**Electronic Supporting Information (ESI)**

# Asymmetric Synthesis of (+)-Teratosphaerone B, its Non-natural Analogue and (+)-Xylarenone using Ene- and Naphthol Reductase Cascade

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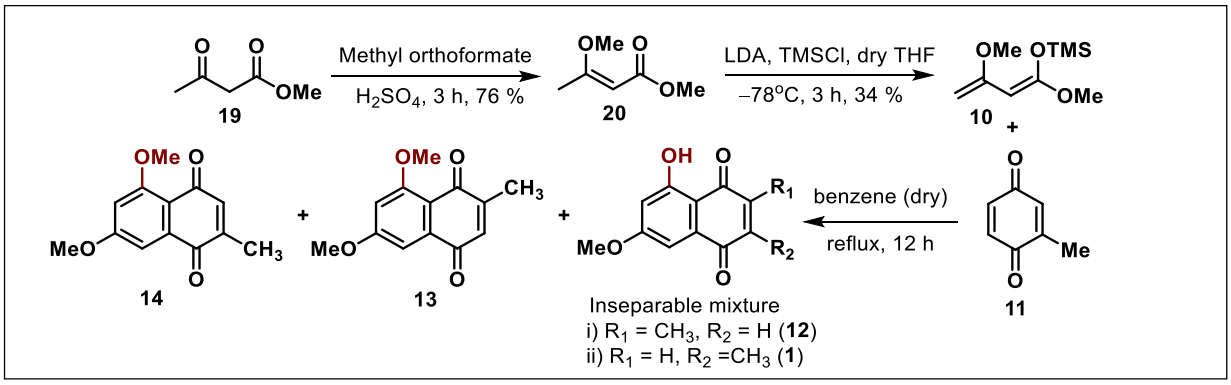
## I. General Remarks

All commercial reagents were obtained from Sigma-Aldrich Chemical Co., Sisco Research Laboratories, Spectrochem Pvt. Ltd, India, TCI Chemicals Pvt. Ltd, India and Avra synthesis Pvt. Ltd, India. Reactions were monitored by thin-layer chromatography (TLC, 0.25 mm E. Merck silica gel plates, 60F254) and the plates were visualized by using UV light. Column chromatography was performed on silica gel 60–120/100-200/230–400 mesh obtained from S. D. Fine Chemical Co., India. Evaporation of solvent was achieved using a Büchi water bath B-481 rotary evaporator under reduced pressure (0 – 1000 mbar) with a bath temperature of 40 °C. Yields represent to chromatographically pure materials; conversions were calculated from gas chromatography-mass spectrometry (GCMS) and Gas Chromatography (GC) of the crude products. $^{1}$H NMR spectra were recorded on Bruker 400 MHz and 400 MHz Ultra Shield instruments using deuterated solvents. Proton coupling constants (*J*) are reported as absolute values in Hz. $^{13}$C NMR spectra were recorded on Bruker 400 MHz Ultra Shield instrument operating at 100 MHz. Chemical shifts ($\delta$) of the $^{1}$H and $^{13}$C NMR spectra are reported in ppm with a solvent resonance as an internal standard. For $^{1}$H NMR: chloroform-$d_1$ 7.26; for $^{13}$C NMR: chloroform-$d_1$ 77.16. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of a doublet, ddd = doublet of a doublet of doublet, t = triplet, dt = doublet of a triplet, q = quartet, quint = quintet, m = multiplet, br = broad, ar = aromatic. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on an Agilent 6530 Accurate-Mass Q-TOF LC/MS system (Agilent Technologies). The concentration of purified enzyme was measured on Nanodrop. Optical rotations were measured on a DigiPol 781 M6U Automatic Polarimeter. UV spectroscopy and activity measurements were performed on Cary 300 UV/Vis spectrophotometer (Agilent Technologies). For determination of the enantiomeric excess (*ee*) the chiral phases Chiralcel OD-H (Daicel Inc., 250 × 4.6 mm, 5 µm) were used on Agilent Technologies 1260 Infinity HPLC system equipped with OpenLAB CDS v2.3 software.

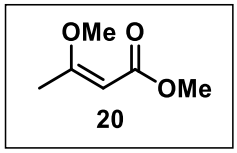
## II. Substrate synthesis

### A. Synthesis of teratosphaerone A (1) using 2-methyl benzoquinone (11)




**Scheme S1:** Synthesis of teratosphaerone A (**1**).

**Methyl (Z/E)-3-methoxybut-2-enoate (20)**[1]

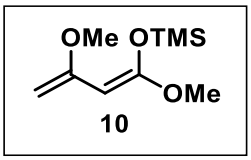


**$C_6H_{10}O_3$**: 130.14 g/mol

To methyl acetoacetate **19** (9.30 mL, 86.0 mmol, 1 equiv.), trimethyl orthoformate (11.88 mL, 111.8 mmol, 1.3 equiv.) and a catalytic amount (4 drops) of conc. $H_2SO_4$ were added, and the solution was stirred at rt. After 24 h, volatile products were removed under reduced pressure, and the crude liquid was purified by vacuum distillation to obtain methyl (Z/ E)-3-methoxybut-2-enoate **20** (8.53 g, 65.6 mmol, 76%) as a colorless liquid.

**GCMS:** Rt = 2.76 min, m/z (%) = 130 (24) [M+], 113 (2), 101 (8), 99 (100), 72 (3), 69 (10), 68 (7), 59(31), 55 (5).

**(Z)-((1,3-dimethoxybuta-1,3-dien-1-yl) oxy) trimethylsilane (10)**[1]



**$C_9H_{18}O_3Si$**: 202.10 g/mol

To a solution of LDA (12.1 mL, 2 M, 24.2 mmol, 1.05 equiv.) in dry THF (25 mL) cooled at -78 °C under argon atmosphere, **20** (3.0 g, 23.1 mmol, 1 equiv.) in dry THF (6 mL) was added slowly. After 30 min, trimethylsilyl chloride (3.5 mL, 27.7 mmol, 1.2 equiv.) in dry THF (6 mL) was added dropwise to the reaction mixture over a period of 15 min. After 1 h, the reaction mixture was brought slowly to rt and stirred for another 1.5 h before removing the solvent. The solvent was then evaporated using rotary evaporator and then, vacuum distilled to obtain (Z)-((1,3-dimethoxybuta-1,3-dien-1-yl) oxy) trimethyl silane **10** (1.59 g, 34% yield).

**GCMS:** Rt = 3.67 min, m/z (%) = 202 (7) [M+], 187 (90), 171 (100), 98 (66), 89 (78), 73 (89), 69 (33), 68 (45), 67 (43), 59 (58).

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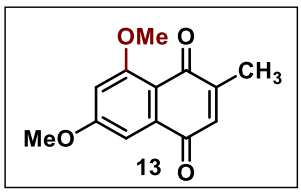
**General Procedure:** 1,4-benzoquinone **11** (200 mg, 1.85 mmol) was dissolved in anhydrous benzene (10 mL) and (*Z*)-4- methoxy-2,2,8,8-tetramethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene **10** (345 mg, 1.85 mmol) was added slowly into the round bottom flask. The reaction mixture was refluxed at 100 °C for 20 h. After complete conversion, reaction mixture was poured into water and extracted with EtOAc (3 x 30 mL). Then the organic layer was concentrated using a rotary evaporator and the residue was purified using column chromatography to obtain **13** and **14**.

**6,8-dimethoxy-2-methylnaphthalene-1,4-dione (13)**




**$C_{13}H_{12}O_4$**: 232.24 g/mol

**TLC** (Hexane/EtOAc, 70:30 v/v): $R_f$ = 0.4

**Column chromatography:** silica gel (100-200 mess size), Hexane: Ethyl acetate: 75:25

**Yield:** 34%

**$^1$H NMR (400 MHz, $CDCl_3$)** $\delta$ (ppm): 7.19 (d, $J$ = 2.4 Hz, 1H), 6.71 – 6.70 (m, 2H), 3.95 (s, 3H), 3.93 (s, 3H), 2.13 (d, $J$ = 1.2 Hz, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$)** $\delta$ (ppm): 185.2, 183.8, 164.7, 162.0, 150.6, 136.4, 133.1, 114.7, 104.2, 102.8, 56.5, 56.0, 17.0.

**HRMS (ESI) m/z: [M + H]** $^+$ Calculated for $[C_{13}H_{13}O_4]^+$ 233.0808; Found 233.0829.

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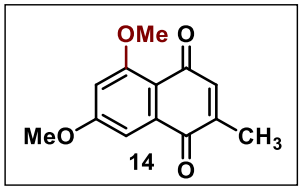
**5,7-dimethoxy-2-methylnaphthalene-1,4-dione (14)**




$C_{13}H_{12}O_4$: 232.24 g/mol

**TLC** (Hexane/EtOAc, 70:30 v/v): $R_f$ = 0.45

**Column chromatography:** silica gel (100-200 mess size), Hexane: Ethyl acetate: 75:25

**Yield:** 10%

**$^1$H NMR (400 MHz, $CDCl_3$)** $\delta$ (ppm): 7.16 (d, $J$ = 2.4 Hz, 1H), 6.64 (d, $J$ = 2.3 Hz, 1H), 6.61 (s, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 2.06 (s, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$)** $\delta$ (ppm): 185.7, 183.4, 164.5, 161.6, 144.7, 138.2, 136.1, 114.5, 104.0, 103.5, 56.4, 55.9, 15.7.

**HRMS (ESI) m/z: [M + H]** $^+$ Calculated for $[C_{13}H_{13}O_4]^+$ 233.0808; Found 233.0824.

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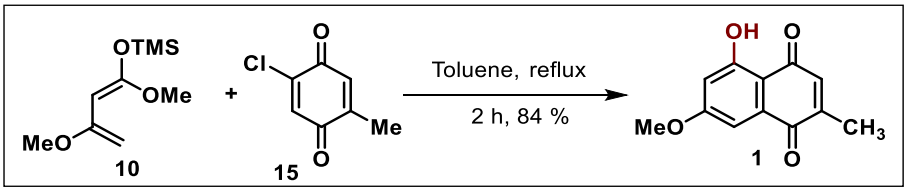
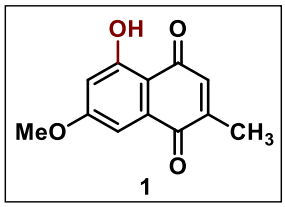
**B. Synthesis of teratosphaerone A (1) using 2-chloro-5-methyl benzoquinone (15)**




**Scheme S2:** Synthesis of teratosphaerone A (**1**).

**5-hydroxy-7-methoxy-2-methylnaphthalene-1,4-dione (teratosphaerone A, 1)**




**$C_{12}H_{10}O_4$**: 218.2080 g/mol

2-Chloro-5-methyl-benzoquinone (**15**) (200 mg, 1.27 mmol) was dissolved in toluene (5 mL) and (Z)-4-methoxy-2,2,8,8-tetramethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene (**10**) (387 mg, 1.91 mmol, 1.5 equiv.) added slowly into the round bottom flask. The reaction mixture was refluxed at 110 °C for 2 h. After complete conversion reaction mixture was poured into water and extracted with EtOAc (3 x 30 mL). Then the organic layer was concentrated using a rotary evaporator and the residue was purified using column chromatography with EtOAc and hexane (10:90 v/v) to obtain teratosphaerone A (**1)** (234 mg) as an orange solid.

**TLC** (Hexane/EtOAc, 70:30 v/v): $R_f$ = 0.80

**Yield:** 84%

**$^1$H NMR (400 MHz, $CDCl_3$)** $\delta$ (ppm): 12.13 (s, 1H, OH), 7.10 (d, $J$ = 2.4 Hz, 1H), 6.70 (q, $J$ = 1.4 Hz, 1H), 6.58 (d, $J$ = 2.4 Hz, 1H), 3.87 (s, 3H), 2.13 (d, $J$ = 1.3 Hz, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$)** $\delta$ (ppm): 188.5, 184.8, 165.9, 164.0, 148.8, 135.9, 133.6, 109.8, 108.0, 106.1, 56.1, 16.5.

**HRMS (ESI) m/z: [M + H]$^+$** Calculated for $[C_{12}H_{11}O_4]^+$ 219.0652; Found 219.0670.

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**Comparison of $^1$H NMR spectroscopic data of natural[2] and synthesized teratosphaerone A.**

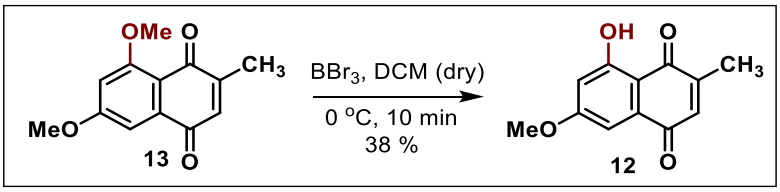
| **$^1$H** | **Natural teratosphaerone A (1) (400 MHz, $CDCl_3$) δ (ppm)** | **Synthesized teratosphaerone A (1) (400 MHz, $CDCl_3$) δ (ppm)** |
|---|---|---|
| **H-3** | 6.73 (q, $J$ = 1.6 Hz, 1H) | 6.70 (q, $J$ = 1.4 Hz, 1H) |
| **H-6** | 6.62 (d, $J$ = 2.4 Hz, 1H) | 6.58 (d, $J$ = 2.4 Hz, 1H) |

| | | |
|---|---|---|
| **H-8** | 7.16 (d, *J* = 2.4 Hz, 1H) | 7.10 (d, *J* = 2.4 Hz, 1H) |
| **C2-CH$_3$** | 2.14 (d, *J* = 1.6 Hz, 3H) | 2.13 (d, *J* = 1.3 Hz, 3H) |
| **C7-OMe** | 3.88 (s, 3H) | 3.87 (s, 3H) |
| **C8-OH** | 12.80 (s, 1H) | 12.13 (s, 1H) |

**Comparison of $^{13}$C NMR spectroscopic data of natural[2] and synthesized teratosphaerone A.**

| $^{13}$C | **Natural teratosphaerone A (100 MHz, CDCl$_3$) δ (ppm)** | **Synthesized teratosphaerone A (100 MHz, CDCl$_3$) δ (ppm)** |
|---|---|---|
| **C-2-Me** | 16.4 | 16.5 |
| **C-1** | 184.8 | 184.8 |
| **C-2** | 148.7 | 148.8 |
| **C-3** | 135.9 | 135.9 |
| **C-4** | 188.5 | 188.5 |
| **C-5** | 164.0 | 164.0 |
| **C-6** | 106.0 | 106.1 |
| **C-7-OMe** | 56.0 | 56.1 |
| **C-7** | 165.8 | 165.9 |
| **C-8** | 107.9 | 108.0 |
| **C-9** | 133.5 | 133.6 |
| **C-10** | 109.7 | 109.8 |

**C. Synthesis of 8-hydroxy-6-methoxy-2-methylnaphthalene-1,4-dione (12)**

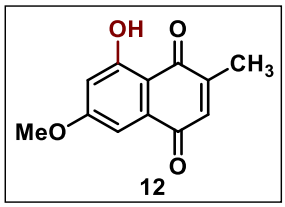



**Scheme S3:** Synthesis of 8-hydroxy-6-methoxy-2-methylnaphthalene-1,4-dione (**12**).

Substate **13** (200 mg, 1.85 mmol) was dissolved in anhydrous DCM (10 mL) and cooled at 0 °C. Then $BBr_3$ solution (345 µL, 1.85 mmol, 1 M in DCM) was added slowly into the round bottom flask. The reaction mixture was stirred at 0 °C for 10 min. After complete conversion

reaction mixture was poured into water and extracted with EtOAc (3 x 30 mL). Then the organic layer was concentrated using a rotary evaporator and the residue was purified by column chromatography to obtain 8-hydroxy-6-methoxy-2-methylnaphthalene-1,4-dione (**12)** (71 mg) as a yellowish orange solid.

**8-hydroxy-6-methoxy-2-methylnaphthalene-1,4-dione (12)**




**$C_{12}H_{10}O_4$**: 218.20 g/mol

**TLC** (Hexane/EtOAc, 70:30 v/v): $R_f$ = 0.80

**Column chromatography:** silica gel (100-200 mess size), Hexane: Ethyl acetate: 75:25

**Yield:** 38%

**$^1$H NMR (400 MHz, $CDCl_3$)** $\delta$ (ppm): 12.28 (s, 1H, OH), 7.13 (d, $J$ = 2.4 Hz, 1H), 6.74 (q, $J$ = 1.4 Hz, 1H), 6.62 (d, $J$ = 2.4 Hz, 1H), 3.90 (s, 3H), 4.0 (s, 1H), 2.17 (s, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$)** $\delta$ (ppm): 189.0, 184.3, 166.2, 164.5, 148.8, 136.0, 134.0, 109.8, 107.5, 106.2, 56.2, 16.1.

**HRMS (ESI) m/z: [M + H]** $^+$ Calculated for $[C_{12}H_{11}O_4]^+$ 219.0652; Found 219.0668.

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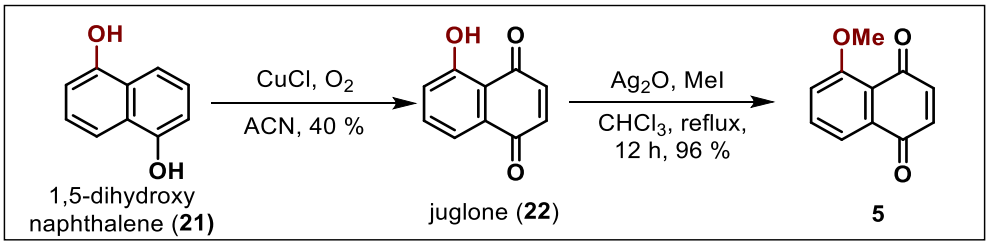
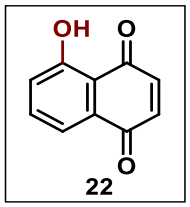
**D. Synthesis of methoxy juglone (5)**




**Scheme S4:** Synthesis of methoxy juglone (**5**).

**5-hydroxynaphthalene-1,4-dione (Juglone, 22)[3]**




**$C_{10}H_6O_3$**: 174.15 g/mol

A suspension of powdered CuCl (2.0 g, 0.02 mole) in acetonitrile (170 mL) was placed in a 250 mL, three-neck flask, fitted with a gas inlet tube and a strong current of air was bubbled through it. The flask was covered with aluminium foil to protect the reaction from light. To this vigorously stirred solution, 1,5-dihydroxynaphthalene **21** (5.0 g, 0.03 mol) was added portion wise over 30 minutes at room temperature. The resultant mixture was stirred overnight (16 h). The mixture was filtered, washed with acetonitrile, and the solvent removed under reduced pressure. The crude product was purified in a Soxhlet extractor with *n*-hexane as a solvent to afford juglone **22** (2.2 g, 40%) as orange-red solid.

**TLC** (Hexane/EtOAc, 70:30 v/v): $R_f$ = 0.80

**$^1$H NMR (400 MHz, $CDCl_3$)** $\delta$ (ppm): 11.90 (s, 1H), 7.67–7.61 (m, 2H), 7.29 (dd, $J$ = 7.7, 1.8 Hz, 1H), 7.96 (s, 2H).

**$^{13}$C NMR (100 MHz, $CDCl_3$)** $\delta$ (ppm): 190.4, 184.4, 161.6, 139.7, 138.8, 136.7, 131.9, 124.6, 119.3, 115.1.

**HRMS (ESI) m/z: [M + H]** $^+$ Calculated for $[C_{10}H_7O_3]^+$ 175.0390; Found 175.0392.

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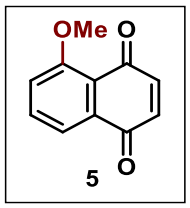
**5-methoxynaphthalene-1,4-dione (5)**




**$C_{11}H_8O_3$**: 188.18 g/mol

Juglone **22** (50 mg, 0.28 mmol) was dissolve in chloroform (5 mL). Then $Ag_2O$ (1.1 eq) and Methyl iodide (MeI, 10 eq) was added to the it and refluxed for 12 h. After complete conversion reaction mixture was poured into water and extracted with EtOAc (3 x 30 mL). Then the reaction mixture was concentrated using a rotary evaporator and the residue was purified using column chromatography with EtOAc in hexane (30:70 v/v) to obtain pure methoxy juglone (**5**) (50 mg, 96%) as an orange solid.

**TLC** (Hexane/EtOAc, 70:30 v/v): $R_f$ = 0.47

**$^1$H NMR (400 MHz, $CDCl_3$)** $\delta$ (ppm): 7.71 (dd, $J$ = 7.6, 1.0 Hz, 1H), 7.66 (t, $J$ = 7.9 Hz, 1H), 7.30 (d, $J$ = 8.0 Hz, 1H), 6.85 (s, 2H), 3.99 (s, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$)** $\delta$ (ppm): 185.3, 184.4, 159.7, 141.0, 136.3, 135.1, 134.1, 119.8, 119.3, 118.0, 56.6.

**HRMS (ESI) m/z: [M + H]** $^+$ Calculated for $[C_{11}H_9O_3]^+$ 189.0546; Found 189.0546.

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## III. Cloning, Expression, and Purification of ene, naphthol and keto- reductases

### Cloning

Synthesized genes encoding Yqjm, GluER, NostocER, OYE-1, OYE-2, OYE-3, MorB, NtDBR cloned into pET22b (+) vector between the NdeI and Xhol restriction sites with N-terminal (YqjM, GluER) 6xHis tag or C-terminal (NostocER, OYE-1, OYE-2, OYE-3, MorB, and NtDBR) 6xHis tag were purchased from Biomatik, Canada. The plasmids for alcohol dehydrogenases and naphthol reductases used in the study were obtained from Prof. Michael Müller, University of Freiburg, Germany. Cloning of $T_4$HNR-*his*, $T_3$HNR-*his* and $T_4$HNRSer156Ala-*his* into the pET-19b vector has been reported elsewhere.[3,4]

### Transformation of the plasmid into *E. coli* cells

Transformation of plasmid DNA to competent *E. coli* BL21 (DE3) cells was performed by applying a heat shock at 42 °C for 45 s. The transformed cells were grown overnight on SOB-agar medium containing 100 µg/mL ampicillin.

### Media and growth conditions

One clone was picked and dispersed in 5 mL of LB-media (Lennox), followed by incubation overnight (37 °C, 220 rpm). Ampicillin (100 µg/mL) was added as required.

### Cultivation and expression

For ene reductases the overnight cultures were diluted to 500 mL of medium each (ampicillin 100 µg/mL) and incubated at 37 °C, 200 rpm. IPTG (0.2 mM) was added to the mid-log phase ($OD_{600}$ = 0.6) was reached, and cultures were incubated for 20 h at 20 °C (for all ene reductases), and for 4 h at 37 ºC (for $T_4$HNR-*his*, $T_3$HNR-*his*, $T_4$HNRSer156Ala-*his*, and GDH) and at 160 rpm.

### Workup and storage

**YqjM**: The harvested *E. coli* cells were resuspended in lysis buffer (50 mM Tris-HCl, 30 mM imidazole, pH 7.0; 2.5 mL per harvested cells of 500 mL medium).
**GluER**: The harvested *E. coli* cells were resuspended in lysis buffer (20 mM KPi, pH 7.0; 2.5 mL per harvested cells of 500 mL medium).

**NtDBR** and **MorB**: The harvested *E. coli* cells were resuspended in lysis buffer (50 mM Tris-base, 300mM NaCl, 10 mM imidazole, pH 7.0; 2.5 mL per harvested cells of 500 mL medium).
**NostocER, OYE-1, OYE-2, OYE-3**: The harvested *E. coli* cells were resuspended in lysis buffer (20 mM Kpi, 300mM NaCl, 30 mM imidazole, pH 7.0; 2.5 mL per harvested cells of 500 mL medium).
**$T_4$HNR-*his*, $T_3$HNR-*his*, $T_4$HNRSer156Ala-*his* and GDH:** The harvested *E. coli* cells were resuspended in lysis buffer (50 mM HEPES, pH 7.5; 2.5 mL per harvested cells of 500 mL culture).

The cells were disrupted by sonication (8 x 10 s, Vibra-Cell Processors, model number VCX500, Sonics), followed by centrifugation (30 min, 12000×*g*, 4 °C). Glycerol (20% v/v) was added, and the crude enzyme preparation was frozen at –20 °C until later use.

**Enzyme purification**

**Ene reductases:** ERED was purified by Ni-NTA affinity chromatography. Non-specifically bound proteins were washed off with 50 mM Tris-HCl, 30 mM imidazole pH 7.0 (for YqjM), 20 mM Kpi, pH 7.0 (for GluER), 50 mM Tris-base, 300mM NaCl, 10 mM imidazole, pH 7.0 (for NtDBR and MorB), 20 mM Kpi, 300 mM NaCl, 30 mM imidazole pH 7.0 (NostocER, OYE-1, OYE-2, OYE-3). Elution was performed with respective washed buffer containing 50-, 100- and 250-mM imidazole. After being analyzed by SDS-PAGE (see below), the fractions containing purified proteins are collected and desalted by gel filtration (Econo-Pac 10 DG desalting gel column, Bio-Rad). The concentration of the protein was performed by ultrafiltration (Vivaspin 20R centrifugal filter units, 10 kDa nominal molecular weight limit, Sartorius). The concentration of the protein was determined by measuring the UV absorption at 280 nm using nanodrop (NanoVue, GE Healthcare).

**Naphthol reductases:** $T_4$HNR-*his* and $T_3$HNR-*his* were purified by Ni-NTA affinity chromatography. Nonspecifically bound proteins were washed off with buffer (50 mM Kpi, pH 7.5) containing 20- and 50-mM imidazole. Elution was performed with 50 mM Kpi buffer (pH 7.5) containing 250 mM imidazole. The eluted solution was desalted by gel filtration (EconoPac 10DG desalting gel column, Bio-Rad). The concentration of the protein was performed by ultrafiltration (Vivaspin 15R centrifugal filter units, 10 kDa nominal molecular weight limit, Sartorius).

HLADH, *Lb*ADH and AOR were produced in *E. coli* as described elsewhere[5,6] and used as a cell-free crude extract.

