Supporting Information

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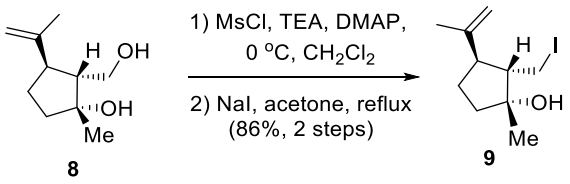
General

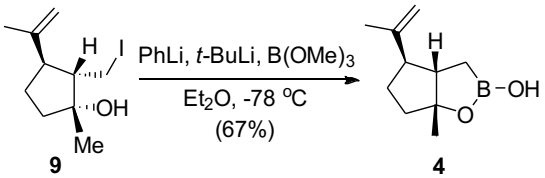
All non-aqueous reactions were performed under a nitrogen atmosphere in oven-dried glassware. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), toluene, and diethyl ether were dried by passing through activated molecular sieves or alumina (solvent purification system). Other solvents and reagents were used as received from commercially available sources. *i*-Pr_2NH and TMSCl were freshly distilled from CaH_2. Deuterated solvents were purchased from either Aldrich or Cambridge Isotopes and used as received. ^{1}H NMR spectra were measured at 600 MHz, 500 MHz, and 400 MHz, referenced relative to residual chloroform (7.26 ppm), and were reported in parts per million. Coupling constants (*J*) were reported in Hertz (Hz), with multiplicity reported following the usual convention: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; ddq, doublet of doublet of quartets; ABq, AB quartet; m, multiplet; bs, broad singlet (prefix app indicates 'apparent'). ^{13}C NMR spectra were measured at 150 MHz, 100 MHz and 75 MHz, referenced relative to residual chloroform (77.23 ppm) or benzene (128.06 ppm), and were reported in parts per million (ppm). Flash column chromatography was performed with 60Å Silica Gel (230-400 mesh) as stationary phase using a gradient solvent system or on an automated Flash column chromatography system (EtOAc/hexanes as eluent unless indicated otherwise). High resolution mass spectra (ESI) were obtained through the Baylor University Mass Spectrometry Center. Thin Layer Chromatography (TLC) was performed using glass-backed silica gel F254 (Silicycle, 250 μm thickness). Visualization of developed plates was performed by fluorescence quenching or by staining with phosphomolybdic acid (PMA), potassium permanganate ($KMnO_4$), *p*-anisaldehyde or cerium sulfate. Fourier Transform Infrared (FTIR) spectra were recorded from thin films on NaCl plates. Optical rotations were recorded on a polarimeter at 589 nm employing a 25 mm cell.



8 **9**

(1*R*,2*S*,3*R*)-2-(iodomethyl)-1-methyl-3-(prop-1-en-2-yl)cyclopentan-1-ol **9**

To an oven dried, round-bottomed flask was added the starting diol **8**[1] (333 mg, 1.96 mmol, 1.00 equiv), 10 mL anhydrous CH_2Cl_2 and 1.0 mg of DMAP as catalyst. The flask was then cooled to 0 ºC with an ice bath and triethylamine (0.35 mL, 2.50 mmol, 1.30 equiv) was added followed by dropwise addition of MsCl (0.16 mL, 2.00 mmol, 1.05 equiv). The reaction mixture was stirred at 0 ºC for 15 min and then allowed to warm to 23 ºC for 1 h until TLC indicated completion. The reaction mixture was then washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The crude mixture was dissolved in acetone and solid NaI (2.40 g, 9.80 mmol, 5.00 equiv) was added. The mixture was heated to reflux overnight and then cooled to ambient temperature, after which it was concentrated under vacuum to remove most of the acetone. The crude reaction was dissolved in water and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated. Flash column chromatography (SiO_2, 10 → 30% EtOAc/hexanes) afforded the iodide **9** (402 mg, 86%) as a colorless oil: TLC (EtOAc: hexanes, 1:10 v/v): R_f = 0.35; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (ddt, *J* = 3.5, 2.0, 1.1 Hz, 2H), 3.29 (dd, *J* = 10.1, 8.8 Hz, 1H), 3.19 (dd, *J* = 10.1, 3.6 Hz, 1H), 2.48 – 2.37 (m, 1H), 1.94 (ddd, *J* = 10.9, 8.8, 3.6 Hz, 1H), 1.88 – 1.73 (m, 3H), 1.72 – 1.69 (m, 3H), 1.63 – 1.52 (m, 2H), 1.50 (s, 1H), 1.47 – 1.39 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.9, 111.7, 79.8, 54.3, 53.2, 42.0, 29.3, 27.6, 19.2, 3.3; IR (thin film): 3320, 2940, 1410, 1245 cm^{-1}; $[\alpha]_D^{24}$ -104 (*c* 1.0, $CHCl_3$); HRMS (ESI+) *m/z* calcd for $C_{10}H_{18}IO$ $[M+H]^+$: 281.0397, found: 281.0385.

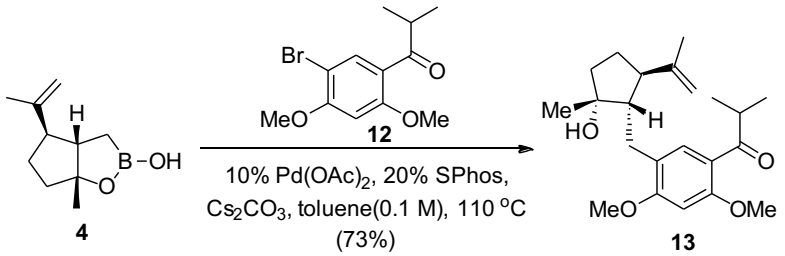


9 **4**

(3a*S*,4*R*,6a*R*)-6a-methyl-4-(prop-1-en-2-yl)hexahydro-2H-cyclopenta[d][1,2]oxaborol-2-ol **4**

To an oven dried, round-bottomed flask was added iodide **9** (1.4 g, 5.0 mmol, 1.0 equiv) and diluted with 20 mL anhydrous ether under an argon atmosphere. The flask was then cooled to -78 ºC with an acetone-dry ice bath and PhLi (3.0 mL of 1.8 M solution in di-*n*-butylether, 5.5 mmol, 1.1 equiv) was added dropwise with a gas tight syringe and then stirred for 15 min. *t*-BuLi (7.4

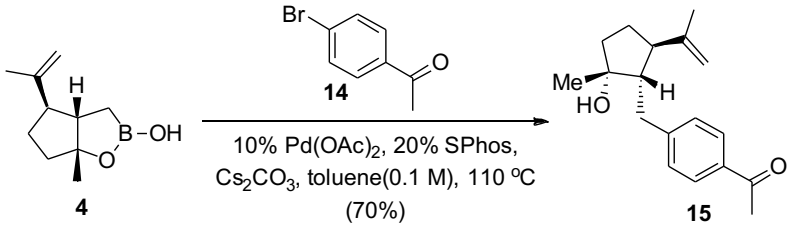
mL of a 1.7 M solution in pentane, 12.5 mmol, 2.5 equiv) was added dropwise and the reaction was stirred for another 20 min. $B(OMe)_3$ (2.8 mL, 25 mmol, 5.0 equiv) was added to the mixture and the reaction was allowed to warm to 23 °C temperature over 4 h. The reaction mixture was carefully quenched with saturated NH_4Cl solution and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Mg_2SO_4 and concentrated. Flash column chromatography (SiO_2, 0 → 30% EtOAc/hexanes) afforded the boronic monoester **4** (559 mg, 67%) as a colorless oil: TLC (EtOAc: hexanes, 1:5 v/v): R_f = 0.15; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (s, 1H), 4.76 – 4.65 (m, 2H), 2.16 – 2.09 (m, 1H), 1.98 (dt, *J* = 9.6, 1.6 Hz, 1H), 1.92 – 1.85 (m, 2H), 1.85 – 1.79 (m, 1H), 1.69 (d, *J* = 0.9 Hz, 3H), 1.50 – 1.39 (m, 1H), 1.32 (s, 3H), 1.26 – 1.18 (m, 1H), 0.88 – 0.82 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3, 110.0, 93.1, 55.5, 51.0, 39.9, 30.5, 28.1, 20.3 (carbon attached to B is not observed); ^{11}B NMR (193 MHz, $CDCl_3$) δ 36.1; IR (thin film): 3356, 3081, 2961, 1430 cm^{-1}; $[\alpha]_D^{24}$ -17.5 (c 1.0, $CHCl_3$); HRMS (ESI+) *m/z* calcd for $C_{10}H_{18}BO_2$ $[M+H]^+$: 181.1394, found: 181.1385.



1-(5-(((1*S*,2*R*,5*R*)-2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)methyl)-2,4-dimethoxyphenyl)-2-methylpropan-1-one **13**

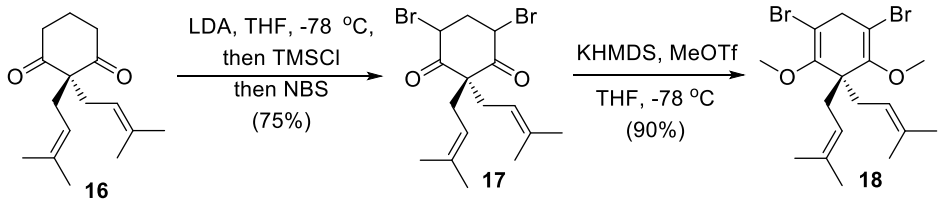
To a 1 dram vial was added the boronic monoester **4** (20 mg, 1.0 equiv), ketone **12** (47 mg, 1.5 equiv) and then dissolved in 2 mL dry toluene. To the solution was added cesium carbonate (110 mg, 3.0 equiv), SPhos (9.0 mg, 0.20 equiv) and palladium acetate (2.5 mg, 0.10 equiv) under a stream of N_2. The vial was capped, and the reaction mixture was stirred at 23 °C) for 15 min and then 100 °C for 16 h until TLC indicated completion. The mixture was concentrated and loaded onto silica gel directly. Flash column chromatography (20% EtOAc/hexanes) gave the product as a colorless solid (28 mg, 73% yield): TLC (EtOAc: hexanes, 1:5 v/v): R_f = 0.55; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (s, 1H), 6.40 (s, 1H), 4.79 – 4.63 (m, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.53 (hept, *J* = 6.8 Hz, 1H), 2.70 (dd, *J* = 14.2, 9.7 Hz, 1H), 2.60 – 2.54 (m, 1H), 2.52 (dd, *J* = 14.2, 4.9 Hz, 1H), 2.31 (s, 1H), 1.89 (ddt, *J* = 12.9, 8.9, 6.9 Hz, 1H), 1.82 – 1.73 (m, 2H), 1.70 – 1.65 (m, 1H), 1.64 (s, 3H), 1.47 – 1.39 (m, 1H), 1.12 (d, *J* = 6.9 Hz, 6H), 0.94 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 205.9, 160.7, 158.5, 147.1, 133.3, 122.1, 120.7, 110.9, 94.6, 79.9, 55.7, 55.6,

52.9, 52.8, 40.8, 39.6, 28.0, 27.8, 26.9, 18.8, 18.8, 18.7; IR (thin film) 2963, 2361, 1660, 1603, cm^{-}; $[\alpha]_D^{24}$ +53.9 (*c* 1.3, $CHCl_3$); HRMS (ESI+) *m/z* calcd for $C_{22}H_{33}O_4$ [M+H]: 361.2373; found: 361.2377.



