

Supporting Information

Bioinspired Total Synthesis of Bussealin E

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General Experimental Details

All non-aqueous reactions were performed under a constant stream of dry nitrogen using glassware that had been oven-dried overnight. Standard practices were employed when handling moisture- and air-sensitive materials.¹

Room temperature (rt) refers to ambient temperature. All temperatures below rt are that of the external bath. Temperatures of 0 °C were maintained using an ice-water bath.

All reagents and solvents were used as received unless otherwise stated. CH₂Cl₂, EtOAc, MeOH, MeCN and toluene was distilled from CaH₂. Tetrahydrofuran (THF) was dried over Na wire and distilled from a mixture of LiAlH₄ and CaH₂ with triphenylmethane as the indicator. Et₂O was distilled from a mixture of LiAlH₄ and CaH₂. Petroleum ether was distilled before use and refers to the fraction between 40-60 °C.

Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Where possible, reactions were monitored by thin layer chromatography (TLC) performed on commercially prepared glass plates pre-coated with Merck silica gel F₂₅₄. Visualisation was by the quenching of ultraviolet (UV) fluorescence (λ_{max} = 254 nm) or by staining with potassium permanganate. Retention factors (R_f) are quoted to the nearest 0.01.

Flash column chromatography was carried out using slurry-packed Merck 9385 Keisegel 60 SiO₂ (230-400 mesh) under a positive pressure of dry nitrogen. Additionally, Combiflash® (Teledyne ISCO), an automated chromatography system, was used for purification of some compounds.

Infrared (IR) spectra were recorded neat on a Perkin-Elmer Spectrum One spectrometer with internal referencing. Selected absorption maxima (ν_{max}) are reported in wavenumbers (cm⁻¹).

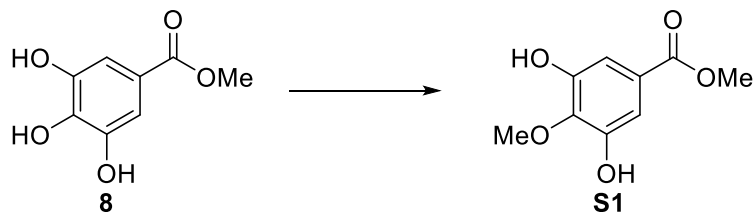
Melting points (m.p.) were obtained on a Büchi B-545 melting point apparatus and are uncorrected.

¹H and ¹³C nuclear magnetic resonance (NMR) spectra were recorded using an internal deuterium lock at ambient probe temperature (unless otherwise stated) on the following instruments: Bruker DPX-400 (400 MHz), Bruker Avance 400 QNP (400 MHz) and Bruker Avance 500 Cryo Ultrashield (500 MHz). NMR spectra assignments are supported by DEPT-135, COSY (2D, ¹H-¹H correlations), HSQC (2D, one bond ¹H-¹³C correlations) and HMBC (2D, multi-bond ¹H-¹³C correlations) where necessary, or by analogy to fully interpreted spectra of related compounds. For ¹H NMR, chemical shifts (δ) are quoted in parts per million (ppm), to the nearest 0.01 ppm, and are referenced to the residual non-deuterated solvent peak. Coupling constants (J) are reported in Hertz (Hz) to the nearest 0.1 Hz. Data are reported as followed: chemical shift, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; qn = quintet; m = multiplet; or as a combination of these, e.g. dd, dt etc.; app = apparent; br = broad), integration and coupling constant(s). The internal standard used was tetramethylsilane. For ¹³C NMR, chemical shifts (δ) are quoted in ppm, to the nearest 0.1 ppm, and are referenced to the solvent peak. Hydrogen multiplicities (C, CH, CH₂, CH₃) obtained from routine DEPT spectra are included. The internal standard used was tetramethylsilane.

High resolution mass spectrometry (HRMS) measurements were recorded on a Bruker Bioapex 4.7e FTICR or a Micromass LCT Premier spectrometer. Mass values are quoted within the error limits of \pm 5 ppm mass units. ESI refers to the electrospray mass ionisation technique.

Experimental Procedures and Characterisation Data

Methyl 3,5-dihydroxy-4-methoxybenzoate, **S1**

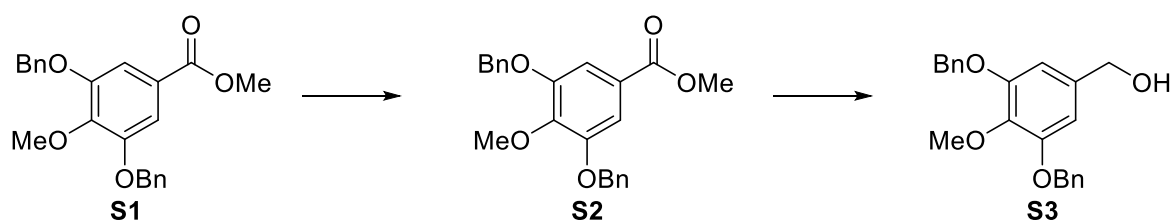


K₂CO₃ (9.28 g, 67.2 mmol) was added to a solution of methyl gallate **8** (10.3 g, 56.0 mmol) in DMF (103 mL) and the mixture heated to 85 °C for 1 h. After cooling to 0 °C, methyl iodide (8.26 g, 58.2 mmol) was added and the mixture stirred at 0 °C for 30 min, before being allowed to warm to rt and stirred for a further 24 h. The mixture was then filtered through Celite and the filtrate diluted with H₂O and EtOAc. The layers were separated and the aqueous phase further extracted with EtOAc (3x). The combined organic fractions were washed with brine, dried over MgSO₄ and evaporated. The residue was purified by flash column chromatography (CHCl₃/MeOH, 49:1) to provide **S1** as a white solid (6.42 g, 32.4 mmol, 58%).

*R*_f = 0.13 (CHCl₃/MeOH, 49:1); ¹H NMR (400 MHz, CDCl₃): δ 7.23 (s, 2H), 5.67 (s, 2H), 3.97 (s, 3H), 3.88 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 166.8 (C), 148.8 (C), 138.6 (C), 126.2 (C), 110.0 (CH), 61.2 (CH₃), 52.4 (CH₃); IR *v*_{max}: 3387, 2998, 2957, 1708, 1594, 1508, 1438.

These data are consistent with those previously reported.²

[3,5-Bis(benzyloxy)-4-methoxyphenyl]methanol, **S3**



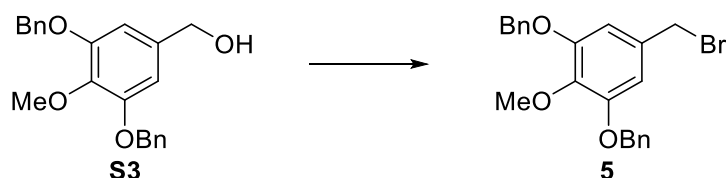
Benzyl bromide (22.2 g, 130 mmol) and Cs₂CO₃ (45.7 g, 130 mmol) were added to a solution of **S1** (6.42 g, 32.4 mmol) in DMF (140 mL) and the mixture heated to 75 °C for 22 h. After cooling, the mixture was filtered through a plug of SiO₂ and the filtrate evaporated. The residue was dissolved in 1:1 H₂O:EtOAc, the layers were separated and the aqueous phase further extracted with EtOAc (2x). The combined organic fractions were successively washed with H₂O, 1.0 M aqueous HCl and brine, then dried over MgSO₄ and evaporated to provide crude product **S2** as a yellow solid. The material was carried forward without further purification. LiAlH₄ (4.82 g, 127 mmol) was added to a solution of the above crude product **S2** in THF (195 mL) and the mixture heated to 65 °C for 18 h. After cooling to 0 °C, the reaction was carefully quenched with 1:1 EtOAc:ice-water and the resultant suspension filtered under suction. The layers of the filtrate were then separated and the aqueous phase extracted with

EtOAc (3x). The combined organic fractions were successively washed with 1.0 M aqueous HCl and brine, then dried over MgSO₄ and evaporated. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 9:1-7:3) to provide **S3** as an off-white solid (9.66 g, 27.6 mmol, 85% over two steps from **S1**).

