

Electronic Supplementary Information

Synthesis of Lamellarin Alkaloids Using Orthoester-Masked α -Keto Acids

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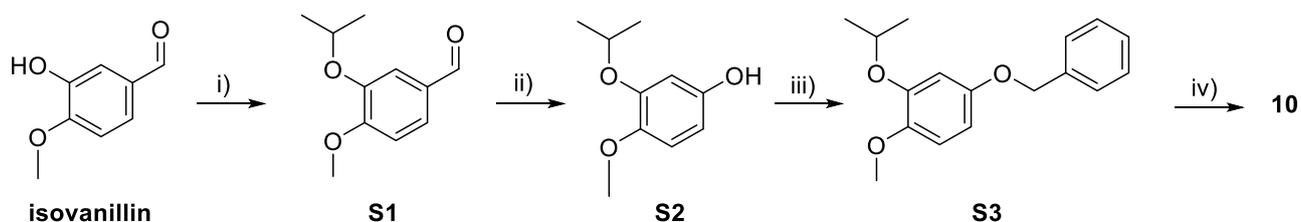
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S1. Alternative Synthesis of 1-(Benzyloxy)-2-bromo-5-isopropoxy-4-methoxybenzene (10)

An alternative synthesis of 1-(benzyloxy)-2-bromo-5-isopropoxy-4-methoxybenzene (**10**) is feasible from **isovanillin**. Initial phenol protection with 2-bromopropane to give **S1**¹ was followed by Baeyer-Villiger oxidation with *m*-CPBA and a B_{Ac}2 cleavage with K₂CO₃ to give phenol **S2** in 83% yield.¹ Protection of the phenol moiety with benzyl bromide gave **S3** in 99% yield,² and subsequent bromination with NBS gave the desired aryl bromide **10** (97% yield).¹



i) K₂CO₃ (2 eq.), *i*PrBr (1.5 eq.), DMSO, 55 °C, 2.5 h, 96%; ii) *m*-CPBA (1.1 eq.), CH₂Cl₂, 0 °C, 4 h, then K₂CO₃ (2.4 eq.), MeOH, rt, 13 h, 83%; iii) K₂CO₃ (2 eq.), BnBr (1.5 eq.), DMF, 0 °C to rt, 13 h, 99%; iv) NBS (1.1 eq.), DMF, 0 °C to rt, 1 h, 97%.

Scheme S1. Alternative synthesis of 1-(benzyloxy)-2-bromo-5-isopropoxy-4-methoxybenzene (**10**)

S2. General Methods and Materials

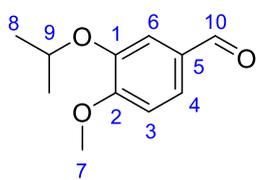
Solvents were dried over 4 Å molecular sieves or activated alumina columns. All commercially available reagents were used without further purification unless otherwise specified. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) was purchased from Alfa Aesar. NaOtBu solution (2 M in THF) was purchased from Sigma-Aldrich (grade ZerO2®). All anhydrous reactions were carried out in flame-dried glassware and under an inert atmosphere of argon unless otherwise specified. Brine refers to a saturated aqueous solution of NaCl. ¹H, ¹³C and ¹⁹F NMR experiments were conducted on a Bruker AVII400 or AVIII400 instrument at 400, 101 and 377 MHz respectively. Chemical shifts, δ, are reported relative to residual solvent peaks and quoted in parts per million (ppm) to the nearest 0.01 ppm with splitting patterns recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), heptet (hept), doublet of doublets (dd), multiplet (m) and broad singlet (br s). Scalar coupling constants, *J*, are measured in Hz accurate to one decimal place. Infrared spectra were recorded as thin films or neat samples on a Bruker Tensor 27 FT-IR spectrometer equipped with Attenuated Total Reflectance sampling accessories. High-resolution mass spectra are given to five decimal places and were recorded on a Bruker MicroTof (resolution = 10000 FWHM) under conditions of electrospray ionization (ESI), electronic ionization (EI), chemical ionization (CI) and atmospheric-pressure chemical ionization (APCI). Melting points were obtained from recrystallized samples using a Leica VMTG heated-stage microscope. The solvent(s) used for recrystallization are quoted in

parentheses after the melting point. Flash column chromatography was performed using silica gel (60 Å, 0.033-0.070 mm, BDH). TLC analysis was performed on Merck Kieselgel 60 F₂₅₄ 0.25 mm pre-coated silica plates. 1-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (**1**),³ and 1-bromo-4-isopropoxybenzene (**19**)⁴ were prepared according to literature procedures.

Systematic names were generated by the computer program ChemDraw. However, the numbering on the structures does not correspond to this systematic name. The NMR assignments follow the numbering system shown on the structures for straightforward comparison of data

S3. Experimental Procedures and Spectroscopic Data

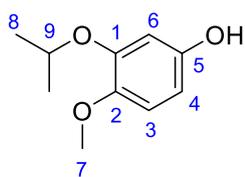
3-Isopropoxy-4-methoxybenzaldehyde (**S1**)



Isovanillin (15.0 g, 98.5 mmol, 1.0 eq.) was dissolved in DMSO (295 mL) in a flame-dried round-bottom flask flushed with argon. Anhydrous K₂CO₃ (27.3 g, 197 mmol, 2.0 eq.) was added to the stirred solution and subsequently, 2-bromopropane (13.8 mL, 148 mmol, 1.5 eq.) was added in one portion at rt,

before the reaction mixture was heated at 55 °C for 2.5 h. The reaction mixture was cooled to rt and diluted with water. The mixture was extracted with Et₂O (3 × 100 mL) and the combined organic extracts were washed successively with 10% aq. NaOH (150 mL), water (150 mL) and brine (100 mL), before being dried over Na₂SO₄. The solvent was evaporated *in vacuo* and the residue was recrystallized to give the *title compound S1* (18.4 g, 96%) as a pale-yellow solid. **m.p.** 32–35 °C (*n*-pentane/Et₂O); **IR** ν_{max} (thin film): 2977, 1687, 1584, 1508, 1435, 1396, 1338, 1264, 1239, 1160, 1132, 1023, 914, 810 cm⁻¹; **¹H NMR (400 MHz, CDCl₃)** δ = 9.83 (1H, s, C(10)HO), 7.44 (1H, d, *J* = 8.1 Hz, HC(4)_{Ar}), 7.41 (1H, s, HC(6)_{Ar}), 6.97 (1H, d, *J* = 8.1 Hz, HC(3)_{Ar}), 4.64 (1H, hept, *J* = 6.1 Hz, OC(9)H), 3.94 (3H, s, OC(7)H₃), 1.40 (6H, d, *J* = 6.1 Hz, C(8)H₃); **¹³C NMR (101 MHz, CDCl₃)** δ = 191.1, 155.7, 148.0, 130.2, 126.7, 112.7, 111.0, 71.4, 56.3, 22.0. Spectroscopic data are consistent with those previously reported in the literature.⁵

3-Isopropoxy-4-methoxyphenol (**S2**)

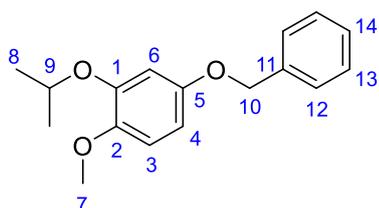


Benzaldehyde **S1** (10.0 g, 51.5 mmol, 1.0 eq.) was dissolved in DCM (100 mL), cooled to 0 °C under argon atmosphere and *m*-chloroperbenzoic acid (25% w/w, 13.2 g, 57.1 mmol, 1.1 eq.) was added in 6 portions every 10 minutes to the stirred solution. After being stirred for 3 h, an additional *m*-chloroperbenzoic acid (0.6 g, 5 mol%, 2.6 mmol) was added. The reaction mixture was left to stir for an additional 1 h

after which time it was quenched by the addition of saturated aq. NaHCO₃ (30 mL). The mixture was

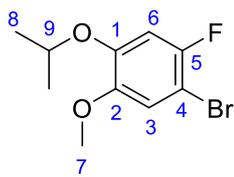
diluted with water and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 , and evaporated *in vacuo*. The residue was dissolved in methanol (200 mL) and K_2CO_3 (17.3 g, 125 mmol, 2.4 eq.) was added in 4 portions over 20 mins to the solution at rt. After being stirred for 13 h, the solvent was evaporated *in vacuo* before water (100 mL) was added to the residue and the product was extracted with Et_2O (3×100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and evaporated *in vacuo*. Recrystallization gave the *title compound S2* (7.8 g, 83%) as a colorless solid. **m.p.** 120–124 °C (*n*-pentane/ Et_2O) [lit.¹ 121–122 °C (*n*-pentane/ Et_2O)]; **IR** ν_{max} (thin film): 3418 (O-H), 2980, 2836, 1605, 1509, 1462, 1374, 1285, 1222, 1163, 1122, 1029, 995, 921, 834 cm^{-1} ; **^1H NMR (400 MHz, CDCl_3)** δ = 6.73 (1H, d, J = 8.5 Hz, $\text{HC}(3)_{\text{Ar}}$), 6.48 (1H, d, J = 2.1 Hz, $\text{HC}(6)_{\text{Ar}}$), 6.34 (1H, dd, J = 8.5, 2.1 Hz, $\text{HC}(4)_{\text{Ar}}$), 4.56 (1H, s, OH), 4.49 (1H, hept, J = 6.1 Hz, $\text{OC}(9)H$), 3.79 (3H, s, $\text{OC}(7)H_3$), 1.37 (6H, d, J = 6.1 Hz, $\text{C}(8)H_3$); **^{13}C NMR (101 MHz, CDCl_3)** δ = 150.3, 148.1, 144.2, 113.5, 106.6, 104.1, 71.4, 56.8, 22.0. Physical and spectroscopic data are consistent with those previous reported in the literature.¹

4-(Benzyloxy)-2-isopropoxy-1-methoxybenzene (S3)



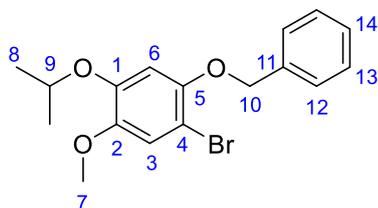
Phenol **S2** (2.0 g, 11 mmol, 1.0 eq.) was dissolved in DMF (22 mL) and cooled to 0 °C before K_2CO_3 (2.3 g, 16.5 mmol, 1.5 eq.) and benzyl bromide (2.2 mL, 18.7 mmol, 1.7 eq.) were subsequently added to the stirred solution. The stirred solution was left to warm to rt over 13 h, after which time it was quenched with saturated aq. NH_4Cl (20 mL) and the product was extracted with Et_2O (3×50 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and filtered. The solvent was evaporated *in vacuo* and the residue was recrystallized to give the *title compound S3* (2.94 g, 99%) as colorless needles. **m.p.** 56–57 °C (*n*-pentane/ Et_2O); **IR** ν_{max} (thin film): 2981, 2889, 1608, 1508, 1457, 1382, 1258, 1227, 1164, 1137, 1080, 1044, 1028, 955 cm^{-1} ; **^1H NMR (400 MHz, CDCl_3)** δ = 7.28 - 7.45 (5H, m, $\text{HC}(12, 13, 14)_{\text{Ar}}$), 6.79 (1H, d, J = 9.1 Hz, $\text{HC}(3)_{\text{Ar}}$), 6.60 (1H, s, $\text{HC}(6)_{\text{Ar}}$), 6.49 (1H, d, J = 9.1 Hz, $\text{HC}(4)_{\text{Ar}}$), 5.00 (2H, s, $\text{OC}(10)H_2\text{Ph}$), 4.49 (1H, hept, J = 6.1 Hz, $\text{OC}(9)H$), 3.81 (3H, s, $\text{OC}(7)H_3$), 1.35 (6H, d, J = 6.1 Hz, $\text{C}(8)H_3$); **^{13}C NMR (101 MHz, CDCl_3)** δ = 153.4, 148.2, 145.0, 137.2, 128.6, 128.0, 127.6, 112.8, 105.0, 104.7, 71.3, 70.7, 56.7, 22.1; **HRMS** (Cl^+) Found $[\text{M}+\text{H}]^+ = 273.1480$; $\text{C}_{17}\text{H}_{21}\text{O}_3$ requires 273.1485, Δ –1.91 ppm.

1-Bromo-2-fluoro-4-isopropoxy-5-methoxybenzene (**S4**)



To a solution of 4-bromo-5-fluoro-2-methoxyphenol (**11**) (1.0 g, 4.5 mmol, 1.0 eq.) in DMSO (10 mL) was added K_2CO_3 (1.9 g, 14 mmol, 3.0 eq.) and 2-bromopropane (1.3 mL, 14 mmol, 3.0 eq.) before a reflux condenser was attached and the stirred mixture was heated at 70 °C for 5 h. After this time, water (100 mL) and DCM (50 mL) were added after cooling to rt, before the organic layer was separated and dried with $MgSO_4$. The residue was dry loaded onto SiO_2 and purified by flash column chromatography (SiO_2 ; *n*-pentane/acetone, 95:5 to 90:10) to give the *title compound* **S4** (1.15 g, 97%) as pale-yellow needles. **m.p.** 52–57 °C (*n*-pentane/acetone); **IR** ν_{max} (thin film): 3115, 2978, 1601, 1500, 1334, 1176, 1109, 1008 cm^{-1} ; **1H NMR (400 MHz, $CDCl_3$)** δ = 6.96 (1H, d, $^4J_{H-F}$ = 6.7 Hz, C(3)H), 6.70 (1H, d, $^3J_{H-F}$ = 10.1 Hz, C(6)H), 4.51–4.42 (1H, m, C(9)H), 3.81 (3H, s, C(7)H₃), 1.36 (6H, d, J = 6.0 Hz, C(8)H₃); **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 153.5 (d, J_{CF} = 238 Hz), 147.6 (d, J_{CF} = 8.6 Hz), 147.2 (d, J_{CF} = 2.3 Hz), 115.8, 104.2 (d, J_{CF} = 25.9 Hz), 97.8 (d, J_{CF} = 23.3 Hz), 72.1, 56.7, 21.9; **^{19}F NMR (377 MHz, $CDCl_3$)** δ -115.9; **HRMS** expected ions not observed.

1-(Benzyloxy)-2-bromo-5-isopropoxy-4-methoxybenzene (**10**)

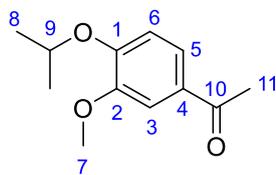


Method A: A solution of **S3** (500 mg, 1.84 mmol, 1.0 eq.) in DMF (2 mL) was cooled to 0 °C before a solution of NBS (340 mg, 1.92 mmol, 1.1 eq.) in DMF (2.5 mL) was added over 30 min *via* a syringe. After being stirred for 1 h, the reaction mixture was diluted with water at 0 °C and then allowed to warm to rt. The product was extracted with Et_2O (3 × 30 mL) and the combined organic extracts were washed with brine, dried over Na_2SO_4 and filtered. The solvent was evaporated *in vacuo*, and recrystallization from *c*-hexane gave the *title compound* **10** (620 mg, 97%) as pale orange needles. **m.p.** 72–73 °C (*c*-hexane); **IR** ν_{max} (thin film): 3034, 2976, 2932, 1581, 1501, 1456, 1441, 1394, 1379, 1311, 1268, 1213, 1177, 1110, 1030, 925, 842 cm^{-1} ; **1H NMR (400 MHz, $CDCl_3$)** δ = 7.28–7.50 (5H, m, HC(12, 13, 14)_{Ar}), 7.04 (1H, s, HC(3)_{Ar}), 6.57 (1H, s, HC(6)_{Ar}), 5.08 (2H, s, OC(10)H₂Ph), 4.39 (1H, hept, J = 6.1 Hz, OC(9)H), 3.80 (3H, s, OC(7)H₃), 1.28 (6H, d, J = 6.1 Hz, C(8)H₃); **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 149.1, 147.0, 145.9, 136.8, 128.6, 128.0, 127.4, 117.0, 106.0, 103.2, 72.3, 72.1, 56.7, 22.0; **HRMS (APCI⁺)** Found $[M+H]^+$ = 351.0583; $C_{17}H_{20}BrO_3$ requires 351.0590, Δ –2.1 ppm.

Method B: To a solution of benzyl alcohol (1.3 mL, 12.5 mmol, 4.0 eq.) in anhydrous NMP (13 mL), NaH (568 mg, 60% in mineral oil, 14.2 mmol, 4.6 eq.) was cautiously added portion wise at rt. After 20 mins the evolution of H_2 had subsided and the mixture was transferred using a syringe, equipped

with a short 10-gauge needle, to an RBF containing a stirred solution of **S4** (808 mg, 3.1 mmol, 1.0 eq.) in NMP (16 mL). The reaction was heated to 100 °C, gradually gaining a dark blue color, with continued stirring for 2 h. After this time the reaction was poured onto a mixture of crushed ice (200 g) and PhMe (200 mL) and allowed to warm to rt. The organic layer was separated, dry loaded onto SiO₂ and flash column chromatography (SiO₂; *n*-pentane/*t*-BuOMe, 95:5 to 90:10) gave the *title compound* **10** (940 mg, 86%) as pale-yellow needles. Data are consistent with those obtained *via* method A.

1-(4-Isopropoxy-3-methoxyphenyl)ethan-1-one (**S5**)

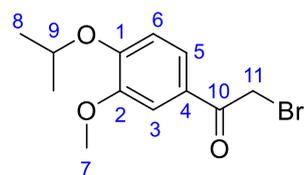


Acetovanillone (500 mg, 3.0 mmol, 1.0 eq.) was dissolved in DMSO (8.7 mL).

