Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

A Lactate-Derived Chiral Aldehyde for Determination of the Enantiopurity of Primary Amines

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General Experimental Information

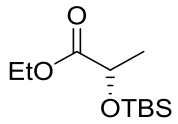
All solvents and chemicals were used as supplied unless otherwise indicated All resins were washed with CH_2Cl_2 and dried under vacuum prior to use. Column chromatography was carried out using silica gel and analytical thin layer chromatography was carried out using aluminium-backed silica plates. Components were visualized using combinations of UV (254 nm) and potassium permanganate. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}, concentration (*c*) in g per 100 mL. ^{1}H NMR spectra were recorded at 300, 400, 500 or 600 MHz in the stated solvent using residual protic solvent $CDCl_3$ (δ = 7.26 ppm, s), DMSO (δ = 2.56 ppm, qn) or MeOD (δ = 4.87, s and 3.31, quintet) as the internal standard. Chemical shifts are quoted in ppm using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet; br, broad or a combination of these. The coupling constants (*J*) are measured in Hertz. ^{13}C NMR spectra were recorded at 150 MHz on a Bruker 600 MHz machine with cryoprobe in the stated solvent using the central reference of $CDCl_3$ (δ = 77.0 ppm, t), DMSO (δ = 39.52 ppm, septet) or MeOD (δ = 49.15 ppm, septet) as the internal standard. Chemical shifts are reported to the nearest 0.1 ppm. Mass Spectrometry data were collected on either TOF or magnetic sector analysers. The ionization method is reported in the experimental data.

The enantiopurity of the commercially available lactates was determined prior to use via formation of the corresponding Mosher's esters as follows: MTPA (40 mg, 0.17 mmol), EDCI.HCl (33 mg, 0.17 mmol) and DMAP (23 mg, 0.19 mmol) were added to a solution of lactate (~0.06 mmol) in CH_2Cl_2 (1 mL). The reaction was stirred overnight, and then concentrated *in vacuo*. The crude mixture was dissolved in MeOD and analysed by ^{1}H NMR. The chemical shifts of the methyl groups at 1.54 and 1.47 ppm were integrated to determine the enantiomeric ratio. Samples of (*R*)-methyl lactate were found to consistently have high enantiopurity (≥99:1), whereas the enantipurity of (*S*)-ethyl lactate was more variable. Typically, most commercial sources of (*S*)-ethyl lactate were found to be not quite enantiopure (97:3 er) with the exception of (*S*)-ethyl lactate (99%) purchased from Alfa Aesar (catalogue number A10900) which was determined to be >99:1 er. In all cases, the enantiopurity of a batch of aldehyde **4** was found to be identical to the enantiopurity of the lactate ester **6** from which it was prepared.

Samples of the aldehydes **4** were stored in the freezer under argon. Although no drop in enantiopurity was observed over the course of 1 month, small amounts of decomposition were observed. It is recommended that aldehyde that has been stored for longer periods is not used for analysis, without first checking both the quality and enantiopurity of the sample.

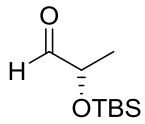
Preparation of Chiral Aldehydes

Ethyl (*S*)-2-((tert-butyldimethylsilyl)oxy)propanoate (*S*)-6a



tert-Butylchlorodimethylsilane (16.0 g, 0.11 mol, 1.2 equiv.), was added to a stirring solution of *S*-ethyl lactate (10 mL, 0.09 mol, 1 equiv.) and imidazole (9.0 g, 0.13 mol, 1.4 equiv.) in DMF (88 mL). The solution was stirred for 30 min at rt, water (150 mL) was added and the reaction mixture extracted with Et_2O (2 × 150 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give **80** as a colourless oil (20.49 g, 0.088 mol, 98%); $[\alpha]_D^{23}$ −21.9 (*c* = 1.33, $CHCl_3$) [lit −28.9 (*c* = 1.26, $CHCl_3$, 23 °C)][1]; δ_H (400 MHz, $CDCl_3$) 0.07 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 1.29 (t, *J* 7.1, CH_2CH_3), 1.40 (d, *J* 6.8, 3H, CH_3CH), 4.17-4.21 (2H, m, CH_2CH_3), 4.31 (q, *J* 6.8, 1H, $CHCH_3$); δ_C (100 MHz, $CDCl_3$) -5.3, -5.0, 14.2, 18.3, 21.3, 25.7, 60.7, 68.5, 174.1.

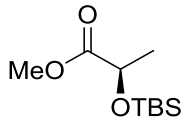
(*S*)-2-((*tert*-Butyldimethylsilyl)oxy)propanal (*S*)-4



Diisobutylaluminium hydride (44 mL, 1.1 M in cyclohexane, 48.4 mmol, 1.6 equiv.) was added dropwise (20 mL/h) to a stirring solution of ester **80** (7 g, 30.1 mmol, 1 equiv.) in Et_2O (200 mL) at -100 °C. After completion of addition, the reaction was stirred for 10 min at -78 °C then quenched by dropwise addition of MeOH (2 mL) and H_2O (5 mL). After warming to rt and stirring for 1.5 h Na_2SO_4 and $MgSO_4$ were added and the suspension stirred for 15 min, then filtered through a short plug of celite and silica eluting with Et_2O. The filtrate was concentrated under reduced pressure and the residue distilled to give aldehyde (*S*)-**81** as a colourless liquid (4.56 g, 24.2 mmol, 80%); bp 79-81 °C (19 Torr) [Lit. 67-68 °C (14 Torr)][2];

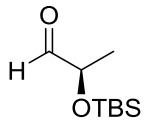
$[\alpha]_D^{23}$ −12.3 (*c* = 1.24, $CHCl_3$) [Lit −11.1, (*c* = 2.7, $CHCl_3$, 22 °C)][2]; δ_H (600 MHz, $CDCl_3$) 0.08 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 1.27 (d, 3H, *J* 6.9, $CHCH_3$), 4.08 (qd, 1H, *J* 1.2, 6.9, $CHCH_3$), 9.60 (d, 1H, *J* 1.2, CHO); δ_C (150 MHz, $CDCl_3$) -4.7, -4.6, 18.3, 18.6, 25.8, 73.9, 204.4.

Methyl (*R*)-2-((*tert*-butyldimethylsilyl)oxy)propanoate (*R*)-6b



tert-Butylchlorodimethylsilane (18.0 g, 0.12 mol, 1.2 equiv.), was added to a stirring solution of *R*-methyl lactate (10 mL, 0.10 mol, 1 equiv.) and imidazole (10.0 g, 0.15 mol, 1.5 equiv.) in DMF (90 mL). The solution was stirred for 30 min at rt, water (150 mL) was added and the reaction mixture extracted with Et_2O (2 × 150 mL). The combined organic layers were washed with brine (150 mL), dried over $MgSO_4$ and concentrated under reduced pressure to give the ester as a colourless oil (17.85 g, 81.7 mmol, 82%); $[\alpha]_D^{24}$ +26.5 (*c* = 2.44, $CHCl_3$) [lit +28.8 (*c* = 2.35, $CHCl_3$, 24 °C][3]; δ_H (600 MHz, $CDCl_3$) 0.05 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.38 (d, *J* 6.8, 3H, CH_3CH), 3.70 (s, 3H, CH_3O), 4.31 (q, *J* 6.8, 1H, $CHCH_3$); δ_C (150 MHz, $CDCl_3$) -5.2, -4.9, 18.4, 21.5, 25.8, 52.0, 68.5, 174.1.

(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)propanal (*R*)-4



Diisobutylaluminium hydride (47 mL, 1.1 M in cyclohexane, 51.7 mmol, 1.6 equiv.) was added dropwise (20 mL/h) to a stirring solution of methyl (*R*)-2-((*tert*-butyldimethylsilyl)oxy)propanoate (7 g, 32.1 mmol, 1 equiv.) in Et_2O (200 mL) at -100 °C. After completion of addition, the reaction was stirred for 10 min at -78 °C then quenched by dropwise addition of MeOH (2 mL) and H_2O (5 mL). After warming to rt and stirring for 1.5 h Na_2SO_4 and $MgSO_4$ were added and the suspension stirred for 15 min, then filtered through a short plug of celite and silica eluting with Et_2O. The filtrate was concentrated under reduced pressure and the residue distilled to give aldehyde (*R*)-**81** as a colourless liquid (4.35 g, 23.1 mmol, 72%); bp 83-86 °C (28 Torr); $[\alpha]_D^{24}$ +15.3 (*c* = 1.59, $CHCl_3$) [Lit. +12.8 (*c* = 1.59, $CHCl_3$) 24 °C][3]; δ_H (600 MHz, $CDCl_3$) 0.08 (s, 3H, $SiCH_3$), 0.09 (s, 3H, $SiCH_3$), 0.91 (s, 9H,

SiC(CH_3)$_3$), 1.27 (d, 3H, *J* 6.9, CHC*H*$_3$), 4.08 (qd, 1H, *J* 1.0, 6.8, C*H*CH$_3$), 9.60 (d, 1H, *J* 1.0, CHO); δ_C (150 MHz, $CDCl_3$) -4.72, -4.66, 18.3, 18.6, 25.8, 73.9, 204.4.

Determination of the Enantiopurity of Aldehyde 4

A solution of phenylalanine methyl ester (54 mg, 0.30 mmol) in C_6D_6 (0.7 mL) was added to the aldehyde (45 mg, 0.24 mmol). The solution was mixed and transferred to an NMR tube and the enantiopurity was determined via ^{13}C NMR as below.

A sample of (*R*)-**4** was analysed via this method after 0, 14, and 31 days (see pages 9-10 for NMR spectra). No drop in enantiopurity (99:1) was observed over this time period, but some impurities were observed in the ^{1}H NMR of **4** after storing for 14 and 30 days (see page 11 for NMR spectra).

General Procedure for Analysis of Chiral Primary Amines

A chiral amine of unknown enantiopurity was weighed into two separate vials (~0.2 mmol in each, 1 equiv.). A solution of (*S*)-**4** (~0.24 mmol, 1.2 equiv.) in MeOD-*d*$_4$ or another appropriate NMR solvent (~0.7 mL) was added to one sample, and a similar solution of (*R*)-**4** was added to the other sample. The resulting solutions of imine were then transferred to NMR tubes and analysed via a 256 scan ^{13}C NMR (600 MHz NMR with cryoprobe; experiment time ~15 minutes). The enantiopurity was determined by integration of the imine carbon signals (ca 160-170 ppm) in each sample. The average enantiomeric ratio from the two samples was taken as the enantiopurity of the sample.

tert-Butyl (1-oxo-1-(propylamino)propan-2-yl)carbamate (7)

Propylamine (82 µL, 1.0 mmol) and B(OCH_2CF_3)$_3$ (616 mg, 2.0 mmol) were added to a solution of (±)-Boc-alanine or Boc-L-alanine (188 mg, 1 mmol) in acetonitrile (2 mL). The reaction was stirred at 80 °C overnight. Dichloromethane (3 mL) and H_2O (1 mL) were added to the reaction mixture. Amberlyst A-26(OH), Amberlyst 15 and Amberlite IRA743 were added and the mixture stirred for 30 min. $MgSO_4$ was added and the mixture was filtered. The solution was concentrated *in vacuo* to give the Boc protected amide as a white solid (228 mg, 0.99 mmol, 99%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.74 (1H, br s, NH), 5.43 (1H, br d, *J* = 6.9, NH), 4.16 (1H, br s, C*H*CH$_3$), 3.14 (2H, q, *J* = 6.9, NHC*H*$_2$), 1.46 (2H, sext, *J* =7.4 , C*H*$_2$CH$_3$), 1.39 (9H, s, tBu), 1.29 (3H, d, *J* = 6.9, CHC*H*$_3$), 0.86 (3H, t, *J* = 7.4, CH$_2$C*H*$_3$); ^{13}C

NMR (150 MHz, $CDCl_3$) δ 173.0, 155.7, 79.9, 50.1, 41.2, 28.4, 22.8, 18.8, 11.4; LRMS (ES+) 231 $[M+H]^+$; mp 82-85 °C (CH_2Cl_2).

The Boc protected amide was deprotected as described below, and then the diastereomeric imines were prepared and analysed via the procedure described above in a range of NMR solvents.

Preparation and analysis of unknown samples (Table 3)

Sample preparation

Samples of 'unknown' enantiopurity were prepared by weighing appropriate amounts of the individual enantiomeric amines into an appropriately size volumetric flask, and preparing a solution in MeOH of approximately 0.4 M concentration.

Each researcher prepared three different samples, and each sample was then analysed independently by two other researchers as described below.

Analysis of 'Unknown' Samples

Two separate 0.5 mL portions of the unknown solution were concentrated into pre-weighed vials to leave ~0.2 mmol of amine in each. A solution of (*S*)-**4** (1.2 equiv) in MeOD-d_4 (~0.7 mL) was added to one vial and a solution of (*R*)-**4** (1.2 equiv) in MeOD-d_4 (~0.7 mL) was added to the other. Both samples were analysed by ^{13}C NMR as described above.

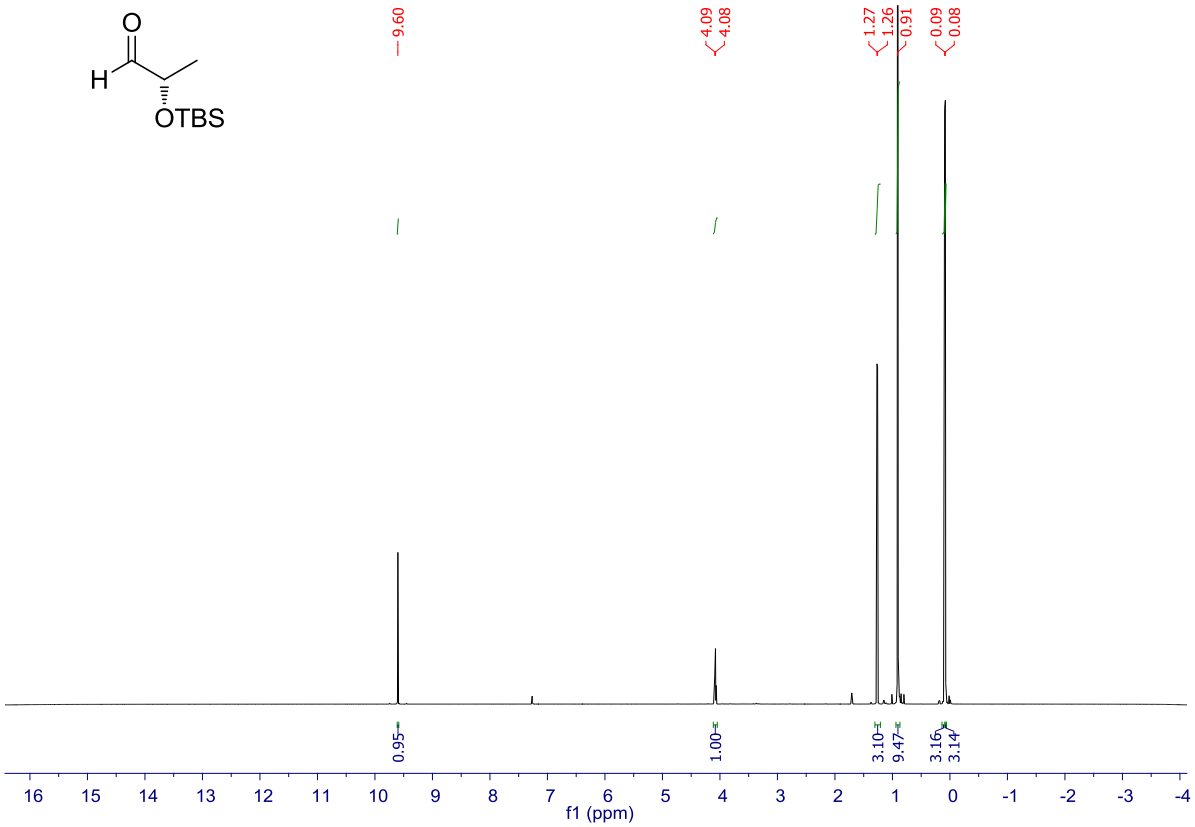
Preparation of Amides 25

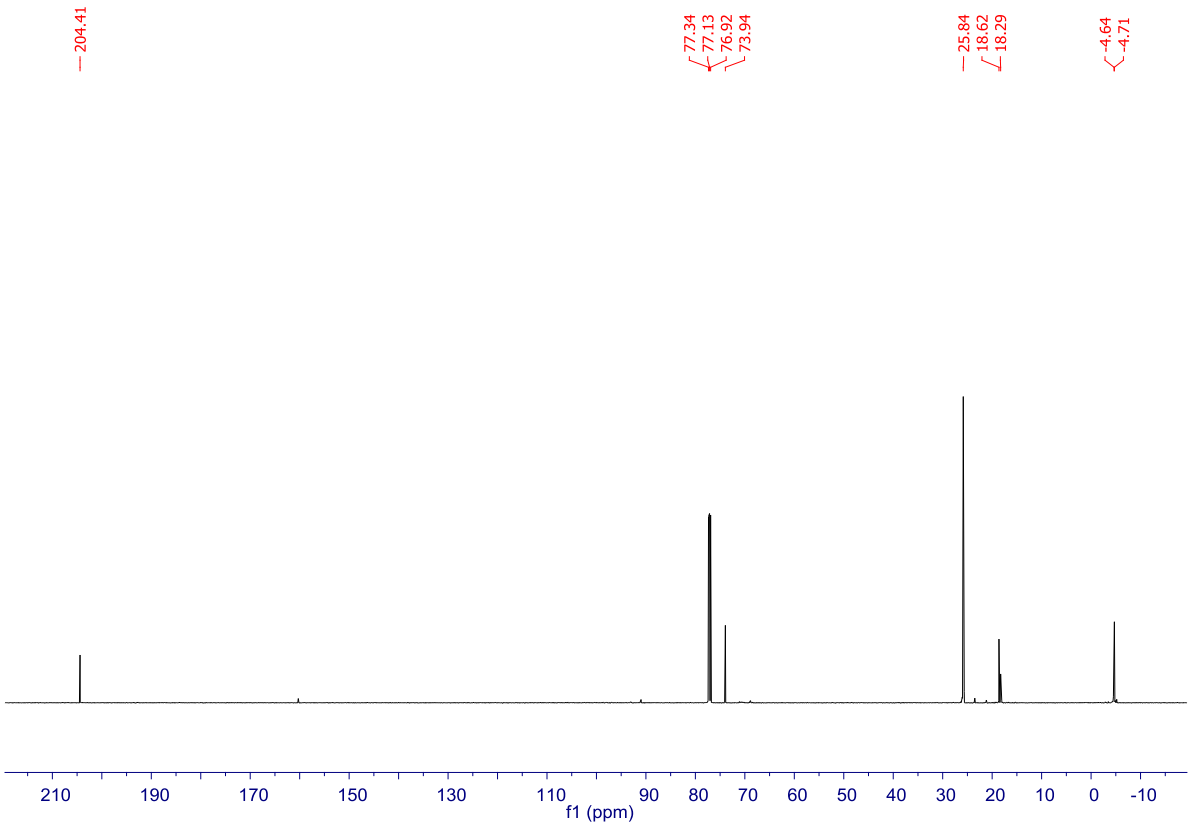
Boc-protected amides **25a**-**25c** were prepared as described previously.[4]

General Procedure for Boc Deprotection and Analysis

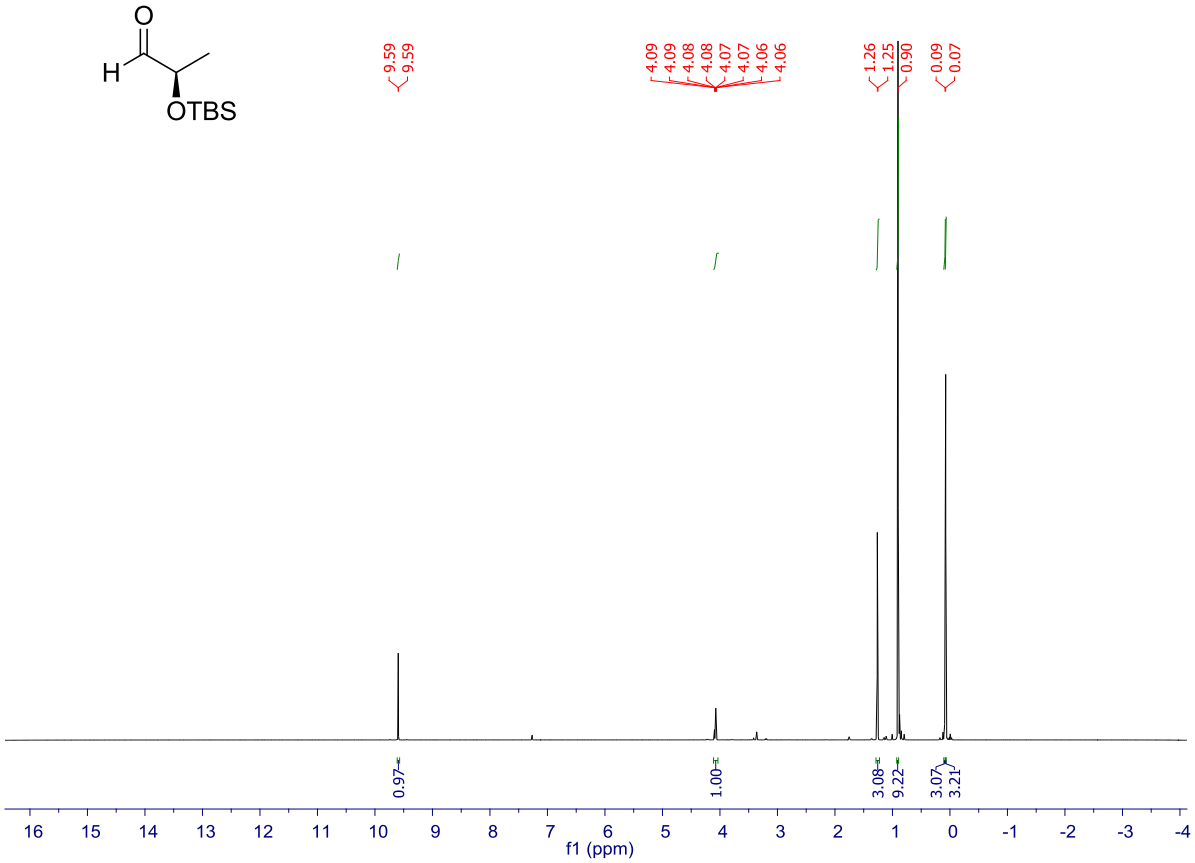
The Boc-protected amino acid amide (~0.25 mmol) was diluted in a 1:1 solution of TFA and CH_2Cl_2 (5 mL, 0.05 M) and stirred at rt for 1 h. The reaction mixture was concentrated in vacuo to give the TFA salt. The salt was redissolved in CH_2Cl_2 and stirred with Amberlite A26(OH) (~50 mg) at rt for 30 min. The resin was then removed by filtration and rinsed three times with CH_2Cl_2 (3 × 10 mL). The filtrate was concentrated under reduced pressure to give the free amino acid amide and the enantiopurity was determined as described above.

