Honokiol-Inspired Analogs as Inhibitors of Oral Bacteria

Amy E. Solinski[1‡], Cristian Ochoa[2‡], Young Eun Lee[2‡], Thomas Paniak[2], Marisa C. Kozlowski[2*] and William M. Wuest[1*]

[1]*Department of Chemistry, Emory University, Atlanta GA 30322, USA*
[2]*Department of Chemistry, University of Pennsylvania, Philadelphia PA, 19104, USA*
[‡]*authors contributed equally*

Table of Contents:

Figure S1: Scaffold A.

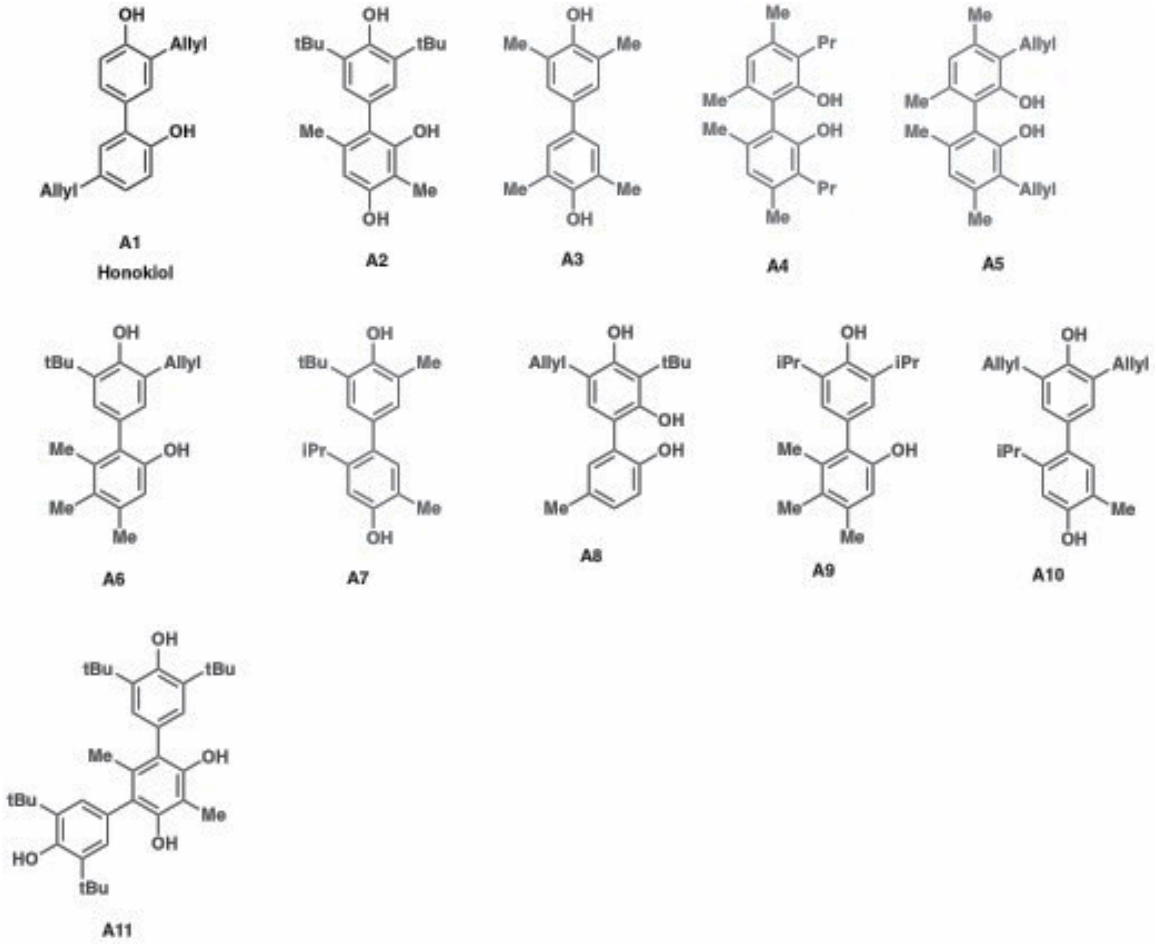


Figure S2: Scaffolds B and C.

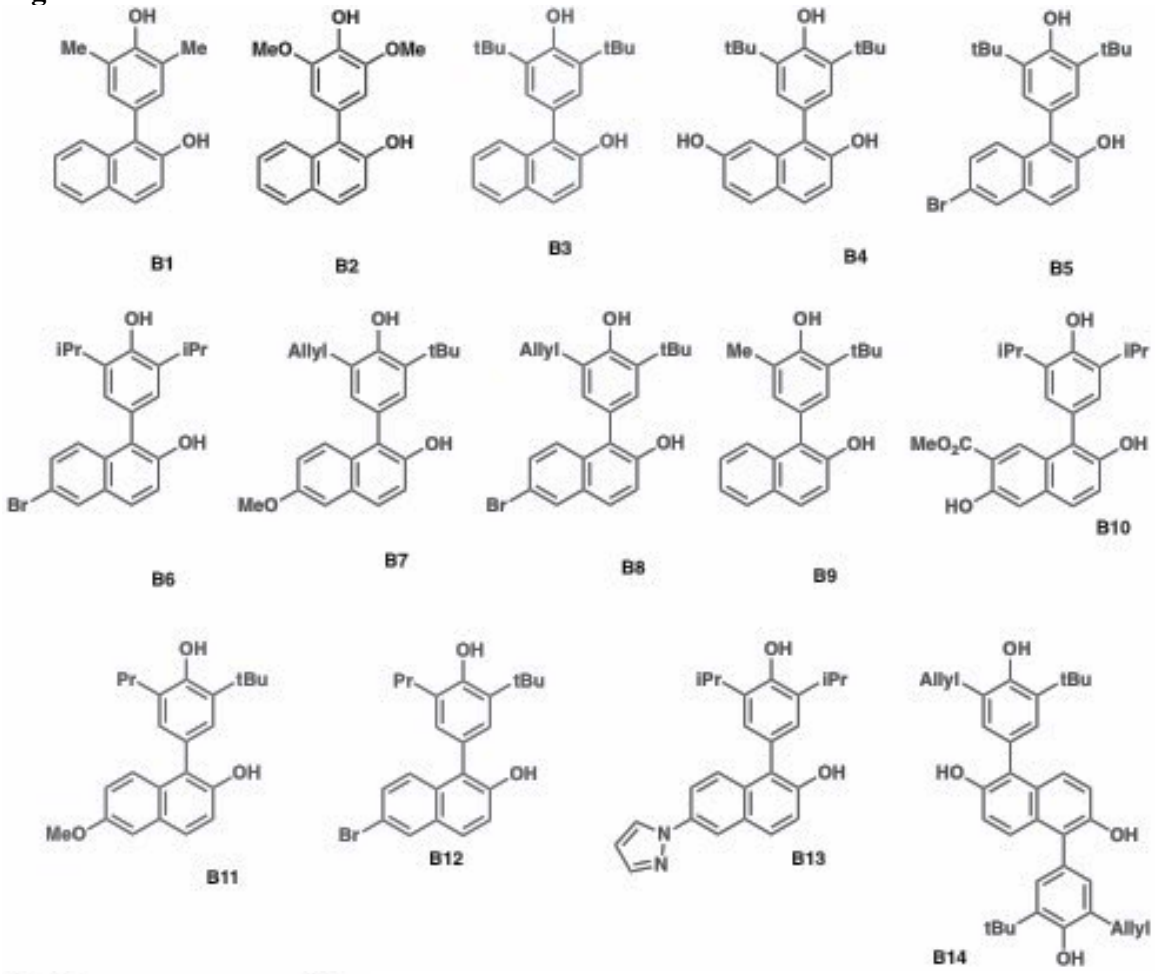


Figure S3: Biofilm Data from crystal violet analysis. Data was analyzed by recording the bacterial growth (OD 600) and the crystal violet stained biofilm (OD 595). Dividing OD 595/OD 600 biofilm mass normalized to bacterial growth was determined. The average of three trials is shown below. The average *S. mutans* biofilm mass value was recorded as 2.26 ± 1.76 (3 biological replicates, 12 technical replicates each). Highlighted in red is biofilm mass that was observed over the average biofilm mass. The purple number represents the MIC value of that analog. Grey values signify wells with no bacterial growth. Analogs were tested in biological triplicate.

Concentration (μM)

	250	125	63	32	16	8	4	2	1	0.5	0.25	0.125
A1	0.00	0.00	3.14	1.47	1.55	1.15	1.55	1.78	1.34	1.58	1.50	2.20
A2	0.00	0.00	0.00	0.00	4.65	2.34	2.92	2.28	1.71	1.76	2.02	1.67
A3	7.00	3.30	1.27	1.64	2.09	3.08	1.15	1.76	1.33	1.44	1.05	1.65
A4	5.08	3.51	2.75	2.39	1.12	1.23	2.58	1.75	2.14	1.44	1.02	2.61
A5	5.22	4.65	2.23	2.54	2.36	1.60	1.88	1.44	1.28	1.75	1.70	2.17
A6	4.99	1.47	1.79	1.58	1.31	0.95	1.53	1.07	3.38	1.21	1.28	2.30
A7	0.00	0.00	0.00	0.00	4.92	1.54	1.19	1.25	1.39	1.00	0.95	2.14
A8	6.35	4.23	3.49	1.53	1.60	1.56	1.65	1.35	1.95	1.74	1.12	1.78
A9	5.56	3.63	2.73	1.47	1.76	2.40	1.91	1.76	1.32	1.53	1.96	2.81
A10	3.22	2.16	1.96	2.05	1.57	2.05	1.79	2.08	1.85	1.99	1.93	2.76
B1	3.19	1.89	1.70	1.34	2.10	2.28	1.79	1.76	2.60	1.63	1.62	1.52
B2	6.59	2.16	0.94	1.45	1.83	1.10	1.54	1.65	3.89	1.01	1.11	1.80
B3	0.00	0.00	0.00	5.92	2.78	1.73	1.63	1.63	2.05	1.23	1.26	2.64
B4	0.00	0.00	5.68	2.38	1.80	1.24	2.93	1.35	1.28	1.49	1.68	1.62
B5	0.000	0.000	0.000	0.000	0.000	0.000	4.990	2.094	1.227	1.775	1.543	2.940
B6	4.372	5.921	5.253	5.279	4.465	4.431	4.898	4.430	1.270	1.622	1.551	1.637
B7	0.000	0.000	3.999	1.438	1.320	2.261	1.719	2.323	1.428	1.784	1.592	2.151
B8	0.000	0.000	0.000	0.000	0.000	6.854	1.939	1.675	1.370	1.220	2.127	2.025
B9	0.000	0.000	0.000	0.000	3.092	2.452	2.564	2.272	1.893	2.306	2.808	2.269
B10	0.000	0.000	0.000	0.000	0.000	6.168	3.285	2.019	1.765	1.812	2.135	2.544
B11	0.000	0.000	0.000	0.000	0.000	4.323	1.864	2.175	1.862	2.552	1.911	2.674
B12	6.183	4.391	3.460	2.380	2.353	1.955	2.069	3.302	2.141	2.015	1.945	2.219
B13	4.539	5.392	6.320	6.827	5.635	3.391	2.104	2.287	2.309	2.163	2.089	2.262
B14	0.000	0.000	0.000	11.091	5.716	2.755	3.090	1.952	2.007	1.628	1.594	2.180
C1	4.756	4.254	3.177	3.095	2.205	2.614	1.449	2.905	2.021	2.281	1.240	1.183
C2	0.000	0.000	0.000	0.000	0.000	0.000	0.000	8.131	2.151	2.066	1.606	1.952

Below: Representative plate from crystal violet MBIC assay.

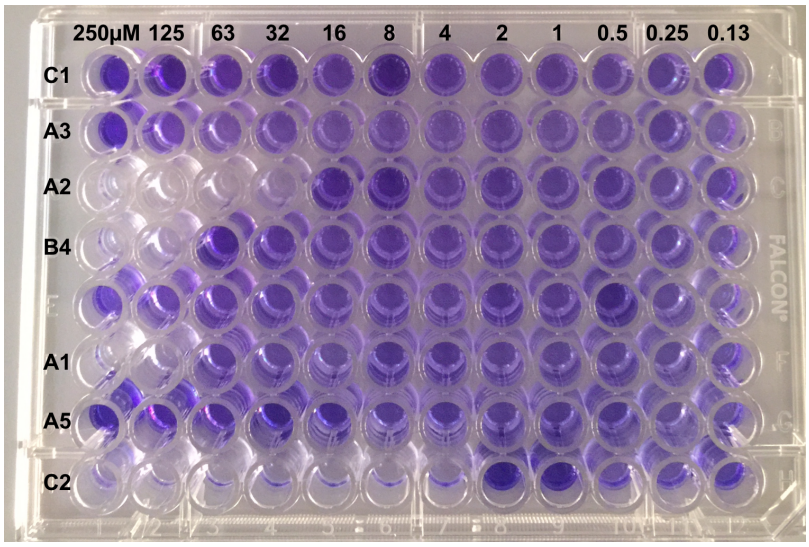
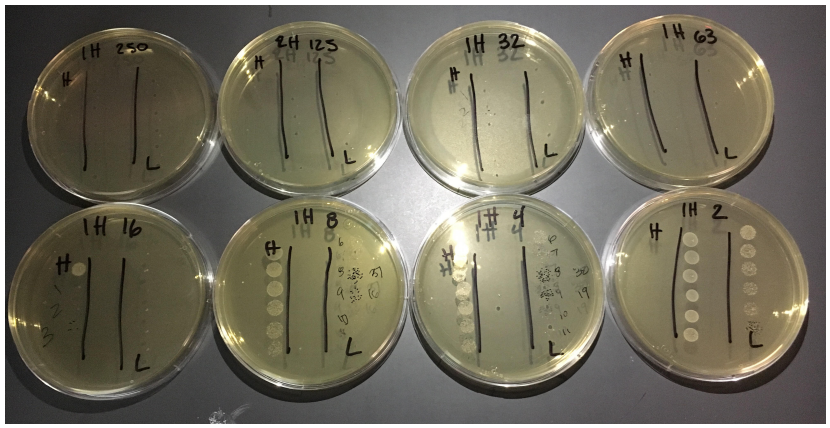


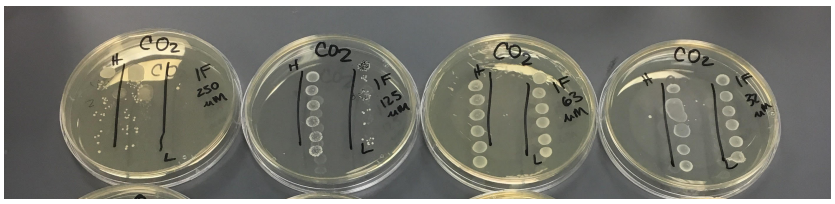
Figure S4: Raw data from MBC colony counts. Colony counts were completed on THB agar plates. The Colony Forming Unit (CFU)/mL were calculated using the equation shown below. Then those numbers were converted to Log value for easy comparison. The standard deviation between the three trials is also shown (See Table). Also shown are representative photos of the THB agar plates that were used for the the colony counts. Photos of Analog C2 [top, labeled 1H] and A1 [bottom, labeled 1F] for comparison. Biological triplicate was performed.

$$(\text{Colony Count}/5\text{uL})*1000\text{uL/mL}*10^{X}$$

X=dilution factor

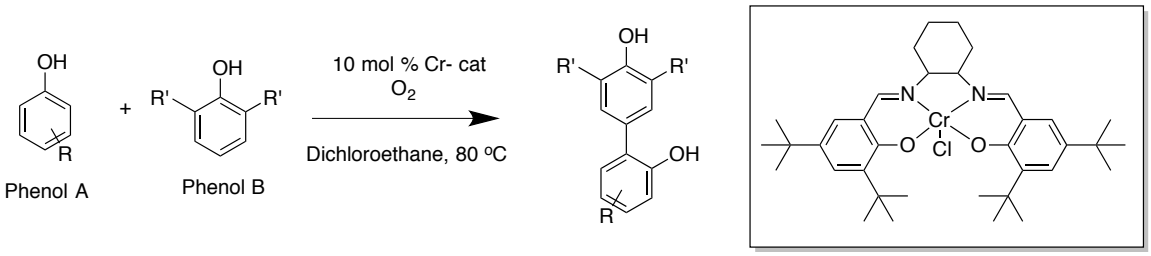
	125 µM	63 µM	16 µM	8 µM	4 µM
A1	7.1±1.0	9.8±0.7	10.3±0.2		
A2	0.0±0.0	5.9±0.8	9.9±0.7		
A7	3.9±0.1	3.8±0.3	8.8±0.7		
B5	4.0±0.5	7.6±0.7	7.0±0.3		
B8	5.8±0.9	6.4±0.5	7.5±0.8		
B11	8.2±1.4	6.25±0.1	8.3±1.1		
C2	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	5.9±1.1
Cells	9.9±0.5				



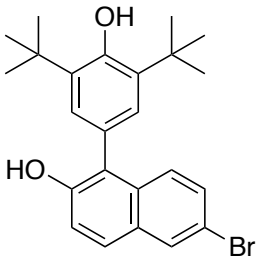


2. Synthetic Procedures

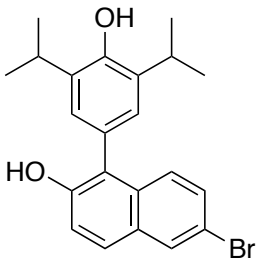
2.1 General Procedure A for Oxidative Coupling of Phenols



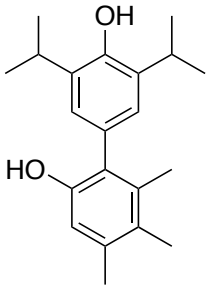
To a 10 mL microwave vial was added phenol A (0.1 mmol), phenol B (0.15 mmol), and Cr-Salen-Cy catalyst (0.01 mmol). The vial was sealed with a septum and $ClCH_2CH_2Cl$ (2.5 mL) was added. Oxygen was added *via* active purge. The septum was replaced with a crimping cap and the vessel was sealed and stirred for the indicated time at 80 °C. After the reaction mixture was filtered through a plug of silica and concentrated, the material was chromatographed using 10-20% ethyl acetate/hexane to afford the product.



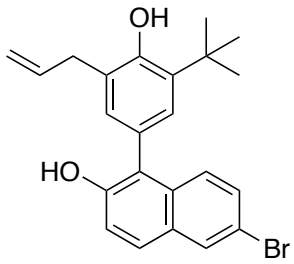
6-Bromo-1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)naphthalen-2-ol (B5). Following general procedure A for 2 d, the cross-coupled product was obtained as a red-orange solid (0.0103 g, 0.0241 mmol) in a 24% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 9.0 Hz, 1H), 7.41 (dd, J = 9.0 Hz, 2.0 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 7.16 (s, 2H), 5.41 (s, 1H), 5.35 (s, 1H), 1.47 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 150.9, 137.5, 132.4, 130.2, 130.0, 129.7, 128.2, 127.6, 127.0, 124.0, 122.3, 118.4, 117.0, 34.7, 30.5; IR (neat) 3632, 3527, 2958, 1615, 1588, 1502, 1437, 1403, 1377, 1362, 1340, 1309, 1236, 1174, 1148, 1120, 958, 885, 821, 511 cm^{-1}; HRMS (ESI-TOF) *m/z* = 425.1116 calc for $C_{24}H_{26}BrO_2$ $[M-H]^-$, found 425.1141.



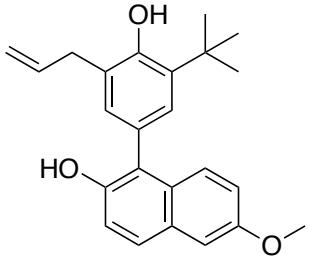
6-Bromo-1-(4-hydroxy-3,5-diisopropylphenyl)naphthalen-2-ol (B6). Following general procedure A for 2 d, the cross-coupled product was obtained as a light orange solid (0.0314 g, 0.0786 mmol) in a 72% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 2.0 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.40 (dd, *J* = 9.0 Hz, 2.0 Hz, 1H) 7.32 (d, *J* = 9.0 Hz, 1H), 7.28 (d, *J* = 9.0 Hz, 1H), 7.06 (s, 2H), 5.32 (s,1H), 5.00 (s, 1H), 3.24 (sept, *J* = 6.9, 2H), 1.30 (d, *J* = 6.8 Hz, 6H), 1.29 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8, 150.5, 135.3, 132.4, 130.2, 130.0, 129.7, 128.2, 126.9, 126.2, 125.1, 122.1, 118.4, 117.1, 27.5, 22.9, 22.8; IR (neat) 3521, 2961, 2927, 1588, 1501, 1461, 1445, 1376, 1362, 1340, 1293, 1258, 1195, 1169, 1148, 1136, 1119, 1071, 882, 825, 812, 470, 452 cm^{-1}; HRMS (ESI-TOF) *m/z* = 397.0803 calc for $C_{22}H_{22}BrO_2$ $[M+H]^+$, found 397.0809.