R_f = 0.37 (petroleum ether/EtOAc, 1:1); ¹H NMR (400 MHz, CDCl₃): δ 7.46-7.44 (m, 4H), 7.40-7.36 (m, 4H), 7.33-7.29 (m, 2H), 6.65 (s, 2H), 5.14 (s, 4H), 4.56 (s, 2H), 3.89 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 152.9 (C), 139.1 (C), 137.3 (C), 136.5 (C), 128.7 (CH), 128.0 (CH), 127.4 (CH), 106.7 (CH), 71.2 (CH₂), 65.6 (CH₂), 61.1 (CH₃); IR *v*_{max}: 3518, 2965, 2934, 2884, 1592, 1502, 1470, 1457, 1437.

These data are consistent with those previously reported.²

1,3-Bis(benzyloxy)-5-(bromomethyl)-2-methoxybenzene, **5**

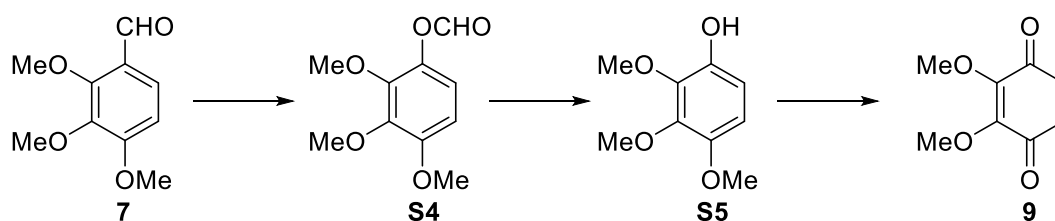


PPh₃ (8.40 g, 32.0 mmol) was added to a solution of **S3** (9.22 g, 26.3 mmol) and CBr₄ (10.6 g, 32.0 mmol) in THF (51 mL) at 0 °C and the reaction stirred for 15 min before being allowed to warm to rt and stirred for a further 17 h. The solvent was then evaporated and the residue re-dissolved in 1:1 H₂O:CH₂Cl₂, the layers separated and the aqueous phase extracted with CH₂Cl₂ (3x). The combined organic fractions were washed with brine, dried over MgSO₄ and evaporated. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 19:1) to provide **5** as an off-white solid (9.60 g, 23.2 mmol, 88%).

R_f = 0.18 (petroleum ether/EtOAc, 19:1); ¹H NMR (400 MHz, CDCl₃): δ 7.46-7.44 (m, 4H), 7.41-7.37 (m, 4H), 7.34-7.30 (m, 2H), 6.67 (s, 2H), 5.13 (s, 4H), 4.39 (s, 2H), 3.89 (s, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 152.8 (C), 139.8 (C), 137.0 (C), 133.1 (C), 128.7 (CH), 128.1 (CH), 127.5 (CH), 109.0 (CH), 71.3 (CH₂), 61.1 (CH₃), 34.3 (CH₂); IR *v*_{max}: 2926, 2855, 1589, 1504, 1439; HRMS (ESI): [M+H]⁺ calcd. for C₂₂H₂₂O₃⁷⁹Br⁺: 413.0747, found: 413.0742.

These data are consistent with those previously reported.³

2,3-Dimethoxy-1,4-benzoquinone, **9**

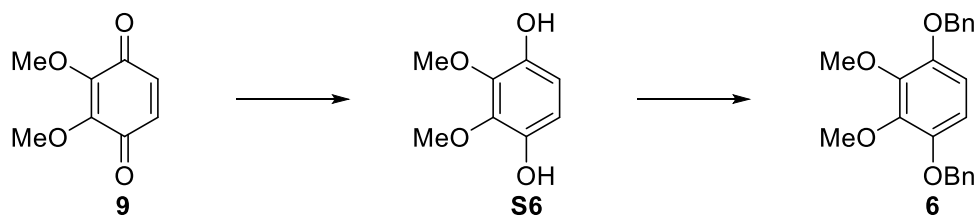


A solution of 2,3,4-trimethoxybenzaldehyde **7** (9.78 g, 49.8 mmol) in CH₂Cl₂ (22 mL) was added slowly to a solution of *m*-CPBA (77 wt%, 12.1 g, 54.0 mmol) in CH₂Cl₂ (88 mL) at 0 °C and the mixture allowed to warm to rt and stirred for 3 h. Saturated aqueous NaHCO₃ (100 mL) was then added and the layers separated. The organic phase was washed with 10% (w/v) aqueous Na₂S₂O₃, dried over Na₂SO₄ and evaporated to provide crude formate ester **S4** as a yellow oil. This residue was re-dissolved in MeOH (50 mL), 10% (w/v) aqueous NaOH (50 mL) was added and the mixture stirred at rt for 16 h. The reaction was then acidified to pH 1 using 6.0 M aqueous HCl and diluted with CH₂Cl₂. The layers were separated and the aqueous phase extracted with CH₂Cl₂ (4x). The combined organic fractions were dried over MgSO₄ and evaporated to provide the crude phenol **S5** as an orange oil. The material was carried forward without further purification. A solution of ceric ammonium nitrate (71.3 g, 130 mmol) in H₂O (65 mL) was added to a flask charged with silica gel (150 g). CH₂Cl₂ (600 mL) was added, followed by a solution of the above crude product **S5** in CH₂Cl₂ (50 mL) and the mixture stirred at rt for 1.5 h. The silica was then removed by suction filtration, rinsing with CH₂Cl₂. The layers of the filtrate were separated and the aqueous phase extracted with CH₂Cl₂ (2x). The combined organic fractions were evaporated. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 19:1) to provide **9** as an orange solid (5.88 g, 35.0 mmol, 70% over two steps from **7**).

R_f = 0.50 (petroleum ether/EtOAc, 1:1); ¹H NMR (400 MHz, CDCl₃): δ 6.61 (s, 2H), 4.03 (s, 6H); ¹³C NMR (101 MHz, CDCl₃): δ 184.3 (C), 145.3 (C), 134.8 (CH), 61.5 (CH₃); IR *v*_{max}: 2953, 1635, 1587, 1454, 1435; HRMS (ESI): [M+H]⁺ calcd. for C₈H₉O₄⁺: 169.0501, found: 169.0505.

These data are consistent with those previously reported.⁴

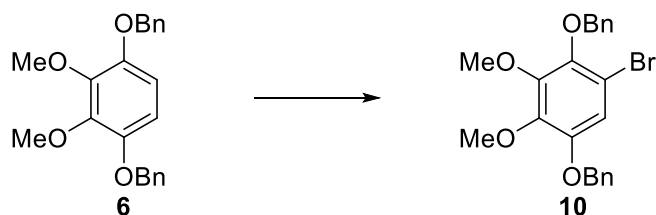
1,4-Bis(benzyloxy)-2,3-dimethoxybenzene, **6**



A solution of **9** (2.86 g, 17.0 mmol) in Et₂O (50 mL) and MeOH (25 mL) was added to a solution of NaBH₄ (3.19 g, 84.3 mmol) in H₂O (90 mL) and the mixture stirred at rt for 2 h. The mixture was then acidified to pH 1 using 2.0 M aqueous HCl and diluted with Et₂O. The layers were separated and the aqueous phase extracted with Et₂O (3x). The combined organic fractions were washed with brine, dried over MgSO₄ and evaporated to provide crude product **S6** as an off-white solid. The material was carried forward without further purification. Benzyl bromide (10.6 g, 62.1 mmol) and Cs₂CO₃ (21.9 g, 62.1 mmol) were added to a solution of the above crude product **S6** in DMF (65 mL) and the mixture heated to 90 °C for 16 h. After cooling, the mixture was filtered through Celite and the filtrate evaporated. The residue was re-dissolved in CH₂Cl₂ and washed successively with H₂O (3x), 1.0 M aqueous HCl (2 x) and brine, then dried over MgSO₄ and evaporated. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 19:1) to provide **6** as a white crystalline solid (4.05 g, 11.6 mmol, 68% over two steps from **9**).

