Corey-Chaykovsky Epoxidation of Twisted Amides: Synthesis and Reactivity of Bridged Spiro-epoxyamines

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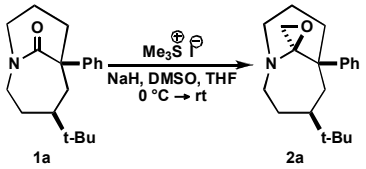
List of Known Compounds

The following compounds are known: lactams **1a-h**.[1-4] Trimethylsulfonium iodide and dimethylsulfoxide were purchased from Aldrich and used as received.

Preparation of Spiro-epoxyamines

General procedure: Round-bottom flask was charged with NaH (60% dispersion in mineral oil) and DMSO was added dropwise at rt. After stirring for 20 min at rt, THF was added and the reaction mixture was cooled to 0 °C. Trimethylsulfonium iodide was added in DMSO, and after stirring for 10 min at 0 °C, twisted amide **1** was added dropwise in THF/DMSO mixture at 0 °C. The reaction mixture was slowly warmed to rt over 4-6 h, and stirred at rt for the remaining time. The reaction was quenched with water (20 mL), extracted with EtOAc (3 x 50 mL), washed with brine (5 x 50 mL), dried, concentrated and chromatographed to afford the final products.

Table 1. *Concentration influence on the Corey-Chaykovsky reaction.*



entry	equiv		time	conc.	conversion	yield
	NaH	Me_3SI	[h]	[M]	[%][a]	[%][b]
1	5.0	2.0	15	0.005	81	ND
2	7.0	2.5	17	0.005	>95	75
3	20.0	5.0	24	0.005	>95	80
4	7.0	2.5	18	0.007	>95	0
5	7.0	2.5	18	0.005	>95	53
6	7.0	2.5	18	0.004	>95	73
7	7.0	2.5	19	0.005	>95	78
8	7.0	2.5	18	0.003	>95	88

[a] Determined by ^{1}H NMR. [b] Isolated yield. ND = not determined.

Entry 1: According to the general procedure, **1a** (0.0200 g, 0.070 mmol, 1.0 equiv) was reacted with NaH (0.014 g, 0.35 mmol, 5.0 equiv), and sulfonium iodide (0.0295 g, 0.14 mmol, 2.0 equiv) in DMSO (3 mL, 1.5 mL and 2 mL) and THF (5 mL and 2 mL) (c_{total} = 0.005 M, c_{ylide} = 0.007 M, c_{amide} = 0.018 M) for 15 h. Analysis of the crude reaction mixture by ^{1}H NMR indicated 81% conversion.

Entry 2: According to the general procedure, the reaction of **1a** (0.0200 g, 0.070 mmol, 1.0 equiv), NaH (0.0196 g, 0.49 mmol, 7.0 equiv), and sulfonium iodide (0.0368 g, 0.18 mmol, 2.5 equiv) in DMSO (3.0 mL, 2.0 mL, and 2.0 mL), and THF (5.0 mL and 3.0 mL) (c_{total} = 0.005 M, c_{ylide} = 0.007 M, c_{amide} = 0.014 M) for 17 h at rt afforded after

chromatography (1/3 EtOAc-hexanes) **2a** in 75% yield (0.0157 g, 0.053 mmol). Analysis of the crude reaction mixture by ^{1}H NMR indicated >95% conversion.

Entry 3. According to the general procedure, the reaction of **1a** (0.0200 g, 0.070 mmol, 1.0 equiv), NaH (0.056 g, 1.40 mmol, 20.0 equiv), and sulfonium iodide (0.0736 g, 0.35 mmol, 5.0 equiv) in DMSO (3.0 mL, 1.5 mL, and 2.0 mL), and THF (5.0 mL and 2.0 mL) (c_{total} = 0.005 M, c_{ylide} = 0.007 M, c_{amide} = 0.018 M) for 24 h at rt afforded after chromatography (1/3 EtOAc-hexanes) **2a** in 80% yield (0.0167 g, 0.056 mmol). Analysis of the crude reaction mixture by ^{1}H NMR indicated >95% conversion.

Entry 4. According to the general procedure, **1a** (0.0300 g, 0.105 mmol, 1.0 equiv) was reacted with NaH (0.0295 g, 0.74 mmol, 7.0 equiv), and sulfonium iodide (0.0552 g, 0.26 mmol, 2.5 equiv) in DMSO (3.0 mL, 2.0 mL, and 2.0 mL), and THF (5.0 mL and 3.0 mL) (c_{total} = 0.007 M, c_{ylide} = 0.011 M, c_{amide} = 0.021 M) for 18 h at rt. Analysis of the crude reaction mixture by ^{1}H NMR indicated only unidentified decomposition products.

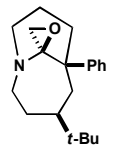
Entry 5. According to the general procedure, **1a** (0.0300 g, 0.105 mmol, 1.0 equiv) was reacted with NaH (0.0295 g, 0.74 mmol, 7.0 equiv), and sulfonium iodide (0.0552 g, 0.26 mmol, 2.5 equiv) in DMSO (5.0 mL, 2.5 mL, and 2.0 mL), and THF (10.0 mL and 3.0 mL) (c_{total} = 0.005 M, c_{ylide} = 0.006 M, c_{amide} = 0.021 M) for 18 h at rt to afford after chromatography (1/3 hexanes/EtOAc) **2a** in 53% yield (0.0276 g, 0.092 mmol). Analysis of the crude reaction mixture by ^{1}H NMR indicated >95% conversion.

Entry 6. According to the general procedure, **1a** (0.0300 g, 0.105 mmol, 1.0 equiv) was reacted with NaH (0.0295 g, 0.74 mmol, 7.0 equiv), and sulfonium iodide (0.0552 g, 0.26 mmol, 2.5 equiv) in DMSO (5.0 mL, 2.5 mL, and 2.0 mL), and THF (10.0 mL and 6.0 mL) (c_{total} = 0.004 M, c_{ylide} = 0.006 M, c_{amide} = 0.013 M) for 18 h at rt to afford after chromatography (1/3 hexanes/EtOAc) **2a** in 73% yield (0.0230 g, 0.077 mmol). Analysis of the crude reaction mixture by ^{1}H NMR indicated >95% conversion.

Entry 7. According to the general procedure, **1a** (0.0500 g, 0.175 mmol, 1.0 equiv) was reacted with NaH (0.0491 g, 1.23 mmol, 7.0 equiv), and sulfonium iodide (0.0920 g, 0.44 mmol, 2.5 equiv) in DMSO (6.0 mL, 2.5 mL, and 2.0 mL), and THF (10.0 mL and 11.0 mL) (c_{total} = 0.0050 M, c_{ylide} = 0.0095 M, c_{amide} = 0.013 M) for 18 h at rt to afford after chromatography (1/3 hexanes/EtOAc) **2a** in 78% yield (0.0408 g, 0.137 mmol). Analysis of the crude reaction mixture by ^{1}H NMR indicated >95% conversion.

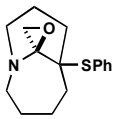
Entry 8. According to the general procedure, **1a** (0.0300 g, 0.105 mmol, 1.0 equiv) was reacted with NaH (0.0295 g, 0.74 mmol, 7.0 equiv), and sulfonium iodide (0.0552 g, 0.26 mmol, 2.5 equiv) in DMSO (5.0 mL, 2.0 mL, and 2.0 mL), and THF (20.0 mL and 3.0 mL) (c_{total} = 0.003 M, c_{ylide} = 0.003 M, c_{amide} = 0.021 M) for 18 h at rt to afford after chromatography (1/3 hexanes/EtOAc) **2a** in 88% yield (0.0276 g, 0.092 mmol). Analysis of the crude reaction mixture by ^{1}H NMR indicated >95% conversion.

Reaction rate: According to the general procedure, **1a** (0.0300 g, 0.105 mmol, 1.0 equiv) was reacted with NaH (0.0295 g, 0.74 mmol, 7.0 equiv), and sulfonium iodide (0.0552 g, 0.26 mmol, 2.5 equiv) in DMSO (5.0 mL, 2.5 mL, and 2.0 mL), and THF (10.0 mL and 6.0 mL) (c_{total} = 0.004 M, c_{ylide} = 0.006 M, c_{amide} = 0.013 M). 3.0 mL aliquots were taken, and analyzed by ^{1}H NMR after aqueous work-up, indicated as follows: 5.9% conversion 10 min after the start of the reaction, 7.1% conversion after 30 min, 12.4% conversion after 2 h, 63% conversion after 6.5 h, 87% conversion after 18 h.



2a

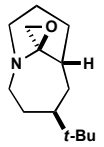
4-*tert*-Butyl-6-phenyl-1-azaspiro[bicyclo[4.3.1]decane-10,2'-oxirane] (2a). According to the general procedure, the reaction of **1a** (0.0300 g, 0.105 mmol, 1.0 equiv), NaH (0.0295 g, 0.74 mmol, 7.0 equiv) and sulfonium iodide (0.0552 g, 2.5 equiv) in DMSO (5.0 mL and 2.0 mL and 2.0 mL) and THF (20.0 mL and 3.0 mL) for 18 h afforded after chromatography (1/4-1/1 EtOAc/hexanes) the title compound as oil (R_f = 0.39, 1/4 EtOAc/hexanes). Yield 88% (0.0276 g, 0.092 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (s, 9H), 1.48-1.55 (m, 1H), 1.59-1.67 (m, 2H), 1.70 (d, *J* = 6.3 Hz, 1H), 1.73-1.80 (m, 2H), 1.88 (m, 1H), 2.00-2.10 (m, 1H), 2.13-2.19 (m, 2H), 2.32 (ddt, *J* = 2.1, 4.3, 13.2 Hz, 1H), 2.48-2.55 (m, 1H), 2.87-2.99 (m, 2H), 3.51 (dt, *J* = 3.9, 13.0 Hz, 1H), 7.08-7.12 (m, 1H), 7.16-7.20 (m, 2H), 7.45 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 27.5, 29.2, 33.9, 36.8, 42.7, 44.1, 48.2, 52.1, 53.2, 53.8, 72.6, 126.0, 126.9, 127.6, 147.0; IR (neat) 3416, 2955, 2922, 2853, 1458, 1365, 1333, 1267. 1163, 1101 cm^{-1}; HRMS calcd for $C_{20}H_{30}NO$ (M^+ + H) 300.2327, found 300.2327.



2b

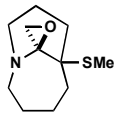
6-(Phenylthio)-1-azaspiro[bicyclo[4.3.1]decane-10,2'-oxirane] (2b). According to the general procedure, the reaction of **1b** (0.0202 g, 0.077 mmol, 1.0 equiv), NaH (0.0217 g, 0.54 mmol, 7.0 equiv) and sulfonium iodide (0.0379 g, 2.5 equiv) in DMSO (5.0 mL and 2.0 mL and 2.0 mL) and THF (10.0 mL and 3.0 mL) for 17 h afforded after chromatography (1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.37, 1/4 EtOAc/hexanes). Yield 81% (0.0171 g, 0.062 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.53 (m, 1H), 1.60-1.72 (m, 2H), 1.77-2.13 (m, 7H), 2.56 (d, *J* = 6.5 Hz, 1H), 2.76 (m, 1H), 2.96-3.12 (m, 2H), 3.20-3.27 (m, 1H), 3.63 (d, *J* = 6.5 Hz, 1H), 7.28-7.35 (m, 3H), 7.56-7.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.2, 24.3, 27.9, 37.4, 40.4, 50.7, 52.6, 52.8, 53.6, 74.4, 128.3, 128.4, 132.4, 136.6; IR (neat) 3057, 2931, 2855, 1474,

1447, 1439, 1329, 1264, 1165, 1017 cm^{-1}; HRMS calcd for $C_{16}H_{22}NOS$ (M^+ + H) 276.1422, found 276.1419.



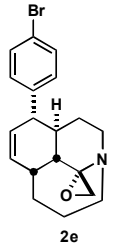
2c

4-*tert*-Butyl-1-azaspiro[bicyclo[4.3.1]decane-10,2'-oxirane] (2c). According to the general procedure, the reaction of **1c** (0.0276 g, 0.132 mmol, 1.0 equiv), NaH (0.0370 g, 0.92 mmol, 7.0 equiv) and sulfonium iodide (0.0694 g, 2.5 equiv) in DMSO (6.0 mL and 2.5 mL and 2.0 mL) and THF (10.0 mL and 8.0 mL) for 18 h afforded after chromatography (5% MeOH/EtOAc) the title compound as oil (R_f = 0.55, 10% MeOH/EtOAc). Yield 41% (0.0121 g, 0.054 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 9H), 1.26-1.84 (m, 9H), 1.94-2.04 (m, 1H), 2.45 (d, *J* = 6.2 Hz, 1H), 2.50 (dt, *J* = 3.4, 12.9 Hz, 1H); 2.64 (d, *J* = 6.2 Hz, 1H), 2.90-3.05 (m, 2H), 3.45 (dt, *J* = 3.5, 13.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 27.6, 28.9, 31.5, 33.1, 33.6, 36.1, 48.7, 522.4, 54.4, 55.3, 71.7; IR (neat) 2939, 2863, 1468, 1448, 1364, 1337, 1263, 1227, 1186, 1149, 1119, 1082 cm^{-1}; HRMS calcd for $C_{14}H_{24}NO$ (M^+ + H) 224.2014, found 224.2004.



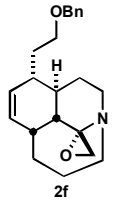
2d

6-(Methylthio)-1-azaspiro[bicyclo[4.3.1]decane-10,2'-oxirane] (2d). To a solution of sulfonium iodide (0.26 g, 1.23 mmol, 10.0 equiv) in THF (15 mL), *n*BuLi (2.5 M in hexanes, 0.38 mL, 0.96 mmol, 8.0 equiv) was added dropwise at 0 °C. After 5 min at 0 °C, amide **1d** (0.0245 g, 0.12 mmol, 1.0 equiv) was added in THF (3.0 mL) dropwise at 0 °C. The reaction mixture was warmed slowly to rt over 3 h, and stirred at rt for additional 2 h. The reaction mixture was quenched with water (20 mL), extracted with EtOAc (3 x 50 mL), washed with brine (1 x 20 mL), dried, concentrated and purified by chromatography (1/3 EtOAc/hexanes) to afford the title compound as oil (R_f = 0.19, 1/4 EtOAc/hexanes). Yield 89% (0.0233 g, 0.11 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44-1.49 (m, 1H), 1.64-1.92 (m, 8H), 1.94 (s, 3H), 2.00-2.08 (m, 1H), 2.24 (d, *J* = 6.8 Hz, 1H), 2,68-2.75 (m, 1H), 2.95-3.11 (m, 2H), 3.20-3.27 (m, 1H), 3.47 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 22.2, 25.4, 29.6, 38.4, 39.1, 48.4, 51.1, 52.4, 53.9, 75.6; IR (neat) 3066, 2919, 2852, 1448, 1330, 1263, 1217, 1164 cm^{-1}; HRMS calcd for $C_{11}H_{20}NOS$ (M^+ + H) 214.1266, found 214.1262. Note: the compound is unstable at rt. The reaction of **1d** under general conditions led to formation of unidentified polymerized material.



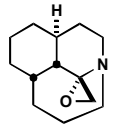
2e

Epoxide 2e. According to the general procedure, the reaction of **1e** (0.0250 g, 0.072 mmol, 1.0 equiv), NaH (0.0202 g, 0.51 mmol, 7.0 equiv) and sulfonium iodide (0.0375 g, 0.18 mmol, 2.5 equiv) in DMSO (5.0 mL and 2.0 mL and 2.0 mL) and THF (10.0 mL and 3.0 mL) for 18 h afforded after chromatography (1/1 EtOAc/hexanes) the title compound as oil (R_f = 0.31, 1/1 EtOAc/hexanes). Yield 70% (0.0183 g, 0.051 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32-1.43 (m, 1H), 1.46-1.53 (m, 1H), 1.60-1.74 (m, 2H), 1.86 (dd, *J* = 4.1, 10.8 Hz, 1H), 2.01-2.11 (m, 1H), 2.16-2.29 (m, 2H), 2.50 (d, *J* = 6.1 Hz, 1H), 2.49-2.56 (m, 1H), 2.59-2.69 (m, 2H), 2.73 (d, *J* = 6.1 Hz, 1H), 3.11 (d, *J* = 10.6 Hz, 1H), 3.38 (dd, *J* = 8.1, 13.5 Hz, 1H), 3.50 (dd, *J* = 4.2, 12.0 Hz, 1H), 5.51 (d, *J* = 9.8 Hz, 1H), 5.98-6.04 (m, 1H), 7.06 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 24.6, 35.0, 35.3, 37.6, 48.1, 50.7, 52.7, 54.7, 58.7, 70.4, 120.3, 129.7, 129.8, 131.5, 134.7, 142.8; IR (neat) 3013, 2916, 2860, 1483, 1441, 1385, 1337, 1298, 1246, 1137, 1071, 1011 cm^{-1}; HRMS calcd for $C_{19}H_{23}BrNO$ (M^+ + H) 360.0963, found 360.0960.



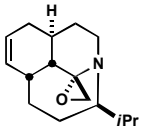
2f

Epoxide 2f. According to the general procedure, the reaction of **1f** (0.0272 g, 0.084 mmol, 1.0 equiv), NaH (0.0234 g, 0.59 mmol, 7.0 equiv) and sulfonium iodide (0.0437 g, 0.21 mmol, 2.5 equiv) in DMSO (5.0 mL and 2.0 mL and 2.0 mL) and THF (10.0 mL and 5.0 mL) for 19 h afforded after chromatography (0-2.5% MeOH/EtOAc) the title compound as oil (R_f = 0.27, EtOAc). Yield 73% (0.0209 g, 0.062 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27-1.67 (m, 5H), 1.84-1.97 (m, 3H), 2.04-2.26 (m, 3H), 2.32-2.44 (m, 1H), 2.44 (d, *J* = 6.1 Hz, 1H), 2.64 (t, *J* = 11.4 Hz, 1H), 2.72 (d, *J* = 6.1 Hz, 1H), 2.72-2.84 (m, 1H), 3.42-3.52 (m, 2H), 2.55-3.63 (m, 2H), 4.53 (s, 2H), 5.51 (d, *J* = 9.9 Hz, 1H), 5.82-5.87 (m, 1H), 7.29-7.38 (m 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 24.7, 32.2, 34.4, 34.8, 35.3, 41.0, 48.3, 53.0, 54.7, 58.8, 68.0, 70.5, 73.1, 127.6, 127.6, 128.4, 130.0, 133.7, 138.5; IR (neat) 3009, 2914, 2860, 1481, 1453, 1385, 1364, 1294, 1258, 1142, 1102, 1053 cm^{-1}; HRMS calcd for $C_{22}H_{30}NO_2$ (M^+ + H) 340.2277, found 340.2256.



