Supporting Information

Enantioselective Synthesis of Azamerone

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1. General Information

All reactions were conducted in oven- or flame-dried glassware under an atmosphere of nitrogen or argon unless otherwise noted. Commercial reagents and solvents were used as received unless otherwise noted with the exception of the following: hexanes (ACS grade, 4.2% various methylpentanes), toluene, tetrahydrofuran, acetonitrile, methanol, benzene, and dichloromethane were dried by passing through a bed of activated alumina in a JC Meyer Solvent System. Flash column chromatography was performed using F60 silica gel (40-63 μm, 230-400 mesh, 60Å) purchased from Silicycle. Analytical thin-layer chromatography (TLC) was carried out on 250 μm 60-F_{254} silica gel plates purchased from EMD Millipore, and visualization was effected by observation of fluorescence-quenching with ultraviolet light and staining with either *p*-anisaldehyde or phosphomolybdic acid (PMA) with cerium sulfate as a developing agent. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian Inova 600, Varian Inova 500, Varian Mercury 400, or Varian Inova 300 spectrometers operating respectively at 600, 500, 400, and 300 MHz for ^{1}H and at 150, 125, 100, and 75 MHz for ^{13}C. Chemical shifts are reported in parts per million (ppm) with respect to residual protonated solvent for ^{1}H ($CDCl_3$ = δ 7.26, CD_3OD = δ 3.31, DMSO-d6 = = δ 2.50) and with respect to carbon resonances of the solvent for ^{13}C ($CDCl_3$ = δ 77.0, CD_3OD = δ 49.0, DMSO-d6 = δ 39.5). Peak multiplicities are annotated as follows: app = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Spectra were processed with exponential line broadening with a factor of 0.2. Infrared (IR) spectra were recorded on a Nicolet 6700 FT-IR spectrometer. LC-MS (ESI) data were collected on a Waters Micromass ZQ or a Waters Micromass LCT Premier mass spectrometer. GC-MS (CI) data were collected on a Waters Micromass GCT Premier mass spectrometer. Isotopic abundance patterns observed alongside each major ion reported matched calculated ratios. Optical rotations were measured using a JASCO P-2000 polarimeter. Chiral high-performance liquid chromatography (HPLC) analysis was performed using an Agilent 1260 with commercial ChiralPak 4.6 x 250 mm columns or a SpectraSystem P1000 with a SpectraSeries UV100 detector. HPLC trace integration was performed by the Agilent OpenLab processing suite. Uncorrected melting point data were collected using a Thomas Hoover Uni-Melt apparatus.

2. Enantioselective Chloroetherification Optimization

General Procedure for Preparation of Racemic *ortho*-Quinone **12**:

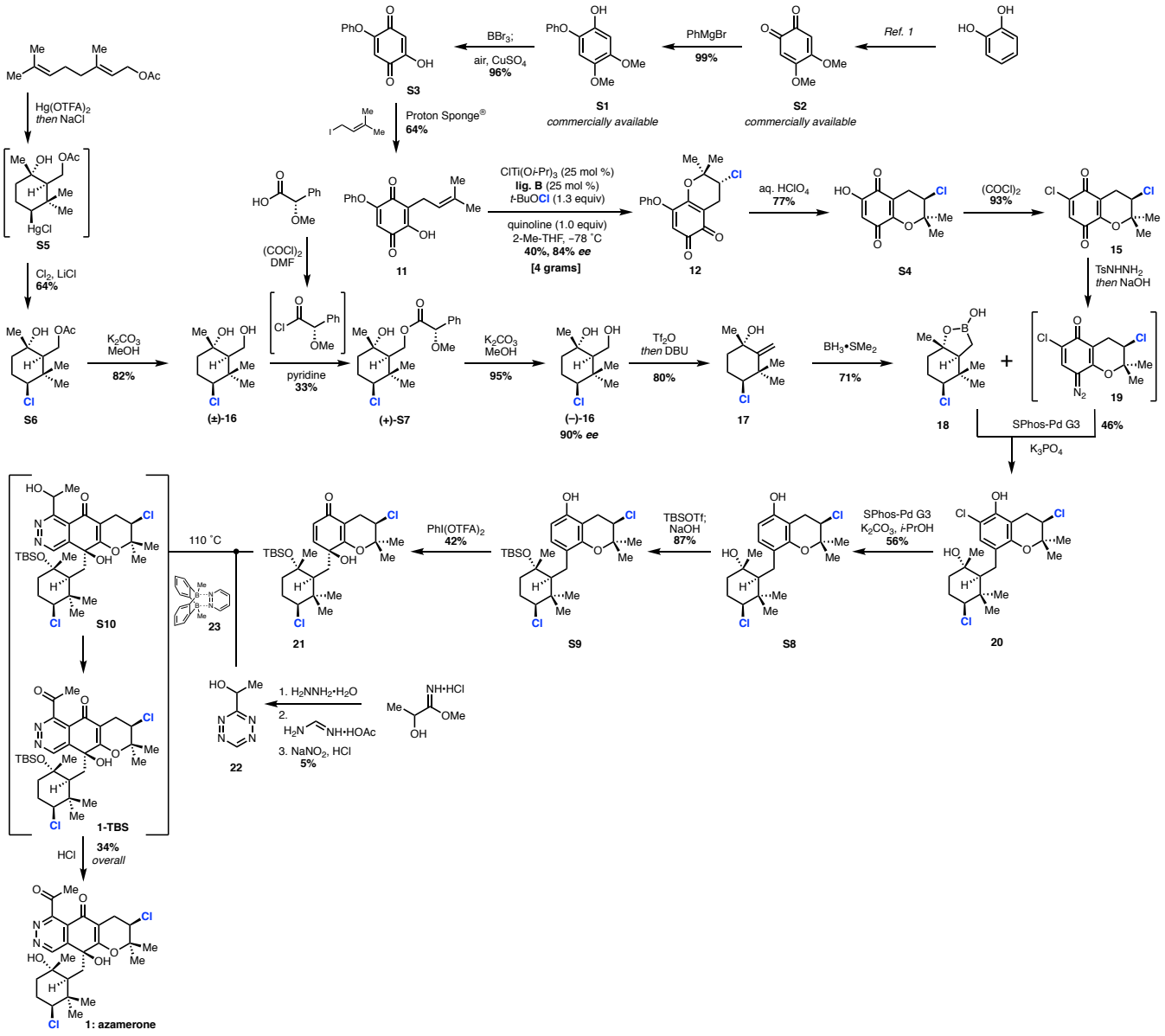
To a flame-dried flask under argon charged with prenyl quinone **11** (1.0 g, 3.5 mmol, 1.0 equiv) was added anhydrous Et_2O (70 mL). The orange solution was cooled to –78 ˚C. *t*-Butyl hypochlorite (0.49 mL, 4.55 mmol, 1.3 equiv) was added dropwise down the side of the flask, and the reaction was allowed to stir at –78 ˚C for one hour before the cooling bath was removed. The reaction was stirred for 3 subsequent hours at room temperature before it was concentrated under reduced pressure. The crude residue was purified via flash column chromatography (silica gel, 10 to 50% EtOAc in hexanes gradient) to yield *ortho*-quinone **12** as an orange foam in 52% yield (586 mg).

General Procedure for the Preparation of Scalemic *ortho*-Quinone **12**:

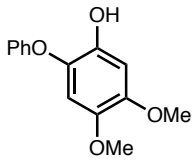
To a solution of $ClTi(O\textit{i}\text{-}Pr)_3$ (2.1 μL, 0.009 mmol, 0.25 equiv) in the stated solvent (0.1 mL) was added the stated ligand (0.009 mmol, 0.25 equiv) as a solution in the stated solvent (0.1 mL) dropwise over 1 minute. This solution was allowed to age for 30 minutes. Separately, prenyl quinone **11** (10 mg, 0.035 mmol, 1.0 equiv) was taken up in the stated solvent (0.5 mL) along with the amine base additive (0.035 mmol, 1.0 equiv) when applicable. The aged titanium ligand complex was added to the quinone solution dropwise over 1 minute, and the resulting dark red solution as allowed to stir at room temperature before it was cooled to –78 ˚C. To this cooled solution was added *t*-butyl hypochlorite (4.2 μL, 0.039 mmol, 1.1 equiv) as a solution in hexanes (0.05 mL) dropwise down the side of the flask. The reaction was allowed to stir for 3 hours, then 1,4-dinitrobenzene (1.5 mg, 0.009 mmol) was added as a stock solution in chloroform (0.035 mL). The reaction was quenched by pouring it into 10% aqueous tartaric acid (10 mL) and then was diluted with Et_2O (5 mL). The biphasic mixture was stirred rapidly for 1 hour, and the layers separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Yields were obtained by ^{1}H-NMR analysis of the crude reaction mixtures as compared to the 1,4-dinitrobenzene standard. Purification by thin layer chromatography (40% EtOAc in hexanes) provided pure samples of **12** for assessment of enantioenrichment by HPLC.

3. Azamerone Synthesis Scheme

Scheme S1. Full synthesis of azamerone



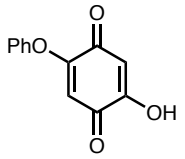
4. Experimental Procedures for the Synthesis of Azamerone



4,5-dimethoxy-2-phenoxyphenol (S1):

Phenol **S1** is commercially available, but it can also be conveniently produced in two steps from catechol. Oxidation of catechol to 4,5-dimethoxycyclohexa-3,5-diene-1,2-dione **S2** has been previously reported.[1]

4,5-Dimethoxycyclohexa-3,5-diene-1,2-dione (60 g, 356 mmol, 1.0 equiv) was dissolved in anhydrous THF (1.2 L) and cooled to –78 ˚C. Phenylmagnesium bromide, prepared freshly from bromobenzene (95 mL, 892 mmol, 2.5 equiv) and magnesium turnings (23 g, 937 mmol, 2.6 equiv) in THF (500 mL), was added dropwise. The reaction was stirred for 1 hour at –78 °C before being warmed to room temperature and allowed to stir overnight (12 hours). The reaction was cooled to 0 °C, quenched by the careful addition of aq. 4M HCl (300 mL), and the THF was removed under reduced pressure. The aqueous layer was extracted with Et_2O (3 x 300 mL), and the combined organics were washed with pH 7 buffer until neutral, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, 0 to 20% EtOAc in hexanes gradient) providing the title compound **S1** in 99% yield (87 g) as a white, waxy solid. Spectral data was in agreement with that previously reported.[2]



2-hydroxy-5-phenoxycyclohexa-2,5-diene-1,4-dione (S3):

4,5-Dimethoxy-2-phenoxyphenol **S1** (87 g, 353 mmol, 1.0 equiv) was dissolved in anhydrous DCM (900 mL) and cooled to –78 ˚C. A 1M solution of BBr_3 in DCM (777 mL, 777 mmol, 2.2 equiv) was added dropwise over 30 minutes. The reaction was stirred at –78 °C for 20 minutes and then warmed to room temperature and stirred for 1 hour. Reaction progress was monitored by TLC. After consumption of starting material, the reaction was carefully poured over crushed ice that itself was cooled by being placed in an external ice/water bath. To this ice slurry was added 10% aq. $CuSO_4$ (1.3 L) and the reaction was vigorously stirred with a mechanical stirrer while aerating the solution. The progress of oxidation was assessed by ^{1}H-NMR analysis of aliquots, and the reaction was worked up after 1 hour. The reaction mixture was filtered, and the aqueous and organic layers were separated. The aqueous layer was extracted with EtOAc (4 x 400 mL) and the combined organic layers were washed with water (2 x 300 mL). The product was extracted from the organic layer with 0.4M pH 8 phosphate buffer (8 x 100 mL). The combined basic layers were acidified to pH 6 with aq. 12M HCl, and the aqueous layer was extracted with EtOAc (5 x 300 mL). The combined organics were washed with sat. aq. NaCl (2 x 200 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the title compound **S3** in 96% yield (73 g).

Physical properties: mustard-yellow solid;

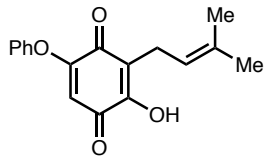
R_f = 0.53 (silica gel, 10% MeOH in DCM, appears as a red spot);

IR (film) ν_{max} 3289, 1644, 1607, 1583, 1487, 1390, 1298, 1193 cm^{-1};

^{1}H NMR (400 MHz, *d_6*-DMSO) δ 11.75 (br s, 1H), 7.56 – 7.42 (m, 2H), 7.34 (ddt, *J* = 8.5, 7.7, 1.1 Hz, 1H), 7.27 – 7.18 (m, 2H), 5.94 (s, 1H), 5.41 (s, 1H);

^{13}C NMR (100 MHz, *d_6*-DMSO) δ 182.99, 182.98, 159.2, 159.1, 152.6, 130.5, 126.5, 120.7, 108.0, 106.5;

LRMS (ESI) calcd. For $C_{12}H_8O_4Na$ $[M + Na]^+$: 239.03, found 239.03;



2-hydroxy-3-(3-methylbut-2-en-1-yl)-5-phenoxycyclohexa-2,5-diene-1,4-dione (11):

Hydroxyquinone **S3** (5.00 g, 23.1 mmol, 1.0 equiv) was dissolved in anhydrous dioxane (230 mL) at room temperature. Proton Sponge® (5.20 g, 24.3 mmol, 1.05 equiv) was added in one portion under a backflow of nitrogen and the mixture was stirred until complete dissolution of reagents was achieved. Freshly prepared prenyl iodide (see below, 5.70 mL, 46.3 mmol, 2.0 equiv) was added dropwise over 15 minutes with a syringe pump and the reaction was stirred for 24 hours over which time a precipitate formed. The reaction was filtered through a pad of Celite and the filter cake was washed with Et_2O (200 mL). The solution was concentrated under reduced pressure and the resulting crude oil was purified by column chromatography (gradient from 2% to 20% ethyl acetate in hexanes). This enriched material was further purified by recrystallization from refluxing hexanes and yielded the title compound **11** in 64% yield (4.21 g).

Preparation of prenyl iodide: sodium iodide (15.23 g, 101.6 mmol, 1.1 equiv) was dissolved in acetone (300 mL) open to air. Prenyl bromide (10.70 mL, 92.4 mmol, 1.0 equiv) was added streamwise. The reaction was stirred for 5 minutes before being filtered and concentrated in a fume hood under reduced pressure (100 Torr). The crude oil was taken up in Et_2O (30 mL), washed with sat. aq. $NaHCO_3$ and sat. aq. $Na_2S_2O_5$ to remove any trace HI or I_2, dried over $MgSO_4$, filtered, and concentrated under reduced pressure and used directly.

Physical properties: crystalline, orange solid;

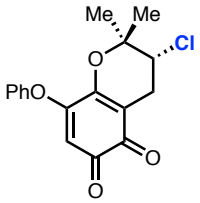
R_f = 0.47 (silica gel, 25% EtOAc in hexanes, appears as a purple spot);

IR (film) ν_{max} 3336, 1659, 1643, 1609, 1581, 1481, 1374, 1354 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (t, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.4, 1H), 7.14 (s, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 5.58 (s, 1H), 5.19 (t, *J* = 7.7 Hz, 1H), 3.20 (d, *J* = 7.5 Hz, 2H), 1.77 (s, 3H), 1.70 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 183.1, 181.4, 160.8, 152.5, 151.0, 133.9, 130.3, 126.8, 120.9, 119.4, 118.2, 105.5, 25.8, 21.9, 17.8;

LRMS (ESI) calcd. for $C_{17}H_{17}O_4$ $[M + H]^+$: 285.11, found 285.03;



(*R*)-3-chloro-2,2-dimethyl-8-phenoxy-3,4-dihydro-2*H*-chromene-5,6-dione (12):

To a 1M solution of ClTi(O*i*-Pr)$_3$ in hexanes (840 μL, 3.52 mmol, 0.25 equiv) in hexanes (3.52 mL) was added TADDOL ligand[3] **B** (2.30 g, 3.52 mmol, 0.25 equiv) as a solution in anhydrous 2-Me-THF (71 mL) via cannula over 10 minutes. This solution was allowed to stir at room temperature for 30 minutes. Separately, hydroxy-prenyl-quinone **11** (4.00 g, 14.07 mmol, 1.0 equiv) was dissolved in anhydrous 2-Me-THF (280 mL) in a 3-neck round bottom flask equipped with an addition funnel. To this solution was added freshly distilled quinoline (1.66 mL, 14.07 mmol, 1.0 equiv). The aged solution of the titanium-ligand complex was then added in a dropwise fashion via the addition funnel over 10 minutes. The resulting dark red solution was allowed to stir for 10 minutes at room temperature before being cooled to –78 ˚C. A solution of freshly prepared *t*-butyl hypochlorite[4] (1.98 mL, 18.29 mmol, 1.30 equiv) in anhydrous hexanes (80 mL) was added to the cooled reaction in a dropwise fashion via the addition funnel over 15 minutes down the side of the flask. The reaction was allowed to stir for 16 hours at –78 ˚C before being quenched by addition of aqueous tartaric acid (10 wt %, 600 mL). The biphasic mixture was stirred rapidly at room temperature for 1 hour. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried with $MgSO_4$, filtered through a pad of Celite, and concentrated under reduced pressure. The resulting crude oil was purified via column chromatography (silica gel, gradient from 0 to 50% ethyl acetate in hexanes) to yield *ortho*-quinone **12** (1.77 g, 40% yield, 84% ee). Enantioenrichment was quantified by chiral HPLC (see below).

Physical properties: orange foam;

R_f = 0.26 (silica gel, 30% EtOAc in hexanes, appears as an orange spot);

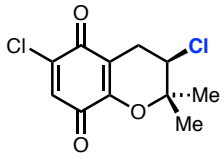
IR (film) ν_{max} 3648, 2361, 2177, 2031, 1966, 1650, 1596, 1583, 1398, 1347, 1206 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.47 – 7.44 (m, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 8.5 Hz, 2H), 5.42 (s, 1H), 4.11 (dd, *J* = 6.8, 5.4 Hz, 1H), 3.02 (dd, *J* = 18.4, 5.3 Hz, 1H), 2.81 (dd, *J* = 18.3, 6.8 Hz, 1H), 1.59 (s, 3H), 1.57 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.2, 177.6, 163.9, 156.1, 152.3, 130.5, 127.1, 121.2, 110.9, 105.5, 81.9, 57.6, 27.0, 25.8, 22.7;

LRMS (ESI) calcd. for $C_{17}H_{16}{}^{35}ClO_4$ $[M + H]^+$: 319.07, found 319.01;

$[\alpha]_D^{23}$ = –24 at 84% ee (*c* = 0.52, $CHCl_3$).



(*R*)-3,6-dichloro-2,2-dimethyl-3,4-dihydro-2*H*-chromene-5,8-dione (15):

ortho-Quinone **12** (950 mg, 2.98 mmol, 1.00 equiv) was dissolved in Et_2O (150 mL) and the resulting orange solution was treated with aqueous $HClO_4$ (60 wt%, 0.42 mL, 3.87 mmol, 1.3 equiv) at room temperature. The reaction was allowed to stir for 1 hour, during which time a color change from dark orange to yellow was observed. Reaction progress was monitored by disappearance of starting material by TLC. Upon completion, the aqueous and organic layers were separated, and the organic layer was washed with water (2 x 10 mL). The washed organic layer was extracted with 1M pH 8 phosphate buffer (3 x 100 mL). The combined dark red basic aqueous layers were washed with diethyl ether (3x 200 mL) and 12M aqueous hydrochloric acid (~3.0 mL) was added to the aqueous layer until the solution was adjusted to pH 7 at which time a color change from dark red to bright yellow was observed. The aqueous layer was extracted with diethyl ether (3 x 200 mL), and the combined organic layers were washed with water (200 mL) and brine (200 mL). The organic layer was dried over $MgSO_4$, filtered through a pad of Celite, and concentrated under reduced pressure to yield intermediate hydroxyquinone **S4** (558 mg, 77% yield).

Anhydrous DMF (130 µL, 1.7 mmol, 1.4 equiv) was added to anhydrous CH_3CN (4.1 mL) at 0 ˚C. To this solution was added oxalyl chloride (120 µL, 1.4 mmol, 1.1 equiv) dropwise over 5 minutes and the reaction was stirred an additional 10 minutes. The intermediate hydroxyquinone **S4** (300 mg, 1.24 mmol, 1.0 equiv) was added in one portion under a backflow of argon, and the reaction progress was monitored by TLC. After 5 minutes, the reaction was diluted with DCM (20 mL) and quenched by the addition of water (10 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica gel, 0 to 26% EtOAc in hexanes gradient) providing the title compound **15** in 93% yield (300 mg).

Physical properties: yellow solid;

R_f = 0.49 (silica gel, 25% EtOAc in hexanes, appears as a yellow spot);

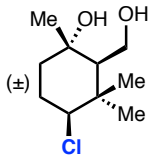
IR (film) ν_{max} 1675, 1657, 1631, 1592, 1392, 1373, 1326, 1187 cm^{-1};

^{1}H NMR (400 MHz, CDCl3) δ 6.89 (s, 1H), 4.05 (dd, *J* = 6.4, 5.2 Hz, 1H), 3.02 (dd, *J* = 18.9, 5.3 Hz, 1H), 2.81 (dd, J = 18.9, 6.4 Hz, 1H), 1.49 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 178.3, 151.7, 144.7, 131.2, 115.2, 80.7, 57.3, 27.4, 25.4, 22.5;

LRMS (ESI) calcd. for $C_{11}H_{11}{}^{35}Cl_2O_3$ $[M + H]^+$: 261.01, found 260.98;

$[\alpha]_D^{23}$ = –12 at 84% ee (*c* = 0.91, $CHCl_3$).



(±)-4-chloro-2-(hydroxymethyl)-1,3,3-trimethylcyclohexan-1-ol ((±)-16):

Mercury trifluoroacetate (75 g, 176 mmol, 1.1 equiv) was taken up in anhydrous $MeNO_2$ (500 mL) and cooled to –15 ˚C under argon. Geranyl acetate (31 g, 158 mmol, 1.0 equiv) was added dropwise over 10 minutes. The reaction was stirred for 3 hours and progress was monitored by TLC. After consumption of starting material, sat. aq. NaCl (1 L) was added and the slurry was stirred overnight (12 hrs) before being diluted with $CHCl_3$ (500 mL) and filtered through a pad of Celite. The aqueous and organic layers were separated, and the aqueous layer was extracted with $CHCl_3$ (4 x 500 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide intermediate organomercurial **S5** (67 g crude mass).

Organomercurial **S5** (67 g crude mass) and anhydrous LiCl (20.2 g, 477 mmol, 3.0 equiv) were taken up in freshly distilled pyridine (3.5 L) and cooled to –40 ˚C under argon. Chlorine gas was bubbled through the solution and reaction progress was monitored by disappearance of starting material by TLC. The reaction was quenched at –40 ˚C by addition of aq. 0.5M $NaSO_3$ (2 L). After quenching, pyridine was removed in a hood under reduced pressure, and the resulting aqueous mixture was extracted with DCM (3 x 250 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, 10 to 100% EtOAc in hexanes gradient) to provide intermediate chlorocycle acetate[5] **S6** in 64% yield over two steps (25.1 g).

The acetate (23 g, 92 mmol, 1.0 equiv) and K_2CO_3 (25.6 g, 185 mmol, 2.0 equiv) were taken up in MeOH (400 mL) and warmed to 50 ˚C. The reaction was stirred for 30 minutes and consumption of starting material was monitored by TLC. Upon completion, the reaction was cooled to room temperature, diluted with water (200 mL), and the methanol was removed under reduced pressure. The resulting emulsion was extracted with EtOAc (3 x 100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, 15 to 75% EtOAc in hexanes gradient) to provide the racemic title compound **(±)-16** in 82% yield (15.7 g).

