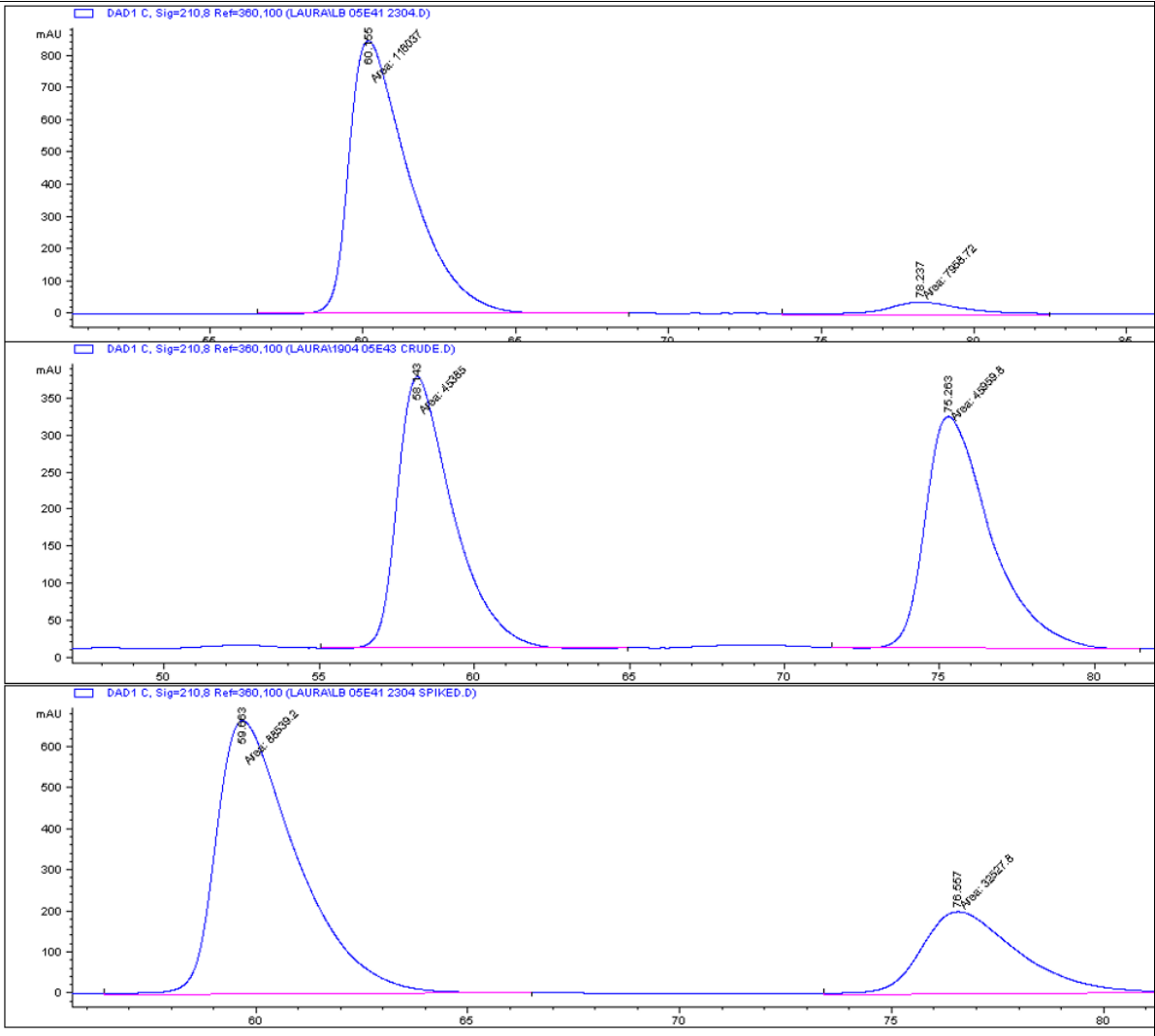
See experimental within main manuscript for details of the organocatalysed reactions.

4. HPLC Traces for Cyclised and Reduced Products

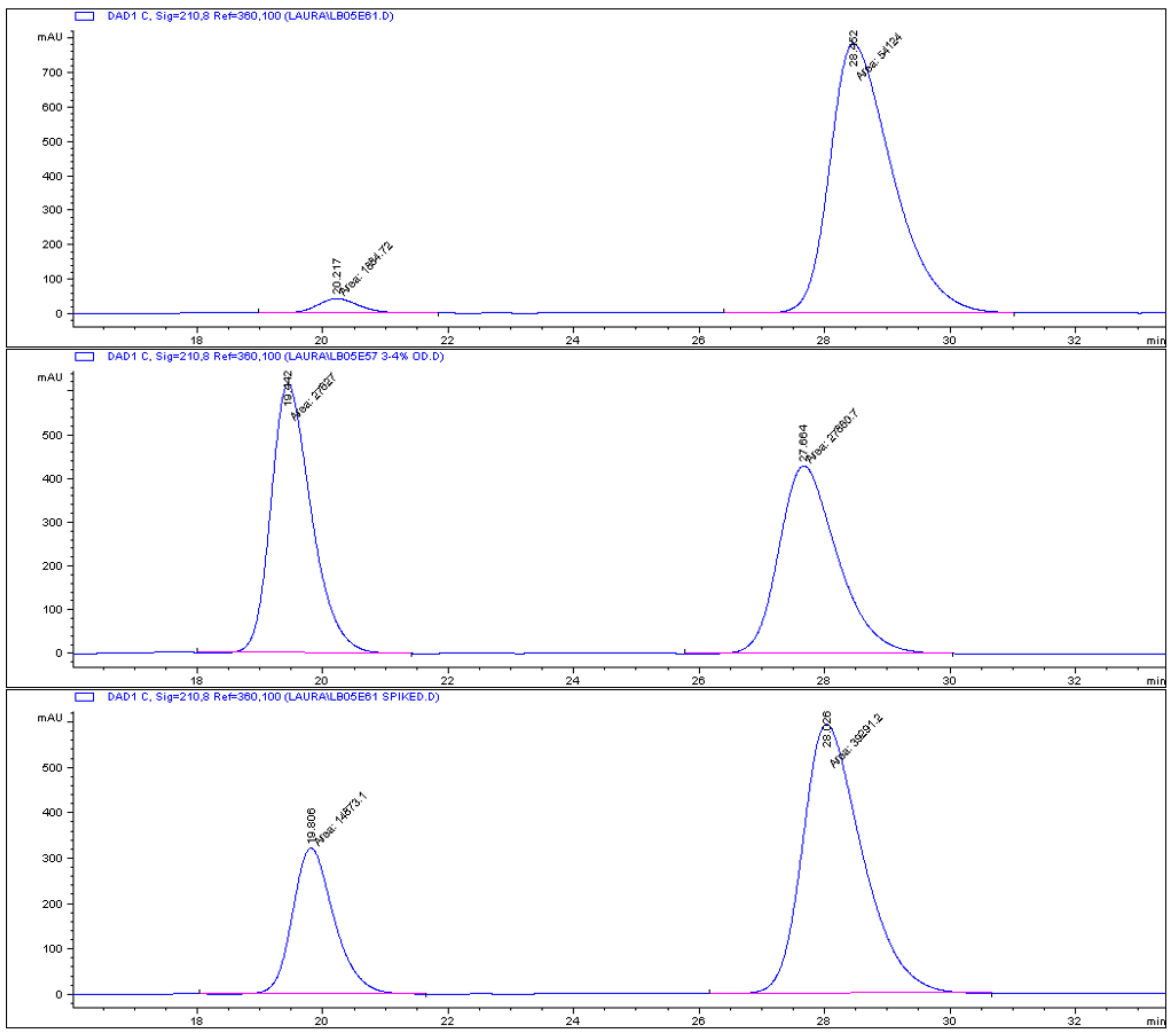
HPLC traces are shown in the order of enantiopure, racemic and spiked samples. The temperature of the HPLC wasn't controlled therefore leading to some fluctuations in retention time between the three traces.



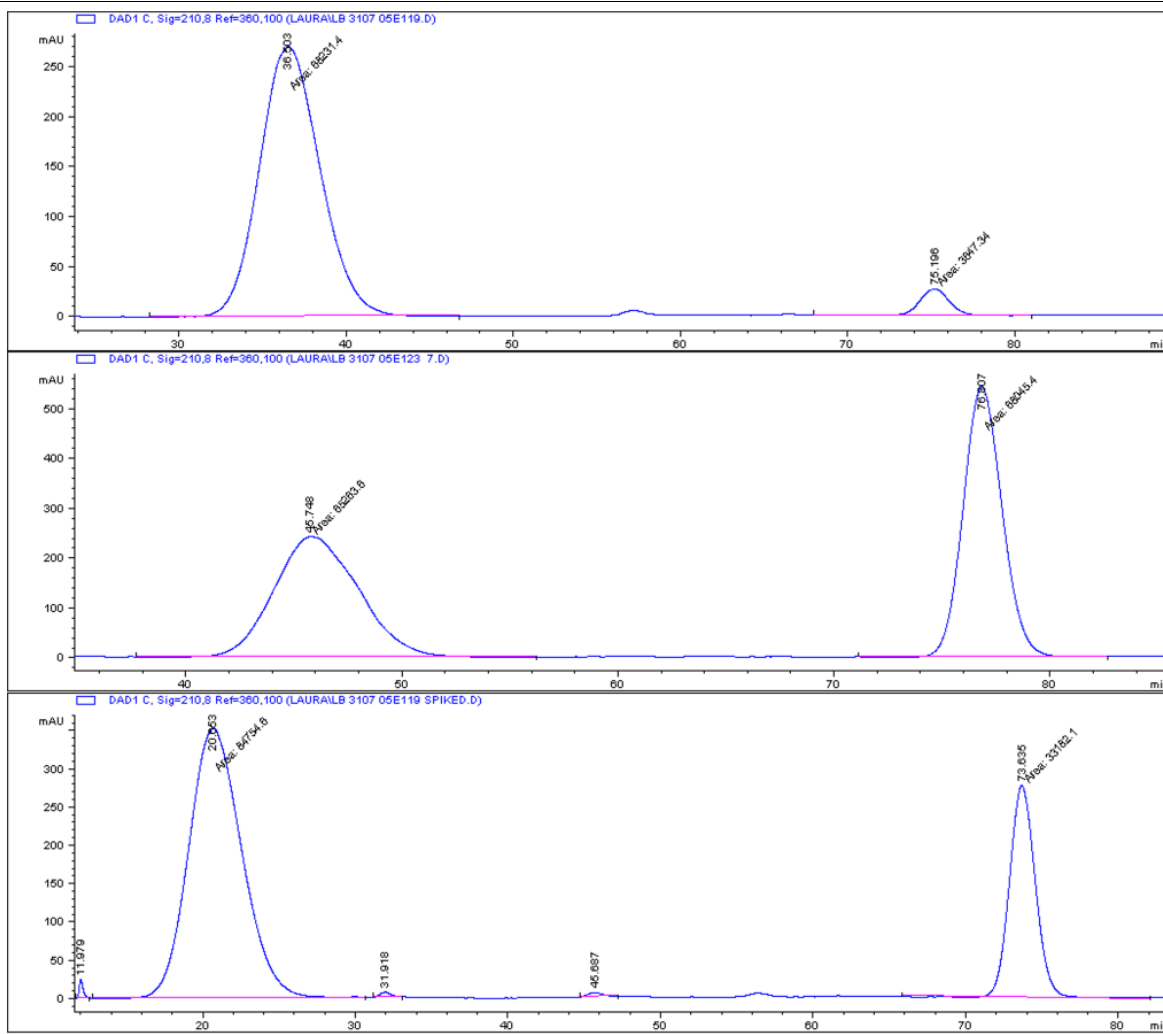
8b



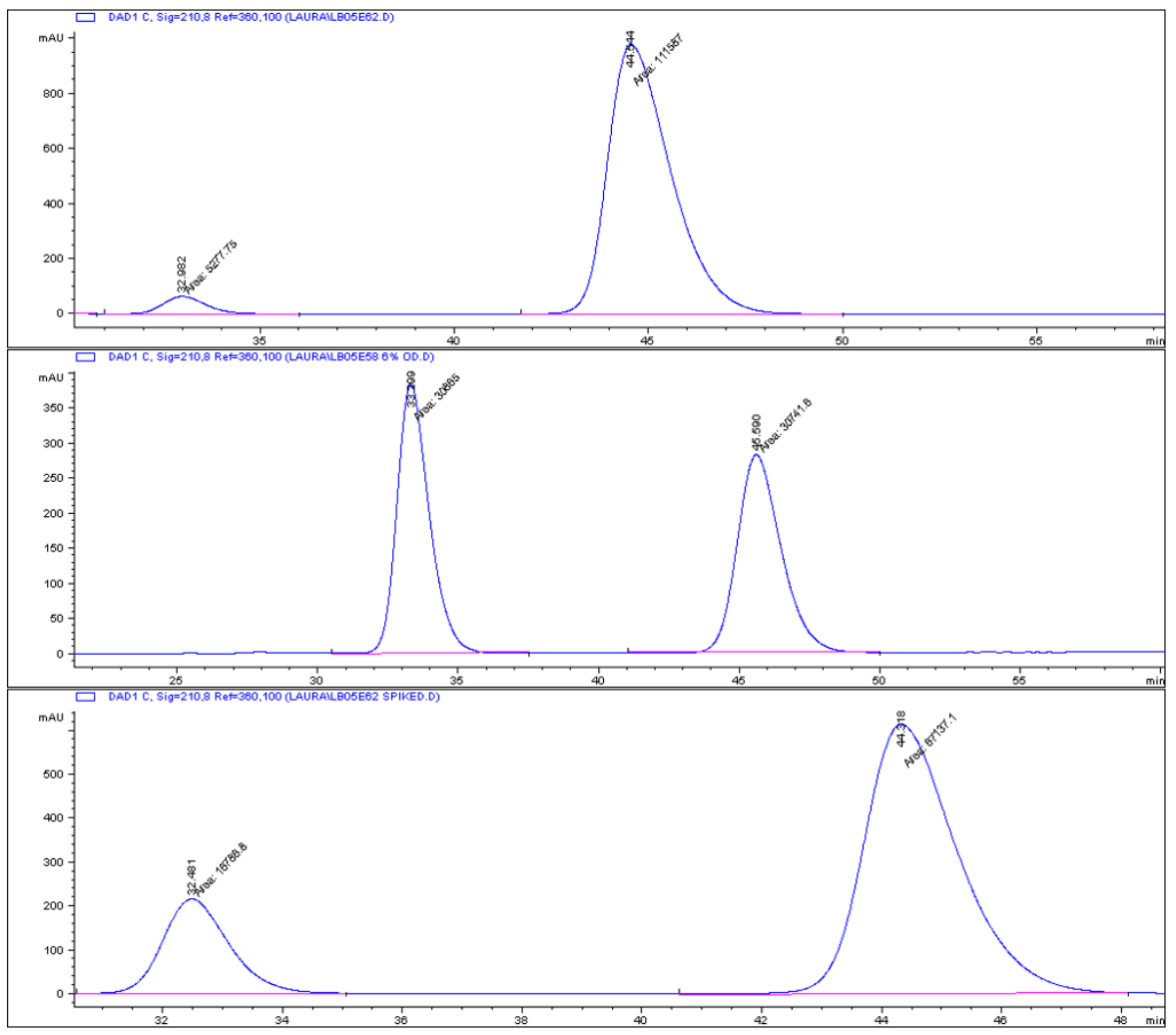
8c



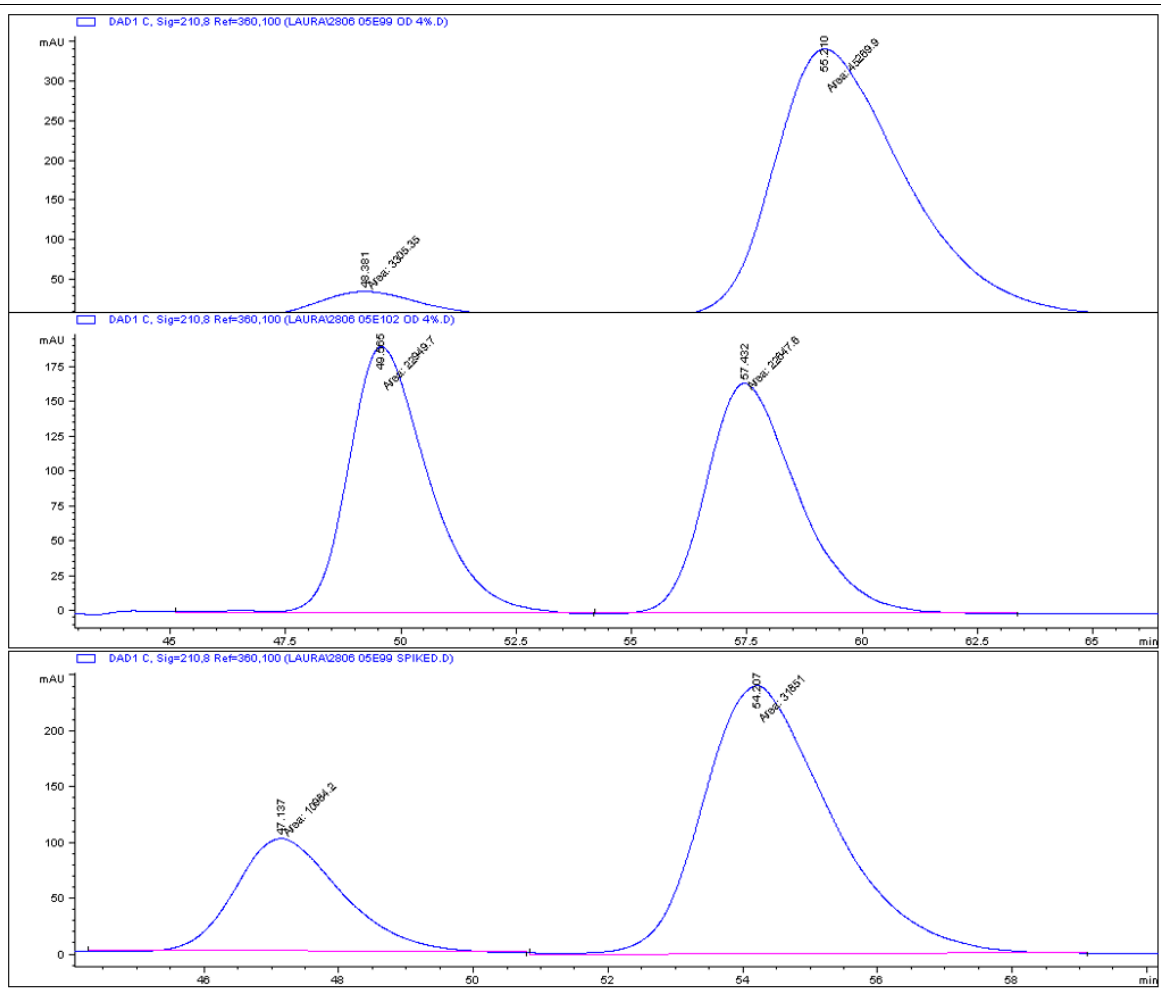
8d



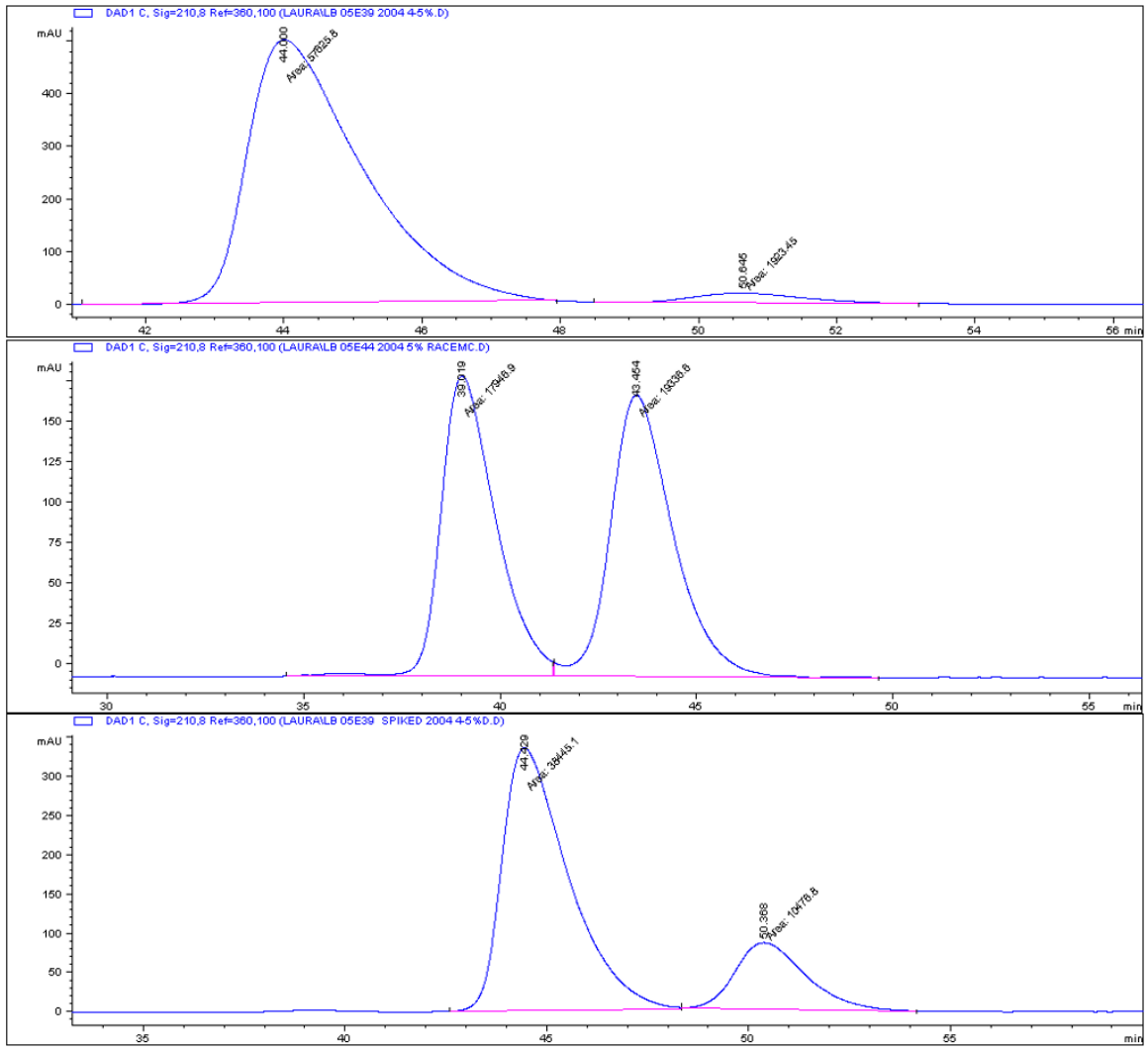
8e



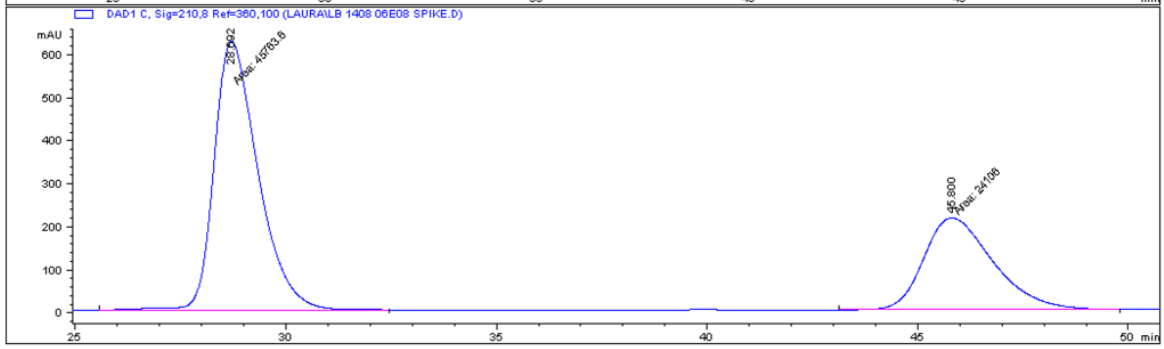
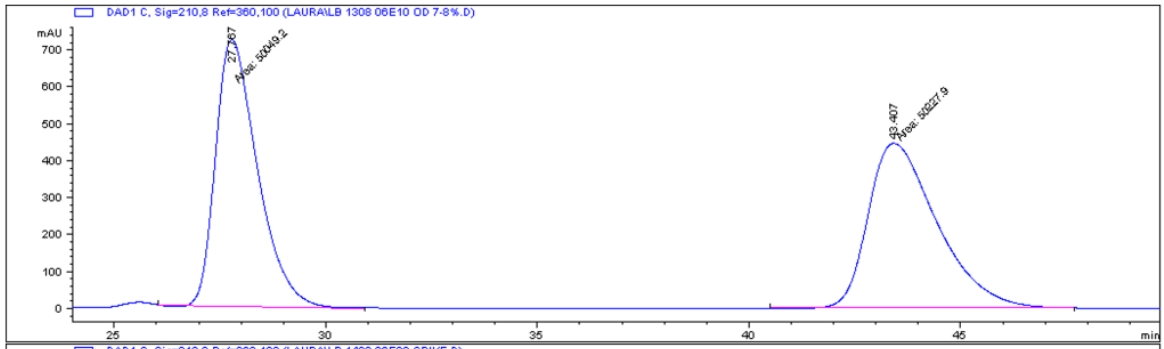
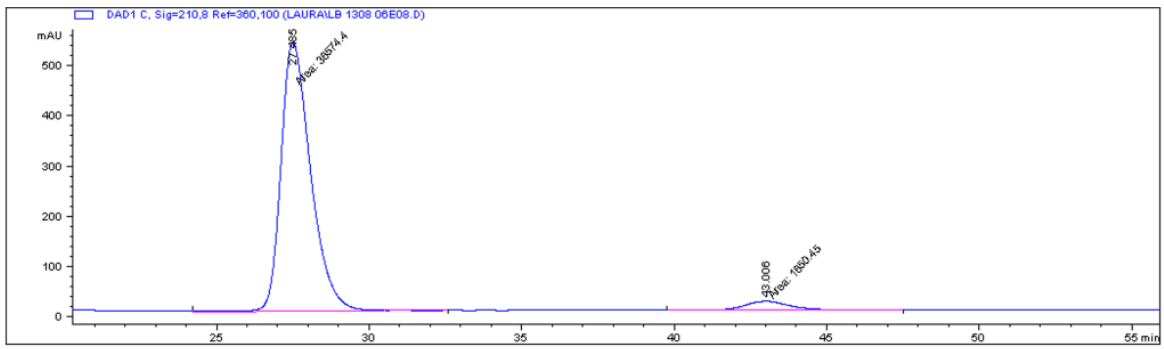
8f

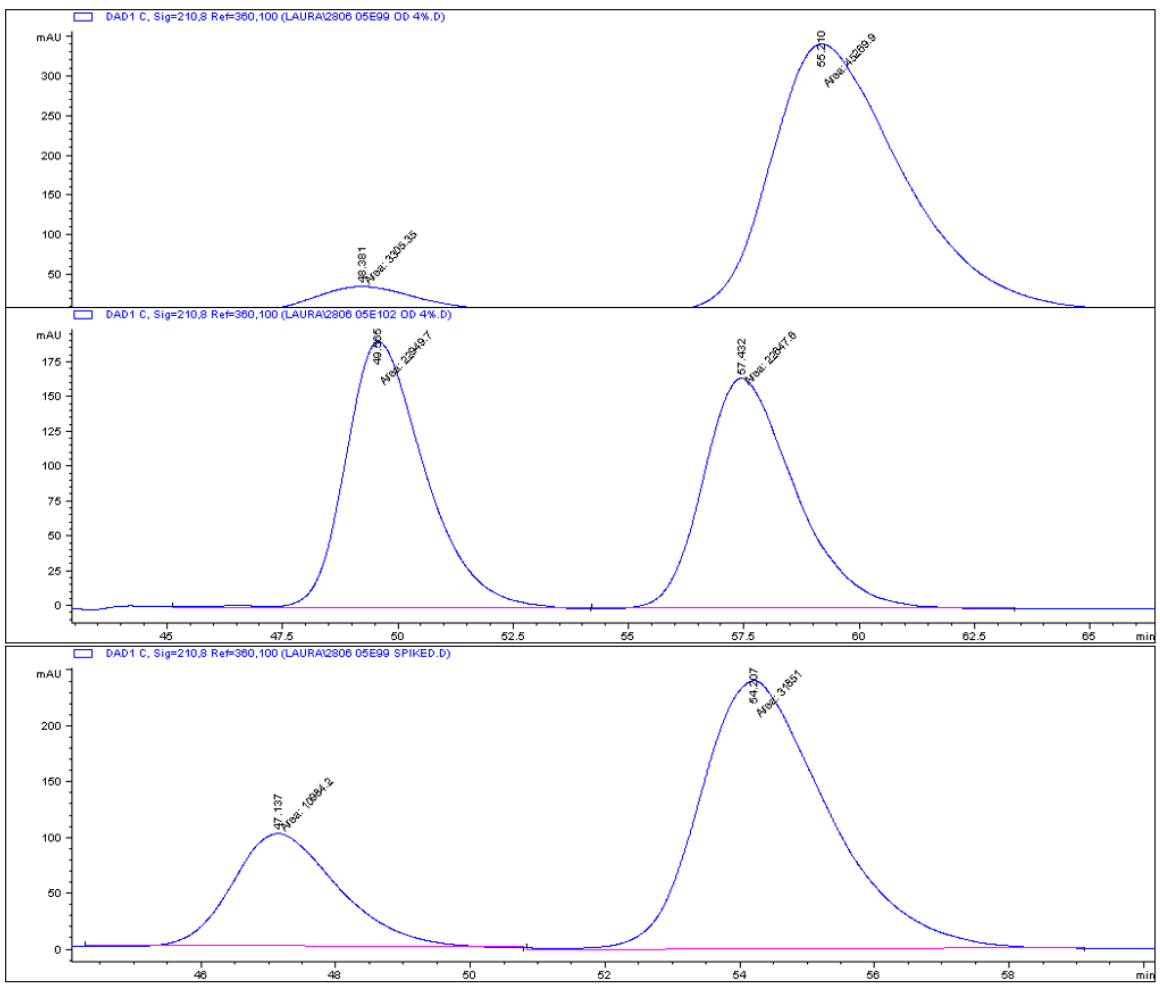


8g

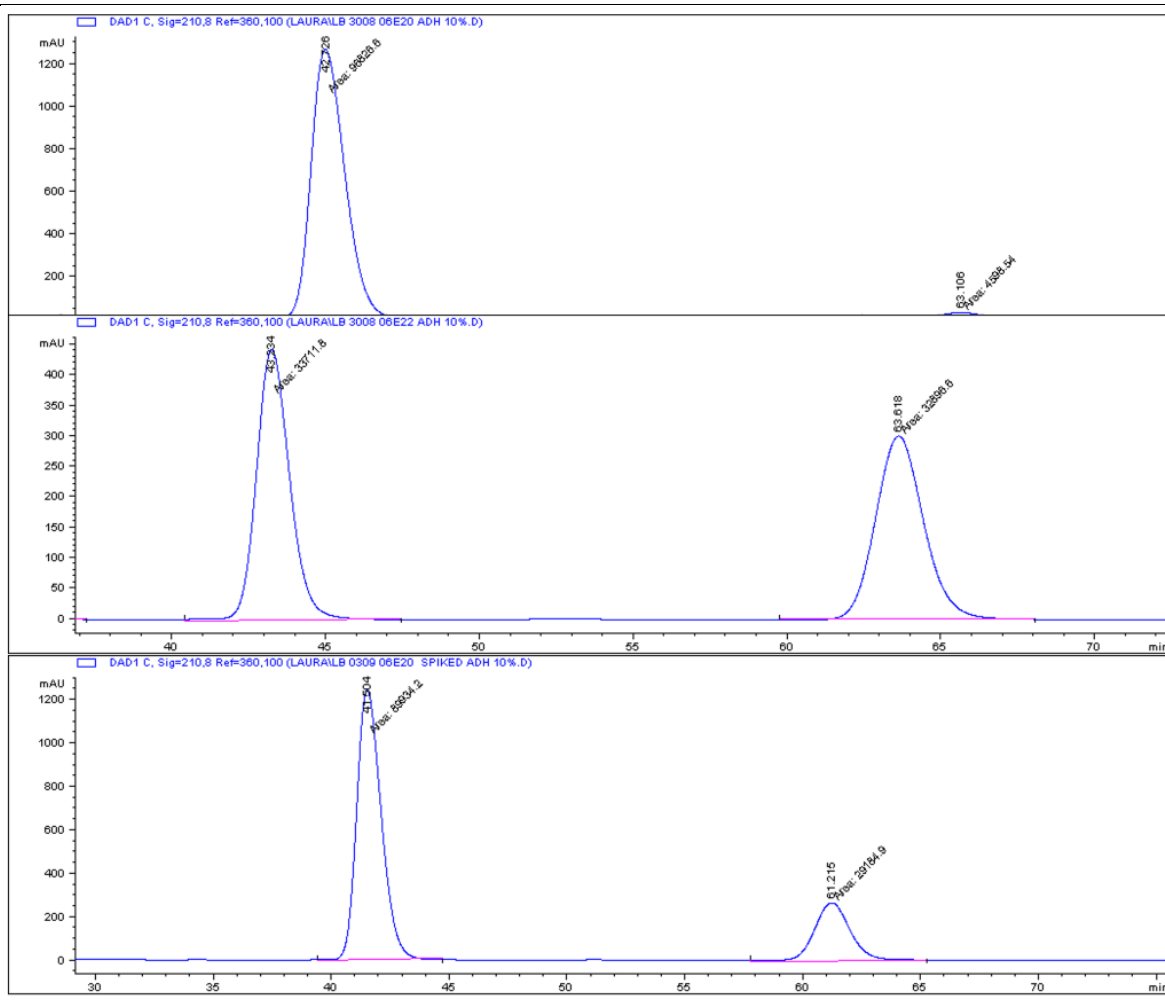


8h

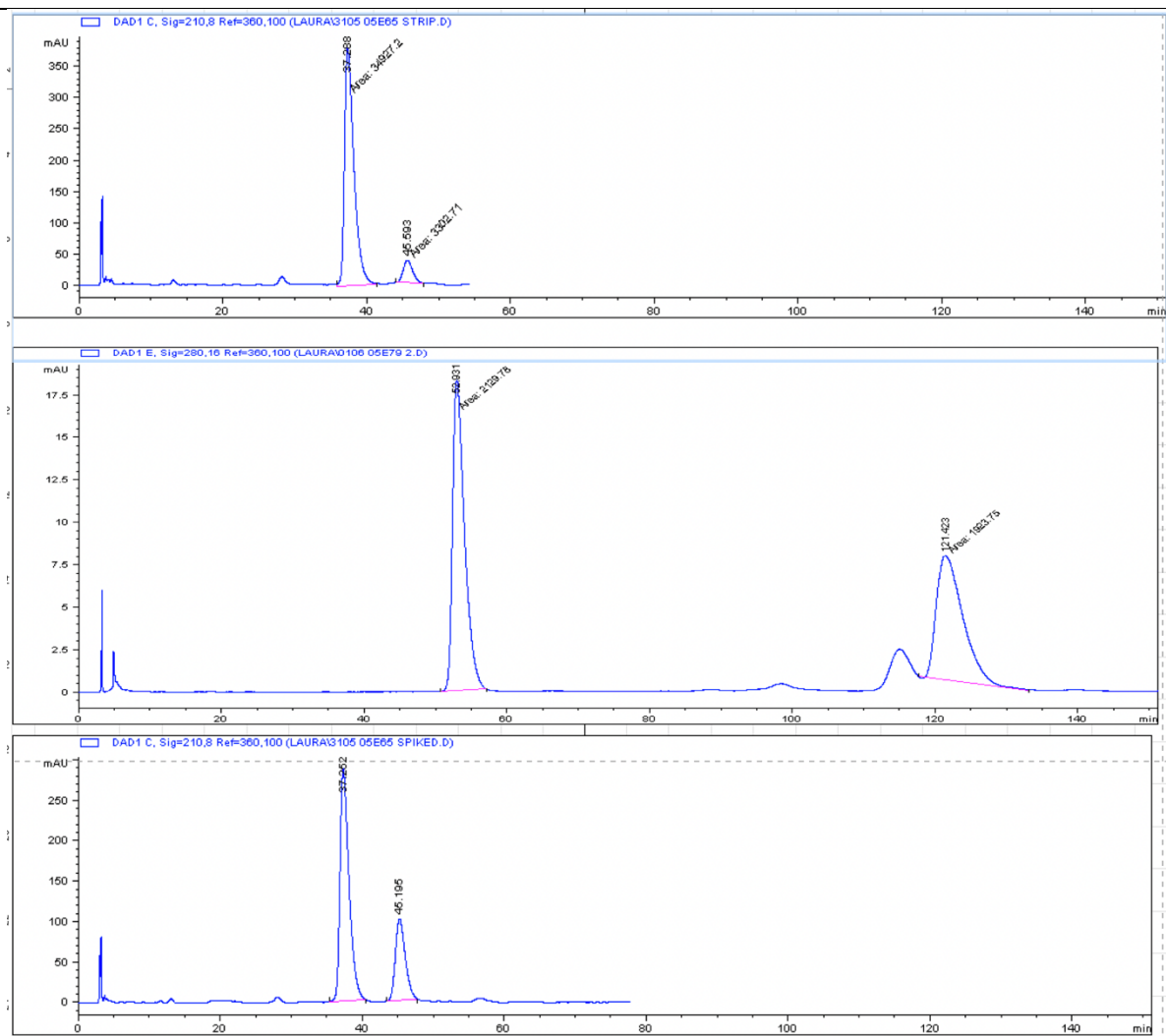




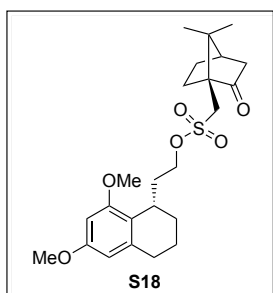
8j



8k



5. Synthesis and characterization of camphorsulfonyl derivative of **8a**



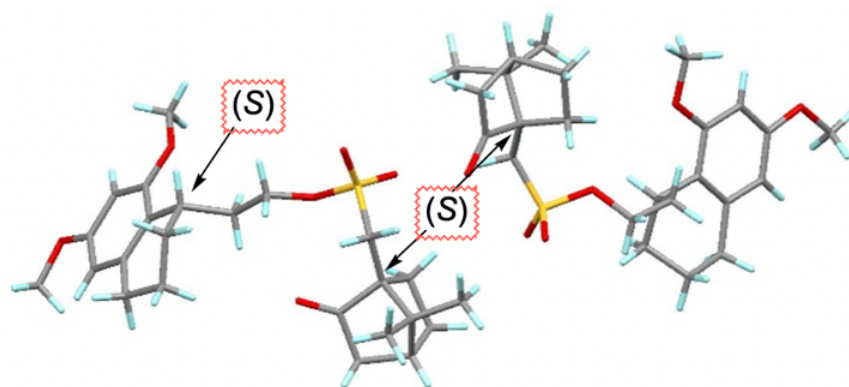
2-((S)-6,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl ((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate **S18** : To a solution of 2-(6,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol **8a** (0.065 g, 0.28 mmol), dry trimethylamine (0.066 mL, 0.48 mmol) in dry THF (1.4 mL) at 0 °C was added (S)- (+)-10-camphorsulfonyl chloride. The solution was warmed to room temperature and stirred for 24 h. The reaction was quenched with saturated sodium bicarbonate (aq) (2.0 mL) and the layers separated. The aqueous phase was extracted with EtOAc (x3). The combined organic phases were dried over MgSO₄. The crude mixture was purified using silica gel on column chromatography (hex/EtOAc, 77.5:22.5) to yield 2-((S)-6,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethyl ((7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate as a clear oil (0.07 g, 57 % yield). The product was recrystallized by

dissolving a small portion in DCM and diluting with MeOH.

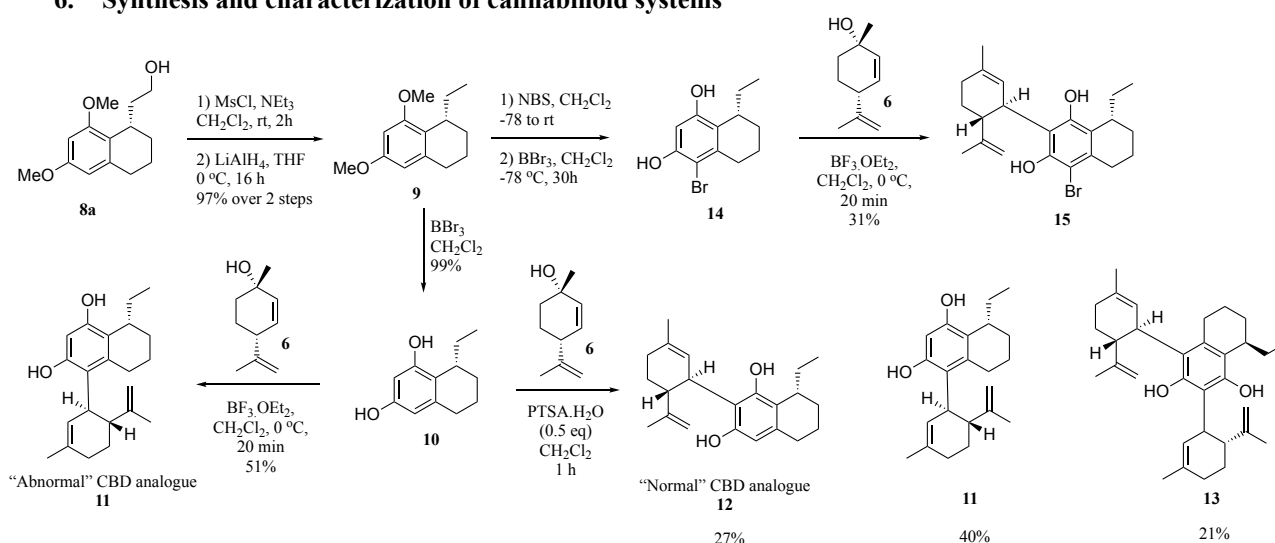
$[\alpha]_D^{20} +9.5$ (c 0.2, MeOH), m.p: 75.4-76.6 °C, ¹H NMR (400 MHz, CDCl₃) δ 6.28 (d, 1 H, J = 2.3 Hz, d-aromatic), 6.21 (d, 1 H, J = 2.3, f-aromatic) 4.44-4.32 (m, 2 H, 1-CH₂), 3.79 (s, 3 H, 7-OMe), 3.77 (s, 3 H, 8-OMe), 3.64 (d, 1 H, J = 15.1 Hz, 9-CHH), 3.08-3.03 (m, 1 H, 3-CH), 2.99 (d, 1 H, J = 15.1 Hz, 9-CHH), 2.78-2.65 (m, 2 H, 6-CH₂), 2.56-2.49 (m, 1 H), 2.43-2.36 (m, 1 H), 2.13-2.02 (m, 3 H), 1.95 (d, 1 H, J = 18.5 Hz), 1.85-1.63 (m, 6 H), 1.47-1.40 (m, 1 H), 1.13 (s, 3 H, 17-CH₃), 0.89 (s, 3 H, 18-CH₂) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 214.67 (11-C), 158.65 (q-aromatic), 158.29 (q-aromatic), 138.69 (a-aromatic), 121.54 (b-aromatic), 104.54 (f-aromatic), 96.29 (d-aromatic), 70.10 (1-C), 58.12 (q-C), 55.37 (8-OMe), 55.34 (7-OMe), 48.06 (q-C), 46.75 (9-C), 42.94, 42.67, 34.15, 29.89, 28.20 (3-C), 27.04, 26.89, 25.01, 20.02 (17-C), 19.85 (18-C), 18.28 ppm; IR (Diamond) ν 2935, 2838, 1745, 1605, 1394, 1198, 856 cm⁻¹ HRMS (ES-Tof) Exact mass calculated for C₂₄H₃₄SO₆ [M+H]⁺ 473.1974, Found 473.1959

Camphorsulfonate derivative **S18** was recrystallized from minimal DCM and hexane. Its single crystal was analysed by X-Ray crystallography using a copper source. The crystal data has not been deposited on CCDC due to the disordered

nature of one of the molecules in the unit cell, but another crystal structure within this manuscript which also confirms the stereochemistry has been.



6. Synthesis and characterization of cannabinoid systems



(R)-1-ethyl-6,8-dimethoxy-1,2,3,4-tetrahydronaphthalene 9 : To a solution of (*S*)-2-(6,8-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-yl)ethan-1-ol **8a** (1.12 g, 4.76 mmol), dry trimethylamine (2.65 mL, 19.02 mmol) in dry DCM (47.5 mL) was added mesyl chloride (1.41 mL, 18.07 mmol) dropwise. The reaction was quenched with 1 M HCl (50 mL) after 2 h of stirring at room temperature. The layers were separated and the aqueous extracted with EtOAc (x2). The combined organic layers were washed with sodium bicarbonate (aq) and dried over Na₂SO₄. After the removal of solvent under reduced pressure, the crude material was dissolved in dry THF (47.5 mL) and cooled to 0 °C. LiAlH₄ (1.19 g, 31.39 mmol) was added to the cooled solution before the temperature was raised to rt. The solution was stirred overnight and quenched at 0 °C with distilled water (1 mL) dropwise, 15 % NaOH (aq) (1 mL) and distilled water (3 mL). The mixture was warmed to room temperature and stirred for 15 min. MgSO₄ was added and stirring continued for a further 2 h. The mixture was filtered and solvent removed under reduced pressure to yield 1-ethyl-6,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (1.0 g, 97 % yield) as an orange oil which required no further purification.

