Supplementary Material (ESI) for Chemical Communications


# SUPPORTING INFORMATION

# Ammonium Ylides for the Diastereoselective Synthesis of Glycidic Amides

**Mario Waser,* Richard Herchl and Norbert Müller**

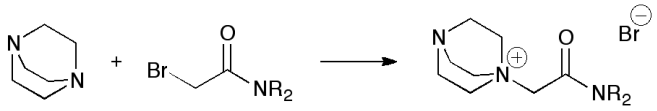
*Institute of Organic Chemistry, Johannes Kepler University Linz, Altenbergerstraße 69, 4040 Linz, Austria. Fax: +43 732 2468 8747; Tel: +43 732 2468 8748;*

*E-mail: Mario.waser@jku.at*

## 1. General Information:

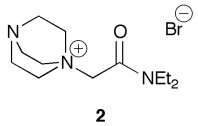
Melting points were measured on a Kofler melting point microscope (Reichert, Vienna). $^{1}$H- and $^{13}$C-NMR spectra were recorded on a Bruker Avance DRX 500 MHz spectrometer using a TXI cryoprobe with z -gradient coil and on a Bruker Avance DPX 200 MHz spectrometer. Typical resolutions and chemical shift precisions were +/- 1 Hz for $^{1}$H and +/- 0.8 Hz for $^{13}$C. All NMR spectra were referenced on the solvent peak. High resolution mass spectra were obtained using an Agilent 6520 Q-TOF mass spectrometer with an ESI source and an Agilent G1607A coaxial sprayer. All analyses were made in the positive ionization mode. Purine (exact mass for $[M+H]^+$ = 121.050873) and 1,2,3,4,5,6-hexakis(2,2,3,3-tetrafluoropropoxy)-1,3,5,2,4,6-triazatriphosphinane (exact mass for $[M+H]^+$ = 922.009798) were used for internal mass calibration. IR spectra were recorded on a Shimadzu IR Affinity-1 fourier transform infrared spectrometer. All chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. All reactions were performed under an Ar-atmosphere.

## 2. Syntheses of DABCO-Ammonium Salts 2, 4, 6, and 8:



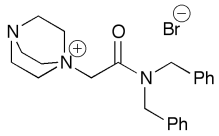

**General Procedure:** One equivalent of DABCO was added to a solution of one equivalent of the α-bromo amide in THF (15 mL / g amide) and stirred for 24 h at room temperature. The resulting suspension was centrifuged, the solid washed 3 times with EtOAc and dried in vacuo to give the product in sufficient purity for the epoxide formation reaction.

**Ammonium Salt 2.** Prepared from 2-bromo-*N*,*N*-diethylacetamide[1] (4.06 g, 20.9 mmol) in 73% (4.65 g, 15.2 mmol). White solid. M.p.: 190-193 °C; $^1$H NMR (500 MHz, δ, $CDCl_3$, 298 K): 1.13 (t, *J* = 7.5 Hz, 3H), 1.22 (t, *J* = 7.5 Hz, 3H), 3.22 (t, *J* = 7.3 Hz, 6H), 3.34 (q, *J* = 7.5 Hz, 2H), 3.48 (q, *J* = 7.5 Hz, 2H), 4.07 (t, *J* = 7.3 Hz, 6H), 4.73 (s, 2H) ppm; $^{13}$C NMR (125 MHz, δ, $CDCl_3$, 298 K): 12.8 ($CH_3$-), 14.4 ($CH_3$-), 41.0 (-$CH_2$-), 42.1 (-$CH_2$-), 45.4 (-$NCH_2$-), 53.0 (-$NCH_2$-) 61.2 (-*C*$H_2$CO-), 162.2 (-CO-) ppm; IR (film): $\bar{\nu}$ = 3532, 3406, 2972, 2941, 2893, 1632, 1489, 1479, 1470, 1431, 1397, 1368, 1310, 1265, 1215, 1109, 1072, 1053, 961, 893, 839 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{12}H_{24}N_3O^+$: 226.1919 [$M^+$]; found: 226.1922.



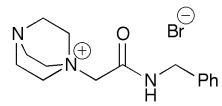
2

**Ammonium Salt 4.** Prepared from 2-bromo-*N*,*N*-dibenzylacetamide[2] (1.56 g, 4.92 mmol) in 78% (1.65 g, 3.84 mmol). White solid. M.p.: decomp > 220 °C; $^1$H NMR (200 MHz, δ, $CDCl_3$, 298 K): 2.91 (t, *J* = 7.0 Hz, 6H), 3.90 (t, *J* = 7.0 Hz, 6H), 4.33 (s, 2H), 4.54 (s, 2H), 5.03 (s, 2H), 7.13-7.20 (m, 10H) ppm; $^{13}$C NMR (50 MHz, δ, $CDCl_3$, 298 K): 45.3 (-$NCH_2$-), 48.8 (-$CH_2$-Ar), 50.7 (-$CH_2$-Ar), 53.0 (-$NCH_2$-), 61.7 (-*C*$H_2$CO-), 127.9 (Ar-C), 128.0 (Ar-C), 128.1 (Ar-C), 128.3 (Ar-C), 129.0 (Ar-C), 129.3 (Ar-C), 135.2 (Ar-$C_{quat}$), 135.8 (Ar-$C_{quat}$), 164.1 (-CO-) ppm; IR (film): $\bar{\nu}$ = 3399, 2974, 2943, 2887, 1655, 1493, 1481, 1449, 1418, 1397, 1364, 1234, 1117, 1057, 1026, 994, 841, 752, 739, 725, 694 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{22}H_{28}N_3O^+$: 350.2232 [$M^+$]; found: 350.2234.



