Total Synthesis of Benzofuran-based Aspergillusene B via Halogenative Aromatization of Enones

*Gennadii A. Grabovyi, Aisha Bhatti, and Justin T. Mohr**

Department of Chemistry, University of Illinois at Chicago
845 West Taylor Street, Chicago, Illinois 60607 USA

Supporting Information

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I. General Information

Unless otherwise stated, reactions were performed in oven-dried glassware using dry, deoxygenated solvents. Anhydrous dichloromethane (CH_2Cl_2), triethylamine (Et_3N), tetrahydrofuran (THF, BHT-free), and *N*,*N*-dimethylformamide (DMF) were purchased from Aldrich, Fisher, or VWR, degassed with argon, and dried by passage through activated drying columns[1] on a Pure Process Technology system. Hexamethylphosphoramide (HMPA) and acrolein were distilled prior being used.

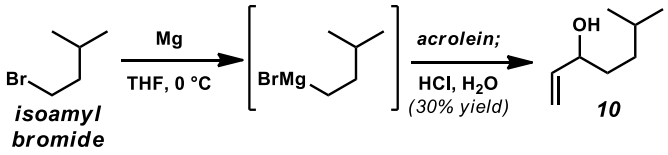
Starting materials and reagents, including isoamyl bromide, Mg flakes, acrolein, diisopropyl azodicarboxylate (DIAD), triphenylphosphine (Ph_3P), hexamethylphosphoramide (HMPA), trifluoromethanesulfonic anhydride (Tf_2O), pyridine, *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), palladium(II) acetate ($Pd(OAc)_2$), tetrabutylammonium chloride ($(n\text{-}Bu)_4NCl$), sodium formate (HCO_2Na), sodium carbonate (Na_2CO_3), xantphos, formic acid (HCO_2H), *N*,*N*′-dicyclohexylcarbodiimide (DCC), bromine (Br_2), acetic acid (AcOH), sulfuric acid (H_2SO_4), nickel(II) chloride ($NiCl_2$),copper (I) chloride (CuCl), and lithium hydroxide hydrate ($LiOH{\bullet}H_2O$) were purchased from Sigma–Aldrich, Alfa Aesar, Oakwood Chemical, or Fisher Scientific and used as received. *p*-Toluenesulfonyl bromide (TsBr) was prepared according to the known procedure.[2] LiHMDS (solid) was purchased from Sigma–Aldrich and stored in a glovebox and used to prepare 1 M solutions in THF by dissolving calculated amount of solid LiHMDS in dry THF immediately before use. Deuterated chloroform ($CDCl_3$, 99.9%, extra dry) was purchased from Cambridge Isotope Laboratories, Inc. and was used without further purification.

Reaction temperatures were controlled by an IKAmag immersion temperature modulator. Thin-layer chromatography (TLC) was performed using Silicycle silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or staining with *p*-anisaldehyde or $KMnO_4$ solutions. Flash chromatography[3] was performed using either SilicycleSiliaFlash® P60 silica gel (40–63 μm particle size) or Al_2O_3 (activated, neutral). ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX-500 (at 500 and 126 MHz, respectively) or DPX-400 instrument (at 400 and 101 MHz, respectively) and are reported relative to Me_4Si (δ 0.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septet, m = multiplet, comp. m = complex multiplet, app. =

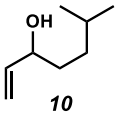
apparent, br s = broad singlet. Data for ^{13}C NMR spectra are reported in terms of chemical shift relative to Me_4Si (δ 0.0). Infrared (IR) spectra were recorded on a Nicolet iS5 FTIR spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were obtained from the University of Illinois at Urbana–Champaign Mass Spectral Facility or from the Cologna laboratory at the University of Illinois at Chicago.

II. 1st Generation Synthesis

*Synthesis of 2° allylic alcohol **10***



A 250 mL round bottomed flask (equipped with magnetic stir bar and rubber septa) was charged with Mg flakes (3.164 g, 130 mmol, 1.3 equiv) and then evacuated and refilled with dry N_2 (3 cycles). Dry THF (33 mL) was then added to the flask, and the mixture was cooled to 0 °C in an ice bath for 10 min. Neat isoamyl bromide (15.13 g, 100 mmol, 1 equiv) was added over 12 min via syringe pump. The ice bath was then removed and the reaction was allowed to stir at 24 °C for another 12 min. The reaction mixture was cooled back to 0 °C in an ice bath for 10 min, followed by addition of a solution of acrolein (5.9 g, 105.2 mmol, 1.05 equiv) in THF (40 mL) over a period of 1 h via syringe pump. The ice bath was then removed and the reaction was allowed to stir at 24 °C for another 40 min, after which the reaction mixture was poured into a glass beaker filled with ice. The solution was then mixed with deionized H_2O (500 mL), saturated aqueous NaCl solution (150 mL), 1 M aqueous HCl solution (50 mL), and EtOAc (300 mL). The aqueous phase was separated and extracted with EtOAc (3 x 100 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by distillation (b.p. 60 °C at ~15 torr) afforded desired alcohol **10** as colorless oil (3.79 g, 30%).



6-Methylhept-1-en-3-ol (10)

TLC (SiO_2) R_f = 0.57 in 3:1 hexanes/EtOAc, UV, *p*-anisaldehyde or $KMnO_4$ stains

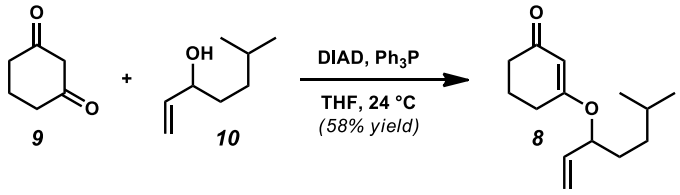
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddd, *J* = 16.9, 10.4, 6.3 Hz, 1H), 5.18 (d, *J* = 17.5 Hz, 1H), 5.06 (d, *J* = 10.4 Hz, 1H), 4.03 (app. q, *J* = 6.5 Hz, 1H), 2.30 (br s, 1H), 1.49 (m, 3H), 1.26 (m, 1H), 1.20–1.11 (m, 1H), 0.86 (d, *J* = 6.7 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.3, 114.5, 73.5, 34.8, 34.4, 28.0, 22.5, 22.5

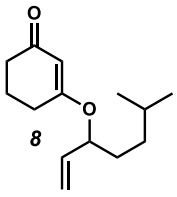
IR (neat) 3353, 2955, 2934, 2870, 1713, 1646, 1468, 1424, 1386, 1367, 1323, 1275, 1171, 1059, 1019, 991, 919, 880, 686 cm^{-1}

HRMS (EI^-) *m/z* calculated for $C_8H_{15}O$ $[M - H]^-$: 127.1123, found 127.1122

*Synthesis of vinylogous ether **8***



A 20 mL round bottomed flask equipped with a magnetic stir bar was charged with Ph_3P (787 mg, 3 mmol, 2 equiv) and THF (7.5 mL). Neat DIAD (0.59 mL, 3 mmol, 2 equiv) was then added dropwise over 40 sec. After 2.5 min a very distinct white solid was formed in the reaction mixture, and then alcohol **10** (0.46 mL, 3 mmol, 2 equiv) was added over a 20 sec period. After stirring at 24 °C for 5 min, a solution of diketone 9 (168 mg, 1.5 mmol, 1 equiv) in THF (3 mL) was added dropwise over 1 min. Immediately after addition of diketone 9 TLC indicated compete formation of the desired product and the reaction was quenched with aqueous NaCl solution (10 mL), deionized H_2O (30 mL), and EtOAc (20 mL). The aqueous phase was separated and extracted with EtOAc (1 x 20 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 4:1) afforded the desired product 8 as a colorless oil (195 mg, 58%).



3-((6-Methylhept-1-en-3-yl)oxy)cyclohex-2-enone (8)

TLC (SiO_2) R_f = 0.56 in 2:1 hexanes/EtOAc, UV, *p*-anisaldehyde or $KMnO_4$ stains

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.68 (dddd, *J* = 17.4, 10.7, 6.7, 1.6 Hz, 1H), 5.32 (s, 1H), 5.23–5.13 (m, 2H), 4.46 (app. q, *J* = 6.5 Hz, 1H), 2.38 (app. td, *J* = 6.3, 2.9 Hz, 2H), 2.33–2.26 (m, 2H), 1.94 (app. p, *J* = 6.5 Hz, 2H), 1.70 (dddd, *J* = 11.7, 10.1, 6.8, 5.2 Hz, 1H), 1.58 (dddd, *J*

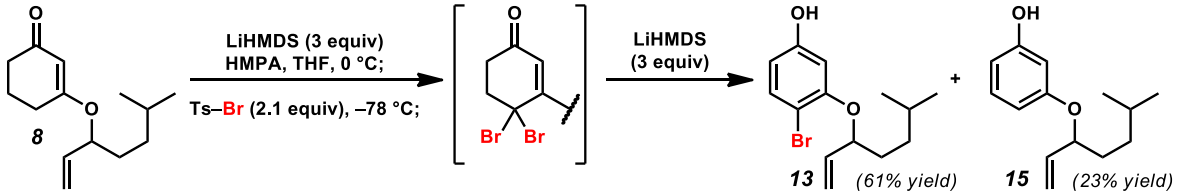
= 11.4, 9.7, 6.5, 5.0 Hz, 1H), 1.51 (app. dtd, J = 13.3, 6.7, 1.5 Hz, 1H), 1.33–1.10 (m, 4H), 0.86 (d, J = 6.7 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.8, 176.9, 136.0, 117.4, 104.0, 79.7, 36.6, 34.0, 32.7, 29.3, 27.8, 22.5, 21.1

IR (neat) 2953, 2870, 1652, 1599, 1457, 1429, 1380, 1347, 1326, 1212, 1180, 1134, 1058, 988, 930, 863, 825, 763, 684 cm^{-1}

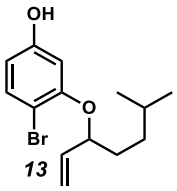
HRMS (ES^+) *m/z* calculated for $C_{14}H_{23}O_2$ $[M + H]^+$: 223.1698, found 223.1696

*Synthesis of bromoarene **13***



A 50 mL glass round bottomed flask (equipped with magnetic stir bar and rubber septa) was evacuated and refilled with dry N_2 (3 cycles). The flask was then charged with vinylogous ester 8 (254 mg, 1.14 mmol, 1 equiv), THF (5.71 mL), and HMPA (0.5 mL). The mixture was cooled to 0 °C in an ice bath for 10 min, followed by addition of LiHMDS solution (1 M solution in THF, 3.43 mL, 3.43 mmol, 3 equiv). The reaction mixture was allowed to stir at 0 °C for 1 h, after which it was cooled to –78 °C by means of a dry ice/acetone bath. After 10 min, a solution of TsBr (563 mg, 2.4 mmol, 2.1 equiv) in THF (4.57 mL) was added dropwise over 10 min, followed by a syringe rinse with THF (1.14 mL). After 45 min, a solution of LiHMDS (1 M solution in THF, 1.14 mL, 1.14 mmol, 1 equiv) was added to the reaction mixture. After 20 min, the mixture was allowed to warm to 24 °C over a period of 25 min. At this point, TLC indicated almost complete conversion of all intermediates to the target aromatic products. Additional LiHMDS solution (1 M solution in THF, 2.28 mL, 2.28 mmol, 1 equiv) was added to promote completion of the reaction. After 20 min, the reaction was quenched with saturated aqueous NaCl solution (15 mL), EtOAc (200 mL), and aqueous HCl solution (1 M, 10 mL). The organic phase was separated and then sequentially washed with deionized H_2O (3 x 50 mL), 1 M aq HCl solution (1 x 50 mL), and saturated aqueous NaCl solution (1 x 50 mL). The organic phase was then dried over Na_2SO_4, decanted, and concentrated in vacuo. Purification by flash

chromatography (SiO_2, hexanes/EtOAc = 20:1 → 10:1) afforded the desired product **13** as a pale yellow oil (160 mg, 61%) and the undesired *des*-bromo resorcinol **15** as an orange oil (58 mg, 23%). Resorcinol **15** decomposed rapidly upon standing at ambient temperature, and was therefore only characterized by TLC, ^{1}H NMR, and ^{13}C NMR.



13

4-Bromo-3-((6-methylhept-1-en-3-yl)oxy)phenol (13)

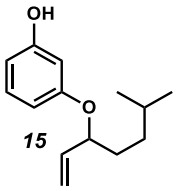
TLC (SiO_2) R_f = 0.27 in 6:1 hexanes/EtOAc, UV, *p*-anisaldehyde or $KMnO_4$ stains

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.5 Hz, 1H), 6.44 (d, *J* = 2.7 Hz, 1H), 6.30 (dd, *J* = 8.6, 2.7 Hz, 1H), 5.85 (ddd, *J* = 17.1, 10.6, 6.3 Hz, 1H), 5.25 (d, *J* = 17.6 Hz, 1H), 5.21 (d, *J* = 10.6 Hz, 1H), 5.06 (br s, 1H), 4.53 (app. q, *J* = 6.4 Hz, 1H), 1.85 (dddd, *J* = 13.6, 11.6, 6.9, 5.0 Hz, 1H), 1.71 (m, 1H), 1.58 (m, 1H), 1.41 (dddd, *J* = 13.2, 11.5, 6.8, 5.0 Hz, 1H), 1.35–1.28 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 137.4, 133.2, 116.8, 108.8, 103.7, 103.7, 81.1, 34.2, 33.3, 29.7, 27.9, 22.6, 22.5

IR (neat) 2955, 2869, 1648, 1617, 1588, 1574, 1495, 1448, 1385, 1342, 1284, 1191, 1158, 1105, 1029, 980, 924, 884, 836, 762, 749, 690 cm^{-1}

HRMS (ESI^-) *m/z* calculated for $C_8H_{15}O$ $[M - H]^-$: 297.0490, found 297.0495



15

3-((6-methylhept-1-en-3-yl)oxy)phenol (15)

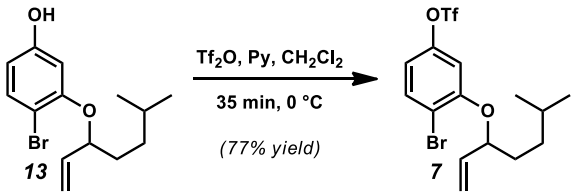
TLC (SiO_2) R_f = 0.44 in 4:1 hexanes/EtOAc, UV, *p*-anisaldehyde or $KMnO_4$ stains

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (t, *J* = 8.1 Hz, 1H), 6.49 (d, *J* = 8.4 Hz, 1H), 6.45–6.36 (m, 2H), 5.84 (ddd, *J* = 17.1, 10.6, 6.2 Hz, 1H), 5.36–5.14 (m, 2H), 4.82 (br. s, 1H), 4.53 (q, *J* =

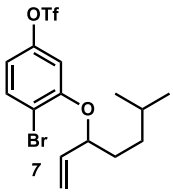
6.3 Hz, 1H), 1.90–1.71 (m, 1H), 1.72–1.50 (m, 2H), 1.45–1.18 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 156.5, 138.1, 129.9, 116.3, 108.5, 107.7, 103.5, 79.4, 34.4, 33.4, 29.7, 27.9, 22.5

Synthesis of aryl triflate 7



A 4 mL glass scintillation vial equipped with a magnetic stir bar was charged with bromoarene **12** (100 mg, 0.334 mmol, 1 equiv), pyridine (54 μL, 0.668 mmol, 2 equiv), and CH_2Cl_2 (0.33 mL). This mixture was then cooled to 0 °C with an ice bath, followed by addition of solution of Tf_2O (67 μL, 0.4 mmol, 1.2 equiv) in CH_2Cl_2 (0.17 mL). After 35 min, TLC indicated reaction completion and the mixture was quenched with saturated aqueous NaCl solution (2 mL) and EtOAc (2 mL). The aqueous phase was separated and extracted with EtOAc (3 x 1 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 20:1) afforded the desired product aryl triflate 7 as colorless oil (111 mg, 77%).



