

De novo synthesis of phenolic dihydroxanthene near-infrared emitting fluorophores

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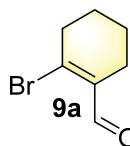
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Supporting Information Available

- I) Experimental Section
- II) Abbreviations
- III) ^1H and ^{13}C NMR Spectra of Compounds

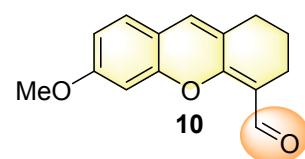
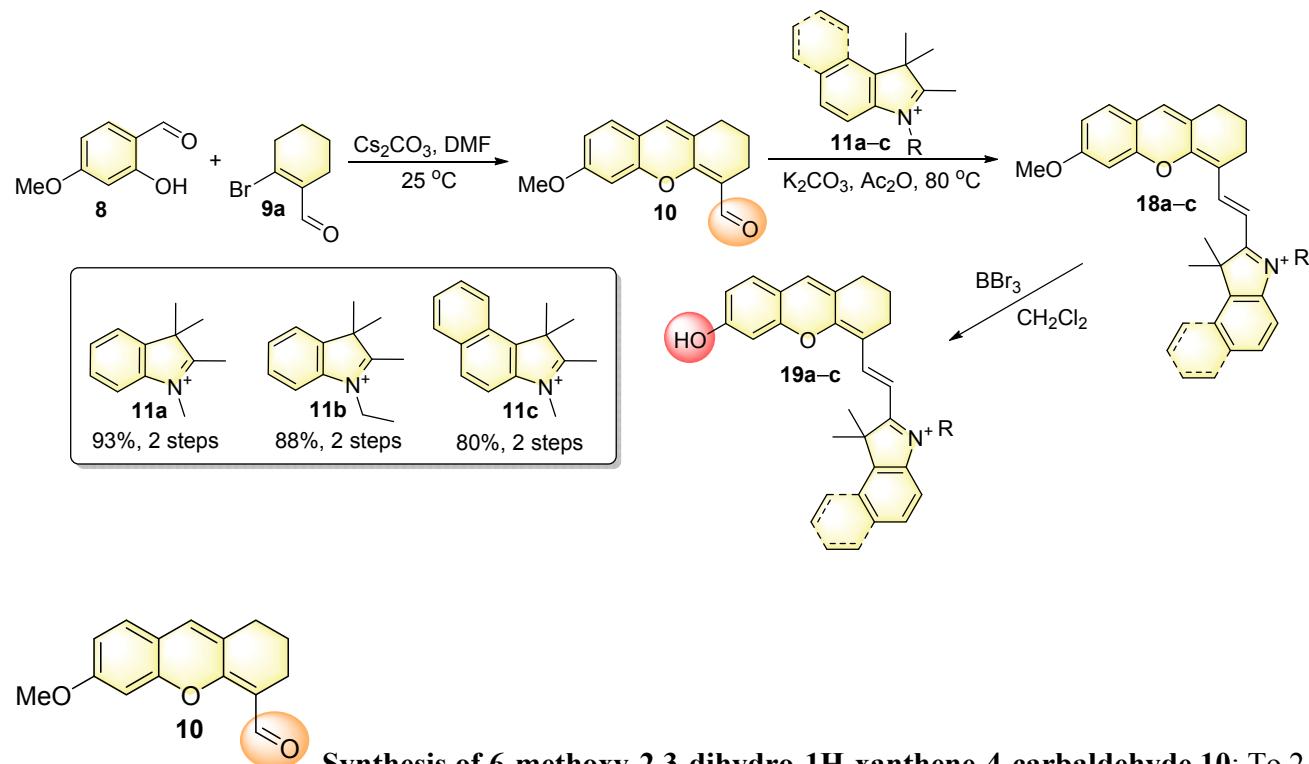
I) Experimental Section

General Procedures. All reactions were carried out under an argon atmosphere unless otherwise noted. *N,N'*-dimethylformamide (DMF) was purchased in anhydrous form and used without further purification. Water, ethyl acetate (EtOAc), diethyl ether (Et₂O), methylene chloride (CH₂Cl₂), and hexanes were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of ammonium molybdate, potassium permanganate and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. NMR spectra were recorded on a Bruker AV-600 instrument and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, pent = pentet, hex = hexet, br = broad. IR spectra were recorded on a Perkin-Elmer Spectrum One FTIR spectrometer with diamond ATR accessory. High-resolution mass spectra (HRMS) were recorded on an Agilent ESI TOF (time of flight) mass spectrometer at 3500 V emitter voltage.



2-bromocyclohex-1-ene-1-carbaldehyde 9a: To DMF (22.4 mL, 290 mmol) and CHCl₃ (100 mL) at 0 °C was slowly added PBr₃ (24.8 mL, 261 mmol). After 45 min, cyclohexanone (10 mL, 96.8 mmol) was added and the mixture was stirred for 16 h at 25 °C. The resulting red solution was then poured onto ice and solid NaHCO₃ was slowly added until pH ~ 7. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (100 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo* to provide a yellow oil (15.4 g) which was pure enough to be used directly in the next step. Enal 9a was found to be rather volatile and unstable at 25 °C but could be stored for months under N₂ at -20 °C.

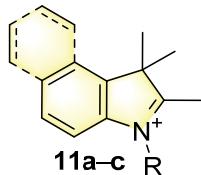
General scheme for the *de novo* synthesis of NIR dyes 19a-c:



Synthesis of 6-methoxy-2,3-dihydro-1H-xanthene-4-carbaldehyde 10: To 2-bromocyclohex-1-ene-1-carbaldehyde 9a (204 mg, 1.08 mmol) in DMF (6 mL) at 25 °C were added 2-hydroxy-4-methoxybenzaldehyde 8 (137 mg, 0.90 mmol) and Cs₂CO₃ (880 mg, 2.7 mmol). The

medium was stirred for 16 h at 25 °C and an intense yellow spot appeared on the TLC plate (TLC hexane/AcOEt : 8/2). The insolubles were then filtered on a pad of silica gel and the filtrate was concentrated. The resulting residue was dissolved in CH₂Cl₂ (30 mL) and washed with H₂O (2 × 15 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification on silica gel (CH₂Cl₂/AcOEt : 9/1) provided 6-methoxy-2,3-dihydro-1H-xanthene-4-carbaldehyde **10** as a deep yellow solid (164 mg, 75%).

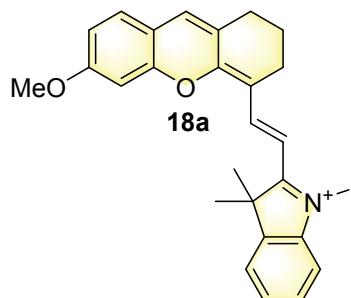
10: R_f = 0.5 (silica gel, hexanes/EtOAc 80:20); IR (film) ν_{max} 2937, 2843, 1627, 1609, 1567, 1507, 1444, 1395, 1357, 1272, 1261, 1203, 1179, 1167, 1125, 1112, 1052, 1029 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ = 10.29 (s, 1H), 7.16–7.09 (m, 1H), 6.76–6.67 (m, 3H), 3.88 (s, 3H), 2.61 (ddd, *J* = 7.7, 5.6, 1.6 Hz, 2H), 2.48 (t, *J* = 6.1 Hz, 2H), 1.81–1.69 (m, 2H); ¹³C NMR (150 MHz, CDCl₃): δ = 187.0, 161.8, 161.7, 153.7, 127.9, 127.8, 126.7, 114.9, 112.5, 111.4, 100.6, 55.9, 30.0, 21.7, 20.5 ppm; HRMS (ESI): *m/z* calcd for C₁₅H₁₅O₃⁺ [M + H]⁺ 243.1021, found 243.1017.



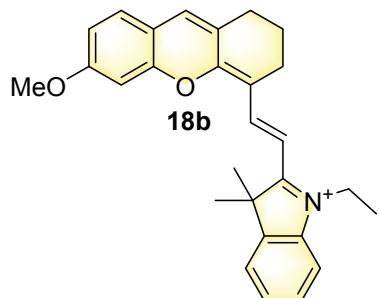
Preparation of indolium species **11a–c:** To a solution of 2,3,3-trimethylindolenine or 1,1,2-trimethylbenz[e]indole in acetonitrile or toluene were added methyl or ethyl iodide (1.5 eq.) and the reaction mixture was heated at reflux for 12 h. The resulting solid was filtered under vacuum, washed with Et₂O and dried to afford pure indolium **11a–c**.

General procedure for the synthesis of OMe-protected NIR dyes **18a–c:** To a solution of 6-methoxy-2,3-dihydro-1H-xanthene-4-carbaldehyde **10** in anhydrous Ac₂O were added K₂CO₃ (2 eq.) and indolium **11a–c** (1.2 eq.). After 16 h at 80 °C the deep blue solution obtained was concentrated and the resulting residue dissolved in CH₂Cl₂ and washed with H₂O. The organic layer was dried over Na₂SO₄,

filtered and concentrated *in vacuo*. Purification on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 2 to 5%) afforded protected NIR fluorophores **18a–c** as blue solids.