4

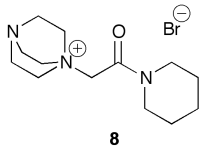
**Ammonium Salt 6.** Prepared from *N*-benzyl-2-bromoacetamide[3] (4.50 g, 19.8 mmol) in 62% (4.15 g, 12.2 mmol). White solid. M.p.: 148-151 °C; $^1$H NMR (500 MHz, δ, $CDCl_3$, 298 K): 3.16 (t, *J* = 7.0 Hz, 6H), 3.74 (t, *J* = 7.0 Hz, 6H), 4.44 (d, *J* = 6.1 Hz, 2H), 4.67 (s, 2H), 7.26 (m, 1H), 7.32 (m, 2H), 7.38 (m, 2H), 9.42 (bs, 1H) ppm; $^{13}$C NMR (125 MHz, δ, $CDCl_3$, 298 K): 43.6 (-$CH_2$-Ar), 45.4 (-$NCH_2$-), 53.5 (-$NCH_2$-), 63.2 (-*C*$H_2$CO-), 127.6 (Ar-C), 128.1 (Ar-C), 128.8 (Ar-C), 137.6 (Ar-$C_{quat}$), 162.8 (-CO-) ppm; IR (film): $\bar{\nu}$ = 3173, 3035, 2962, 2951, 2912, 2884, 1663, 1553, 1495, 1452, 1431, 1367, 1331, 1315, 1294, 1223, 1103, 1055, 1026, 993, 841, 729, 708, 607 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{15}H_{22}N_3O^+$: 260.1763 [$M^+$]; found: 260.1757.



6

[1] T. Hama, X. Liu, D. A. Culkin and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 11176.
[2] P. M. P. Gois and C. A. M. Afonso, *Eur. J. Org. Chem.*, 2003, 3798.
[3] A. M. R. Smith, H. S. Rzepa, A. J. P. White, D. Billen and K. K. (M.) Hii, *J. Org. Chem.*, 2010, **75**, 3085.

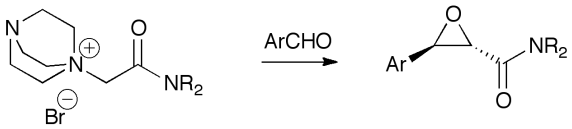
**Ammonium Salt 8.** Prepared from 2-bromo-1-(piperidin-1-yl)ethanone[4] (1.10 g, 5.36 mmol)



8

in 70% (1.19 g, 3.75 mmol). Hygroscopic white solid. M.p.: 164-167 °C; $^1$H NMR (500 MHz, δ, $CDCl_3$, 298 K): 1.27-1.37 (m, 6H), 2.93 (m, 6H), 3.15-3.34 (m, 4H), 3.83 (m, 6H), 4.65 (s, 2H) ppm; $^{13}$C NMR (125 MHz, δ, $CDCl_3$, 298 K): 23.8 (-$CH_2$-), 25.1 (-$CH_2$-), 26.0 (-$CH_2$-), 42.6 (-CON-*C*$H_2$-), 45.2 (-$NCH_2$-), 46.1 (-CON-*C*$H_2$-), 52.4 (-$NCH_2$-), 60.9 (-*C*$H_2$CO-), 161.1 (-CO-) ppm; IR (film): $\tilde{\nu}$ = 2930, 2856, 1638, 1472, 1435, 1402, 1346, 1323, 1248, 1229, 1061, 1017, 990, 848, 787, 745 cm$^{-1}$; HRMS (ESI): *m/z* calcd for $C_{13}H_{24}N_3O^+$: 238.1919 [$M^+$]; found: 238.1925.

## 3. Syntheses of Glycidic Amides:

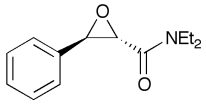



**General procedure for the preparation of epoxides using homogeneous or liquid/solid conditions (Table 1, entries 1-8):** 1.2 equiv. of *t*-BuOK (or other base) were added to a mixture of ammonium salt **2** in THF (or other solvent) at 0 °C and stirred for 5 min. After addition of the indicated amount of aldehyde **1** the mixture was stirred at 0 °C for 1 h followed by stirring at 25 °C for 23 h. After extraction with EtOAc and $NH_4Cl$ the organic layer was washed with brine, dried over $Na_2SO_4$ and evaporated to dryness. Column chromatography (silica gel, hexanes/EtOAc = 7:3) gave **3** in the reported yields.

**Optimized procedure for the preparation of epoxides under biphasic conditions (using 2 equiv. of aldehyde):** A vigorously stirred solution of ammonium salt (2 mmol) in $CH_2Cl_2$ (30 mL) was cooled to 0 °C, followed by addition of 50% NaOH (15 mL). After 5 min the aldehyde (4 mmol) was added in one portion. The biphasic mixture was warmed to 25 °C over 1 h and vigorously stirred for 23 h. After extraction with EtOAc the organic layer was washed with brine, dried over $Na_2SO_4$ and evaporated to dryness. Column chromatography (silica gel, hexanes/EtOAc = 7:3) gave the glycidic amides in the reported yields (For copies of NMR spectra of 2 representative *trans*-epoxide products see chapter 5).

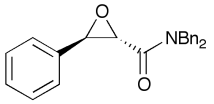
[4] B. C. Gorske, B. L. Bastian, G. D. Geske, and H. E. Blackwell, *J. Am. Chem. Soc.*, 2007, **129**, 8928.

***trans-N,N*-diethyl-3-phenyloxirane-2-carboxamide (3).** Obtained in 67% using the biphasic procedure as a white to yellow solid. Analytical data are in full accordance with those reported in literature.[5] $^1$H NMR (500 MHz, δ, $CDCl_3$, 298 K): 1.16 (t, *J* = 7.3 Hz, 3H), 1.20 (t, *J* = 7.3 Hz, 3H), 3.40-3.51 (m, 4H), 3.58 (d, *J* = 1.4 Hz, 1H), 4.09 (d, *J* = 1.4 Hz, 1H), 7.32-7.39 (m, 5H) ppm; $^{13}$C NMR (125 MHz, δ, $CDCl_3$, 298 K): 13.1, 15.0, 41.0, 41.6, 57.3, 57.7, 125.8, 128.6, 128.7, 135.9, 165.8 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_{17}NO_2$: 220.1332 $[M+H]^+$; found: 220.1329.



