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Supplementary Information

Total Synthesis of 1-Hydroxydehydroherbarin and Ascomycones A, B, Naphthoquinone Antibiotics

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Experimental

General methods

NMR spectra were recorded with tetramethylsilane as the internal standard. TLC was performed on glass-backed silica plates. Column chromatography was performed using silica gel (200-300 mesh) eluting with ethyl acetate and petroleum ether. ^{1}H NMR spectra were recorded at 400 MHz, and ^{13}C NMR spectra were recorded at 100 MHz (Bruker Avance). Chemical shifts (δ) are reported in ppm downfield from $CDCl_3$ (δ 7.26 ppm) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ 77.0 ppm) for ^{13}C NMR spectroscopy. Coupling constants (*J*) are given in Hz. ESI-HRMS spectrometer was measured with a Finnigan LCQ^{DECA} ion trap mass spectrometer.

Synthesis of 2-(3-chloro-2,5-dimethoxyphenyl)-1,3- dioxane (**11**)[1]

To a solution of 3-chloro-2,5-dimethoxybenz-aldehyde (2.02 g, 10.12 mmol) in toluene (25 mL), 1,3-propanediol (3.08 g, 40.48 mmol, 4 equiv.) and *para*-toluenesulphonic acid (0.018 g; 0.10 mmol; 0.01 equiv.) were added. The reaction was heated under reflux for 4 h using a Dean-Stark apparatus. Subsequently, the reaction mixture was washed with aq. satd. $NaHCO_3$ (15 mL) and brine (20 mL). The organic layer was extracted with ethyl acetate, dried ($MgSO_4$) and evaporated, which was further purified by means of column chromatography on silica gel with petroleum ether/ethyl acetate (15:1), **11** was obtained as a yellow oil (2.40 g, 92%), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.08 (d, 1H, *J* 3.1 Hz), 6.92 (d, 1H, *J* 3.0 Hz), 5.78 (s, 1H), 4.27-4.23 (m, 2H), 4.04-3.98 (m, 2H), 3.83 (s, 3H), 3.78 (s, 3H), 2.30-2.18 (m, 1H), 1.45 (d, 1H, *J* 13.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 156.1, 147.3, 134.1, 128.1, 117.0, 110.3, 97.2, 67.5, 67.5, 62.0, 55.8, 25.7; IR (KBr) ν_{max}/cm^{-1}: 1661, 1591; ESI-HRMS: calc. for $C_{12}H_{15}ClO_4$ +H 259.0731, found 259.0736.

Synthesis of 2-chloro-6-(1,3-dioxan-2-yl)cyclohexa-2,5-diene-1,4-dione (**8b**)

Compound **11** (1.29 g, 5.00 mmol) was dissolved in CH_3CN (20 mL), and a solution of CAN (8.22 g, 15.00 mmol, 3 equiv.) in water (20 mL) was added in one portion. The reaction mixture was stirred for 3 min at room temperature and subsequently poured in a mixture of 20 mL of ethyl acetate and 20 mL of brine. The organic layer was washed with brine (20 mL) and extracted with ethyl acetate, dried ($MgSO_4$) and evaporated, which was further purified by column chromatography on silica gel with petroleum ether/ethyl acetate (15:1), **8b** was obtained as a yellow solid (0.89 g, 78%), mp 60-62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.99 (s, 1H), 6.99 (s, 1H), 5.58 (s, 1H), 4.23-4.19 (m, 2H), 4.00-3.93 (m, 2H), 2.24-2.12 (m, 1H), 1.45 (d, 1H, *J* 13.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 185.1, 177.8, 144.1, 143.2, 133.4, 133.3, 94.6, 67.5, 67.5, 25.6; ESI-HRMS: calc. for $C_{10}H_9ClO_4$+H 229.0262, found 229.0265.

Synthesis of *N*-(methylcarbonylmethyl)pyridinium chloride (**13**)

To a stirred solution of dry pyridine (0.41 mL, 5.00 mmol) in dry THF (30 mL) under an argon atmosphere was added chloroacetone (0.40 mL, 5.00 mmol, 1equiv.), and the reaction mixture was stirred for 6 h at 25 °C. The solvent was removed in vacuo, and the solid product obtained was purified by recrystallization from ethanol/acetone (1:1, v/v), **13** was obtained as a white solid (0.38 g, 44%), mp 202-204 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 9.07 (d, 2H, *J* 3.8 Hz), 8.70 (t, 1H, *J* 7.7 Hz), 8.25 (t, 2H, *J* 6.9 Hz), 6.06 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6)) δ (ppm) 199.9, 146.6, 146.4, 128.1, 68.5, 27.6; IR (KBr) ν_{max}/ cm^{-1}: 1658; ESI-HRMS: calc. for $C_{13}H_{10}ClN_5O$+Na 310.0474, found 310.0477.

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Synthesis of 2-(1,3-dioxan-2-yl)-8-hydroxy-6-methoxy-naphthalene-1,4-dione (**7b**)

To a stirred solution of compound **8b** (1.14 g, 5.00 mmol) in dry THF (30 mL) under an argon atmosphere was added Brassard's diene (1.01 g, 5.00 mmol) at −30 °C. The mixture was allowed to warm to ambient temperature after 30 min and stirred for another 1 h. Then the solvent was removed and the residue was poured into 30 mL of DCM. After that, deactivated silica gel (5.00 g) was added in one portion and was stirred for 14 h, then dried with Na_2SO_4 and evaporated in vacuo. **7b** was obtained by recrystallization from ethanol as a yellow solid (0.90 g, 62%), mp 192-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 12.2 (s, 1H), 7.15 (s, 1H), 7.12(s, 1H), 6.64 (d, 1H, *J* 1.8Hz), 5.71 (s, 1H), 4.27-4.23 (m, 2H), 4.09-3.98 (m, 2H), 3.90 (s, 3H), 2.26-2.16 (m, 1H), 1.46 (d, 1H, *J* 14.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 186.8, 184.6, 166.2, 164.5, 145.4, 135.6, 133.4, 109.6, 107.6, 106.4, 94.5, 67.6, 67.6, 56.0, 25.7; IR (KBr) ν_{max}/cm^{-1}: 3429, 1644, 1598; ESI-HRMS: calc. for $C_{15}H_{14}O_6$ +H 291.0863, found 291.0864.