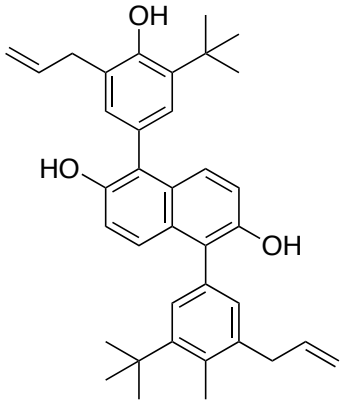
3',5'-Diisopropyl-4,5,6-trimethyl-[1,1'-biphenyl]-2,4'-diol (A9). Following general procedure A for 2 d, the cross-coupled product was obtained as a white solid (0.0056 g, 0.0179 mmol) in an 18% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (s, 2H), 6.72 (s, 1H), 4.90 (s, 1H), 4.73 (s, 1H), 3.19 (sept, *J* = 7.0 Hz, 2H), 2.30 (s, 3H), 2.16 (s, 3H), 2.00 (s, 3H), 1.27-1.25 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 149.7, 136.7, 135.5, 134.7, 127.7, 126.8, 126.6, 125.7, 113.6, 27.2, 22.8, 22.7, 20.8, 17.8, 15.4; IR (neat) 3426, 2960, 2927, 2870, 1589, 1465, 1383, 1363, 1292, 1251, 1199, 1173, 1150, 1112, 1042, 938, 882, 786, 726, 660 cm^{-1}; HRMS (ESI-TOF) *m/z* = 313.2168 calc for $C_{21}H_{29}O_2$ $[M+H]^+$, found 313.2191.



1-(3-Allyl-5-(*tert*-butyl)-4-hydroxyphenyl)-6-bromonaphthalen-2-ol (B8). Following general procedure A for 2 d, the cross-coupled product was obtained as a red-orange solid (0.0681 g, 0.1656 mmol) in an 85% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 2.0 Hz, 1H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.40 (dd, *J* = 7.0 Hz, 2.0 Hz, 1H), 7.32 (d, *J* = 9.0 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 7.01 (d, *J* = 2.0 Hz, 1H), 6.07 (m, 1H), 5.47 (s, 1H), 5.31 (m, 3H), 3.49 (d, *J* = 6.0 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 150.8, 138.5, 136.0, 132.4, 130.7, 130.2, 130.0, 129.7, 128.5, 128.3, 126.9, 126.5, 124.7, 121.7, 118.4, 118.0, 117.1, 36.4, 35.1, 29.9; IR (neat) 3517, 2956, 1725, 1587, 1500, 1475, 1414, 1376, 1362, 1339, 1263, 1226, 1196, 1170, 1144, 1068, 1043, 957, 892, 878, 820, 737, 465, 455 cm^{-1}; HRMS (ESI-TOF) *m/z* = 411.0960 calc for $C_{23}H_{24}BrO_2$ $[M+H]^+$, found 411.0939.

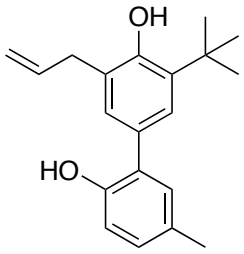


1-(3-Allyl-5-(*tert*-butyl)-4-hydroxyphenyl)-6-methoxynaphthalen-2-ol (B7). Following general procedure A for 2 d, the cross-coupled product was obtained as a dark yellow solid (0.0181 g, 0.0499 mmol) in a 49% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 9.0 Hz, 1H) 7.37 (d, *J* = 9.0 Hz, 1H), 7.23 (d, *J* = 9.0 Hz, 1H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 7.04 (dd, *J* = 9.3 Hz, 2.3 Hz, 1H), 7.02 (s, 1H), 6.07 (m, 1H), 5.42 (s, 1H), 5.30 (m, 2H), 5.13 (s, 1H), 3.91 (s, 3H), 3.49 (d, *J* = 6.5 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 153.9, 148.9, 138.3, 136.1, 130.8, 129.9, 129.0, 128.6, 127.9, 126.5, 126.2, 125.5, 121.7, 119.0, 117.9, 117.7, 55.5, 36.4, 35.1, 29.9; IR (neat) 3530, 2956, 1600, 1515, 1464, 1426, 1374, 1350, 1235, 1170, 1139, 1115, 1073, 1040, 922, 851, 825, 650, 596 cm^{-1}; HRMS (ESI-TOF) *m/z* = 363.1960 calc for $C_{24}H_{27}O_3$ $[M+H]^+$, found 363.1974.

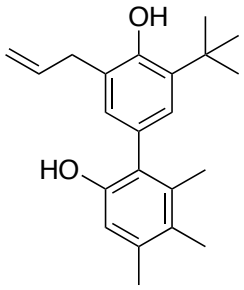


1,5-Bis(3-allyl-5-(*tert*-butyl)-4-hydroxyphenyl)naphthalene-2,6-diol (B14). Following general procedure A for 2 d, the cross-coupled product was obtained as a

purple solid (0.0112 g, 0.0209 mmol) in a 21% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 9.1, 2H), 7.23 (s, 2H), 7.14 (d, *J* = 9.1, 2H), 7.05 (s, 2H), 6.07 (m, 2H), 5.44 (s, 2H), 5.33 (m, 4H), 5.11 (s, 2H), 3.50 (d, *J* = 6.4, 4H), 1.44 (s, 18H); ^{13}C ,NMR (125 MHz, $CDCl_3$) δ 174.3, 153.9, 148.6, 138.3, 136.1, 130.8, 129.0, 128.7, 126.3, 126.1, 125.6, 121.8, 117.9, 117.5, 36.5, 35.1, 29.9; IR (neat) 3420, 3302, 2958, 1596, 1514, 1467, 1400, 1362, 1332, 1187, 1114, 1000, 917, 818, 677, 600 cm^{-1}; HRMS (ESI-TOF) *m/z* = 537.3005 calc for $C_{36}H_{41}O_4$ $[M+H]^+$, found 537.2991.

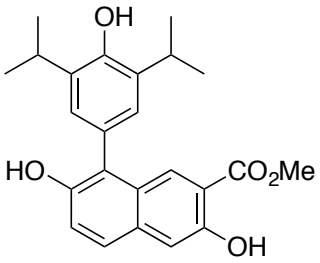


3'-Allyl-5'-(*tert*-butyl)-5-methyl-[1,1'-biphenyl]2,4'-diol (A8). Following general procedure A, phenol A (0.5 mmol), phenol B (0.1 mmol), and Cr-Salen-Cy (0.01 mmol) in $ClCH_2CH_2Cl$ (2.5 mL) were heated at 50 °C for 1 d, and the cross-coupled product was obtained as a red-orange amorphous solid (0.0109 g, 0.0368 mmol) in 28% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 2.8 Hz, 1H), 7.07 (d, *J* = 2.2 Hz, 1H), 7.04-7.02 (m, 2H), 6.87 (d, *J* = 7.9 Hz, 1H), 6.08-6.02 (m, 1H), 5.34 (s, 1H), 5.31-5.26 (m, 2H), 5.13 (s, 1H), 3.46 (d, *J* = 6.0 Hz, 2H), 2.31 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 150.3, 137.9, 135.9, 130.6, 129.8, 129.1, 128.7, 128.7, 128.1, 126.6, 125.9, 117.7, 115.3, 36.3, 34.9, 29.8, 20.5; IR (neat) 3533, 2954, 2919, 2867, 1497, 1471, 1449, 1392, 1361, 1323, 1253, 1230, 1209, 1175, 1125, 999, 919, 876, 815, 712 cm^{-1}; HRMS (ESI) *m/z* = 295.1698 calc for $C_{20}H_{23}O_2$ $[M-H]^-$, found 295.1715.

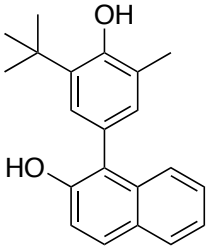


3'-Allyl-5'-(*tert*-butyl)-4,5,6-trimethyl-[1,1'-biphenyl]2,4'-diol (A6). Following general procedure A, phenol A (0.5 mmol), phenol B (0.1 mmol), and Cr-Salen-Cy (0.01 mmol) in $ClCH_2CH_2Cl$ (2.5 mL) were heated at 50 °C for 1 d, and the cross-coupled product was obtained as a yellow solid (0.0113 g, 0.0348 mmol) in a 33% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, *J* = 2.0 Hz, 1H), 6.87 (d, *J* = 2.0 Hz, 1H), 6.71 (s, 1H), 6.09-6.01 (m, 1H), 5.32 (s, 1H), 5.29-5.25 (m, 2H), 4.69 (s, 1H), 3.44 (d, *J* = 6.5 Hz, 2H), 2.30 (s, 3H), 2.16 (s, 3H), 2.00 (s, 3H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 150.7, 138.0, 136.9, 136.2, 135.7, 130.2, 128.2, 127.3, 127.0, 126.4, 126.0, 117.7, 113.8, 36.4, 35.0, 29.9, 21.0, 18.0, 15.5; IR (neat) 3532, 2956, 2925, 2870, 1600, 1443,

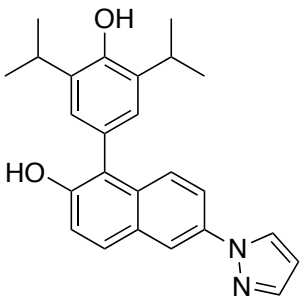
1391, 1362, 1201, 1087, 1037, 999, 919, 798, 748, 701 cm^{-1}; HRMS (EI-TOF) *m/z* = 324.2089 calc for $C_{22}H_{28}O_2$ $[M]^+$, found 324.2095.



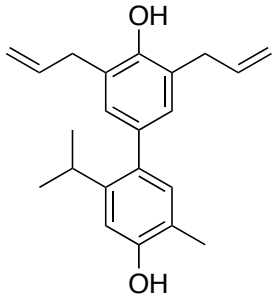
Methyl 3,7-dihydroxy-8-(4-hydroxy-3,5-diisopropylphenyl)-2-naphthoate (B10). Following general procedure A at 55 °C for 2 d, the cross-coupled product was obtained as a yellow solid (0.022 g, 0.056 mmol) in a 56% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.20 (s, 1H), 7.63 (d, J = 9 Hz, 1H), 7.32 (d, J = 9 Hz, 1H), 7.31 (s, 1H), 7.12 (s, 1H), 5.32 (s, 1H), 5.01 (s, 1H), 3.89 (s, 3H), 3.27 (septet, J = 6.9 Hz, 2H), 1.32 (d, J = 7.1 Hz, 6H) 1.28 (d, J = 7.5, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 154.6, 150.2, 148.6, 135.2, 133.7, 129.2, 127.3, 127.0, 126.2, 125.1, 122.2, 121.2, 114.3, 112.1, 52.3, 27.3, 22.9, 22.7; IR (neat) 3521, 2961, 1682, 1523, 1472, 1442, 1415, 1386, 1346, 1323, 1294, 1243, 1198, 1171, 1150, 1122 cm^{-1}; HRMS (EI-TOF) *m/z* = 394.1906 calc for $C_{24}H_{26}O_5$ $[M]^+$, found 394.1905.



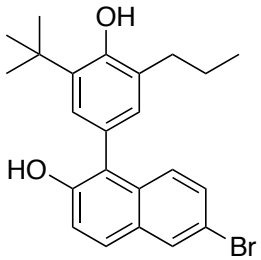
1-(3-(*tert*-Butyl)-4-hydroxy-5-methylphenyl)naphthalen-2-ol (B9). Following general procedure A at 55 °C for 2 d, the cross-coupled product was obtained as a white solid (4.4 mg, 0.0144 mmol) in a 13% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (m, 2H), 7.46 (d, J = 7.0 Hz, 1H), 7.33 (m, 2H), 7.26 (d, J = 8.5 Hz, 1H), 7.17 (d, J = 0.75 Hz, 1H), 7.06 (d, J = 0.75 Hz, 1H), 5.27 (s, 1H), 4.96 (s, 1H), 2.34 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 150.4, 137.1, 133.7, 131.0, 129.1, 128.9, 128.0, 127.9, 126.3, 125.0, 124.8, 124.3, 123.1, 121.4, 117.1, 34.8, 29.8, 16.1; IR (neat) 3523, 2956, 2924, 1620, 1597, 1481, 1465, 1435, 1389, 1362, 1345, 1313, 1263, 1223, 1190, and 1174 cm^{-1}; HRMS (EI-TOF) *m/z* = 306.1620 calc for $C_{21}H_{22}O_2$ $[M]^+$, found 306.1632.



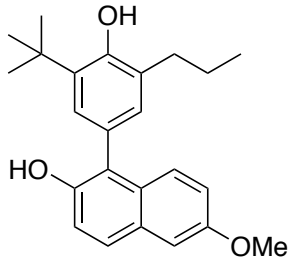
1-(4-Hydroxy-3,5-diisopropylphenyl)-6-(1*H*-pyrazol-1-yl)naphthalen-2-ol (B13). Modifying general procedure A, 2 equiv of phenol A (0.0113 g, 0.0634 mmol) and 1.5 equiv of phenol B[2](0.010 g, 0.0476 mmol were treated at 55 °C for 2 d, and the cross-coupled product was obtained as a brown solid (6.9 mg, 0.0179 mmol) in a 28% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 1H), 8.00 (s, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.75 (d, J = 0.8 Hz, 1H), 7.73 (dd, J = 9.0, 1.2 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.31 (d, J = 9.0 Hz, 1H), 7.11 (s, 2H), 6.49 (t, J = 2.0 Hz, 1H), 5.34 (s, 1H), 5.05 (s, 1H), 3.26 (septet, J = 7.0 , 2H), 1.31 (d, J = 5.5 Hz, 6H), 1.30 (d, J = 6.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 150.5, 141.2, 135.9, 135.3, 132.3, 129.1, 129.1, 127.1, 126.6, 126.3, 125.3, 122.0, 119.2, 118.5, 117.0, 107.7, 27.5, 23.0, 22.9; IR (neat) 3244, 2962, 2928, 2871, 1603, 1519, 1471, 1397, 1352, 1263, 1198, 1168, 1144, 1043, 954, 918 cm^{-1}; HRMS (ESI-TOF) *m/z* = 387.2073 calc for $C_{25}H_{26}N_2O_2$ $[M]^+$, found 387.2086.



3',5'-Diallyl-2-isopropyl-5-methyl-[1,1'-biphenyl]-4,4'-diol (A10). Following general procedure A at 55 °C for 2 d, the cross-coupled product was obtained as a yellow oil (1.1 mg, 0.0034 mmol) in a 4% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (s, 1H), 6.90 (s, 2H), 6.76 (s, 1H), 6.04 (m, 2H), 5.12-5.2 (m 5H), 4.57 (s, 1H), 3.43 (d, J = 7.5 Hz, 4H), 3.00 (septet, J = 7.0 Hz, 1H), 2.22 (s, 3H), 1.12 (d, J = 7.0 Hz, 6H); IR (neat) 3376, 2960, 1780, 1659, 1600, 1514, 1464, 1374, 1234, 1166, 1038, 909, 852, 824, 732, 704 cm^{-1}.

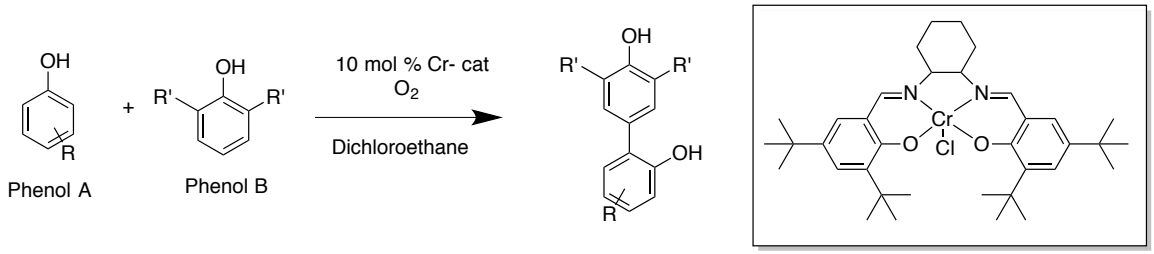


6-Bromo-1-(3-(*tert*-butyl)-4-hydroxy-5-propylphenyl)naphthalen-2-ol (B12). To a solution of 1-(3-allyl-5-(*tert*-butyl)-4-hydroxyphenyl)-6-bromonaphthalen-2-ol (0.010 g, 0.024 mmol) in ethanol (1 mL, 0.02 M) at room temperature was added hydrazine monohydrate (0.010 g, 0.194 mmol). The mixture heated to reflux and stirred for 22 h. After concentration, the resulting solid was treated with H_2O and extracted using ethyl acetate (5 x 10 mL). The combined organic fractions were dried over Na_2SO_4, concentrated, and chromatographed (hexane/EtOAc, 10:1)[2]. The reduced product was obtained as a tan solid (9.3 mg, 0.0225 mmol) in a 93% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 2.0 Hz, 1H), 7.68 (d, J = 9.0 Hz, 1H), 7.40 (dd, J = 9.0, 1 Hz, 1H), 7.33 (d, J = 9.0 Hz, 1H) 7.27 (d, J = 8.5 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H), 7.01 (d, J = 2.0 Hz, 1H), 5.32 (broad, 1H), 5.08 (broad, 1H), 2.62 (dd, J = 6.5, 1.5 Hz, 2H), 1.71 (m, 2H), 1.45 (s, 9H), 1.03 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6, 150.6, 137.3, 132.2, 130.0, 129.9, 129.8, 129.4, 128.9, 128.0, 127.5, 126.7, 124.2, 121.7, 118.2, 116.8, 34.7, 32.0, 29.6, 22.6, 14.0; IR (neat) 3520, 2957, 2925, 1588, 1446, 1377, 1362, 1339, 1316, 1262, 1223, 1186, 1168, 1144, 1122, 1068, 1016 cm^{-1}; HRMS (EI-TOF) *m/z* = 412.1038 calc for $C_{23}H_{25}BrO_2$ $[M]^+$, found 412.1059.

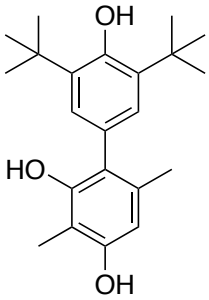


1-(3-(*tert*-Butyl)-4-hydroxy-5-propylphenyl)-6-methoxynaphthalen-2-ol (B11). To a stirring solution of allylated phenol (0.012 g, 0.033 mmol) in dry methanol (0.8 mL) was added Pd/C (0.010 mg). The reaction flask was evacuated and backfilled with H_2 (3 times). The reaction was stirred under H_2 atmosphere for 36 hours. The reaction mixture was then filtered through Celite and concentrated. Chromatography (hexane/EtOAc, 10:1) provided the reduced product was obtained as a tan solid (0.0021 g, 0.0058 mmol) in a 18% yield (~15% impure): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, J = 8.5 Hz, 1H), 7.37 (d, J = 9.0 Hz, 1H), 7.23 (d, J = 9.0 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 7.13 (d, J = 2.0 Hz, 1H) 7.03 (m, 2H), 5.14 (broad, 1H), 5.04 (s, 1H), 3.91 (s, 3H), 2.62 (dd, J = 7.0, 1.5 Hz, 2H), 1.72 (m, 2H), 1.45 (s, 9H), 1.03 (t, J = 7.5 Hz, 3H); IR (neat) 3522, 2959, 1601, 1516, 1465, 1374 cm^{-1} HRMS (ESI-TOF) *m/z* = 363.1960 calc for $C_{24}H_{28}O_3$ $[M-H]^-$, found 363.1944.

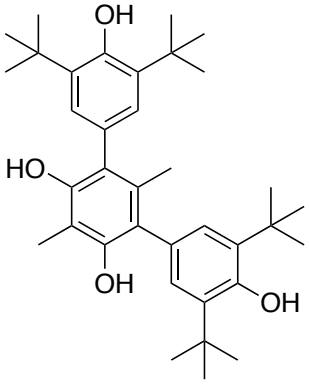
2.2 General Procedure B for Oxidative Coupling of Phenols



To a 5-mL microwave vial was added phenol A (0.3 mmol), phenol B (0.25 mmol) and Cr-Salen-Cy catalyst (0.025 mmol). The vial was sealed with a septum and $ClCH_2CH_2Cl$ (2.5 mL) was added. Oxygen was added via active purge. The septum was replaced with a crimping cap and the vessel was sealed and stirred at the indicated temperature and time. The reaction mixture was filtered through a plug of silica and concentrated. The residue was chromatographed using 10% ethyl acetate/hexane to afford the product.