1-(4-(((1*S*,2*R*,5*R*)-2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)methyl)phenyl)ethan-1-one **15:**

To a 1 dram vial was added the boronic monoester (10 mg, 1.0 equiv) and ketone (17 mg, 1.5 equiv) and then dissolved in 2 mL anhydrous toluene. To the solution was added cesium carbonate (38 mg, 3.0 equiv), SPhos (4.6 mg, 0.2 equiv) and palladium acetate (1.2 mg, 0.1 equiv) under a steam of N_2. The vial was capped, and the reaction mixture was stirred at ambient temperature for 15 min and then 100 ºC for 16 h until TLC indicated completion. The mixture was concentrated and loaded on to silica directly. Flash column chromatography (20% EtOAc/hexanes) gave the product as a white solid (10 mg, 70% yield): TLC (EtOAc: hexanes, 1:6 v/v): R_f = 0.41; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 – 7.80 (m, 2H), 7.32 – 7.28 (m, 2H), 4.74 (dt, *J* = 2.3, 0.8 Hz, 1H), 4.67 (dq, *J* = 2.9, 1.5 Hz, 1H), 2.83 (dd, *J* = 14.1, 8.1 Hz, 1H), 2.70 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.66 – 2.59 (m, 1H), 2.58 (s, 3H), 1.92 (ddt, *J* = 13.2, 8.9, 6.9 Hz, 1H), 1.85 (ddd, *J* = 11.0, 8.2, 5.4 Hz, 1H), 1.81 – 1.70 (m, 2H), 1.59 (dd, *J* = 1.4, 0.8 Hz, 3H), 1.48 (dddd, *J* = 13.1, 9.9, 8.4, 5.4 Hz, 1H), 1.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 197.9, 148.1, 146.6, 134.9, 129.4 (2), 128.3 (2), 111.5, 80.4, 53.3, 52.8, 41.5, 34.4, 27.9, 27.7, 26.6, 18.6; IR (thin film): 2966, 2361, 1681, 1603 cm^{-1}; $[\alpha]_D^{23}$ +15.1 (*c* 0.45, $CHCl_3$); HRMS (ESI+) *m/z* calcd for $C_{18}H_{25}O_2$ $[M+H]^+$: 273.1849, found: 273.1851.



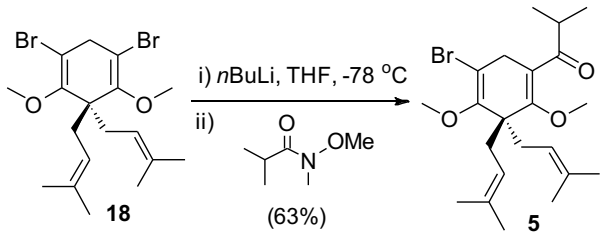
1,5-dibromo-2,4-dimethoxy-3,3-bis(3-methylbut-2-en-1-yl)cyclohexa-1,4-diene **18**

Note: The quality of KHMDS (a relatively new bottle), NBS (freshly recrystallized), and TMSCl (freshly distilled) is vital to the success of this reaction.

To an oven dried, round-bottomed flask was added *i*-Pr_2NH (2.6 mL, 18.6 mmol, 3.3 equiv) and 30 mL anhydrous THF under argon atmosphere. The flask was then cooled to -78 ºC with an acetone-dry ice bath and *n*-BuLi (7.0 mL of a 2.5 M solution in hexanes, 5.5 mmol, 3.1 equiv) was added dropwise and then stirred for 30 min. Dry DMPU (2.0 mL, about 5% volume of the solvent) was added, followed by dropwise addition of a 6 mL THF solution of **16** (1.4 g, 5.6 mmol, 1.0 equiv). The reaction was allowed to warm to 23 ºC over 2 h and then cooled to -78 ºC again. Freshly distilled TMSCl (2.0 mL, 23 mmol, 4.0 equiv) was added to the mixture and the reaction was stirred at -78 ºC for 0.5 h. The reaction was warmed to 23 ºC and stirred for an additional 1 h until TLC indicated completion. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with ether (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Mg_2SO_4 and concentrated. The crude was dissolved in 40 mL THF and covered with alumina foil. At 0 ºC, solid NBS (2.0 g, 11 mmol, 2.0 equiv) was added to the reaction and stirred for 15 min. The mixture was diluted with ethyl acetate and washed with saturated $Na_2S_2O_3$ solution, brine, after which it was dried over anhydrous Na_2SO_4 and concentrated. Very rapid purification by flash column chromatography in the dark (SiO_2, 0 → 10% EtOAc/hexanes) afforded the dibromide **17** (1.7 g, 75%) as a yellow oil, which is rather unstable (sensitive to air and light) and was taken immediately to the next step without full characterization: MS (ESI+) *m/z* calcd for $C_{16}H_{23}Br_2O_2$ $[M+H]^+$: 405.01, found: 405.01.

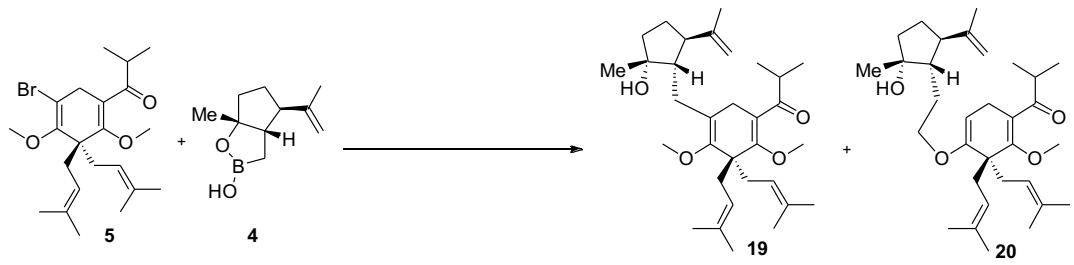
To an oven dried, round-bottomed flask was added 40 mL anhydrous THF and 5 mL dry DMPU under argon atmosphere. The flask was then cooled to -78 ºC with an acetone-dry ice bath and KHMDS (12.6 mL of 1 M solution in THF, 12.6 mmol, 3.0 equiv) was added. After stirring at -78 ºC for 15 min, a THF (6 mL) solution of dibromide **17** (1.7 g, 4.2 mmol, 1.0 equiv) was added to the solution via a syringe pump (the syringe was covered with alumina foil to protect the light-sensitive dibromide **17**) in 40 min to afford a dark brown solution. It is advised that the addition needle touch the flask wall to ensure cooling of the di-bromo solution before reaching the reaction solution. The reaction was stirred at -78 ºC for an additional 2 h and quenched by slow addition of MeOTf (2.3 mL, 21 mmol, 5.0 equiv). The reaction mixture was then allowed to warm to 23 ºC over 2 h, during which time the reaction mixture slowly turned bright red. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Mg_2SO_4 and concentrated. Flash column chromatography (basic alumina, 0 → 5% EtOAc/hexanes) afforded

the dibromo dimethylether **18** (1.64 g, 90%) as a light yellow oil: TLC (EtOAc:hexanes, 1:10 v/v): R_f = 0.75. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.93 (br t, *J* = 6.6 Hz, 2H), 3.75 (s, 6H), 3.43 (s, 2H), 2.33 (br d, *J* = 6.6 Hz, 4H), 1.66 (q, *J* = 1.5 Hz, 6H), 1.59 (d, *J* = 1.4 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.8(2), 133.8(2), 119.7(2), 102.5(2), 61.1(2), 55.1, 43.8, 34.4(2), 26.1(2), 18.4(2); IR (thin film): 2969, 1716, 1454, 1214 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{18}H_{27}Br_2O_2$ $[M+H]^+$: 433.0372, found: 433.0364.



1-(5-bromo-2,4-dimethoxy-3,3-bis(3-methylbut-2-en-1-yl)cyclohexa-1,4-dien-1-yl)-2-methylpropan-1-one **5**:

To an oven dried, round-bottomed flask was added **18** (0.89 g, 2.0 mmol, 1.0 equiv), 15 mL anhydrous THF under argon atmosphere (nitrogen atmosphere gives inferior results). The flask was then cooled to -78 ºC with an acetone-dry ice bath and n-BuLi (0.91 mL of 2.5 M solution in hexanes, 2.2 mmol, 1.1 equiv) was added dropwise and then stirred for 1.5 h. The Weinreb amide (0.39 g, 3.0 mmol, 1.5 equiv) was then added dropwise to the solution and the reaction was warmed to 23 °C over 3 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ether (3 × 20 mL). The combined organic layers were washed with brine, dried over anhydrous Mg_2SO_4 and concentrated. Flash column chromatography (gradient SiO_2, 0 → 10% EtOAc/hexanes) afforded the ketone **5** (527 mg, 63%) as a light yellow oil: TLC (EtOAc: hexanes, 1:10 v/v): R_f = 0.65; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.97 (br t, *J* = 6.7 Hz, 2H), 3.77 (s, 3H), 3.55 (s, 3H), 3.27 – 3.21 (m, 3H), 2.41 – 2.32 (m, 4H), 1.65 (d, *J* = 1.6 Hz, 6H), 1.60 (d, *J* = 1.3 Hz, 6H), 1.08 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.2, 160.3, 151.7, 133.6(2), 119.9(2), 119.0, 103.9, 63.3, 61.0, 53.7, 39.5, 37.1, 34.43(2), 25.9(2), 18.4(2), 18.3(2) IR (thin film): 2968, 1680, 1447, 1241 cm^{-1}; HRMS (ESI+) *m/z* calcd for $C_{22}H_{34}BrO_3$ $[M+H]^+$: 425.1686, found: 425.1687.



General procedure for cross coupling:

To a sealed pressure tube was added boronic monoester **4** (1.0 equiv), vinyl bromide **5** (1.2 equiv) and anhydrous toluene (concentrations specified below). To the solution was added a base (3.0 equiv), ligand (0.2 equiv) and palladium catalyst (0.1 equiv). The reaction mixture was stirred at ambient temperature (23 ^{o}C) for 15 min followed by the indicated temperature for 10 h. The crude reaction mixture was concentrated and loaded onto silica gel directly. Flash column chromatography (SiO_2, 0 → 20% EtOAc/hexanes) provided the products which were analyzed by NMR.

Optimized conditions favoring normal cross-coupling:

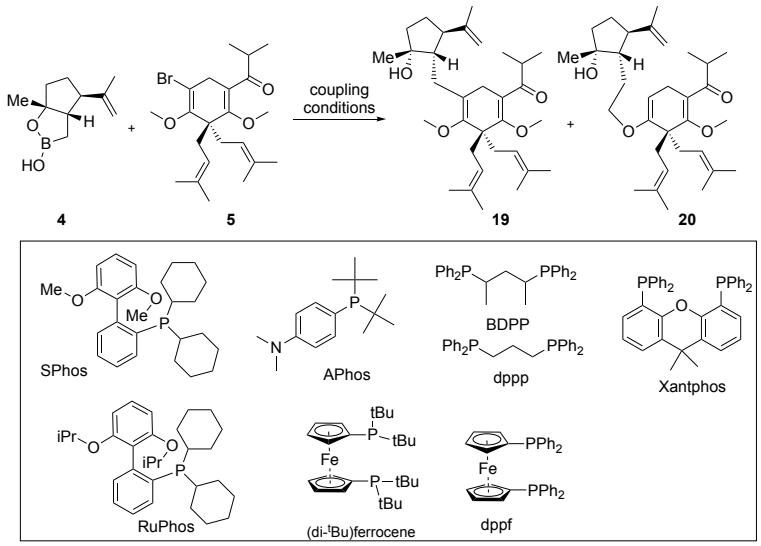
To a sealed tube was added the boronic monoester **4** (140 mg, 0.78 mmol, 1.0 equiv), vinyl bromide **5** (400 mg, 0.94 mmol, 1.2 equiv), Cs_2CO_3 (32 mg, 0.10 mmol, 3.0 equiv), and then anhydrous toluene (4.0 mL, 0.20 M). To the above solution was added Cs_2CO_3 (0.76 g, 2.3 mmol, 3.0 equiv), Aphos (21 mg, 0.078 mmol, 0.10 equiv) and palladium acetate (8.7 mg, 0.040 mmol, 0.05 equiv). Protected under nitrogen, the reaction mixture was stirred at ambient temperature (23 ^{o}C) for 15 min (Note: immediate heating, *i.e.* without premixing at ambient temperature, resulted in rapid darkening of the reaction mixture and gave inferior results) and then heated to 65 ^{o}C for 10 h. The crude reaction mixture was filtered through a pad of Celite, concentrated, and loaded onto silica gel directly for flash column chromatography (SiO_2, 0 → 20% EtOAc/hexanes) which afforded the cross-coupled product **19** (287 mg, 74% yield) as a colorless oil as the major product with only trace amount of the C-H insertion side-product **20**. Data **19**: TLC (EtOAc: hexanes, 1:10 v/v): R_f= 0.25; ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.04 – 4.98 (m, 2H), 4.75 (d, *J* = 1.3 Hz, 2H), 3.69 (s, 3H), 3.57 (s, 3H), 3.32 (hept, *J* = 6.9 Hz, 1H), 2.88 (d, *J* = 21.0 Hz, 1H), 2.79 (d, *J* = 21.0 Hz, 1H), 2.57 – 2.37 (m, 5H), 2.35 – 2.23 (m, 2H), 1.85 – 1.71 (m, 4H), 1.68 (d, *J* = 1.1 Hz, 3H), 1.63 (d, *J* = 1.6 Hz, 3H), 1.60 (s, 3H), 1.59 (d, *J* = 1.3 Hz, 6H), 1.45 – 1.38 (m, 1H), 1.25 (s, 3H), 1.10 (d, *J* = 6.9 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.8, 161.6, 149.2, 147.0, 133.1, 132.9, 121.2, 121.1, 120.3, 119.0, 111.0, 79.1, 63.5, 62.1, 53.7, 51.0, 49.1, 41.1, 39.5, 35.9, 34.6, 31.0, 29.5, 28.7, 28.4, 25.99, 25.96, 19.0, 18.8, 18.4, 18.1, 18.0; IR (thin

film): 2966, 2358, 1685, 1446 cm^{-1} ; $[\alpha]_D^{23}$ +25.0 (c 1.0, $CHCl_3$); HRMS (ESI+) *m/z* calcd for $C_{32}H_{51}O_4$ $[M+H]^+$: 499.3782, found: 499.3783.

Optimized conditions favoring C-H insertion:

To a 1 dram vial under nitrogen was added the boronic monoester **4** (6.0 mg, 0.03 mmol, 1.0 equiv), vinyl bromide **5** (18 mg, 0.04 mmol, 1.3 equiv) and then anhydrous toluene (3.0 mL, 0.01 M). A separate solution was prepared in 0.3 mL of dry toluene of Cs_2CO_3 (32 mg, 0.10 mmol, 3.0 equiv), Sphos (2.9 mg, 0.007 mmol, 0.2 equiv) and palladium acetate (0.7 mg, 0.003 mmol, 0.1 equiv). This catalyst mixture was stirred at ambient temperature (23 ºC) for 15 min. The reaction vessel containing **4** and **5** was sealed and heated to 65 ºC. The catalyst mixture was added to this 65 °C solution via a syringe pump over 3 h. The stirring was continued at that temperature for an additional 10 h. The mixture was then filtered through a small pad of Celite, concentrated and loaded on to silica gel directly. Flash column chromatography (SiO_2, 0 → 20% EtOAc/hexanes) afforded the C_{sp3}-C_{sp3} cross coupling product **20** (8.3 mg, 51% yield) as the major product with only trace amount of **19**. Data for C-H activation product **20**: colorless residue, TLC (EtOAc: hexanes, 1:10 v/v): Rf = 0.27. ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.02 – 4.96 (m, 2H), 4.77 (dt, *J* = 1.6, 0.8 Hz, 1H), 4.73 – 4.68 (m, 2H), 3.66 (dt, *J* = 9.4, 5.8 Hz, 1H), 3.60 (ddd, *J* = 9.2, 7.5, 5.0 Hz, 1H), 3.55 (s, 3H), 3.29 (hept, *J* = 6.9 Hz, 1H), 2.87 (d, *J* = 3.7 Hz, 2H), 2.52 (dt, *J* = 10.7, 8.8 Hz, 1H), 2.39 – 2.30 (m, 4H), 1.93 – 1.83 (m, 2H), 1.78 – 1.72 (m, 2H), 1.67 (s, 3H), 1.65 – 1.63 (m, 1H), 1.62 (t, *J* = 1.4 Hz, 6H), 1.61 (s, 1H), 1.58 (d, *J* = 1.3 Hz, 6H), 1.49 – 1.41 (m, 1H), 1.30 (s, 3H), 1.07 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 211.3, 160.4, 152.5, 147.3, 132.4, 132.3, 120.8, 120.7, 119.7, 110.9, 93.0, 80.1, 65.6, 63.1, 53.0, 49.6, 48.9, 41.1, 39.5, 34.5, 34.4, 28.2, 27.9, 27.9, 27.5, 25.9, 25.9, 18.6, 18.5, 18.4, 18.1, 18.1; IR (thin film): 2967, 2349, 1687,1371 cm^{-1} ; $[\alpha]_D^{24}$ +47 (c 1.0, $CHCl_3$); HRMS (ESI+) *m/z* calcd for $C_{32}H_{51}O_4$ $[M+H]^+$: 499.3782, found: 499.3789.

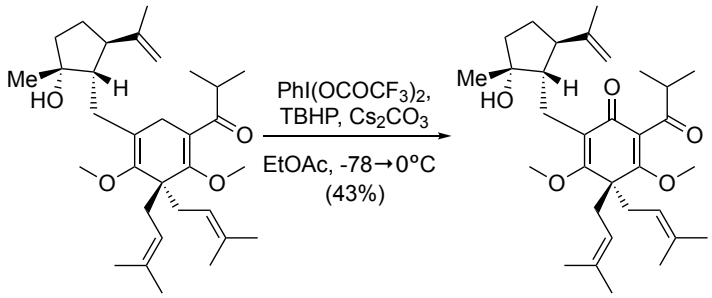
Table 1. Optimization Table for both Suzuki-Miyaura Coupling and C-H Insertion



entry	Pd source (0.1 equiv)	Ligand (0.2 equiv)	Base (3 equiv)	Solvent [concentration]	Temp.	Suzuki-Miyaura coupling[b]	C-H insertion[b]
1	$Pd(OAc)_2$	SPhos	Cs_2CO_3	PhMe (0.24 M)	65 ºC	18%	17%
2	$Pd(OAc)_2$	SPhos	Cs_2CO_3	PhMe (0.03 M)	65 ºC	11%	35%
3	$Pd(OAc)_2$	APhos	Cs_2CO_3	PhMe (0.1 M)	65 ºC	40%	12%
4	$Pd(OAc)_2$	BDPP	Cs_2CO_3	PhMe (0.1 M)	65 ºC	--[a]	--
5	$Pd(OAc)_2$	(di-^{t}Bu) ferrocene	Cs_2CO_3	PhMe (0.1 M)	65 ºC	32%	5%
6	$Pd(OAc)_2$	RuPhos	Cs_2CO_3	PhMe (0.1 M)	65 ºC	--	--
7	$Pd(OAc)_2$	RuPhos	K_2CO_3	PhMe (0.1 M)	65 ºC	21%	--
8	$Pd(OAc)_2$	RuPhos	K_3PO_4	PhMe (0.1 M)	65 ºC	23%	--
9	$Pd(OAc)_2$	SPhos	Cs_2CO_3	PhMe (0.1 M)	65 ºC	20%	32%
10	$Pd(OAc)_2$	SPhos	CsF	PhMe (0.1 M)	65 ºC	--	--
11	$Pd(OAc)_2$	APhos	K_2CO_3	PhMe (0.1 M)	65 ºC	36%	10%
12	$Pd(OAc)_2$	APhos	K_3PO_4	PhMe (0.1 M)	65 ºC	--	--
13	$Pd(OAc)_2$	APhos	CsF	PhMe (0.1 M)	65 ºC	--	--
14	$Pd(OAc)_2$	APhos	Cs_2CO_3	PhMe (0.1 M)	23 ºC	--	--

[a]Denotes only trace or no product detected

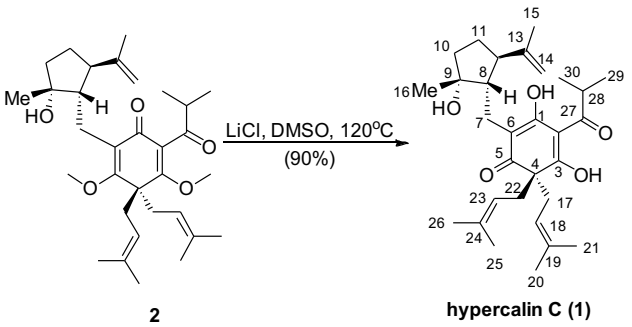
[b]Yields refer to purified, isolated products.



19 **2**

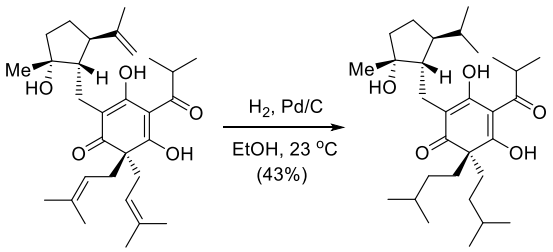
2-(((*1S*,2*R*,5*R*)-2-hydroxy-2-methyl-5-(prop-1-en-2-yl)cyclopentyl)methyl)-6-isobutyryl-3,5-dimethoxy-4,4-bis(3-methylbut-2-en-1-yl)cyclohexa-2,5-dien-1-one **2**:

To an oven-dried, round-bottomed flask was added cyclohexadiene **19** (50 mg, 0.10 mmol, 1.0 equiv) and 1.0 mL HPLC grade EtOAc (saturated with O_2 by bubbling through for 30 min before use). To this solution was added Cs_2CO_3 (130 mg, 0.40 mmol, 4.0 equiv), $PhI(OCOCF_3)_2$ (129 mg, 0.30 mmol, 3.0 equiv), and 4 Å molecular sieves. The flask was then cooled to -78 ºC (acetone-dry ice bath) and O_2 was bubbled in using a needle continuously and then TBHP (40 µL of a 5 M solution in decane, 0.20 mmol, 2.0 equiv) was added dropwise. After complete addition, the reaction was slowly warmed to 0 ºC over 1h, quenched with 0.1 mL dimethyl sulfide, and stirred at ambient temperature (23 ºC) for 0.5 h. The mixture was concentrated and loaded directly on a flash column for purification (SiO_2, 0 → 20% EtOAc/hexanes) to afford the dienone **2** (21 mg, 43%) as a colorless oil: TLC (EtOAc: hexanes, 1:5 v/v): R_f = 0.25; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.76 – 4.73 (m, 2H), 4.72 (dt, *J* = 2.6, 1.4 Hz, 1H), 4.68 (ddt, *J* = 6.3, 2.9, 1.4 Hz, 1H), 4.19 (s, 1H), 3.80 (s, 3H), 3.56 (s, 3H), 2.88 (hept, *J* = 7.1 Hz, 1H), 2.57 – 2.43 (m, 6H), 2.32 (dd, *J* = 14.6, 3.1 Hz, 1H), 1.83 (ddt, *J* = 12.3, 8.7, 6.5 Hz, 1H), 1.76 (ddd, *J* = 13.9, 8.7, 5.3 Hz, 1H), 1.65 (q, *J* = 1.2 Hz, 3H), 1.58 (ddt, *J* = 10.0, 6.4, 1.8 Hz, 1H), 1.53 (d, *J* = 1.4 Hz, 3H), 1.52 (s, 6H), 1.50 (d, *J* = 1.4 Hz, 3H), 1.38 (dddd, *J* = 13.5, 8.3, 6.8, 3.5 Hz, 1H), 1.22 – 1.15 (m, 1H), 1.08 (d, *J* = 7.1 Hz, 3H), 1.07 (d, *J* = 7.1 Hz, 3H), 1.04 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 209.3, 190.2, 171.5, 171.2, 147.3, 134.6, 134.5, 125.2, 121.2, 118.5, 118.1, 111.6, 78.5, 62.2, 60.6, 54.4, 54.0, 52.8, 42.3, 41.5, 36.1, 36.0, 28.6, 27.4, 25.8, 25.8, 21.4, 18.4, 18.2, 18.1, 18.03, 17.95; IR (thin film): 2920, 1739, 1590, 1261 cm^{-1}; $[\alpha]_D^{24}$ +57 (c 0.30, $CHCl_3$); HRMS (ESI+) *m/z* calcd for $C_{32}H_{49}O_5$ $[M+H]^+$: 513.3575, found: 513.3572.