**Activity measurement:** $T_4$HNR-*his*, $T_3$HNR-*his*, $T_4$HNRSer156Ala-*his* and GDH were assayed as described elsewhere.[3,4] All ene reductases were assayed as described.[5-7]

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***Bacillus subtilis* NADPH dehydrogenase (YqjM)**

**Protein Sequence**

MMARKLFTPITIKDMTLKNRIVMSPMCMYSSHEKDGKLTPFHMAHYISRAIGQVGLI
IVEASAVNPQGRITDQDLGIWSDEHIEGFAKLTEQVKEQGSKIGIQLAHAGRKAELEG
DIFAPSAIAFDEQSATPVEMSAEKVKETVQEFKQAAARAKEAGFDVIEIHAAHGYLIH
EFLSPLSNHRTDEYGGSPENRYRFLREIIDEVKQVWDGPLFVRVSASDYTDKGLDIAD
HIGFAKWMKEQGVDLIDCSSGALVHADINVFPGYQVSFAEKIREQADMATGAVGMI
TDGSMAEEILQNGRADLIFIGRELLRDPFFARTAAKQLNTEIPAPVQYERGW

***Gluconobacter oxydans* Ene-Reductase (GluER)**

**Protein sequence:**

MPTLFDPIDFGPIHAKNRIVMSPLTRGRADKEAVPTPIMAEYYAQRASAGLIITEATGI
SREGLGWPFAPGIWSDAQVEAWKPIVAGVHAKGGKIVCQLWHMGRMVHSSVTGT
QPVSSSATTAPGEVHTYEGKKPFEQARAIDAADISRILNDYENAARNAIRAGFDGVQI
HAANGYLIDEFLRNGTNHRTDEYGGVPENRIRFLKEVTERVIAAIGADRTGVRLSPN
GDTQGCIDSAPETVFVPAAKLLQDLGVAWLELREPGPNGTFGKTDQPKLSPQIRKVF
LRPLVLNQDYTFEAAQTALAEGKADAIAFGRKFISNPDLPERFARGIALQPDDMKTW
YSQGPEGYTDYPSATSGPN

**Ene-reductase 1 from Nostoc sp. PCC7120 (NostocER)**

**Protein sequence:**

MSDEAERQRGNNLYKNSPLLPVSISQVSTSQLRETEIMSTNINLFSSYQLGELELPNRV
MAPLTRQRAGEGNVPHQLNAIYYGQRASAGLIIAEATQVTPQGQGYPHTPGIHSPEQ
VAGWKLVTDTVHQQGGRIFLQLWHVGRISHPDLQPDGGLPVAPSAIAPKGEVLTYE
GKKPYVTPRALDTSEIPAIVEQYRQGAANALAAGFDGVEIHAANGYLIDQFLRDGTN
QRTDEYGGAIENRARLLLEVTEAITSVWDSQRVGVRLSPSGTFNDIRDSHPLETFGYV
AQALNRFNLSYLHIFEAIDADIRHGGTVVPTSHLRDRFTGTLIVNGGYTREKGDTVIA
NKAADLVAFGTLFISNPDLPERLEVNAPLNQADPTTFYGGGEKGYTDYPFLAVANKL
E

**Old Yellow Enzyme 1 (OYE1)**

**Protein Sequence:**

MSFVKDFKPQALGDTNLFKPIKIGNNELLHRAVIPPLTRMRALHPGNIPNRDWAVEY
TQRAQRPGTMIITEGAFISPQAGGYDNAPGVWSEEQMVEWTKIFNAIHEKKSFVWV
QLWVLGWAAFPDNLARDGLRYDSASDNVFMDAEQEAKAKKANNPQHSLTKDEIK
QYIKEYVQAAKNSIAAGADGVEIHSANGYLLNQFLDPHSNTRTDEYGGSIENRARFT
LEVVDALVEAIGHEKVGLRLSPYGVFNSMSGGAETGIVAQYAYVAGELEKRAKAGK
RLAFVHLVEPRVTNPFLTEGEGEYEGGSNDFVYSIWKGPVIRAGNFALHPEVVREEV
KDKRTLIGYGRFFISNPDLVDRLEKGLPLNKYDRDTFYQMSAHGYIDYPTYEEALKL
GWDKK

**Old yellow enzyme 2 (OYE2)**

**Protein Sequence:**

MPFVKDFKPQALGDTNLFKPIKIGNNELLHRAVIPPLTRMRAQHPGNIPNRDWAVEY
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LWVLGWAAFPDTLARDGLRYDSASDNVYMNAEQEEKAKKANNPQHSITKDEIKQY
VKEYVQAAKNSIAAGADGVEIHSANGYLLNQFLDPHSNNRTDEYGGSIENRARFTLE
VVDAVVDAIGPEKVGLRLSPYGVFNSMSGGAETGIVAQYAYVLGELERRAKAGKRL
AFVHLVEPRVTNPFLTEGEGEYNGGSNKFAYSIWKGPIIRAGNFALHPEVVREEVKD
PRTLIGYGRFFISNPDLVDRLEKGLPLNKYDRDTFYKMSAEGYIDYPTYEEALKLGW
DKN

**Old yellow enzyme 3 (OYE3)**

**Protein Sequence:**

MPFVKGFEPISLRDTNLFEPIKIGNTQLAHRAVMPPLTRMRATHPGNIPNKEWAAVY
YGQRAQRPGTMIITEGTFISPQAGGYDNAPGIWSDEQVAEWKNIFLAIHDCQSFAWV
QLWSLGWASFPDVLARDGLRYDCASDRVYMNATLQEKAKDANNLEHSLTKDDIKQ
YIKDYIHAAKNSIAAGADGVEIHSANGYLLNQFLDPHSNKRTDEYGGTIENRARFTL
VVDALIETIGPERVGLRLSPYGTFNSMSGGAEPGIIAQYSYVLGELEKRAKAGKRLAF
VHLVEPRVTDPSLVEGEGEYSEGTNDFAYSIWKGPIIRAGNYALHPEVVREQVKDPR
TLIGYGRFFISNPDLVYRLEEGLPLNKYDRSTFYTMSAEGYTDYPTYEEAVDLGWNK
N

**Morphinone reductase (MorB)**

**Protein Sequence:**

MPDTSFSNPGLFTPLQLGSLSLPNRVIMAPLTRSRTPDSVPGRLQQIYYGQRASAGLII
SEATNISPTARGYVYTPGIWTDAQEAGWKGVVEAVHAKGGRIALQLWHVGRVSHE
LVQPDGQQPVAPSALKAEGAECFVEFEDGTAGLHPTSTPRALETDEIPGIVEDYRQA
QRAKRAGFDMVEVHAANACLPNQFLATGTNRRTDQYGGSIENRARFPLEVVDAVA
EVFGPERVGIRLTPFLELFGLTDDEPEAMAFYLAGELDRRGLAYLHFNEPDWIGGDIT
YPEGFREQMRQRFKGGLIYCGNYDAGRAQARLDDNTADAVAFGRPFIANPDLPERF
RLGAALNEPDPSTFYGGAEVGYTDYPFLDNGHDRLG

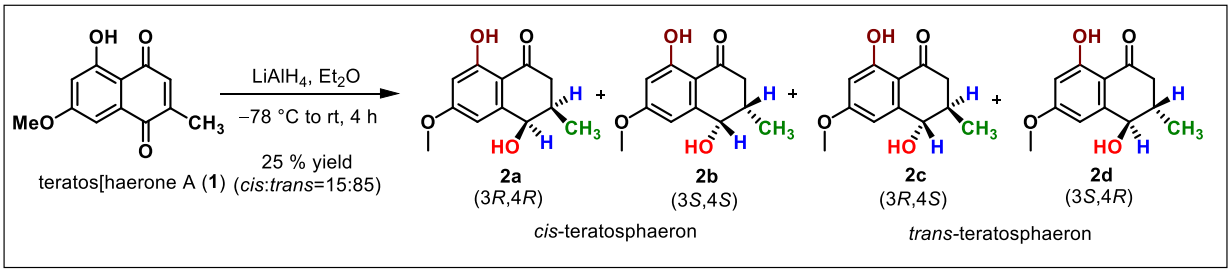
***Nicotiana tabacum* Double Bond Reductase (NtDBR)**

**Protein Sequence:**

MAEEVSNKQVILKNYVTGYPKESDMEIKNVTIKLKVPEGSNDVVVKNLYLSCDPYM
RSRMRKIEGSYVESFAPGSPITGYGVAKVLESGDPKFQKGDLVWGMTGWEEYSIITP
TQTLFKIHDKDVPLSYYTGILGMPGMTAYAGFHEVCSPKKGETVFVSAASGAVGQL
VGQFAKMLGCYVVGSAGSKEKVDLLKSKFGFDEAFNYKEEQDLSAALKRYFPDGID
IYFENVGGKMLDAVLVNMKLYGRIAVCGMISQYNLEQTEGVHNLFCLITKRIRMEG
FLVFDYYHLYPKYLEMVIPQIKAGKVVYVEDVAHGLESAPTALVGLFSGRNIGKQV
VMVSRELE

## IV. Synthesis of racemic products

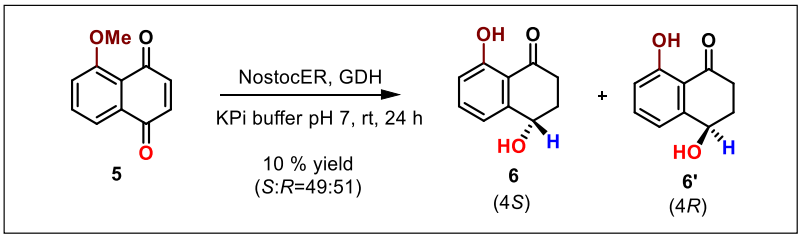
### A. Synthesis of racemic *cis*- and *trans*-teratosphaerone B (2)




**Scheme S5:** Racemic synthesis of teratosphaerone B (**2**).

40 mg (183 mmol) teratosphaerone A (**1**) was reduced with $LiAlH_4$ (50 mg, 1.8 mmol, 10 equiv.) in $Et_2O$ (10 mL) at −78 °C. The solution was stirred for 4 h while warming up to room temperature, then 0.1 N HCl was added until pH 5 was reached. The mixture was extracted with $Et_2O$ and the organic extract was washed with $H_2O$, dried over $MgSO_4$ and the solvent was evaporated in vacuo. And the residue was purified using column chromatography with EtOAc and hexane (15:85 v/v) to obtain racemic teratosphaerone B (10 mg) as a viscous yellow oil. The product was characterized by NMR and compared with reported data of natural product.[2]

### B. Enzyme catalysed synthesis of racemic xylarenone (6)




**Scheme S6:** Racemic synthesis of xylarenone (**6**).

To a 100 mL round bottom flask, $NADP^+$ (8.4 mg, 0.010 mmol, 0.1 equiv.), glucose (95.7 mg, 0.50 mmol, 5 equiv.) and GDH (100 U) were added into 40 mL Kpi buffer solution (50 mM, EDTA = 1.0 mM, DTT = 1.0 mM, pH 7) at room temperature. Then the substrate, methoxy juglone (**5**) (20.0 mg, 0.10 mmol, 1 equiv.) in DMSO (4 mL, 10% v/v) was added slowly, while stirring. At last, ene reductase NostocER cell-free extract (1 mL, 4U) was added to the reaction

mixture and kept stirring at 100 rpm at room temperature under argon atmosphere. After 14 h, the reaction was stopped by the addition of ethyl acetate and was filtered through a celite pad and washed with diethyl ether. The solution was extracted with ethyl acetate (EtOAc, 3 x 25 mL), dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. Racemic product was characterized by NMR compared with reported data of natural product.[8]

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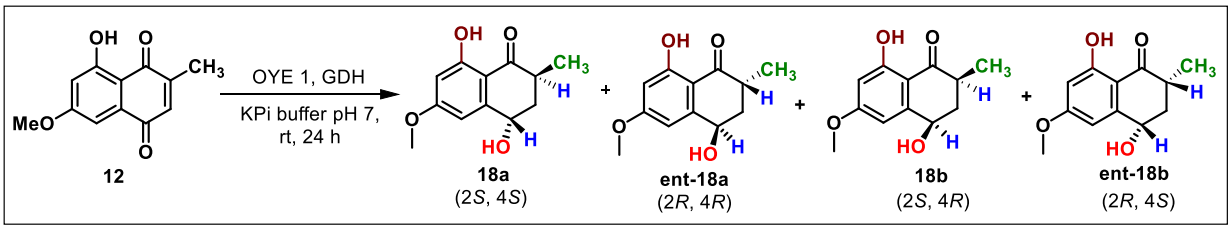
**C. Enzyme catalysed synthesis of all possible stereoisomers of 18**




**Scheme S7:** Synthesis of all possible stereoisomers of **18**.

To a 100 mL round bottom flask, $NADP^+$ (7.22 mg, 0.009 mmol, 0.1 equiv.), glucose (82.0 mg, 0.48 mmol, 5 equiv.) and GDH (100 U) were added into 40 mL Kpi buffer solution (50 mM, EDTA = 1.0 mM, DTT = 1.0 mM, pH 7) at room temperature. After that substrate **12** (20.0 mg, 0.09 mmol, 1 equiv.) in DMSO (4 mL, 10% v/v) was added slowly, while stirring. Then, cell-free extract of ene reductase OYE 1 (1 mL, 4U) was added to the reaction mixture and kept stirring at 100 rpm at room temperature under argon. After 14 h, the reaction was stopped by the addition of ethyl acetate and was filtered through a celite pad and washed with diethyl ether. The solution was extracted with ethyl acetate (EtOAc, 3 x 25 mL), dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. Product was characterized by NMR and mass.

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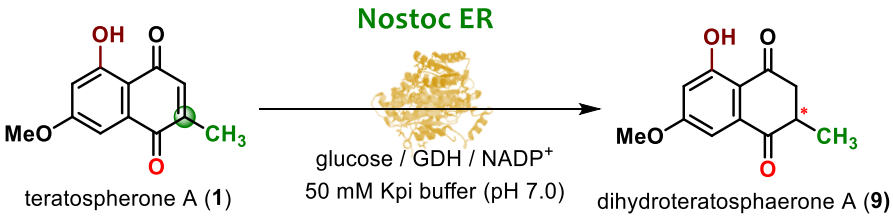
## V. Biocatalytic cascade synthesis of teratosphaerone B (2)

### A. Ene reductase (ERED) catalysed C=C bond reduction of teratosphaerone A (1):




**Scheme S8:** Synthesis of dihydroteratosphaerone A (**9**).

### A1. Ene reductase (ERED) screening

Analytical scale enzyme catalysed reactions were performed using cell-free extract of ERED and GDH (used for cofactor recycling). Total volume of 5 mL of buffer was taken in a 10 mL round bottom flask and stirred at 100 rpm for 3 h at room temperature under argon atmosphere, before being quenched and extracted with ethyl acetate (2 x reaction volume). The organic fractions were combined, dried over $Na_2SO_4$, and the solvent was removed under reduced pressure, and analyses using NMR spectroscopy in $CDCl_3$ (Table 1)

### A2. Optimisation of substrate concentration:

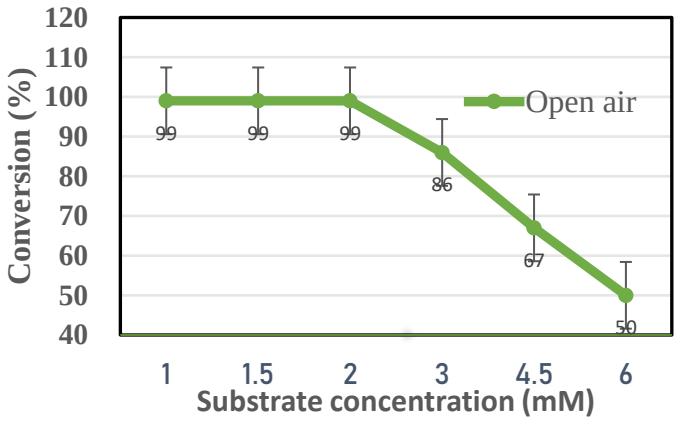



**Figure S1:** concentration optimisation

Conversion was determined by $^1$H-NMR. Reaction conditions: 1.0 – 6.0 mM substrate (**1**), 50 µM cell-free extract of Nostoc ER, 10 U GDH, 0.1 equiv. $NADP^+$, 5 equiv. glucose, 10% v/v

DMSO, 50 mM potassium phosphate buffer (1 mM EDTA, 1 mM DTT, pH 7.0). Open air reaction condition, rt, 3 h.

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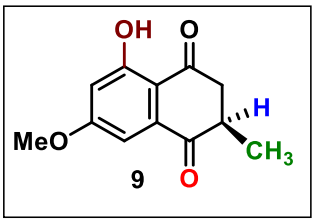
**A3. Ene reductase (ERED) catalysed C=C bond reduction of teratosphaerone A (1) on large scale.**

To a 100 mL round bottom flask, $NADP^+$ (7.22 mg, 0.009 mmol, 0.1 equiv.), glucose (82.0 mg, 0.48 mmol, 5 equiv.) and GDH (50 U) were added into 40 mL Kpi buffer solution (50 mM, EDTA =1.0 mM, DTT = 1.0 mM, pH 7) at room temperature. After that substrate teratosphaerone A (**1**) (20.0 mg, 0.09 mmol, 1 equiv.) in DMSO (4 mL, 10% v/v) was added slowly, while stirring. Finally, cell-free extract of NostocER (1 mL, 4U) was added to the reaction mixture and reaction was stirred at 100 rpm at room temperature under argon atmosphere. After 3 h, the reaction was stopped by the addition of ethyl acetate and was filtered through a celite pad and washed with diethyl ether. The solution was extracted with ethyl acetate (EtOAc, 3 x 25 mL), dried over $Na_2SO_4$, and the solvent was removed under reduced pressure to obtain pure **9** (no purification required).

**(2*R*)-5-hydroxy-7-methoxy-2-methyl-2,3-dihydronaphthalene-1,4-dione (dihydroteratosphaerone A (9))**




**$C_{12}H_{12}O_4$**: 220.22 g/mol

**TLC** (Hexane/EtOAc, 90:10 v/v): $R_f$ = 0.80

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ (ppm) 12.37 (narrow, OH), 7.04 (d, $J$ = 2.5 Hz, 1H), 6.64 (dd, $J$ = 2.5 Hz, 1H), 3.89 (s, 3H), 3.16–3.02 (m, 2H), 2.81 (dd, $J$ = 16.7, 10.5 Hz, 1H), 1.31 (d, $J$ = 6.4 Hz, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ (ppm) 200.7, 198.4, 166.5, 164.5, 137.2, 112.6, 106.4, 105.8, 56.1, 44.5, 42.3, 15.6.

**CD (*c* = 2.0 mM, *l* = 0.1 mm, methanol): λ [nm] (CD mdeg)** 200 (5.63), 207 (6.99), 216 (2.70), 219 (0.10), 223 (–3.48), 231 (–6.44), 240 (–3.32), 251 (0.14), 267 (–1.38), 289 (–0.64), 311 (–4.49), 324 (–6.86), 340 (–3.05), 346 (–0.64), 359 (1.54), 378 (0.25).

**[$\alpha^{25}_D$]** = –32.50 (*c* = 0.08, MeOH).

**HRMS (ESI) m/z: [M + H]** $^+$ Calculated for $[C_{12}H_{13}O_4]^+$ 221.0808; Found 221.0823.

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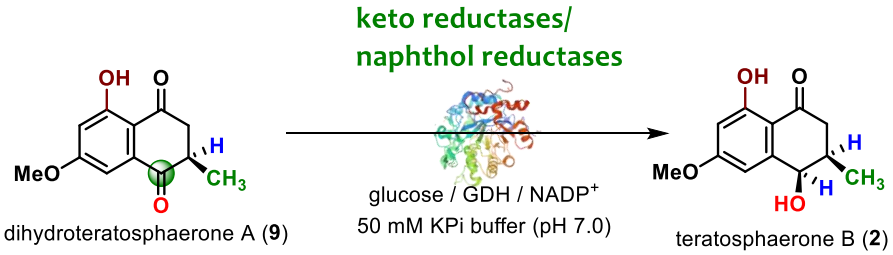
**B. Biocatalytic C=O bond reduction of dihydroteratosphaerone A (9)**

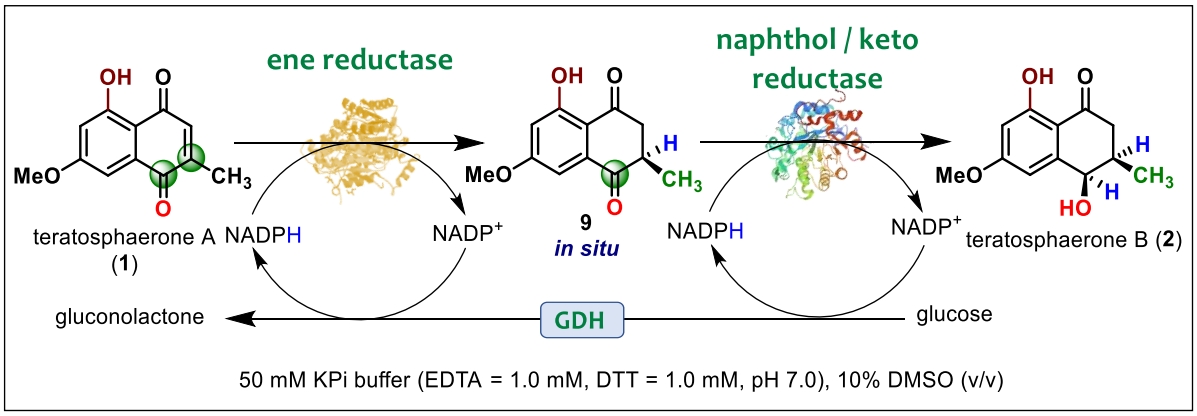
Analytical scale enzymatic reactions were performed using cell-free extract of keto/naphthol reductases (KRs/NRs) and GDH (used for cofactor recycling). All reactions were performed taking 5 mL of Kpi buffer in a 10 mL round bottom flask and stirred at 100 rpm for 14 h at room temperature under argon atmosphere. The reaction was quenched using ethyl acetate and extracted in the same solvent (2 x reaction volume). The organic fractions were combined, dried over $Na_2SO_4$, solvent was removed under reduced pressure. The conversion was determined by measuring the $^1$H NMR of the crude reaction mixture in $CDCl_3$ (Table S1)




| Table-S1: Optimisation table for selective keto reduction | | |
|---|---|---|
| **Entry** | **Keto reductase** | **Conversion (%)** |
| **1** | HLADH | 18 |
| **2** | LBADH | 43 |
| **3** | AOR | - |
| **4** | $T_4$HNR | 10 |
| **5** | $T_4$HNR-S156A | 46 |
| **6** | **$T_3$HNR** | **99** |

The conversion was determined by $^1$H-NMR after 14 h. Reaction conditions: 2 mM substrate (**9**), 50 µM cell-free extract of keto/naphthol reductase, 10 U GDH, 0.2 mM $NADP^+$, 10 mM glucose, 10% v/v DMSO, reaction volume 5 mL, 50 mM potassium phosphate buffer pH 7. Open air

**C. One-pot bienzyme cascade reduction of teratosphaerone A (1)**




**Scheme S9:** Cascade synthesis of teratosphaerone B (**2**).

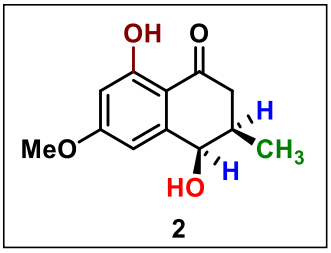
Biotransformations were performed using crude cell-free extract of various EREDs and keto reductases/ naphthol reductases added together along with GDH (used for cofactor recycling). All reactions were performed using 20 mL of buffer and reaction was stirred at 100 rpm at room temperature for 14 h using optimized reaction condition and the product formed was extracted into ethyl acetate (2 x reaction volume) as mentioned in earlier enzymatic procedures. The organic fractions were combined, dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. To determine the conversion and diastereomeric ratio of *cis* and *trans* isomer of the synthesized teratosphaerone B (**2**) crude $^1$H-NMR was taken. After that, the crude reaction mixture was subjected to column chromatography to afford the pure product and calculate the corresponding isolated yield whereas enantioselectivity was determined using chiral HPLC. (Table 2)

**D. One-pot synthesis of teratosphaerone B (2) using NostocER-T$_3$HNR cascade**

To a 100 mL round bottom flask, $NADP^+$ (7.22 mg, 0.009 mmol, 0.1 equiv.), glucose (82.5 mg, 0.48 mmol, 5 equiv.) and GDH (50 U) were added into 40 mL KPi buffer solution (50 mM, EDTA=1.0 mM, DTT=1.0 mM, pH 7) at room temperature. After that substrate teratosphaerone A (**1**) (20.0 mg, 0.09 mmol, 1 equiv.) in DMSO (4 mL, 10% v/v) was added slowly, while stirring. Finally, cell-free extract of Nostoc-ER (1 mL, 4 U) and T$_3$HNR-*his* (1 mL, 6 U) were added to the reaction mixture which was stirred at 100 rpm at room temperature under argon atmosphere. After 14 h, the reaction was stopped by the addition of ethyl acetate and was filtered through a celite pad and washed with ethyl acetate. The solution was extracted

with ethyl acetate (EtOAc, 3 x 20 mL), dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. The crude reaction mixture was subjected to column chromatography to afford the pure product as yellowish solid.

**(3*R*,4*R*)-4,8-dihydroxy-6-methoxy-3-methyl-3,4-dihydronaphthalen-1(2*H*)-one ((+)-teratosphaerone B, (2))**




2

**$C_{12}H_{14}O_4$**: 222.24 g/mol

**TLC** (Hexane/EtOAc, 70:30 v/v): $R_f$ = 0.40

**Column chromatography:** silica gel (100-200 mess size), Hexane: Ethyl acetate: 75:25

**Yield:** 92%

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ (ppm) 12.38 (s, 1H, OH), 6.49 (d, $J$ = 2.3 Hz, 1H), 6.36 (d, $J$ = 2.4 Hz, 1H), 4.67 (d, $J$ = 2.8 Hz, 1H), 3.84 (s, 3H), 2.77 (dd, $J$ = 17.6 Hz, 10.2 Hz, 1H), 2.53 (dd, $J$ = 17.6 Hz, 4.4 Hz, 1H), 2.44–2.34 (m, 1H), 1.13 (d, $J$ = 6.9 Hz, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ (ppm) 202.5, 166.5, 165.8, 146.9, 109.5, 107.2, 100.6, 71.5, 55.8, 40.8, 34.6, 15.9.

**CD (*c* = 2.0 mM, *l* = 0.1 mm, methanol): λ [nm] (CD mdeg)** 201 (–22.50), 206 (–34.04), 211 (–39.18), 221 (–20.57), 229 (–0.24), 236 (3.40), 247 (0.43), 267 (3.87), 289 (6.37), 314 (4.05), 331 (2.26), 343 (0.56), 358 (0.20).

