Asymmetric Total Synthesis of (-)-Variabilin and (-)-Glycinol

Michael A. Calter* and Na Li
Department of Chemistry, Wesleyan University, Middletown, Connecticut, 06459
mcalter@wesleyan.edu

Supporting Information

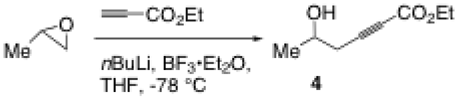
Table of Contents

General Procedures

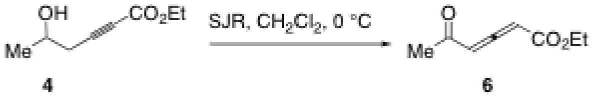
Unless otherwise indicated, all commercial materials were used as received. Chlorotrimethylsilane (TMSCl), N,N'-dimethylethylenediamine, N,N,N'-trimethyl ethylenediamine, dibutyl ether and 1,3-propanediol were distilled over calcium hydride and kept in storage flasks under Ar. THF, DMF, toluene, pyridine, dimethoxy ethane and diethyl ether were used from a solvent purification system by filtering through an activated alumina column. Dichloromethane and diisopropylamine were distilled over CaH_2 before use.

Flash column chromatography was performed on Silicycle 60 Å, 32-63 μm or Dynamic Adsorbents 60 Å, 32-63 μm silica gel, and Dynamic Adsorbents 60 Å, 32-63 μm basic alumina activity III. Thin-layer chromatography (TLC) was accomplished with SiliCycle 0.25 mm, 60 Å pore size silica gel plates or basic alumina (III) plates. TLC plates were visualized using a ceric ammonium molybdate stain or by a UV/Vis lamp.

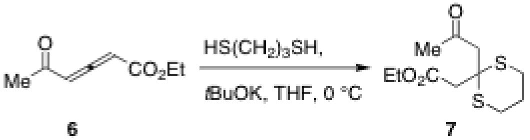
A Varian-300 (300 Hz and 75 Hz) or Varian-400 (400 Hz and 100 Hz) NMR spectrometer were used for ^{1}H and ^{13}C spectra. Specific rotations were taken on a Perkin-Elmer 241 Polarimeter. HPLC analyses were obtained from a Thermo Separation Product Spectra Series P200 HPLC equipped with a Spectra 100 variable UV/Vis detector and a Hewlett Packard HP-3394a integrator. A Perkin Elmer 1605 FT-IR spectrometer was used to collect IR spectra. Atlantic Microlab performed elemental analyses. The UC Riverside Mass Spec Facility performed the mass spectra.



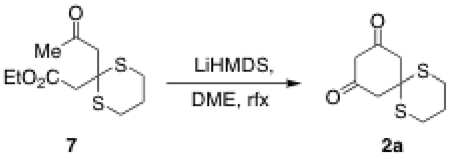
Ethyl 5-hydroxyhex-2-ynoate (4): *n*BuLi (32 ml of a 1.6 M solution in hexanes, 51 mmol) was added dropwise to a solution of ethyl propiolate (5.2 ml, 51 mmol) in THF (90 ml) at -78 °C. The reaction mixture was allowed to stir at this temperature for 30 min. Propylene oxide (1.80 ml, 25.5 mmol) was then added dropwise, immediately followed by boron trifluoride diethyl etherate (6.4 ml, 51 mmol). After an additional 2 h at -78 °C, the solvents were removed under reduced pressure, the residue was diluted with CH_2Cl_2 (100 ml) and then washed with saturated NH_4Cl (80 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 ml). The combined organic layers were dried over Na_2SO_4 and the solvents were evaporated under vacuum. Gradient silica gel flash chromatography (5:1 to 1:1 hexanes:EtOAc) afforded **4** (3.46 g, 87%) as a colorless oil. This compound has been characterized before.[1]



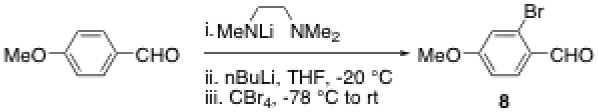
1-Ethylcarboxylate-3-acetoallene (6): 100 ml of Jones reagent (2.5 M, 250 mmol) was added slowly to 120 g of silica gel in a three-neck round bottom flask equipped with a mechanical stirrer. This silica gel-supported Jones reagent (SJR) was stirred until a fine orange powder was formed. CH_2Cl_2 (500 ml) was then added and the suspension was cooled to 0 °C. **4** (7.8 g, 50 mmol) in CH_2Cl_2 (50 ml) was added over 10 min and the suspension was stirred at 0 °C for 30 min. The suspension was filtered through a plug of celite and washed with CH_2Cl_2 (2 × 100 ml). The filtrate was dried over Na_2SO_4 and concentrated under reduced pressure at room temperature to give **6** as a bright yellow oil (7.7 g, 100%): IR (neat) 1948, 1719, 1685, 1255, 1153 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.08 (d, J = 6.0 Hz, 1H), 6.01 (d, J = 6.0 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 2.23 (s, 3H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 221.4, 195.3, 163.1, 100.5, 92.3, 61.7, 27.5, 14.2.



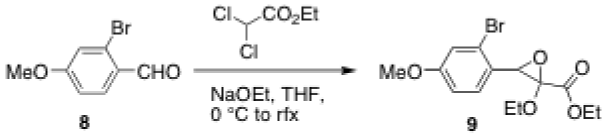
5-Oxo-3-(1,3-dithiane)-hexanoic acid ethyl ester (7): Potassium *t*-butoxide (2.50 g, 22.4 mmol) was added in portions to a solution of **6** (6.90 g, 44.8 mmol) and 1,3-propanedithiol (5.0 ml, 49 mmol) in THF (80 ml) at 0 °C. After 1 h at 0 °C, the solvents were removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (100 ml) and washed with saturated NH_4Cl (100 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 100 ml). The organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Silica gel flash chromatography (4:1 hexanes:EtOAc) yielded **7** (9.74 g, 83%) as a white solid. This compound has been characterized before.[2]



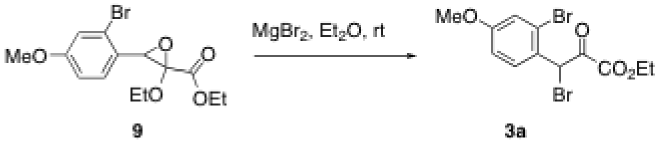
5-(1,3-Dithiane)-1,3-cyclohexadione (2a): **7** (2.65 g, 10.1 mmol) in dimethoxy ethane (10 ml) was added to a solution of LiHMDS (10.1 ml of a 1.0 M solution in THF, 10.1 mmol) in 30 ml of dimethoxy ethane at 0 °C. The reaction mixture was heated to reflux for 12 h. The solvents were removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (40 ml). The organic layer was washed with 2 N acetic acid (10 ml) and the aqueous layer was extracted with CH_2Cl_2 (2 × 40 ml). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo.* Recrystallization from hexanes/EtOAc afforded **2a** (1.42 g, 65%) as a white solid: IR (neat) 1585, 1501, 1321, 1230, 1106 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 11.32 (bs, 1H), 5.18 (s, 1H), 2.82-2.89 (m, 8H), 1.84 (m, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 102.7, 47.3, 44.9, 25.8, 24.8.



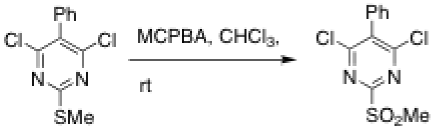
2-Bromo-4-methoxybenzaldehyde (8): This procedure was reported before.[3] To a solution of N,N,N'-trimethyl ethylenediamine (0.620 ml, 4.85 mmol) in THF (10 ml) at -20 °C was added nBuLi (2.90 ml of a 1.6 M solution in hexanes, 4.63 mmol). After 15 min, 4-methoxybenzaldehyde (0.600 g, 4.41 mmol) was added at -20 °C. The mixture was stirred for 15 min, and *n*BuLi (8.20 ml of a 1.6 M solution in hexanes, 13.2 mmol) was added. After another 30 min at -20 °C, the mixture was put in a fridge (-7 °C) for 22 h. The reaction mixture was then cooled to -78 °C and treated with carbon tetrabromide (4.70 g, 14.1 mmol). The reaction mixture was allowed to warm to room temperature. 10% aqueous HCl (20 ml) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 ml). The combined organic phases were dried over Na_2SO_4 and the solvents were removed *in vacuo*. Silica gel flash chromatography (9:1 hexanes:EtOAc,) afforded **8** (0.5 g, 53%) as a white solid. This compound has been previously characterized.[3]



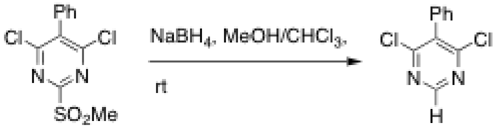
Ethyl 3-(2-bromo-4-methoxyphenyl)-2-ethoxyoxirane-2-carboxylate (9): To a solution of sodium ethoxide, made by dissolving 0.960 g of sodium (41.7 mmol) in 26 ml of anhydrous ethanol, was added a solution of **8** (4.50 g, 20.9 mmol) and ethyl dichloroacetate (3.60 ml, 29.3 mmol) in THF (42 ml) at 0 °C via cannula. The suspension was then heated at reflux for 6 h. After removing all the solvent *in vacuo*, the residue was diluted with CH_2Cl_2 (50 ml) and washed with saturated NH_4Cl (40 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 40 ml). The combined organic layers were dried (Na_2SO_4) and the solvents were evaporated *in vacuo*. Silica gel flash chromatography (85:15 hexanes:EtOAc) provided **9** (5.0 g, 72%) as a colorless oil: IR (neat) 1738, 1605, 1498, 1305, 1181, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20 (d, *J* = 8.7 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.83 (dd, *J* = 2.4, 8.7 Hz, 1H), 4.46 (s, 1H), 4.28-4.34 (m, 2H), 3.72-3.80 (m, 5H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.9, 160.2, 129.4, 124.2, 123.1, 117.5, 113.1, 82.9, 77.6, 77.2, 76.7, 64.2, 63.7, 62.3, 55.5, 15.0, 14.2.



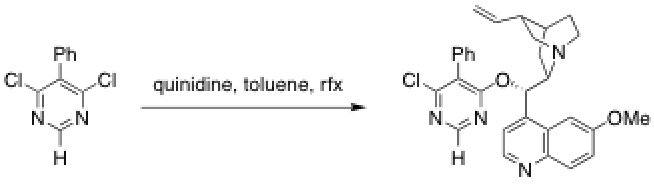
Ethyl 3-bromo-3-(2-bromo-4-methoxyphenyl)-2-oxopropanoate (3a): To a solution of **9** (1.25 g, 3.72 mmol) in Et_2O (37 ml) was added magnesium bromide (1.37 g, 7.45 mmol) in portions at room temperature for 2 h. Deionized water (30 ml) was then added and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 × 40 ml). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Silica gel flash chromatography (3:1 hexanes:EtOAc) provided **3a** as a light yellow oil (1.1 g, 80%): IR (neat) 1726, 1597, 1492, 1298, 1235, 1055, 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43 (d, *J* = 8.7 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.70 (s, 1H), 4.29-4.37 (m, 2H), 3.80 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.1, 160.9, 159.8, 132.4, 125.0, 124.8, 118.6, 114.5, 63.4, 55.8, 49.6, 14.0.



4,6-Dichloro-2-(methylsulfonyl)-5-phenylpyrimidine: 4,6-Dichloro-2-thiomethyl-5-phenylprimidine (3.00 g, 11.1 mmol) was dissolved in 30 ml of $CHCl_3$ at room temperature. MCPBA (6.00 g of 70% mixture, 24.3 mmol) was added in portions over a period of 5 min. The reaction mixture was held overnight and then washed with saturated $NaHCO_3$ (2 × 30 ml). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford a white powder: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.56 (m, 3H), 7.32 (m, 2H), 3.41 (s, 3H).

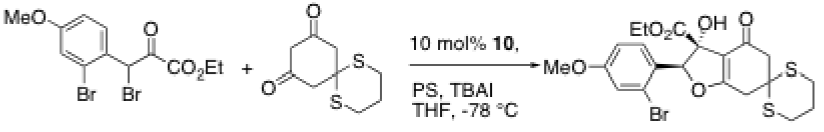


4,6-Dichloro-5-phenylpyrimidine: Sodium borohydride (0.750 g, 19.8 mmol) was added to sulfone (6.00 g, 19.8 mmol) in MeOH (80 ml) and $CHCl_3$ (80 ml) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 30 min. The solvents were evaporated under vacuum and the residue was redissolved in CH_2Cl_2 (100 ml) and H_2O (100 ml) was added with vigorous stirring. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 ml). The combined organic layers were dried over Na_2SO_4 and the concentrated *in vacuo*. Silica gel flash chromatography (7:3 hexanes:diethyl ether) provided the product as a white powder (3.6 g, 81%): ^1H NMR ($CDCl_3$, 400 MHz) δ 8.80 (s, 1H), 7.53 (m, 3H), 7.32 (m, 2H).



10

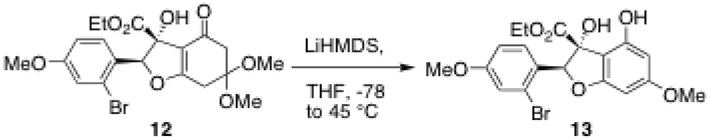
6-Chloro-5-Phenylpyrimidine-4-(9-O-quinidine) ether (10): Powdered potassium hydroxide (0.20 g, 3.6 mmol) was added to quinidine (0.58 g, 1.8 mmol) in toluene (40 ml) and the mixture was heated to reflux in a Dean-Stark apparatus for 1 h. 4,6-Dichloro-5-phenylpyrimidine (0.48 g, 2.1 mmol) was added and the mixture continued to stir at reflux for 1 h, after which time additional powdered potassium hydroxide (0.10 g, 1.8 mmol) was added. The reaction mixture was held for another hour at reflux. The solvents were then removed *in vacuo* and the residue was dissolved in CH_2Cl_2 (50 ml) and washed with H_2O (3 × 30 ml). The organic layer was dried over Na_2SO_4 and the solvents were removed under reduced pressure. Flash column chromatography (basic alumina (III), 1:1 hexanes:EtOAc) produced **10** (0.74 g, 81%) as a white solid: $[\alpha]_D^{23}$ = -101.8° (*c* 1.0, CH_2Cl_2); IR (neat) 2933, 1536, 1418, 1227, 991 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.68 (d, *J* = 4.5 Hz, 1H),8.36 (s, 1H), 8.00 (d, *J* = 9 Hz, 1H), 7.46-7.56 (m, 3H), 7.30-7.39 (m, 4H), 7.21 (d, *J* = 4.5 Hz, 1H), 6.95 (bs, 1H), 5.32-5.44 (m, 1H), 4.88-4.97 (m, 2H), 3.84 (s, 3H), 3.14-3.22 (m, 1H), 2.60-2.87 (m, 4H), 2.07-2.16 (m, 1H), 1.68-1.76 (m, 2H), 1.64 (s, 1H), 1.41-1.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6, 159.8, 157.9, 156.3, 147.4, 144.7, 143.5, 140.2, 131.9, 131.6, 129.8, 128.8, 128.7, 126.7, 121.8, 121.4, 118.6, 114.8, 101.5, 78.1, 59.2, 55.6, 50.0, 49.6, 40.3, 28.2, 26.2, 22.6; HRMS: *m/z* Calcd for $C_{30}H_{30}N_4O_2ClH^+$, 513.2052; Found, 513.2051.



3a 2a 11

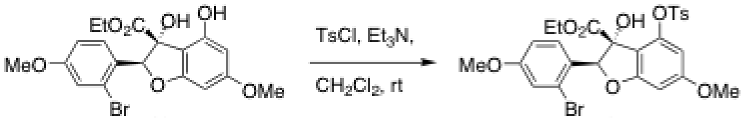
Ethyl 2-(2-bromo-4-methoxyphenyl)-2,3,4,5,6,7-hexahydro-3-hydroxy-4-oxo-6-(1,3-dithiane)benzofuran-3-carboxylate (11): To a solution of **2a** (0.711 g, 3.29 mmol), proton sponge (1.42 g, 6.58 mmol), **10** (0.17 g, 0.33 mmol) and tetrabutylammonium iodide (2.43 g, 6.58 mmol) in THF (30 ml) at -78 °C was added **3a** (2.50 g, 6.58 mmol) in 5 ml of THF (also at -78 °C) via cannula dropwise. The reaction mixture was held for 30 min at -78 °C and then concentrated *in vacuo*. The residue was redissolved in CH_2Cl_2 (50 ml) and washed with saturated $NaHCO_3$ (30 ml). The separated organic layer was washed again with 1 N $NaHSO_4$ (15 ml). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo.* ^1H NMR analysis of the unpurified reaction mixture showed an 8.5:1 *E*:*Z* mixture of diastereomers. Silica gel chromatography (9.5:0.5:0.05 CH_2Cl_2:EtOAc:MeOH,) gave **11** (0.83 g, 49%) as a white foam as a mixture of diastereomers (9:1 *E*:*Z*). Data for the pure *E*-isomer: $[\alpha]_D^{23}$ = +31.2° (*c* 1.0, CH_2Cl_2); IR (neat) 1733, 1647, 1495, 1239, 1212, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.05-7.11 (m, 2H), 6.84 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.15 (s, 1H), 4.32 (s, 1H), 3.84-3.91 (m, 1H), 3.78 (s, 3H), 3.54-3.61 (m, 1H), 3.24 (s, 2H), 2.85-3.12 (m, 6H), 2.00-2.10 (m, 2H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.8, 176.0, 170.4, 160.2, 129.1, 126.4, 122.5, 117.5, 114.9, 113.6, 95.6, 84.7, 77.4, 62.6, 55.8, 49.4, 48.3, 38.1, 26.9, 24.9, 13.7; Anal. Calcd. for $C_{21}H_{23}BrO_6S_2$ (515.4): C, 48.93; H, 4.50. Found: C, 49.02; H, 4.58.

Ethyl 2-(2-bromo-4-methoxyphenyl)-2,3,4,5,6,7-hexahydro-3-hydroxy-6,6-dimethoxy-4-oxobenzofuran-3-carboxylate (12): PIFA (1.63 g, 3.80 mmol) was added to a solution of **11** (0.700 g, 1.35 mmol) in 27 ml of anhydrous MeOH. After 30 min, triethylamine (2 ml) was added. After removal of the solvents under reduced pressure, silica gel column chromatography (4:6 hexanes:EtOAc) yielded **12** (0.42 g, 67%) as a mixture of diastereomers (9:1 *E*:*Z*): $[\alpha]_D^{23}$ = +34.7° (*c* 1.0, CH_2Cl_2); IR (neat) 1734, 1648, 1495, 1237, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31 (d, *J* = 8.7 Hz, 1H *Z*), 7.06-7.10 (m, 1H *Z* and 2H *E*), 6.90 (dd, *J* = 2.4, 8.7 Hz, 1H *Z*), 6.84 (dd, *J* = 2.4, 8.7 Hz, 1H *E*), 6.26 (s, 1H *Z)*, 6.14 (s, 1H *E*), 4.31-4.40 (m, 2H *Z*), 4.30 (s, 1H *E*), 3.82-3.91 (m, 1H *E*), 3.78 (s, 3H *Z* and 3H *E*), 3.50-3.61 (m, 1H *E*), 3.27 (s, 6H *Z*), 3.25 (s, 6H, *E*), 2.89-3.04 (m, 2H *Z* and 2H *E*), 2.71-2.83 (m, 22H *Z* and 2H *E*), 1.32 (t, *J* = 7.2 Hz, 3H *Z*), 0.88 (t, *J* = 7.2 Hz, 3H *E*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.6, 189.5, 177.4, 176.9, 172.6, 170.5, 160.5, 160.2, 130.6, 128.9, 126.6, 124.6, 122.7, 122.5, 117.6, 116.7, 115.4, 113.7, 113.6, 101.5, 101.4, 95.7 92.4, 84.8, 79.8, 77.4, 63.5, 62.5, 55.7, 48.9, 48.8, 45.4, 34.1, 33.9, 14.3, 13.6.



12 **13**

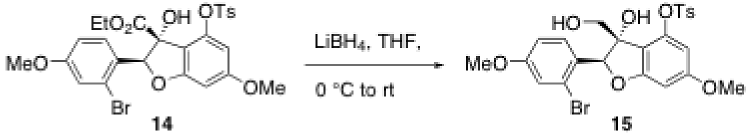
Ethyl 2-(2-bromo-4-methoxyphenyl)-2,3-dihydro-3,4-dihydroxy-6-methoxybenzofuran-3-carboxylate (13): To a solution of **12** (0.37 g, 0.78 mmol) in anhydrous THF (8 ml) at -78 °C was added LiHMDS (3.2 ml of a 1 M solution in THF, 3.2 mmol) was added dropwise. The reaction mixture was allowed to warm to -45 °C over a period of 10 min and stirred for 1 h at -45 °C. The mixture was then diluted with CH_2Cl_2 (20 ml) and washed with saturated NH_4Cl (10 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 ml). The combined organic layers were dried (Na_2SO_4) and the solvents were removed *in vacuo*. Silica gel flash chromatography (6:4 hexanes:EtOAc) gave **13** (0.29 g, 84%) as a white foam as a mixture of diastereomers (9:1 *E*:*Z*): $[\alpha]_D^{23}$ = +66.9° (*c* 1.0, CH_2Cl_2); IR (neat) 3394, 1727, 1603, 1235, 1140 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40 (d, *J* = 8.7 Hz, 1H *Z*), 7.33 (d, *J* = 8.7 Hz, 1H *E*), 7.08 (d, *J* = 2.4 Hz, 1H *Z* and 1H *E*), 6.89 (dd, *J* = 2.4, 8.7 Hz, 1H *Z*), 6.82 (dd, *J* = 2.4, 8.7 Hz, 1H *E*), 6.30 (s, 1H *Z*), 6.15 (d, *J* = 1.8 Hz, 1H *Z* and 1H *E*), 6.13 (s, 1H, *E*), 6.02 (d, *J* = 1.8 Hz, 1H *Z* and 1H *E*), 4.35-4.40 (m, 2H *Z*), 3.82-3.93 (m, 1H *E*), 3.78 (s, 3H *Z* and 3H *E*), 3.64-3.73 (m, 1H *E*), 1.34 (t, *J* = 7.2 Hz, 3H, *Z*), 0.91 (t, *J* = 7.2 Hz, 3H *E*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.6, 171.8, 164.2, 162.9, 160.3, 160.2, 154.2, 153.9, 130.4, 129.3, 127.9, 126.5, 122.7, 117.8, 117.7, 113.8, 113.7, 105.9, 105.6, 95.9, 93.5, 89.6, 89.5, 89.4, 86.1, 81.2,77.4, 63.6, 62.8, 60.6, 55.8, 55.7, 14.3, 13.7.



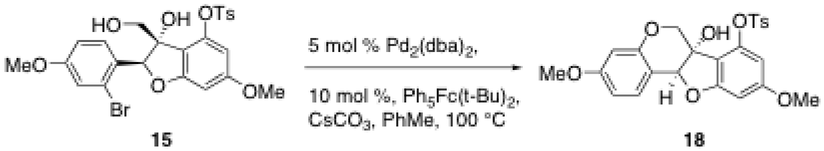
13 **14**

3-(Ethoxycarbonyl)-2-(2-bromo-4-methoxyphenyl)-2,3-dihydro-3-hydroxy-6-methoxybenzofuran-4-yl 4-methylbenzenesulfonate (14): To a solution of **13** (0.27 g, 0.61 mmol) and triethylamine (0.340 ml, 2.44 mmol) in CH_2Cl_2 (6.1 ml) was added tosyl chloride (0.18 g, 0.92 mmol). The reaction solution was stirred for 3 h at room temperature, after which time the solvent was removed under reduced pressure. Silica gel flash chromatography (4:6 hexanes:diethyl ether,) produced **14** (0.31 g, 85%) as a white foam. The enantiomeric excess and diastereomeric ratio were determined by analytical

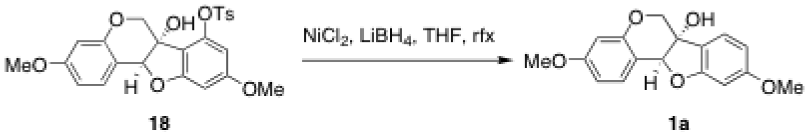
HPLC (Chiralpak AD column, 80:20 hexanes:*i*PrOH, 1.0 ml/min, 280 nm) $R_{t(2R,3S)}$ = 27.3 min, $R_{t(2S,3S)}$ = 33.7 min, $R_{t(2S,3R)}$ = 41.9 min, $R_{t(2R,3R)}$ = 46.8 min, ee = 94%, dr = 95:5 (*E*/*Z*), data for the mixture of diastereomers: $[\alpha]_D^{23}$ = +28.7° (*c* 1.0, CH_2Cl_2); IR (neat) 1732, 1627, 1494, 1237, 1131 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.82 (d, *J* = 8.1 Hz, 2H *Z* and 2H *E*), 7.47 (d, *J* = 8.7 Hz, 1H *Z*), 7.34 (d, *J* = 8.1 Hz, 2H *Z* and 2H *E*), 7.18 (d, *J* = 8.7 Hz, 1H *E*), 7.05 (d, *J* = 2.4 Hz, 1H *Z* and 1H *E*), 6.89 (dd, *J* = 2.4, 8.7 Hz, 1H *Z*), 6.78 (dd, *J* = 2.4, 8.7 Hz, 1H *E*), 6.46 (d, *J* = 1.8 Hz, 1H *Z* and 1H *E*), 6.39 (d, *J* = 1.8 Hz, 1H *E*), 6.28 (s, 1H *Z*), 6.24 (d, *J* = 1.8 Hz, 1H *Z*), 6.12 (s, 1H *E*), 4.35 (s, 1H *E*), 4.29-4.32 (m, 2H *Z*), 3.78-3.89 (m, 1H *E*), 3.76 (s, 3H *Z* and 3H *E*), 3.60-3.72 (m, 1H *E*), 2.44 (s, 3H *Z* and 3H *E*), 1.28 (t, *J* = 7.2 Hz, 3H *Z*), 0.83 (t, *J* = 7.2 Hz, 3H *E*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.4, 170.7, 163.4, 163.3, 163.1, 162.5, 160.3, 160.1, 146.3, 145.9, 145.8, 132.8, 132.6, 131.4, 129.9, 129.3, 128.9, 128.8, 128.7, 127.8, 125.6, 122.6, 122.4, 117.6, 117.5, 113.6, 113.5, 112.8, 101.7, 101.6, 95.3, 94.9, 94.5, 91.0, 84.6, 79.6, 77.4, 63.4, 62.7, 56.0, 55.7, 21.7, 14.1, 13.6; Anal. Calcd. for $C_{26}H_{25}BrO_9S$ (593.4): C, 52.62; H, 4.25. Found: C, 52.89; H, 4.27.