$[\alpha]_D^{20} +11.0$ (c 0.2, MeOH) ¹H NMR (400 MHz, CDCl₃) δ 6.21 (d, 1 H, J = 2.3 Hz, d-aromatic), 6.13 (d, 1 H, J = 2.3 Hz, f-aromatic), 3.73-3.69 (m, 6 H, 7-OMe and 8-OMe), 2.75-2.68 (m, 1 H, 3-CH), 2.67-2.59 (m, 2 H, 6-CH₂), (m, 1 H, 4-CHH), 1.76-1.46 (m, 4 H, 2-CHH, 4-CHH, 5-CH₂), 1.32-1.20 (m, 1 H, 2-CHH), 0.87 (t, 3 H, J = 7.4 Hz, 1-CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 158.52 (c-aromatic), 158.20 (e-aromatic), 138.49 (a-aromatic), 123.70 (b-aromatic), 104.35 (f-aromatic), 96.30 (d-aromatic), 55.34 (7-OMe), 55.33 (8-OMe), 33.27 (3-C), 30.25 (6-C), 27.17 (2-C), 25.36 (4-C), 18.24 (5-C), 12.70 (1-C) ppm; IR (Diamond) ν 2958, 2933, 2869, 1605, 1590, 1486, 1458, 861 cm⁻¹ Exact mass calculated for C₁₄H₂₀O₂ [M+H]⁺ 221.1542, Found 221.1550

(R)-5-bromo-1-ethyl-6,8-dimethoxy-1,2,3,4-tetrahydronaphthalene 14 : To a solution of (*R*)-1-ethyl-6,8-dimethoxy-1,2,3,4-tetrahydronaphthalene **9** (0.33 g, 1.50 mmol) in anhydrous DCM (35.0 mL) at -78 °C was added N-bromosuccinimide (0.27 g, 1.50 mmol) in one portion. After 1 h of stirring at -78 °C, the temperature of the solution was raised to room temperature. After 2 h the reaction was quenched with saturated sodium bicarbonate solution (aq)

and the organic layer washed with 5 % sodium thiosulphate solution (aq) before being dried over MgSO₄. The resultant thick orange oil taken forward without further purification (3.3 g, 72 % yield).

$[\alpha]_D^{20} +9.0$ (c 0.2, DCM) ¹H NMR (400 MHz, CDCl₃) δ 6.39 (s, 1 H, d-aromatic), 3.89 (s, 3 H, 8-OMe), 3.83 (s, 3 H, 7-OMe), 2.93-2.82 (m, 2 H, 3-CH and 6-CHH), 2.59-2.50 (m, 1 H, 6-CHH), 1.94-1.88 (m, 1 H, 4-CHH), 1.80-1.73 (m, 2 H, 5-CH₂), 1.65-1.57 (m, 1 H, 2-CHH), 1.53-1.44 (m, 1 H, 4-CHH), 1.37-1.29 (m, 1 H, 2-CHH), 0.85 (t, 3 H, J = 7.4 Hz, 1-CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 157.17 (c-aromatic), 154.25 (e-aromatic), 137.78 (a-aromatic), 125.71 (b-aromatic), 105.50 (f-aromatic), 94.38 (d-aromatic), 56.60 (8-OMe), 55.64 (7-OMe), 33.49 (3-C), 30.91 (6-C), 26.89 (2-C), 24.42 (4-C), 17.91 (5-C), 12.65 (1-C) ppm; IR (Diamond) ν 2952, 2933, 2870, 2836, 1591, 804 cm⁻¹ HRMS (ES-Tof) Exact mass calculated for C₁₄H₁₉BrO₂ [M+H]⁺ 299.0647, Found 299.0645

(R)-4-bromo-8-ethyl-5,6,7,8-tetrahydronaphthalene-1,3-diol 15: To a solution of (R)-5-bromo-1-ethyl-6,8-dimethoxy-1,2,3,4-tetrahydronaphthalene **14** (0.31 g, 1.05 mmol) in dry DCM (2.8 mL) at -78 °C was added BBr₃ (1.0 M, 2.84 mL, 2.84 mmol) dropwise. The temperature was raised to room temperature and the reaction stirred overnight. After 30 h, the reaction was quenched with ice and the layers separated. The aqueous was extracted with DCM (x3) and EtOAc (x2). The organic layers were combined and dried over MgSO₄. The crude material was purified using silica gel on column chromatography (Hex/EtOAc, 7:3) to yield 4-bromo-8-ethyl-5,6,7,8-tetrahydronaphthalene-1,3-diol as a brown crystalline solid (0.13 g, 31% yield).

$[\alpha]_D^{20} +32.3$ (c 0.2, DCM), m.p: 123.4-124.6 °C ¹H NMR (400 MHz, CDCl₃) δ 6.40 (s, 1 H, d-aromatic), 5.49 (s, 1 H, e-OH), 4.73 (s, 1 H, c-OH), 2.85-2.78 (m, 1 H, 6-CHH), 2.74 (dtd, 1 H, J = 8.0, 5.5 and 3.0 Hz, 3-CH), 2.57-2.48 (m, 1 H, 6-CH), 1.98-1.91 (m, 1 H, 4-CHH), 1.84-1.74 (m, 2 H, 5-CH₂), 1.72-1.62 (m, 1 H, 2-CHH), 1.55-1.49 (m, 1 H, 4-CHH), 1.40 (ddq, 1 H, J = 14.3, 10.43, 7.2 Hz, 2-CHH), 0.99 (t, 1 H, J = 7.4 Hz, 1-CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 153.57 (c-aromatic), 150.46 (e-aromatic), 137.15 (a-aromatic), 123.21 (b-aromatic), 104.66 (f-aromatic), 100.70 (d-aromatic), 33.74 (3-C), 30.77 (6-C), 26.73 (2-C), 24.42 (4-C), 17.74 (5-C), 12.58 (1-C) ppm; IR (Diamond) ν 3464, 3415, 2959, 2935, 2866, 1592, 835, 820 cm⁻¹ HRMS (ES-Tof) Exact mass calculated for C₁₂H₁₇NO₂ [M+H]⁺ 269.0177, Found 269.0187

(R)-8-ethyl-5,6,7,8-tetrahydronaphthalene-1,3-diol 10 : BBr₃ (1.0 M, 10.12 mL, 10.12 mmol) was added dropwise over 4 mins to a solution of 1-ethyl-6,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (0.86 g, 3.89 mmol) in dry DCM at -78 °C. The reaction temperature was raised to 0 °C after 30 min. After 24 h the temperature of the reaction was raised to room temperature due to incomplete consumption of starting material. After a further 3 h of stirring, the reaction was quenched at 0 °C with MeOH (25 mL). The layers were separated and the aqueous extracted with EtOAc (x3). The combined organic layers were washed with saturated NaHCO₃ (aq), distilled water, brine and dried over MgSO₄. The crude mixture was purified using silica gel on column chromatography (Hex/EtOAc/DCM, 65:25:10) to yield 8-ethyl-5,6,7,8-tetrahydronaphthalene-1,3-diol as a brown oil (0.74 g, 99 % yield).

¹H NMR (400 MHz, CDCl₃) δ 6.15 (s, 2 H, d and f-aromatic), 4.83-4.72 (m, 2 H, 7 and 8-OH), 4.27-2.60 (m, 3 H, 3-CH and 6-CH₂), 1.96-1.90 (m, 1 H, 4-CHH), 1.83-1.58 (m, 4 H, 2-CHH, 4-CHH, 5-CH₂), 1.48-1.37 (m, 1 H, 2-CHH), 0.99 (t, 3 H, J = 7.6 Hz, 1-CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 154.50 (c-aromatic), 153.91 (e-aromatic), 139.55 (a-aromatic), 121.12 (b-aromatic), 107.90 (f-aromatic), 100.57 (d-aromatic), 33.48 (3-C), 29.83 (6-C), 27.03 (2-C), 25.44 (4-C), 18.09 (5-C), 12.59 (1-C) ppm; HRMS (Es-Tof) Exact mass calculated for C₁₂H₁₆O₂ [M+H]⁺ 191.1067, Found 191.1072 IR (Diamond) ν 3478, 3243, 2960, 2937, 2870, 1608, 1590, 839 cm⁻¹

(R)-8-ethyl-4-((1R,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl)-5,6,7,8-tetrahydronaphthalene-1,3-diol 11 : BF₃·OEt₂ METHOD : To a solution of 8-ethyl-5,6,7,8-tetrahydronaphthalene-1,3-diol (0.14 g, 0.70 mmol) and BF₃·OEt₂ (0.009 mL, 0.07 mmol) in dry DCM (2.5 mL) at 0 °C was added (1S, 4R)-1-methyl-4-(prop-1-en-2-yl)cyclohex-2-en-1-ol (0.11 g, 0.7 mmol) dropwise in dry DCM (1.0 mL) over 1 min. The reaction was quenched after 20 min with saturated sodium bicarbonate solution (aq) (3.5 mL). The layers were separated and the aqueous was extracted with DCM (x2). The combined organic layers were combined and dried over MgSO₄. The crude material was purified using silica gel on column chromatography (the sample was dry loaded, gradient, Hex/ Et₂O, 97.5:2.5, 9:1, 65:35) to yield a brown solid (0.16 g, 51 % yield).

$[\alpha]_D^{20} -40.0$ (c 0.2, DCM), m.p: 48.0-49.5 °C ¹H NMR (400 MHz, CDCl₃) δ 6.19 (s, 1 H, 3'-CH), 6.02 (s, 1 H, 2'-OH), 5.57 (s, 1 H, 2-CH), 4.62-4.61 (m, 1 H, 10-CHH), 4.52 (s, 1 H, 4'-OH), 4.44 (s, 1 H, 10-CHH), 3.62-3.59 (m, 1 H, 3-CH), 2.73-2.62 (m, 2 H, 1''-CHH and 4''-CH), 2.50-2.38 (m, 2 H, 1''-CHH and 4-CH), 2.24-2.16 (m, 1 H, 6-CHH), 2.10-2.04 (m, 1 H, 6-CHH), 1.89-1.63 (m, 9 H, 2''-CH₂, 3''-CHH, 5-CH₂, 5''-CHH and 7-CH₃), 1.53-1.35 (m, 5 H, 3''-CHH, 5''-CHH and 9-CH₃), 0.98 (t, 3 H, J = 7.5 Hz, 6''-CH₃) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 153.84 (2'-C), 152.60 (4'-C), 147.99 (8-C), 139.43 (1-C), 137.28 (6'-C), 125.15 (2-C), 120.91 (5'-C), 120.15 (1'-C), 111.41 (10-C), 102.11 (3'-C), 44.96 (4-C), 39.67 (3-C), 33.95 (4''-C), 30.26 (6-C), 28.19 (5-C), 27.74 (1''-C), 27.03 (5''-C), 24.53 (3''-C), 23.76 (7-C), 21.38 (9-C), 18.32 (2''-C), 12.68 (6''-C) ppm; IR (Diamond) ν 3425, 2982, 2958, 2929, 2869, 2832, 1642, 890, 862 cm⁻¹ HRMS (Es-Tof) Exact mass calculated for C₂₂H₃₀O₂ [M+H]⁺ 327.2324, Found 327.232

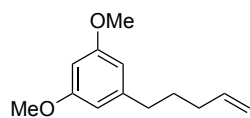
(R)-8-ethyl-2-((1R,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl)-5,6,7,8-tetrahydronaphthalene-1,3-diol 13 and **(R)-8-ethyl-4-((1R,6R)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl)-5,6,7,8-tetrahydronaphthalene-1,3-diol 11** : **TsOH METHOD** : To an ice-cold suspension of **(R)-8-ethyl-5,6,7,8-tetrahydronaphthalene-1,3-diol 10** (0.51 g, 2.66 mmol) and *p*-toluenesulfonic acid monohydrate (253 mg, 1.33 mmol) in anhydrous dichloromethane (16 mL) was added a solution of (1*S*,4*R*)-menthadienol (404 mg, 2.66 mmol) in anhydrous dichloromethane (5 mL) over 1 h and the mixture was stirred for 10 min at 0 °C. The reaction mixture was quenched with saturated aqueous sodium bicarbonate (15 mL) and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 15 mL) and the combined organic layers were washed with saturated brine (50 mL), dried (MgSO₄) and concentrated to give an off-white foam. This material was purified using a Biotage Isolera automated chromatography system under normal phase conditions (silica column, gradient of 0 → 100 % diethyl ether in petrol) with detection at 270 nm to give normal CBD cyclohexyl analogue **12** (486 mg, 27 %), as a white solid and abnormal CBD cyclohexyl analogue **11** (0.72 g, 40 %), as a white solid. Compound **13** is a proposed but un-isolated structure based on the LC-MS profile.

¹H NMR (500 MHz, CDCl₃) δ 6.28 – 5.81 (2 H, m, 3, 7), 5.60 – 5.51 (1 H, s, 10), 4.79 – 4.40 (3 H, m, 8, 17), 3.91 – 3.79 (1 H, s, 9), 2.78 – 2.54 (3 H, s, 19', 19'', 22), 2.45 – 2.31 (1 H, s, 14), 2.31 – 2.16 (1 H, m, 12'), 2.14 – 2.05 (1 H, d, *J* 15.3, 12''), 1.95 – 1.86 (1 H, d, *J* 14.2, 13''), 1.86 – 1.69 (6 H, s, 13', 15, 20), 1.69 – 1.49 (6 H, m, 18, 21, 23''), 1.46 – 1.29 (1 H, m, 23'), 0.99 – 0.91 (3 H, t, *J* 7.4, 24).; ¹³C NMR (126 MHz, CDCl₃) δ 153.73, 153.45, 151.40, 150.03, 149.43, 140.23, 140.05, 136.40, 124.18, 122.93, 122.79, 120.20, 114.09, 113.72, 110.78, 110.71, 109.45, 107.42, 46.00, 38.38, 37.31, 33.80, 33.56, 30.46, 30.36, 29.33, 28.40, 26.75, 26.62, 25.60, 24.95, 23.80, 22.62, 21.20, 20.56, 20.45, 17.87, 12.61.

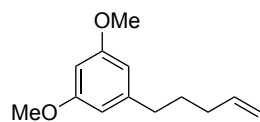
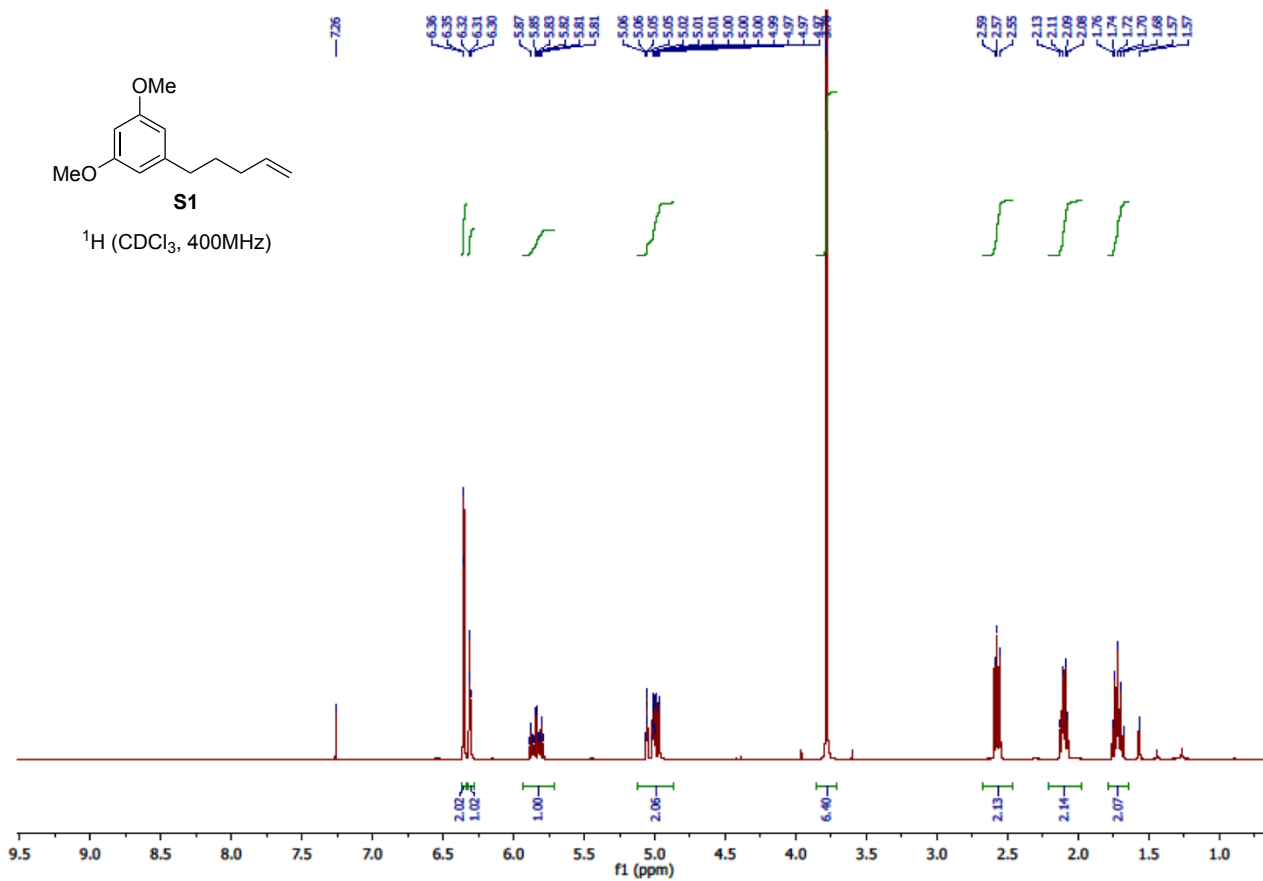
¹H NMR (500 MHz, d₆-DMSO) δ 8.33 (1 H, s br, H-8), 6.91 (1 H, s br, H-7), 5.98 (1 H, s, H-3), 5.21 (1 H, m, H-10), 4.48 (1 H, m, H-17'), 4.43 (1 H, m, H-17''), 3.90 (1 H, m, H-9), 2.87 (1 H, m, H-14), 2.75 (1 H, m, H-22), 2.53 – 2.48* (2 H, m, H-19', 19''), 2.16 (1 H, m, H-12'), 1.97 (1 H, m, H-12''), 1.81 (1 H, m, H-21'), 1.76 – 1.46 (11 H, m, H-13', 13'', H-15, H-18, H-20', 20'', H-21'', H-23'), 1.25 (1 H, m, H-23''), 0.89 (3 H, t, *J* 7.3, H-24). *masked underneath DMSO peak.

¹³C NMR (126 MHz, d₆-DMSO) δ 54.07 (C-2), 153.77 (C-6), 149.18 (C-16), 134.59 (C-4), 132.53 (C-11), 126.87 (C-10), 120.35 (C-5), 115.62 (C-1), 110.26 (C-17), 107.71 (C-3), 44.87 (C-14), 36.60 (C-9), 33.05 (C-22), 30.71 (C-12), 29.74 (C-13), 29.45 (C-19), 27.02 (C-23), 25.75 (C-21), 23.74 (C-15), 19.85 (C-18), 18.25 (C-20), 12.50 (C-24).

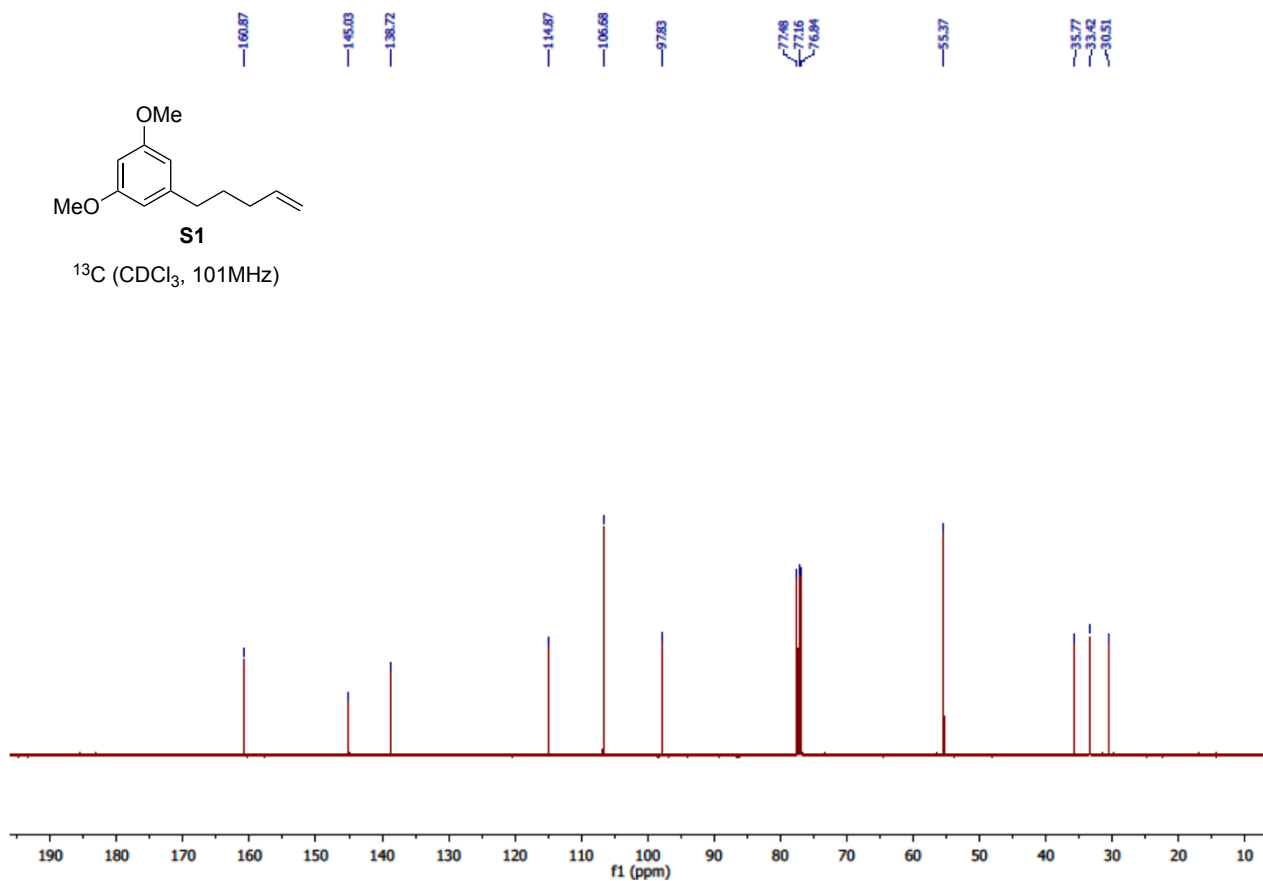
7. NMR Spectra

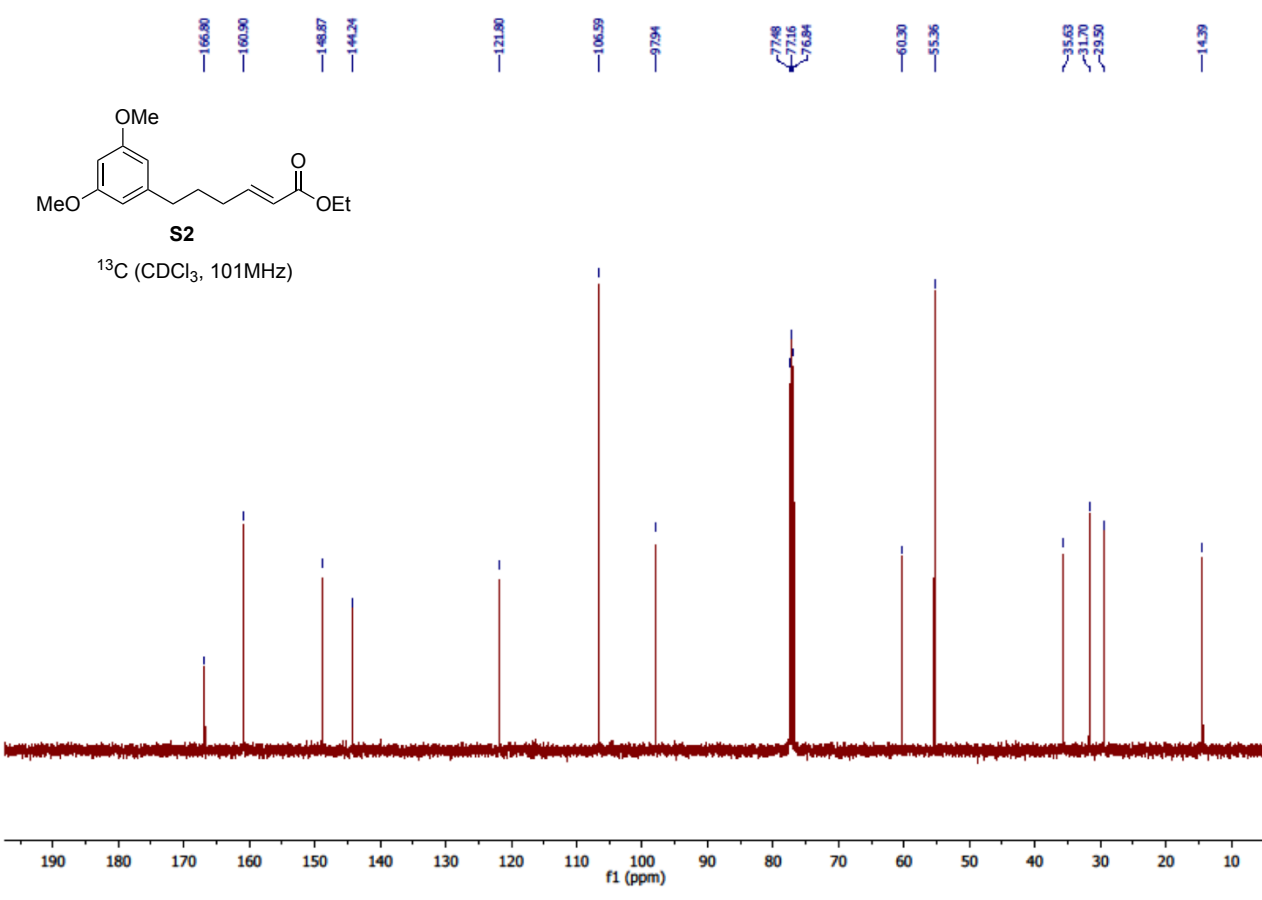
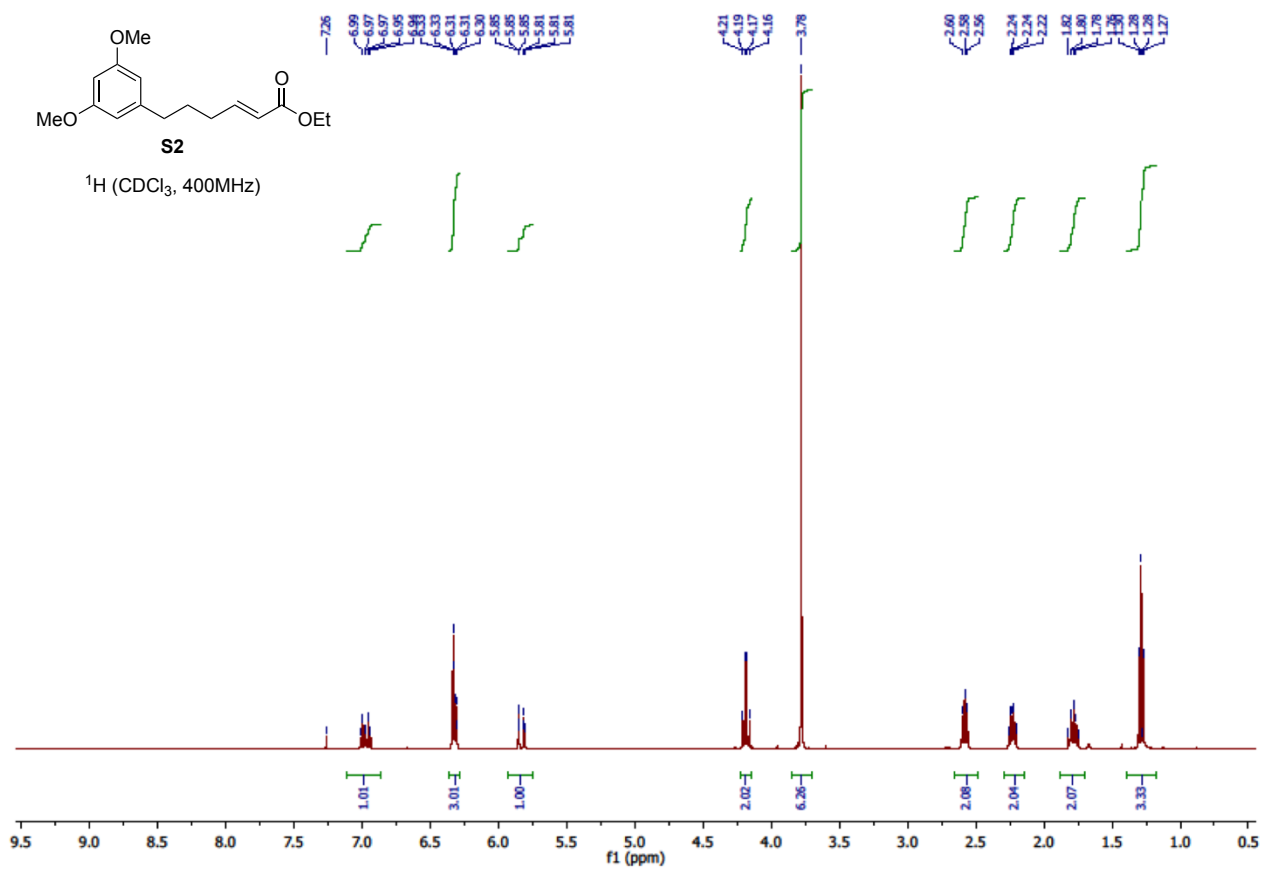


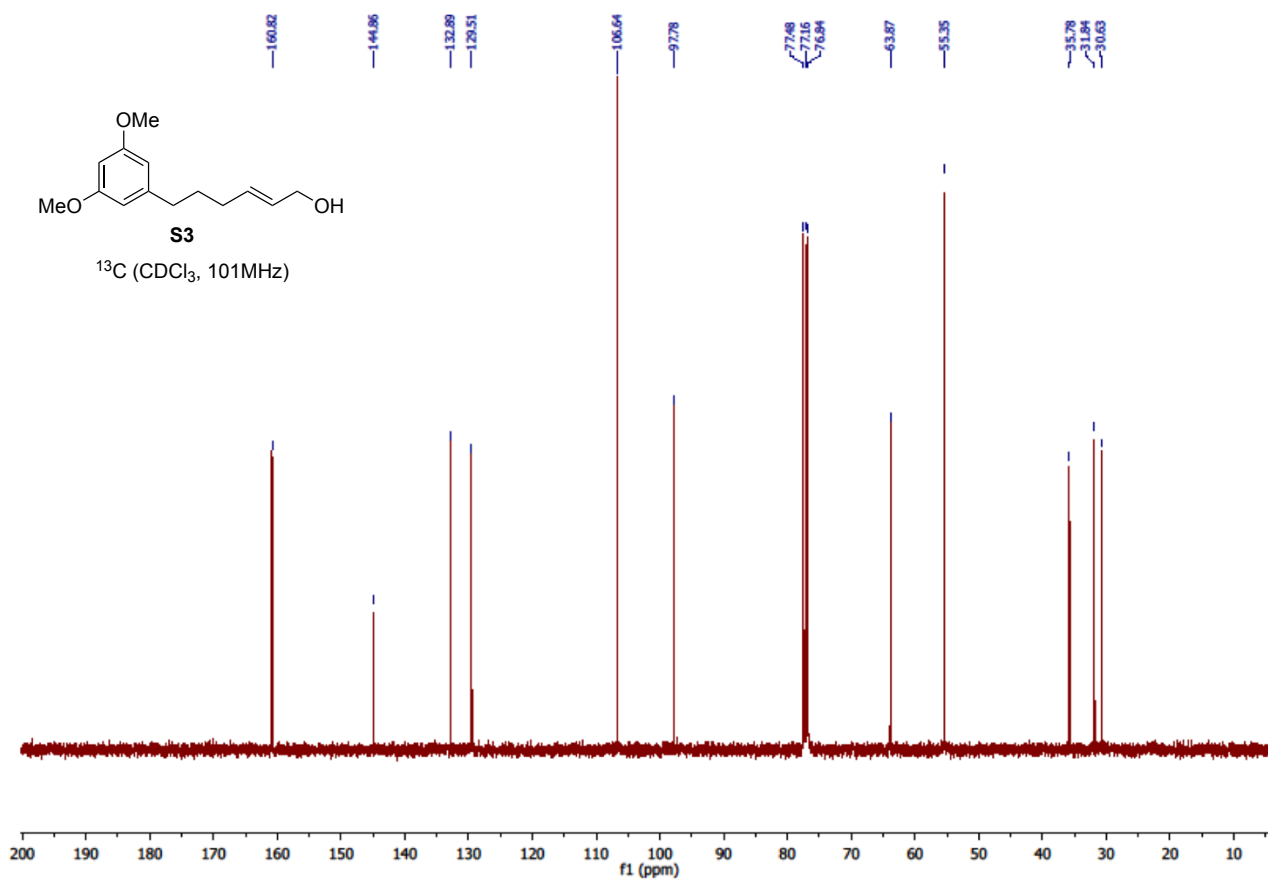
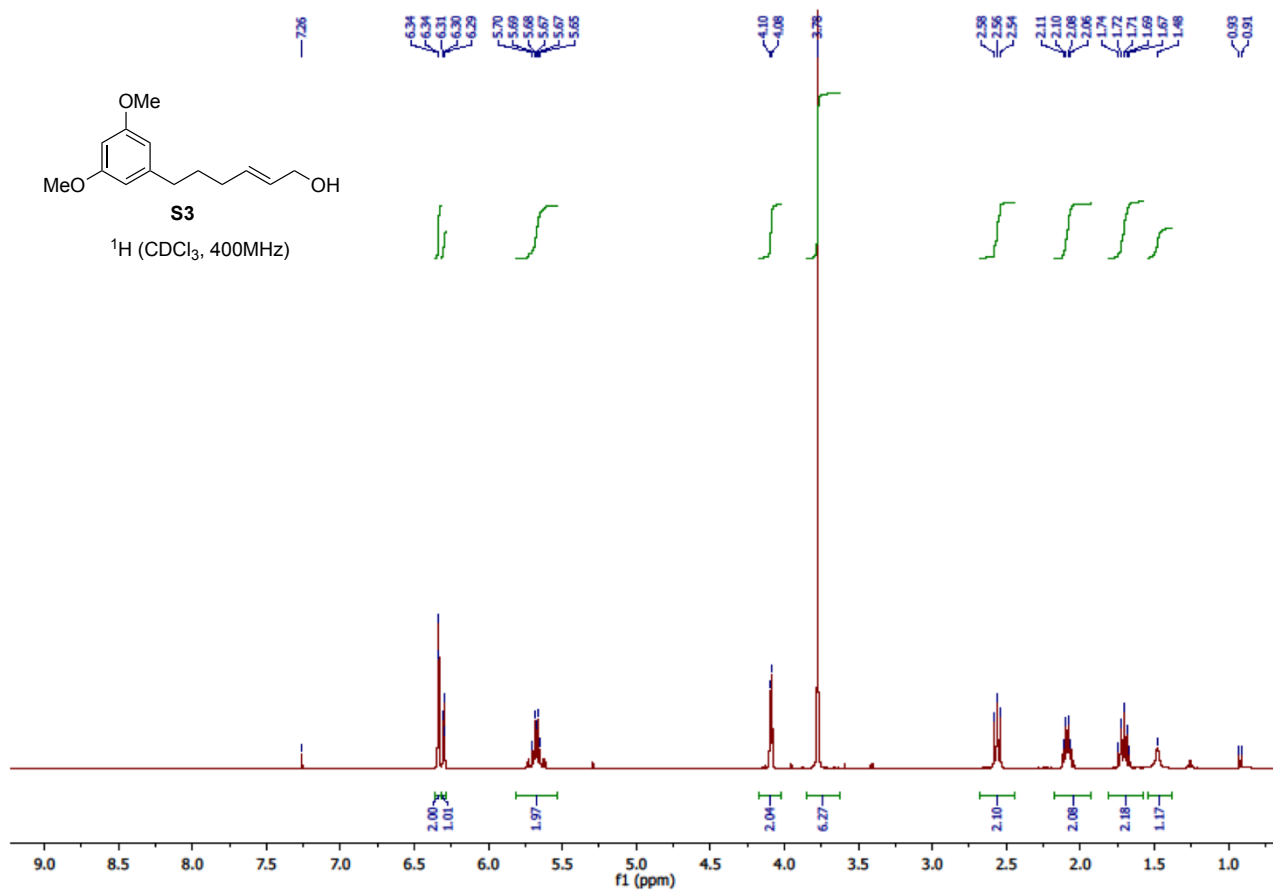
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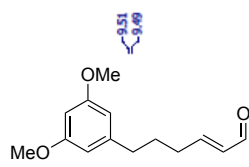


^{13}C (CDCl_3 , 101MHz)

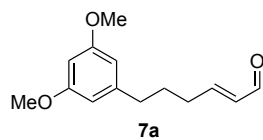
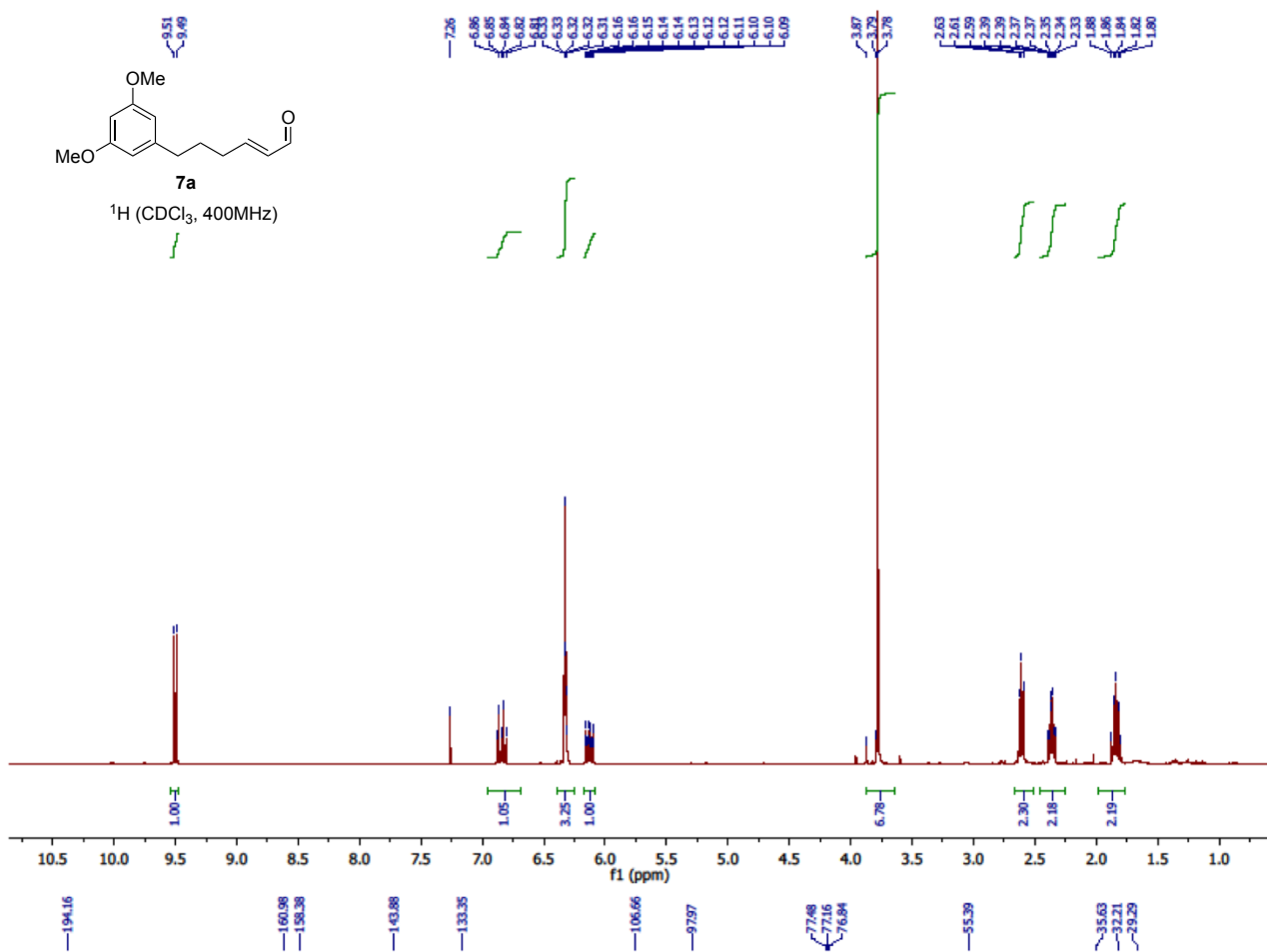




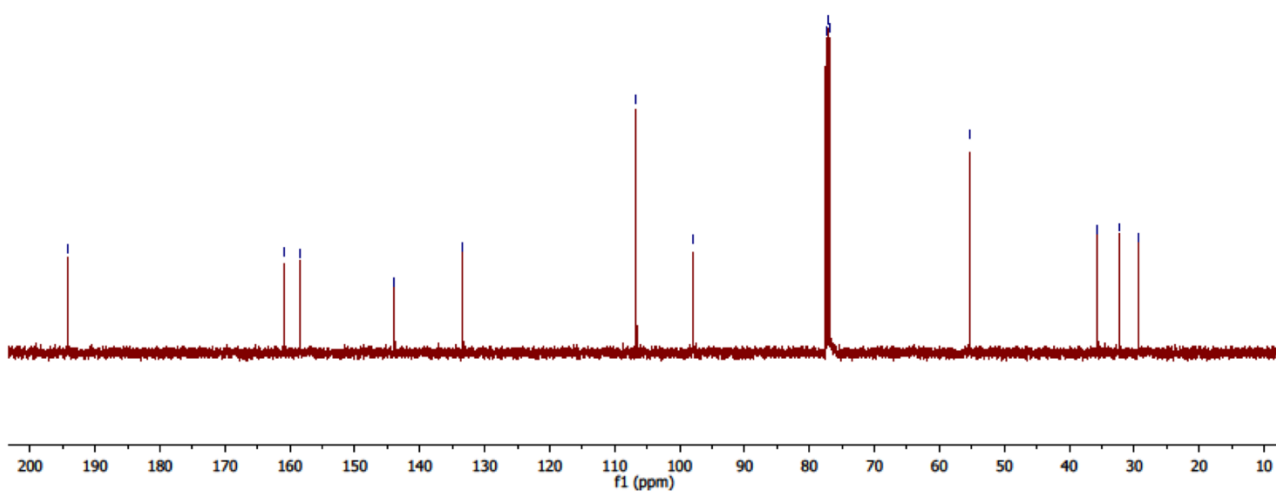


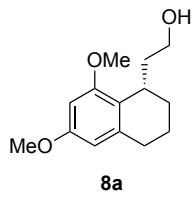


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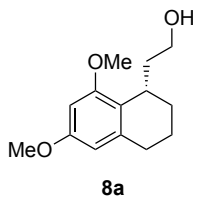
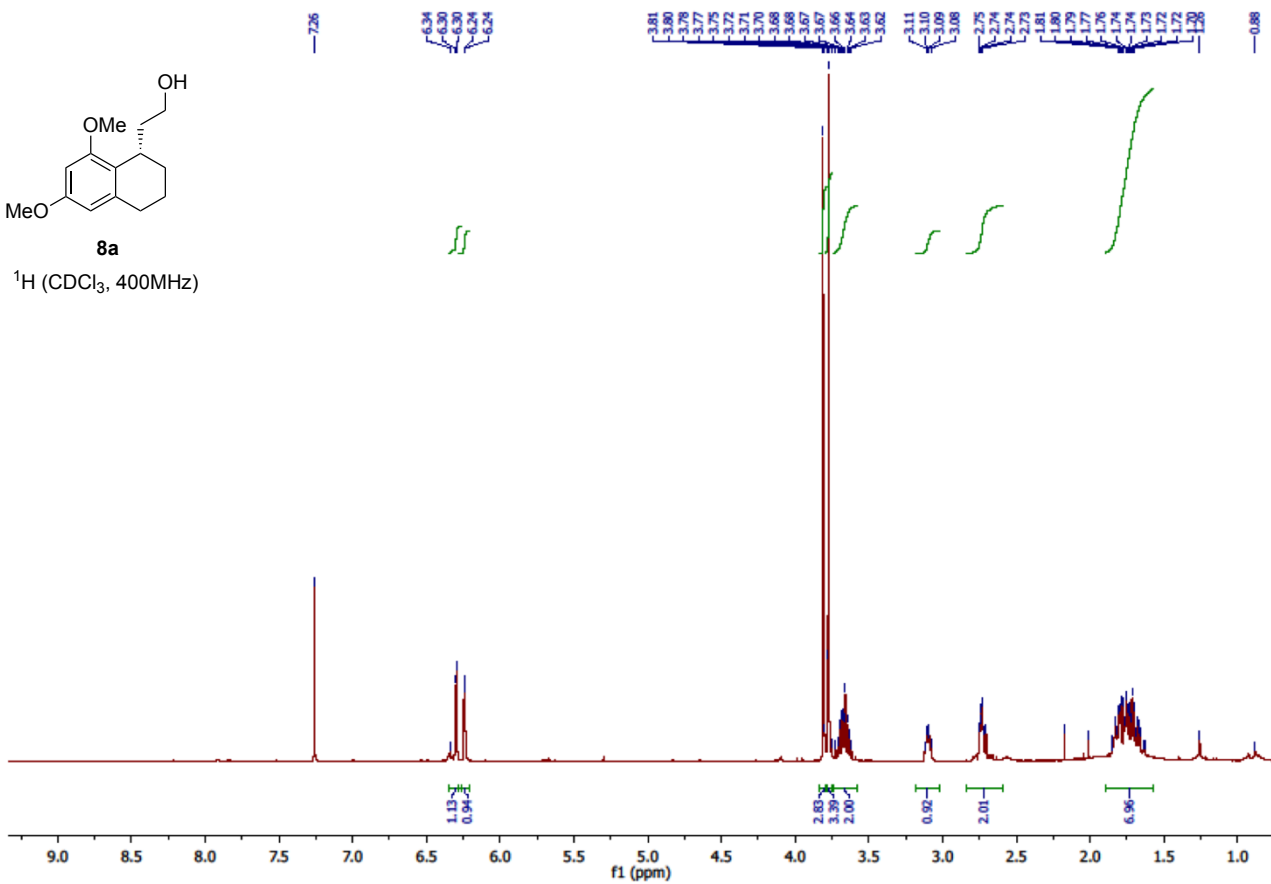