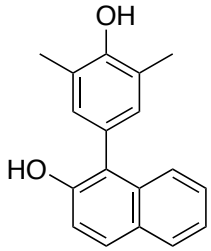


3',5'-Di-*tert*-3,6-methyl-[1,1'-biphenyl]-2,4,4'-triol (A2). Following the general procedure B at 80 °C for 18 h, the product was obtained in 38% yield (15 mg, 0.044 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (s, 2H), 6.34 (s, 1H), 5.29 (s, 1H), 5.09 (s, 1H), 4.66 (s, 1H), 2.16 (s, 3H), 2.01 (s, 3H), 1.44 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 153.3, 152.0, 136.9, 134.8, 127.2, 126.0, 121.5, 108.2, 107.1, 34.5, 30.4, 20.2, 8.2; IR (film) 3536, 3525, 2959, 1727, 1416, 1234, 1080, 908, 734 cm^{-1}; HRMS (ESI-TOF) *m/z* = 341.2117 calc for $C_{24}H_{29}O_3$ $[M-H]^-$, found 341.2115.

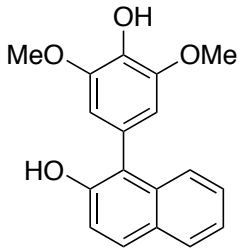


3,3",5,5"-Tetra-*tert*-butyl,2',5'-dimethyl-[1,1':3',1"-terphenyl]-4,4',4",6'-tetraol (A11). Following general procedure B at 80°C for 18 h, the product was obtained in a 29% yield (18 mg, 0.034 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (s, 4H), 5.29 (s,

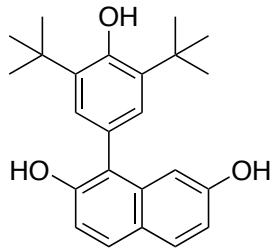
2H), 5.07 (s, 2H), 2.22 (s, 3H), 1.76 (s, 3H), 1.45 (s, 36H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 151.2, 136.9, 132.7, 127.4, 126.5, 121.0, 107.1, 34.5, 30.4, 18.4, 8.7; IR (film) 3638, 3531, 2959, 1616, 1438, 1415, 1234, 1085, 909, 734 cm^{-1}; HRMS (ESI-TOF) *m/z* = 547.3787 calc for $C_{36}H_{51}O_4$ $[M+H]^+$, found 547.3803.



1-(4-Hydroxy-3,5-dimethylphenyl)naphthalene-2-ol (B1). Following general procedure B at 80°C for 18 h, the product was obtained in a 65% yield (20 mg, 0.076 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80-7.76 (m, 2H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.36-7.29 (m, 2H), 7.25 (d, *J* = 9.0 Hz, 1H), 7.03 (s, 2H), 5.24 (s, 1H), 4.79 (s, 1H), 2.23 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 150.3, 133.6, 131.2, 129.1, 128.9, 128.0, 127.0, 126.3, 124.8, 124.3, 123.1, 121.9, 117.2, 16.0; IR (neat) 3638, 3531, 2959, 1616, 1438, 1415, 1234, 1085, 909, 734 cm^{-1}; HRMS (ESI-TOF) *m/z* = 264.1150 calc for $C_{18}H_{16}O_2$ $[M]^+$, found 264.1148.

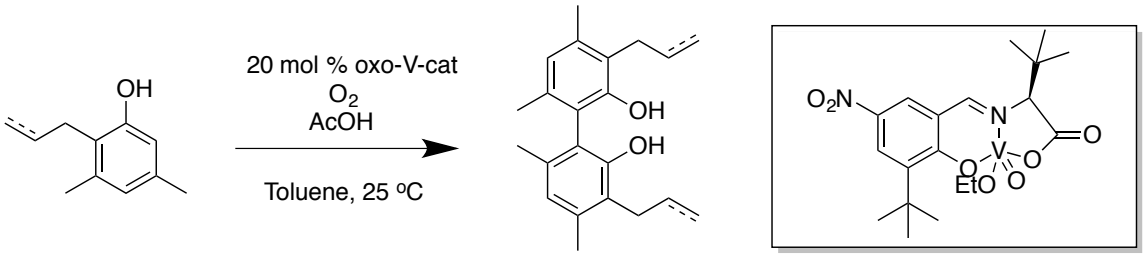


1-(4-Hydroxy-3,5-dimethoxyphenyl)naphthalen-2-ol (B2). Following the general procedure B at 80 °C for 24 h, product was obtained in 72% yield (20 mg, 0.067 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) 7.82 (d, *J* = 5.0 Hz, 1H), 7.80 (d, *J* = 6.5 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.39-7.34 (m, 2H), 7.27 (d, *J* = 9.0 Hz, 1H), 6.64 (s, 2H), 5.70 (s, 1H), 5.30 (s, 1H), 3.90 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 150.3, 148.0, 134.7, 133.5, 129.4, 128.8, 128.0, 126.5, 124.6, 124.5, 123.3, 121.0, 117.2, 107.4, 56.4; IR (film) 3466, 1620, 1518, 1465, 1393, 1335, 1212, 1114, 817, 735, 634 cm^{-1}; HRMS (ESI) *m/z* = 297.1127 calc for $C_{18}H_{17}O_4$ $[M+H]^+$, found 297.1132.

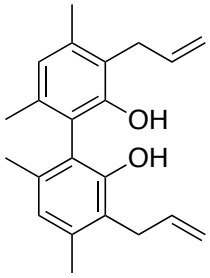


1-(3,5-Di-*tert*-butyl-4-hydroxyphenol)naphthalene-2-7-diol (B4). Following general procedure B at 80°C for 18 h, the product was obtained in a 88% yield (30 mg, 0.083 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, J = 2.0 Hz, 1H), 7.70 (d, J = 3.0 Hz, 1H), 7.16 (s, 2H), 7.11 (d, J = 9.0 Hz, 1H), 6.93 (dd, J = 9.0 Hz, 2.0 Hz, 1H), 6.74 (d, J = 2.0 Hz, 1H), 5.39 (s, 1H), 5.26 (s, 1H), 4.88 (s, 1H), 1.47 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 151.1, 137.3, 135.2, 130.0, 128.9, 127.5, 124.5, 124.3, 120.7, 114.8, 114.6, 107.1, 34.5, 30.4; IR (film) 3498, 2959, 1625, 1516, 1434, 1172, 831, 738 cm^{-1}; HRMS (ESI-TOF) *m/z* = 363.1960 calc for $C_{24}H_{27}O_3$ $[M-H]^-$, found 363.1946.

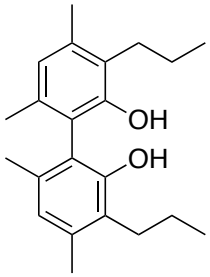
2.3 General Procedure C for Oxidative Coupling of Phenols



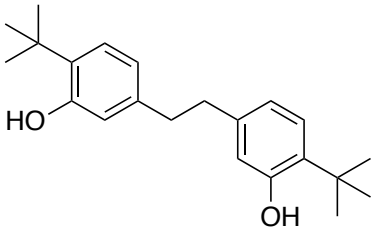
To a microwave vial was added phenol, 20 mol % oxovanadium catalyst, and acetic acid (6.25 equiv). The vial was sealed and toluene (0.5 M) was added. Oxygen was added via active purge. The mixture was stirred for the specified time at 25 °C, and then concentrated. The residue was chromatographed to yield the homo-coupled product.



3,3'-Diallyl-4,4',6,6'-tetramethyl-[1,1'-biphenyl]-2,2'diol (A5). Following the general procedure C, 2-allyl-3,5-dimethylphenol (0.2 mmol) after 3 d afforded the product as a white solid (18 mg, 0.06 mmol) in 56% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (s, 2H), 5.99-5.92 (m, 2H), 5.00-4.93 (m, 4H), 4.77 (s, 2H), 3.44-3.42 (m, 4H), 2.30 (s, 6H), 1.93 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 138.6, 136.0, 135.9, 124.2, 121.9, 117.2, 114.4, 30.6, 19.4, 19.2; IR (film) 3524, 3077, 2922, 1637, 1564, 1457, 1302, 1258, 1191, 1144, 1110, 1050, 995, 909, and 851 cm^{-1}; HRMS (ESI-TOF) *m/z* = 323.2011 calc for $C_{22}H_{27}O_2$ $[M+H]^+$, found 323.2020.

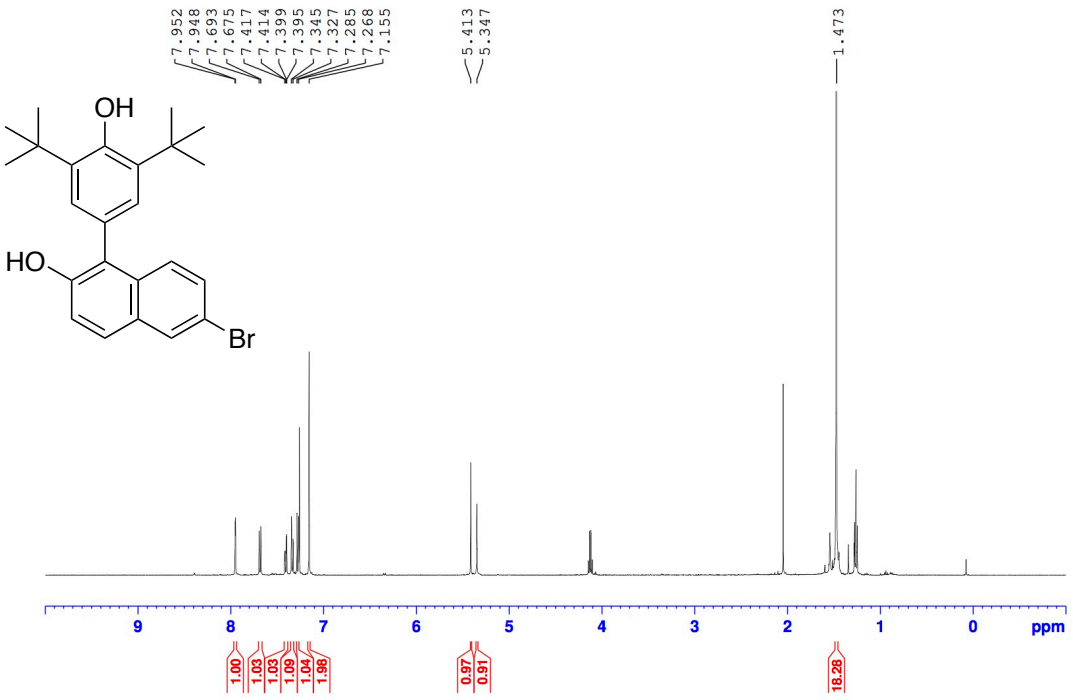


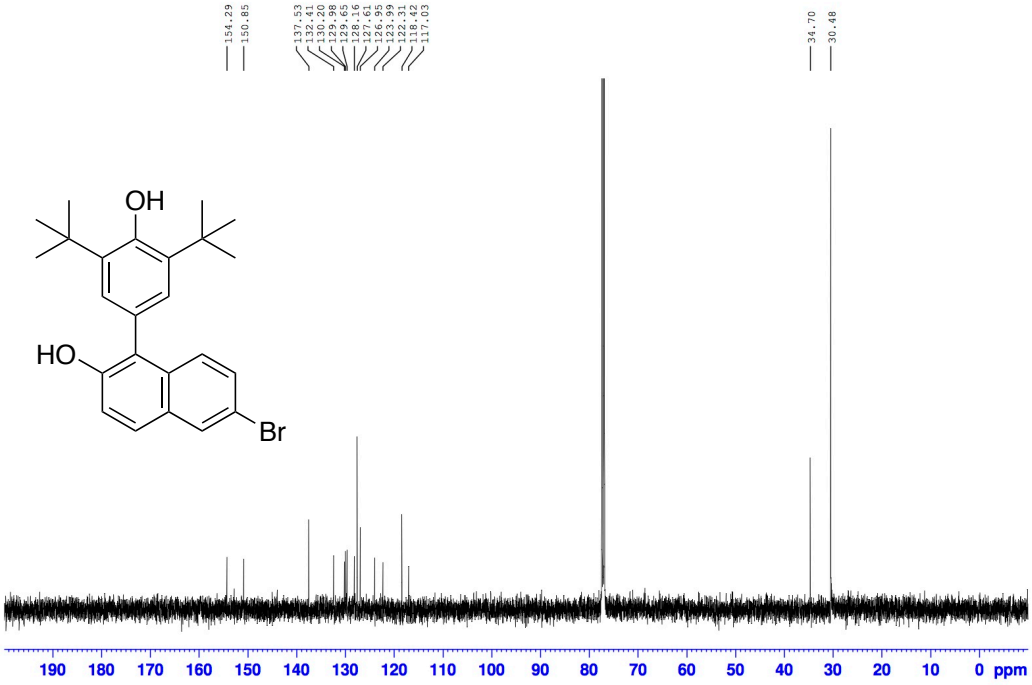
4,4',6,6'-Tetramethyl-3,3'-dipropyl-[1,1'-diphenyl]2,2'diol (A4). Following the general procedure C, 3,5-dimethyl-2-propylphenol (0.2 mmol) after 3 d afforded the product as a white solid (26 mg, 0.08 mmol) in 80% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.72 (s, 2H), 4.72 (s, 2H), 2.64-2.61 (m, 4H), 2.32 (s, 6H), 1.92 (s, 6H), 1.58-1.53 (m, 4H), 0.98-0.95 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 138.0, 135.2, 125.2, 124.0, 117.1, 28.5, 22.4, 19.4, 19.2, 14.3; IR (film) 3524, 2959, 2871, 1616, 1563, 1453, 1394, 1296, 1260, 1205, 1146, 1103, 1039, 954, 850 cm^{-1}; HRMS (ESI-TOF) *m/z* = 327.2324 calc for $C_{22}H_{31}O_2$ $[M+H]^+$, found 327.2323.

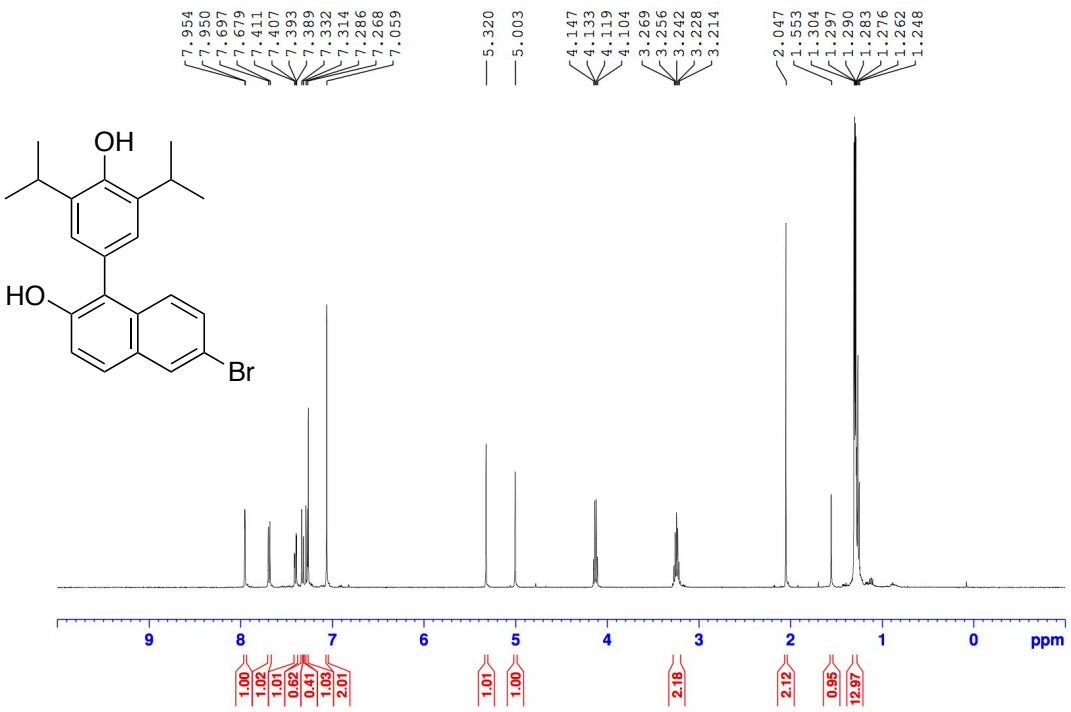


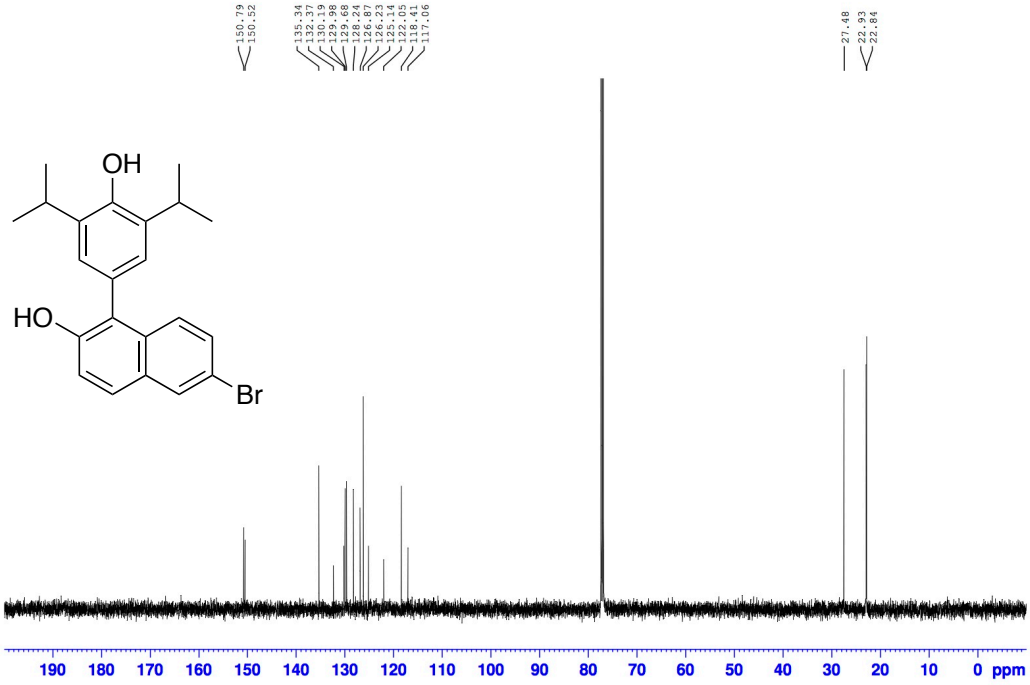
5,5'-(Ethane-1,2-diyl)bis(2-(*tert*-butyl)phenol) (C2). To a solution of 3,3'-ethane-1,2-diyl)diphenol[1] (166 mg, 0.77 mmol) in CH_2Cl_2 (4 mL, 0.2 M) at 0 °C was added *tert*-butanol (62 mg, 2.4 equiv) and conc H_2SO_4 (80 mg, 2.4 equiv). The mixture was allowed to warm to room temperature and stirred for 24 h. It was quenched with $NaHCO_3$ (5 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic fractions were dried over $MgSO_4$, concentrated and chromatographed (hexane/EtOAc, 8:1). The product was obtained in 57% yield as a white solid (0.1570 g, 0.4809 mmol): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, *J* = 8.0 Hz, 2H), 6.74 (dd, *J* = 8.0 Hz, 1.5 Hz, 2H), 6.52 (d, *J* = 1.5 Hz, 2H), 4.71(s, 2H), 2.81 (s, 4H), 1.41 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 141.2, 133.9, 127.2, 120.4, 116.7, 36.9, 34.5, 29.9; IR (neat) 3513, 2955, 2869, 1709, 1615, 1483, 1468, 1416, 1390, 1375, 1362, 1297, 1260, 1201, 1184, 1137, 1079, 1043, 858, 816, 573 cm^{-1}; HRMS (ESI-TOF) *m/z* = 327.2324 calc for $C_{22}H_{31}O_2$ $[M+H]^+$, found 327.2296.

