Supplementary Material for Organic & Biomolecular Chemistry

Supporting information for

"Organocatalytic Regioselective Michael Additions of Cyclic Enones via Asymmetric Phase Transfer Catalysis."

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Experimental Section

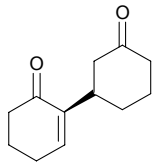
General methods. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz respectively. The chemical shifts are reported in ppm downfield to TMS ($\delta = 0$) for ^{1}H NMR and for ^{13}C NMR relative to the central $CDCl_3$ resonance ($\delta = 77.5$). Flash chromatography (FC) was carried out using Merck silica gel 60 (230-400 mesh). The enantiomeric excess (ee) of the products was determined by HPLC (CHIRALPAK IB or whelk O1 (R,R) columns, see below for the single compounds) or CSP-GC using a GC-FID 5890 Hawlett-Packard series II. Chiral column: MEGA (diacetyl *t*-butylsilyl β-CAX 30%) 25m x 0.25 mm; head column pressure: 100 kPa, gas carrier He, isoterm at 180°C.

Materials. Analytical grade solvents were used as received. All commercially available reagents were used as received. Compounds **1**, **4**, **5**, **7**, **8**, **10**, **3a, 3b, 3c, 3d, 3e** are commercially available and were used as received.

These compounds were prepared according to standard literature procedures (reaction of cinchonine with the corresponding commercially available benzyl bromides in refluxing toluene and precipitation of the ammonium salt upon addition of ether) : **3f,**[1] **3g,** [2] **3h,**[3] **3i**. A new procedure has been used for catalysts : **3j**,[4] **3k**, **3l**, **3m**[3], **3n**, **3o**. Compound **10** has been prepared according to standard literature procedure.[5]

General procedure for the enantioselective dimerization of enones catalyzed by 3a-o.

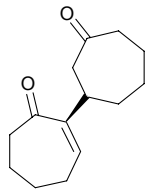
Catalysts **3a-o** (0.065 mmoles, 12.5 mol%, see table 1) and enones **1**, **4, 5, 7, 8** were placed in a test tube and toluene (4 mL) was added. After 5 minutes, a solution of 50% KOH (2 mL) was added dropwise taking care that the temperature of the reaction mixture did not exceed 30 C. The resulting biphasic mixture was stirred at rt for 24 h. In the case of enone **1**, no starting material could be detected after 6 h with most of the catalysts employed. The organic layer was separated and directly purified by FC on silica gel (petrol ether, then petrol ether: ether 50: 50). The resulting dimerization products **2**, **6**, **9** were analyzed to determine ee by CSP-GC or HLPC.



2

2: Yields and ee: see table 1. ee was determined by CSP-GC using a chiral MEGA (diacetyl *t*-butylsilyl β-CAX 30%) 25m x 0.25 mm column: isoterm 180 °C for 16 min; **2**: τ_{minor} = 15.0 min, τ_{major} =15.4 min; (employing catalyst **3a**, 47%ee). The spectral data for this compund were indentical to that reported in the literature.[see ref. 7b in the manuscript]

$[\alpha]^{rt}_{D}$ = -3 (sample with 47% ee, prepared using general procedure at rt and employing as the catalyst **3a,** benzyl cinchoninium chloride); (c= 0.0035 g/ 1 mL, CH_2Cl_2)



6

6: The ee was determined by HPLC using Whelk O1 column (hexane/*i*-PrOH 80:20); flow rate 0.75 mL/min; **6**: τ_{major} = 25.3 min; τ_{minor} = 29.8 min. (employing catalyst **3a**, 40%ee); **6**: τ_{minor} = 25.3 min; τ_{major} = 29.8 min. (employing catalyst **3o**, -73%ee); **6**: τ_{major} = 25.3 min; τ_{minor} = 29.8 min. (employing catalyst **3n**, 87%ee).

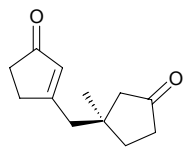
Yield: 80% with catalyst **3n** and 75% with catalyst **3o**;

^{1}H NMR δ ($CDCl_3$) 6.42 (t, 1H, J 6.4 Hz), 2.90 – 2.80 (m, 1H), 2.59 –2.29 (m 6H), 1.95 – 1.38 (m, 12H).

^{13}C NMR ($CDCl_3$) 213.54, 204.61, 148.38, 139.50, 49.86, 43.69, 42.69, 38.18, 37.34, 29.35, 27.18, 24.78, 24.26, 21.37.

$[\alpha]^{rt}_{D}$ = +18 (sample with -73% ee, prepared using general procedure at rt and emplyoing as the catalyst **3o,** 3,5,4-trimethoxybenzyl cinchonidinium bromide); (c= 0.0035 g/ 1 mL, CH_2Cl_2)

HRMS calc. $C_{14}H_{20}O_2^+$: 220.1463; found: 220.1464.



9

9: Yields and ee: see table 2. ee was determined by CSP-GC using a chiral MEGA (diacetyl *t*-butylsilyl β-CAX 30%) 25m x 0.25 mm column: isoterm 180 °C for 30 min; **9**: τ_{major} = 23.0 min, τ_{minor} =25.9 min; (employing catalyst **3a**, 47%ee).

^{1}H NMR δ ($CDCl_3$) : 5.95 (t, 1H, J 1.6 Hz), 2.40 – 2.23 (m, 4H), 1.97 – 1.91 (m, 2H), 1.45 – 1.04 (m, 3H) 1.20 (s, 3H).

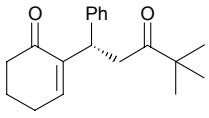
^{13}C NMR ($CDCl_3$) 218.04, 209.75, 179.89, 129.87, 53.04, 52.62, 44.37, 41.49, 36.75, 35.89, 32.27, 26.89.

$[\alpha]^{rt}_D$ = -6.5 (sample with 47% ee prepared using general procedure at rt and employing as the catalyst **3a**, benzyl cinchonidinium chloride); (c= 0.0046 g/ 1 mL, CH_2Cl_2)

HRMS calc. $C_{12}H_{16}O_2^+$: 192.1150; found: 192.1152.

Procedure for the addition of 2-cyclohexenone 1 to 10:

Catalyst **3n** or **3o** (0.065 mmoles, 12.5 mol%), enones **10** (0.52 mmol, 1eq.) and **1** (0.52 mmol, 1eq.) were placed in a test tube and toluene (4 mL) was added. After 5 minutes, a solution of 50% KOH (2 mL) was added dropwise taking care that the temperature of the reaction mixture did not exceed 30 ºC. More 2-cyclohexenone (0.52 mmol, 1eq.) was added twice after 5 and 10 hours. The resulting biphasic mixture was stirred at rt for 24 h. The organic layer was separated and directly purified by FC on silica gel (petrol ether, then petrol ether: ether 50: 50). The resulting products **11** was analyzed to determine ee. 1.20 And 1.15 eq. of **2** were isolated as well employing catalyst **3n** or **3o**, respectively.



11

The ee was determined by HPLC using Chiralpak IB column (hexane/*i*-PrOH 90:10); flow rate 0.75 mL/min; **11**: τ_{major} = 8.0 min; τ_{minor} = 8.8 min. (employing catalyst **3n**, 47%ee); **11**: τ_{minor} = 8.0 min; τ_{major} = 8.8 min. (employing catalyst **3m**, 65%ee);

Yield: 95% with catalysts **3n** and 94% with catalysts **3m**.

^{1}H NMR δ ($CDCl_3$) 7.28 – 7.13 (m, 5H), 6.76 (t, 1H, J 4.2 Hz), 4.54 (t,1H J 5.9Hz), 2.45 – 2.35 (m 4H), 2.02 (d, 2H, J 5.9Hz), 1.13-1.08 (m, 2H), 1.10 (s, 9H).

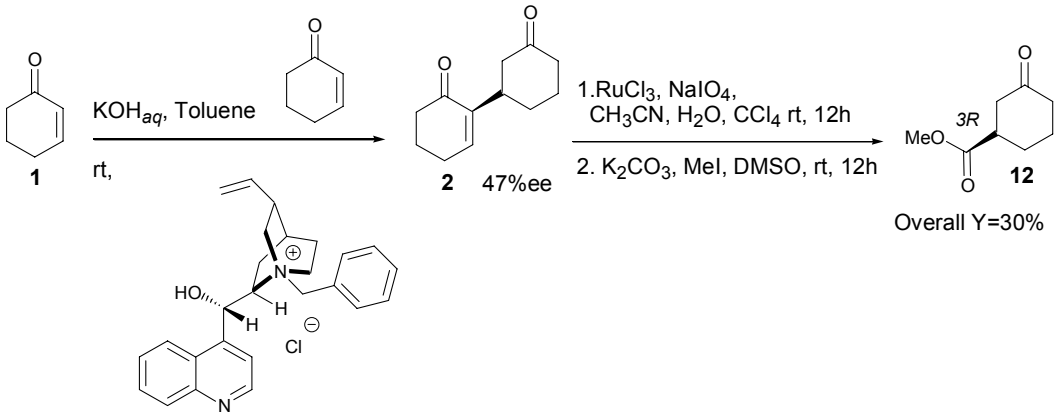
^{13}C NMR ($CDCl_3$) 212.91, 197.98, 145.02, 142.77, 141.66, 128.06 (2C), 127.78 (2C), 126.04, 43.89, 40.81, 39.90, 38.70, 26.10 (3C), 25.98, 22.56.

$[\alpha]^{rt}_D$ = -22 (sample with 47% ee, prepared using general procedure at rt and employing as the catalyst **3n,** 3,5,4-tribenzyloxybenzyl cinchoninium bromide) (c= 0.0305 g/ 1 mL, CH_2Cl_2)

HRMS calc. $C_{19}H_{25}O_2^+$: 285.1855; found: 285.1854.

