Supplementary Material (ESI) for Chemical Communications

Electronic Supplementary Information

Construction of Perhydro Indol-2-ones by a Methoxide Catalyzed Deacetylation / Michael / Aldol Cascade

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Contents

General Experimental

For all reactions conducted under anhydrous conditions glassware was dried in an oven at 100^{o}C and carried out under a nitrogen atmosphere, unless otherwise stated.

Solvents and Reagents

Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. Reagents used were obtained from commercial suppliers or purified according to standard procedures. Petrol refers to distilled light petroleum of fraction (40 – 65 °C). Anhydrous tetrahydrofuran and diethyl ether were freshly distilled from sodium-benzophenone.

Chromatography

Flash column chromatography was performed with commercial solvents using Merck Kieselgel 60 silica gel (200-400 mesh). Thin layer chromatography (TLC) was performed on aluminium or glass plates pre-coated with Merck Kieselgel 60 F254 and visualised by ultra-violet radiation or by staining with either aqueous basic potassium permanganate or vanillin. Enantiomeric excesses were determined using high performance liquid chromatography (HPLC) performed on a Hewlett-Packard Series 1050 series system (column conditions are given with the compound).

Melting Points

Melting points were recorded on a Gallenkamp melting point apparatus with the sample contained in a thin glass tube at ambient pressure and are uncorrected.

Infra-Red Spectroscopy

Infrared spectra were recorded on a Perkin Elmer Spectrum RX1 FTIR spectrometer (thin film deposited onto a sodium chloride plate). Only selected absorbencies (ν_{max}) are reported.

NMR Spectroscopy

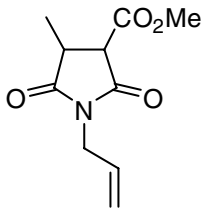
^{1}H, ^{13}C, DEPT, COSY and HMQC NMR spectra were recorded on Bruker 500, 400 MHz and Varian 300 MHz spectrometers. Chemical shifts (δ_H) are quoted in parts per million (ppm + 0.01 ppm) downfield of tetramethylsilane, relative to the residual protiosolvent (δ_H (C**H**Cl$_3$) = 7.26 ppm) against an internal deuterium lock. Coupling constants (*J*) are given in Hertz (Hz + 0.1 Hz). The ^{1}H NMR spectra are reported as follows: δ / ppm (multiplicity, number of protons, coupling constants *J* / Hz, assignment). DEPT and two-dimensional NMR

spectroscopy (COSY and HMQC) were used where appropriate to assist the assignment of the signals in the ^{1}H NMR and ^{13}C NMR spectra.

Mass Spectrometry

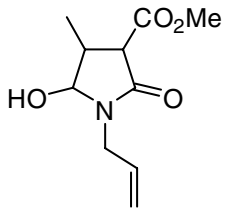
Low resolution mass spectrometry (electron impact / chemical ionisation) was recorded on a Micromass Trio 2000 quadropole mass spectrometer and (electrospray) on a Micromass Platform II spectrometer. High resolution mass spectra (accurate mass) were recorded on a Thermo Finnigan Mat95XP mass spectrometer.

(±)-Methyl-1-allyl-4-methyl-2,5-dioxopyrrolidine-3-carboxylate 5:



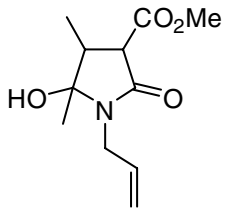
To a stirred solution of 1-allyl-3-methylpyrrolidine-2,5-dione[1] (1.03 g, 6.73 mmol) and methyl chloroformate (1.27 mL, 13.5 mmol) in dry tetrahydrofuran (10 mL) was added a 1.6 M solution of lithium hexamethyldisilazane (8.4 mL, 13.5 mmol) dropwise at −78 °C. The reaction was stirred at −78 °C until complete consumption of starting material occurred (approx. 30 minutes). The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride solution (5 mL) and allowed to warm to room temperature. The reaction mixture was partitioned between dichloromethane (50 mL) and distilled water (50 mL). The layers were separated and the aqueous layer further extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with brine (1 × 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product. Purification by column chromatography [SiO_2, Et_2O–light petroleum ether (1:1-3:1)] afforded **5** (1.2 g, 86%) as a colourless oil. **IR** ν_{max} (oil): 2959 (CH), 1785 (C=O), 1735 (C=O) and 1702 (C=O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.79-5.66 (m, 1H, NCH_2CHCH_2), 5.19-5.06 (m, 2H, NCH_2CHCH_2), 4.06 (m, 2H, NCH_2CHCH_2), 3.78 (s, 3H, CO_2CH_{3major}), 3.76 (s, 3H, CO_2CH_{3minor}), 3.37 (d, 1H, *J* 5.4Hz, $CHCO_2Me$), 3.22-3.14 (m, 1H, $CHCH_{3major}$), 3.14-3.08 (m, 1H, $CHCH_{3minor}$), 1.35 (d, 3H, *J* 7.5Hz, $CHCH_{3major}$), 1.24 (d, 3H, *J* 7.5Hz, $CHCH_{3minor}$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 177.9 ($C{=}O_{major}$), 177.7 ($C{=}O_{minor}$), 171.8 ($C{=}O_{minor}$), 170.9 ($C{=}O_{major}$), 168.0 ($C{=}O_{major}$), 167.3 ($C{=}O_{minor}$), 130.0 (allyl-*C*), 118.4 (allyl-C_{major}), 118.1 (allyl-C_{minor}), 54.1 (CO_2CH_{3major}), 53.2 ($CHCO_2Me_{major}$), 52.5(CO_2CH_{3minor}), 51.2 ($CHCO_2Me_{minor}$), 41.3 (allyl-C_{major}), 41.2 (allyl-C_{minor}), 39.1 ($CHCH_{3major}$), 37.4 ($CHCH_{3minor}$), 15.4 ($CHCH_{3major}$) and 11.1 ($CHCH_{3minor}$); **MS** ***m/z*** (ES+): 234.2 ($[M+Na]^+$); **HRMS** Found $[M+Na]^+$ 234.0735 ($C_{10}H_{13}O_4NNa$) requires (M) 234.0737.

(±)-Methyl 1-allyl-5-hydroxy-4-methyl-2-oxopyrrolidine-3-carboxylate 2a:



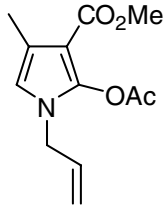
A solution of **5** (2.0 g, 9.48 mmol) in dry tetrahydrofuran (80 mL) was added dropwise *via* cannula to a stirred suspension of sodium hydride (0.228 g, 9.48 mmol) in dry tetrahydrofuran (80 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 min and then cooled to −78 °C before di*iso*butylaluminium hydride (1.0 M solution in cyclohexane, 19.9 mL, 19.9 mmol) was added dropwise. The solution was stirred for 1 h at −78 °C, followed by quenching with addition of a saturated solution of sodium potassium tartrate (20 mL). The reaction mixture was stirred at room temperature until the two layers were clearly visible. The layers were separated and the aqueous layer extracted with dichloromethane (2 × 100 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by column chromatography [SiO_2, EtOAc–light petroleum ether (1:1-3:1)] to afford **2a** (1.43 g, 6.71 mmol, 71%) as a colourless oil. **IR** ν_{max} (oil): 3369 (OH), 2958 (CH), 1741 (C=O), 1681 (C=O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.74 (ddt, 1H, *J* 17.1Hz, 10.1Hz, and 5.3Hz, NCH_2CHCH_2), 5.21 (dddd, 2H, *J* 12.6Hz, 10.1Hz, 2.7Hz and 1.3Hz, NCH_2CHCH_2), 5.11 (t, 1H, *J* 5.8Hz, C*H*OH), 4.17 (td, 2H, *J* 5.3Hz and 1.6Hz, NCH_2CHCH_2), 3.8 (s, 3H, OCH_3), 3.27 (d, 1H, *J* 10.4Hz, C=OC*H*CO_2Me), 2.8 (dqd, 1H, *J* 10.2Hz, 7.0Hz and 5.8Hz, C*H*CH_3), 2.38 (d, 1H, *J* 5.9Hz, O*H*), 1.18 (d, 3H, *J* 7.0Hz, $CHCH_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 170.0 (*C*=O), 169.9 (*C*=O), 132.4 (allyl-*C*), 118.6 (allyl-*C*), 82.9 (*C*HOH), 53.5 (*C*HCO_2Me), 52.7 (CO_2CH_3), 43.3(*C*HCH_3), 37.3 (allyl-*C*), 12.7 (CH*C*H_3); **MS *m/z*** (ES+): 236 ($[M+Na]^+$). **HRMS** Found $[M+Na]^+$ 236.1003 ($C_{10}H_{15}O_4NNa$) requires (M) 236.1001.

(±)-Methyl 1-allyl-5-hydroxy-4,5-dimethyl-2-oxopyrrolidine-3-carboxylate 2b:



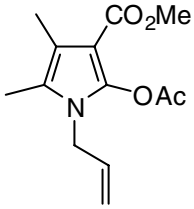
A solution of **5** (2.9 g, 14.0 mmol) in dry tetrahydrofuran (115 mL) was added dropwise *via* cannula to a stirred suspension of sodium hydride (0.56 g, 14.0 mmol) in dry tetrahydrofuran (115 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 min and then cooled to −78 °C before methylmagnesium bromide (3.0 M solution in diethyl ether, 21.0 mL, 63.0 mmol) was added dropwise. The solution was warmed to room temperature and stirred for a further 2 hours. The reaction mixture was quenched by addition of a saturated solution of ammonium chloride (1 × 50 mL). The layers were separated and the aqueous layer extracted with dichloromethane (2 × 100 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by column chromatography [SiO_2, EtOAc–light petroleum ether (1:1-3:1)] to afford **2b** (1.90 g, 8.37 mmol, 60%) as a colourless oil. **IR** ν_{max} (oil); 3600-3200 (OH), 1742 (C=O), 1690 (C=O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.84 (ddt, 1H, *J* 17.1Hz, 10.6Hz and 5.9Hz, NCH_2CHCH_2), 5.22 (d, 1H, *J* 17.1Hz, 1 of NCH_2CHCH_2), 5.15 (d, 1H, *J* 10.6Hz, 1 of NCH_2CHCH_2), 3.82-3.97 (m, 2H, NCH_2CHCH_2), 3.79 (s, 3H, CO_2CH_3), 3.30 (d, 1H, *J* 10.7Hz, $CHCO_2Me$), 3.02-2.78 (br. s, 1H, OH), 2.57 (dq, 1H, *J* 10.7Hz and 6.9Hz, $CHCH_3$), 1.51 (s, 3H, CCH_3), 1.14 (d, 1H, *J* 6.9Hz, $CHCH_3$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 170.1 (*C*=O), 170.0 (*C*=O), 134.0 (allyl-*C*), 117.3 (allyl-*C*), 89.8 (quaternary-*C*), 53.6 ($CHCO_2Me$), 52.7 (CO_2CH_3), 42.8 ($CHCH_3$), 42.1 (allyl-*C*), 24.7 (CCH_3) and 11.9 ($CHCH_3$); **MS *m/z*** (ES+): 250.3 ($[M+Na]^+$); **HRMS** Found $[M+Na]^+$ 250.1054 ($C_{11}H_{17}O_4NNa$) requires (M) 250.1050.

Methyl 2-acetoxy-1-allyl-4-methyl-1H-pyrrole-3-carboxylate 6a:



Pyridine (2.20 mL, 28.2 mmol) and acetic anhydride (1.40 mL, 14.1 mmol) were added to a stirred solution of **2a** (0.200 g, 0.94 mmol) in dry tetrahydrofuran (15 mL). The reaction mixture was refluxed for 3 days and then allowed to cool to room temperature. The reaction mixture was quenched by addition of a saturated aqueous copper sulfate solution (15 mL). The organic layer was washed further with another portion of saturated aqueous copper sulfate solution (15 mL), followed by saturated sodium hydrogen carbonate solution (15 mL). The layers were separated and the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography [SiO_2, Et_2O–light petroleum ether (1:1)] gave a yellow oil, which was titurated with light petroleum ether to afford **6a** (151 mg, 68%) as an off-white solid; **m.p.** 59-61 °C. **IR** ν_{max}(solid) 2950 (CH), 1787 (C=O), 1702 (C=O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 6.15 (s, 1H, pyrrole-*H*), 5.82 (ddt, 1H, *J* 16.5Hz, 10.2Hz and 5.6Hz, NCH_2CHCH_2), 5.19 (d, 1H, *J* 10.2Hz, 1 of NCH_2CHCH_2), 5.11 (d, 1H, *J* 16.5Hz, 1 of NCH_2CHCH_2), 4.23 (d, 2H, *J* 5.6Hz, NCH_2CHCH_2), 3.74 (s, 3H, CO_2CH_3), 2.32 (s, 3H, acetate-CH_3) and 2.19 (s, 3H, 4-CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 168.4 (*C*=O), 164.4 (*C*=O), 139.4 (pyrrole-*C*), 132.5 (allyl-*C*), 119.1 (pyrrole-*C*), 118.0 (allyl-*C*), 113.9 (pyrrole-*C*), 101.1 (pyrrole-*C*), 50.6 (CO_2CH_3), 47.4 (allyl-*C*), 20.4 (acetate-CH_3) and 12.6 (4-CH_3); **MS *m/z*** (CI+): 260 ($[M+Na]^+$); **HRMS** Found $[M+H]^+$ 238.1067 ($C_{12}H_{16}O_4N$) requires (M) 238.1074. Analysis calculated for $C_{12}H_{16}O_4N$: C, 60.75; H, 6.37; N, 5.90; O, 26.98. Found: C, 60.23; H, 6.22; N, 5.75.

Methyl 2-acetoxy-1-allyl-4,5-dimethyl-1H-pyrrole-3-carboxylate 6b:

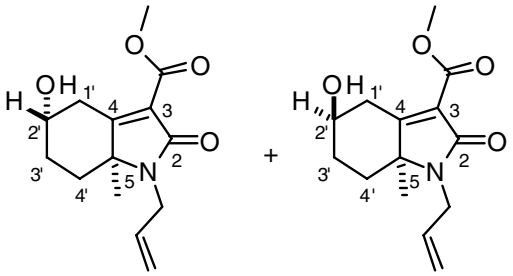


Pyridine (13.0 mL, 0.16 mol) and acetic anhydride (7.60 mL, 0.81 mol) were added to a stirred solution of **2b** (1.22 g, 5.37 mmol) in dry tetrahydrofuran (88 mL). The reaction mixture was refluxed for 3 days and then allowed to cool to room temperature. The reaction mixture was quenched by addition of a saturated aqueous copper sulfate solution (50 mL). The organic layer was washed further with another portion of saturated aqueous copper sulfate solution (50 mL), followed by saturated sodium hydrogen carbonate solution (50 mL). The layers were separated and the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography [SiO_2, Et_2O–light petroleum ether (4:6)] gave a yellow oil, which was triturated with light petroleum ether to afford **6b** (569 mg, 45%) as an off-white solid; **m.p.** 51-54 °C. **IR** ν_{max}(solid) 3085, 2985, 2950 (CH), 1788 (C=O), 1690 (C=O); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ_H 5.78 (ddt, 1H, *J* 17.0Hz, 10.1Hz and 4.8Hz, NCH_2CHCH_2), 5.14 (d, 1H, *J* 10.1Hz, 1 of NCH_2CHCH_2), 4.92 (d, 1H, *J* 17.0Hz, 1 of NCH_2CHCH_2), 4.28-4.25 (m, 2H, NCH_2CHCH_2), 3.73 (s, 3H, CO_2CH_3), 2.32 (s, 3H, acetate-CH_3), 2.16 (s, 3H, 5-CH_3) and 2.04 (s, 3H, 4-CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 168.8 (*C*=O), 164.6 (*C*=O), 138.7 (pyrrole-*C*), 132.5 (allyl-*C*), 120.3 (pyrrole-*C*), 116.8 (allyl-*C*), 114.3 (pyrrole-*C*), 100.1 (pyrrole-*C*), 50.6 (CO_2CH_3), 44.5 (allyl-*C*), 20.5 (acetate-CH_3), 10.8 (5-CH_3) and 8.9 (4-CH_3); **MS *m/z*** (CI+): 252 ($[M+H]^+$); **HRMS** Found $[M+H]^+$ 252.1223 ($C_{13}H_{18}O_4N$) requires (M) 252.1230. Analysis calculated for $C_{13}H_{18}O_4N$: C, 62.14; H, 6.82; N, 5.57. Found: C, 61.97; H, 7.55; N, 5.60.

General Procedure A for the Michael−Aldol Reaction

To a stirred solution of **6b** (1.5 equiv.) in MeOH (0.2 M) was added an α,β-unsaturated ketone (1.0 equiv.) and K_2CO_3 (0.2 equiv.) at room temperature. The reaction was stirred until t.l.c analysis showed complete consumption of starting material (approx. between 0.5 and 12 hours). The reaction was quenched by addition of acetic acid (0.4 equiv.) and concentrated *in vacuo*. Purification by column chromatography [SiO_2, Et_2O (100%)] gave the Michael−Aldol product as a yellow oil.

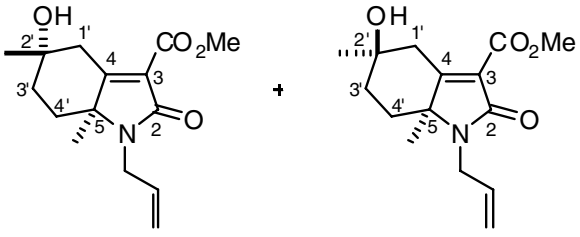
(±)-Methyl 1-allyl-5-hydroxy-7a-methyl-2-oxo-2,4,5,6,7,7a-hexahydro-1H-indole-3-carboxylate 8a,b



a b

Following general procedure A the reaction was carried out on a 0.27 mmol scale to give **8** (50 mg, 71%) as a 1:1 mixture of diastereoisomers. **IR** ν_{max}(oil) 3387 (OH), 2920 (CH), 1741, (C=O), 1680 (C=O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.82 (m, 1H, NCH_2CHCH_2), 5.21 (d, 1H, *J* 17.2Hz, 1 of NCH_2CHCH_2), 5.12 (d, 1H, *J* 10.0Hz, 1 of NCH_2CHCH_2), 4.40 (br-s, 1H, O*H*), 4.11 (dd, 1H, *J* 15.8Hz and 5.8Hz, $NCH_AH_BCHCH_2$), 3.92 (dd, 1H, *J* 15.9Hz and 6.4Hz, $NCH_AH_BCHCH_2$), 3.85 (s, 3H, CO_2CH_3), 3.75-3.72 (m, 1H, b-1'-CH_AH_B), 3.7 (dt, 1H, *J* 14.2Hz and 2.6, a-1'-CH_AH_B), 3.4-3.28 (m, 1H, 2'-C*H*OH), 2.48 (dd, 1H, *J* 14.2Hz and3.2 Hz, a-1'-CH_AH_B), 2.30 (dd, 1H, *J* 10.9Hz, *J* 12.6Hz, b-1'-CH_AH_B), 2.20-2.15 (m, 1H, 1 of b-3'-CH_2), 2.02-2.04 (m, 1H, a-1 of 3'-CH_2), 2.03-1.97 (m 1H, b-1 of 3'-CH_2), 1.9-1.66 (m, 3H, 1 of a-3'-CH_2 and a-4'-CH_2 and 1 of b-4'-CH_2), 1.64-1.54 (m, 1H, 1 of b-4'-CH_2), 1.37 (s, 3H, a-5-CH_3), 1.33 (s, 3H, b-5-CH_3); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 171.5 (2-C=O), 171.1 (2-C=O), 165.5 (C=O), 165.5 (C=O), 163.8 (quat. C=C), 163.3 (quat. C=C), 134.6 ($HC=CH_2$), 134.4 ($HC=CH_2$), 124.0 (quat. C=C), 121.9 (quat. C=C), 117.3 ($HC=CH_2$), 117.1 ($HC=CH_2$), 71.7 (2'-OH), 68.7 (2'-OH), 64.0 (5-C), 63.5 (5-C), 52.0 (OCH_3), 52.0 (OCH_3), 42.1, 42.0, 35.0, 34.7, 33.0, 30.4, 29.7, 28.4, 21.1, 20.4; **MS** *m/z* (ES+): 266 ($[M+H]^+$); **HRMS** Found $[M+H]^+$ 266.1385 ($C_{14}H_{20}O_4N$) requires (M) 266.1387.

