Proximity Effects in Nucleophilic Addition Reactions to Medium-Bridged Twisted Lactams: Remarkably Stable Tetrahedral Intermediates

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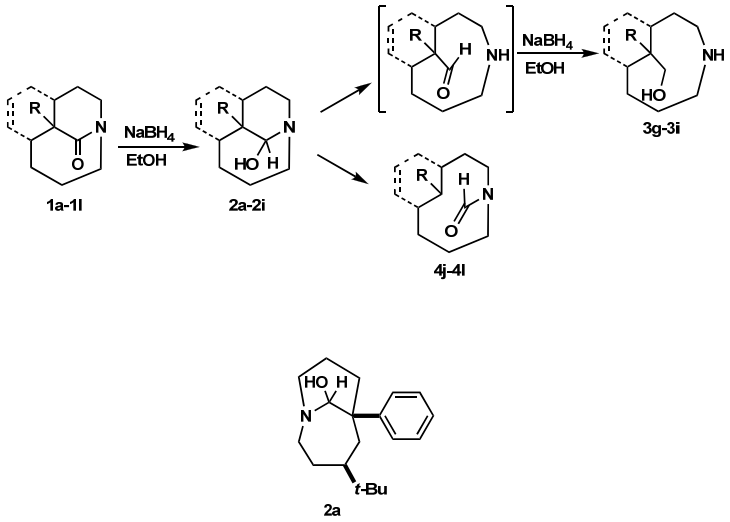
List of Known Compounds

The following compounds are known: bridged lactams **1a**, **1b**, **1g**, **1m**,[1] **1e**, **1f**, **1l**,[2] **1h**, **1i**, **1j**.[3] Lactams **1c**, **1d** and **1k** were prepared in a manner analogous to **1a** and **1b**. Full details will be reported separately.[4] Fused lactams **11**[1] and **13**.[2]

Hydride Addition to Bridged Amides

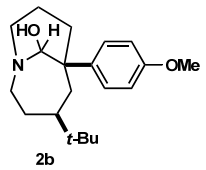
General procedure: To a solution of bridged amide (1.0 equiv) in EtOH, $NaBH_4$ (3.0 equiv) was added at rt, and the reaction mixture was stirred at rt for 20-24 h. The reaction was quenched with sat. NH_4Cl (5 mL), extracted with CH_2Cl_2 (3 x 50 mL), washed with brine (1 x 10 ml), dried and concentrated. Chromatography ($MeOH/CH_2Cl_2$) afforded the final products.

Scheme A. *Synthesis of Compounds **2a-4l** (Table 1 and Scheme 1).*



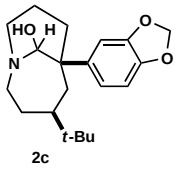
(4R,6R)-4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decan-10-ol (2a). According to the general procedure, the reaction of amide **1a** (0.0250 g, 0.088 mmol, 1.0 equiv) and $NaBH_4$ (0.010 g, 0.26 mmol, 3.0 equiv) in EtOH (5.0 mL) for 21 h at rt afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title compound as oil (R_f = 0.43, 1/10/90 $NH_4OH/MeOH/CH_2Cl_2$). Yield 90% (0.02228 g, 0.079 mmol), 80:20 mixture of inseparable diastereoisomers. ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 0.87 (s, 9H), 1.38-1.61 (m, 3H), 1.73-1.92 (m, 3H), 1.99-2.21 (m, 2H), 2.43-2.53 (m, 2H), 2.65 (dt, *J* = 5.0, 13.4 Hz, 1H), 3.48 (dt, *J* = 3.9, 13.5 Hz, 1H), 3.63-3.70 (m, 1H), 5.13 (s, 1H), 7.16-7.42 (m, 5H); (minor isomer, diagnostic peaks) δ 0.95 (s, 9H), 2.93 (d, *J* = 7.9 Hz, 1H), 4.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 21.3, 27.5, 29.9, 30.8, 33.8, 42.8, 45.2, 47.1, 47.5, 53.1, 83.5, 125.4, 125.5, 128.2, 150.6; (minor isomer, diagnostic peaks) δ 21.4, 27.8, 29.4, 34.0, 38.0, 38.1, 43.4, 46.2, 50.2, 51.9, 88.3, 126.0, 128.0,

151.2; IR (neat) 3400, 2057, 2957, 2941, 2866, 1468, 1445, 1366, 733, 696 cm^{-1}; HRMS calcd for $C_{19}H_{30}NO$ (M^+ + H) 288.2327, found 288.2330.



2b

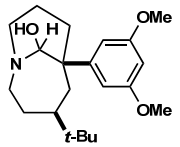
(4R,6R)-4-*tert*-Butyl-6-(4-methoxyphenyl)-1-azabicyclo[4.3.1]decan-10-ol (2b). According to the general procedure, the reaction of amide **1b** (0.0335 g, 0.11 mmol, 1.0 equiv) and $NaBH_4$ (0.0121 g, 0.32 mmol, 3.0 equiv) in EtOH (5.0 mL) for 20 h at rt afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.40, 1/10/90 NH_4OH/MeOH/CH_2Cl_2). Yield 91% (0.0318 g, 0.10 mmol), 77:23 mixture of inseparable diastereoisomers. ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 0.86 (s, 9H), 1.38-1.58 (m, 3H), 1.73-1.95 (m, 3H), 1.98-2.21 (m, 2H), 2.37-2.53 (m, 2H), 2.64 (dt, *J* = 5.0, 12.8 Hz, 1H), 3.47 (dt, *J* = 4.1, 13.8 Hz, 1H), 3.62-3.73 (m, 1H), 3.81 (s, 3H), 5.08 s, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 7.30 (d, *J* = 8.9 Hz, 2H); (minor isomer, diagnostic peaks) δ 0.94 (s, 9H), 2.93 (d, *J* = 7.1 Hz, 1H), 4.91 (s, 1H), 7.52 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 21.2, 27.5, 30.0, 30.7, 33.8, 42.2, 45.1, 47.2, 47.5, 53.1, 55.2, 83.5, 113.3, 126.4, 142.7, 157.2; (minor isomer, diagnostic peaks) δ 27.8, 34.0, 38.1, 38.3, 42.8, 46.2, 50.4, 51.9, 88.6, 113.3, 127.1, 142.7; IR (neat) 3440, 2955, 2988, 1610, 1512, 1250, 1186, 825, 731 cm^{-1}; HRMS calcd for $C_{20}H_{32}NO_2$ (M^+ + H) 318.2433, found 318.2429.



2c

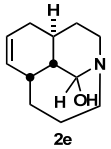
(4R,6R)-6-(Benzo[d][1,3]dioxol-5-yl)-4-*tert*-butyl-1-azabicyclo[4.3.1]decan-10-ol (2c). According to the general procedure, the reaction of amide **1c** (0.0335 g, 0.10 mmol, 1.0 equiv) and $NaBH_4$ (0.0116 g, 0.30 mmol, 3.0 equiv) in EtOH (5.0 mL) for 18 h at rt afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.79, 1/10/90 NH_4OH/MeOH/CH_2Cl_2). Yield 94% (0.0313 g, 0.094 mmol), 78:22 mixture of inseparable diastereoisomers. ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 0.86 (s, 9H), 1.37-1.50 (m, 2H), 1.51-1.59 (m, 1H), 1.71-1.81 (m, 2H), 1.86 (d, *J* = 11.8 Hz, 1H), 1.93-2.22 (m, 2H), 2.38 (dt, *J* = 6.5, 12.6 Hz, 1H), 2.49 (dd, *J* = 4.8, 14.1 Hz, 1H), 2.64 (dt, *J* = 4.9, 13.2 Hz, 1H), 3.46 (dt, *J* = 4.0, 13.7 Hz, 1H), 3.61-3.69 (m, 1H), 5.03 (s, 1H), 5.94 (s, 2H), 6.73-6.84 (m, 2H), 6.90 (s, 1H); (minor isomer, diagnostic peaks) δ 0.94 (s, 9H), 2.92 (d, *J* = 7.5 Hz, 1H), 4.86 (s, 1H), 5.93 (s, 2H), 7.06 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 21.2, 27.5, 30.3, 30.7, 33.8, 42.7, 45.0, 47.2, 47.4, 53.0, 83.5, 100.8, 106.4, 107.9, 118.2, 144.9, 145.1, 147.5; (minor isomer, diagnostic peaks) δ 21.3, 27.8, 30.4, 38.2, 38.5, 43.4,

46.1, 50.3, 51.8, 88.5, 100.7, 107.3, 107.6, 118.9, 144.9, 145.4, 147.2; IR (neat) 3400, 2959, 2941, 2868, 1504, 1489, 1234, 1042, 912, 733 cm^{-1}; HRMS calcd for $C_{20}H_{30}NO_3$ (M^+ + H) 332.2226, found 332.2225.



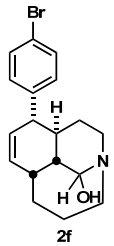
2d

(4R,6R)-4-*tert*-Butyl-6-(3,5-dimethoxyphenyl)-1-azabicyclo[4.3.1]decan-10-ol (2d). According to the general procedure, the reaction of amide **1d** (0.0571 g, 0.17 mmol, 1.0 equiv) and $NaBH_4$ (0.0188 g, 0.50 mmol, 3.0 equiv) in EtOH (5.0 mL) for 18 h at rt afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.53, 1/10/90 NH_4OH/MeOH/CH_2Cl_2). Yield 95% (0.0561 g, 0.16 mmol), 77:23 mixture of inseparable diastereoisomers. ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 0.86 (s, 9H), 1.38-1.60 (m, 3H), 1.71-1.91 (m, 3H), 1.93-2.22 (m, 2H), 2.36-2.52 (m, 2H), 2.64 (dt, *J* = 5.0, 12.6 Hz, 1H), 3.48 (dt, *J* = 4.1, 13.8 Hz, 1H), 3.59-3.69 (m, 1H), 3.82 (s, 9H), 5.05 (s, 1H), 6.32 (t, *J* = 2.0 Hz, 1H), 6.54 (d, *J* = 2.2 Hz, 2H); (minor isomer, diagnostic peaks) δ 0.94 (s, 9H), 1.66 (m, 2H), 2.92 (d, *J* = 7.2 Hz, 2H), 4.90 (s, 1H), 6.81 (d, *J* = 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 21.3, 27.5, 30.0, 30.7, 33.8, 43.0, 45.0, 46.7, 47.4, 52.9, 55.2, 83.5, 96.8, 104.5, 153.3, 160.5; (minor isomer, diagnostic peaks) δ 21.3, 27.8, 29.2, 34.0, 38.0, 43.7, 46.1, 50.3, 51.8, 55.2, 88.2, 97.0, 105.1, 153.9, 160.3; IR (neat) 3400, 3088, 2955, 2868, 1595, 1456, 1308, 1204, 1151, 1069, 910, 733 cm^{-1}; HRMS calcd for $C_{21}H_{34}NO_3$ (M^+ + H) 348.2539, found 348.2538.



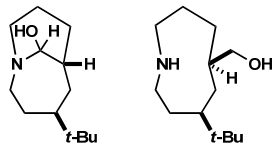
2e

Hemiaminal 2e. According to the general procedure, amide **1e** (0.060 g, 0.31 mmol, 1.0 equiv) was reacted with $NaBH_4$ (0.036 g, 0.94 mmol, 3.0 equiv) in EtOH for 18 h at rt. Saturated NH_4Cl (ca. 1 mL) was added and after stirring for 5 min, the solution was dried with Na_2SO_4, filtered, and concentrated. Chromatography (1/9 MeOH/CH_2Cl_2) afforded the title compound as oil. Yield 91% (0.0550 g, 0.29 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 1.21-1.25 (m, 1H), 1.82-2.16 (complex, 11H), 2.30-2.40 (m, 1H), 2.90-2.98 (m, 2H), 3.91-3.95 (m, 1H), 4.05-4.10 (m, 1H), 5.37 (s, 1H), 5.60-5.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 23.5, 27.6, 32.9, 34.0, 36.6, 46.6, 49.9, 56.5, 82.0, 126.5, 132.3; IR (neat): 3370 cm^{-1}; HRMS calcd for $C_{12}H_{20}NO$ (M^++1) 194.1545, found 194.1530.



2f

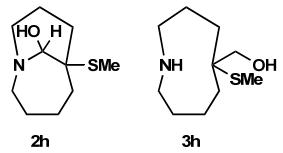
Hemiaminal 2f. According to the general procedure, the reaction of amide **1f** (0.100 g, 0.29 mmol, 1.0 equiv) and $NaBH_4$ (0.033 g, 0.87 mmol, 3.0 equiv) in EtOH for 18 h at rt afforded after chromatography (1/9 $MeOH/CH_2Cl_2$) the title compound as oil. Yield 88% (0.0892 g, 0.26 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 1.58-1.90 (complex, 4H), 2.00-2.12 (m, 2H), 2.27-2.30 (m, 2H), 2.54-2.56 (m, 1H), 2.75-2.85 (m, 2H), 3.20-3.23 (m, 1H), 3.87-3.93 (m, 1H), 4.01-4.06 (m, 1H), 5.43 (s, 1H), 5.57-5.59 (m, 1H), 5.96-6.00 (m, 1H), 7.01-7.03 (m, 2H), 7.45-7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 23.4, 33.2, 35.7, 36.5, 46.3, 50.0, 50.7, 56.4, 82.0, 120.9, 129.7, 130.4, 131.8, 133.4, 141.1; IR (neat): 3370 cm^{-1}; HRMS calcd for $C_{18}H_{23}BrNO$ (M^++1) 348.0963, found 348.0964.



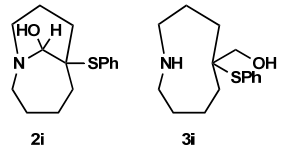
2g 3g

(4R,6R)-4-*tert*-Butyl-1-azabicyclo[4.3.1]decan-10-ol (2g) and ((7R)-7-*tert*-Butylazonan-5-yl)methanol (3g). According to the general procedure, the reaction of amide **1g** (0.100 g, 0.47 mmol, 1.0 equiv) and $NaBH_4$ (0.0545 g, 1.44 mmol, 3.0 equiv) in EtOH (20 mL) for 18 h at rt afforded after chromatography (1/20/80 $NH_4OH/MeOH/CH_2Cl_2$) **2g** as oil (R_f = 0.52, 1/10/90 $NH_4OH/MeOH/CH_2Cl_2$), yield 24% (0.0240 g, 0.11 mmol), 80:20 mixture of inseparable diastereoisomers, and **3g** as oil (R_f = 0.24, 1/10/90 $NH_4OH/MeOH/CH_2Cl_2$), yield 52% (0.0522 g, 0.25 mmol). Analysis of the crude reaction mixture by ^1H NMR indicated 30:70 mixture of **2g** to **3g**. Compound **2g**: ^1H NMR (400 MHz, $CDCl_3$) (major isomer) δ 0.89 (s, 9H), 0.99 (td, *J* = 3.5, 14.0 Hz, 1H), 1.21-1.55 (m, 4H), 1.70-1.88 (m, 2H), 2.05-2.16 (m, 1H), 2.16-2.24 (m, 2H), 2.57 (dd, *J* = 4.7, 14.4 Hz, 1H), 2.85 (td, *J* = 2.8, 14.7 Hz, 1H), 3.03 (dt, *J* = 3.4, 14.5 Hz, 1H), 3.44 (td, *J* = 4.0, 13.8 Hz, 1H), 4.66 (s, 1H); (minor isomer, diagnostic peaks) δ 0.90 (s, 9H), 2.38-2.46 (m, 2H), 2.48-2.54 (m, 1H), 4.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 19.4, 24.3, 27.6, 30.5, 31.9, 33.7, 33.9, 44.7, 45.8, 54.8, 81.4; (minor isomer, diagnostic peaks) δ 19.3, 24.8, 27.6, 29.8, 33.5, 34.7, 35.3, 45.3, 48.1, 51.4, 81.2; IR (neat) 3400, 3125, 2937, 1468, 1450, 1366, 1053, 986 cm^{-1}; HRMS calcd for $C_{13}H_{26}NO$ (M^+ + H) 212.2014, found 212.2009. Compound **3g**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 9H), 1.18-1.80 (m, 9H), 1.81-1.92 (m, 1H), 2.03 (br, 2H), 2.53 (td, *J* = 3.9, 13.1 Hz, 1H), 2.64-2.78 (m, 2H), 2.82-2.92 (m, 1H), 3.38-3.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 26.7, 27.7, 28.5, 32.9, 34.2, 34.8, 40.6, 42.9, 49.5, 67.5;

IR (neat) 3350, 2939, 2866, 1477, 1364, 1140, 1030 cm^{-1}; HRMS calcd for $C_{13}H_{28}NO$ (M^+ + H) 214.2171, found 214.2170.

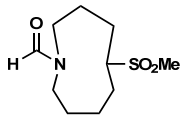


6-(Methylthio)-1-azabicyclo[4.3.1]decan-10-ol (2h) and (5-(Methylthio) azonan-5-yl)methanol (3h). According to the general procedure, the reaction of amide **1h** (0.0322 g, 0.16 mmol, 1.0 equiv) and $NaBH_4$ (0.018 g, 0.48 mmol, 3.0 equiv) in EtOH (10 mL) for 18 h at rt afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) **2h** as oil (R_f = 0.65, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 40% (0.0129 g, 0.064 mmol), and **3h** as oil (R_f = 0.17, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 48% (0.0161 g, 0.079 mmol). Compound **2h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43-1.73 (m, 5H), 1.74-2.05 (m, 5H), 2.12 (s, 3H), 2.34-2.42 (m, 1H), 2.58 (dd, *J* = 4.8, 14.2 Hz, 1H), 2.94-3.08 (m, 2H), 3.34-3.45 (m, 1H), 4.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1, 22.6, 25.9, 31.7, 32.0, 38.6, 43.7, 50.9, 55.1, 80.9; IR (neat) 2400, 2920, 2856, 1450, 1163, 1155, 1113 cm^{-1}; HRMS calcd for $C_{10}H_{20}NOS$ (M^+ + H) 202.1266, found 202.1263. Compound **3h**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.55 (m, 4H), 1.58-1.78 (m, 5H), 1.78-1.95 (m, 3H), 1.91 (s, 3H), 2.07-2.85 (m, 4H), 3.33 (q, *J* = 11.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.5, 17.5, 20.5, 25.6, 26.1, 28.4, 41.9, 47.7, 56.7, 63.6; IR (neat) 3400, 2920, 2862, 1480, 1157, 1123, 748 cm^{-1}; HRMS calcd for $C_{10}H_{22}NOS$ (M^+ + H) 204.1422, found 204.1420.



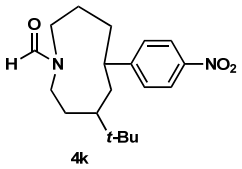
6-(Phenylthio)-1-azabicyclo[4.3.1]decan-10-ol (2i) and (5-(Phenylthio)azonan-5-yl)methanol (3i). According to the general procedure, the reaction of amide **1i** (0.0245 g, 0.093 mmol, 1.0 equiv) and $NaBH_4$ (0.011 g, 0.28 mmol, 3.0 equiv) in EtOH (5 mL) for 18 h at rt afforded after chromatography (1/5/95 NH_4OH/MeOH/CH_2Cl_2) **2i** as oil (R_f = 0.50, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 62% (0.0151 g, 0.057 mmol), 83:17 mixture of diastereoisomers, and **3i** as oil (R_f = 0.31, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 34% (0.0083 g, 0.031 mmol). Analysis of the crude reaction mixture by ^{1}H NMR indicated 63:37 mixture of **2i** to **3i**. Compound **2i**: ^{1}H NMR (400 MHz, $CDCl_3$) (major isomer) δ 1.02-1.16 (m, 1H), 1.48-1.65 (m, 5H), 1.78-1.91 (m, 3H), 2.18 (td, *J* = 4.6, 12.4 Hz, 1H), 2.34 (ddd, *J* = 3.4, 6.2, 15.8 Hz, 1H), 2.55 (dd, *J* = 4.9, 14.1 Hz, 1H), 2.86-2.99 (m, 2H), 3,44 (td, *J* = 3.5, 13.7 Hz, 1H), 4.50 (s, 1H), 7.30-7.42 (m, 3H), 7.60 (dd, *J* = 1.8, 7.9 Hz, 2H); (minor isomer, diagnostic peaks) δ 2.68-2.75 (m, 1H), 4.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 22.9, 24.8, 31.2, 32.4, 38.1, 43.5, 54.5, 55.8, 81.9, 128.8, 129.0, 130.9, 136.7; IR (neat) 3450, 3071, 3057, 2924, 2855, 1450, 1437,

1350, 1150, 750 cm^{-1}; HRMS calcd for $C_{15}H_{22}NOS$ (M^+ + H) 264.1422, found 264.1422. Compound **3i**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.39-1.65 (m, 6H), 1.65-2.16 (m, 6H), 2.63-2.71 (m, 1H), 2.73-2.87 (m, 3H), 3.24 (q, *J* = 11.6 Hz, 2H), 7.33-7.43 (m, 3H), 7.51 (dd, *J* = 1.4, 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 20.7, 25.9, 26.3, 28.5, 41.5, 47.6, 62.3, 64.3, 128.9, 129.1, 130.0, 137.3; IR (neat) 3400, 3057, 2918, 2849, 1474, 1437, 1410, 1050, 750 cm^{-1}; HRMS calcd for $C_{15}H_{24}NOS$ (M^+ + H) 266.1579, found 266.1577.



4j

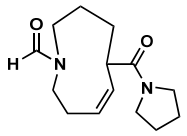
5-(Methylsulfonyl)azonane-1-carbaldehyde (4j). According to the general procedure, the reaction of amide **1j** (0.0110 g, 0.048 mmol, 1.0 equiv) and $NaBH_4$ (0.0054 g, 0.14 mmol, 3.0 equiv) in EtOH (4 mL) for 18 h at rt afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) **4j** as oil (R_f = 0.35, 1/10/90 NH_4OH/MeOH/CH_2Cl_2). Yield 98% (0.0110 g, 0.047 mmol). ^1H NMR (400 MHz, $CDCl_3$) (60:40 mixture of rotamers) δ 1.61-1.99 (m, 7H), 2.06-2.37 (m, 3H), 2.84 (s, 3H, minor rotamer), 2.85 (s, 3H, major rotamer), 2.89-3.02 (m, 1H), 3.08-3.37 (m, 2H), 3.42-3.56 (m, 1H), 3.68-3.77 (m, 1H), 8.15 (s, 1H, major rotamer), 8.20 (s, 1H, minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 23.5, 23.8, 24.3, 24.4, 25.3, 25.4, 25.6, 26.0, 26.6, 26.8, 37.7, 37.9, 45.1, 45.7, 49.6, 50.4, 62.1, 62.2, 163.9, 164.3; IR (neat) 1651, 1283, 1128 cm^{-1}; HRMS calcd for $C_{10}H_{20}NO_3S$ (M^+ + H) 234.1164, found 234.1167.



4k

4-*tert*-Butyl-6-(4-nitrophenyl)azonane-1-carbaldehyde (4k). According to the general procedure, the reaction of amide **1k** (0.0221 g, 0.067 mmol, 1.0 equiv) and $NaBH_4$ (0.008 g, 0.20 mmol, 3.0 equiv) in EtOH (10 mL) for 20 h at rt afforded **4k** as 42:68 mixture of diastereoisomers (determined by ^1H NMR of the crude reaction mixture). PTLC (1/10/90 NH_4OH/MeOH/CH_2Cl_2) afforded minor diastereoisomer **4ka** as oil (R_f = 0.54, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 36% (0.0081 g, 0.024 mmol), and major diastereoisomer **4kb** as oil (R_f = 0.46, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 46% (0.0103 g, 0.031 mmol). Compound **4ka**: ^1H NMR (400 MHz, $CDCl_3$) (64:36 mixture of rotamers) δ 0.91 (s, 9H, major rotamer), 0.94 (s, 9H, minor rotamer), 1.58-2.8 (m, 10H), 3.21-3.69 (m, 4H), 7.62-7.68 (m, 2H), 8.16-8.22 (m, 2H), 8.32 (s, 1H, minor rotamer); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 21.8, 21.9, 27.6, 30.2, 33.4, 34.6, 34.7, 36.8, 37.7, 39.1, 40.8, 42.5, 44.1, 45.8, 48.9, 50.1, 75.6, 76.2, 123.6, 123.6, 125.5, 125.7, 146.8, 157.6, 164.0, 164.1; IR (neat) 2959, 2870, 1661, 1518, 1348, 733 cm^{-1};

HRMS calcd for $C_{19}H_{29}N_2O_3$ (M^+ + H) 333.2178, found 333.2159. Compound **4kb**: ^{1}H NMR (400 MHz, $CDCl_3$) (55:45 mixture of rotamers) δ 0.45 (s, 9H, minor rotamer), 0.55 (s, 9H, major rotamer), 0.96-1.02 (m, 1H), 1.48-2.44 (m, 9H), 3.26-3.43 (m, 2H), 3.46-3.58 (m, 1H), 3.61-3.71 (m, 1H, minor rotamer), 3.83 (td, J = 4.3, 13.8 Hz, 1H, major rotamer), 7.66-7.73 (m, 2H), 8.16-8.20 (m, 2H), 8.22 (s, 1H, minor rotamer), 8.29 (s, 1H, major rotamer); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 20.2, 20.8, 27.3, 27.5, 29.7, 31.2, 32.0, 33.2, 34.1, 34.3, 39.4, 39.6, 40.9, 42.6, 42.9, 43.7, 47.7, 48.8, 123.3, 126.7, 127.0, 146.9, 155.9, 156.0, 163.9, 164.5; IR (neat) 2961, 2872, 1659, 1518, 1349, 1076, 912, 856, 733 cm^{-1}; HRMS calcd for $C_{19}H_{28}N_2O_3Na$ (M^+ + Na) 355.1997, found 355.2019.



4l

(Z)-5-(Pyrrolidine-1-carbonyl)-2,3,4,5,8,9-hexahydro-1H-azonine-1-carbaldehyde (4l). According to the general procedure, the reaction of amide **1l** (0.080 g, 0.32 mmol, 1.0 equiv) and $NaBH_4$ (0.037 g, 0.97 mmol, 3.0 equiv) in EtOH for 18 h at rt afforded after chromatography (20% EtOH/EtOAc) **4l** as oil in 99% yield (0.0801 g, 0.32 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) (88:12 mixture of rotamers) δ 1.50-1.54 (m, 2H), 1.73-2.00 (complex, 5H), 2.00-2.10 (m, 1H), 2.53-2.55 (m, 1H), 2.64-2.70 (m, 1H), 3.14 (m, 1H), 3.28-3.41 (complex, 6H), 3.91-3.96 (m, 1H), 5.38-5.44 (m, 1H), 5.87-5.93 (m, 1H), 8.09 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 22.9, 23.0, 24.2, 26.1, 28.3, 42.7, 45.8, 45.9, 46.0, 50.6, 129.9, 130.0, 162.9, 171.8; IR (neat): 3370, 1655, 1630 cm^{-1}; HRMS calcd for $C_{14}H_{23}N_2O_2$ (M^++1) 251.1760, found 251.1747.

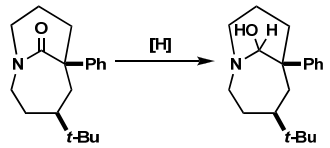
Role of Hydride Source and Reaction Conditions on Formation and Fates of Stable Hemiaminals

Reaction of **1a** with a number of different hydride sources[5] afforded stable hemiaminal **2a** (Table A). Interestingly, the reduction rate with $NaBH_4$[6] was found to be qualitatively slower in methanol as a solvent than in ethanol (entry 2), which contrasts with the reduction of typical carbonyl groups by $NaBH_4$.[7] In addition, the reduction of **1a** was suppressed when $CeCl_3$ was utilized as an additive (entry 3).[8] Hydrogen bonding or coordination to the amide bond nitrogen could be responsible for decreased reaction rates in these cases.

Tributoxyaluminum hydride[9] and L-Selectride[10] (entries 5 and 6) did not reduce **34**, while $LiAlH_4$,[11] Red-Al and DIBAL-H[12] smoothly provided hemiaminal **238** (entries 7-9). In contrast, $LiEt_3BH$[13] promoted the collapse of **238** to the aldehyde (entry 11), indicating that the outcome of the reduction of one-carbon bridged lactams could also be modified by changes in reaction conditions (vs. substrate modification).

Importantly, when a one-carbon higher homologue of **1a** ([5.3.1] ring system) was treated with $NaBH_4$, reduction was not observed, indicating that the [5.3.1] scaffold is not sufficiently distorted to permit hydride addition under these conditions (Scheme B).[6]

Table A. *Reduction of Lactam **1a**.*



1a 2a

entry	reagent	solvent	temp. [°C]	time [h]	yield [%]	dr[a]
1	$NaBH_4$	EtOH	24	20	96	80:20
2	$NaBH_4$[b]	MeOH	24	20	32[c]	86:14
3	$NaBH_4/CeCl_3$	EtOH	24	20	31[c]	81:19
4	$LiBH_4$	EtOH	24	20	94	82:18
5	$LiAl(OtBu)_3H$	THF	24	24	<5[d]	nd
6	L-Selectride	THF	24	24	<5[d]	nd
7	$LiAlH_4$	Et_2O	24	5	99	82:18
8	Red-Al	PhMe	110	2	96	80:20
9	DIBAL-H	PhMe	110	2	97	81:19
10	BH_3	THF	66	24	47	74:26
11	$LiEt_3BH$	THF	24	3	92[e]	84:16

[a] Determined by ^1H NMR; [b] 4-$MeOC_6H_4$ derivative was used; [c] Conversion; [d] Only starting material was observed by ^1H NMR; [e] Combined yield of hemiaminal and primary alcohol **3a** (isolated in 38% and 54% yield, respectively); nd = not determined.

Entry 2: According to the general procedure amide **1b** (0.0205 g, 0.065 mmol, 1.0 equiv) was reacted with $NaBH_4$ (0.0074 g, 0.20 mmol, 3.0 equiv) in MeOH (3 mL) for 20 h at rt. Analysis of the reaction mixture by ^1H NMR indicated 32% conversion to the aminal **2a**, dr = 86:14.

Entry 3: To a solution of amide **1a** (0.0150 g, 0.053 mmol, 1.0 equiv) in EtOH (10 mL), $CeCl_3$ (0.019 g, 0.053 mmol, 1.0 equiv) was added, followed by $NaBH_4$ (0.006 g, 0.16 mmol, 3.0 equiv), and the resulting mixture was stirred at rt for 24 h. Analysis of the crude reaction mixture by ^1H NMR indicated 31% conversion to the aminal **2a**, dr = 81:19.

Entry 4: According to the general procedure amide **1a** (0.0150 g, 0.053 mmol, 1.0 equiv) was reacted with $LiBH_4$ (0.0037 g, 0.16 mmol, 3.0 equiv) in EOH (10 mL) for 20 h at rt, to afford aminal **2a**, yield 94% (0.0143 g, 0.050 mmol), dr = 82:18.

Entry 5: To a solution of amide **1a** (0.0150 g, 0.053 mmol, 1.0 equiv) in THF (5 mL), LiAlO*t*Bu (0.068 g, 0.26 mmol, 5.0 equiv) was added at rt, and the reaction mixture

was stirred at rt for 24 h. After aqueous work-up, analysis of the crude reaction mixture indicated only the presence of the starting material.

Entry 6: To a solution of amide **1a** (0.0150 g, 0.053 mmol, 1.0 equiv) in THF (5 mL), L-Selectride (1.0 M in THF, 0.26 mL, 0.26 mmol, 5.0 equiv) was added at rt, and the reaction mixture was stirred at rt for 24 h. After aqueous work-up, analysis of the crude reaction mixture indicated only the presence of the starting material.

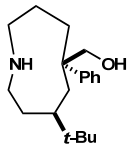
Entry 7: To a solution of amide **1a** (0.0150 g, 0.053 mmol, 1.0 equiv) in Et_2O (5 mL), $LiAlH_4$ (1.0 M in Et_2O, 0.16 mL, 0.16 mmol, 3.0 equiv) was added at 0 °C, and the reaction mixture was stirred at rt for 5 h. Fieser and Fieser work-up, followed by chromatography afforded **2a**, yield 99% (0.0150 g, 0.052 mmol), dr = 82:18.

Entry 8: To a solution of amide **1a** (0.0181 g, 0.064 mmol, 1.0 equiv) in toluene (5 mL), Red-Al (65% in toluene, 0.10 mL, 0.31 mmol, 5.0 equiv) was added at rt, and the reaction mixture was heated to reflux for 2 h. Fieser and Fieser work-up, followed by chromatography afforded **2a**, yield 96% (0.0177 g, 0.062 mmol), dr = 80:20.

Entry 9: To a solution of amide **1a** (0.0150 g, 0.053 mmol, 1.0 equiv) in toluene (5 mL), DIBAL-H (1.0 M in toluene, 0.26 mL, 0.26 mmol, 5.0 equiv) was added at rt, and the reaction mixture was heated to reflux for 2 h. Fieser and Fieser work-up, followed by chromatography afforded **2a**, yield 97% (0.0147 g, 0.051 mmol), dr = 81:19.

Entry 10: To a solution of amide **1a** (0.040 g, 0.14 mmol, 1.0 equiv) in THF (10 mL), BH_3•Me_2S (2.0 M in THF, 0.35 mL, 0.70 mmol, 5.0 equiv) was added at rt, and the reaction mixture was heated to reflux for 24 h. The reaction was quenched with water, extracted with CH_2Cl_2, washed with brine, dried and concentrated. Chromatography afforded **2a**, yield 47% (0.0187 g, 0.065 mmol), dr = 74:26. The remaining mass balance consisted of an unidentified compound (0.0209 g, possibly polymer, R_f = 0.83, 1/4 EtOAc/hexanes).

Entry 11: To a solution of amide **1a** (0.0150 g, 0.05 mmol, 1.0 equiv) in THF (10 mL), $LiEt_3BH$ (1.0 M in THF, 0.26 mL, 0.26 mmol, 5.0 equiv) was added dropwise at rt, and the resulting mixture was stirred for 3 h at rt. Aqueous work-up (quench with water, extraction with CH_2Cl_2), followed by chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) afforded aminal **2a** (R_f = 0.45, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 38% (0.0055 g, 0.019 mmol), and alcohol **3a** (R_f = 0.13, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 54% (0.0078 g, 0.027 mmol).

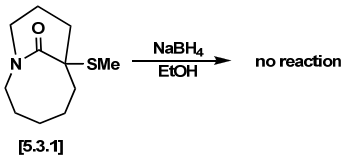


3a

((7R)-7-*tert*-Butyl-5-phenylazonan-5-yl)methanol (3a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.40 (s, 9H), 1.25-1.99 (m, 10H), 2.56 (d, *J* = 13.9 Hz, 1H), 2.65-2.90 (m, 4H),

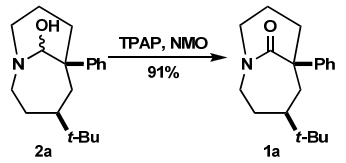
3.54 (d, *J* = 11.4 Hz, 1H), 3.78 (dd, *J* = 1.4, 11.3 Hz, 1H), 7.12 (t, *J* = 7.3 Hz, 1H), 7.27 (t, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 23.3, 27.2, 34.2, 34.6, 37.7, 38.8, 47.2, 47.4, 47.8, 68.4, 126.3, 127.5, 128.6, 145.4; IR (neat) 3350, 2947, 2870, 1557, 1487, 1445, 1366, 1034, 911 cm^{-1}; HRMS calcd for $C_{19}H_{32}NO$ (M^+ + H) 290.2484, found 290.2462. Note: a number of other reductants were also tried (for example, Bu_3SnH/SiO_2, Ph_3SiH, $NaBH_4/BF_3$, $NaBH_4/TiCl_4$, $NaCNBH_3$), however no reaction or complex reactions mixtures were obtained.

Scheme B. *Attempted Reduction of [5.3.1] Bridged System.*

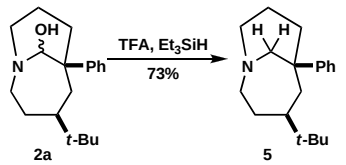


According to the general procedure for reduction of bridged amides, amide [5.3.1][3] (0.0383 g, 0.18 mmol, 1.0 equiv) was reacted with $NaBH_4$ (0.0205 g, 0.54 mmol, 3.0 equiv) in EtOH (10 mL) at rt for 18 h. Analysis of the crude reaction by NMR indicated only the presence of the staring material.

Synthetic Transformations of Bridged Hemiaminals

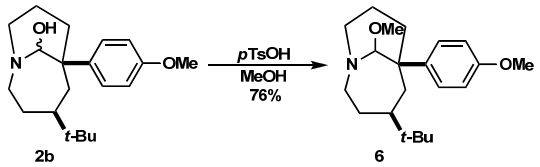


(4R,6R)-4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decan-10-one (1a). To a solution of alcohol **2a** (0.0150 g, 0.052 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) containing some MS 4Å, NMO (0.0122 g, 0.104 mmol, 2.0 equiv) and TPAP (0.004 g, 0.01 mmol, 0.2 equiv) were added, and the resulting mixture was stirred at rt for 2 h. After solvent removal, chromatography (1/4 EtOAc/hexanes) afforded the title lactam. Yield 91% (0.0135 g, 0.047 mmol). Spectroscopic properties matched those previously described.[1]

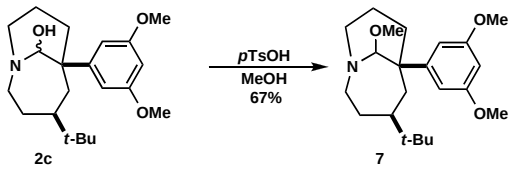


(4R,6R)-4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decane (5). To a solution of aminal **2a** (0.0252 g, 0.088 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) TFA (1.0 mL, excess) was added at rt, followed by Et_3SiH (0.014 mL, 10 equiv) after 15 min. The reaction

mixture was warmed stirred at rt for 12 days. Quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2 (3 x 20 mL), washed with brine (1 x 20 mL), dried, and concentrated. Chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) afforded the title product as oil (R_f = 0.33, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 73% (0.0174 g, 0.064 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 9H), 1.25-1.36 (m, 1H), 1.42-1.61 (m, 2H), 1.70 (t, *J* = 12.4 Hz, 1H), 1.78-2.01 (m, 3H), 2.04-2.16 (m, 1H), 2.30 (d, *J* = 13.0 Hz, 1H), 2.61 (td, *J* = 3.6, 13.4 Hz, 1H), 2.91 (d, *J* = 7.2 Hz, 2H), 3.04 (d, *J* = 14.2 Hz, 1H), 3.61-3.72 (m, 2H), 7.18-7.24 (m, 1H), 7.31-7.42 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 27.5, 30.0, 33.8, 36.1, 37.4, 46.8, 48.3, 53.3, 54.1, 54.2, 124.6, 125.8, 128.3, 151.9; IR (neat) 3056, 2944, 2917, 2849, 1576, 1540, 1470, 1366, 1100, 1036, 992 cm^{-1}; HRMS calcd for $C_{19}H_{30}N$ (M^+ + H) 272.2378, found 272.2373.



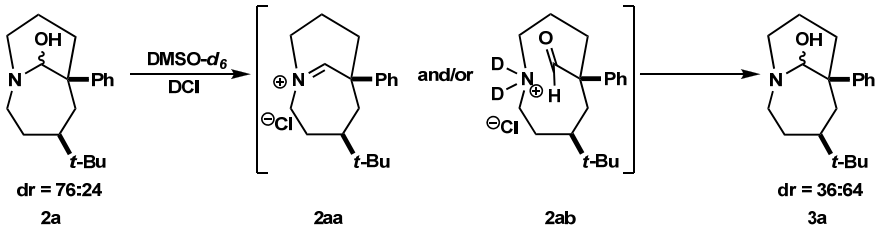
(4R,6R)-4-*tert*-Butyl-10-methoxy-6-(4-methoxyphenyl)-1-azabicyclo[4.3.1] decane (6). To a solution of hemiaminal **2b** (0.0280 g, 0.088 mmol, 1.0 equiv) in MeOH (5 mL), *p*TsOH (0.020 g, 0.11 mmol, 1.2 equiv) was added and the reaction mixture was stirred at rt. After 5 h 1.2 equiv of *p*TsOH was added, and the reaction was stirred for the next 19 h. The reaction was quenched with sat. $NaHCO_3$, solvent was removed under reduced pressure, the aqueous layer was extracted with Et_2O (3 x 30 mL), dried and concentrated. Chromatography (100% EtOAc) afforded the title product as oil (R_f = 0.90, EtOAc, R_f = 0.63, 1/10/90 NH_4OH/MeOH/CH_2Cl_2), yield 76% (0.0221 g, 0.067 mmol). Single diastereoisomer, structure not determined. ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 9H), 1.24-1.44 (m, 2H), 1.46-1.52 (m, 1H), 1.73-1.88 (m, 3H), 2.02-2.17 (m, 2H), 2.26-2.36 (m, 1H), 2.50 (dd, *J* = 4.7, 15.0 Hz, 1H), 2.73 (td, *J* = 5.6, 13.0 Hz, 1H), 3.12-3.24 (m, 1H), 3.19 (s, 3H), 3.67 (dd, *J* = 5.2, 13.6 Hz, 1H), 3.81 (s, 3H), 4.41 (s, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 27.6, 31.1, 31.4, 33.7, 42.1, 45.2, 47.4, 48.1, 53.9, 54.0, 55.2, 90.7, 113.3, 126.0, 143.6, 156.8; IR (neat) 2914, 2866, 1512, 1251, 1186, 1086 cm^{-1}; HRMS calcd for $C_{21}H_{34}NO_2$ (M^+ + H) 332.2590, found 332.2585.