2g

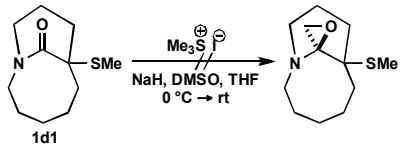
Epoxide 2g. According to the general procedure, the reaction of **1g** (0.0090 g, 0.047 mmol, 1.0 equiv), NaH (0.0130 g, 0.33 mmol, 7.0 equiv) and sulfonium iodide (0.0240 g, 0.12 mmol, 2.5 equiv) in DMSO (5.0 mL and 2.0 mL and 2.0 mL) and THF (10.0 mL and 3.0 mL) for 18 h afforded after chromatography (10% MeOH/EtOAc) the title compound as oil (R_f = 0.36, 10% MeOH/EtOAc). Yield 77% (0.0075 g, 0.036 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01-1.14 (m, 1H), 1.32-1.78 (m, 10H), 1.85-2.05 (m, 2H), 2.14-2.25 (m, 2H), 2.43 (dd, *J* = 2.3, 6.1 Hz, 1H), 2.69 (dd, *J* = 1.9, 6.2 Hz, 1H), 2.76-2.85 (m, 2H), 3.35 (dd, *J* = 8.4, 13.4 Hz, 1H), 3.49-3.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.5, 25.0, 28.2, 30.9, 31.0, 32.0, 33.2, 33.8, 52.1, 52.8, 54.6, 58.7, 71.0; IR (neat) 2918, 2859, 1484, 1453, 1443, 1383, 1321, 1285, 1242, 1152 cm^{-1}; HRMS calcd for $C_{13}H_{22}NO$ (M^+ + H) 208.1701, found 208.1694.



2h

Epoxide 2h. According to the general procedure, the reaction of **1h** (0.0258 g, 0.11 mmol, 1.0 equiv), NaH (0.0310 g, 0.78 mmol, 7.0 equiv) and sulfonium iodide (0.0572 g, 0.28 mmol, 2.5 equiv) in DMSO (5.0 mL and 2.0 mL and 2.0 mL) and THF (10.0 mL and 6.0 mL) for 18 h afforded after chromatography (2.5% EtOAc/hexanes) the title compound as oil (R_f = 0.84, 1/10 EtOAc/hexanes). Yield 70% (0.0190 g, 0.077 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (dd, *J* = 2.6, 6.8 Hz, 6H), 1.37-1.61 (m, 5H), 1.65-1.72 (m, 1H), 1.80-1.89 (m, 1H), 1.97 (dd, *J* = 2.0, 13.3 Hz, 1H), 2.01-2.17 (m, 3H), 2.35-2.43 (m, 1H), 2.41 (d, *J* = 6.6 Hz, 1H), 2.62 (dd, *J* = 1.8, 11.2 Hz, 1H), 2.68 (d, *J* = 6.6 Hz, 1H), 2.74-2.84 (m, 1H), 3.41 (dd, *J* = 8.0, 13.3 Hz, 1H), 5.55-5.63 (m, 1H), 5.77-5.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 18.3, 25.6, 27.9, 29.9, 33.5, 33.7, 34.8, 36.1, 48.6, 53.4, 54.8, 69.9, 74.7, 126.0, 133.8; IR (neat) 3015, 2954, 2927, 2669, 1463, 1451, 1393, 1378, 1341, 1291, 1260, 1064 cm^{-1}; HRMS calcd for $C_{16}H_{26}NO$ (M^+ + H) 248.2014, found 248.2015.

Scheme A. *Attempted synthesis from 1-carbon higher homologue of **1d**.*



According to the general procedure, **1d1** (0.0228 g, 0.11 mmol, 1.0 equiv) was reacted with NaH (0.0300 g, 0.75 mmol, 7.0 equiv) and sulfonium iodide (0.0563 g, 0.27 mmol, 2.5 equiv) in DMSO (5.0 mL and 2.0 mL and 2.0 mL) and THF (10.0 mL and 6.0 mL) for 17 h. Analysis of the crude reaction mixture by NMR indicated only presence of the starting material.

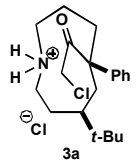
As expected, the twist of amide bonds is important for the Corey-Chaykovsky reaction. As evidenced by spectroscopic properties, the amide **1d1** having [5.3.1] ring is less distorted than amide **1d** having [4.3.1] ring system. The behavior of the latter is consistent with less "amide-like" and greater "ketone-like" nature of the carbonyl group.[5] Evaluation of the effect of strain embedded in other ring systems on reactivity of amide bonds (including the Corey-Chaykovsky reaction) is a part of our research program.[1-5]

We have also attempted Corey-Chaykovsky epoxidations using a number of other sulfur ylides, including dimethylsulfoxonium methylide,[6] diphenylsulfonium ethylide,[7] diphenylsulfonium cyclopropylide,[8] tetrahydrothiophenium 1-carbomethoxylide[9] and benzylide[10] under variety of conditions, however the formation of the corresponding epoxyamines has not been observed so far. In most cases, analysis of the reaction mixtures indicated only the presence of starting materials, however decomposition was also noticed in several instances. In these reactions, the addition of ylides to amide carbonyls is complicated by (1) lower nucleophilicity of the ylides (vs. dimethylsulfonium methylide) and (2) decreased stability of some ylides (vs. dimethylsulfonium methylide).[11] We think that the resulting zwitterions are sometimes formed, however that the zwitterions revert to the starting materials instead of undergoing the rearrangement to spiro-epoxyamines. Work to address these points is underway.

An additional point that needs to be emphasized is that the vital factor allowing for the epoxidation of one-carbon bridged amides is their superior hydrolytic stability as compared to other twisted amides, for example quinuclidone derivatives.[3] Under Corey-Chaykovsky reaction conditions, quinuclidone-based twisted amides would be expected to undergo hydrolysis to amino acids or collapse after ylide addition. Transannular interactions between amine and ketone groups in these systems are much weaker than in 9-membered heterocycles, in which the ketone is placed at the carbon adjacent directly to the ring.[3]

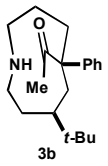
Reactivity of Spiro-epoxyamines

*Transformations of **2a** under acidic and reductive conditions.*



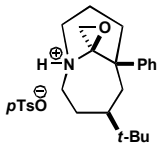
3a

4-*tert*-Butyl-6-(2-chloroacetyl)-6-phenylazonanium chloride (3a). To a 10 ml round bottom flask charged with epoxide **2a** (0.0041 g, 0.014 mmol, 1.0 equiv) and MeOH (5.0 mL), HCl (4.0 M, dioxane, 0.40 mL, 1.6 mmol, 100 equiv) was added dropwise at rt, and the resulting reaction mixture was stirred at rt. After 19 h the solvent was removed to provide the title compound as a white solid (m.p = 230-5 °C). Yield 99% (0.0050 g, 0.0135 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.34 (s, 9H), 1.28-1.48 (m, 3H), 1.60 (m, 1H), 1.83 (m, 1H), 1.95 (m, 1H), 2.05 (m, 1H), 2.17 (m, 1H), 2.57 (m, 1H), 3.00 (m, 2H), 3.14 (m, 2H), 4.12 (d, *J* = 16.0 Hz, 1H), 4.48 (d, *J* = 16.0 Hz, 1H), 7.19 (d, *J* = 7.4 Hz, 2H), 7.30 (t, *J* = 7.1 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 8.76 (br, 1H), 9.51 (br, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 17.9, 24.6, 27.2, 29.1, 33.9, 34.3, 37.9, 41.7, 44.6, 57.1, 59.6, 127.9, 128.0, 129.3, 142.1, 204.6; IR (KBr) 3423, 2931, 1725, 1574, 1466, 1290, 1124, 1075 cm^{-1}; HRMS calcd for $C_{20}H_{31}ClNO$ (M^+) 336.2094, found 336.2093. Note: the reaction of **2a** (0.0163 g, 0.055 mmol) and HCl (4.0 M, dioxane, 4.0 mL), w/o MeOH, afforded **3a** in 97% yield.



3b

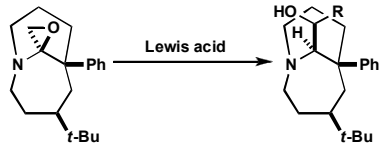
7-*tert*-Butyl-5-phenylazonan-5-yl)ethanone (3b). To a solution of epoxide **2a** (0.0157 g, 0.053 mmol, 1.0 equiv) in Et_2O (10 mL), $LiAlH_4$ (1.0 M, Et_2O, 0.26 mL, 0.26 mmol, 5.0 equiv) was added at rt. After stirring for 20 h at rt, the reaction was quenched at 0 °C by sequential addition of H_2O, 15% NaOH, H_2O and Na_2SO_4 according to the procedure by Fieser and Fieser. Purification by chromatography (1/10/90 NH_3/MeOH/CH_2Cl_2) afforded the title compound as oil (R_f = 0.31-0.62, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 91% (0.0144 g, 0.048 mmol). ^{1}H NMR (500 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 (125 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.



3c

Salt 3c. To a solution of epoxide **2a** (0.0146 g, 0.049 mmol, 1.0 equiv) in acetone (2.0 mL), *p*TsOH (0.0093 g, 0.049 mmol, 1.0 equiv) was added in acetone (0.5 mL). Et_2O (2.5 mL) wad added and the reaction mixture was kept for 5 days at -20 °C. The solvent was removed to afford the title compound as white foam. Yield 99% (0.0238 g, 0.049 mmol). Note: the compound is unstable. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (s, 9H), 1.72 (m, 1H), 1.84 (d, *J* = 14.0 Hz, 1H), 2.06-2.21 (m, 5H), 2.32-2.45 (m, 2H), 2.34 (s, 3H), 2.62 (m, 1H), 3.05 (m, 1H), 3.47 (d, *J* = 3.9 Hz, 1H), 3.63 (d, *J* = 7.7 Hz, 2H), 4.21-4.29 (m, 1H), 7.18 (d, *J* = 7.9 Hz, 2H), 2.27-7.38 (m, 3H), 7.45 (m, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 11.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 21.4, 26.7, 27.3, 33.6, 34.0, 42.1, 43.2, 47.4, 50.5, 55.0, 55.4, 74.4, 126.0, 126.0, 127.6, 128.6, 128.9, 140.4, 141.3, 142.7; IR (neat) 3352, 2954, 2918, 2848, 1718, 1458, 1365, 1273, 1226, 1165, 1120 cm^{-1}; HRMS calcd for $C_{20}H_{30}NO$ (M^+) 300.2327, found 300.2337.

Table 2. *Reactions of* ***2a*** *under Lewis acidic conditions, including additional examples.*



2a 3d

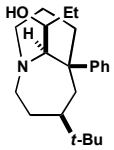
entry	acid/additive	R	yield [%]
1	Et_2AlCl	Et (**3d**)	92
2	Me_2AlCl	Me (**3d1**)	58
3	Me_3Al	Me (**3d1**)	45
4	Et_2AlCl/TMSCN	CN (**3d2**)	70
5	Et_2AlCl/Et_3SiH	H (**3d3**)	56
6	Et_2AlCl/allylTMS	Et (**3d**)	87
7	$MeAlCl_2$	Ar[a] (**3d4**)	68
8	BF_3•Et_2O	H, (CHO)[b] (**3d5**)	0

[a] Friedel-Crafts product, see below. [b] Aldehyde is the expected product of this transformation, see below.

As stated in the main text, we established that bridged spiro-epoxyamines participate in a number of Lewis acid catalyzed reactions not typical to traditional epoxides (Table 2). For example, upon exposure of **2a** to Et_2AlCl or Me_2AlCl conversion to aldehyde and subsequent alkyl transfer is observed (Table 2, entry 1 and 2). When additives such as TMSCN and Et_3SiH are utilized, closely-related cyano and hydroxyl derivatives are formed (entry 4 and 5), however allyl trimethylsilane does not capture the aldehyde (entry 6), while the use of $MeAlCl_2$ resulted in the formation of Friedel-Crafts product (entry 7). This contrasts with traditional epoxides, which typically undergo ring

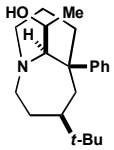
opening and alkyl transfer when exposed to alkylaluminum compounds. Selected relevant examples of reactivity of epoxides upon exposure to Lewis acids can be found in references 12-24 in the Supporting Information. Investigation of Lewis acid-promoted reactions as well as of the exact mechanism of the aluminum promoted rearrangement is underway.

General procedure: To a round-bottom flask charged with epoxide **2a** and CH_2Cl_2, Lewis acid was added at rt, unless indicated otherwise. If an additive was used, it was added before the Lewis acid. After the reaction mixture was stirred for a specified time, the reaction was quenched with sat. $NaHCO_3$, extracted with CH_2Cl_2, washed with brine, dried, concentrated and chromatographed to afford the final products. Stereochemistry (migration with retention of configuration) was determined by 2D NMR correlations.



3d

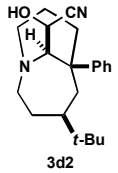
4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decan-10-yl)propan-1-ol (3d). According to the general procedure, the reaction of **2a** (0.0147 g, 0.049 mmol, 1.0 equiv) and Et_2AlCl (1.8 M, toluene, 0.055 mL, 0.10 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) for 15 h at rt, afforded after chromatography (1/10/90 NH_3/MeOH/CH_2Cl_2) the title compound as oil (R_f = 0.33, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 92% (0.0149 g, 0.045 mmol), dr = 59:41. ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 0.40 (t, *J* = 6.9 Hz, 3H, minor isomer), 0.65 (t, *J* = 7.3 Hz, 3H, major isomer), 0.89 (s, 9H), 1.53-2.05 (m, 16H), 2.08-2.31 (m, 4H), 2.48 (dt, *J* = 4.1, 13.6 Hz, 1H), 2.59 (dd, *J* = 4.8, 14.6 Hz, 1H), 2.67-2.81 (m, 3H), 2.92-3.03 (m, 3H), 3.09-3.22 (m, 2H), 3.32-3.41 (m, 1H), 3.53 (dd, *J* = 6.2, 11.0 Hz, 1H), 3.62 (dd, *J* = 4.6, 13.9 Hz, 1H), 3.69 (dd, *J* = 3.7, 13.7 Hz, 1H), 7.19-7.49 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 10.3, 21.4, 21.7, 27.5, 27.5, 28.6, 30.1, 30.2, 31.0, 31.6, 33.8, 34.0, 41.1, 46.2, 48.1, 48.2, 48.2, 48.5, 49.6, 56.6, 57.5, 59.0, 62.8, 67.7, 125.7, 125.9, 126.0, 127.9, 128.2, 149.1, 149.2; IR (neat) 3304, 2959, 2870, 1720, 1663, 1599, 1497, 1460, 1366, 1225. 1099 cm^{-1}; HRMS calcd for $C_{22}H_{36}NO$ (M^+ + H) 330.2797, found 330.2767.



3d1

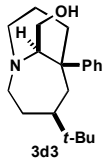
4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decan-10-yl)ethanol (3d1). According to the general procedure, the reaction of **2a** (0.0126 g, 0.042 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 M, hexanes, 0.084 mL, 0.084 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) for 13 h at rt, afforded after chromatography (1/10/90-1/30/70 NH_3/MeOH/CH_2Cl_2) the title

compound as oil (R_f = 0.31, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 58% (0.0076 g, 0.024 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.26 (d, *J* = 5.9 Hz, 3H), 0.90 (s, 9H), 1.54-1.63 (m, 3H), 1.78-1.93 (m, 5H), 2.16-2.26 (m, 1H), 2.39-2.48 (m, 1H), 2.66-2.80 (m, 2H), 2.96 (d, *J* = 8.8 Hz, 1H), 3.16 (dt, *J* = 4.4, 14.1 Hz, 1H), 3.54-3.61 (m, 1H), 3.62-3.70 (m, 1H), 7.18-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 22.7, 27.5, 30.0, 31.5, 34.0, 40.9, 47.8, 48.2, 48.6, 57.6, 62.8, 66.0, 126.0, 126.1, 128.0, 149.2; IR (neat) 3255, 2960, 2870, 1652, 1465, 1446, 1367, 1224, 1112, 1084 cm^{-1}; HRMS calcd for $C_{21}H_{34}NO$ (M^+ + H) 316.2641, found 316.2644. Note: the reaction of **2a** (0.0124 g, 0.041 mmol, 1.0 equiv) with Me_3Al (2.0 M, toluene, 0.10 mL, 0.21 mmol, 5.0 equiv) in CH_2Cl_2 (10 mL) added at -78 °C, and slowly warmed to rt over 16 h, afforded **3d1** in 45% yield (Table 2, entry 3).



3d2

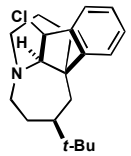
4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decan-10-yl)-2-hydroxyacetonitrile (3d2). According to the general procedure, the reaction of **2a** (0.0156 g, 0.052 mmol, 1.0 equiv), TMSCN (0.071 mL, 0.52 mmol, 10.0 equiv) and Et_2AlCl (1.8 M, toluene, 0.060 mL, 0.10 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) for 15 h at rt, afforded after chromatography (1/1 EtOAc/hexanes) the title compound as oil (R_f = 0.60, 1/1 EtOAc/hexanes). Yield 70% (0.0119 g, 0.037 mmol), dr = 65:35. ^{1}H NMR (400 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 0.89 (s, 9H, major isomer), 0.92 (s, 9H, minor isomer), 1.46-2.01 (m, 16H), 2.14-2.41 (m, 3H), 2.64-2.86 (m, 5H), 3.06-3.18 (m, 1H), 3.37 (dt, *J* = 3.9, 14.9 Hz, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.65-3.74 (m, 2H), 3.92 (d, *J* = 9.1 Hz, 1H, minor isomer), 4.02 (d, *J* = 6.5 Hz, 1H, major isomer), 7.22-7.48 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) (mixture of diastereoisomers) δ 20.6, 20.7, 27.5, 27.5, 29.1, 29.8, 30.0. 30.8, 33.8, 34.0, 39.6, 40.5, 47.1, 47.5, 47.9, 48.1, 48.2, 50.8, 56.3, 56.6, 56.8, 56.9, 60.8, 61.6, 119.6, 121.4, 126.4, 126.6, 127.5, 128.6, 128.7, 144.8, 146.3; IR (neat) 3305, 2959, 2870, 1720, 1669, 1600, 1463, 1446, 1366, 1227, 1094 cm^{-1}; HRMS calcd for $C_{21}H_{30}N_2O$ (M^+ + H) 327.2436, found 327.2404.



