Asymmetric Total Synthesis of Nigerone

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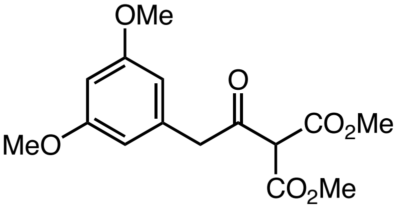
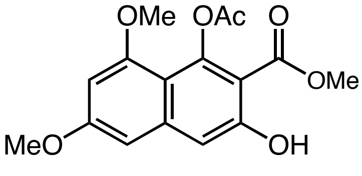
General Considerations. Unless otherwise noted, all non-aqueous reactions were carried out under an atmosphere of dry N_2 in dried glassware. When necessary, solvents and reagents were dried prior to use. Toluene and CH_2Cl_2 were de-oxygenated by purging with N_2 and then dried by passing through activated alumina. THF was distilled from sodium benzophenone ketyl. CH_3CN, TMEDA, and hexanes were distilled from CaH_2. Benzene was distilled from sodium. Solvents for the preparation of the catalyst complexes and for the oxidative coupling reactions were usually used without purification although acid-free halogenated solvents are required (if necessary, trace acid can be removed by filtering through basic Al_2O_3). Enantiomerically pure diaza-*cis*-decalin was prepared as previously described.[1] The Cu(TMEDA)Cl(OH) catalyst was prepared[2] and used in the oxidative biaryl coupling reactions to prepare the racemic samples of the biaryl products.

Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica-gel 60-F plates. Visualization was accomplished with UV light. Chromatography was performed using a forced flow of the indicated solvent system on EM Reagents Silica Gel 60 (230-400 mesh).[3] Enantiomeric excesses were determined using analytical high performance liquid chromatography (HPLC), performed on a Waters 600 HPLC with UV detection at 254 nm. An analytical Chiralpak AD column (0.46 cm x 25 cm) from Daicel was used. ^1H NMR spectra were recorded on Bruker AM-500 (500 MHz), AM-360 (360 MHz), AM-250 (250 MHz), or AM-200 (200 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane (0 ppm) or from the solvent resonance ($CDCl_3$ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m =

multiplet), coupling constants, and number of protons. Decoupled ^{13}C NMR spectra were recorded on a Bruker AM-500 (125 MHz) spectrometer. IR spectra were taken on a Perkin-Elmer FT-IR spectrometer using a thin film on NaCl plates or a $CHCl_3$ solution. Melting points were obtained on Thomas Scientific Unimelt apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer Polarimeter 341 with a sodium lamp and are reported as follows $[\alpha]^{T}_{\lambda}$, (c g/100 mL, solvent).



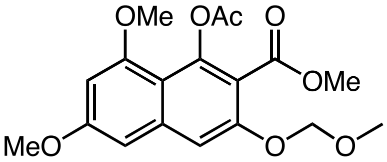
Methyl-1,3-dihydroxy-6,8-dimethoxynapthalene-2-carboxylate (6). To a solution of phenyl acetic acid **5** (0.429 g, 2.19 mmol) in CH_2Cl_2, $SOCl_2$ (0.319 mL) was added. After 1 h at reflux, the solution was concentrated. To a suspension of NaH (0.156 g, 6.5 mmol) in THF (51 mL) was added dimethyl malonate (0.838 g, 6.35 mmol). After stirring for 1 h a solution of the unpurified acid chloride in THF was added. After 1 h at room temperature, 1 M HCl and EtOAc were added. The layers were separated and the aqueous layer was extracted three times with EtOAc. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2; 85%hexanes/EtOAc) to afford the intermediate tricarbonyl (0.650 g) as a clear oil.



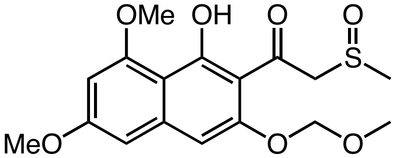
Methyl-1-acetoxy-3-hydroxy-6,8-dimethoxynapthalene-2-carboxylate (7). To a solution of the intermediate tricarbonyl in methane sulfonic acid (10 mL), was added P_2O_5 (0.600 g). After 3 h at room temperature, ice was added and the resulting precipitate was filtered and dried in an oven overnight to yield naphthalene diol (0.500 g) in 82% yield (from the phenylacetic acid **5**) as a grey solid: mp 162-164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ), 11.13 (s, 1H), 10.70 (s, 1H), 6.64 (s, 1H), 6.48 (d, *J* = 2.2 Hz, 1H), 6.28 (d, *J* = 2.2 Hz, 1H), 4.05 (s, 3H), 4.02 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 160.7, 158.8, 157.7, 141.1, 105.1, 102.0, 97.9, 97.4, 95.8, 56.1, 55.3, 52.4; IR (film) 3443, 3304, 2953, 1664, 1594 cm^{-1}; HRMS (ES) calcd for $C_{14}H_{14}O_6$ (MH^+) 279.0868, found 279.0880. This sequence matches that of another synthesis but no experimental procedures or characterizations were reported.[4]