(4R,6R)-4-*tert*-Butyl-6-(3,5-dimethoxyphenyl)-10-methoxy-1-azabicyclo[4.3.1] decane (7). According to the procedure described above, the reaction of the corresponding hemiaminal **2c** (0.0416 g, 0.12 mmol, 1.0 equiv) and pTsOH (0.0227 g,

0.12 mmol, 1.0 equiv) in MeOH (10 mL) at rt for 36 h, afforded after chromatography (EtOAc) the title product as oil (R_f = 0.72, EtOAc, R_f = 0.78, 1/10/90 $NH_4OH/MeOH/CH_2Cl_2$), yield 67% (0.0290 g, 0.080 mmol). Single diastereoisomer, structure not determined. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 9H), 1.26-1.51 (m, 3H), 1.74-1.88 (m, 3H), 1.99-2.13 (m, 2H), 2.24-2.35 (m, 1H), 2.49 (dd, *J* = 5.0, 14.4 Hz, 1H), 2.71 (td, *J* = 5.7, 13.4 Hz, 1H), 3.18 (td, *J* = 4.2, 13.3 Hz, 1H), 3.20 (s, 3H), 3.62-3.69 (m, 1H), 3.82 (s, 6H), 6.31 (t, J = 2.0 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 27.6, 31.1, 31.4, 33.8, 42.9, 45.1, 47.4, 47.6, 53.9, 54.0, 55.2, 90.7, 96.4, 104.2, 154.0, 160.2; IR (neat) 2941, 2866, 1595, 1456, 1204, 1151, 1084 cm^{-1}; HRMS calcd for $C_{22}H_{36}NO_3$ (M^+ + H) 362.2695, found 362.2694.

Scheme C. *Epimerization of Hemiaminal **2a** upon Treatment with Acid.*

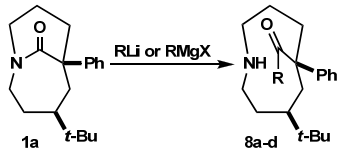


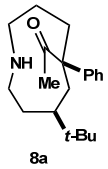
^{1}H NMR reference spectrum of **2a** in DMSO-d_6 indicated dr = 76:24 favoring the same diastereoisomer as in $CDCl_3$. A vial was charged with **2a** (0.010 g, 0.025 mmol), DMSO-d_6 (0.30 mL), and DCl (1.0 *N* in D_2O, 0.3 mL). The vial was heated with a heat gun until a clear solution was obtained (~10-15 s). ^{1}H NMR indicated dr = 36:64 favoring the opposite epimer. The NMR tube was heated with heat gun for ~5 min. NMR indicated no change in dr. DCl (1.0 *N* in D_2O, 0.1 mL) was added directly to the NMR tube, and the reaction was heated with a heat gun for ~ 1 min. NMR indicated no change in the dr. Note: a similar change in dr (from 71:29 to 38:62) was observed when CD_3CN was used as a solvent. The epimerization of **2a** could occur either via the intermediate bridged iminium ion **2aa** or through the acid-promoted opening to the aldehyde **2ab** and re-closure to the more thermodynamically favored isomer.

Organometallic Addition to Bridged Amides

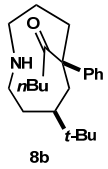
General procedure: To a solution of bridged amide (1.0 equiv) in Et_2O at -78 °C, organometallic reagent (3.0 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for 1 h, allowed to warm slowly to rt, quenched with water (10 mL) after 2 h, extracted with ether (3 x 50 mL), washed with brine (1 x 10 ml) and dried. Chromatography ($MeOH/CH_2Cl_2$) afforded the final products.

Scheme D. *Synthesis of Compounds **8a-8d** (Table 2).*



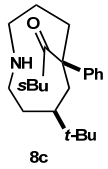


1-((5R,7R)-7-*tert*-Butyl-5-phenylazonan-5-yl)ethanone (8a). According to the general procedure, the reaction of **1a** (0.0100 g, 0.035 mmol, 1.0 equiv) and MeLi (1.6 M in Et_2O, 0.070 mL, 0.11 mmol, 3.0 equiv) in Et_2O (5.0 mL), afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title compound as oil (R_f = 0.31-0.62, 1/10/90 $NH_3/MeOH/CH_2Cl_2$). Yield 89% (0.0094 g, 0.031 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 0.38 (s, (9H), 1.38-1.99 (m, 9H), 1.91 (s, 3H), 2.18 (dd, *J* = 3.8, 12.7 Hz, 1H), 2.68-2.96 (m, 4H), 7.18-7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 24.0, 26.4, 27.4, 33.4, 33.8, 34.0, 37.6, 43.3, 46.4, 60.5, 126.8, 127.6, 128.5, 144.1, 211.7; IR (neat) 2947, 2868, 1701, 1477, 1364, 1169, 1144 cm^{-1}; HRMS calcd for $C_{20}H_{32}NO$ (M^+ + H) 302.2484, found 302.2474. Note: the reaction of **1a** (0.0100 g, 0.035 mmol, 1.0 equiv) and MeLi•LiBr (1.5 M, Et_2O, 0.070 mL, 0.11 mmol, 3.0 equiv) in Et_2O (5 mL) afforded 8**a** in 85% yield (0.0090 g, 0.030 mmol). Resubmission of **8a** (0.0094 g, 0.031 mmol) to the reaction with MeLi (1.6 M, Et_2O, 0.06 mL, 3.0 equiv) in Et_2O (10 mL) for 3 h led to quantitative recovery of **8a**, suggesting that the further addition does not occur due to the steric hindrance around the ketone. Note: the reaction of **1a** (0.010 g, 0.035 mmol, 1.0 equiv) and MeMgI (3.0 M in Et_2O, 0.035 mL, 0.11 mmol, 3.0 equiv) in Et_2O (10 mL) for 24 h, afforded **8a** in 73% yield (0.0077 g, 0.026 mmol) (Table 2, entry 2).



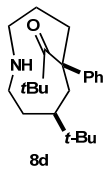
8b

1-((5R,7R)-7-*tert*-Butyl-5-phenylazonan-5-yl)pentan-1-one (8b). According to the general procedure, the reaction of **1a** (0.0200 g, 0.070 mmol, 1.0 equiv) and *n*BuLi (2.3 M in hexanes, 0.090 mL, 0.21 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.73, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 83% (0.0200 g, 0.058 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.40 (s, 9H), 0.80 (t, *J* = 7.3 Hz, 3H), 1.09-1.22 (m, 2H), 1.26-1.35 (m, 1H), 1.37-1.58 (m, 5H),1.64 (d, *J* = 16.0 Hz, 1H), 1.72-1.84 (m, 1H), 1.98-2.10 (m, 1H), 2.11-28 (m, 4H), 2.69-2.95 (m, 5H), 7.18-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.3, 22.4, 24.0, 26.8, 27.3, 33.3, 34.0, 34.1, 37.5, 37.9, 43.4, 46.4, 60.3, 126.8, 127.7, 128.5, 144.1, 213.7; IR (neat) 3369, 2955, 2870, 1701, 1474, 1364, 1130, 702 cm^{-1}; HRMS calcd for $C_{23}H_{38}NO$ (M^+ + H) 344.2954, found 344.2944.



8c

1-((5R,7R)-7-*tert*-Butyl-5-phenylazonan-5-yl)-2-methylbutan-1-one (8c). According to the general procedure, the reaction of **1a** (0.0200 g, 0.070 mmol, 1.0 equiv) and *sec*-BuLi (1.4 M in cyclohexane, 0.15 mL, 0.21 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.54, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 93% (0.0223 g, 0.065 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.44, 0.46 (s, 9H), 0.59 (t, *J* = 7.5 Hz, 1H), 0.78-0.85 (m, 3H), 0.99 (d, *J* = 6.7 Hz, 2H), 1.19-1.68 (m, 7H), 1.70-1.81 (m, 2H), 2.01-2.13 (m, 1H), 2.28-2.41 (m, 2H), 2.64-2.93 (m, 4H), 2.97-3.09 (m, 1H), 7.18-7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of rotamers) δ 11.3, 11.4, 17.6, 18.5, 23.1, 23.9, 24.2, 27.3, 27.4, 27.5, 28.4, 34.2, 34.3, 35.6, 35.9, 37.5, 37.7, 42.7, 43.1, 46.3, 46.4, 47.4, 60.8, 60.9, 126.8, 126.8, 128.1, 128.2, 128.3, 128.3, 142.9, 143.1, 217.7, 217.8; IR (neat) 3373, 2961, 2873, 1699, 1464, 1366, 1148, 1013, 733, 702 cm^{-1}; HRMS calcd for $C_{23}H_{38}NO$ (M^+ + H) 344.2954, found 344.2939.

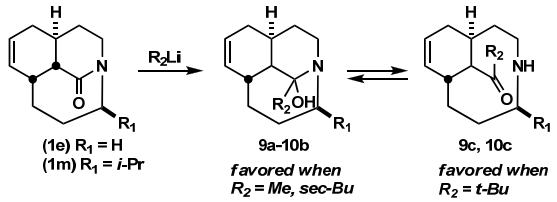


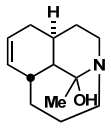
8d

1-((5R,7R)-7-*tert*-Butyl-5-phenylazonan-5-yl)-2,2-dimethylpropan-1-one (8d). According to the general procedure, the reaction of **1a** (0.0200 g, 0.070 mmol, 1.0 equiv) and *tert*-BuLi (1.7 M in pentanes, 0.12 mL, 0.21 mmol, 3.0 equiv) in Et_2O (10 mL),

afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title compound as oil (R_f = 0.37, 1/10/90 $NH_3/MeOH/CH_2Cl_2$). Yield 80% (0.0192 g, 0.056 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 0.39 (s, 9H), 0.98 (s, 9H), 1.24-1.44 (m, 2H), 1.45-1.66 (m, 3H), 1.77-1.88 (m, 1H), 2.21-2.34 (m, 1H), 2.36 (dd, *J* = 5.2, 15.8 Hz, 1H), 2.75-3.04 (m, 6H), 7.18-7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 22.5, 27.2, 30.3, 33.7, 34.2, 37.2, 38.0, 45.0, 46.1, 46.5, 61.0, 126.8, 127.9, 128.3, 143.4, 217.4; IR (neat) 3377, 2959, 2870, 1680, 1479, 1364, 1146, 1090, 1005, 910, 735, 704 cm^{-1}; HRMS calcd for $C_{23}H_{38}NO$ (M^+ + H) 344.2954, found 344.2924.

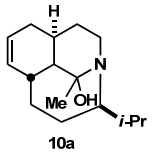
Scheme E. *Synthesis of Compounds **9a-10c** (Table 3).*





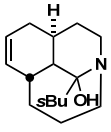
9a

Hemiaminal 9a. According to the general procedure, the reaction of **1e** (0.0189 g, 0.099 mmol, 1.0 equiv) and MeLi (1.6 M in Et_2O, 0.20 mL, 0.30 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title compound as solid (Mp = 107-108 °C, R_f = 0.10, 1/10/90 $NH_3/MeOH/CH_2Cl_2$). Yield 95% (0.0194 g, 0.094 mmol), dr > 10:1, structure not determined. ^1H NMR (400 MHz, $CDCl_3$) δ 1.23-1.41 (m, 2H), 1.52 (s, 3H), 1.64-1.82 (m, 3H), 1.84-1.95 (m, 2H), 1.96-2.11 (m, 2H), 2.35 (q, *J* = 14.4 Hz, 1H), 2.40-2.48 (m, 1H), 2.54-2.77 (m, 2H), 2.86 (s, 1H), 3.05 (t, *J* = 13.5 Hz, 1H), 3.34-3.50 (m, 1H), 5.65 (s, 1H), 5.74 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.4, 25.8, 27.3, 31.4, 34.7, 34.9, 35.3, 49.4, 51.8, 52.6, 86.5, 127.6, 134.9; IR (neat) 3350, 3011, 2949, 2914, 2866, 1462, 1447, 1369, 1292, 1163, 1134, 1018, 924, 731, 708 cm^{-1} Note: ketone peak not detected in the IR spectrum; HRMS calcd for $C_{13}H_{22}NO$ (M^+ + H) 208.1701, found 208.1706.



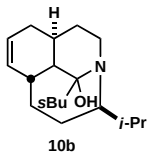
10a

Hemiaminal 10a. According to the general procedure, the reaction of **1m** (0.0200 g, 0.086 mmol, 1.0 equiv) and MeLi (1.6 M in Et_2O, 0.17 mL, 0.26 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title compound as oil (R_f = 0.20, 1/10/90 $NH_3/MeOH/CH_2Cl_2$). Yield 92% (0.0196 g, 0.079 mmol), dr > 10:1, structure not determined. ^1H NMR (500 MHz, $CDCl_3$) δ 0.68-0.93 (m, 6H), 1.26 (d, *J* = 13.8 Hz, 1H), 1.31-1.42 (m, 1H), 1.49 (s, 3H), 1.57 (m, 4H), 1.71-1.83 (m, 2H), 1.86-1.92 (m, 1H), 1.97 (dt, *J* = 4.0, 16.9 Hz, 1H), 2.22-2.43 (m, 2H), 2.54-2.66 (m, 2H), 2.69-2.78 (m, 1H), 3.22-3.33 (m, 1H), 5.47 (s, 1H), 5.75 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 19.3, 24.9, 26.5, 28.5, 32.9, 34.5, 35.5, 35.8, 49.6, 50.2, 73.5, 86.1, 125.4, 135.6; IR (neat) 3589, 3460, 3011, 2951, 2914, 1968, 1713 (vw), 1632, 1464, 1371, 1219, 1169, 1113, 1055, 943, 703 cm^{-1}; HRMS calcd for $C_{16}H_{28}NO$ (M^+ + H) 250.2171, found 250.2164.



9b

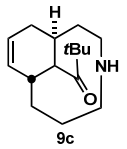
Hemiaminal 9b. According to the general procedure, the reaction of **1e** (0.0164 g, 0.086 mmol, 1.0 equiv) and *sec*-BuLi (1.4 M in cyclohexane, 0.18 mL, 0.26 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/10/90 $NH_4OH/MeOH/CH_2Cl_2$) the title compound as oil (R_f = 0.57, 1/10/90 $NH_3/MeOH/CH_2Cl_2$). Yield 80% (0.0172 g, 0.069 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 0.78-2.25 (m, 19H), 2.31-2.52 (m, 2H), 2.582-.67 (m, 2H), 2.702-.85 (m, 1H), 3.38-3.46 (m, 1H), 5.48-5.67 (m, 2H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 10.7, 11.4, 11.8, 13.6, 20.7, 23.7, 23.7, 24.4, 25.1, 25.2, 33.3, 33.4, 33.9, 34.3, 34.4, 37.5, 37.9, 48.6, 48.7, 50.5, 50.6, 88.2, 88.4, 126.4, 134.1, 134.1 IR (neat) 3591, 3450, 3013, 2963, 2916, 2870, 1653, 1540, 1456, 1379, 1292, 1259, 1113, 1057, 1021, 912, 802, 744 cm^{-1} Note: ketone peak not detected in the IR spectrum; HRMS calcd for $C_{16}H_{28}NO$ (M^+ + H) 250.2171, found 250.2185.



10b

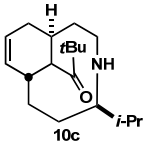
Hemiaminal 10b. According to the general procedure, the reaction of **1m** (0.0200 g, 0.086 mmol, 1.0 equiv) and *sec*-BuLi (1.4 M in cyclohexane, 0.18 mL, 0.26 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/1 EtOAc/hexanes) the title compound as oil (R_f = 0.26, 1/1 EtOAc/hexanes). Yield 88% (0.0219 g, 0.075 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 0.82-1.07 (m, 12H), 1.21-1.46 (m, 3H), 1.58-1.86 (m, 6H),

1.92-2.17 (m, 4H), 2.26-2.38 (m, 1H), 2.47 (q, *J* = 13.6 Hz, 1H), 2.53-2.62 (m, 1H), 2.68-2.82 (m, 2H), 3.06-3.19 (m, 1H), 5.51-5.58 (m, 1H), 5.84-5.92 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (mixture of rotamers) δ 13.2, 13.3, 14.1, 18.4, 18.5, 18.8, 19.0, 23.4, 24.2, 26.1, 26.3, 27.8, 28.1, 28.5, 32.8, 35.2, 35.3, 35.5, 35.6, 35.7, 44.3, 44.5, 45.8, 49.7, 49.8, 73.2, 88.2, 88.4, 125.3, 136.1; IR (neat) 3595, 3013, 3959, 3013, 2959, 2870, 2829, 1705 (vw), 1634, 1464, 1381, 1258, 1163, 1107, 1061, 1011, 808, 704 cm^{-1}; HRMS calcd for $C_{19}H_{34}NO$ (M^+ + H) 292.2641, found 292.2642.



9c

1-((1S,8R)-4-Azabicyclo[6.3.1]dodec-9-en-12-yl)-2,2-dimethylpropan-1-one (9c). According to the general procedure, the reaction of **1e** (0.0200 g, 0.105 mmol, 1.0 equiv) and *tert*-BuLi (1.7 M in pentanes, 0.18 mL, 0.31 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.14, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 90% (0.0235 g, 0.094 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 9H), 1.17-1.34 (m, 3H), 1.56-1.68 (m, 1H), 1.72-1.96 (m, 4H), 2.07-2.17 (m, 1H), 2.46 (s, 1H), 2.67-2.84 (m, 2H), 2.89-2.97 (m, 1H), 3.18-3.27 (m, 2H), 3.36-3.46 (m, 1H), 5.51-5.58 (m, 1H), 5.85-5.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of ketone and enol tautomers) δ 26.4, 28.8, 29.2, 29.6, 30.6, 38.6, 42.5, 45.6, 49.9, 50.8, 52.6, 130.7, 132.5, 218.5; IR (neat) 3391, 3015, 2951, 2918, 2868, 1705, 1541, 1477, 1441, 1389, 1364, 1317, 1099, 916, 735 cm^{-1}; HRMS calcd for $C_{16}H_{28}NO$ (M^+ + H) 250.2171, found 250.2175. Note: after chromatography partial closure to the hemiaminal was observed (^{13}C NMR, δ 81.4 ppm).

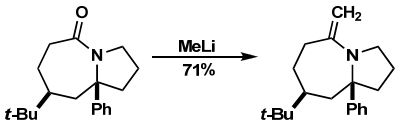


10c

1-((1S,5R,8R)-5-Isopropyl-4-azabicyclo[6.3.1]dodec-9-en-12-yl)-2,2-dimethyl propan-1-one (10c). According to the general procedure, the reaction of **1m** (0.0200 g, 0.086 mmol, 1.0 equiv) and *tert*-BuLi (1.7 M in pentanes, 0.15 mL, 0.26 mmol, 3.0 equiv) in Et_2O (10 mL), afforded after chromatography (1/10/90 NH_4OH/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.27, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 90% (0.0226 g, 0.078 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88-0.98 (m, 6H), 1.13 (s, 9H), 1.21-1.37 (m, 3H), 1.52-1.81 (m, 3H), 1.86-2.29 (M, 5H), 2.31-2.80 (m, 4H), 3.16-3.32 (m, 1H), 5.57-5.71 (m, 1H), 5.82-5.95 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (mixture of slowly equilibrating ketone and enol tautomers) δ 19.9, 21.4, 21.7, 24.7, 26.0, 26.1, 26.4, 28.8, 29.7, 30.2, 30.9, 32.5, 34.0, 36.6, 37.2, 38.8, 40.9, 43.1, 43.2, 45.7, 46.0, 50.9, 52.8, 130.4, 131.2, 132.7, 132.9, 219.2, 220.5; IR (neat) 3597, 3375, 3013, 2955, 2924, 2868, 1697, 1626, 1466, 1387, 1366, 1261, 1099, 910, 804 cm^{-1}; HRMS calcd for $C_{19}H_{34}NO$

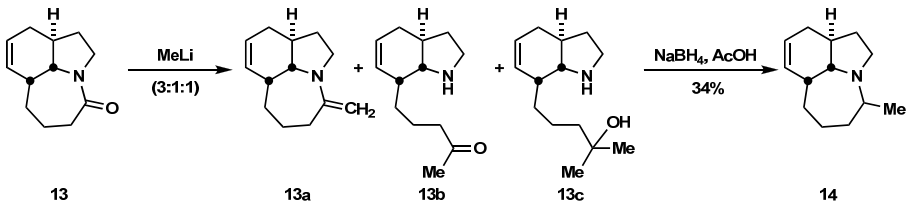
(M^+ + H) 292.2641, found 292.2636. Note: we have observed a similar keto-enol equilibration in analogous 9-membered heterocycles, in which α-position relative to the ketone is unsubstituted (for example, compounds resulting from organometallic addition to bridged bicyclic lactam **1g**). We think that the unusually high contribution from the enol tautomer arises from a transannular stabilization of the enol by the amine placed on the opposite side of the medium-sized ring. We are investigating this and related interactions between amines and electrophilic components moved one-carbon away from the medium-sized rings in a broader context.

Organometallic Addition to Planar Analogues of Bridged Amides



11 **12**

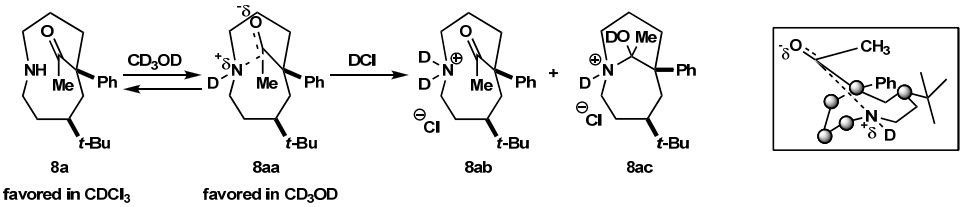
(8S,9aR)-8-*tert*-Butyl-5-methylene-9a-phenyloctahydro-1H-pyrrolo[1,2-a] azepine (12). According to the general procedure, the reaction of planar amide **11** (0.0200 g, 0.070 mmol, 1.0 equiv) and MeLi•LiBr (1.5 M in Et_2O, 0.14 mL, 0.21 mmol, 3.0 equiv) in Et_2O (5 mL) for 18 h, afforded after chromatography (1/15/85 NH_4OH/MeOH/CH_2Cl_2) the title product as oil (R_f = 0.28, NH_4OH/MeOH/CH_2Cl_2), yield 71% (0.0141 g, 0.050 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84 (s, 9H), 1.12-1.78 (m, 7H), 1.85-2.35 (m, 5H), 2.84-3.61 (m, 3H), 7.02-7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 27.2, 27.7, 29.3, 31.7, 32.6, 39.8, 41.0, 43.3, 49.2, 69.1, 74.5, 125.1, 126.1, 126.7, 128.1, 150.6, 151.8; IR (neat) 2959, 2866, 1632, 1445, 1366, 731, 702 cm^{-1}; HRMS calcd for $C_{20}H_{30}N$ (M^+ + H) 284.2378, found 284.2373. The structure of enamine was confirmed by reduction under acidic conditions to the corresponding amine ($NaBH_4$, AcOH, THF, rt, 5 h, 83% yield). Note: the dehydration was not general and for example, addition of *n*-BuLi to **1a** resulted in a complex mixture of products including starting material, ketone, enamine, and alcohol. Furthermore, we determined that in the case of planar amides, the reaction time was longer than with the bridged lactams (for example, after 3 h of the reaction with MeLi, bridged **1a** >95% conversion vs. fused **11** ~70% conversion).



Amine **14**. According to the general procedure for addition of organometallic reagents, the planar amide **13** (0.080 g, 0.43 mmol, 1.0 equiv) was reacted with MeLi•LiBr (1.5 M in Et_2O, 0.84 mL, 1.26 mmol, 3.0 equiv) in Et_2O (10 mL) for 18 h. Analysis of the crude reaction mixture indicated presence of enamine **13a**, ketone **13b** and alcohol **13c** in 3:1:1 ratio as judged by ^{1}H NMR. Due to the very similar and high polarity the products could not be separated at this stage. Diagnostic peaks: Compound **13a**: ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 26.4, 28.7, 29.9, 31.2, 37.1, 38.3, 47.4, 64.2, 74.7, 126.0, 131.5, 151.8; HRMS calcd for $C_{13}H_{20}N$ (M^+ + H) 190.1596, found 190.1597. Compounds **13b** and **13c**: ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 22.7, 29.0, 29.3, 29.9, 31.0, 32.2, 35.7, 38.0, 38.1, 44.0, 44.1, 44.8, 63.6, 63.7, 70.8, 126.8, 127.1, 130.5, 130.9, 209.0; HRMS calcd for $C_{13}H_{22}NO$ (M^+ + H) 208.1701, found 208.1734; HRMS calcd for $C_{14}H_{26}NO$ (M^+ + H) 224.2014, found 224.2036. IR (neat) 3339, 3017, 2920, 2868, 1715, 1613, 1408, 1356, 1161 cm^{-1}. The above crude reaction mixture was taken in THF (5 mL), $NaBH_4$ (0.005 g, 0.13 mmol, 5.0 equiv), followed by AcOH (0.05 mL, 0.86 mmol, 20 equiv) were added at rt, and the resulting mixture was stirred at rt for 5 h. The reaction was diluted with ether (15 mL), quenched with sat. $NaHCO_3$, washed with brine, dried and concentrated. Chromatography (1/4 EtOAc/hexanes) afforded **3c** as oil (R_f = 0.82, 1/4 EtOAc/hexanes), yield 34% (2 steps, 0.0271 g, 0.14 mmol). Single diastereoisomer, structure not determined. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18-2.22 (m, 10 H, 1.35 (d, J = 6.8 Hz, 3H), 2.33 (dt, J = 4.5, 17.4 Hz, 1H), 2.65 (s, 1H), 2.86-3.08 (m, 2H), 3.14-3.26 (m, 1H), 3.87 (dd, J = 4.0, 13.2 Hz, 1H), 5.34-5.43 (m, 1H), 5.57-5.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 29.0, 30.7, 31.8, 32.8, 33.8, 35.3, 37.8, 54.9, 67.2, 79.2, 124.5, 132.8; IR (neat) 3019, 2920, 2851, 2352, 1450, 1383, 1196, 1163, 1084, 1013, 849 cm^{-1}; HRMS calcd for $C_{13}H_{22}N$ (M^+ + H) 192.1752, found 192.1763.

Transannular Interaction in Bicyclic System

Scheme F. *Transannular N···C=O Interaction in Bicyclic System.*



According to the general procedure for addition of organometallic reagents, amide **1a** (0.0300 g, 0.105 mmol, 1.0 equiv) was reacted with MeLi•LiBr (1.5 M in Et_2O, 0.36 mL, 0.53 mmol, 5.0 equiv). After aqueous work-up, crude NMR ($CDCl_3$) indicated the presence of **8a** as a single major product. Purification by chromatography (1/10/90 NH_3/MeOH/CH_2Cl_2) afforded **8a** in 99% yield (0.0313 g, 0.104 mmol). ^{1}H NMR and ^{13}C NMR ($CDCl_3$, 0.75 mL, 1000 scans) were identical with the previously described for **8a**; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.38 (s, (9H), 1.38-1.99 (m, 9H), 1.91 (s, 3H), 2.18 (dd, *J* = 3.8, 12.7 Hz, 1H), 2.68-2.96 (m, 4H), 7.18-7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 24.0, 26.4, 27.4, 33.4, 33.8, 34.0, 37.6, 43.3, 46.4, 60.5, 126.8, 127.6, 128.5, 144.1, 211.7; no change was observed in comparison with the crude spectra, indicating that standard purification on SiO_2 does not influence the interaction between the ketone and the amine groups.

The solvent was removed, sample was dissolved in MeOD-*d*$_4$ (0.75 mL), and NMR spectra were recorded after ~3 min. Major changes were not observed in ^{1}H NMR, however ^{13}C NMR indicated significant broadening of 7 peaks. Despite much longer acquisition time (23 700 scans) ketone peak was not detected. Compound **8aa**: ^{1}H NMR (400 MHz, CD_3OD) δ 0.47 (s, 9H), 1.44 (s, 2H), 1.63 (d, *J* = 15.5 Hz, 3H), 1.78-1.92 (m, 1H), 1.83 (s, 3H), 2.20 (dd, *J* = 4.8, 15.6 Hz, 2H), 2.58 (d, *J* = 14.0 Hz, 1H), 2.71-2.84 (m, 2H), 2.84-3.02 (m, 2H), 7.19-7.38 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 20.3, 25.0 (br), 25.2, 26.5, 31.2, 33.5, 34.5 (br), 38.6 (br), 43.2 (br), 45.8, 58.7 (br), 126.6, 127.2, 128.3, 144.5 (br). 2D NMR correlations allowed for assignment of carbons corresponding to the broadened peaks, suggesting that the transannular interaction takes place over the western part of the amino-ketone (Scheme F, box, shaded circles).

24 h after dissolution of **8a** in MeOD-*d*$_4$, ^{1}H NMR was identical to the described above, for t = ~3 min. Next, 0.75 mL of MeOD-*d*$_4$ was added to the NMR tube, and 1/2 of the resulting mixture was transferred to 5 mL round bottom flask, evaporated to dryness, and dissolved in $CDCl_3$. NMR was identical to the described above for **8a** in $CDCl_3$, indicating that the interaction is reversible. To the remaining part of **8aa** in MeOD-*d*$_4$, 0.2 mL of 1.0 *N* DCl in D_2O was added, the NMR tube was wrapped in parafilm, and the reaction was mixed by turning the NMR tube upside down 5 times, followed by gentle shaking. NMR (recorded ~5 min after addition of acid) indicated 89:11 mixture of the protonated **8ab** and hemiaminal **8ac**. As expected, upon addition of acid peaks were much sharper than in MeOD-*d*$_4$ alone indicating that this time the interaction does not occur; ^{13}C NMR (0.60 mL, 4000 scans) showed a sharp ketone peak

at 213.4 ppm, and a hemiaminal peak at 94.0 ppm. The ratio of **8ab** to **8ac** did not change after the next 24 h.

Protonated **8ab**: ^{1}H NMR (400 MHz, CD_3OD) δ 0.42 (s, 9H), 1.31 (s, 1H), 1.52-1.73 (m, 2H), 1.78 (d, *J* = 16.2, 1H), 1.92-2.05 (m, 1H), 1.98 (s, 3H), 2.14 (td, *J* = 5.1, 16.4 Hz, 1H), 2.40-2.49 (m, 2H), 3.19-3.41 (m, 5H), 7.20-7.42 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ 17.7, 24.9, 25.6, 26.2, 28.6, 33.6, 33.8, 39.0, 42.3, 44.8, 59.9, 127.3, 127.4, 128.8, 142.3, 213.4. Hemiaminal **8ac**: ^{1}H NMR (400 MHz, CD_3OD) (diagnostic peaks) δ 0.89 (s, 9H), 1.87 (t, *J* = 11.5 Hz, 1H), 2.30-2.40 (m, 2H), 2.60-2.72 (m, 1H), 3.11-3.21 (m, 1H), 3.54 (td, *J* = 5.0, 14.1 Hz, 1H), 4.01-4.09 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 17.7, 24.4, 26.5, 27.0, 30.1, 33.5, 41.6, 45.2, 46.1, 50.0, 53.0, 94.1, 126.5, 127.3, 128.1, 147.1.

Note: we determined that a similar interaction does not occur upon dissolution of **8a** in C_6D_6 and CD_3CN, however in DMSO-d_6 NMR indicated formation of a ca. 3:1 mixture of amino ketone **8a** and hemiaminal **8ac**. Further studies addressing this type of transannular interactions are in progress.

Compound **8a** in C_6D_6.^{1}H NMR (400 MHz, C_6D_6) δ 0.61 (s, 9H), 1.21 (s, 2H), 1.48 (s, 1H), 1.62-1.78 (m, 4H), 1.85 (s, 3H), 1.92 (d, *J* = 16.3 Hz, 1H), 2.38-2.72 (m, 5H), 3.10 (d, *J* = 11.6 Hz, 1H), 7.07-7.40 (m, 5H); ^{13}C NMR (100 MHz, C_6D_6) δ 21.4, 23.9, 25.9, 27.5, 33.7, 33.9, 34.5, 37.6, 43.3, 46.3, 60.5, 126.7, 144.8, 209.1.

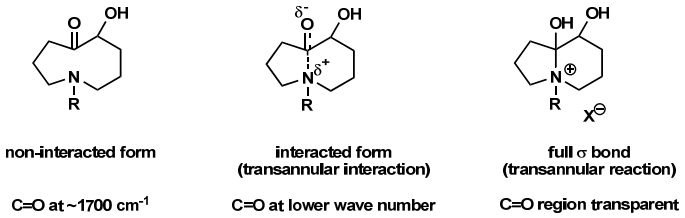
Compound **8a** in CD_3CN.^{1}H NMR (400 MHz, CD_3CN) δ 0.41 (s, 9H), 1.21-1.65 (m, 6H), 1.76 (s, 1H), 1.86 (s, 3H), 2.18-2.36 (m, 2H), 2.60-2.85 (m, 4H), 2.94-3.06 (m, 1H), 7.18-7.37 (m, 5H); ^{13}C NMR (100 MHz, CD_3CN) δ 21.4, 24.0, 25.6, 26.8, 33.4, 33.6, 34.3, 37.6, 43.7, 46.2, 60.4, 126.7, 127.6, 128.4, 144.5, 210.7.

Compound **8a** in DMSO-d_6. (~3:1 mixture of ketone **8a** and hemiaminal **8ac)** ^{1}H NMR (400 MHz, DMSO-d_6) (diagnostic peaks) δ 0.34 (s, 9H), 1.41-1.52 (m, 2H), 1.84 (s, 3H), 2.06-2.14 (m, 1H), 2.93 (d, *J* = 12.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.8, 24.4, 26.6, 27.6, 31.8, 32.7, 34.5, 37.7, 43.5, 46.0, 60.3, 127.3, 127.7, 130.1, 144.2, 210.6. Hemiaminal **8ac**.^{1}H NMR (400 MHz, DMSO-d_6) (diagnostic peaks) δ 0.82 (s, 9H), 3.15 (t, *J* = 13.0 Hz, 1H), 3.67 (d, *J* = 12.6 Hz, 1H), 5.26 (s, 1H), 7.68 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) (diagnostic peaks) δ 22.1, 28.5, 31.2, 42.7, 45.7, 49.4, 51.7, 59.8, 88.2, 125.4, 151.5.

Additional Discussion Regarding IR Spectra

Leonard and coworkers have determined that infrared spectroscopy can be used effectively to detect transannular interactions between N and C_{CO} in cyclic amino acyloins and amino ketones (Figure A).[14-16]

Figure A. *Infrared Spectroscopy in Detection of Transannular Interactions.*



Accordingly, for cyclic amino ketones, in which the reactive moieties are not involved in a transannular interaction, the C=O absorption band appears at about 1700-1705 cm^{-1}, as expected for a typical medium-sized cyclic ketone (Figure A, non-interacted form).

However, for cyclic amino ketones in which a transannular interaction takes place the C=O absorption band moves toward lower wave numbers, which is indicative of a decreased electron density at the carbonyl carbon (Figure A, interacted form).

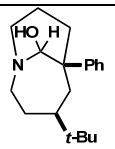
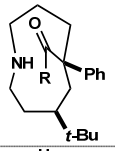
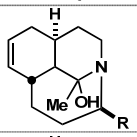
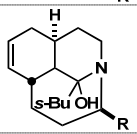
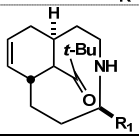
Interestingly, for certain amino ketones, the infrared carbonyl region separates into two distinct bands, the one at higher wave number corresponding to a transannular non-interacted form, and the one at lower wave number corresponding to the transannular interacted form.[14]

Finally, when a full bonding between the amine and the carbonyl functionality is formed, the carbonyl region is fully transparent in the infrared spectrum (Figure A, full σ bond).

Thus, IR is a convenient method for determining a difference between a *transannular interaction* between the amine and carbonyl group (n_N electrons involved in homoconjugation with π^*_{CO} orbital, forming a partial bond between the reactive moieties), from a *transannular reaction* between the amine and carbonyl group (full σ bond between the reactive functionalities).

The following Table B summarizes the infrared characteristics of compounds **2a**, **8a-8d**, **9a-10c** formed upon addition of nucleophiles to one-carbon bridged twisted lactams. IR spectra of compounds **2a**, **8a, 8c-d**, **9a-10c** are reproduced on pages 71-75.

Table B. *Carbonyl Absorption of Selected Compounds Resulting from Nucelophilic Addition to Bridged Lactams.*

entry	compound	structure	$\nu_{C=O}$ [cm-1]
1	**2a**		-
2	**8a**, R = Me		1701 (s)
3	**8b**, R = *n*-Bu		1701 (s)
4	**8c**, R = *sec*-Bu		1699 (s)
5	**8d**, R = *tert*-Bu		1680 (s)
6	**9a**, R = H		-
7	**10a**, R = *i*-Pr		1713 (vw), 1632 (w)
8	**9b**, R = H		1653 (w)
9	**10b**, R = *i*-Pr		1705 (vw), 1633 (w)
10	**9c**, R = H		1705 (s)
11	**10c**, R = *i*-Pr		1697 (s), 1626 (m)

As expected, hemiaminal **2a** is characterized by a fully transparent carbonyl region in the infrared spectrum, indicating that a full σ bond between the amine and carbonyl present in this compound (Table B, entry 1).

By contrast, amino ketones **8a-8c** show maximum absorption at ~1700 cm^{-1}, a frequency typical for alkyl ketones (entries 2-4). This is indicative of an absence of the transannular interaction in these cases. However, amino ketone **8d** (entry 5) absorbs at significantly lower frequency than amino ketones **8a-8c**, which suggests the presence of a transannular interaction between the amine and the *tert*-butyl ketone in **8d** (compare this frequency with entries 10 and 11). It is possible that in the case of **8d** a steric interaction between the *tert*-butyl substituent placed on the nine-membered ring and the *tert*-butyl ketone favors the orientation of the reactive amine and ketone moieties on the same side of the medium-sized ring.

Next, more substituted but contained in a tricyclic scaffold hemiaminal **9a** (entry 6) is fully transparent in the carbonyl absorption region in the infrared spectrum, in a fashion similar to hemiaminal **2a** (entry 1).

Very interestingly, however, in the case of hemiaminal **10a** (entry 7) two weak absorption bands are visible in the carbonyl region in the infrared spectrum. We ascribe these bands to the presence of the transannular non-interacted species (characterized by absorption at 1713 cm^{-1}) and the transannular interacted species (characterized by absorption at 1632 cm^{-1}). These species are likely in equilibrium with the fully-closed hemiaminal form. As judged from ^{13}C NMR and from the relative intensities of the

absorption bands in the IR spectrum the fully-closed hemiaminal form seems to be the major species present in this equilibrium.

The carbonyl absorption bands corresponding to hemiaminals **9b** and **10b** (entries 8 and 9) mirror the IR spectrum of hemiaminal **10a** (entry 7). As expected, the bands corresponding to the hemiaminal **10b**, which is substituted with a sterically demanding *i*-propyl substituent near the hemiaminal carbon (entry 9), are more intense than the carbonyl absorption bands corresponding to hemiaminal **9a** (entry 8, compare with the tendency in entries 2-5).

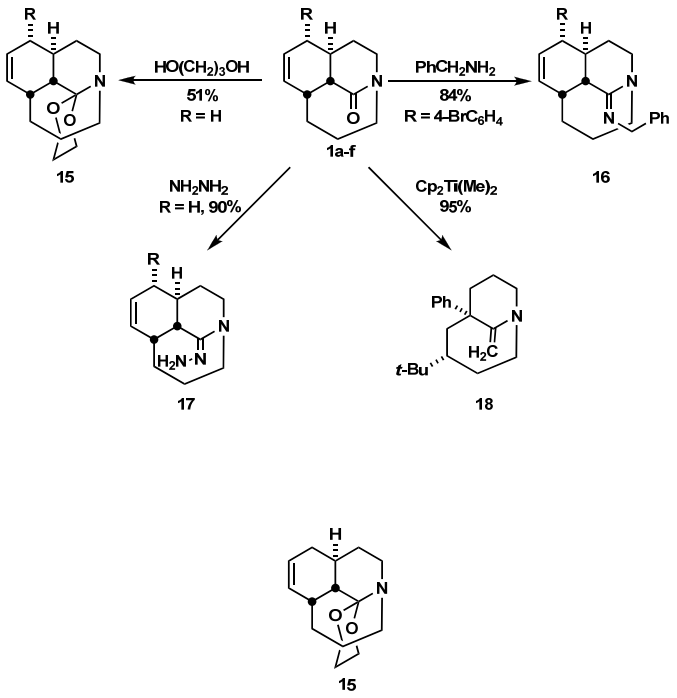
Finally, although the unsubstituted **9c** (entry 10) shows only one maximum in the carbonyl region clearly corresponding to the non-interacted amino ketone (compare with entry 2), the carbonyl frequency of the *i*-Pr substituted **10c** (entry 11) reveals a tendency towards equilibrium of the non-interacted amino ketone with the species participating in a transannular interaction (as evidenced by a lower frequency of the ketone absorption band at 1697 cm^{-1} and the appearance of a weak band at 1632 cm^{-1}).

We also recorded IR spectrum of **8a** in solution ($CDCl_3$). In agreement with the previous observations, the carbonyl absorption maximum was shifted towards lower wave numbers (1697 cm^{-1} in $CDCl_3$ vs. 1701 cm^{-1} when spectrum was recorded as a film), however this difference was smaller than in the above examples and could also arise from experimental errors.