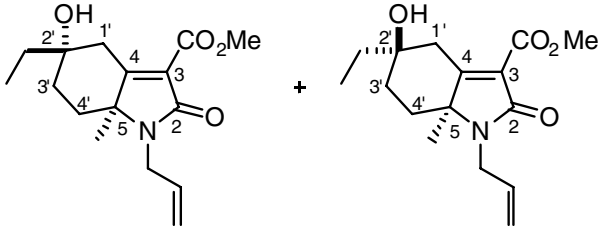
(±)-Methyl-1-allyl-5-hydroxy-5,7a-dimethyl-2-oxo-2,4,5,6,7,7a-hexahydro-1H-indole-3-carboxylate 7a,b:



major minor

Following general procedure A the reaction was carried out on a 0.27 mmol scale to give **7** (55 mg, 74%) as a 2:1 mixture of diastereoisomers. **IR** ν_{max} (oil) 3550-3200 (OH), 2950 (CH), 1759 (C=O), 1690 (C=O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.86-5.77 (m, 1H, NCH_2CHCH_2), 5.20 (d, 1H, *J* 17.1Hz, 1 of NCH_2CHCH_2), 5.11 (d, 1H, *J* 10.1Hz, 1 of NCH_2CHCH_2), 4.10 (dd, 1H, *J* 15.6Hz and 6.6Hz, $NCH_AH_BCHCH_2$), 3.89 (dd, 1H, *J* 15.6Hz and 6.6Hz, $NCH_AH_BCHCH_2$), 3.84 (s, 3H, CO_2CH_3), 3.61 (d, 1H, *J* 12.8Hz, 1'-CH_AH_{Bmajor}), 3.54 (d, 1H, *J* 13.9Hz, 1'-CH_AH_{Bminor}), 2.47 (d, 1H, *J* 12.8Hz, 1'-CH_AH_{Bmajor}), 2.34 (d, 1H, *J* 13.9Hz, 1'-CH_AH_{Bminor}), 2.12 (dt, 1H, *J* 13.3Hz and 2.9Hz, 3'-CH_AH_{Bmajor}), 2.04-2.00 (m, 1H, 3'-CH_AH_{Bminor}), 1.82 (dt, 1H, *J* 14.1Hz, 4.1Hz, 4'-CH_AH_B), 1.76-1.66 (m, 1H, 4'-CH_AH_B), 1.40 (s, 3H, 2'-CH_{3minor}), 1.37 (s, 3H, 5-CH_{3major}), 1.31 (s, 3H, 5-CH_{3minor}), 1.28-1.22 (m, 1H, 3'-CH_AH_B), 1.12 (s, 3H, 2'-CH_{3major}); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 172.6 (*3-C*), 172.0 (*4-C*), 165.6 (C=O_{major}), 165.5(C=O_{minor}), 163.8 (CO_2CH_{3minor}), 163.1(CO_2CH_{3major}), 134.4 (allyl-C_{minor}), 134.3 (allyl-C_{major}), 117.2 (allyl-C_{major}), 117.1 (allyl-C_{minor}), 74.7 (2'-C_{major}), 73.8 (2'-C_{minor}), 63.8 (5-*C*), 52.0 (CO_2CH_{3minor}), 51.9 (CO_2CH_{3major}), 42.2 (allyl-C_{major}), 42.1(allyl-C_{minor}), 39.5 (1'-C_{major}), 38.4 (1'-C_{minor}), 35.6 (3'-C_{major}), 35.5 (4'-C_{major}), 35.3 (3'-C_{minor}), 34.4 (4'-C_{minor}), 30.7 (5-C-CH_{3minor}), 25.8 (5-C-CH_{3major}), 21.1(2'-C-CH_{3major}), 20.5 (2'-C-CH_{3minor}); **MS** *m/z* (ES+): 302 ($[M+Na]^+$); **HRMS** Found $[M+H]^+$ 280.1549 ($C_{15}H_{22}O_4N$) requires (M) 280.1543.

(±)-Methyl-1-allyl-5-ethyl-5-hydroxy-7a-methyl-2-oxo-2,4,5,6,7,7a-hexahydro-1H-indole-3-carboxylate 9a,b:

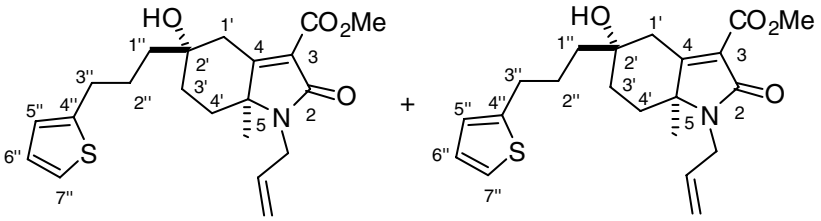


major minor

Following general procedure A the reaction was carried out on a 0.27 mmol scale to give **9** (52 mg, 67%) as a 4:1 mixture of diastereoisomers. **IR** ν_{max}(oil) 3550-3200 (OH), 2900, 2800 (CH), 1720 (C=O), 1685 (C=O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 5.86-5.76 (1H, m, NCH_2CHCH_2), 5.19 (d, 1H, *J* 17.1Hz, 1 of NCH_2CHCH_2), 5.10 (d, 1H, *J* 10.1Hz, 1 of NCH_2CHCH_2), 4.09 (dd, 2H, *J* 15.8Hz, 5.9Hz, $NCH_AH_BCHCH_2$), 3.87 (dd, 2H, *J* 15.8Hz and 6.7Hz, $NCH_AH_BCHCH_2$), 3.84 (s, 3H, OCH_{3minor}), 3.83 (s, 3H, OCH_{3major}), 3.67 (d, 1H, *J* 13.0Hz, 1'-CH_AH_{Bmajor}), 3.51 (d, 1H, *J* 13.8Hz, 1'-CH_AH_{Bminor}), 2.41 (d, 1H, *J* 13.0Hz, 1'-

CH_AH_{Bmajor}), 2.28 (d, 1H, *J* 13.9Hz, 1'-CH_AH_{Bminor}), 2.08 (dt, 1H, *J* 13.3Hz, 4.0Hz, 3'-CH_AH_B), 1.83-1.76 (m, 1H, 4'-CH_AH_B), 1.73 (dt, 1H, *J* 14.0Hz, 4.0Hz, 4'-CH_AH_{Bmajor}), 1.64 (q, 1H, *J* 7.6Hz, CH_2CH_{3minor}), 1.53 (m, 1H, 4'-CH_AH_{Bminor}), 1.43-1.37 (1H, m, CH_2CH_{3major}), 1.37 (s, 3H, 5-CH_{3major}), 1.34 (q, 1H, *J* 7.4Hz, CH_2CH_{3major}), 1.30 (s, 3H, 5-CH_{3minor}), 1.19 (m, 1H, 3'-CH_AH_B), 0.97 (t, 3H, *J* 7.5Hz, CH_2CH_{3minor}), 0.85 (t, 3H, *J* 7.4Hz, CH_2CH_{3major}); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 173.0 (3-*C*), 172.0 (4-*C*), 165.6 (*C*=O), 163.9 (CO_2CH_{3minor}), 163.1(CO_2CH_{3major}), 134.4 (allyl-C_{minor}), 134.3(allyl-C_{major}), 122.1, 117.2 (allyl-C_{major}), 117.0 (allyl-C_{minor}), 76.4 (2'-C_{major}), 76.1 (2'-C_{minor}), 64.1 (5-C_{major}), 63.8 (5-C_{minor}), 52.0 (CO_2CH_{3minor}), 51.8 (CO_2CH_{3major}), 42.1 (allyl-*C*), 37.6 (1'-C_{major}), 36.3 (1'-C_{minor}), 36.0 (CH_2CH_{3minor}), 35.4 (3'-C_{minor}), 34.8 (3'-C_{major}), 32.8 (4'-C_{major}), 32.0 (4'-C_{minor}), 29.4 (CH_2CH_{3major}), 21.4 (5-CH_{3major}), 20.3 (5-CH_{3minor}), 7.7 (CH_2CH_{3minor}), 6.7 (CH_2CH_{3major}); **MS** *m/z* (ES+): 294 ($[M+H]^+$); **HRMS** Found $[M+H]^+$ 294.1705 ($C_{16}H_{24}O_4N$) requires (M) 294.1700.

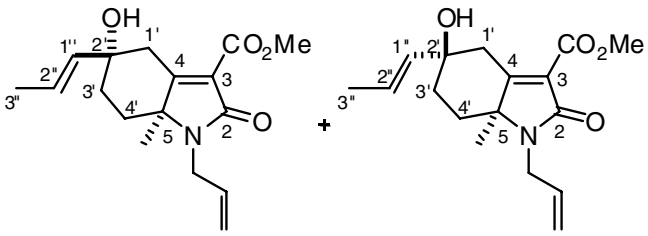
(±)-Methyl 1-allyl-4,5-dimethyl-2-oxo-5-(3-(thiophen-2-yl)propyl)-2,5-dihydro-1H-pyrrole-3-carboxylate 10a,b:



Following general procedure A the reaction was carried out on a 0.14 mmol scale to give **10** (36 mg, 69%) as a 4:1 mixture of diastereoisomers. **IR** ν_{max} (oil) 3700-3200 (OH), 2948, (CH), 1736 (C=O), 1690 (C=O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H 7.12 (d, 1H, *J* 5.1Hz, 7''-CH_{minor}), 7.10 (d, 1H, *J* 5.1Hz, 7''-CH_{major}), 6.92 (dd, 1H, *J* 5.1Hz and 3.5Hz, 6''-CH_{minor}), 6.89 (dd, 1H, *J* 5.1Hz and 3.4Hz, 6''-CH_{minor}), 6.80 (d, 1H, *J* 2.8Hz, 5''-CH_{minor}), 6.75 (d, 1H, *J* 2.8Hz, 5''-CH_{major}), 5.83 (ddt, 1H, *J* 16.9Hz, 10.2Hz, 6.0Hz, NCH_2CHCH_2), 5.21 (d, 1H, *J* 16.9Hz, 1 of NCH_2CHCH_2), 5.13 (d, 1H, *J* 10.2Hz, 1 of NCH_2CHCH_2), 4.11 (dd, 1H, *J* 16.1Hz, 6.0Hz, $NCH_AH_BCHCH_{2major}$), 4.09 (dd, 1H, *J* 16.1Hz, 6.0Hz, $NCH_AH_BCHCH_{2minor}$), 3.93 (dd, 1H, *J* 16.1Hz, 6.0Hz, $NCH_AH_BCHCH_{2minor}$), 3.90 (dd, 1H, *J* 16.1Hz, 6.0Hz, $NCH_AH_BCHCH_2$ major), 3.86 (s, 3H, CO_2CH_{3minor}), 3.85 (s, 3H, CO_2CH_{3major}), 3.71 (d, 1H, *J* 13.0Hz, 1'-CH_AH_{Bmajor}), 3.54 (d, 1H, *J* 13.8Hz, 1'-CH_AH_{Bminor}), 2.87 (t, 2H, *J* 7.3Hz, 3''-H_{2minor}), 2.84-2.71 (m, 2H, 3''-CH_{2major}), 2.40 (d, 1H, *J* 13.0Hz, 1'-CH_AH_{Bmajor}), 2.30 (d, 1H, *J*

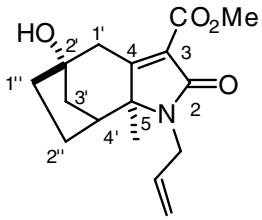
13.8Hz, 1'-CH_AH_{Bminor}), 2.09 (dt, 1H, *J* 13.3Hz and 3.5Hz, 3'-CH_AH_B), 1.88-1.77 (m, 3H, 4'-CH_2 and 2"-CH_AH_B), 1.73 (dt, 1H, *J* 14.1Hz, 4.0Hz, 2"-CH_AH_B), 1.48-1.36 (m, 2H, 1"-CH_2), 1.39 (s, 3H, 5-CH_{3major}), 1.31 (s, 3H, 5-CH_{3minor}), 1.20 (dt, 1H, *J* 12.6Hz, 5.1Hz, 3'-CH_AH_B). **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 172.1 (3-*C*), 171.5 (4-*C*), 165.6 (2-*C*=O), 163.1 (CO_2CH_3), 144.7 (4"-*C*), 134.4 (allyl-*C*), 126.8 (6"-CH_{minor}), 126.7 (6"-CH_{major}), 124.3 (5"-CH_{minor}), 124.2 (C5"-CH_{major}), 123.2 (7"-CH_{minor}), 123.1 (7"-CH_{major}), 117.3 (allyl-*C*), 76.4 (2'-*C*), 63.7 (5-*C*), 52.0 (CO_2CH_3), 42.2 (allyl-C_{major}), 42.1 (allyl-C_{minor}), 37.9 (1'-CH_{2major}), 36.8 (1'-CH_{2minor}), 36.3 (5-CH_3), 35.5 (3'-CH_{2minor}), 35.0 (C3'-CH_{2major}), 33.6 (4'-CH_2), 29.9 (3"-CH_2), 25.0 (2"-CH_2), 21.4 (1"-CH_2); **MS** *m/z* (ES+): 412 ($[M+Na]^+$); **HRMS** Found $[M+Na]^+$ 412.1540 ($C_{21}H_{27}O_4NNaS$) requires (M) 412.1553.

(±)-(E)-methyl-1-allyl-5-hydroxy-7a-methyl-2-oxo-5-(prop-1-enyl)-2,4,5,6,7,7a-hexahydro-1H-indole-3-carboxylate 11a,b:



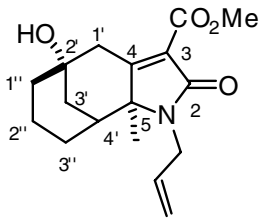
Following general procedure A the reaction was carried out on a 0.14 mmol scale to give **11** (28 mg, 70%) as a 6:1 mixture of diastereoisomers. **IR** ν_{max} (oil) 3600-3300 (OH), 2948 (CH), 1741 (C=O), 1714 (C=O), 1679 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.92-5.75 (m, 2H, NCH_2CHCH_2 and 1"-C*H*), 5.65 (app. dd, 1H, *J* 15.5Hz, 1.5Hz, 2"-C*H*), 5.26-5.19 (m, 1H, 1 of NCH_2CHCH_2), 5.12 (dd, 1H, *J* 10.1Hz, 1.3Hz, 1 of NCH_2CHCH_2), 4.11 (ddt, 1H, *J* 15.7Hz, 5.8Hz, 1.5Hz, $NCH_AH_BCHCH_2$), 3.98-3.89 (m, 1H, $NCH_AH_BCHCH_2$), 3.87 (s, 3H, CO_2CH_3), 3.55 (dd, 1H, *J* 13.9Hz, 2.1Hz, 1'-CH_AH_B), 2.53 (d, 1H, *J* 13.1Hz, 1'-CH_AH_{Bminor}), 2.44 (d, 1H, *J* 13.9Hz, 1'-CH_AH_{Bmajor}), 2.20-2.03 (m, 1H, 3'-CH_AH_B), 1.73 (dd, 3H, *J* 6.4Hz, 1.5Hz, 3"-CH_3), 1.71-1.58 (m, 3H, 3'-CH_AH_B, 4'-CH_2), 1.39 (s, 3H, 5-CH_{3minor}), and 1.34 (s, 3H, 5-CH_{3major}); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 172.7 (3-*C*), 172.0 (4-*C*), 165.5 (2-*C*=O), 163.9 (CO_2CH_3), 137.1 (1"-*C*H), 134.6 (allyl-*C*), 127.6 (2"-*C*H), 117.1 (allyl-*C*), 75.4 (2'-*C*), 63.7 (5-*C*), 52.1 (CO_2CH_3), 42.1 (allyl-*C*), 37.3 (1'-CH_2), 35.3 (3'-CH_2), 33.5 (4'-CH_2), 20.4 (5-CH_3) and 17.6 (3"-CH_3); **MS** *m/z* (ES+): 328 ($[M+Na]^+$); **HRMS** Found $[M+Na]^+$ 328.1527 ($C_{17}H_{23}O_4NNa$) requires (M) 328.1519

Methyl 8-hydroxy-2-methyl-4-oxo-3-(prop-2-en-1-yl)-3-azatricyclo[6.2.1.0^{2,6}]undec-5-ene-5-carboxylate 12:



Following general procedure A the reaction was carried out on a 0.27 mmol scale to give **12** (56 mg, 72%) as a single diastereoisomer. **IR** ν_{max}(oil) 3325 (OH), 2928 (CH), 1741, (C=O), 1730 (C=O), 1684 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.79 (dddd, 1H, *J* 5.8Hz, *J* 7.2Hz, *J* 10.0Hz, *J* 17.2Hz, NCH_2CHCH_2), 5.23 (dd, 1H, *J* 1.4Hz, *J* 17.1Hz, 1 of NCH_2CHCH_2), 5.12 (dd, 1H, *J* 1.2Hz, *J* 10.1Hz, 1 of NCH_2CHCH_2), 4.16 (tdd, 1H, *J* 1.5Hz, *J* 5.8Hz, *J* 15.5Hz, 1 of NCH_2CHCH_2), 3.87 (s, 3H, OCH_3), 3.75 (dd, 1H, *J* 7.2Hz, *J* 15.5Hz, 1 of NCH_2CHCH_2), 3.57 (dd, 1H, *J* 3.0Hz, *J* 13.3Hz, 1 of 1'-CH_2), 2.69 (d, 1H, *J* 13.3Hz, 1 of 1'-CH_2) 2.44 (t, 1H, *J* 5.0Hz, *J* 11.3Hz, 4'-CH), 2.02-1.86 (m, 2H, 3'-CH_2), 1.66-1.62 (m, 1H, 1 of 2''-CH_2), 1.55-1.49 (m, 2H, 1''-CH_2), 1.42 (s, 3H, 5-CH_3), 1.16-1.08 (m, 1H, 1 of 2''-CH_2); **^{13}C NMR** (125 MHz; $CDCl_3$) 171.2 (2-C=O), 166.5 (C=O), 163.4 (quat. C=C), 134.0 ($HC=CH_2$), 123.8 (quat. C=C), 117.9 ($HC=CH_2$), 80.5 (2'-OH), 67.3, 52.1(OCH_3), 42.6, 42.5, 41.1, 40.9, 35.7, 23.1, 22.0 **MS** *m/z* (ES+): 314 ($[M+Na]^+$); **HRMS** Found $[M+H]^+$ 292.1541 $C_{16}H_{22}O_4N$ requires M 292.1543