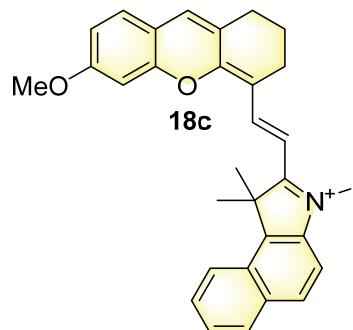


18a: $R_f = 0.5$ (silica gel, $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 90:10); IR (film) ν_{\max} 3406, 2920, 1709, 1645, 1614, 1537, 1490, 1458, 1407, 1371, 1276, 1232, 1176, 1130, 1115, 1020, 947, 926, 748 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ = 8.63 (d, J = 14.7 Hz, 1H), 7.47 (dd, J = 13.2, 7.5 Hz, 2H), 7.43–7.32 (m, 3H), 7.26 (s, 1H), 6.93–6.80 (m, 2H), 6.51 (d, J = 14.7 Hz, 1H), 4.03 (s, 3H), 3.96 (s, 3H), 2.79 (t, J = 6.3 Hz, 2H), 2.73 (t, J = 6.3 Hz, 2H), 1.92 (t, J = 6.3 Hz, 2H), 1.79 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3): δ = 177.6, 163.2, 161.9, 154.6, 145.8, 142.3, 141.6, 133.9, 129.3, 128.9, 127.5, 127.3, 122.4, 115.9, 115.4, 113.4, 112.8, 104.6, 101.0, 56.3, 50.6, 34.6, 29.4, 28.3 (2C), 24.8, 20.4 ppm; HRMS (ESI): m/z calcd for $\text{C}_{27}\text{H}_{28}\text{N}_2\text{O}^+$ $[\text{M}^*]^+$ 398.2115, found 398.2133.



18b: $R_f = 0.5$ (silica gel, $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 90:10); IR (film) ν_{\max} 3417, 1771, 1625, 1568, 1526, 1440, 1421, 1371, 1275, 1244, 1213, 1184, 1174, 1115, 1080 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ = 8.61 (d, J = 14.7 Hz, 1H), 7.52–7.48 (m, 1H), 7.45 (td, J = 7.8, 1.3 Hz, 1H), 7.38 (dt, J = 22.6, 7.8 Hz, 3H), 7.30 (s, 1H), 6.87 (dd, J = 8.6, 2.4 Hz, 1H), 6.82 (d, J = 2.4 Hz, 1H), 6.45 (d, J = 14.7 Hz, 1H), 4.49 (q, J = 7.4 Hz, 2H), 3.94 (s, 3H), 2.78–2.71 (m, 4H), 1.96–1.87 (m, 2H), 1.78 (s, 6H), 1.50 (t, J = 7.4 Hz, 3H);

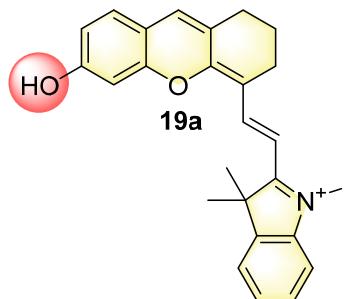
¹³C NMR (150 MHz, CDCl₃): δ = 176.6, 163.2, 162.0, 154.5, 145.7, 141.8, 141.1, 134.3, 129.3, 129.0, 127.3(2), 127.2(8), 122.7, 115.8, 115.1, 113.4, 112.5, 103.5, 100.8, 56.5, 50.6, 41.5, 29.2, 28.3 (2C), 24.8, 20.3, 13.0 ppm; HRMS (ESI): *m/z* calcd for C₂₈H₃₀N₂O⁺[M*]⁺ 412.2271, found 412.2283.



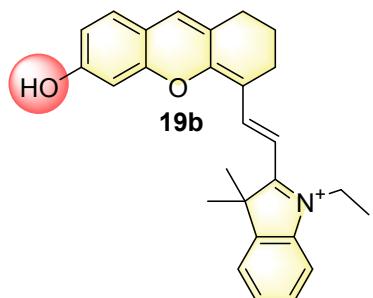
18c: R_f = 0.5 (silica gel, CH₂Cl₂/CH₃OH 90:10); IR (film) ν_{max} 3415, 2935, 1625, 1568, 1532, 1508, 1478, 1447, 1412, 1372, 1359, 1299, 1279, 1259, 1243, 1209, 1174, 1123, 1066, 1017, 941 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ = 8.74 (d, *J* = 15.0 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.8 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 1H), 7.67 (ddd, *J* = 8.5, 6.7, 1.3 Hz, 1H), 7.55 (dd, *J* = 8.0, 6.7 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.15 (s, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.63 (d, *J* = 15.0 Hz, 1H), 4.21 (s, 3H), 3.99 (s, 3H), 2.80 (t, *J* = 6.2 Hz, 2H), 2.72 (t, *J* = 6.2 Hz, 2H), 2.05 (s, 6H), 1.94 (t, *J* = 6.2 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃): δ = 179.2, 163.1, 161.1, 154.7, 145.0, 139.9, 135.5, 133.0(1), 132.9(5), 131.4, 130.4, 128.6, 128.2, 127.8, 127.6, 126.3, 122.5, 115.8, 115.1, 113.2, 111.9, 104.5, 101.1, 56.4, 52.4, 34.3, 29.4, 27.8 (2C), 24.5, 20.5 ppm; HRMS (ESI): *m/z* calcd for C₃₁H₃₀N₂O⁺[M*]⁺ 448.2271, found 448.2275.

General procedure for the synthesis of NIR dyes 19a-c: To a CH₂Cl₂ solution of the protected dyes **18a-c** obtained above was added BBr₃ (20 eq.) at 0 °C and the medium was stirred for 16 h at 25 °C. Quenching with a saturated solution of NaHCO₃ at 0 °C was followed by extraction of the aqueous layer with CH₂Cl₂. The organic layer was then washed with H₂O, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Purification on silica gel (CH₂Cl₂/MeOH 5 to 10%) afforded NIR dyes **19a-c** as

blue solids.

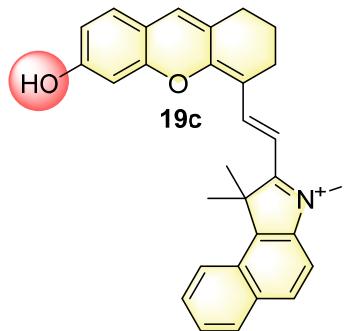


19a: $R_f = 0.4$ (silica gel, $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 90:10); IR (film) ν_{\max} 3377, 2300, 1626, 1457, 1367, 1191, 1172, 1112, 1019 cm^{-1} ; ^1H NMR (600 MHz, CD_3OD) δ = 8.62 (d, $J = 14.4$ Hz, 1H), 7.59 (d, $J = 7.5$ Hz, 1H), 7.52 (s, 1H), 7.48 (t, $J = 7.7$ Hz, 1H), 7.42–7.39 (m, 2H), 7.35 (t, $J = 7.4$ Hz, 1H), 6.82 (dd, $J = 8.6$, 2.2 Hz, 1H), 6.74 (d, $J = 2.2$ Hz, 1H), 6.27 (d, $J = 14.4$ Hz, 1H), 3.73 (s, 3H), 2.79 (t, $J = 6.2$ Hz, 2H), 2.72 (t, $J = 6.2$ Hz, 2H), 1.95 (t, $J = 6.2$ Hz, 2H), 1.81 (s, 6H); ^{13}C NMR (150 MHz, CD_3OD): δ = 177.0, 171.0, 164.6, 158.4, 145.1, 144.6, 144.4, 139.5, 131.6, 130.8, 127.7, 125.9, 124.3, 120.2, 117.0, 116.8, 113.2, 104.2, 102.3, 51.7, 32.8, 30.6, 29.4 (2C), 26.1, 22.8 ppm; HRMS (ESI): m/z calcd for $\text{C}_{26}\text{H}_{26}\text{NO}_2^+ [\text{M}]^+$ 384.1958, found 384.1964.



19b: $R_f = 0.4$ (silica gel, $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 90:10); IR (film) ν_{\max} 3394, 2300, 1625, 1530, 1438, 1372, 1278, 1256, 1213, 1188, 1114, 1081 cm^{-1} ; ^1H NMR (600 MHz, CD_3OD) δ = 8.72 (d, $J = 14.6$ Hz, 1H), 7.65 (d, $J = 7.3$ Hz, 1H), 7.58–7.48 (m, 2H), 7.48–7.32 (m, 3H), 6.96–6.74 (m, 2H), 6.43 (d, $J = 14.6$ Hz, 1H), 4.37 (q, $J = 7.3$ Hz, 2H), 2.80 (t, $J = 6.1$ Hz, 2H), 2.74 (t, $J = 6.1$ Hz, 2H), 2.02–1.91 (m, 2H), 1.83 (s, 6H), 1.49 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD): δ = 178.0, 166.6, 164.5, 157.5,

146.7, 144.0, 143.6, 137.8, 131.4, 131.0, 128.6, 127.6, 124.6, 117.8, 117.1, 116.5, 113.9, 103.9, 103.7, 52.4, 41.9, 30.7, 29.3 (2C), 26.0, 22.6, 13.6 ppm; HRMS (ESI): m/z calcd for $C_{27}H_{28}N_2O^+ [M^*]^+$ 398.2115, found 398.2125.