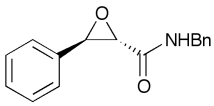
3

***trans-N,N*-dibenzyl-3-phenyloxirane-2-carboxamide (5).** Obtained in 72% using the biphasic procedure as a white to yellow solid. Analytical data are in full accordance with those reported in literature.[6] $^1$H NMR (500 MHz, δ, $CDCl_3$, 298 K): 3.70 (d, *J* = 1.2 Hz, 1H), 4.14 (d, *J* = 1.2 Hz, 1H), 4.55 (s, 2H), 4.69 (d, *J* = 4.8 Hz, 2H), 7.15-7.41 (m, 15H) ppm; $^{13}$C NMR (125 MHz, δ, $CDCl_3$, 298 K): 48.8, 49.4, 57.5, 58.2, 125.8, 126.7, 127.8, 128.0, 128.4, 128.6, 128.7, 128.8, 129.2, 135.4, 135.9, 136.5, 167.3 ppm; HRMS (ESI): *m/z* calcd for $C_{23}H_{21}NO_2$: 344.1645 $[M+H]^+$; found: 344.1644.



5

***trans-N*-benzyl-3-phenyloxirane-2-carboxamide (7).** Obtained in 24% using the biphasic procedure as a white solid. Analytical data are in full accordance with those reported in literature.[7] $^1$H NMR (500 MHz, δ, $CDCl_3$, 298 K): 3.58 (d, *J* = 1.2 Hz, 1H), 3.90 (d, *J* = 1.2 Hz, 1H), 4.49 (m, 2H), 6.57 (bs, 1H), 7.26-7.36 (m, 10H) ppm; $^{13}$C NMR (125 MHz, δ, $CDCl_3$, 298 K): 43.0, 59.1, 59.2, 125.9, 127.8, 127.9, 128.8, 128.9, 129.2, 134.9, 137.6, 167.4 ppm; HRMS (ESI): *m/z* calcd for $C_{16}H_{15}NO_2$: 276.0995 $[M+Na]^+$; found: 276.0997.



7

[5] Y.-G. Zhou, X.-L. Hou, L.-X. Dai, L.-J. Xia and M.-H. Tang, *J. Chem. Soc., Perkin Trans. 1*, 1999, 77.
[6] O. Meth-Cohn, C. Moore, and H. C. Taljaard, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2663.
[7] T. Nemoto, T. Ohshima and M. Shibasaki, *J. Am. Chem. Soc.,* 2001, **123**, 9474.

***trans*-(3-phenyloxiran-2-yl)(piperidin-1-yl)methanone (9).** Obtained in 58% using the biphasic procedure as a yellowish oil. Analytical data are in full accordance with those reported in literature.[8] $^1$H NMR (500 MHz, δ, $CDCl_3$, 298 K): 1.57-1.67 (m, 6H), 3.46-3.65 (m, 4H), 3.61 (d, *J* = 1.9 Hz, 1H), 4.05 (d, *J* = 1.9 Hz, 1H), 7.26-7.38 (m, 5H) ppm; $^{13}$C NMR (125 MHz, δ, $CDCl_3$, 298 K): 24.5, 25.5, 26.6, 43.4, 46.1, 57.6, 57.7, 125.7, 128.7, 128.8, 135.9, 164.9 ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_{17}NO_2$: 232.1332 $[M+H]^+$; found: 232.1330.

**9**

***trans*-*N*,*N*-diethyl-3-(*p*-tolyl)oxirane-2-carboxamide (11).** Obtained in 68% using the biphasic procedure white to yellow solid. Analytical data are in full accordance with those reported in literature.[5] $^1$H NMR (500 MHz, δ, $CDCl_3$, 298 K): 1.15 (t, *J* = 7.1 Hz, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 2.34 (s, 3H), 3.38-3.49 (m, 4H), 3.57 (d, *J* = 1.7 Hz, 1H), 4.03 (d, *J* = 1.7 Hz, 1H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H) ppm; $^{13}$C NMR (125 MHz, δ, $CDCl_3$, 298 K): 13.0, 15.0, 21.3, 40.9, 41.5, 57.2, 57.7, 125.7, 129.4, 132.8, 138.7, 165.9 ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_{19}NO_2$: 234.1489 $[M+H]^+$; found: 234.1494.

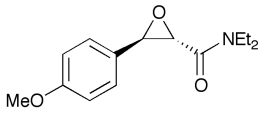
**11**

***trans*-3-(4-chlorophenyl)-*N*,*N*-diethyloxirane-2-carboxamide (13).** Obtained in 72% using the biphasic procedure as a white solid. Analytical data are in full accordance with those reported in literature.[5] $^1$H NMR (500 MHz, δ, $CDCl_3$, 298 K): 1.16 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.2 Hz, 3H), 3.38-3.48 (m, 4H), 3.53 (d, *J* = 1.3 Hz, 1H), 4.07 (d, *J* = 1.3 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H) ppm; $^{13}$C NMR (125 MHz, δ, $CDCl_3$, 298 K): 12.5, 14.5, 40.5, 41.1, 56.5, 56.7, 126.5, 128.4, 133.9, 134.1, 164.9 ppm; HRMS (ESI): *m/z* calcd for $C_{13}H_{16}ClNO_2$: 276.0762 $[M+Na]^+$; found: 276.0762.

**13**

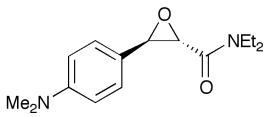
[8] T. Satoh, T. Shimura, and K. Sakai, *Heterocycles*, 2003, **59**, 137.

***trans*-*N*,*N*-diethyl-3-(4-methoxyphenyl)oxirane-2-carboxamide (15).** Obtained in 47% using the biphasic procedure at 25 °C as a bright yellow solid. Analytical data are in full accordance with those reported in literature.[9] $^1$H NMR (200 MHz, δ, $CDCl_3$, 298 K): 1.11-1.23 (m, 6H), 3.37-3.52 (m, 4H), 3.58 (d, *J* = 1.8 Hz, 1H), 3.80 (s, 3H), 4.02 (d, *J* = 1.8 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H) ppm; $^{13}$C NMR (50 MHz, δ, $CDCl_3$, 298 K): 12.6, 14.8, 40.8, 41.4, 55.2, 57.0, 57.5, 114.1, 127.0, 127.7, 160.0, 165.8 ppm; HRMS (ESI): *m/z* calcd for $C_{14}H_{19}NO_3$: 272.1257 $[M+Na]^+$; found: 272.1251.