Methyl 8-hydroxy-2-methyl-4-oxo-3-(prop-2-en-1-yl)-3-azatricyclo[6.3.1.0^{2,6}]dodec-5-ene-5-carboxylate 13:



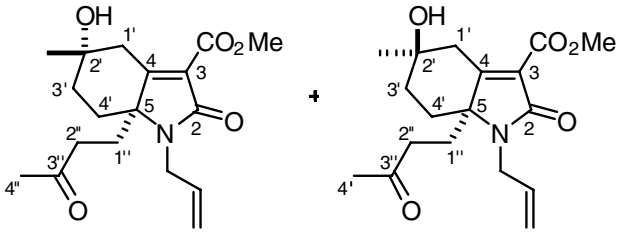
Following general procedure A the reaction was carried out on a 0.27 mmol scale to give **13** (55 mg, 68%) as a single diastereoisomer. **IR** ν_{max}(oil) 3390 (OH), 2919 (CH), 1736, (C=O), 1713 (C=O), 1674 (C=O); **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H 5.94 (tdd, 1H, *J* 6.5Hz, *J* 10.1Hz, *J* 16.6Hz, NCH_2CHCH_2), 5.24 (dd, 1H, *J* 1.4Hz, *J* 17.1Hz, 1 of NCH_2CHCH_2), 5.14 (dd, 1H, *J* 1.2Hz, *J* 10.1Hz, 1 of NCH_2CHCH_2), 4.02 (tdd, 1H, *J* 1.3Hz, *J* 6.3Hz, *J* 15.3Hz, 1 of NCH_2CHCH_2), 3.91 (dd, 1H, *J* 6.5Hz, *J* 15.4Hz, 1 of NCH_2CHCH_2), 3.86 (s, 3H, OCH_3), 3.70 (dd, 1H, *J* 2.7Hz, *J* 14.8Hz, 1 of 1'-CH_2), 2.65 (dd, 1H, *J* 1.8Hz, *J* 14.8Hz, 1 of 1'-CH_2),

2.41 (m, 1H, 4'-C*H*), 2.13 (ddd, 1H, *J* 2.8Hz, *J* 5.2Hz, *J* 13.1Hz, 1 of 3'-CH_2), 1.85 (dd, 1H, *J* 2.8Hz, *J* 11.9Hz, 1 of 3'-CH_2), 1.68 (td, 1H, *J* 3.0Hz, *J* 13.1Hz, 1 of 3''-CH_2), 1.63-1.48 (m, 2H, 1 of 1''-C*H* and 3''-C*H*), 1.46 (s, 3H, 5-CH_3), 1.35 (m, 4H, 1''-C*H*, 2''-CH_2 and 3''-C*H*); **^{13}C NMR** (125 MHz; $CDCl_3$) 174.5 (2-C=O), 166.8 (C=O), 163.3 (quat. C=C), 133.9 (H*C*=CH_2), 121.5 (quat. C=C), 117.7 (HC=*C*H_2), 72.7 (2'-OH), 67.2, 51.9 (OCH_3), 42.8, 40.9, 40.5, 39.0, 38.8, 25.8, 25.2, 20.8; **MS** *m/z* (ES+): 328 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 328.1520 ($C_{17}H_{23}O_4NNa$) requires (M) 328.1519

General Procedure B for the Michael−Michael−Aldol Reaction

To a stirred solution of **6a** (1 equiv.) in MeOH (0.2 M) was added an α,β-unsaturated ketone (4.4 equiv) and K_2CO_3 (0.2 equiv.) at room temperature. The reaction was stirred until t.l.c analysis showed complete consumption of starting material (approx 30 minutes). The reaction was quenched by addition of acetic acid (0.4 equiv.) and concentrated *in vacuo*. Purification by column chromatography [SiO_2, Et_2O (100%)] gave the Michael−Michael−Aldol product as a yellow oil.

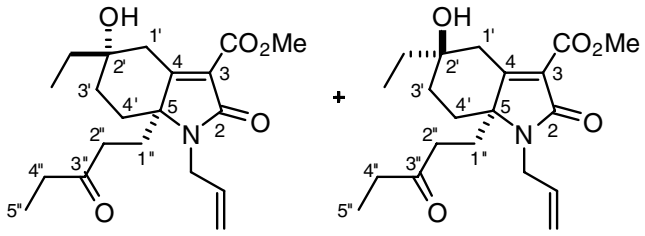
(±)-Methyl 1-allyl-2'-hydroxy-2'-methyl-2-oxo-5-(3''-oxobutyl)-2,4,5,6,7,7a-hexahydro-1H-indole-3-carboxylate 14a,b:



Following general procedure B the reaction was carried out on a 0.4 mmol scale to give **14** (112 mg, 76%) as a 3:1 mixture of diastereoisomers. **IR** ν_{max} (oil) 3550-3200 (OH), 2953 (CH), 1760 (C=O), 1715 (C=O) 1686 (C=O); **^{1}H NMR** (500 MHz; $CDCl_3$) δ_H 5.87-5.77 (m, 1H, NCH_2CHCH_2), 5.22 (d, 1H, *J* 17.1Hz, 1 of NCH_2CHCH_2), 5.11 (d, 1H, *J* 10.0Hz, 1 of NCH_2CHCH_2), 4.06 (dd, 1H, *J* 15.3Hz, 5.4Hz, $NCH_AH_BCHCH_2$), 3.86 (s, 3H, CO_2CH_3), 3.74 (dd, 1H, *J* 15.3Hz, 6.7Hz, $NCH_AH_BCHCH_2$), 3.59 (d, 1H, *J* 12.6Hz, 1'-CH_AH_{Bmajor}), 3.50 (d, 1H, *J* 13.8Hz, 1'-CH_AH_{Bminor}), 2.34 (dd, 1H, *J* 13.8Hz, 8.4Hz, 1"-CH_AH_B), 2.31 (d, 1H, *J* 12.6Hz, 1'-CH_AH_{Bmajor}), 2.23 (d, 1H, *J* 13.8Hz, 1'-CH_AH_{Bminor}), 2.20-2.18 (m, 2H, 4'-CH_2), 2.10-1.96 (m, 2H, 2"-CH_AH_B and 1"-CH_AH_B), 2.05 (s, 3H, 4"-CH_{3major}), 2.03 (s, 3H, 4"-CH_{3minor}), 1.89 (dd, 1H, *J* 15.0Hz, 10.3Hz, 2"-CH_AH_B), 1.77-1.67 (m, 1H, 3'-CH_AH_B), 1.40 (s,

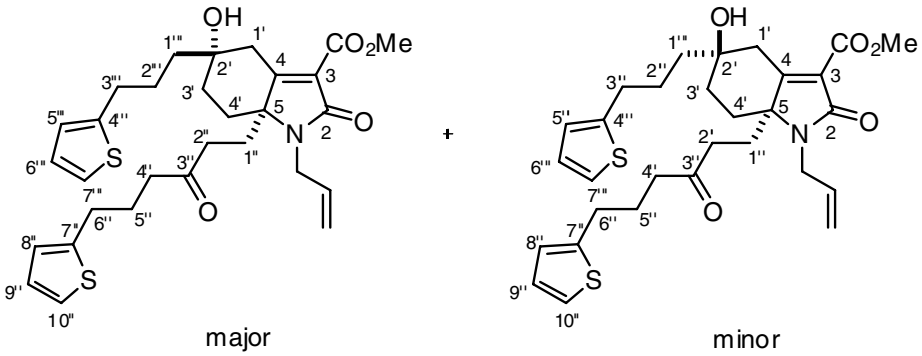
3H, 2'-CH_{3major}), 1.31 (dt, 1H, *J* 14.0Hz, 4.4Hz, 3'-CH_AH_B) and 1.13 (s, 3H, 2'-CH_{3minor}); **^{13}C NMR** (125 MHz; $CDCl_3$) δ_C 206.9 (3"-*C*=O), 170.3 (4-*C*), 166.2 (2-*C*=O), 162.8 (*C*O_2CH_3), 133.7 (allyl-C_{minor}), 133.5 (allyl-C_{major}), 123.7 (3-*C*), 118.2 (allyl-C_{major}), 118.0 (allyl-C_{minor}), 74.9 (2'-C_{major}), 74.0 (2'-C_{minor}), 66.0 (5-*C*), 52.0 (CO_2CH_3), 42.3 (allyl-*C*), 39.7 (1'-*C*H_2), 36.5 (4"-*C*H_3), 35.6 (2"-*C*H_2), 34.2 (C3'-*C*H_2), 30.2 (4'-*C*H_2), 25.9 (2'-*C*H_3) and 25.7 (1"-*C*H_2); **MS** *m/z* (ES+): 358 ([M+Na]$^+$); **HRMS** Found [M+Na]$^+$ 358.1617 ($C_{18}H_{25}O_5Na$) requires (M) 358.1625.

(±)-Methyl 1-allyl-5-ethyl-5-hydroxy-2-oxo-7a-(3-oxopentyl)-2,4,5,6,7,7a-hexahydro-1H-indole-3-carboxylate 15a,b:



Following general procedure B the reaction was carried out on a 0.4 mmol scale to give **15** (115 mg, 75%) as a 3:1 mixture of diastereoisomers. **IR** ν_{max}(oil) 3700-3300 (OH), 2940 (CH), 1760 (C=O), 1710 (C=O) 1690 (C=O); **^{1}H NMR** (300 MHz, $CDCl_3$) δ_H 5.92-5.71 (m, 1H, NCH_2CHCH_2), 5.20 (d, 1H, *J* 17.1Hz, NCH_2CHCH_2), 5.09 (d, 1H, *J* 10.1Hz, NCH_2CHCH_2), 4.04 (dd, 1H, *J* 15.4Hz, 6.4Hz, $NCH_AH_BCHCH_2$), 3.84 (s, 3H, CO_2CH_3), 3.75 (dd, 1H, *J* 14.4Hz, 6.4Hz, $NCH_AH_BCHCH_2$), 3.63 (d, 1H, *J* 13.5Hz, 1'-CH_AH$_{Bmajor}$), 3.46 (d, 1H, *J* 15.1Hz, 1'-CH_AH$_{Bminor}$), 2.31-2.27 (m, 4H, 2"-CH_2 and 4"-CH_2), 2.26-2.23 (m, 1H, 1'-CH_AH_{Bmajor}), 2.16 (d, 1H, *J* 13.5Hz, 1'-CH_AH_{Bminor}), 2.12-1.55 (m, 5H, 3'-CH_AH$_B$, 1"-CH_2 and 4'-CH_2), 1.44-1.27 (m, 2H, 2'-CH_2CH$_3$), 1.26-1.12 (m, 1H, 3'-CH_AH_B), 0.96 (t, 6H, *J* 7.4Hz, 2 × CH_2CH_{3major}) and 0.84 (t, 6H, *J* 7.4Hz, 2 × CH_2CH_{3minor}); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C 209.8 (3"*C*=O$_{major}$), 209.6 (3"*C*=O$_{minor}$), 171.4 (4-C_{major}), 170.3 (4-C_{minor}), 166.2 (2-*C*=O), 163.5 (*C*O_2CH_{3major}), 162.8 (*C*O_2CH_{3minor}), 133.7 (allyl-C_{major}), 133.6 (allyl-C_{minor}), 125.0 (3-C_{major}), 123.9 (3-C_{minor}), 118.1 (allyl-C_{major}), 117.9 (allyl-C_{minor}), 76.6 (2'-C_{major}), 76.4 (2'-C_{minor}), 66.5 (5-C_{major}), 66.1 (5-C_{minor}), 52.1 ($CO_2CH_{3\ major}$), 52.0 ($CO_2CH_{3\ minor}$), 42.3 (allyl-C_{major}), 42.2 (allyl-C_{minor}), 37.9 (4''-*C*H_{2major}), 36.5 (4''-*C*H_{2minor}), 36.2 (*C*$H_2CH_{3\ major}$), 35.7 (*C*$H_2CH_{3\ minor}$), 35.2 (*C*H_{2major}), 35.0 (*C*H_{2minor}), 34.8 (*C*H_2), 32.9 (*C*H_2), 32.0 (*C*H_2), 29.6 (2'-*C*H_2CH_3), 26.2 (*C*H_2), 25.2 (*C*H_2), 7.7 (5''-CH_2CH_3) and 6.8 (CH_2CH_3); **MS** *m/z* (ES+): 364 ([M+H]$^+$); **HRMS** Found [M+H]$^+$ 364.2129 ($C_{20}H_{30}O_5N$) requires (M) 364.2118.

(±)-Methyl-1-allyl-2'-hydroxy-2-oxo-5-(3''-oxo-6''-(thiophen-2-yl)hexyl)-2'-(3'''-(thiophen-2-yl)propyl)-hexahydro-1H-indole-3-carboxylate 16a,b:



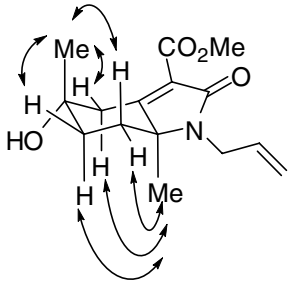
Following general procedure B the reaction was carried out on a 0.2 mmol scale to give **16** (88 mg, 79%) as a separable 3:1 mixture of diastereoisomers. **IR** ν_{max}(oil) 3600-3100 (OH), 2948 (CH), 1736, (C=O), 1714 (C=O), 1677 (C=O); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H Major diastereoisomer: 7.11 (dd, 1H, *J* 5.1Hz, 1.0Hz, thiophene-*H*), 6.90 (ddd, 1H, *J* 5.1Hz, 3.4Hz, thiophene-*H*), 6.89 (dd, 1H, *J* 5.1Hz, 3.4Hz, thiophene-*H*), 6.75 (d, 2H, *J* 3.4Hz, thiophene-*H*), 5.81 (ddt, 1H, *J* 17.0Hz, 10.1Hz, 6.5Hz, NCH_2CHCH_2), 5.22 (dd, 1H, *J* 17.0Hz, 1.1Hz, 1 of NCH_2CHCH_2), 5.11 (d, 1H, *J* 10.1Hz, 1 of NCH_2CHCH_2), 4.05 (dd, 1H, *J* 15.4Hz, 6.2Hz, $NCH_AH_BCHCH_2$), 3.85 (s, 3H, CO_2CH_3), 3.72 (dd, 1H, *J* 15.4Hz, 6.8Hz, $NCH_AH_BCHCH_2$), 3.66 (d, 1H, *J* 12.8Hz, 1'-CH_AH_B), 2.78 (dd, 4H, *J* 14.8Hz, 7.5Hz, 3'''-CH_2 and 6''-CH_2), 2.34 (t, 4H, *J* 7.4Hz, 2''-CH_2 and 4''-CH_2), 2.25 (d, 1H, *J* 12.8Hz, 1'-CH_AH_B), 2.16-2.08 (m, 1H, 3'-CH_AH_B), 2.04-1.95 (m, 1H, 4'-CH_AH_B), 1.87 (m, 4H, 1''-CH_2 and 4''-CH_2), 1.85-1.73 (m, 1H, 4'-CH_AH_B), 1.71-1.58 (m, 4H, 2'''-CH_2 and 5''-CH_2), 1.40 (m, 2H, 1'''-CH_2) and 1.24 (ddd, 1H, *J* 13.2Hz, 7.6Hz, 4.7Hz, 3'-CH_AH_B); **^{1}H NMR** (500 MHz, $CDCl_3$) δ_H Minor diastereoisomer: 7.12 (dd, 1H, *J* 5.3Hz, 0.8Hz, thiophene-*H*), 6.92 (dd, 1H, *J* 5.3Hz, 3.6Hz, thiophene-*H*), 6.90 (dd, 1H, *J* 5.3Hz, 3.6Hz, thiophene-*H*), 6.79 (d, 1H, *J* 3.6Hz, thiophene-*H*), 5.83 (ddt, 1H, *J* 17.0Hz, 10.0Hz, 6.5Hz, NCH_2CHCH_2), 5.22 (d, 1H, *J* 17.0Hz, 1 of NCH_2CHCH_2), 5.10 (d, 1H, *J* 10.0Hz, 1 of NCH_2CHCH_2), 4.04 (dd, 1H, *J* 15.4Hz, 6.5Hz, $NCH_AH_BCHCH_2$), 3.86 (s, 3H, CO_2CH_3), 3.76 (dd, 1H, *J* 15.4Hz, 6.5Hz, $NCH_AH_BCHCH_2$), 3.48 (d, 1H, *J* 13.6Hz, 1'-CH_AH_B), 2.87 (t, 2H, *J* 7.3Hz, 6''-CH_2), 2.79 (t, 2H, *J* 7.3Hz, 3'''-CH_2), 2.33 (t, 2H, *J* 7.3Hz, 2''-CH_2), 2.26-2.18 (m, 1H, 3'-CH_AH_B), 2.17 (d, 1H, *J* 13.6Hz, 3'-CH_AH_B), 2.11-2.06 (m, 2H, 4''-CH_2), 1.98-1.89 (m, 2H, 4'-CH_2), 1.88 (t, 2H, *J* 7.3Hz, 2'''-CH_2), 1.85-1.74 (m, 3H, 5''-CH_2) and 1.73-1.62 (m, 5H, 1'''-CH_2, 3'-CH_AH_B and 1''-CH_2); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C Major diastereoisomer: 208.5 (3''*C*=O), 169.7 (4-*C*), 166.0 (2-*C*=O), 162.7 (CO_2CH_3), 144.7 (thiophene-*C*), 144.0 (thiophene-*C*), 133.5 (allyl-*C*), 126.8 (thiophene-*C*), 126.7 (thiophene-*C*), 124.5 (thiophene-*C*), 124.2 (3-*C*), 124.1 (thiophene-*C*), 123.3 (thiophene-*C*), 123.1

(thiophene-*C*), 118.1 (allyl-*C*), 76.3 (2'-*C*), 65.9 (5-*C*), 52.0 ($CO_2C\mathit{H}_3$), 42.3 (allyl-*C*), 41.8 (4"-$C\mathit{H}_2$), 38.1 (1"-$C\mathit{H}_2$), 36.3 (2"'-$C\mathit{H}_2$), 35.3 (3"-$C\mathit{H}_2$), 35.0 (6"'-$C\mathit{H}_2$), 33.5 (3'-$C\mathit{H}_2$), 29.9 (4'-$C\mathit{H}_2$), 28.9 ($C\mathit{H}_2$), 26.0 ($C\mathit{H}_2$), 25.3 ($C\mathit{H}_2$) and 25.0 (1"'-$C\mathit{H}_2$); **^{13}C NMR** (125 MHz, $CDCl_3$) δ_C Minor diastereoisomer: 208.6 (3"-*C*=O), 170.8 (4-*C*), 166.0 (2-*C*=O), 163.5 ($C\mathit{O}_2CH_3$), 144.6 (thiophene-*C*), 144.0 (thiophene-*C*), 133.7 (allyl-*C*), 126.8 (thiophene-*C*), 125.2 (3-*C*), 124.5 (thiophene-*C*), 124.4 (thiophene-*C*), 123.3 (thiophene-*C*), 123.1 (thiophene-*C*), 117.9 (allyl-*C*), 76.1 (2'-*C*), 66.4 (5-*C*), 52.1 ($CO_2C\mathit{H}_3$), 42.8 (allyl-*C*), 42.2 , 41.8 (4"-$C\mathit{H}_2$), 36.9 (2"'-$C\mathit{H}_2$), 35.7 (3"-$C\mathit{H}_2$ and 6"'-$C\mathit{H}_2$), 32.4 (3'-$C\mathit{H}_2$), 30.0 (4'-$C\mathit{H}_2$), 28.9 ($C\mathit{H}_2$), 25.6 ($C\mathit{H}_2$), 25.3 ($C\mathit{H}_2$) and 25.0 (1"'-$C\mathit{H}_2$); **MS** *m/z* (ES+): 578 ($[M+Na]^+$); **HRMS** Found $[M+Na]^+$ 578.2016 ($C_{30}H_{37}O_5NNaS_2$) requires (M) 578.2005.