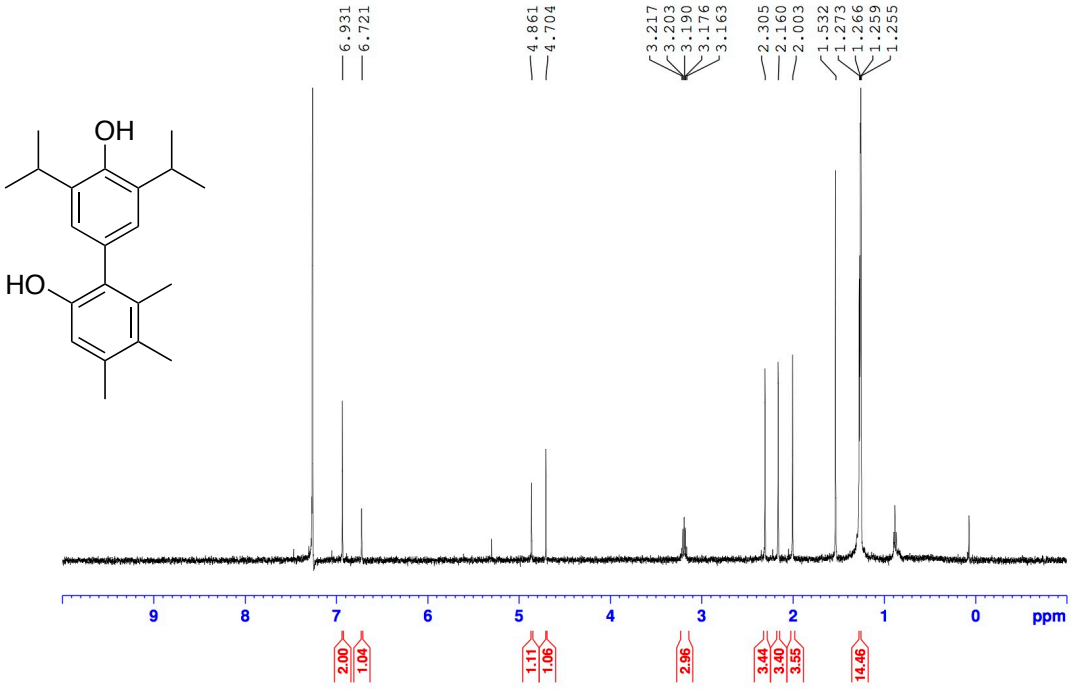
3. Experimental Spectra



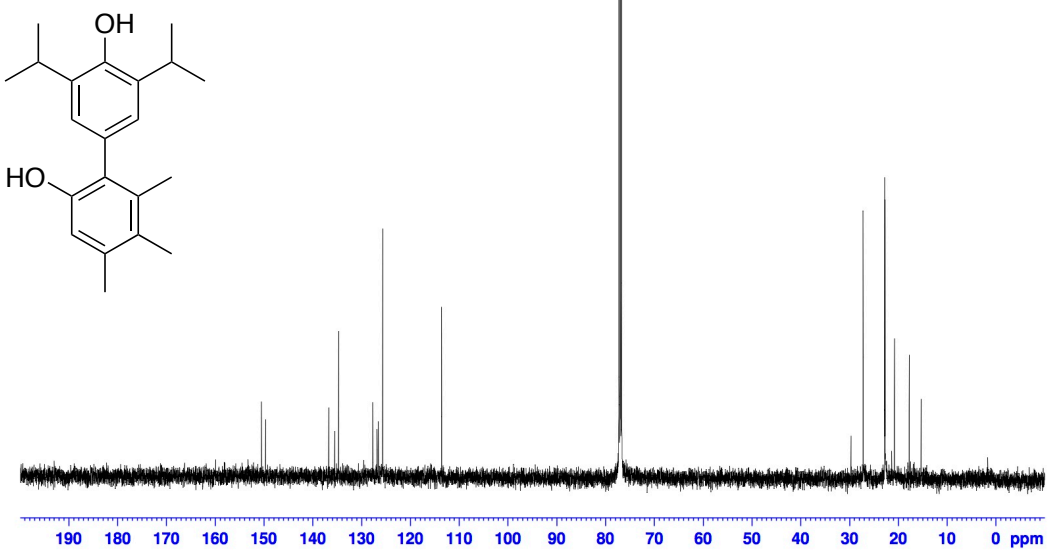


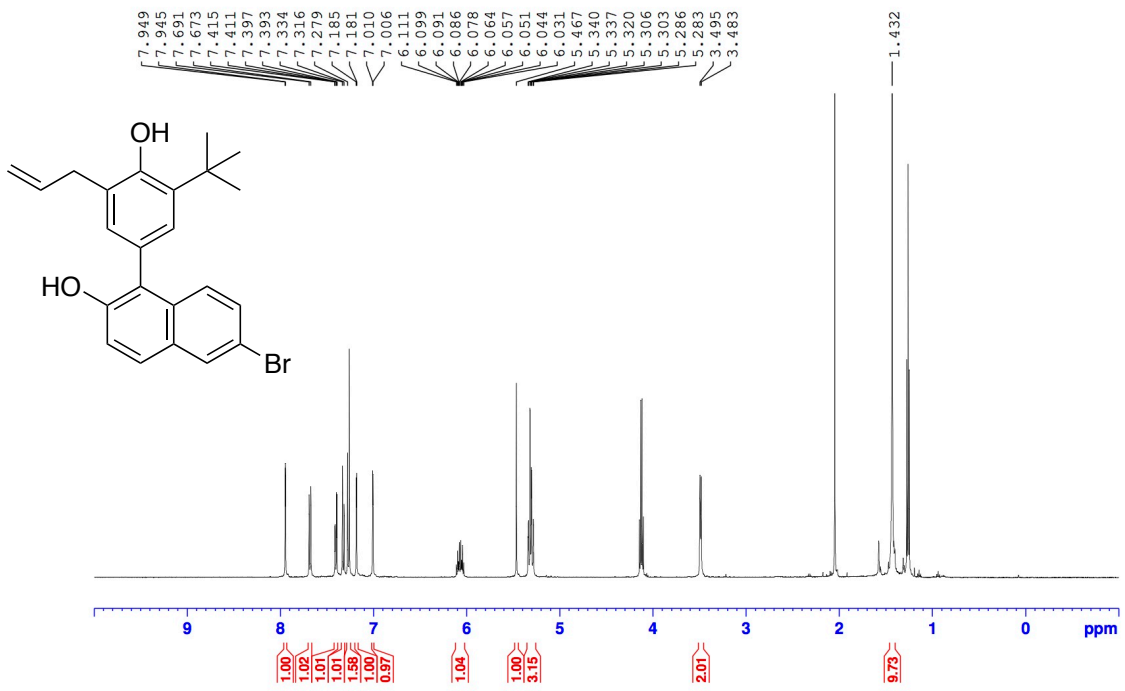

7.954
7.950
7.697
7.679
7.411
7.407
7.393
7.389
7.332
7.314
7.286
7.268
7.059
5.320
5.003
4.147
4.133
4.119
4.104
3.269
3.256
3.242
3.228
3.214
2.047
1.553
1.304
1.297
1.290
1.283
1.276
1.262
1.248
OH
HO
Br
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.02
1.01
0.62
0.41
1.03
2.01
1.01
1.00
2.18
2.12
0.95
12.97

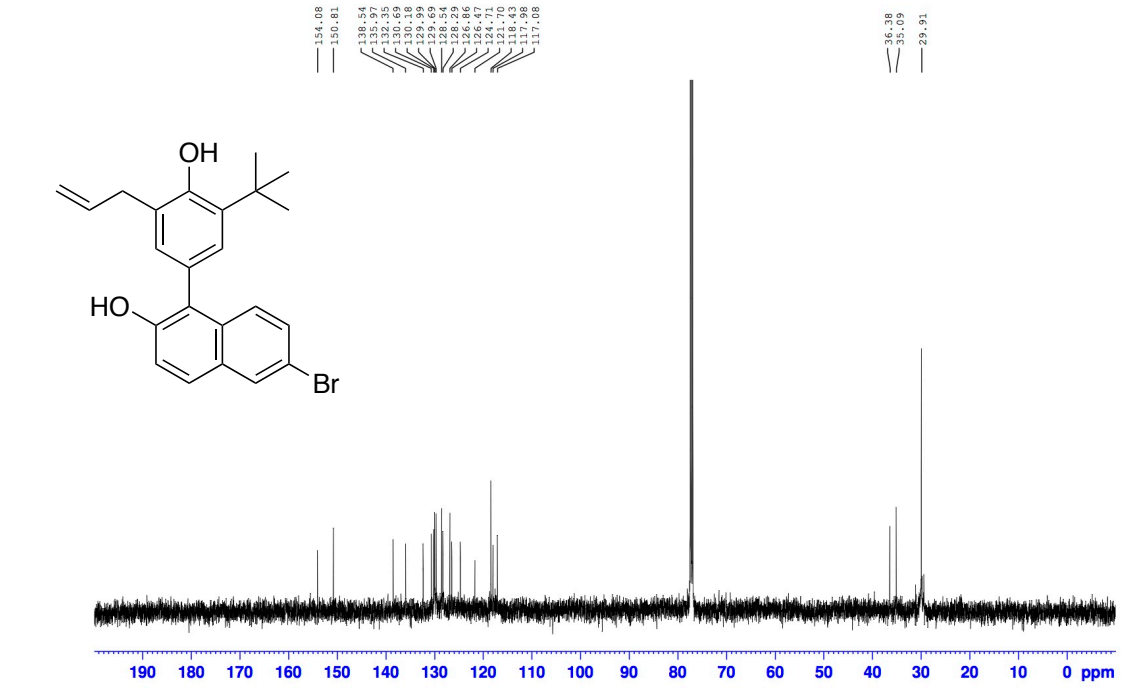

150.79
150.52
135.34
132.37
130.19
129.98
129.68
128.24
126.87
126.23
125.14
122.05
118.41
117.06
27.48
22.93
22.84
OH
HO
Br
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

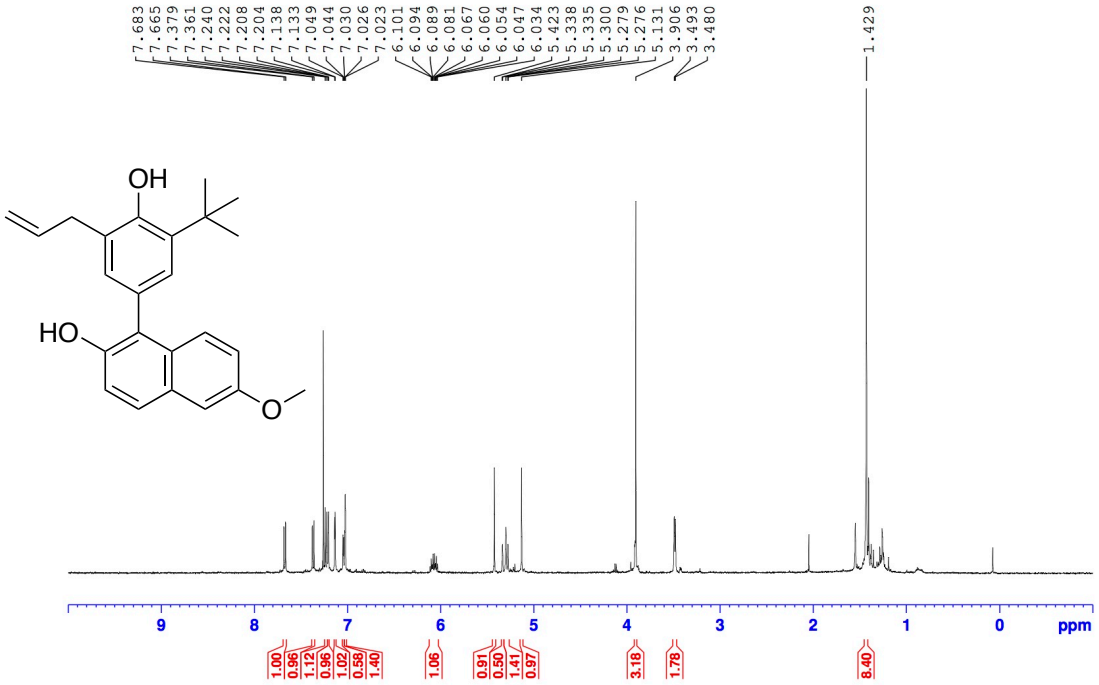

OH
HO
6.931
6.721
4.861
4.704
3.217
3.203
3.190
3.176
3.163
2.305
2.160
2.003
1.532
1.273
1.266
1.259
1.255
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.04
1.11
1.06
2.96
3.44
3.40
3.55
14.46

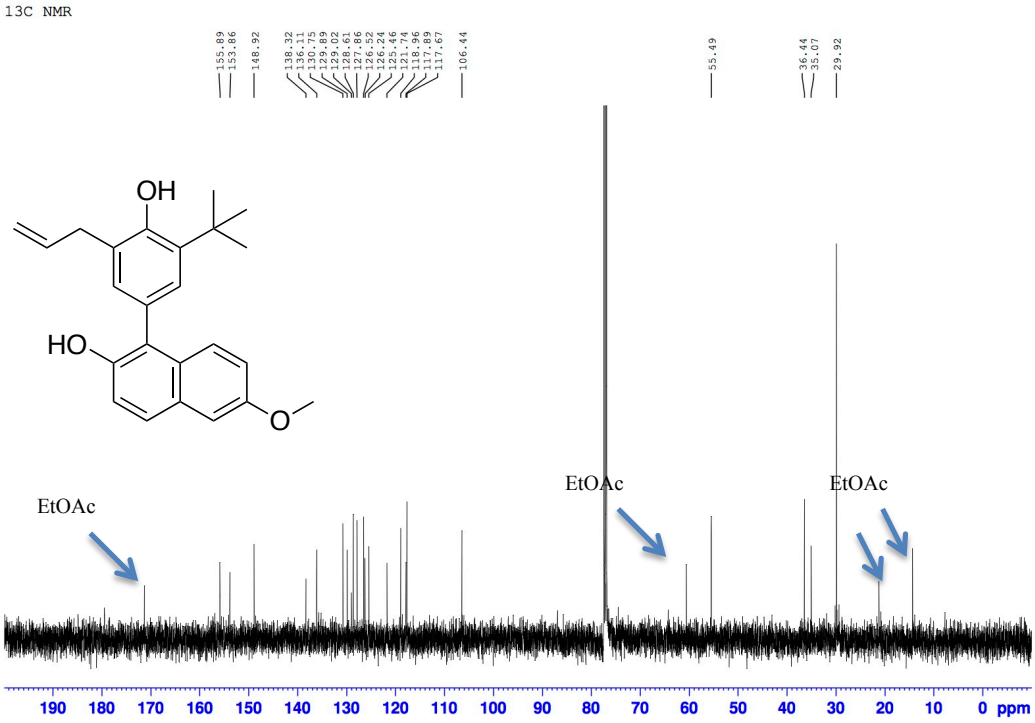
13C NMR

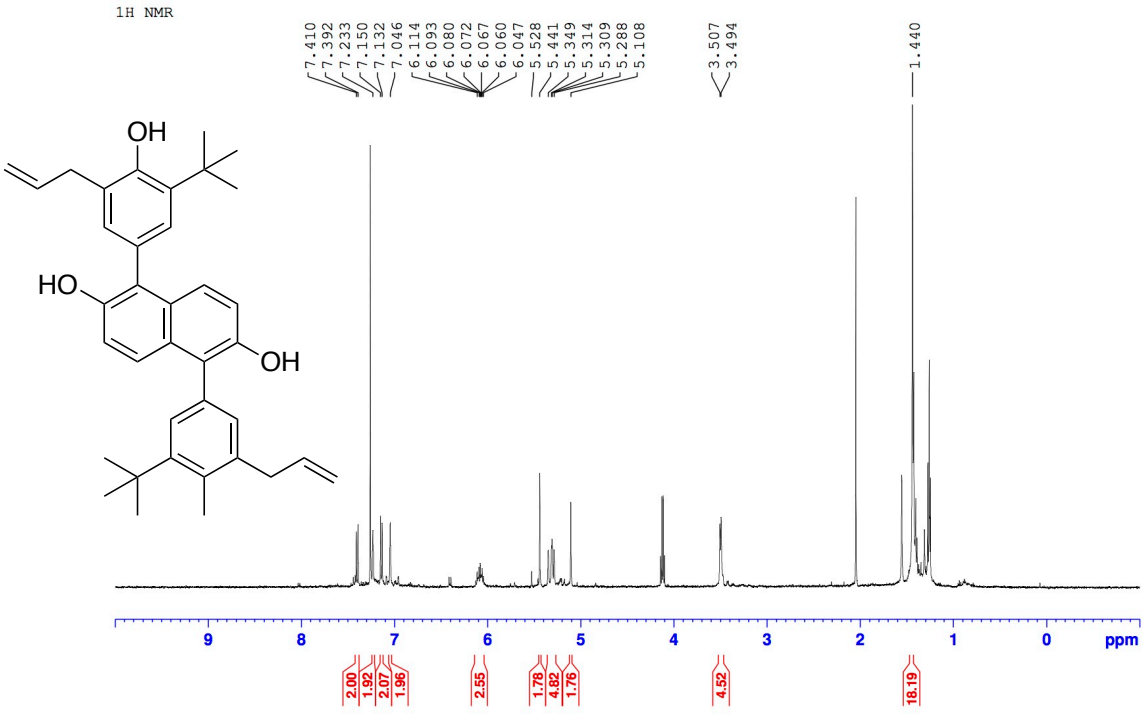

OH
HO
150.54
149.67
136.73
135.53
134.71
127.72
126.84
126.60
125.67
113.62
29.71
27.23
22.83
22.73
20.82
17.79
15.35
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

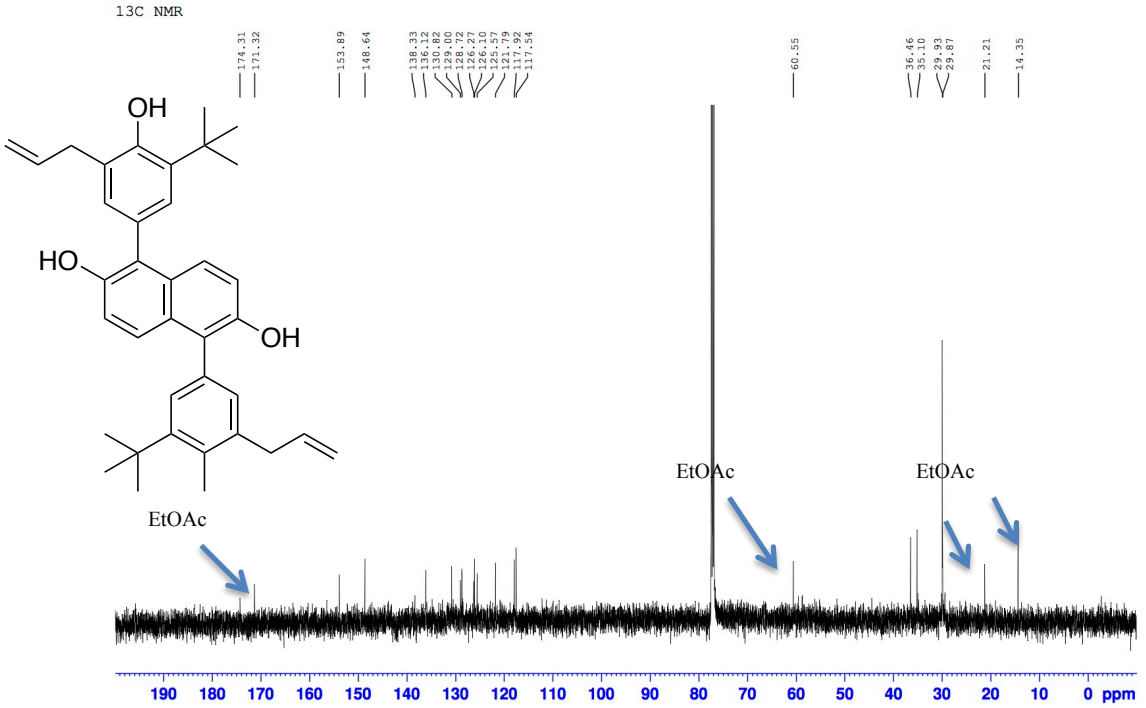

7.949
7.945
7.691
7.673
7.415
7.411
7.397
7.393
7.334
7.316
7.279
7.185
7.181
7.010
7.006
6.111
6.099
6.091
6.086
6.078
6.064
6.057
6.051
6.044
6.031
5.467
5.340
5.337
5.320
5.306
5.303
5.286
5.283
3.495
3.483
1.432
OH
HO
Br
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.02
1.01
1.01
1.58
1.00
0.97
1.04
1.00
3.15
2.01
9.73


154.08
150.81
138.54
135.97
132.35
130.69
130.18
129.99
129.69
128.54
128.29
126.66
126.47
124.71
121.70
118.43
117.98
117.08
36.38
35.09
29.91
OH
HO
Br
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