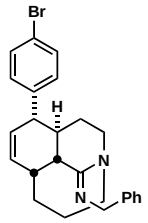
Overall, these results clearly demonstrate a potential one-carbon bridged lactams to monitor the transition from stable tetrahedral intermediates to N···C=O interactions to unstable tetrahedral intermediates. We are currently investigating this point in more detail.

Reactions with Additional Nucleophiles

Scheme G. *Synthesis of compounds **15-18**.*



Aminoketal 15. To a mixture of 1,3-pentanediol (0.19 g, 2.5 mmol) and *p*-TsOH (2 mg, 0.06 mmol) in benzene was added bridged lactam **1e** (0.030 g, 0.16 mmol) at room temperature, and the reaction mixture was allowed to reflux for 3 days. The reaction mixture was partitioned between water and EtOAc, the organic layer was washed with saturated $NaHCO_3$ and brine, dried with Na_2SO_4, filtered, and concentrated. Chromatography (60% EtOAc/hexanes) afforded the title compound as oil. Yield 51% (0.020 g, 0.08 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37-1.45 (m, 3H), 1.60-1.67 (m, 3H), 1.80-1.84 (m, 2H), 1.96-2.11 (m, 5H), 2.62-2.75 (m, 3H), 2.99-3.11 (m, 1H), 3.27-3.31 (m, 1H), 3.71-3.73 (m, 2H), 4.10-4.33 (m, 2H), 5.65-5.70 (complex, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 24.9, 26.9, 32.3, 32.7, 34.0, 34.1, 49.6, 52.5, 53.0, 59.1, 59.7, 105.1, 126.8, 134.7; IR (neat) 2957, 1085 cm^{-1}; HRMS calcd for $C_{15}H_{24}NO_2$ (M^++1) 250.1802, found 250.1798. Note: attempted ketalization of bicyclic lactam **1b** and **1l** under identical reaction conditions did not afford the desired products (only starting materials were observed by NMR).



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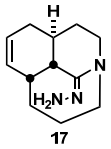
Bridged imine 16. Lactam **1f** (0.0100 g, 0.029 mmol, 1.0 equiv), benzylamine (0.063 mL, 0.058 mmol, 20.0 equiv) and *p*TsOH (1 crystal) were heated in toluene (20 mL) under Dean-Stark trap for 23 h. Solvent removal and chromatography (2/1 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.44, 1/1 EtOAc/hexanes). Yield 84% (0.0106 g, 0.024 mmol). The compound was obtained as a single imine isomer. Geometry was determined by HSQC, HMBC and NOESY correlations. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25-1.72 (m, 5H), 1.86 (q, *J* = 11.0 Hz, 1H), 2.06-2.15 (m, 1H), 2.48-2.62 (m, 2H), 2.70-2.80 (m, 1H), 2.91 (dd, *J* = 4.4, 10.8 Hz, 1H), 3.17 (d, *J* = 10.8 Hz, 1H), 3.45 (dd, *J* = 6.1, 11.8 Hz, 1H), 3.54 (dt, *J* = 3.2, 11.9, 1H), 4.29 (d, *J* = 14.6 Hz, 1H), 4.87 (d, *J* = 14.5 Hz, 1H), 5.56 (d, *J* = 9.8 Hz, 1H), 5.90-5.97 (m, 1H), 7.05 (d, *J* = 8.3 Hz, 2H), 7.19-7.36 (m, 5H), 7.45 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 26.0, 33.8, 39.4, 40.6, 49.6, 53.3, 53.7, 55.8, 56.2, 120.2, 126.4, 128.1, 128.3, 129.8, 130.7, 131.5, 134.0, 140.8, 142.6, 165.8; IR (neat) 3021, 2922, 2855, 1655, 1487, 1451, 1405, 1073 cm^{-1}; HRMS calcd for $C_{25}H_{28}BrN_2$ (M^+ + H) 435.1436, found 435.1410. Note: the reaction of bicyclic amide **1a** under similar conditions did not afford the desired imine (only starting material was observed by NMR). Under more forcing conditions only decomposition of the starting material was observed.



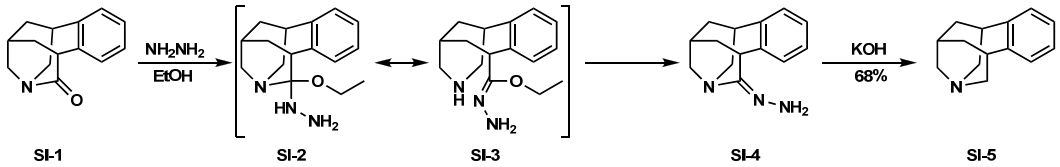
17

Aminohydrazone 17. Lactam **1e** (0.050 g, 0.26 mmol) was dissolved in methylene glycol, treated with hydrazine (0.084 g, 2.6 mmol), and the reaction mixture was heated to 100 °C for 20 h. The reaction was cooled to rt, KOH (0.031 g, 0.55 mmol) was added and heating was continued for 2 h at 195 °C. The reaction was cooled to rt, partitioned between water and $CHCl_3$, the organic layer was washed with saturated $NaHCO_3$ and brine, dried with Na_2SO_4, filtered, and concentrated. Chromatography (10/90 MeOH/CH_2Cl_2) afforded the title product as an oil. Mixture of isomers. Yield 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15-1.80 (complex, 11H), 1.96-1.99 (m, 1H), 2.23-2.27 (m, 1H), 2.50-2.62 (m, 1H), 2.77-2.83 (m, 1H), 3.21-3.25 (m, 0.7H), 3.38-3.39 (m, 0.4H), 3.49-3.52 (m, 1H), 5.48-5.57 (complex, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 26.6, 28.5, 30.8, 32.2, 32.9, 40.0, 53.9, 54.2, 57.7, 127.1, 133.4, 152.8; (minor isomer) δ 26.0, 27.7, 30.7, 33.5, 34.4, 41.3, 50.8, 55.4, 57.3, 151.2. IR (neat) 3371, 1627 cm^{-1}; HRMS calcd for $C_{12}H_{20}N_3$ (M^++1) 206.1657, found 206.1662.

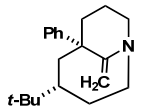
Note: This particular reaction was also performed to allow comparison of one-carbon bridged lactams with an adamantane-type bridged amide reported by Coe and

coworkers (Scheme H).[17] Interestingly, although in the latter case a subsequent full reduction to the corresponding amine was carried out, we were unable to reduce **17** under Wolff-Kishner conditions.

Scheme H. *Reduction of Adamantane-type Twisted Amide under Wolff-Kishner Conditions.*[14]



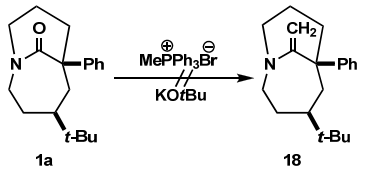
Coe and coworkers have observed by APCI MS analysis that in the course of the reaction the mixed ethanol-aminohydrazine intermediate **SI-2** is formed, which probably exists in equilibrium with the open amino-hydrazonate **SI-3**.[17] It is possible that in the case of one-carbon bridged lactam **1e** a similar ring opening occurs, with the closure being facilitated by inside-outside isomerism exhibited by the open amino-hydrazonate form of the lactam **1e**.[18] It should be noted that **SI-1** represents one of the very few examples of reactive and stable to alcoholic conditions twisted amides.[19]



18

(4R,6R)-4-*tert*-Butyl-10-methylene-6-phenyl-1-azabicyclo[4.3.1]decane (18). 25 mL round bottom flask was charged with amide **1a** (0.0214 g, 0.75 mmol, 1.0 equiv), toluene (6.0 mL), pyridine (0.06 mL) and Petasis reagent[20] (0.58 M in toluene, 0.65 mL, 0.38 mmol, 5.0 equiv), sealed with septum, and the resulting reaction mixture was heated at 105 °C for 10 h. The reaction was cooled to rt, diluted with Et_2O (5 mL) and hexanes (5 mL), stirred for 10 min, and filtered through a short plug of celite (eluting with Et_2O). Chromatography (1/4 EtOAc/hexanes) afforded the title compound as oil (R_f = 0.21, 1/4 EtOAc/hexanes). Yield 95% (0.0201 g, 0.071 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 9H), 1.57-1.81 (m, 6H), 1.86-1.98 (m, 1H), 2.07-2.19 (m, 1H), 2.30 (d, *J* = 9.9 Hz, 1H), 2.59-2.71 (m, 1H), 2.99-3.09 (m, 1H), 3.39-3.48 (m, 1H), 3.52-3.59 (m, 1H), 4.19 (s, 1H), 4.76 (s, 1H), 7.20 (tt, *J* = 1.1, 6.7 Hz, 1H), 7.29-7.36 (m, 2H), 7.46-7.53 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 27.8, 28.1, 34.0, 39.9, 43.9, 45.0, 47.0, 54.6, 55.4, 110.6, 125.6, 127.2, 127.7, 151.7, 157.0; IR (neat) 3088, 3055, 3028, 2943, 2866, 1628, 1555, 1443, 1393, 1366, 1101, 866, 762 cm^{-1}; HRMS calcd for $C_{20}H_{30}N$ (M^+ + H) 284.2378, found 284.2375.

Scheme I. *Attempted Wittig Olefinations of One-carbon Bridged Lactams.*



1a 18

*Attempted Wittig Olefination of Amide **1a**.* According to the procedure by Fitjer for demanding olefinations.[21] To a solution of triphenyl methyl triphenylphosphonium bromide (0.256 g, 0.70 mmol, 10.0 equiv) in toluene (5 mL) KO*t*Bu (0.089 g, 0.70 mmol, 10.0 equiv) was added and the resulting mixture was heated at 105 °C for 1 h. The reaction was cooled to rt, amide **1a** (0.0200 g, 0.070 mmol, 1.0 equiv) in toluene (2 mL) was added, and the reaction was heated at 105 °C for 24 h. The reaction was quenched with water (5 mL), extracted with ether (3 x 20 mL), washed with water (1 x 10 mL), brine (1 x 10 mL), dried and concentrated. Analysis of the crude reaction mixture by NMR indicated only the presence of the starting material. Enamine **18** was not present in the reaction mixture. Similarly, the reaction of amide **1e** with triphenyl methyl triphenylphosphonium bromide (10.0 equiv) and KO*t*Bu (10.0 equiv) for 22 h at 105 °C did not afford the bridged enamine. In addition, the reaction of amide **1f** with 3.0 equiv of triphenylphosphonium methylide (generated from methyl triphenylphosphonium bromide and *n*BuLi) in refluxing THF for 24 h did not afford the desired product.[22] Analysis of the crude reaction mixtures indicated only the presence of the starting materials.

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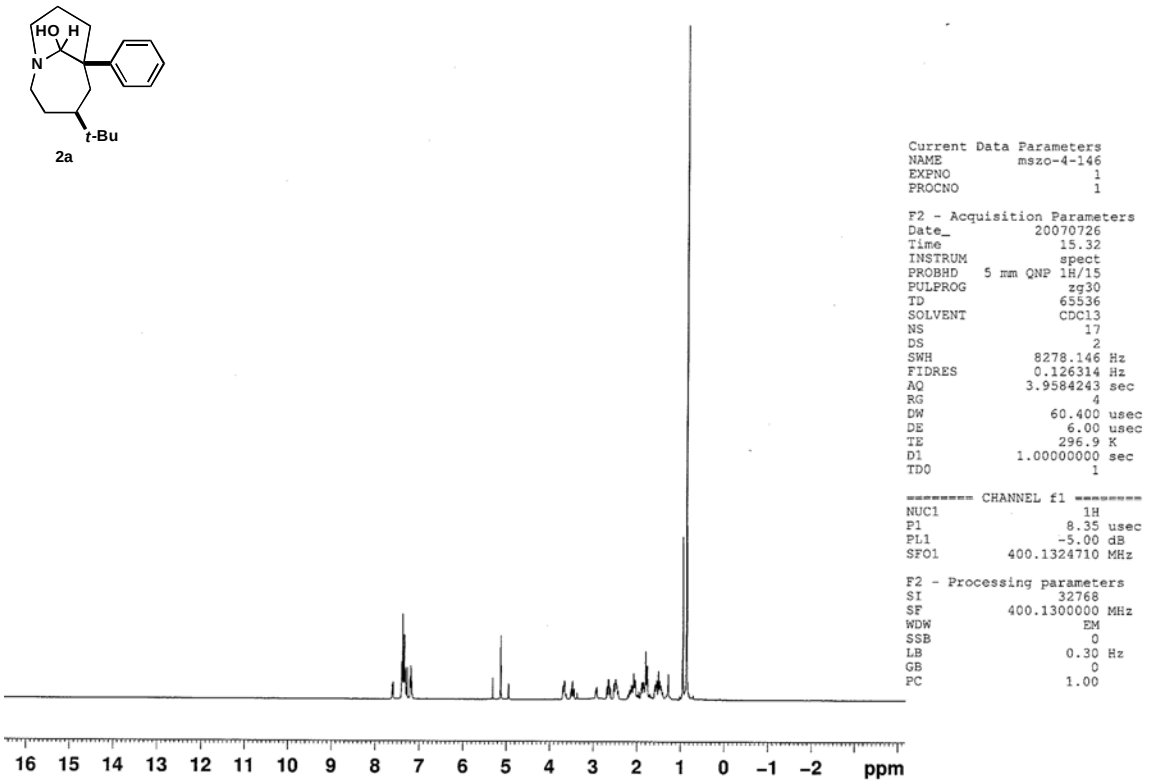
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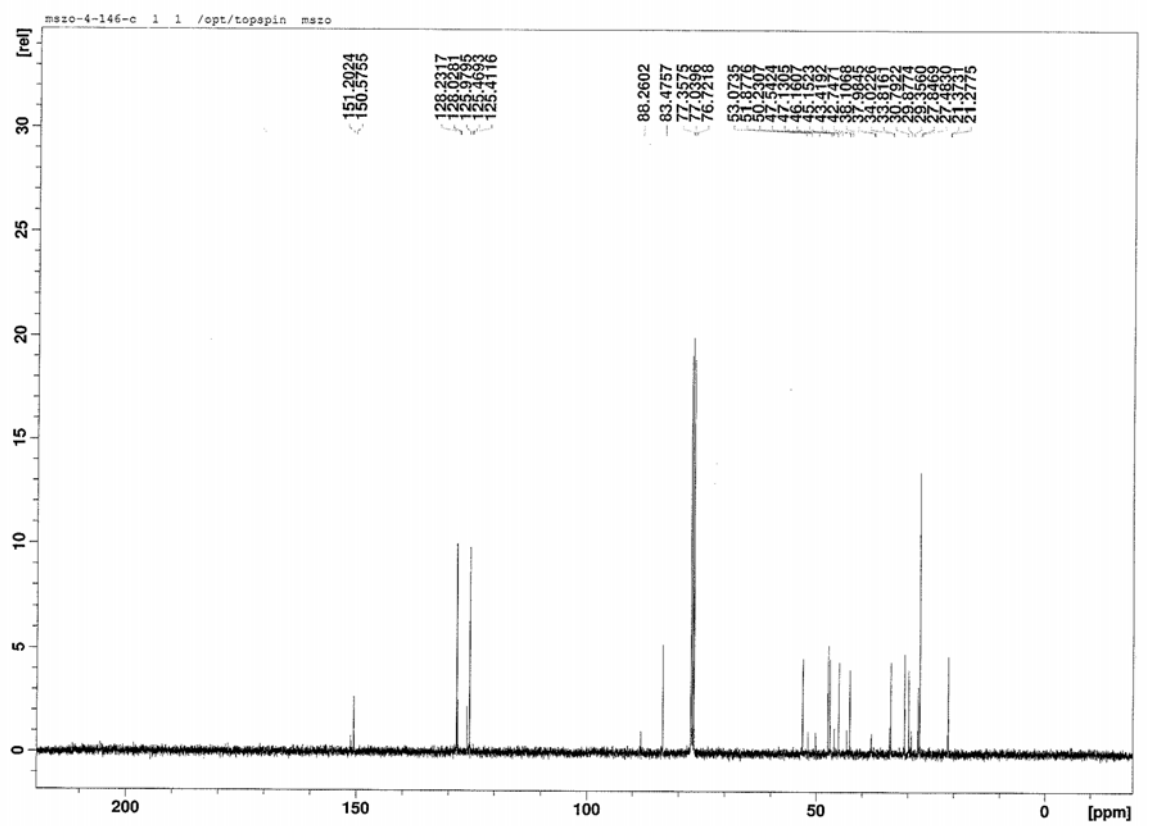
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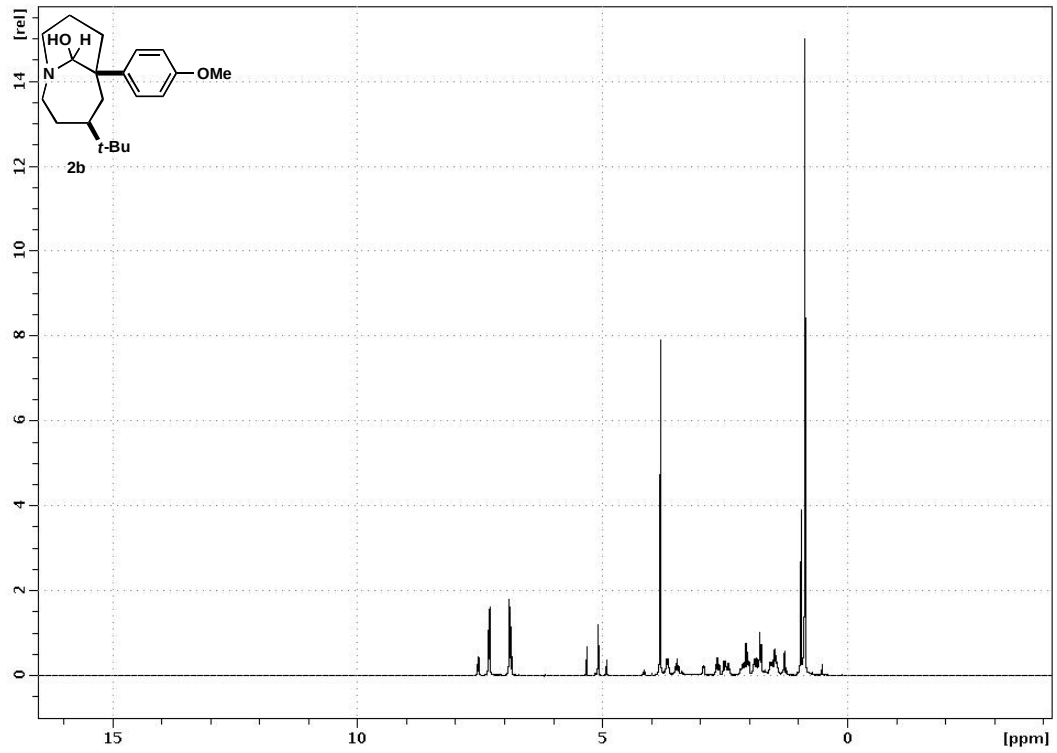
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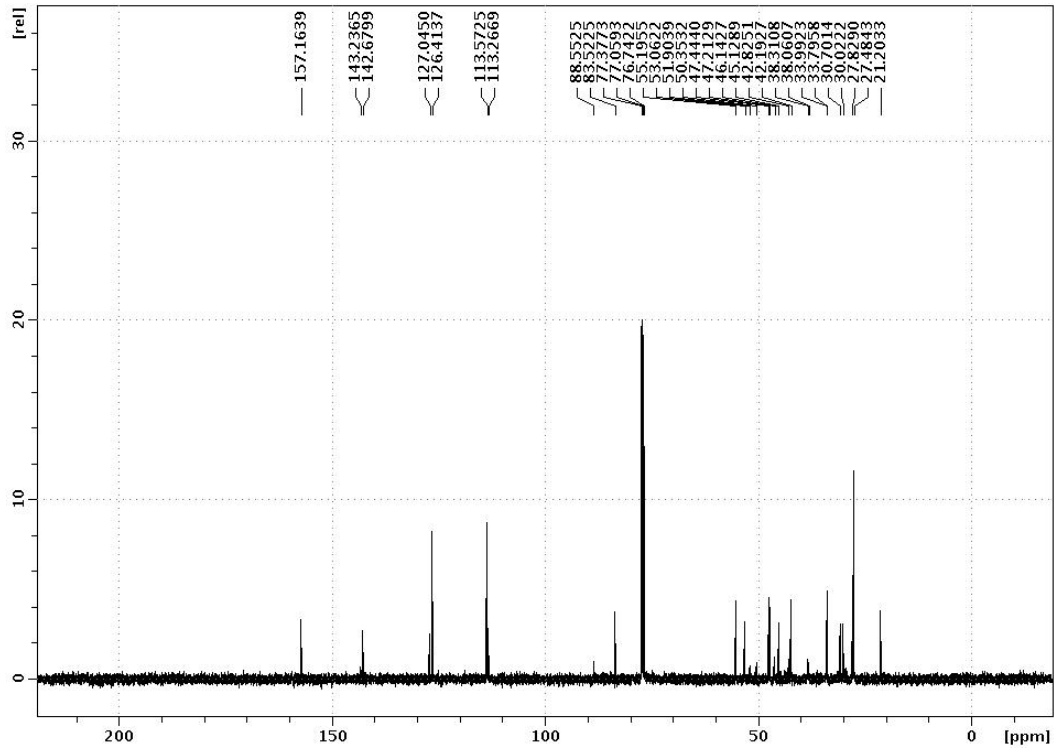
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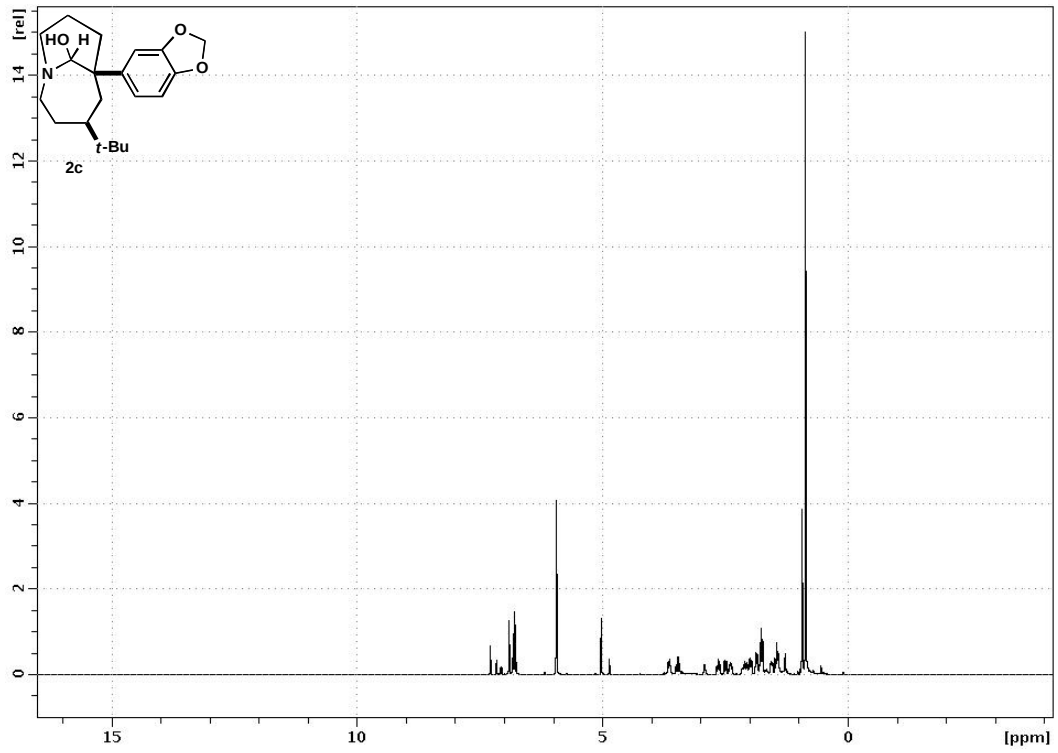
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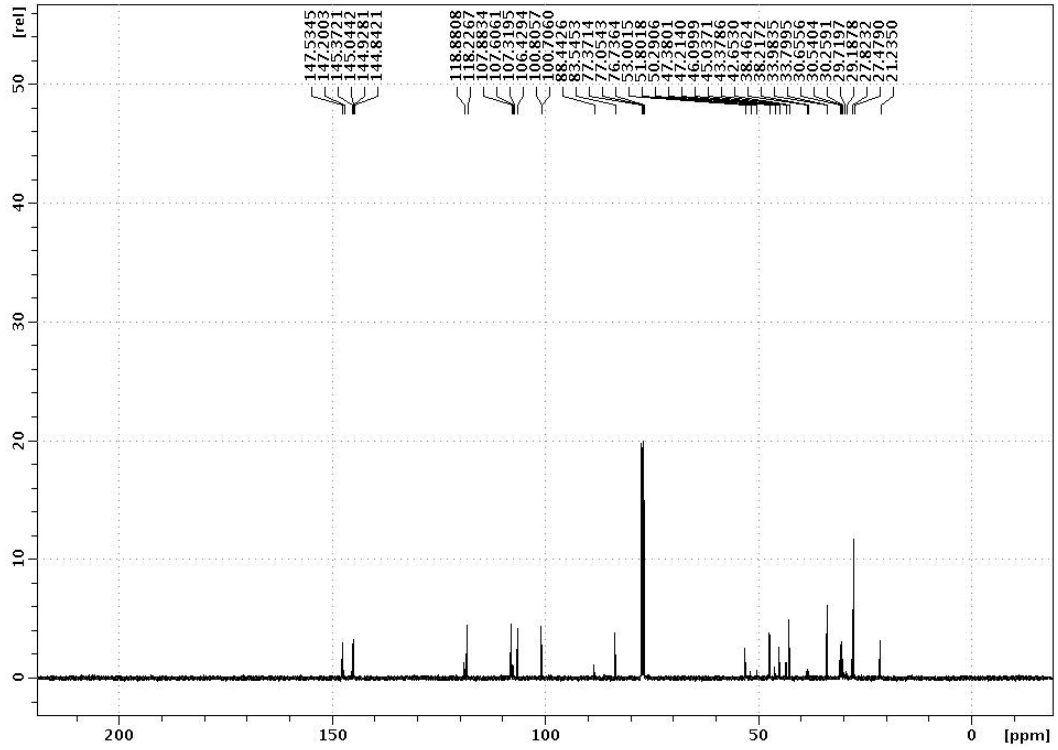
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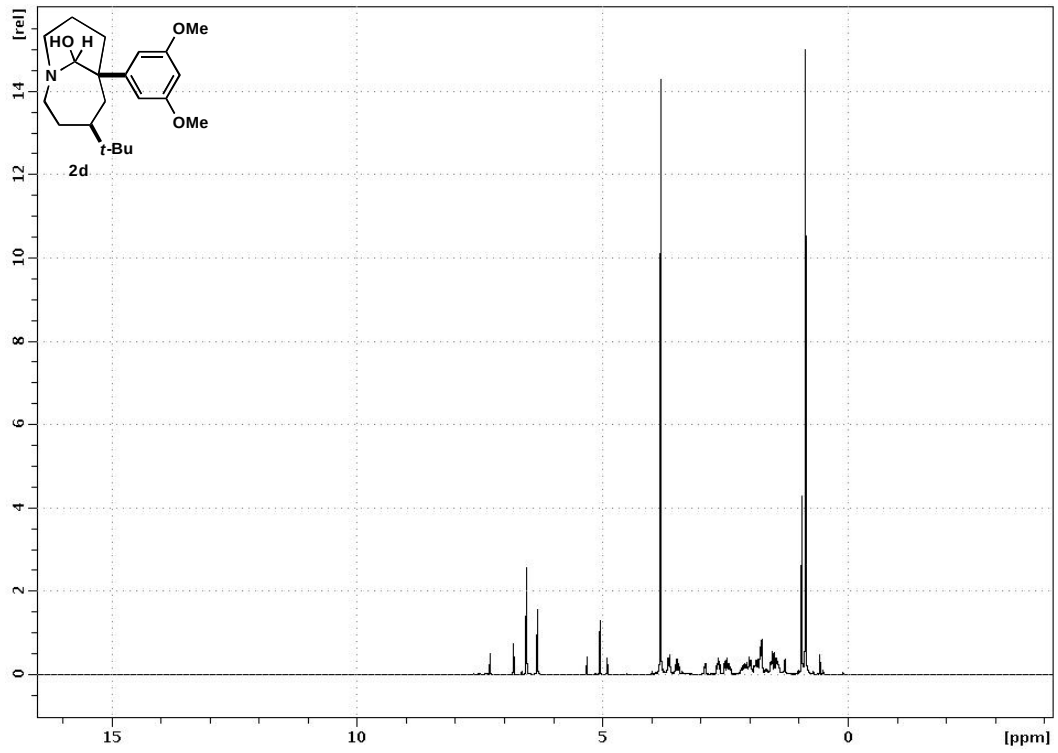
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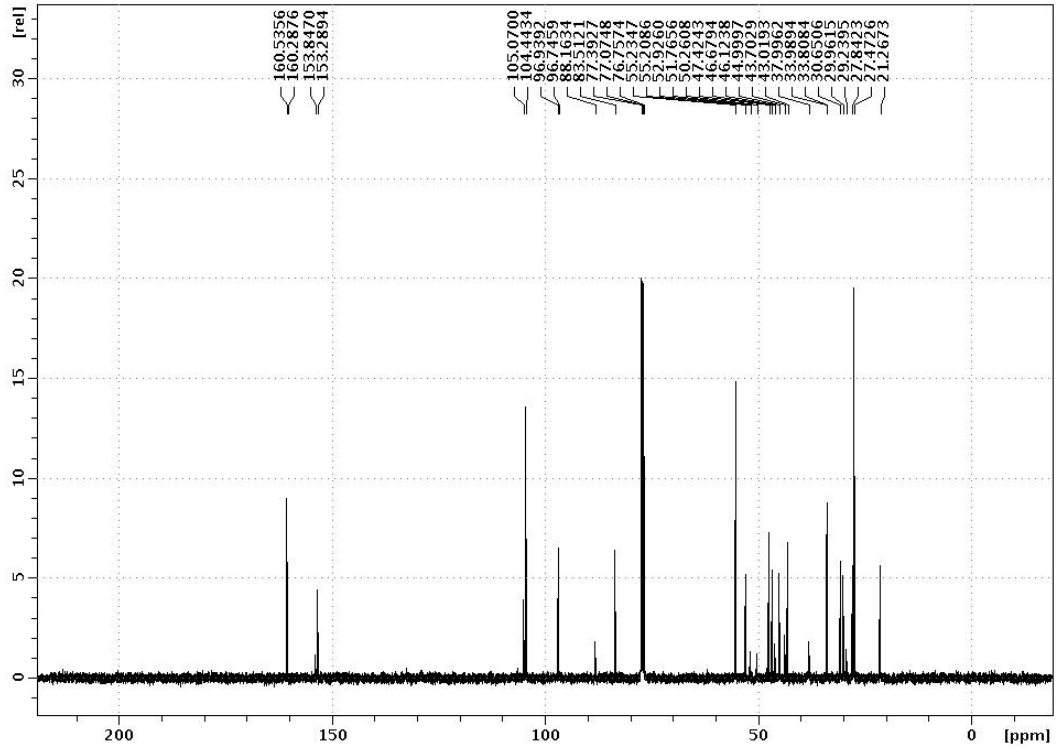
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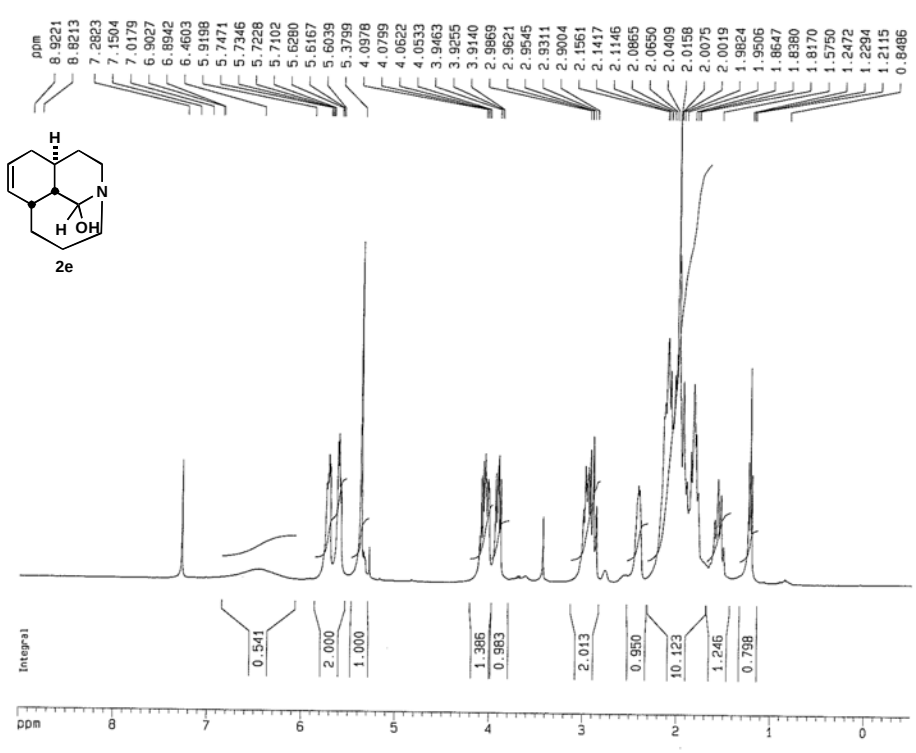


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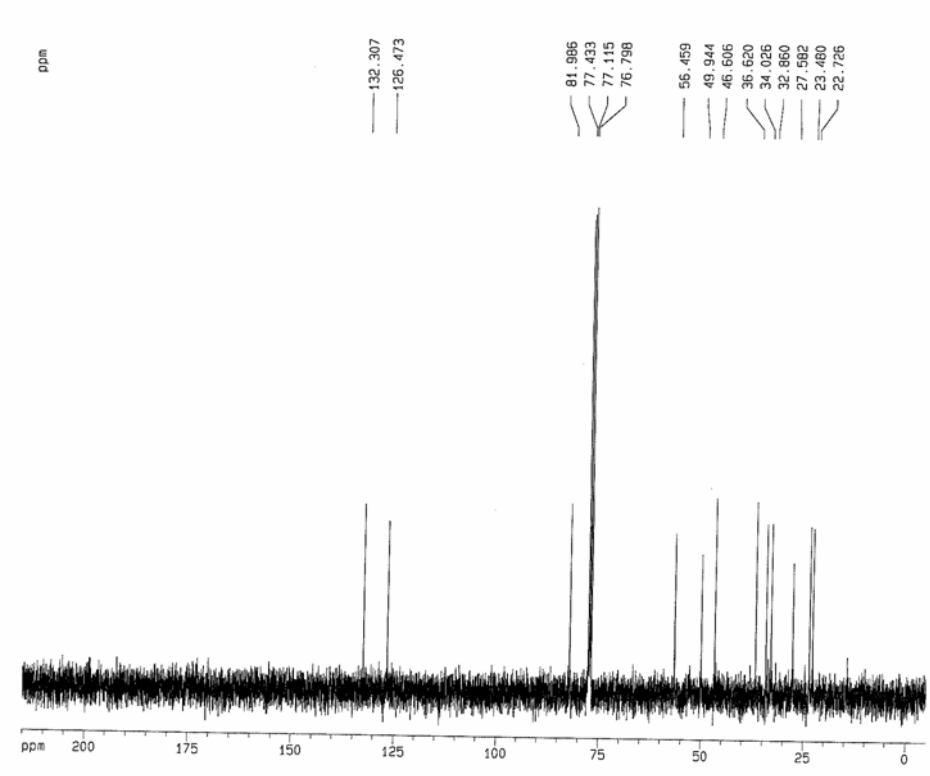


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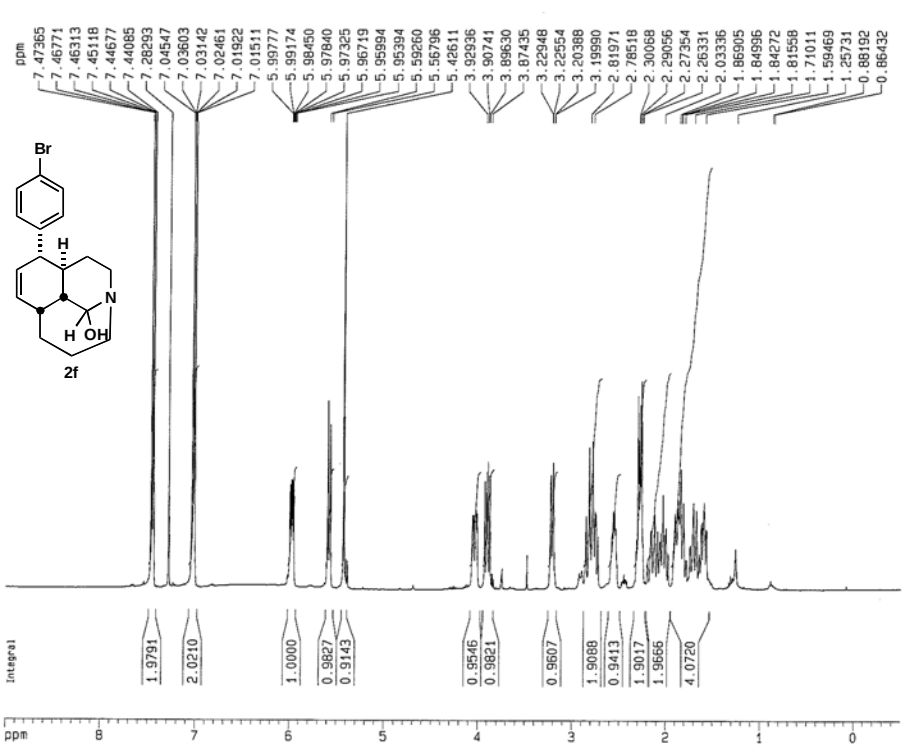


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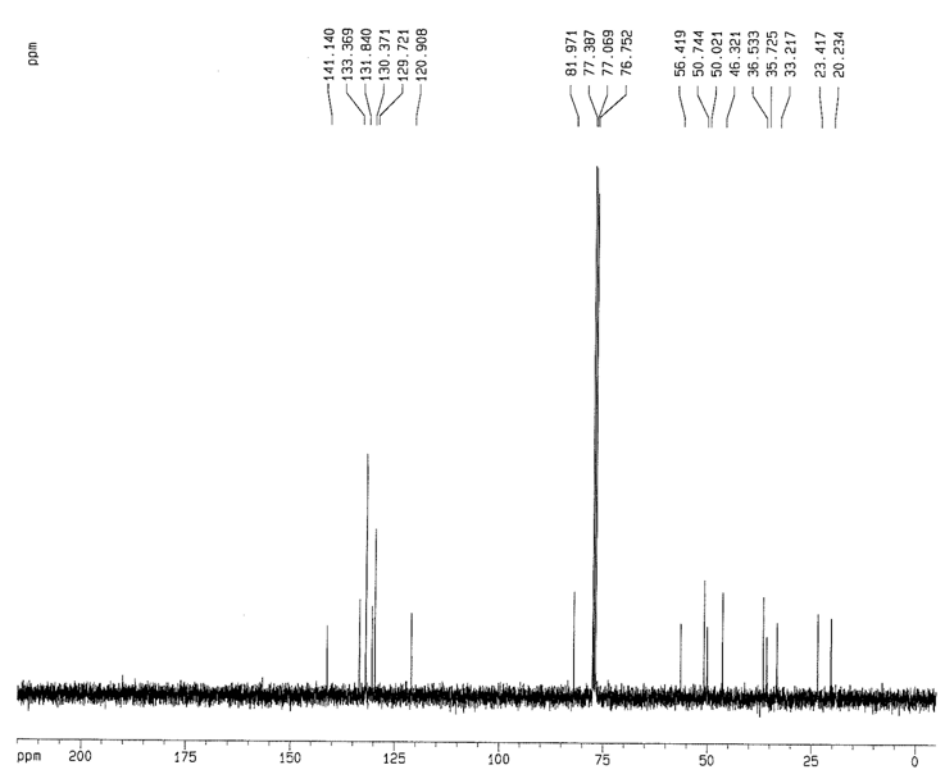