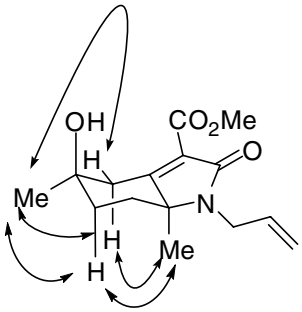
Determination of Relative Stereochemistry of 7

The relative configuration of both diastereoisomers of compound **7** were determined by nOe effects.

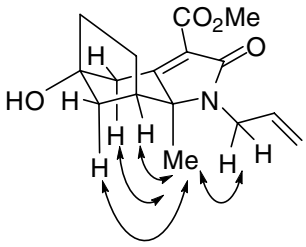
nOe effects of 7a (major diastereoisomer):



nOe effects of 7b (minor diastereoisomer):



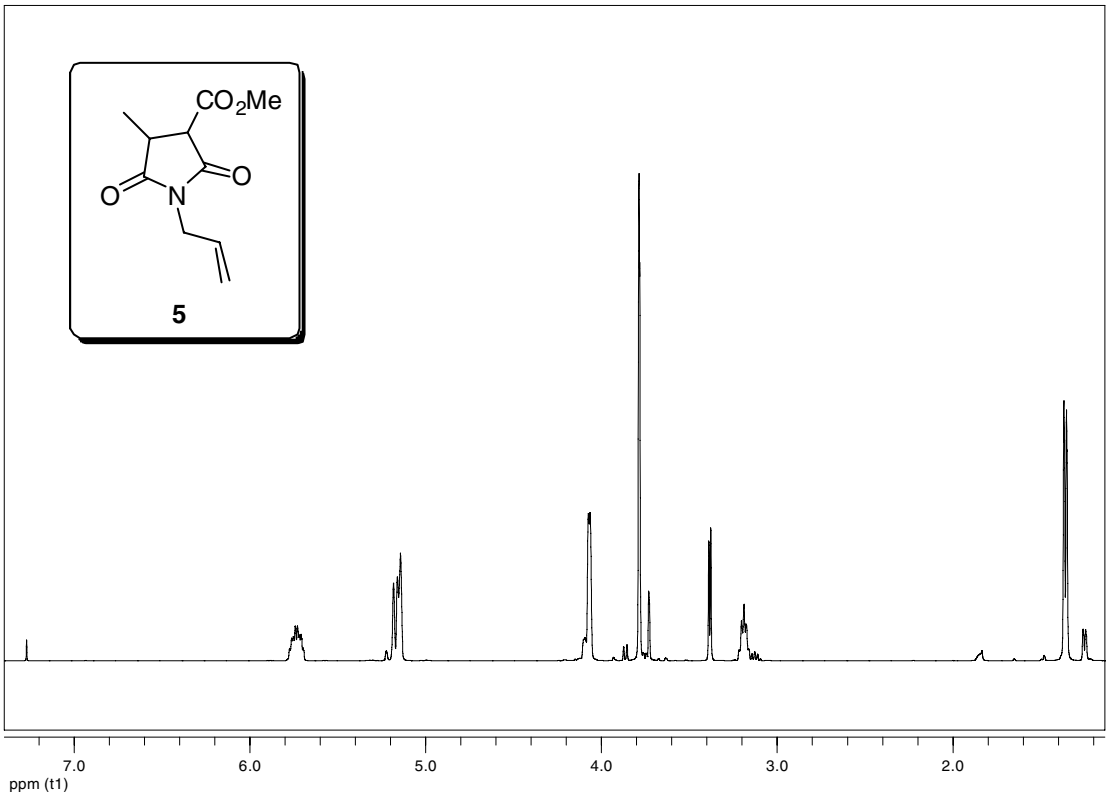
Determination of Relative Stereochemistry of 12

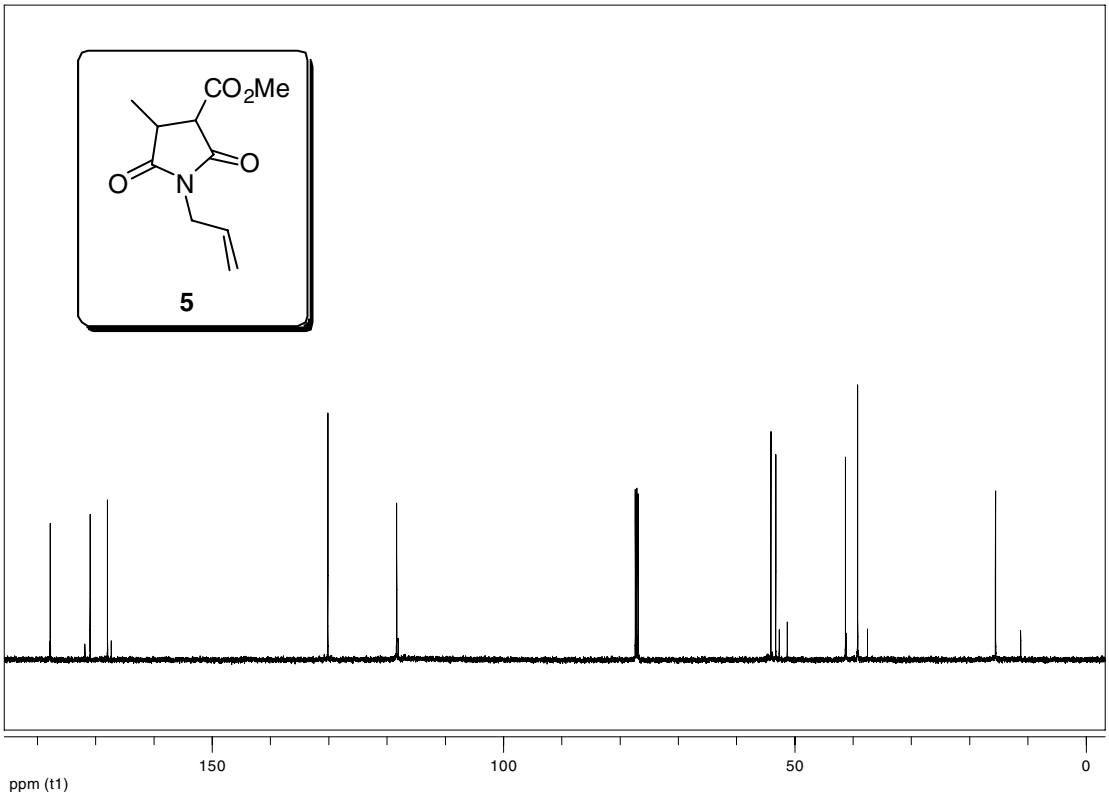


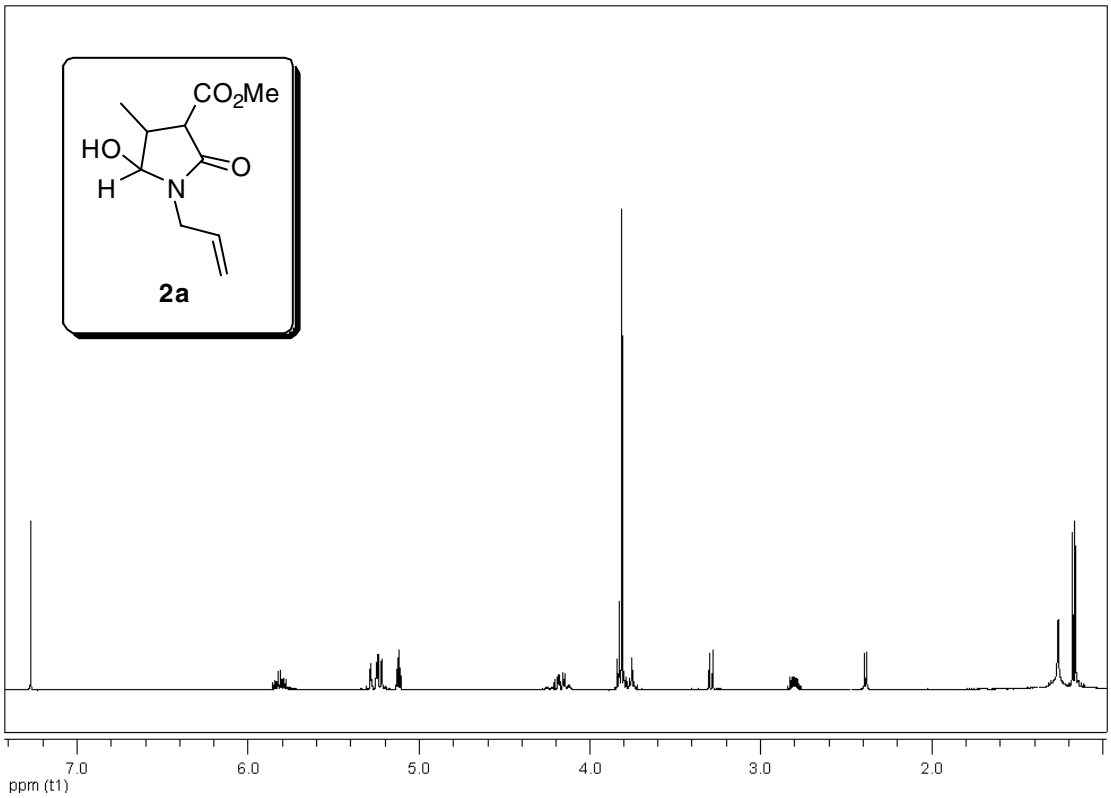
References

1) Davies, S. G.; Dixon, D. J. *J. Chem. Soc. Perkin Trans. I* **2002**, 1869.