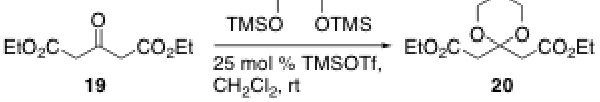
2-(2-Bromo-4-methoxyphenyl)-2,3-dihydro-3-hydroxy-3-(hydroxymethyl)-6-methoxybenzofuran-4-yl 4-methylbenzenesulfonate (15): Lithium borohydride (0.46 ml of a 2 M solution in THF, 0.92 mmol) was added dropwise to a solution of **14** (0.27 g, 0.46 mmol) in THF (5 ml) at 0 °C. The mixture was held at room temperature overnight. Saturated NH_4Cl (5 ml) was added slowly and the solution was extracted with CH_2Cl_2 (3 × 10 ml). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The unpurified mixture was subjected to a second reduction and work-up under identical conditions. Silica gel flash chromatography (6:4 hexanes:EtOAc with 1% added triethylamine) provided **15** (0.21 g, 83%) as a white foam with as a mixture of diastereomers (9:1 *E*:*Z*): $[\alpha]_D^{23}$ = -42.2° (*c* 1.0, CH_2Cl_2); IR (neat) 3500, 1626,1596, 1352, 1137, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.86 (d, *J* = 8.1 Hz, 2H *Z* and 2H *E*), 7.39 (d, *J* = 8.1 Hz, 2H *Z* and 2H *E*), 7.12 (d, *J* = 2.4 Hz, 1H *Z* and 1H *E*), 7.08 (d, *J* = 8.7 Hz, 1H *Z* and 1H *E*), 6.89 (dd, *J* = 2.4, 8.7 Hz, 1H *Z*), 6.78 (dd, *J* = 2.4, 8.7 Hz, 1H *E*), 6.44 (d, *J* = 1.8 Hz, 1H *Z* and 1H *E*), 6.12 (s, 1H *Z*), 6.10 (s, 1H *E*), 5.97 (d, *J* = 2.1 Hz, 1H *Z*), 5.95 (d, *J* = 2.1 Hz, 1H *E*), 4.07-4.10 (m, 1H *Z*), 3.98-4.01 (m, 1H *Z*), 3.83 (s, 1H *E*), 3.80 (s, 3H *Z*), 3.78 (s, 3H *E*), 3.68 (s, 3H *Z* and 3H *E*), 3.53-3.60 (m, 1H *E*), 2.48 (s, 3H *Z* and 3H *E*), 2.14 (bs, 1H *Z*), 1.76 (bs, 1H *E*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.5, 163.3, 162.9, 160.3, 160.1, 146.5, 146.4, 146.3, 132.3, 132.2, 131.4, 130.2, 128.9, 128.7, 127.9, 126.1, 123.9, 117.9, 117.8, 114.0, 113.8, 113.7, 113.6, 102.0, 101.9, 95.9, 95.7, 93.4, 88.5, 83.9, 81.8, 77.4, 65.1, 64.7, 55.9, 55.7, 21.9.



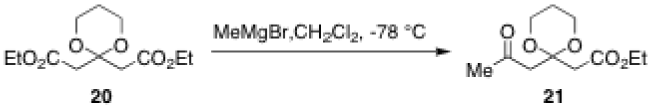
6a,11a-Dihydro-6a-hydroxy-3,9-dimethoxy-6*H*-benzofuro[3,2-*c*]chromen-7-yl 4-methylbenzenesulfonate (18): A 50 ml round bottom flask was charged with **15** (135 mg, 0.240 mmol), $Pd_2(dba)_3$ (13.0 mg, 0.012 mmol), $Ph_5FcP(t\text{-}Bu)_2$ (17.0 mg, 0.024 mmol) and Cs_2CO_3 (120 mg, 0.360 mmol). The flask was placed into a preheated 100 °C oil bath and anhydrous toluene (16 ml) was added in three aliquots. The mixture was held at 100 °C for 3 h under Ar. After removing all solvents *in vacuo*, the residue was diluted with CH_2Cl_2 (15 ml) and washed with saturated brine (15 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel flash chromatography (6:4 hexanes:EtOAc) afforded **18** (81 mg, 70%) as a white foam: $[\alpha]_D^{23}$ = -314.4° (*c* 1.0, CH_2Cl_2); IR (neat) 1620, 1593, 1350, 1130, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.87 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 1H), 6.60 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.37 (d, *J* = 2.4 Hz, 1H), 6.29 (d, *J* = 2.1 Hz, 1H), 5.78 (d, *J* = 2.1 Hz, 1H), 5.52 (s, 1H), 4.60 (d, *J* = 11.4 Hz, 1H), 4.16 (d, *J* = 11.4 Hz, 1H), 3.90 (s, 1H), 3.73 (s, 3H), 3.58 (s, 3H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.1, 163.0, 161.1, 156.3, 146.4, 146.2, 131.9, 131.7, 130.2, 128.9, 113.4, 113.3, 109.8, 102.1, 101.6, 96.7, 86.6, 76.7, 68.7, 55.8, 55.4, 21.9; HRMS: *m/z* Calcd for $C_{24}H_{22}O_8SNa^+$, 493.0928; Found, 493.0926.



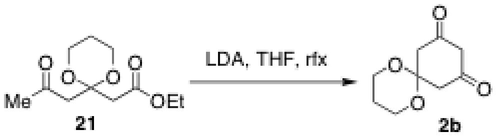
6a,11a-Dihydro-3,9-dimethoxy-6*H*-benzofuro[3,2-*c*]chromen-6a-ol ((-)-variabilin, 1a): Lithium borohydride (0.32 ml of a 2 M solution in THF, 0.65 mmol) was added dropwise to a mixture of **18** (0.06 g, 0.13 mmol) and nickel (II) chloride (0.016 g, 0.130 mmol) in THF (10 ml). The solution turned to black slowly and was heated at reflux for 4 h, after which time nickel (II) chloride (0.008 g, 0.065 mmol) and lithium borohydride (0.13 ml, 0.26 mmol) were added again. The mixture was stirred at reflux for additional 3 h. After cooling to room temperature, saturated NH_4Cl (5 ml) was added dropwise. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Silica gel flash chromatography (8:92 acetone:toluene,) provided variabilin **1a** (34 mg, 90%) as a white foam: $[\alpha]_D^{23}$ = -236° (*c* 0.68, $CHCl_3$); IR (neat) 3437, 1618, 1598, 1496, 1160, 1027, 956 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39 (d, J = 8.4 Hz, 1H),7.24 (d, *J* = 8.4 Hz, 1H), 6.65 (dd, *J* = 2.1, 8.4 Hz, 1H), 6.52 (dd, *J* = 1.8, 8.4 Hz, 1H), 6.44 (d, *J* = 2.1 Hz, 1H), 6.40 (d, *J* = 1.8 Hz, 1H), 5.29 (s, 1H), 4.20 (d, *J* = 11.4 Hz, 1H), 4.01 (d, *J* = 11.4 Hz, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 2.54 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.7, 161.2, 161.0, 155.9, 132.0, 124.0, 120.2, 112.5, 109.9, 107.8, 101.8, 97.2, 85.1, 76.9, 69.8, 55.7, 55.5. This compound has been reported before.[4]



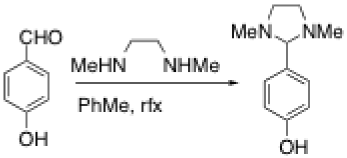
Diethyl 3-(1,3-dioxane)pentanedioate (20): To a solution of **19** (4.45 g, 22.0 mmol) and 1,3-bis(trimethylsilyloxy)propane (6.32 g, 28.6 mmol) in 110 ml of CH_2Cl_2 was added trimethylsilane trifluoromethanesulfonate (0.990 ml, 5.45 mmol) at -20 °C. The reaction was then warmed to rt and held at this temperature for 24 h. Pyridine (9.9 ml) was then added to the reaction solution at 0 °C. Saturated aqueous $NaHCO_3$ (50 ml) was then added and the mixture extracted with CH_2Cl_2 (3 × 50 ml). The combined organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel flash chromatography (7:3 hexanes:EtOAc) gave **20** (4.4 g, 77%) as a colorless oil: IR (neat) 1729, 1095, 1025 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.11 (q, *J* = 7.2 Hz, 4H), 3.92 (t, *J* = 5.4 Hz, 4H), 3.06 (s, 4H), 1.69 (q, *J* = 5.4 Hz, 2H), 1.22 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 97.2, 60.5, 60.1, 39.8, 24.8, 14.2.□



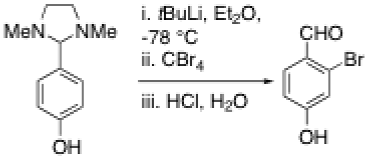
Ethyl 2-(2-(2-oxopropyl)-1,3-dioxan-2-yl)acetate (21): Methyl magnesium bromide (3.0 ml of a 3 M solution in diethyl ether, 9.0 mmol) was added dropwise to a solution of **20** (2.0 g, 7.7 mmol) in CH_2Cl_2 (77 ml) at -78 °C. After an additional 12 h at -78 °C, saturated NH_4Cl (20 ml) was added and the mixture was allowed to warm to rt. The mixture was extracted with CH_2Cl_2 (3 × 30 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Silica gel flash chromatography (6:4 hexanes:EtOAc) gave recovered **20** (880 mg, 44%) and **21** (890 mg, 50%) as a colorless oil: IR (neat) 1726, 1072 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.02 (q, *J* = 7.2 Hz, 2H), 3.91 (m, 2H), 3.76 (m, 2H), 2.92 (s, 4H), 2.11 (s, 3H), 1.78 (m, 1H), 1.44 (m, 1H), 1.13 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.5, 169.0, 97.3, 60.4, 59.8, 50.4, 37.6, 31.8, 24.6, 14.0. Anal. Calcd. for $C_{11}H_{18}O_5$ (230.26): C, 57.38; H, 7.88. Found: C, 57.3; H, 7.97.



5-(1,3-Dioxane)-1,3-cyclohexadione (2b): *n*BuLi (1.43 ml of a 1.6 M solution in hexanes, 2.30 mmol) was added to a solution of diisopropylamine (0.32 ml, 2.3 mmol) in THF (5 ml) at -78 °C. The reaction mixture was allowed to warm to 0 °C in 30 min and was added to **21** (0.50 g, 2.2 mmol) in 40 ml of THF via cannula at -78 °C. After warming to room temperature, the solution was heated at reflux for 3 h. The solvents were removed *in vacuo* and the residue was diluted with CH_2Cl_2 (20 ml) and washed with 2 N acetic acid (5 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 ml). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Recrystallization from EtOAc/hexanes gave **2b** (0.24 g, 59%) as a white solid: IR (neat) 1584, 1230, 1103, 1024 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.20 (bs, 1H), 5.12 (s, 1H), 3.83 (m, 4H), 2.69 (s, 4H), 1.59 (m, 2H); ^{13}C NMR (MeOH-d_4, 100 MHz) δ 102.2, 98.2, 59.9, 41.0, 25.1.

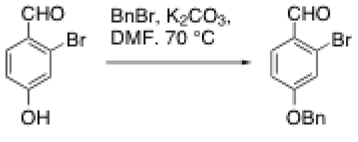


4-(1,3-Dimethylimidazolidin-2-yl)phenol: A solution of 4-hydroxybenzaldehyde (6.0 g, 49 mmol) and N,N'-dimethylethylenediamine (6.3 ml, 59 mmol) in toluene (100 ml) was heated at reflux for 3 h in a Dean-Stark apparatus. The solvents were then removed *in vacuo* to afford the aminal as a pale yellow solid (9.4 g, 100%): IR (neat) 1243 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.53 (bs, 1H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.62 (d, *J* = 8.7 Hz, 2H), 3.36-3.41 (m, 2H), 3.28 (s, 1H), 2.53-2.57 (m, 2H), 2.19 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.9, 130.1, 128.2, 116.0, 92.0, 52.9, 39.6.



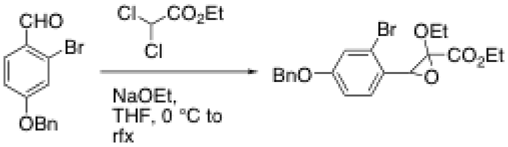
22

2-Bromo-4-hydroxybenzaldehyde (22): *t*-Butyl lithium (58.5 ml of a 1.6 M solution in pentane, 93.6 mmol) was added slowly to a solution of 4-(1,3-Dimethylimidazolidin-2-yl)phenol (6.0 g, 31 mmol) in Et_2O (220 ml) at -78 °C. The mixture was held under Ar at rt for 24 h. After cooling to -78 °C, carbon tetrabromide (31.0 g, 93.6 mmol) was added in portions. The mixture was then held at rt overnight. Aqueous HCl (3 N, 100 ml) was then added and the mixture stirred at room temperature for 2 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (3 × 100 ml). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel flash chromatography (1:99 MeOH :CH_2Cl_2) produced **22** (2.9 g, 46%) as a white solid: IR (neat) 3425, 1657, 1561, 1491, 1239 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) δ 10.14 (s, 1H), 9.81 (bs, 1H), 7.80 (d, *J* = 8.7 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 7.01 (dd, *J* = 2.4, 8.7 Hz, 1H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 190.2, 164.1, 132.4, 128.8, 127.1, 120.9, 116.5.



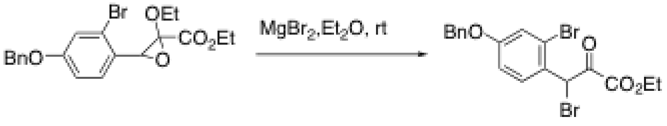
22 **23**

4-Benzyloxy-2-bromobenzaldehyde (23): A solution of **22** (2.0 g, 10 mmol), K_2CO_3 (1.8 g, 13 mmol) and BnBr (1.4 ml, 12 mmol) in DMF (50 ml) was heated to 70 °C for 6 h. After cooling to room temperature, the solution was diluted with H_2O (60 ml). The aqueous layer was extracted with Et_2O (3 × 60 ml). The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo.* Silica gel chromatography (8:2 hexanes:diethyl ether) gave **23** (2.6 g, 90%) as a white solid. This compound has been characterized before.[5]



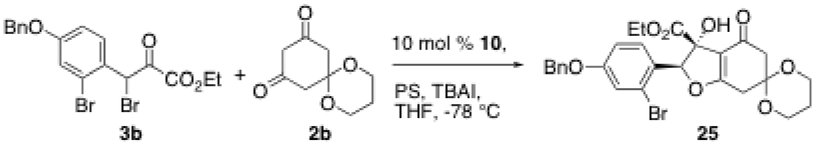
23 **24**

Ethyl 3-(4-benzyloxy-2-bromophenyl)-2-ethoxyoxirane-2-carboxylate (24): A mixture of **23** (2.1 g, 7.2 mmol) and ethyl dichloroacetate (0.97 ml, 7.9 mmol) in THF (14 ml) was cooled to 0 °C. A solution of sodium ethoxide, prepared from the addition of sodium (0.332 g, 14.4 mmol) to anhydrous ethanol (9 ml), was added via cannula. The suspension was then heated at reflux for 6 h. After removing all solvents *in vacuo*, the residue was diluted with CH_2Cl_2 (30 ml) and washed with saturated NH_4Cl (20 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 ml). The combined organic layers were dried (Na_2SO_4) and the solvents were evaporated *in vacuo*. The product **24** (pale yellow oil) was used without purification in the next step: IR (neat) 1743, 1604, 1495, 1278, 1180, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.41 (m, 5H), 7.25 (d, *J* = 8.7 Hz, 1H), 7.18 (d, *J* = 2.4 Hz, 1H), 6.93 (dd, *J* = 2.4, 8.7 Hz, 1H), 5.05 (s, 2H), 4.50 (s, 1H), 4.30-4.41 (m, 2H), 3.80 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.0, 159.4, 136.3, 129.6, 128.8, 128.3, 127.7, 124.6, 123.2, 118.6, 113.9, 83.0, 70.4, 64.4, 63.8, 62.5, 15.2, 14.3.



24 **3b**

Ethyl 3-(4-benzyloxy-2-bromophenyl)-3-bromo-2-oxopropanoate (3b): Magnesium bromide (2.65 g, 14.4 mmol) was added to a solution of **24** in Et_2O (72 ml) in portions. After 2 h at room temperature, H_2O (50 ml) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 × 50 ml). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. Silica gel flash chromatography (7:3 hexanes/EtOAc) afforded **3b** (1.84 g, 56% for 2 steps) as a colorless oil: IR (neat) 1734, 1598, 1490, 1229, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, *J* = 8.7 Hz, 1H), 7.35-7.41 (m, 5H), 7.22 (d, *J* = 2.4 Hz, 1H), 6.97 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.70 (s, 1H), 5.06 (s, 2H), 4.34 (m, 2H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 184.1, 160.1, 159.8, 135.9, 132.5, 128.9, 128.5, 127.7, 125.3, 124.8, 119.5, 115.2, 70.6, 63.4, 49.5, 14.4.

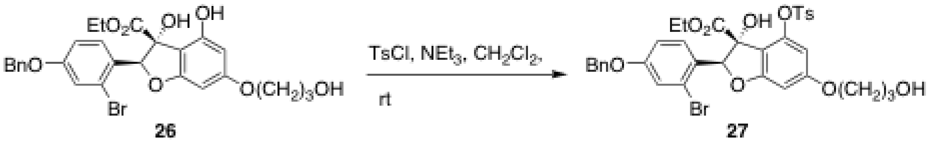


3b **2b** **25**

Ethyl 2-(4-benzyloxy-2-bromophenyl)-2,3,4,5,6,7-hexahydro-3-hydroxy-6-(1,3-dioxane)-4-oxobenzofuran-3-carboxylate (25): To a solution of **2b** (81 mg, 0.44 mmol) in THF (8 ml), was added **10** (22 mg, 0.04 mmol), proton sponge (0.28 g, 1.3 mmol) and tetrabutylammonium iodide (0.49 g, 1.3 mmol). After cooling to -78 °C, **3b** (0.60 g, 1.3 mmol) in 1 ml of THF (also at -78 °C) was added dropwise via cannula. The mixture was held at -78 °C for 30 min. The solvents were removed and the residue was redissolved in CH_2Cl_2 (10 ml) and washed with saturated $NaHCO_3$ (5 ml). The separated organic layer was washed with 1 N $NaHSO_4$ (5 ml). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo.* ^1H NMR analysis of the unpurified reaction mixture showed a 10:1 *E*:*Z* mixture of diastereomers. Silica gel chromatography (4:6 hexanes:EtOAc) gave **25** (115 mg, 46%) as a white foam as a mixture of diastereomers (10:1 *E*:*Z*): $[\alpha]_D^{23}$ = +7.6° (*c* 1.0, CH_2Cl_2); IR (neat) 1734, 1650, 1240, 1211, 1101 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32-7.37 (m, 5H *Z* and 5H *E*), 7.15 (d, *J* = 2.4 Hz, 2H *Z* and 2H *E*), 7.08 (d, *J* = 8.7 Hz, 1H *Z* and 1H *E*), 6.97 (dd, *J* = 2.4, 8.7 Hz, 1H *Z*), 6.89 (dd,

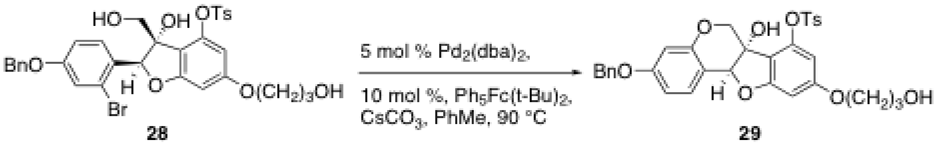
J = 2.4, 8.7 Hz, 1H *E*), 6.27 (s, 1H *Z*), 6.13 (s, 1H *E*), 5.04 (s, 2H *Z* and 2H *E*), 4.32-4.37 (m, 2H *Z*), 4.30 (s, 1H *E*), 3.88-4.02 (m, 4H *Z* and 4H *E*), 3.78-3.86 (m 1H *E*), 3.47-3.58 (m, 1H *E*), 2.86-3.11 (m, 4H *Z* and 4H *E*), 1.88-1.97 (m, 1H *Z* and 1H *E*), 1.64-1.67 (m, 1H *Z* and 1H *E*), 1.32 (t, J = 7.2 Hz, 3H *Z*), 0.81 (t, J = 7.2 Hz, 3H *E*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.4, 177.2, 176.7, 172.6, 170.5, 159.6, 159.2, 136.2, 136.1, 130.8, 129.0, 128.8, 128.4, 127.7, 127.5, 126.9, 124.8, 122.7, 122.4, 118.8, 118.5, 116.3, 115.0, 114.4, 114.2, 99.2, 99.1, 95.6, 92.4, 84.8, 79.7, 77.3, 70.5, 70.4, 63.5, 62.5, 60.4, 60.3, 44.1, 36.0, 35.9, 25.1, 14.3, 13.6. Anal. Calcd. for $C_{27}H_{27}BrO_8$ (559.4): C, 57.97; H, 4.86. Found: C, 57.92; H, 4.92.

Ethyl 6-(3-hydroxypropoxy)-2-(4-(benzyloxy)-2-bromophenyl)-2,3-dihydro-3,4-dihydroxybenzofuran-3-carboxylate (26): Potassium *t*-butoxide (0.21 g, 1.8 mmol) was added to a solution of **25** (0.94 g, 1.7 mmol) in THF (33 ml) at 0 °C. The mixture was stirred at 0 °C for 2 h. After removing all solvents under reduced pressure, the residue was redissolved in CH_2Cl_2 (30 ml) and washed with saturated NH_4Cl (20 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 ml). The organic layers were then combined, dried (Na_2SO_4) and concentrated *in vacuo*. Silica gel flash chromatography (7:3 hexanes:EtOAc) yielded **26** (0.78 g, 83%) as a white foam: $[\alpha]_D^{23}$ = +71.6° (c 1.0, CH_2Cl_2); IR (neat) 3446, 1727, 1629, 1492, 1234, 1147, 1014 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.40 (m, 5H), 7.27 (d, J = 8.7 Hz, 1H), 7.16 (d, J = 2.4 Hz, 1H), 6.86 (dd, J = 2.4, 8.7 Hz, 1H), 6.12 (s, 2H), 5.97 (s, 1H), 5.03 (s, 2H), 4.46 (bs, 1H), 4.04 (m, 2H), 3.76-3.86 (m, 3H), 3.60-3.67 (m, 1H), 2.40 (bs, 1H), 2.00 (m, 2H), 0.83 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.9, 163.1, 159.1, 154.3, 136.2, 129.3, 128.8, 128.4, 128.3, 127.6, 122.5, 118.8, 114.3, 106.0, 96.1, 93.8, 89.6, 85.8, 77.4, 70.4, 66.1, 62.8, 60.4, 31.8, 13.7.

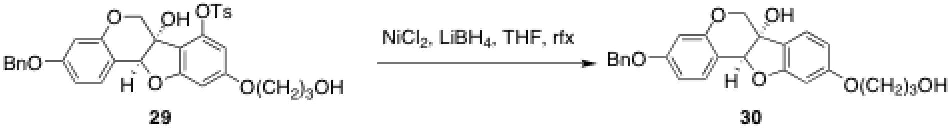


3-(Ethoxycarbonyl)-6-(3-hydroxypropoxy)-2-(4-(benzyloxy)-2-bromophenyl)-2,3-dihydro-3-hydroxybenzofuran-4-yl 4-methylbenzenesulfonate (27): To a solution of **26** (0.56 g, 1.0 mmol) and NEt_3 (0.56 ml, 4.0 mmol) in CH_2Cl_2 (10 ml) was added TsCl (0.21g, 1.1 mmol). After 3 h at room temperature, the solvents were removed under reduced pressure. Silica gel flash chromatography (4:6 hexanes:EtOAc) produced **27** as a white foam (0.64 g, 89%). The enantiomeric excess and diastereomeric ratio were determined by analytical HPLC (Chiralpak AD column, 60:40 hexanes:*i*PrOH, 0.8 ml/min, 280 nm) $R_{t(2R,3S)}$ = 19.7 min, $R_{t(2S,3R)}$ = 30.3 min, $R_{t(2S,3S)}$ = 34.8 min, $R_{t(2R,3R)}$ = 45.4 min, ee = 93%, dr = 96:4 (*E*/*Z*). Data for the *E*-isomer: $[\alpha]_D^{23}$ = +17.7° (*c* 1.0, CH_2Cl_2); IR (neat) 1732, 1601, 1493, 1236, 1136 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.83 (d, *J* = 8.1 Hz, 2H), 7.31-7.37 (m, 7H), 7.17 (d, *J* = 8.7 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 6.84 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.47 (d, *J* = 1.8 Hz, 1H), 6.44 (d, *J* = 1.8 Hz, 1H), 6.10 (s, 1H), 5.03 (s, 2H), 4.33 (s, 1H), 4.07 (t, *J* = 6 Hz, 2H), 3.76-3.86 (m, 3H), 3.55-3.62 (m, 1H), 2.45 (s, 3H), 2.03 (q, *J* = 6 Hz, 2H), 1.63 (bs, 1H), 0.78 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 163.4, 162.5, 159.1, 146.2, 145.9, 136.2, 132.6, 129.9, 129.3, 128.8, 128.7, 128.4, 128.1, 127.6, 122.3, 118.8, 114.2, 112.8, 102.0, 95.4, 94.4, 84.6, 70.3, 66.1, 62.7, 60.0, 31.9, 21.9, 13.6; Anal. Calcd. for $C_{34}H_{33}BrO_{10}S$ (713.6): C, 57.23; H, 4.66. Found: C, 56.97; H, 4.62.

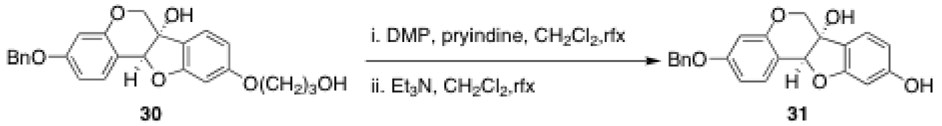
6-(3-Hydroxypropoxy)-2-(4-(benzyloxy)-2-bromophenyl)-2,3-dihydro-3-hydroxy-3-(hydroxymethyl)benzofuran-4-yl 4-methylbenzenesulfonate (28): Lithium borohydride (2 M in THF, 0.70 ml, 1.4 mmol) was added dropwise to a solution of **27** (0.50 g, 0.7 mmol) in THF (7 ml) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight. Saturated NH_4Cl (5 ml) was added slowly to quench the reaction and the solution was extracted with CH_2Cl_2 (3 × 15 ml). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The unpurified reaction mixture was resubmitted to the exact same reduction conditions and work-up. Silica gel flash chromatography (4:6 hexanes:EtOAc with 1% added triethylamine) gave **28** (0.40 g, 85%) as a white foam: $[\alpha]_D^{23}$ = -28.5° (*c* 1.0, CH_2Cl_2); IR (neat) 3501, 1627, 1599, 1493, 1143, 1012 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.86 (d, *J* = 8.1 Hz, 2H), 7.33-7.40 (m, 7H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 6.85 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.45 (d, *J* = 2.1 Hz, 1H), 6.10 (s, 1H), 6.01 (d, *J* = 2.1 Hz, 1H), 5.02 (s, 2H), 3.94-4.00 (m, 2H), 3.79-3.83 (m, 4H), 3.52-3.60 (m, 1H), 2.48 (s, 3H), 1.98 (m, 2H), 1.76 (bs, 1H), 1.60 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.4, 162.1, 159.3, 146.4, 146.3, 136.2, 132.0, 130.2, 128.9, 128.8,128.7, 128.4, 128.1, 127.1, 123.9, 118.9, 114.6, 113.9, 102.4, 96.3, 93.3, 83.8, 70.4, 66.0, 64.6, 60.0, 31.9, 21.9.