Determination of absolute configuration:

The absolute configuration of **2** has been determined by correlation with known compound **12**, according to the scheme below:

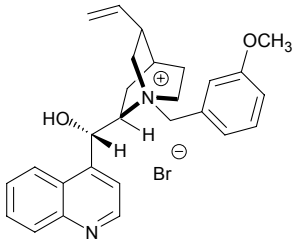


12: $[\alpha]^{rt}_{560}$ = - 24 (c= 0.059 g/ 1 mL, EtOH) [ref 6]

12: $[\alpha]^{rt}_{D}$ = - 2 (c= 0.059 g/ 1 mL, EtOH) [ref 6]

Since compound **12** has been reported to have negative rotation by several authors[6] we assigned the absolute configuration to our product to be (*R*).

Catalyst 3i :



3i

Yield: 72%;

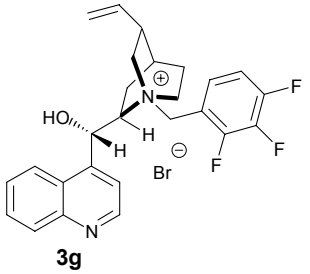
^{1}H NMR δ (MeOD) 8.85 (d, 1H, J 4.6 Hz), 8.25 - 8.20 (m, 1H), 8.04 - 7.99 (m, 1H), 7.87 (d, 1H, J 4.6 Hz), 7.80 – 7.70 (m, 2H), 7.43 – 7.35 (m, 1H), 7.25 – 7.17 (m, 2H), 7.04 – 7.02 (m, 1H), 6.52 (s, 1H), 6.05 – 5.88 (m, 1H), 5.22 (d, 1H, J 6.0 Hz), 5.14 (m, 1H), 5.03 (m, 2H), 4.37 – 4.25 (m, 1H), 3.97 – 3.79 (m, 6H), 3.64 (dd, 1H, J 11.4, 11.6 Hz), 3.1 (m, 1H), 2.60 – 2.31 (m, 2H), 1.84 – 1.71 (m, 3H), 1.11 – 0.80 (m, 1H).

^{13}C NMR (DMSO) 159.11, 149.95, 149.86, 147.36, 144.79, 136.86, 129.66, 129.44, 129.08, 127.15, 125.72, 124.09, 123.95, 119.84, 119.28, 116.72, 115.39, 66.81, 64.26, 61.56, 55.87, 55.27, 53.66, 36.44, 26.10, 22.80, 20.60.

$[\alpha]^{rt}_{D}$ = + 139 (c= 0.042 g/ 1 mL, CH_3OH)

HRMS calc. $C_{27}H_{31}N_2O_2^+$: 415.2386; found: 415.2360.

Catalyst 3g:



3g

Yield: 76%;

^{1}H NMR δ (DMSO) 8.88 (d, 1H, J 4.37 Hz), 8.37 (d, 1H, J 8.03 Hz), 8.00 (d, 1H, J 8.03 Hz), 7.75 – 7.40 (m, 5H), 6.81 (d, 1H, J 3.1Hz), 6.41 (s, 1H), 5.98 - 5.80 (m, 1H), 5.24 – 5.00 (m, 4H), 4.15 – 3.89 (m, 3H), 3.40 – 3.35 (m, 1H), 3.15-3.00 (m, 1H), 2.58-2.45 (m, 1H), 2.21- 2.09 (m, 1H), 1.75-1.66 (m, 3H), 0.97 – 0.82 (m, 1H).

^{13}C NMR (DMSO) 159.09, 149.83, 147.34, 144.77, 136.84, 129.62, 129.41,129.02, 127.13, 125.71, 124.07, 123.92, 119.82, 119.25, 116.70, 115.36, 66.82, 64.26, 61.53, 55.86, 55.25, 53.64, 36.44, 26.09, 22.84, 20.60.

$[\alpha]^{rt}_{D}$ = + 135 (c= 0.046 g/ 1 mL, CH_3OH)

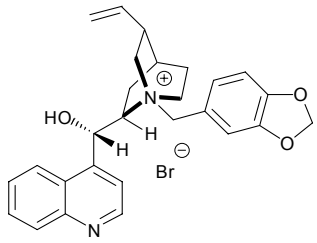
HRMS calc. $C_{26}H_{26}F_3N_2O^+$: 439.1992; found: 439.1962.

General procedure for the Preparation of catalysts 3k-o:

CAUTION: alkoxy substituted benzyl bromides are unstable in basic solutions and if solvent is removed. They are very lachrymatory and their preparation must be done in fume hood. This procedure allows using directly the toluene solution of the corresponding bromides.

Either piperonyl alcohol, (for catalysts **3k**) 3,4 dibenzyloxy alcohol,[7] (for catalysts **3l**) or 3,4,5,-trimethoxybenzyl alcohol,[8] (for catalysts **3m** and **3o**) or 3,4,5-tribenzyloxybenzyl alcohol[9] (for catalysts **3n**) (1 mmol) was placed in a flask, dissolved in 10 mL of toluene and 5 mL of HBr were added dropwise at rt. The reaction mixture was stirred for 0.5 h and the organic layer separated and added in a separate flask to cinchonine (for catalysts **3k-n**) or cinchonidine (for catalysts **3o**) (0.7 mmol). 4 mL of DMF was added in the preparation of catalysts **3k-o.** The suspension was refluxed for 5 hours. After a TLC check showed that all cinchonine reacted, the reaction was cooled at rt, diethyl ether was added to precipitate the ammonium salts. The precipitate was filtered, washed twice with a 1: 1 mixture ether: petrol ether to remove DMF, toluene and traces of benzyl bromides dried and used.

Catalyst 3k:



3k

Yield: 85%;

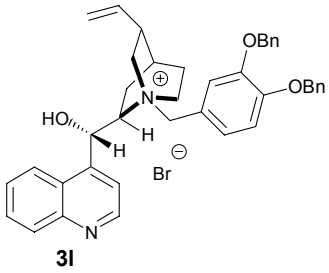
^{1}H NMR δ (MeOD) 8.86 (d, 1H, J 4.3 Hz), 8.25 - 8.20 (m, 1H), 8.05 – 8.00 (m, 1H), 7.87 (d, 1H, J 4.5 Hz), 7.81 – 7.70 (m, 2H), 7.14 – 7.09 (m, 2H), 6.93 (d, 1H, J 7.1 Hz), 6.51 (s, 1H), 6.02 – 5.88 (m, 4H), 5.25 (d, 1H, J 6.0 Hz), 5.15 (d, 1H, J 1.6 Hz), 4.89 (m, 2H), 4.32 – 4.28 (m, 1H), 3.94 – 3.71 (m, 2H), 3.61 (dd, 1H, J=12.4, 12.6 Hz), 3.12 - 2.96 (m, 1H), 2.61 – 2.31 (m, 2H), 1.86 – 1.71 (m, 3H), 1.04 – 0.81 (m, 1H).

^{13}C NMR (DMSO) 149.85, 148.47, 148.11, 147.33, 144.88, 136.92, 129.42, 129.09, 128.04, 127.15, 124.10, 123.91, 120.91, 119.83, 116.71, 113.22, 118.26, 101.49, 66.72, 64.29, 61.60, 55.60, 53.36, 36.46, 26.16, 22.82, 20.57.

$[\alpha]^{rt}_{D}$ = + 99 (c= 0.047 g/ 7 mL, CH_3OH)

HRMS calc. $C_{27}H_{29}N_2O_3^+$: 429.2173; found: 429.2175.

Catalyst 3l:



3l

Yield: 80%;

^{1}H NMR δ ($CDCl_3$) 8.79 (d, 1H, J 4.5 Hz), 8.22 - 8.17 (m, 1H), 7.81 (d, 1H, J 4.5 Hz), 7.60 (d, 2H, J 7.0 Hz), 7.49 – 7.44 (m, 1H), 7.41 – 7.29 (m, 8H), 7.22 – 7.11 (m, 2H), 6.96 – 6.91 (m, 1H), 6.83 – 6.73 (m, 1H), 6.56 (m, 2H), 6.40 (m, 1H), 5.96 – 5.68 (m, 2H), 5.31 – 5.02 (m, 8H), 4.28 – 4.17 (m, 1H), 4.07 – 3.17 (m, 1H), 3.79 – 3.67 (m, 1H), 3.10 – 2.99 (m, 1H), 2.13 – 1.92 (m, 3H), 1.50 – 1.34 (m, 2H), 0.79 – 0.59 (m, 1H).

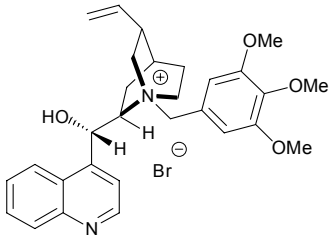
^{13}C NMR ($CDCl_3$) 149.79, 149.21, 147.10, 146.82, 144.33, 137.11, 136.90, 135.37, 129.27, 128.37 (3C), 128.20 (2C), 128.08, 127.67 (2C), 127.46, 127.16 (3C), 127.05, 126.83, 123.32, 123.14,

119.50, 119.06, 117.79, 112.97, 70.43, 69.86, 66.30, 65.44, 61.27, 55.78, 53.17, 37.81, 27.09, 23.67, 21.60.

$[\alpha]^{rt}_{D}$ = + 83 (c= 0.049 g/ 1.5 mL, CH_3OH)

HRMS calc. $C_{40}H_{41}N_2O_3^+$: 597.3117; found: 597.3114.

Catalyst 3m:



3m

Yield: 95 %;

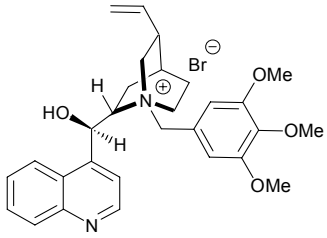
^{1}H NMR δ ($CDCl_3$) 8.86 (d, 1H, J 4.7 Hz), 8.34 (d, 1H, J 6.3 Hz), 7.98 – 7.95 (m, 1H,), 7.76 (d, 1H, J 7.2 Hz), 7.18 – 7.10 (m, 2H), 6.98 (m, 2H), 6.79 (s, 1H), 6.46 (s, 1H), 6.04 – 5.77 (m, 2H), 5.33 – 5.16 (m, 3H), 4.16 – 3.99 (m, 2H), 3.87 (m, 12H), 3.53 – 3.42 (m, 1H), 2.42 – 2.28 (m, 1H), 1.80 – 1.67 (m, 3H), 0.76 – 0.62 (m, 1H).