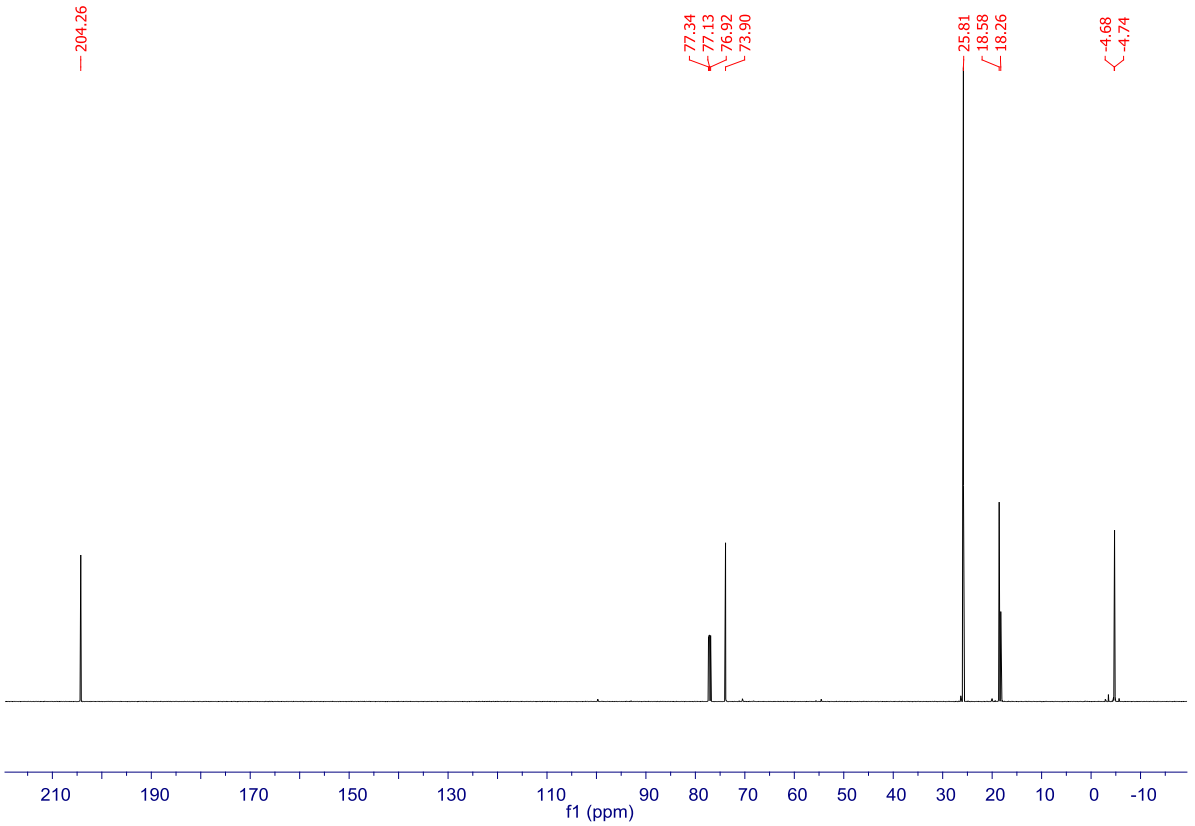
(*S*)-2-((*tert*-Butyldimethylsilyl)oxy)propanal (*S*)-4



