Supporting Information

Investigation of Lewis Acid Catalyzed Asymmetric Aza-Diels-Alder Reactions of 2*H*-Azirines

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Content:

General Methods.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with the residual peak of $CHCl_3$ (^{1}H NMR δ 7.26 and ^{13}C NMR δ 77.0) as internal standard. The chemical shifts are reported in the δ-scale with multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant (Hz), and integration. Optical rotations, $[\alpha]_D$, were measured at the sodium D-line. Analytical TLC plates were visualized with UV light, iodine in methanol or phosphomolybdic acid (5% in ethanol). Air- and moisture sensitive reactions were performed with oven- or flame-dried equipment under an atmospheric pressure of nitrogen or argon. All liquid reagents were transferred using oven-dried cannulas. The solvents were dried by distillation immediately before use, CH_2Cl_2 from CaH_2 and toluene from sodium/benzophenone. The DMF was dried over 4 Å molecular sieves.

(1*R*,2*S*,4*S*)-*N*-(2,3-dibromopropionyl)-bornane-2,10-sultam 25a: Following a literature procedure[1] compound **25a** was obtained in 81% yield as colorless crystals. Analytical data for the diastereomeric mixture: mp: decomposition before melting; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13(m, 1H), 4.06(dd, *J* = 11.1, 9.8 Hz, 1H), 4.01(dd, *J* = 7.6, 5.0 Hz, 1H, major isomer), 3.94(dd, *J* = 8.1, 5.0 Hz, 1H, minor isomer), 3.72(dd, *J* = 9.6, 4.3 Hz, 1H, minor isomer), 3.67(dd, *J* = 9.6, 4.0 Hz, 1H, major isomer), 3.52(m, 2H), 2.05-2.17(m, 2H), 1.86-1.98(m, 3H), 1.34-1.48(m, 2H), 1.18(s, 3H, minor isomer), 1.17(s, 3H, major isomer), 0.98(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 65.6, 64.9, 52.9, 48.9, 47.9, 44.4, 40.0, 39.5, 37.8, 37.3, 32.8, 32.6, 30.5, 28.2, 26.41, 26.36, 20.7, 20.5, 19.91, 19.86 HRMS (FAB+) calculated for $C_{13}H_{20}Br_2NO_3S$ (M+H): 427.9531, found: 427.9534.

(1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl-(2,3-dibromo)-propionate 25b: To a solution of **24a** (0.46 g, 1.6 mmol) in CH_2Cl_2 (7 mL) was added Br_2 (90 μL, 1.8 mmol). The reaction mixture was heated to 50 °C in a sealed tube for 30 min and then allowed to reach room temperature before addition of $Na_2S_2O_3$ (aq) until no color remained. The resulting bi-phase mixture was filtered through an Extrelute® tube, which was rinsed with CH_2Cl_2 (15 mL). The resulting organic phase was concentrated before purification by filtration through a plug of SiO_2 (pentane–Et_2O). Dibromide **25b** was obtained as a mixture of diastereomers in 95% yield (0.68 g) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31(br d, *J* = 4.3 Hz, 4H), 7.18(m, 1H), 4.83(td, *J* = 10.6, 4.3 Hz, 1H, major isomer), 3.97(dd, *J* = 9.8, 4.8 Hz, 1H, minor isomer), 3.61-3.73(m, 2H), 3.47-3.53(m, 1H), 2.0-2.11(m, 1H), 1.94-2.0(m, 1H), 1.58-1.73(m, 2H), 1.43-1.53(m, 1H), 1.36(s, 3H, minor isomer), 1.34(s, 3H, major isomer), 1.25(s, 3H, minor isomer), 1.24(s, 3H, major isomer), 0.97-1.15(m, 2H), 0.89(d, *J* = 6.3 Hz, 3H, major isomer), 0.88(d, *J* = 6.5 Hz, 3H, minor isomer), 0.84-0.93(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.73, 166.68, 151.3, 151.1, 128.0, 125.6, 125.5, 125.2, 125.1, 78.1, 77.05, 50.4, 50.2, 43.3, 41.3, 41.1, 40.2, 39.9, 39.6, 34.4, 31.3, 31.2, 30.9, 29.7, 27.6, 26.8, 26.53, 26.49, 25.2, 21.7 HRMS (FAB+) calculated for $C_{19}H_{27}Br_2O_2$ (M+H): 445.0378, found: 445.0363.

(1*R*,2*S*,4*S*)-*N*-(2-azidopropenoyl)-bornane-2,10-sultam 26a: A solution of dibromide **25a** (190 mg, 0.44 mmol) in DMF (2.5 mL) was added to a pre-heated (60 °C) suspension of NaN_3 (58 mg, 0.89 mmol) in dry DMF (2.5 mL). The reaction mixture was heated at 60 °C for 8 min before addition of an ice and water mixture (20 mL). The resulting mixture was extracted with Et_2O and the organic phase then washed with H_2O and brine and then dried over $MgSO_4$, filtered and evaporated. Purification by chromatography (SiO_2, pentane–Et_2O–CH_2Cl_2) gave **26a** as a white semi-solid in 56% yield (76 mg). $[\alpha]_D^{25}$ = +185 (c = 0.1, CH_2Cl_2); IR (neat): ν_{max} = 2111, 1679, 1616, 1340, 1171, 1134; ^1H NMR (400 MHz, $CDCl_3$) δ 5.55(d, *J* = 2.5 Hz, 1H), 5.45(d, *J* = 2.5 Hz, 1H), 4.11(dd, *J* = 7.8, 4.7 Hz, 1H), 3.55(A-part of ABq, *J* = 13.6 Hz,1H), 3.44(B-part of ABq, *J* = 13.6 Hz, 1H), 1.91-2.11(m, 5H), 1.34-1.47(m, 2H), 4.22(s, 3H), 1.01(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9, 138.2, 111.3, 65.7, 53.7, 48.1, 47.8, 45.3, 38.1, 33.3, 26.4, 21.3, 19.8; HRMS (FAB+) calculated for $C_{13}H_{19}N_4O_3S$ (M+H): 311.1178, found: 311.1179.

(1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl-(2-azido)-acrylate 26b: A solution of dibromide **25b** (640 mg, 1.43 mmol) in DMF (6 mL) was added to a pre-heated (85 °C) suspension of NaN_3 (196 mg, 3.0 mmol) in dry DMF (10 mL). The reaction mixture was heated at 85 °C for exactly 20 min before addition of an ice and water mixture (50 mL). The resulting mixture was extracted with Et_2O and the resulting organic phase was then washed with H_2O and brine and dried over $MgSO_4$ before filtration and concentration. Purification by chromatography (SiO_2, pentane–Et_2O) gave **26b** as a colorless oil in 65% yield (305 mg). $[\alpha]_D^{25}$ = -63 (c = 0.42, CH_2Cl_2); IR (film): ν_{max} = 2955, 2923, 2125, 1716, 1615, 1254; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.29(m, 4H), 7.08-7.13(m, 1H), 5.10(d, *J* = 1.3 Hz, 1H), 4.99(d, *J* = 1.5 Hz, 1H), 4.95(td, *J* = 10.8, 4.5 Hz, 1H), 2.12(ddd, *J* = 12.3, 10.8, 3.8 Hz, 1H), 1.88-1.93(m, 1H), 1.77(dq, *J* = 13.3, 3.5 Hz, 1H), 1.65-1.71(m, 1H), 1.44-1.56(m, 1H), 1.32(s, 3H), 1.22(s, 3H), 1.15(app qd, *J* = 13.1, 3.3 Hz, 1H), 1.04(app q, *J* = 11.1 Hz, 1H), 0.85-0.86(m, 1H), 0.89(d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 151.3, 135.6, 128.1, 125.3, 125.1, 110.8, 76.3, 50.3, 41.4, 39.6, 34.4, 31.3, 28.4, 26.5, 24.6, 21.7; HRMS (FAB+) calculated for $C_{19}H_{26}N_3O_2$ (M+H): 328.2025, found: 328.2024.

General Procedure for the Synthesis of 3-Substituted-2H-azirines 1a and 1b from Vinyl Azides 26a and 26b.[2]

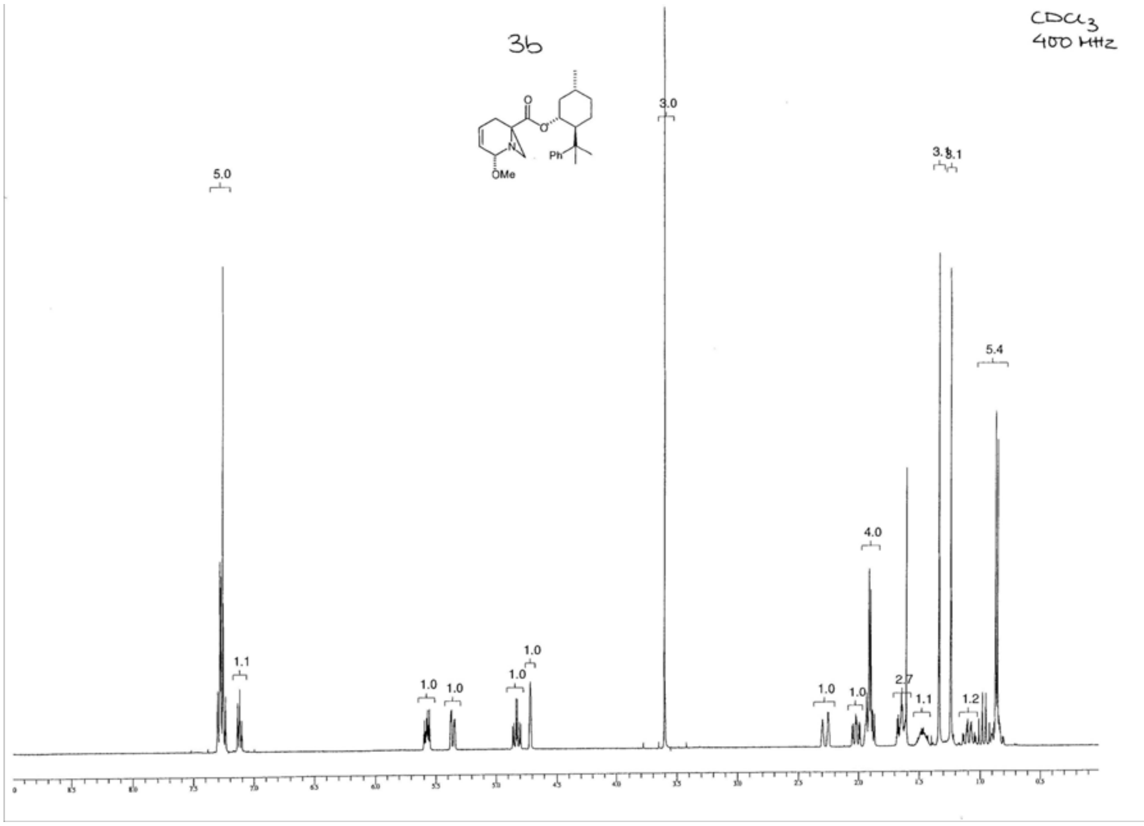
(1*R*,2*S*,5*R*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexyl-2*H*-azirine-3-carboxylate 1b: Vinyl azide **26b** (70 mg, 0.21 mmol) was dissolved in dry CH_2Cl_2 (3.0 mL) and heated in a sealed tube at 150 °C for 20 min and then cooled to 0 °C. CAUTION! Heating azides may cause explosion. Evaporation gave **1b** in quantitative yield and in high purity (no purification necessary). $[\alpha]_D^{25}$ = +7 (c = 0.27, CH_2Cl_2); IR (neat): ν_{max} = 2923, 2955, 1746, 1716, 1210; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.27 (m, 2 H), 7.19(m, 2 H), 7.05(tt, J = 7.2, 1.3 Hz, 1 H), 5,11(td, J = 10.8, 4.9 Hz, 1 H), 2.17(ddd, J = 12.3, 10.8, 3.7 Hz, 1 H), 1.91-1.97(m, 1 H), 1.87(app dq, J = 13.6, 3.6 Hz, 1 H), 1.68-1.74(m, 1 H), 1.65(A-part of ABq, J = 8.3 Hz, 1 H), 1.60(B-part of ABq, J = 8.3 Hz, 1 H), 1.47-1.56(m, 1 H), 1.35(s, 3 H), 1.25(s, 3 H), 1.18-1.26(m, 1H), 1.15(app q, J = 12.1 Hz, 1H), 0.88-0.99(m, 1 H), 0.91(d, J = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 157.5, 150.8, 127.9, 125.3, 125.2, 77.2, 50.3, 41.4, 39.5, 34.2, 31.4, 29.0, 26.3, 24.2, 23.7, 21.7.

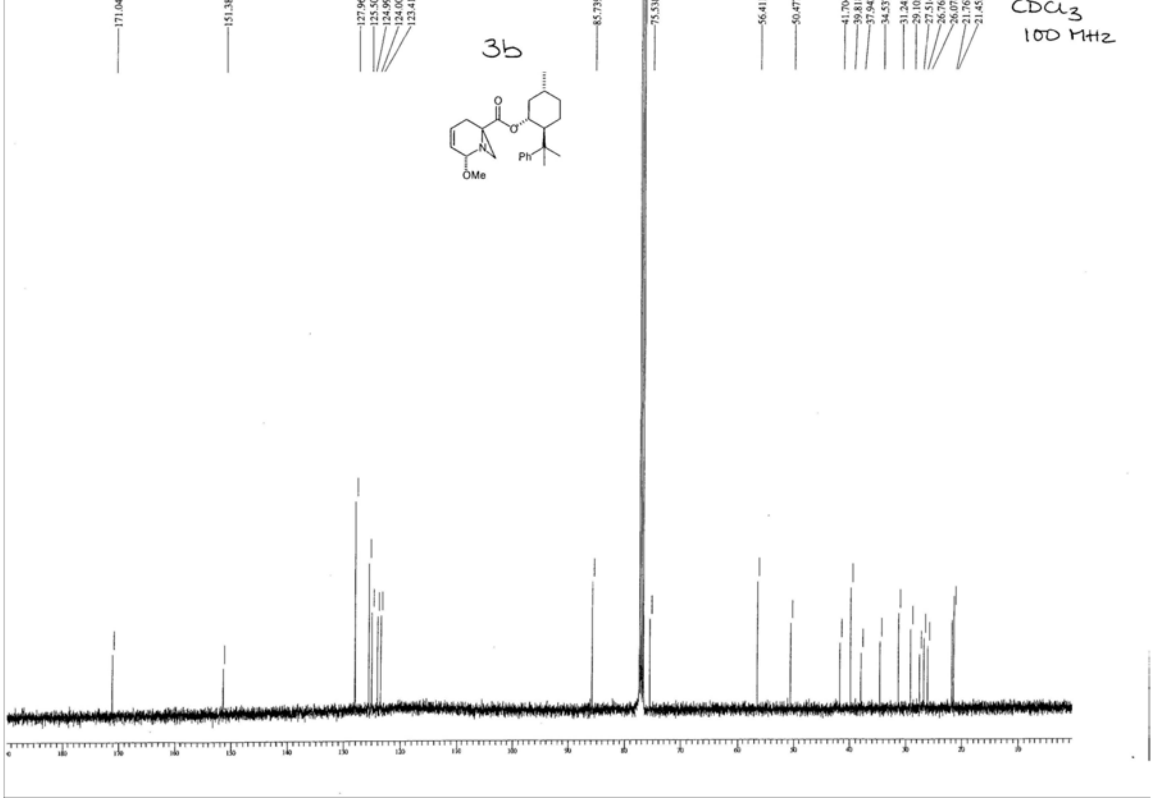
(1*R*,2*S*,4*S*)-*N*-(2*H*-azirine-3-carbonyl)-bornane-2,10-sultam 1a: Prepared from **26a** as described for **1b** and obtained in quantitative yield and in high purity (no purification necessary). $[\alpha]_D^{25}$ = +93 (c = 0.55, CH_2Cl_2); IR (neat): ν_{max} = 1723, 1678, 1341, 1169, 1142; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08(dd, J = 7.8, 5.0 Hz, 1H), 3.58(A-part of ABq, J

= 13.6 Hz, 1H), 3.49(B-part of ABq, *J* = 13.8 Hz, 1H), 2.14-2.30(m, 4H), 1.9-2.03(m, 3H), 1.37-1.50(m, 2H), 1.20(s, 3H), 1.01(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 155.9, 65.0, 53.2, 49.5, 47.9, 44.9, 38.0, 33.1, 27.7, 26.3, 21.0, 19.8.

(1) Garner, P.; Dogan, O.; Pillai, S. *Tetrahedron Lett.* **1994**, *35*, 1653-1656.

(2) Sjöholm Timén, Å.; Risberg, E.; Somfai, P. *Tetrahedron Lett.* **2003**, *44*, 5339-5341.