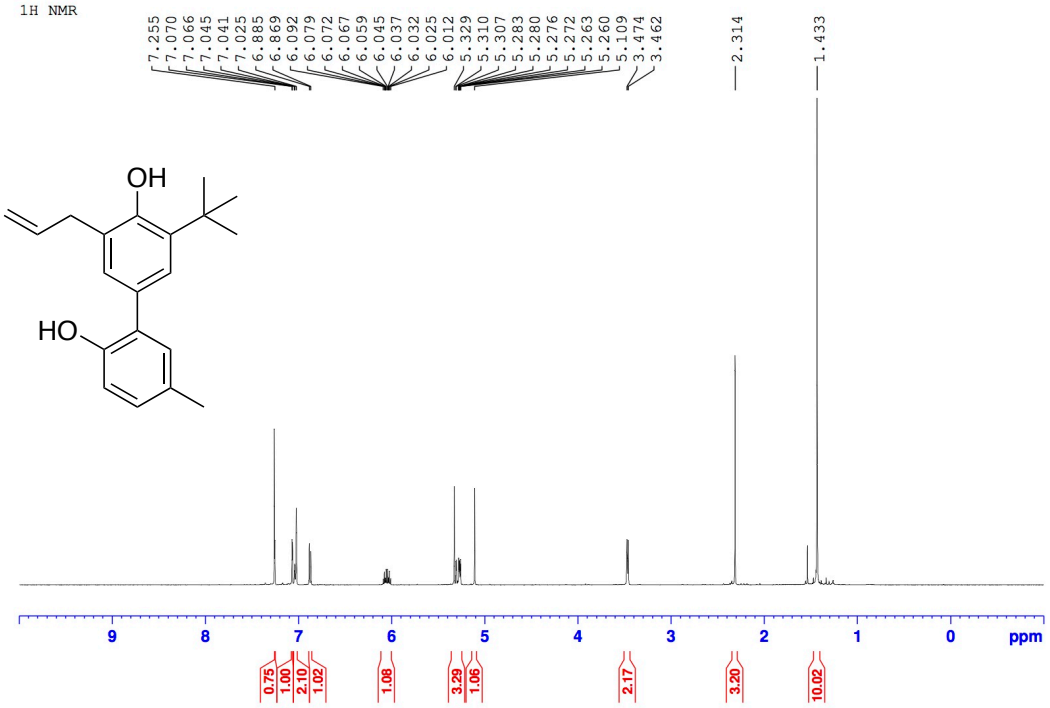

7.683
7.665
7.379
7.361
7.240
7.222
7.208
7.204
7.138
7.133
7.049
7.044
7.030
7.026
7.023
6.101
6.094
6.089
6.081
6.067
6.060
6.054
6.047
6.034
5.423
5.338
5.335
5.300
5.279
5.276
5.131
3.906
3.493
3.480
1.429
OH
HO
O
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.96
1.12
0.96
1.02
0.58
1.40
1.06
0.91
0.50
1.41
0.97
3.18
1.78
8.40


13C NMR
155.89
153.86
148.92
138.32
136.11
130.75
129.89
129.02
128.61
127.86
126.52
126.24
125.46
123.78
118.96
117.89
117.67
106.44
55.49
36.44
35.07
29.92
OH
HO
O
EtOAc
EtOAc
EtOAc
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

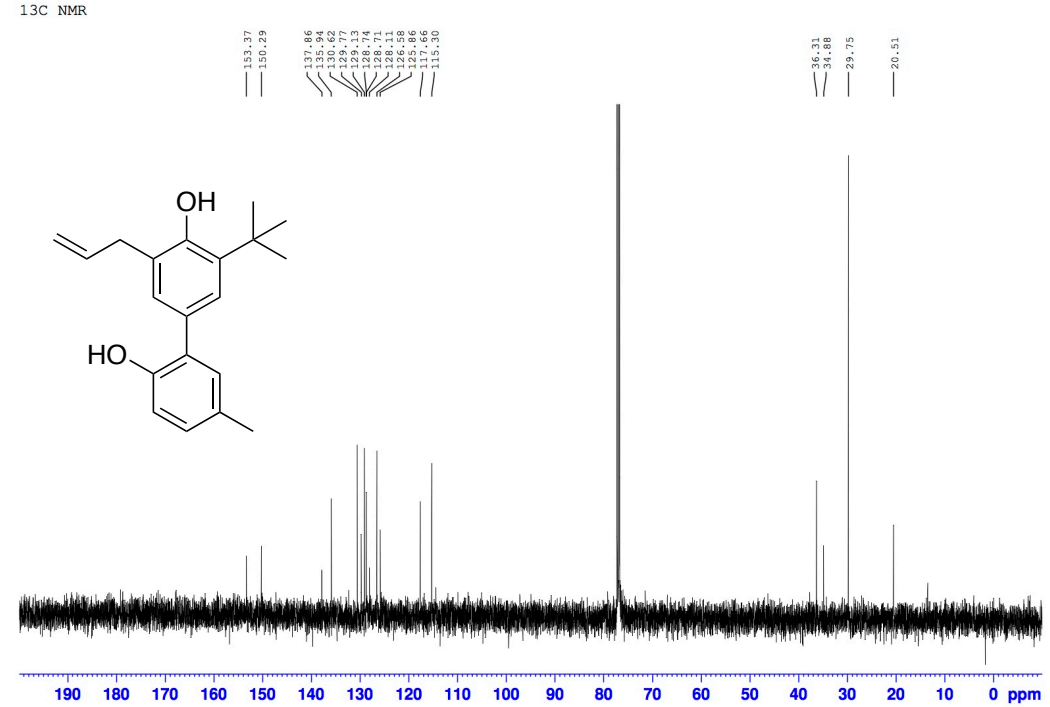

1H NMR
7.410
7.392
7.233
7.150
7.132
7.046
6.114
6.093
6.080
6.072
6.067
6.060
6.047
5.528
5.441
5.349
5.314
5.309
5.288
5.108
3.507
3.494
1.440
OH
HO
OH
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.92
2.07
1.96
2.55
1.78
4.82
1.76
4.52
18.19

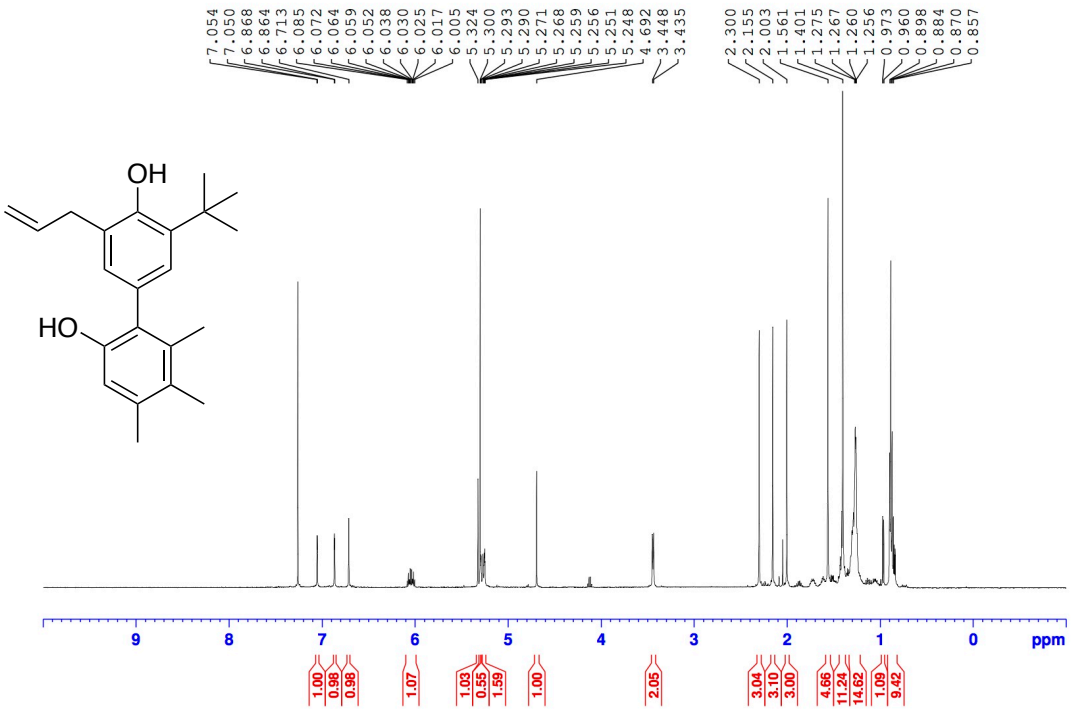

13C NMR
174.31
171.32
153.89
148.64
138.33
136.12
130.82
129.00
128.72
126.27
126.10
125.57
121.79
117.92
117.54
60.55
36.46
35.10
29.93
29.87
21.21
14.35
OH
HO
OH
EtOAc
EtOAc
EtOAc
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

1H NMR

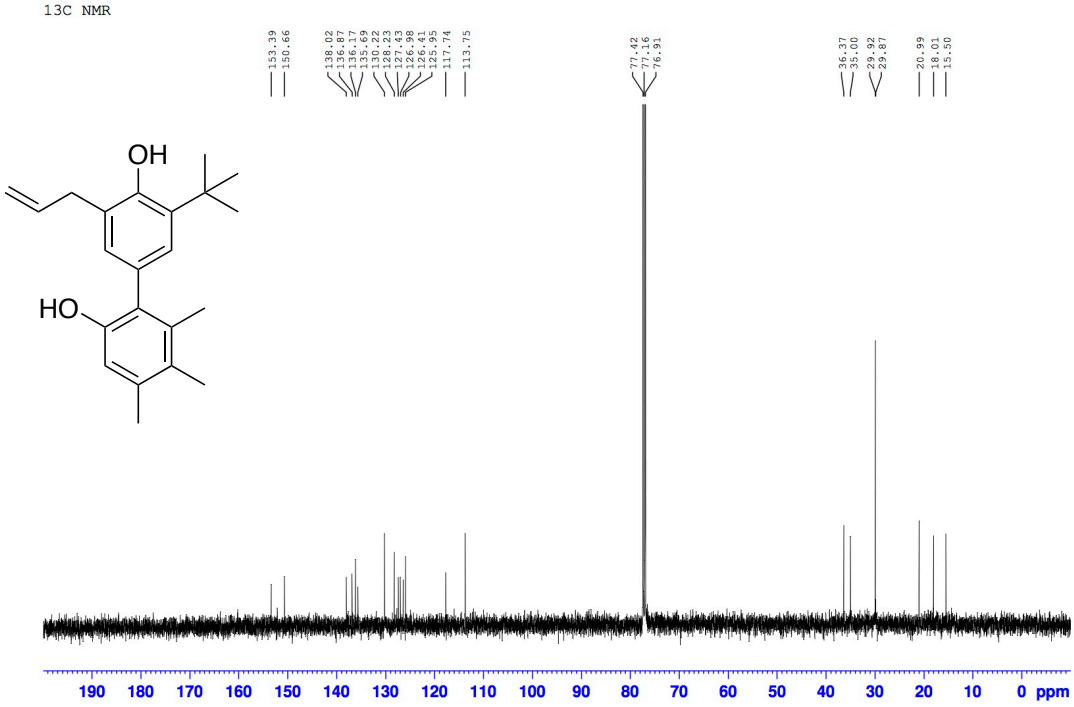


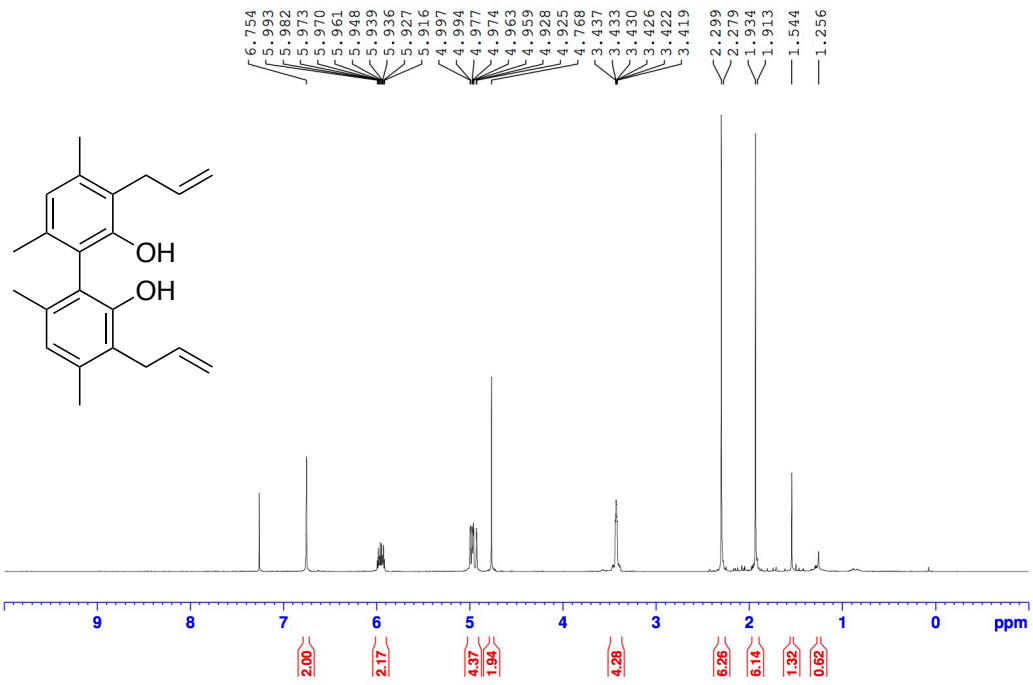
13C NMR



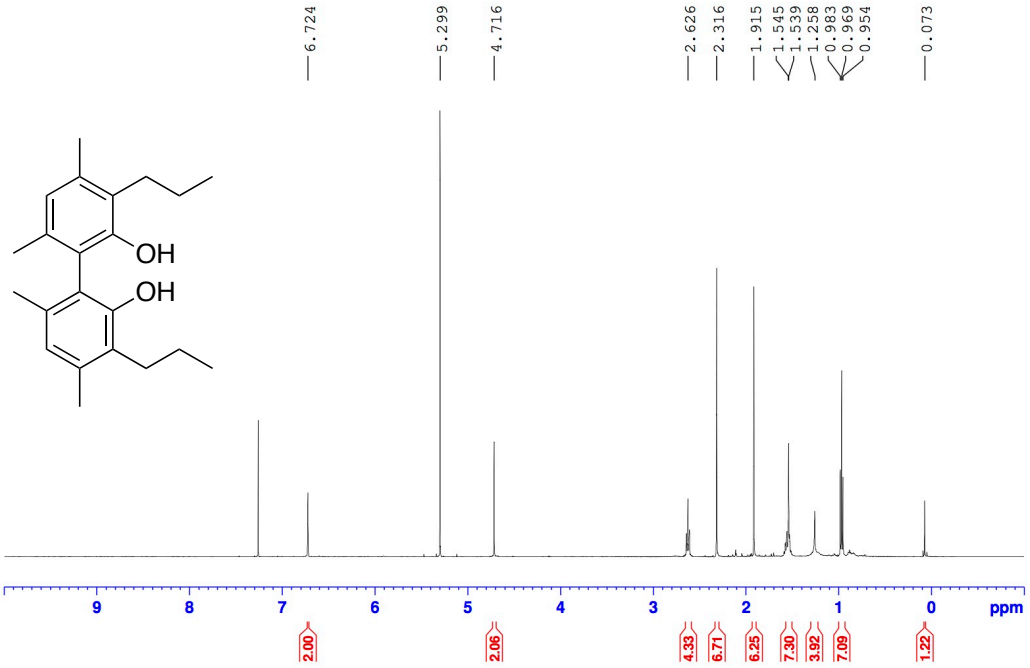

7.054
7.050
6.868
6.864
6.713
6.085
6.072
6.064
6.059
6.052
6.038
6.030
6.025
6.017
6.005
5.324
5.300
5.293
5.290
5.271
5.268
5.259
5.256
5.251
5.248
4.692
3.448
3.435
2.300
2.155
2.003
1.561
1.401
1.275
1.267
1.260
1.256
0.973
0.960
0.898
0.884
0.870
0.857
OH
HO
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.98
0.98
1.07
1.03
0.55
1.59
1.00
2.05
3.04
3.10
3.00
4.66
11.24
14.62
1.09
9.42

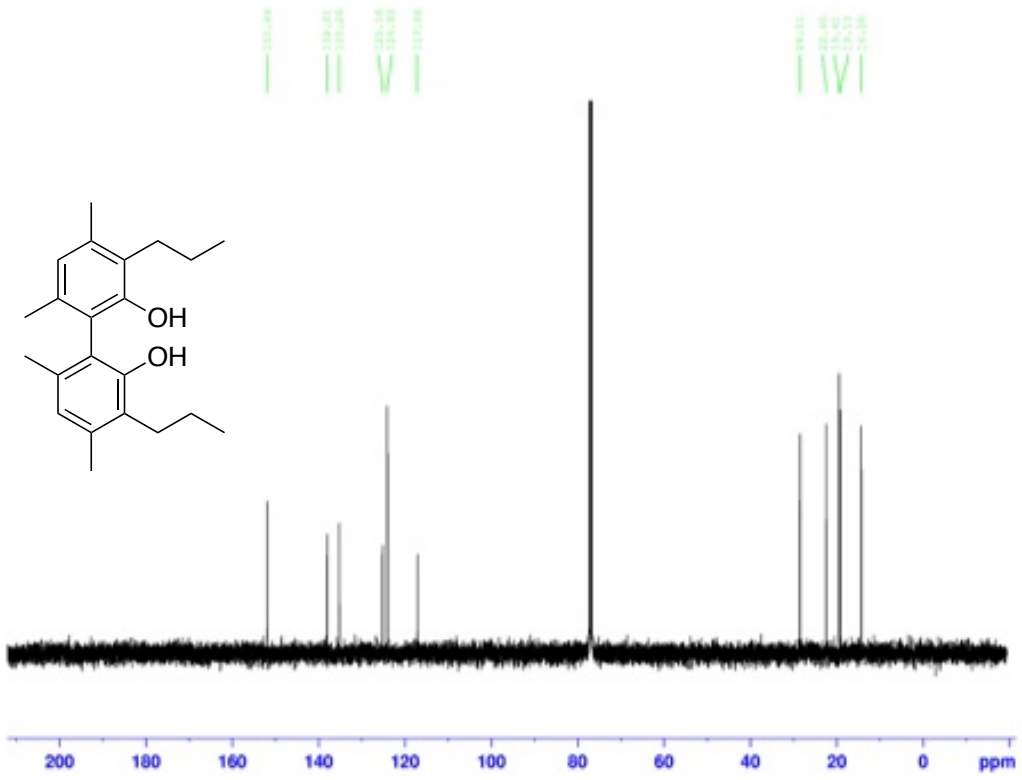
13C NMR

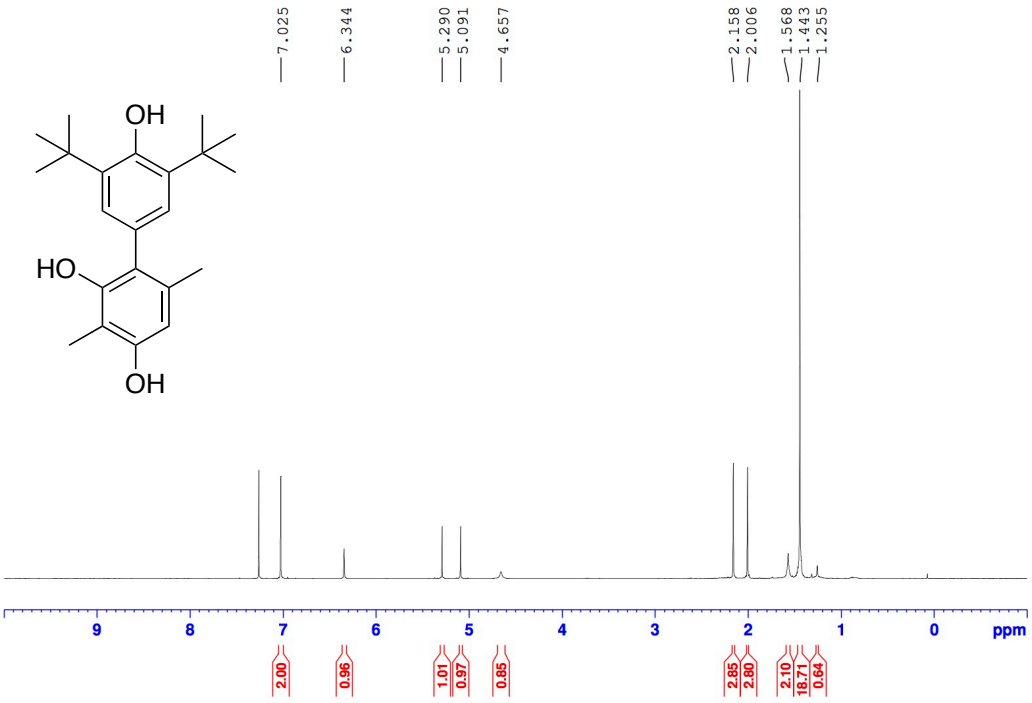

153.39
150.66
138.02
136.87
136.17
135.69
130.22
128.33
127.43
126.98
126.41
125.95
117.74
113.75
77.42
77.16
76.91
36.37
35.00
29.92
29.87
20.99
18.01
15.50
OH
HO
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