Synthesis of 2-(1,3-dioxan-2-yl)-6,8-dimethoxy-naphthalene-1,4-dione (**12**)

To a solution of compound **7b** (0.73 mg, 2.50 mmol) in 10 mL of chloroform was added iodomethane (3.50 g, 25.00 mmol) and silver(I) oxide (5.70 g, 25.00 mmol). The mixture was refluxed for 5h, under protection from light by covering the flask with aluminum foil. After cooling, the reaction mixture was filtered over celite and evaporated in vacuo, which was further purified by column chromatography on silica gel with petroleum ether/ethyl acetate (2:1), **12** was obtained as a yellow solid (0.71 g, 93%), mp 165-168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.20 (d, 1H, *J* 2.4 Hz), 7.06 (s, 1H), 6.72 (d, 1H, *J* 2.3 Hz) 5.73 (s, 1H), 4.24-4.20 (m, 2H), 4.02-3.97 (m, 2H), 3.95 (s, 3H), 3.94 (s, 3H), 2.25-2.13 (m, 1H), 1.44 (d, 1H, *J* 13.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 185.6, 181.5, 164.7, 162.0, 146.6, 135.8, 132.4, 114.5, 104.4, 102.8, 95.1, 67.6, 67.6, 56.4, 55.9, 25.8; IR (KBr) ν_{max}/cm^{-1}: 1642, 1599; ESI-HRMS: calc. for $C_{16}H_{16}O_6$+H 305.1019, found 305.1016.

Synthesis of 3-(1,3-dioxan-2-yl)-5,7-dimethoxy-2-(2-oxopropyl)-naphthalene-1,4-dione (**6b**)

N-(methyl-carbonylmethyl)pyridinium chloride (**13**) (0.20 g, 1.20 mmol) was suspended at room temperature in acetonitrile (10 mL) containing compound **12** (0.31 g, 1.00 mmol) under argon, then a solution of triethylamine (0.12 g, 1.20 mmol) in acetonitrile (2 mL) was added. The mixture was stirred for 12 h, under protection from light by covering the flask with aluminum foil, the reaction was poured into 5 mL of water, the resulting solution was extracted with trichloromethane, dried ($MgSO_4$) and evaporated, which was further purified by column chromatography on silica gel with petroleum ether/ethyl acetate (2:1), **6b** was obtained as a yellow solid (0.30, 85%), mp 168-171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.22 (d, 1H, *J* 2.4 Hz), 6.72 (d, 1H, *J* 2.4 Hz), 6.07 (s, 1H), 4.19-4.16(m, 2H), 4.15(s, 2H), 3.96 (s, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 2.24 (s, 3H), 2.22-2.12 (m, 1H), 1.45 (d, 1H, *J* 13.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.5, 185.7, 180.8, 164.6, 161.9, 142.1, 141.6, 135.5, 114.4, 104.6, 103.1, 96.5, 67.7, 67.7, 56.4, 55.9, 41.2, 29.8, 26.1; IR (KBr) ν_{max}/cm^{-1}: 1727, 1642, 1608; ESI-HRMS: calc. for $C_{19}H_{20}O_7$+H 361.1281, found 361.1279.

Synthesis of 1-(3-hydroxypropoxy)-7,9-dimethoxy-3-methyl-1*H*-benzo[*g*]isochromene- 5,10-dione (**14**)

To a solution of compound **6b** (0.28 mg, 0.80 mmol) in 10 mL of toluene was added triethylamine (0.08 g, 0.80 mmol). The mixture was refluxed for 6 h, under protection from light by covering the flask with aluminum foil. After cooling, the reaction mixture was poured in water, celite and evaporated, which was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (2:3), **14** was obtained as a orange solid (0.23 g, 81%), mp 152-155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27 (d, 1H, *J* 2.4 Hz), 6.73 (d, 1H, *J* 2.4 Hz), 6.31 (s, 1H), 6.06 (s, 1H), 4.14-4.08 (m, 1H), 4.00-3.97 (m, 1H), 3.96 (s, 1H), 3.95 (s, 1H), 3.76-3.68 (m, 2H), 2.13 (s, 3H), 1.91-1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 183.3, 181.1, 164.3, 161.8, 160.2, 135.7, 134.3, 122.8, 114.6, 104.6, 103.5, 94.9, 93.5, 67.1, 60.3, 56.4, 55.9, 32.0, 20.7; IR (KBr) ν_{max}/cm^{-1}: 3497, 1662, 1581; ESI-HRMS: calc. for $C_{19}H_{20}O_7$+Na 383.1101, found 383.1108.

Synthesis of 1-hydroxydehydroherbarin (**3**)

Compound **14** (0.18 g, 0.50 mmol) was dissolved in THF (5 mL) to which aqueous HCl (2 mol L^{-1}, 2 mL) was added and the reaction mixture was stirred for 2 h at room temperature, shielded from light by means of aluminum foil. The reaction mixture was poured in brine (5 mL) and extracted with chloroform, dried ($MgSO_4$) and evaporated, which was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (1:1), **3** was obtained as a orange solid (0.14 g, 95%), mp 156-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.28 (d, 1H, *J* 2.4 Hz), 6.74 (d, 1H, *J* 2.4 Hz), 6.66 (s, 1H), 6.07 (s, 1H), 3.96 (s, 3H), 3.95 (s, 3H), 3.53 (bs, 1H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 183.3, 180.9, 164.3, 161.6, 160.2, 135.5, 133.7, 123.6, 114.6, 104.5, 103.4, 93.0, 88.3, 56.3, 55.9,

20.8; IR (KBr) ν_{max}/ cm^{-1}: 3450, 2920, 1680; ESI-HRMS: calc. for $C_{16}H_{14}O_6$+Na 325.0683, found 325.0679.

Synthesis of ascomycone B (**2**)

To a solution of compound **3** (0.09 g, 0.30 mmol) in 10 mL of dry dichloromethane was added dropwise boron(III) bromide (0.37 g, 1.50 mmol) under a nitrogen atmosphere at −78 °C. After 30 min, the reaction was allowed to warm till room temperature. After stirring for 2 additional hours, the reaction was quenched with water and poured into 5 mL NaOH (2 mol L^{-1}). HCl (1 mol L^{-1}) was added in portions until the colour of the reaction mixture turned yellow. The resulting solution was extracted with dichloromethane, dried ($MgSO_4$), evaporated, then it was purified by column chromatography on silica gel with petroleum ether/ethyl acetate (3:1), ascomycone B (**2**) was obtained as a amorphous red solid (0.07 g, 83%), decomposition 175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 12.4 (s, 1H), 7.18 (d, 1H, *J* 2.5 Hz), 6.67 (s, 1H), 6.64 (d, 1H, *J* 2.4 Hz), 6.15 (s, 1H), 3.90 (s, 3H), 3.66 (bs, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 185.9, 182.1, 165.4, 163.8, 162.2, 136.7, 133.2, 121.4, 108.4, 107.5, 106.7, 93.8, 87.9, 55.8, 20.9; IR (KBr) ν_{max}/cm^{-1}: 3349, 2840, 1715; ESI-HRMS: calc. for $C_{15}H_{12}O_6$+Na 311.0532, found 311.0542.

