

Supporting Information for:

**Multicomponent Asymmetric Reactions
Mediated by Proline-Lithium Salt.**

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1. General methods

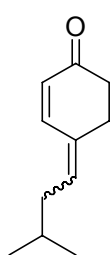
^1H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz or at 200 MHz and 50 MHz respectively. Chemical shifts are reported in ppm relative to the resonance of CHCl_3 ($\delta = 7.26$) for ^1H NMR and to the central peak of CDCl_3 ($\delta = 77.5$) for ^{13}C NMR. Flash chromatography (FC) was carried out using Merck silica gel 60 (230-400 mesh) using mixtures of petroleum ether 30-50° C (PE) and diethyl ether for compounds **7** or a mixture of ethyl acetate/methanol for compounds **10**.

1.1 Materials

Analytical grade solvents were used as received. All commercially available reagents were employed as received including aldehydes **7**, proline **4**, 2-cyclohexen-1-one **2**. Proline-**4** lithium salt has been prepared accordingly to standard literature procedures.

2. General procedure for the vinylogous aldol condensation of 2-cyclohexen-1-one and aldehydes **7** leading to compounds **8**.

2-Cyclohexen-1-one **2** (1 g, 10.4 mmol, 1 eq) and aldehydes **7a-d** (20.8 mmols, 2 eq) were added to a stirred suspension of proline **4**-lithium salt (1.26 g, 1 eq) in toluene (20 mL). After 24 h water (40 mL) was added and the mixture extracted twice with ethyl acetate (100 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent removed *in vacuo*. The crude material was purified by FC (eluant: PE:diethyl ether from the ratio 10:1 to 1:3) to afford compounds **8a-d** in yield % accordingly to scheme 2.



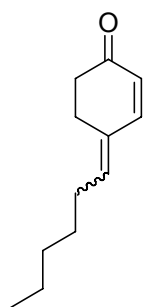
8a

Mixture of *E-Z* isomers in the ratio 3:1

$^1\text{H-NMR}$ (200 MHz); δ (CDCl_3): 7.43 (d, 1H, $J = 10$ Hz *Z*-isomer), 7.01 (d, 1H, $J = 10.2$ Hz *E*-isomer), 5.86 (m, 2H), 2.73 (m, 2H), 2.52 (m, 2H), 1.70 (m, 1H), 0.92 (d, 6H).

$^{13}\text{C-NMR}$ (50 MHz); δ (CDCl_3): 207.29, 199.64, 149.78, 142.11, 137.41, 134.18, 133.60, 132.00, 127.1, 125.52, 68.55, 63.45, 37.84, 36.70, 28.76, 26.70, 24.58, 23.48, 22.43, 21.86, 21.04, 20.06.

HRMS calc. ($\text{C}_{11}\text{H}_{16}\text{NaO}^+$): 187.1099; found: 187.1089

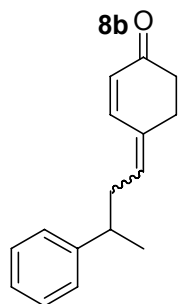


Mixture of *E-Z* isomers in the ratio 4:1

$^1\text{H-NMR}$ (300 MHz); δ (CDCl_3): 7.43 (d, 1H, $J = 10$ Hz *Z*-isomer), 7.41 (d, 1H, $J = 10.2$ Hz, *E*-isomer), 5.87 (m, 2H), 2.70 (m, 2H), 2.50 (m, 2H), 2.18 (m, 2H), 1.2 (m, 6H), 0.88 (m, 3H).

$^{13}\text{C-NMR}$ (75 MHz); δ (CDCl_3): 200.1, 200.0, 150.3, 142.5, 139.1, 135.9, 133.3, 131.2, 127.5, 125.9, 38.4, 35.5, 37.1, 32.0, 31.9, 31.5, 29.7, 29.3, 29.1, 28.4, 24.0, 22.9, 14.5, 14.4.

HRMS calc. ($\text{C}_{12}\text{H}_{18}\text{NaO}^+$): 201.1255; found: 201.1270



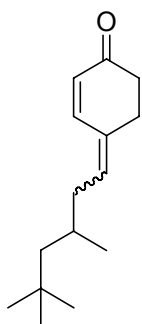
rac-8c

Mixture of *E-Z* isomers in the ratio 5:1

$^1\text{H-NMR}$ (200 MHz); δ (CDCl_3): 7.27 (m, 6H), 6.9 (d, 1H), 5.9 (m, 1H), 2.8 (m, 2H), 2.4 (m, 5H), 1.3 (d, 3H).

$^{13}\text{C-NMR}$ (50 MHz); δ (CDCl_3): 199.9, 199.4, 149.4, 146.2, 141.7, 136.1, 135.9, 134.0, 133.0, 132.4, 130.9, 128.5, 127.3, 127.1, 126.4, 126.2, 125.7, 40.2, 39.9, 39.7, 37.9, 37.5, 36.7, 36.6, 31.2, 29.8, 23.7, 21.7.

HRMS calc. ($\text{C}_{16}\text{H}_{18}\text{NaO}^+$): 249.1255; found: 249.1258



rac-8d

Mixture of *E-Z* isomers in the ratio 5:1

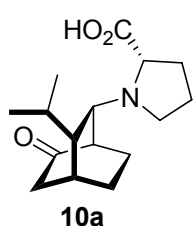
¹H-NMR (200 MHz); δ (CDCl₃): 7.40(d, 1H, *J*= 10 Hz *Z*-isomer), 7 (d, 1H, *J*= 10 Hz *E*-isomer), 5.85 (m, 2H), 2.7 (m, 2H), 2.5(m, 2H), 2.1(m, 3H), 0.98 (d, 3H), 0.90 (s, 9H).

¹³C-NMR (50 MHz); δ (CDCl₃): 200.0, 199.6, 149.8, 142.2, 137.6, 134.4, 133.7, 132.0, 127.2, 125.5, 65.9, 50.9, 50.7, 38.3, 38.0, 37.5, 36.7, 31.2, 31.2, 30.4, 30.4, 30.33, 30.09, 29.97, 29.79, 29.74, 23.86, 22.71, 22.65, 15.34.

HRMS calc. (C₁₅H₂₄NaO⁺): 243.1725; found: 243.1701.