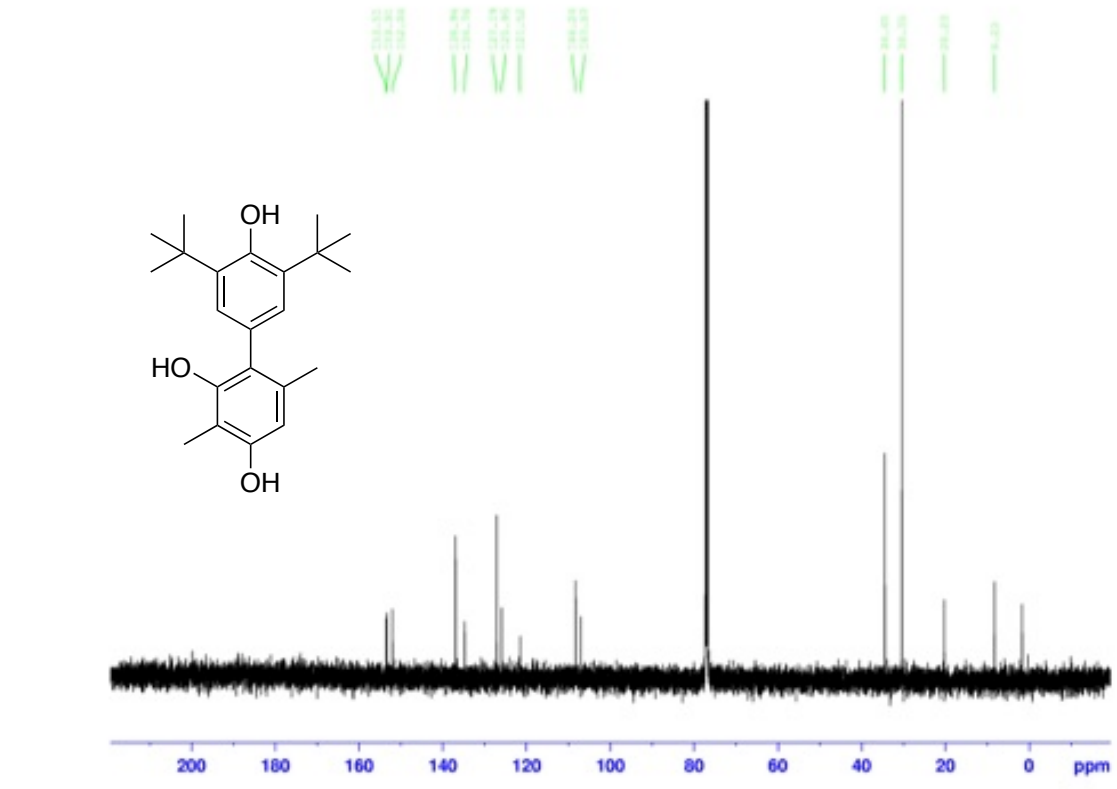

6.754
5.993
5.982
5.973
5.970
5.961
5.948
5.939
5.936
5.927
5.916
4.997
4.994
4.977
4.974
4.963
4.959
4.928
4.925
4.768
3.437
3.433
3.430
3.426
3.422
3.419
2.299
2.279
1.934
1.913
1.544
1.256
OH
OH
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.17
4.37
1.94
4.28
6.26
6.14
1.32
0.62

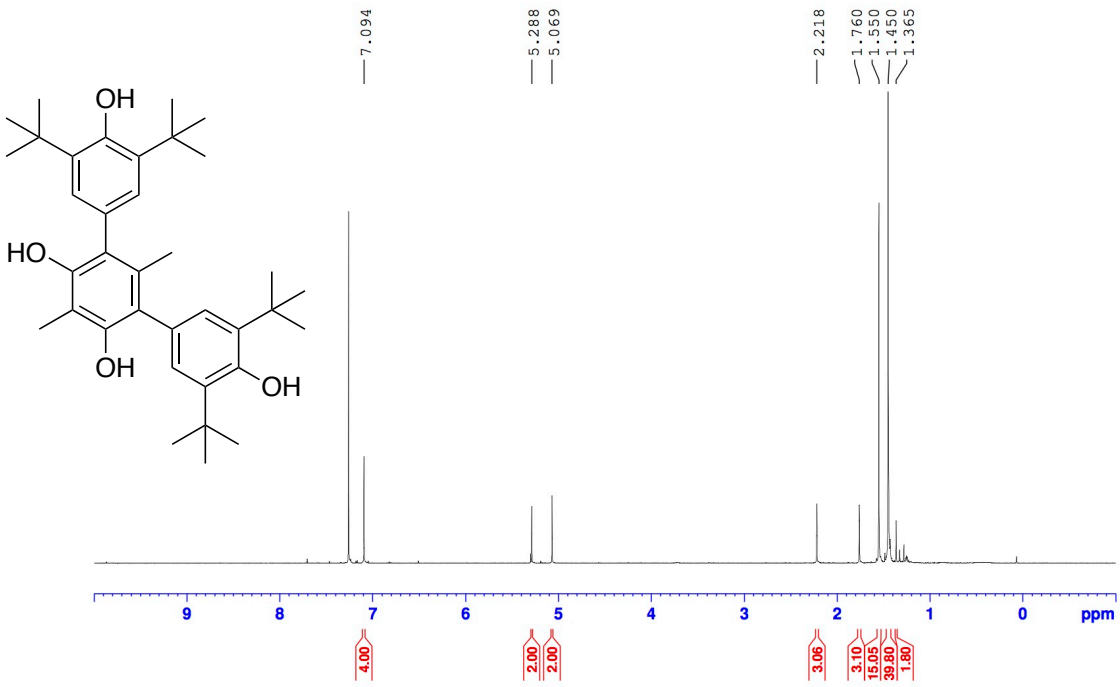
1H NMR

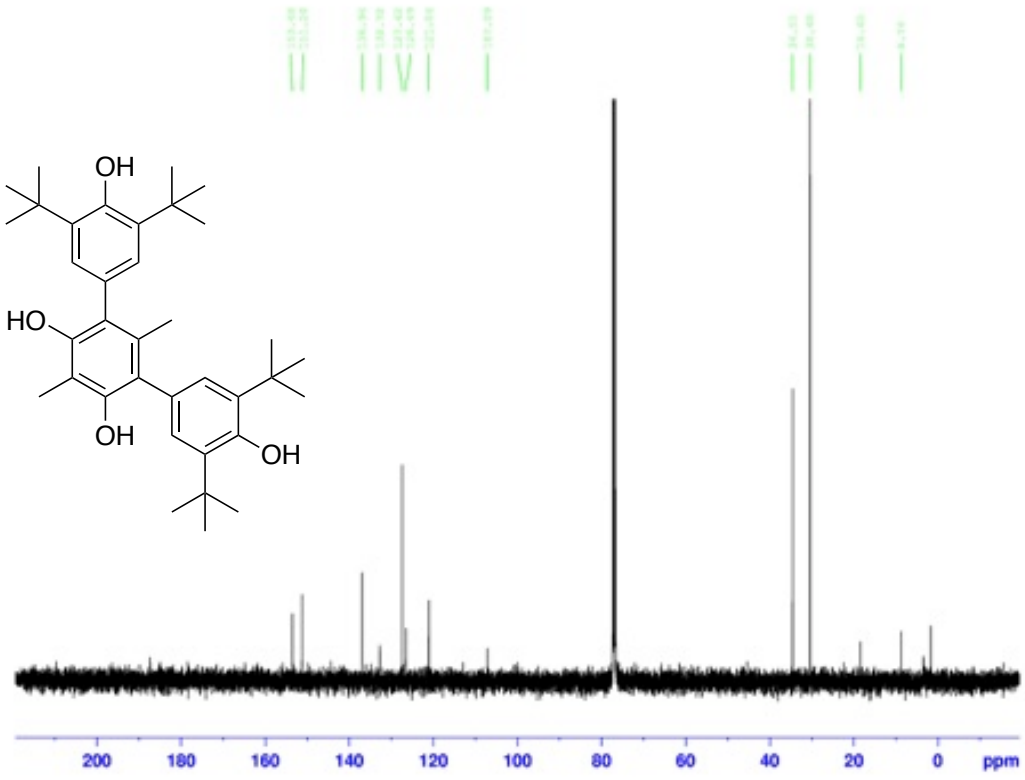

6.724
5.299
4.716
2.626
2.316
1.915
1.545
1.539
1.258
0.983
0.969
0.954
0.073
OH
OH
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.06
4.33
6.71
6.25
7.30
3.92
7.09
1.22

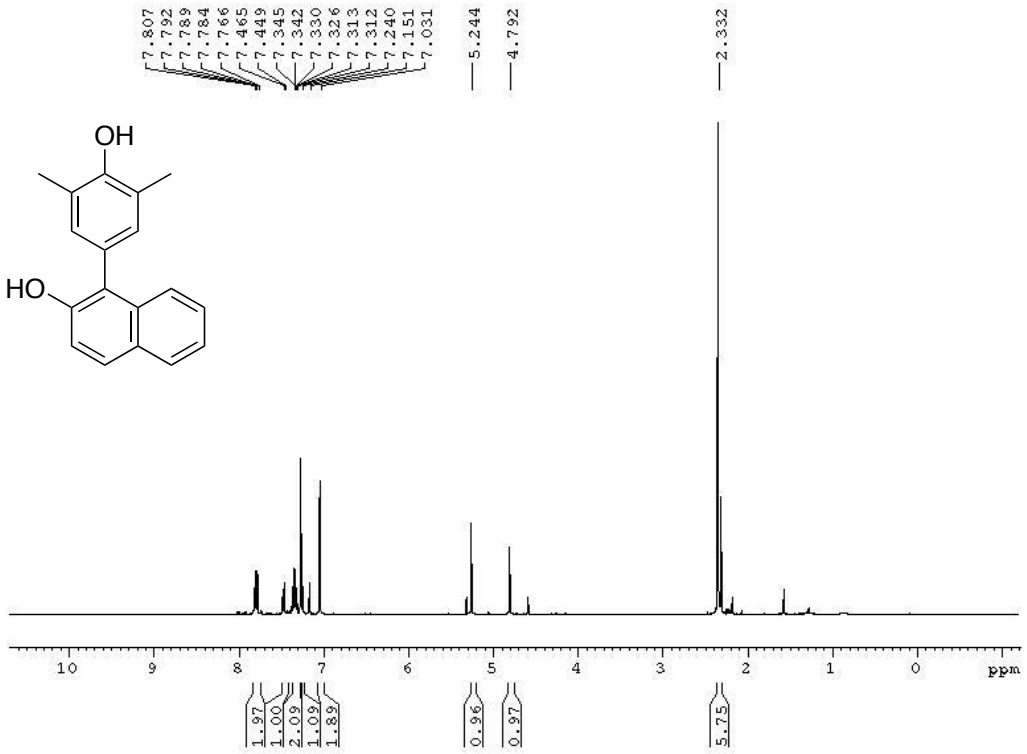

OH
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

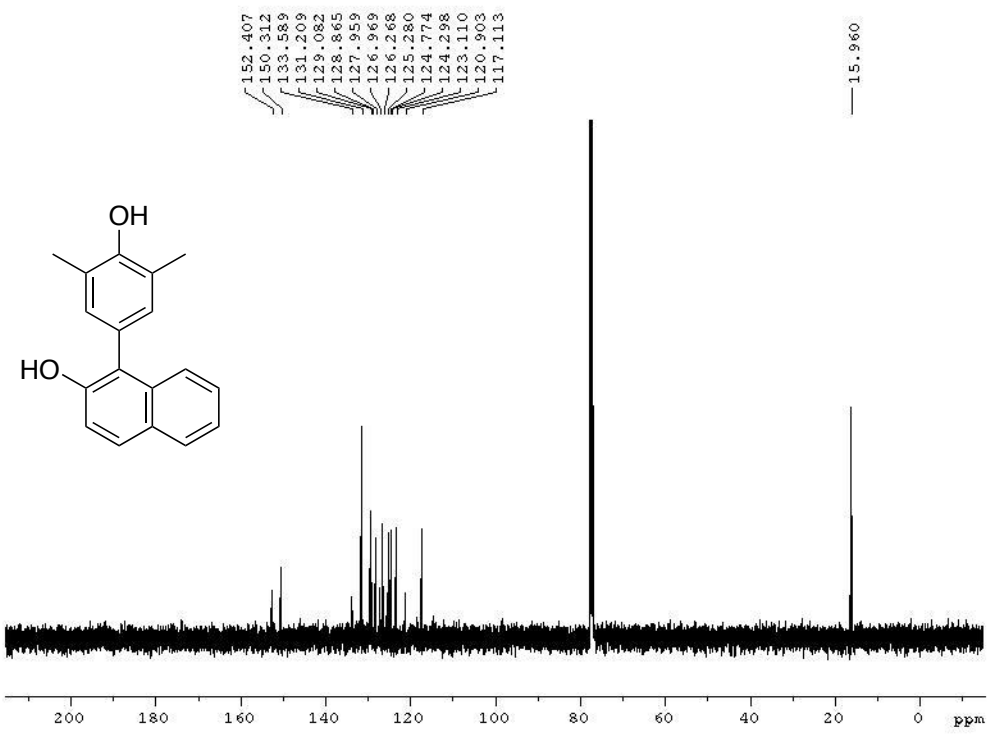

7.025
6.344
5.290
5.091
4.657
2.158
2.006
1.568
1.443
1.255
OH
HO
OH
9
8
7
6
5
4
3
2
1
0
ppm
2.00
0.96
1.01
0.97
0.85
2.85
2.80
2.10
18.71
0.64

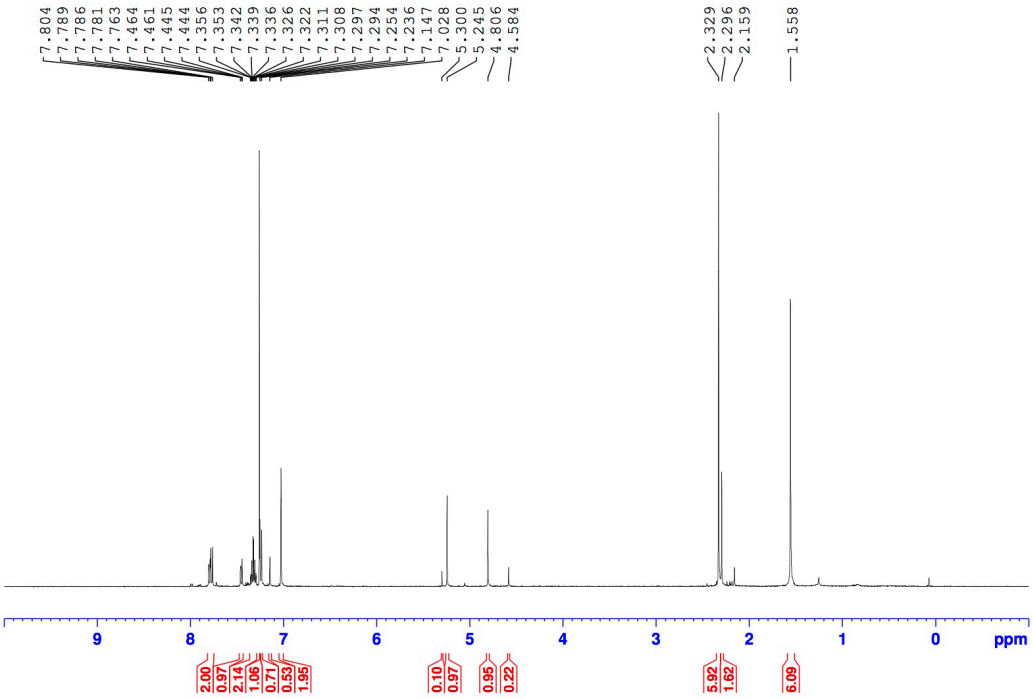

OH
HO
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

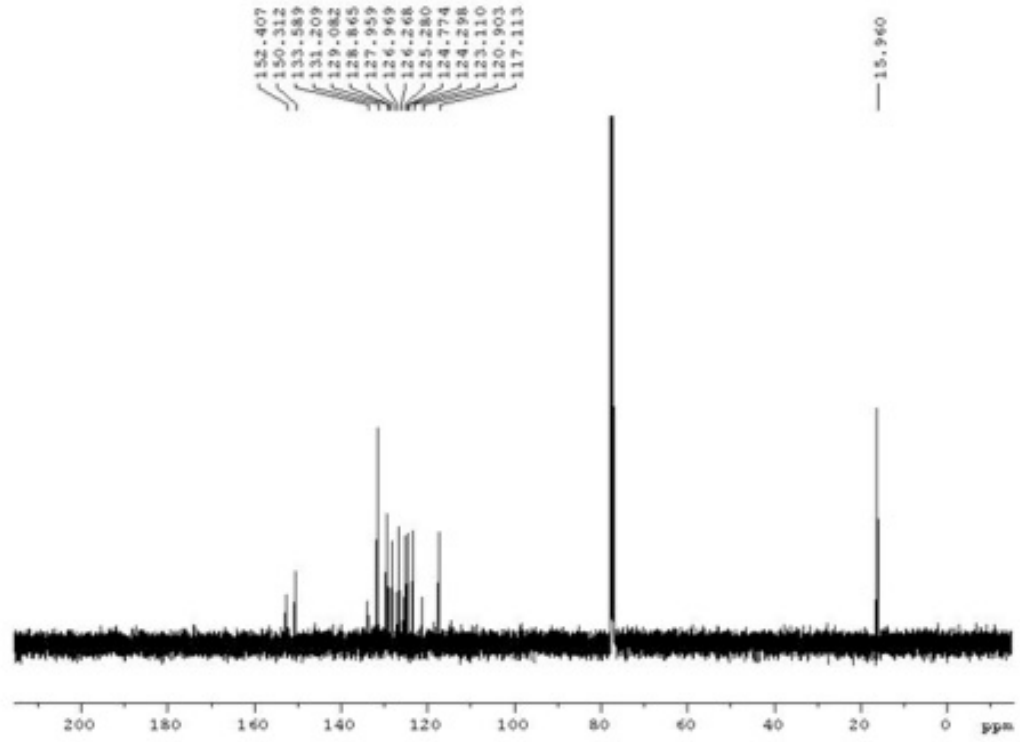

7.094
5.288
5.069
2.218
1.760
1.550
1.450
1.365
OH
HO
OH
OH
9
8
7
6
5
4
3
2
1
0
ppm
4.00
2.00
2.00
3.06
3.10
15.05
39.80
1.80

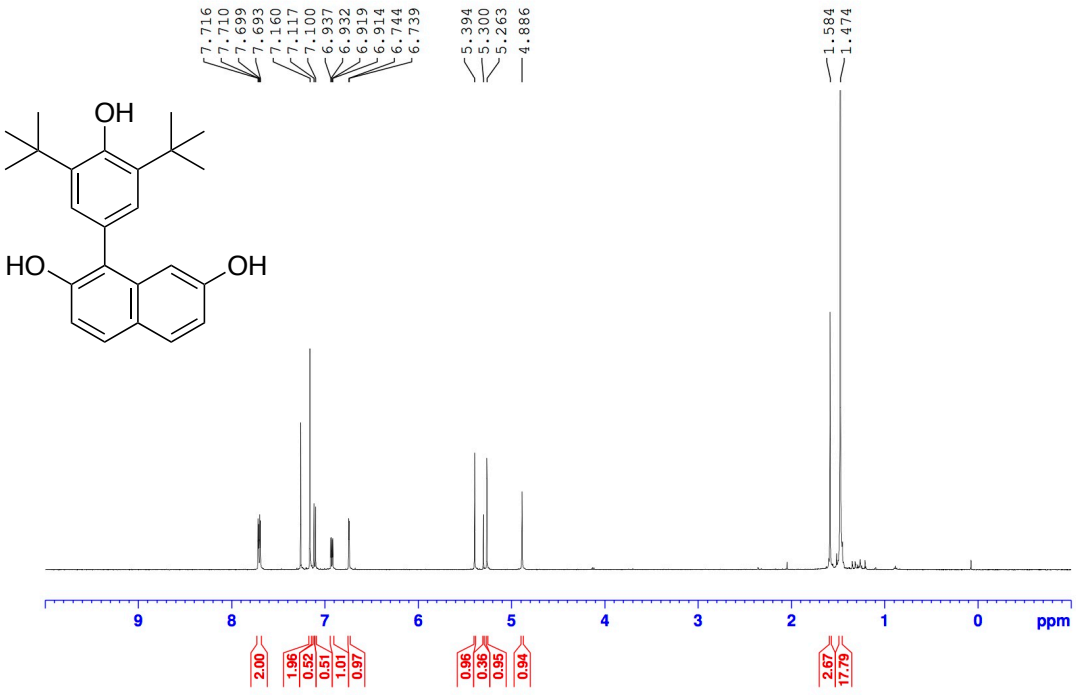

OH
HO
OH
OH
200
180
160
140
120
100
80
60
40
20
0
ppm

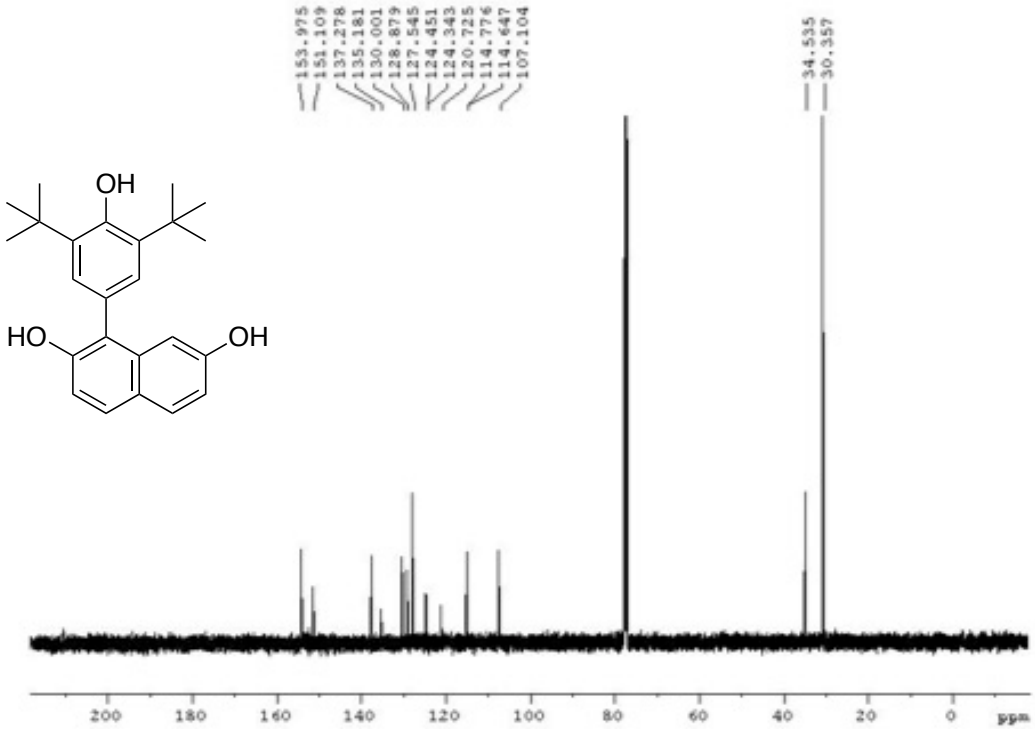

7.807
7.792
7.789
7.784
7.766
7.465
7.449
7.345
7.342
7.330
7.326
7.313
7.312
7.240
7.151
7.031
5.244
4.792
2.332
OH
HO
10
9
8
7
6
5
4
3
2
1
0
ppm
1.97
1.00
2.09
1.09
1.89
0.96
0.97
5.75