9-(3-Hydroxypropoxy)-3-(benzyloxy)-6a,11a-dihydro-6a-hydroxy-6*H*-benzofuro[3,2-*c*]chromen-7-yl 4-methylbenzenesulfonate (29): A 100 ml round bottom flask was charged with **28** (0.40 g, 0.59 mmol), $Pd_2(dba)_3$ (31 mg, 0.03 mmol), $Ph_5FcP(t\text{-}Bu)_2$ (42 mg, 0.06 mmol) and Cs_2CO_3 (0.29 g, 0.89 mmol). The flask was placed into a pre-heated 90 °C oil bath and anhydrous toluene (50 ml) was added in four aliquots. The mixture was held at 90 °C for 7 h under Ar. After removing all solvents *in vacuo*, the residue was diluted with CH_2Cl_2 (30 ml) and washed with saturated brine (30 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 ml) and the combined organic layers were dried over Na_2SO_4 and concentrated. Silica gel flash chromatography (4:6 hexanes:EtOAc) afforded **29** as a white foam (0.26 g, 73%): $[\alpha]_D^{23}$ = -250.3° (*c* 1.0, CH_2Cl_2); IR (neat) 1619, 1594, 1497, 1133, 1017 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.88 (d, *J* = 8.1 Hz, 2H), 7.30-7.43 (m, 8H), 6.68 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 6.29 (d, *J* = 1.8 Hz, 1H), 5.85 (d, *J* = 1.8 Hz, 1H), 5.50 (s, 1H), 4.98 (s, 2H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.15 (d, *J* = 11.4 Hz, 1H), 3.94 (s, 1H), 3.81-3.91 (m, 2H), 3.73 (bs, 2H), 2.49 (s, 3H), 1.90 (m, 2H), 1.65 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.0, 162.1, 160.2, 156.2, 146.5, 146.0, 136.7, 131.7, 130.2, 128.9, 128.7, 128.2, 127.6, 113.5, 113.4, 110.4, 102.6, 102.5, 97.2, 86.4, 76.6, 70.1, 68.7, 65.9, 59.8, 31.8, 21.9; HRMS: *m/z* Calcd for $C_{32}H_{30}O_9SNa^+$, 613.1503; Found, 613.1494.



9-(3-Hydroxypropoxy)-3-(benzyloxy)-6a,11a-dihydro-6*H*-benzofuro[3,2-*c*]chromen-6a-ol (30): Lithium borohydride (0.25 ml of a 2 M solution in THF, 0.50 mmol) was added dropwise to a solution of **29** (60 mg, 0.10 mmol) and nickel (II) chloride (13 mg, 0.10 mmol) in THF (8 ml). The solution turned black slowly and was heated at reflux for 4 h, after which time nickel (II) chloride (6.0 mg, 0.05 mmol) and lithium borohydride (0.1 ml, 0.2 mmol) were added again. The mixture was held at reflux for another 3 h. After it cooled to room temperature, saturated NH_4Cl (5 ml) was added dropwise. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 ml) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Silica gel flash chromatography (2:8 acetone:toluene) provided **30** (38 mg, 89%) as a white foam: $[\alpha]_D^{23}$ = -144.9° (*c* 1.0, CH_2Cl_2); IR (neat) 3344, 1618, 1598, 1497, 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.42 (m, 6H),7.21 (d, *J* = 8.1 Hz, 1H), 6.71 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.48-6.52 (m, 2H), 6.38 (d, *J* = 1.8 Hz, 1H), 5.27 (s, 1H), 5.01 (s, 2H), 4.18 (d, *J* = 11.4 Hz, 1H), 3.78-4.04 (m, 4H), 3.76-3.81 (m, 2H), 2.95 (bs, 1H), 1.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.7, 160.9, 160.3, 155.8, 136.7, 132.0, 128.7, 128.2, 127.6, 124.0, 120.4, 112.8, 110.6, 108.3, 102.8, 97.7, 85.0, 76.6, 70.2, 69.8, 65.9, 60.3, 31.9. Anal. Calcd. for $C_{25}H_{24}O_6$ (420.4): C, 71.41; H, 5.75. Found: C, 71.38; H, 5.82.



3-Benzyloxy-6a,11a-dihydro-6*H*-benzofuro[3,2-*c*]chromene-6a,9-diol (31): To a solution of **30** (73 mg, 0.17 mmol) and pyridine (0.11 ml, 1.4 mmol) in CH_2Cl_2 (9 ml) was added Dess-Martin periodinane (146 mg, 0.340 mmol). The reaction mixture was heated at reflux for 1h, cooled to rt and then washed with saturated $NaHCO_3$ (5 ml) and saturated $Na_2S_2O_3$ (5 ml). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 ml). The organic layers were combined and dried over Na_2SO_4 and the solvents were removed under vacuum. The crude residue was redissolved in CH_2Cl_2 (9 ml) and of triethylamine (1.2 ml, 8.6 mmol) was added to the mixture. The reaction solution was heated at reflux for 40 min. After cooling to room temperature, the solution was washed with 1 N

$NaHSO_4$ (10 ml). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 10ml). The organic layers were combined, dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel flash chromatography (1:1 hexanes:EtOAc) provided **31** as a white foam (52 mg, 83%). The spectra data of this compound were taken on the *E* isomer: $[\alpha]_D^{23}$ = -179.7° (*c* 1.0, acetone); IR (neat) 3204, 1621, 1172, 1024, 965 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 8.46 (bs, 1H), 7.31-7.48 (m, 6H),7.21 (d, *J* = 8.1 Hz, 1H), 6.72 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.49 (d, *J* = 2.4 Hz, 1H), 6.43 (dd, *J* = 1.8, 8.1 Hz, 1H), 6.25 (d, *J* = 1.8 Hz, 1H), 5.29 (s, 1H), 5.10 (s, 2H), 4.96 (s, 1H), 4.15 (d, *J* = 11.4 Hz, 1H), 4.05 (d, *J* = 11.4 Hz, 1H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 162.0, 161.0, 160.8, 157.1, 138.2, 133.1, 129.3, 128.7, 128.4, 125.1, 121.4, 114.6, 110.6, 109.0, 103.1, 98.7, 85.8, 76.7, 70.6, 70.5. HRMS: *m/z* Calcd for $C_{22}H_{29}O_5H^+$, 363.1227; Found, 363.1213.

31 1b

6a,11a-Dihydro-6*H*-benzofuro[3,2-*c*]chromene-3,6a,9-triol ((-)-glycinol, 1b): 1,4-cyclohexadiene (0.10 ml, 1.1 mmol) was added to a solution of **31** (40 mg, 0.11 mmol) and Pd/C (40 mg) in 2 ml of anhydrous EtOH. After 24 h at room temperature, the suspension was filtered through celite and washed with MeOH (3 x 5 ml). The filtrate was dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel flash chromatography (3:7 hexanes:EtOAc) provided (-)-glycinol **1b** (26 mg, 90%) as a white solid: $[\alpha]_D^{23}$ = -228° (*c* 0.3, MeOH); IR (neat) 3336, 1621, 1259, 1037, 963 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 8.55 (bs, 1H), 8.46 (bs, 1H), 7.30 (d, J = 8.7 Hz, 1H),7.2 (d, *J* = 8.1 Hz, 1H), 6.54 (dd, *J* = 2.4, 8.7 Hz, 1H), 6.42 (dd, *J* = 1.8, 8.1 Hz, 1H), 6.32 (d, *J* = 2.4 Hz, 1H), 6.24 (d, *J* = 1.8 Hz, 1H), 5.26 (s, 1H), 4.93 (s, 1H), 4.12 (d, *J* = 11.4 Hz, 1H), 4.02 (d, *J* = 11.4 Hz, 1H); ^{13}C NMR (acetone-d_6, 75 MHz) δ 162.0, 160.7, 159.6, 157.2, 133.2, 125.2, 121.5, 113.4, 110.7, 108.9, 103.8, 98.7, 86.0, 76.8, 70.6. HRMS: *m/z* Calcd for $C_{15}H_{13}O_5H^+$, 273.0758; Found, 273.0749.

---

[1] Tan, N. P. H.; Donner, C. D. *Tetrahedron*, **2009**, *65*, 4007-4012.

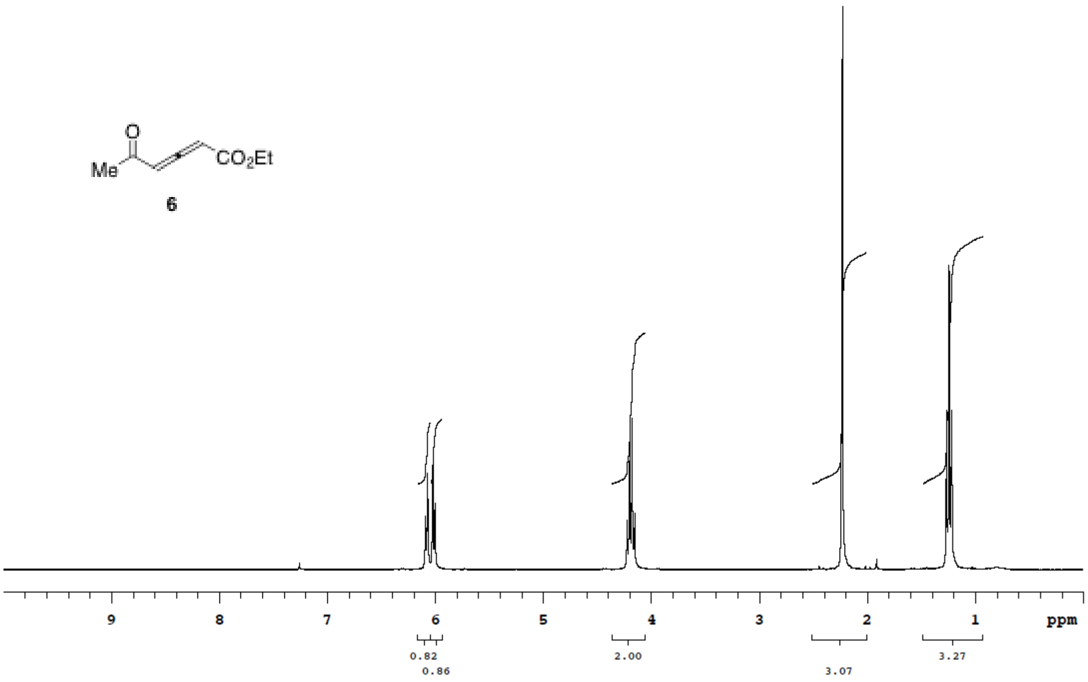
[2] Ibrahim-Oauli, M.; Missoum, A.; Sinibaldi, M-E.; Troin, Y.; Gramail, J-C. *Synth. Comm*. 1**996**, *26*, 657-670.

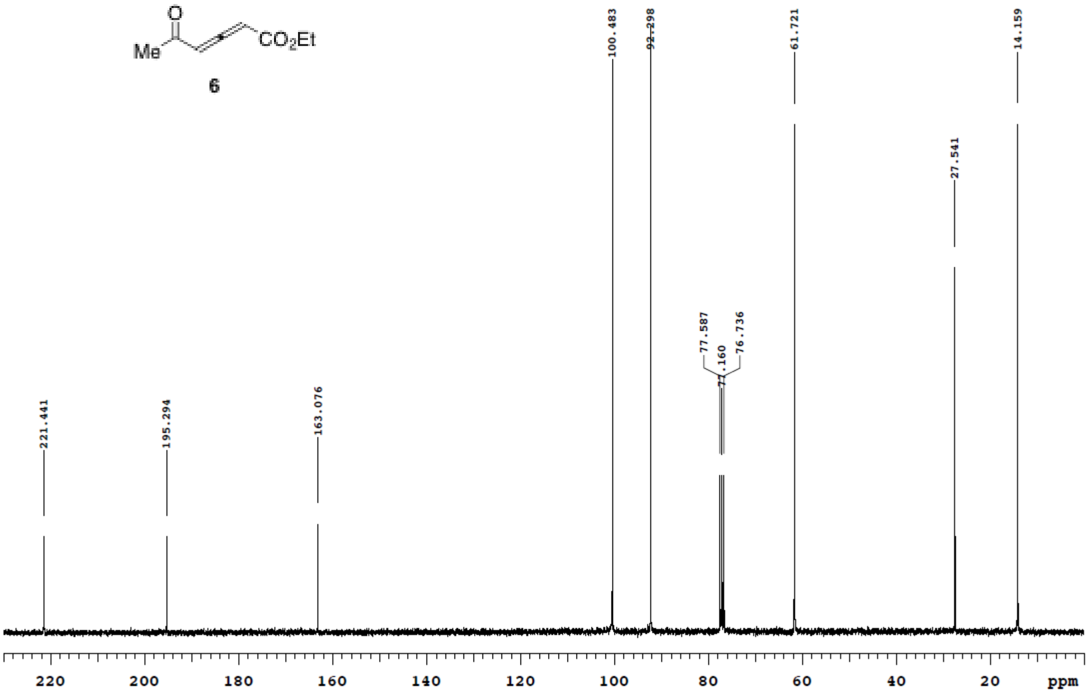
---

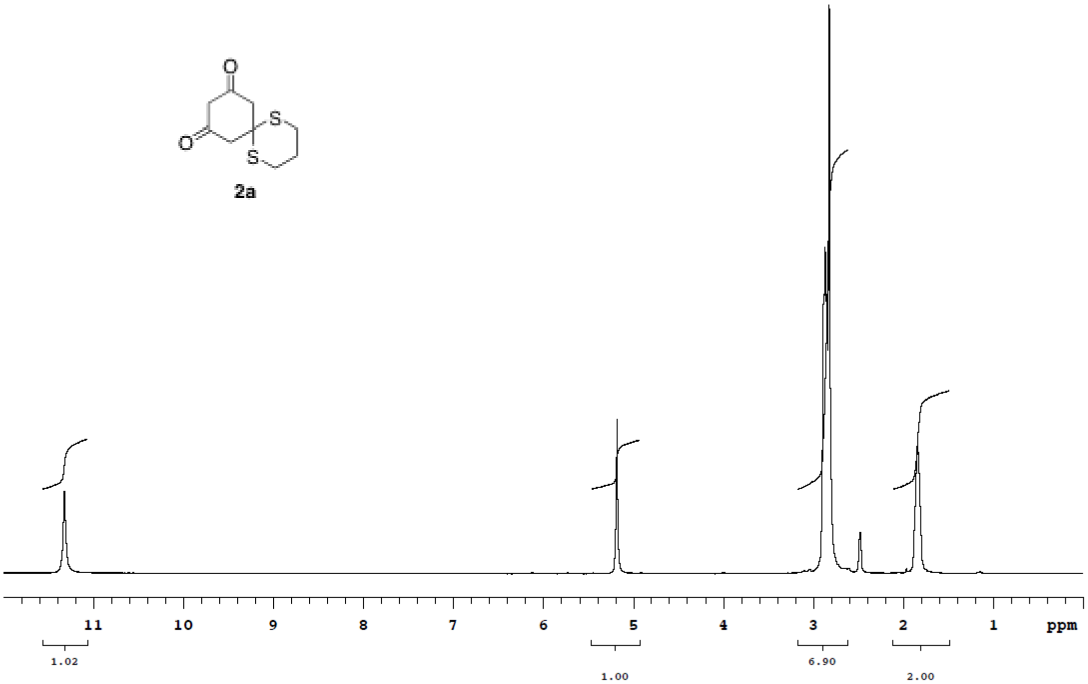
[3] Lear, Y.; Durst, T. *Can. J. Chem*. **1997**, *75*, 817-824.

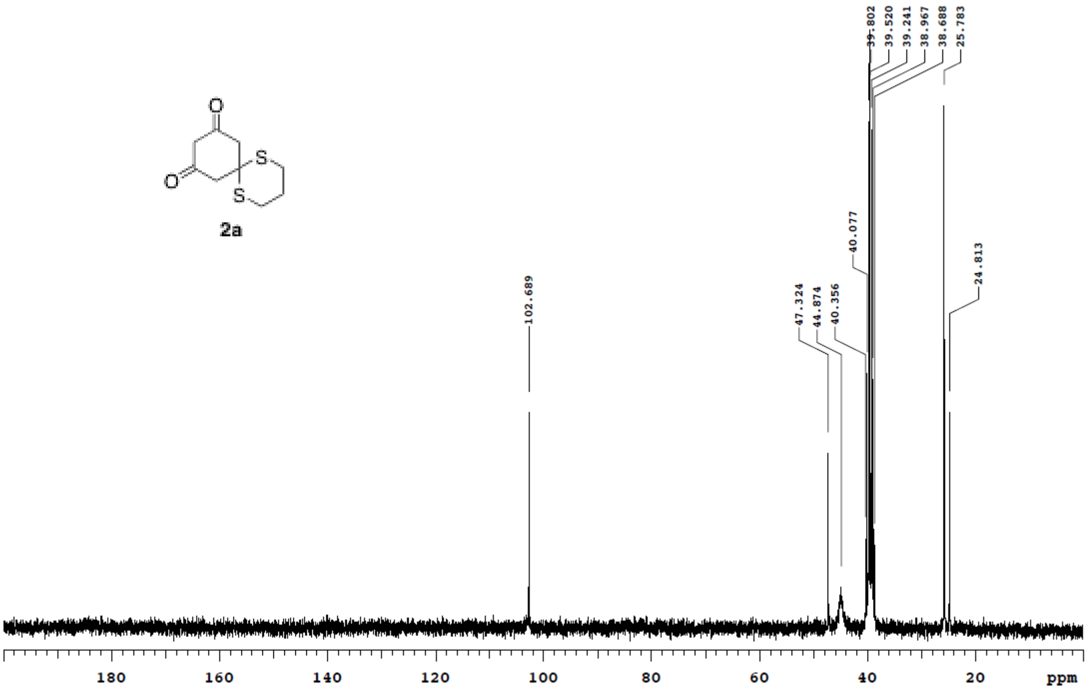
[4] van Aardt, T. G.; van Rensburg, H.; Ferreira, D. *Tetrahedron*, **2001**, *57*, 7113-7126.

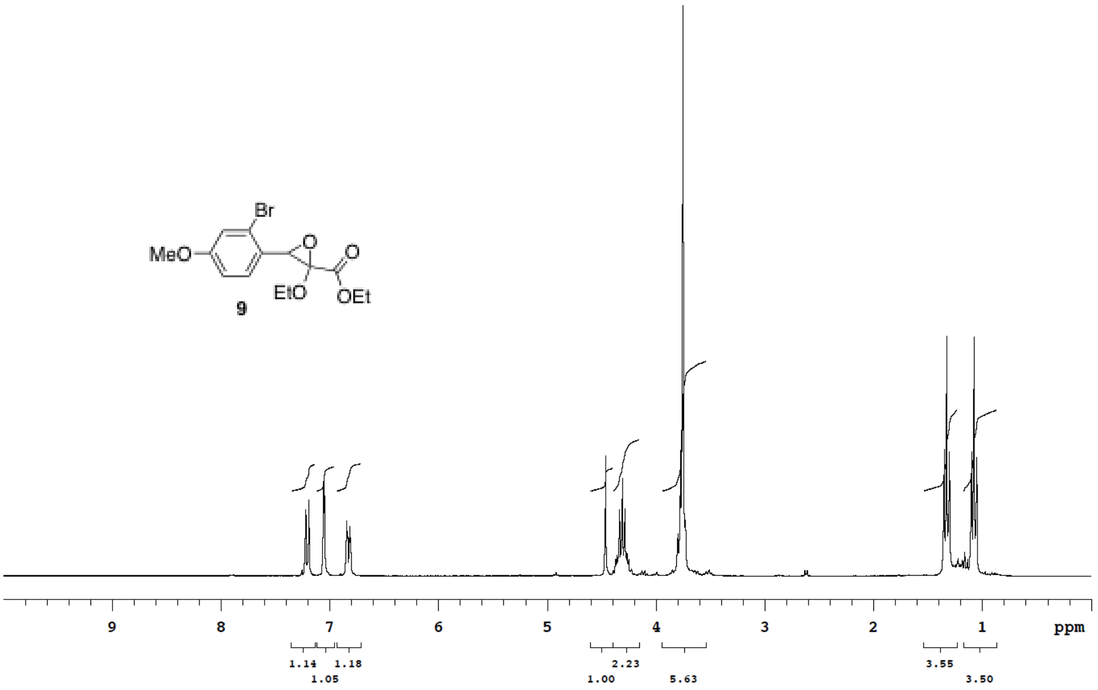
[5] Couture, A.; Deniau, E.; Lebrum, S.; Hoarau, C.; Grandclaudon, P. *Natural Product Lett*. **1999**, *13*(1), 33-40.

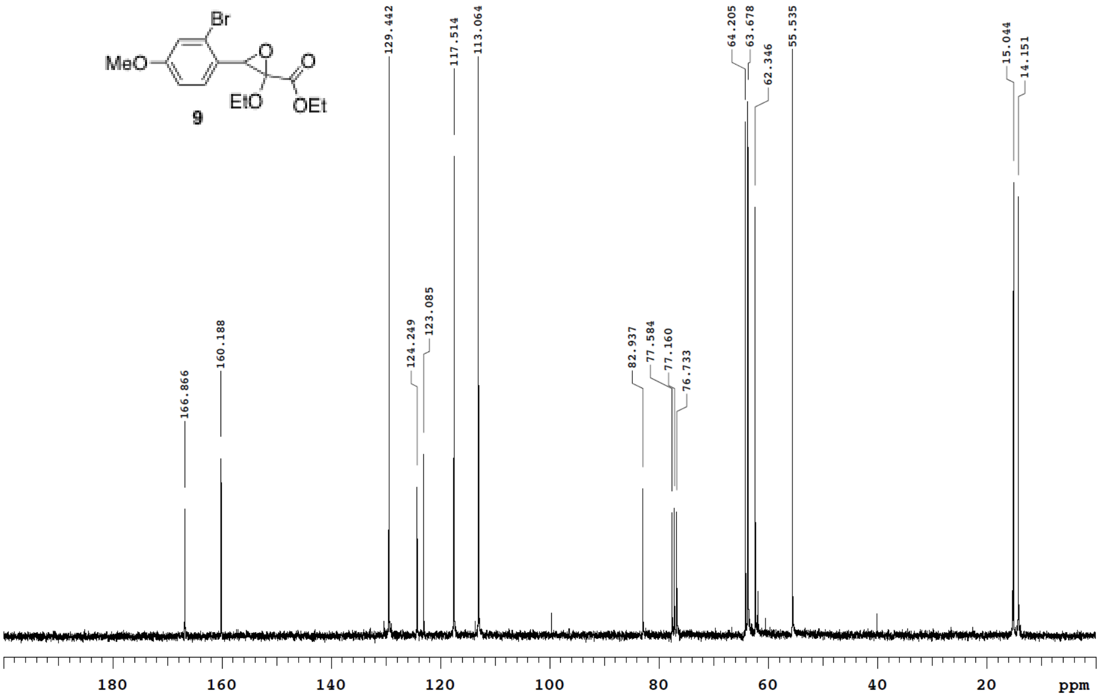

Me
O
CO2Et
6
9
8
7
6
5
4
3
2
1
ppm
0.82
0.86
2.00
3.07
3.27

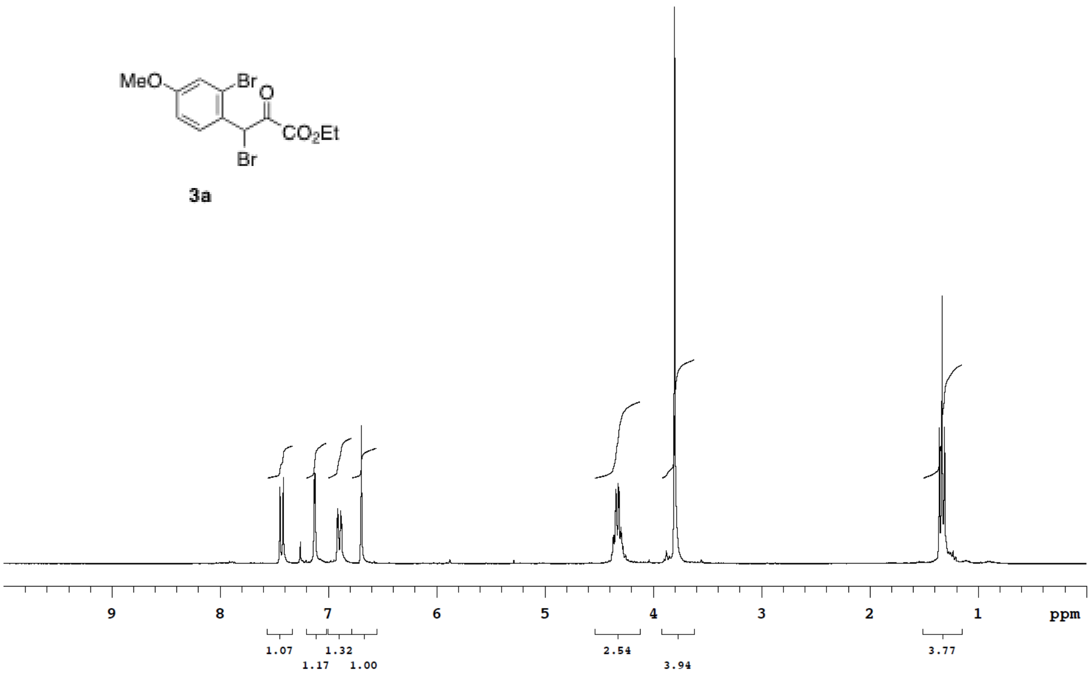

Me
O
CO2Et
6
221.441
195.294
163.076
100.483
92.298
77.587
77.160
76.736
61.721
27.541
14.159
220
200
180
160
140
120
100
80
60
40
20
ppm