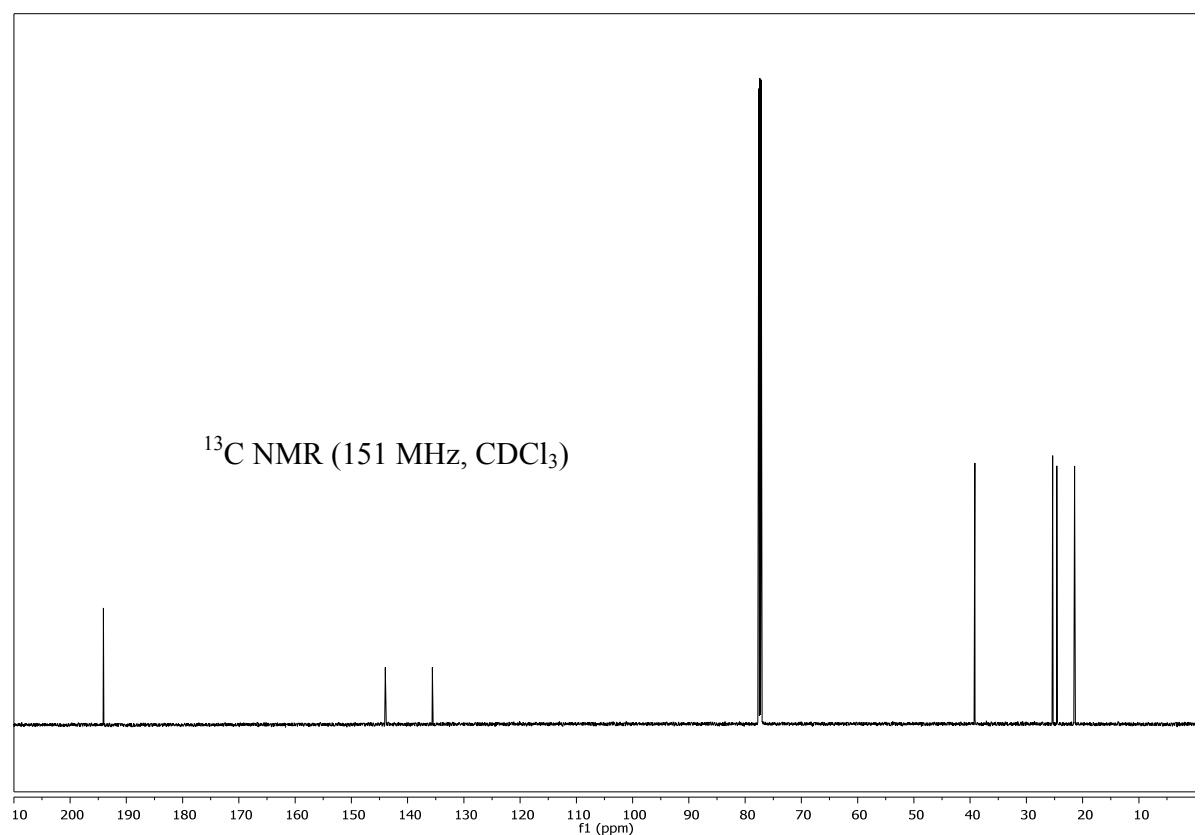
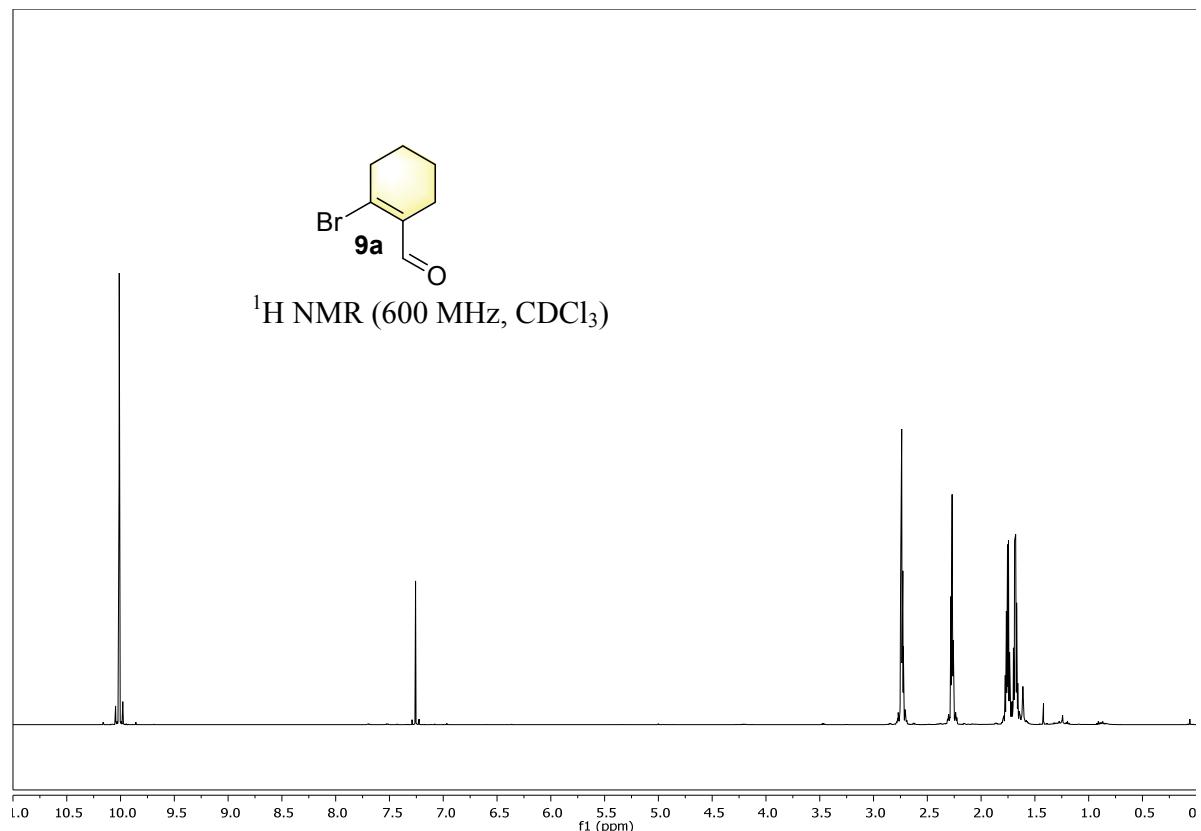


19c: $R_f = 0.4$ (silica gel, CH_2Cl_2/CH_3OH 90:10); IR (film) ν_{max} 3406, 1626, 1560, 1508, 1469, 1445, 1416, 1360, 1295, 1255, 1191, 1122, 940 cm^{-1} ; 1H NMR (600 MHz, CD_3OD) δ = 8.82 (d, J = 14.8 Hz, 1H), 8.37 (d, J = 8.7 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 8.08 (d, J = 8.2 Hz, 1H), 7.85–7.66 (m, 2H), 7.64–7.48 (m, 1H), 7.48–7.25 (m, 2H), 6.94–6.69 (m, 2H), 6.45 (d, J = 14.8 Hz, 1H), 3.94 (s, 3H), 2.81 (t, J = 6.2 Hz, 2H), 2.77 (t, J = 6.2 Hz, 2H), 2.19 (s, 3H), 2.11 (s, 3H), 2.01–1.94 (m, 2H); ^{13}C NMR (150 MHz, CD_3OD): δ = 179.8, 168.2, 164.0, 157.8, 145.1, 142.3, 137.8, 136.8, 134.8, 132.8, 132.1, 131.3, 130.0, 129.9, 127.6, 127.0, 124.4, 118.5, 117.0, 116.4, 113.2, 104.1, 103.5, 53.9, 33.5, 30.7, 28.9 (2C), 26.0, 22.7 ppm; HRMS (ESI): m/z calcd for $C_{30}H_{28}N_2O^+ [M^*]^+$ 434.2115, found 434.2130.

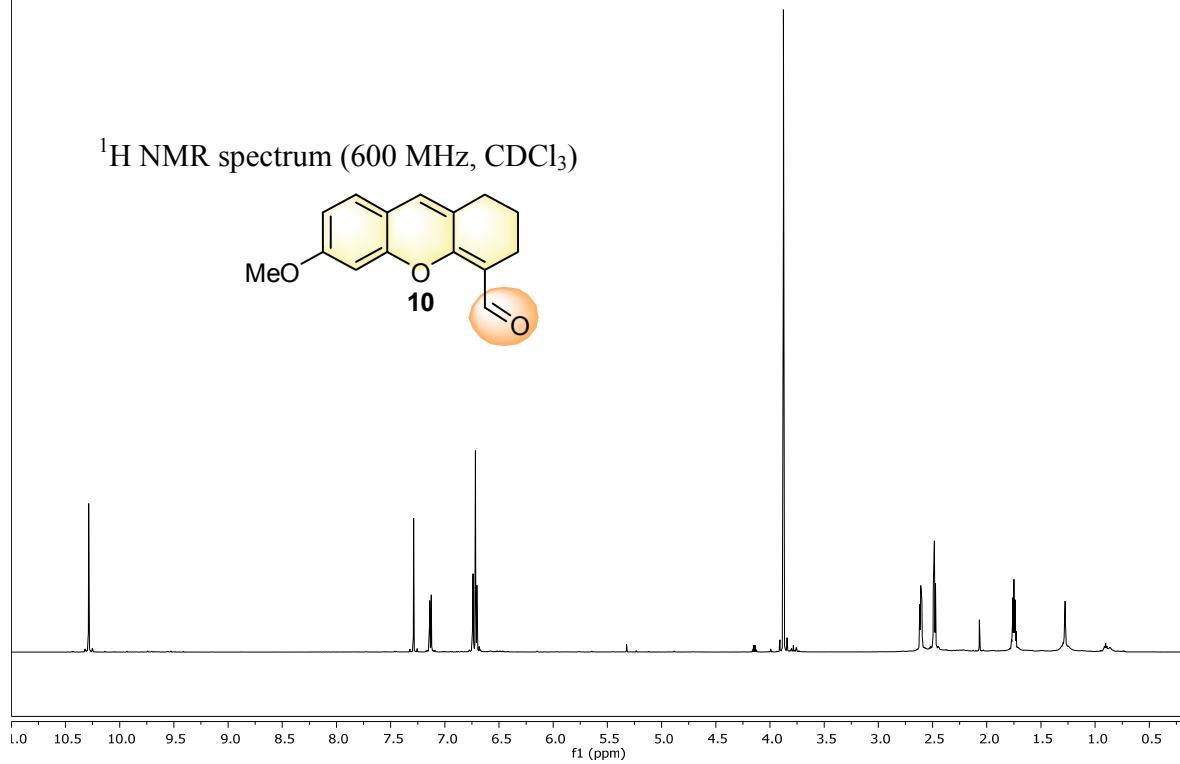
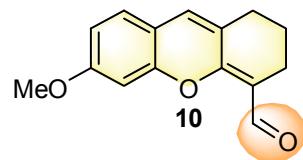
II) Abbreviations