^{13}C NMR ($CDCl_3$) 152.57 (2C), 149.12, 146.72, 144.11, 138.84, 135.17, 129.14, 128.24, 127.15, 123.17, 122.99, 121.57 (2C), 119.39, 117.85, 110.83, 66.61, 65.20, 61.86, 60.26, 56.27 (3C), 53.64, 37.82, 26.82, 25.54, 21.36.

$[\alpha]^{rt}_{D}$ = + 121 (c= 0.023 g/ 1 mL, $CHCl_3$)

HRMS calc. $C_{29}H_{35}N_2O_4^+$: 475.2591; found: 475.2599.

Catalyst 3o:



3o

Yield: 95 %;

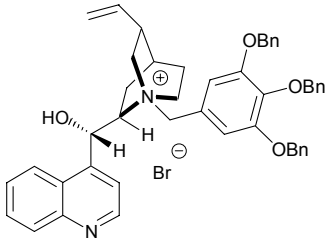
^{1}H NMR δ ($CDCl_3$) 8.84 (d, 1H, J 4.5 Hz), 8.10 – 8.06 (m,1H), 7.80 (d, 1H, J 4.6 Hz), 7.76 – 7.71 (m, 1H), 7.06 (m, 2H), 6.51 (m, 2H), 5.63 (m, 2H), 5.43 – 5.35 (m, 1H), 5.27 – 5. 19 (m, 1H), 4.96 – 4.90 (m, 1H), 4.02 – 3.94 (m, 2H), 3.86 (m, 12H), 3.79 - 3.64 (m, 2H), 3.25 – 3.20 (m, 1H), 2.58 – 2.46 (m, 1H), 1.99 – 1.88 (m, 3H), 1.13 – 1.00 (m, 1H).

^{13}C NMR ($CDCl_3$): 152.85 (2C), 149.33, 147.14, 144.42, 139.12, 136.11, 129.52, 128.66, 127.50, 123.50, 122.82, 121.80, 119.66, 117.62, 67.33, 64.53, 62.70, 60.44, 56.52 (3C) , 50.70, 37.79, 26.33, 24.98, 21.97.

$[\alpha]^{rt}_D$ = - 120 (c= 0.016 g/ 1 mL, $CHCl_3$)

HRMS calc. $C_{29}H_{35}N_2O_4^+$: 475.2591; found: 475.2570.

Catalyst 3n:



3n

Yield: 75 %;

^{1}H NMR δ ($CDCl_3$) 8.87 (d, 1H, J 4.5 Hz), 8.28 - 8.23 (m, 1H), 7.92 (d, 1H, J 4.5 Hz), 7.61 – 7.50 (m, 6H), 7.33 – 7.18 (m, 13H), 7.08 – 7.03 (m, 2H), 6.79 – 6.76 (m, 1H), 6.46 (s,1H), 6.06 (d, 1H, J 11.4 Hz), 5.91 – 5.74 (m, 1H), 5.31 – 5.01 (m, 10H), 4.33 – 4.23 (m, 1H), 4.09 – 4.00 (m, 1H), 3.71 – 3.60 (m, 1H), 3.14 (1H, J 11.8 Hz), 2.17 – 1.98 (m, 1H), 1.59 – 1.30 (m, 3H), 0.72 – 0.59 (m, 1H).

^{13}C NMR ($CDCl_3$) 151.72 (2C), 148.79, 146.21, 145.16, 139.44, 138.08, 136.85, 135.37, 128.96, 128.55, 128.28 (4C), 128.09 (2C), 128.00(2C), 127.77(4C), 127.73, 127.65 (2C), 127.42 (2C), 123.39, 123.14, 121.48, 119.64, 118.05, 112.92, 74.85, 70.39 (2C), 66.67, 65.59, 61.80, 56.15, 53.51, 37.91, 27.10, 23.87, 21.77.

$[\alpha]^{rt}_D$ = + 100 (c= 0.0115 g/ 1 mL, CH_3OH)

HRMS calc. $C_{47}H_{47}N_2O_4^+$: 703.3536; found: 703.3541.

References

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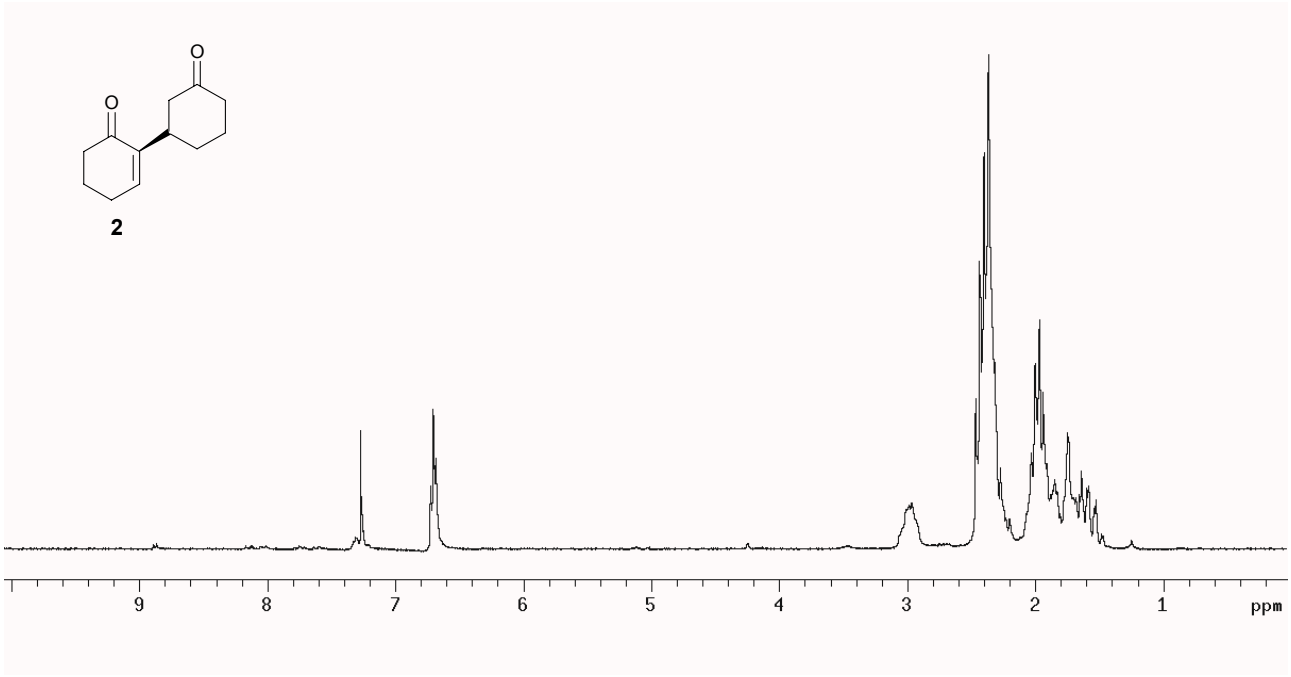
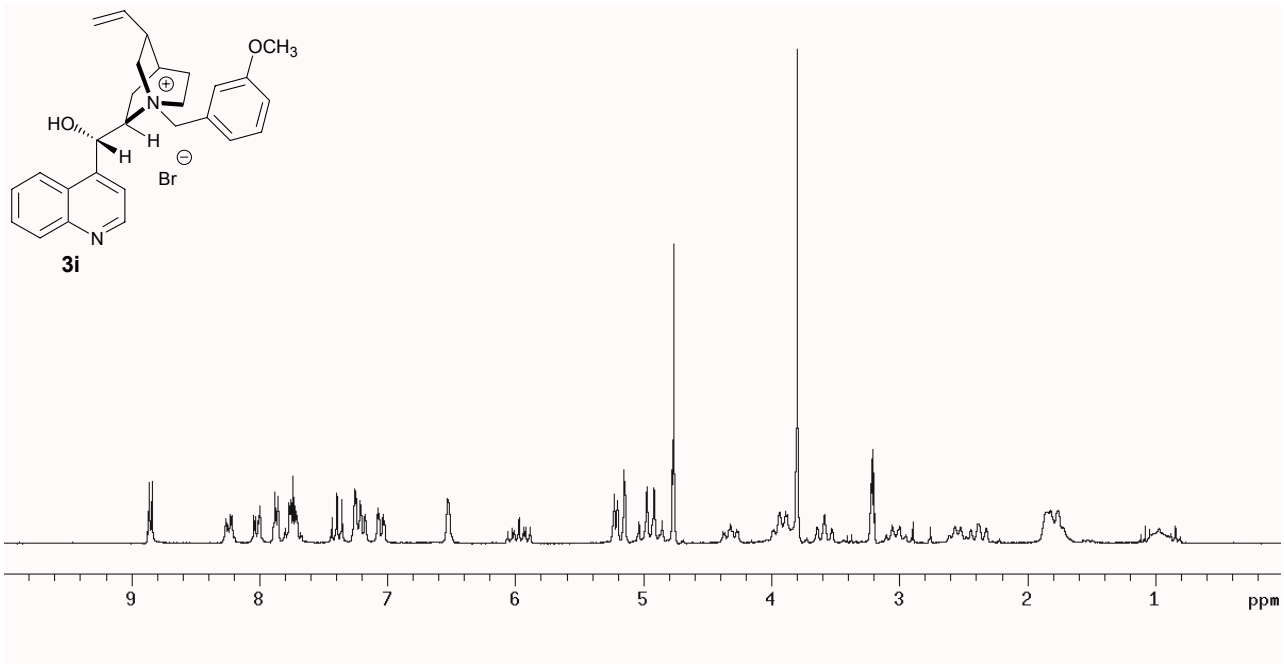
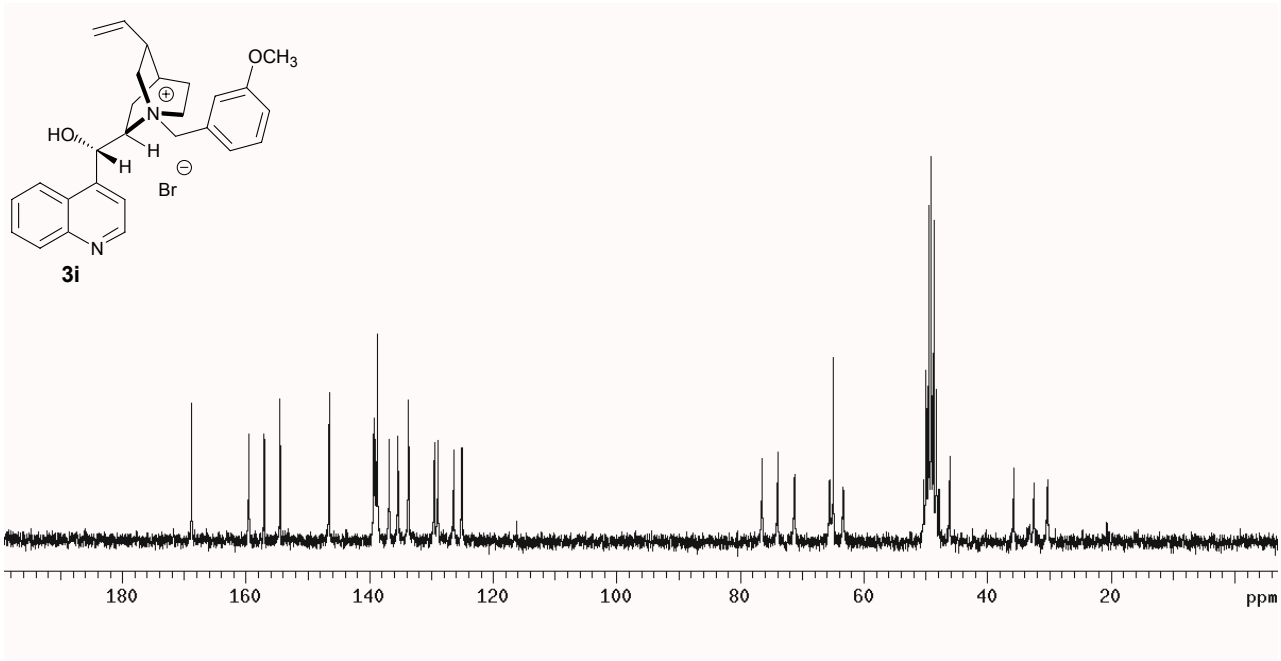
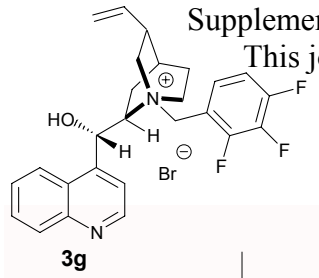
Copies of NMR Spectra:









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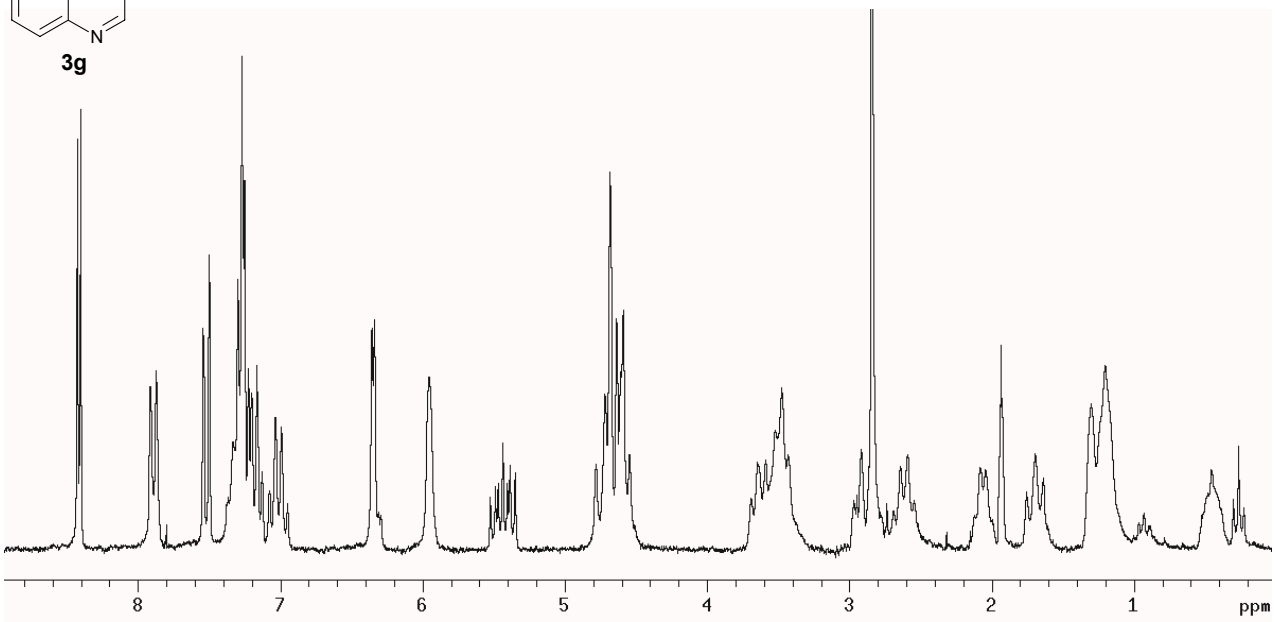

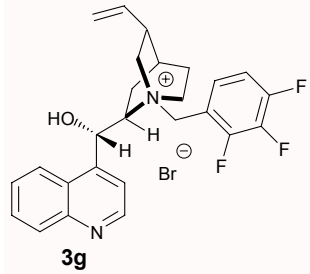

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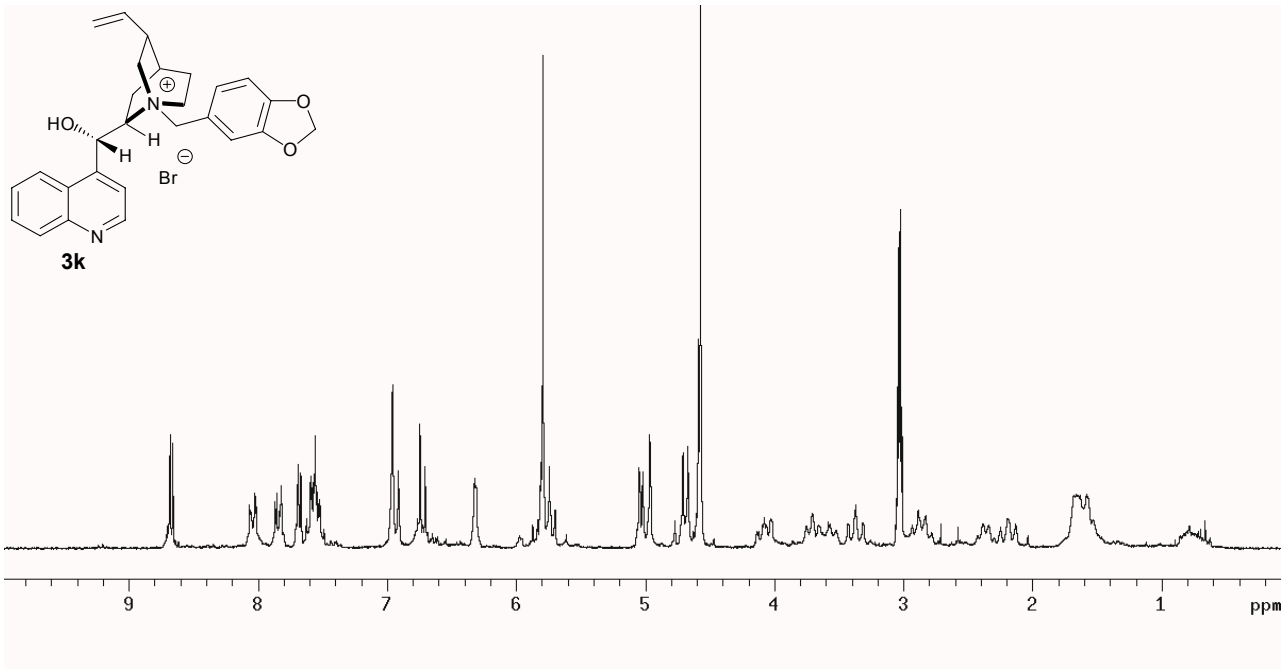