4-Bromo-3-((6-methylhept-1-en-3-yl)oxy)phenyl trifluoromethanesulfonate (7)

TLC (SiO_2) R_f = 0.79 in 6:1 hexanes/EtOAc, UV, *p*-anisaldehyde or $KMnO_4$ stains

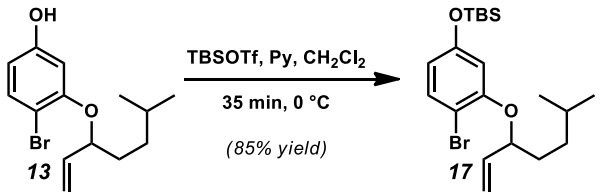
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.7 Hz, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 6.75 (dd, *J* = 8.7, 2.7 Hz, 1H), 5.84 (ddd, *J* = 17.2, 10.3, 6.5 Hz, 1H), 5.29 (d, *J* = 11.5 Hz, 1H), 5.28 (d, *J* = 16.4 Hz, 1H), 4.58 (app. q, *J* = 6.4 Hz, 1H), 1.89 (dddd, *J* = 13.7, 11.7, 6.9, 5.1 Hz, 1H), 1.76 (m, 1H), 1.60 (m, *J* = 13.3, 6.7 Hz, 1H), 1.51–1.23 (m, 2H), 0.92 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 148.8, 136.5, 133.8, 118.7 (q, $J_{C–F}$ = 321.0 Hz), 117.7, 114.1, 112.7, 108.9, 81.8, 34.1, 33.2, 27.9, 22.5, 22.4

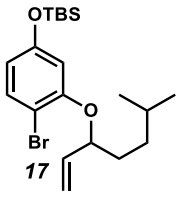
IR (neat) 2956, 2872, 1599, 1574, 1476, 1426, 1413, 1368, 1270, 1244, 1208, 1139, 1117, 1042, 992, 975, 932, 890, 851, 836, 799, 759, 728, 666, 612, 596 cm^{-1}

HRMS (ES^+) *m/z* calculated for $C_{15}H_{18}BrF_3O_4S$ $[M]^+$: 430.0061, found 430.0053

*Synthesis of aryl silyl ether **17***



A 4 mL glass scintillation vial equipped with a magnetic stir bar was charged with bromoarene **13** (100 mg, 0.334 mmol, 1 equiv), pyridine (54 µL, 0.668 mmol, 2 equiv), and CH_2Cl_2 (0.33 mL). This mixture was then cooled to 0 °C with an ice bath, followed by addition of a solution of TBSOTf (92 µL, 0.4 mmol, 1.2 equiv) in CH_2Cl_2 (0.17 mL). After 35 min, TLC indicated reaction completion and the mixture was quenched with saturated aqueous NaCl solution (2 mL) and EtOAc (2 mL). The aqueous phase was separated and extracted with EtOAc (3 x 1 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 20:1) afforded the desired aryl silyl ether **17** as a colorless oil (117 mg, 85%).



(4-Bromo-3-((6-methylhept-1-en-3-yl)oxy)phenoxy)(*tert*-butyl)dimethylsilane (17)

TLC (SiO_2) R_f = 0.85 in 6:1 hexanes/EtOAc, UV, *p*-anisaldehyde or $KMnO_4$ stains

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 8.6 Hz, 1H), 6.43 (d, *J* = 2.6 Hz, 1H), 6.33 (dd, *J* = 8.5, 2.6 Hz, 1H), 5.87 (ddd, *J* = 17.1, 10.6, 6.4 Hz, 1H), 5.33–5.17 (m, 2H), 4.53 (app. q, *J* =

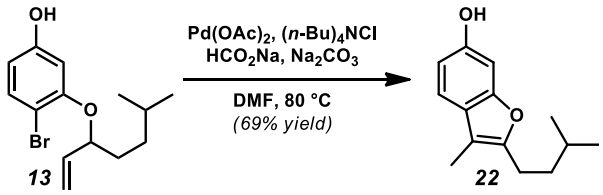
6.4 Hz, 1H), 1.87 (dddd, J = 13.4, 11.5, 6.8, 5.0 Hz, 1H), 1.73 (m, 1H), 1.60 (m, 1H), 1.50–1.23 (m, 2H), 0.98 (s, 9H), 0.92 (app. d, J = 6.6 Hz, 6H), 0.18 (app. s, 6H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8, 155.3, 137.7, 132.9, 116.7, 113.7, 108.5, 104.6, 81.0, 34.2, 33.4, 27.9, 25.7, 25.6, 22.6, 22.5, 18.2, –4.5, –4.5

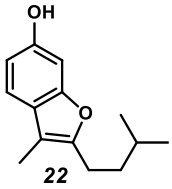
IR (neat) 2954, 2929, 2858, 1580, 1471, 1411, 1363, 1294, 1253, 1181, 1118, 1092, 1040, 1003, 925, 896, 838, 779, 713, 670, 636, 576, 558 cm^{-1}

HRMS (ES^+) *m/z* calculated for $C_{20}H_{35}BrO_2Si$ $[M + H]^+$: 413.1511, found 413.1495

*Synthesis of benzofuran **22***



A 20 mL glass scintillation vial equipped with a magnetic stir bar was charged with aryl bromide **13** (299 mg, 1 mmol, 1 equiv), $Pd(OAc)_2$ (45 mg, 0.2 mmol, 20 mol %), (n-Bu)$_4$NCl (278 mg, 1 mmol, 1 equiv), HCO_2Na (68 mg, 1 mmol, 1 equiv), Na_2CO_3 (212 mg, 2 mmol, 2 equiv), and DMF (13.9 mL) in a glovebox under inert (N_2) atmosphere. The reaction vial was then sealed with a plastic cap, removed from a glovebox, and placed in an aluminum heating block that was preheated to 80 °C. After 23 h, the reaction was cooled to 24 °C and quenched with deionized H_2O (30 mL) and EtOAc (50 mL). The organic phase was separated, washed with deionized H_2O (3 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 10:1) afforded the desired product benzofuran **22** as colorless oil (150 mg, 69%).



2-Isopentyl-3-methylbenzofuran-6-ol (22)

TLC (SiO_2) R_f = 0.24 in 10:1 hexanes/EtOAc, UV, p-anisaldehyde or $KMnO_4$ stains

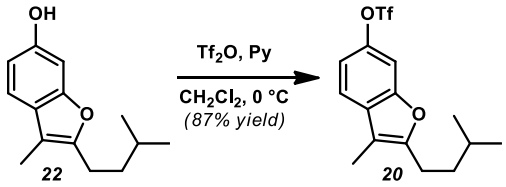
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.3 Hz, 1H), 6.90 (d, *J* = 2.2 Hz, 1H), 6.75 (dd, *J* = 8.3, 2.2 Hz, 1H), 5.13 (s, 1H), 2.69 (t, *J* = 7.2 Hz, 2H), 2.13 (s, 3H), 1.59 (dt, *J* = 6.9, 3.5 Hz, 3H), 0.96 (d, *J* = 5.9 Hz, 6H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 153.7, 152.7, 124.3, 118.7, 110.7, 108.9, 98.0, 37.2, 27.6, 24.2, 22.4, 7.9

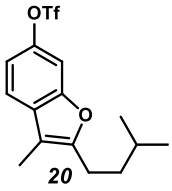
IR (neat) 3370, 2955, 2927, 2869, 1706, 1621, 1490, 1449, 1385, 1367, 1344, 1292, 1150, 1132, 1114, 1048, 959, 908, 837, 805, 767, 732, 699, 631 cm^{-1}

HRMS (ES^+) *m/z* calculated for $C_{14}H_{19}O_2$ $[M + H]^+$: 219.1749, found 219.1747

*Synthesis of aryl triflate **20***



A 4 mL glass scintillation vial equipped with a magnetic stir bar was charged with benzofuran **22** (140 mg, 0.334 mmol, 1 equiv), pyridine (103 μL, 1.282 mmol, 2 equiv), and CH_2Cl_2 (1.92 mL). This mixture was then cooled to 0 °C with an ice bath, followed by addition of a solution of Tf_2O (129 μL, 0.769 mmol, 1.2 equiv) in CH_2Cl_2 (0.32 mL). After 4.5 h, TLC indicated reaction completion and the reaction mixture was diluted with CH_2Cl_2 (10 mL). The solution was washed with deionized H_2O (3 x 3 mL) and saturated aqueous NaCl solution (3 x 3 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated in vacuo thus affording the desired product aryl triflate **20** as a colorless oil (194 mg, 87%).



2-Isopentyl-3-methylbenzofuran-6-yl trifluoromethanesulfonate (20)

TLC (SiO_2) R_f = 0.65 in 10:1 hexanes/EtOAc, UV, *p*-anisaldehyde or $KMnO_4$ stains

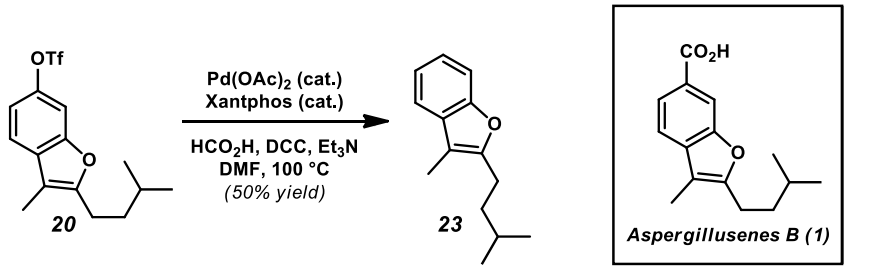
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 2.2 Hz, 1H), 7.13 (dd, J = 8.5, 2.2 Hz, 1H), 2.74 (t, J = 7.3 Hz, 2H), 2.17 (s, 3H), 1.60 (dt, J = 7.6, 3.8 Hz, 3H), 0.96 (d, J = 6.1 Hz, 6H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 153.1, 145.8, 130.6, 119.0, 118.7 (q, $J_{C–F}$ = 320.9 Hz), 115.4, 109.3, 104.6, 36.9, 27.6, 24.3, 22.3, 7.7

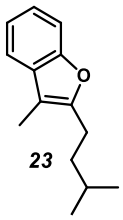
IR (neat) 2958, 2872, 1633, 1599, 1478, 1421, 1368, 1345, 1317, 1238, 1204, 1140, 1091, 1048, 943, 861, 829, 809, 774, 750, 715, 628, 602 cm^{-1}

HRMS (ES^+) *m/z* calculated for $C_{15}H_{17}F_3O_4S$ $[M]^+$: 350.0799, found 350.0786

*Accidental synthesis of benzofuran **23***



A 4 mL glass scintillation vial equipped with a magnetic stir bar was charged with aryl triflate **20** (35 mg, 0.1 mmol, 1 equiv), $Pd(OAc)_2$ (1.2 mg, 0.005 mmol, 5 mol %), xantphos (2.9 mg, 0.005 mmol, 5 mol %), DCC (4.1 mg, 0.02 mmol, 20 mol %), HCO_2H (26 μL, 0.7 mmol, 7 equiv), Et_3N (28 μL, 0.2 mmol, 2 equiv), and DMF (0.2 mL) in a glovebox under inert (N_2) atmosphere. The reaction vial was then sealed with a plastic cap, removed from the glovebox, and placed in an aluminum heating block that was preheated to 100 °C. After 19.5 h, the reaction was cooled to 24 °C and then quenched with saturated aqueous NaCl solution (3 mL), deionized H_2O (15 mL), and EtOAc (1 mL). The aqueous phase was separated and extracted with EtOAc (5 x 3 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 1:1) afforded the undesired product benzofuran **23** as colorless oil (10.1 mg, 50%).



23

2-Isopentyl-3-methylbenzofuran (23)

TLC (SiO_2) R_f = 0.83 in 10:1 hexanes/EtOAc, UV, *p*-anisaldehyde or $KMnO_4$ stains

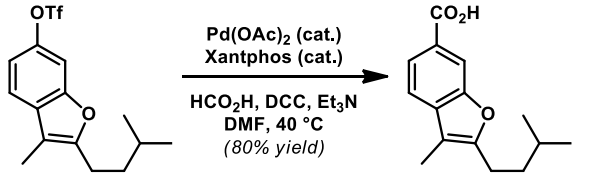
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.35 (m, 2H), 7.26–7.15 (m, 2H), 2.74 (t, *J* = 7.3 Hz, 2H), 2.17 (s, 3H), 1.68–1.56 (m, 3H), 0.96 (d, *J* = 6.1 Hz, 6H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 153.8, 130.5, 122.9, 121.9, 118.5, 110.5, 109.2, 37.1, 29.7, 27.6, 24.2, 22.4, 7.9

IR (neat) 2955, 2923, 2868, 1633, 1455, 1385, 1366, 1318, 1277, 1255, 1209, 1177, 1136, 1108, 1072, 1049, 1007, 922, 858, 822, 741, 689, 562 cm^{-1}

HRMS (ES^+) *m/z* calculated for $C_{14}H_{19}O$ $[M + H]^+$: 203.1436, found 203.1433

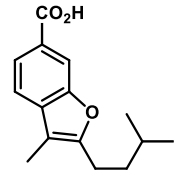
Total synthesis of aspergillusene B



20 ***Aspergillusene B (1)***

A 4 mL glass scintillation vial equipped with a magnetic stir bar was charged with aryl triflate **20** (35 mg, 0.1 mmol, 1 equiv), $Pd(OAc)_2$ (2.9 mg, 0.012 mmol, 12 mol %), xantphos (7.0 mg, 0.012 mmol, 12 mol %), DCC (9.2 mg, 0.045 mmol, 45 mol %), HCO_2H (26 µL, 0.7 mmol, 7 equiv), Et_3N (28 µL, 0.2 mmol, 2 equiv), and DMF (0.2 mL) in a glovebox under inert (N_2) atmosphere. The reaction vial was then sealed with a plastic cap, removed from the glovebox, and placed in an aluminum heating block that was preheated to 40 °C. After 19.5 h, the reaction was cooled to 24 °C and then quenched with saturated aqueous NaCl solution (3 mL), deionized H_2O (15 mL), and EtOAc (1 mL). The aqueous phase was separated and extracted with EtOAc (5 x 3 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in

vacuo. Purification by flash chromatography (SiO_2, hexanes/EtOAc = 1:1) afforded the desired natural product aspergillusene B (1) as a white amorphous solid (19.1 mg, 80%).[4]



Aspergillusene B (1)

2-Isopentyl-3-methylbenzofuran-6-carboxylic acid (1)

TLC (SiO_2) R_f = 0.15 in 10:1 hexanes/EtOAc, UV, *p*-anisaldehyde or $KMnO_4$ stains

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.20 (s, 3H), 1.62 (m, 3H), 0.96 (d, *J* = 5.7 Hz, 6H)

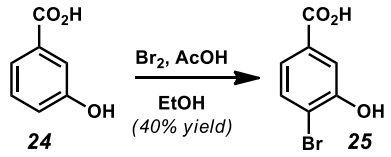
^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 158.9, 153.2, 135.7, 124.2, 123.9, 118.2, 112.7, 110.0, 36.9, 27.7, 24.5, 22.3, 7.8

IR (neat) 3319, 2954, 2924, 2851, 2571, 1674, 1608, 1578, 1498, 1466, 1434, 1391, 1363, 1348, 1304, 1265, 1231, 1186, 1125, 1093, 1071, 1046, 967, 933, 887, 867, 843, 792, 769, 745, 725, 699, 641, 605, 571 cm^{-1}

HRMS (ES^-) *m/z* calculated for $C_{15}H_{17}O_3$ $[M - H]^-$: 245.1178, found 245.1178

III. 2nd Generation Synthesis

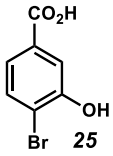
*Synthesis of aryl bromide **25***



24 ***25***

A 250 mL round bottomed flask equipped with a magnetic stir bar was charged with 3-hydroxybenzoic acid **24** (5 g, 36.2 mmol, 1 equiv), EtOH (20 mL), and acetic acid (10 mL) at 24 °C. The mixture was then treated with Br_2 (3.7 mL, 72.2 mmol, 2 equiv). After 30 min, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution (50 mL). The crude product mixture was diluted with EtOAc (100 mL), separated from the aqueous phase, and washed with deionized H_2O (3 x 50 mL). The organic phase was then dried over Na_2SO_4, filtered, and

concentrated in vacuo, thus affording the desired product aryl bromide **25** as a white amorphous solid (3.1228 g, 40%).



