Skeletal Diversity *via* Cationic Rearrangements of Substituted Dihydropyrans

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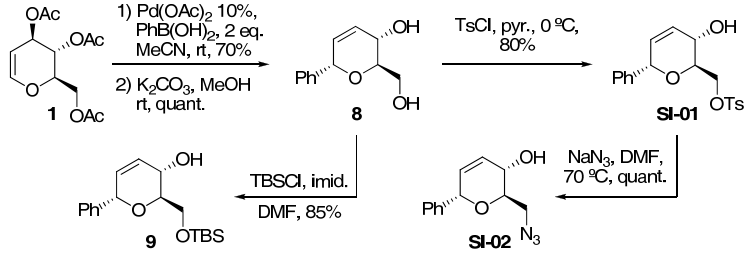
Supporting Information

I. General Experimental Information

All reactions were carried out in a flame-dried apparatus under an Ar atmosphere. Solvents (methylene chloride, THF, and acetonitrile) were dried by passage through columns of neutral alumina (Innovative Technologies, MA). Nitromethane was used as supplied by Sigma-Aldrich. All other reagents and solvents were used as provided by TCI, Strem Chemicals, and Sigma-Aldrich. Flash column chromatography was performed using Isco Combiflash Companion with CombiFlash silica gel cartridges (www.isco.com). Analytical thin layer chromatography was performed on 0.25 mm SiO_2 60-F plates. ^{1}H NMR spectra were recorded on a 400 MHz Varian Mercury spectrometer at ambient temperature. Chemical shifts are reported in ppm relative to the solvent ($CDCl_3$ at 7.26 ppm or C_6D_6 at 7.16 ppm). Proton decoupled ^{13}C NMR were recorded at 100.0 MHz at ambient temperature and the chemical shifts are relative to the solvent $CDCl_3$ at 77.0 ppm. Data for ^{1}H NMR are reported as: chemical shift, integration, multiplicity (app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet) and coupling constants (J in Hz). Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. Optical rotations were recorded on an AUTOPOL III digital polarimeter at 589 nm and are recorded as $[\alpha]^D$(concentration in grams/100 mL solvent). Low and high-resolution mass spectra were obtained in the Boston University Mass Spectrometry Laboratory using a Waters Q-TOF mass spectrometer. Microwave reactions were carried out using the CEM Explorer/Discover (www.cem.com) system equipped with a dynamic cooling valve. The Arthur™ Suite Reaction Planner (Symyx Technologies, Inc.) was used for experimental procedure planning.

II. Synthesis of Dihydropyran Substrates



(2R,3S,6S)-2-(Hydroxymethyl)-6-phenyl-3,6-dihydro-2H-pyran-3-ol (8)
Dihydropyran diol **8** was synthesized from *tri*-O-acetyl-D-glucal following the two step reported procedure in 70% overall yield. Spectroscopic data for **8** matched the reported data.[1]

(2R,3S,6S)-3-Hydroxy-6-phenyl-3,6-dihydro-2H-pyran-2-yl)methyl-4-methylbenzenesulfonate (**SI-01**) A solution of diol **8** (1 g, 4.9 mmol) in pyridine (5 mL) and CH_2Cl_2 (10 mL) was cooled to 0 °C. Tosyl chloride (0.92 g, 4.9 mmol) was added

[1] Yeager, A.R.; Min, G.K.; Porco Jr., J.A.; Schaus, S.E. *Org. Lett.* **2006**, *8*, 5065.

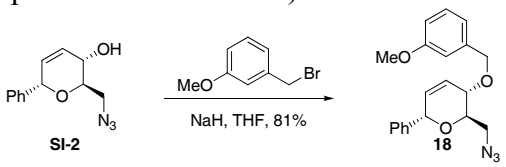
under nitrogen and the mixture was stirred at the same temperature for 17 h. Saturated $NH_4Cl_{(aq)}$ (25 mL) was then added and the mixture was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The resulting residue was purified *via* flash column chromatography (hexane:EtOAc = 5:1) to afford the *p*-toluenesulfonate ester **SI-01** (1.4 g, 80% yield). $[\alpha]^{25}_D$ = –80.4° (c 0.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 2H), 7.28-7.34 (m, 7H), 6.06 (ddd, J = 10.4, 2.8, 1.6 Hz, 1H), 6.12 (ddd, J = 10.4, 2.0, 2.0, Hz, 1H), 5.22 (dd, J = 4.8, 2.4 Hz, 1H), 4.32 (dd, J = 11.2, 4.8 Hz, 1H), 4.25 (dddd, J = 13.6, 7.6, 2.0, 1.6 Hz, 1H), 4.10 (ddd, J = 10.8, 4.0, 2.8 Hz, 1H), 3.49 (ddd, J = 7.6, 4.8, 2.8 Hz, 1H), 2.42 (s, 3H), 2.01 (d, J = 7.2 Hz, 1H); ^{13}C NMR (100.0 MHz, $CDCl_3$) δ 144.9, 138.8, 132.7, 129.8, 129.4, 129.1, 128.4, 128.1, 127.94, 127.88, 74.0, 71.2, 69.1, 62.9, 21.6; IR (neat) 3524, 3062, 3032, 2954, 2891, 1598, 1494, 1453, 1361, 1190, 1174, 1097, 990, 930 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{19}H_{20}O_5SNa$: 383.0929, observed 383.0905.

(2R,3S,6S)-2-(Azidomethyl)-6-phenyl-3,6-dihydro-*2H*-pyran-3-ol (**SI-02**): To a flask charged with tosylate **SI-01** (2.03 g, 5.63 mmol) under N_2 was added DMF (30 mL). To the solution was added NaN_3 (3.66 g, 56.3 mmol). The reaction mixture was stirred at 75 °C for 20 h. The crude reaction mixture was quenched with the addition of saturated, $NaHCO_{3(aq)}$. The mixture was extracted with Et_2O, and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified via flash column chromatography (hexane:EtOAc = 4:1 to 2:1), to afford azide **SI-02** (1.31 g, quant). $[\alpha]^{25}_D$ = –183.0° (c 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.43 (m, 5H), 6.13 (ddd, J = 10.2, 3.0, 1.8 Hz, 1H), 6.02 (ddd, J = 10.5, 2.1, 2.1 Hz, 1H), 5.29 (dd, J = 5.1, 2.4 Hz, 1H), 4.12-4.21 (m, 1H), 3.48-3.53(m, 1H), 3.40-3.47 (m, 2 H),1.61 (d, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 129.4, 129.3, 128.4, 128.1, 127.9, 73.8, 72.3, 64.5, 51.7; IR (neat) 3395, 3062, 3032, 2921, 2890, 2100, 1493, 1452, 1289, 1262, 1068, 1030, 864 cm^{-1}; HRMS $[M+H]^+$: calculated for $C_{12}H_{14}N_3O_2$: 232.1086, observed 232.1081.

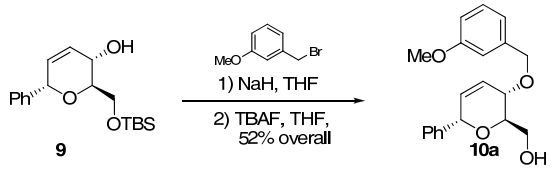
(2R,3S,6S)-2-((Tert-butyldimethylsilyloxy)methyl)-6-phenyl-3,6-dihydro-*2H*-pyran-3-ol (9) To a solution of diol **8** (3 g, 14.55 mmol) in DMF (45 mL), imidazole (1.07g, 15.72 mmol) and *t*-butyldimethylsilyl chloride (2.4g, 15.7 mmol) were added at room temperature. The solution was stirred under nitrogen for 15 h, after which time H_2O (150 mL) was added. The aqueous layer was extracted with EtOAc (2 x 150mL). The combined organic layers were washed with H_2O (2 x 100 mL) and sat. $NaCl_{(aq)}$ (100 mL). The organic portion was then dried over Na_2SO_4, filtered, and the solvent removed under reduced pressure. The crude material was purified by flash column chromatography (EtOAc:petroleum ether = 3:7) to afford the silyl ether **7** (4.0 g, 85% yield). $[\alpha]^{25}_D$ = –63.5° (c 2.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.44 (m, 5H), 5.93 - 6.16 (m, 2 H), 5.25 (s, 1 H), 4.27 (dd, *J*=7.8, 1.6 Hz, 1 H), 3.84 (dd, *J*=9.8, 5.1 Hz, 1 H), 3.72 (dd, *J*=9.8, 7.8 Hz, 1 H), 3.47 (ddd, *J*=7.8, 7.8, 5.1 Hz, 1 H), 2.89 (s(br), 1 H), 0.91 (s, 9 H), 0.08 (s, 3 H), 0.06(s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 129.4, 128.4, 128.3, 128.0, 128.0, 77.3, 76.7, 73.9, 71.0, 67.2, 65.8, 25.8, 18.2, -5.6; IR (neat) 3423, 3062, 3032, 2954, 2962, 2884, 2857, 1602, 1493, 1256, 1073, 837 cm^{-1}; HRMS $[2M+Na]^+$: calculated for $C_{36}H_{56}O_6Si_2Na$: 663.3616, observed 663.3513.

III. General Procedure A: Etherification of Allylic Alcohols 9 and SI-02

A dry round bottom flask fitted with a nitrogen balloon was charged with NaH (1.0 mmol, 2.0 eq, 60% dispersion in oil). THF (1 mL) was added and the suspension was cooled to 0 °C. To the suspension was added a solution of the allylic alcohol (0.5 mmol, 1 equiv.) in THF (1 mL) and the reaction mixture was stirred at room temperature for 30 min. After cooling back to 0 ºC, the benzylic or allylic bromide (2.0 equiv.) dissolved in THF (1 mL) was added to the reaction and stirring was continued at room temperature for 4 h. Sat. $NH_4Cl_{(aq)}$ (10 mL) was then added to quench the reaction; after dilution with H_2O (10 mL), the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. In the case of azido dihydropyran **SI-02**, the crude product was isolated by flash column chromatography to afford **18**. In case of silyl ether **7**, the crude product was treated with TBAF (2.0 equiv.) in THF (2 mL) without further purification. After the silyl group cleavage, the corresponding primary alcohols (**10a–10d**) were isolated in pure form by flash column chromatography (EtOAc: petroleum ether = 3:7).

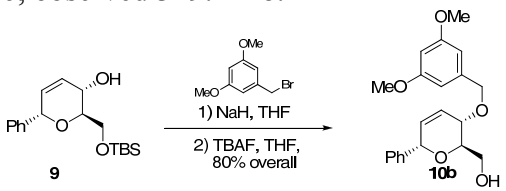


(2R,3S,6S)-2-(Azidomethyl)-3-(3-methoxybenzyloxy)-6-phenyl-3,6-dihydro-2H-pyran (**18)** was prepared (140 mg, 81% yield) from alcohol **SI-02** (114 mg, 0.5 mmol) following general procedure **A**. $[\alpha]^{25}_D$ = –36.5° (c 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J=7.0 Hz, 2 H), 7.35 (m, 3 H), 7.27 (d, J=8.2 Hz, 1 H), 6.92 (d, J=7.8 Hz, 1 H), 6.89 (s, 1 H), 6.86 (dd, J=8.2, 2.7 Hz, 1 H), 6.17 (d, J=11.0 Hz, 1 H), 6.11-6.15 (m, 1 H), 5.32 (br. s., 1 H), 4.68 (d, J=12.0 Hz, 1 H), 4.54 (d, J=11.7 Hz, 1 H), 4.05 (dd, J=8.2, 1.6 Hz, 1 H), 3.82 (s, 3 H), 3.67 (m, 1 H), 3.40 (d, J=4.3 Hz, 2 H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 139.4, 138.9, 129.6, 129.4, 128.4, 128.2, 128.1, 126.8, 120.2, 113.5, 113.4, 74.2, 71.0, 70.9, 70.3, 55.2, 51.8; IR(neat) 3060, 3031, 3002, 2918, 2883, 2836, 2359, 2099, 1587, 1490, 1389, 1267, 1155, 1087, 952, 863 cm^{-1}; HRMS $[M+H]^+$: calculated for $C_{20}H_{21}N_3O_3Na$: 352.1661, observed 352.1672.

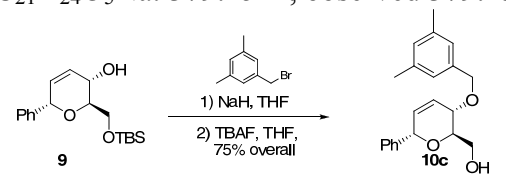


((2R,3S,6S)-3-(3-Methoxybenzyloxy)-6-phenyl-3,6-dihydro-2H-pyran-2-yl)methanol (10a) was prepared (1.07 g, 52% overall yield) from allylic alcohol **9** (2 g, 0.5 mmol) following general procedure **A**. $[\alpha]^{25}_D$ = +53.7° (c 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 - 7.34 (m, 6 H), 6.81 - 6.86 (m, 2 H), 6.75 (dd, J=8.4, 2.1 Hz, 1 H), 6.08 (dt, J=10.16, 1.95 Hz, 1 H), 6.02 (ddd, J=10.55, 3.13, 1.56 Hz, 1 H), 5.19 (d, 1 H), 4.61 (d, J=11.7 Hz, 1 H), 4.49 (d, J=11.7 Hz, 1 H), 4.02 (dd, J=8.21 1.95 Hz, 1 H), 3.72 (s, 3 H), 3.69 - 3.60 (m, 2 H), 3.47 - 3.53 (m, 1 H), 1.95 (br s, 1 H)^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 139.6, 139.1, 129.5, 129.2, 128.4, 128.1, 127.2, 120.1, 113.4, 113.2,

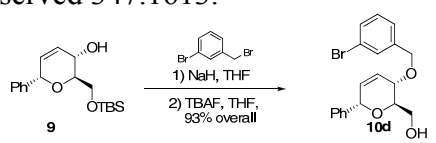
71.0, 70.9, 70.2, 62.5, 55.2. IR (neat) 3455, 3031, 3455, 3031, 3002, 2879, 2836, 1602, 1490, 1454, 1437, 1391, 1267, 1155, 1082, 925, 870 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{20}H_{22}O_4Na$: 349.1446, observed 349.1428.



(2R,3S,6S)-3-(3,5-Dimethoxybenzyloxy)-6-phenyl-3,6-dihydro-2H-pyran-2-yl)methanol (**10b**) was prepared from allylic alcohol **9** (254 mg, 0.79 mmol) following general procedure **A** and isolated in 80% yield (225 mg). $[\alpha]^{25}_D$ = +33.2° (c 5.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$)δ 7.43 (d, J=7.4 Hz, 2 H), 7.29 - 7.40 (m, 3 H), 6.53 (d, J=2.0 Hz, 2 H), 6.41 (t, J=2.3 Hz, 1 H), 6.20 (m, 1 H), 6.08 (m, 1 H), 5.29 (d, J=2.0 Hz, 1 H), 4.65 (d, J=11.7 Hz, 1 H), 4.55 (d, J=11.7 Hz, 1 H), 4.11 (dd, J=8.2, 1.6 Hz, 1 H), 3.80 (s, 6 H), 3.76 (dd, J=11.3, 3.5 Hz, 1 H), 3.73 (dd, J=11.3, 4.6 Hz, 1 H), 3.58 - 3.64 (m, 1 H), 2.10 (s, 1 H).^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 140.4, 139.1, 129.2, 128.4, 128.0, 127.2, 105.5, 99.8, 74.1, 71.0, 70.9, 70.2, 62.5, 55.3; IR (neat) 3462, 3001, 2937, 2884, 2839, 1653, 1598, 1559, 1457, 1345, 1298, 1205, 1154, 1089, 921, 835 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{21}H_{24}O_5Na$: 379.1521, observed 379.1508.

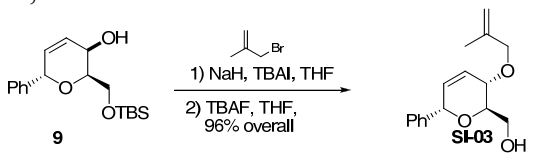


((2R,3S,6S)-3-(3,5-Dimethylbenzyloxy)-6-phenyl-3,6-dihydro-2H-pyran-2-yl)methanol (**10c**) was prepared from allylic alcohol **9** (160 mg, 0.5 mmol) following general procedure **A** and isolated in 75% overall yield (121 mg). $[\alpha]^{25}_D$ = +10.0° (c 3.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J=7.4 Hz, 2 H), 7.29 - 7.39 (m, 3 H), 6.98 (s, 2 H), 6.95 (s, 1 H), 6.20 (dt, J=10.1, 1.9 Hz, 1 H), 6.10 (ddd, J=10.1, 3.1, 1.9 Hz, 1 H), 5.29 (d, J=2.3 Hz, 1 H), 4.66 (d, J=10.9 Hz, 1 H), 4.53 (d, J=10.9, 1 H), 4.11 (ddd, J=8.2, 3.9, 2.0 Hz, 1 H), 3.77 (dd, J=11.3, 3.1 Hz, 1 H), 3.71 (dd, J=11.3, 4.7 Hz, 1 H), 3.60 (ddd, 3.77 (dd, J=8.2, 4.7, 3.1 Hz, 1 H), 2.34 (s, 6 H), 1.89 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 138.1, 137.7, 129.5, 129.1, 128.4, 128.1, 128.0, 127.4, 125.8, 74.2, 71.2, 70.8, 70.2, 62.6, 21.3; IR (neat) 3447, 3060, 3029, 2918, 2873, 1608, 1493, 1453, 1310, 1261, 1158, 1087, 925, 870, 847 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{21}H_{24}O_3Na$: 347.1623, observed 347.1613.

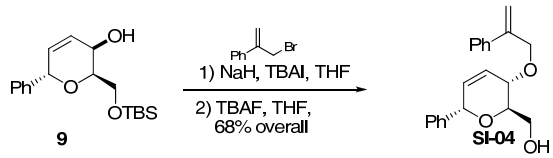


((2R,3S,6S)-3-(3-Bromobenzyloxy)-6-phenyl-3,6-dihydro-2H-pyran-2-yl)methanol (**10d**) was prepared from allylic alcohol **9** (320 mg, 1.0 mmol) following general procedure **A** (350 mg, 93% overall yield). $[\alpha]^{25}_D$ = +31.0° (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1 H), 7.28-7.44 (m, 7 H), 7.22 (d, J=7.4 Hz, 1 H), 6.17 (dt, J=10.6, 1.0 Hz, 1 H), 6.11 (ddd, J=10.6, 2.7, 1.0 Hz, 1 H), 5.29-5.30 (m, 1 H), 4.68 (d,

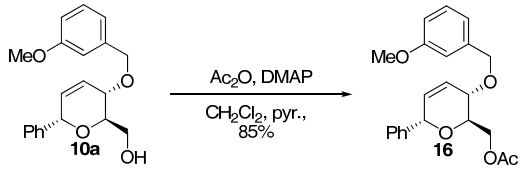
J=12.5 Hz, 1 H), 4.57 (d, J=12.5 Hz, 1 H), 4.12 (ddd, J=8.2, 3.5, 1.8 Hz, 1 H), 3.68 - 3.79 (m, 3 H), 3.59 (ddd, J=8.1, 4.8, 3.5 Hz, 1 H), 1.91 (t, J=6.3 Hz, 1 H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 139.0, 130.9, 130.7, 130.0, 129.5, 128.5, 128.2, 128.1, 127.0, 126.2, 122.6, 74.2, 70.9, 70.5, 70.2, 62.5; IR (neat) 3835, 3744, 3447, 3061, 3031, 2878, 2360, 1571, 1474, 1394, 1310, 1201, 1082, 1001 cm^{-1}; HRMS $[2M+Na]^+$: calculated for $C_{38}H_{38}O_6Br_2Na$: 771.0933, observed 771.0931.



((2R,3S,6S)-3-(2-Methylallyloxy)-6-phenyl-3,6-dihydro-2H-pyran-2-yl)methanol (**SI-03**) was prepared (125 mg, 96% overall yield) from allylic alcohol **9** (160 mg, 0.5 mmol) using a slight modification of general procedure **A** (5% tetrabutyl ammonium iodide (TBAI) was added at the time of addition of the allylic bromide). $[\alpha]^{25}_D$ = +13.9° (c 3.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 - 7.44 (m, 5 H), 6.18 (dt, J=10.6, 2.0 Hz, 1 H), 6.11 (ddd, J=10.6, 3.1, 1.9 Hz, 1 H), 6.07 - 6.12 (m, 1 H), 5.29 (d, J=2.3 Hz, 1 H), 5.00 (s, 1 H), 4.92 (s, 1 H, 4.08 (d, J=12.1 Hz, 1 H), 4.04 (dd, J=8.4, 1.8 Hz, 1 H), 3.98 (d, J=12.1 Hz, 1 H), 3.78 (d, J=11.7, 3.1 Hz, 1 H), 3.72 (d, J=11.7, 5.1 Hz, 1 H), 3.56 (ddd, J=8.2, 4.9, 3.3 Hz, 1 H), 2.07 (br. s., 1 H), 1.78 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 139.1, 129.0, 128.4, 128.0, 127.3, 112.7, 74.1, 73.1, 70.9, 70.2, 62.6, 19.6; IR (neat) 3453, 3031, 2915, 2883, 1452, 1375, 1309, 1259, 1193, 1087, 900, 869, 813, 738, 698 cm^{-1}; HRMS $[M+H]^+$: calculated for $C_{16}H_{21}O_3$: 261.1491, observed 261.1503.

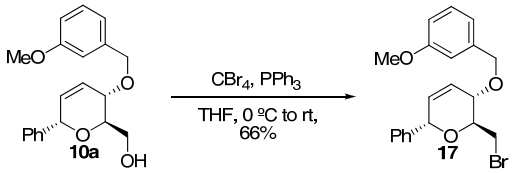


((2R,3S,6S)-6-Phenyl-3-(2-phenylallyloxy)-3,6-dihydro-2H-pyran-2-yl)methanol (SI-04) was Prepared (680 mg, 68% overall yield) from allylic alcohol **9** (1 g, 3.12 mmol) using modified general procedure **A** (5% TBAI was added at the time of addition of the allylic bromide). $[\alpha]^{25}_D$ = +4.5° (c 3.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J*=7.4 Hz, 2 H), 7.28-7.41 (m, 8 H), 6.16 (dt, *J*=10.6, 1.6 Hz, 4 H), 6.08 (ddd, *J*=10.6, 3.1, 1.6 Hz, 5 H), 5.55 (s, 1 H), 5.36 (s, 1 H), 5.27 (d, *J*=2.3 Hz, 1 H), 4.60 (d, *J*=12.5 Hz, 1 H), 4.47 (d, *J*=12.5 Hz, 1 H), 4.09 - 4.12 (m, 1 H), 3.49-3.61 (m, 3 H), 1.81 (br.s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 139.1, 138.4, 129.2, 128.4, 128.1, 128.0, 127.1, 126.2, 115.2, 74.2, 70.9, 70.8, 69.8, 62.5; IR (neat) 3449, 3058, 3029, 2919, 2876, 1623, 1598, 1573, 1494, 1452, 1390, 1307, 1260, 1189, 1073, 910, 870, 779, 698 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{21}H_{22}O_3Na$: 345.1467, observed 345.1464.



((2R,3S,6S)-3-(3-Methoxybenzyloxy)-6-phenyl-3,6-dihydro-2H-pyran-2-yl)methyl acetate (**16**): To a solution of alcohol **10a** (200 mg, 0.61 mmol) in CH_2Cl_2:pyridine (3:1, 3 mL) acetic anhydride (0.12 mL, 1.22 mmol) and dimethylaminopyridine (15 mg, 0.12

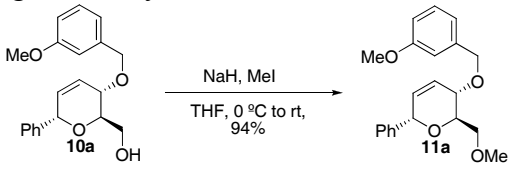
mmol) were added at room temperature. After 6 h, sat. $NaHCO_{3(aq)}$ (10 mL) was added and the mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with H_2O (2 x 20 mL) and sat. $NaCl_{(aq)}$ (10 mL) and dried over Na_2SO_4. After removal of the volatiles under reduced pressure, acetate **16** was purified by flash column chromatography (191 mg, 85% yield). $[\alpha]^{25}_D$ = +13.2° (c 3.5, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.45 (m, 2 H), 7.31 - 7.40 (m, 1 H), 7.27 (m, J=8.2 Hz, 1 H), 6.90 - 6.95 (m, 2 H), 6.85 (dd, J=8.2, 2.3 Hz, 1 H), 6.13 - 6.21 (m, 2 H), 5.32 (s, 1 H), 4.67 (d, J=11.7 Hz, 1 H), 4.55 (d, J=11.7 Hz, 1 H), 4.31 (dd, J=11.9, 5.3 Hz, 1 H), 4.17 (dd, J=11.9, 2.7 Hz, 1 H), 4.05 (d, J=7.8 Hz, 1 H), 3.82 (s, 3 H), 3.75 (ddd, J=7.9, 5.4, 2.7 Hz, 1 H), 2.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 159.7, 139.3, 139.1, 129.7, 129.5, 128.4, 128.0, 128.0, 126.5, 120.3, 113.5, 113.3, 74.1, 70.7, 69.5, 69.3, 63.5, 55.2, 20.8; IR (neat) 3031, 2952, 1740, 1587, 1491, 1453, 1368, 1235, 1155, 1049, 957, 871 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{22}H_{24}O_5Na$: 391.1521, observed 391.1510.



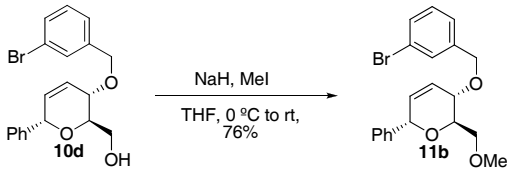
(2S,3S,6S)-2-(Bromomethyl)-3-(3-methoxybenzyloxy)-6-phenyl-3,6-dihydro-2H-pyran (17) Alcohol **10a** (150 mg, 0.46 mmol) was disolved in THF. To this solution, carbon tetrabromide (229 mg, 0.69 mmol) and triphenylphosphine (181 mg, 0.69 mmol) were added in that order. Stirring was continued under nitrogen at room temperature. Solvent was removed under reduced pressure and the crude material purified by flash column chromatography to afford bromide **17** (118 mg, 66% yield). $[\alpha]^{25}_D$ = +0.9° (c 3.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J=6.6 Hz, 2 H), 7.16 - 7.30 (m, 4 H), 6.85 (d, J=7.4 Hz, 1 H), 6.82 (s, 1 H), 6.76 (dd, J=8.2, 2.7 Hz, 1 H), 6.00 - 6.08 (m, 2 H), 5.24 (s, 1 H), 4.61 (d, J=11.7 Hz, 1 H), 4.52 (d, J=11.7Hz, 1 H), 4.06 (d, J=7.4 Hz, 1 H), 3.72 (s, 3 H), 3.62(ddd, J=7.8, 4.7, 3.1 Hz, 1 H), 3.50 (dd, J=10.9, 5.1 Hz 1 H), 3.47 (dd, J=10.9, 3.5 Hz 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 139.4, 138.9, 129.5, 128.4, 128.1, 126.4, 120.2, 113.5, 113.4, 74.2, 71.9, 71.1, 70.1, 55.2, 33.9; IR (neat) 3060, 3031, 3002, 2957, 2937, 2869, 2835, 1604, 1490, 1465, 1436, 1309, 1266 1155, 1051, 1004 HRMS $[M+Na]^+$ calculated for $C_{20}H_{21}BrO_3Na$ 411.0572; observed 411.0586.

IV. General Procedure B: Preparation of Pyran Methyl Ethers (11a-e)

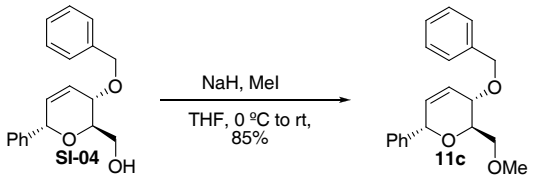
Dihydropyran alcohol (1 mmol) was dissolved in THF (2 mL) and MeI (2 mmol) was added. This solution was cooled to 0 ºC before NaH (2.8 mmol of 60% dispersion in oil) was added in one portion. The reaction was stirred at room temperature for 4 h before sat. $NH_4Cl_{(aq)}$ (10 mL) was added. The mixture was diluted with H_2O (10 mL), extracted with EtOAc (2 x 20 mL) and the combined organic layers were dried over Na_2SO_4. Removal of solvent under reduced pressure and purification *via* flash column chromatography afforded the corresponding C6 methyl ether.



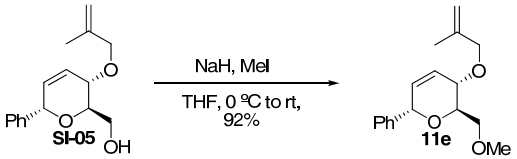
(2R,3S,6S)-3-(3-Methoxybenzyloxy)-2-(methoxymethyl)-6-phenyl-3,6-dihydro-2H-pyran (**11a**) was prepared (294 mg, 94% yield) from pyran alcohol **10a** (300 mg, 0.36 mmol) following general procedure **B**. $[\alpha]^{25}_{D}$ = +9.7° (c 3.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J=7.0 Hz, 2 H), 7.28 - 7.37 (m, 4 H), 6.92 (m, 2 H), 6.84 (dd, J=8.2, 2.3 Hz, 1 H), 6.13 (m, 1 H), 6.10 (dd, J=2.9, 1.4 Hz, 2 H), 5.30 (d, J=1.6 Hz, 1 H), 4.66 (d, J=11.7 Hz, 1 H), 4.57 (d, J=11.7 Hz, 1 H), 4.18 (dd, J=8.0, 1.8 Hz, 1 H), 3.81 (s, 3 H), 3.62-3.67 (m, 1 H), 3.58 (dd, J=10.2, 3.9 Hz, 1 H), 3.51 (dd, J=10.2, 2.3 Hz, 1 H), 3.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 139.8, 139.4, 129.5, 129.4, 128.3, 128.1, 127.9, 127.2, 120.2, 113.4, 113.3, 74.2, 71.7, 71.1, 70.2, 70.0, 59.2, 55.2; IR (neat) 3031, 2925, 2889, 2836, 1722, 1693, 1684, 1587, 1490, 1465, 1394, 1267, 1193, 1050, 967, 868 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{21}H_{24}O_4Na$: 363.1572, observed 363.1556.



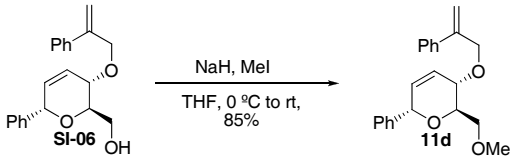
(2R,3S,6S)-3-(3-Bromobenzyloxy)-2-(methoxymethyl)-6-phenyl-3,6-dihydro-2H-pyran (11b) was prepared (80 mg, 76% yield) from pyran alcohol **10d** (100 mg, 0.27 mmol) following general procedure **B**. $[\alpha]^{25}_{D}$ = +66.7° (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1 H), 7.35 (m, 2 H), 7.25 (m, 3 H), 7.17 (d, J=9.4 Hz, 1 H), 7.14 (d, J=7.8 Hz, 1 H), 6.04 - 6.06 (m, 2 H), 5.23 (s, 1 H), 4.58 (d, J=12.9 Hz, 1 H), 4.48 (d, J=12.9 Hz, 1 H), 4.11 (d, J=7.8 Hz, 1 H), 3.54-3.58 (m, 1 H), 3.51 (dd, J=10.6, 3.9 Hz, 1 H), 3.43 (dd, J=10.6, 2.7 Hz, 1 H), 3.27 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 139.3, 130.8, 130.0, 129.7, 128.5, 128.4, 128.1, 128.0, 126.9, 126.3, 122.5, 74.2, 71.6, 70.2, 70.1, 59.3; IR (neat) 3859, 3790, 3642, 3371, 3061, 3031, 2980, 2922, 2886, 1952, 1885, 1724, 1598, 1494, 1452, 1311, 1196, 1091, 957, 870 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{20}H_{21}B_rO_3Na$: 411.0572, found 411.0590.



(2R,3S,6S)-3-(benzyloxy)-2-(methoxymethyl)-6-phenyl-3,6-dihydro-2H-pyran (**11c**) was prepared (134 mg, 85% yield) from pyran alcohol **SI-04** (150 mg, 0.51 mmol) following general procedure **B**. $[\alpha]^{25}_{D}$ = +27.6° (c 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J=7.0 Hz, 2 H), 7.32 (m, 8 H), 6.14 (dt, J=10.6, 2.0 Hz, 1 H), 6.11 (ddd, J=10.6, 3.1, 1.6 Hz, 1 H), 5.31 (d, J=2.0 Hz, 1 H), 4.69 (d, J=11.3 Hz, 1 H), 4.60 (d, J=11.3 Hz, 1 H), 4.17 - 4.22 (m, 2 H), 3.62 - 3.66 (m, 1 H), 3.58 (dd, J=10.6, 4.7 Hz, 1 H), 3.52 (dd, J=10.6, 2.7 Hz, 1 H), 3.32 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 138.2, 129.4, 128.4, 128.1, 128.0, 127.9, 127.8, 127.3, 74.2, 71.7, 71.2, 70.2, 69.9, 59.2; IR (neat) 3062, 3031, 2887, 1495, 1453, 1304, 1262, 1194, 1091, 1028, 921 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{20}H_{22}O_3Na$: 333.1467, observed 333.1467.

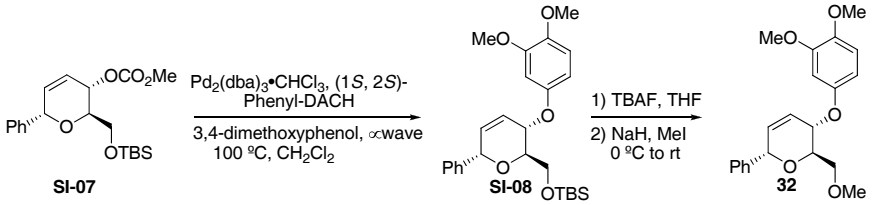


(2R,3S,6S)-2-(Methoxymethyl)-3-(2-methylallyloxy)-6-phenyl-3,6-dihydro-2H-pyran (**11e**) was prepared (217 mg, 92% yield) from pyran alcohol **SI-05** (237 mg, 0.91 mmol) following general procedure **B**. $[\alpha]^{25}_{D}$ = +13.9° (c 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 - 7.44 (m, 5H), 6.06 - 6.15 (m, 2H), 5.29 (s, 1H), 4.98 (s, 1H), 4.90 (s, 1H), 4.08 (d, J=7.4 Hz, 1H), 4.05 (d, J=12.5 Hz, 1H), 3.96 (d, J=12.1, 1H), 3.60 (app dd, J=11.7, 4.3 Hz, 2H), 3.50 (app dd, J=11.9, 4.4 Hz, 1H), 3.36 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 139.3, 129.1, 128.1, 127.9, 127.7, 127.1, 112.5, 74.0, 73.0, 71.6, 70.2, 69.7, 59.0, 19.4; IR (neat) 3345, 3062, 3031, 2978, 2889, 2360, 1956, 1891, 1811, 1654, 1577, 1452, 1310, 1194, 1093, 1031, 956, 900, 871 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{17}H_{22}O_3Na$: 297.1467, observed 297.1454.



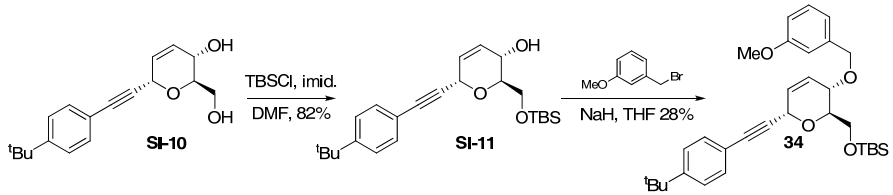
(2R,3S,6S)-2-(Methoxymethyl)-6-phenyl-3-(2-phenylallyloxy)-3,6-dihydro-2H-pyran (**11d**) was prepared (62 mg, 85% yield) from pyran alcohol **SI-06** (70 mg, 0.22 mmol) following general procedure **B**. $[\alpha]^{25}_{D}$ = +24.4° (c 6.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 - 7.44 (m, 5 H), 6.18 (dt, J=10.6, 2.0 Hz, 1 H), 6.11 (ddd, J=10.6, 3.1, 1.9 Hz, 1 H), 6.07 - 6.12 (m, 1 H), 5.29 (d, J=2.3 Hz, 1 H), 5.00 (s, 1 H), 4.92 (s, 1 H, 4.08 (d, J=12.1 Hz, 1 H), 4.04 (dd, J=8.4, 1.8 Hz, 1 H), 3.98 (d, J=12.1 Hz, 1 H), 3.78 (d, J=11.7, 3.1 Hz, 1 H), 3.72 (d, J=11.7, 5.1 Hz, 1 H), 3.56 (ddd, J=8.2, 4.9, 3.3 Hz, 1 H), 2.07 (br. s., 1 H), 1.78 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 139.1, 129.0, 128.4, 128.0, 127.3, 112.7, 74.1, 73.1, 70.9, 70.2, 62.6, 19.6. IR (neat) 3393, 3084, 3059, 3031, 2981, 2888, 2360, 2342, 1956, 1811, 1653, 1575, 1495, 1395, 1263, 1117, 1002, 916, 870 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{22}H_{20}O_3Na$: 359.1623, observed 359.1614.