Physical properties: white solid;

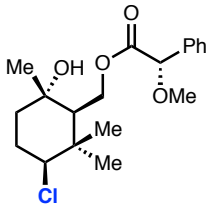
R_f = 0.57 (silica gel, 80% EtOAc in hexanes, visualized with anisaldehyde stain);

IR (film) ν_{max} 3213, 2971, 2944, 2875, 1457, 1380, 1371, 1346 cm^{-1};

^{1}H NMR (400 MHz, CDCl3) δ 3.97 – 3.92 (m, 3H), 3.78 (dd, J = 12.2, 4.1 Hz, 1H), 3.73 (br s, 1H), 2.05 – 1.95 (m, 1H), 1.89 – 1.74 (m, 2H), 1.68 (t, J = 6.8 Hz, 1H), 1.65 – 1.54 (app dt, J = 14.0, 4.0 Hz, 1H), 1.34 (s, 3H), 1.16 (s, 3H), 0.83 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 73.6, 70.9, 61.9, 56.0, 41.7, 38.9, 30.6, 29.0, 23.5, 16.0;

LRMS (ESI) calcd. for $C_{11}H_{19}{}^{35}ClNO_2$ $[M + CN]^-$: 232.11, found 232.13;



((1*R*,3*S*,6*S*)-3-chloro-6-hydroxy-2,2,6-trimethylcyclohexyl)methyl (*S*)-2-methoxy-2-phenylacetate ((+)-S7):

Anhydrous DMF (6.2 mL, 80 mmol, 1.5 equiv) was taken up in anhydrous CH_3CN (180 mL) at 0 ˚C. To this solution was added oxalyl chloride (5.4 mL, 64 mmol, 1.2 equiv) dropwise over 5 minutes and the reaction was stirred an additional 10 minutes. (*S*)-(+)-α-Methoxyphenylacetic acid (9.8 g, 58 mmol, 1.1 equiv) was added in one portion under a backflow of argon and the reaction was stirred 5 minutes. Racemic diol **(±)-16** (11 g, 53 mmol, 1.0 equiv) was taken up in anhydrous pyridine (15 mL) and added to the reaction in a dropwise fashion over 5 minutes. The reaction was stirred for 20 minutes and reaction progress was monitored by TLC. The reaction was diluted with Et_2O (200 mL) and washed with aq. 1M HCl (200 mL). The aqueous layer was extracted with Et_2O (3 x 100 mL) and the combined organics were sequentially washed with sat. aq. $NaHCO_3$ (200 mL) and sat. aq. NaCl (100 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (100 g silica gel per 1 g crude, 30 to 100% Et_2O in hexanes gradient), first eluting the non-desired diastereomer (8.15 g, 43%), then mixed fractions (1.20 g, 6%), then the title compound **(+)-S7** in 33% yield (6.20 g).

Physical properties: white solid;

R_f = 0.30 (desired) (silica gel, 70% Et_2O in hexanes, visualized with anisaldehyde stain);

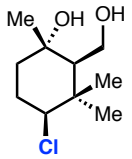
IR (film) ν_{max} 3527, 3369, 2969, 2943, 1744, 1454, 1397, 1373 cm^{-1};

^{1}H NMR (400 MHz, CDCl3) δ 7.45 – 7.30 (m, 5H), 4.75 (s, 1H), 4.45 – 4.34 (m, 2H), 3.74 – 3.70 (dd, *J* = 4.0, 12.1 Hz, 1H), 3.38 (s, 3H), 2.55 (s, 1H), 2.05 – 1.95 (m, 1H), 1.88 – 1.74 (m, 2H), 1.65 (t, *J* = 5.5 Hz, 1H), 1.61 – 1.49 (m, 1H), 1.17 (s, 3H), 0.95 (s, 3H), 0.89 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 135.6, 128.9, 128.7, 127.1, 82.6, 71.5, 70.5, 63.9, 57.3, 55.2, 41.6, 39.6, 30.6, 28.7, 23.8, 16.1;

LRMS (ESI) calcd. for $C_{19}H_{27}{}^{35}ClO_4Na$ $[M + Na]^+$: 377.15, found 377.07;

$[\alpha]_D^{23}$ = +27 (*c* = 1.0, $CHCl_3$).



(1*S*,2*R*,4*S*)-4-chloro-2-(hydroxymethyl)-1,3,3-trimethylcyclohexan-1-ol ((–)-16):

(S)-α-Methoxyphenylacetic ester **(+)-S7** (5.0 g, 14 mmol, 1.0 equiv) and K_2CO_3 (3.9 g, 28 mmol, 2.0 equiv) were taken up in MeOH (60 mL) and warmed to 50 ˚C. The reaction was stirred for 30 minutes and consumption of starting material was monitored by TLC. Upon completion, the reaction was cooled to room temperature, diluted with water (60 mL), and the methanol was removed under reduced pressure. The resulting emulsion was extracted with EtOAc (3 x 50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, 20 to 90% EtOAc in hexanes gradient) to provide the enantioenriched title compound **(–)-16** in 95% yield (2.76 g, 90% ee). Enantioenrichment was assessed by chiral HPLC of the benzoate derivative (see below).

Physical properties: white solid;

R_f = 0.57 (silica gel, 80% EtOAc in hexanes, visualized with anisaldehyde stain);

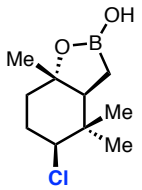
IR (film) ν_{max} 3213, 2971, 2944, 2875, 1457, 1380, 1371, 1346 cm^{-1};

^{1}H NMR (400 MHz, CDCl3) δ 3.97 – 3.92 (m, 3H), 3.78 (dd, J = 12.2, 4.1 Hz, 1H), 3.73 (s, 1H), 2.05 – 1.95 (m, 1H), 1.89 – 1.74 (m, 2H), 1.68 (t, J = 6.8 Hz, 1H), 1.65 – 1.54 (app dt, J = 14.0, 4.0 Hz, 1H), 1.34 (s, 3H), 1.16 (s, 3H), 0.83 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 73.6, 70.9, 61.9, 56.0, 41.7, 38.9, 30.6, 29.0, 23.5, 16.0;

LRMS (ESI) calcd. for $C_{11}H_{19}{}^{35}ClNO_2$ $[M + CN]^-$: 232.11, found 232.13;

$[\alpha]_D^{23}$ = –5.7 at 96% ee (*c* = 0.53, $CHCl_3$).



(3a*S*,5*S*,7a*S*)-5-chloro-4,4,7a-trimethylhexahydrobenzo[*d*][1,2]oxaborol-2(3*H*)-ol (18):

Enantioenriched diol **(–)-16** (5.40 g, 26.1 mmol, 1.0 equiv) was taken up in anhydrous DCM (104 mL). Distilled 2,6-lutidine (3.53 mL, 31.3 mmol, 1.2 equiv) was added and the reaction was cooled to –78 ˚C. Tf_2O (4.61 mL, 27.4 mmol, 1.05 equiv) was added dropwise over 5 minutes. The reaction was stirred for 30 minutes and then a solution of DBU (9.77 mL, 65.3 mmol, 2.5 equiv) in DCM (15 mL) was added dropwise over 10 minutes. The resulting solution was warmed to room temperature and stirred overnight (12 hours). The reaction was diluted with DCM (100 mL) and washed with aq. 1M HCl (100 mL). The aqueous layer was extracted with DCM (3 x 25 mL) and the combined organics were washed with sat. aq. $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered, and gingerly concentrated under reduced pressure to avoid loss of the volatile product. The resulting crude oil was purified by flash column chromatography (silica gel, 5 to 60% Et_2O in pentane gradient) to provide allylic alcohol product **17** in 80% yield (3.96 g).

Allylic alcohol **17** (823 mg, 4.36 mmol, 1.0 equiv) was dissolved in anhydrous THF (20 mL) and cooled to 0 ˚C under argon. To this solution was added $BH_3{\cdot}SMe_2$ (0.574 mL, 6.05 mmol, 1.4 equiv) dropwise over 5 minutes. The reaction was allowed to slowly warm to room temperature, stirred overnight (18 hours), and checked by TLC where it was judged to be incomplete. The reaction was cooled to 0 ˚C and $BH_3{\cdot}SMe_2$ (0.25 mL, 2.64 mmol, 0.6 equiv) was added dropwise over 5 minutes. The reaction was allowed to slowly warm to room temperature, stirred overnight (12 hours), quenched by the slow addition of water (0.6 mL), and stirred an additional 30 minutes. The biphasic mixture were concentrated under reduced pressure, and the resulting aqueous suspension was extracted with DCM (4 x 20 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting crude oil was purified by flash column chromatography (silica gel, 15 to 60% EtOAc in hexanes gradient) with the more polar, desired boronic hemiester diastereomer eluting after an undesired diastereomer, to provide **18** in 71% yield (672 mg).

Physical properties: white solid;

R_f = 0.48 (silica gel, 50% EtOAc in hexanes, visualized with anisaldehyde stain);

IR (film) ν_{max} 3291, 2954, 2871, 1458, 1436, 1406, 1393, 1381 cm^{-1};

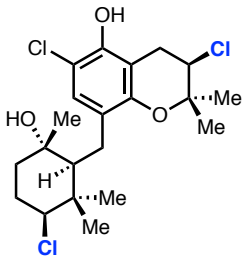
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (s, 1H), 3.75 (dd, *J* = 12.0, 4.7 Hz, 1H), 2.20 – 2.10 (m, 1H), 1.96 – 1.82 (m, 2H), 1.72 – 1.60 (m, 2H), 1.21 (s, 3H), 1.03 (s, 3H), 0.92 (s, 3H; obscured m, 4H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 82.6, 70.5, 57.4, 39.9, 39.2, 32.0, 29.2, 29.1, 22.1, 15.5;

^{11}B NMR (96 MHz, $CDCl_3$) δ 36.6;

LRMS (ESI) calcd. for $C_{11}H_{18}B^{35}ClNO_2$ $[M + CN]^-$: 242.11, found 242.07;

$[\alpha]_D^{23}$ = –0.72 at 88% ee (*c* = 1.3, $CHCl_3$).



(*R*)-3,6-dichloro-8-(((1*S*,3*S*,6*S*)-3-chloro-6-hydroxy-2,2,6-trimethylcyclohexyl)methyl)-2,2-dimethylchroman-5-ol (20):

Quinone **15** (34 mg, 0.126 mmol, 1.0 equiv) and *p*-toluenesulfonyl hydrazide (26 mg, 0.138 mmol, 1.1 equiv) were taken up in methanol (1 mL). The suspension was allowed to stir at room temperature and the reaction mixture gradually became homogeneous and dark orange. Consumption of the starting material was monitored by TLC, and after 30 minutes the methanol was removed under reduced pressure. The residue was taken back up in DCM (5 mL) and treated with aq. 1M NaOH (1M, 3 mL). The biphasic mixture was shaken vigorously for 3 minutes, turning a dark green, before the layers were separated. The aqueous layer was washed with DCM (5 mL), and the combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the crude quinone diazide **19**, which was carried into the next step without further purification. (Note: exposure of quinone diazide **19** to $MgSO_4$ or Celite, as well as prolonged standing led to depressed yields, presumably due to the decomposition of **19**).

A flame-dried vial was charged with the crude quinone diazide **19** from above, boronic hemiester **18** (30 mg, 0.138 mmol, 1.1 equiv), (SPhos)Pd-G3 (10 mg, 0.0126 mmol, 0.1 equiv), and K_3PO_4 (35 mg, 0.164 mmol, 1.3 equiv). The vial was evacuated and purged with argon three times. Dioxane (1 mL) was sparged with argon for 30 minutes, added to the vial, and the contents were warmed in a 60 ˚C oil bath with rapid stirring for 90 minutes. The reaction was then cooled to room temperature and diluted with 1M HCl (5 mL) and DCM (3 mL). The layers were separated and the aqueous layer was extracted with DCM (2 x 3 mL). The combined organics were washed with sat. aq. $NaHCO_3$ (5 mL) and brine (5 mL), then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (silica gel, 3 to 26% EtOAc in hexanes gradient) to afford **20** in 46% yield (25 mg, 10:1 dr).

Physical properties: light brown foam;

R_f = 0.56 (silica gel, 30% EtOAc in hexanes, visualized with anisaldehyde stain);

IR (film) ν_{max} 2983, 2948, 1602, 1473, 1371, 1200, 1159, 1134, 1081, 1063 cm^{-1};

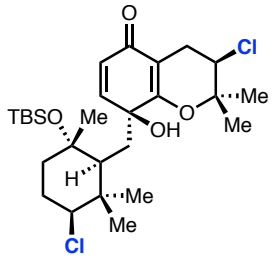
^{1}H NMR Major (600 MHz, $CDCl_3$) δ 7.04 (s, 1H), 5.49 (s, 1H), 4.14 (dd, *J* = 6.2, 5.6 Hz, 1H), 3.77 (dd, *J* = 12.4, 4.1 Hz, 1H), 3.21 (dd, *J* = 18.0, 5.5 Hz, 1H), 3.04 (dd, *J* = 17.8, 6.3 Hz, 1H), 2.87 (dd, *J* = 14.9, 6.9 Hz, 1H), 2.62 (dd, *J* = 14.9, 3.8 Hz, 1H), 2.47 (s, 1H), 2.02 (dq, *J* = 13.6, 3.8 Hz, 1H), 1.92 – 1.82 (m, 1H), 1.82 – 1.74 (m, 2H), 1.53 (q, *J* = 4.5, 3.9 Hz, 1H), 1.47 (s, 3H), 1.46 (s, 3H), 1.35 (s, 3H), 1.17 (s, 3H), 0.99 (s, 3H);

^{1}H NMR Minor [where distinguishable] (600 MHz, $CDCl_3$) δ 7.04 (s, 1H), 5.50 (s, 1H), 4.09 (dd, *J* = 9.0, 5.8 Hz, 1H), 3.79 (obscured by major, 1H), 3.26 (obscured by major, 1H), 2.95 – 2.91 (m, 1H), 2.81 (dd, *J* = 15.0, 6.5 Hz, 1H), 2.65 (obscured by major, 1H), 2.41 (s, 1H), 1.70 (dd, *J* = 6.5, 4.0 Hz, 2H), 1.50 (obscured by major, 2H), 1.39 (s, 3H), 1.34 (s, 3H), 1.16 (s, 3H), 1.09 (s, 3H), 0.90 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.9, 147.6, 127.9, 124.6, 111.3, 107.8, 73.1, 71.7, 59.1, 58.6, 41.5, 41.3, 31.0, 29.9, 28.8, 25.7, 25.6, 25.5, 23.7, 23.2, 16.1;

LRMS (ESI) calcd. for $C_{21}H_{28}{}^{35}Cl_3O_3$ $[M - H]^-$: 433.11, found 433.17;

$[\alpha]_D^{23}$ = +14 (*c* = 0.94, $CHCl_3$).



(3*R*,8*S*)-8-(((1*S*,3*S*,6*S*)-6-((*tert*-butyldimethylsilyl)oxy)-3-chloro-2,2,6-trimethylcyclohexyl)methyl)-3-chloro-8-hydroxy-2,2-dimethyl-2,3,4,8-tetrahydro-5*H*-chromen-5-one (21):

A flame-dried flask charged with chlorophenol **20** (157 mg, 0.36 mmol, 1.0 equiv), (SPhos)Pd-G3 (28 mg, 0.036 mmol, 0.1 equiv), and K_2CO_3 (99 mg, 0.72 mmol, 2.0 equiv) was evacuated and backfilled with argon three times. Separately, isopropanol (3.6 mL) was sparged with argon for 30 minutes and then added to the reaction vessel. The vial was sealed and heated in a 90 ˚C oil bath for 50 minutes. Upon the formation of palladium black, the reaction was cooled to room temperature and diluted with ethyl acetate (5 mL) and 1M HCl (5 mL). (Note: reaction is not run to full consumption of **20** as judged by TLC and NMR, however, allowing the reaction to stir after formation of palladium black leads to significantly depressed yields.) The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 x 3 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The crude residue was purified via flash column chromatography (silica gel, 6 to 50% EtOAc in hexanes gradient) to yield the desired phenol product **S8** as an amorphous white powder in 56% yield (81 mg).

Phenol **S8** (80 mg, 0.20 mmol, 1.0 equiv) was taken up in anhydrous DCM at room temperature. To this stirred solution was added *i*-Pr_2NEt (140 μL, 0.80 mmol, 4.0 equiv) at once, followed by *tert*-butyldimethylsilyl trifluormethanesulfonate (137 μL, 0.60 mmol, 3.0 equiv) dropwise over 5 minutes. The reaction was allowed to stir under argon for 18 hours, at which point it was quenched with 1M HCl (2 mL). The layers were separated and the aqueous layer was extracted with DCM (2 x 3 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then taken up in isopropanol (3 mL) and treated with 3M NaOH (0.5 mL). The solution was stirred rapidly for 3 hours before it was diluted with 1M HCl (3 mL) and DCM (3 mL). The layers were separated and the aqueous layer extracted with DCM (2 x 3 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried with Na_2SO_4, filtered, and

concentrated under reduced pressure. The crude residue was purified via flash column chromatography (silica gel, 1 to 14% EtOAc in hexanes) to yield the desired product **S9** as a white foam in 87% yield (87 mg).

The TBS-protected phenol **S9** (14 mg, 0.027 mmol, 1.0 equiv) was taken up in acetonitrile (1.0 mL) and water (0.3 mL) with rapid stirring under ambient atmosphere. [Bis(trifluoroacetoxy)iodo]benzene (13 mg, 0.029 mmol, 1.1 equiv) was added as a single portion and the reaction was allowed to stir for 30 seconds (Note: reaction times longer than 30 seconds were found to be deleterious to the yield of the desired product; reactions were often complete after 10 seconds). The reaction was quenched with 1:1 saturated aq. $NaHCO_3$ and 1M Na_2S_2O5 (5 mL) and diluted with EtOAc (1 mL). The layers were separated and the aqueous was extracted with EtOAc (3 x 1 mL). The combined organic layers were washed with saturated aq. $NaHCO_3$ (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (silica gel, 3 to 24% EtOAc in hexanes gradient) to afford the title compound **21** in 42% yield (6 mg).

Physical properties: off-white foam;

R_f = 0.58 (silica gel, 30% EtOAc in hexanes, visualized with anisaldehyde stain);

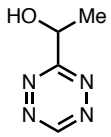
IR (film) ν_{max} 3313, 2930, 2855, 1663, 1607, 1464, 1385, 1256, 1094, 959 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.73 (d, *J* = 10.2 Hz, 1H), 6.05 (d, *J* = 10.2 Hz, 1H), 5.50 (s, 1H), 3.94 (dd, *J* = 10.1, 5.8 Hz, 1H), 3.80 (dd, *J* = 12.4, 3.9 Hz, 1H), 2.98 (dd, *J* = 17.1, 5.8 Hz, 1H), 2.56 – 2.33 (m, 2H), 2.09 (dt, *J* = 10.0, 4.7 Hz, 2H), 1.92 – 1.78 (m, 2H), 1.69 (td, J = 14.8, 13.8, 3.7 Hz, 1H), 1.55 (s, 3H; obscured m, 1H), 1.36 (s, 3H), 1.34 (s, 3H), 1.06 (s, 3H), 0.94 (s, 9H), 0.85 (s, 3H), 0.26 (s, 3H), 0.24 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 185.2, 169.0, 148.7, 125.6, 107.9, 80.2, 78.2, 70.4, 68.4, 59.4, 50.9, 41.8, 41.6, 36.5, 31.1, 31.0, 26.8, 26.6, 23.6, 19.6, 18.6, 17.2, 0.2, –0.90, –0.93;

LRMS (ESI) calcd. For $C_{23}H_{33}{}^{35}Cl_2NO_3Na$ $[M - OH - TBS + Na + CH_3CN]^+$: 464.17, found 464.17; calcd. For $C_{24}H_{36}{}^{35}ClNO_5Na$ $[M - Cl - TBS + MeOH + Na + CH_3CN]^+$: 476.22, found 476.22;

$[\alpha]_D^{23}$ = –55 (*c* = 0.96, $CHCl_3$).



1-(pyridazin-3-yl)ethan-1-ol (22):

Methyl 2-hydroxypropanimidate hydrochloride[6] (20.0 g, 143 mmol, 1.0 equiv) was taken up in methanol (400 mL) at 0 ˚C. Hydrazine hydrate (ca. 55 wt%, 22 mL, 389 mmol, 2.5 equiv) was added dropwise, and the solution was allowed to stir for 10 minutes. Formamidine acetate (40.0 g, 384 mmol, 2.5 equiv) was added portion-wise over 5 minutes at 0 ˚C. The reaction was allowed to stir for 1 hour at 0 ºC and then warmed to room temperature for 2 hours. The reaction was concentrated under reduced pressure to remove methanol and then taken up in H_2O (200 mL). Sodium nitrite (80 g, 1160 mmol, 8.0 equiv) was added in a single portion and the reaction mixture was cooled to 0 ˚C. 12 M HCl (90 mL) was added dropwise over 30 minutes. The reaction was stirred at 0 ˚C for 2 hours, then warmed to RT for 1 hour. The reaction was diluted with EtOAc (300 mL), and the layers separated. The aqueous layer was extracted with EtOAc (3 x 500 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (silica gel, 12 to 96% EtOAc in hexanes gradient) to yield the title compound **22** as a pink oil in 5% yield (939 mg). While low-yielding, the efficiency of this synthesis is consistent with literature syntheses of other tetrazines.[7]

Physical properties: pink oil;

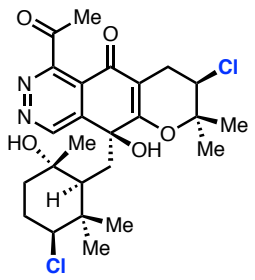
R_f = 0.16 (silica gel, 30% EtOAc in hexanes, appears as a pink spot);

IR (film) ν_{max} 3442, 1723, 1448, 1372, 1284, 1124, 1095, 1015 cm^{-1};

^{1}H NMR (600 MHz, $CDCl_3$) δ 10.31 (s, 1H), 5.46 (q, *J* = 6.7 Hz, 1H), 1.79 (d, *J* = 6.7 Hz, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 159.0, 68.8, 22.9;

LRMS (CI) calcd. for $C_4H_6N_4O$ $[M]^+$: 126.05, found 126.00;



Azamerone (1):

To a flame-dried vial under argon charged with bisboron Lewis acid[8] **23** (5 mg, 0.018 mmol, 1.0 equiv) and tetrazine **22** (11 mg, 0.090 mmol, 5.0 equiv) was added **21** (9.6 mg, 0.018 mmol, 1.0 equiv) as a solution in anhydrous CF_3Ph (1.0 mL). The vial was sealed and the reaction was heated to 110 ˚C for two days. Further equivalents of bisboron Lewis acid **23** (5 mg, 0.018 mmol, 1.0 equiv) and tetrazine **22** (11 mg, 0.090 mmol, 5.0 equiv) were added, and the reaction was allowed to stir for two more days before it was cooled to room temperature, diluted with methanol and concentrated. The crude residue was purified via flash column chromatography (silica gel, 0 to 30% EtOAc in hexanes gradient) to yield the desired product **1-TBS** in 40% yield, 55% BRSM (4.5 mg).