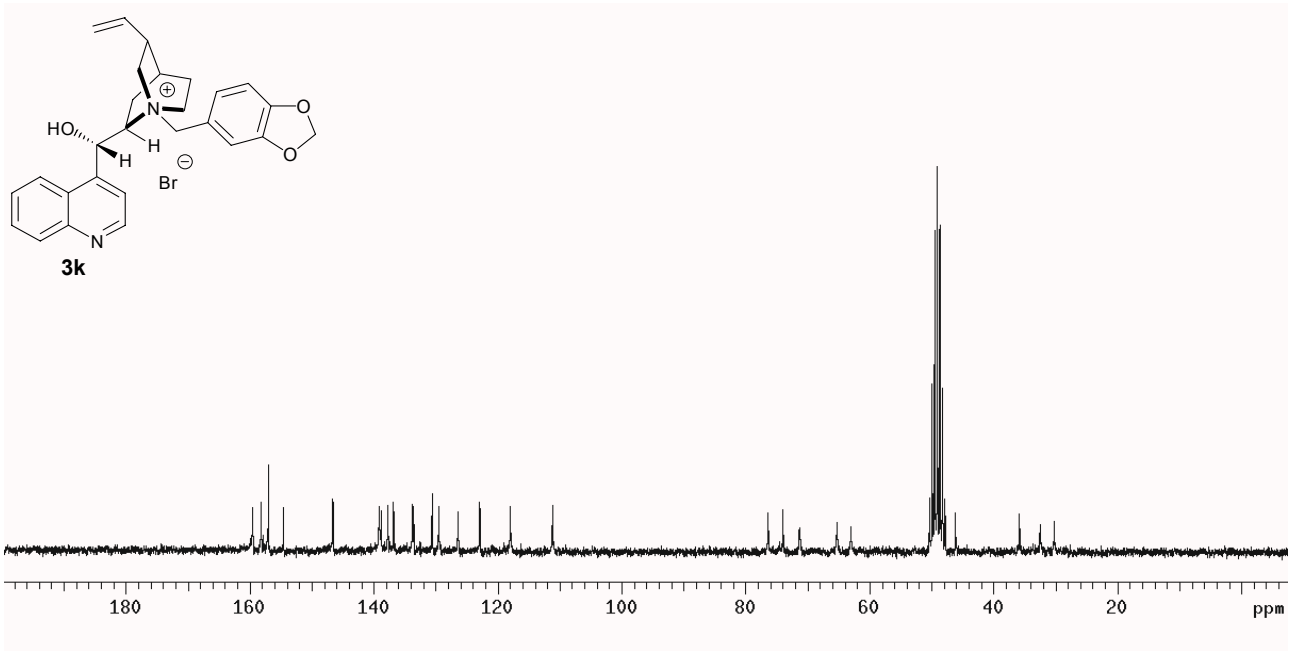

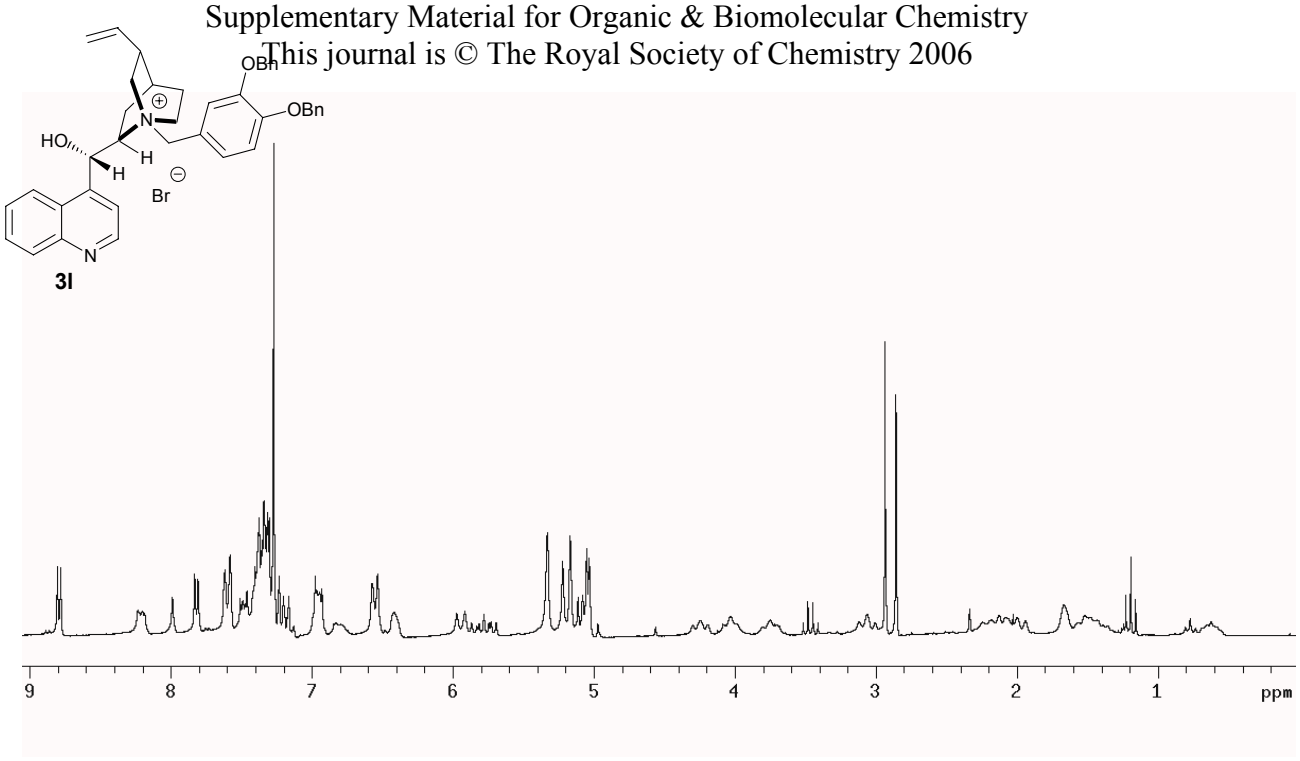

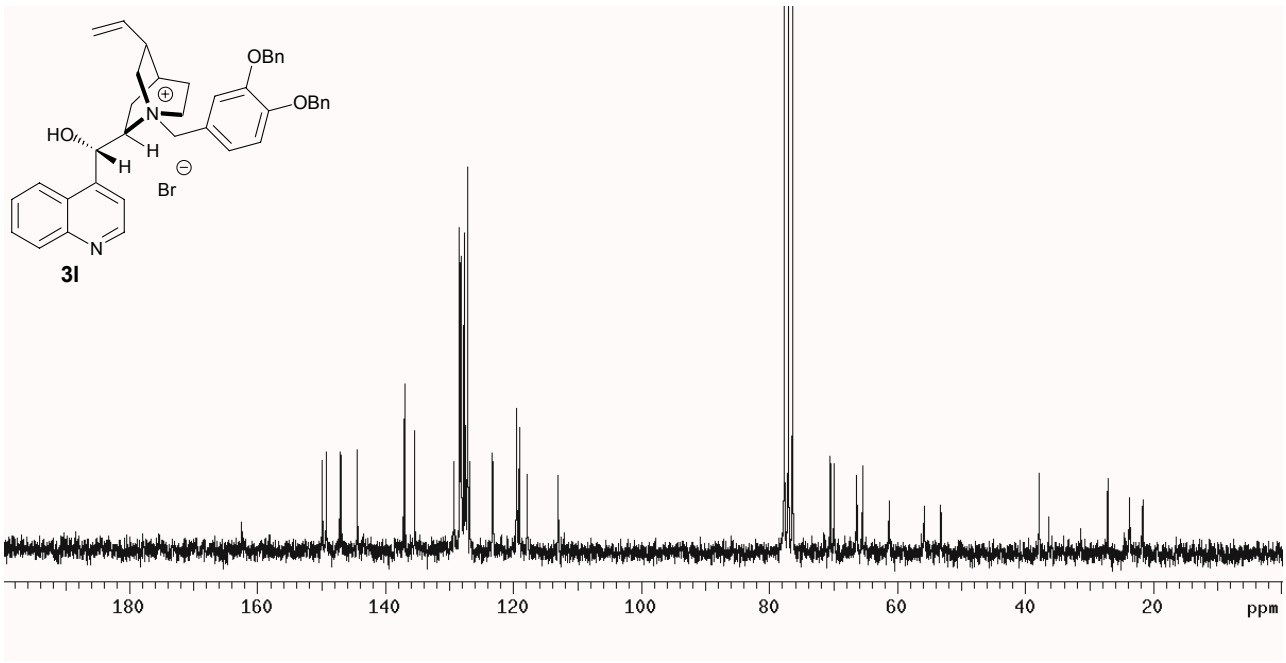

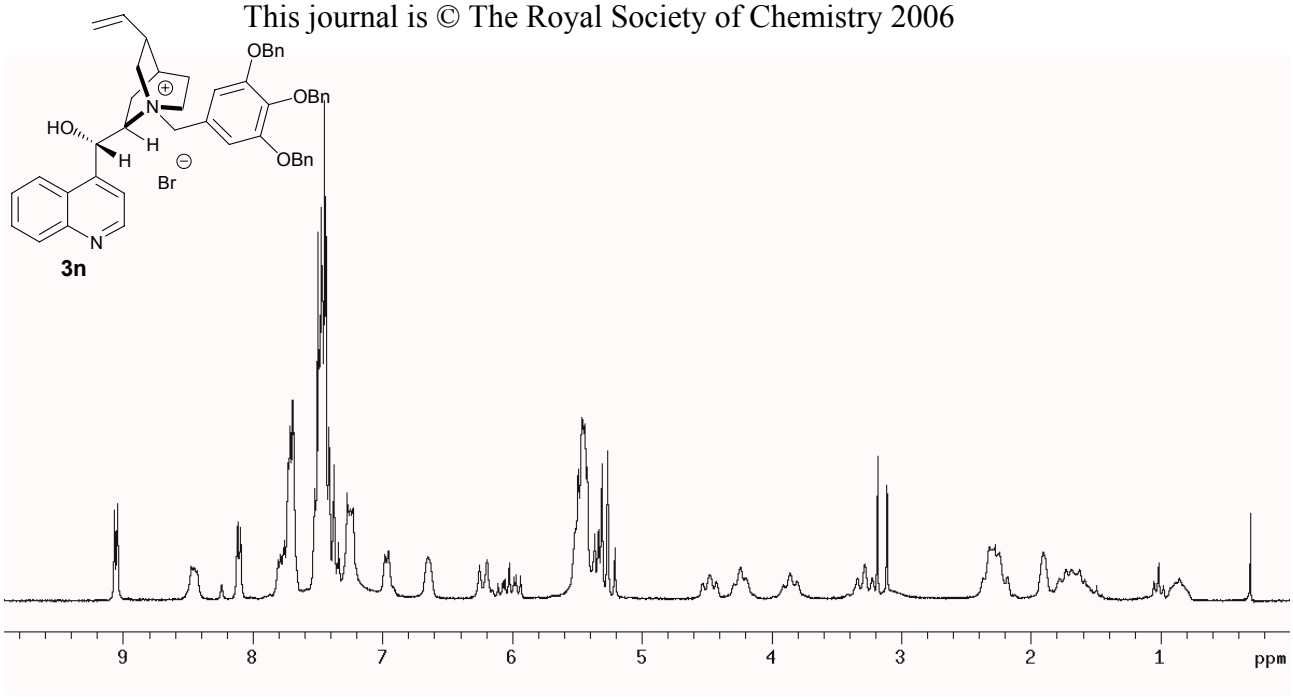

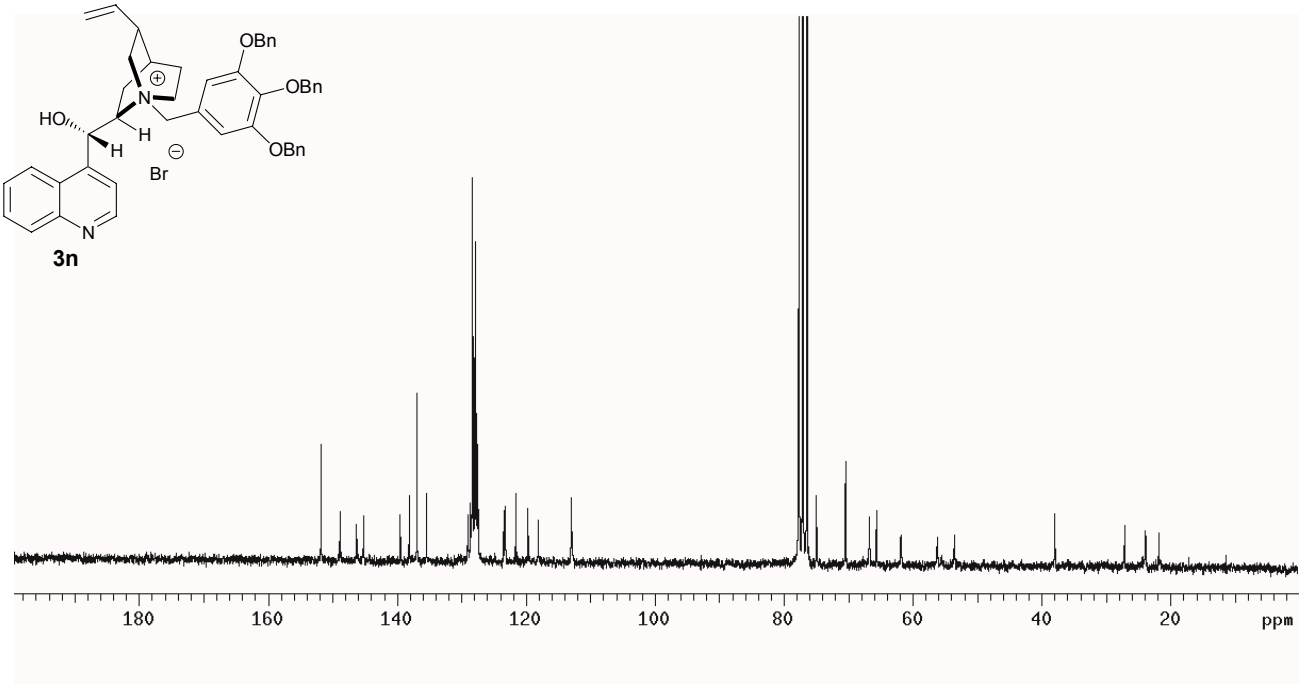