NMR Spectra



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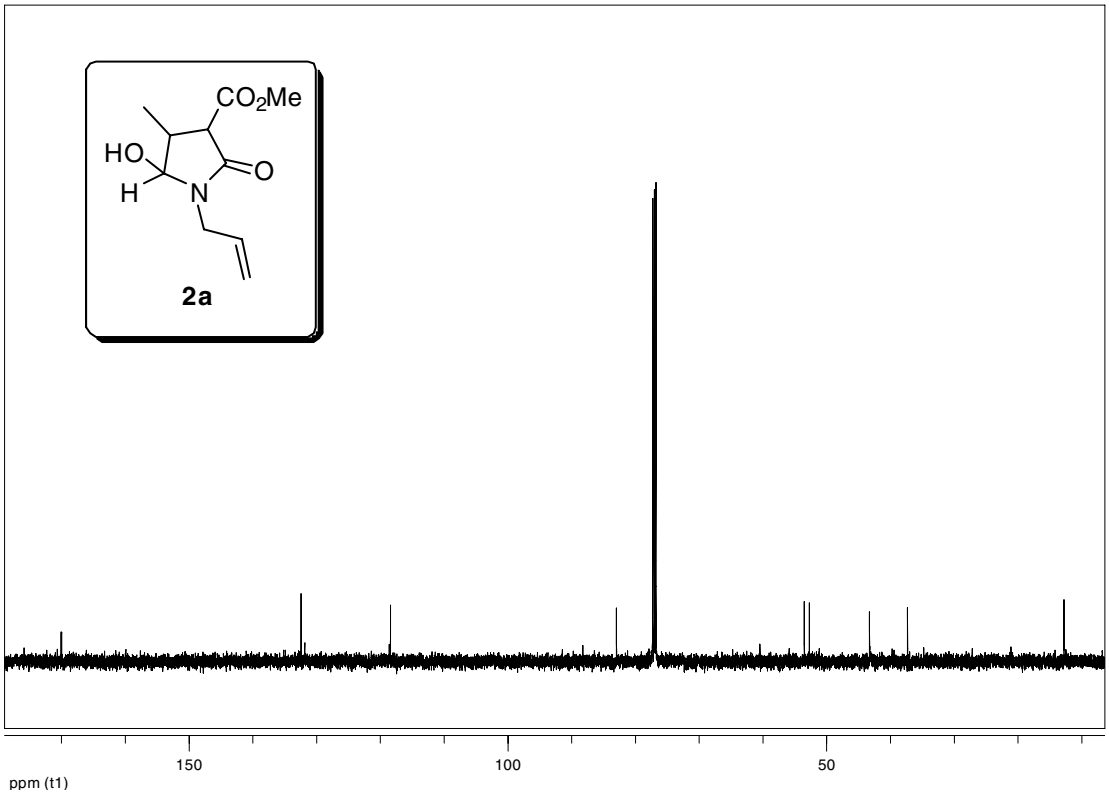
2.0
ppm (t1)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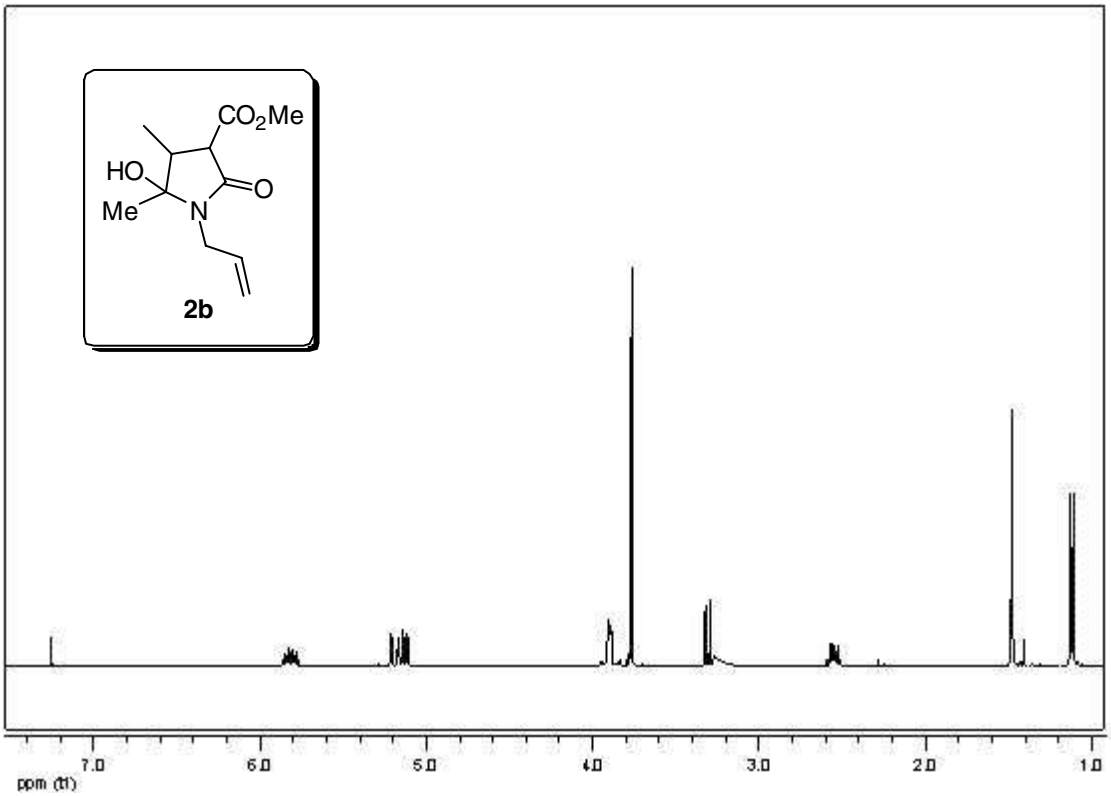
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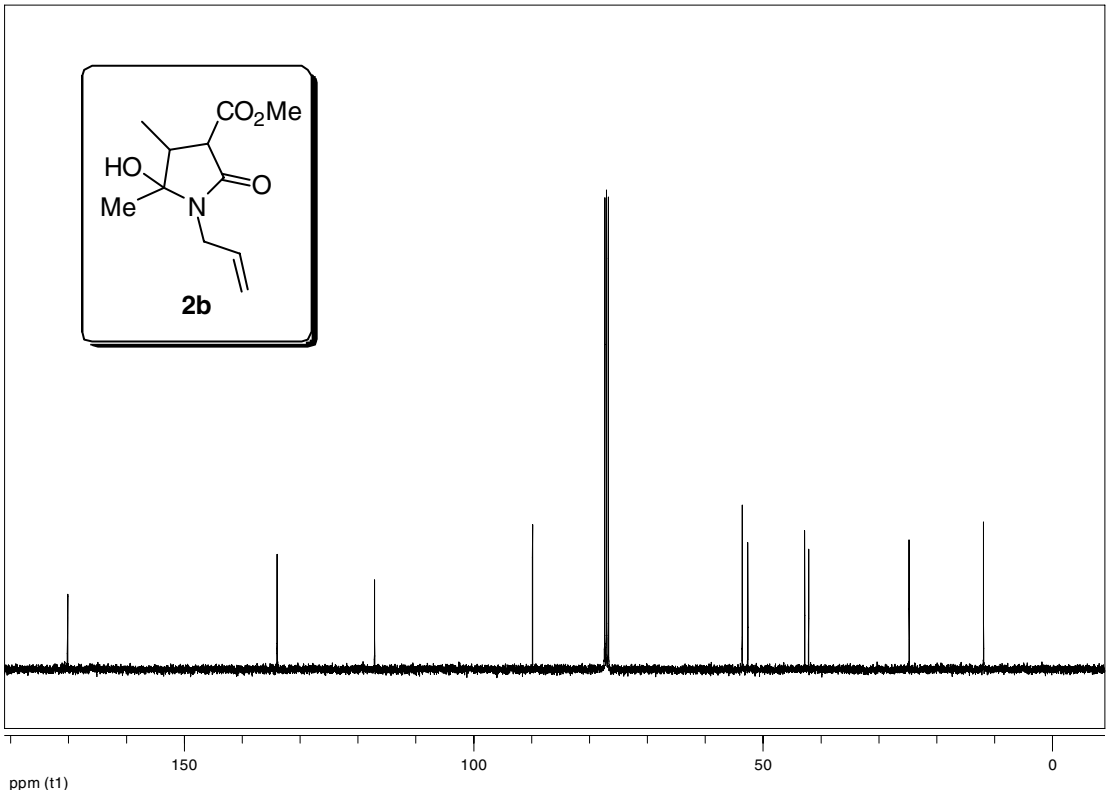
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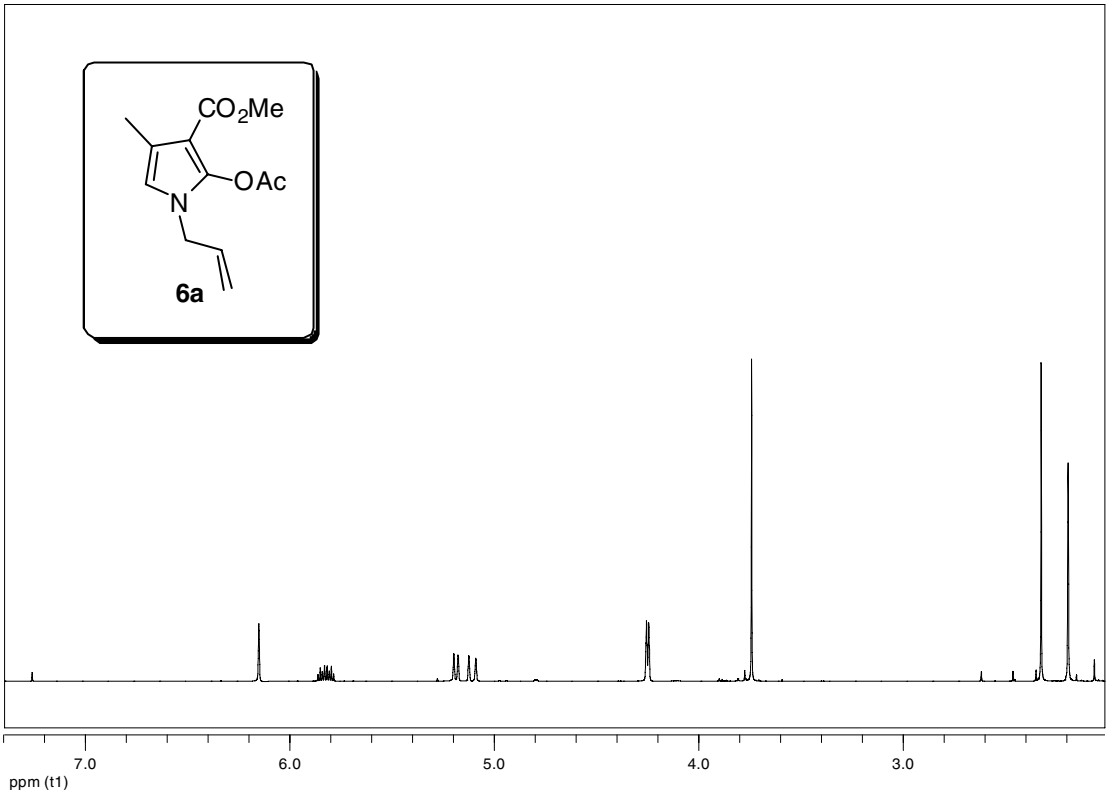
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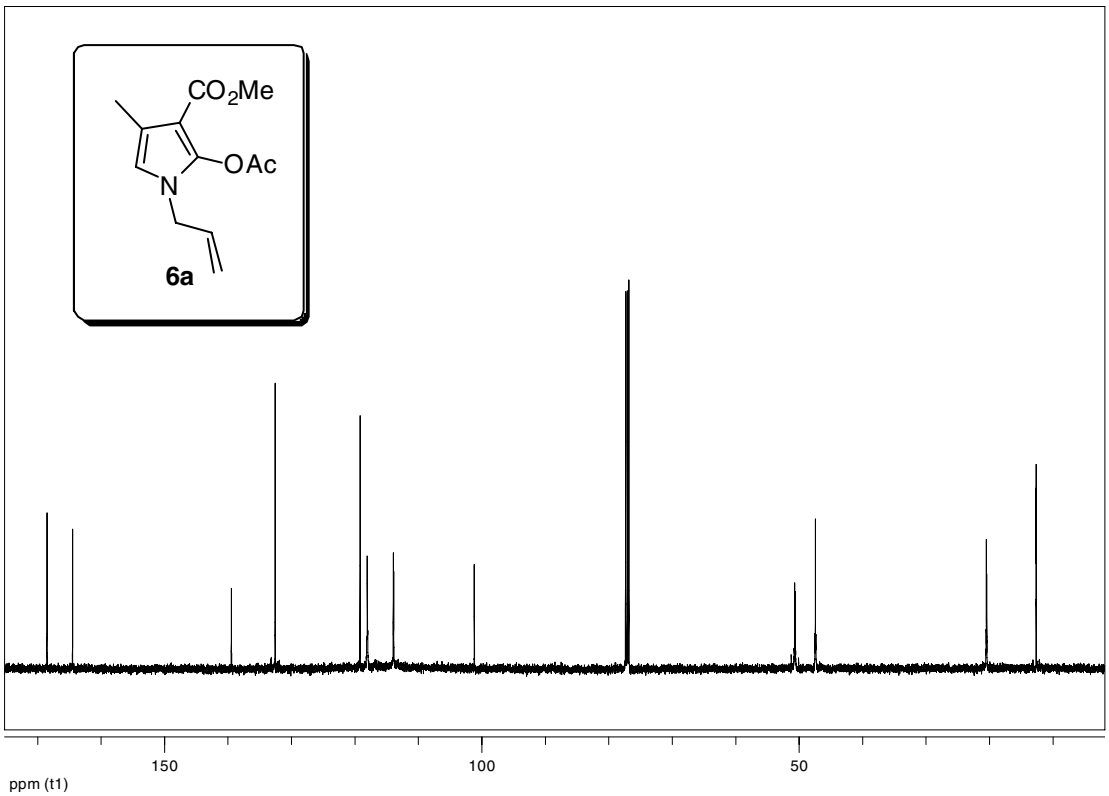
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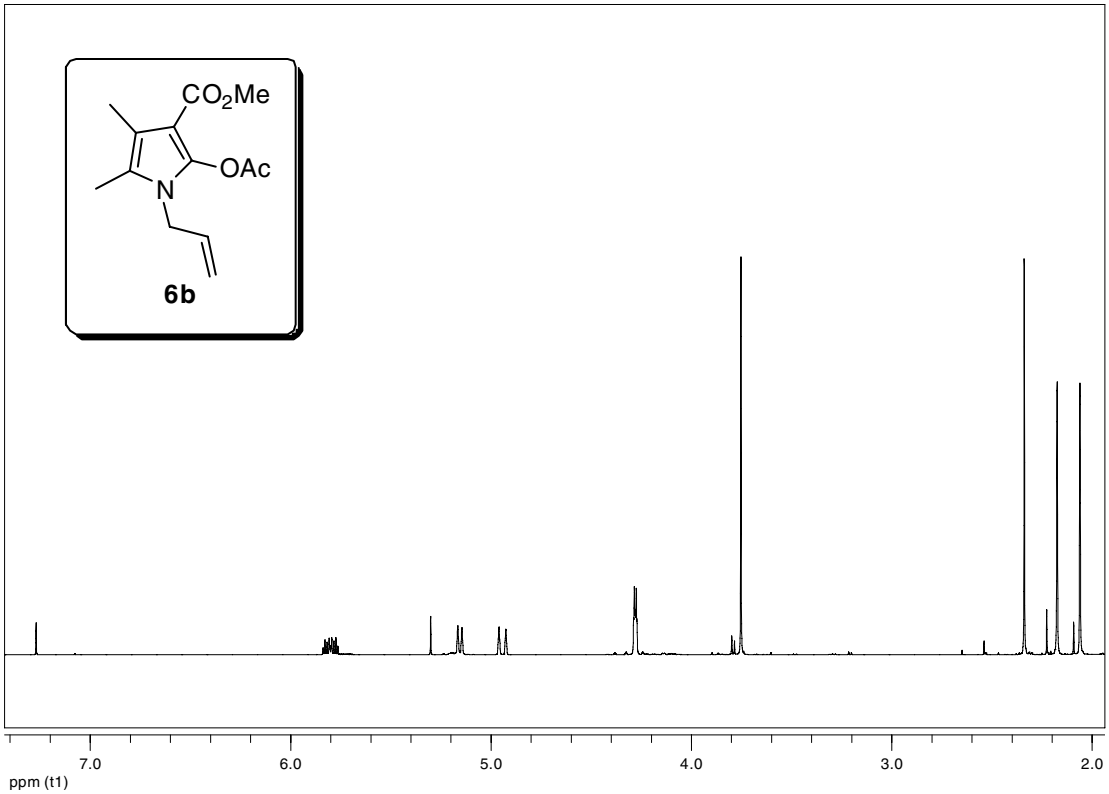
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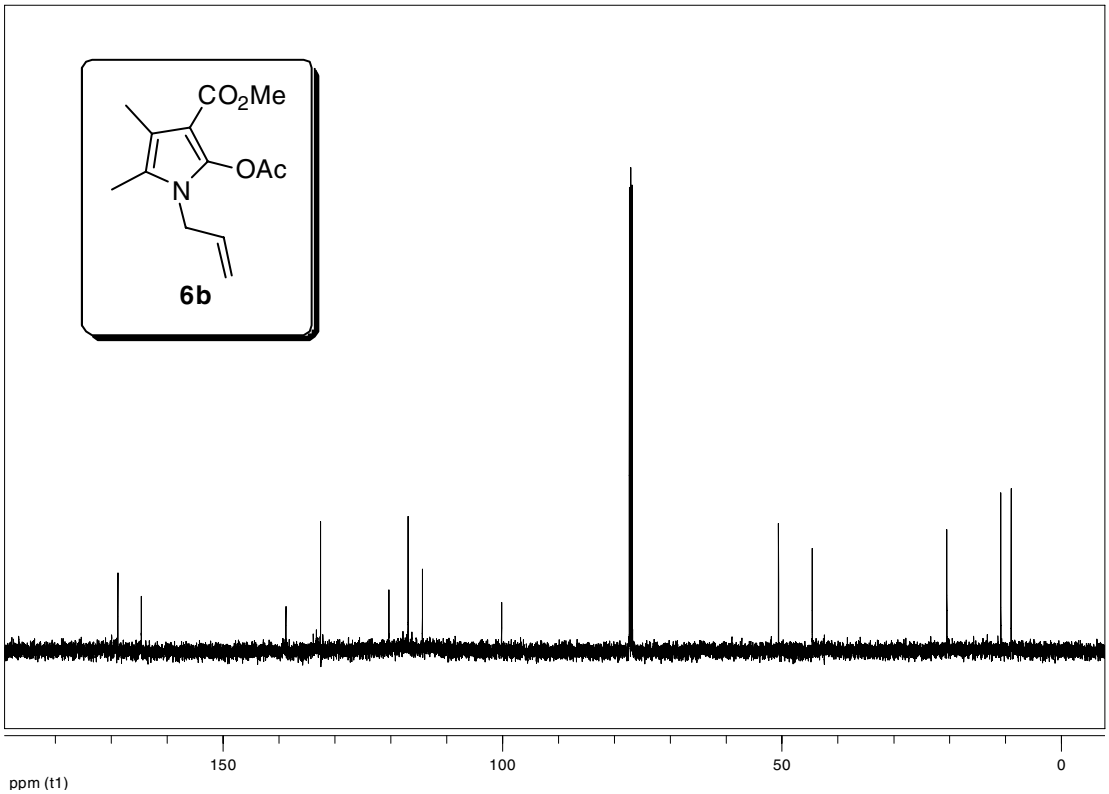