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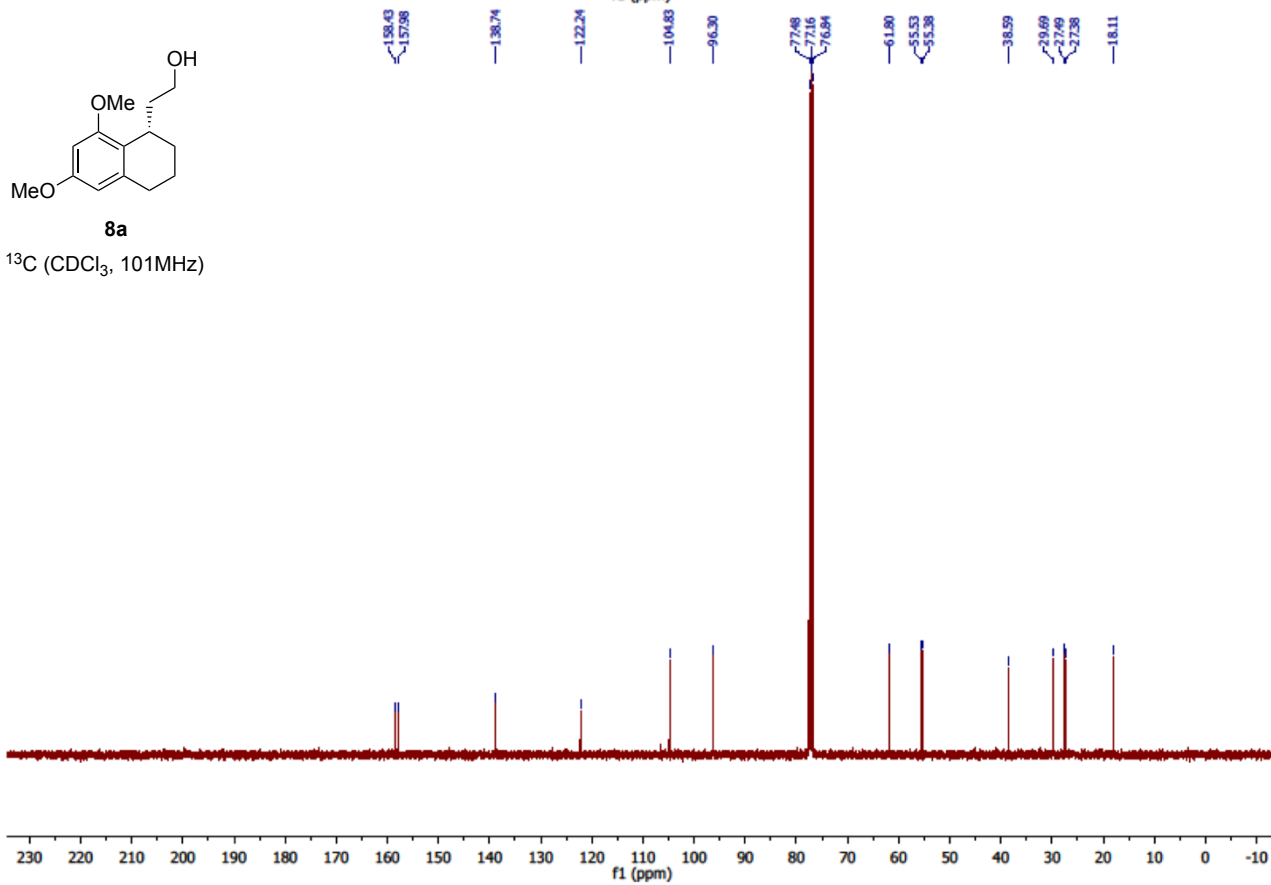


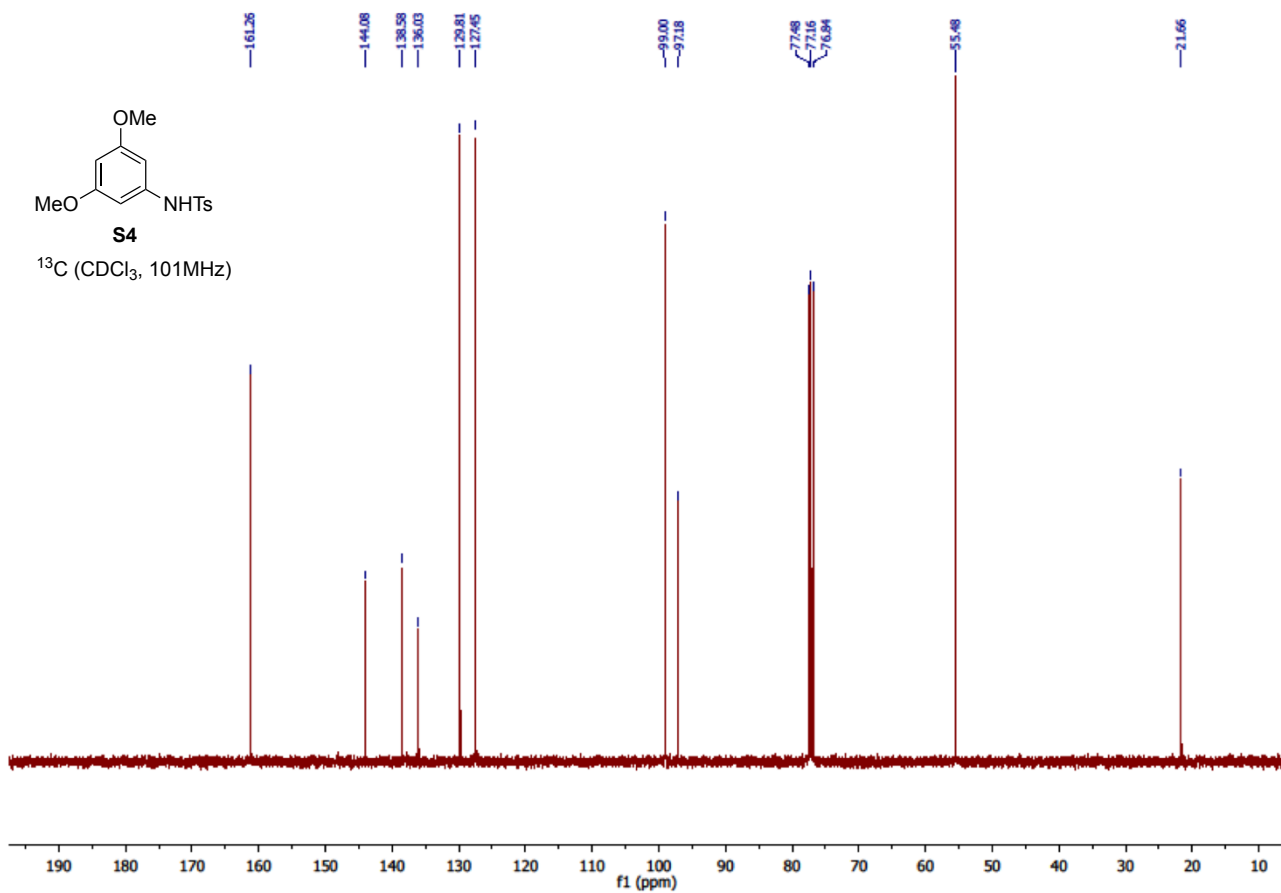
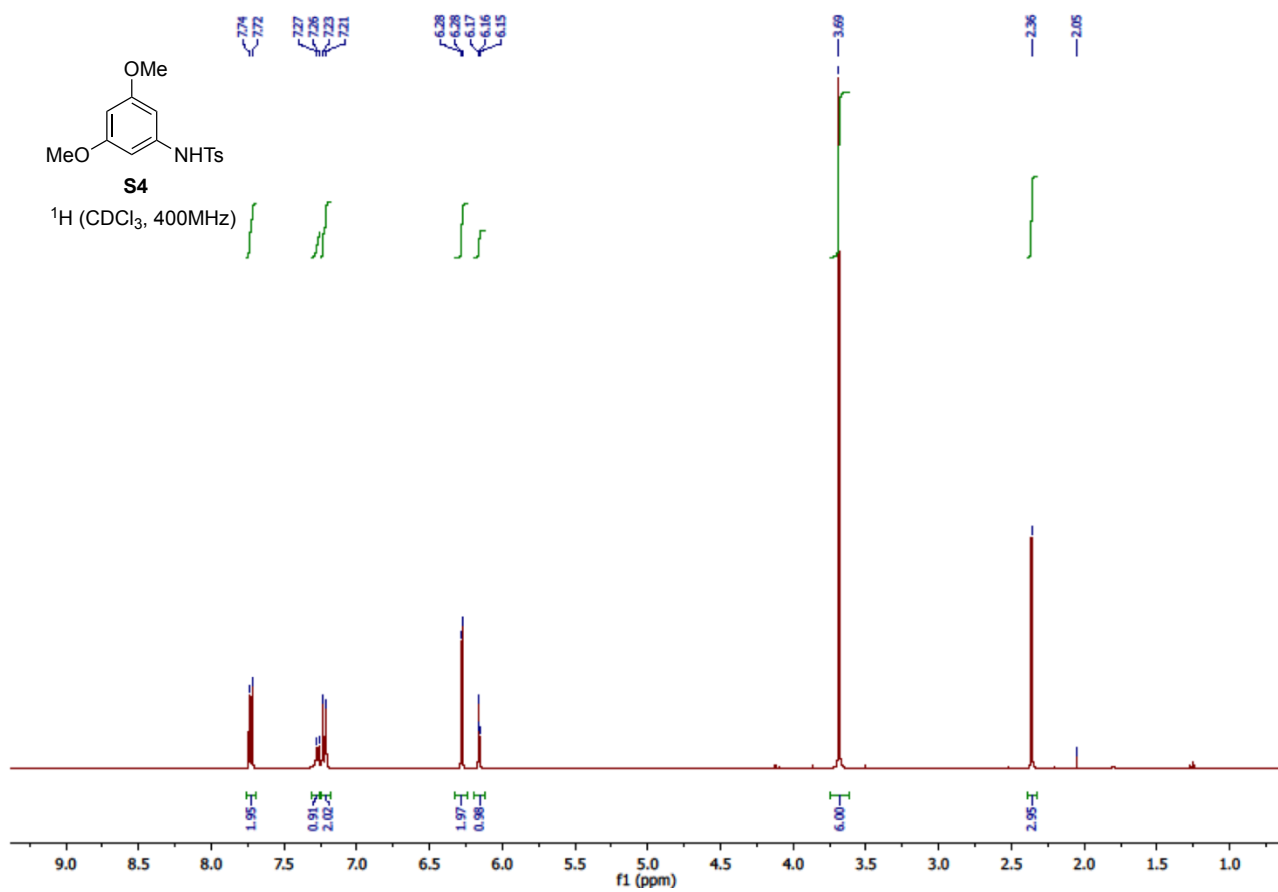


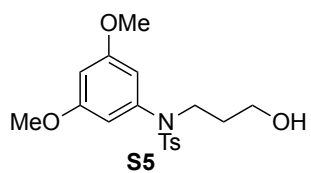
¹H (CDCl₃, 400MHz)



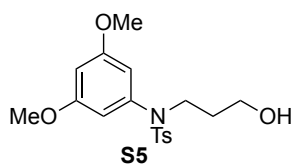
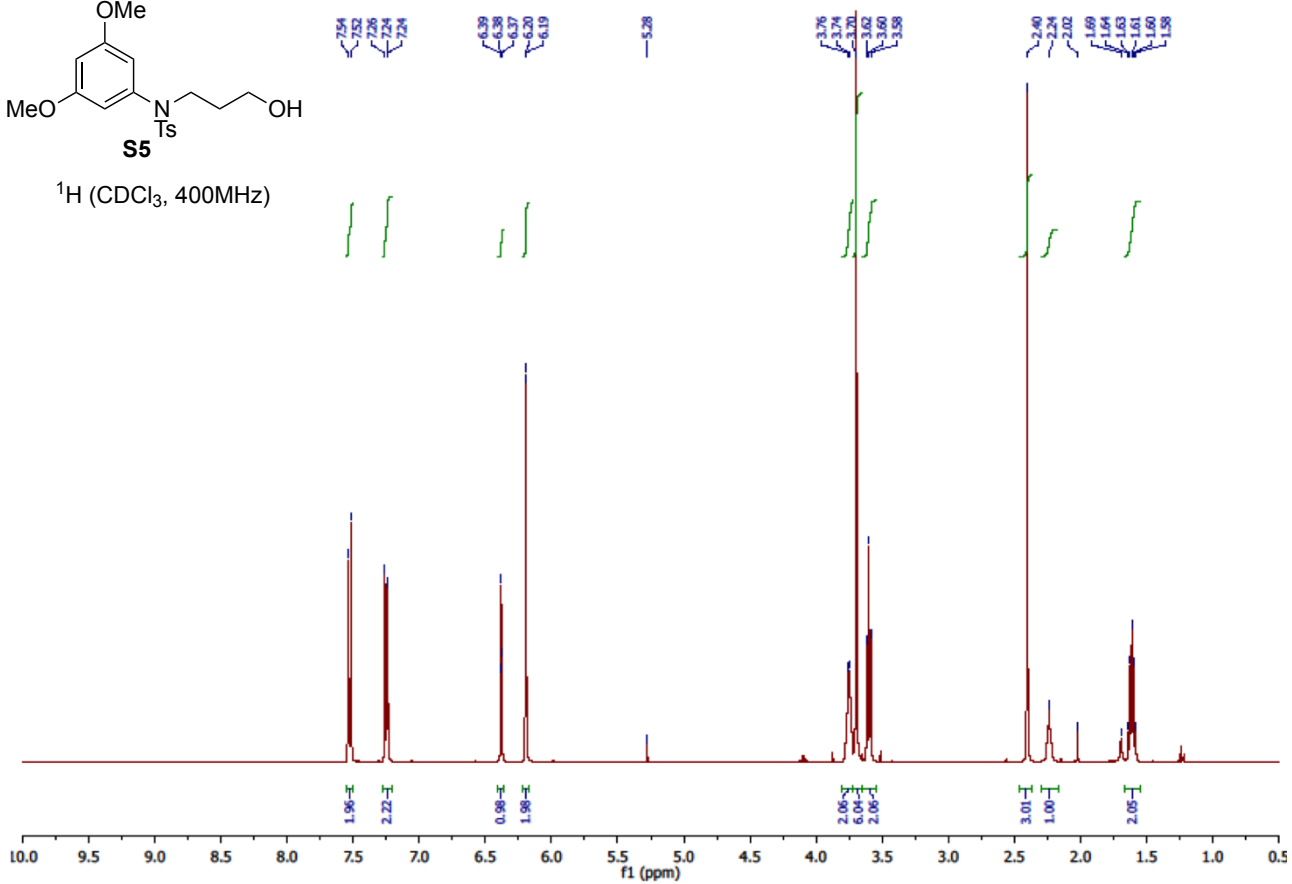
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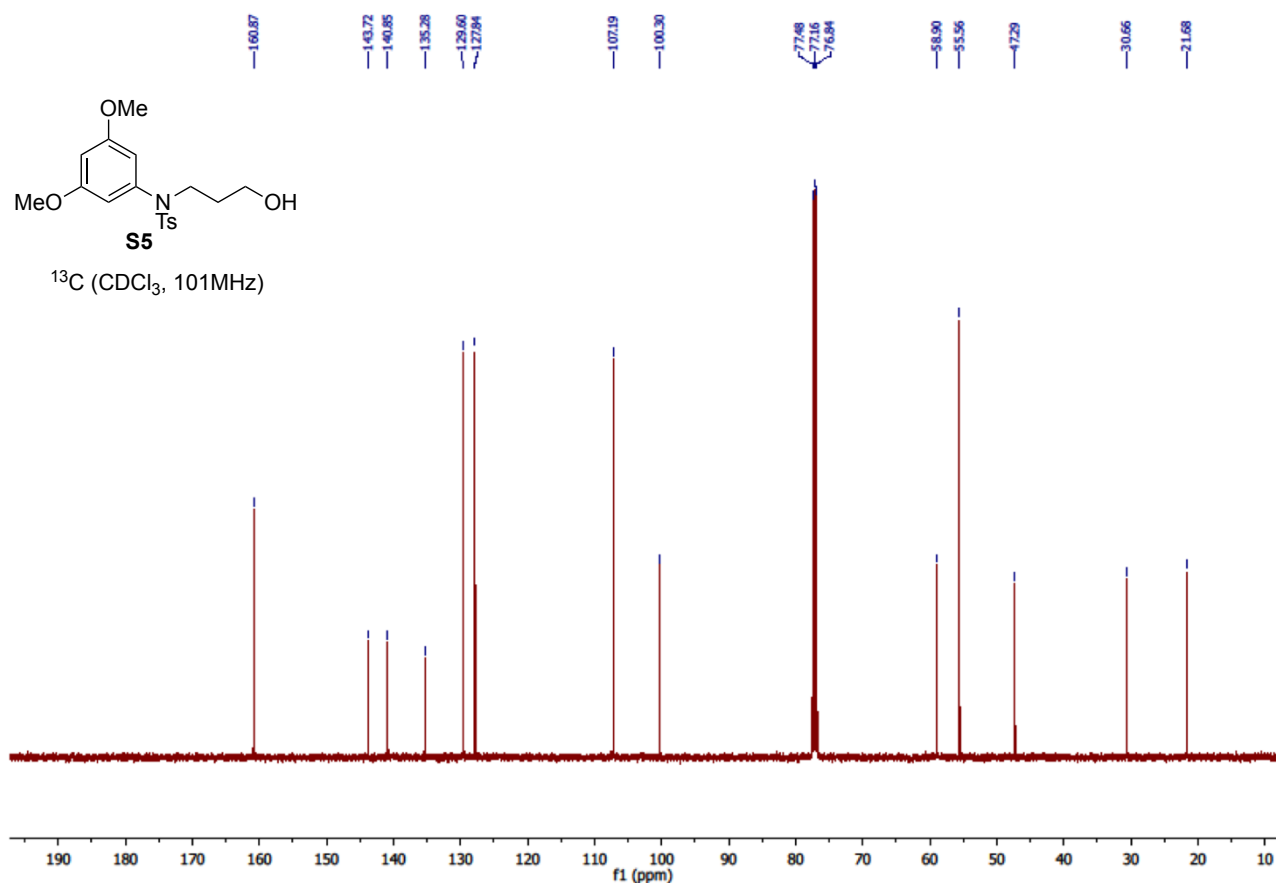


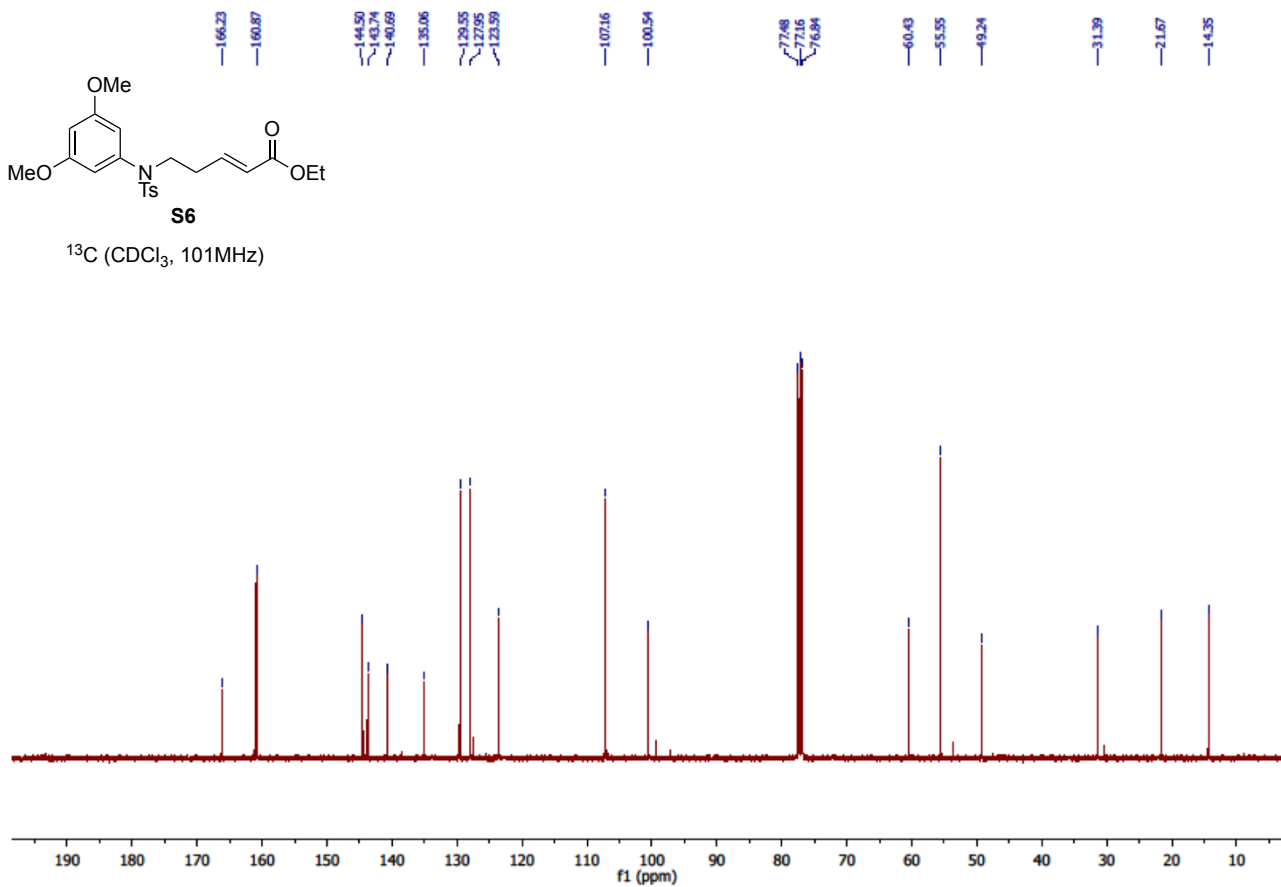
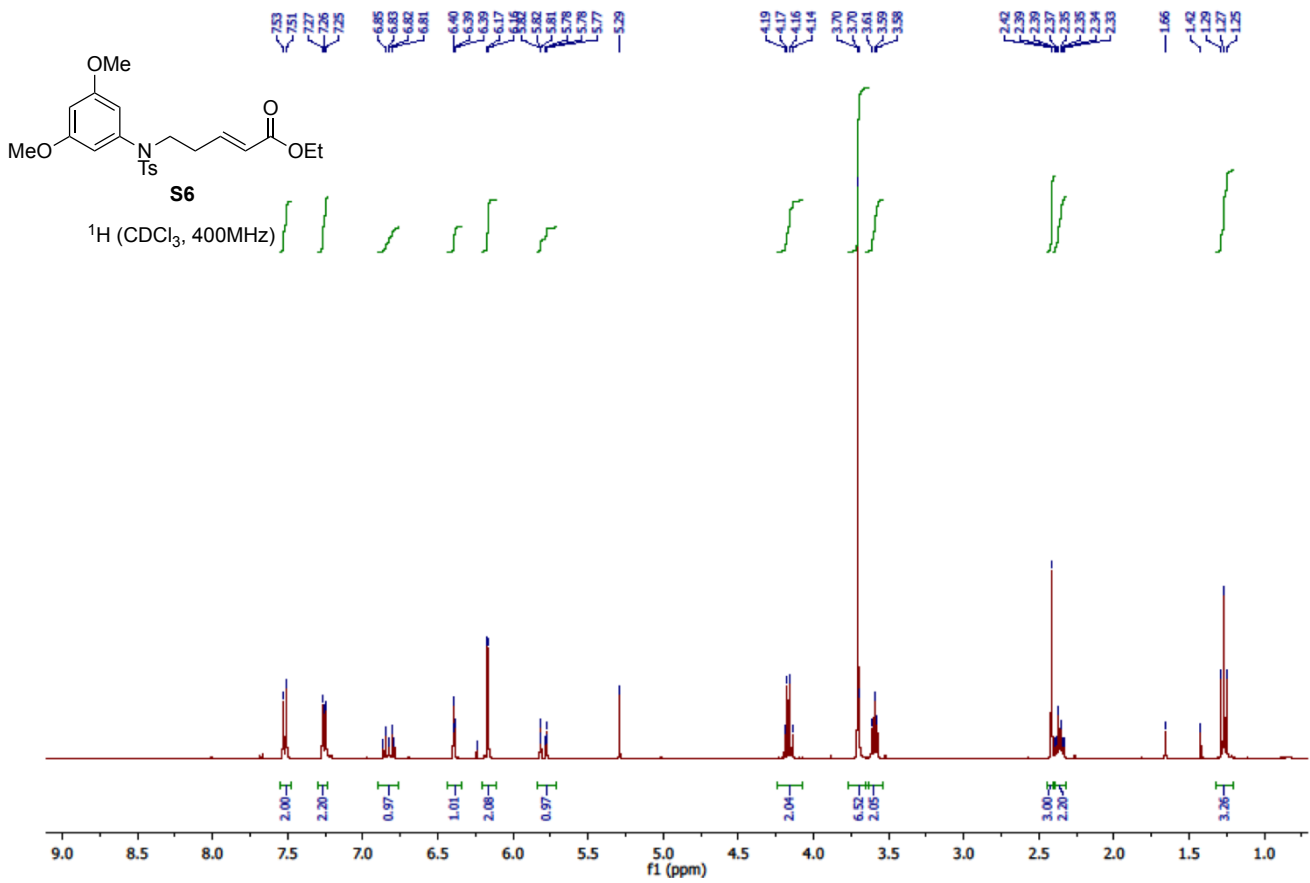


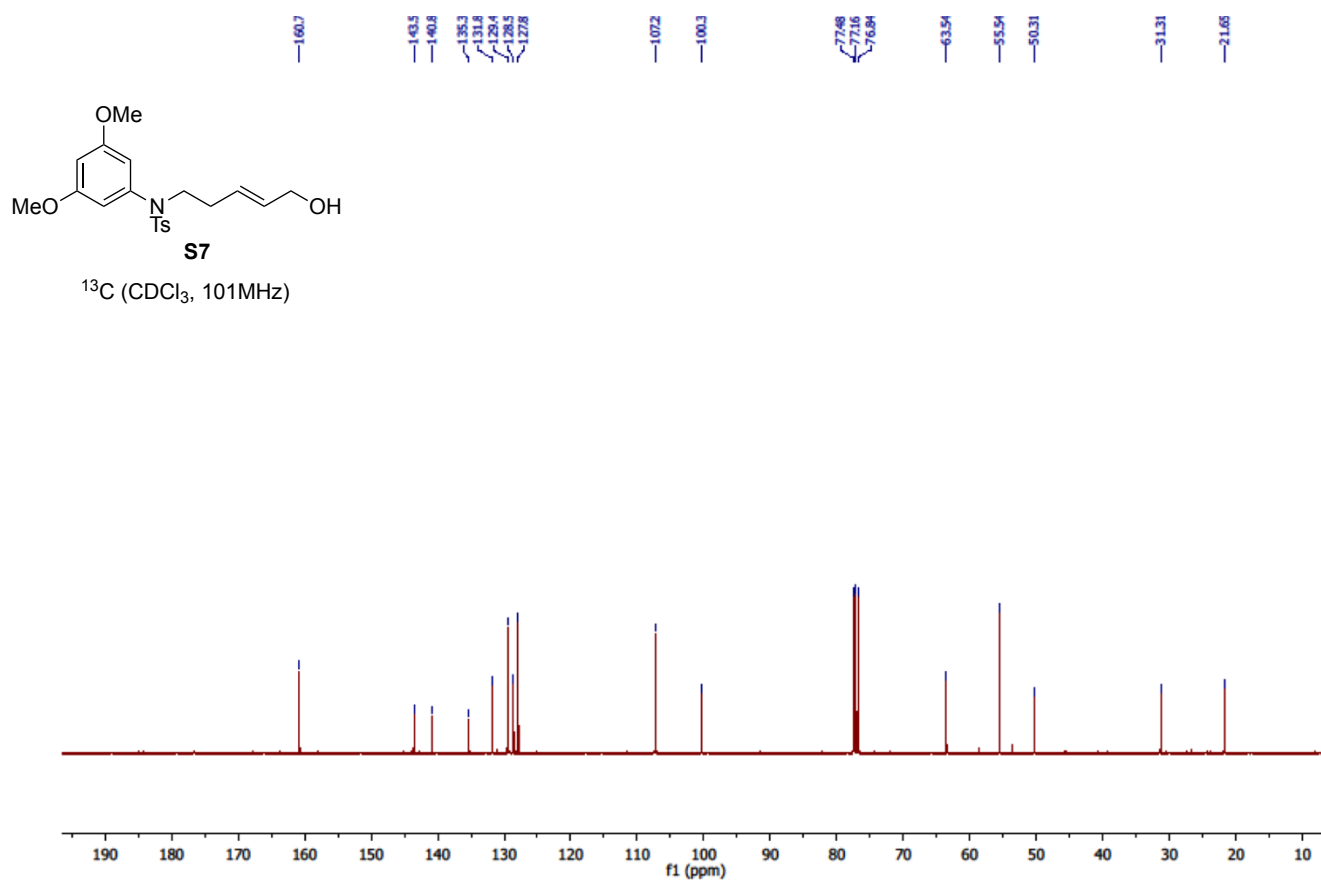
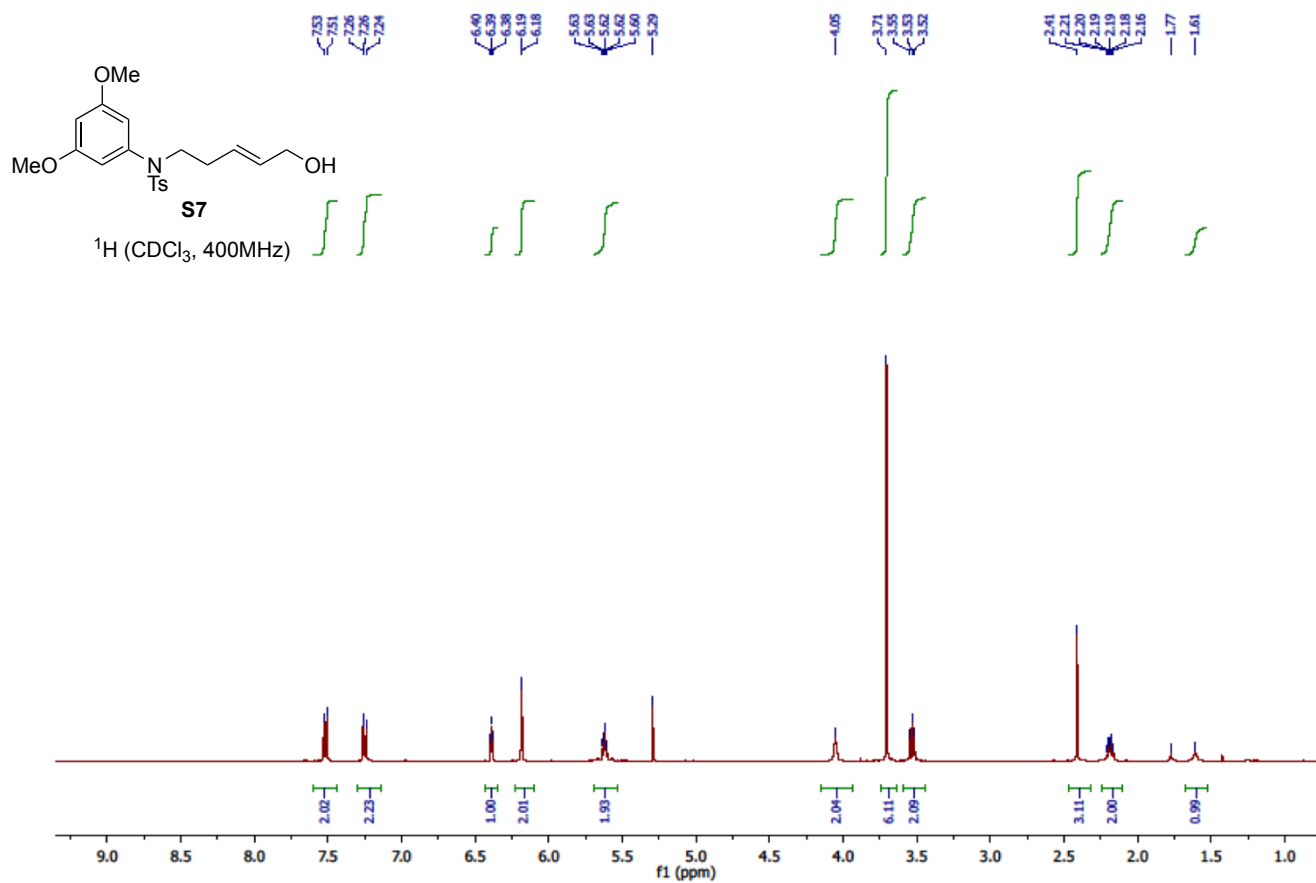
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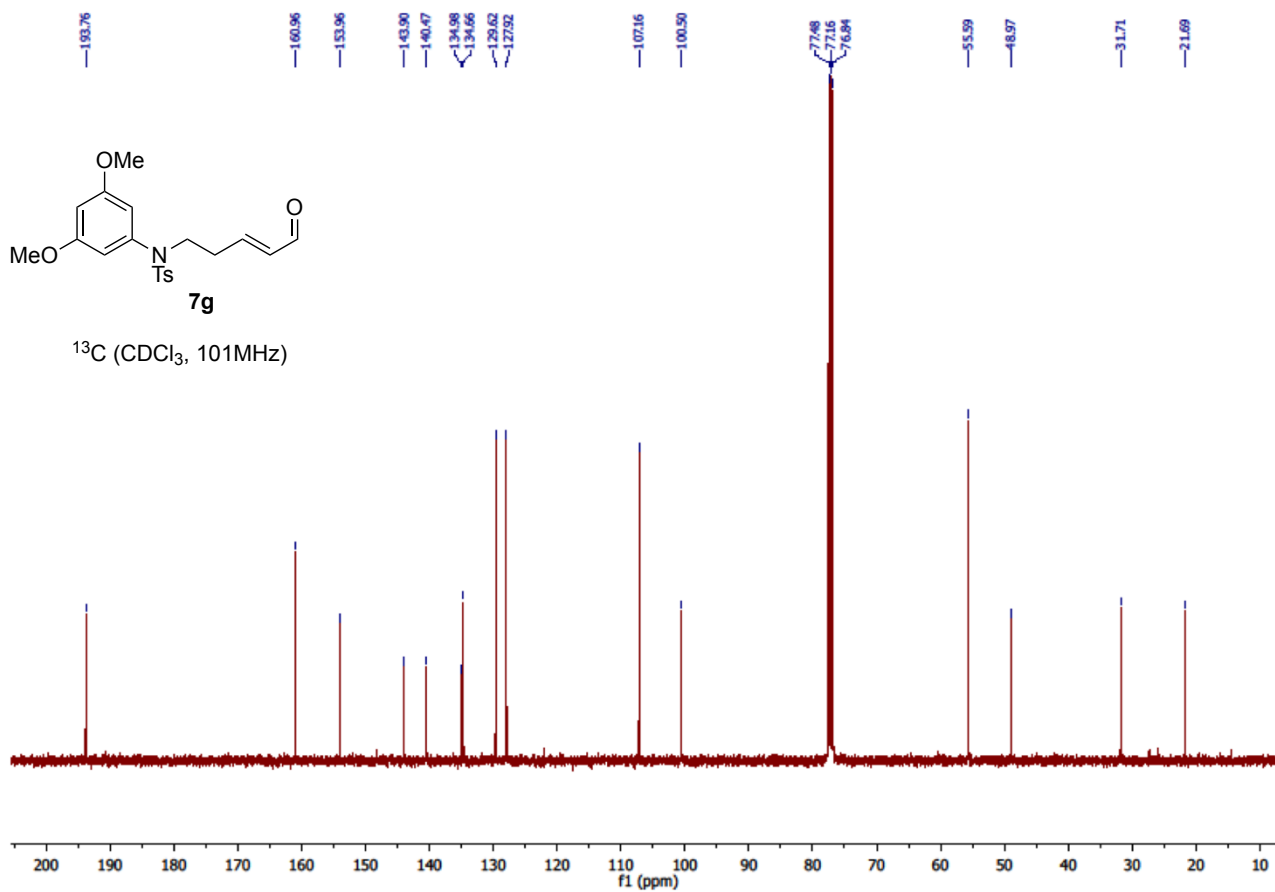
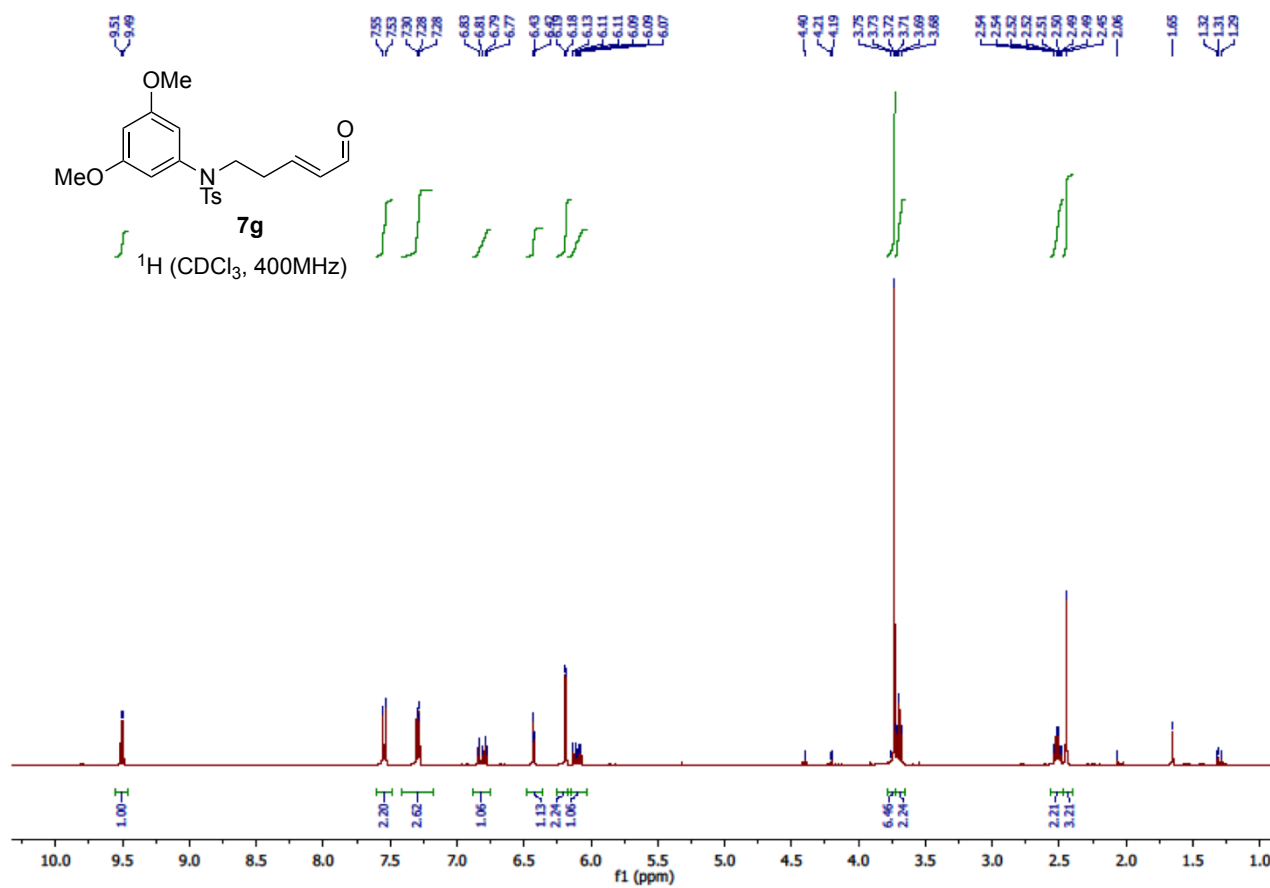


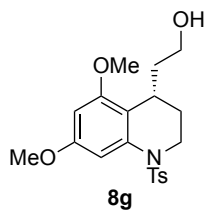
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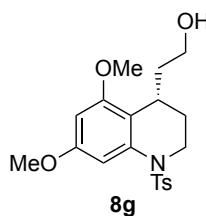
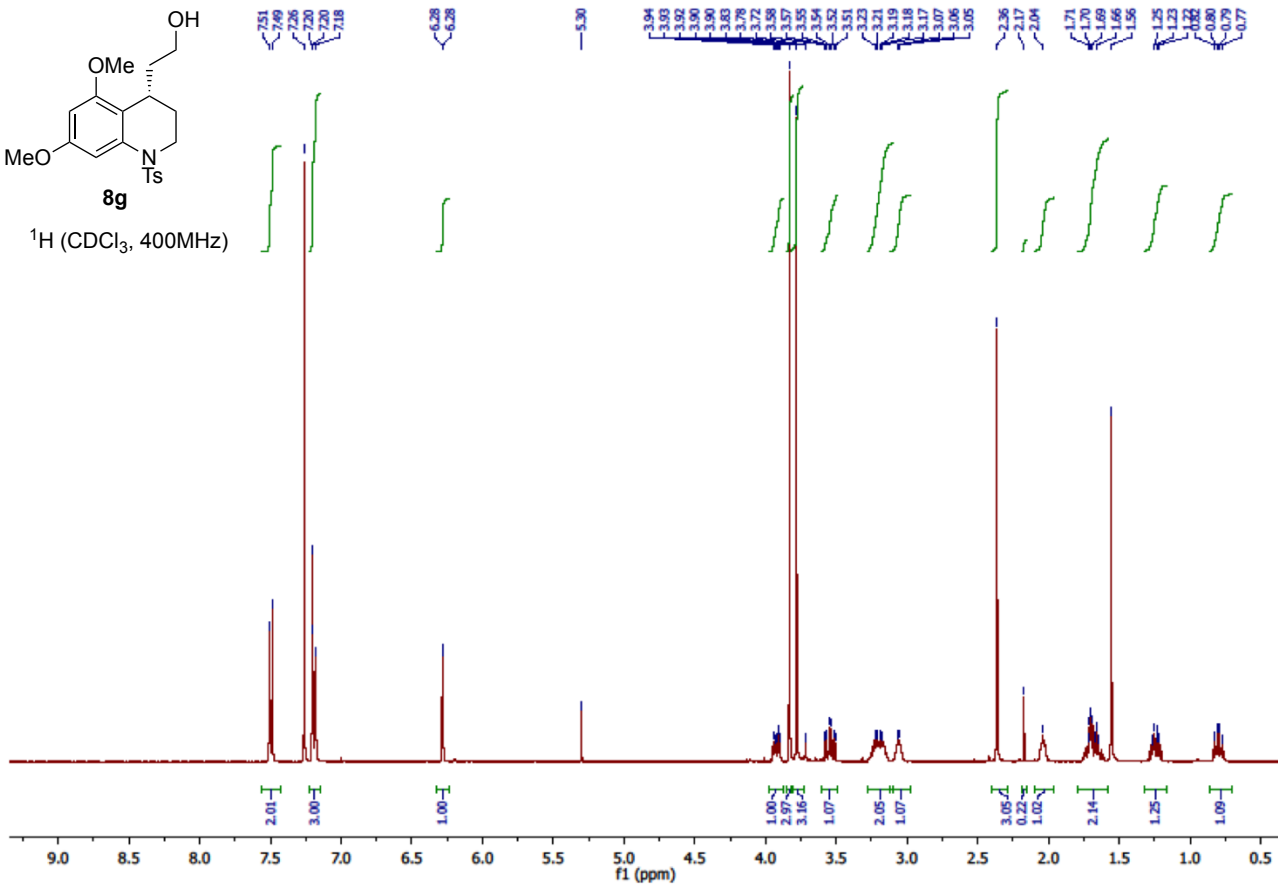




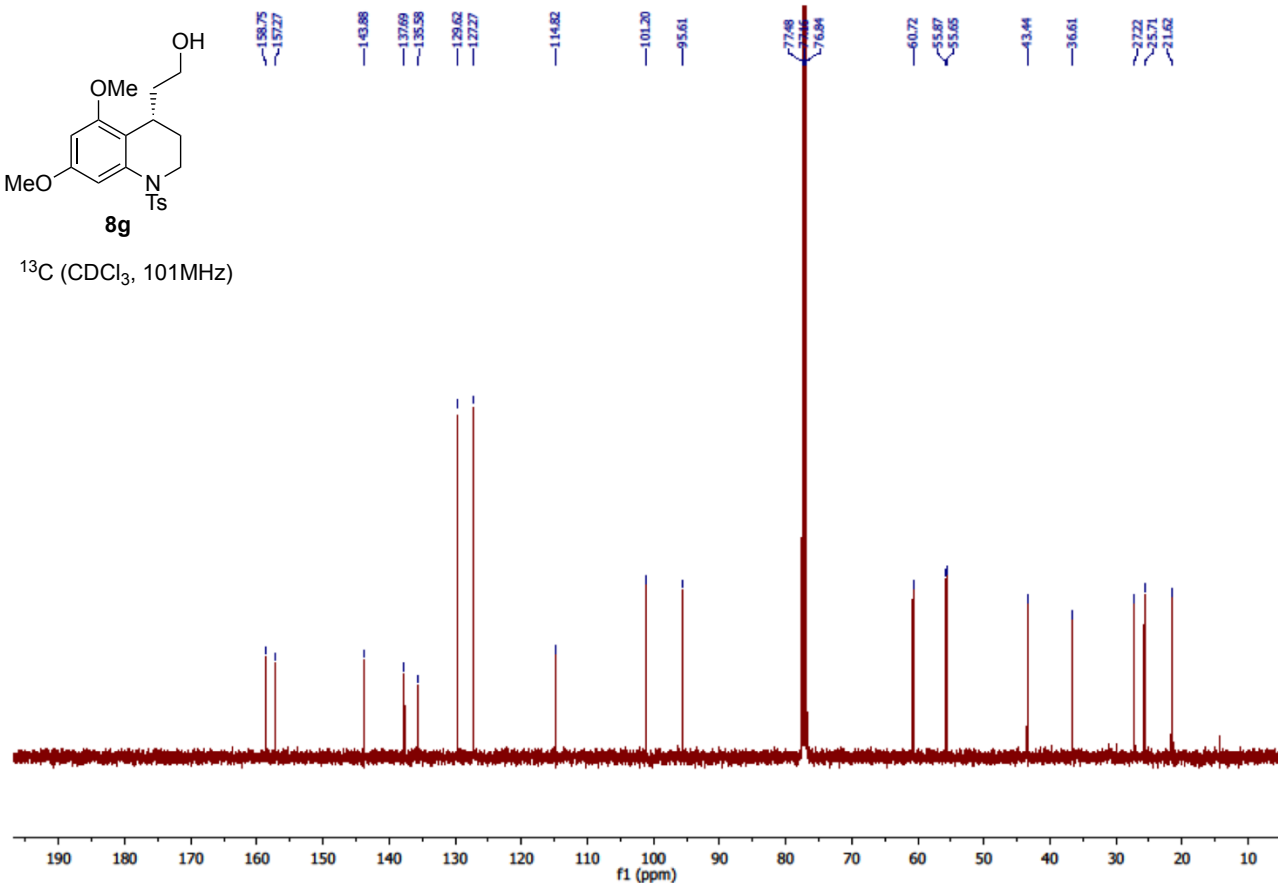


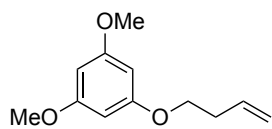


¹H (CDCl₃, 400MHz)