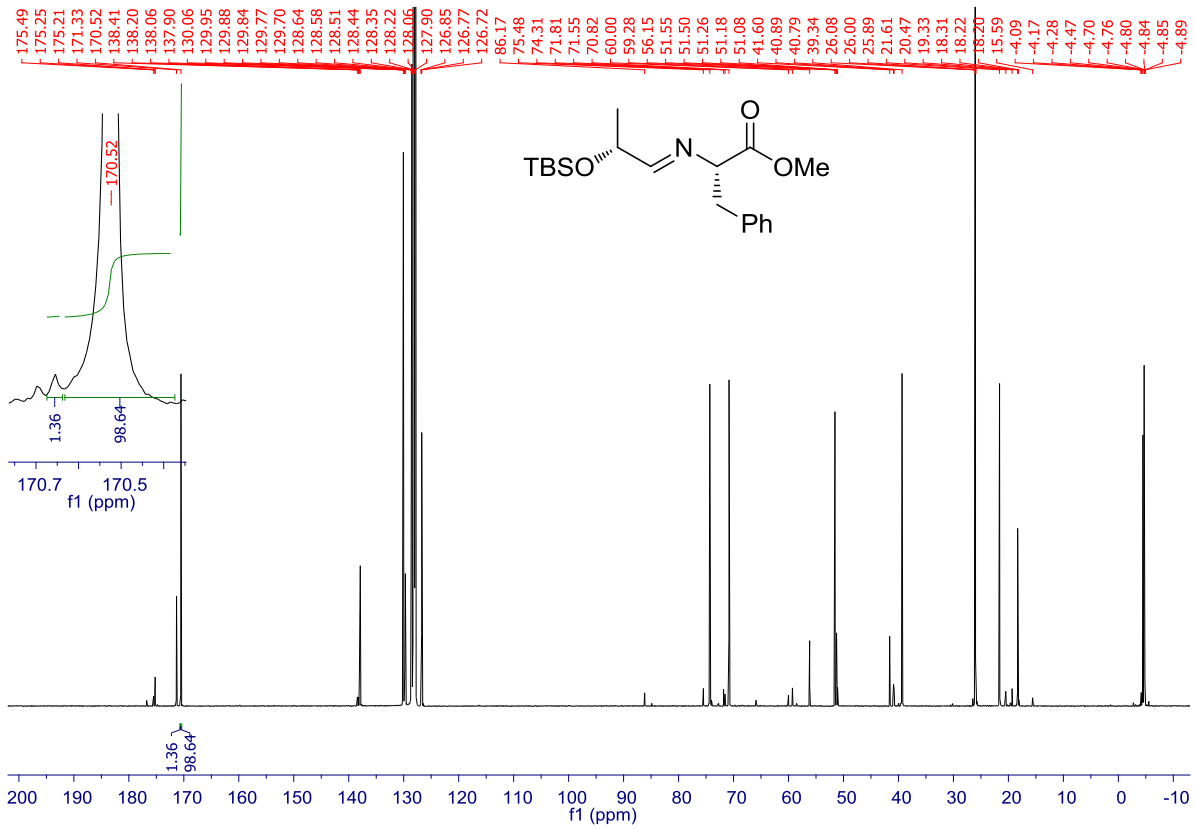


(*R*)-2-((*tert*-Butyldimethylsilyl)oxy)propanal (*R*)-4

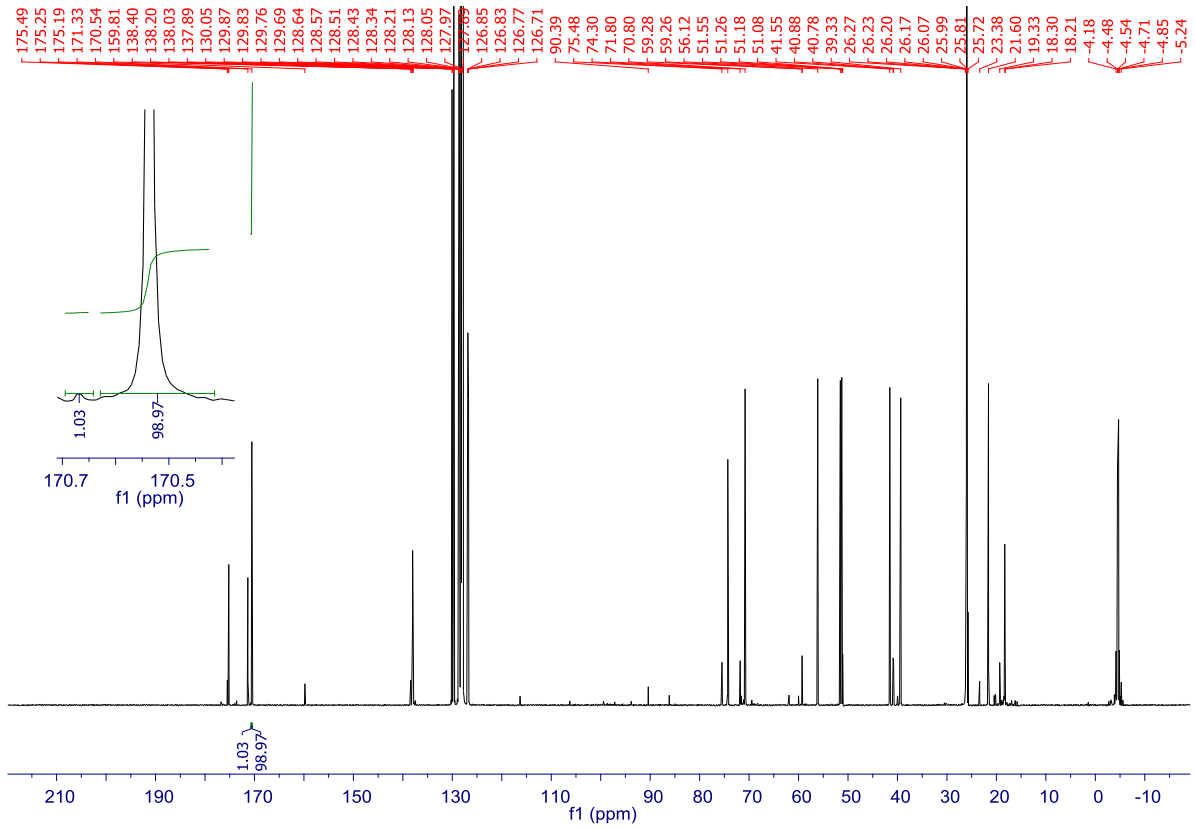




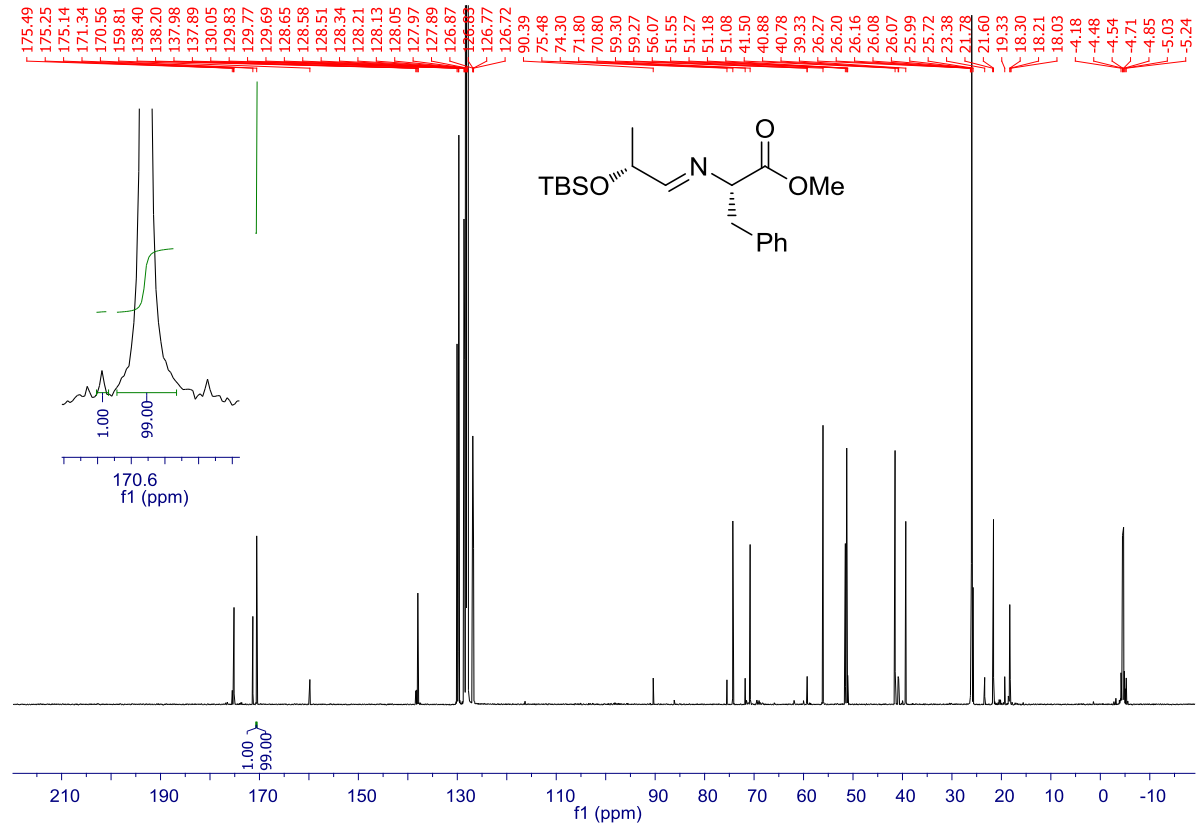
(*R*)-4 and H-Phe-OMe, C_6D_6 0 days



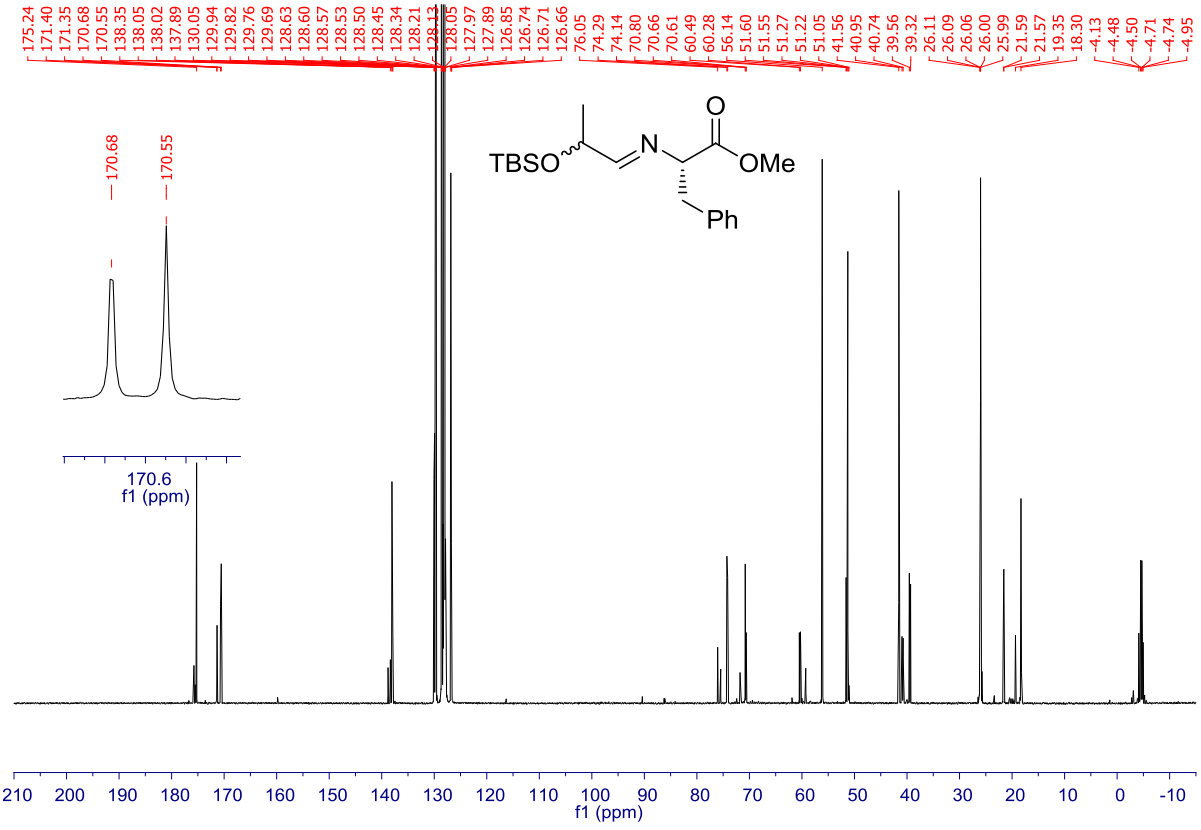
14 days



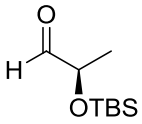
31 days

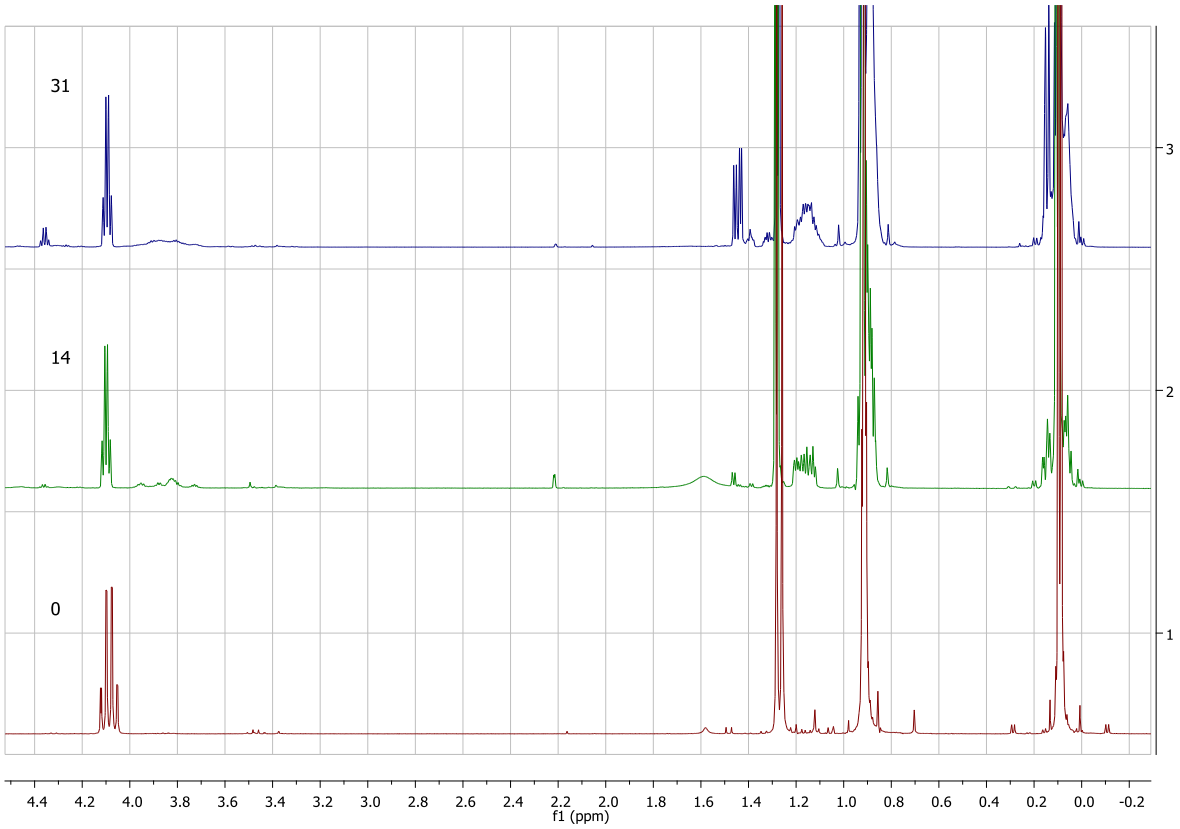


Mixture of (*R*)-4 and (*S*)-4 with H-Phe-OMe



^{1}H NMR of (*R*)-4 after 0, 14 and 31 days





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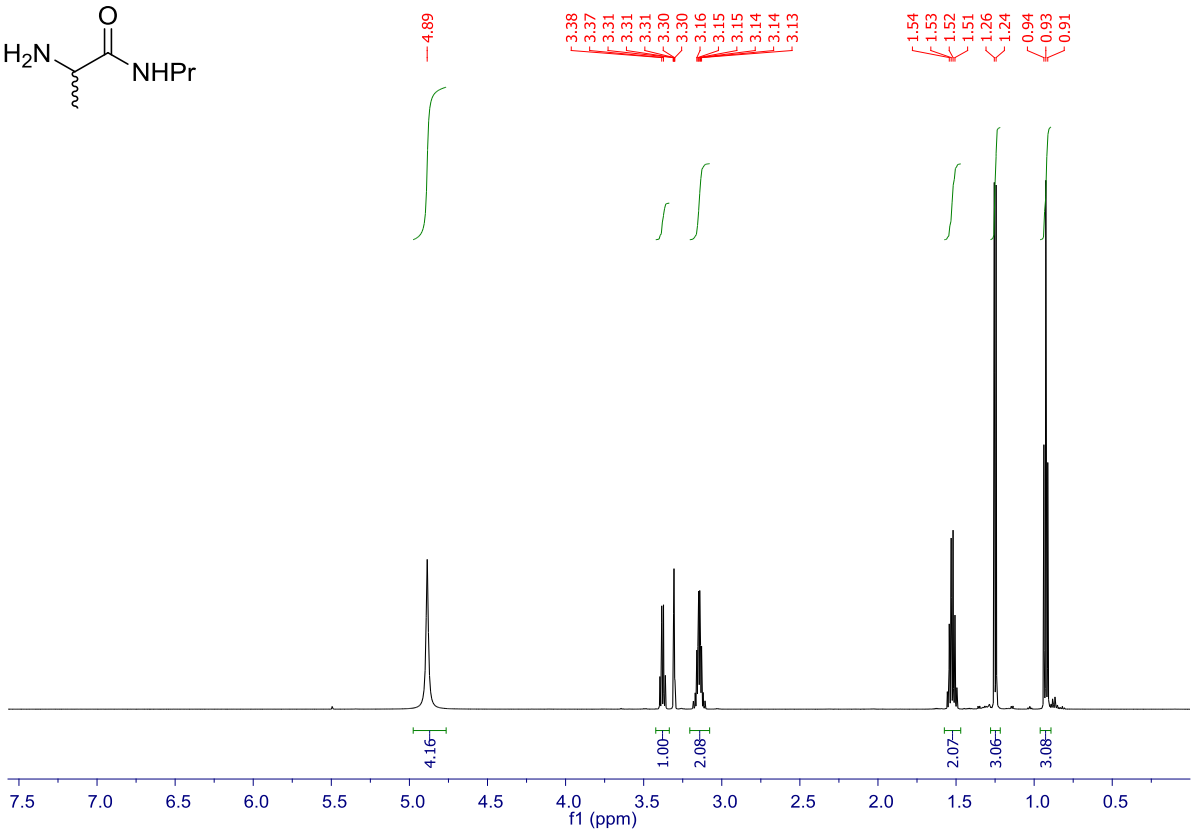
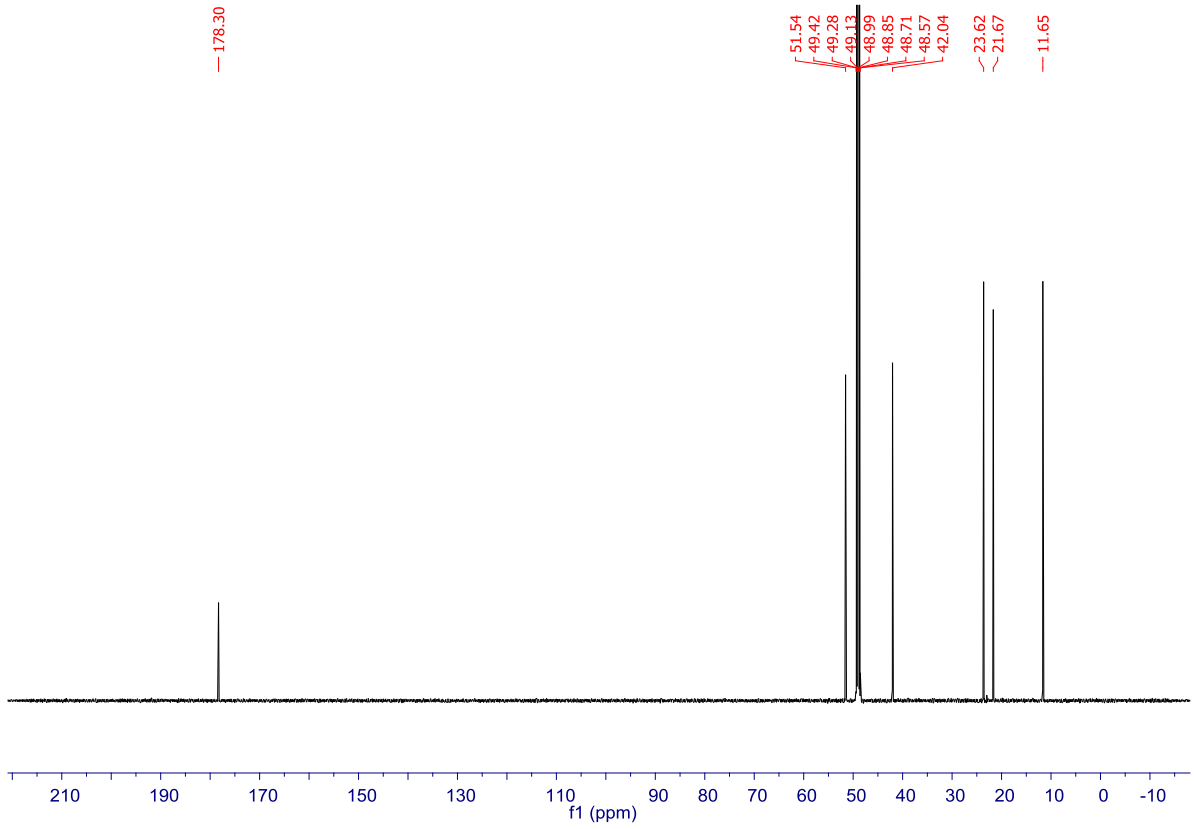
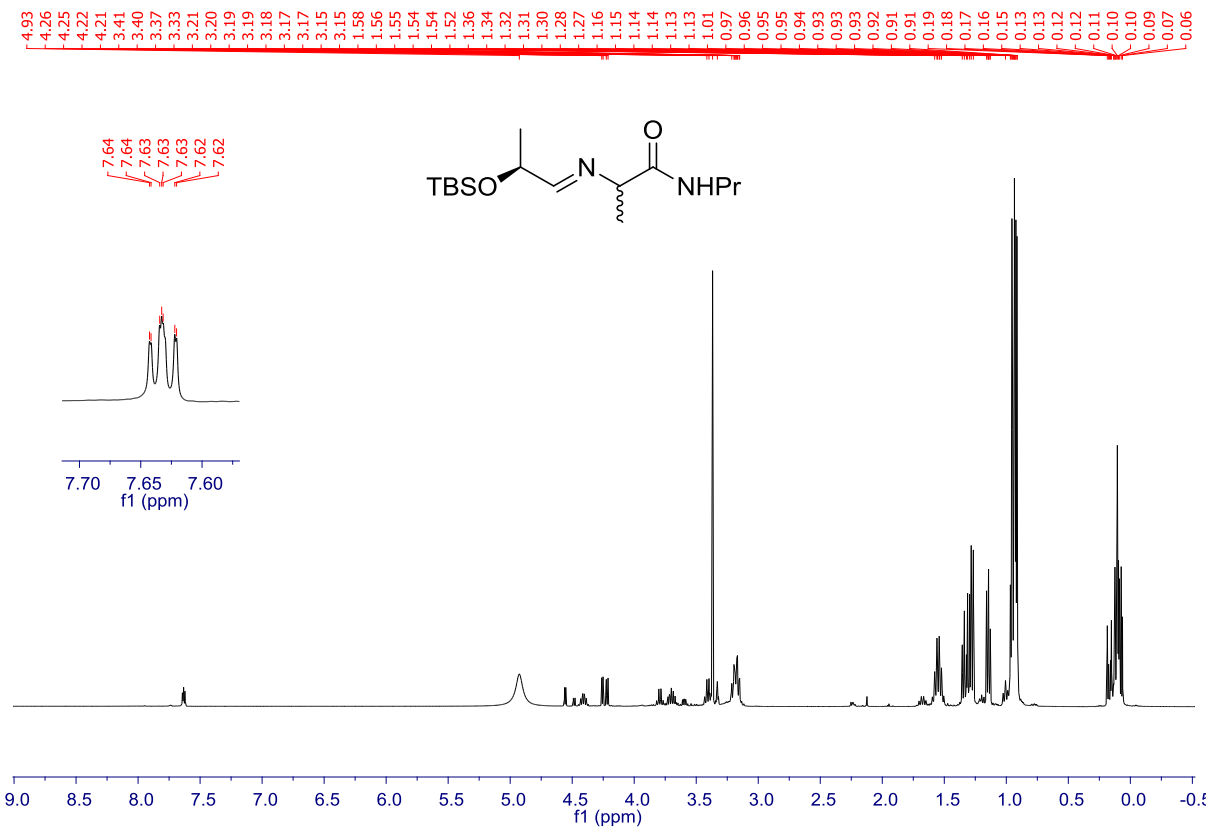
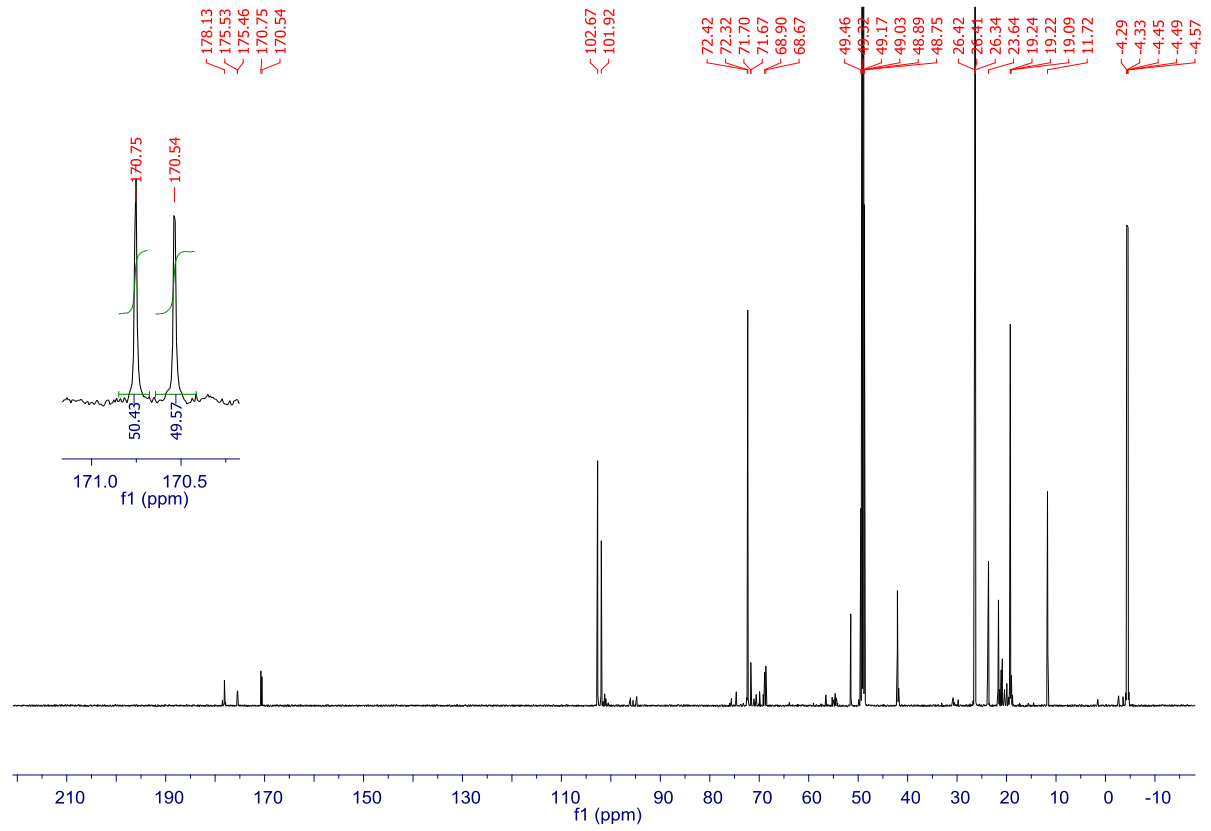




(±)-7 and (*S*)-4, d_4-MeOH





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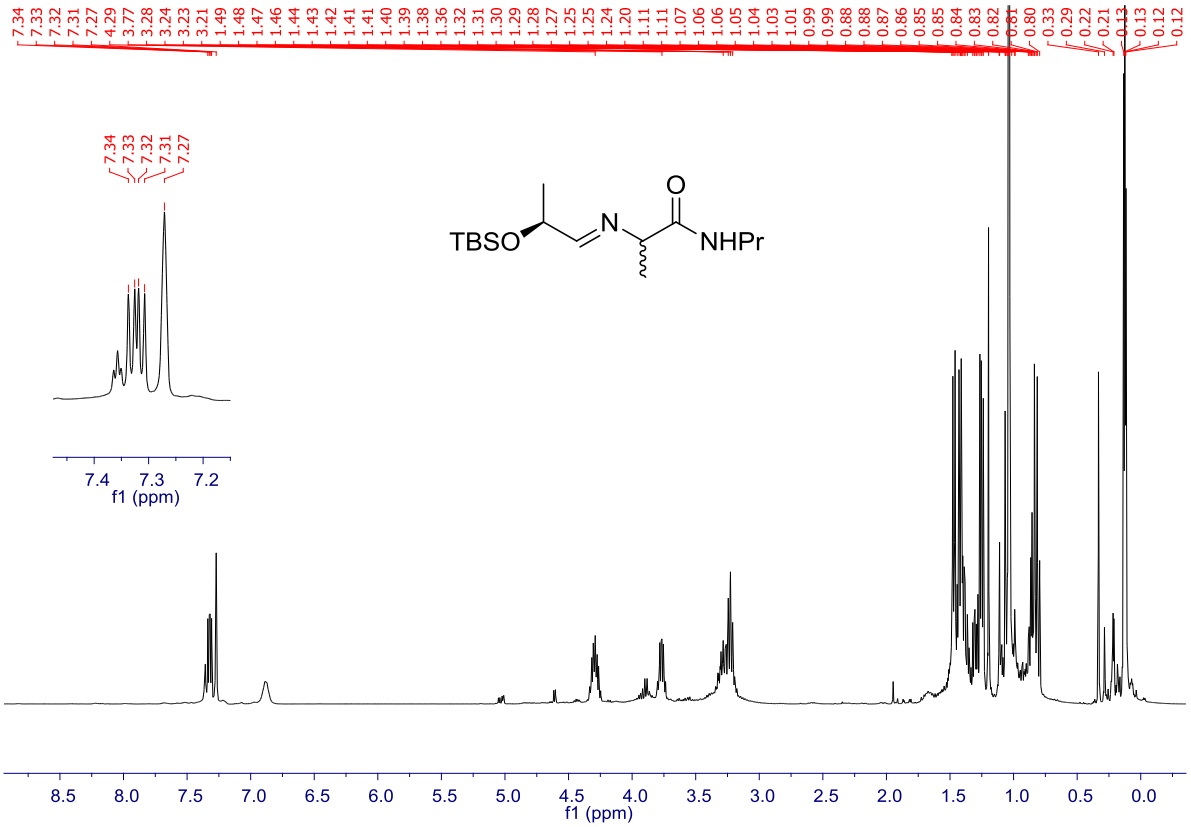

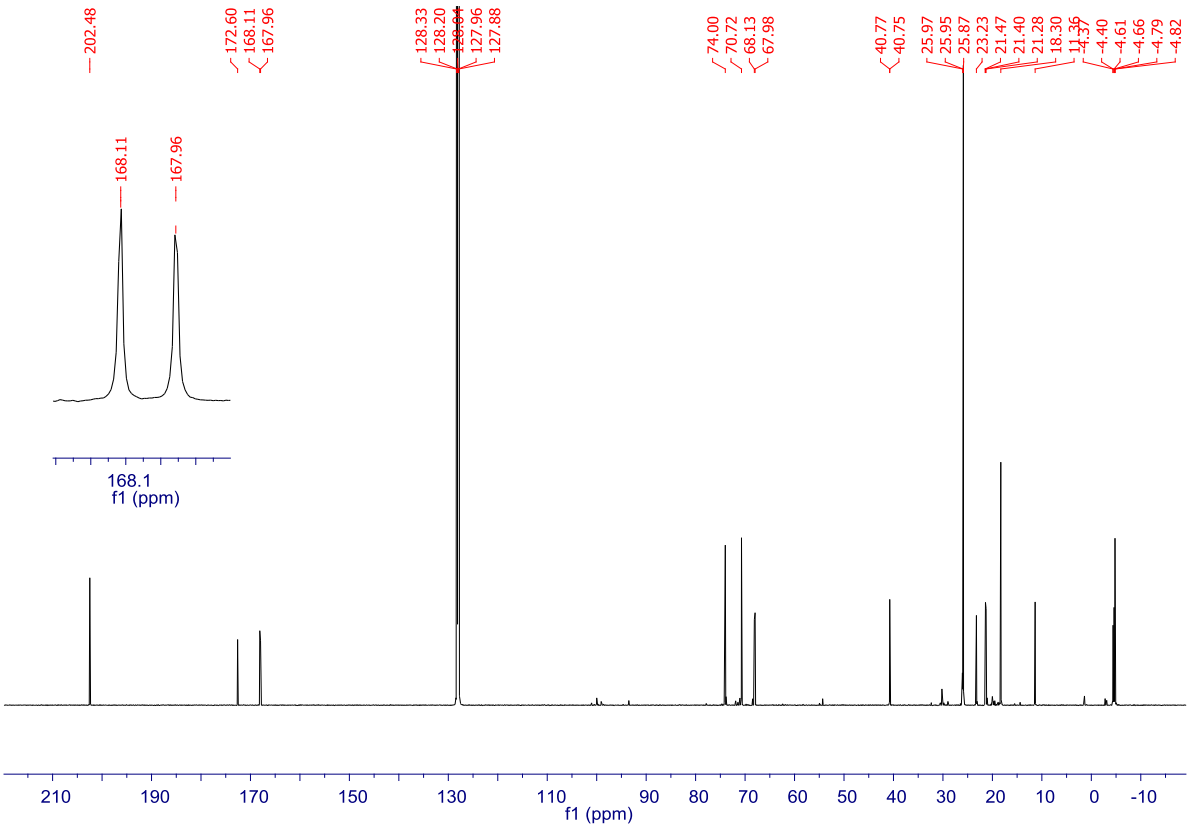

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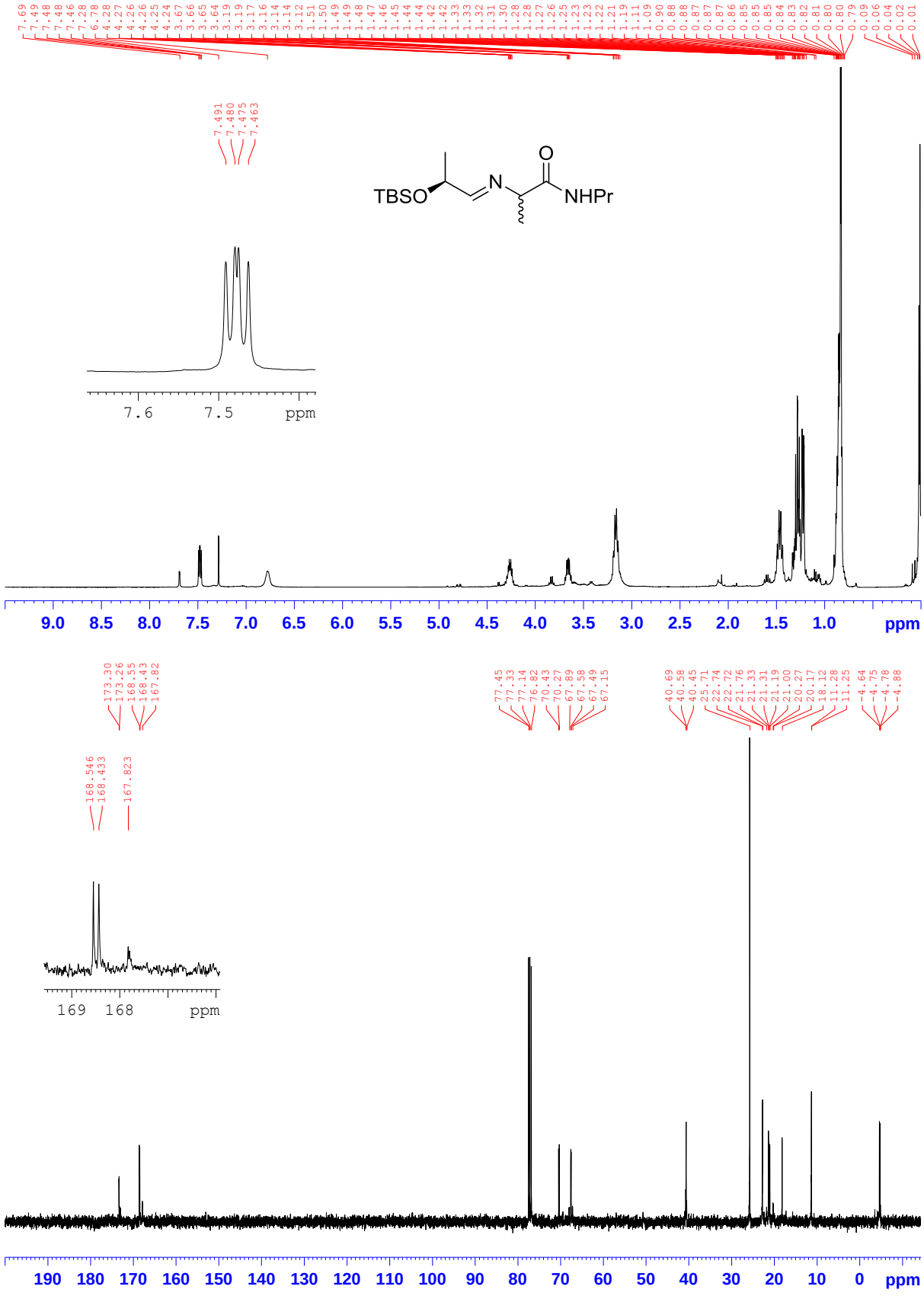

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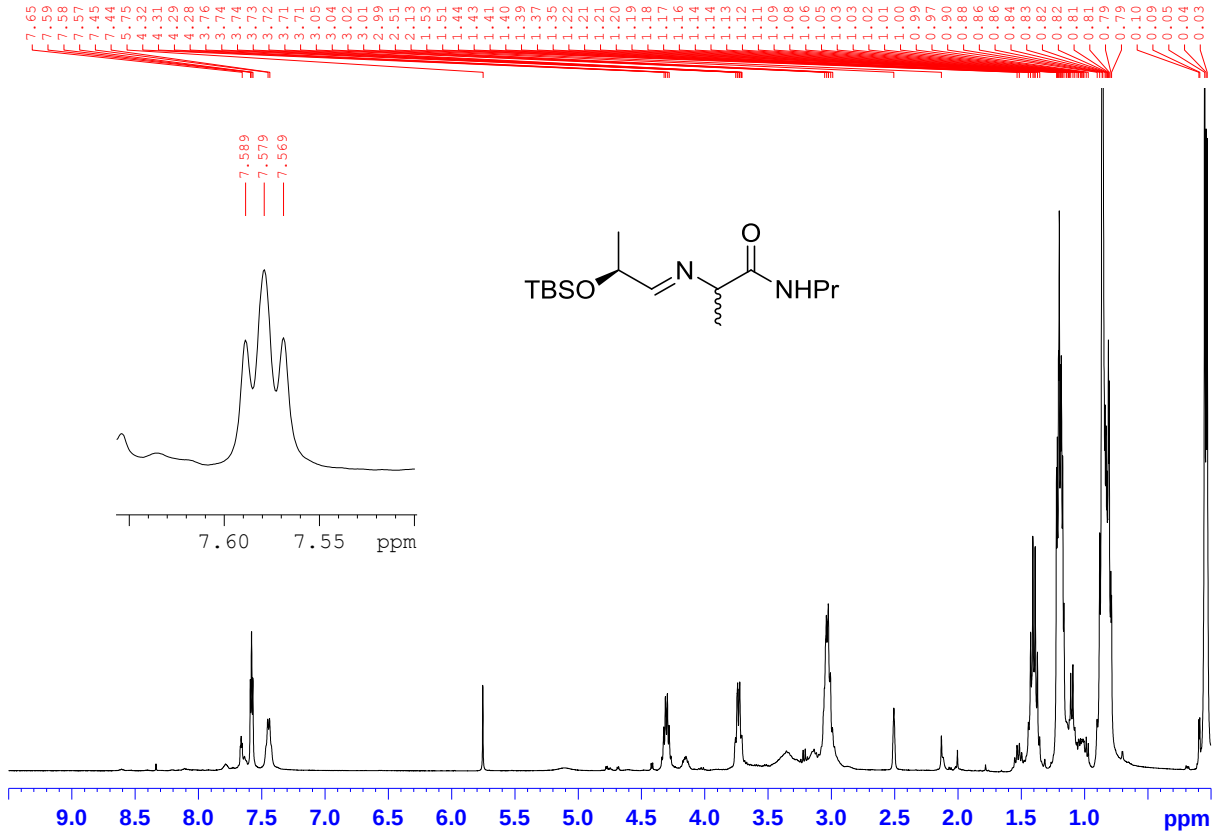
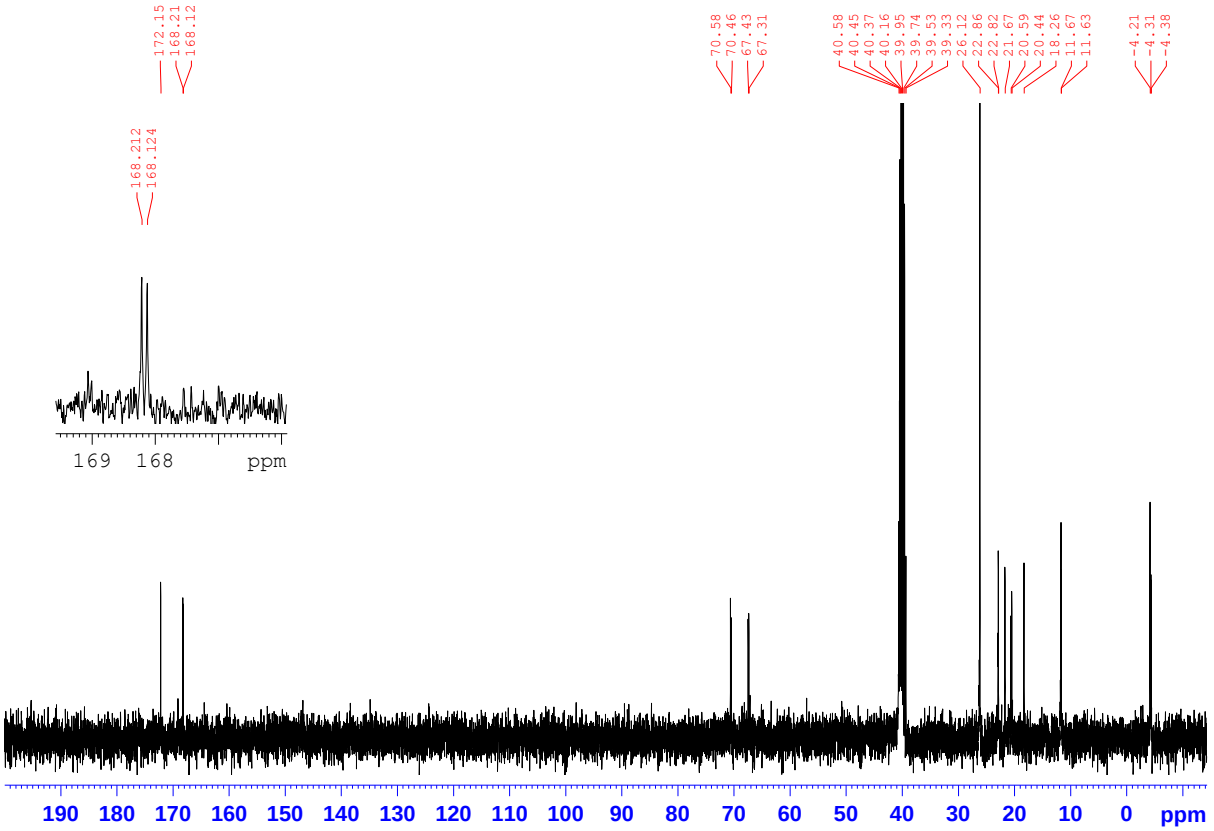
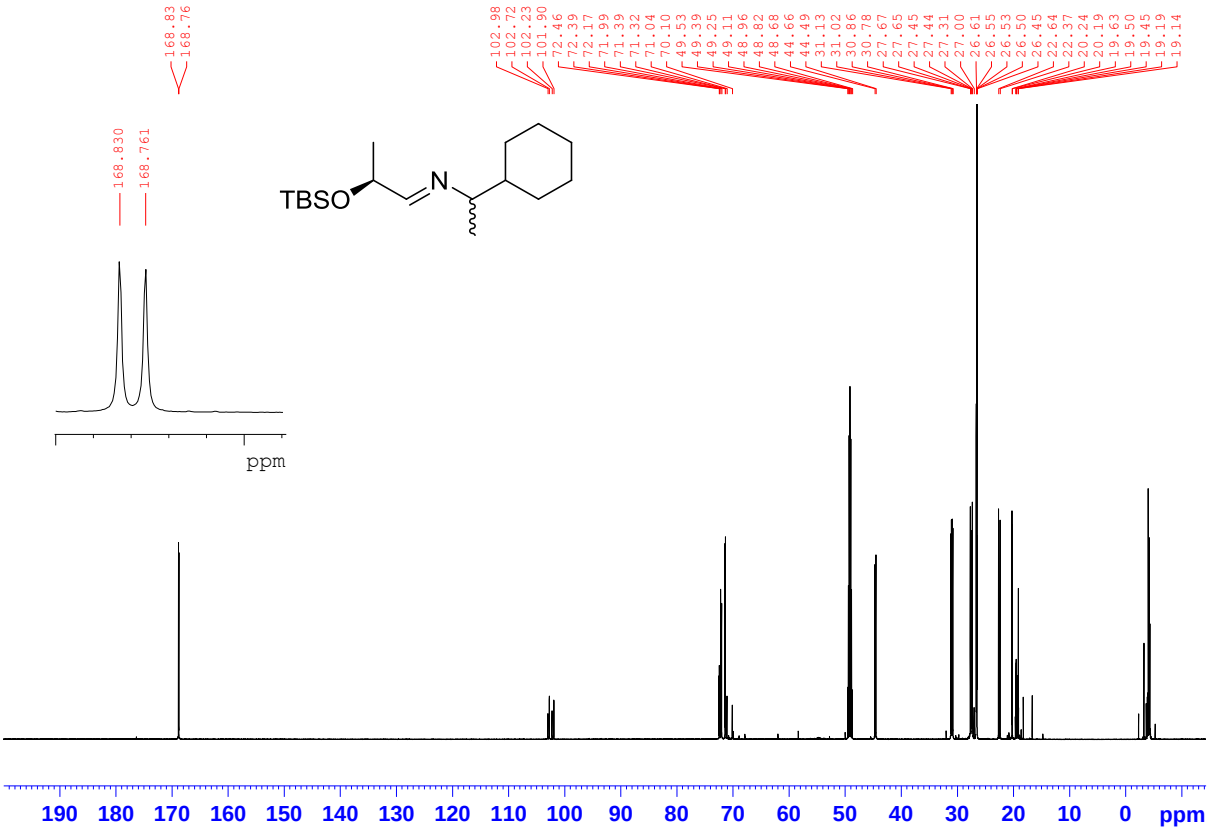