3. General procedure for the three component reaction of 2-cyclohexen-1-one, 2 aldehydes 7, and proline 4 leading to bicyclic adducts 10.

2-Cyclohexen-1-one **2** (1gr, 10.4 mmol, 1 eq) and aldehydes **7a-b** and **7e-g** (20.8 mmols, 2 eq) were added to a suspension of proline **4**-lithium salt (1.26 gr, 1eq) in toluene (20 mL). The reaction was stirred at rt up to 5 days (scheme 2). Without performing any aqueous workup DCM was added to the crude reaction mixture. After the time indicated in table 1, the suspension was filtered over a pad of celite in order to remove any unreacted salt of proline. The solvent was then removed *in vacuo* and the products were purified by FC (eluant: diethyl ether first, then ethyl acetate and last ethyl acetate: methanol from the ratio 100:1 to 4:1), to afford compounds **10** as described in table 1. Compounds **10** were further purified by crystallization.



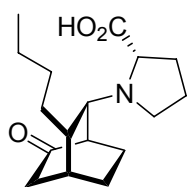
10a

¹H-NMR (200 MHz); δ (D₂O): 3.76 (m, 1H), 3.38 (m, 1H), 3.29 (m, 1H), 2.57 (m, 1H), 2.38 (m, 1H), 1.97 (m, 4H), 1.69 (m, 2H), 1.43 (m, 6H), 0.99 (m, 2H), 0.72 (d, 3H *J*=6.0 Hz), 0.59 (d, 3H, *J*=6.0 Hz).

¹³C-NMR (50 MHz); δ (D₂O): 219.8, 173.2, 67.9, 66.6, 65.2, 52.2, 51.9, 45.9, 45.1, 45.0, 30.0, 29.2, 23.2, 22.3, 20.4, 19.2, 18.3.

$[\alpha]_D^{25} = -14.2$ (c= 9 mg / mL. CH₂Cl₂)

HRMS calc. (C₁₆H₂₅NNaO₃⁺): 302.1732; found: 302.1720.



10b

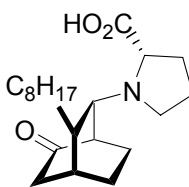
¹H-NMR (300 MHz); δ (CDCl₃): 6.7 (bs, 1H), 3.9-3.7 (m, 2H), 3.0-2.8 (m, 1H), 2.8 (m, 1H), 2.5-2.6 (m, 1H), 2.4-1.3 (m, 16 H), 0.9 (t, 3H, *J*=6.6).

¹³C-NMR (75 MHz); δ (CDCl₃): 213.4, 173.6, 67.6, 66.8, 54.0, 47.5, 42.0, 39.0, 34.8, 30.8, 30.1, 30.0, 25.6, 24.6, 23.1, 17.6, 14.7.

$[\alpha]_D^{25} = -163.2$ (c= 5 mg / mL. CH₂Cl₂)

HRMS calc. (C₁₇H₂₇NNaO₃⁺): 316.1889; found: 316.1892.

Melting point: 97.2-98.5



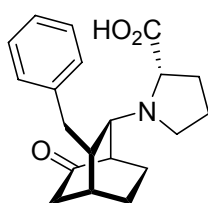
10c

¹H-NMR (300 MHz); δ (CDCl₃): 3.8-3.6 (m, 2H), 3.0-2.8 (m, 1H), 2.7 (m, 1H), 2.5 (m, 1H), 2.4-1.2 (m, 24H), 0.88 (t, *J*= 6Hz),

¹³C-NMR (75 MHz); δ (CDCl₃): 213.2, 173.6, 67.5, 66.6, 53.9, 51.3, 42.4, 39.0, 35.2, 32.3, 30.8, 30.1, 30.0, 29.9, 29.7, 28.0, 25.7, 24.8, 23.1, 17.5, 14.5.

$[\alpha]_D^{25} = -2.6$ (c= 35mg / mL. CH₂Cl₂)

HRMS calc. (C₂₁H₃₅NNaO₃⁺): 372.2515; found: 372.2518.