Synthesis of ascomycone A (**1**)

Ascomycone B (**2**) (0.05 g, 0.17 mmol) was dissolved in methanol (2 mL), to which one drop of concentrated sulfuric acid was added. The reaction mixture was stirred for 2 h at room temperature. Then the reaction mixture was poured in brine (10 mL). The resulting solution was extracted with chloroform, dried ($MgSO_4$), evaporated, then it was purified by column chromatography on silica gel with chloroform. ascomycone A (**1**) was obtained as a red crystalline solid (0.04 g, 80%), mp 80-83 °C; The NMR data was identical to that reported in the literature,[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 12.5 (s, 1H), 7.19 (d, 1H, *J* 2.5 Hz), 6.65 (d, 1H, *J* 2.4 Hz), 6.26 (s, 1H), 6.14 (s, 1H), 3.89 (s, 3H), 3.61 (s, 1H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 186.1, 182.4, 165.4, 163.9, 162.3, 137.1, 133.1, 120.8, 109.8, 107.9, 106.7, 95.1, 94.6, 52.9, 55.8, 20.9; IR (KBr) ν_{max}/cm^{-1}: 3439, 2913, 1649; ESI-HRMS: calc. for $C_{16}H_{14}O_6$+H 303.0863, found 303.0871.

Reference

1. Sargent, M. V.; Wangchareontrakul, S.; *J. Chem. Soc., Perkin Trans.* **1990**, *1*, 129.

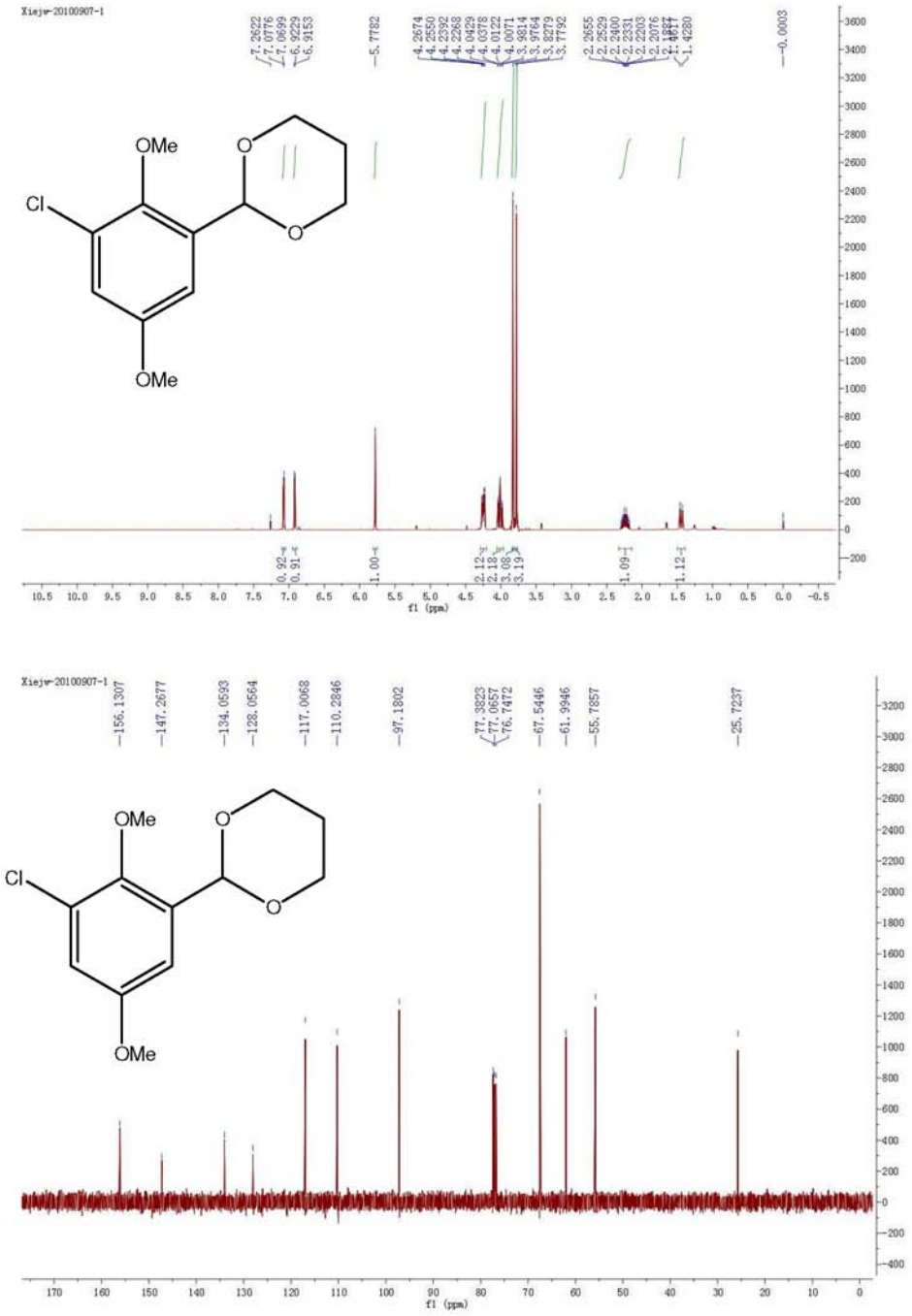

Figure S1. NMR spectra of compound **11**.