(±)-1-cyclohexylethylamine-(9) and (*S*)-4, d_4-MeOH



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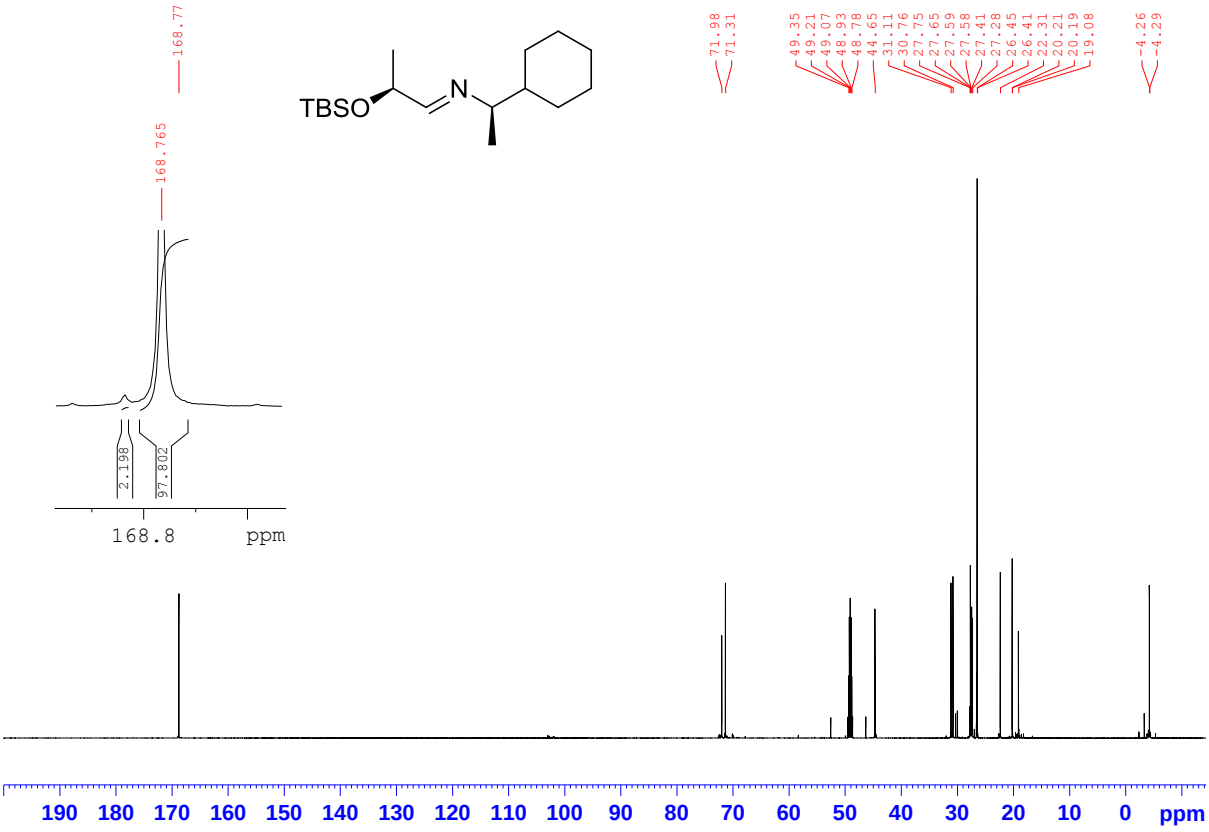
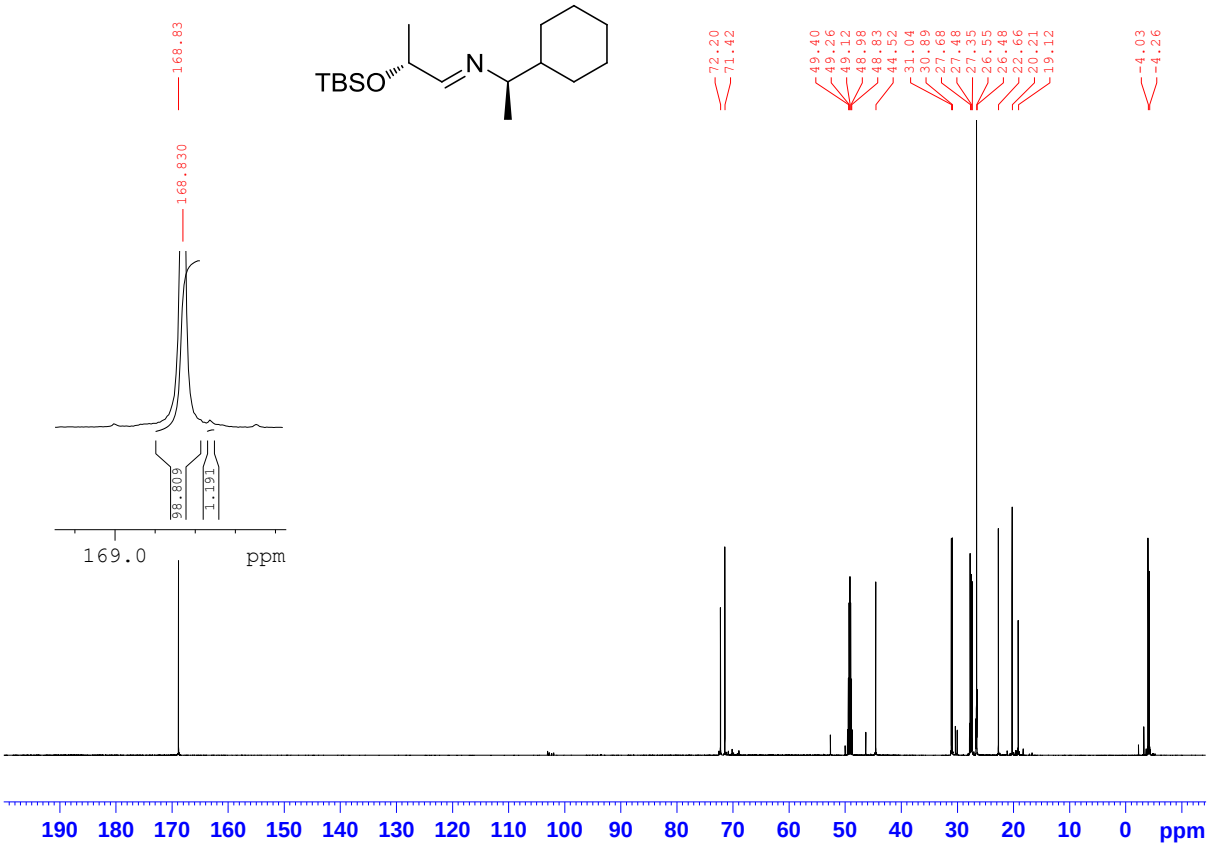
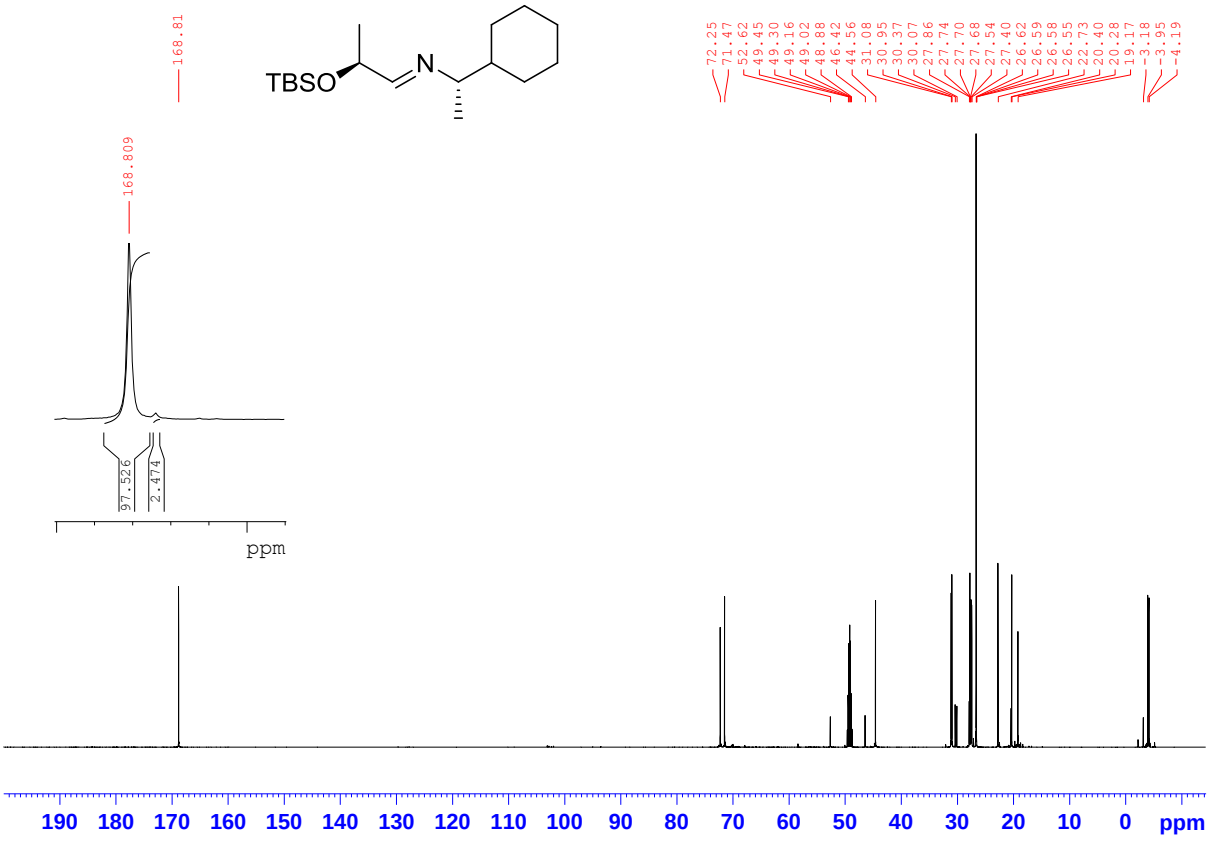


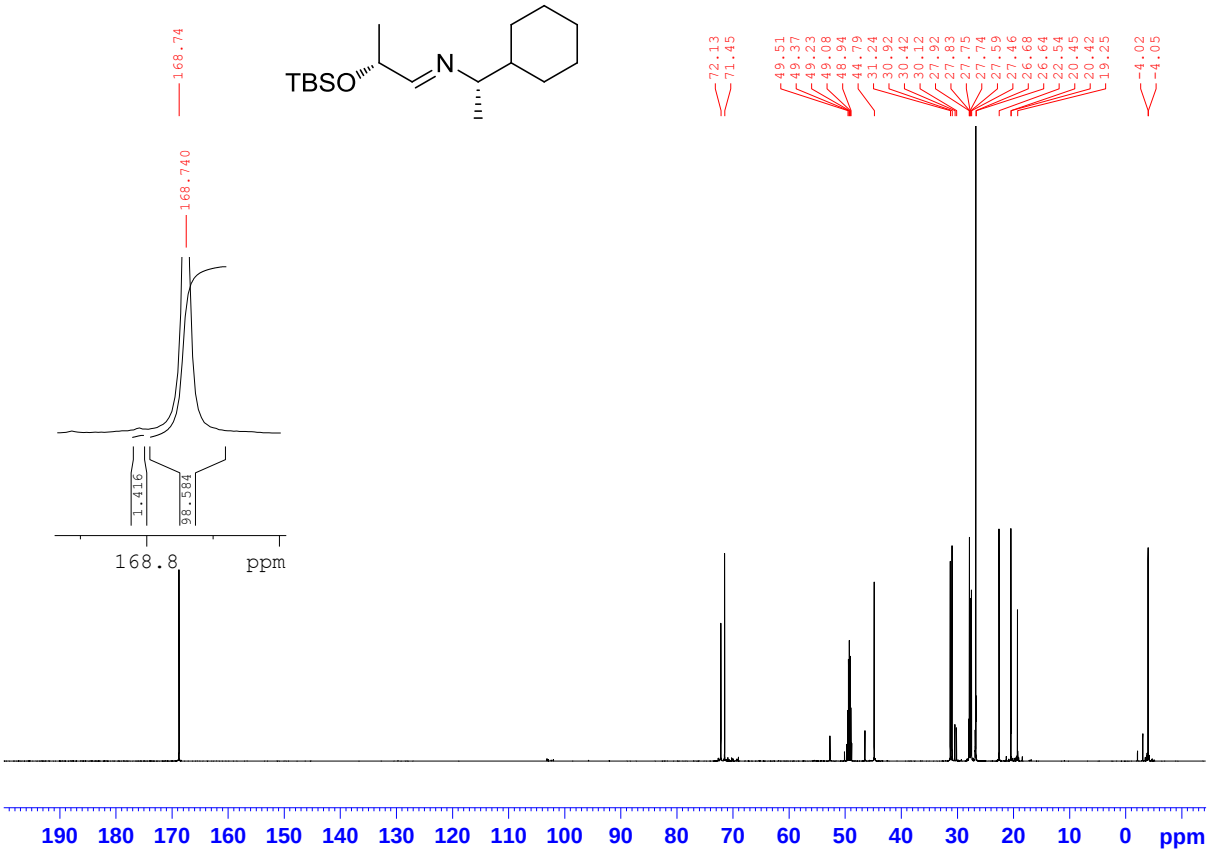
(*R*)-1-cyclohexylethylamine-(9) and (*R*)-4, d_4-MeOH



(*S*)-1-cyclohexylethylamine-(9) and (*S*)-4, d_4-MeOH

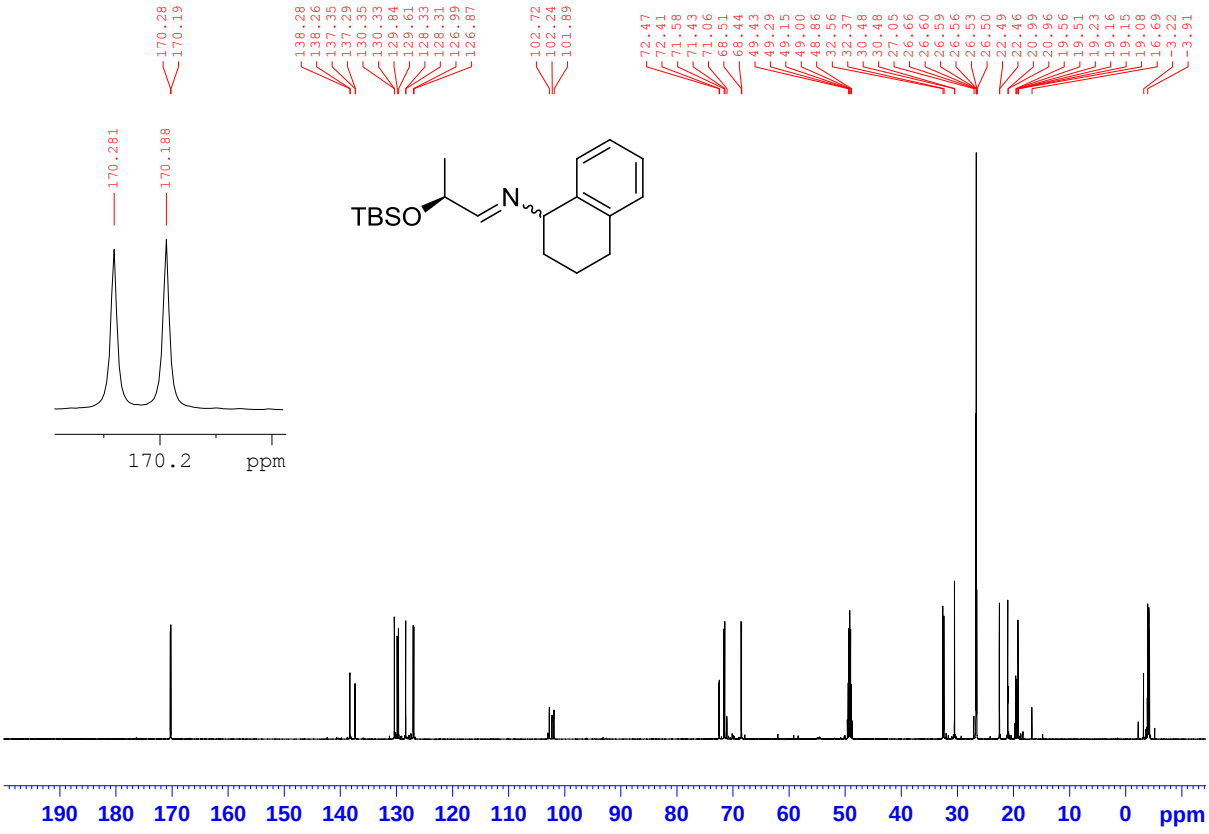


(*S*)-1-cyclohexylethylamine-(9) and (*R*)-4, d_4-MeOH

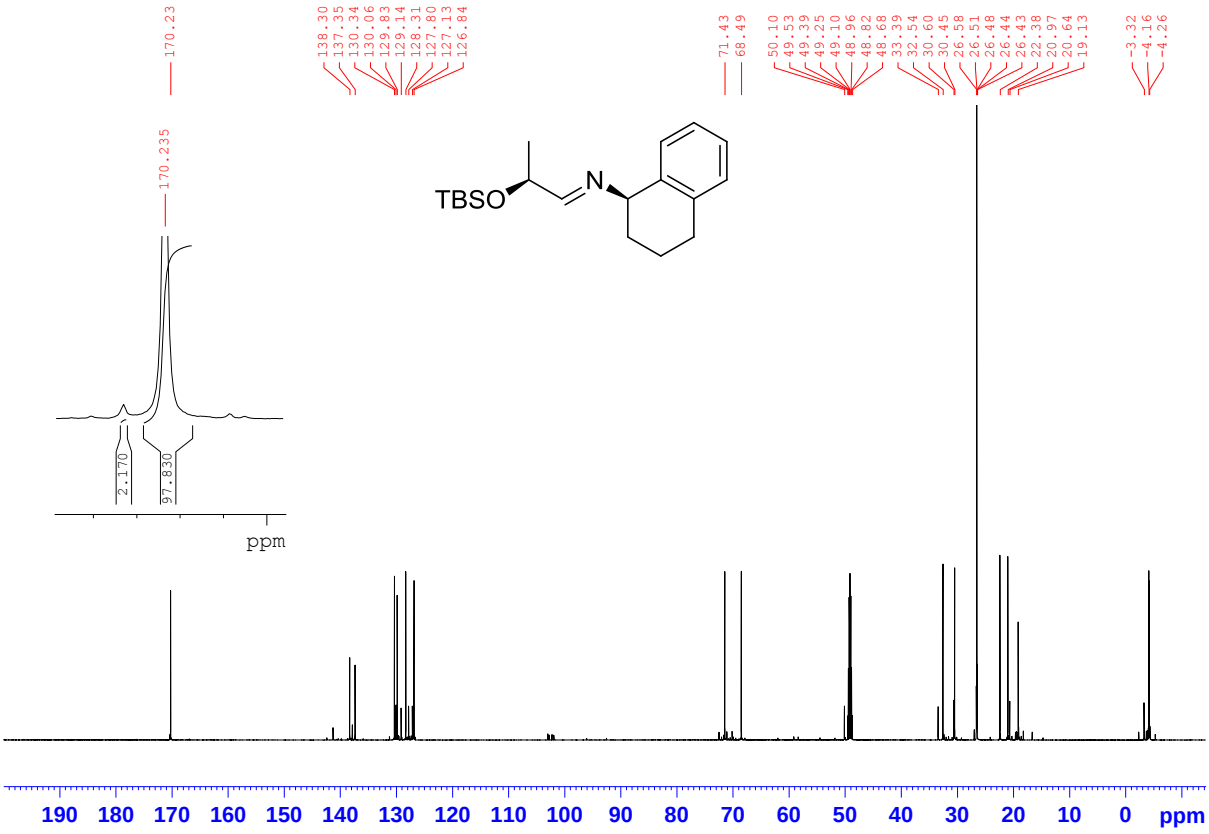


1-cyclohexyethylamine (9)	**Aldehyde (4)**	*S*	*R*
R		2:98	99:1
S		98:2	1:99

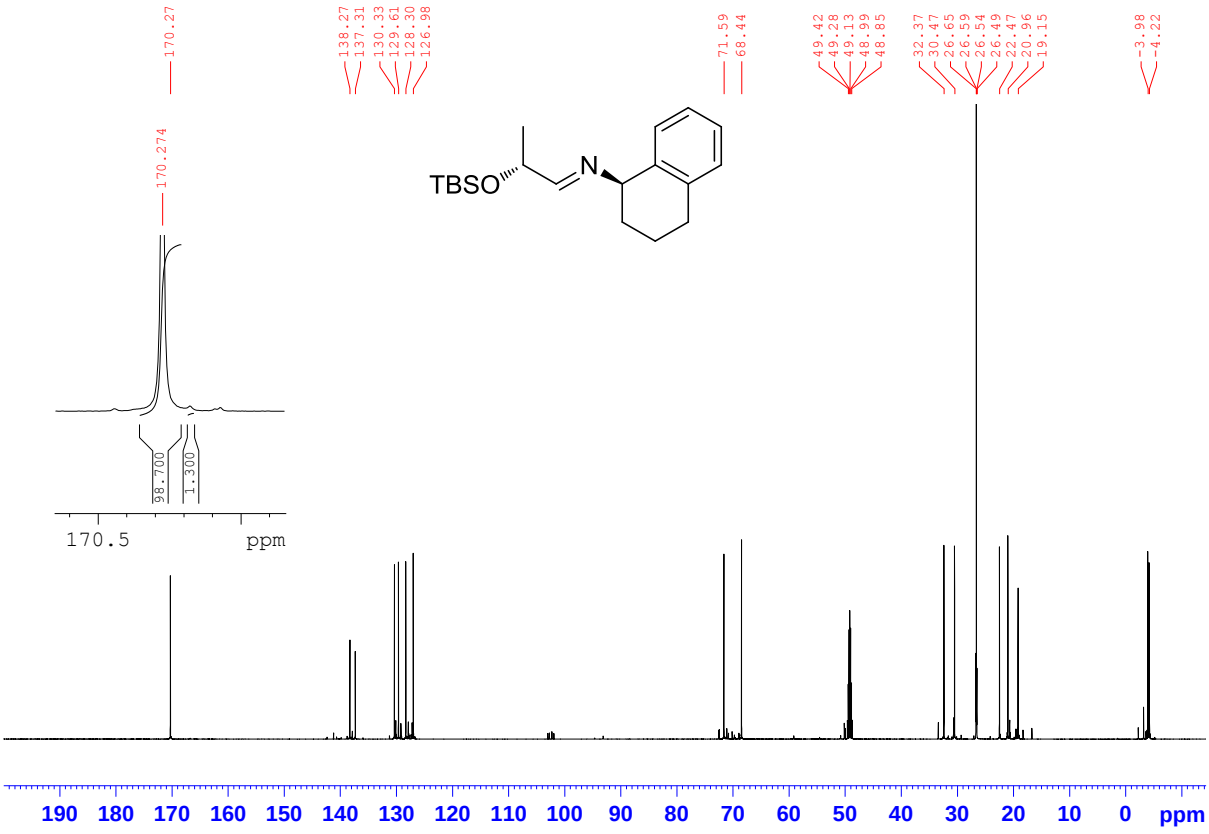
(±)-tetrahydro-1-naphthylamine-(10) and (*S*)-4, d_4-MeOH