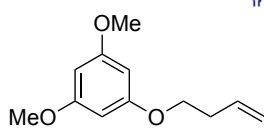
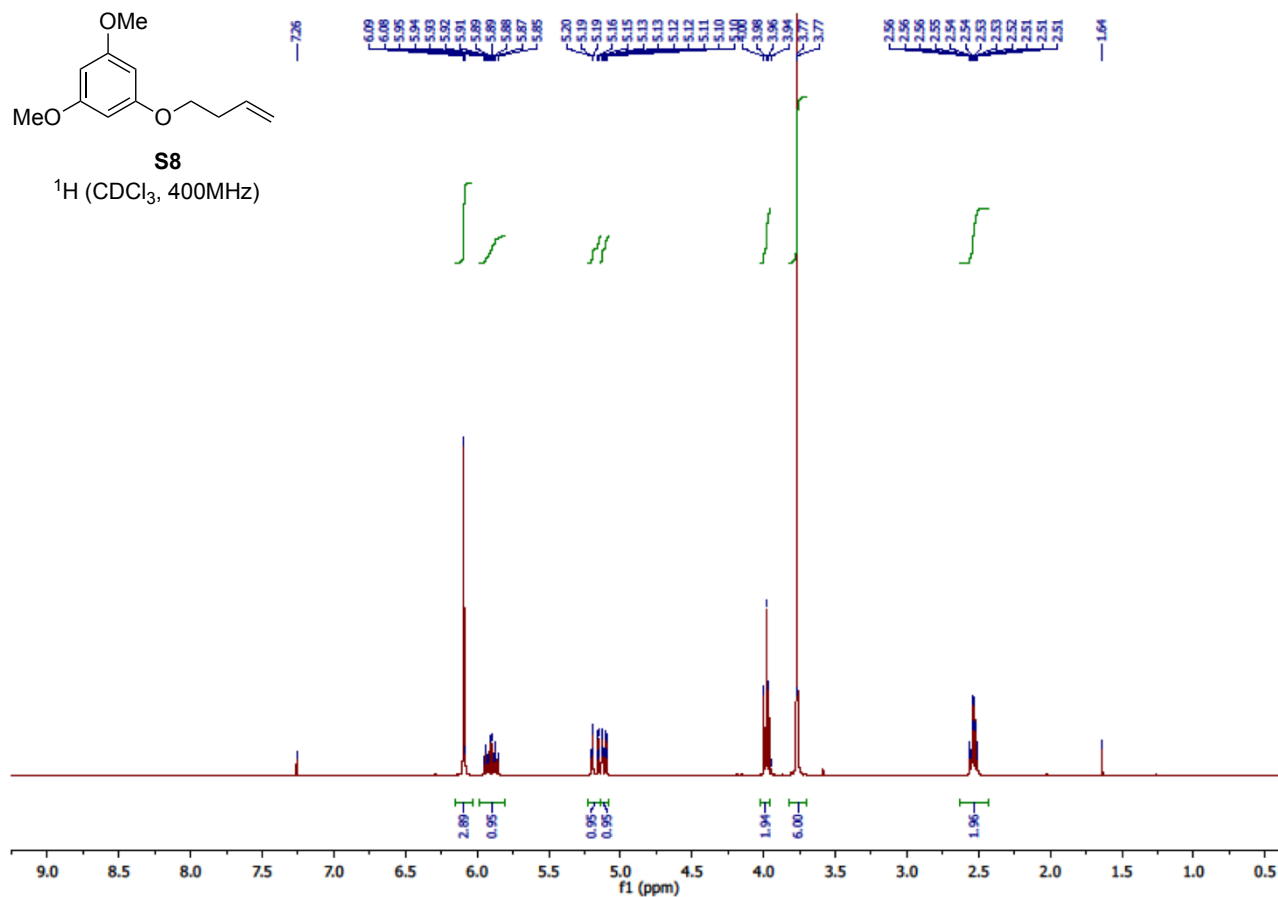


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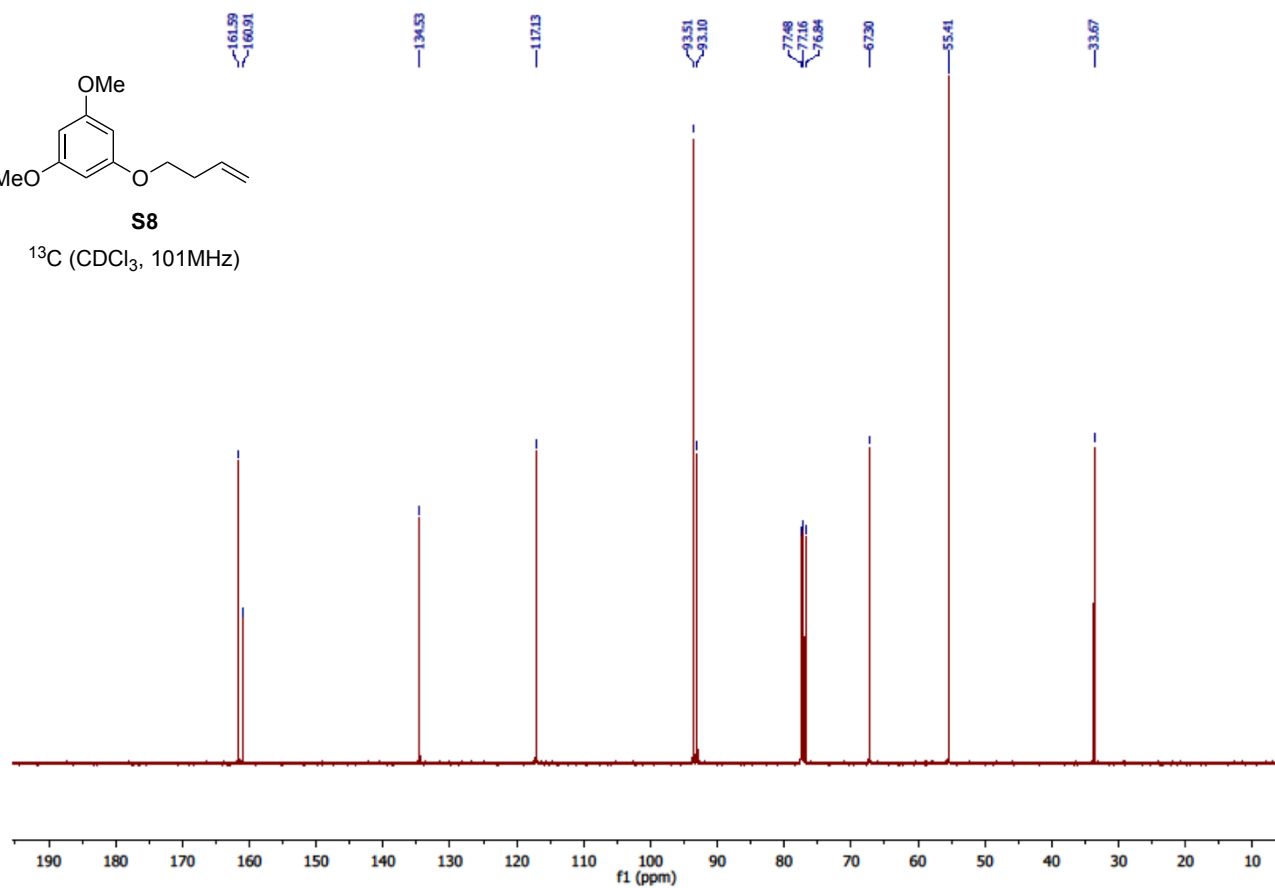


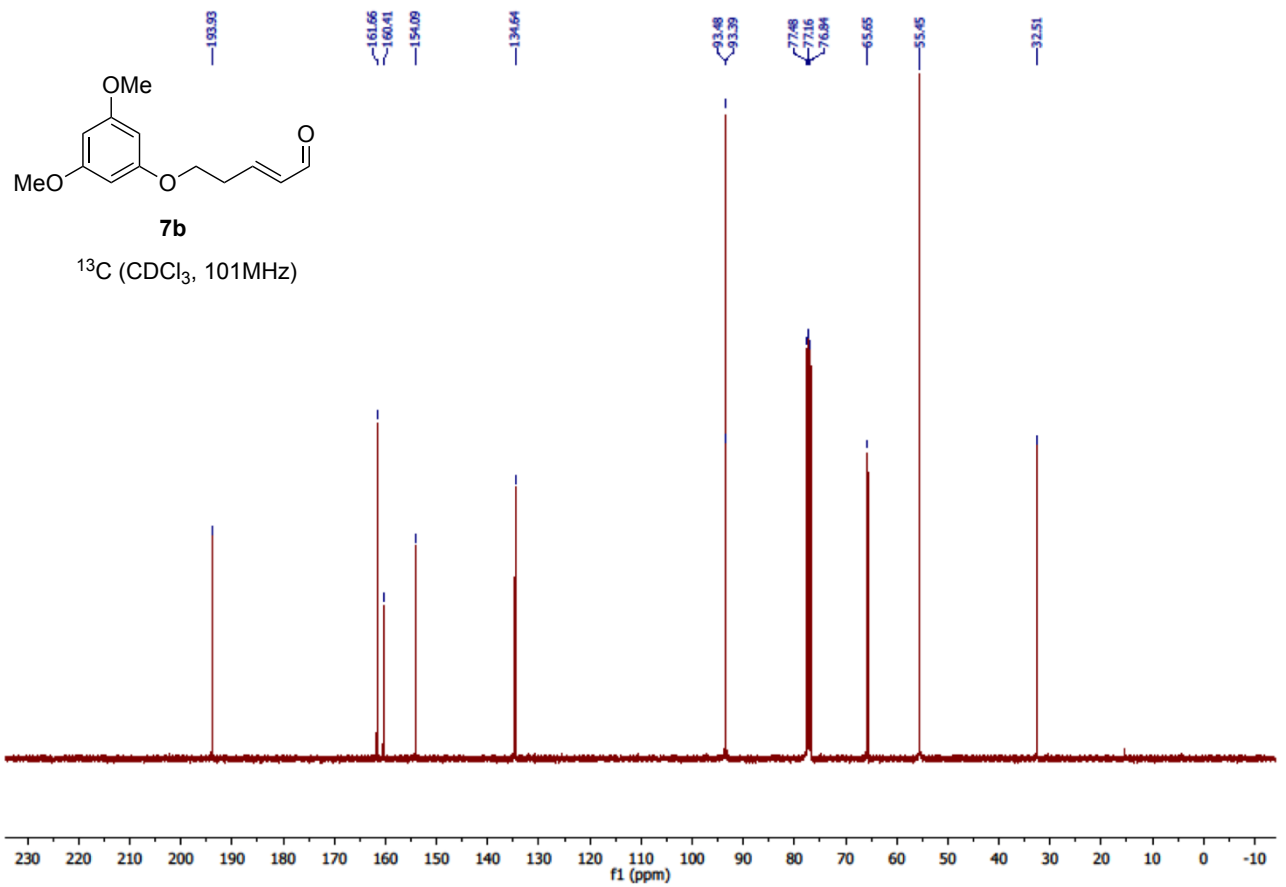
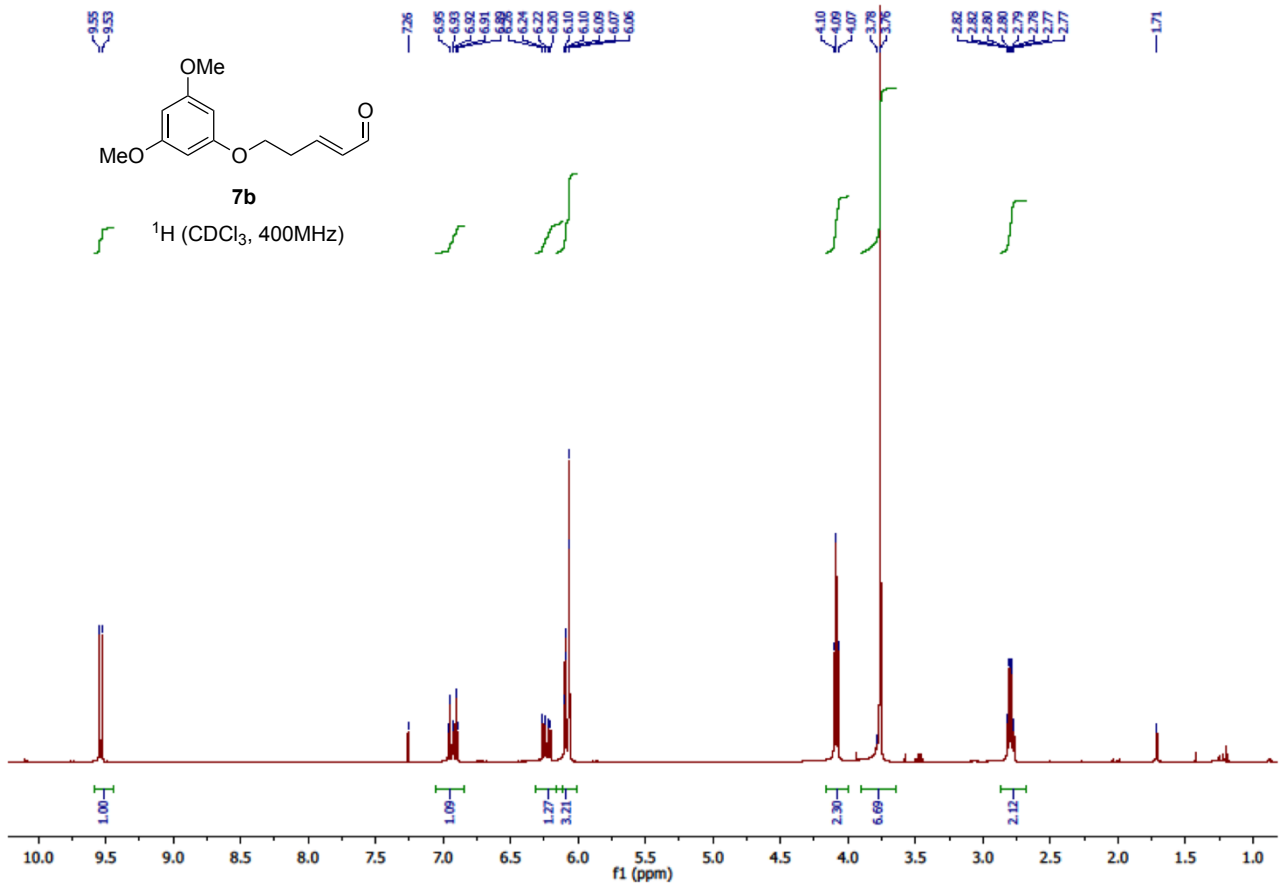


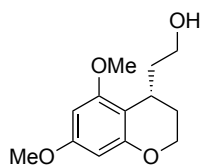
S8
¹H (CDCl₃, 400MHz)



S8
¹³C (CDCl₃, 101MHz)

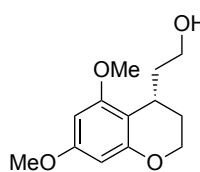
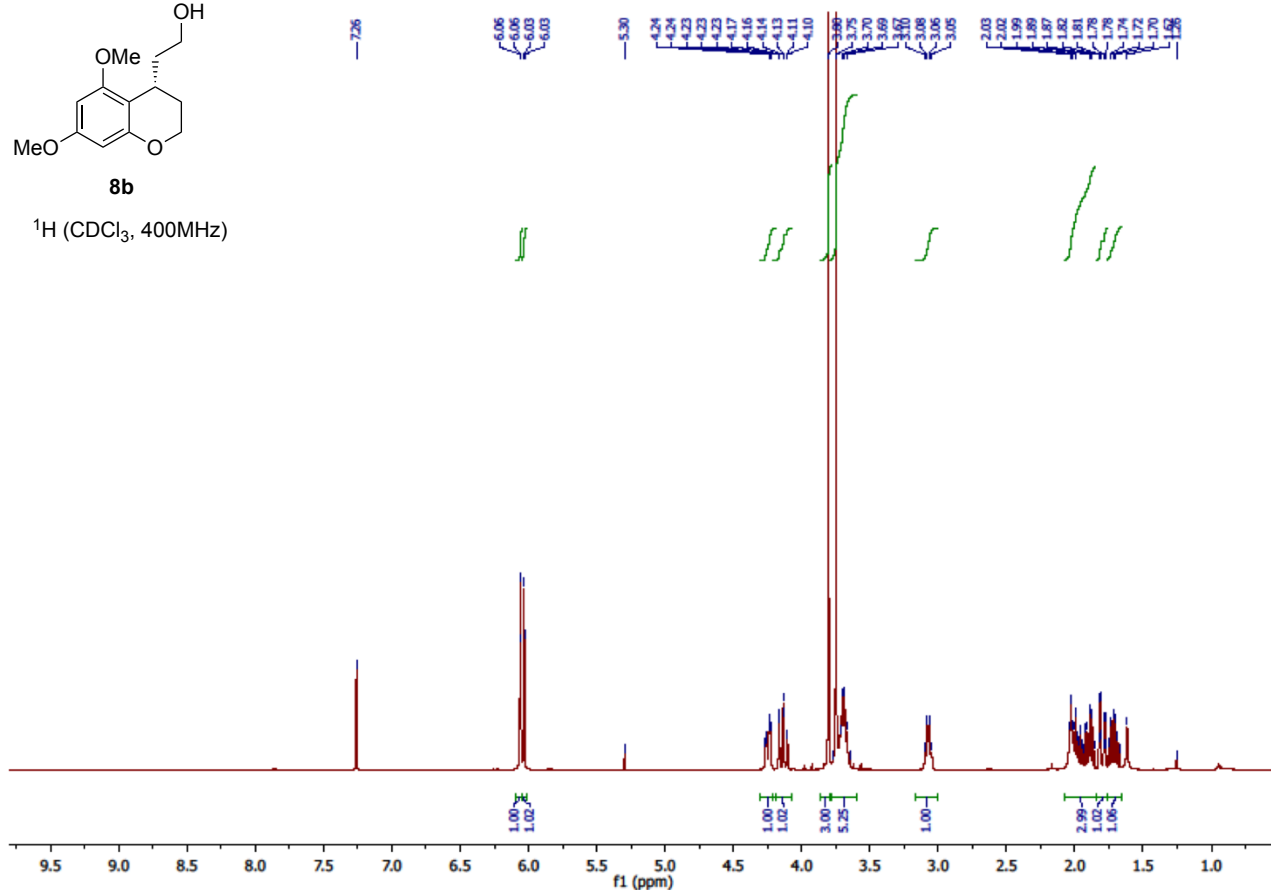






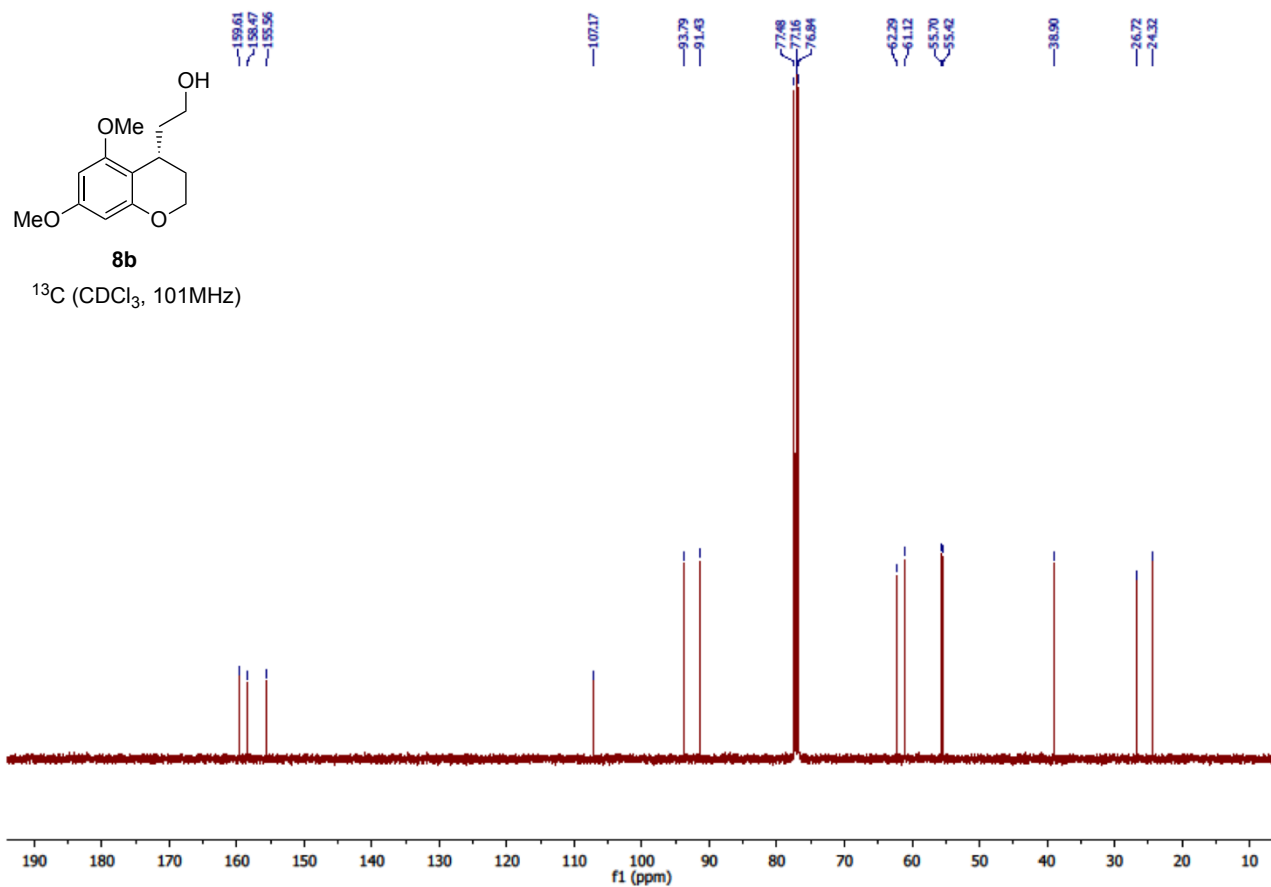
8b

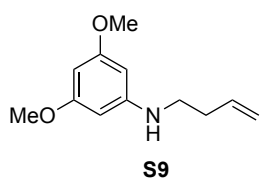
^1H (CDCl_3 , 400MHz)



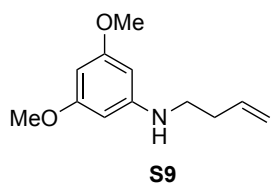
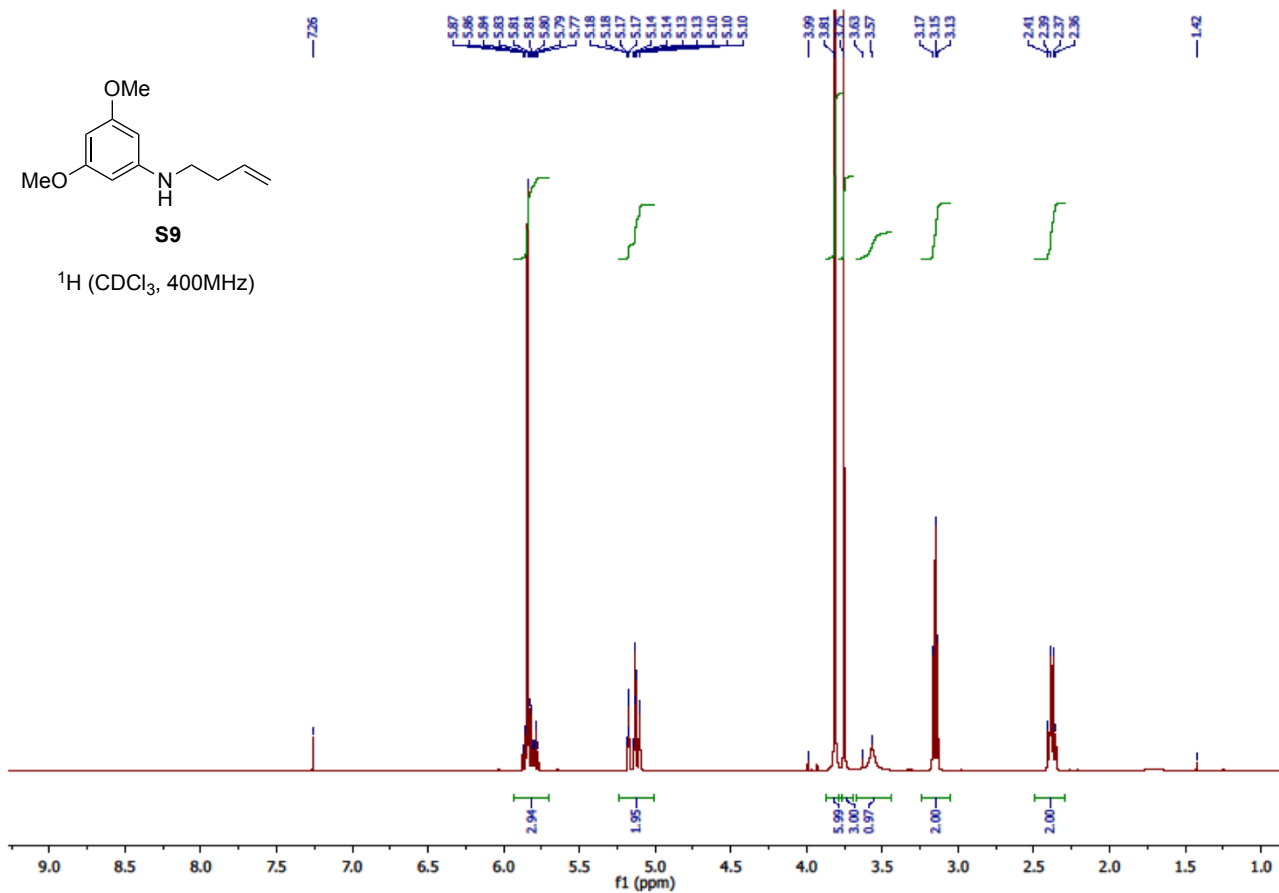
8b

^{13}C (CDCl_3 , 101MHz)

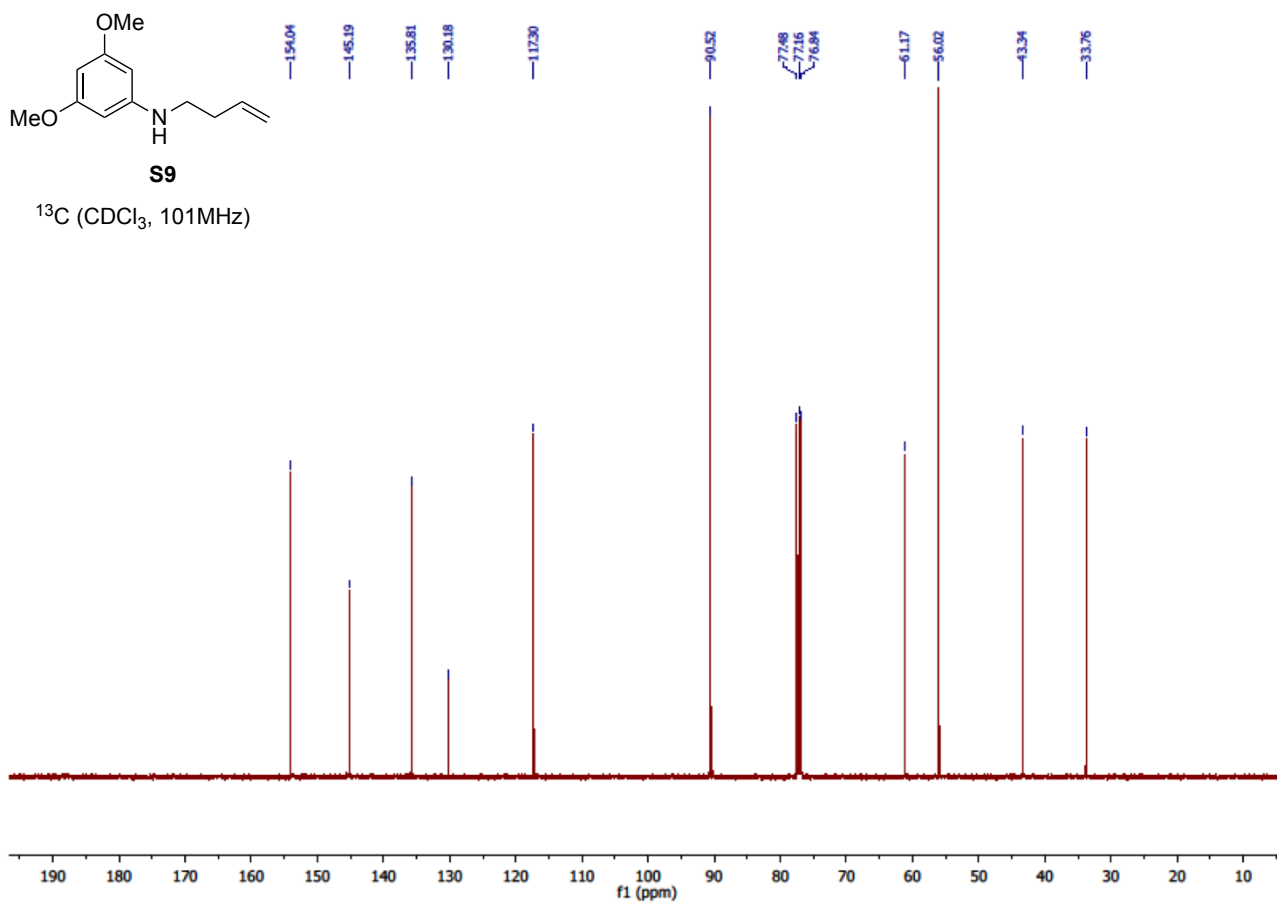


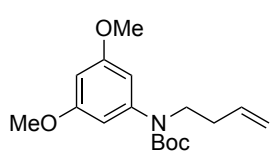


^1H (CDCl_3 , 400MHz)



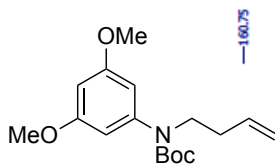
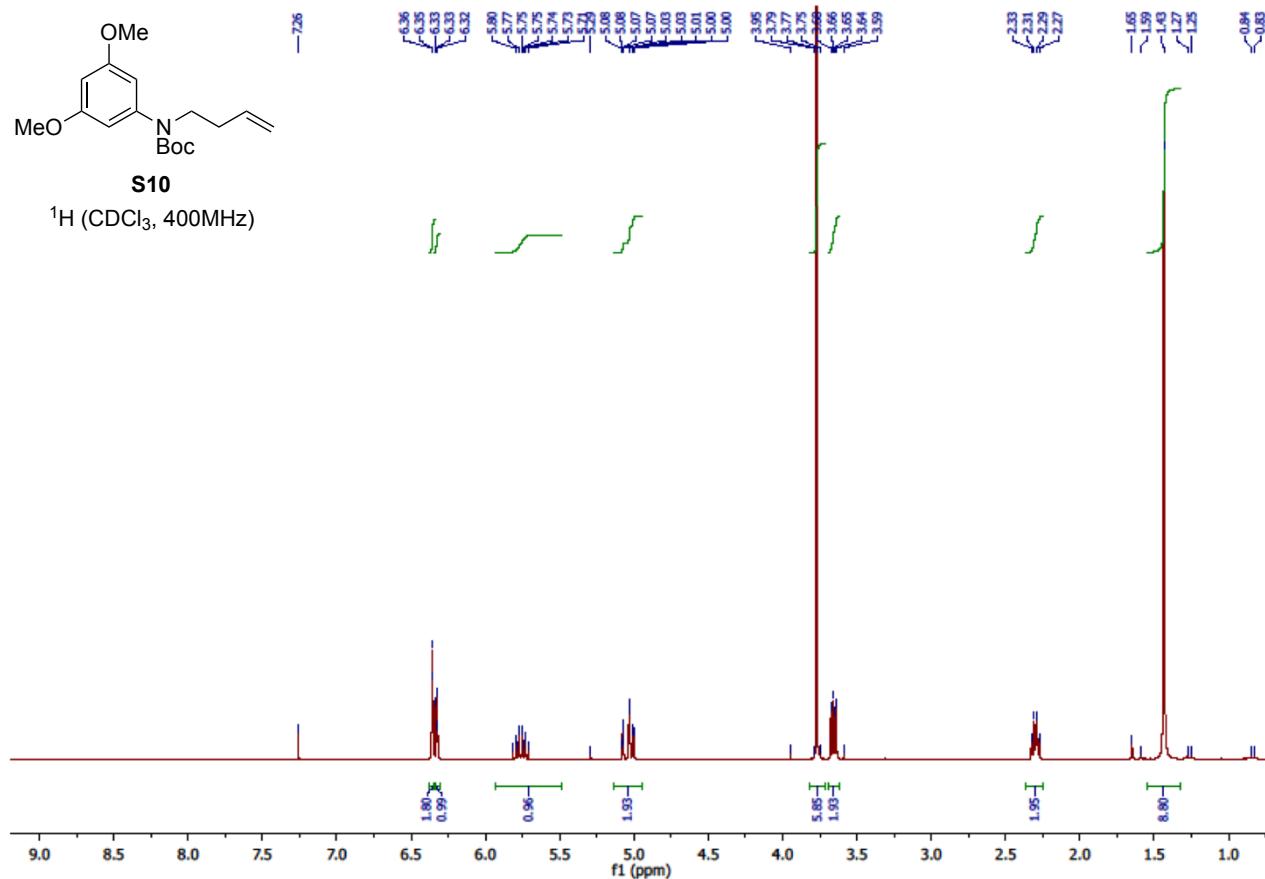
^{13}C (CDCl_3 , 101MHz)





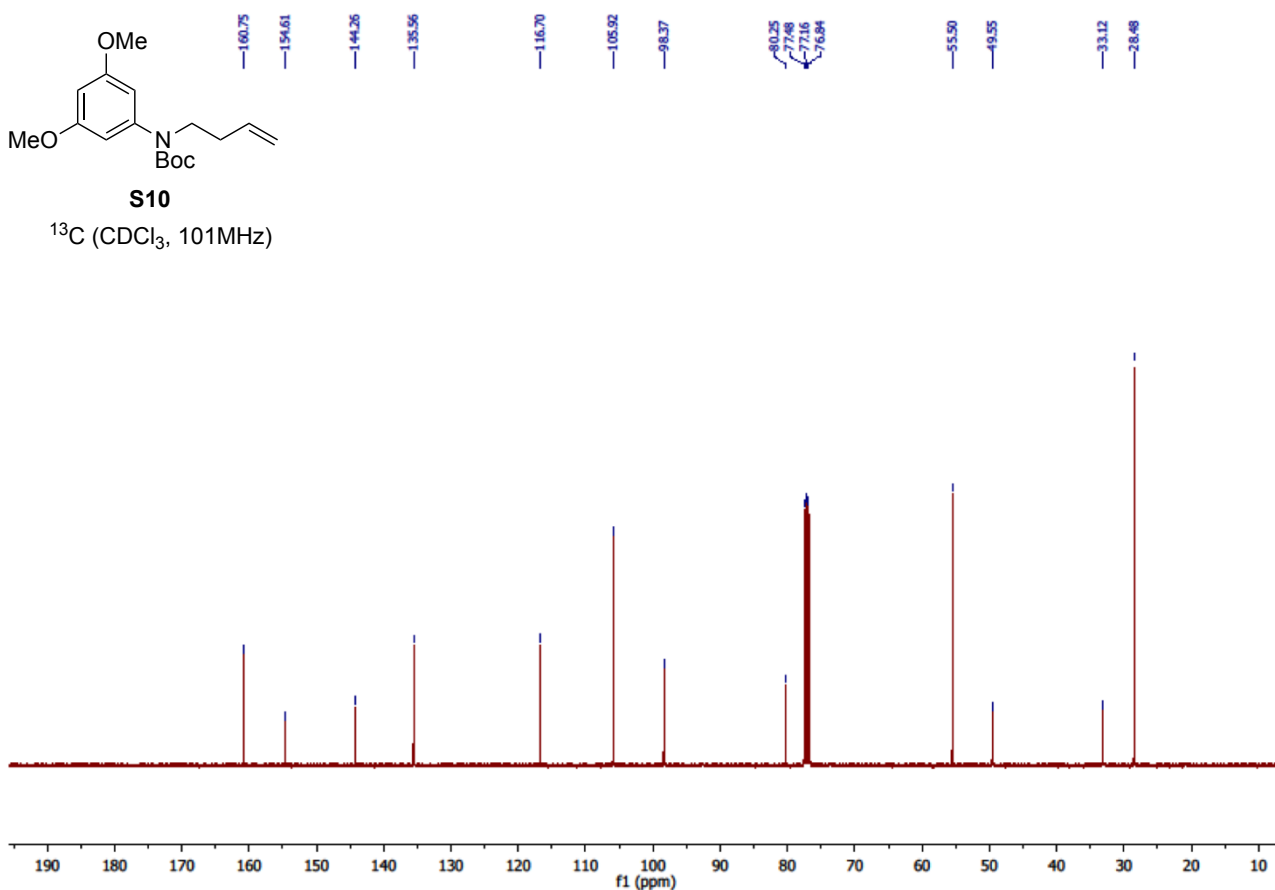
S10

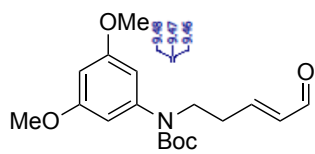
¹H (CDCl₃, 400MHz)



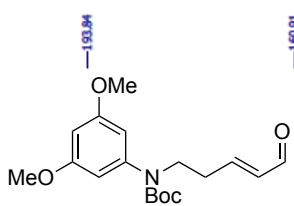
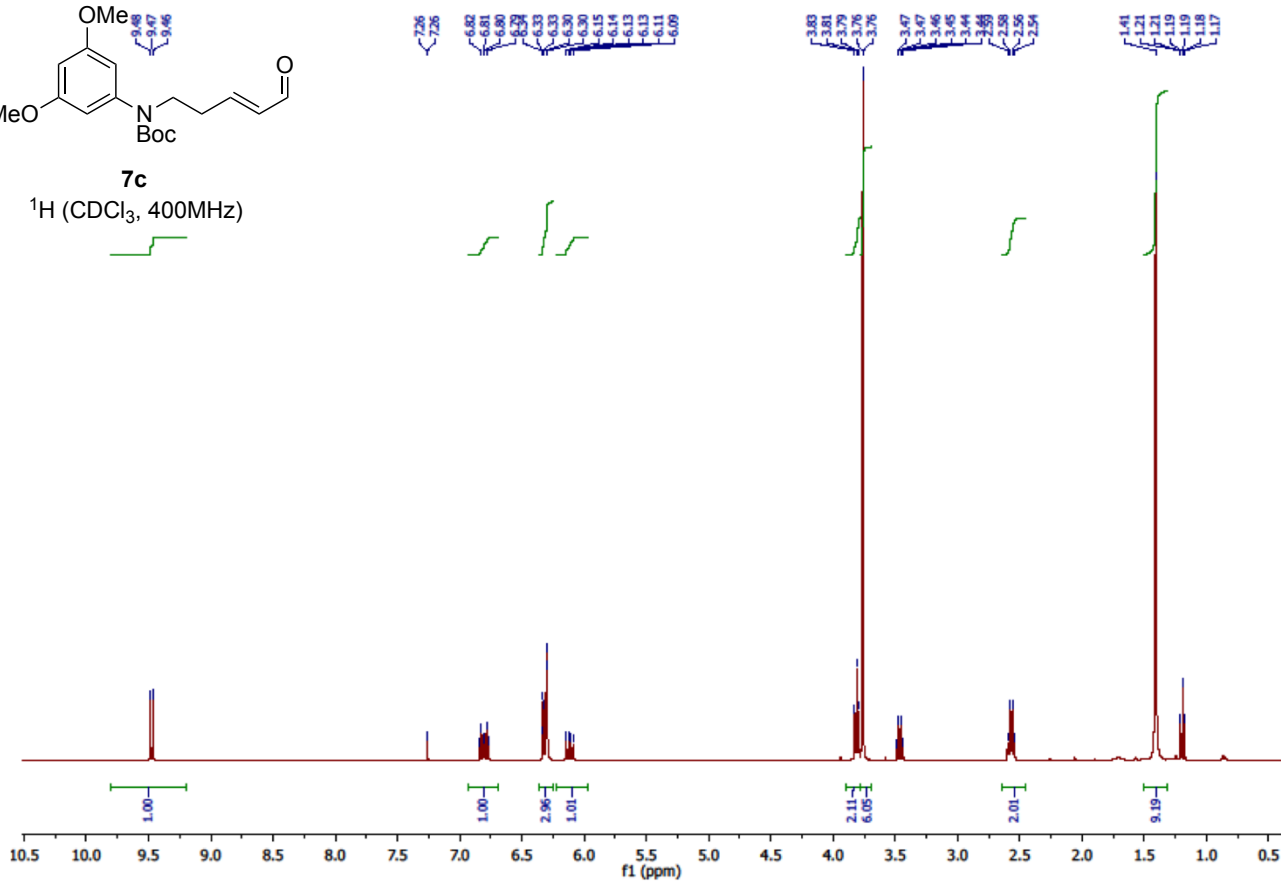
S10

¹³C (CDCl₃, 101MHz)

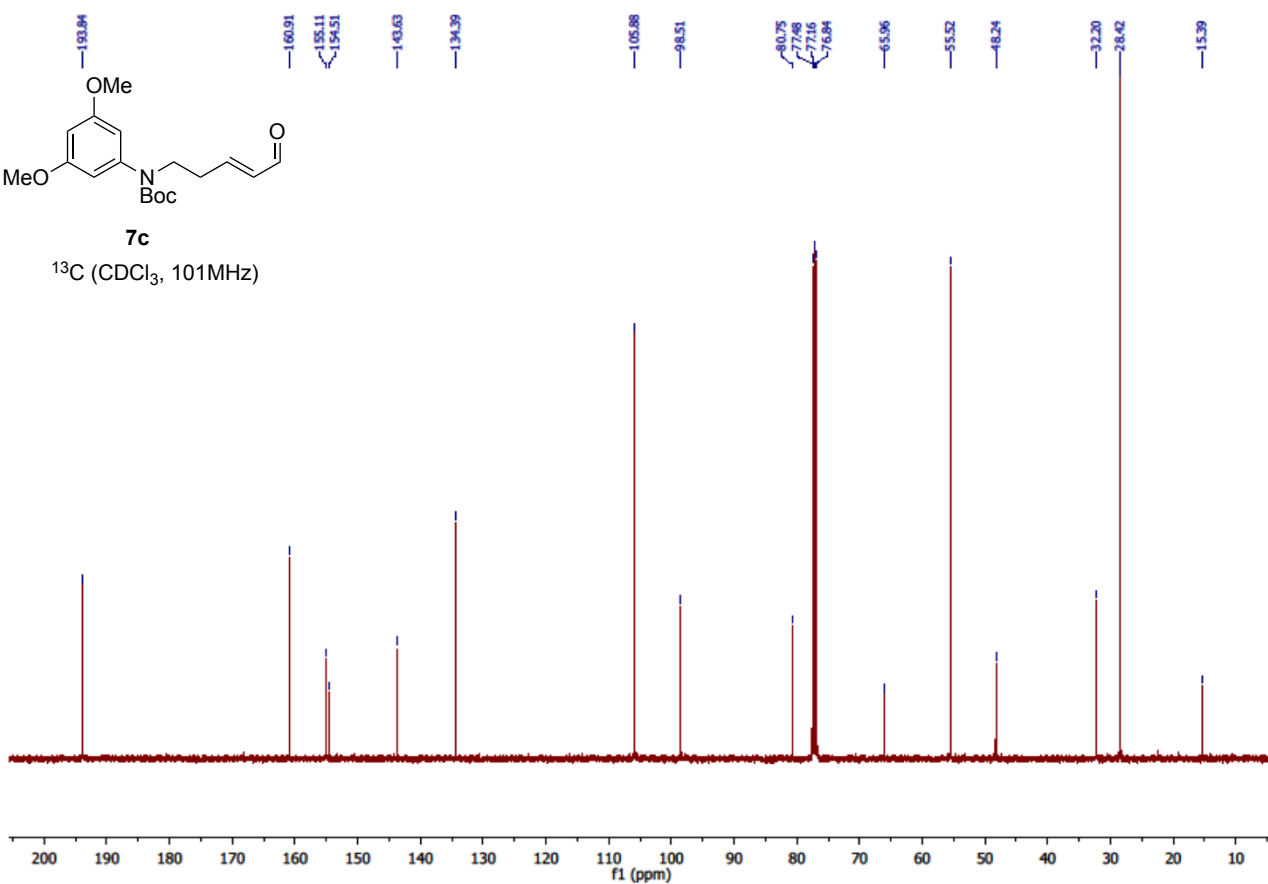


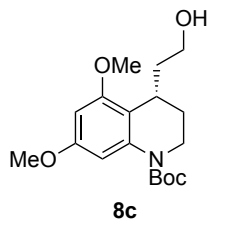


7c
¹H (CDCl₃, 400MHz)