V. Synthesis of Dihydropyrans 32 and 34



(2R,3S,6S)-3-(3,4-Dimethoxyphenoxy)-2-(methoxymethyl)-6-phenyl-3,6-dihydro-2H-pyran (**32**): 3,4-dimethoxy aryl ether **SI-08** was synthesized from methylcarbonate **SI-07** (377 mg, 1.0 mmol) following the reported procedure using 3,4-dimethoxyphenol as the nucleophile.[1] The crude reaction mixture was filtered through a pad of silica gel using EtOAc. The filtrate was concentrated and dissolved in THF (5 mL). A solution of TBAF (1.0M in THF, 1.5mL) was added at room temperature. The mixture was stirred for 30

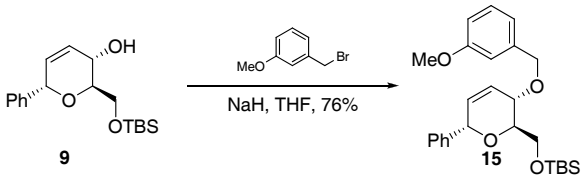
min at the same temperature, at which time it was diluted with EtOAc (5 mL) and H_2O (5 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL) and dried over $MgSO_4$. The solution was concentrated *in vacuo* and advanced to the next step without further purification. Crude **SI-08** was dissolved in THF (5 mL) and iodomethane (93 μL, 1.5 mmol) was added in one portion. The solution was cooled to 0 ºC before adding NaH (60 mg, 1.5 mmol). The reaction was stirred at room temperature for 30 min and subsequently quenched by addition of H_2O (5 mL). The mixture was diluted with EtOAc (5 mL), the aqueous layer extracted with EtOAc (3 × 5 mL), and the combined organic layers were dried over $MgSO_4$. The mixture was concentrated *in vacuo* and the crude material purified *via* flash column chromatography (70:30, hexanes:EtOAc) to provide **32** (145 mg, 41% yield, 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (app d, J=7.0 Hz, 2H), 7.39 (app t, J=7.2 Hz, 2H), 7.34 (app d, J=7.4 Hz, 1H), 6.80 (d, J=9.0 Hz, 1H), 6.58 (d, J=2.7 Hz, 1H), 6.51 (dd, J=9.0, 2.7 Hz, 1H), 6.17 (s, 2H), 5.38 (s, 1H), 4.94 (dd, J=8.2, 1.9 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.77 (ddd, J=7.8, 3.1, 3.1 Hz, 1H), 3.62–3.54 (m, 2H), 3.35 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 149.9, 143.8, 139.1, 130.1, 128.4, 128.1, 128.0, 126.4, 111.8, 105.7, 101.9, 71.4, 70.1, 69.0, 59.3, 56.4, 55.8 ppm; IR (neat) 2994, 2939, 2894, 2832, 1596, 1511, 1452, 1230, 1197, 1160, 1027 cm^{-1}; HRMS $[M+H]^+$: calculated for $C_{21}H_{25}O_5$: 357.1702, observed 357.1712.



(2R,3S,6S)-2-((tert-Butyldimethylsilyloxy)methyl)-6-((4-tert-butylphenyl)ethynyl)-3,6-dihydro-2H-pyran-3-ol (**SI-11**): was obtained from diol **SI-10**[1] following the procedure used for preparation of silyl ether **9** (*vide supra*). **SI-11** was isolated in 82% yield (345 mg) from **SI-10** (300 mg, 286.37 mmol). $[\alpha]^{25}_D$ = –17.3° (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J*=8.6 Hz, 2 H), 7.24 (d, *J*=8.6 Hz, 2 H), 5.77 (s, 2 H), 4.99-5.00 (m, 1 H), 4.16 (dd, *J*=8.2, 2.3 Hz, 1 H), 3.91 (dd, *J*=9.8, 4.7 Hz, 1 H), 3.76 (dt, *J*=11.3, 5.1 Hz, 1 H), 3.66 (dd, *J*=9.8, 7.4 Hz, 1 H), 1.20 (m, 9 H), 0.82 (m, 9 H), 0.02 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 131.6, 128.7, 127.1, 125.2, 119.3, 86.1, 84.9,72.4, 67.1, 65.8, 64.1, 34.8, 31.1, 25.8, 18.2, -5.5, -5.6 ppm: IR (neat) 3446, 2957, 2929, 2904, 2685, 2857, 1515, 1505, 1363, 1255, 1115, 1018, 924, 836 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{24}H_{36}O_3SiNa$: 423.2331, found 423.2327.

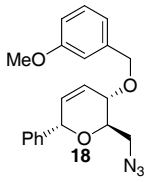
***tert*-butyl(((2R,3S,6S)-6-((4-tert-butylphenyl)ethynyl)-3-(3-methoxybenzyloxy)-3,6-dihydro-2H-pyran-2-yl)methoxy)dimethylsilane (34**) was prepared (73 mg, 28% yield) from **SI-11** following the general procedure **A** (for **SI-2**). $[\alpha]^{25}_D$ = –191.0° (c 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 - 7.30 (m, 5 H), 6.82 - 6.86 (m, 2 H), 6.73 - 6.76 (m, 1 H), 5.88 (dt, *J*=10.2, 1.6 Hz, 1 H), 5.79 (ddd, *J*=10.2, 3.5, 1.6 Hz, 1 H), 5.03-5.05 (m, 1 H), 4.55 (d, *J*=11.0 Hz, 1 H), 4.47 (d, *J*=11.0 Hz, 1 H), 4.04-4.07 (m, 1 H), 3.83 (m, 3 H), 3.72 (s, 3 H), 1.21 (m, 9 H), 0.82 (m, 9 H), 0.01 (s, 3 H), 0.00 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 151.6, 139.8, 131.5, 129.4, 128.1, 126.9, 125.3, 120.1, 119.5, 113.4, 110.0, 86.0, 85.2, 73.7, 71.9, 71.1, 69.8, 64.4, 63.0, 55.2, 34.8, 31.2, 26.0, 18.5, -5.1, -5.2; IR (neat) 3853, 3675, 3393, 3038, 2956, 2929, 2857, 2360, 1603, 1464,

1267, 1097, 836 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{32}H_{44}O_4SiNa$: 543.2907, observed 543.2902.

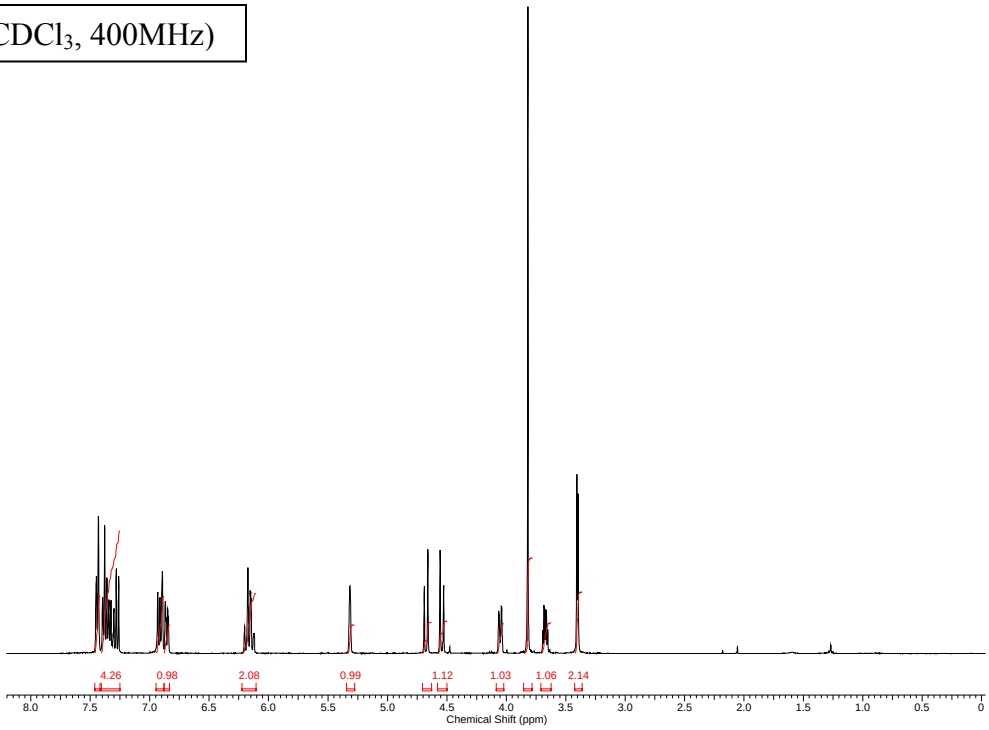


***tert*-Butyl(((2R,3S,6S)-3-(3-methoxybenzyloxy)-6-phenyl-3,6-dihydro-2H-pyran-2-yl)methoxy)dimethylsilane** (**15**): A mixture of the allylic alcohol **9** (2.0 g, 6.24 mmol) and 3-methoxybenzyl bromide (1.7 mL, 12.5 mmol) was dissolved in THF (20 mL) and cooled to 0 ºC. NaH (494 mg of 60% dispersion in oil) was added to this solution in one portion. The reaction was then warmed to room temperature and stirred for 4 h under nitrogen. After cooling back to 0 °C, the reaction was quenched by addition of H_2O (10 mL). The mixture was diluted with sat. $NaHCO_{3(aq)}$ and extracted with diethyl ether (2 x 100 mL). The combined organic layers were dried, concentrated, and purified by flash column chromatography (EtOAc: petroleum ether = 1:9) to afford methoxybenzyl ether **15** (2.09 g, 76% yield). $[\alpha]^{25}_D$ = +4.3° (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J=7.4 Hz, 2 H), 7.35 (d, J=6.6 Hz, 2 H), 7.24 - 7.31 (m, 2 H), 6.92 (d, 2 H), 6.83 (dd, J=8.2, 2.7 Hz, 1 H), 6.09 - 6.16 (m, 2 H), 5.28 (s, 1 H), 4.66 (d, J=11.7 Hz, 1 H), 4.58 (d, J=11.7 Hz, 1 H), 4.05 (d, J=7.4 Hz, 1 H), 3.77 - 3.84 (m, 5 H), 3.66 (s, 9 H), 0.06 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 140.0, 139.8, 130.2, 129.4, 128.3, 127.8, 127.6, 126.5, 120.0, 113.3, 113.1, 73.6, 70.7, 70.0, 63.1, 55.2, 25.9, 18.3, -5.3; IR (neat) 2953, 2928, 2883, 2856, 1587, 1490, 1266, 1091, 836 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{20}H_{22}O_4Na$: 349.1416, observed 349.1428 .

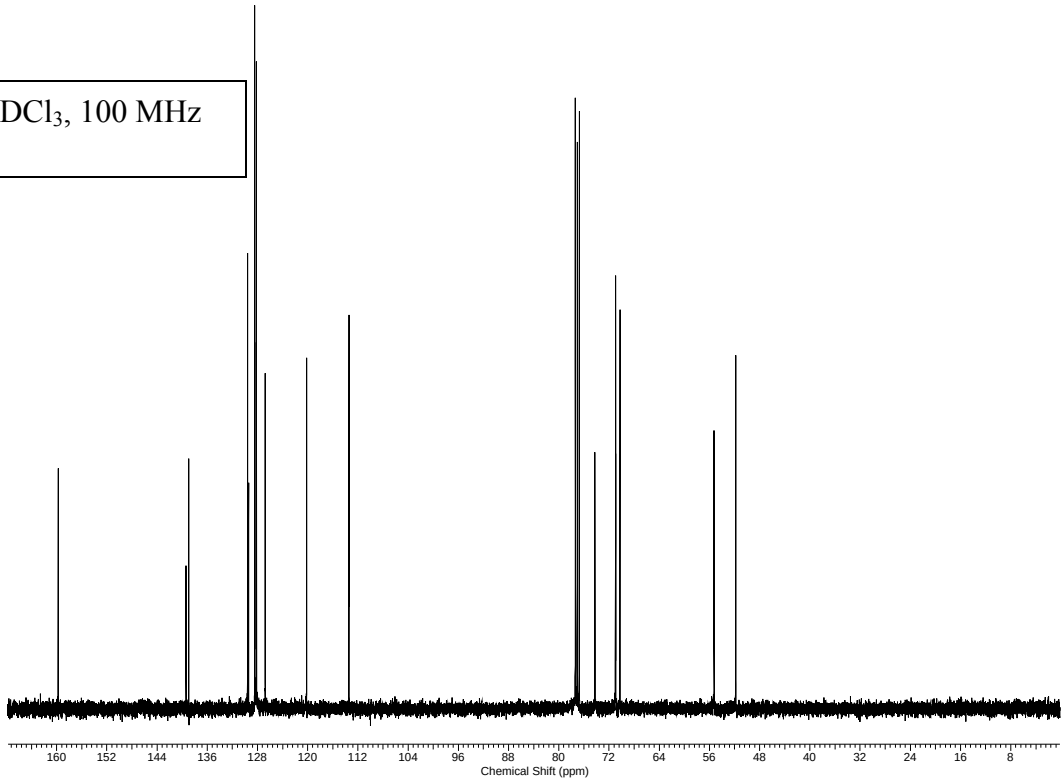
VI. ^{1}H and ^{13}C NMR Spectra of Dihydropyran Substrates

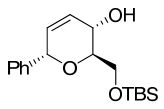


($CDCl_3$, 400MHz)



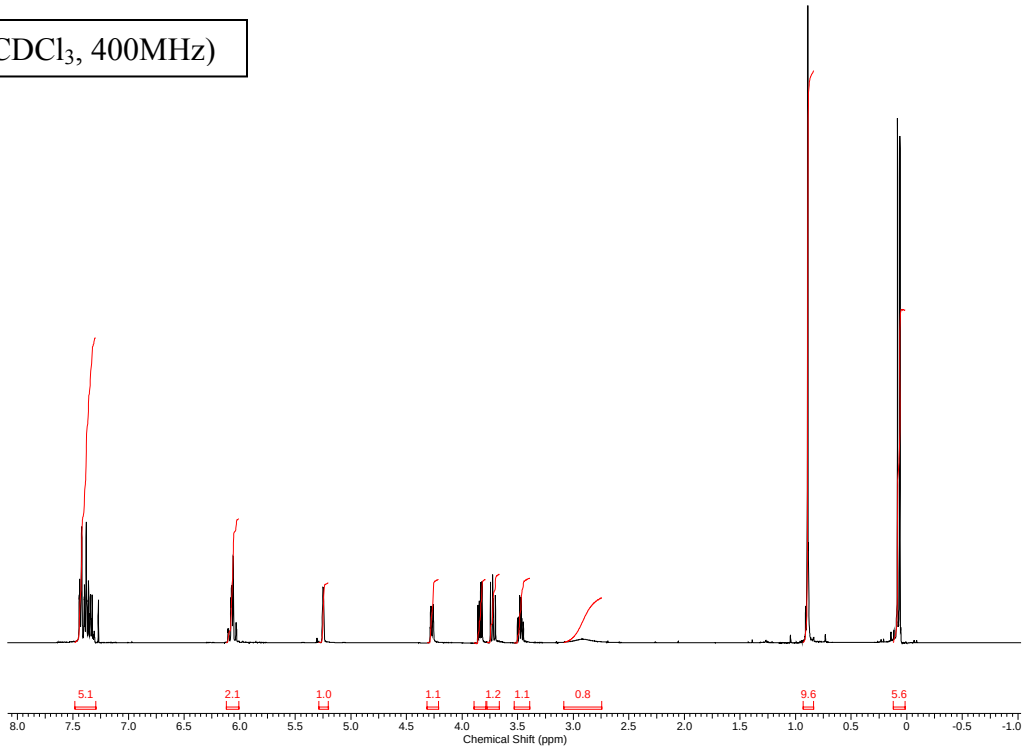
$CDCl_3$, 100 MHz





9

($CDCl_3$, 400MHz)



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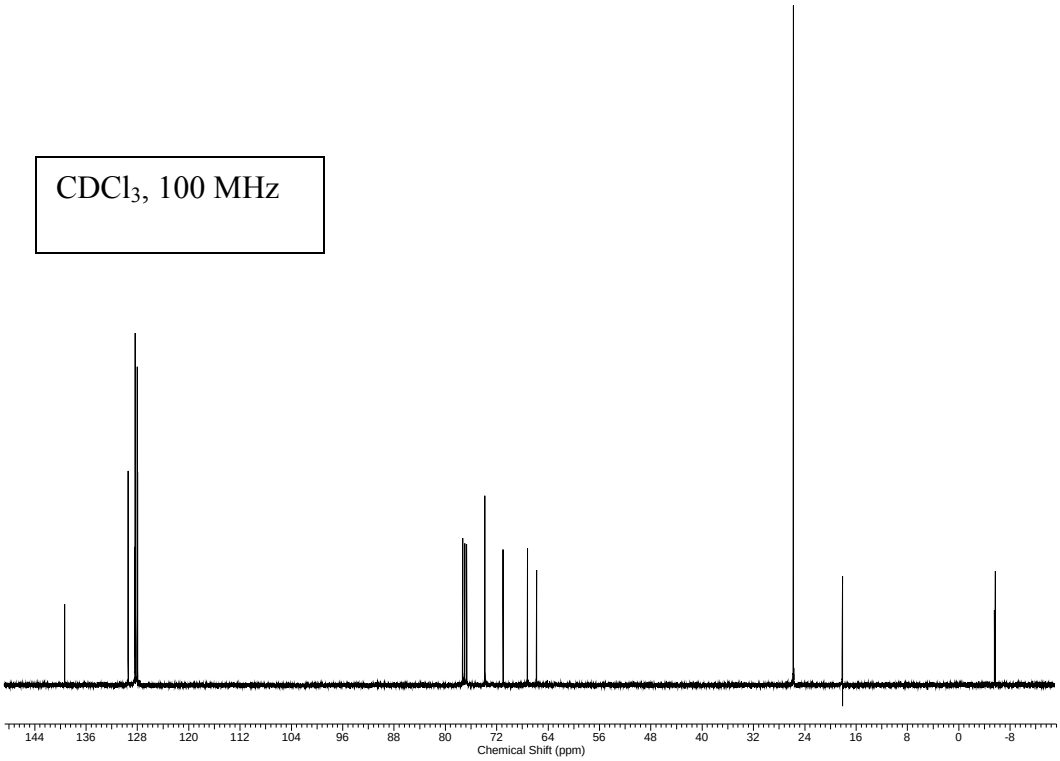

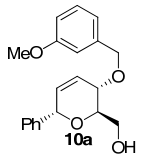

10a

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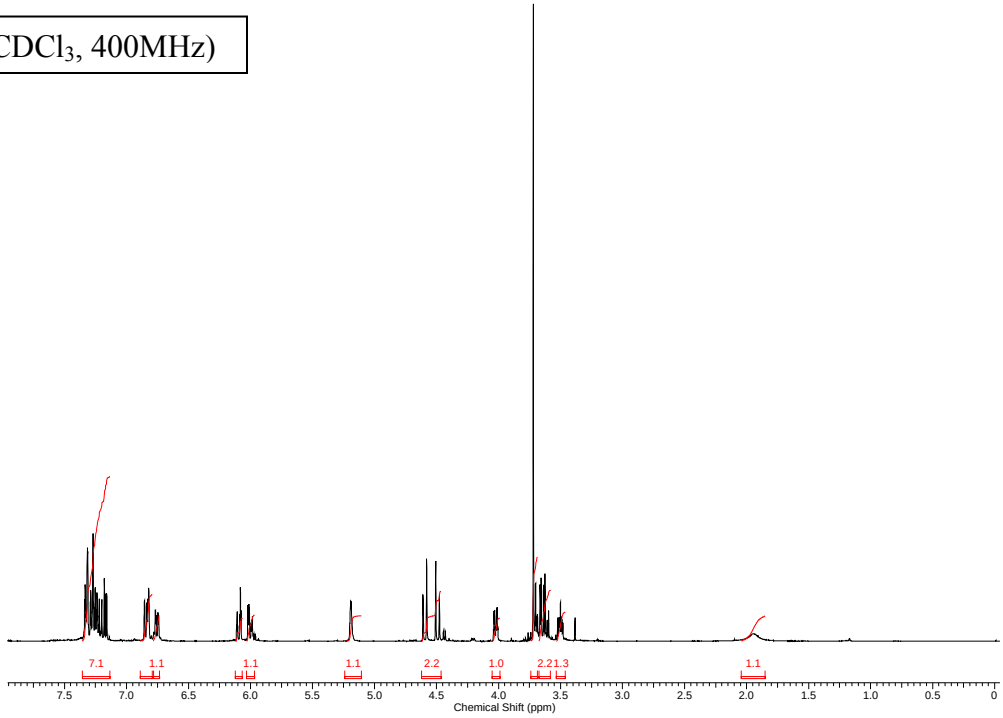

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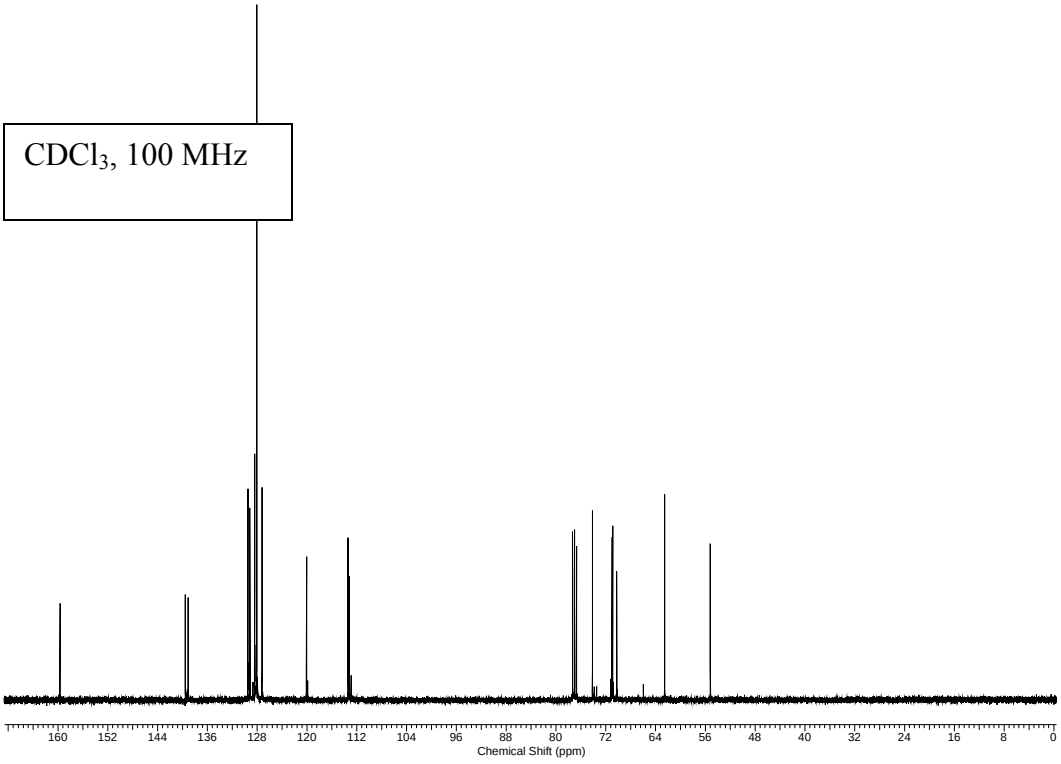
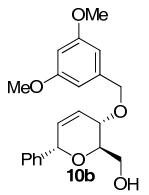
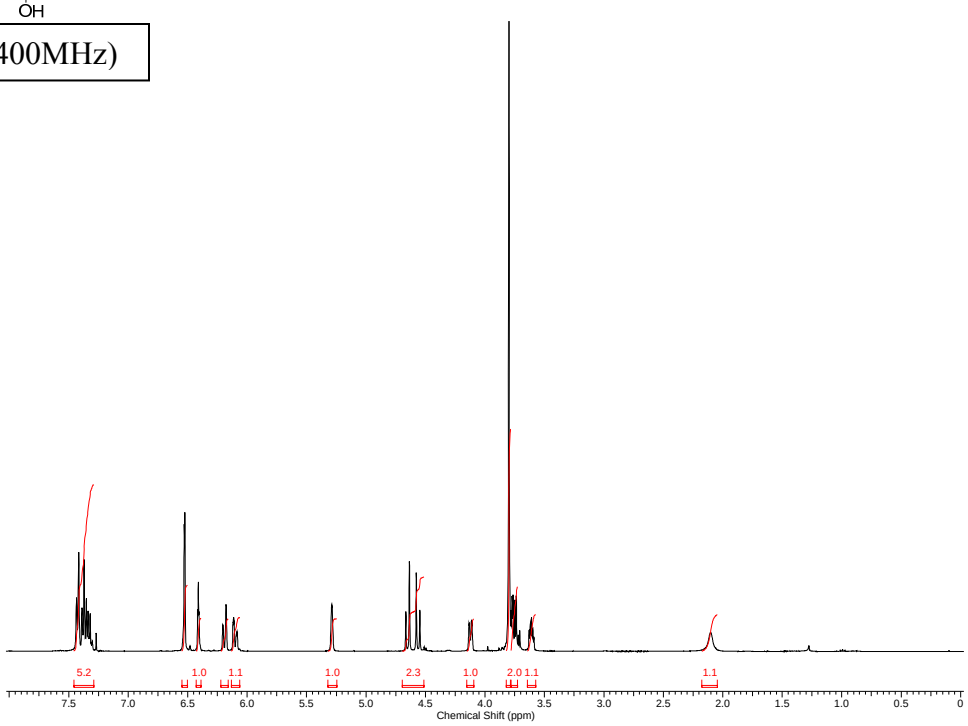




($CDCl_3$, 400MHz)



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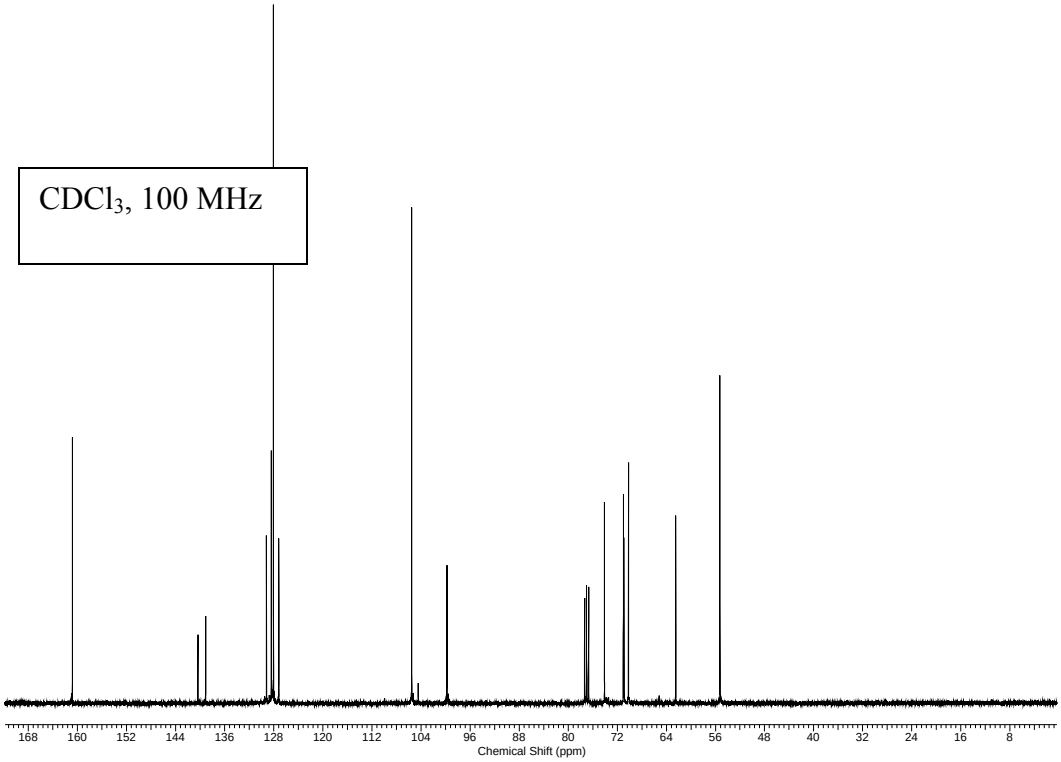

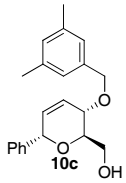

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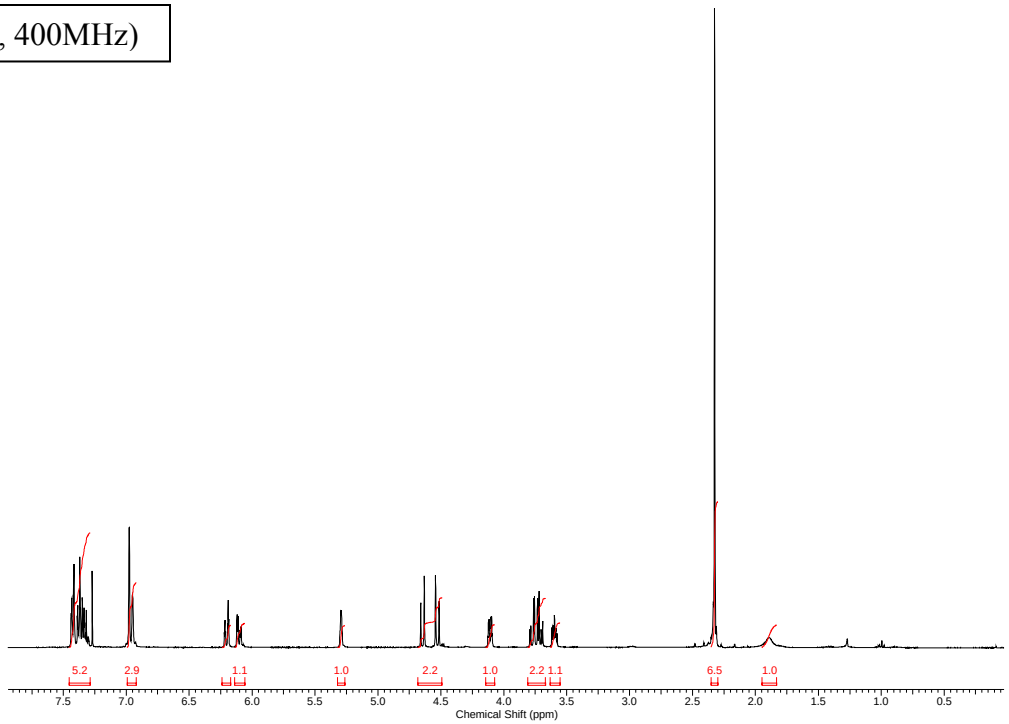

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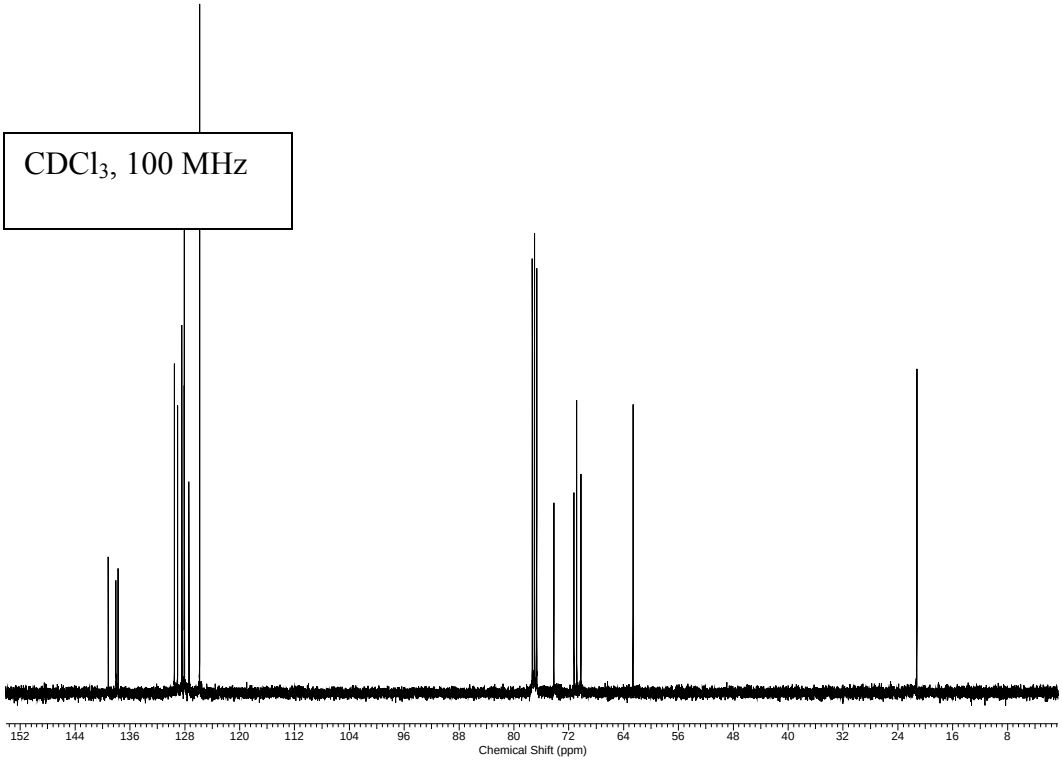

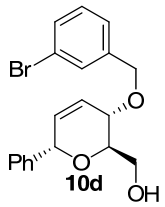

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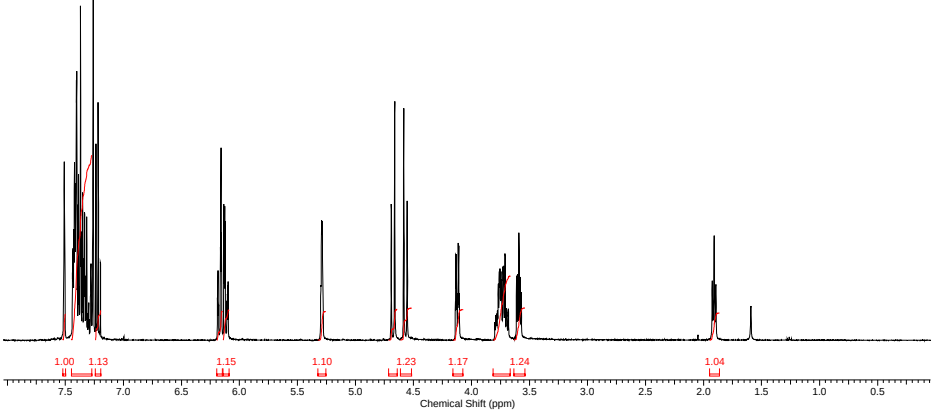

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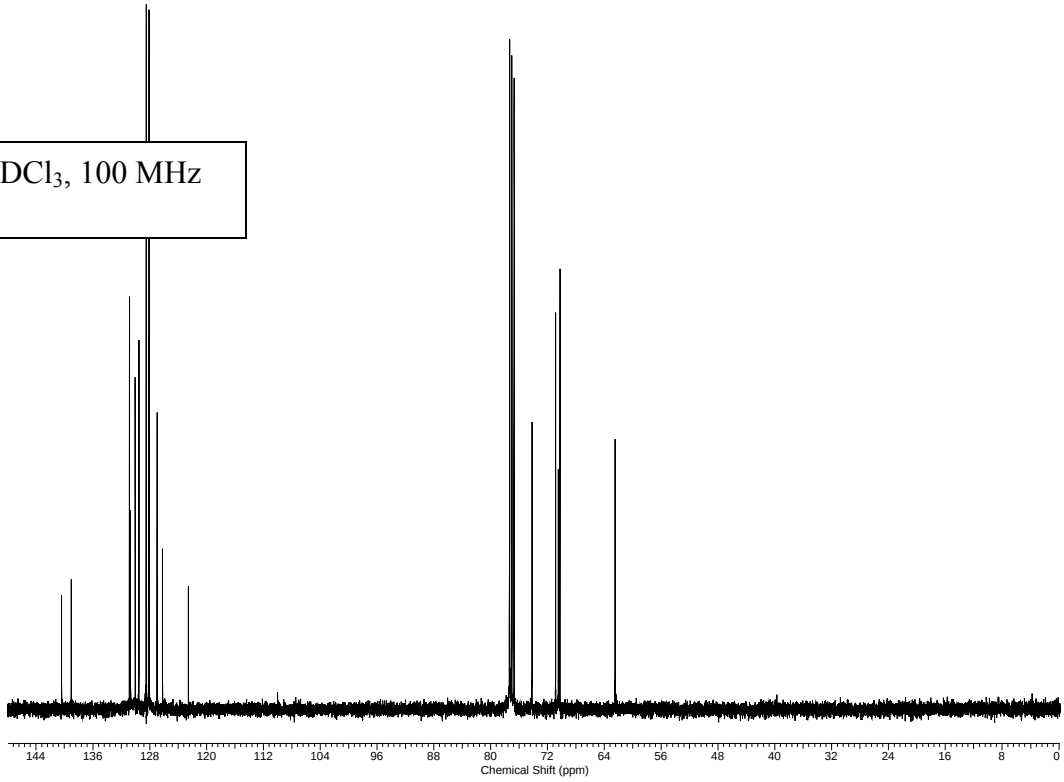

