Palladium-catalyzed aryl halide carbonylation/intramolecular *O*-enolate acylation: Efficient isocoumarin synthesis, including the synthesis of thunberginol A

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Electronic Supporting Information

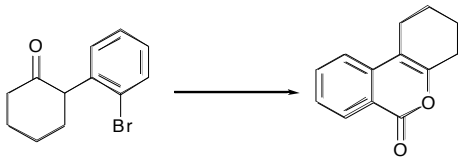
General considerations

Reactions were conducted with continuous magnetic stirring under an inert nitrogen or argon atmosphere with anhydrous solvents unless otherwise stated. Nitrogen and argon were passed through a Drierite® filled drying tube before use. Glassware was oven-dried at >200 °C and allowed to cool to room temperature under a positive nitrogen pressure or vacuum. Reagents were purchased from Sigma-Aldrich Chemical Co. Ltd., Acros Organics Ltd, Avocado, Fluorochem or Lancaster Synthesis Ltd. and used as supplied. Although commercially available, 2-Bromo-3-iodo-phenol was prepared by a known procedure by Sanz *et al*.[1] Toluene, tetrahydrofuran and dichloromethane were collected fresh from the in house solvent purification system having been passed through anhydrous alumina columns. Dry dimethylformamide was purchased from Romil and stored as received over 4Å molecular sieves. Dimethoxyethane was distilled prior to use and stored over 4Å molecular sieves. Flash column chromatography was carried out

using Zeochem ZEOprep hyd. 40-63 micron silica with pre-absorption of the crude product onto silica. Pressure was applied at the column head via hand bellows.

^{1}H, and ^{13}C nuclear magnetic resonance experiments were carried out using Bruker DQX-400 or AVC-500 spectrometers. Chemical shifts are reported in parts per million (ppm) from the residual solvent peak and coupling constants (*J*) in Hertz (Hz). Proton multiplicity is assigned using the following abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), septet (sep), multiplet (m), broad (br.) and apparent (ap.). Melting points were determined using a Leica Galen III hot-stage microscope and are reported uncorrected. Infrared measurements were carried out using a Bruker Tensor 27 FT-IR with internal calibration in the range 4000-600 cm^{-1}. Accurate mass measurements were carried out on a Bruker MicroTOF mass spectrometer by the internal service at the Department of Organic Chemistry, University of Oxford. Elemental analysis was performed by the service at London Metropolitan University.

General Procedure A exemplified by the preparation of 1,2,3,4-tetrahydro-benzo[c]chromen-6-one, 7



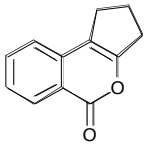
Cesium carbonate (463 mg, 1.42 mmol) was added to an oven dried Schlenk tube (30 mL) charged with Pd_2dba_3 (13.0 mg, 0.014 mmol), DPE-phos (15.3 mg, 0.028 mmol) and 2-(2-bromophenyl)cyclohexanone (120 mg, 0.474 mmol) under argon. To this anhydrous toluene (1.0 mL) was added. A balloon fitted with a glass tap attachment was filled with

argon and evacuated three times. The balloon was then filled with carbon monoxide from a lecture bottle (Aldrich) and attached to the top of the Schlenk tube. The inert atmosphere was then exchanged for carbon monoxide by briefly exposing the reaction vessel to vacuum (1-2 seconds) through the side arm of the Schlenk tube and filling the vessel with carbon monoxide through the balloon on the top. The evacuation of the atmosphere and filling with carbon monoxide was performed three times. The reaction was then left open to the balloon and stirred vigorously, heating at 110 °C for 16 hours. After this time the Schlenk tube was allowed the cool and the carbon monoxide balloon removed. The reaction mixture was then diluted with ethyl acetate (ca. 10 mL), filtered through a celite pad, washing with ethyl acetate (ca. 40 mL), and concentrated under reduced pressure. The crude material was purified *via* flash column chromatography (4:1 hexane:ethyl acetate) to yield the *isocoumarin* (86.0 mg, 91%) as a white solid: mp 110-111 °C. ν_{max} (KBr)/cm^{-1} 2935, 2868, 2842, 1724, 1652, 1603, 1488, 1454, 1368, 1324, 1305, 1236, 1186, 1063, 1028, 987, 899, 755, 689; δ_H (500 MHz; $CDCl_3$) 8.29 (1H, d, *J* 7.8, Ar-*H*), 7.72 (1H, dd, (ap. t) *J* 7.7, Ar-*H*), 7.47-7.44 (2H, m, Ar-*H*), 2.60-2.58 (4H, m, $CH_2C{=}CCH_2$), 1.87-1.85 (4H, m, 2 × CH_2); δ_C (125 MHz; $CDCl_3$) 162.7, 152.4, 138.0, 134.5, 129.7, 127.1, 121.3, 120.6, 109.3, 27.4, 22.7, 22.0, 22.0; *m/z* LRMS (ES^+) 201.4 (M+H, 50); HRMS (ES^+) 223.0734 ($[M+Na]^+$. $C_{13}H_{12}NaO_2$ requires 223.0730); Anal. Calc. for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 78.05; H, 5.95%. Data consistent with literature.[2]

One-pot procedure for the synthesis of 1,2,3,4-tetrahydro-benzo[c]chromen-6-one (7): tandem palladium-catalysed α-arylation and carbonylation

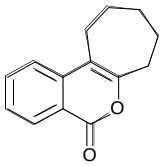
Cesium carbonate (1.152g, 3.53 mmol) was added to an oven dried Schlenk tube (30 mL) charged with Pd_2dba_3 (19.4 mg, 0.021 mmol), Xantphos (24.5 mg, 0.042 mmol) under argon. The reagents were suspended in anhydrous toluene (1.4 mL) and 1-bromo-2-iodobenzene (200 mg, 0.707 mmol, 0.091 mL) and cyclohexanone (138.8 mg, 1.419 mmol, 0.147 mL) were added under argon and the reaction was heated to 80 °C for 24 hours. After this time, a balloon filled with carbon monoxide was attached to the top of the Schlenk tube. The inert atmosphere was then exchanged for carbon monoxide by briefly exposing the reaction vessel to vacuum (1-2 seconds) through the side arm of the Schlenk tube and filling the vessel with carbon monoxide through the balloon on the top. The evacuation of the atmosphere and filling with carbon monoxide was performed three times. The reaction was then left open to the balloon and stirred vigorously, heating at 110 °C for 20 hours. After this time the Schlenk tube was allowed the cool and the carbon monoxide balloon removed. The reaction mixture was then diluted with ethyl acetate (ca. 10 mL), filtered through a celite pad, washing with ethyl acetate (ca. 60 mL), and concentrated under reduced pressure. The crude material was purified *via* flash column chromatography (4:1 hexane:ethyl acetate) to yield the *isocoumarin* (61.0 mg, 43%) as a white solid.