R_f = 0.66 (petroleum ether/EtOAc, 1:1); **m.p.** 71.9-72.6 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.45-7.43 (m, 4H), 7.40-7.36 (m, 4H), 7.33-7.29 (m, 2H), 6.58 (s, 2H), 5.06 (s, 4H), 3.94 (s, 6H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 147.4 (C), 144.4 (C), 137.5 (C), 128.6 (CH), 128.0 (CH), 127.5 (CH), 109.3 (CH), 71.8 (CH_2), 61.5 (CH_3); **IR** ν_{max} : 2939, 2908, 2860, 1595, 1488, 1476; **HRMS** (ESI): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{22}\text{H}_{23}\text{O}_4^+$: 351.1596, found: 351.1613.

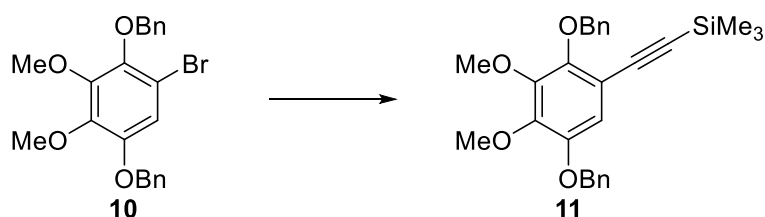
1,4-Bis(benzyloxy)-5-bromo-2,3-dimethoxybenzene, **10**



NH_4Br (1.13 g, 11.5 mmol) and Oxone (7.10 g, 11.5 mmol) were added to a solution of **6** (4.04 g, 11.5 mmol) in MeOH (115 mL) and the mixture stirred at rt for 2 h. The reaction was then filtered under suction and the filtrate evaporated. The residue was re-suspended in CH_2Cl_2 , filtered to remove insoluble impurities and the filtrate evaporated. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 9:1) to provide **10** as a white solid (4.71 g, 11.0 mmol, 95%).

R_f = 0.25 (petroleum ether/EtOAc, 9:1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.57-7.54 (m, 2H), 7.46-7.43 (m, 2H), 7.42-7.38 (m, 4H), 7.37-7.32 (m, 2H), 6.92 (s, 1H), 5.06 (s, 2H), 4.99 (s, 2H), 3.94 (s, 3H), 3.91 (s, 3H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 149.6 (C), 148.6 (C), 144.4 (C), 143.5 (C), 137.2 (C), 136.6 (C), 128.8 (CH), 128.7 (CH), 128.5 (CH), 128.31 (CH), 128.26 (CH), 127.5 (CH), 113.0 (CH), 111.2 (C), 75.6 (CH_2), 71.6 (CH_2), 61.7 (CH_3), 61.5 (CH_3); **IR** ν_{max} : 2941, 1661, 1595, 1495, 1453; **HRMS** (ESI): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{22}\text{H}_{22}\text{O}_4^{79}\text{Br}^+$: 429.0701, found: 429.0720.

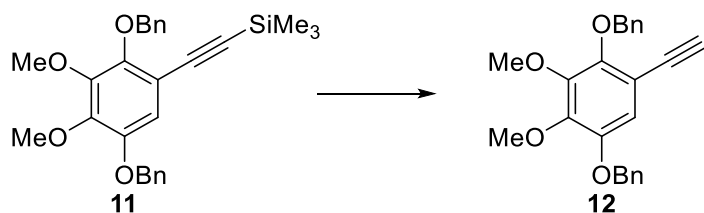
1,4-Bis(benzyloxy)-2,3-dimethoxy-5-[(trimethylsilyl)ethynyl]benzene, **11**



$\text{P}(t\text{-Bu})_3$ (1.0 M in toluene, 0.513 mL, 0.513 mmol) and ethynyltrimethylsilane (3.62 mL, 25.6 mmol) were added successively to a solution of **10** (1.10 g, 2.57 mmol), $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (180 mg, 0.257 mmol) and CuI (49.0 mg, 0.257 mmol) in toluene (16 mL) and Et_3N (8 mL) and the mixture heated to reflux for 18 h. After cooling, the reaction was filtered through Celite and the filtrate evaporated. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 1:0-99:1) to provide **11** as a yellow oil (818 mg, 1.83 mmol, 71%).

R_f = 0.25 (petroleum ether/EtOAc, 9:1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.56-7.54 (m, 2H), 7.46-7.44 (m, 2H), 7.42-7.32 (m, 6H), 6.82 (s, 1H), 5.08 (s, 2H), 5.06 (s, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 0.23 (s, 9H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 149.0 (C), 148.7 (C), 147.6 (C), 145.2 (C), 137.6 (C), 136.9 (C), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.15 (CH), 128.12 (CH), 127.6 (CH), 113.0 (CH), 112.5 (C), 101.1 (C), 98.1 (C), 75.8 (CH_2), 71.5 (CH_2), 61.6 (CH_3), 61.5 (CH_3), 0.1 (CH_3); $\text{IR } \nu_{\text{max}}$: 2959, 2152, 1588, 1566, 1483, 1451, 1434, 1412; HRMS (ESI): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{27}\text{H}_{31}\text{O}_4^{28}\text{Si}^+$: 447.1992, found: 447.1995.

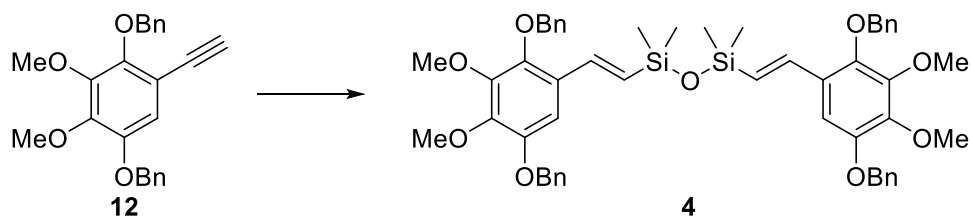
1,4-Bis(benzyloxy)-5-ethynyl-2,3-dimethoxybenzene, **12**



TBAF (1.0 M in THF, 1.66 mL, 1.66 mmol) was added to a solution of **11** (740 mg, 1.66 mmol) in THF (12 mL) and the mixture stirred at rt for 1 h. The solvent was evaporated and the residue purified by flash column chromatography (petroleum ether/EtOAc, 1:0-49:1) to provide **12** as a yellow oil (552 mg, 1.47 mmol, 89%).

R_f = 0.68 (petroleum ether/EtOAc, 1:1); $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 7.54-7.52 (m, 2H), 7.45-7.43 (m, 2H), 7.41-7.31 (m, 6H), 6.81 (s, 1H), 5.08 (s, 2H), 5.06 (s, 2H), 3.93 (s, 3H), 3.91 (s, 3H), 3.22 (s, 1H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 149.2 (C), 148.7 (C), 147.6 (C), 145.4 (C), 137.5 (C), 136.8 (C), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 128.2 (CH), 127.5 (CH), 113.2 (CH), 111.5 (C), 80.9 (CH), 80.0 (C), 76.0 (CH_2), 71.5 (CH_2), 61.6 (CH_3), 61.5 (CH_3); $\text{IR } \nu_{\text{max}}$: 3280, 2934, 2107, 1591, 1567, 1483, 1451, 1434, 1412; HRMS (ESI): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{24}\text{H}_{23}\text{O}_4^+$: 375.1591, found: 375.1582.