Anhydrous K₂CO₃ (830 mg, 6.0 mmol, 2.0 eq.) was added to the stirred solution, and subsequently 2-bromopropane (420 μL, 4.5 mmol, 1.5 eq.) was added in one portion at rt, before the reaction mixture was heated at 55 °C

for 3.5 h. The reaction mixture was cooled to rt and diluted with water. The biphasic mixture was extracted with Et₂O (3 × 50 mL) and the combined organic extracts were washed successively with 10% aq. NaOH (30 mL), water (30 mL), and brine (30 mL), before being dried over Na₂SO₄. The solvent was evaporated *in vacuo* and recrystallization of the residue gave the *title compound* **S5** (600 mg, 96%) as a pale yellow waxy solid. **m.p.** 31–32 °C (*n*-pentane/Et₂O); **IR** ν_{\max} (thin film): 2978, 2935, 1672 (C=O), 1585, 1507, 1464, 1416, 1385, 1374, 1356, 1264, 1218, 1175, 1149, 1133, 1108, 1078, 1032, 951, 876, 847, 810 cm⁻¹; **¹H NMR (400 MHz, CDCl₃)** δ = 7.55 (1H, d, *J* = 8.3 Hz, HC(5)_{Ar}), 7.53 (1H, s, HC(3)_{Ar}), 6.88 (1H, d, *J* = 8.3 Hz, HC(6)_{Ar}), 4.66 (1H, hept, *J* = 6.1 Hz, OC(9)*H*), 3.91 (3H, s, OC(7)*H*₃), 2.56 (3H, s, C(11)*H*₃), 1.41 (6H, d, *J* = 6.1 Hz, C(8)*H*₃); **¹³C NMR (101 MHz, CDCl₃)** δ = 197.0, 152.0, 150.0, 130.3, 123.3, 112.8, 110.8, 71.3, 56.2, 26.4, 22.0; **HRMS (ESI⁺)** Found [M+H]⁺ = 209.11729; C₁₂H₁₇O₃ requires 209.11722, Δ +0.33 ppm.

2-Bromo-1-(4-isopropoxy-3-methoxyphenyl)ethan-1-one (**8**)

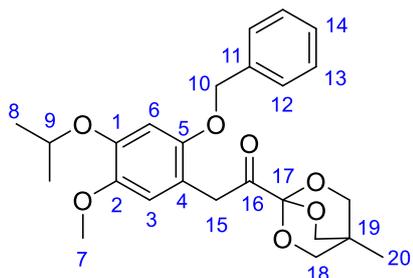


Acetophenone **S5** (139 mg, 0.67 mmol, 1.0 eq.) and (±)-10-camphorsulfonic acid (300 mg, 1.29 mmol, 1.9 eq.) were added to a flame-dried RBF containing acetonitrile (5 mL) over flame-dried 3 Å molecular sieves (*ca.* 500 mg). To the strongly stirred mixture was added NBS (119 mg, 0.67 mmol,

1.0 eq.) before refluxing at 85 °C for 1.5 h. After this time the mixture was cooled to rt before SiO₂ (*ca.* 3.0 g) was added and the solvent was removed *in vacuo*. The solid mixture was loaded onto a column for purification (SiO₂, *n*-pentane/acetone, 80:20) to give the *title compound* **8** (175 mg, 91%) as pale-yellow crystals. **m.p.** 70–71 °C (*c*-hexane); **IR** ν_{\max} (thin film): 2976, 1666, 1583, 1514, 1469,

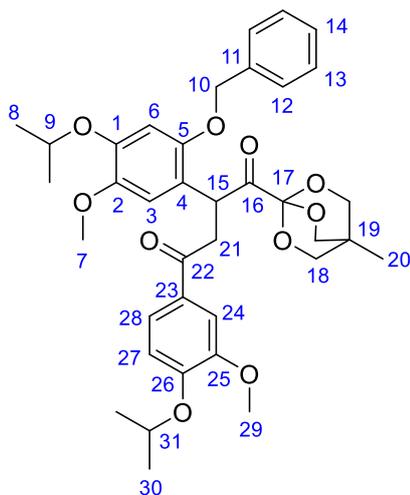
1421, 1388, 1290, 1239, 1153, 1111, 1024, 956, 860 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.57 (1H, d, J = 8.3 Hz, $\text{HC}(5)_{\text{Ar}}$), 7.53 (1H, s, $\text{HC}(3)_{\text{Ar}}$), 6.89 (1H, d, J = 8.3 Hz, $\text{HC}(6)_{\text{Ar}}$), 4.67 (1H, hept, J = 6.1 Hz, $\text{OC}(9)\text{H}$), 4.40 (2H, s, $\text{C}(11)\text{H}_2\text{Br}$), 3.90 (3H, s, $\text{OC}(7)\text{H}_3$), 1.41 (6H, d, J = 6.1 Hz, $\text{C}(8)\text{H}_3$); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 190.1, 152.8, 150.1, 126.7, 123.9, 112.6, 111.5, 71.4, 56.2, 30.6, 22.0; **HRMS** (ESI^+) Found $[\text{M}+\text{H}]^+$ = 287.02780; $\text{C}_{12}\text{H}_{16}\text{O}_3\text{Br}$ requires 287.02773, Δ +0.24 ppm.

2-[2-(Benzyloxy)-4-isopropoxy-5-methoxyphenyl]-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)ethan-1-one (9)



In a flame-dried Biotage[®] microwave vial flushed with argon, was added **10** (225 mg, 0.64 mmol, 1.1 eq.) methyl-OBO-ketone **1** (150 mg, 0.87 mmol, 1.5 eq.), $\text{Pd}(\text{dtbpf})\text{Cl}_2$ (19 mg, 29 μmol , 5 mol%) and THF (5.1 mL). After this NaOtBu (2M in THF, 720 μL , 1.45 mmol, 2.5 eq.) was added to the stirred solution and the vial was flushed with argon for 5 mins after which time the vial was sealed with an aluminium microwave vial cap (Reseal[™] septum). The solution was heated at 50 $^\circ\text{C}$ for 24 h. The resulting mixture was filtered through a short plug of SiO_2 using EtOAc as eluent, concentrated *in vacuo*, dry-loaded onto SiO_2 and purified by column chromatography (*n*-pentane/EtOAc, 60:40) to give the *title compound 9* (212 mg, 75%) as pale-yellow needles. **m.p.** 122–124 $^\circ\text{C}$ (*n*-pentane/Et₂O); **IR** ν_{max} (thin film): 3657, 2981, 2886, 1753 ($\text{C}=\text{O}$), 1509, 1462, 1383, 1252, 1220, 1154, 1075, 1051, 1004, 955 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.27–7.43 (5H, m, $\text{HC}(12, 13, 14)_{\text{Ar}}$), 6.64 (1H, s, $\text{HC}(3)_{\text{Ar}}$), 6.52 (1H, s, $\text{HC}(6)_{\text{Ar}}$), 4.97 (2H, s, $\text{OC}(10)\text{H}_2\text{Ph}$), 4.38 (1H, hept, J = 5.9 Hz, $\text{OC}(9)\text{H}$), 4.01 (6H, s, $\text{OC}(18)\text{H}_2$), 3.99 (2H, s, $\text{C}(15)\text{H}_2$), 3.77 (3H, s, $\text{OC}(7)\text{H}_3$), 1.29 (6H, d, J = 6.1 Hz, $\text{C}(8)\text{H}_3$), 0.87 (3H, s, $\text{C}(20)\text{H}_3$); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 195.9, 150.9, 146.9, 144.6, 137.5, 128.4, 127.6, 127.3, 115.9, 115.0, 103.9, 103.8, 73.1, 71.9, 71.4, 56.7, 37.9, 30.9, 22.2, 14.3; **HRMS** (APCI^+) Found $[\text{M}+\text{H}]^+$ = 443.20633; $\text{C}_{25}\text{H}_{31}\text{O}_7$ requires 443.20643, Δ –0.23 ppm.

2-[2-(Benzyloxy)-4-isopropoxy-5-methoxyphenyl]-4-(4-isopropoxy-3-methoxyphenyl)-1-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)butane-1,4-dione (7)



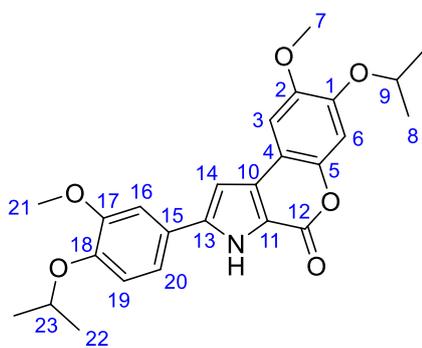
Method A: In a flame-dried RBF flushed with argon, **9** (44.3 mg, 0.10 mmol, 1.0 eq.) was dissolved in THF (1.0 mL) before NaOtBu (2M in THF, 60 μ L, 0.12 mmol, 1.2 eq.) was added and the resulted solution was left stirring for 20 mins. A solution of **8** (34.5 mg, 0.12 mmol, 1.2 eq.) in THF (1.0 mL) was added dropwise to the stirred solution of **9** *via* a syringe (addition rate: 6 mL/h). After complete addition, the solution was left to stir for an additional 1.5 h, after which time it was quenched with saturated aq. NH₄Cl (5 mL) and extracted with DCM (3 \times 30 mL). The combined organic extracts

were dried with Na₂SO₄, filtered, and the solvent was evaporated *in vacuo*. The residue was dry-loaded onto SiO₂ and purified by column chromatography (*n*-pentane/acetone, 80:20) to give the *title compound 7* (64.9 mg, 100%) as colorless needles.

Method B (one-pot): To a flame-dried Biotage[®] microwave vial flushed with argon was added **10** (112.4 mg, 0.32 mmol, 1.1 eq.), methyl-OBO-ketone **1** (75 mg, 0.44 mmol, 1.5 eq.), Pd(dtbpf)Cl₂ (9.5 mg, 14.5 μ mol, 5 mol%) and THF (2.5 mL). Subsequently, NaOtBu (2 M in THF, 360 μ L, 0.73 mmol, 2.5 eq.) was added *via* a syringe and the vial was flushed with argon for 5 mins after which time the vial was sealed with an aluminium microwave vial cap (Reseal[™] septum). The solution was heated at 50 $^{\circ}$ C for 52 h, after which time a solution of **8** (184 mg, 0.64 mmol, 2.0 eq.) in anhydrous THF (5 mL) was added dropwise *via* a syringe (addition rate: 5 mL/h). After complete addition, the solution was left to stir for an additional 30 min at 50 $^{\circ}$ C, after which time it was left to cool to rt, quenched with saturated aq. NH₄Cl (10 mL) and extracted with DCM (3 \times 30 mL). The combined organic extracts were dried with MgSO₄, filtered, and the solvent was evaporated *in vacuo*. The residue was dry-loaded onto SiO₂ and purified by column chromatography (*n*-pentane/acetone, 75:25) to give the *title compound 7* (161 mg, 78%) as colorless needles. **m.p.** 151–154 $^{\circ}$ C (*n*-pentane/Et₂O); **IR** ν_{\max} (thin film): 2976, 2935, 2880, 1741, 1674, 1593, 1508, 1464, 1417, 1263, 1213, 1106, 1069, 1035, 1002, 950 cm^{-1} ; **¹H NMR (400 MHz, CDCl₃)** δ = 7.52 (1H, d, J = 8.3 Hz, HC(28)_{Ar}), 7.50 (1H, s, HC(24)_{Ar}), 7.27 – 7.45 (5H, m, HC(12, 13, 14)_{Ar}), 6.80 (1H, d, J = 8.3 Hz, HC(27)_{Ar}), 6.65 (1H, s, HC(3)_{Ar}), 6.53 (1H, s, HC(6)_{Ar}), 5.37 (1H, dd, J = 9.9, 4.2 Hz, C(15)H), 5.05 (2H, s, OC(10)H₂), 4.62 (1H, hept, J = 6.1 Hz, OC(31)H), 4.41 (1H, hept, J = 6.1 Hz, OC(9)H), 3.91 (6H, s, OC(18)H₂), 3.84 (3H, s, OC(29)H₃), 3.80 (1H, dd, J = 17.8, 9.9 Hz, C(21)H₂), 3.75 (3H, s, OC(7)H₃), 3.17 (1H, dd, J = 17.8, 4.2 Hz, C(21)H₂), 1.39 (6H,

d, $J = 6.1$ Hz, C(30)H₃), 1.30 (6H, dd, $J = 6.1, 3.8$ Hz, C(8)H₃), 0.78 (3H, s, C(20)H₃); ¹³C NMR (101 MHz, CDCl₃) $\delta = 198.2, 196.1, 151.7, 150.0, 149.7, 146.6, 144.9, 137.5, 129.5, 128.5, 127.7, 127.2, 122.7, 118.9, 113.1, 112.7, 111.0, 104.4, 104.1, 73.0, 71.8, 71.7, 71.1, 56.5, 56.0, 41.9, 40.8, 30.8, 22.2, 22.1, 22.0, 21.9, 14.3$; HRMS (ESI⁺) Found [M+H]⁺ = 649.30023; C₃₇H₄₅O₁₀ requires 649.30072, $\Delta = -0.76$ ppm.

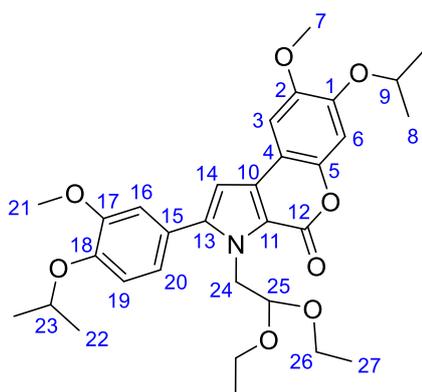
7-Isopropoxy-2-(4-isopropoxy-3-methoxyphenyl)-8-methoxychromeno[3,4-*b*]pyrrol-4(3*H*)-one (13a)



In a flame-dried RBF flushed with argon were added the 1,4-dicarbonyl **7** (65 mg, 0.10 mmol, 1.0 eq.) and NH₄OAc (77.1 mg, 1.0 mmol, 10.0 eq.) before the addition of AcOH (3 mL). A reflux condenser was attached, and the solution was heated at 110 °C for 30 min. The reaction mixture was left to cool to rt and then poured onto crushed ice. The mixture was neutralised by the

careful addition of solid K₂CO₃ (as judged by litmus paper). The aqueous layer was extracted with DCM (3 × 30 mL) and the combined organic extracts were dried with MgSO₄, filtered and the solvent was evaporated *in vacuo*. The residue was transferred to an RBF and dissolved in EtOH (5 mL). To the stirred solution was added Pd/C (10% wt. loading, 24.0 mg) and the flask was flushed H₂ and left to stir under an atmosphere of H₂ (balloon) at rt for 6.5 h. After complete consumption of the starting material (as observed by TLC), the solution was filtered through filter paper using EtOH as eluent, and the solvent was evaporated *in vacuo*. The residue was dissolved in EtOH (4 mL) and powdered K₂CO₃ (28.0 mg, 0.20 mmol, 2 eq.) was added to the stirred solution and heated at 90 °C for 2 h. The solution was left to cool to rt and the solvent was evaporated *in vacuo*. The product was extracted with DCM (3 × 30 mL) and the extract was washed with brine (30 mL), dried over MgSO₄ and evaporated *in vacuo* to give the *title compound* **13a** (42 mg, 95%) as colorless needles. **m.p.** 263–264 °C (EtOH); IR ν_{max} (thin film): 3264, 2975, 2934, 2872, 2840, 1697, 1623, 1607, 1595, 1519, 1494, 1472, 1447, 1415, 1384, 1276, 1258, 1231, 1220, 1206, 1169, 1148, 1110, 1067, 1027, 1001, 941, 868, 842 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) $\delta = 11.05$ (1H, s, NH), 7.58 (1H, d, $J = 2.1$ Hz, HC(16)_{Ar}), 7.37 (1H, dd, $J = 8.4, 2.1$ Hz, HC(20)_{Ar}), 7.22 (1H, s, HC(3)_{Ar}), 6.99 (1H, d, $J = 8.4$ Hz, HC(19)_{Ar}), 6.92 (1H, s, HC(6)_{Ar}), 6.87 (1H, d, $J = 2.3$ Hz, C(14)H), 4.62 (2H, hept, $J = 6.1$ Hz, OC(9, 23)H), 4.13 (3H, s, OC(21)H₃), 3.98 (3H, s, OC(7)H₃), 1.43 (12H, d, $J = 6.1$ Hz, C(8, 22)H₃); ¹³C NMR (101 MHz, CDCl₃) $\delta = 156.2, 150.8, 148.2, 148.0, 147.6, 146.2, 143.5, 132.1, 123.9, 118.8, 116.4, 115.4, 110.4, 109.6, 105.1, 103.9, 98.9, 71.8, 71.5, 56.6, 56.5, 22.2, 22.0$; HRMS (APCI⁺) Found [M+H]⁺ = 438.19061; C₂₅H₂₈O₆N requires 438.19111, $\Delta = -1.14$ ppm.

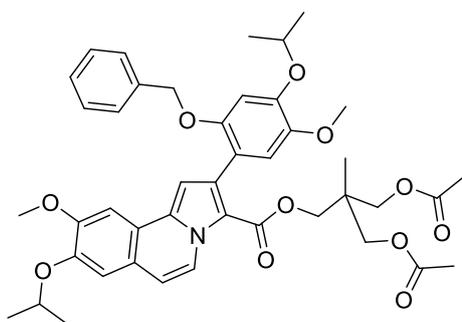
3-(2,2-Diethoxyethyl)-7-isopropoxy-2-(4-isopropoxy-3-methoxyphenyl)-8-methoxychromeno[3,4-*b*]pyrrol-4(3*H*)-one (13b)



In a flame-dried Biotage[®] microwave vial flushed with argon, **13a** (100 mg, 0.23 mmol, 1.0 eq.) was dissolved in DMF (5 mL). To the stirred solution, Cs₂CO₃ (483 mg, 1.48 mmol, 6.5 eq.) and 2-bromo-1,1-diethoxyethane (225 μ L, 1.50 mmol, 6.6 eq.) were added and the vial was then flushed with argon for 5 min after which time the vial was sealed with a microwave vial cap (Reseal[™] septum). The solution was heated at 110 °C for 24 h. The resulting

mixture was allowed to cool to rt and the product was extracted with DCM (3 \times 30 mL) and the extract was washed with brine (30 mL), dried over MgSO₄ and evaporated *in vacuo*. The residue was dry-loaded onto SiO₂ and purified by column chromatography (SiO₂; *n*-pentane/acetone, 50:10) to yield the *title compound* **13b** (108 mg, 86%) as an unstable yellow oil. Installation of the acetal was confirmed by ¹H NMR (400 MHz, CDCl₃) Diagnostic resonances δ = 5.05 (1H, t, *J* = 5.6 Hz, HC(25)), 4.49 (2H, d, *J* = 5.6 Hz, H₂C(24)), 3.67 (2H, q, *J* = 7.0 Hz, OC(26)H₂), 3.42 (2H, q, *J* = 7.0 Hz, OC(26)H₂) and 1.10 (6H, t, *J* = 7.0 Hz, H₃C(27)).