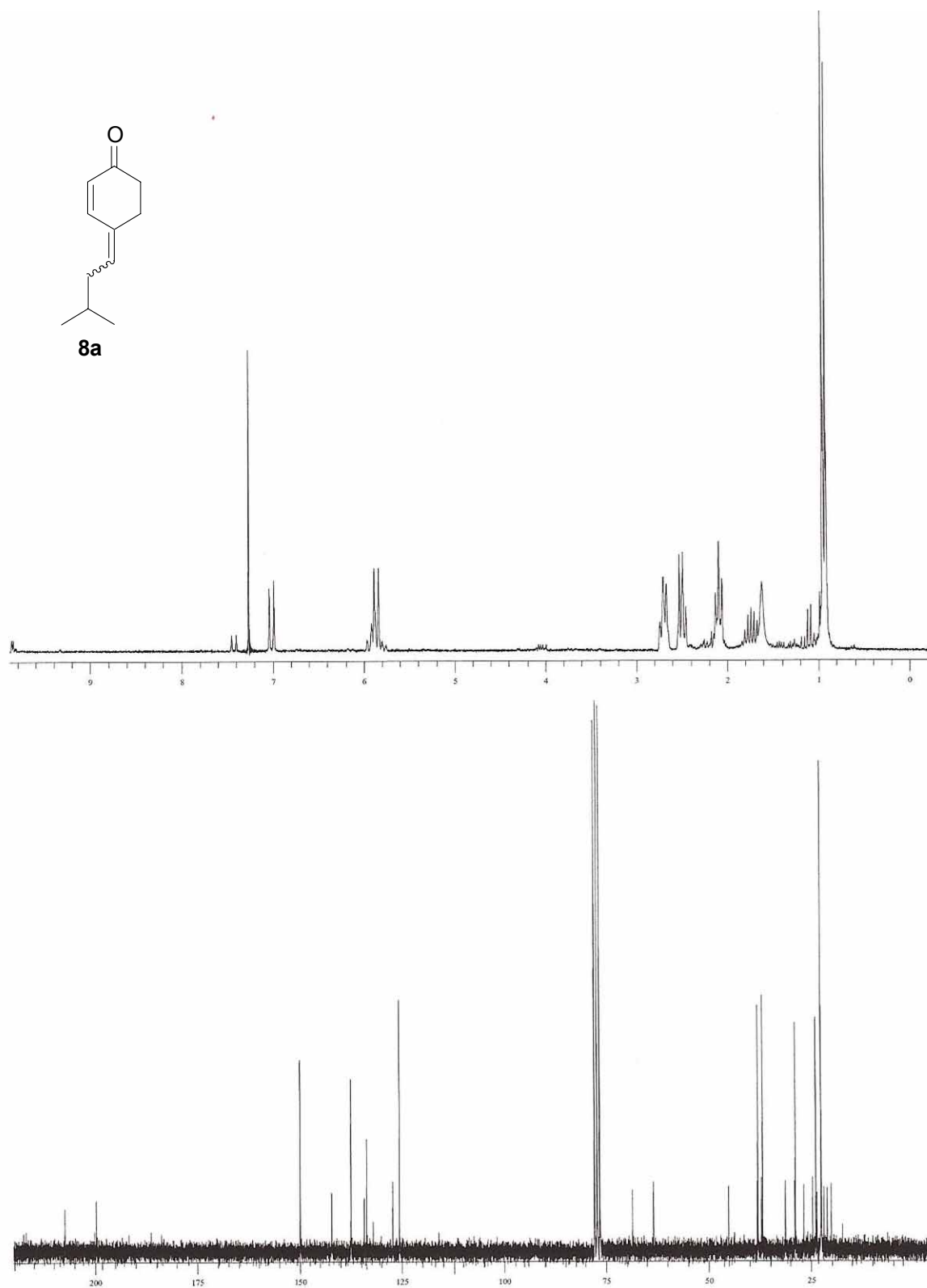
10d

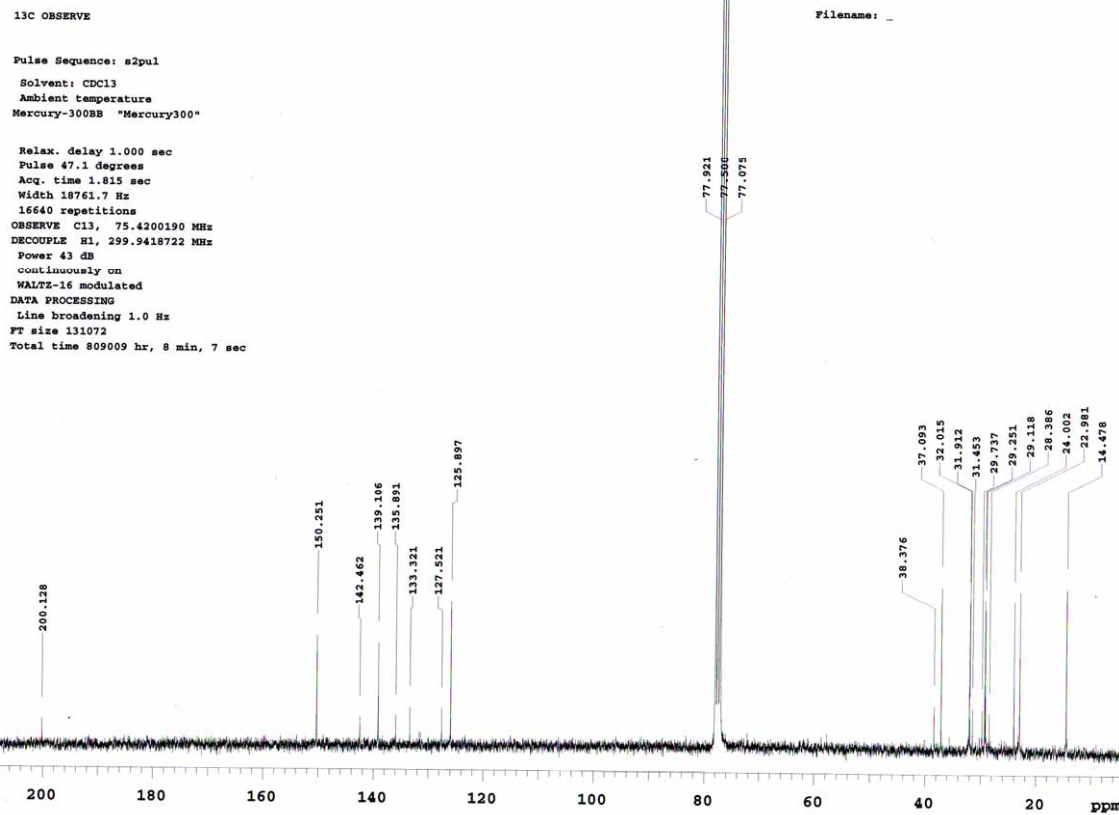
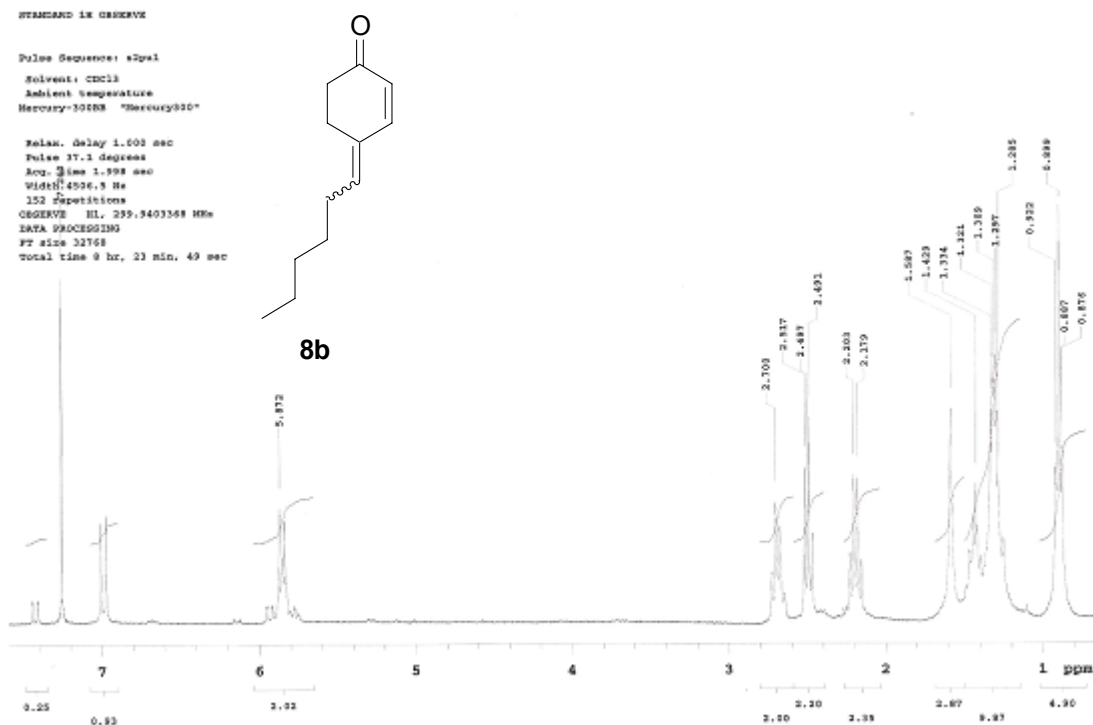
¹H-NMR (300 MHz); δ (DMSO-*d*₆): 7.2 (m, 5H). 3.5 (m, 1H), 3.3 (m, 1H), -2.8-1.2 (m, 17H)