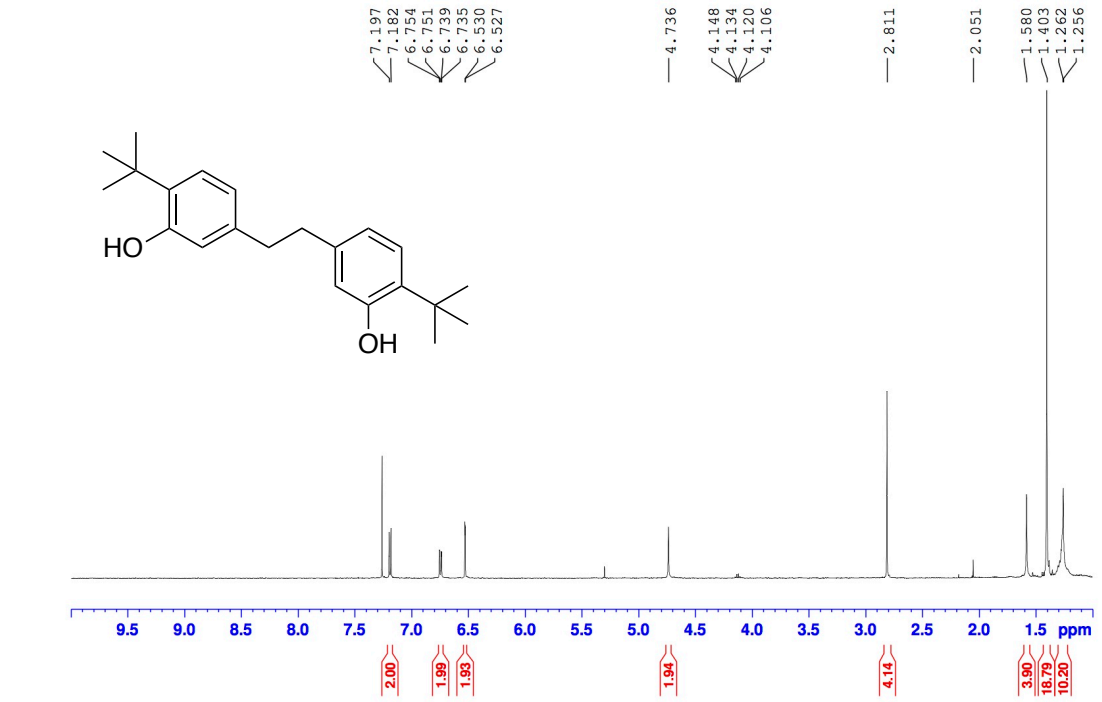

152.407
150.312
133.589
131.209
129.082
128.865
127.959
126.969
126.268
125.280
124.774
124.298
123.110
120.903
117.113
15.960
OH
HO
200
180
160
140
120
100
80
60
40
20
0
ppm

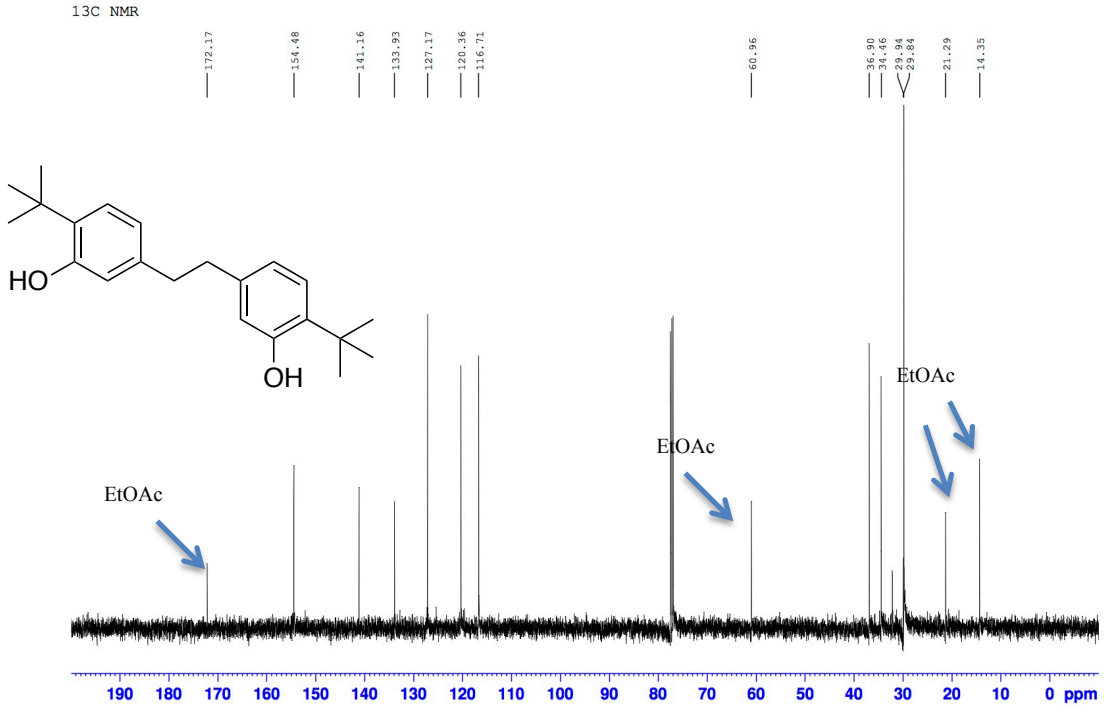

7.804
7.789
7.786
7.781
7.763
7.464
7.461
7.445
7.444
7.356
7.353
7.342
7.339
7.336
7.326
7.322
7.311
7.308
7.297
7.294
7.254
7.236
7.147
7.028
5.300
5.245
4.806
4.584
2.329
2.296
2.159
1.558
9
8
7
6
5
4
3
2
1
0
ppm
2.00
0.97
2.14
1.06
0.71
0.53
1.95
0.10
0.97
0.95
0.22
5.92
1.62
6.09

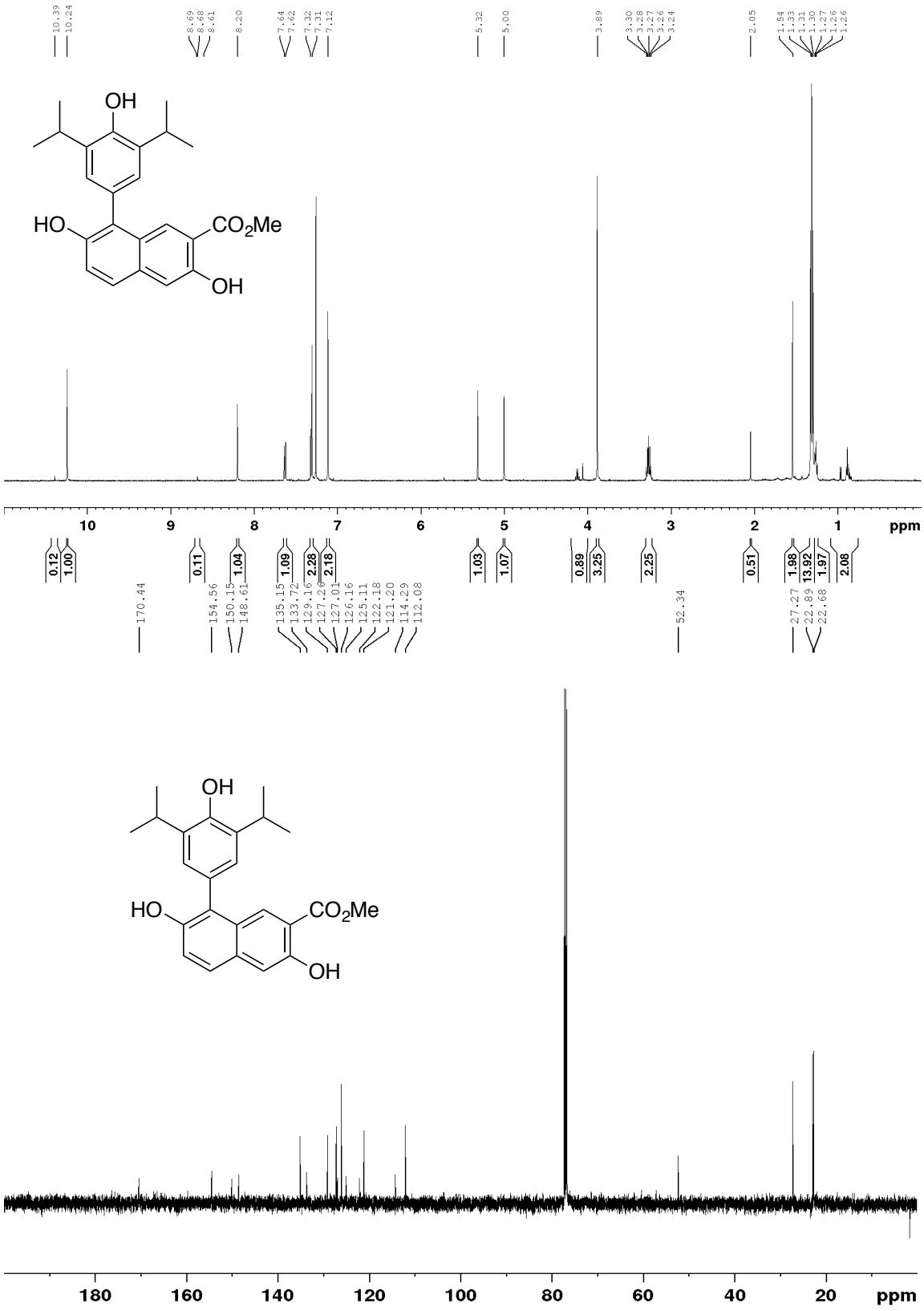

152.407
150.312
133.589
131.209
129.082
128.865
127.959
126.969
126.268
125.280
124.774
124.298
123.110
120.903
117.113
15.960
200
180
160
140
120
100
80
60
40
20
0
ppm


7.716
7.710
7.699
7.693
7.160
7.117
7.100
6.937
6.932
6.919
6.914
6.744
6.739
5.394
5.300
5.263
4.886
1.584
1.474
OH
HO
OH
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.96
0.52
0.51
1.01
0.97
0.96
0.36
0.95
0.94
2.67
17.79

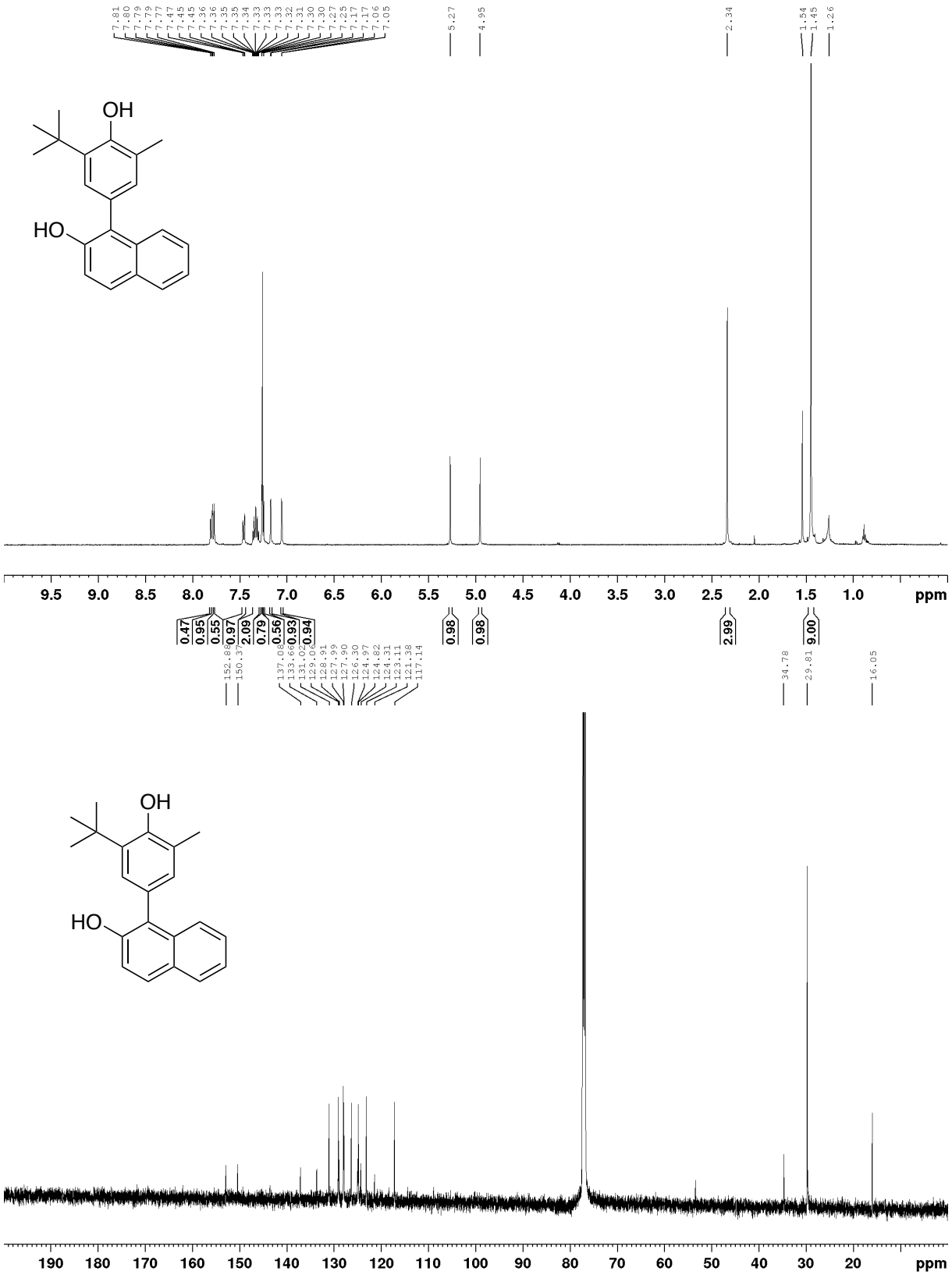

153.975
151.109
137.278
135.181
130.001
128.879
127.545
124.451
124.343
120.725
114.776
114.647
107.104
34.535
30.357
OH
HO
OH
200
180
160
140
120
100
80
60
40
20
0
ppm


7.197
7.182
6.754
6.751
6.739
6.735
6.530
6.527
4.736
4.148
4.134
4.120
4.106
2.811
2.051
1.580
1.403
1.262
1.256
HO
OH
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
2.00
1.99
1.93
1.94
4.14
3.90
18.79
10.20

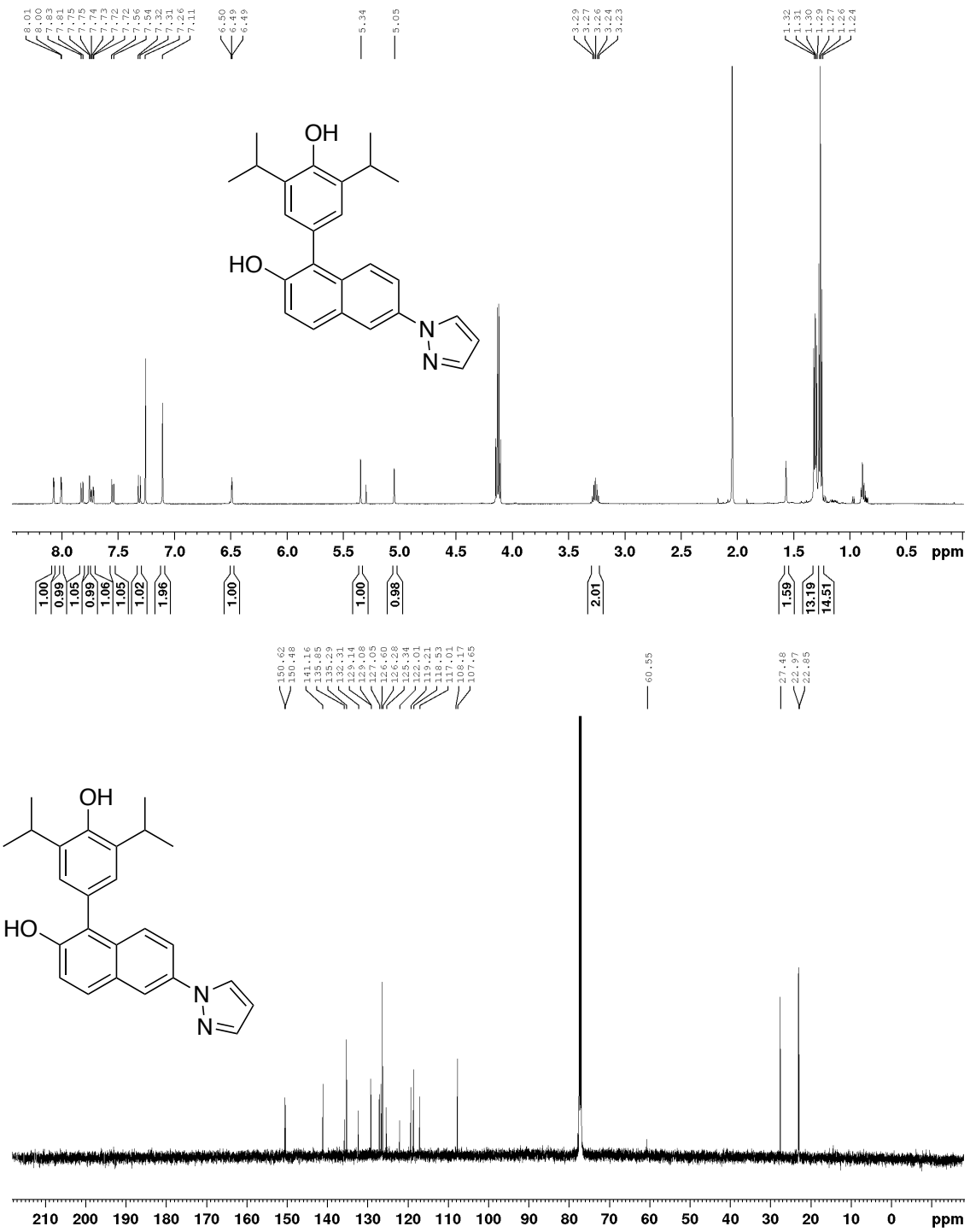

13C NMR
172.17
154.48
141.16
133.93
127.17
120.36
116.71
60.96
36.90
34.46
29.94
29.84
21.29
14.35
HO
OH
EtOAc
EtOAc
EtOAc
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