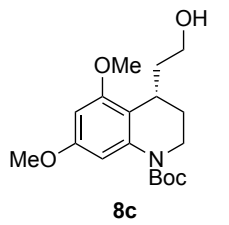
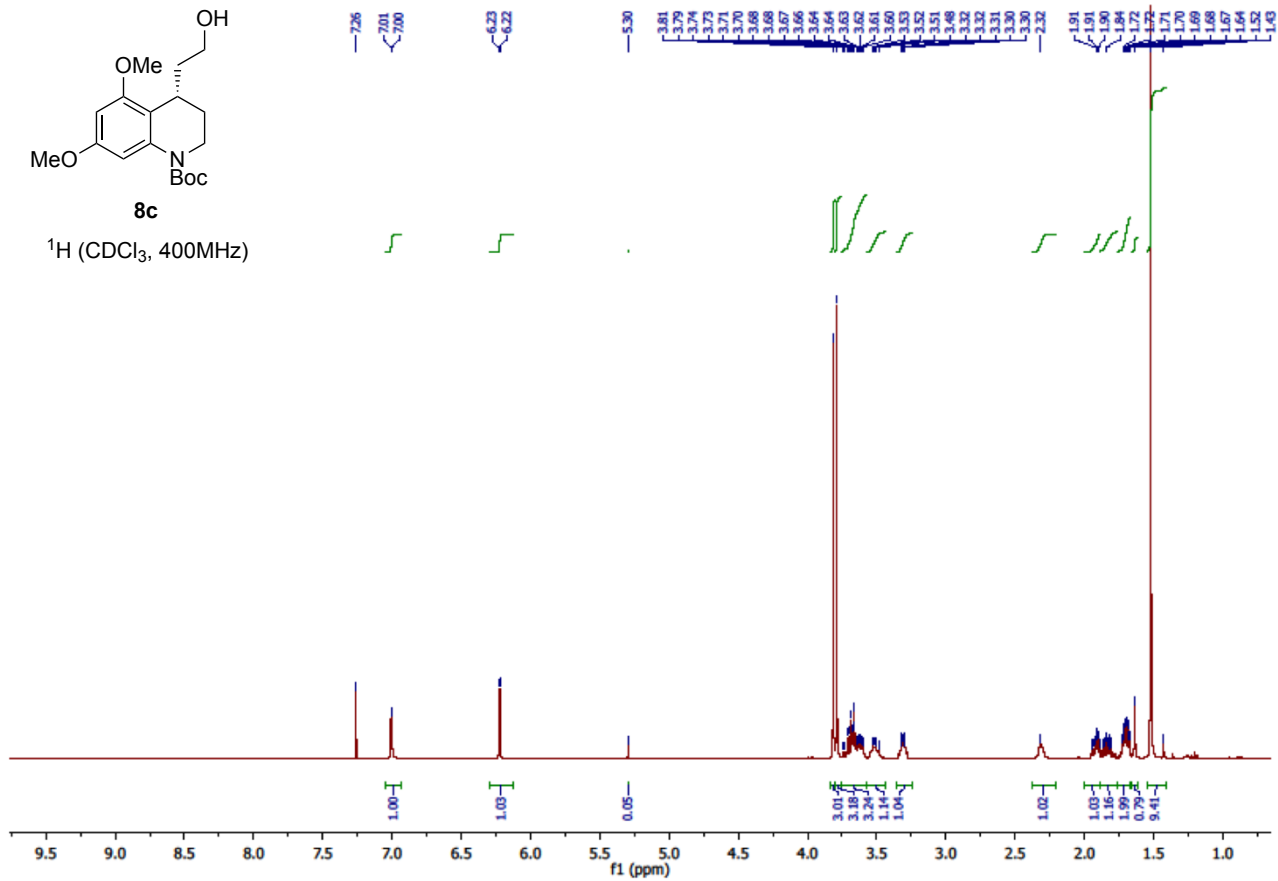


7c
¹³C (CDCl₃, 101MHz)

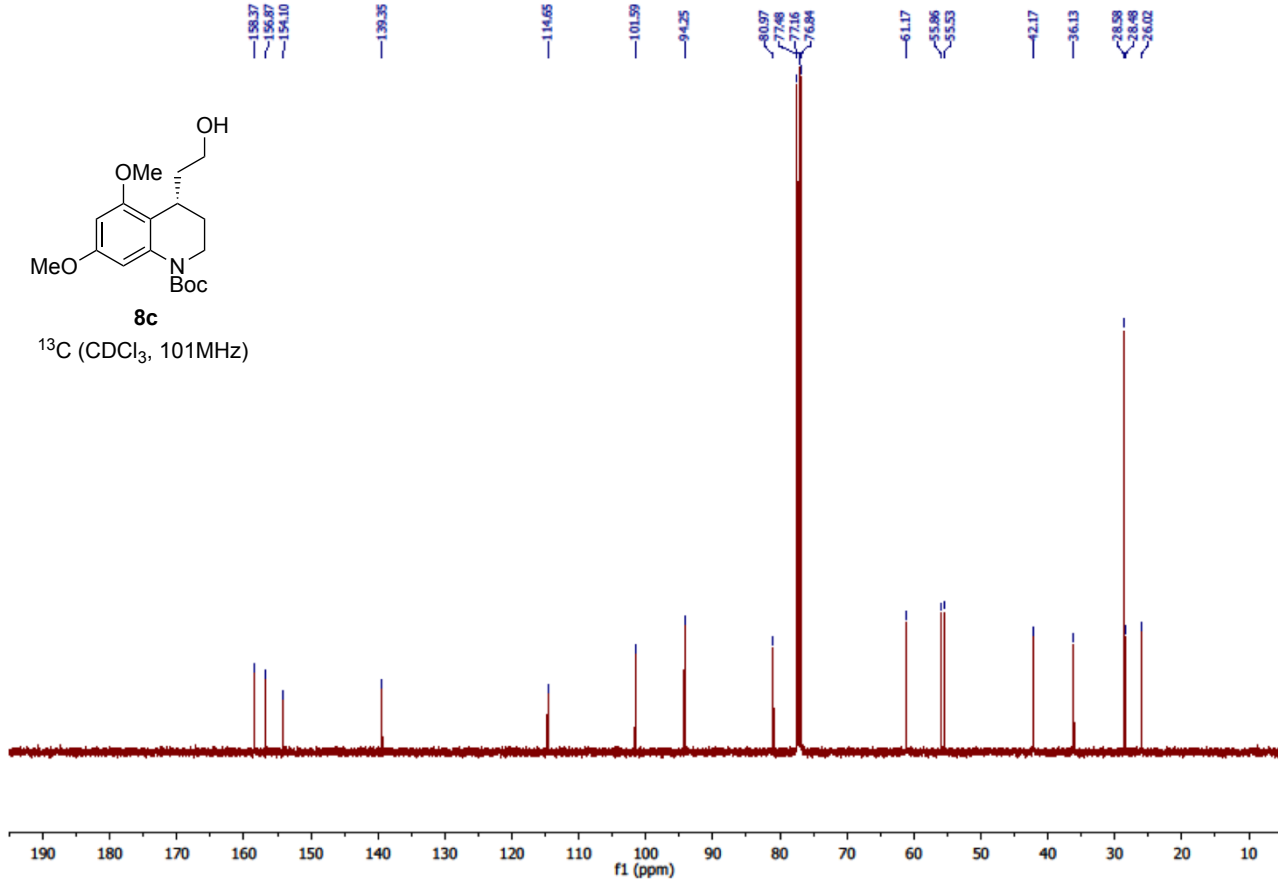


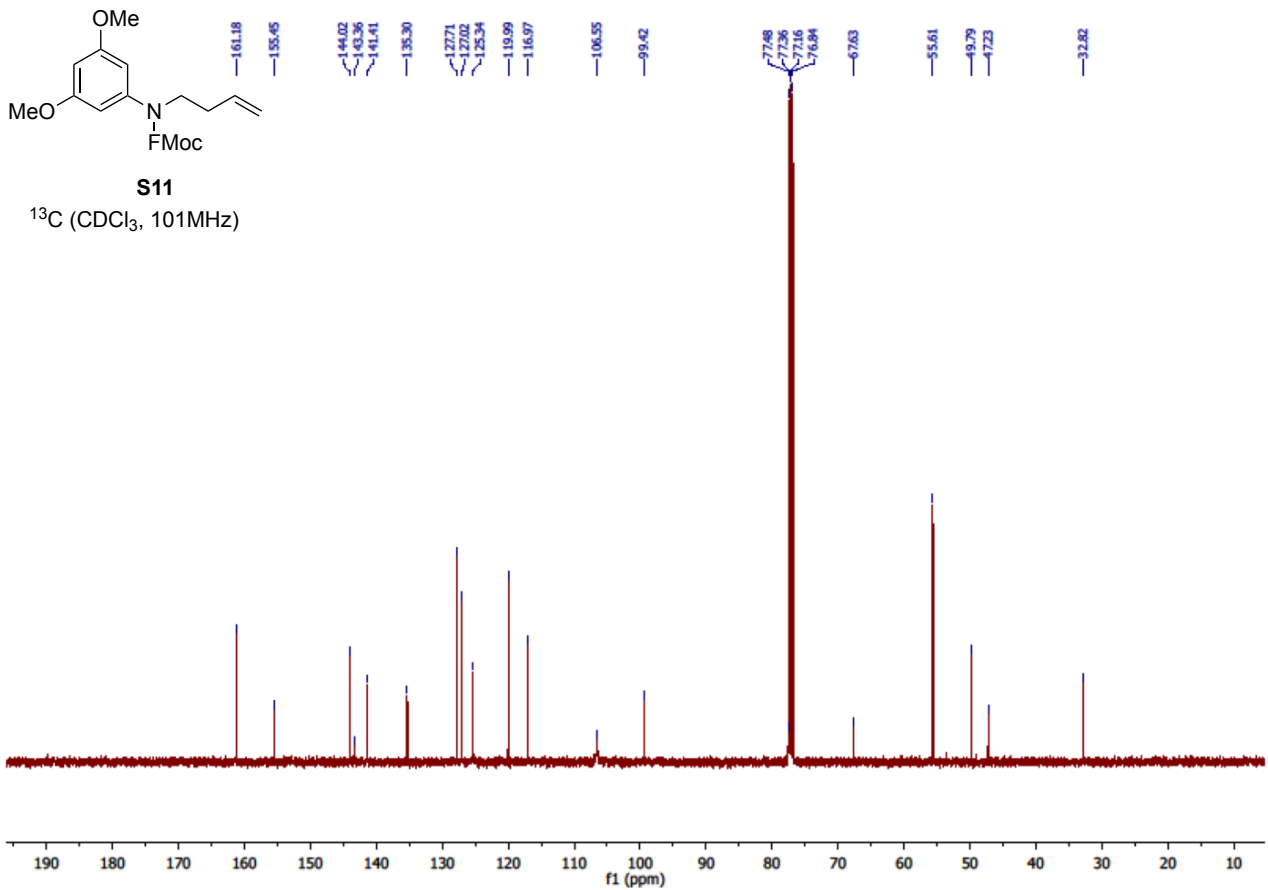
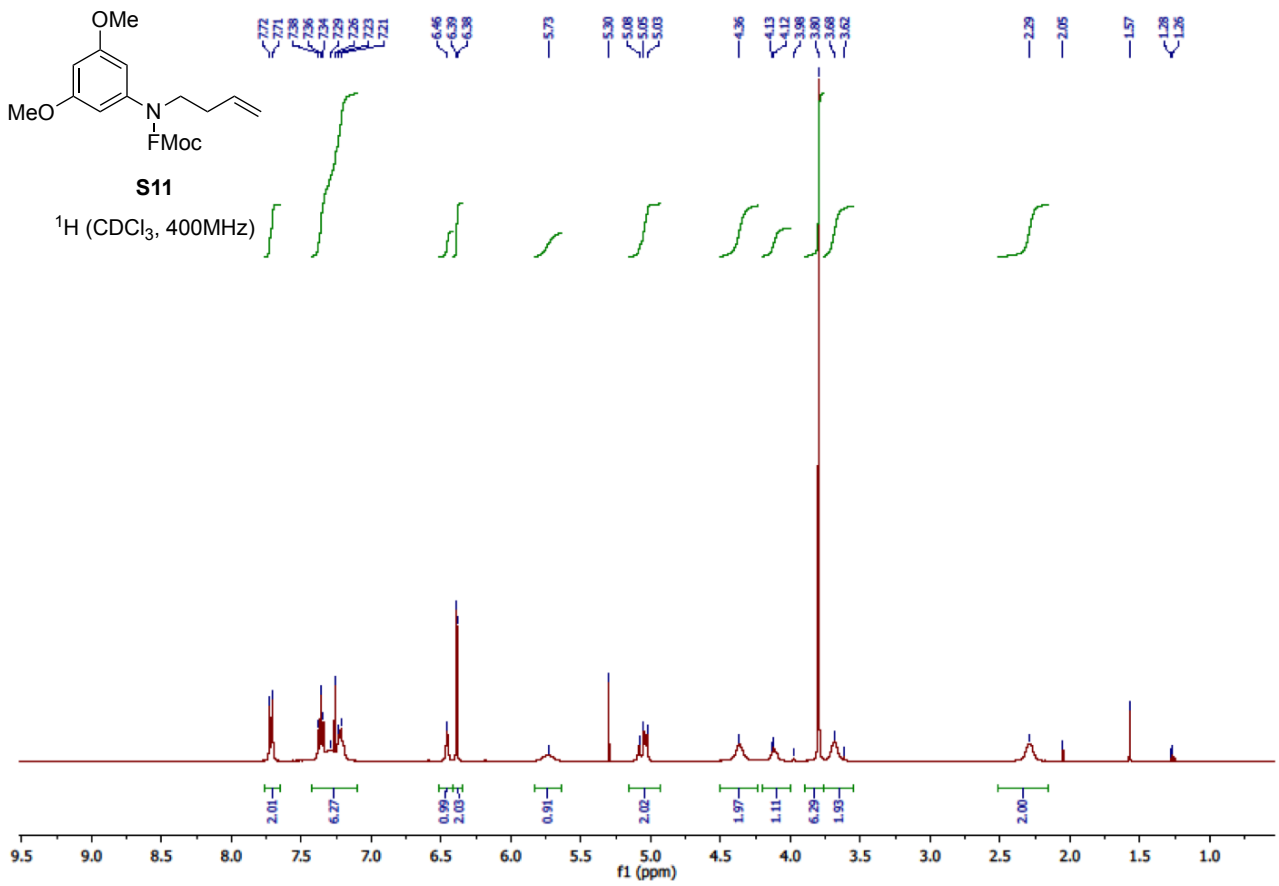


¹H (CDCl₃, 400MHz)

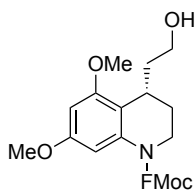


¹³C (CDCl₃, 101MHz)

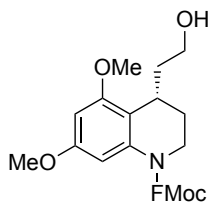
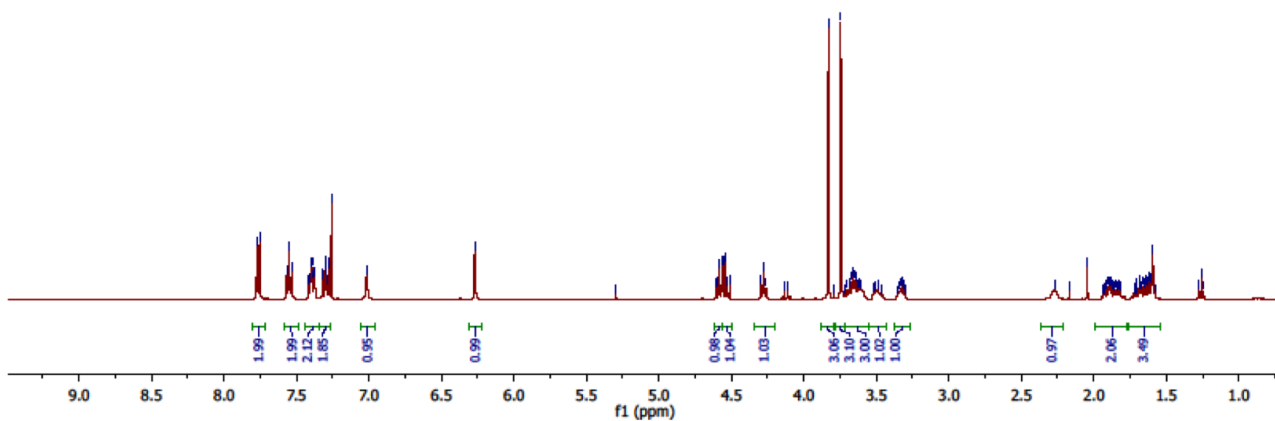




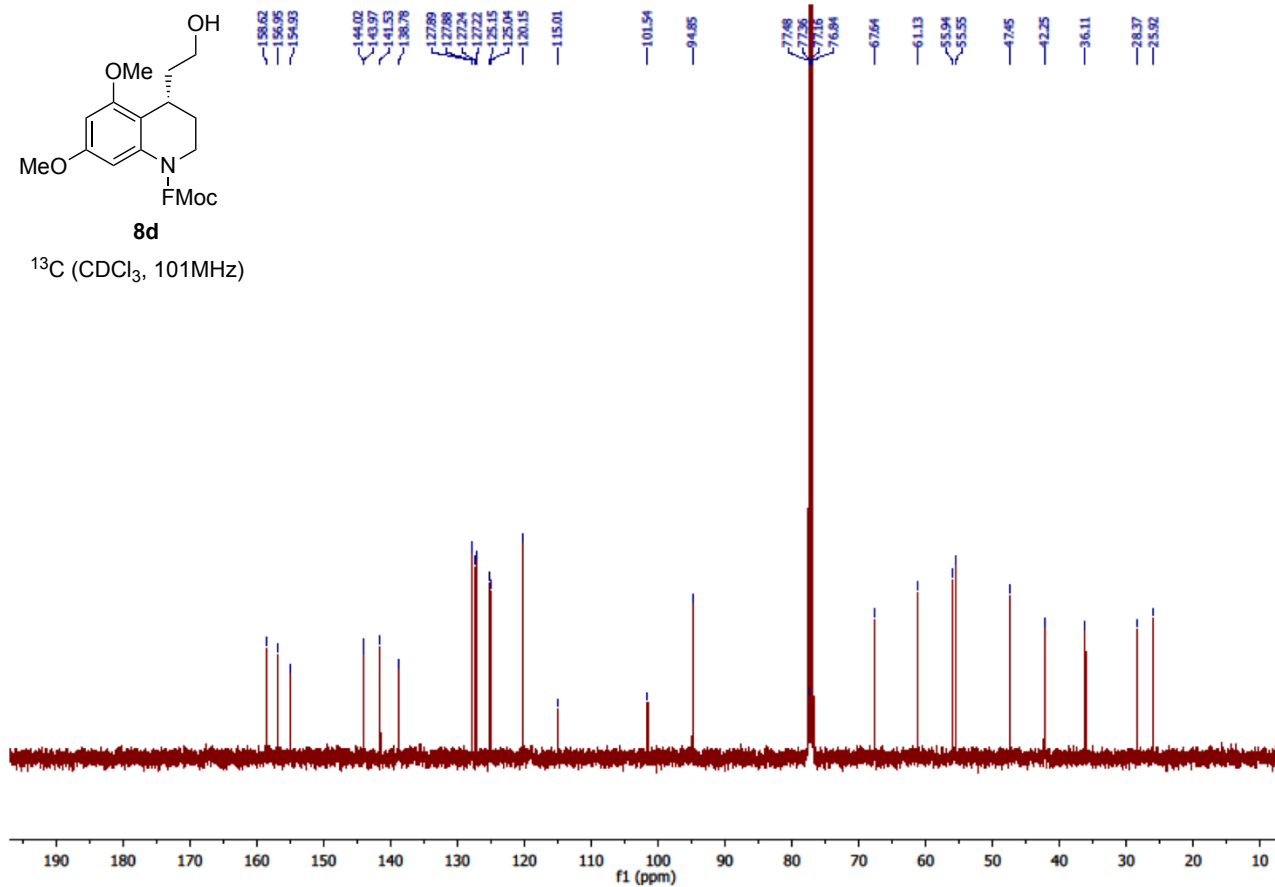
7.77 7.75 7.57 7.55 7.53 7.42 7.41 7.40 7.39 7.38 7.37 7.32 7.30 7.00 7.00 7.00 7.29 7.28 7.26 7.01 6.27 6.27 4.61 4.59 4.58 4.56 4.56 4.54 4.53 4.51 4.29 4.28 4.26 4.13 4.11 3.83 3.74 3.70 3.69 3.67 3.66 3.66 3.65 3.63 3.62 3.61 3.61 3.51 3.49 3.34 3.33 3.32 3.31 2.27 2.17 2.04 1.91 1.90 1.89 1.89 1.88 1.86 1.86 1.85 1.83 1.83 1.82 1.80 1.79 1.68 1.67 1.67 1.64 1.63 1.62 1.61 1.59 1.28 1.26 1.24

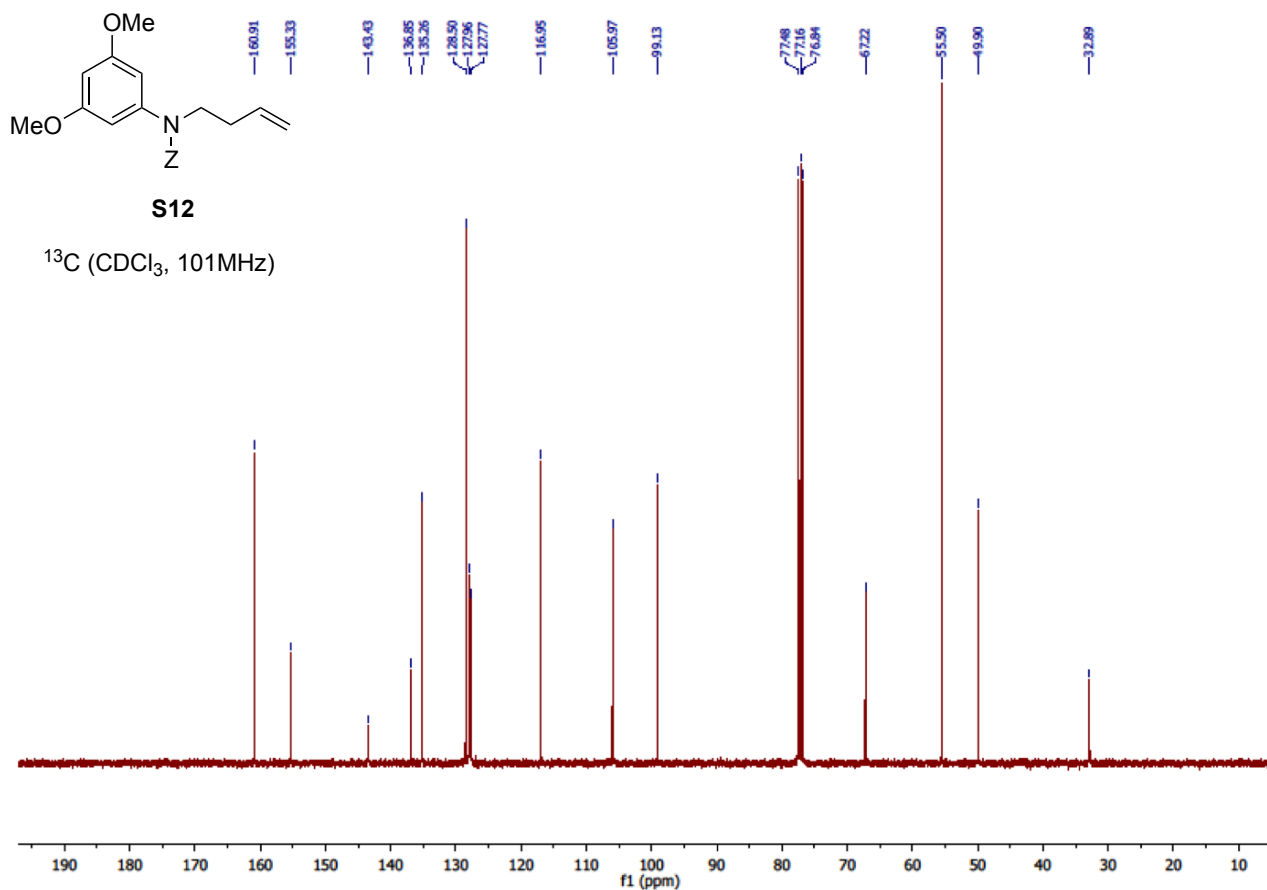
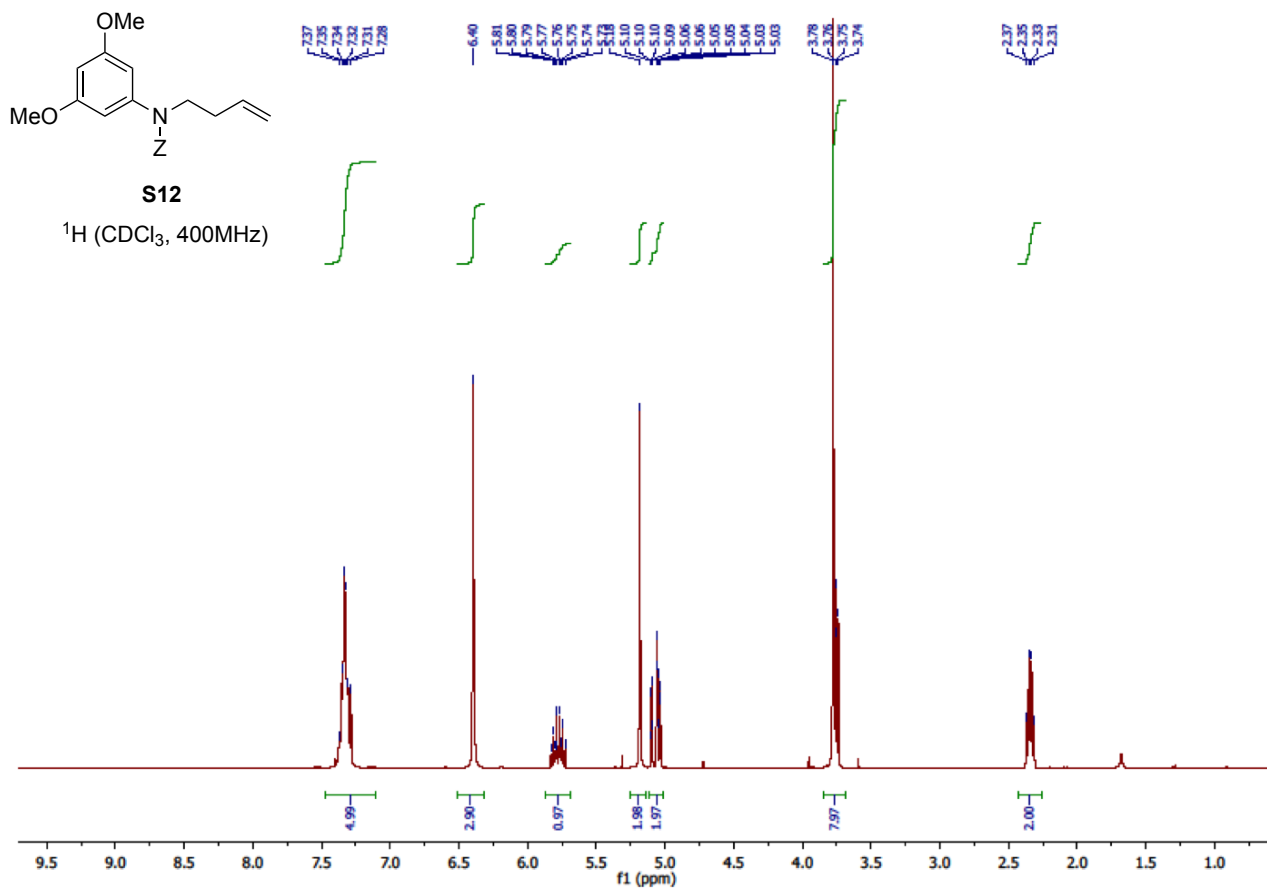


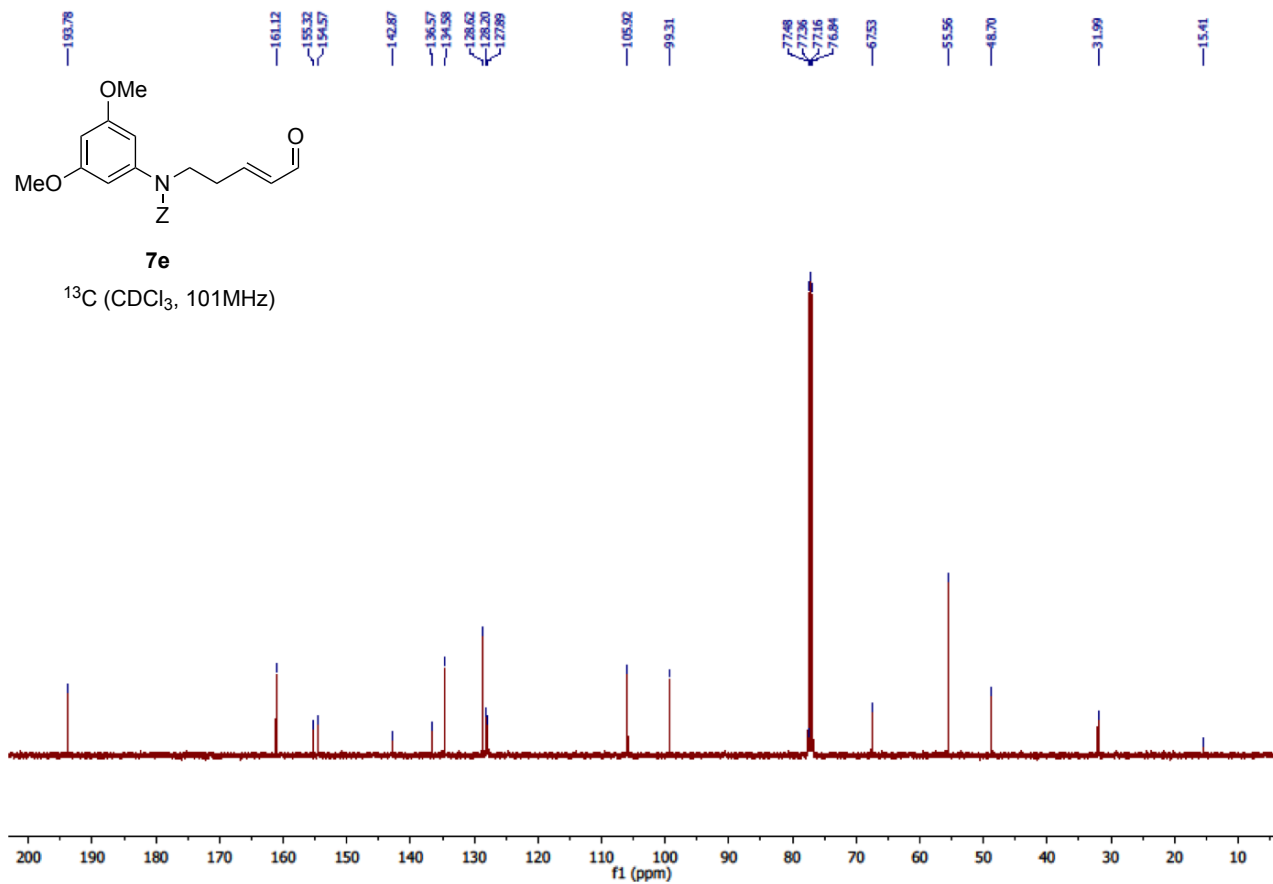
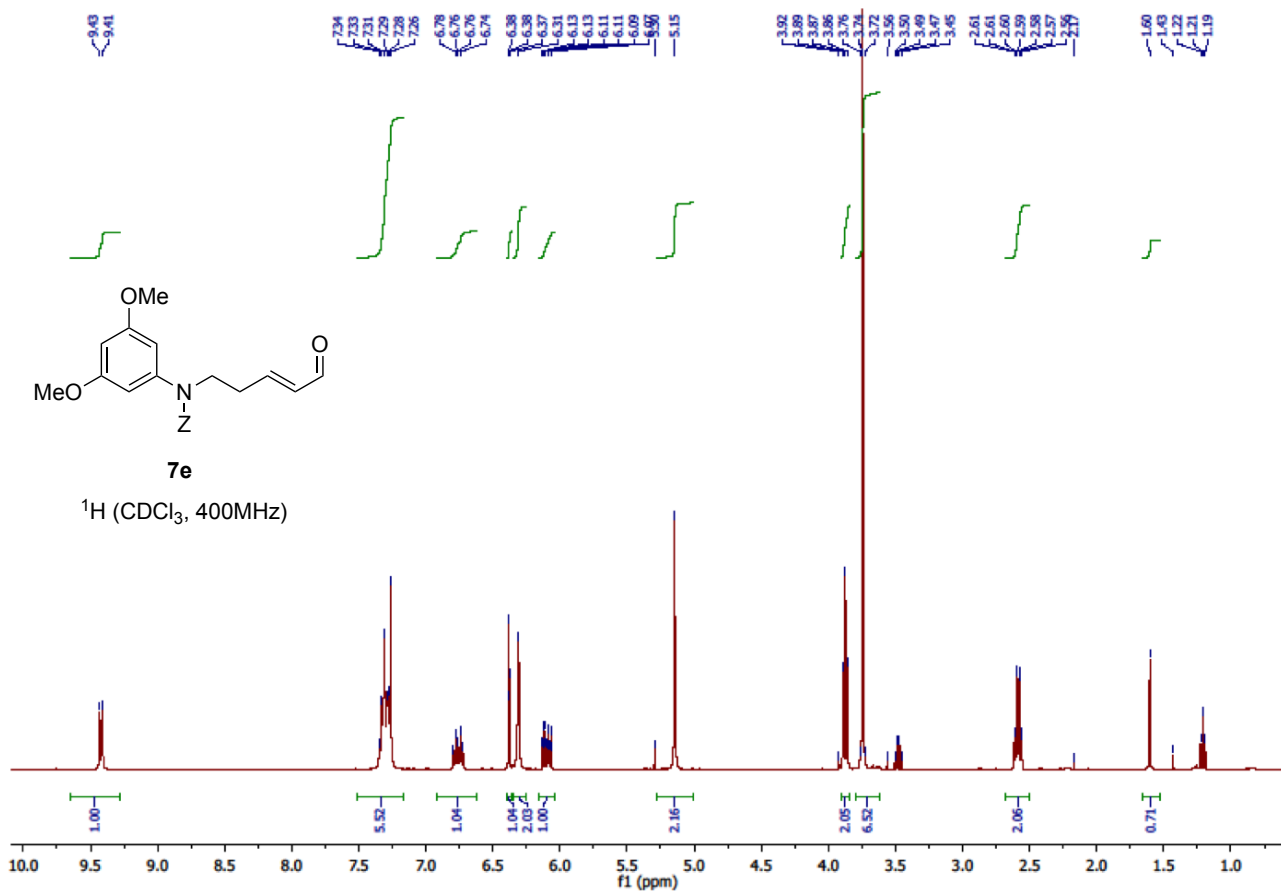
8d
 ^1H (CDCl₃, 400MHz)

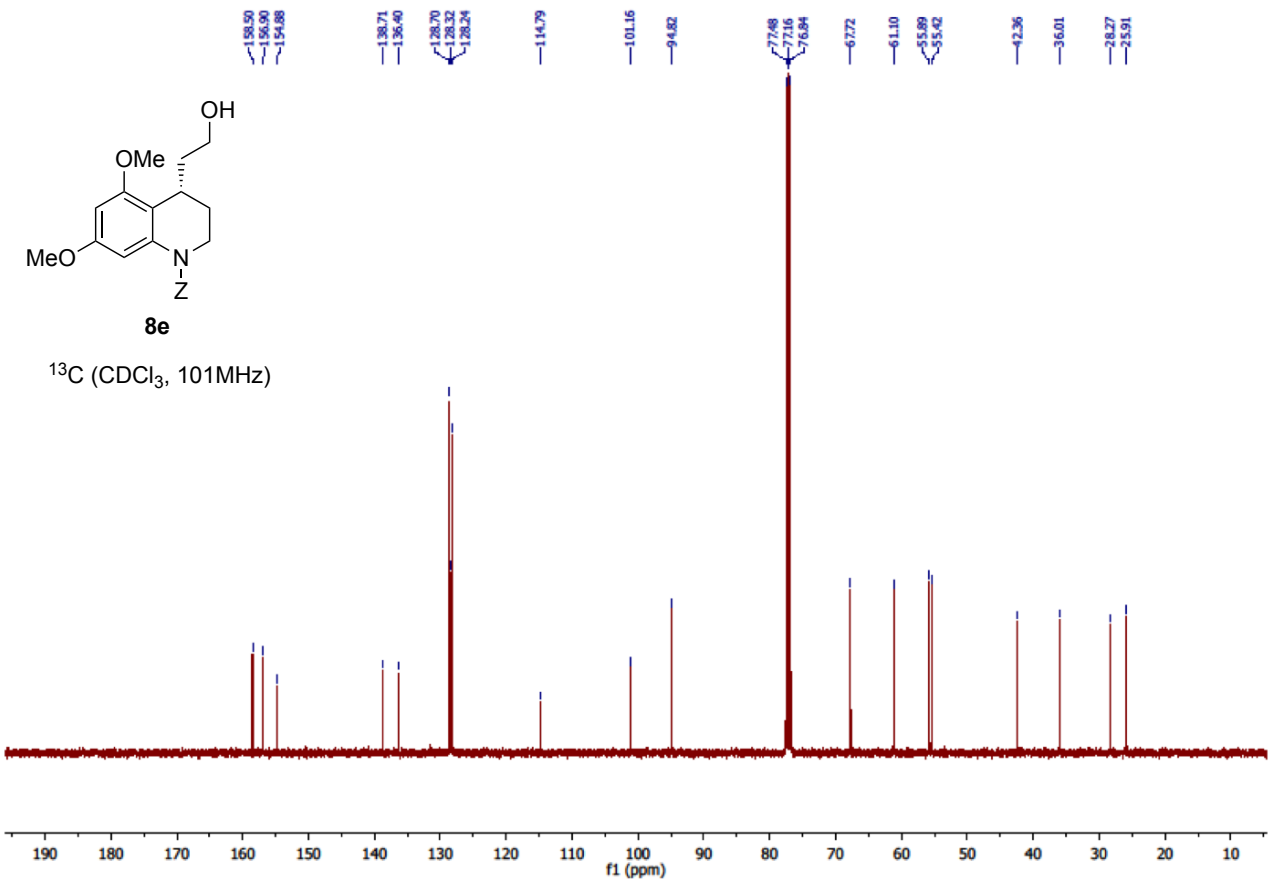
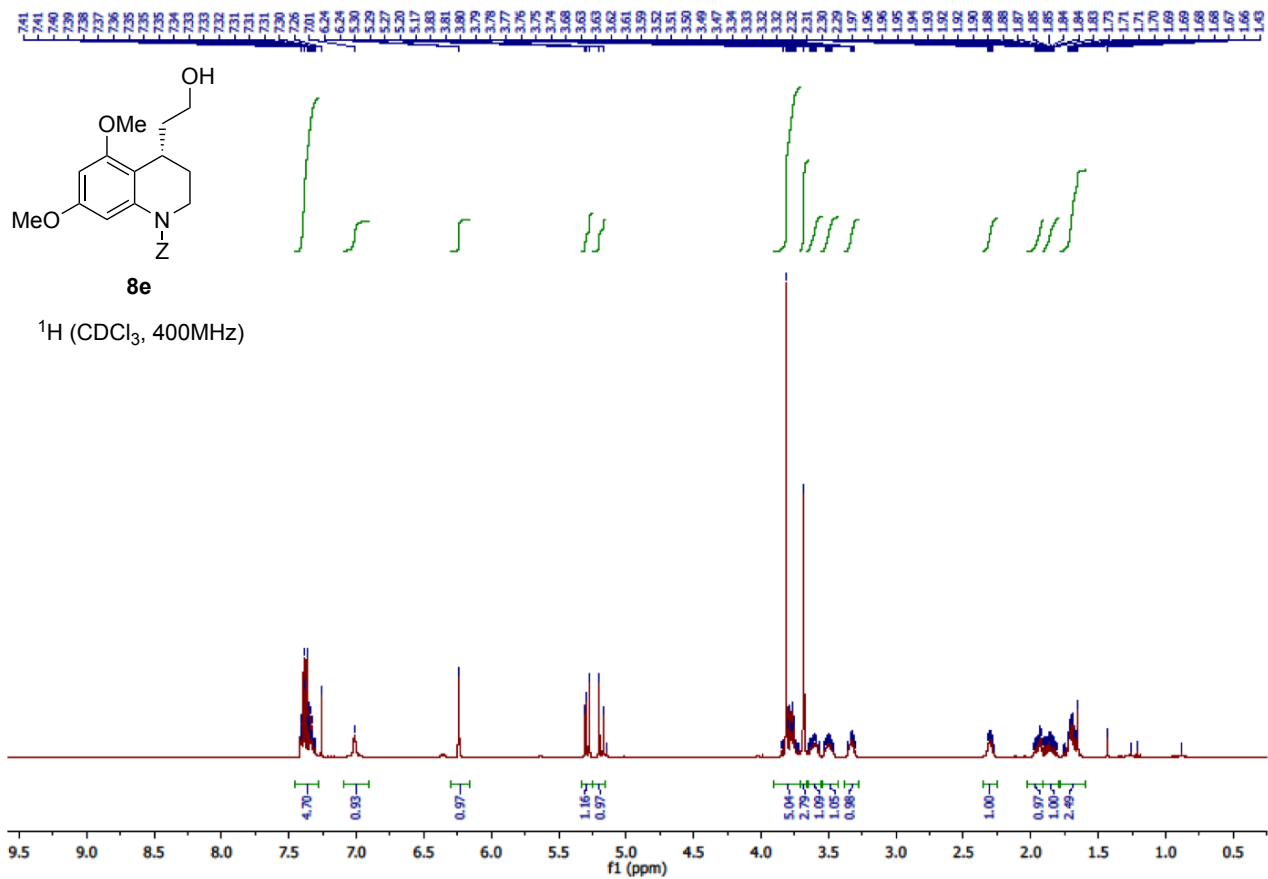


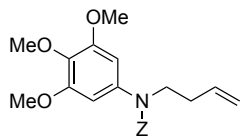
8d
 ^{13}C (CDCl₃, 101MHz)





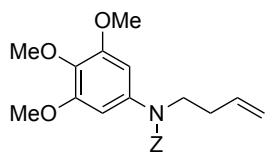
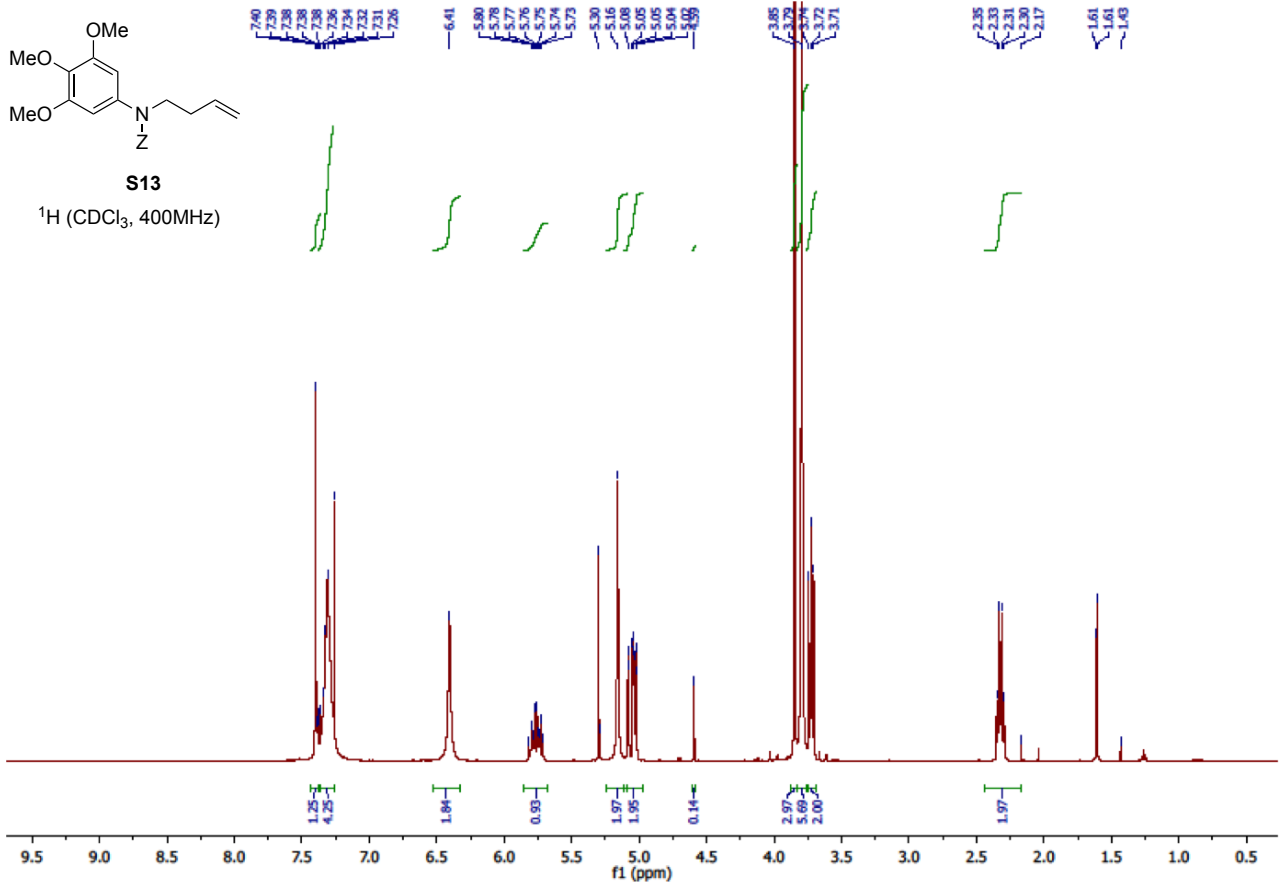