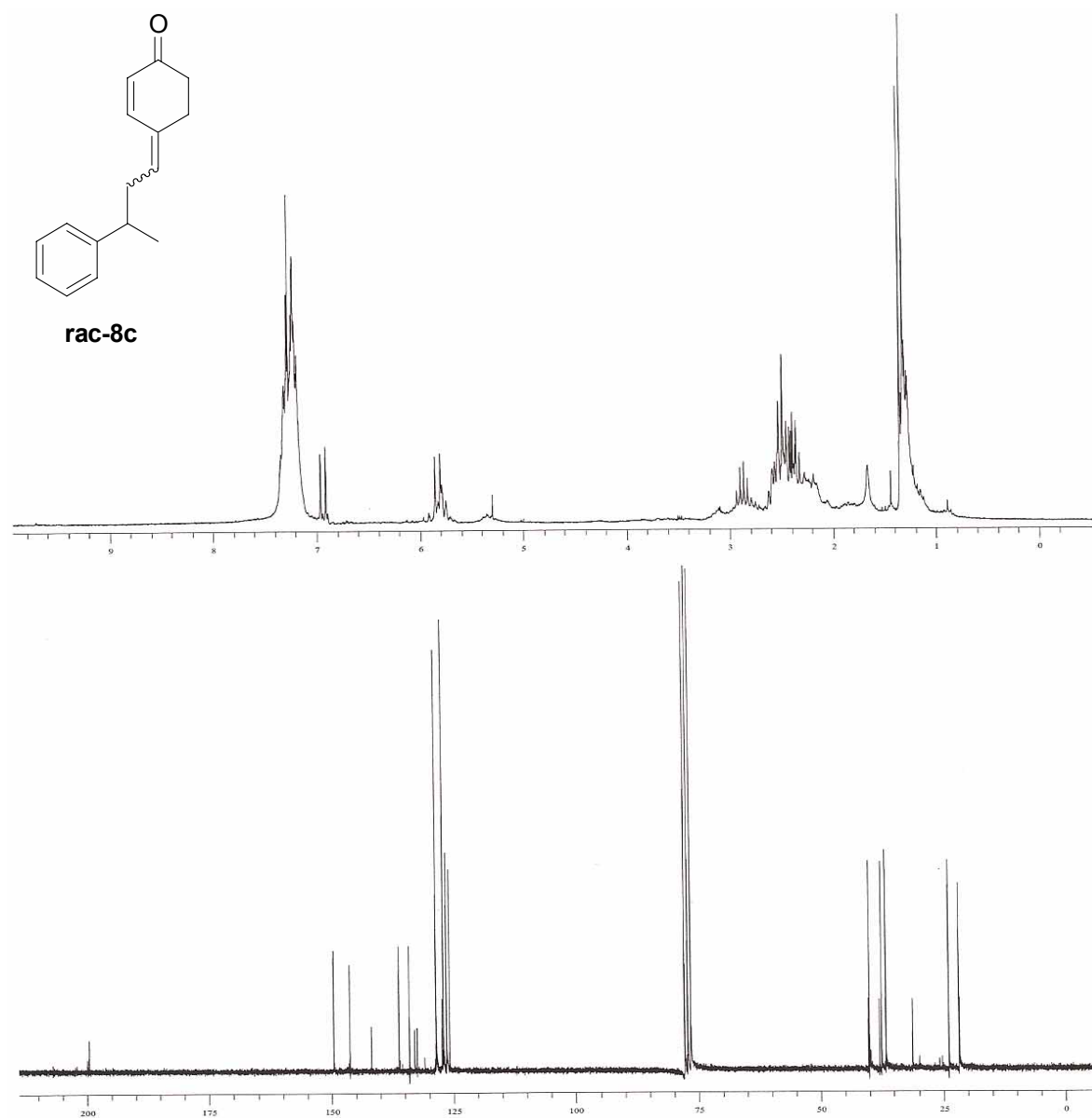
¹³C-NMR (75 MHz); δ (DMSO-*d*₆): 215.1, 176.1, 140.8.2, 129.4, 129.0, 126.7, 64.3, 64.2, 51.9, 48.5, 44.0, 40.8, 39.3, 30.5, 29.5, 25.6, 23.9, 16.8.

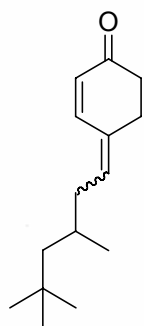
$[\alpha]_D^{25} = -18.4$ (c= 29 mg / mL. CH₂Cl₂)

HRMS calc. (C₂₀H₂₅NNaO₃⁺): 350.1732; found: 350.1711.