2-[(2-[2-(Benzyloxy)-4-isopropoxy-5-methoxyphenyl]-8-isopropoxy-9-methoxypyrrolo[2,1-*a*]-isoquinoline-3-carbonyl)oxy)methyl]-2-methylpropane-1,3-diyl diacetate (14)

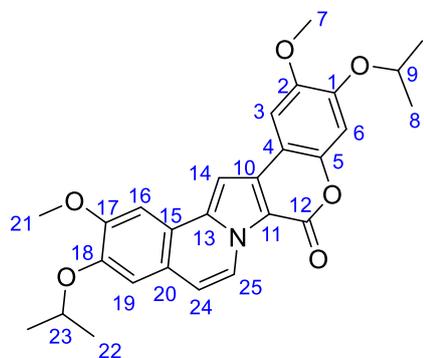


To an RBF containing **7** (100 mg, 0.16 mmol, 1.0 eq.) and aminoacetaldehyde diethyl acetal (**6**) (200 mg, 1.50 mmol, 9 eq.) was added a solution of AcOH (10 mL, with added 1 mol% water and *ca.* 0.001 mol% formic acid) *via* syringe, before a reflux condenser was attached and the stirred solution was heated at 100 °C over 16 h. After this time the solution was allowed to cool to rt and poured onto crushed ice, before adjustment to pH 7-8 by the portion wise

addition of K₂CO₃ (as judged by litmus paper). The aqueous layer was extracted with EtOAc (20 mL), the organic layer was collected, dried over MgSO₄ and filtered. The filtrate was directly dry-loaded onto SiO₂ and purified by flash column chromatography (SiO₂, *n*-pentane/acetone, 80:20) to give the *title compound* **14** as yellow oil (108 mg, 89%). IR ν_{max} (thin film) 2978, 2930, 1700, 1616, 1509, 1486, 1466, 1418, 1385, 1324, 1223, 1179, 1137, 1038, 1018, 945 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ = 9.29 (1H, d, *J* = 7.5 Hz), 7.42 (1H, s), 7.22-7.14 (5H, m), 7.09 (1H, s), 6.94 (1H, d, *J* = 7.5 Hz), 6.88 (1H, s), 6.79 (1H, s), 6.68 (1H, s), 4.93 (2H, s), 4.71 (1H, hept, *J* = 6.1 Hz, O*i*Pr), 4.50 (1H, hept, *J* = 6.1 Hz, O*i*Pr), 4.05 (2H, s, CH₂), 3.98 (3H, s, OMe), 3.82 (3H, s, OMe), 3.68 (4H, s, 2 \times CH₂), 1.97 (6H, s, 2 \times OAc), 1.46 (6H, d, *J* = 6.1 Hz, O*i*Pr), 1.36 (6H, d, *J* = 6.1 Hz, O*i*Pr), 0.66 (3H, s, Me); ¹³C NMR (101 MHz, CDCl₃) δ = 170.8, 162.1, 151.1, 150.1, 148.5, 147.2, 145.0, 137.7, 134.5, 132.9, 128.4, 127.6,

127.2, 123.9, 123.1, 120.1, 119.2, 115.6, 113.2, 112.1, 110.7, 105.4, 104.4, 103.4, 72.0, 71.5, 66.0, 65.7, 56.8, 56.2, 37.9, 22.3, 22.1, 20.8, 16.8. **HRMS** (ESI⁺) Found [M+H]⁺ = 756.33699; C₄₃H₅₀O₁₁N requires 756.33784, Δ−1.14 ppm.

3,11-Diisopropoxy-2,12-dimethoxy-6H-chromeno[4',3':4,5]pyrrolo[2,1-a]isoquinolin-6-one (**5**)



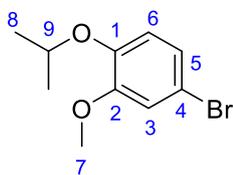
Method A: In a flame-dried RBF flushed with argon, **13b** (63 mg, 0.11 mmol, 1.0 eq.) was dissolved in DCM (5 mL). In a flame-dried pear-shaped flask flushed with argon, an emulsion of TfOH in DCM (1.0 M, 1 mL) was made and stirred vigorously at rt. Two drops of the TfOH emulsion were added *via* a syringe to the stirred solution containing **13b** at −10 °C. After 6 h, a further two drops of TfOH emulsion was added and the solution was allowed to warm to −5

°C over 18 h. After complete consumption of the starting material as observed by TLC (25 h), the reaction was quenched by addition of NaHCO₃ (139 mg, 1.65 mmol, 15 eq.) and EtOH (0.6 mL) before warming to rt and then the solvent was evaporated *in vacuo*. The residue was dry-loaded onto SiO₂ and purified by column chromatography (*n*-pentane/acetone, 80:20) to give the *title compound 5* (46.1 mg, 88%) as colorless needles.

Method B: To a RBF containing **14** (100 mg, 0.13 mmol, 1.0 eq.) and 1,4-cyclohexadiene (0.3 mL, 3.2 mmol, 25 eq.) in MeOH (5 mL) and EtOAc (0.5 mL) was added 20% Pd(OH)₂ on carbon (Pearlman's catalyst) (88 mg). After flushing with N₂, the mixture was heated to 60 °C over 6 h. After this time K₂CO₃ (1.0 g) was added before cooling to rt and mixture was filtered over a 5 cm pad of diatomaceous earth, eluting with DCM (50 mL) into an RBF. The filtrate was directly dry-loaded onto SiO₂ and purified by flash column chromatography (SiO₂, *n*-pentane/acetone, 80:20) to give the *title compound 5* (54 mg, 89%) as an off-white solid. **IR** ν_{\max} (thin film): 3469, 3375, 2978, 2950, 2349, 2154, 1695 (C=O), 1666, 1619, 1594, 1499, 1438, 1420, 1365, 1336, 1317, 1297, 1235, 1190, 1144, 1100, 1031, 1009, 991, 964, 924, 855 cm⁻¹; **¹H NMR (400 MHz, CDCl₃)** δ = 9.07 (1H, d, *J* = 7.3 Hz, HC(25)), 7.54 (1H, s, HC(16)_{Ar}), 7.32 (1H, s, HC(3)_{Ar}), 7.13 (1H, s, HC(14)_{Ar}), 7.12 (1H, s, HC(19)_{Ar}), 6.99 (1H, d, *J* = 7.3 Hz, HC(24)_{Ar}) overlaps with 6.99 (1H, s, HC(6)_{Ar}), 4.74 (1H, hept, *J* = 6.1 Hz, OC(23)*H*), 4.61 (1H, hept, *J* = 6.1 Hz, OC(9)*H*), 4.07 (3H, s, OC(21)*H*₃), 4.00 (3H, s, OC(7)*H*₃), 1.48 (6H, d, *J* = 6.1 Hz, C(22)*H*₃), 1.45 (6H, d, *J* = 6.1 Hz, C(8)*H*₃); **¹³C NMR (101 MHz, CDCl₃)** δ = δ 155.6, 151.3, 149.4, 148.7, 147.4, 146.8, 138.6, 132.4, 124.3, 123.5, 118.5, 112.3, 110.7, 109.8, 109.3, 105.4, 104.8, 103.8, 91.4, 77.5, 77.2, 76.8, 71.7, 71.5, 56.7, 56.3, 27.1, 22.1, 22.0. **HRMS** (ESI⁺) Found [M+H]⁺ = 462.19095;

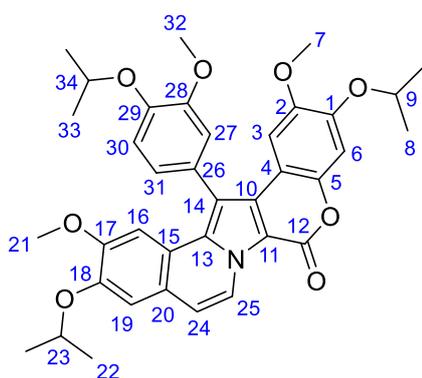
C₂₇H₂₈O₆N requires 462.19111, Δ−0.36 ppm. Spectroscopic data are consistent with those previously reported.⁶

4-Bromo-1-isopropoxy-2-methoxybenzene (4)



To a suspension of KOtBu (898 mg, 8.0 mmol, 4.0 eq.) in PhMe (2 mL) was added 2-propanol (690 μL, 9.0 mmol, 4.5 eq.) in anhydrous DMPU (2 mL) before the mixture was heated at 80 °C for 30 mins. After this time, 5-bromo-2-fluoroanisole **15** (410 mg, 2.0 mmol, 1.0 eq.) in anhydrous DMPU (1 mL) was added (syringe washed with further 0.2 mL DMPU), before a reflux condenser was immediately attached and the solution was stirred at 80 °C for a further 3 h. After this time, the mixture was cooled to rt before brine (20 mL) and *n*-pentane (20 mL) were sequentially added. After vigorous shaking of the biphasic mixture in a separating funnel, the organic layer was separated and filtered through a 5 cm plug of SiO₂ and washed with *n*-pentane (20 mL). The solvent was evaporated to give the *title compound 4* (401 mg, 82%) as colorless oil. IR ν_{max} (thin film): 2975, 2933, 2830, 1585, 1493, 1464, 1444, 1397, 1383, 1372, 1322, 1290, 1248, 1221, 1178, 1133, 1107, 1028, 951, 868, 835, 813 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ = 6.97 (1H, dd, *J* = 9.1, 2.3 Hz, HC(5)_{Ar}) overlaps with 6.96 (1H, d, *J* = 2.3 Hz, HC(3)_{Ar}), 6.74 (1H, d, *J* = 9.1 Hz, HC(6)_{Ar}), 4.45 (1H, hept, *J* = 6.1 Hz, OC(9)*H*), 3.81 (3H, s, OC(7)*H*₃), 1.32 (6H, d, *J* = 6.1 Hz, C(8)*H*₃); ¹³C NMR (101 MHz, CDCl₃) δ = 151.3, 146.5, 123.4, 117.2, 115.4, 113.2, 71.8, 56.1, 22.0. Spectroscopic data are consistent with those previously reported.¹

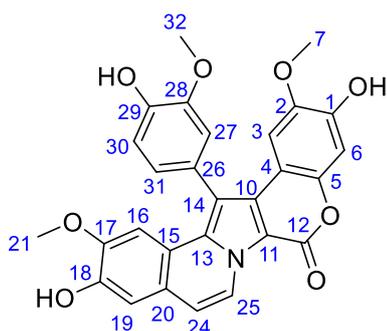
3,11-Diisopropoxy-14-(4-isopropoxy-3-methoxyphenyl)-2,12-dimethoxy-6*H*-chromeno[4',3':4,5]-pyrrolo[2,1-*a*]isoquinolin-6-one (16)



In a flame-dried Biotage[®] microwave vial containing DMA (0.3 mL) were added **5** (23.8 mg, 51.6 μmol, 1.0 eq.), Pd(PPh₃)₂Cl₂ (2 mg, 2.8 μmol, 5 mol%), anhydrous KOAc (10 mg, 102 μmol, 2.0 eq.), and **4** (23 μL, 129 μmol, 2.5 eq.) under argon. The vial was then flushed with argon for 5 min after which time the vial sealed with an aluminium microwave vial cap (Reseal[™] septum) and the solution was heated at 150 °C for 22 h. The resulting mixture was allowed to cool to rt and diluted with water (10 mL). The aqueous layer was extracted with DCM (3 × 20 mL) and the combined organic extracts were washed with brine (30 mL), dried over MgSO₄, and evaporated *in vacuo*. The residue was dry-loaded onto SiO₂ and purified by column chromatography (*n*-pentane/acetone, 85:15) to yield the *title compound 16* (25.7 mg, 80%) as off-white needles. *m.p.* 192–194 °C [lit.⁶ 191–192 °C (DCM/Et₂O)]; IR ν_{max} (thin film): 2976, 2934, 1704 (C=O), 1614, 1534,

1509, 1486, 1465, 1431, 1418, 1385, 1334, 1266, 1223, 1179, 1162, 1137, 1110, 1038, 1018, 945, 857 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 9.20 (1H, d, J = 7.3 Hz, $\text{HC}(25)$), 7.17 (1H, s, $\text{HC}(16)_{\text{Ar}}$), 7.16 (1H, s, $\text{HC}(31)_{\text{Ar}}$) overlaps with 7.16 (1H, s, $\text{HC}(30)_{\text{Ar}}$), 7.13 (1H, s, $\text{HC}(27)_{\text{Ar}}$), 7.09 (1H, s, $\text{HC}(19)_{\text{Ar}}$), 7.01 (1H, d, J = 7.3 Hz, $\text{HC}(24)_{\text{Ar}}$), 6.95 (1H, s, $\text{HC}(6)_{\text{Ar}}$), 6.75 (1H, s, $\text{HC}(3)_{\text{Ar}}$), 4.69 (1H, hept, J = 6.1 Hz, $\text{OC}(23)\text{H}$), 4.63 (1H, hept, J = 6.1 Hz, $\text{OC}(34)\text{H}$), 4.56 (1H, hept, J = 6.1 Hz, $\text{OC}(9)\text{H}$), 3.84 (3H, s, $\text{OC}(32)\text{H}_3$), 3.44 (3H, s, $\text{OC}(7)\text{H}_3$), 3.43 (3H, s, $\text{OC}(21)\text{H}_3$), 1.43 (12H, d, J = 6.1 Hz, $\text{C}(22, 33)\text{H}_3$), 1.39 (6H, d, J = 6.1 Hz, $\text{C}(8)\text{H}_3$); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 155.6, 151.4, 150.2, 148.5, 147.9, 147.2, 146.6, 146.5, 134.4, 129.4, 128.8, 124.7, 123.9, 123.2, 119.0, 116.9, 115.0, 112.3, 111.0, 110.4, 110.0, 107.8, 105.7, 105.5, 103.4, 71.8, 71.5, 71.2, 56.2, 55.5, 55.2, 21.8–21.9 (6 \times CHCH_3); **HRMS** (ESI^+) Found $[\text{M}+\text{H}]^+$ = 626.27460; $\text{C}_{37}\text{H}_{40}\text{O}_8\text{N}$ requires 626.27484, Δ –0.39 ppm. Spectroscopic data are consistent with those previously reported.⁶

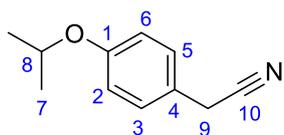
3,11-Dihydroxy-14-(4-hydroxy-3-methoxyphenyl)-2,12-dimethoxy-6H-chromeno[4',3':4,5]pyrrolo-[2,1- α]isoquinolin-6-one, Lamellarin D



In a flame-dried RBF flushed with argon, **16** (25.7 mg, 41.1 μmol , 1.0 eq.) was dissolved in DCM (6 mL) and then cooled to -78°C . BCl_3 (1.0 M in *n*-heptane, 370 μL , 9.0 eq.) was then added *via* a syringe to the stirred solution. After 30 minutes, the solution was allowed to warm to rt and left to stir for a further 3 h, after which time it was quenched by the addition of saturated aq. NaHCO_3 (2 mL). The product was

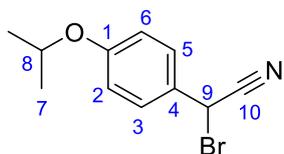
extracted with EtOAc (3 \times 20 mL) and the combined organic extracts were dried over MgSO_4 and evaporated *in vacuo*. The residue was dry-loaded onto SiO_2 and purified by column chromatography (SiO_2 ; EtOAc) to yield **lamellarin D** (20.4 mg, 99%) as a pale green solid. $^1\text{H NMR}$ (700 MHz, $\text{DMSO-}d_6$) δ = 9.94 (1H, s), 9.84 (1H, s), 9.34 (1H, s), 8.99 (1H, d, J = 7.4 Hz), 7.20 (1H, d, J = 7.4 Hz), 7.18 (1H, s), 7.15 (1H, d, J = 2.0 Hz), 7.13 (1H, s), 7.09 (1H, d, J = 7.9 Hz), 7.00 (1H, dd, J = 2.0, 7.9 Hz), 6.86 (1H, s), 6.71 (1H, s), 3.77 (3H, s), 3.38 (3H, s) and 3.38 (3H, s) overlap with H_2O resonance; $^{13}\text{C NMR}$ (101 MHz, $\text{DMSO-}d_6$) δ = 154.4, 148.7, 148.5, 148.4, 147.9, 146.9, 146.4, 144.6, 134.1, 129.0, 125.5, 124.7, 123.9, 122.1, 117.6, 116.5, 115.1, 112.4, 111.6, 110.9, 108.4, 106.4, 105.8, 105.4, 103.8, 56.0, 55.1, 54.6; **HRMS** (ESI^+) Found $[\text{M}+\text{Na}]^+$ = 522.11591; $\text{C}_{28}\text{H}_{21}\text{O}_8\text{N}^{23}\text{Na}$ requires 522.11594, Δ –0.06 ppm. Spectroscopic data are consistent with those previously reported.⁵

2-(4-Isopropoxyphenyl)acetonitrile (**22**)



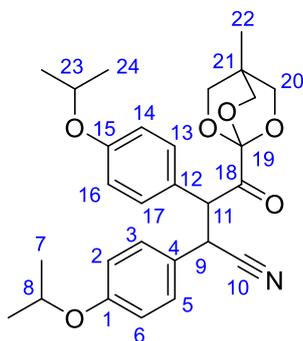
2-Bromopropane (14 mL, 0.15 mol, 1.5 eq.) was added to a mixture of 4-hydroxyphenylacetonitrile (13.3 g, 0.1 mol, 1.0 eq.) and K_2CO_3 (28 g, 0.2 mol, 2.0 eq.) in DMSO (50 mL). The reaction mixture was stirred at 60 °C for 21 h and then left to cool to rt. Water (100 mL) was added and the aqueous layer extracted with DCM (4 × 80 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4 , filtered and concentrated *in vacuo* to give the *title compound* **22** (17 g, >99%) as pale-yellow needles. **m.p.** 26-28 °C (*n*-pentane/ Et_2O); **IR** ν_{max} 3042, 2976 and 2906, 2248, 1611, 1581, 1508, 1469, 1452, 1416, 1380, 1373, 1352, 1333, 1304, 1286, 1246, 1205, 1180, 1137, 1117, 1103, 1013, 953, 925, 902, 863, 832, 806 cm^{-1} ; **1H NMR (400 MHz, $CDCl_3$)** δ = 7.21 (2H, d, J = 8.7 Hz, HC_{Ar}), 6.88 (2H, d, J = 8.7 Hz, HC_{Ar}), 4.54 (1H, hept, J = 6.1 Hz, OC(8)H), 3.67 (2H, s, C(9) H_2 CN), 1.33 (6H, d, J = 6.0 Hz, C(7) H_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 157.6, 129.1, 121.5, 118.2, 116.4, 70.0, 22.8, 21.9; **HRMS:** Found $[M+Na]^+$ = 198.08925, $C_{11}H_{13}ON^{23}Na$ requires 198.08894, Δ = +1.58 ppm.