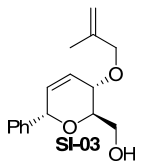

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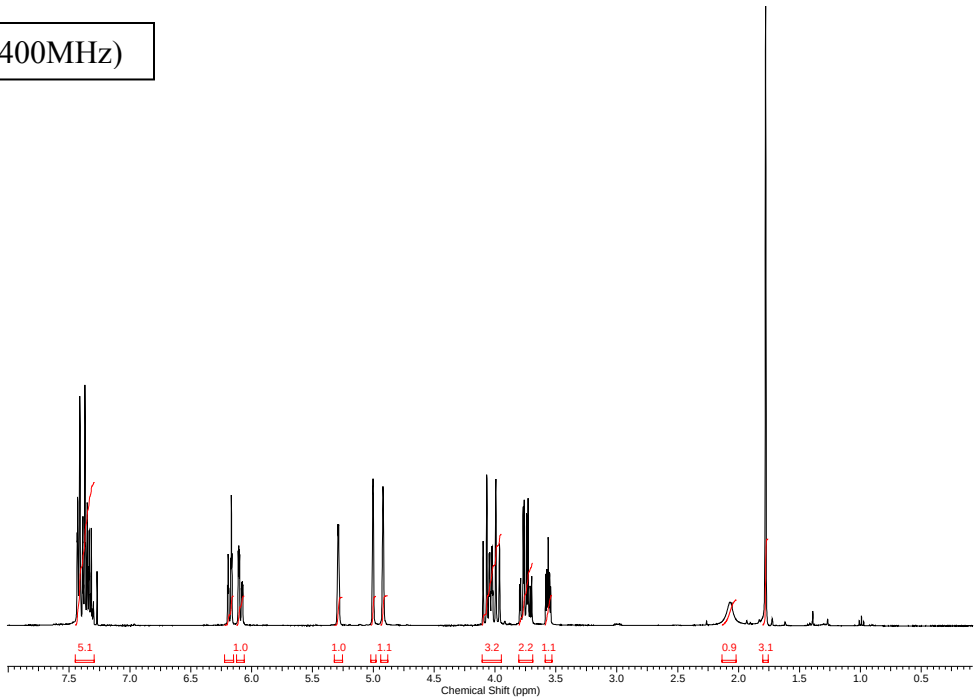

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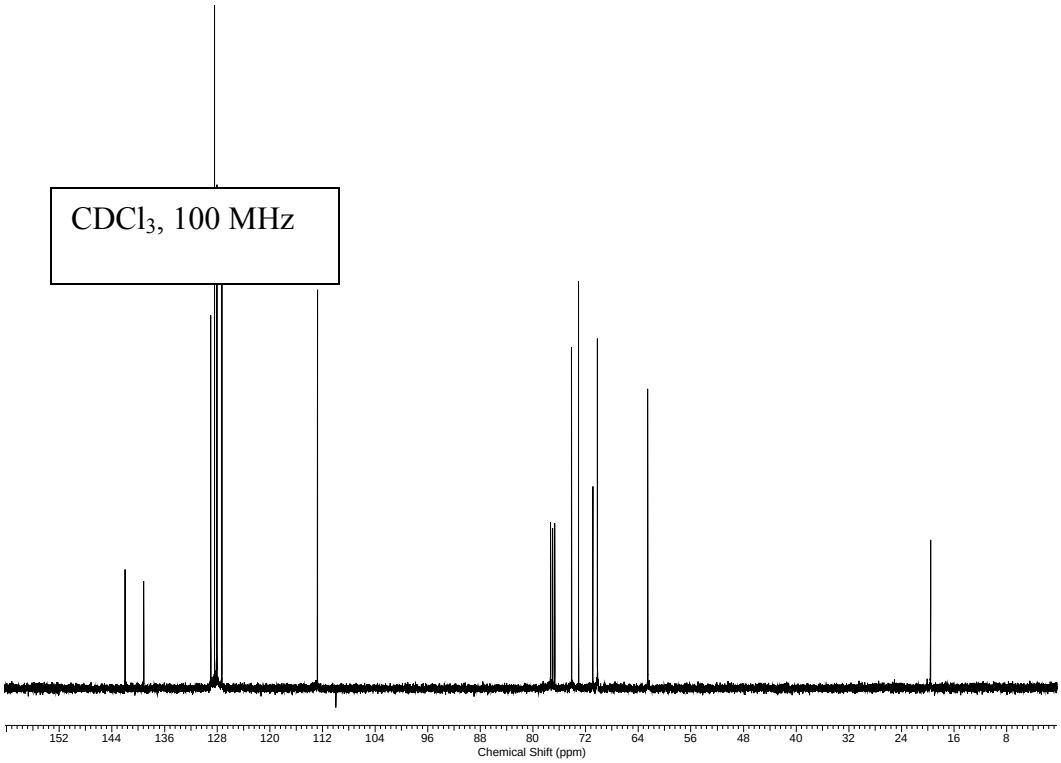

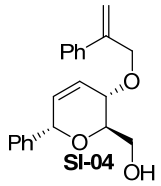

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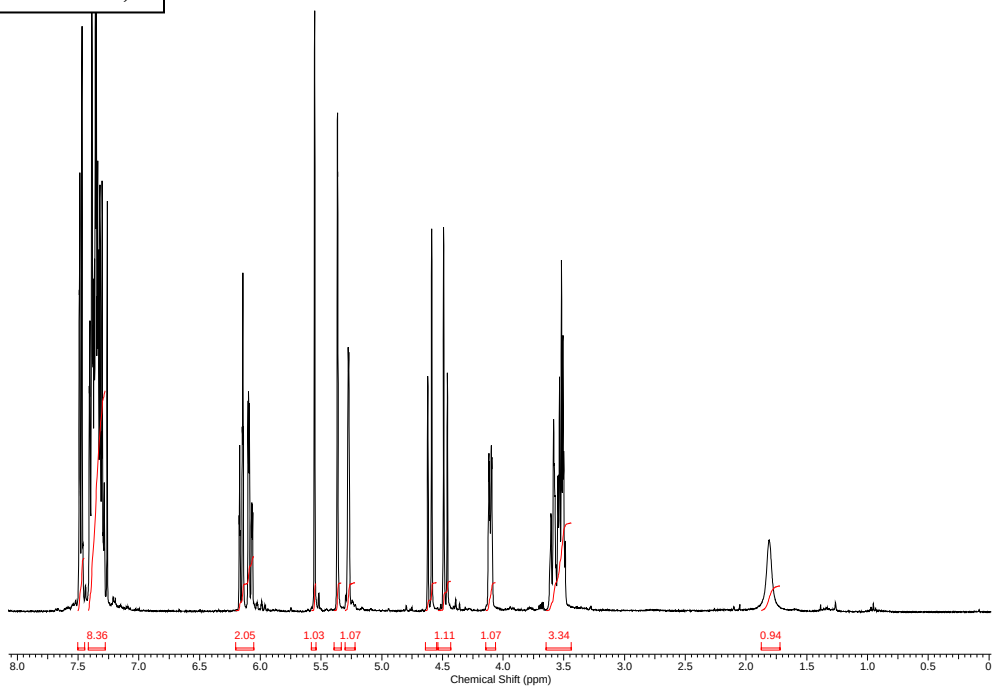
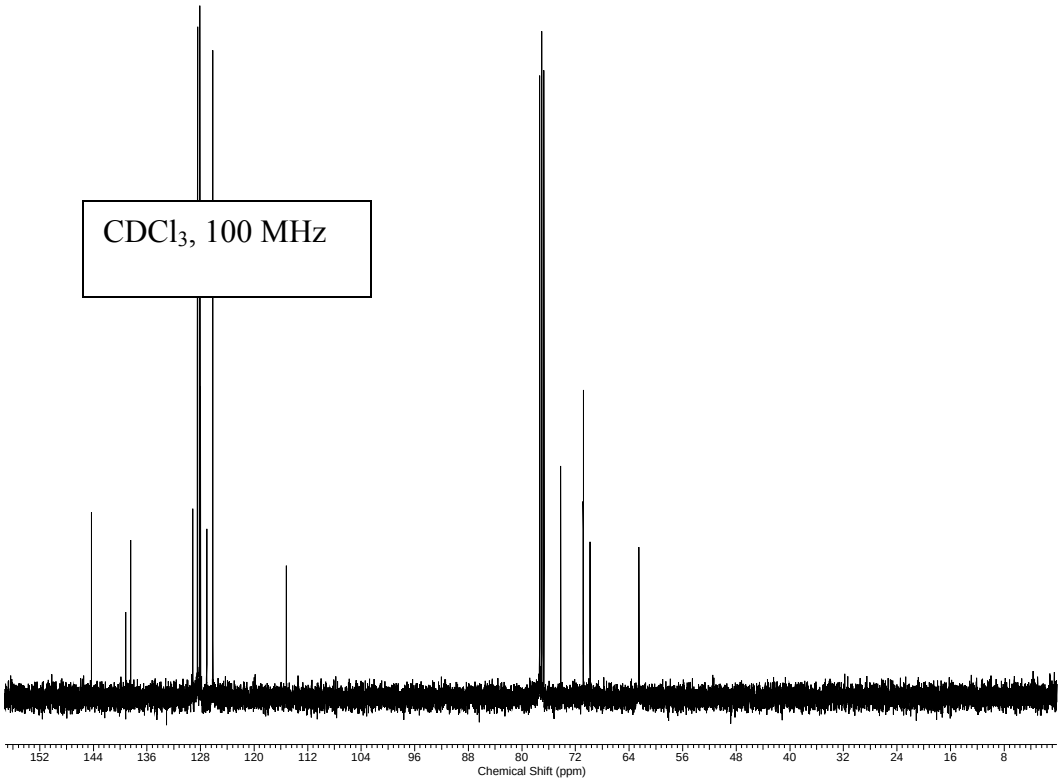
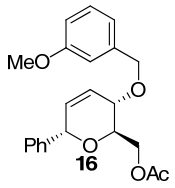
(CDCl$_3$, 400MHz)



CDCl$_3$, 100 MHz





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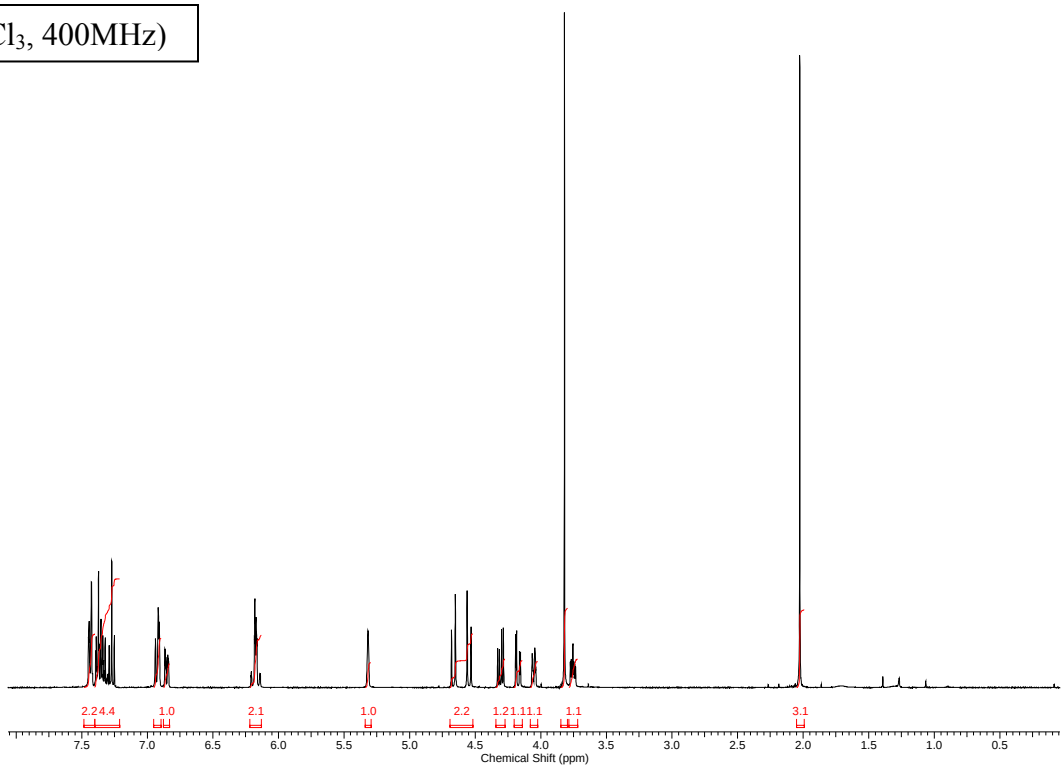

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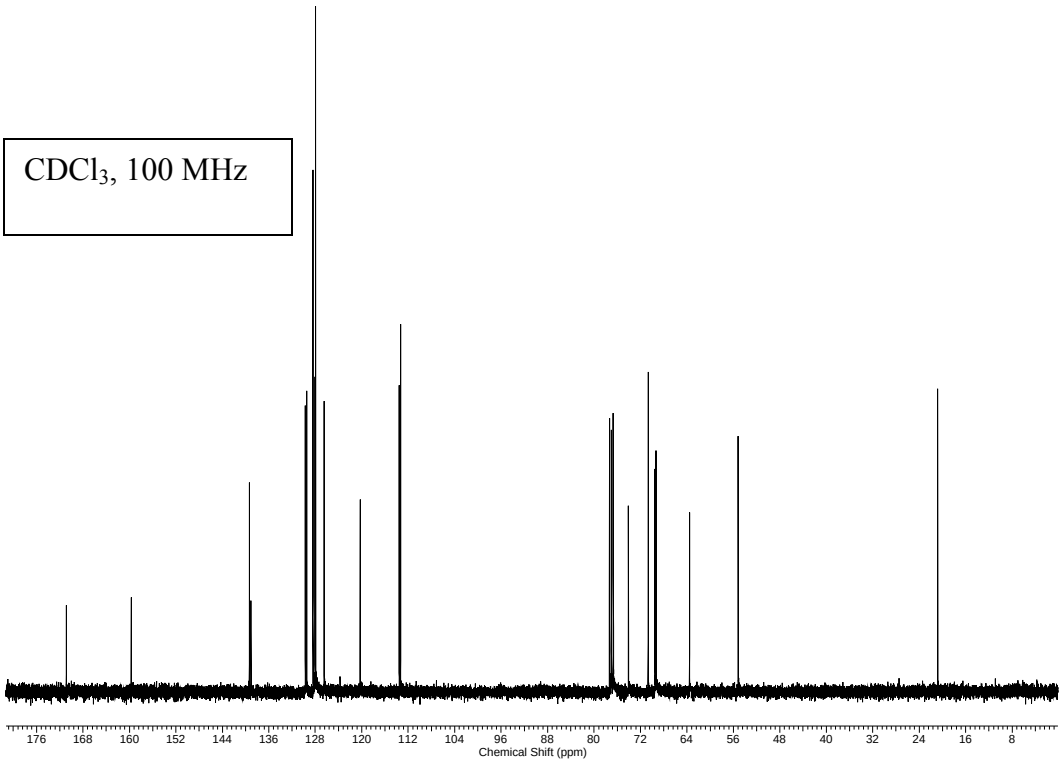

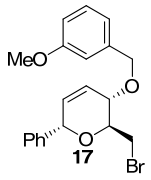

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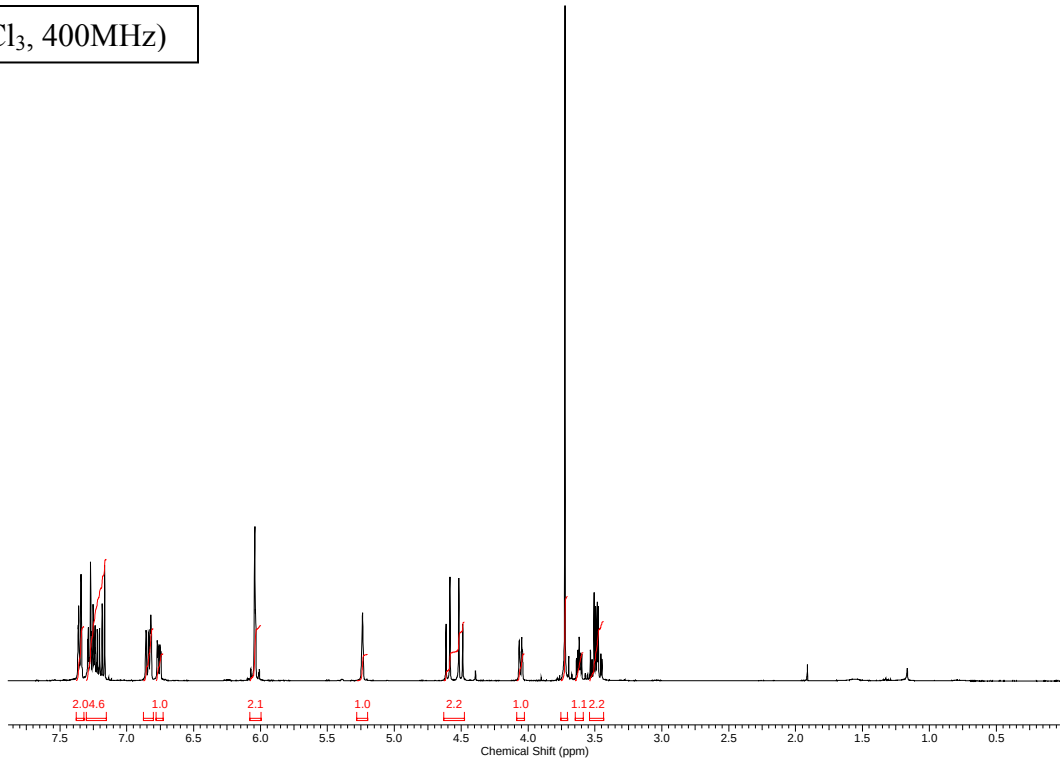

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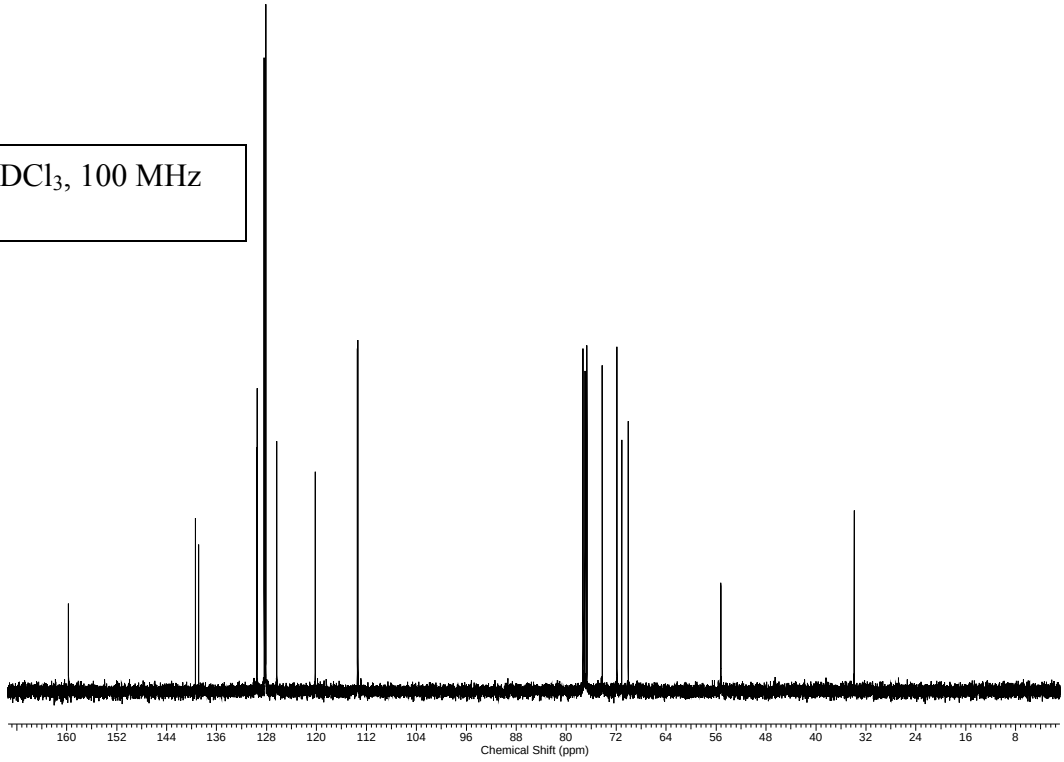

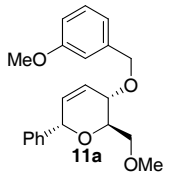

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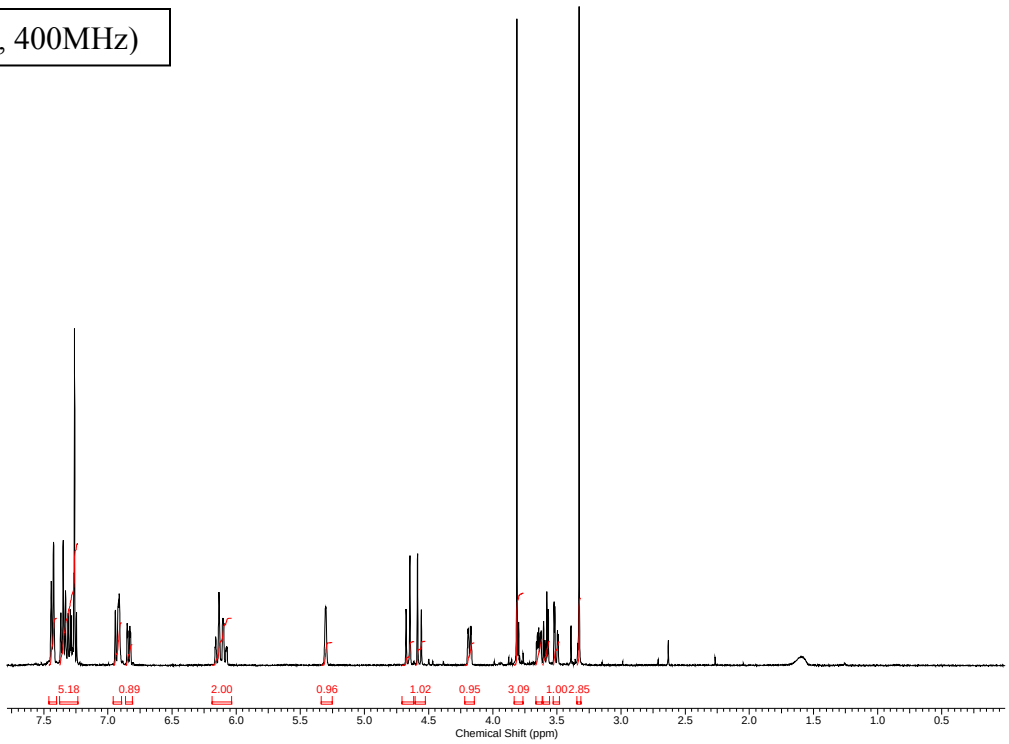

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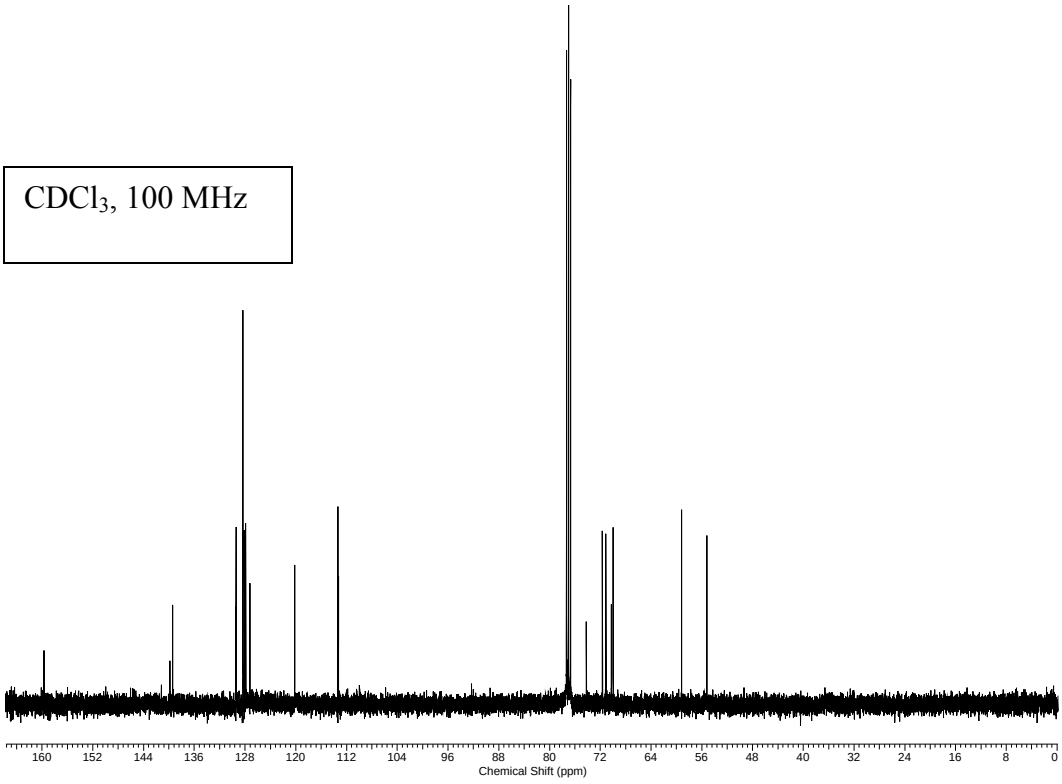

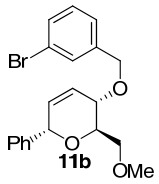

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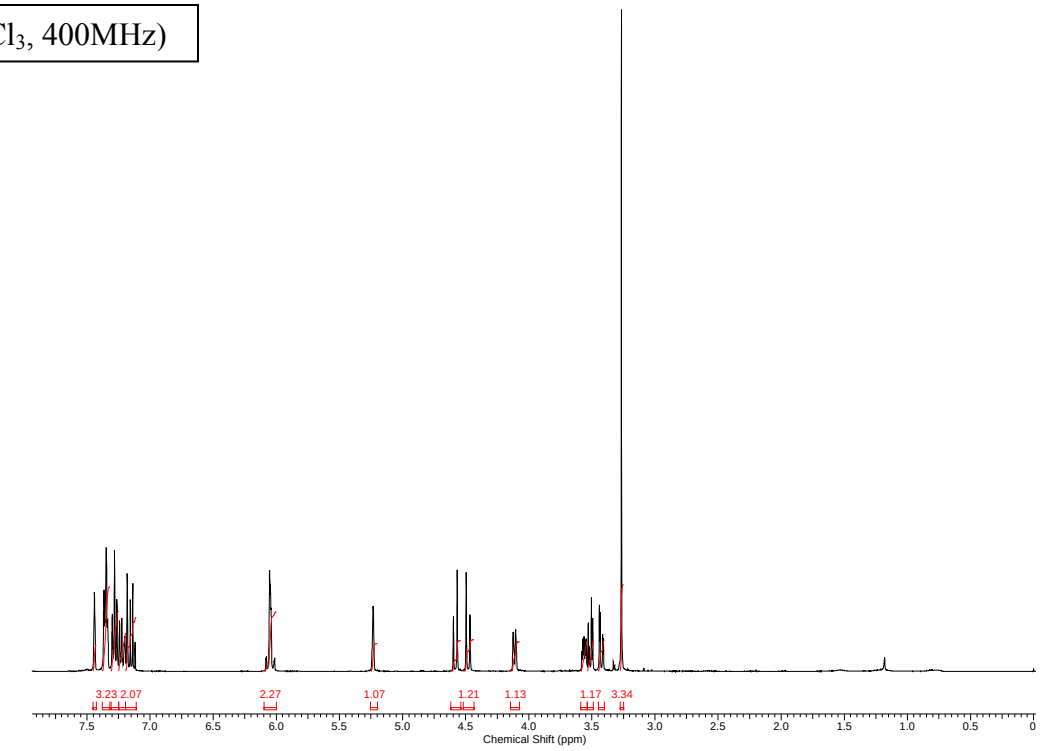

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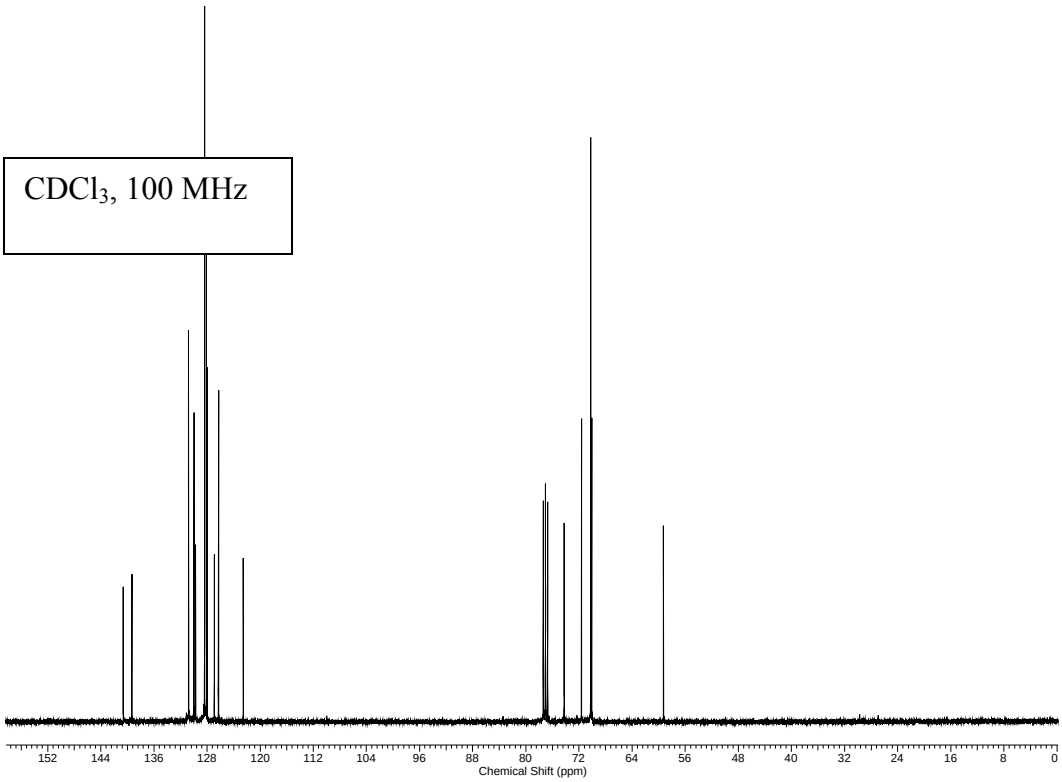
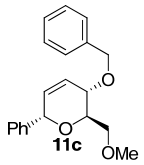
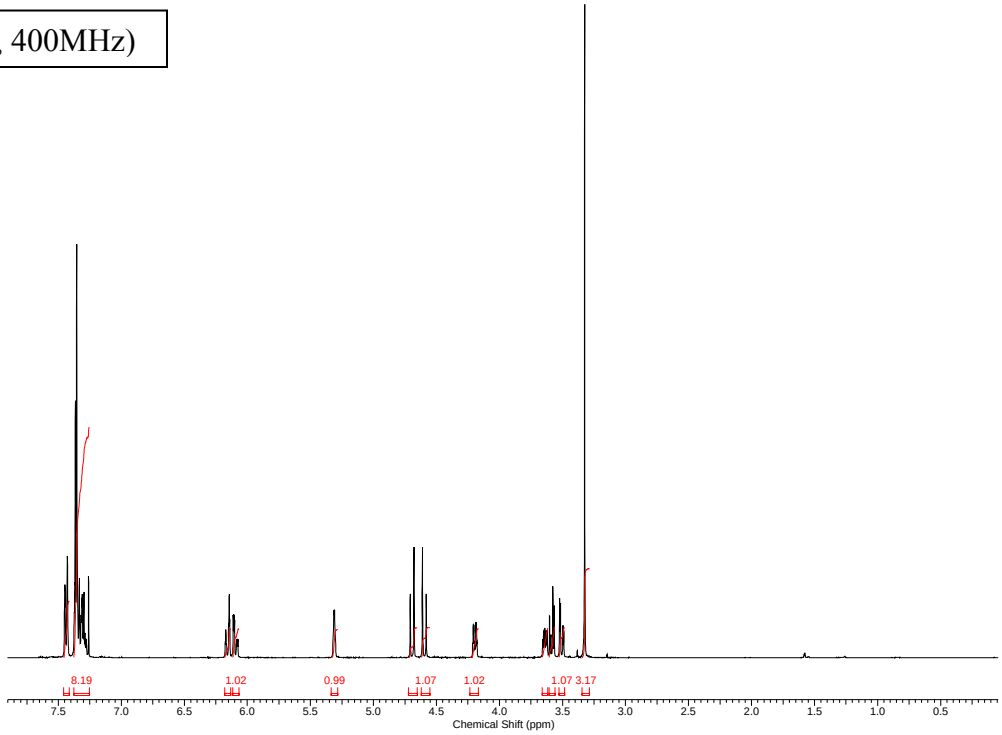
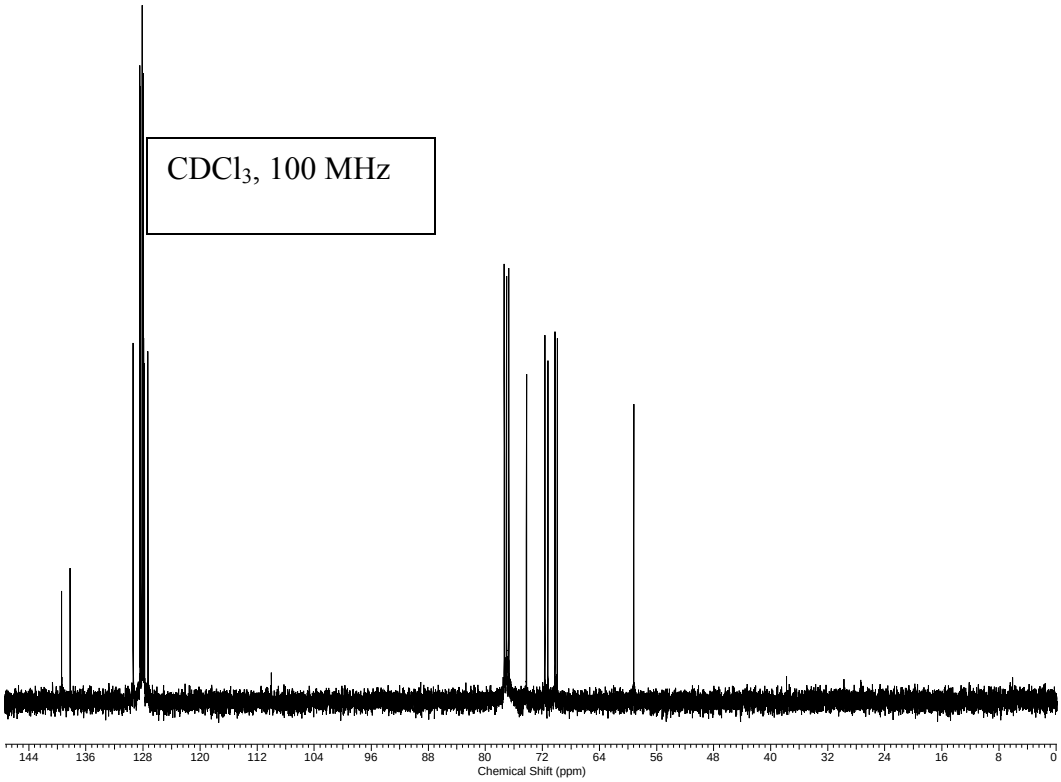


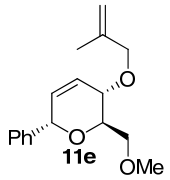


(CDCl$_3$, 400MHz)