3d3

4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decan-10-yl)methanol (3d3). According to the general procedure, the reaction of **2a** (0.0138 g, 0.046 mmol, 1.0 equiv), Et_3SiH (0.074 mL, 0.46 mmol, 10.0 equiv) and Et_2AlCl (1.8 M, toluene, 0.051 mL, 0.09 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) for 18 h at rt, afforded after chromatography (1/4 MeOH/EtOAc) the title compound as oil (R_f = 0.34, 20% MeOH/EtOAc). Yield 56% (0.0077 g, 0.026 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 9H), 1.54-1.66 (m, 3H),

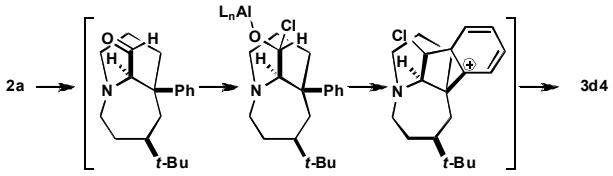
1.76-1.90 (m, 3H), 1.97 (d, *J* = 12.1 Hz, 1H), 2.05-2.31 (m, 2H), 2.59 (dd, *J* = 4.4, 14.3 Hz, 1H), 2.73 (dt, *J* = 4.8, 13.7 Hz, 1H), 2.91-3.02 (m, 2H), 3.14 (t, *J* = 10.7 Hz, 2H), 3.53 (dd, *J* = 5.6, 10.8 Hz, 1H), 3.69 (dd, *J* = 5.0, 14.5 Hz, 1H), 7.12-7.55 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 27.5, 30.1, 31.0, 33.8, 39.6, 46.2, 48.2, 49.6, 56.6, 56.6, 59.0, 125.7, 125.9, 128.2, 149.1; IR (neat) 3357, 2957, 2944, 1459, 1366, 1324, 1274, 1226, 1037 cm^{-1}; HRMS calcd for $C_{20}H_{32}NO$ (M^+ + H) 302.2484, found 302.2481. Note: the reaction of **2a** (0.0174 g, 0.058 mmol, 1.0 equiv), allyltrimethylsilane (0.094 mL, 0.58 mmol, 10.0 equiv) and Et_2AlCl (1.8 M, toluene, 0.064 mL, 0.11 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) at rt for 14 h, afforded **3d** in 87% (Table 2, entry 6).



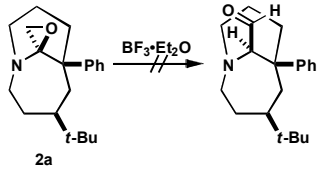
3d4

Compound 3d4. According to the general procedure, the reaction of **2a** (0.0129 g, 0.043 mmol, 1.0 equiv) and $MeAlCl_2$ (1.0 M, hexanes, 0.086 mL, 0.086 mmol, 2.0 equiv) in CH_2Cl_2 (5.0 mL) for 13 h at rt, afforded after chromatography (2/1 EtOAc/hexanes) the title compound as oil (R_f = 0.48, EtOAc). Yield 68% (0.0093 g, 0.029 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.42-1.55 (m, 2H), 1.72-2.07 (m, 6H), 2.36 (dt, *J* = 2.5, 13.0 Hz, 1H), 2.65 (dt, *J* = 4.0, 13.6 Hz, 1H), 2.75-2.83 (m, 1H), 31.4 (dt, *J* = 3.4, 12.7 Hz, 1H), 3.61 (d, *J* = 9.6 Hz, 1H), 3.67-3.77 (m, 1H), 5.51 (d, *J* = 9.6 Hz, 1H), 7.13-7.18 (m, 1H), 7.25-7.32 (m, 2H), 7.46-7.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 27.7, 29.8, 33.8, 35.8, 41.2, 41.8, 47.7, 47.7, 54.9, 60.8, 72.7, 121.7, 125.4, 126.9, 128.7, 138.4, 152.0; IR (neat) 2943, 2866, 1471, 1458, 1363, 1095 cm^{-1}; HRMS calcd for $C_{20}H_{29}NCl$ (M^+ + H) 318.1988, found 318.1983.

Scheme B. *Proposed mechanism for the formation of **3d4**.*



Scheme C. *Attempted rearrangement of **2a** using BF_3•Et_2O (Table 2, entry 8).*

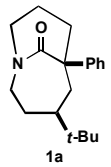


2a

According to the general procedure, **2a** (0.0152 g, 0.051 mmol, 1.0 equiv) was reacted with BF_3•Et_2O (10 drops, excess) in CH_2Cl_2 (5.0 mL) for 18 h at rt. Analysis of

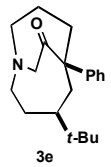
the crude reaction mixture indicated only presence of the starting material. Note: the use of **2a** (0.0073 g, 0.024 mmol, 1.0 equiv), Et_3SiH (0.040 mL, 0.24 mmol, 10.0 equiv) and $BF_3•Et_2O$ (0.10 mL, excess) in CH_2Cl_2 (5.0 mL) for 14 h at rt, according to the procedure for **3d3** also resulted in <5% conversion. Note: the use of other acids known to promote Meinwald rearrangement, also resulted in no conversion. For example, **2a** (0.0129 g, 0.043 mmol, 1.0 equiv) was reacted with $Cu(BF_4)_2•H_2O$[8b, main text] (0.0509 g, 0.22 mmol, 5.0 equiv) in CH_2Cl_2 (5.0 mL) for 15 h, and **2a** (0.0121 g, 0.041 mmol, 1.0 equiv) was reacted with $Sc(OTf)_3$[24, SI] (0.0299 g, 0.061 mmol, 1.5 equiv) in CH_2Cl_2 (5.0 mL) for 17 h at rt. Analysis of the crude reaction mixtures indicated only the presence of the starting material.

*Transformations of **2a** under thermal conditions.*



1a

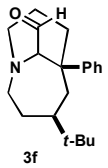
Lactam 1a. A solution of epoxide **2a** (0.0106 g, 0.035 mmol, 1.0 equiv), KCN (0.0455 g, 0.70 mmol, 20.0 equiv) in DMF (10 mL) was heated at 110 °C for 24 h. The reaction mixture was cooled to rt, diluted with EtOAc (50 mL), washed with water (4 x 20 mL), brine (1 x 20 mL), dried, concentrated and purified by chromatography (1/2 EtOAc/hexanes) the title compound. Yield 86% (0.0086 g, 0.030 mmol). Spectroscopic properties matched those previously described. Note: the reaction of **2a** (0.0252 g, 0.084 mmol) with KCN (0.0279 g, 0.42 mmol, 5.0 equiv) and $LiClO_4$ (0.0447 g, 0.42 mmol, 5.0 equiv) in CH_3CN (10 mL) at 70 °C for 80 h afforded **1a** in 45% yield at 70% conversion.



3e

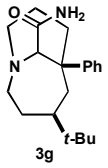
4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.2]undecan-11-one (3e). According to the procedure for **1a**, the reaction of **2a** (0.0170 g, 0.057 mmol, 1.0 equiv) and NaI (0.17 g, 1.1 mmol, 20.0 equiv) in DMF (10 mL) at 110 °C for 16 h, afforded after chromatography (1/4 EtOAc/hexanes) the title compound as oil (R_f = 0.22, 1/4 EtOAc/hexanes). Yield 51% (0.0087 g, 0.029 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H), 1.32-1.49 (m, 2H), 1.78-2.-2 (m, 3H), 2.14 (dd, *J* = 2.0, 13.0 Hz, 1H), 2.33 (tt, *J* = 2.6, 13.4 Hz, 1H), 2.41-2.52 (m, 1H), 2.59 (dd, *J* = 3.7, 13.1 Hz, 1H), 2.76 (dt, *J* = 4.0, 13.2 Hz, 1H), 3.14-3.31 (m, 2H), 3.59 (dt, *J* = 3.0, 14.5 Hz, 1H), 3.73 (q, *J* = 16.9 Hz, 2H), 7.13-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 28.4, 31.5, 35.2, 40.9, 42.0, 46.6, 56.9, 57.1, 58.6, 65.5, 126.0, 126.2, 128.1, 151.6, 203.1; IR (neat) 2960, 2918,

2870, 1697, 1444, 1365, 1163, 1116 cm^{-1}; HRMS calcd for $C_{20}H_{30}NO$ (M^+ + H) 300.2327, found 300.2304.



3f

4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decane-10-carbaldehyde (3f). 10 mL MW vial (Biotage) was charged with epoxide **2a** (0.0046 g, 0.015 mmol, 1.0 equiv) and toluene (3.0 mL, 0.005 M), the vial was sealed and heated to 200 °C for 10 h. The solvent was removed and the reaction was analyzed by NMR. Yield 81% (vs. nitromethane as the internal standard), dr = 86:14. Note: the compound is very unstable, it decomposes rapidly over time, attempted purification led only to decomposition products. (R_f = ~0.50, 1/1 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) (major diastereoisomer) δ 0.88 (s, 9H), 1.53 (m, 3H), 1.80 (m, 2H), 1.86-1.96 (m, 1H), 2.02-2.20 (m, 2H), 2.35-2.44 (m, 1H), 2.72 (dt, *J* = 4.7, 13.5 Hz, 2H), 2.93 (dt, *J* = 3.9, 13.4 Hz, 1H), 3.77 (ddd, *J* = 1.8, 5.2, 13.6 Hz, 1H), 4.09 (s, 1H), 7.17-7.55 (m, 5H), 9.44 (s, 1H); (minor diastereoisomer, diagnostic peaks) δ 4.20 (s, 1H), 9.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) (major diastereoisomer) δ 21.6, 27.5, 30.4, 32.5, 33.8, 38.9, 48.2, 49.3, 49.7, 56.3, 66.9, 125.1, 125.6, 128.4, 150.1, 199.7; IR (neat) 2956, 2943, 2706, 1726, 1444, 1365, 1224, 1155, 1099 cm^{-1}; HRMS calcd for $C_{20}H_{30}NO$ (M^+ + H) 300.2327, found 300.2301. Note: the reaction carried out in DMF (120 °C, 14 h) resulted in decomposition; in MeOH (150 °C, 2 h) (MW) a complex mixture was formed (27% yield of **3f**); in $PhCH_3$ (110 °C, 15 h) <5% conversion; in $PhCH_3$ (150 °C, 14 h) 23% conversion; in $PhCH_3$ (180 °C, 5 h) 38% conversion. All reactions at c = 0.005 M.

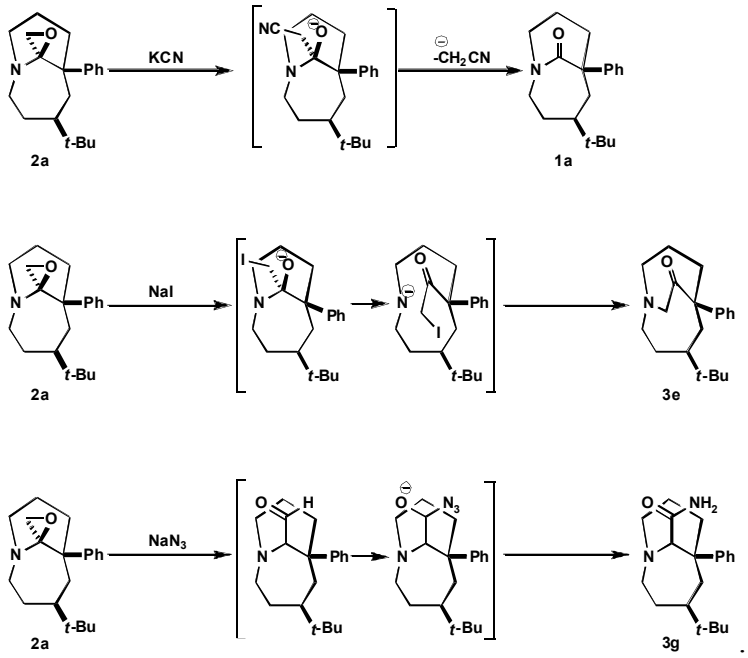


3g

4-*tert*-Butyl-6-phenyl-1-azabicyclo[4.3.1]decane-10-carboxamide (3g). A solution of epoxide **2a** (0.0221 g, 0.074 mmol, 1.0 equiv), NaN_3 (0.21 g, 3.3 mmol, 50 equiv) and DMF (10 mL) was heated at 110 °C for 21 h. The reaction mixture was cooled to rt, diluted with EtOAc (50 mL), washed with water (4 x 20 mL), brine (1 x 20 mL), dried, concentrated and purified by chromatography (1/10/90 NH_3/MeOH/CH_2Cl_2) to afford the the title compound as oil (R_f = 0.40, 1/10/90 NH_3/MeOH/CH_2Cl_2). Yield 62% (0.0143 g, 0.045 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 9H), 1.46-1.76 (m, 6H), 1.91 (dd, *J* = 6.9, 15.0 Hz, 1H), 2.11-2.29 (m, 2H), 2.34 (d, *J* = 14.6 Hz, 1H), 2.57-2.72 (m, 2H), 2.04 (d, *J* = 15.0 Hz, 1H), 3.83 (dt, *J* = 2.8, 15.2 Hz, 1H), 4.40 (dd, *J* = 4.8, 13.7 Hz, 1H), 4.29 (s, 1H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 26.2, 28.4, 34.0, 35.9, 39.3, 44.8, 48.9,

49.8, 51.1, 59.9, 126.1, 126.9, 128.5, 149.7, 177.5; IR (neat) 3387, 2959, 2926, 1661, 1480, 1430, 1366, 1220, 1156, 1100 cm^{-1}; HRMS calcd for $C_{20}H_{31}N_2O$ (M^+ + H) 315.24361, found 315.2430.