To a round bottom flask containing the naphthalene diol (0.50 g, 1.80 mmol), Ac_2O (2.54 mL) and pyridine (2.50 mL) were added. After 4 h at room temperature, The solution was poured over ice to quench any excess Ac_2O. EtOAc was added and the organic layer was subsequently washed with 1M HCl, water, brine, dried over $MgSO_4$, filtered, and concentrated. Methanol was added to this diacetate material along with sufficient 1M NaOMe solution until TLC analysis indicated no remaining diacetate. 1 M HCl was subsequently added and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2; 70%hexanes/EtOAc) to afford naphthol **7** (0.44 g) in 76% yield as a yellow solid: mp 168-169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.83 (s, 1H), 7.06 (s, 1H), 6.52 (d, *J* = 2.2 Hz, 1H), 6.29 (d, *J* = 2.2 Hz, 1H), 3.98 (s, 3H) 3.89 (s, 3H), 3.88 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

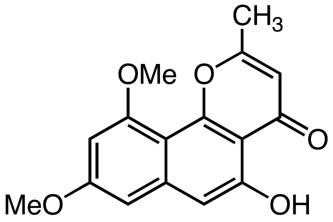
170.0, 169.5, 161.1, 158.1, 157.4, 149.9, 141.1, 111.2, 109.3, 107.3, 97.8, 97.1, 56.1, 55.4, 52.9, 20.9; IR (film) 3134, 3007, 2957, 2845, 1760, 1671, 1629, 1571 cm^{-1}; HRMS (ES) calcd for $C_{16}H_{16}O_7Na$ (MNa$^+$) 343.0794, found (MNa$^+$) 343.0797.



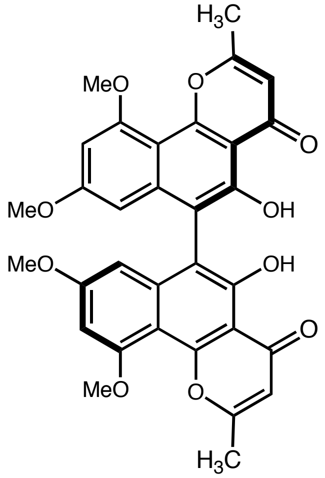
Methyl-1-acetoxy-6,8-dimethoxy-3-(methoxymethoxy)naphthalene-2-carboxylate (8). A solution of **7** (0.250 g, 0.780 mmol) in DMF (4 mL) was cooled to 0 °C at which time NaH (0.028 g, 1.17 mmol) was added. After 20 min, MOMCl (0.099 mL) was added in one portion. After 2 h at room temperature, EtOAc and 1 M HCl were added. The organic layer was washed three times with water and brine to remove DMF. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2; 70% hexanes/EtOAc) to afford **8** (0.270 g) in 94% yield as a white powder: mp 140-141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (s, 1H), 6.65 (d, *J* = 2.2 Hz, 1H), 6.39 (d, *J* = 2.2 Hz, 1H), 5.28 (s, 2H), 3.92 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.51 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.3, 165.8, 159.9, 157.3, 152.5, 145.6, 138.8, 116.8, 110.4, 107.9, 98.8, 98.6, 95.1, 56.6, 56.3, 55.6, 52.7, 20.9; IR (film) 3067, 2989, 1772, 1714, 1629, 1586 cm^{-1}; HRMS (ES) calcd for $C_{18}H_{20}O_8Na$ (MNa$^+$) 364.1158, found 364.1164.