2-Bromo-2-(4-isopropoxyphenyl)acetonitrile (**20**)



To a two-neck RBF was added dibenzoyl peroxide (97 mg, 0.04 mmol, 4 mol%), 2-(4-isopropoxyphenyl)acetonitrile **22** (1.75 g, 10 mmol, 1.0 eq.) and NBS (2.67 g, 15 mmol, 1.5 eq.). Diethyl carbonate (which had been degassed by freeze-pump-thaw cycles) (50 mL) was added under argon before heating to 100 °C, over 24 h. The reaction mixture was left to cool to rt and concentrated *in vacuo*. The residue was triturated with pentane/ Et_2O , filtered and washed with Et_2O . The filtrate was concentrated *in vacuo* and flash column chromatography (SiO_2 ; *n*-pentane/acetone, 96:4) gave the *title compound* **20** (1.53 g, 60%) as orange oil. **IR** ν_{max} 2978 and 2935, 2247, 1606, 1582, 1509, 1466, 1454, 1428, 1385, 1375, 1331, 1305, 1250, 1180, 1120, 1106, 950, 863, 834 cm^{-1} ; **1H NMR (400 MHz, $CDCl_3$)** δ = 7.46 (2H, d, J = 8.8 Hz, HC_{Ar}), 6.90 (2H, d, J = 8.8 Hz, HC_{Ar}), 5.49 (1H, s, C(9)H), 4.58 (1H, hept, J = 6.0 Hz, C(8)H), 1.35 (6H, d, J = 6.0 Hz, C(7) H_3); **^{13}C NMR (101 MHz, $CDCl_3$)** δ = 159.5, 129.4, 124.9, 116.5, 116.3, 70.2, 27.8, 21.9; **HRMS:** Expected ions were not observed.

2,3-Bis(4-isopropoxyphenyl)-4-(4-methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)-4-oxobutanenitrile (18)

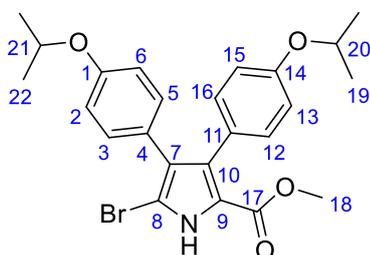


To a stirring solution of **1** (100 mg, 0.58 mmol, 1.0 eq.), **19** (201 mg, 0.93 mmol, 1.6 eq.) and Pd(dtbpf)Cl₂ (38 mg, 0.058 mmol, 0.1 eq.) in THF (5 mL) was added NaOtBu (2M in THF, 0.72 mL, 2.5 eq.) at rt. The solution was then heated at 55 °C over 20 h. After this time, a solution of freshly prepared **20** (223 mg, 0.79 mmol, 1.4 eq.) in THF (1 mL) was added dropwise and the mixture was left stirring for additional 3 h. After this time Et₂O (7 mL), saturated aq. NH₄Cl (1 mL) and water (1.5 mL) were added. The

aqueous layer was extracted with Et₂O (2 x 10 mL), dried over MgSO₄ and filtered. The filtrate was dry loaded onto SiO₂ and purification by flash column chromatography (SiO₂; *n*-pentane/EtOAc, 80:20) gave the *title compound* **18** as a single diastereoisomer (208 mg, 75%), as pale-yellow crystals.

m.p. 151-153 °C (*n*-pentane/Et₂O); **IR** ν_{\max} 3070, 3038, 2977, 2929, 2887, 2236, 1751, 1610, 1581, 1508, 1469, 1399, 1384, 1372, 1350, 1301, 1243, 1178, 1119, 1106, 1083, 1065, 103, 1003, 954, 879, 858, 843 cm⁻¹; **¹H NMR (400 MHz, CDCl₃)** δ = 7.20 (2H, d, *J* = 8.8 Hz, HC_{Ar}), 7.19 (2H, d, *J* = 8.8 Hz, HC_{Ar}), 6.84 (2H, d, *J* = 8.7 Hz, HC_{Ar}), 6.81 (2H, d, *J* = 8.7 Hz, HC_{Ar}), 4.62 (1H, d, *J* = 10.0 Hz, CH), 4.58–4.49 (2H, m, C(8)H & C(23)H), 4.46 (1H, d, *J* = 10.0 Hz, CH), 3.80 (6H, s, C(20)H₂), 1.38–1.24 (12H, m, OCH(C(24)H₃)₂ & OCH(C(7)H₃)₂), 0.74 (3H, s, C(22)H₃); **¹³C NMR (101 MHz, CDCl₃)** δ = 194.4, 158.0, 157.7, 130.2, 129.6, 125.8, 125.4, 119.7, 116.1, 115.9, 103.6, 72.9, 69.9, 69.8, 56.0, 40.6, 30.8, 22.07, 22.06, 22.0, 14.1; **HRMS:** Found [M+H]⁺ = 480.23810, C₂₈H₃₄NO₆, requires 480.23806 Δ +0.07 ppm.

Methyl 5-bromo-3,4-bis(4-isopropoxyphenyl)-1H-pyrrole-2-carboxylate (24)

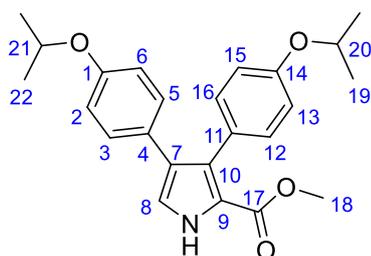


A solution of **18** (143.9 mg, 0.3 mmol) in DCM/Et₂O (1:1, 2 mL) was added dropwise to a solution of 33% HBr in AcOH (920 μ L) at 0 °C and the mixture left stirring at this temperature for 30 min. After this time, the mixture left to warm to rt. After 3 h the reaction mixture was poured onto crushed ice and adjusted to *ca.* pH 7-8 (as judged by pH indicator paper) by slow addition of K₂CO₃. The solution was then

extracted with DCM (4 x 50 mL), and the combined organic extracts dried with Na₂SO₄, filtered and concentrated *in vacuo*. The remaining residue was dissolved in MeOH (9 mL) and K₂CO₃ (82.9 mg, 0.6 mmol, 2 eq.) was added. The mixture heated at 65 °C for 4 h. Then the mixture left to cool to rt, dry loaded onto SiO₂ and purified by flash column chromatography (SiO₂; *n*-pentane/Et₂O, 80:20) to give the *title compound* **24** (87.3 mg, 62%) as colorless plates. **m.p.** 153-154 °C (*c*-hexane); **IR** ν_{\max} 3247

(N-H), 2975 and 2933 (alkyl C-H), 1678, 1610, 1573, 1549, 1530, 1507, 1461, 1441, 1417, 1385, 1335, 1305, 1283, 1238, 1181, 1171, 1136, 1118, 1020, 1004, 953, 859, 843 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 9.13 (1H, s, NH), 7.07 (2H, d, J = 8.7 Hz, HC_{Ar}), 7.01 (2H, d, J = 8.8 Hz, HC_{Ar}), 6.75 (4H, d, J = 8.7 Hz, HC_{Ar}), 4.57–4.45 (2H, hept, J = 6.0 Hz, $\text{OCH}(\text{CH}_3)_2$), 3.74 (3H, s, $\text{C}(18)\text{H}_3$), 1.32 (6H, d, J = 6.1 Hz, $\text{OCH}(\text{CH}_3)_2$), 1.32 (6H, d, J = 6.1 Hz, $\text{OCH}(\text{CH}_3)_2$); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 160.6, 157.0, 156.7, 131.8, 131.3, 131.1, 125.8, 125.1, 124.8, 119.4, 115.1, 114.8, 104.2, 69.70, 69.67, 51.4, 22.1; HRMS: Found $[\text{M}+\text{Na}]^+$ = 494.09372, $\text{C}_{24}\text{H}_{26}\text{BrNO}_4\text{Na}$ requires 494.09374, Δ –0.05 ppm.

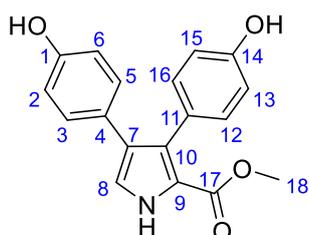
Methyl 3,4-bis(4-isopropoxyphenyl)-1H-pyrrole-2-carboxylate (**25**)



A mixture of methyl 5-bromo-3,4-bis(4-isopropoxyphenyl)-1H-pyrrole-2-carboxylate (**24**) (47.2 mg, 0.1 mmol, 1.0 eq.), NaOAc (20 mg, 0.21 mmol, 2.1 eq.) and 10 mol% Pd/C (16 mg) in MeOH (5 mL) was purged with H_2 and stirred under an atmosphere of H_2 (balloon) at rt for 1 h. The reaction mixture was filtered, and the filtrate was

concentrated *in vacuo* to give the *title compound* **25** (33 mg, >99%) as colorless plates. **m.p.** 143–144 $^\circ\text{C}$ (*n*-pentane/ Et_2O) [lit.⁷ 141–141.5 $^\circ\text{C}$ (*n*-hexane/ EtOAc)]; IR ν_{max} 3357 (NH), 2975 and 2939 (alkyl C-H), 1700, 1611, 1572, 1554, 1536, 1506, 1481, 1438, 1419, 1370, 1306, 1282, 1238, 1182, 1150, 1135, 1118, 1104, 1087, 1025, 1008, 947, 921, 859 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 9.12 (1H, br s, NH), 7.17 (2H, d, J = 8.7 Hz, HC_{Ar}), 7.02 (1H, d, J = 3.1 Hz, $\text{C}(8)\text{H}$), 7.00 (2H, d, J = 8.8 Hz, HC_{Ar}), 6.82 (2H, d, J = 8.7 Hz, HC_{Ar}), 6.72 (2H, d, J = 8.7 Hz, HC_{Ar}), 4.55 (1H, hept, J = 6.1 Hz, $\text{OCH}(\text{CH}_3)_2$), 4.48 (1H, hept, J = 6.1 Hz, $\text{OCH}(\text{CH}_3)_2$), 3.73 (3H, s, $\text{OC}(18)\text{H}_3$), 1.35 (6H, d, J = 6.0 Hz, $\text{OCH}(\text{CH}_3)_2$), 1.31 (6H, d, J = 6.1 Hz, $\text{OCH}(\text{CH}_3)_2$); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ = 161.5, 156.8, 156.3, 131.9, 129.4, 129.1, 126.8, 126.5, 126.1, 120.0, 119.3, 115.5, 115.0, 69.8, 69.7, 51.2, 22.14, 22.08; HRMS: Found $[\text{M}+\text{Na}]^+$ = 416.18304, $\text{C}_{24}\text{H}_{27}\text{NO}_4^{23}\text{Na}$, requires 416.18323, Δ –0.44 ppm. Spectroscopic data are consistent with those previously reported in the literature.⁷

Methyl 3,4-bis(4-hydroxyphenyl)-1H-pyrrole-2-carboxylate, Lamellarin Q



To a stirred solution of methyl 3,4-bis(4-isopropoxyphenyl)-1H-pyrrole-2-carboxylate (**25**) (20 mg, 0.06 mmol, 1.0 eq.) in DCM (5 mL) under argon atmosphere at -78°C was added BBr_3 (1M in DCM, 0.2 mL, 0.18 mmol, 3.0 eq.). After complete addition the solution was left to warm to rt. After 3 h the reaction was quenched by the addition of saturated aq. NaHCO_3 (1 mL)

and extracted with DCM (2×5 mL). The combined organic extracts were dried with MgSO_4 , filtered and evaporated *in vacuo*. Flash column chromatography (SiO_2 , *n*-pentane/acetone, 80:20) gave

lamellarin Q (16 mg, >99%) as unstable yellow needles. **m.p.** 218-221 °C with decomposition (lit.⁸ 220-222 °C with decomposition). **¹H NMR (400 MHz, acetone-*d*₆)** δ = 10.88 (1H, br s, NH), 8.21 (1H, s, OH), 8.13 (1H, s, OH), 7.13 (1H, d, J = 3.2 Hz, C(8)H), 7.05 (2H, d, J = 8.6 Hz, HC_{Ar}), 6.95 (2H, d, J = 8.6 Hz, HC_{Ar}), 6.75 (2H, d, J = 8.5 Hz, HC_{Ar}), 6.66 (2H, d, J = 8.6 Hz, HC_{Ar}), 3.64 (3H, s, OC(8)H₃). **¹³C NMR (100 MHz, acetone-*d*₆)** 161.9, 157.0, 156.5, 132.8, 130.2, 129.7, 127.4, 126.93, 126.88, 121.4, 120.0, 115.8, 115.2, 51.0; **HRMS** (ESI⁺) Found [M+H]⁺ = 310.10748; C₁₈H₁₆O₄N requires 310.10739, Δ +0.32 ppm. Physical and spectroscopic data are consistent with those previously reported.⁸

S4. ^{13}C NMR Data Lamellarin D and Q Compared to Previously Reported Data

Table 1. Comparison of ^{13}C NMR data of lamellarin D in DMSO- d_6 with a synthetic sample reported by Jia *et al.*⁵

Literature δ_c^5	This report δ_c	$\Delta\delta_c$
54.5	54.6	+0.1
55.1	55.1	
56.0	56.0	
103.7	103.8	+0.1
105.4	105.4	
105.8	105.8	
106.4	106.4	
108.3	108.4	+0.1
110.7	110.9	+0.2
111.5	111.6	+0.1
112.3	112.4	+0.1
115.1	115.1	
116.4	116.5	+0.1
117.5	117.6	+0.1
121.9	122.1	+0.2
123.8	123.9	+0.1
124.6	124.7	+0.1
125.5	125.5	
128.9	129.0	+0.1
134.0	134.1	+0.1
144.5	144.6	+0.1
146.3	146.4	+0.1
146.8	146.9	+0.1
147.8	147.9	+0.1
148.2	148.4	+0.2
148.4	148.5	+0.1
148.7	148.7	
154.3	154.4	+0.1

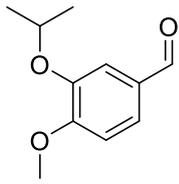
Table 2. Comparison of ^{13}C NMR data of lamellarin Q in acetone- d_6 with a synthetic sample reported by Vazquez *et al.*⁸

Literature δ_{C}^8	This report δ_{C}	$\Delta\delta_{\text{C}}$
161.9	161.9	
157.0	157.0	
156.5	156.5	
132.8	132.8	
130.2	130.2	
129.7	129.7	
127.4	127.4	
127.0	126.9	-0.1
126.8	126.9	+0.1
121.4	121.4	
120.0	120.0	
115.9	115.8	-0.1
115.2	115.2	
51.0	51.0	