**$[\alpha^{25}_D]$** = + 21.0 (*c* = 0.14, MeOH).

**HRMS (ESI) m/z: [M + H]$^+$** Calculated for $[C_{12}H_{15}O_4]^+$ 223.0965; Found 223.0976.

**HPLC:** (*rac*) [Flow rate: 0.5 mL/min; Typical injection volume: 5 µL; Isocratic: 90% *n*-hexane, 10% isopropanol; DAD: 280 nm (bandwidth = 4 nm); Column: Chiralcel OD-H, 5 µm,4.6 mm (ϕ) x 250 mm (L) mm, Temperature: 25 °C.]: Retention time (Rt), Rt ((3*S*, 4*S*)-**2b**) = 17.80 min, $R_t$ ((3*R*, 4*R*)-**2a**) = 18.92 min; $R_t$ ((3*R*, 4*S*)-**2c**) =19.86, $R_t$ ((3*S*, 4*R*)-**2d**) = 21.68.

**HPLC:** (3*R*, 4*R*)-**2a**) [Flow rate: 0.5 mL/min; Typical injection volume: 10 µL; Isocratic: 90% *n*-hexane, 10% isopropanol; DAD: 280 nm (bandwidth = 4 nm); Column: Chiralcel OD-H, 5 µm,4.6 mm (ϕ) x 250 mm (L) mm, Temperature: 25 °C.]: Retention time (Rt), $R_t$ ((3*R*, 4*R*)-**2a**) = 18.42 min; Enantiomeric excess (ee) = >99%, Diastereomeric ratio (cis/trans) = 100:0. (Determined by comparison to *rac*emic).

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**Comparison of $^1$H NMR spectroscopic data of natural and synthesized (+)-teratosphaerone B (2).**[2]

| **$^1$H** | **Natural (+)-teratosphaerone B (2) (400 MHz, $CDCl_3$) δ (ppm)** | **Synthesized (+)-teratosphaerone B (2) (400 MHz, $CDCl_3$) δ (ppm)** |
|---|---|---|
| **H-2** | 2.50 (dd, *J* = 17.6, 4.4 Hz, 1H) | 2.53 (dd, *J* = 17.6 Hz, 4.4 Hz, H) |
| | 2.74 (dd, *J* = 17.6, 10.0 Hz, 1H) | 2.77 (dd, *J* = 17.6 Hz, 10.2 Hz, 1H) |
| **H-3** | 2.36 (m, 1H) | 2.44–2.34 (m, 1H) |
| **C3-$CH_3$** | 1.11 (d, *J* = 6.8 Hz, 3H) | 1.13 (d, *J* = 6.9 Hz, 3H) |
| **H-4** | 4.64 (d, *J* = 2.8 Hz, 1H) | 4.67 (d, *J* = 2.8 Hz, 1H), |
| **H-5** | 6.46 (d, *J* = 2.4 Hz, 1H) | 6.49 (d, *J* = 2.3 Hz, 1H) |
| **H-7** | 6.33 (d, *J* = 2.4 Hz, 1H) | 6.36 (d, *J* = 2.4 Hz, 1H) |
| **C6-OMe** | 3.83 (s, 3H) | 3.84 (s, 3H) |
| **C8-OH** | 12.80 (s, 1H) | 12.38 (s, 1H) |

**Comparison of $^{13}$C NMR spectroscopic data of natural and synthesized (+)-teratosphaerone B.**[2]

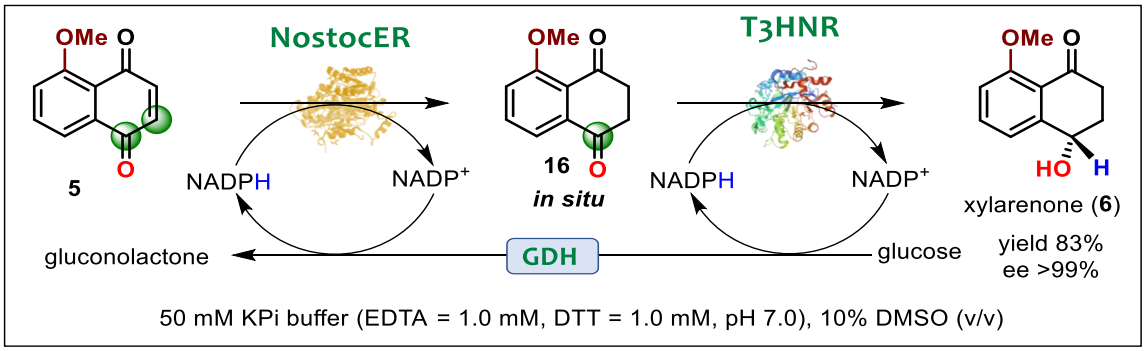
| **$^{13}$C** | **Natural (+)-teratosphaerone B (2) (100 MHz, $CDCl_3$) δ (ppm)** | **Synthesized (+)-teratosphaerone B (2) (100 MHz, $CDCl_3$) δ (ppm)** |
|---|---|---|

| | | |
|---|---|---|
| **C-3-Me** | 15.8 | 15.9 |
| **C-1** | 202.4 | 202.5 |
| **C-2** | 40.6 | 40.8 |
| **C-3** | 34.4 | 34.6 |
| **C-4** | 71.3 | 71.5 |
| **C-5** | 107.1 | 107.2 |
| **C-6** | 166.3 | 166.5 |
| **C-6-Ome** | 55.6 | 55.8 |
| **C-7** | 100.4 | 100.6 |
| **C-8** | 165.6 | 165.8 |
| **C-9** | 109.3 | 109.5 |
| **C-10** | 146.7 | 146.9 |

**E. Preparative scale synthesis of (+)-teratosphaerone B (2)**

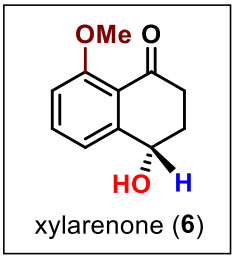
To a 1 L round bottom flask, $NADP^+$ (78 mg, 0.1 mmol, 0.1 equiv.), glucose (900 mg, 5 mmol, 5 equiv.) and GDH (120 U) were added into 400 mL Kpi buffer solution (50 mM, EDTA=1.0 mM, DTT=1.0 mM, pH 7) at room temperature. After that substrate teratosphaerone A (**1)** (218.0 mg, 1 mmol, 1 equiv.) in DMSO (20 mL) was added slowly, while stirring. Finally, the cell-free extract of Nostoc-ER (3 mL, 12 U) and $T_3$HNR-*his* (4 mL, 24 U) were added to the reaction mixture which was stirred at 100 rpm at room temperature under argon atmosphere. After 14 h, the reaction was stopped by the addition of ethyl acetate and was filtered through a celite pad and washed with ethyl acetate. The solution was extracted with ethyl acetate (EtOAc, 3 x 20 mL), dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. The crude reaction mixture was subjected to column chromatography to afford teratosphaerone B **2** (151 mg, 0.68 mmol, 68%) the pure product as yellowish solid.

## VI. Synthesis of (+)-xylarenone (6) using bienzyme cascade




**Scheme S10:** Cascade synthesis of (+)-xylarenone (**6**) using NostocER and $T_3$HNR.

To a 100 mL round bottom flask, NADP+ (8.4 mg, 0.01 mmol, 0.1 equiv.), glucose (95.7 mg, 0.53 mmol, 5 equiv.) and GDH (50 U) were added into 40 mL Kpi buffer solution (50 mM, 1.0 mM EDTA, 1.0 mM DTT, pH 7) at room temperature. Then the substrate **5** (20.0 mg, 0.11 mmol, 1 equiv.) in DMSO (4 mL, 10% v/v) was added slowly, while stirring. Finally, cell-free extract of Nostoc-ER (1 mL, 4 U) and $T_3$HNR-*his* (1 mL, 6 U) were added to the reaction mixture and stirred at 100 rpm at room temperature under argon atmosphere. After 14 h, the reaction was stopped by the addition of ethyl acetate and was filtered through a celite pad and washed with ethyl acetate. The solution was extracted with ethyl acetate (EtOAc, 3 x 20 mL), dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. The crude reaction mixture was subjected to column chromatography to afford the pure **6** as yellowish solid.




**$C_{11}H_{12}O_3$**: 192.21 g/mol

**TLC** (Hexane/EtOAc, 50:50 v/v): $R_f$ = 0.40

**Column chromatography:** silica gel (100-200 mess size), Hexane: Ethyl acetate: 70:30

**Yield:** 83%

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ (ppm) 7.52 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 4.90 (dd, *J* = 7.8, 3.7 Hz, 1H), 3.92 (s, 3H), 2.91 (ddd, *J* = 17.4 Hz, 7.7, 5.1 Hz, 1H), 2.58 (ddd, *J* = 17.3, 8.6, 5.1 Hz, 1H), 2.36–2.29 (m, 1H), 2.19–2.10 (m, 1H),

**$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ (ppm) 196.7, 160.2, 147.9, 134.9, 120.7, 118.9, 112.0, 68.6, 56.3, 36.5, 31.4.

**CD (*c* = 2.0 mM, *l* = 0.1 mm, methanol): λ [nm] (CD mdeg)** 200 (6.69), 204 (16.05), 209 (26.48), 219 (14.51), 222 (5.39), 227 (–4.31), 235 (–2.30), 252 (–11.07), 265 (–7.05), 277 (–0.64), 305 (–0.53), 338 (1.96), 367 (0.29), 394 (0.29).

**$[\alpha^{25}_{D}]$** = + 26.67 (*c* = 0.06, $CHCl_3$).

**HRMS (ESI) m/z: [M + H]** $^{+}$ Calculated for $[C_{11}H_{13}O_3]^{+}$ 193.0859; Found 193.0852.

**HPLC:** (*rac*) [Flow rate: 1 mL/min; Typical injection volume: 5 µL; Isocratic: 90% *n*-hexane, 10% isopropanol; DAD: 210 nm (bandwidth = 4 nm); Column: Chiralcel OD-H, 5 µm,4.6 mm (ϕ) x 250 mm (L) mm, Temperature: 25 °C.]: Retention time (Rt), Rt (4*S*) = 23.91 min, $R_t$ (4*R*) =26.02.

**HPLC:** (4*S*)-**7**) [Flow rate: 1 mL/min; Typical injection volume: 10 µL; Isocratic: 90% *n*-hexane, 10% isopropanol; DAD: 210 nm (bandwidth = 4 nm); Column: Chiralcel OD-H, 5 µm,4.6 mm (ϕ) x 250 mm (L) mm, Temperature: 25 °C.]: Retention time (Rt), Rt (4*S*)) = 23.78 min. Enantiomeric excess (ee) = >99%. (Determined by comparison to *rac*emic).

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**Comparison of $^{1}$H NMR spectroscopic of natural and synthesized (+)-xylarenone (6).**[8]

| **$^{1}$H** | **Natural (+)-xylarenone (6). (300 MHz, $CDCl_3$) δ (ppm)** | **Synthesized (+)-xylarenone (6) (400 MHz, $CDCl_3$) δ (ppm)** |
|---|---|---|
| **H-2** | 2.52 (ddd, *J* = 18.0, 9.0, 3.0 Hz, 1H) | 2.58 (ddd, *J* = 17.3, 8.6, 5.1 Hz, H) |
| | 2.85 (ddd, *J* = 18.0, 9.0, 3.0 Hz, 1H) | 2.91 (ddd, *J* = 17.4, 7.7, 5.1 Hz, 1H) |
| **H-3** | 2.10 (m, 1H) | 2.19–2.10 (m, 1H) |
| | 2.25 (m, 1H) | 2.36–2.29 (m, 1H) |
| **H-4** | 4.83 (dd, *J* = 9.0, 6.0 Hz, 1H) | 4.90 (dd, *J* = 7.8, 3.7 Hz, 1H) |
| **H-5** | 7.11 (d, *J* = 6.0 Hz, 1H) | 7.17 (d, *J* = 7.6 Hz, 1H) |

| | | |
|---|---|---|
| **H-6** | 7.46 (dd, *J* = 9.0, 6.0 Hz, 1H) | 7.52 (t, *J* = 7.8 Hz, 1H) |
| **H-7** | 6.91 (d, *J* = 9.0 Hz, 1H) | 6.96 (d, J = 8.4 Hz, 1H) |
| **C8-OMe** | 3.86 (s, 3H) | 3.92 (s, 3H) |

**Comparison of $^{13}$C NMR spectroscopic of natural and synthesized (+)-xylarenone (6).**[8]

| $^{13}$C | Natural (+)-xylarenone (6) (75 MHz, $CDCl_3$) δ (ppm) | Synthesized (+)-xylarenone (6) (100 MHz, $CDCl_3$) δ (ppm) |
|---|---|---|
| **C-1** | 197.0 | 196.7 |
| **C-2** | 36.3 | 36.5 |
| **C-3** | 31.3 | 31.4 |
| **C-4** | 68.5 | 68.6 |
| **C-5** | 118.8 | 118.9 |
| **C-6** | 134.7 | 134.9 |
| **C-8-Ome** | 56.1 | 56.3 |
| **C-7** | 112.0 | 112.0 |
| **C-8** | 160.1 | 160.2 |
| **C-9** | 120.1 | 120.7 |
| **C-10** | 147.8 | 147.9 |

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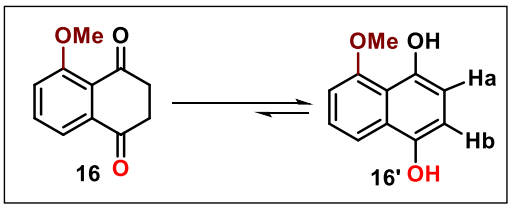
**Characterization of intermediate 16**

For the characterization of intermediated **16**, substrate **5** was incubated with NostocER under optimized reaction condition, in presence of NADPH (regenerated using glucose/glucose dehydrogenase). After 30 minutes the reaction mixture was extracted with ethyl acetate, dried over $Na_2SO_4$, the solvent was removed under reduced pressure and the crude reaction mixture was directly subjected to NMR spectroscopy in $CDCl_3$. Although presence of **16** could not be detected but its more stable enol tautomer **16'** was characterized by $^{1}$H and $^{13}$C NMR experiments.



**Crude $^{1}$H-NMR of 16 (400 MHz, $CDCl_3$)**

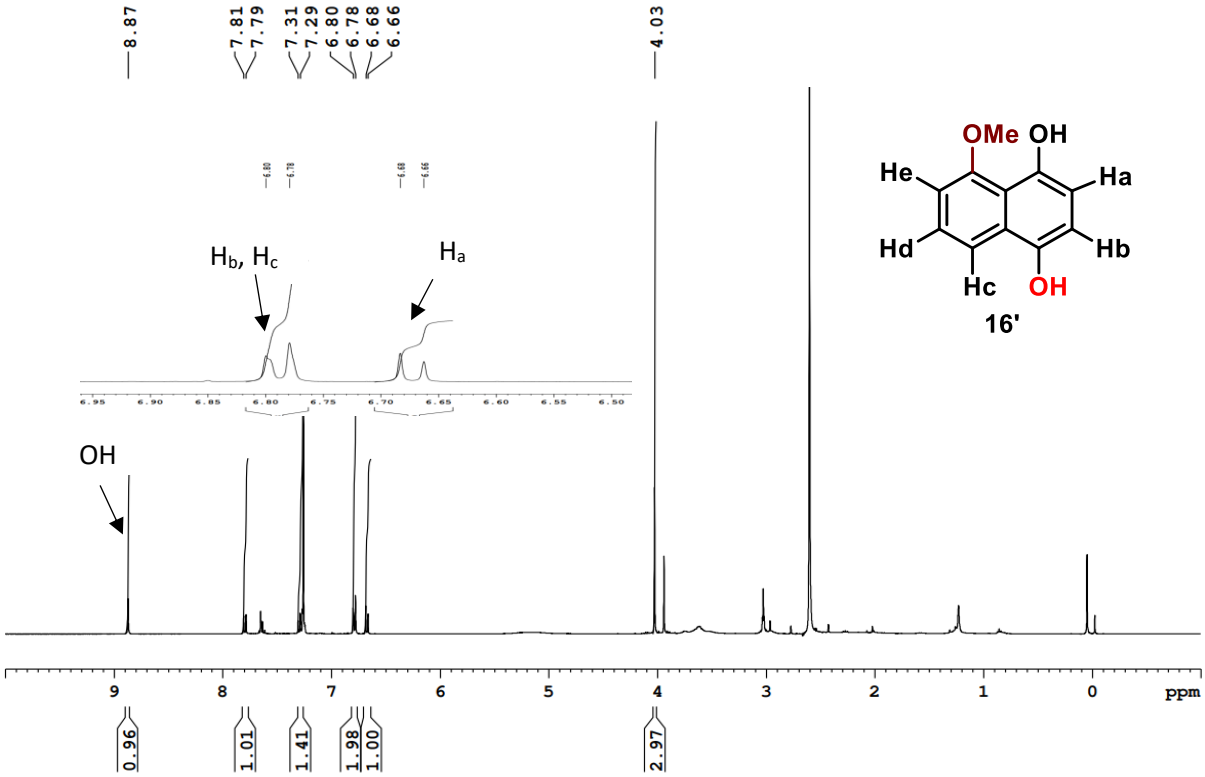



**Figure S2:** $^{1}$H NMR spectra of intermediate **16'**

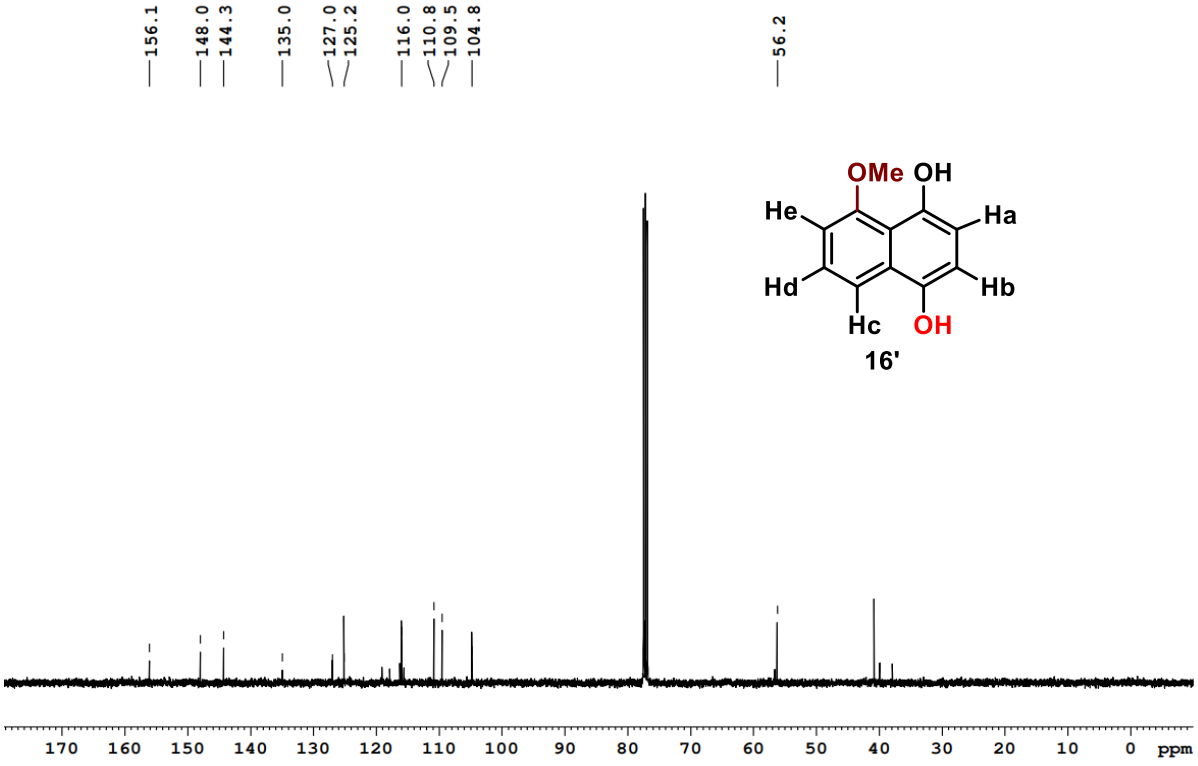
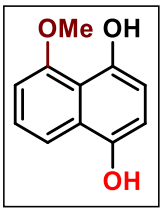



**Figure S3:** $^{13}$C NMR spectra of intermediate **16'**

**5-methoxynaphthalene-1,4-diol (16')**



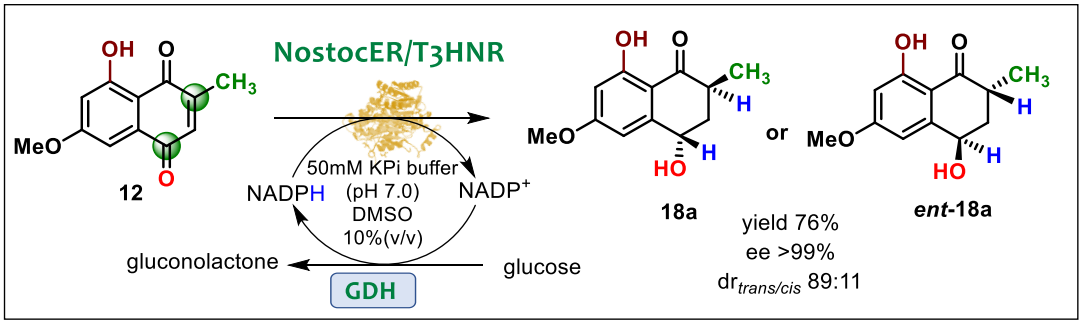

**$C_{11}H_{10}O_3$**: 190.19 g/mol

**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ (ppm) δ 8.87 (s, OH), 7.80 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 6.79 (d, *J* = 8.2, 1.0 Hz, 2H), 6.67 (d, *J* = 8.5 Hz, 1H), 4.03 (s, 3 H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ (ppm) δ 156.1, 148.0, 144.3, 135.0, 127.0, 125.2, 116.0, 110.8, 109.5, 104.8, 56.2.

## VII. Reduction of non-natural substrate 12 by Nostoc-ER and naphthol reductase cascades

### A. NostocER and T3HNR cascade catalysed reduction of 12




**Scheme S11:** Cascade synthesis of *trans*-4,8-dihydroxy-6-methoxy-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**18a** or **ent-18a**).

To a 100 mL round bottom flask, $NADP^+$ (7.22 mg, 0.009 mmol, 0.1 equiv.), glucose (82.5 mg, 0.48 mmol, 5 equiv.) and GDH (50 U) were added into 40 mL Kpi buffer solution (50 mM, EDTA = 1.0 mM, DTT = 1.0 mM, pH 7) at room temperature. Then the substrate **12** (20.0 mg, 0.09 mmol, 1 equiv.) in DMSO (4 mL, 10% v/v) was added slowly, while stirring. Finally, cell-free extract of Nostoc-ER (1 mL, 4 U) and $T_3$HNR-*his* (1 mL, 6 U) were added to the reaction mixture and stirred at 100 rpm at room temperature under argon atmosphere. After 14 h, the reaction was stopped by the addition of ethyl acetate and was filtered through a celite pad and washed with ethyl acetate. The solution was extracted with ethyl acetate (EtOAc, 3 x 20 mL), dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. The crude reaction mixture was subjected to column chromatography to afford the pure product as yellowish solid.

***Trans*-4,8-dihydroxy-6-methoxy-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (18a or ent-18a)**

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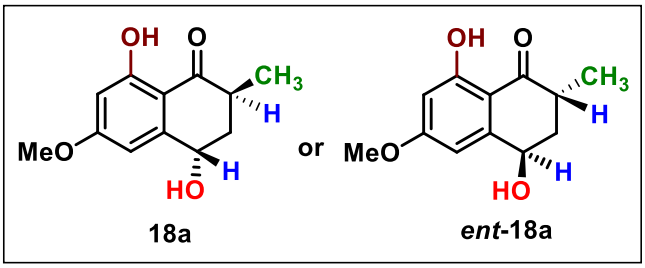



**$C_{12}H_{14}O_4$**: 222.24 g/mol

**TLC** (Hexane/EtOAc, 70:30 v/v): $R_f$ = 0.48

**Column chromatography:** silica gel (100-200 mess size), Hexane: Ethyl acetate: 7:3

**Yield:** 76%

**$^1$H NMR (800 MHz, $CDCl_3$):** $\delta$ (ppm) 12.97 (s, 1H, OH), 6.46 (dd, *J* = 2.1, 0.4 Hz, 1H), 6.36 (d, *J* = 2.4 Hz, 1H), 4.85 (dd, *J* = 4.8, 3.2 Hz, 1H), 3.83 (s, 3H), 3.14–3.05 (m, 1H), 2.27 (dt, *J* = 13.7, 5.0 Hz 1H), 2.05 (ddd, *J* = 13.7, 10.5, 3.2 Hz, 1H), 1.28 (d, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR (200 MHz, $CDCl_3$):** $\delta$ (ppm) 205.2, 166.3, 166.0, 146.6, 116.3, 107.1, 100.8, 66.9, 55.8, 38.4, 36.5, 15.4.

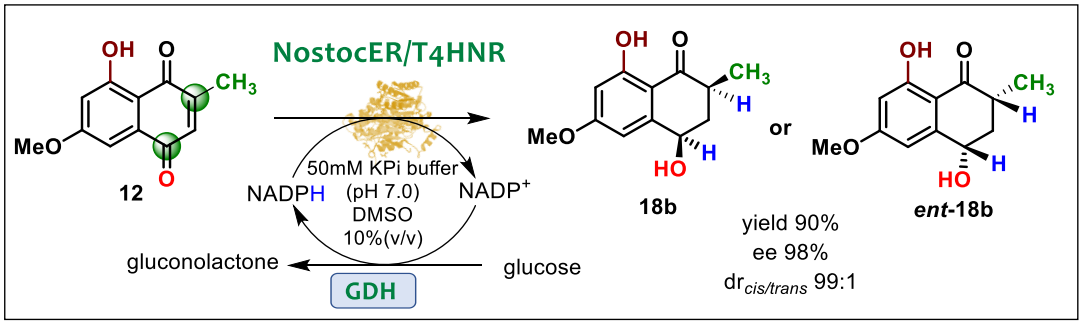
**HRMS (ESI) m/z: [M + H]** $^+$ Calculated for $[C_{12}H_{15}O_4]^+$ 223.0965; Found 223.0978.