TBS-protected azamerone **1-TBS** (4.5 mg, 0.0072 mmol, 1.0 equiv) was taken up in 2:1 methanol/DCM (1.5 mL). To this was added aq. 12M HCl (50 μL), and the solution was allowed to stir for 5 hours. The reaction was diluted with DCM (2 mL) and quenched with saturated aq. $NaHCO_3$ (5 mL). The layers were separated and the aqueous layer was washed with DCM (3 x 1 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (silica gel, 10 to 60% EtOAc in hexanes gradient) to yield **1** in 84% yield (3.1 mg). The purified compound was spectroscopically in agreement with that previously reported,[9] as well as in comparison to an authentic sample (see below).

3 step procedure:

To a flame-dried vial under argon charged with bisboron Lewis acid **23** (16 mg, 0.056 mmol, 1.0 equiv) and tetrazine **22** (36 mg, 0.28 mmol, 5.0 equiv) was added CF_3Ph (0.5 mL) and the suspension was stirred rapidly at RT for 10 minutes. **21** (30 mg, 0.056 mmol, 1.0 equiv) as a solution in anhydrous CF_3Ph (1.0 mL) was then added streamwise. The vial was sealed and the reaction was heated to 110 ˚C for 24 hours. Further equivalents of bisboron Lewis acid **23** (8 mg, 0.028 mmol, 0.5 equiv) and tetrazine **22** (36 mg, 0.28 mmol, 5.0 equiv) were added, and the reaction was allowed to stir for 24 hours. A final addition of bisboron Lewis acid **23** (8 mg, 0.028 mmol, 0.5 equiv) and tetrazine **22** (36 mg, 0.28 mmol, 5.0 equiv) was carried out and the reaction stirred for 24 hours before it was cooled to room temperature, diluted with methanol, and concentrated. The crude residue was purified via flash column chromatography (silica gel, 0 to 60% EtOAc in hexanes gradient) to yield the desired product in ca. 57% yield as a 1.5:1 mixture of **1-TBS**/**S10** (20 mg crude mass).

The mixed phthalazinone products **1-TBS**/**S10** (20 mg crude mass, 0.032 mmol, 1.0 equiv) were taken up in DCM (1 mL). The reaction was cooled to 0 ˚C and $NaHCO_3$ (33 mg, 0.39 mmol, 12.0 equiv) was added. To this stirred suspension was added Dess–Martin periodinane (82 mg, 0.19 mmol, 6.0 equiv) portion-wise over 5 minutes. The reaction was allowed to stir for 5 minutes and then was warmed to RT and stirred for 2.5 hours. The reaction was quenched with 1:1 saturated aq. $NaHCO_3$/1M $Na_2S_2O_5$, and then diluted with DCM (2 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 2 mL). The combined organic layers were sequentially washed with saturated aq. $NaHCO_3$ (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was then taken back up in 4:1 MeOH/DCM (2.5 mL). To this was added aq. 12M HCl (0.1 mL) and the reaction was allowed to stir at RT for 2.5 hours. The reaction was diluted with DCM (2 mL) and quenched with saturated aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous was extracted with DCM (3 x 2 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (silica gel, 12 to 100% EtOAc in hexanes) to yield **1** in 38% yield (6.2 mg).

Physical properties: white solid;

R_f = 0.23 (silica gel, 50% EtOAc in hexanes, visualized with anisaldehyde);

IR (film) ν_{max} 3209, 2994, 2861, 1708, 1638, 16121394, 1240, 1123, 1082, 1053, 950 cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.72 (s, 1H), 4.04 (dd, *J* = 8.4, 5.5 Hz, 1H), 3.64 (dd, *J* = 11.8, 4.0 Hz, 1H), 3.10 (dd, *J* = 17.4, 5.5 Hz, 1H), 2.70 (s, 3H), 2.65 – 2.55 (m, 2H), 2.10 – 2.04 (m, 1H), 1.96 – 1.88 (m, 1H), 1.87 – 1.82 (m, 2H), 1.78 (td, *J* = 12.9, 12.2, 2.2 Hz, 2H), 1.59 (s, 3H), 1.48 (s, 3H), 1.34 (s, 3H), 0.69 (s, 3H), 0.23 (s, 3H);

^{1}H NMR (500 MHz, CD_3OD) δ 9.76 (s, 1H), 4.33 (dd, *J* = 7.7, 5.5 Hz, 1H), 3.80 (dd, *J* = 12.1, 4.1 Hz, 1H), 3.09 (dd, *J* = 17.2, 5.4 Hz, 1H), 2.66 – 2.57 (m, 2H), 2.60 (s, 3H), 1.98 (dd, *J* = 8.9, 2.5 Hz, 1H), 1.96 – 1.93 (m, 1H), 1.89 – 1.78 (m, 2H), 1.70 (d, *J* = 6.2 Hz, 1H), 1.66 (dd, *J* = 13.3, 3.8 Hz, 1H), 1.60 (s, 3H), 1.48 (s, 3H), 1.21 (s, 3H), 0.78 (s, 3H), 0.50 (s, 3H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.6, 180.2, 172.3, 157.6, 150.6, 143.5, 123.1, 108.3, 81.8, 73.3, 70.1, 69.4, 58.1, 49.5, 42.1, 41.5, 40.9, 30.8, 30.0, 28.4, 26.6, 26.1, 24.6, 21.5, 16.4;

^{13}C NMR (126 MHz, CD_3OD) δ 202.5, 181.6, 172.8, 158.8, 152.1, 146.5, 124.8, 110.0, 82.7, 72.4, 71.7, 71.4, 59.3, 51.4, 42.7, 41.9, 41.7, 32.0, 30.0, 29.2, 27.7, 26.1, 23.8, 21.8, 16.5;

LRMS (ESI) calcd. for $C_{25}H_{33}{}^{35}Cl_2N_2O_5$ $[M + H]^+$: 511.18, found 511.12;

$[\alpha]_D^{23}$ = –7 (*c* = 0.1, MeOH); lit.[8] for **1** **$[\alpha]_D$** = –8.8 (*c* = 0.0025, MeOH).

5. NMR Comparison Tables of Synthetic and Natural Azamerone

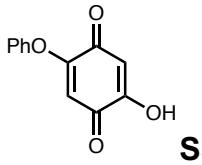
Table S1. ^{1}H NMR comparison for azamerone.

Synthetic 1 (500 MHz, CD_3OD)	Natural 1[8] (500 MHz, CD_3OD)
9.76, s	9.76, s
4.33, dd (*J* = 7.7, 5.5 Hz)	4.33, dd (*J* = 7.5 Hz, 5.5 Hz)
3.80, dd (*J* = 12.1, 4.1 Hz)	3.79, dd (*J* = 12.0 Hz, 4.0 Hz)
3.09, dd (*J* = 17.2, 5.4 Hz)	3.09, dd (*J* = 17.5 Hz, 5.5 Hz)
2.66 – 2.57, m	2.63, dd (*J* = 15.0 Hz, 7.0 Hz)
	2.61, dd (*J* = 17.5 Hz, 7.5 Hz)
2.60, s	2.60, s
1.98, dd, (*J* = 8.9, 2.5 Hz)	1.99, m
1.96 – 1.93, m	1.95, dd (*J* = 15.0 Hz, 2.0 Hz)
1.89 – 1.78, m	1.85, m
	1.81, td (*J* = 14.0 Hz, 3.5 Hz)
1.70, d, (*J* = 6.2 Hz)	1.70, dd (*J* = 7.0 Hz, 2.0 Hz)
1.66 dd (*J* = 13.3, 3.8 Hz)	1.65, dt (*J* = 14.0 Hz, 3.5 Hz)
1.60, s	1.60, s
1.48, s	1.48, s
1.21, s	1.22, s
0.78, s	0.78, s
0.50, s	0.50, s

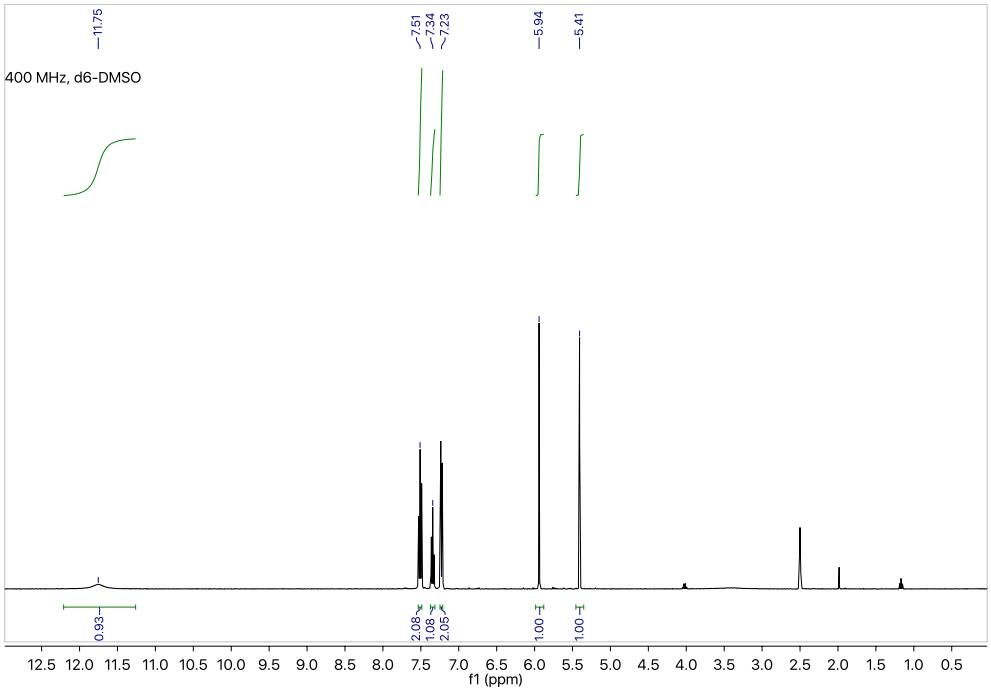
Table S2. ^{13}C NMR comparison for azamerone.

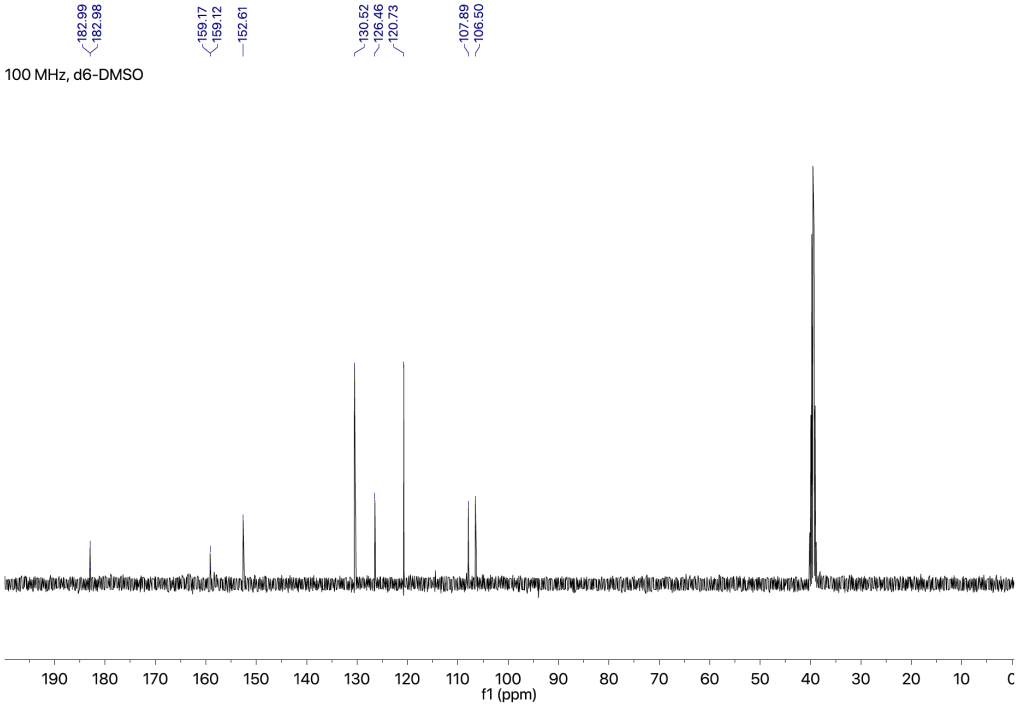
Synthetic 1 (126 MHz, CD_3OD)	Natural 1[8] (125 MHz, CD_3OD)
202.5	202.5
181.6	181.6
172.8	172.8
158.8	158.8
152.1	152.2
146.5	146.5
124.8	124.8
110.0	110.0
82.7	82.7
72.4	72.4
71.7	71.6
71.4	71.4
59.3	59.3
51.4	51.3
42.7	42.6
41.9	41.9
41.7	41.6
32.0	31.9
30.0	30.0
29.2	29.2
27.7	27.7
26.1	26.1
23.8	23.8
21.8	21.9
16.5	16.4