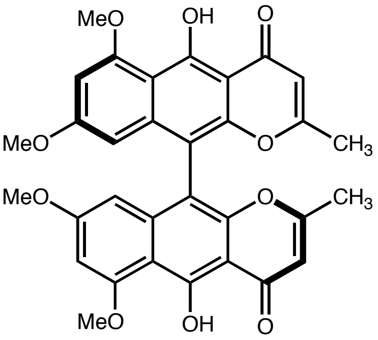
1,3-dimethoxy-6-(methoxymethoxy)-7-(2-(methylsulfinyl)acetyl)naphthalene-8-yl-acetate (9). Benzene (10 mL) and DMSO (3.1 mL) were added to a round bottom flask containing NaH (0.296 g, 12.33 mmol). After 1 h at reflux, the reaction mixture was allowed to cool to room temperature and a solution of **8** (0.642 g, 1.76 mmol) in benzene was added. After 1 h at 45 °C, the solution was concentrated at which time water and acetic acid were added dropwise until a precipitate formed. The precipitate was filtered and dried to afford **9** (0.600 g) in 96% yield as a yellow powder: mp 145-146 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.05 (s, 1H), 6.73 (s, 1H), 6.54 (d, *J* = 2.2 Hz, 1H), 6.36 (d, *J* = 2.2 Hz, 1H), 5.35 (dd, *J* = 9.7, *J* = 6.8, 2H), 4.84 (d, *J* = 14 Hz, 1H), 4.30 (d, *J* = 14 Hz, 1H), 3.98 (s, 3H), 3.89 (s, 3H), 3.56 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.6, 165.3, 162.3, 160.7, 154.0, 141.6, 108.1, 107.3, 100.2, 99.1, 97.2, 94.8, 68.6, 56.8, 56.2, 55.4, 39.9; IR (film) 3003, 2968, 3397, 1625, 1583 cm^{-1}; HRMS (ES) calcd for $C_{17}H_{20}O_7SNa$ (MNa^+) 368.0930, found 368.0937.



Flavasperone (4). To a solution of **9** (0.192 g, 0.523 mmol) in toluene (10 mL), one drop of piperdine was added. The solution was warmed to 45 °C and newly purchased acetaldehyde (0.375 mL) was added. After 3 h at reflux, the mixture was allowed to cool to room temperature upon which time EtOAc and 1 M HCl were added. The organic layer was washed with water and brine. To the unpurified product was added CH_2Cl_2 (3.80 mL) and the reaction mixture was cooled to –78 °C. The cooled solution was treated with BCl_3 (0.476 mL, 3.00 mmol) and was allowed to stir for 20 minutes at which time $NaHCO_3$ was added. The reaction mixture was then allowed to warm to room temperature. The organic layer was washed with water and brine. The residue was chromatographed (SiO_2; 4% EtOAc/CH_2Cl_2) to afford **4** (0.036 g) in 65% yield as a yellow solid: (500 MHz, $CDCl_3$) δ 12.83 (s, 1H), 6.89 (s, 1H), 6.60 (d, *J* = 2.2 Hz, 1H), 6.41 (d, *J* = 2.2 Hz, 1H), 6.29 (s, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.9, 166.4, 161.7, 159.6, 155.9, 154.7, 140.6, 110.6, 110.4, 108.6, 105.2, 97.0, 96.8, 56.0, 55.2, 20.5. ^1H NMR matches that of reported compound.[5]