DMF = *N,N*-Dimethylformamide

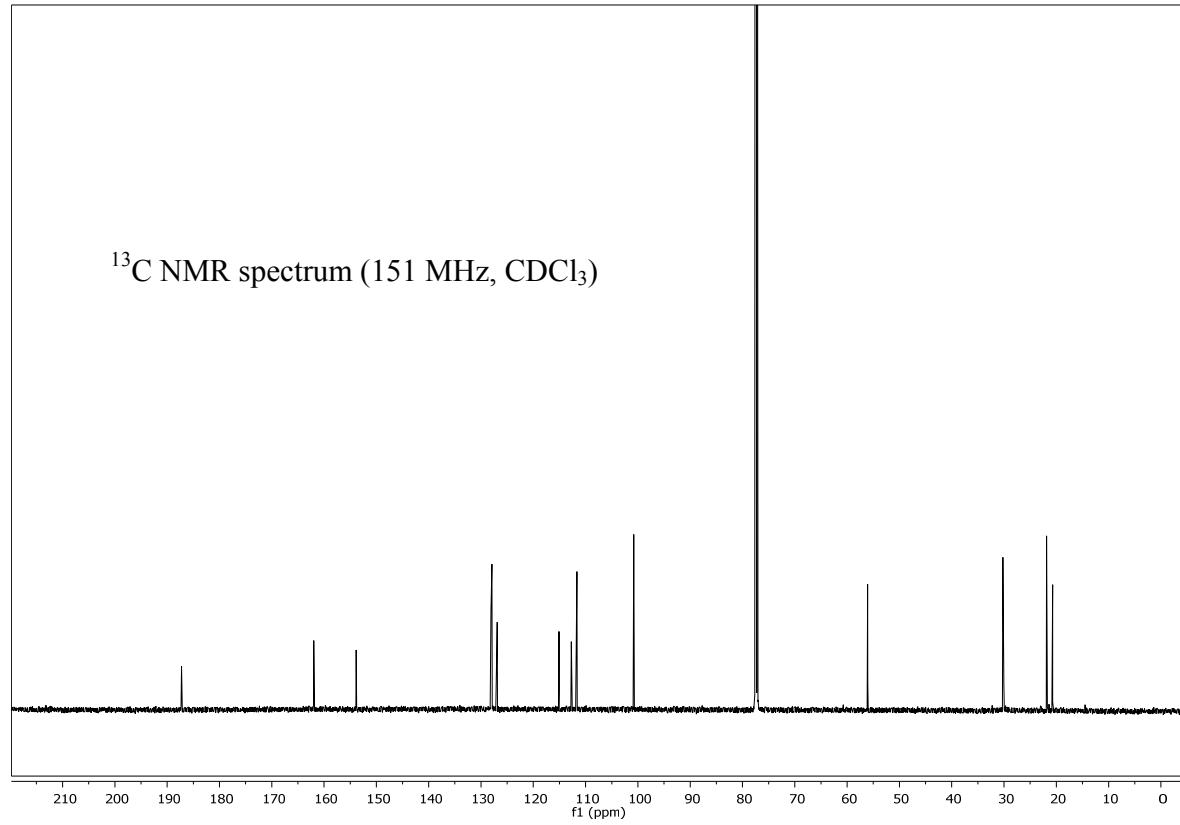
III) ^1H and ^{13}C NMR Spectra of Compounds

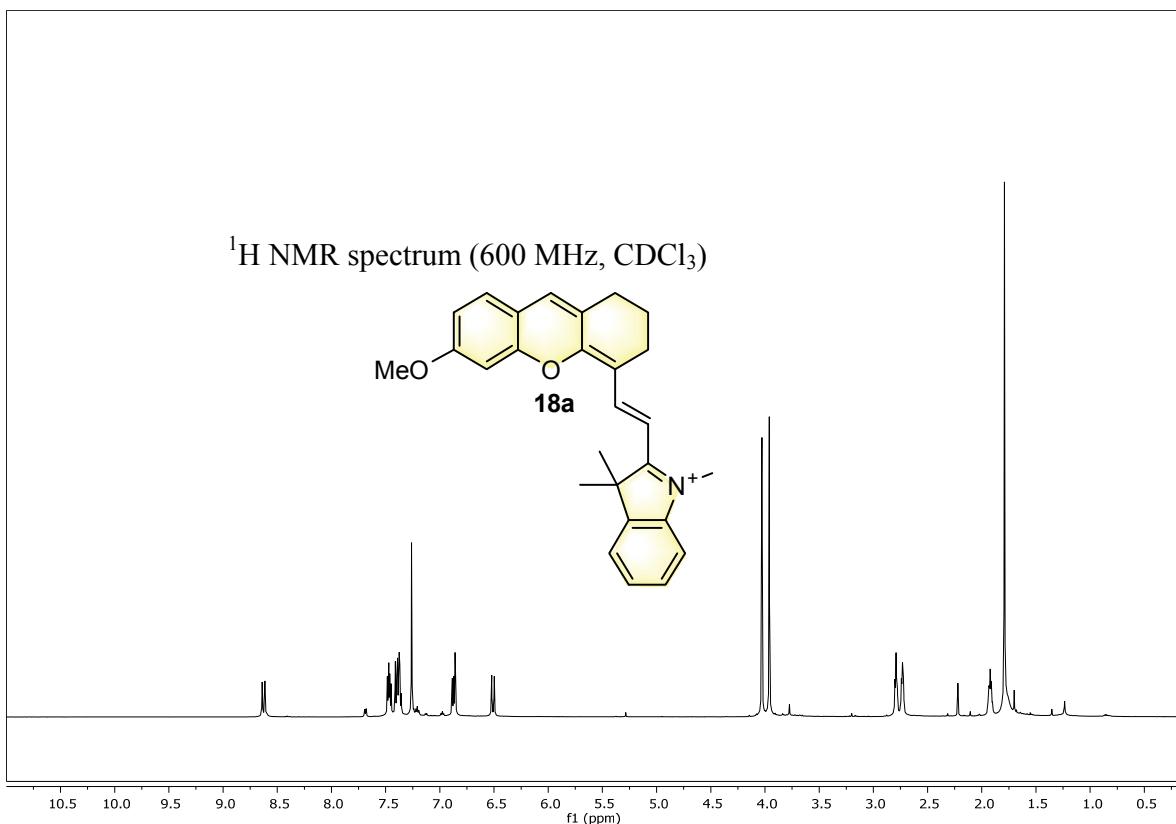


^1H NMR spectrum (600 MHz, CDCl_3)