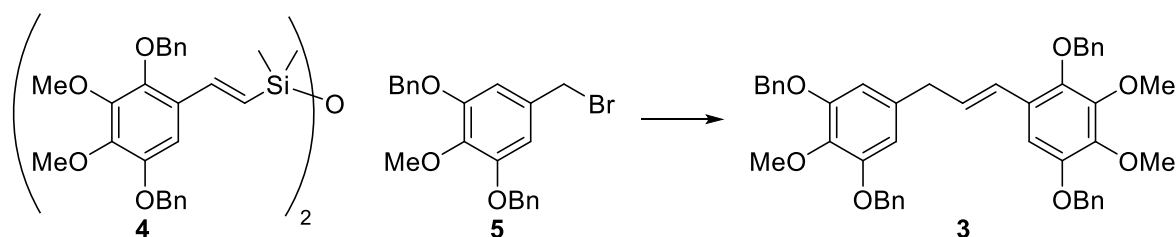
1,3-Bis[(E)-2-(2,5-bis(benzyloxy)-3,4-dimethoxyphenyl)vinyl]-1,1,3,3-tetramethyldisiloxane, **4**



$\text{P}(t\text{-Bu})_3$ (1.0 M in toluene, 22 μL , 22 μmol) was added to $\text{Pt}(\text{DVDS})$ (0.1 M in xylenes, 22 μL , 2.2 μmol) at 0 °C and stirred for 5 min. 1,1,3,3-Tetramethyldisiloxane (145 mg, 1.08 mmol) was then added. After stirring for 5 min at 0 °C, a solution of **12** (810 mg, 2.16 mmol) in toluene (6 mL) was added and the mixture heated to 40 °C for 16 h. After cooling, the solvent was evaporated and the residue purified by flash column chromatography (petroleum ether/EtOAc, 1:0-9:1) to provide **4** as a white solid (769 mg, 0.871 mmol, 81%).

R_f = 0.44 (petroleum ether/EtOAc, 3:1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.45–7.43 (m, 8H), 7.39–7.30 (m, 12H), 7.23 (d, 2H, J = 19.4 Hz), 6.89 (s, 2H), 6.23 (d, 2H, J = 19.4 Hz), 5.05 (s, 4H), 4.91 (s, 4H), 3.92 (s, 6H), 3.91 (s, 6H), 0.18 (s, 12H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 149.1 (C), 147.5 (C), 144.9 (C), 144.2 (C), 138.2 (CH), 137.5 (C), 137.2 (C), 128.7 (CH), 128.7 (CH), 128.6 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.2 (C), 105.6 (CH), 76.3 (CH_2), 71.5 (CH_2), 61.5 (CH_3), 61.5 (CH_3), 1.0 (CH_3); **IR** ν_{max} : 3030, 2941, 1592, 1569, 1485, 1450, 1435, 1418; **HRMS** (ESI): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{52}\text{H}_{58}\text{O}_9^{28}\text{Si}_2\text{Na}^+$: 905.3517, found: 905.3513.

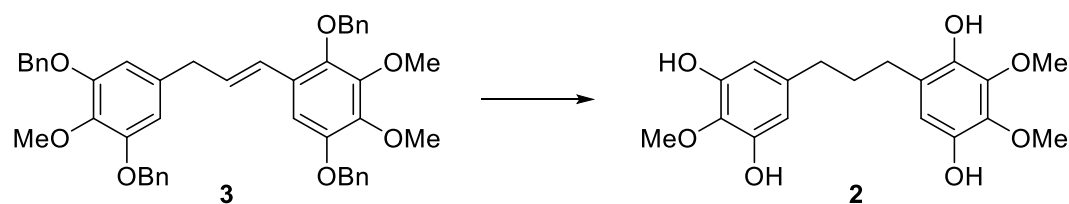
1,4-Bis(benzyloxy)-5-[(1*E*)-3-(3,5-bis(benzyloxy)-4-methoxyphenyl)prop-1-en-1-yl]-2,3-dimethoxybenzene, **3**



TBAF (1.0 M in THF, 0.83 mL, 0.83 mmol) was added to a solution of **4** (244 mg, 0.276 mmol), **5** (171 mg, 0.414 mmol) and allyl palladium chloride dimer (5.0 mg, 0.014 mmol) in THF (0.25 mL) and the mixture stirred at rt for 16 h. The reaction was then filtered through a plug of SiO_2 and the filtrate evaporated. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 97:3-19:1) to provide **3** as a pale yellow oil (235 mg, 0.332 mmol, 80%).

R_f = 0.34 (petroleum ether/EtOAc, 3:1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.47–7.27 (m, 20H), 6.79 (s, 1H), 6.65 (d, 1H, J = 15.8 Hz), 6.50 (s, 2H), 6.12 (dt, 1H, J = 15.8, 6.9 Hz), 5.09 (s, 4H), 5.08 (s, 2H), 4.92 (s, 2H), 3.96 (s, 3H), 3.94 (s, 3H), 3.89 (s, 3H), 3.38 (d, 2H, J = 6.5 Hz); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 152.7 (C), 149.1 (C), 147.6 (C), 144.3 (C), 143.4 (C), 138.1 (C), 137.6 (C), 137.4 (C), 137.2 (C), 135.8 (C), 129.4 (CH), 128.7 (CH_2), 128.6 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 126.4 (C), 125.4 (CH), 108.5 (CH), 106.1 (CH), 76.0 (CH_2), 71.6 (CH_2), 71.3 (CH_2), 61.6 (CH_3), 61.5 (CH_3), 61.1 (CH_3), 39.9 (CH_2); **IR** ν_{max} : 3032, 2933, 1590, 1498, 1487, 1454, 1434; **HRMS** (ESI): $[\text{M}+\text{Na}]^+$ calcd. for $\text{C}_{46}\text{H}_{44}\text{O}_7\text{Na}^+$: 731.2985, found: 731.2981.

1,4-Dihydroxy-5-[3-(3,5-dihydroxy-4-methoxyphenyl)propyl]-2,3-dimethoxybenzene, **2**

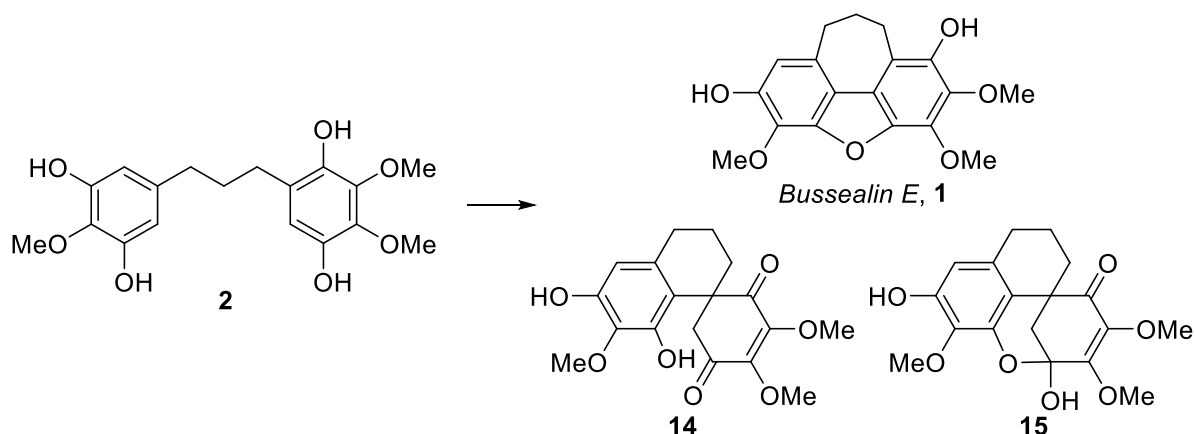


Pd/C (5 wt% Pd, 71 mg, 0.033 mmol) was added to a solution of **3** (235 mg, 0.332 mmol) in EtOAc (3 mL). A H_2 balloon was applied and the reaction stirred at rt for 24 h. The mixture was then filtered

through Celite and the filtrate evaporated. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 3:1-2:3) to provide **2** as a pale yellow oil (90 mg, 0.257 mmol, 77%).

