

# **A Concise Enantioselective Synthesis of the Anticancer Rotenoid Deguelin Enabled by a Tandem Knoevenagel/Asymmetric Conjugate Addition/Decarboxylation Sequence**

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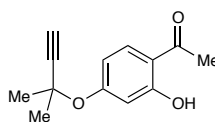
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## General Synthetic Information

All reactions were carried out under a nitrogen atmosphere in flame-dried glassware with magnetic stirring. Solvents were purified by passage through a bed of activated alumina.<sup>1</sup> Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.<sup>2</sup> Purification of reaction products was carried out by flash column chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and ceric ammonium nitrate, p-anisaldehyde, phosphomolybdic acid (PMA) or potassium permanganate stain followed by heating. Infrared spectra were recorded on a Bruker Tensor 37 FT-IR spectrometer (MiD IR/ATR). Optical rotations were measured on a Perkin Elmer Model 341 polarimeter with a sodium lamp and are reported as follows:  $[\alpha]_{\lambda T}^{\circ C}$  (c = g/100 mL, solvent). <sup>1</sup>H NMR spectra were recorded on a Varian INOVA 500 (500 MHz) spectrometer and Bruker AVANCE III 500 (500 MHz) spectrometer with direct cryoprobe and are reported in ppm using solvent as an internal standard (CDCl<sub>3</sub> at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad). All coupling constants (*J*) are reported in Hz. Proton-decoupled <sup>13</sup>C NMR spectra were recorded on Varian INOVA 500 (125 MHz) spectrometer and Bruker AVANCE III 500 (125 MHz) spectrometer with direct cryoprobe and are reported in ppm using solvent as an internal standard (CDCl<sub>3</sub> at 77.21 ppm). Mass spectra were obtained on a Waters Acquity Ultra High Performance Liquid Chromatography Mass Spectrometry system or a Thermo Finnegan LCQ mass spectrometer (LRMS – ESI).

## Synthesis of Beta-Ketoester Substrates



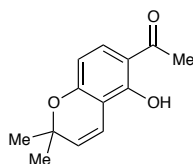
**1-(2-hydroxy-4-((2-methylbut-3-yn-2-yl)oxy)phenyl)ethanone (8):** Compound **8** was synthesized according to a modified procedure by Bell.<sup>3</sup> To a 100 mL flame-dried round bottom flask was added 2',4'-dihydroxyacetophenone (**7**, 50 mmol, 7.61 g), K<sub>2</sub>CO<sub>3</sub> (100 mmol, 13.82 g), KI (85 mmol, 14.11 g) and copper(I) iodide (2.5 mmol, 476 mg). The flask was purged with N<sub>2</sub>, then dry DMF (40 mL) was added via syringe. After approximately 5 minutes of stirring under N<sub>2</sub>, 3-chloro-3-methylbutyne (90 mmol, 10.1 mL) was added via syringe, at which point the slightly peach colored reaction turned yellow and bubbled slightly. The reaction was then equipped with a reflux condenser and was heated to 65 °C overnight. After stirring for approximately 15 h, the reaction was quenched by the addition of 100 mL of water, and the aqueous layer was extracted with 100 mL EtOAc. The aqueous layer was then acidified with 2 M HCl, then was extracted 2x100 mL with EtOAc. The combined organic layers were washed with 100 mL water, then brine, and were dried over Na<sub>2</sub>SO<sub>4</sub>. The dark orange-yellow organic layers were then concentrated *in vacuo* and purified by flash column chromatography (SiO<sub>2</sub>, 5%

<sup>1</sup> Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmer, F. J. *Organometallics* **1996**, *15*, 1518-1520.

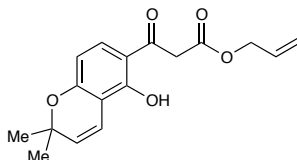
<sup>2</sup> Perrin, D. M.; Armarego, W. L. *Purification of Laboratory Chemicals*; 3<sup>rd</sup> ed.; Pergamon Press: Oxford, 1988.

<sup>3</sup> Bell, D.; Davies, M. R.; Geen, G. R.; Mann, I. S. *Synthesis* **1995**, 707-712.

EtOAc/hexanes) to yield the desired compound **8** (8.72 g, 80%) as a light yellow solid. Analytical data for **8**: IR (film) 3290, 2991, 2938, 1634, 1575, 1499, 1369, 1331, 1271, 1253, 1173, 1129, 1066, 991, 888, 854, 804, 652, 622  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  12.61 (s, 1H), 7.63 (d,  $J = 8.9$  Hz, 1H), 6.89 (d,  $J = 2.4$  Hz, 1H), 6.65 (dd,  $J = 8.9, 2.4$  Hz, 1H), 2.66 (s, 1H), 2.56 (s, 3H), 1.71 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  202.8, 164.3, 162.6, 131.8, 114.5, 111.0, 106.4, 84.7, 75.1, 72.3, 29.5, 26.4; LRMS (ESI): Mass calcd for  $\text{C}_{13}\text{H}_{14}\text{O}_3$   $[\text{M}+\text{H}]^+$ , 219. Found 219.



**1-(5-hydroxy-2,2-dimethyl-2H-chromen-6-yl)ethanone (9)**: To a 10-12 mL microwave vial was added the starting alkyne **8** (12 mmol, 2.62 g) and dry toluene (12 mL). The vial was capped and the reaction was heated in a Biotage Initiator microwave reactor at 180  $^\circ\text{C}$  for 30 minutes at 1-2 bar. After 30 minutes, the dark brown-amber reaction was concentrated to a dark brown oil that crystallized on the high vacuum to yield the desired product **9** (2.62 g, 100%) as a light brown solid. Analytical data for **9**: IR (film) 2977, 1643, 1623, 1487, 1426, 1391, 1330, 1273, 1211, 1166, 1122, 1073, 898, 805, 790, 730  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  12.97 (s, 1H), 7.51 (d,  $J = 8.8$  Hz, 1H), 6.71 (dd,  $J = 10.1, 0.8$  Hz, 1H), 6.33 (dd,  $J = 8.8, 0.7$  Hz, 1H), 5.58 (d,  $J = 10.0$  Hz, 1H), 2.54 (s, 3H), 1.45 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  202.8, 159.7, 159.6, 131.7, 128.2, 115.8, 113.8, 109.2, 108.3, 77.8, 28.3, 26.2; LRMS (ESI): Mass calcd for  $\text{C}_{13}\text{H}_{14}\text{O}_3$   $[\text{M}+\text{H}]^+$ , 219. Found 219.

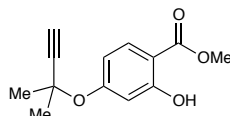


**allyl 3-(5-hydroxy-2,2-dimethyl-2H-chromen-6-yl)-3-oxopropanoate (10)**: To a 250 mL flame-dried round bottom flask was added dry THF (18 mL) and freshly distilled hexamethyldisilazane (24 mmol, 5 mL).<sup>4,5</sup> The system was purged with  $\text{N}_2$ , then was cooled in a dry ice/acetone bath to  $-78$   $^\circ\text{C}$ .  $n\text{BuLi}$  (2.44 M, 24 mmol, 9.84 mL) was then added dropwise such that the temperature did not go above  $-69$   $^\circ\text{C}$ , as monitored by a thermocouple. The solution of LiHMDS was then warmed to  $0$   $^\circ\text{C}$  in an ice/water bath and stirred for 1 h. After that time, the reaction was cooled back to  $-78$   $^\circ\text{C}$ , and the starting acetophenone (**9**) (6 mmol, 1.31 g) in 22.5 mL of dry THF was cannulated into the solution of LiHMDS. The reaction was allowed to stir at  $-78$   $^\circ\text{C}$  for 1 h, then  $-20$   $^\circ\text{C}$  (ice/salt bath) for 2 h. After that time, the reaction was cooled to  $-78$   $^\circ\text{C}$  and diallyl carbonate (24 mmol, 3.44 mL) in 2.25 mL THF was added quickly via syringe. The reaction was then allowed to slowly warm to  $23$   $^\circ\text{C}$  overnight. After stirring for approximately 16 h, the reaction was poured over a mixture of ice (75 g) and concentrated HCl (3 mL), then was extracted with  $\text{CHCl}_3$  (3x100 mL). The combined organic layers were washed with brine (100 mL) and dried over  $\text{Na}_2\text{SO}_4$ , then were concentrated *in vacuo* and purified by

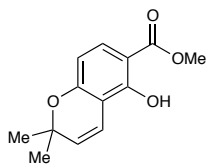
<sup>4</sup> Biddle, M. M.; Lin, M.; Scheidt, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3830-3831.

<sup>5</sup> Farmer, R. L.; Biddle, M. M.; Nibbs, A. E.; Huang, X. K.; Bergan, R. C.; Scheidt, K. A. *ACS Med. Chem. Lett.* **2010**, *1*, 400-405.

flash column chromatography (SiO<sub>2</sub>, 5% EtOAc/hexanes) to yield the beta-ketoester **10** (1.31 g, 72%) as a bright yellow oil. Analytical data for **10**: IR (film) 2976, 1934, 1741, 1641, 1618, 1578, 1487, 1426, 1377, 1353, 1301, 1282, 1232, 1163, 1115, 990, 939, 897, 805, 786, 728 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 12.52 (s, 1H), 7.44 (d, *J* = 8.9 Hz, 1H), 6.70 (dd, *J* = 9.9, 0.8 Hz, 1H), 6.35 (dd, *J* = 8.7, 0.8 Hz, 1H), 5.90 (ddt, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.59 (d, *J* = 10.1 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.5, 1.3 Hz, 1H), 4.66 (dt, *J* = 5.8, 1.4 Hz, 2H), 3.94 (s, 2H), 1.45 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 196.1, 166.9, 160.4, 160.0, 131.5, 131.4, 128.4, 118.9, 115.6, 113.1, 109.3, 108.9, 78.1, 66.2, 45.4, 28.4; LRMS (ESI): Mass calcd for C<sub>17</sub>H<sub>18</sub>O<sub>5</sub> [M+H]<sup>+</sup>, 303. Found 303.

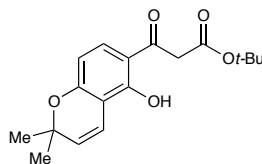


**methyl 2-hydroxy-4-((2-methylbut-3-yn-2-yl)oxy)benzoate (11):** Compound **11** was synthesized in an analogous manner to alkyne **8**, using the modified procedure reported by Bell.<sup>3</sup> To a flame-dried 50 mL RBF was added CuI (0.75 mmol, 143 mg), followed by methyl 2,4-dihydroxybenzoate (15 mmol, 2.52 g), K<sub>2</sub>CO<sub>3</sub> (30 mmol, 4.15 g) and KI (25.5 mmol, 4.23 g). The system was purged with N<sub>2</sub>, then dry DMF (12 mL) was added via syringe. The slightly pink solution was allowed to stir under N<sub>2</sub> for an additional 5 minutes, then 3-chloro-3-methylbutyne (27 mmol, 3 mL) was added via syringe. The reaction turned a bright yellow upon addition of the alkyne. The reaction was then equipped with a reflux condenser and heated to 65 °C overnight. After stirring for approximately 16 h, the reaction was cooled to 23 °C and was quenched by the addition of 100 mL H<sub>2</sub>O. The aqueous layer was neutralized to pH 7 with 2 M HCl, then was extracted 2x100 mL with EtOAc. The combined yellow-orange organic layers were then washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The organic material was concentrated *in vacuo* and purified by flash column chromatography (SiO<sub>2</sub>, 10% EtOAc/hexanes) to give **11** (2.60 g, 74%) as an orange oily solid. Analytical data for **11**: IR (film) 3290, 2992, 2955, 1672, 1621, 1579, 1499, 1441, 1348, 1256, 1224, 1191, 1172, 1132, 989, 963, 889, 855, 781, 697, 667 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 10.89 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 6.66 (dd, *J* = 8.9, 2.4 Hz, 1H), 3.91 (s, 3H), 2.65 (s, 1H), 1.70 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 170.4, 163.0, 162.0, 130.7, 111.5, 106.5, 84.9, 74.9, 72.2, 52.1, 29.6; LRMS (ESI): Mass calcd for C<sub>13</sub>H<sub>14</sub>O<sub>4</sub> [M+H]<sup>+</sup>, 235. Found 235.