3b
CDCl3
400 MHz
OMe
Ph
N
O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127.965
125.509
124.991
124.009
123.415
85.739
75.538
56.411
50.477
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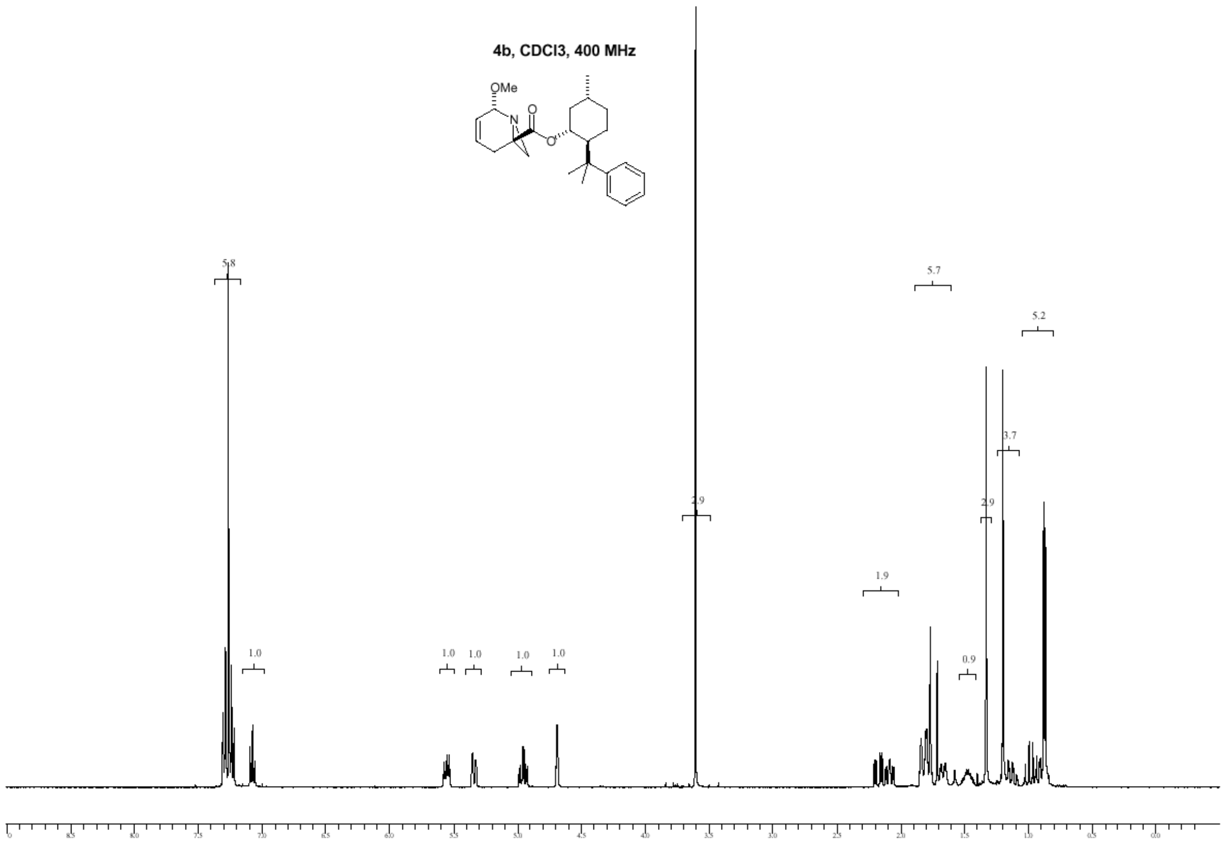
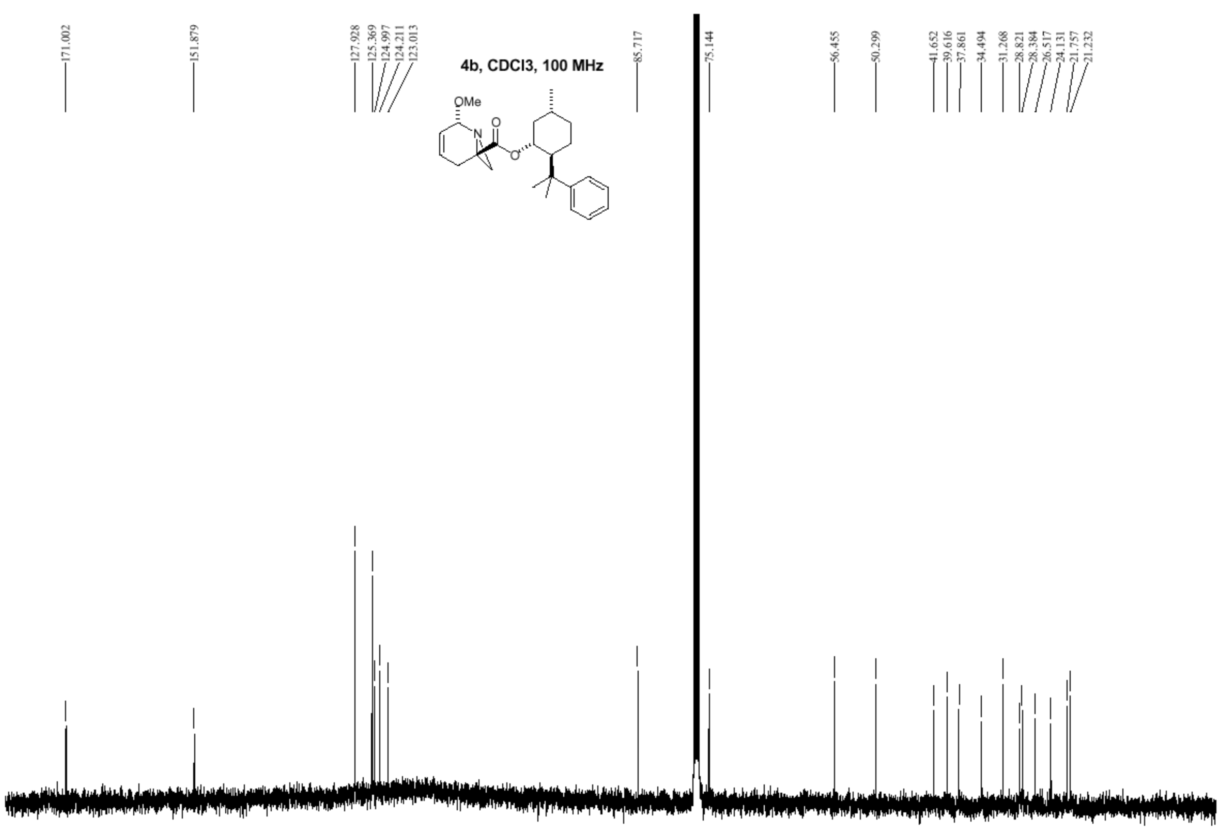
39.818
37.942
34.537
31.245
29.105
27.514
26.762
26.078
21.767
21.455


4b, CDCl3, 400 MHz
OMe
N
O
5.8
1.0
1.0
1.0
1.0
1.0
2.9
1.9
5.7
0.9
2.9
3.7
5.2


171.002
151.879
127.928
125.369
124.997
124.211
123.013
4b, CDCl3, 100 MHz
OMe
N
O
85.717
75.144
56.455
50.299
41.652
39.616
37.861
34.494
31.268
28.821
28.384
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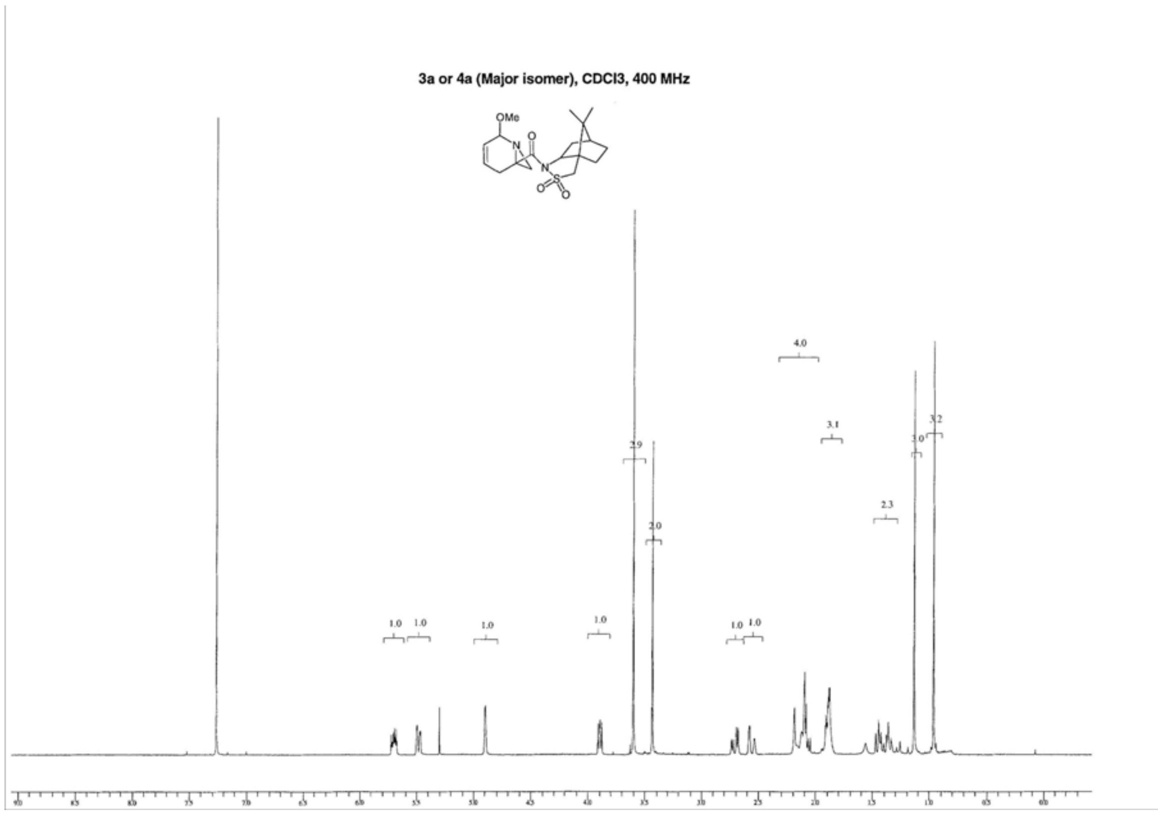
24.131
21.757
21.232


3a or 4a (Major isomer), CDCl3, 400 MHz
OMe
N
O
N
S
O
O
4.0
3.1
3.2
3.0
2.9
2.3
2.0
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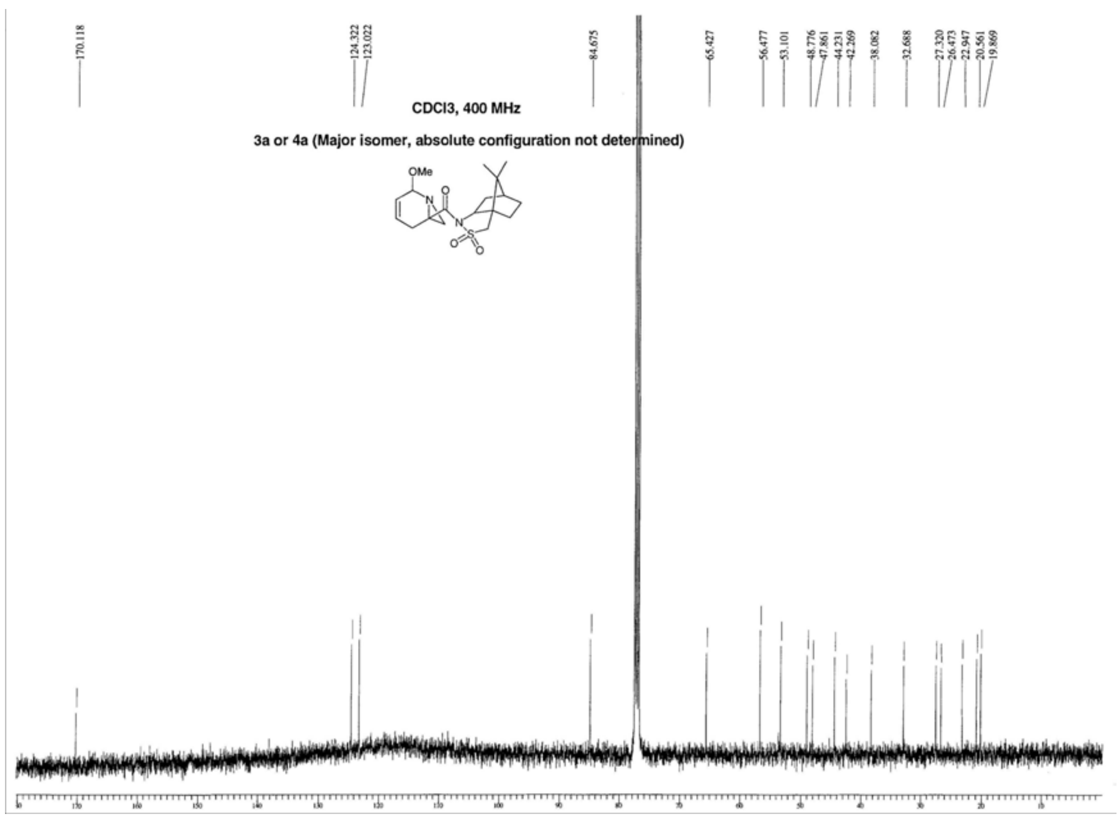
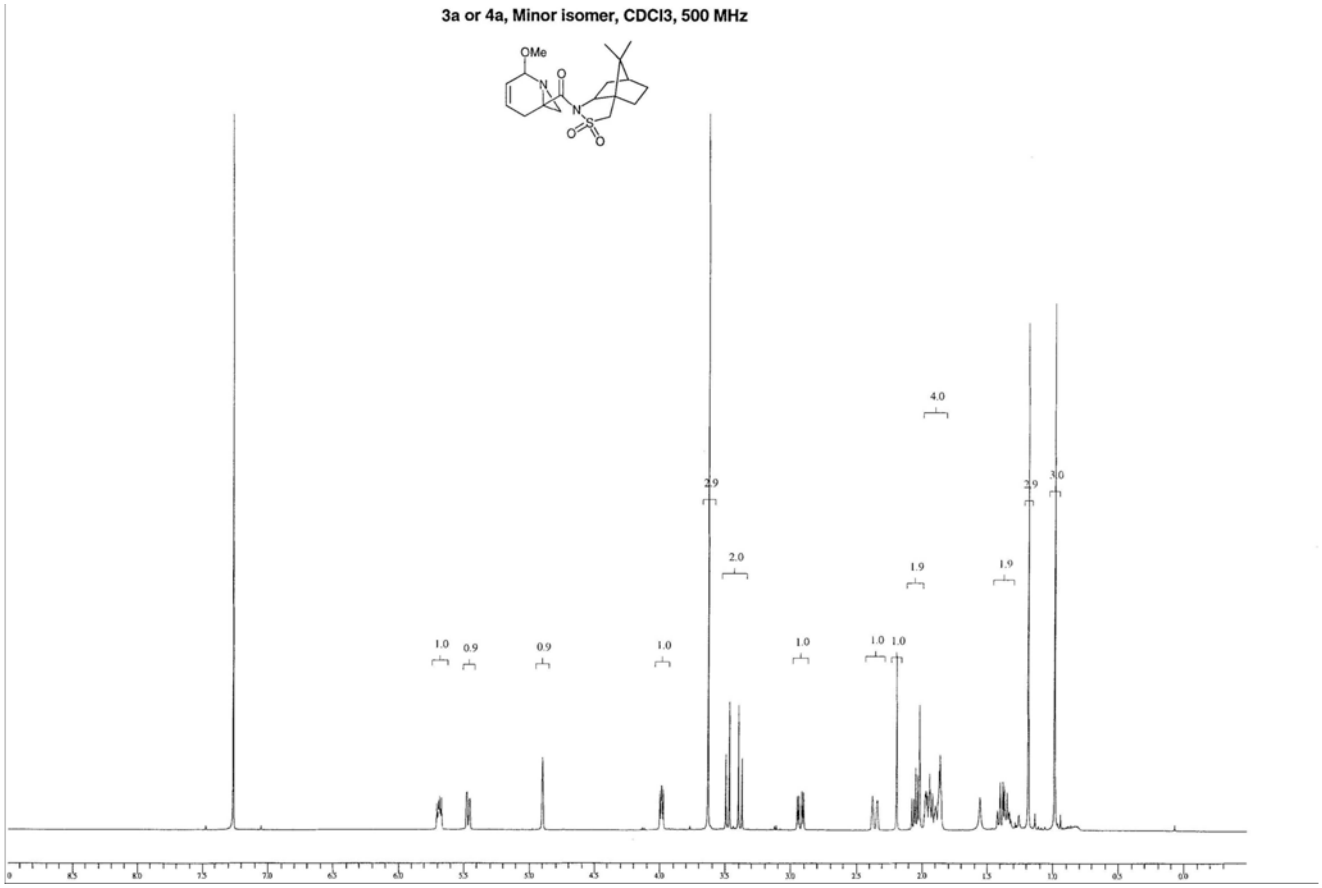
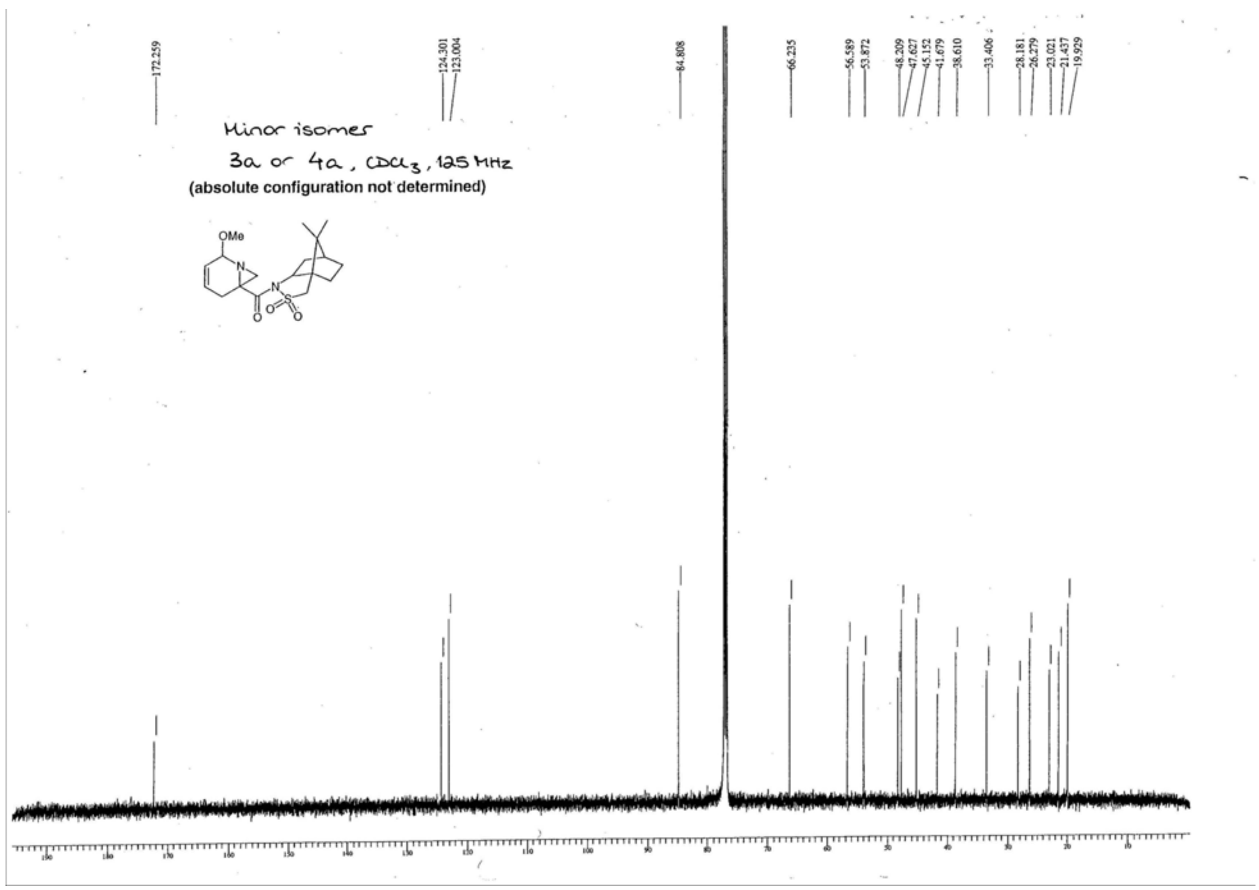
1.0
1.0
1.0