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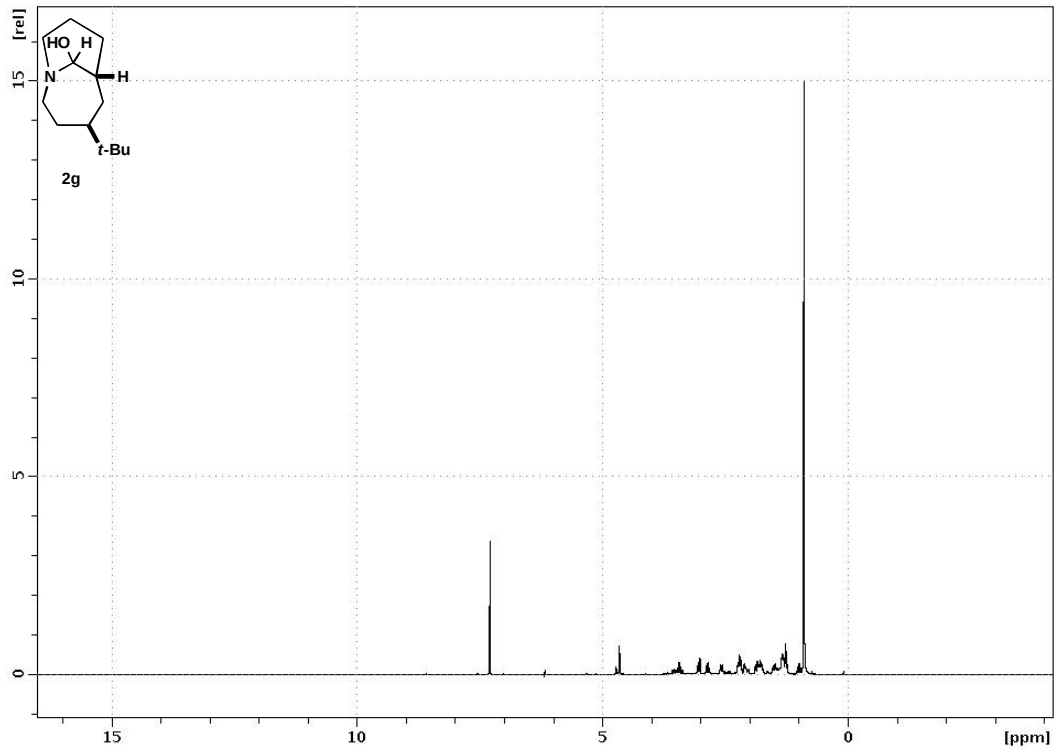
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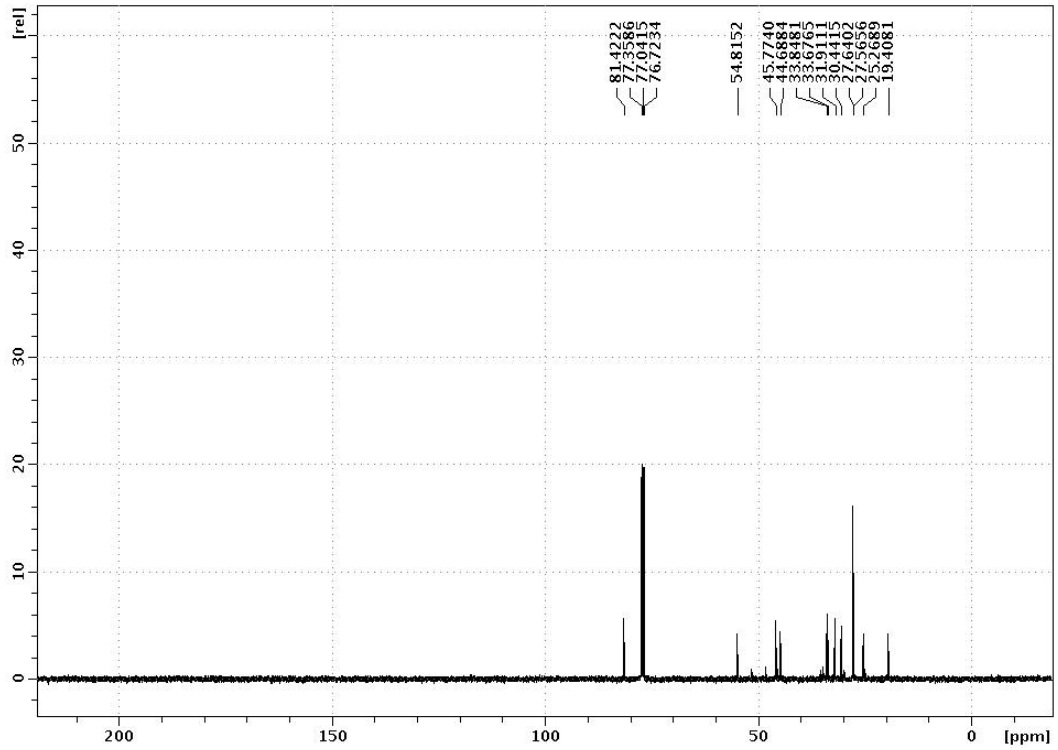
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29.6402
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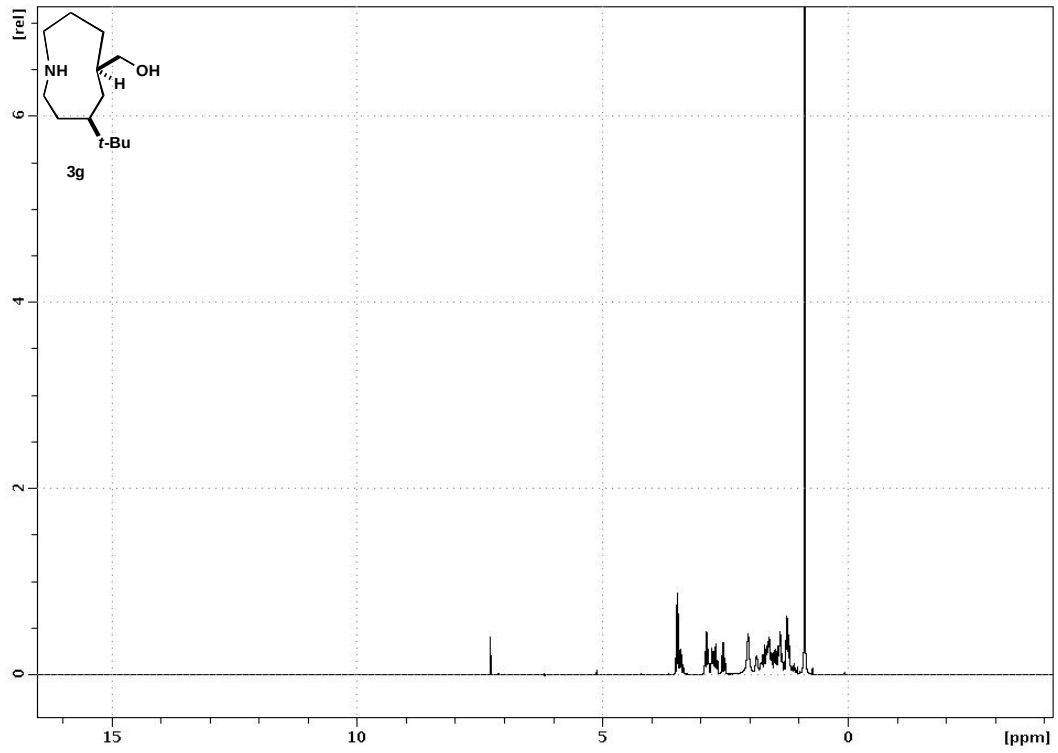
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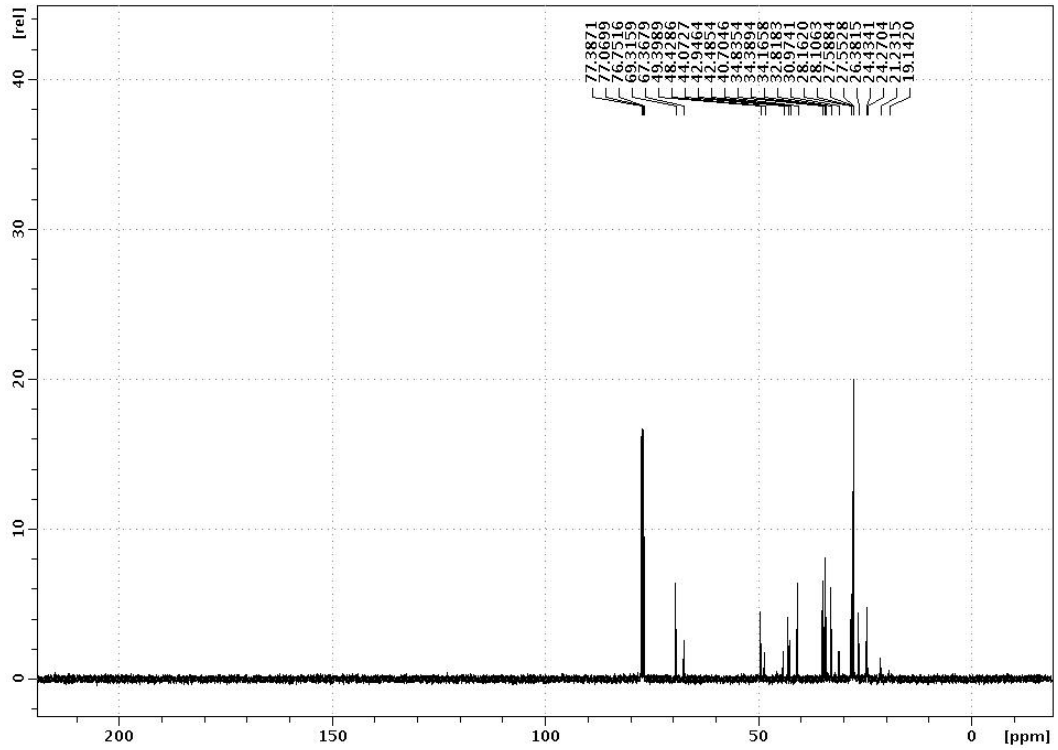
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34.1658
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28.1620
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27.5884
27.5528
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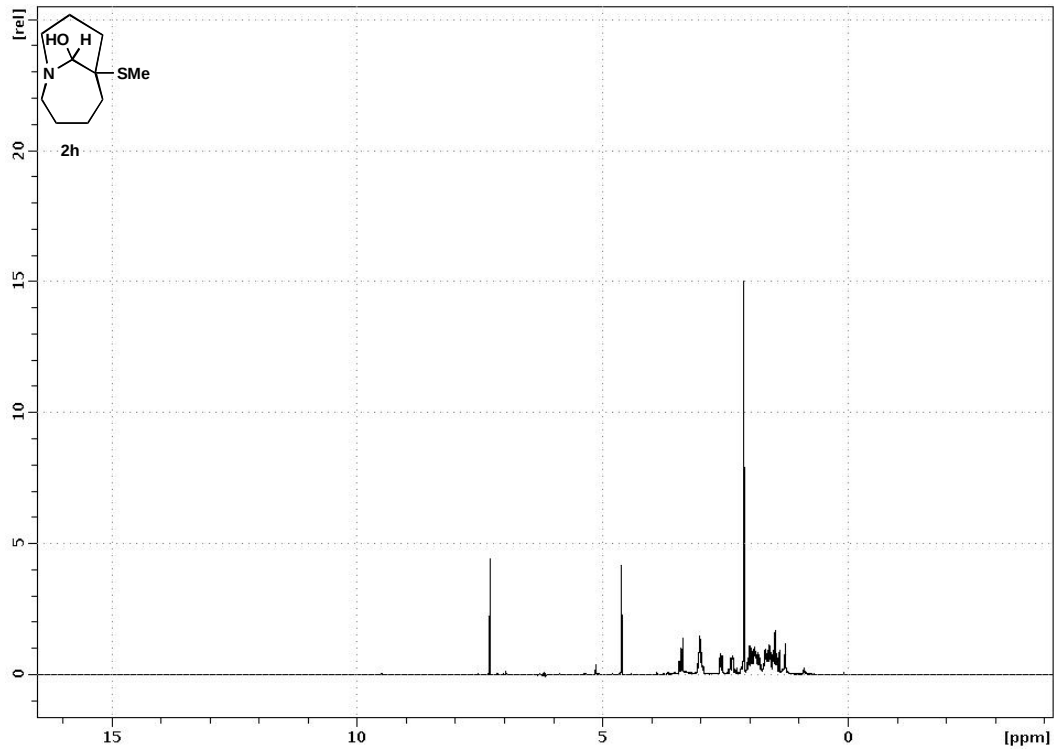
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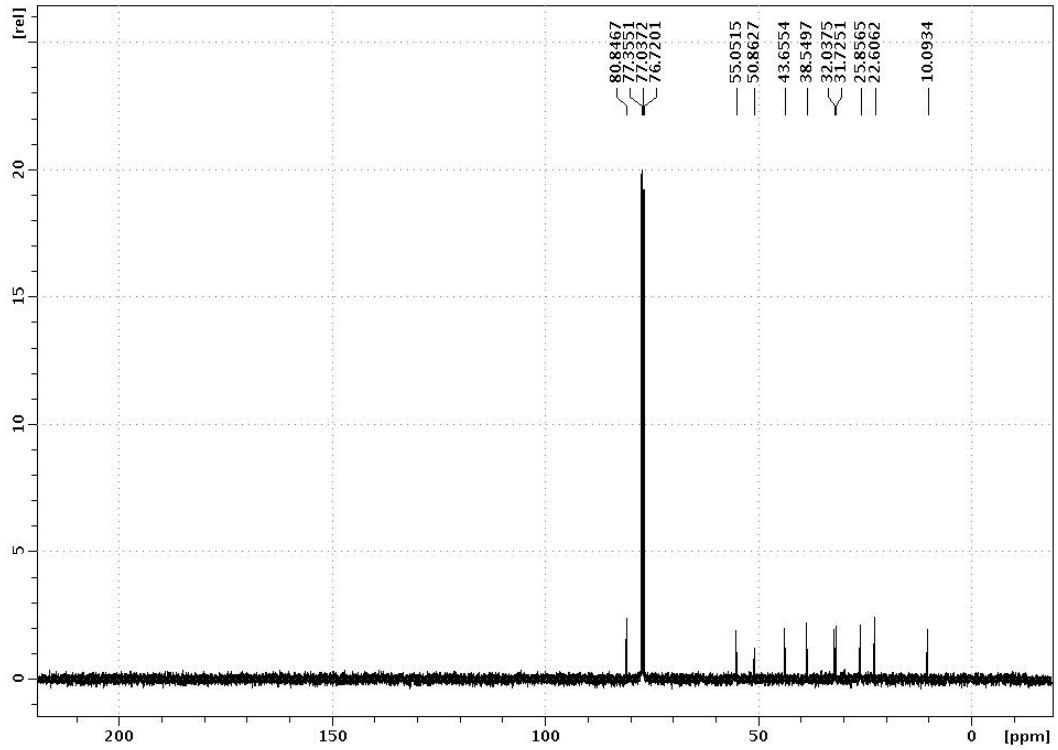
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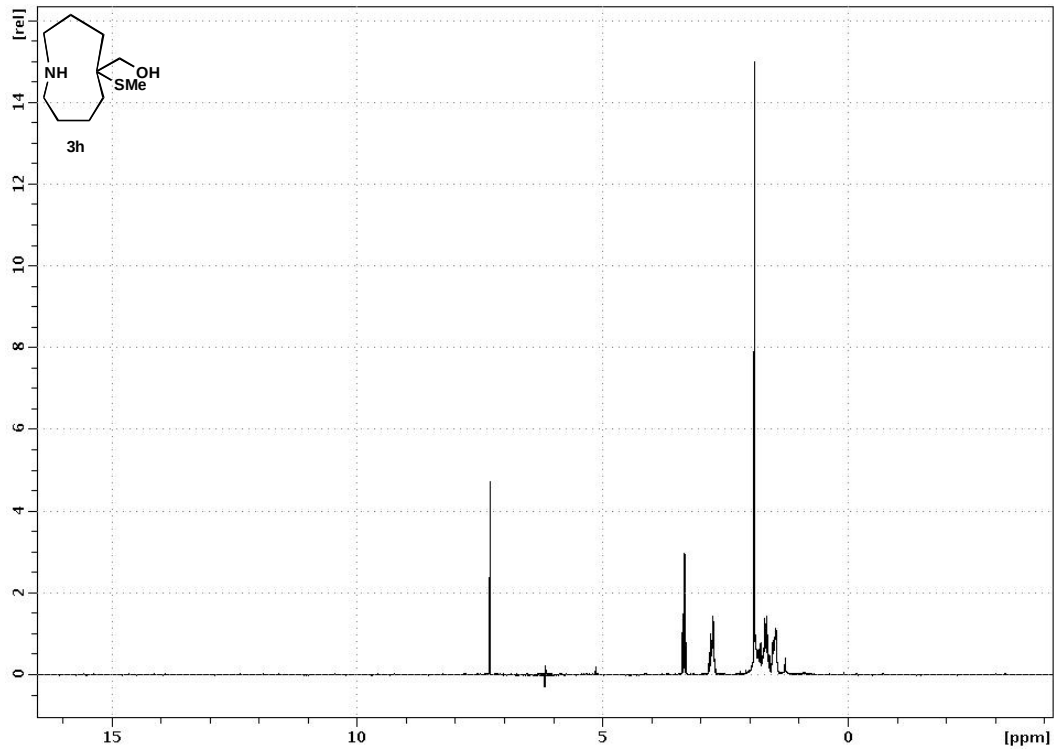
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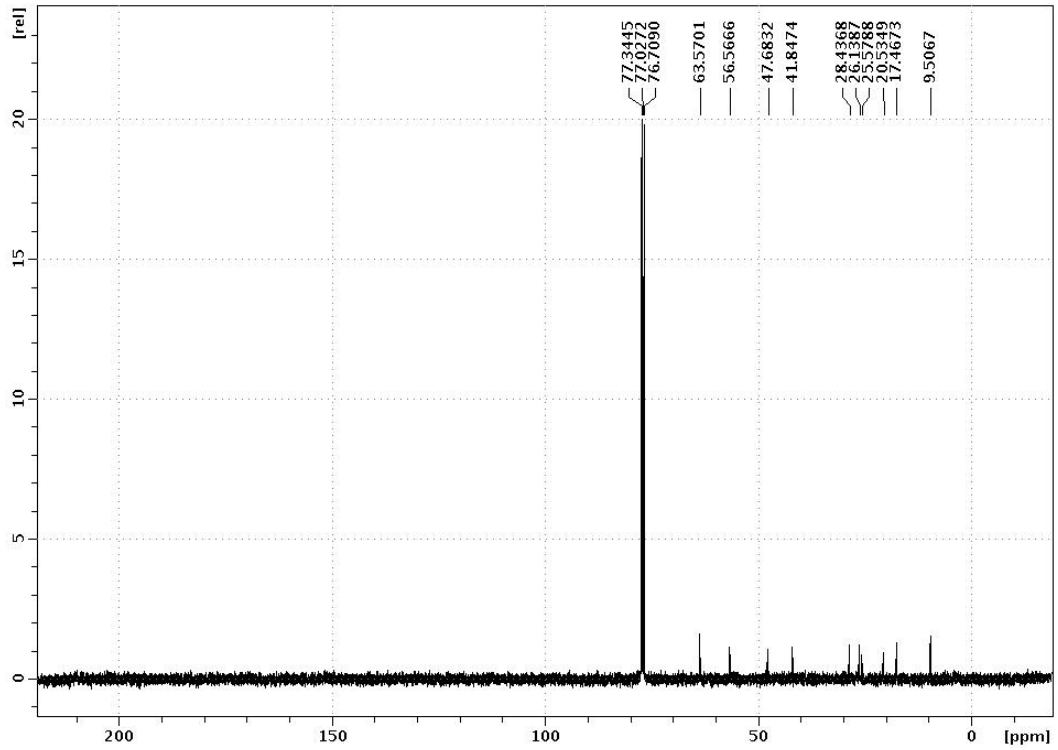
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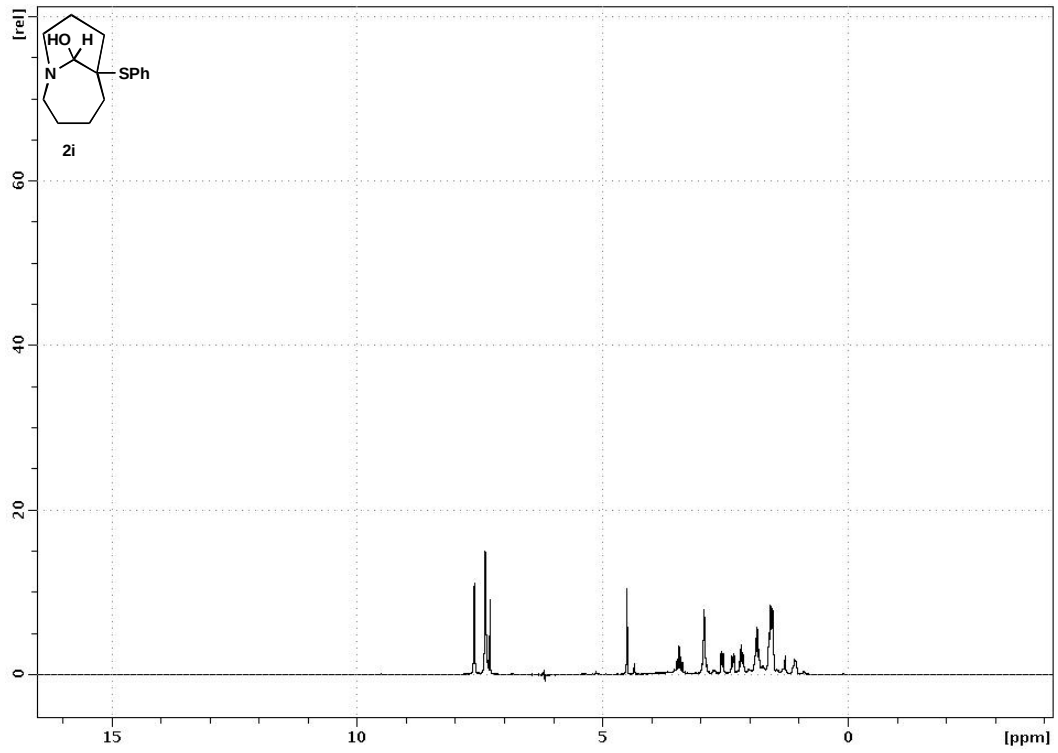
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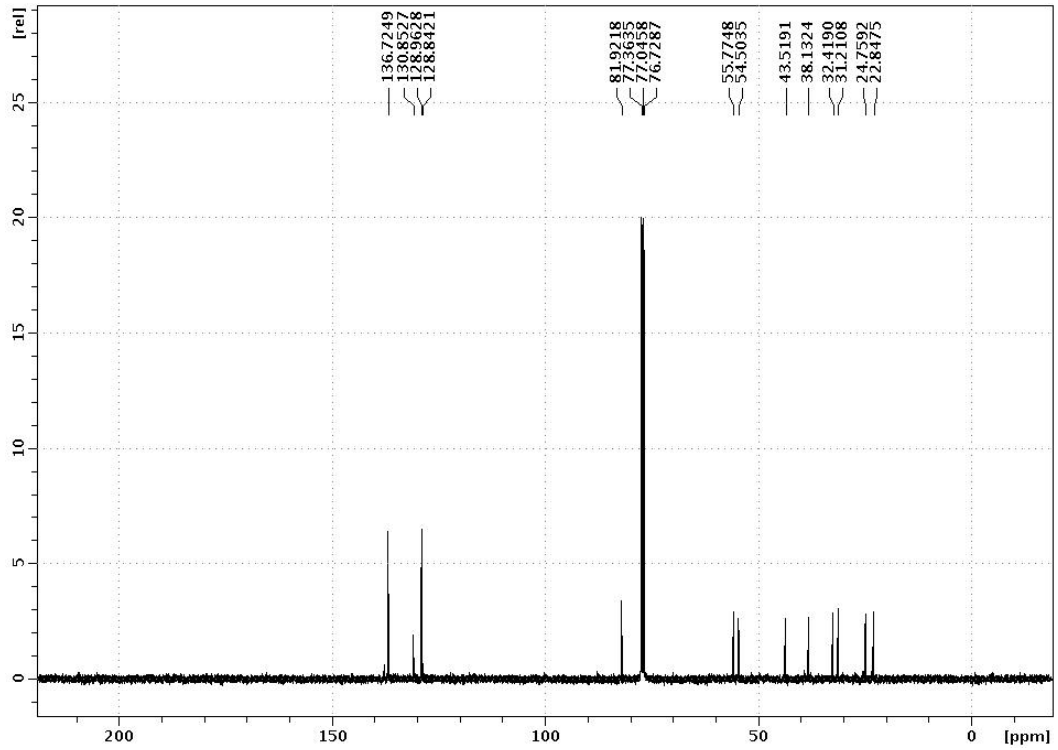
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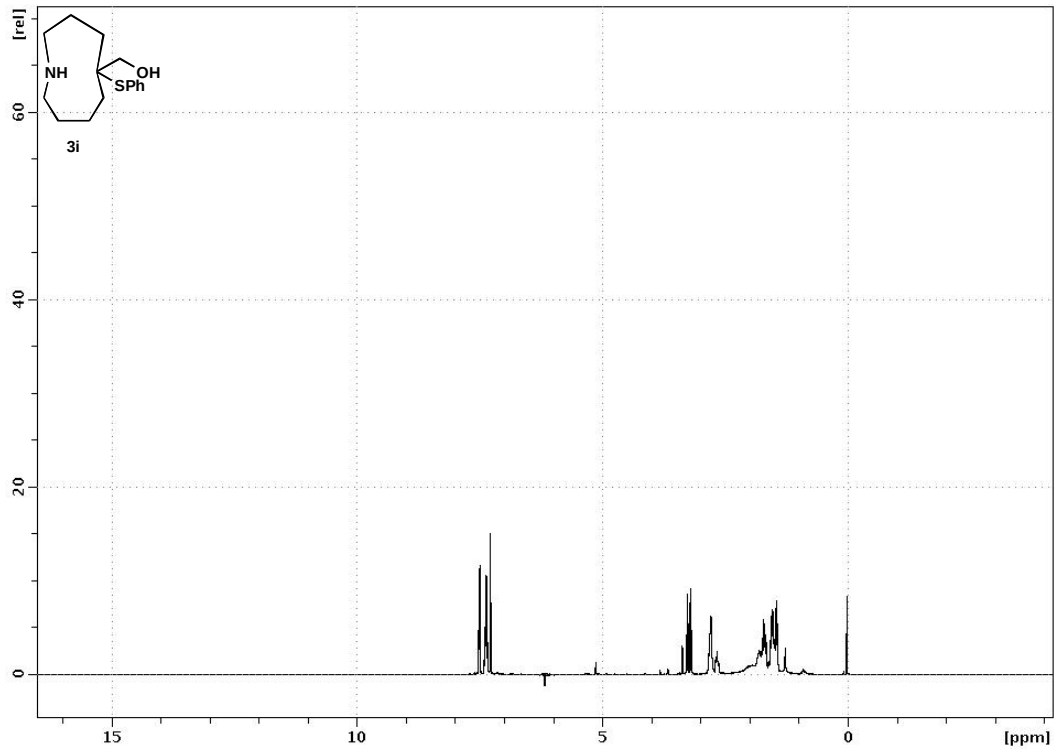
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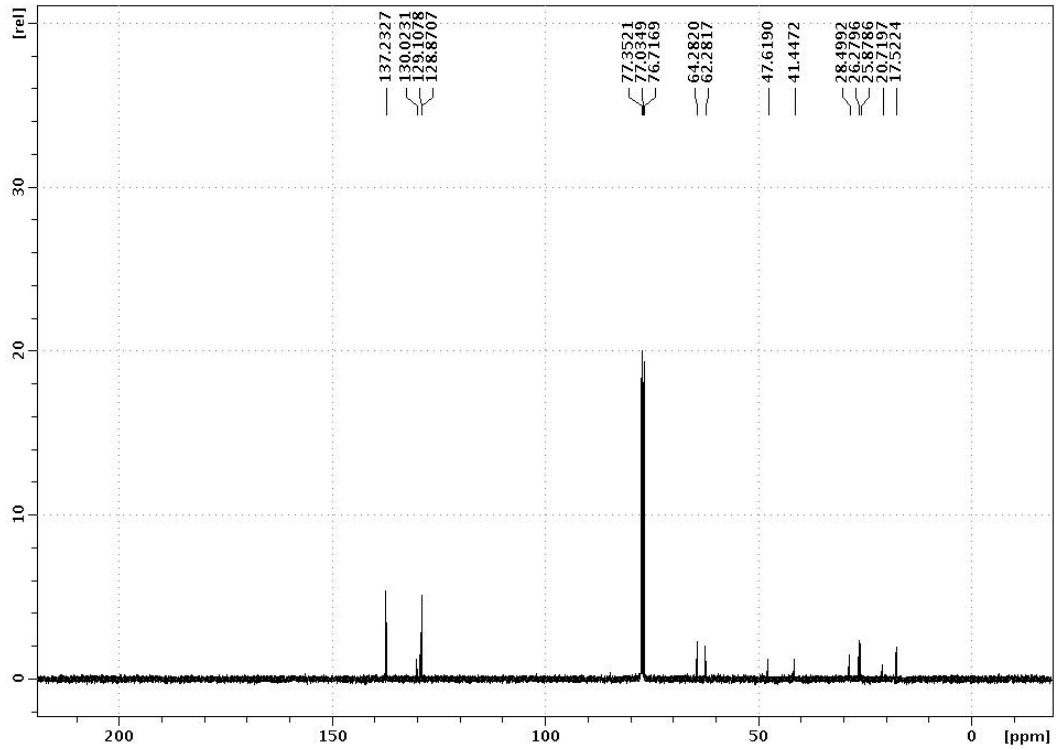
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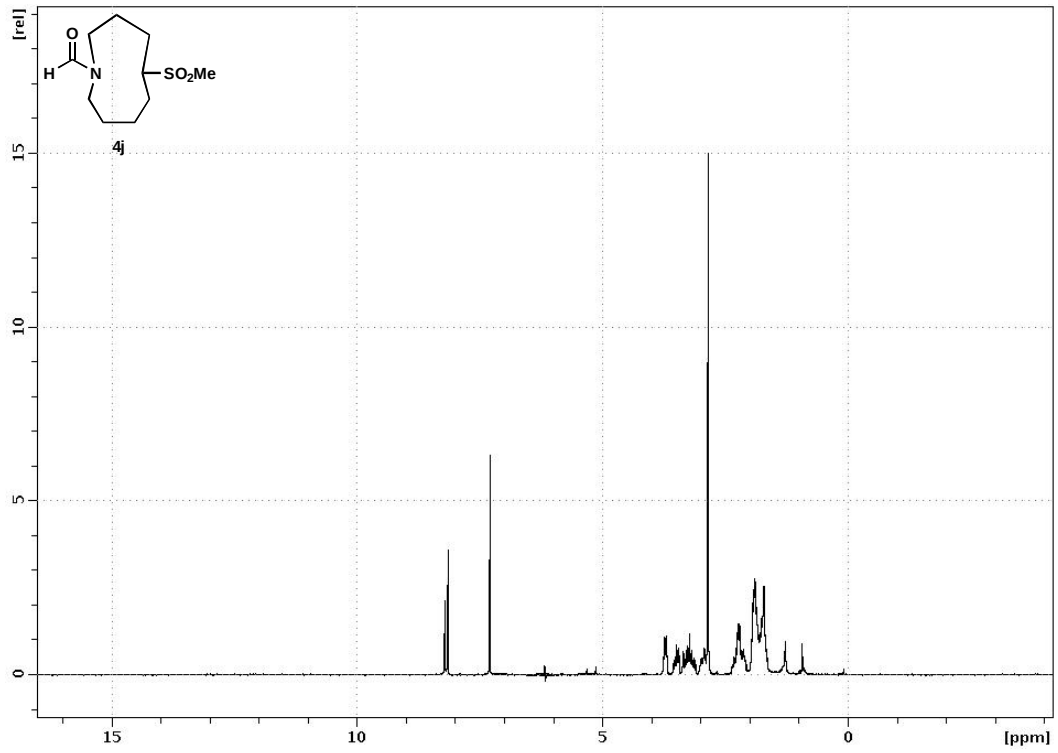
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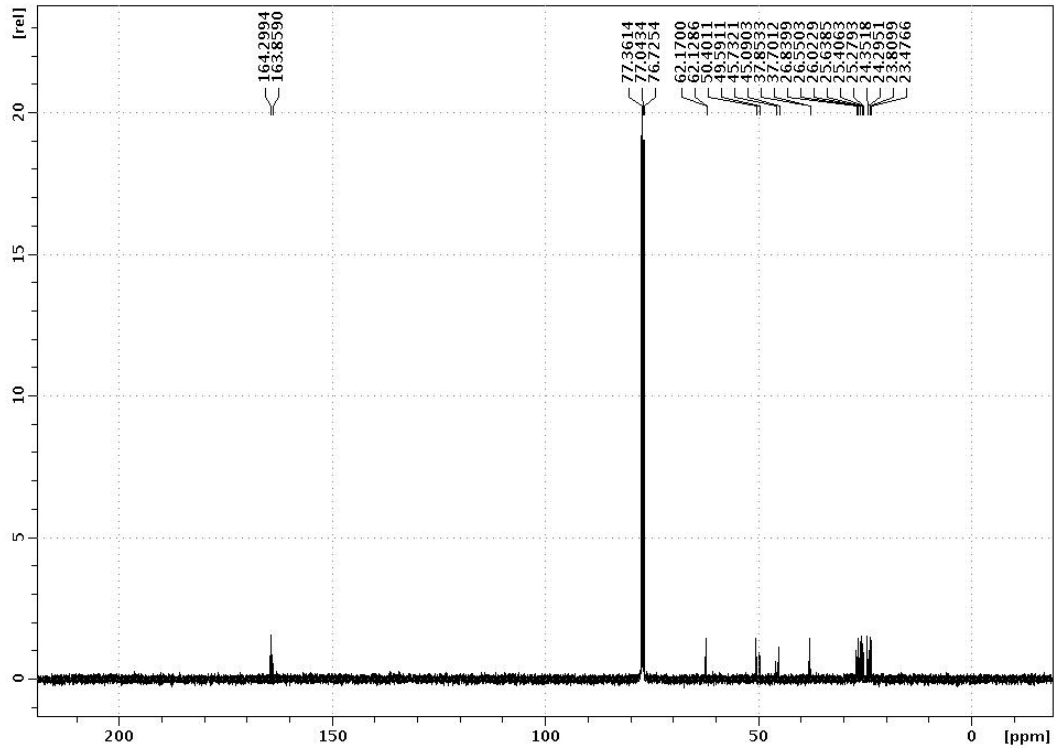
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26.8399
26.5503
26.0229
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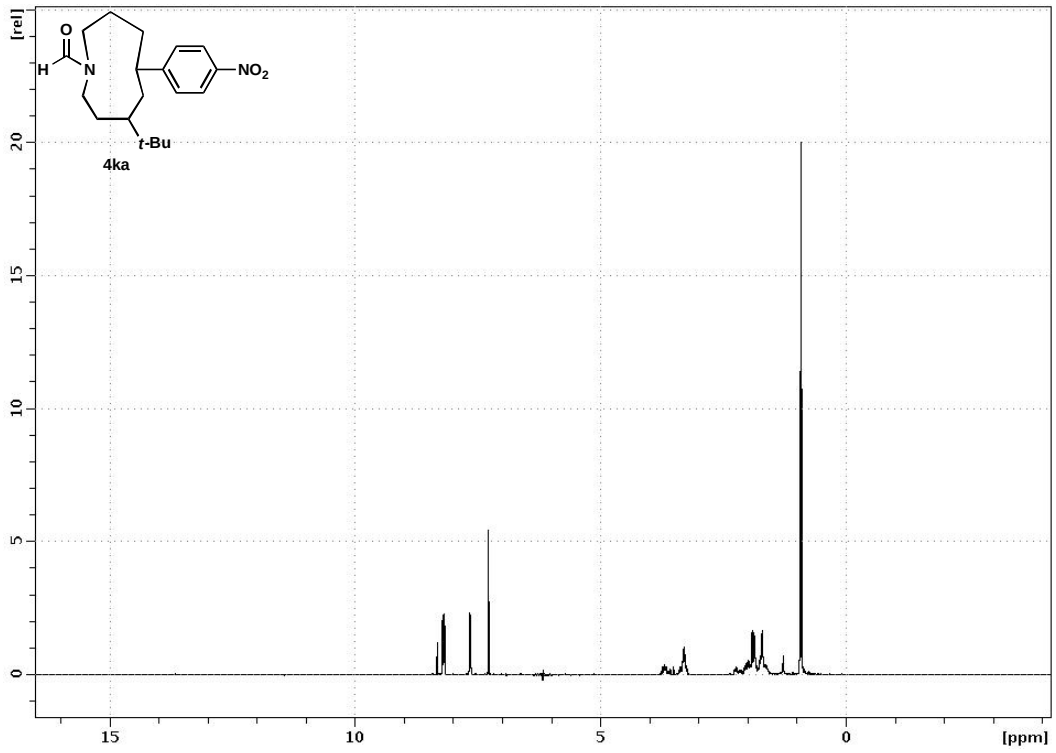
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NO2
t-Bu
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10
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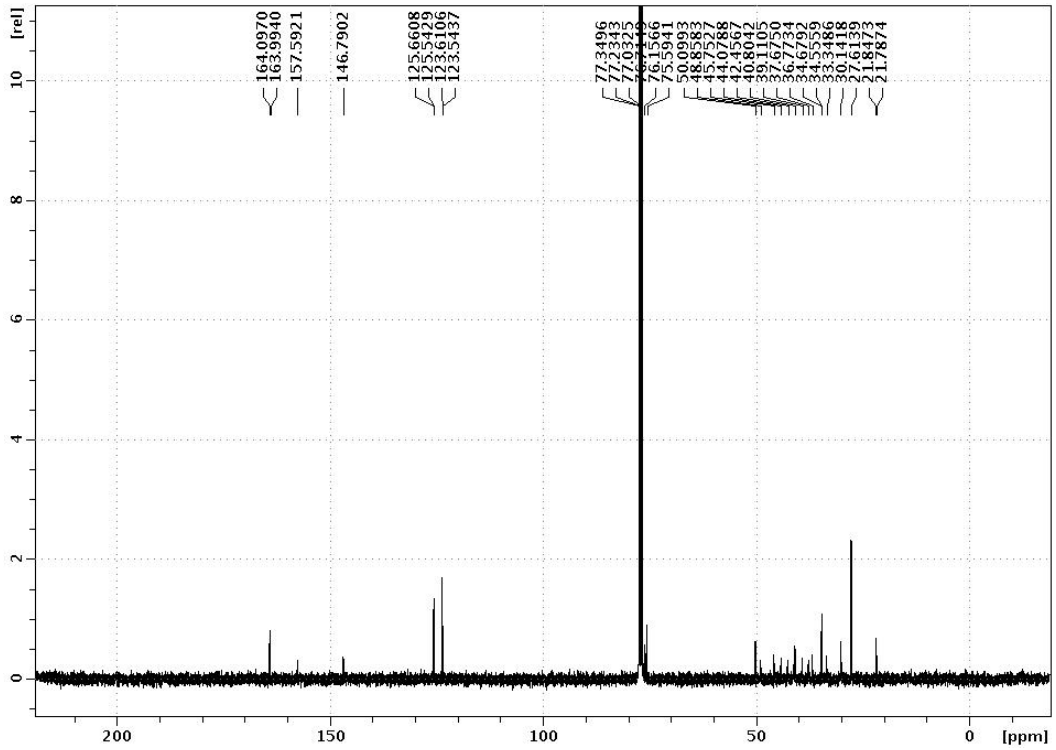
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44.0788
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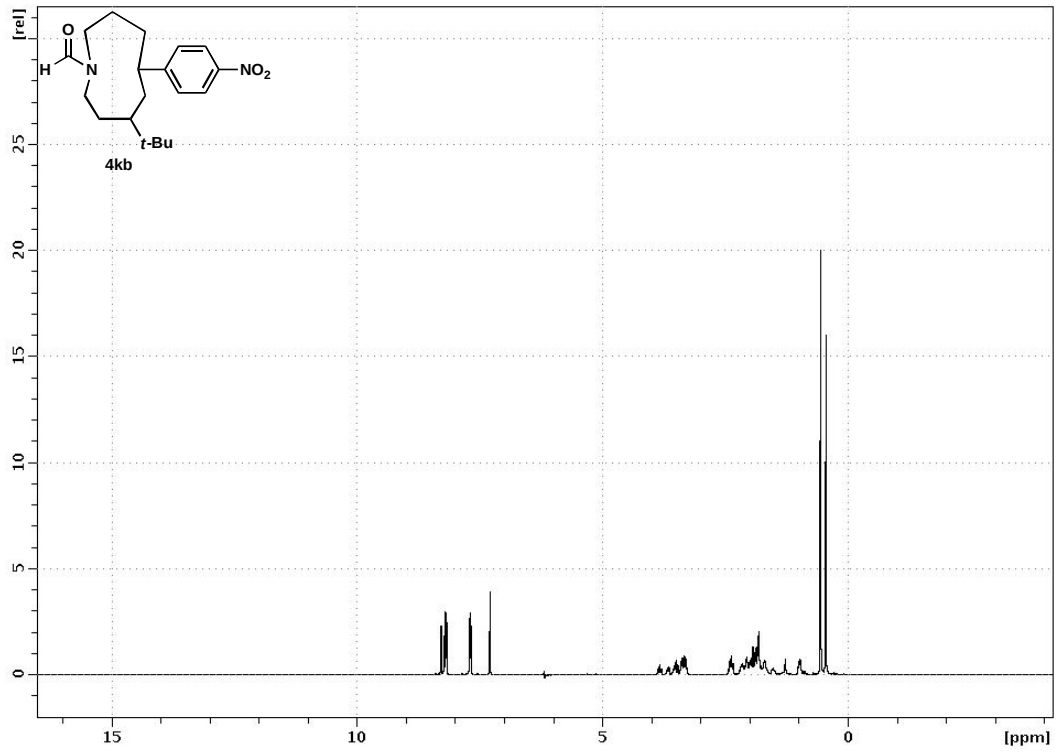
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N
NO2
t-Bu
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10
5
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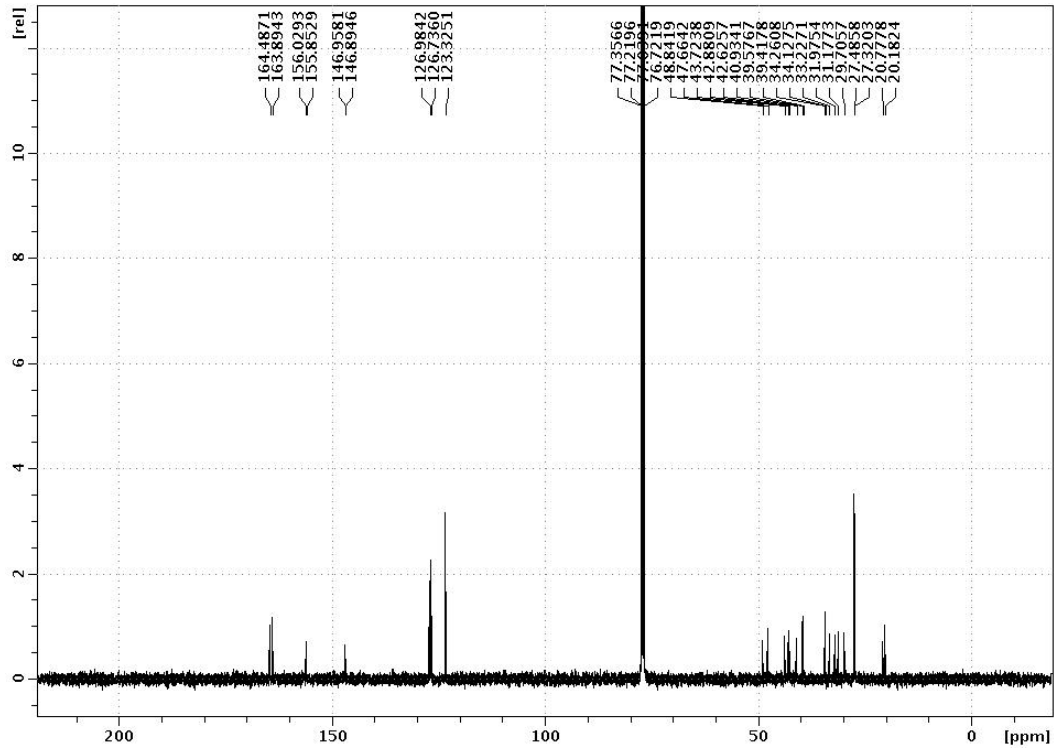
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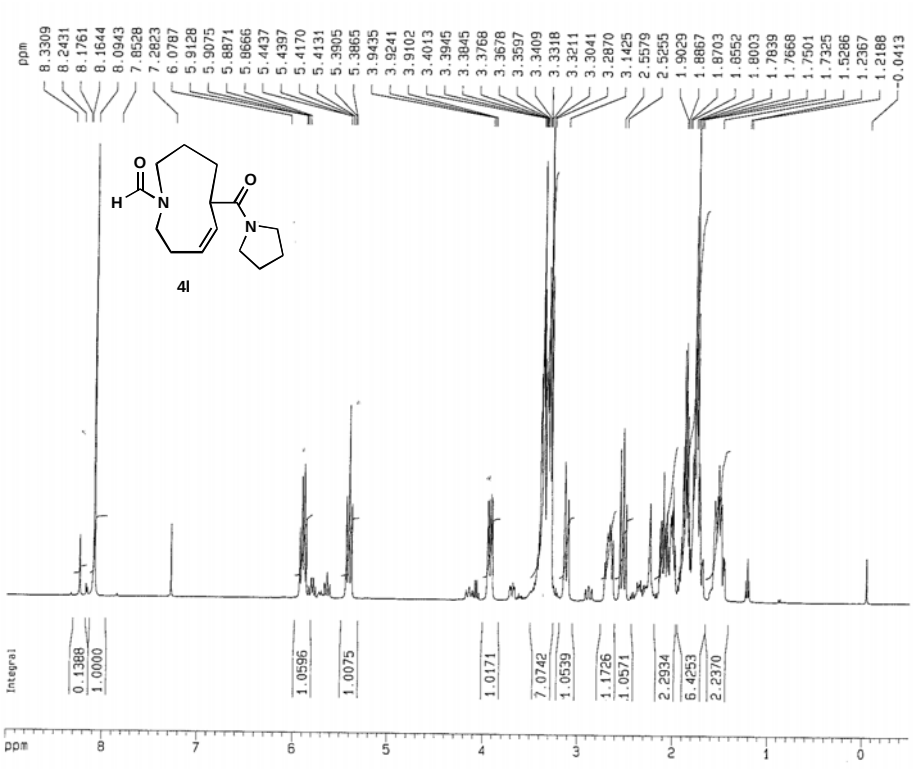