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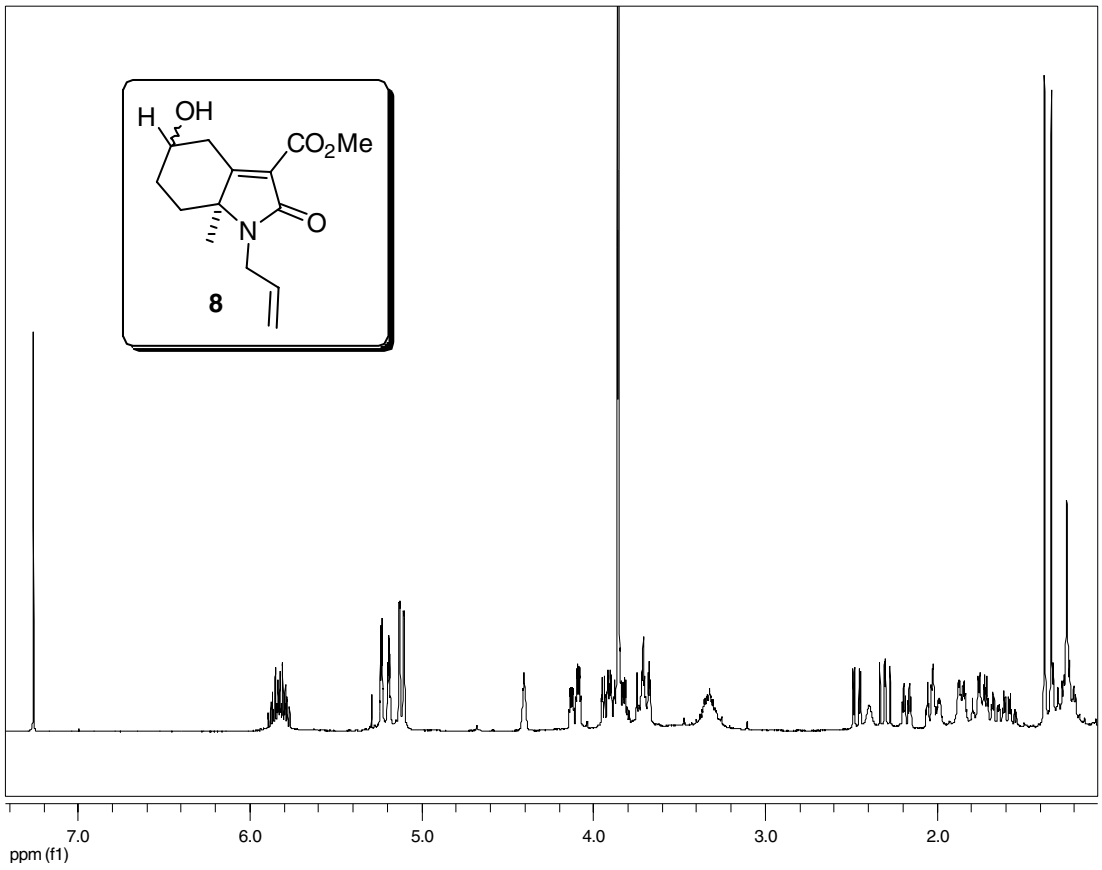
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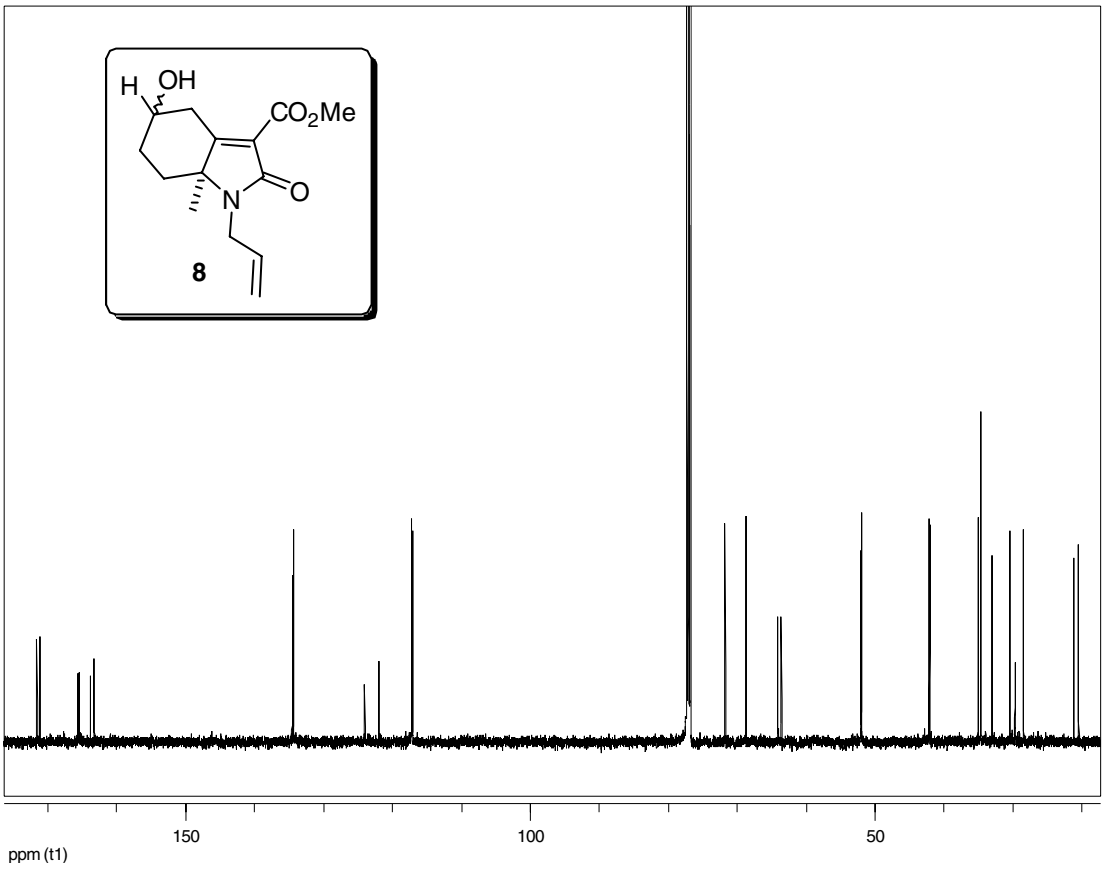
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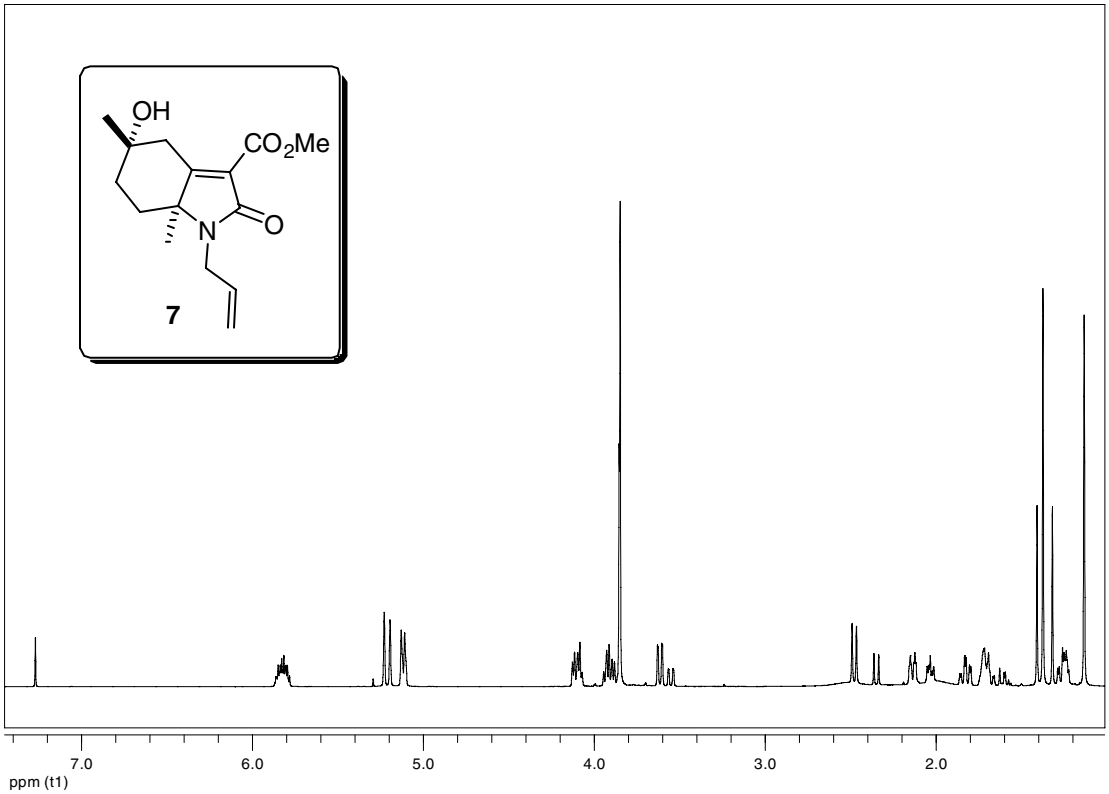
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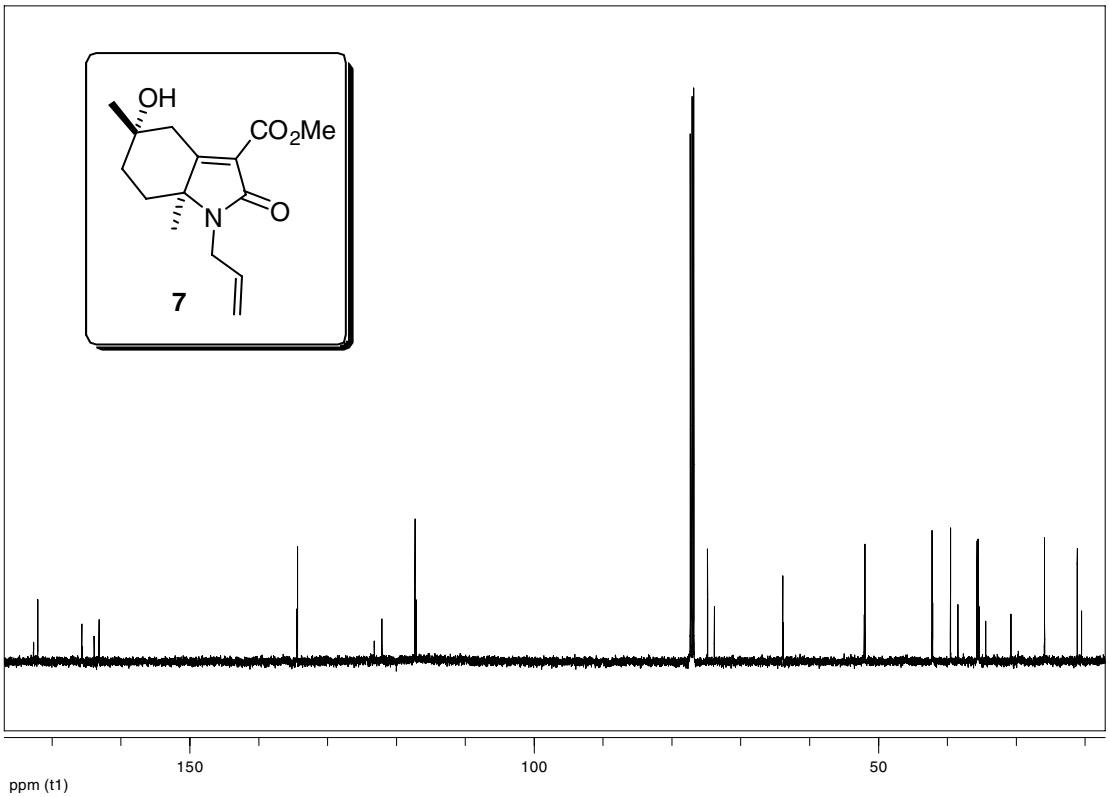
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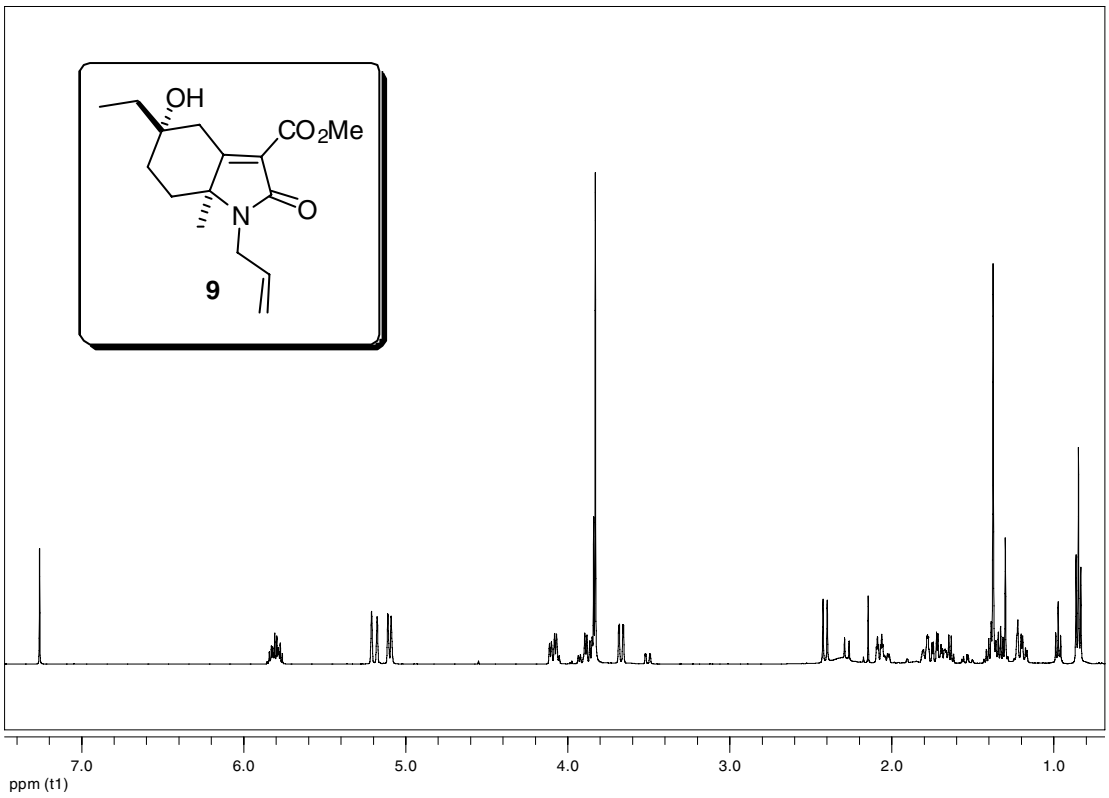
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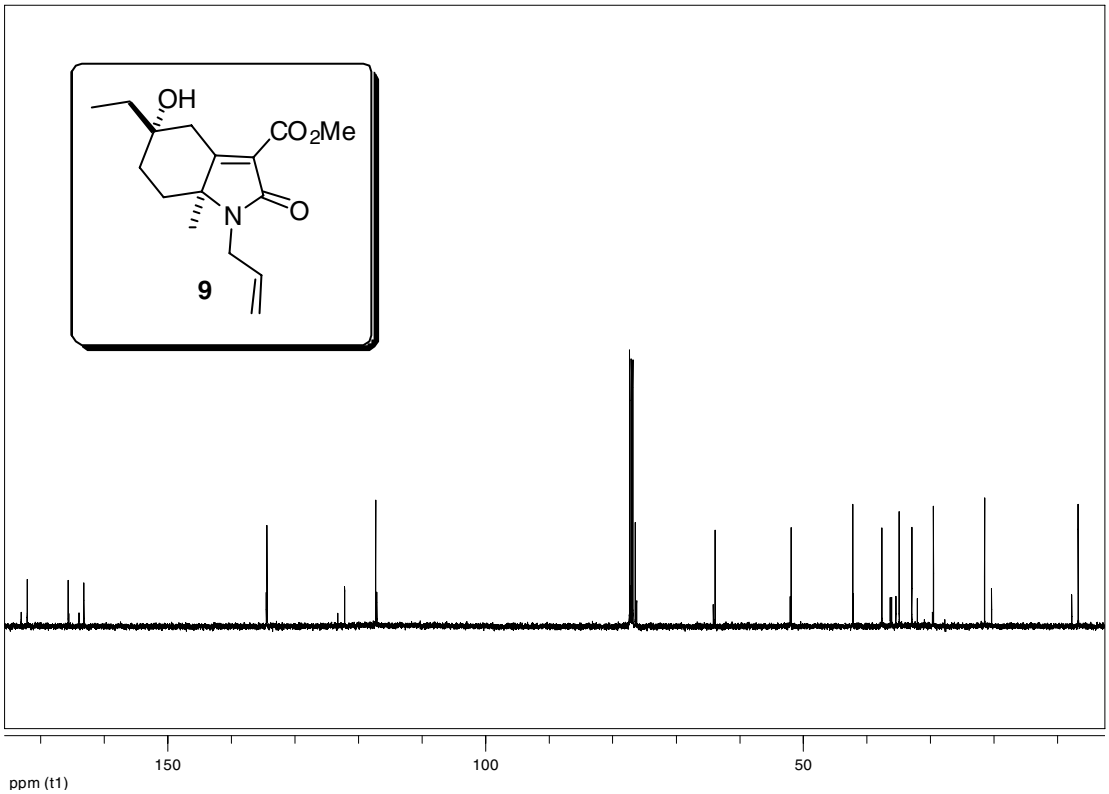
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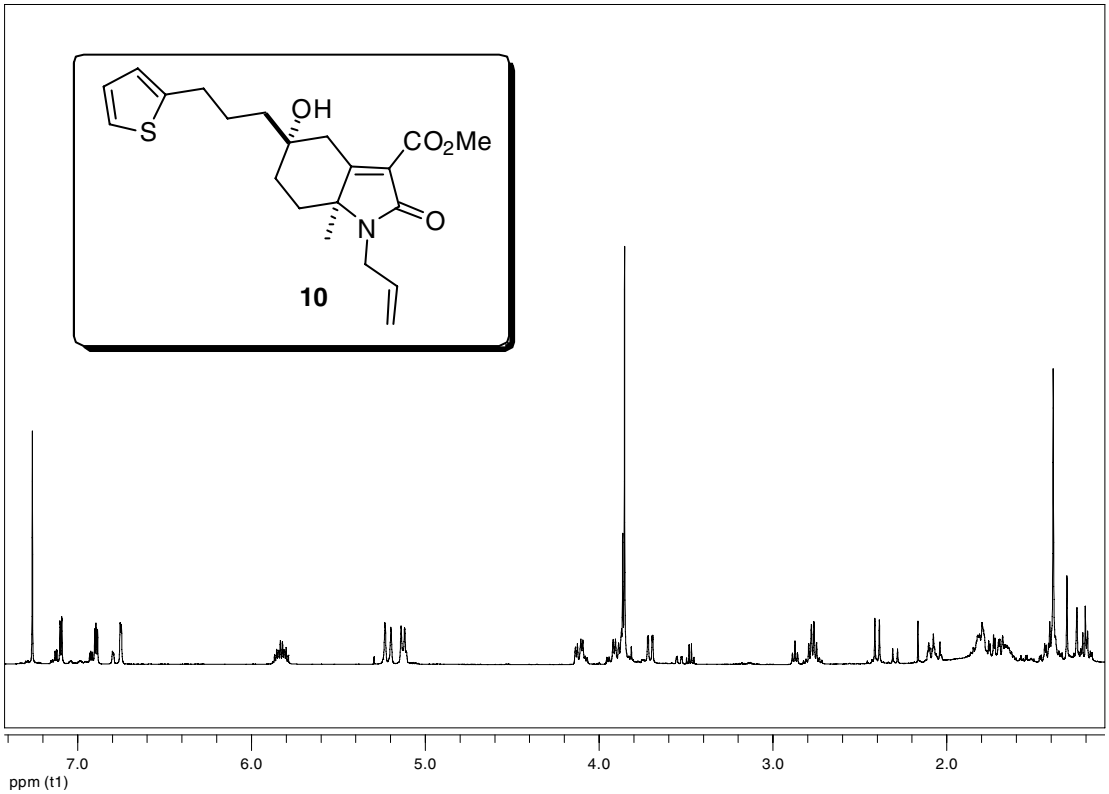
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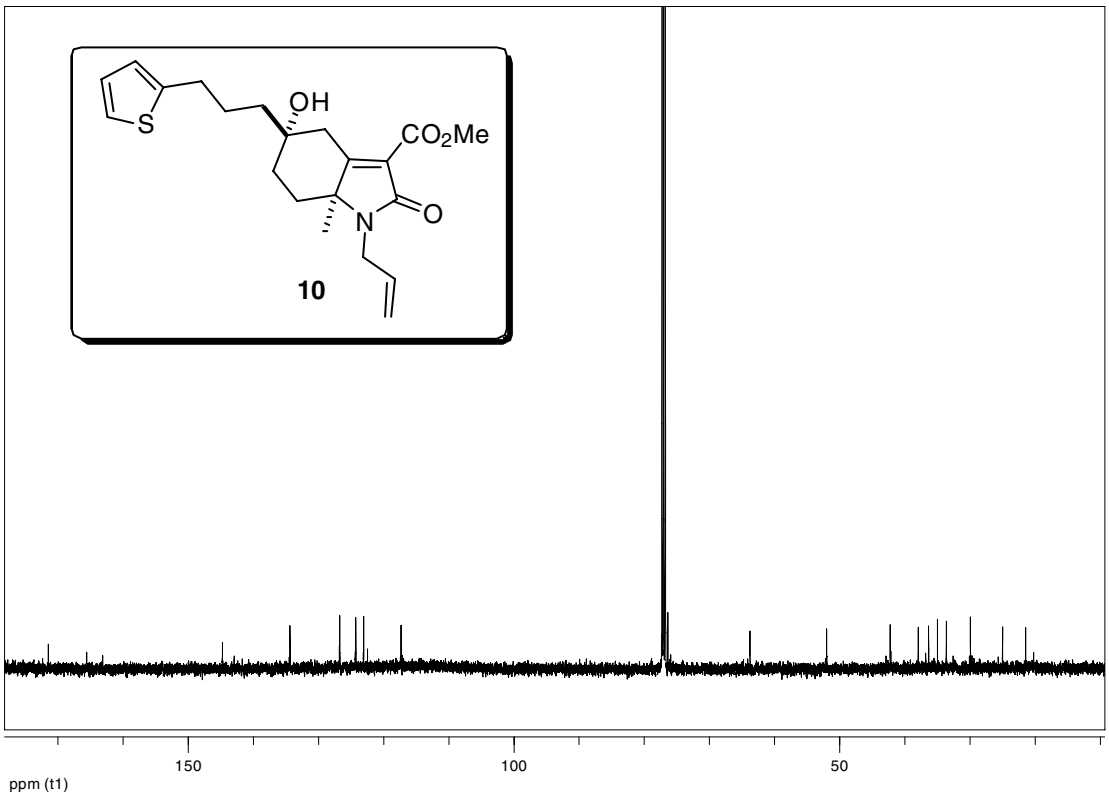