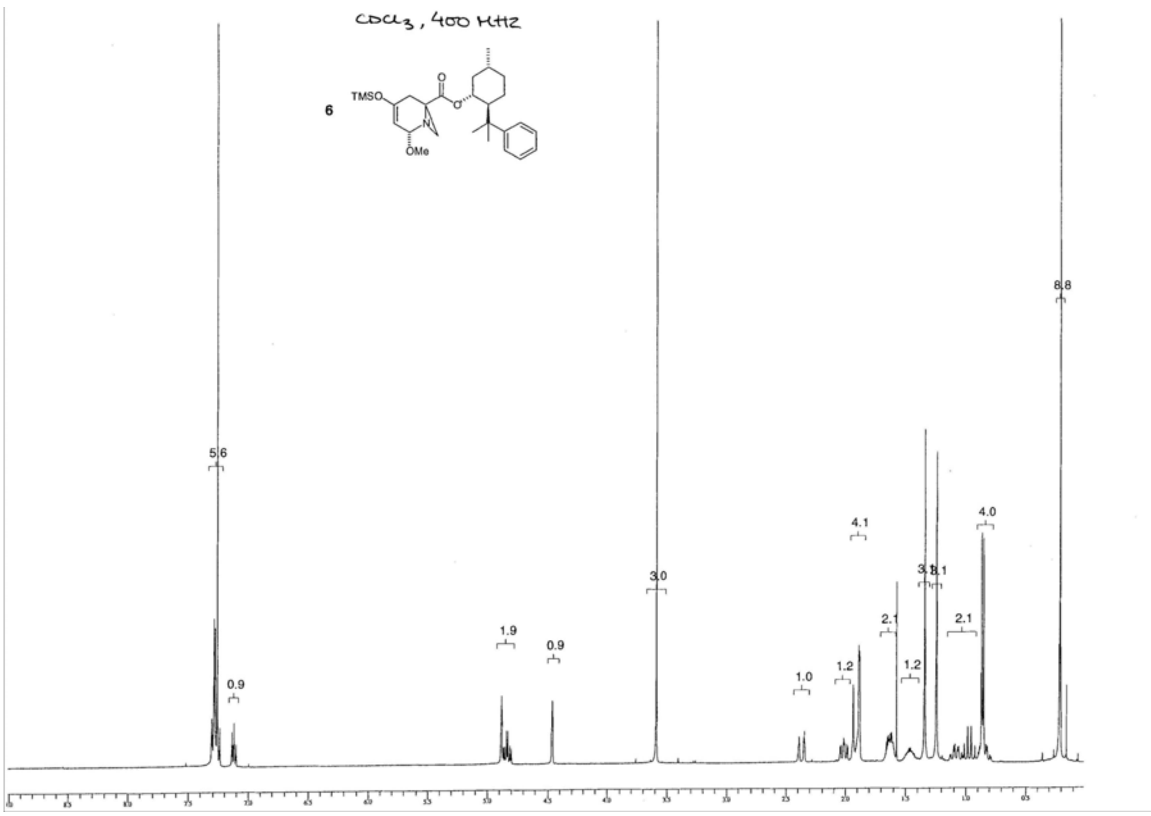

170.118
124.322
123.022
84.675
65.427
56.477
53.101
48.776
47.861
44.231
42.269
38.082
32.688
27.320
26.473
22.947
20.561
19.869
CDCl3, 400 MHz
3a or 4a (Major isomer, absolute configuration not determined)
OMe
N
O
N
S
O
O

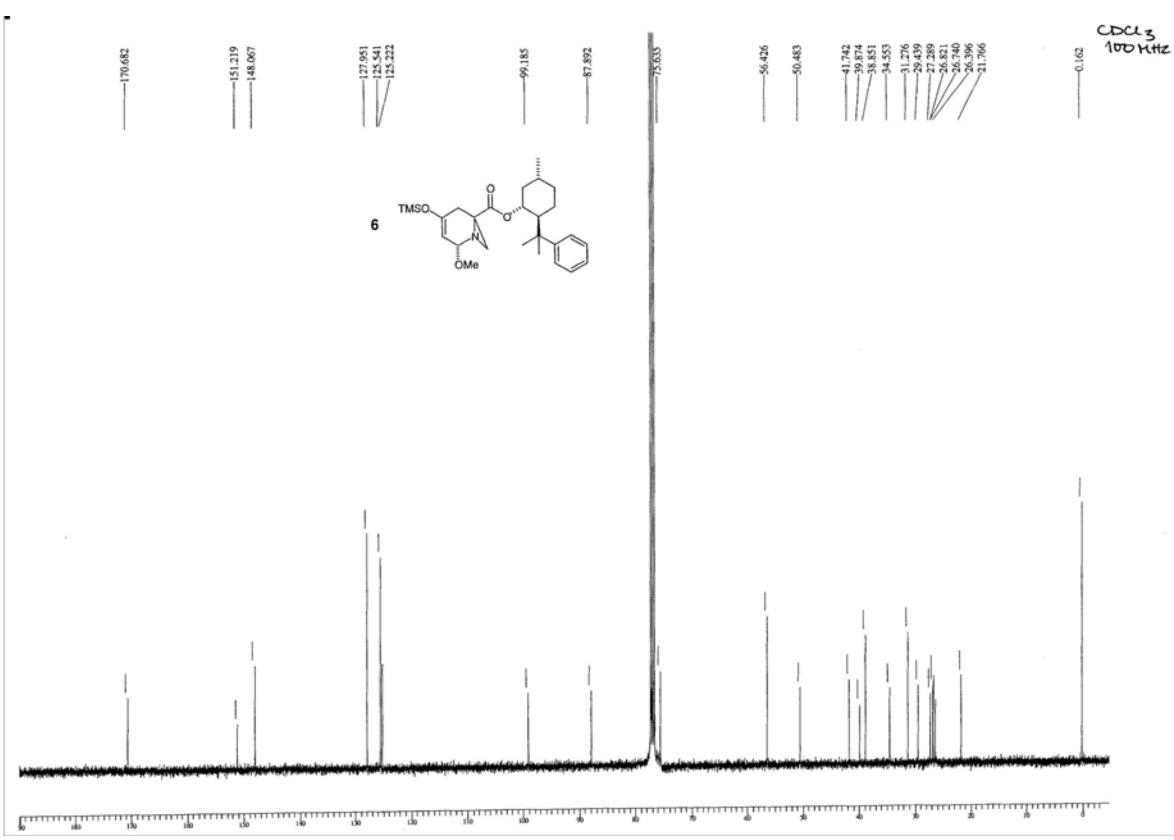


3a or 4a, Minor isomer, CDCl3, 500 MHz
OMe
1.0
0.9
0.9
1.0
2.9
2.0
1.0
1.0
1.0
4.0
1.9
1.9
2.9
3.0



172.259
124.301
123.004
84.808
66.235
56.589
53.872
48.209
47.627
45.152
41.679
38.610
33.406
28.181
26.279
23.021
21.437
19.929
Minor isomer
3a or 4a, CDCl3, 125 MHz
(absolute configuration not determined)
OMe


CDCl3, 400 MHz
6
TMSO
OMe
N
O
5.6
0.9
1.9
0.9
3.0
1.0
1.2
4.1
2.1
1.2
3.1
3.1
2.1
4.0
8.8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127.951
125.541
125.222
99.185
87.892
75.635
56.426
50.483
41.742
39.874
38.851
34.553
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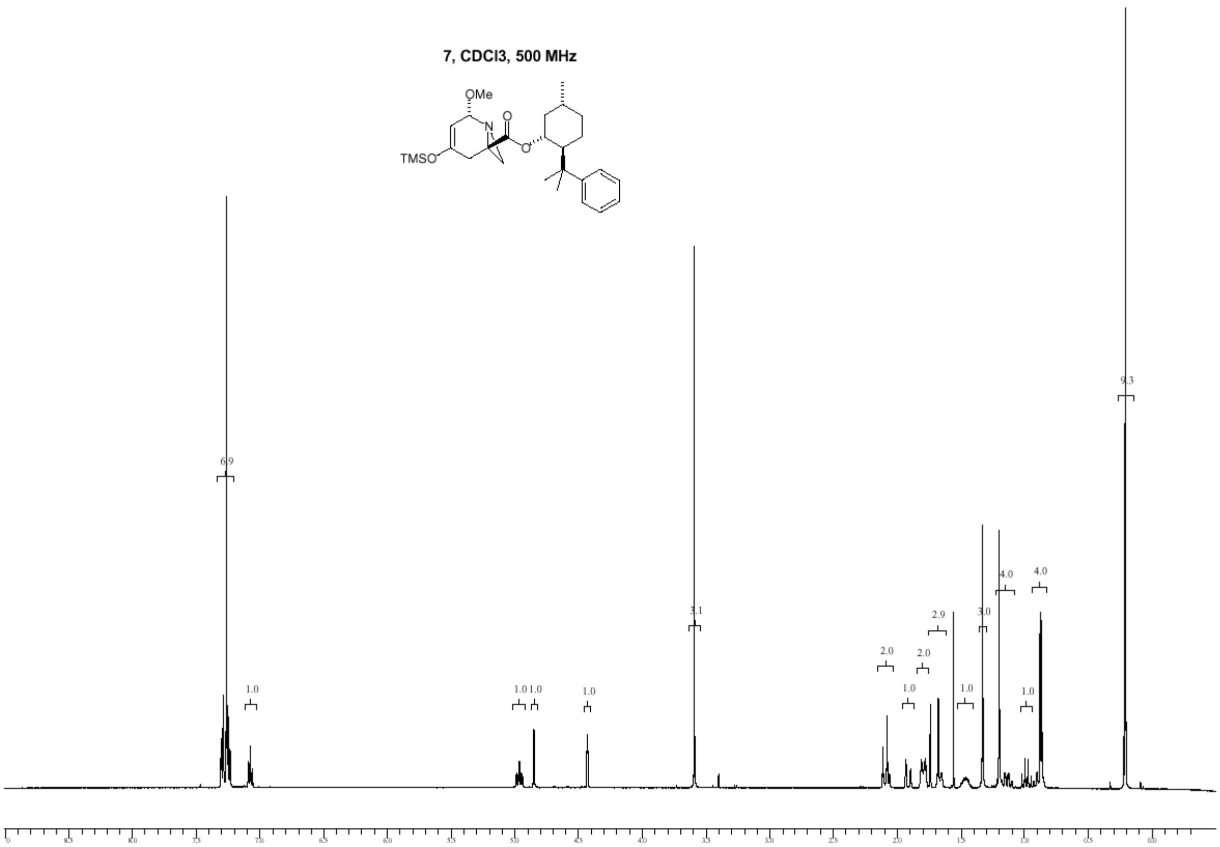
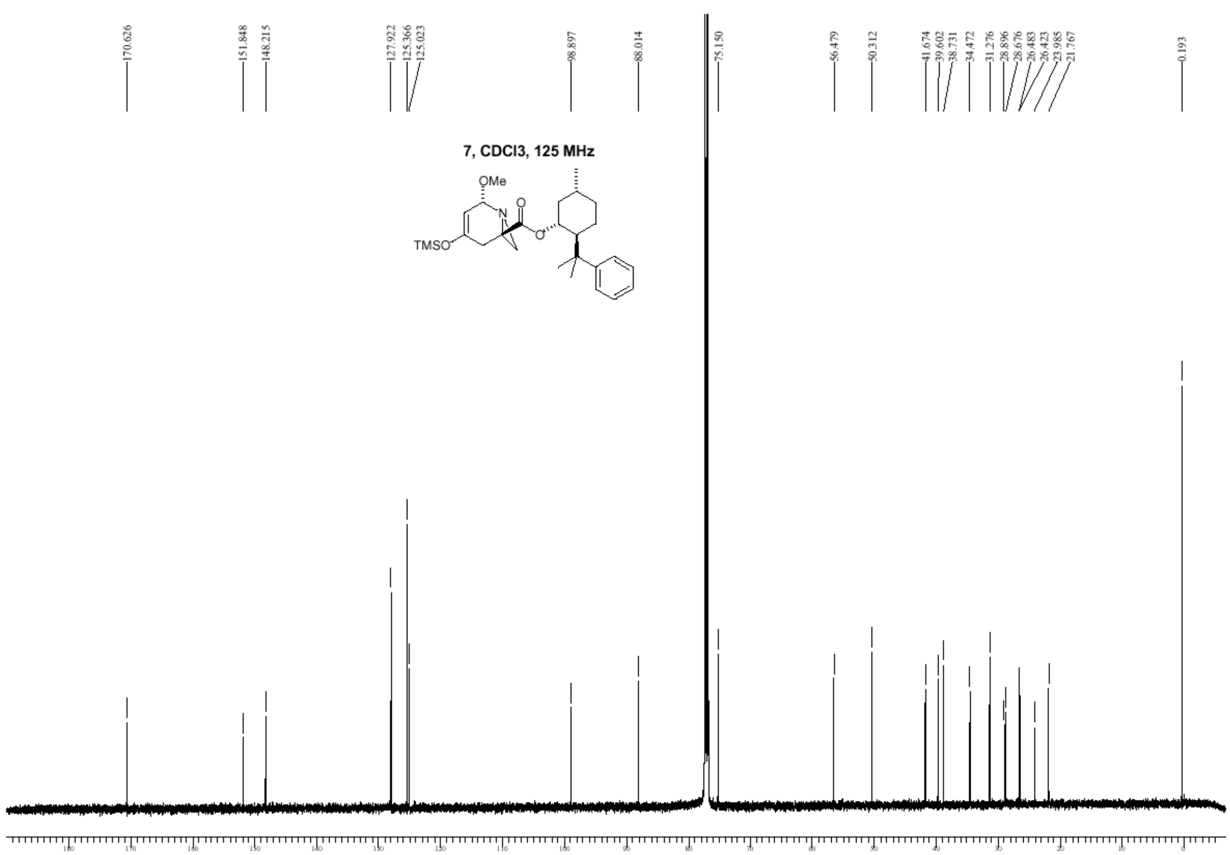
29.439
27.289
26.821
26.740
26.396
21.766
0.162
6
TMSO
OMe


7, CDCl3, 500 MHz
OMe
TMSO
N
O
6.9
1.0
1.0 1.0
1.0
3.1
2.0
2.0
1.0
2.9
1.0
3.0
4.0
1.0
4.0
9.3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148.215
127.922
125.366
125.023
98.897
88.014
75.150
56.479
50.312
41.674
39.602
38.731
34.472
31.276
28.896
28.676
26.483
26.423
23.985
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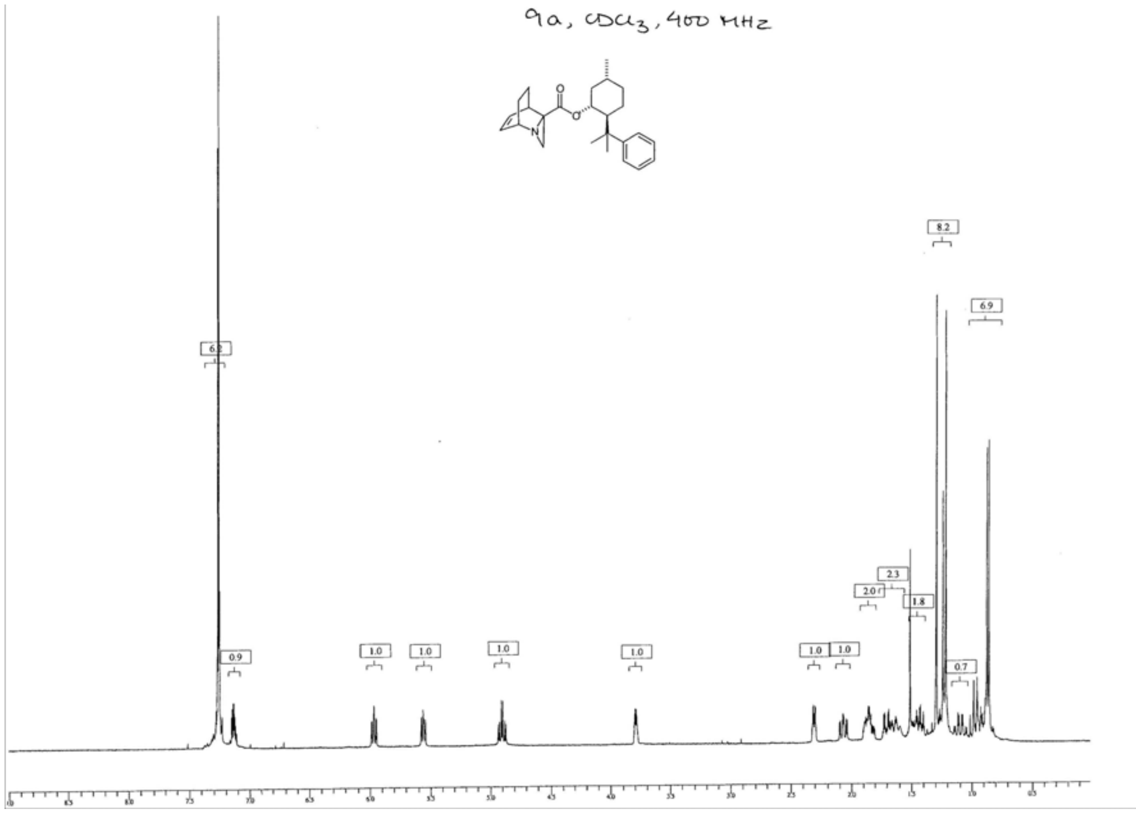
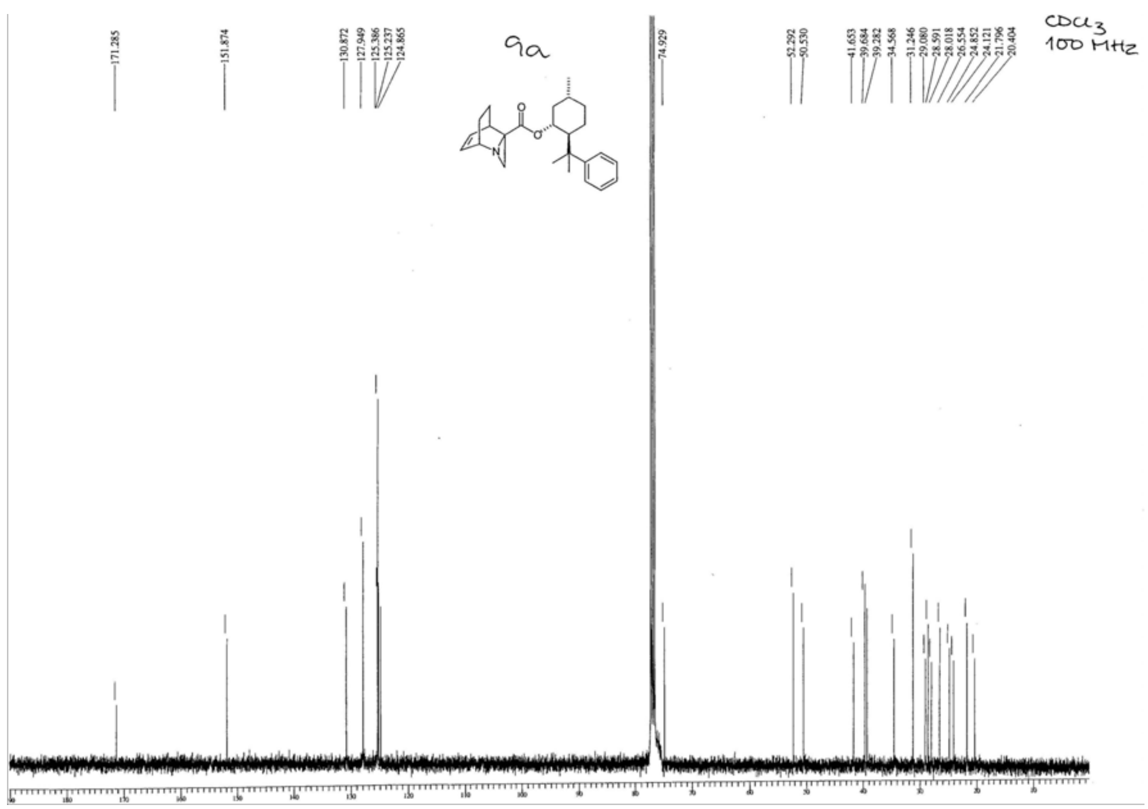
7, CDCl3, 125 MHz
OMe
TMSO
N
O