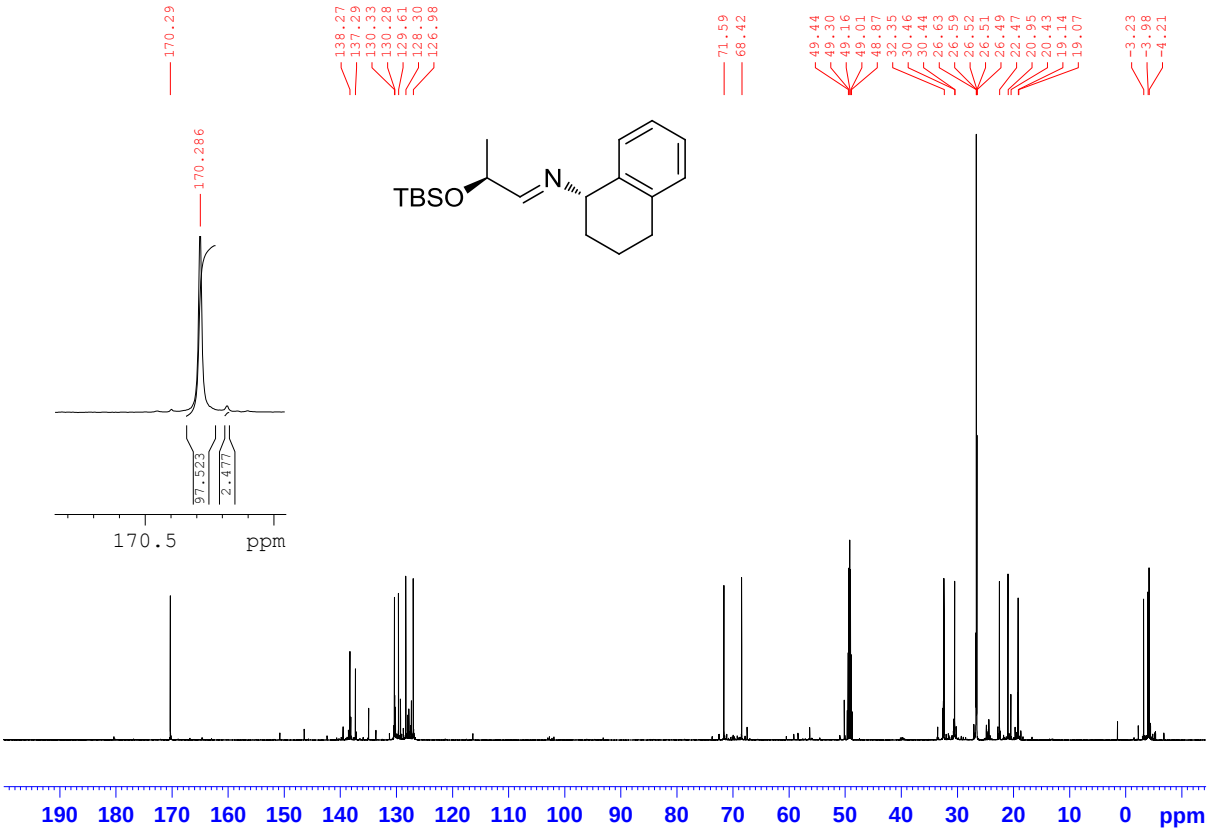
(*R*)-Tetrahydro-1-naphthylamine-(10) and (*S*)-4, d_4-MeOH



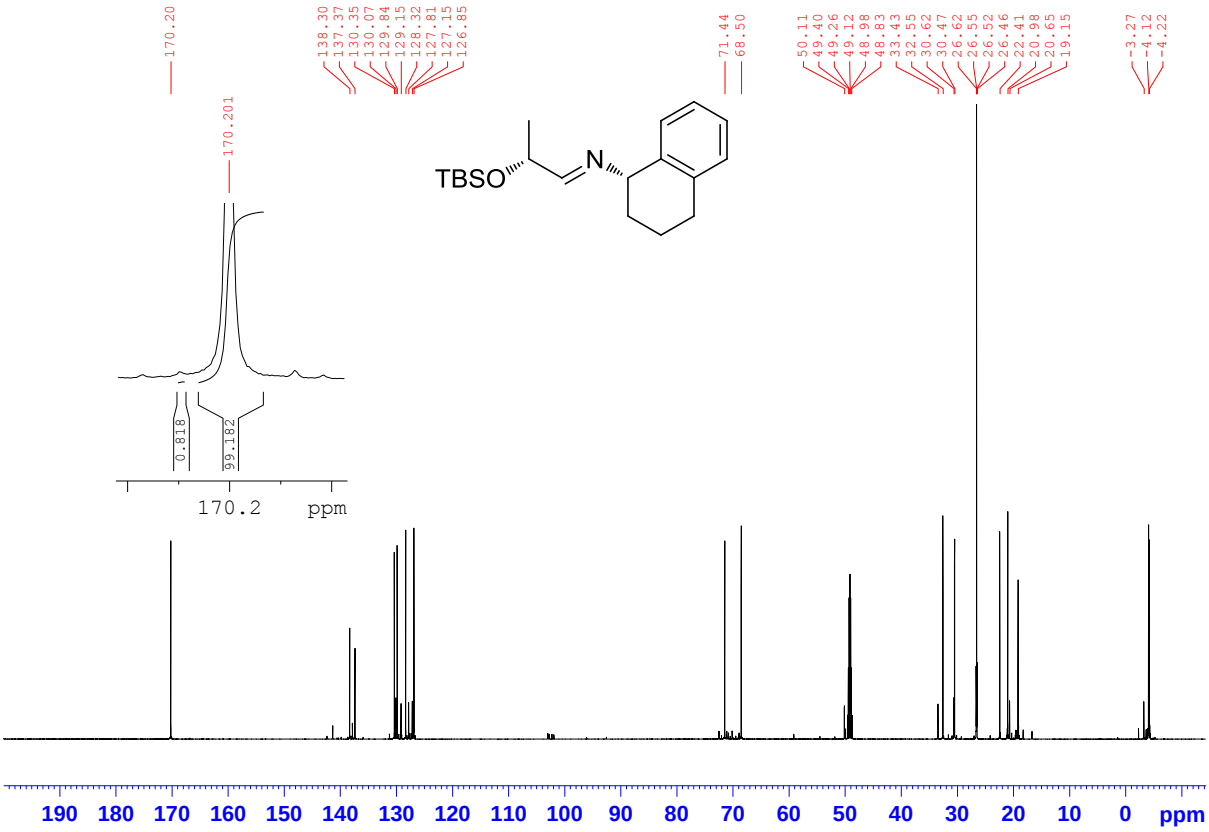
(*R*)-tetrahydro-1-naphthylamine-(10) and (*R*)-4, d_4-MeOH



(*S*)-tetrahydro-1-naphthylamine-(10) and (*S*)-4, d_4-MeOH

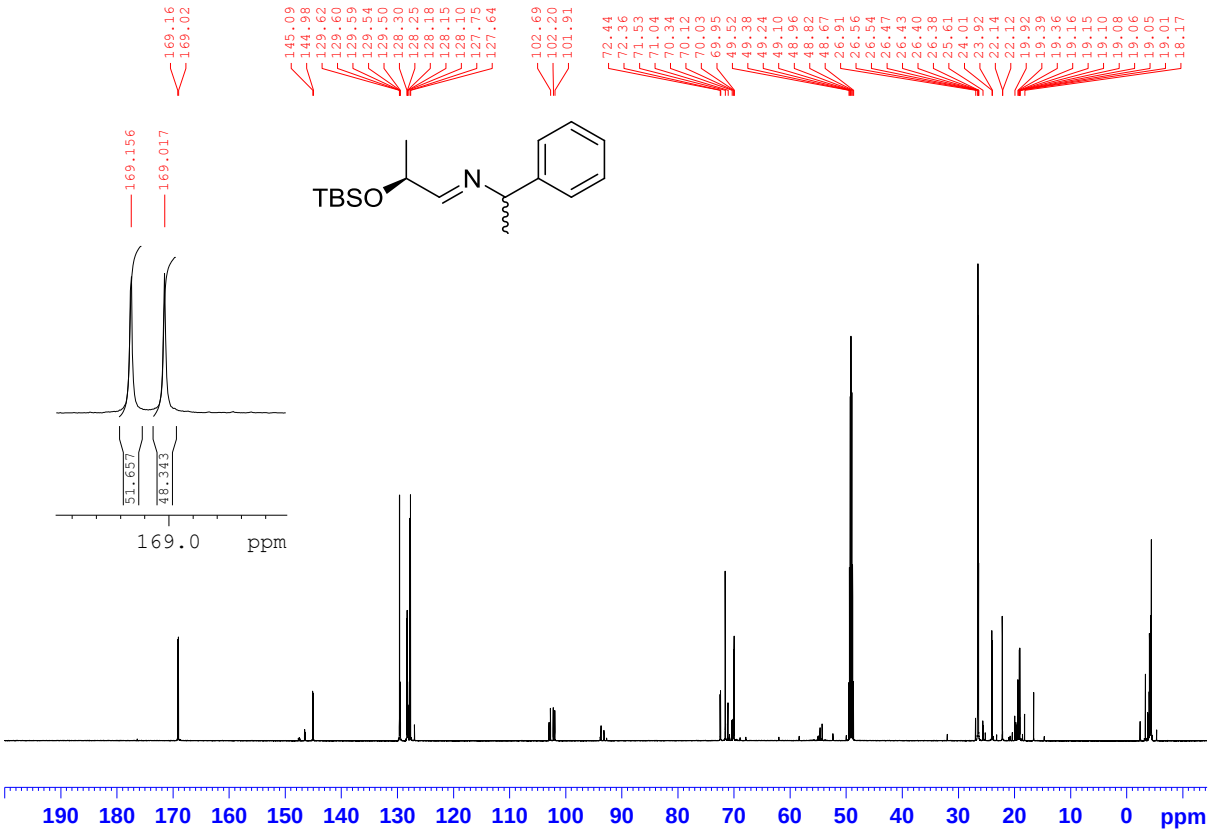


(*S*)-tetrahydro-1-naphthylamine-(10) and (*R*)-4, d_4-MeOH

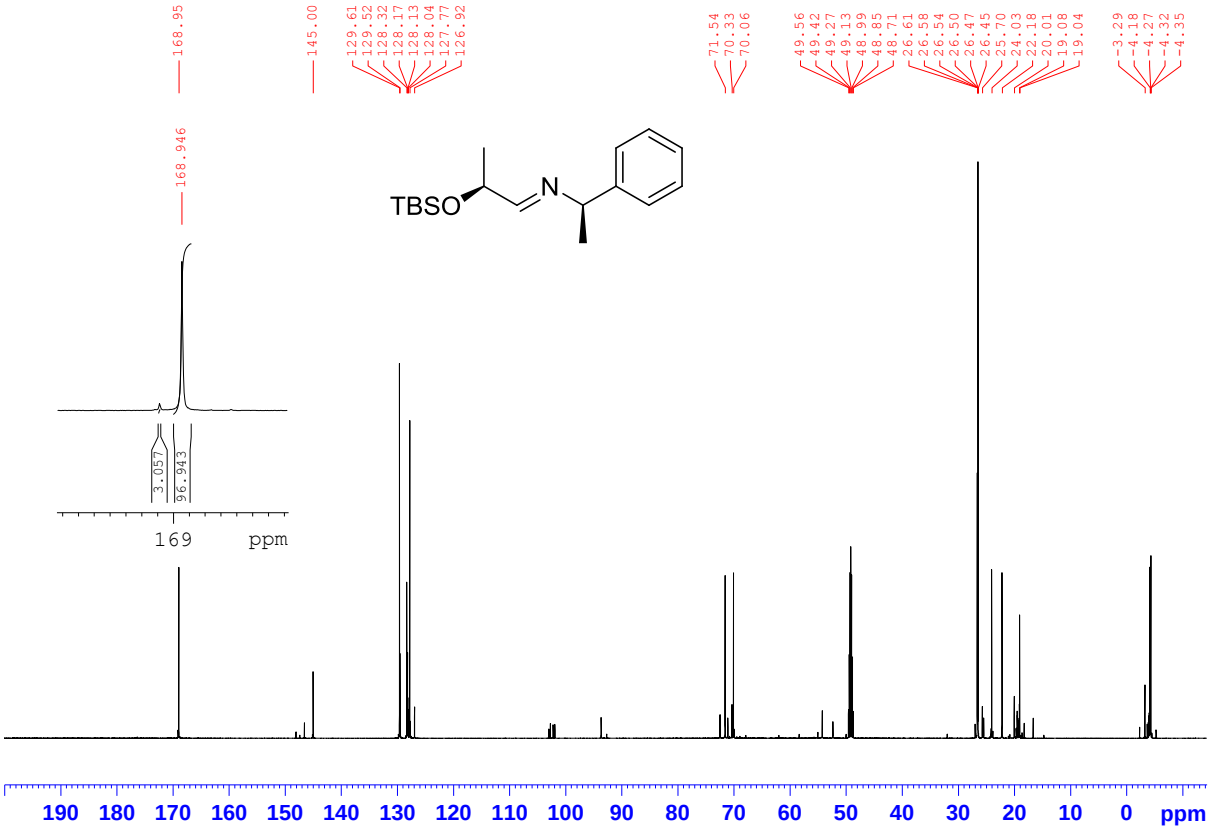


1,2,3,4-tetrahydro-1-naphthylamine (10)	Aldehyde (4)	*S*	*R*
R		2:98	99:1
S		98:2	1:99

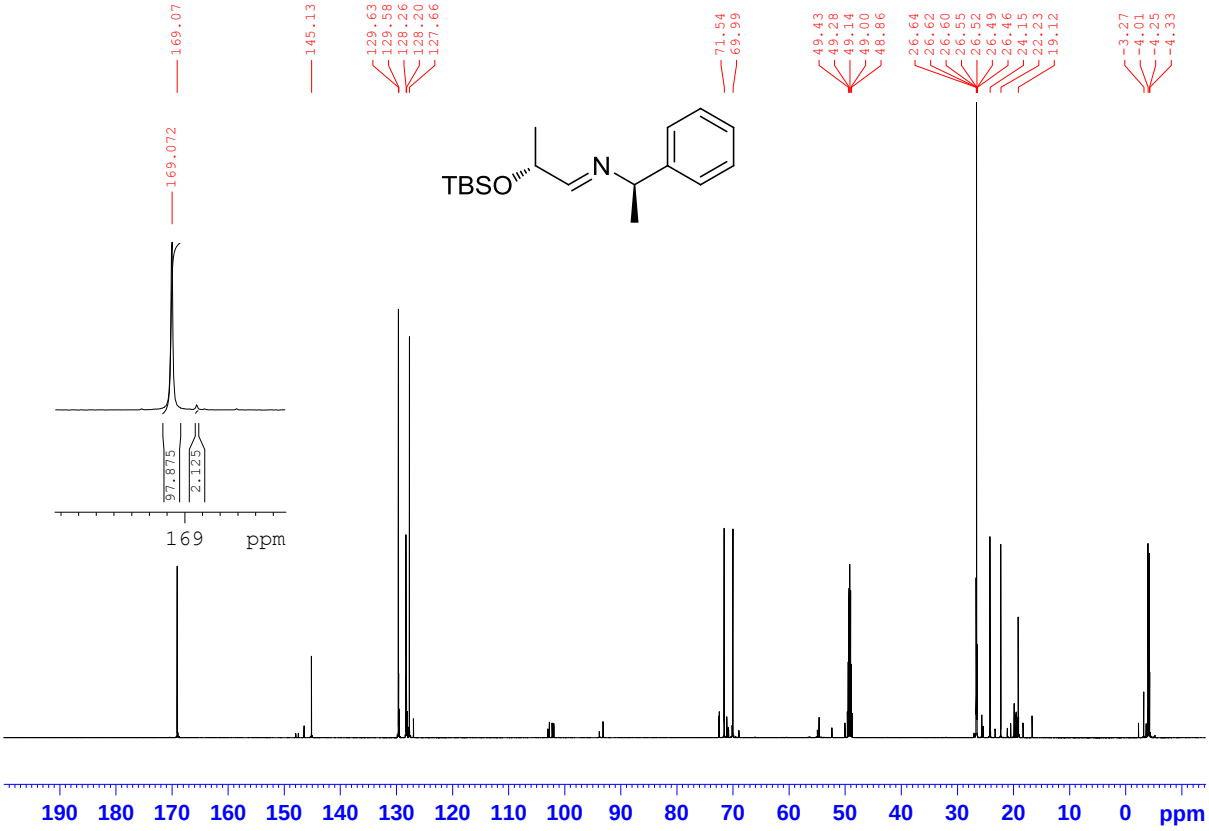
(±)-α-methylbenzylamine-(11) and (*S*)-4, d_4-MeOH



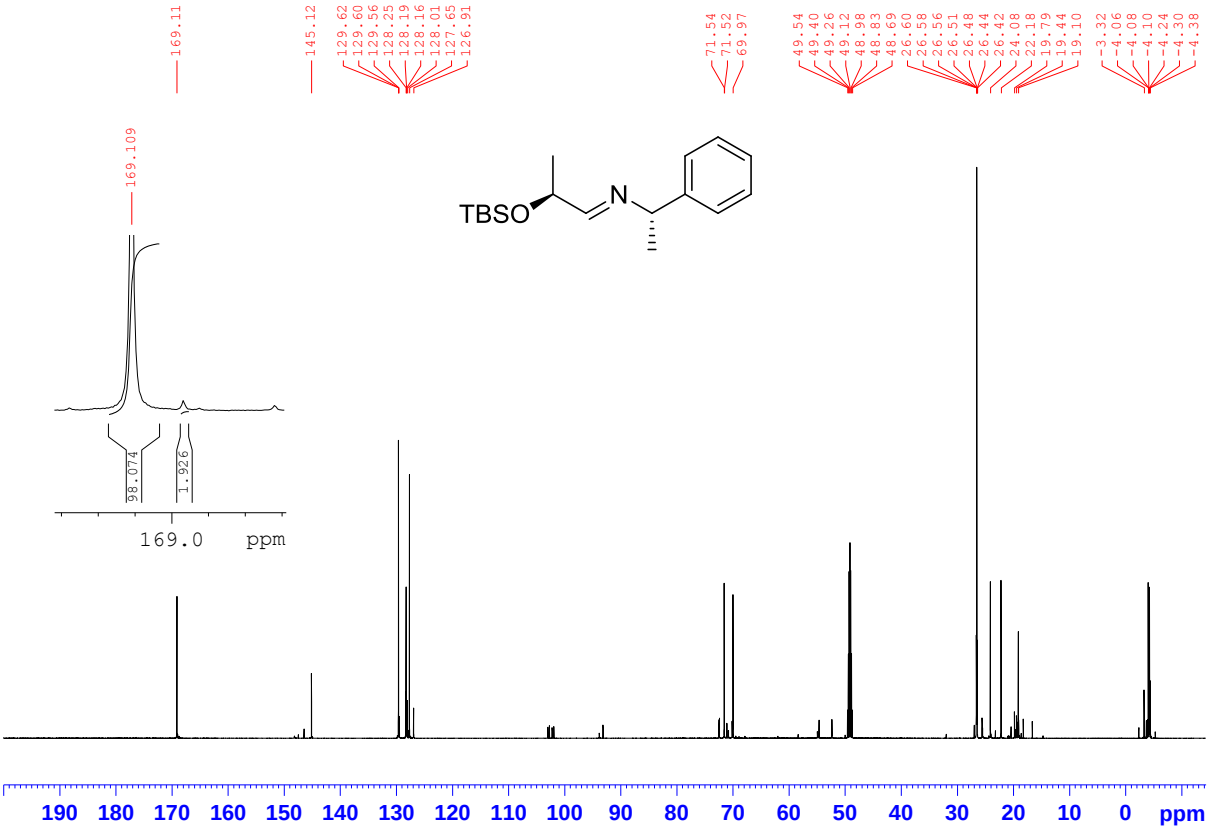
(*R*)-α-methylbenzylamine-(11) and (*S*)-4, d_4-MeOH



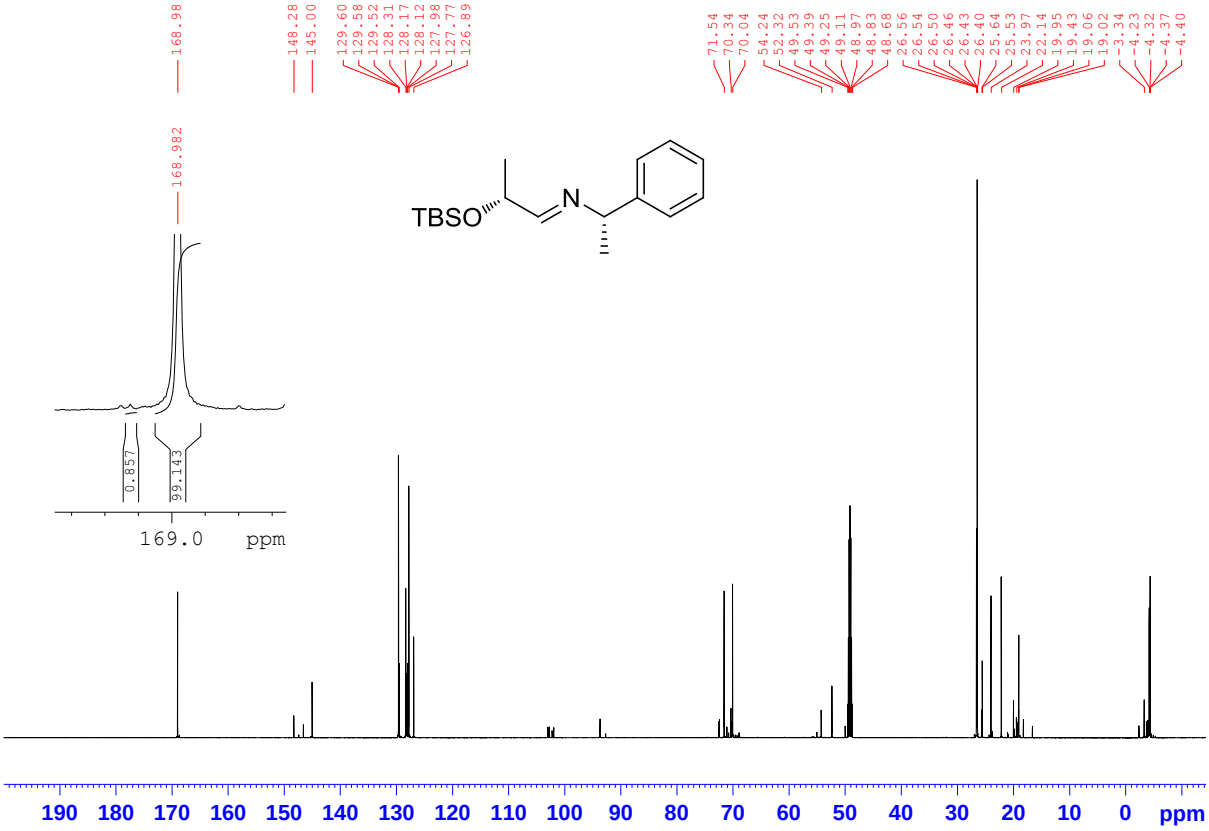
(*R*)-α-methylbenzylamine-(11) and (*R*)-4, d_4-MeOH