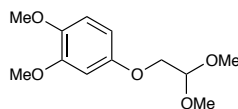
**methyl 5-hydroxy-2,2-dimethyl-2H-chromene-6-carboxylate (12):** Compound **12** was synthesized using the same protocol as acetophenone **9**. To a 10-12 mL microwave vial was added the starting alkyne **11** (12 mmol, 2.81 g) and dry toluene (12 mL). The vial was capped and the reaction was heated in a Biotage Initiator microwave reactor at 180 °C for 30 minutes at 1-2 bar. After 30 minutes, the dark brown-amber reaction was concentrated to yield the desired product **12** (2.81 g, 100%) as an amber oil. Analytical data for **12**: IR (film) 2976, 2955, 2930, 2856, 1668, 1620, 1578, 1487, 1438, 1375, 1341, 1271, 1201, 1165, 1143, 1113, 1074, 990, 763

$\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  11.18 (s, 1H), 7.62 (d,  $J = 8.8$  Hz, 1H), 6.71 (dd,  $J = 10.0$ , 0.6 Hz, 1H), 6.33 (dd,  $J = 8.8$ , 0.7 Hz, 1H), 5.58 (d,  $J = 10.0$  Hz, 1H), 3.91 (s, 3H), 1.45 (s, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.6, 159.0, 158.2, 130.4, 128.3, 116.0, 109.2, 108.5, 105.3, 52.0, 28.2; LRMS (ESI): Mass calcd for  $\text{C}_{13}\text{H}_{14}\text{O}_4$   $[\text{M}+\text{H}]^+$ , 235. Found 235.



**tert-butyl 3-(5-hydroxy-2,2-dimethyl-2H-chromen-6-yl)-3-oxopropanoate (13):** Freshly distilled HMDS (30 mmol, 6.3 mL) and dry THF (10 mL) were added to a flame-dried 100 mL RBF, and the system was purged with  $\text{N}_2$ .<sup>4</sup> The solution was cooled to  $-78$  °C in a dry ice/acetone bath, then  $n\text{BuLi}$  (30 mmol, 1.77 M, 17 mL) was added dropwise such that the reaction temperature did not exceed  $-66$  °C, as monitored by a thermocouple. The LiHMDS solution was then warmed to  $0$  °C for 1 h. After that time, the reaction was cooled back down to  $-78$  °C, and  $t\text{-BuOAc}$  (17.5 mmol, 2.36 mL) in 5 mL of dry THF was cannulated into the reaction dropwise. The reaction was allowed to stir at  $-78$  °C for another 1.5 h, then the ester **12** (5 mmol, 1.17 g) in 5 mL of dry THF was added via syringe. The bright orange reaction was then allowed to warm slowly to  $23$  °C overnight. After stirring for approximately 15 h, the reaction was quenched with saturated  $\text{NH}_4\text{Cl}$  (100 mL) and the aqueous layer was extracted with EtOAc (50 mL). The aqueous layer was neutralized to pH 7 with 2 M HCl, then was back-extracted with EtOAc (2x100 mL). The combined organic layers were then washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The organic material was concentrated *in vacuo* and purified by flash column chromatography ( $\text{SiO}_2$ , 10% EtOAc/hexanes) to yield **13** (1.12 g, 70%) as a bright orange oil. Analytical data for **13**: IR (film) 2978, 2933, 1731, 1641, 1579, 1514, 1368, 1304, 1282, 1251, 1212, 1147, 1115, 827, 805, 787, 668  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  12.60 (s, 1H), 7.44 (d,  $J = 8.8$  Hz, 1H), 6.69 (dd,  $J = 10.0$ , 0.7 Hz, 1H), 6.33 (dd,  $J = 8.8$ , 0.8 Hz, 1H), 5.57 (d,  $J = 10.1$  Hz, 1H), 3.80 (s, 2H), 1.44 (s, 15H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  197.0, 166.5, 160.1, 160.0, 131.4, 128.3, 115.7, 113.2, 109.3, 108.7, 82.3, 78.0, 46.9, 28.4, 28.0; LRMS (ESI): Mass calcd for  $\text{C}_{18}\text{H}_{22}\text{O}_5$   $[\text{M}+\text{Na}]^+$ , 341. Found 341.

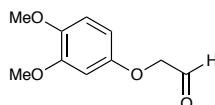
### Synthesis of Aldehyde Coupling Partner



**4-(2,2-dimethoxyethoxy)-1,2-dimethoxybenzene (15):** To a 100 mL flame-dried RBF was added 3,4-dimethoxyphenol (**14**, 40 mmol, 6.16 g) and dry DMF (36 mL).<sup>6</sup> The flask was purged with  $\text{N}_2$ , then  $\text{K}_2\text{CO}_3$  (240 mmol, 33.2 g) and bromoacetaldehyde dimethyl acetal (56 mmol, 6.62 mL) were added. The reaction was equipped with a reflux condenser and heated to  $150$  °C overnight. After approximately 16 h, the reaction was cooled to  $23$  °C and the salts that had

<sup>6</sup> Tummatorn, J.; Khorphueng, P.; Petsom, A.; Muangsin, N.; Chaichit, N.; Roengsumran, S. *Tetrahedron* **2007**, *63*, 11878-11885.

formed in the reaction were dissolved in H<sub>2</sub>O (150 mL). The aqueous layer was neutralized to pH 7 with 2 M HCl, then it was extracted 3x100 mL with EtOAc. The combined organic layers were washed once with brine (100 mL), then were dried over Na<sub>2</sub>SO<sub>4</sub>. The organic material was concentrated *in vacuo* and purified by flash column chromatography (SiO<sub>2</sub>, 50% EtOAc/hexanes) to yield the desired product **15** (9.37 g, 97%) as a pale yellow oily solid. Analytical data for **15**: IR (film) 2935, 2832, 1611, 1513, 1451, 1283, 1229, 1202, 1165, 1134, 1076, 1026, 835, 680, 668 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 6.76 (d, *J* = 8.7 Hz, 1H), 6.58 (d, *J* = 2.8 Hz, 1H), 6.40 (dd, *J* = 8.7, 2.8 Hz, 1H), 4.72 (t, *J* = 5.2 Hz, 1H), 3.96 (d, *J* = 5.2 Hz, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.46 (s, 6H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 153.0, 149.8, 143.8, 111.5, 103.6, 102.1, 101.1, 67.9, 56.4, 55.9, 54.1; LRMS (ESI): Mass calcd for C<sub>12</sub>H<sub>18</sub>O<sub>5</sub> [M+H]<sup>+</sup>, 243. Found 243.

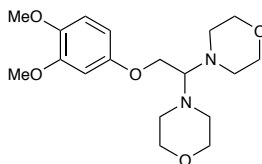


**2-(3,4-dimethoxyphenoxy)acetaldehyde (6):** A flame-dried 250 mL RBF was charged with dimethyl acetal **15** (15 mmol, 3.63 g), which was then dissolved in a 5:1 mixture of MeCN and water (180 mL).<sup>7,8</sup> The system was equipped with a reflux condenser and was purged with N<sub>2</sub>, then Amberlyst-15 beads (1.5 g) were added. The heterogeneous reaction was then heated to reflux (85 °C) for 20 h. TLC in 1:1 hexanes/EtOAc demonstrated that the starting material had been consumed, so the reaction was cooled to 23 °C and was diluted with DCM (200 mL). The remaining Amberlyst-15 beads were removed by vacuum filtration, and the organic filtrate was washed with brine (2x100 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The clear organic layers were then concentrated *in vacuo* and purified by flash column chromatography (SiO<sub>2</sub>, 50% EtOAc/hexanes) to give **6** (2.62 g, 88%) as an off-white viscous oil. This material was stored under benzene at -78 °C to prevent decomposition, which occurred readily at room temperature. Analytical data for **6**: IR (film) 3000, 2938, 2835, 1737, 1599, 1513, 1453, 1283, 1261, 1230, 1201, 1165, 1143, 1068, 1025, 957, 939, 835, 794, 767 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 9.85 (s, 1H), 6.77 (d, *J* = 8.8 Hz, 1H), 6.59 (d, *J* = 2.8 Hz, 1H), 6.33 (dd, *J* = 8.6, 2.9 Hz, 1H), 4.54 (s, 2H), 3.87 (s, 3H), 3.84 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 199.5, 152.2, 150.1, 144.4, 111.6, 103.7, 101.1, 73.3, 56.4, 55.9; LRMS (ESI): Mass calcd for C<sub>10</sub>H<sub>12</sub>O<sub>4</sub> [M+H]<sup>+</sup>, 197. Found 197.

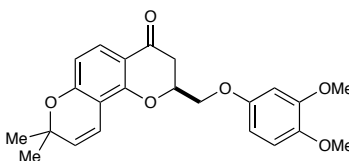
<sup>7</sup> Phillips, E. M.; Wadamoto, M.; Roth, H. S.; Ott, A. W.; Scheidt, K. A. *Org. Lett.* **2009**, *11*, 105-108.

<sup>8</sup> Speranza, G.; Mueller, B.; Orlandi, M.; Morelli, C. F.; Manitto, P.; Schink, B. *Helv. Chim. Acta* **2003**, *86*, 2629-2636.

### Synthesis of Enantioenriched Chromanone **3** and (-)-Deguelin

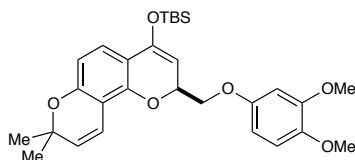


**4,4'-(2-((3,4-dimethoxyphenoxy)ethane-1,1-diyl)dimorpholine (16):** Compound **16** was synthesized according to the procedure used in the synthesis of the abyssinone natural products.<sup>5</sup> To a flame-dried 25 mL RBF was added the starting aldehyde **6** (2.55 mmol, 500 mg) and benzene (5.1 mL). The flask was purged with N<sub>2</sub> for 5 minutes, then morpholine (5.10 mmol, 444 μL) was added via a syringe. The reaction was then equipped with a Dean-Stark trap and a reflux condenser and was heated to 110 °C. After stirring at that temperature for 1 h, the reaction was checked by <sup>1</sup>H NMR, which demonstrated that the aldehyde had been consumed. The reaction was then cooled to 23 °C and was concentrated *in vacuo* to give a light yellow oil which was dried on the high vacuum and then stored at -20 °C. 832 mg recovered, 93% yield. No analytical data was collected for this compound since it could never be isolated from the enamine contaminants that were also formed during the course of the reaction.