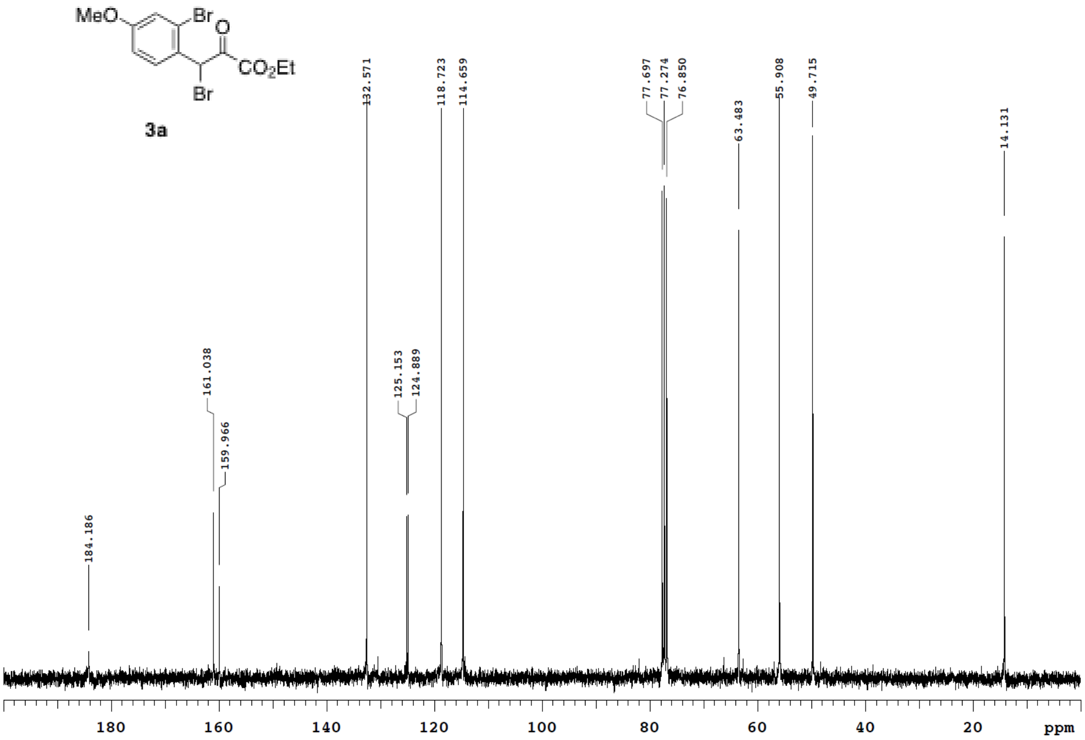

2a
11
10
9
8
7
6
5
4
3
2
1
ppm
1.02
1.00
6.90
2.00

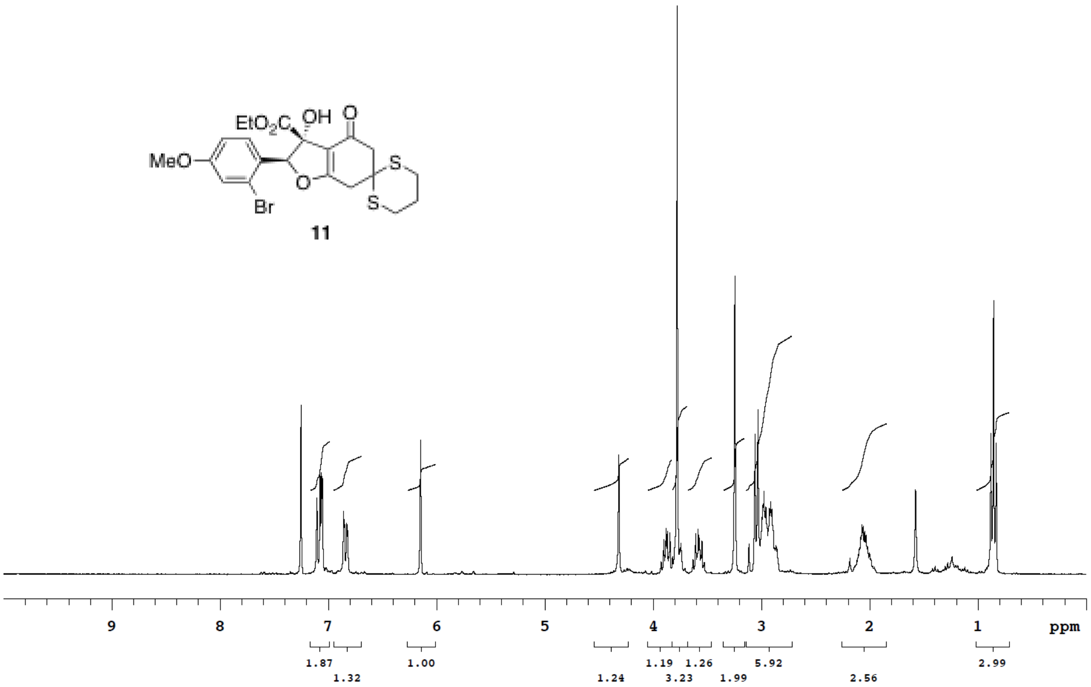

2a
102.689
47.324
44.874
40.356
40.077
39.802
39.520
39.241
38.967
38.688
25.783
24.813
180
160
140
120
100
80
60
40
20
ppm

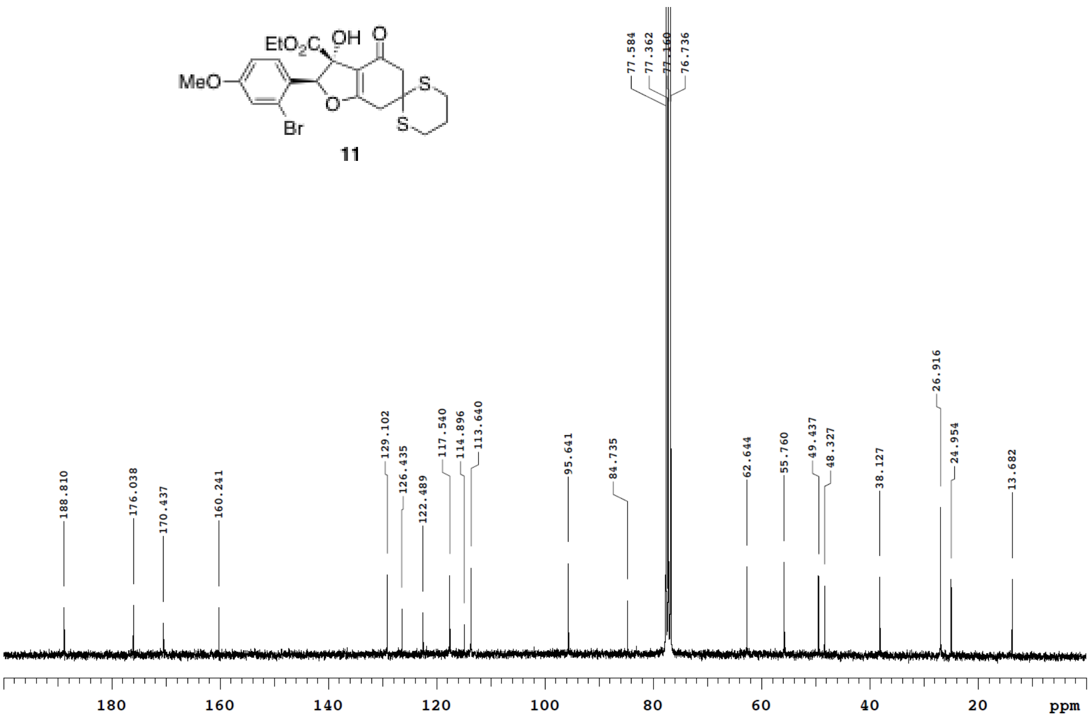

Br
MeO
O
O
EtO
OEt
9
1.14
1.05
1.18
1.00
2.23
5.63
3.55
3.50
9
8
7
6
5
4
3
2
1
ppm

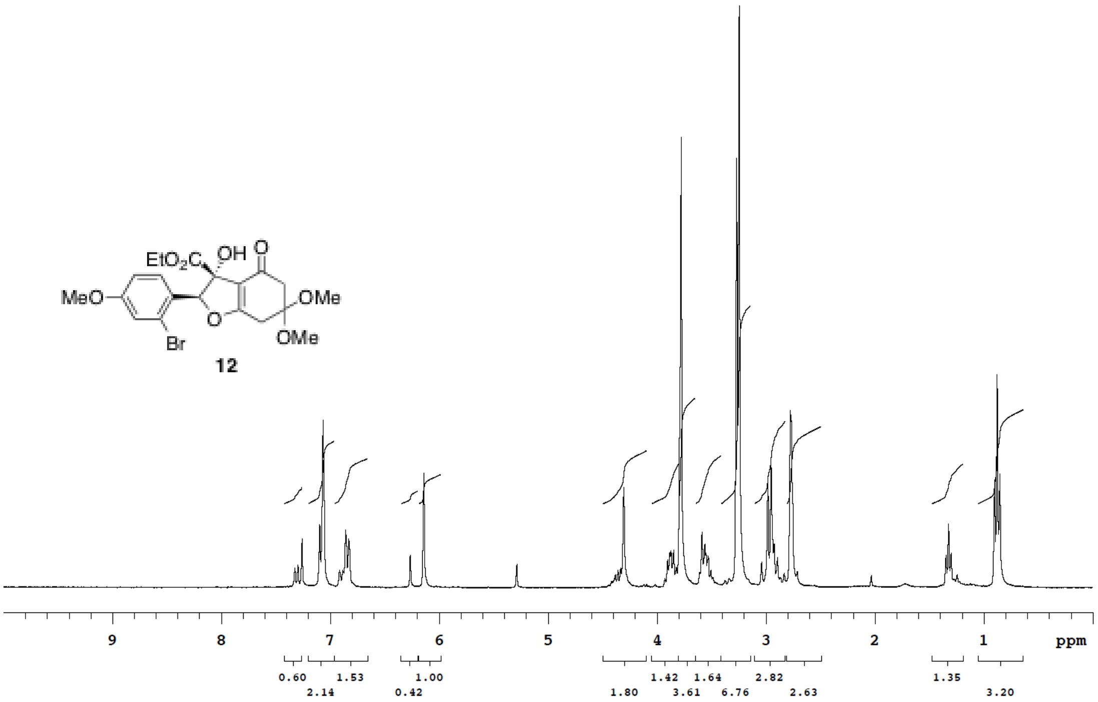

Br
MeO
O
O
EtO
OEt
9
166.866
160.188
129.442
124.249
123.085
117.514
113.064
82.937
77.584
77.160
76.733
64.205
63.678
62.346
55.535
15.044
14.151
180
160
140
120
100
80
60
40
20
ppm

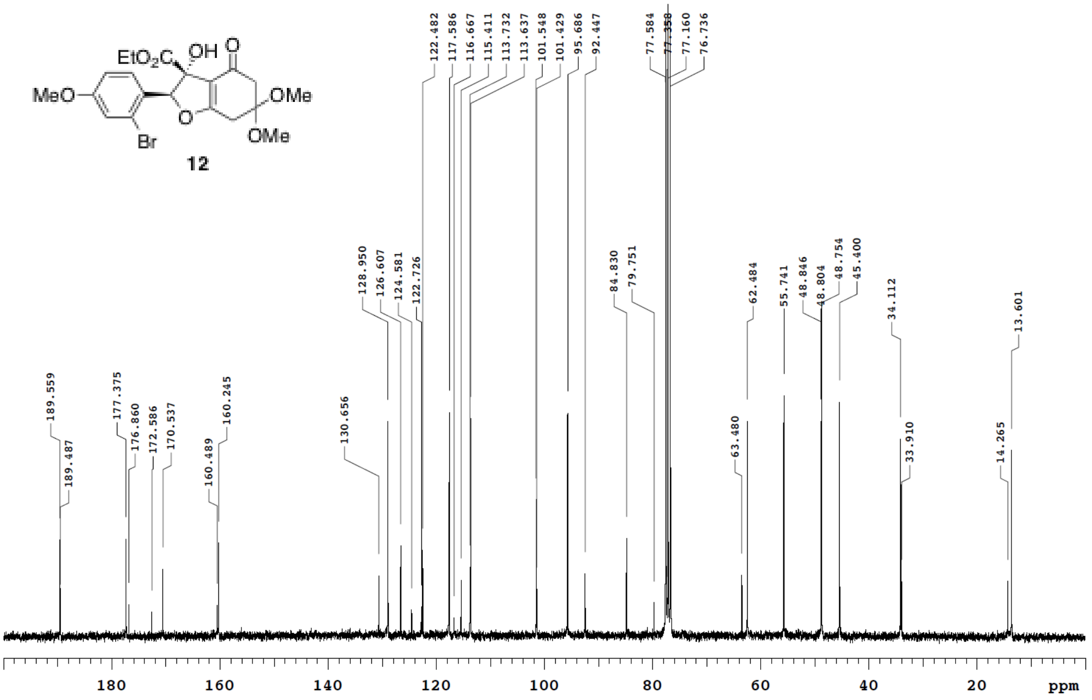

MeO
Br
O
CO2Et
Br
3a
9
8
7
6
5
4
3
2
1
ppm
1.07
1.17
1.32
1.00
2.54
3.94
3.77

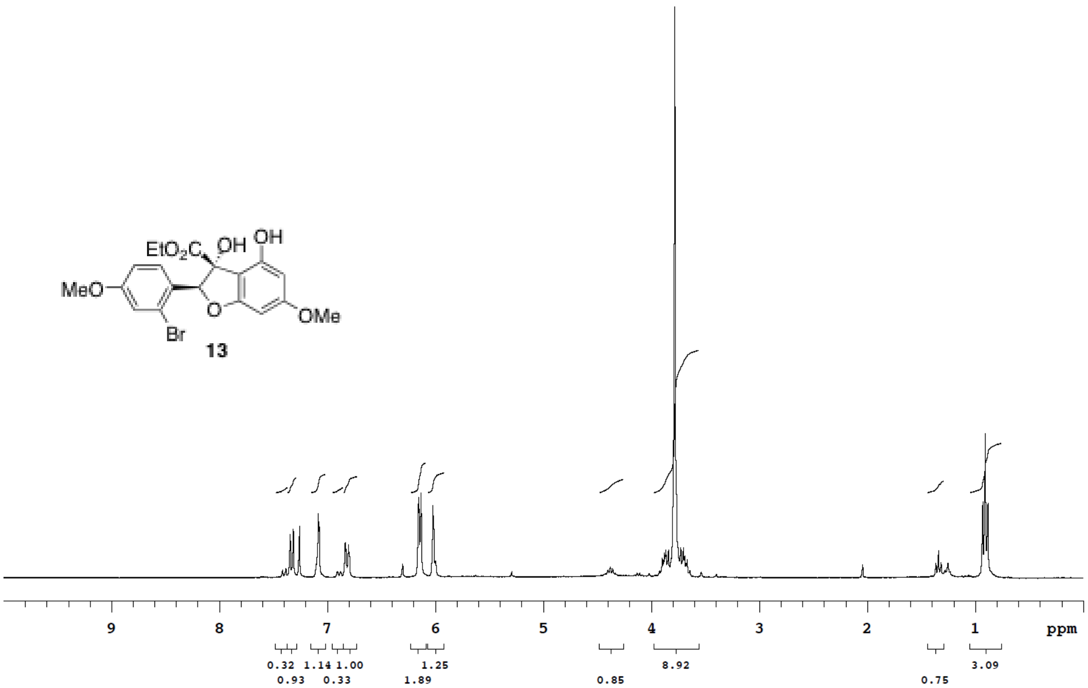

MeO
Br
O
CO2Et
Br
3a
184.186
161.038
159.966
132.571
125.153
124.889
118.723
114.659
77.697
77.274
76.850
63.483
55.908
49.715
14.131
180
160
140
120
100
80
60
40
20
ppm

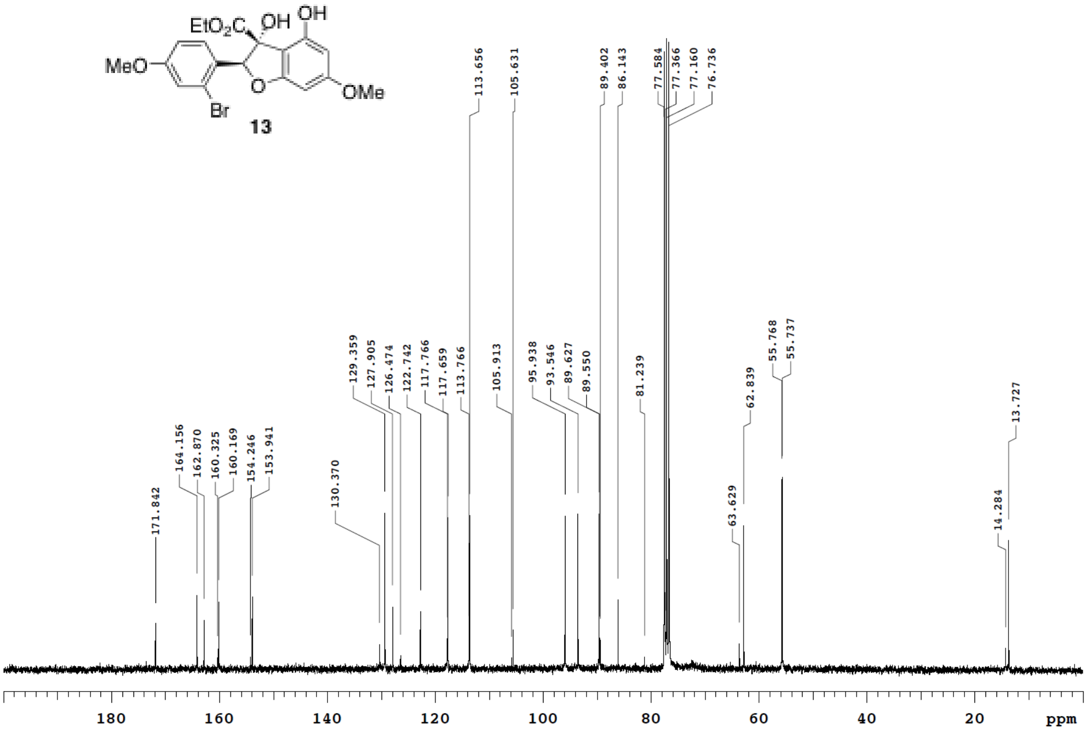

EtO2C
OH
O
MeO
S
O
S
Br
11
9
8
7
6
5
4
3
2
1
ppm
1.87
1.32
1.00
1.24
1.19
3.23
1.26
1.99
5.92
2.56
2.99

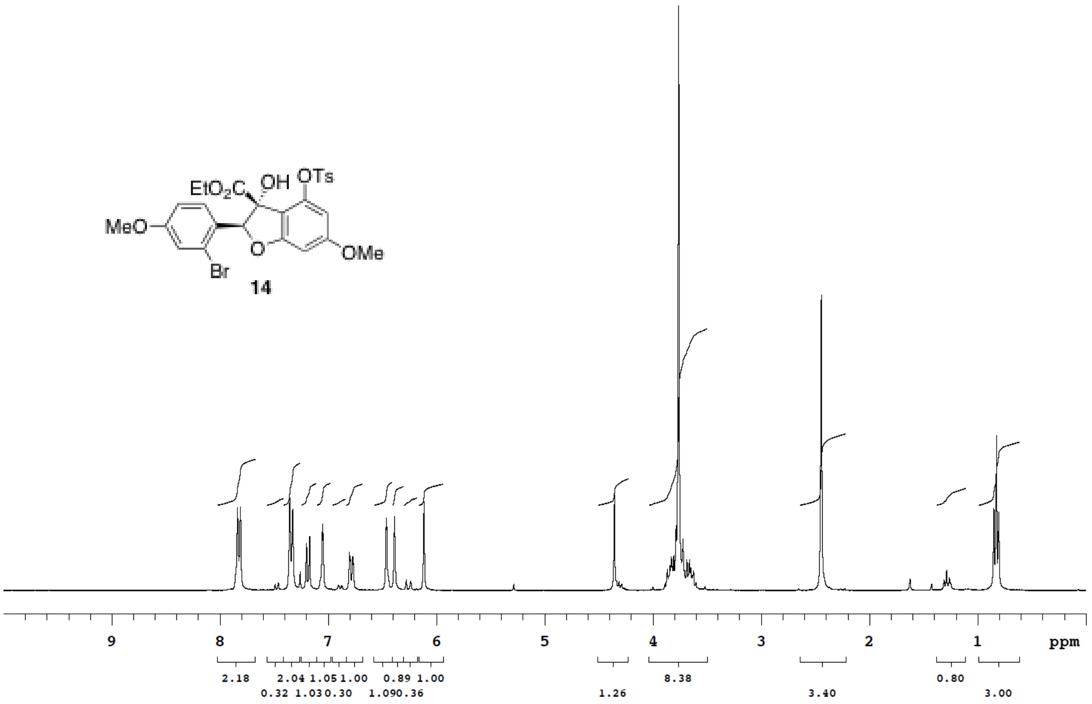

EtO2C
OH
O
MeO
S
O
S
Br
11
77.584
77.362
77.160
76.736
188.810
176.038
170.437
160.241
129.102
126.435
122.489
117.540
114.896
113.640
95.641
84.735
62.644
55.760
49.437
48.327
38.127
26.916
24.954
13.682
180
160
140
120
100
80
60
40
20
ppm

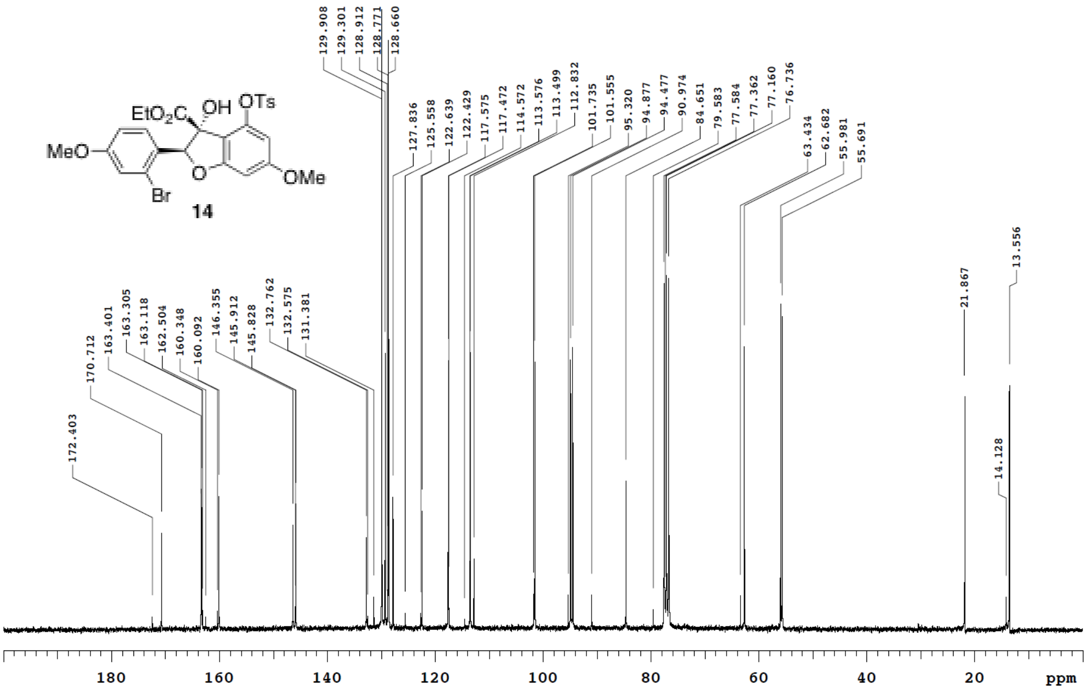

EtO2C
OH
O
MeO
OMe
OMe
Br
O
12
9
8
7
6
5
4
3
2
1
ppm
0.60
2.14
1.53
0.42
1.00
1.80
1.42
3.61
1.64
6.76
2.82
2.63
1.35
3.20

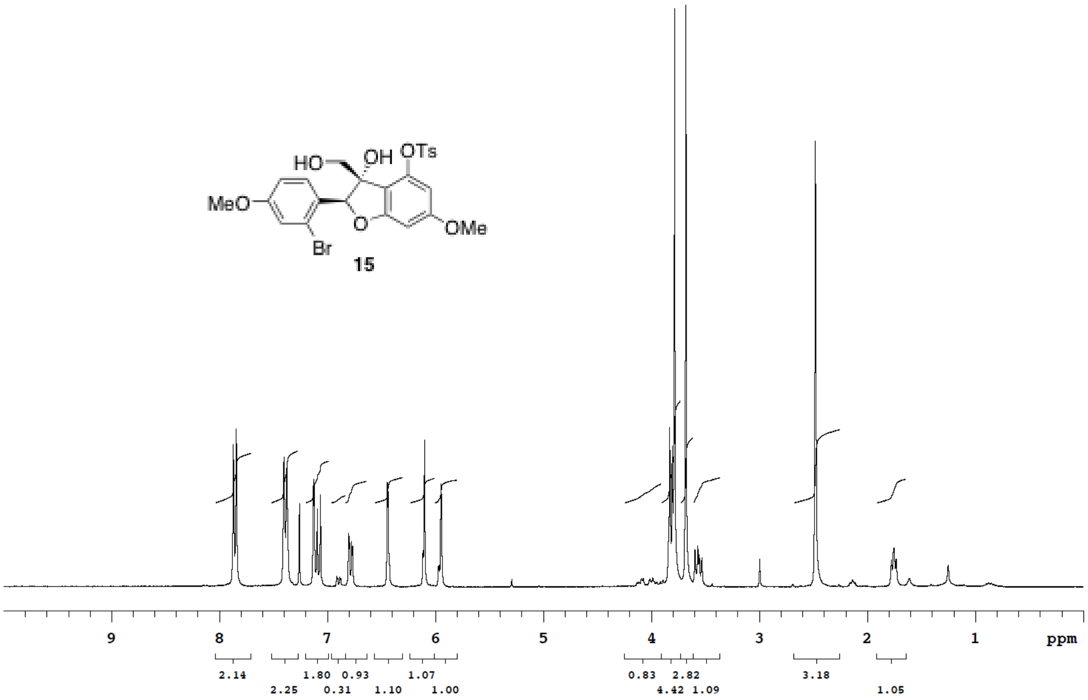

EtO2C
OH
O
MeO
OMe
OMe
Br
O
12
189.559
189.487
177.375
176.860
172.586
170.537
160.489
160.245
130.656
128.950
126.607
124.581
122.726
122.482
117.586
116.667
115.411
113.732
113.637
101.548
101.429
95.686
92.447
84.830
79.751
77.584
77.358
77.160
76.736
63.480
62.484
55.741
48.846
48.804
48.754
45.400
34.112
33.910
14.265
13.601
180
160
140
120
100
80
60
40
20
ppm

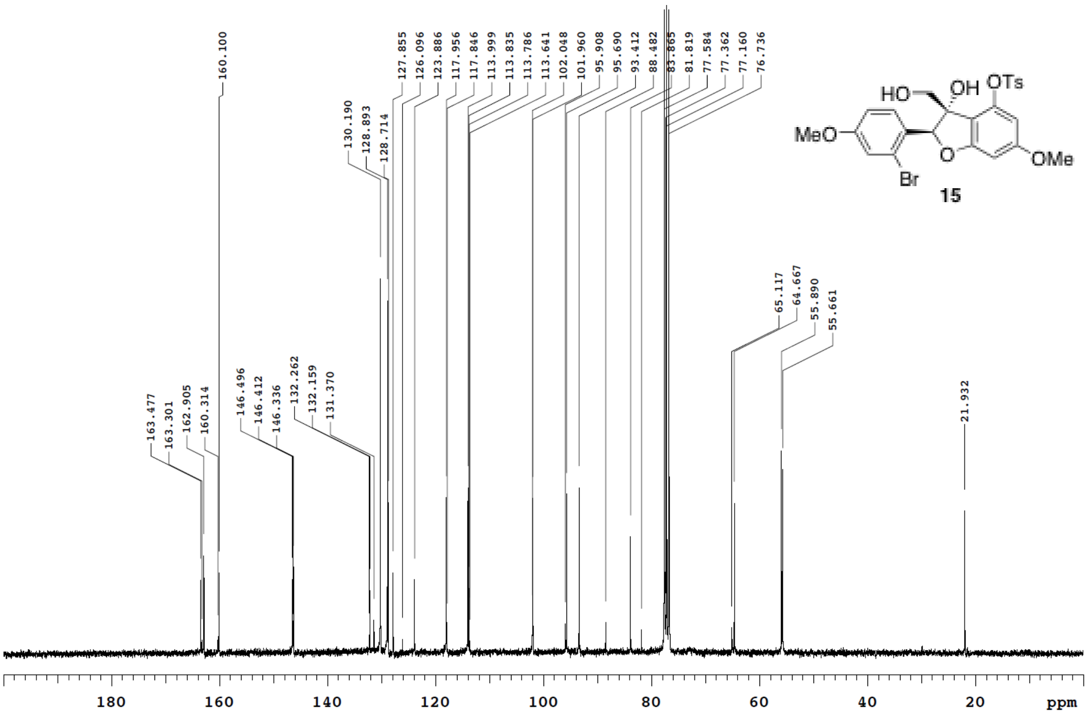

EtO2C
OH
OH
MeO
O
OMe
Br
13
9
8
7
6
5
4
3
2
1
ppm
0.32
0.93
1.14
0.33
1.00
1.89
1.25
0.85
8.92
0.75
3.09