CDCl$_3$, 100 MHz





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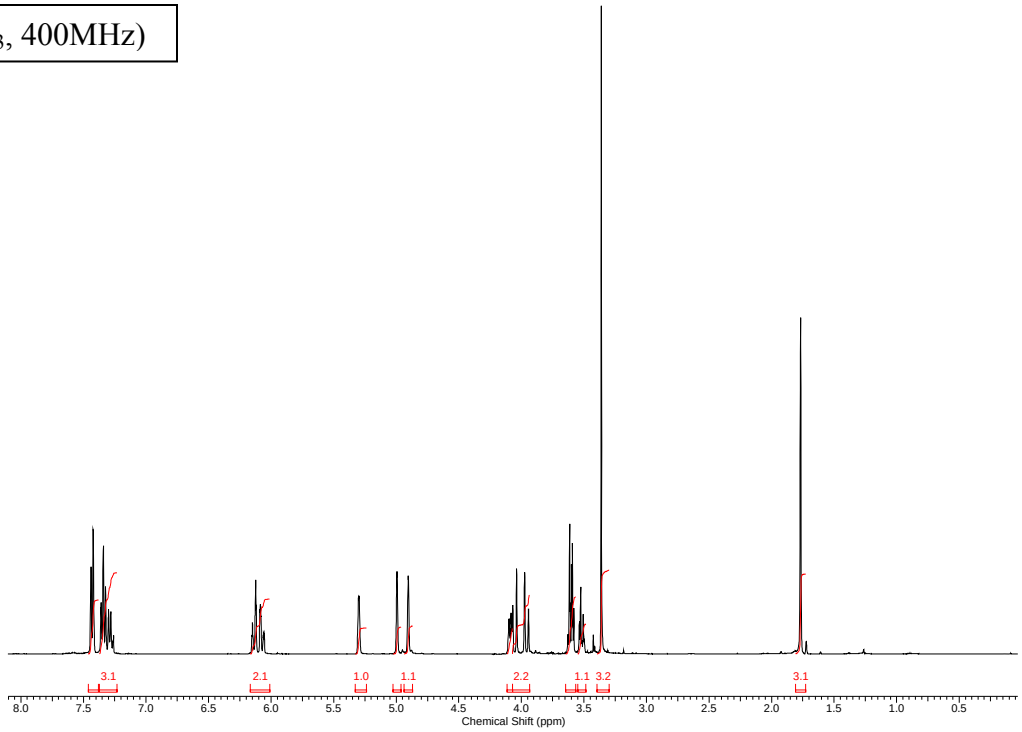

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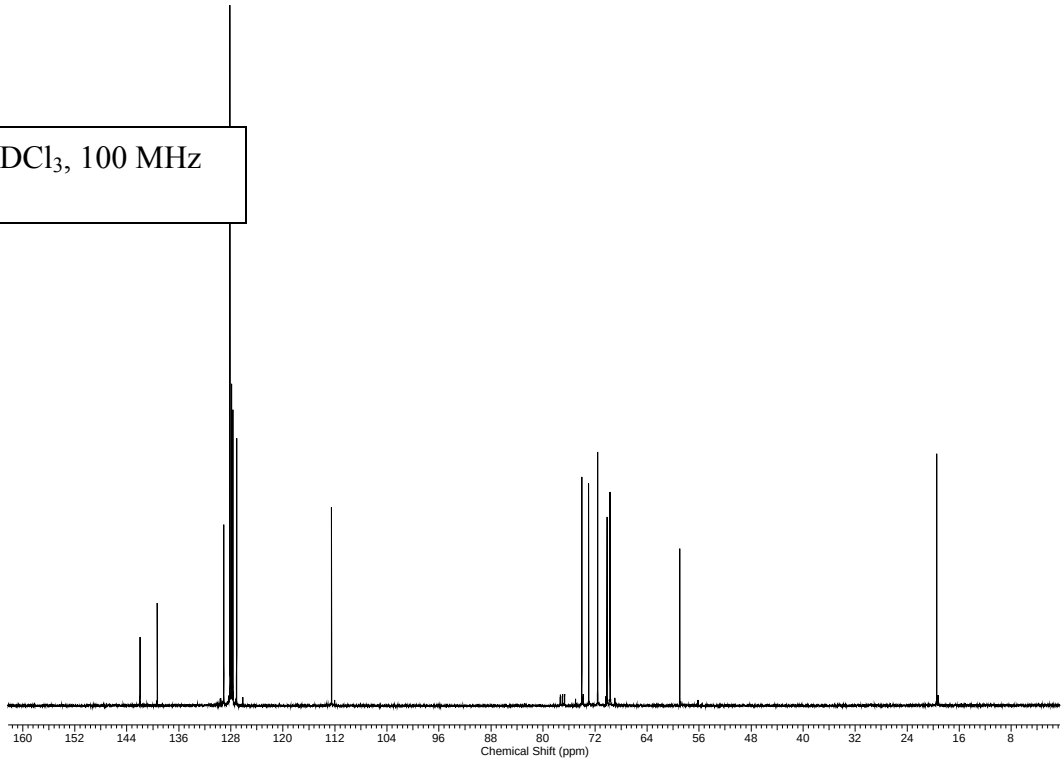
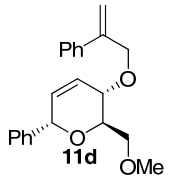
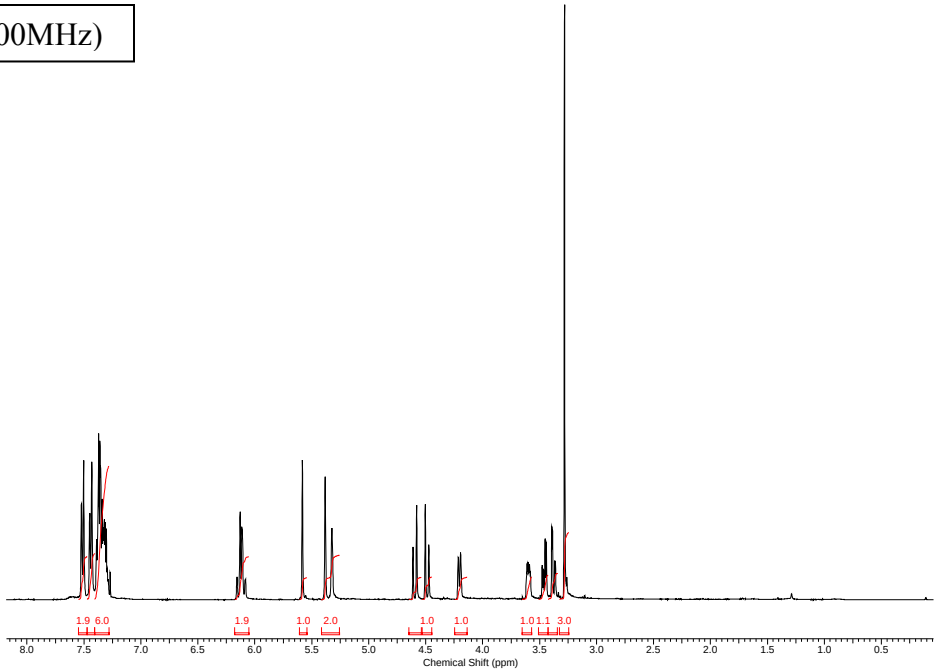
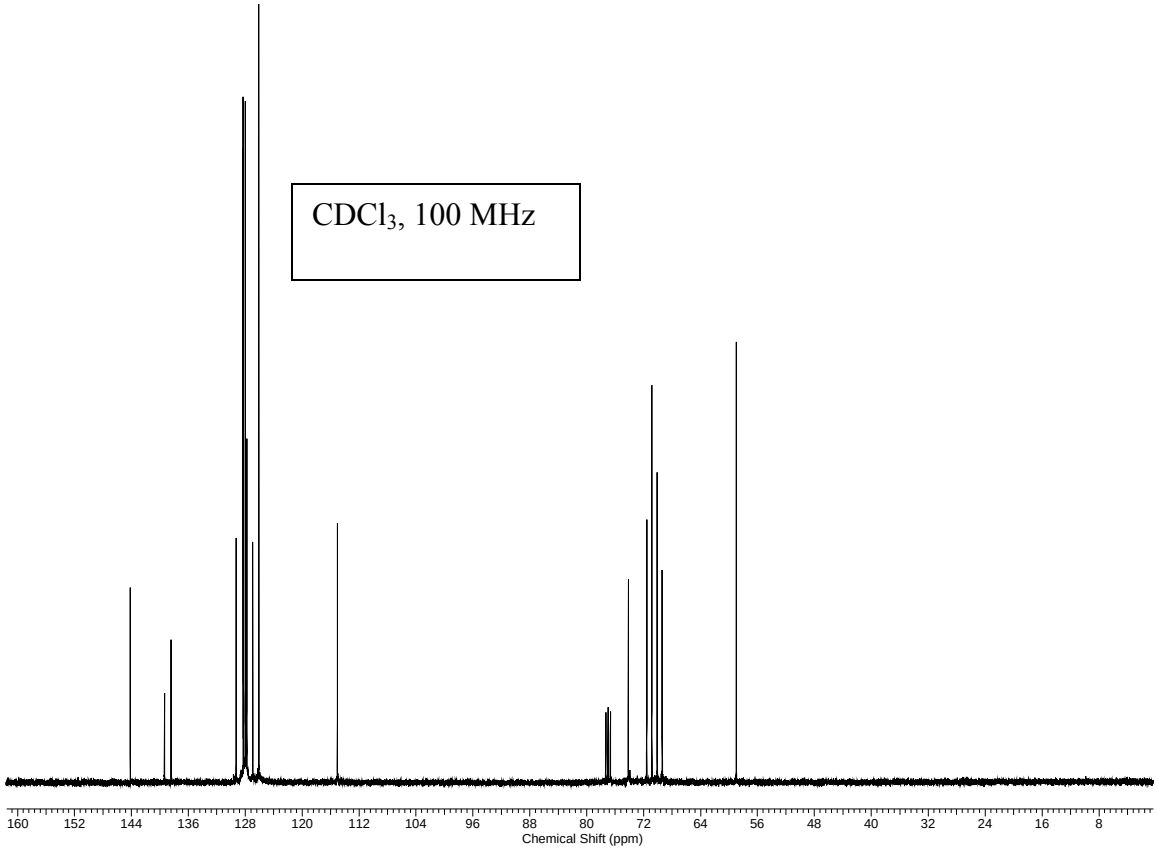


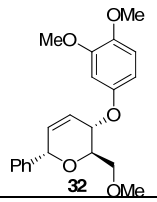


(CDCl$_3$, 400MHz)



CDCl$_3$, 100 MHz





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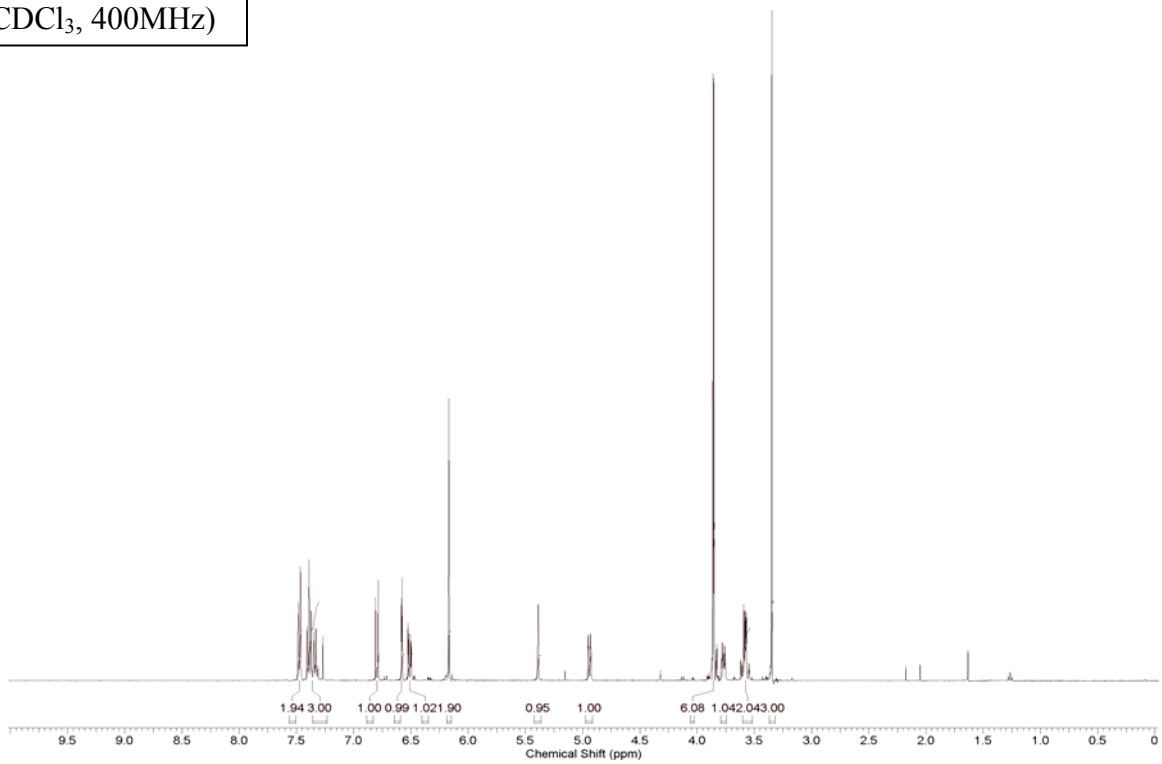
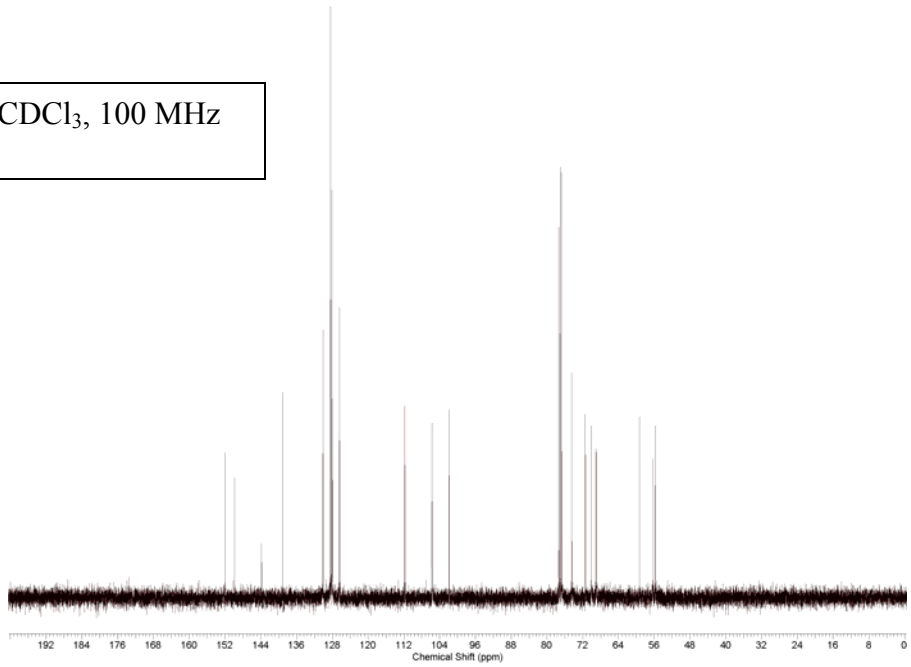
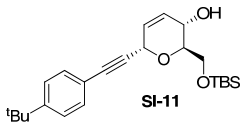
($CDCl_3$, 400MHz)



$CDCl_3$, 100 MHz





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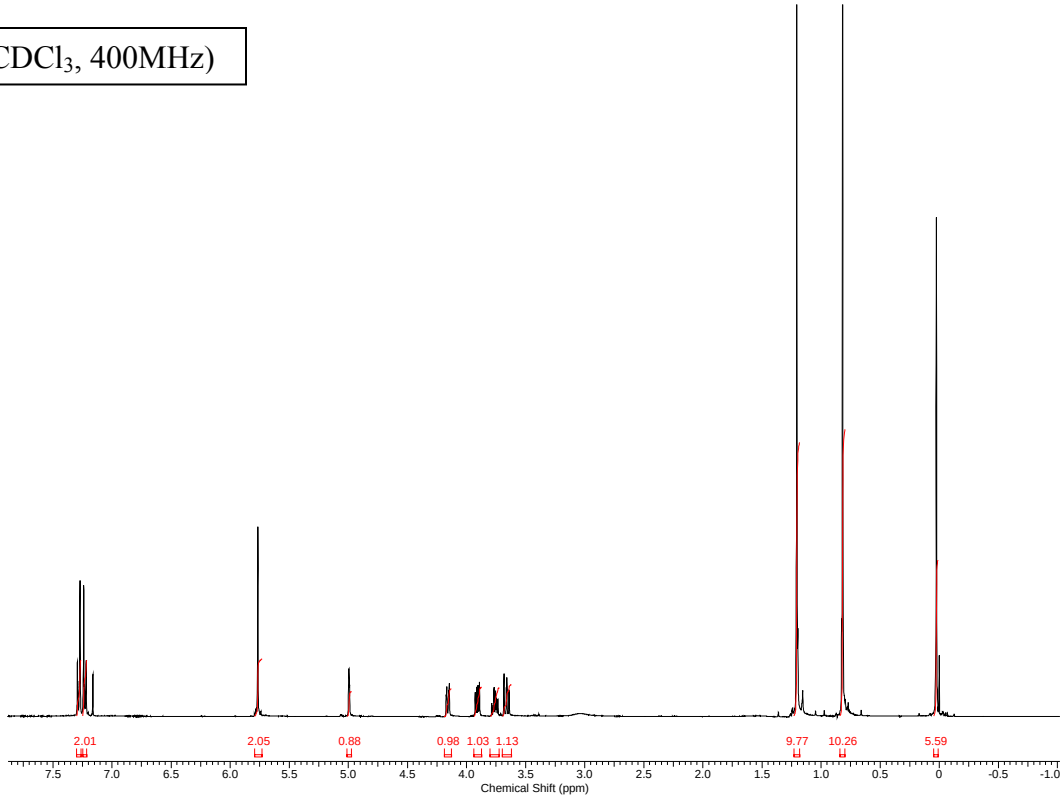
($CDCl_3$, 400MHz)



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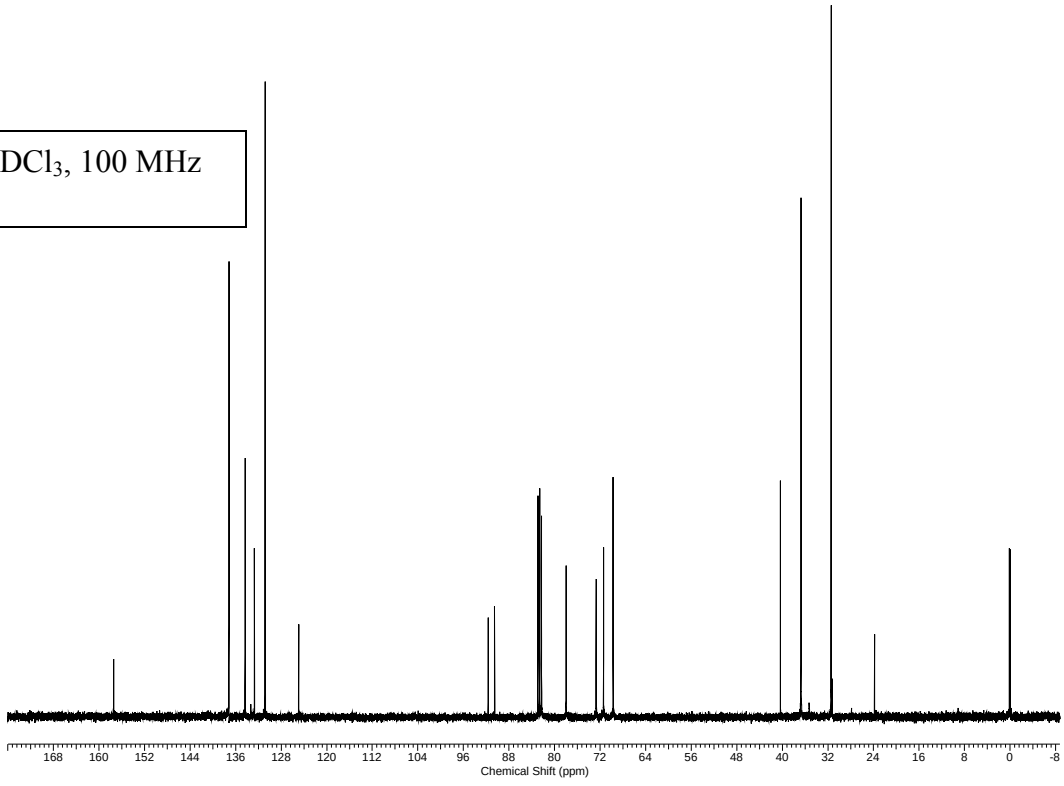

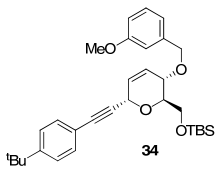

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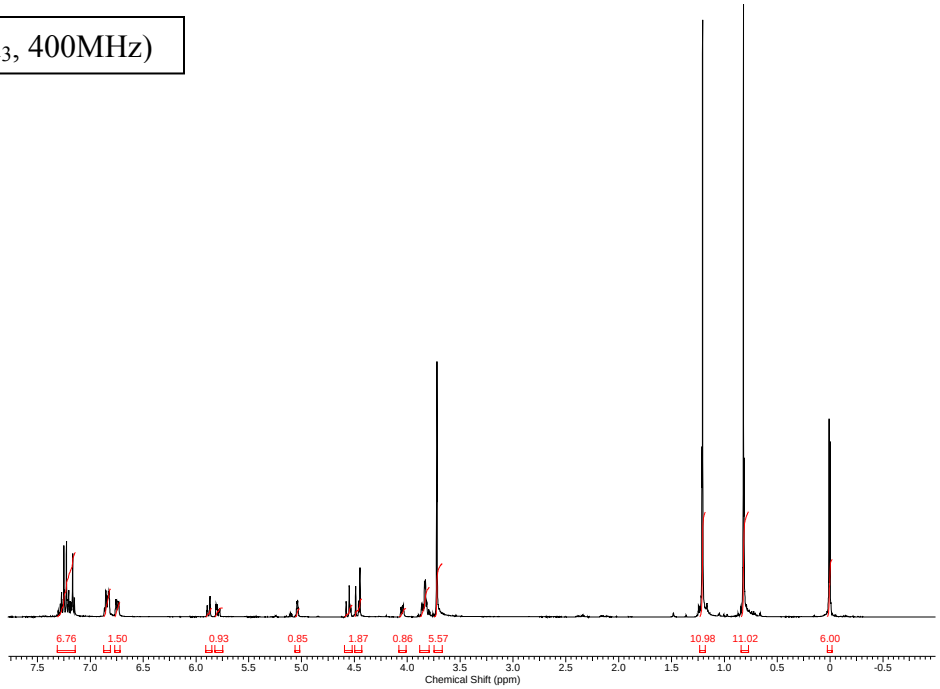
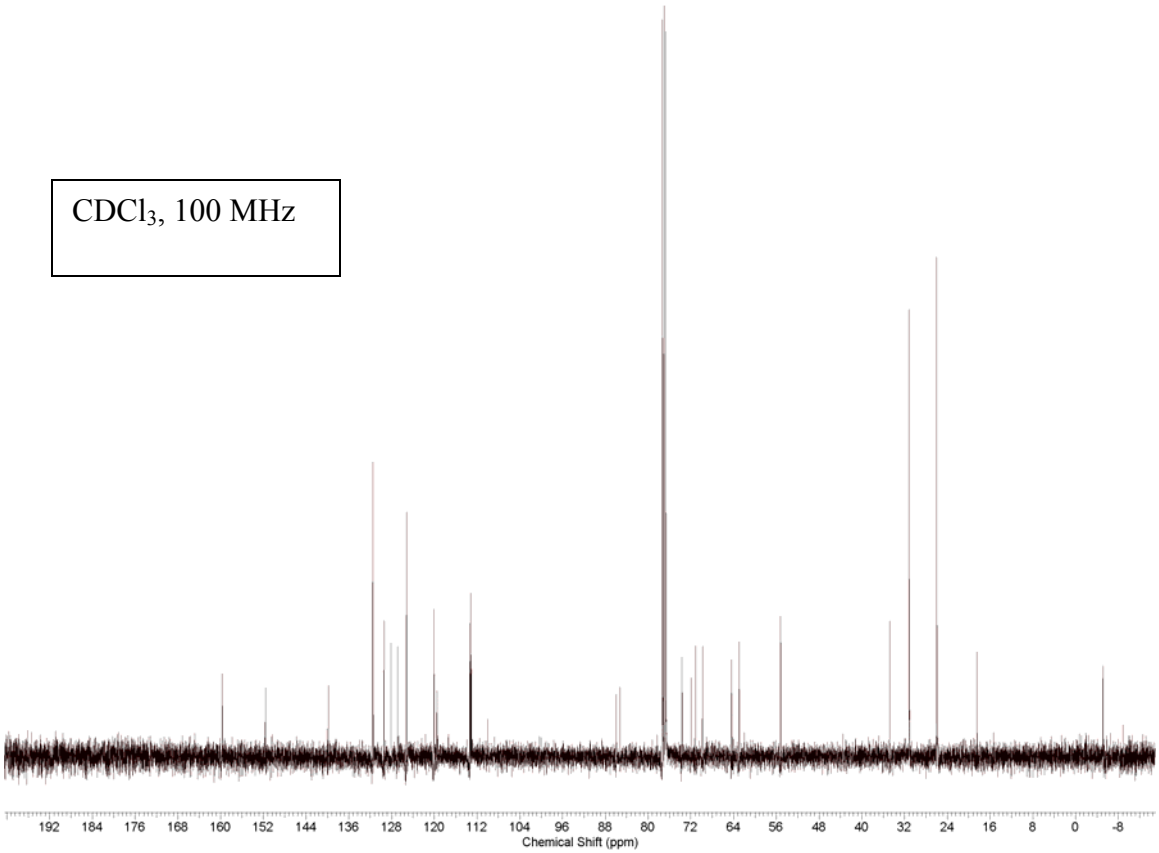
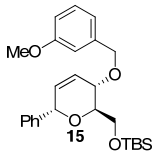
(CDCl$_3$, 400MHz)



CDCl$_3$, 100 MHz





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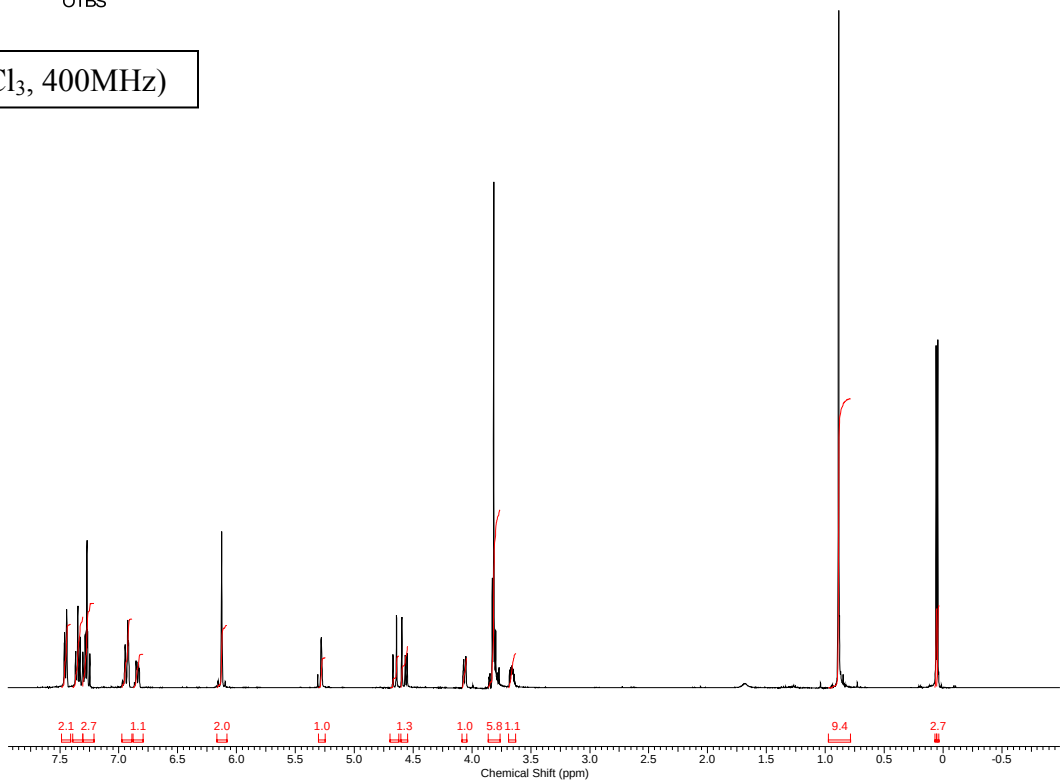
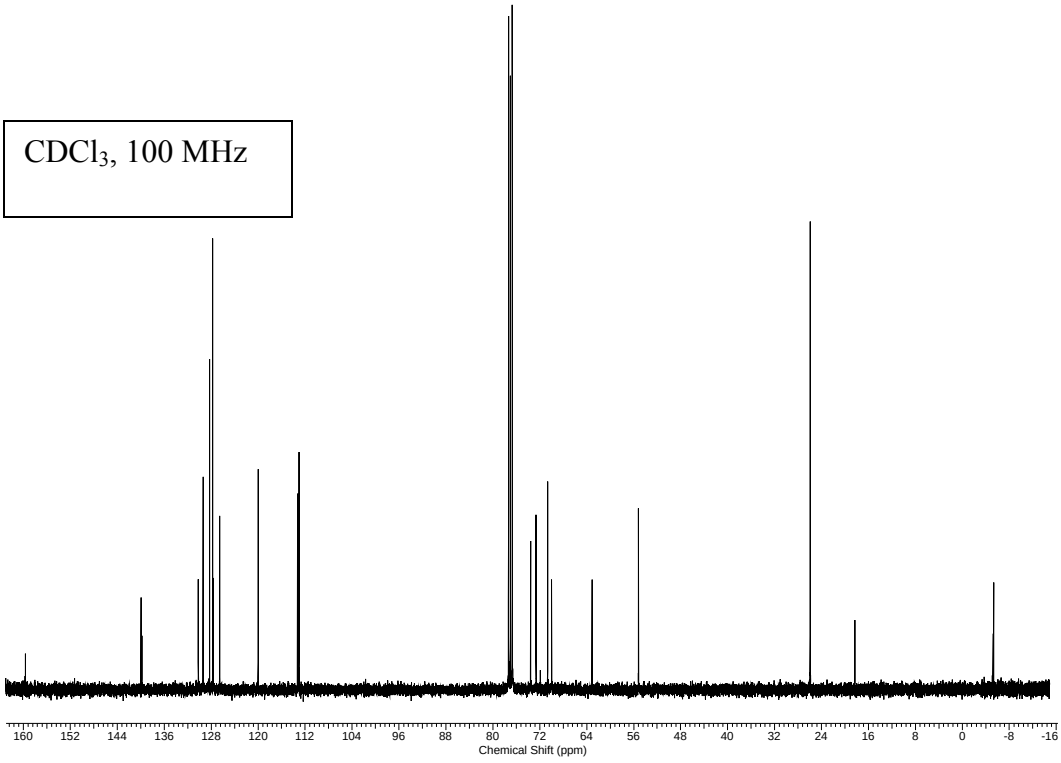


$CDCl_3$, 100 MHz



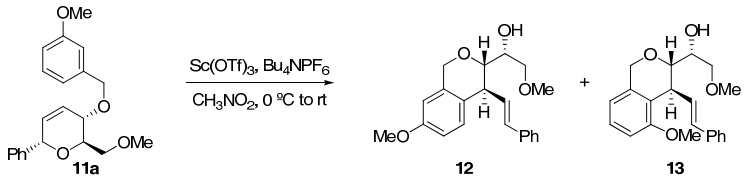
VII. General Procedure C: Reactions Using Stoichiometric $Sc(OTf)_3$

A solution of dihydropyran **11a** (34.0 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) was cooled to 0 ºC. $Sc(OTf)_3$ (49.0 mg, 0.10 mmol) was added and the reaction was warmed to room temperature over 2 h. The reaction was quenched with sat. $NaHCO_{3(aq)}$ (2 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (gradient elution, hexanes:EtOAc = 100:1 to 1:1) to provide isochroman **12** (27 mg, 79% yield) and **13** (5.5 mg 16% yield).

VIII. General Procedure D: Reactions Using Catalytic $Sc(OTf)_3$

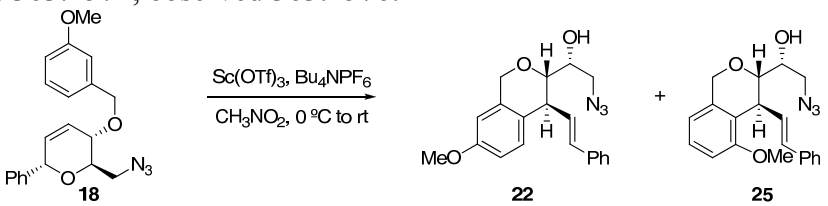
Substrate dihydropyran (0.1 mmol) was dissolved in CH_3NO_2 (0.3 mL) and the solution was cooled to 0 ºC. $Sc(OTf)_3$ (0.02 mmol) and Bu_4NPF_6 (0.02 mmol) were added upon which the solution turned yellow. Stirring was continued at the same temperature for 40 min. Sat. $NaHCO_{3(aq)}$ (10 mL) was added and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (EtOAc: petroleum ether).

The reactions shown in entries 7–9 in Table 1 were conducted according to General Procedure D with the following modifications:
Entry 7: Triflic acid (20 mol%, added as a 1M solution in CH_3NO_2) was substituted for $Sc(OTf)_3$. Bu_4NPF_6 was not added to the reaction.
Entry 8: 2,6-di-*tert*-butyl-4-methylpyridine was added to the reaction mixture before the addition of $Sc(OTf)_3$.
Entry 9: The nitromethane was refluxed over $MgSO_4$, distilled, and stored over 3Å molecular sieves prior to use in the reaction. The reaction was conducted in the presence of flame dried 3Å molecular sieves (3:1, w/w).



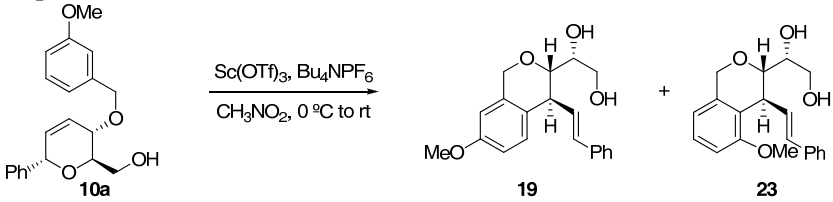
Isochromans **12** and **13** were obtained as a separable mixture (3.6:1; 95% isolated yield) from dihydropyran **11a** using general procedure **D**.
12: $[\alpha]^{25}_D$ = +63.0° (c 5.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J=7.0 Hz, 2 H), 7.32 (t, J=7.4 Hz, 2 H), 7.25 (d, J=7.0 Hz, 1 H), 7.16 (d, J=8.2 Hz, 1 H), 6.75 (dd, J=8.2, 2.7 Hz, 1 H), 6.61 (d, J=15.6 Hz, 1 H), 6.56 (d, J=2.5 Hz, 1 H), 6.05 (dd, J=15.6, 9.4 Hz, 1 H), 4.85 (s, 2 H), 4.08-4.10 (m, 1 H), 3.80-3.84 (m, 1 H), 3.78 (s, 3 H), 3.68-3.72 (m, 2 H), 3.59-3.64 (m, 1 H), 3.40 (s, 3 H), 2.58 (br s., 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 136.8, 135.1, 133.6, 130.2, 129.3, 128.6, 128.6, 127.6, 126.9, 126.3, 113.1, 108.8, 80.1, 72.7, 70.9, 68.5, 59.2, 55.3, 42.8; IR (neat) 3458, 3081, 3057, 3025, 2931, 2834, 2067, 1805, 1735, 1611, 1500, 1256, 1038, 969, 870 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{21}H_{24}O_4Na$: 363.1572, observed 363.1566.

13: $[\alpha]^{25}_D$ = –4.9° (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J=7.4 Hz, 2 H), 7.26 (t, J=7.4 Hz, 3 H), 7.18 (m, 2 H), 6.74 (d, J=8.2 Hz, 1 H), 6.65 (d, J=7.4 Hz, 1 H), 6.43 (d, J=16.4 Hz, 1 H), 6.29 (dd, J=16.0, 8.2 Hz, 1 H), 4.75 (d, J=15.6 Hz, 1 H), 4.73 (d, J=15.6 Hz, 1 H), 4.08 (dd, J=8.0, 3.9 Hz, 1 H), 3.89 - 3.95 (m, 2 H), 3.78 (s, 3 H), 3.67 (dd, J=9.8, 2.7 Hz, 1 H), 3.57 (dd, J=9.8, 6.6 Hz, 1 H), 3.41 (s, 3 H), 2.43 (d, J=3.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 137.7, 135.3, 131.2, 130.6, 128.4, 127.1, 126.9, 126.2, 122.9, 116.5, 108.9, 78.4, 73.6, 69.6, 65.2, 59.2, 55.4, 36.1; IR (neat) 3447, 3024, 2928, 2836, 1591, 1472, 1263, 1091, 964 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{21}H_{24}O_4Na$: 363.1572, observed 363.1576.