*trans*-configuration is assigned based on the chemical shift and coupling constant of the $^1$H NMR spectra of **18a** or *ent*-**18a**. But for *trans* isomer splitting pattern is different from *cis* isomer. Here, both H-3 have three different magnetically equivalent protons. That's' why it should give doublet for each proton and doublet of doublet of doublet (ddd) will observe. We observed one ddd for one H-3 at 2.05 ppm with coupling constant 13.7 Hz for cis coupling, 10.5 Hz for geminal coupling and 3.2 Hz for trans coupling but another proton H-3 splitted into dt at 2.27 ppm *J* = 13.7, 5.0 Hz.

**HPLC:** (*rac*) [Flow rate: 1 mL/min; Typical injection volume: 5 µL; Isocratic: 97.5% *n*-hexane, 2.5% isopropanol; DAD: 280 nm (bandwidth = 4 nm); Column: Chiralcel OD-H, 5 µm,4.6 mm (ϕ) x 250 mm (L) mm, Temperature: 25 °C.]: Retention time (Rt), Rt (*trans*) = 27.97 min, 33.20 min, $R_t$ (*cis*) = 36.48 min, 40.93 min.

**HPLC:** *trans*-**18a**/*ent*-**18a** [Flow rate: 1 mL/min; Typical injection volume: 5 µL; Isocratic: 97.5% *n*-hexane, 2.5% isopropanol; DAD: 280 nm (bandwidth = 4 nm); Column: Chiralcel OD-H, 5 µm,4.6 mm (ϕ) x 250 mm (L) mm, Temperature: 25 °C.]: Retention time (Rt), Rt (*trans*) = 33.04 min (major), Rt (*cis*) = 36.35 min (minor), 40.72 (minor). Enantiomeric excess (ee) = >99%, Diastereomeric ratio (*trans*: *cis*) = 89:11. (Determined by comparison to *rac*emic).

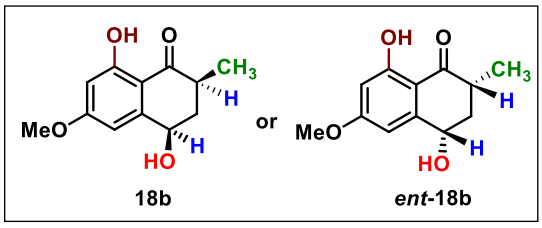
### B. NostocER and T$_4$HNR cascade catalysed reduction of 12




**Scheme S12:** Cascade synthesis of *cis*-4,8-dihydroxy-6-methoxy-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**18b** or ***ent*-18b**).

To a 100 mL round bottom flask, $NADP^+$ (7.22 mg, 0.009 mmol, 0.1 equiv.), glucose (82.5 mg, 0.48 mmol, 5 equiv.) and GDH (50 U) were added into 40 mL KPi buffer solution (50 mM, EDTA = 1.0 mM, DTT = 1.0 mM, pH 7) at room temperature. Then the substrate **12** (20.0 mg, 0.09 mmol, 1 equiv.) in DMSO (4 mL, 10% v/v) was added slowly, while stirring. Finally, cell-free extract of Nostoc-ER (1 mL, 4 U) and $T_4$HNR-*his* (1 mL, 6 U) were added to the reaction mixture and stirred at 100 rpm at room temperature under argon atmosphere. After 14 h, the reaction was stopped by the addition of ethyl acetate and was filtered through a celite pad and washed with ethyl acetate. The solution was extracted with ethyl acetate (EtOAc, 3 x 20 mL), dried over $Na_2SO_4$, and the solvent was removed under reduced pressure. The crude reaction mixture was subjected to column chromatography to afford the pure product as yellowish solid.

***Cis*-4,8-dihydroxy-6-methoxy-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (18b or *ent*-18b)**




**$C_{12}H_{14}O_4$**: 222.24 g/mol

**TLC** (Hexane/EtOAc, 70:30 v/v): $R_f$ = 0.48

**Column chromatography:** silica gel (100-200 mess size), Hexane: Ethyl acetate: 7:3

**Yield:** 90%

**$^{1}$H NMR (400 MHz, $CDCl_3$):** $\delta$ (ppm) 12.94 (s, 1H, OH), 6.72 (dd, *J* = 2.3, 0.8 Hz, 1H), 6.34 (d, *J* = 2.3 Hz, 1H), 4.87 (dd, *J* = 12.0, 4.4 Hz, 1H), 3.85 (s, 3H), 2.69–2.64 (m, 1H), 2.40 (dt, *J* = 12.2, 4.5 Hz, 1H), 1.97 (s, 1H, OH), 1.82 (dt, *J* = 12.6, 12.2 Hz, 1H), 1.13 (d, *J* = 6.7 Hz, 3H).

**$^{13}$C NMR (100 MHz, $CDCl_3$):** $\delta$ (ppm) 204.2, 166.5, 165.7, 149.8, 109.6, 104.0, 100.1, 68.4, 55.8, 41.5, 40.6, 15.4.

*cis*-configuration is assigned based on the chemical shift and coupling constant of the $^{1}$H NMR spectra of **18b** or *ent*-**18b**. H-3 has one geminal proton H'-3, two magnetically equivalent protons H-2 and H-4. It should give doublet for H'-3 (*J* = 12.2 Hz) and triplet for H-2 and H-4 (*J* = 4.5 Hz) and the splitting pattern is doublet of triplet (dt) at 2.40 ppm. Similar spectrum is observed for H'-3 i.e., dt (*J* = 12.6, 12.2 Hz) at 1.82 ppm.

**CD (*c* = 2.0 mM, *l* = 0.1 mm, methanol): λ [nm] (CD mdeg)** 200 (7.67), 204 (16.85), 211 (29.05), 222 (12.01), 227 (0.58), 235 (–7.28), 248 (–1.10), 265 (–5.83), 278 (–12.38), 290 (–2.42), 308 (9.11), 328 (3.87), 344 (0.32), 375 (0.32).

**$[\alpha^{25}{}_{D}]$** = + 55.00 (*c* = 0.08, MeOH).

**HRMS (ESI) m/z: [M + H]** $^{+}$ Calculated for $[C_{12}H_{15}O_4]^{+}$ 223.0965; Found 223.0978.

**HPLC:** (*rac*) [Flow rate: 1 mL/min; Typical injection volume: 5 µL; Isocratic: 97.5% *n*-hexane, 2.5% isopropanol; DAD: 280 nm (bandwidth = 4 nm); Column: Chiralcel OD-H, 5 µm,4.6 mm (ϕ) x 250 mm (L) mm, Temperature: 25 °C.]: Retention time (Rt), Rt (*trans*) = 27.97 min, 33.20 min, $R_t$ (*cis*) = 36.48 min, 40.93 min.

**HPLC:** *cis*-**18b**/*ent*-**18b** [Flow rate: 1 mL/min; Typical injection volume: 5 µL; Isocratic: 97.5% *n*-hexane, 2.5% isopropanol; DAD: 280 nm (bandwidth = 4 nm); Column: Chiralcel OD-H, 5 µm,4.6 mm (ϕ) x 250 mm (L) mm, Temperature: 25 °C.]: Retention time (Rt), Rt (*cis*) = 36.44 min (major), 40.94 min (minor). Enantiomeric excess (ee) = 98%, Diastereomeric ratio (*cis*: *trans*) = 99:1. (Determined by comparison to *rac*emic).

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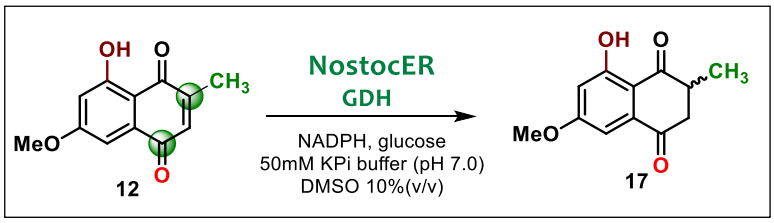
**Characterization of intermediate 17**

For the characterization of intermediated **17**, substrate **12** was incubated with NostocER under optimized reaction condition, in presence of NADPH (regenerated using glucose/glucose dehydrogenase). After 30 minutes the reaction mixture was extracted with ethyl acetate, dried over $Na_2SO_4$, the solvent was removed under reduced pressure and the crude reaction mixture was used directly without purification for characterization using NMR.




**$^1$H-NMR of 22 (400 MHz, $CDCl_3$)**

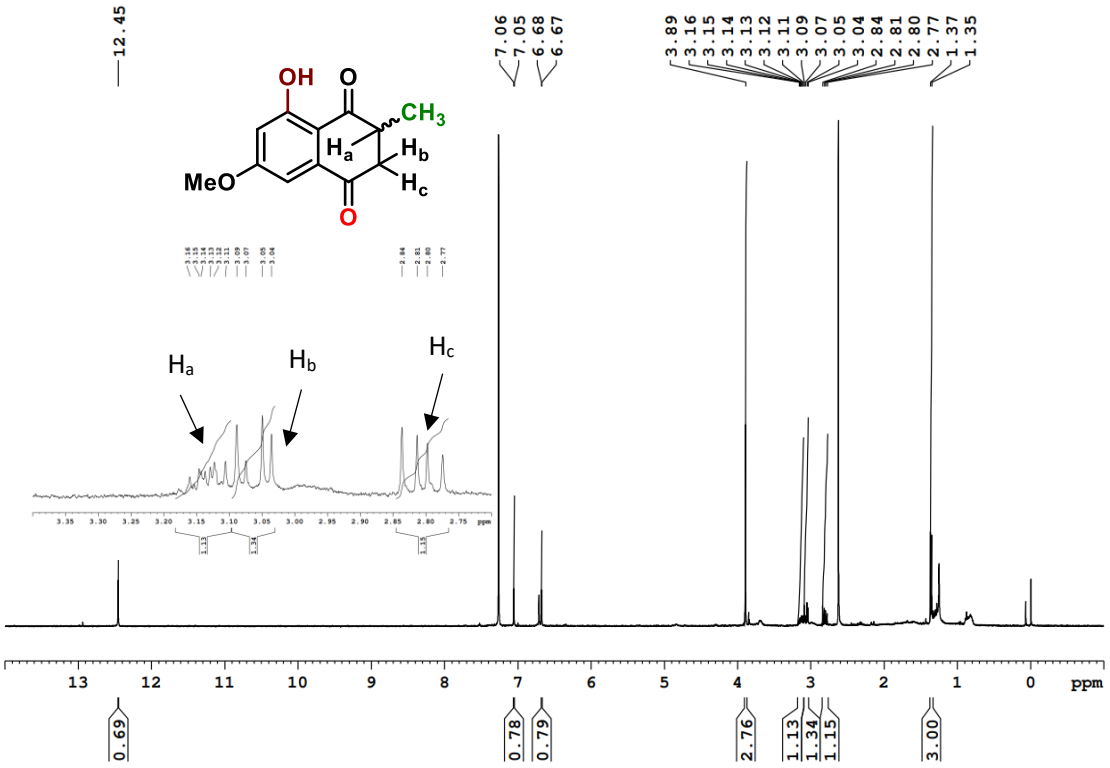
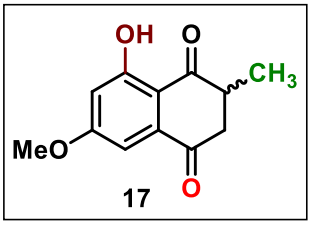



**Figure S4:** $^1$H NMR spectra of intermediate **17**

**8-hydroxy-6-methoxy-2-methyl-2,3-dihydronaphthalene-1,4-dione (17)**

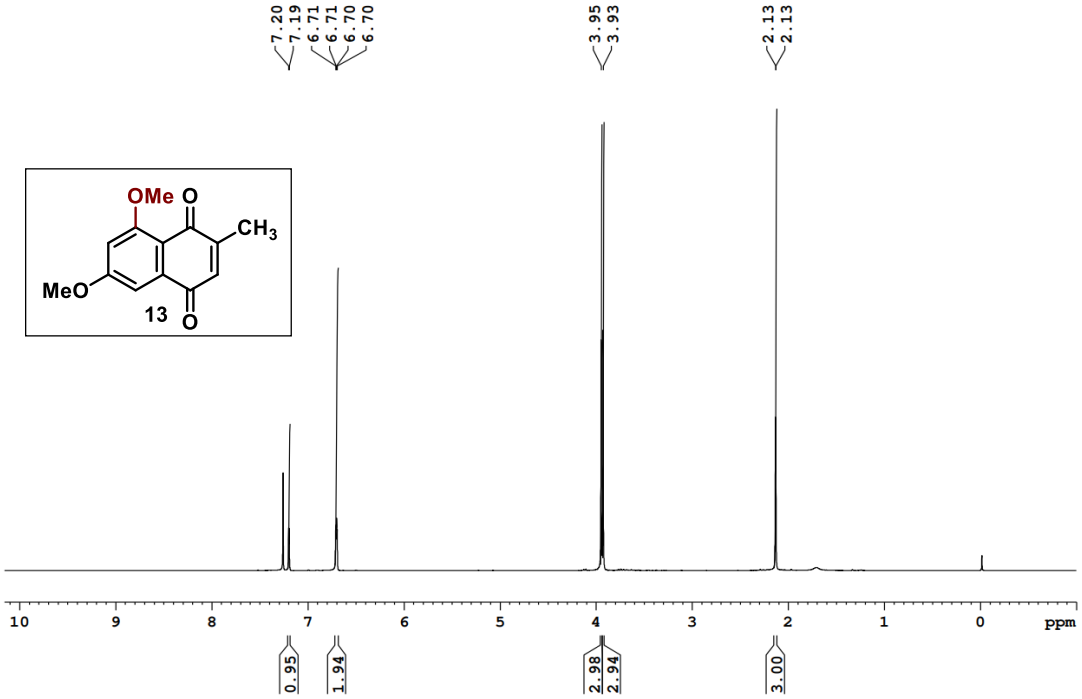


**$C_{12}H_{12}O_4$**: 220.22 g/mol

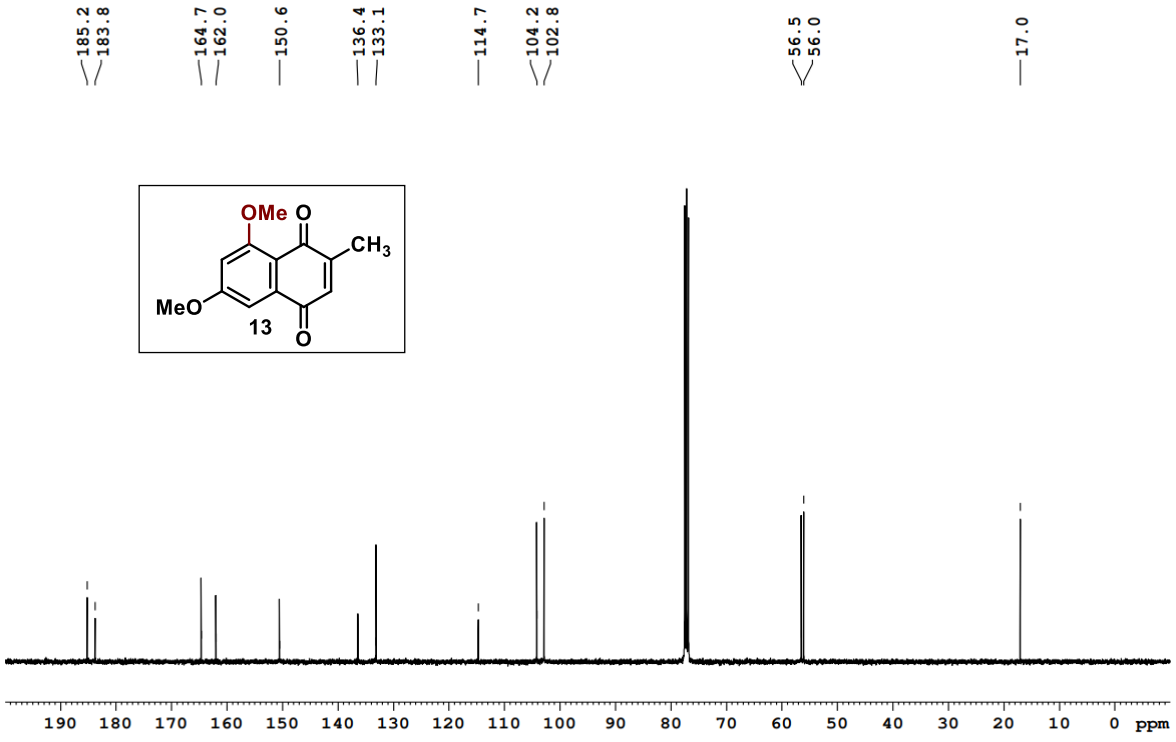
**$^1$H NMR (400 MHz, $CDCl_3$):** $\delta$ (ppm) δ 12.45 (s, OH), 7.05 (d, *J* = 2.5 Hz, 1H), 6.67 (d, *J* = 2.5 Hz, 1H), 3.89 (s, 3 H), 3.16–3.09 (m, 1H), 3.06 (dd, *J* = 15.5, 8.7 Hz, 1H), 2.80 (dd, *J* = 15.5, 9.4 Hz, 1H), 1.36 (d, *J* = 6.8 Hz, 3H).

## VIII. NMR Spectra

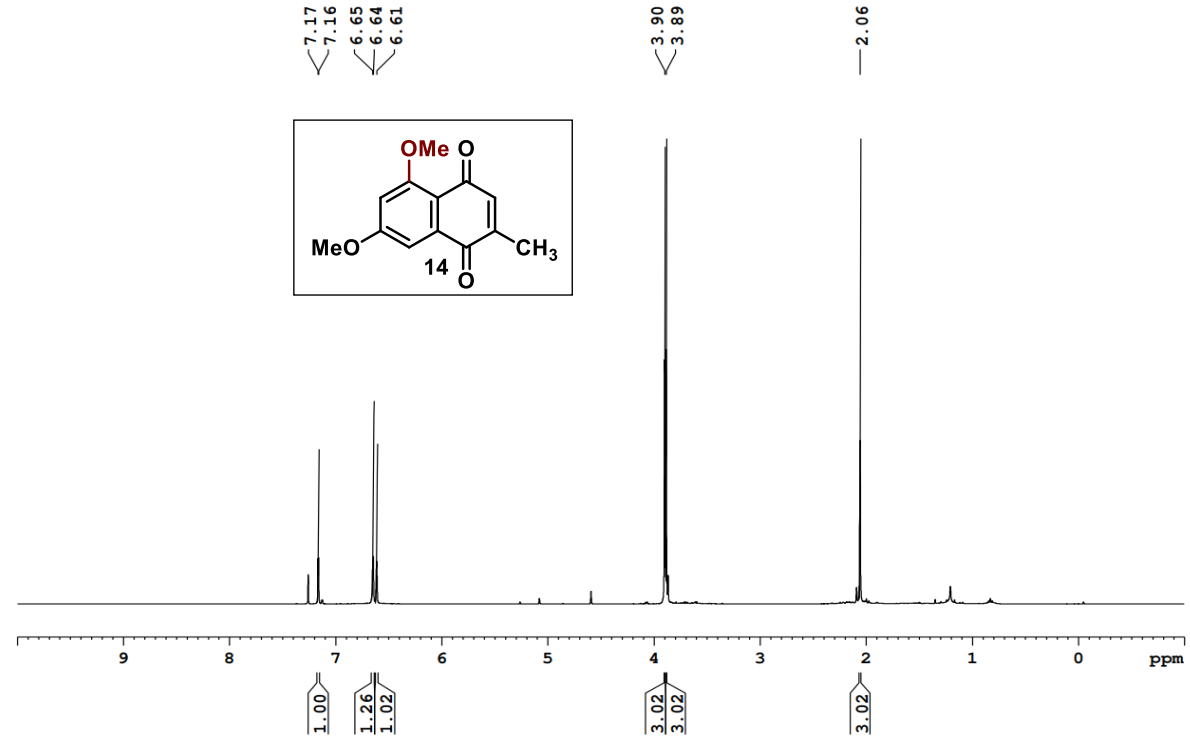
### $^{1}$H NMR (400 MHz, $CDCl_3$)