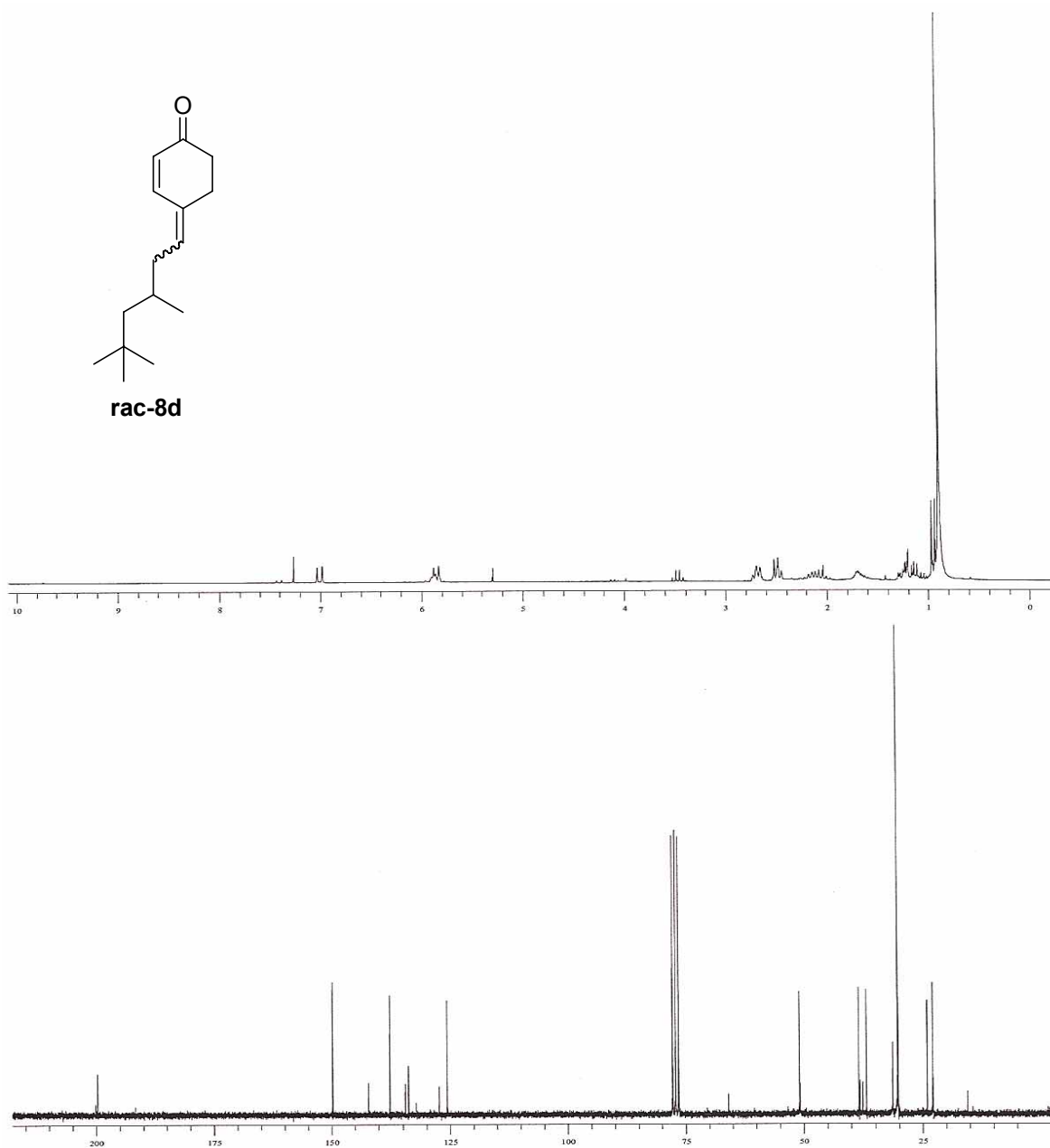


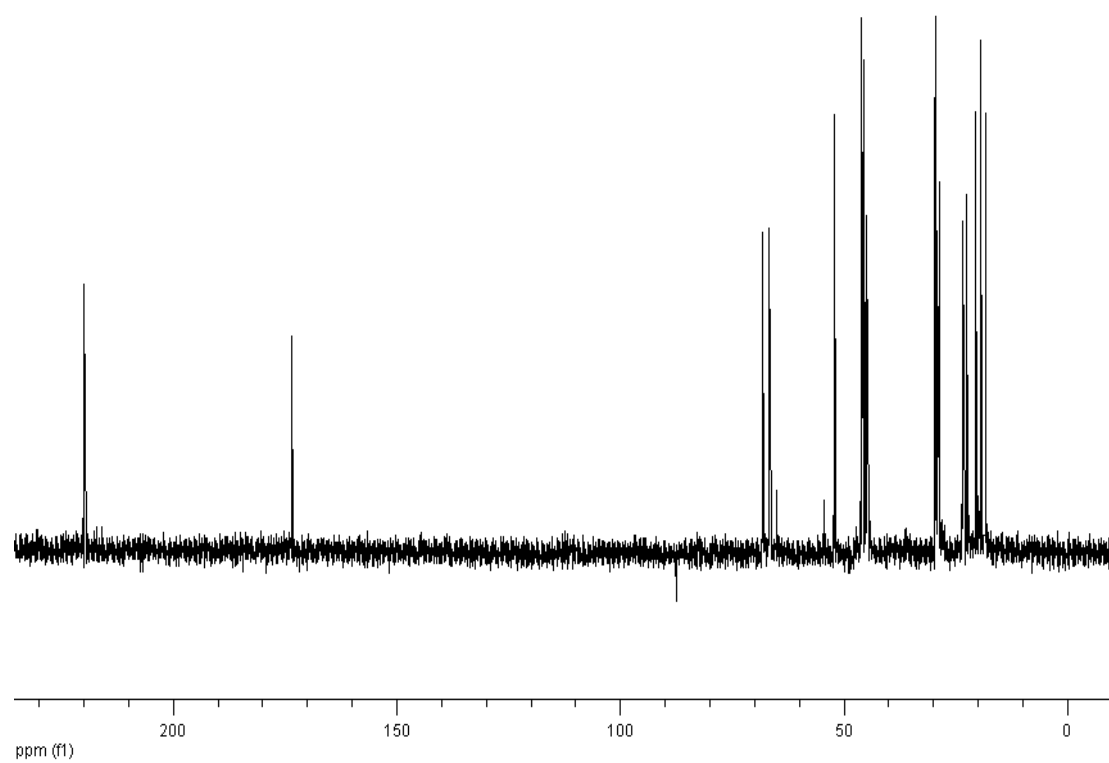
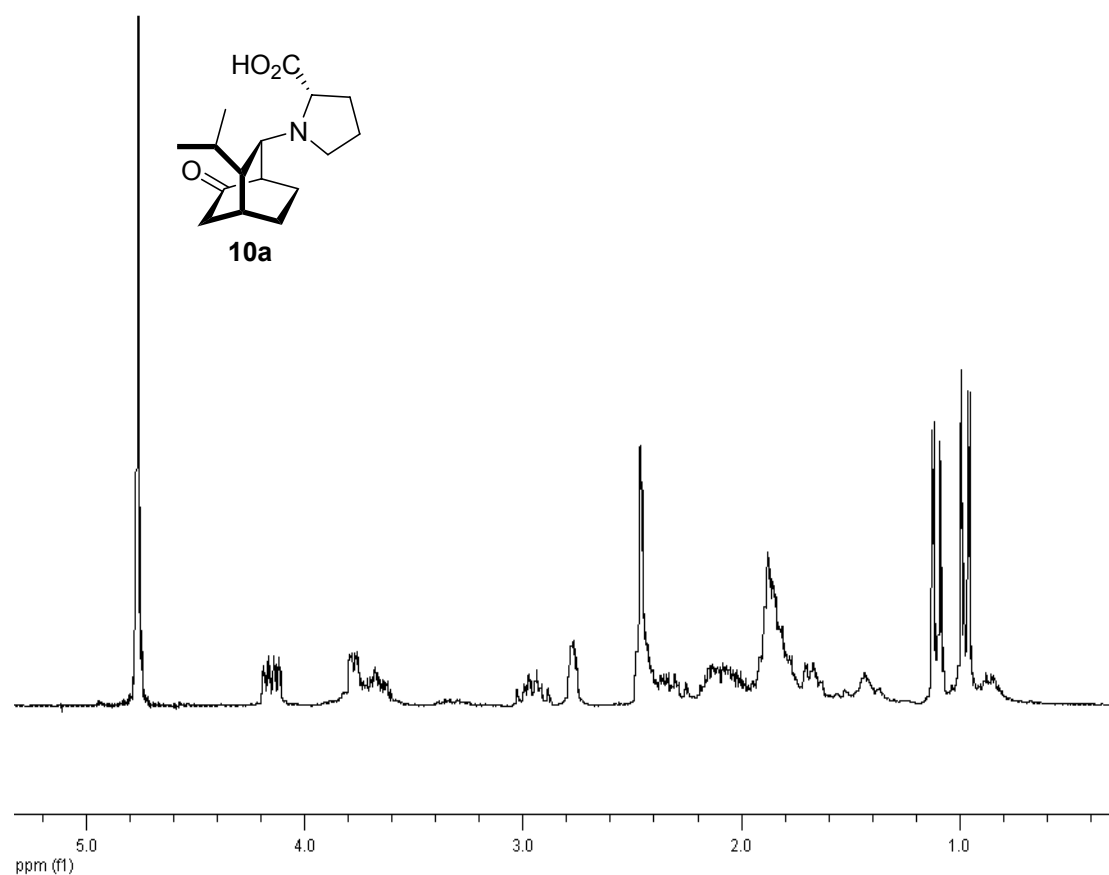