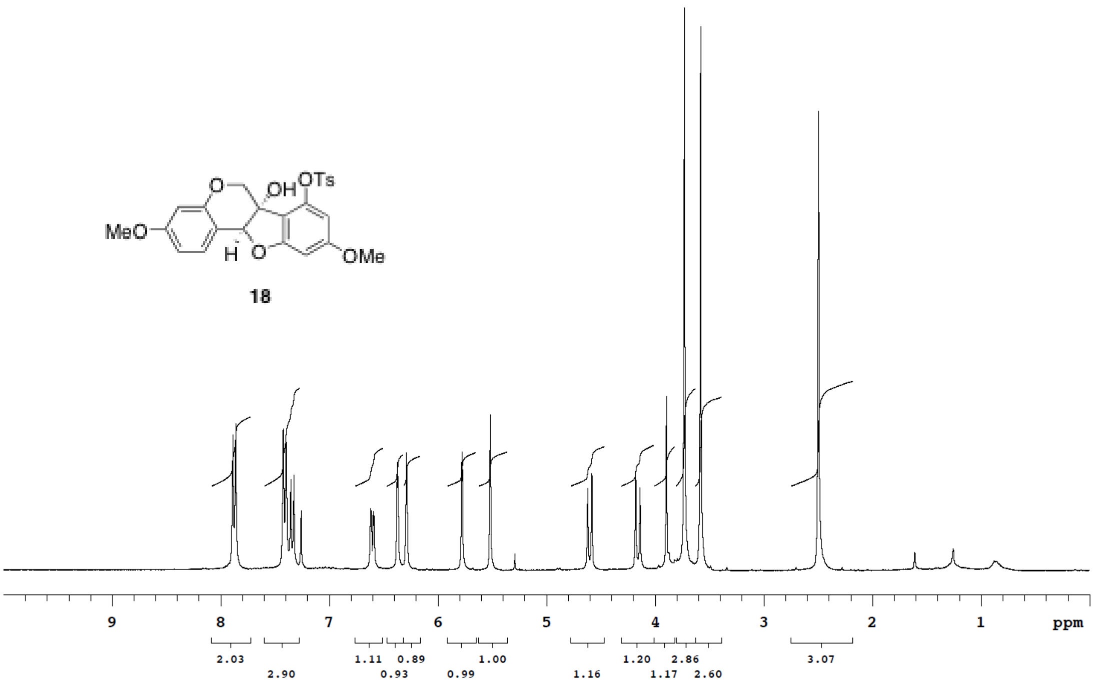

EtO2C
OH
OH
MeO
O
OMe
Br
13
113.656
105.631
89.402
86.143
77.584
77.366
77.160
76.736
171.842
164.156
162.870
160.325
160.169
154.246
153.941
130.370
129.359
127.905
126.474
122.742
117.766
117.659
113.766
105.913
95.938
93.546
89.627
89.550
81.239
63.629
62.839
55.768
55.737
14.284
13.727
180
160
140
120
100
80
60
40
20
ppm

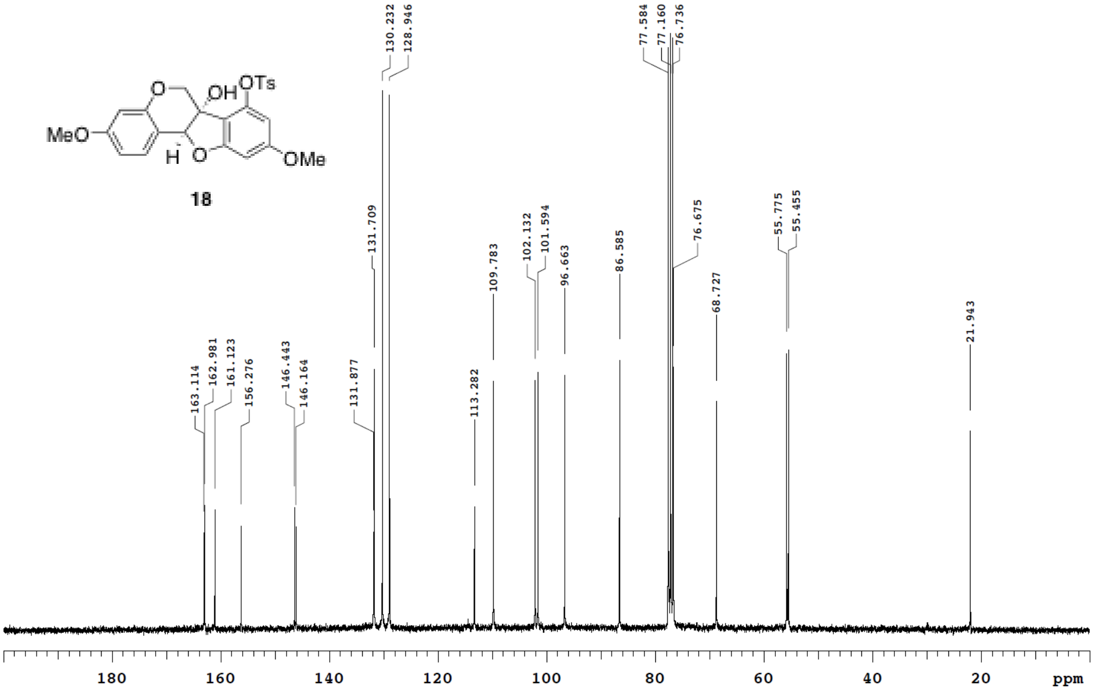

EtO2C
OH
OTs
MeO
O
OMe
Br
14
9
8
7
6
5
4
3
2
1
ppm
2.18
2.04
1.05
1.00
0.89
1.00
0.32
1.03
0.30
1.09
0.36
1.26
8.38
3.40
0.80
3.00

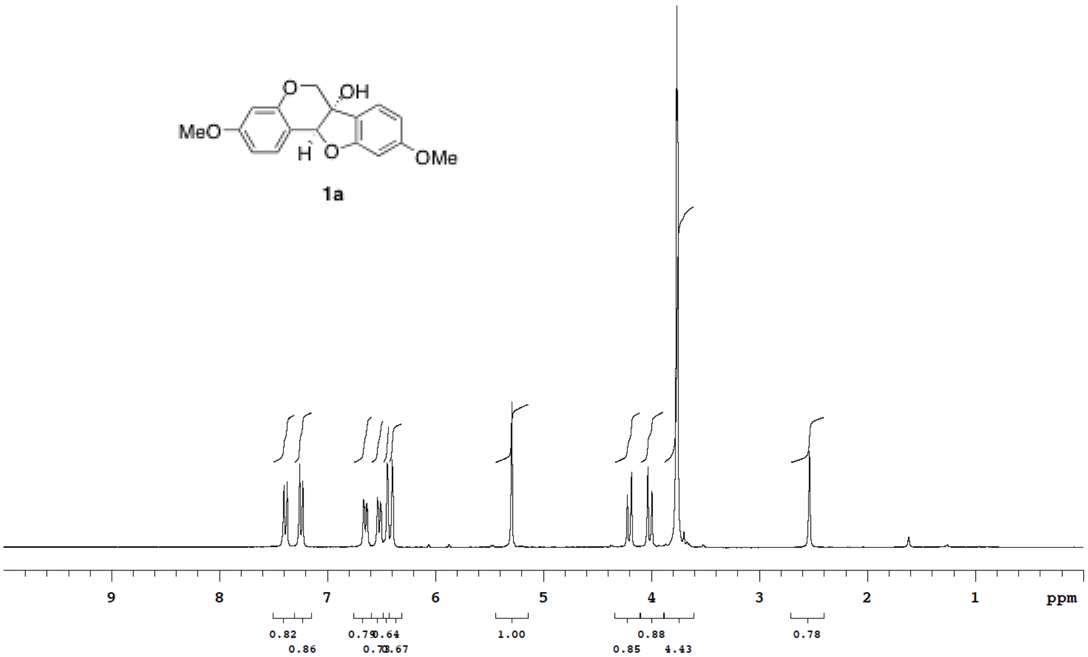

129.908
129.301
128.912
128.771
128.660
127.836
125.558
122.639
122.429
117.575
117.472
114.572
113.576
113.499
112.832
101.735
101.555
95.320
94.877
94.477
90.974
84.651
79.583
77.584
77.362
77.160
76.736
63.434
62.682
55.981
55.691
EtO2C
OH
OTs
MeO
O
OMe
Br
14
13.556
21.867
14.128
172.403
170.712
163.401
163.305
163.118
162.504
160.348
160.092
146.355
145.912
145.828
132.762
132.575
131.381
180
160
140
120
100
80
60
40
20
ppm

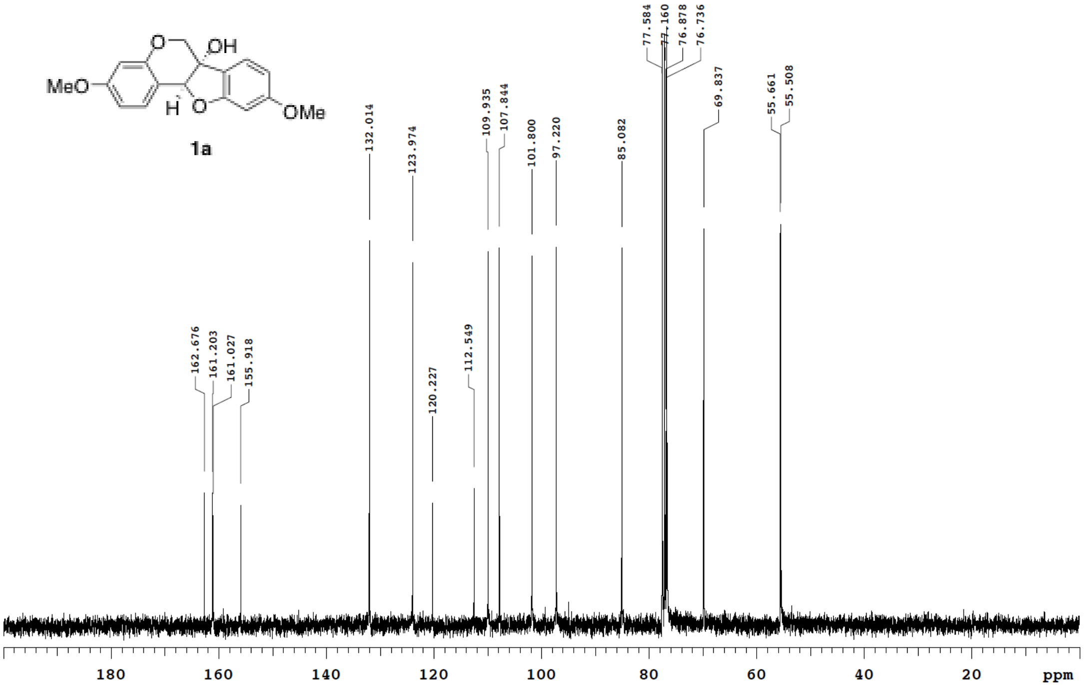

HO
OH
OTs
MeO
O
OMe
Br
15
9
8
7
6
5
4
3
2
1
ppm
2.14
2.25
1.80
0.31
0.93
1.10
1.07
1.00
0.83
4.42
2.82
1.09
3.18
1.05

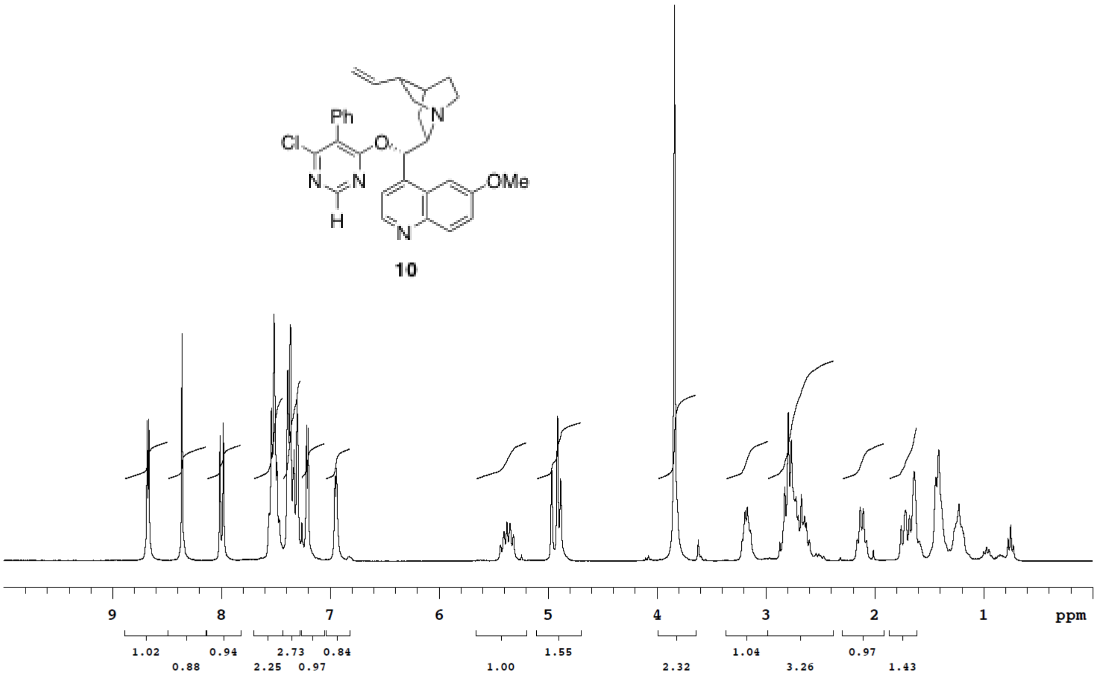

163.477
163.301
162.905
160.314
160.100
146.496
146.412
146.336
132.262
132.159
131.370
130.190
128.893
128.714
127.855
126.096
123.886
117.956
117.846
113.999
113.835
113.786
113.641
102.048
101.960
95.908
95.690
93.412
88.482
83.865
81.819
77.584
77.362
77.160
76.736
65.117
64.667
55.890
55.661
21.932
HO
OH
OTs
MeO
O
OMe
Br
15
180
160
140
120
100
80
60
40
20
ppm


MeO
O
OH
OTs
H
O
OMe
18
9
8
7
6
5
4
3
2
1
ppm
2.03
2.90
1.11
0.93
0.89
0.99
1.00
1.16
1.20
1.17
2.86
2.60
3.07

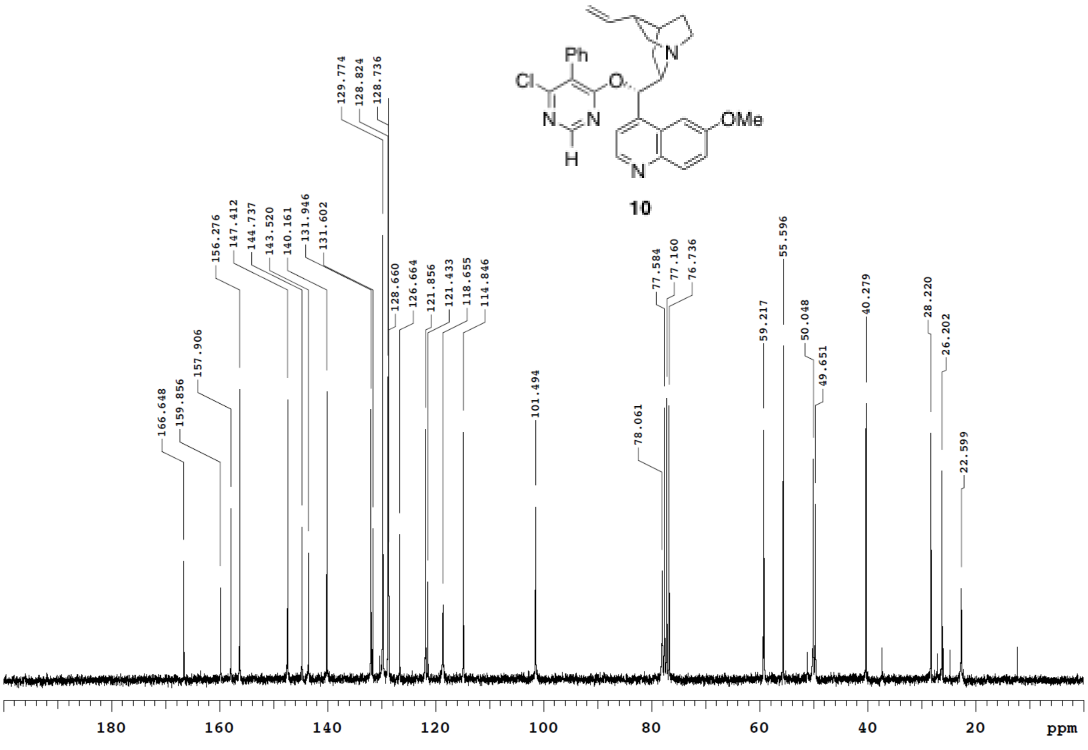

MeO
O
OH
OTs
H
O
OMe
18
163.114
162.981
161.123
156.276
146.443
146.164
131.877
131.709
130.232
128.946
113.282
109.783
102.132
101.594
96.663
86.585
77.584
77.160
76.736
76.675
68.727
55.775
55.455
21.943
180
160
140
120
100
80
60
40
20
ppm


OH
MeO
H
O
OMe
1a
9
8
7
6
5
4
3
2
1
ppm
0.82
0.86
0.79
0.73
0.64
0.67
1.00
0.88
0.85
4.43
0.78

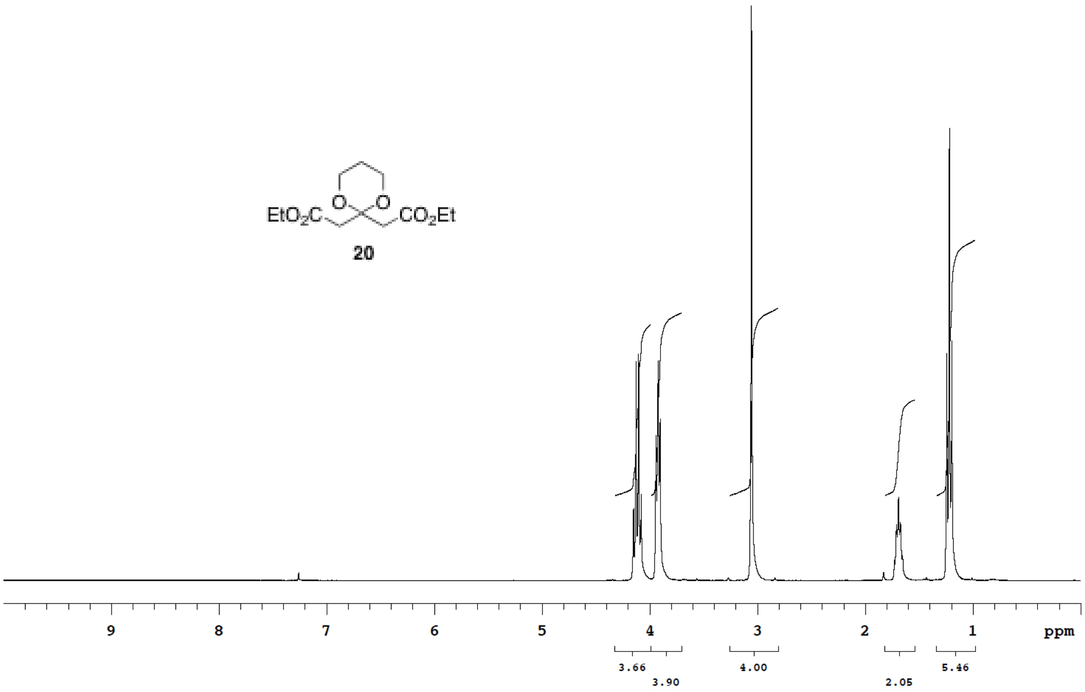

OH
MeO
H
O
OMe
1a
162.676
161.203
161.027
155.918
132.014
123.974
120.227
112.549
109.935
107.844
101.800
97.220
85.082
77.584
77.160
76.878
76.736
69.837
55.661
55.508
180
160
140
120
100
80
60
40
20
ppm

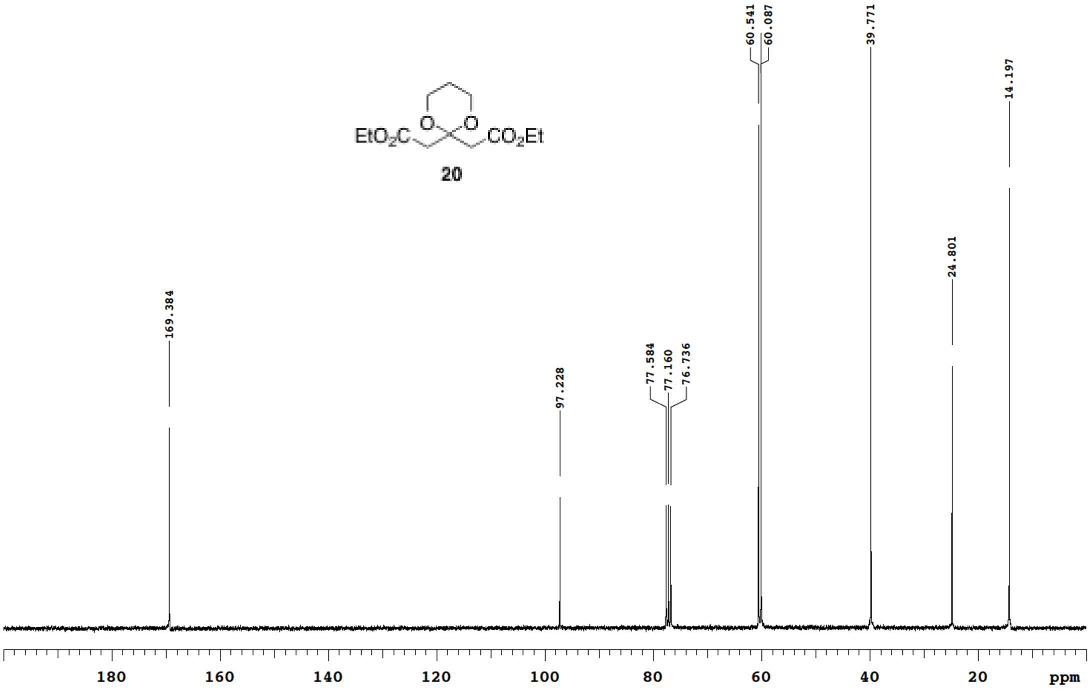

Ph
Cl
O
N
N
N
H
N
OMe
9
8
7
6
5
4
3
2
1
ppm
1.02
0.88
0.94
2.25
2.73
0.97
0.84
1.00
1.55
2.32
1.04
3.26
0.97
1.43

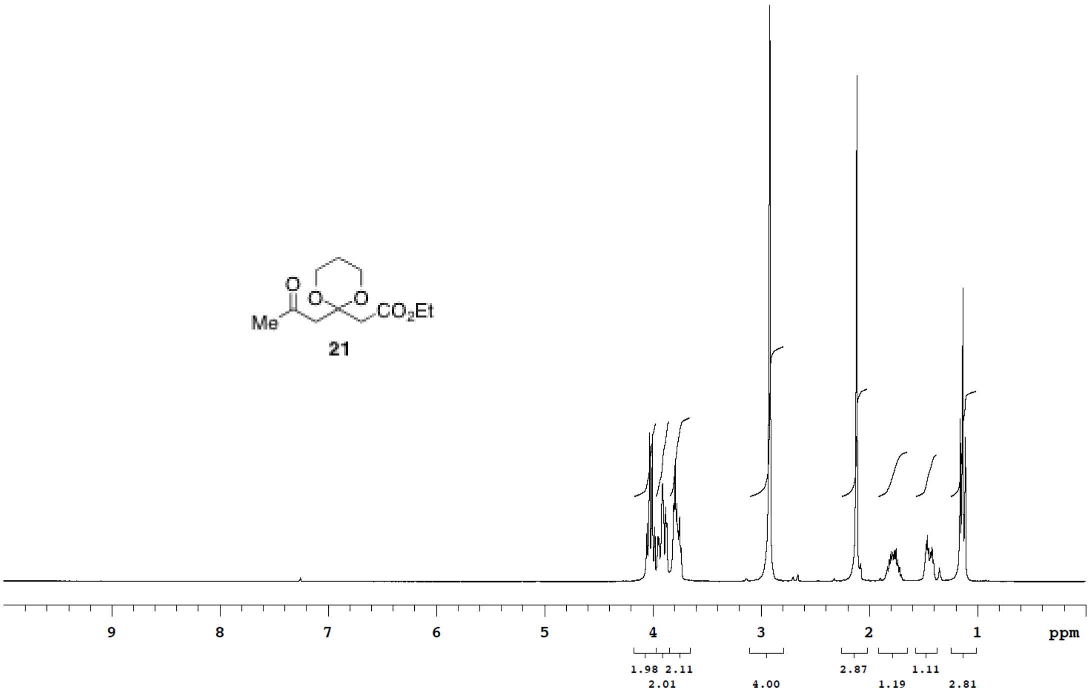
10


Ph
Cl
O
N
N
N
H
N
OMe
166.648
159.856
157.906
156.276
147.412
144.737
143.520
140.161
131.946
131.602
129.774
128.824
128.736
128.660
126.664
121.856
121.433
118.655
114.846
101.494
78.061
77.584
77.160
76.736
59.217
55.596
50.048
49.651
40.279
28.220
26.202
22.599
180
160
140
120
100
80
60
40
20
ppm

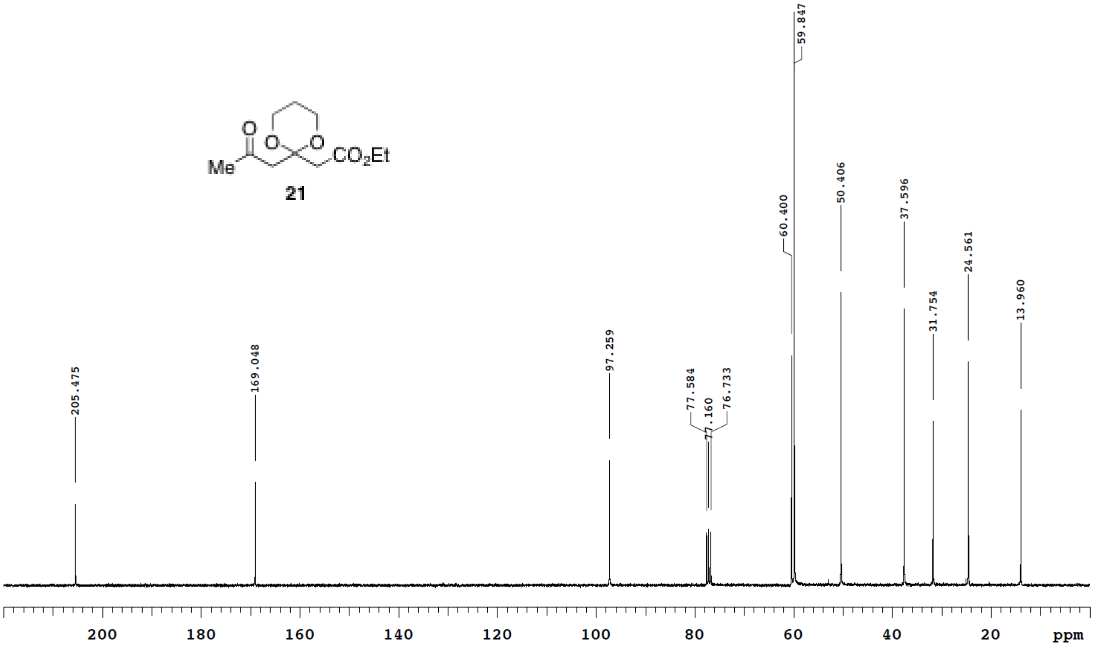
10


EtO2C
CO2Et
20
9
8
7
6
5
4
3
2
1
ppm
3.66
3.90
4.00
2.05
5.46

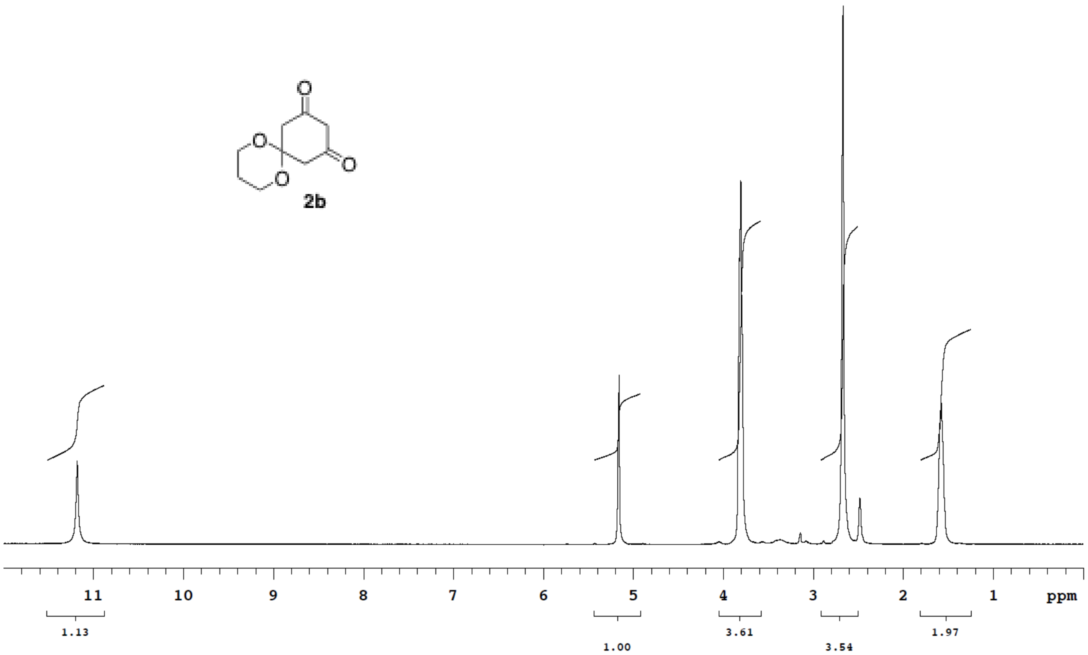

EtO2C
CO2Et
20
169.384
97.228
77.584
77.160
76.736
60.541
60.087
39.771
24.801
14.197
180
160
140
120
100
80
60
40
20
ppm