Hypercalin C (**1**):

To an oven-dried, round-bottomed flask was added **21** (22 mg, 0.04 mmol, 1.0 equiv), 1.0 mL DMSO and LiCl (17 mg, 0.40 mmol, 10 equiv). The flask was purged with nitrogen and heated to 120 ºC for 20 h. The reaction was cooled to ambient temperature (23 ºC) diluted with water (5 mL) and then extracted with Et_2O (5 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous Mg_2SO_4 and concentrated. Flash column chromatography (gradient SiO_2, 0 → 30% EtOAc/hexanes) afforded (+)- hypercalin C (**1**, 19 mg, 90%) as a white solid: TLC (EtOAc: hexanes, 1:5 v/v): R_f = 0.25; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.93 – 4.85 (m, 1H), 4.83 (t, *J* = 1.8 Hz, 1H), 4.82 – 4.77 (m, 2H), 4.04 (hept, *J* = 6.8 Hz, 1H), 2.73 – 2.57 (m, 4H), 2.49 (dd, *J* = 13.6, 7.8 Hz, 1H), 2.42 (dt, *J* = 10.8, 7.0 Hz, 1H), 2.12 (dd, *J* = 14.7, 11.6 Hz, 1H), 1.99 (ddd, *J* = 13.3, 9.1, 3.4 Hz, 1H), 1.82 (dt, *J* = 13.4, 4.3 Hz, 2H), 1.77 (s, 3H), 1.58 (s, 3H), 1.57 – 1.56 (m, 1H), 1.54 (s, 3H), 1.53 (s, 3H), 1.51 (s, 3H), 1.53 – 1.51 (m, 1H), 1.28 (s, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.44, 195.91, 190.29, 174.22, 146.14, 134.77, 133.89, 119.58, 118.11, 111.74, 109.73, 107.09, 81.19, 57.69, 54.37, 49.92, 43.78, 38.85, 37.34, 35.59, 29.25, 28.81, 25.88, 25.80, 21.61, 18.89, 18.80, 18.47, 18.03, 17.87; IR (thin film):3400, 2960, 1630, 1560, 1470, 1340 cm^{-1} ; $[\alpha]_D^{24}$ +142 (*c* 0.50, $CHCl_3$) (literature value: $[\alpha]_D^{24}$ +185 (*c* 0.5, $CHCl_3$)[2]; HRMS (ESI+) *m/z* calcd for $C_{30}H_{45}O_5$ $[M+H]^+$: 485.3262, found: 485.3264.



hypercalin C (1) **22**

Hexahydrohypercalin C **22**:

To a 1 dram vial was added **1** (2.0 mg, 0.004 mmol, 1.0 equiv), 1.0 mL EtOH, and Pd/C (0.4 mg, 20%). The vial was purged with H_2 and a hydrogen balloon was attached. The reaction was stirred at 23 ºC for 24 h, then concentrated and directly loaded onto a flash column for purification (SiO_2, 0 → 30% EtOAc/hexanes) to afford tetrahydrohypercalin C **22** (0.8 mg, 43%) as a colorless film: TLC (EtOAc: hexanes, 1:5 v/v): R_f = 0.28; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.23 (s, 1H), 4.07 (hept, *J* = 6.8 Hz, 1H), 2.71 (dd, *J* = 14.6, 3.0 Hz, 1H), 2.30 – 2.20 (m, 1H), 1.97 – 1.87 (m, 3H), 1.85 – 1.72 (m, 5H), 1.70 – 1.61 (m, 3H), 1.43 – 1.36 (m, 4H), 1.30 (s, 3H), 1.17 (dd, *J* = 6.7, 1.7 Hz, 2H), 1.15 (s, 1H), 1.14 (s, 3H), 1.13 (d, *J* = 2.4 Hz, 1H), 1.03 – 0.90 (m, 13H), 0.81 (d, *J* = 6.7 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.6, 196.5, 190.3, 174.6, 110.1, 107.3, 82.2, 57.6, 52.3, 51.5, 49.6, 43.5, 37.9, 35.7, 33.8, 33.4, 29.6, 29.2, 28.5, 28.2, 24.0, 23.2, 22.6, 22.42, 22.41, 22.3, 21.6,18.9, 18.8, 17.7; IR (thin film): 3409, 2964, 1632, 1560 cm^{-1}; $[\alpha]_D^{24}$ +16.0 (c 0.05, $CHCl_3$); HRMS (ESI+) *m/z* calcd for $C_{30}H_{51}O_5$ $[M+H]^+$: 491.3731, found: 491.3740.

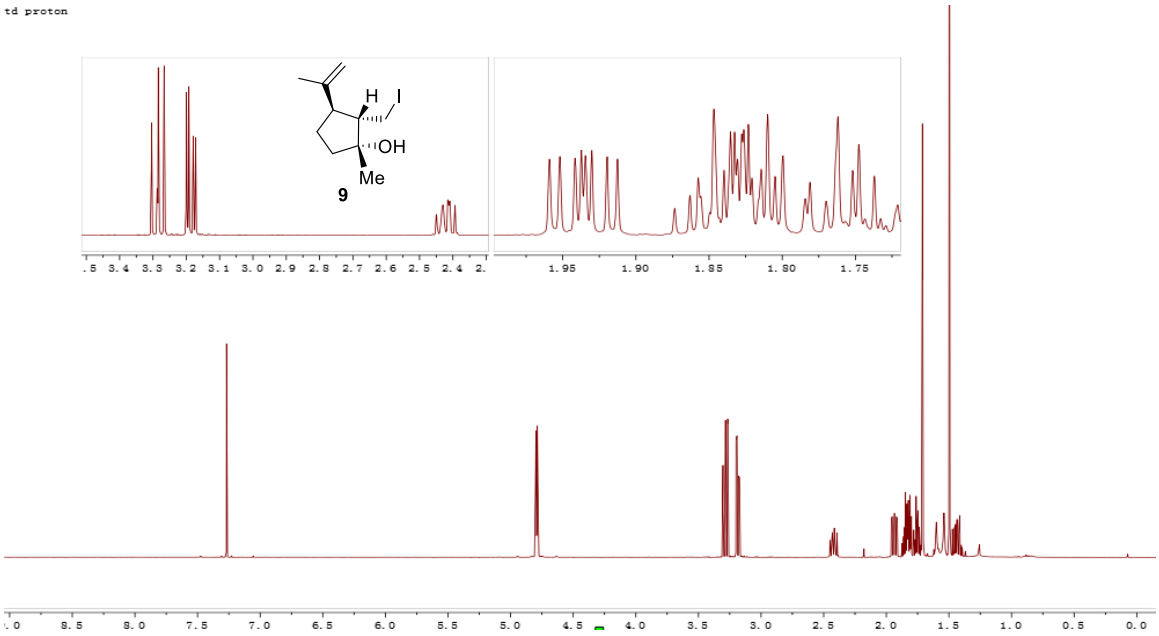
1. G. Liu, D. Romo, *Angew. Chem. Int. Ed.* **2011**, *50*, 7537-7540.
2. L. A. Decosterd, H. Stoeckli‐Evans, J. C. Chapuis, B. Sordat, K. Hostettmann, *Helv. Chim. Acta* **1989**, *72*, 1833-1845.

Cytotoxicity Assays

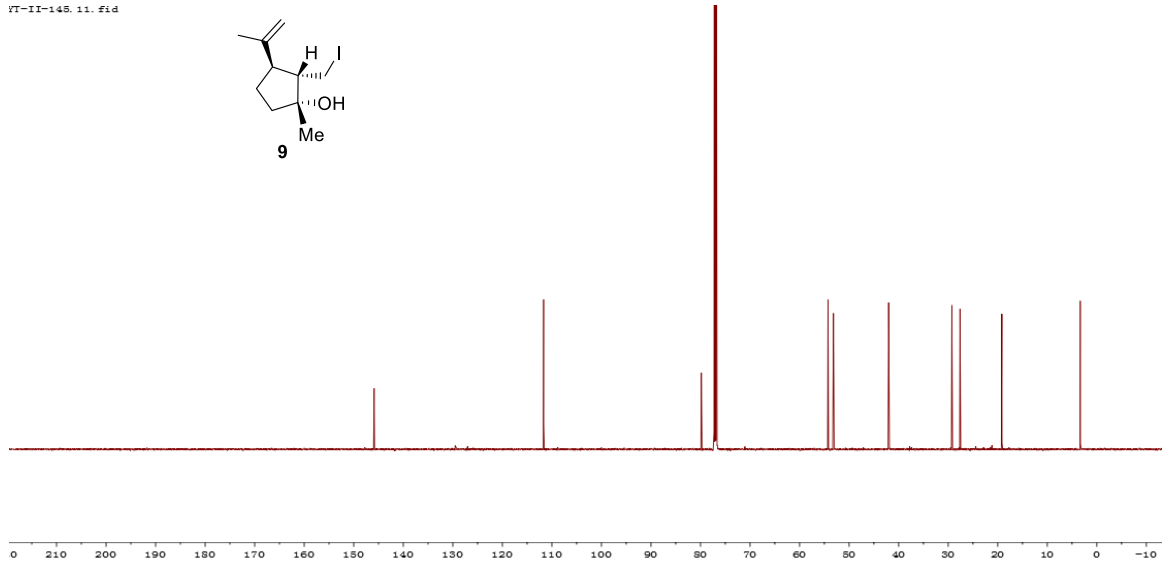
Solids and oils to be assayed were re-suspended in DMSO to yield a final concentration of 100 mM and aliquots were stored at -80^{o}C. HCT116 and MDA MB 231 cells were plated on 96-well plates with 2,000 cells per well in McCoy's 5a media and DMEM media, respectively, with 10% FBS. Twenty-four hours later, compounds were added to media and allowed to incubate for 72 h at 37 ^{o}C, 5% CO_2. Relative cell metabolic activity was assessed by incubation with MTS assay reagent for 3 h (CellTiter 96 Aqueous One Solution Cell Proliferation Assay, Promega) according to the manufacturer's protocol. Background absorbance (media only) was subtracted from all other wells and absorbance was then normalized to DMSO treatment at matching concentrations. The normalized relative viability values were graphed against the drug dosage and IC_{50} (drug concentration eliciting 50% of the maximum inhibition) values were calculated for each tested cell line using the "log(inhibitor) vs. response -- Variable slope (four parameters)" function in Prism6 (Graphpad).