2,3-Dihydro-1*H*-cyclopenta[c]isochromen-5-one, table 1, entry 1



Prepared following general procedure A using 2-(2-bromo-phenyl)-cyclopentanone (113.4 mg, 0.474 mmol). The crude material was purified *via* flash column chromatography (4:1 hexane:ethyl acetate) to yield the *isocoumarin* (69.6 mg, 79%) as a white solid: mp 148-149 °C. ν_{max} (KBr)/cm^{-1} 2969, 2920, 2864, 1715, 1659, 1605, 1488, 1462, 1383, 1322, 1205, 1074, 1055, 1019, 959, 777, 693; δ_H (500 MHz; $CDCl_3$) 8.28 (1H ,d, *J* 7.9, Ar-*H*), 7.71 (1H, dd (ap. t) *J* 7.7, Ar-*H*), 7.44 (1H, dd (ap. t) *J* 7.9, Ar-*H*), 7.28 (1H, d, *J* 7.7, Ar-*H*), 2.88-2.82 (4H, m, C*H*$_2$C=CC*H*$_2$), 2.22-2.16 (2H, m, C*H*$_2$); δ_C (125 MHz; $CDCl_3$) 163.8, 155.9, 136.4, 134.8, 130.4, 127.0, 122.5, 119.6, 113.2, 31.0, 26.5, 19.8; *m/z* LRMS (ES$^+$) 187.1 (M+H, 100); HRMS (ES$^+$) 209.0572 ([M+Na]$^+$. $C_{12}H_{10}NaO_2$ requires 209.0573).

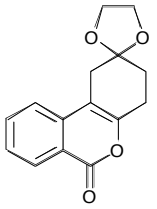
8,9,10,11-Tetrahydro-7*H*-6-oxa-cyclohepta[a]naphtalen-5-one, table 1, entry 2



Prepared following general procedure A using 2-(2-bromo-phenyl)-cycloheptanone (126.6 mg, 0.474 mmol). The crude material was purified *via* flash column chromatography (4:1 hexane:ethyl acetate) to yield the *isocoumarin* (71.0 mg, 70%) as a cream coloured solid: mp 128-129 °C. ν_{max} (KBr)/cm^{-1} 2949, 2851, 1721, 1640, 1602, 1487, 1317, 1225, 1185, 1098, 1071, 1065, 961, 779, 704; δ_H (500 MHz; $CDCl_3$) 8.33

(1H, dd, *J* 7.8 and 1.3, Ar-*H*), 7.73 (1H, ddd, *J* 8.2, 7.8 and 1.3, Ar-*H*), 7.59 (1H, d, *J* 8.2, Ar-*H*), 7.45 (1H, dd (ap. t) *J* 7.8, Ar-*H*), 2.80-2.74 (4H, m, C*H*$_2$C=CC*H*$_2$), 1.89-1.84 (2H, m, C*H*$_2$), 1.75-1.67 (4H, m, 2 × C*H*$_2$); δ_C (125 MHz; $CDCl_3$) 162.9, 157.1, 138.0, 134.6, 130.0, 126.8, 121.9, 120.3, 114.4, 33.3, 31.2, 25.9, 24.8, 24.5; *m/z* LRMS (ES^+) 451.1 (2M+Na, 100), 215.1 (M+H, 75); HRMS (ES^+) 237.0890 ($[M+Na]^+$. $C_{14}H_{14}NaO_2$ requires 237.0886); Anal. Calc. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.57; H, 6.58%.

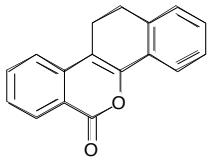
3,4-Dihydro-1H,6H-spiro[benzo[c]chromene-2,2'-[1,3]dioxolan]-6-one, table 1, entry 3



Prepared following general procedure A using 7-(2-bromo-phenyl)-1,4-dioxa-spiro[4,5]decan-8-one (147.5 mg, 0.474 mmol). The crude material was purified *via* flash column chromatography (3:2 hexane:ethyl acetate) to yield the *isocoumarin* (90.5 mg, 76%) as a cream solid: mp 104-105 °C. ν_{max} (KBr)/cm^{-1} 2888, 1732, 1658, 1605, 1490, 1432, 1369, 1304, 1275, 1186, 1118, 1089, 1060, 1030, 946, 891, 852, 766, 692; δ_H (500 MHz; $CDCl_3$) 8.28 (1H, dd, *J* 7.8 and 1.1 Ar-*H*), 7.71 (1H, ddd, *J* 8.2, 7.8 and 1.1, Ar-*H*), 7.46 (1H, dd (ap. t) *J* 7.8, Ar-*H*), 7.35 (1H, d, *J* 8.2, Ar-*H*), 4.09-4.02 (4H, m, OC*H*$_2$C*H*$_2$O), 2.82-2.78 (4H, m, C*H*$_2$C=CC*H*$_2$), 2.00 (2H, t, *J* 6.6, C=CCH$_2$C*H*$_2$); δ_C (125 MHz; $CDCl_3$) 162.4, 151.0, 137.4, 134.7, 129.8, 127.4, 121.2, 120.2, 107.2, 107.1, 64.7, 33.2, 30.5, 26.2; *m/z* LRMS (ES^+) 259.1 (M+H, 65); HRMS (ES^+) 281.0785 ($[M+Na]^+$.

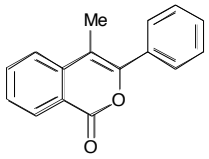
$C_{15}H_{14}NaO_4$ requires 281.0784); Anal. Calc. for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.72; H, 5.43%.

11,12-Dihydro-dibenzo[*c*,*h*]chromen-6-one, table 1, entry 4



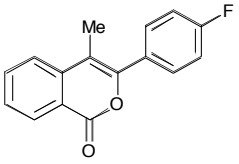
Prepared following general procedure A using 2-(2-bromo-phenyl)-3,4-dihydro-2*H*-naphthalen-1-one (142.8 mg, 0.474 mmol). The crude material was purified *via* flash column chromatography (4:1 hexane:ethyl acetate) to yield the *isocoumarin* (113.9 mg, 95%) as a white solid: mp 174-175 °C. ν_{max} (KBr)/cm^{-1} 3031, 2945, 1715, 1654, 1629, 1606, 1487, 1162, 1090, 1022, 729, 683; δ_H (500 MHz; $CDCl_3$) 8.39 (1H, dd, *J* 7.8 and 1.2, Ar-*H*), 7.90 (1H, dd, *J* 7.3 and 1.3, Ar-*H*), 7.78 (1H, ddd, *J* 7.9, 7.8, 1.2, Ar-*H*), 7.63 (1H, d, *J* 7.9, Ar-*H*), 7.51 (1H, dd (ap. t) *J* 7.8, Ar-*H*), 7.35-7.29 (2H, m, Ar-*H*), 7.25 (1H, d, *J* 7.9, Ar-*H*), 3.07-3.04 (2H, m, CH_2), 2.97-2.94 (2H, m, CH_2); δ_C (125 MHz; $CDCl_3$) 162.1, 148.1, 137.4, 136.4, 134.8, 130.3, 129.2, 128.7, 127.64, 127.56, 127.0, 122.9, 122.2, 121.0, 109.6, 27.3, 21.1; *m/z* LRMS (ES^+) 249.1 (M+H, 90). Data consistent with literature.[3]