21

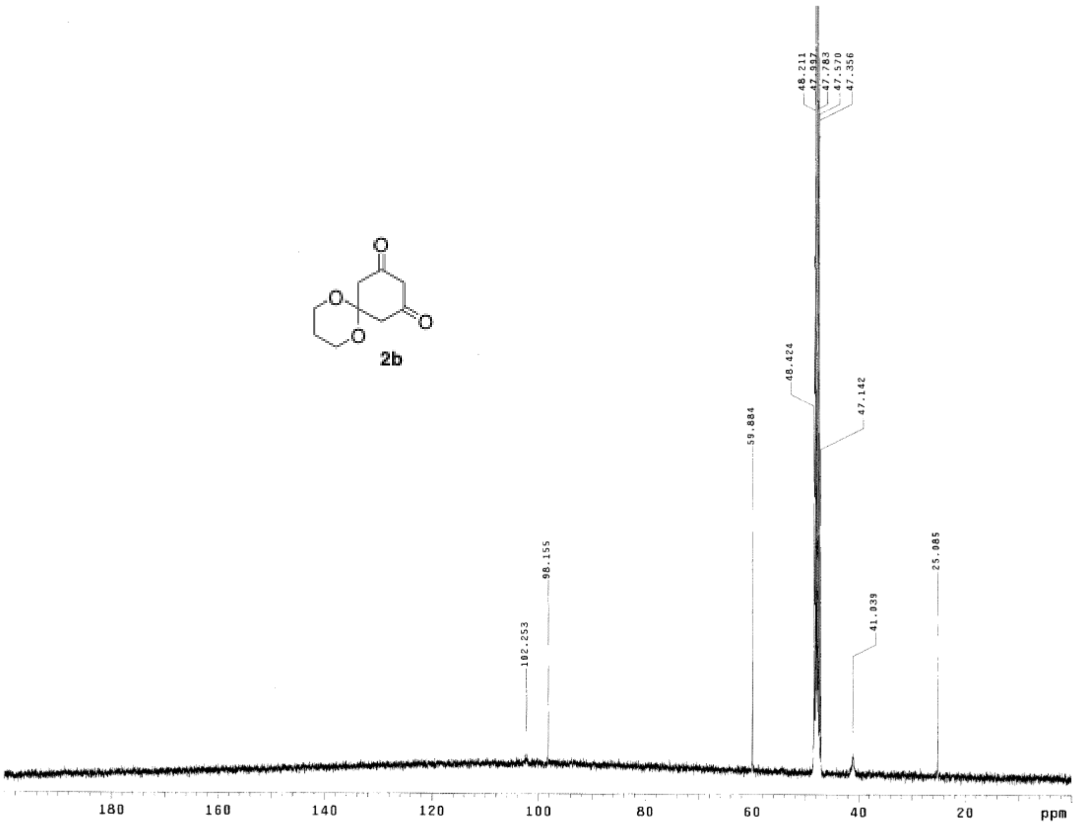
Me
O
CO2Et
9
8
7
6
5
4
3
2
1
ppm
1.98
2.11
2.01
4.00
2.87
1.19
1.11
2.81


21

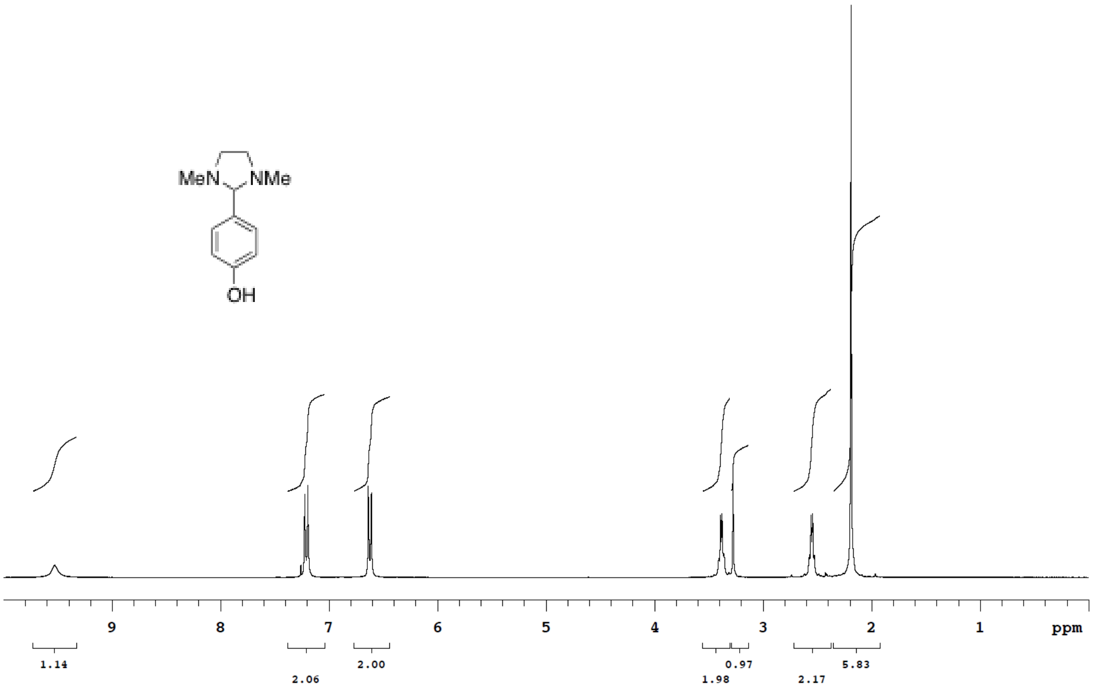
Me
O
CO2Et
205.475
169.048
97.259
77.584
77.160
76.733
60.400
59.847
50.406
37.596
31.754
24.561
13.960
200
180
160
140
120
100
80
60
40
20
ppm

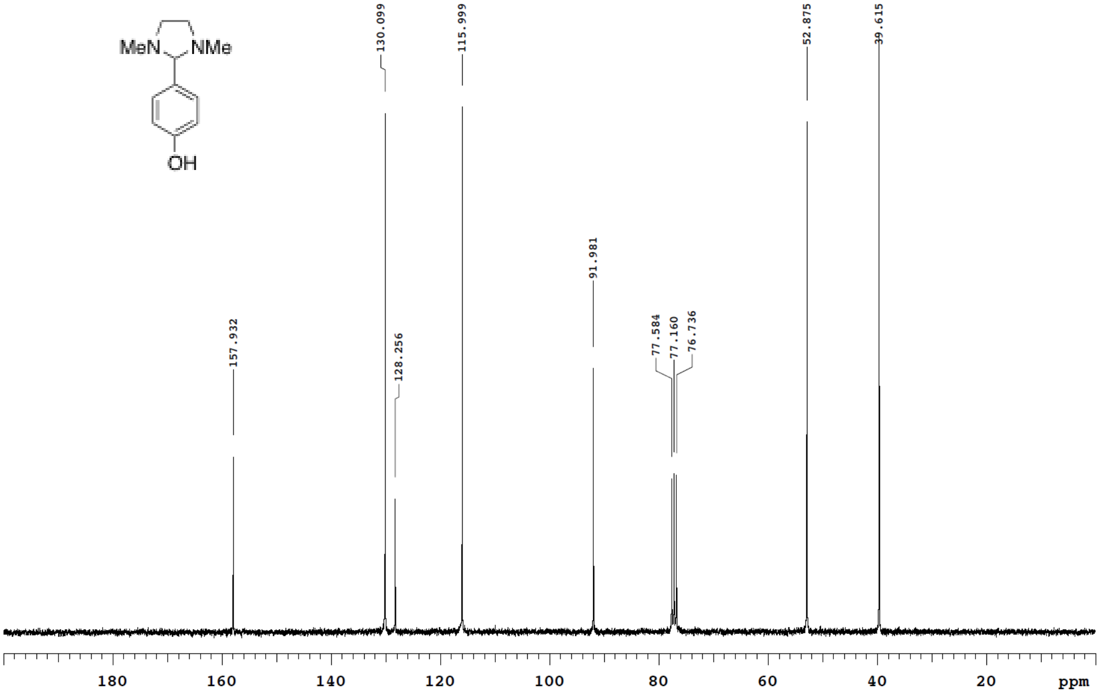


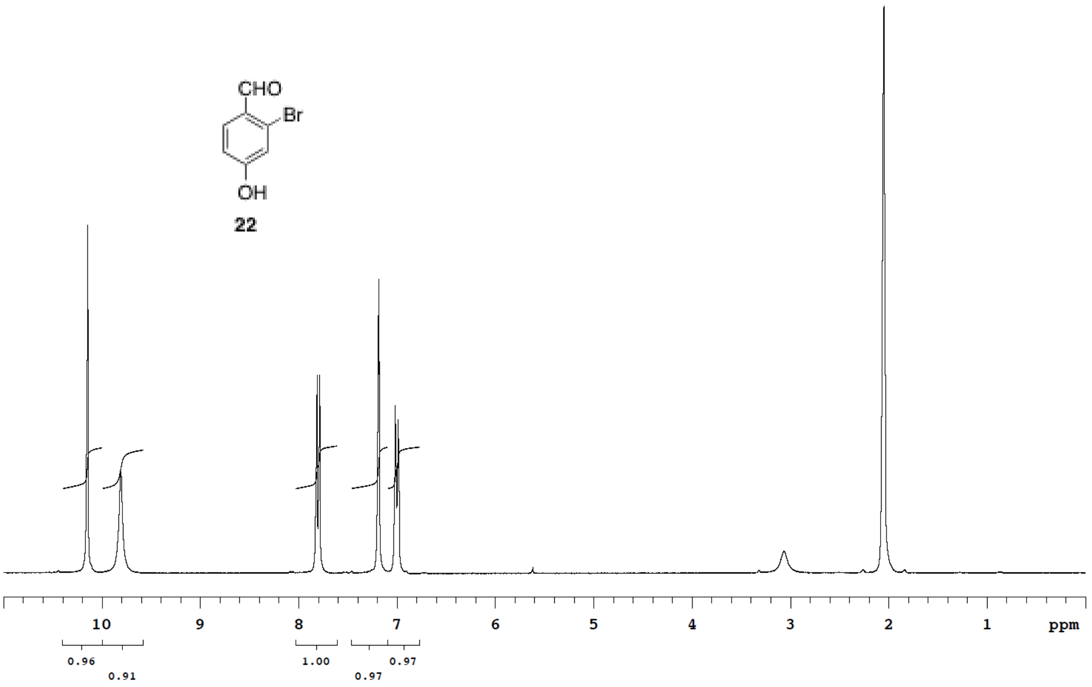
O
O
O
O
2b
11
10
9
8
7
6
5
4
3
2
1
ppm
1.13
1.00
3.61
3.54
1.97

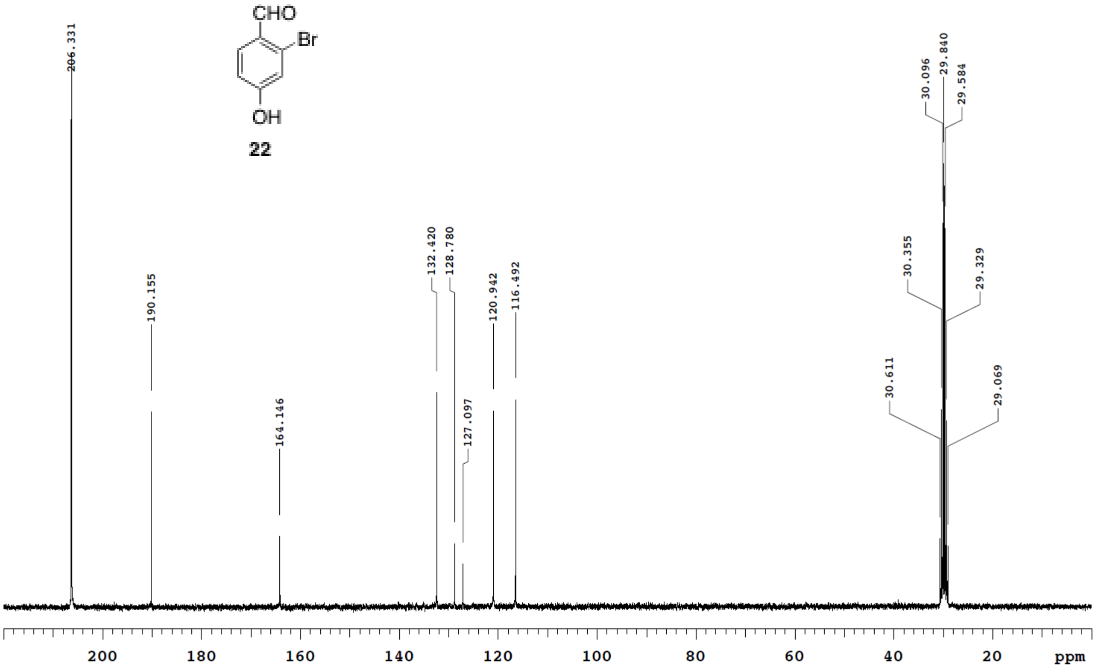


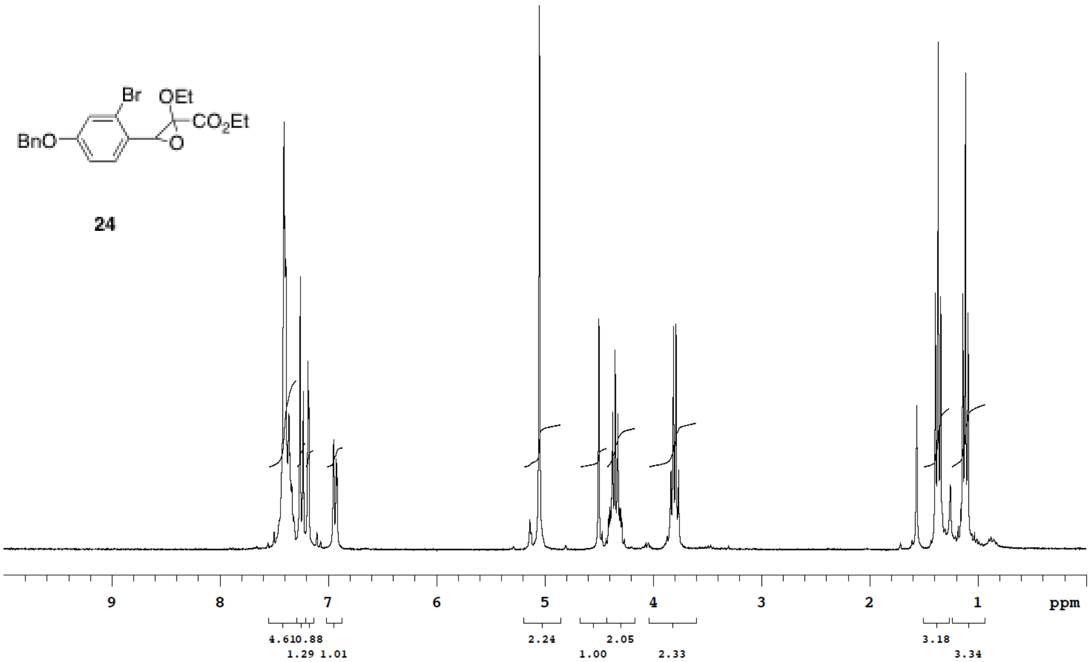
48.211
47.997
47.783
47.570
47.356
O
O
O
O
2b
48.424
47.142
59.884
98.155
102.253
41.039
25.085
180
160
140
120
100
80
60
40
20
ppm


MeN
NMe
OH
9
8
7
6
5
4
3
2
1
ppm
1.14
2.06
2.00
1.98
0.97
2.17
5.83

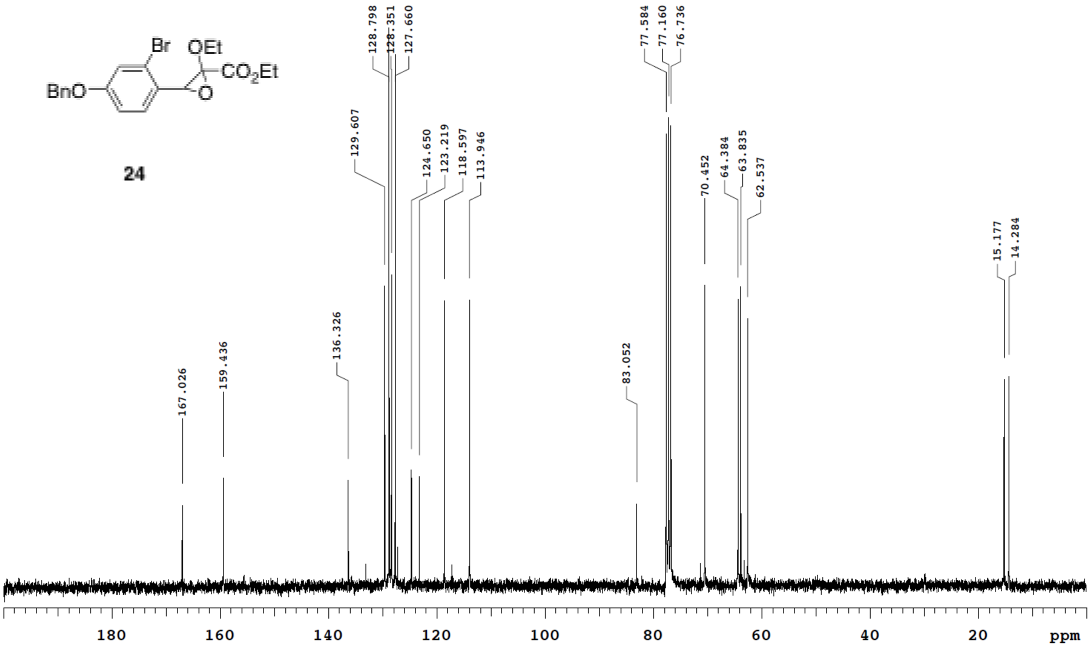

MeN
NMe
OH
157.932
130.099
128.256
115.999
91.981
77.584
77.160
76.736
52.875
39.615
180
160
140
120
100
80
60
40
20
ppm


CHO
Br
OH
22
10
9
8
7
6
5
4
3
2
1
ppm
0.96
0.91
1.00
0.97
0.97

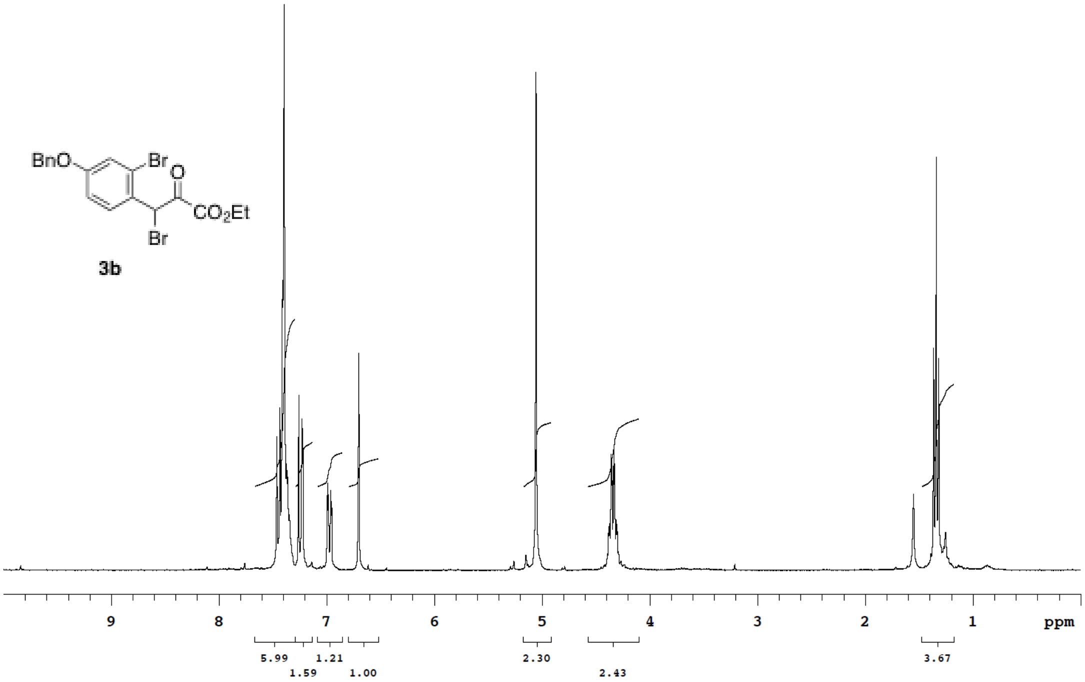

CHO
Br
OH
22
206.331
190.155
164.146
132.420
128.780
127.097
120.942
116.492
30.611
30.355
30.096
29.840
29.584
29.329
29.069
200
180
160
140
120
100
80
60
40
20
ppm

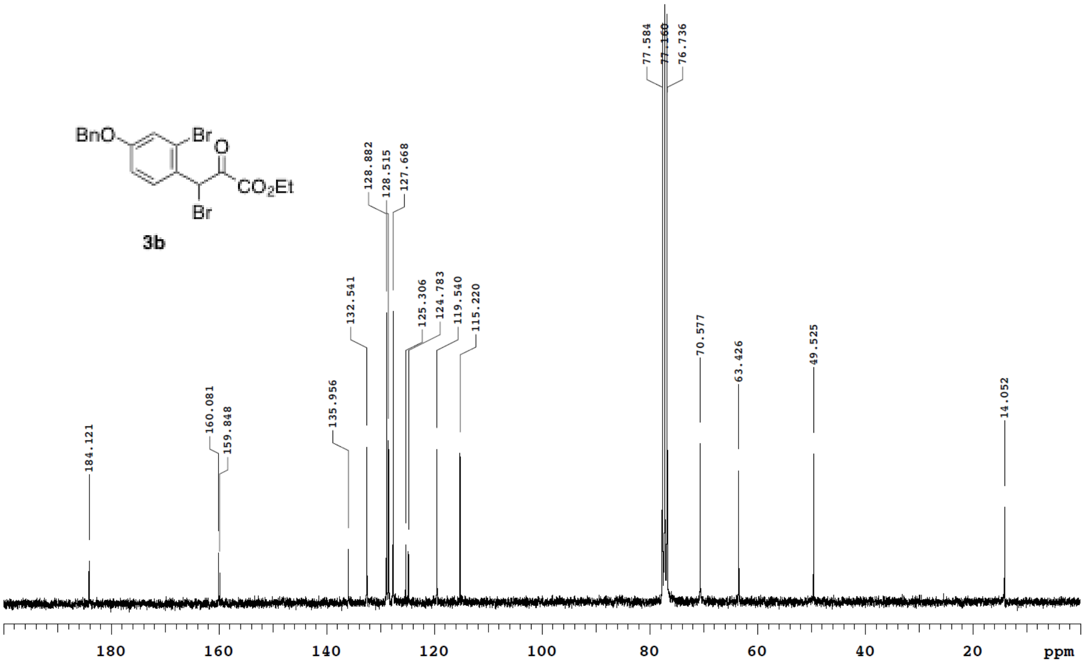

Br
OEt
CO2Et
BnO
O
9
8
7
6
5
4
3
2
1
ppm
4.61
0.88
1.29
1.01
2.24
2.05
1.00
2.33
3.18
3.34

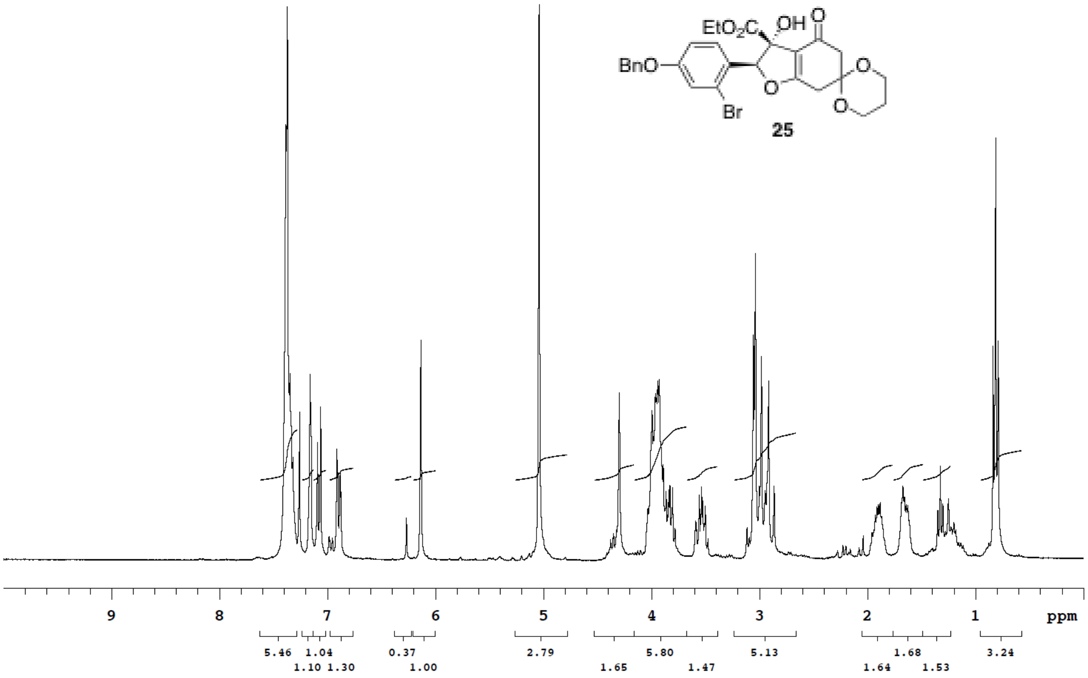
24


Br
OEt
CO2Et
BnO
O
167.026
159.436
136.326
129.607
128.798
128.351
127.660
124.650
123.219
118.597
113.946
83.052
77.584
77.160
76.736
70.452
64.384
63.835
62.537
15.177
14.284
180
160
140
120
100
80
60
40
20
ppm