Table S1: ^{13}C NMR Comparison of Synthetic and Literature Values for Hypercalin C (**1**)

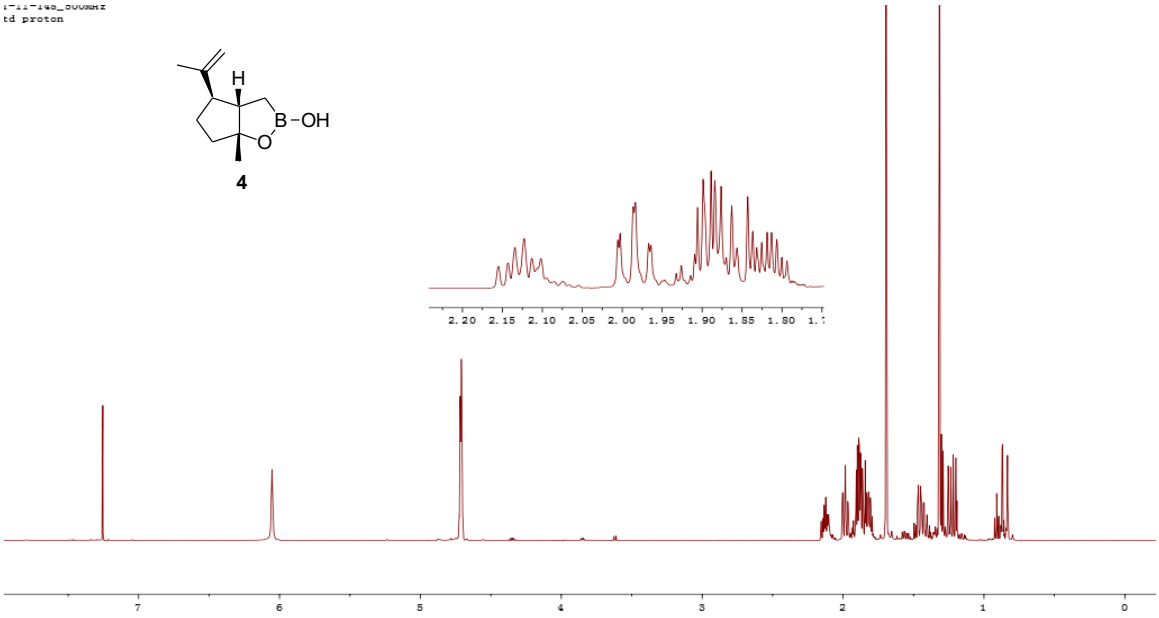
hypercalin C (C#'s)	^{13}C NMR Chemical Shifts		Δ
	Natural	Synthetic	
C27	207.4	207.44	0.04
C3	195.9	195.91	0.01
C1	190.3	190.29	-0.01
C5	174.2	174.21	0.01
C13	146.1	146.14	0.04
C24	134.8	134.77	-0.03
C19	133.9	133.89	-0.01
C18	119.5	119.58	0.08
C23	118.1	118.11	0.01
C14	111.8	111.74	-0.06
C6	109.7	109.73	0.03
C2	107.1	107.09	-0.01
C9	81.2	81.19	-0.01
C4	57.7	57.69	-0.01
C12	54.4	54.37	-0.03
C8	49.9	49.92	0.02
C10	43.8	43.77	-0.03
C22	38.8	38.84	0.04
C17	37.3	37.35	0.05
C28	35.6	35.59	-0.01
C16	29.2	29.25	0.05
C11	28.8	28.81	0.01
C25	25.9	25.86	-0.04
C21	25.8	25.80	0
C7	21.6	21.61	0.01
C30	18.9	18.89	-0.01
C29	18.8	18.80	0
C15	18.4	18.47	0.07
C26	18	18.03	0.03
C20	17.9	17.87	-0.03



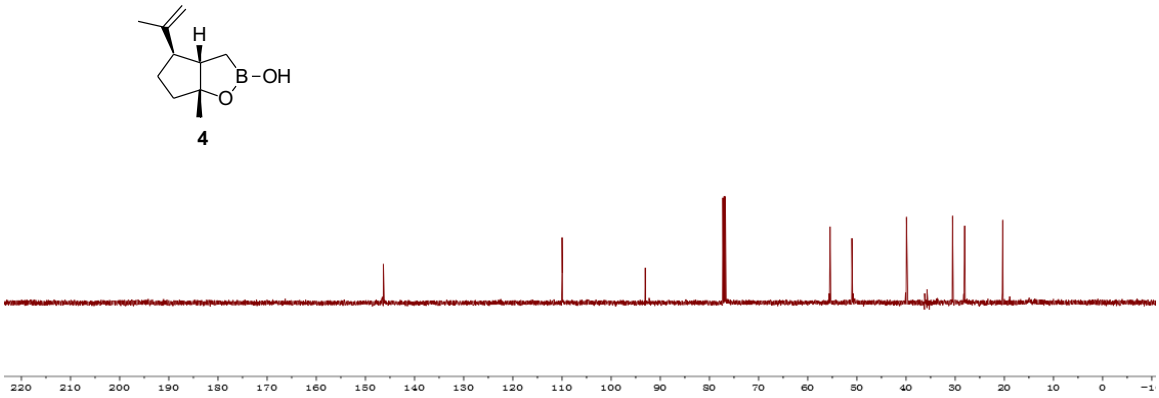
^{1}H NMR (500 MHz, $CDCl_3$) of iodide **9**



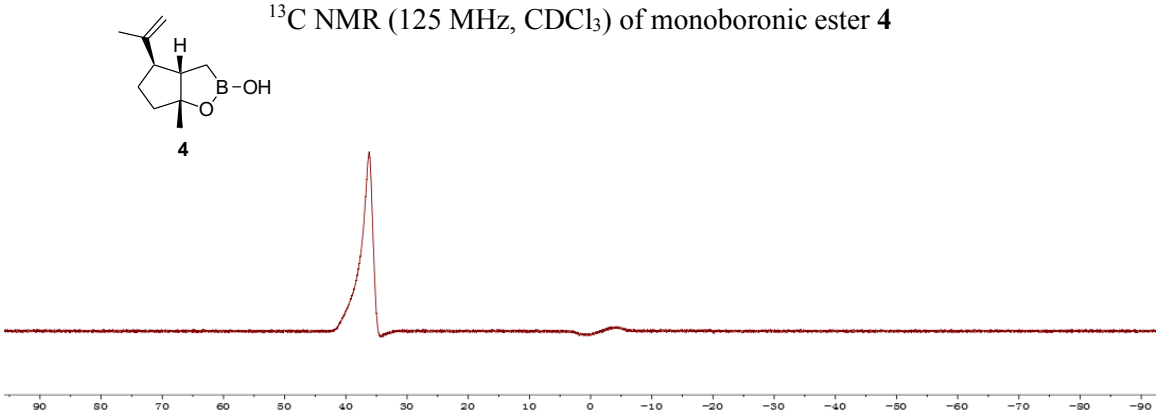
^{13}C NMR (150 MHz, $CDCl_3$) of iodide **9**



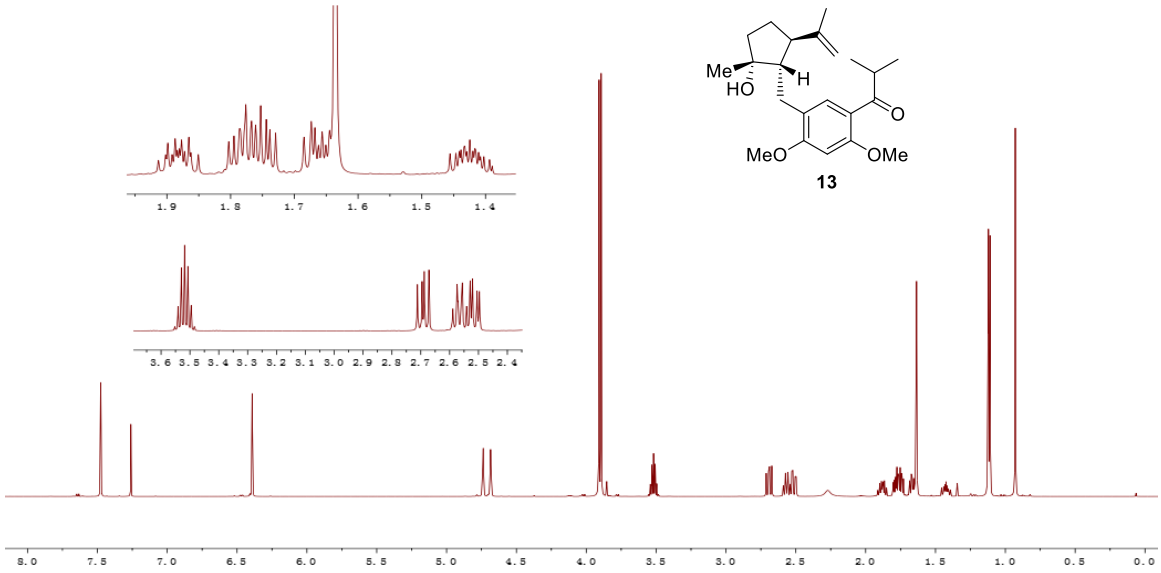
^{1}H NMR (500 MHz, $CDCl_3$) of monoboronic ester **4**



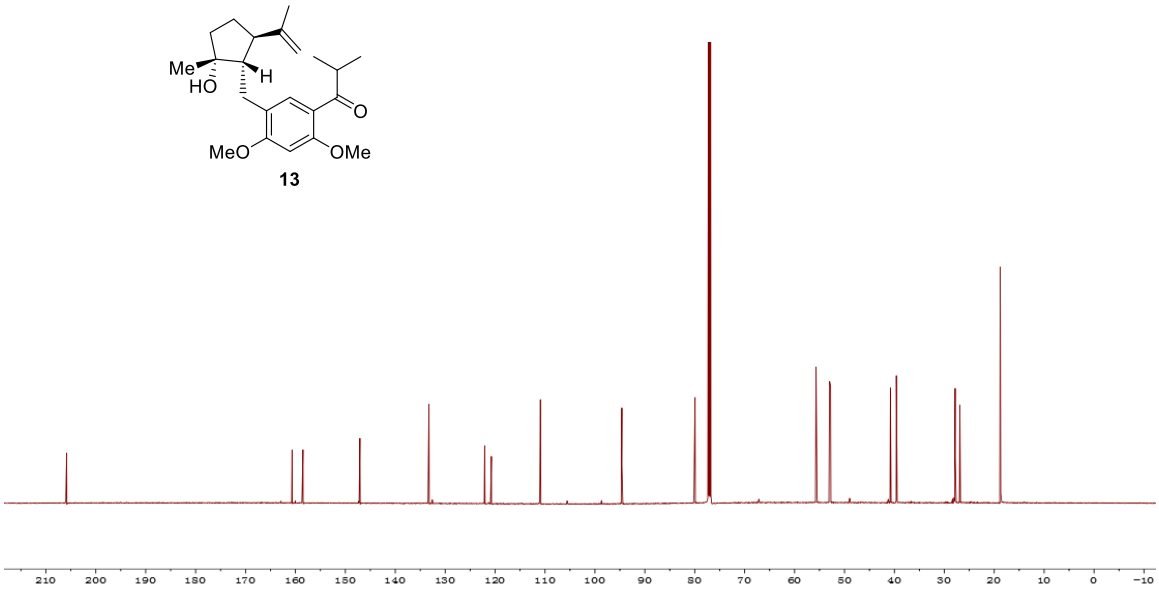
^{13}C NMR (125 MHz, $CDCl_3$) of monoboronic ester **4**