4-Bromo-3-hydroxybenzoic acid (25)

TLC (SiO_2) R_f = 0.46 in 20:10:1 hexanes/EtOAc/AcOH, UV, *p*-anisaldehyde or $KMnO_4$ stains

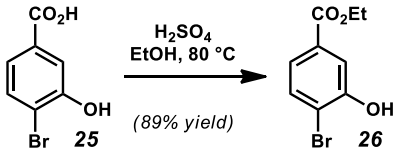
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.01 (s, 1H), 11.36–10.01 (m, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.50 (s, 1H), 7.27 (d, J = 8.2 Hz, 1H)

^{13}C NMR (101 MHz, DMSO-d_6) δ 167.2, 154.6, 133.5, 131.7, 121.6, 117.0, 115.0

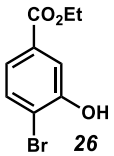
IR (neat) 3457, 2823, 2538, 1674, 1601, 1571, 1483, 1445, 1421, 1324, 1300, 1273, 1182, 1104, 1030, 933, 888, 827, 771, 759, 677, 577 cm^{-1}

HRMS (ES^-) *m/z* calculated for $C_7H_4BrO_3$ $[M - H]^-$: 214.9344, found 214.9346

*Synthesis of aryl ester **26***



A 50 mL round bottomed flask equipped with a magnetic stir bar was charged with benzoic acid **25** (3 g, 36.2 mmol, 1 equiv), EtOH (30 mL), and H_2SO_4 (1.27 mL) at 24 °C. The reaction mixture was then brought to reflux. After 10.5 h, the mixture was cooled and then quenched with saturated aqueous $NaHCO_3$ solution (200 mL) and EtOAc (200 mL). The organic phase was separated and washed with deionized H_2O (3 x 100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the desired product aryl ester **26** as a white amorphous solid (2.6355 g, 89%).



Ethyl 4-bromo-3-hydroxybenzoate (26)

TLC (SiO_2) R_f = 0.24 in 6:1 hexanes/EtOAc, UV, *p*-anisaldehyde or $KMnO_4$ stains

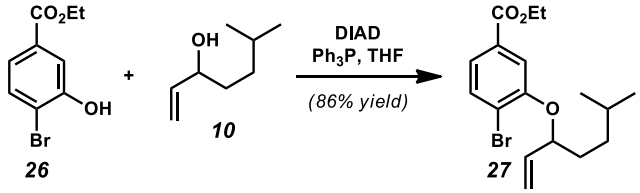
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 2.0 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 1H), 7.47 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.01 (s, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 152.5, 132.2, 131.5, 122.6, 117.1, 115.5, 61.4, 14.2

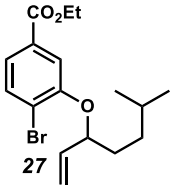
IR (neat) 3376, 2989, 1691, 1595, 1497, 1472, 1442, 1420, 1396, 1373, 1354, 1293, 1250, 1205, 1127, 1109, 1032, 1014, 955, 887, 866, 840, 812, 756, 705, 685, 619 cm^{-1}

HRMS (ES^-) *m/z* calculated for $C_9H_8BrO_3$ $[M - H]^-$: 242.9657, found 242.9656

*Synthesis of allylic ether **27***



A 50 mL round bottomed flask was equipped with a magnetic stir bar and charged with Ph_3P (1.238 g, 4.75 mmol, 2.25 equiv) and THF (21.1 mL). This mixture was then cooled to 0 °C and treated sequentially with DIAD (881 µL, 4.475 mmol, 2.12 equiv), aryl bromide **26** (519 mg, 2.11 mmol, 1 equiv), and alcohol **10** (406 mg, 3.167 mmol, 1.5 equiv). The reaction mixture was then allowed to warm to 24 °C over a period of 24 h. The crude mixture was then concentrated in vacuo. The residue was diluted with EtOAc (10 mL) and deionized H_2O (5 mL) and then treated with aqueous H_2O_2 solution (30 % w/v, 2.6 mL). The organic phase was separated and washed with deionized H_2O (3 x 10 mL) and saturated aqueous NaCl solution (3 x 10 mL). The organic phase was then dried over Na_2SO_4, filtered, and concentrated in vacuo. The mixture was then diluted with hexanes (10 mL), the precipitated solids were filtered, and the filtrate was concentrated in vacuo. This process was repeated 3 more times until no more solid matter precipitated upon addition of hexanes. The desired allylic ether **27** was thus isolated as a colorless oil (648 mg, 86%).



Ethyl 4-bromo-3-((6-methylhept-1-en-3-yl)oxy)benzoate (27)

TLC (SiO_2) R_f = 0.56 in 10:1 hexanes/EtOAc, UV, *p*-anisaldehyde or $KMnO_4$ stains

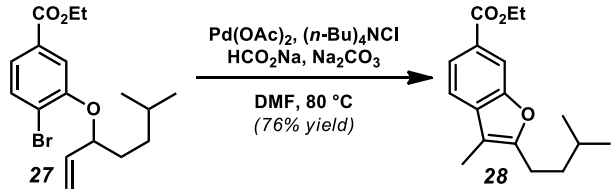
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.53 (m, 2H), 7.46 (dd, *J* = 8.2, 1.9 Hz, 1H), 5.86 (ddd, *J* = 17.2, 10.6, 6.4 Hz, 1H), 5.38–5.16 (m, 2H), 4.69 (app. q, *J* = 6.4 Hz, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.88 (dddd, *J* = 13.7, 11.5, 6.9, 5.2 Hz, 1H), 1.74 (m, 1H), 1.59 (m, 1H), 1.49–1.24 (m, 2H), 1.37 (app. t, *J* = 7.1 Hz, 3H), 0.91 (dd, *J* = 6.6 Hz, 6H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 154.7, 137.1, 133.2, 130.6, 122.6, 118.6, 117.2, 116.0, 81.0, 61.2, 34.1, 33.2, 27.9, 22.6, 22.5, 14.3

IR (neat) 2955, 2870, 1719, 1588, 1575, 1476, 1412, 1367, 1284, 1228, 1172, 1142, 1104, 1023, 991, 927, 879, 828, 758, 692, 616, 576, 559 cm^{-1}

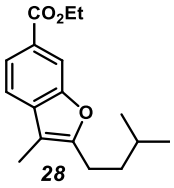
HRMS (ES^+) *m/z* calculated for $C_{17}H_{24}BrO_3$ $[M + H]^+$: 355.0909, found 355.0898

*Synthesis of benzofuran **28***



A 20 mL glass scintillation vial equipped with a magnetic stir bar was charged with aryl bromide **27** (356 mg, 1 mmol, 1 equiv), $Pd(OAc)_2$ (45 mg, 0.2 mmol, 20 mol %), (n-Bu)$_4$NCl (278 mg, 1 mmol, 1 equiv), HCO_2Na (68 mg, 1 mmol, 1 equiv), Na_2CO_3 (212 mg, 2 mmol, 2 equiv), and DMF (13.9 mL) in a glovebox under inert (N_2) atmosphere. The reaction vial was then sealed with a plastic cap, removed from the glovebox, and placed in an aluminum heating block that was preheated to 80 °C. After 23 h, the reaction was cooled to 24 °C and then quenched with deionized H_2O (30 mL) and EtOAc (50 mL). The organic phase was separated, washed with deionized H_2O (3 x 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo.

Purification by flash chromatography (SiO_2, hexanes/EtOAc = 50:1) afforded the desired product benzofuran **28** as a colorless oil (208 mg, 76%).



28

Ethyl 2-isopentyl-3-methylbenzofuran-6-carboxylate (28)

TLC (SiO_2) R_f = 0.60 in 10:1 hexanes/EtOAc, UV, *p*-anisaldehyde or $KMnO_4$ stains

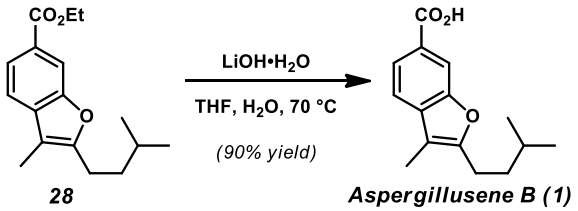
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.92 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 2.75 (t, *J* = 7.4 Hz, 2H), 2.17 (s, 3H), 1.67–1.54 (m, 3H), 1.41 (t, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 6.0 Hz, 6H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 158.2, 153.2, 134.7, 125.3, 123.5, 118.0, 112.0, 109.8, 60.8, 36.9, 27.6, 24.4, 22.3, 14.4, 7.8

IR (neat) 2956, 2870, 1713, 1610, 1582, 1467, 1430, 1387, 1367, 1279, 1223, 1199, 1119, 1085, 1048, 1020, 937, 889, 831, 769, 745, 611, 559 cm^{-1}

HRMS (ES^+) *m/z* calculated for $C_{17}H_{23}O_3$ $[M + H]^+$: 275.1647, found 275.1649

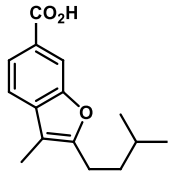
Total synthesis of aspergillusene B



28 ***Aspergillusene B (1)***

A 4 mL glass scintillation vial equipped with a magnetic stir bar was charged with aryl ester **28** (12 mg, 0.044 mmol, 1 equiv), $LiOH•H_2O$ (6 mg, 0.144 mmol, 3.3 equiv), THF (0.2 mL), and H_2O (0.05 mL). The reaction vial was then sealed with a plastic cap and placed in an aluminum heating block that was preheated to 70 °C. After 16.5 h, the reaction was cooled to 24 °C and quenched with 1 M aq HCl solution (2 mL) and EtOAc (2 mL). The aqueous phase was separated and extracted with EtOAc (6 x 2 mL). The combined organic phases were dried over

Na_2SO_4, filtered, and concentrated in vacuo thus affording the desired natural product aspergillusene B (1) as a white amorphous solid (9.7 mg, 90%).



Aspergillusene B (1)

2-Isopentyl-3-methylbenzofuran-6-carboxylic acid (1)

TLC (SiO_2) R_f = 0.15 in 10:1 hexanes/EtOAc, UV, *p*-anisaldehyde or $KMnO_4$ stains

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.20 (s, 3H), 1.62 (m, 3H), 0.96 (d, *J* = 5.7 Hz, 6H)

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 158.9, 153.2, 135.7, 124.2, 123.9, 118.2, 112.7, 110.0, 36.9, 27.7, 24.5, 22.3, 7.8

IR (neat) 3319, 2954, 2924, 2851, 2571, 1674, 1608, 1578, 1498, 1466, 1434, 1391, 1363, 1348, 1304, 1265, 1231, 1186, 1125, 1093, 1071, 1046, 967, 933, 887, 867, 843, 792, 769, 745, 725, 699, 641, 605, 571 cm^{-1}

HRMS (ES^-) *m/z* calculated for $C_{15}H_{17}O_3$ $[M - H]^-$: 245.1178, found 245.1178

IV. References and Notes

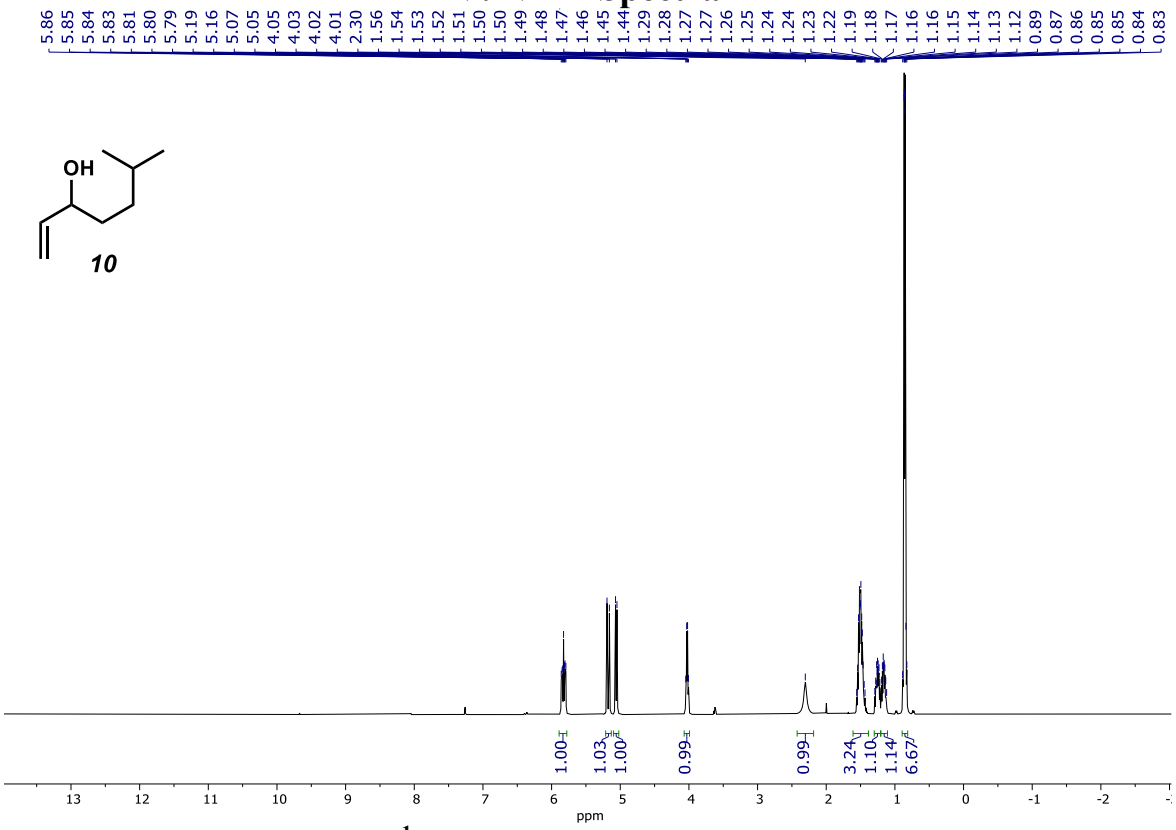
[1] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. *J. Organometallics* **1996**, *15*, 1518–1520.

[2] Lennartson, A.; Quant, M.; Moth-Poulsen, K. *Synlett* **2015**, *26*, 1501–1504.

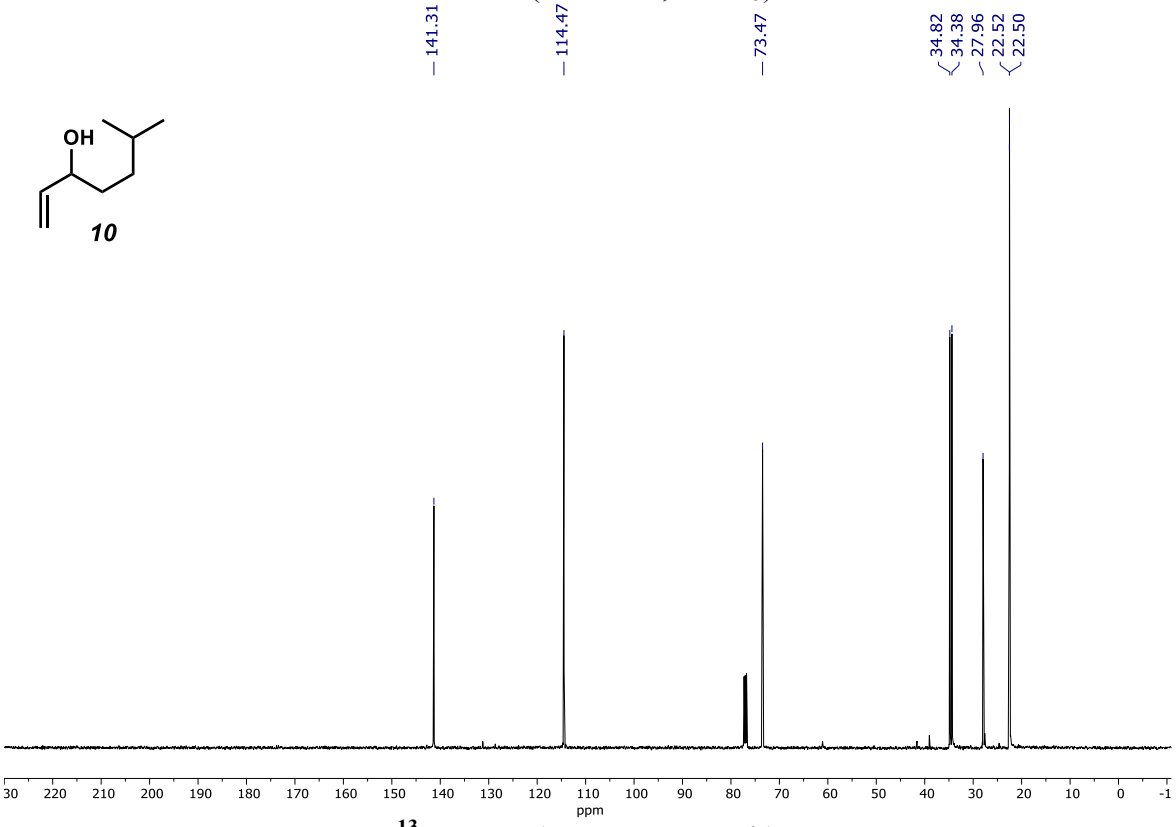
[3] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