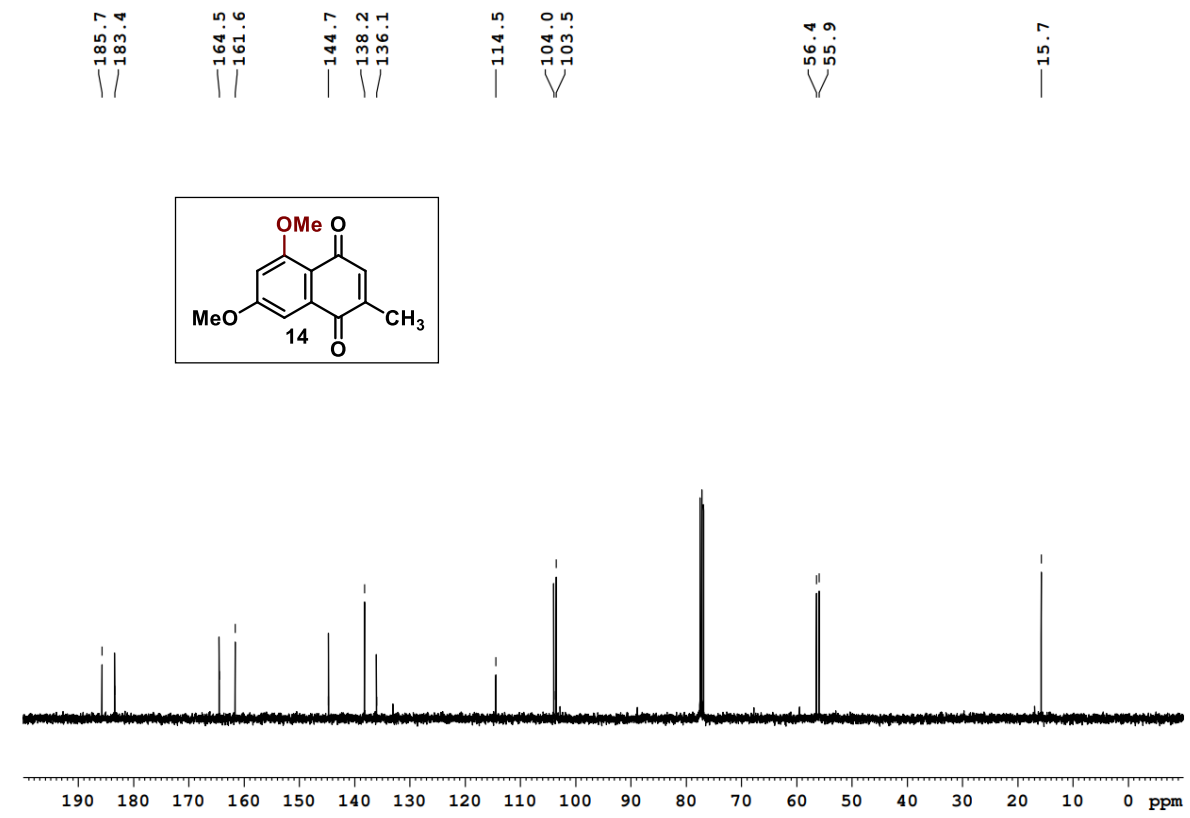

### $^{13}$C NMR (100 MHz, $CDCl_3$)



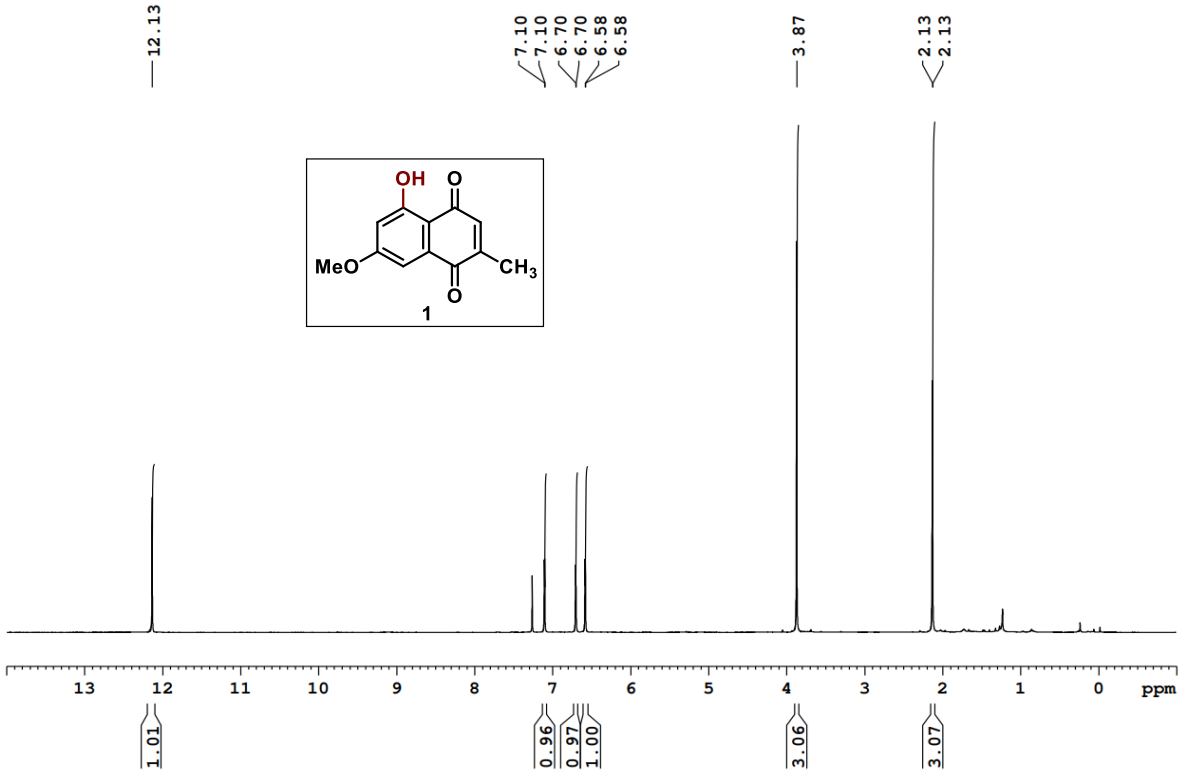
**$^{1}$H NMR (400 MHz, $CDCl_3$)**



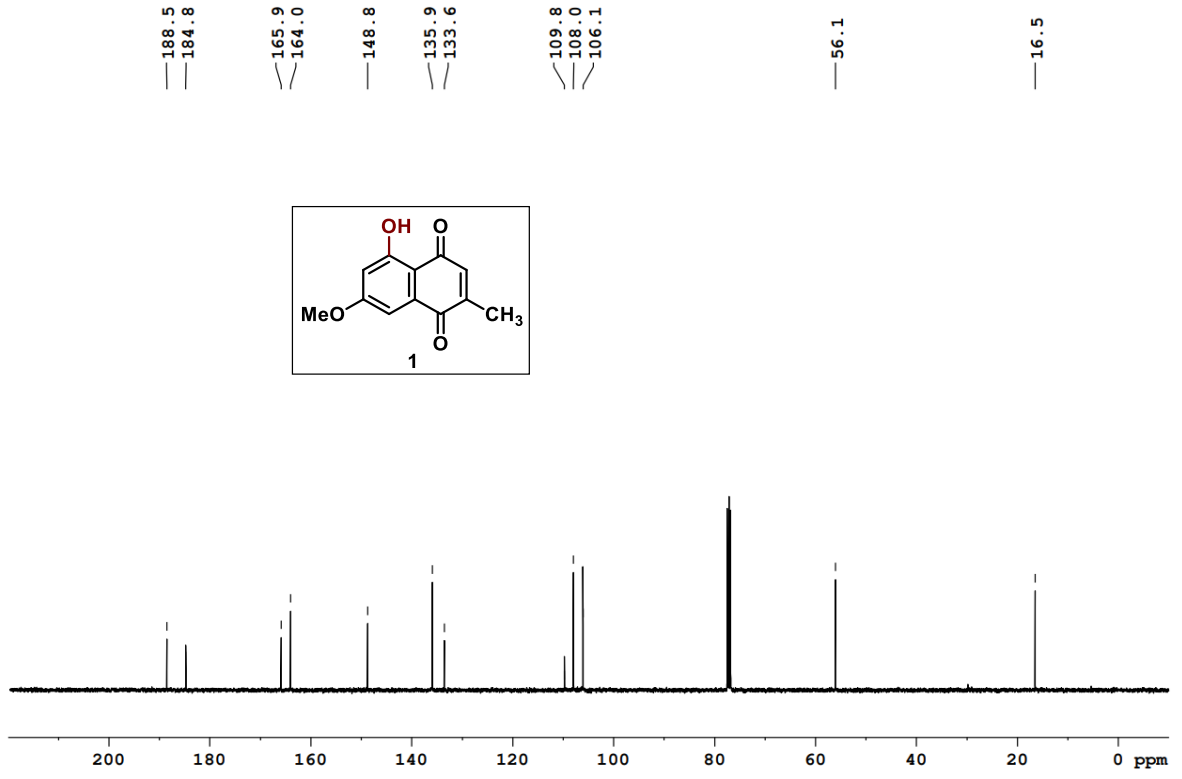

**$^{13}$C NMR (100 MHz, $CDCl_3$)**



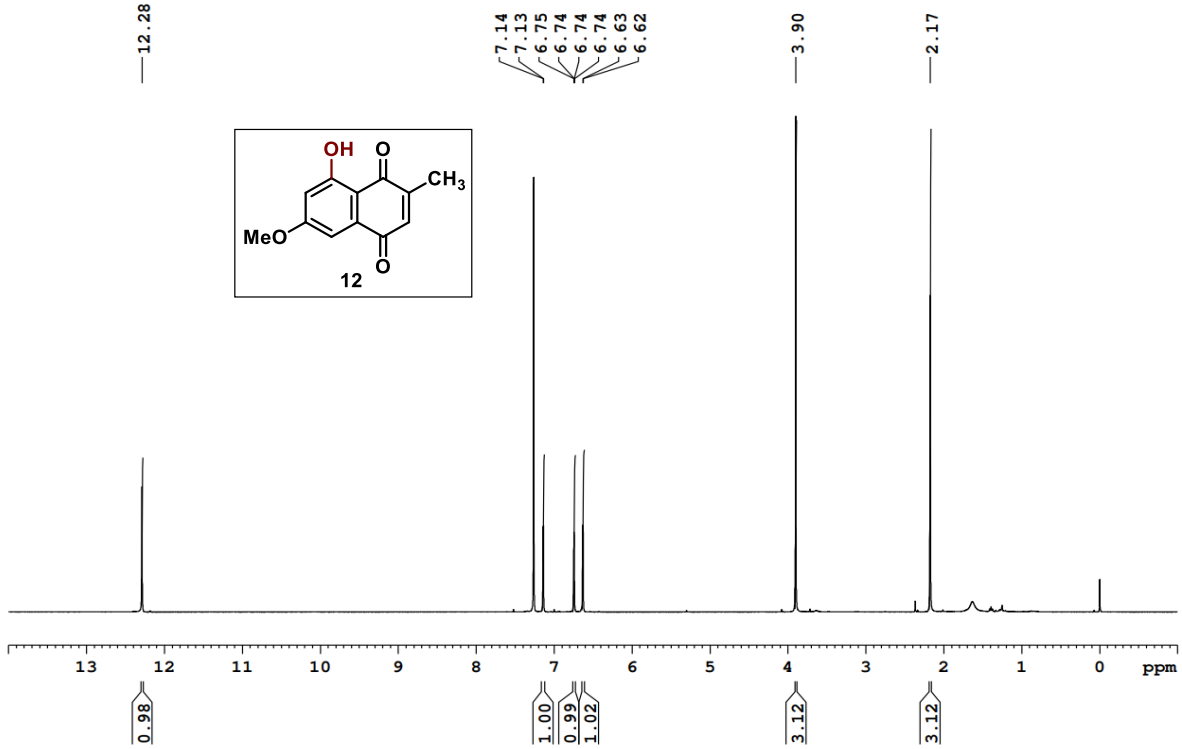
**$^{1}$H NMR (400 MHz, $CDCl_3$)**



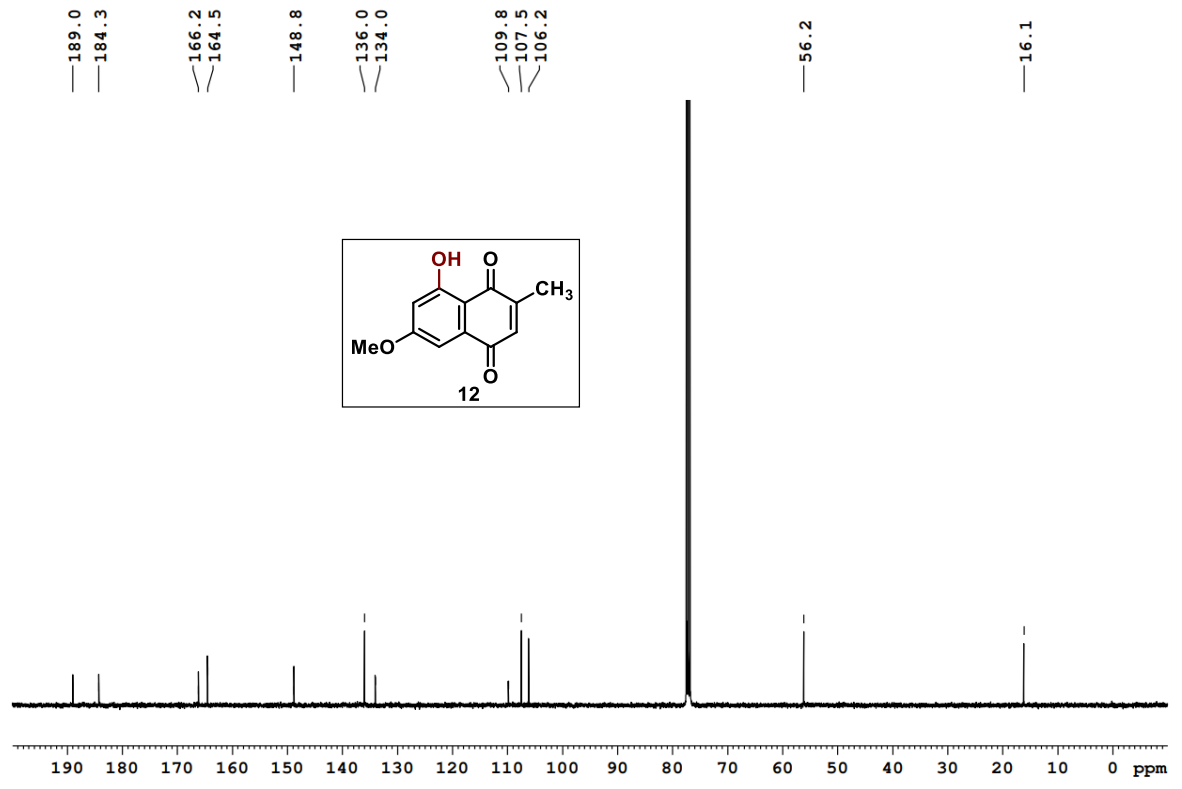

**$^{13}$C NMR (100 MHz, $CDCl_3$)**



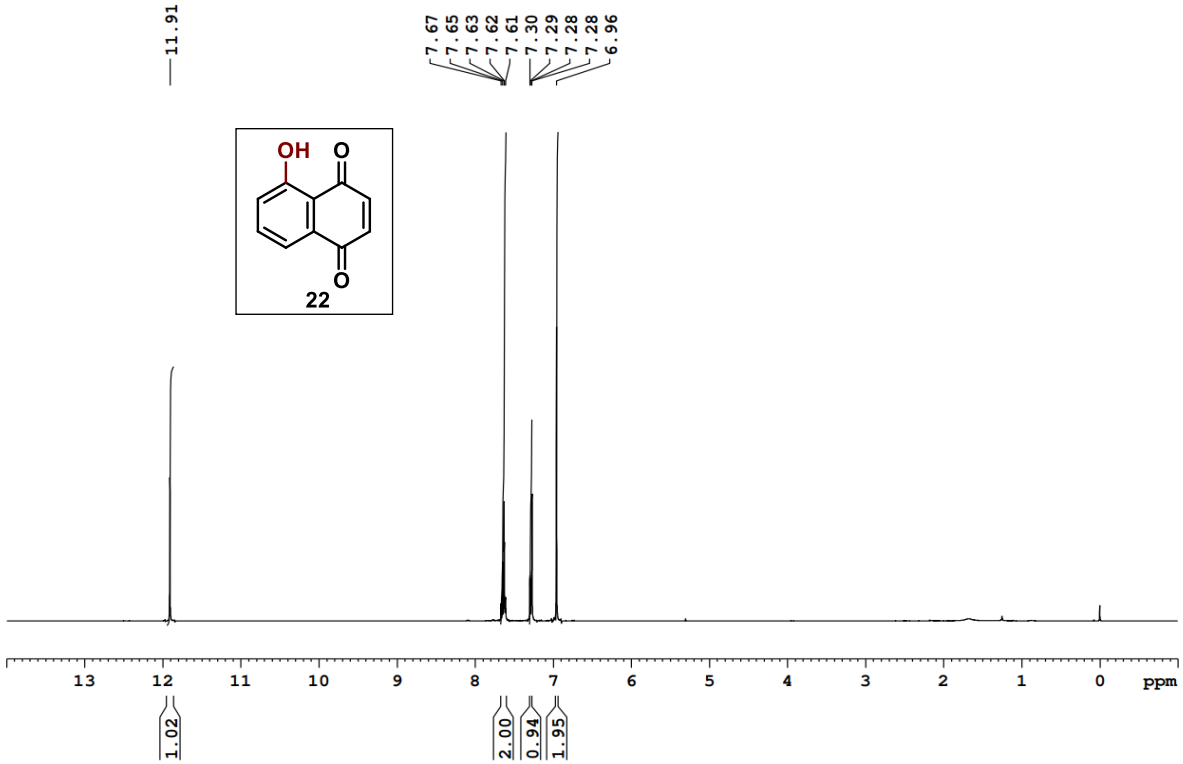
**$^{1}$H NMR (400 MHz, $CDCl_3$)**



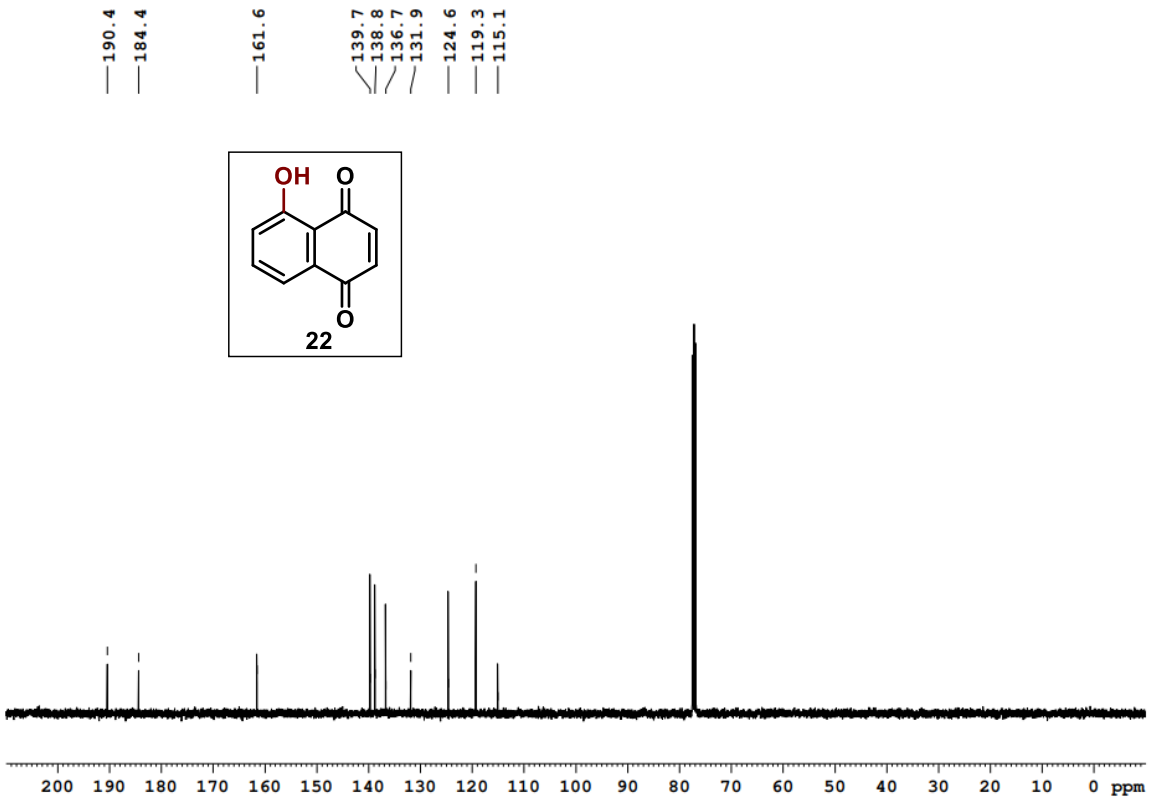

**$^{13}$C NMR (100 MHz, $CDCl_3$)**



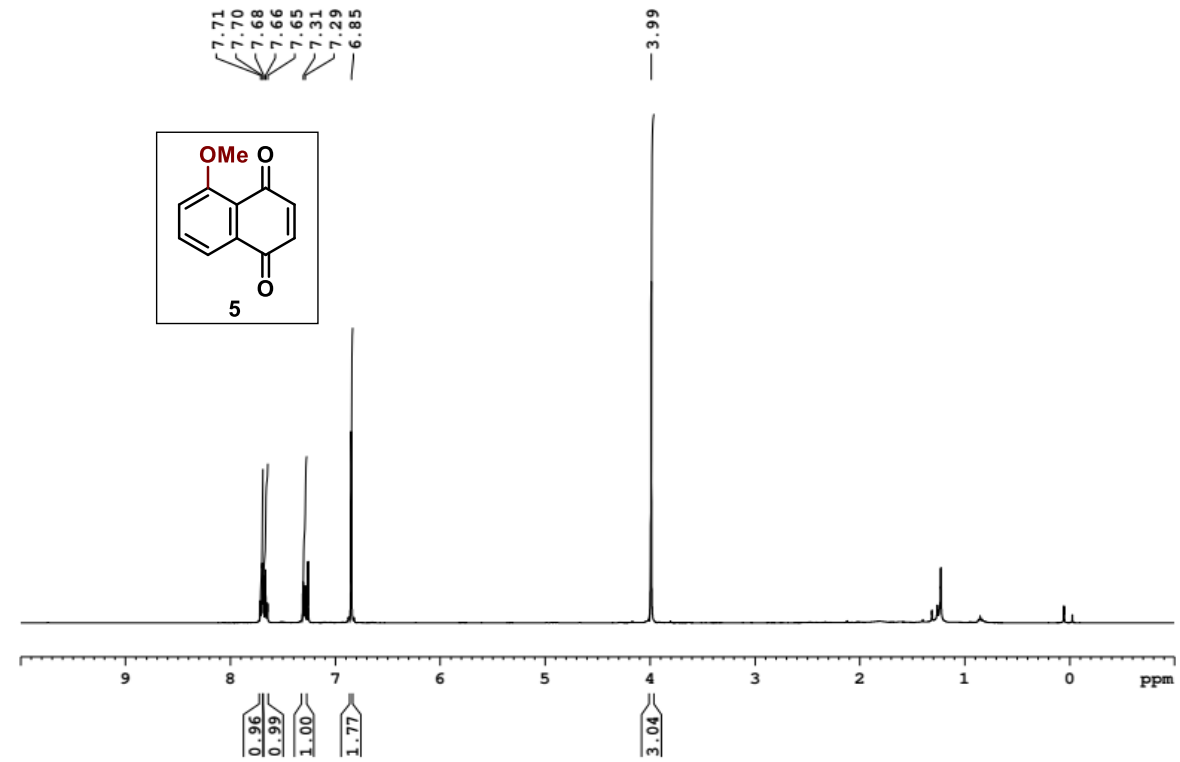
**$^{1}$H NMR (400 MHz, $CDCl_3$)**



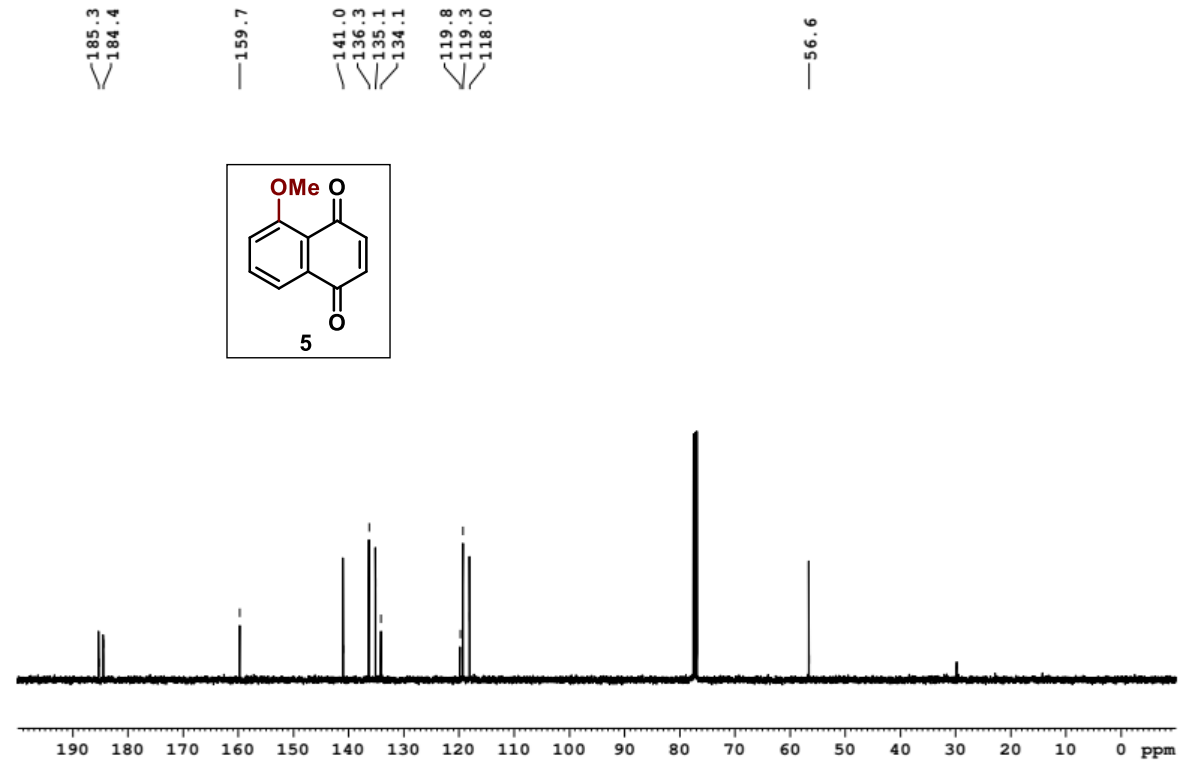