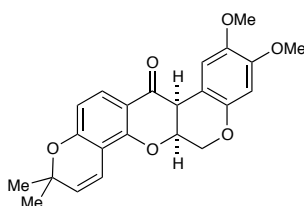


**(-)-2-((3,4-dimethoxyphenoxy)methyl)-8,8-dimethyl-2,3-dihydropyrano[2,3-f]chromen-4(8H)-one ((-)-3):** To a flame-dried 25 mL RBF was added the starting *t*-butyl beta-ketoester **13** (0.499 mmol, 159 mg), the bis-morpholine aminal **16** (0.999 mmol, 352 mg) and the Hiemstra catalyst **18** (0.10 mmol, 67 mg). The system was purged with N<sub>2</sub>, then 5 mL of dry toluene was added. After 5 minutes, acetic acid (1.998 mmol, 114 μL) was added via a Hamilton syringe to the bright yellow reaction, and it was stirred at 23 °C for 3 days. TLC in 30% EtOAc/hexanes demonstrated that the reaction had gone mostly to completion, with a slight amount of beta-ketoester **13** still left in the reaction. The reaction was diluted with EtOAc (40 mL), then was washed with brine (25 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. The bright yellow organic layers were then concentrated to give a dark orange foamy solid (248 mg) that was taken onto the next step without further purification. The unpurified material was added to a 25 mL RBF, then *para*-toluenesulfonic acid (0.250 mmol, 48 mg) and 5 mL of dry toluene were added. The reaction was purged with N<sub>2</sub>, then was equipped with a reflux condenser and heated to 80 °C overnight. After 16 h, TLC in 30% acetone/hexanes demonstrated that the product had formed, so the reaction was cooled to 23 °C and was diluted with EtOAc (10 mL). The organic material was washed with brine (2x10 mL), then was dried over Na<sub>2</sub>SO<sub>4</sub>. Purified by passage through a short silica plug with 1:1 hexanes/EtOAc as the eluent to give (-)-**3** (90.1 mg, 46%, 87:13 er) as a yellow oil. Analytical data for **3**: IR (film) 1682, 1638, 1596, 1578, 1512, 1442, 1393, 1377, 1348, 1279, 1229, 1201, 1163, 1112, 1067, 1026, 820, 681, 668 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.72 (d, *J* = 8.7 Hz, 1H), 6.79 (d, *J* = 8.8 Hz, 1H), 6.67 – 6.59 (m, 1H), 6.58 (d, *J* = 2.8 Hz, 1H), 6.48 (dd, *J* = 8.7, 0.7 Hz, 1H), 6.45 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.58 (d, *J* = 10.0 Hz, 1H), 4.80 (dtd, *J* = 12.6, 4.6, 3.2 Hz, 1H), 4.24 (d, *J* = 4.5 Hz, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 2.96 (dd, *J* = 16.8, 12.9 Hz,

1H), 2.73 (dd,  $J = 16.9, 3.0$  Hz, 1H), 1.47 (s, 3H), 1.43 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  190.3, 159.7, 157.2, 153.0, 149.9, 144.0, 128.9, 127.9, 115.8, 114.7, 111.6, 111.2, 109.4, 103.9, 101.2, 76.5, 69.9, 56.4, 55.9, 39.2, 28.4, 28.1; LRMS (ESI): Mass calcd for  $\text{C}_{23}\text{H}_{24}\text{O}_6$   $[\text{M}+\text{H}]^+$ , 397. Found 397. Optical rotation was measured and found to be  $[\alpha]_{\text{D}}^{20} = -7.6$  ( $c = 0.38$ ,  $\text{CHCl}_3$ ).



**(-)-tert-butyl((2-((3,4-dimethoxyphenoxy)methyl)-8,8-dimethyl-2,8-dihydropyrano[2,3-f]chromen-4-yl)oxy)dimethylsilane ((-)-**20**):** Compound **20** was synthesized according to a modified procedure by Dratch.<sup>9</sup> To a flame-dried 25 mL RBF was added the starting chromanone **3** (0.227 mmol, 90.1 mg) and dry MeCN (2.3 mL). The system was purged with  $\text{N}_2$ , then TEA (0.545 mmol, 76  $\mu\text{L}$ ) was added. The light yellow/orange reaction turned a darker orange upon addition of the base. After 5 minutes of stirring at room temperature, TBSCl (0.545 mmol, 82 mg) and NaI (0.545 mmol, 82 mg) were added and the system was purged again with  $\text{N}_2$ . The reaction was then allowed to stir for 16 h at 23  $^\circ\text{C}$ . TLC in 3:2 hexanes/EtOAc demonstrated that the reaction had gone to completion, so it was quenched with satd.  $\text{NaHCO}_3$  (10 mL) and was then extracted 2x50 mL with hexanes. The organic layers were combined and dried over  $\text{Na}_2\text{SO}_4$ , then were concentrated *in vacuo* to give a dark orange oil. Purified by flash column chromatography ( $\text{SiO}_2$ , 30% EtOAc/hexanes) to give **20** (68 mg, 58%) as a light orange, viscous oil. Analytical data for **20**: IR (film) 2955, 2931, 2858, 1646, 1602, 1512, 1465, 1377, 1359, 1279, 1261, 1229, 1199, 1164, 1145, 1113, 1050, 1029, 950, 902, 833, 784, 733  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.13 (d,  $J = 8.3$  Hz, 1H), 6.75 (d,  $J = 8.8$  Hz, 1H), 6.59 (dd,  $J = 10.0, 0.8$  Hz, 1H), 6.54 (d,  $J = 2.7$  Hz, 1H), 6.39 (dd,  $J = 8.7, 2.8$  Hz, 1H), 6.36 (dd,  $J = 8.4, 0.8$  Hz, 1H), 5.54 (d,  $J = 10.0$  Hz, 1H), 5.27 (dt,  $J = 7.4, 3.9$  Hz, 1H), 4.72 (d,  $J = 3.9$  Hz, 1H), 4.15 (dd,  $J = 10.3, 7.2$  Hz, 1H), 3.94 (dd,  $J = 10.3, 3.9$  Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.00 (s, 9H), 0.22 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  154.4, 153.4, 149.84, 149.77, 147.4, 143.7, 129.1, 122.6, 116.6, 114.3, 111.6, 109.9, 108.7, 104.4, 101.2, 95.1, 76.2, 75.1, 70.8, 56.4, 55.9, 28.1, 27.8, 25.8, 18.3, -4.5; LRMS (ESI): Mass calcd for  $\text{C}_{29}\text{H}_{38}\text{O}_6\text{Si}$   $[\text{M}+\text{H}]^+$ , 511. Found 511.



**(-)-degeulin ((-)-**1**):** Compound **1** was made by an oxidative alpha-arylation protocol adapted from Snider.<sup>10</sup> To a flame-dried 10 mL RBF was added  $\text{Cu}(\text{OTf})_2$  (from glovebox, 0.265 mmol, 96 mg) and  $\text{Cu}_2\text{O}$  (0.463 mmol, 66 mg). The flask was purged with  $\text{N}_2$ , then dry MeCN (1 mL) was added, followed by DTBP (0.529 mmol, 119  $\mu\text{L}$ ). The reaction was then cooled to  $-30$   $^\circ\text{C}$  in an MeCN/dry ice bath. In a separate teardrop flask was added the silyl enol ether starting material **20** (0.132 mmol, 68 mg), which was dissolved in 1.6 mL of dry MeCN and then cooled

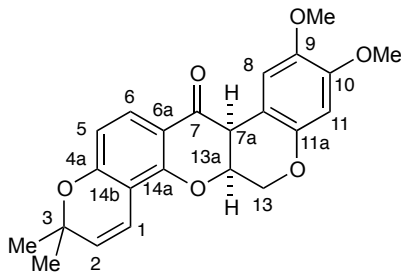
<sup>9</sup> Dratch, S.; Charnikhova, T.; Saraber, F. C. E.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2003**, *59*, 4287-4295.

<sup>10</sup> Snider, B. B.; Kwon, T. *J. Org. Chem.* **1992**, *57*, 2399-2410.



to  $-30\text{ }^{\circ}\text{C}$ . The SEE material **20** was cannulated dropwise into the vessel containing the  $\text{Cu}(\text{OTf})_2/\text{Cu}_2\text{O}$  mixture, and TLC in 30% EtOAc/hexanes demonstrated that the reaction was complete immediately after the completion of the cannulation. The reaction was quenched with water (5 mL), then was extracted 2x25 mL with EtOAc, and the organic layers were dried over  $\text{Na}_2\text{SO}_4$ . Purified by flash column chromatography ( $\text{SiO}_2$ , 20% hexanes/EtOAc) to give (-)-**IV-1** (13 mg, 25%, 82:18 er) as a light yellow film. Analytical data for (-)-**1**: IR (film) 2966, 2929, 2857, 1674, 1637, 1597, 1578, 1513, 1443, 1393, 1378, 1346, 1276, 1234, 1214, 1199, 1166, 1112, 1095, 1078, 1061, 1011, 911, 893, 818, 771, 704, 679, 668, 656, 609  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.74 (d,  $J = 8.7$  Hz, 1H), 6.78 (s, 1H), 6.64 (d,  $J = 10.1$  Hz, 1H), 6.48 – 6.35 (m, 2H), 5.55 (d,  $J = 10.1$  Hz, 1H), 4.92 (tt,  $J = 3.2, 1.3$  Hz, 1H), 4.64 (dd,  $J = 12.0, 3.1$  Hz, 1H), 4.19 (d,  $J = 12.1$  Hz, 1H), 3.84 (d,  $J = 4.1$  Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  189.3, 160.1, 157.0, 149.4, 147.4, 143.8, 128.70, 128.58, 115.8, 112.8, 111.5, 110.3, 109.2, 104.7, 100.9, 77.7, 72.4, 66.3, 56.3, 55.9, 44.4, 28.5, 28.2; LRMS (ESI): Mass calcd for  $\text{C}_{23}\text{H}_{22}\text{O}_6$   $[\text{M}+\text{H}]^+$ , 395. Found 395. Optical rotation was measured and found to be  $[\alpha]_{\text{D}}^{20} = -9.6$  ( $c = 0.98$ ,  $\text{CHCl}_3$ ).

## Comparison of NMR Shifts for Isolated and Synthetic (-)-Deguelin



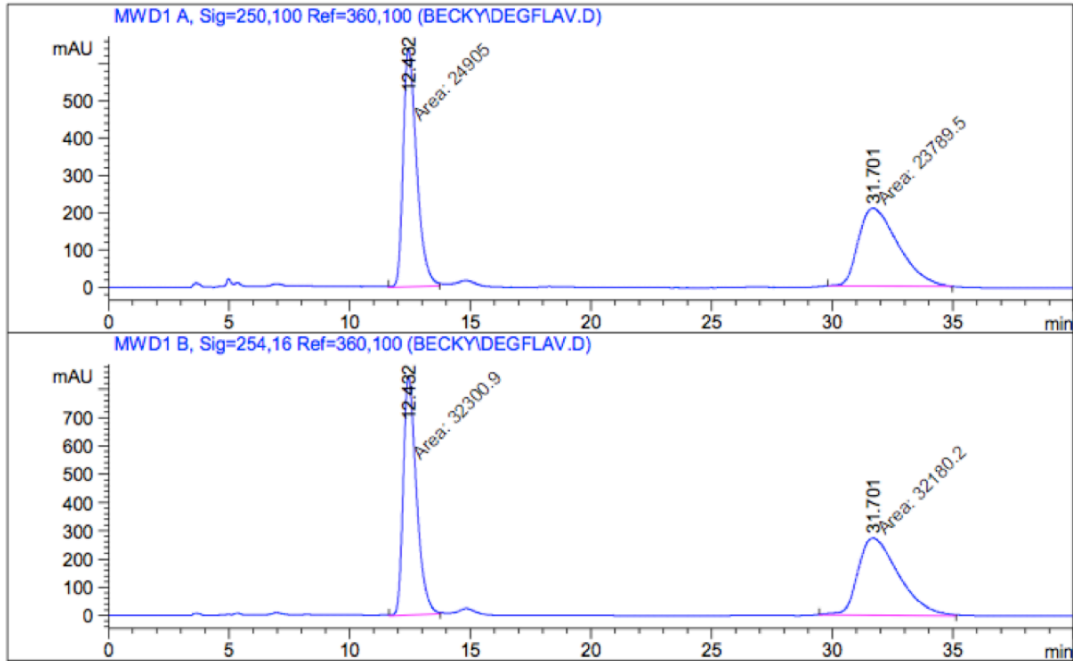
position	<sup>1</sup> H-NMR (CDCl <sub>3</sub> ), <i>J</i> in Hz		<sup>13</sup> C-NMR (CDCl <sub>3</sub> ), <i>J</i> in Hz	
	isolated <sup>a</sup>	synthetic	isolated <sup>a</sup>	synthetic
1	6.64 (d, 9.8)	6.64 (d, 10.1)	115.3	115.8
2	5.55 (d, 9.8)	5.55 (d, 10.1)	128.1	128.6
3	--	--	77.3	77.7
3-Me	1.36, 1.45	1.38, 1.45	27.7, 28.1	28.2, 28.5
4a	--	--	159.7	160.1
5	6.45 (d, 8.6)	6.48-6.35 (m)	111.1	111.5
6	7.51 (d, 8.6)	7.74 (d, 8.7)	128.3	128.7
6a	--	--	112.4	112.8
7	--	--	188.9	189.3
7a	3.83 (d, 4.0)	3.84 (d, 4.1)	43.9	44.4
7b	--	--	104.4	104.7
8	6.79	6.78	110.0	110.3
9	--	--	143.4	143.8
9-OMe	3.77	3.80	55.4	55.9
10	--	--	149.0	149.4
10-OMe	3.74	3.77	55.9	56.3
11	6.45	6.48-6.35 (m)	100.5	100.9
11a	--	--	147.0	147.4
13 <sub>α</sub>	4.82 (dd, 12.0, 3.1)	4.64 (dd, 12.0, 3.1)	65.9	66.3
13 <sub>β</sub>	4.17 (d, 12.0)	4.19 (d, 12.0)	--	--
13a	4.92 (br s)	4.92 (tt, 3.2, 1.3)	72.0	72.4
14a	--	--	156.5	157.0
14b	--	--	108.7	109.2

<sup>a</sup>L. Luyengi, I. S. Lee, W. Mar, H. H. S. Fong, J. M. Pezzuto, A. D. Kinghorn, *Phytochemistry*, 1994, **36**, 1523-1526.