Isochromans **22** and **25** were obtained as a separable mixture (4.5:1, 80% isolated yield) from dihydropyran **18** following general procedure **D**.

22: $[\alpha]^{21}_D$ = -3.9° (c 0.64, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 - 7.35 (m, 2H), 7.23 - 7.28 (m, 2H), 7.15 - 7.19 (m, 2H), 6.73 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 6.42 (d, J = 15.6 Hz, 1H), 6.22 (dd, J = 15.6, 7.6 Hz, 1H), 4.75 (d, J = 15.2 Hz, 1H), 4.68 (d, J = 15.2 Hz, 1H), 4.01 (dd, J = 7.6, 3.6 Hz, 1H), 3.86 - 3.90 (m, 2H), 3.76 (s, 3H), 3.54 - 3.57 (m, 2H), 2.22 (d, J = 4.4 Hz, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$) δ 157.8, 137.4, 135.2, 131.1, 130.6, 128.4, 127.4, 127.1, 126.2, 116.6, 109.1, 79.1, 70.8, 65.6, 55.4, 54.0, 36.5; IR (neat) 3399, 2920, 2100, 1589, 1472, 1439, 1316, 1264, 1086 cm^{-1}; HRMS $[M+Na]^+$ Calculated for $C_{20}H_{21}N_3O_3Na$: 352.1661, observed 352.1678.

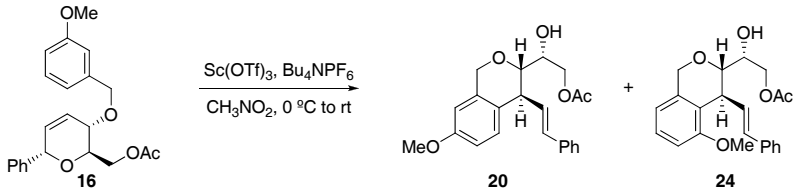


Isochromans **19** and **23** were obtained as a separable mixture (2.8:1, 83% isolated yield) from dihydropyran **10a** following general procedure **D**.

19: $[\alpha]^{25}_D$ = +28.0° (c 2.0, $CHCl_3$); ^{1}H NMR (400MHz , $CDCl_3$) δ 7.32 (d, J = 7.0 Hz, 2 H), 7.25 (t, J = 7.0 Hz, 2 H), 7.19 (d, J = 7.0 Hz, 1 H), 7.07 (d, J = 8.6 Hz, 1 H), 6.68 (dd, J = 2.7, 8.6 Hz, 1 H), 6.53 (d, J = 16.0 Hz, 1 H), 6.47 (d, J = 2.7 Hz, 1 H), 5.93 (dd, J = 9.6, 15.8 Hz, 1 H), 4.78 (d, J = 14.8 Hz, 1 H), 4.77 (d, J = 14.8 Hz, 1 H), 3.94 - 3.72 (m, 4 H), 3.70 (s, 3 H), 3.56 (t, J = 11.0 Hz, 1 H), 2.65 (br s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 136.5, 134.7, 134.3, 130.1, 128.7, 128.3, 127.8, 126.6, 126.3, 113.2, 108.9, 82.2, 71.3, 68.9, 62.6, 55.3, 43.6; IR (neat) 3415, 3025, 2935, 2836, 1612, 1500, 1257, 1036, 969 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{20}H_{22}O_4Na$: 349.1416, observed 349.1418.

23: $[\alpha]^{25}_D$ = –9.3° (c 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 4 H), 7.19 (m, 2 H), 6.75 (d, J=8.2 Hz, 1 H), 6.67 (d, J=7.4 Hz, 1 H), 6.45 (d, J=16.0 Hz, 1 H), 6.19 (dd, J=16.0, 7.8 Hz, 1 H), 4.75 (s, 2 H), 3.89 (m, 5 H), 3.76 (s, 3 H), 2.62 (br s, 1 H), 2.19 (br s., 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 137.4, 135.6, 131.4, 130.5, 128.4 , 127.3, 127.1, 126.1, 122.9, 116.6, 109.2, 81.0, 70.9, 66.6, 63.4, 55.4, 37.3; IR (neat)

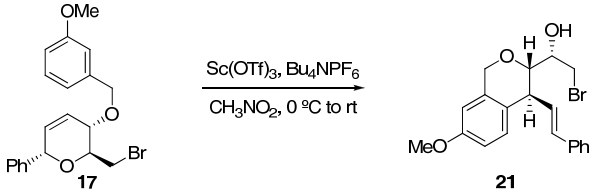
3393, 3081, 3023, 2929, 2849, 2283, 1589, 1469, 1262, 1081, 971 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{20}H_{22}O_4Na$: 349.1416, observed 349.1404.



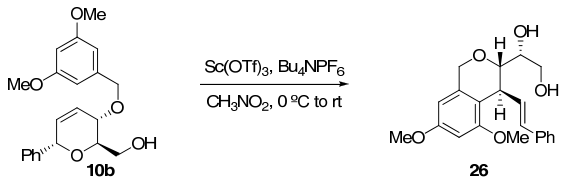
Isochromans **20** and **24** were obtained as a separable mixture (5.5:1, 95% yield) from dihydropyran **16** (50 mg, 0.14 mmol) using general procedure **D**.

20: $[\alpha]^{25}_D$ = +52.8° (c 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J=7.4 Hz, 2 H), 7.26 (t, J=7.4 Hz, 2 H), 7.20 (m, 1 H), 7.08 (d, J=8.6 Hz, 1 H), 6.68 (dd, J=8.6, 2.3 Hz, 1 H), 6.60 (d, J=15.6 Hz, 1 H), 6.49 (d, J=2.3 Hz, 1 H), 5.97 (dd, J=15.6, 9.4 Hz, 1 H), 4.78 (s, 2 H), 4.39 (dd, J=11.9, 2.9 Hz, 1 H), 4.22 (dd, J=11.9, 8.0 Hz, 1 H), 4.03 (m, 1 H), 3.73 (m, 1 H), 3.71 (s, 3 H), 3.64 (app t, J=9.4 Hz, 1 H), 2.43 (br s., 1 H), 2.03 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 158.3, 136.6, 134.9, 134.2, 130.1, 128.7, 128.5, 127.8, 126.6, 126.3, 113.2, 108.8, 80.3, 70.9, 68.6, 65.2, 55.3, 43.1, 21.0; IR (neat) 3464, 3025, 2953, 2836, 1737, 1500, 1251, 1097, 1038 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{22}H_{24}O_5Na$: 391.1521, observed 391.1521.

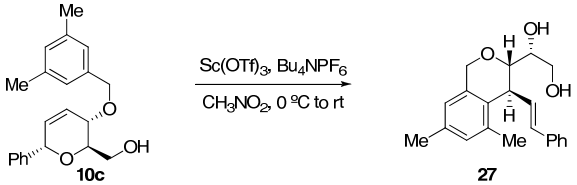
24: $[\alpha]^{25}_D$ = +2.2° (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J=7.0 Hz, 2 H), 7.26 (m, 2 H), 7.19 (m, 2 H), 6.74 (d, J=8.2 Hz, 1 H), 6.67 (d, J=7.8 Hz, 1 H), 6.45 (d, J=16.0 Hz, 1 H), 6.27 (dd, J=16.0, 7.8 Hz, 1 H), 4.76 (s, 2 H), 4.49 (dd, J=11.9, 2.5 Hz, 1 H), 4.21 (dd, J=11.9, 6.8 Hz, 1 H), 4.08 (dd, J=7.8, 4.3 Hz, 1 H), 3.95-4.00 (m, 1 H), 3.93 (dd, J=6.6, 4.3 Hz, 1 H), 3.78 (m, 3 H), 2.38 (d, J=5.9 Hz, 1 H), 2.10 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 157.9, 137.5, 135.2, 131.0, 130.7, 128.4, 127.3, 127.1, 126.3, 126.2, 122.6, 116.5, 108.9, 78.5, 69.7, 66.4, 65.4, 55.4, 36.2, 21.0; IR (neat) 3442, 2946, 2837, 1738, 1472, 1263, 1093, 965 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{22}H_{24}O_5Na$: 391.1521, observed 391.1516.



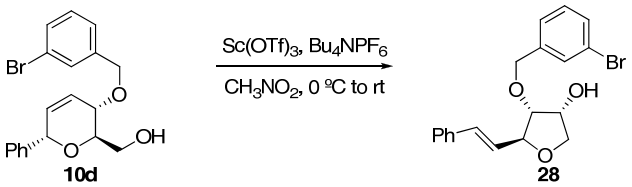
Isochroman **21** was obtained as a single regioisomer (93% yield) from pyran **17** (40 mg, 0.1 mmol) following general procedure **D**. $[\alpha]^{25}_D$ = +58.9° (c 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J=7.4 Hz, 2 H), 7.26 (t, J=7.4 Hz, 2 H), 7.17 - 7.21 (m, 1 H), 7.09 (d, J=8.2 Hz, 1 H), 6.68 (dd, J=8.6, 2.7 Hz, 1 H), 6.56 (d, J=15.6 Hz, 1 H), 6.49 (d, J=2.7 Hz, 1 H), 6.01 (dd, J=15.6, 9.4 Hz, 1 H), 4.78 (s, 2 H), 3.99 - 4.03 (m, 1 H), 3.74 (dd, J=9.4, 4.3 Hz, 1 H), 3.71 (s, 3 H), 3.64-3.69 (m, 2 H), 3.59 (dd, J=10.9, 8.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.3, 136.5, 134.8, 133.8, 130.1, 129.0, 128.7, 127.8, 126.4, 113.2, 110.0, 108.9, 80.1, 72.7, 68.3, 55.3, 43.6, 35.9; IR (neat) 3454, 3081, 3058, 3025, 2934, 2835, 1734, 1611, 1500, 1429, 1256, 1036, 970, 843 cm^{-1}; HRMS $[M+H]^+$: calculated for $C_{20}H_{22}BrO_3$: 389.0752, observed 389.0761.



Isochroman **26** was obtained as a single diastereomer (29 mg, 98% yield) from dihydropyran **10b** (30 mg, 0.08 mmol) following general procedure **D**. $[\alpha]^{25}_{D} = -10.3°$ (c 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 - 7.35 (m, 4 H), 7.20 (t, J=7.0 Hz, 1 H), 6.44 (d, J=16.0 Hz, 1 H), 6.36 (d, J=2.0 Hz, 1 H), 6.21 (d, J=2.0 Hz, 1 H), 6.18 (dd, J=16.0, 7.8 Hz, 1 H), 4.72 (s, 2 H), 3.83 - 3.96 (m, 4 H), 3.81 (s, 3 H), 3.75 (s, 3 H), 2.38 (br. s., 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 159.1, 137.4, 136.0, 131.1, 130.8, 128.4, 127.1, 126.1, 115.3, 99.9, 97.6, 81.0, 70.8, 66.8, 63.4, 55.4, 55.3, 37.0; IR (neat) 3408, 3024, 2933, 2840, 1607, 1493, 1359, 1200, 1149, 1048, 965, 830 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{21}H_{24}O_5Na$: 379.1521, found 379.1516.

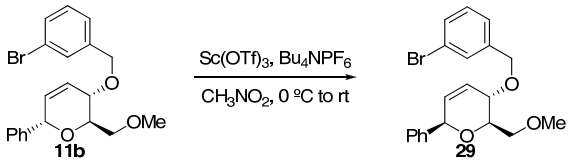


Isochroman **27** was obtained as a single diastereomer (43 mg, 81% yield) from dihydropyran **10c** (53 mg, 0.17 mmol) following general procedure **D.** $[\alpha]^{25}_{D} = -2.2°$ (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (m, 4 H), 7.14 (m, 1 H), 6.83 (s, 1 H), 6.66 (s, 1 H), 6.28 (d, J=16.4 Hz, 1 H), 6.10 (dd, J=16.4, 8.2 Hz, 1 H), 4.65 (d, J=15.0 Hz, 1 H), 4.64 (d, J=15.0 Hz, 1 H), 3.73-3.88 (m, 5 H), 2.55 (br s, 1 H), 2.22 (s, 3 H), 2.18 (s, 3 H), 2.13 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 136.9, 136.0, 134.1, 131.9, 130.5, 130.3, 129.2, 128.5, 127.4, 126.2, 122.8, 80.9, 70.8, 66.7, 63.6, 39.9, 20.9, 19.5; IR (neat) 3397, 3024, 2923, 2855, 2360, 1448, 1091, 968 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{21}H_{24}O_3Na$: 347.1623, observed 347.1635.

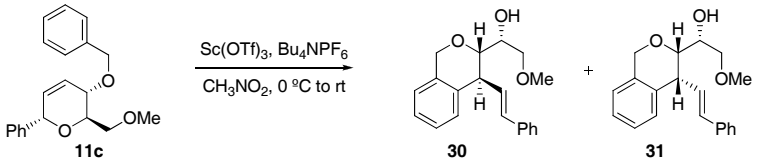


Tetrahydrofuran **28** was obtained (9 mg, 30% yield) from dihydropyran **10d** (30 mg, 0.8 mmol) following general procedure **D**.[2] $[\alpha]^{25}_{D} = -26.7°$ (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1 H), 7.24 - 7.38 (m, 7 H), 7.11-7.15 (m, 1 H), 6.62 (d, J=16.0 Hz, 1 H), 6.07 (dd, J=16.0, 7.2 Hz, 1 H), 4.57 (d, J=12.1 Hz, 1 H), 4.56 (d, J=12.1 Hz, 1 H), 4.40 (t, J=6.8 Hz, 1 H), 4.25 - 4.28 (m, 1 H), 4.09 (dd, J=10.0, 4.9 Hz, 1 H), 3.81 (dd, J=10.0, 3.3 Hz, 1 H), 3.71 (dd, J=6.6, 5.1 Hz, 1 H), 2.57 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 136.3, 132.8, 131.3, 130.2, 128.8, 128.6, 127.9, 127.1, 126.6, 126.3, 122.7, 83.5, 80.9, 73.2, 71.9, 70.0; IR (neat) 3853, 3432, 3059, 3026, 2918, 2850, 1734, 1494, 1260, 1070, 966, 837 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{19}H_{19}BrO_3Na$: 397.0415, observed 397.0404.

[2] Compound **10d** was found to be unstable to the conditions described in general procedure **D**.



Epimerized dihydropyran **29** was recovered in 40 % yield from dihydropyran **11b** (40 mg, 0.1 mmol) following general procedure **D**. $[\alpha]^{25}_{D}$ = +61.0° (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1 H), 7.44 (d, J=7.8 Hz, 1 H), 7.33-7.34 (m, 4 H), 7.28 (m, 3 H), 5.99 (dt, J=10.0, 2.0 Hz, 1 H), 5.88 (dt, J=10.0, 1.0 Hz, 1 H), 5.19 (d, J=1.6 Hz, 1 H), 4.69 (d, J=12.1 Hz, 1 H), 4.56 (d, J=12.0 Hz, 1 H), 4.13 - 4.16 (m, 1 H), 3.82-3.78 (m, 1 H), 3.70 (dd, J=10.9, 2.0 Hz, 1 H), 3.65 (dd, J=10.9, 5.5 Hz, 1 H), 3.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 132.0, 130.9, 130.8, 130.0, 128.5, 128.0, 127.3, 126.3, 125.6, 122.6, 77.6, 77.5, 72.4, 70.6, 70.3, 59.5; IR (neat) 3853, 2923, 2369, 1734, 1647, 1506, 1273, 1085 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{22}H_{29}BrO_3Na$: 443.1198, found 443.1202.



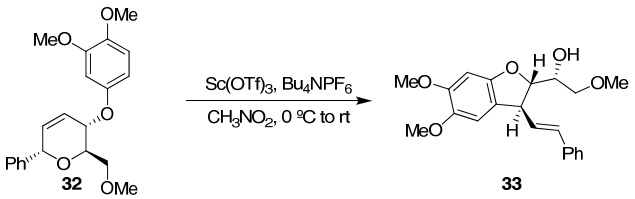
Isochromans **30** and **31** were obtained (2:1, 78% yield) from dihydropyran **11c** (75 mg, 0.24 mmol) following general procedure **D**.

30: $[\alpha]^{25}_{D}$ = −102.1° (c 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J=7.4 Hz, 7 H), 7.19 (d, J=7.8 Hz, 2 H), 7.09 - 7.13 (m, 4 H), 6.94 - 6.97 (m, 1 H), 6.49 (d, J=16.0 Hz, 1 H), 6.36 (dd, J=16.0, 9.4 Hz, 1 H), 4.87 (d, J=15.2 Hz, 1 H), 4.78 (d, J=15.2 Hz, 1 H), 3.77-3.83 (m, 1 H), 3.70 (dd, J=9.0, 2.3 Hz, 1 H), 3.63 (ddd, J=9.4, 6.4, 2.7 Hz, 2 H), 3.49 (dd, J=9.6, 6.4 Hz, 1 H), 3.34 (s, 3 H), 2.32 (d, J=5.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.0, 133.7, 131.2, 130.1, 129.5, 128.4, 127.2, 126.7, 126.6, 126.3, 124.0, 73.9, 69.9, 68.7, 59.2, 43.2, 29.7; IR (neat) 3902, 3457, 3024, 2917, 2360, 1491, 1093, 967 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{20}H_{22}O_3Na$: 333.1467, observed 333.1482.

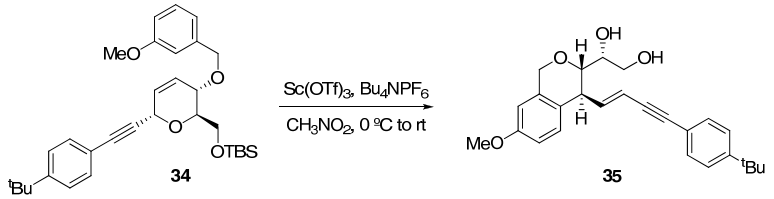
31: $[\alpha]^{25}_{D}$ = +32.4° (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, J=7.8, 1.0 Hz, 2 H), 7.25 (t, J=7.4 Hz, 2 H), 7.16 (m, 4 H), 6.96 (m, 1 H), 6.56 (d, J=16.0 Hz, 1 H), 6.02 (dd, J=15.8, 9.2 Hz, 1 H), 4.81 (s, 2 H), 4.03 (m, 1 H), 3.79 (dd, J=9.8, 3.5 Hz, 1 H), 3.68 - 3.73 (m, 1 H), 3.63 (dd, J=10.0, 3.5 Hz, 1 H), 3.55 (dd, J=10.0, 7.8 Hz, 1 H), 3.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 134.9, 133.9, 129.1, 129.0, 128.6, 127.7, 126.9, 126.5, 126.3, 124.2, 79.8, 72.6, 70.9, 68.3, 59.2, 43.3: IR (neat) 3446, 3060, 3025, 2924, 2360, 1734, 1449, 1099, 968 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{20}H_{22}O_3Na$: 333.1467, observed 333.1476.

*Determination of the relative stereochemistry for compounds **30** and **31*** (see page SI-52–53)**.**

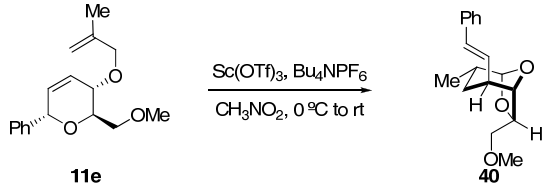
Compounds **30** and **31** were converted to the respective secondary acetates using typical conditions. NOE difference experiments were performed in benzene-d_6 (degassed *via* the freeze-pump-thaw method) using a Varian 500 MHz NMR. Peak identities were determined *via* COSY experiments.



Dihydrobenzofuran **33** (45 mg, 50% yield) was obtained from dihydropyran **32** (90 mg) following general procedure **D**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (app d, J=7.4 Hz, 2H), 7.27 (app t, J=7.4 Hz, 2H), 7.16 (app t, J=7.4 Hz, 1H), 6.71 (s, 1H), 6.61 (s, 1H), 6.18 (ddd, J=12.1, 7.4, 2.7Hz, 1H), 5.79 (d, J=12.5 Hz, 1H), 4.51–4.47 (m, 2H), 3.99–3.94 (m, 1H), 3.86 (s, 3H), 3.84, (s, 3H), 3.64 (dd, J=9.7, 7.4 Hz, 1H), 3.57 (dd, J=9.7, 7.4 Hz, 1H), 3.41 (s, 3H), 2.59 (d, J=5.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 148.4, 145.4, 143.4, 131.1, 128.7, 128.4, 127.5, 127.3, 126.2, 112.6, 106.3, 80.6, 72.8, 72.6, 59.1, 56.2, 56.0, 50.1 ppm; IR (neat) 3461, 2931, 1610, 1510, 1450, 1407, 1265, 1195, 1124, 1076, 1020, 815, 736, 701 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{19}H_{20}O_4Na$:, observed.



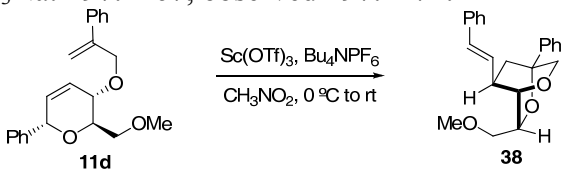
Isochroman **35** was obtained (18 mg, 50% yield) from pyran **34** (36 mg, 0.07 mmol) following general procedure **D**. $[\alpha]^{25}_D$ = +12.0° (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J*=9.0 Hz, 2 H), 7.34 (d, *J*=9.0 Hz, 2 H), 7.14 (d, *J*=8.6 Hz, 1 H), 6.79 (dd, *J*=8.6, 2.3 Hz, 1 H), 6.55 (d, *J*=2.3 Hz, 1 H), 5.99 (dd, *J*=15.6, 8.6 Hz, 1 H), 5.94 (d, *J*=15.6 Hz, 1 H), 4.85 (d, *J*=14.8 Hz, 1 H), 4.79 (d, *J*=14.8 Hz, 1 H), 3.97 (dd, *J*=11.3, 4.7 Hz, 1 H), 3.88-3.92 (m, 1 H), 3.79-3.83 (m, 2 H), 3.79 (s, 3 H), 3.59 (t, *J*=8.2 Hz, 1 H), 2.79 (d, *J*=8.2 Hz, 1 H), 2.34 (d, *J*=7.8 Hz, 1 H), 1.31 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 151.6, 141.3, 134.6, 131.2, 130.1, 125.7, 125.4, 114.3, 113.2, 109.0, 90.2, 86.5, 81.8, 71.1, 68.7, 62.5, 55.3, 43.7, 34.8, 31.2; IR (neat) 3404, 2961, 2869, 2360, 1501, 1259, 1037, 835 cm^{-1}; HRMS $[M+H]^+$: calculated for $C_{26}H_{30}O_4Na$: 407.2222, observed 407.2227.



Dioxabicyclo[3.2.1]octane **40** was obtained in 50% yield from pyran **11e** under the conditions described in general procedure **D**.[3] $[\alpha]^{25}_D$ = −131.4° (c 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, C_6D_6) δ 7.02 (d, *J*=7.4 Hz, 2 H), 6.85 - 6.89 (m, 2 H), 6.76 - 6.79 (m, 1 H),

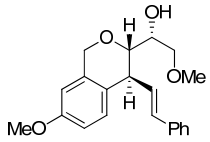
[3]Trace amounts of isomers of **40,** which were inseparable by flash column chromatography, UPLC, and HPLC analysis were detected in the NMR spectra.

6.30 (dd, *J*=16.0, 8.2 Hz, 1 H), 6.08 (d, *J*=16.0 Hz, 1 H), 5.01 (s, 1 H), 4.03 (dt, *J*=6.8, 4.7 Hz, 1 H), 3.87 (d, *J*=4.7 Hz, 1 H), 3.30 (dd, *J*=9.8, 6.8 Hz, 1 H), 3.13 (dd, *J*=9.8, 6.8 Hz, 1 H), 2.81 (s, 3 H), 1.96 (app t, *J*=7.4 Hz, 1 H), 1.45-1.53 (m, 1 H), 1.27-1.35 (m, 1 H), 1.05-1.11 (m, 1 H), 0.44 (d, *J*=7.0 Hz, 3 H); ^{13}C NMR (100 MHz, C_6D_6) δ 138.4, 132.8, 130.6, 129.2, 127.8, 126.9, 106.1, 78.2, 78.1, 70.7, 59.4, 38.0, 33.0, 31.9, 17.3; IR (neat) 3057, 3026, 2957, 2931, 2341, 1493, 1105, 1054, 933 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{17}H_{22}O_3Na$: 297.1467, observed 297.1472.



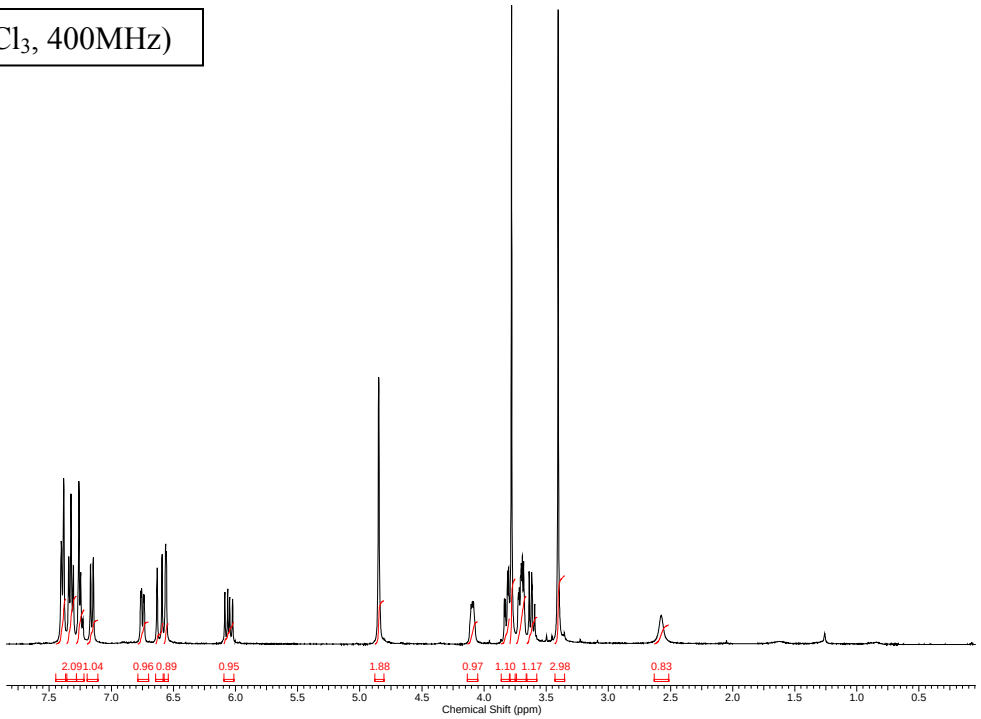
Dioxabicyclo[2.2.1]octane **38** was isolated in 63% yield from dihydropyran **11d** following the conditions described in general procedure **D**. $[\alpha]^{25}_D$ = –9.8° (c 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 - 7.45 (m, 4 H), 7.24 - 7.37 (m, 6 H), 6.56 (dd, *J*=15.6, 7.0 Hz, 1 H), 6.54 (s, *J*=15.6 Hz, 1 H), 4.72-4.76 (m, 1 H), 4.22 (dd, *J*=9.8, 3.1 Hz, 1 H), 4.05 (d, *J*=9.8 Hz, 1 H), 3.88 (s, 1 H), 3.65 (dd, *J*=10.2, 6.3 Hz, 1 H), 3.56 (dd, *J*=10.2, 7.0 Hz, 1 H), 3.44 (s, 3 H), 2.92 - 2.98 (m, 1 H), 2.44 (ddd, *J*=13.7, 10.9, 3.1 Hz, 1 H), 2.10 (dd, *J*=13.7, 5.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 137.2, 132.0, 130.2, 128.5, 128.3, 127.6, 127.3, 126.2, 125.1, 76.3, 74.4, 73.1, 71.2, 59.5, 37.8, 36.4; IR (neat) 3057, 3026, 2926, 2871, 1494, 1093, 966 cm^{-1}; HRMS $[M+Na]^+$: calculated for $C_{22}H_{24}O_3Na$: 359.1623, observed 359.1635.

IX. ^{1}H and ^{13}C NMR and representative 2-D and 1-D NOE Spectra for Isochroman and Dioxabicyclooctane scaffolds

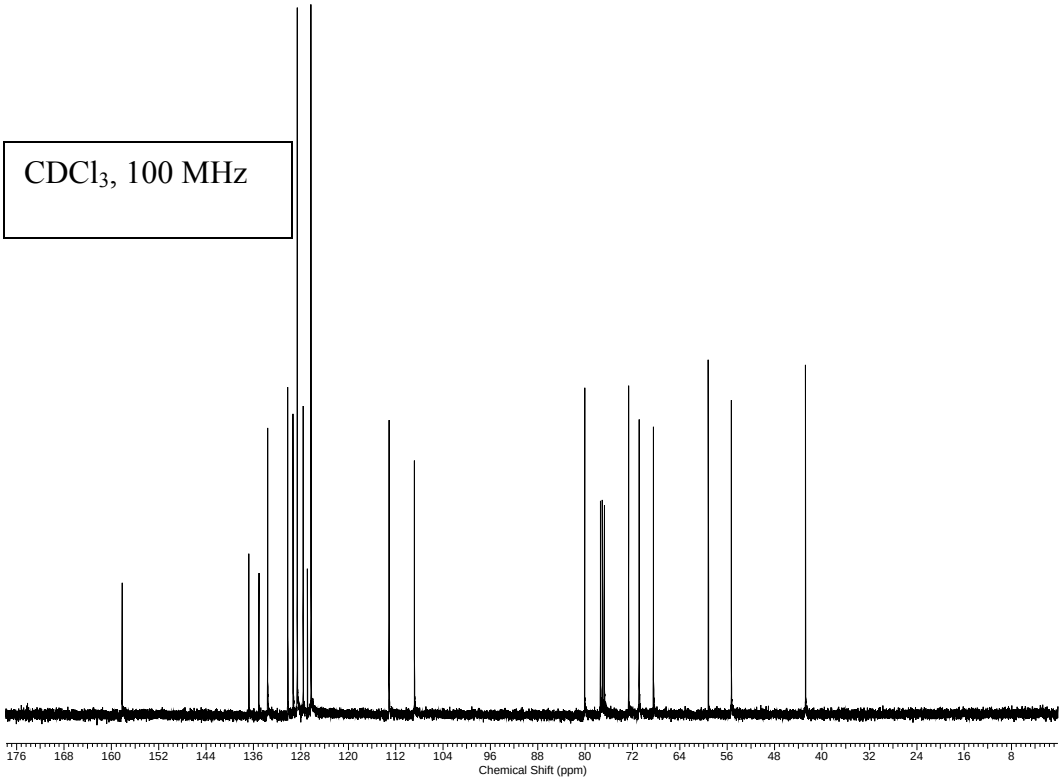


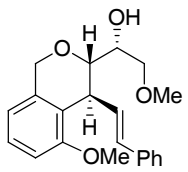
12

($CDCl_3$, 400MHz)

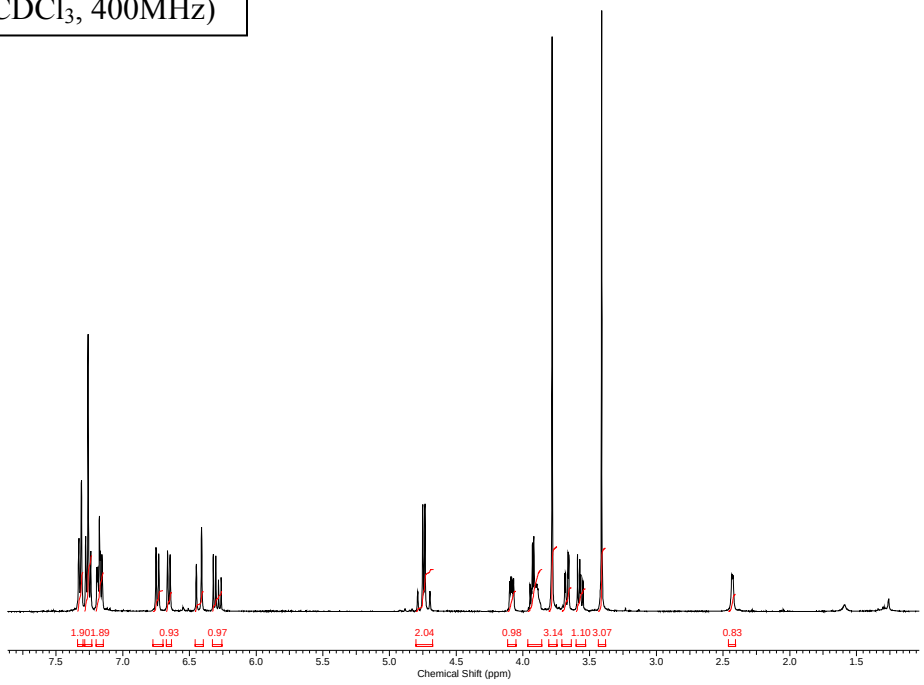


$CDCl_3$, 100 MHz

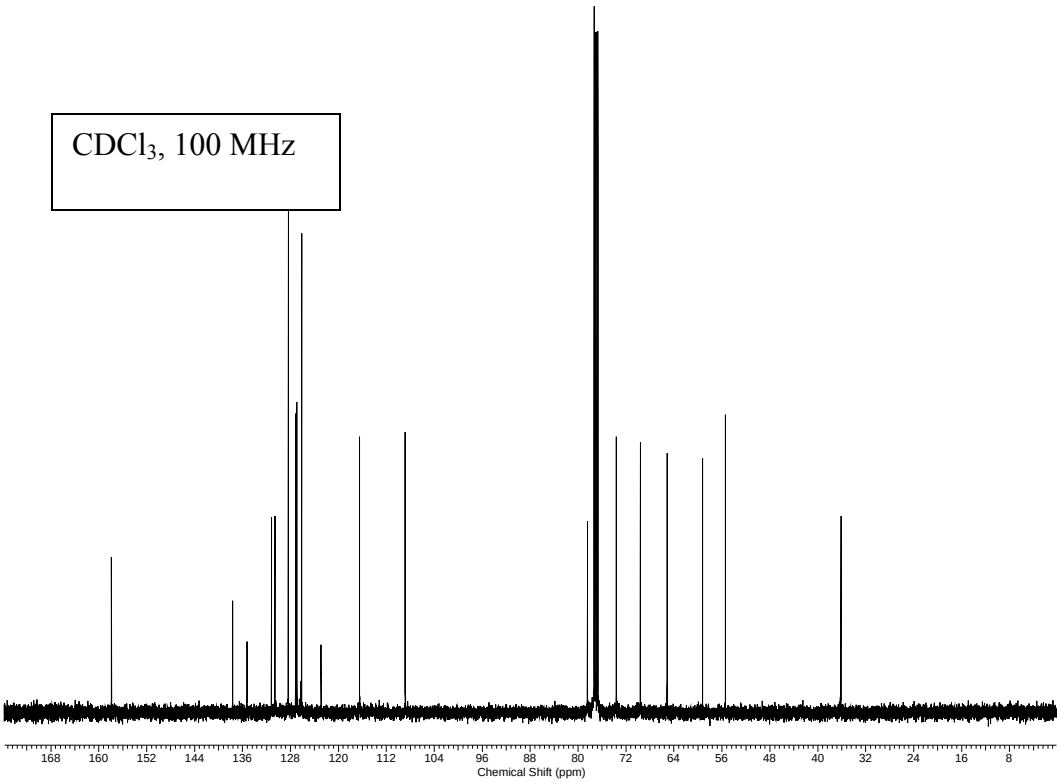


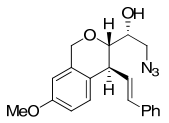


(CDCl$_3$, 400MHz)