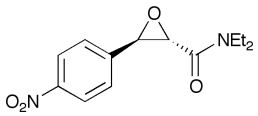
**15**

***trans*-*N*,*N*-diethyl-3-(4-dimethylaminophenyl)oxirane-2-carboxamide (17).** $^1$H NMR of the crude product showed less than 20% of **17** besides unreacted starting material **16**. The product decomposed during column chromatography. $^1$H NMR and HRMS of the crude product were consistent with formation of the *trans*-epoxide: $^1$H NMR (200 MHz, δ, $CDCl_3$, 298 K): 1.18 (m, 6H), 2.89 (s, 6 H), 3.37 (m, 4H), 3.58 (d, *J* = 1.7 Hz, 1H), 3.92 (d, *J* = 1.7 Hz, 1H), 6.61 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H) ppm; HRMS (ESI): *m/z* calcd for $C_{15}H_{22}N_2O_2$: 263.1754 $[M+Na]^+$; found: 263.1756.



**17**

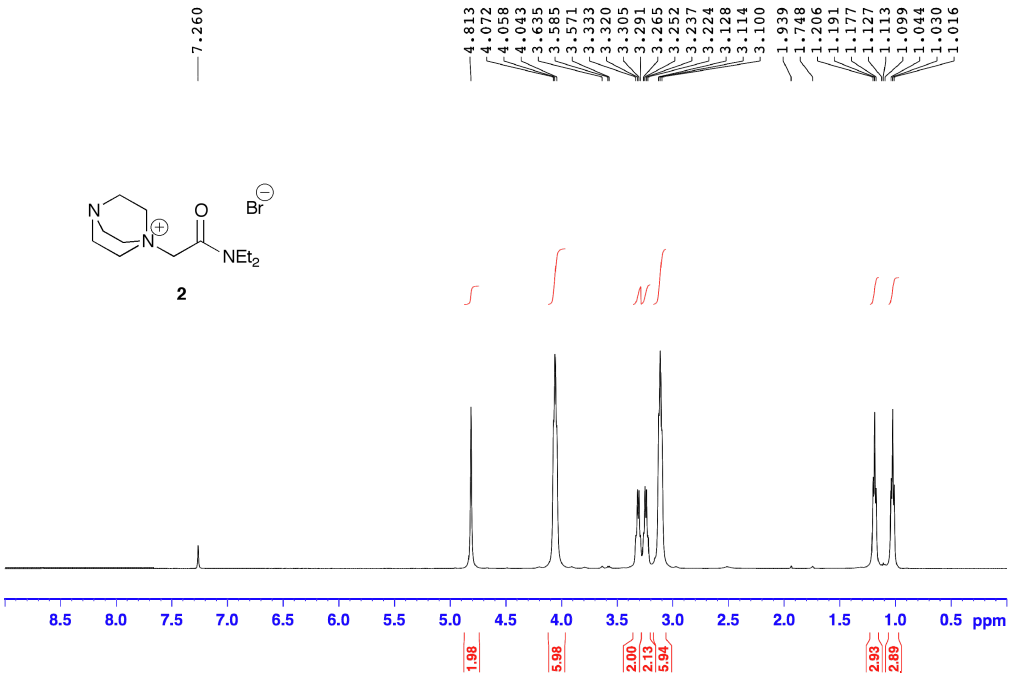
***trans*-*N*,*N*-diethyl-3-(4-nitrophenyl)oxirane-2-carboxamide (19).** $^1$H NMR of the crude product showed less than 10% of **19** and the corresponding Cannizzaro disproportionation products. $^1$H NMR signals of the *trans*-oxirane ring are in accordance with literature.[5] The formation of the product was also evidenced by HRMS. HRMS (ESI): *m/z* calcd for $C_{13}H_{16}N_2O_4$: 287.1002 $[M+Na]^+$; found: 287.1002.