Scheme D. *Proposed intermediates in formation of **1a**, **3e** and **3g**.*



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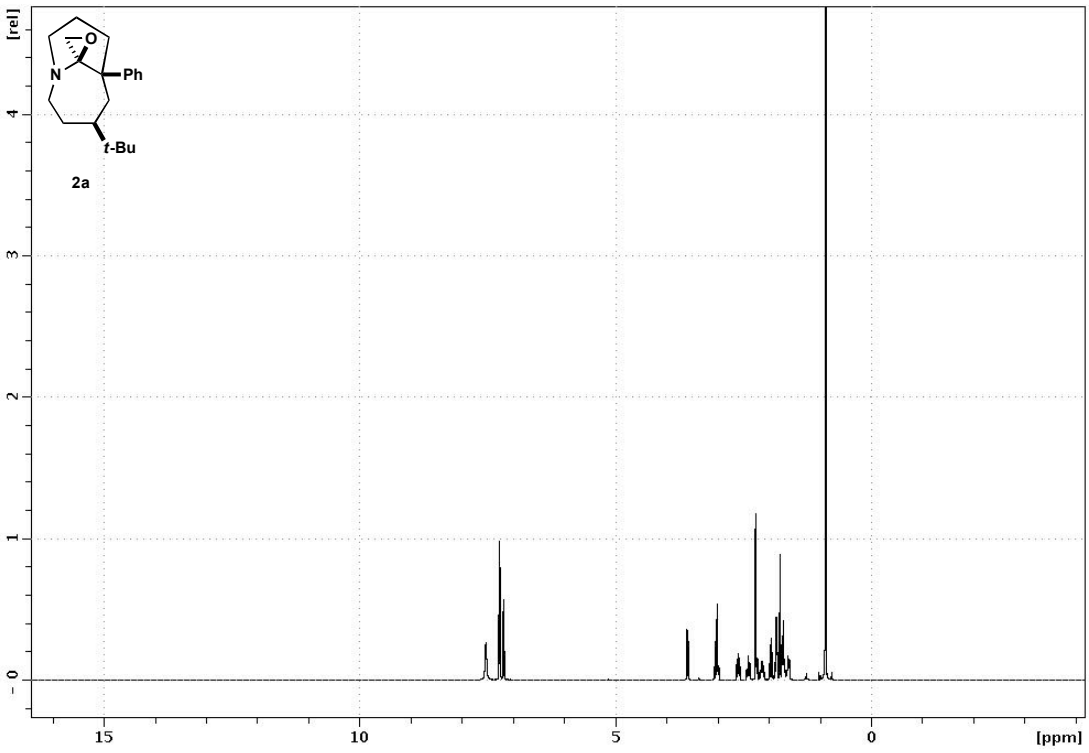
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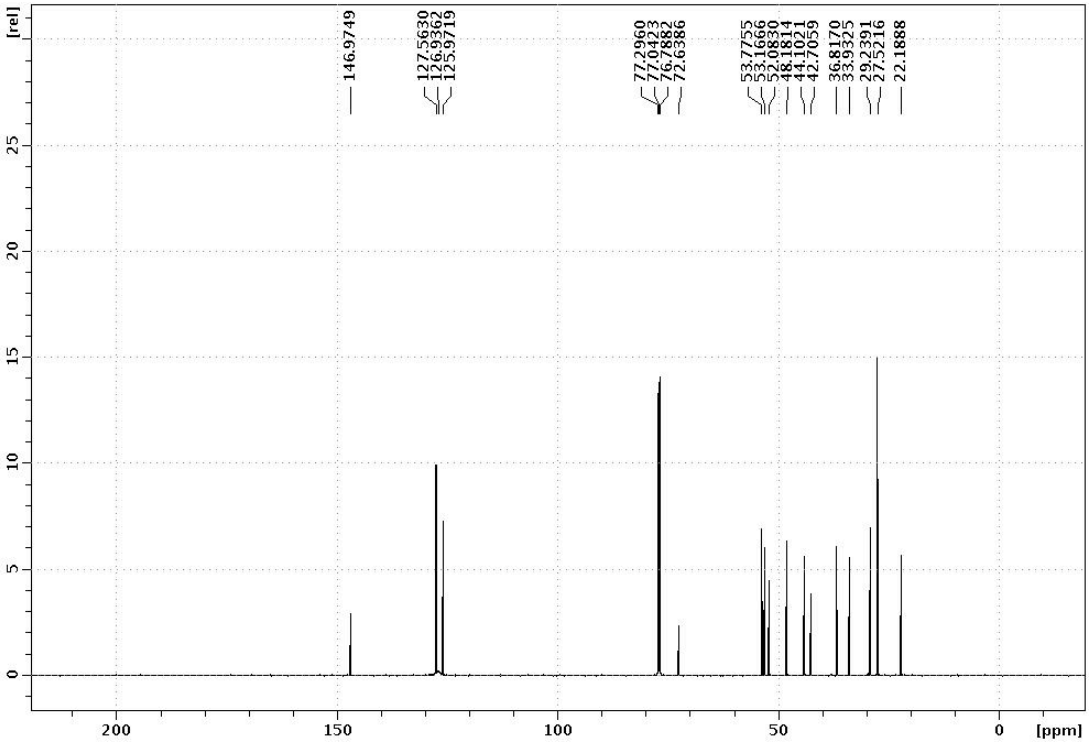
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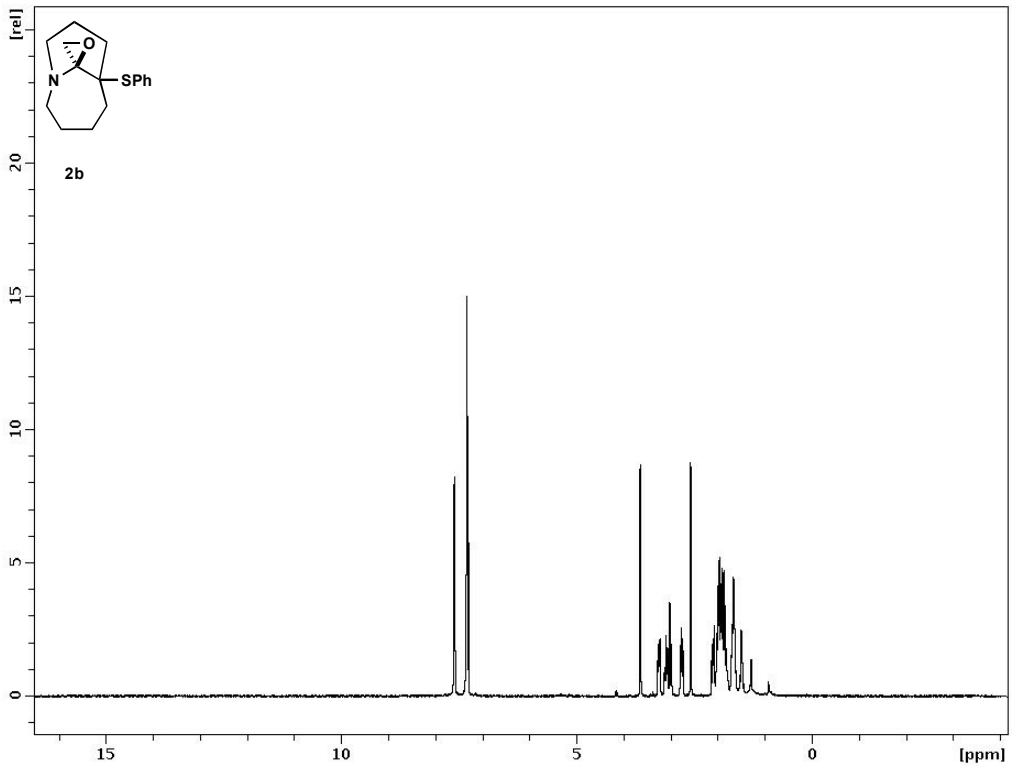
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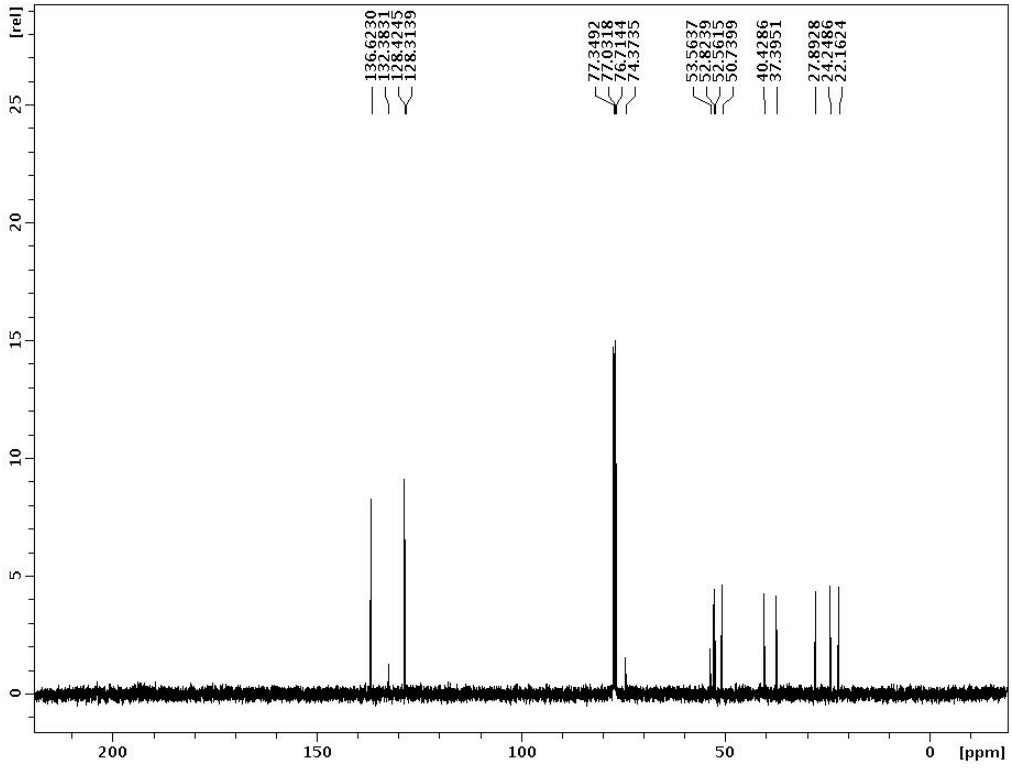
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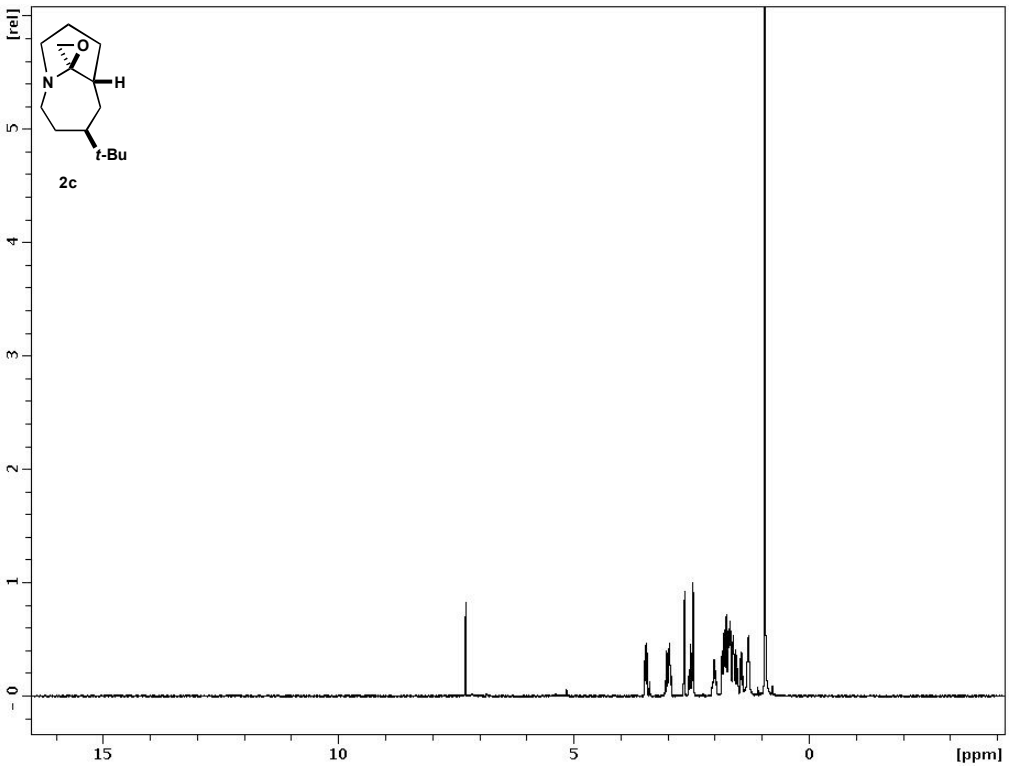
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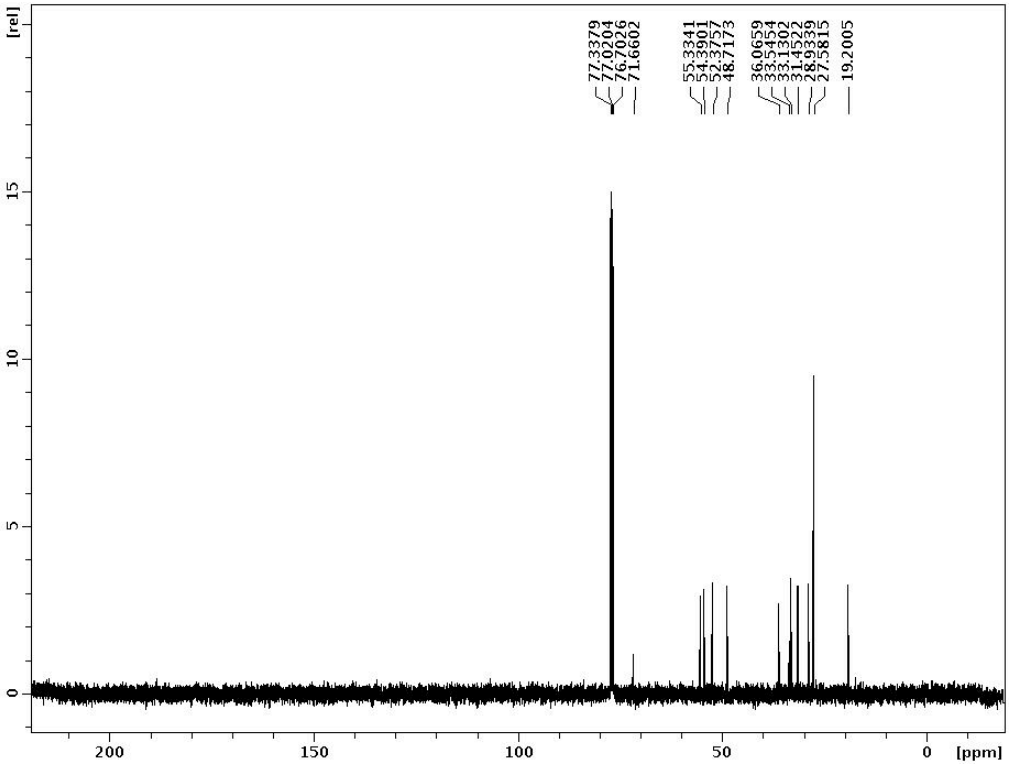
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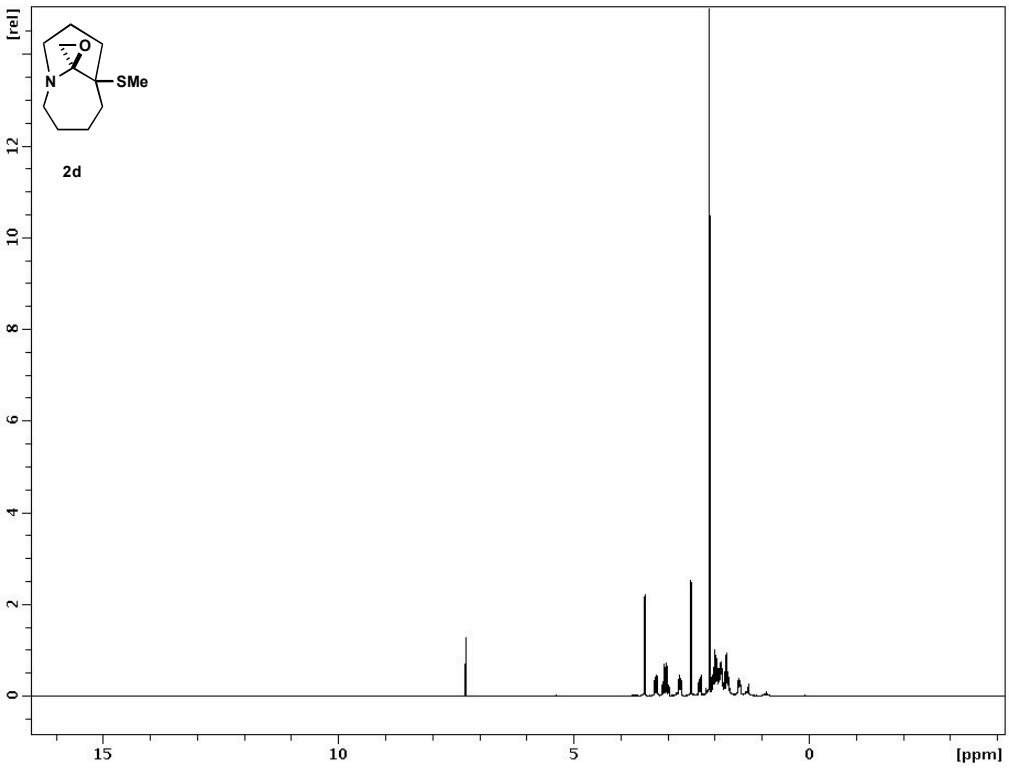
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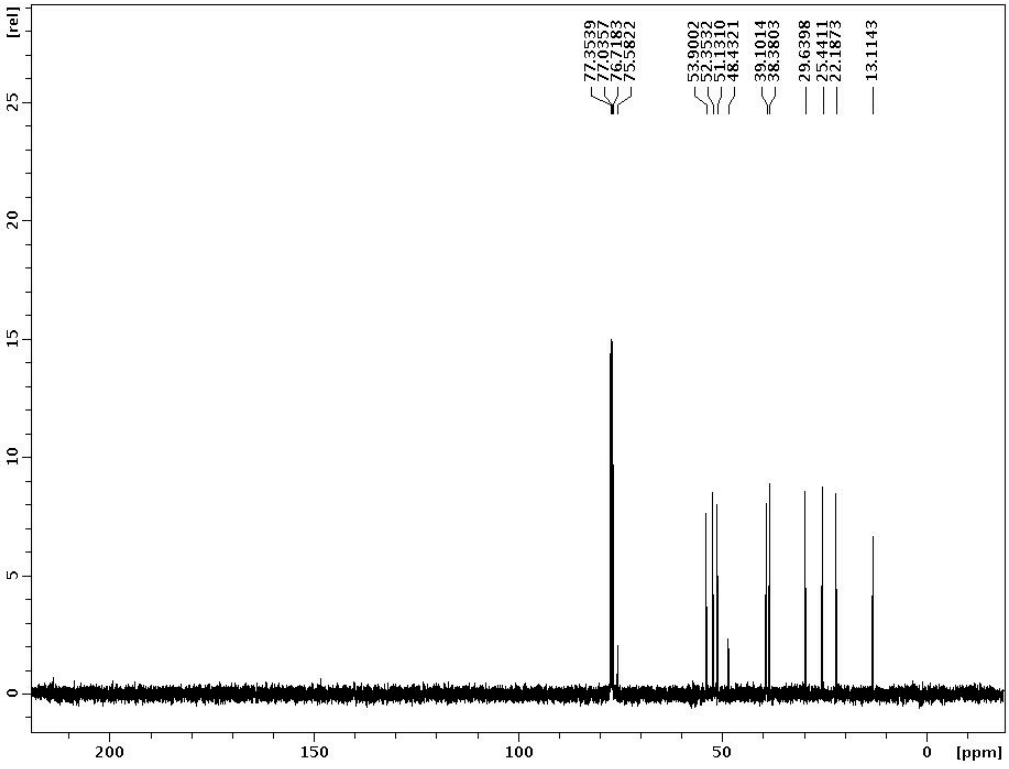
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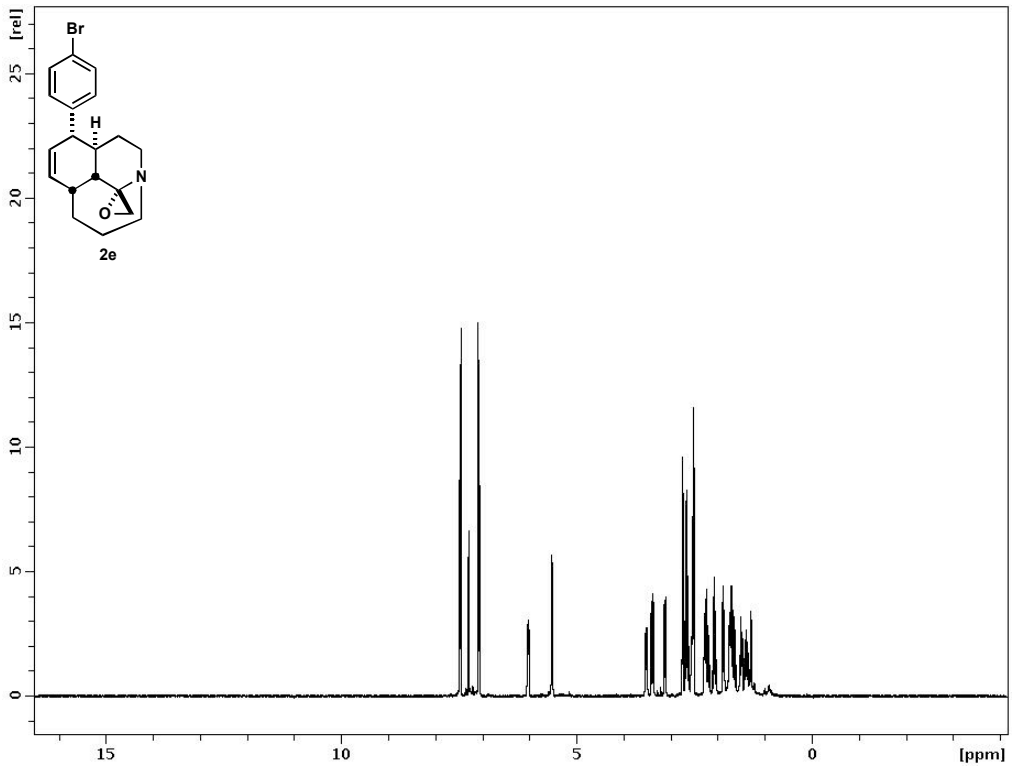
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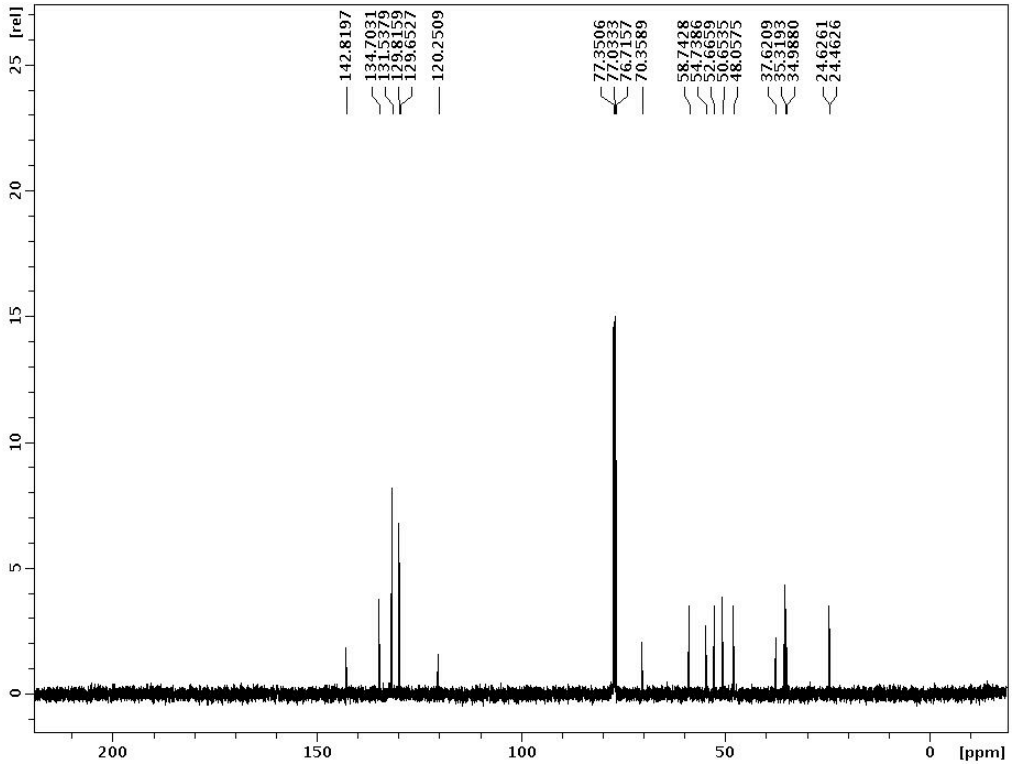
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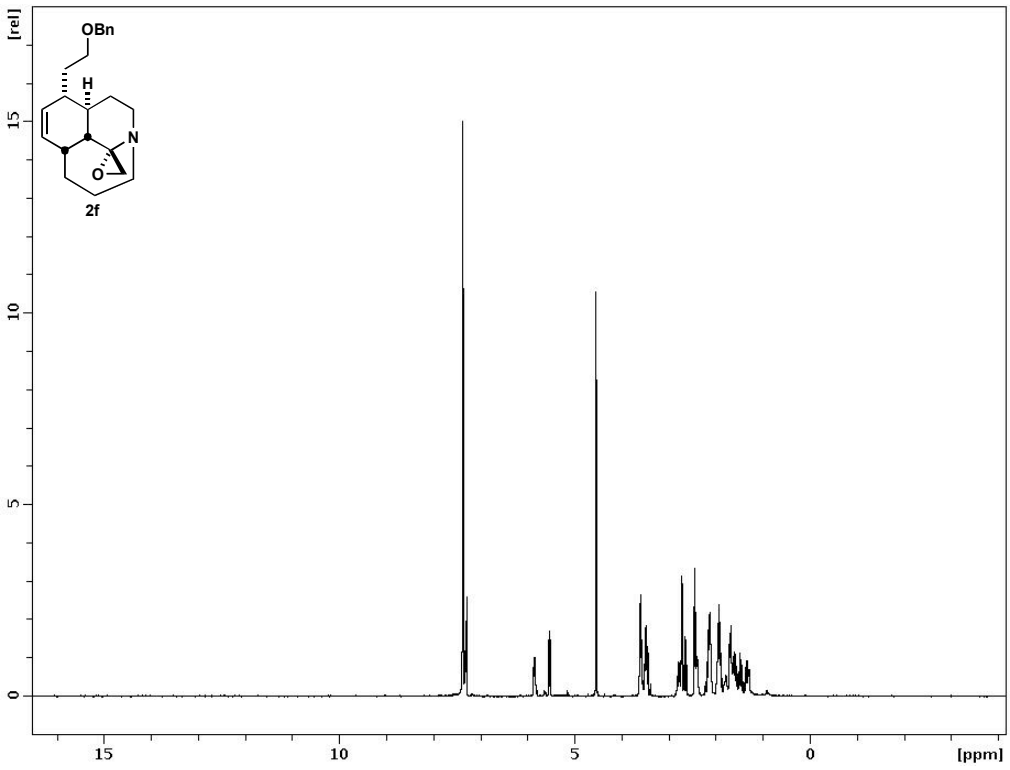
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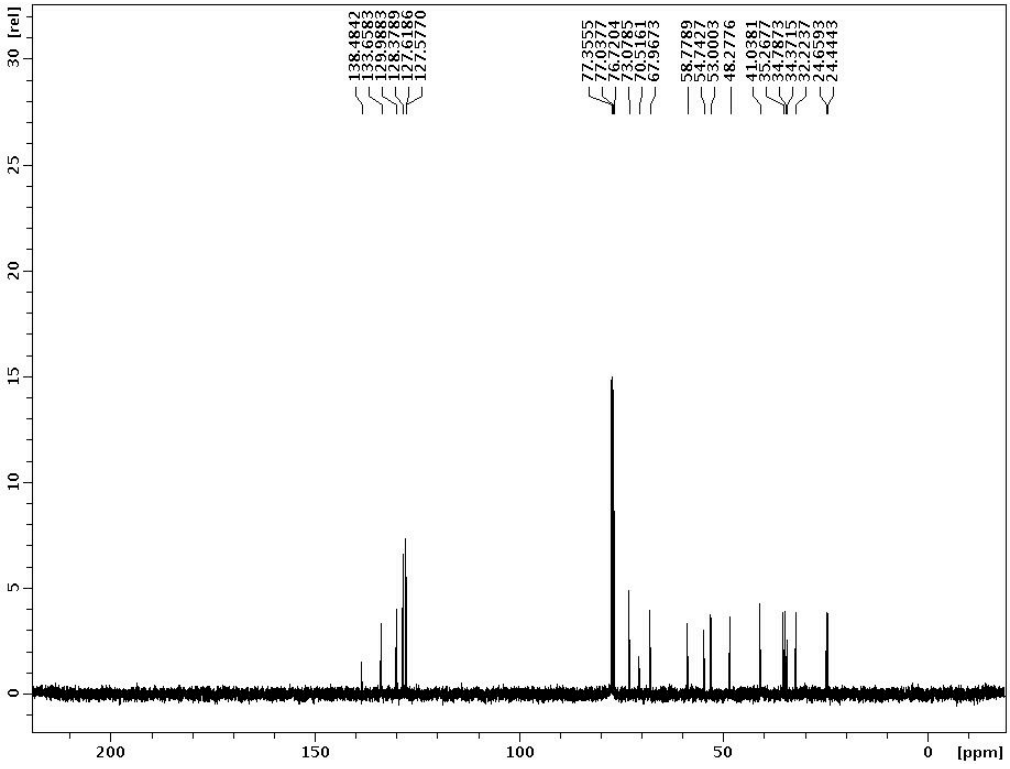
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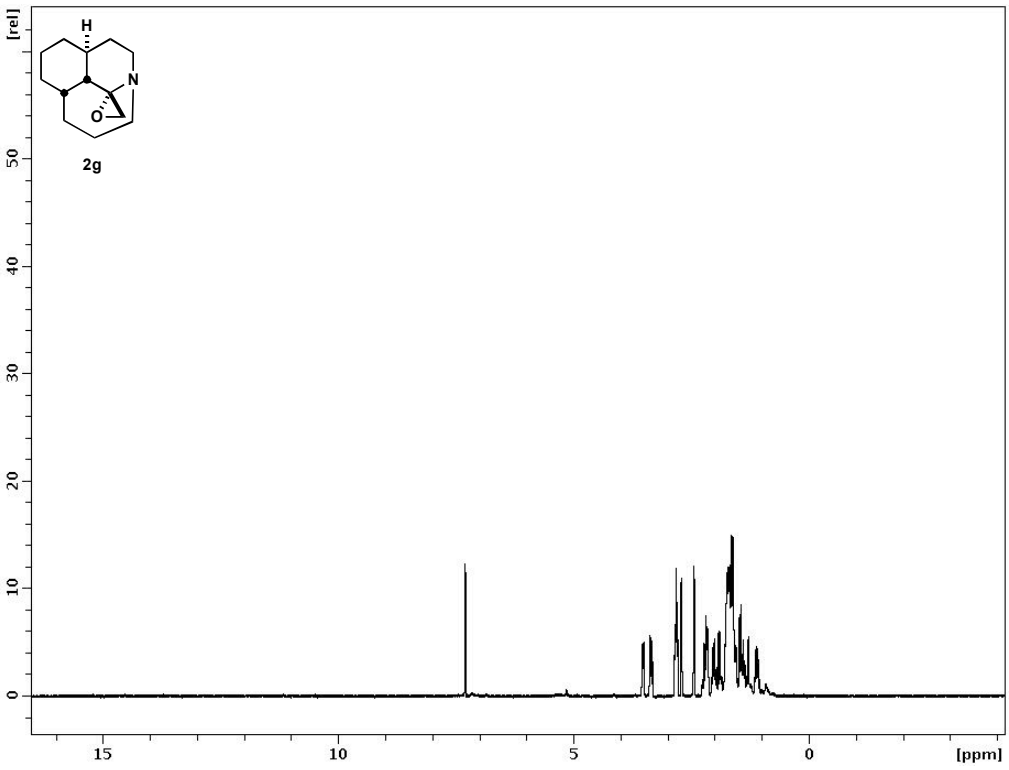
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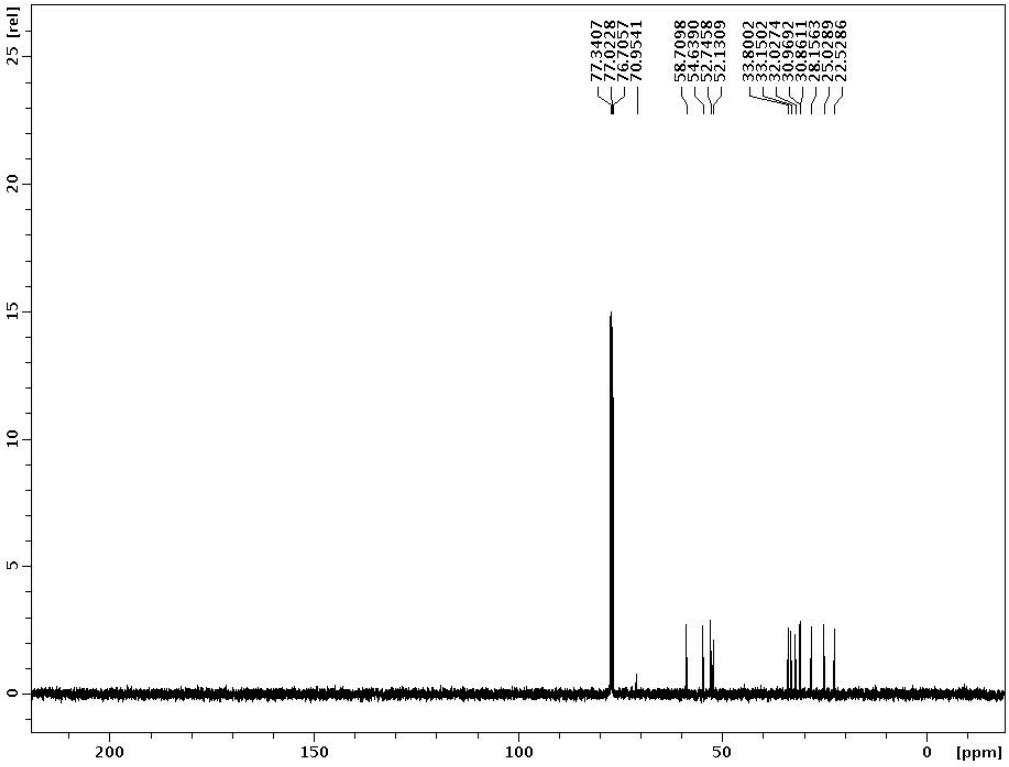