9a, CDCl3, 400 MHz
6.2
0.9
1.0
1.0
1.0
1.0
1.0
1.0
2.0
2.3
1.8
8.2
0.7
6.9



9a
CDCl3
100 MHz
171.285
151.874
130.872
127.949
125.386
125.237
124.865
74.929
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50.530
41.653
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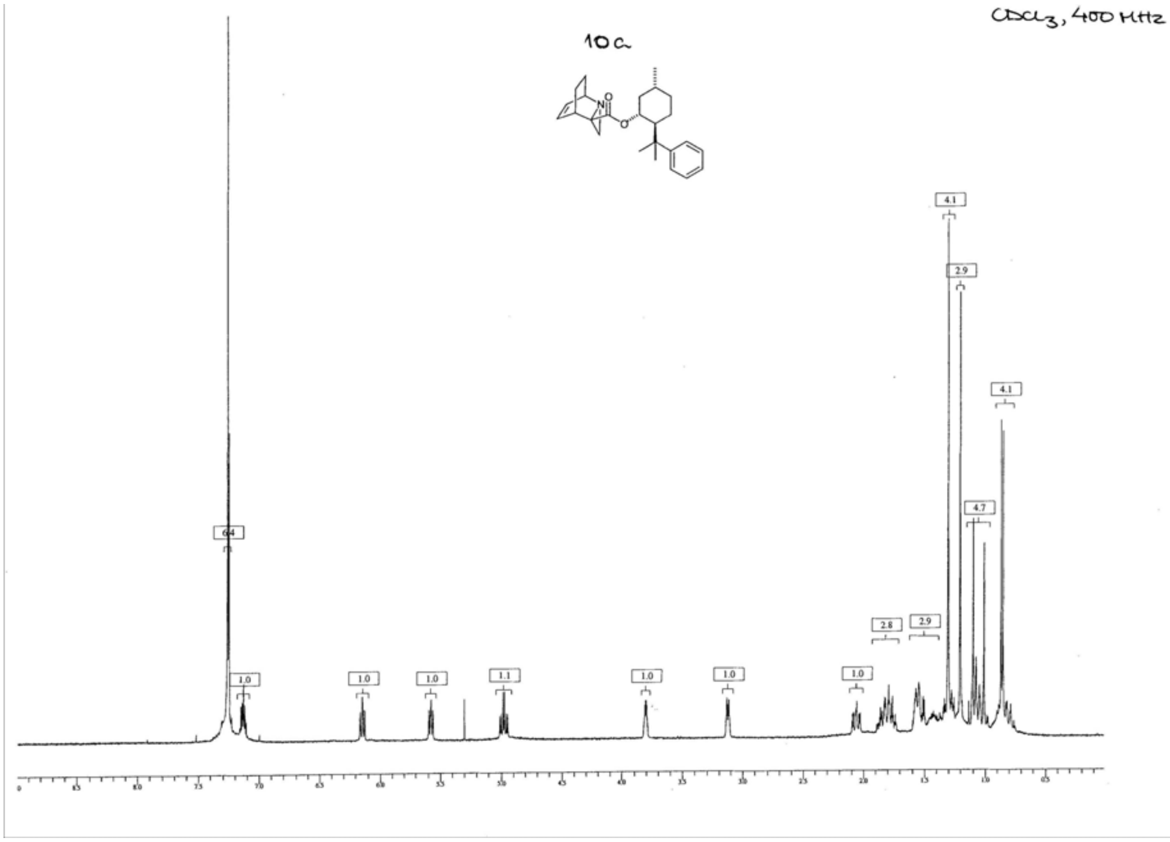
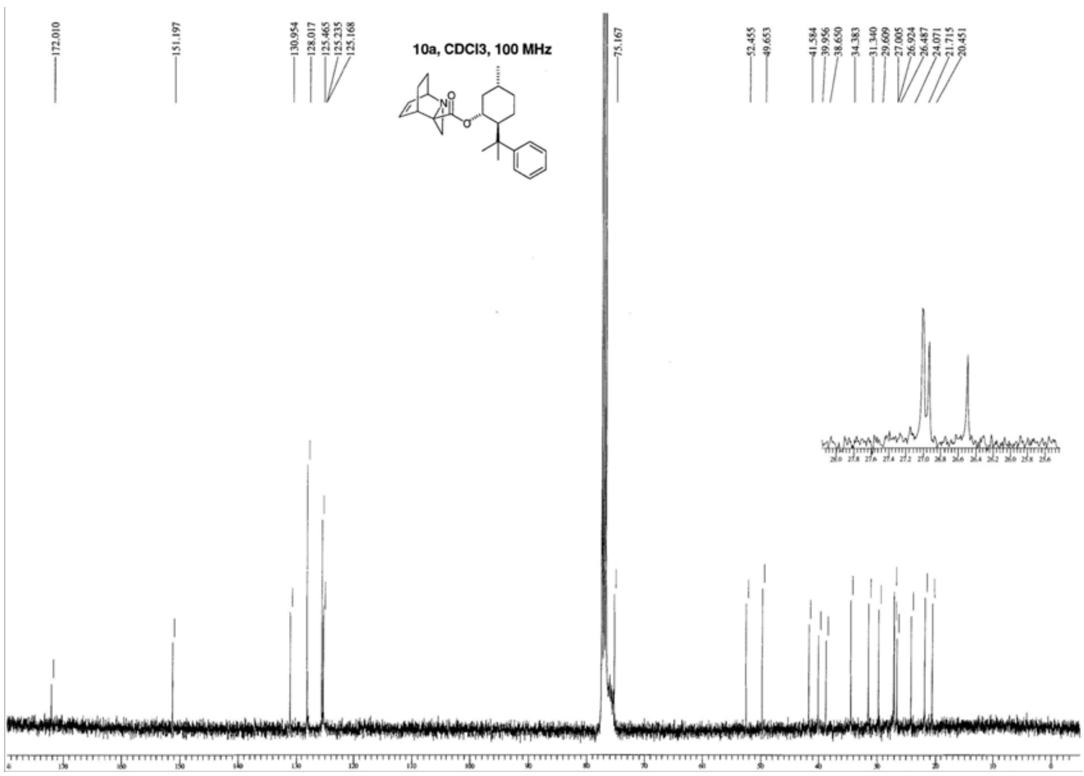
24.121
21.796
20.404


CDCl3, 400 MHz
10a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130.954
128.017
125.465
125.235
125.168
75.167
52.455
49.653
41.584
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34.383
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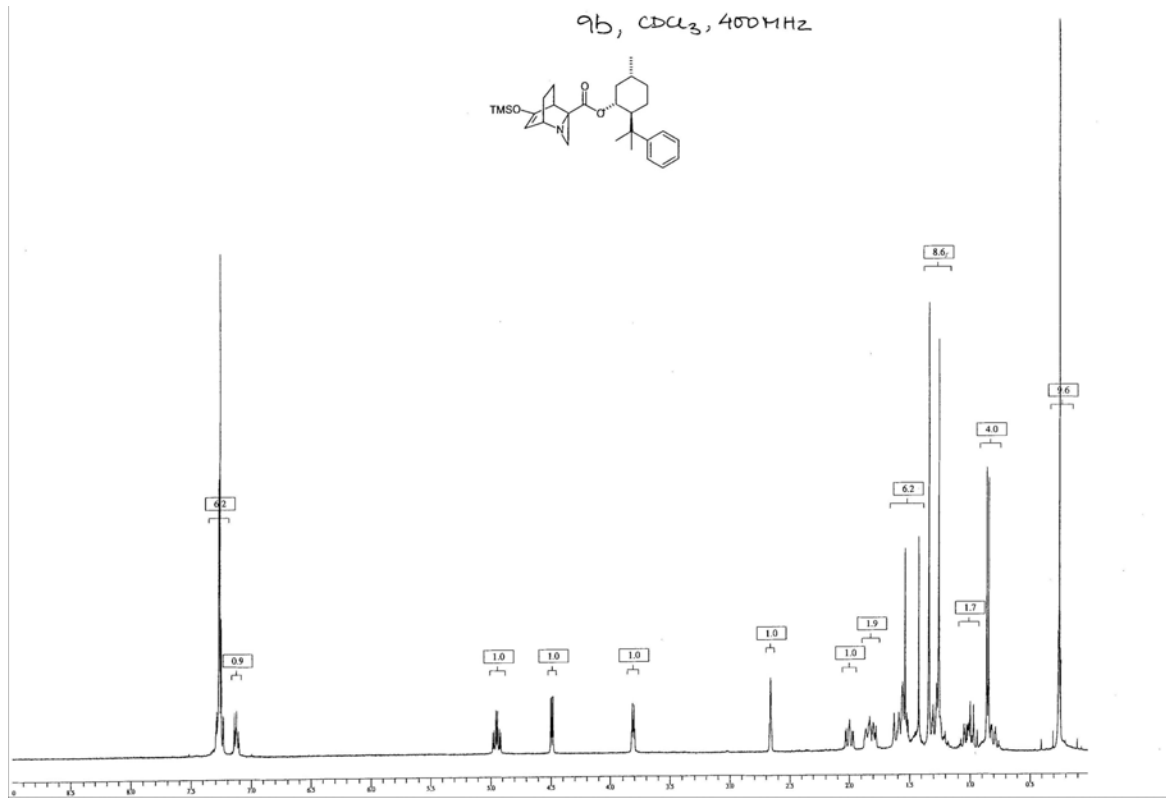
26.924
26.487
24.071
21.715
20.451


9b, CDCl3, 400MHz
TMSO
N
O
O
6.2
0.9
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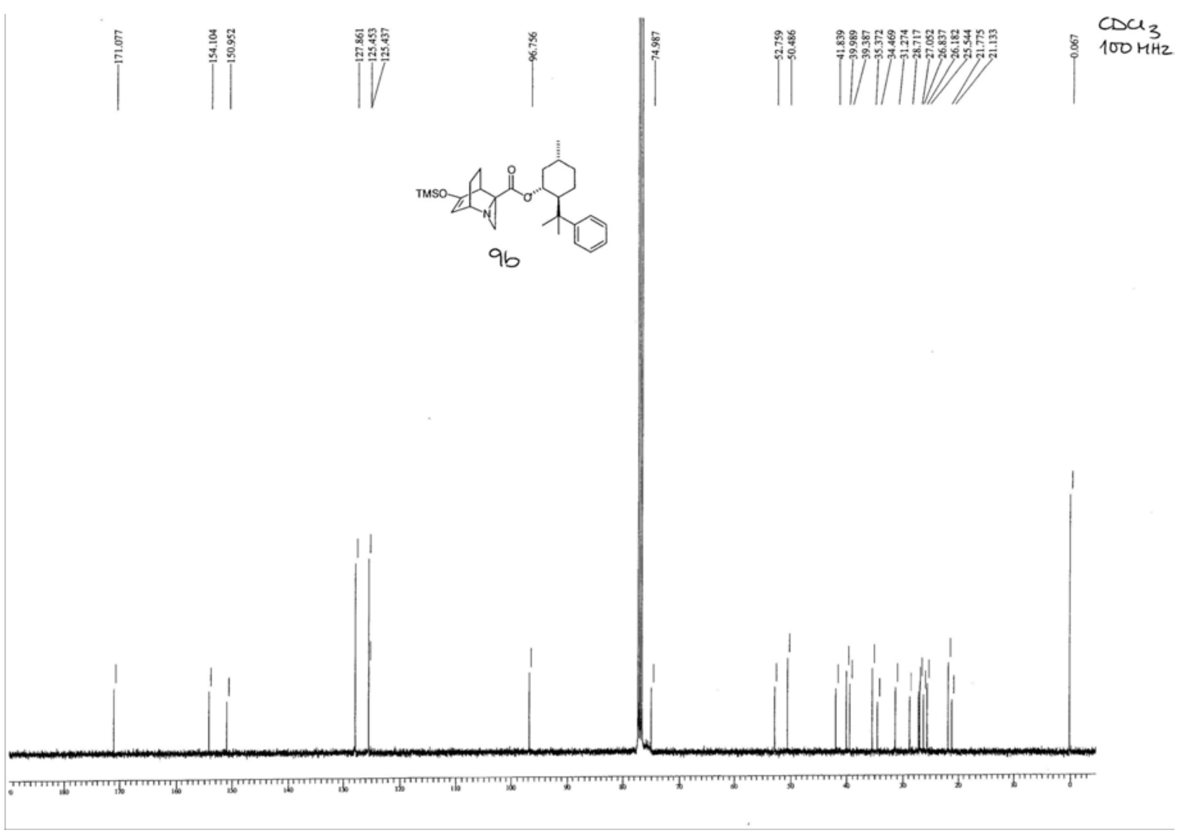
1.0
1.0
1.0
1.0
1.9
6.2
8.6
1.7
4.0
9.6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100 MHz
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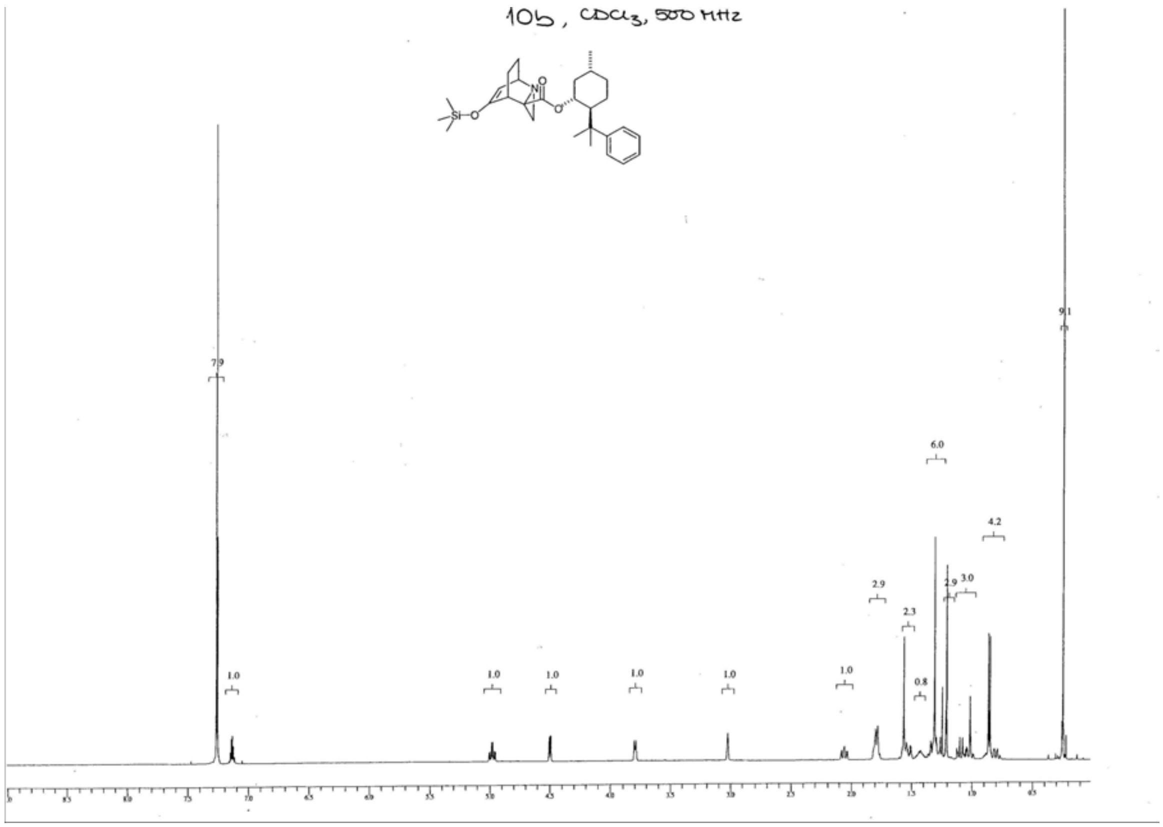
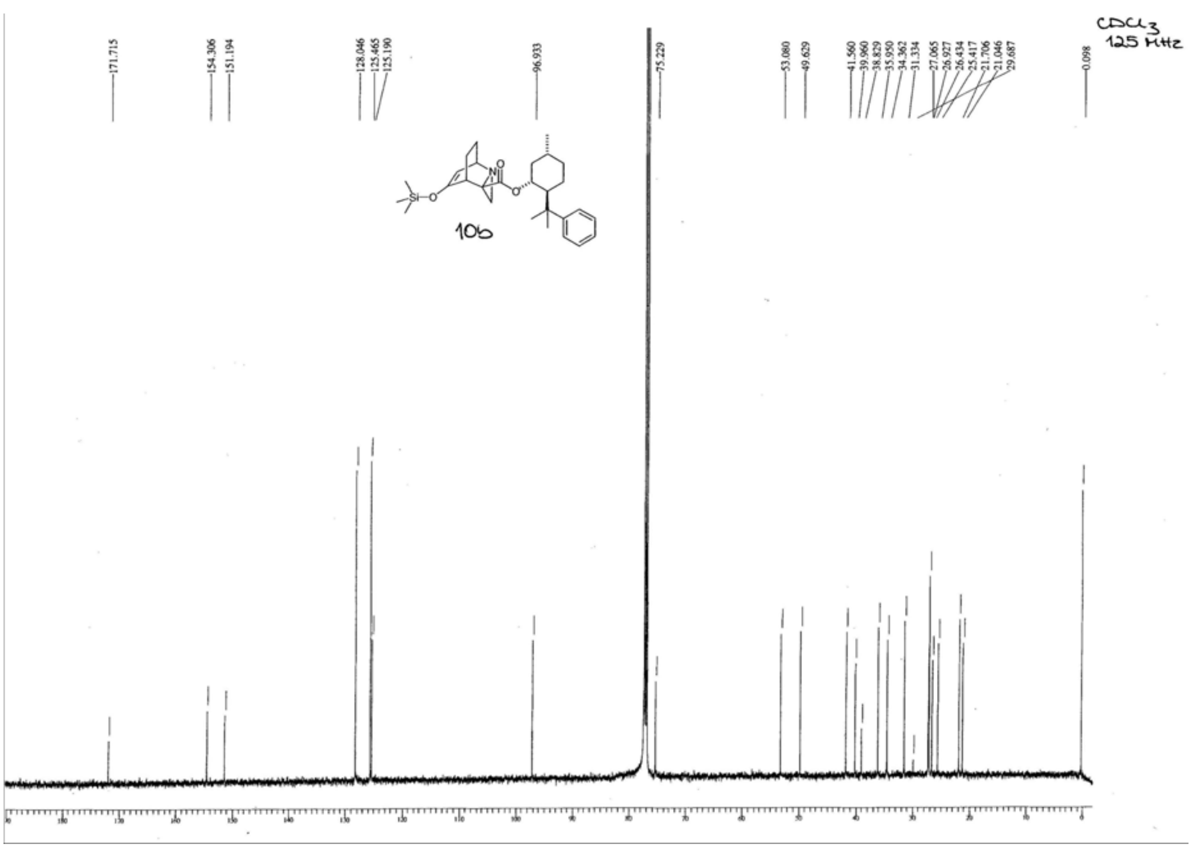
154.104
150.952
127.861
125.453
125.437
96.756
74.987
52.759
50.486
41.839
39.989
39.387
35.372
34.469
31.274
28.717
27.052
26.837
26.182
25.544
21.775
21.133
0.067
TMSO
N
O
O
9b