**$^{13}$C NMR (100 MHz, $CDCl_3$)**



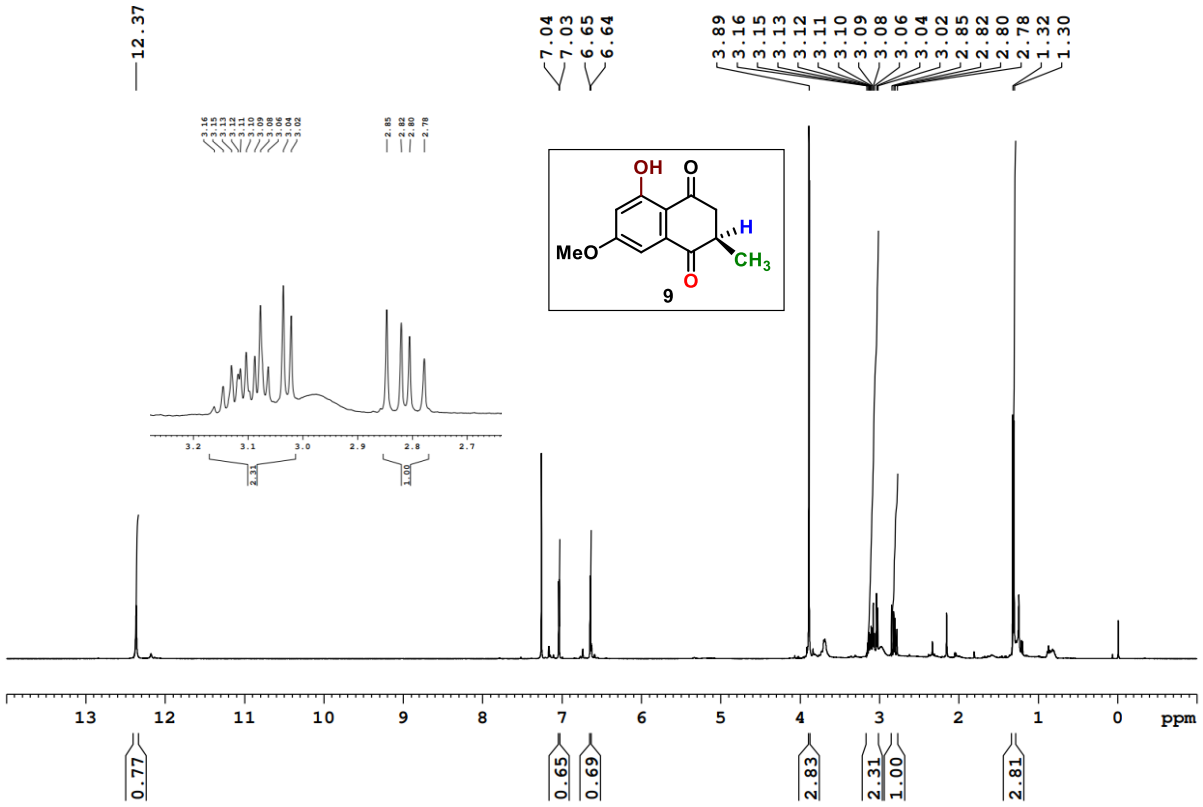
**$^{1}$H NMR (400 MHz, $CDCl_3$)**



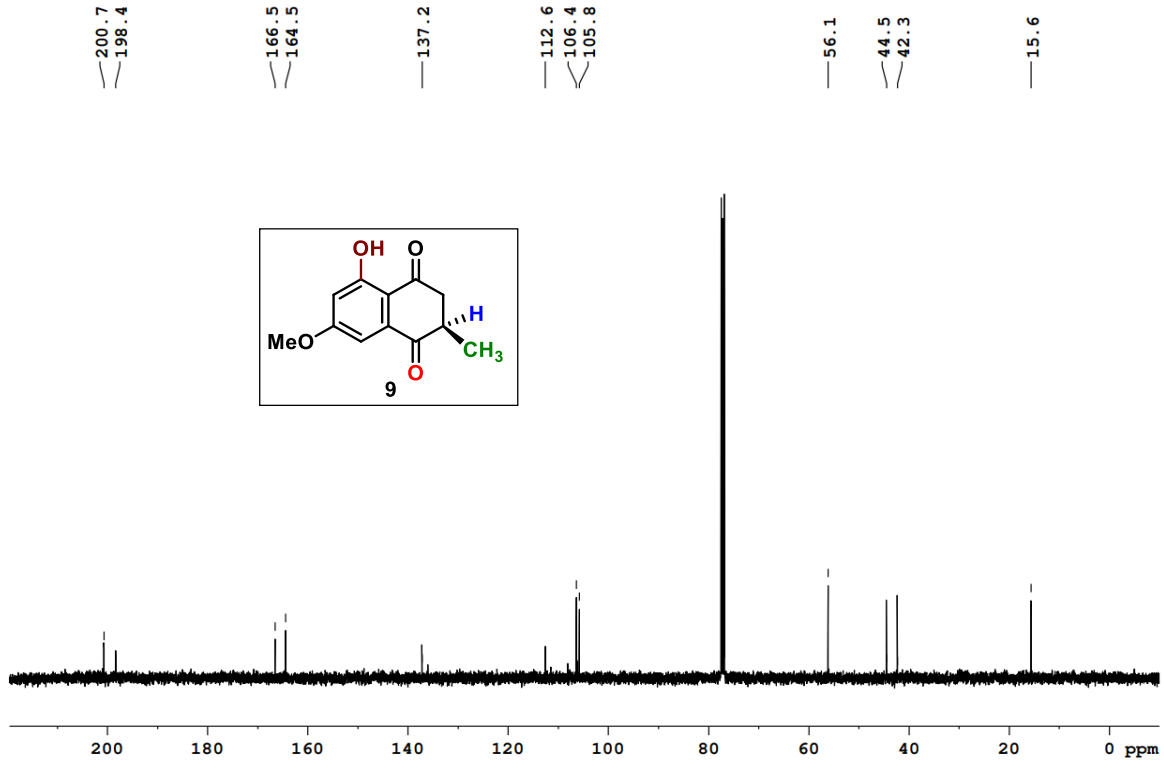

**$^{13}$C NMR (100 MHz, $CDCl_3$)**



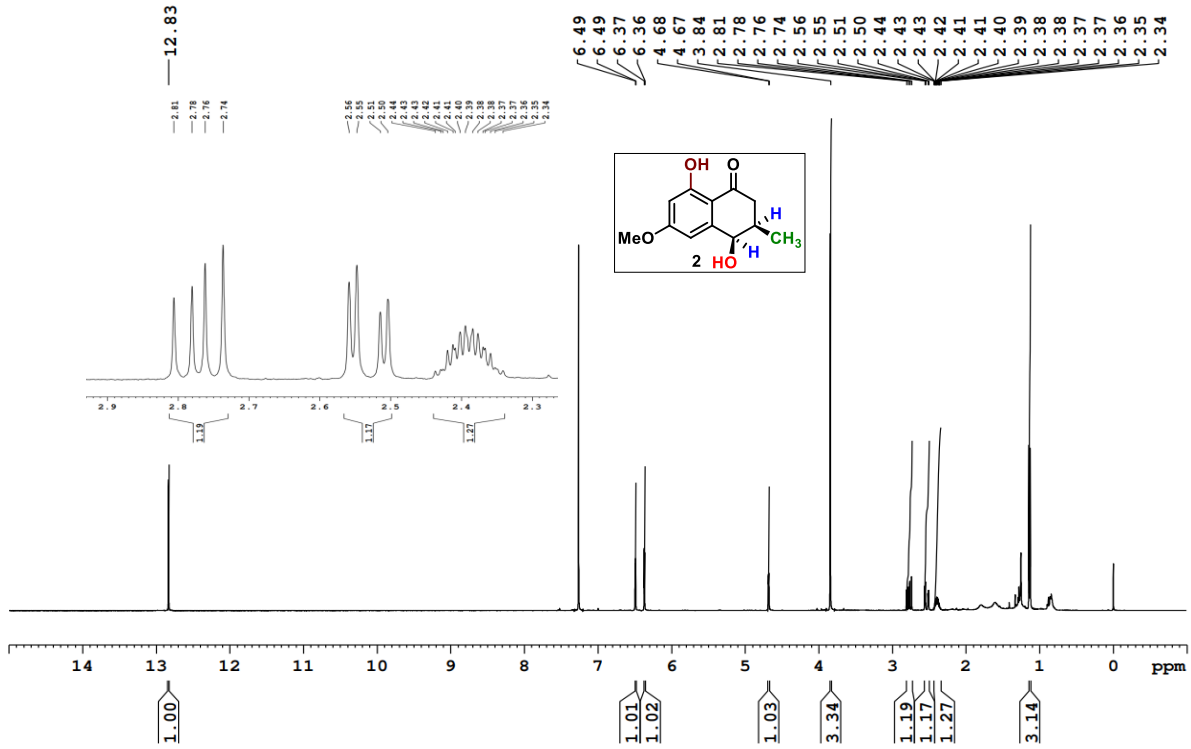
**$^{1}$H NMR (400 MHz, $CDCl_3$)**



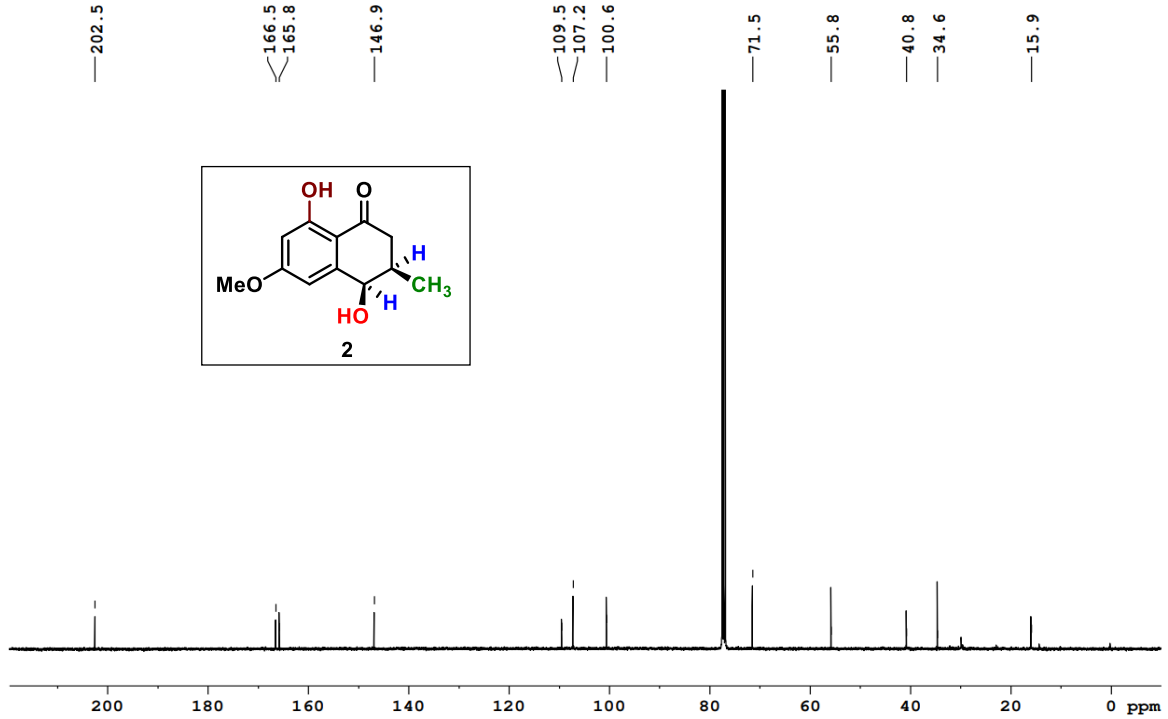

**$^{13}$C NMR (100 MHz, $CDCl_3$)**



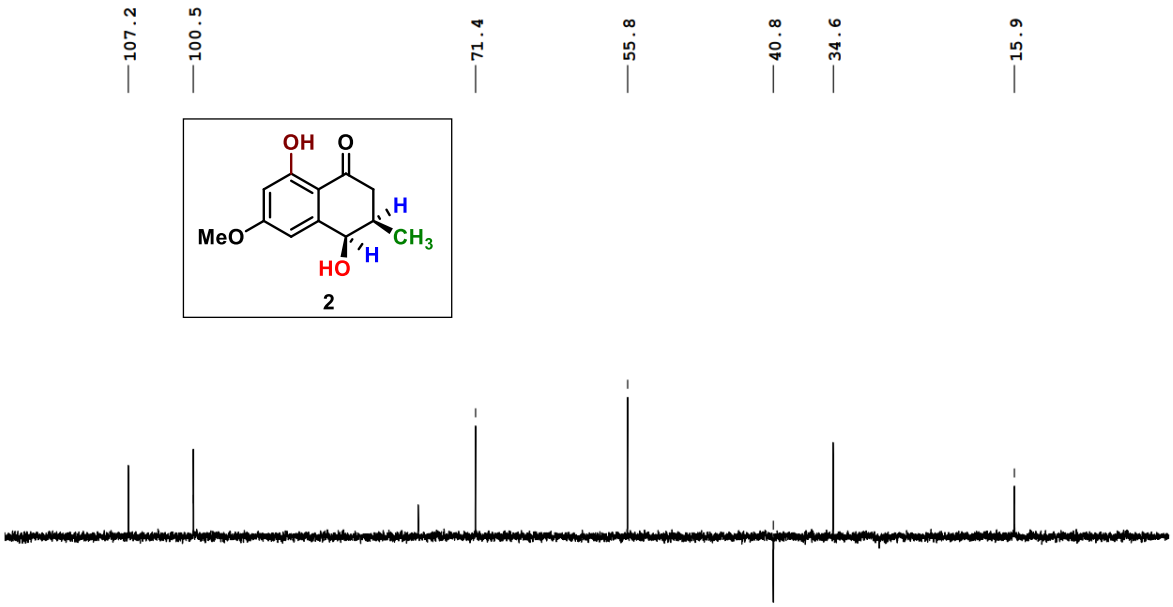
**$^{1}$H NMR (400 MHz, $CDCl_3$)**



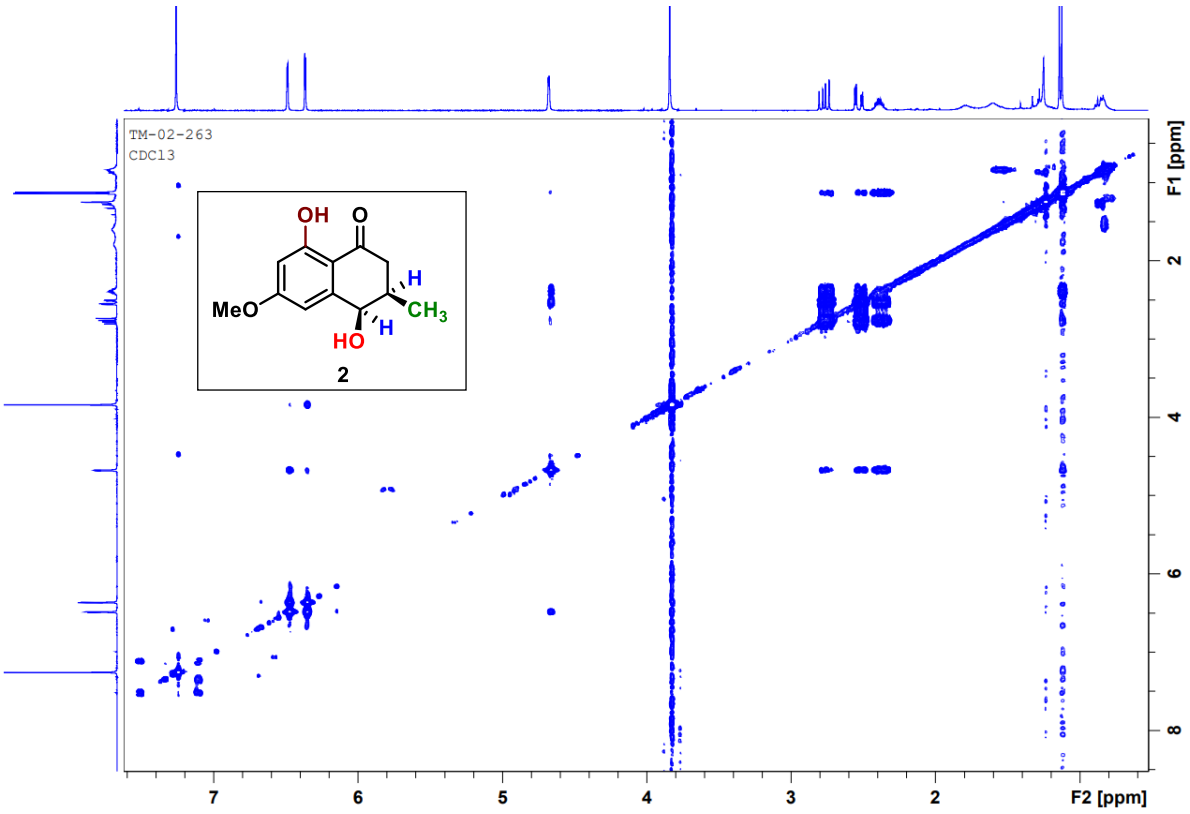

**$^{13}$C NMR (100 MHz, $CDCl_3$)**



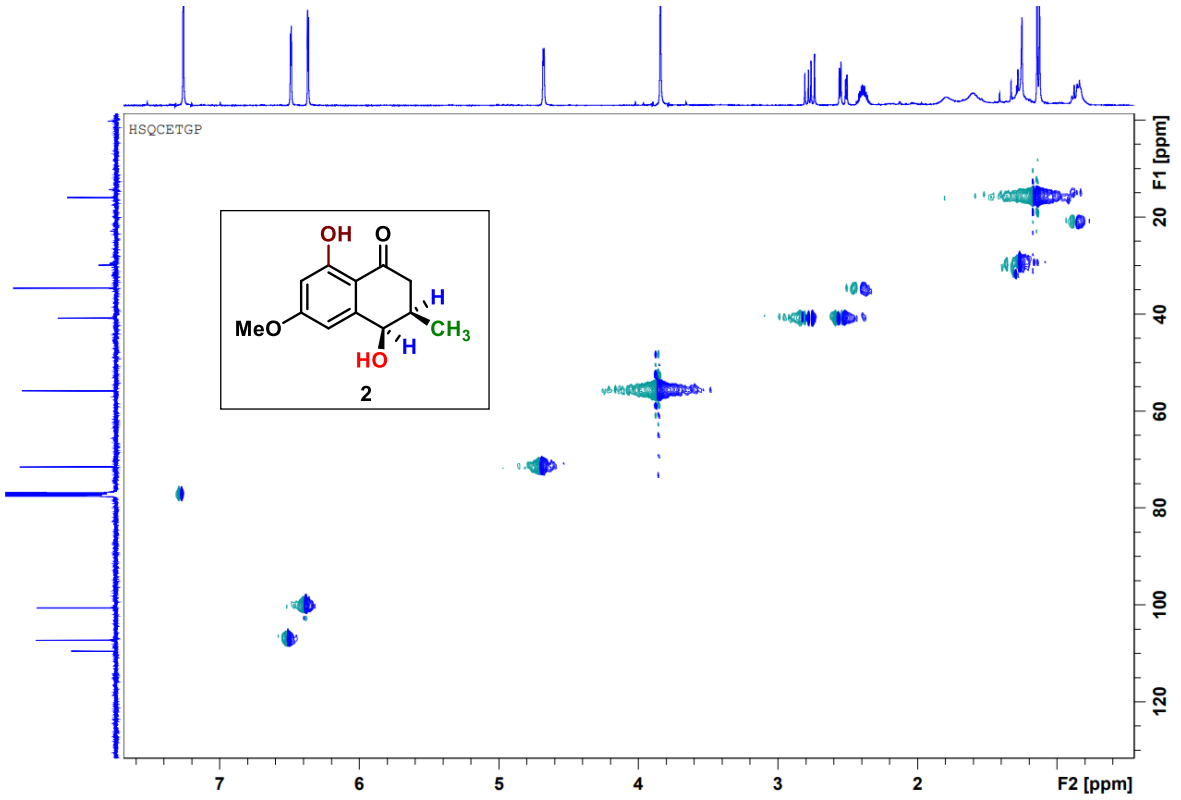
**DEPT NMR (100 MHz, $CDCl_3$)**



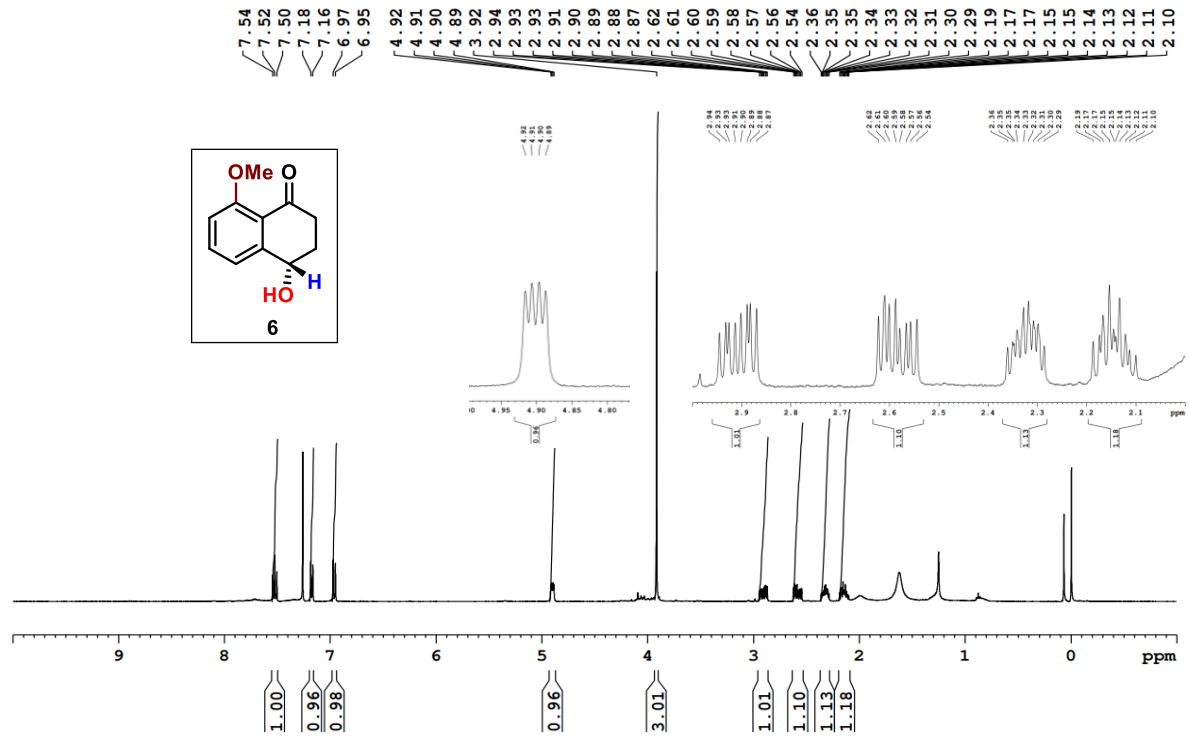

**COSY NMR (400 MHz, $CDCl_3$)**



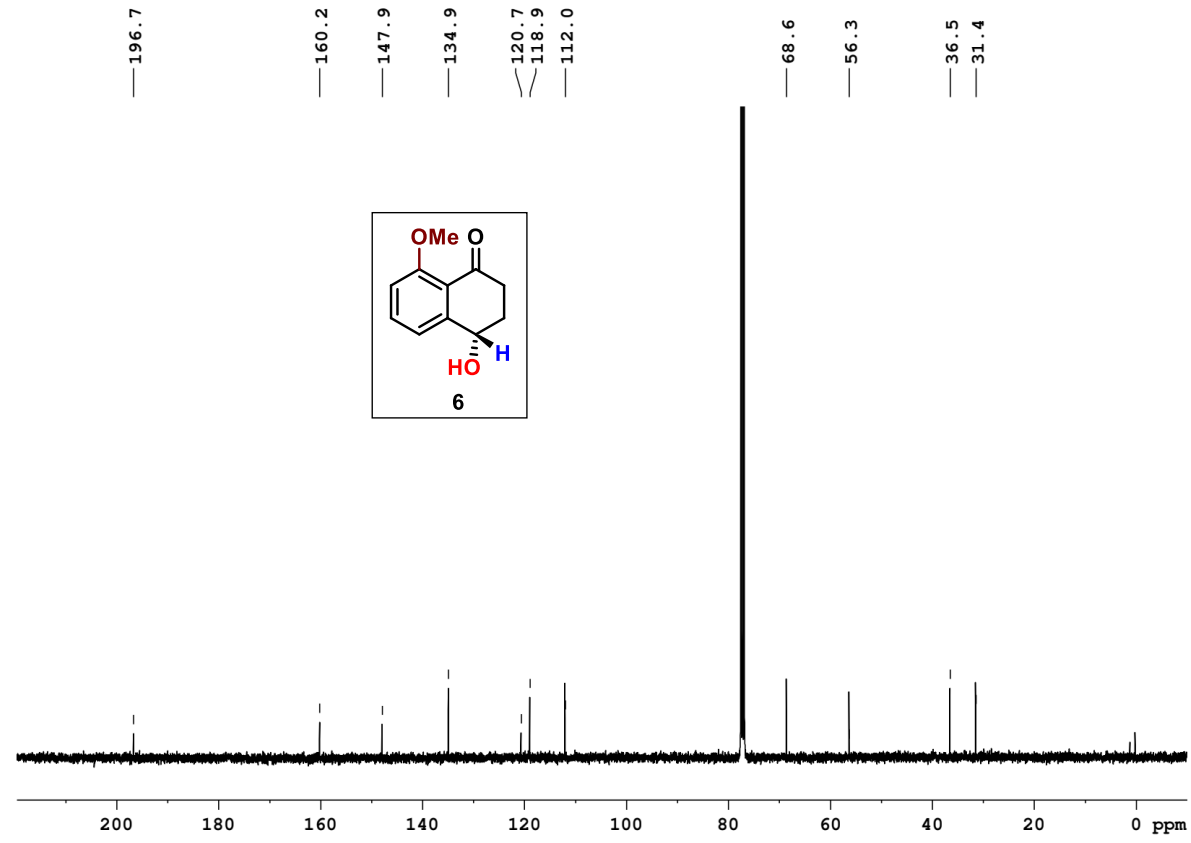
## HSQC NMR (400 MHz, $CDCl_3$)