R_f = 0.15 (petroleum ether/EtOAc, 1:1); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.48 (s, 1H), 6.36 (s, 2H), 5.34 (s, 2H), 5.33 (s, 1H), 5.20 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H), 2.57 (t, 2H, J = 7.6 Hz), 2.51 (t, 2H, J = 7.7 Hz), 1.90-1.82 (m, 2H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3): δ 148.7 (C), 141.7 (C), 140.4 (C), 139.8 (C), 139.2 (C), 137.4 (C), 132.7 (C), 123.7 (C), 110.6 (CH), 108.2 (CH), 61.3 (CH_3), 60.94 (CH_3), 60.90 (CH_3), 35.3 (CH_2), 31.0 (CH_2), 29.4 (CH_2); $\text{IR } \nu_{\text{max}}$: 3390, 2939, 1597, 1525, 1498, 1463, 1436; HRMS (ESI): $[\text{M}+\text{H}]^+$ calcd. for $\text{C}_{18}\text{H}_{23}\text{O}_7^+$: 351.1438, found: 351.1429.

9,10-Dihydro-2,7-dihydroxy-3,5,6-trimethoxy-8*H*-cyclohepta[*klm*]dibenzofuran, Bussealin E, **1**; 6',8'-dihydroxy-3,4,7'-trimethoxy-3',4'-dihydro-2'*H*-spiro[cyclohexane-1,1'-naphthalen]-3-ene-2,5-dione, **14**; and 2,10-dihydroxy-3,4,11-trimethoxy-7,8-dihydro-6*H*-2,5a-methanonaphtho[1,8-*bc*]oxocin-5(2*H*)-one, **15**



Preparation of $\text{FeCl}_3/\text{SiO}_2$:

Silica gel (3.30 g) was added to a solution of FeCl_3 (500 mg, 3.08 mmol) in Et_2O (6.3 mL) and MeOH (0.7 mL). The solvent was removed *in vacuo* to provide a yellow solid with the consistency of silica, $\text{FeCl}_3/\text{SiO}_2$ (0.8 mmol FeCl_3/g).

Reaction:

$\text{FeCl}_3/\text{SiO}_2$ (560 mg, 0.450 mmol FeCl_3) was added in one portion to a solution of **2** (75.0 mg, 0.214 mmol) in CH_2Cl_2 (1.6 mL) and the mixture was stirred at rt for 3.5 h. The mixture was then filtered and the filtrate evaporated. The residue was re-dissolved in toluene (3 mL) and MeOH (0.5 mL), *p*-TsOH $\cdot\text{H}_2\text{O}$ (102 mg, 0.535 mmol) was added and the reaction heated to reflux for 18 h. After cooling, the solvent was evaporated and the residue purified by flash column chromatography (petroleum ether/EtOAc, 9:1) to provide **1** as an off-white solid (7.0 mg, 0.021 mmol, 10%) and **14**, which exists as a 3:1 mix with **15** in solution, as an off-white solid (32 mg, 0.092 mmol, 43%).

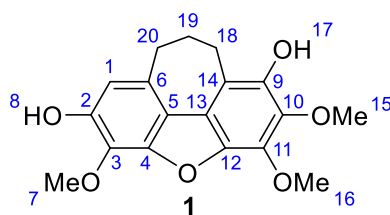
1: R_f = 0.14 (petroleum ether/EtOAc, 4:1); $^1\text{H NMR}$ (500 MHz, CDCl_3): δ 6.69 (s, 1H), 5.74 (s, 1H), 5.69 (s, 1H), 4.233 (s, 3H), 4.231 (s, 3H), 4.00 (s, 3H), 3.13-3.10 (4H, m), 2.18-2.15 (m, 2H); $^{13}\text{C NMR}$ (126 MHz, CDCl_3): δ 146.5 (C), 146.2 (C), 142.3 (C), 140.7 (C), 136.4 (C), 135.5 (C), 132.0 (C), 129.7 (C), 120.5

(C), 118.2 (C), 115.0 (C), 110.1 (CH), 61.7 (CH₃), 60.81 (CH₃), 60.78 (CH₃), 35.5 (CH₂), 28.7 (CH₂), 24.3 (CH₂); **IR** ν_{max} : 3440, 2928, 1635, 1608, 1523, 1449, 1408; **HRMS** (ESI): [M-H]⁻ calcd. for C₁₈H₁₇O₆⁻: 329.1031, found: 329.1031.

These data are consistent with those previously reported.⁵

14/15 (labelled as A/B respectively for NMR data): **R_f** = 0.29 (petroleum ether/EtOAc, 1:3); **¹H NMR** (500 MHz, CDCl₃): δ 6.38 (s, 0.33H, B), 6.27 (s, 1H, A), 5.70 (s, 1H, A), 5.65 (s, 0.33H, B), 5.22 (br s, 1H, A), 4.74 (s, 0.33H, B), 4.08 (s, 1H, B), 4.04 (s, 3H, A), 4.00 (s, 3H, A), 3.87 (s, 1H, B), 3.82 (s, 3H, A), 3.56 (s, 1H, B), 3.44 (dd, 1H, *J* = 16.1, 1.0 Hz, A), 2.87 (d, 1H, *J* = 16.0 Hz, A), 2.73-2.61 (m, 2.33H, A/B), 2.58-2.49 (m, 0.66H, B), 2.40-2.32 (m, 0.33H, B), 2.30 (d, 0.33H, *J* = 12.8 Hz, B), 2.08 (d, 0.33H, *J* = 12.8 Hz, B), 1.91-1.81 (m, 3H, A), 1.77-1.68 (m, 1H, A), 1.64-1.61 (m, 0.33H, B), 1.40-1.34 (m, 0.33H, B); **¹³C NMR** (126 MHz, CDCl₃): δ 198.3 (C^A), 196.1 (C^B), 194.1 (C^A), 153.2 (C^B), 149.2 (C^A), 148.7 (C^B), 148.4 (C^A), 147.5 (C^A), 145.9 (C^A), 145.5 (C^B), 136.15 (C^B), 136.10 (C^B), 134.8 (C^A), 133.21 (C^B), 133.17 (C^A), 117.3 (C^A), 110.9 (C^B), 108.5 (CH^A), 107.6 (CH^B), 95.2 (C^B), 61.5 (CH₃^A), 61.4 (CH₃^B), 61.1 (CH₃^B), 60.9 (CH₃^A), 60.85 (CH₃^B), 60.77 (CH₃^A), 49.3 (C^A), 47.5 (CH₂^A), 44.5 (C^B), 39.6 (CH₂^B), 36.1 (CH₂^A), 29.6 (CH₂^A), 28.0 (CH₂^B), 27.8 (CH₂^B), 20.3 (CH₂^B), 19.3 (CH₂^A); **IR** ν_{max} : 3267, 2936, 1695, 1657, 1595, 1519, 1454, 1435; **HRMS** (ESI): [M+H]⁺ calcd. for C₁₈H₂₁O₇⁺: 349.1282, found: 349.1271.