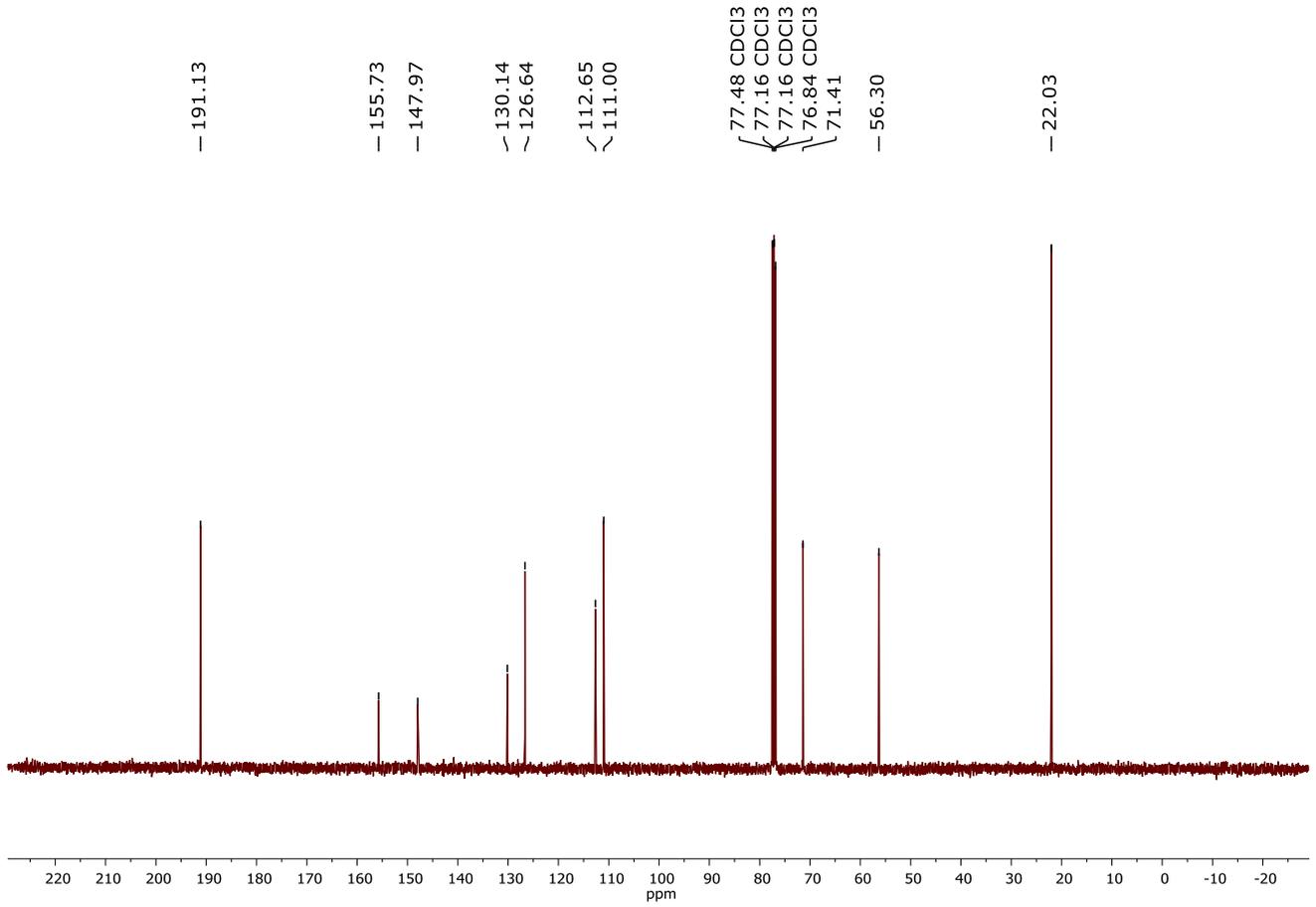
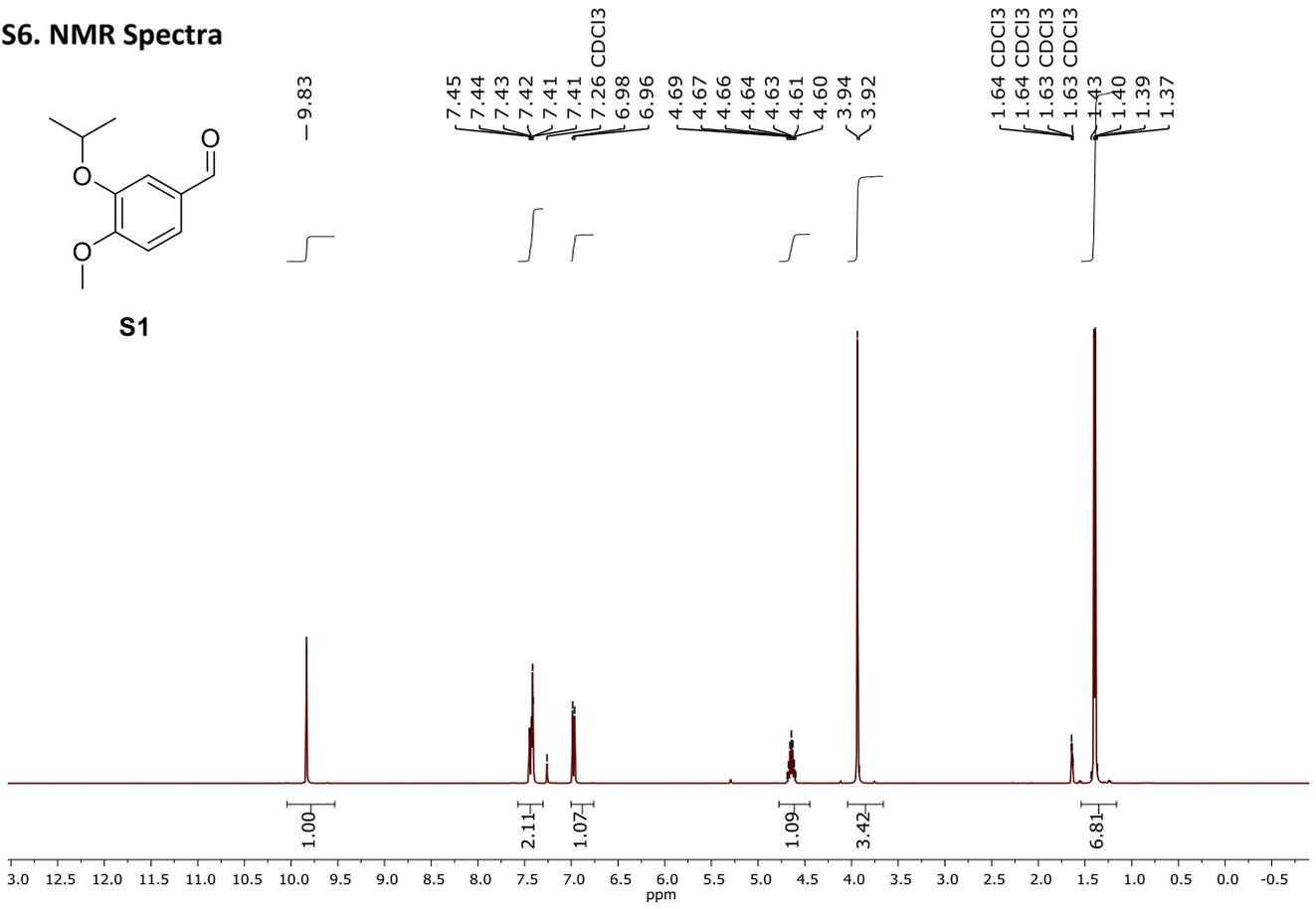
S5. References

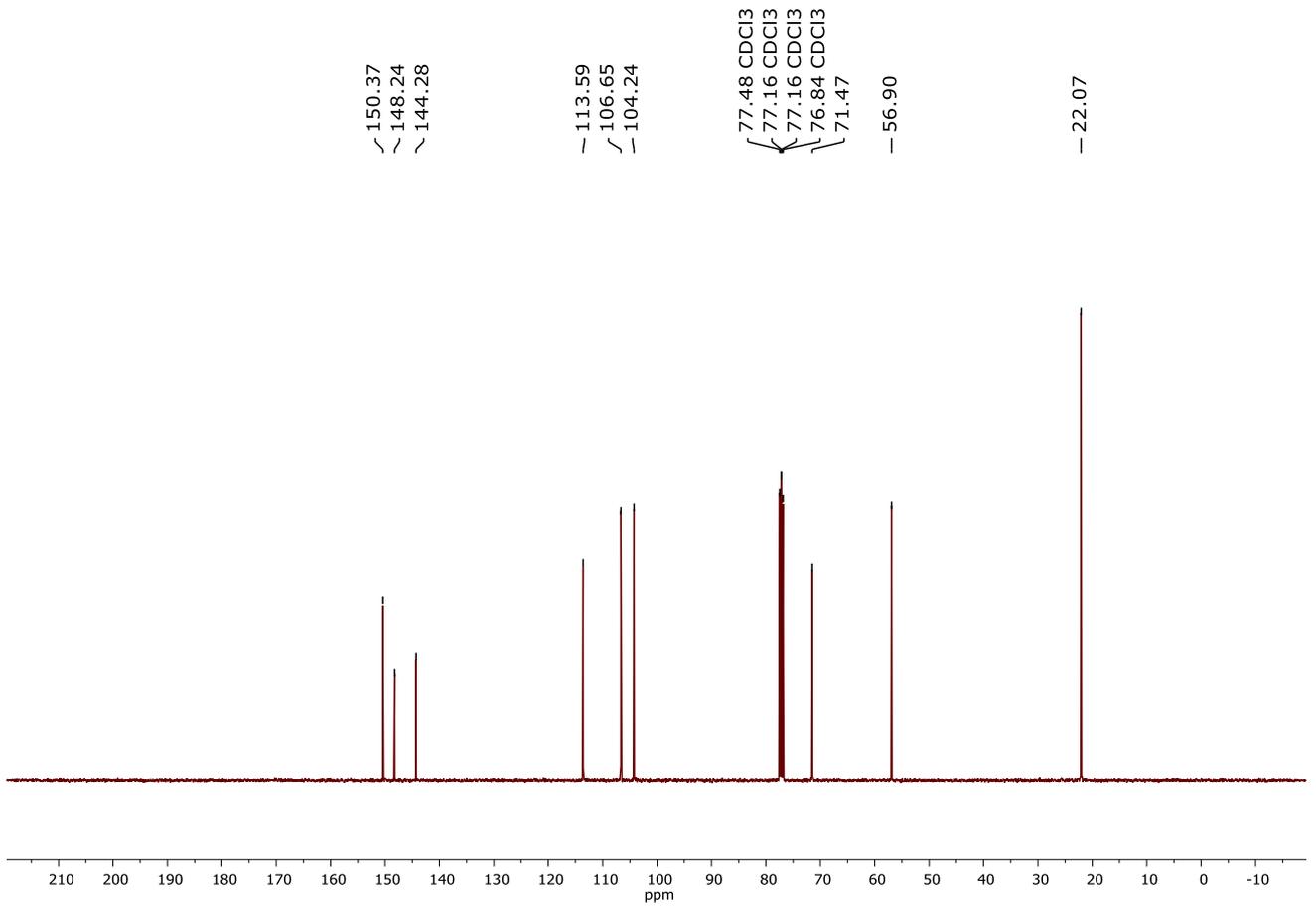
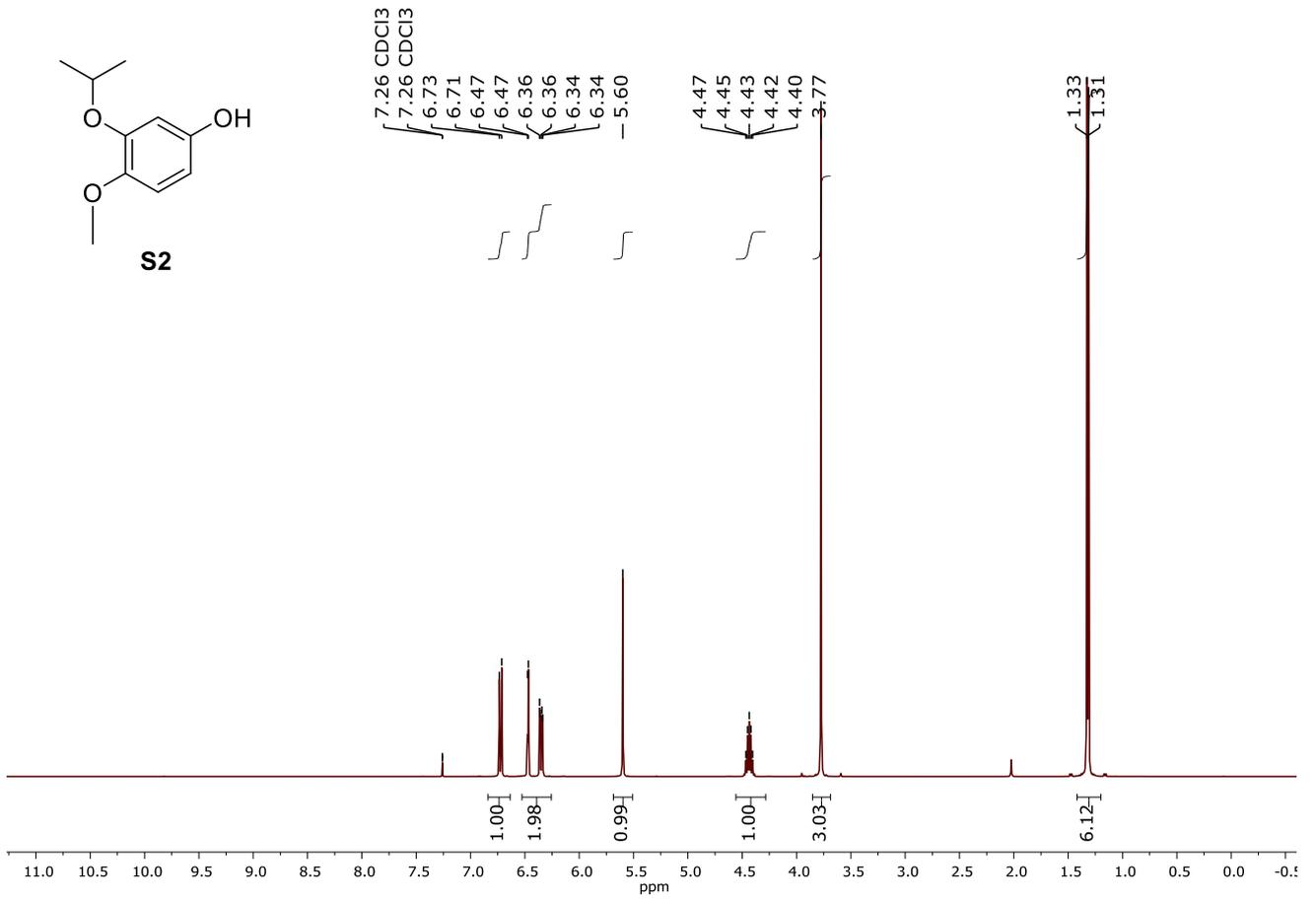
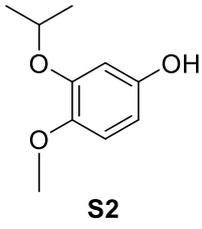
1. N. Fujikawa, T. Ohta, T. Yamaguchi, T. Fukuda, F. Ishibashi, M. Iwao, *Tetrahedron*, 2006, **62**, 594.
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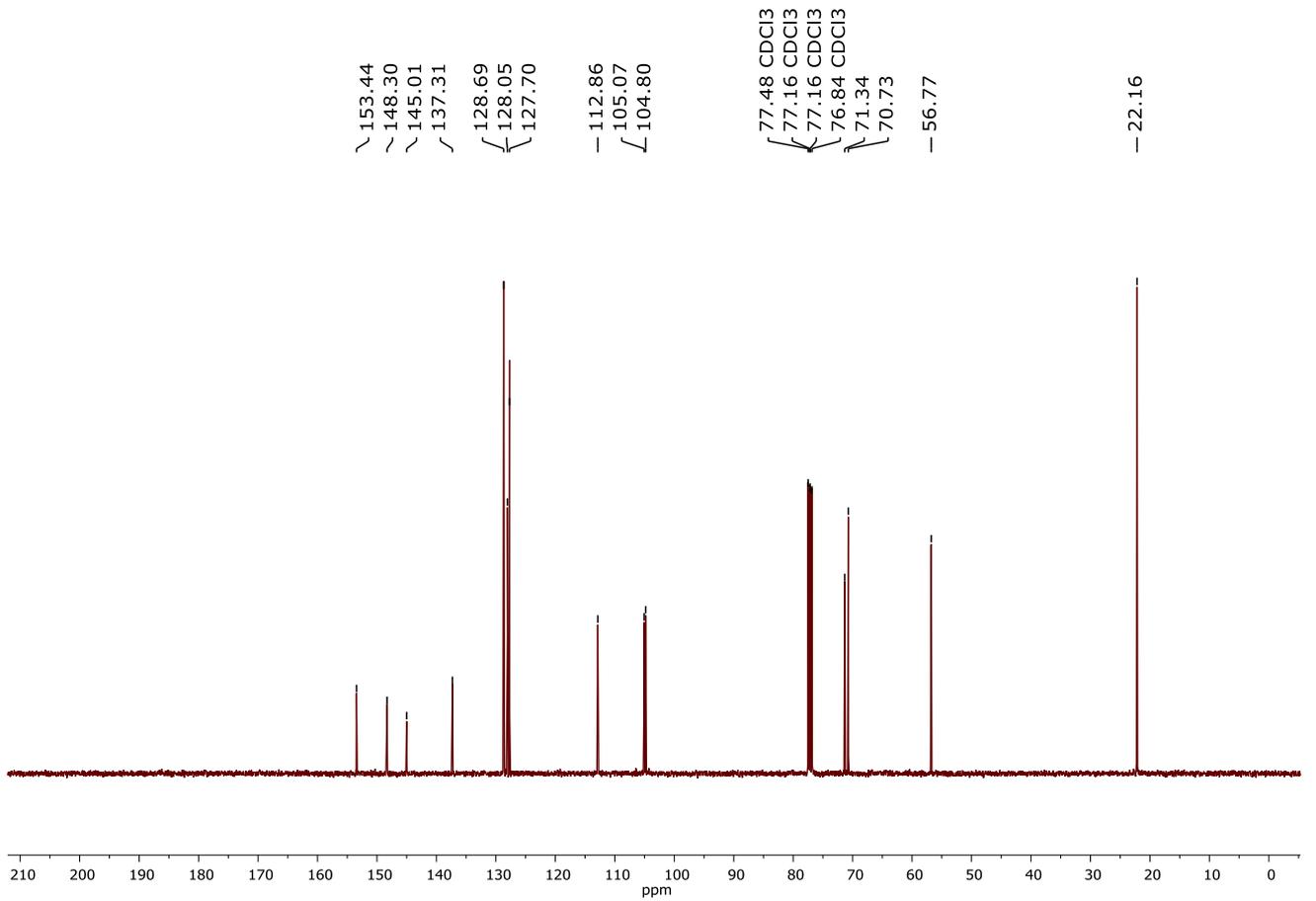
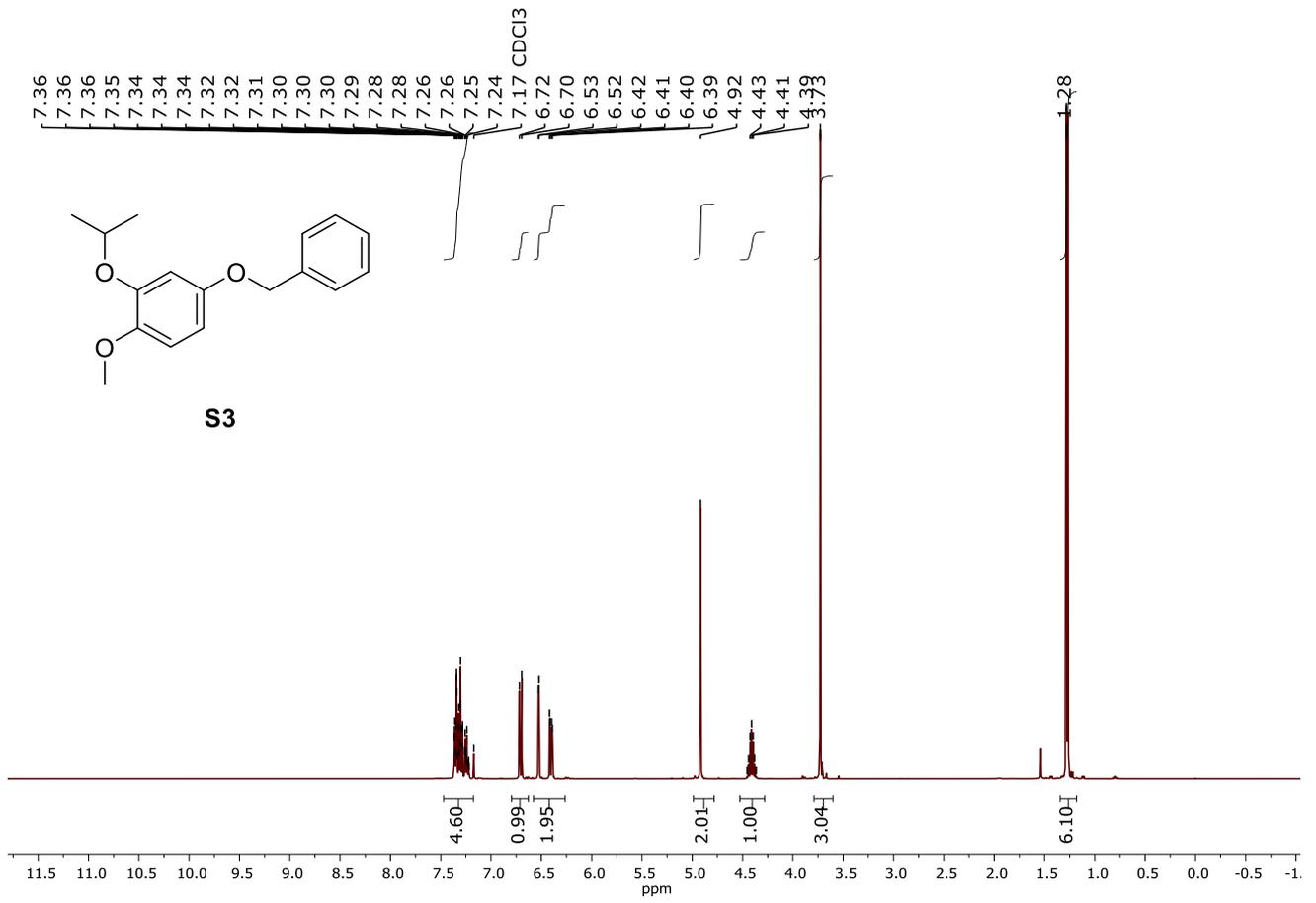
S6. NMR Spectra