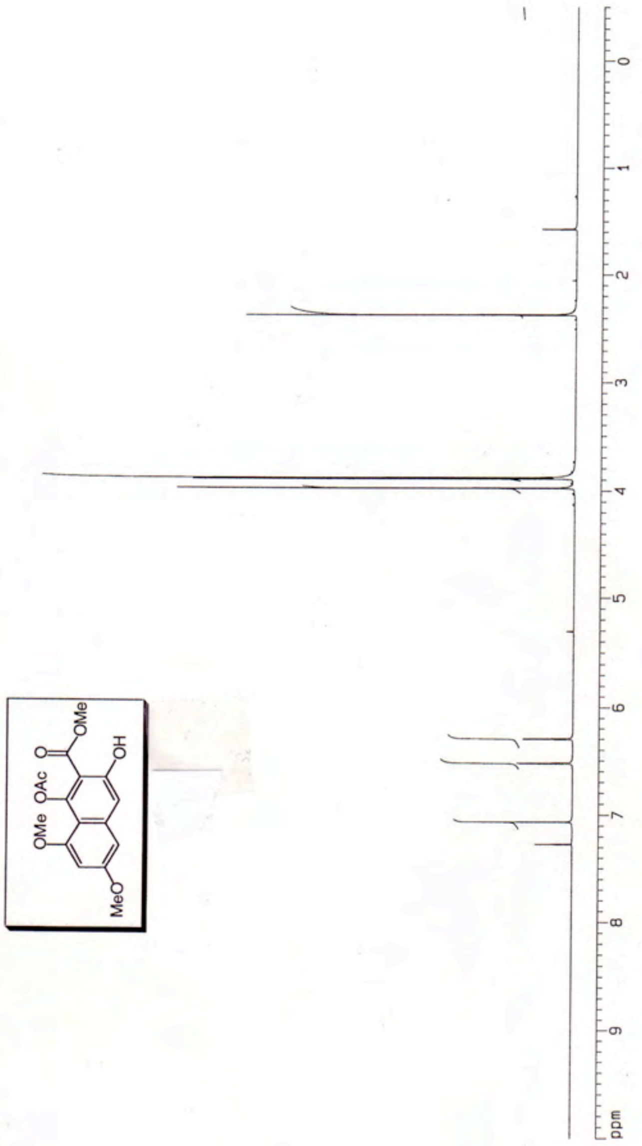


Bisisonigerone (3). To a solution of **4** (0.030 g, 0.010 mmol) in 1:1 CH_3CN/CH_2Cl_2 (3 mL), CuI·(*S,S*)-1,5-diaza-*cis* decalin catalyst (0.036 g, 0.010 mmol) was added. After 6 d at 40 °C, 1 M HCl was added and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2; 60% hexanes/EtOAc) to afford **3** (0.018 g) in 60% yield along with **4** (0.009 g, 80% ee) as a yellow solid: mp 180-185 °C decomposition; $[\alpha]_D^{23}$ +72.58 (*c* 0.25, 80% ee, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 13.19 (s, 1H), 6.45 (d, *J* = 2.2 Hz, 1H), 6.33 (s, 1H), 6.21 (d, *J* = 2.2 Hz, 1H), 4.02 (s, 3H), 3.55 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.9, 166.4, 161.7, 159.7, 156.1, 154.6, 140.5, 110.5, 110.3, 108.6, 104.3, 96.9, 96.7, 56.0, 55.2, 29.7, 20.5; IR (film) 3366, 3003, 2926, 1656, 1610, 1579, 1517 cm^{-1}; HRMS (ES) calcd for $C_{32}H_{26}O_{10}Na$ (MNa^+) 571.1604, found 571.1624; CSP HPLC (Chiralpak AD, 1.0 mL/min, 90:10 hexanes:*i*-PrOH): t_R(*S*) = 40.6 min, t_R(*R*) = 109.9 min.



Nigerone (1). A solution of **3** (0.026 g, 80% ee) in MeOH (22 mL) was heated with sat. aq. NaOH solution (0.22 mL) and was placed in a 70 °C oil bath. After 18 h, 1M HCl was added and the aqueous layer was extracted three times with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2; 60% hexanes/EtOAc) to afford **1** (0.013 g, 77% ee) in 50% yield as yellow solid: mp > 200 °C decomposition; ^1H NMR (500 MHz, $CDCl_3$) δ 15.31 (s, 1H), 6.44 (d, *J* = 7 Hz, 2H), 6.07 (d, *J* = 7 Hz, 1H), 6.00 (s, 1H), 4.06 (s, 3H), 3.49 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.5, 167.6, 163.1, 161.9, 161.2, 151.3, 140.7, 108.8, 107.3 105.5, 104.3, 97.2, 96.5, 56.2, 55.2, 20.6; IR (film) 3377, 2930, 2853, 1652, 1610, 1586, 1409; HRMS (ES) calcd for $C_{32}H_{26}O_{10}Na$ (MNa^+) 571.1604, found 571.1624; CSP HPLC (Chiralpak AD, 1.0 mL/min, 90:10 hexanes:*i*-PrOH): t_R(*S*) = 31.7 min, t_R(*R*) = 38.7 min.