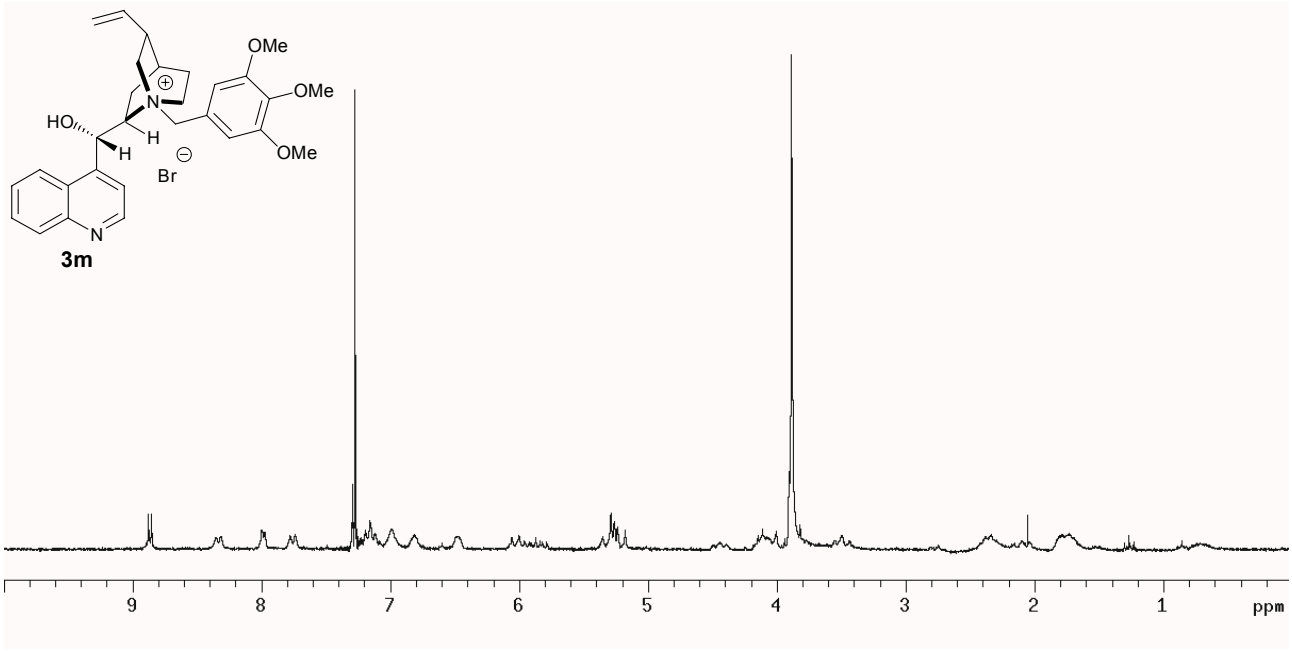
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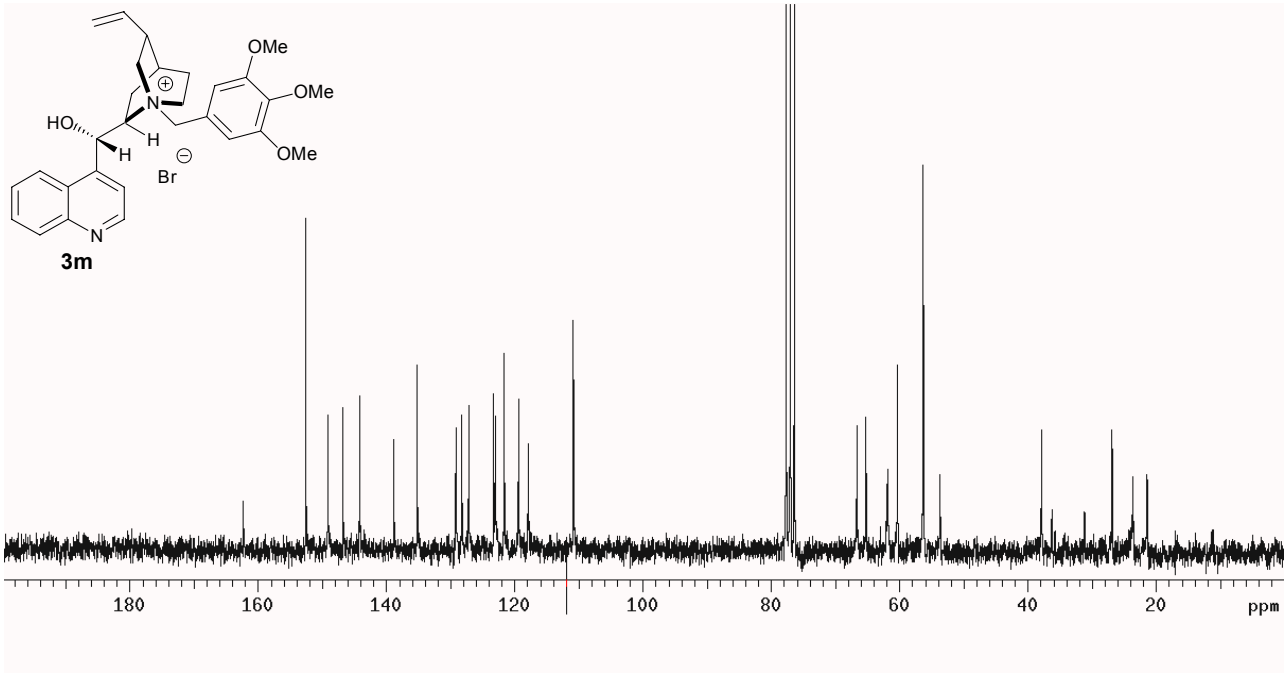
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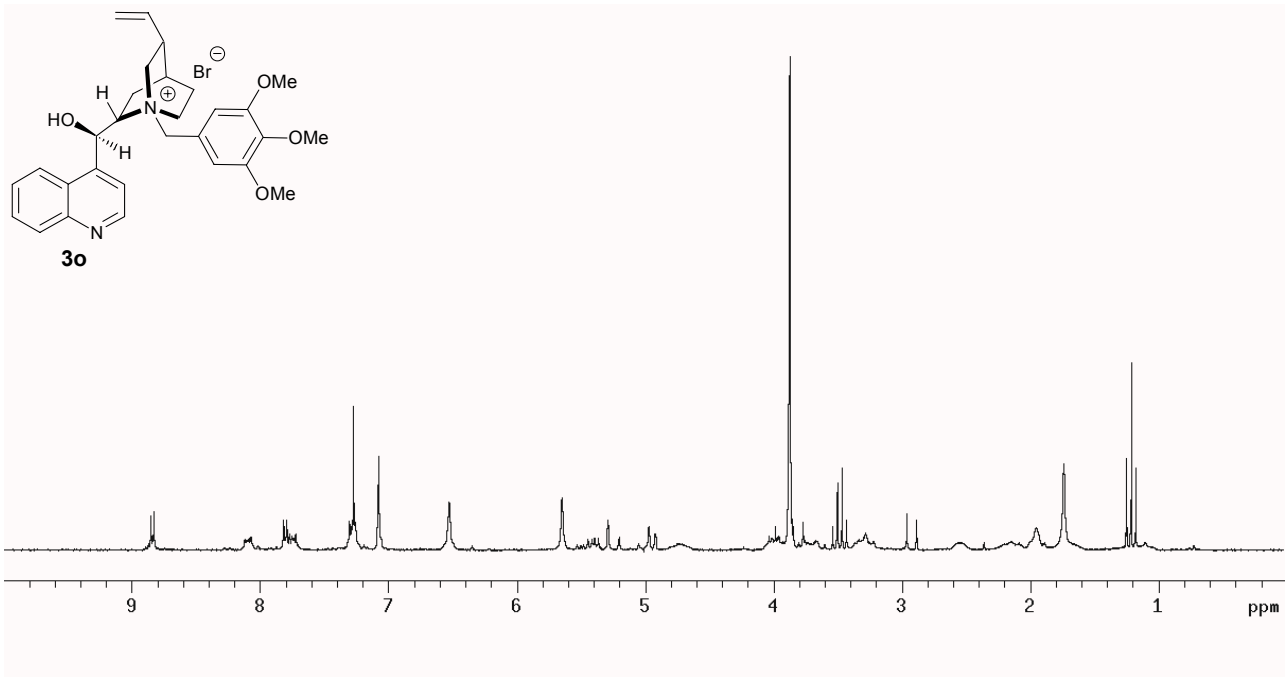