(*S*)-α-methylbenzylamine-(11) and (*S*)-4, d_4-MeOH

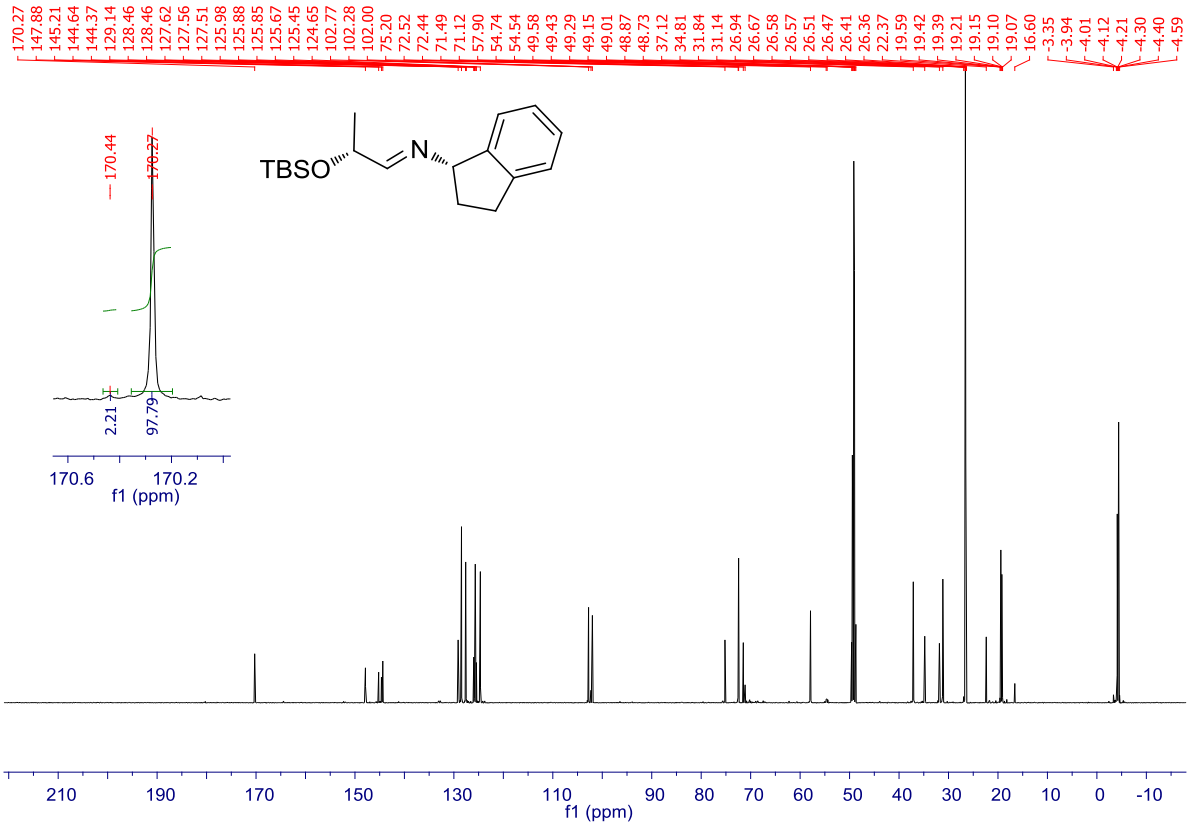


(*S*)-α-methylbenzylamine-(11) and (*R*)-4, d_4-MeOH

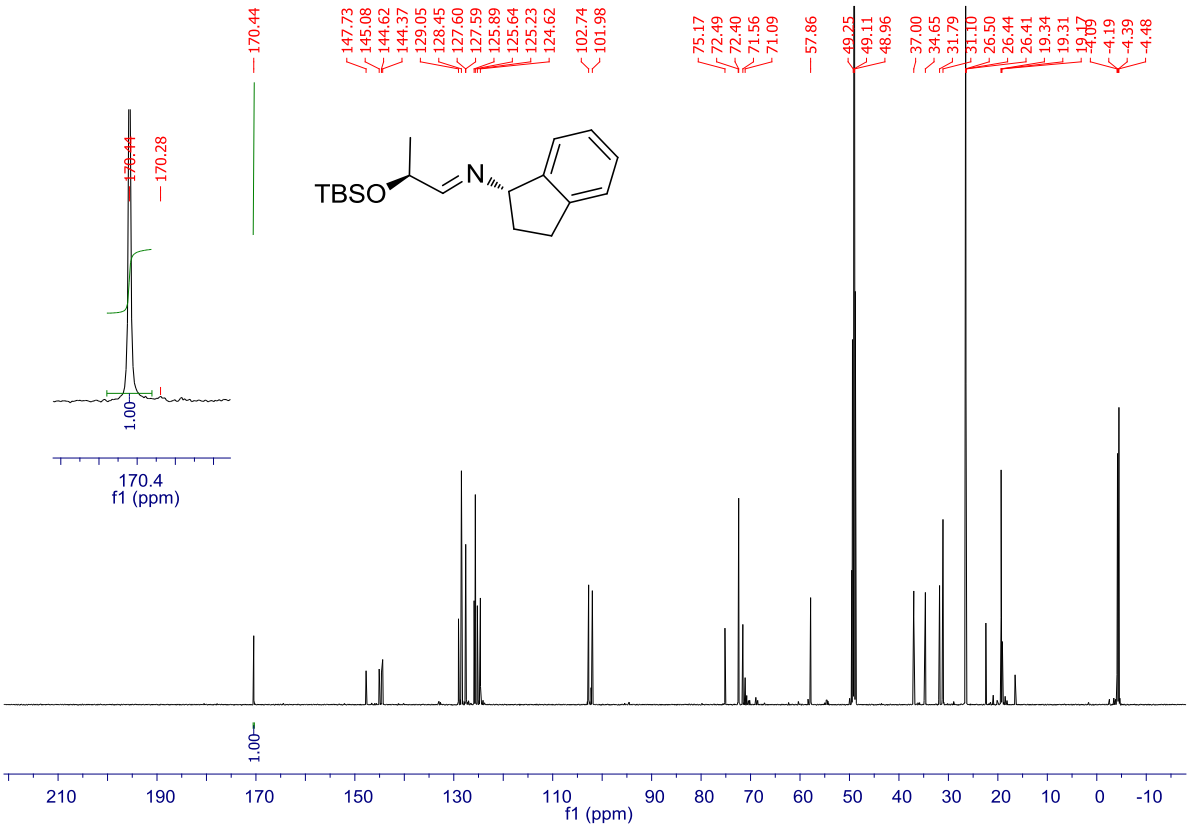


α-methylbenzylamine (11)	Aldehyde (4)	*S*	*R*
R		3:97	98:2
S		98:2	1:99

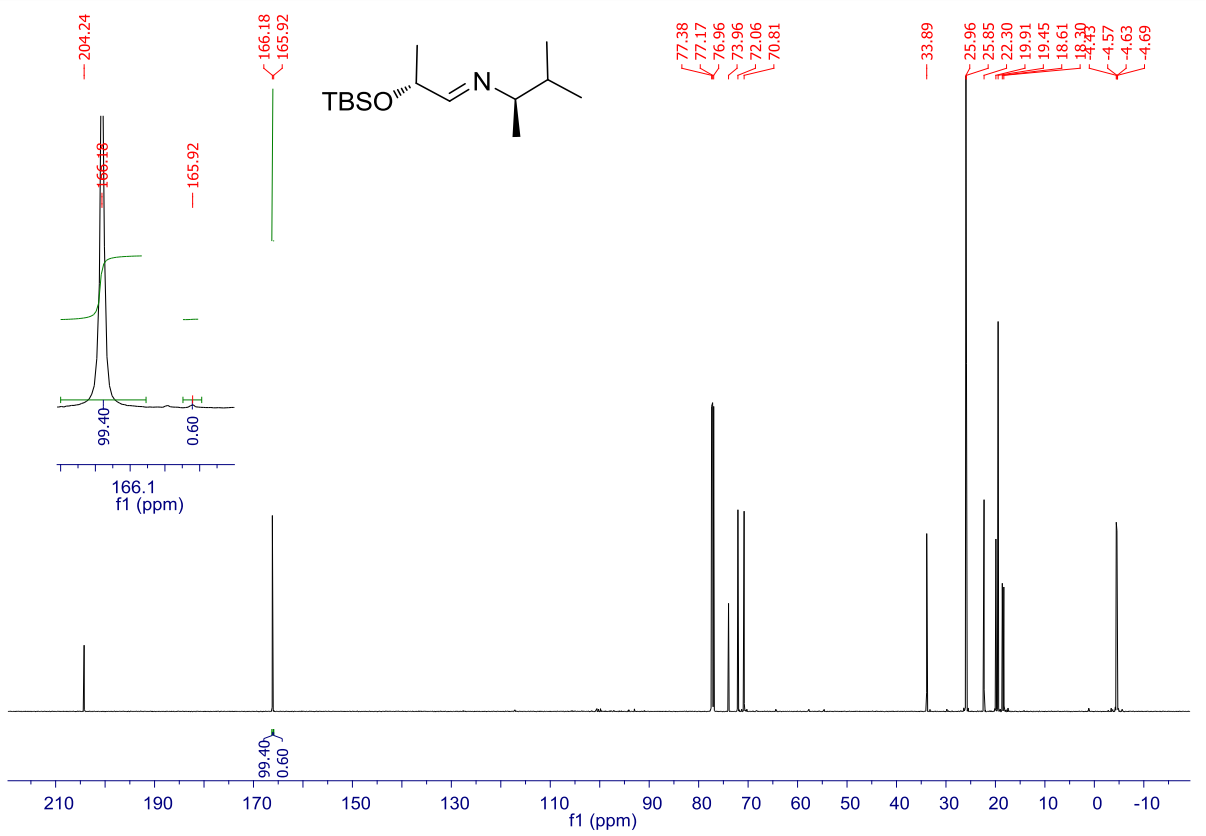
(*S*)-(+)-1-Aminoindan-(12) and (*R*)-4, d_4-MeOH



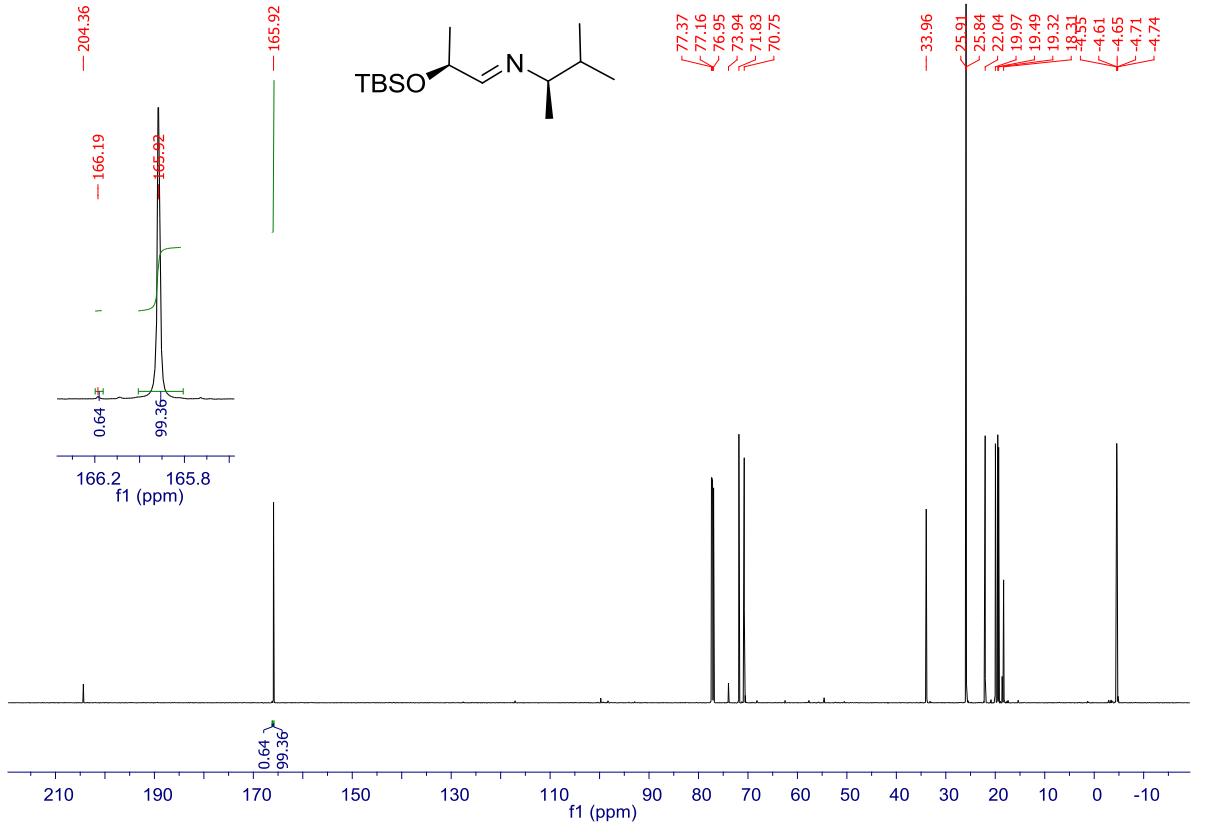
(*S*)-(+)-1-Aminoindan-(12) and (*S*)-4, d_4-MeOH



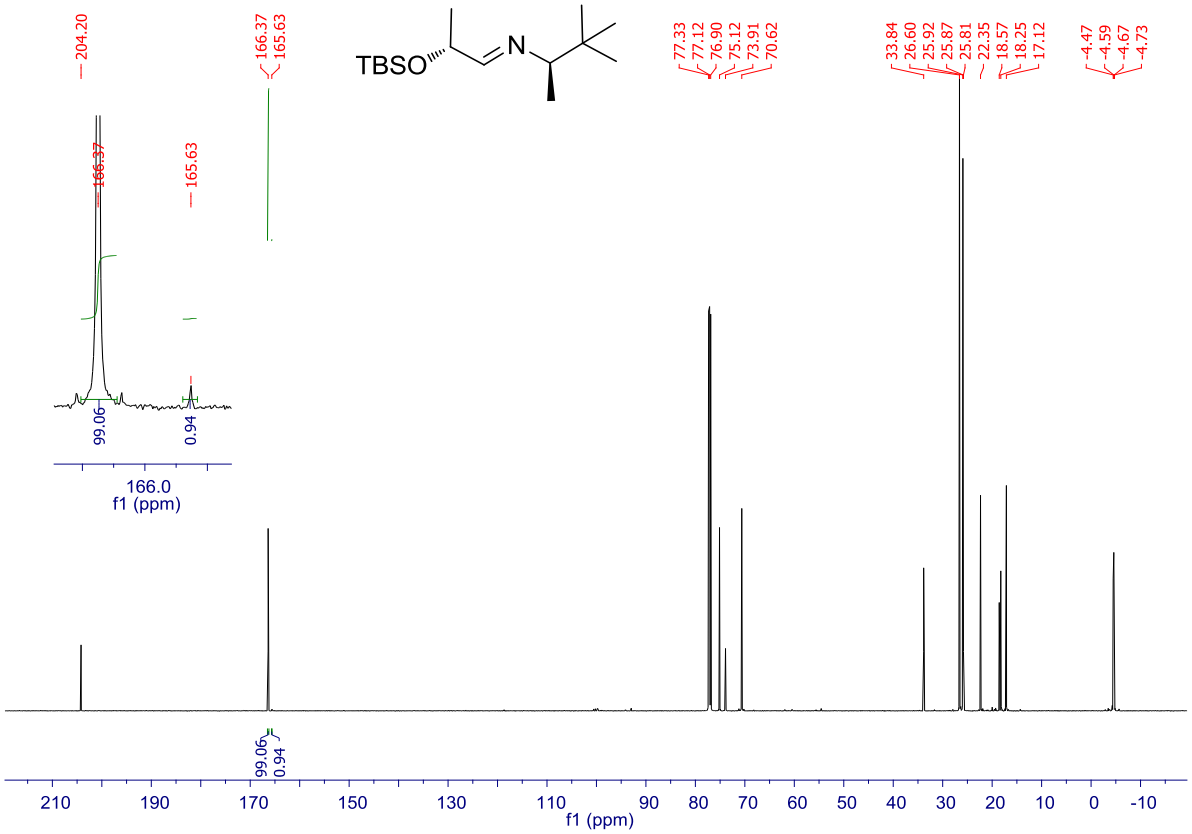
(*R*)-(−)-2-Amino-3-methylbutane-(13) and (*R*)-4, $CDCl_3$



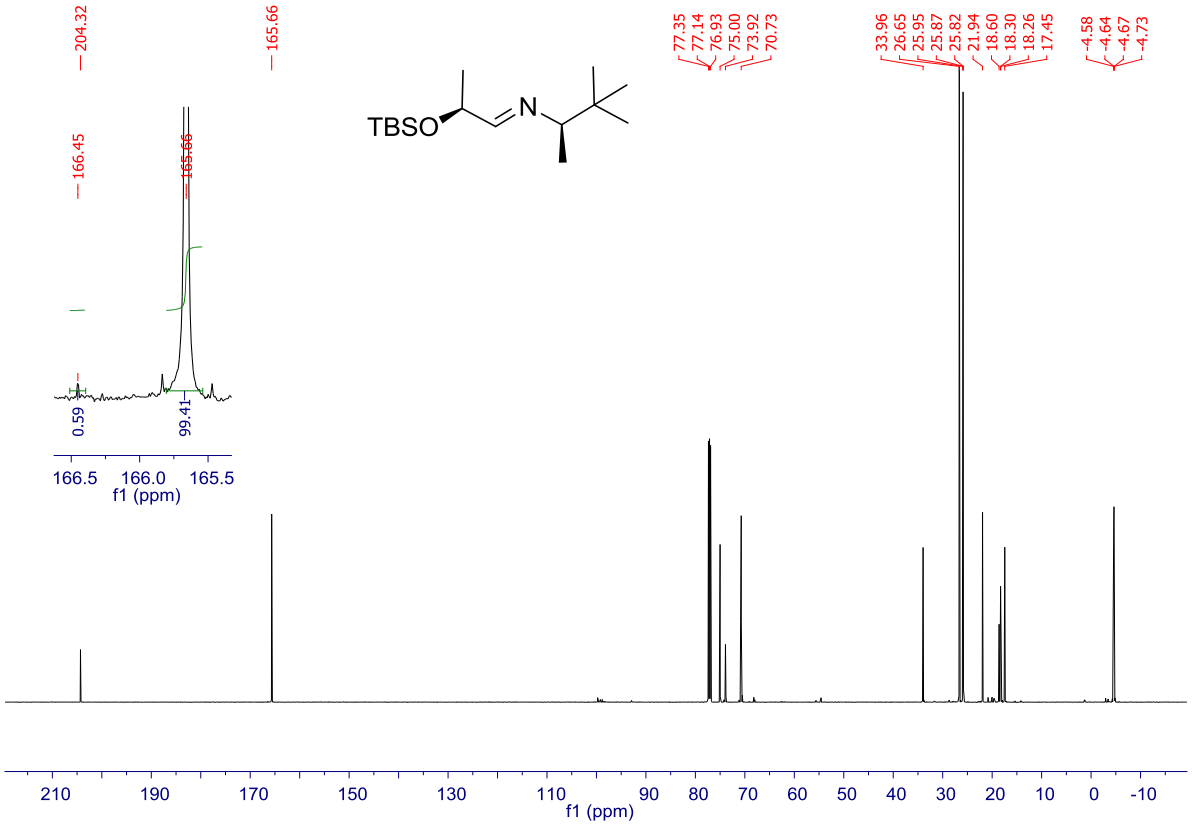
(*R*)-(−)-2-Amino-3-methylbutane-(13) and (*S*)-4, $CDCl_3$



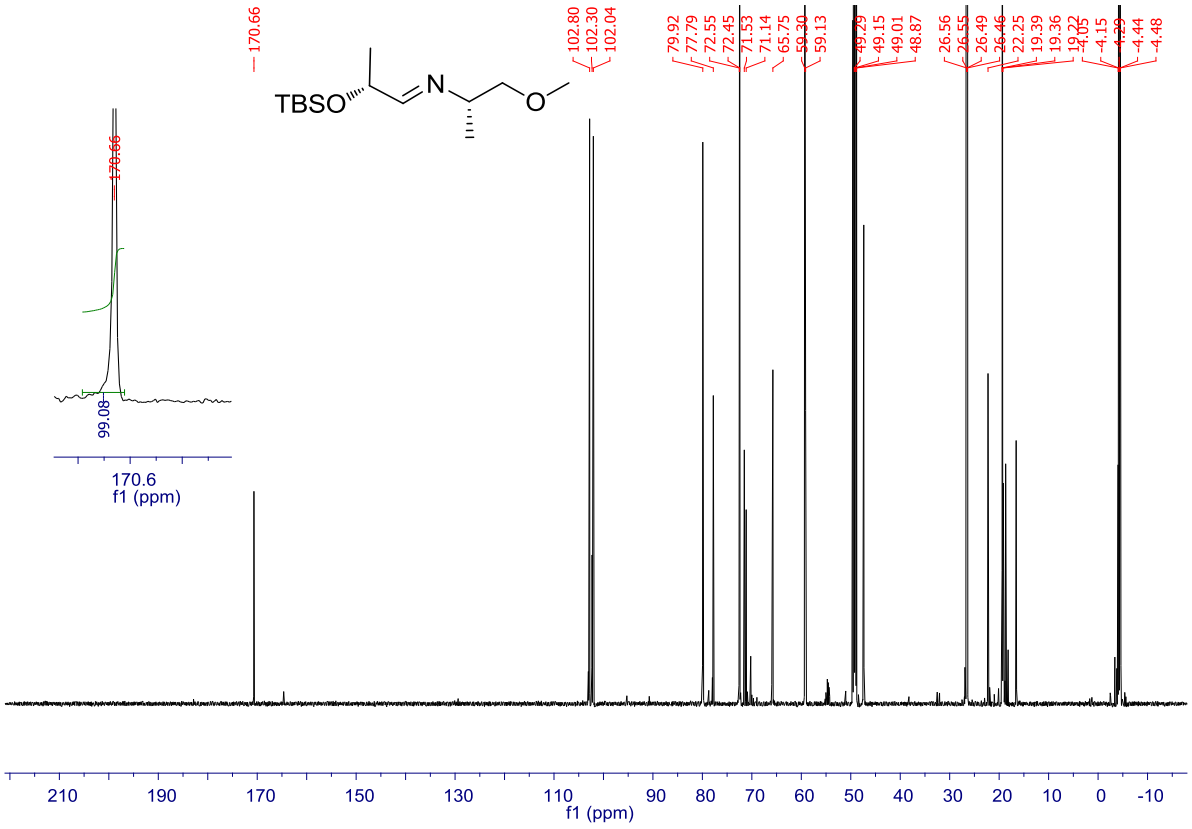
(*R*)-(−)-3,3-Dimethyl-2-butylamine-(14) and (*R*)-4, $CDCl_3$