Table SI1: NMR comparison table of natural and synthetic samples



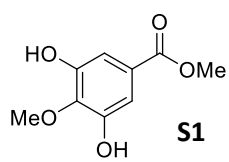
Bussealin E

Position	Reported ^1H , δ (ppm) ^a	Observed ^1H , δ (ppm) ^b	$\Delta\delta$ (ppm)	Reported ^{13}C , δ (ppm) ^a	Observed ^{13}C , δ (ppm) ^b	$\Delta\delta$ (ppm)
1	6.70 s	6.69 s	-0.01	110.1	110.1	0
2				146.5	146.5	0
3				129.7	129.7	0
4				146.2	146.2	0
5				118.2	118.2	0
6				131.7	132.0	+0.3
7	4.24 s	4.23 s	-0.01	60.8	60.8	0
8	5.69 s	5.69 s	0			
9				142.3	142.3	0
10				136.5	136.4	-0.1
11				135.6	135.5	-0.1
12				140.7	140.7	0
13				120.6	120.5	-0.1
14				115.0	115.0	0
15	4.01 s	4.00 s	-0.01	61.7	61.7	0
16	4.24 s	4.23 s	-0.01	60.8	60.8	0
17	5.75 s	5.74 s	-0.01			
18	3.13 m	3.13-3.10 m	0	28.7	28.7	0
19	2.17 m	2.18-2.15 m	0	24.3	24.3	0
20	3.12 m	3.13-3.10 m	0	35.5	35.5	0

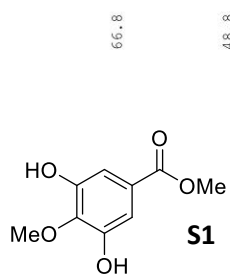
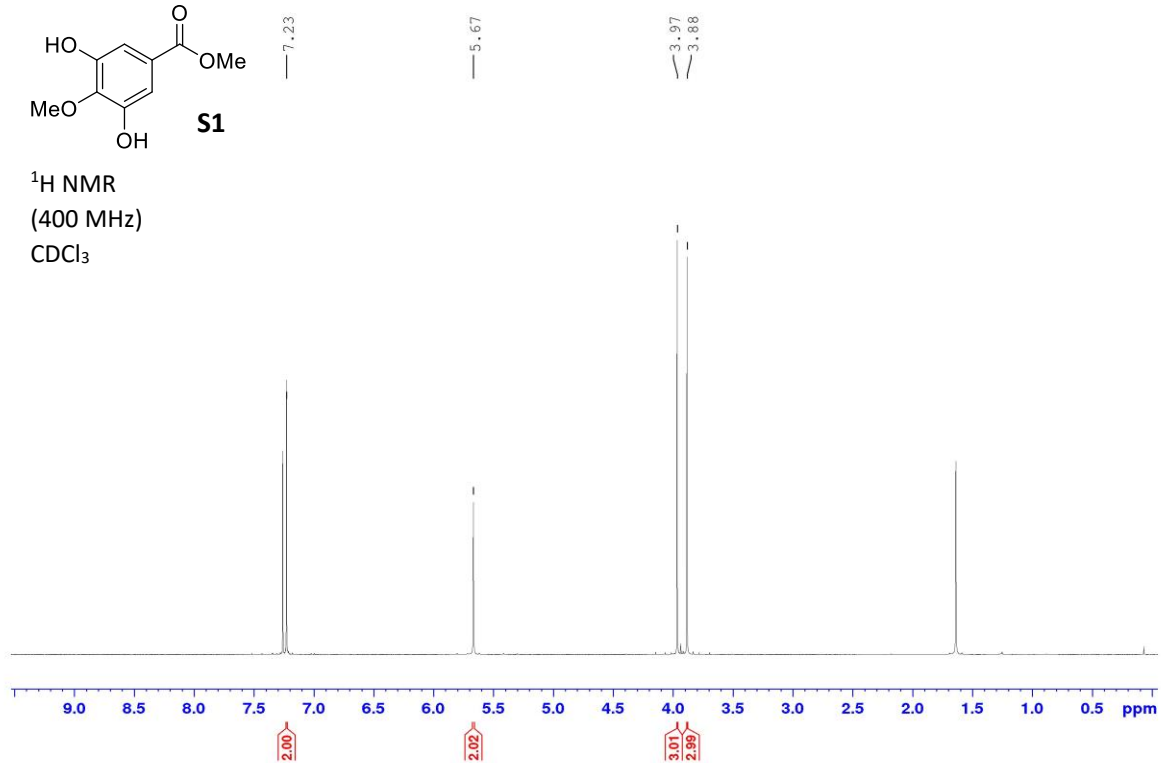
^a ^1H NMR (600 MHz, CDCl_3) and ^{13}C NMR (150 MHz, CDCl_3) data reported following isolation by Pan *et al.*; ^b ^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR (126 MHz, CDCl_3) data reported following synthesis in this report.