4-methyl-3-phenyl-isochromen-1-one, table 1, entry 5



Prepared following general procedure A using 2-(2-bromo-phenyl)-1-phenyl-propan-1-one (137.1 mg, 0.474 mmol). The crude material was purified *via* flash column chromatography (4:1 hexane:diethyl ether) to yield the *isocoumarin* (77.4 mg, 69%) as a cream solid: mp 110-111 °C. ν_{max} (KBr)/cm^{-1} 3068, 2923, 2871, 1721, 1691, 1634, 1607, 1486, 1444, 1336, 1243, 1097, 1078, 1057, 925, 826, 694; δ_H (500 MHz; $CDCl_3$) 8.38 (1H, d, *J* 7.9, Ar-*H*), 7.82-7.79 (1H, m, Ar-*H*), 7.65 (1H, d, *J* 7.9, Ar-*H*), 7.61-7.53 (3H, m, Ar-*H*), 7.49-7.44 (3H, m, Ar-*H*), 2.32 (3H, s, C*H*$_3$); δ_C (125 MHz; $CDCl_3$) 162.4, 151.1, 138.7, 134.7, 133.2, 129.7, 129.5, 129.3, 128.2, 127.9, 123.3, 120.7, 109.1, 13.5; *m/z* LRMS (ES$^+$) 495.1 (2M+Na, 100), 237.1 (M+H, 80). Data consistent with literature.[4]

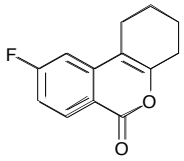
3-(4-Fluoro-phenyl)-4-methyl-isochromen-1-one, table 1, entry 6



Prepared following general procedure A using 2-(2-bromo-phenyl)-1-(4-fluoro-phenyl)-propan-1-one (145.6 mg, 0.474 mmol). The crude material was purified *via* flash column chromatography (4:1 hexane:diethyl ether) to yield the *isocoumarin* (88.3 mg, 73%) as a cream solid: mp 116-117 °C. ν_{max} (KBr)/cm^{-1} 3065, 2958, 2929, 1723, 1690, 1640, 1602, 1509, 1485, 1320, 1244, 1163, 1095, 1057, 1030, 854, 798, 766, 692; δ_H (500 MHz; $CDCl_3$) 8.38 (1H, dd, *J* 7.9 and 1.0, Ar-*H*), 7.83-7.80 (1H, m, Ar-*H*), 7.64 (1H, d, *J* 8.2,

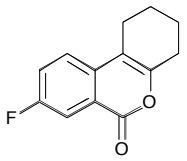
Ar-*H*), 7.60-7.54 (3H, m, Ar-*H*), 7.18-7.14 (2H, m, Ar-*H*), 2.30 (3H, s, CH_3); δ_C (125 MHz; $CDCl_3$) 163.1 (d, $^1J_{CF}$ 249.8), 162.4, 150.1, 138.6, 134.8, 131.5, (d, $^3J_{CF}$ 8.6), 129.8, 129.4 (d, $^4J_{CF}$ 3.8), 128.0, 123.4, 120.8, 115.4 (d, $^2J_{CF}$ 21.9), 109.2, 13.5; *m/z* LRMS (ES^+) 531.1 (2M+Na, 100), 255.1 (M+H, 80); HRMS (ES^+) 277.0631 ($[M+Na]^+$. $C_{16}H_{11}FNaO_2$ requires 277.0635); Anal. Calc. for $C_{16}H_{11}FO_2$: C, 75.58; H, 4.36. Found: C, 75.67; H, 4.43%.

9-Fluoro-1,2,3,4-tetrahydro-benzo[c]chromen-6-one, table 1, entry 7



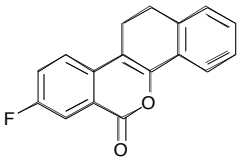
Prepared following general procedure A using 2-(2-bromo-5-fluoro-phenyl)-cyclohexanone (128.5 mg, 0.474 mmol). The crude material was purified *via* flash column chromatography (4:1 hexane:ethyl acetate) to yield the *isocoumarin* (98.5 mg, 95%) as a white solid: mp 128-129 °C. ν_{max} (KBr)/cm^{-1} 2935, 2866, 1719, 1652, 1615, 1574, 1486, 1372, 1296, 1256, 1237, 1193, 1159, 1135, 1059, 1006, 859, 833, 776, 686; δ_H (500 MHz; $CDCl_3$) 8.29 (1H, dd, *J* 8.7 and 5.7, Ar-*H*), 7.12 (1H, ddd (ap. td) *J* 8.7 and 2.5, Ar-*H*), 7.05 (1H, dd, *J* 9.8 and 2.5, Ar-*H*), 2.58-2.52 (4H, m, CH_2C=CCH_2), 1.89-1.83 (4H, m, 2 × CH_2); δ_C (125 MHz; $CDCl_3$) 166.8 (d, $^1J_{CF}$ 255.5), 161.7, 153.9, 141.0 (d, $^3J_{CF}$ 10.5), 133.0 (d, $^3J_{CF}$ 10.5), 117.0 (d, $^4J_{CF}$ 1.9), 115.2 (d, $^2J_{CF}$ 22.9), 109.0 (d, $^4J_{CF}$ 2.9), 107.6 (d, $^2J_{CF}$ 22.9), 27.4, 22.6, 21.86, 21.85; *m/z* LRMS (ES^+) 219.1 (M+H, 100); HRMS (ES^+) 241.0635 ($[M+Na]^+$. $C_{13}H_{11}FNaO_2$ requires 241.0635); Anal. Calc. for $C_{13}H_{11}FO_2$: C, 71.55; H, 5.08. Found: C, 71.63; H, 5.03%.