[4] NMR spectra of synthetic aspergillusene B (1) match those reported by Rukachaisirikul, see: Trisuwan, K.; Rukachaisirikul, V.; Kaewpet, M.; Phongpaichit, S.; Hutadilok-Towatana, N.; Preedanon, S.; Sakayaroj, J. *J. Nat. Prod.* **2011**, *74*, 1663–1667

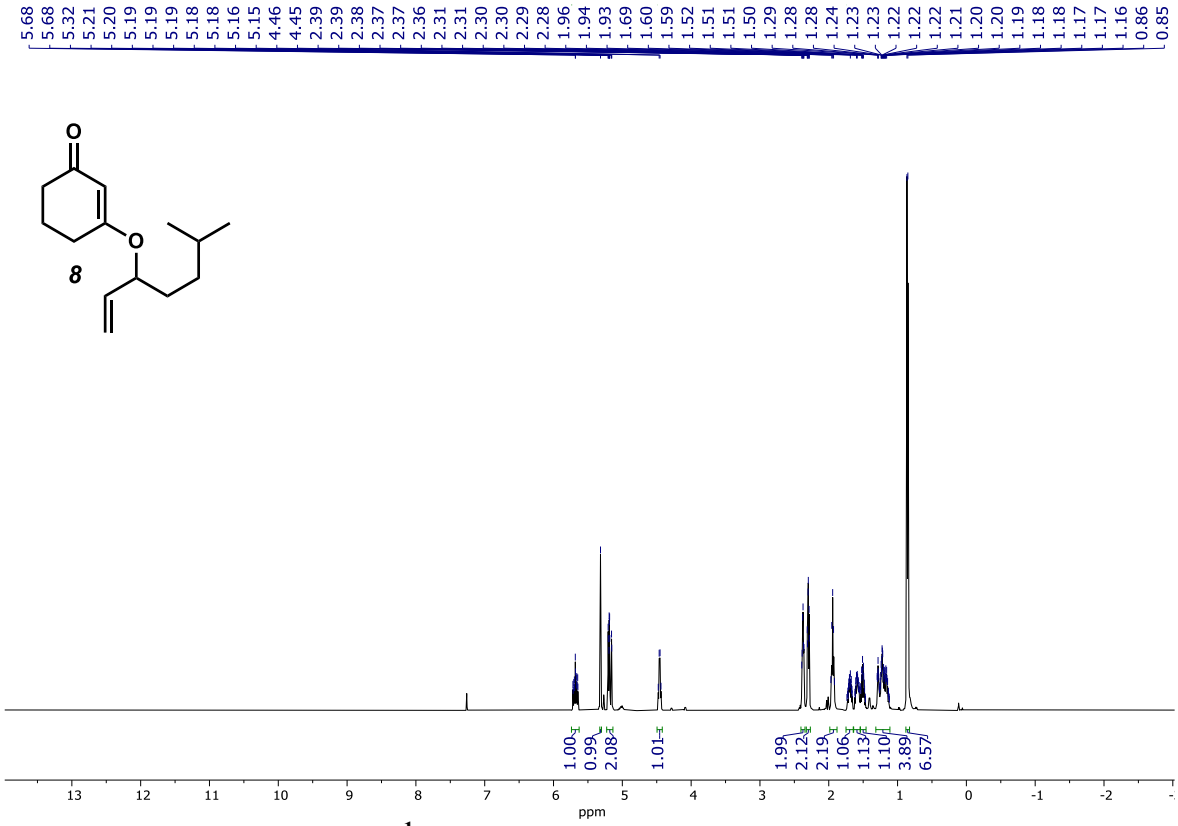
V. NMR Spectra



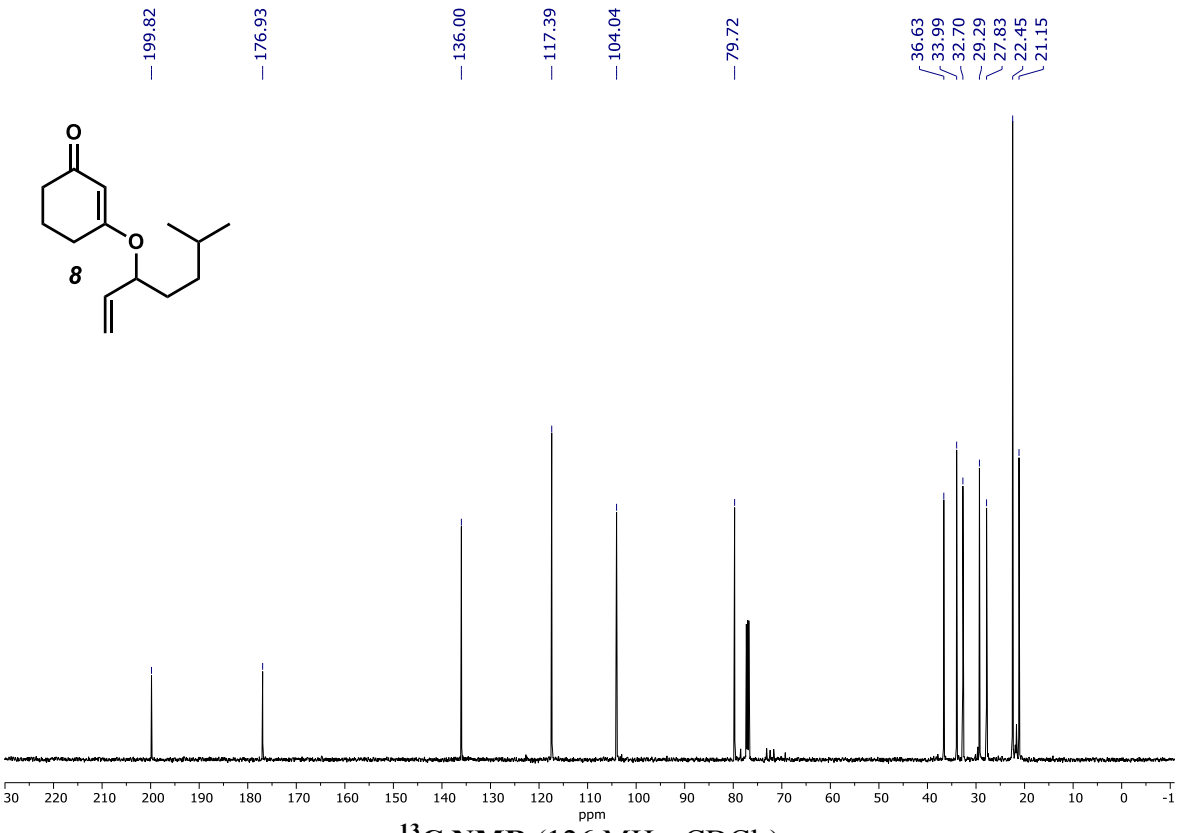
^{1}H NMR (500 MHz, $CDCl_3$)



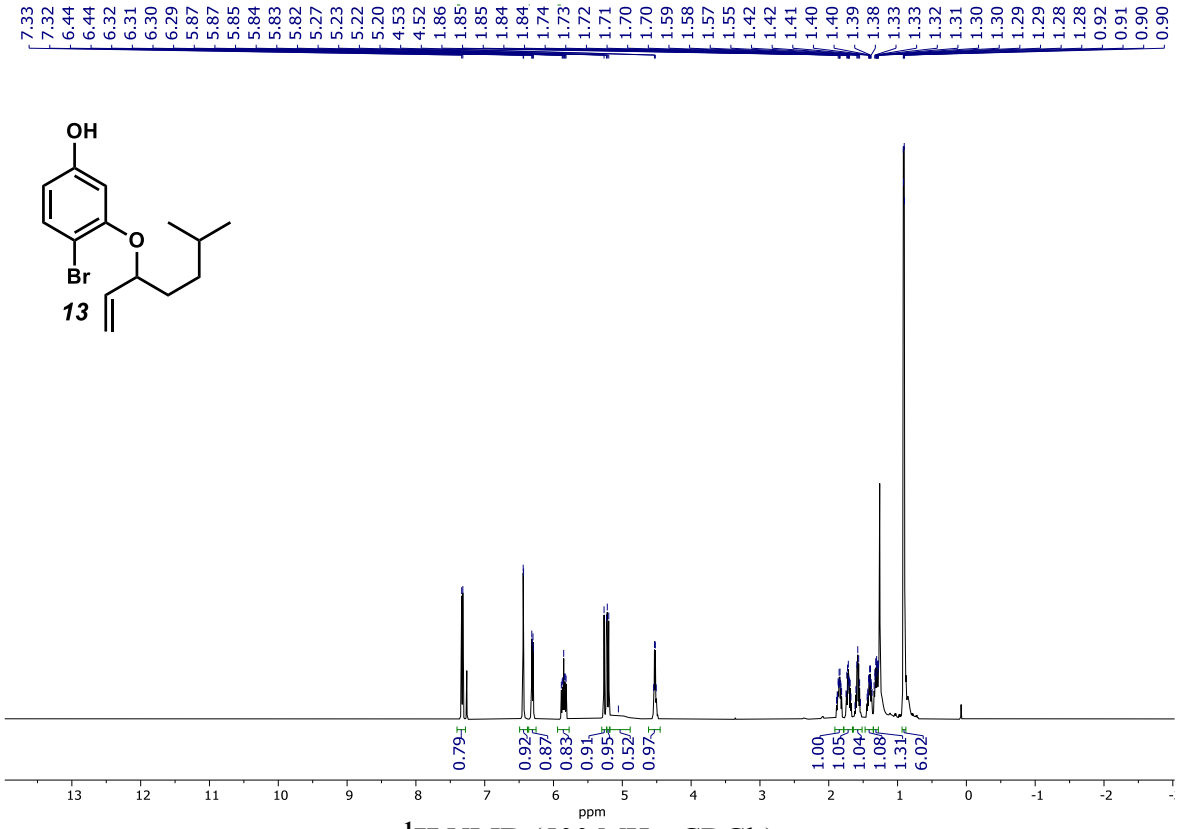
^{13}C NMR (126 MHz, $CDCl_3$)



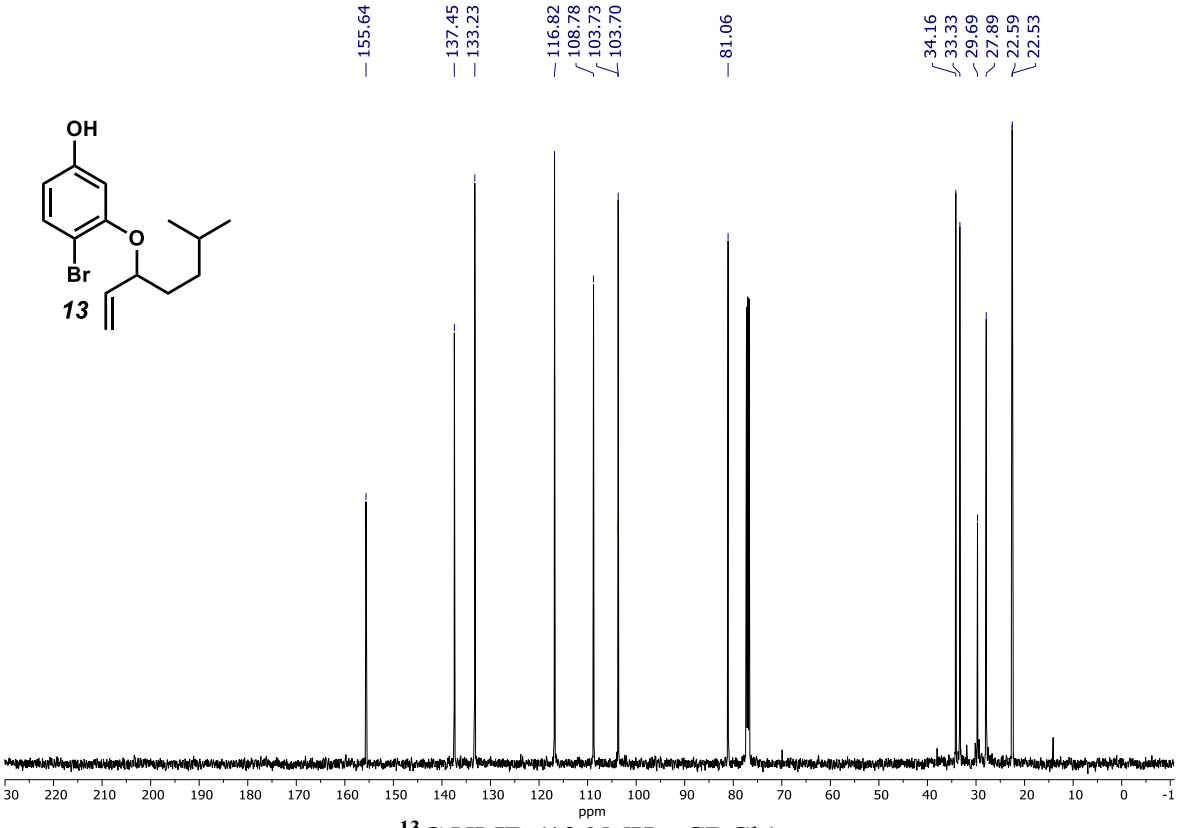
^{1}H NMR (500 MHz, $CDCl_3$)



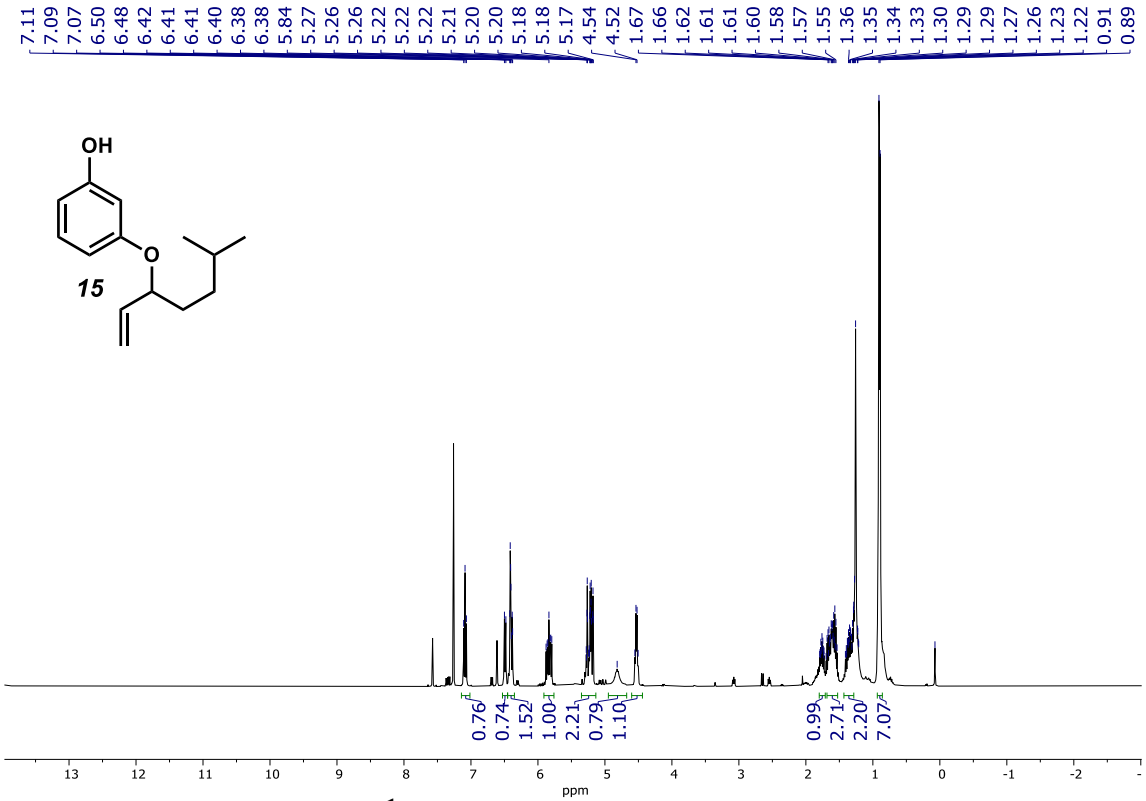
^{13}C NMR (126 MHz, $CDCl_3$)