CDCl$_3$, 100 MHz





22

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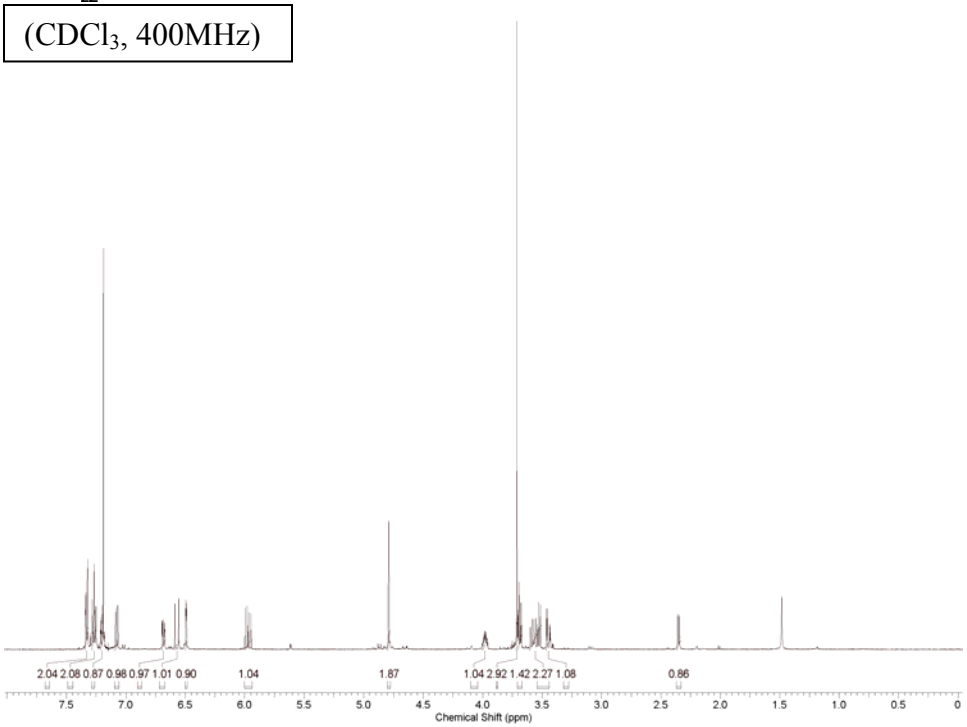

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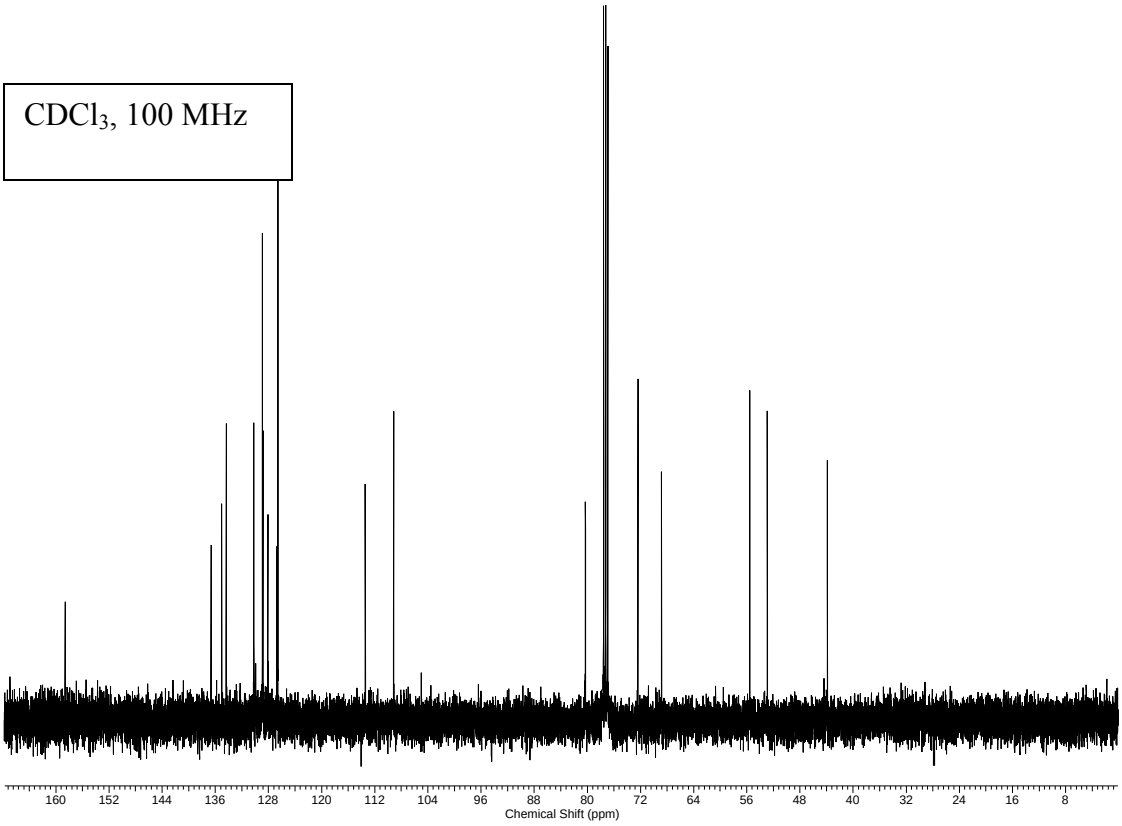
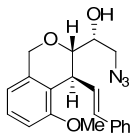
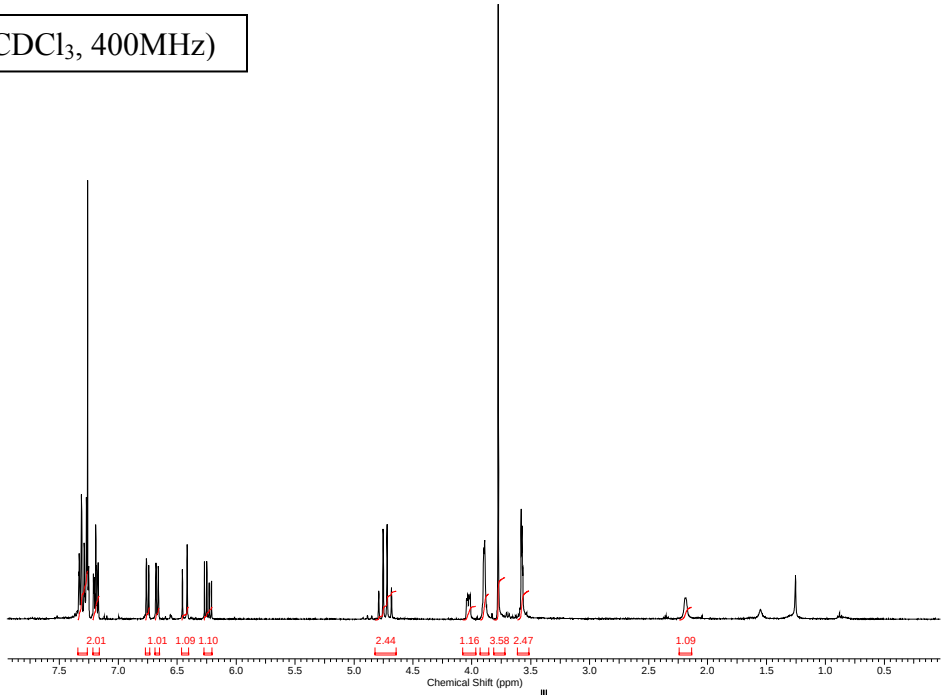


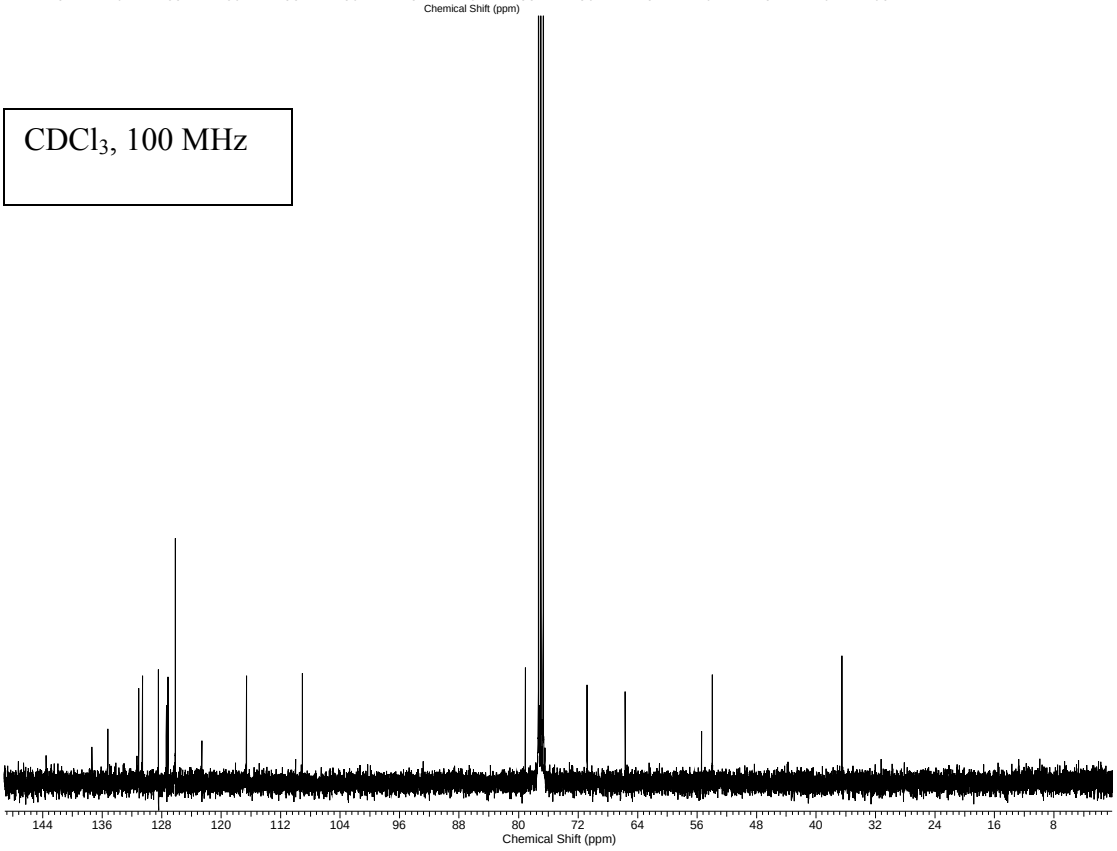


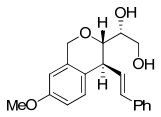
25

($CDCl_3$, 400MHz)



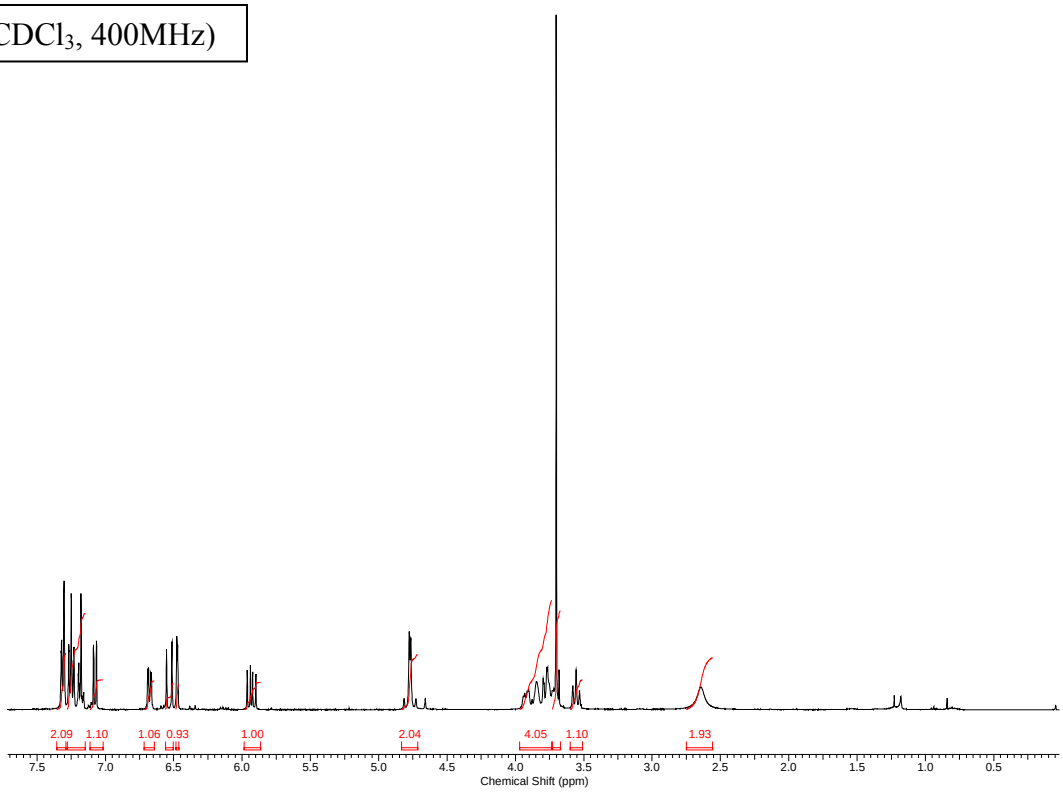
$CDCl_3$, 100 MHz



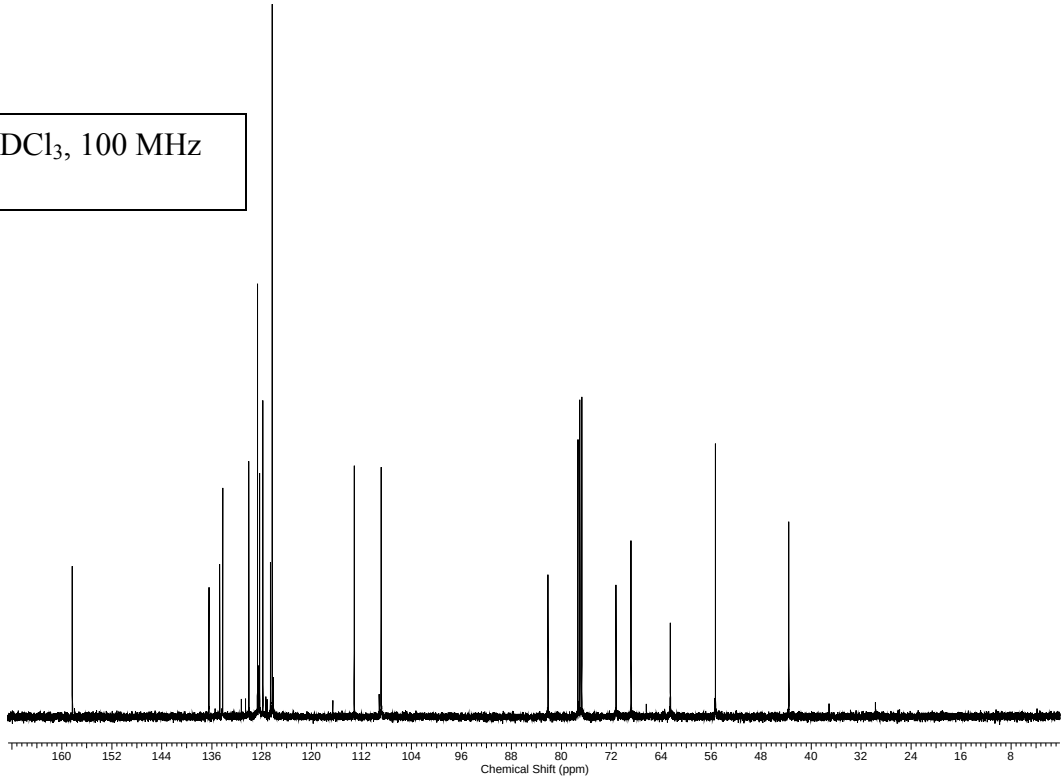


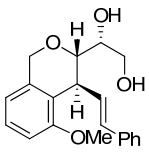
19

($CDCl_3$, 400MHz)



$CDCl_3$, 100 MHz





23

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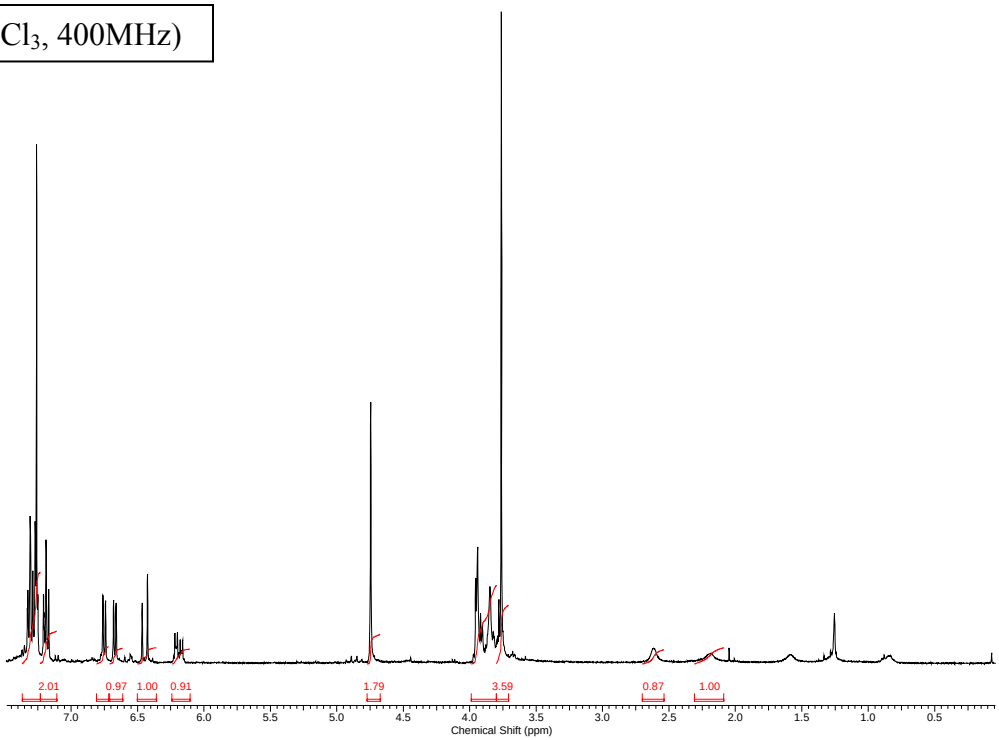
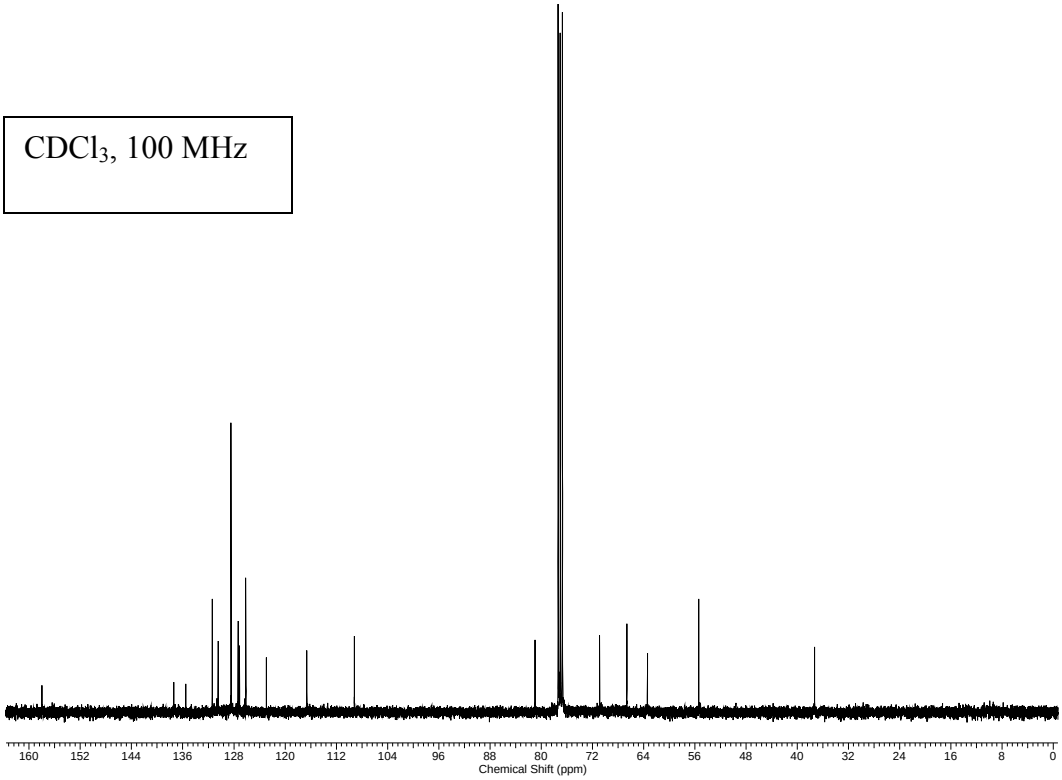
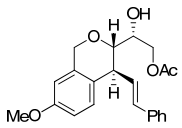


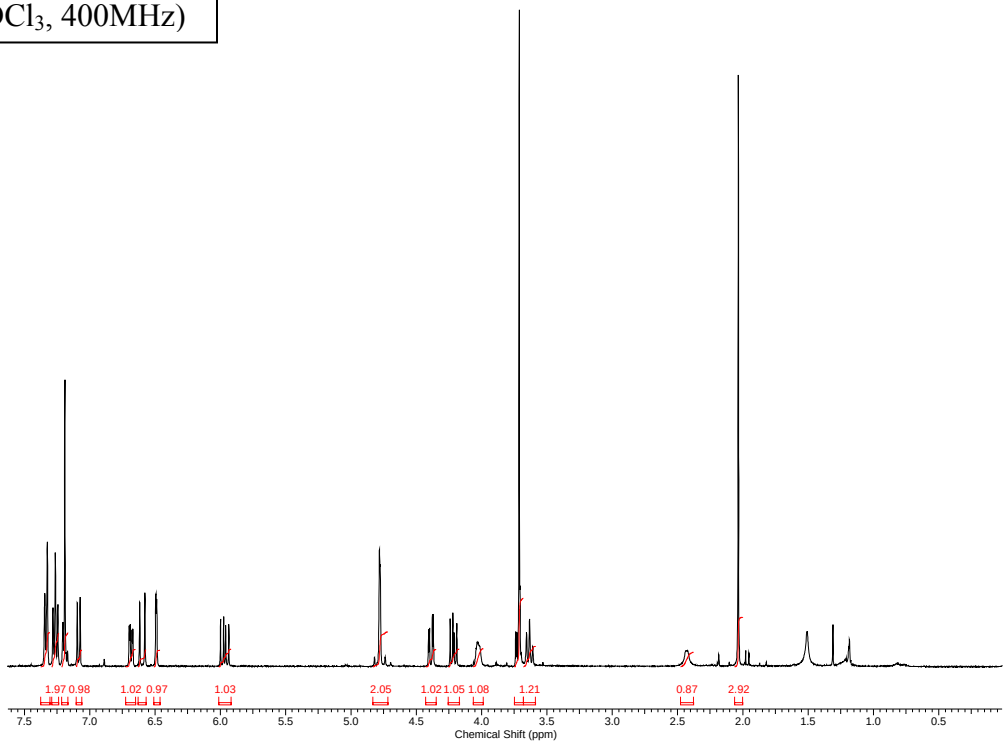
$CDCl_3$, 100 MHz



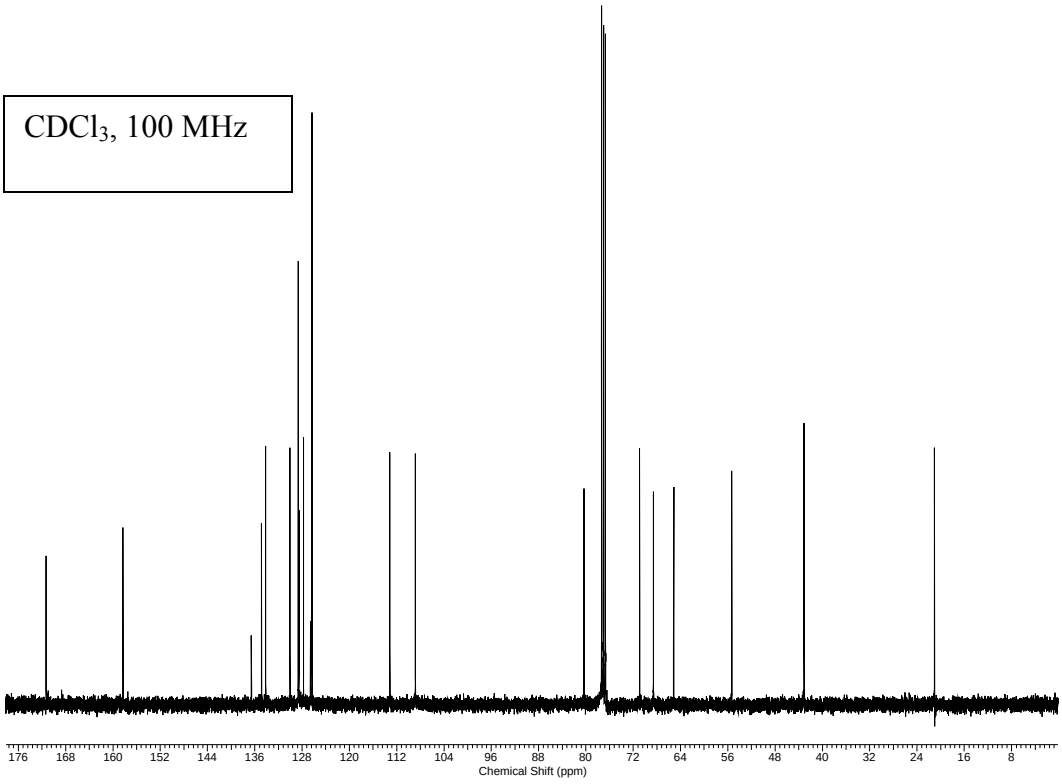


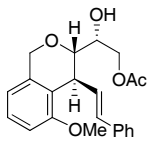
20

(CDCl$_3$, 400MHz)



CDCl$_3$, 100 MHz





24

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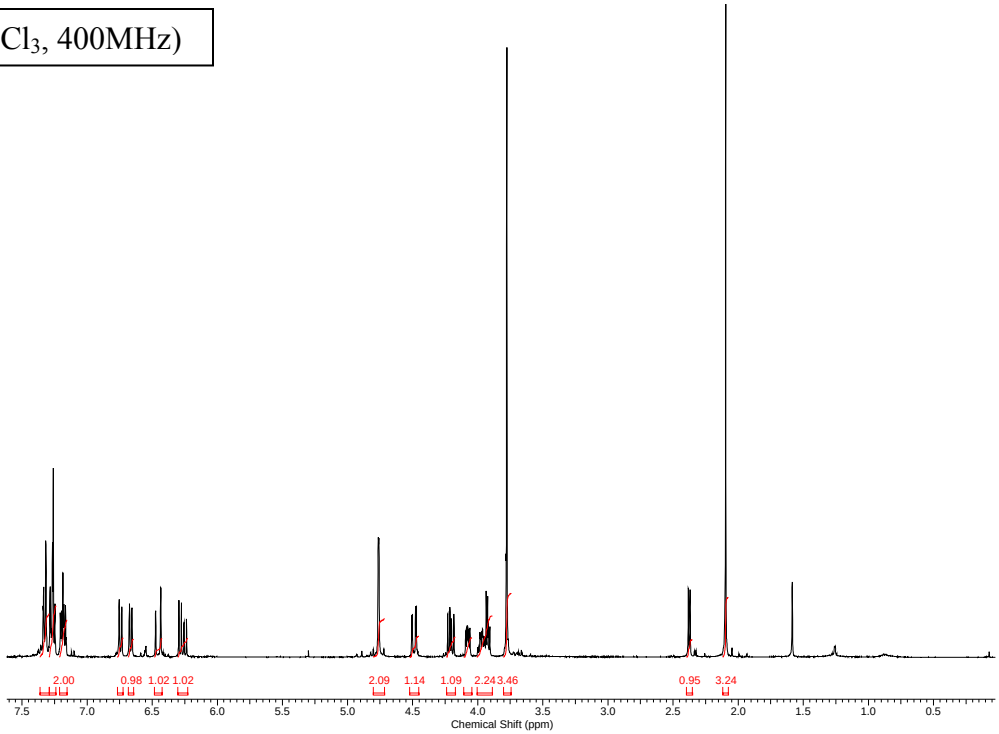
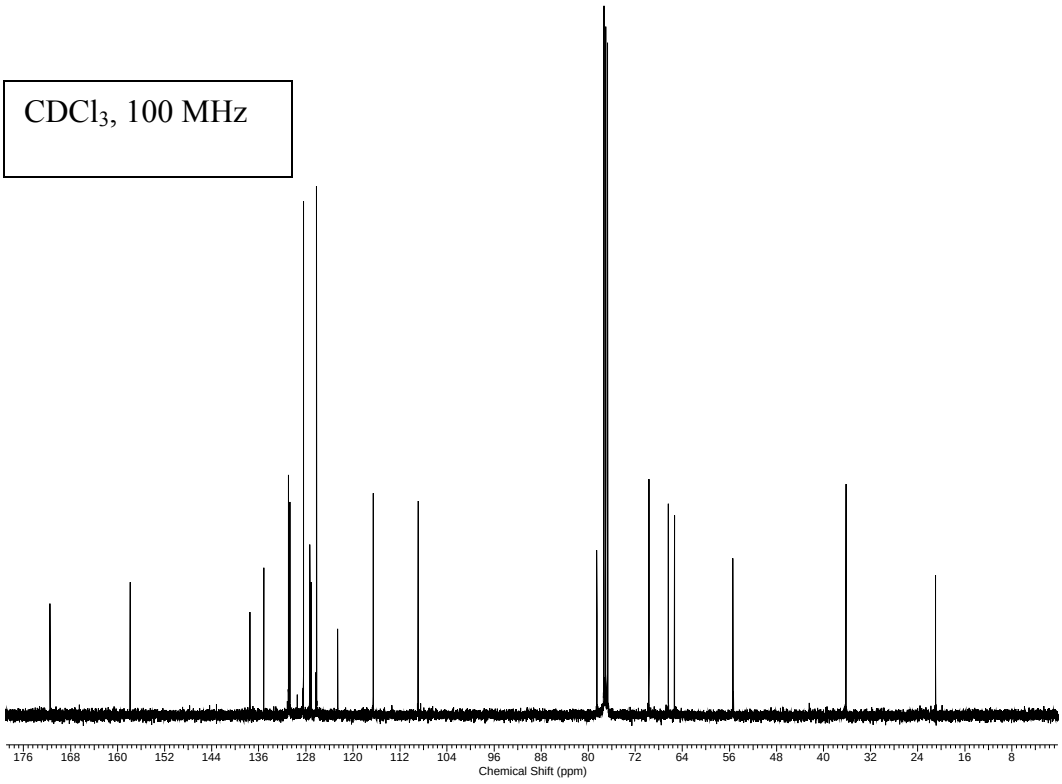
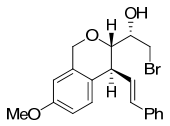


$CDCl_3$, 100 MHz





21

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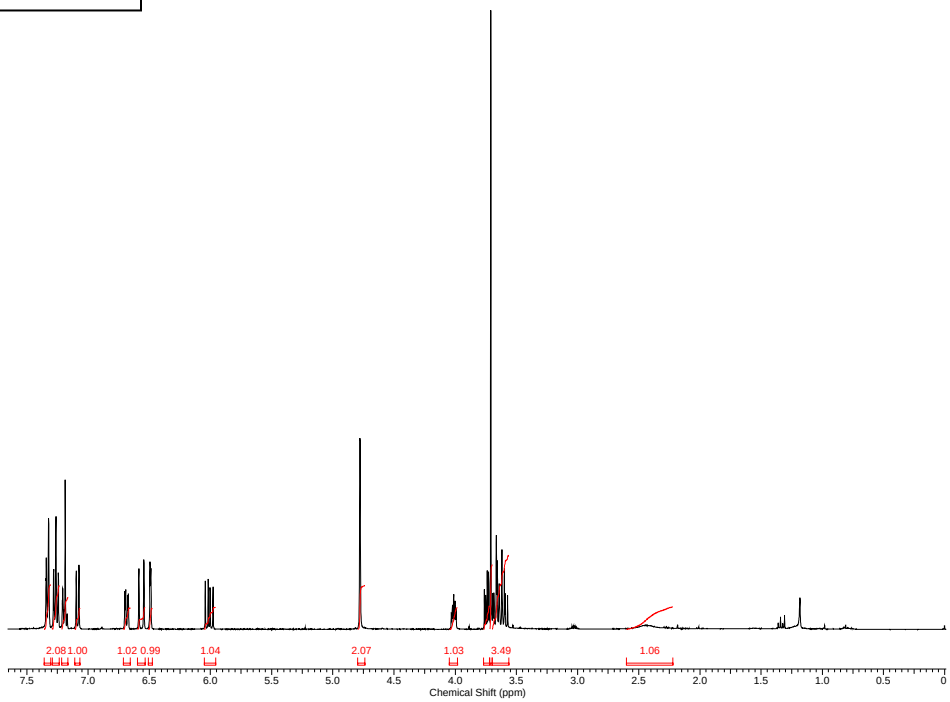
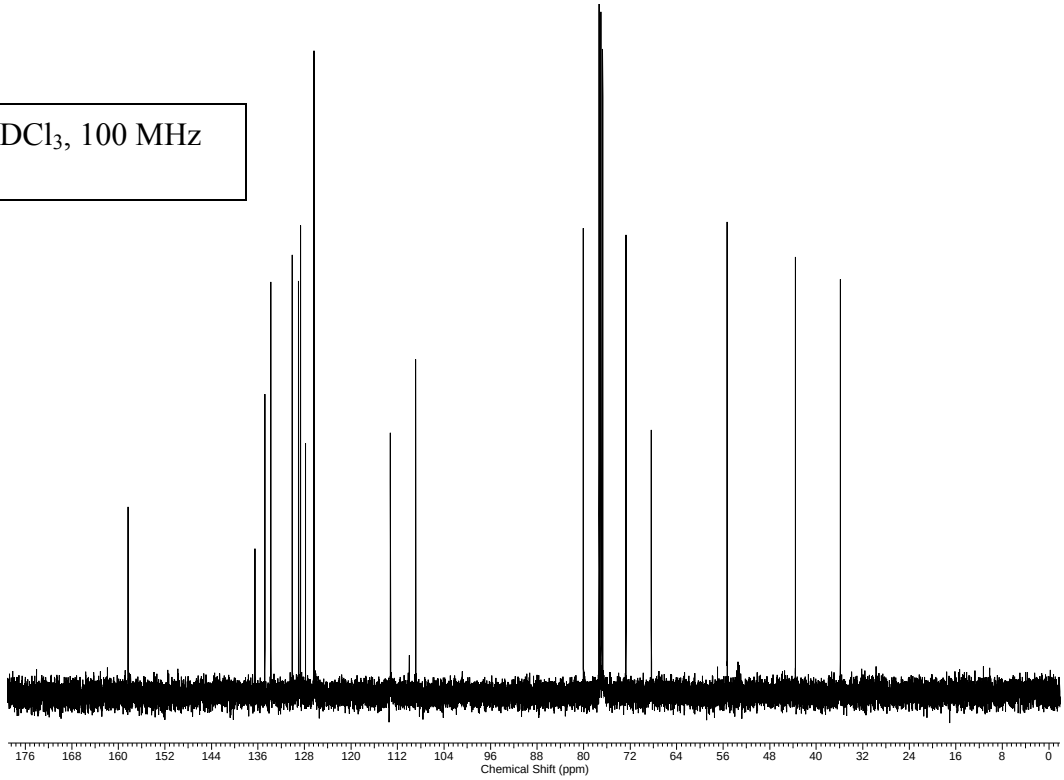
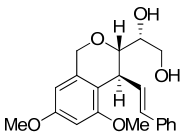