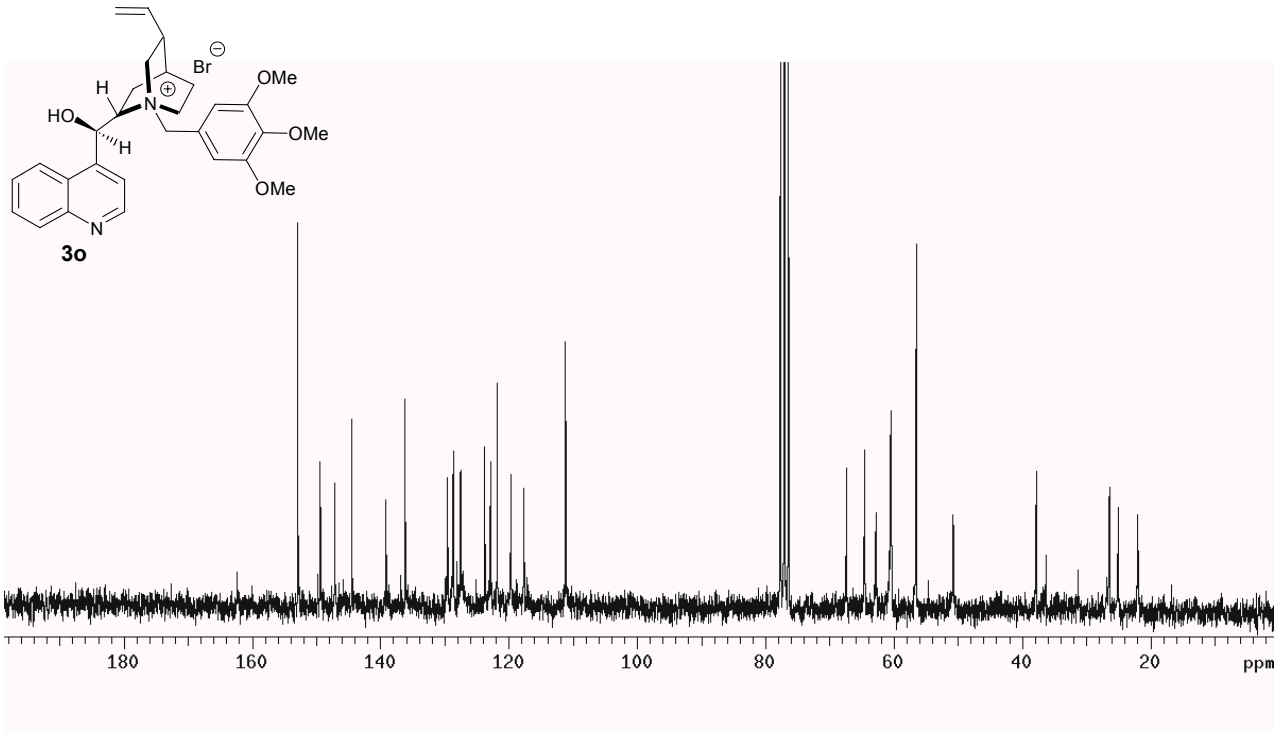

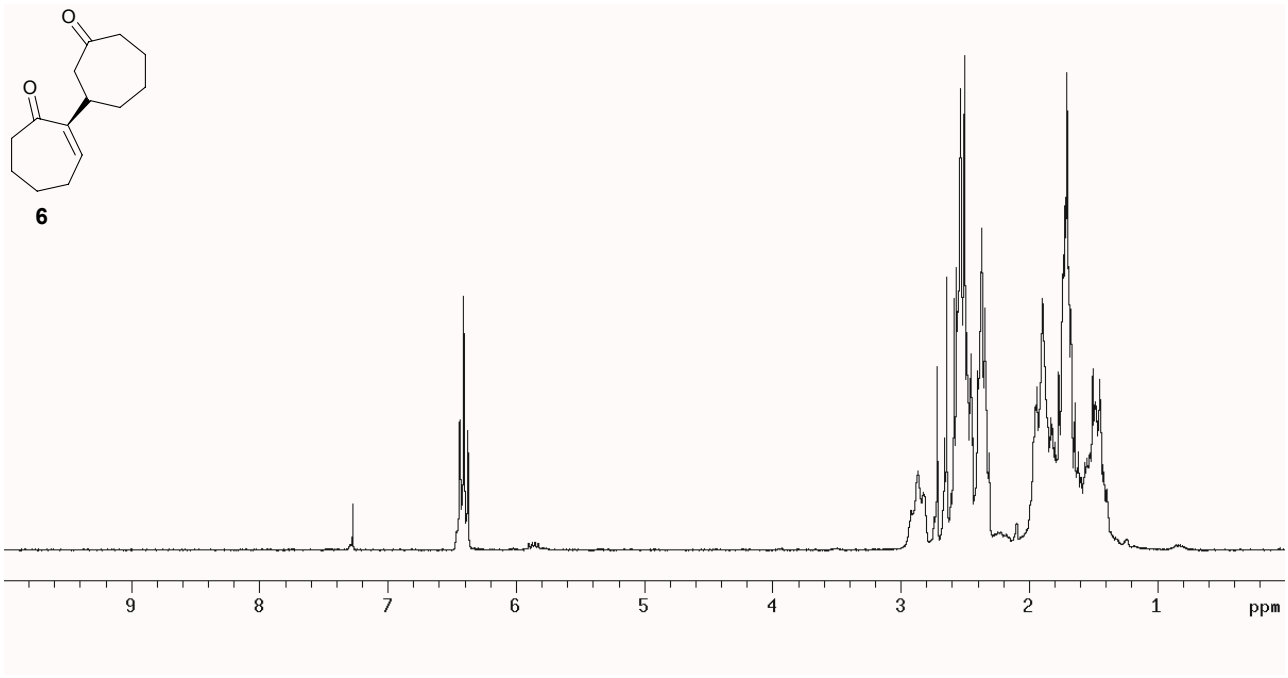

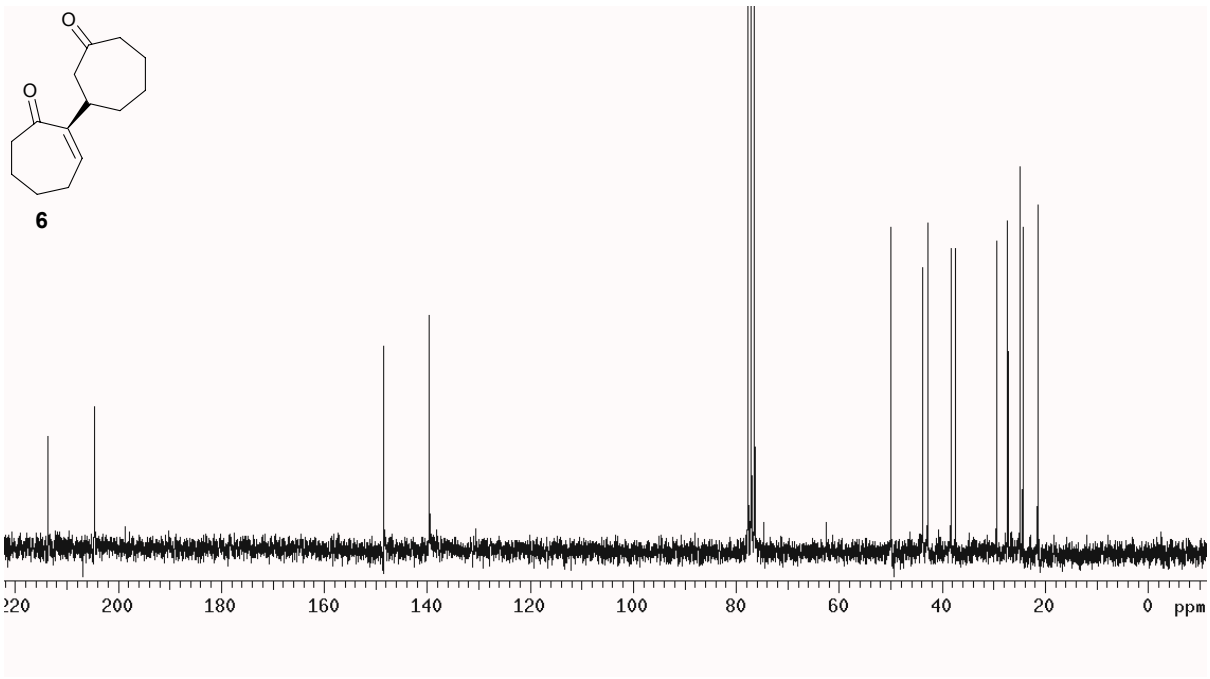

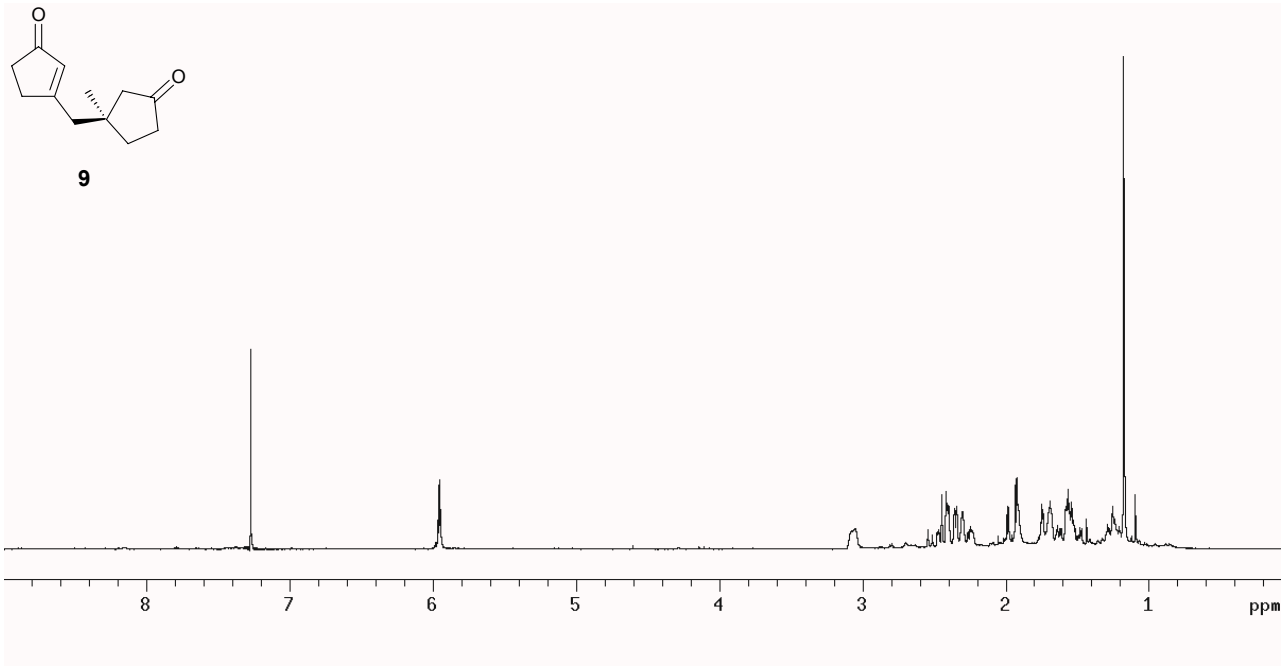

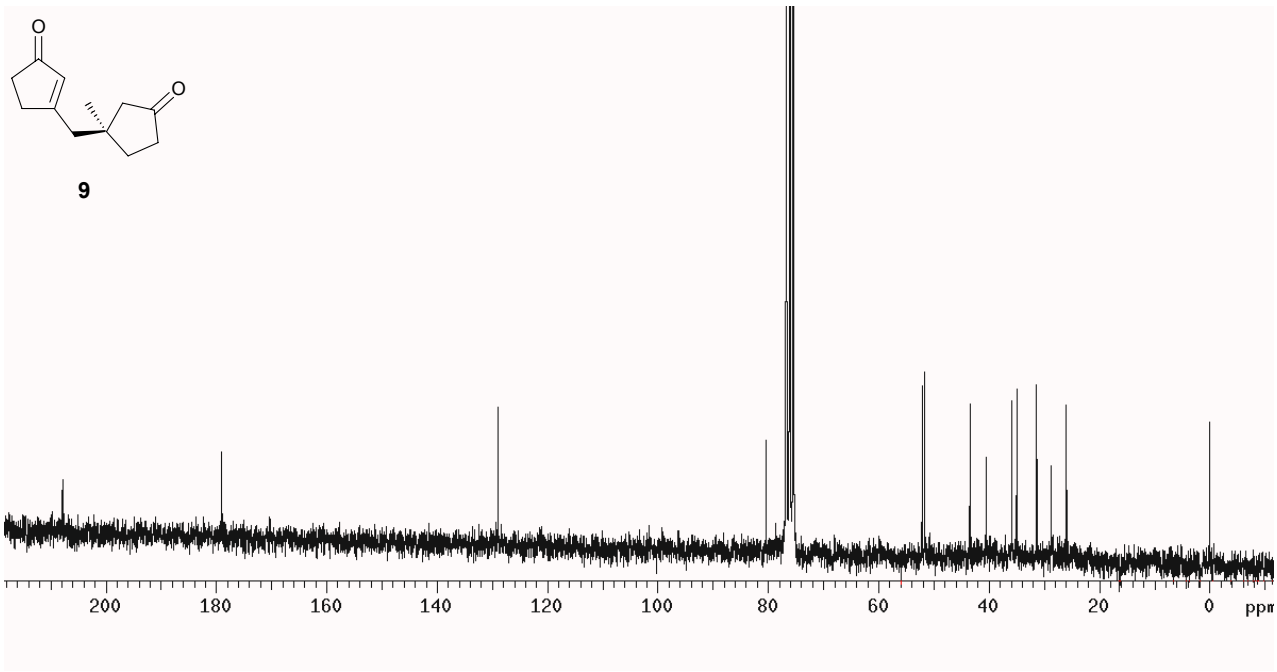