10b, CDCl3, 500 MHz
Si
O
N
O
O
7.9
1.0
1.0
1.0
1.0
1.0
1.0
2.9
2.3
0.8
6.0
2.9
3.0
4.2
9.1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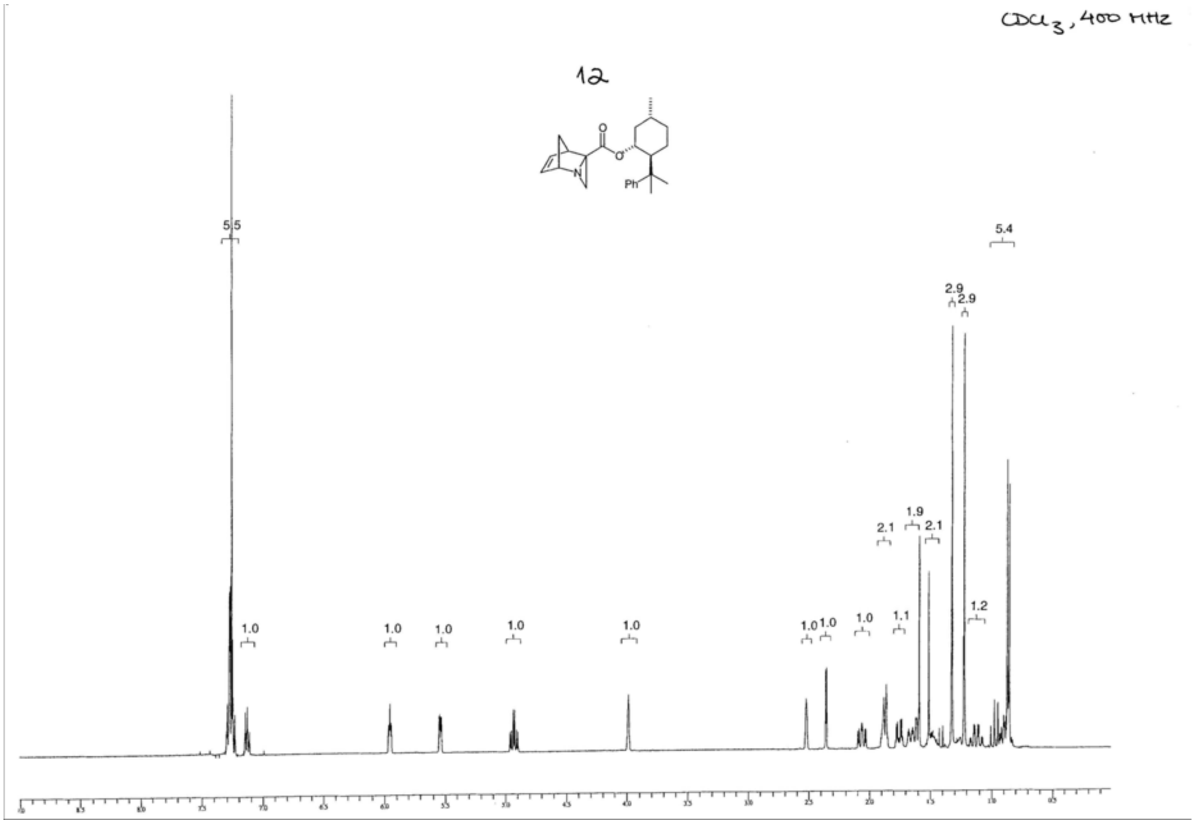
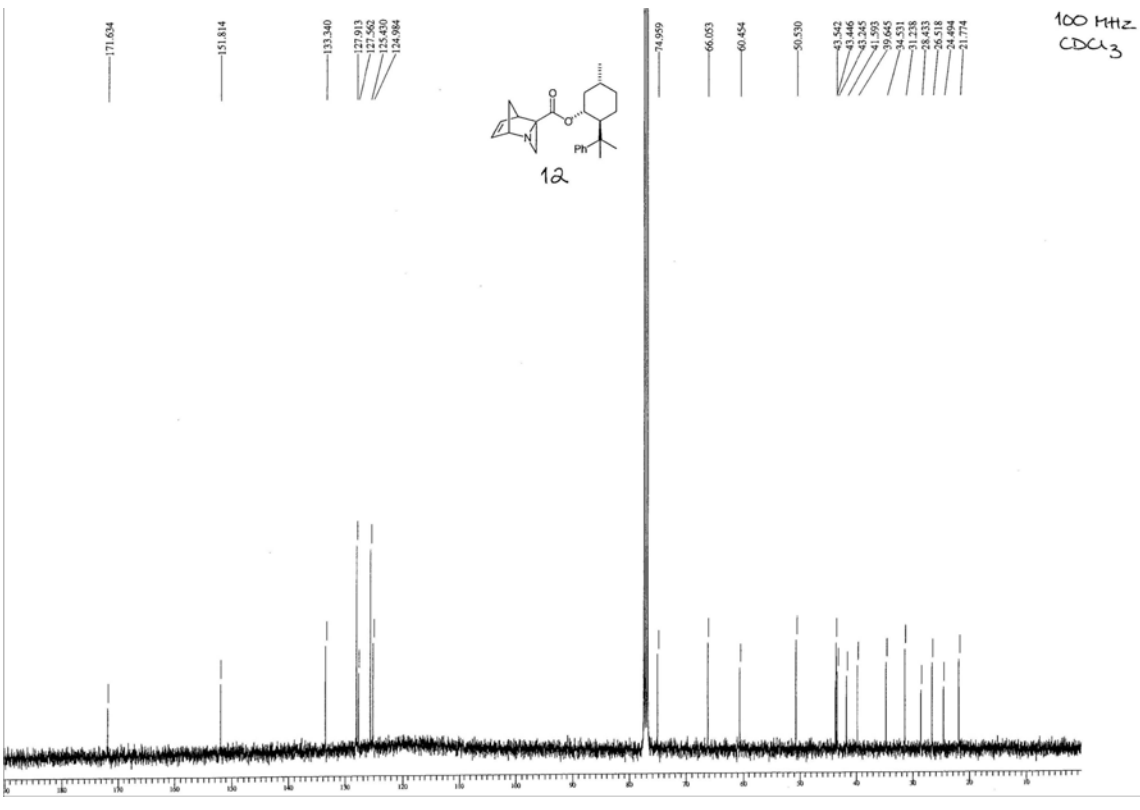
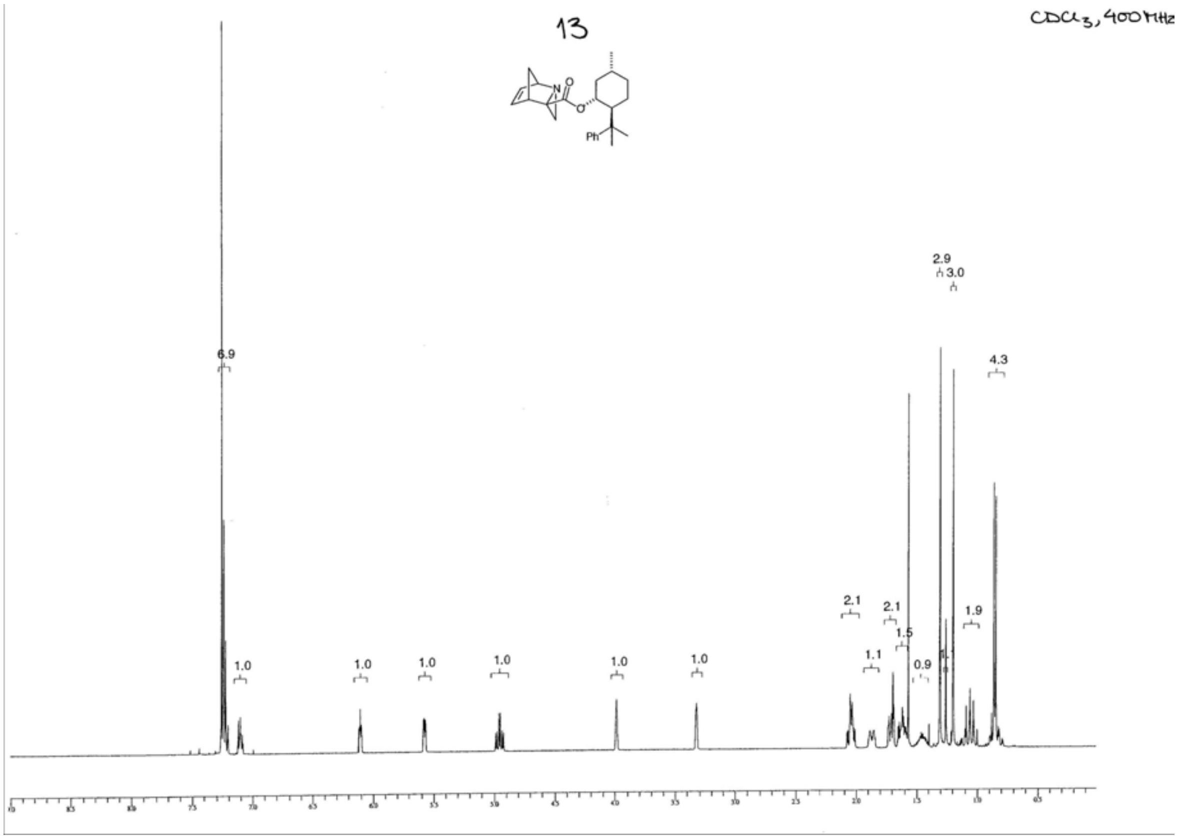
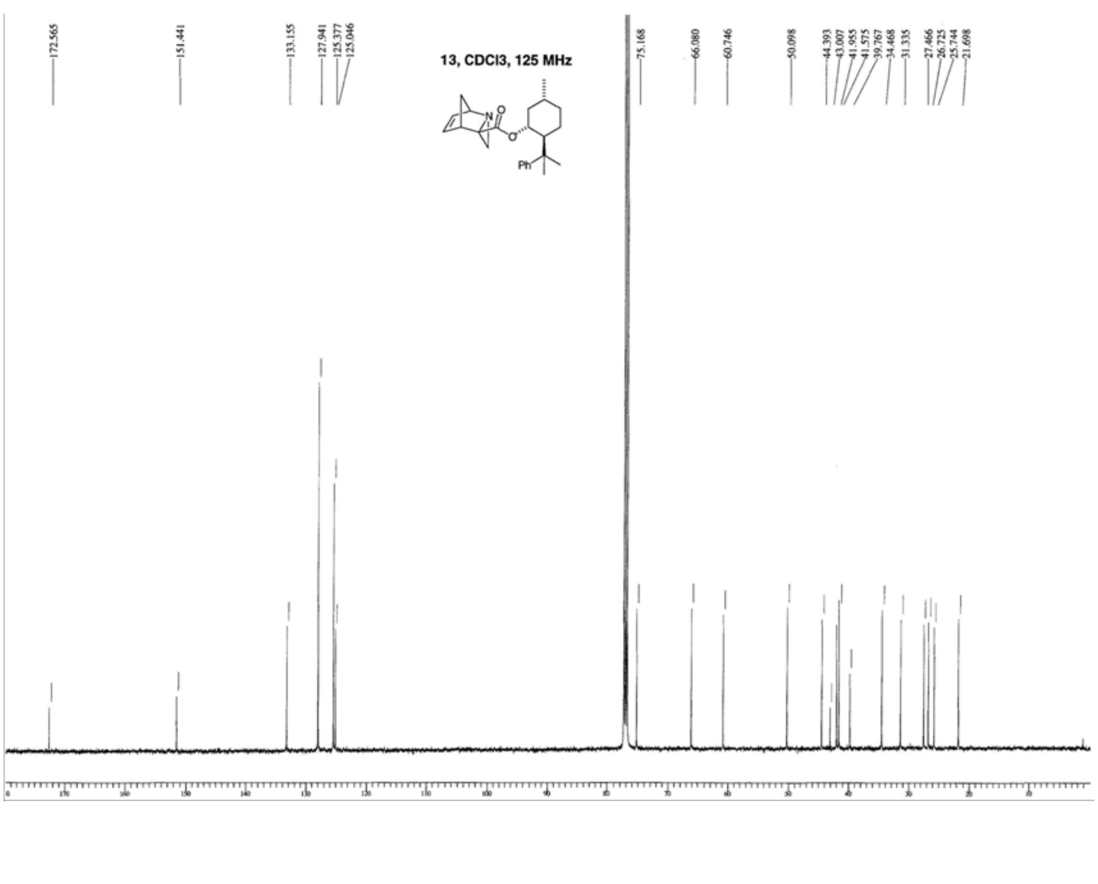
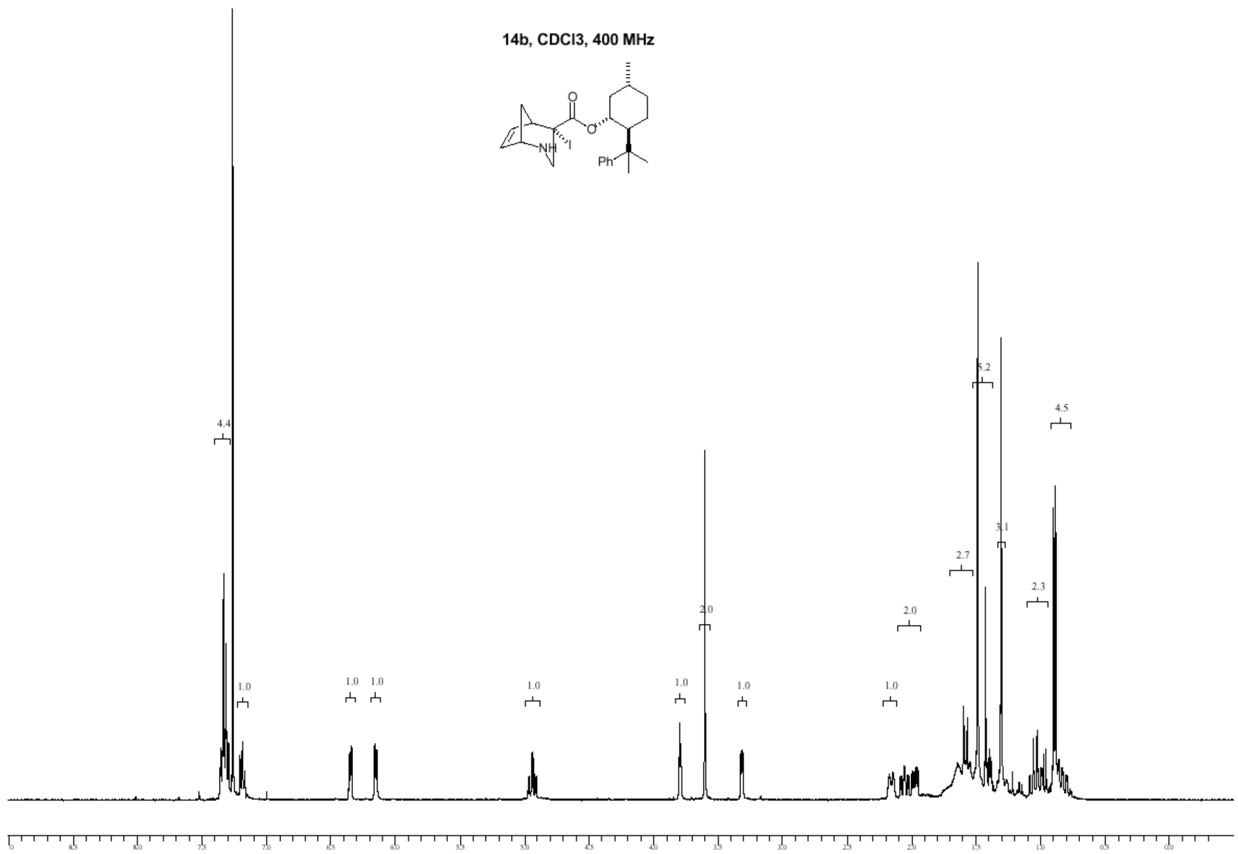
154.306
151.194
128.046
125.465
125.190
96.933
75.229
53.080
49.629
41.560
39.960
38.829
35.950
34.362
31.334
27.065
26.927
26.434
25.417
21.706
21.046
29.687
0.098
Si
O
N
O
O
10b