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Current Data Parameters
NAME                  YL-V-P009
EXPNO                         3
PROCNO                        1

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Date_                  20050519
Time                      13.24
INSTRUM                   spect
PROBHD   5 mm QNP 1H/15
PULPROG                   zg30
TD                       32768
SOLVENT                  CDCl3
NS                           16
DS                            2
SWH                    4789.272 Hz
FIDRES                 0.146157 Hz
AQ                     3.4210291 sec
RG                         80.6
DW                      104.400 usec
DE                        6.00 usec
TE                       297.3 K
D1                  1.00000000 sec
MCREST              0.00000000 sec
MCWRK               0.01500000 sec

======== CHANNEL f1 ========
NUC1                         1H
P1                         7.05 usec
PL1                       -3.00 dB
SFO1                400.1320007 MHz

F2 - Processing parameters
SI                           32768
SF                  400.1300000 MHz
WDW                             EM
SSB                              0
LB                            0.30 Hz
GB                               0
PC                            1.00

1D NMR plot parameters
CX                           20.00 cm
CY                            0.00 cm
F1P                           9.000 ppm
F1                         3601.17 Hz
F2P                          -0.500 ppm
F2                         -200.07 Hz
PPMCM                      0.47500 ppm/cm
HZCM                     190.06175 Hz/cm
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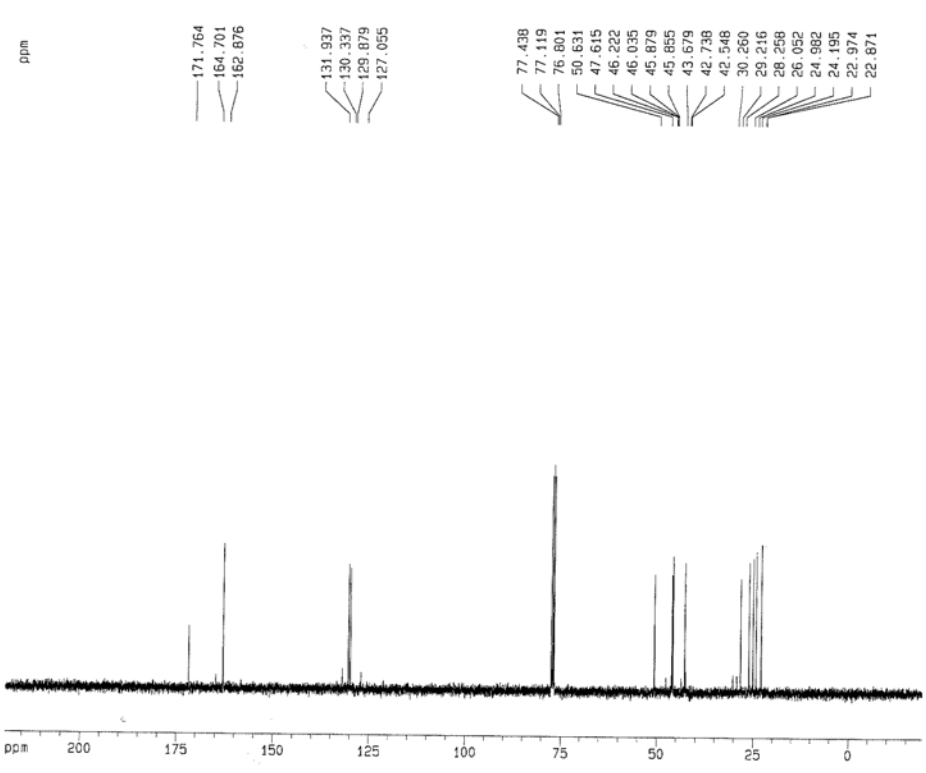


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Current Data Parameters
NAME                  YL-V-P009
EXPNO                         4
PROCNO                        1

F2 - Acquisition Parameters
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Time                      13.27
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PULPROG                 zgpg30
TD                       65536
SOLVENT                  CDCl3
NS                           81
DS                            4
SWH                   23980.814 Hz
FIDRES                0.365918 Hz
AQ                    1.3664756 sec
RG                         2048
DW                       20.850 usec
DE                        6.00 usec
TE                       297.3 K
D1                  0.15000001 sec
d11                 0.03000000 sec
DELTA               0.05000000 sec
MCREST              0.00000000 sec
MCWRK               0.01500000 sec

======== CHANNEL f1 ========
NUC1                         13C
P1                         7.20 usec
PL1                       -2.00 dB
SFO1                100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2                 waltz16
NUC2                         1H
PCPD2                     98.40 usec
PL2                       -3.00 dB
PL12                      19.96 dB
PL13                     120.00 dB
SFO2                400.1316005 MHz

F2 - Processing parameters
SI                           32768
SF                  100.6127690 MHz
WDW                             EM
SSB                              0
LB                            1.00 Hz
GB                               0
PC                            1.40

1D NMR plot parameters
CX                           20.00 cm
CY                            5.00 cm
F1P                         219.169 ppm
F1                        22051.21 Hz
F2P                         -19.179 ppm
F2                        -1929.61 Hz
PPMCM                     11.91738 ppm/cm
HZCM                    1199.04077 Hz/cm
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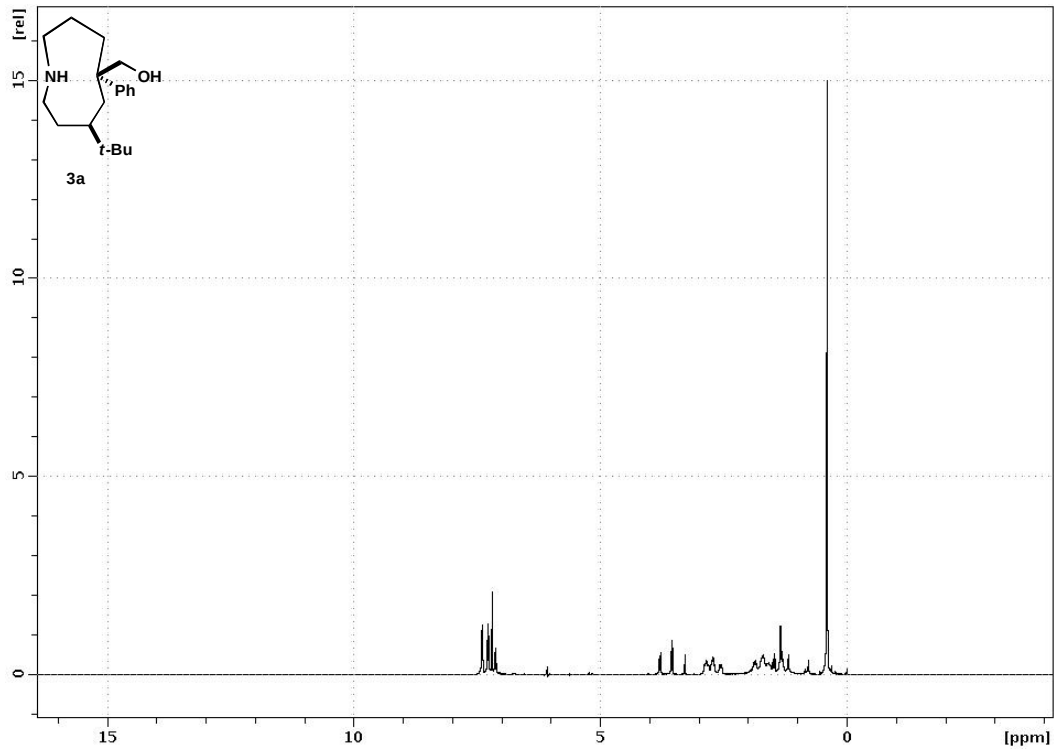
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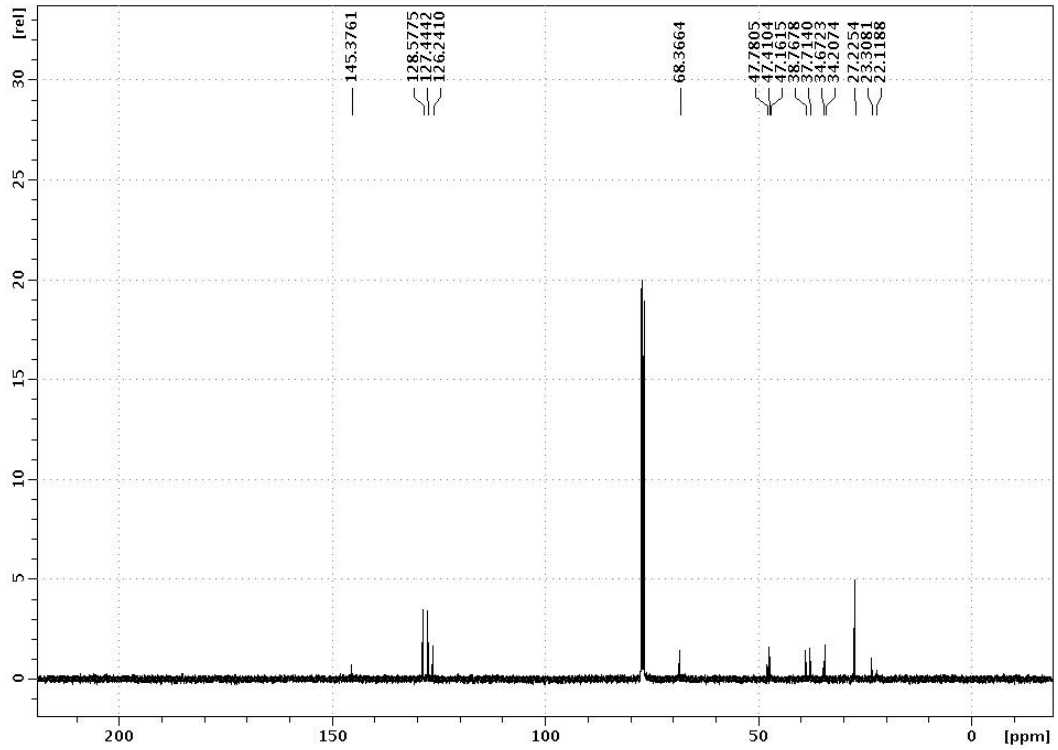
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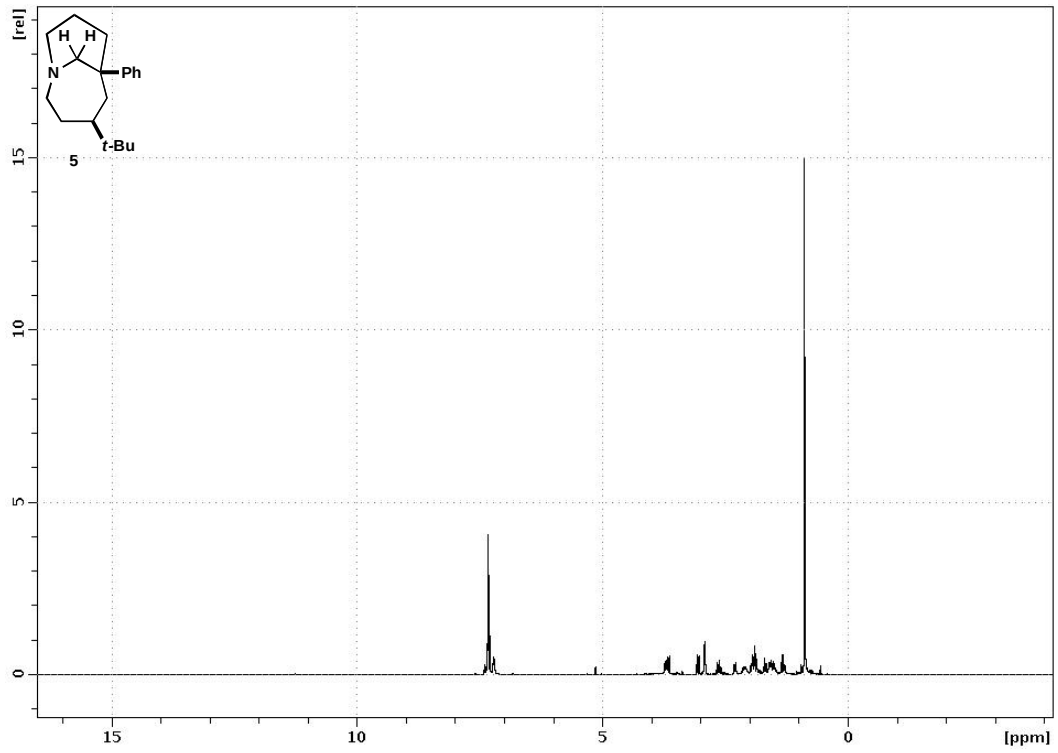
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H
N
Ph
t-Bu
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5
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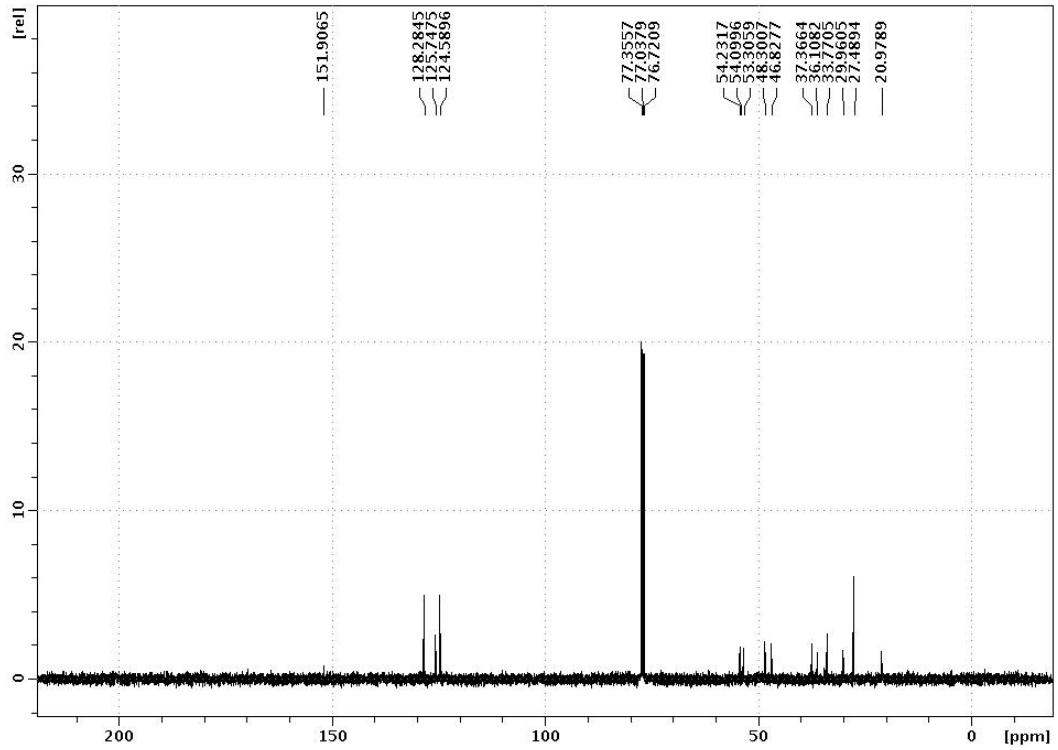
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37.3664
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33.7705
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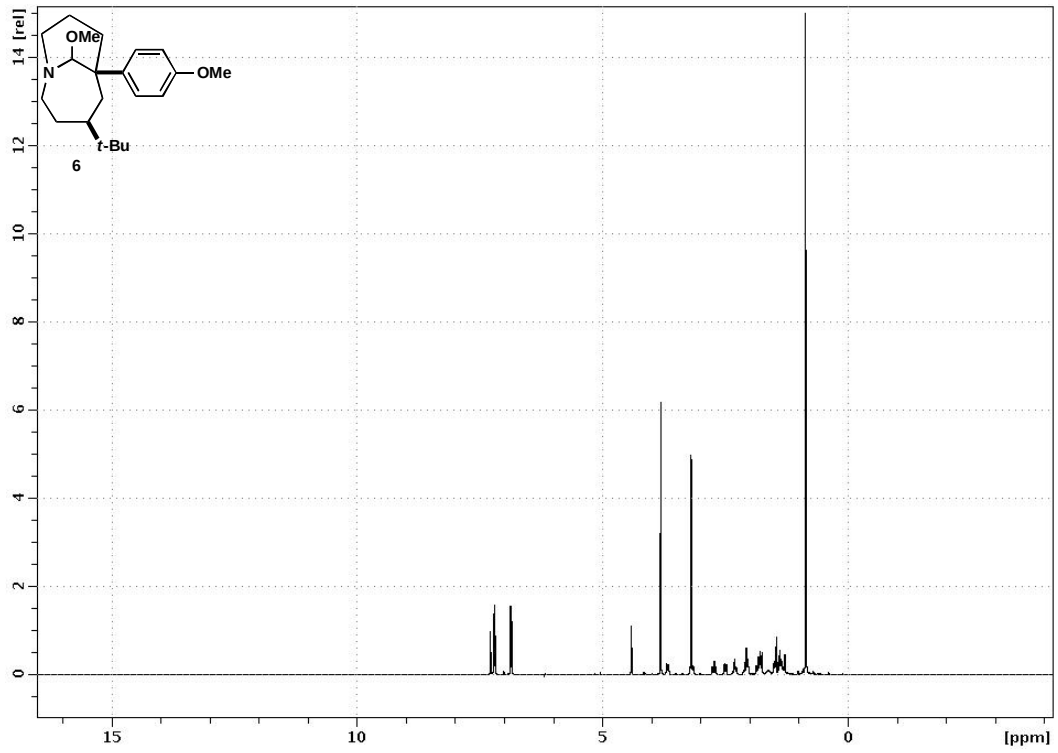
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OMe
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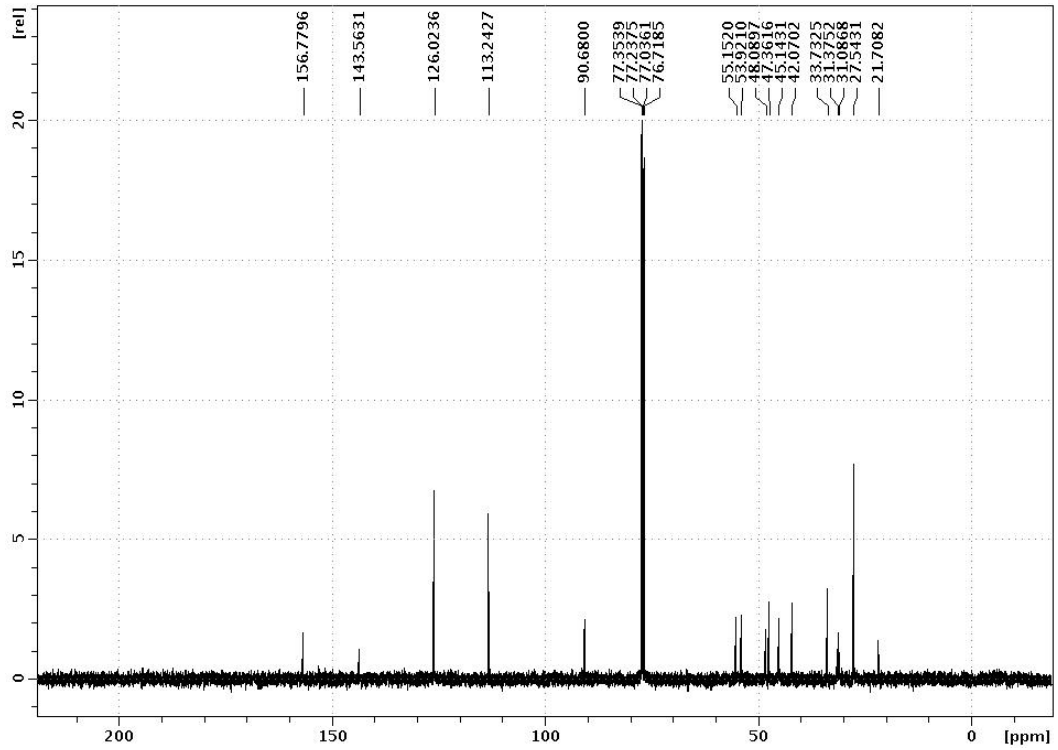
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47.3616
45.1431
42.0702
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20
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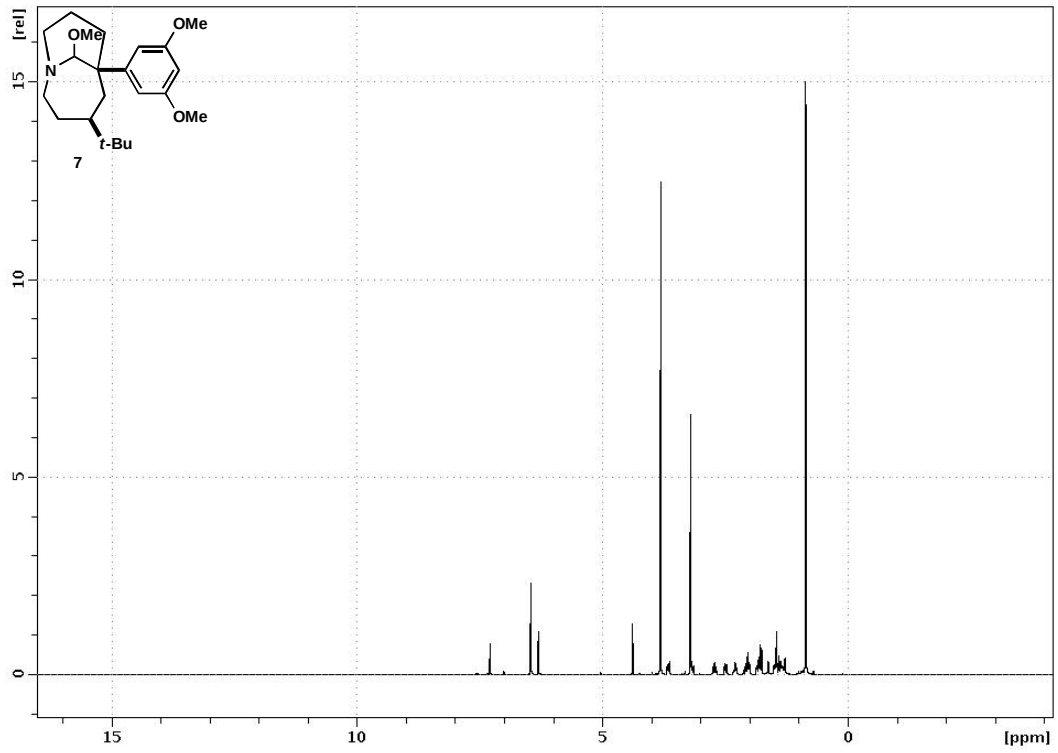
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OMe
OMe
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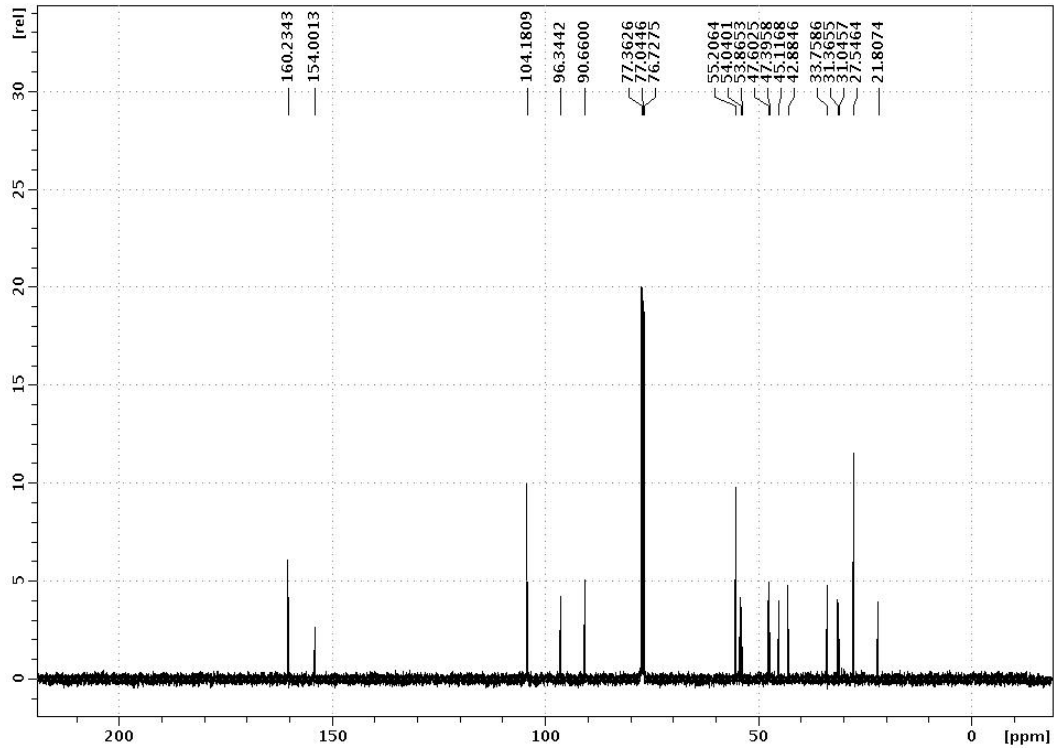
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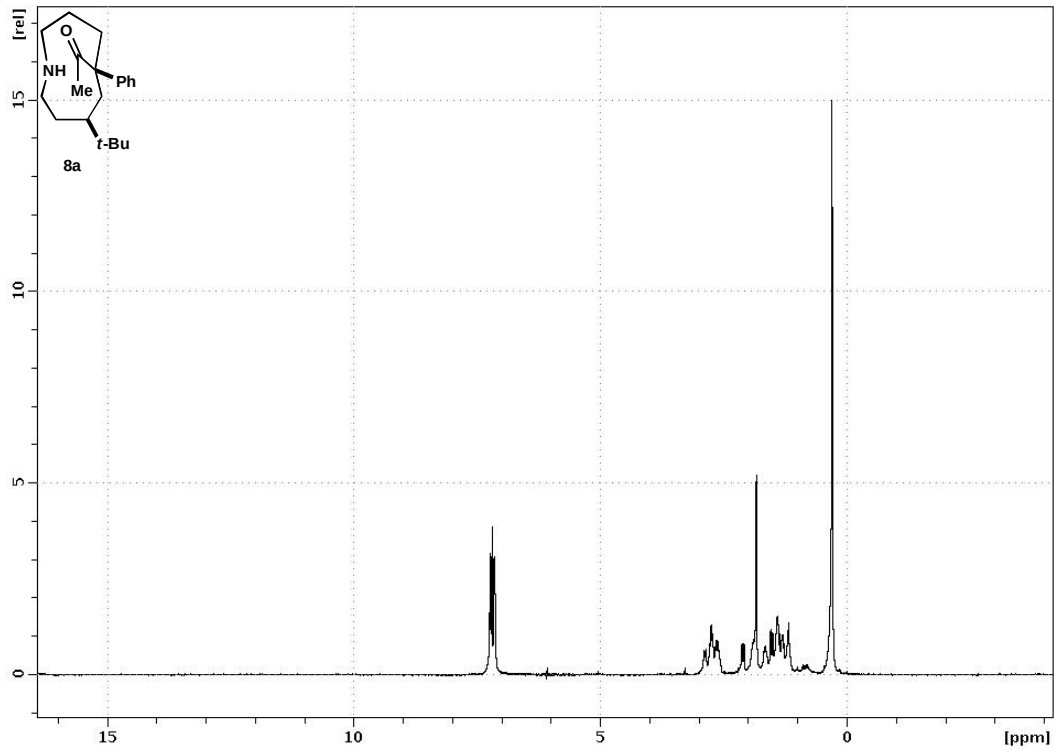
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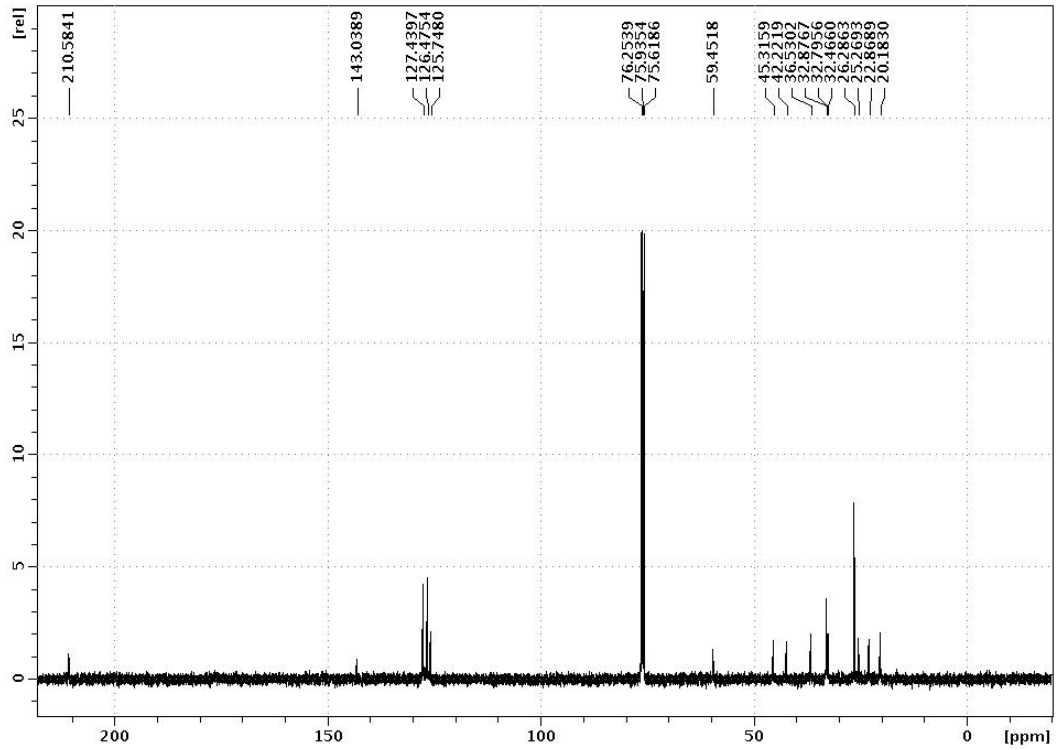
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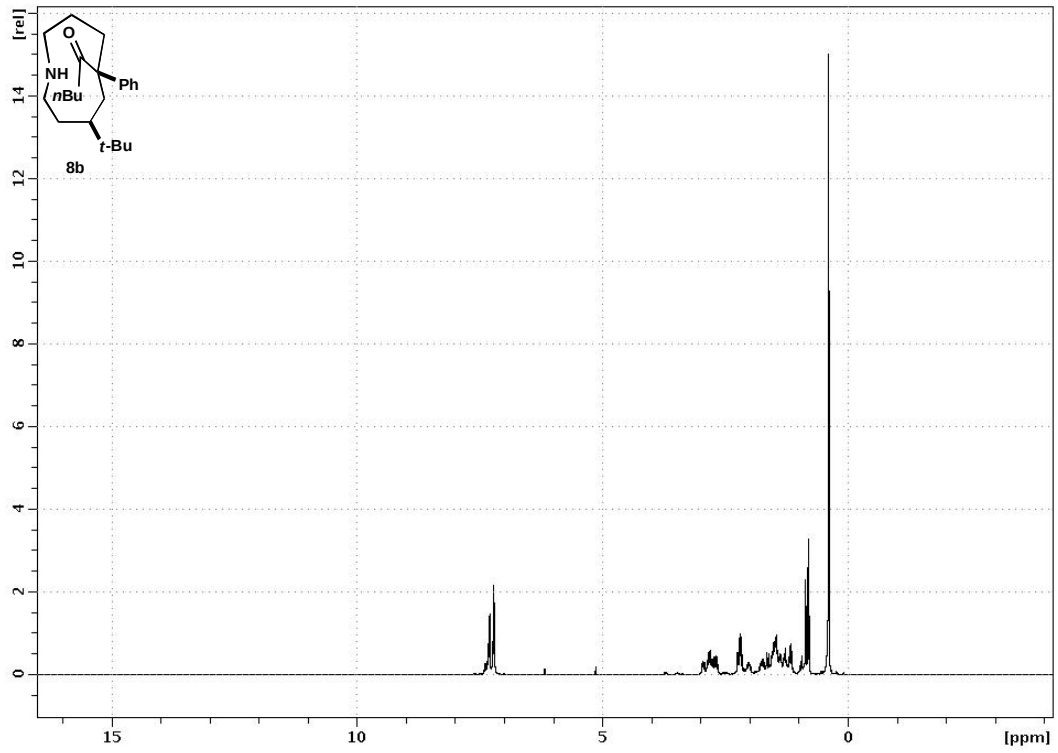
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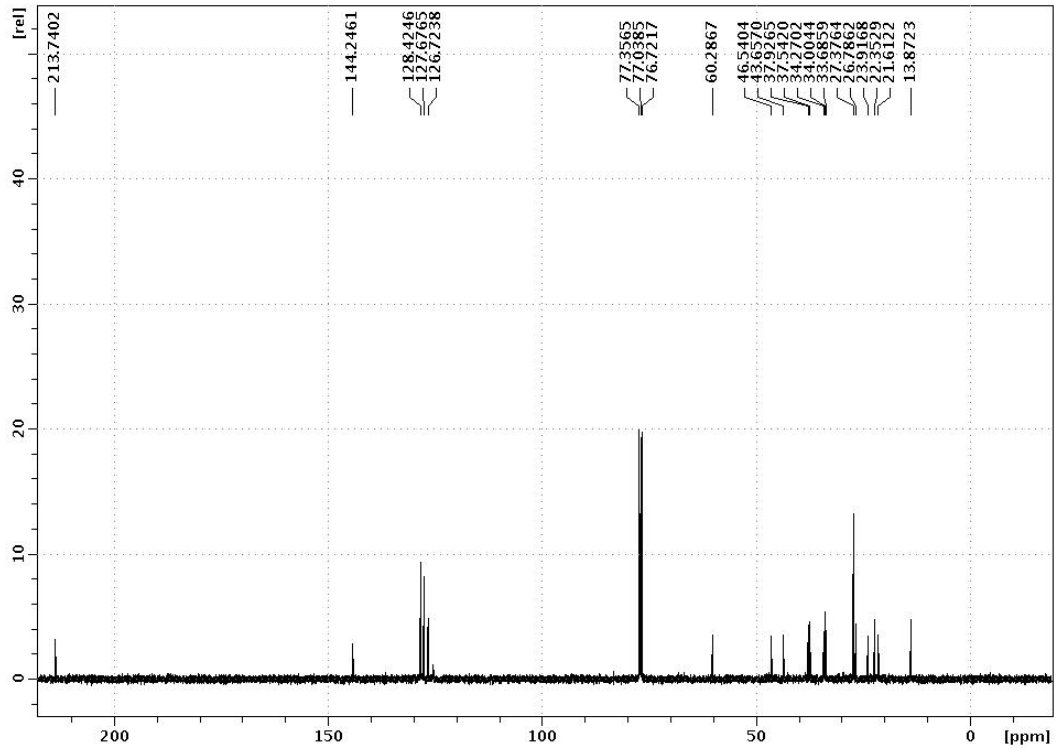
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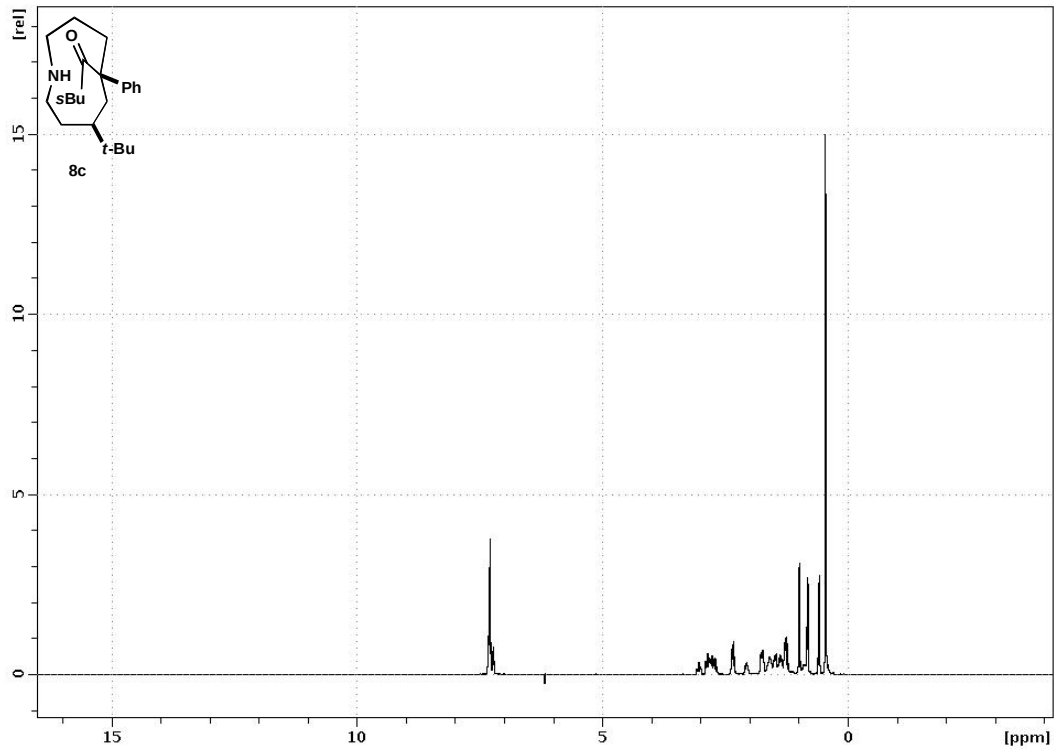
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8c
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10
5
0
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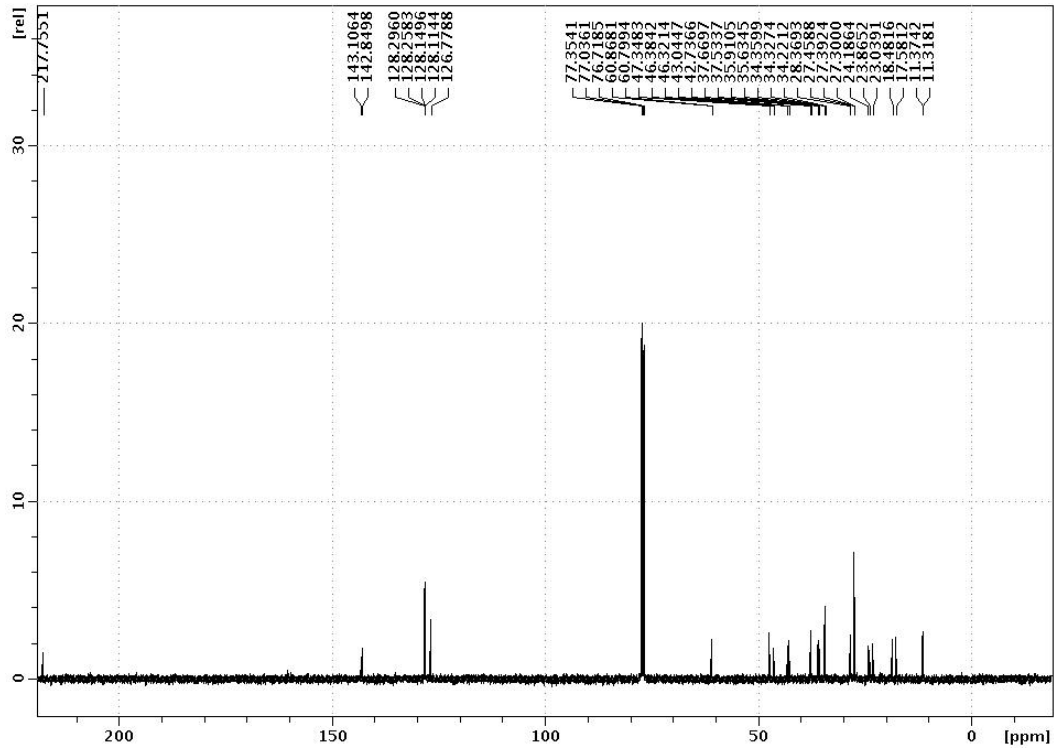
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142.8498
128.2960
128.2583
128.1496
128.1144
126.7788
77.3541
77.0361
76.7185
60.9681
47.3483
46.3843
46.3214
43.0447
42.7366
37.6697
37.5337
35.9105
35.6345
34.3599
34.3274
34.2212
28.3693
27.4588
27.3924
27.3000
24.1864
23.0391
18.4816
17.5815
11.3742
11.3181
30
20
10
0
200
150
100
50
0
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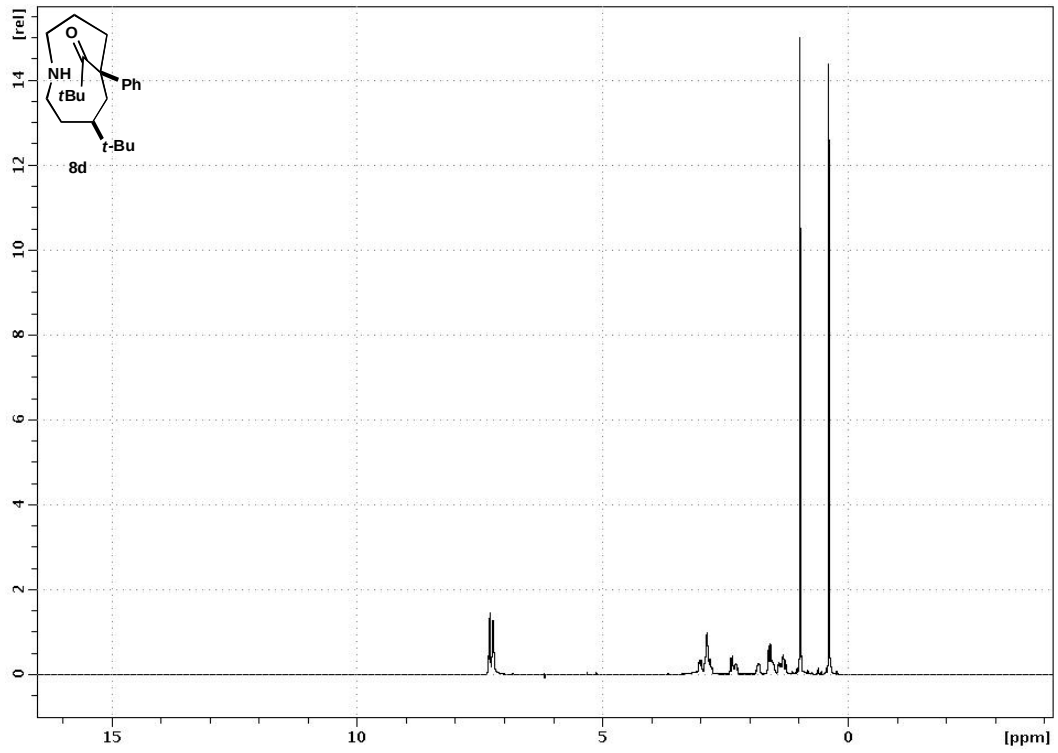
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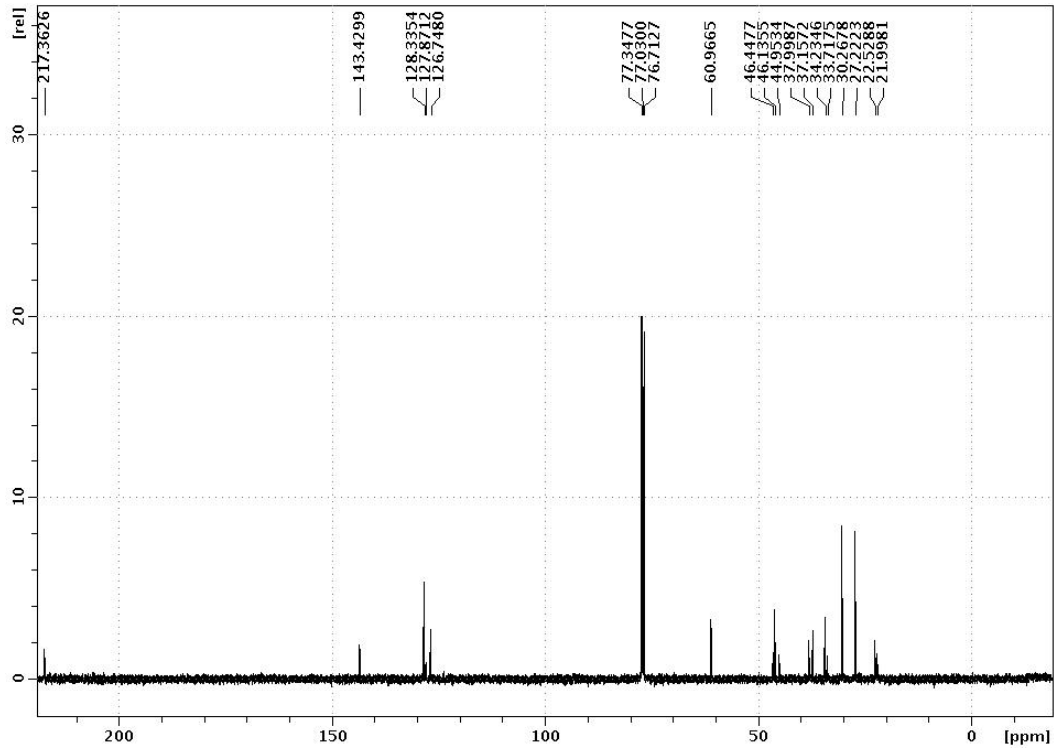
O
NH
tBu
Ph
t-Bu
8d
[ppm]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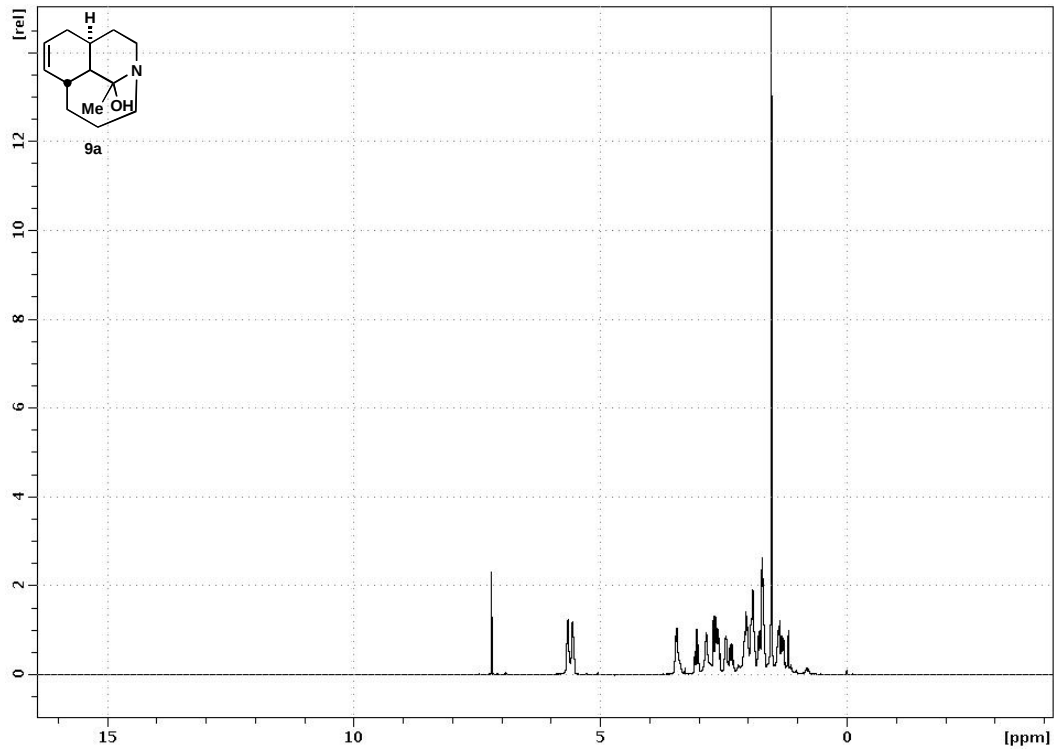
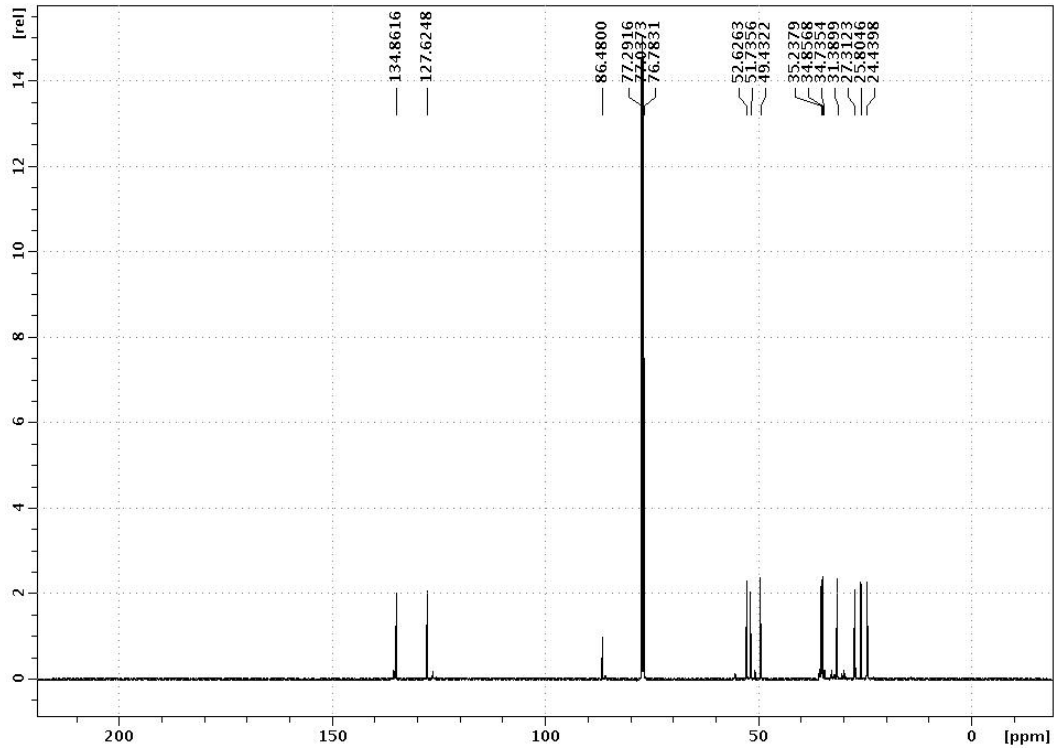
127.8712
126.7480
77.3477
77.0300
76.7127
60.9665
46.4477
46.1355
44.9534
37.9987
37.1572
34.2346
33.7175
30.2678
27.2223
22.5288
21.9981
[ppm]