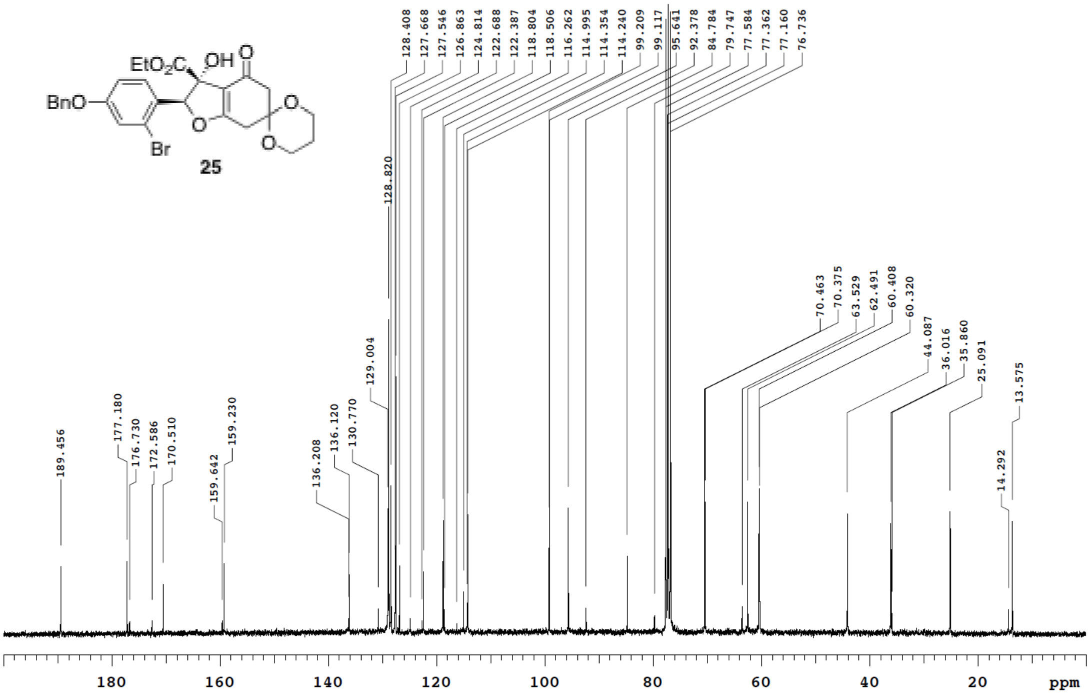
24


BnO
Br
O
CO2Et
Br
3b
9
8
7
6
5
4
3
2
1
ppm
5.99
1.59
1.21
1.00
2.30
2.43
3.67

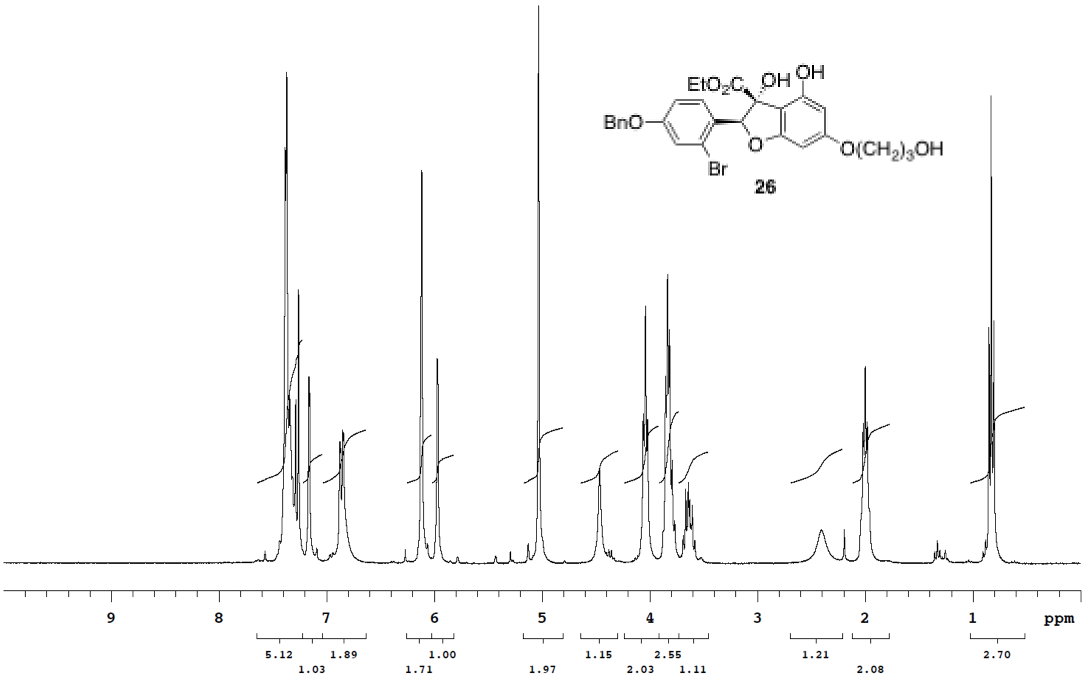

BnO
Br
O
CO2Et
Br
3b
184.121
160.081
159.848
135.956
132.541
128.882
128.515
127.668
125.306
124.783
119.540
115.220
77.584
77.160
76.736
70.577
63.426
49.525
14.052
180
160
140
120
100
80
60
40
20
ppm



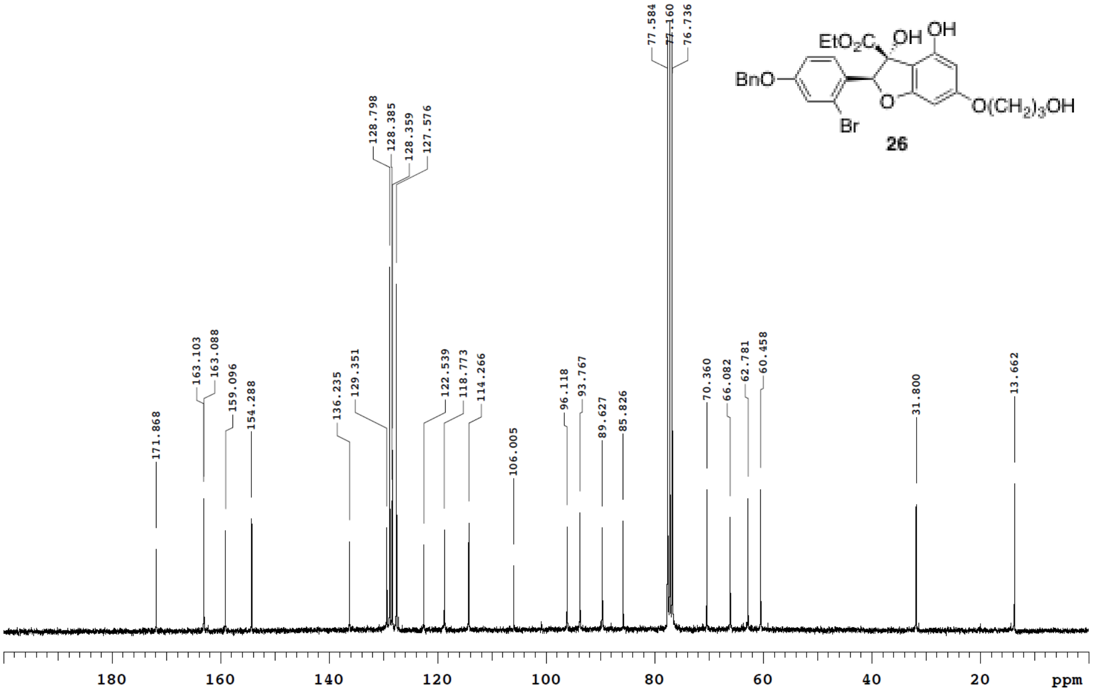
EtO$_2$C
OH
O
BnO
O
O
Br
25
9
8
7
6
5
4
3
2
1
ppm
5.46
1.04
1.10
1.30
0.37
1.00
2.79
1.65
5.80
1.47
5.13
1.64
1.68
1.53
3.24



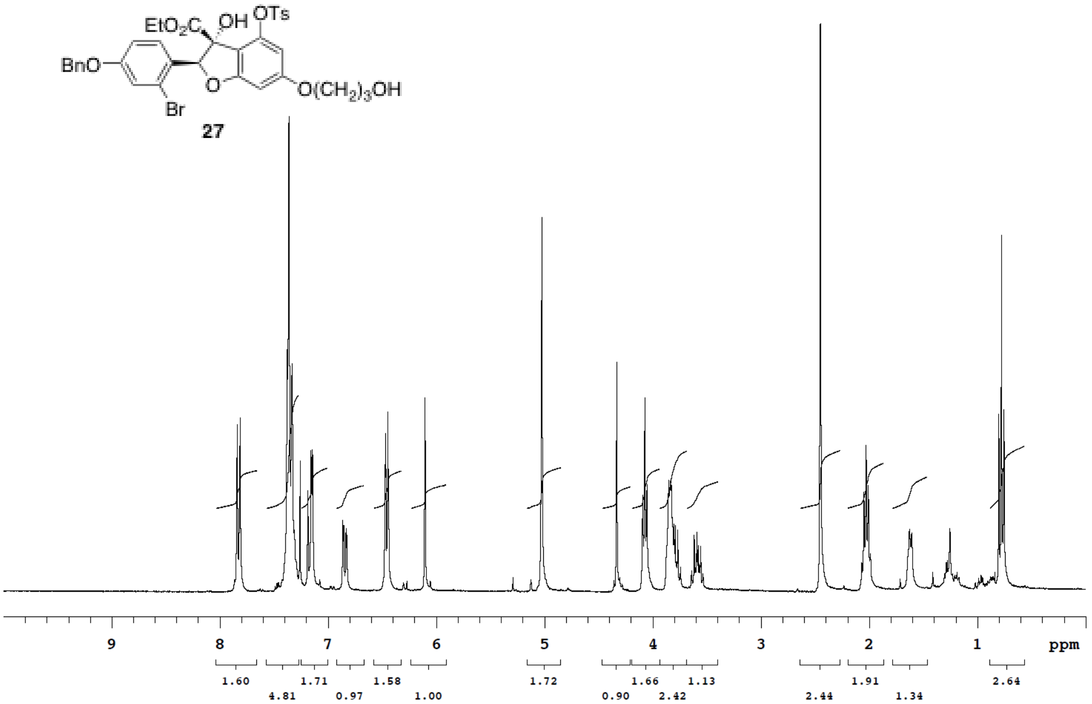
EtO$_2$C
OH
O
BnO
O
O
Br
25
128.408
127.668
127.546
126.863
124.814
122.688
122.387
118.804
118.506
116.262
114.995
114.354
114.240
99.209
99.117
95.641
92.378
84.784
79.747
77.584
77.362
77.160
76.736
128.820
129.004
189.456
177.180
176.730
172.586
170.510
159.642
159.230
136.208
136.120
130.770
70.463
70.375
63.529
62.491
60.408
60.320
44.087
36.016
35.860
25.091
13.575
14.292
180
160
140
120
100
80
60
40
20
ppm

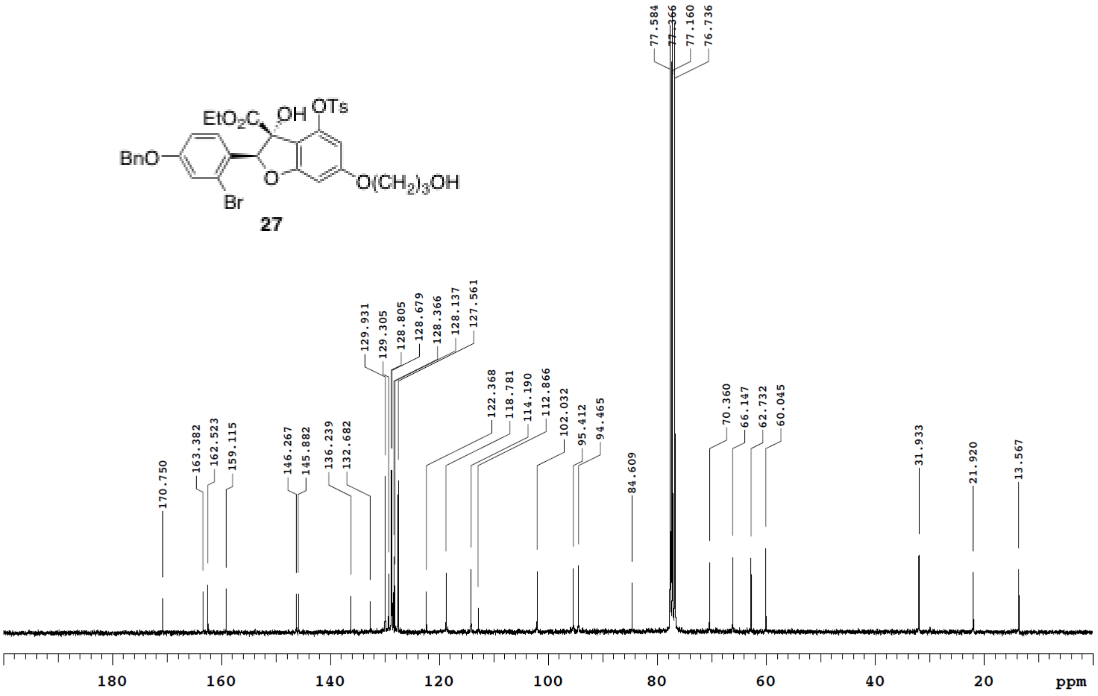


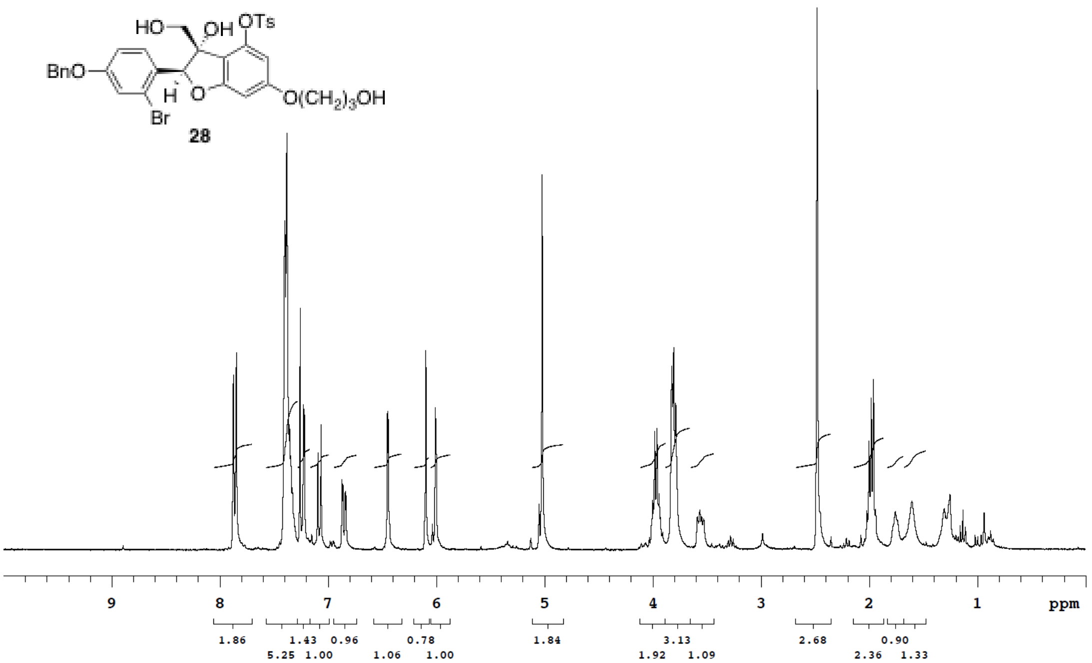
EtO2C
OH
OH
BnO
O
O(CH2)3OH
Br
26
9
8
7
6
5
4
3
2
1
ppm
5.12
1.03
1.89
1.71
1.00
1.97
1.15
2.03
2.55
1.11
1.21
2.08
2.70



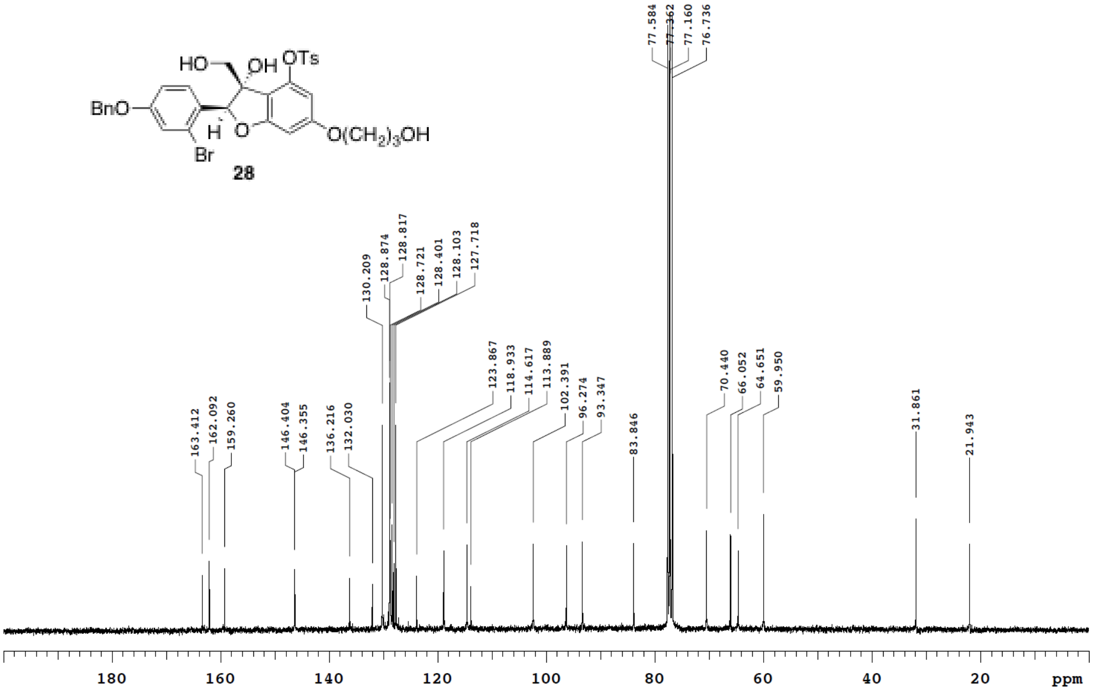
77.584
77.160
76.736
EtO2C
OH
OH
BnO
O
O(CH2)3OH
Br
26
128.798
128.385
128.359
127.576
171.868
163.103
163.088
159.096
154.288
136.235
129.351
122.539
118.773
114.266
106.005
96.118
93.767
89.627
85.826
70.360
66.082
62.781
60.458
31.800
13.662
180
160
140
120
100
80
60
40
20
ppm


EtO2C
OH
OTs
BnO
O
O(CH2)3OH
Br
27
9
8
7
6
5
4
3
2
1
ppm
1.60
4.81
1.71
0.97
1.58
1.00
1.72
0.90
1.66
2.42
1.13
2.44
1.91
1.34
2.64

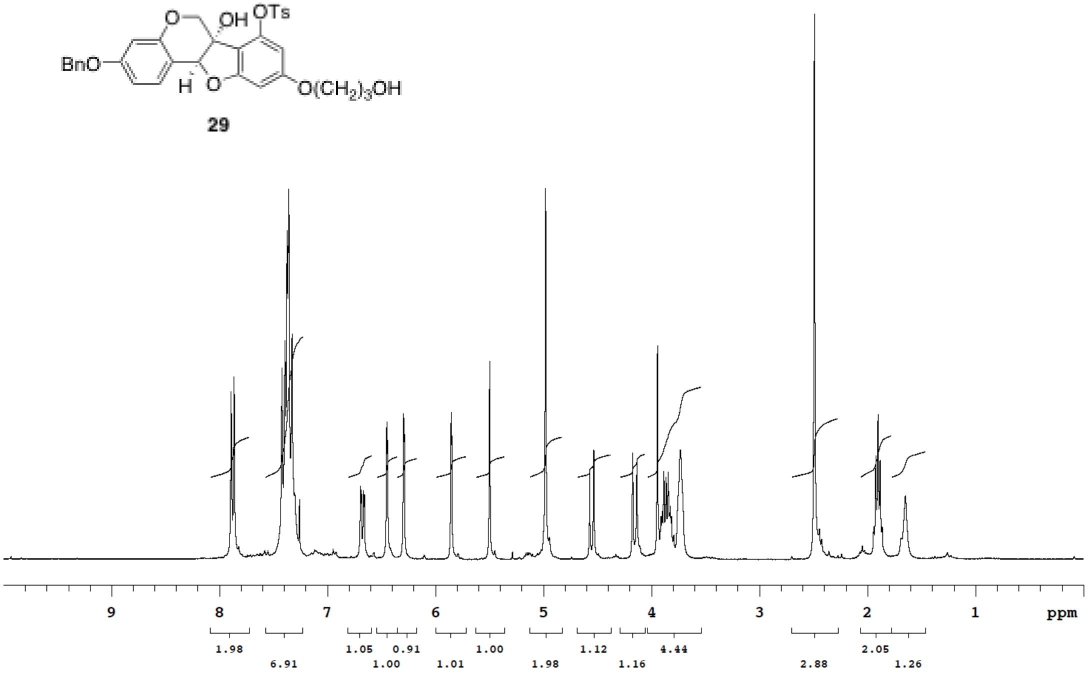

EtO2C
OH
OTs
BnO
O
O(CH2)3OH
Br
27
170.750
163.382
162.523
159.115
146.267
145.882
136.239
132.682
129.931
129.305
128.805
128.679
128.366
128.137
127.561
122.368
118.781
114.190
112.866
102.032
95.412
94.465
84.609
77.584
77.366
77.160
76.736
70.360
66.147
62.732
60.045
31.933
21.920
13.567
180
160
140
120
100
80
60
40
20
ppm



HO
OH
OTs
BnO
H
O
Br
O(CH₂)₃OH
28
1.86
5.25
1.43
1.00
0.96
1.06
0.78
1.00
1.84
1.92
3.13
1.09
2.68
2.36
0.90
1.33
9
8
7
6
5
4
3
2
1
ppm

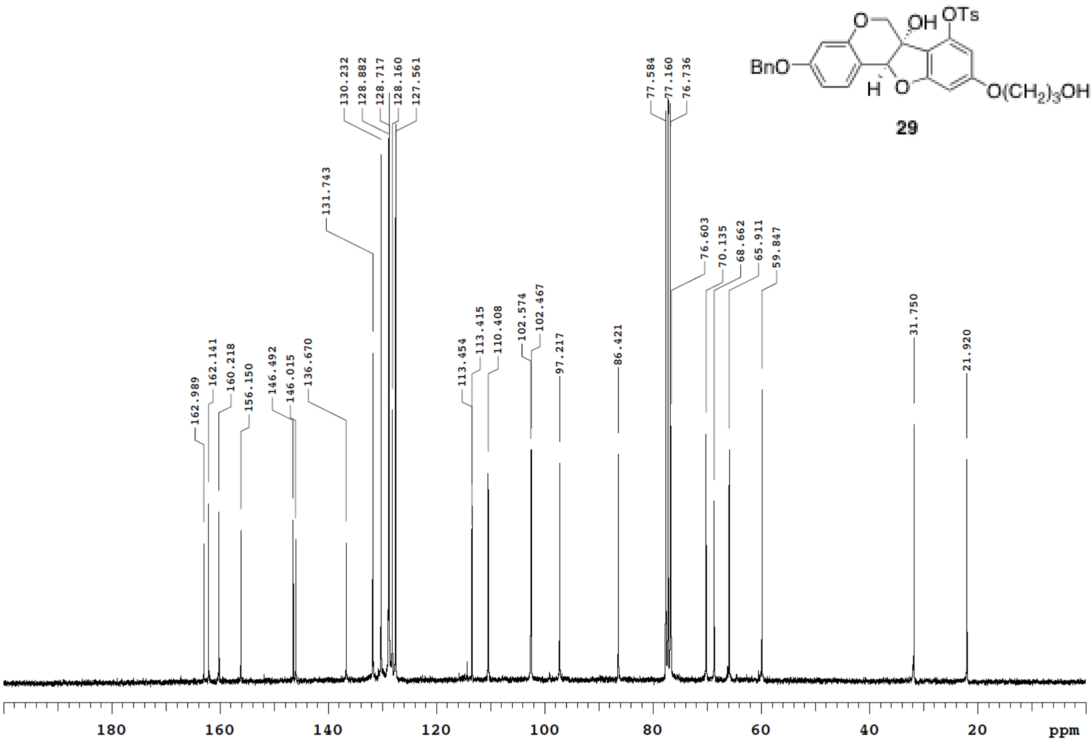


HO
OH
OTs
BnO
H
O
Br
O(CH₂)₃OH
28
163.412
162.092
159.260
146.404
146.355
136.216
132.030
130.209
128.874
128.817
128.721
128.401
128.103
127.718
123.867
118.933
114.617
113.889
102.391
96.274
93.347
83.846
77.584
77.362
77.160
76.736
70.440
66.052
64.651
59.950
31.861
21.943
180
160
140
120
100
80
60
40
20
ppm



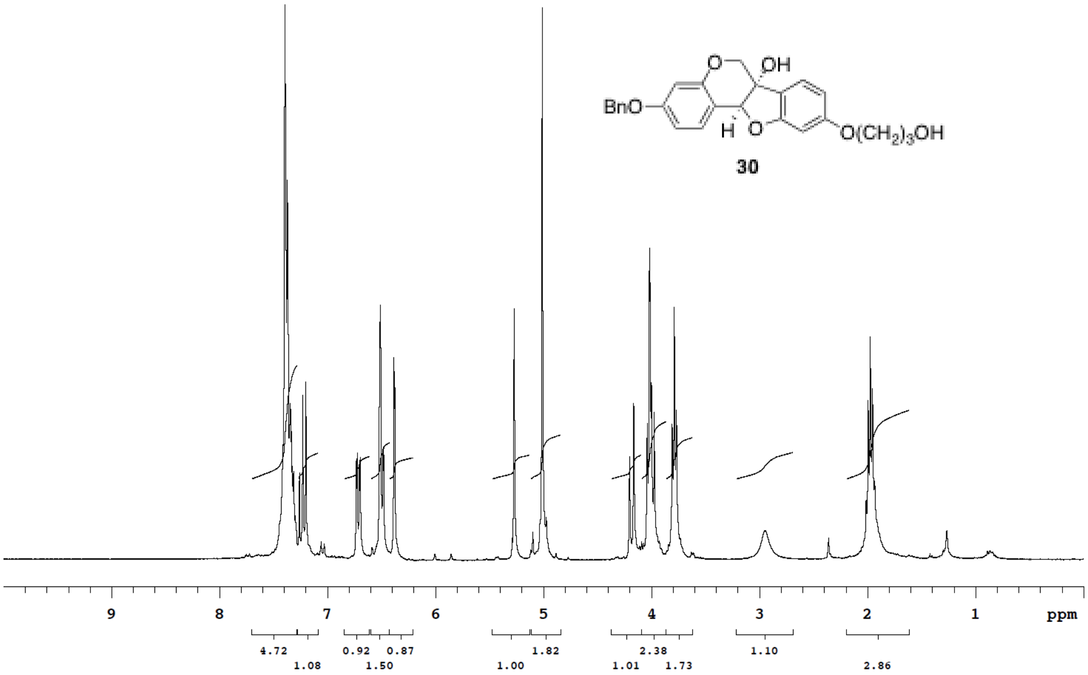
BnO
O
OH
OTs
H
O(CH₂)₃OH
9
8
7
6
5
4
3
2
1
ppm
1.98
6.91
1.05
1.00
0.91
1.01
1.00
1.98
1.12
1.16
4.44
2.88
2.05
1.26