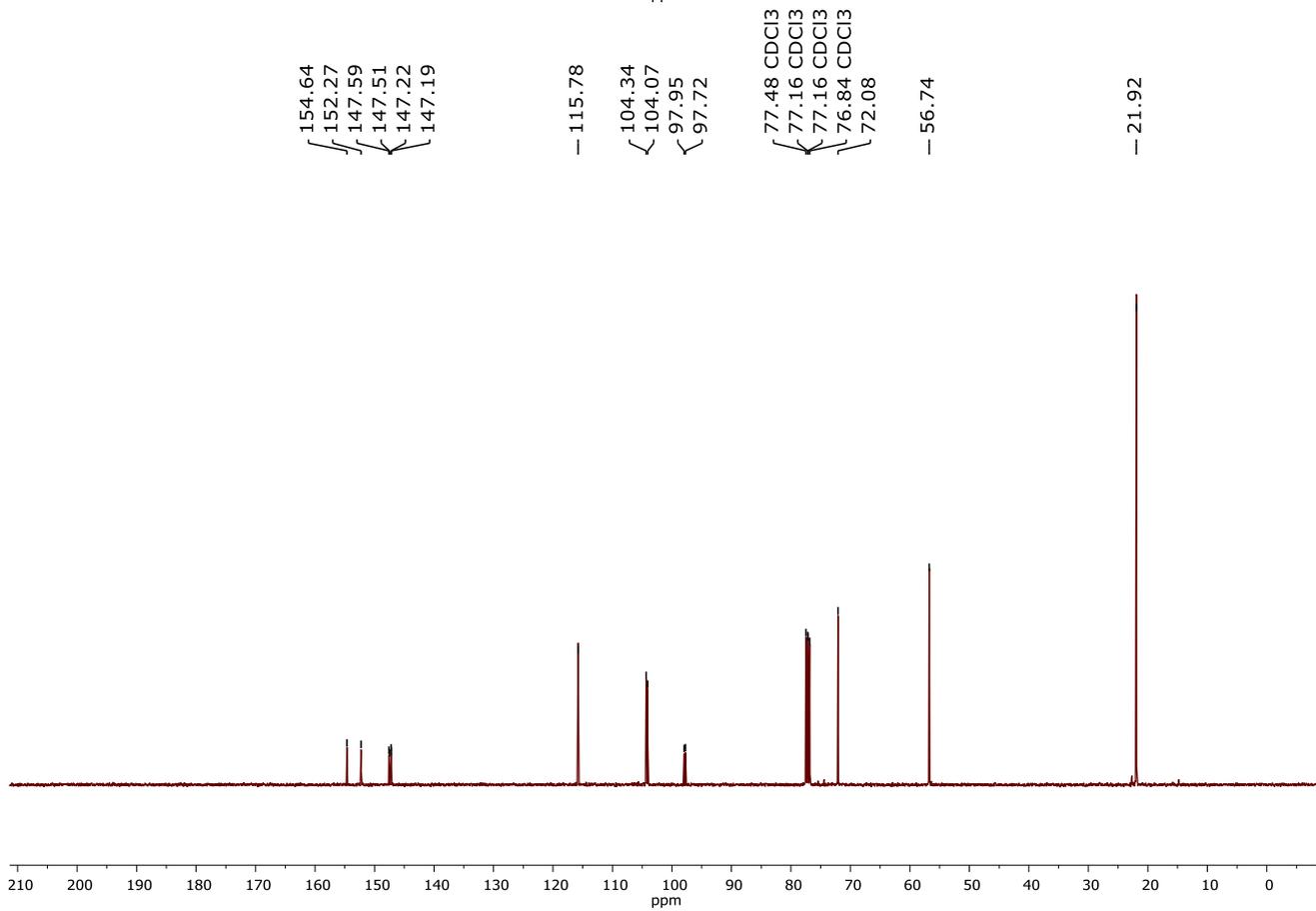
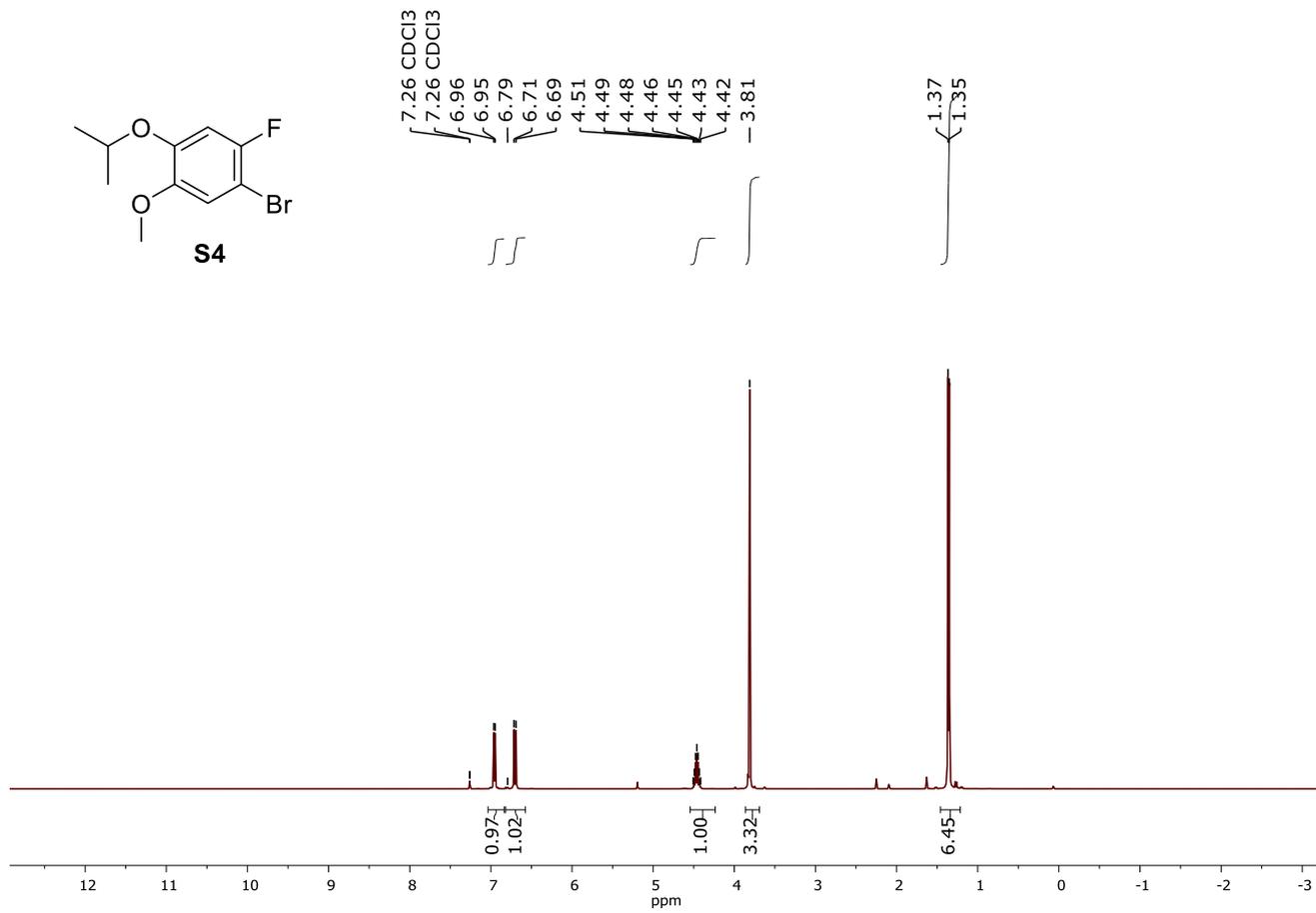
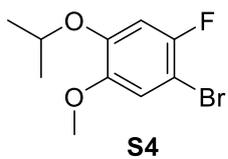


S1

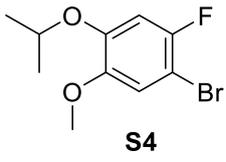




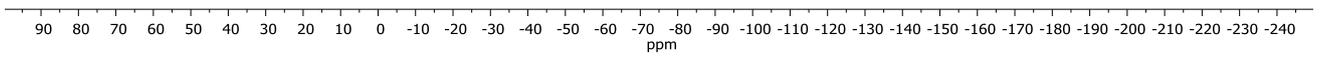


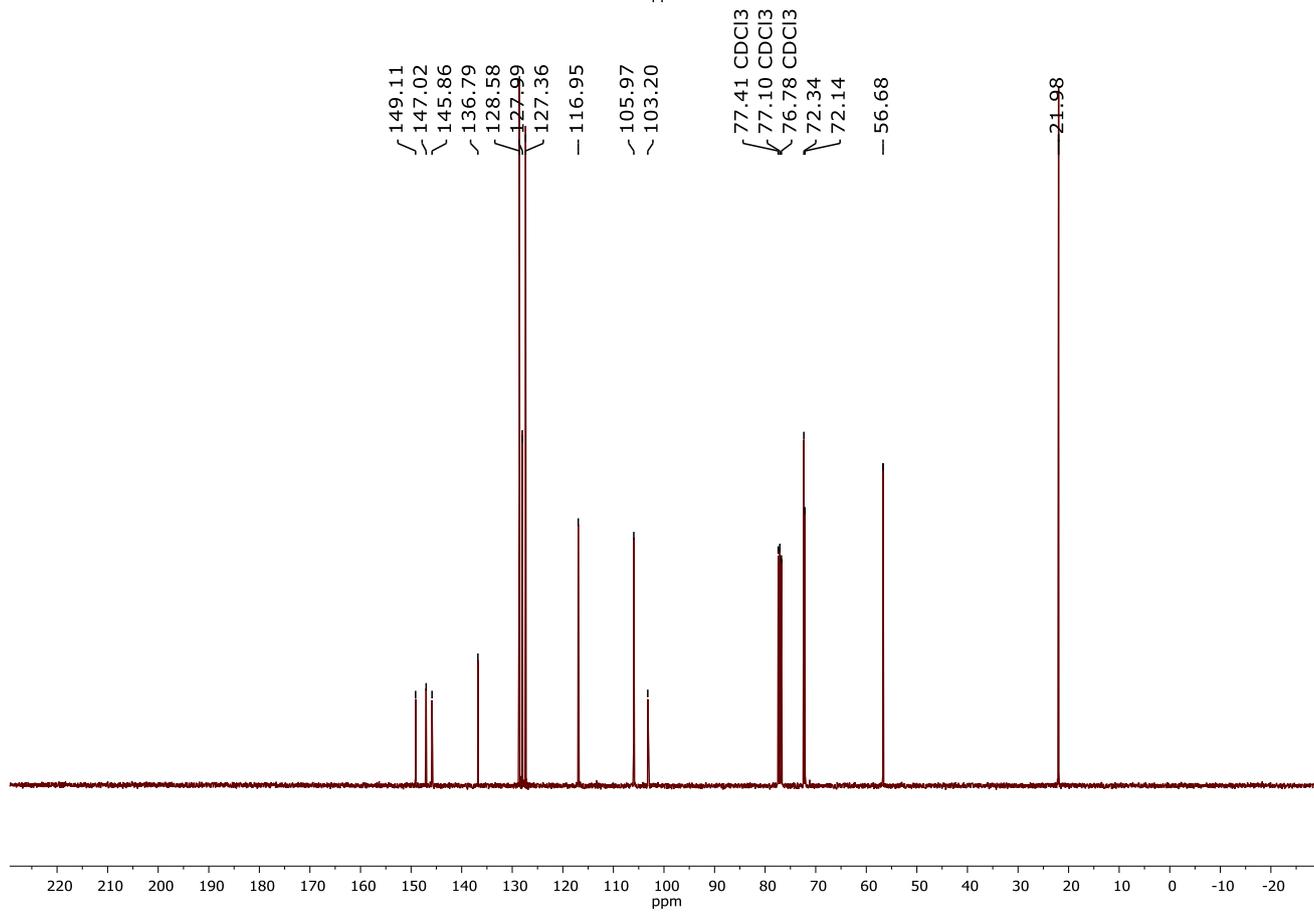
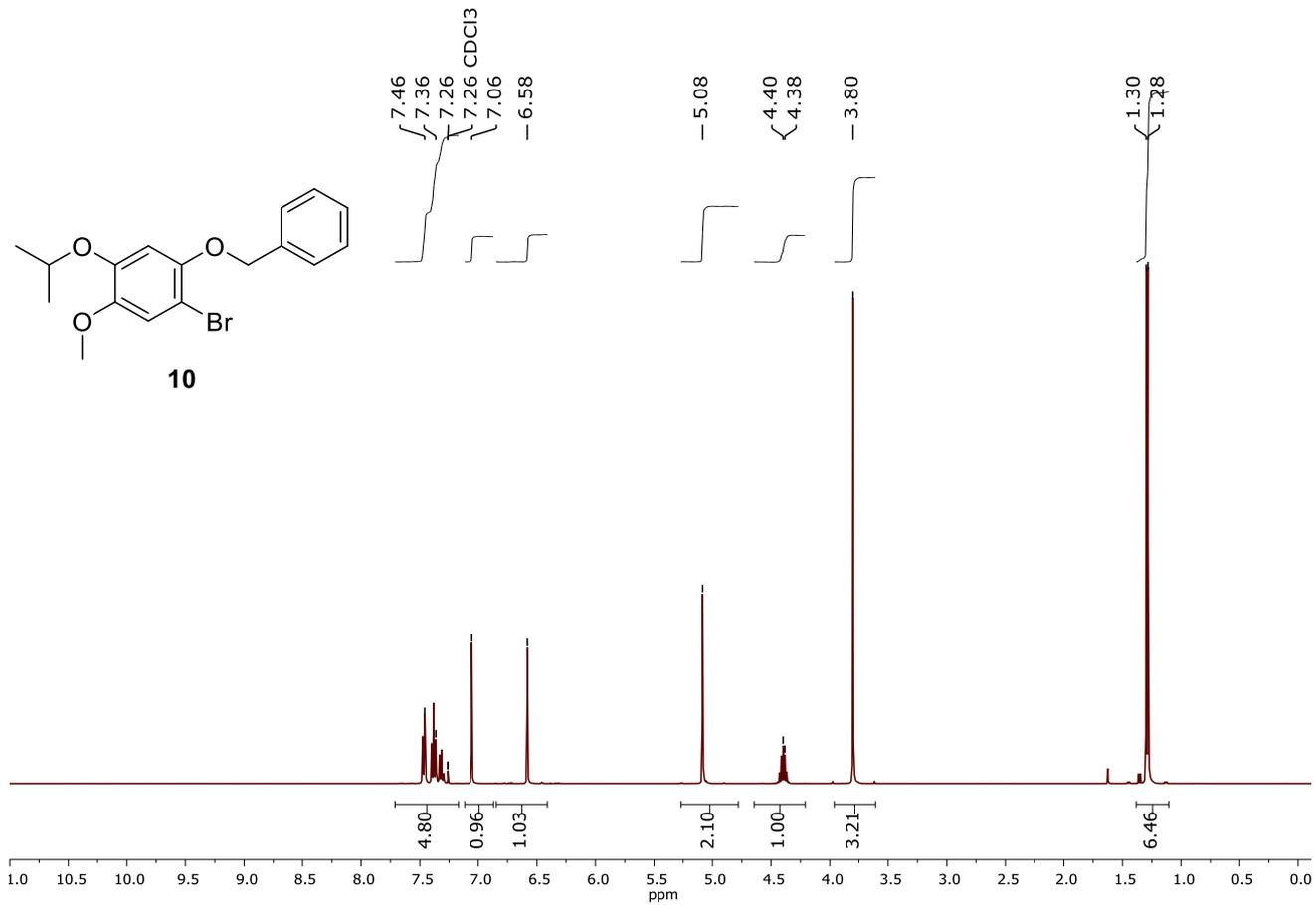