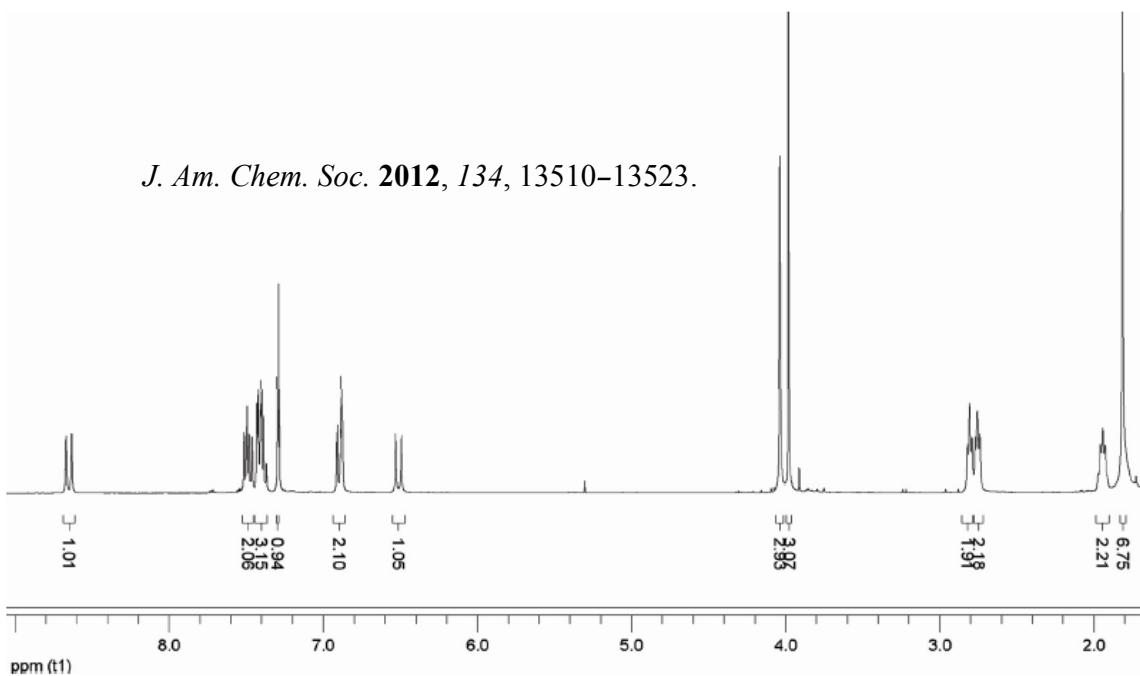


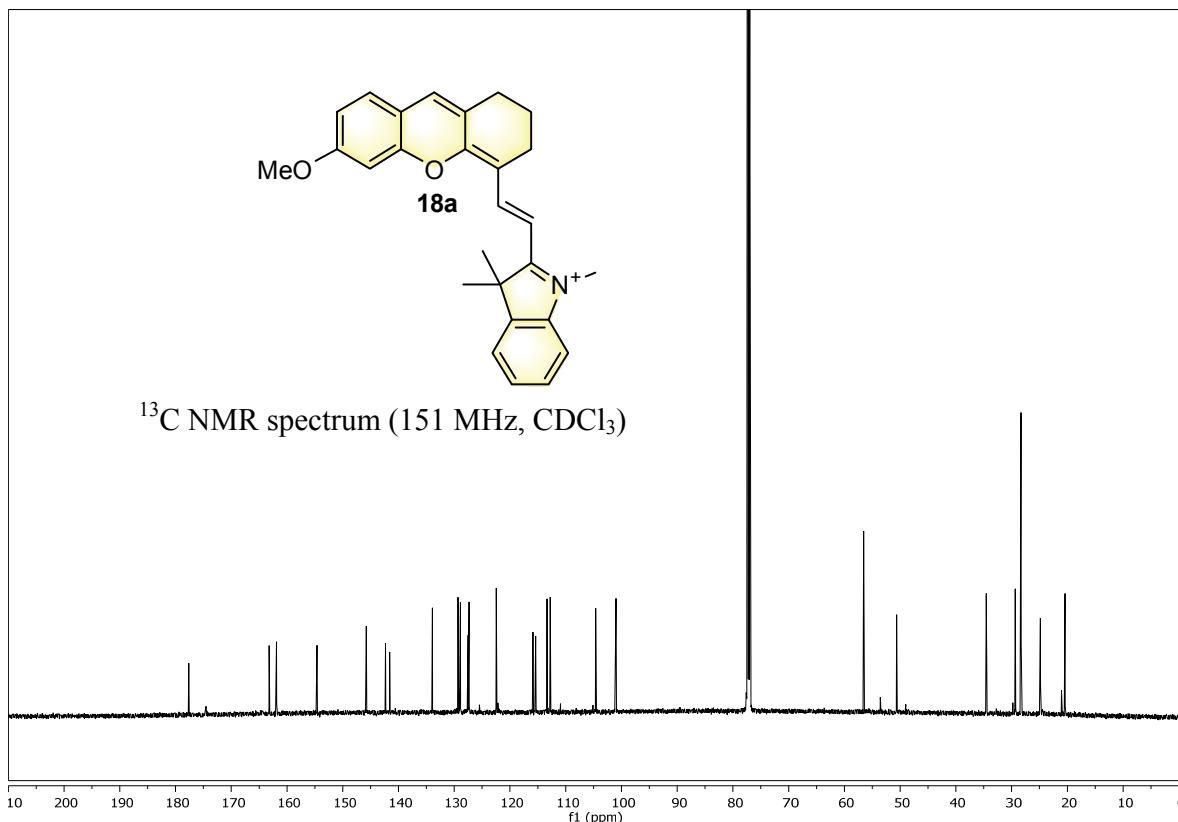
^{13}C NMR spectrum (151 MHz, CDCl_3)



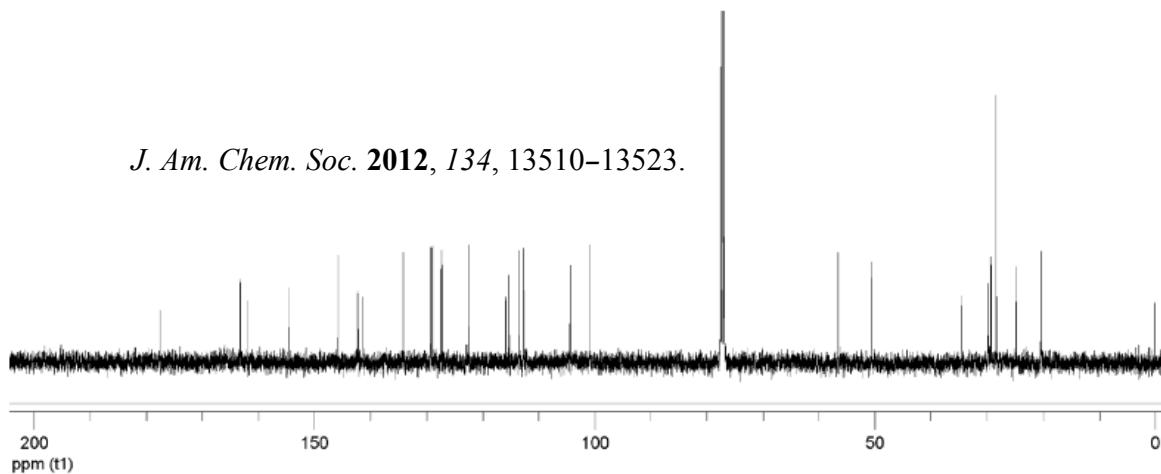


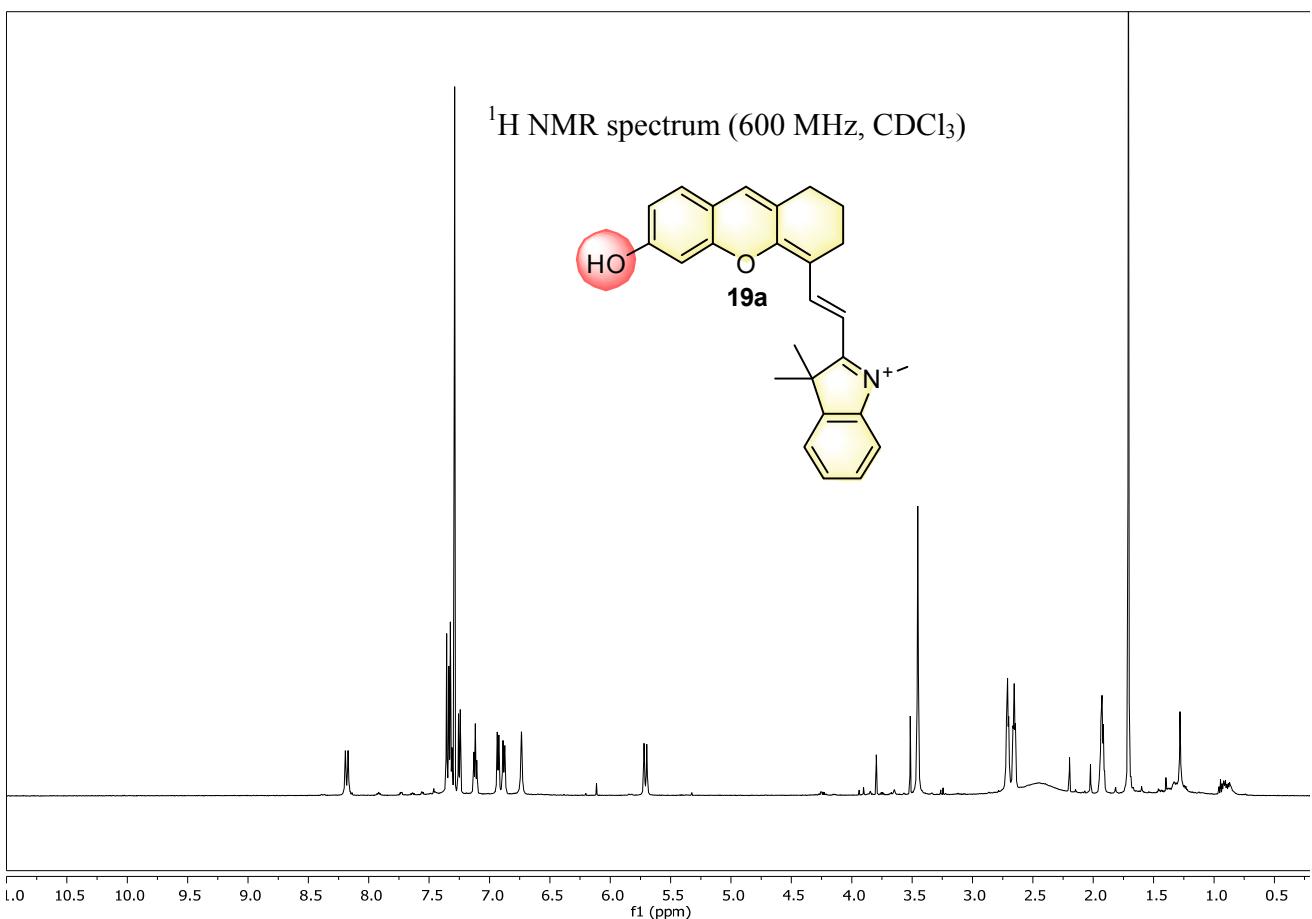
Comparison of the ¹H NMR with the material prepared by Prof. Weiyang Lin and co-workers:



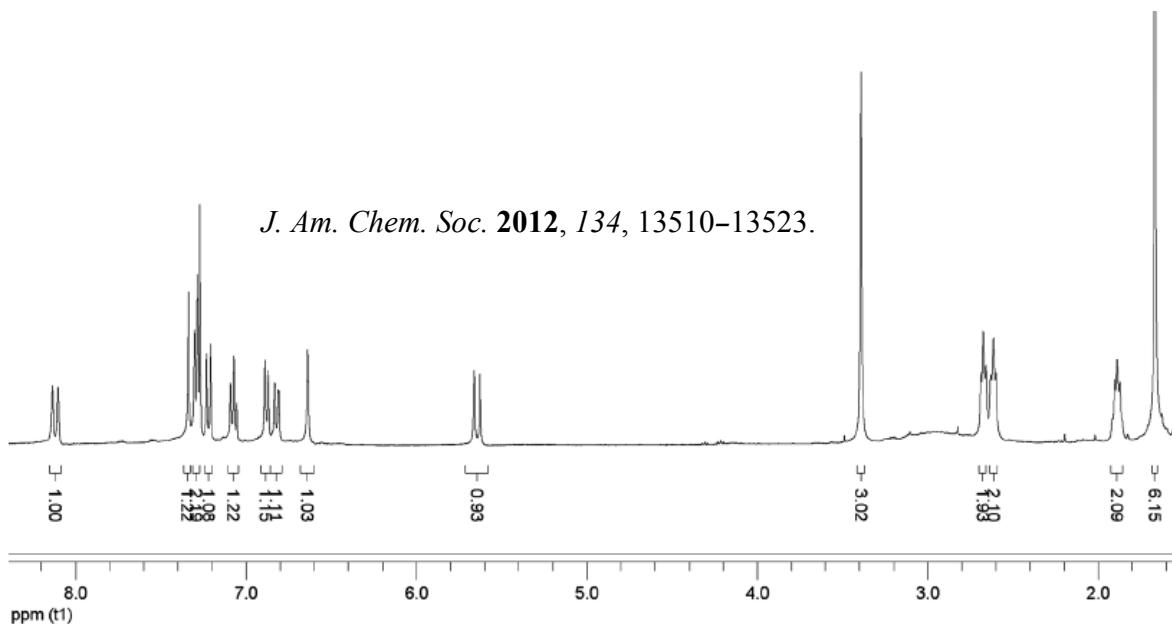


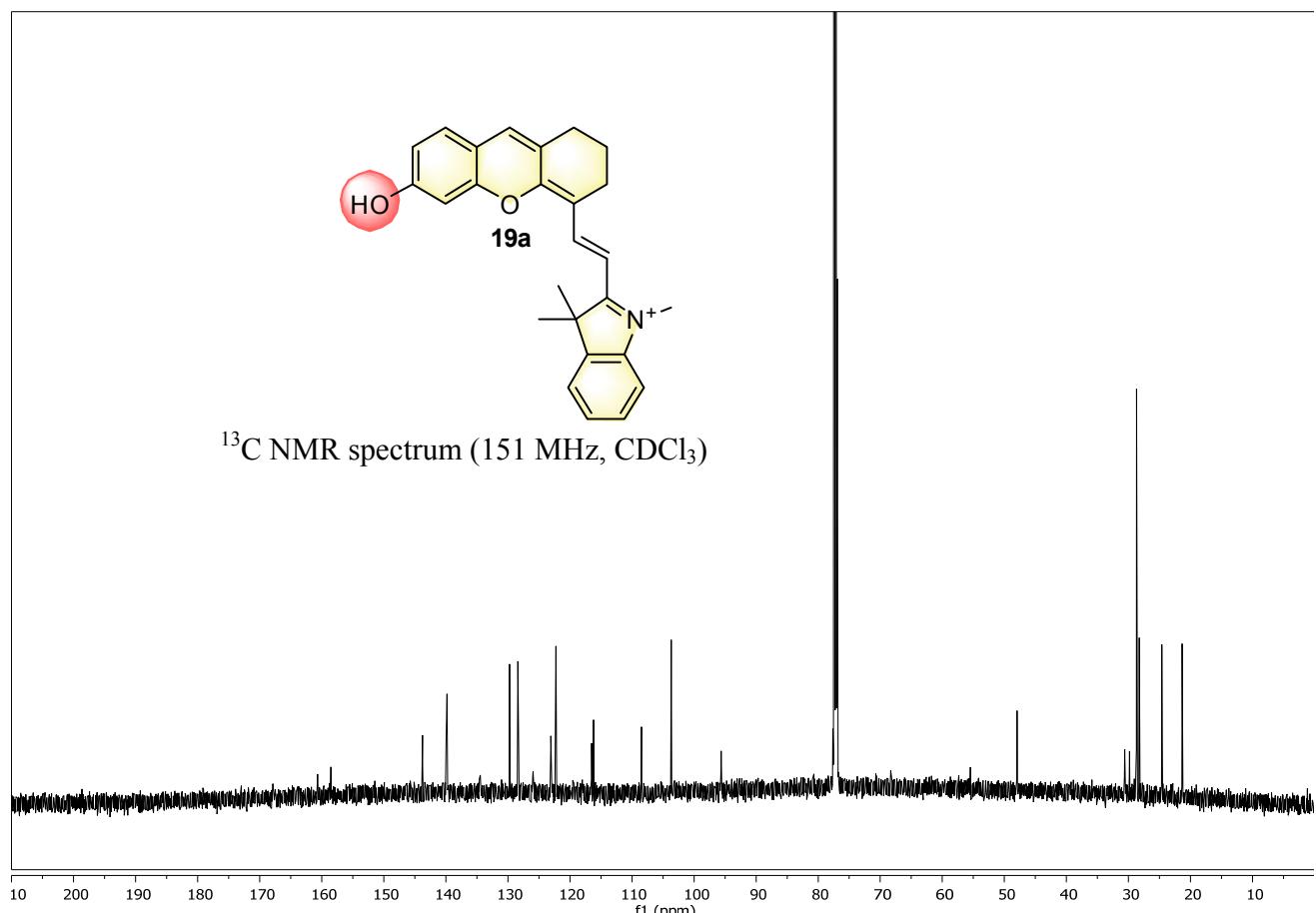
Comparison of the ^{13}C NMR with the material prepared by Prof. Weiying Lin and co-workers:



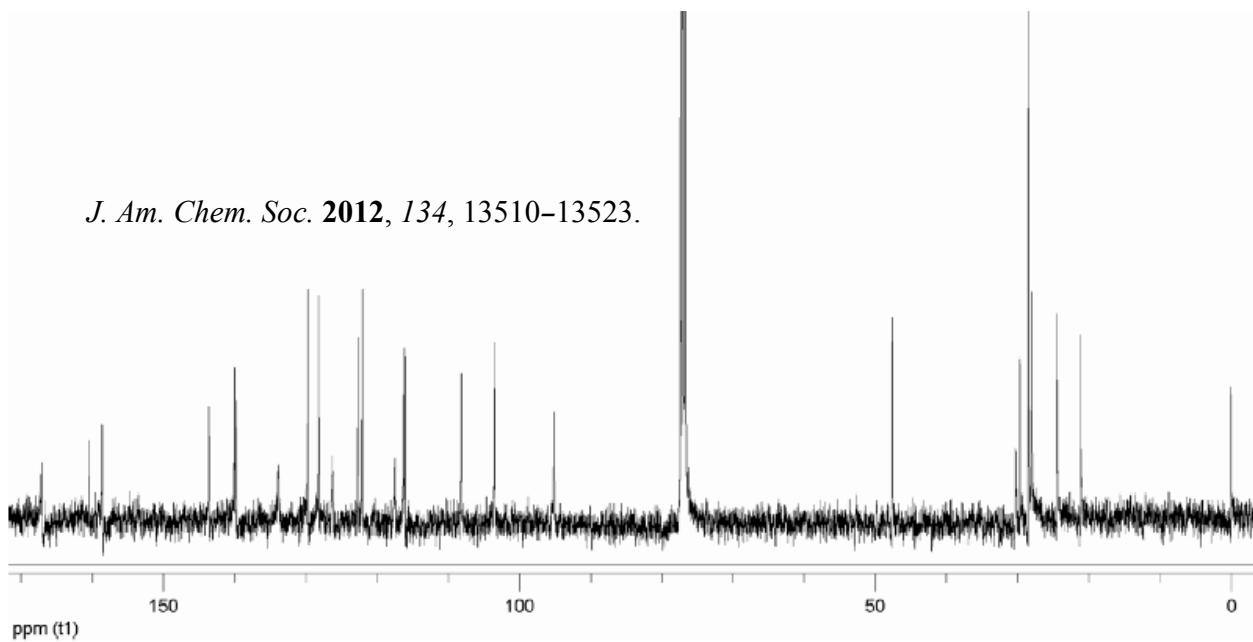


Comparison of the ¹H NMR with the material prepared by Prof. Weiying Lin and co-workers:

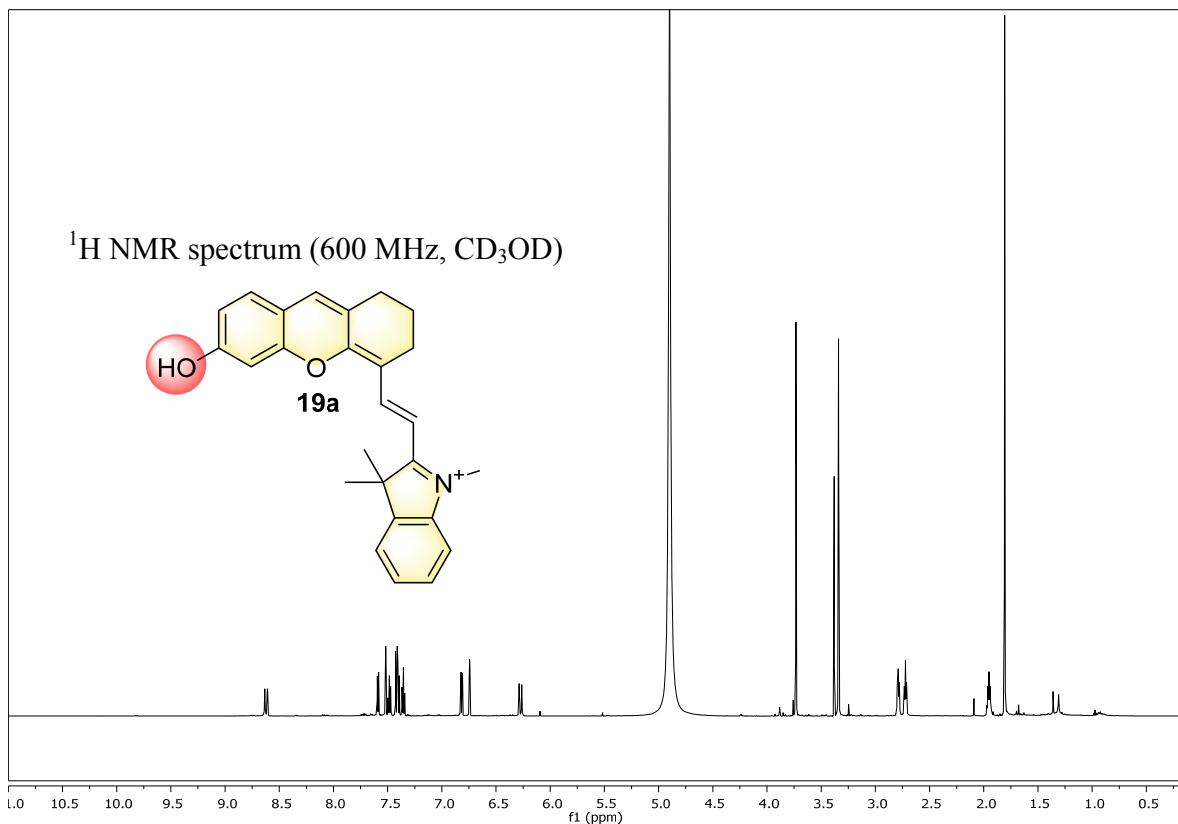




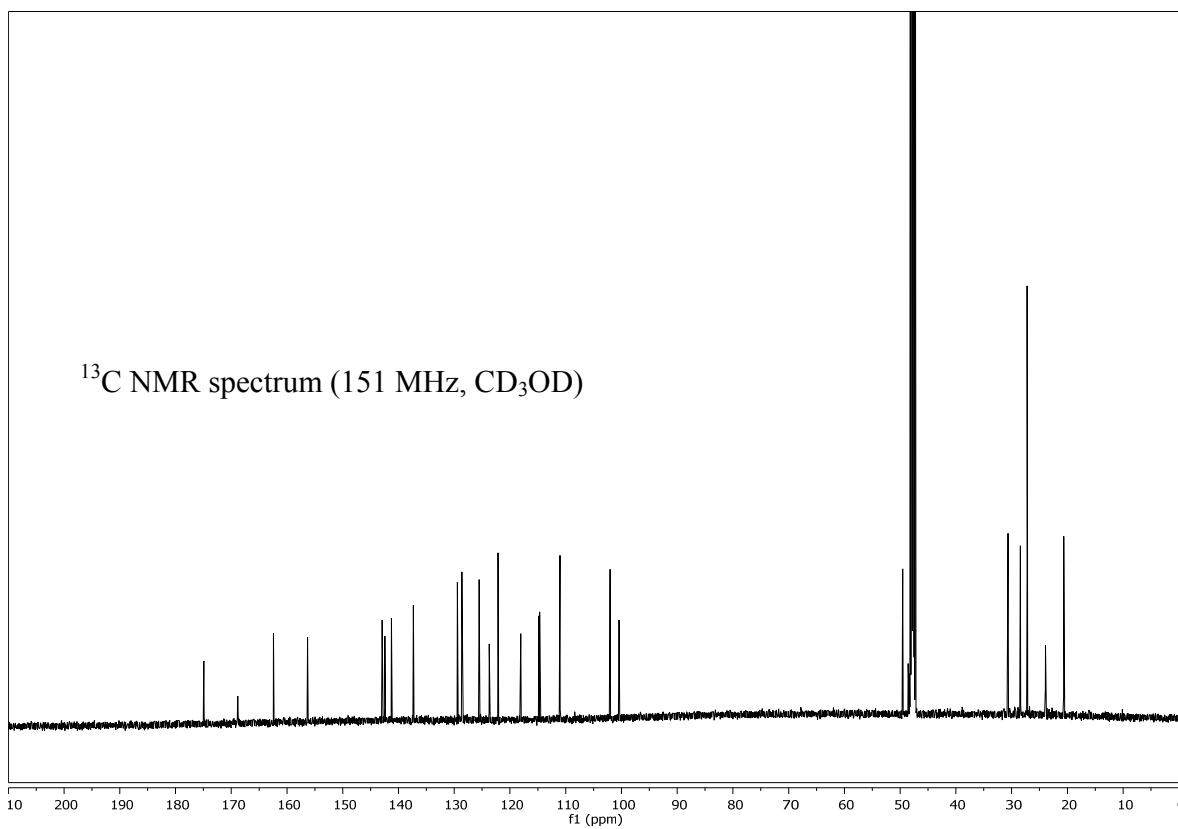
Comparison of the ^{13}C NMR with the material prepared by Prof. Weiying Lin and co-workers:



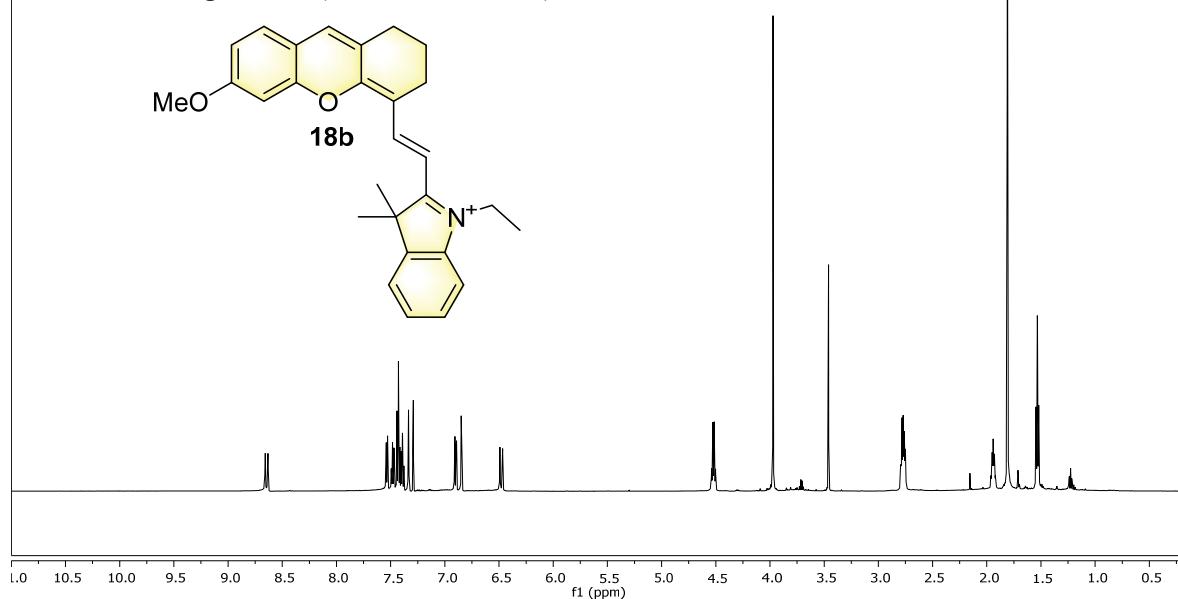
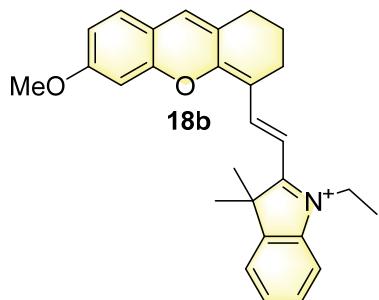
J. Am. Chem. Soc. **2012**, *134*, 13510–13523.



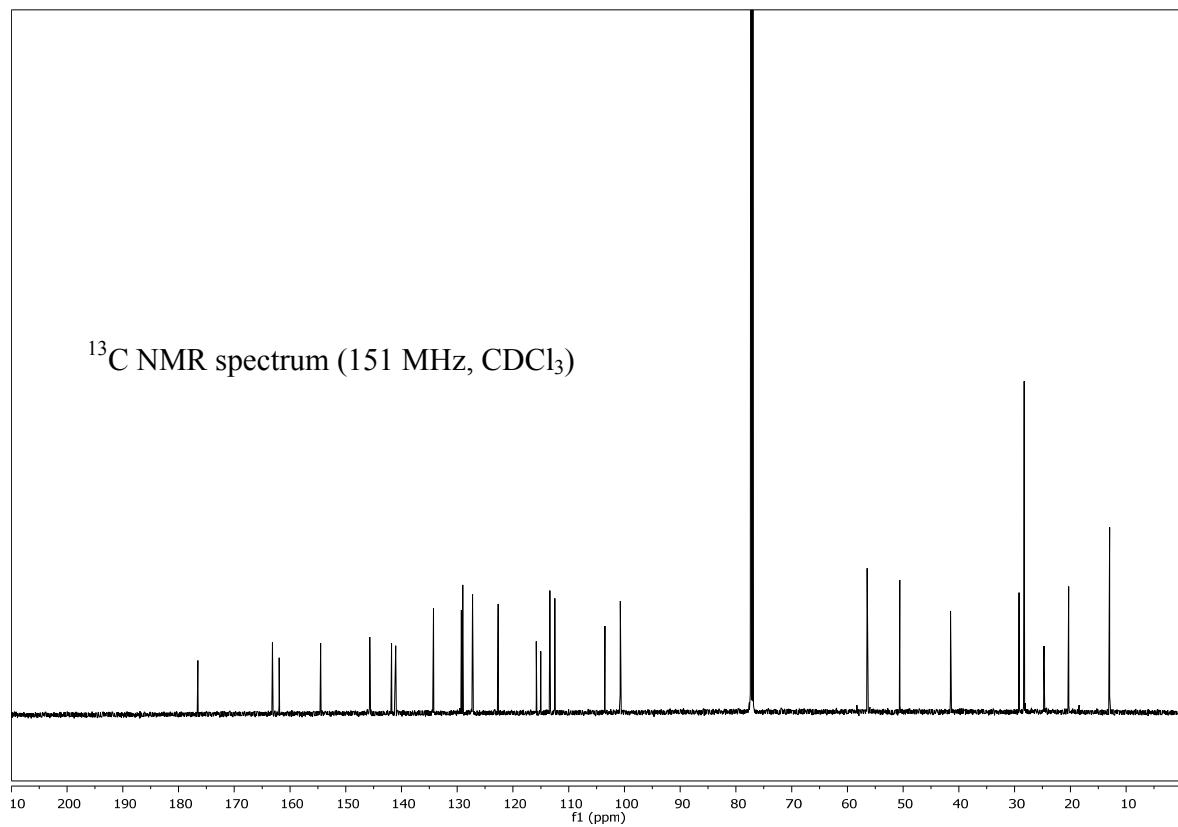
Much better spectra were obtained when the ¹H and ¹³C NMRs were recorded in CD₃OD.