29

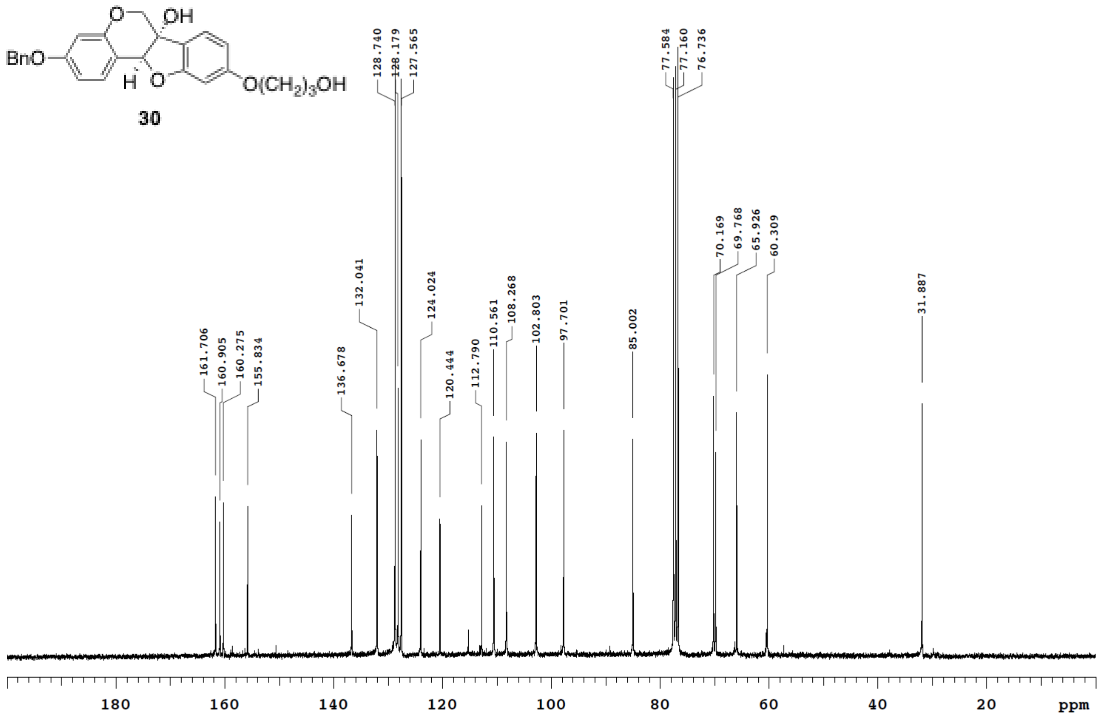


BnO
O
OH
OTs
H
O(CH₂)₃OH
162.989
162.141
160.218
156.150
146.492
146.015
136.670
131.743
130.232
128.882
128.717
128.160
127.561
113.454
113.415
110.408
102.574
102.467
97.217
86.421
77.584
77.160
76.736
76.603
70.135
68.662
65.911
59.847
31.750
21.920
180
160
140
120
100
80
60
40
20
ppm

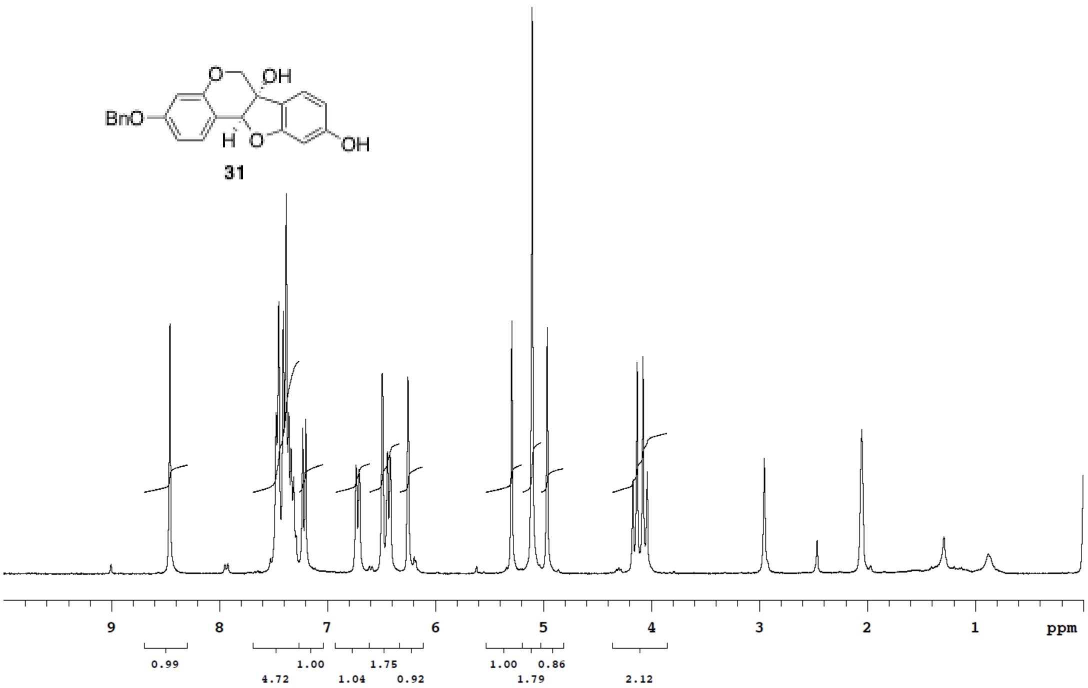
29



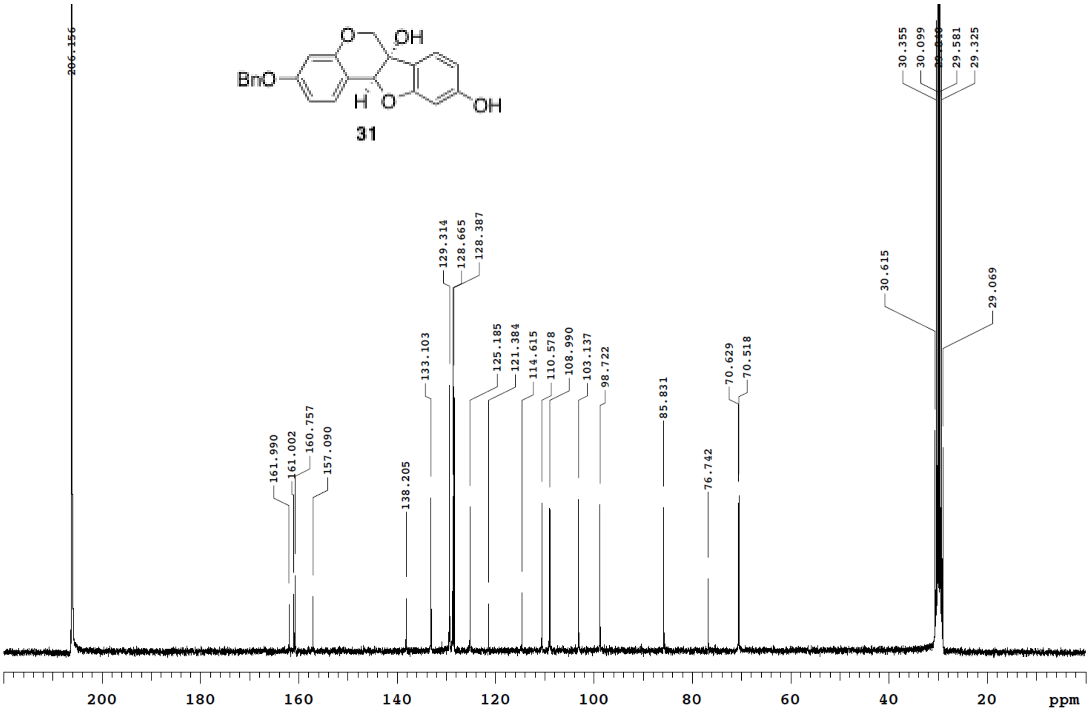
BnO
OH
H
O
O(CH2)3OH
30
9
8
7
6
5
4
3
2
1
ppm
4.72
1.08
0.92
1.50
0.87
1.00
1.82
1.01
2.38
1.73
1.10
2.86



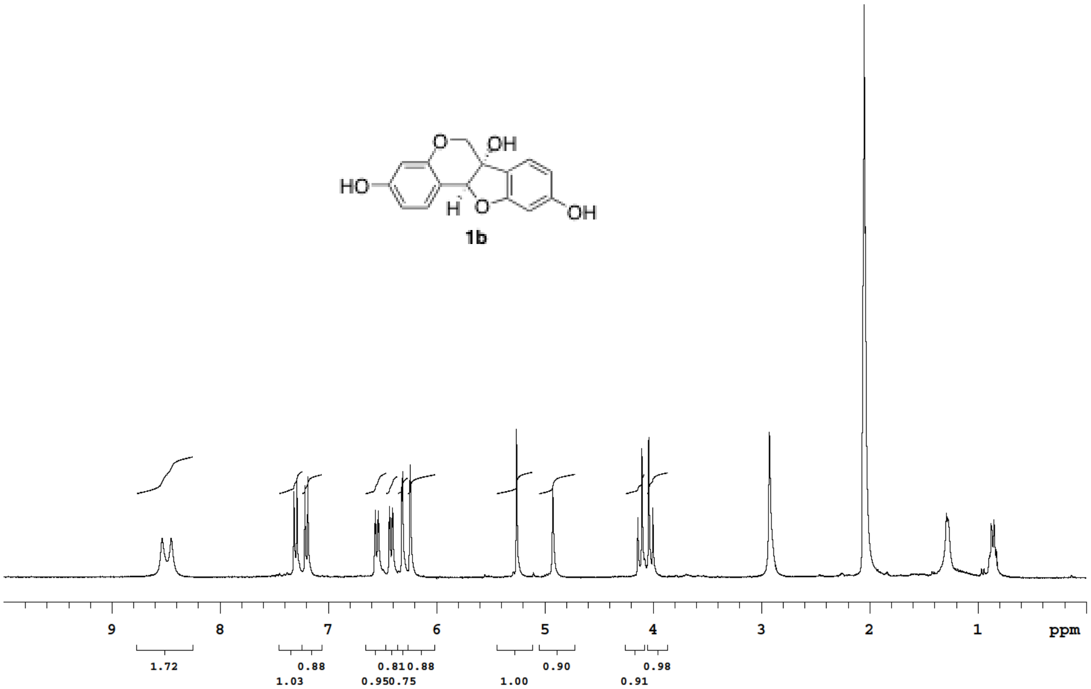
BnO
OH
H
O
O(CH2)3OH
30
161.706
160.905
160.275
155.834
136.678
132.041
128.740
128.179
127.565
124.024
120.444
112.790
110.561
108.268
102.803
97.701
85.002
77.584
77.160
76.736
70.169
69.768
65.926
60.309
31.887
180
160
140
120
100
80
60
40
20
ppm

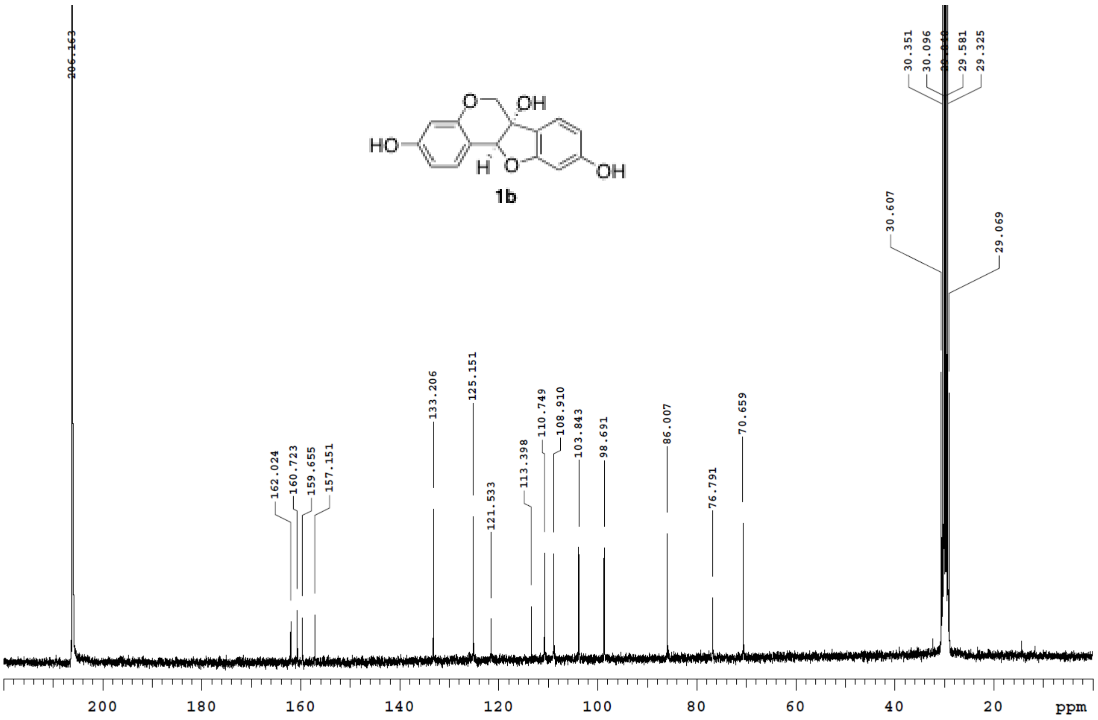


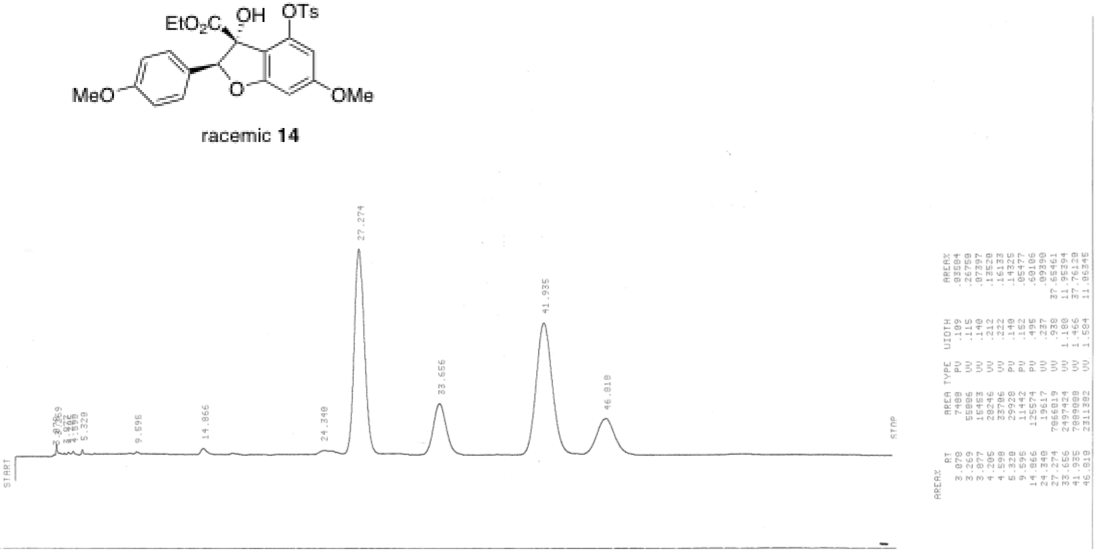
BnO
OH
H
O
O
OH
31
9
8
7
6
5
4
3
2
1
ppm
0.99
1.00
4.72
1.04
1.75
0.92
1.00
0.86
1.79
2.12



206.156
BnO
OH
H
O
O
OH
31
30.355
30.099
29.581
29.325
30.615
29.069
129.314
128.665
128.387
133.103
125.185
121.384
114.615
110.578
108.990
103.137
98.722
85.831
70.629
70.518
161.990
161.002
160.757
157.090
138.205
76.742
200
180
160
140
120
100
80
60
40
20
ppm

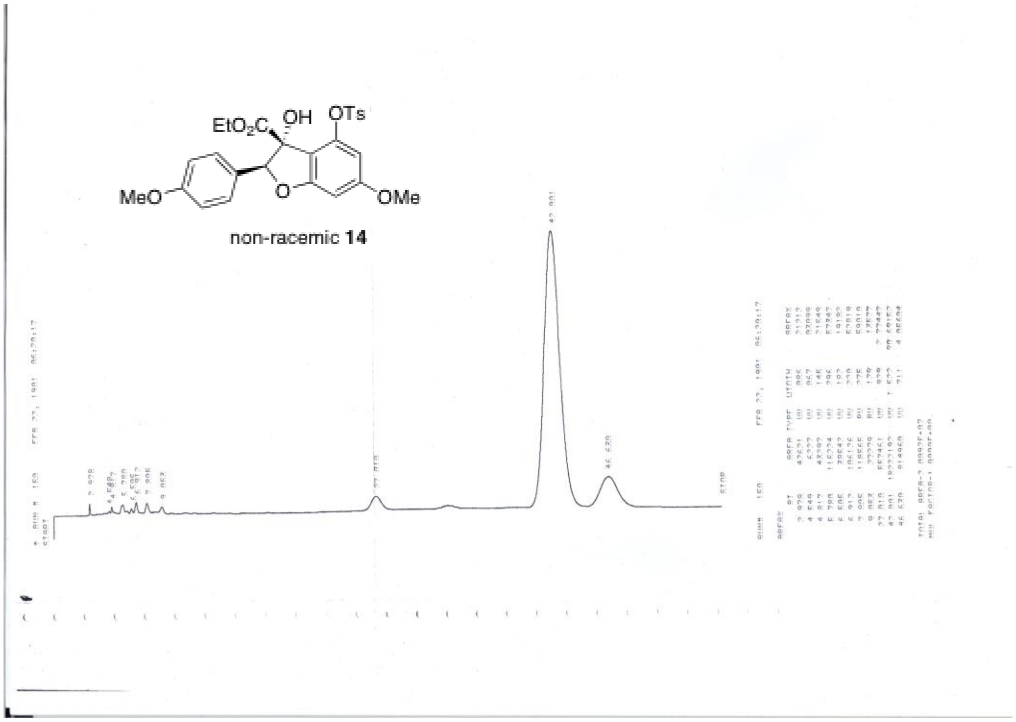

HO
O
OH
H
O
OH
1b
9
8
7
6
5
4
3
2
1
ppm
1.72
0.88
1.03
0.81
0.88
0.95
0.75
1.00
0.90
0.91
0.98


206.163
30.351
30.096
29.581
29.325
30.607
29.069
HO
O
OH
H
O
OH
1b
162.024
160.723
159.655
157.151
133.206
125.151
121.533
113.398
110.749
108.910
103.843
98.691
86.007
76.791
70.659
200
180
160
140
120
100
80
60
40
20
ppm



racemic **14**

```
AREA%
     RT        AREA TYPE  WIDTH       AREA%
   3.078       7488   PV   .109      .03584
   3.269      55806   VV   .115      .26759
   3.877      15453   VV   .140      .07397
   4.205      28246   VV   .212      .13520
   4.598      33706   VV   .222      .16133
   5.328      29928   PV   .140      .14325
   9.595      11442   PV   .152      .05477
  14.866     125574   PV   .495      .60106
  24.340      19617   VV   .237      .09390
  27.274    7866819   VV   .938    37.65461
  33.656    2497424   VV  1.180    11.95394
  41.935    7889088   VV  1.466    37.76120
  46.818    2311382   VV  1.584    11.06345
```

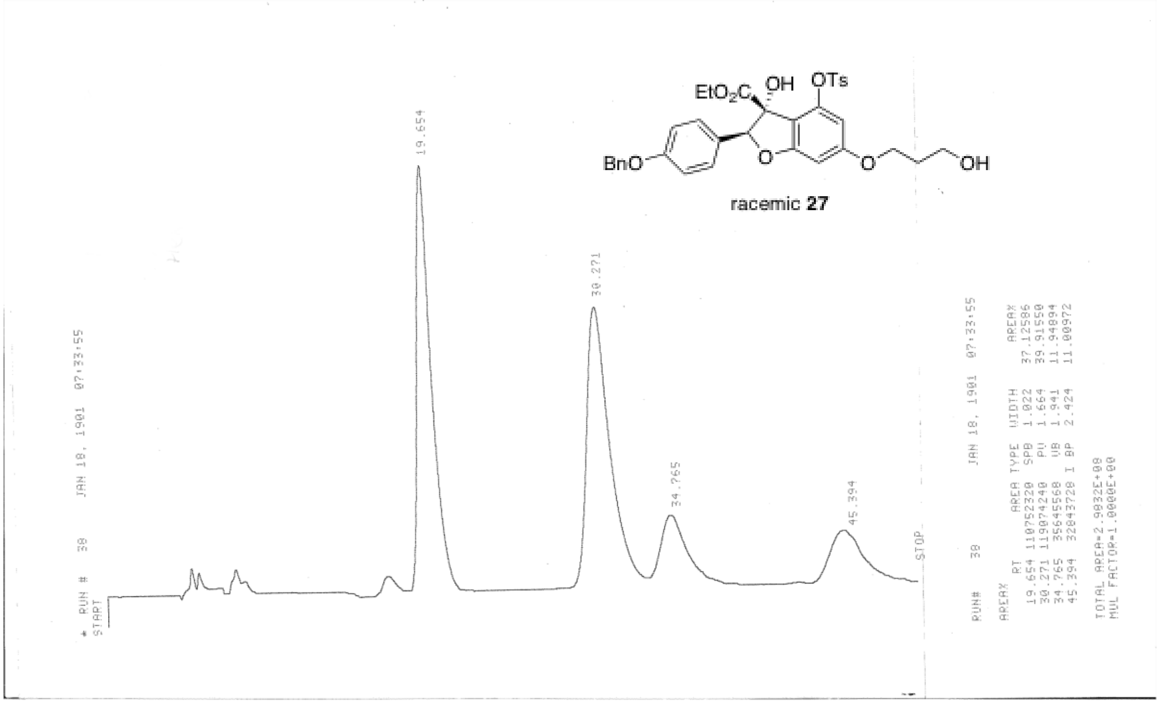


non-racemic **14**

```
RUN#   150            FEB 22, 1991  06:20:17

AREA%
     RT        AREA TYPE  WIDTH       AREA%
   2.929      47671   VV   .096      .21212
   4.549       6227   VV   .067      .03099
   4.917      47297   VV   .145      .21540
   5.798     115224   VV   .296      .57747
   6.505      38542   VV   .182      .19192
   6.917     106126   VV   .220      .52819
   7.905     118565   PV   .275      .59010
   9.053      27279   PV   .129      .13577
  27.818     557461   VV   .928     2.77447
  42.001   18222192   VV  1.522    90.68152
  46.630     914960   VV   .711     4.95694

TOTAL AREA=2.0093E+07
MUL FACTOR=1.0000E+00
```



racemic **27**

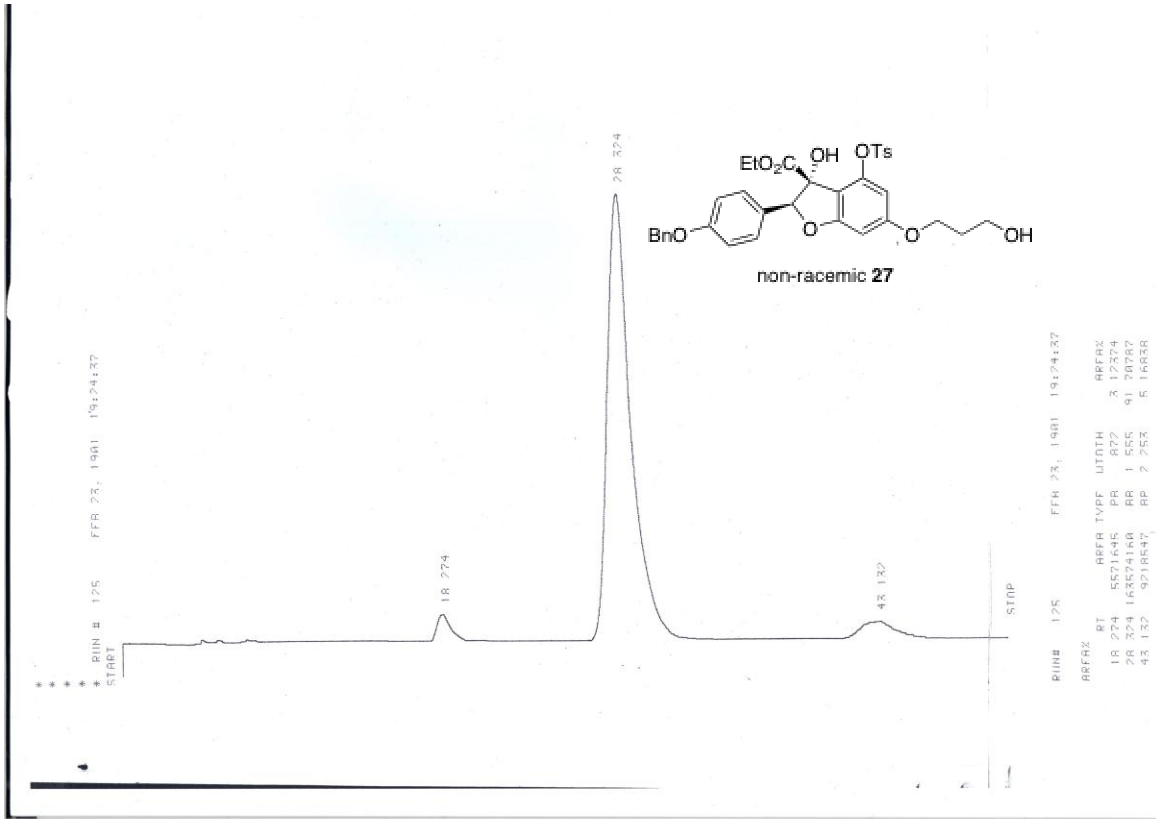
```
* RUN #   38      JAN 18, 1901  07:33:55
START

STOP

RUN#    38            JAN 18, 1901  07:33:55

AREA%
      RT        AREA TYPE  WIDTH      AREA%
  19.654 110752320  SPB  1.022   37.12586
  30.271 119074240   PU  1.664   39.91550
  34.765  35645568   VB  1.941   11.94894
  45.394  32843728 I BP  2.424   11.00972

TOTAL AREA=2.9832E+08
MUL FACTOR=1.0000E+00
```



non-racemic **27**

```
*
*
*
*
* RUN #  125      FFR 23, 1901  19:24:37
START

STOP

RIIN#   125           FFR 23, 1901  19:24:37

ARFA%
      RT        ARFA TYPF  WTDTH      ARFA%
  18 274   5571645   PR    872    3 12374
  28 324 163574160   RR  1 555   91 70787
  43 132   9218547   RP  2 253    5 16838
```