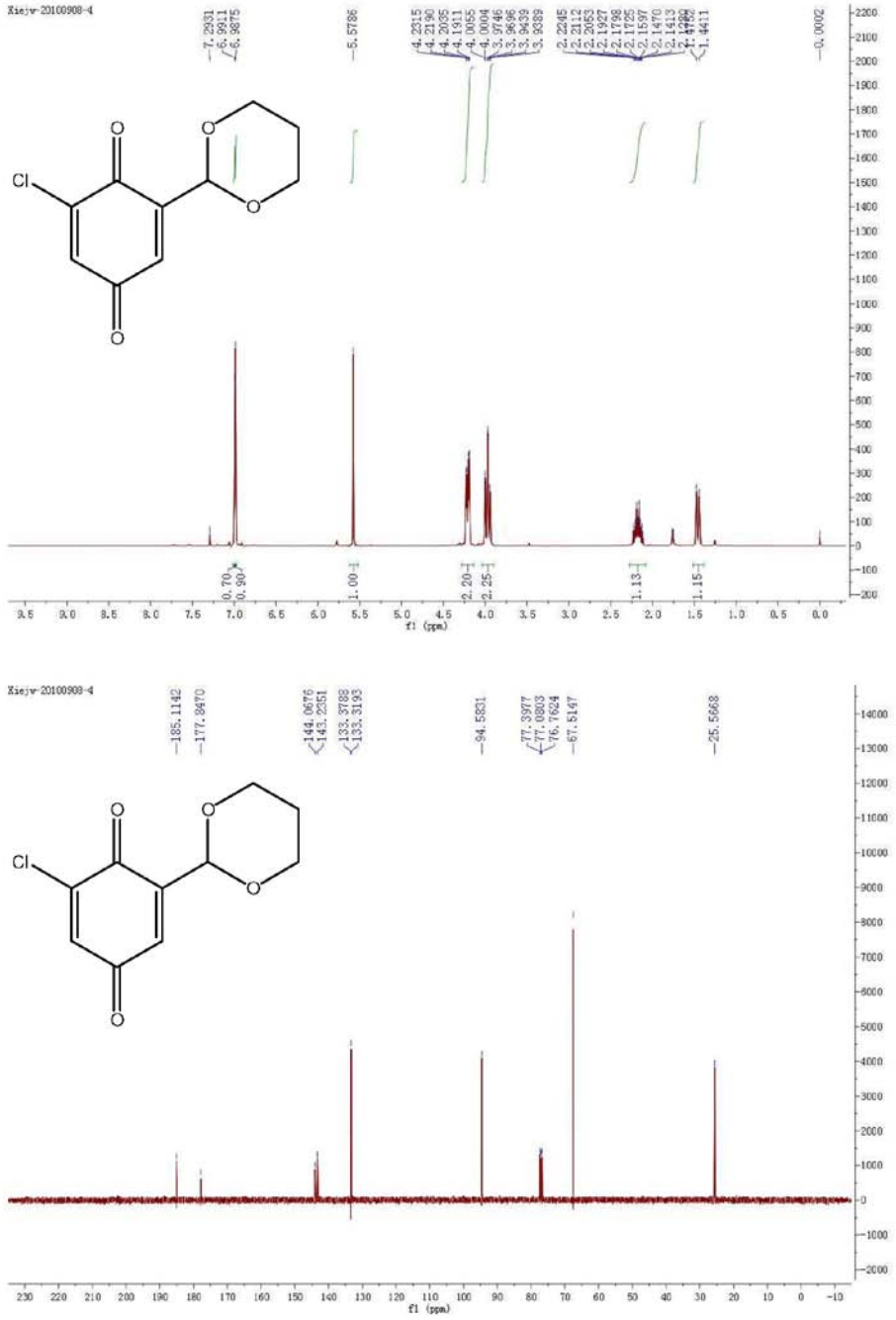

Figure S2. NMR spectra of compound **8b**.

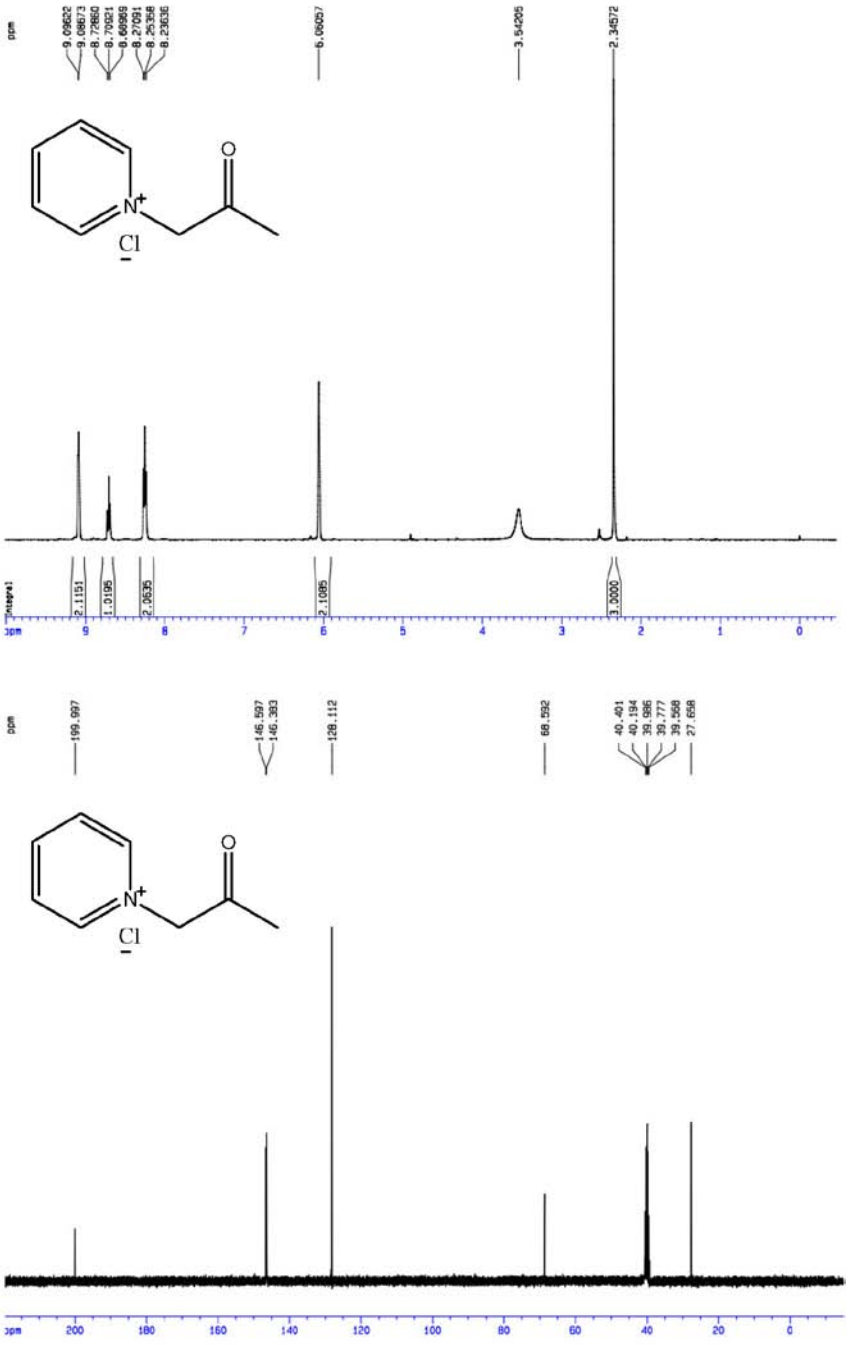

Figure S3. NMR spectra of compound **13**.