Trituration of this material with EtOAc provided **1** with 90% *ee*: $[\alpha]_D^{23}$: –223 (*c* 0.018 g/100 mL, CH_2Cl_2, 90% *ee*), literature (ref 3a, main text) $[\alpha]_D^{20}$: –287.7 (*c* 1.00, $CHCl_3$).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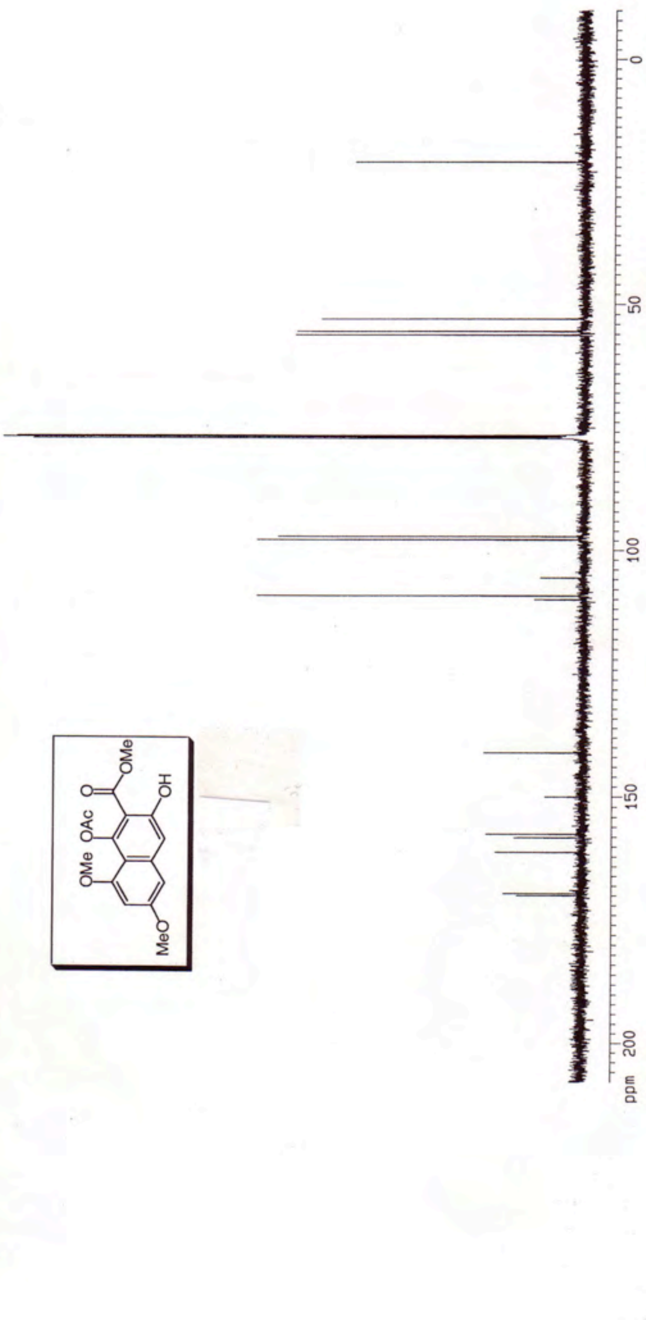
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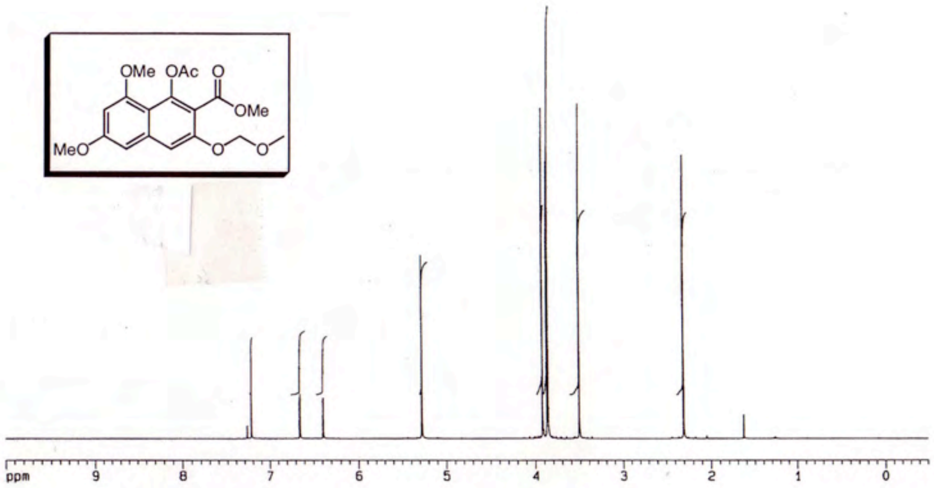
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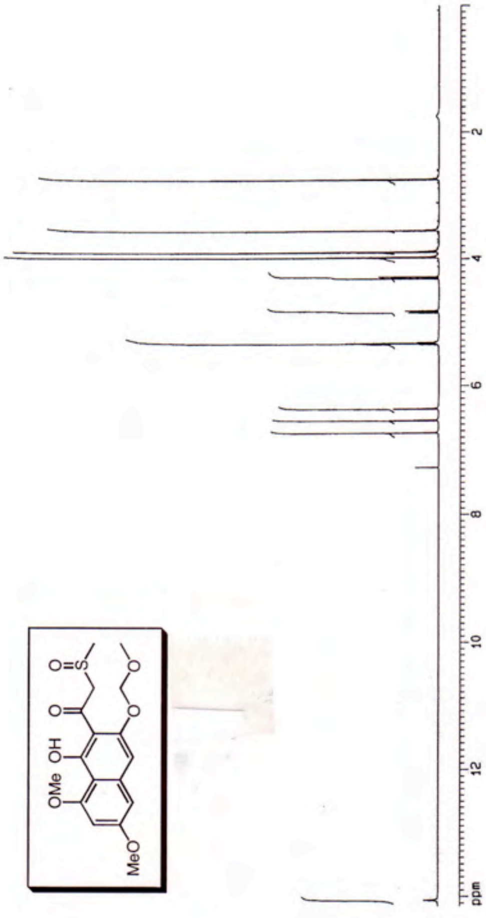