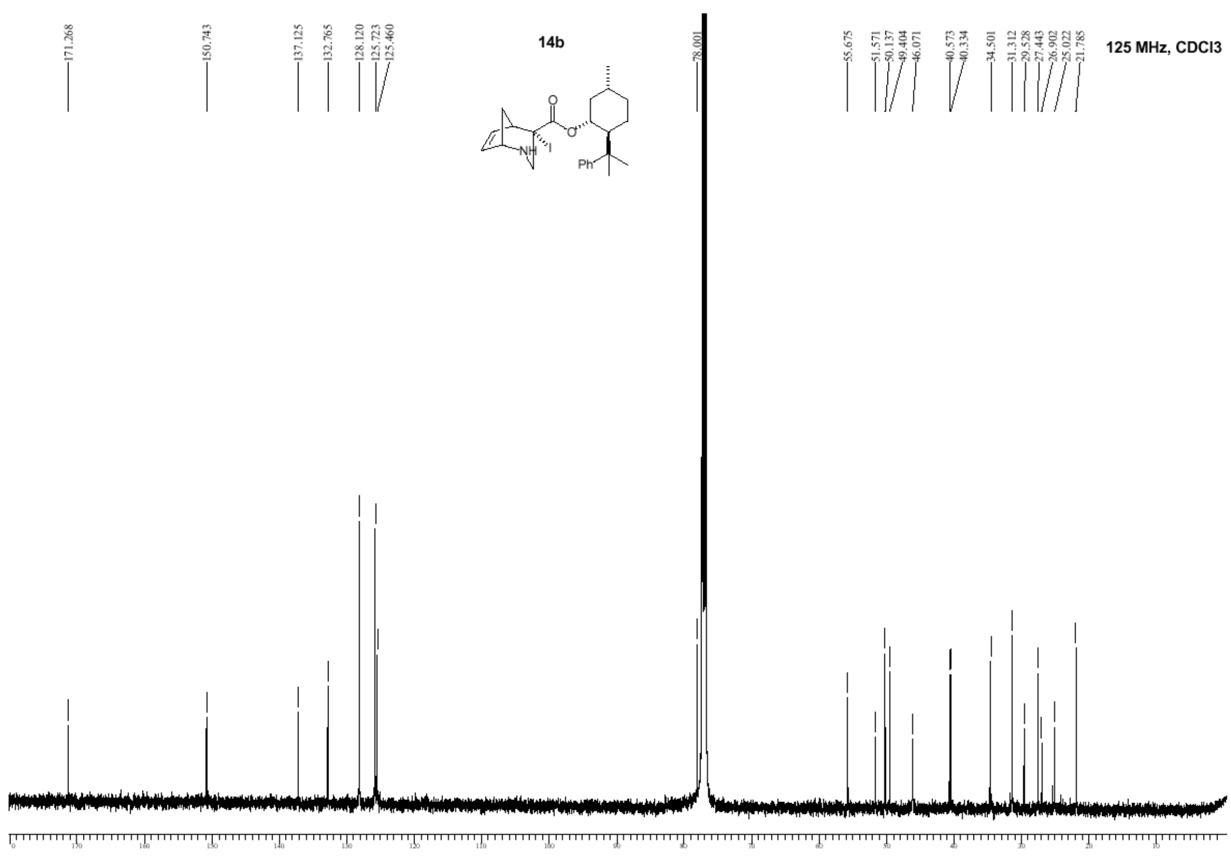

CDCl3, 400 MHz
12
Ph
5.5
1.0
1.0
1.0
1.0
1.0
1.0
1.0
1.0
1.1
2.1
1.9
2.1
2.9
2.9
1.2
5.4

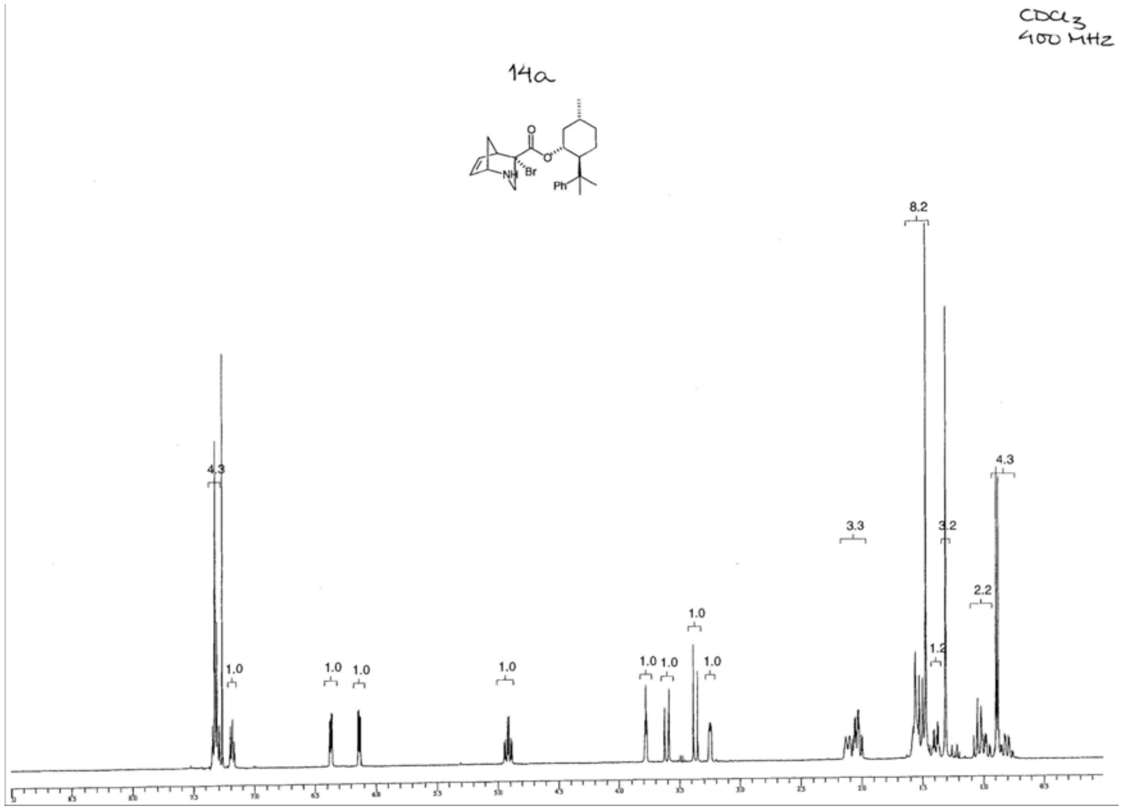

171.634
151.814
133.340
127.913
127.562
125.430
124.984
74.959
66.053
60.454
50.530
43.542
43.446
43.245
41.593
39.645
34.531
31.238
28.433
26.518
24.494
21.774
100 MHz
CDCl3
Ph
12

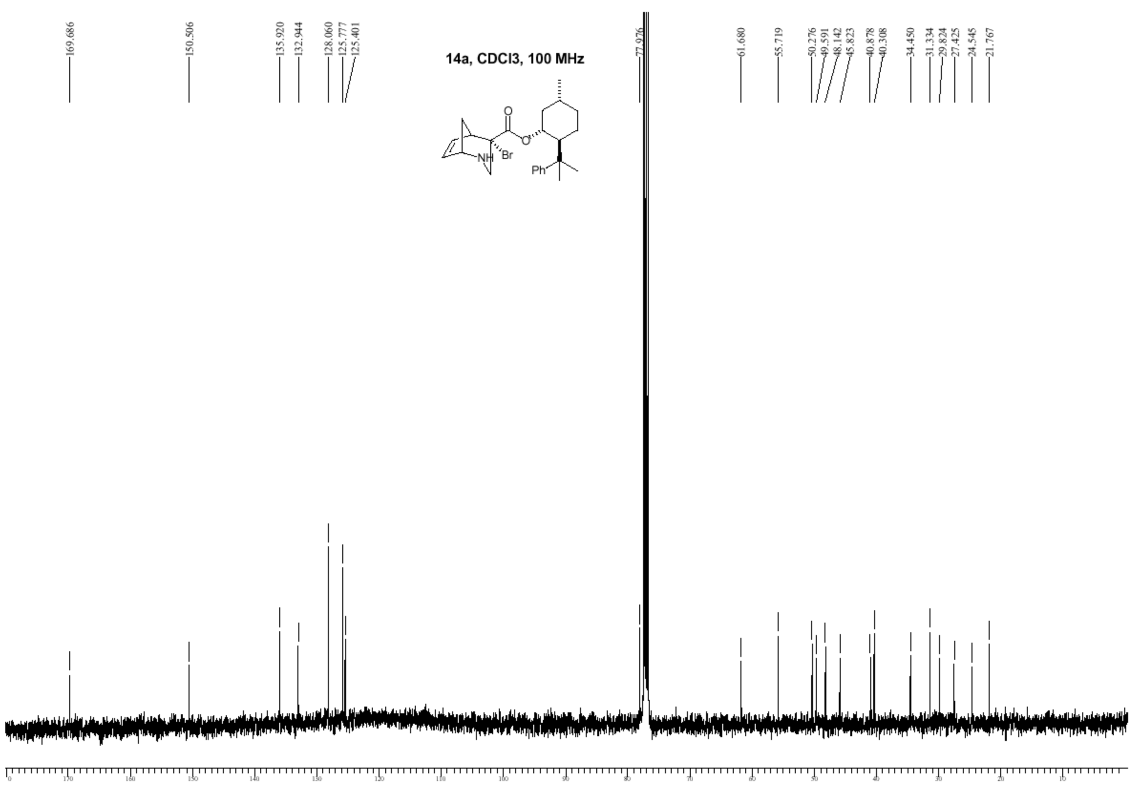

13
CDCl3, 400 MHz
Ph
6.9
1.0
1.0
1.0
1.0
1.0
1.0
2.1
1.1
2.1
1.5
0.9
2.9
3.0
1.9
4.3

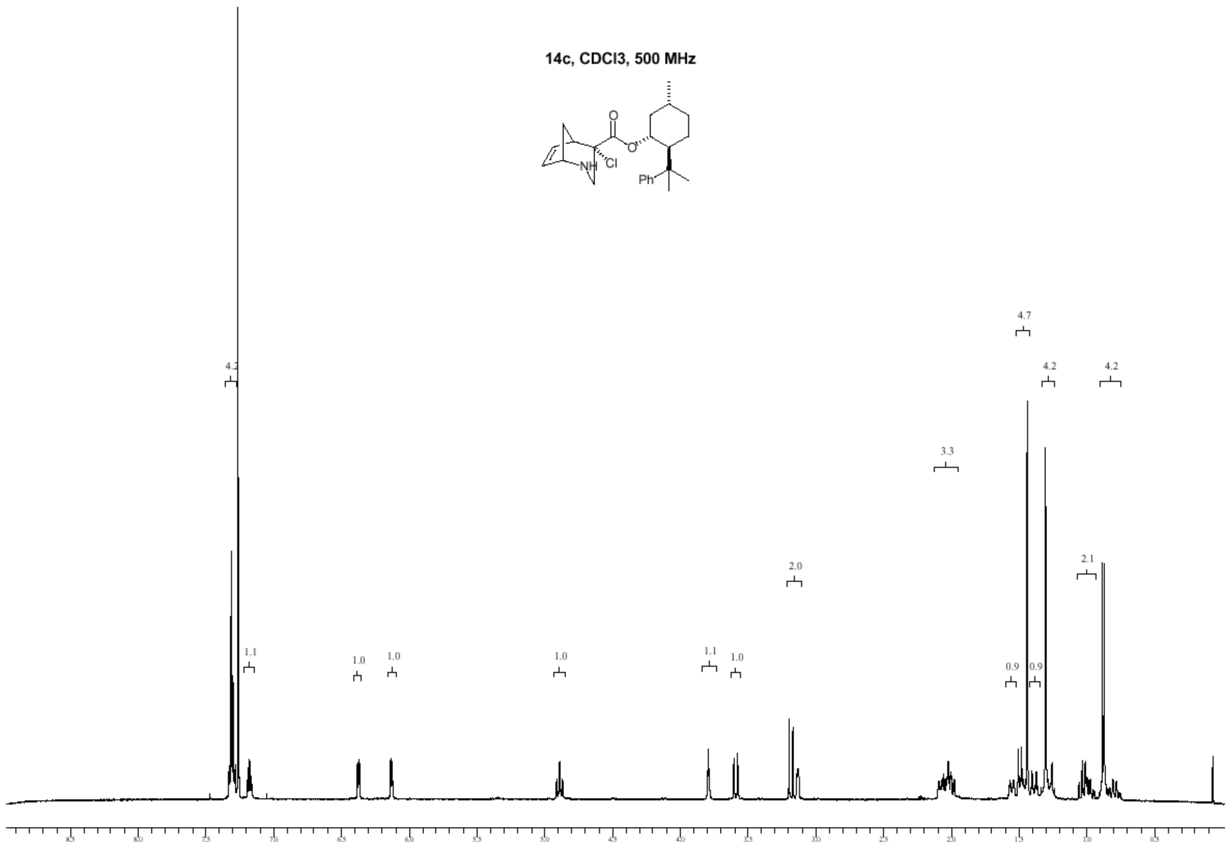

13, CDCl3, 125 MHz
Ph
172.565
151.441
133.155
127.941
125.377
125.046
75.168
66.080
60.746
50.098
44.393
43.007
41.955
41.575
39.767
34.468
31.335
27.466
26.725
25.744
21.698

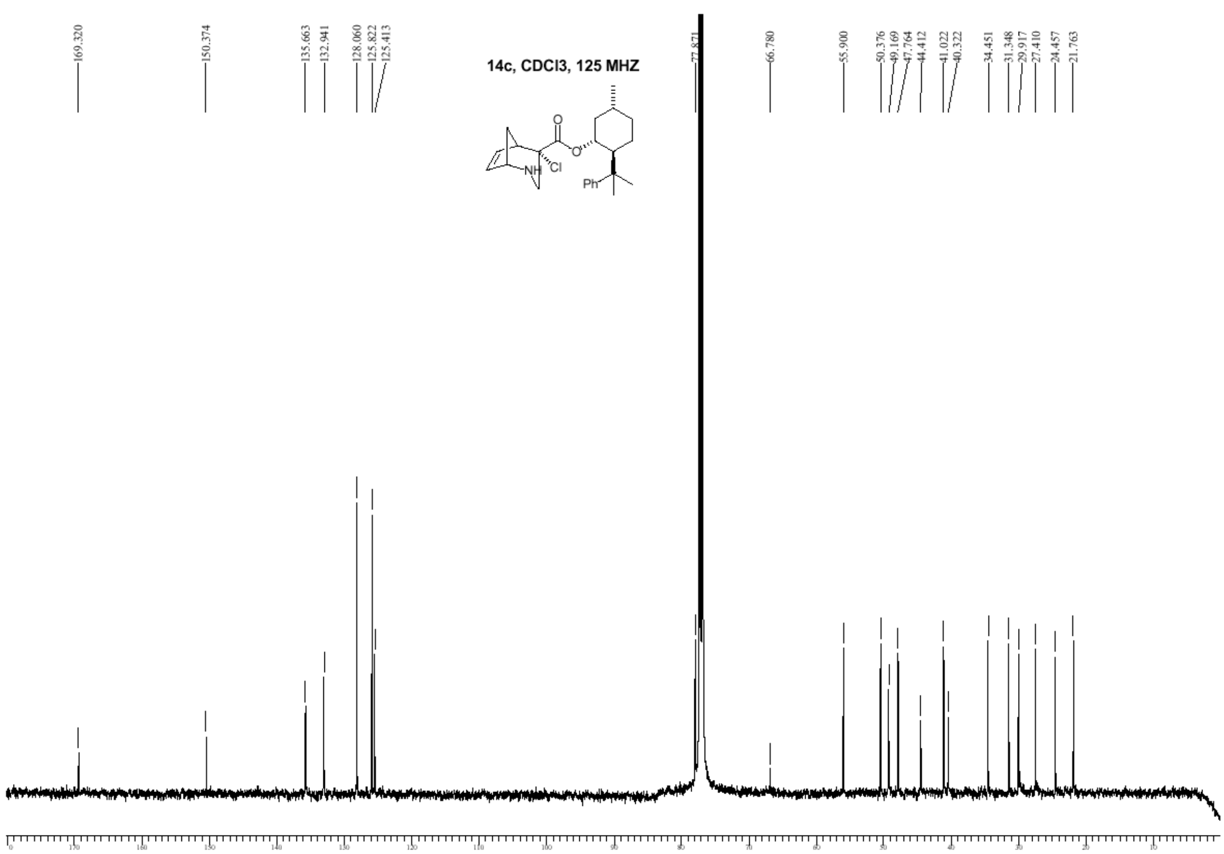

14b, CDCl3, 400 MHz
NH
I
O
O
Ph

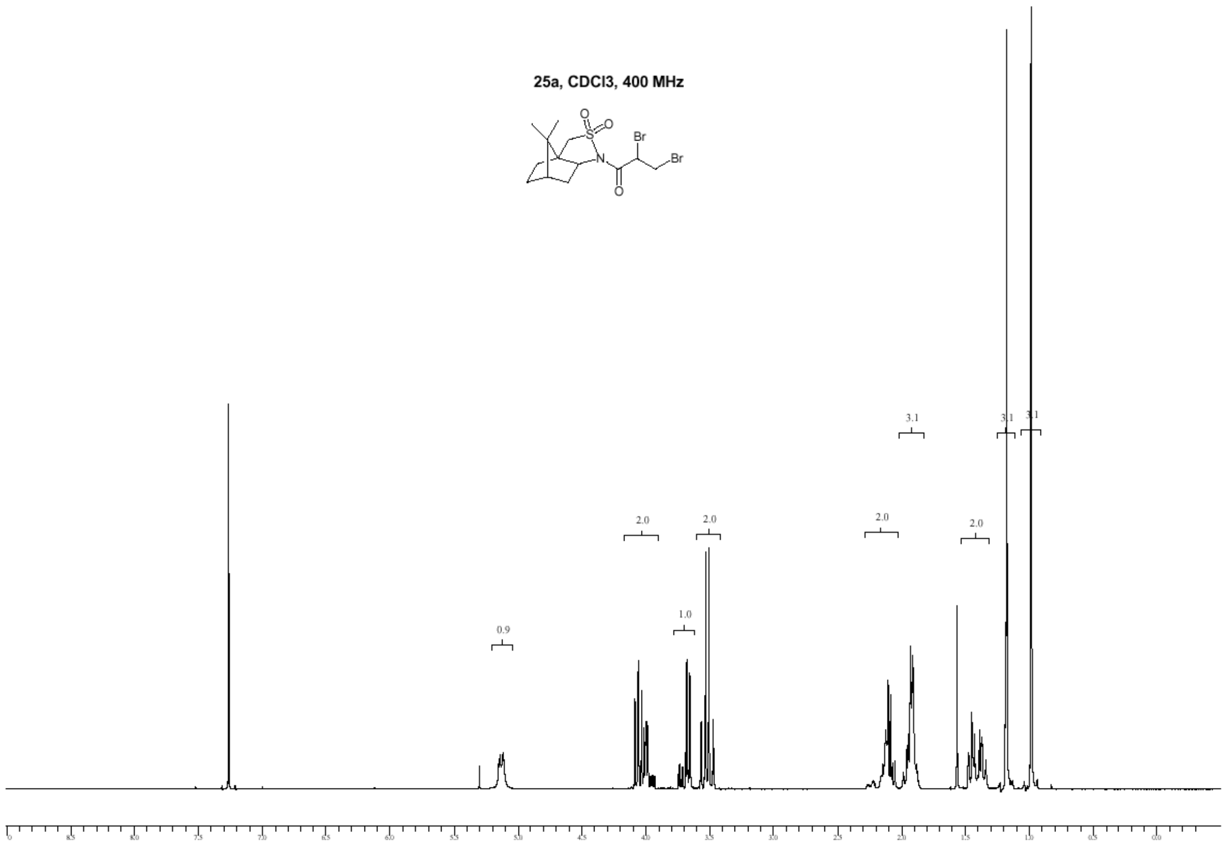

171.268
150.743
137.125
132.765
128.120
125.723
125.460
14b
78.001
55.675
51.571
50.137
49.404
46.071
40.573
40.334
34.501
31.312
29.528
27.443
26.902
25.022
21.785
125 MHz, CDCl3
NH
I
O
O
Ph