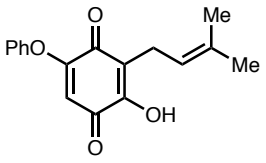
6. ^{1}H and ^{13}C NMR Spectra



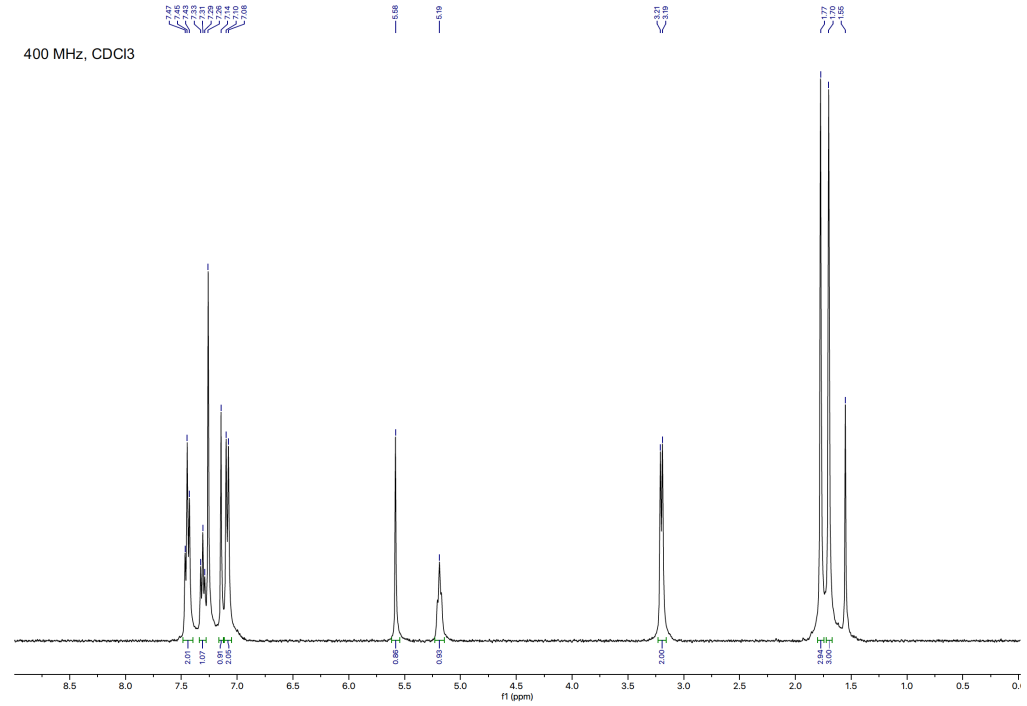
S3

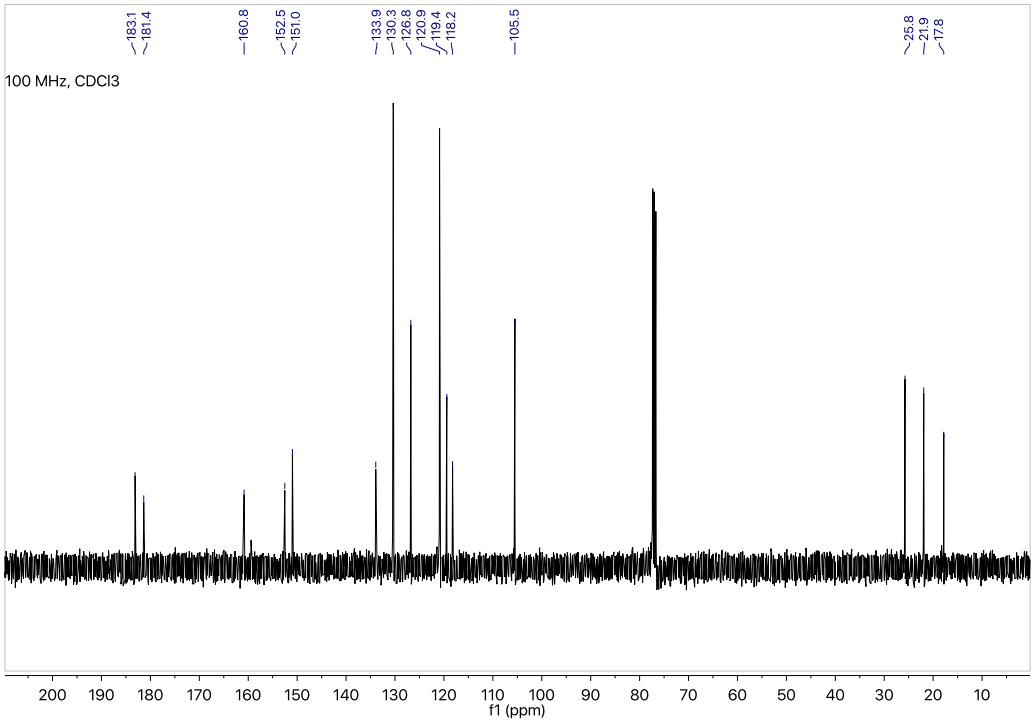


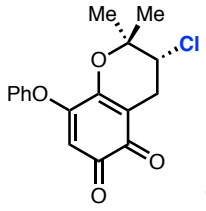




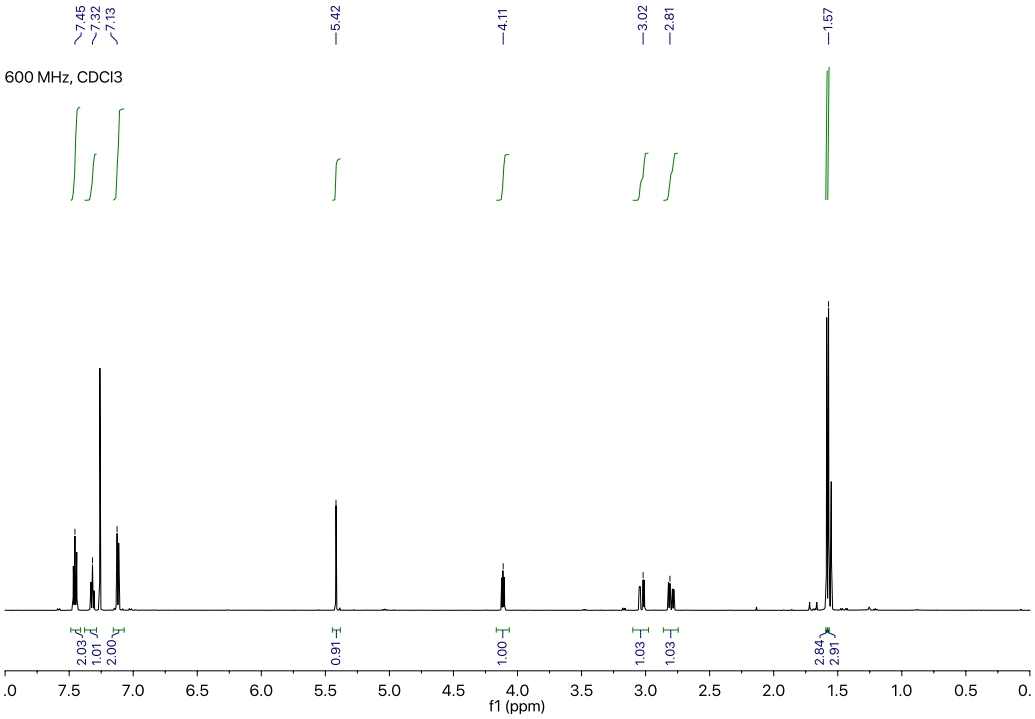
11

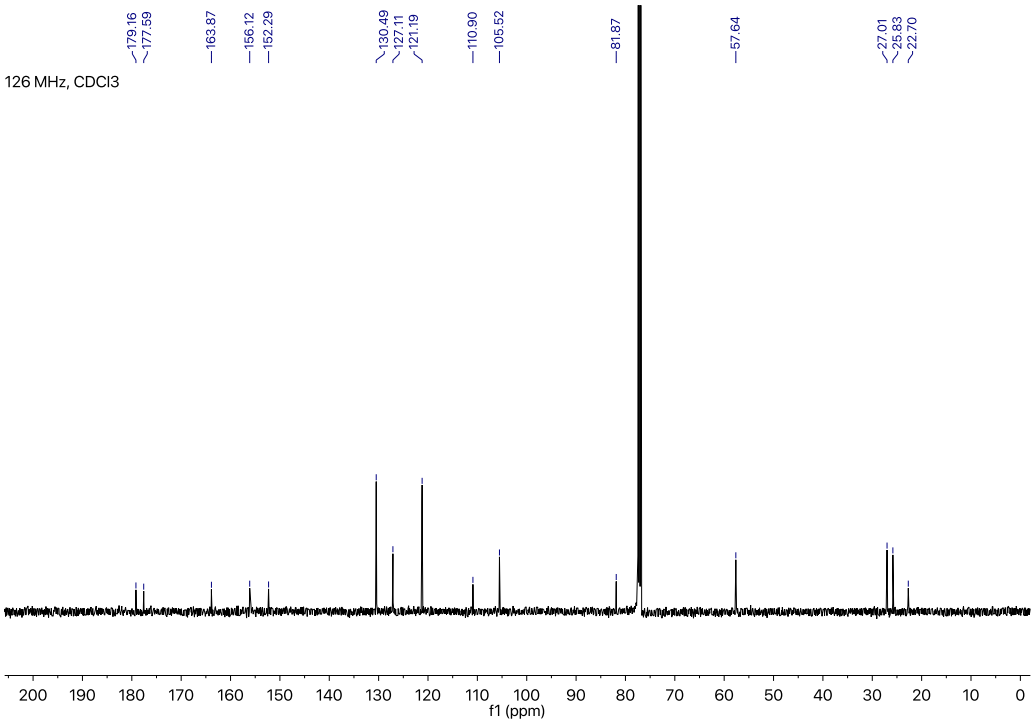


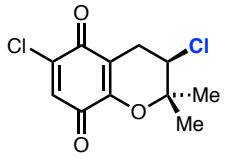



Me
Me
Cl
O
PhO
O
O

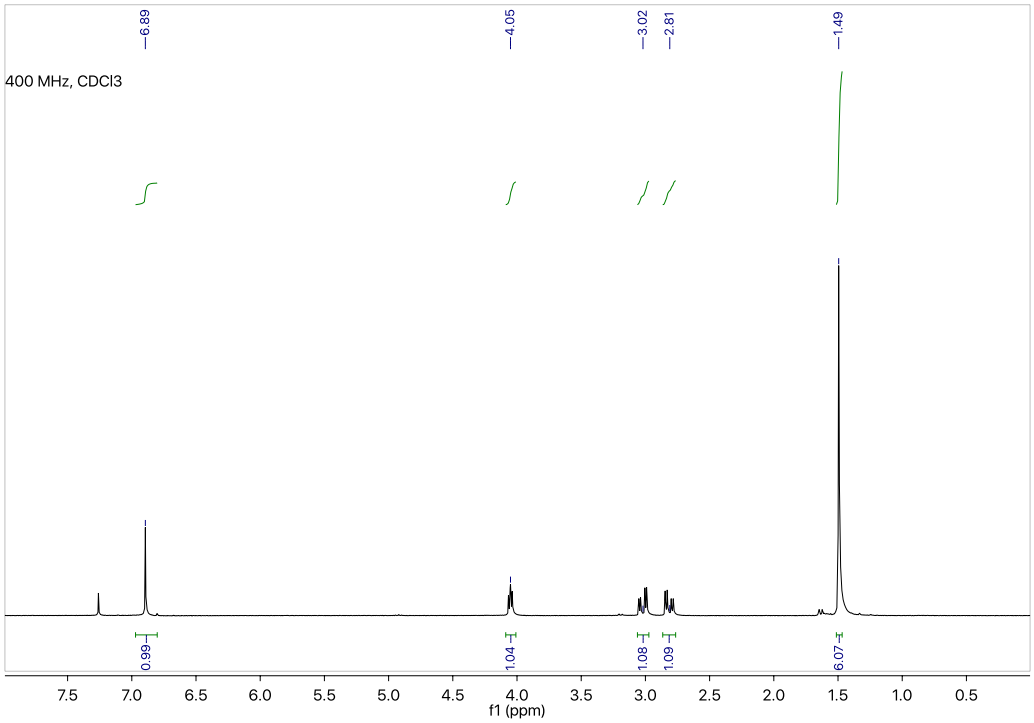
12

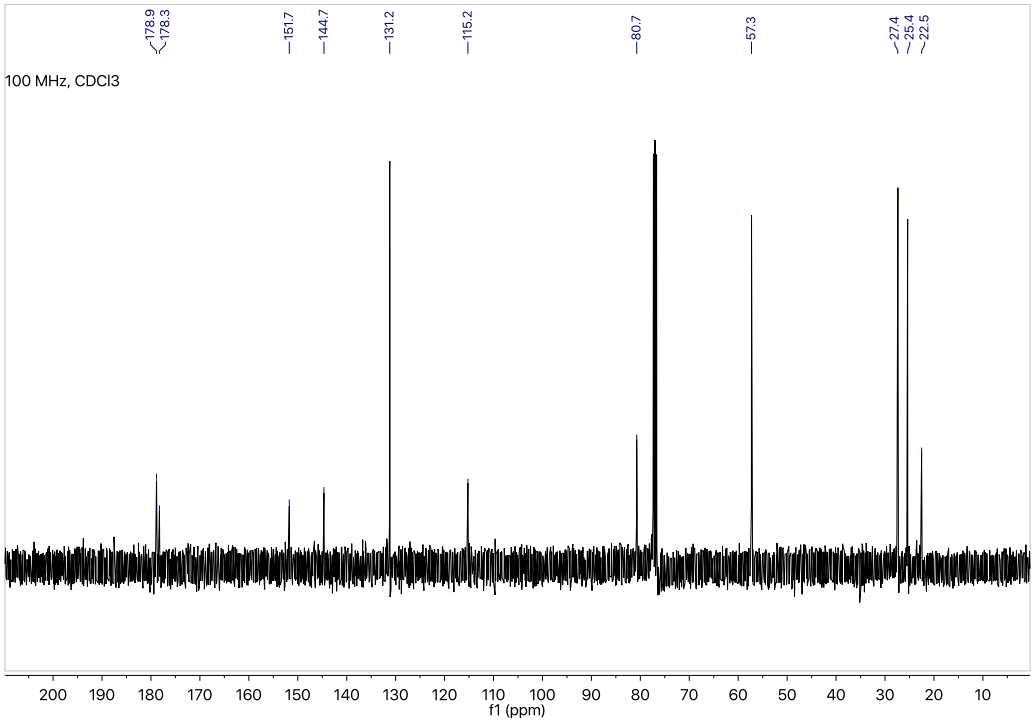

7.45
7.32
7.13
5.42
4.11
3.02
2.81
1.57
600 MHz, CDCl3
2.03
1.01
2.00
0.91
1.00
1.03
1.03
2.84
2.91
f1 (ppm)

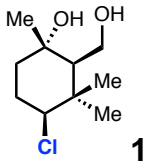

179.16
177.59
163.87
156.12
152.29
130.49
127.11
121.19
110.90
105.52
81.87
57.64
27.01
25.83
22.70
126 MHz, CDCl3
f1 (ppm)


O
Cl
Cl
Me
O
Me
O

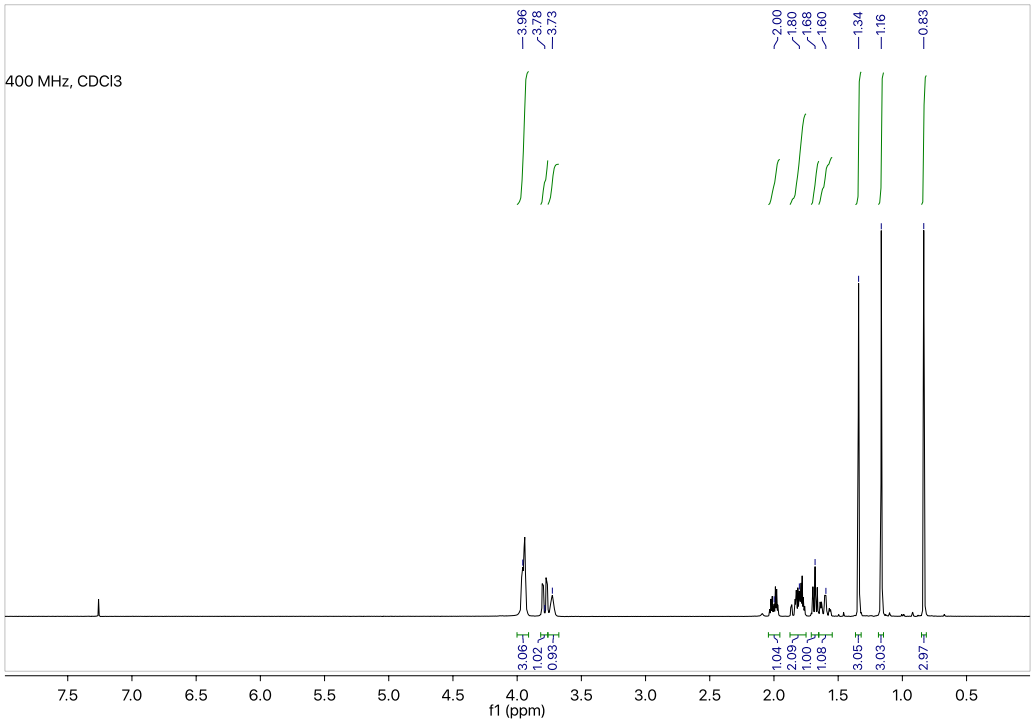
S4

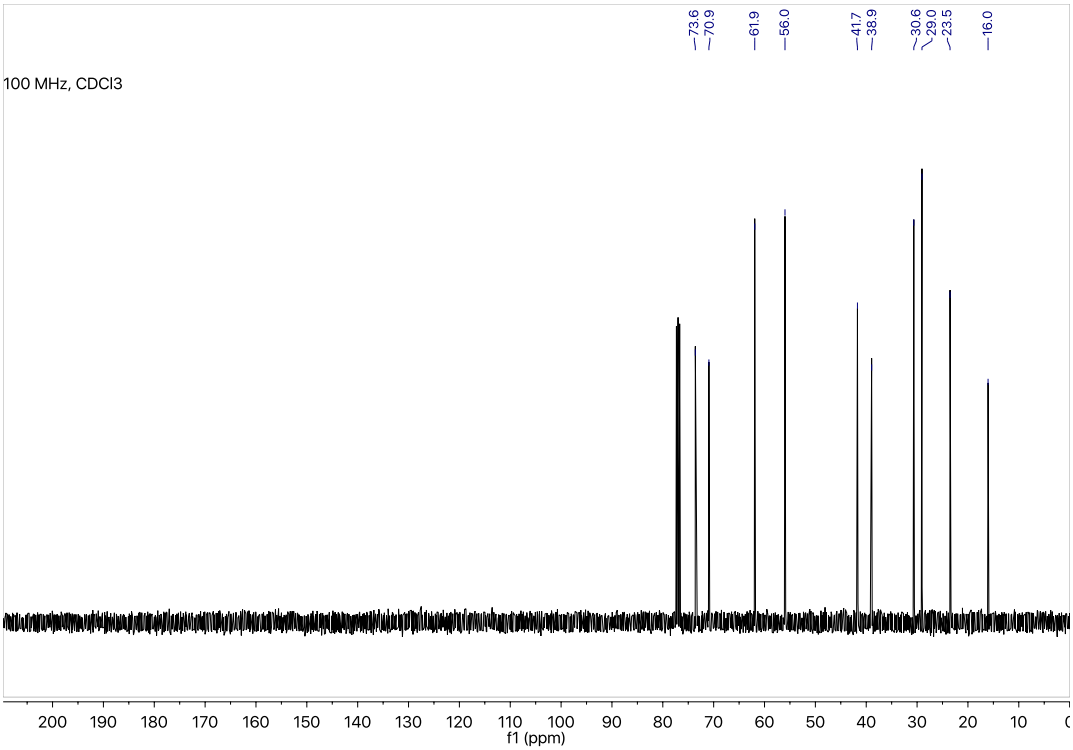

6.89
4.05
3.02
2.81
1.49
400 MHz, CDCl3
0.99
1.04
1.08
1.09
6.07
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

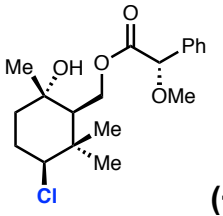

178.9
178.3
151.7
144.7
131.2
115.2
80.7
57.3
27.4
25.4
22.5
100 MHz, CDCl3
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


Me
OH
OH
Me
Me
Cl

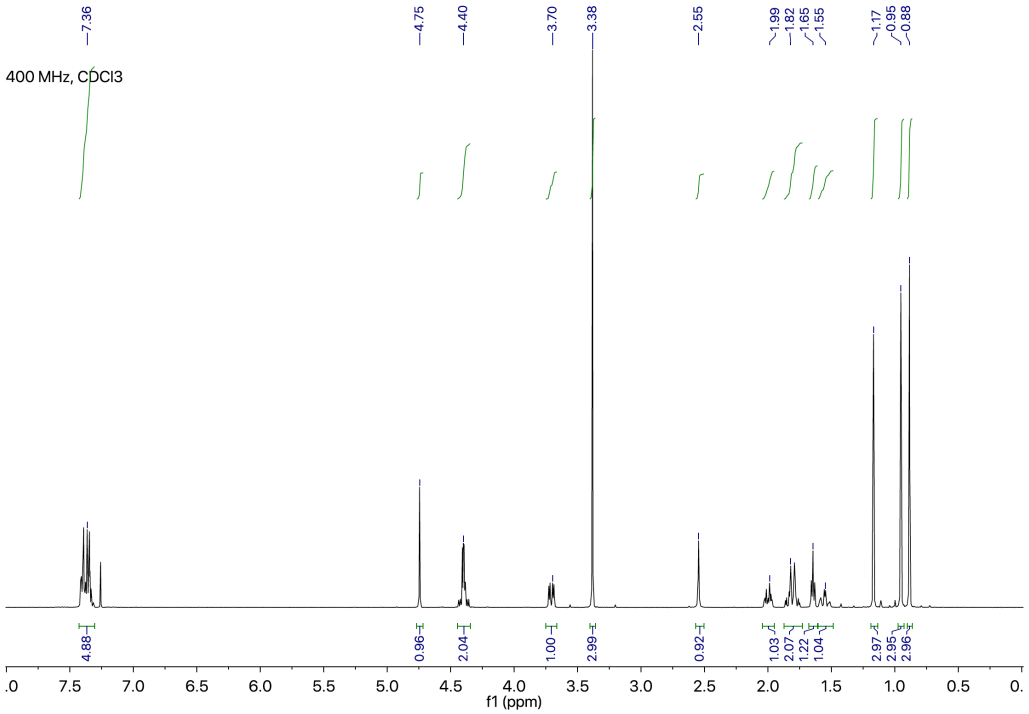
16

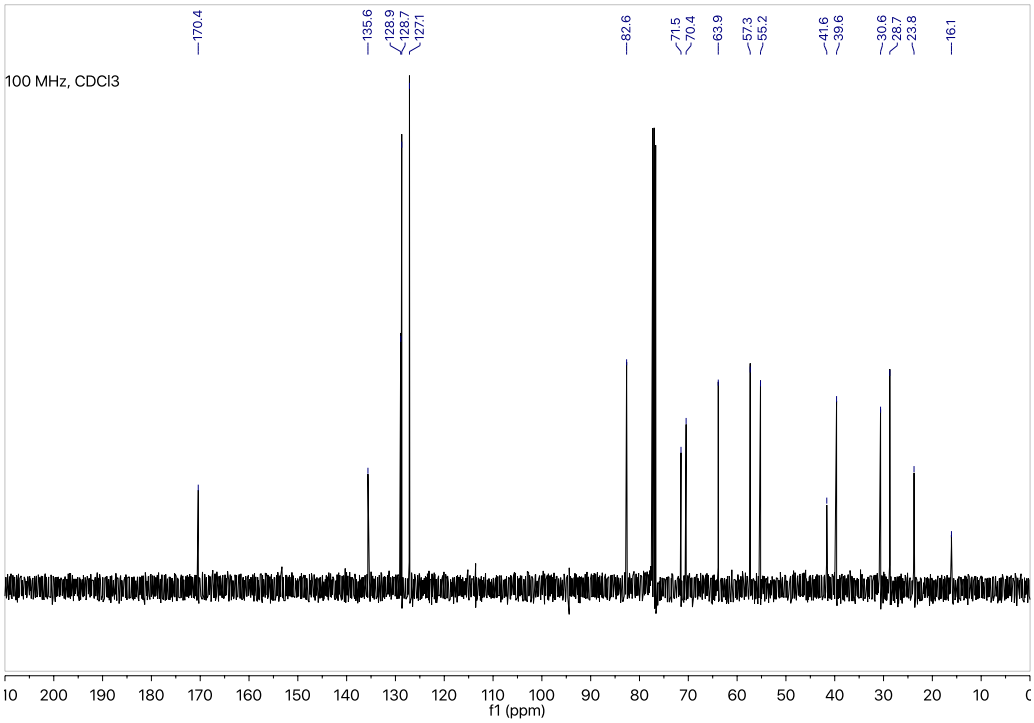

400 MHz, CDCl3
3.96
3.78
3.73
2.00
1.80
1.68
1.60
1.34
1.16
0.83
3.06
1.02
0.93
1.04
2.09
1.00
1.08
3.05
3.03
2.97
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

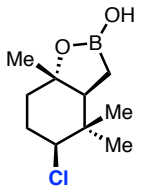

100 MHz, CDCl3
73.6
70.9
61.9
56.0
41.7
38.9
30.6
29.0
23.5
16.0
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


O
Ph
Me
OH
O
OMe
Me
Me
Cl

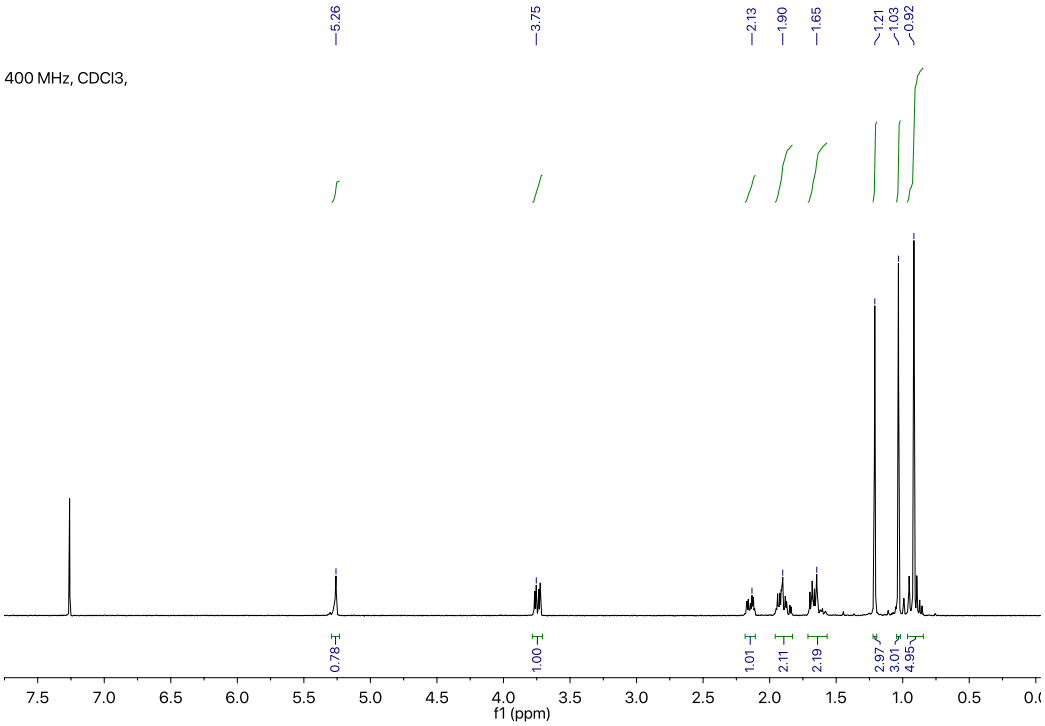
(+)-S7

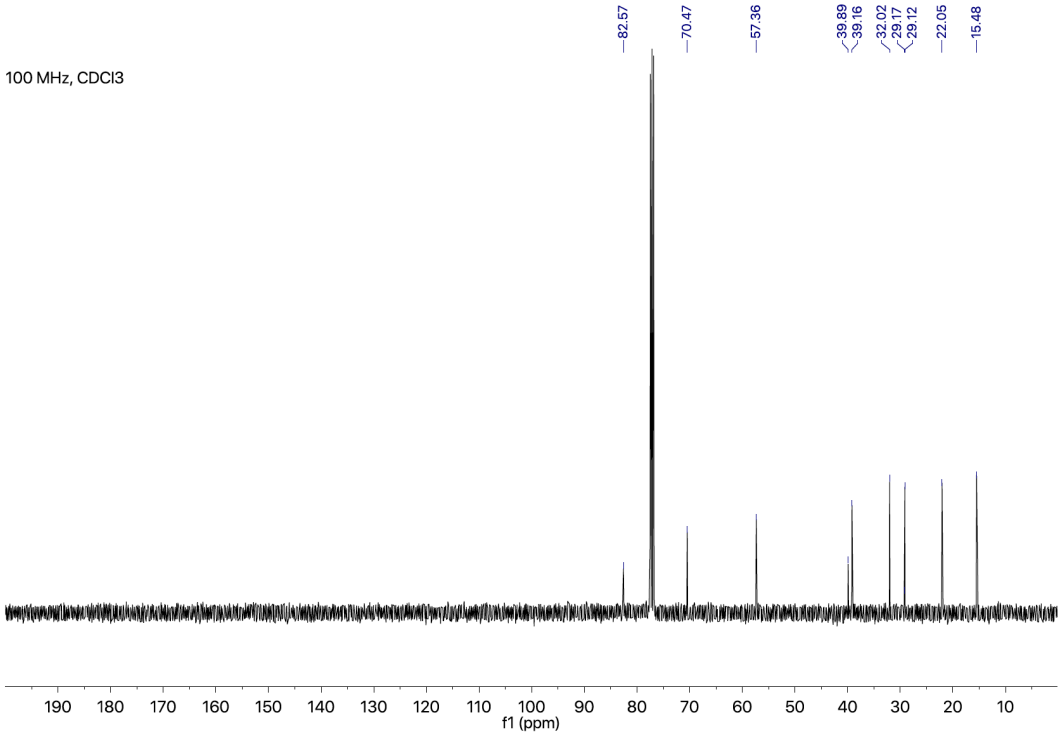

400 MHz, CDCl3
7.36
4.75
4.40
3.70
3.38
2.55
1.99
1.82
1.65
1.55
1.17
0.95
0.88
4.88
0.96
2.04
1.00
2.99
0.92
1.03
2.07
1.22
1.04
2.97
2.95
2.96
f1 (ppm)