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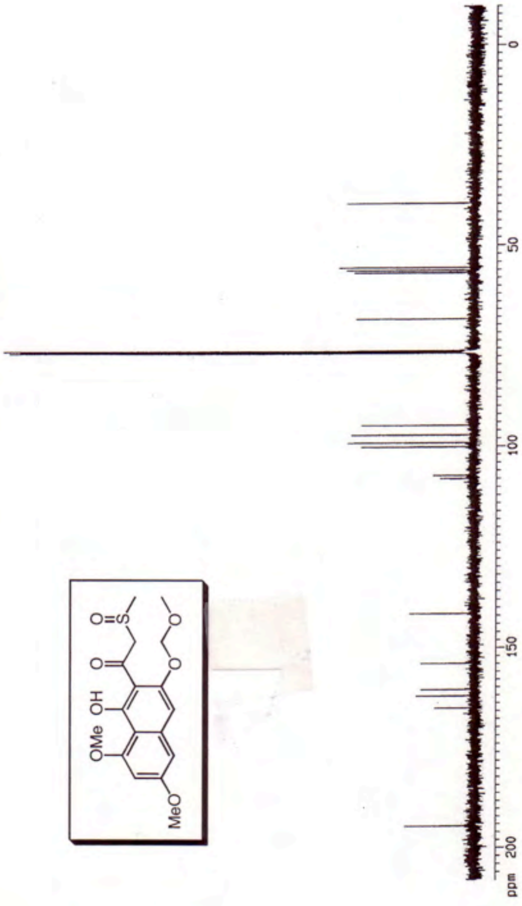
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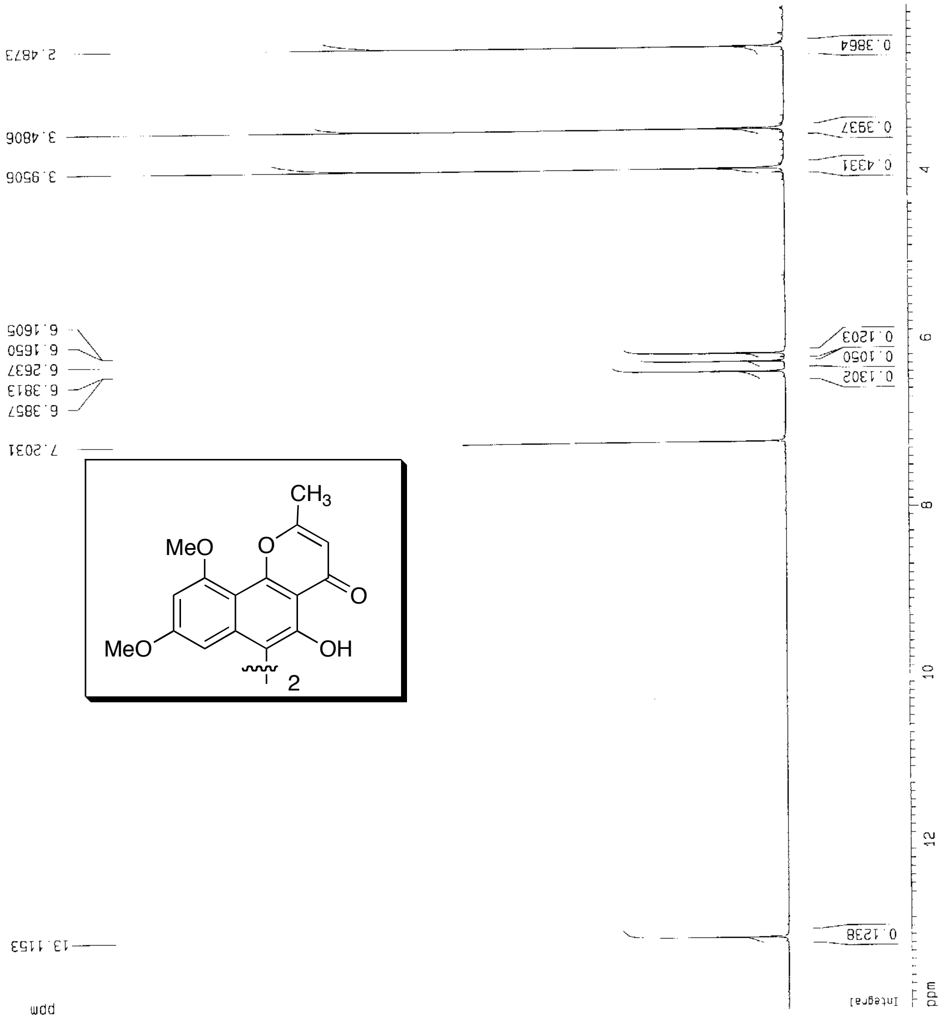
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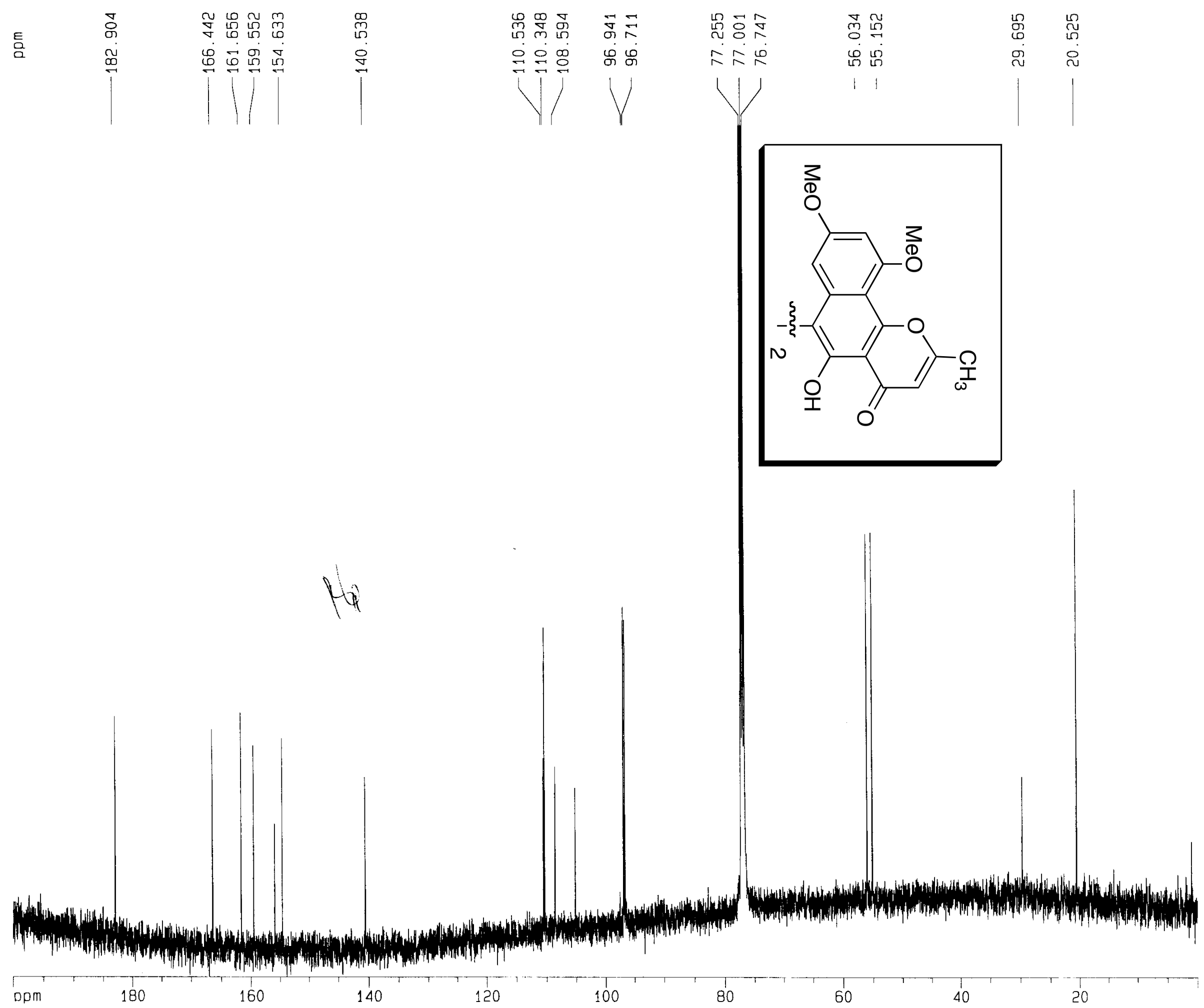