H
N
Me
OH
9a
[rel]
0
2
4
6
8
10
12
15
10
5
0
[ppm]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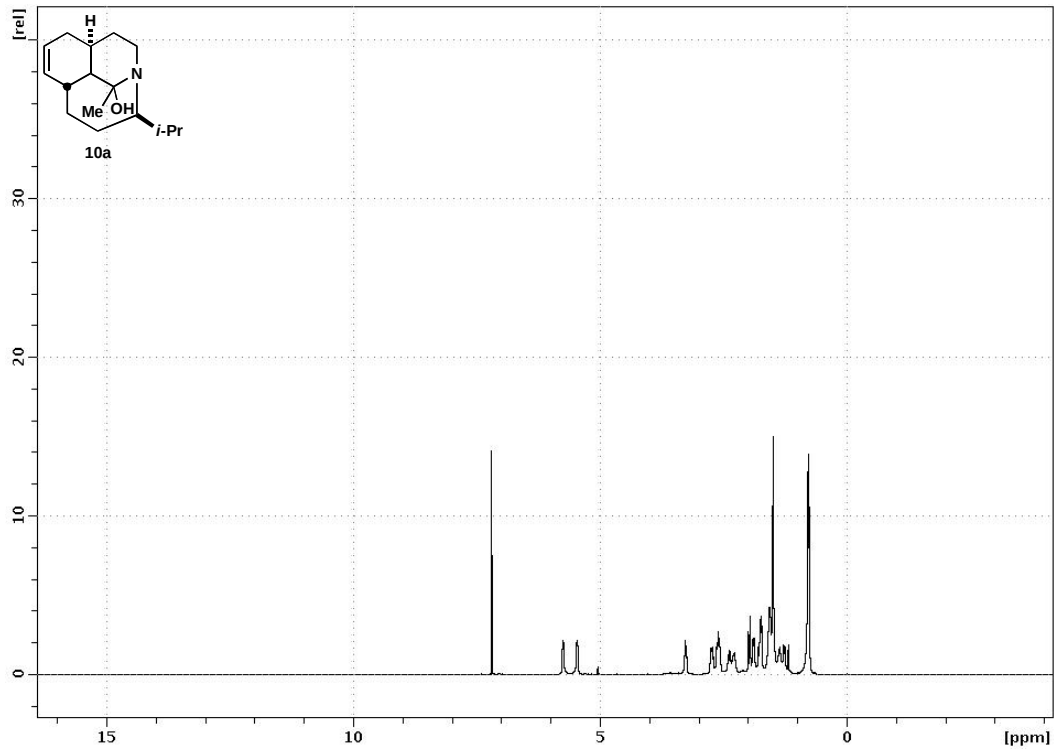
86.4800
77.2916
77.0373
76.7831
53.6263
51.7356
49.4322
35.2379
34.9368
34.6358
31.3894
27.3123
25.5804
24.4398
[rel]
0
2
4
6
8
10
12
14
200
150
100
50
0
[ppm]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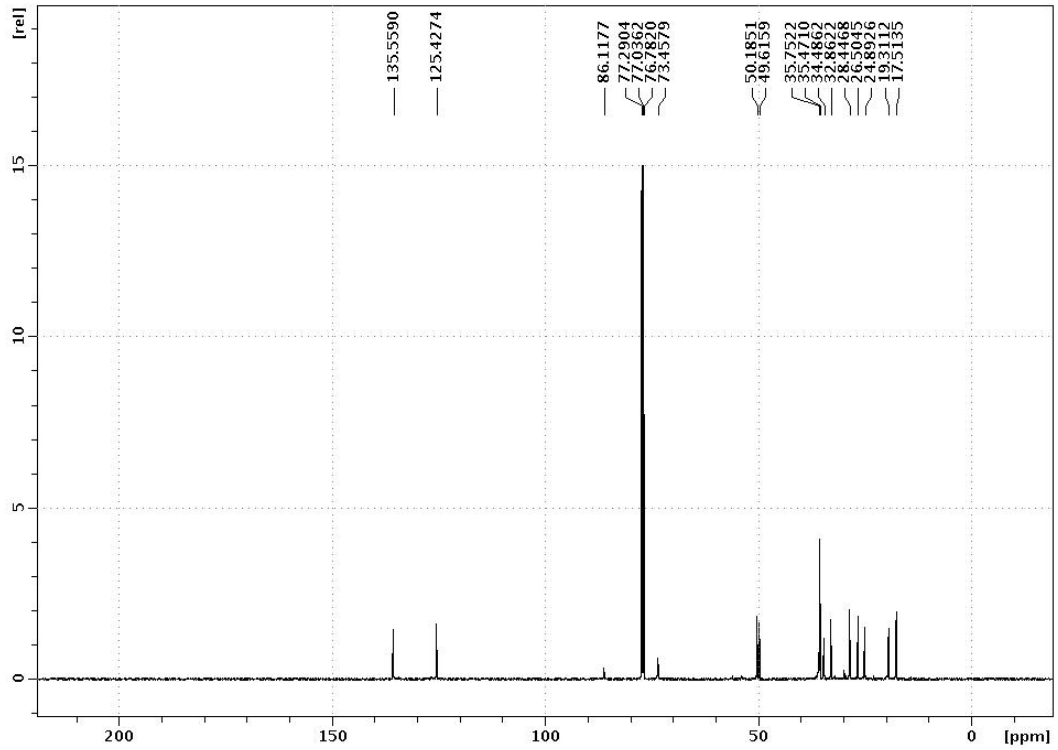
H
N
Me
OH
i-Pr
10a
30
20
10
0
15
10
5
0
[ppm]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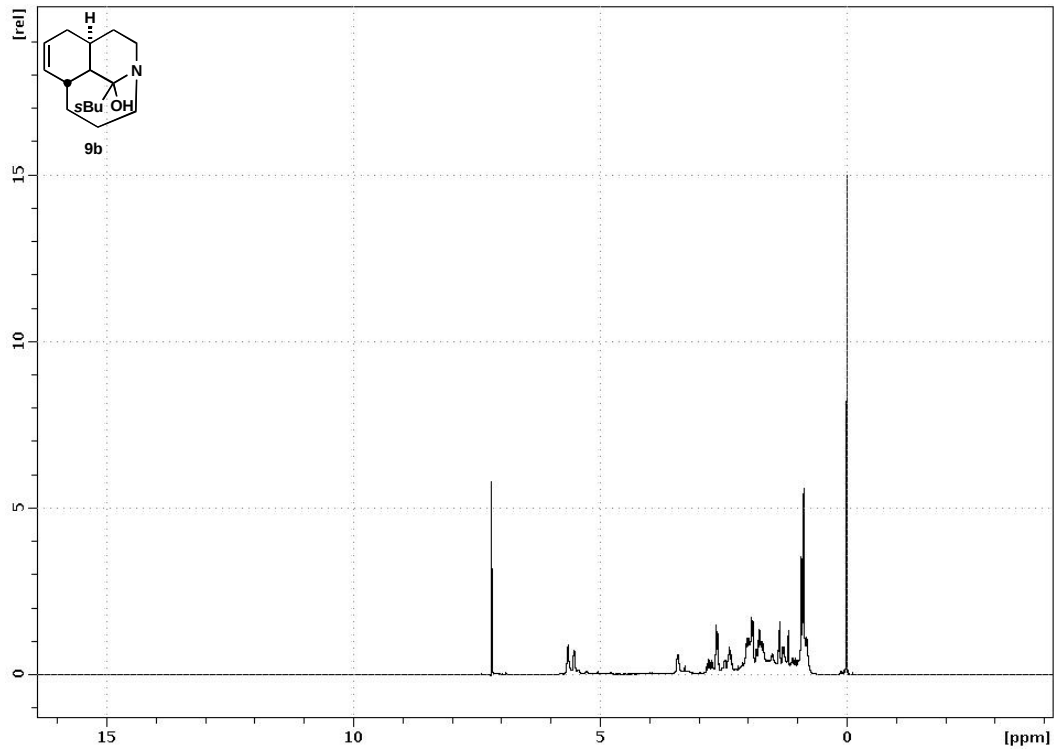
86.1177
77.2904
77.0362
76.7820
73.4579
50.1851
49.6159
35.7522
33.4710
33.4862
32.8622
28.4468
26.5045
24.8926
19.3112
17.5135
15
10
5
0
200
150
100
50
0
[ppm]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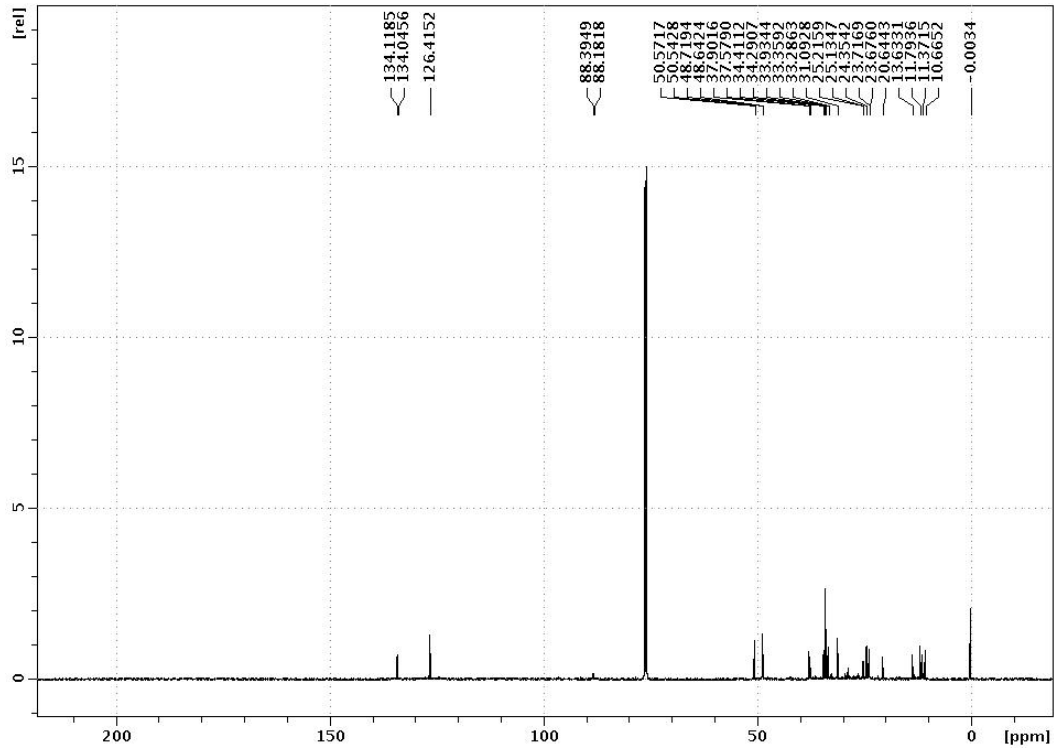
H
N
sBu
OH
9b
15
10
5
0
15
10
5
0
[ppm]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134.0456
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88.1818
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48.7194
48.6424
37.9016
37.5790
34.4112
34.2907
33.3544
33.3362
33.2863
31.6928
25.2159
25.1347
24.3542
23.7169
23.6760
20.6443
13.6331
11.7936
11.3715
10.6652
0.0034
15
10
5
0
200
150
100
50
0
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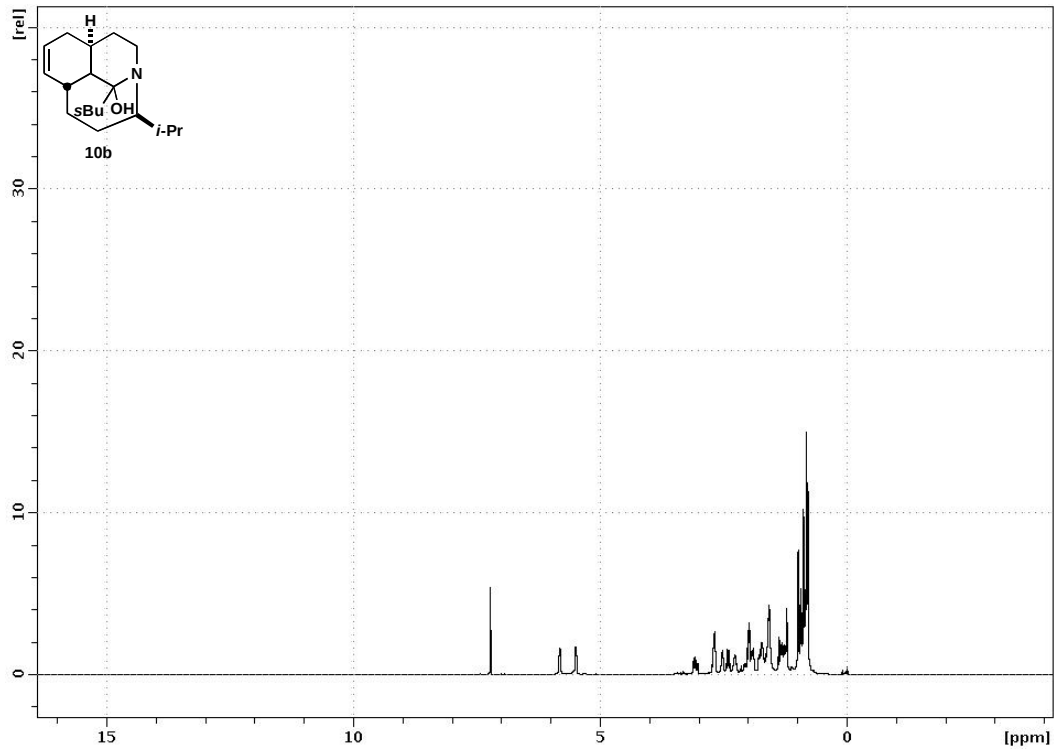
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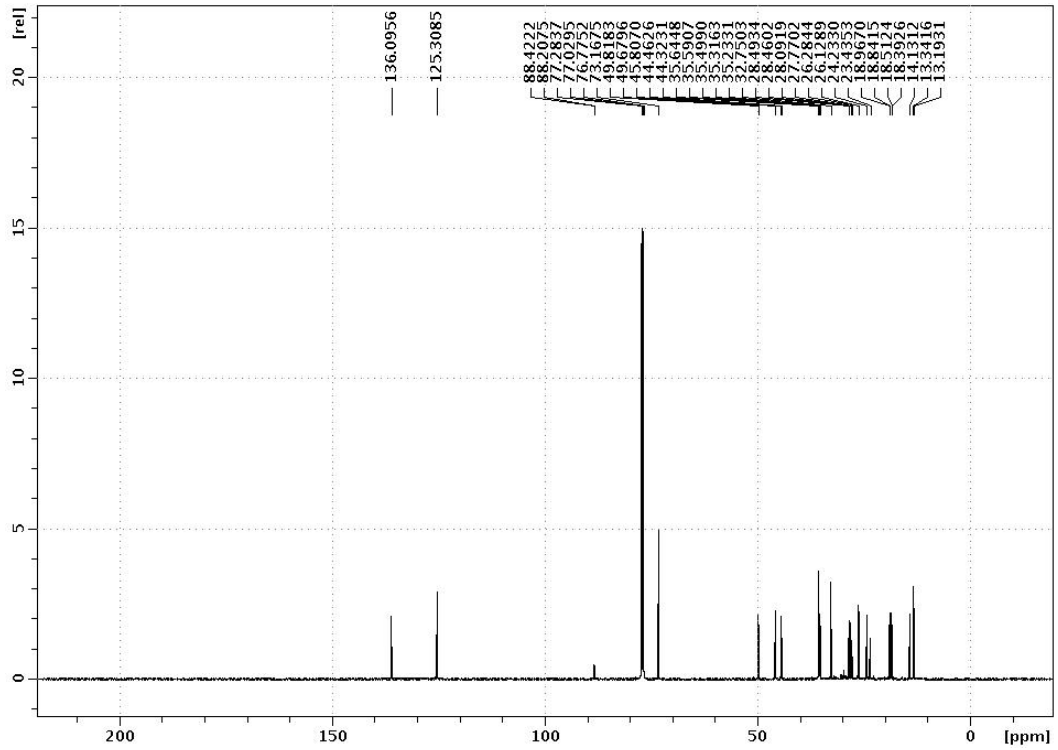
H
N
sBu
OH
i-Pr
10b
30
20
10
0
15
10
5
0
[ppm]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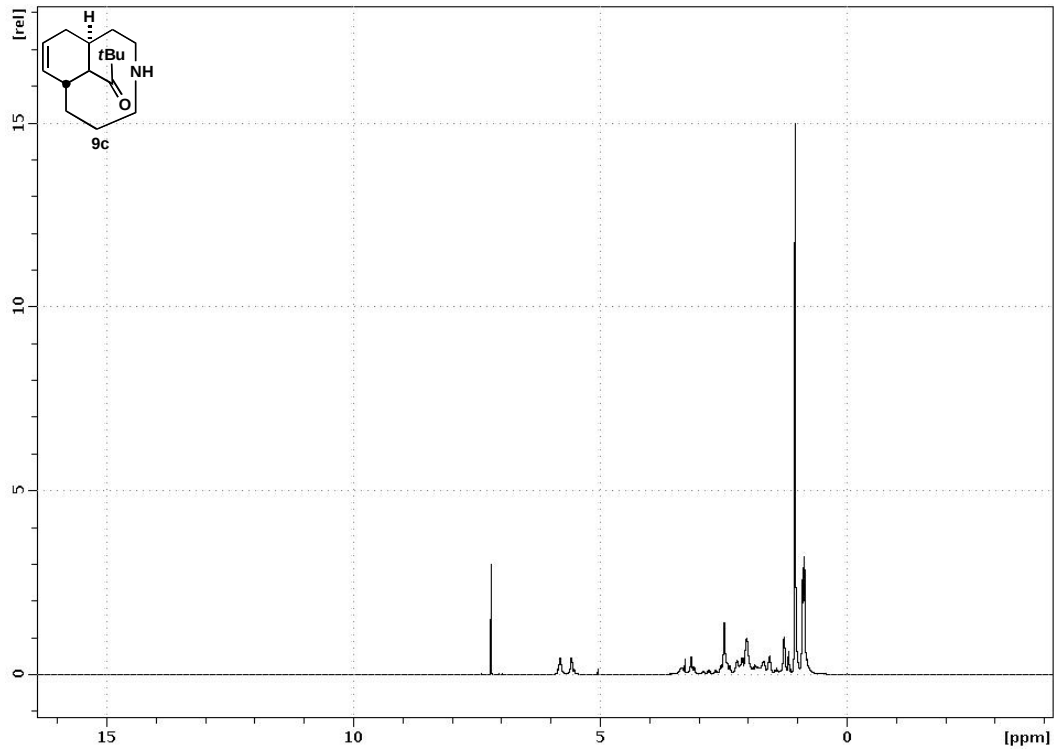
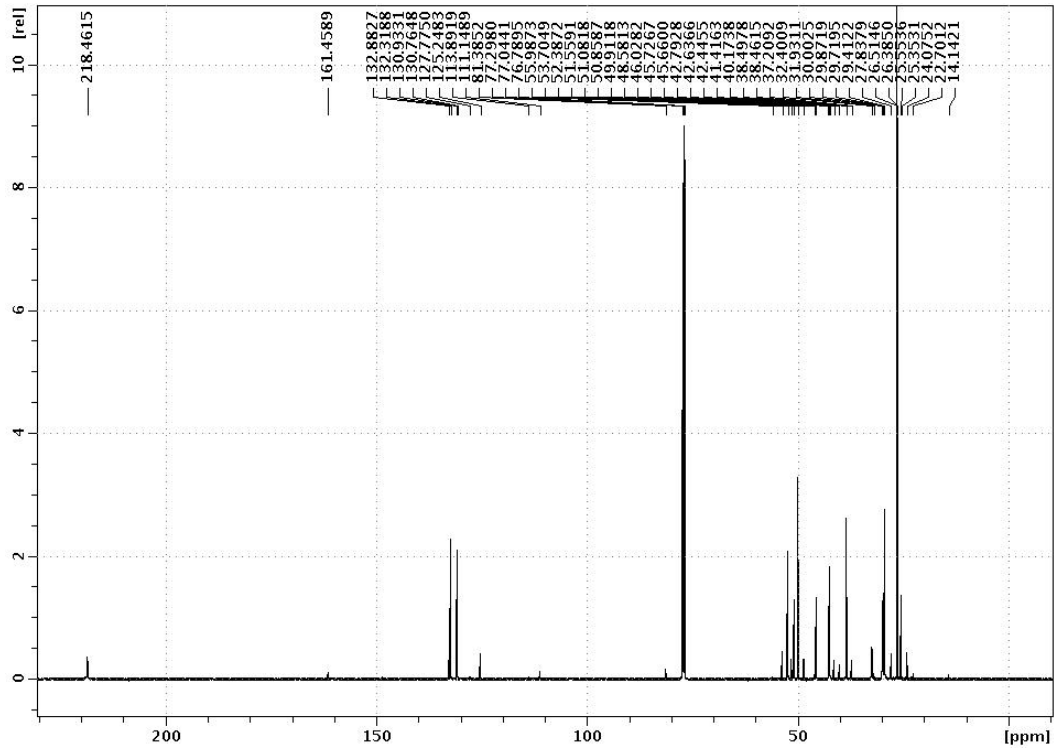
88.2075
77.6837
77.0795
76.7572
73.1672
49.8183
49.6796
45.8070
44.4626
44.3231
35.6448
35.5907
35.4990
35.3163
35.2331
32.7503
28.4934
28.4602
28.0919
27.7702
26.7844
24.1330
23.4359
18.9670
18.8415
18.5124
18.3926
14.1312
13.3416
13.1931
20
15
10
5
0
200
150
100
50
0
[ppm]


H
tBu
NH
O
9c
[rel]
0
5
10
15
15
10
5
0
[ppm]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132.3188
130.9331
130.7648
127.7750
125.2483
113.8919
111.1489
81.3852
77.2980
77.0441
76.7895
55.9873
53.7049
52.3872
51.5591
51.0818
49.8587
48.5813
46.0282
45.7267
45.5600
42.7928
42.6366
42.4455
41.4163
40.1738
38.4978
38.4615
32.2092
32.4009
31.9311
30.0025
29.8719
28.4195
27.8372
26.5146
26.3850
25.5536
25.3531
24.0752
22.7012
14.1421
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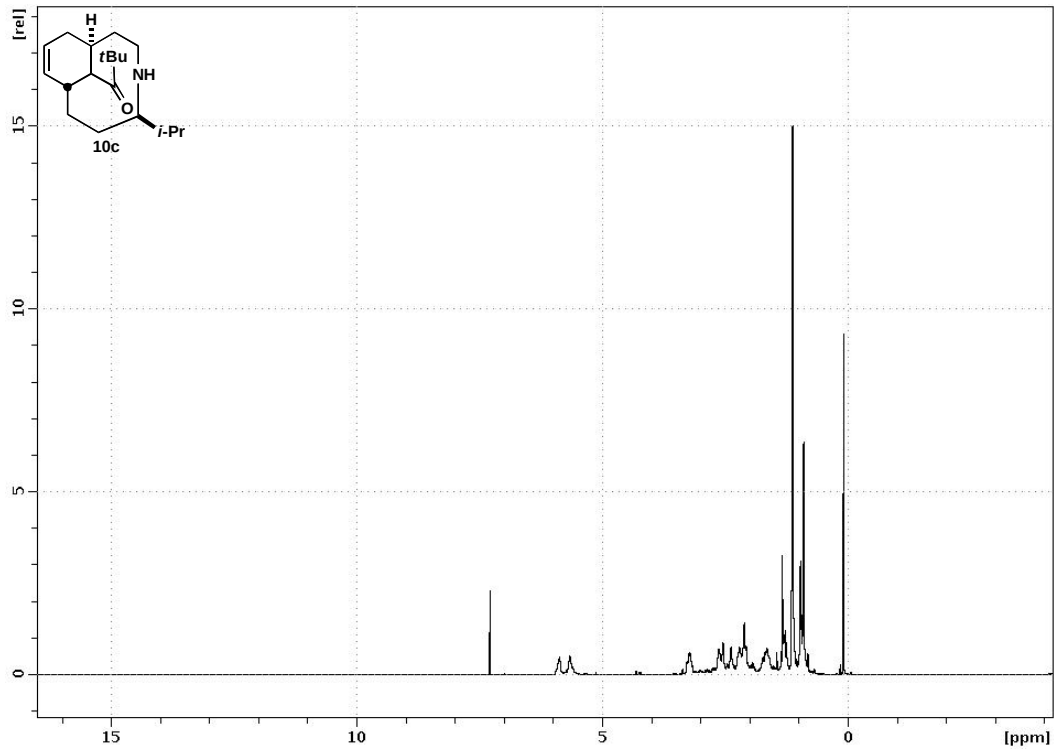
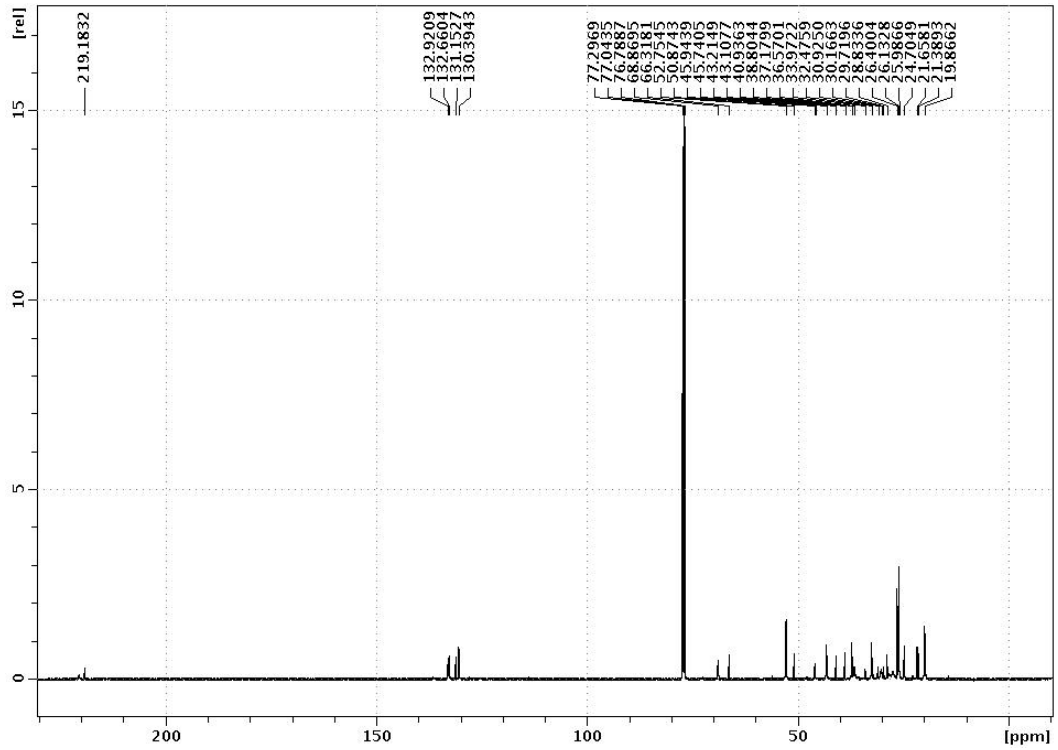
0
2
4
6
8
10
200
150
100
50
[ppm]