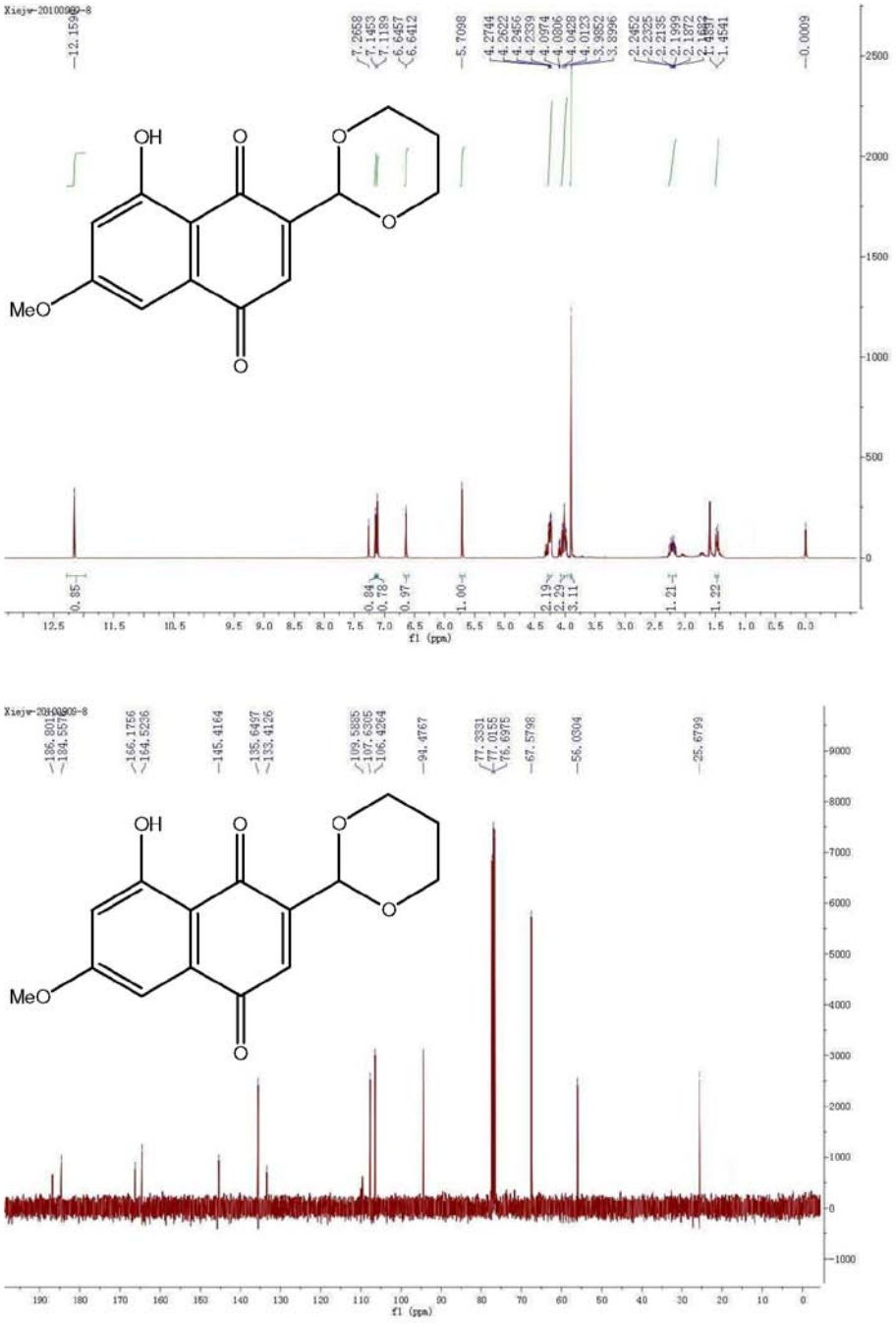

Figure S4. NMR spectra of compound **7b**.

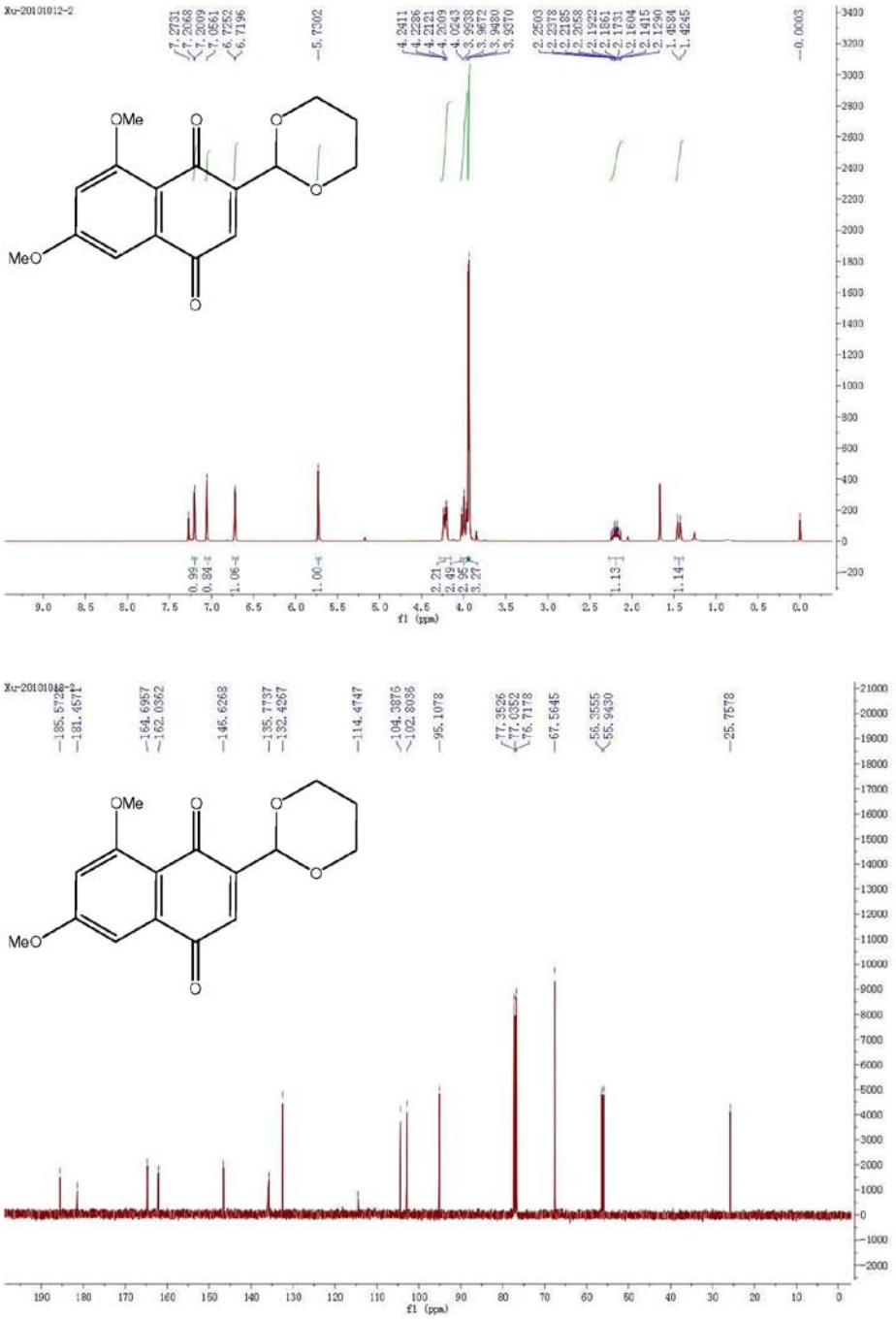

Figure S5. NMR spectra of compound **12**.