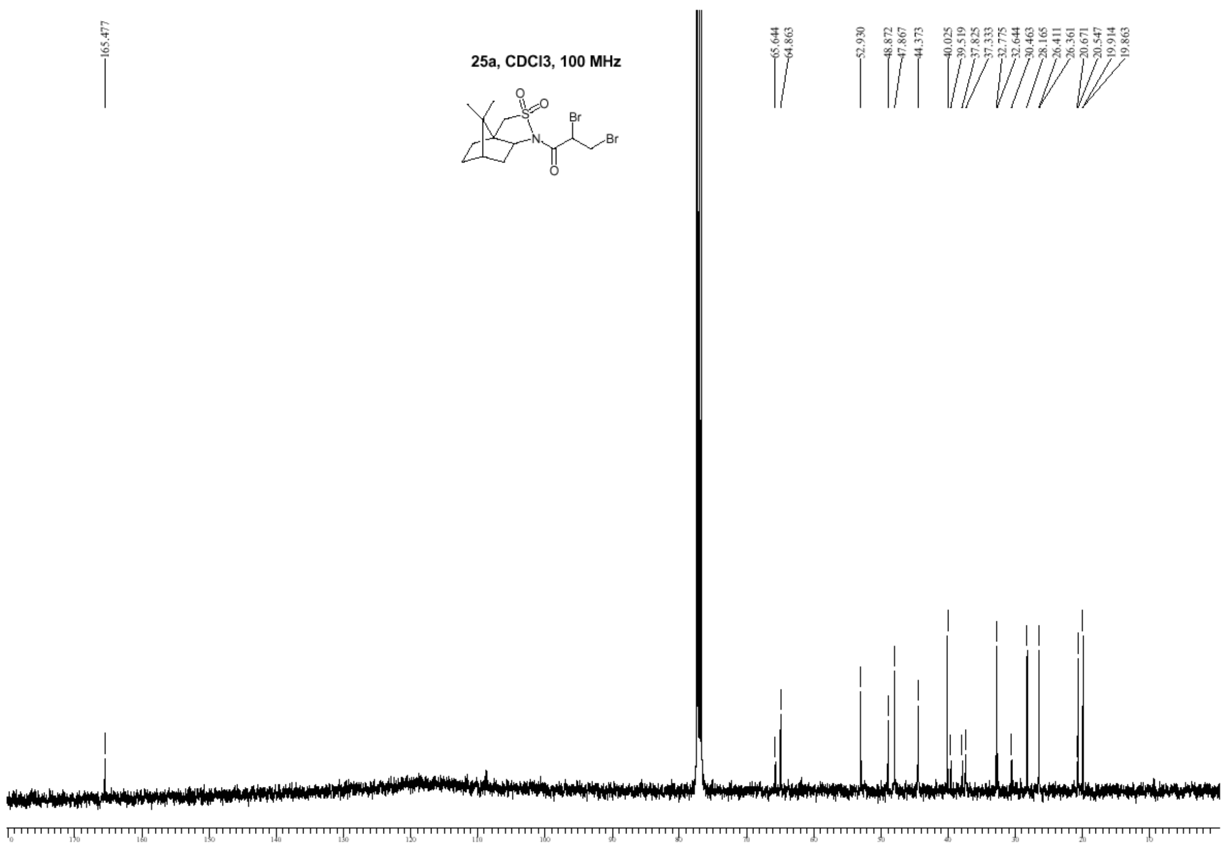

CDCl3
400 MHz
14a
NH
Br
Ph
4.3
1.0
1.0 1.0
1.0
1.0 1.0
1.0
1.0
3.3
8.2
1.2
3.2
2.2
4.3

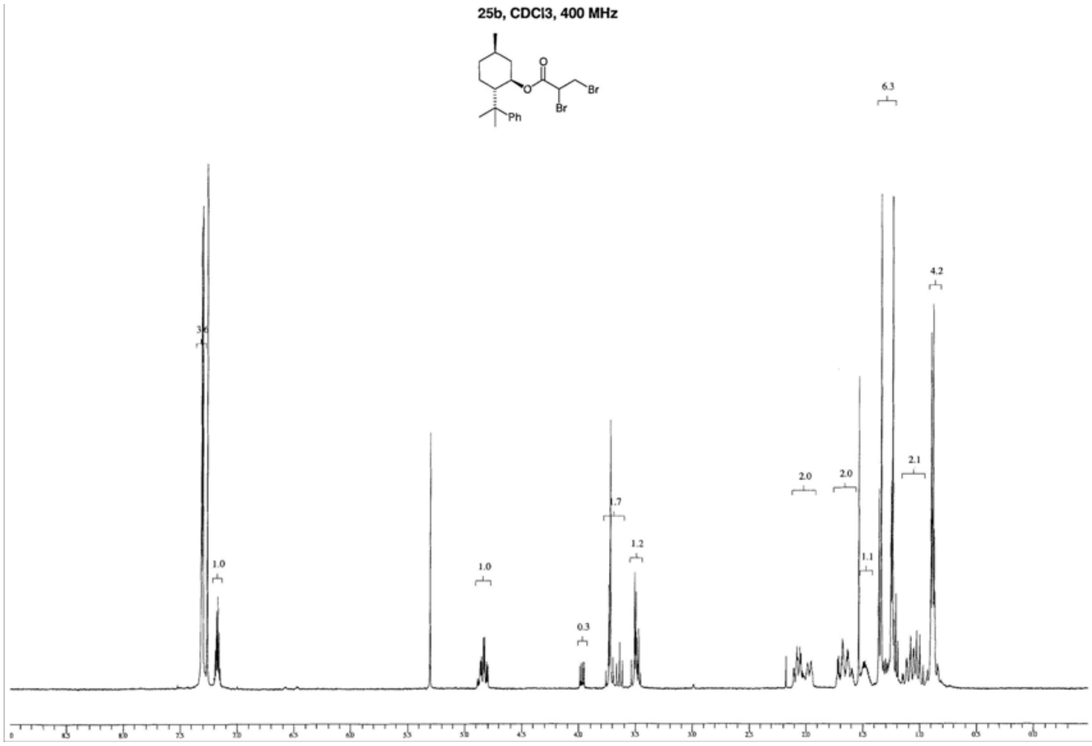

169.686
150.506
135.920
132.944
128.060
125.777
125.401
77.926
61.680
55.719
50.276
49.591
48.142
45.823
40.878
40.308
34.450
31.334
29.834
27.425
24.545
21.767
14a, CDCl3, 100 MHz
NH
Br
Ph

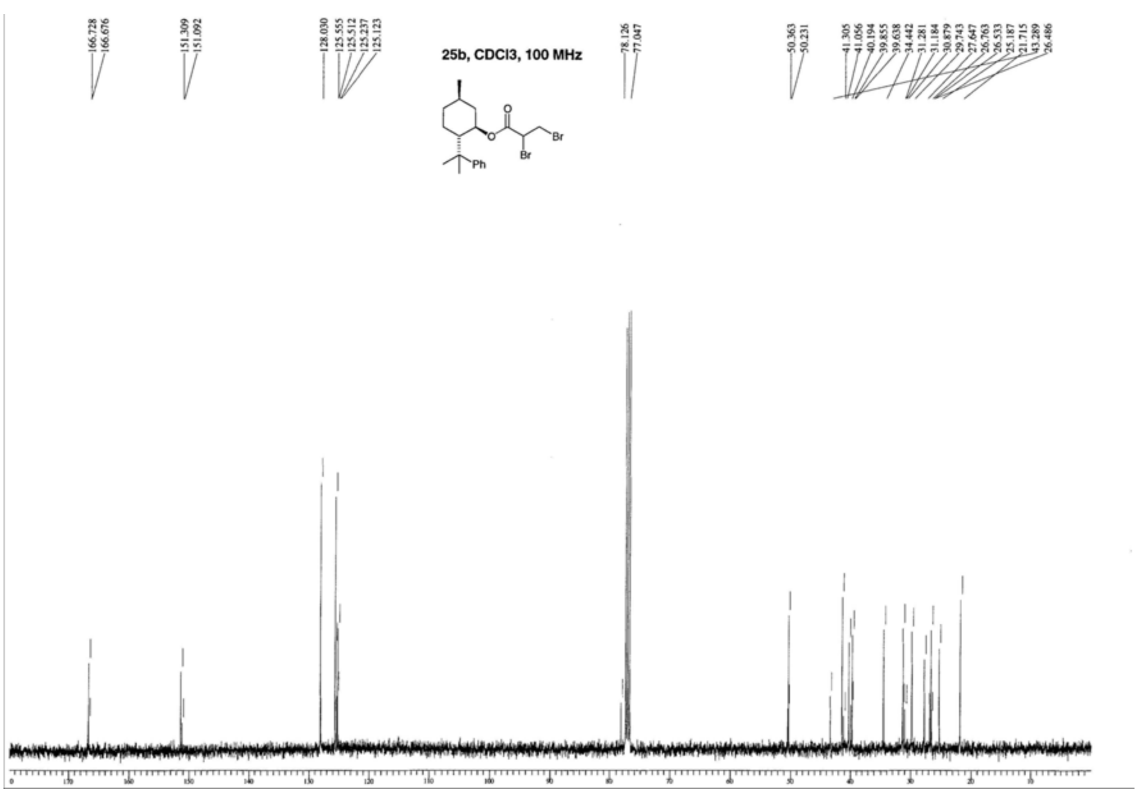

14c, CDCl3, 500 MHz
NH
Cl
Ph
4.2
1.1
1.0
1.0
1.0
1.1
1.0
2.0
3.3
0.9
4.7
0.9
4.2
2.1
4.2

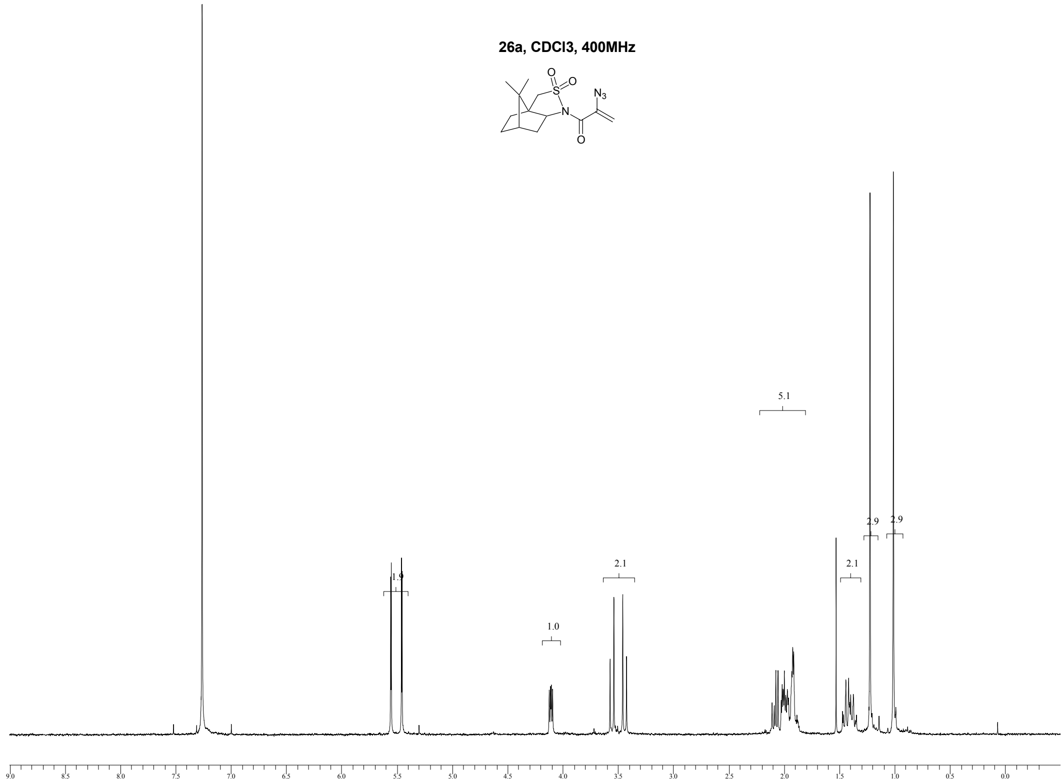

169.320
150.374
135.663
132.941
128.060
125.822
125.413
14c, CDCl3, 125 MHZ
77.871
66.780
55.900
50.376
49.169
47.764
44.412
41.022
40.322
34.451
31.348
29.917
27.410
24.457
21.763
NH
Cl
Ph

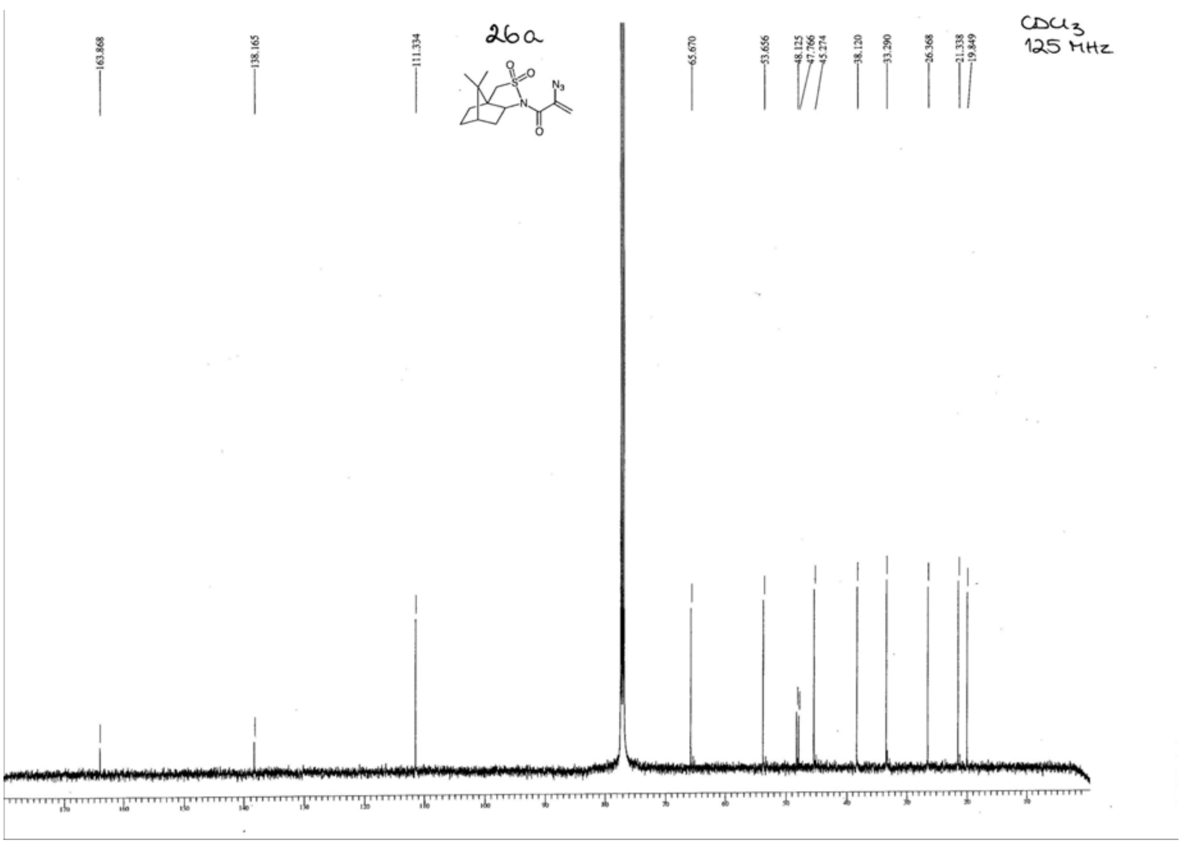

25a, CDCl3, 400 MHz
0.9
2.0
1.0
2.0
2.0
3.1
2.0
3.1
3.1


25a, CDCl3, 100 MHz
165.477
65.644
64.863
52.930
48.872
47.867
44.373
40.025
39.519
37.825
37.333
32.775
32.644
30.463
28.165
26.411
26.361
20.671
20.547
19.914
19.863