## HPLC Traces for Chromanone 3 and (-)-Deguelin

### HPLC Trace for (±)-3

Column conditions: Chiralcel OD-H, 1 ml/min, 1:1 hexanes:IPA



Signal 1: MWD1 A, Sig=250,100 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.432	MM	0.6482	2.49050e4	640.34094	51.1454
2	31.701	MM	1.9061	2.37895e4	208.01096	48.8546

Totals : 4.86944e4 848.35190

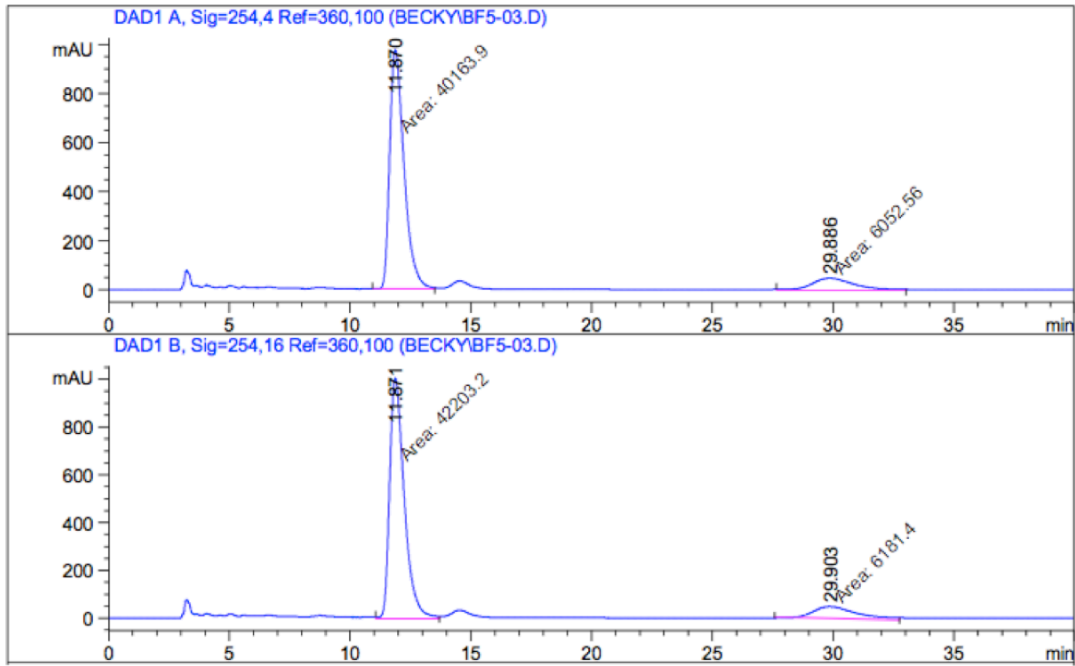
Signal 2: MWD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.432	MM	0.6367	3.23009e4	845.47882	50.0936
2	31.701	MM	1.9633	3.21802e4	273.17432	49.9064

Totals : 6.44811e4 1118.65314

**HPLC Trace for (-)-3**

Column conditions: Chiralcel OD-H, 1 ml/min, 1:1 hexanes:IPA



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.870	MM	0.6866	4.01639e4	974.96948	86.9039
2	29.886	MM	2.0635	6052.56152	48.88594	13.0961

Totals : 4.62164e4 1023.85542

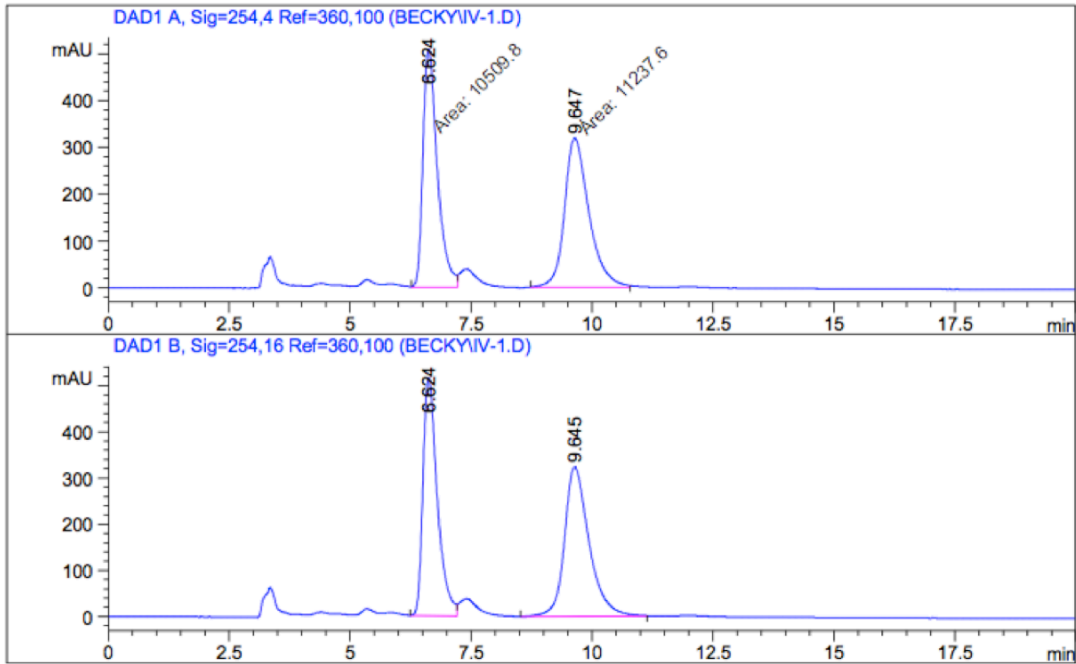
Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.871	MM	0.6986	4.22032e4	1006.81433	87.2245
2	29.903	MM	2.0832	6181.39893	49.45440	12.7755

Totals : 4.83846e4 1056.26873

**HPLC Trace for (±)-Deguelin ((±)-1)**

Column conditions: Chiralcel OD-H, 1 ml/min, 1:1 hexanes:IPA



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.624	MM	0.3442	1.05098e4	508.86926	48.3265
2	9.647	MM	0.5876	1.12376e4	318.77029	51.6735

Totals : 2.17474e4 827.63956

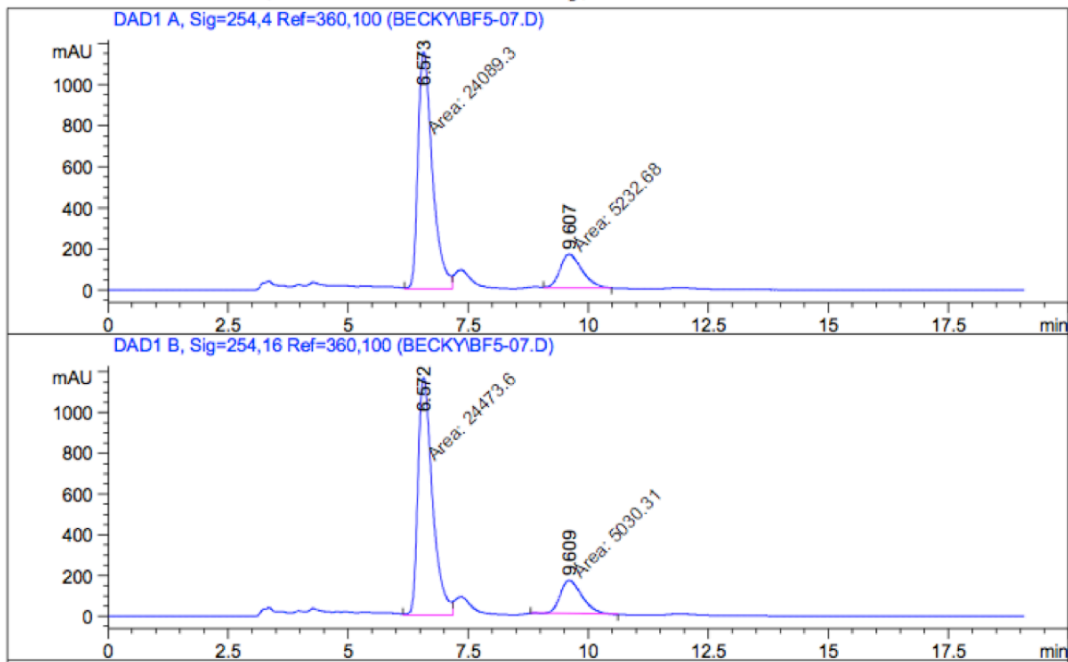
Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.624	VV	0.3096	1.05808e4	515.26740	48.0715
2	9.645	VB	0.5270	1.14297e4	322.90799	51.9285

Totals : 2.20105e4 838.17538

**HPLC Trace for (-)-Deguelin ((-)-1)**

Column conditions: Chiralcel OD-H, 1 ml/min, 1:1 hexanes:IPA



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.573	MM	0.3475	2.40893e4	1155.23438	82.1544
2	9.607	MM	0.5342	5232.68408	163.24812	17.8456