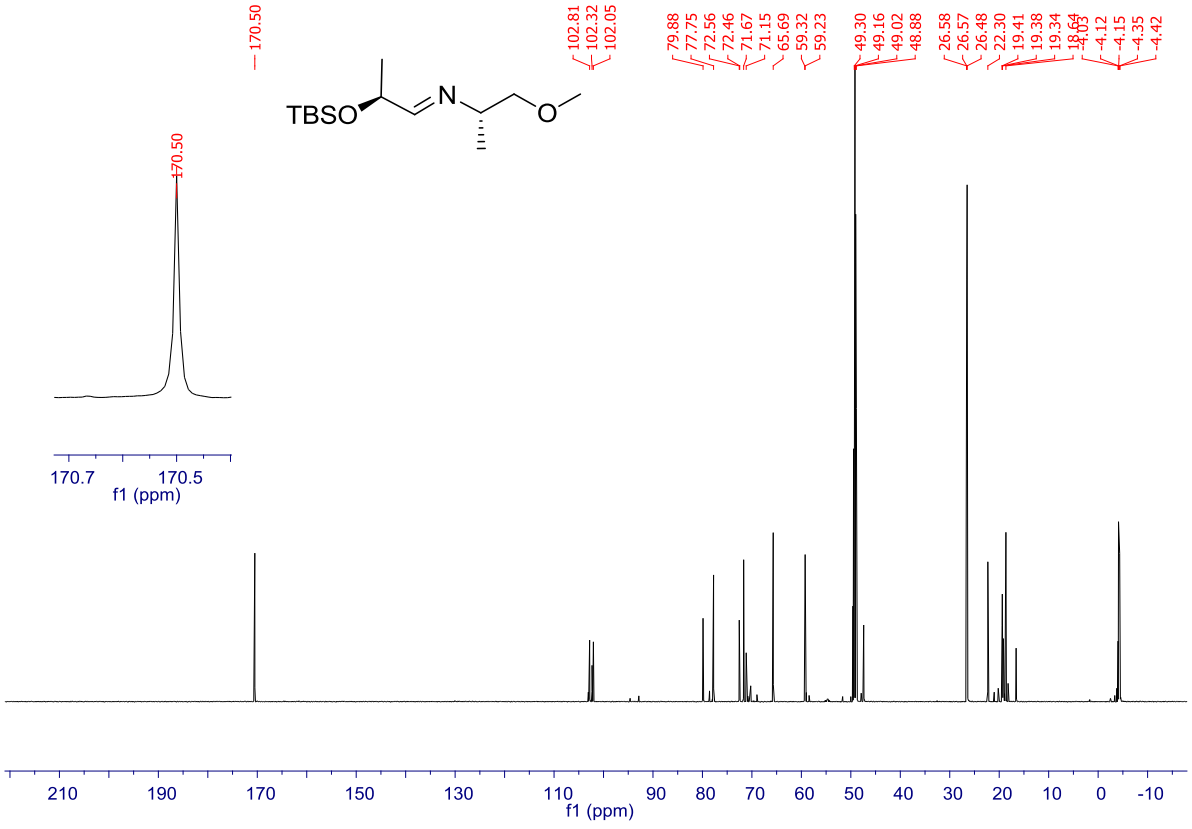
(*R*)-(−)-3,3-Dimethyl-2-butylamine-(14) and (*S*)-4, $CDCl_3$



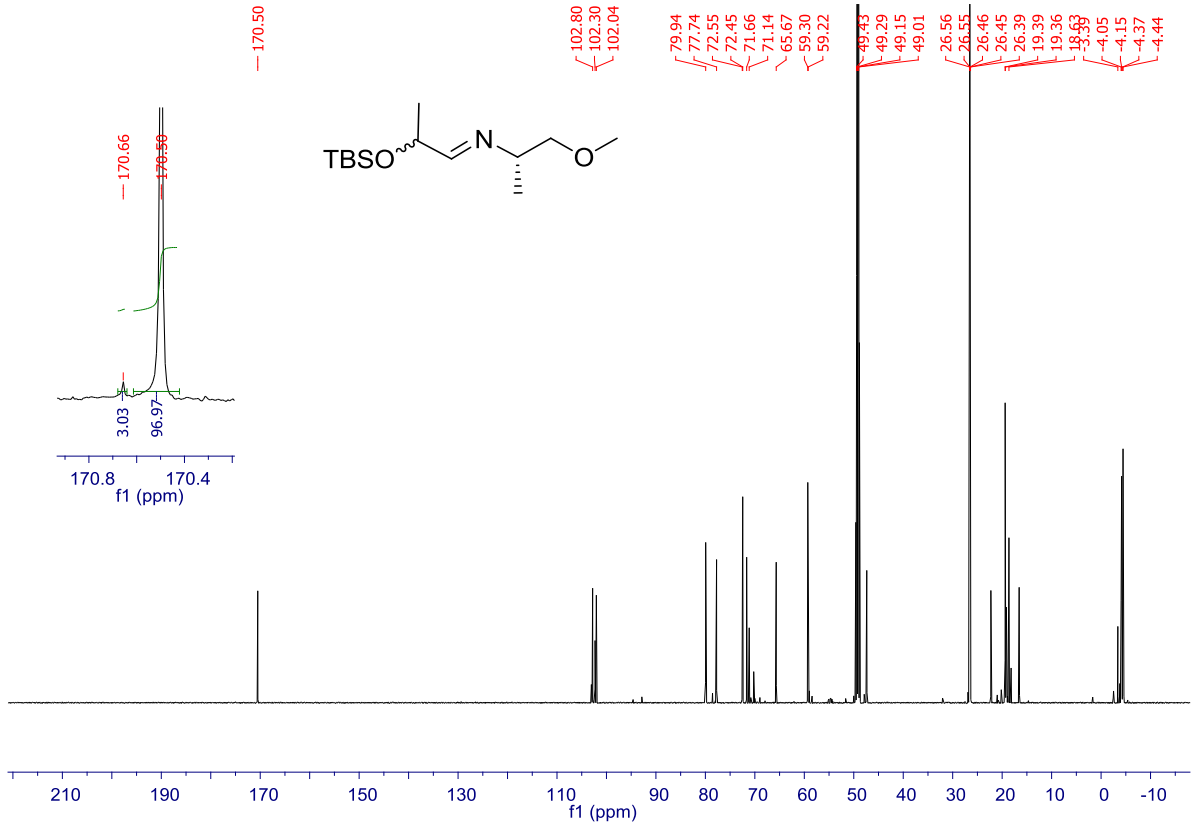
(*S*)-1-Methoxy-2-propylamine-(15) and (*R*)-4, d_4-MeOH



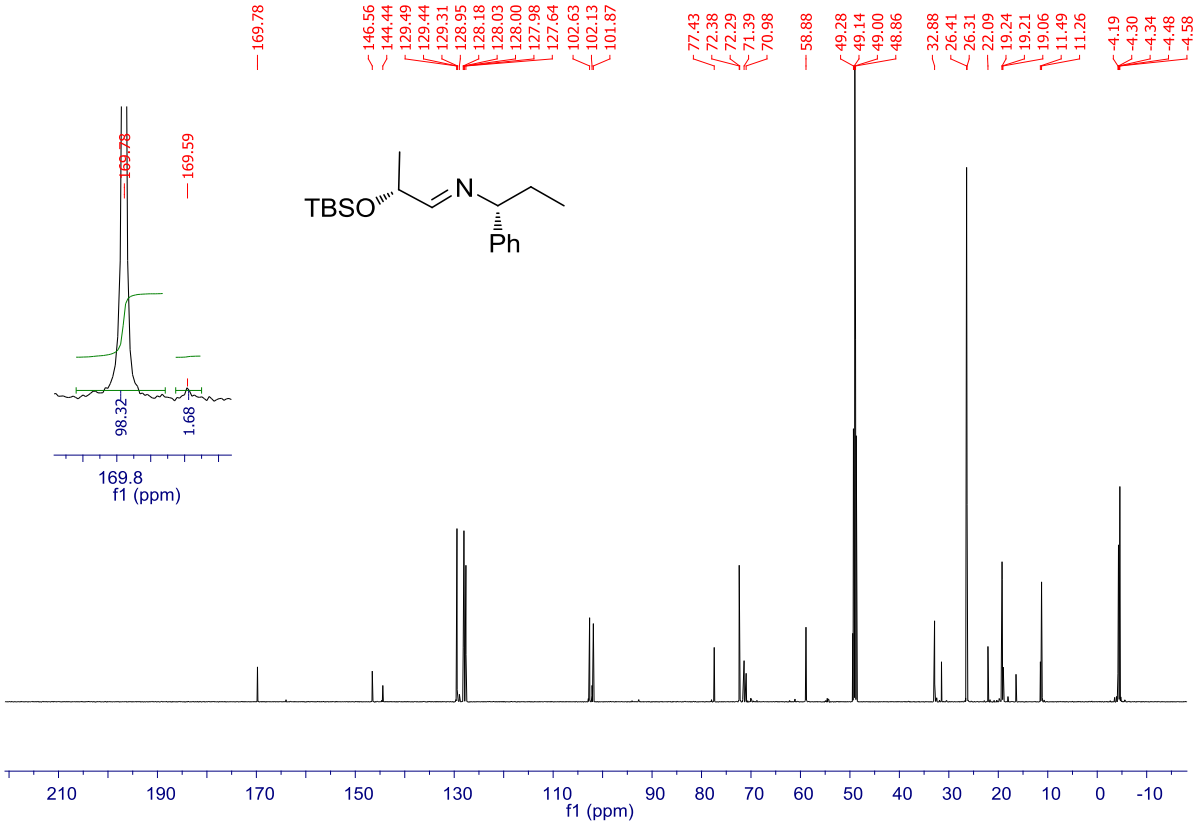
(*S*)- 1-Methoxy-2-propylamine-(15) and (*S*)-4, d_4-MeOH



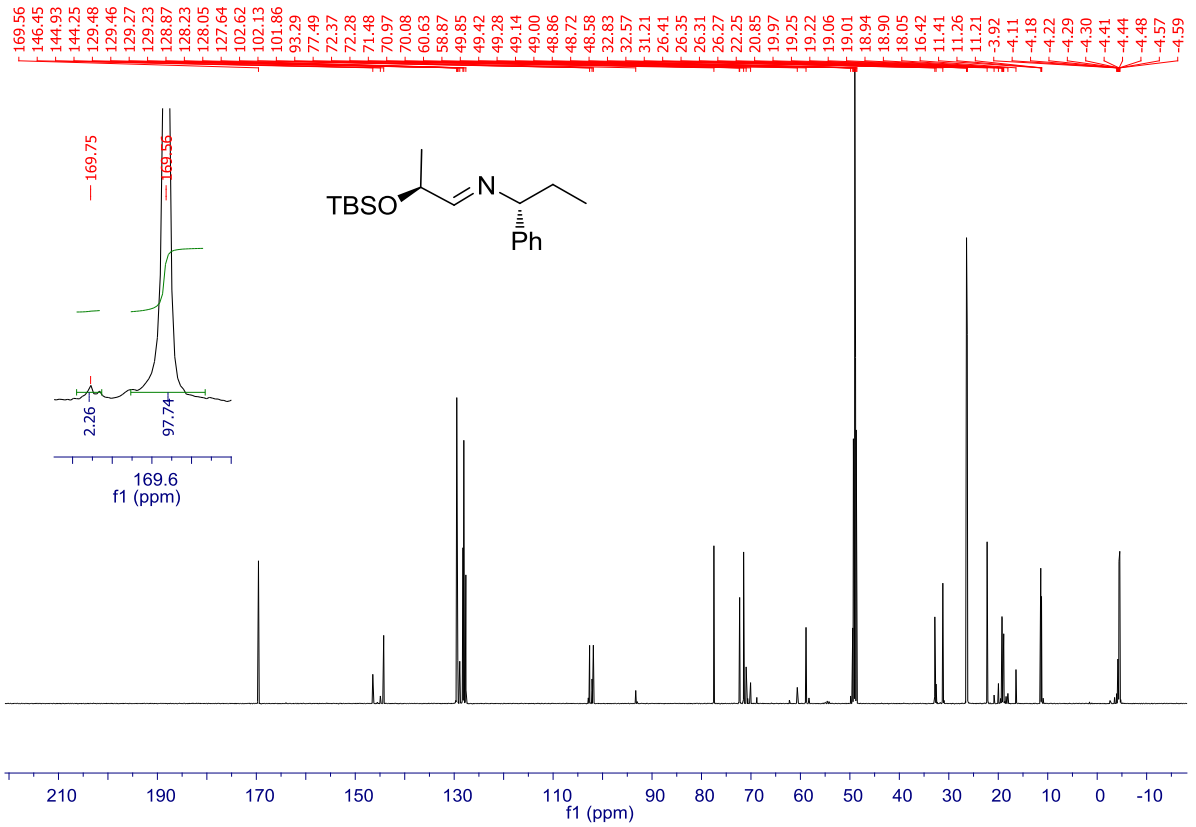
(*S*)- 1-Methoxy-2-propylamine-(15) and (*R*)-4:(*S*)-4 3:97



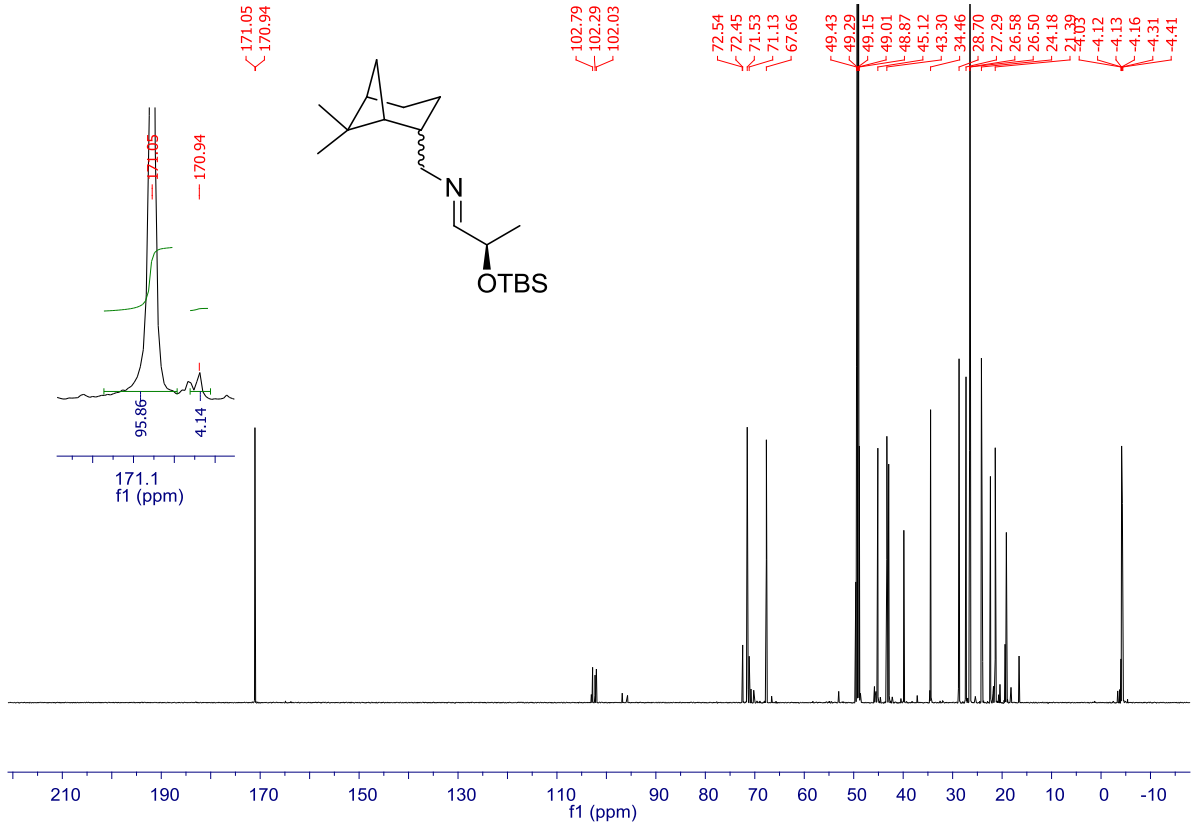
(*R*)-(+)-α-Ethylbenzylamine-(16) and (*R*)-4, d_4-MeOH



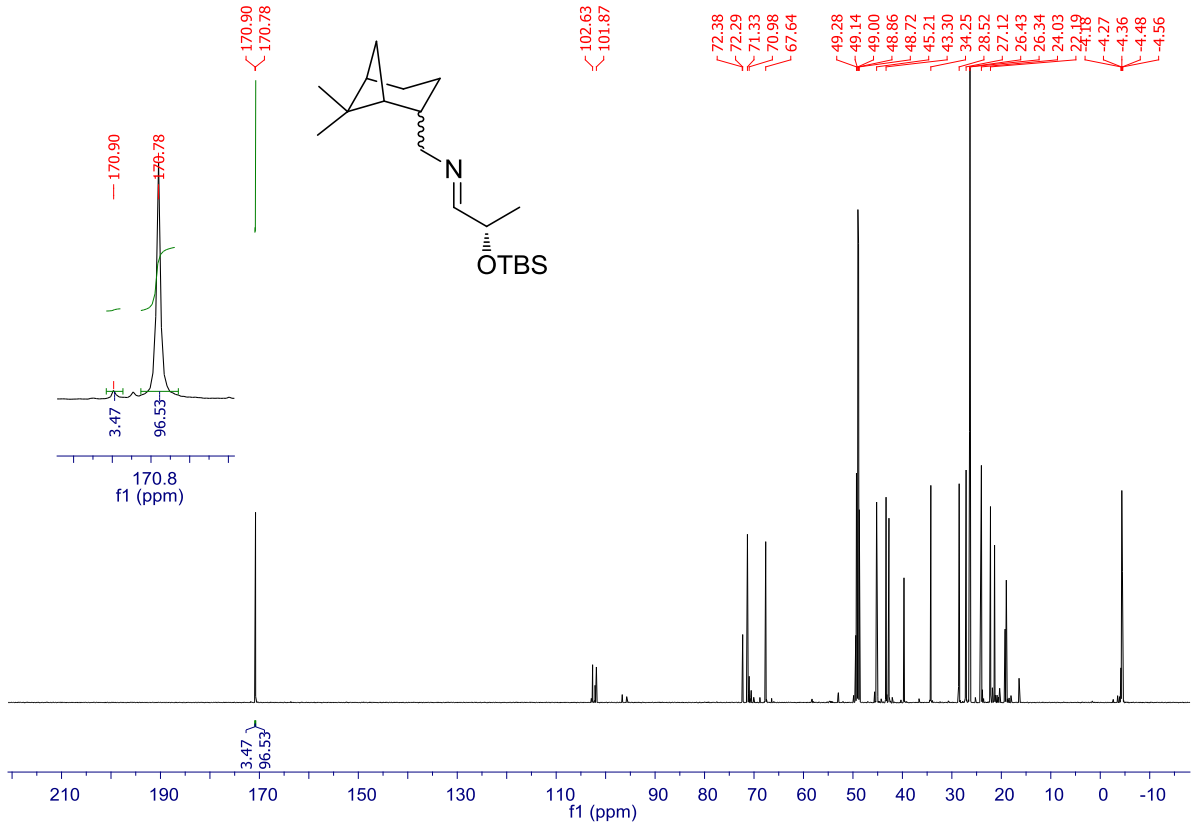
(*R*)-(+)-α-Ethylbenzylamine-(16) and (*S*)-4, d_4-MeOH



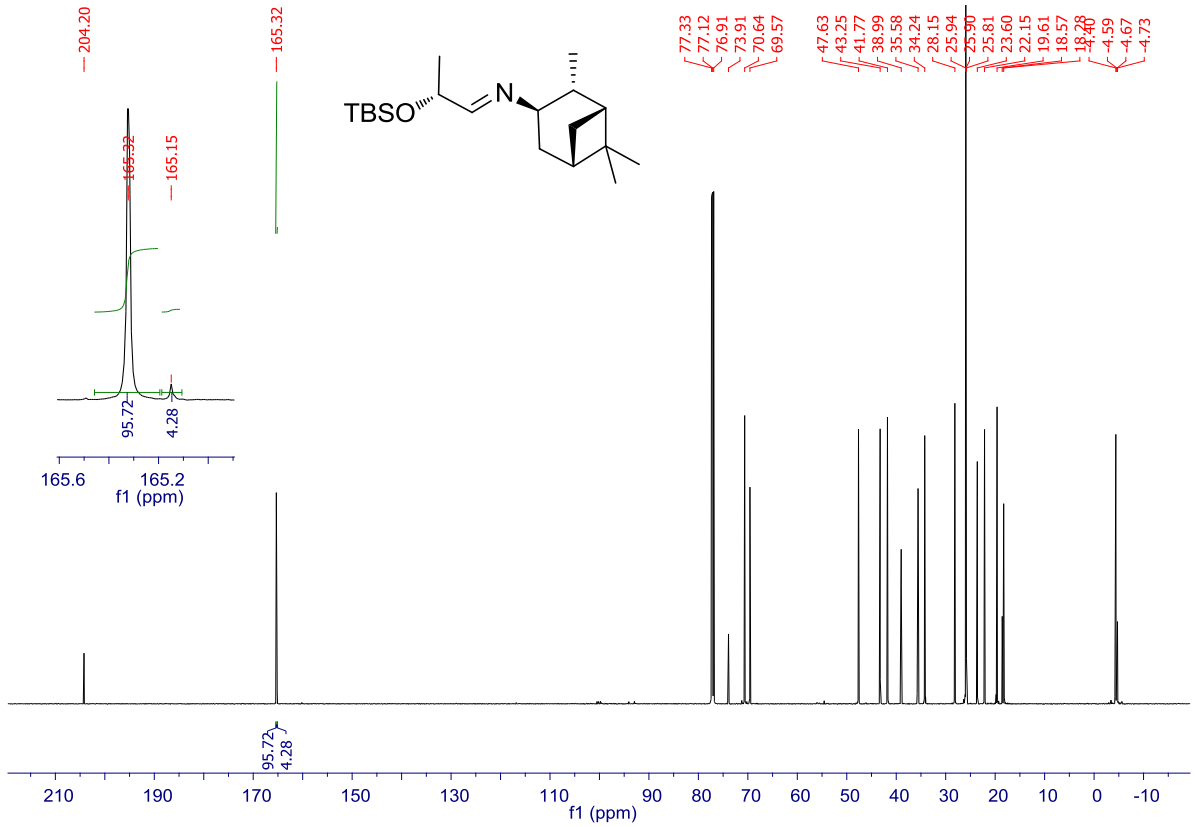
(−)-*cis*-Myrtanylamine (±)-(17) and (*R*)-4, d_4-MeOH



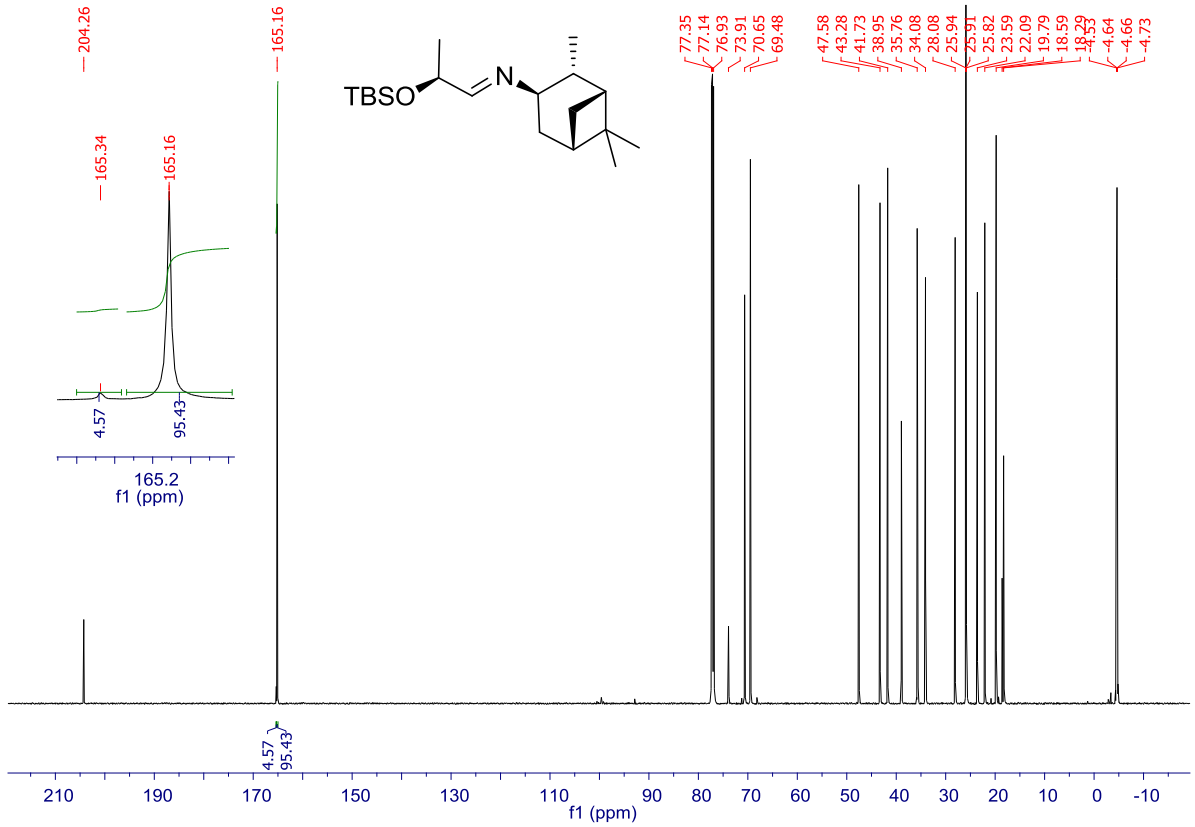
(−)-*cis*-Myrtanylamine(±)-(17) and (*S*)-4, d_4-MeOH