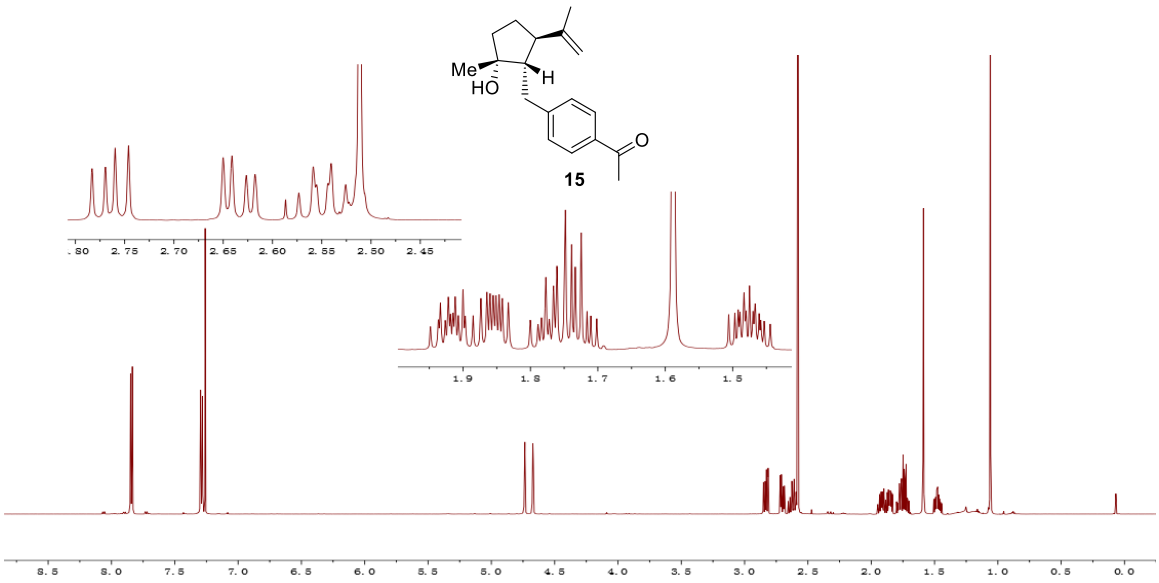
^{11}B NMR (193 MHz, $CDCl_3$) of monoboronic ester **4**



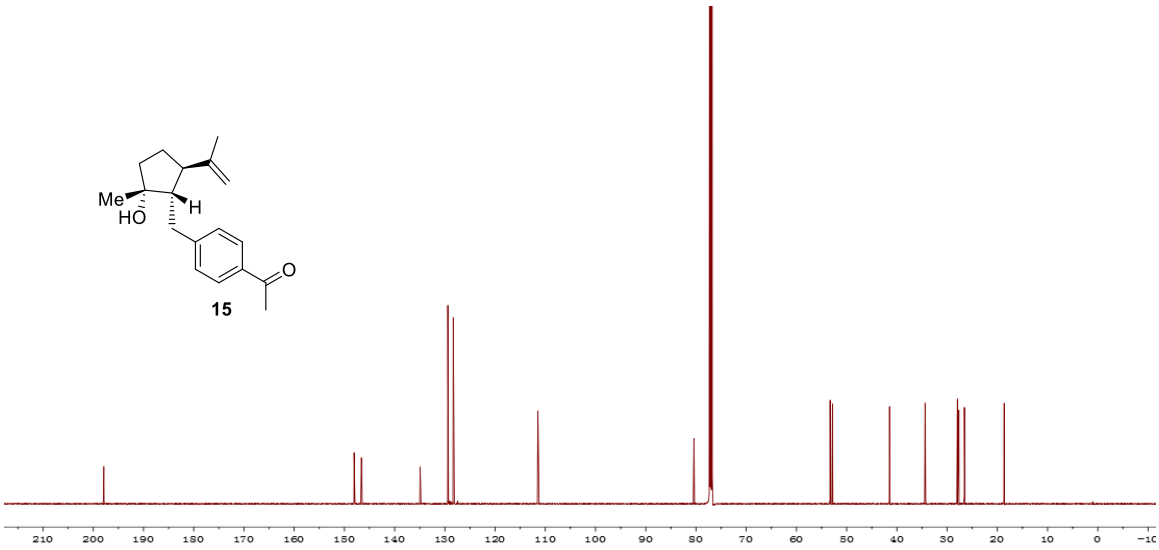
^{1}H NMR (600 MHz, $CDCl_3$) of aryl cyclopentane **13**



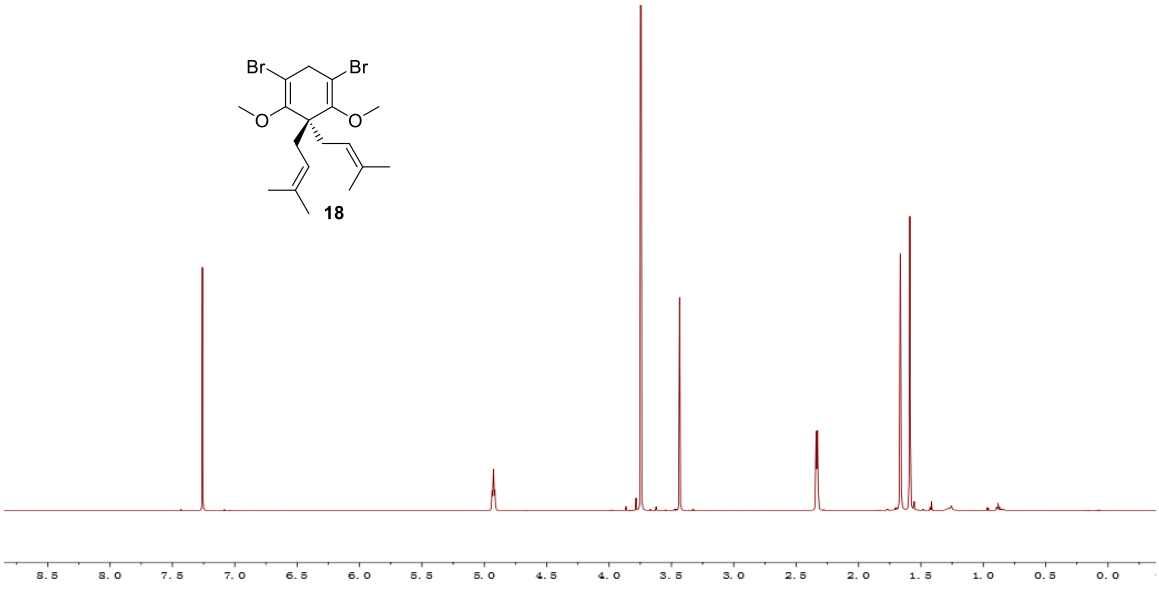
^{13}C NMR (150 MHz, $CDCl_3$) of aryl cyclopentane **13**



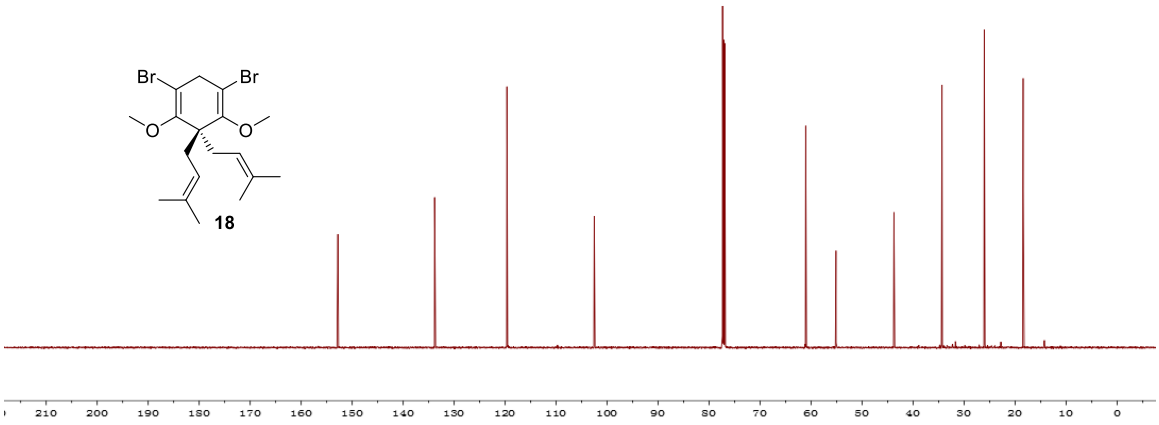
^{1}H NMR (600 MHz, $CDCl_3$) of aryl cyclopentane **15**



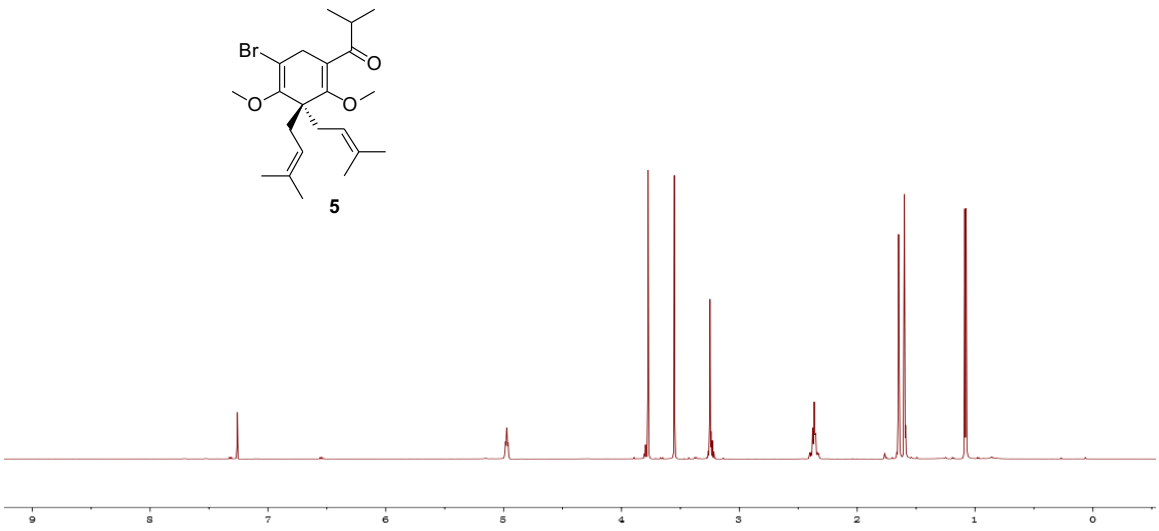
^{13}C NMR (150 MHz, $CDCl_3$) of aryl cyclopentane **15**



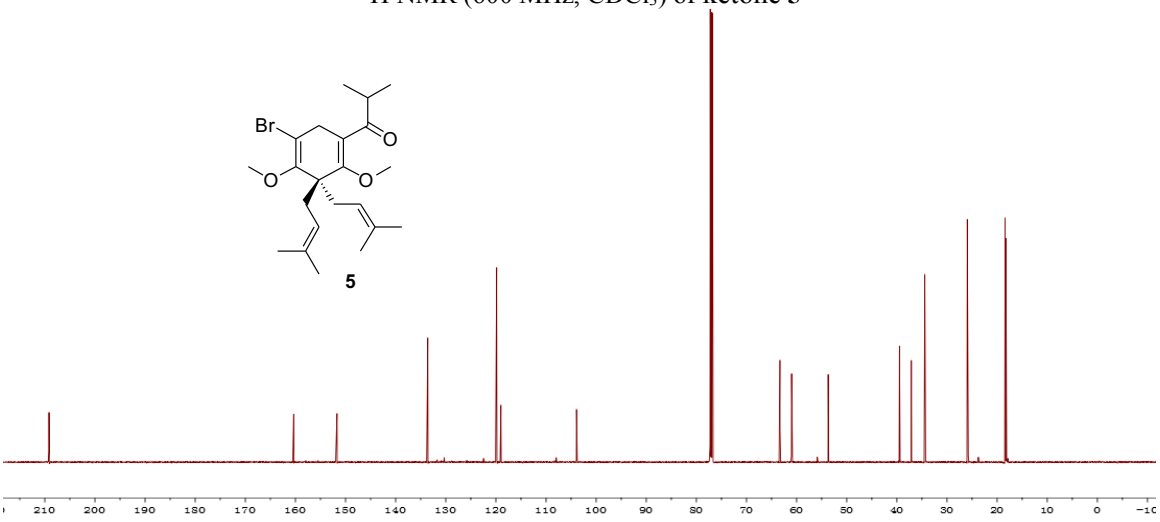
^{1}H NMR (600 MHz, $CDCl_3$) of bis-bromoenolether **18**