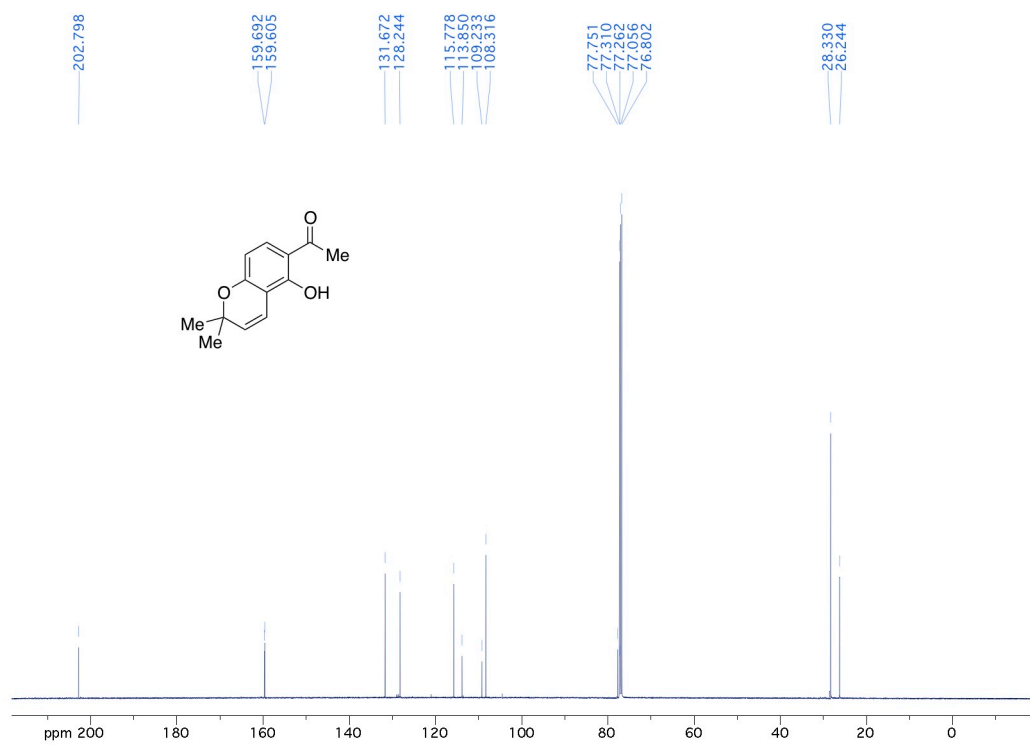
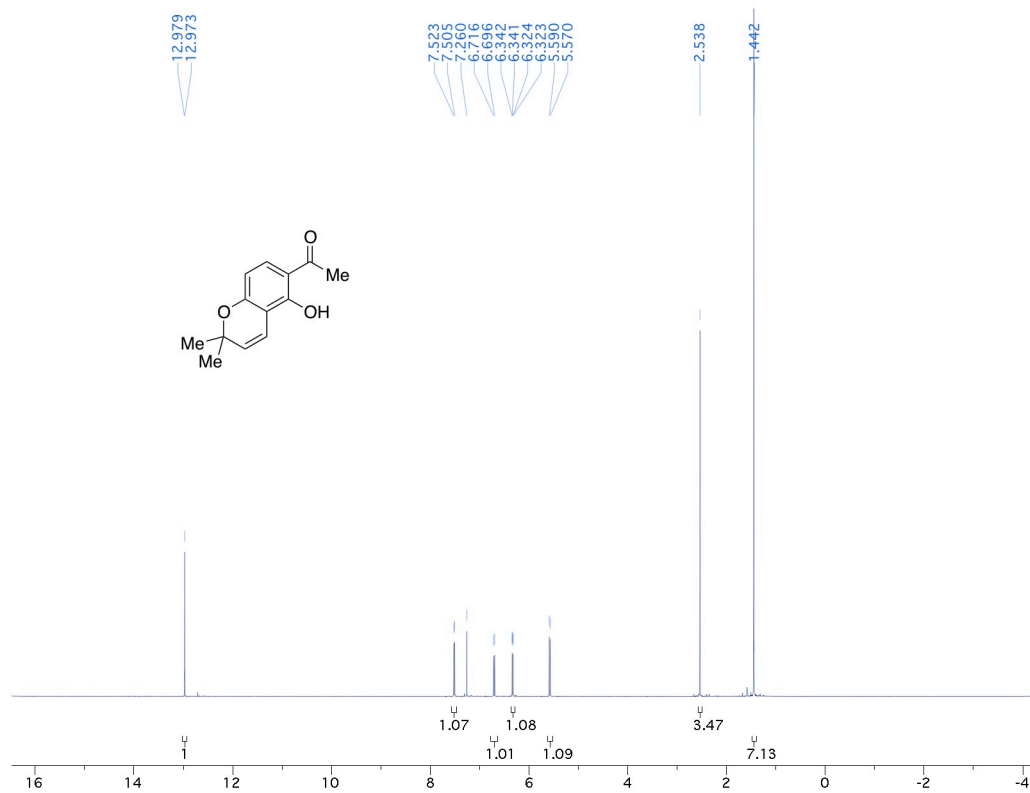
Totals : 2.93220e4 1318.48250

Signal 2: DAD1 B, Sig=254,16 Ref=360,100

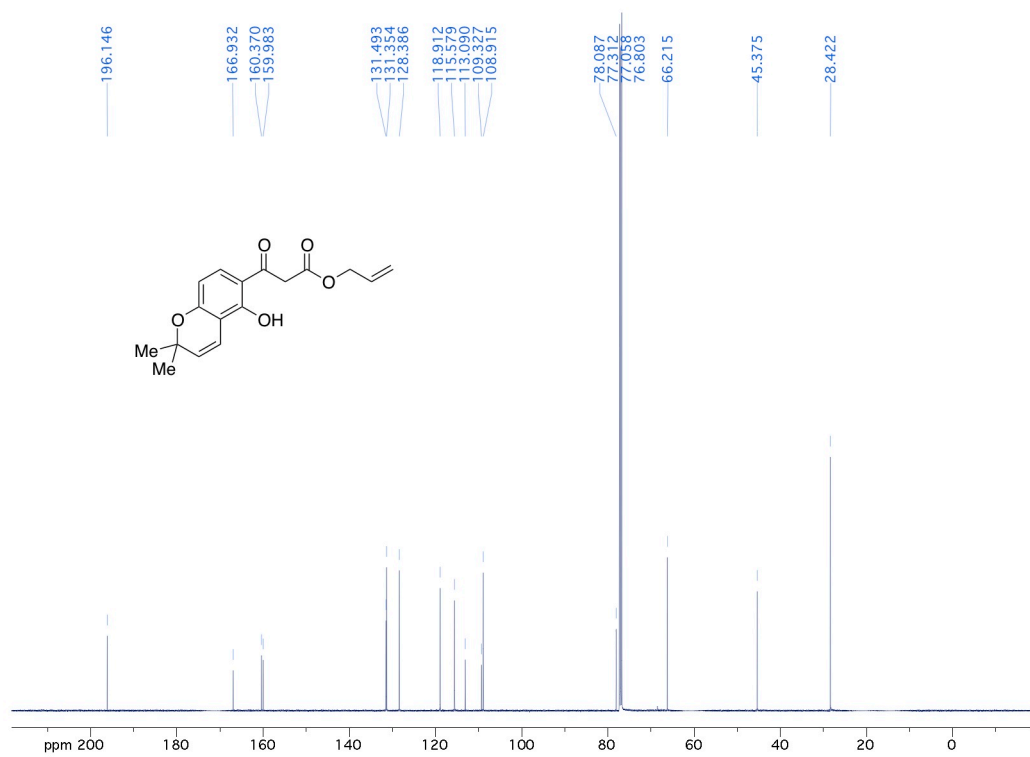
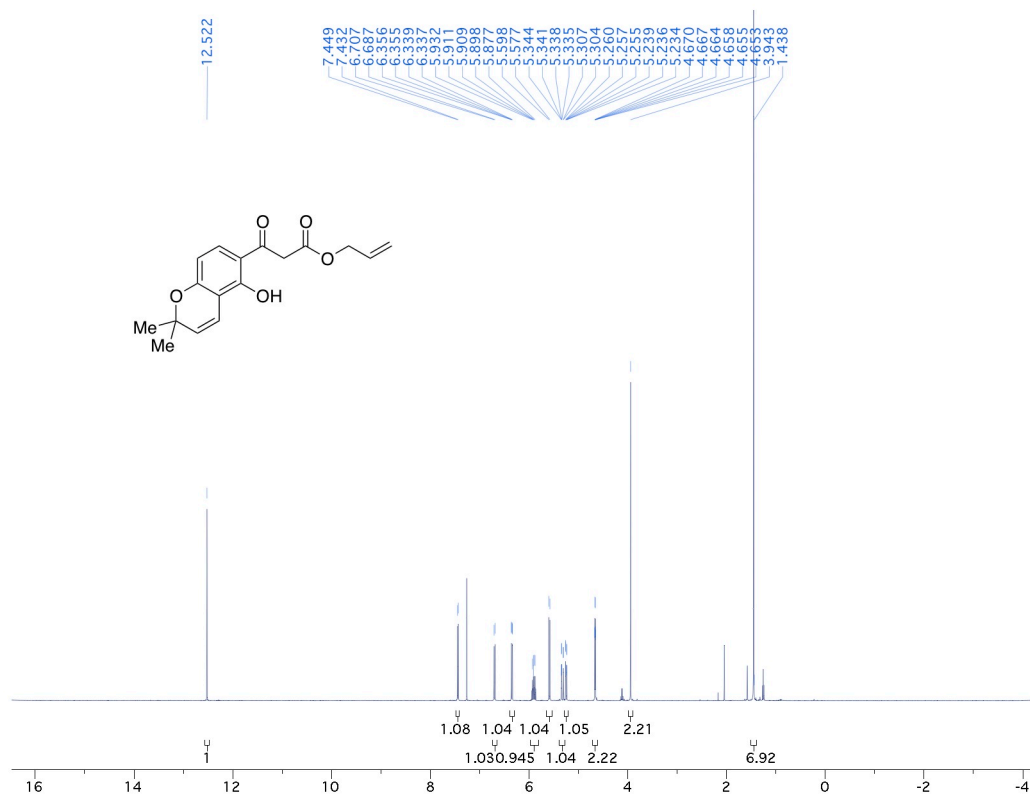
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.572	MM	0.3495	2.44736e4	1167.06934	82.9504
2	9.609	MM	0.5179	5030.31055	161.86787	17.0496