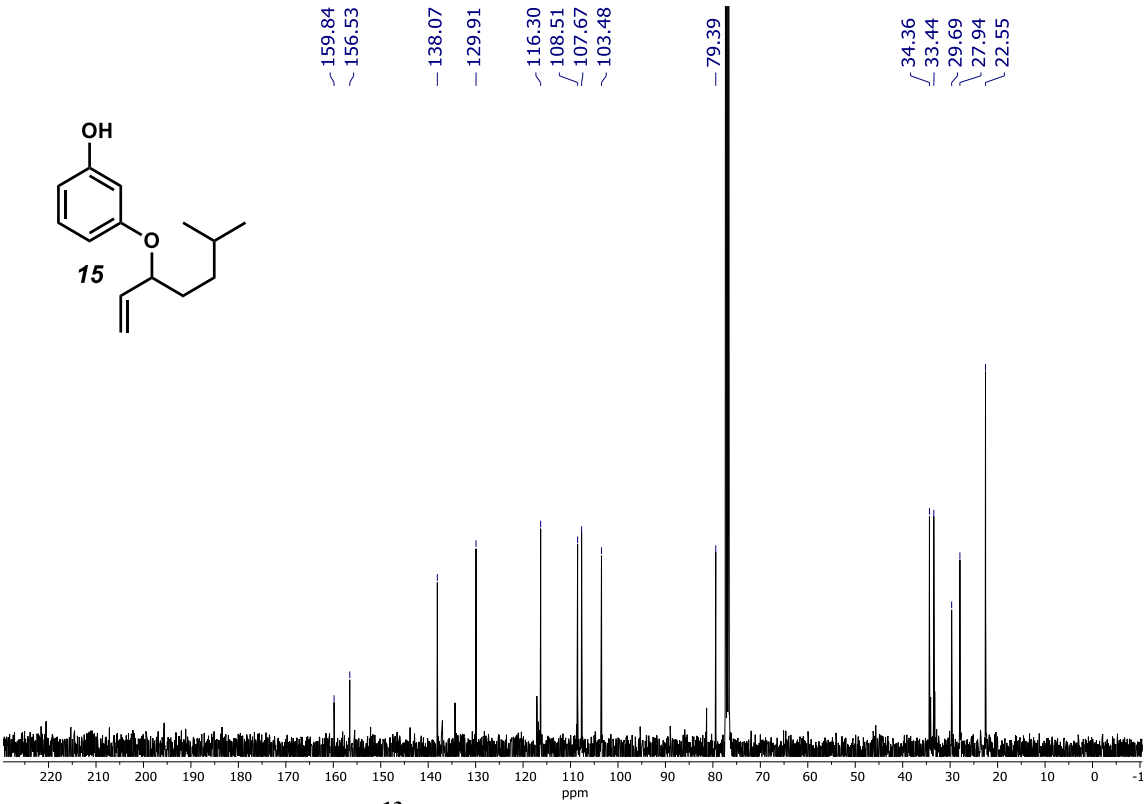
^{1}H NMR (500 MHz, $CDCl_3$)



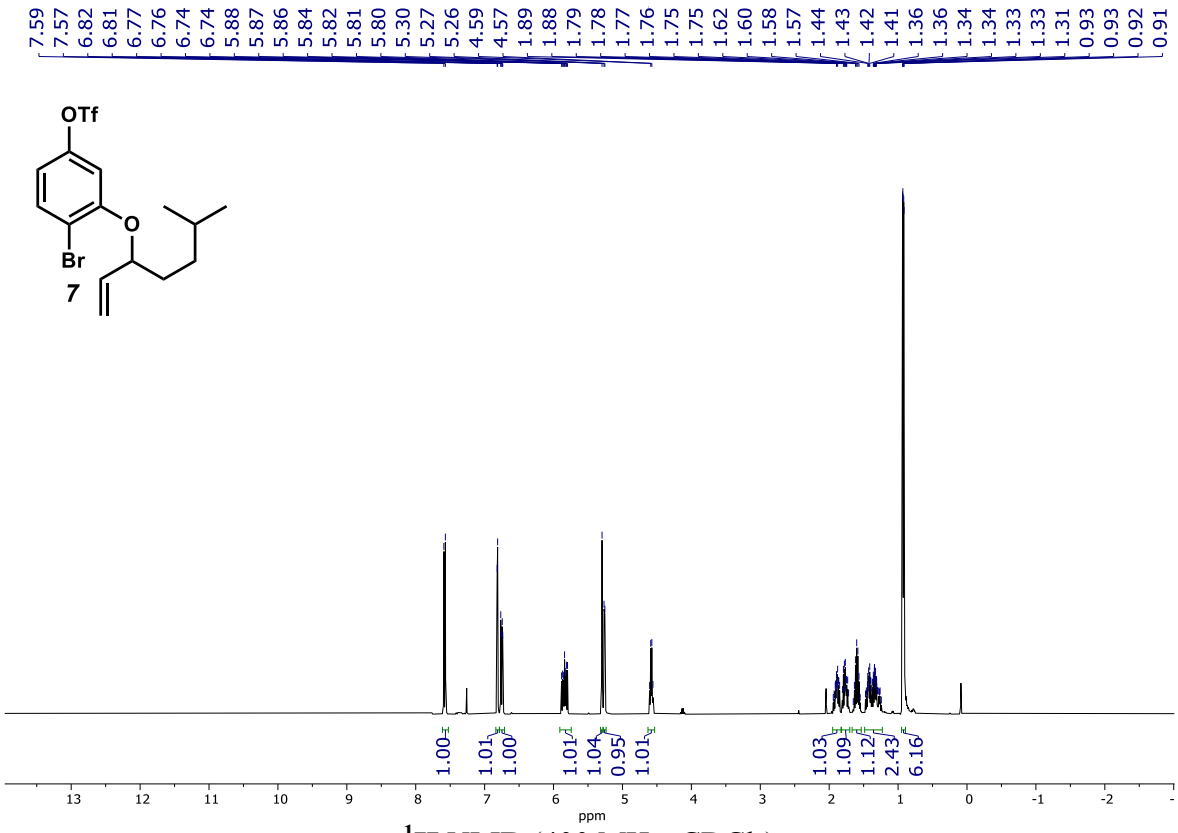
^{13}C NMR (126 MHz, $CDCl_3$)



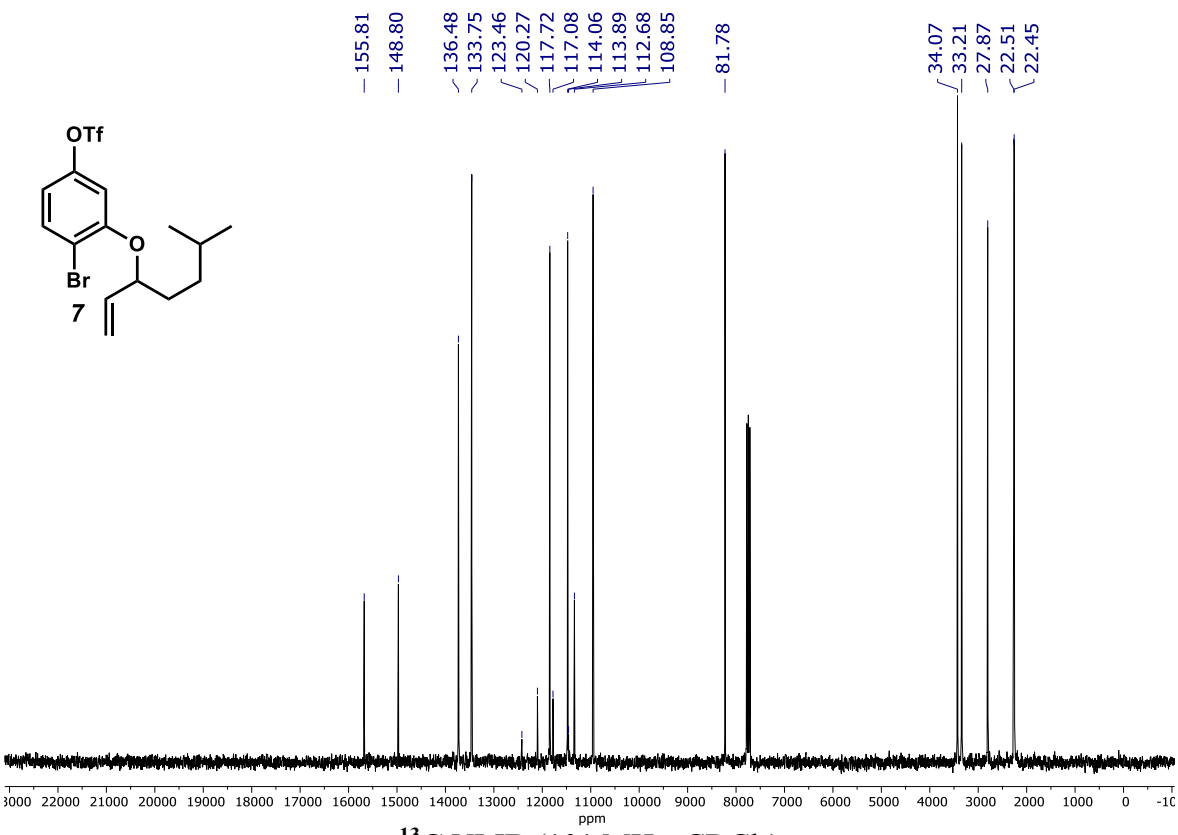
^{1}H NMR (400 MHz, $CDCl_3$)



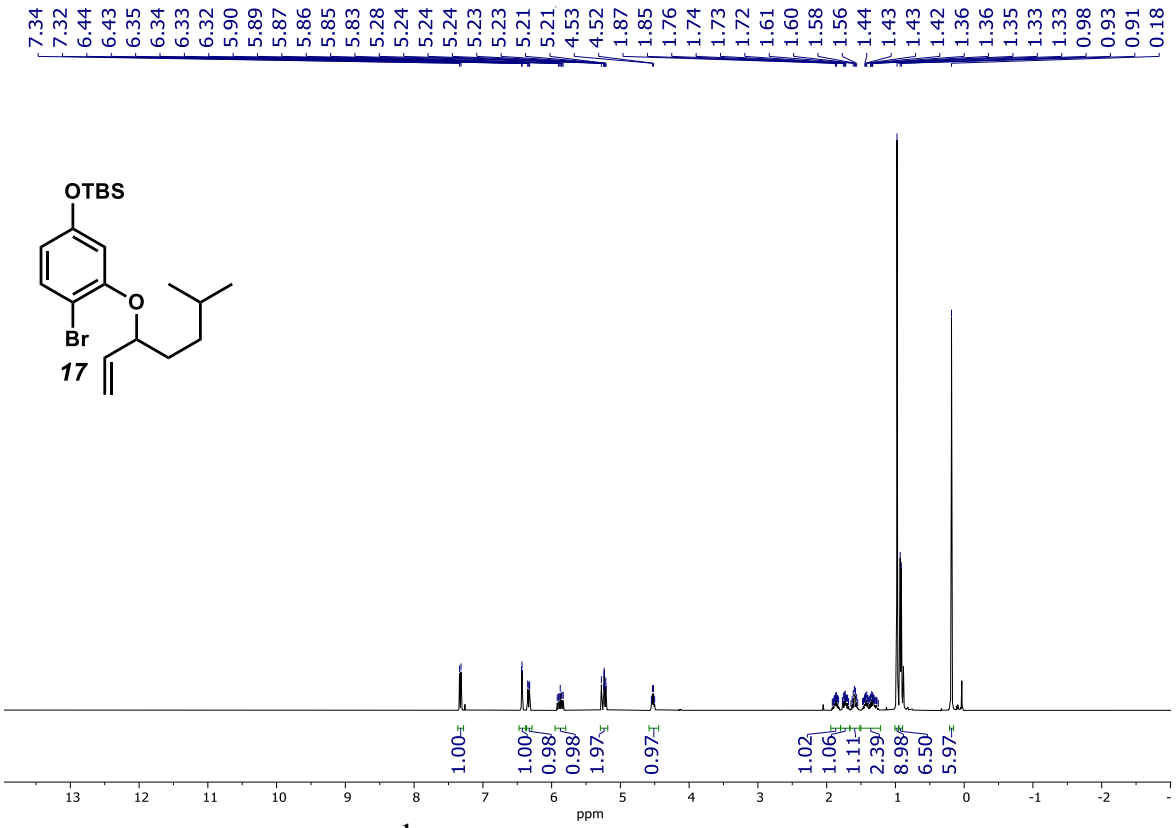
^{13}C NMR (101 MHz, $CDCl_3$)



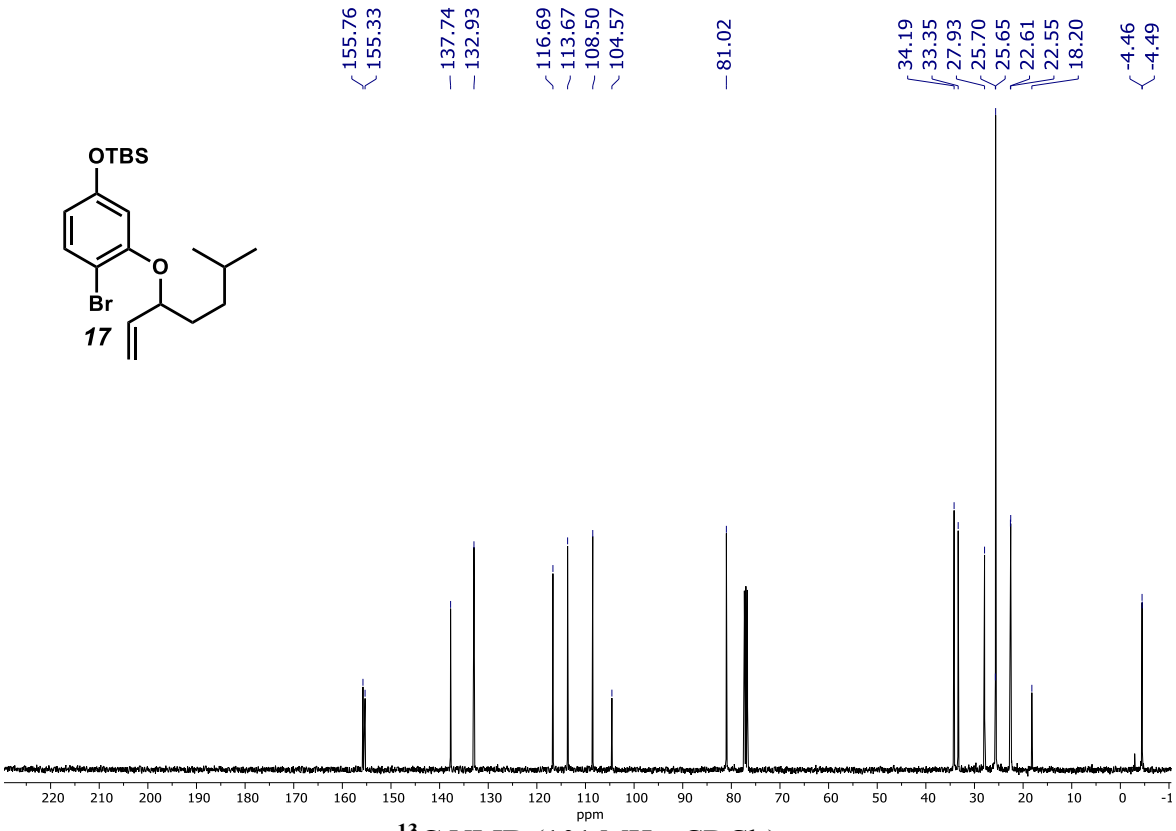
^{1}H NMR (400 MHz, $CDCl_3$)