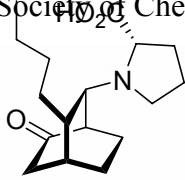




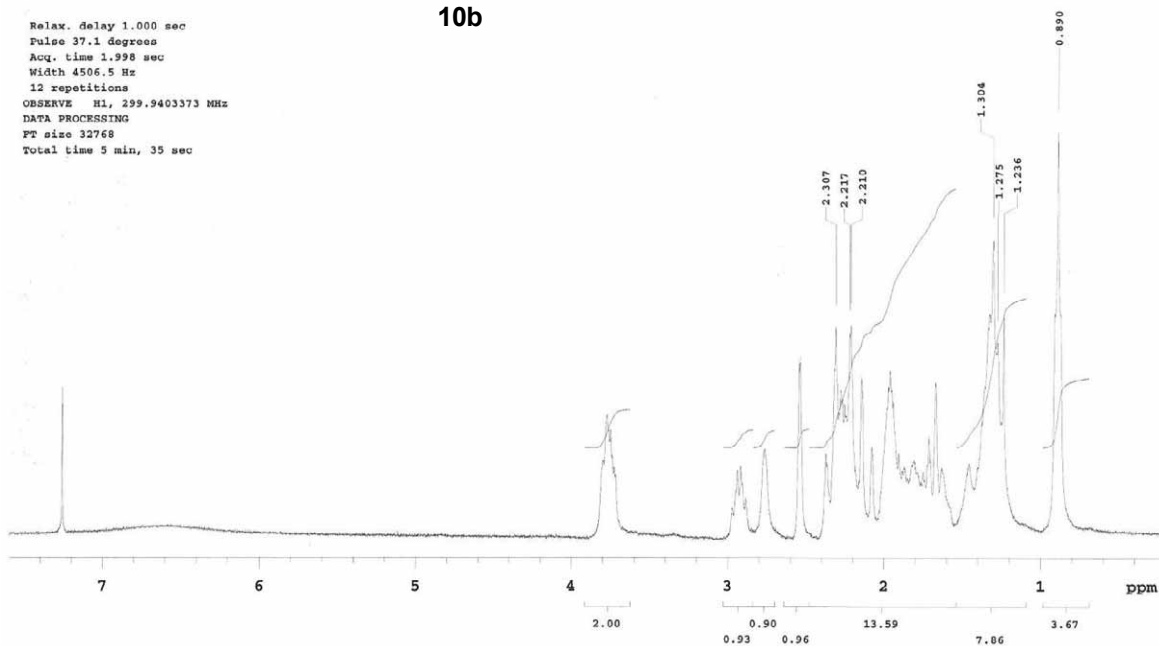
rac-8d