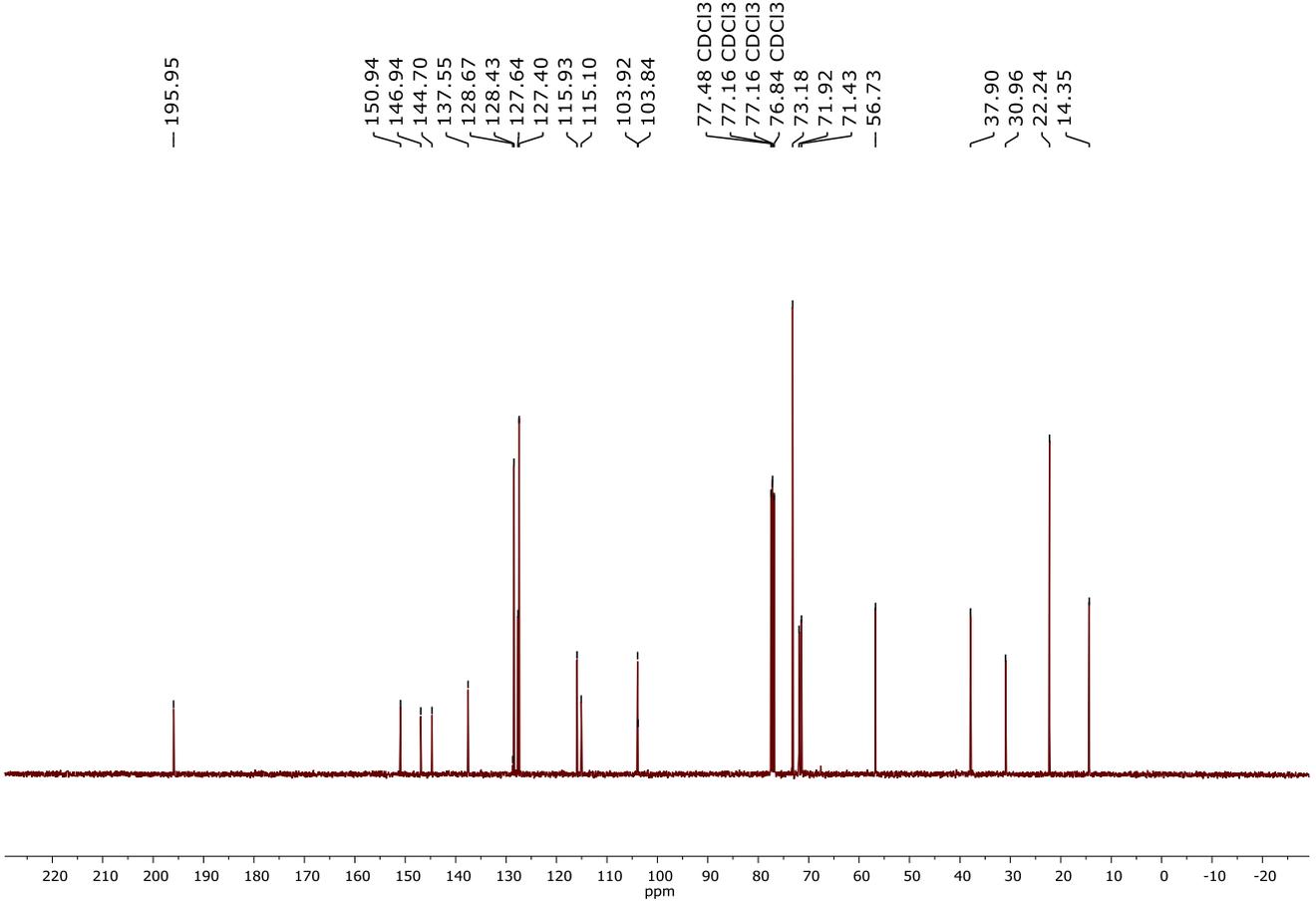
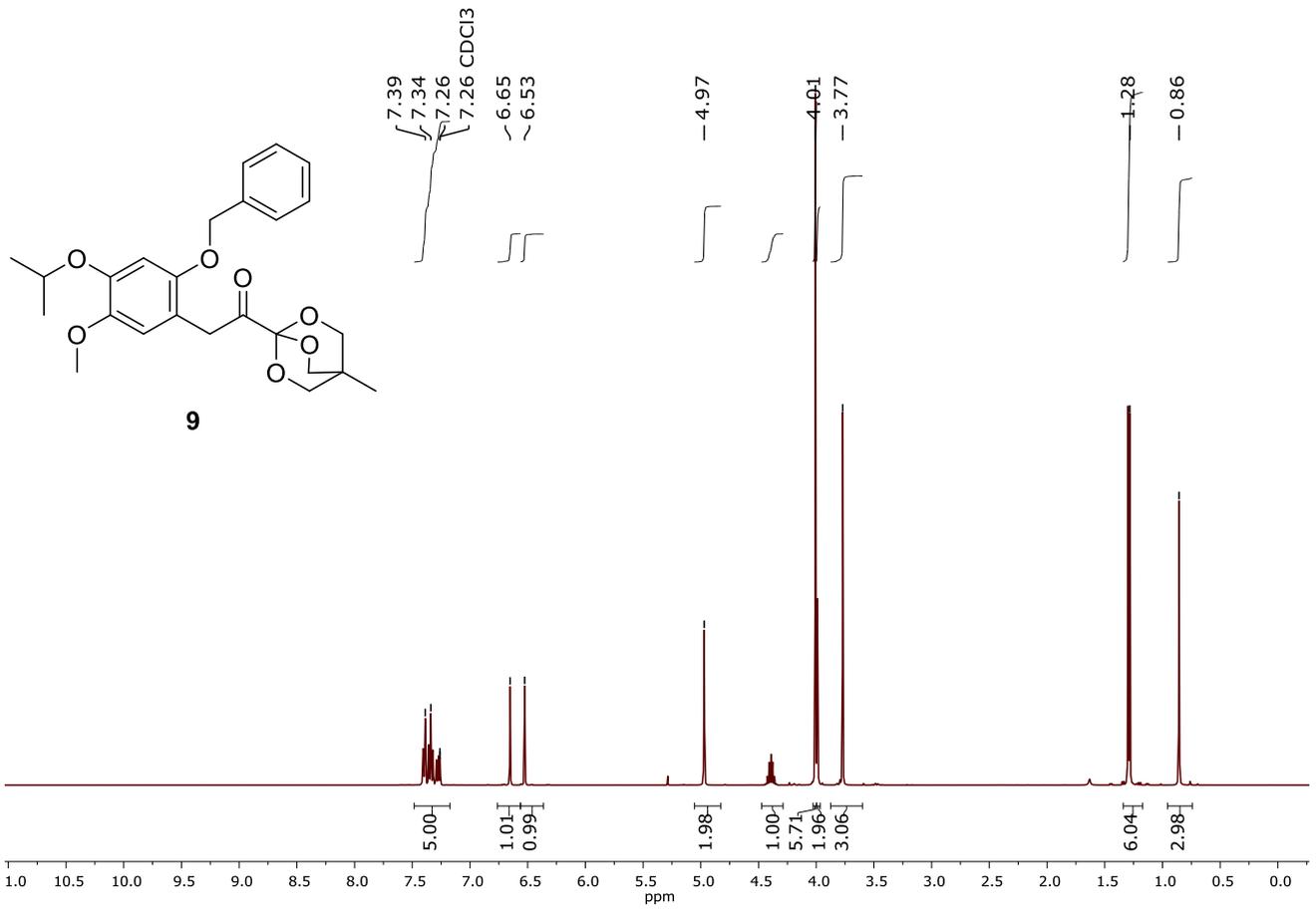
¹⁹F

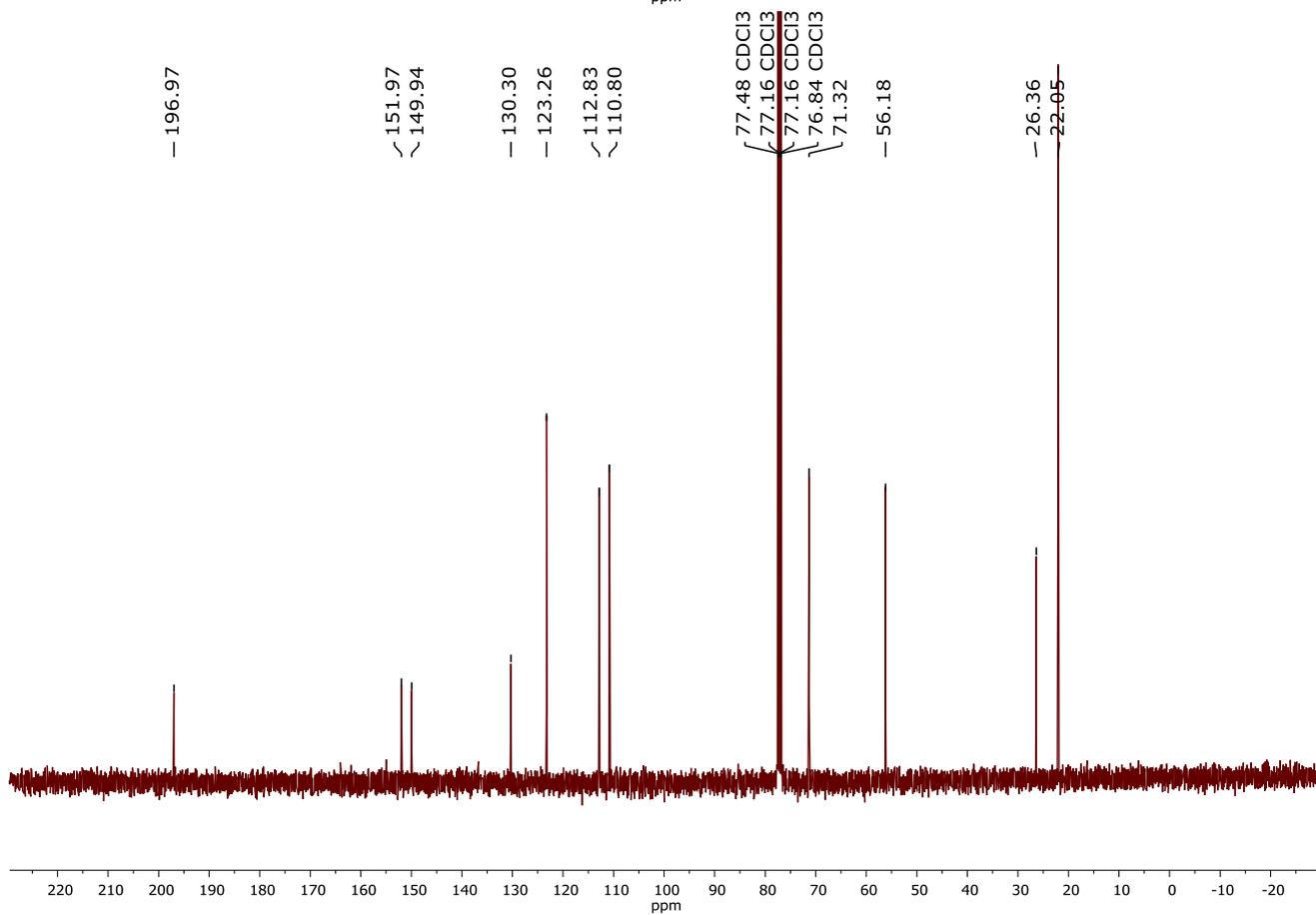
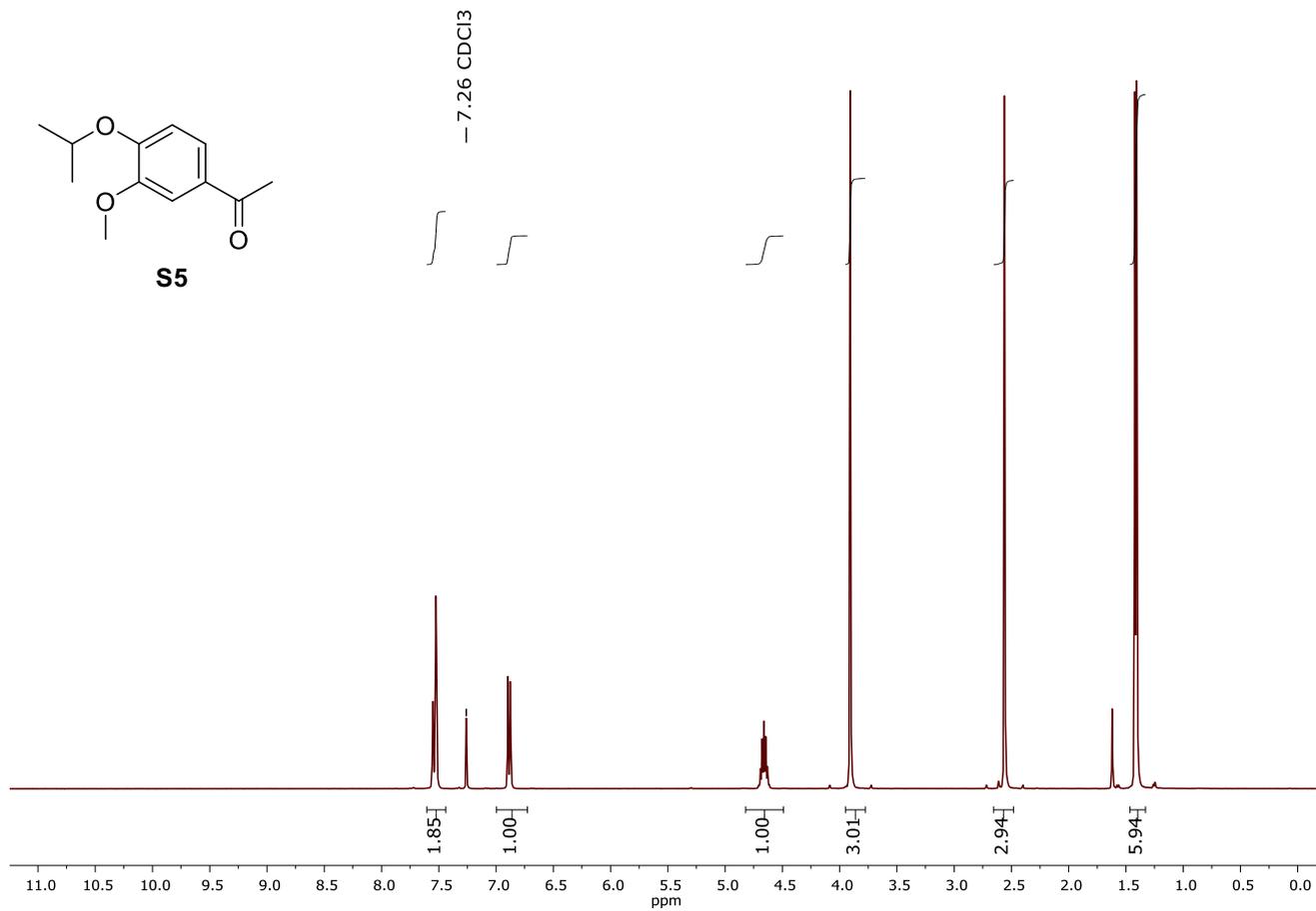
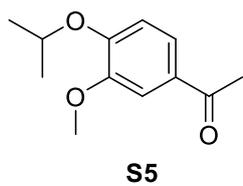