H
tBu
NH
O
i-Pr
10c
[rel]
15
10
5
0
15
10
5
0
[ppm]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130.3943
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77.0435
76.7887
68.8695
66.3181
52.7545
50.8743
45.9439
45.7405
43.2149
43.1077
40.9363
38.8044
37.1709
33.9701
33.4752
30.9250
30.1663
29.7196
28.8336
26.4004
26.1328
25.9866
24.7049
21.6581
21.3893
19.8662
[rel]
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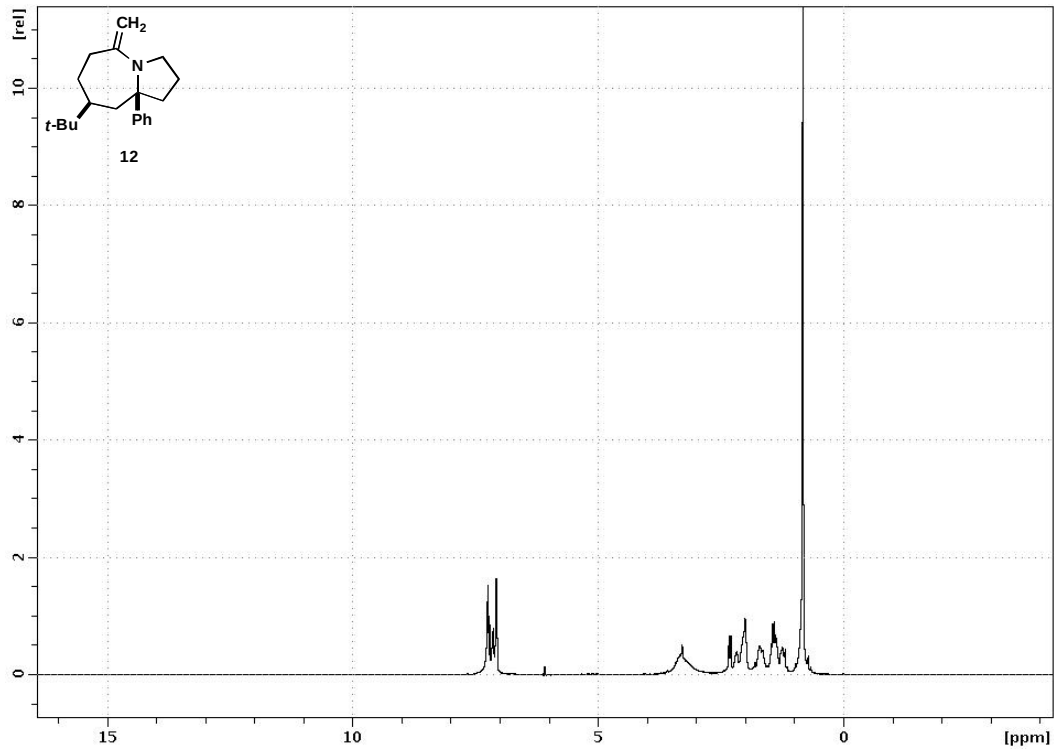
10
5
0
200
150
100
50
[ppm]


CH2
N
t-Bu
Ph
12
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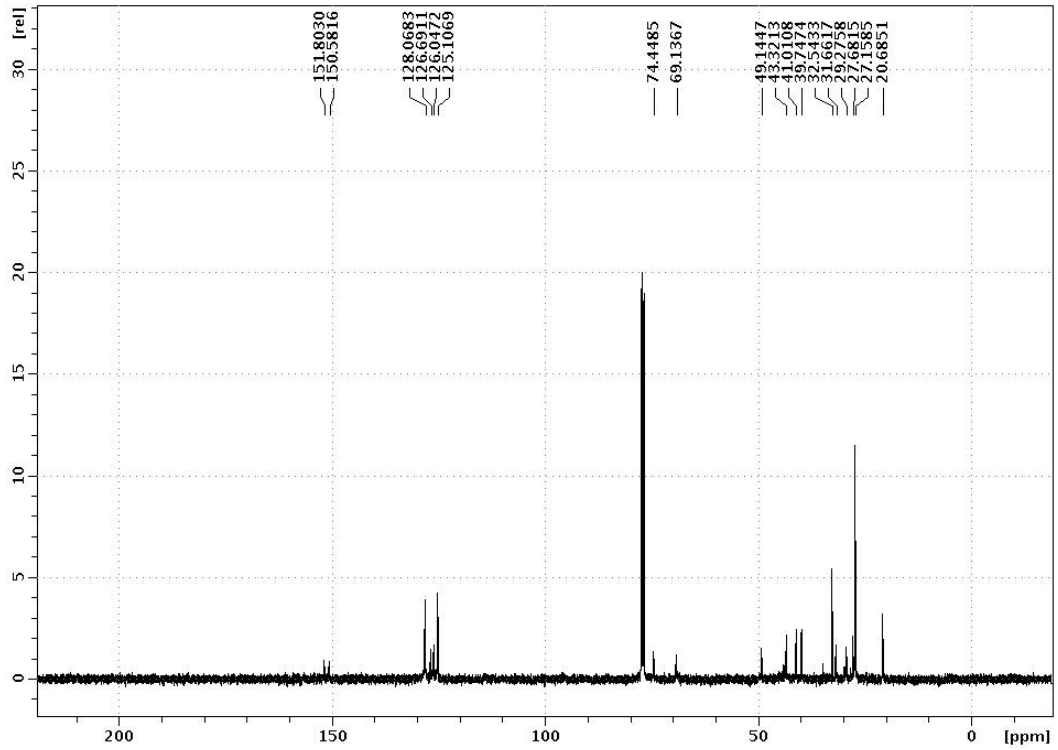
[ppm]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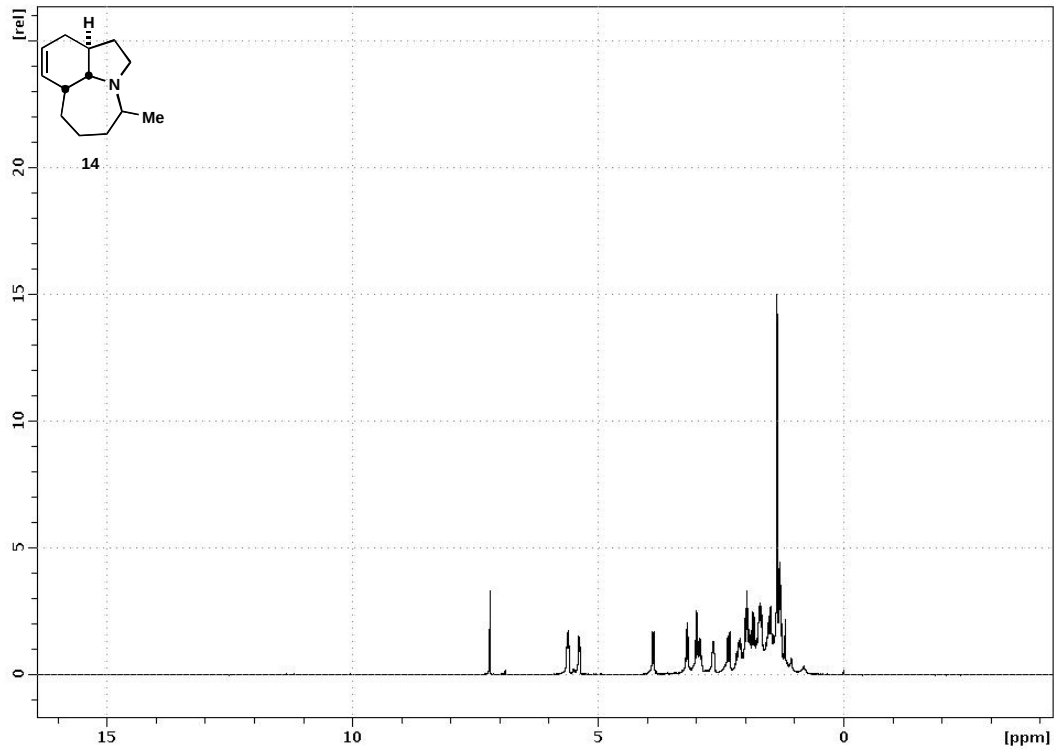
128.0683
126.6911
126.0472
125.1069
74.4485
69.1367
49.1447
43.3213
41.0108
38.7474
32.5433
31.6617
29.2758
27.6815
27.1585
20.6851
[rel]
[ppm]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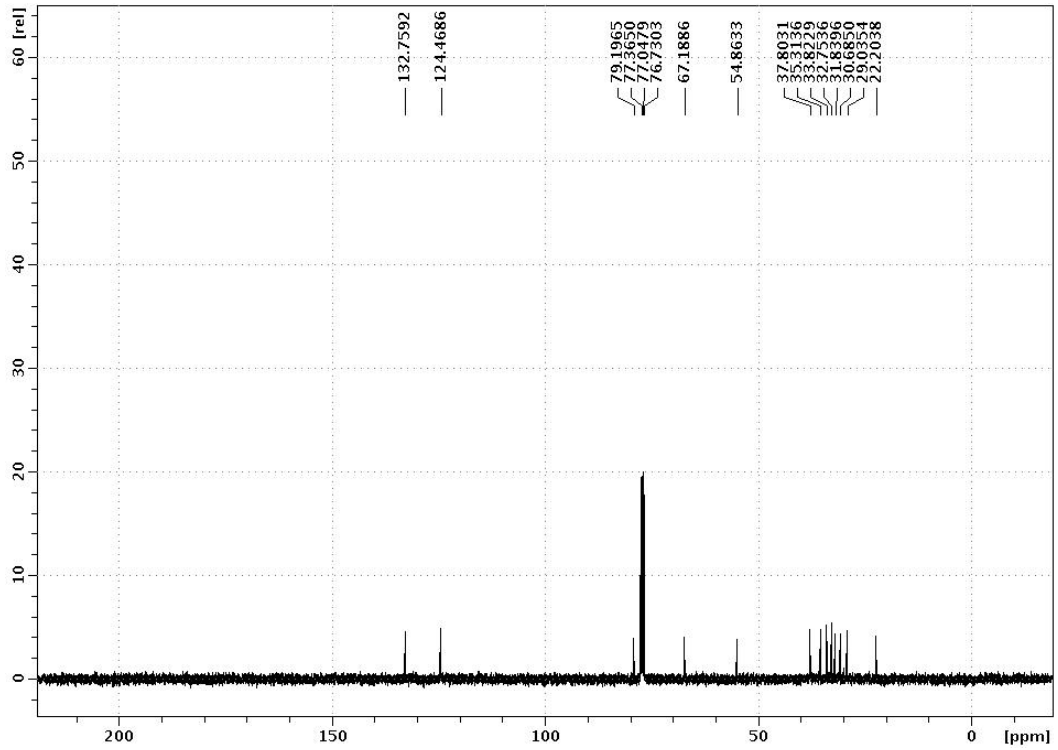
H
N
Me
14
0
5
10
15
20
15
10
5
0
[ppm]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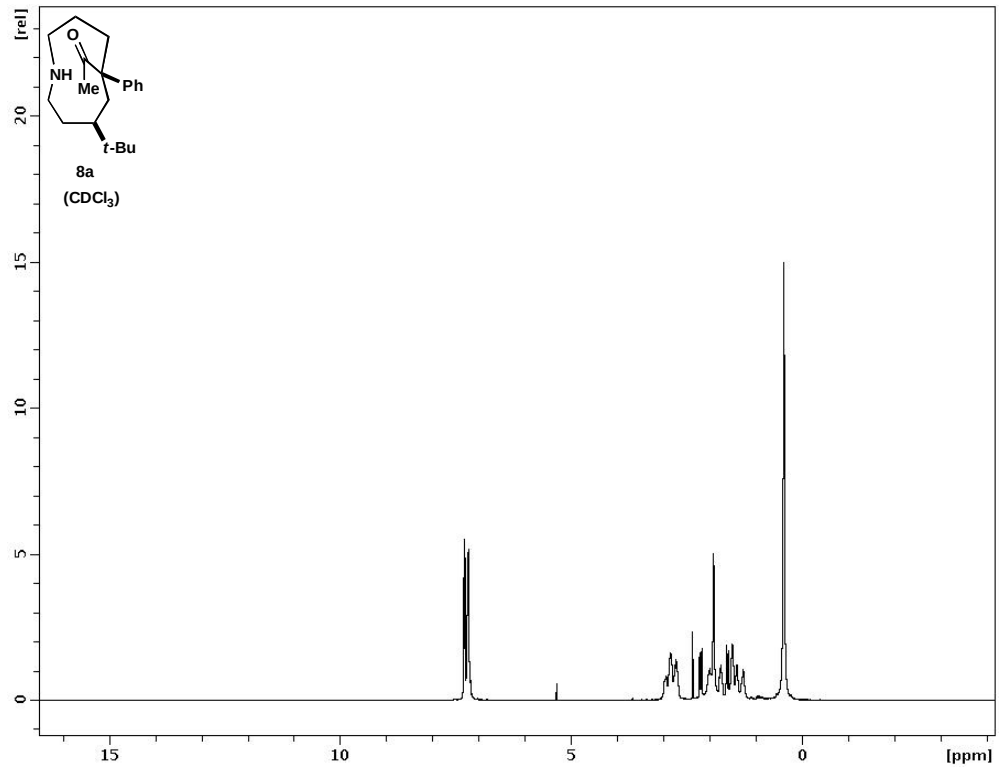
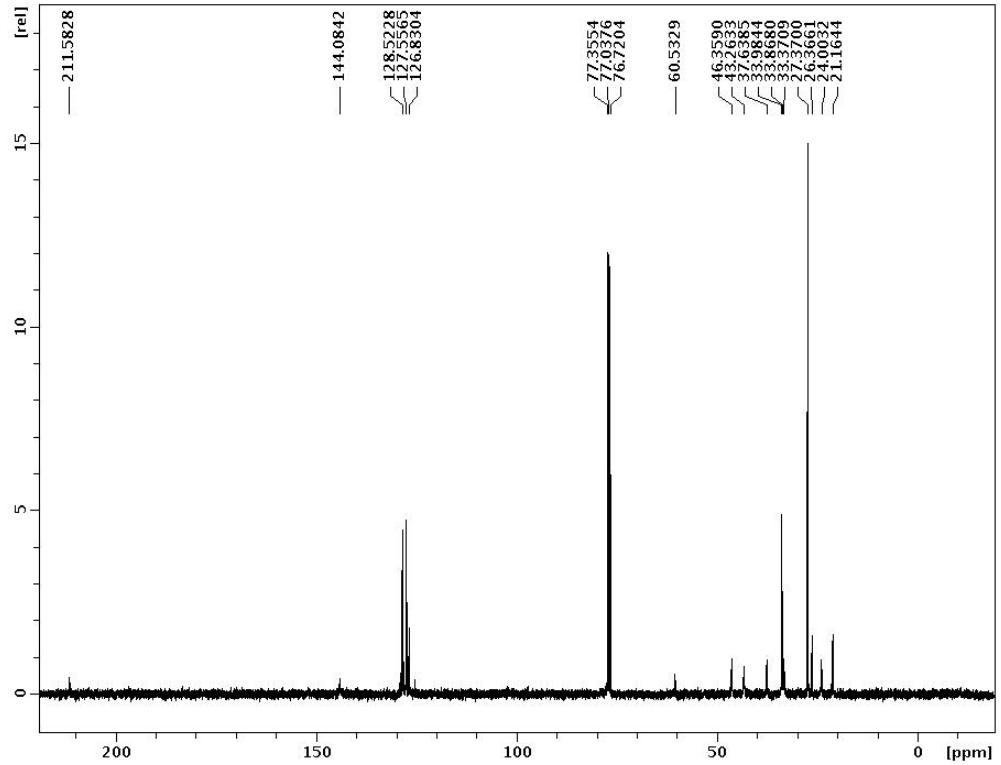
77.0479
76.7303
67.1886
54.8633
37.8031
33.3136
33.8229
32.7536
31.8396
30.0850
29.0354
22.2038
0
10
20
30
40
50
60
200
150
100
50
0
[ppm]


[rel]
O
NH
Me
Ph
t-Bu
8a
(CDCl3)
0
5
10
15
20
15
10
5
0
[ppm]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77.0376
76.7204
60.5329
46.3590
43.2633
37.6385
33.9844
33.8680
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27.3700
26.3661
24.0032
21.1644
0
5
10
15
200
150
100
50
0
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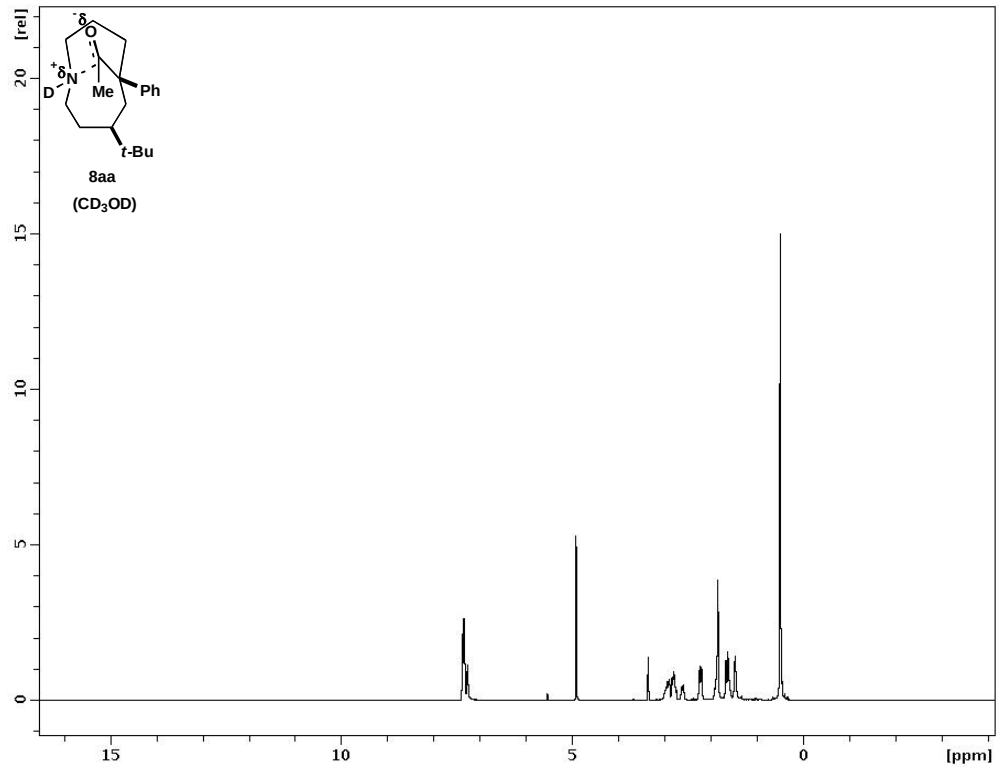
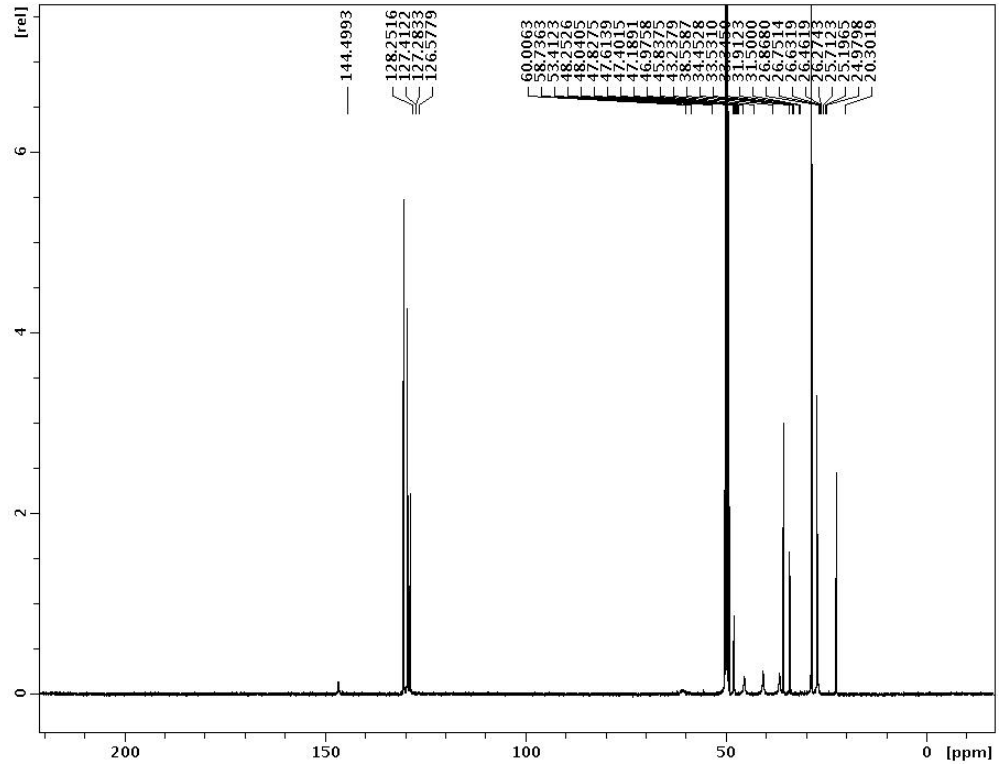

[rel]
20
15
10
5
0
15
10
5
0
[ppm]
δ-
O
δ+
N
D
Me
Ph
t-Bu
8aa
(CD3OD)


[rel]
6
4
2
0
200
150
100
50
0
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126.5779
60.0063
58.7383
53.4193
48.2526
48.0405
47.8275
47.6139
47.4015
47.1891
46.9758
45.8375
43.2379
38.5587
34.4528
33.5310
31.9123
31.5080
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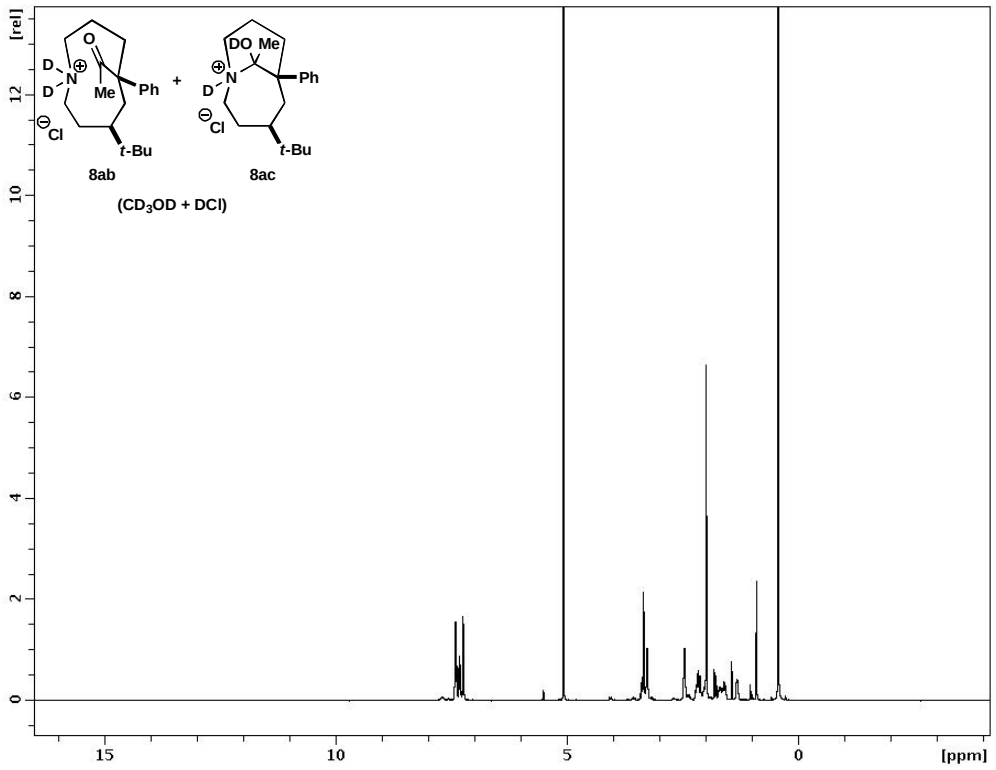
26.2743
25.7123
25.1965
24.9798
20.3019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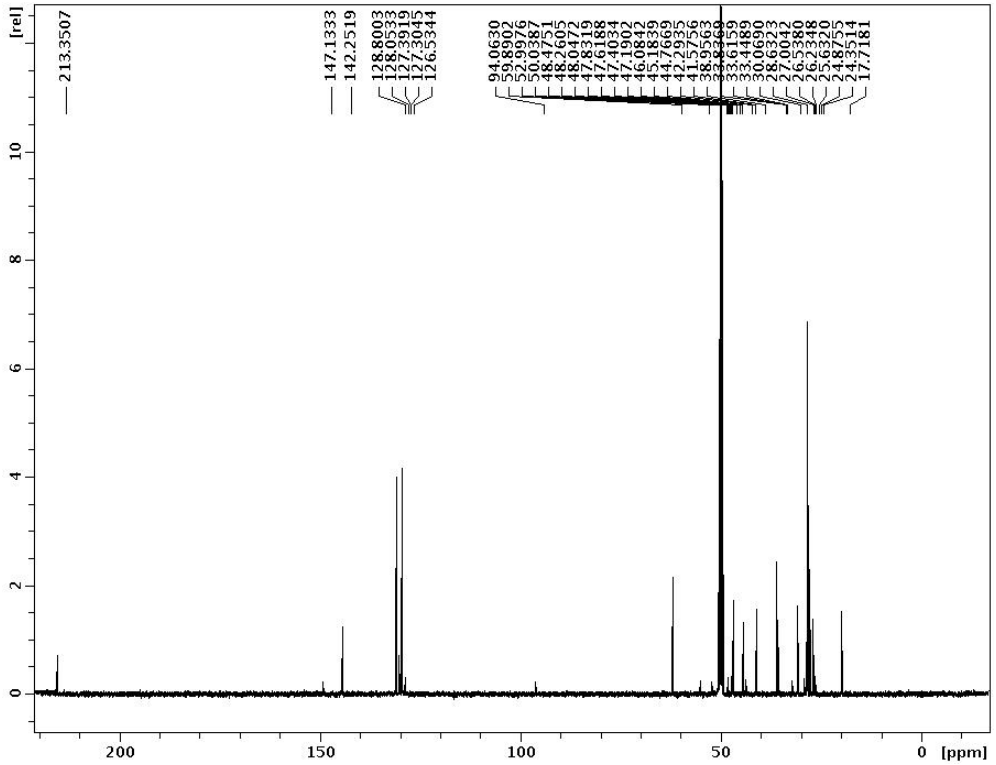
8ab
8ac
(CD3OD + DCl)
[ppm]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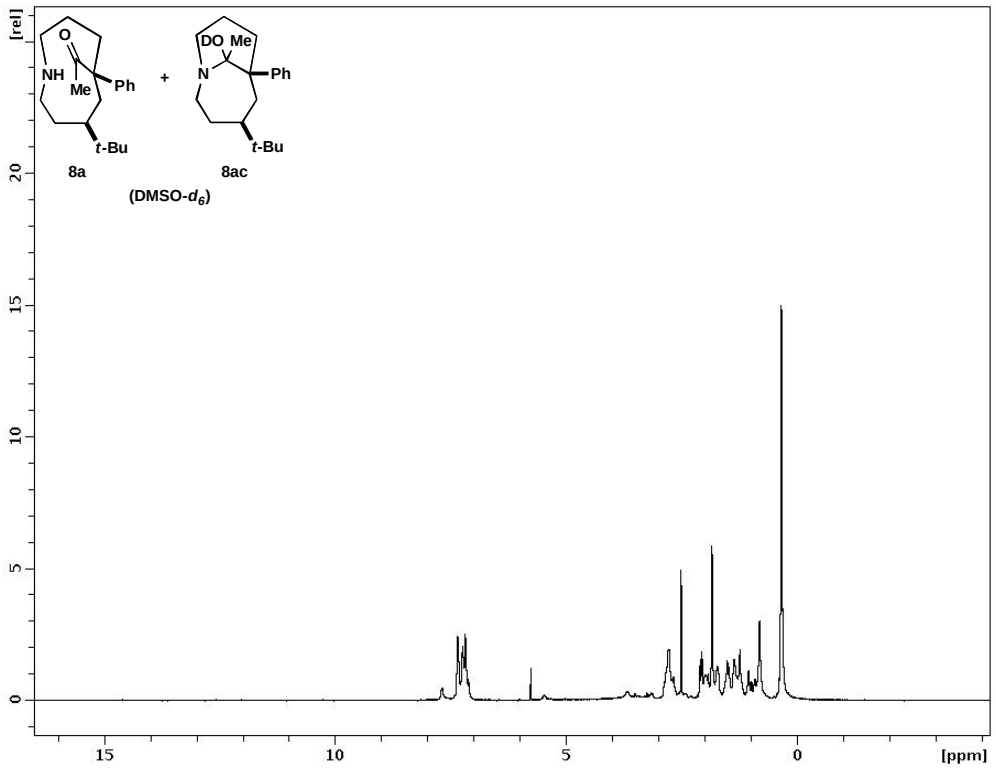
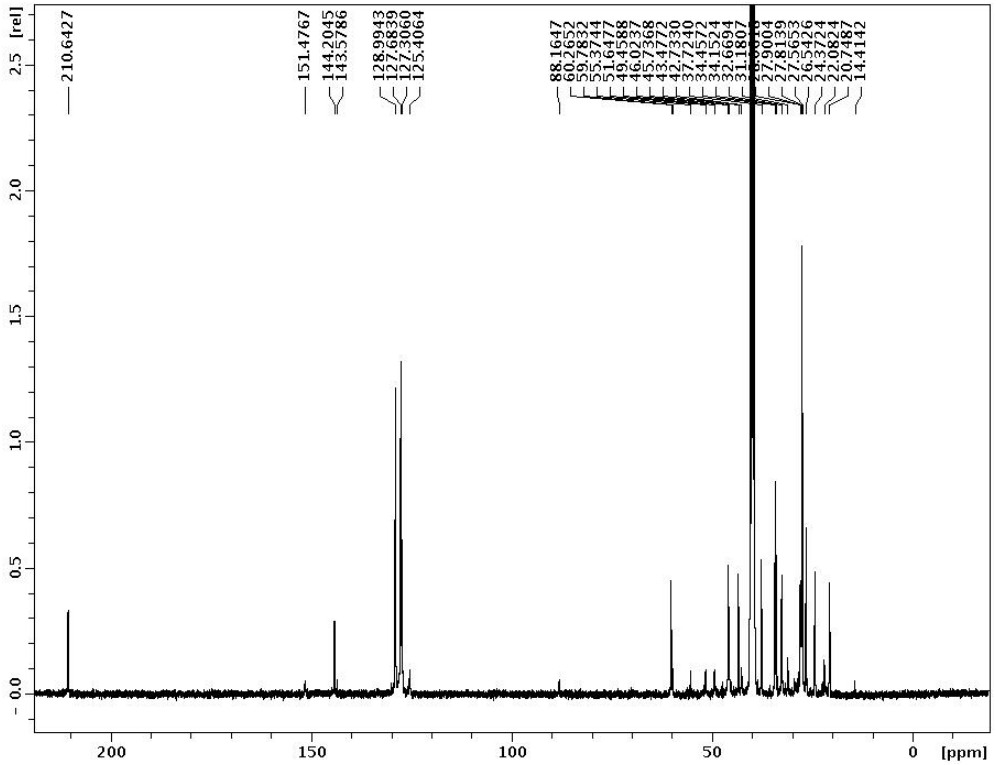
142.2519
128.8003
128.0533
127.3919
127.3045
126.5344
[ppm]


[rel]
O
NH
Me
Ph
t-Bu
8a
+
DO Me
N
Ph
t-Bu
8ac
(DMSO-d_6)
0
5
10
15
20
15
10
5
0
[ppm]


[rel]
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143.5786
128.9943
127.6839
127.3060
125.4064
88.1647
60.2652
59.7832
55.3744
51.6477
49.4588
46.0237
45.7398
43.7372
43.4340
37.7240
34.4572
34.1524
32.6694
31.1807
27.9004
27.8139
27.5653
26.5426
24.3724
22.0824
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2.0
2.5
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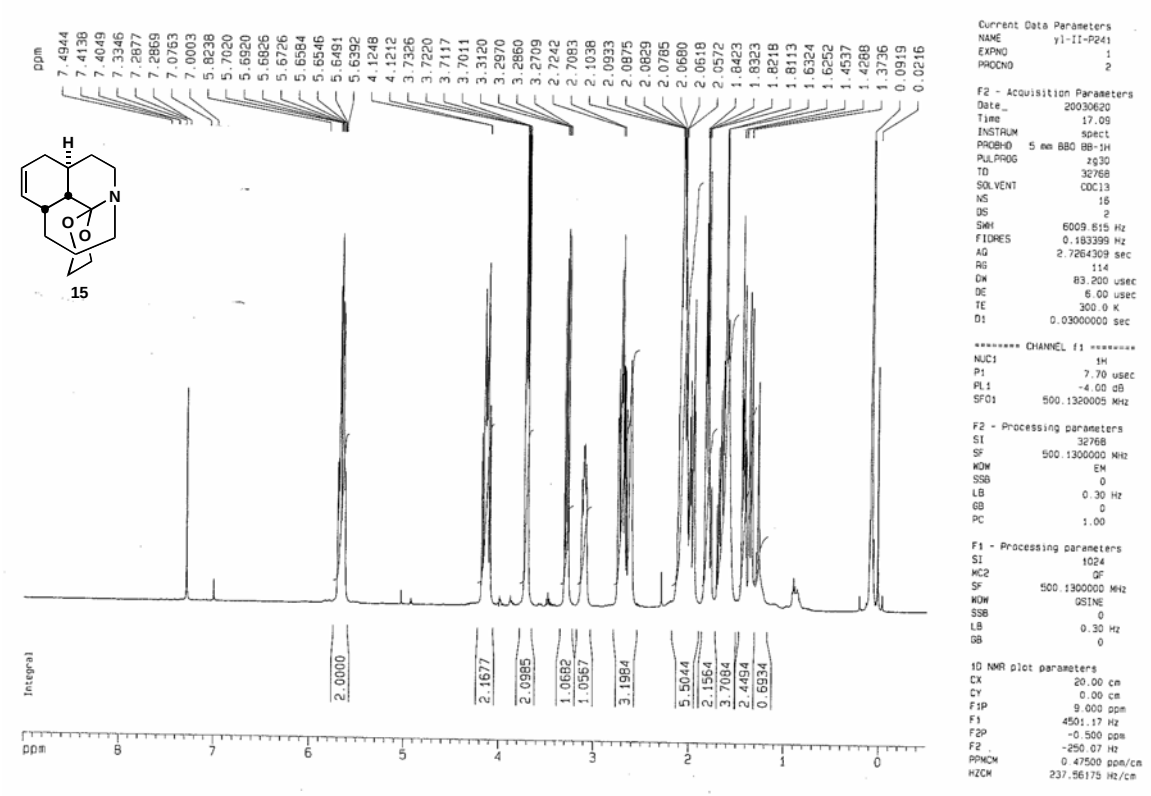
150
100
50
0
[ppm]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7.4049
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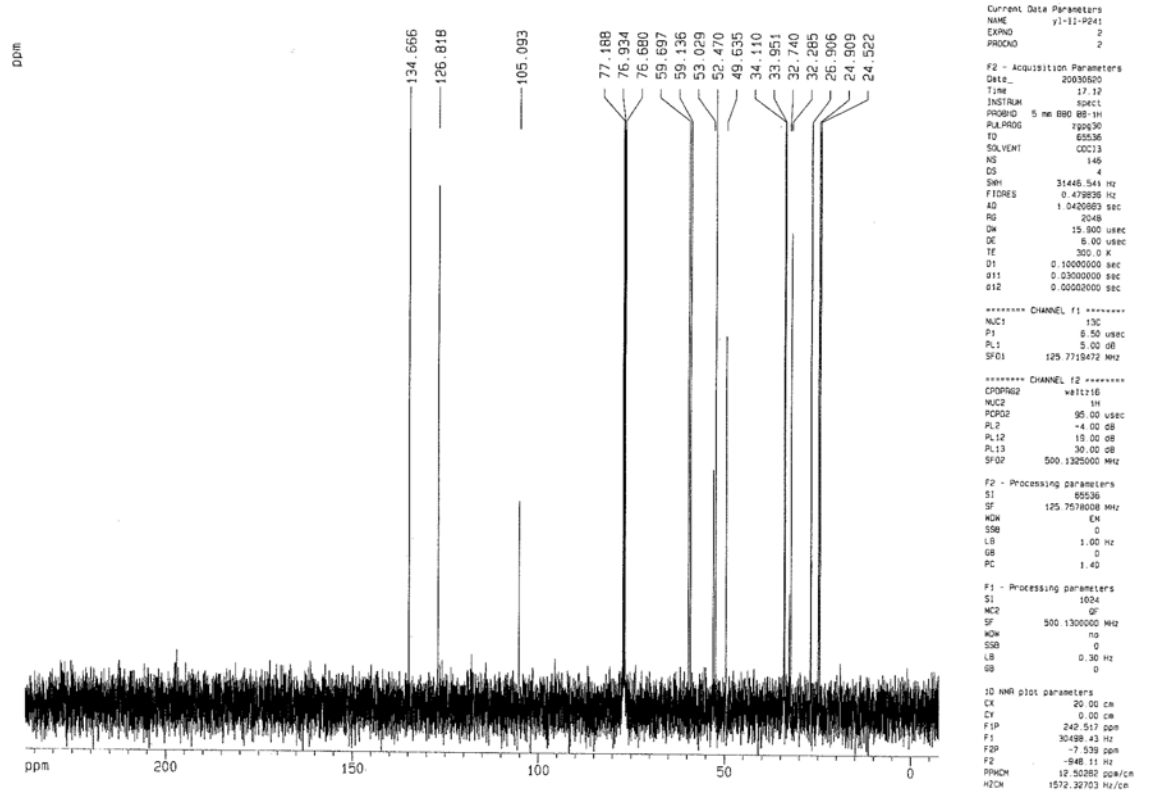
7.2877
7.2869
7.0763
7.0003
5.8238
5.7020
5.6920
5.6826
5.6726
5.6584
5.6546
5.6491
5.6392
4.1248
4.1212
3.7326
3.7220
3.7117
3.7011
3.3120
3.2970
3.2860
3.2709
2.7242
2.7083
2.1038
2.0933
2.0875
2.0829
2.0785
2.0680
2.0618
2.0572
1.8423
1.8323
1.8218
1.8113
1.6324
1.6252
1.4537
1.4288
1.3736
0.0919
0.0216
H
N
O
O
15
Integral
2.0000
2.1677
2.0985
1.0682
1.0567
3.1984
5.5044
2.1564
3.7084
2.4494
0.6934
ppm
8
7
6
5
4
3
2
1
0
Current Data Parameters
NAME yl-II-P241
EXPNO 1
PROCNO 2
F2 - Acquisition Parameters
Date_ 20030620
Time 17.09
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 6009.615 Hz
FIDRES 0.183399 Hz
AQ 2.7264309 sec
RG 114
DW 83.200 usec
DE 6.00 usec
TE 300.0 K
D1 0.03000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.70 usec
PL1 -4.00 dB
SFO1 500.1320005 MHz
F2 - Processing parameters
SI 32768
SF 500.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
F1 - Processing parameters
SI 1024
MC2 QF
SF 500.1300000 MHz
WDW QSINE
SSB 0
LB 0.30 Hz
GB 0
1D NMR plot parameters
CX 20.00 cm
CY 0.00 cm
F1P 9.000 ppm
F1 4501.17 Hz
F2P -0.500 ppm
F2 -250.07 Hz
PPMCM 0.47500 ppm/cm
HZCM 237.56175 Hz/cm