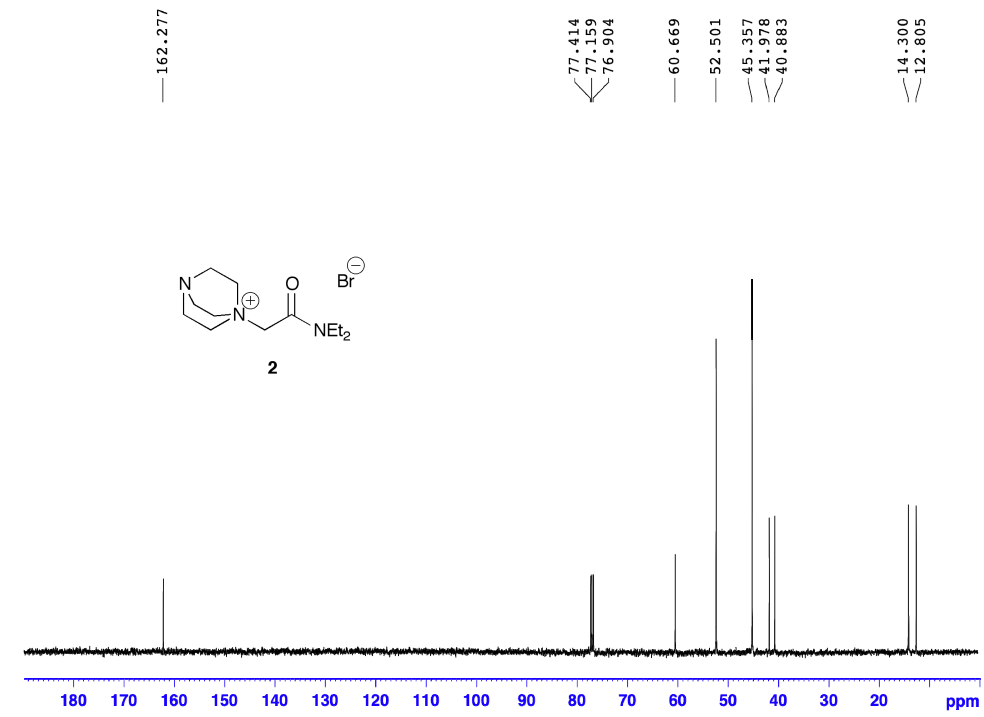


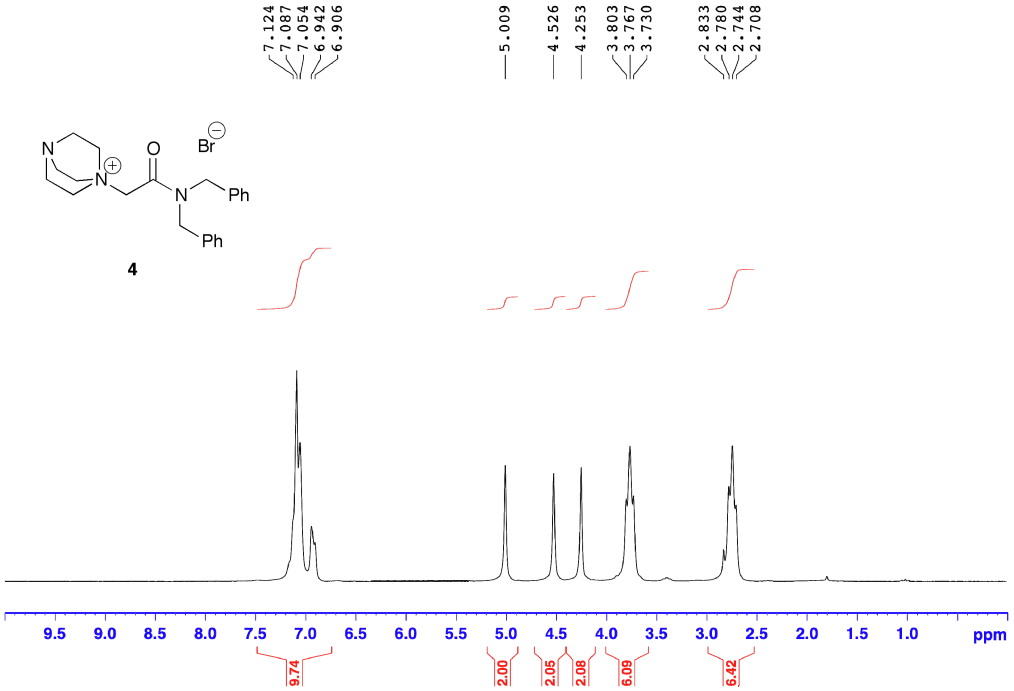
**19**

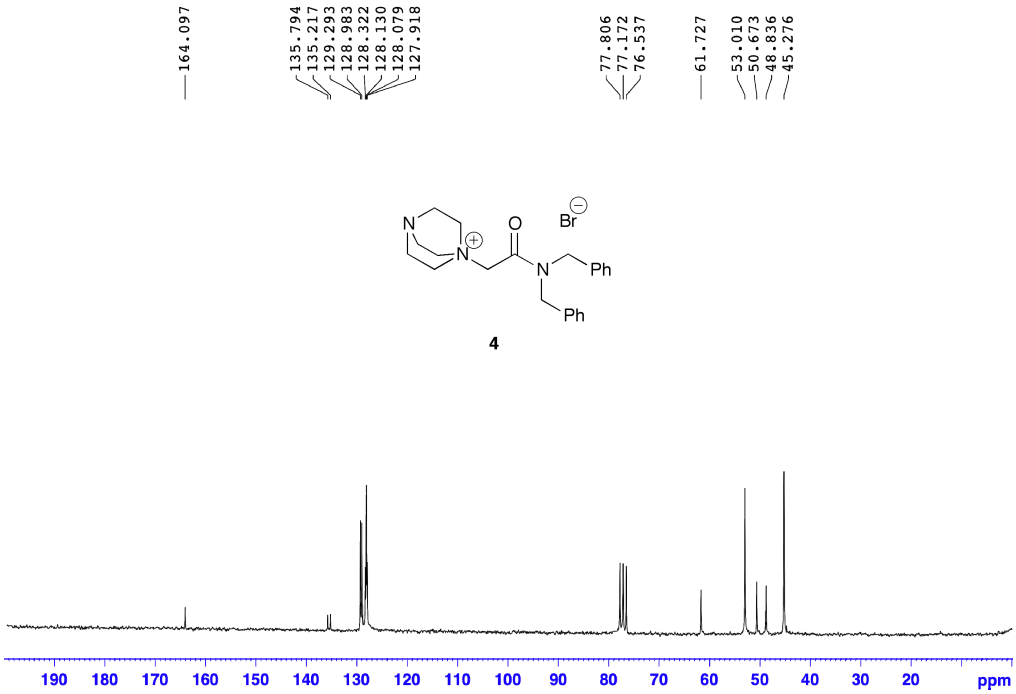
[9] R. Imashiro and M. Seki, *J. Org. Chem.*, 2004, **69**, 4216.

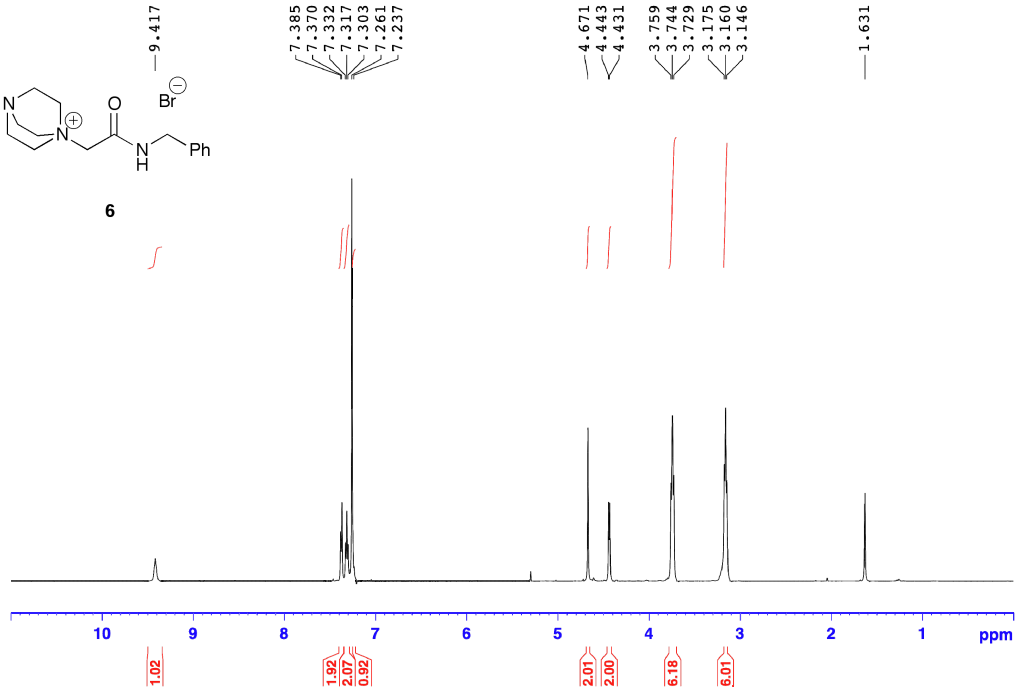
# 4. NMR Spectra of the Novel Ammonium Salts 2, 4, 6, and 8:



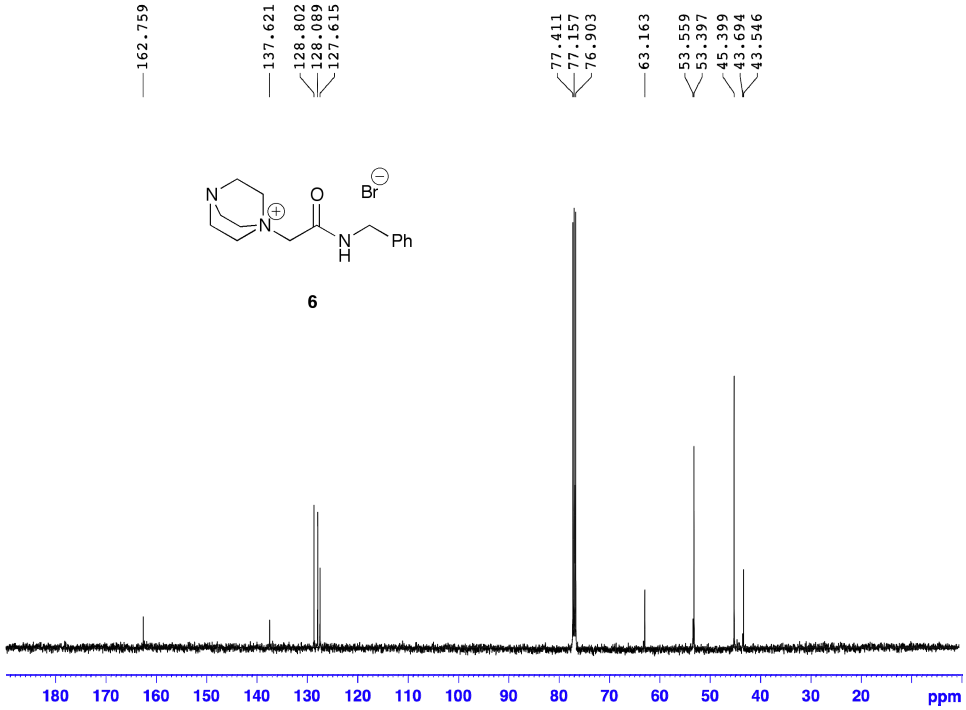




7.124
7.087
7.054
6.942
6.906
5.009
4.526
4.253
3.803
3.767
3.730
2.833
2.780
2.744
2.708
N
O
Br
N
N
Ph
Ph
4
9.74
2.00
2.05
2.08
6.09
6.42
ppm

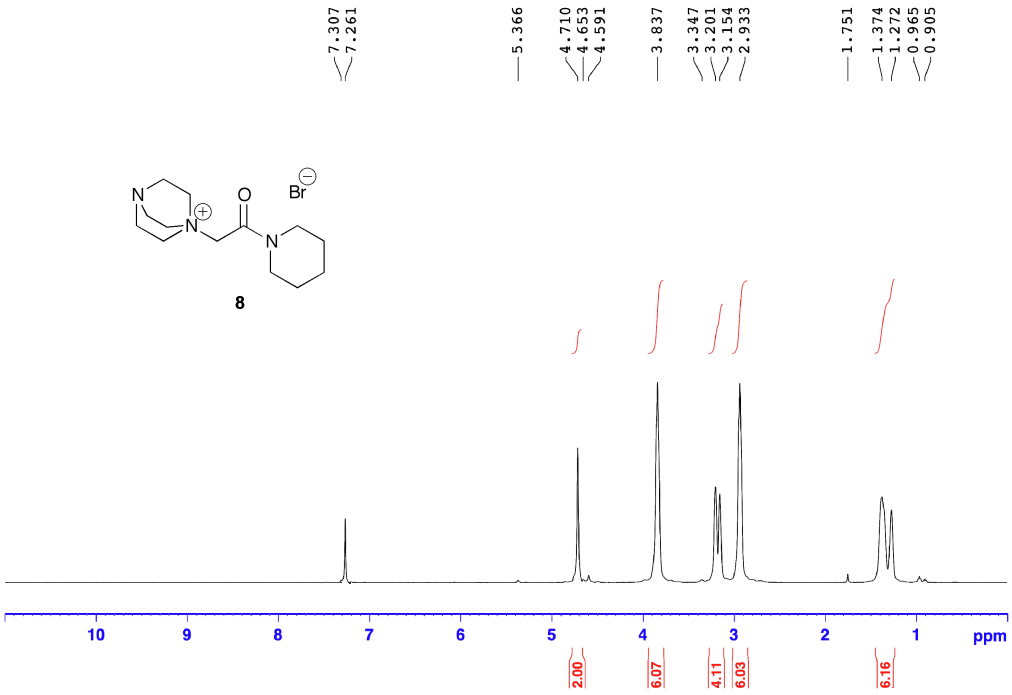

164.097
135.794
135.217
129.293
128.983
128.322
128.130
128.079
127.918
77.806
77.172
76.537
61.727
53.010
50.673
48.836
45.276
N
O
Br
N
N
Ph
Ph
4
ppm