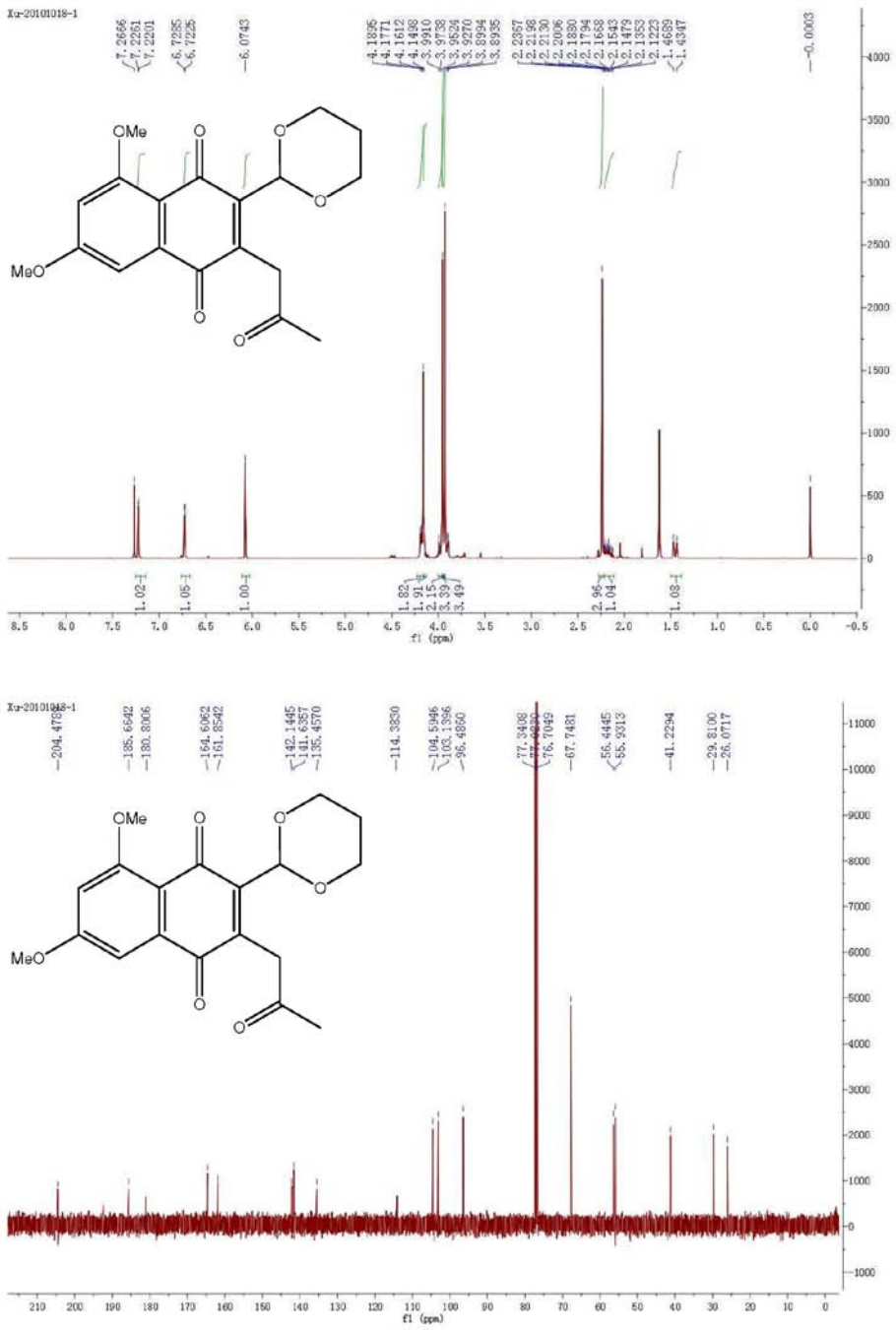

Figure S6. NMR spectra of compound **6b**.