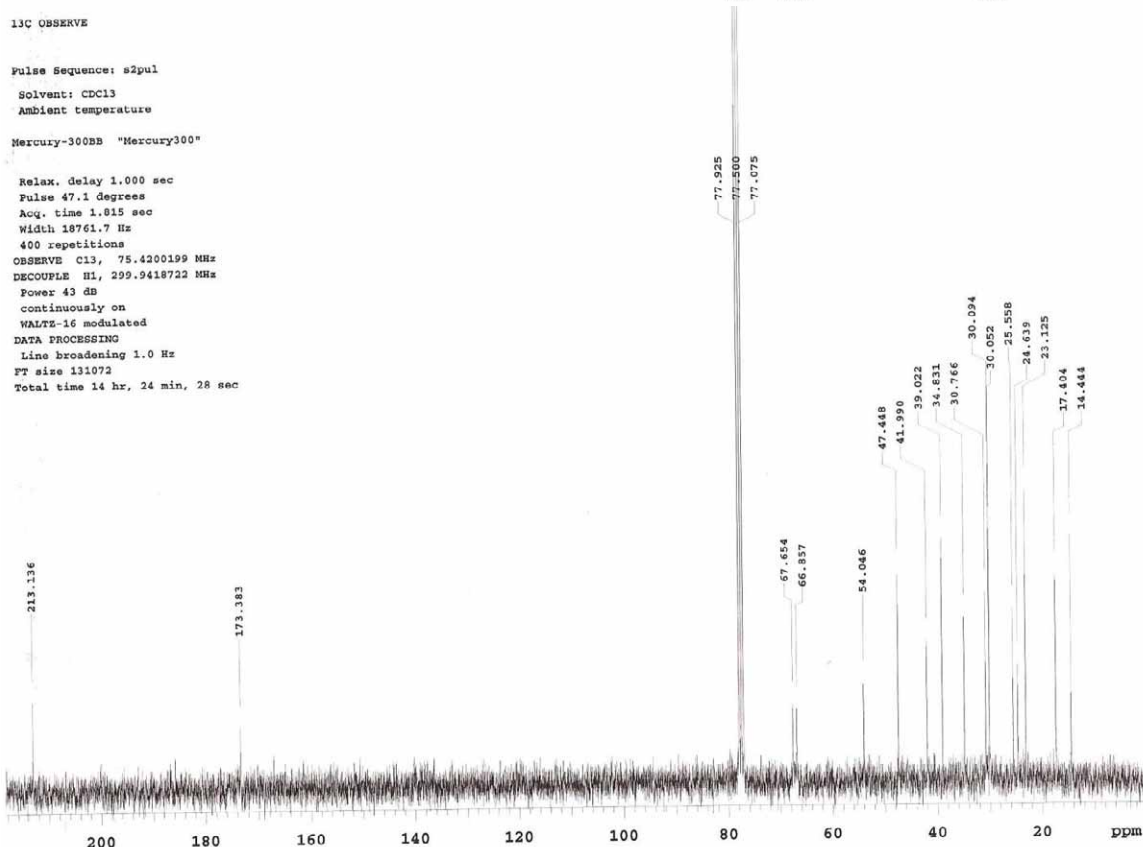


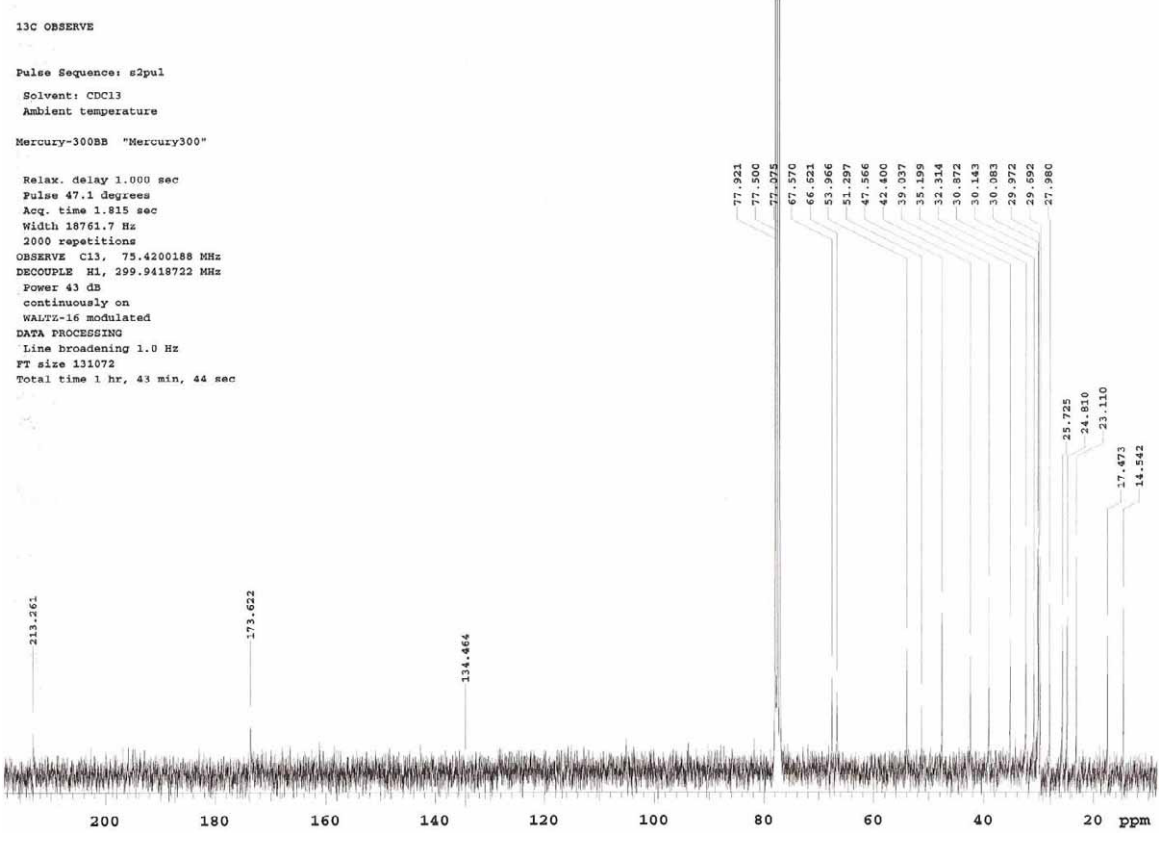
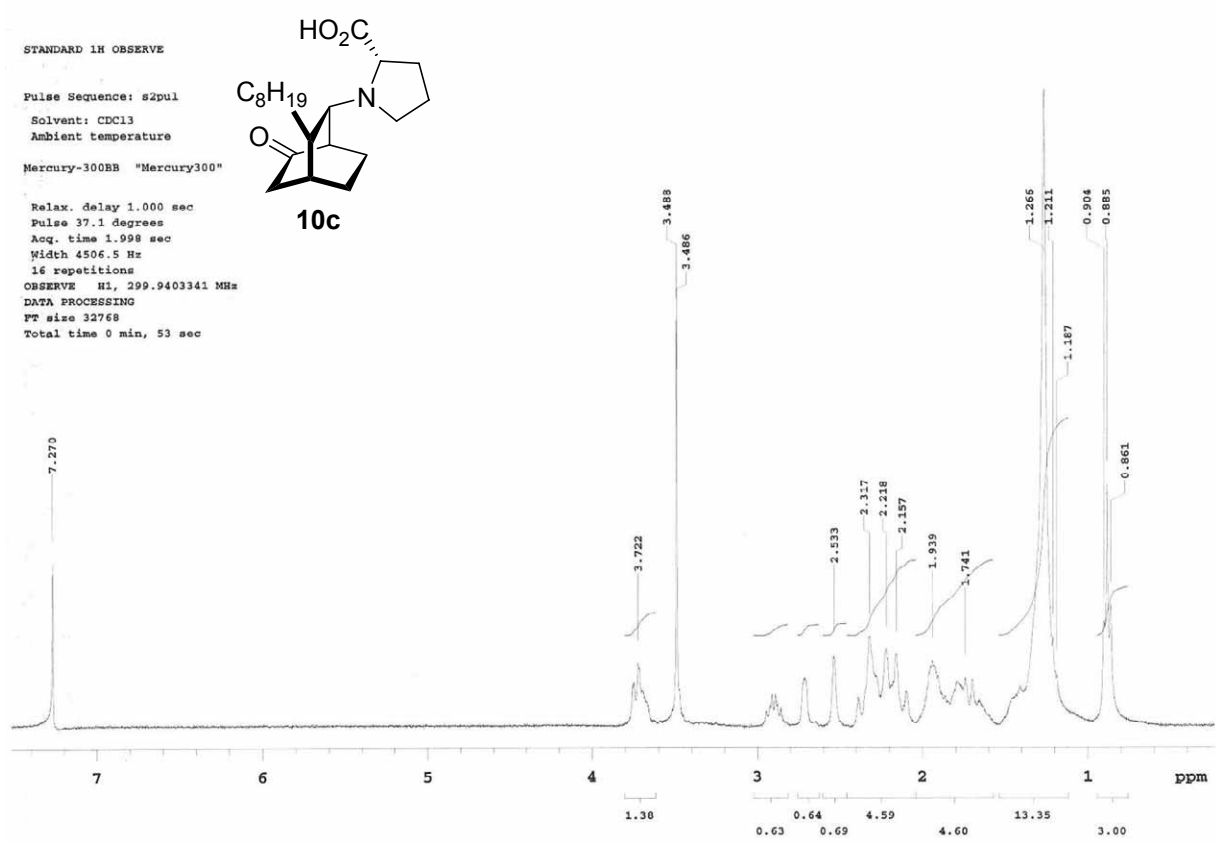