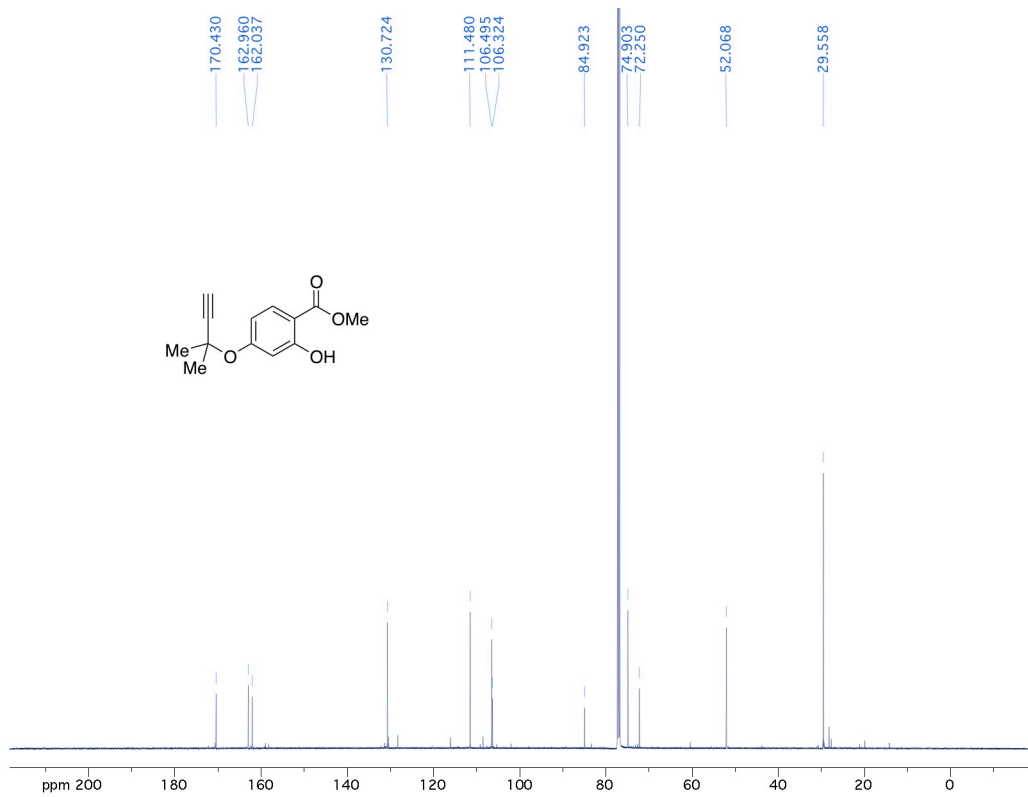
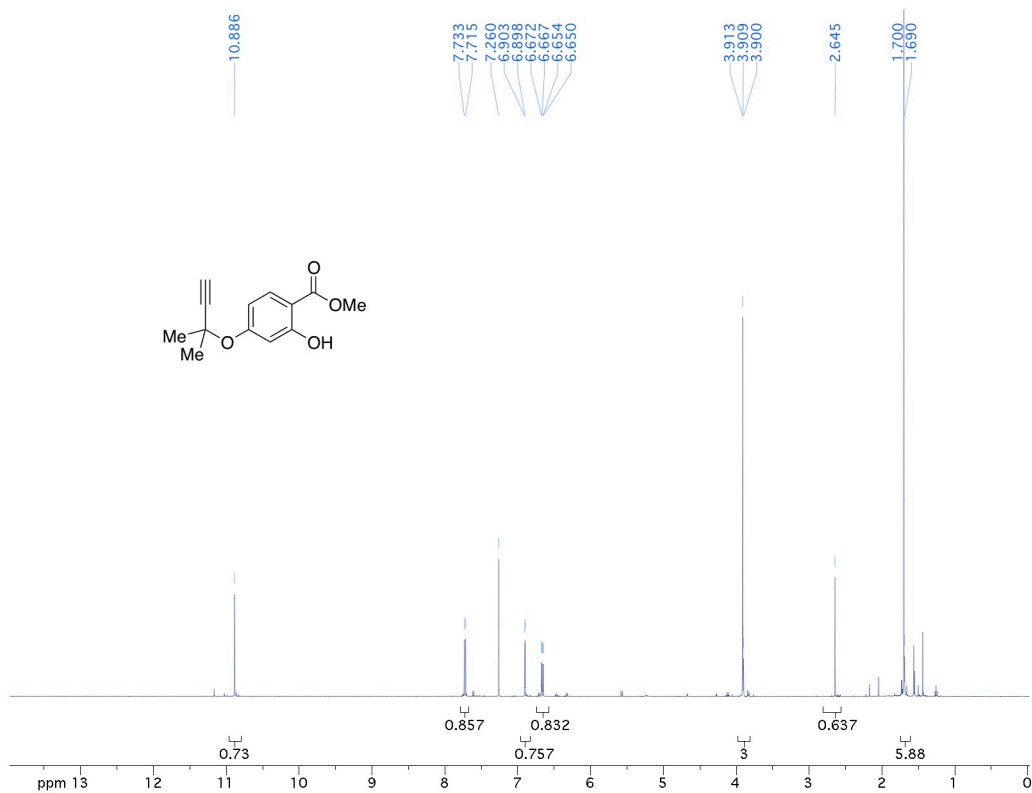
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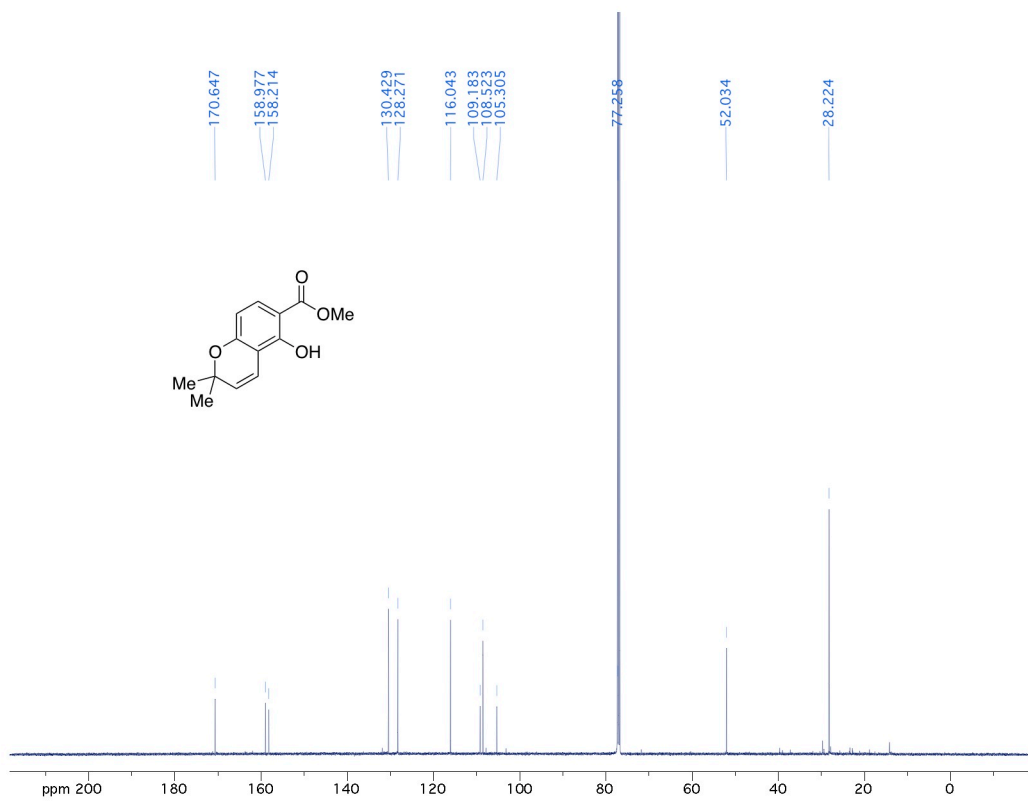
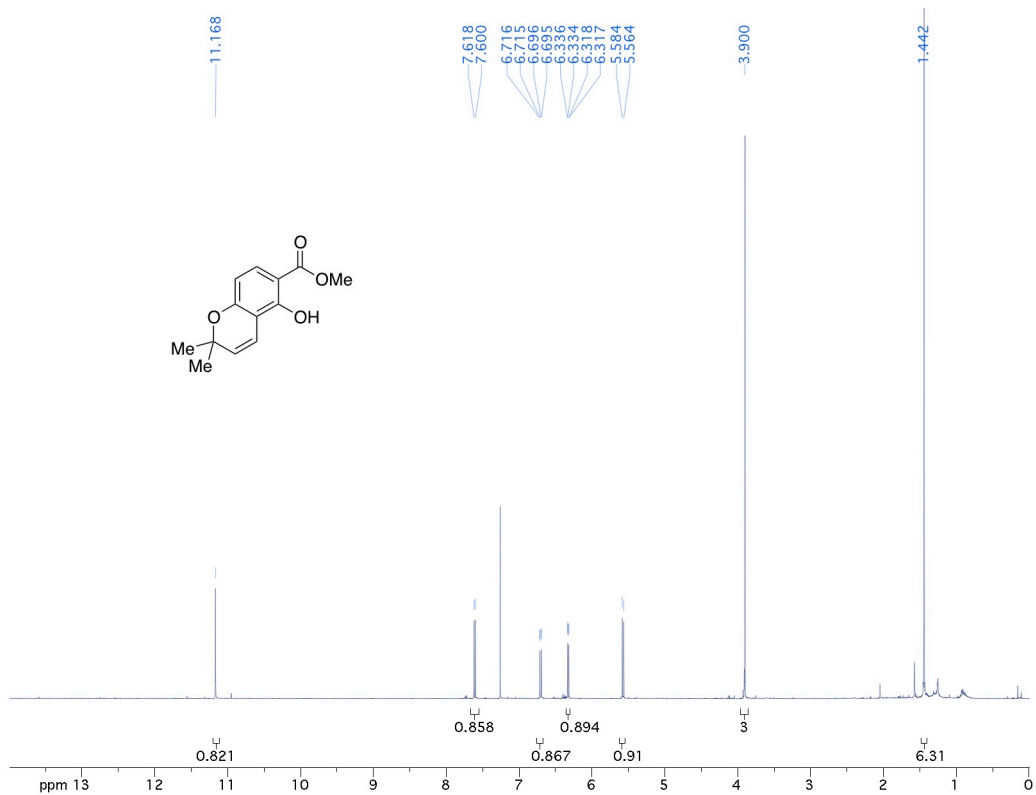


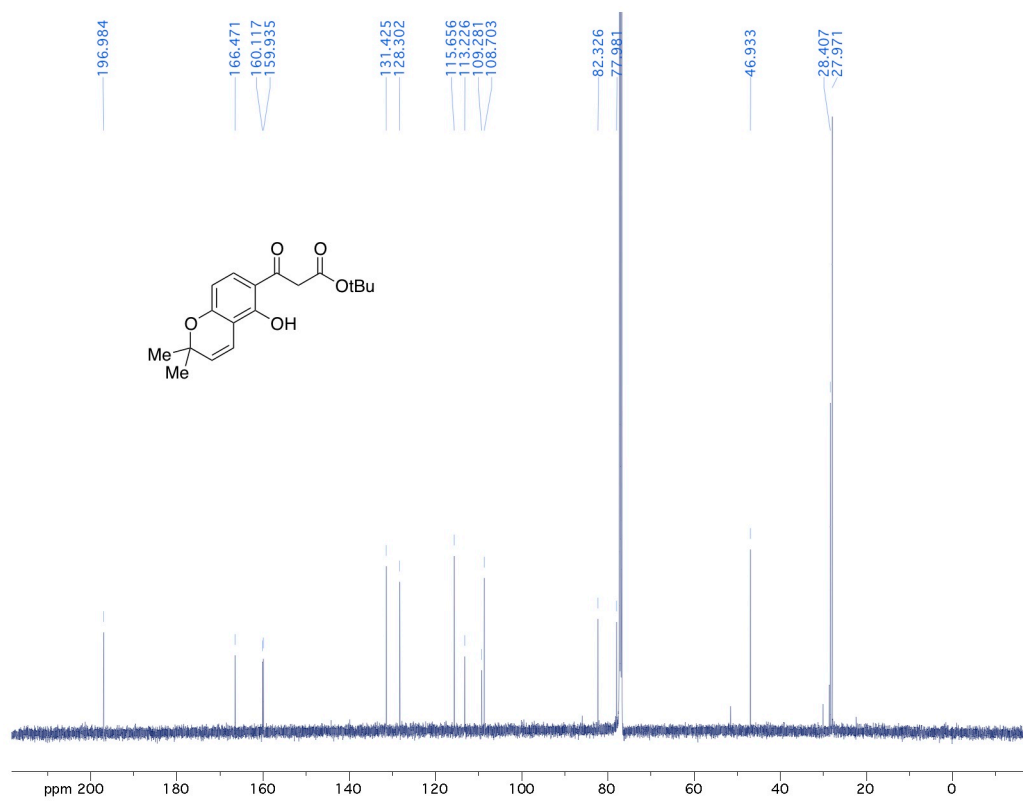
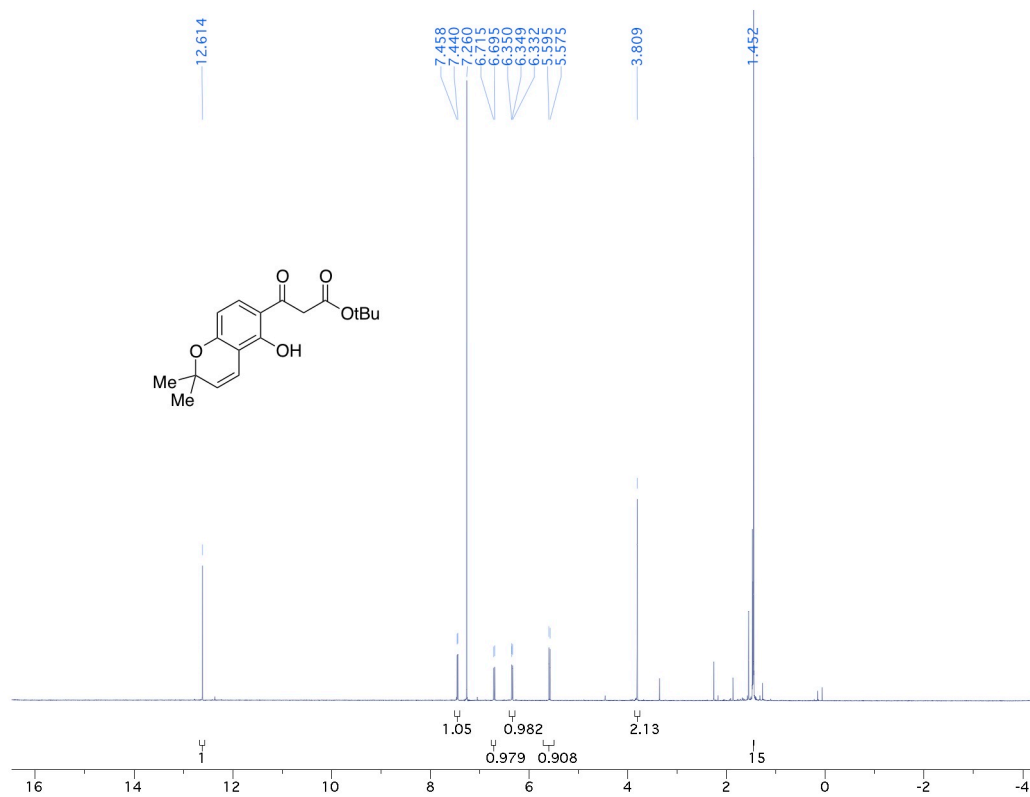