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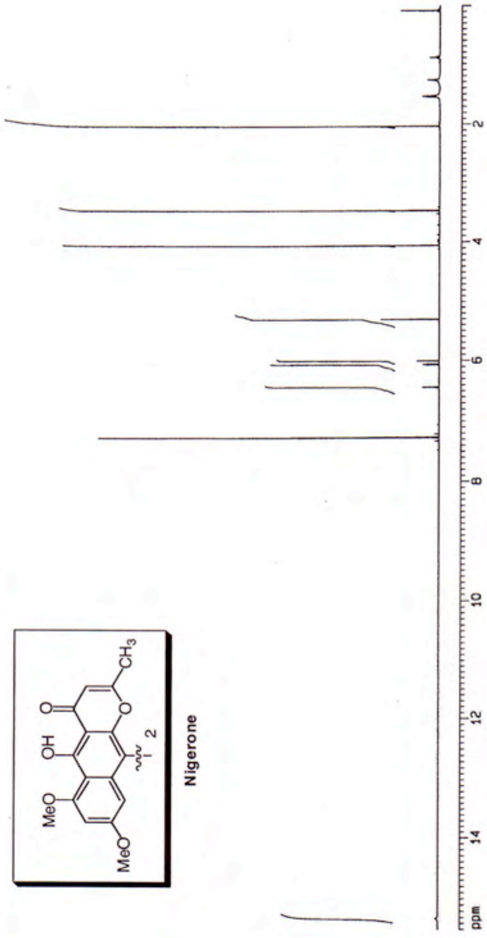
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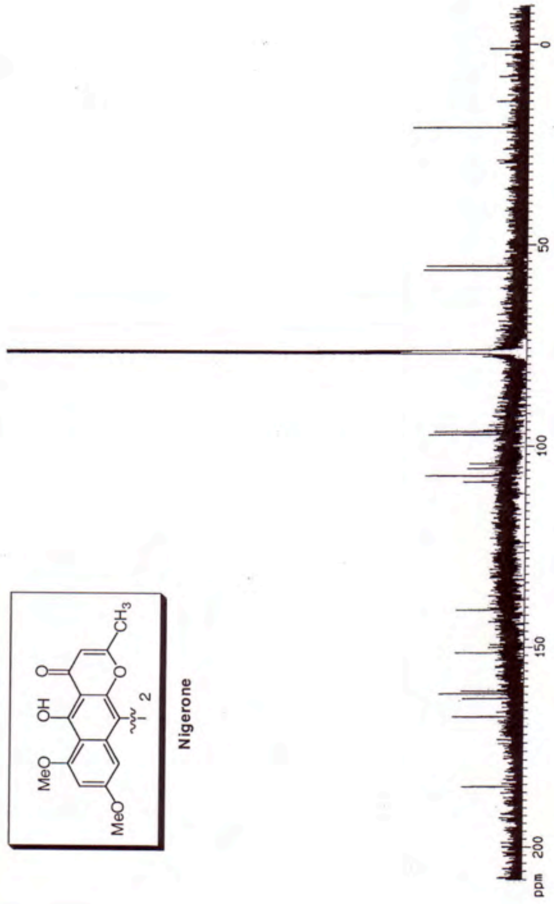

Nigerone

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