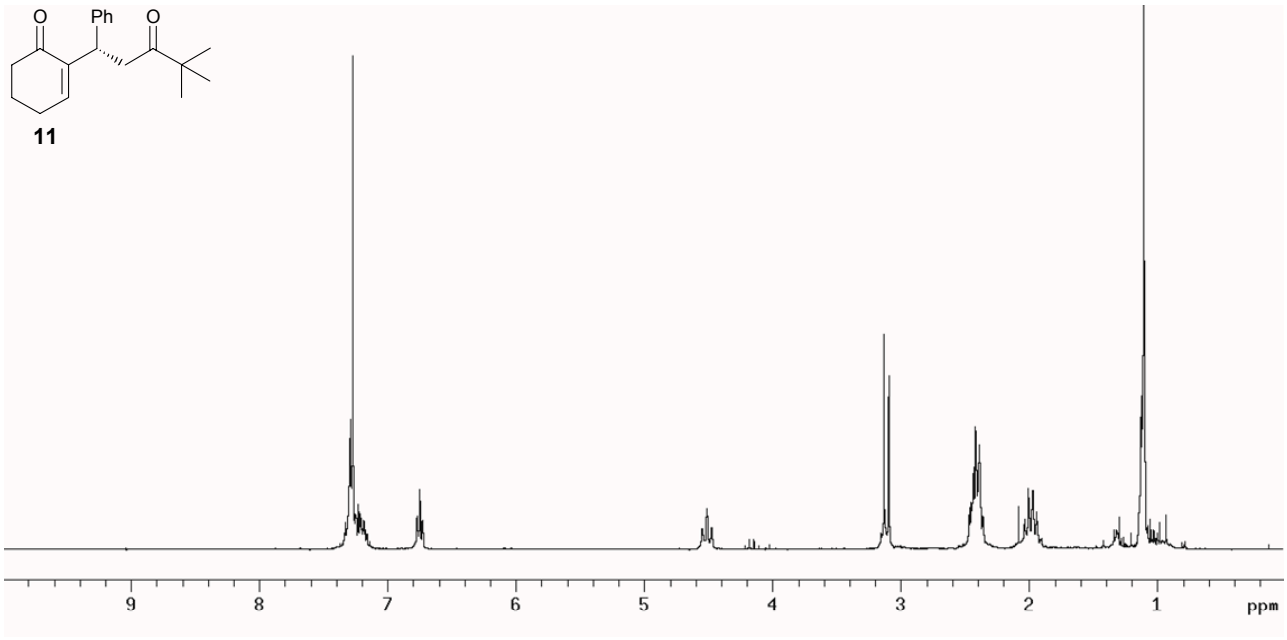
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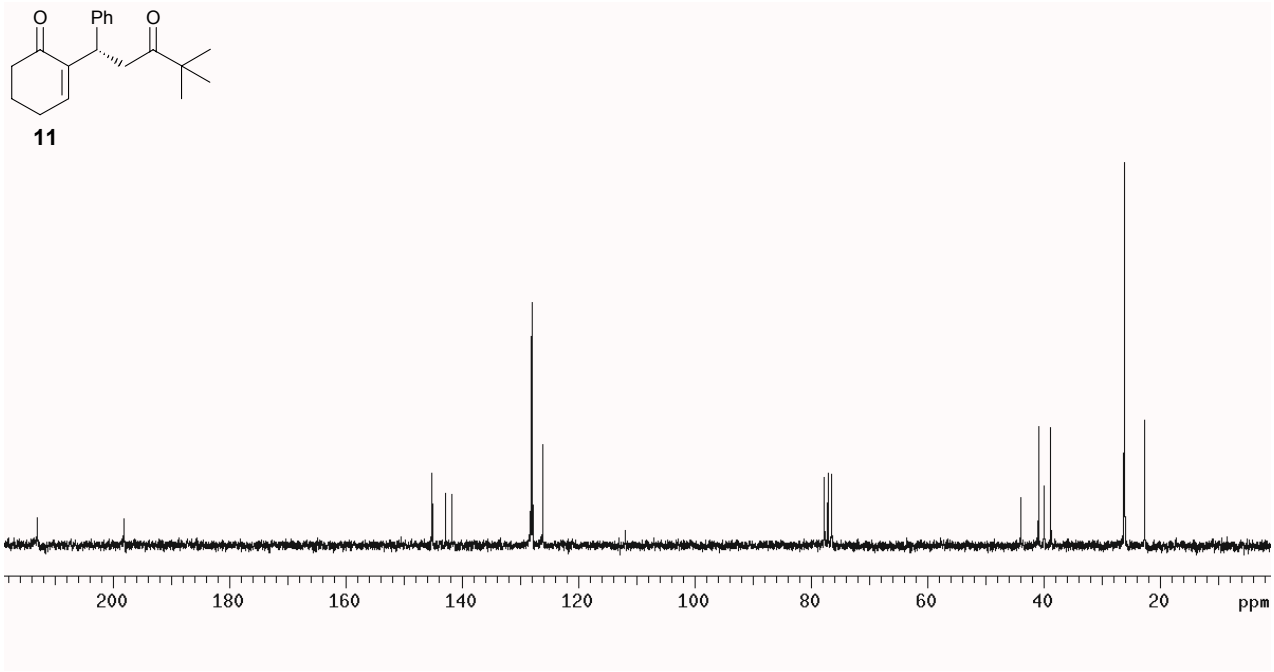
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