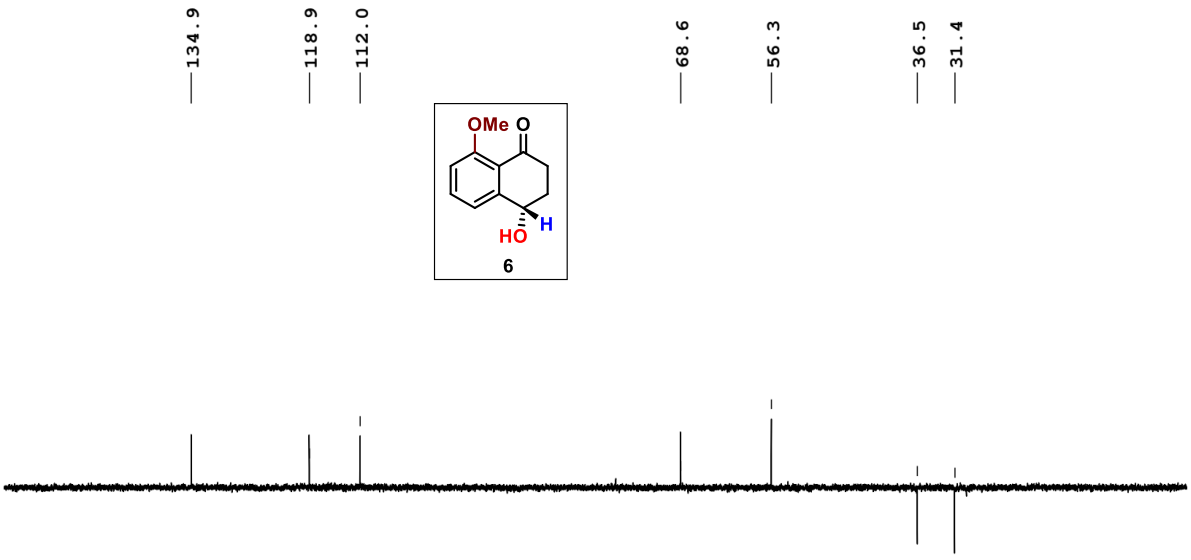

## $^1$H NMR (400 MHz, $CDCl_3$)



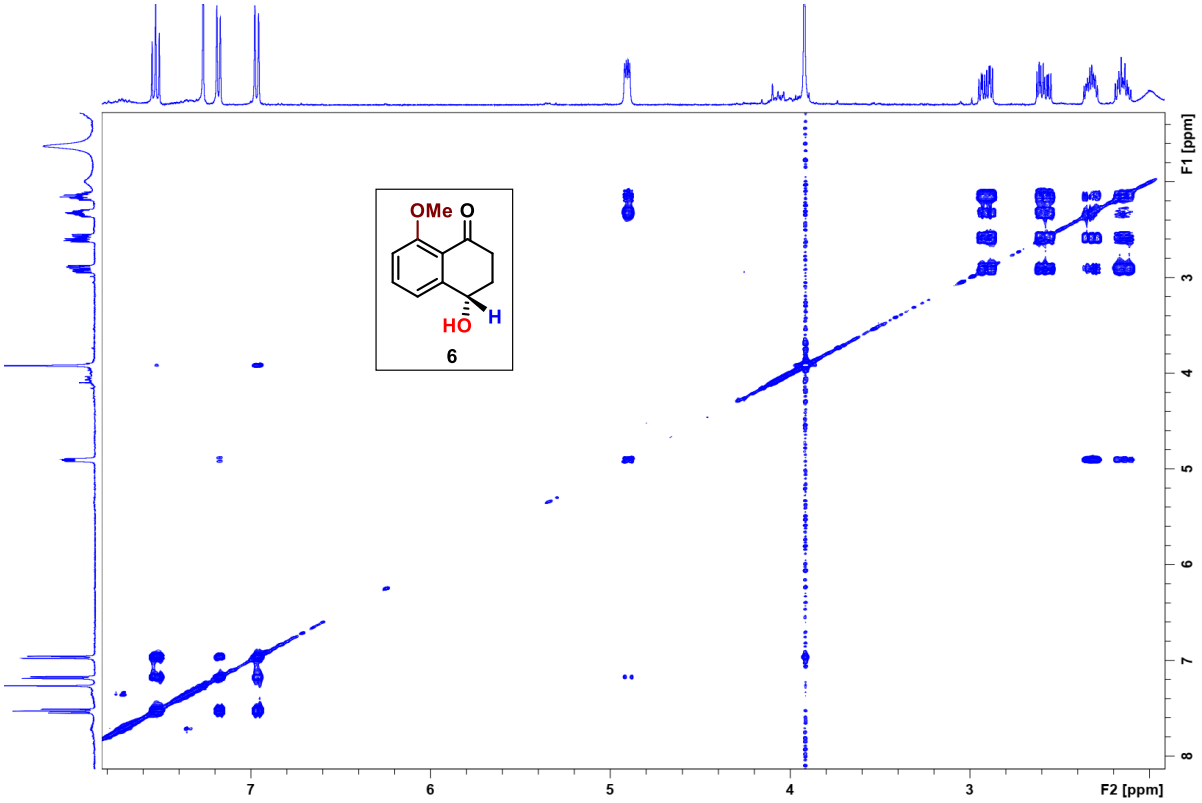
**$^{13}$C NMR (100 MHz, $CDCl_3$)**



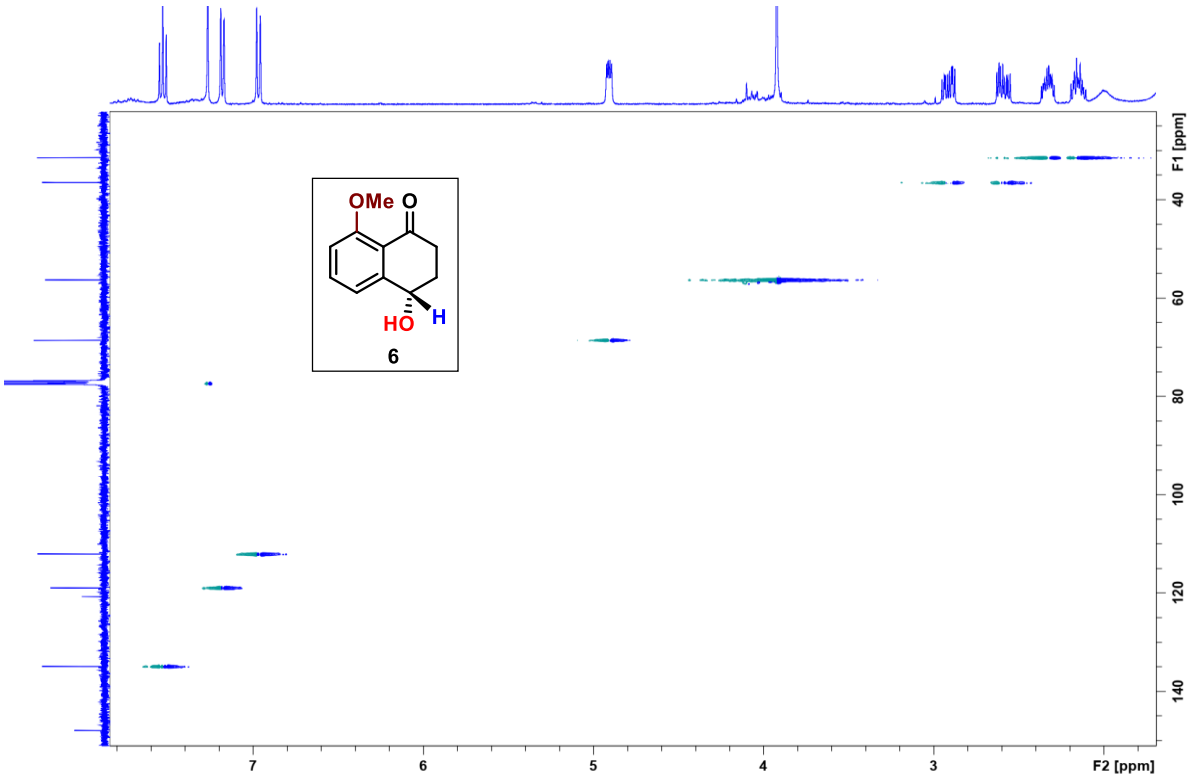

**DEPT NMR (100 MHz, $CDCl_3$)**



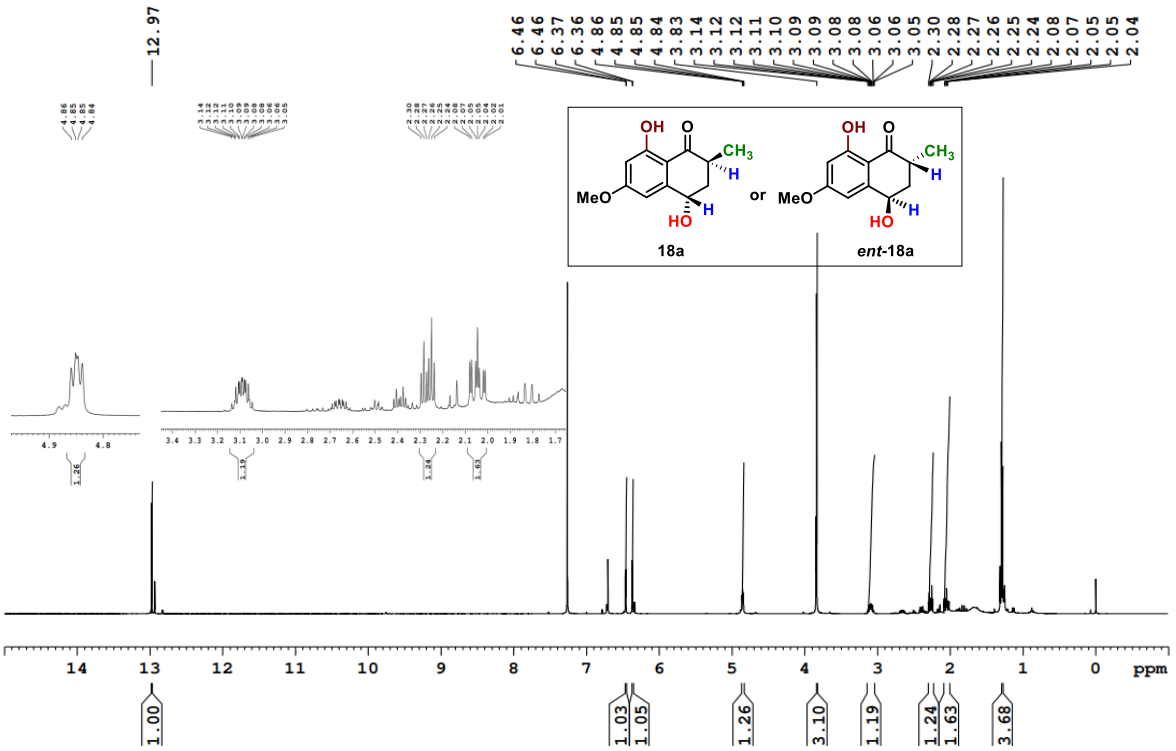
**COSY NMR (400 MHz, $CDCl_3$)**



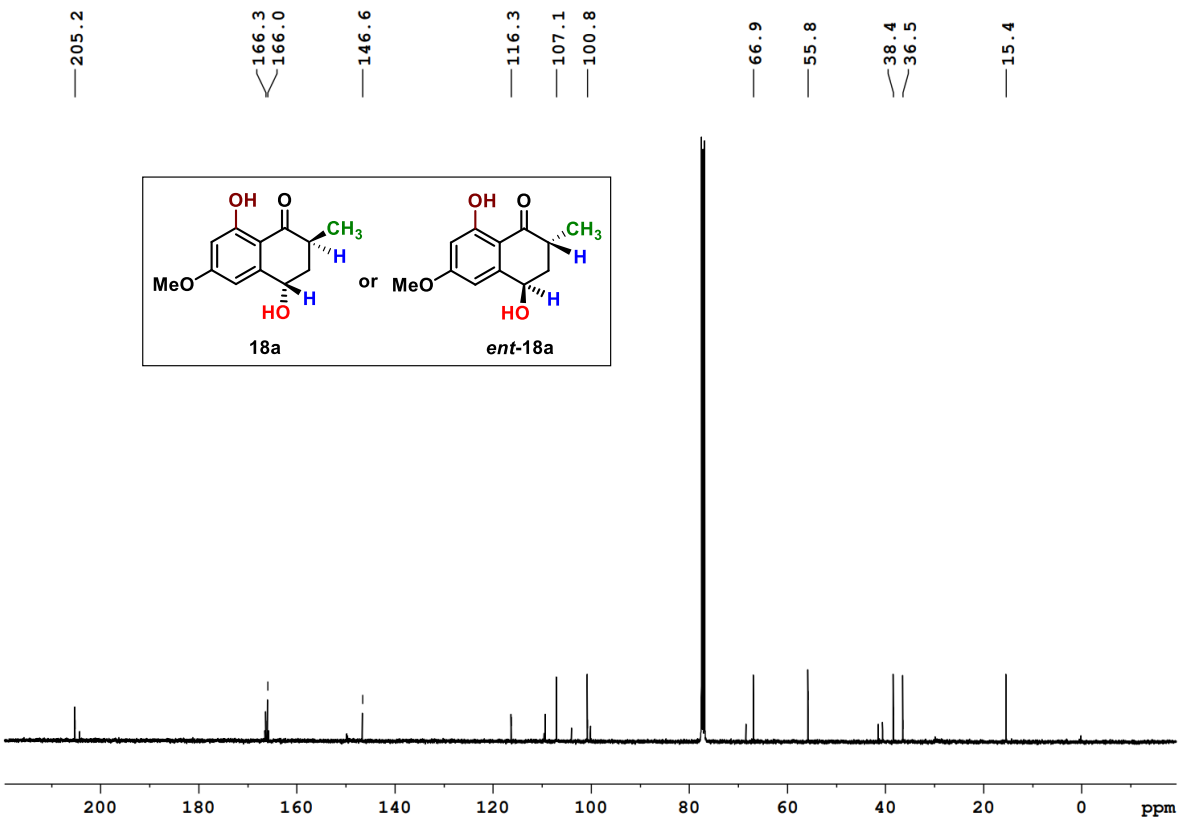

**HSQC NMR (400 MHz, $CDCl_3$)**



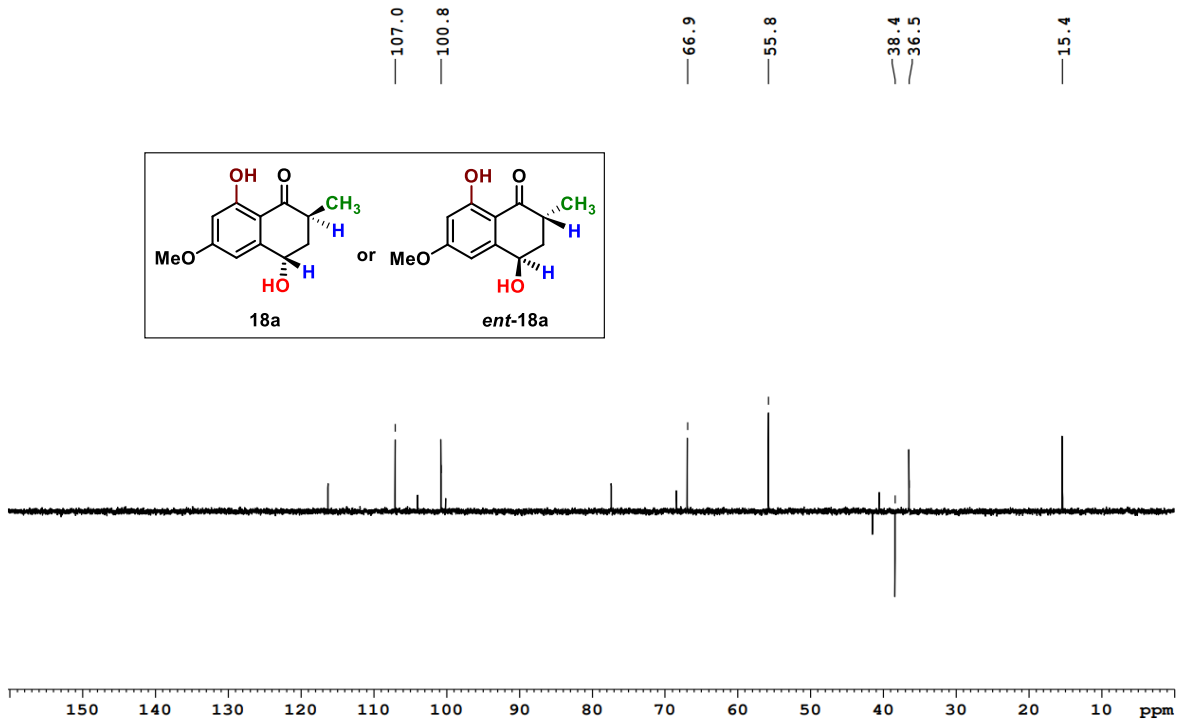
## $^{1}$H NMR (400 MHz, $CDCl_3$)



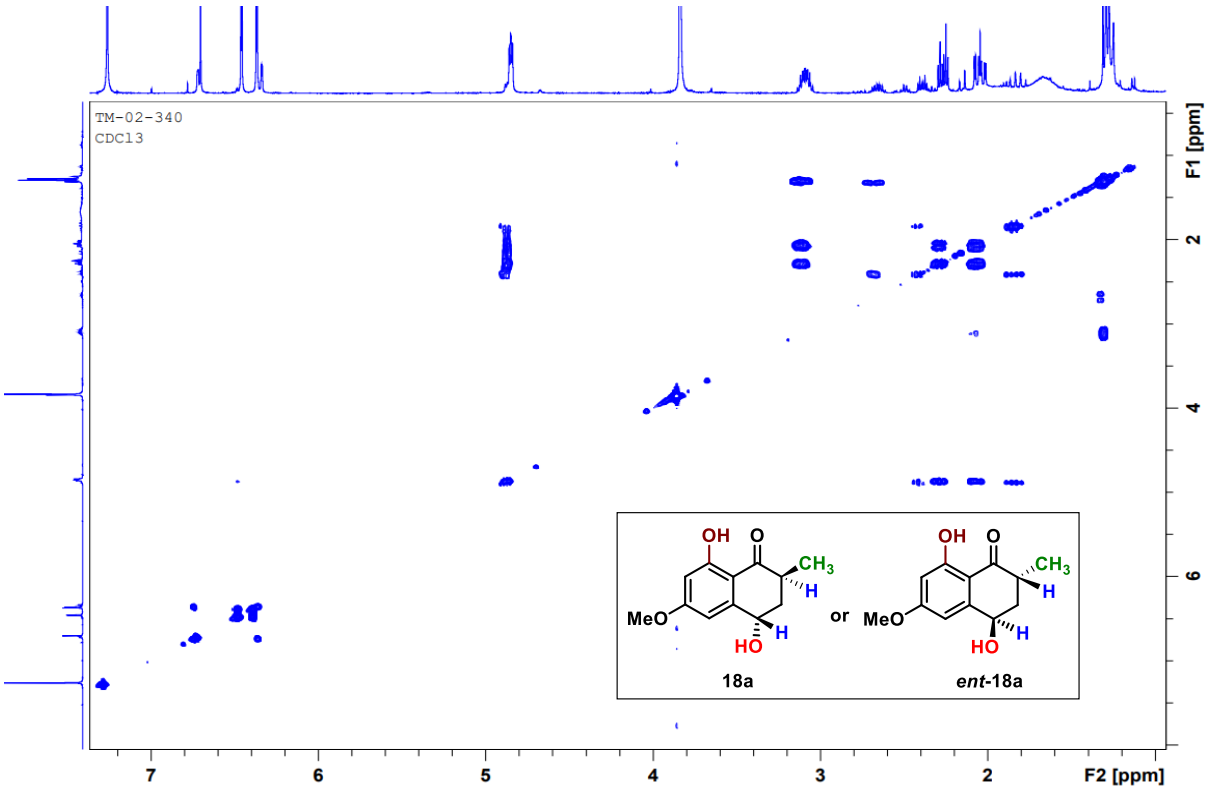

## $^{13}$C NMR (100 MHz, $CDCl_3$)



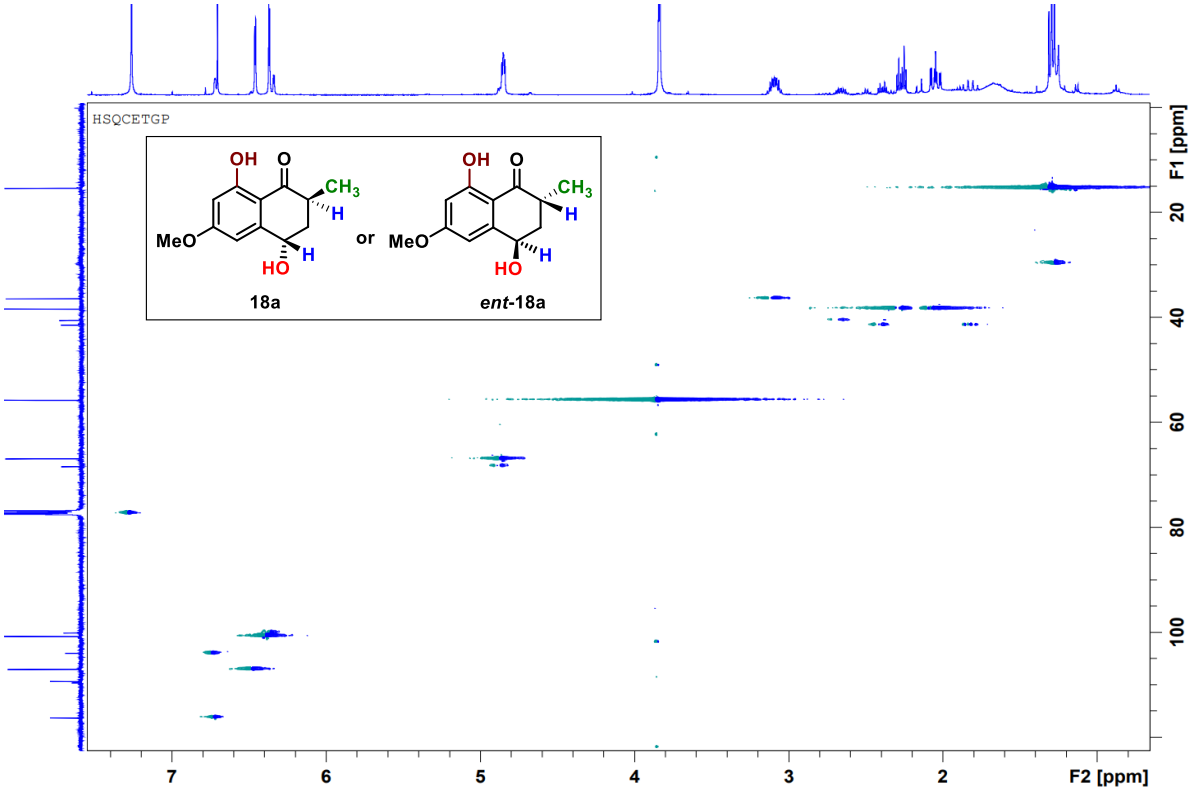
## DEPT NMR (100 MHz, $CDCl_3$)



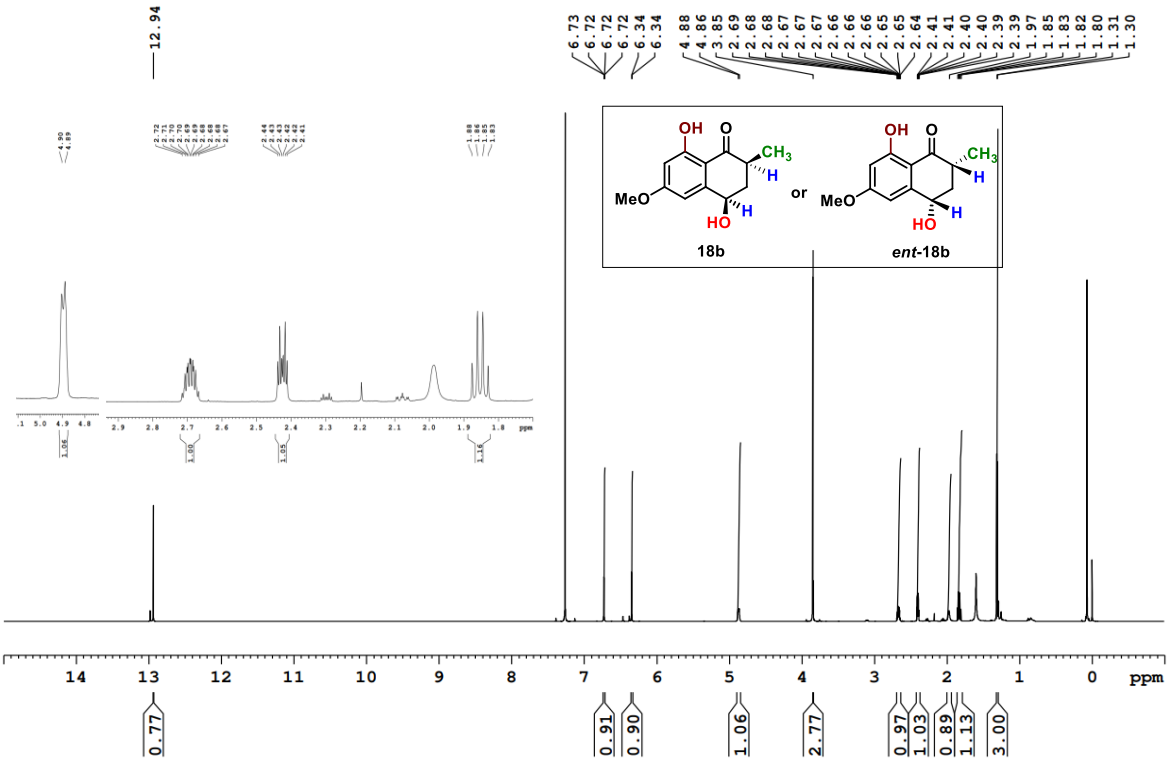

## COSY NMR (400 MHz, $CDCl_3$)



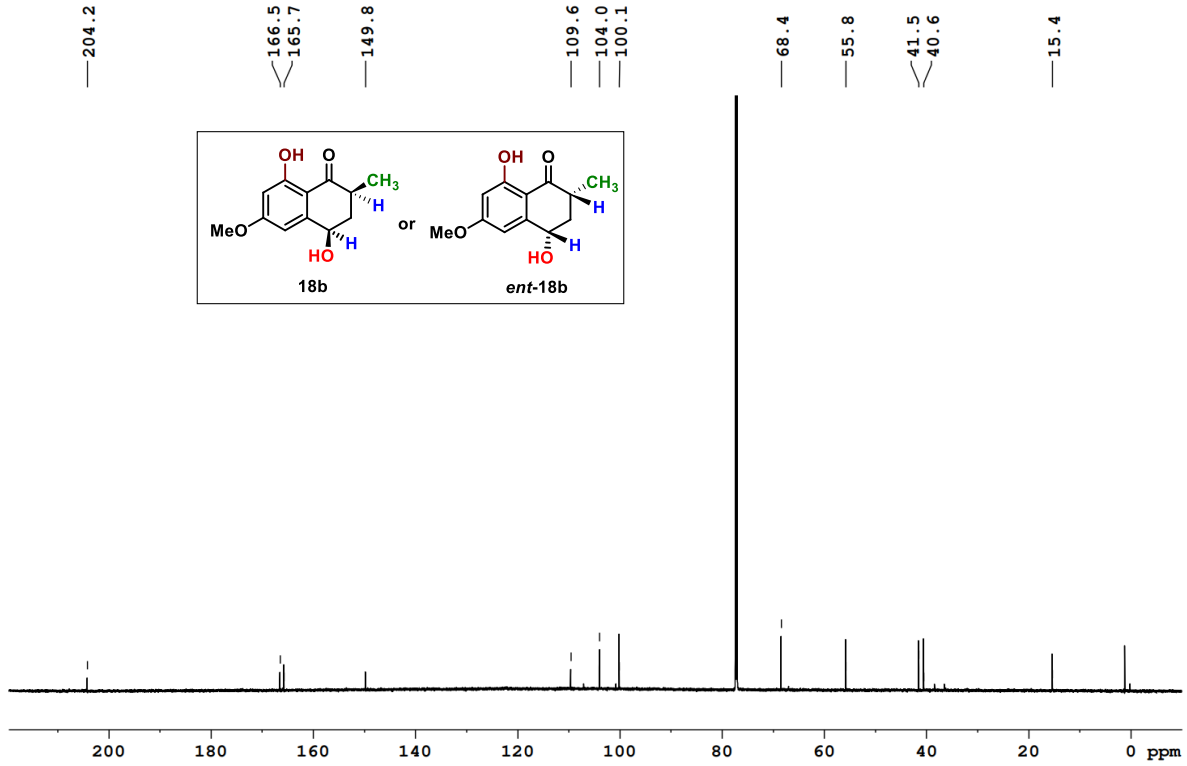
## HSQC NMR (400 MHz, $CDCl_3$)



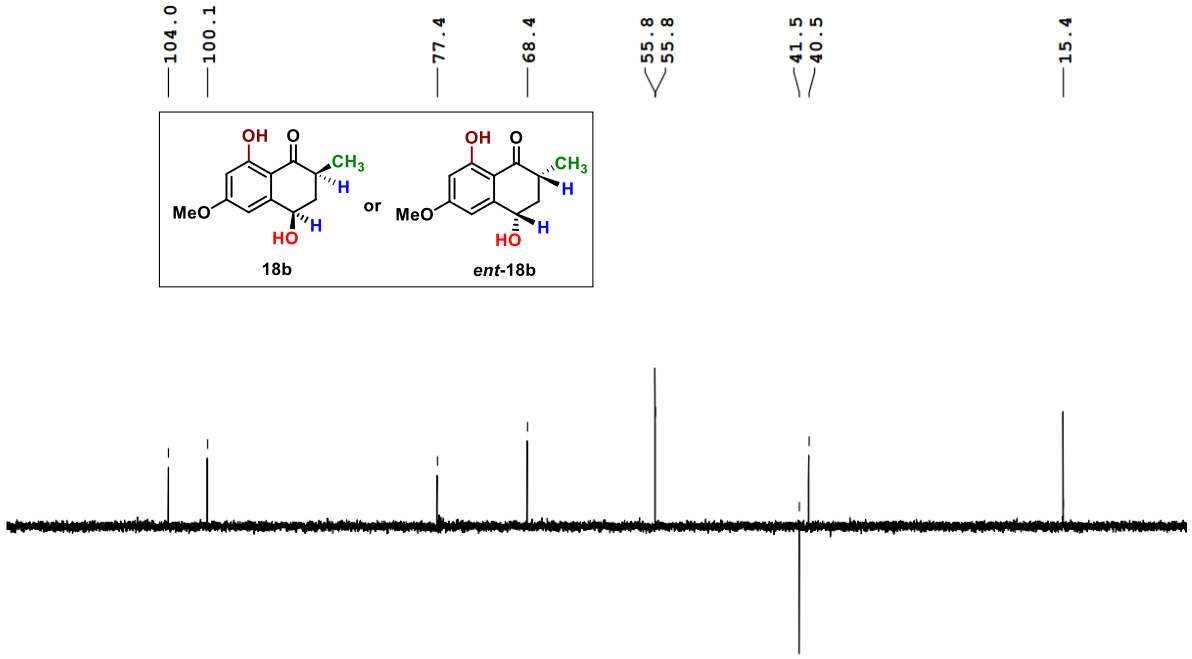

## $^1$H NMR (800 MHz, $CDCl_3$)



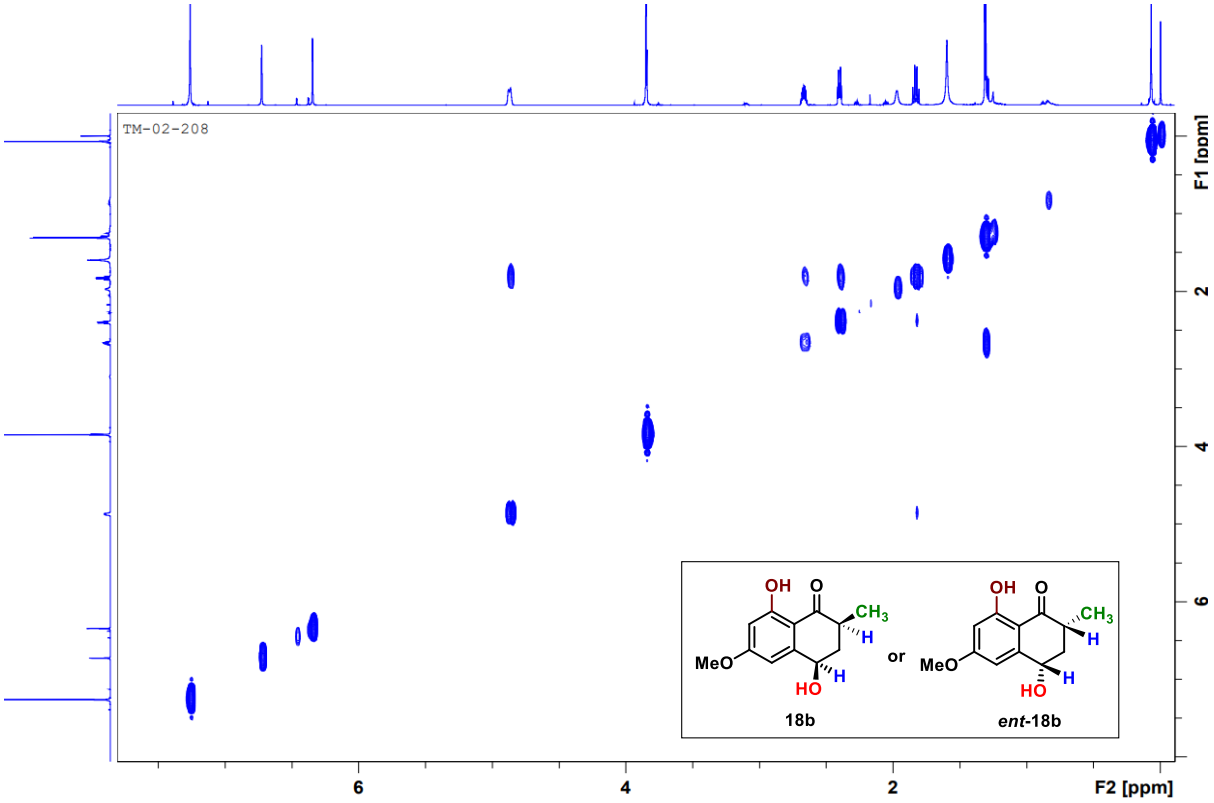
## $^{13}$C NMR (200 MHz, $CDCl_3$)