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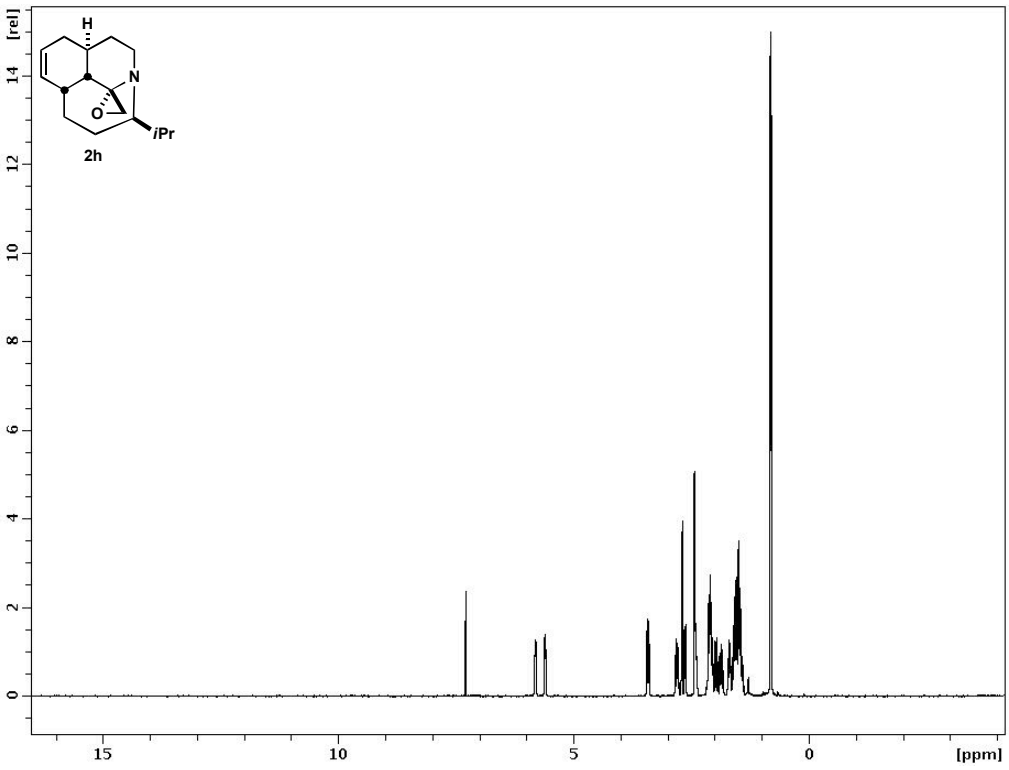
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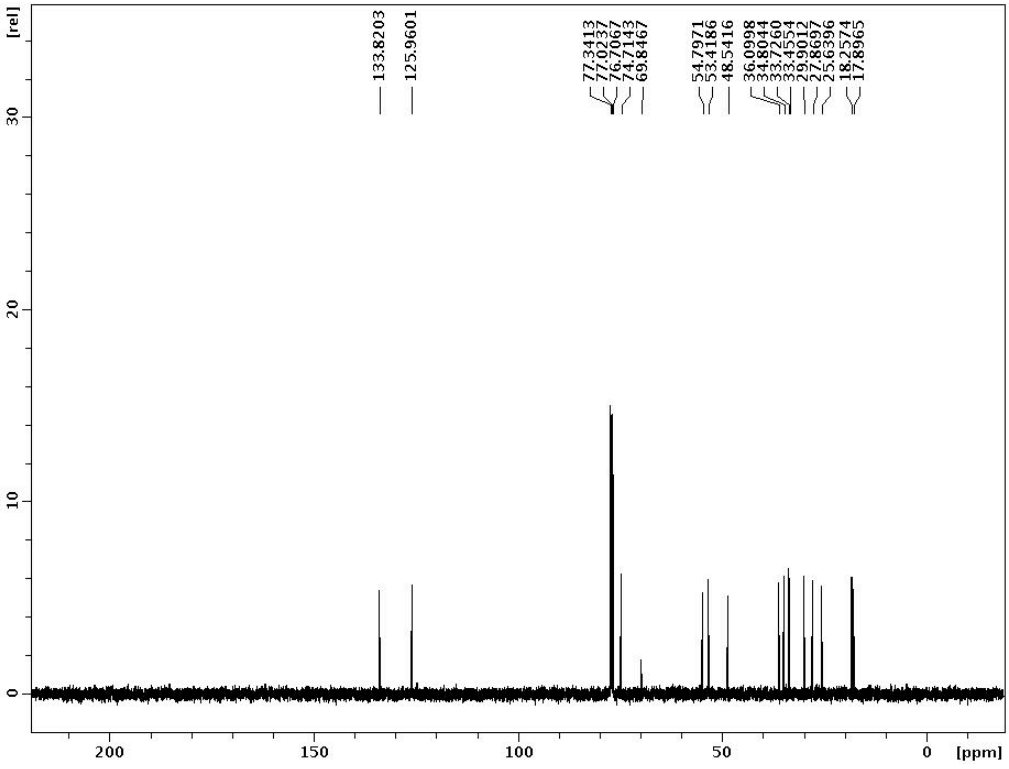
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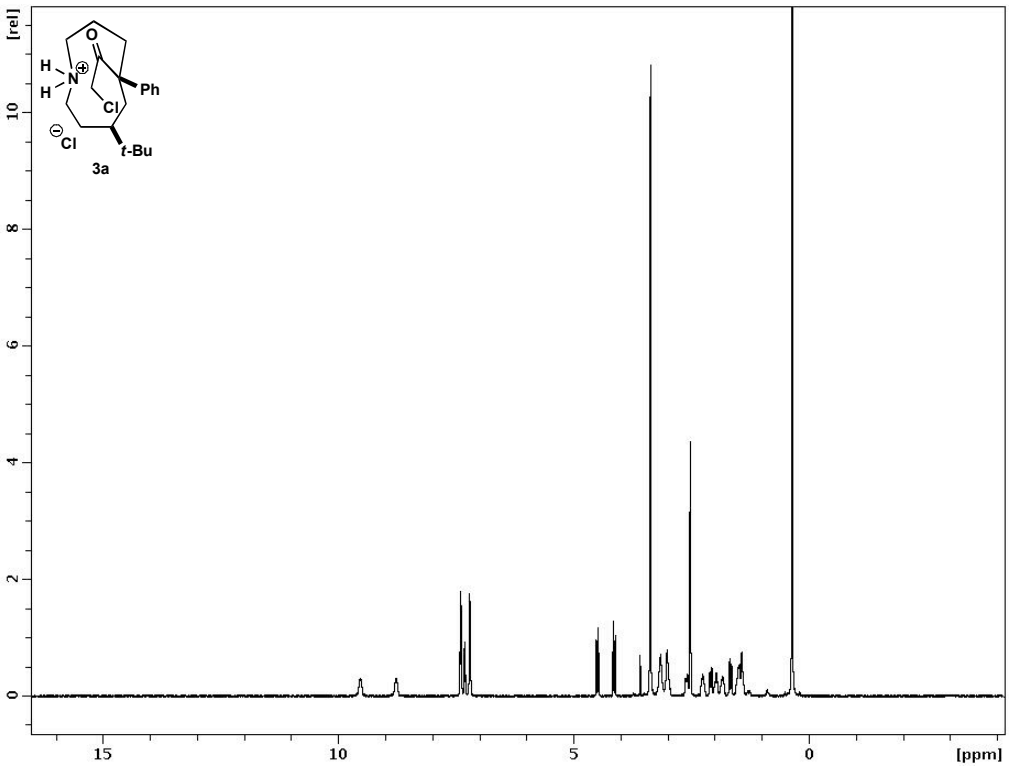
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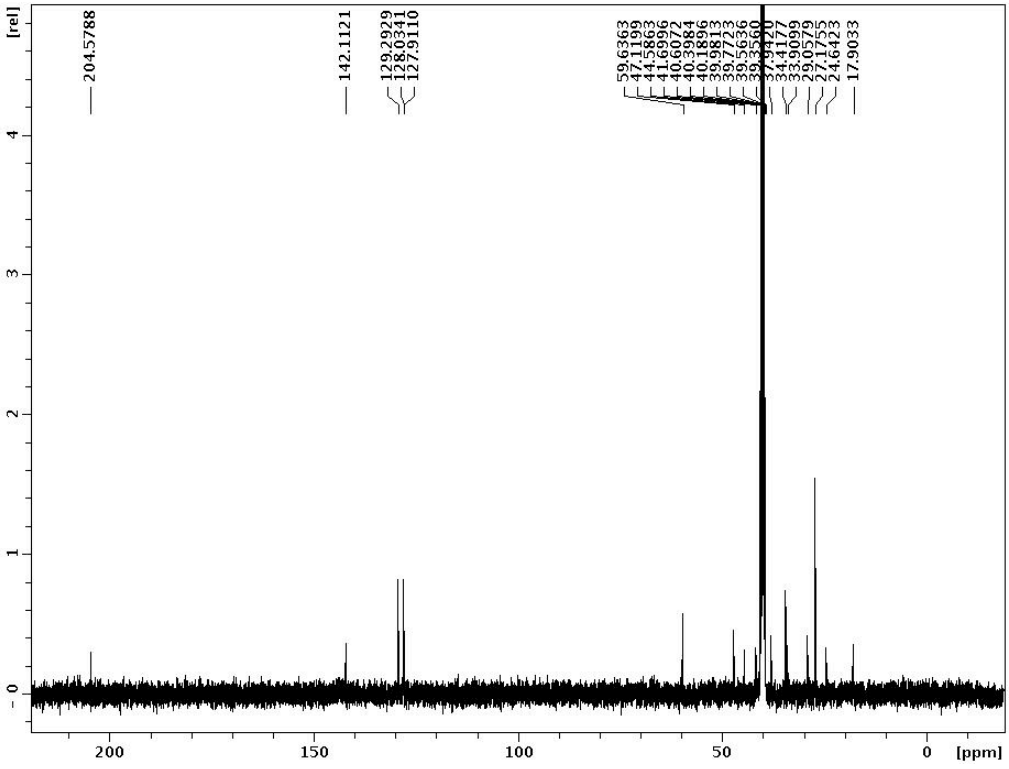
N
H
Cl
Ph
Cl
t-Bu
3a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2
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127.9110
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41.6996
40.6072
40.3984
40.1896
39.9813
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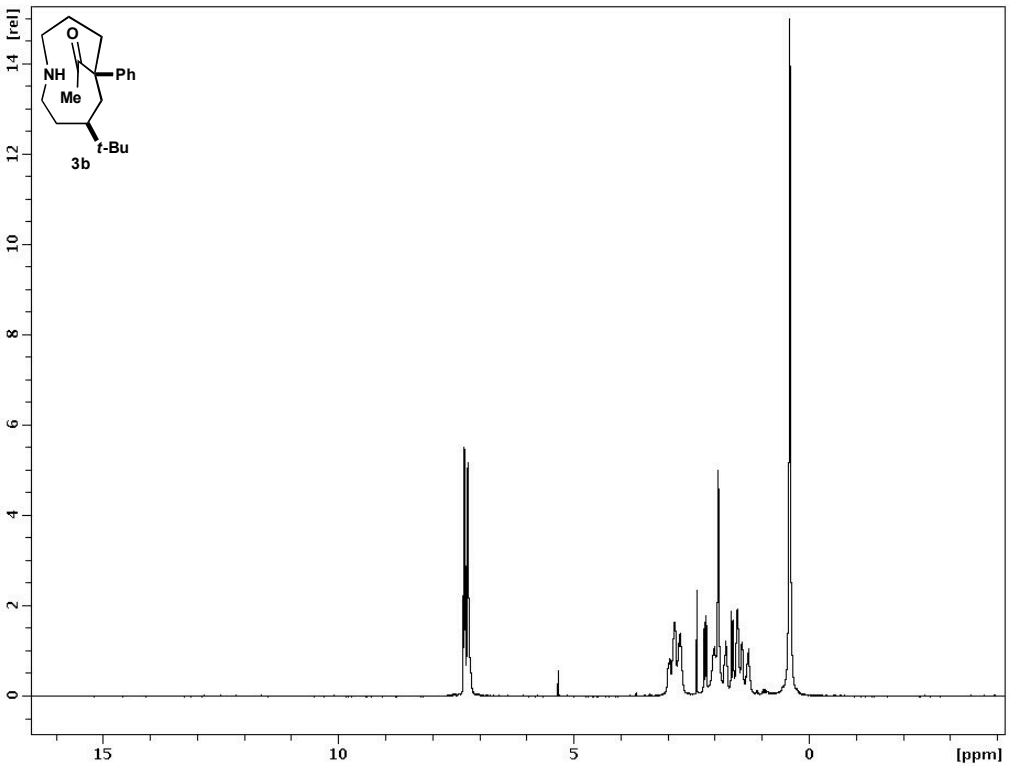
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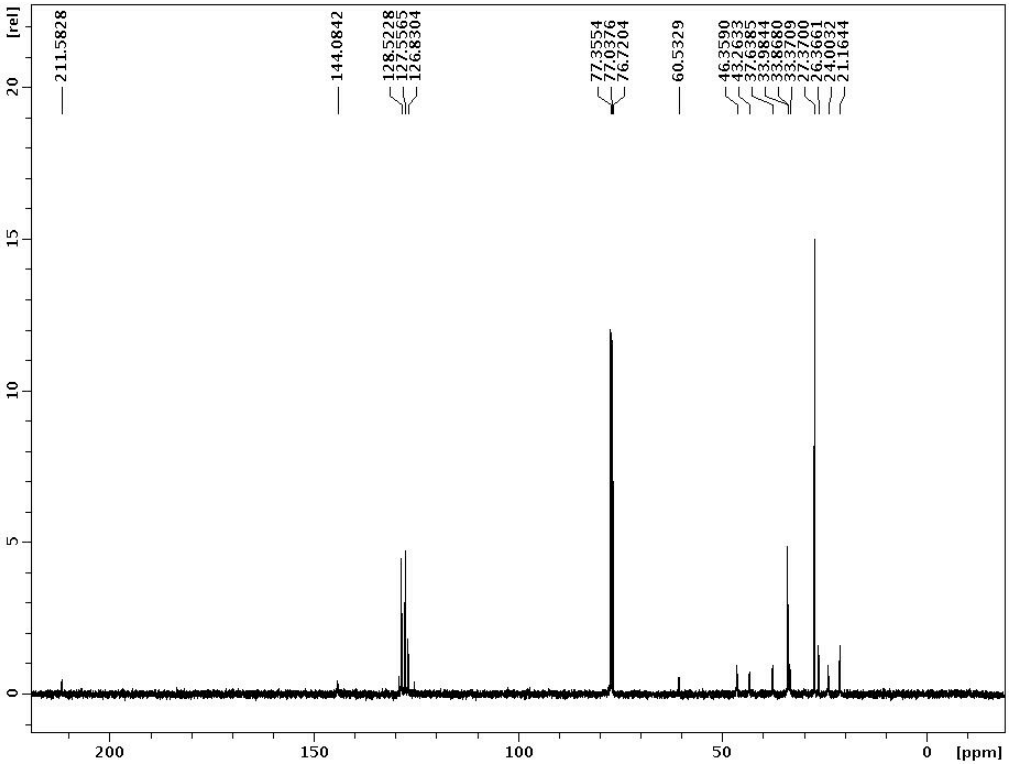
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60.5329
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43.2633
37.6385
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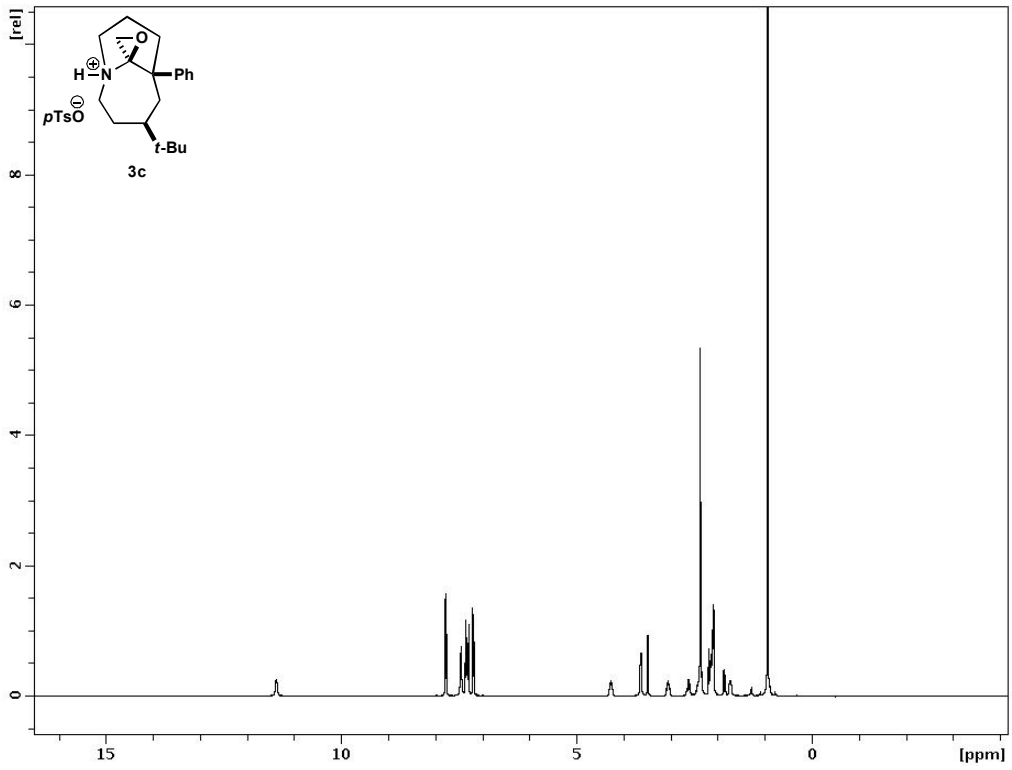
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pTsO
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3c
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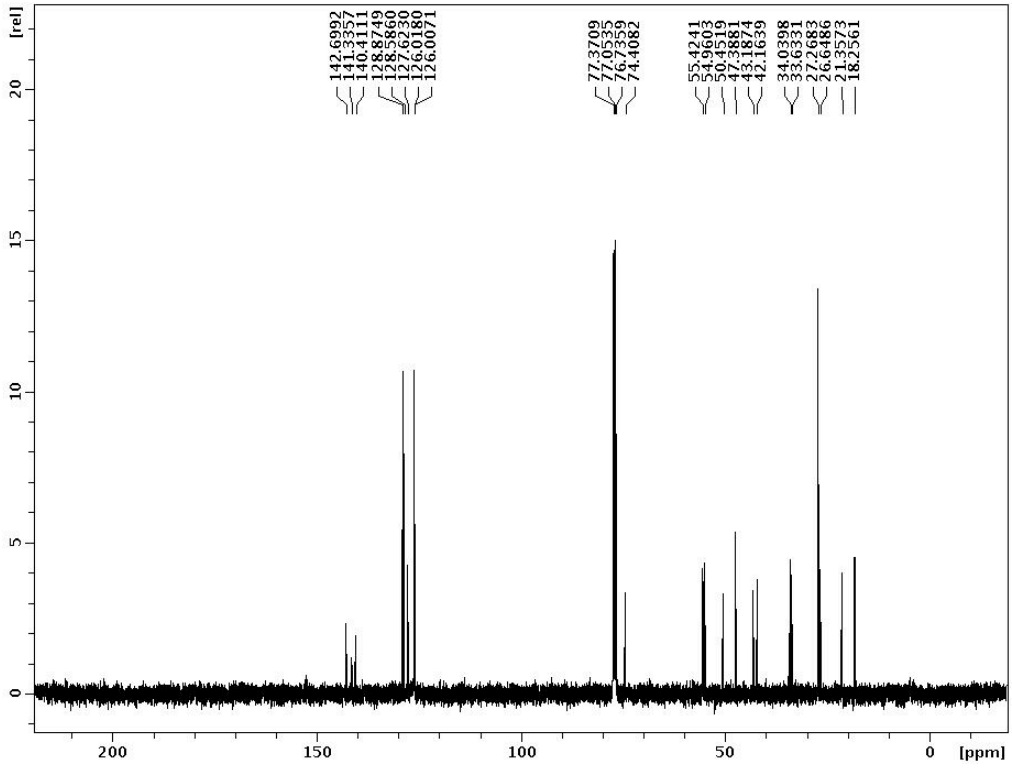
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74.4082
55.4241
54.9603
50.4519
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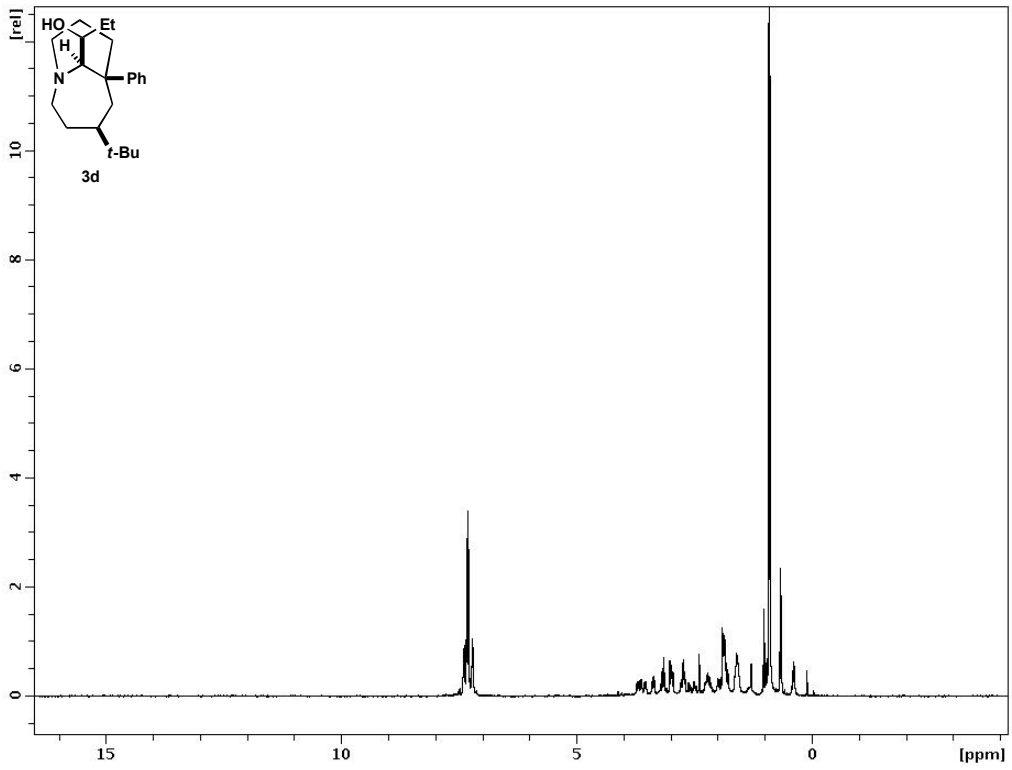