STANDARD 1H OBSERVE
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 Mercury-300BB "Mercury300"
 Relax. delay 1.000 sec
 Pulse 37.1 degrees
 Acq. time 1.998 sec
 Width 4506.5 Hz
 12 repetitions
 OBSERVE H1, 299.9403373 MHz
 DATA PROCESSING
 FT size 32768
 Total time 5 min, 35 sec

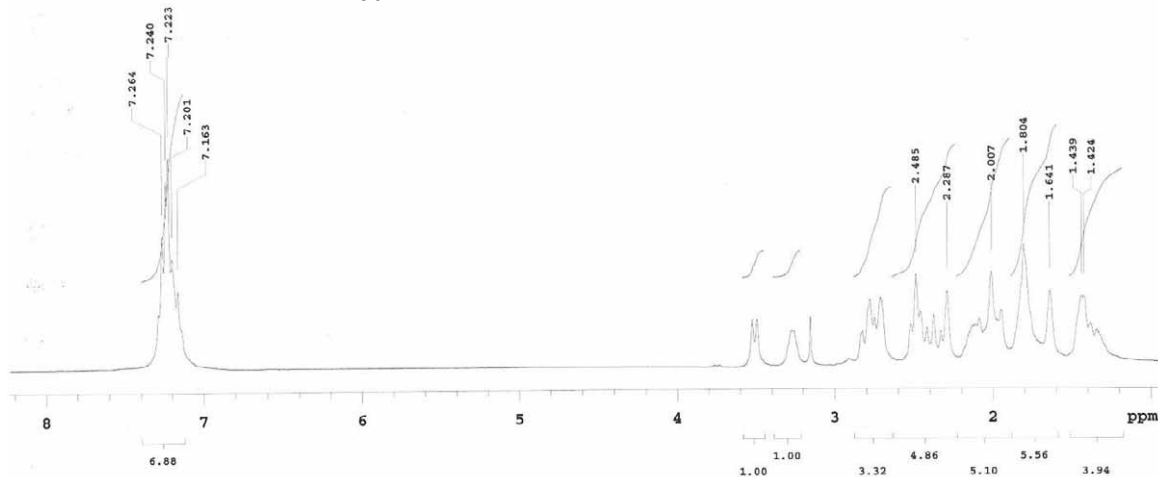
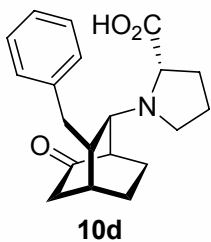


13C OBSERVE
 Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 Mercury-300BB "Mercury300"
 Relax. delay 1.000 sec
 Pulse 47.1 degrees
 Acq. time 1.815 sec
 Width 18761.7 Hz
 400 repetitions
 OBSERVE C13, 75.4200199 MHz
 DECOUPLE H1, 299.9418722 MHz
 Power 43 dB
 Continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 1.0 Hz
 FT size 131072
 Total time 14 hr, 24 min, 28 sec





STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
Mercury-300DB "Mercury300"
Relax. delay 1.000 sec
Pulse 37.1 degrees
Acq. time 1.998 sec
Width 4506.5 Hz
12 repetitions
OBSERVE H1, 299.9417621 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 53 sec



13C OBSERVE
Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
Mercury-300DB "Mercury300"
Relax. delay 1.000 sec
Pulse 47.1 degrees
Acq. time 1.815 sec
Width 18761.7 Hz
240 repetitions
OBSERVE C13, 75.4203981 MHz
DECOUPLE H1, 299.9432969 MHz
Power 43 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 131072
Total time 518 hr, 41 min, 12 sec