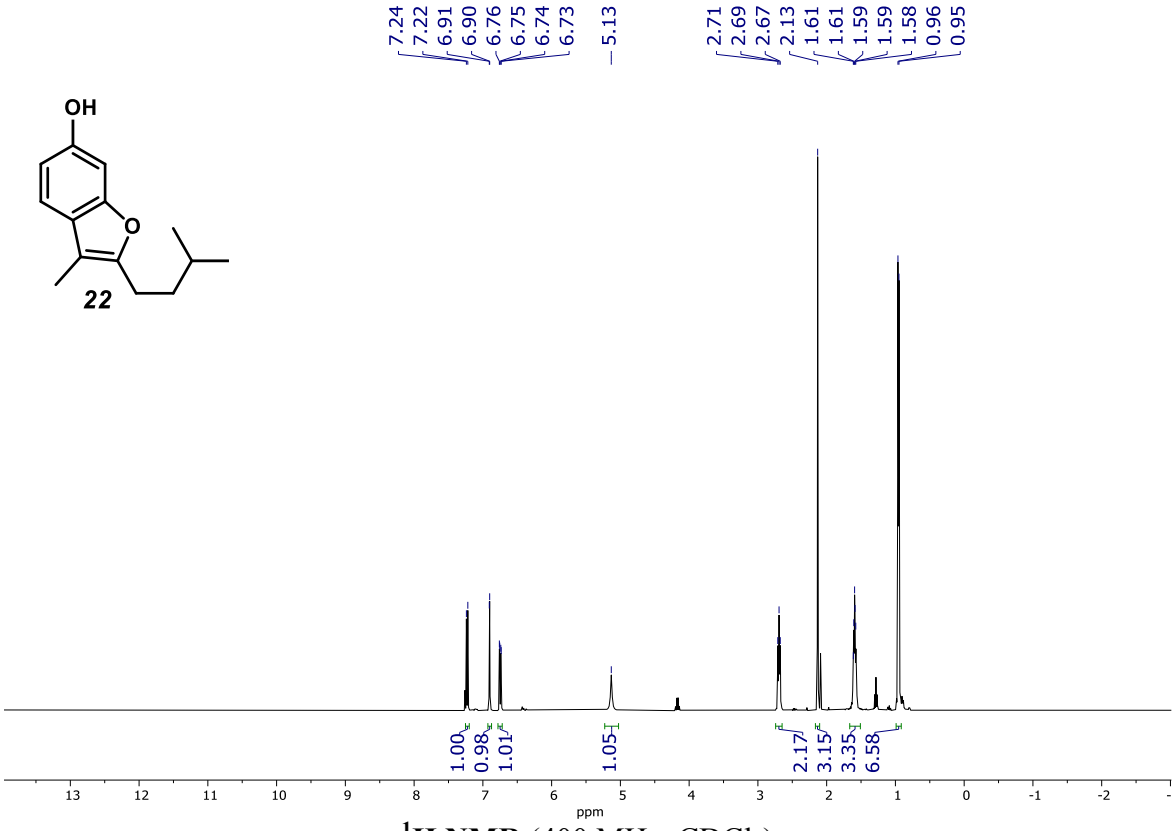
^{13}C NMR (101 MHz, $CDCl_3$)



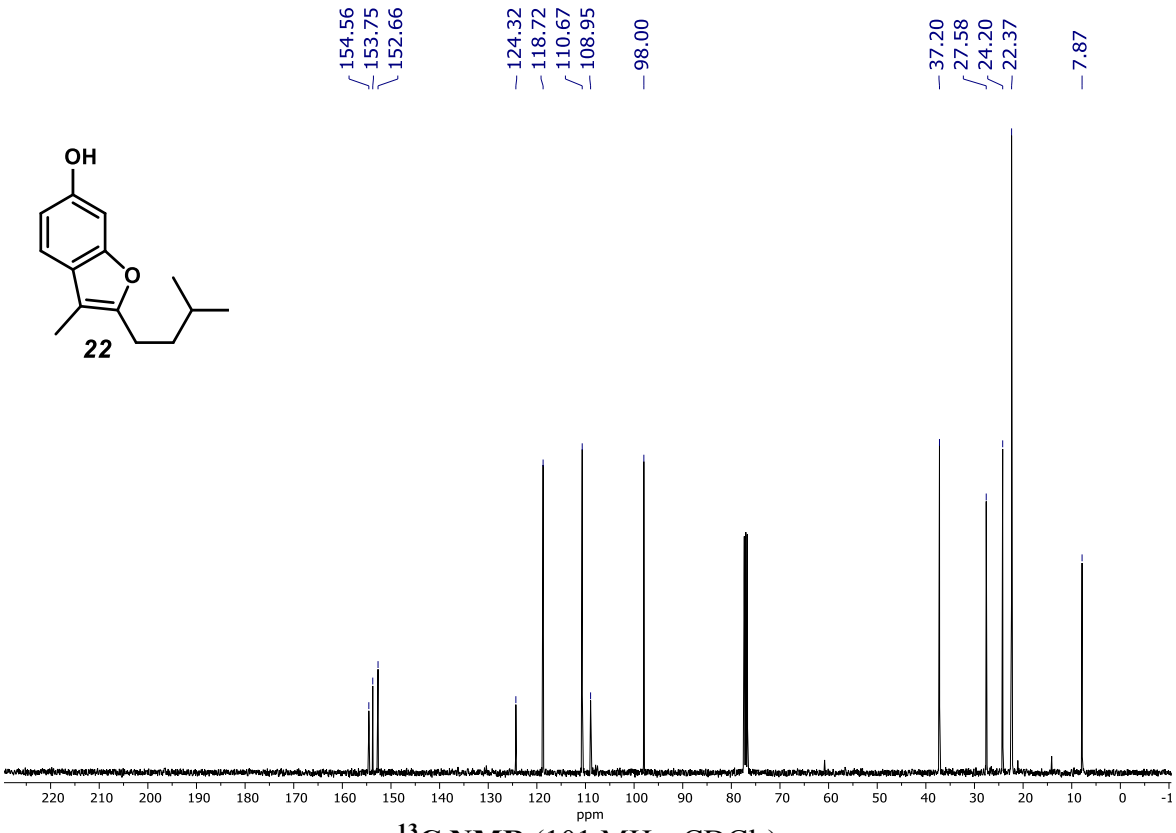
^{1}H NMR (400 MHz, $CDCl_3$)



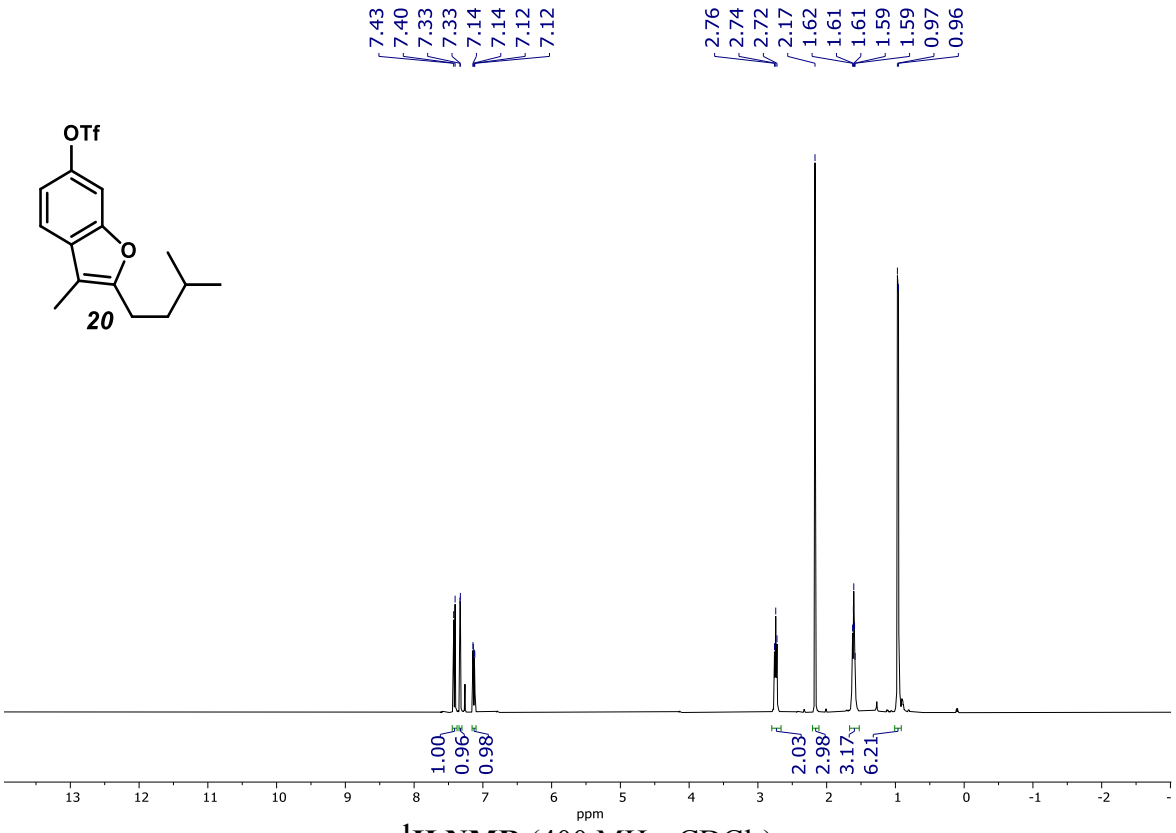
^{13}C NMR (101 MHz, $CDCl_3$)



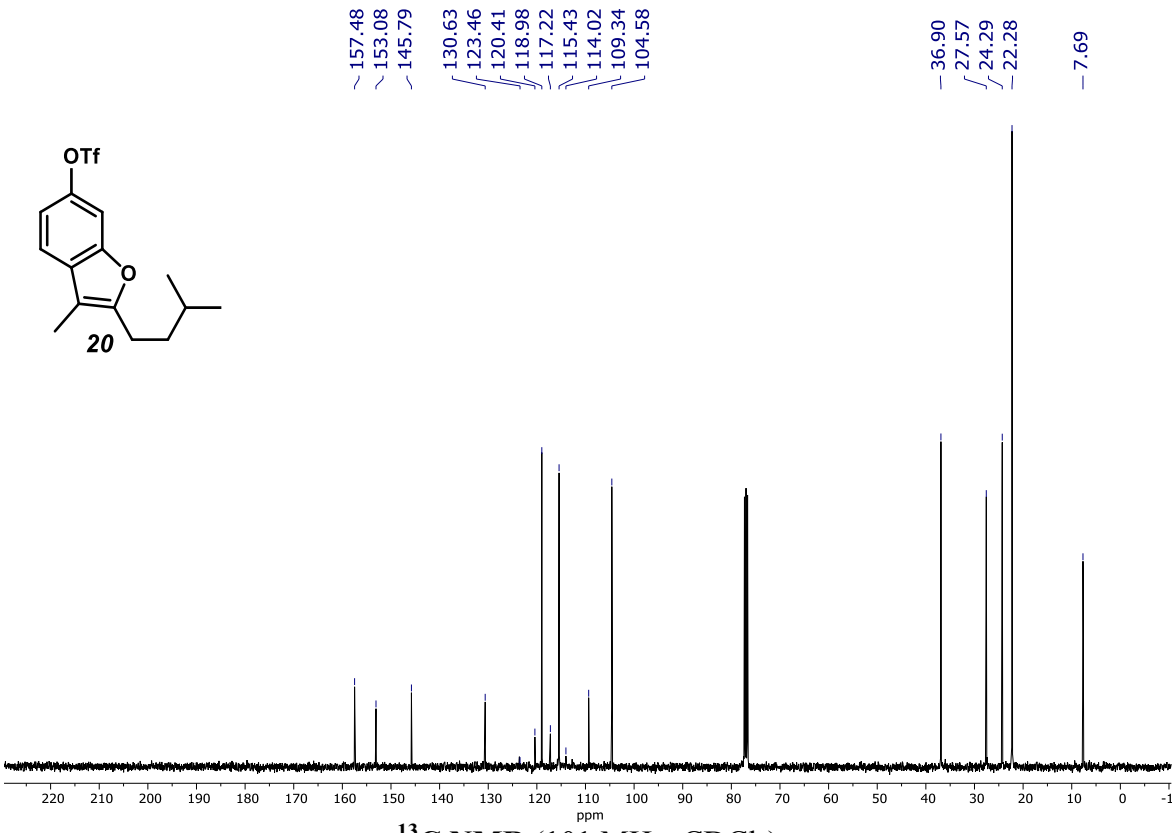
^{1}H NMR (400 MHz, $CDCl_3$)



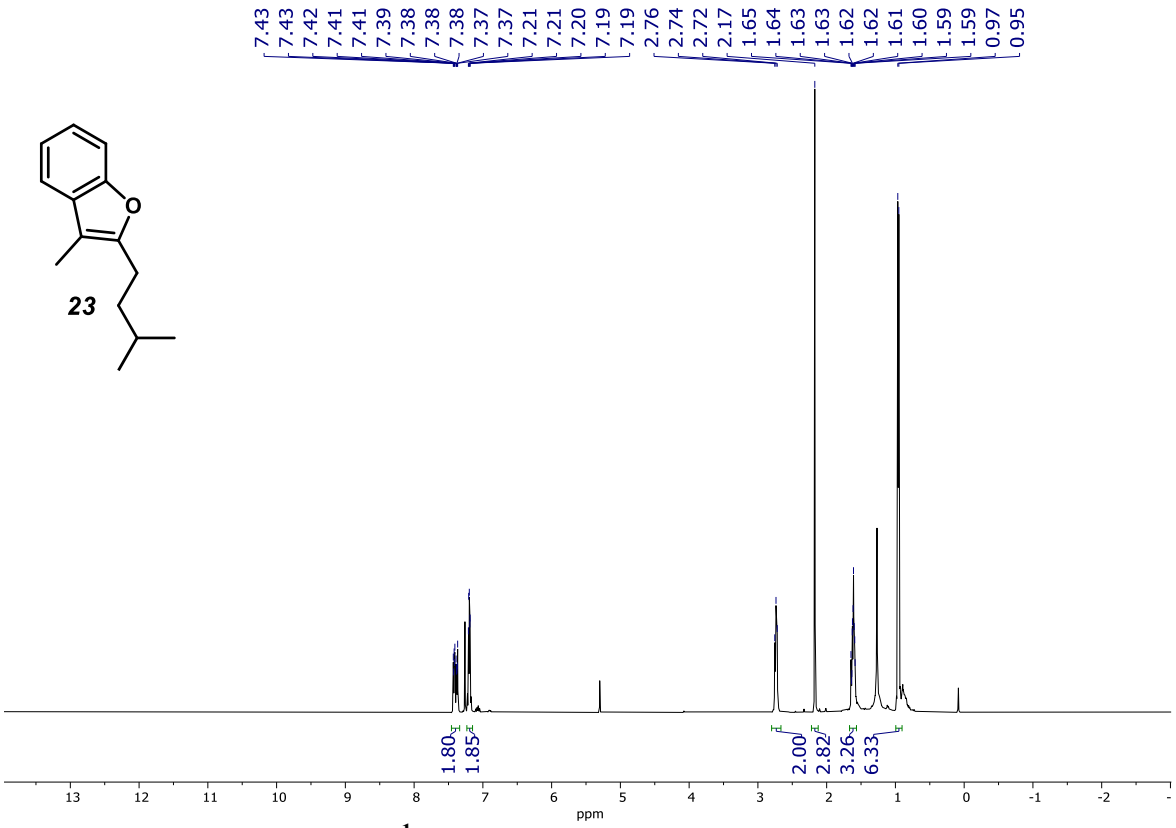
^{13}C NMR (101 MHz, $CDCl_3$)



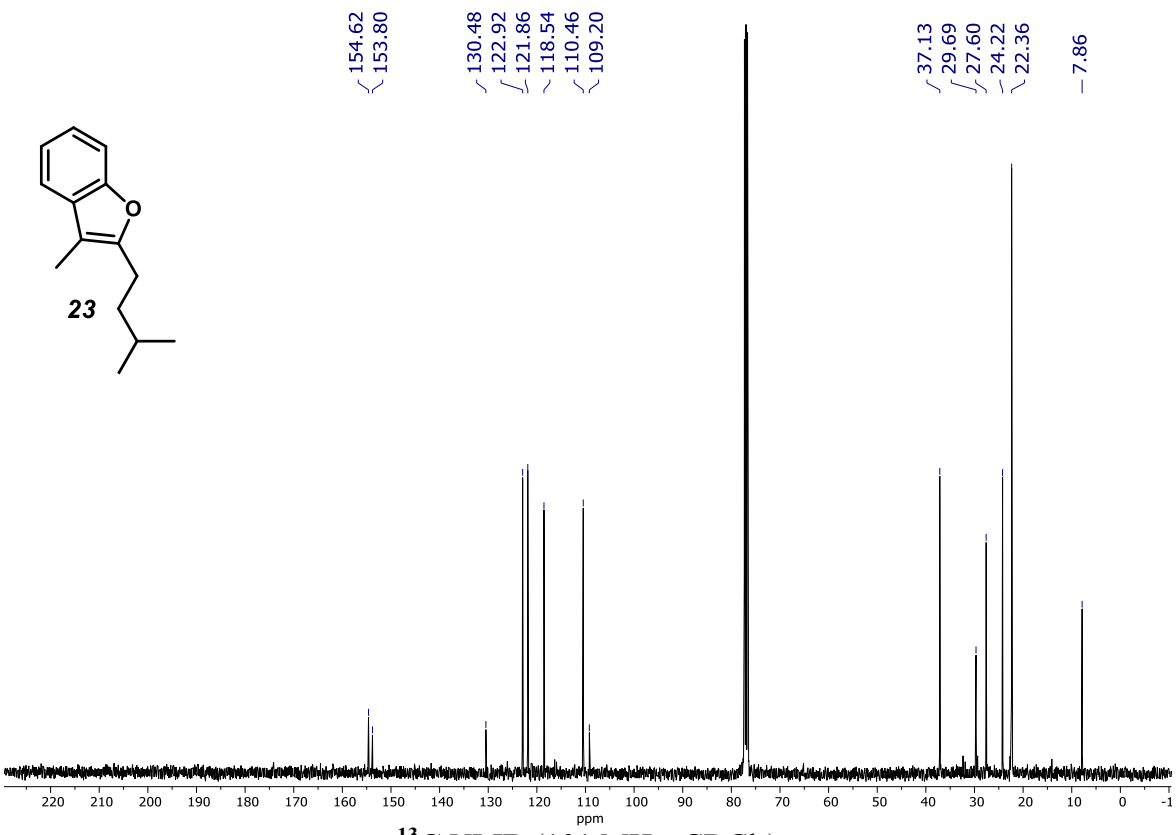
^{1}H NMR (400 MHz, $CDCl_3$)