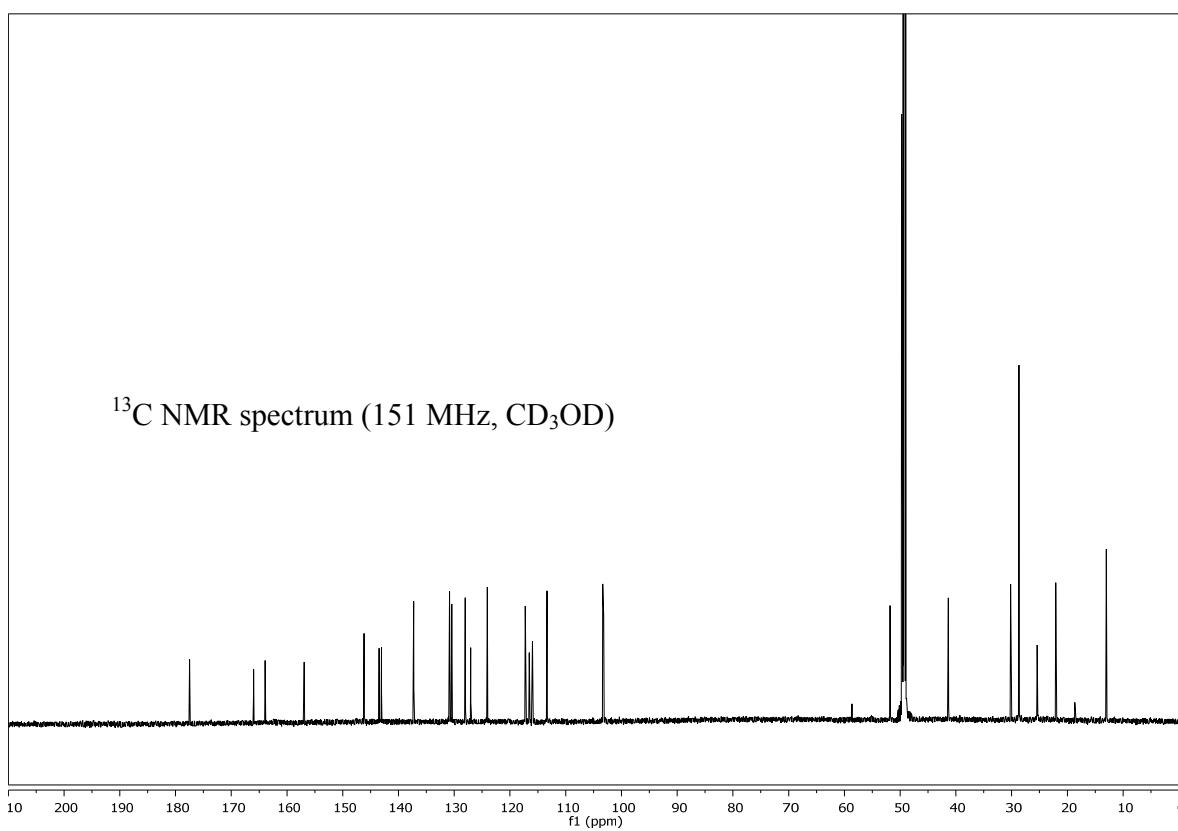
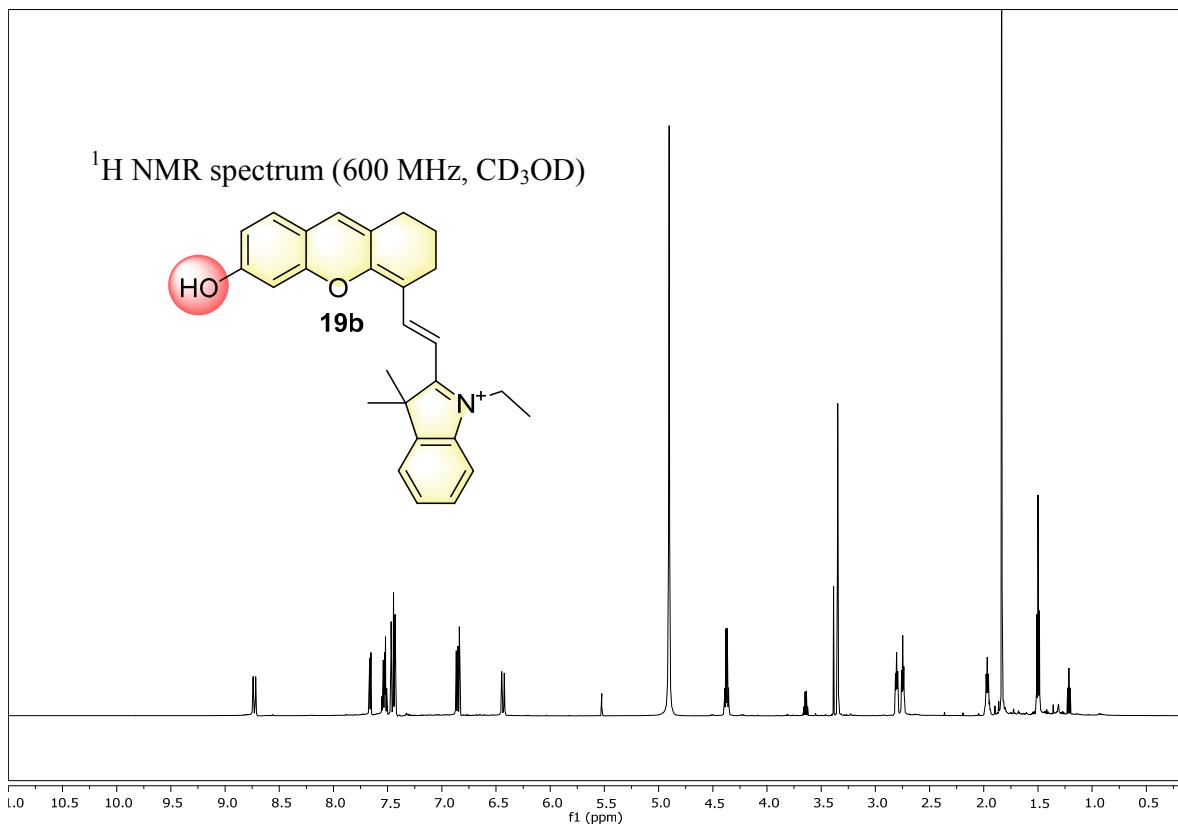


¹H NMR spectrum (600 MHz, CDCl₃)

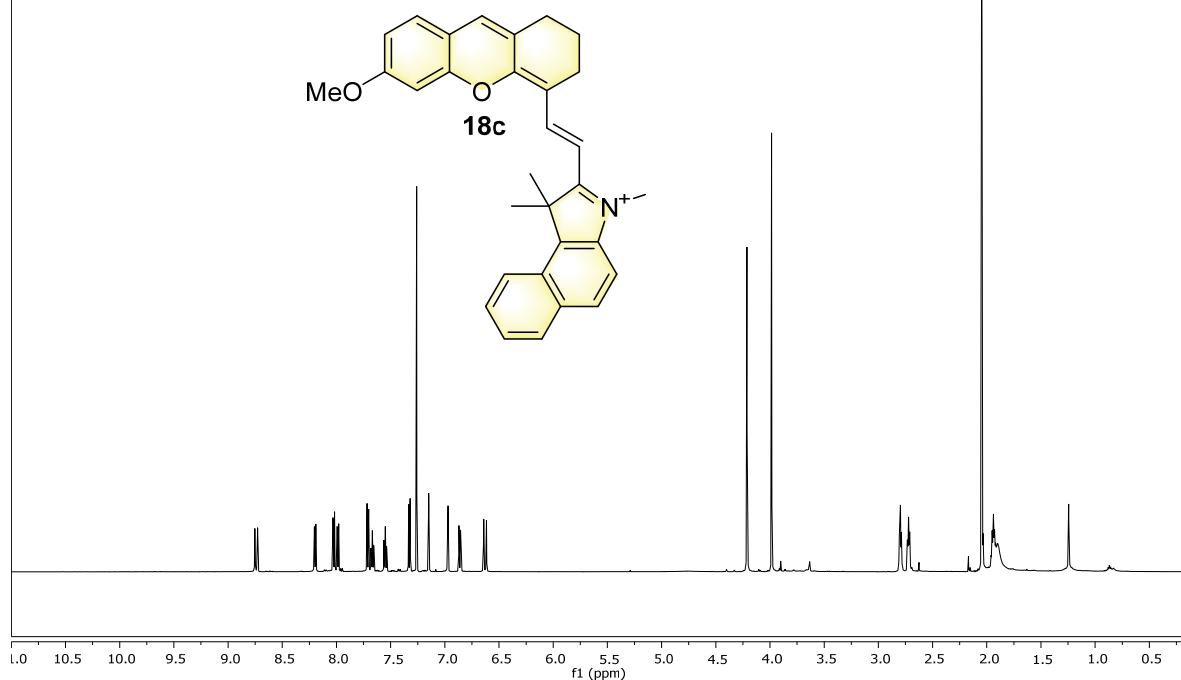


¹³C NMR spectrum (151 MHz, CDCl₃)





^1H NMR spectrum (600 MHz, CDCl_3)



^{13}C NMR spectrum (151 MHz, CDCl_3)