References

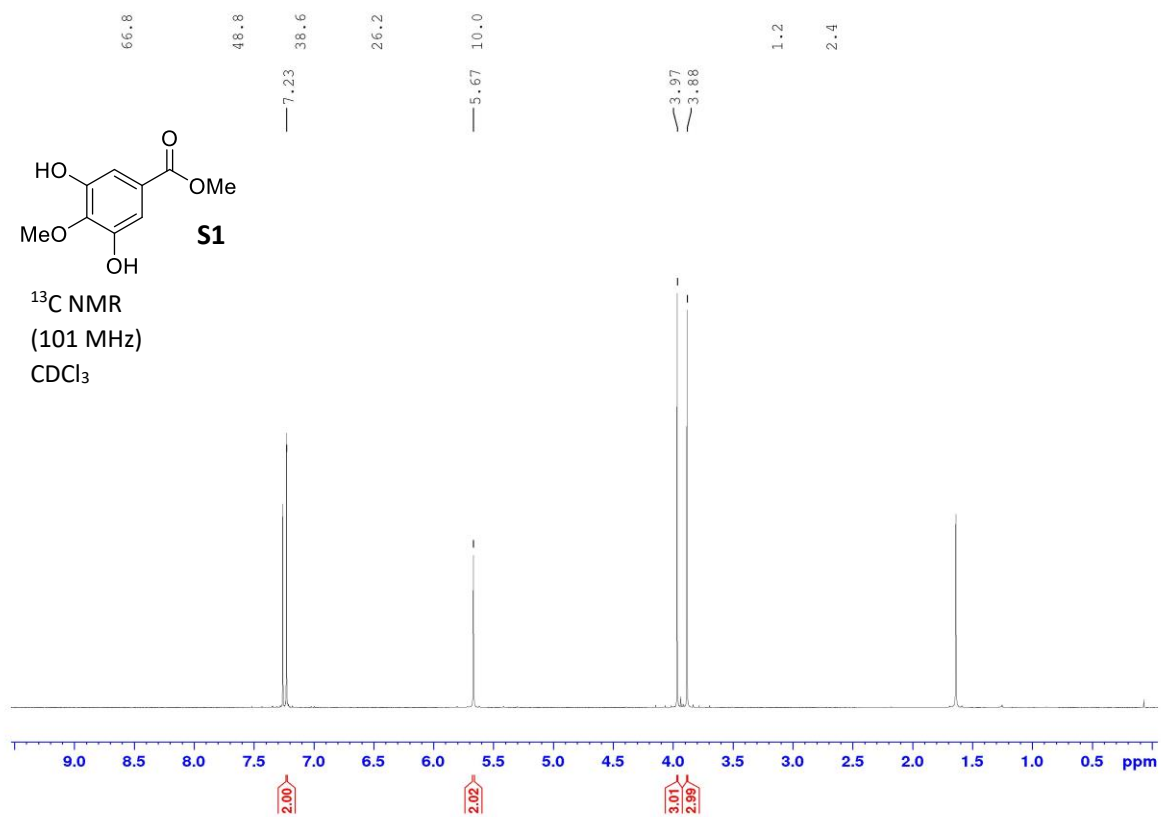
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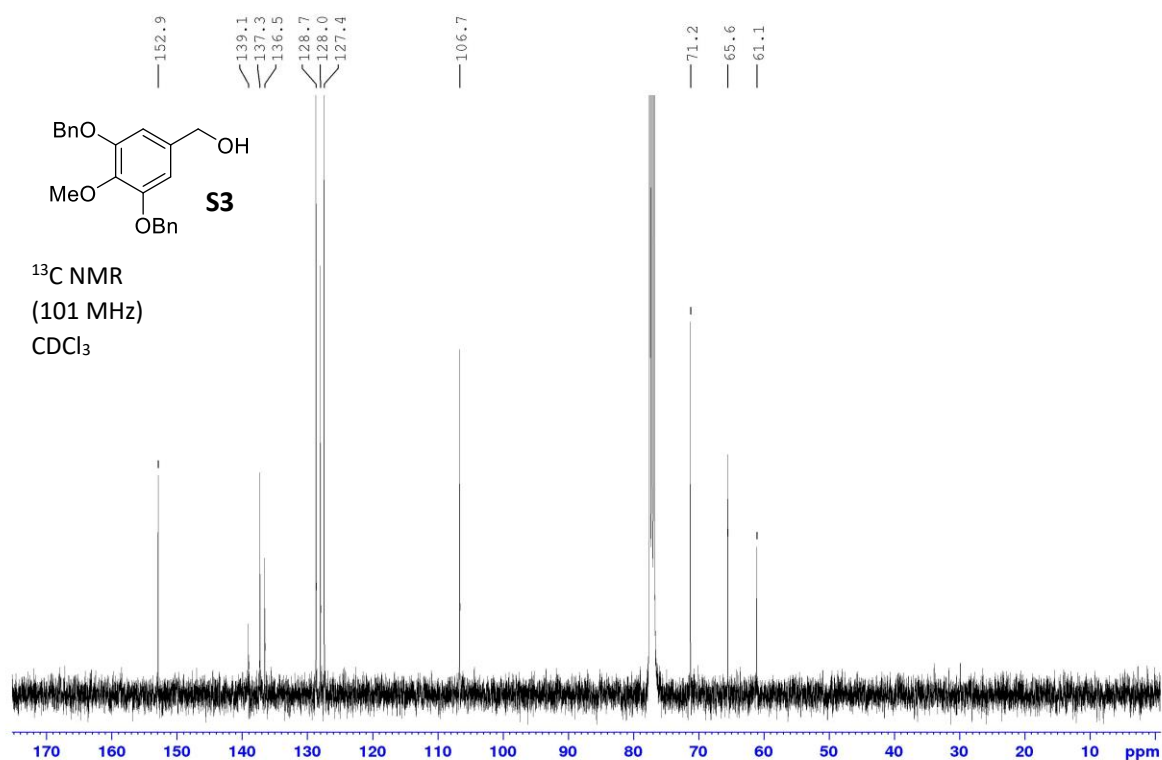
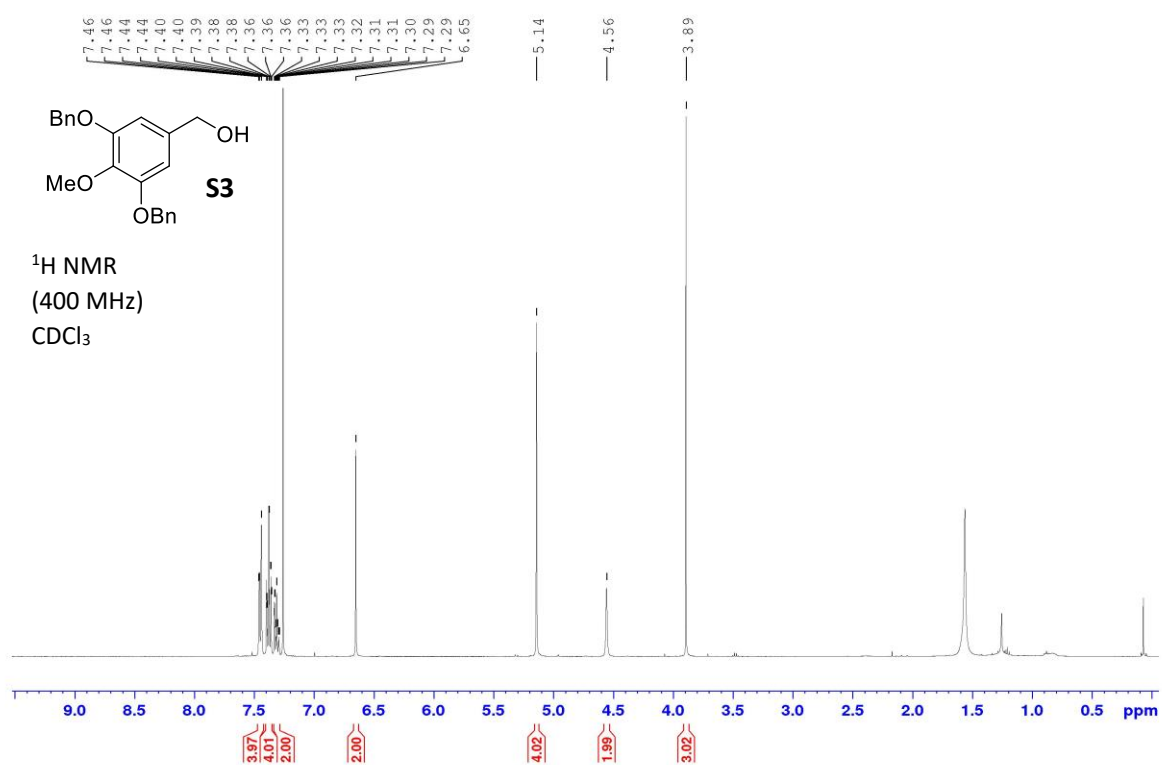