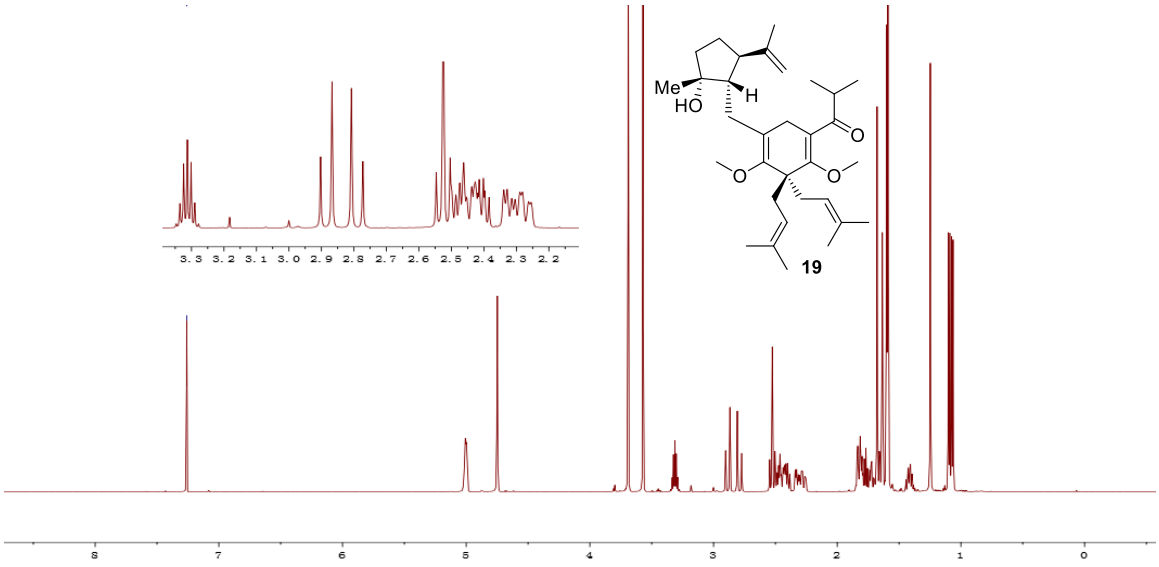
^{13}C NMR (150 MHz, $CDCl_3$) of bis-bromoenolether **18**



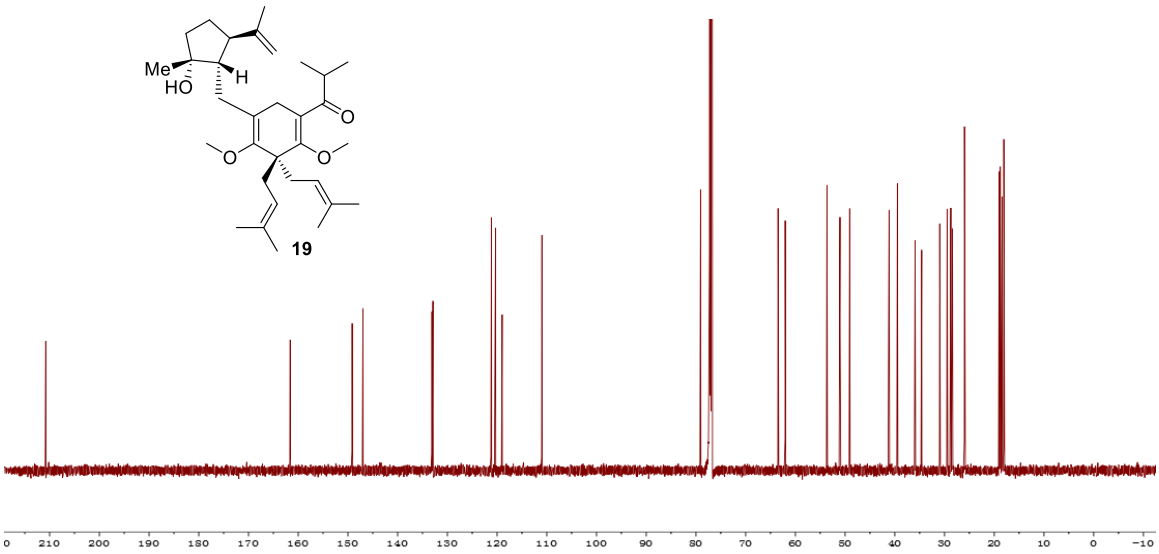
^{1}H NMR (600 MHz, $CDCl_3$) of ketone **5**



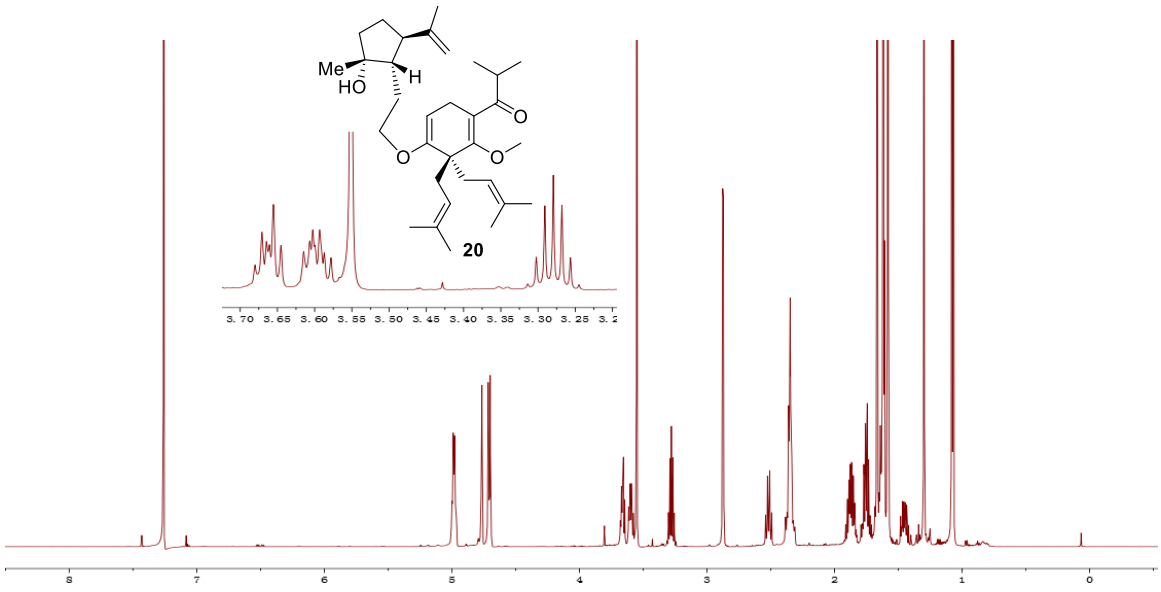
^{13}C NMR (150 MHz, $CDCl_3$) of ketone **5**



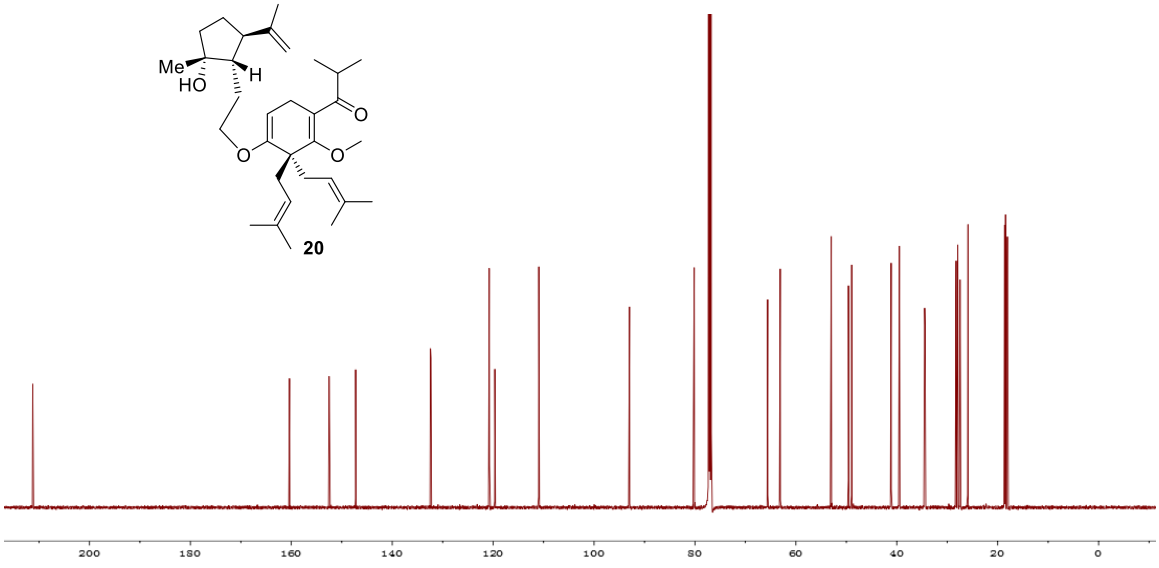
^{1}H NMR (600 MHz, $CDCl_3$) of cyclohexadiene **19**



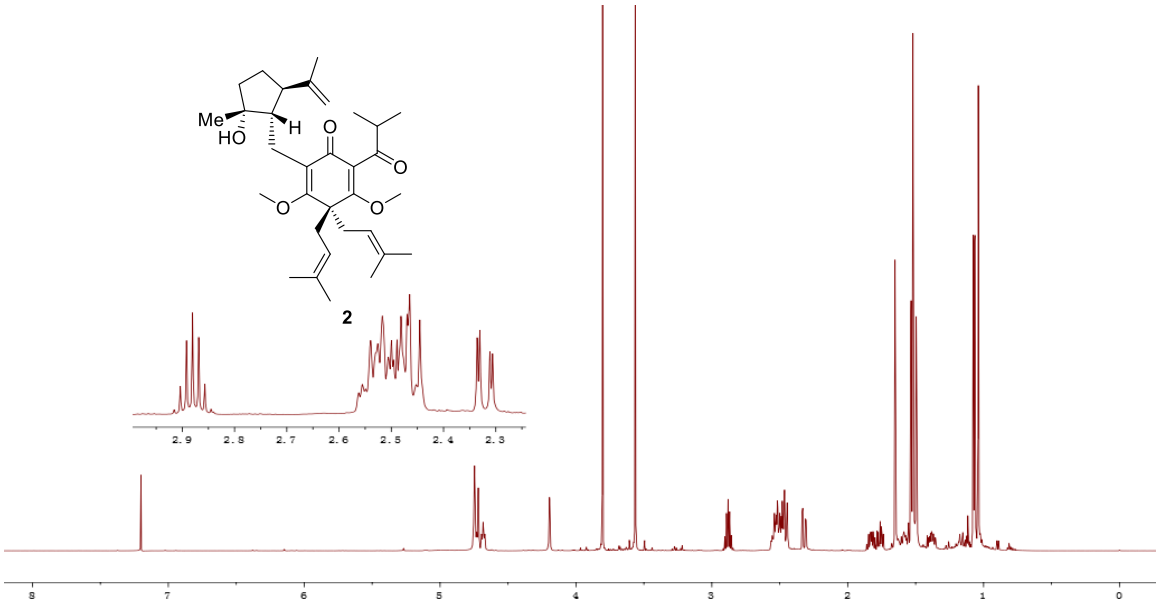
^{13}C NMR (150 MHz, $CDCl_3$) of cyclohexadiene **19**