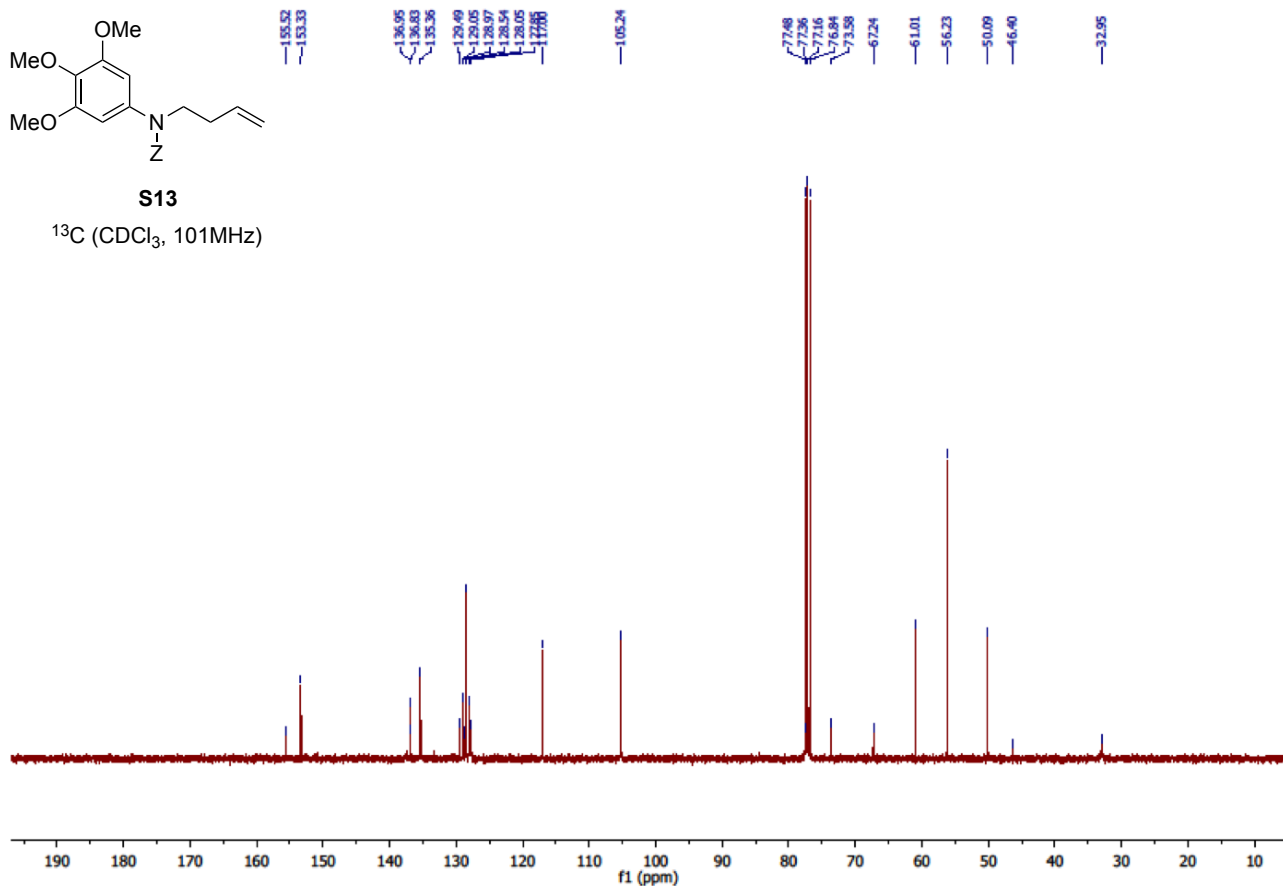
S13

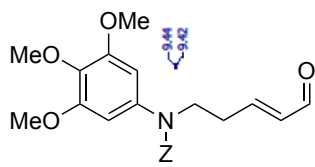
¹H (CDCl₃, 400MHz)



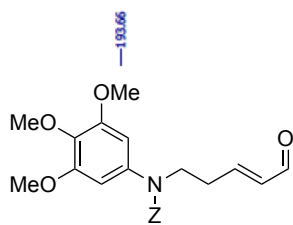
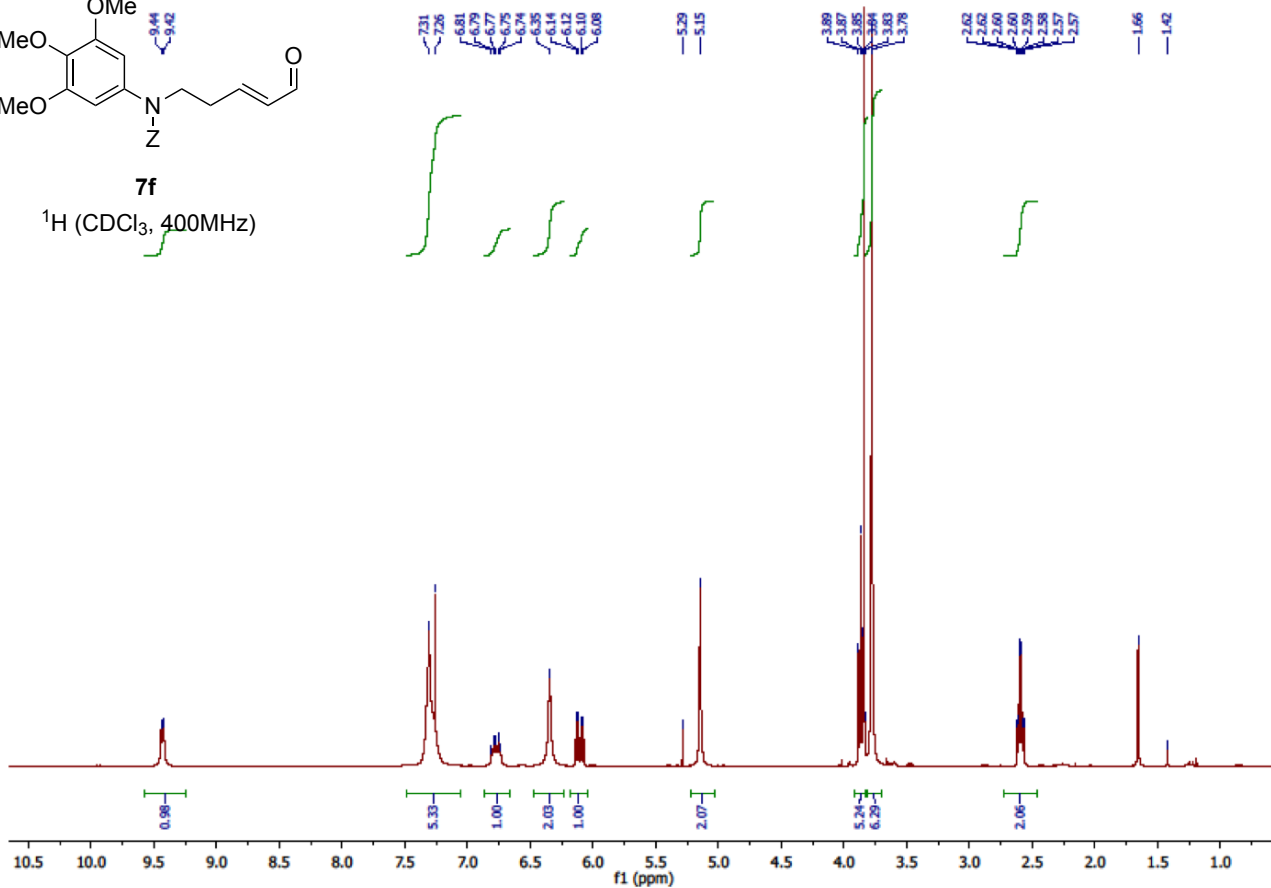
S13

¹³C (CDCl₃, 101MHz)

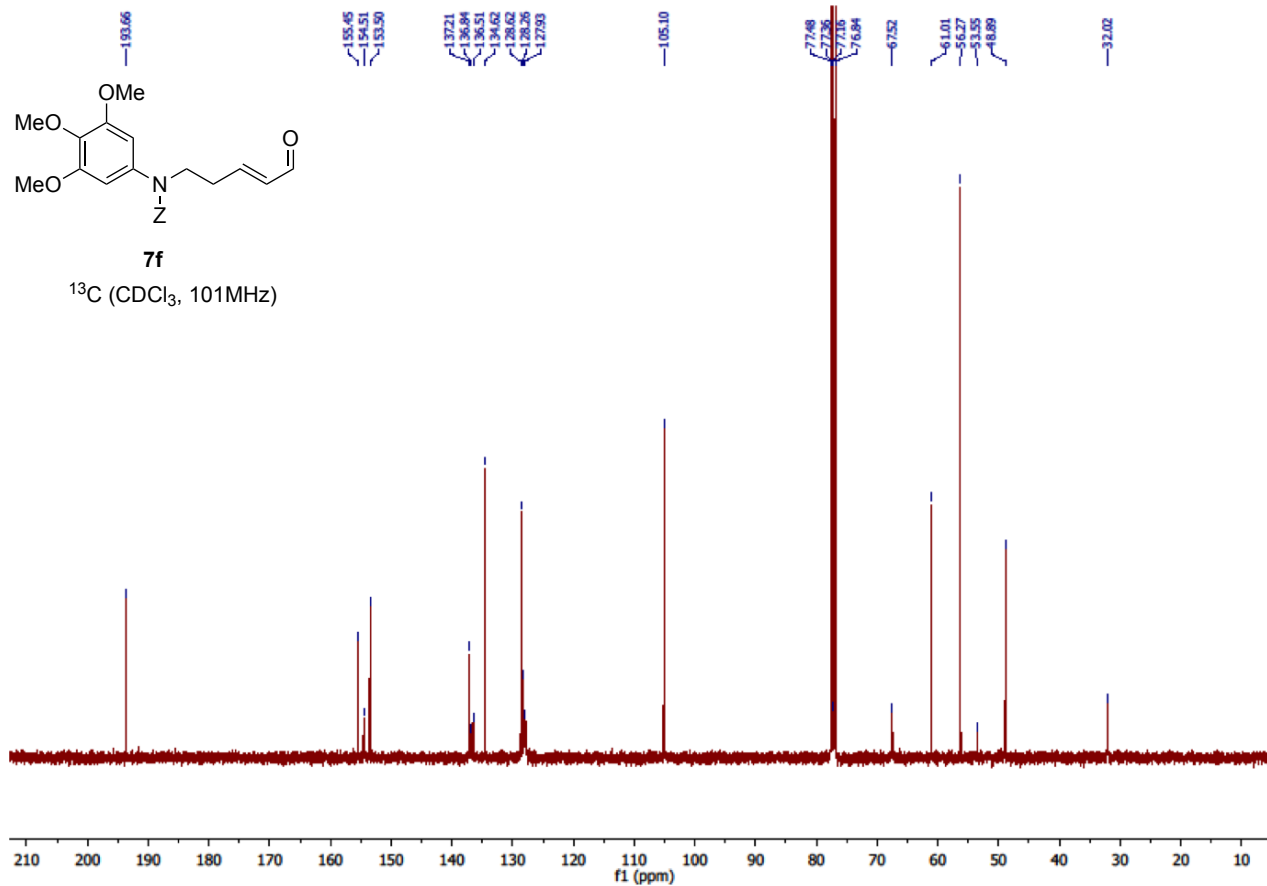


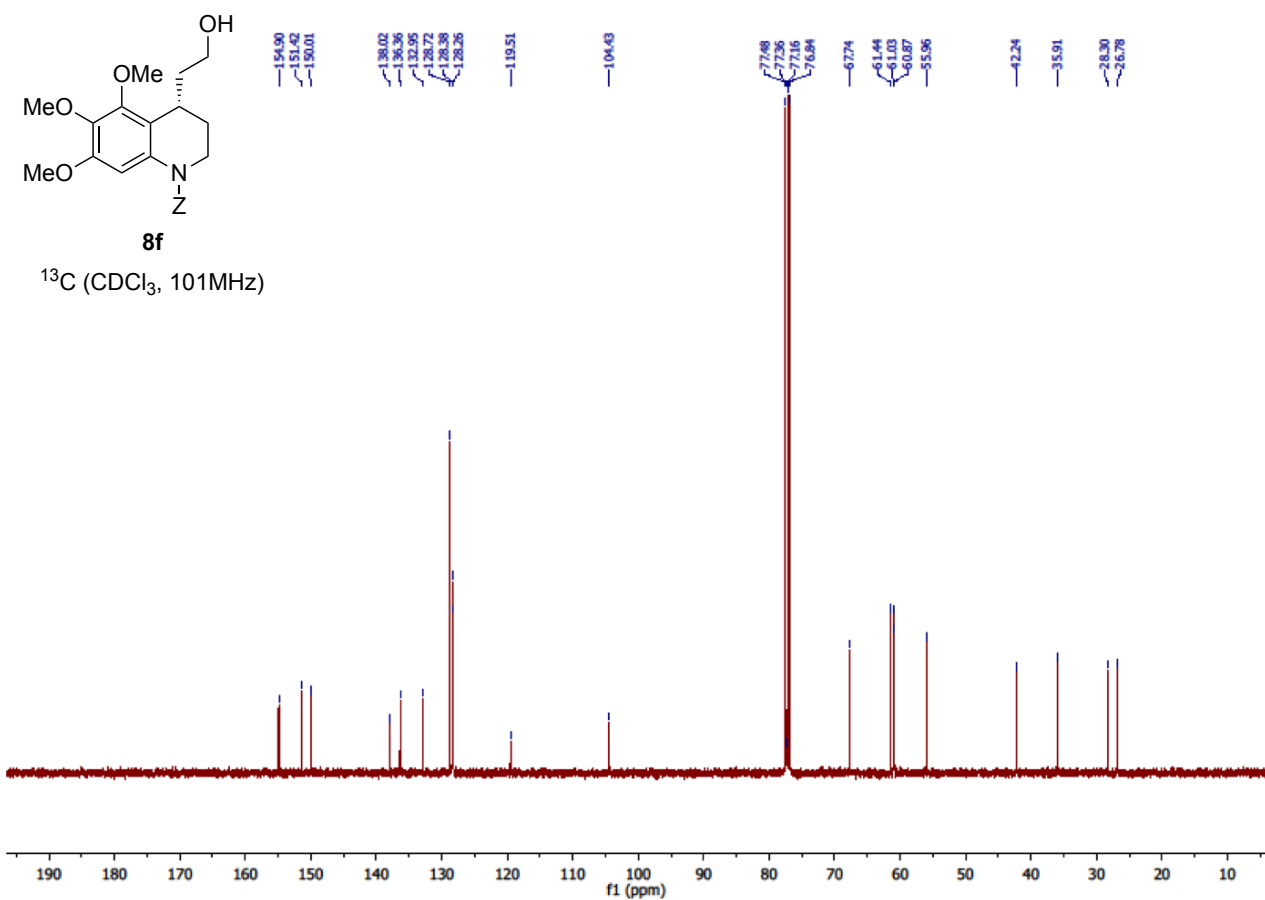
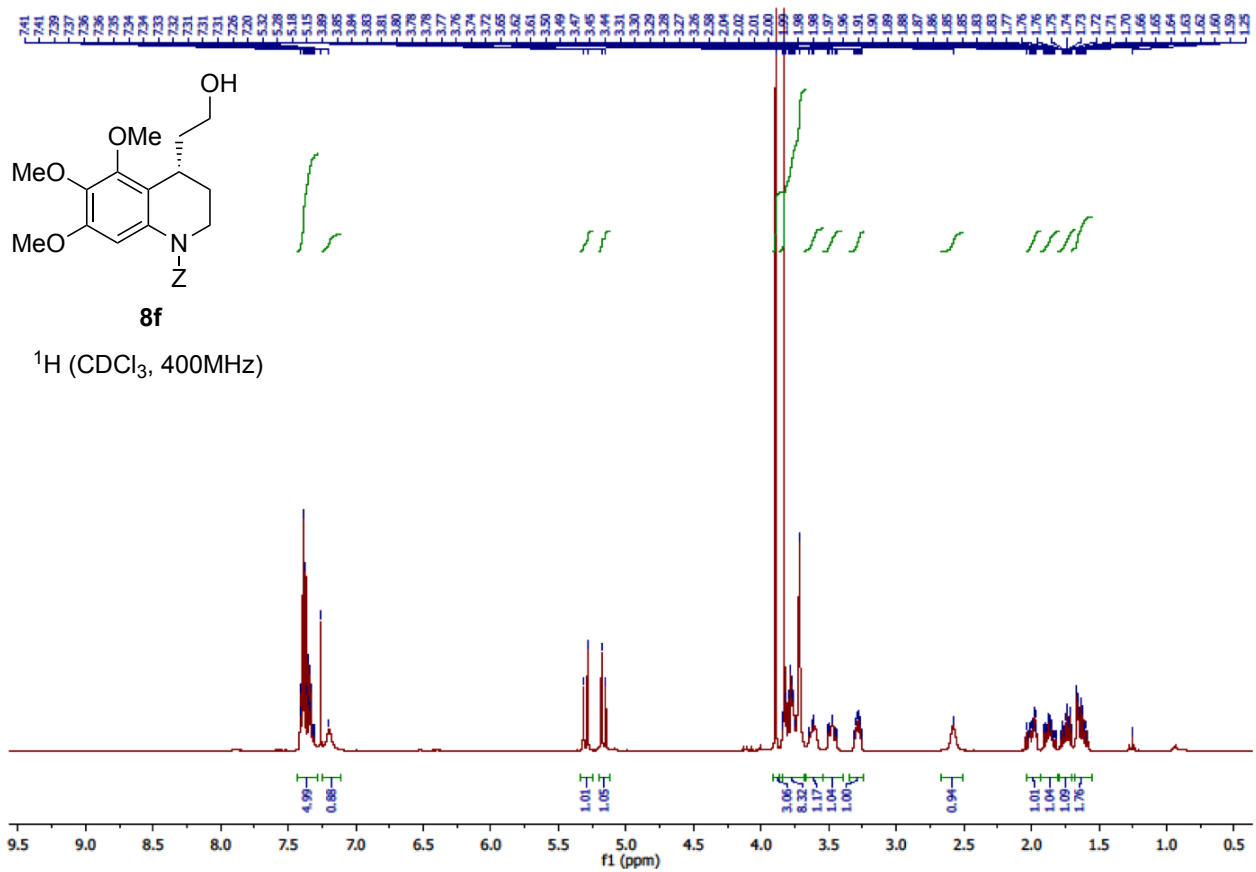


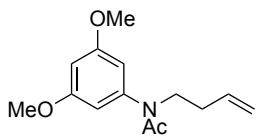
7f
¹H (CDCl₃, 400MHz)



7f
¹³C (CDCl₃, 101MHz)

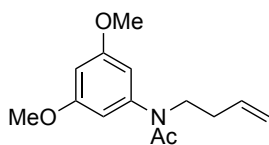
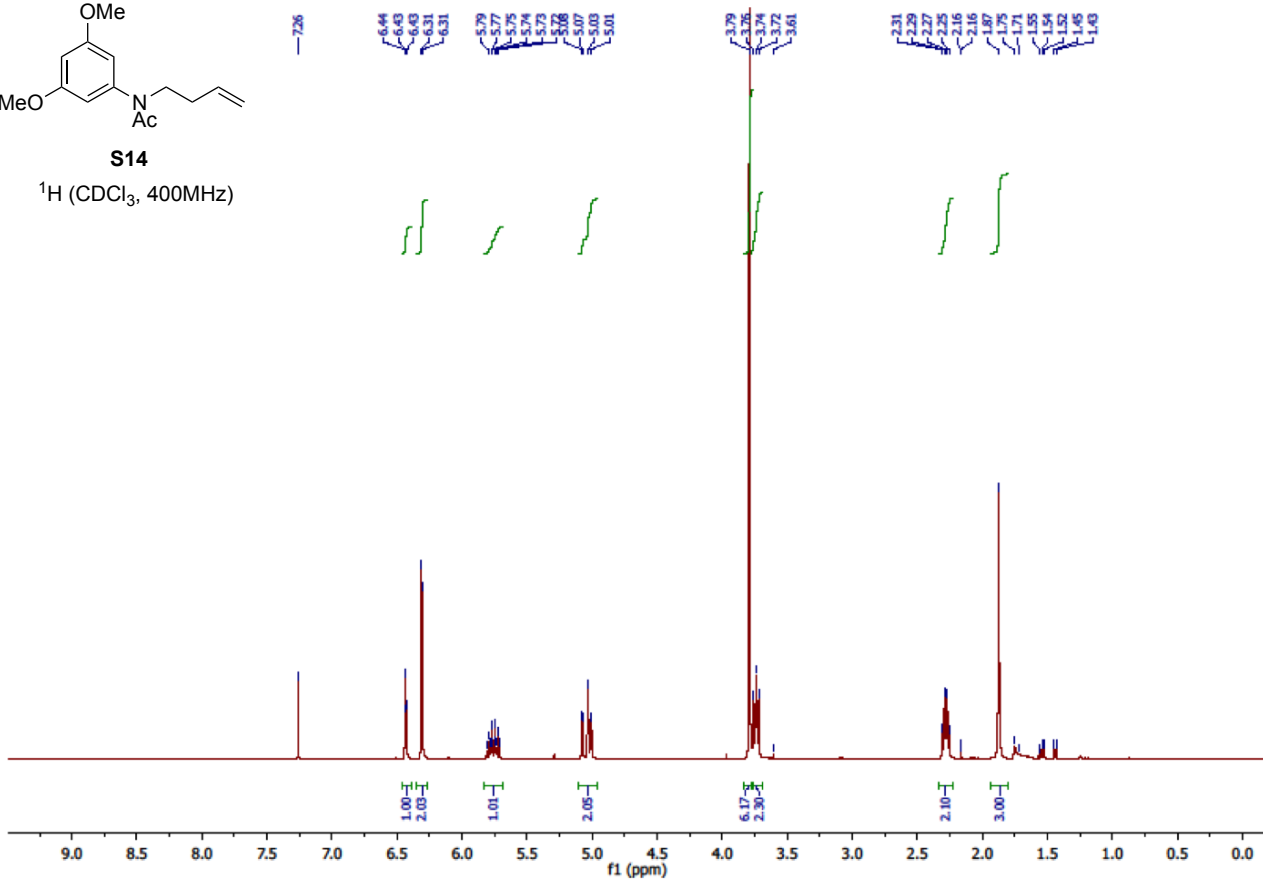






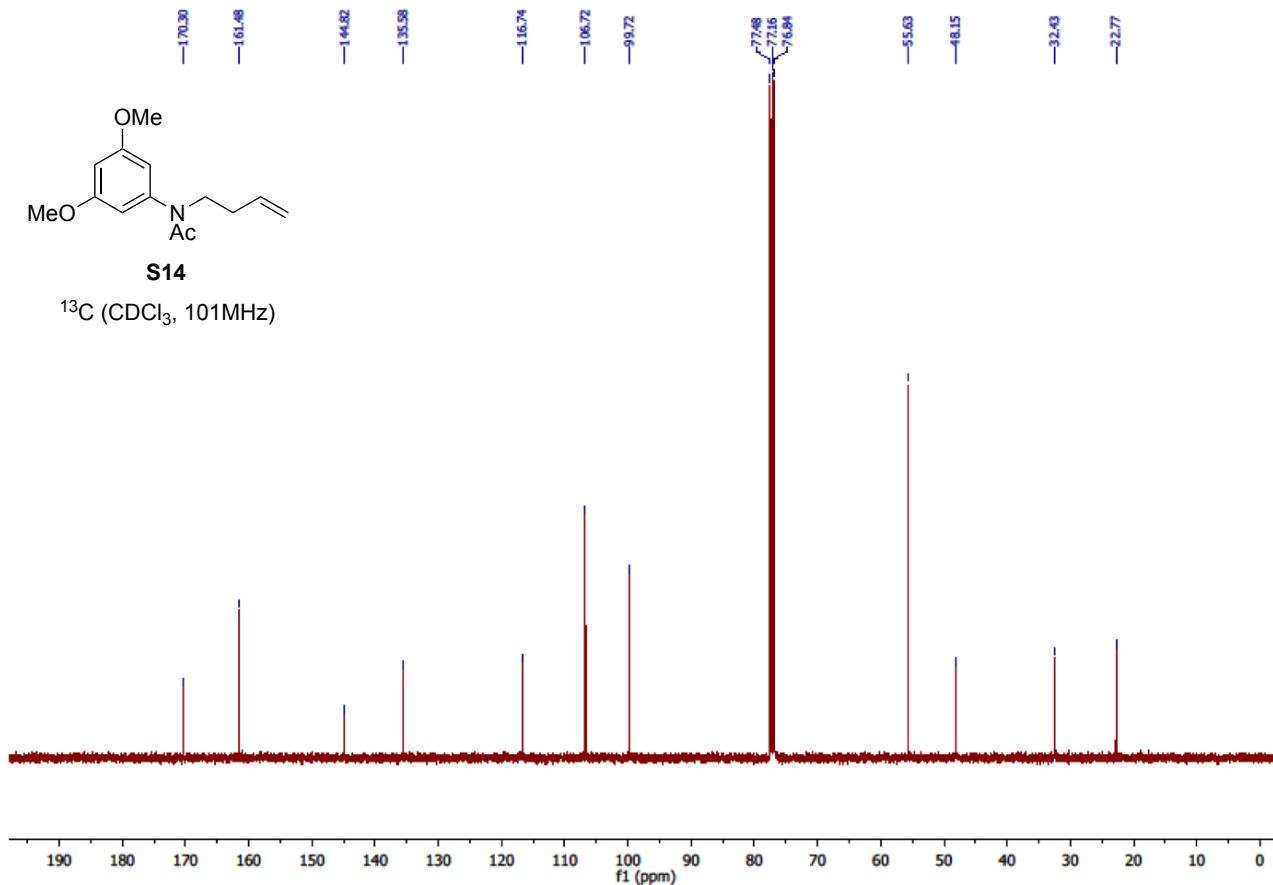
S14

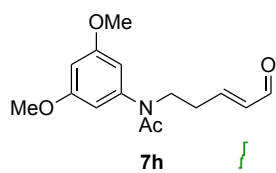
^1H (CDCl_3 , 400MHz)



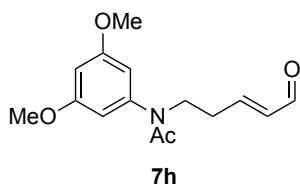
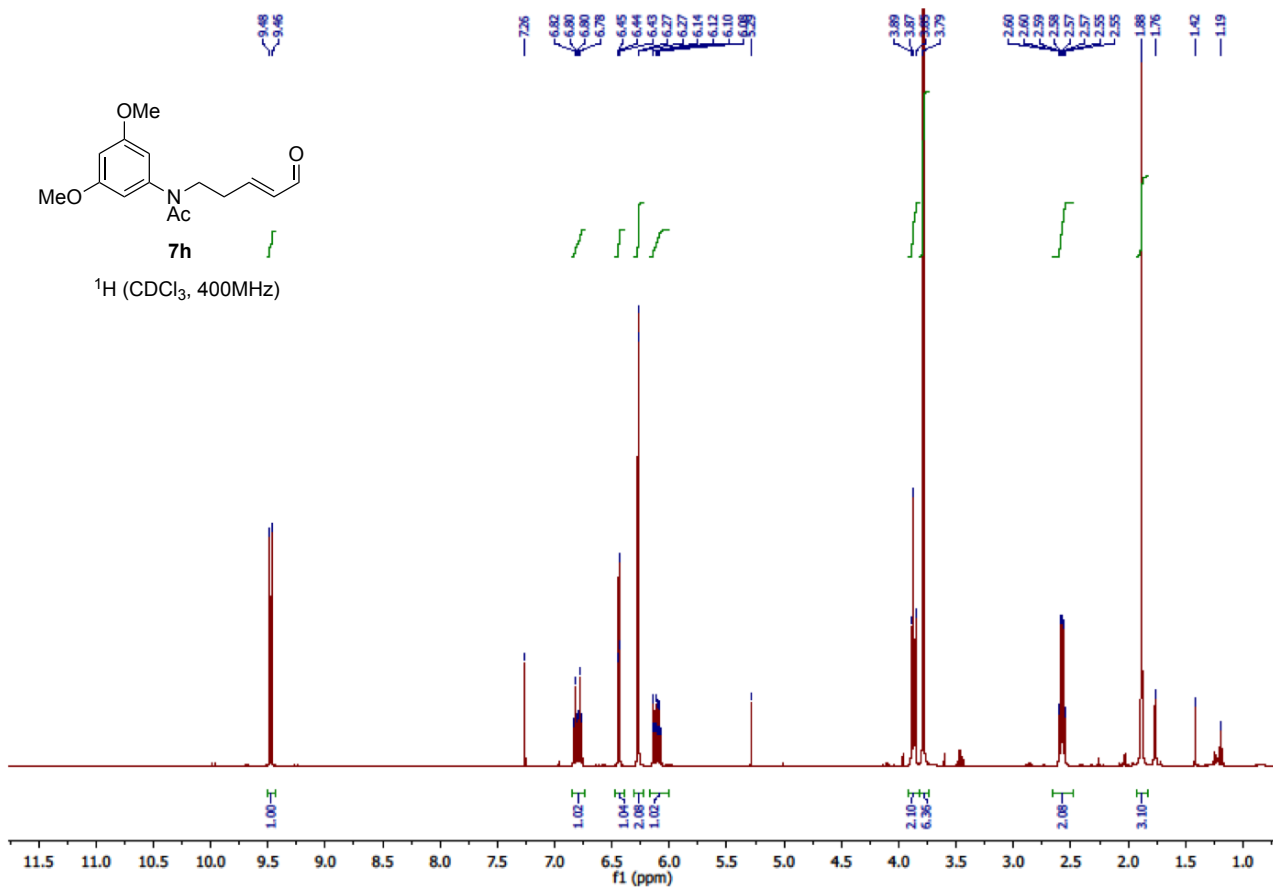
S14

^{13}C (CDCl_3 , 101MHz)

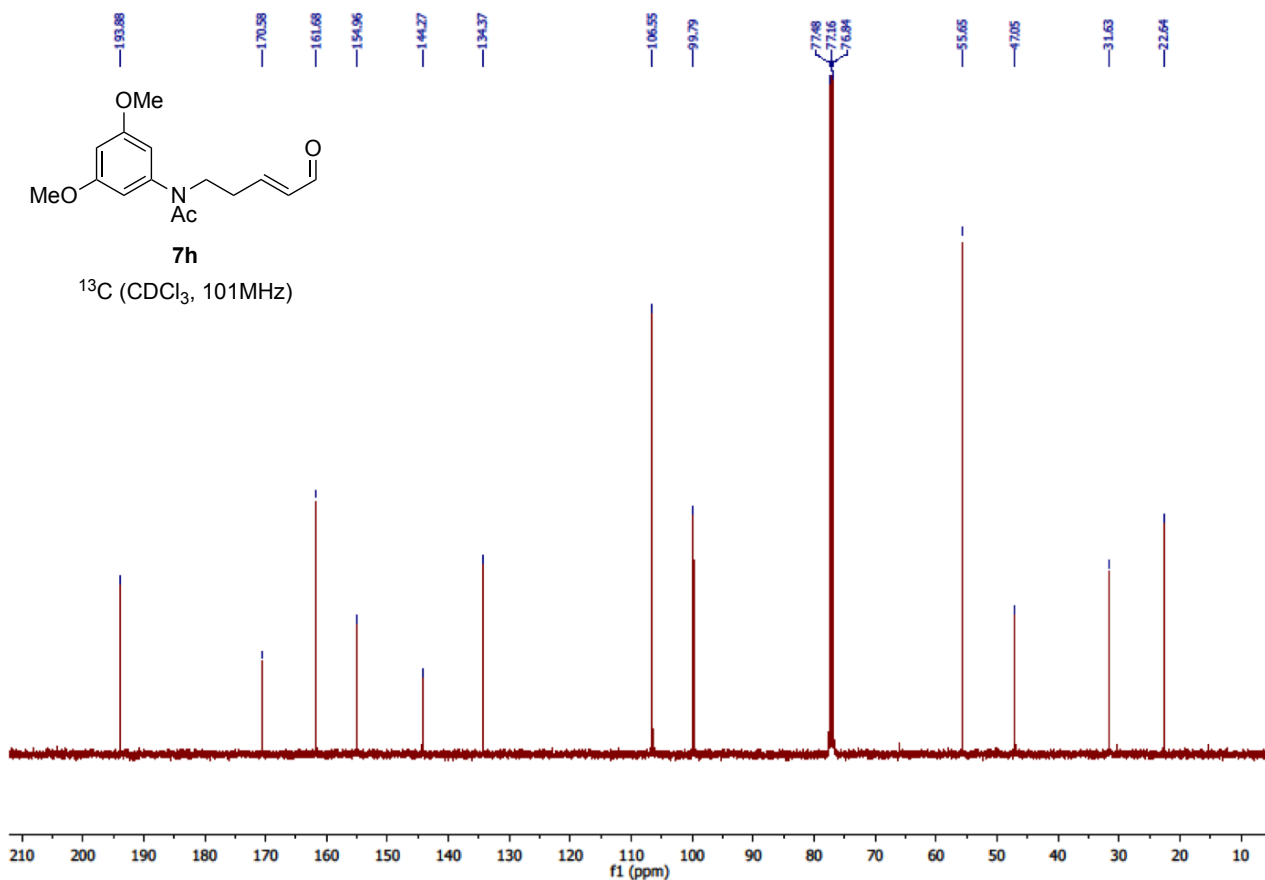


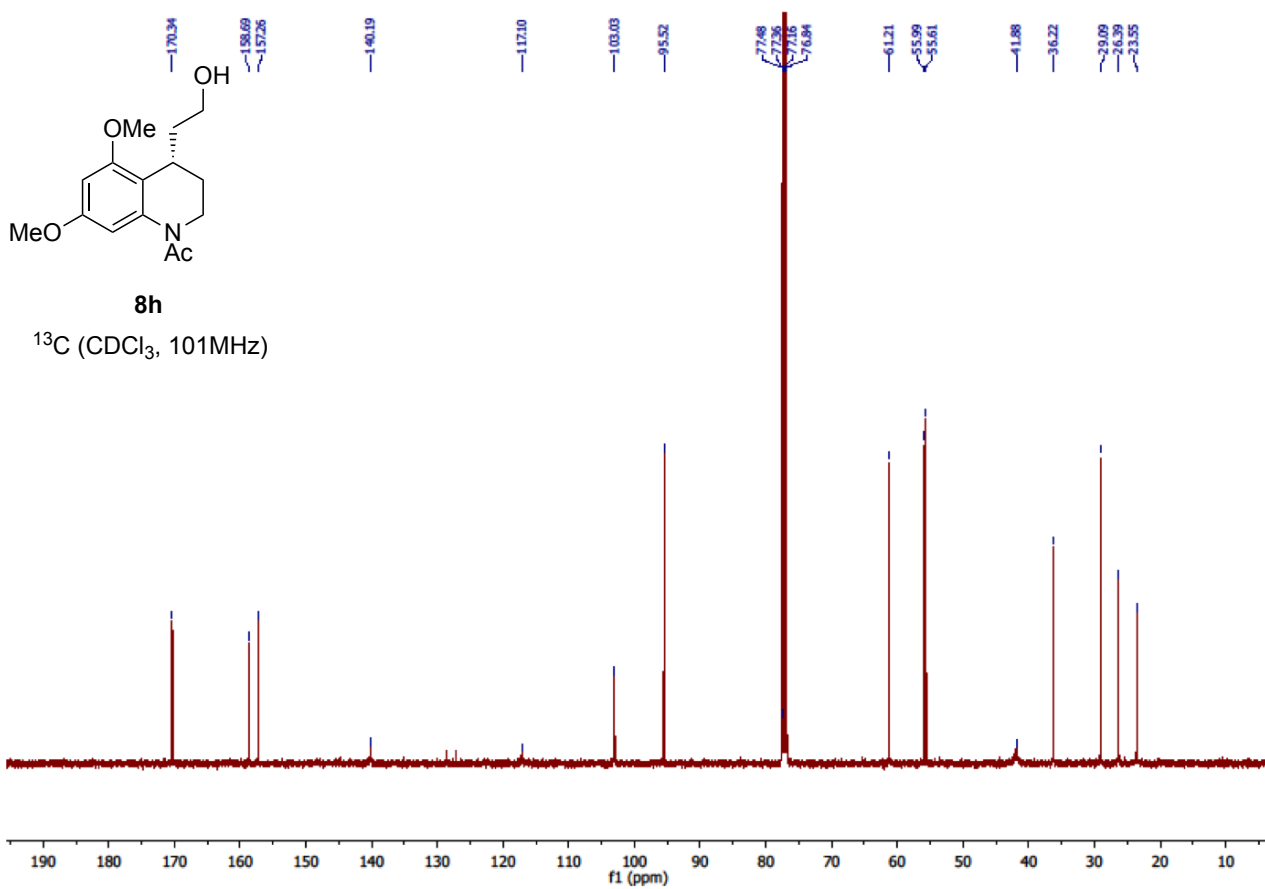
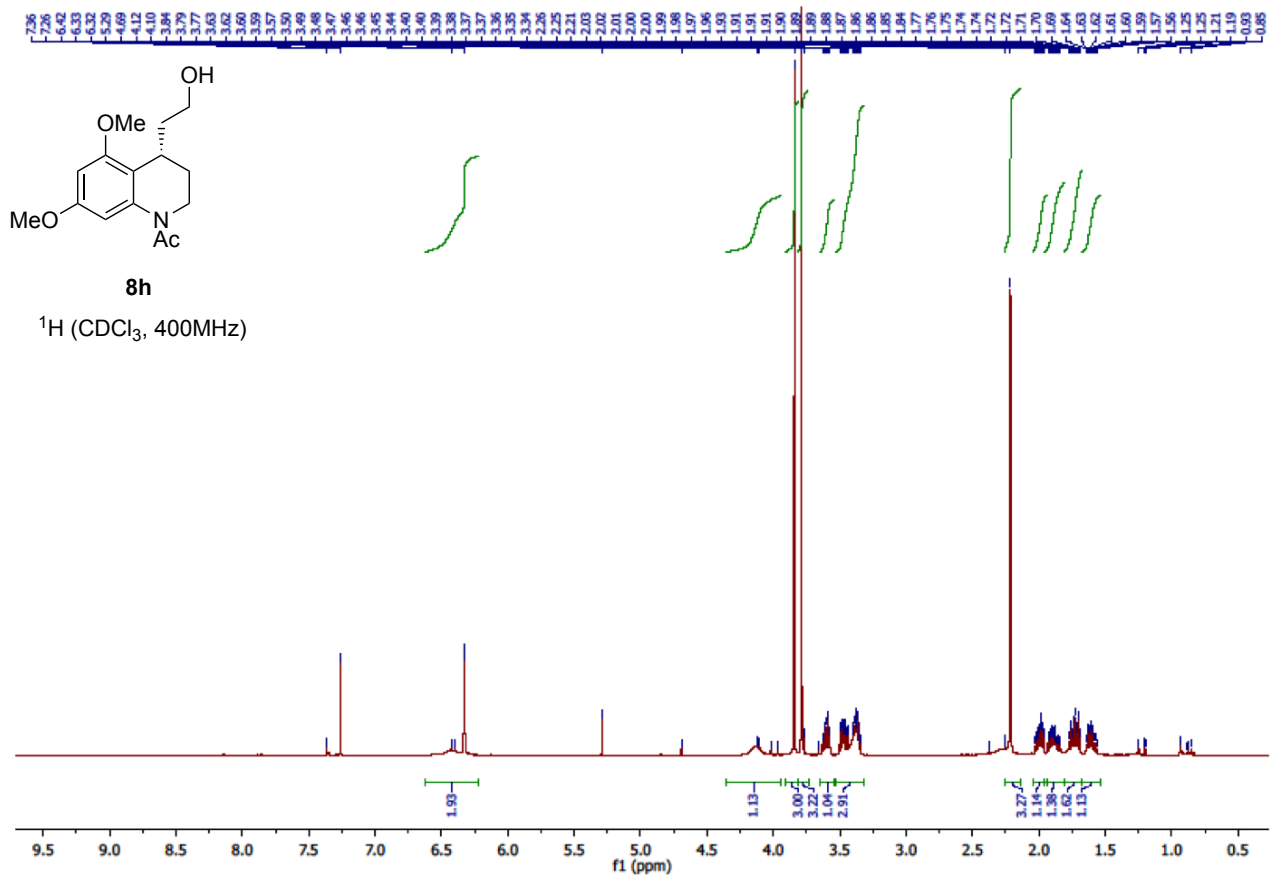


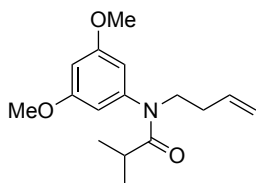
^1H (CDCl₃, 400MHz)



^{13}C (CDCl₃, 101MHz)

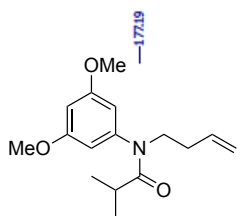
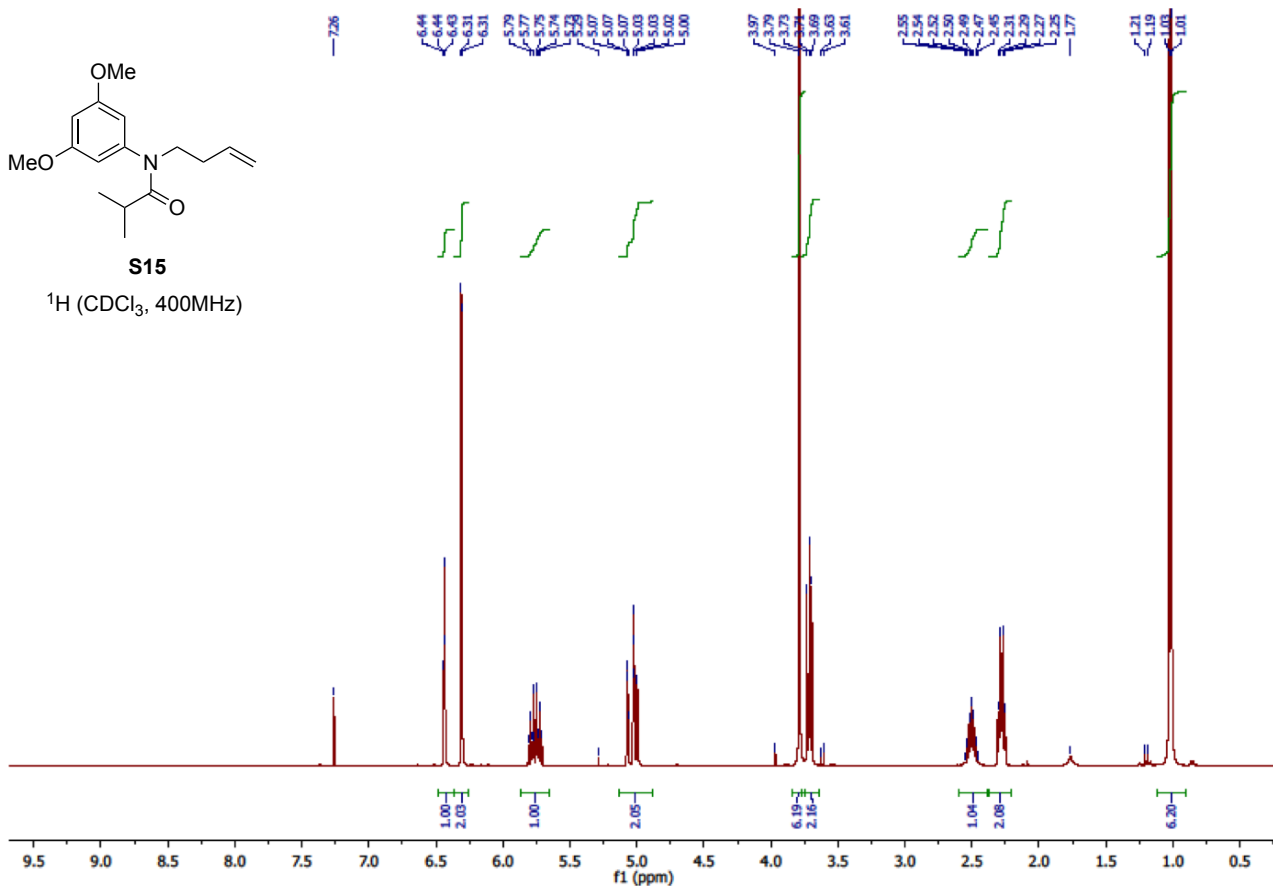