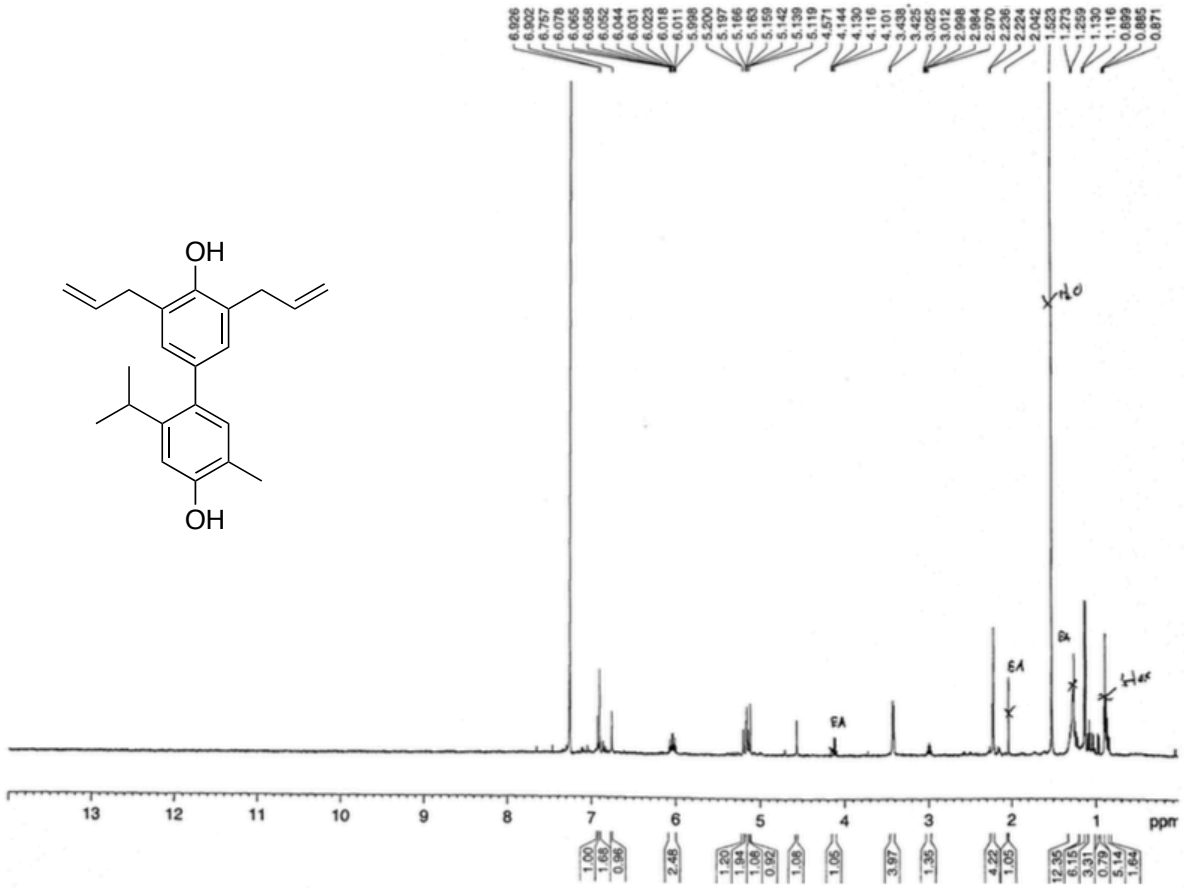
Methyl 3,7-dihydroxy-8-(4-hydroxy-3,5-diisopropylphenyl)-2-naphthoate



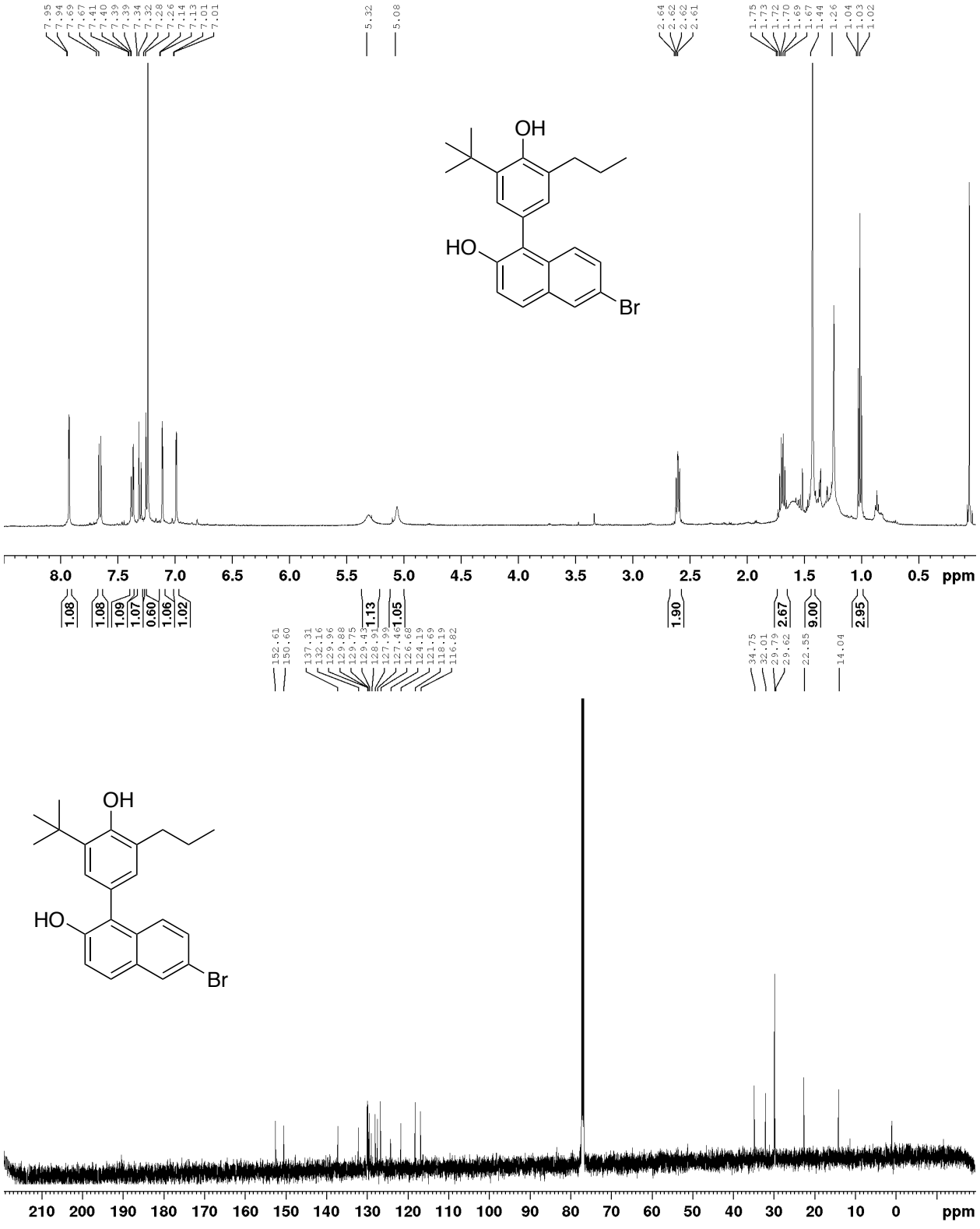
1-(3-(*tert*-Butyl)-4-hydroxy-5-methylphenyl)naphthalen-2-ol



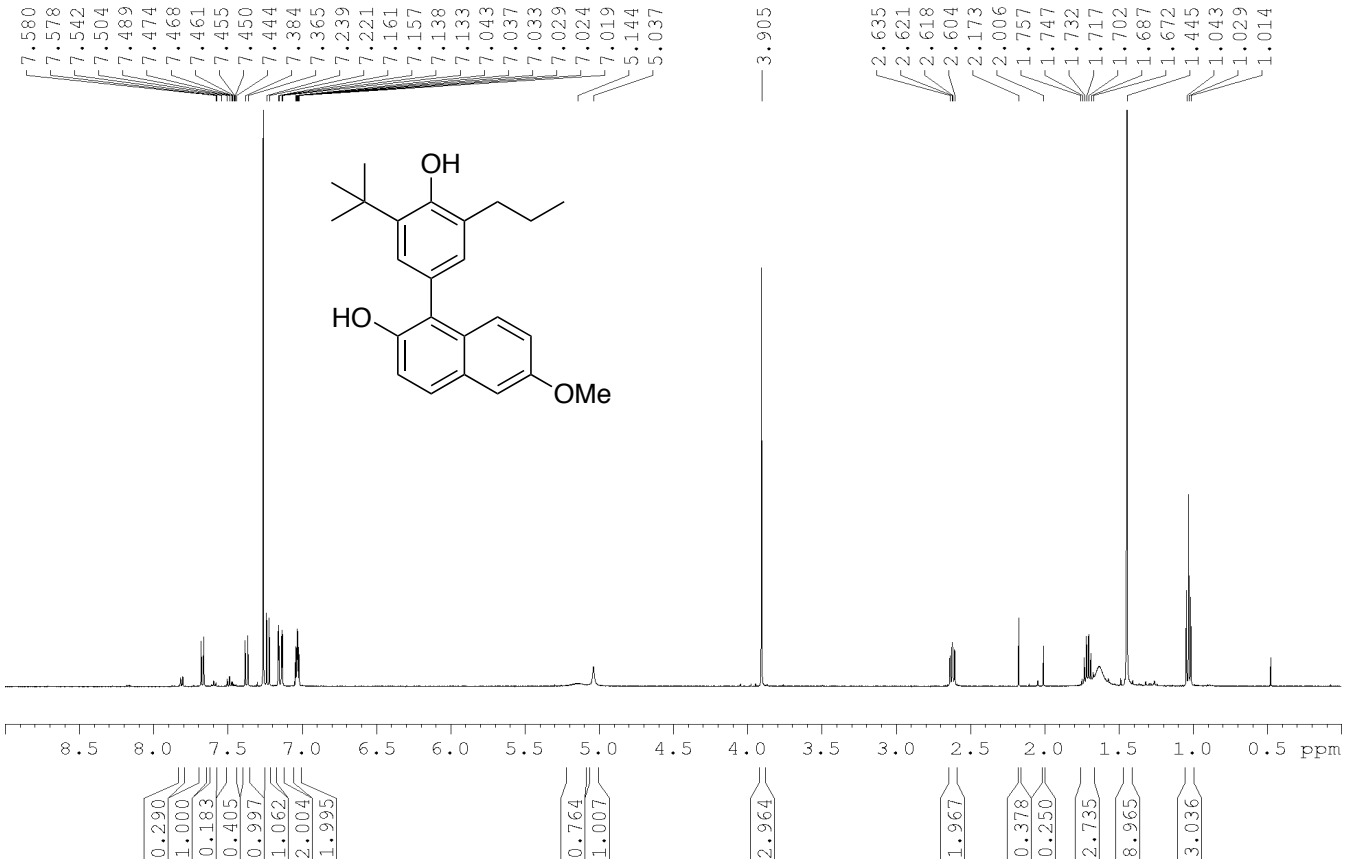
1-(4-Hydroxy-3,5-diisopropylphenyl)-6-(1*H*-pyrazol-1-yl)naphthalen-2-ol



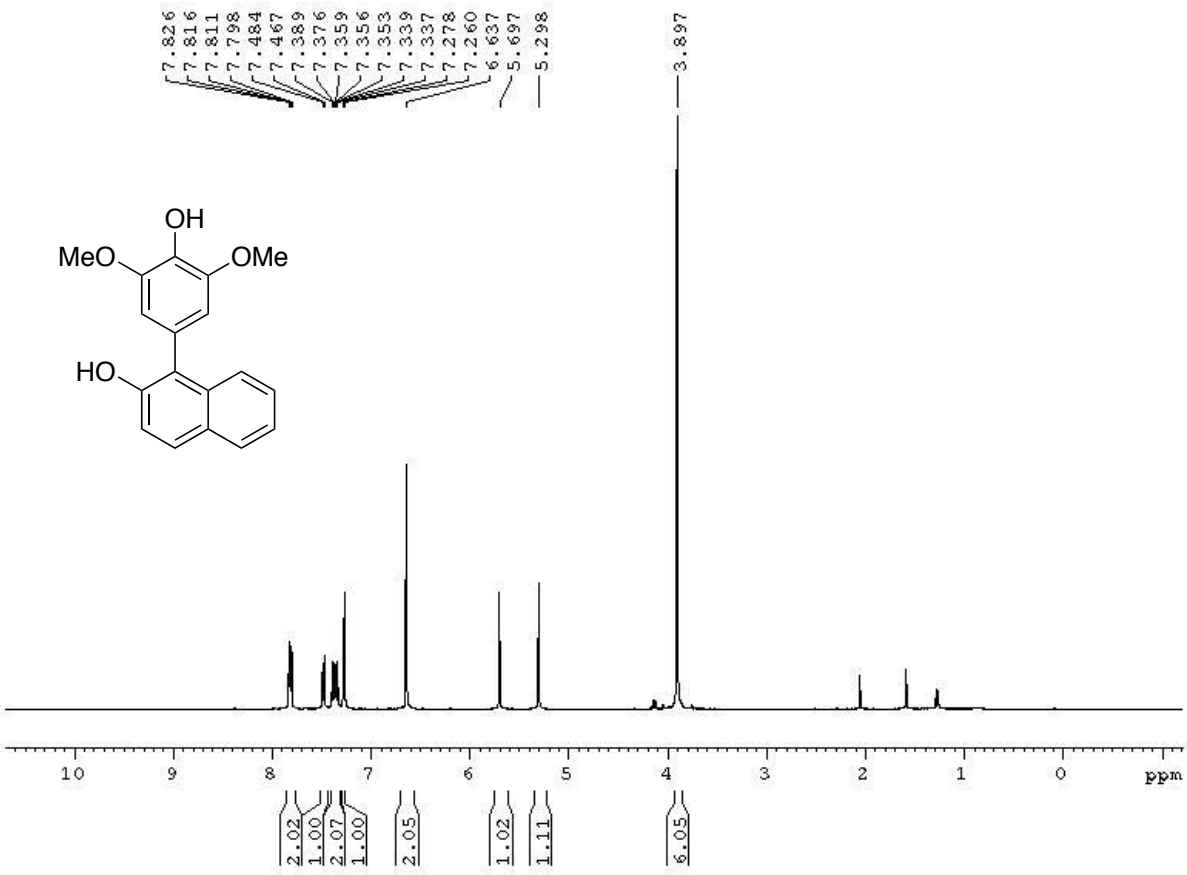
3',5'-Diallyl-2-isopropyl-5-methyl-[1,1'-biphenyl]-4,4'-diol



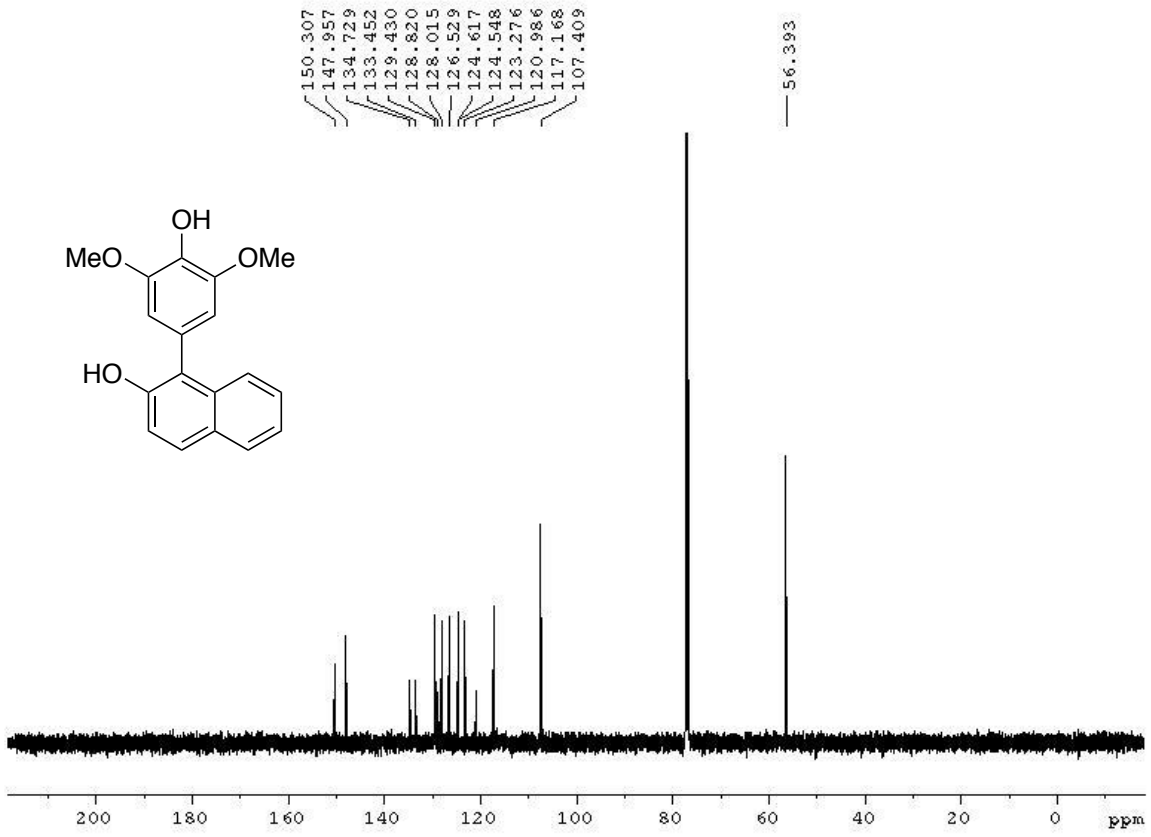
6-Bromo-1-(3-(*tert*-butyl)-4-hydroxy-5-propylphenyl)naphthalen-2-ol



1-(3-(*tert*-Butyl)-4-hydroxy-5-propylphenyl)-6-methoxynaphthalen-2-ol



1-(4-Hydroxy-3,5-dimethoxyphenyl)naphthalen-2-ol



1-(4-Hydroxy-3,5-dimethoxyphenyl)naphthalen-2-ol

4. Biological Methods

Materials. *Streptococcus mutans* wild-type strain UA159 was used for all bacterial cultures and was provided by Dr. Bettina Buttaro from Temple University Medical School, Philadelphia, PA. *Streptococcus gordonii* strain DL1 and *Streptococcus sanguinis* strain 10904 were provided by Dr. Robert G. Quivey from University of Rochester Medical School. Bacteria were routinely maintained on in BactoTM Todd- Hewitt (TH) agar plates and liquid cultures were grown in in BactoTM Todd-Hewitt broth (THB). For growth of biofilms, THB was supplemented with 0.1% sucrose. Incubation was stagnant at 37 °C.

S. *mutans* MIC assay. Stock solution of honokiol analogs, 10 mM, were serial diluted in THB media in flat-bottom 96-well microtiter plates (total volume 100 µL). Bacterial cultures are grown to mid-exponential phase, back diluted to an OD of 0.1 and then inoculated into the 96-well plate to reach a final volume of 200 µL. Plates are incubated at 37 °C in 5% CO_2 for 20-24 hours upon which time wells are evaluated visually for bacterial growth. The MIC is determined as the lowest concentration of compound resulting in no bacterial growth visible to the naked eye. DMSO controls corresponding to each test concentration were performed. Biological triplicates were performed to confirm results.

***S. mutans* biofilm model.** Stock solution of honokiol analogs, 10 mM, were serial diluted in THB media supplemented with 0.1% sucrose (w/v) in flat-bottom 96-well microtiter plates (total volume 100 µL). Bacterial cultures are grown to mid-exponential phase, back diluted to an OD of 0.1 and then inoculated into the 96-well plate to reach a final volume of 200 µL. Plates are incubated at 37 °C in 5% CO_2 for 20 hours (early stage biofilm) upon which time wells are evaluated visually for bacterial growth. DMSO vehicle controls corresponding to each test concentration were performed. Biological triplicates were performed to confirm results.

Crystal Violet (biofilm mass). Biofilm assay is performed (above) and wells are washed with 200 µL of DI H_2O and dried for 24 hours at 37°C. Dried plates were incubated for 10 minutes at room temperature with 200 µL of 1% w/v crystal violet (10% ethanol in H_2O). Excess crystal violet was removed via aspiration. 200 µL of DI H_2O was added to each well and aspirated (repeat until all excess crystal violet is removed). Plates were then inverted and dried at 37°C for 3-5 hours. Crystal violet stain biofilm mass was dissolved with 200 µL of 30% acetic acid, 100 µL of which was then transferred to a fresh flat-bottom 96-well plate for absorbance measurements at 595 nm. DMSO controls corresponding to each test concentration were performed. Biological triplicate was performed to confirm results.

S. *mutans* MBC assay. MIC assay is performed (above) and each well is diluted (log-dilution) into a new 96-well microtiter plate. 5 µL from each dilution is then plated on THB agar plates and incubated for 24 hours. Colony counts are

performed to determine MBC which is defined as the concentration which there is a 3-log reduction in CFU count which corresponds to 99.9% bacterial death.

5. References

(1) Hata, K., Baba, K., and Kozawa, M. *Chem. Pharm. Bull* **1979**, *27*, 984.