8-Fluoro-1,2,3,4-tetrahydro-benzo[c]chromen-6-one, table 1, entry 8



Prepared following general procedure A using 2-(2-bromo-4-fluoro-phenyl)-cyclohexanone (128.5 mg, 0.474 mmol). The crude material was purified *via* flash column chromatography (4:1 hexane:ethyl acetate) to yield the *isocoumarin* (90.0 mg, 87%) as a white solid: mp 177-178 °C. ν_{max} (KBr)/cm^{-1} 2941, 2870, 1712, 1651, 1608, 1500, 1427, 1329, 1300, 1273, 1234, 1196, 1098, 915, 893, 835, 818, 783; δ_H (500 MHz; $CDCl_3$) 7.95-7.92 (1H, m, Ar-*H*), 7.46-7.43 (2H, m, Ar-*H*), 2.61-2.55 (4H, m, C*H*$_2$C=CC*H*$_2$), 1.89-1.83 (4H, m, 2 × C*H*$_2$); δ_C (125 MHz; $CDCl_3$) 161.9 (d, $^4J_{CF}$ 3.8), 161.3 (d, $^1J_{CF}$ 247.9), 151.9, 134.6 (d, $^4J_{CF}$ 1.9), 123.8 (d, $^3J_{CF}$ 7.6), 122.7 (d, $^2J_{CF}$ 22.9), 122.2 (d, $^3J_{CF}$ 7.6), 115.2 (d, $^2J_{CF}$ 22.9), 108.9, 27.2, 22.8, 22.04, 21.99; *m/z* LRMS (ES$^+$) 219.1 (M+H, 90); HRMS (ES$^+$) 241.0635 ([M+Na]$^+$. $C_{13}H_{11}FNaO_2$ requires 241.0635); Anal. Calc. for $C_{13}H_{11}FO_2$: C, 71.55; H, 5.08. Found: C, 71.60; H, 5.00%.

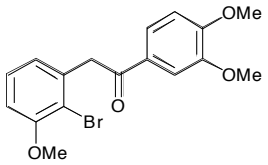
8-Fluoro-11,12-dihydro-dibenzo[*c*,*h*]chromen-6-one, table 1, entry 9



Prepared following general procedure A using 2-(2-bromo-4-fluoro-phenyl)-3,4-dihydro-2*H*-naphthalen-1-one (151.3 mg, 0.474 mmol). The crude material was purified *via* flash column chromatography (4:1 hexane:ethyl acetate) to yield the *isocoumarin* (123.6 mg, 98%) as a cream solid: mp 188-189 °C. ν_{max} (KBr)/cm^{-1} 3081, 2950, 1716, 1627, 1497,

1338, 1265, 1100, 1052, 935, 883, 827, 755; δ_H (500 MHz; $CDCl_3$) 8.04 (1H, dd, *J* 8.7 and 2.8, Ar-*H*), 7.89-7.87 (1H, m, Ar-*H*), 7.65-7.61 (1H, m, Ar-*H*), 7.50 (1H, ddd, *J* 8.6, 8.4 and 2.8, Ar-*H*), 7.35-7.29 (2H, m, Ar-*H*), 7.25-7.23 (1H, m, Ar-*H*), 3.05 (2H, t, *J* 7.9, CH_2), 2.96-2.93 (2H, m, CH_2); δ_C (125 MHz; $CDCl_3$) 161.6 (d, $^1J_{CF}$ 249.8), 161.2 (d, $^4J_{CF}$ 3.8), 147.7 (d, $^3J_{CF}$ 2.9), 136.2, 134.0 (d, $^4J_{CF}$ 1.9), 129.3, 128.4, 127.6, 127.1, 124.7 (d, $^3J_{CF}$ 7.6), 123.0 (d, $^2J_{CF}$ 22.9), 122.74, 122.67, 115.8 (d, $^2J_{CF}$ 23.8), 109.0, 27.2, 21.2; *m/z* LRMS (ES^+) 267.1 (M+H, 80); HRMS (ES^+) 289.0628 ($[M+Na]^+$. $C_{17}H_{11}FNaO_2$ requires 289.0635); Anal. Calc. for $C_{17}H_{11}FO_2$: C, 76.68; H, 4.16. Found: C, 76.78; H, 4.09%.

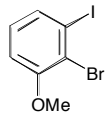
2-(2-Bromo-3-methoxy-phenyl)-1-(3,4-dimethoxy-phenyl)-ethanone, 8



2-Bromo-1-iodo-3-methoxy-benzene (150 mg, 0.479 mmol), 3',4'-dimethoxyacetophenone (57.7 mg, 0.320mmol) and sodium *tert*-butoxide (67.6 mg, 0.703 mmol) were added to an oven dried round bottom flask charged with Pd_2dba_3 (14.6 mg, 0.016 mmol) and Dave-phos (12.6 mg, 0.032 mmol) under argon. To this anhydrous 1,2-dimethoxyethane (0.6 mL) was added and the reaction heated at 80 °C for 5 hours under argon. After this time, the reaction mixture was allowed to cool and diluted with dichloromethane (ca. 5 mL) and filtered through a celite pad, washing with dichloromethane (ca. 40 mL). The filtrate was reduced *in vacuo*. The product was purified *via* flash column chromatography (93:7 toluene:diethyl ether) to yield the *ketone* (74.6 mg, 64%) as a pale brown solid: mp 126-128 °C. ν_{max} (KBr)/cm^{-1} 3002, 2968,

2935, 2837, 1679, 1663, 1596, 1573, 1513, 1467, 1435, 1303, 1266, 1158, 1068, 1027, 867, 812, 769, 745; δ_H (500 MHz; $CDCl_3$) 7.70 (1H, dd, *J* 8.5 and 2.1, Ar-*H*), 7.58 (1H, d, *J* 2.1, Ar-*H*), 7.24 (1H, dd (ap. t) *J* 7.9, Ar-*H*), 6.91 (1H, d, *J* 8.5, Ar-*H*), 6.88 (1H, d, *J* 7.9, Ar-*H*), 6.84 (1H, d, *J* 7.9, Ar-*H*), 4.45 (2H, s, C*H*$_2$), 3.95 (3H, s, OC*H*$_3$), 3.93 (3H, s, OC*H*$_3$), 3.91 (3H, s, OC*H*$_3$); δ_C (125 MHz; $CDCl_3$) 195.1, 156.2, 153.4, 149.0, 137.1, 129.8, 127.9, 123.4, 123.1, 114.5, 110.45, 110.41, 110.0, 56.3, 56.1, 56.0, 45.7; *m/z* LRMS (ES^+) 367.1 (^{81}Br-M+H, 100), 365.1 (^{79}Br-M+H, 95); HRMS (ES^+) 365.0381 ([^{79}Br-M+H]$^+$. $C_{17}H_{18}{}^{79}BrO_4$ requires 365.0383).