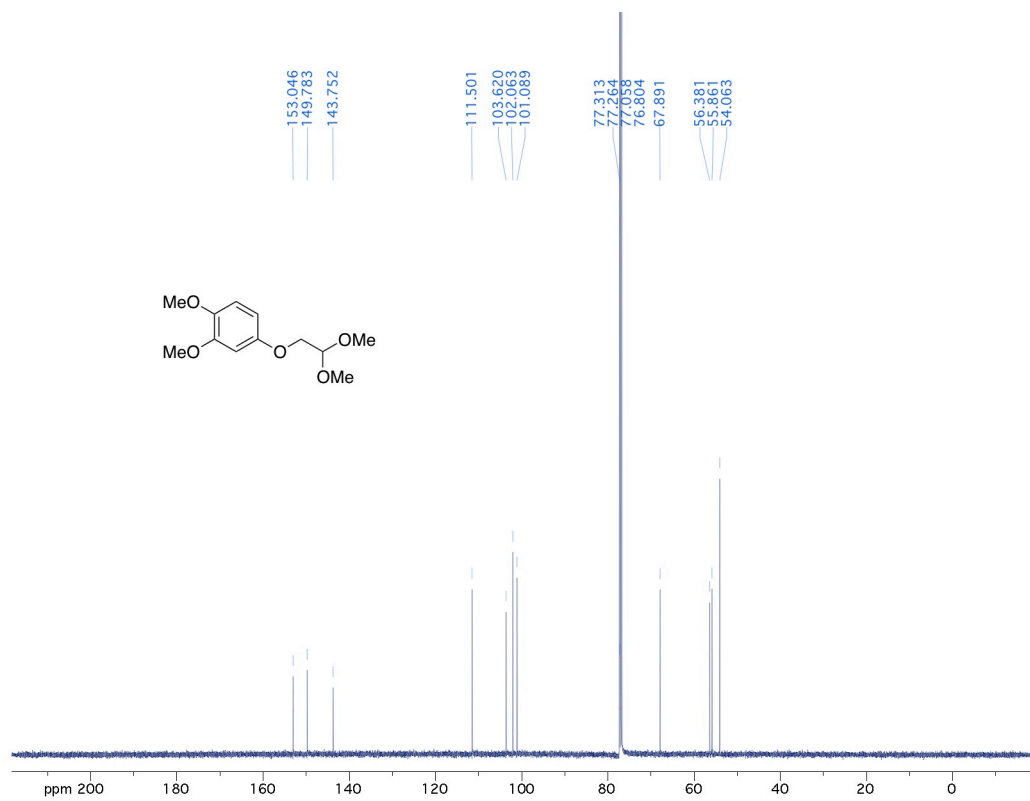
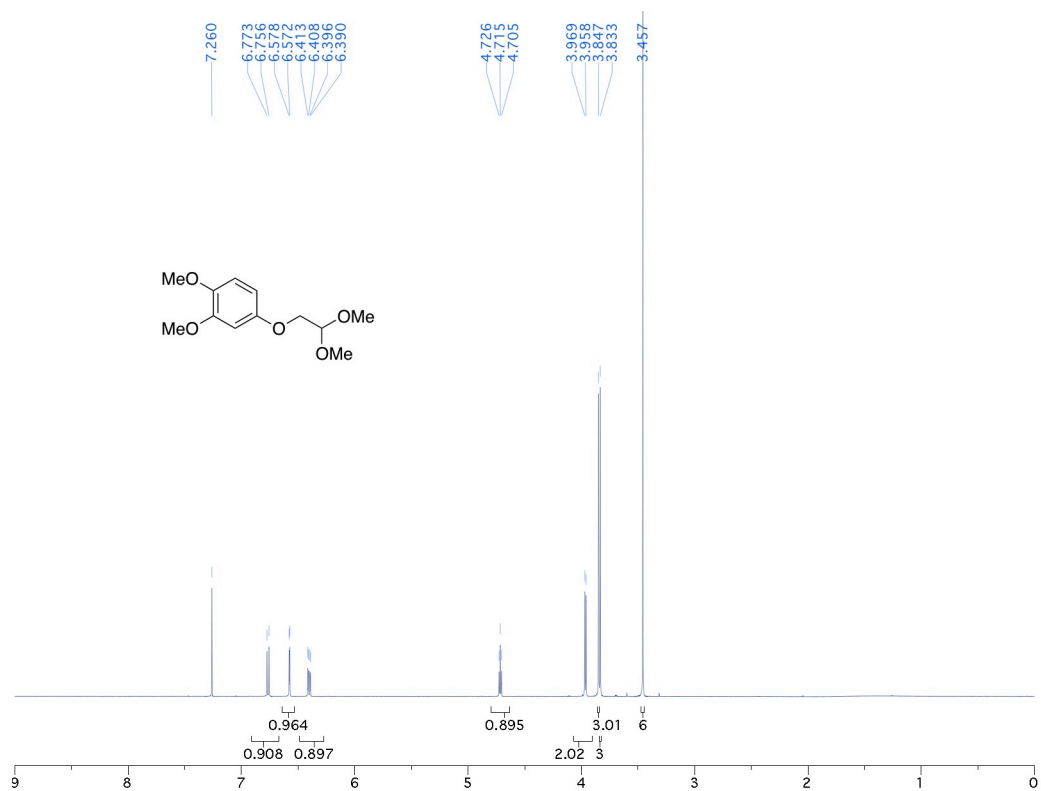


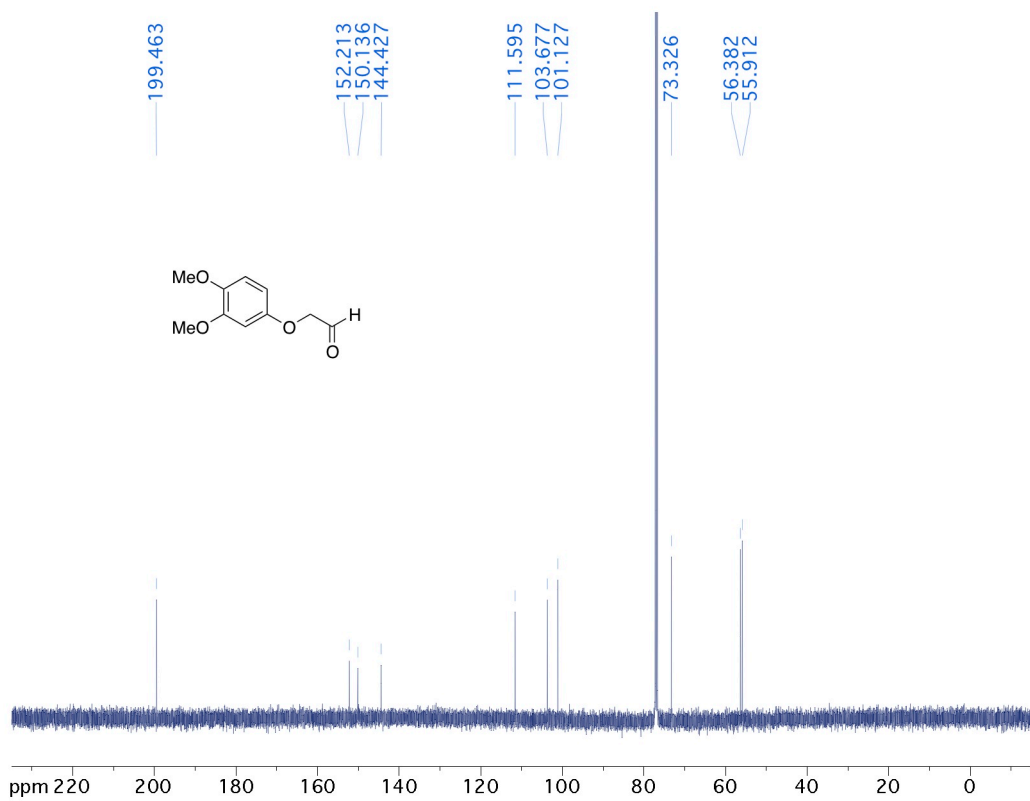
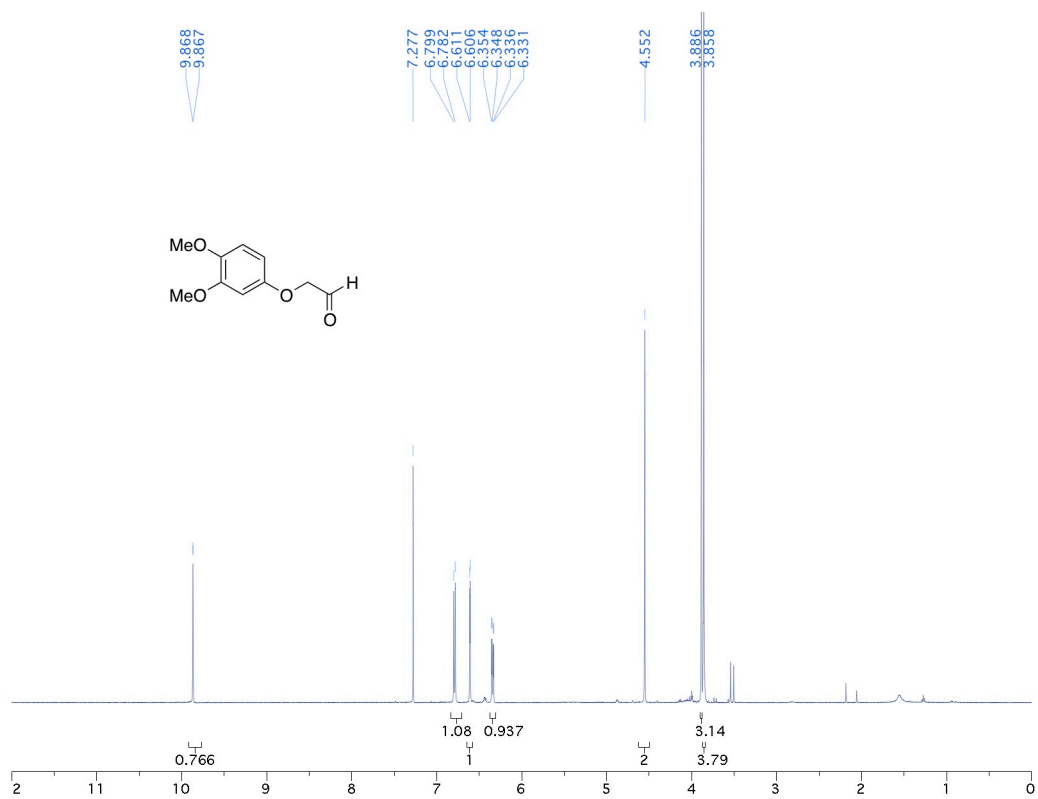