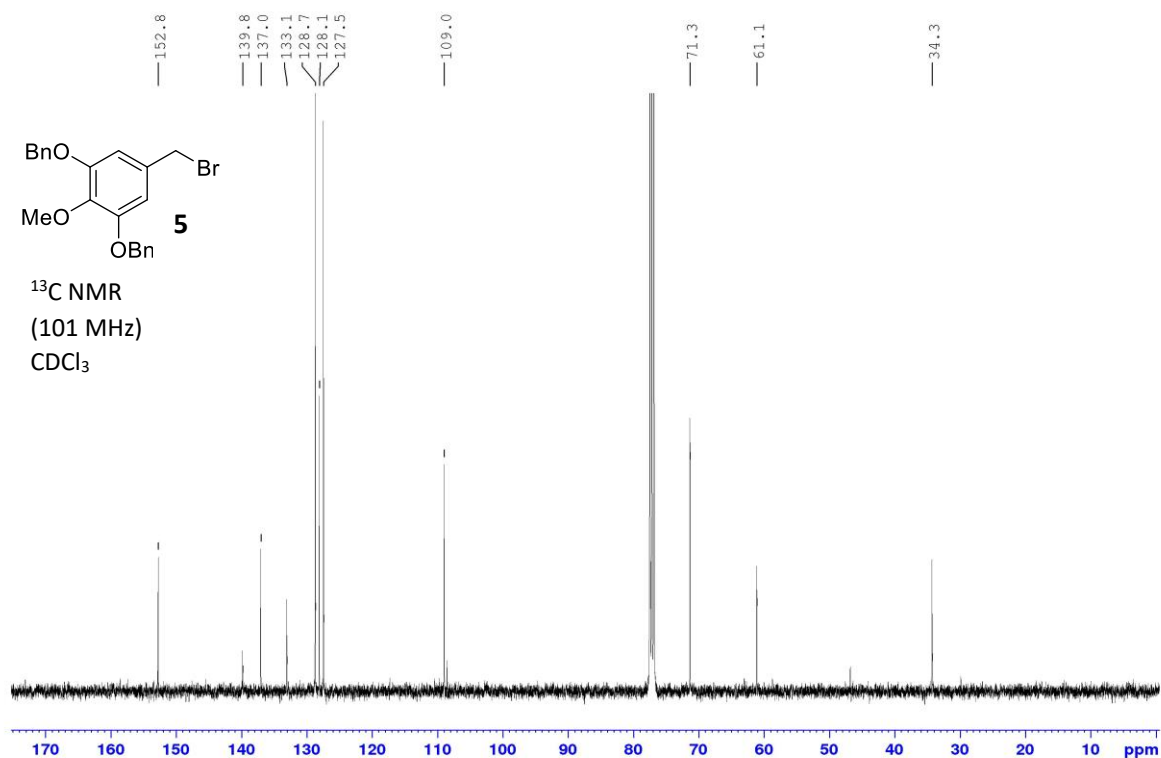
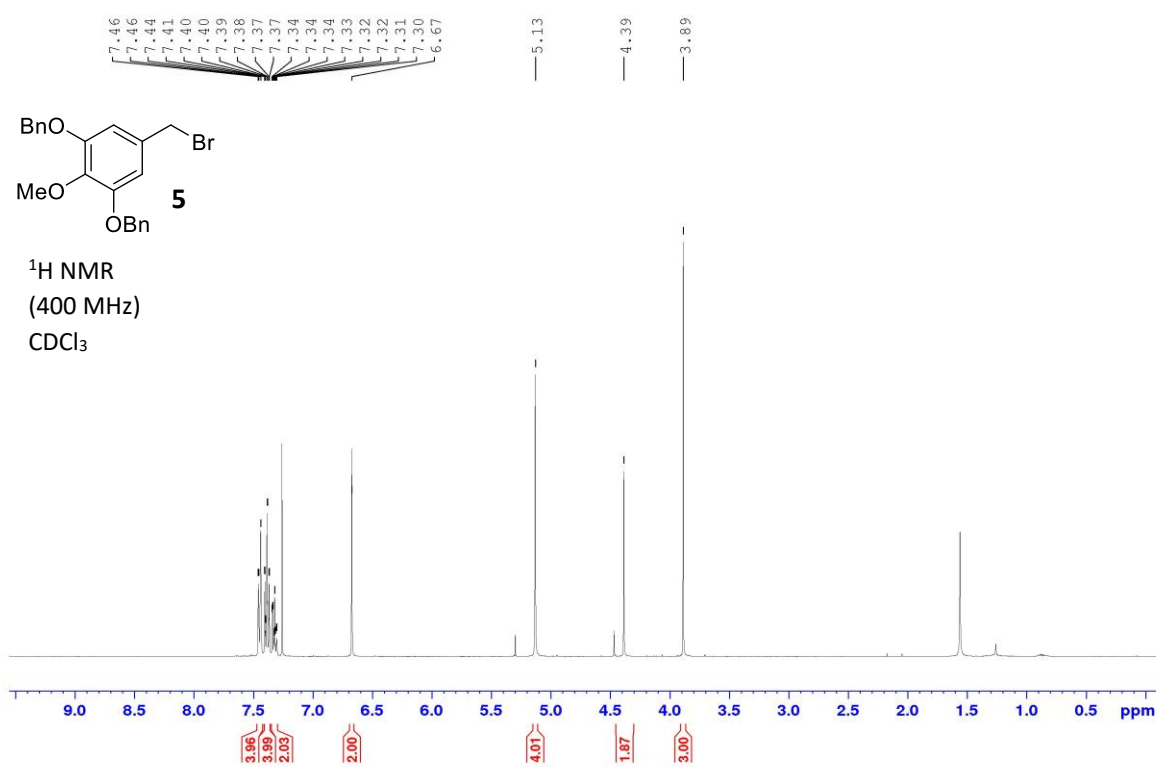
¹H NMR
(400 MHz)
CDCl₃

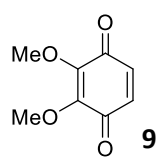


¹³C NMR
(101 MHz)
CDCl₃

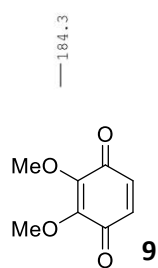
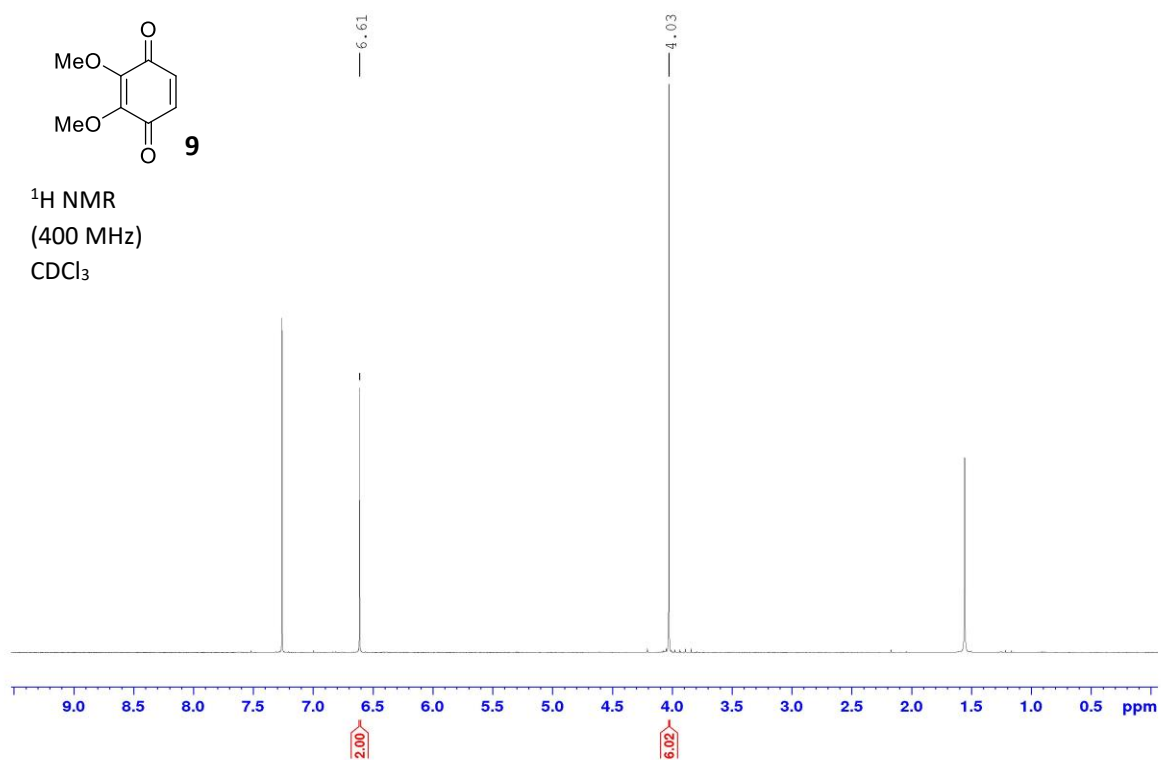








¹H NMR
(400 MHz)
CDCl₃



¹³C NMR
(101 MHz)
CDCl₃