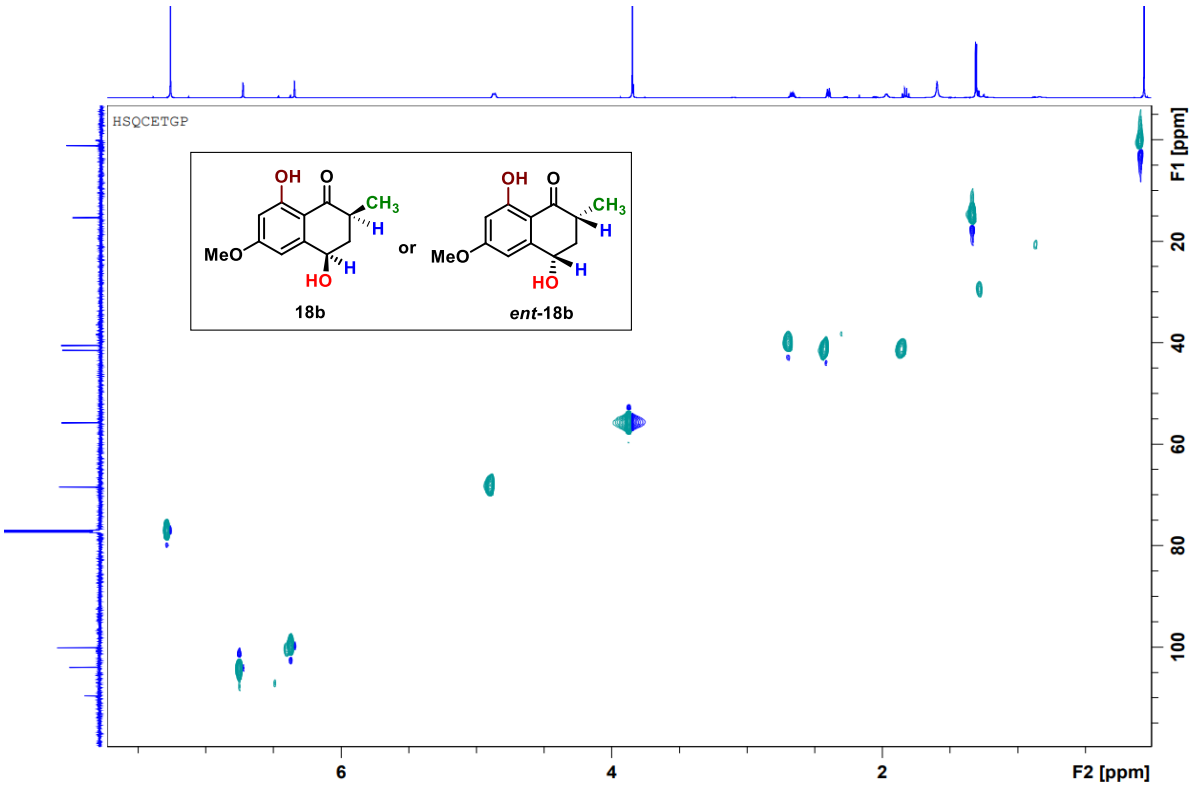

## DEPT NMR (200 MHz, $CDCl_3$)



## COSY NMR (800 MHz, $CDCl_3$)

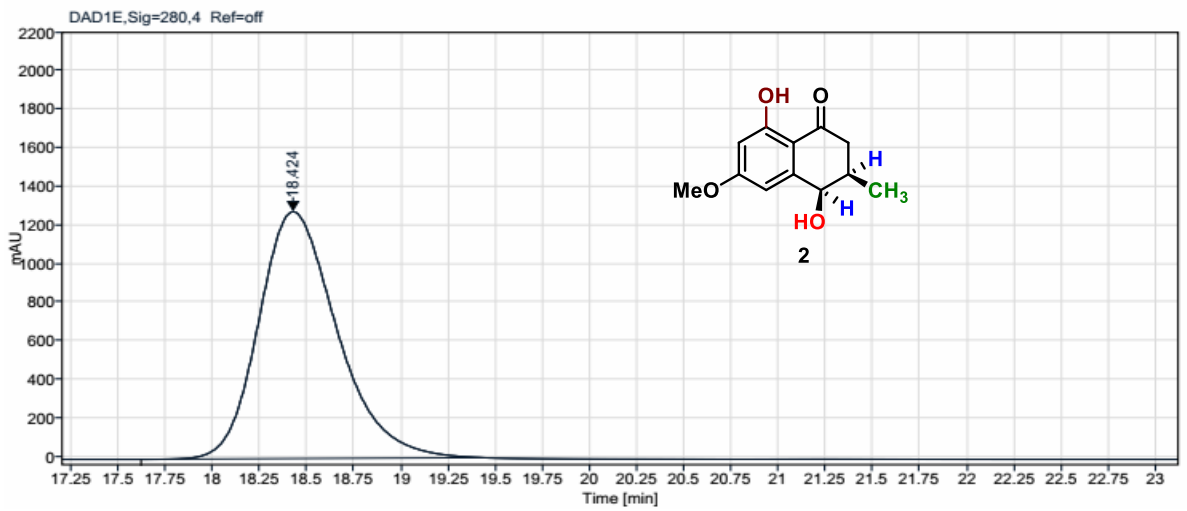



## HSQC NMR (800 MHz, $CDCl_3$)

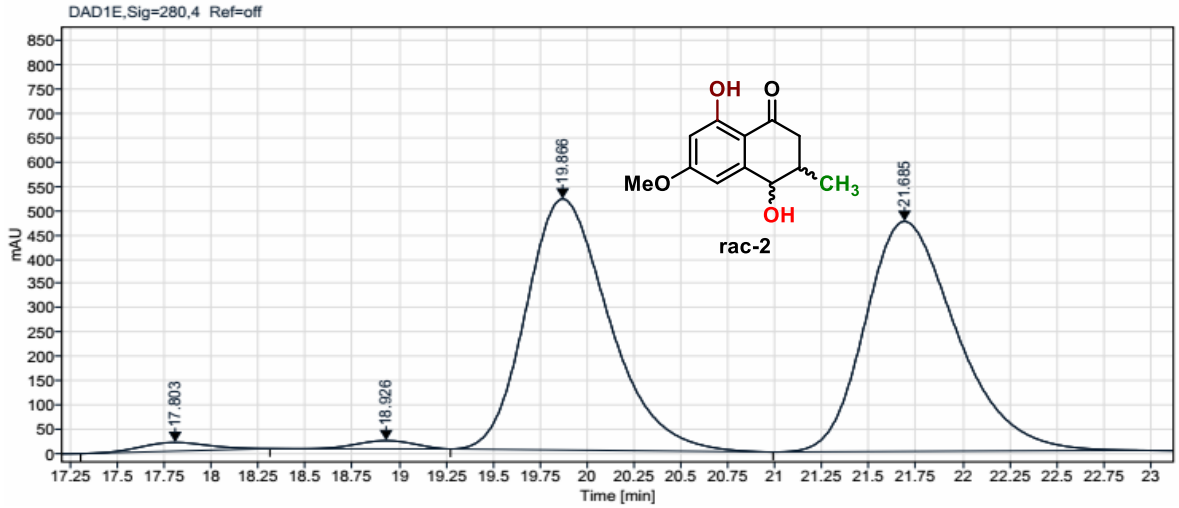


## IX. HPLC Chromatogram

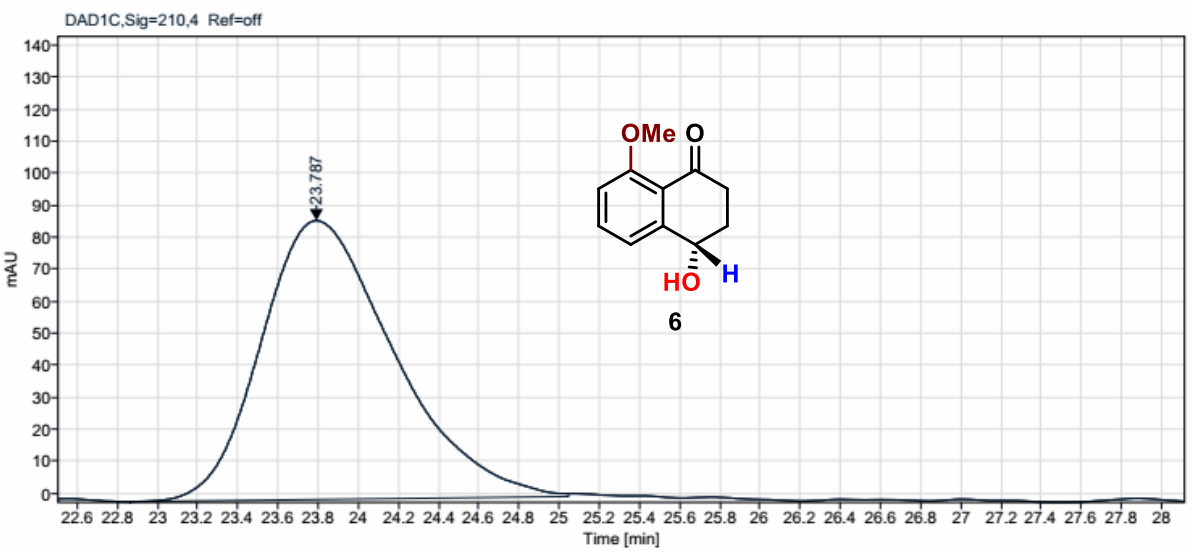
### (+)-teratosphaerone B (2)



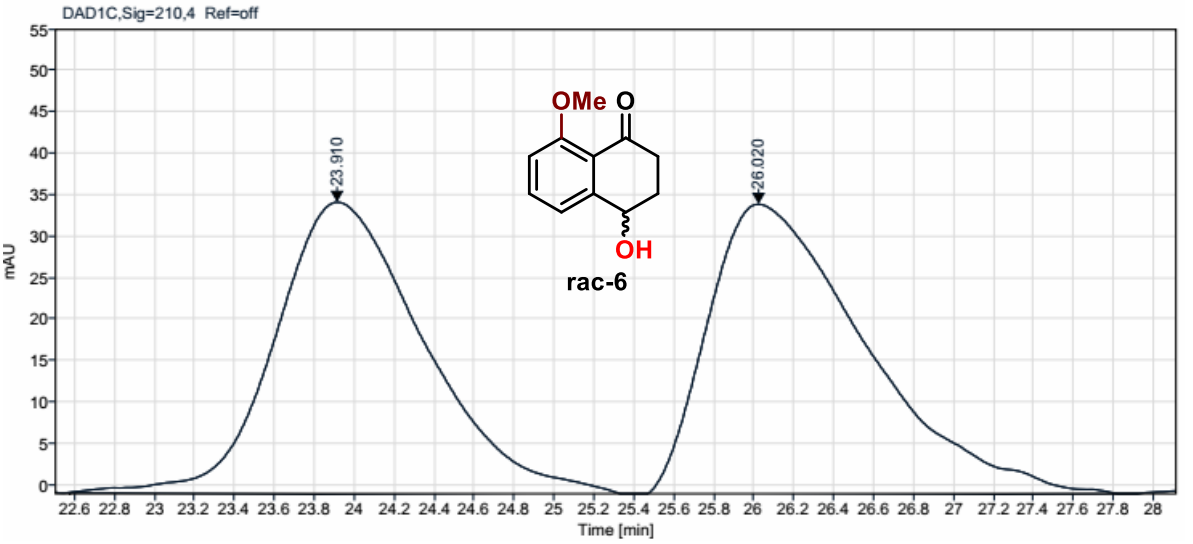

### (rac)-teratosphaerone B (2)



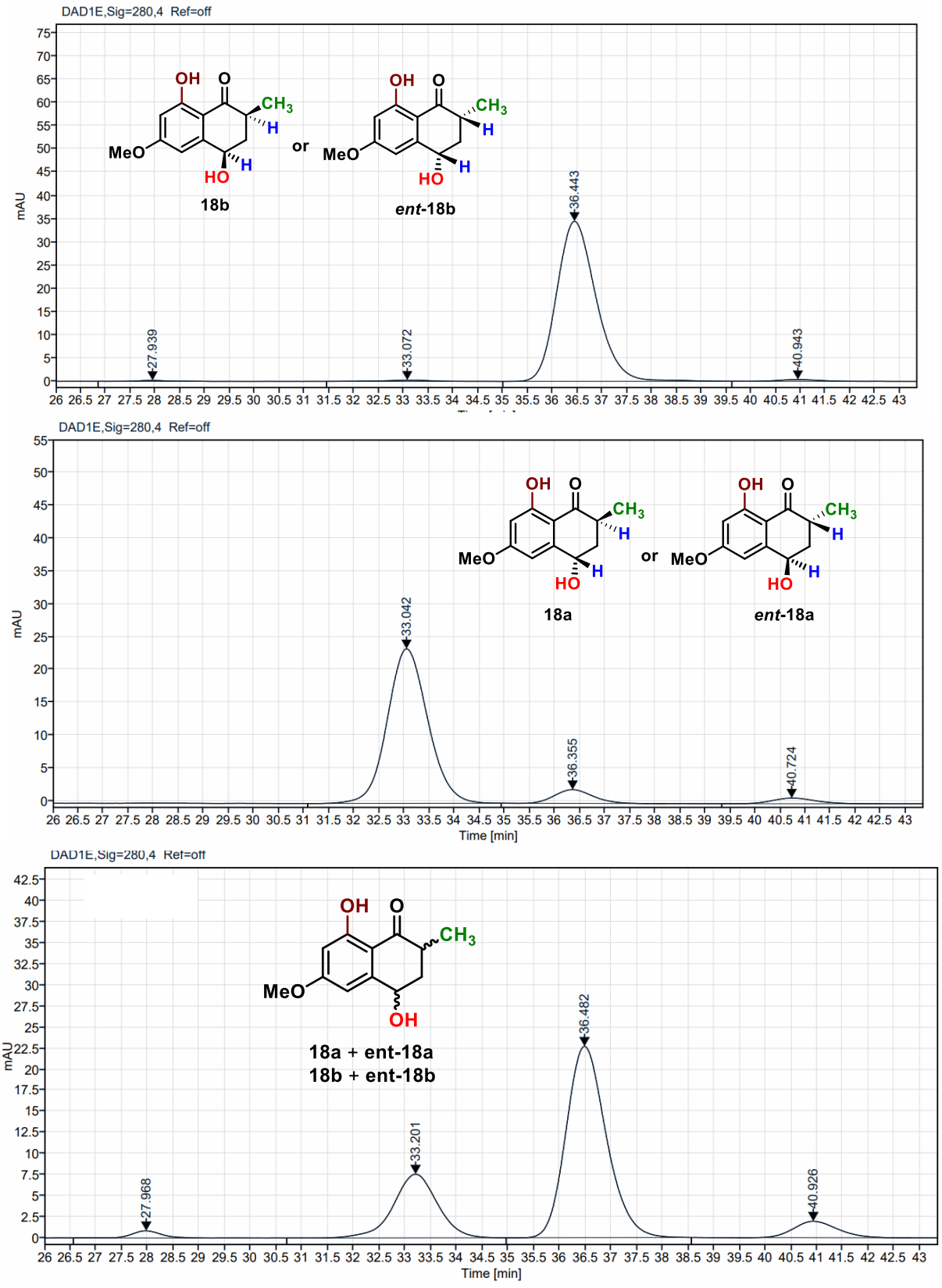
**(+)-xylarenone (6)**




**(rac)-xylarenone (6)**

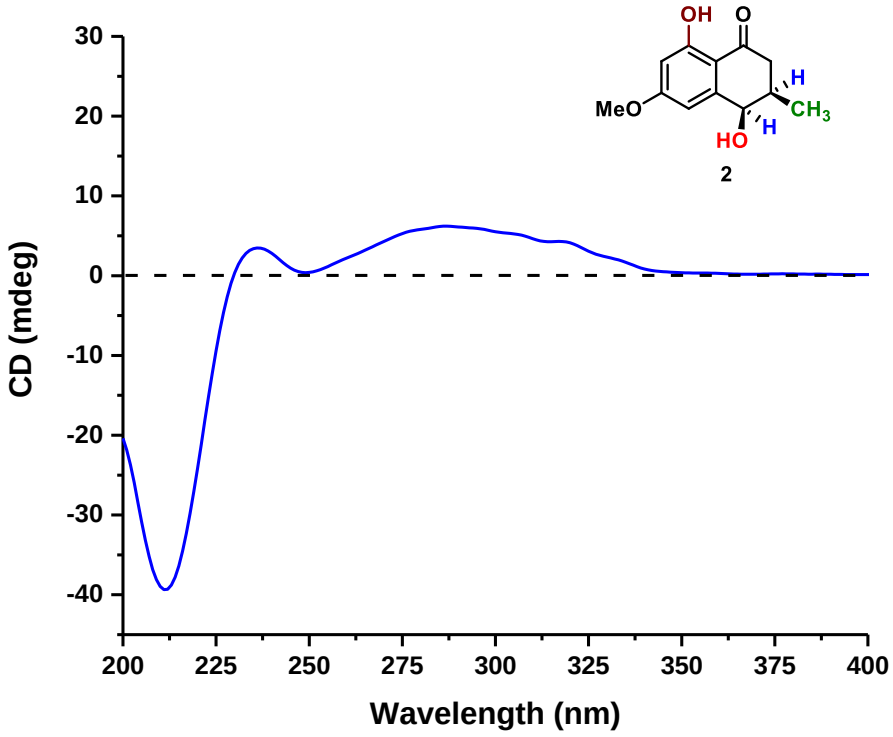


**4,8-dihydroxy-6-methoxy-2-methyl-3,4-dihydronaphthalen-1(2H)-one (17)**

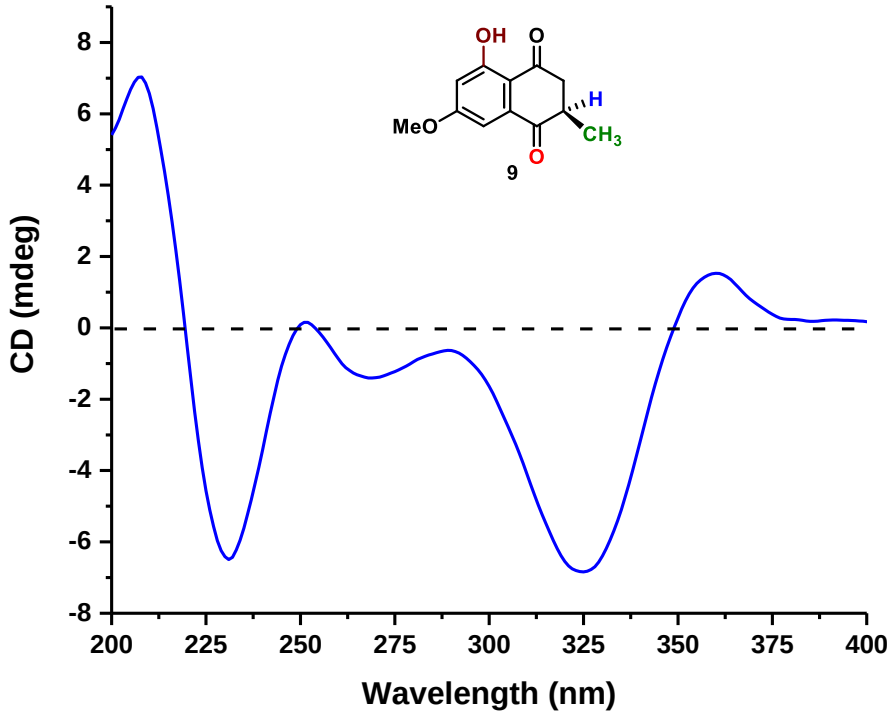


## X. CD Spectra

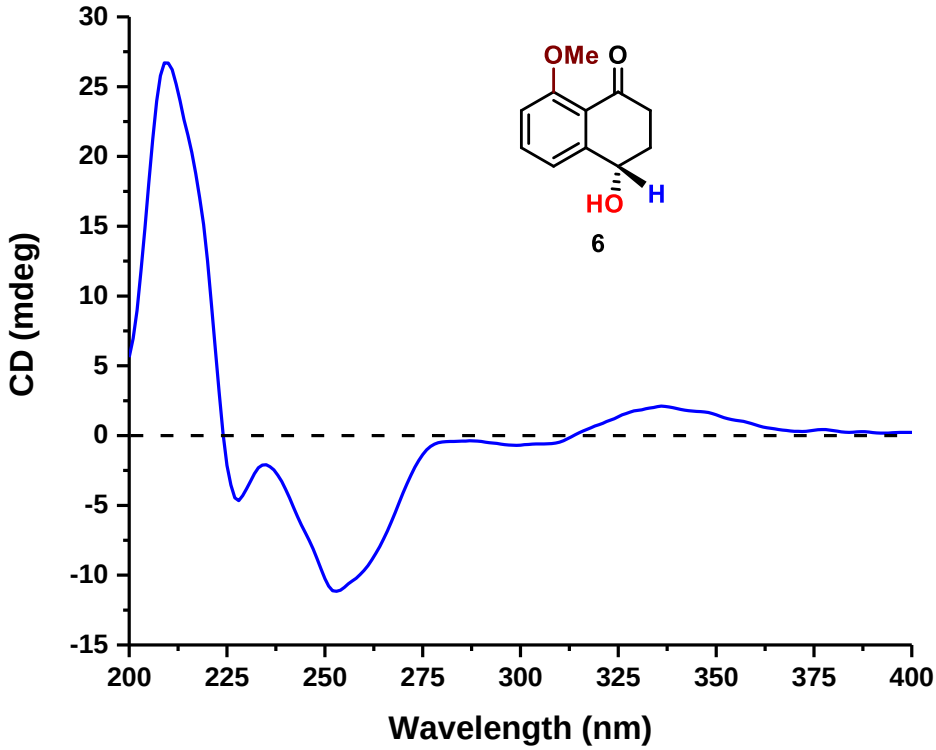
**(+)-teratosphaerone B (2)**



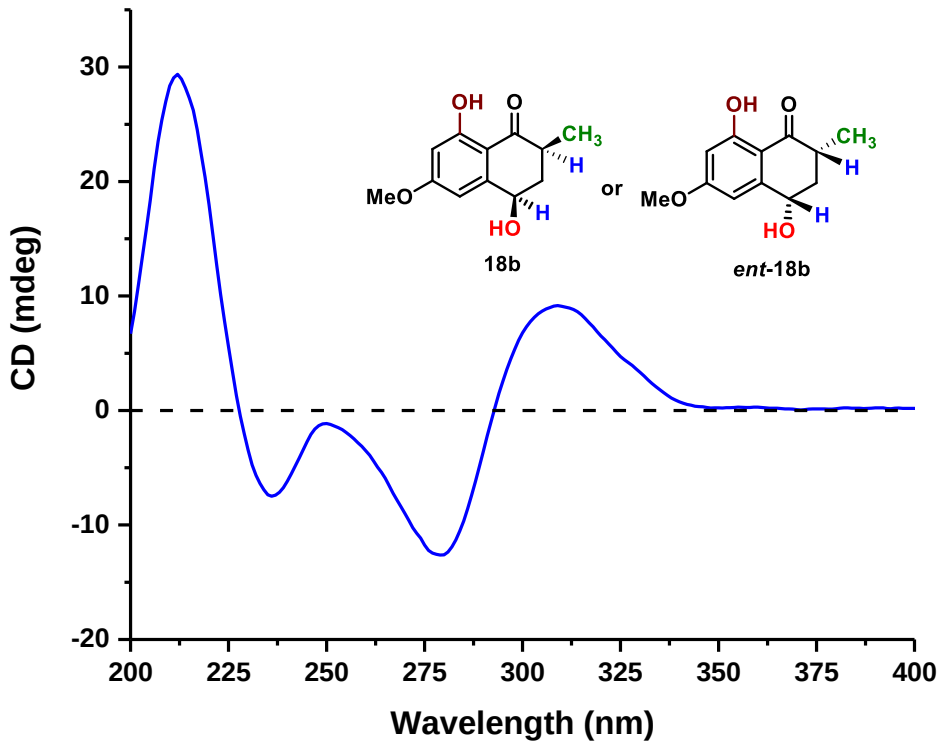

**(R)-5-hydroxy-7-methoxy-2-methyl-2,3-dihydronaphthalene-1,4-dione (9)**



**(+)-xylarenone (6)**




**(+)-*cis*-4,8-dihydroxy-6-methoxy-2-methyl-3,4-dihydronaphthalen-1(2H)-one (18b or *ent*-18b)**



## XI. References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