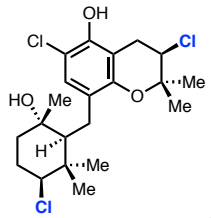

100 MHz, CDCl3
170.4
135.6
128.9
128.7
127.1
82.6
71.5
70.4
63.9
57.3
55.2
41.6
39.6
30.6
28.7
23.8
16.1
f1 (ppm)


OH
O
B
Me
Me
Me
Cl

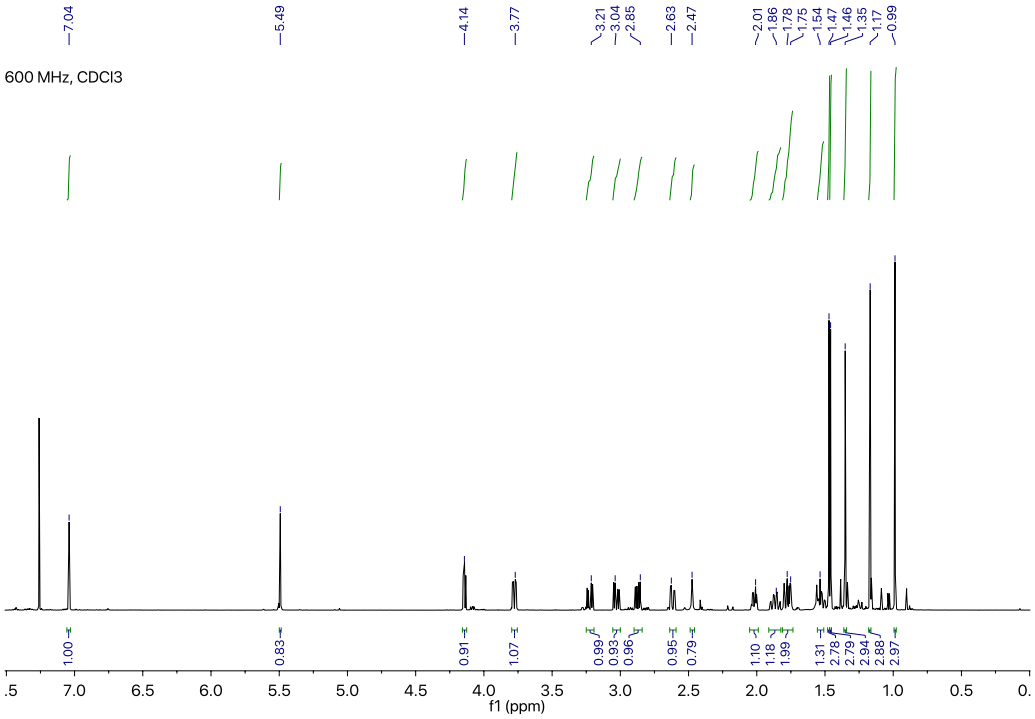
18

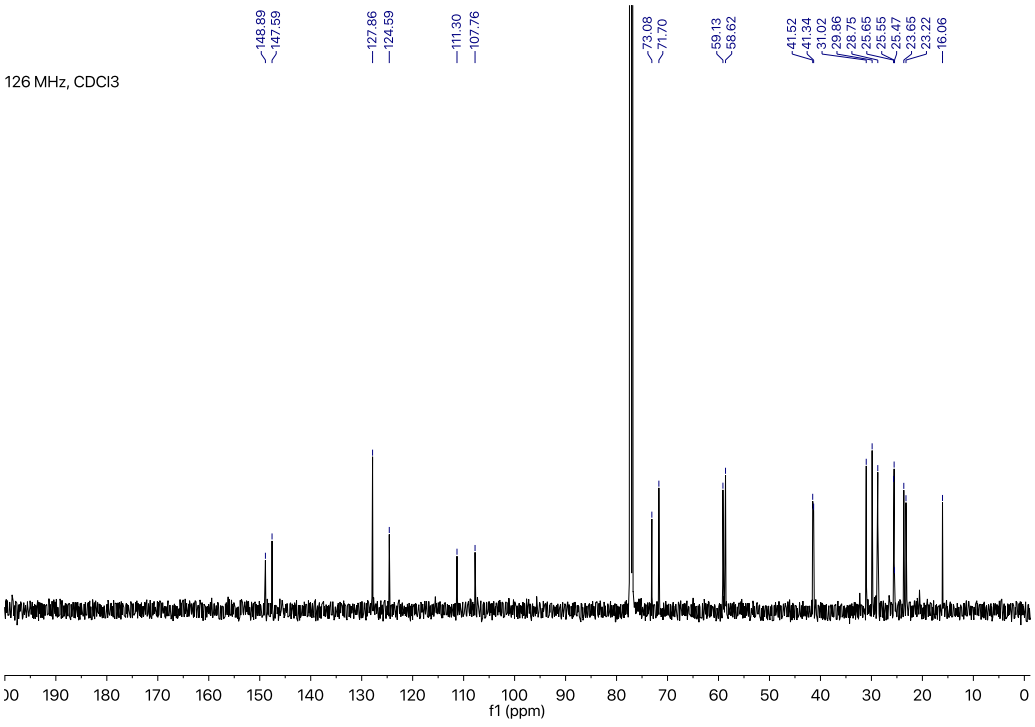

400 MHz, CDCl3,
5.26
3.75
2.13
1.90
1.65
1.21
1.03
0.92
0.78
1.00
1.01
2.11
2.19
2.97
3.01
4.95
f1 (ppm)

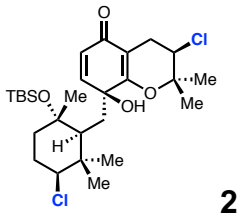

100 MHz, CDCl3
82.57
70.47
57.36
39.89
39.16
32.02
29.17
29.12
22.05
15.48
f1 (ppm)


OH
Cl
Cl
Me
Me
HO
Me
O
H
Me
Me
Cl

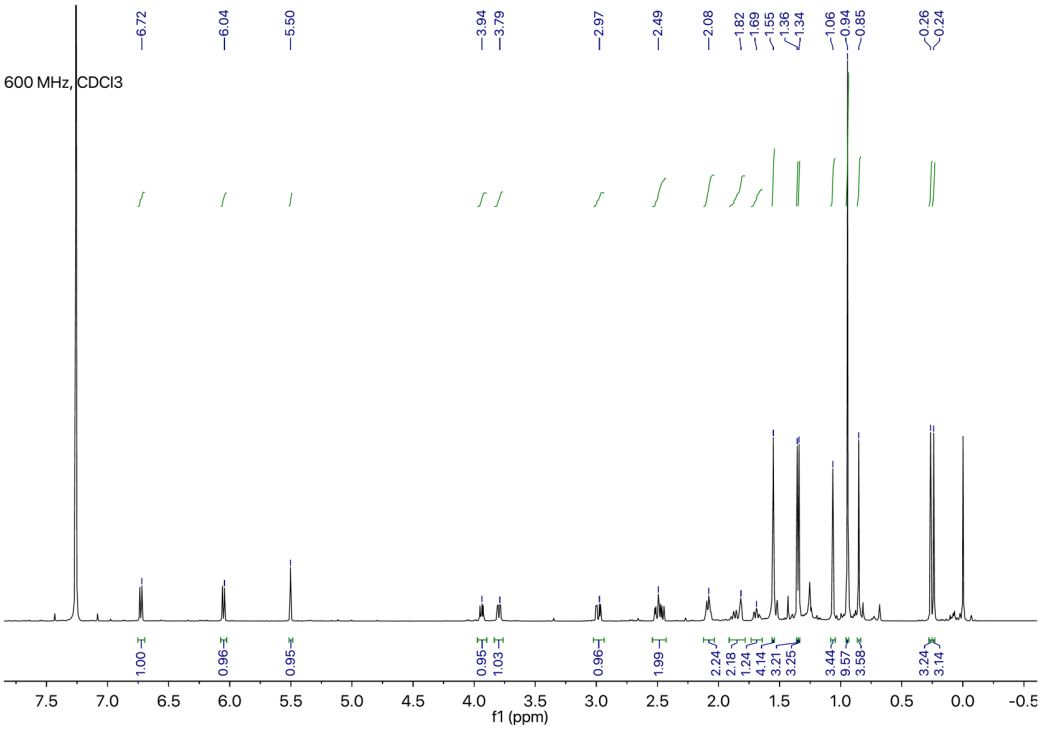
20

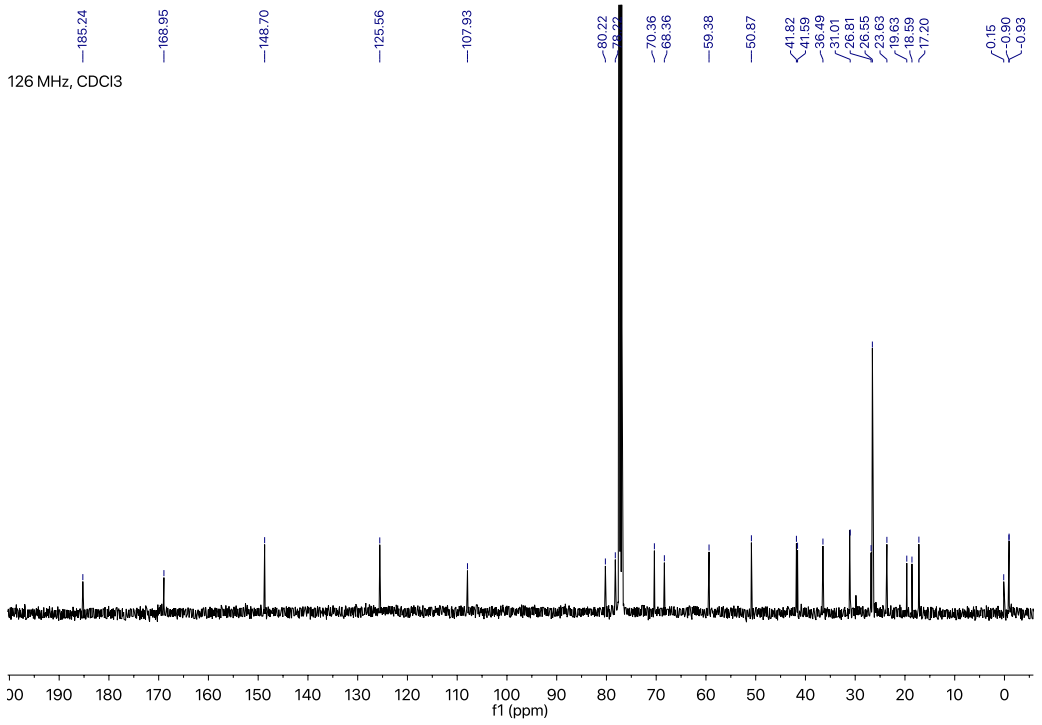

7.04
5.49
4.14
3.77
3.21
3.04
2.85
2.63
2.47
2.01
1.86
1.78
1.75
1.54
1.47
1.46
1.35
1.17
0.99
600 MHz, CDCl3
1.00
0.83
0.91
1.07
0.99
0.93
0.96
0.95
0.79
1.10
1.18
1.99
1.31
2.78
2.79
2.94
2.88
2.97
f1 (ppm)

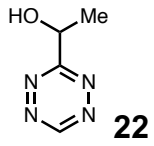

148.89
147.59
127.86
124.59
111.30
107.76
73.08
71.70
59.13
58.62
41.52
41.34
31.02
29.86
28.75
25.65
25.55
25.47
23.65
23.22
16.06
126 MHz, CDCl3
f1 (ppm)


O
Cl
Me
Me
TBSO
Me
OH
O
H
Me
Me
Cl

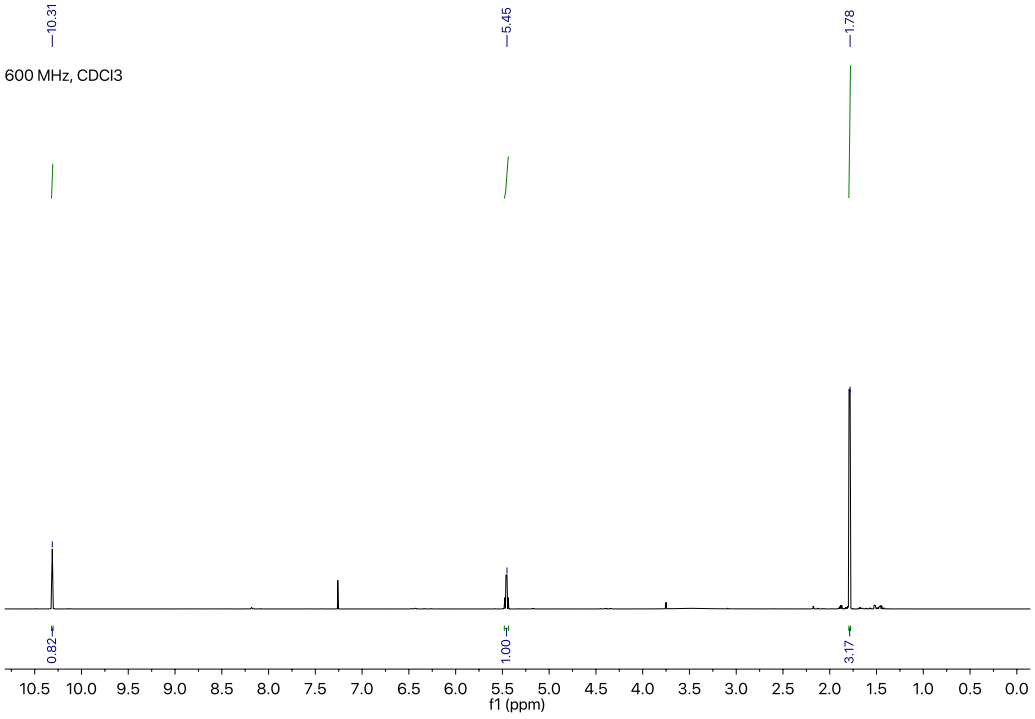
21

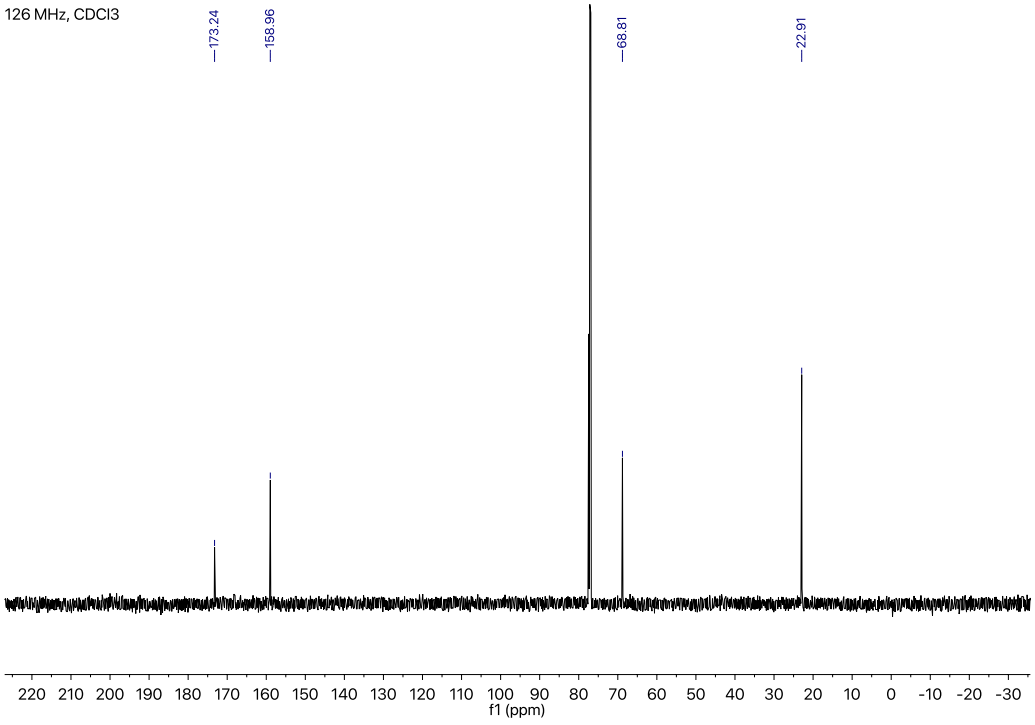

600 MHz, CDCl3
6.72
6.04
5.50
3.94
3.79
2.97
2.49
2.08
1.82
1.69
1.55
1.36
1.34
1.06
0.94
0.85
0.26
0.24
1.00
0.96
0.95
0.95
1.03
0.96
1.99
2.24
2.18
1.24
4.14
3.21
3.25
3.44
9.57
3.58
3.24
3.14
f1 (ppm)


126 MHz, CDCl3
185.24
168.95
148.70
125.56
107.93
80.22
79.22
70.36
68.36
59.38
50.87
41.82
41.59
36.49
31.01
26.81
26.55
23.63
19.63
18.59
17.20
0.15
-0.90
-0.93
f1 (ppm)

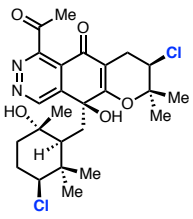

HO
Me
N
N
N
N
N

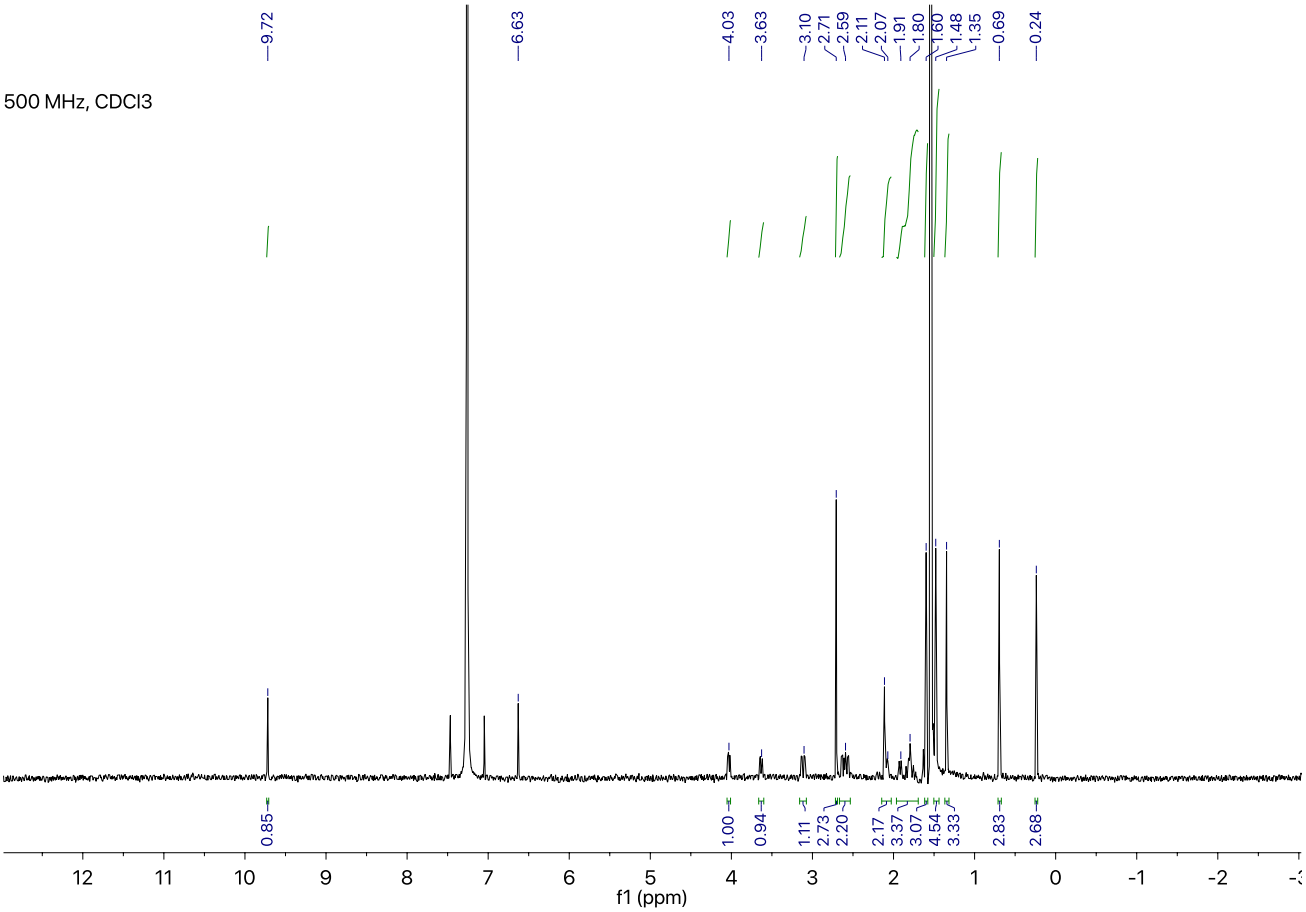
22


10.31
5.45
1.78
600 MHz, CDCl3
0.82
1.00
3.17
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

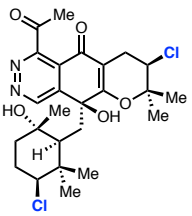

126 MHz, CDCl3
173.24
158.96
68.81
22.91
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)

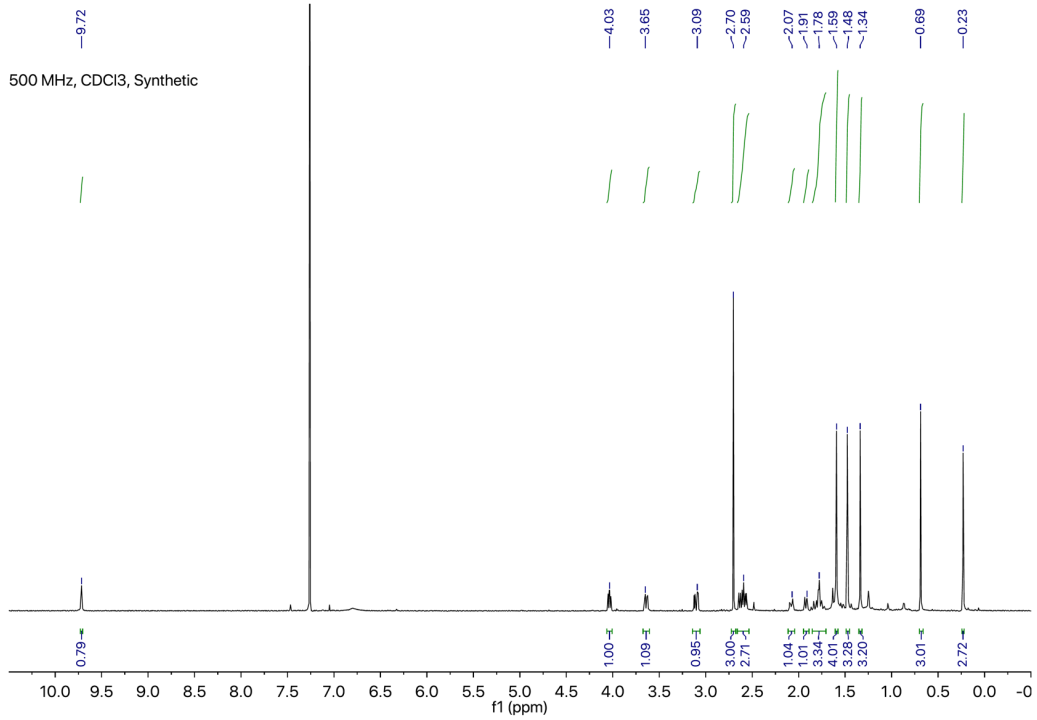
Natural azamerone ($CDCl_3$):

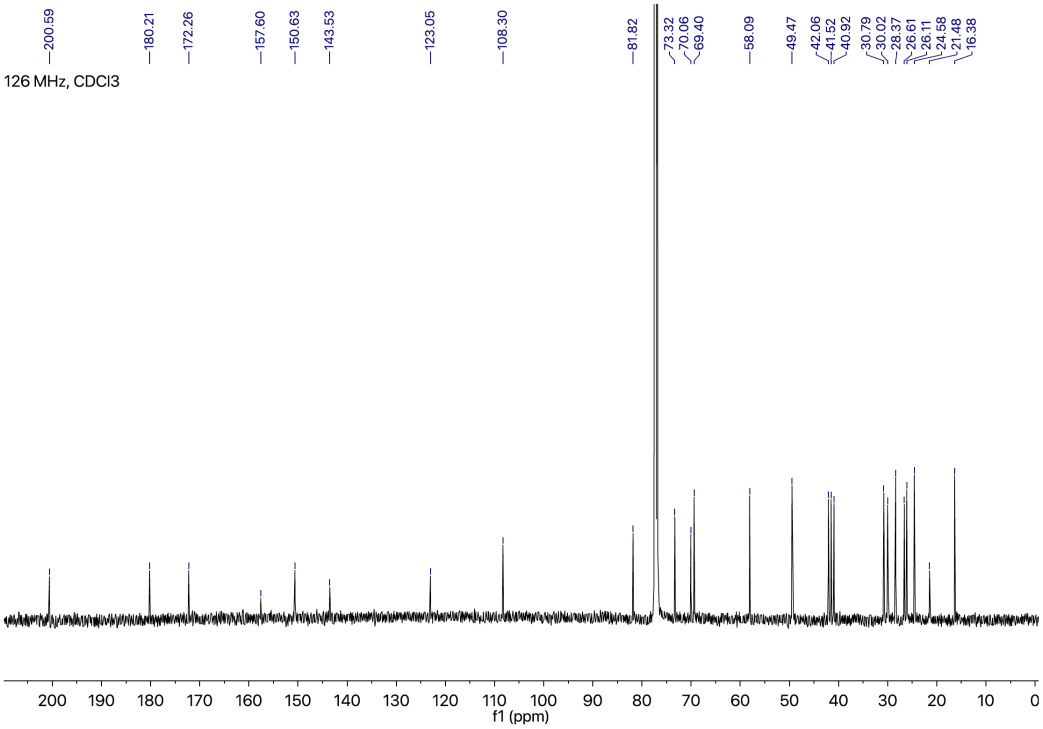




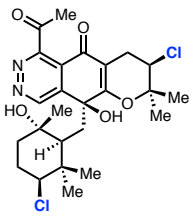
Synthetic azamerone ($CDCl_3$):