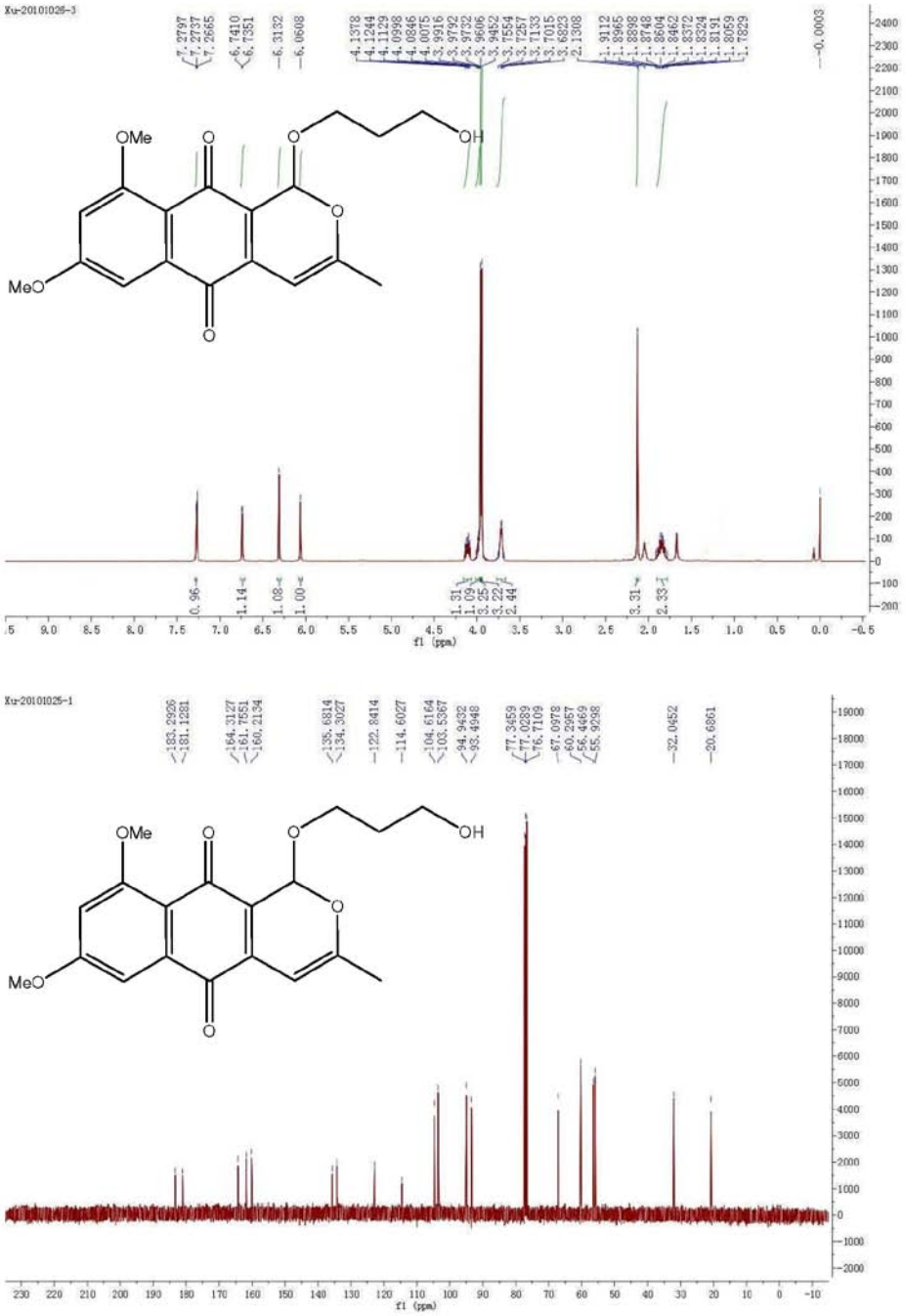

Figure S7. NMR spectra of compound **14**.

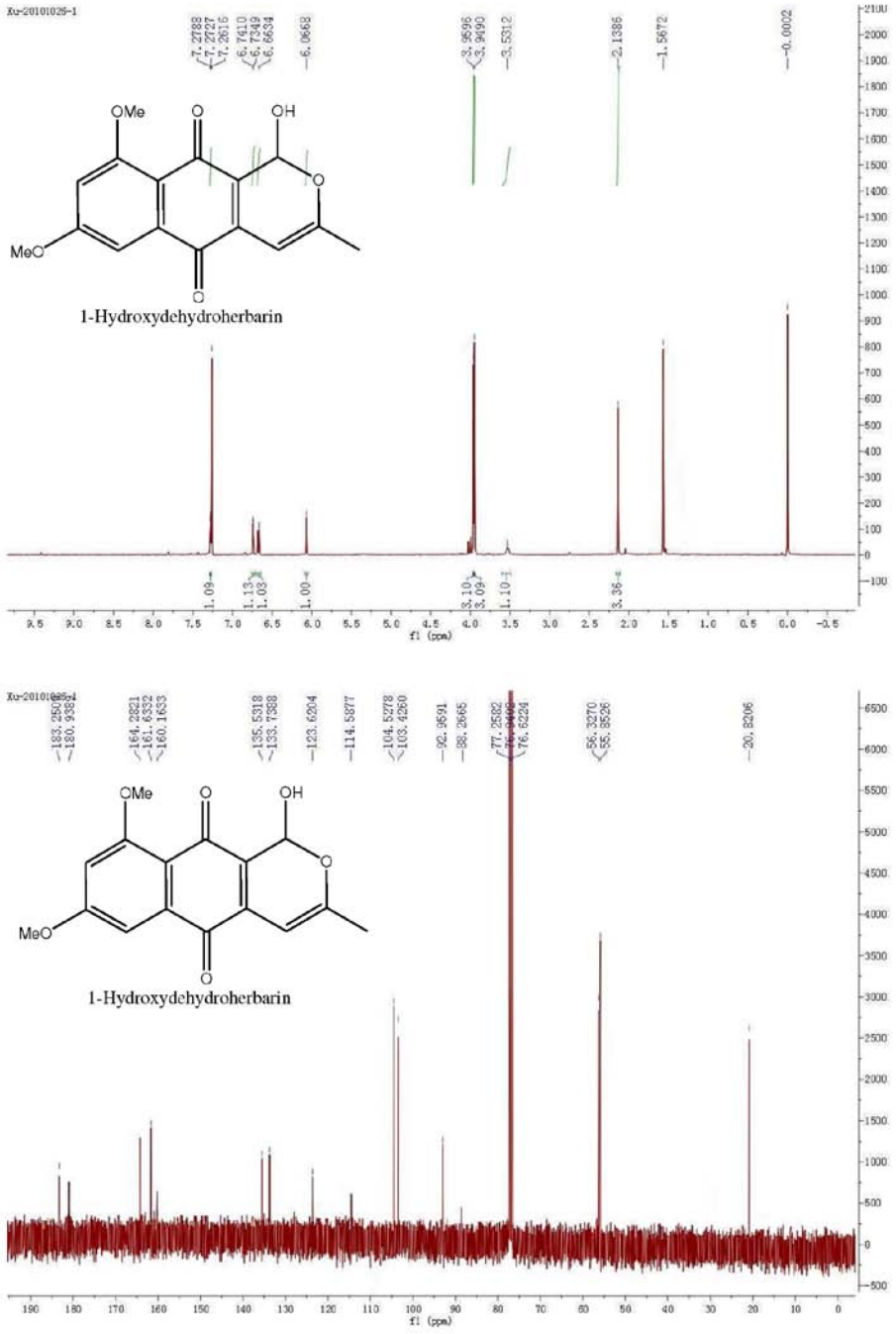

Figure S8. NMR spectra of compound **3**.