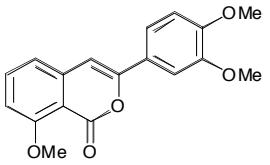
2-Bromo-1-iodo-3-methoxy-benzene, 9



2-Bromo-3-iodo-phenol (1.51 g, 5.05 mmol) and potassium carbonate (1.40 g, 10.1 mmol) were added to a round bottom flask under nitrogen. THF (20 mL) and iodomethane (5.74 g, 2.52 mL, 40.4 mmol) were then added. The reaction was stirred at room temperature for 24 hours under nitrogen. After this time the reaction mixture was diluted with dichloromethane (ca. 20 mL), filtered through a celite pad, washing with ethyl acetate (ca. 100 mL), and concentrated under reduced pressure. The crude material was purified *via* flash column chromatography (4:1 petroleum ether:diethyl ether) to yield the *aryl iodide* (1.57 g, 99%) as a white solid. mp 43-45 °C. δ_H (400 MHz; $CDCl_3$) 7.49 (1H, dd, *J* 7.8 and 1.2, Ar-*H*), 7.01 (1H, dd, *J* 8.2 and 7.8, Ar-*H*), 6.86 (1H, dd, *J* 8.2 and 1.2, Ar-*H*), 3.88 (3H, s, OC*H*$_3$); δ_C (100 MHz; $CDCl_3$) 156.7, 132.0, 129.4, 119.3,

111.1, 103.1, 56.6; *m/z* LRMS (FI^+) 313.9 (^{81}Br-M^+, 95), 311.9 (^{79}Br-M^+, 100). Data consistent with literature.[5]

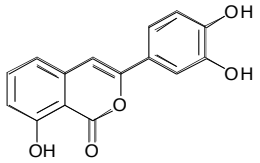
3-(3,4-Dimethoxy-phenyl)-8-methoxy-isochromen-1-one, 10



Cesium carbonate (463 mg, 1.42 mmol) was added to an oven dried Schlenk tube (30 mL) charged with Pd_2dba_3 (21.7 mg, 0.024 mmol), DPE-phos (25.5 mg, 0.047 mmol) and 2-(2-bromo-3-methoxy-phenyl)-1-(3,4-dimethoxy-phenyl)-ethanone (173.1 mg, 0.474 mmol) under argon. To this anhydrous toluene (1.0 mL) was added. A balloon fitted with a glass tap attachment was filled with argon and evacuated three times. The balloon was then filled with carbon monoxide from a lecture bottle (Aldrich) and attached to the top of the Schlenk tube. The inert atmosphere was then exchanged for carbon monoxide by briefly exposing the reaction vessel to vacuum (1-2 seconds) through the side arm of the Schlenk tube and filling the vessel with carbon monoxide through the balloon on the top. The evacuation of the atmosphere and filling with carbon monoxide was performed three times. The reaction was then left open to the balloon and stirred vigorously, heating at 110 °C for 15 hours. After this time the Schlenk tube was allowed the cool and the carbon monoxide balloon removed. The reaction mixture was then diluted with ethyl acetate (ca. 10 mL), filtered through a celite pad, washing with ethyl acetate (ca. 40 mL), and concentrated under reduced pressure. The crude material was purified *via* flash column chromatography (1:1 petroleum ether:ethyl acetate) to yield the *isocoumarin* (93.0 mg, 64%) as a pale orange solid: mp 142-144 °C (lit. 148-150 °C). ν_{max} (KBr)/cm^{-1}

1732, 1639, 1567, 1517, 1477, 1257, 1208, 1169, 1145, 1108, 1023, 810; δ_H (500 MHz; $CDCl_3$) 7.60 (1H, dd (ap. t) *J* 8.1, Ar-*H*), 7.47 (1H, dd, *J* 8.5 and 2.0, Ar-*H*), 7.36 (1H, d, *J* 2.0, Ar-*H*), 7.01 (1H, d, *J*, 8.1, Ar-*H*), 6.92 (1H, d, *J* 8.5, Ar-*H*), 6.91 (1H, d, *J* 8.1, Ar-*H*), 6.75 (1H, s, C=C*H*), 4.02 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 3.94 (3H, s, OCH_3); δ_C (125 MHz; $CDCl_3$) 161.6, 159.1, 153.9, 150.6, 149.1, 140.7, 135.7, 124.7, 118.6, 117.8, 111.0, 109.4, 108.9, 108.2, 100.6, 56.3, 56.2, 56.0; *m/z* LRMS (ES^+) 647.2 (2M+Na, 100), 313.1 (M+H, 80). Data consistent with literature.[6]

Thunberginol A



A mixture of 3-(3,4-dimethoxy-phenyl)-8-methoxy-isochromen-1-one (45.0 mg, 0.144 mmol) and a 1M dichloromethane solution of BBr_3 (5.2 eq., 0.75 mL, 0.749 mmol) was stirred at room temperature under nitrogen for 2 hours. The solution was then poured into ice water (ca. 10 mL) and the mixture extracted with ethyl acetate (6 × 15 mL). The organic extract was washed with brine (10 mL), dried over magnesium sulphate and reduced *in vacuo*. The product was purified *via* flash column chromatography (90:9:1 chloroform:methanol:water) to yield the *natural product* (38.0 mg, 98%) as a pale orange solid. mp 247-248 °C (lit. 249-252 °C). ν_{max} (KBr)/cm^{-1} 2925, 2854, 1665, 1611, 1566, 1525, 1453, 1262, 1217, 1160, 1105, 1072, 1015, 818; δ_H (500 MHz; DMSO-d_6) 10.86 (1H, s, O*H*), 9.59 (1H, s, O*H*), 9.32 (1H, s, O*H*), 7.69 (1H, dd, *J* 8.1 and 8.0, Ar-*H*), 7.29 (1H, d, *J* 2.2, Ar-*H*), 7.25-7.23 (2H, m, C=C*H* and Ar-*H*), 7.10 (1H, d, *J* 8.1, Ar-*H*), 6.93 (1H, d, *J* 8.0, Ar-*H*), 6.87 (1H, d, *J* 8.1, Ar-*H*); δ_C (125 MHz; $CDCl_3$) 165.2, 160.4, 152.8,

147.8, 145.7, 138.6, 137.6, 122.3, 117.0, 116.6, 116.0, 114.0, 112.2, 105.2, 100.6; *m/z* LRMS (ES^-) 540.1 (2M, 30), 539.1 (2M-H, 100), 270.1 (M, 20), 269.1 (M-H, 60); HRMS (ES^+) 271.0598 ($[M+H]^+$. $C_{15}H_{11}O_5$ requires 271.0601). Data consistent with literature.[6]

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1. R. Sanz, M. P. Castroviejo, Y. Fernndez, F. J. Faans, *J. Org. Chem*., 2005, **70**, 6548-6551.