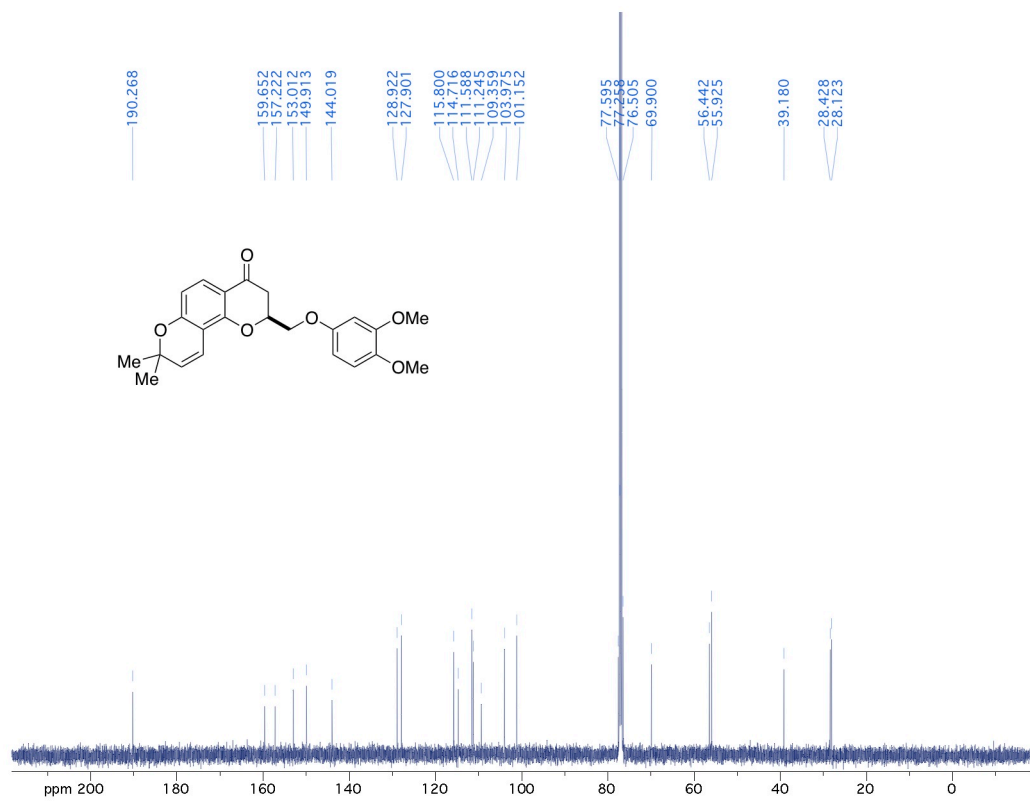
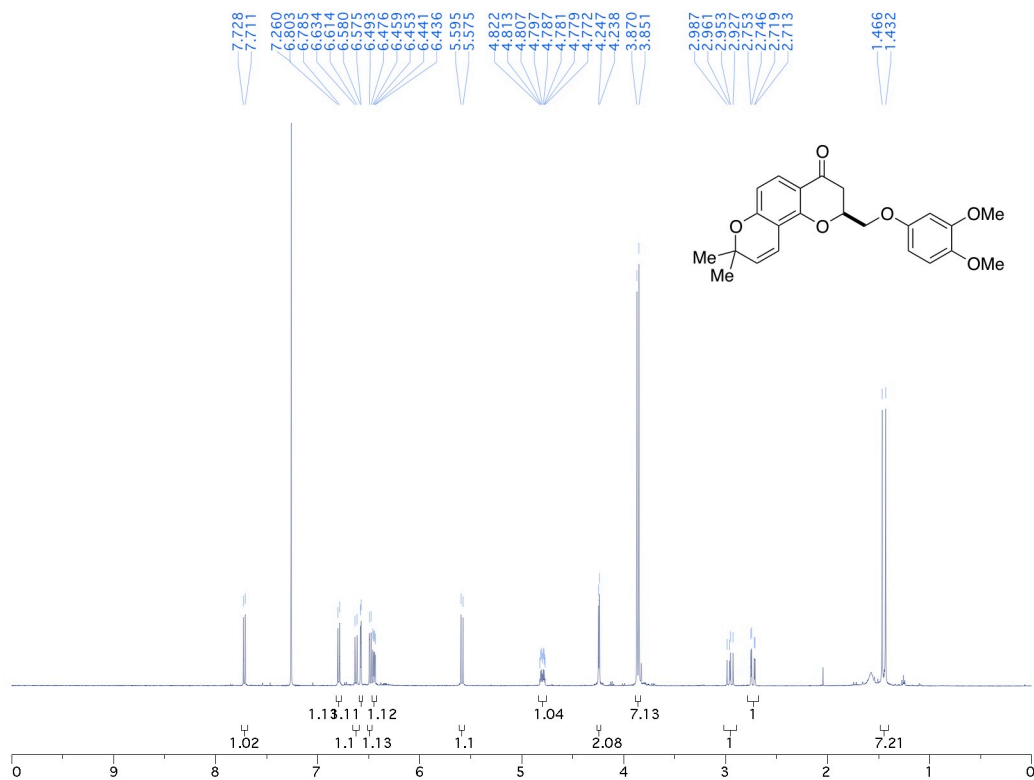






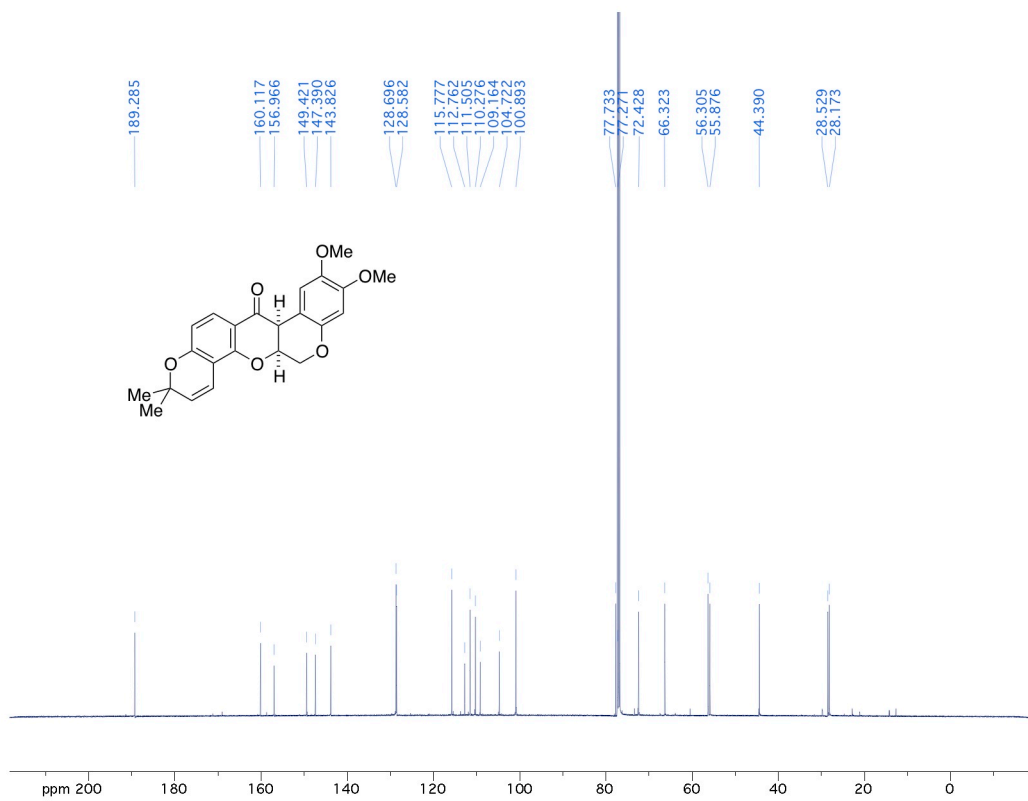
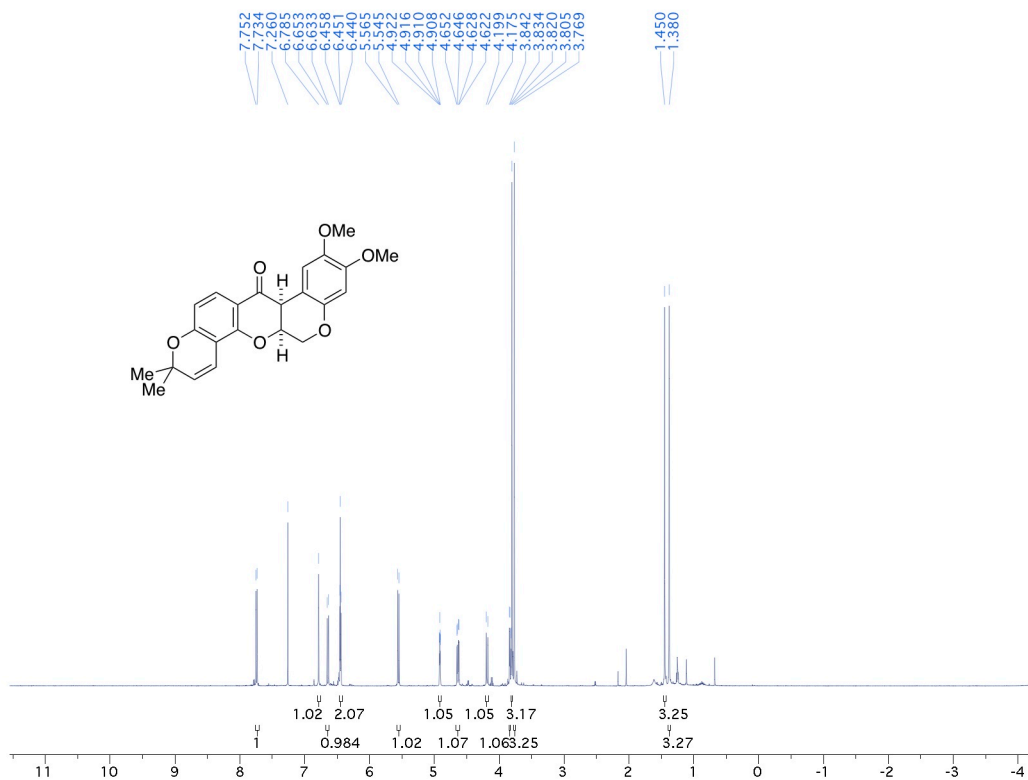












## Procedure for Cell Toxicity Screen

**Cell culture.** All cell lines used for screening were grown in Roswell Park Memorial Institute (RPMI) 1640 media, supplemented with 10% FBS and 2 mM glutamine (all supplied by GIBCO, Life Technologies, Grand Island, NY). Cells were maintained at 37 °C in a humidified atmosphere of 5% carbon dioxide, with media changes occurring three times per week. Cells were also maintained in the exponential growth phase, and routinely certified as mycoplasma free.

**48-hour cell toxicity/IC<sub>50</sub> assays.** 48-hour growth inhibition assays were performed in Greiner Bio-One black 96 well plates (Greiner Bio-One, Monroe, NC). First, each cell line was plated at the given density shown below in 90 µL of cell culture media (RPMI supplemented with 5% FBS and 50 µg/mL gentamycin). The cells were then allowed to attach for 24 hours (for the adherent cell lines). After the overnight incubation, the three test compounds, (±)-deguelin, (-)-deguelin and (+)-deguelin were suspended in culture media at the range of desired concentrations (10µL of 10<sup>-6</sup>-10<sup>2</sup> µM) and added to the wells to give a final volume of 100 µL per well. All of the test compounds were suspended in DMSO and stored at -20 °C prior to use. The final DMSO concentration did not exceed 0.5% in any experiment. The treated cells were then incubated for an additional 48 hours, then the plates were equilibrated for 30 minutes at room temperature. To each well was added 100µL of Cell Titer Glo reagent (Promega, Verona, WI) to a total volume of 200 µL. The plates were shaken for 2 minutes on an orbital shaker and then allowed to stand for 10 minutes to stabilize the luminescence signal. Plates were read on Biotek Synergy H1 reader (Biotek Instruments, Winooski, VT) on luminescence program. Each treatment condition was performed in triplicate, and the average results were used for analysis. Analysis was completed using Graph Pad Prism 5 (Graph Pad Prism 5, La Jolla, CA).

Plating densities:

PC-3 – 7.5x10<sup>3</sup> cells/mL

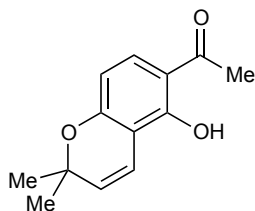
MCF-7 – 1.5x10<sup>4</sup> cells/mL

HepG2 – 2.0x10<sup>4</sup> cells/mL

Jurkat – 4.0x10<sup>4</sup> cells/mL

**X-ray Crystallographic Data**

The structure of **9** was determined by the X-ray diffraction.



X-ray diffraction was performed at  $-120\text{ }^{\circ}\text{C}$  and raw frame data were processed using Bruker SAINT. Molecular structure was solved using direct methods and refined by F2 by full-matrix least-squares techniques. The GOF = 1.06 for 201 variables refined to  $R1 = 0.036$  for 2664 reflections with  $I > 2\sigma(I)$ . Further information is contained in the CIF file. Data was deposited to the CCDC (number 924171).