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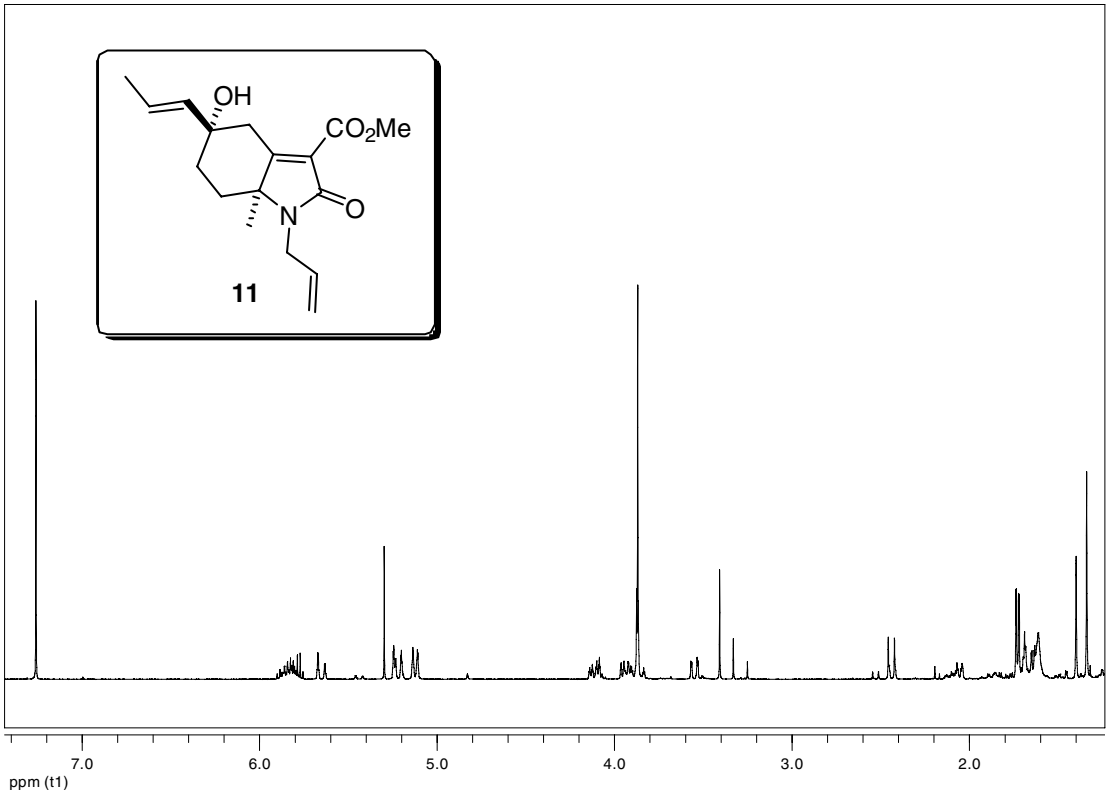
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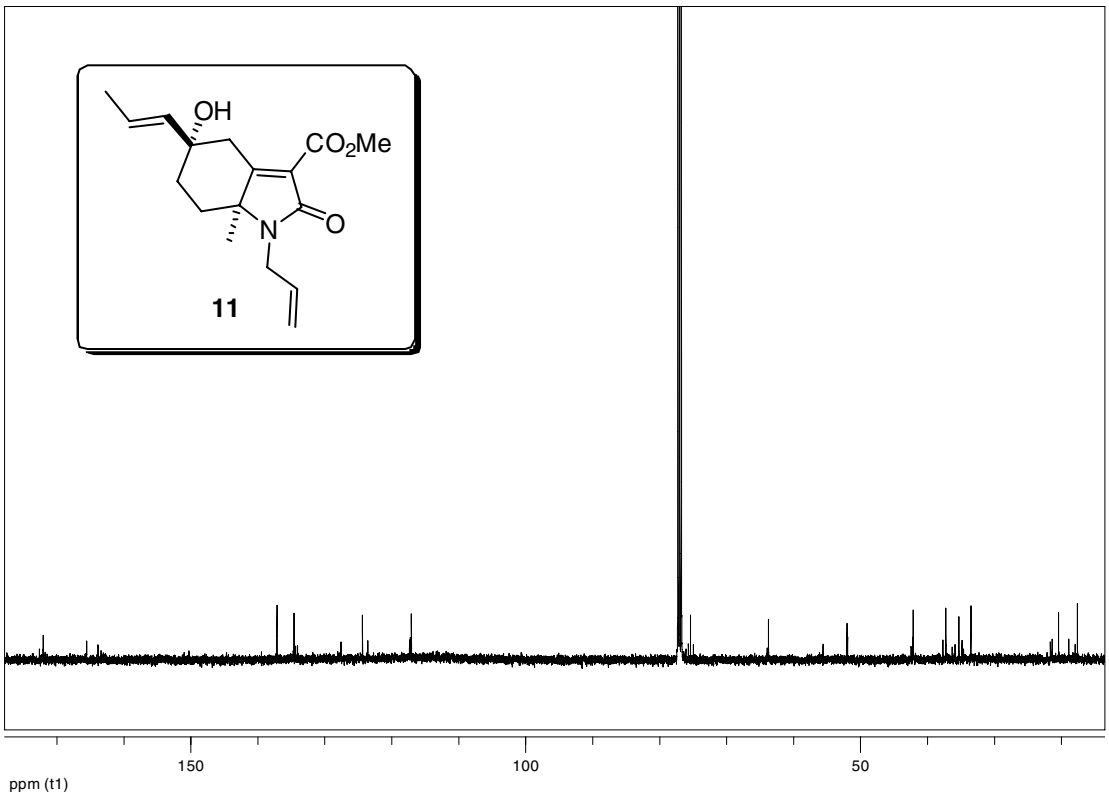
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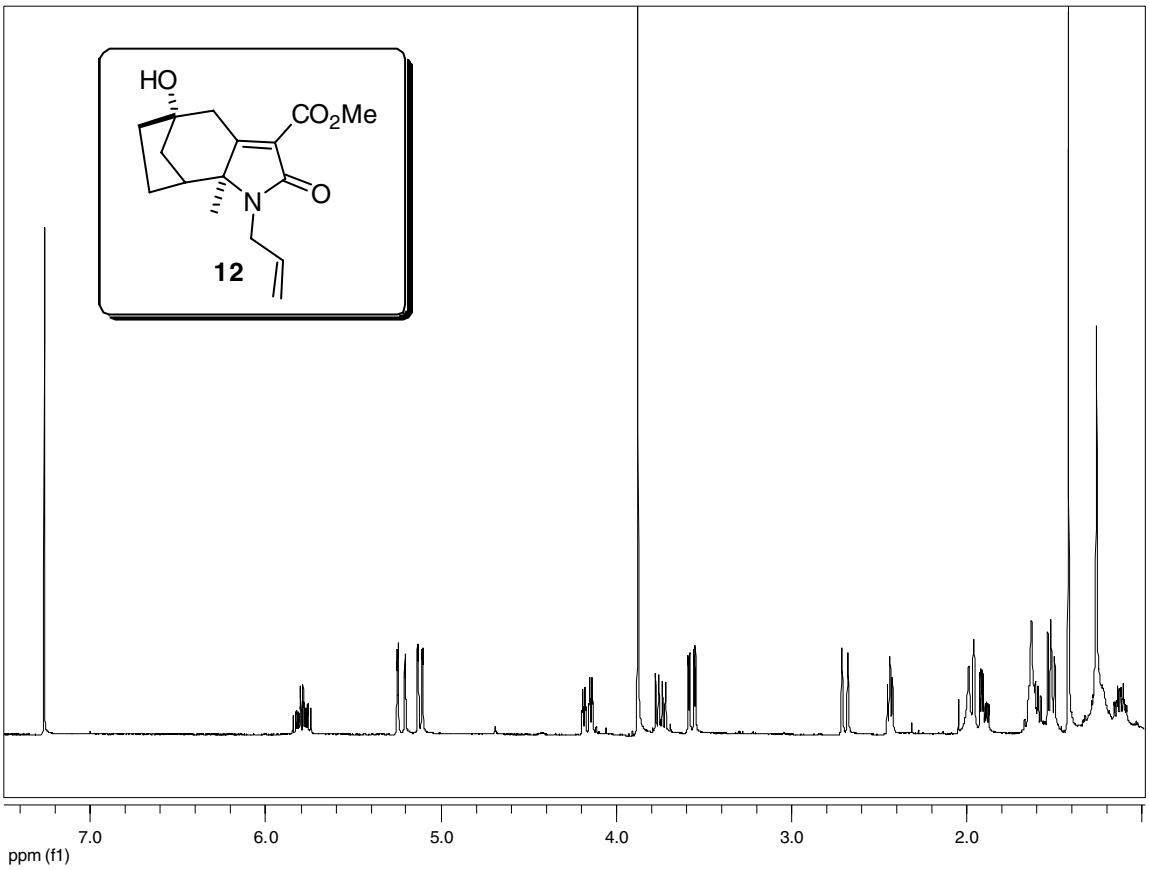
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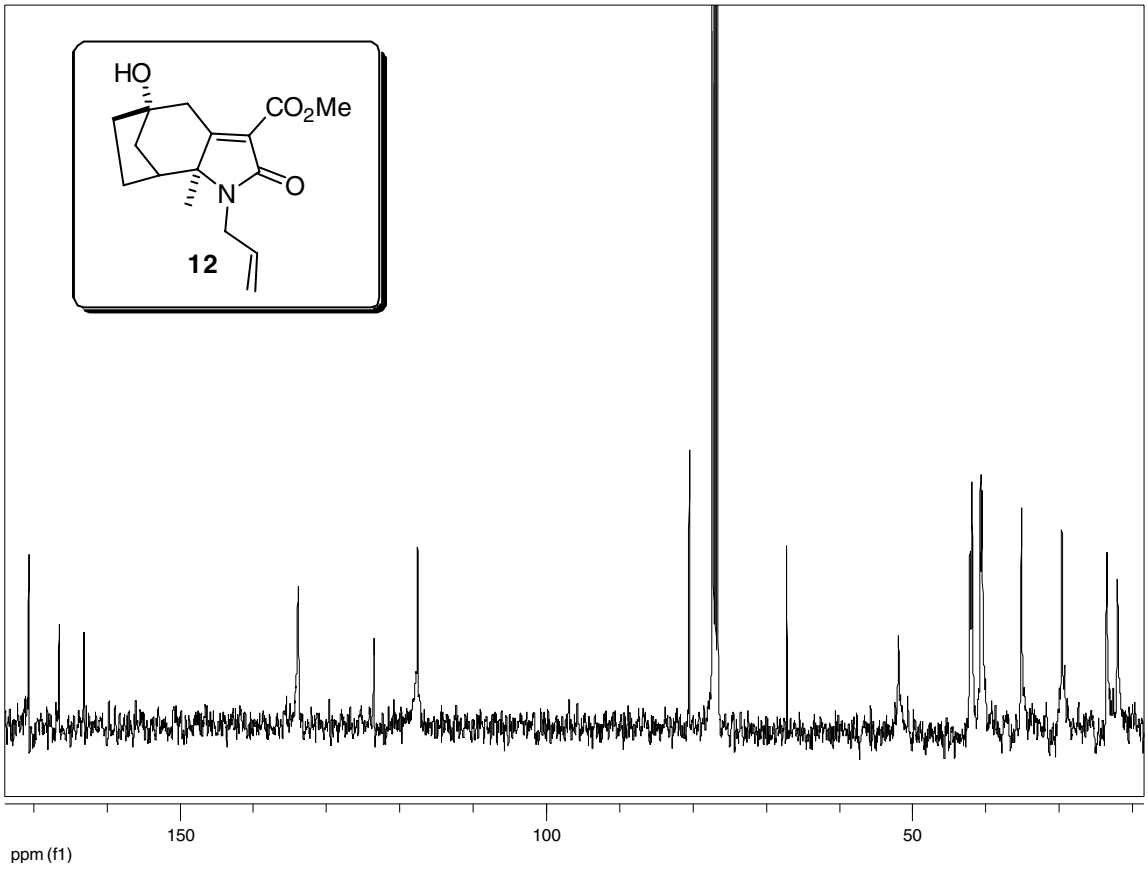
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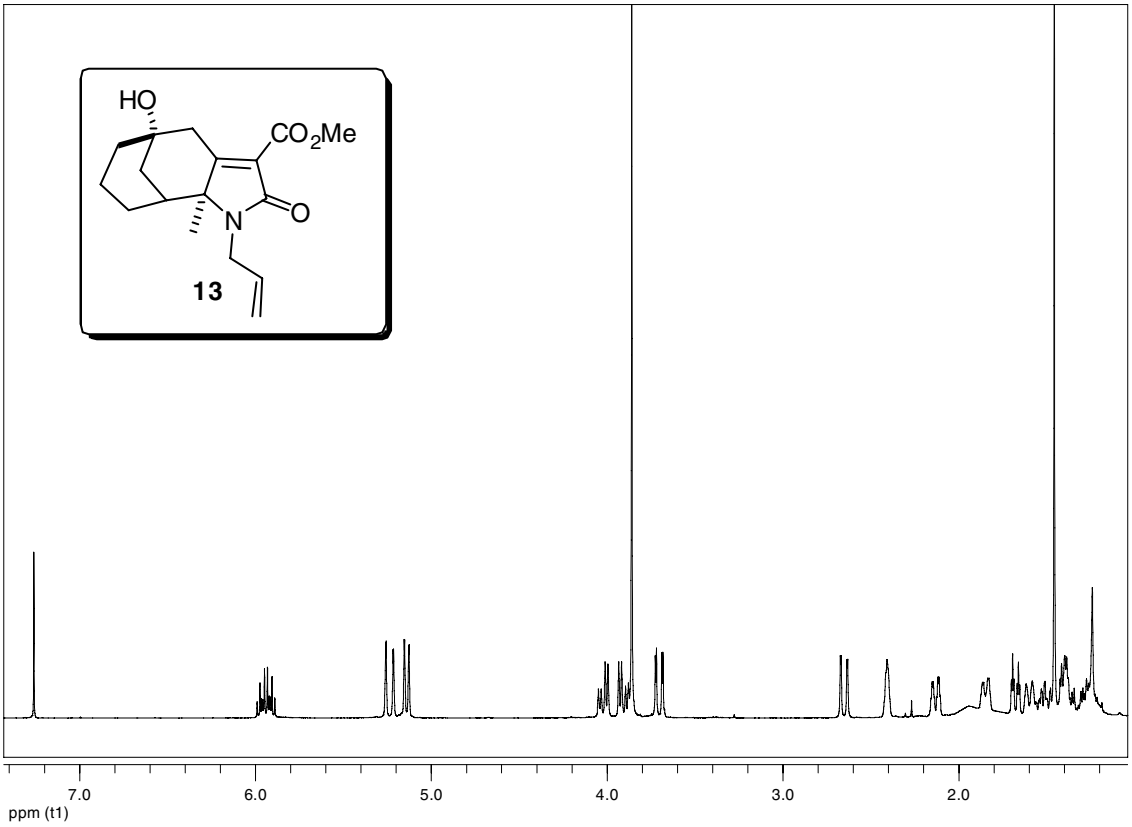
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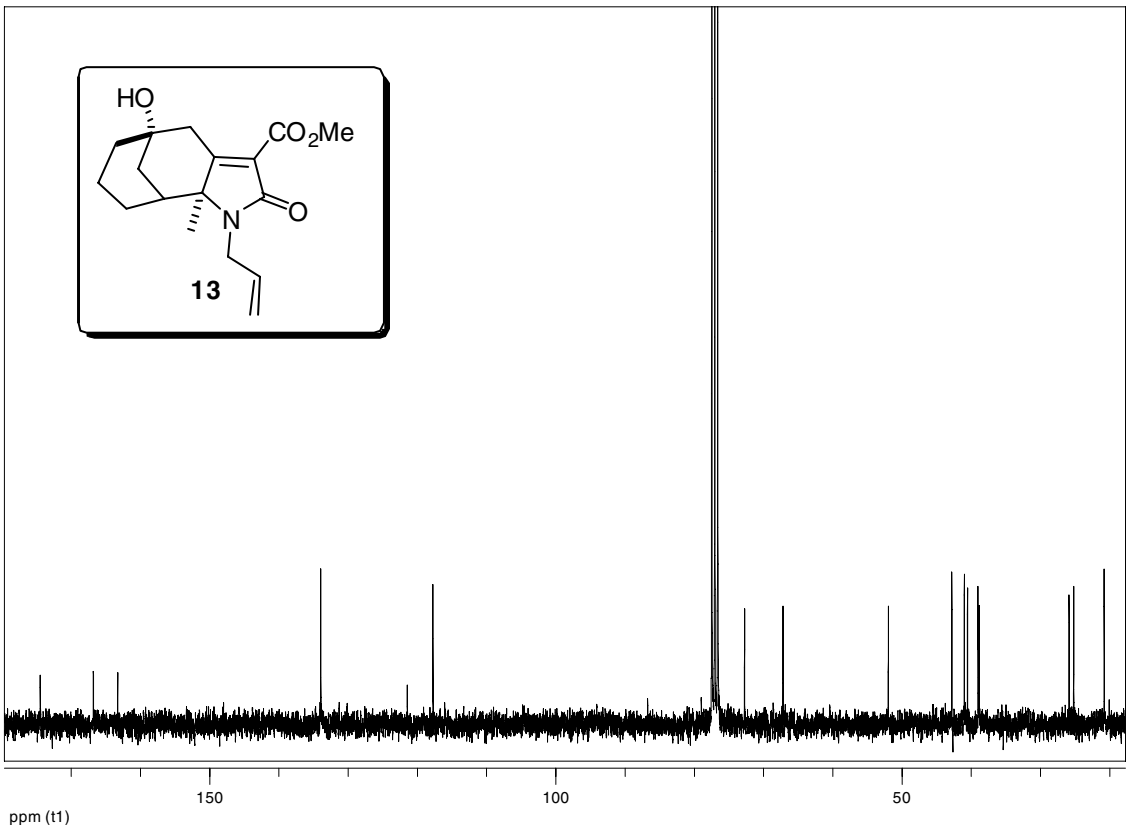
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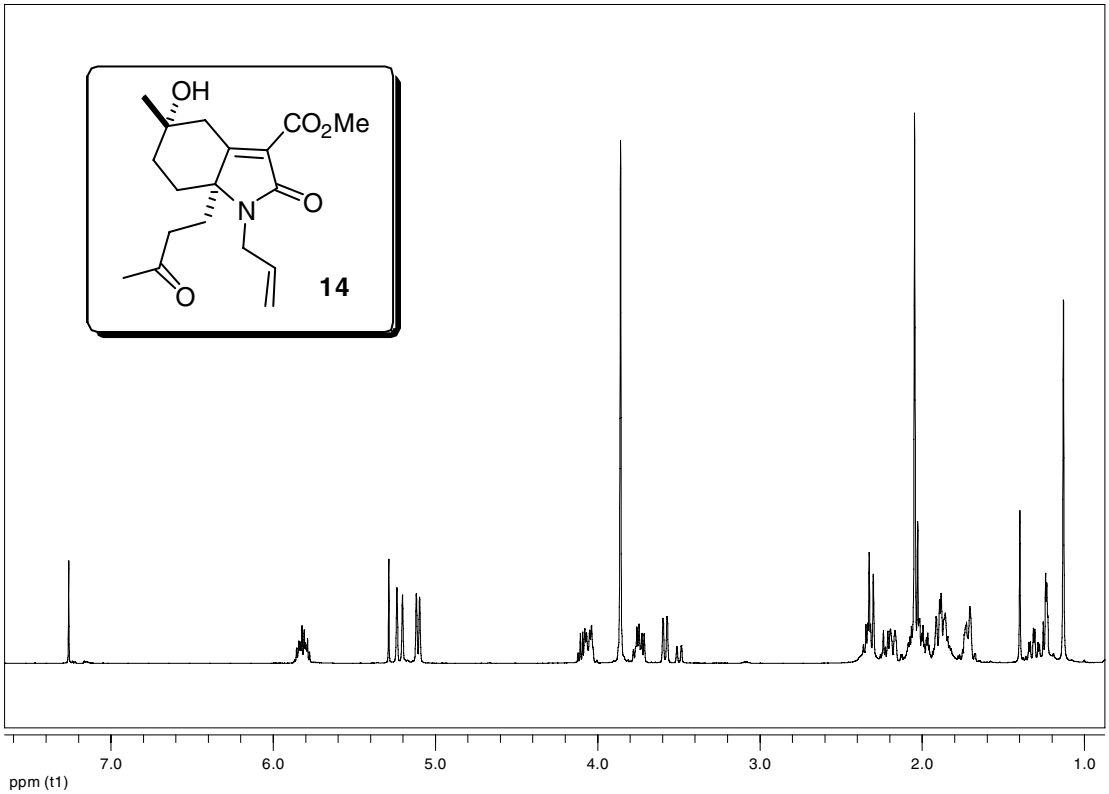