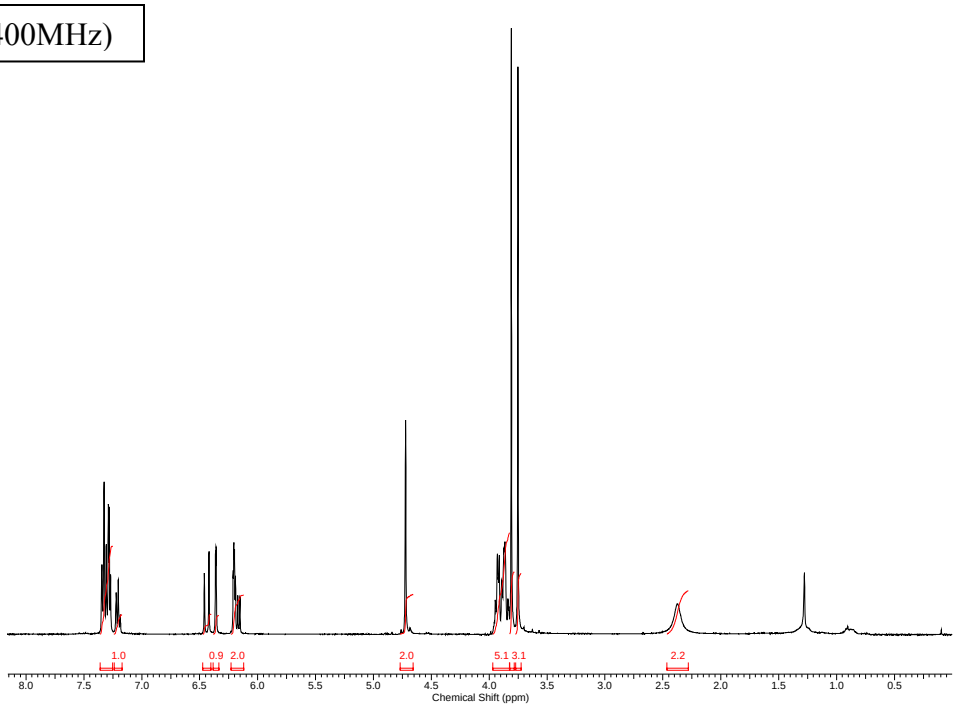
CDCl$_3$, 100 MHz



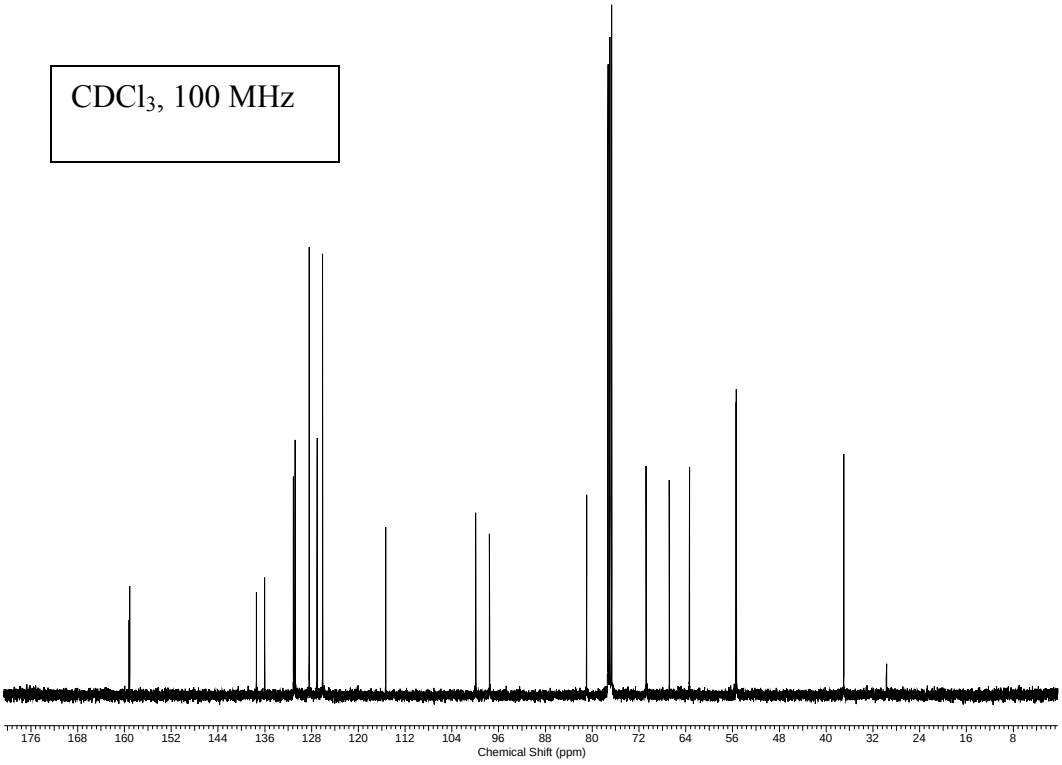


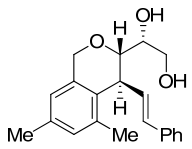
26

($CDCl_3$, 400MHz)



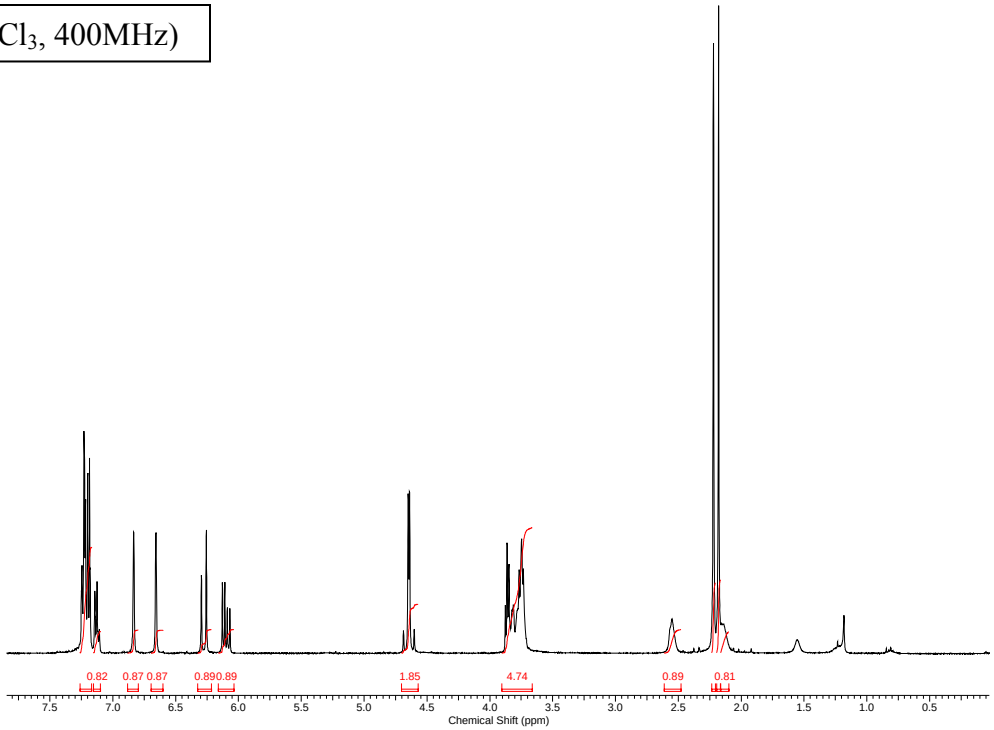
$CDCl_3$, 100 MHz



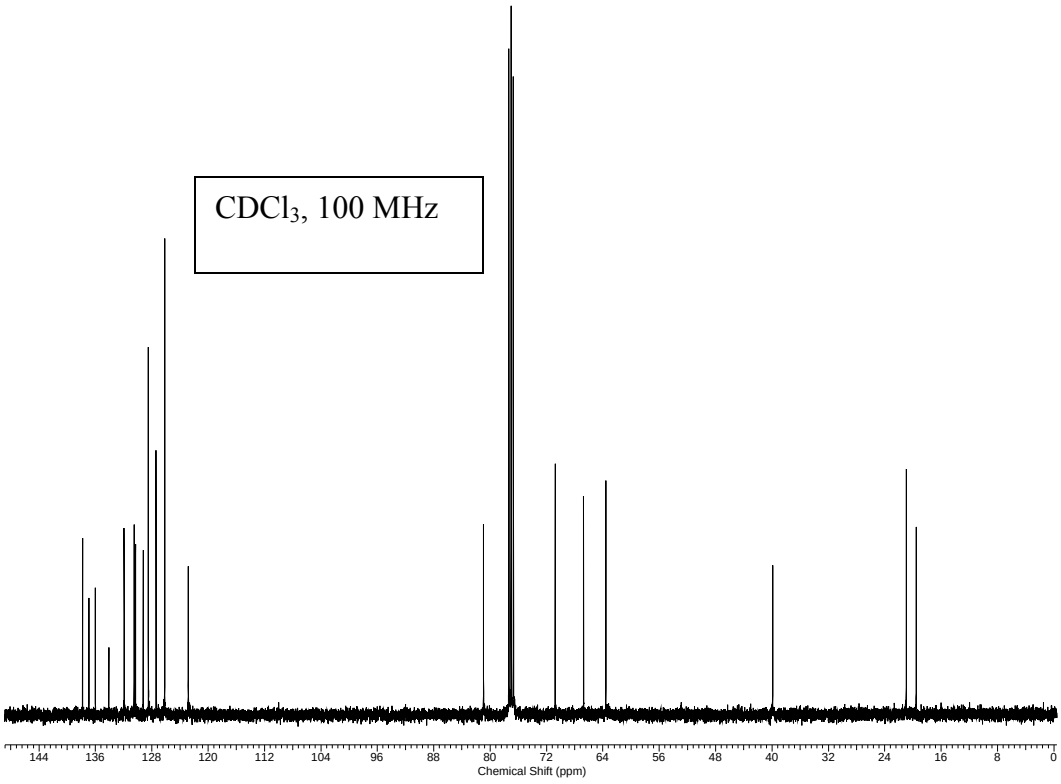


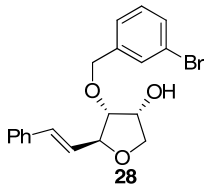
27

($CDCl_3$, 400MHz)



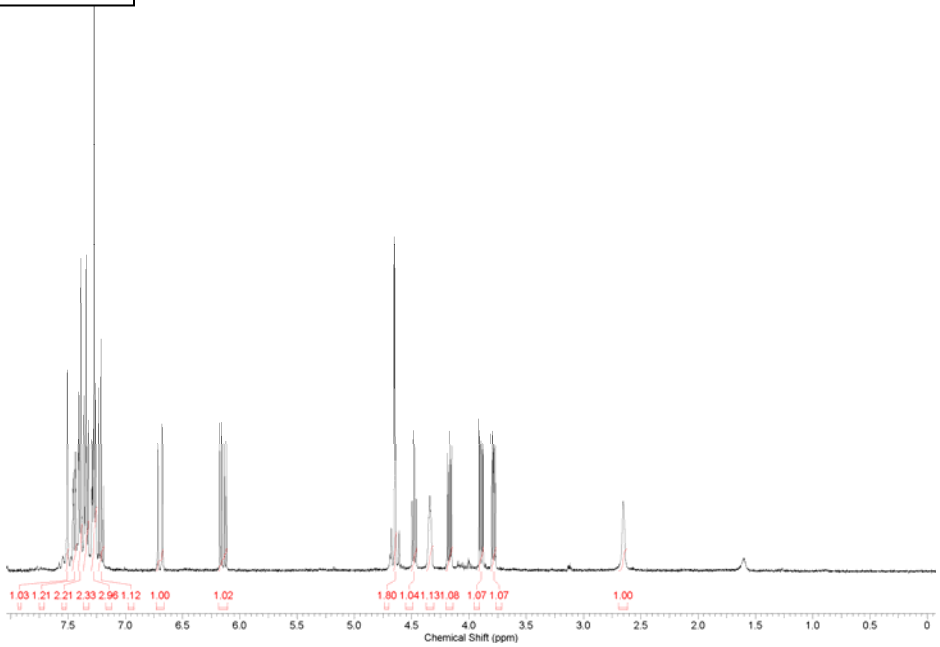
$CDCl_3$, 100 MHz



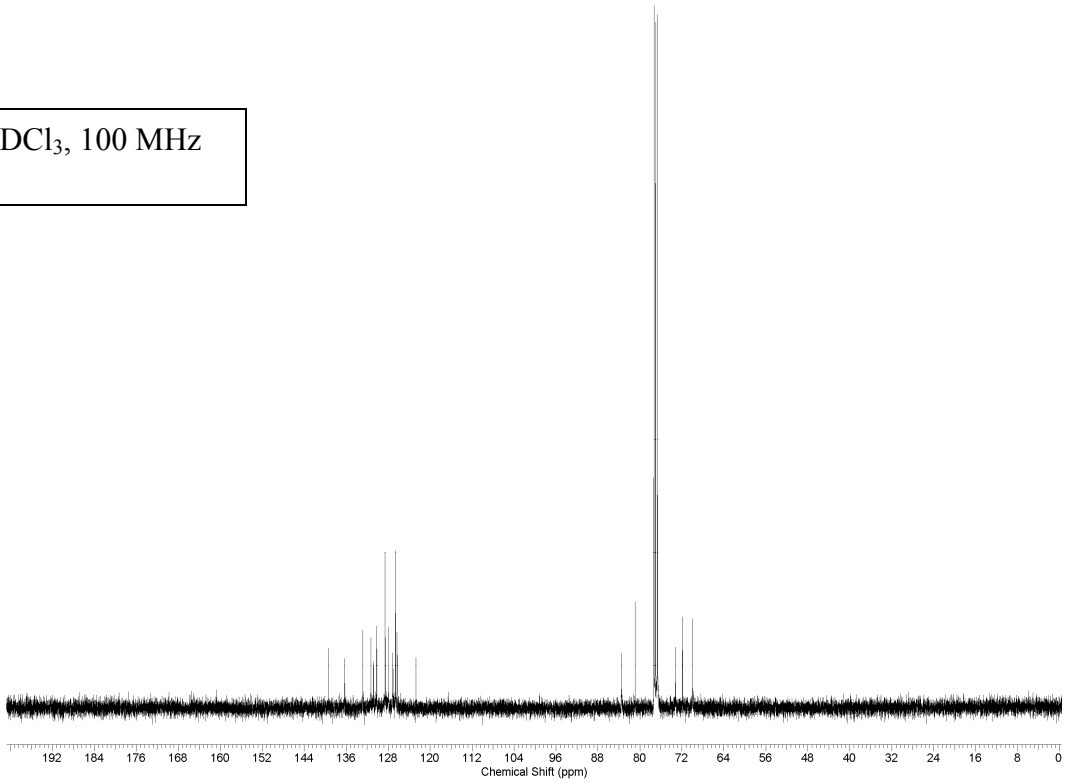


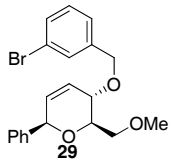
28

($CDCl_3$, 400MHz)



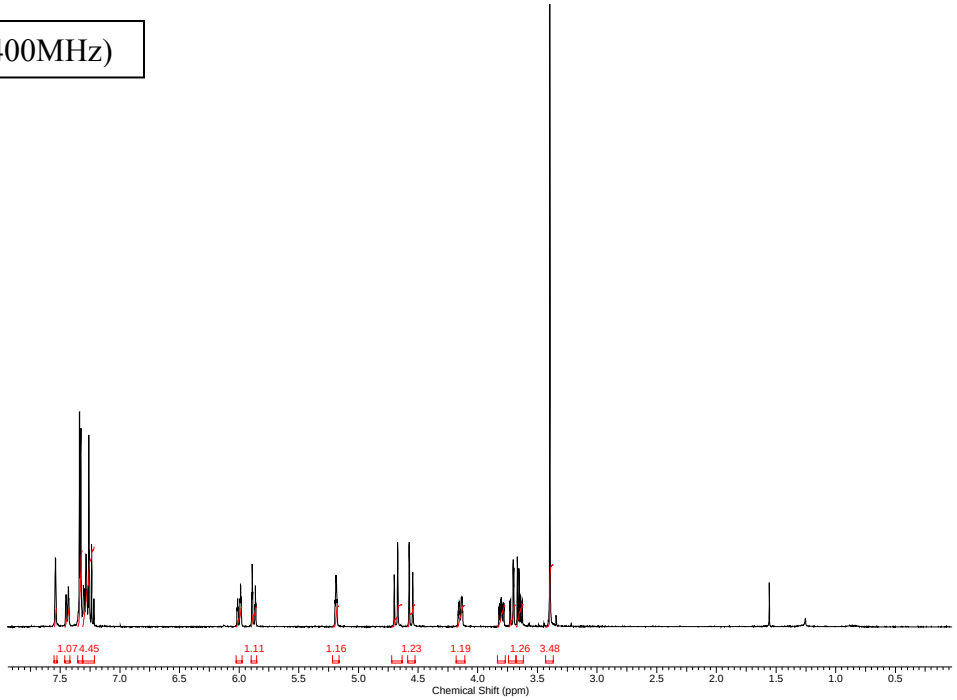
$CDCl_3$, 100 MHz



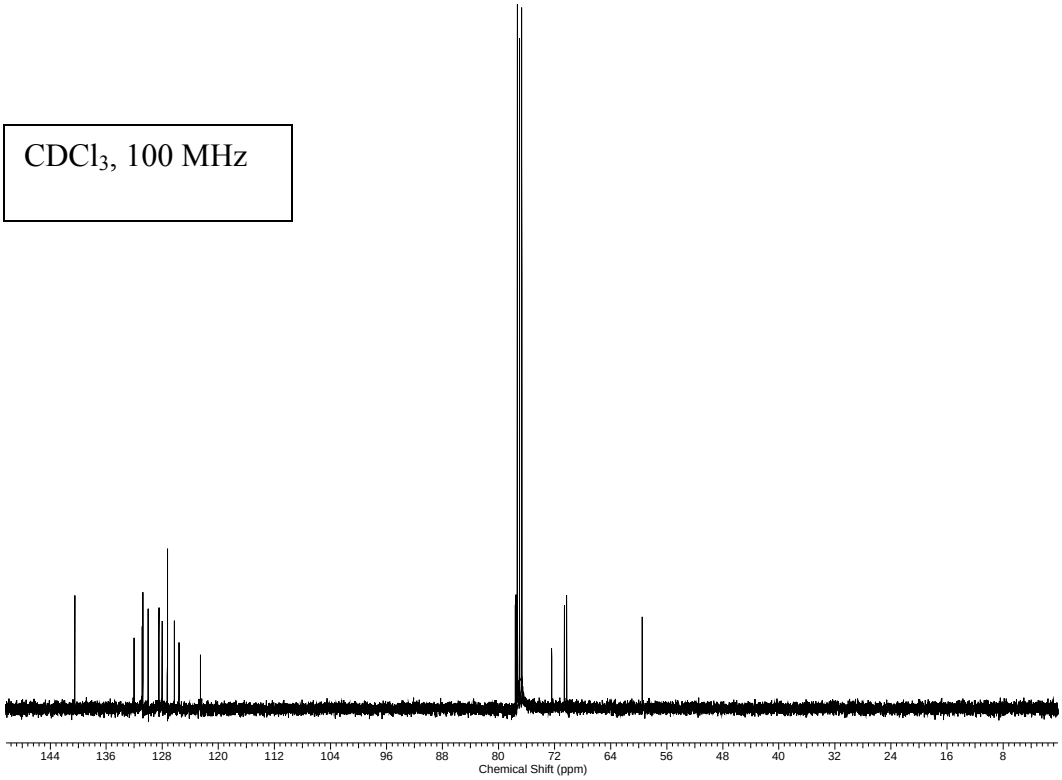


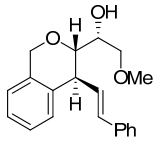
29

($CDCl_3$, 400MHz)



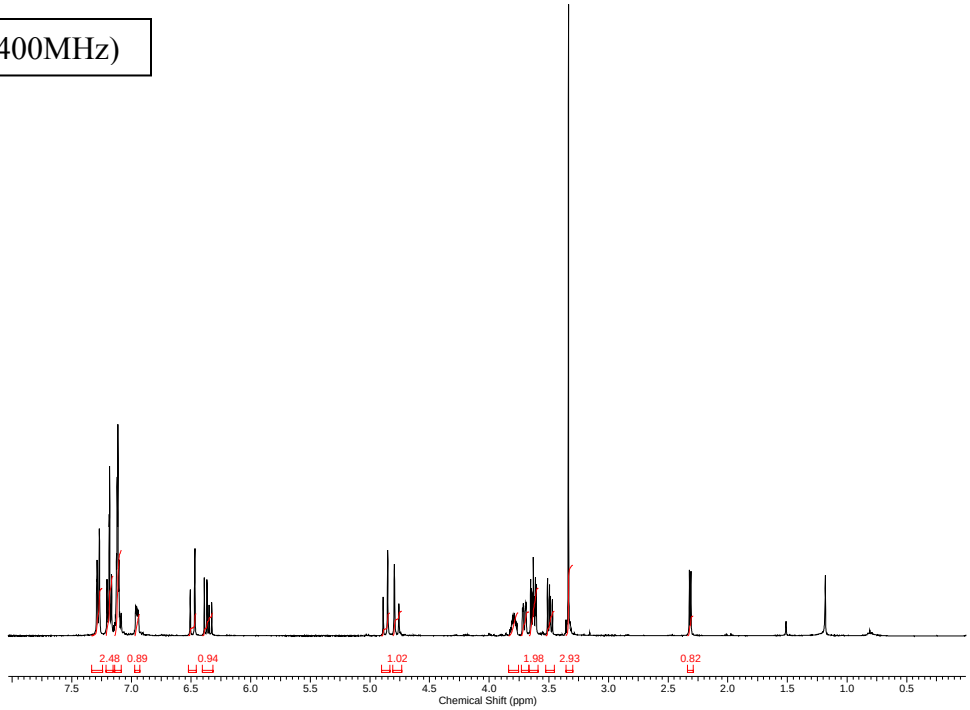
$CDCl_3$, 100 MHz



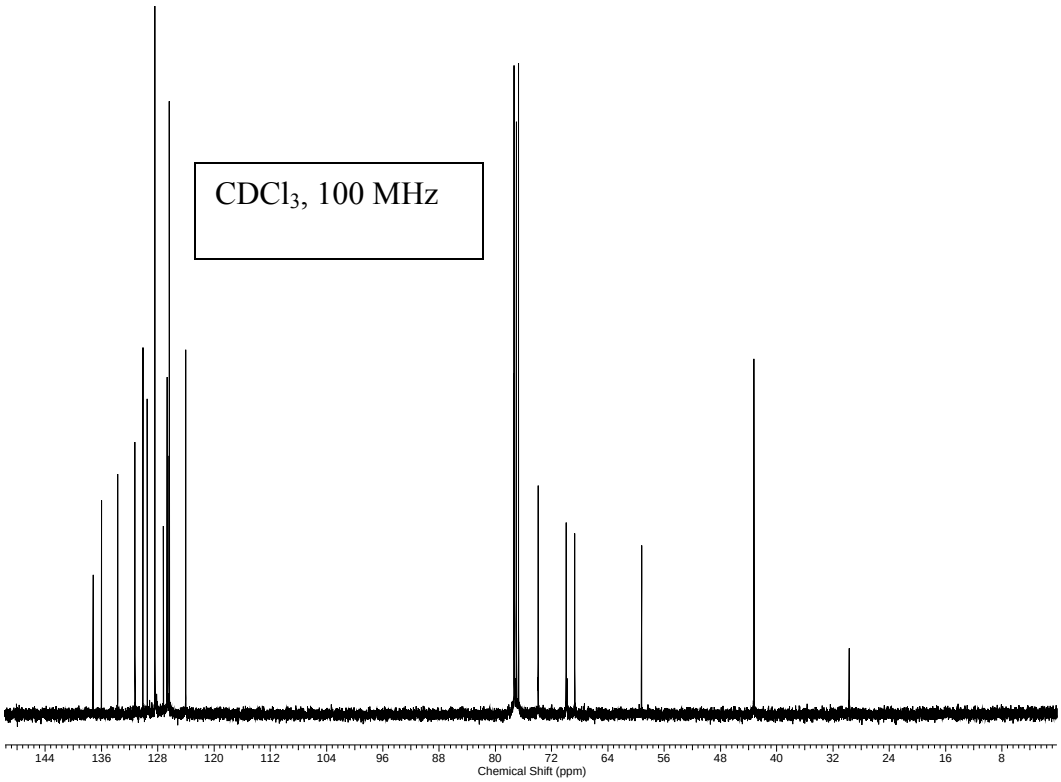


30

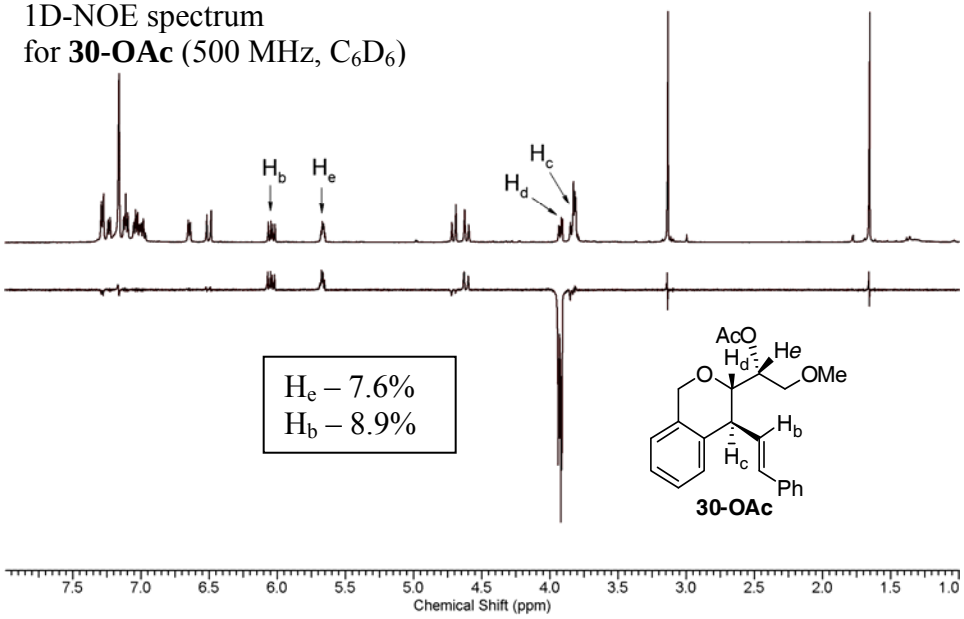
($CDCl_3$, 400MHz)



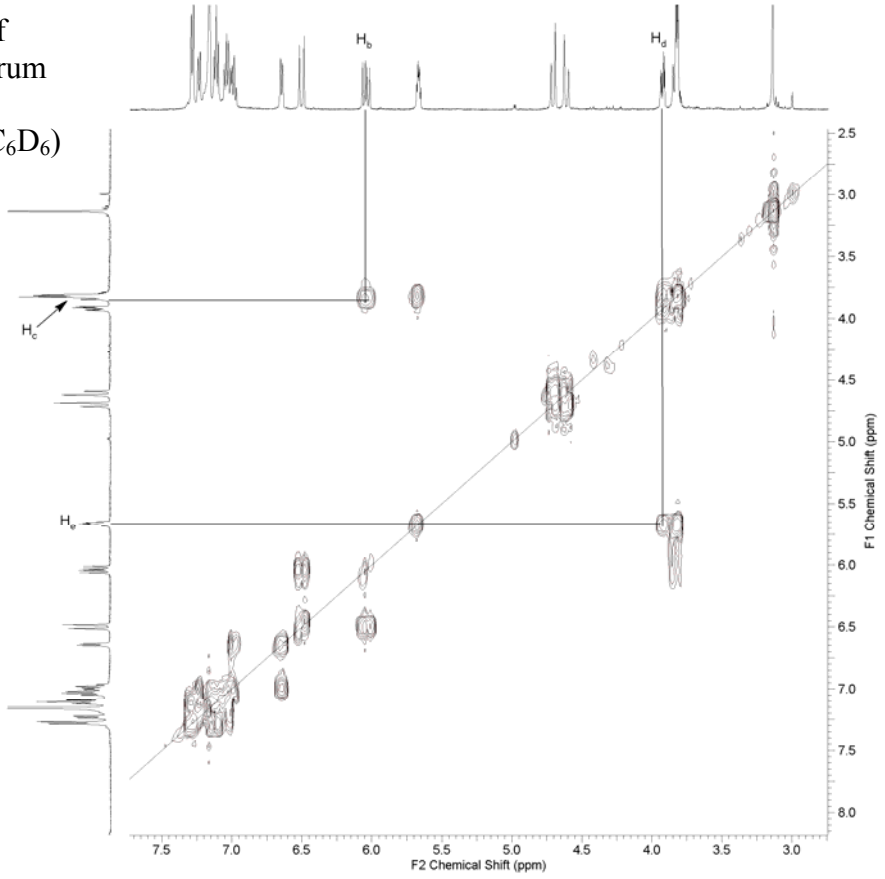
$CDCl_3$, 100 MHz



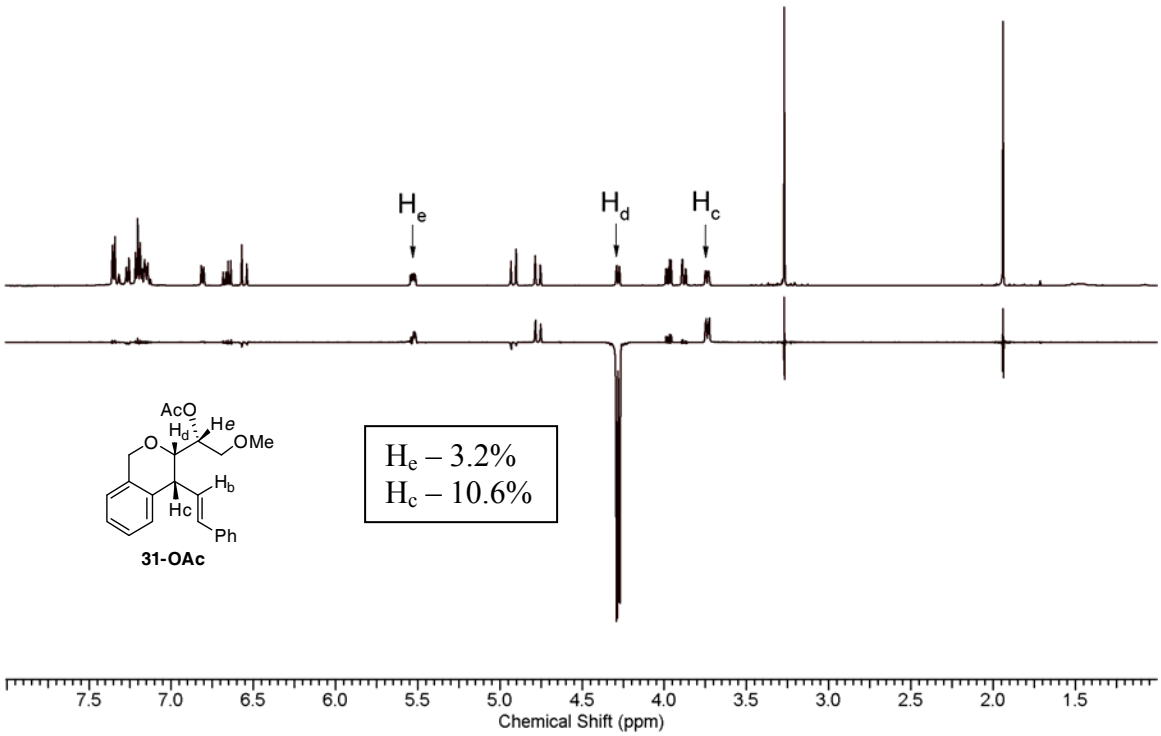
1D-NOE spectrum
for **30-OAc** (500 MHz, C_6D_6)



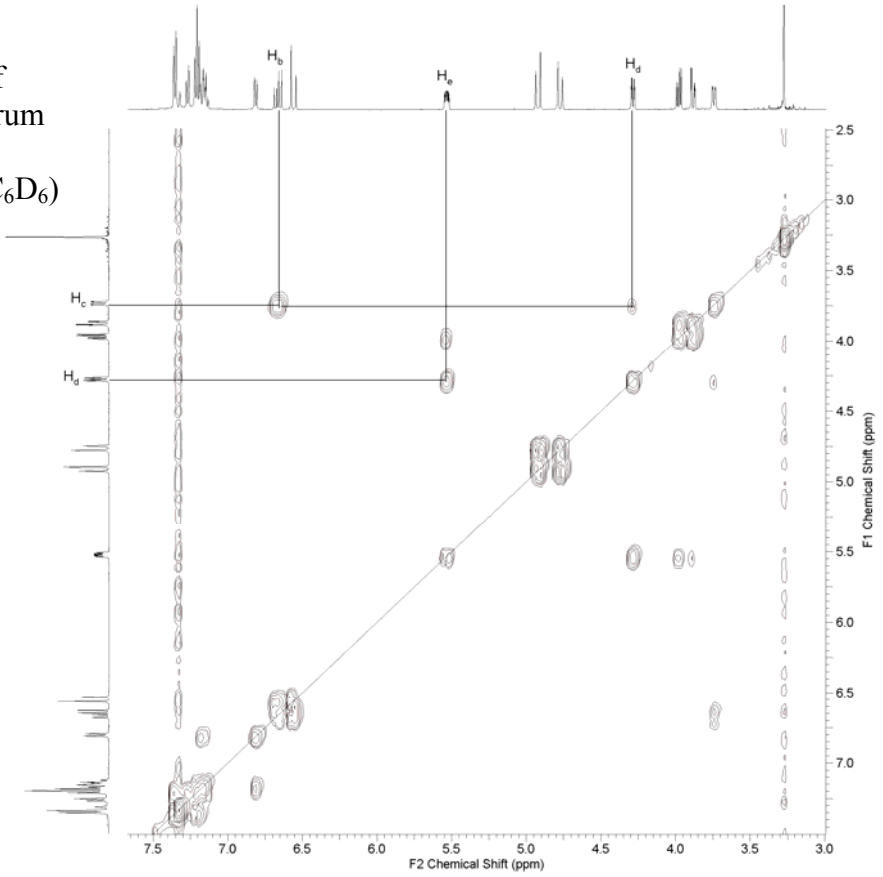
Expansion of
COSY spectrum
for **30-OAc**
(500 MHz, C_6D_6)

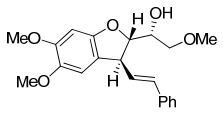


1D-NOE spectrum
for **31-OAc** (500 MHz, C_6D_6)



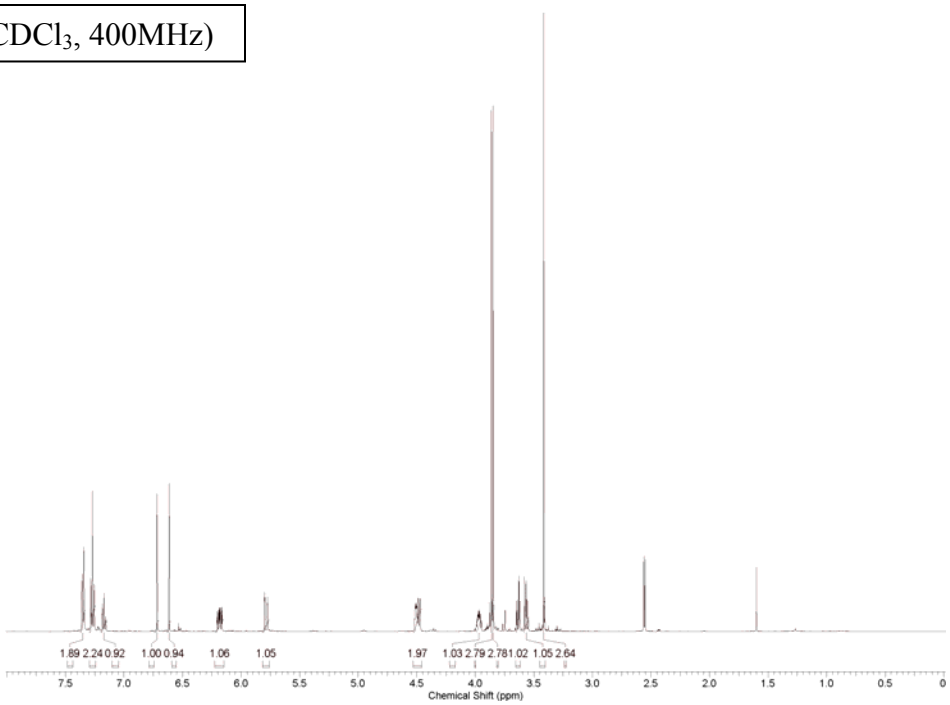
Expansion of
COSY spectrum
for **31-OAc**
(500 MHz, C_6D_6)