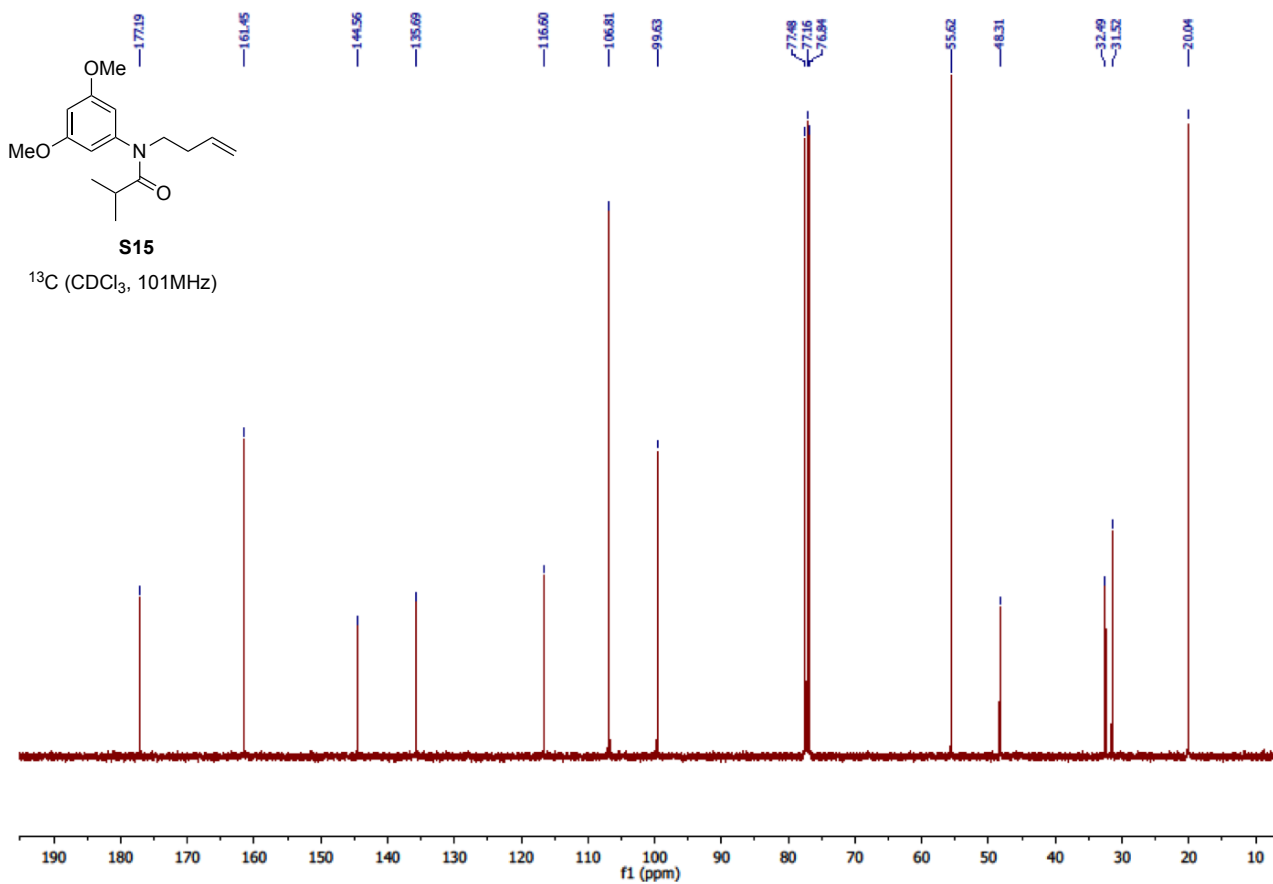
S15

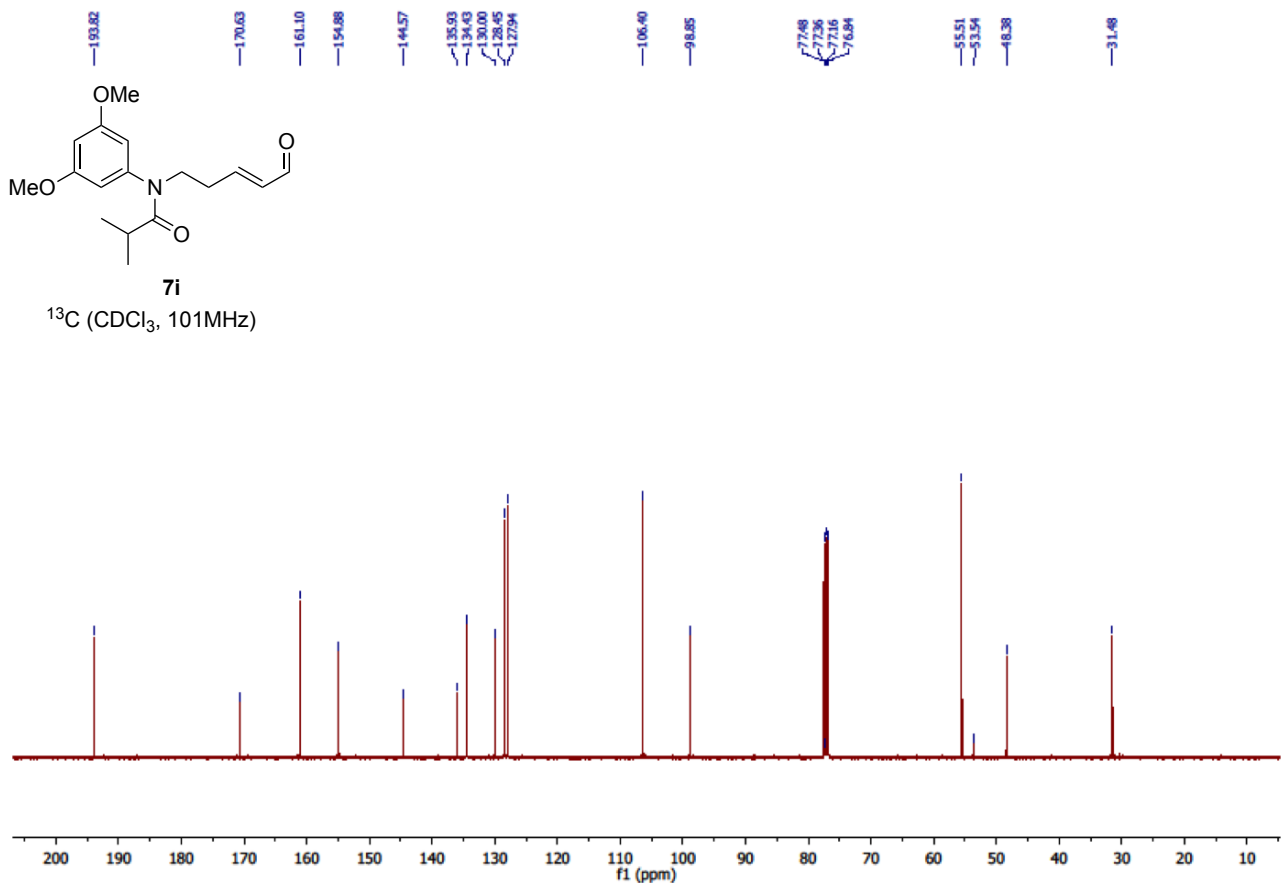
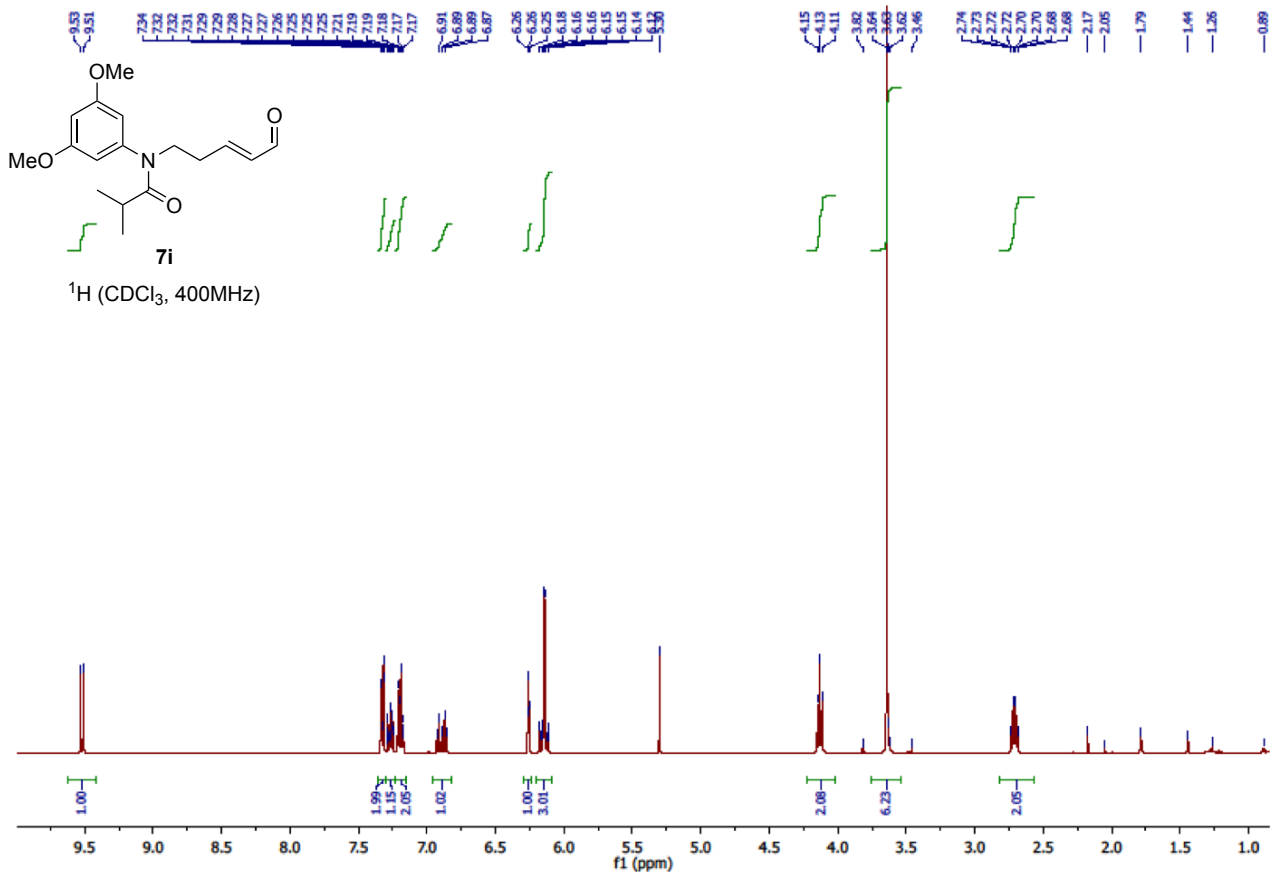
¹H (CDCl₃, 400MHz)

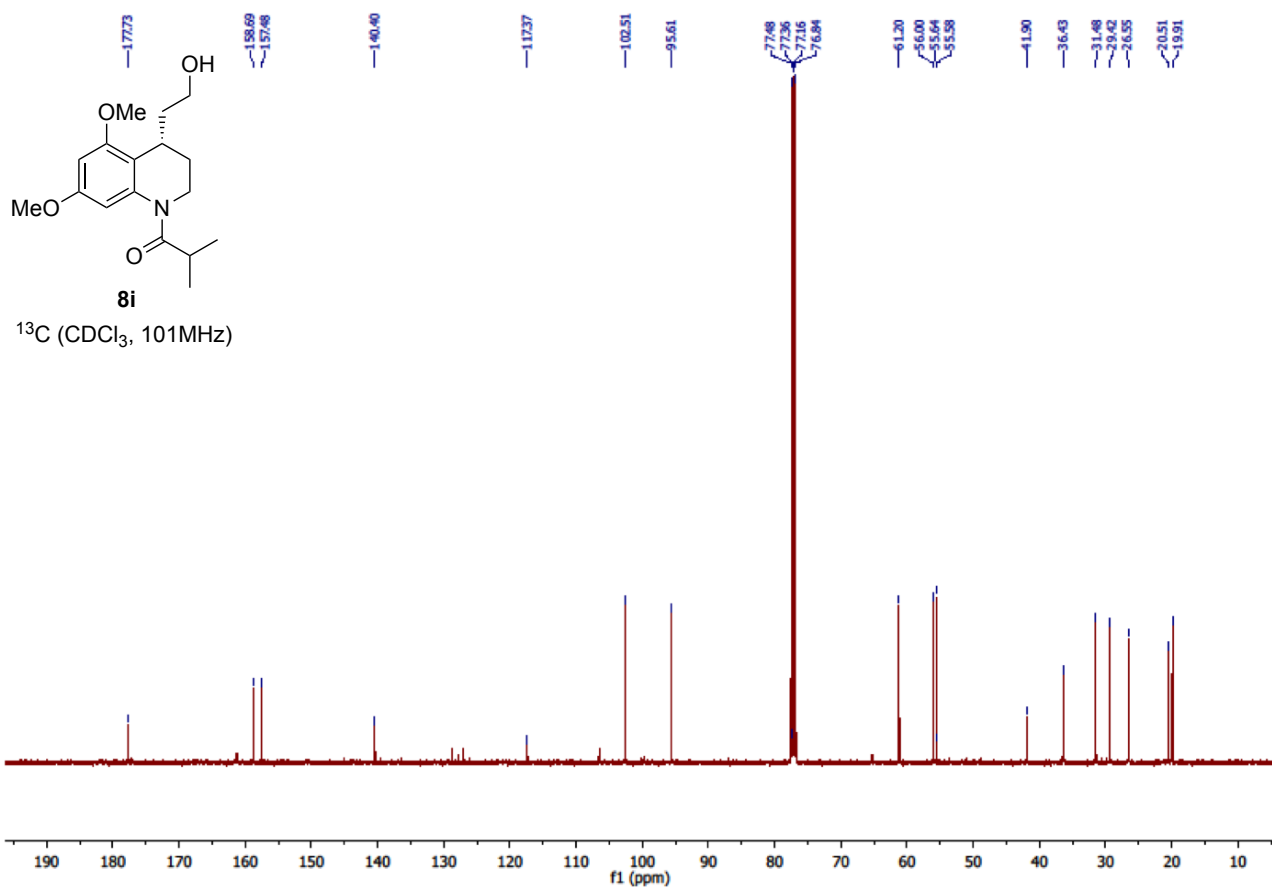
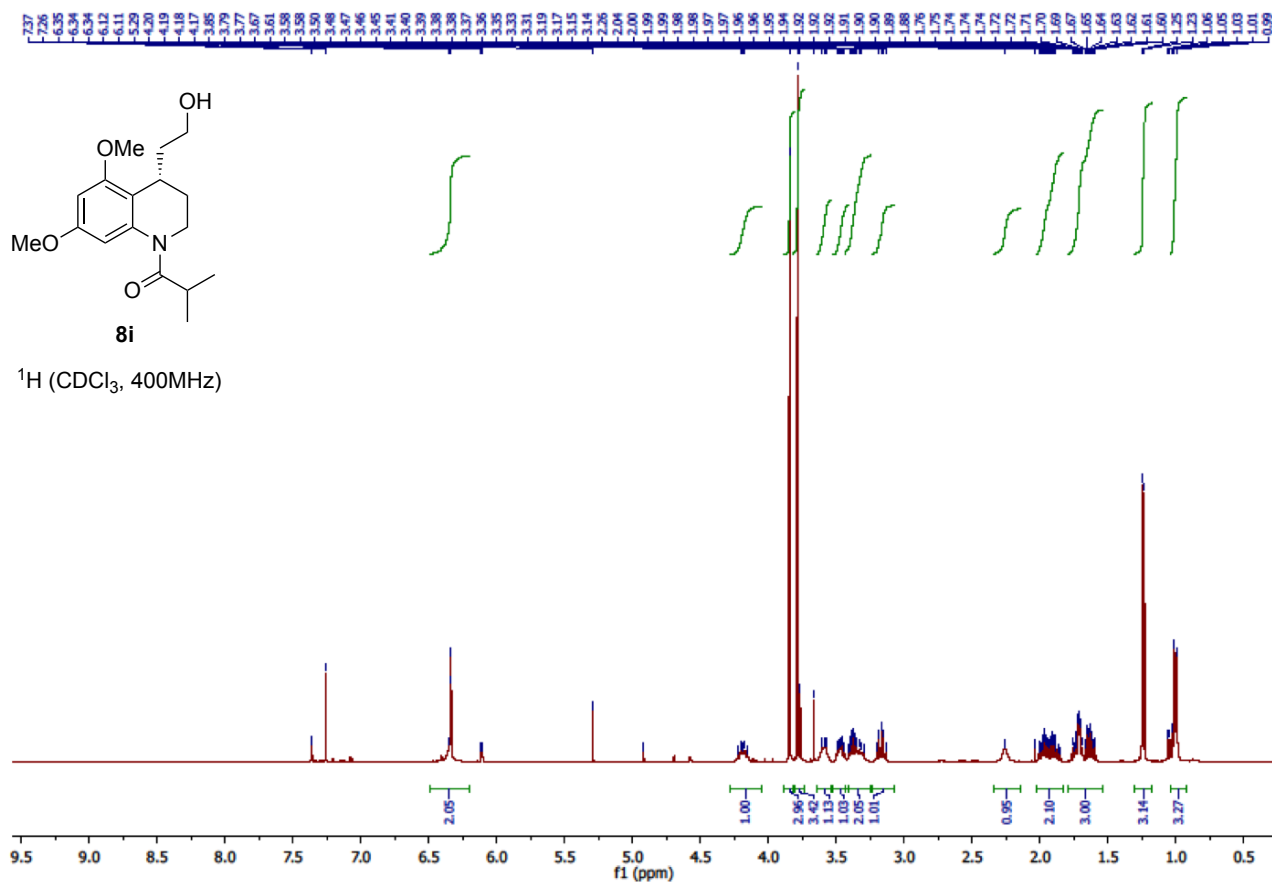


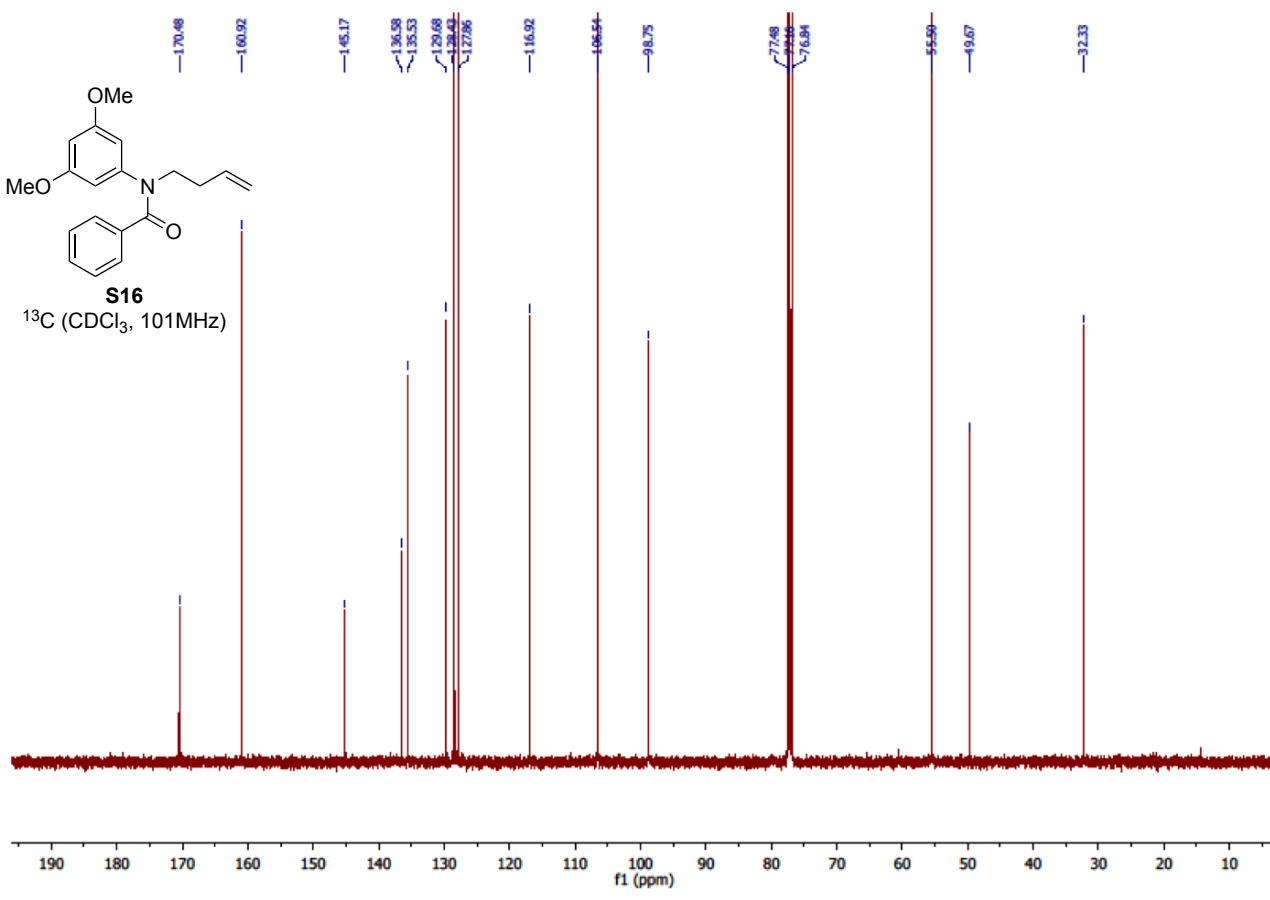
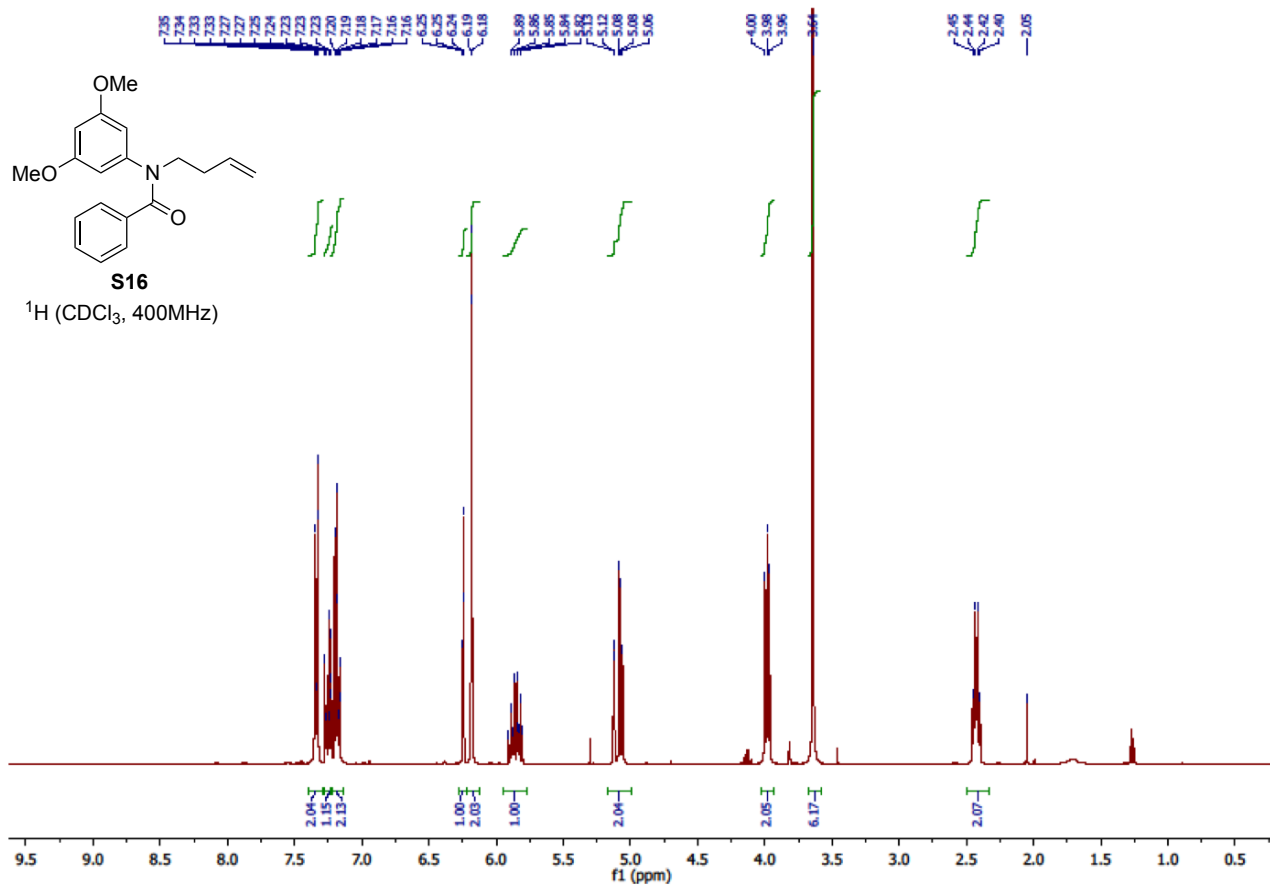
S15

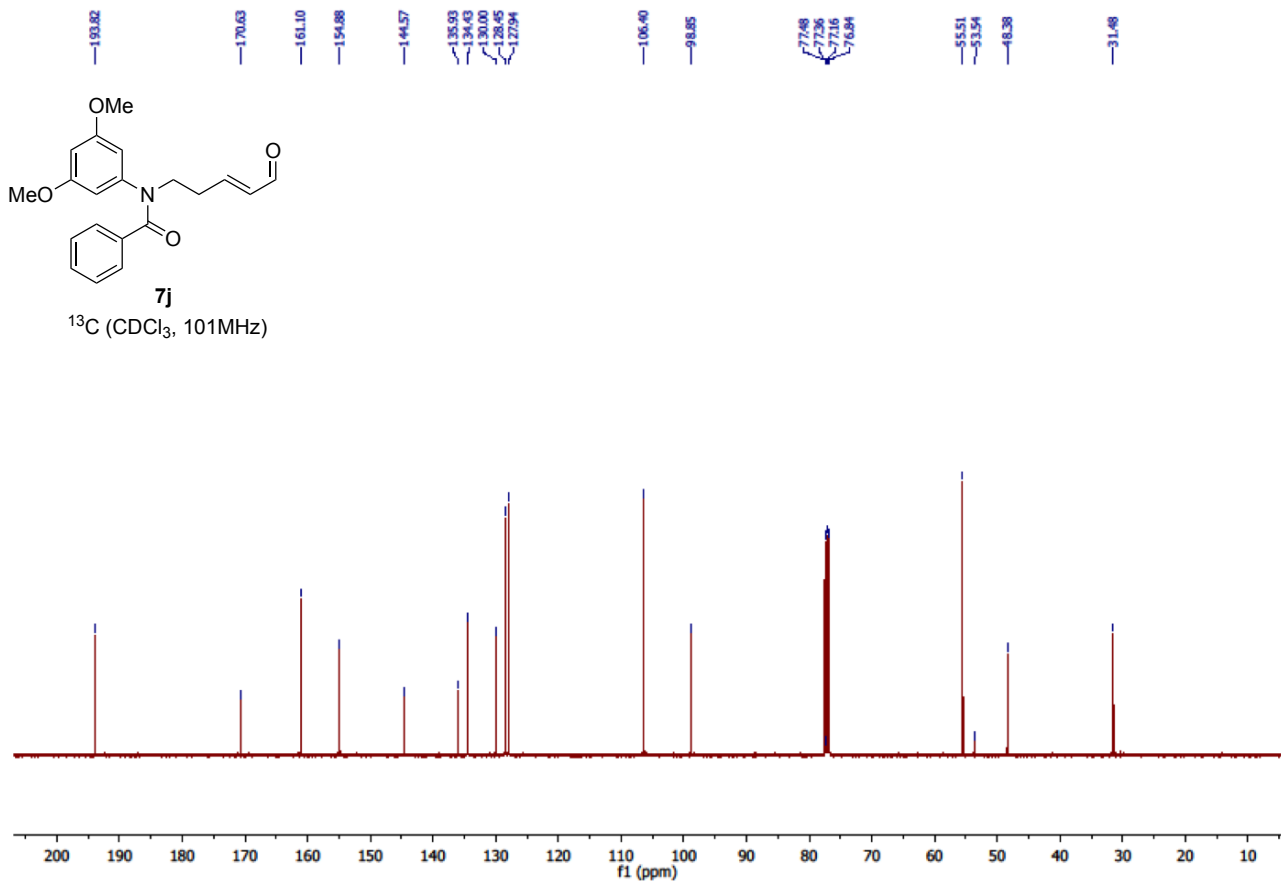
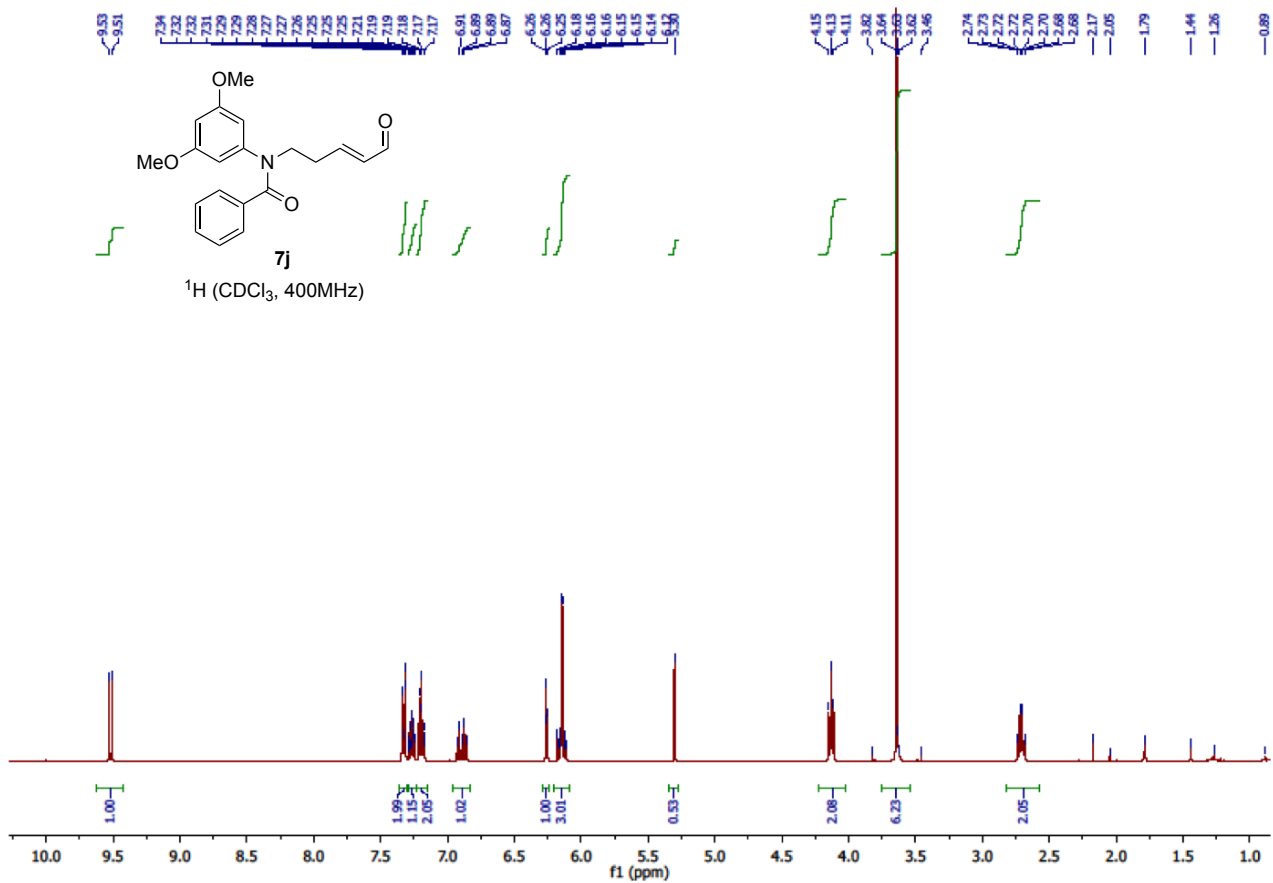
¹³C (CDCl₃, 101MHz)

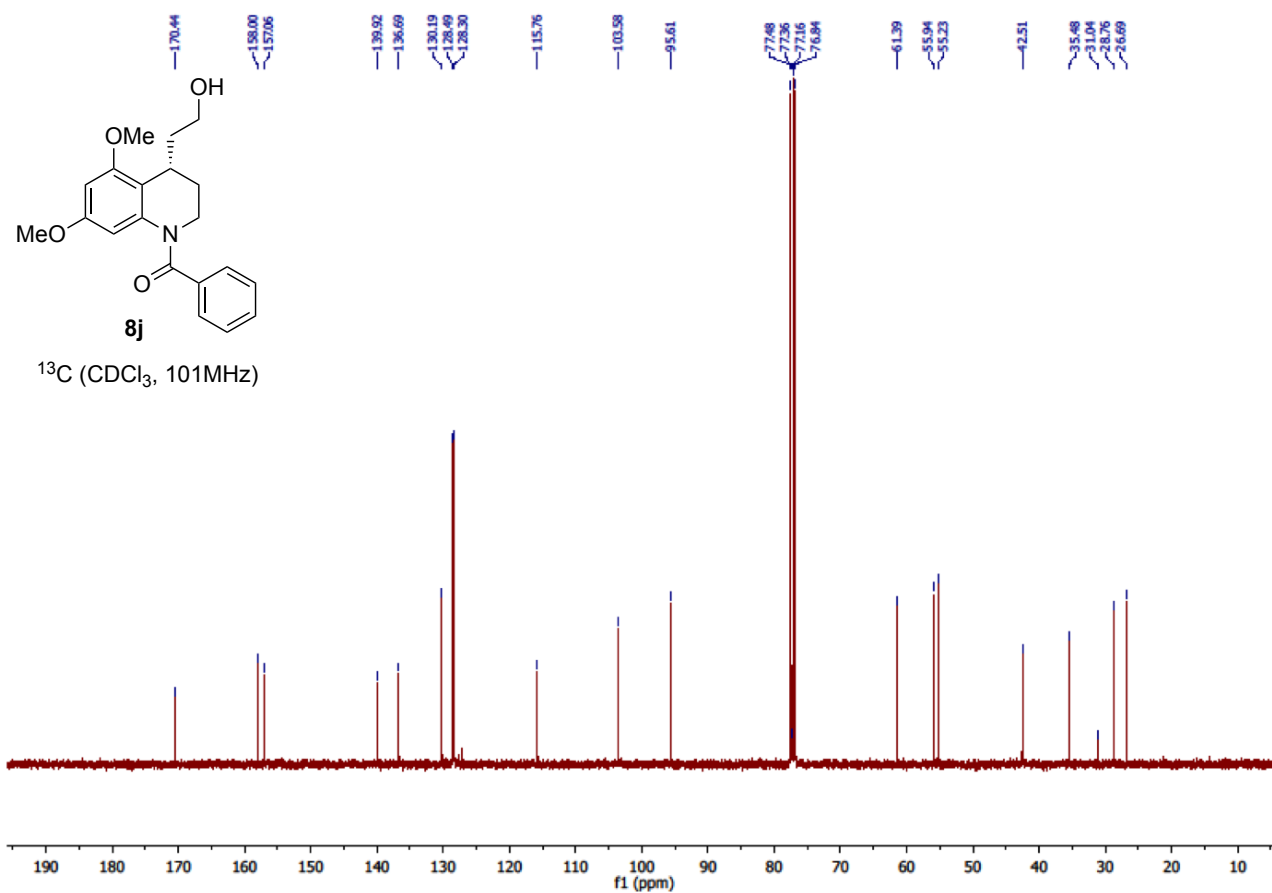
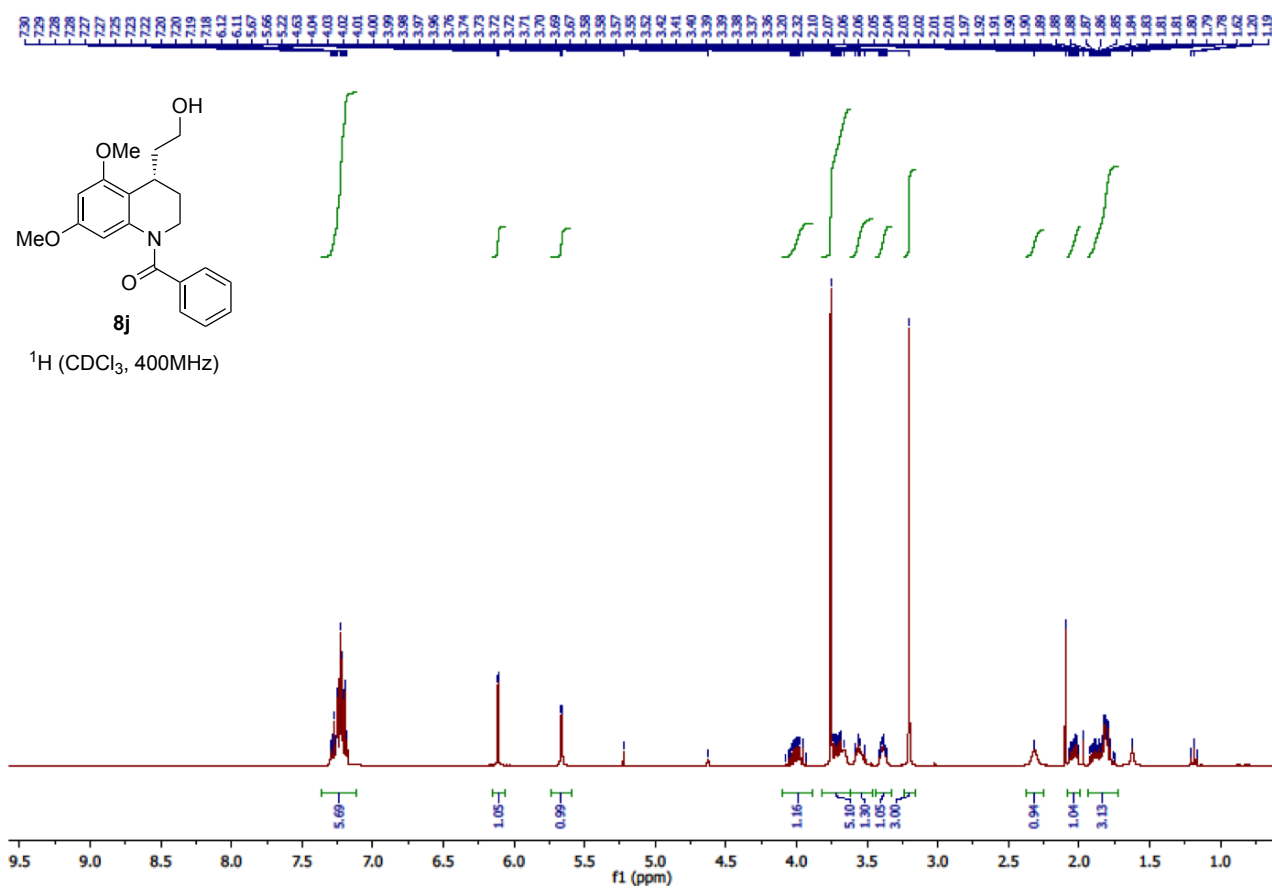


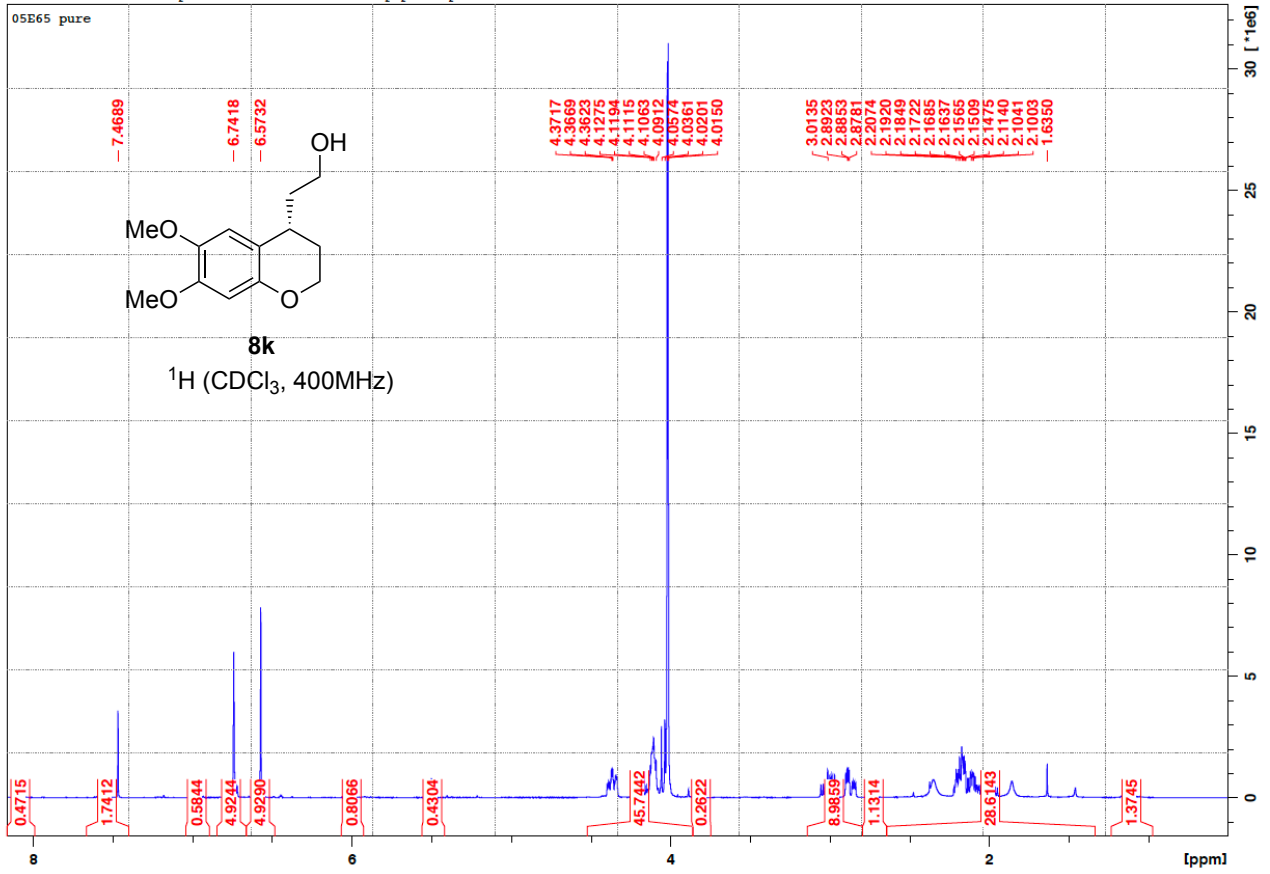


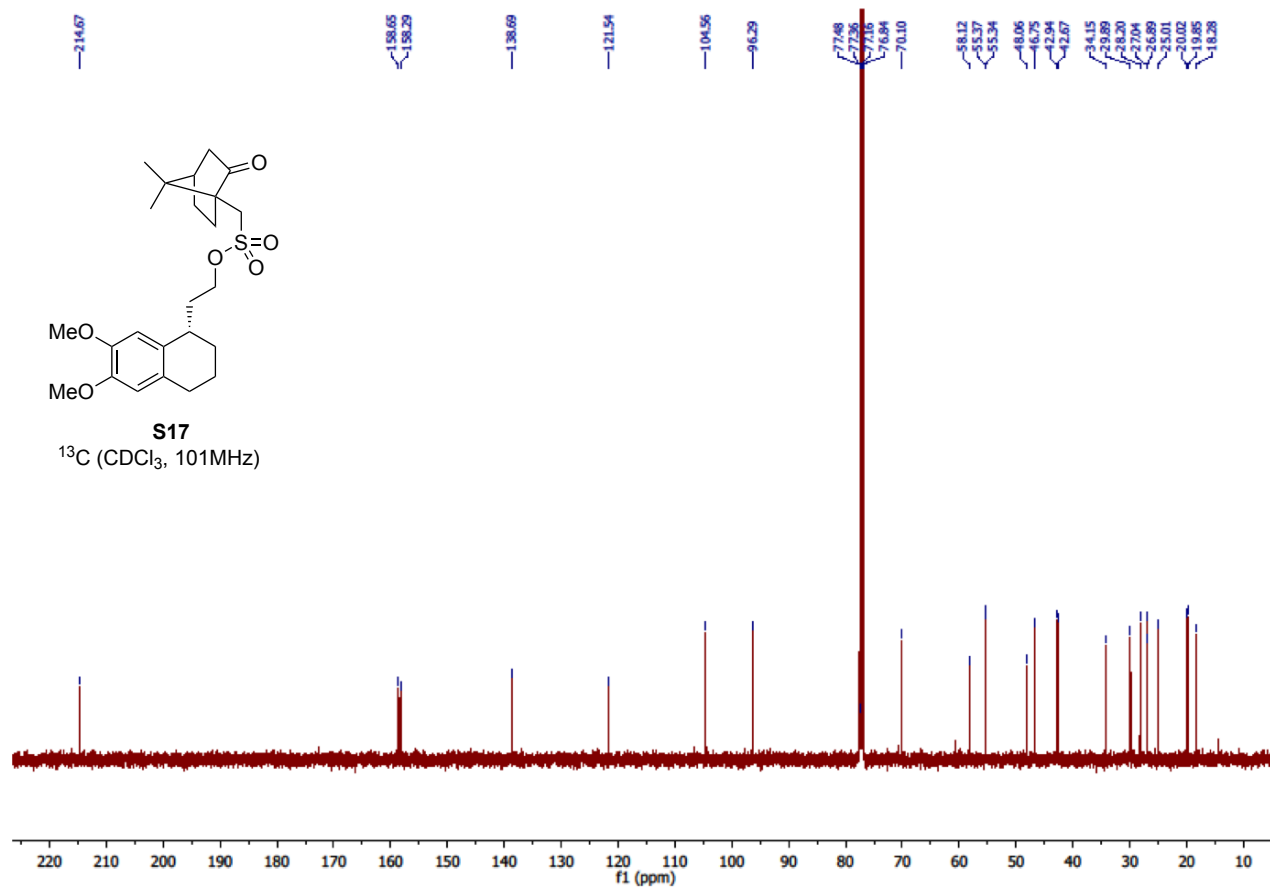
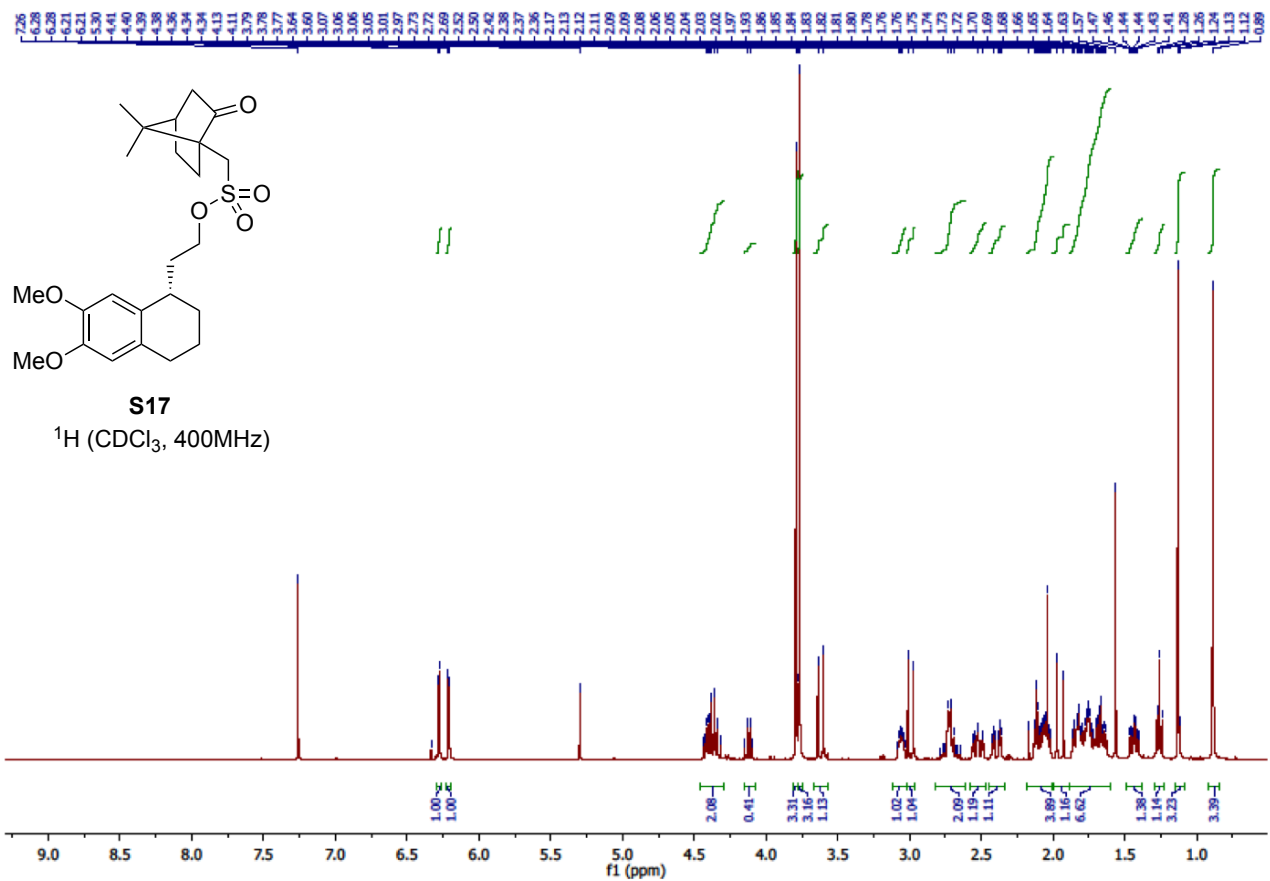