2. R. C. Larock, S. Varaprath, H. H. Lau, C.A. Fellows, *J. Am. Chem. Soc.*, 1984, **106**, 5274-5284.

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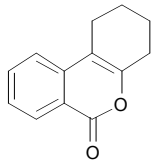
071120060_010000fid



^{1}H NMR (500 MHz, $CDCl_3$)
Structure 7

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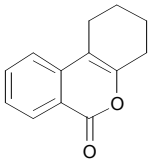

^{13}C NMR (125 MHz, $CDCl_3$)
Structure 7

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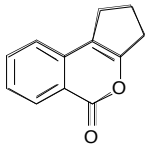

^{1}H NMR (500 MHz, $CDCl_3$)
Table 1, entry 1

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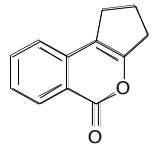

^{13}C NMR (125 MHz, $CDCl_3$)
Table 1, entry 1

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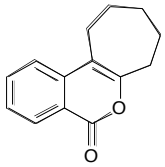

^{1}H NMR (500 MHz, $CDCl_3$)
Table 1, entry 2

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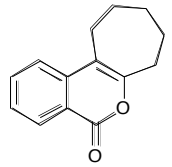

^{13}C NMR (125 MHz, $CDCl_3$)
Table 1, entry 2

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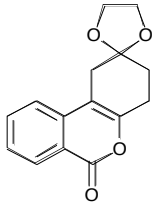

^{1}H NMR (500 MHz, $CDCl_3$)
Table 1, entry 3

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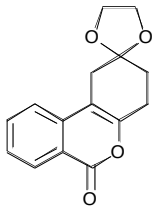

^{13}C NMR (125 MHz, $CDCl_3$)
Table 1, entry 3

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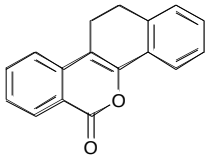

^{1}H NMR (500 MHz, $CDCl_3$)
Table 1, entry 4

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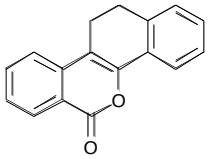

^{13}C NMR (125 MHz, $CDCl_3$)
Table 1, entry 4

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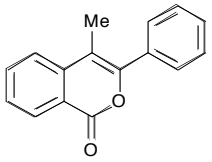

^{1}H NMR (500 MHz, $CDCl_3$)
Table 1, entry 5

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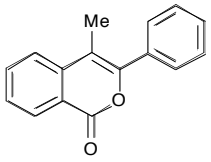

^{13}C NMR (125 MHz, $CDCl_3$)
Table 1, entry 5

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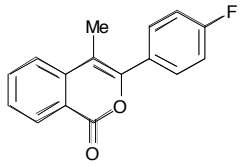

^{1}H NMR (500 MHz, $CDCl_3$)
Table 1, entry 6

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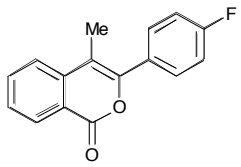

^{13}C NMR (125 MHz, $CDCl_3$)
Table 1, entry 6

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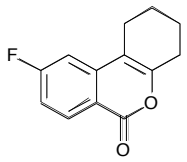

^{1}H NMR (500 MHz, $CDCl_3$)
Table 1, entry 7

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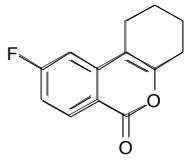

^{13}C NMR (125 MHz, $CDCl_3$)
Table 1, entry 7

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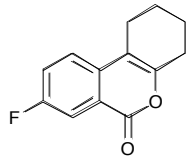

^{1}H NMR (500 MHz, $CDCl_3$)
Table 1, entry 8

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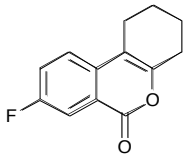

^{13}C NMR (125 MHz, $CDCl_3$)
Table 1, entry 8

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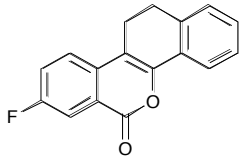
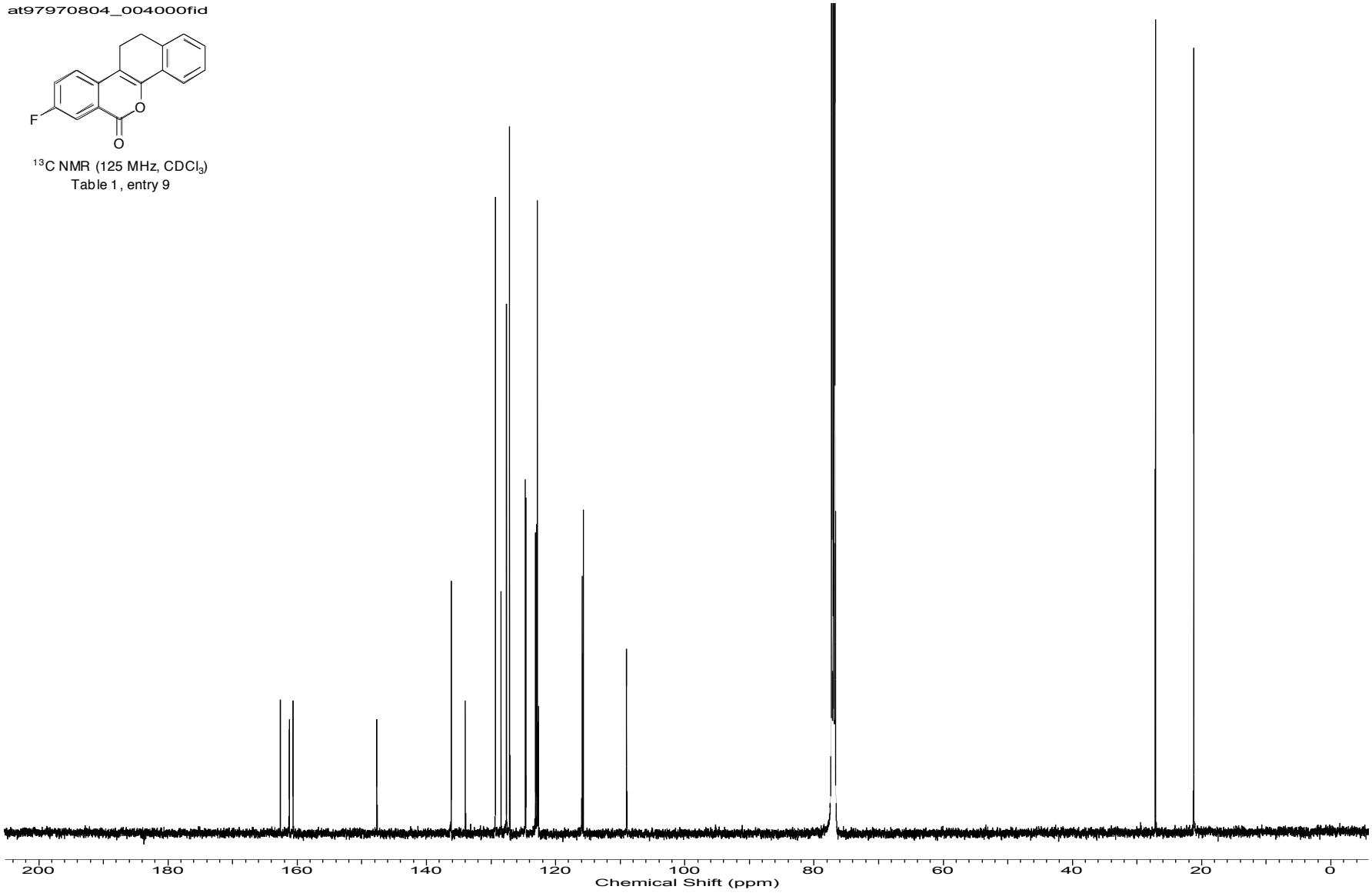