ppm
134.666
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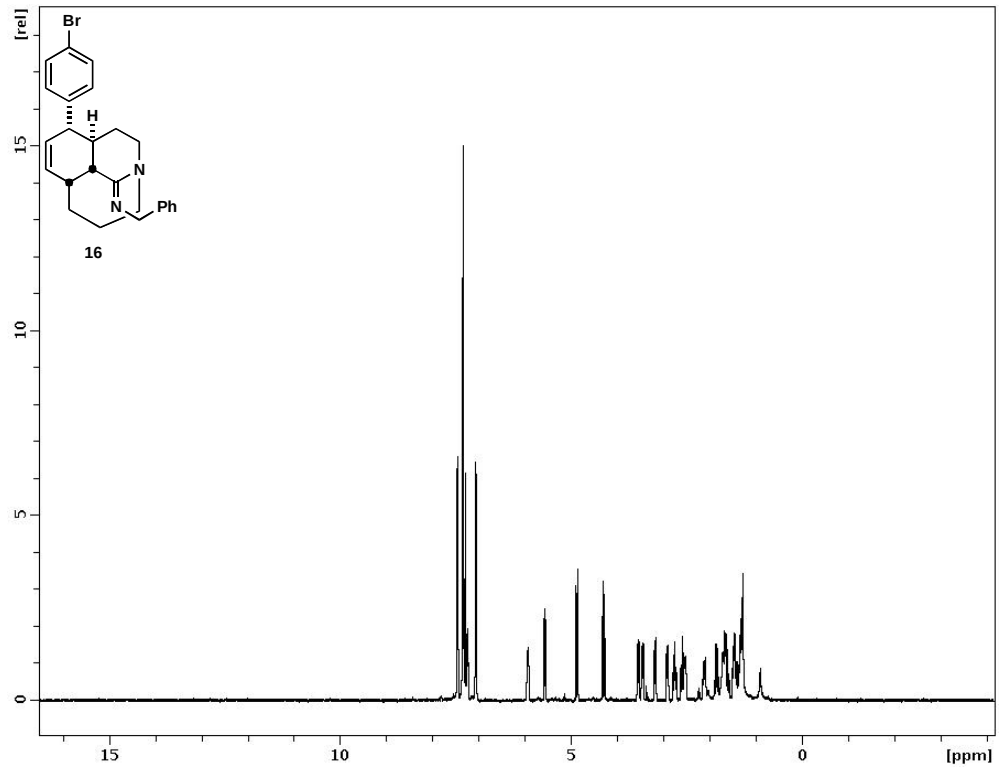
105.093
77.188
76.934
76.680
59.697
59.136
53.029
52.470
49.635
34.110
33.951
32.740
32.265
26.906
24.909
24.522
ppm
200
150
100
50
0
Current Data Parameters
NAME yl-II-P241
EXPNO 2
PROCNO 2
F2 - Acquisition Parameters
Date_ 20030620
Time 17.12
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 149
DS 4
SWH 31446.541 Hz
FIDRES 0.479836 Hz
AQ 1.0420883 sec
RG 2048
DW 15.900 usec
DE 6.00 usec
TE 300.0 K
D1 0.10000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 8.50 usec
PL1 5.00 dB
SFO1 125.7719472 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 95.00 usec
PL2 -4.00 dB
PL12 19.00 dB
PL13 30.00 dB
SFO2 500.1325000 MHz
F2 - Processing parameters
SI 65536
SF 125.7578008 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 1024
MC2 QF
SF 500.1300000 MHz
WDW no
SSB 0
LB 0.30 Hz
GB 0
1D NMR plot parameters
CX 20.00 cm
CY 0.00 cm
F1P 242.517 ppm
F1 30498.43 Hz
F2P -7.539 ppm
F2 -948.11 Hz
PPMCM 12.50282 ppm/cm
HZCM 1572.32703 Hz/cm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H
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N
Ph
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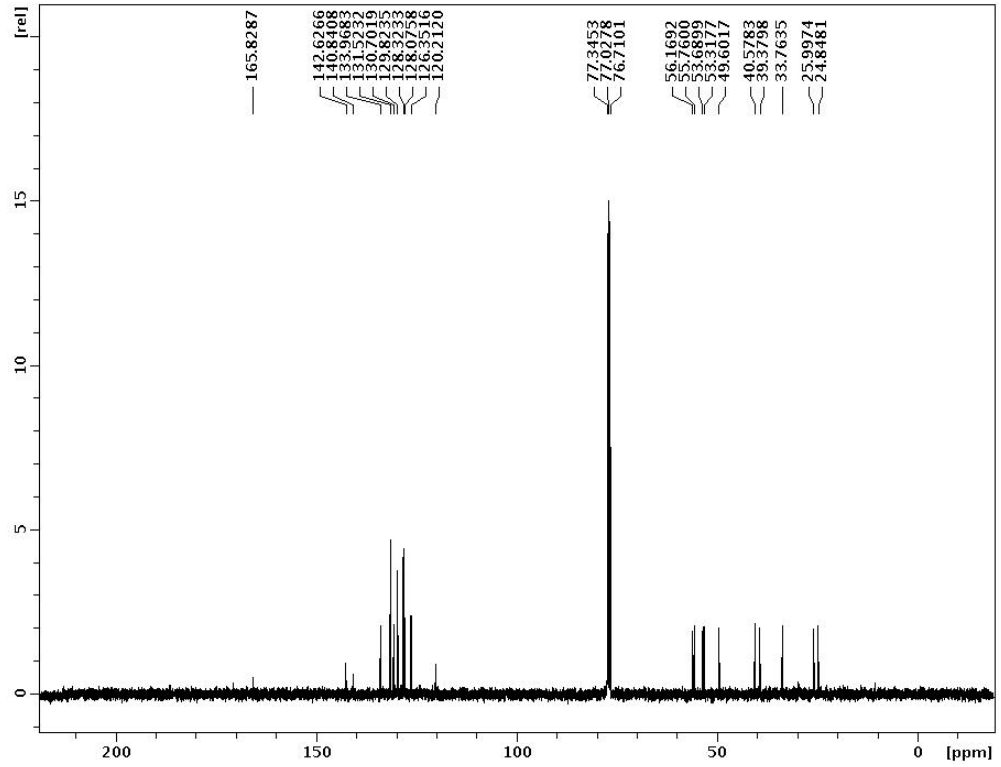
0
5
10
15
15
10
5
0
[ppm]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142.6366
140.8408
133.9983
131.7617
130.7619
129.8235
128.3233
128.0758
126.3516
120.2120
77.3453
77.0278
76.7101
56.1692
55.7600
53.6899
53.3177
49.6017
40.5783
39.3798
33.7635
25.9974
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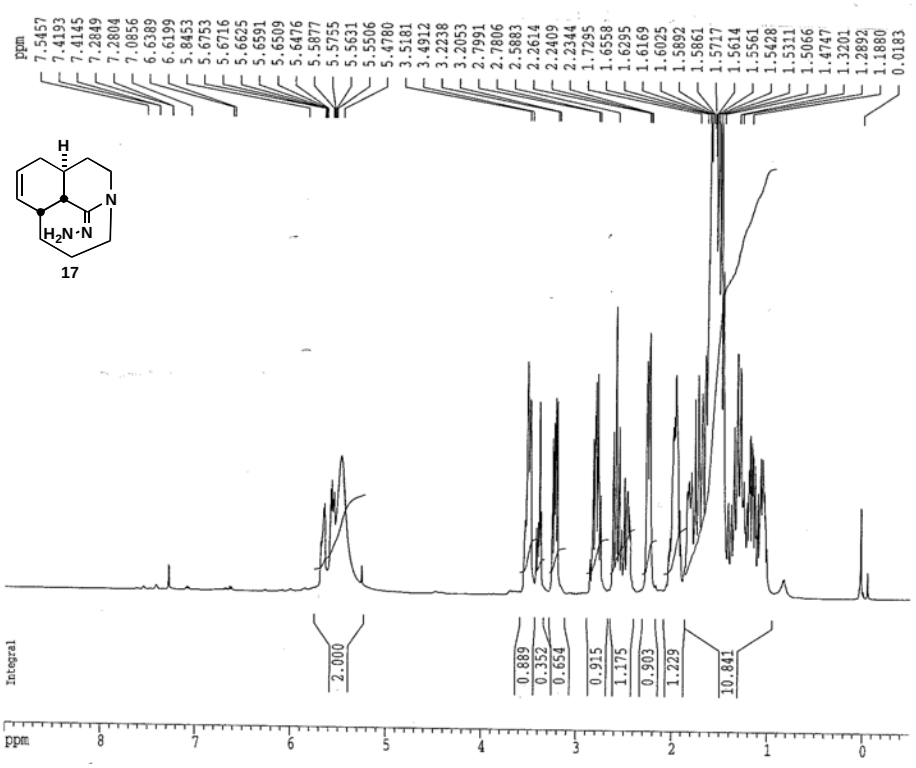
0
5
10
15
200
150
100
50
0
[ppm]




```
urrent Data Parameters
NAME          yl-II-P190
EXPNO                  3
PROCNO                 1

F2 - Acquisition Parameters
Date_           20030529
Time                9.51
INSTRUM          drx400
PROBHD   5 mm Multinucl
PULPROG             zg30
TD                 32768
SOLVENT             CDCl3
NS                     16
DS                      2
SWH           4789.272 Hz
FIDRES        0.146157 Hz
AQ            3.4210291 sec
RG                     32
DW              104.400 usec
DE                4.50 usec
TE                300.0 K
D1           1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                 7.70 usec
PL1                -6.00 dB
SFO1        400.1320007 MHz

F2 - Processing parameters
SI                     16384
SF          400.1300000 MHz
WDW                    EM
SSB                     0
LB                 0.30 Hz
GB                      0
PC                   1.00

1D NMR plot parameters
CX                  20.00 cm
CY                  12.50 cm
F1P                 9.000 ppm
F1                3601.17 Hz
F2P                -0.500 ppm
F2                -200.07 Hz
PPMCM             0.47500 ppm/cm
HZCM          190.06175 Hz/cm
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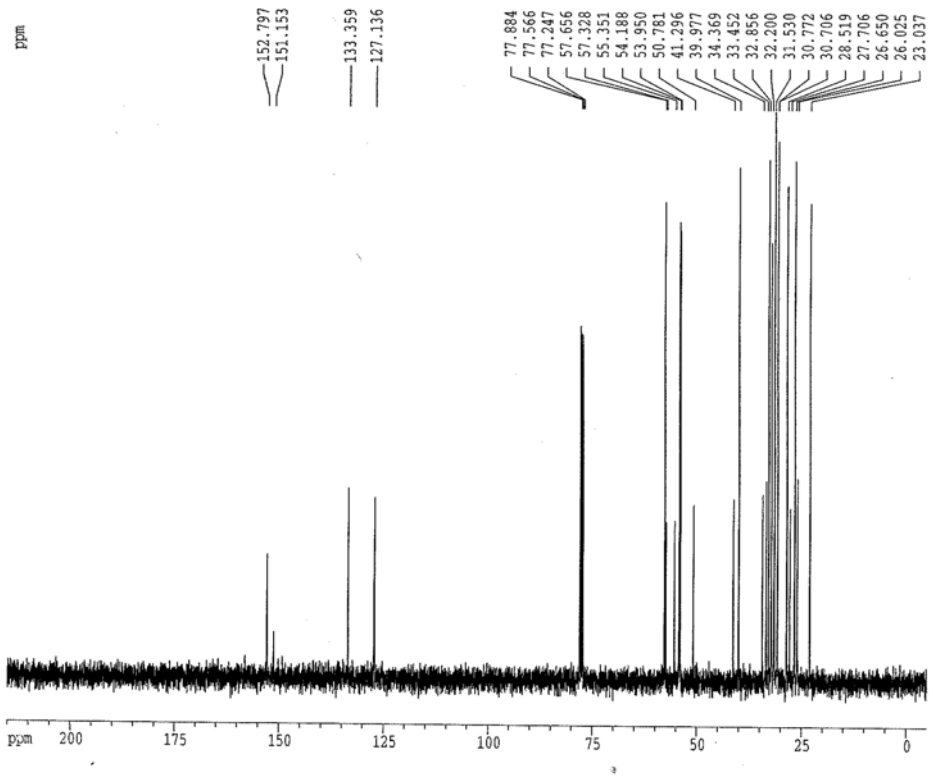


```
Current Data Parameters
NAME          yl-II-P190
EXPNO                  4
PROCNO                 1

F2 - Acquisition Parameters
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Time                9.53
INSTRUM          drx400
PROBHD   5 mm Multinucl
PULPROG           zgpg30
TD                 65536
SOLVENT             CDCl3
NS                     50
DS                      2
SWH          23148.148 Hz
FIDRES        0.353213 Hz
AQ            1.4156276 sec
RG                 32768
DW              21.600 usec
DE                4.50 usec
TE                300.0 K
D1           0.05000000 sec
d11          0.03000000 sec
d12          0.00002000 sec

======== CHANNEL f1 ========
NUC1                   13C
P1                12.30 usec
PL1                2.00 dB
SFO1        100.6232933 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                   1H
PCPD2           100.00 usec
PL2                0.00 dB
PL12              18.00 dB
PL13              18.00 dB
SFO2        400.1316005 MHz

F2 - Processing parameters
SI                 32768
SF          100.6127290 MHz
WDW                    EM
SSB                     0
LB                 1.00 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                  20.00 cm
CY                  12.50 cm
F1P                215.000 ppm
F1              21631.74 Hz
F2P                -5.000 ppm
F2              -503.06 Hz
PPMCM            11.00000 ppm/cm
HZCM          1106.73999 Hz/cm
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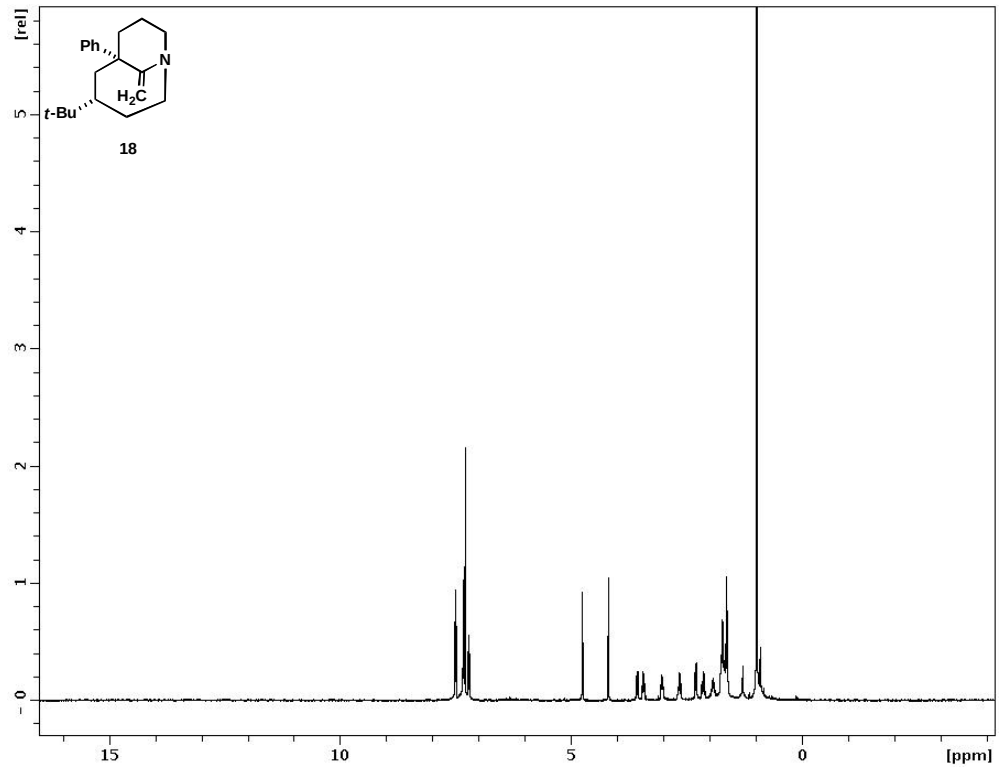
Ph
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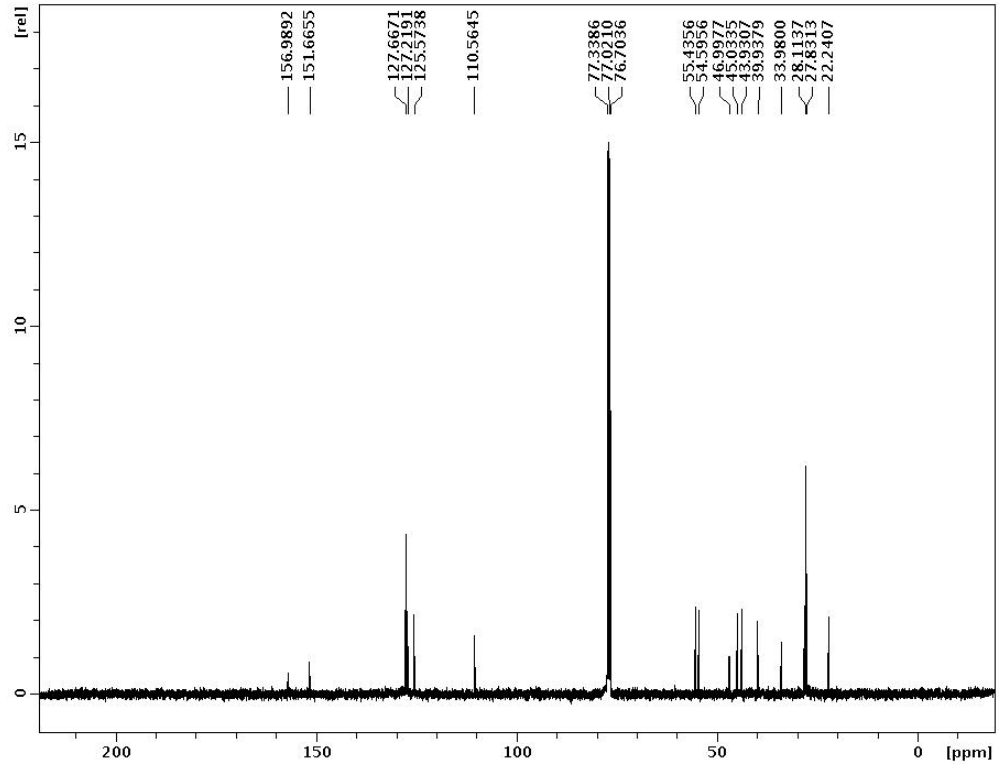
H2C
t-Bu
18
[rel]
[ppm]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127.2191
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110.5645
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76.7036
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54.5956
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43.9307
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33.9800
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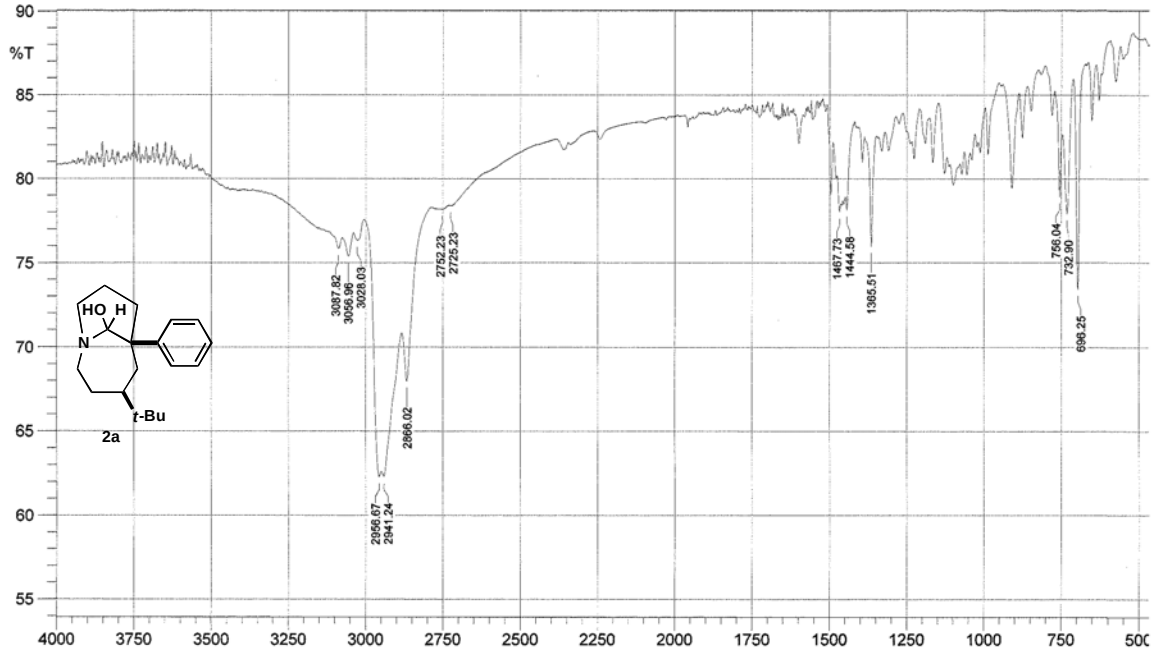
27.8313
22.2407
[rel]
[ppm]


%T
HO H
N
t-Bu
2a
3087.82
3056.96
3028.03
2956.67
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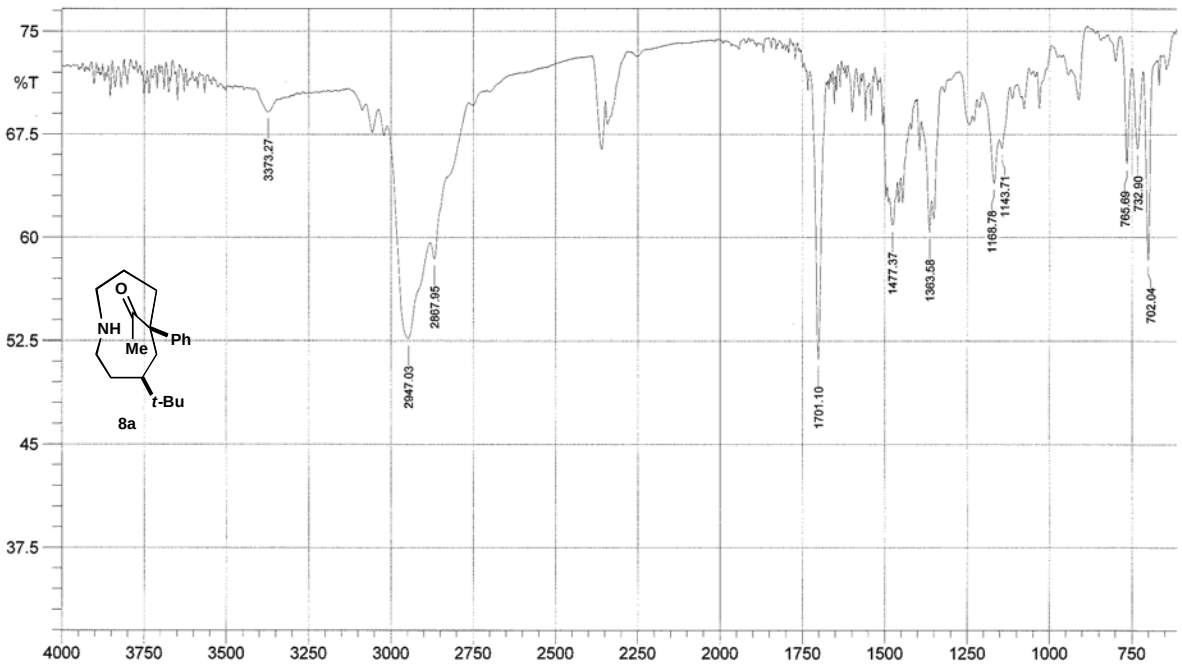
2752.23
2725.23
1467.73
1444.56
1365.51
766.04
732.90
698.25


%T
O
NH
Me
Ph
t-Bu
8a
3373.27
2947.03
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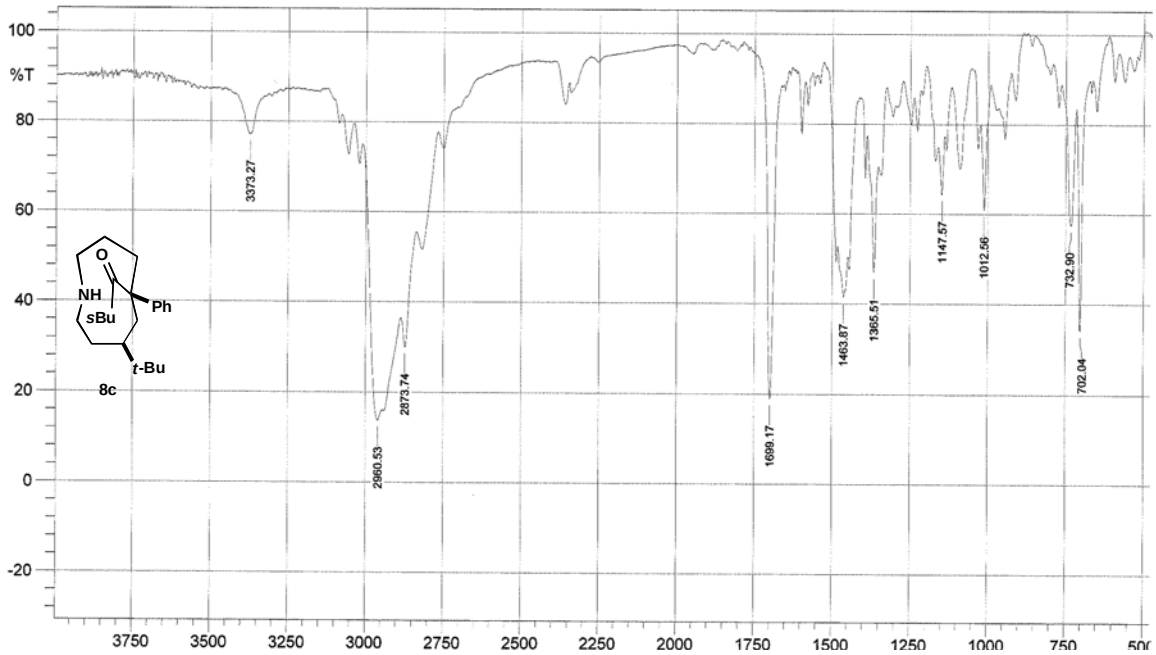
1168.78
1143.71
765.69
732.90
702.04


100
%T
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40
20
0
-20
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1699.17
1463.87
1365.51
1147.57
1012.56
732.90
702.04
3750
3500
3250
3000
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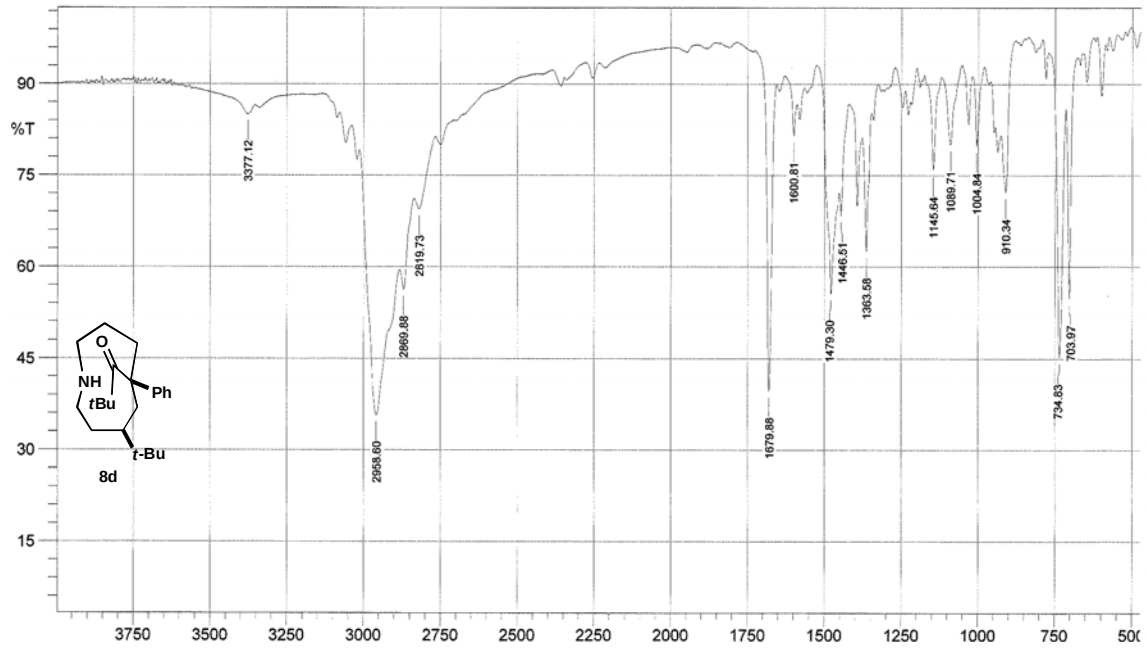
2500
2250
2000
1750
1500
1250
1000
750
O
NH
sBu
Ph
t-Bu
8c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%T
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45
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15
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2958.60
2869.88
2819.73
1679.88
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1479.30
1446.61
1363.58
1145.64
1089.71
1004.84
910.34
734.83
703.97
3750
3500
3250
3000
2750
2500
2250
2000
1750
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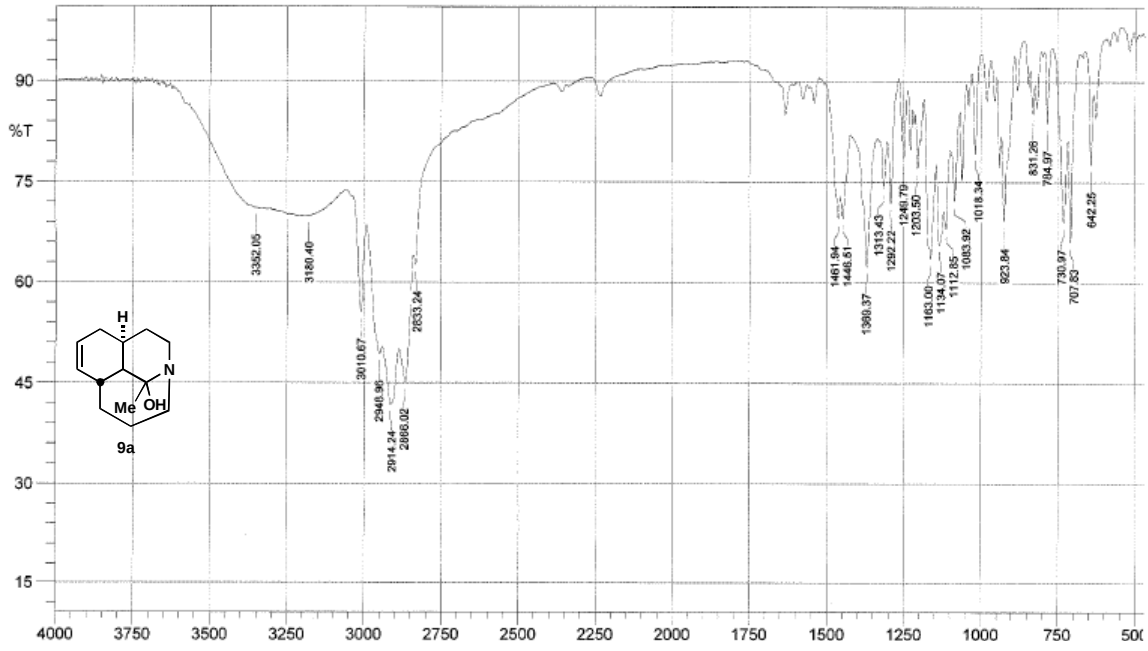
1000
750
O
NH
tBu
Ph
t-Bu
8d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3250
3000
2750
2500
2250
2000
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1250
1000
750
3392.05
3180.40
3010.67
2948.96
2914.24
2866.02
2633.24
1461.94
1448.51
1380.37
1313.43
1292.22
1246.79
1203.50
1163.00
1134.07
1112.65
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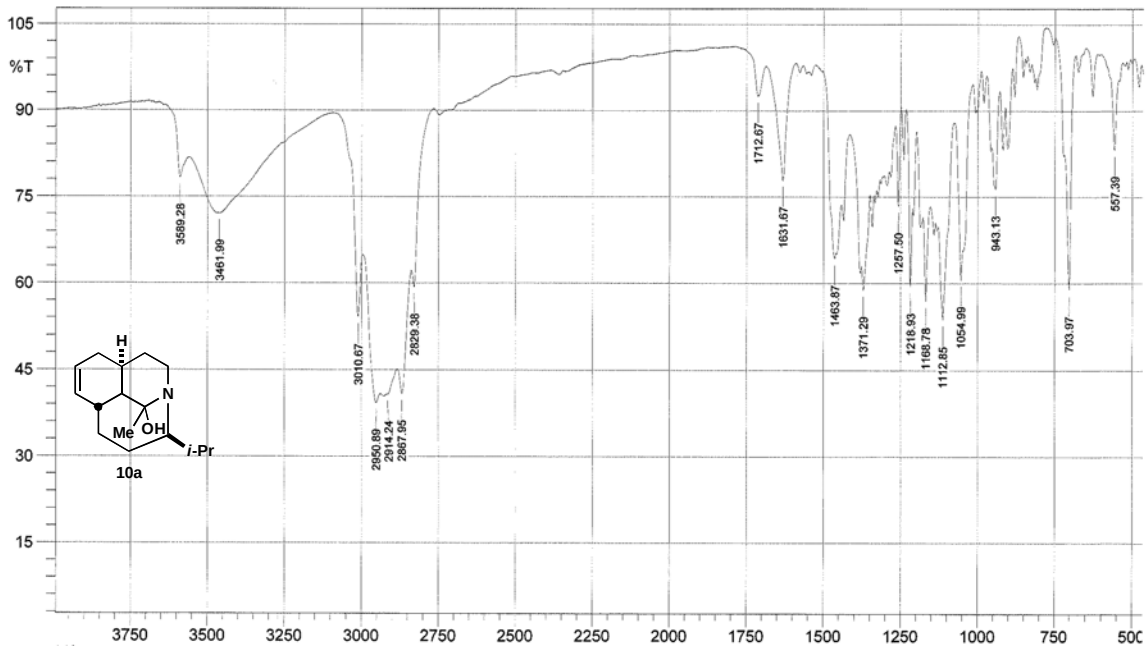
Me
OH
9a


%T
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3750
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3000
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2500
2250
2000
1750
1500
1250
1000
750
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3461.99
3010.67
2950.89
2914.24
2867.95
2829.38
1712.67
1631.67
1463.87
1371.29
1257.50
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1054.99
943.13
703.97
557.39
H
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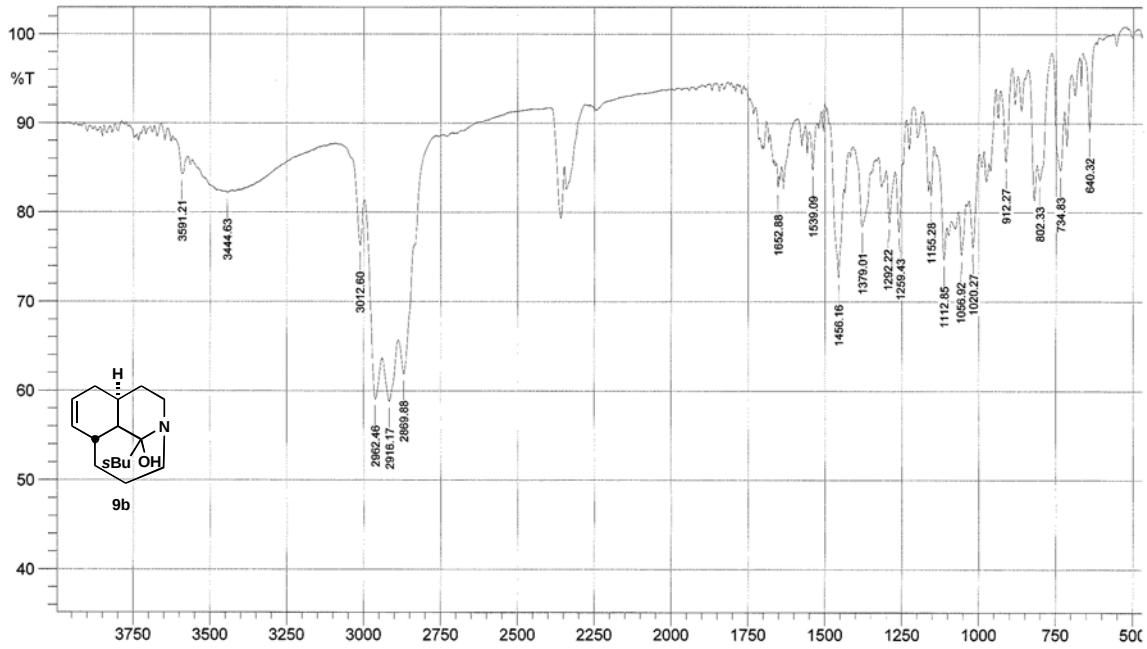
Me
OH
i-Pr
10a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2869.88
1652.88
1539.09
1456.16
1379.01
1292.22
1259.43
1155.28
1112.85
1056.92
1020.27
912.27
802.33
734.83
640.32
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1000
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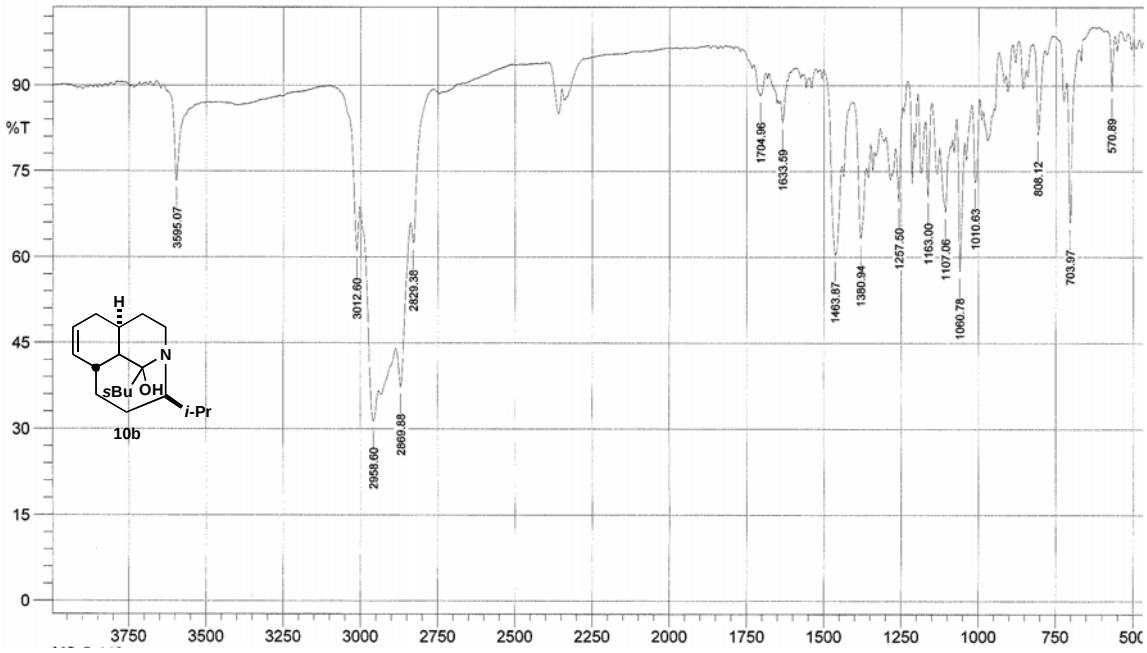
N
sBu
OH
9b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570.89
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3500
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3000
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2500
2250
2000
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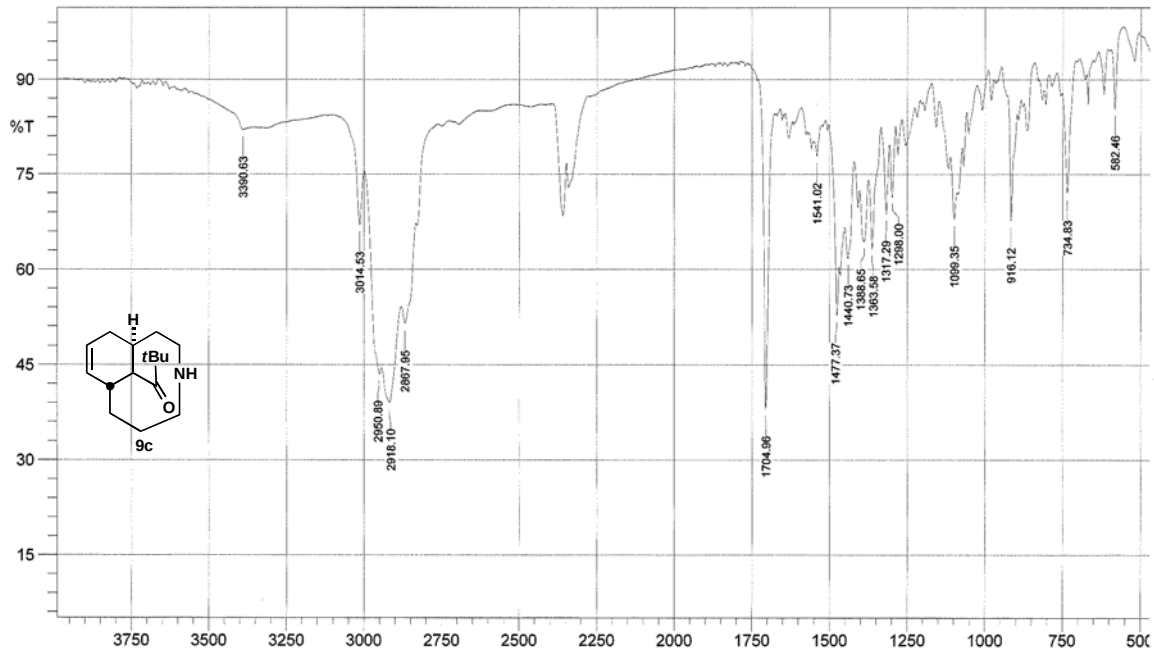
1500
1250
1000
750
H
N
sBu
OH
i-Pr
10b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1317.29
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1099.35
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582.46
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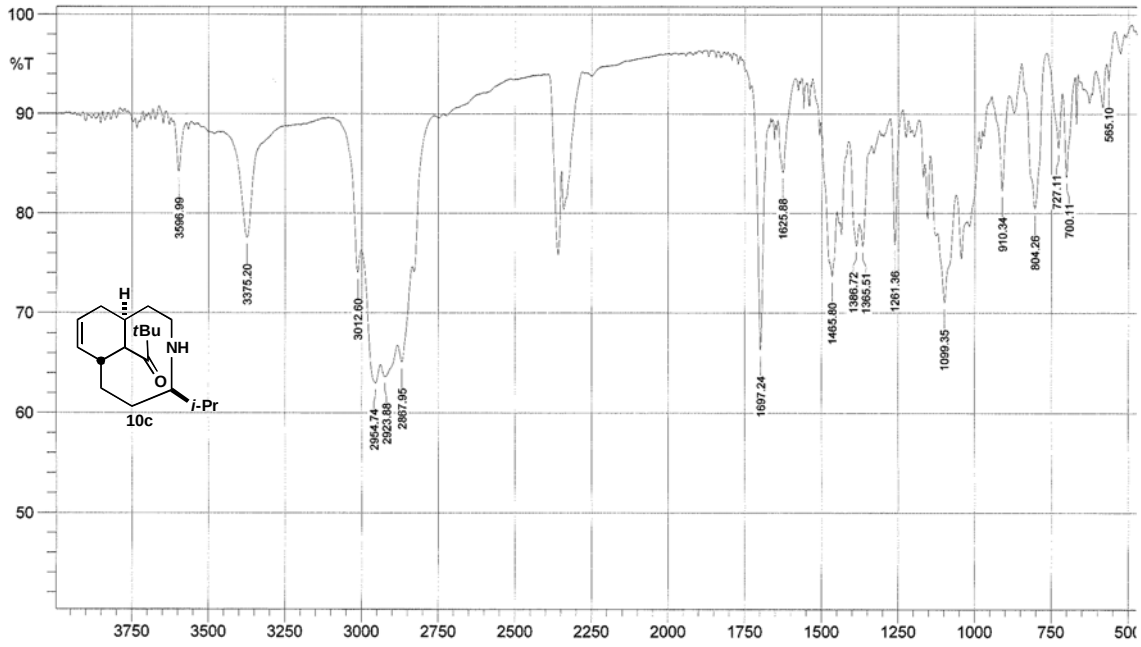
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700.11
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NH
O
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3000
2750
2500
2250
2000
1750
1500
1250
1000
750