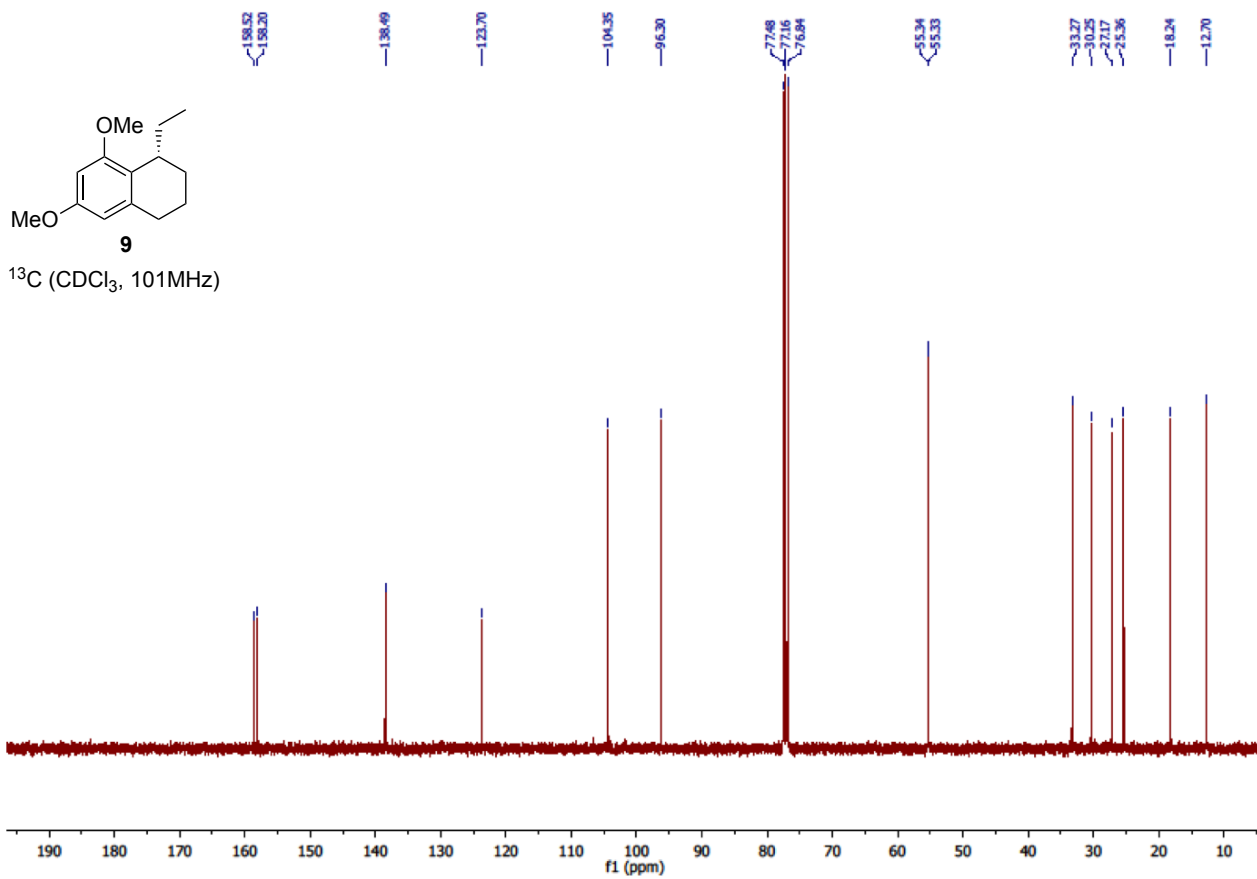
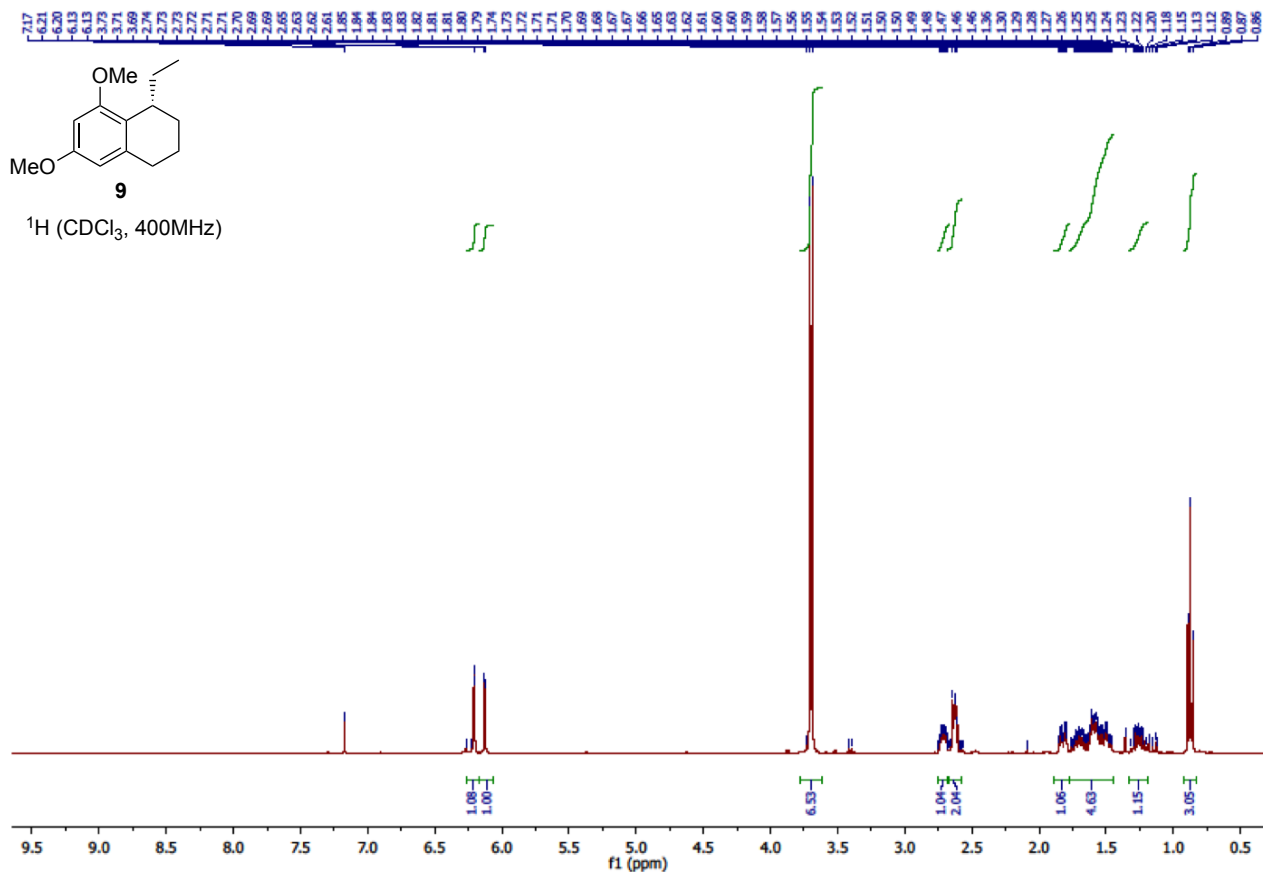


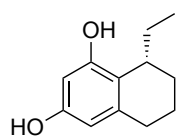






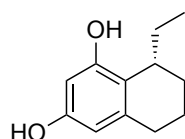
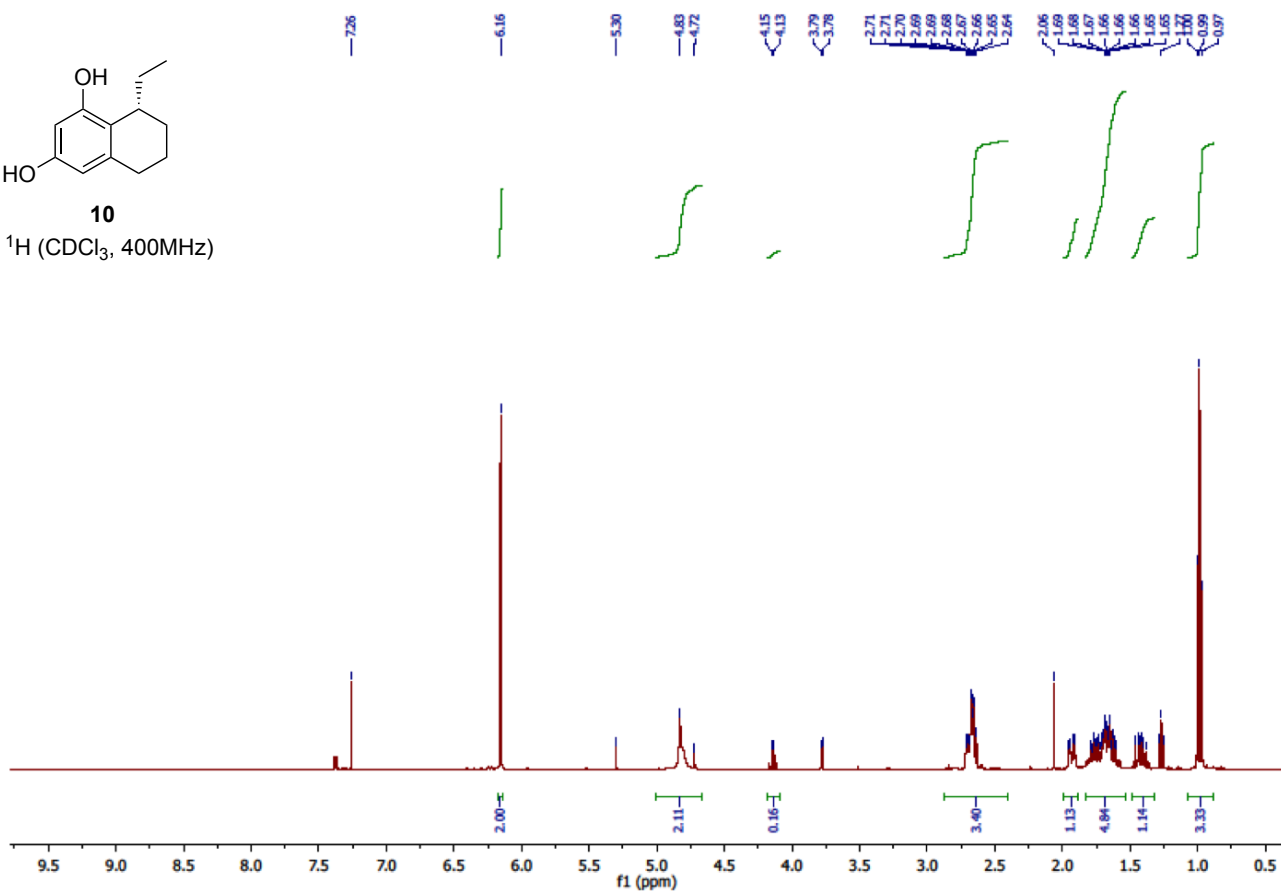






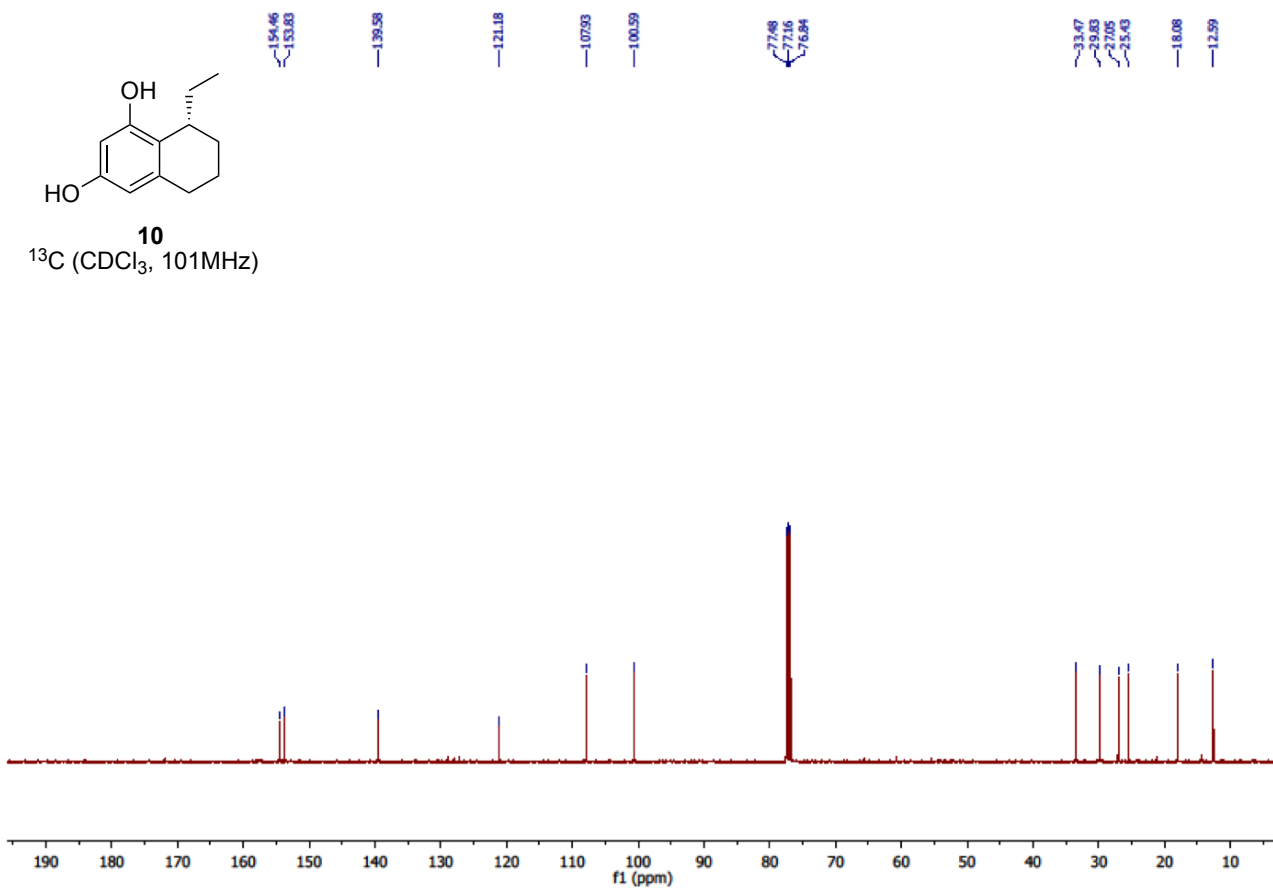
10

¹H (CDCl₃, 400MHz)

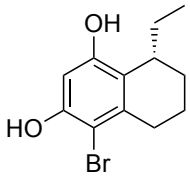


10

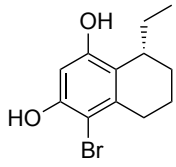
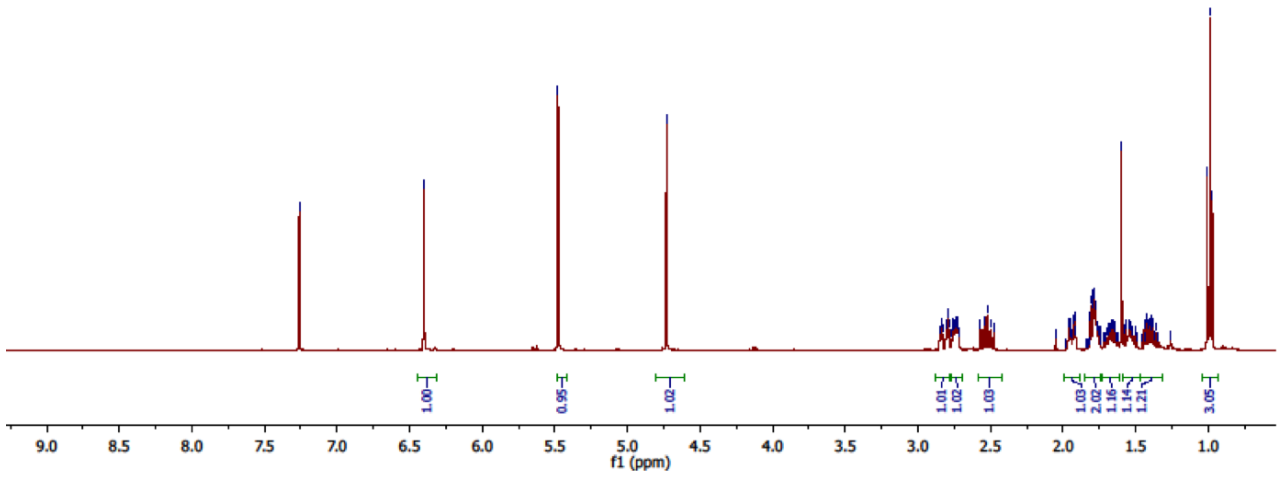
¹³C (CDCl₃, 101MHz)



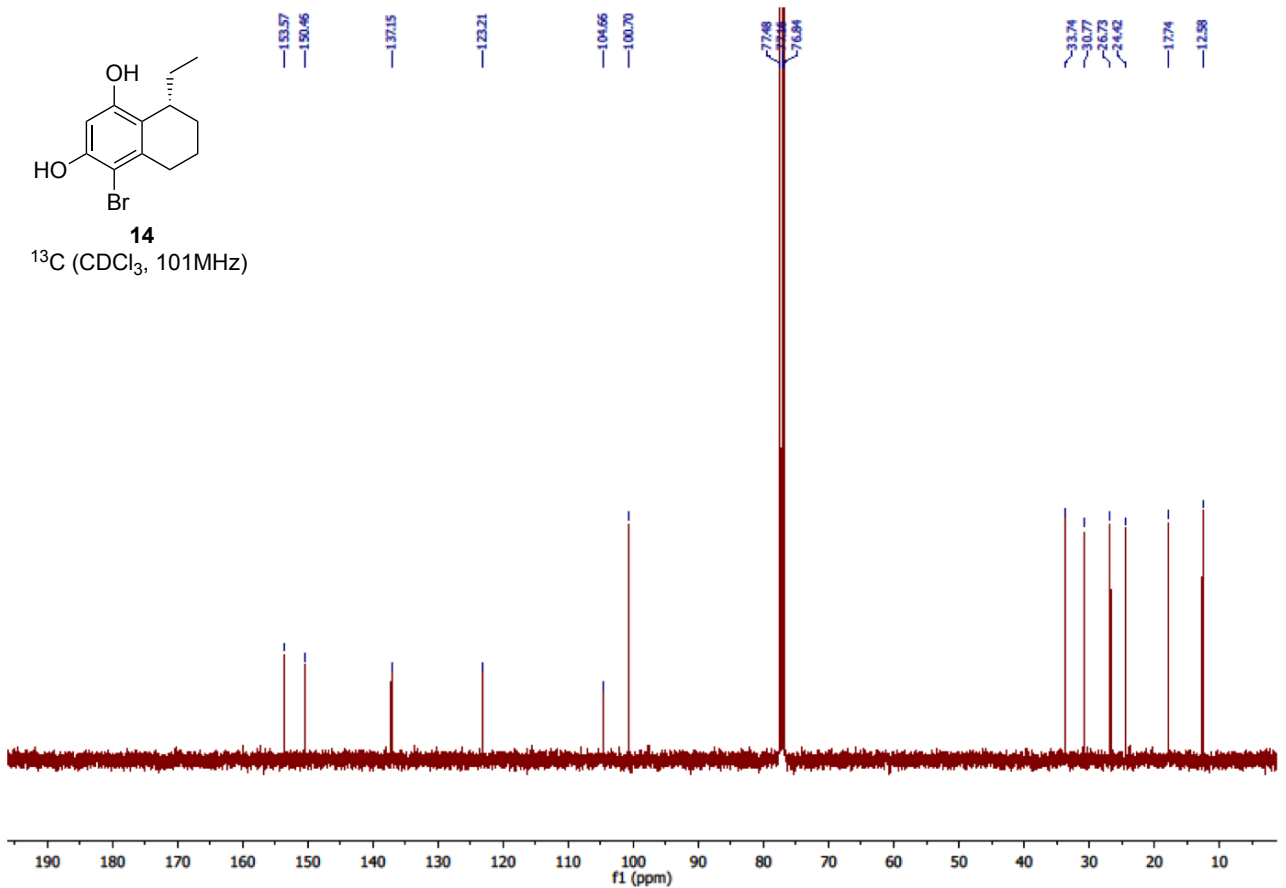
7.26 6.40 5.48 4.73 2.85 2.84 2.83 2.80 2.79 2.78 2.77 2.76 2.75 2.74 2.73 2.72 2.71 2.57 2.54 2.52 2.50 2.48 2.05 1.96 1.95 1.93 1.92 1.91 1.82 1.81 1.80 1.79 1.78 1.77 1.76 1.75 1.74 1.72 1.71 1.70 1.69 1.68 1.67 1.66 1.66 1.65 1.64 1.64 1.63 1.62 1.60 1.58 1.58 1.55 1.53 1.52 1.52 1.50 1.49 1.46 1.44 1.43 1.42 1.41 1.41 1.40 1.39 1.38 1.38 1.37 1.36 1.34 1.26 1.01 0.99 0.97

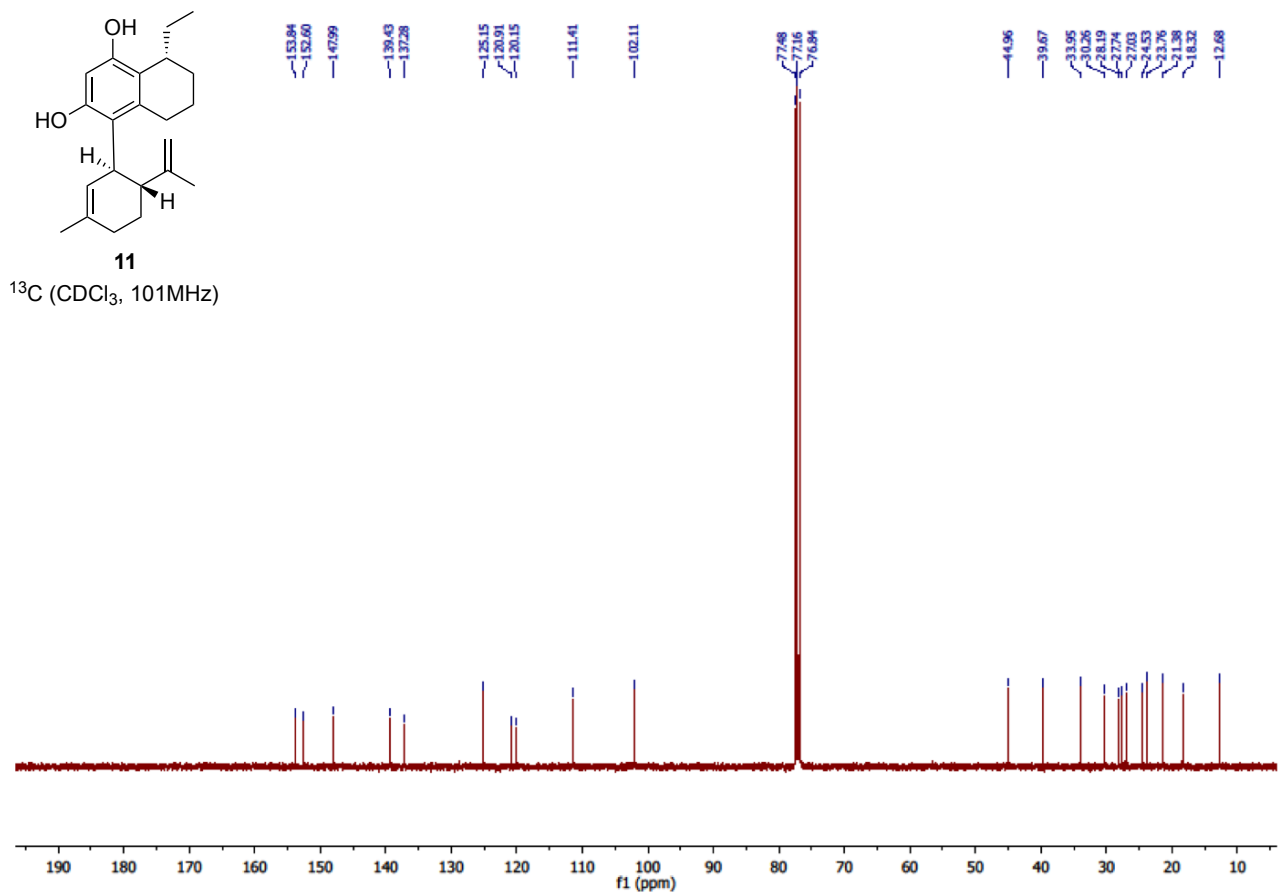
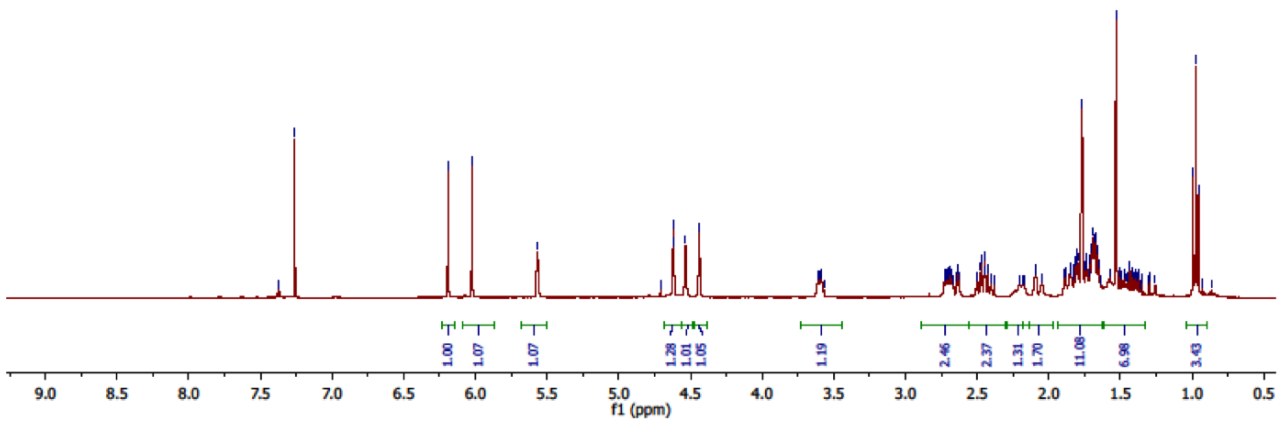


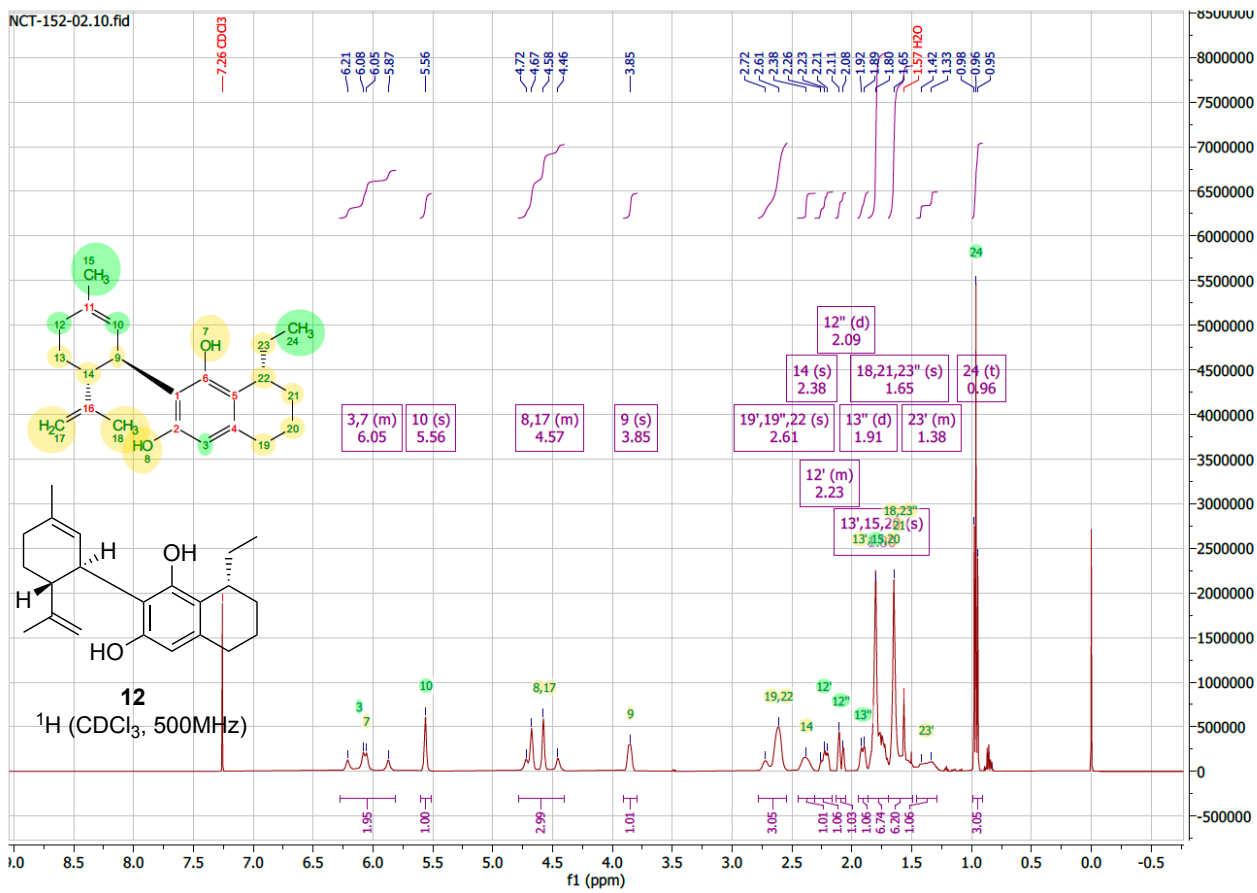
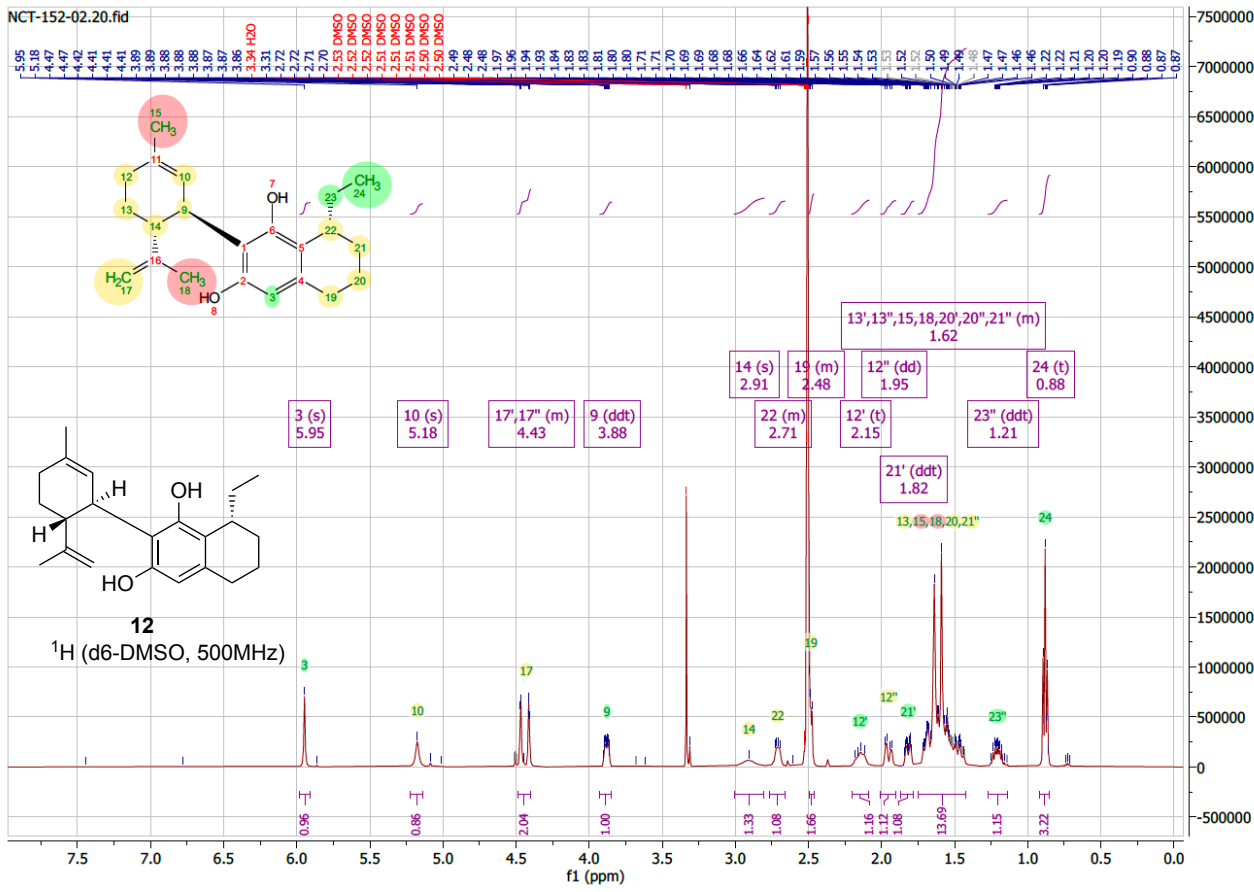
14
 ^1H (CDCl_3 , 400MHz)

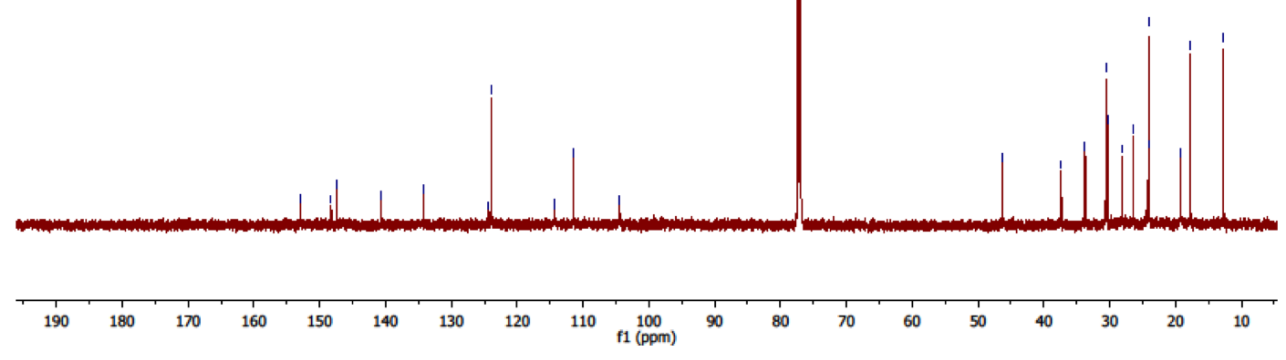
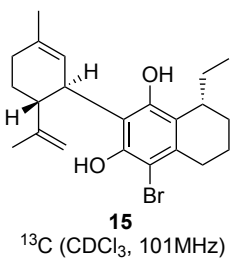
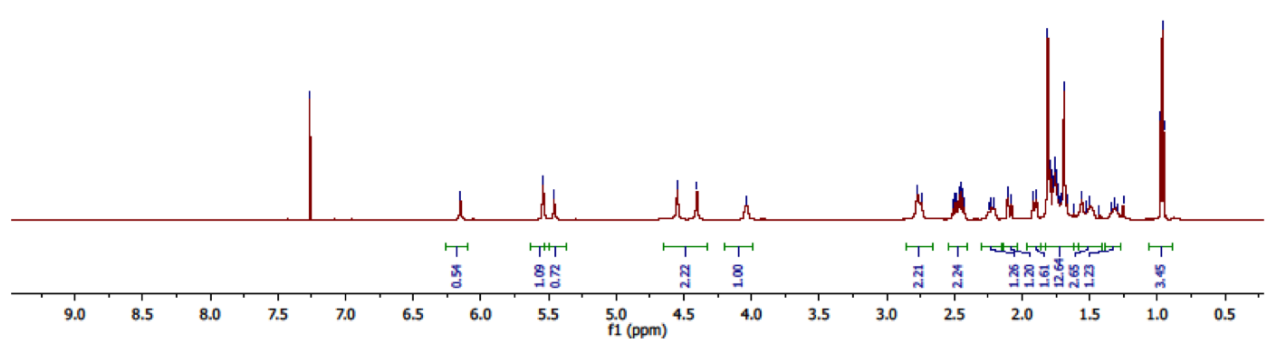
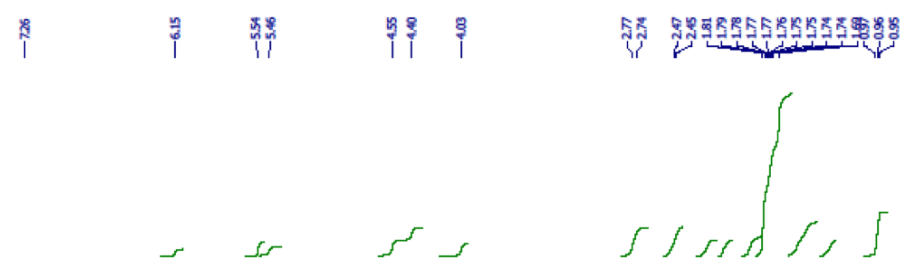
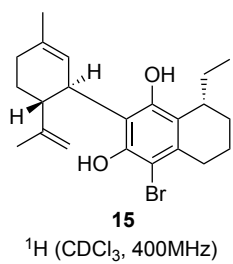


14
 ^{13}C (CDCl_3 , 101MHz)









8. XRD CheckCIF Data of Compound 17

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) LB0637

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. [CIF dictionary](#) [Interpreting this report](#)

Datablock: LB0637

Bond precision: C-C = 0.0068 Å Wavelength=0.71073
Cell: a=9.2254(3) b=9.4586(3) c=12.0829(4)
 alpha=90 beta=110.572(4) gamma=90
Temperature: 150 K

	Calculated	Reported
Volume	987.11(6)	987.11(6)
Space group	P 21	P 1 21 1
Hall group	P 2yb	P 2yb
Moiety formula	C22 H29 Br O2	C22 H29 Br O2
Sum formula	C22 H29 Br O2	C22 H29 Br O2
Mr	405.35	405.36
Dx, g cm ⁻³	1.364	1.364
Z	2	2
Mu (mm ⁻¹)	2.094	2.094
F000	424.0	424.0
F000'	423.58	
h,k,lmax	12,13,16	12,12,16
Nref	5363[2835]	4558
Tmin,Tmax	0.951,0.979	0.881,1.000
Tmin'	0.901	

Correction method= # Reported T Limits: Tmin=0.881 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 1.61/0.85 Theta(max)= 29.245

R(reflections)= 0.0412(4058) wR2(reflections)= 0.0827(4558)

S = 1.033 Npar= 231

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
 Click on the hyperlinks for more details of the test.

Alert level B

[PLAT420 ALERT 2 B](#) D-H Bond Without Acceptor 01 --H1 . Please Check

Author Response: H atom orientation obtained from electron density, so we are confident that the orientation is correct

Alert level C

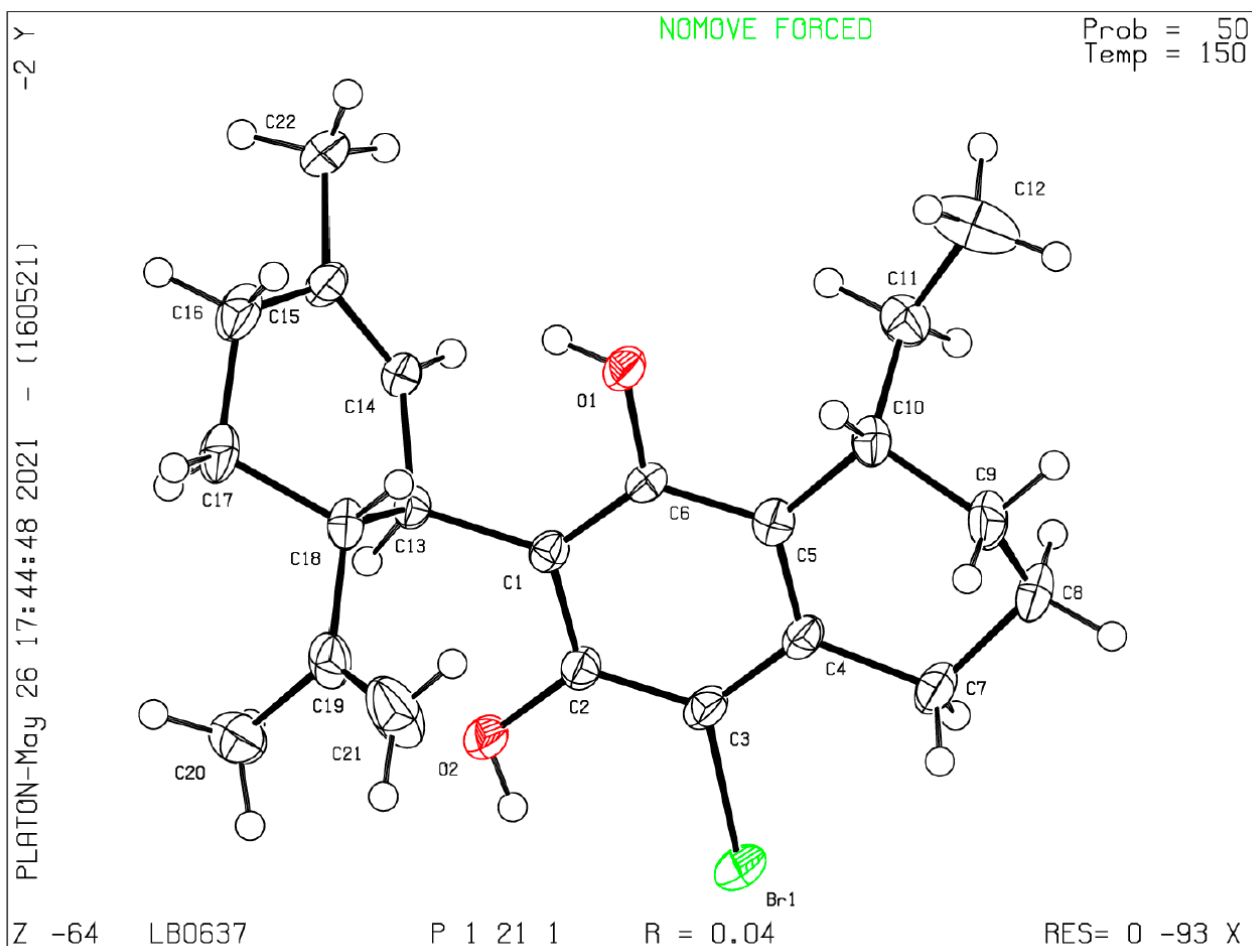
[PLAT220 ALERT 2 C](#) NonSolvent Resd 1 C Ueq(max)/Ueq(min) Range 3.2 Ratio
[PLAT341 ALERT 3 C](#) Low Bond Precision on C-C Bonds 0.00679 Ang.

Alert level G

[PLAT007 ALERT 5 G](#) Number of Unrefined Donor-H Atoms 2 Report
[PLAT380 ALERT 4 G](#) Incorrectly? Oriented X(sp2)-Methyl Moiety C22 Check
[PLAT791 ALERT 4 G](#) Model has Chirality at C10 (Sohnke SpGr) R Verify
[PLAT791 ALERT 4 G](#) Model has Chirality at C13 (Sohnke SpGr) S Verify
[PLAT791 ALERT 4 G](#) Model has Chirality at C18 (Sohnke SpGr) R Verify
[PLAT910 ALERT 3 G](#) Missing # of FCF Reflection(s) Below Theta(Min). 4 Note
[PLAT912 ALERT 4 G](#) Missing # of FCF Reflections Above STh/L= 0.600 299 Note
[PLAT941 ALERT 3 G](#) Average HKL Measurement Multiplicity 4.5 Low
[PLAT978 ALERT 2 G](#) Number C-C Bonds with Positive Residual Density. 0 Info

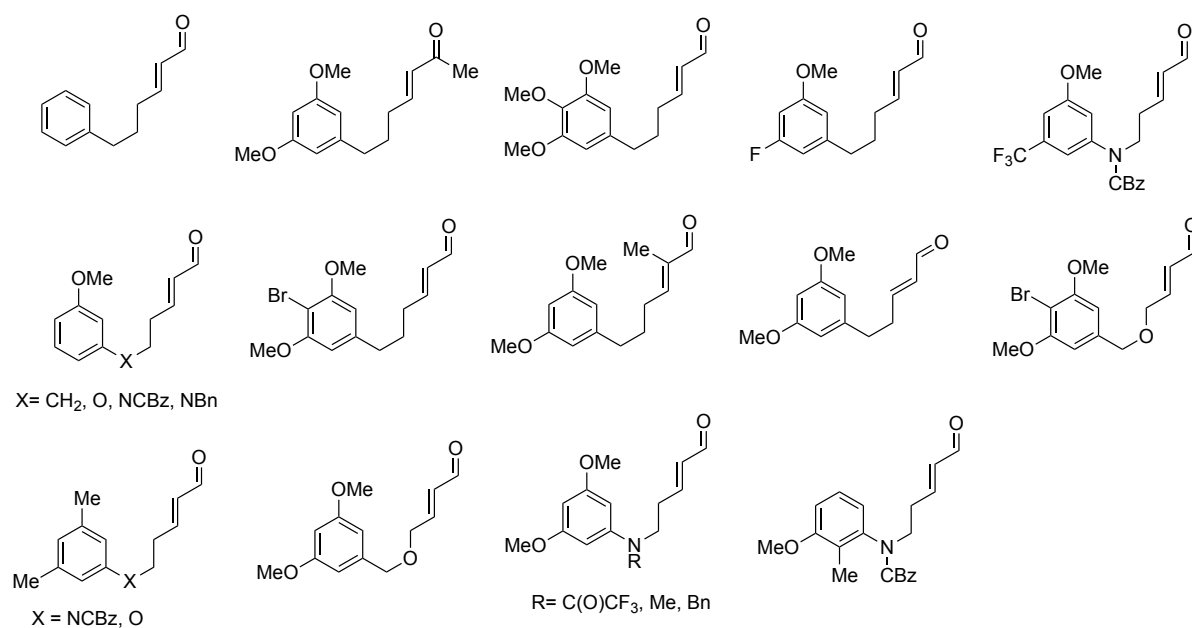
- 0 **ALERT level A** = Most likely a serious problem - resolve or explain
- 1 **ALERT level B** = A potentially serious problem, consider carefully
- 2 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
- 9 **ALERT level G** = General information/check it is not something unexpected

- 0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
- 3 ALERT type 2 Indicator that the structure model may be wrong or deficient
- 3 ALERT type 3 Indicator that the structure quality may be low
- 5 ALERT type 4 Improvement, methodology, query or suggestion
- 1 ALERT type 5 Informative message, check



9. Unsuccessful Substrates

In the interests of balance we present below the substrates that did not cyclize, or gave minimal product.



10. References

- Lee, D.; Chang, S. *Chem. Eur. J.* **2015**, *21*, 5364
- Mizukami, M.; Wada, K.; Sato, G.; Ishii, Y.; Kawahara, N.; Nagumo, S. *Tetrahedron*, **2013**, *69*, 4120