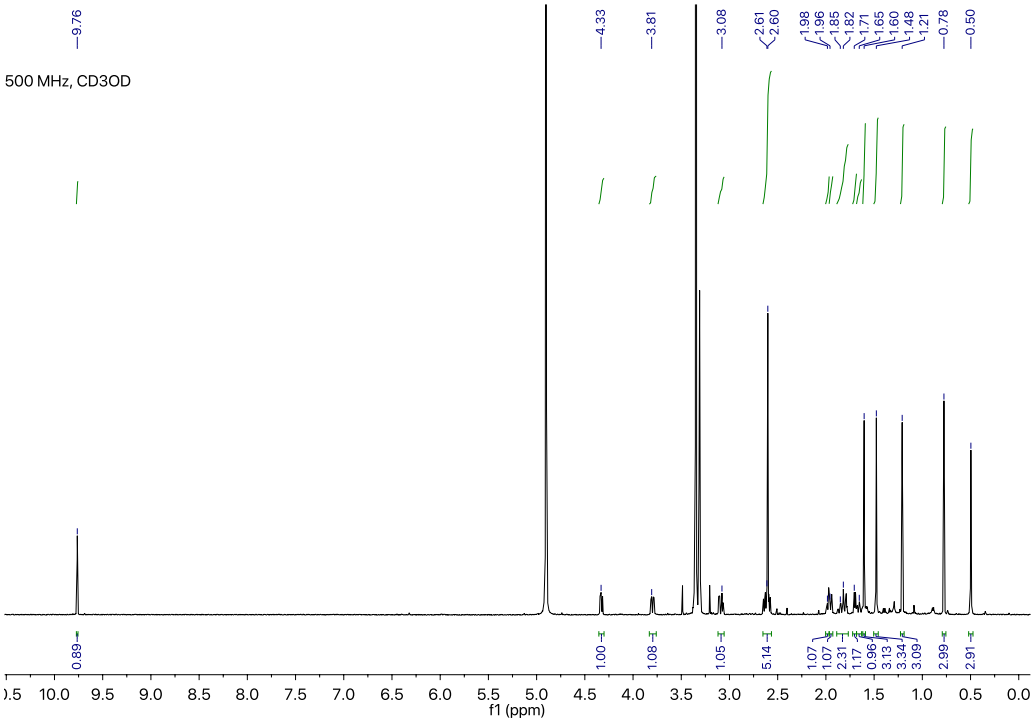


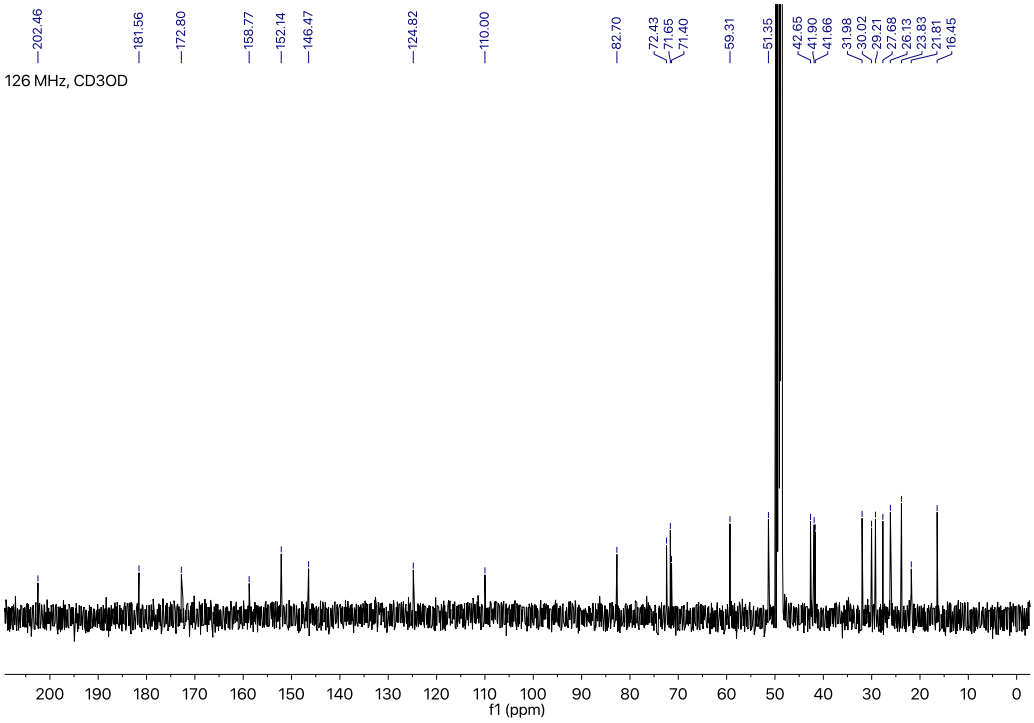




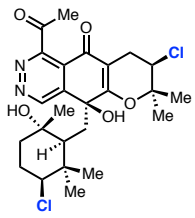
Synthetic azamerone (CD_3OD):

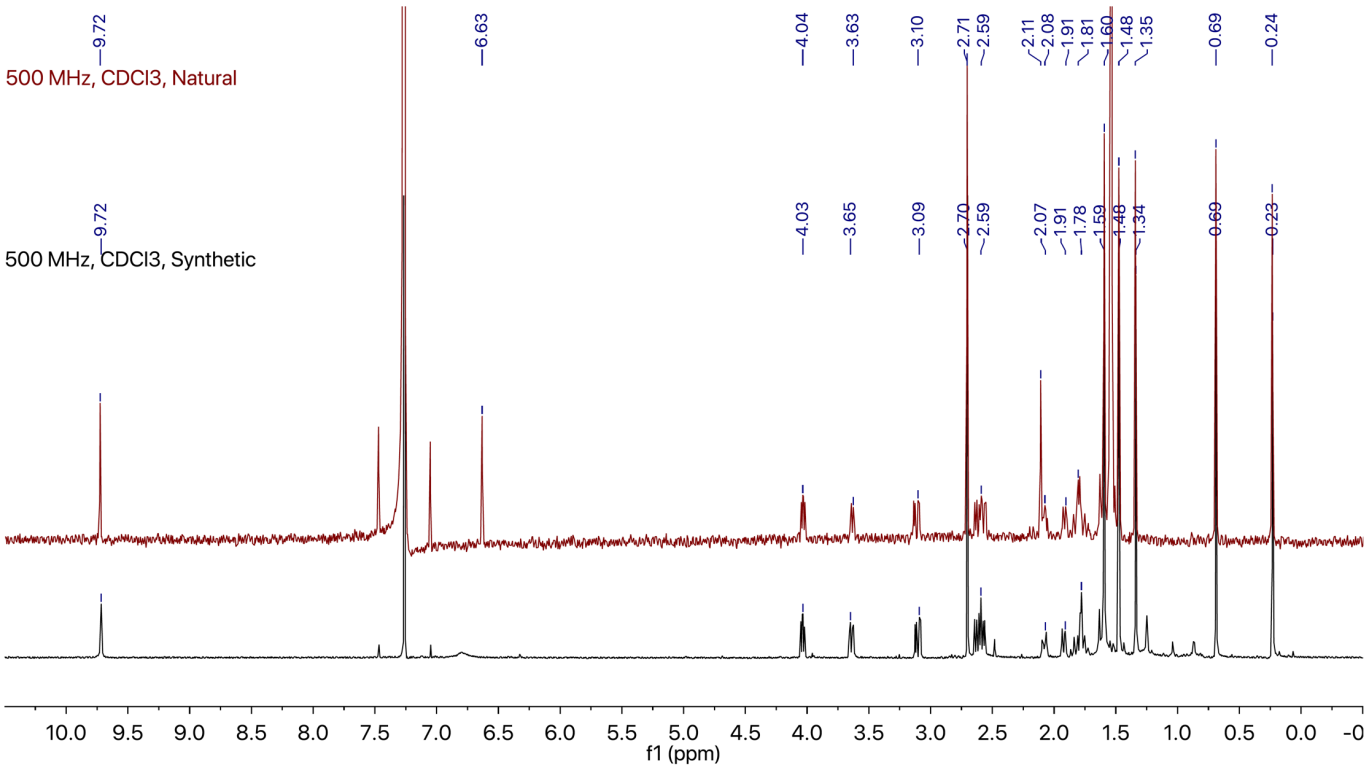




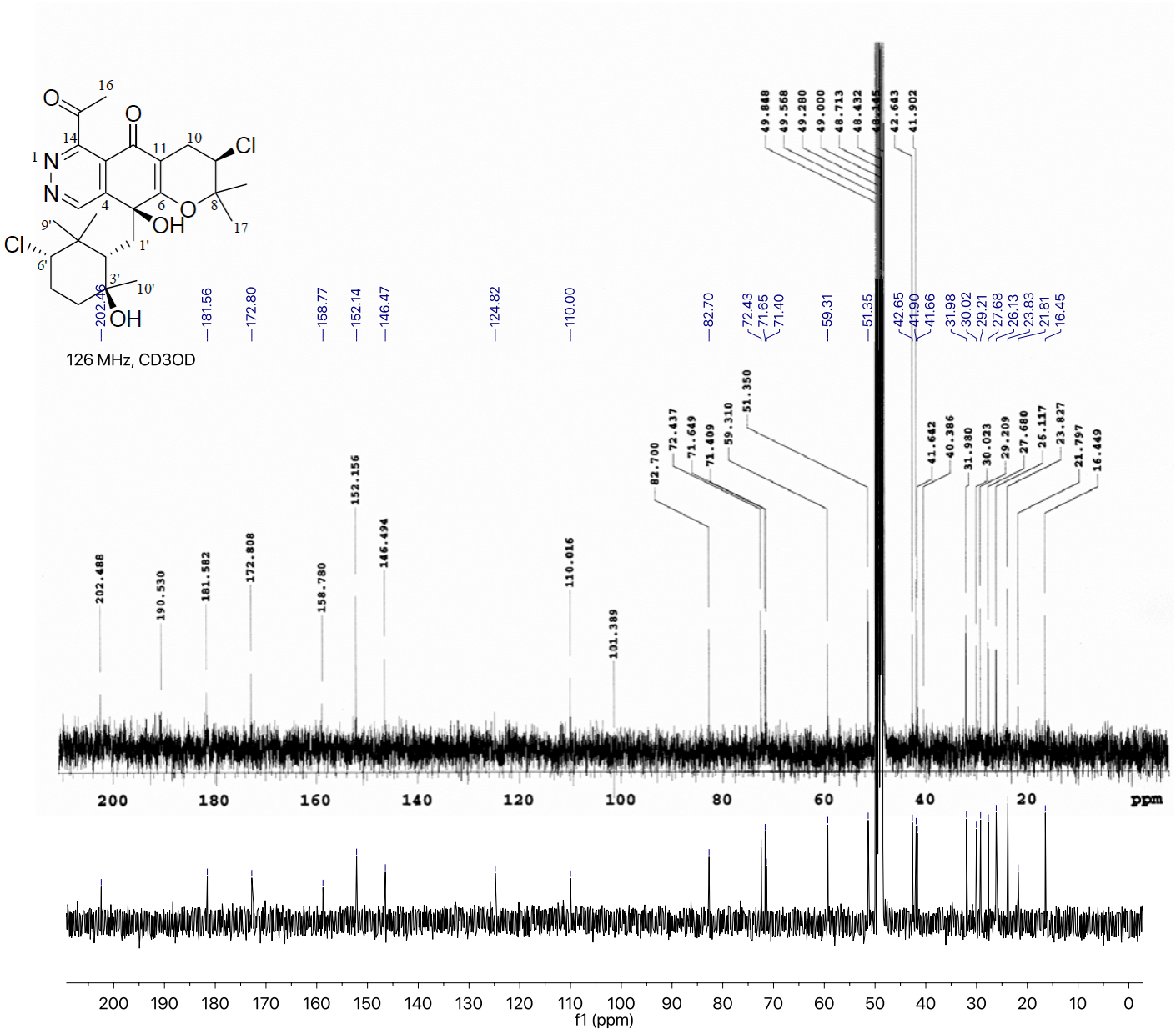


^{1}H-NMR spectra overlay of natural (top) and synthetic (bottom) azamerone (500 MHz, $CDCl_3$):

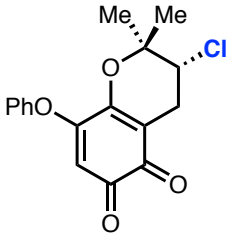




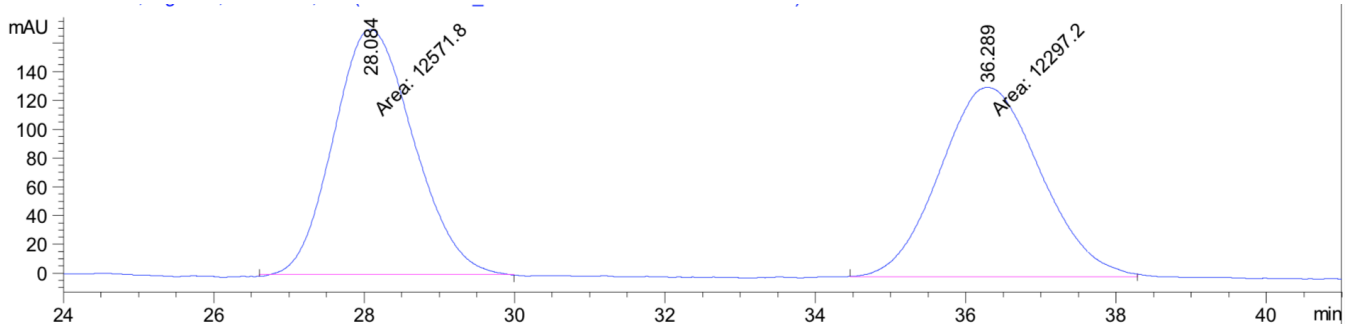
^{13}C-NMR spectra overlay of natural (top, 125 MHz) and synthetic (bottom, 126 MHZ) azamerone (CD_3OD):



7. HPLC Traces

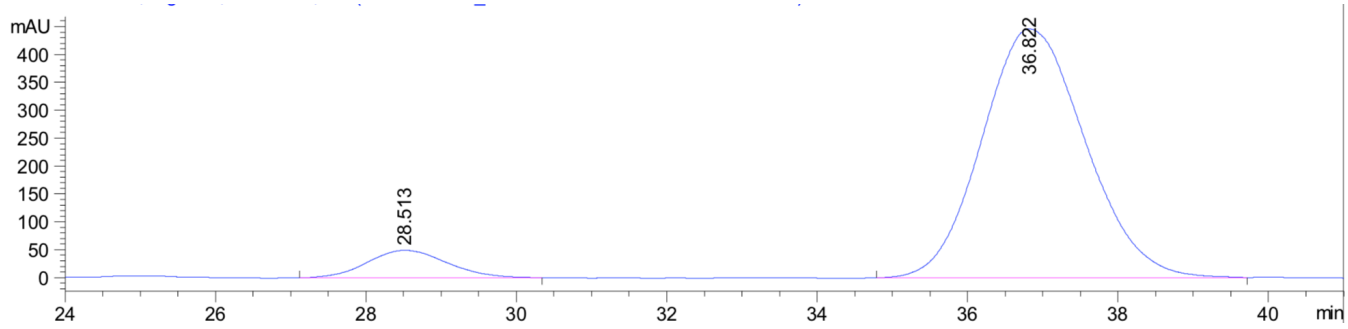


Racemic Sample: Chiralpak AS-H column, 30% *i*-PrOH in hexanes, 1 mL/min, 210 nm

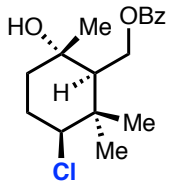


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.084	MM	1.2312	1.25718e4	170.18613	50.5520
2	36.289	MM	1.5545	1.22972e4	131.84886	49.4480
Totals :				2.48690e4	302.03499	

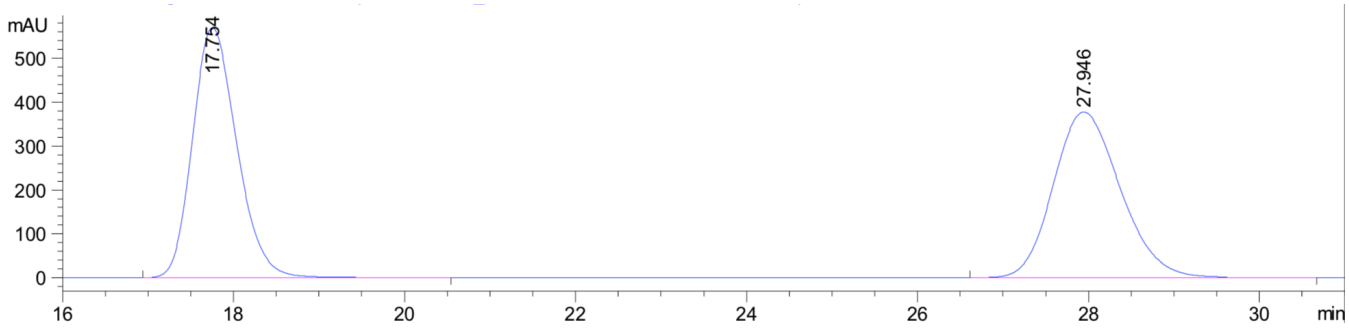
Scalemic Sample: Chiralpak AS-H column, 30% *i*-PrOH in hexanes, 1 mL/min, 210 nm



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.513	BB	0.9016	3634.44580	49.21397	7.8746
2	36.822	BB	1.2459	4.25197e4	446.15707	92.1254
Totals :				4.61541e4	495.37105	

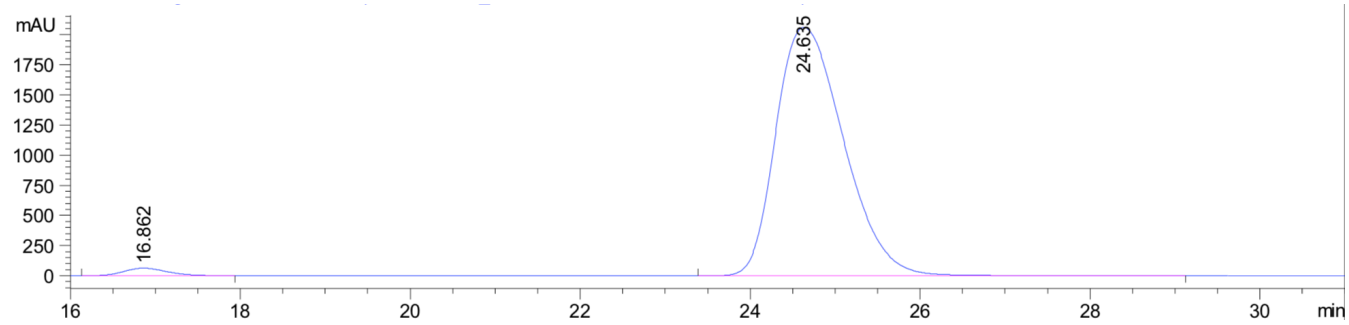


Racemic Sample: Chiralpak AS-H column, 3% *i*-PrOH in hexanes, 1 mL/min, 230 nm



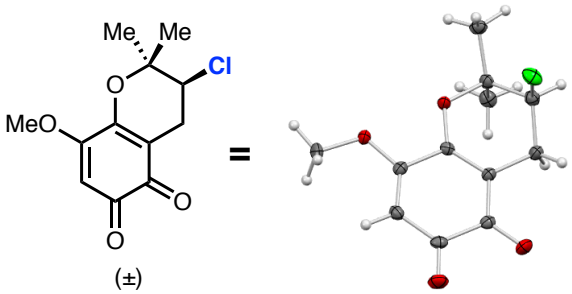
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.754	BB	0.5587	2.04139e4	568.78845	49.9487
2	27.946	BB	0.8476	2.04558e4	376.65546	50.0513
Totals :				4.08697e4	945.44391	

Scalemic Sample: Chiralpak AS-H column, 3% *i*-PrOH in hexanes, 1 mL/min, 230 nm



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.862	BB	0.5411	2139.05078	61.60521	1.8443
2	24.635	BB	0.8668	1.13845e5	2059.92188	98.1557
Totals :				1.15984e5	2121.52709	

8. X-Ray Crystallographic Information



su1411a

The compound crystallizes as yellow block-like crystals from a benzene / hexanes solution. There are two crystallographically independent molecules of the chromenedione and one and a half molecules of benzene of crystallization in the unit cell of the primitive, centrosymmetric triclinic space group P-1.

The connectivity of the two chromenedione molecules is as expected and the compound is: 3-chloro-6-methoxy-2,2-dimethyl-3,4-dihydro-2*H*-chromene-5,8-dione (see Figures). Though the molecules are crystallographically independent they are chemically identical (see Tables of Bond Distances and Angles for differences). They differ primarily in orientation and proximity to the benzene molecules. An overlay of the two molecules shows a high degree of mutual orientation.

One benzene molecule is located on a center of symmetry at [0, 0.5, 0.5] while the other is in a general position.

Bond distances and angles within the molecules are as expected.

CRYSTAL SUMMARY

Crystal data for $C_{33}H_{35}Cl_2O_8$; $M_r = 630.51$; Triclinic; space group P-1; $a = 10.7112(13)$ Å; $b = 11.6880(14)$ Å; $c = 12.6327(15)$ Å; $\alpha = 89.4701(18)°$; $\beta = 89.1293(19)°$; $\gamma = 79.0974(19)°$; $V = 1552.8(3)$ Å^3; $Z = 2$; $T = 120(2)$ K; λ(Mo-Kα) = 0.71073 Å; μ(Mo-Kα) = 0.260 mm^{-1}; d_{calc} = 1.349g.cm^{-3}; 36352 reflections collected; 6189 unique ($R_{int} = 0.0347$); giving $R_1 = 0.0372$, $wR_2 = 0.0892$ for 4954 data with [I>2σ(I)] and $R_1 = 0.0515$, $wR_2 = 0.0961$ for all 6189 data. Residual electron density (e$^-$.Å^{-3}) max/min: 0.469/-0.215.

An arbitrary sphere of data were collected on a yellow block-like crystal, having approximate dimensions of 0.139 × 0.093 × 0.081 mm, on a Bruker APEX-II diffractometer using a combination of ω- and φ-scans of 0.5° [1]. Data were corrected for absorption and polarization effects and analyzed for space group determination. The structure was solved by intrinsic phasing methods and expanded routinely [2]. The model was refined by full-matrix least-squares analysis of F^2 against all reflections. All non-hydrogen atoms were refined with anisotropic thermal displacement parameters. Unless otherwise noted, hydrogen atoms were included in calculated positions. Thermal parameters for the hydrogens were tied to the isotropic thermal parameter of the atom to which they are bonded (1.5 × for methyl, 1.2 × for all others).

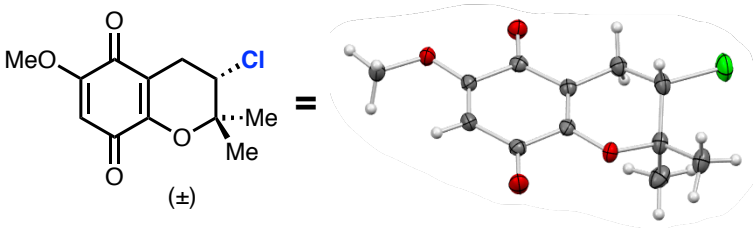
REFERENCES

[1] Bruker AXS. (2008). *APEX-2*. Bruker-Nonius AXS, Madison, Wisconsin, USA.

[2] G. M. Sheldrick, *Acta Cryst.*, **2008**, *A64*, 112.

Crystal data and structure refinement for su1411a.

Identification code	su1411a
Empirical formula	$C_{33}H_{35}Cl_2O_8$
Formula weight	630.51
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 10.7112(13) Å α = 89.4701(18)°
	b = 11.6880(14) Å β = 89.1293(19)°
	c = 12.6327(15) Å γ = 79.0974(19)°
Volume	1552.8(3) Å^3
Z	2
Density (calculated)	1.349 g.cm^{-3}
Absorption coefficient (μ)	0.260 mm^{-1}
F(000)	662
Crystal color, habit	yellow, block
Crystal size	0.139 × 0.093 × 0.081 mm^3
θ range for data collection	1.612 to 26.114°
Index ranges	$-13 \le h \le 13$, $-14 \le k \le 14$, $-15 \le l \le 15$
Reflections collected	36352
Independent reflections	6189 [R_{int} = 0.0347]
Completeness to θ = 25.242°	100.0 %
Absorption correction	Numerical
Max. and min. transmission	1.0000 and 0.9408
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6189 / 0 / 394
Goodness-of-fit on F^2	1.028
Final R indices [I>2σ(I)]	R_1 = 0.0372, wR_2 = 0.0892
R indices (all data)	R_1 = 0.0515, wR_2 = 0.0961
Largest diff. peak and hole	0.469 and -0.215 e$^-$.Å^{-3}



su1412

The compound, 3-chloro-8-methoxy-2,2-dimethyl-3,4-dihydro-2*H*-chromene-5,6-dione, crystallizes as orange block-like crystals from a benzene / hexanes solution. There are four molecules of the compound in the unit cell of the primitive, centrosymmetric, monoclinic space group $P2_1/n$.