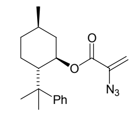

25b, CDCl3, 400 MHz
Br
Br
Ph
6.3
4.2
2.0
2.0
2.1
1.7
1.2
1.1
1.0
1.0
0.3

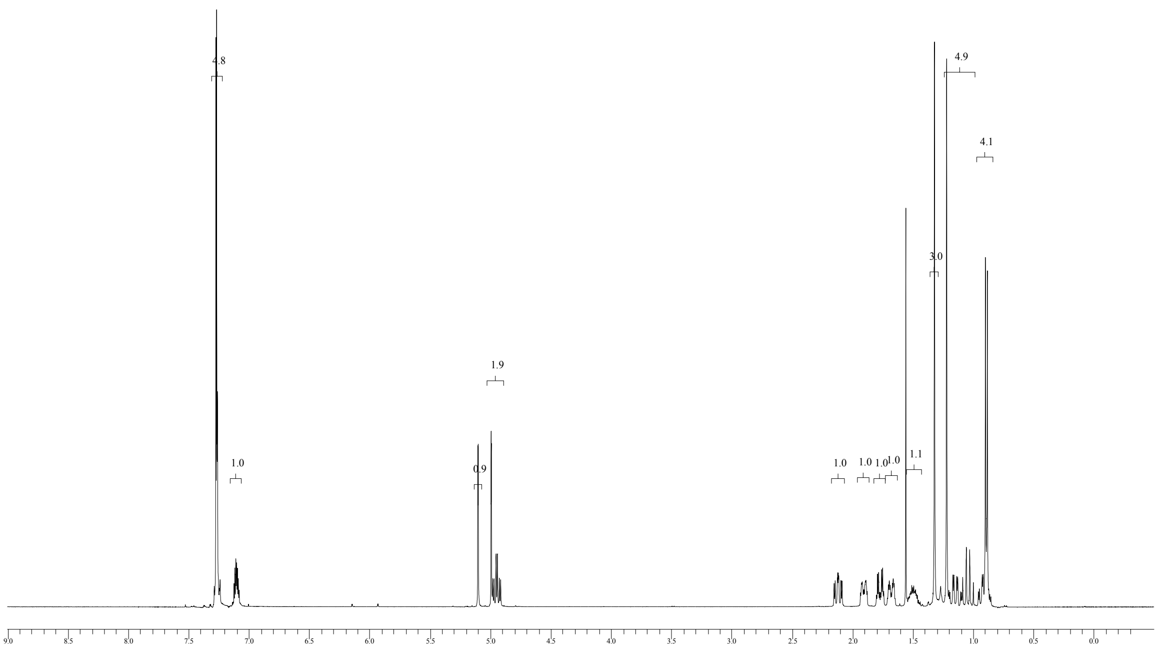

25b, CDCl3, 100 MHz
Br
Br
Ph
166.728
166.676
151.309
151.092
128.030
125.555
125.512
125.237
125.123
78.126
77.047
50.363
50.231
41.305
41.056
40.194
39.855
39.638
34.442
31.281
31.184
30.879
29.743
27.647
26.763
26.533
25.187
21.715
43.289
26.486

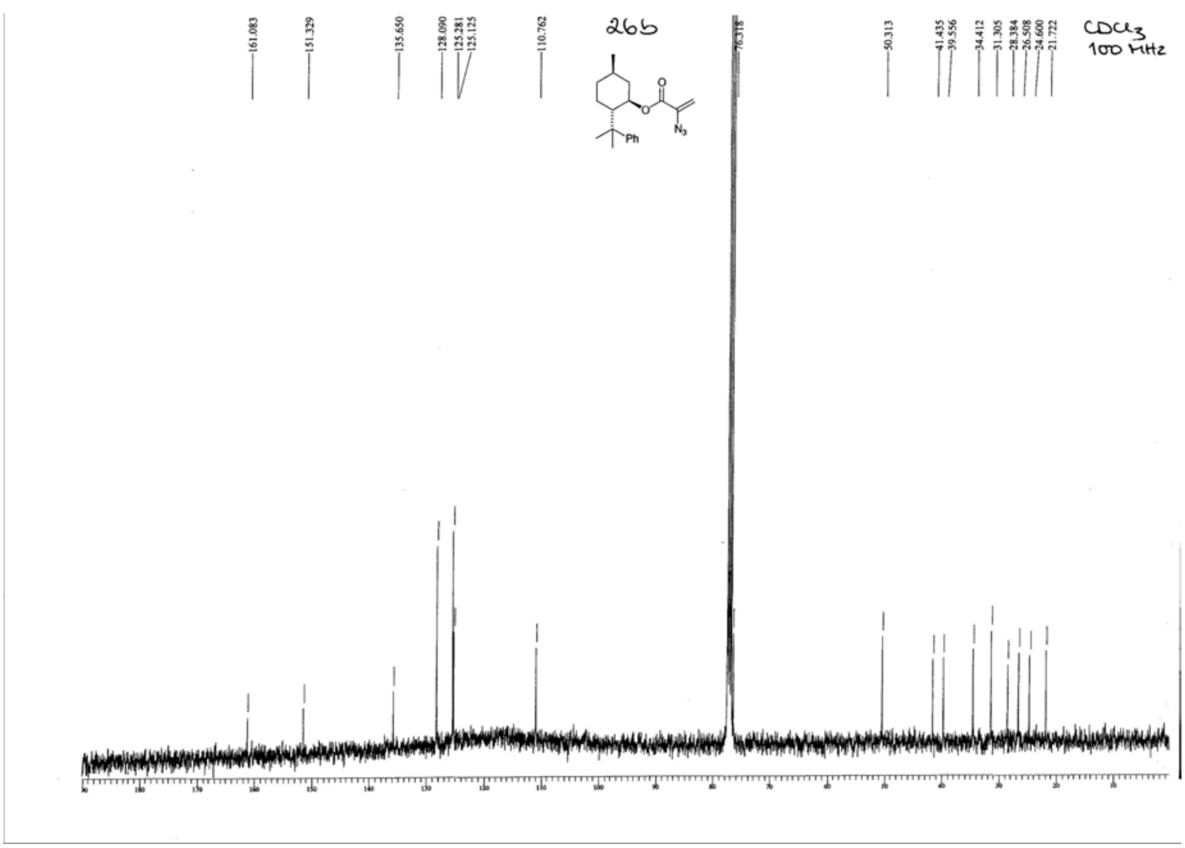

26a, CDCl3, 400MHz
N3
5.1
2.9
2.9
2.1
2.1
1.0
1.9

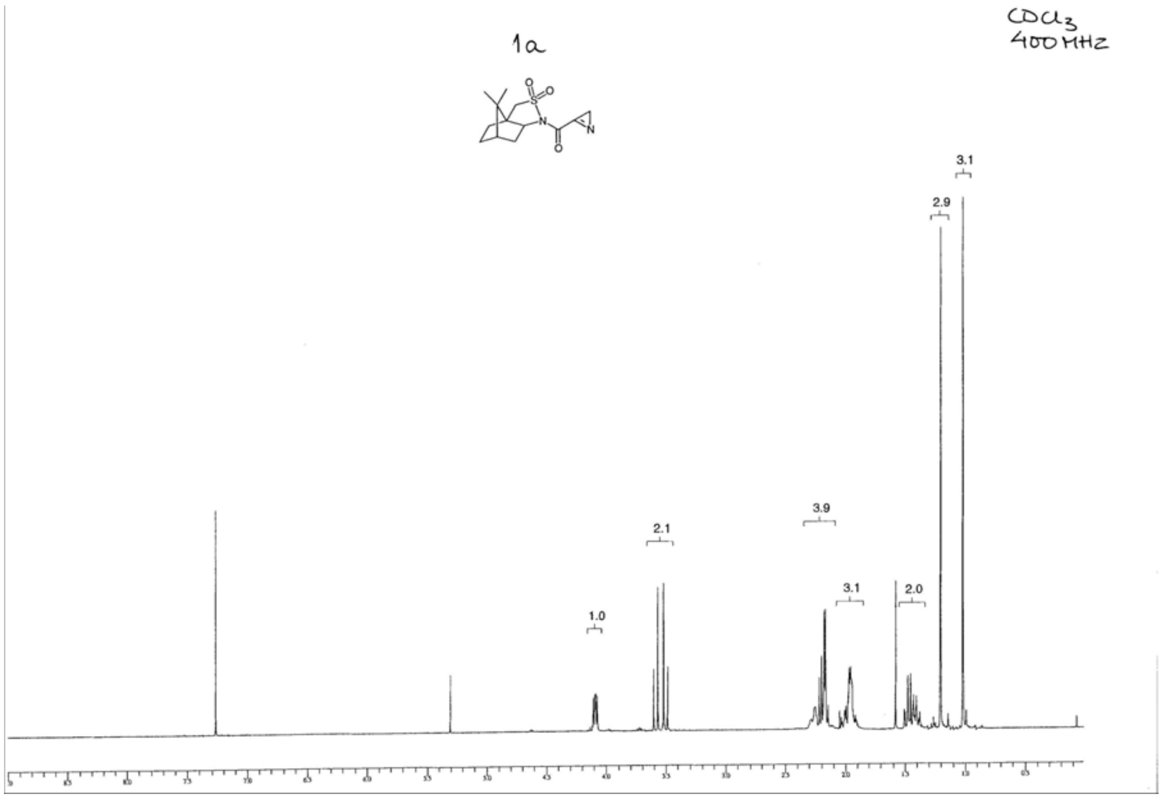

26a
N3
CDCl3
125 MHz
163.868
138.165
111.334
65.670
53.656
48.125
47.766
45.274
38.120
33.290
26.368
21.338
19.849

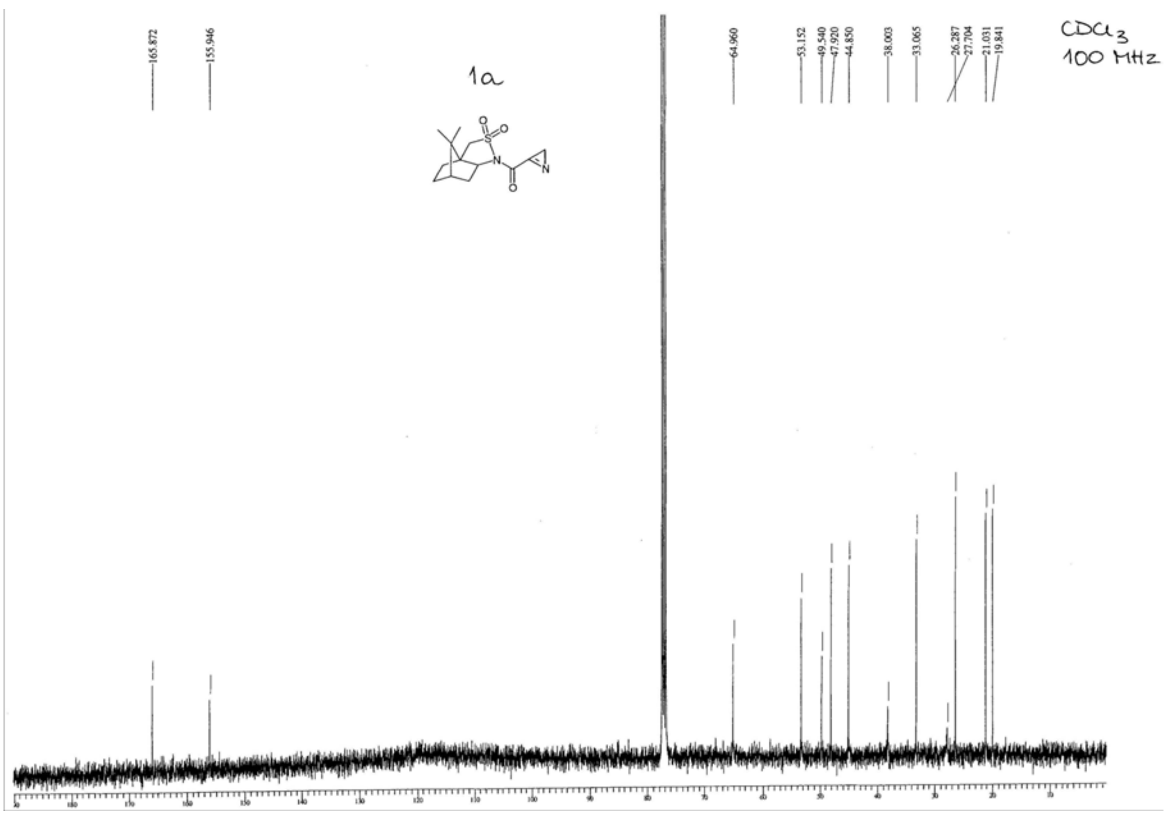
26b, CDCl3, 400 MHz

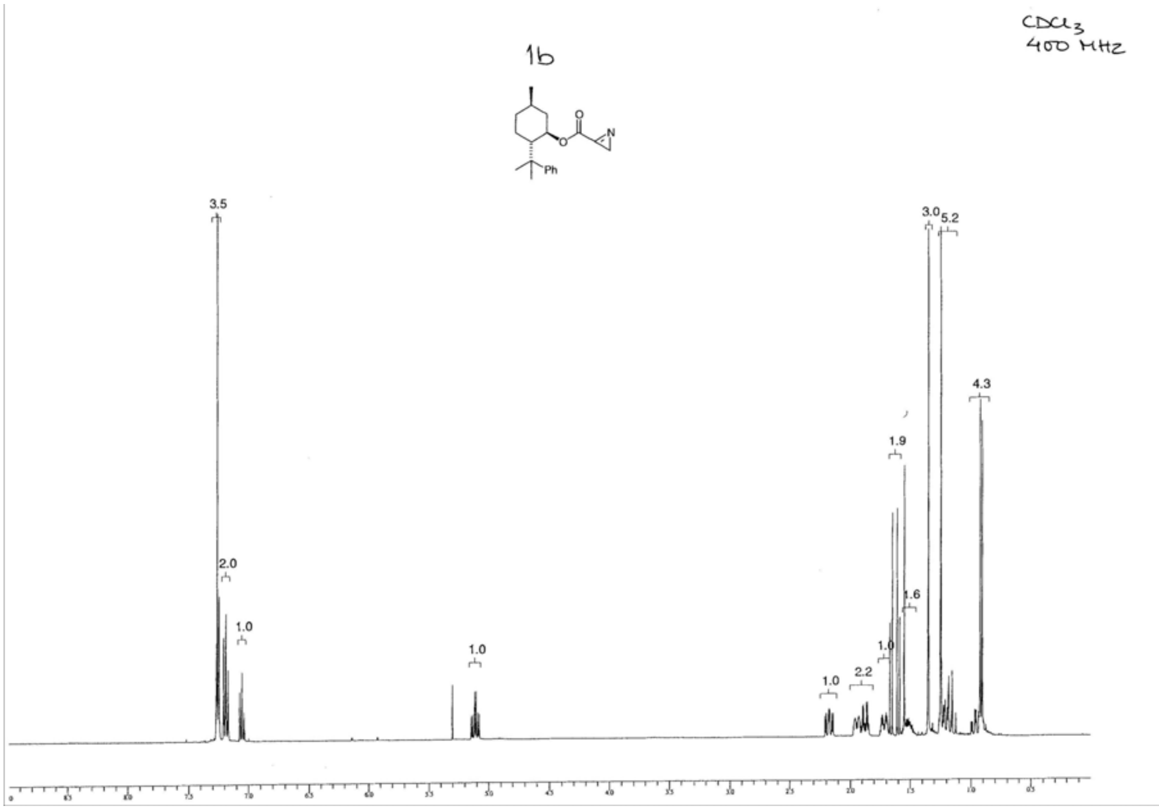




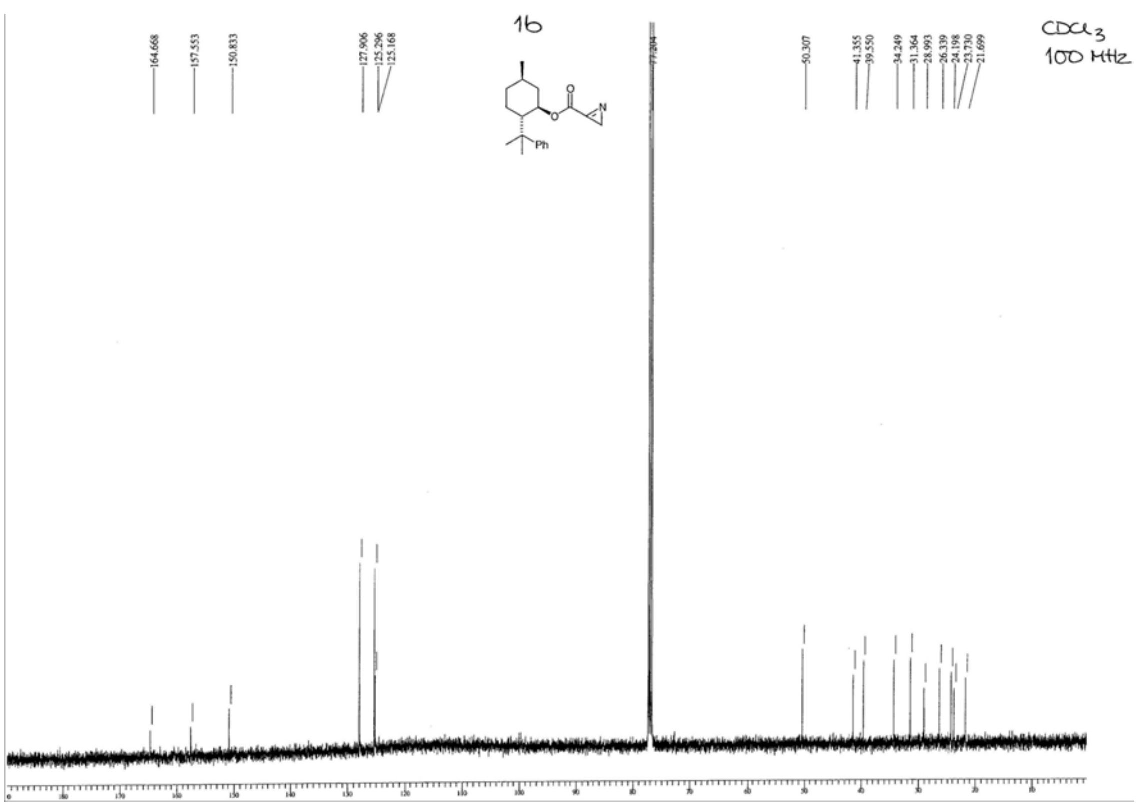



1a
CDCl3
400 MHz
3.1
2.9
2.1
3.9
3.1
2.0
1.0


165.872
155.946
64.960
53.152
49.540
47.920
44.850
38.003
33.065
26.287
27.704
21.031
19.841
1a
CDCl3
100 MHz



CDCl3
400 MHz
1b
Ph
N
O
3.5
2.0
1.0
1.0
1.0
2.2
1.0
1.6
1.9
3.0
5.2
4.3



1b
CDCl3
100 MHz
164.668
157.553
150.833
127.906
125.296
125.168
77.204
50.307
41.355
39.550
34.249
31.364
28.993
26.339
24.198
23.730
21.699