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N
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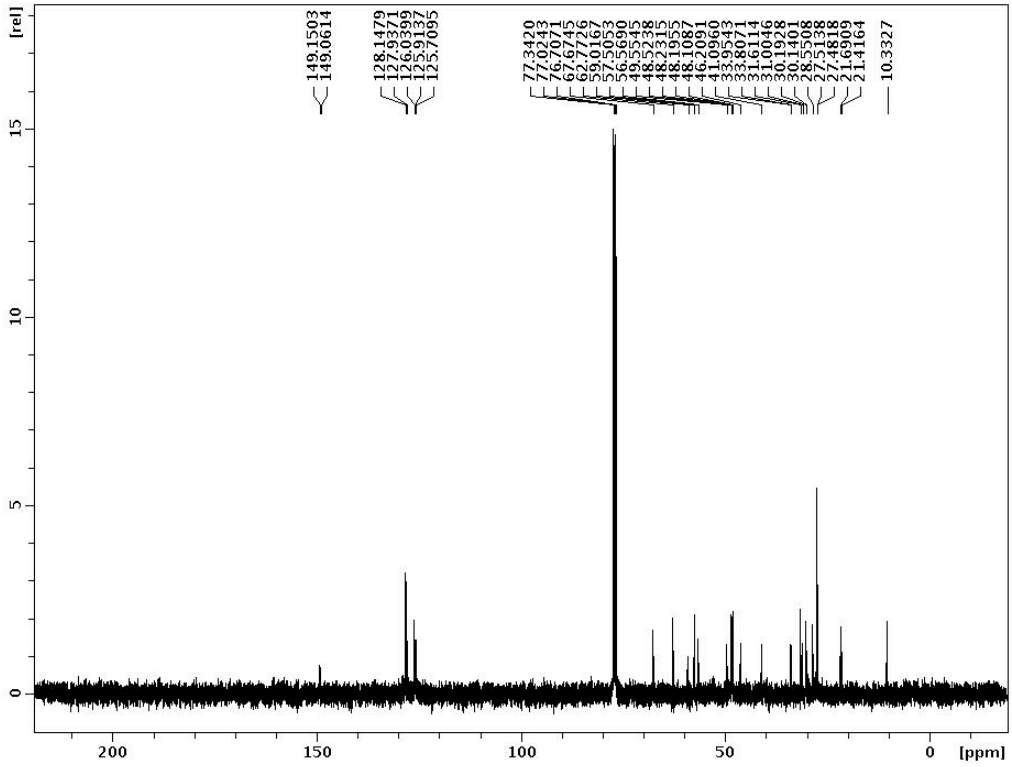
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76.7071
67.6745
62.7726
59.0167
57.5053
56.5690
49.5545
48.5238
48.2315
48.1057
46.2081
41.0960
33.9543
33.8071
31.6114
31.0046
30.1928
30.1401
28.5508
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27.4818
21.6909
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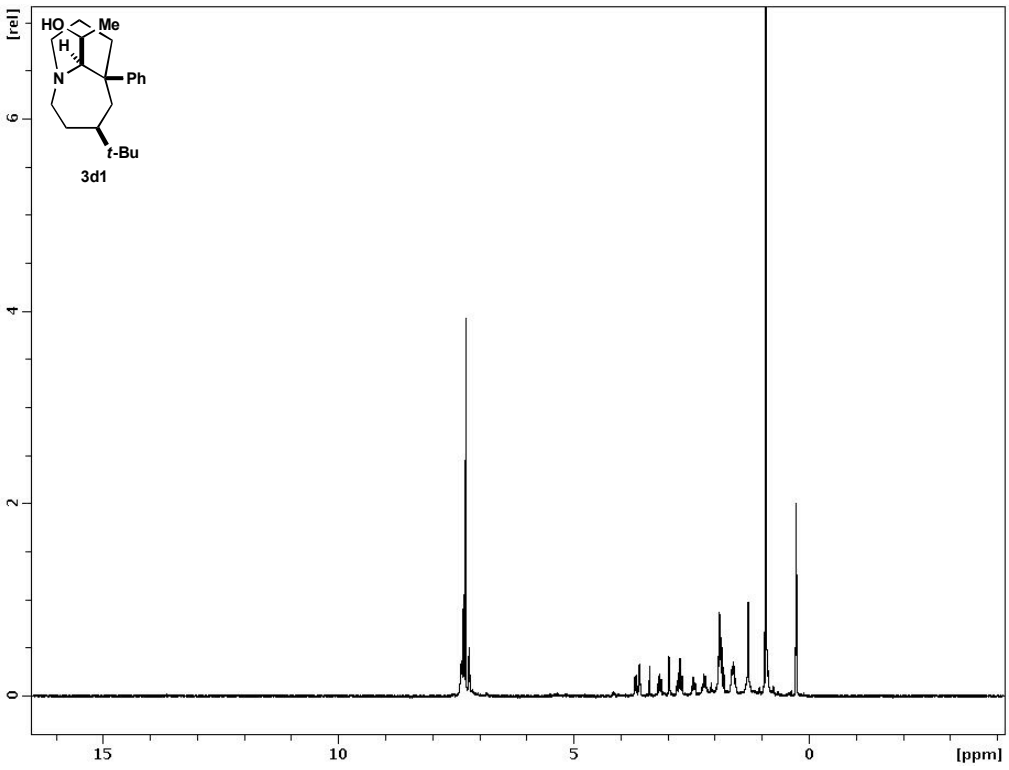
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Me
H
N
Ph
t-Bu
3d1
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6
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10
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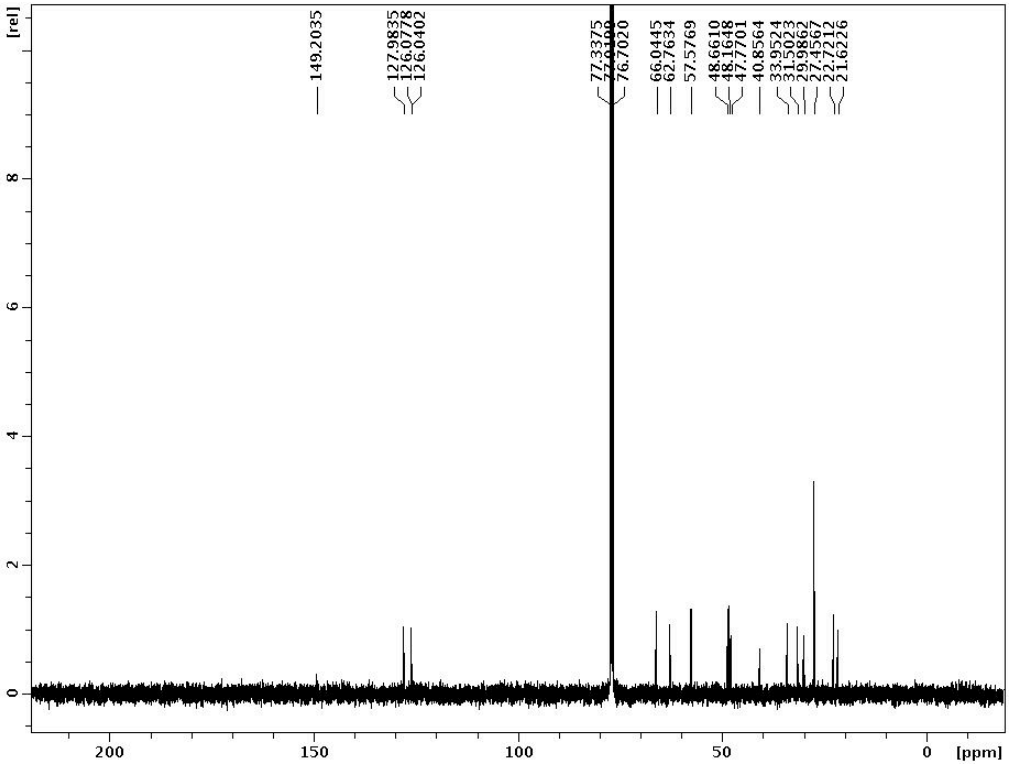
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77.0100
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66.0445
62.7634
57.5769
48.6610
48.1648
47.7701
40.8564
33.9524
31.5023
29.9862
27.4567
22.7212
21.6226
0
2
4
6
8
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150
100
50
0
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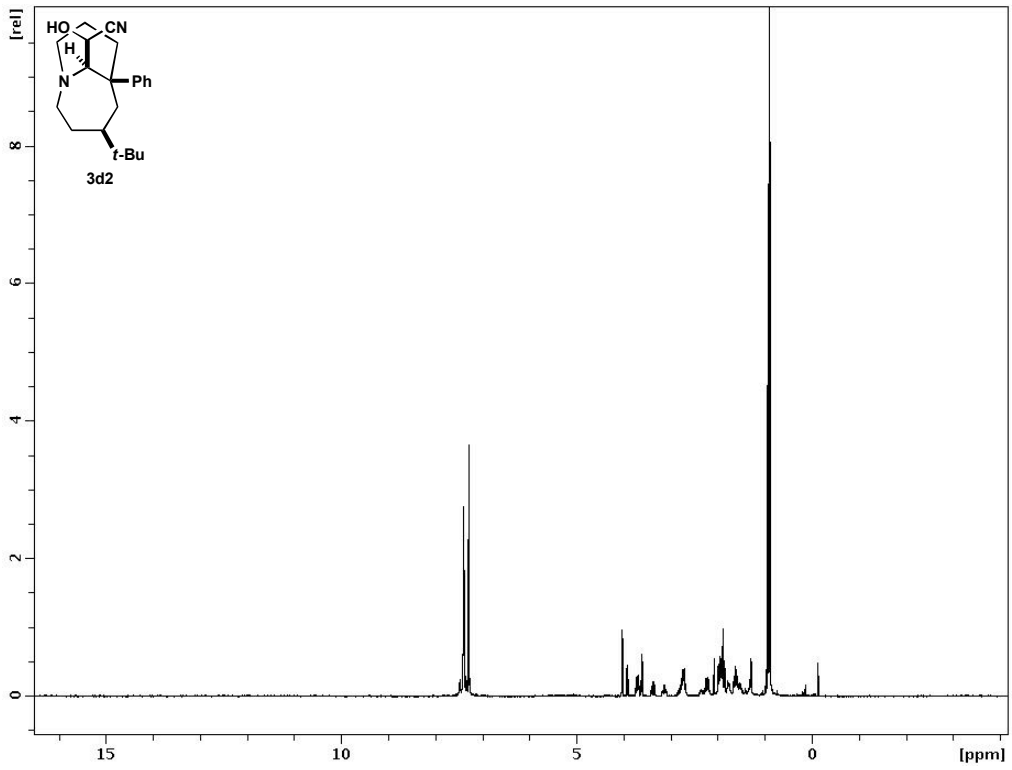
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CN
H
N
Ph
t-Bu
3d2
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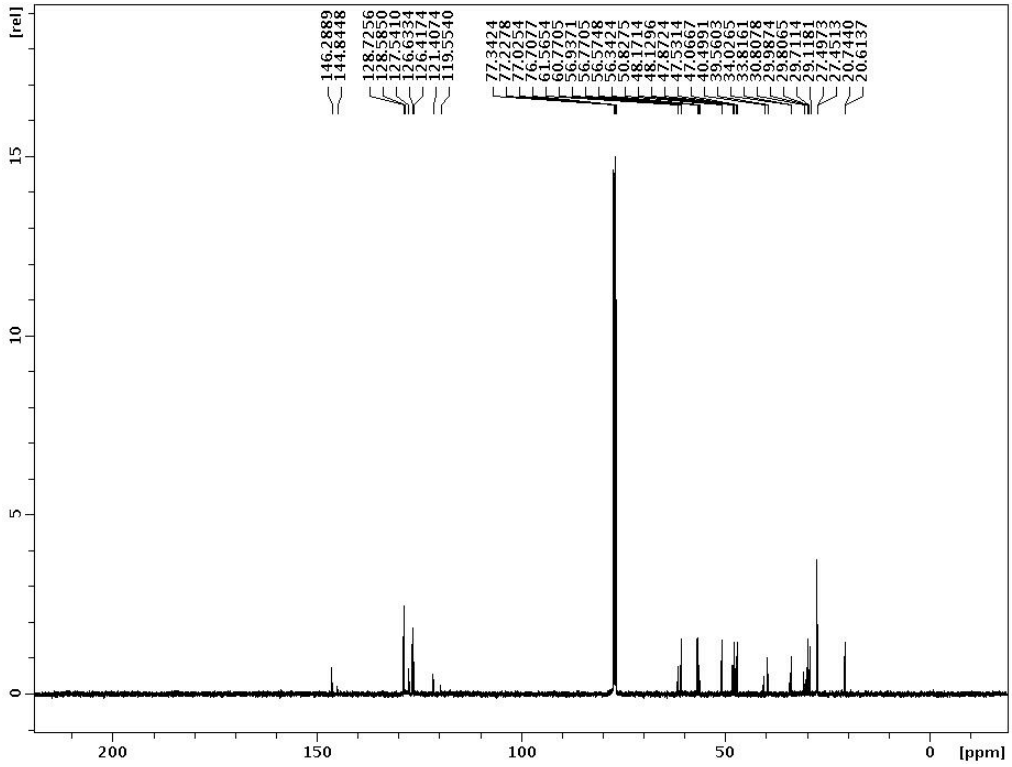