The structure of the chromene dione is as expected. Localization of the double bonds is evidenced by the C4-C9 and C7-C8 bond distances (~1.36 Å, see Table of Bond Distances).

CRYSTAL SUMMARY

Crystal data for C12 H13 Cl O4; M_r = 256.67; Monoclinic; space group $P2_1/n$; a = 10.1102(13) Å; b = 11.1721(13) Å; c = 11.1221(14) Å; α = 90°; β = 115.225(3)°; γ = 90°; V = 1136.5(2) Å^3; Z = 4; T = 120(2) K; λ(Mo-Kα) = 0.71073 Å; μ(Mo-Kα) = 0.336 mm^{-1}; d_{calc} = 1.500g.cm^{-3}; 18072 reflections collected; 2535 unique (R_{int} = 0.0503); giving R_1 = 0.0407, wR_2 = 0.0949 for 1934 data with [I>2σ(I)] and R_1 = 0.0613, wR_2 = 0.1046 for all 2535 data. Residual electron density (e$^-$.Å^{-3}) max/min: 0.549/-0.301.

An arbitrary sphere of data were collected on a orange block-like crystal, having approximate dimensions of 0.15 × 0.12 × 0.10 mm, on a Bruker Kappa X8-APEX-II diffractometer using a combination of ω- and φ-scans of 0.5° [1]. Data were corrected for absorption and polarization effects and analyzed for space group determination. The structure was solved by intrinsic phasing methods and expanded routinely [2]. The model was refined by full-matrix least-squares analysis of F^2 against all reflections. All non-hydrogen atoms were refined with anisotropic thermal displacement parameters. Unless otherwise noted, hydrogen atoms were included in calculated positions. Thermal parameters for the hydrogens were tied to the isotropic thermal parameter of the atom to which they are bonded (1.5 × for methyl, 1.2 × for all others).

REFERENCES

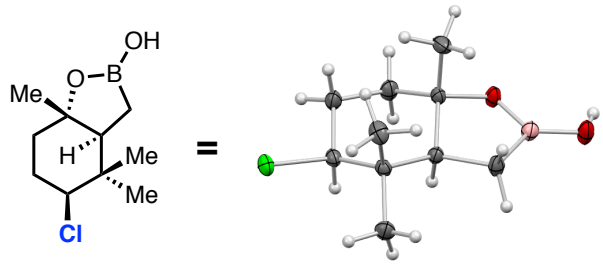
[1] Bruker AXS. (2008). *APEX-2*. Bruker-Nonius AXS, Madison, Wisconsin, USA.

[2] G. M. Sheldrick, *Acta Cryst.*, **2008**, *A64*, 112.

Crystal data and structure refinement for su1412.

Identification code	su1412
Empirical formula	C12 H13 Cl O4
Formula weight	256.67
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$

Unit cell dimensions	a = 10.1102(13) Å α = 90°
	b = 11.1721(13) Å β = 115.225(3)°
	c = 11.1221(14) Å γ = 90°
Volume	1136.5(2) Å^3
Z	4
Density (calculated)	1.500 g.cm^{-3}
Absorption coefficient (μ)	0.336 mm^{-1}
F(000)	536
Crystal color, habit	orange, block
Crystal size	0.15 × 0.12 × 0.10 mm^3
θ range for data collection	2.283 to 27.201°
Index ranges	-12 ≤ h ≤ 12, -11 ≤ k ≤ 14, -14 ≤ l ≤ 14
Reflections collected	18072
Independent reflections	2535 [R_{int} = 0.0503]
Completeness to θ = 25.242°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7455 and 0.6971
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2535 / 0 / 157
Goodness-of-fit on F^2	1.056
Final R indices [I>2σ(I)]	R_1 = 0.0407, wR_2 = 0.0949
R indices (all data)	R_1 = 0.0613, wR_2 = 0.1046
Extinction coefficient	n/a
Largest diff. peak and hole	0.549 and -0.301 e$^-$.Å^{-3}



18 **su1713**

The compound crystallizes as colorless block-like crystals from an evaporated chloroform solution. There are two molecules of the compound in the unit cell of the primitive, centrosymmetric, triclinic space group P-1.

The structure and relative stereochemistry of the compound are as predicted (see Figures). There are no exceptional bond distances or angles within the molecule. The boryl hydrogen (bonded to O2) was located from a difference Fourier map and refined freely. It forms a hydrogen bond to oxygen, O1, of a neighboring molecule via inversion symmetry, resulting in a hydrogen-bonded dimer within the lattice.

CRYSTAL SUMMARY

Crystal data for $C_{10}H_{18}BClO_2$; M_r = 216.50; Triclinic; space group P-1; a = 7.3390(7) Å; b = 7.6739(7) Å; c = 11.4931(10) Å; α = 105.065(2)°; β = 95.119(2)°; γ = 114.634(2)°; V = 553.57(9) Å^3; Z = 2; T = 120(2) K; λ(Mo-Kα) = 0.71073 Å; μ(Mo-Kα) = 0.316 mm^{-1}; d_{calc} = 1.299 g.cm^{-3}; 16616 reflections collected; 2788 unique (R_{int} = 0.0201); giving R_1 = 0.0434, wR_2 = 0.1122 for 2509 data with [I>2σ(I)] and R_1 = 0.0485, wR_2 = 0.1157 for all 2788 data. Residual electron density (e$^-$.Å^{-3}) max/min: 1.283/-0.332.

An arbitrary sphere of data was collected on a colorless block-like crystal, having approximate dimensions of 0.238 × 0.171 × 0.110 mm, on a Bruker Kappa X8-APEX-II diffractometer using a combination of ω- and φ-scans of 0.5° [1]. Data were corrected for absorption and polarization effects and analyzed for space group determination [2]. The structure was solved by dual-space methods and expanded routinely [3]. The model was refined by full-matrix least-squares analysis of F^2 against all reflections [4]. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Unless otherwise noted, hydrogen atoms were included in calculated positions. Atomic displacement parameters for the hydrogens were tied to the equivalent isotropic displacement parameter of the atom to which they are bonded (U_{iso}(H) = 1.5U_{eq}(C) for methyl, 1.2U_{eq}(C) for all others).

REFERENCES

[1] *APEX-3*. Bruker AXS. Madison, Wisconsin, USA. **2016**.

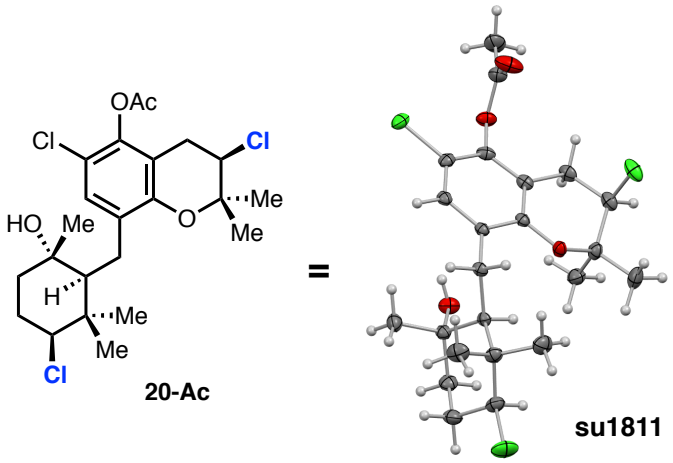
[2] L. Krause, R. Herbst-Irmer, G. M. Sheldrick, & D. Stalke. *J. Appl. Cryst.* **2015** *48*, 3.

[3] G. M. Sheldrick. *Acta Cryst.*, **2015**, *A71*, 3.

[4] G. M. Sheldrick. *Acta Cryst.*, **2015**, *C71*, 3.

Crystal data and structure refinement for su1713.

Identification code	su1713
Empirical formula	$C_{10}H_{18}BClO_2$
Formula weight	216.50
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.3390(7) Å α = 105.065(2)°
	b = 7.6739(7) Å β = 95.119(2)°
	c = 11.4931(10) Å γ = 114.634(2)°
Volume	553.57(9) $Å^3$
Z	2
Density (calculated)	1.299 $g.cm^{-3}$
Absorption coefficient (μ)	0.316 mm^{-1}
F(000)	232
Crystal color, habit	colorless, block
Crystal size	0.238 × 0.171 × 0.110 mm^3
θ range for data collection	1.883 to 28.437°
Index ranges	$-9 \le h \le 9$, $-10 \le k \le 10$, $-15 \le l \le 15$
Reflections collected	16616
Independent reflections	2788 [R_{int} = 0.0201]
Completeness to θ = 25.242°	100.0 %
Absorption correction	Numerical
Max. and min. transmission	0.9939 and 0.9327
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2788 / 0 / 134
Goodness-of-fit on F^2	1.085
Final R indices [I>2σ(I)]	R_1 = 0.0434, wR_2 = 0.1122
R indices (all data)	R_1 = 0.0485, wR_2 = 0.1157
Extinction coefficient	n/a
Largest diff. peak and hole	1.283 and -0.332 $e^-.Å^{-3}$



The chromanyl compound crystallizes as colorless block-like crystals. There are two molecules of the chromanyl in the unit cell of the primitive, acentric, monoclinic space group $P2_1$. The correct, absolute stereochemistry was determined by comparison with the known configuration of the molecule and by comparison of intensities of Friedel pairs of reflections. The Flack *x* parameter [0.049(4); 5] and Hooft *y* parameter [0.050(1); 6] are in agreement with the known absolute configuration that is shown in the Figures.

The structure of the chromanyl is as expected. The hydroxyl hydrogen atom was located from a difference Fourier map and refined freely. Surprisingly it is not involved in hydrogen bonding with possible acceptor atoms. Rather, it appears to be oriented towards the nearby phenyl ring of the chromanyl moiety. However, it is not well-oriented to form a non-classical O-H···π interaction. Presumably steric hindrance prevents reasonable hydrogen-bonding interactions.

Bond distances and angles within the molecule are as expected.

CRYSTAL SUMMARY

Crystal data for $C_{23}H_{31}Cl_3O_4$; $M_r = 477.83$; Monoclinic; space group $P2_1$; $a = 10.9120(5)$ Å; $b = 9.4971(5)$ Å; $c = 11.5555(6)$ Å; $\alpha = 90°$; $\beta = 99.171(2)°$; $\gamma = 90°$; $V = 1182.22(10)$ Å^3; $Z = 2$; $T = 120(2)$ K; λ(Cu-Kα) = 1.54184 Å; μ(Cu-Kα) = 3.726 mm^{-1}; $d_{calc} = 1.342$ g.cm^{-3}; 19514 reflections collected; 4561 unique ($R_{int} = 0.0364$); giving $R_1 = 0.0289$, $wR_2 = 0.0763$ for 4526 data with [I>2σ(I)] and $R_1 = 0.0291$, $wR_2 = 0.0764$ for all 4561 data. Residual electron density (e$^-$.Å^{-3}) max/min: 0.616/-0.252.

An arbitrary sphere of data was collected on a colorless block-like crystal, having approximate dimensions of 0.164 × 0.151 × 0.139 mm, on a Bruker APEX-II diffractometer using a combination of ω- and φ-scans of 0.5° [1]. Data were corrected for absorption and polarization effects and analyzed for space group determination [2]. The structure was solved by dual-space methods and expanded routinely [3]. The model was refined by full-matrix least-squares analysis of F^2 against all reflections [4]. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Unless otherwise noted, hydrogen atoms were included in calculated positions. Atomic displacement parameters for the hydrogens were tied to the equivalent isotropic displacement parameter of the atom to which they are bonded (U_{iso}(H) = 1.5U_{eq}(C) for methyl, 1.2U_{eq}(C) for all others).

REFERENCES

[1] *APEX-3*. Bruker AXS. Madison, Wisconsin, USA. **2016**.

[2] L. Krause, R. Herbst-Irmer, G. M. Sheldrick, & D. Stalke. *J. Appl. Cryst.* **2015** *48*, 3.

[3] G. M. Sheldrick. *Acta Cryst.*, **2015**, *A71*, 3.

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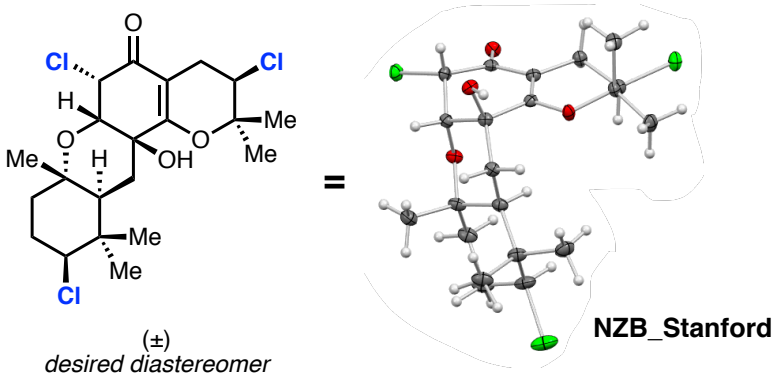
Crystal data and structure refinement for su1811.

Identification code	su1811	
Empirical formula	$C_{23}H_{31}Cl_3O_4$	
Formula weight	477.83	
Temperature	120(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 10.9120(5) Å	α = 90°
	b = 9.4971(5) Å	β = 99.171(2)°
	c = 11.5555(6) Å	γ = 90°
Volume	1182.22(10) Å^3	
Z	2	
Density (calculated)	1.342 g.cm^{-3}	
Absorption coefficient (μ)	3.726 mm^{-1}	
F(000)	504	
Crystal color, habit	colorless, block	
Crystal size	0.164 × 0.151 × 0.139 mm^3	
θ range for data collection	3.875 to 72.443°	
Index ranges	$-13 \le h \le 12$, $-11 \le k \le 10$, $-14 \le l \le 14$	
Reflections collected	19514	
Independent reflections	4561 [R_{int} = 0.0364]	
Completeness to θ = 67.679°	99.5 %	
Absorption correction	Numerical	
Max. and min. transmission	0.7149 and 0.6056	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4561 / 1 / 281	
Goodness-of-fit on F^2	1.037	
Final R indices [I>2σ(I)]	R_1 = 0.0289, wR_2 = 0.0763	
R indices (all data)	R_1 = 0.0291, wR_2 = 0.0764	
Absolute structure parameter	0.049(4)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.616 and -0.252 e$^-$.Å^{-3}	

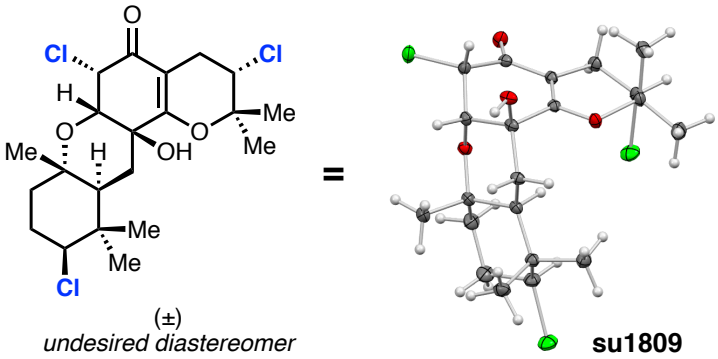


(±)
desired diastereomer

Crystal data and structure refinement for nzb_stanford.

Identification code	NZB_Stanford	
Empirical formula	C21 H29 Cl3 O4	
Formula weight	451.79	
Temperature	100(2) K	
Wavelength	0.71073 ≈	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 7.22880(10) ≈	α= 75.3280(10)∞.
	b = 10.3110(2) ≈	β= 87.2510(10)∞.
	c = 15.9253(3) ≈	γ = 72.8190(10)∞.
Volume	1096.60(3) ≈^{3}	
Z	2	
Density (calculated)	1.368 Mg/m^3	
Absorption coefficient	0.442 mm^{-1}	
F(000)	476	
Crystal size	0.100 x 0.100 x 0.080 mm^3	
Theta range for data collection	1.322 to 25.367∞.	
Index ranges	-8<=h<=8, -12<=k<=12, -19<=l<=19	
Reflections collected	29024	
Independent reflections	4023 [R(int) = 0.0297]	
Completeness to theta = 25.000∞	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.745 and 0.698	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4023 / 0 / 262	
Goodness-of-fit on F^2	1.067	

Final R indices [I>2sigma(I)]	R1 = 0.0320, wR2 = 0.0835
R indices (all data)	R1 = 0.0366, wR2 = 0.0867
Extinction coefficient	n/a
Largest diff. peak and hole	0.350 and -0.201 e.$\approx^{-3}$



The compound crystallizes as colorless tablet-shaped crystals from a chloroform / pentanes solution. There are two molecules of the compound in the unit cell of the primitive, centrosymmetric, triclinic space group P-1.

The structure of the compound is not as predicted. It is a fused tetra-cyclic compound (see Figures). Formally the compound is: 3,6,10-trichloro-12a-hydroxy-2,2,7a,11,11- pentamethyltetradecahydro-2H,5H- pyrano[2,3-a]xanthen-5-one. Because the compound is in a centrosymmetric space group, only the relative stereochemistry is presented.

The hydroxyl, O17, forms a hydrogen bond to the carbonyl O6 on a neighboring molecule (see Table of Hydrogen bonds for details).

The C—C—C bond angles at C3 and C7 are slightly more constrained than is normally expected, but only slightly. No other exceptional bond distances or angles are observed within the molecule.

CRYSTAL SUMMARY

Crystal data for $C_{21}H_{29}Cl_3O_4$; M_r = 451.79; Triclinic; space group P-1; a = 7.2805(2) Å; b = 11.3131(3) Å; c = 13.8979(4) Å; α = 78.5640(10)°; β = 78.6160(10)°; γ = 85.2340(10)°; V = 1098.75(5) Å^3; Z = 2; T = 120(2) K; λ(Cu-Kα) = 1.54184 Å; μ(Cu-Kα) = 3.976 mm^{-1}; d_{calc} = 1.366 g.cm^{-3}; 33410 reflections collected; 4157 unique (R_{int} = 0.0334); giving R_1 = 0.0277, wR_2 = 0.0746 for 3877 data with [I>2σ(I)] and R_1 = 0.0294, wR_2 = 0.0756 for all 4157 data. Residual electron density (e$^-$.Å^{-3}) max/min: 0.347/-0.279.

An arbitrary sphere of data was collected on a colorless tablet-like crystal, having approximate dimensions of 0.144 × 0.116 × 0.052 mm, on a Bruker APEX-II diffractometer using a combination of ω- and φ-scans of 0.5° [1]. Data were corrected for absorption and polarization effects and analyzed for space group determination [2]. The structure was solved by dual methods and expanded routinely [3]. The model was refined by full-matrix least-squares analysis of F^2 against all reflections [4]. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Unless otherwise noted, hydrogen atoms were included in calculated positions. Atomic displacement parameters for the hydrogens were tied to the equivalent isotropic displacement parameter of the atom to which they are bonded (U_{iso}(H) = 1.5U_{eq}(C) for methyl, 1.2U_{eq}(C) for all others).

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[3] G. M. Sheldrick. *Acta Cryst.*, **2015**, *A71*, 3.

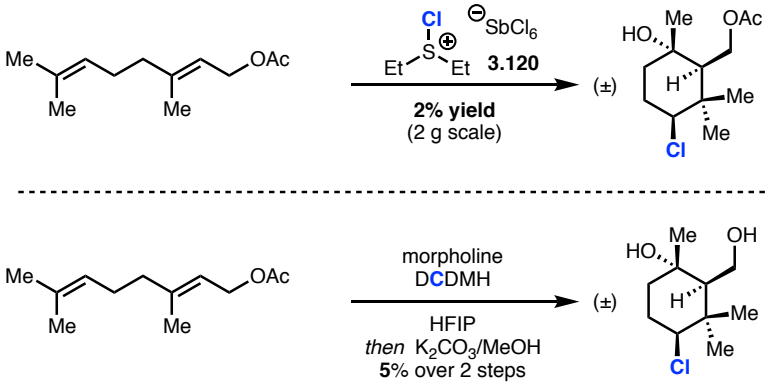
[4] G. M. Sheldrick. *Acta Cryst.*, **2015**, *C71*, 3.

Crystal data and structure refinement for su1809.