^{1}H NMR (500 MHz, $CDCl_3$)
Table 1, entry 9


at97970804_004000fid
F
O
O
^{13}C NMR (125 MHz, $CDCl_3$)
Table 1, entry 9
200
180
160
140
120
100
80
60
40
20
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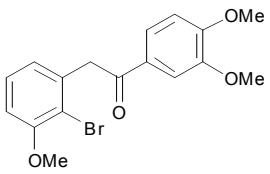
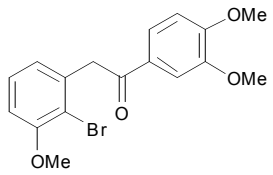
Chemical Shift (ppm)

at11032807_001000fid



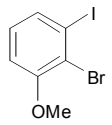
^{1}H NMR (500 MHz, $CDCl_3$)
Structure 8

at11032807_004000fid

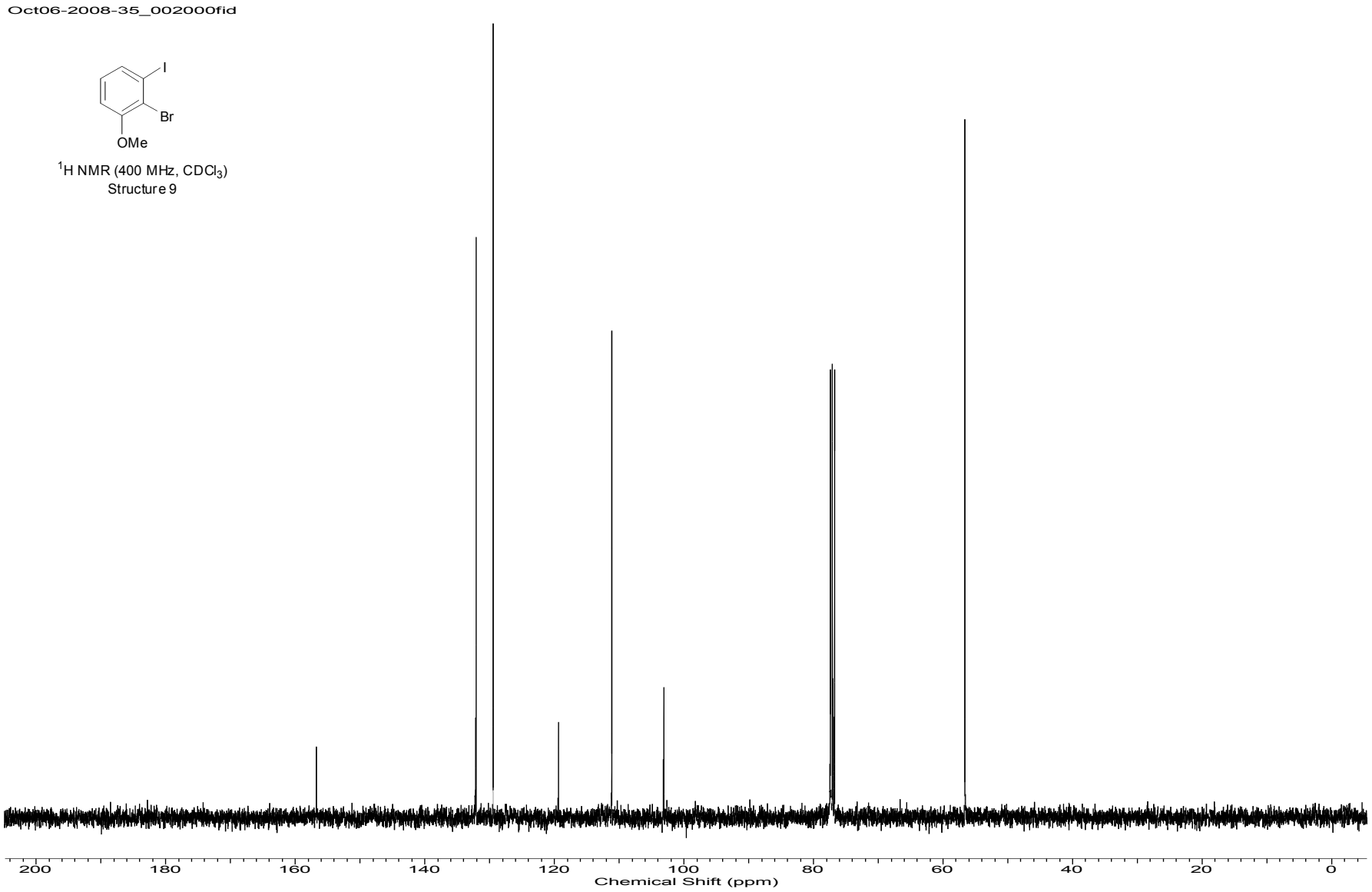


^{13}C NMR (125 MHz, $CDCl_3$)
Structure 8

Oct06-2008-35_001000fid



^{1}H NMR (400 MHz, $CDCl_3$)
Structure 9


Oct06-2008-35_002000fid
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Br