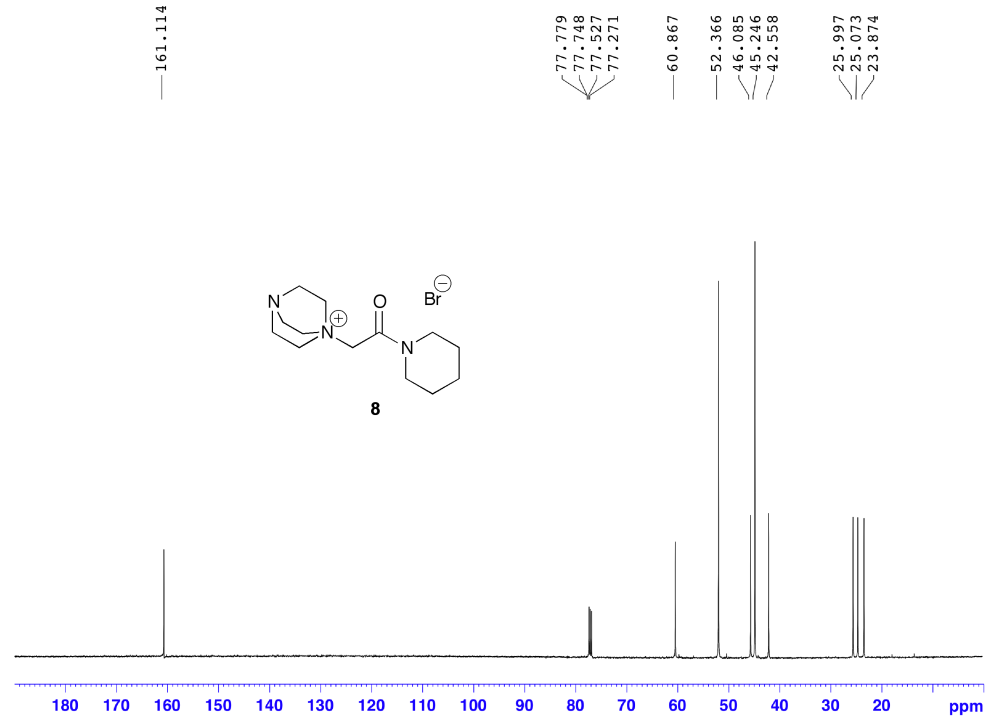

9.417
7.385
7.370
7.332
7.317
7.303
7.261
7.237
4.671
4.443
4.431
3.759
3.744
3.729
3.175
3.160
3.146
1.631
Br
N
O
N
H
Ph
10
9
8
7
6
5
4
3
2
1
ppm
1.02
1.92
2.07
0.92
2.01
2.00
6.18
6.01

**6**

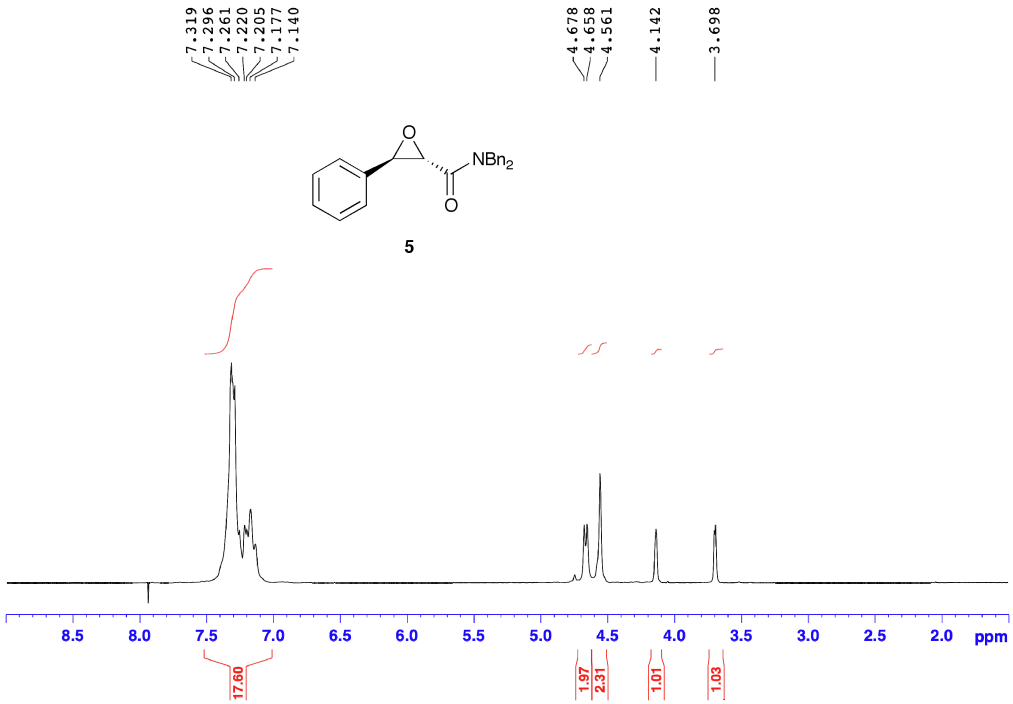

162.759
137.621
128.802
128.089
127.615
77.411
77.157
76.903
63.163
53.559
53.397
45.399
43.694
43.546
Br
N
O
N
H
Ph
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