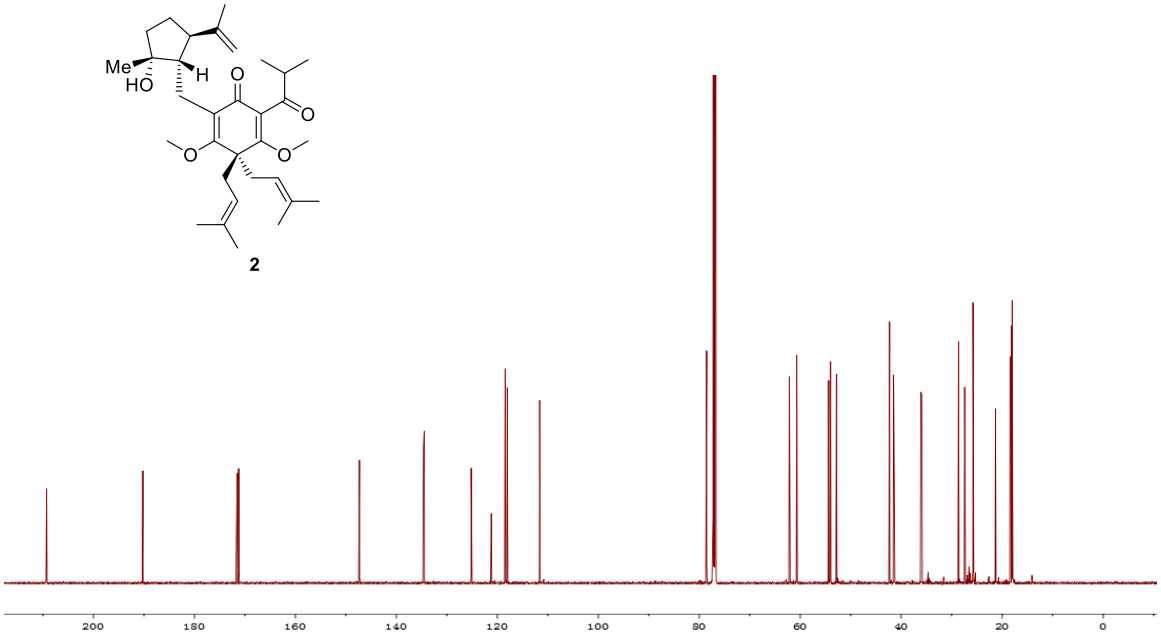
^{1}H NMR (600 MHz, $CDCl_3$) of ether **20**



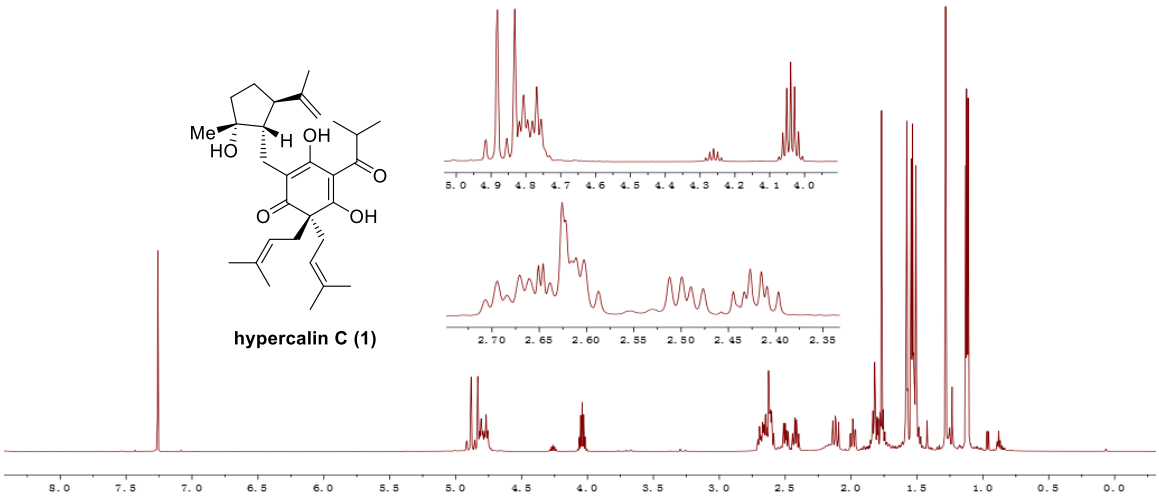
^{13}C NMR (150 MHz, $CDCl_3$) of ether **20**



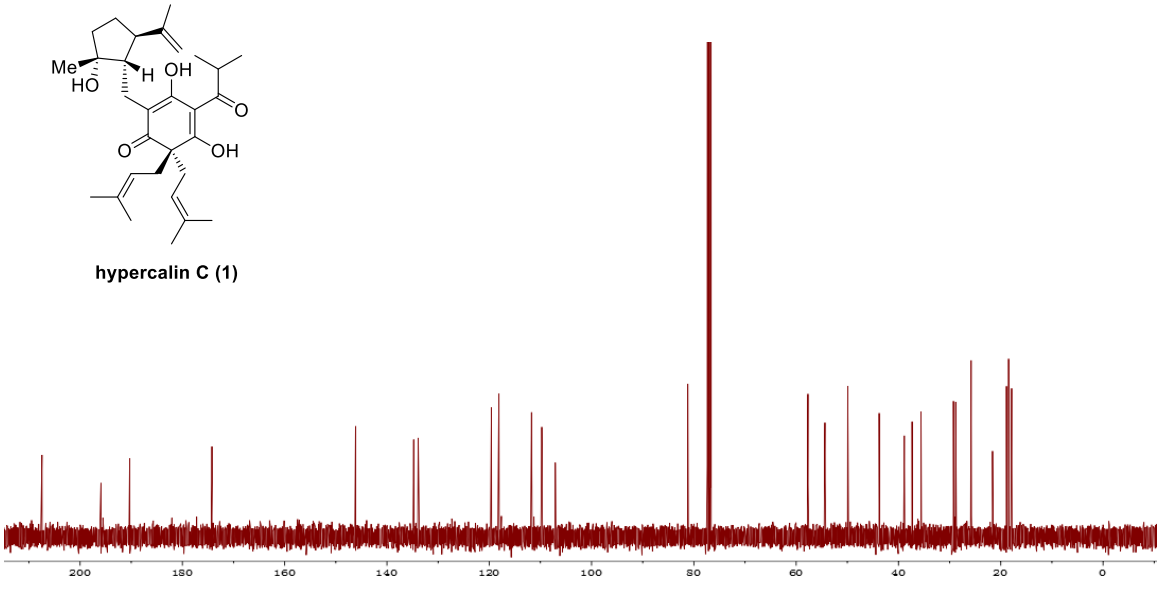
^{1}H NMR (600 MHz, $CDCl_3$) of dienone **2**



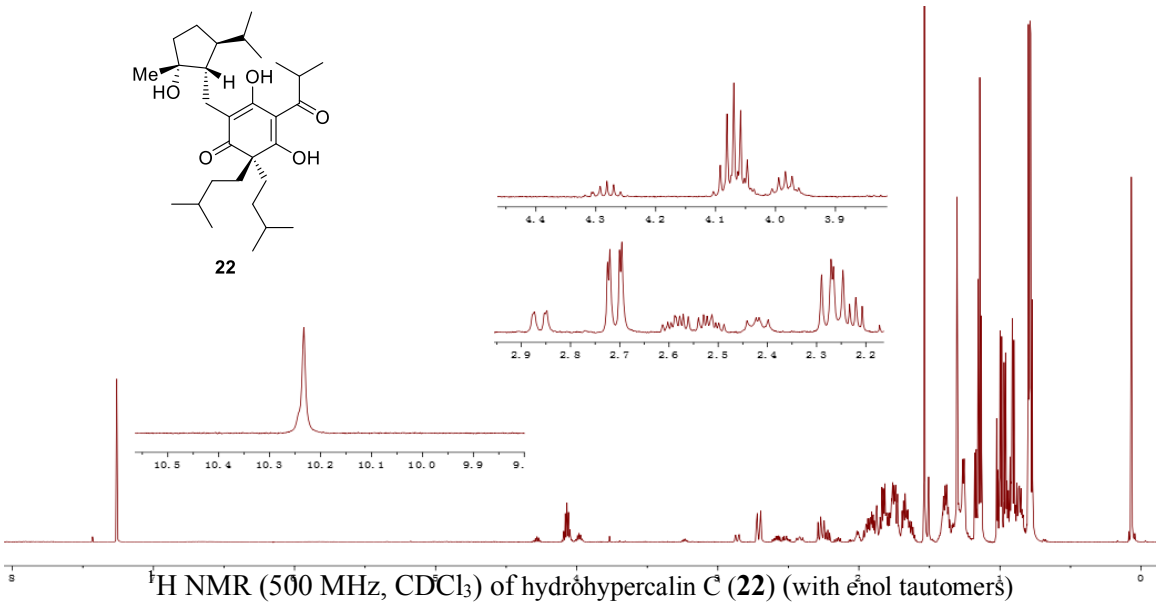
^{13}C NMR (150 MHz, $CDCl_3$) of dienone **2**



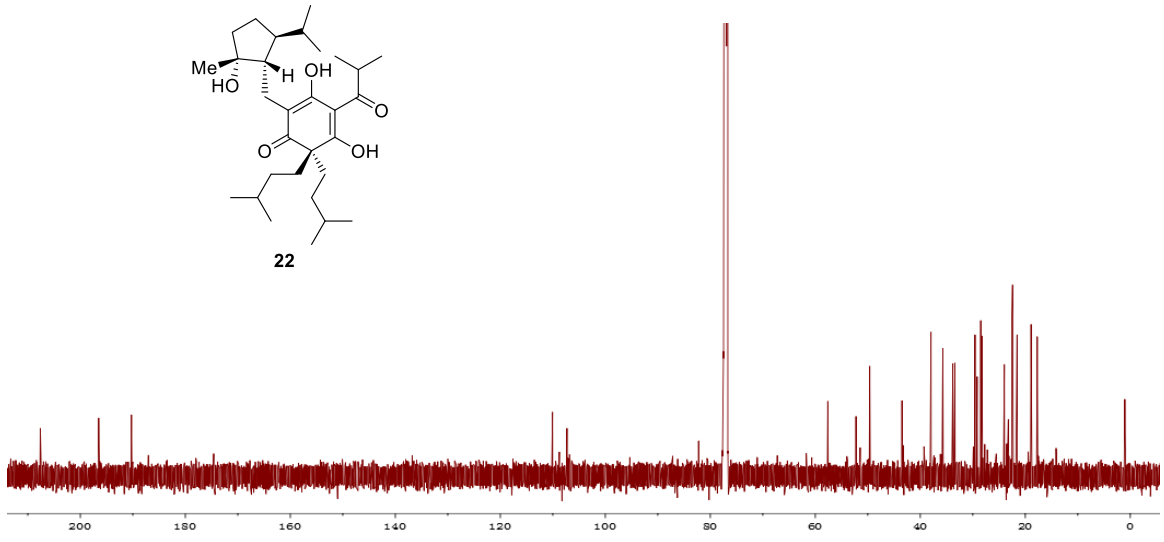
^{1}H NMR (600 MHz, $CDCl_3$) of hypercalin C **(1)** (with enol tautomers)



^{13}C NMR (100 MHz, $CDCl_3$) of hypercalin C **(1)** (with enol tautomers)



^{1}H NMR (500 MHz, $CDCl_3$) of hydrohypercalin C (**22**) (with enol tautomers)



^{13}C NMR (150 MHz, $CDCl_3$) of hydrohypercalin C (**22**) (with enol tautomers)