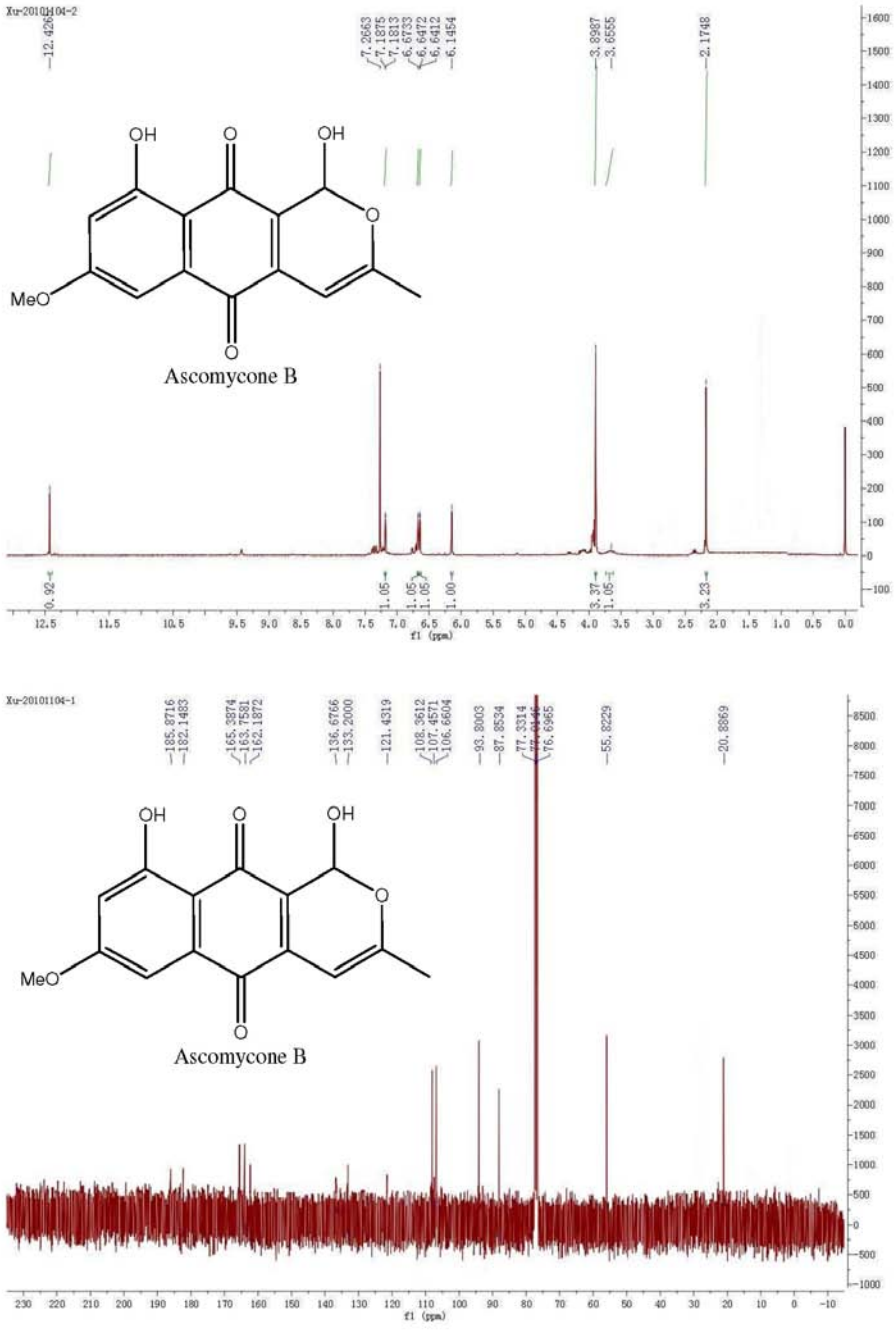

Figure S9. NMR spectra of compound ascomycones B.

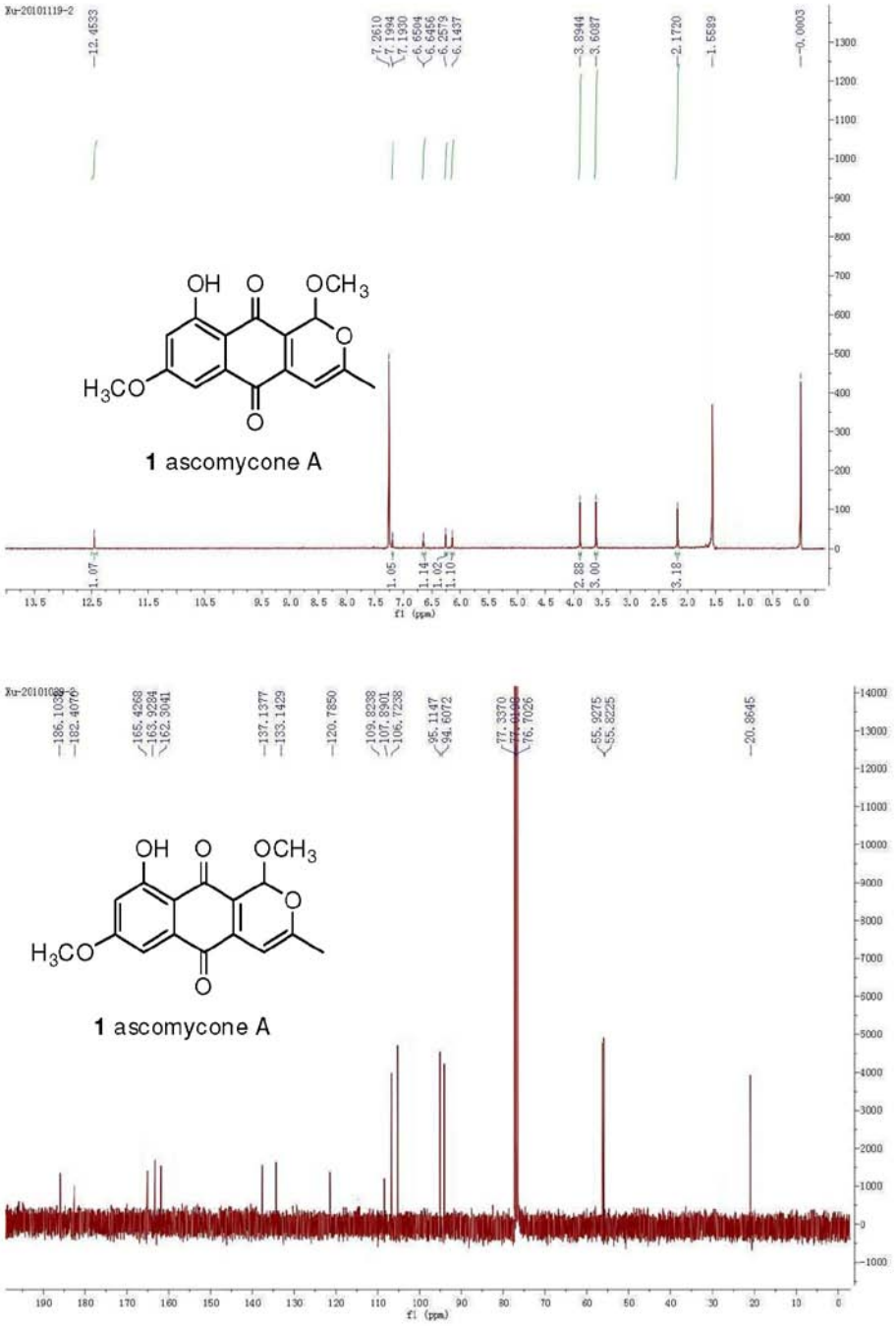

Figure S10. NMR spectra of compound ascomycones A.