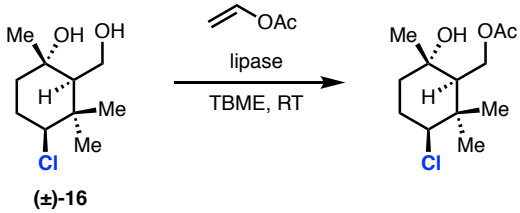
Identification code	su1809	
Empirical formula	$C_{21}H_{29}Cl_3O_4$	
Formula weight	451.79	
Temperature	120(2) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.2805(2) Å	α = 78.5640(10)°
	b = 11.3131(3) Å	β = 78.6160(10)°
	c = 13.8979(4) Å	γ = 85.2340(10)°
Volume	1098.75(5) Å^3	
Z	2	
Density (calculated)	1.366 g.cm^{-3}	
Absorption coefficient (μ)	3.976 mm^{-1}	
F(000)	476	
Crystal color, habit	colorless, tablet	
Crystal size	0.144 × 0.116 × 0.052 mm^3	
θ range for data collection	3.301 to 72.417°	
Index ranges	$-8 \le h \le 8$, $-13 \le k \le 13$, $-17 \le l \le 16$	
Reflections collected	33410	
Independent reflections	4157 [R_{int} = 0.0334]	
Completeness to θ = 67.679°	96.8 %	
Absorption correction	Numerical	
Max. and min. transmission	0.8928 and 0.7084	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4157 / 0 / 262	
Goodness-of-fit on F^2	1.083	
Final R indices [I>2σ(I)]	R_1 = 0.0277, wR_2 = 0.0746	
R indices (all data)	R_1 = 0.0294, wR_2 = 0.0756	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.347 and -0.279 e$^-$.Å^{-3}	

9. Alternative and Failed Routes

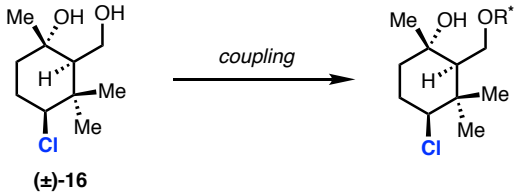
Scheme S2. Alternative racemic chloropolyene cyclizations

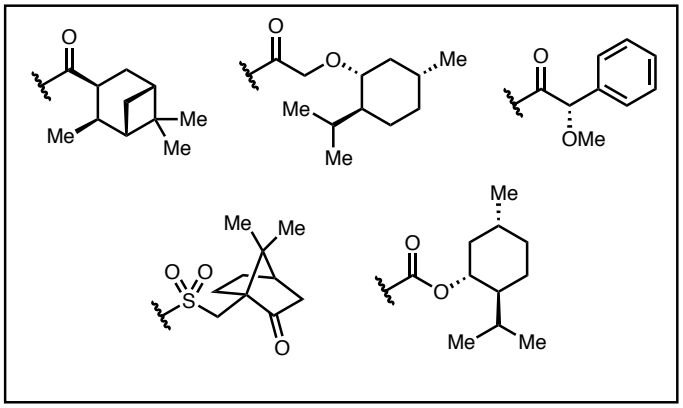


Scheme S3. Failed resolutions of (±)-16

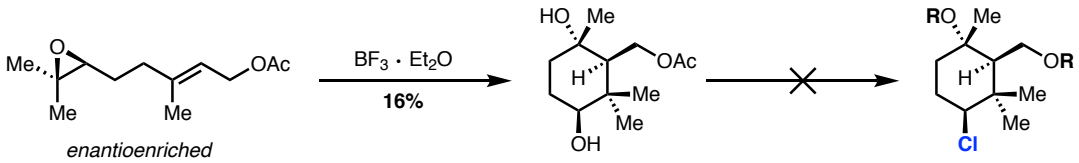


lipase	% conv., %*ee* **SM**
Amano Lipase PS	46%, 8% ee
Lipase Type II; from Porcine Pancreas	23%, 9% ee

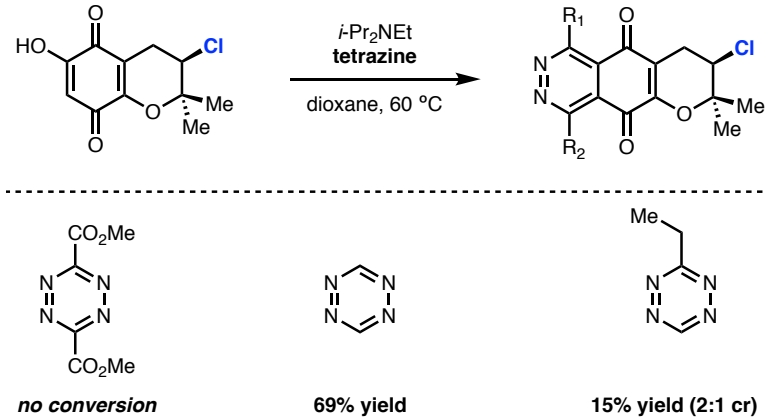




Scheme S4. Failure to converter secondary alcohol to the corresponding chloride

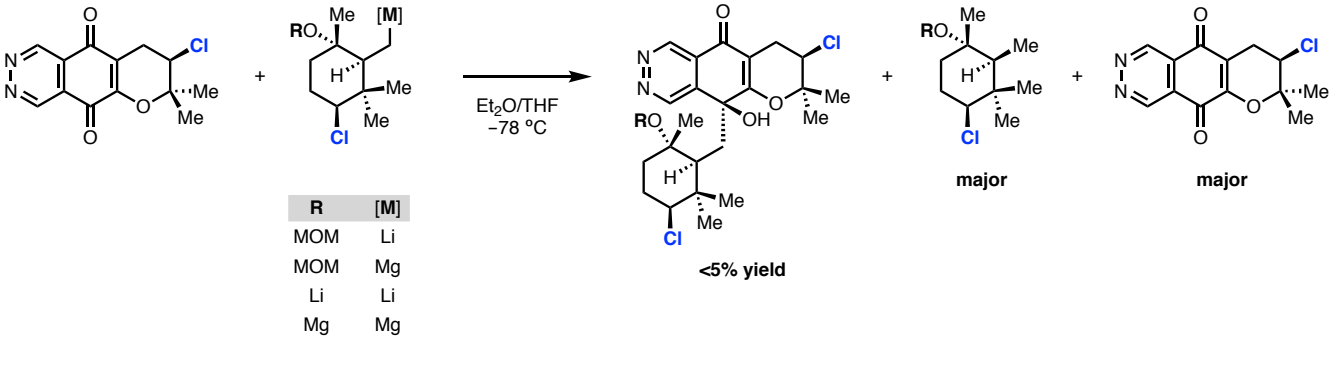


Scheme S5. Boger tetrazine Diels–Alder reactions with hydroxyquinone



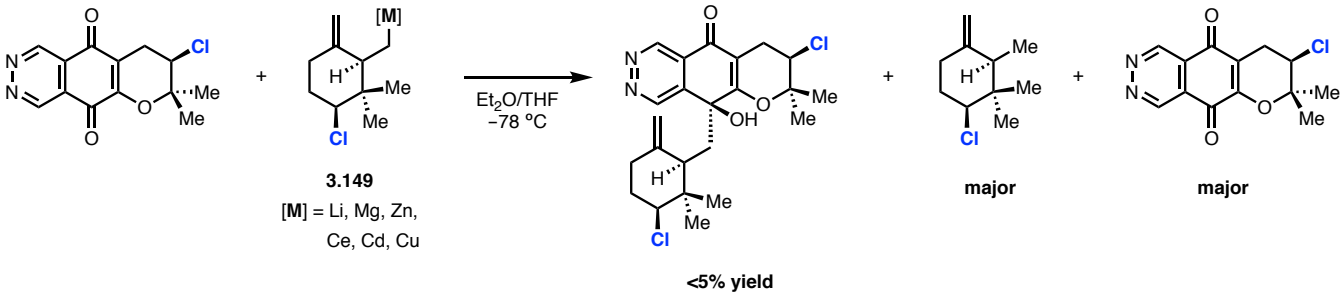
no conversion | **69% yield** | **15% yield (2:1 cr)**

Scheme S6. Failed nucleophilic additions to phthalazinone core



R	[M]
MOM	Li
MOM	Mg
Li	Li
Mg	Mg

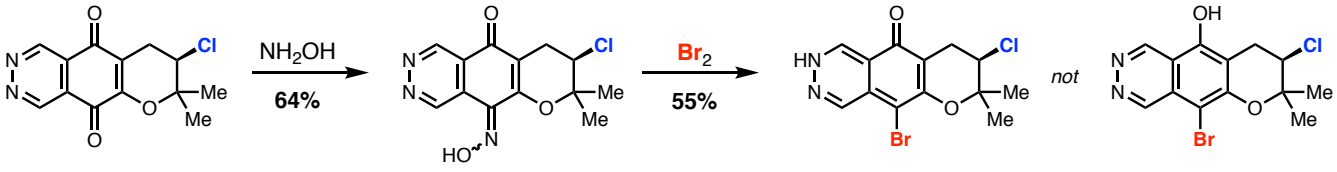
<5% yield



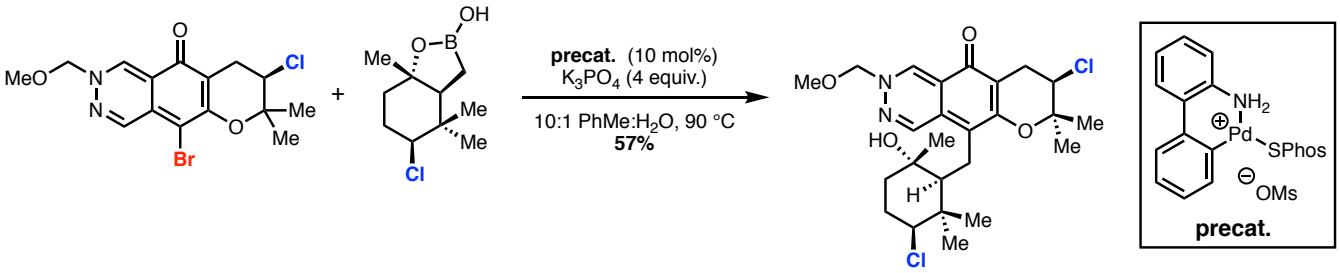
3.149
[M] = Li, Mg, Zn, Ce, Cd, Cu

<5% yield

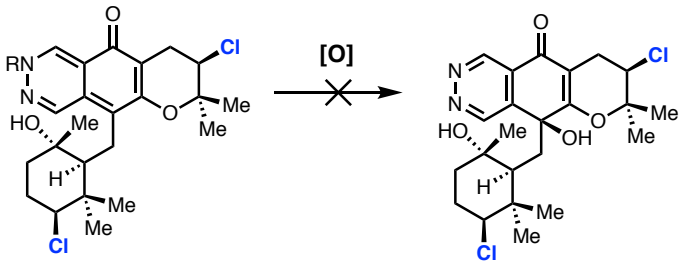
Scheme S7. Oxime-mediated bromination of phthalazinone core



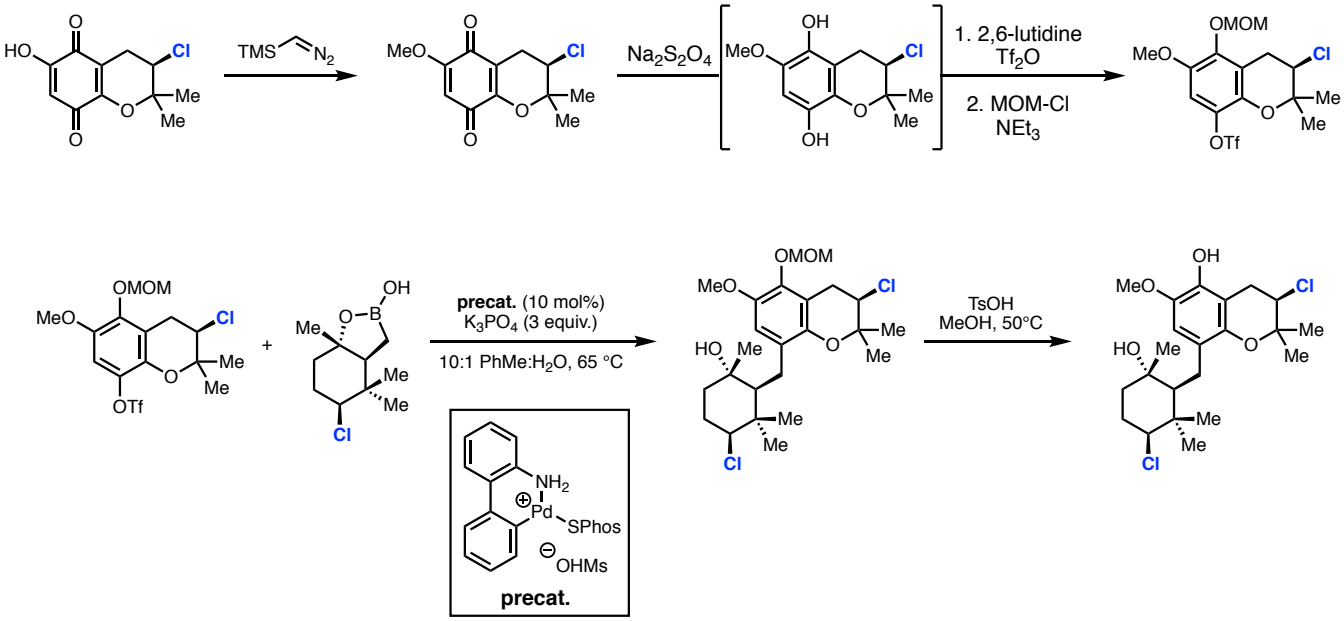
Scheme S8. Successful Suzuki cross coupling of brominated phthalazinone



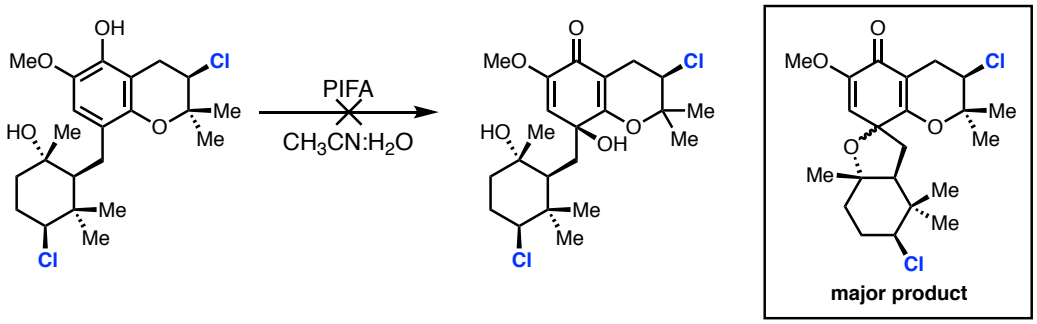
Scheme S9. Failure to effect oxidation of coupled product



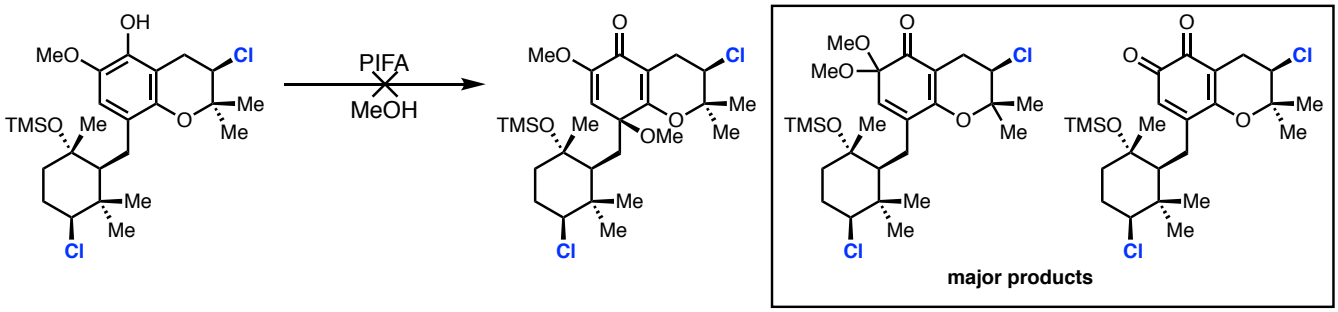
Scheme S10. Lengthier Suzuki cross coupling sequence



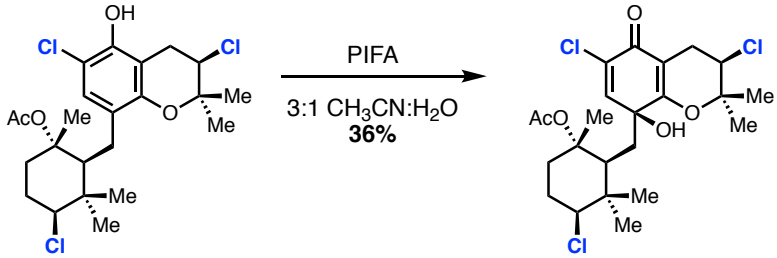
Scheme S11. Unwanted spirocyclization in phenol oxidation



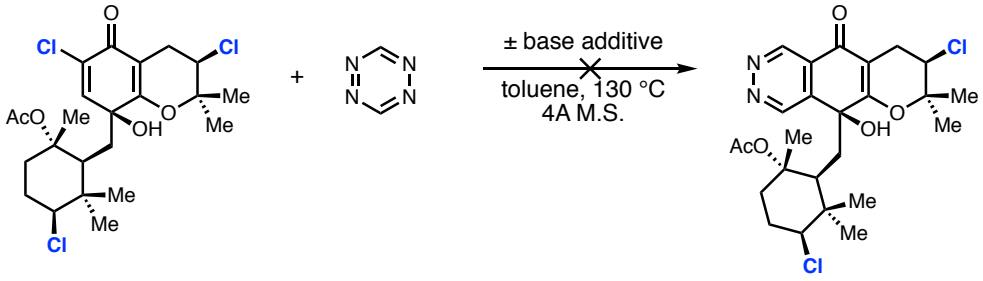
Scheme S12. Failed phenol oxidations of methoxyphenol



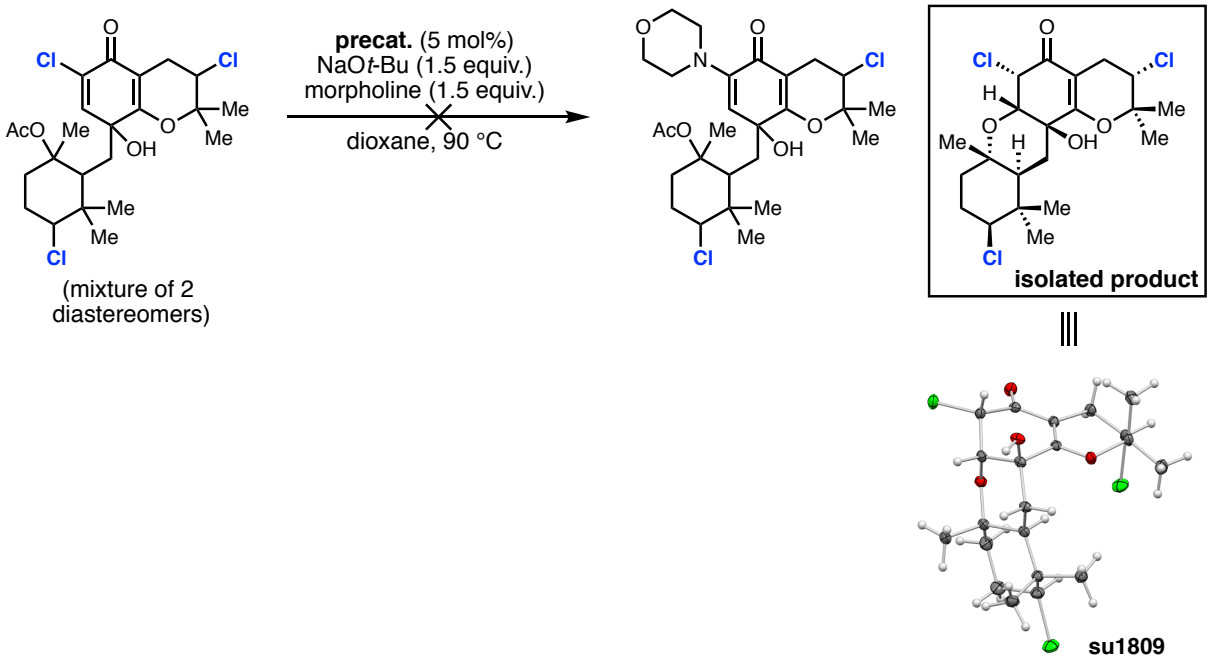
Scheme S13. Successful oxidation of chlorophenol



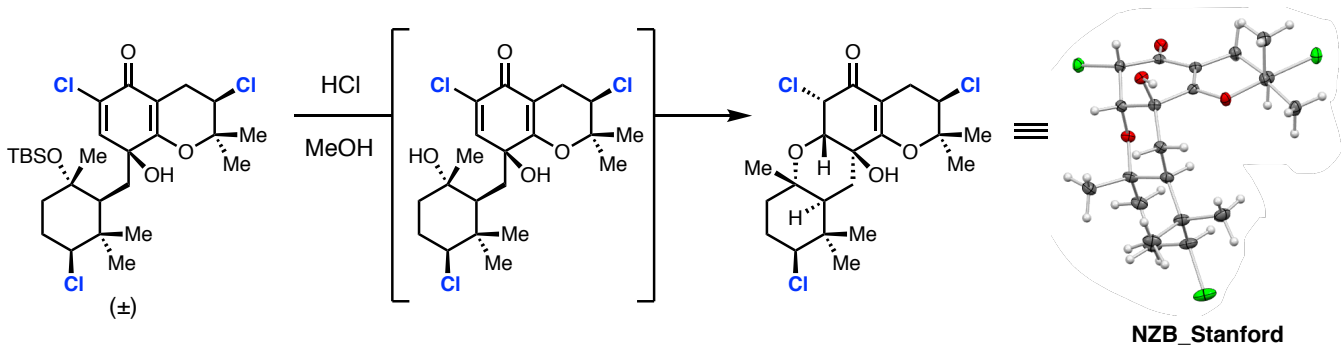
Scheme S14. Failed Boger Diels–Alder on oxidized chlorophenol



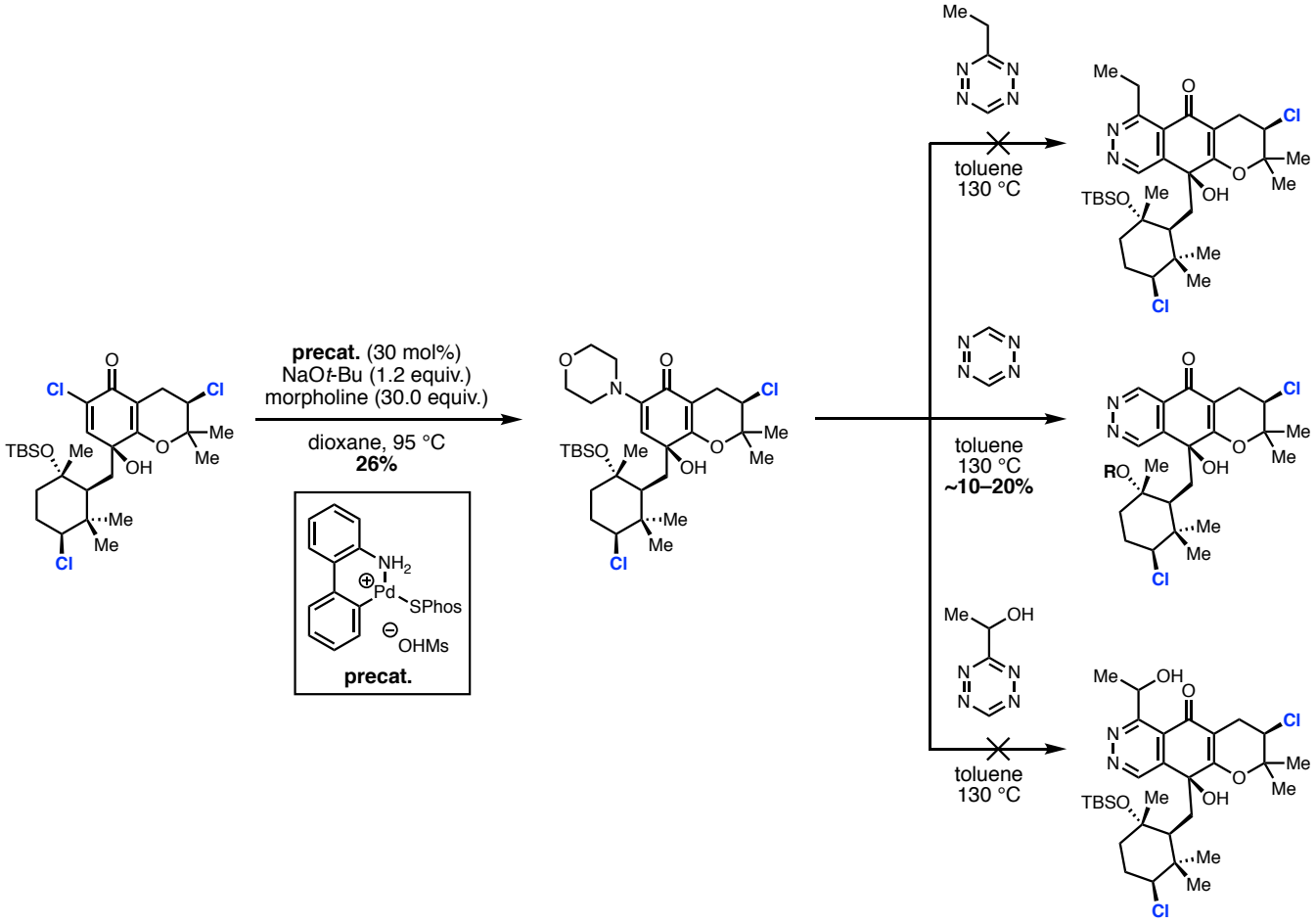
Scheme S15. Attempted amination of oxidized chlorophenol aids stereochemical assignment via isolation of an oxa-Michael product



Scheme S16. Oxa-Michael of oxidized TBS-protected chlorophenol aids stereochemical assignment



Scheme S17. Successful amination of TBS-protected oxidized chlorophenol and attempts at Boger Diels–Alder reactions



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