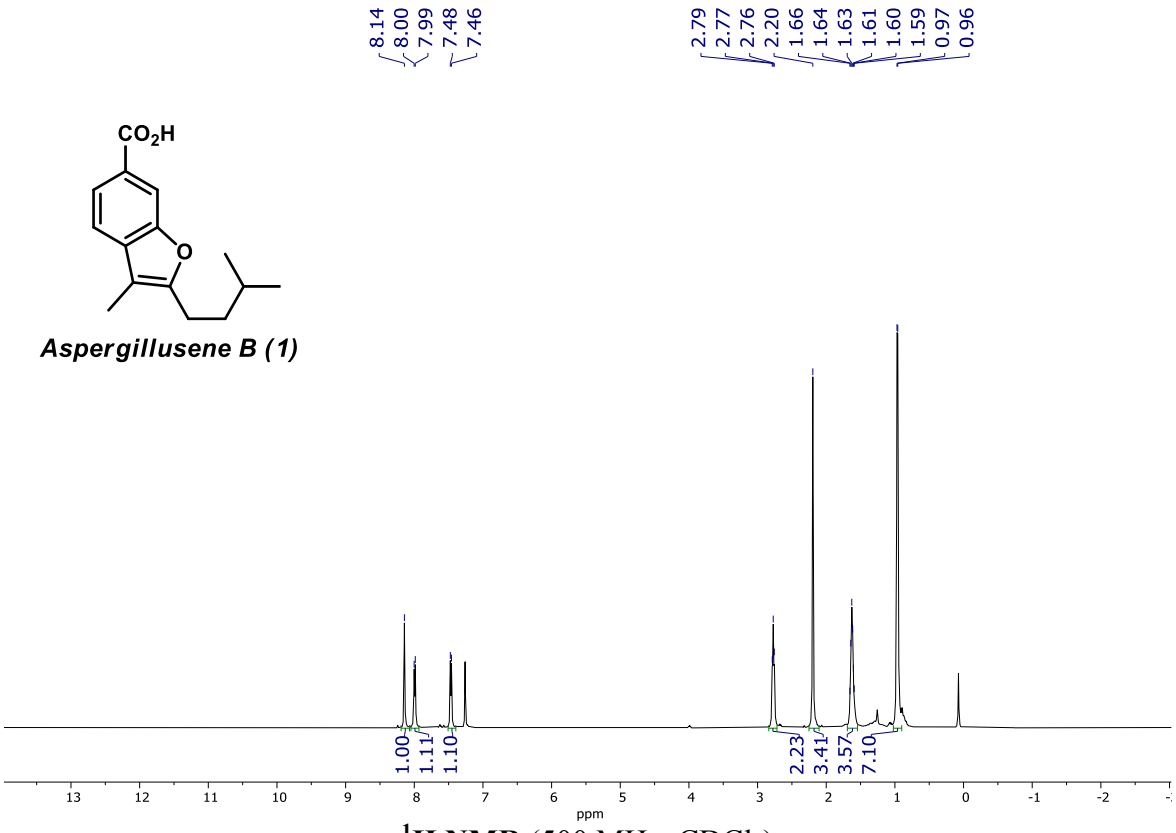
^{13}C NMR (101 MHz, $CDCl_3$)



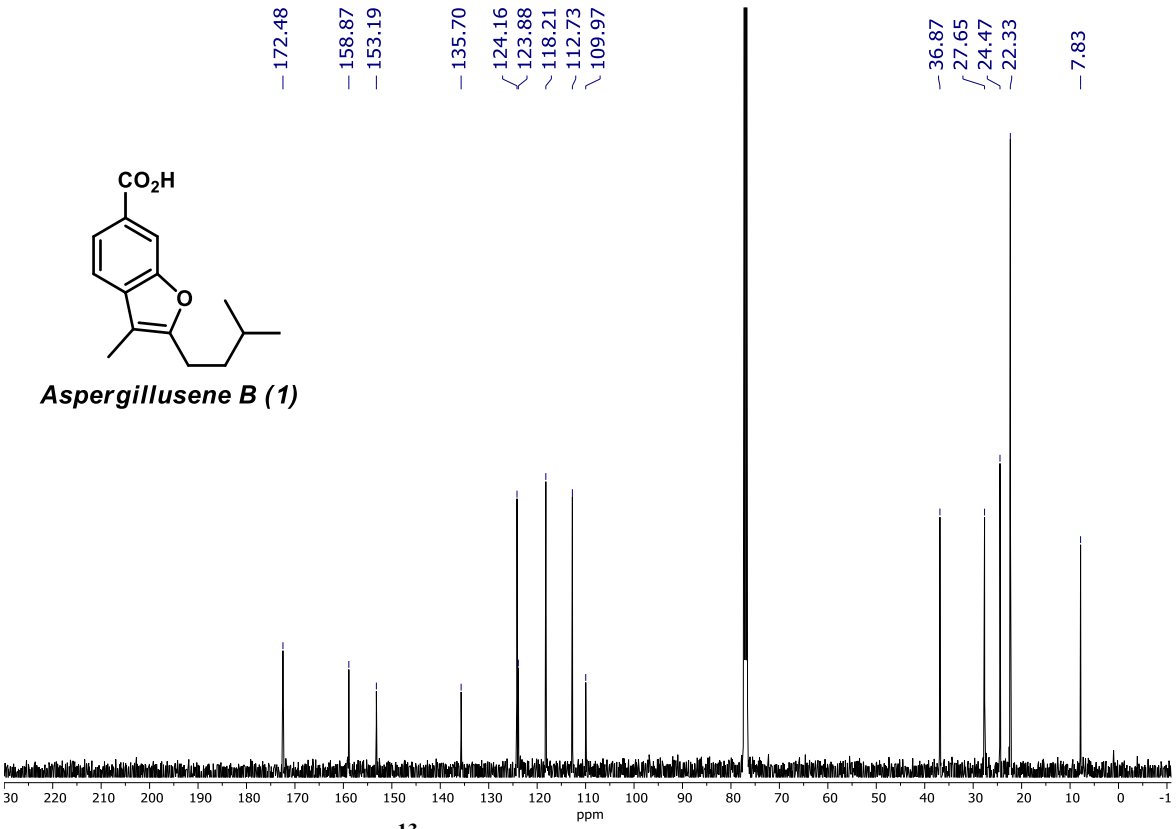
^{1}H NMR (400 MHz, $CDCl_3$)



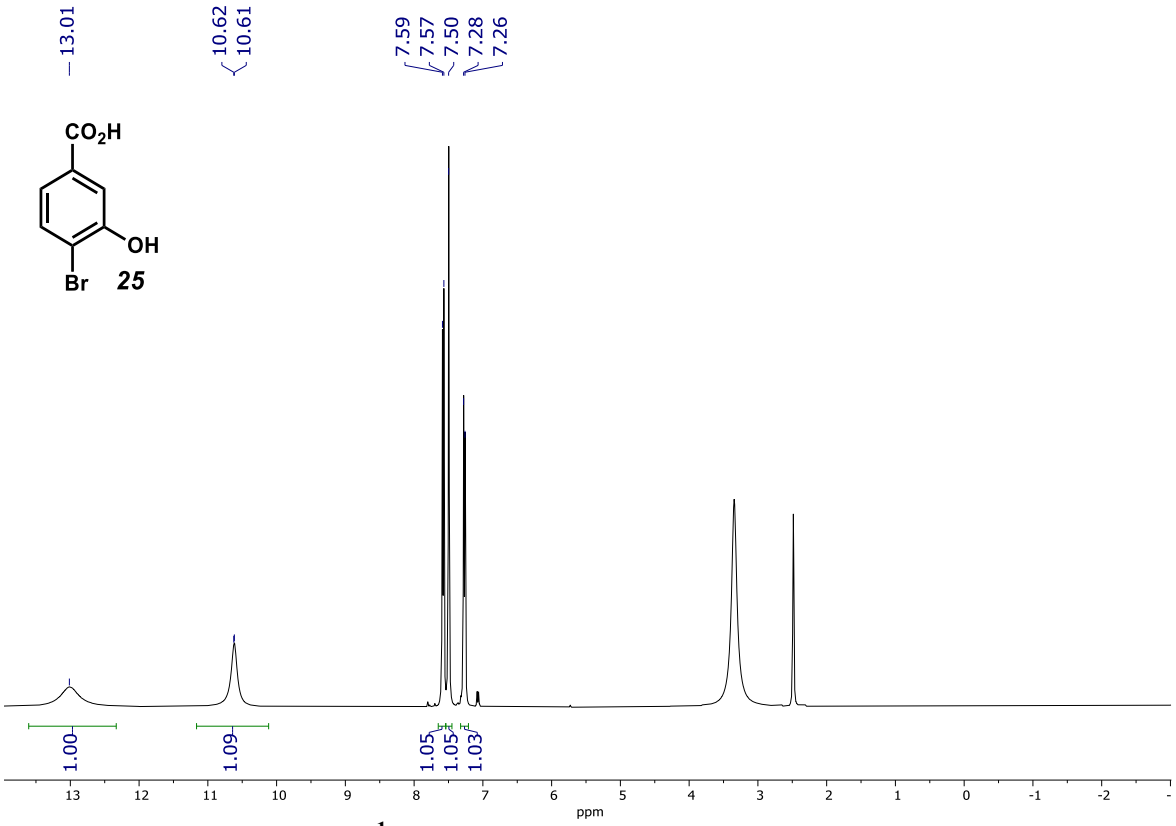
^{13}C NMR (101 MHz, $CDCl_3$)



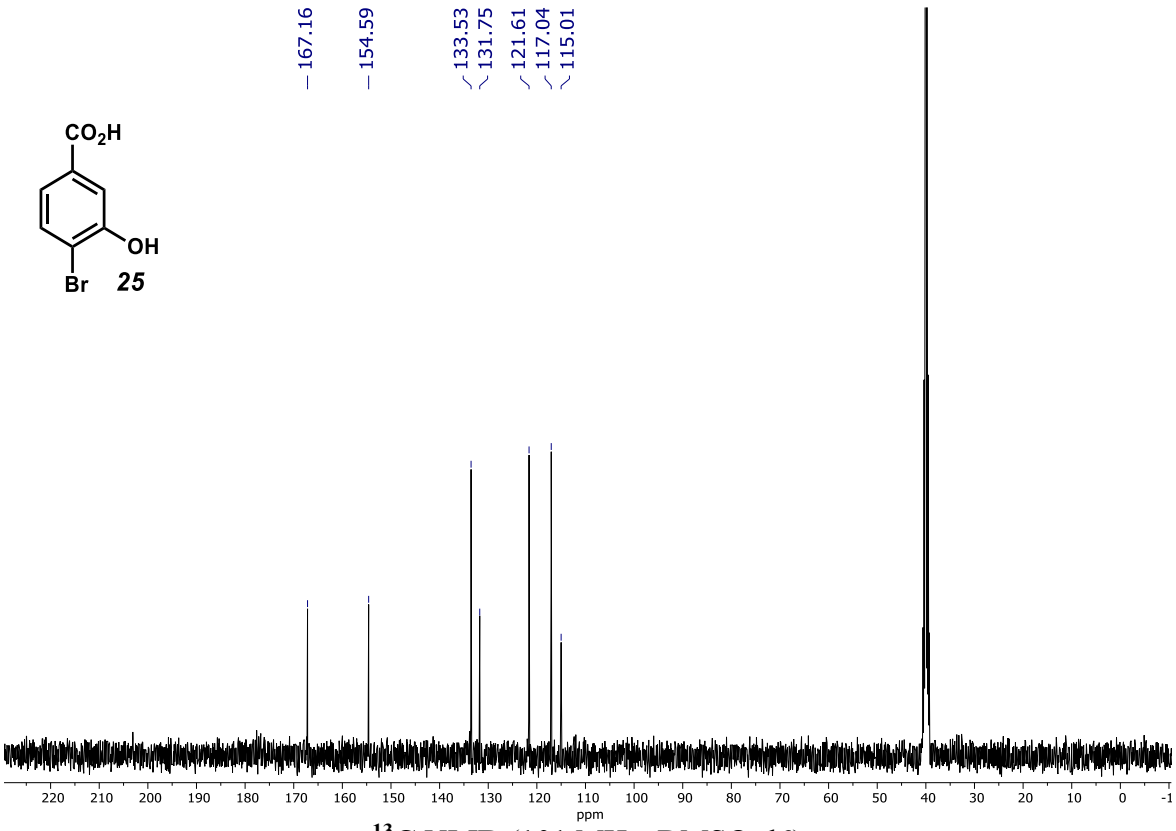
^{1}H NMR (500 MHz, $CDCl_3$)



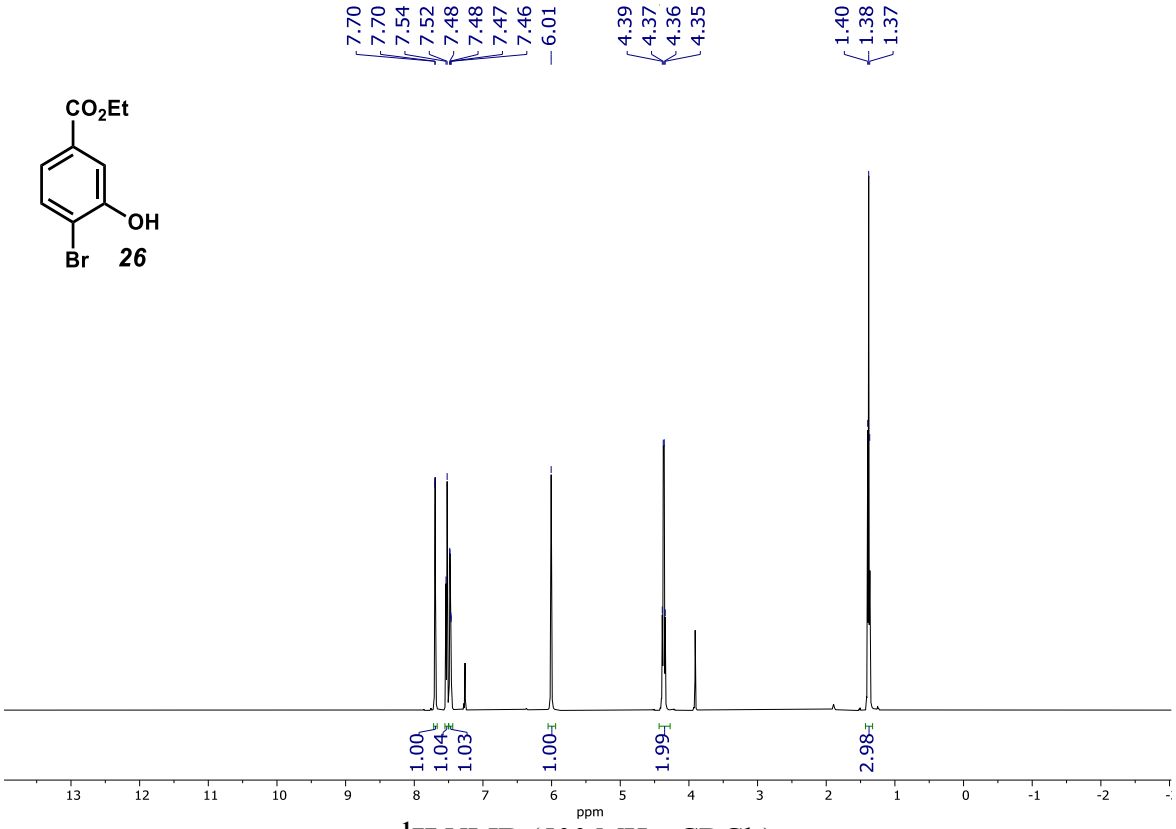
^{13}C NMR (126 MHz, $CDCl_3$)