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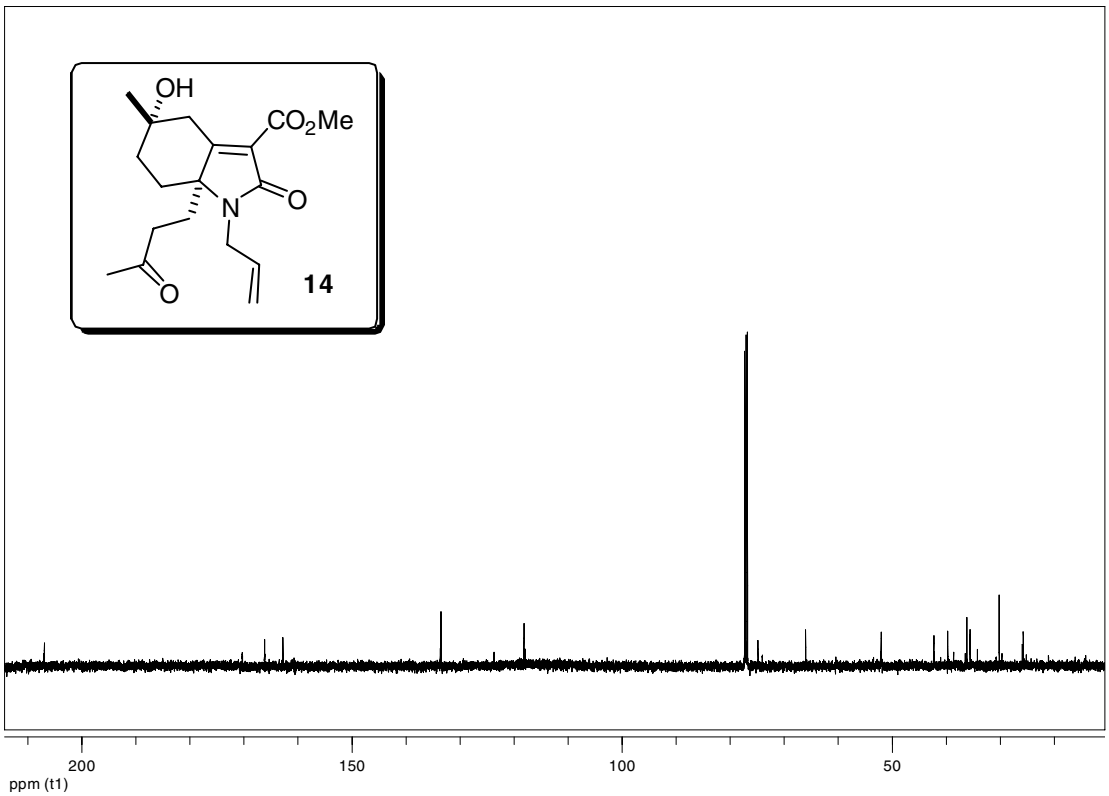
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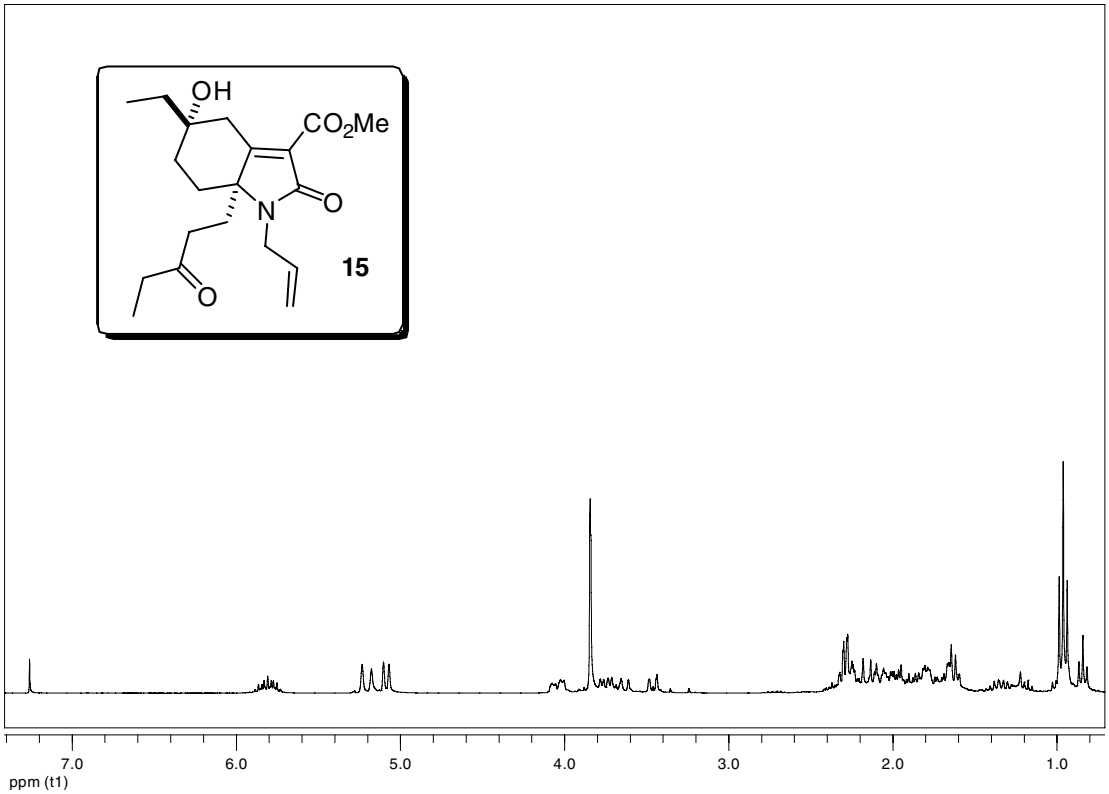
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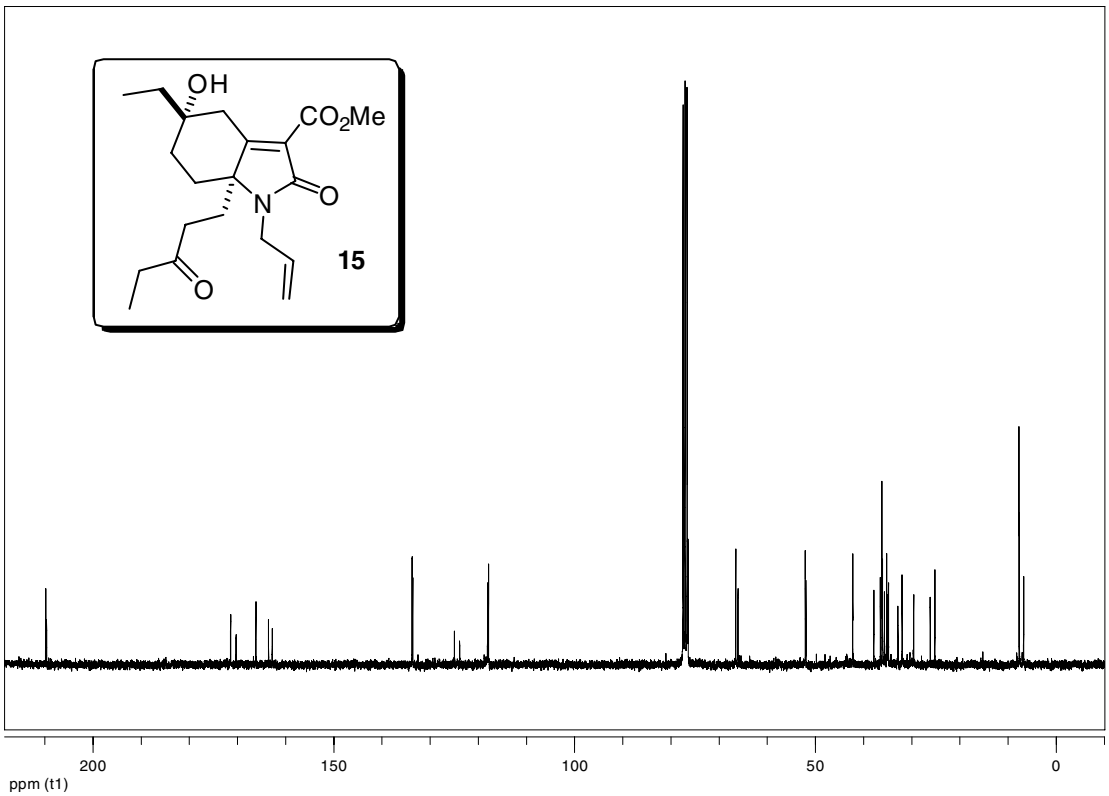
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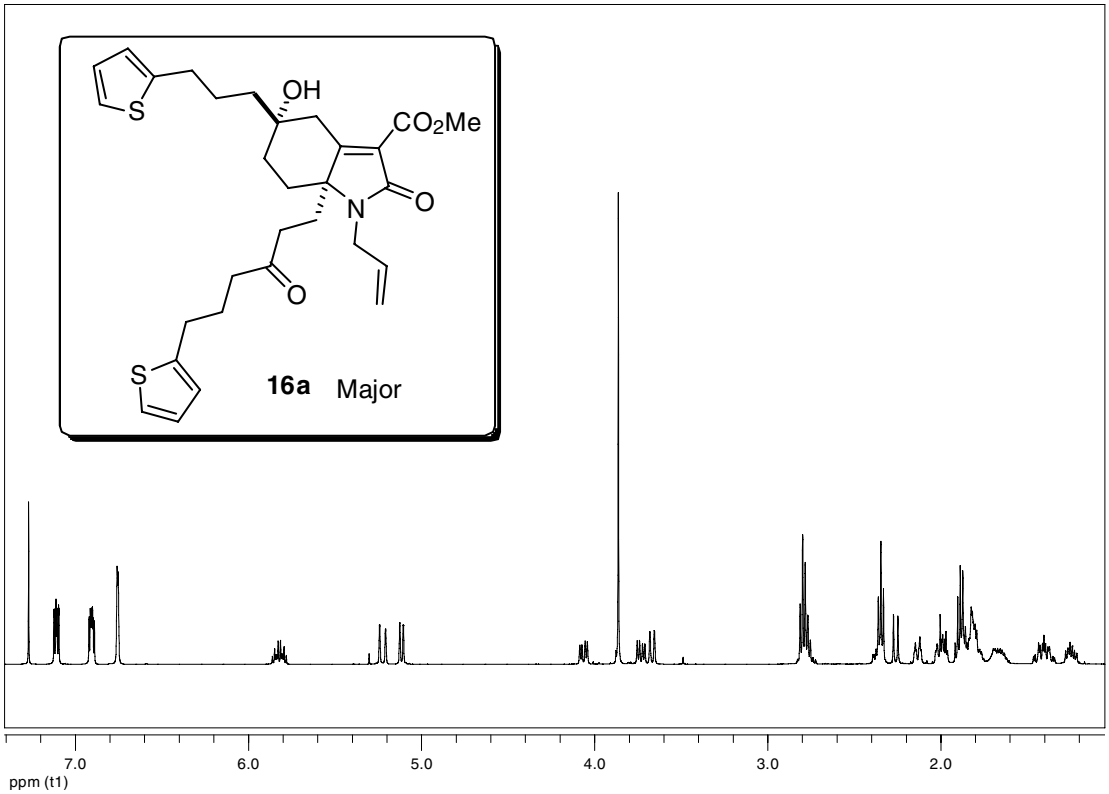
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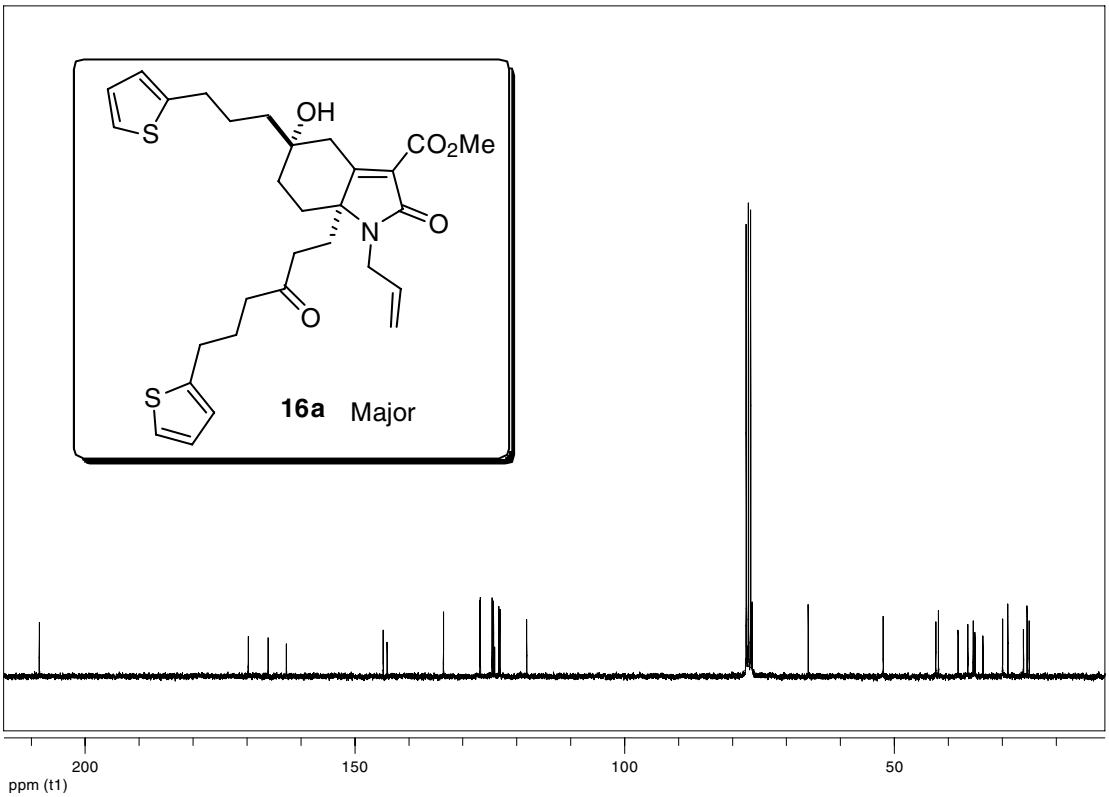
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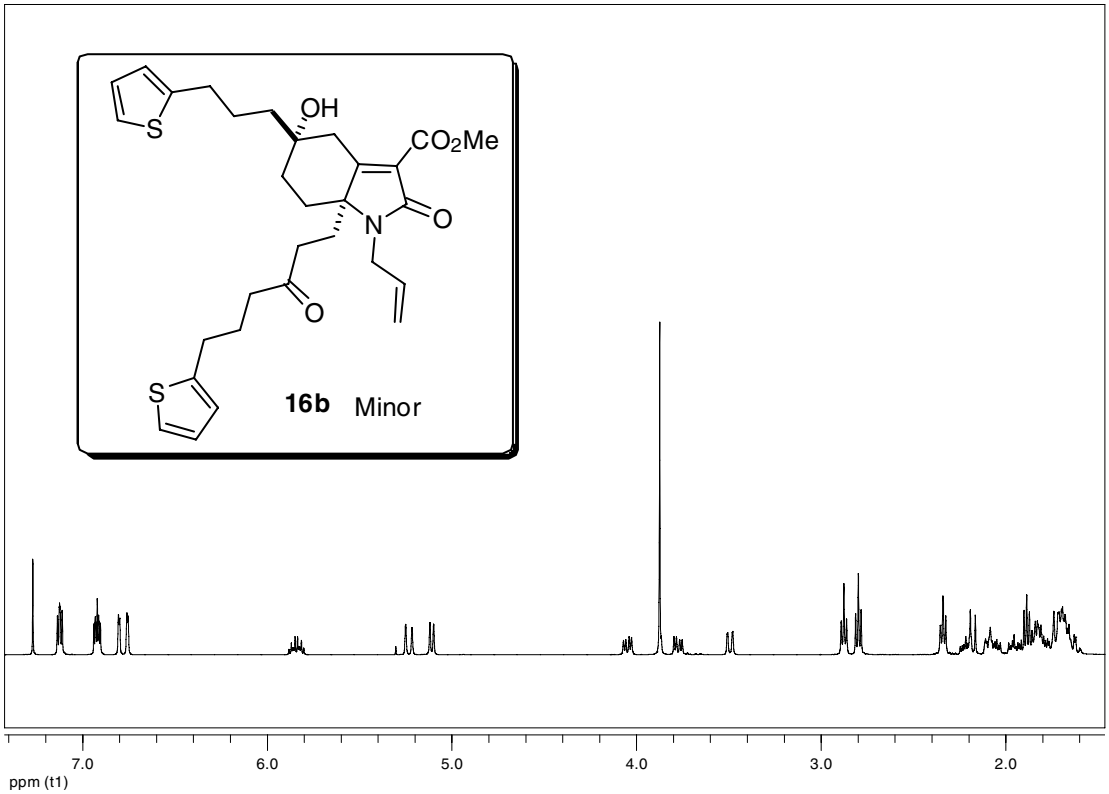
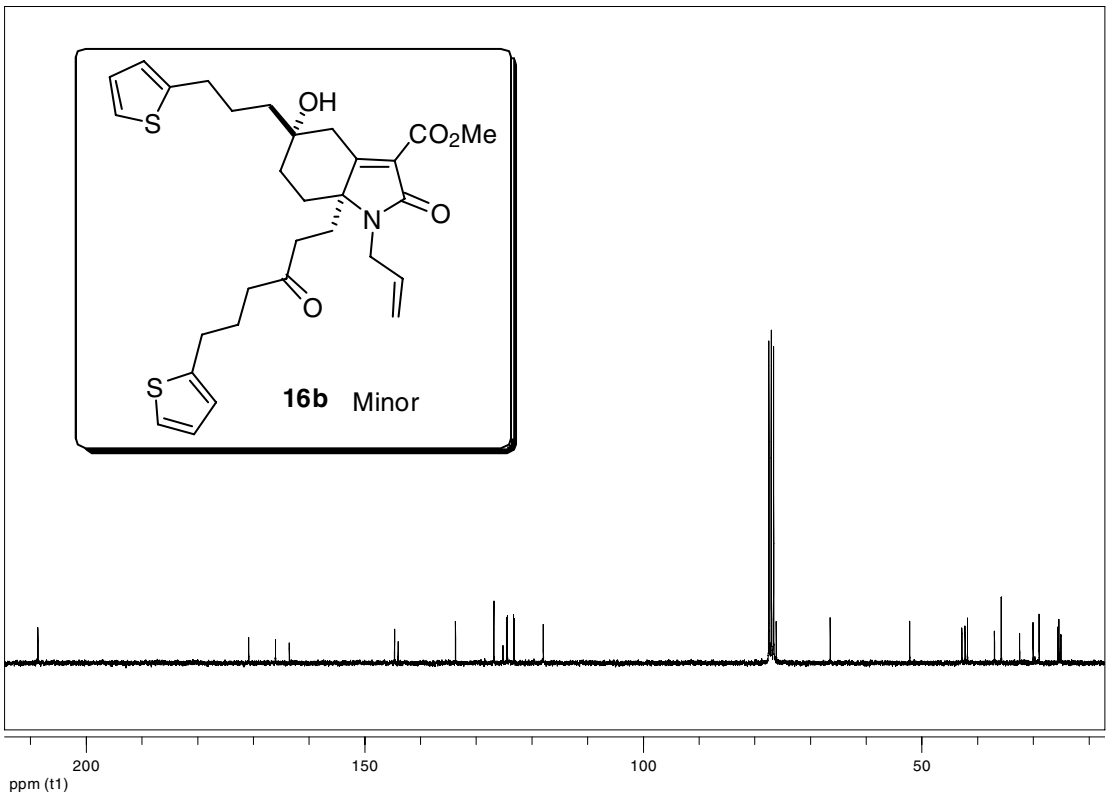

OH
CO2Me
N
O
O
S
S
16b Minor
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t1)


OH
CO2Me
N
O
O
S
S
16b Minor
200
150
100
50
ppm (t1)