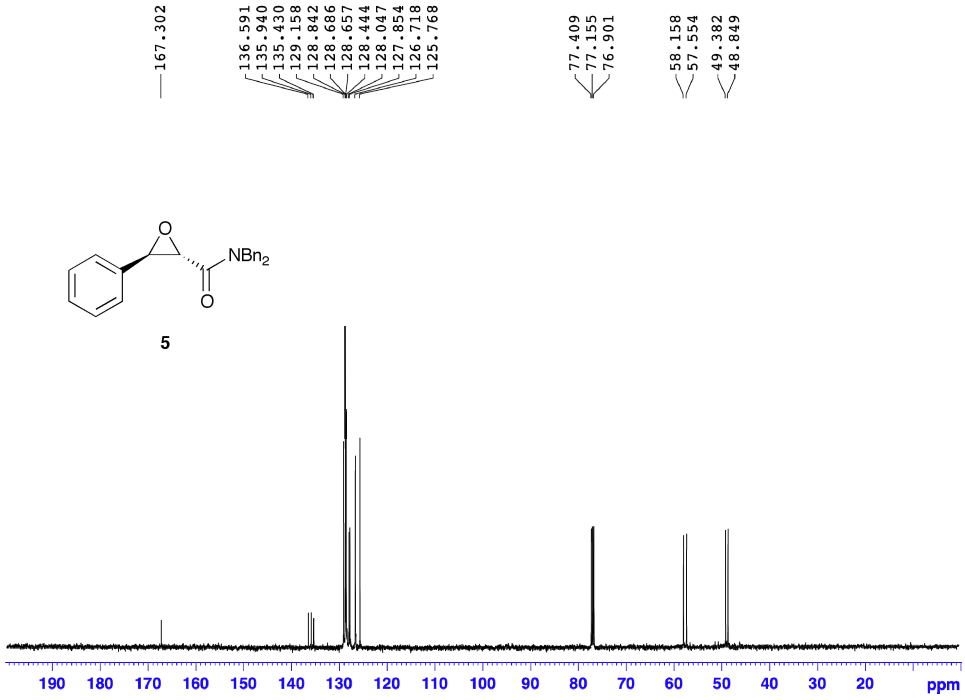
**6**

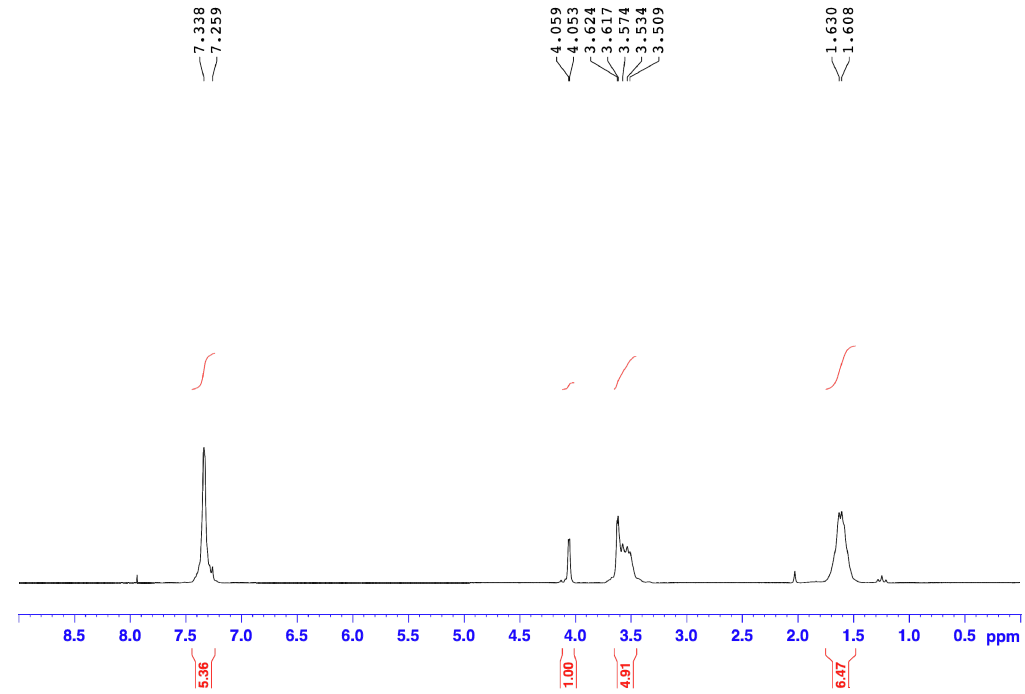

7.307
7.261
5.366
4.710
4.653
4.591
3.837
3.347
3.201
3.154
2.933
1.751
1.374
1.272
0.965
0.905
N
O
Br
N
N
8
10
9
8
7
6
5
4
3
2
1
ppm
2.00
6.07
4.11
6.03
6.16

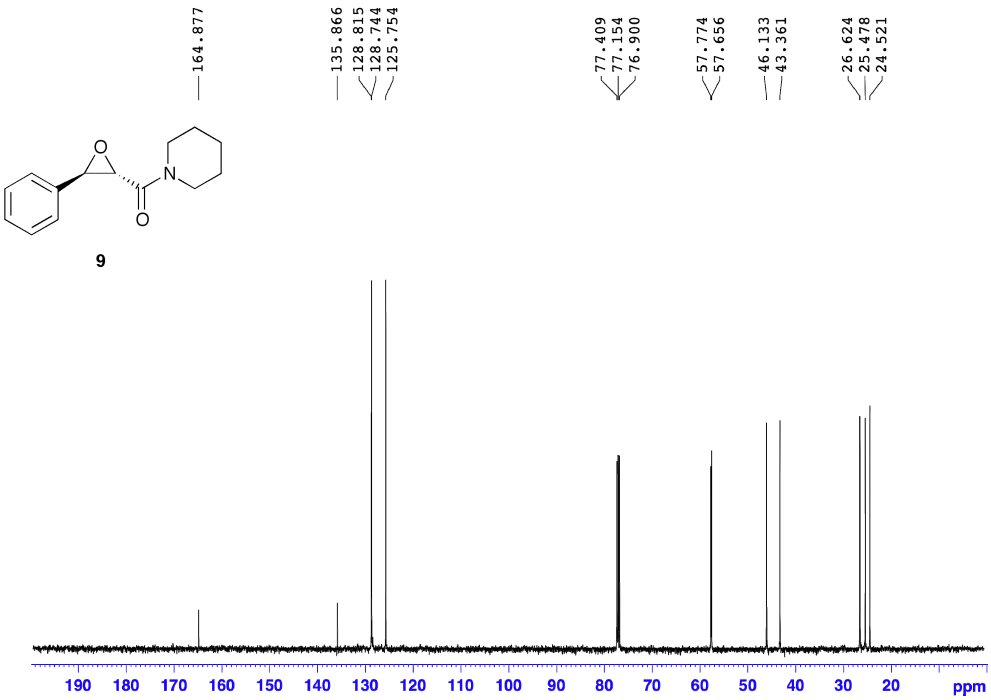

161.114
77.779
77.748
77.527
77.271
60.867
52.366
46.085
45.246
42.558
25.997
25.073
23.874
N
O
Br
N
N
8
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

# 5. Representative NMR Spectra for *trans*-Epoxide Products:




7.338
7.259
4.059
4.053
3.624
3.617
3.574
3.534
3.509
1.630
1.608
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.36
1.00
4.91
6.47


164.877
135.866
128.815
128.744
125.754
77.409
77.154
76.900
57.774
57.656
46.133
43.361
26.624
25.478
24.521
O
N
O
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

**9**