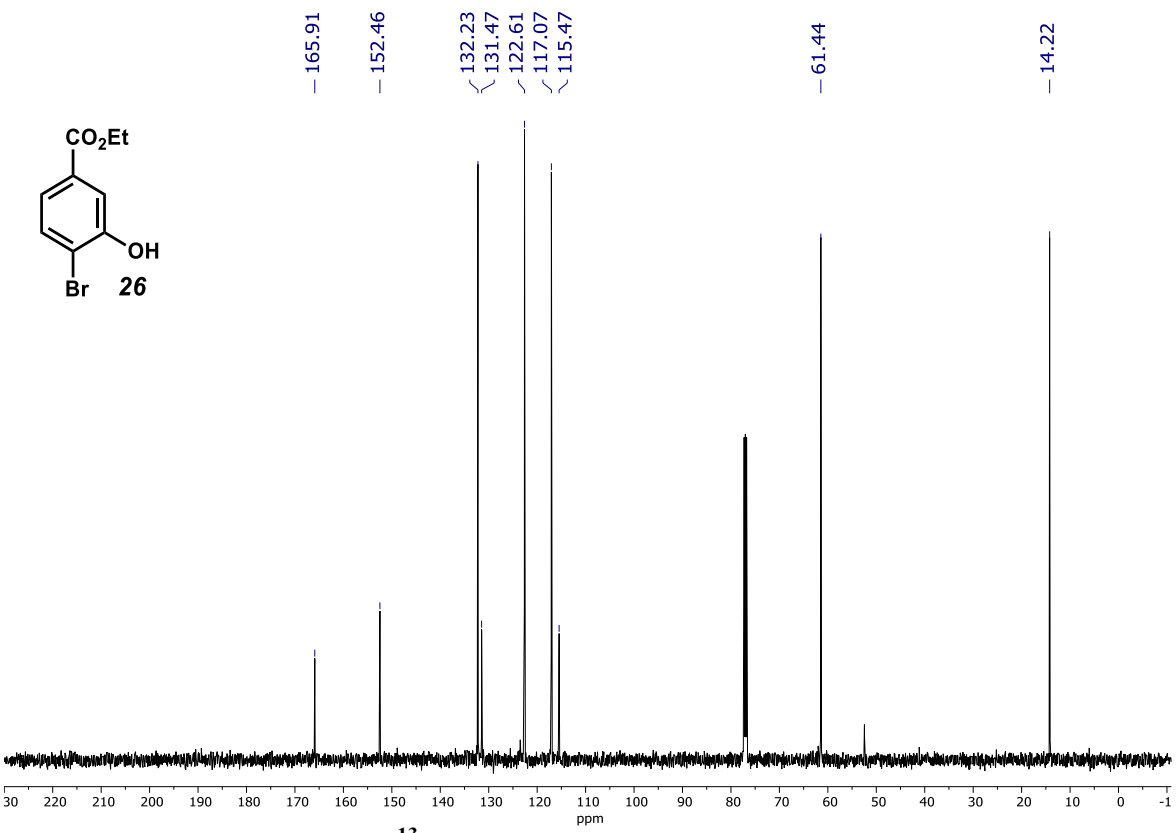
^{1}H NMR (400 MHz, DMSO-d6)



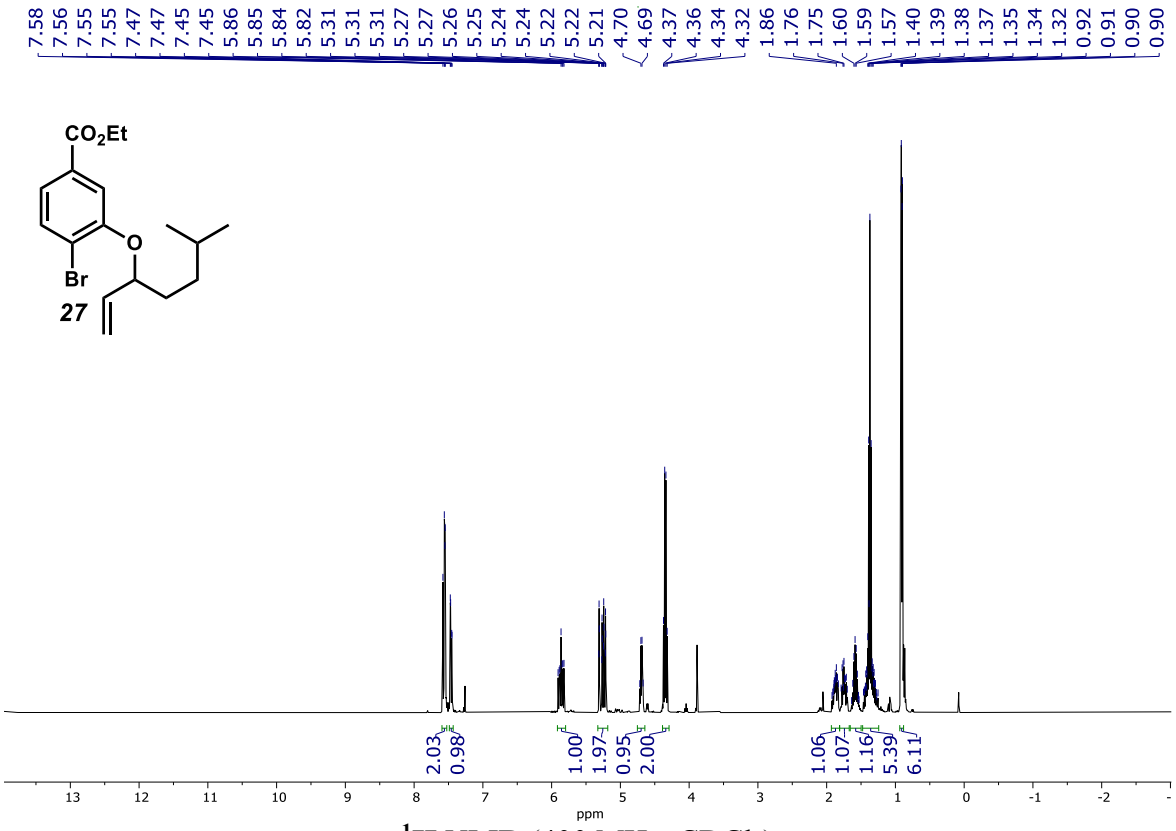
^{13}C NMR (101 MHz, DMSO-d6)



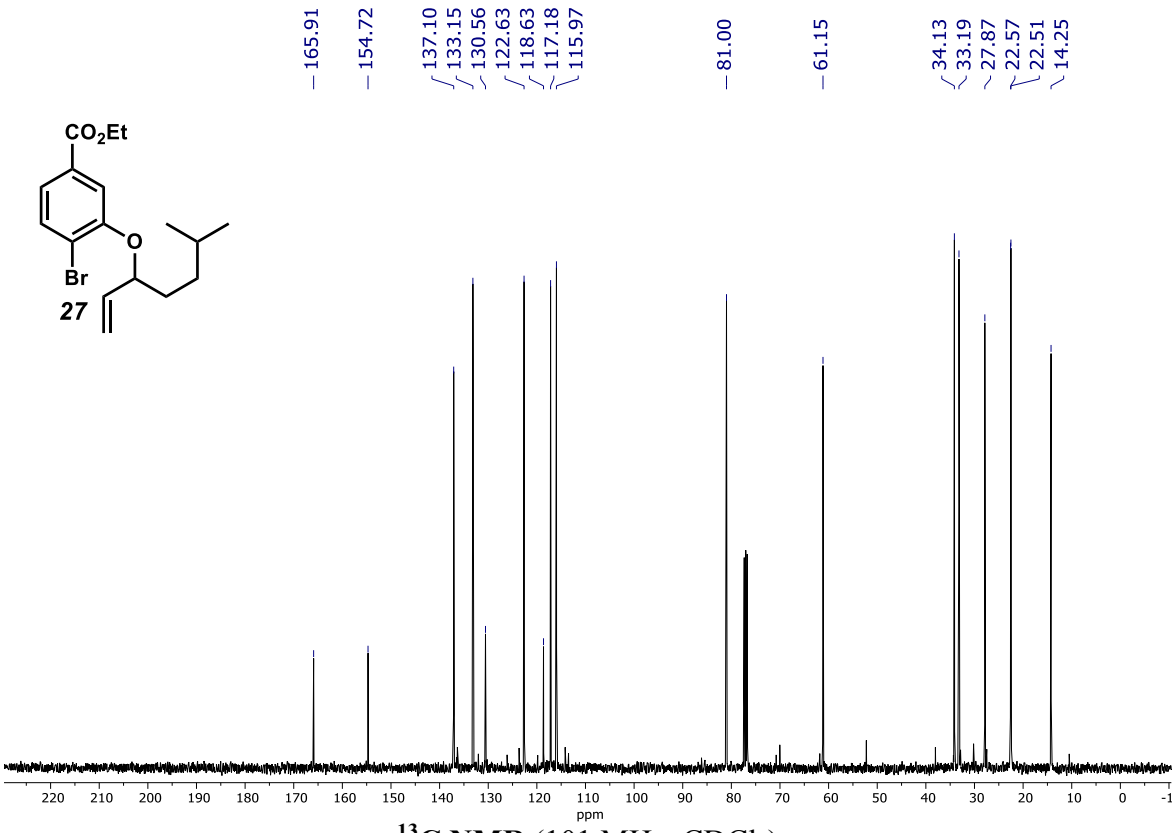
^{1}H NMR (500 MHz, $CDCl_3$)



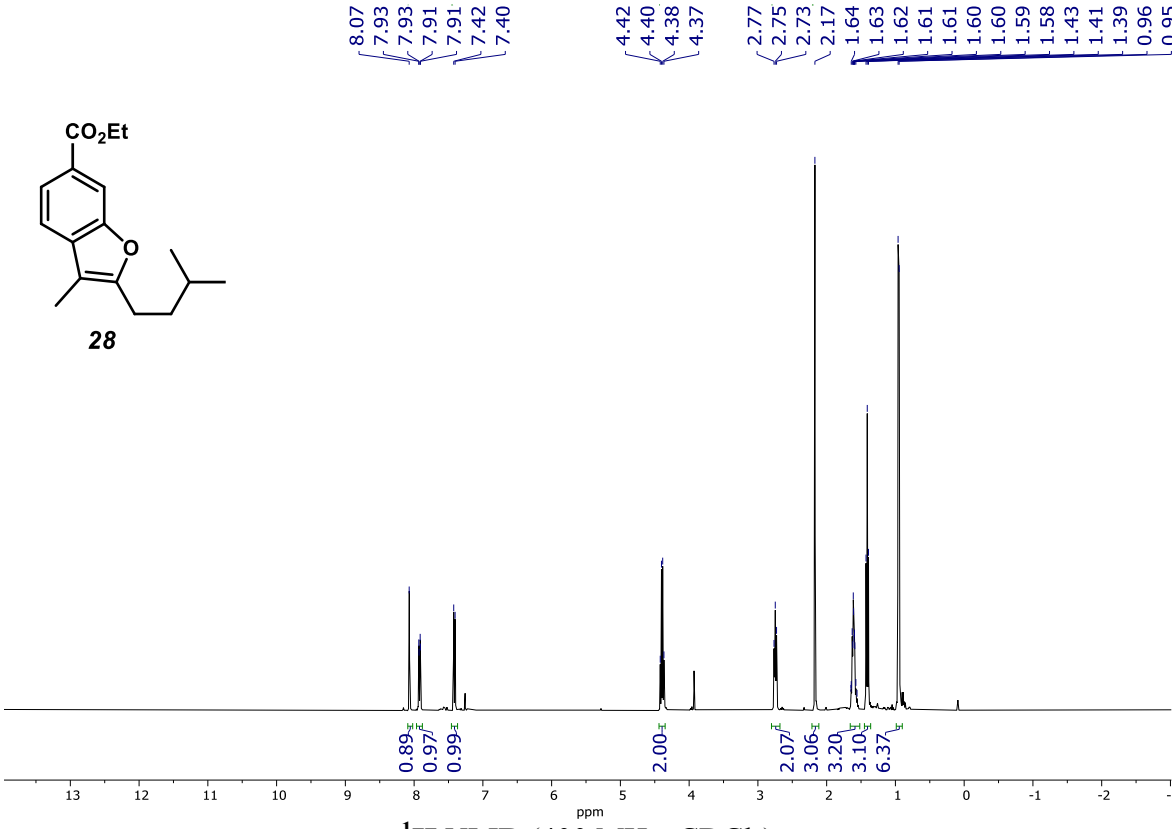
^{13}C NMR (126 MHz, $CDCl_3$)



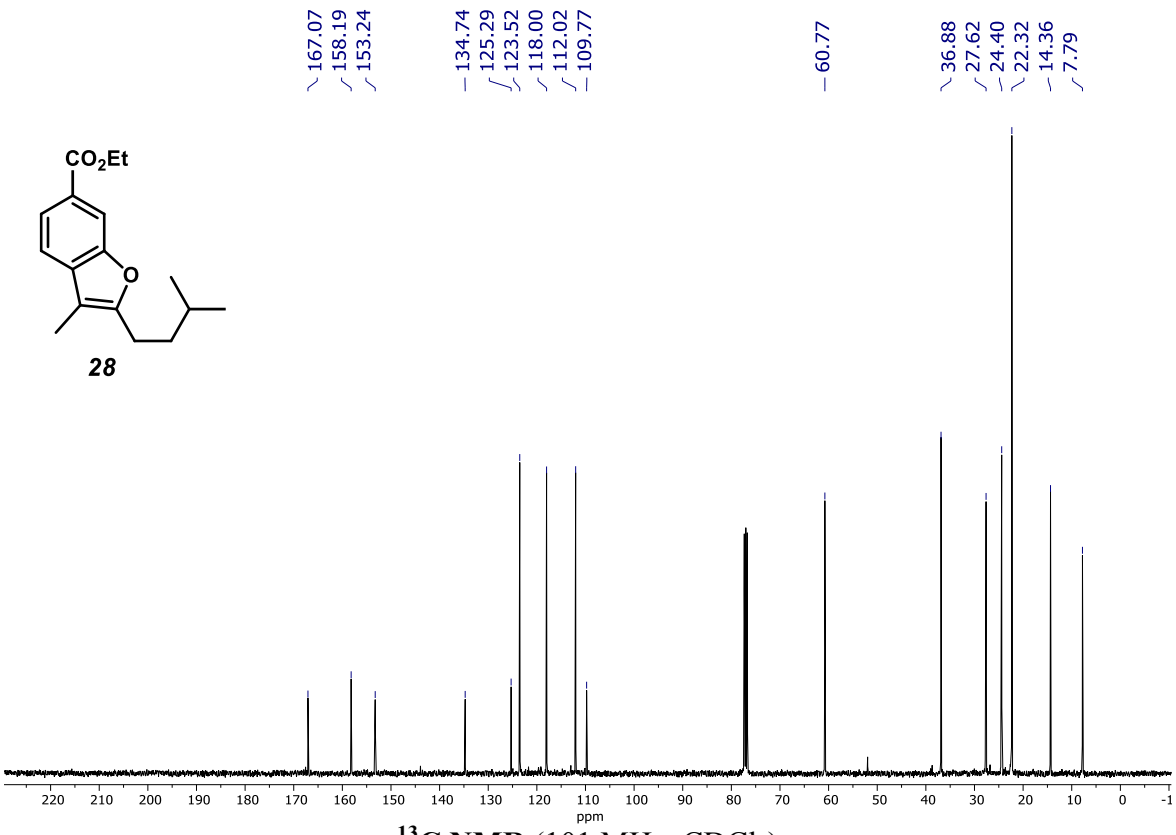
^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)



^{1}H NMR (400 MHz, $CDCl_3$)



^{13}C NMR (101 MHz, $CDCl_3$)