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77.0254
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61.5654
60.7705
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56.7705
56.5748
56.3424
50.8275
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39.5693
34.0165
33.8161
30.8078
29.9874
29.8065
29.7114
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10
15
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100
50
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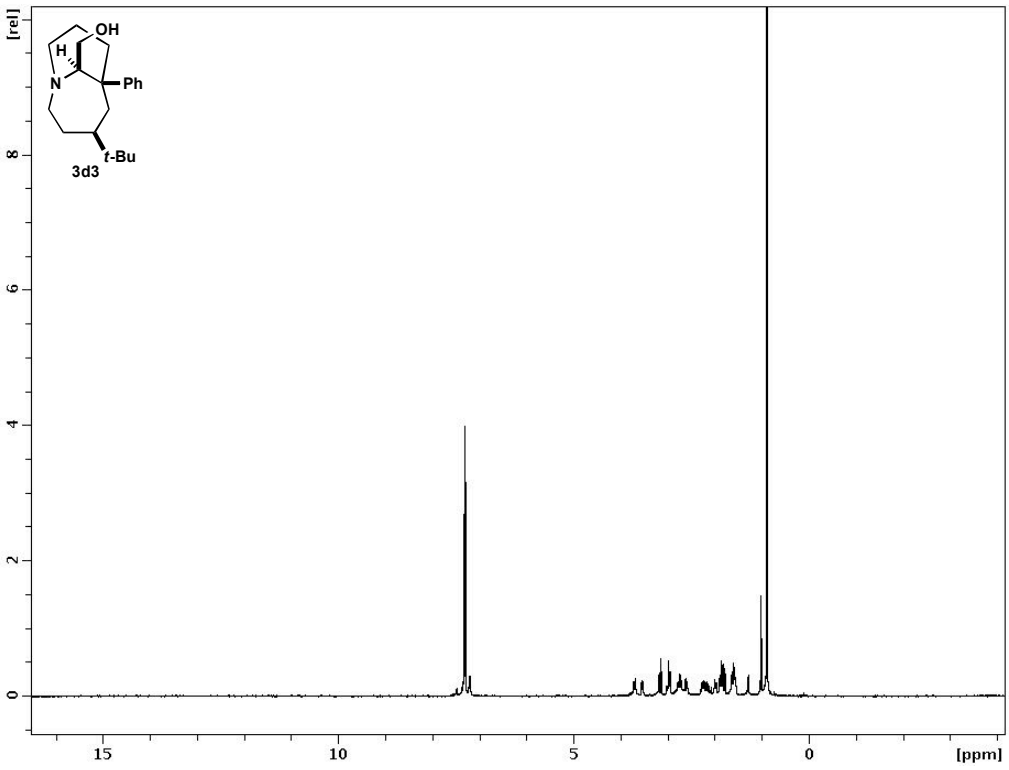
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N
Ph
t-Bu
3d3
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6
8
15
10
5
0
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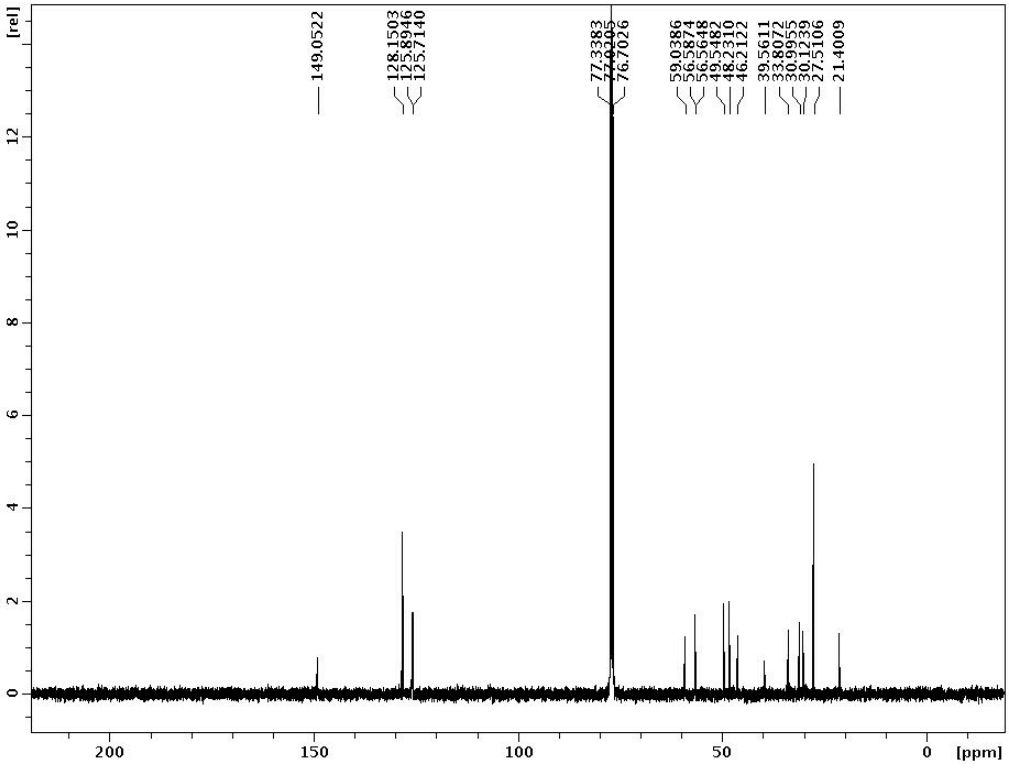
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48.2310
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39.5611
33.8072
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2
4
6
8
10
12
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100
50
0
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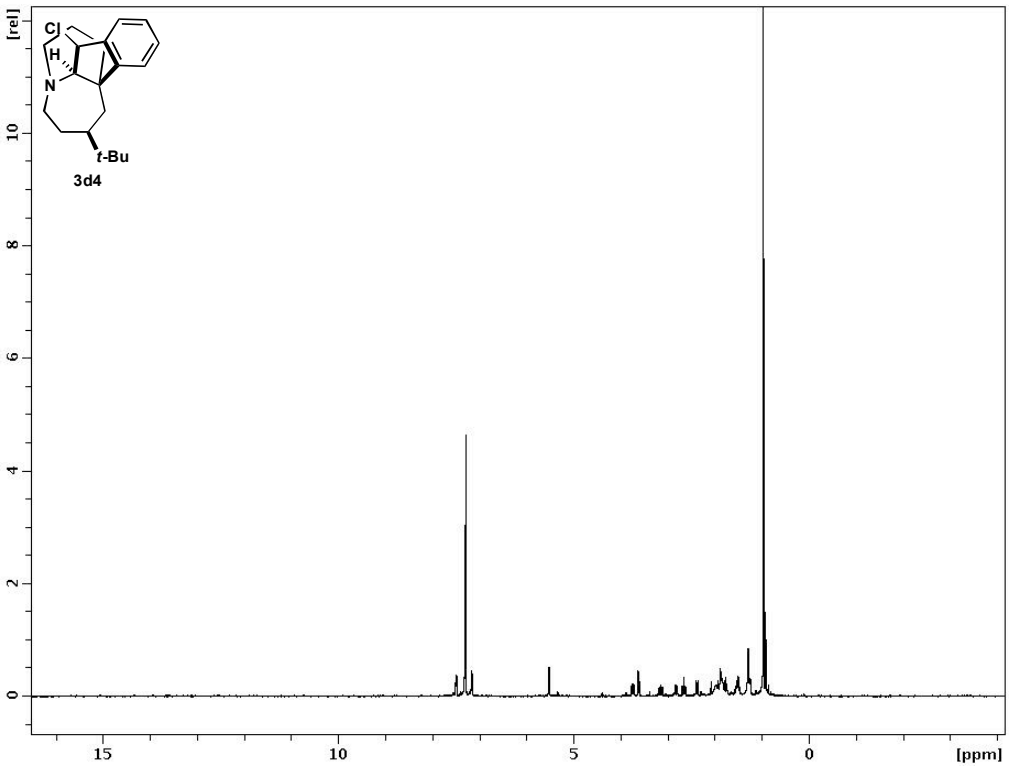
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t-Bu
3d4
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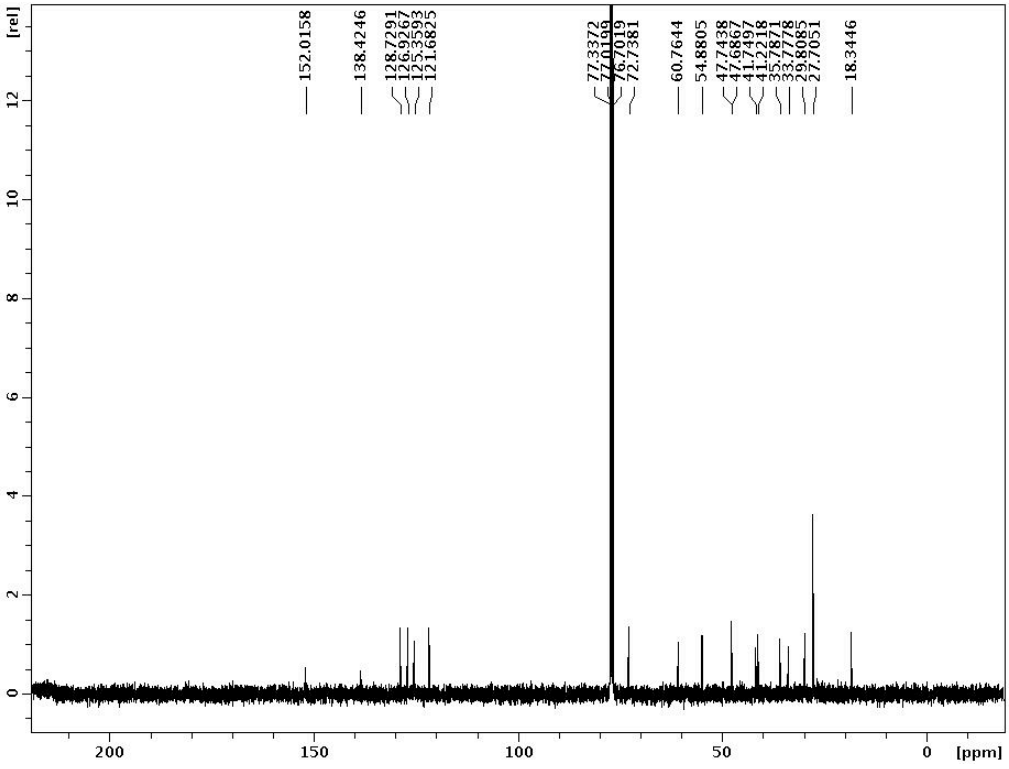
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54.8805
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47.6867