OMe
^{1}H NMR (400 MHz, $CDCl_3$)
Structure 9
200
180
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140
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100
80
60
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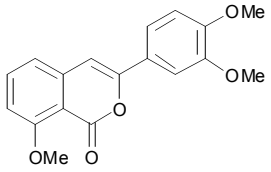
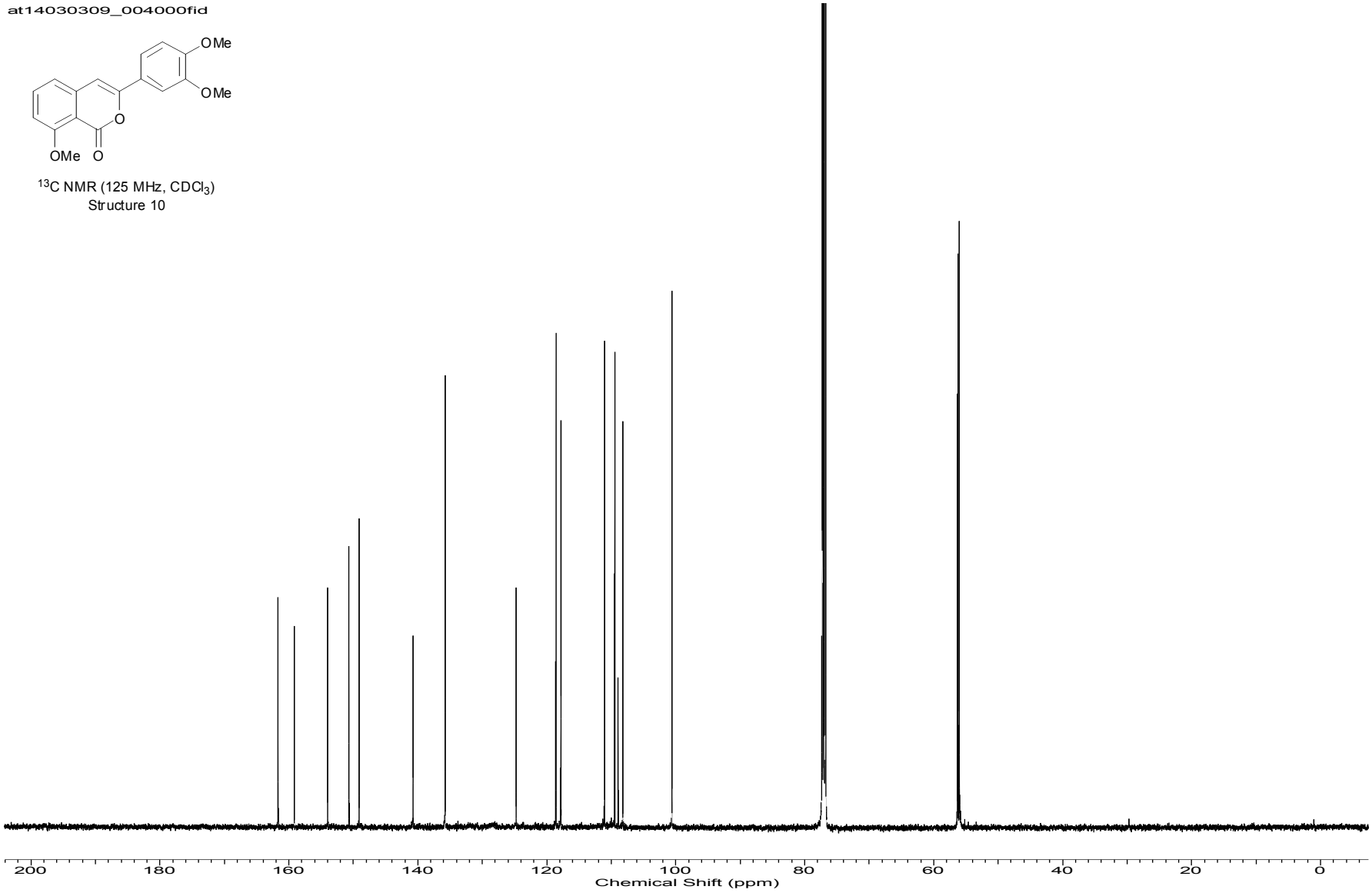
Chemical Shift (ppm)

at14030309_001000fid



^{1}H NMR (500 MHz, $CDCl_3$)
Structure 10



^{13}C NMR (125 MHz, $CDCl_3$)
Structure 10

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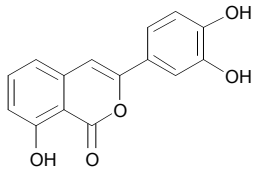
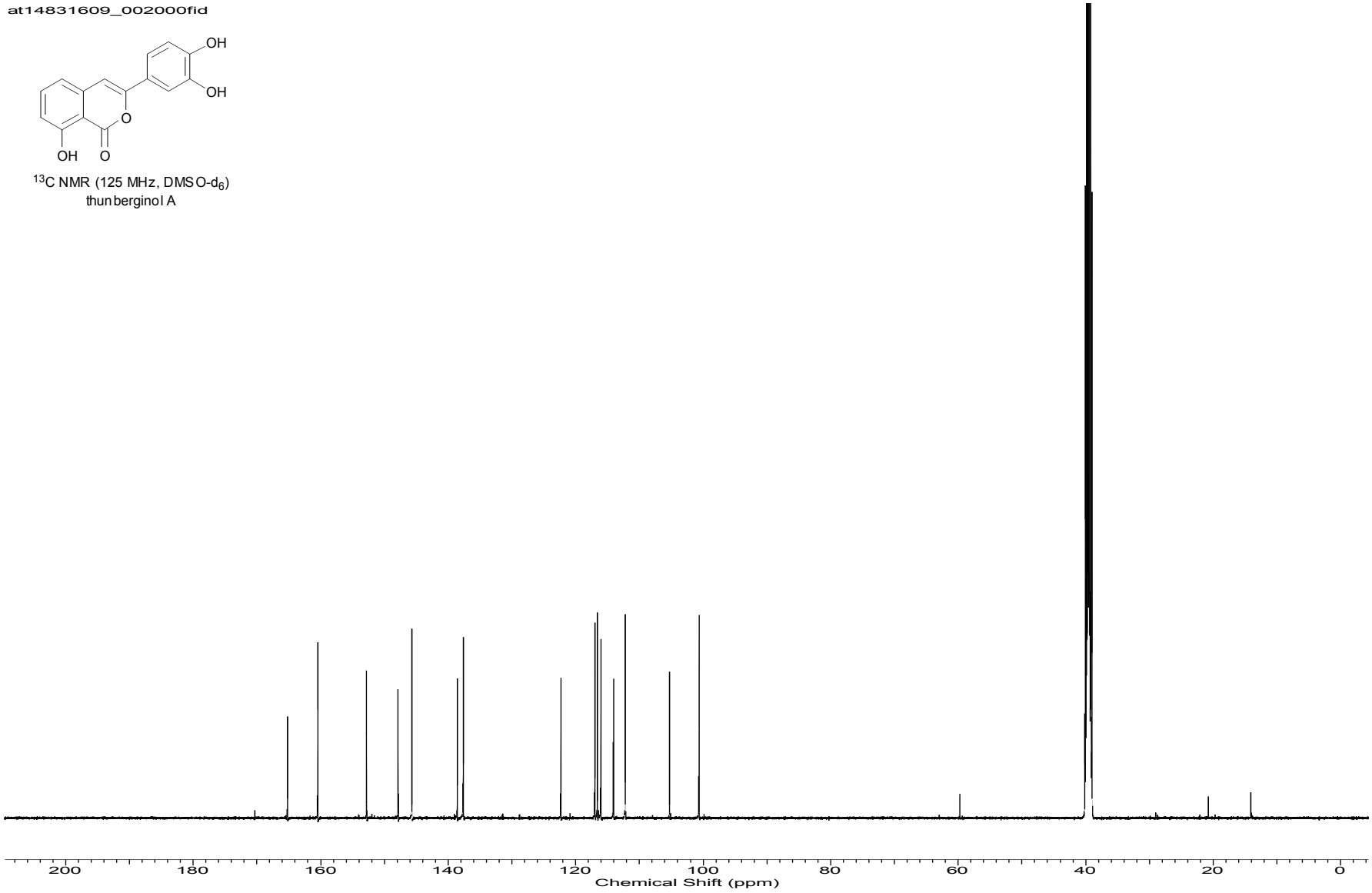


^{1}H NMR (500 MHz, DMSO-d_6)
thunberginol A



^{13}C NMR (125 MHz, DMSO-d_6)
thunberginol A