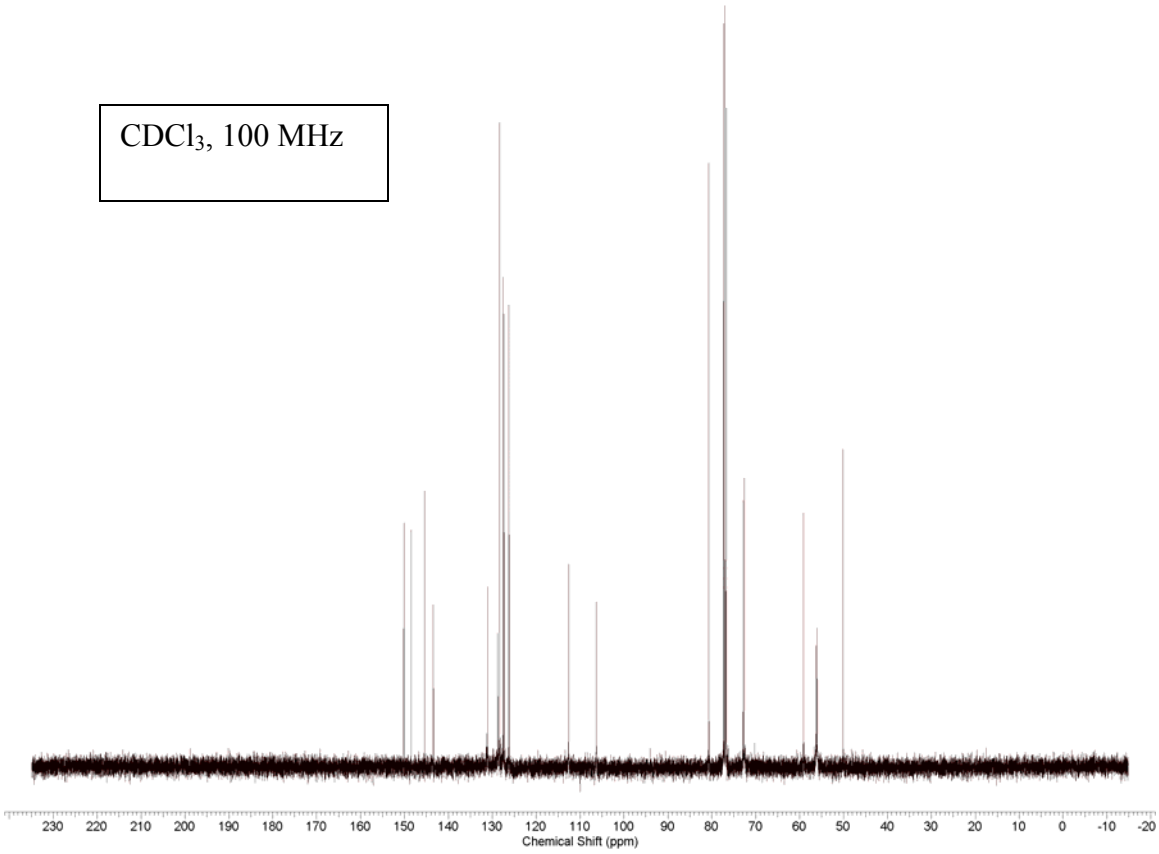


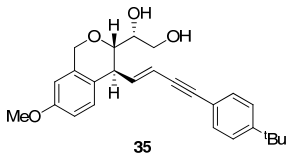
33

($CDCl_3$, 400MHz)



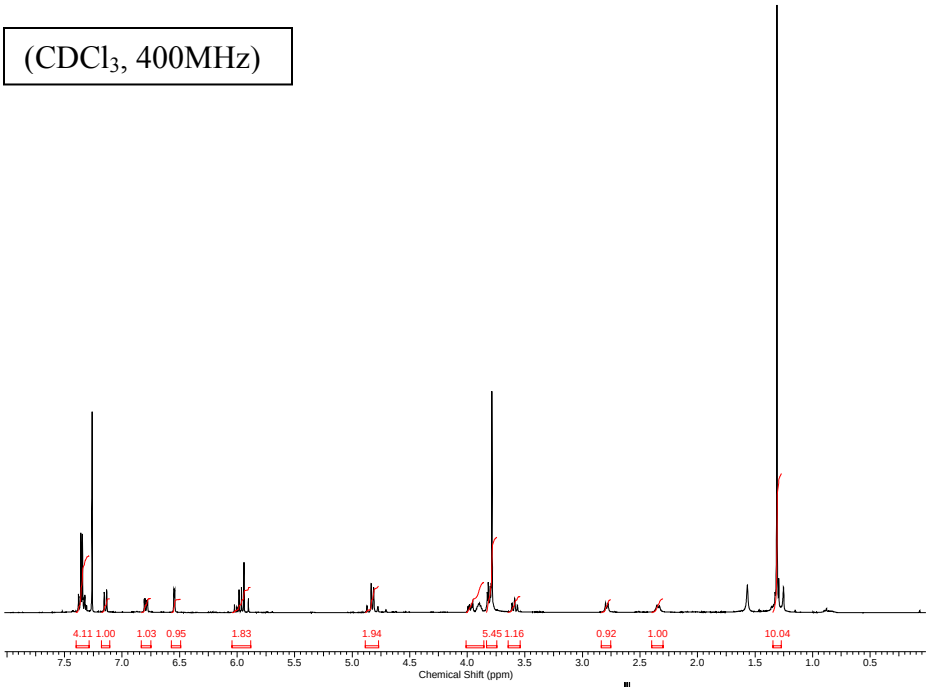
$CDCl_3$, 100 MHz



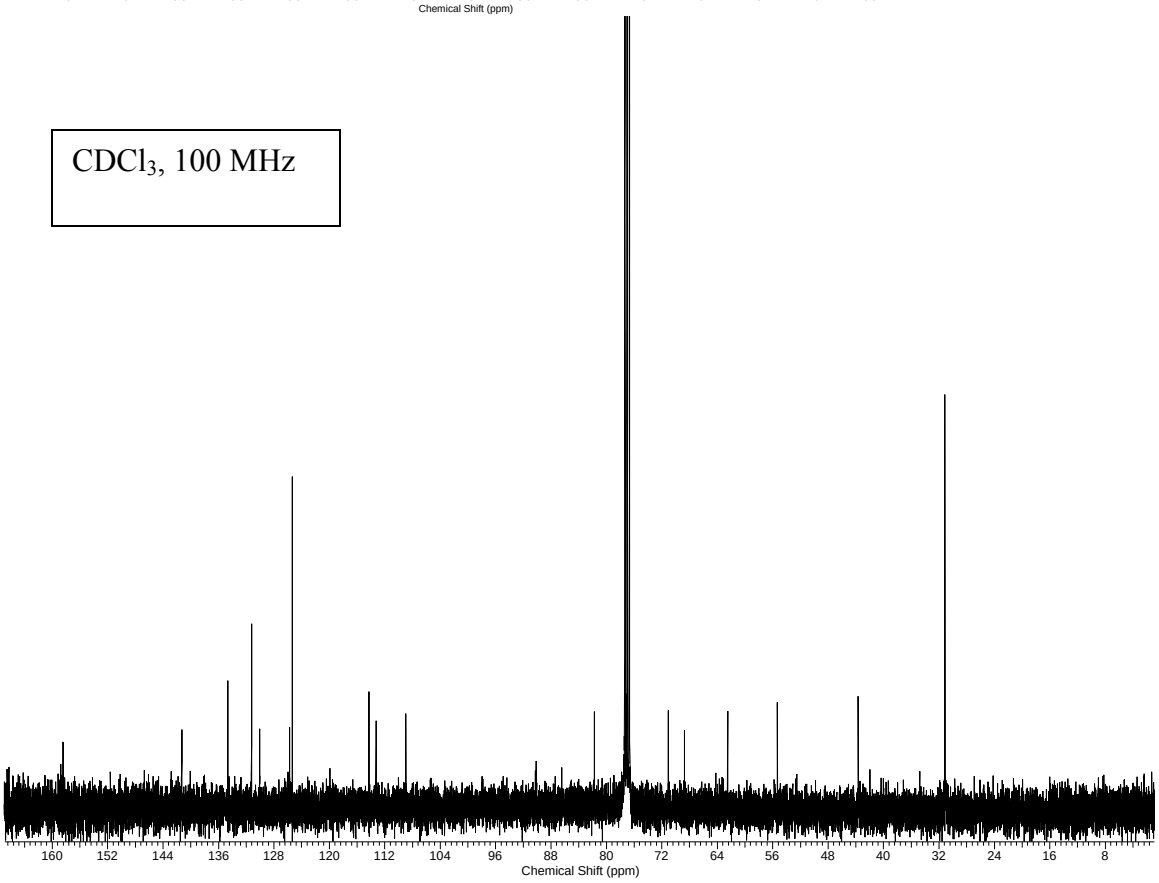


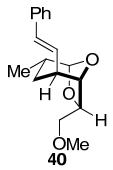
35

($CDCl_3$, 400MHz)



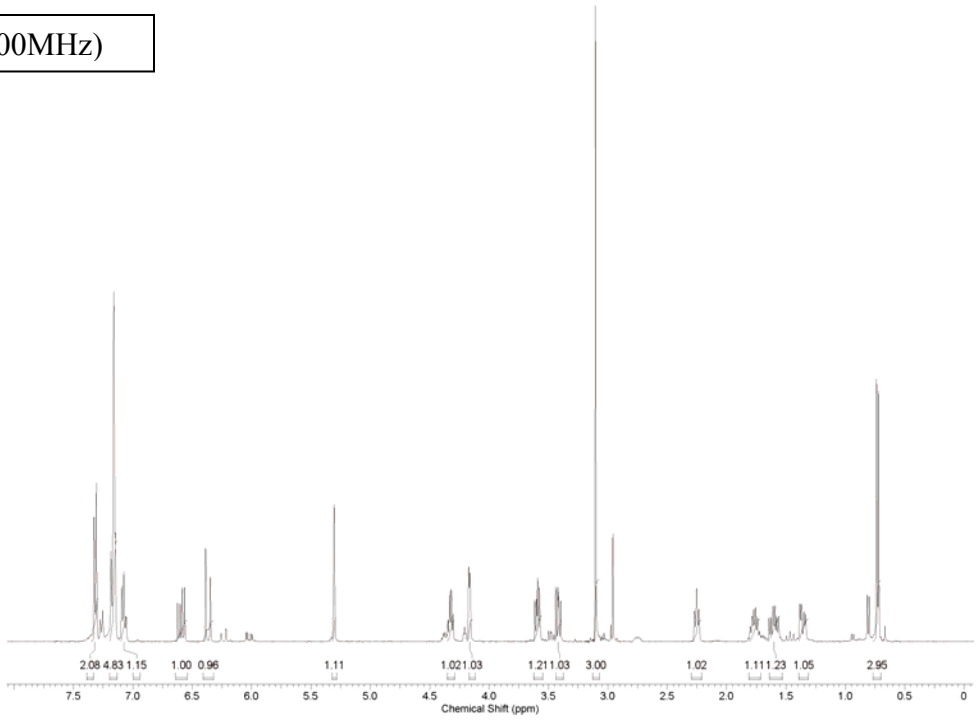
$CDCl_3$, 100 MHz



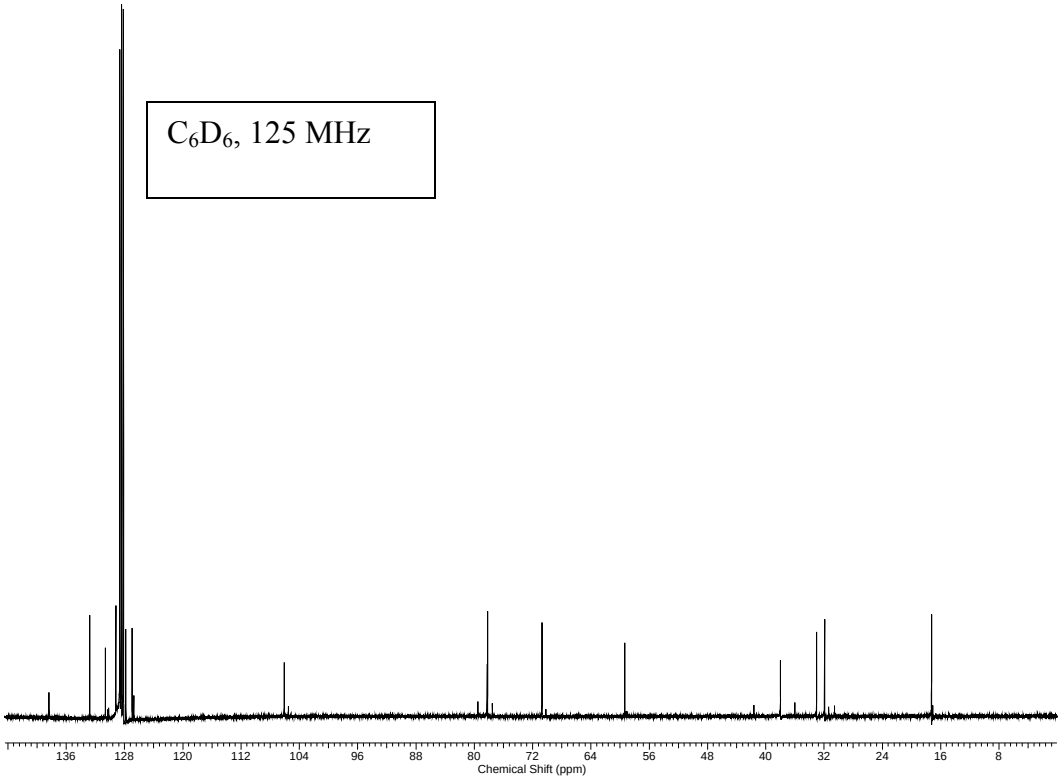


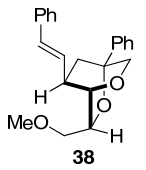
40

(C_6D_6, 500MHz)



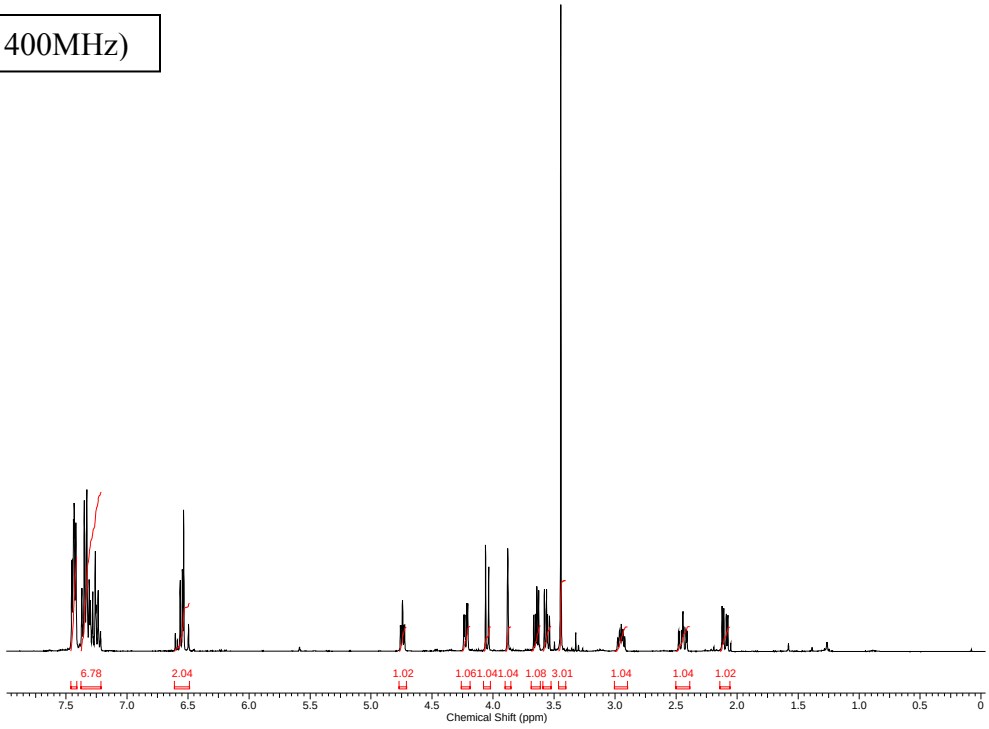
C_6D_6, 125 MHz



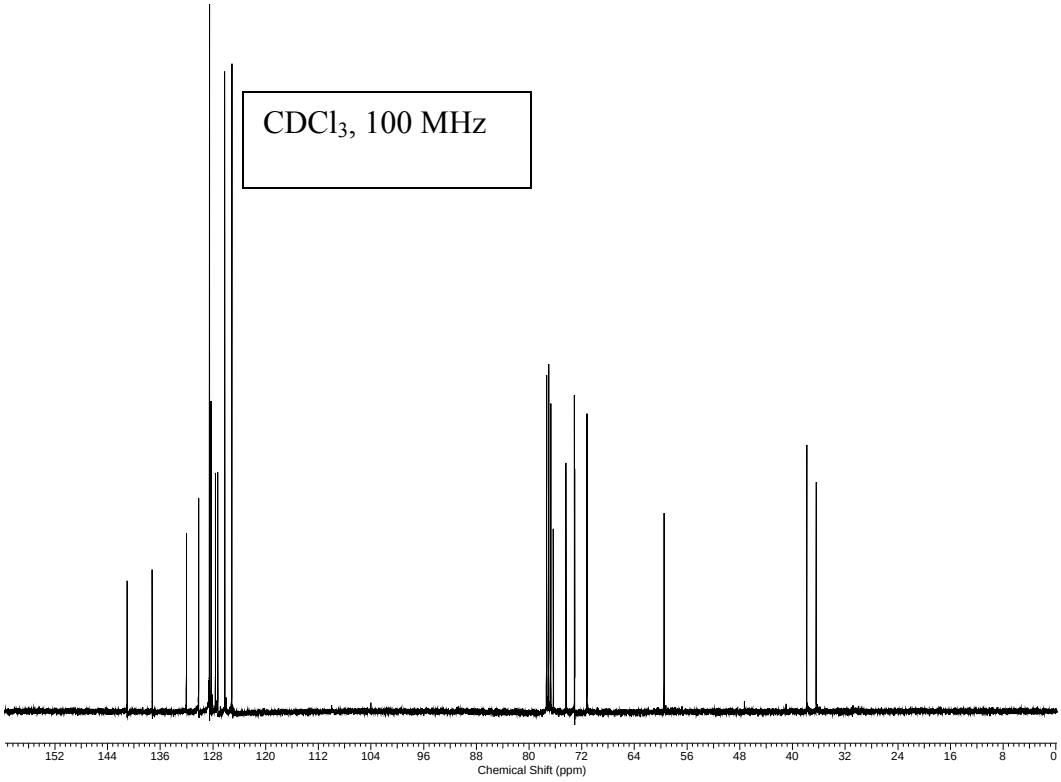


38

($CDCl_3$, 400MHz)



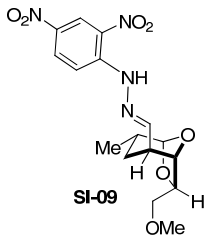
$CDCl_3$, 100 MHz



X. Preparation of SI-09 and X-Ray Crystallographic Data

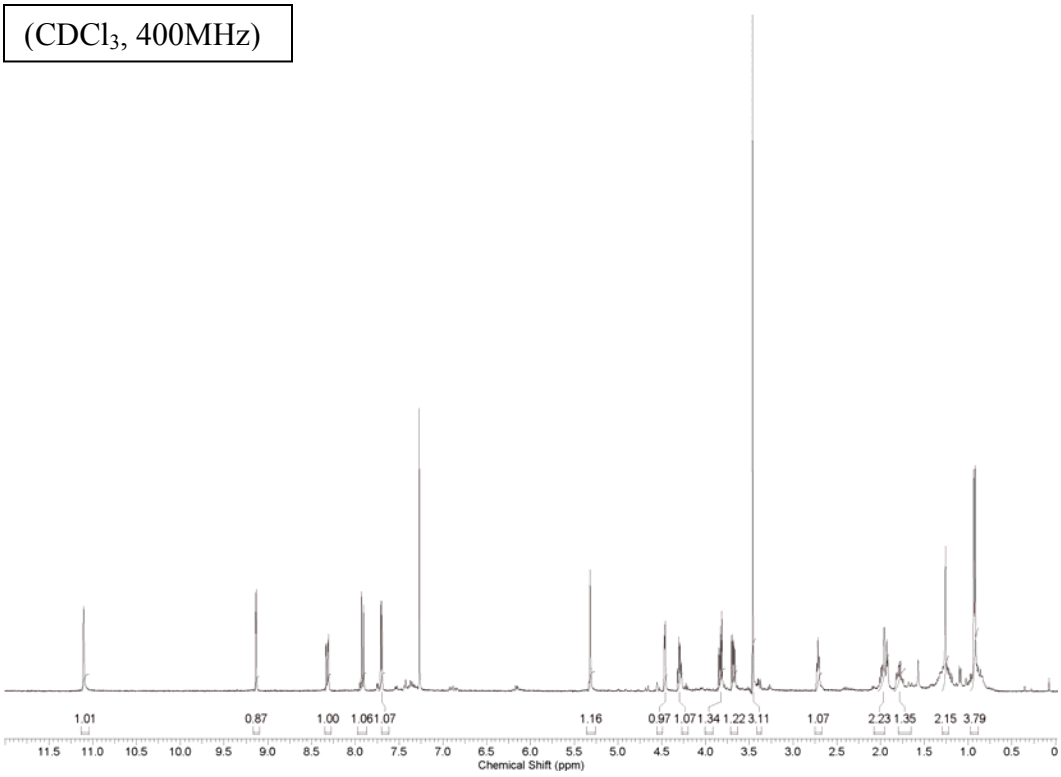
Preparation of (*E*)-1-(2,4-Dinitrophenyl)-2-(((1*S*,2*R*,4*S*,5*S*,7*R*)-7-(methoxymethyl)-4-methyl-6,8-dioxabicyclo[3.2.1]octan-2-yl)methylene)hydrazine (SI-09).
Olefin **40** (230 mg, 0.84 mmol) was dissolved in a mixture of acetone:water (8 mL, 10:1). To this solution was added 2,6-lutidine (195 μL, 1.7 mmol), *N*-methylmorpholine-*N*-oxide (148 mg, 1.3 mmol), and osmium tetraoxide (2.5% in *tert*-BuOH, 0.02 equiv). The reaction was stirred for 12 h in a flask opened to the atmosphere. $PhI(OAc)_2$ (405 mg, 1.3 mmol) was then added and the reaction stirred at room temperature until complete consumption of the intermediate diol was observed by TLC. The reaction was quenched by the addition of 10% aqueous sodium thiosulfate (5 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with saturated aqueous copper sulfate (1 × 10 mL), dried over Na_2SO_4, and concentrated in vacuo.[4] The crude residue was dissolved in absolute EtOH (0.50 mL). To this solution was added 2,4-dinitrophenylhydrazine (183 mg, 0.92 mmol) and the reaction was stirred for 12 hours at room temperature. The crude reaction mixture was concentrated in vacuo and purified by flash chromatography (gradient elution, 99:1 to 60:40, hexanes:EtOAc) to provide **SI-09** (140 mg, 40% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.1 (s, 1H), 9.13 (d, J=2.3 Hz, 1H), 8.32 (app dd, J=9.4, 2.3 Hz, 1H). 7.92 (d, J=9.4 Hz, 1H), 7.70 (d, J=5.1 Hz, 1H), 5.32 (s, 1H), 4.47 (d, J=3.9 Hz, 1H), 4.29 (dd, J=10.9, 6.6 Hz, 1H), 3.83 (dd, J=9.7, 6.6 Hz, 1H), 3.68 (dd, J=9.7, 6.6 Hz, 1H), 3.46 (s, 3H), 2.72 (app t, J=5.7 Hz, 1H), 2.01–1.92 (m, 2H), 1.82–1.76 (m, 1H), 0.93 (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 145.0, 138.0, 130.0, 123.4, 116.4, 105.7, 77.1, 75.4, 69.9, 59.6, 37.2, 32.5, 28.1, 16.6; IR (neat) 3299, 3111, 2929, 1614, 1589, 1515, 1422, 1326, 1306, 1275, 1135, 1098, 1055, 919, 832, 742 cm^{-1}; HRMS $[M+H]^+$: 381.1410 calculated for $C_{16}H_{21}N_4O_7$, observed 381.1489.

[4] Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Org. Lett.* **2010**, *12*, 1552.

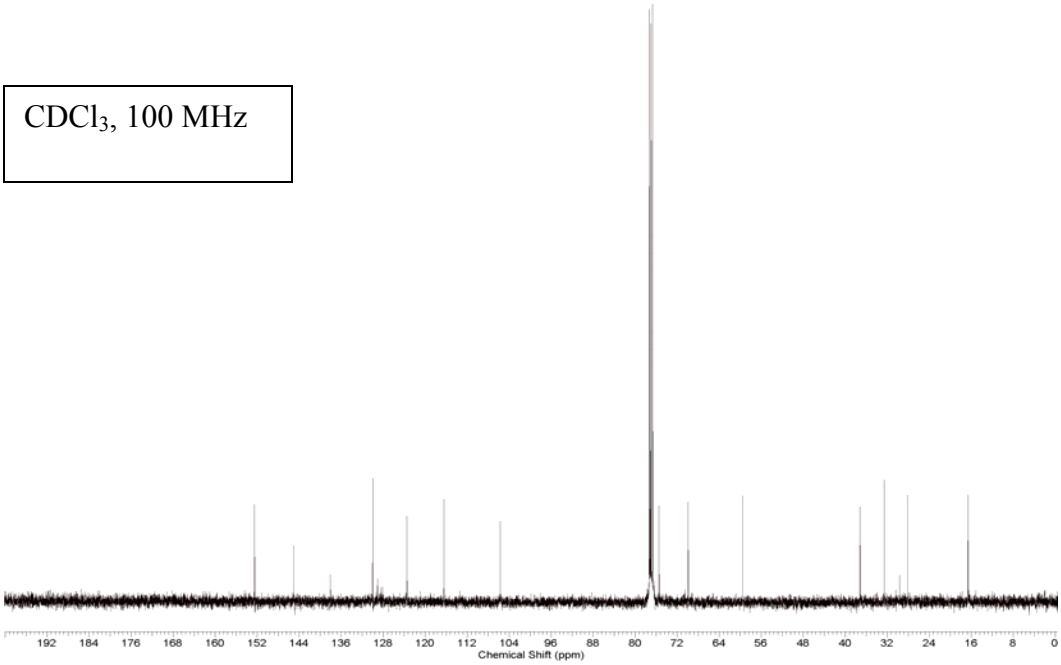


SI-09

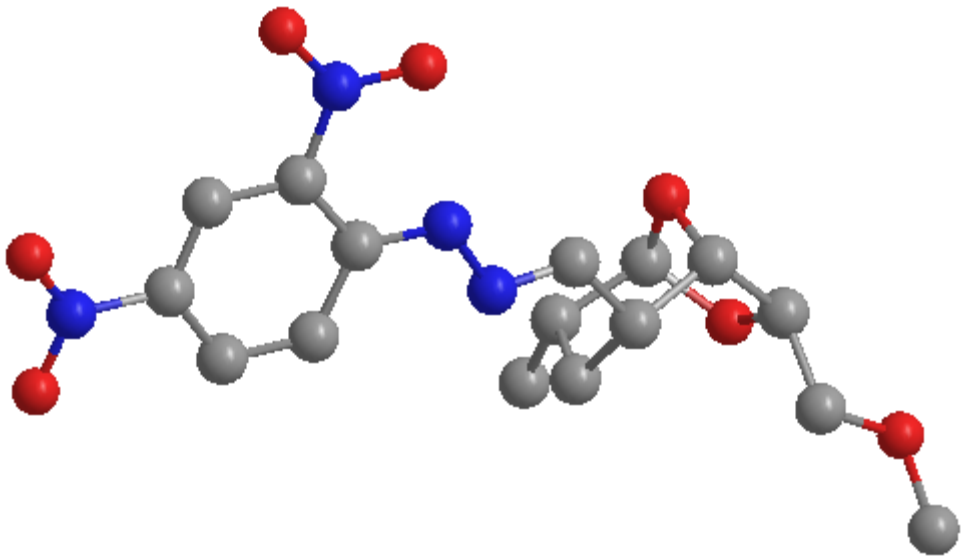
($CDCl_3$, 400MHz)



$CDCl_3$, 100 MHz



X-ray crystallographic data for (*E*)-1-(2,4-dinitrophenyl)-2-(((1*S*,2*R*,4*S*,5*S*,7*R*)-7-(methoxymethyl)-4-methyl-6,8-dioxabicyclo[3.2.1]octan-2-yl)methylene)hydrazine (SI-09)



Crystals suitable for X-ray crystallographic analysis were obtained by slow evaporation of a dilute solution in methanol. CCDC 773799 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table SI-1. Crystal data and structure refinement for compound **SI-09**.

Identification code	Compound **SI-09**
Empirical formula	C16 H20 N4 O7
Formula weight	380.36
Temperature	100(2) K
Wavelength	1.54178 A
Crystal system, space group	Monoclinic, P21
Unit cell dimensions	a = 9.757(8) A alpha = 90 deg. b = 29.99(2) A beta = 98.610(19) deg. c = 11.970(9) A gamma = 90 deg.
Volume	3463(4) A^3
Z, Calculated density	8, 1.459 Mg/m^3
Absorption coefficient	0.987 mm^-1
F(000)	1600
Crystal size	0.30 x 0.14 x 0.12 mm
Theta range for data collection	3.73 to 64.84 deg.
Limiting indices	-11<=h<=11, -35<=k<=29, -14<=l<=12

Reflections collected / unique	26648 / 10178 [R(int) = 0.0259]
Completeness to theta = 64.84	98.9 %
Absorption correction	Analytical
Max. and min. transmission	0.9513 and 0.8340
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	10178 / 1 / 982
Goodness-of-fit on F^2	1.044
Final R indices [I>2sigma(I)]	R1 = 0.0238, wR2 = 0.0628
R indices (all data)	R1 = 0.0242, wR2 = 0.0631
Absolute structure parameter	0.00(7)
Largest diff. peak and hole	0.246 and -0.179 e.A^-3

Table SI-2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for compound SI-09. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	-11222(1)	-1959(1)	-10640(1)	26(1)
O(2)	-5410(1)	1040(1)	-3410(1)	29(1)
O(3)	-8033(1)	1185(1)	-9162(1)	22(1)
O(4)	-7350(1)	1764(1)	-8151(1)	31(1)
O(5)	-5284(1)	1654(1)	-4354(1)	32(1)
O(6)	-12250(1)	-493(1)	-9876(1)	23(1)
O(7)	-12592(1)	-1228(1)	-9528(1)	21(1)
N(1)	-5621(1)	1262(1)	-4290(1)	22(1)
N(15)	-8719(1)	-35(1)	-8094(1)	21(1)
N(2)	-7588(1)	1363(1)	-8237(1)	20(1)
N(16)	-8304(1)	405(1)	-8188(1)	19(1)
C(1)	-10382(2)	-2341(1)	-10427(2)	30(1)
C(2)	-10564(2)	-1569(1)	-10158(1)	22(1)
C(3)	-11598(2)	-1195(1)	-10308(1)	21(1)
C(4)	-11023(2)	-724(1)	-10090(1)	20(1)
C(5)	-9899(2)	-672(1)	-9055(1)	20(1)
C(6)	-9403(2)	-197(1)	-8991(1)	20(1)
C(9)	-7651(1)	618(1)	-7267(1)	18(1)
C(10)	-7308(1)	1081(1)	-7246(1)	18(1)
C(11)	-6658(1)	1289(1)	-6273(1)	19(1)
C(12)	-6307(2)	1040(1)	-5307(1)	20(1)
C(13)	-7256(2)	378(1)	-6240(1)	20(1)
C(14)	-6599(1)	583(1)	-5288(1)	20(1)
C(15)	-10428(2)	-835(1)	-7967(1)	22(1)
C(16)	-11958(2)	-721(1)	-7938(1)	23(1)

C(17)	-12563(2)	-996(1)	-7058(1)	31(1)
C(18)	-12772(2)	-787(1)	-9112(1)	23(1)
O(8)	-10577(1)	1236(1)	-7953(1)	24(1)
O(9)	-15513(1)	-2060(1)	-14275(1)	29(1)
O(10)	-10868(1)	1846(1)	-8930(1)	28(1)
O(11)	-16441(1)	-543(1)	-14389(1)	32(1)
O(12)	-16899(1)	-1243(1)	-13794(1)	27(1)
O(13)	-12430(1)	1157(1)	-13803(1)	21(1)
O(14)	-11836(1)	1774(1)	-12917(1)	27(1)
N(3)	-10910(1)	1438(1)	-8846(1)	19(1)
N(4)	-12845(1)	428(1)	-12698(1)	19(1)
N(5)	-13287(1)	-2(1)	-12521(1)	21(1)
N(6)	-12102(1)	1373(1)	-12915(1)	18(1)
C(19)	-11383(1)	1178(1)	-9860(1)	18(1)
C(20)	-11543(1)	1388(1)	-10886(1)	18(1)
C(21)	-12013(1)	1138(1)	-11854(1)	18(1)
C(22)	-12381(1)	682(1)	-11794(1)	18(1)
C(23)	-13702(2)	-226(1)	-13405(1)	23(1)
C(24)	-14192(2)	-701(1)	-13329(1)	21(1)
C(25)	-15208(2)	-802(1)	-14409(1)	26(1)
C(26)	-15813(2)	-1275(1)	-14486(1)	26(1)
C(27)	-14805(2)	-1646(1)	-14117(1)	26(1)
C(28)	-14605(2)	-2425(1)	-14007(2)	35(1)
C(29)	-12209(2)	487(1)	-10695(1)	19(1)
C(30)	-11706(2)	728(1)	-9754(1)	19(1)
C(31)	-17079(2)	-777(1)	-13568(2)	30(1)
C(32)	-16391(2)	-659(1)	-12390(1)	27(1)
C(33)	-14862(2)	-790(1)	-12260(1)	23(1)
C(34)	-17123(2)	-887(1)	-11496(2)	37(1)
O(15)	-3276(1)	3290(1)	-12840(1)	38(1)
O(16)	-10749(1)	-161(1)	-15597(1)	33(1)
O(17)	-3996(1)	2040(1)	-10631(1)	24(1)
O(18)	-3354(1)	2767(1)	-10726(1)	23(1)
O(19)	-9385(1)	-8(1)	-11725(1)	28(1)
O(20)	-8807(1)	624(1)	-10914(1)	23(1)
O(21)	-10870(1)	411(1)	-16721(1)	24(1)
N(7)	-7646(1)	1710(1)	-12376(1)	20(1)
N(8)	-8273(1)	1315(1)	-12142(1)	20(1)
N(9)	-10580(1)	238(1)	-15784(1)	21(1)
N(10)	-9137(1)	392(1)	-11773(1)	19(1)
C(35)	-3217(2)	3635(1)	-12038(2)	44(1)
C(36)	-4246(2)	2951(1)	-12704(1)	28(1)
C(37)	-3668(2)	2596(1)	-11866(1)	22(1)
C(38)	-4609(2)	2198(1)	-11728(1)	21(1)
C(39)	-6144(2)	2316(1)	-11685(1)	19(1)
C(40)	-6926(2)	1898(1)	-11529(1)	20(1)

C(41)	-8860(1)	1054(1)	-13009(1)	18(1)
C(42)	-9099(1)	1224(1)	-14130(1)	19(1)
C(43)	-9677(1)	969(1)	-15024(1)	19(1)
C(44)	-10018(1)	523(1)	-14841(1)	18(1)
C(45)	-3835(2)	2442(1)	-9994(1)	24(1)
C(46)	-5212(2)	2579(1)	-9663(1)	25(1)
C(47)	-6258(2)	2658(1)	-10738(1)	23(1)
C(48)	-9267(1)	606(1)	-12867(1)	18(1)
C(49)	-9822(1)	340(1)	-13778(1)	18(1)
C(50)	-5072(2)	2989(1)	-8918(1)	33(1)
O(22)	-9585(1)	3656(1)	-7076(1)	32(1)
O(23)	-15878(1)	602(1)	-11207(1)	33(1)
O(24)	-9023(1)	2209(1)	-5517(1)	23(1)
O(25)	-8710(1)	2959(1)	-5291(1)	23(1)
O(26)	-16071(2)	16(1)	-10177(1)	42(1)
O(27)	-14040(1)	-20(1)	-6366(1)	26(1)
O(28)	-13297(1)	575(1)	-5441(1)	22(1)
N(11)	-12731(1)	1777(1)	-6667(1)	21(1)
N(12)	-13093(1)	1337(1)	-6502(1)	20(1)
N(13)	-15704(1)	401(1)	-10296(1)	27(1)
N(14)	-13790(1)	380(1)	-6334(1)	18(1)
C(51)	-9208(2)	3900(1)	-6058(2)	35(1)
C(52)	-10292(2)	3254(1)	-6914(1)	24(1)
C(53)	-9346(2)	2877(1)	-6450(1)	21(1)
C(54)	-10024(2)	2419(1)	-6363(1)	20(1)
C(55)	-11441(2)	2425(1)	-5935(1)	20(1)
C(56)	-11922(2)	1954(1)	-5854(1)	21(1)
C(57)	-13734(1)	1102(1)	-7388(1)	18(1)
C(58)	-14080(2)	642(1)	-7356(1)	19(1)
C(59)	-14720(2)	415(1)	-8302(1)	20(1)
C(60)	-15039(2)	641(1)	-9304(1)	22(1)
C(61)	-8791(2)	2549(1)	-4686(1)	22(1)
C(62)	-9978(2)	2558(1)	-3994(1)	23(1)
C(63)	-11342(2)	2662(1)	-4781(1)	22(1)
C(64)	-14722(2)	1093(1)	-9386(1)	22(1)
C(65)	-14099(2)	1318(1)	-8456(1)	21(1)
C(66)	-9737(2)	2899(1)	-3045(1)	31(1)