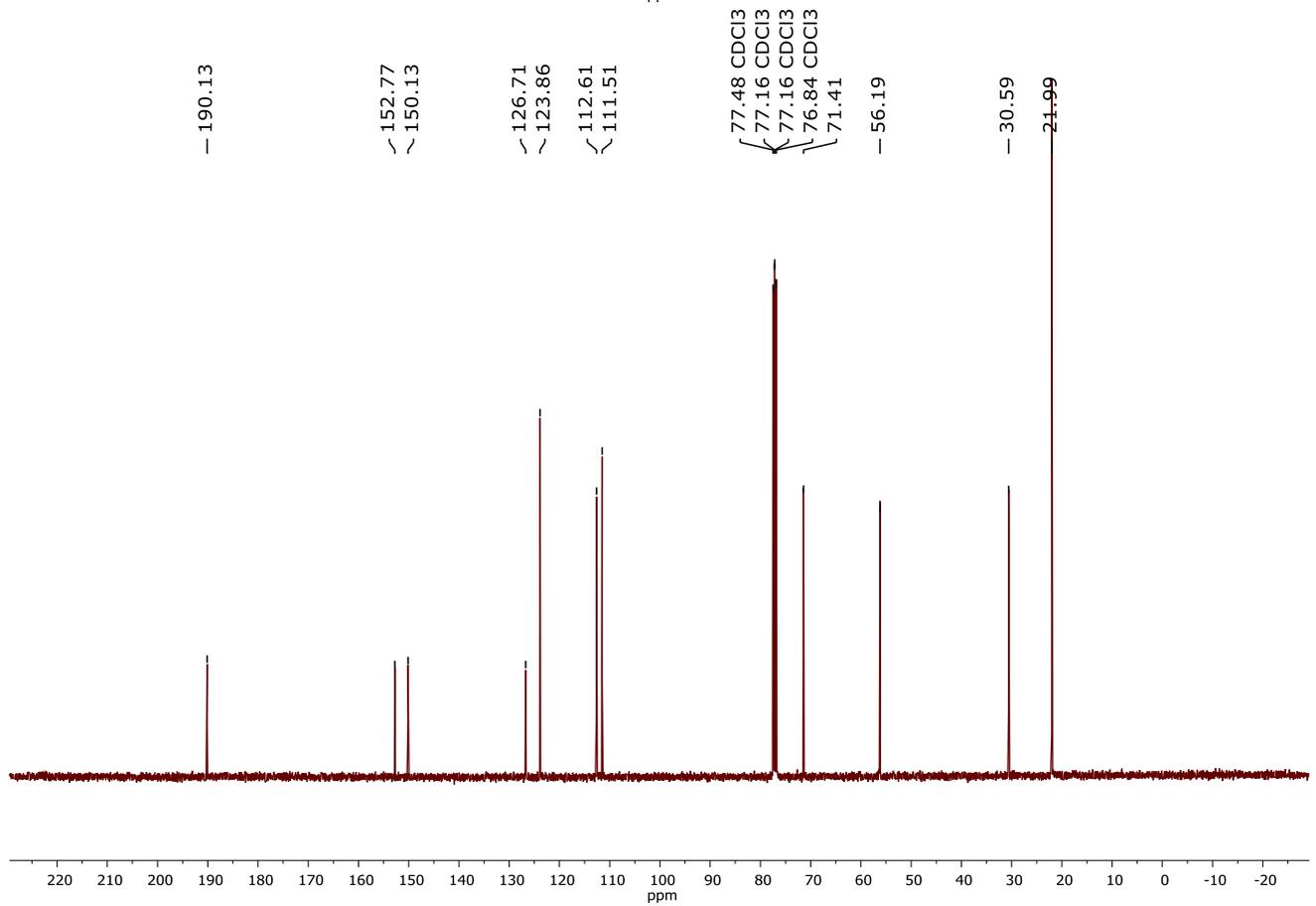
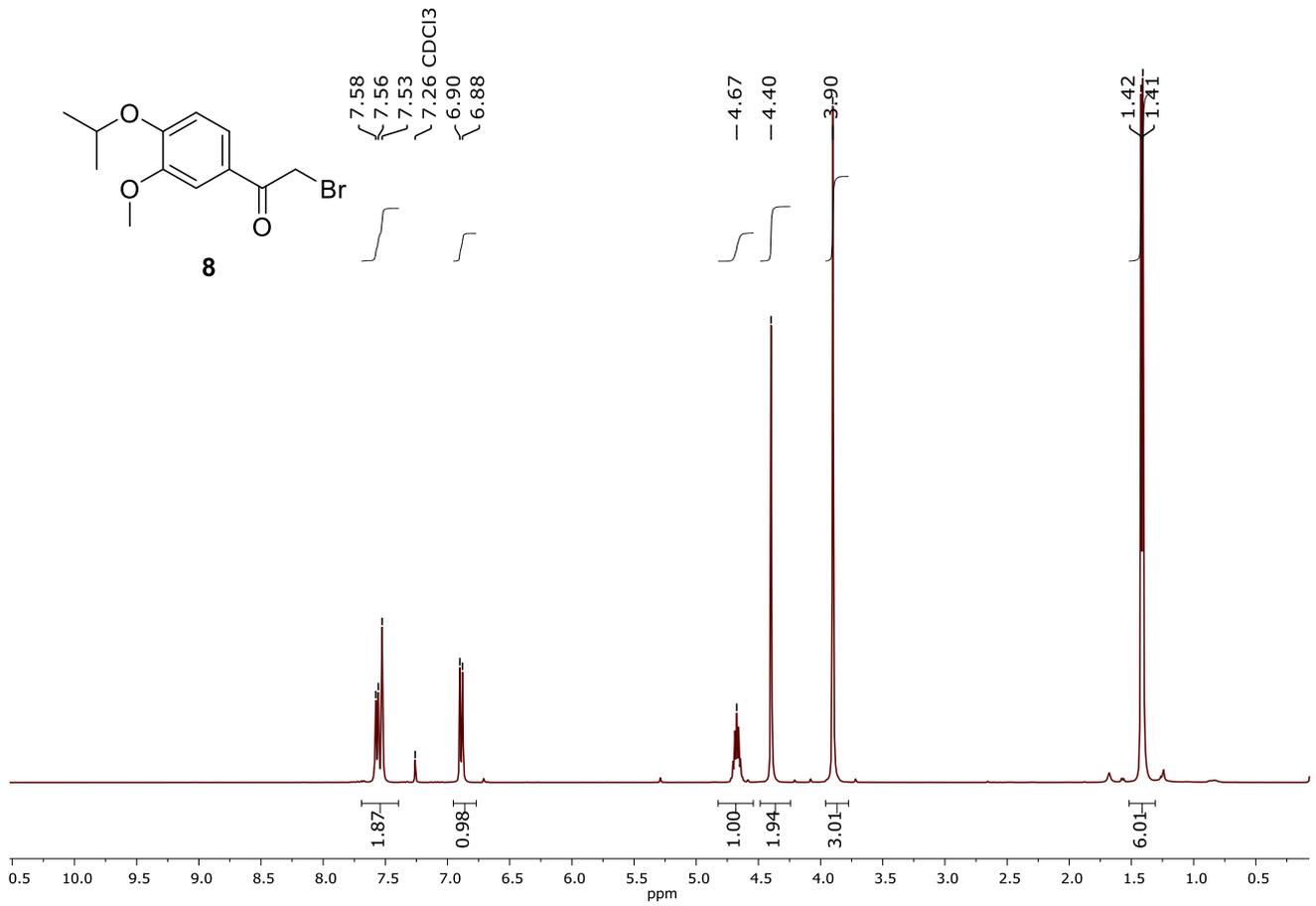
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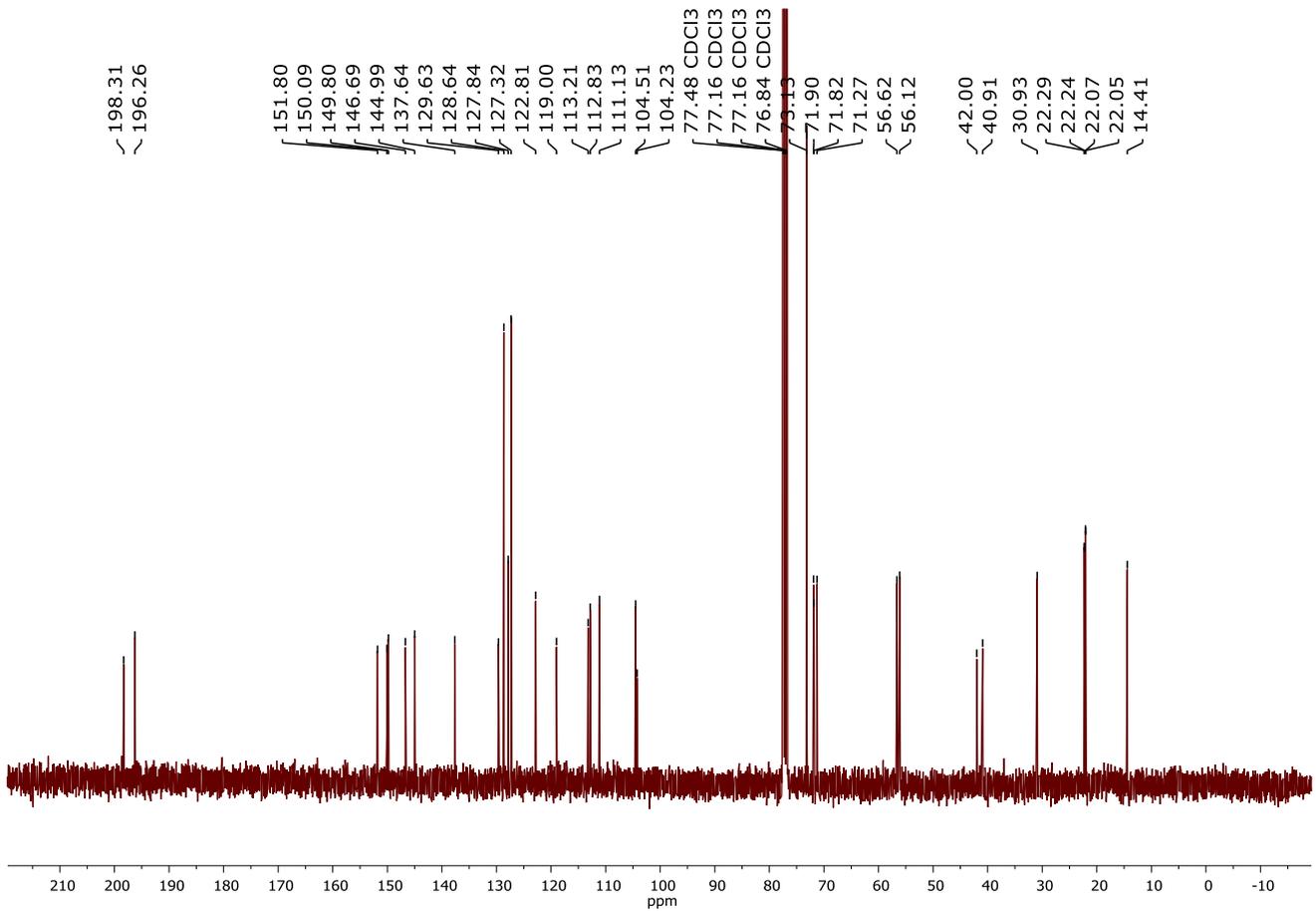
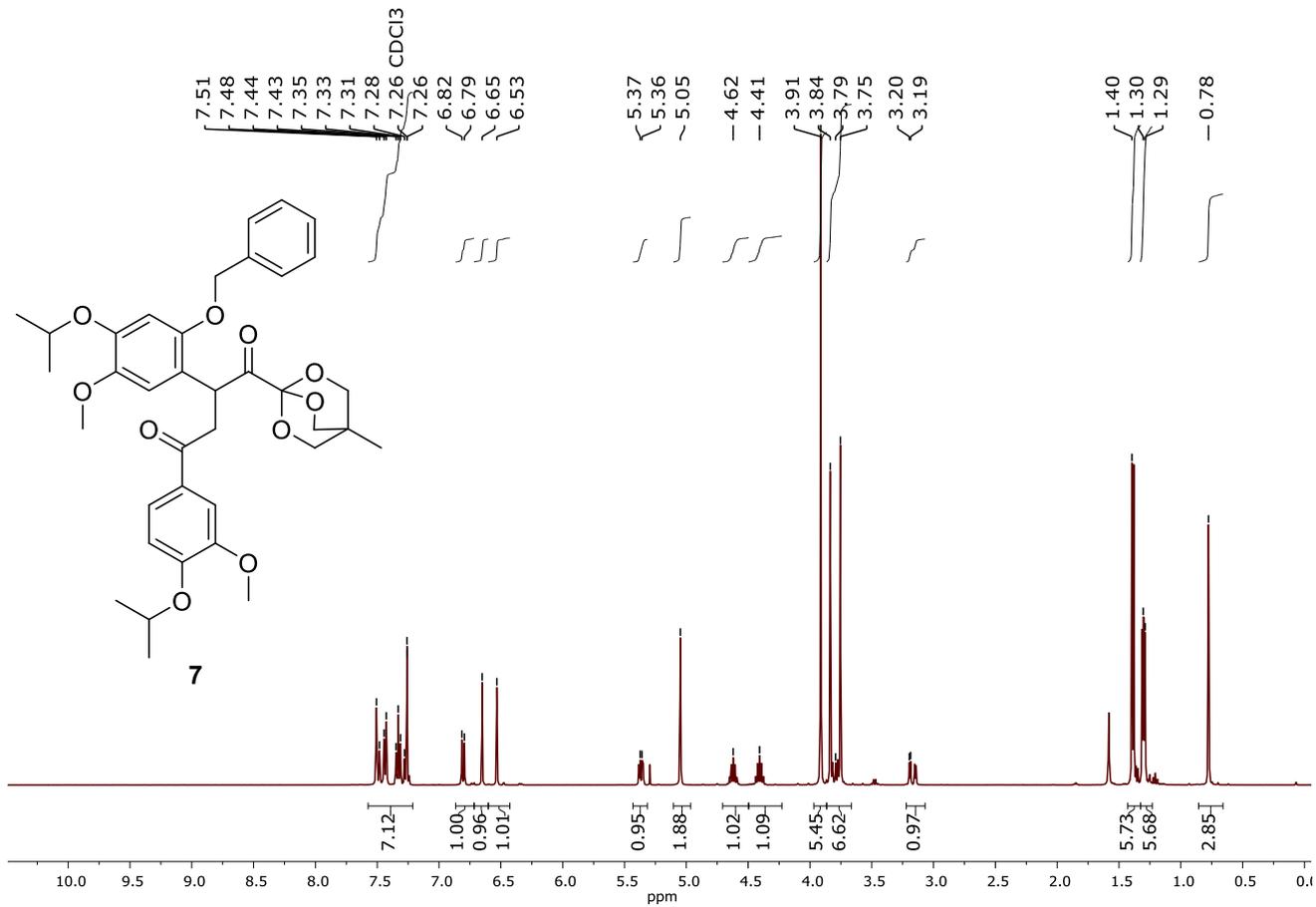


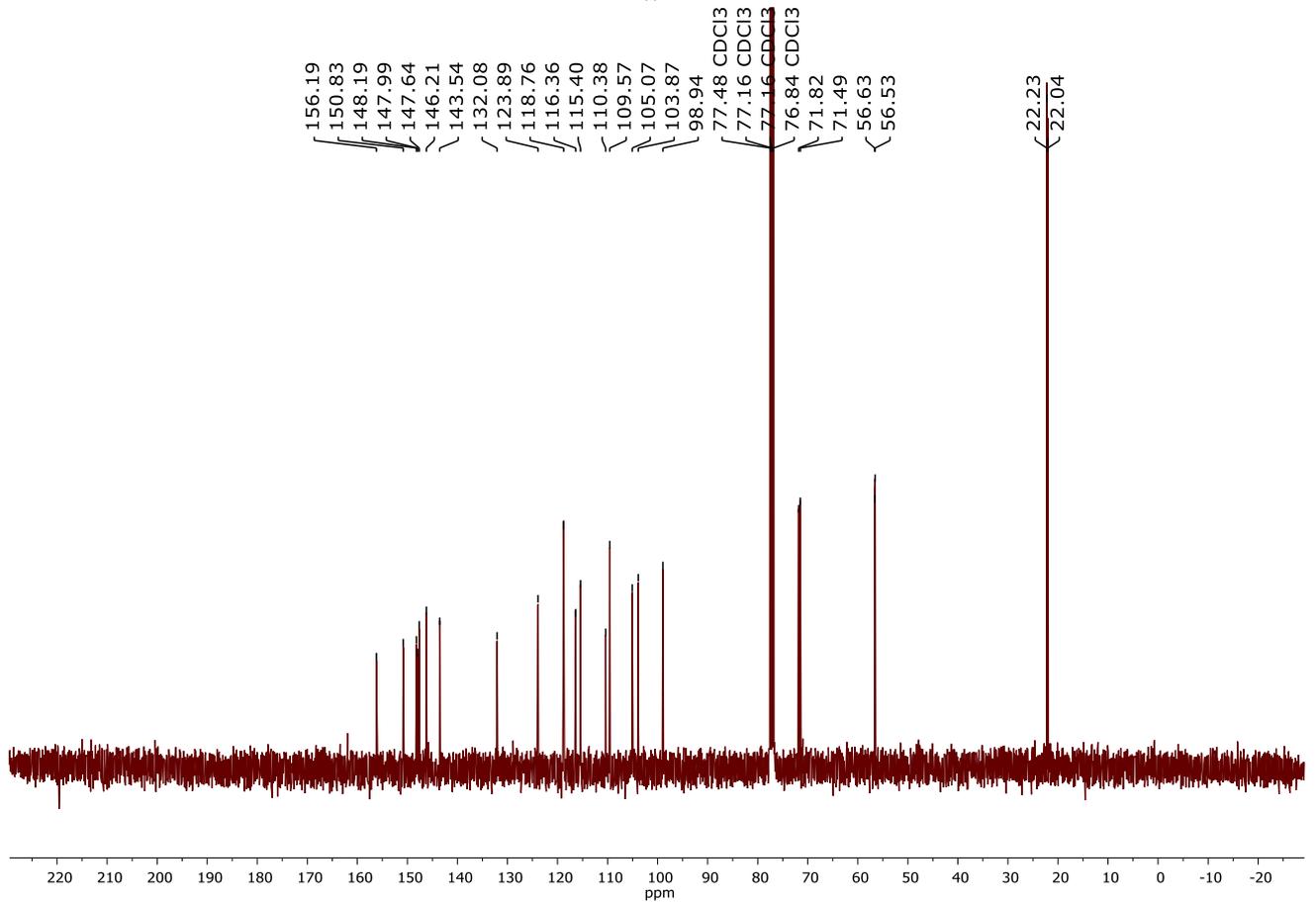
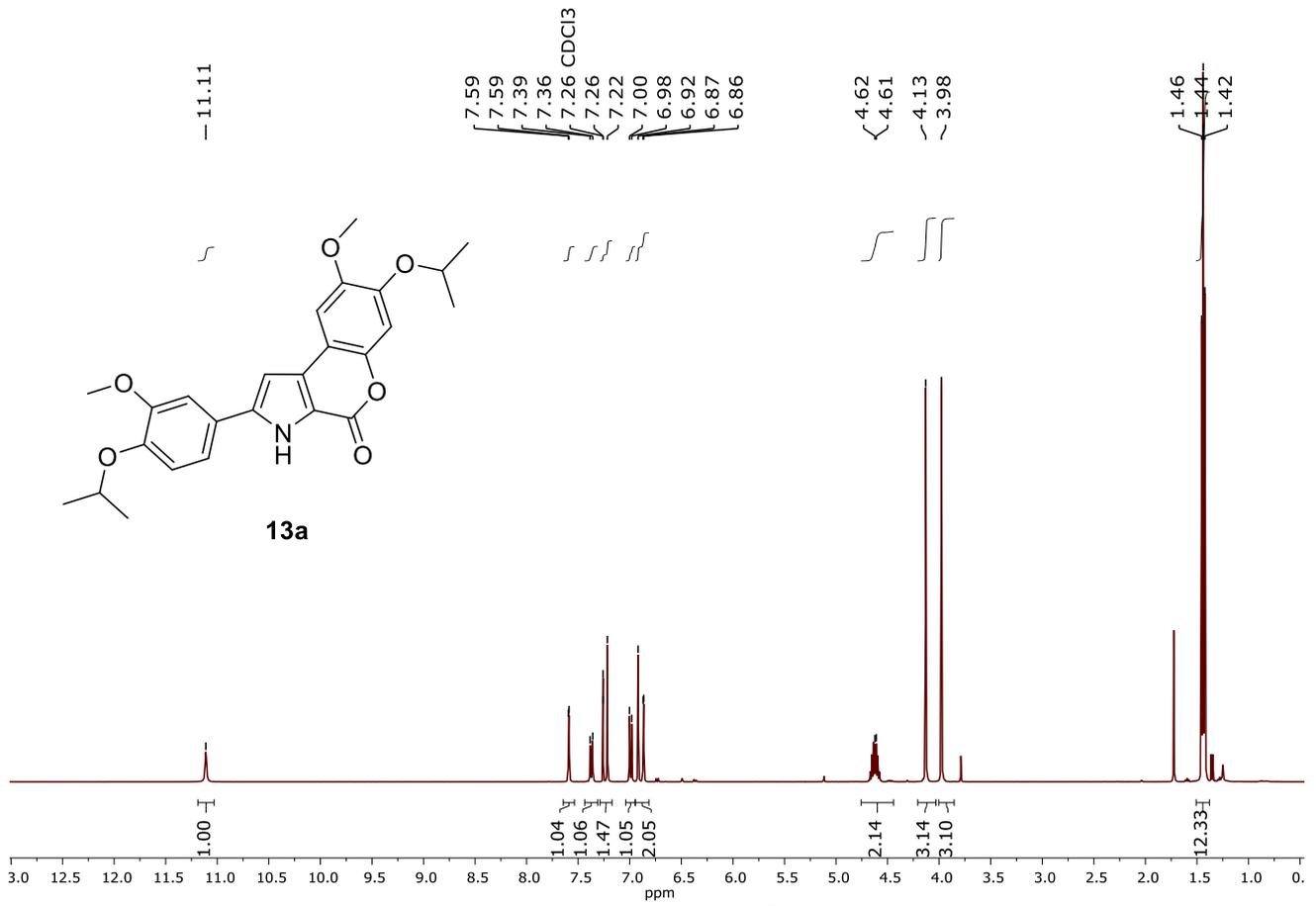


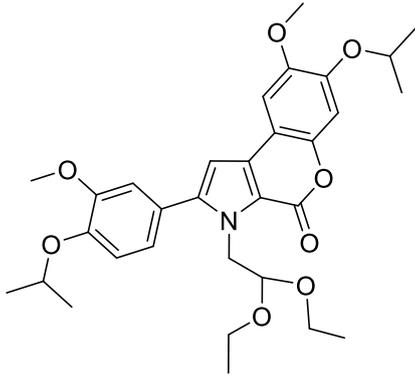












13b
unstable oil