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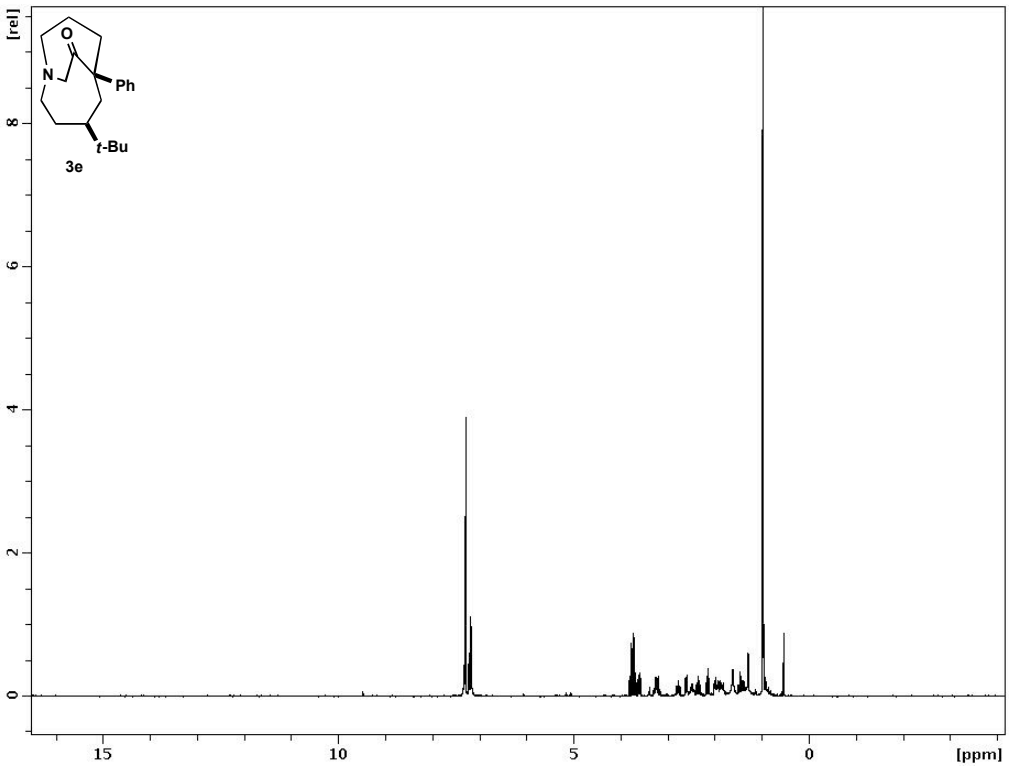
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N
Ph
t-Bu
3e
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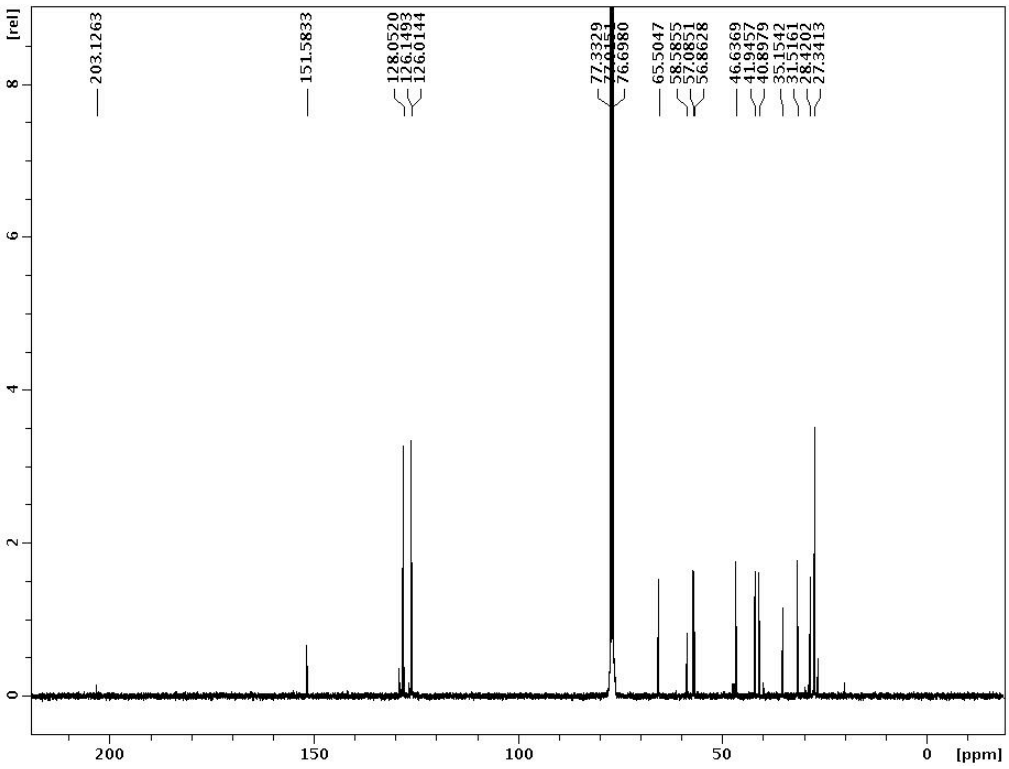
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57.0851
56.8628
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27.3413
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0
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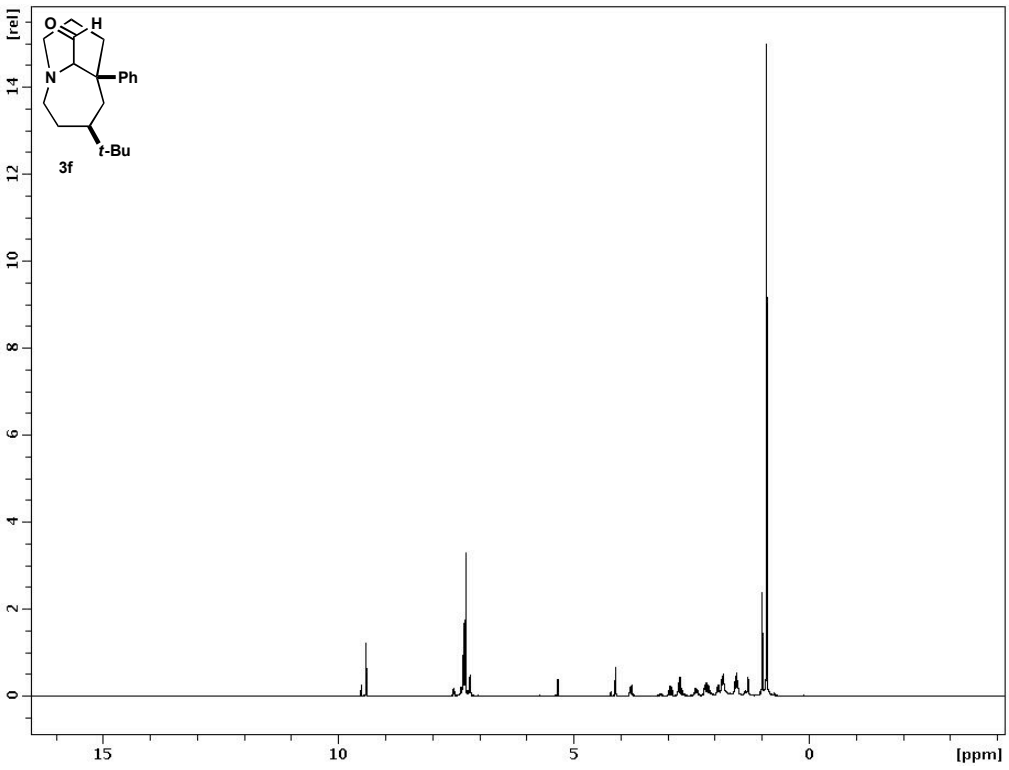
O
H
N
Ph
t-Bu
3f
[rel]
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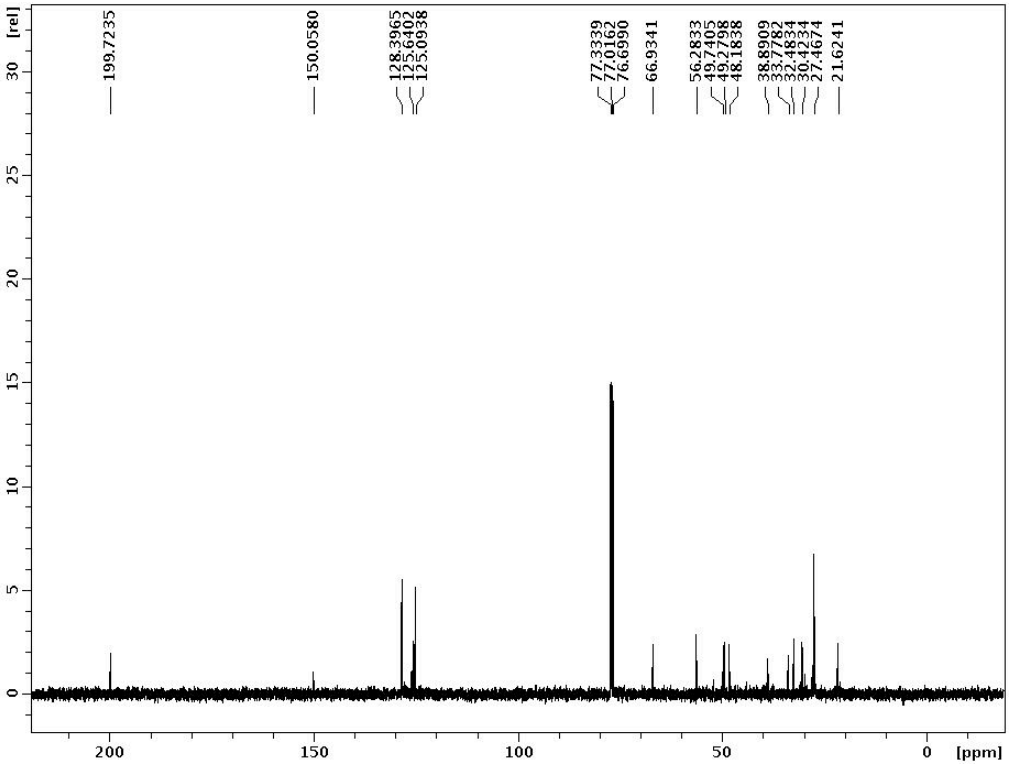
4
6
8
10
12
14
15
10
5
0
[ppm]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66.9341
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48.1838
38.8909
33.7782
32.4834
30.4234
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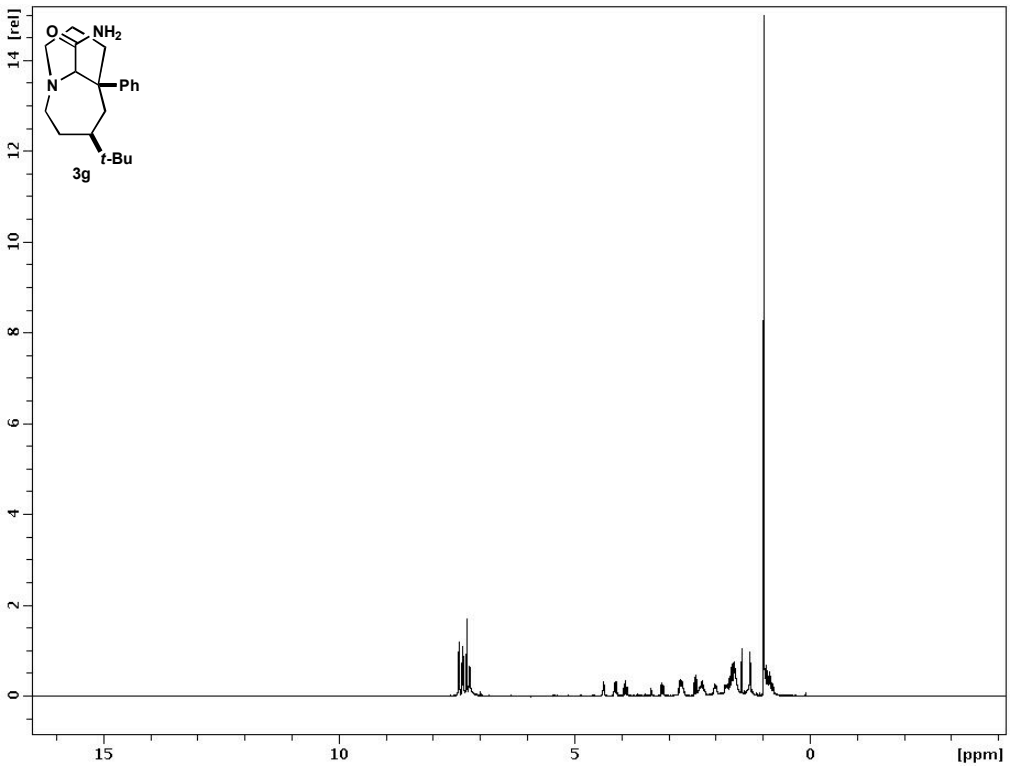
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N
Ph
t-Bu
3g
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5
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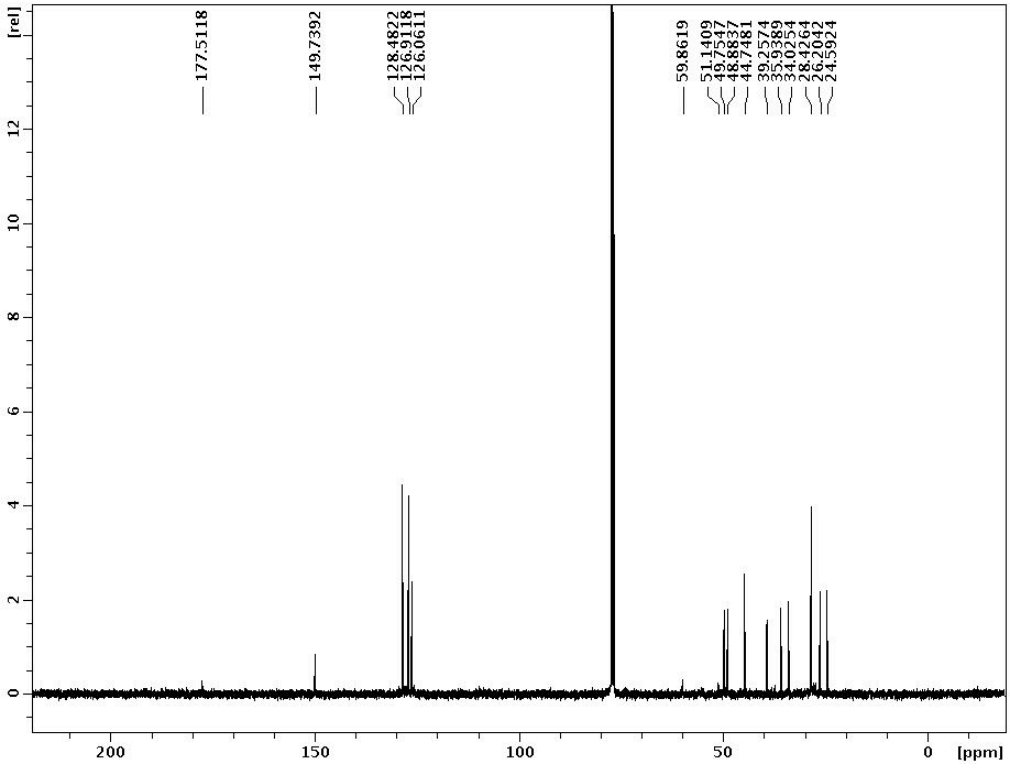
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35.9389
34.0254
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26.2042
24.5924
[rel]
12
10
8
6
4
2
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200
150
100
50
0
[ppm]