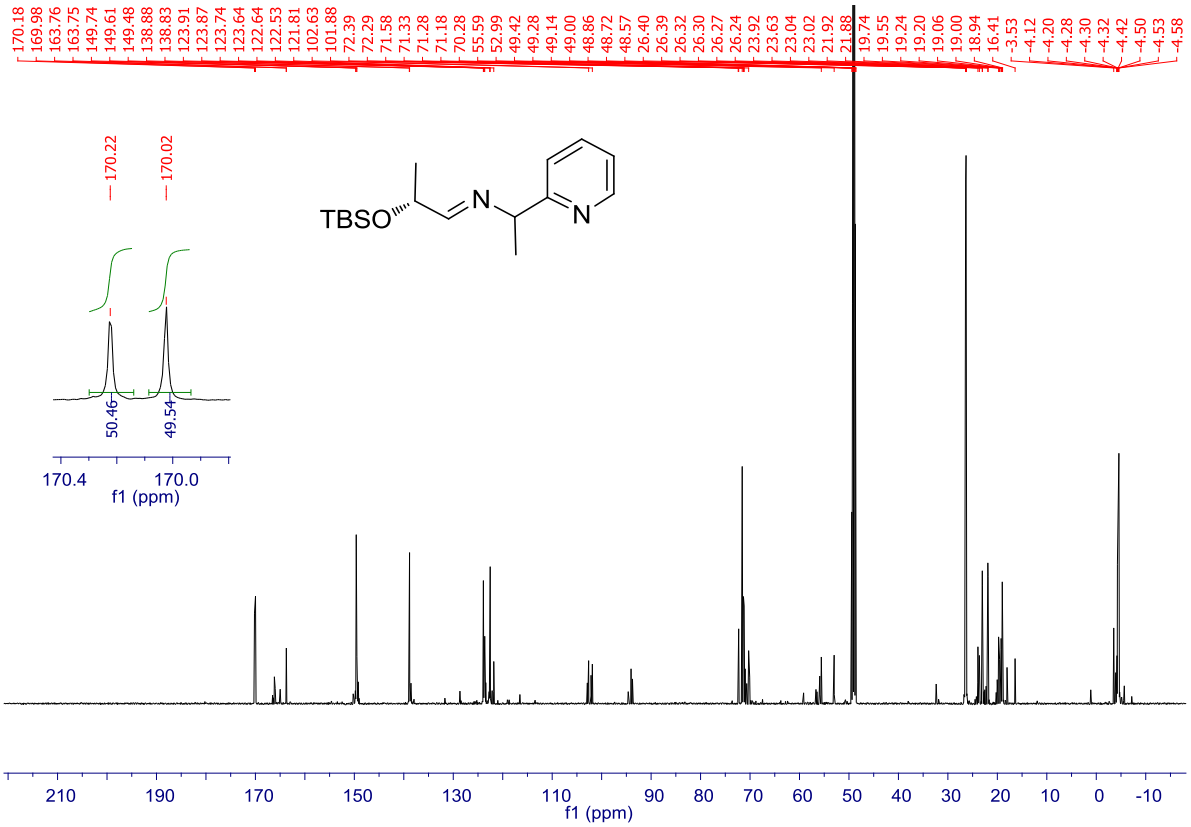
(1*R*,2*R*,3*R*,5*S*)-(−)-Isopinocampheylamine-(18) and (*R*)-4, $CDCl_3$



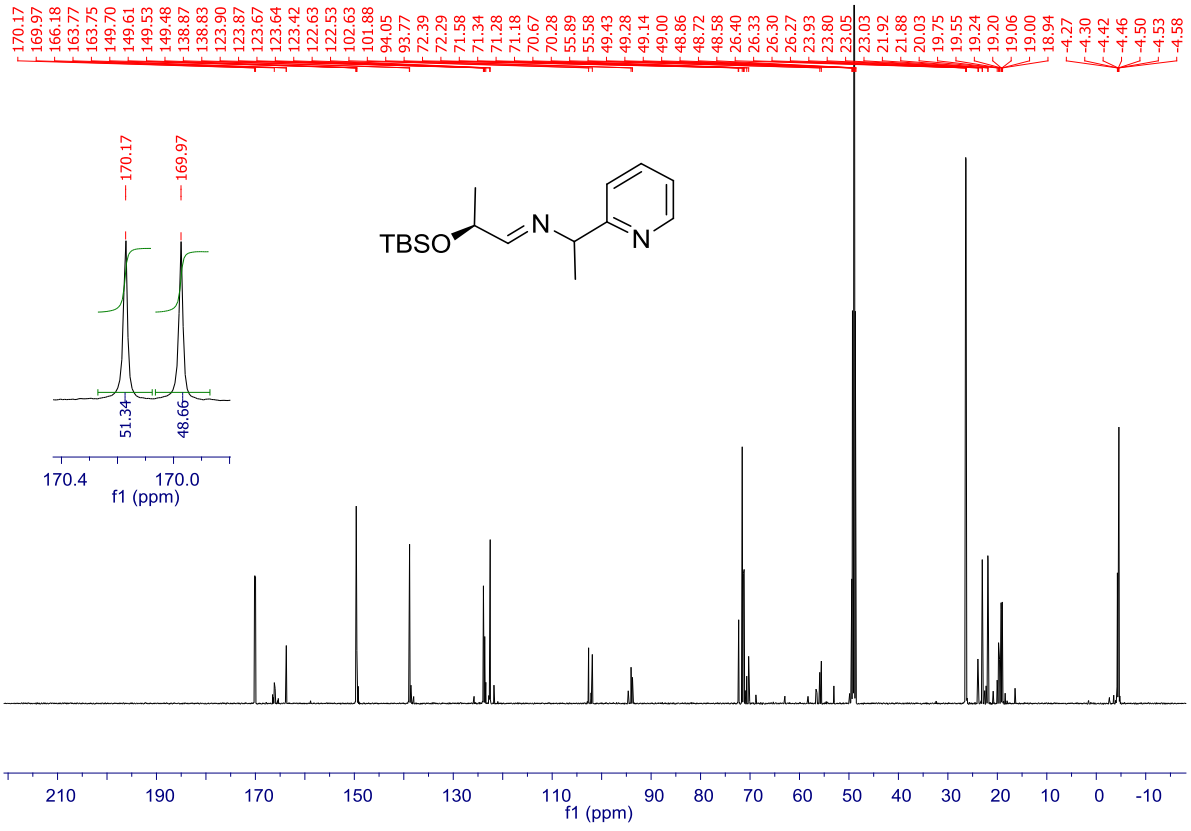
(1*R*,2*R*,3*R*,5*S*)-(−)-Isopinocampheylamine-(18) and (*S*)-4, $CDCl_3$



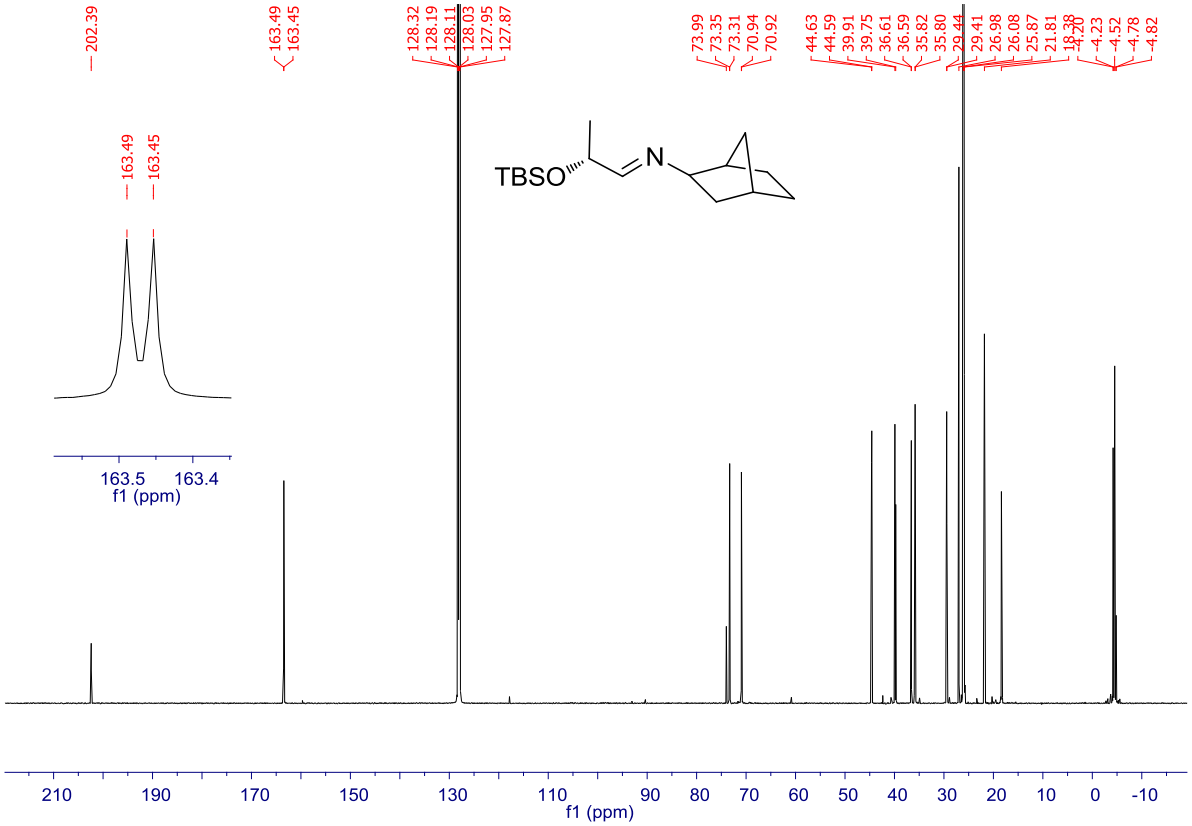
(±)-2-(1-Aminoethyl)pyridine-(19) and (*R*)-4, d_4-MeOH



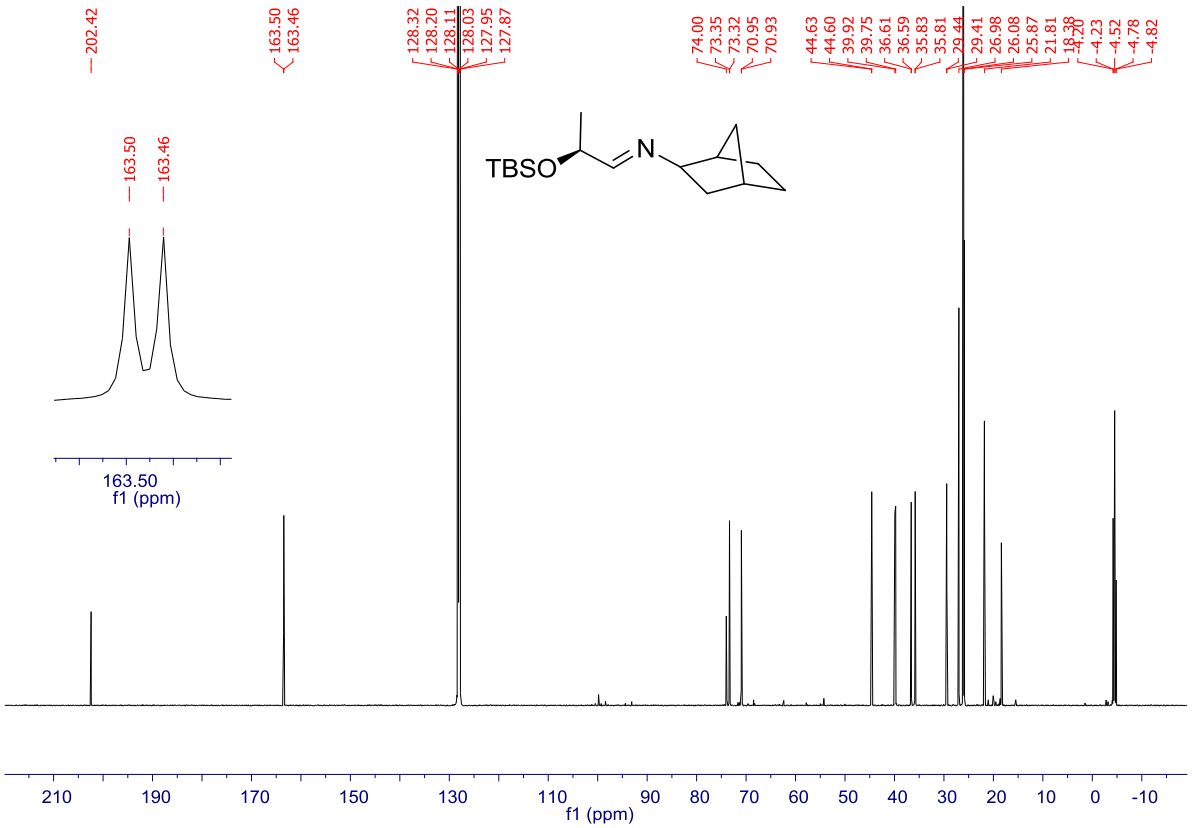
(±)-2-(1-Aminoethyl)pyridine-(19) and (*S*)-4, d_4-MeOH



(±)-exo-2-Aminonorbornane-(20) and (*R*)-4, C_6D_6



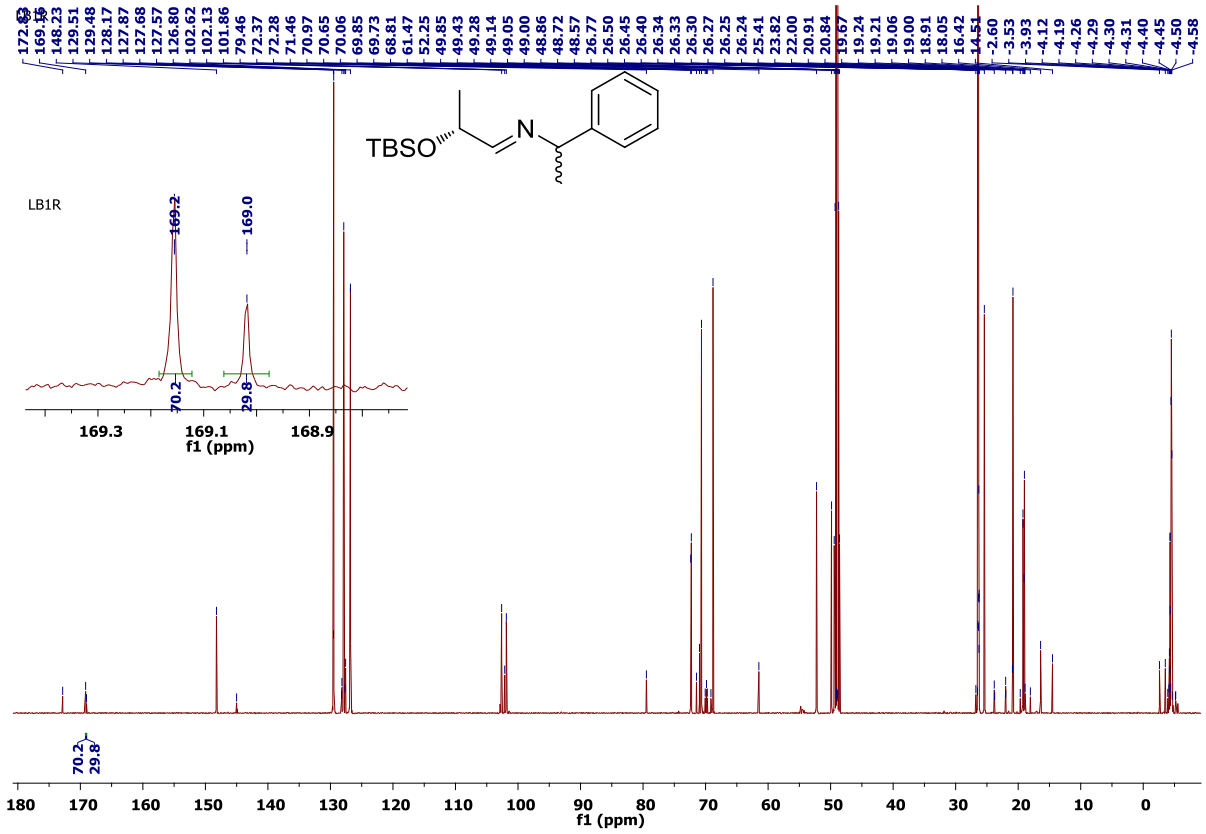
(±)-exo-2-Aminonorbornane-(20) and (*S*)-4, C_6D_6

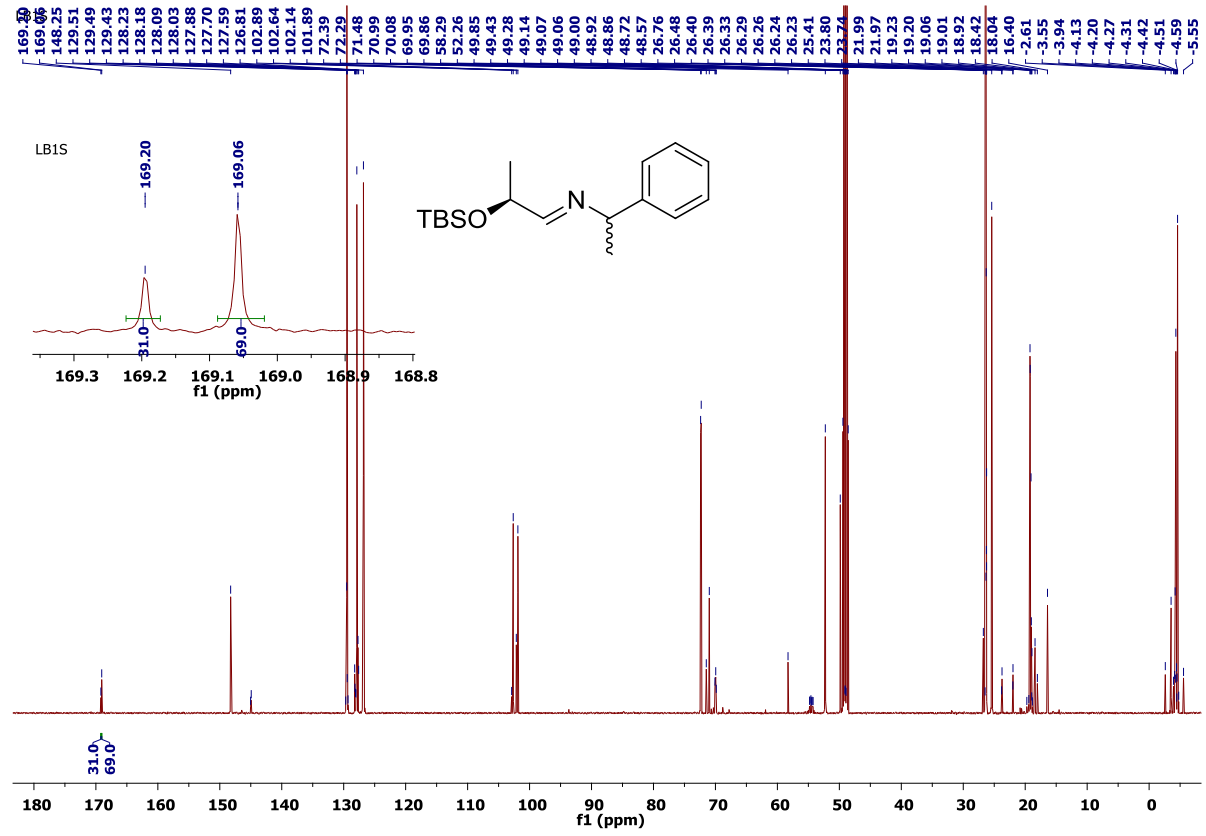


Analysis of 'Unknown' Samples (Table 3)

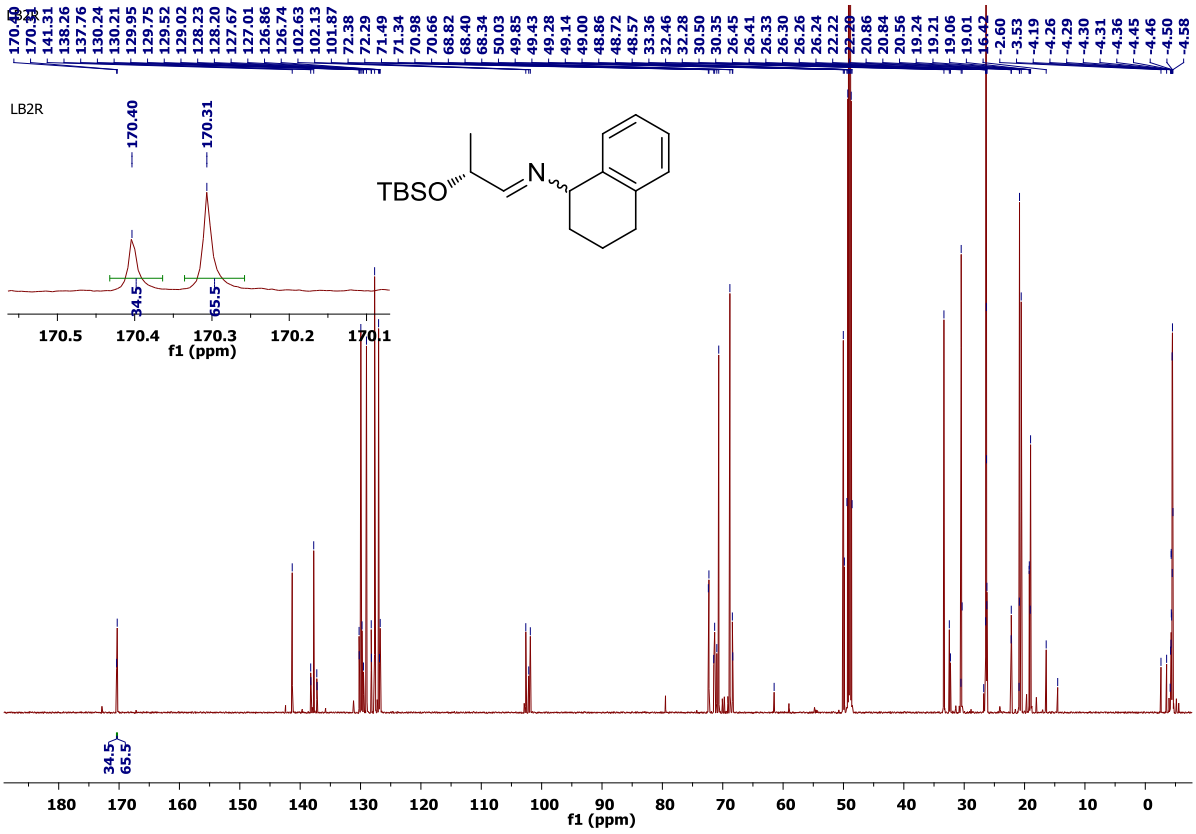
Sample	Prepared by	Actual er *R*:*S*	Researcher 1		Researcher 2	
			(*S*)-4	(*R*)-4	(*S*)-4	(*R*)-4
1	*RML*	69:31	*LB*		*SMG*	
			69:31	69:31	70:30	68:32
2	*RML*	34:66	*LB*		*SMG*	
			35:65	35:65	35:65	35:65
3	*RML*	77:23	*LB*		*SMG*	
			78:22	78:22	77:23	79:21
4	*LB*	6:94	*RML*		*SMG*	
			9:91	8:92	10:90	8:92
5	*LB*	86:14	*RML*		*SMG*	
			86:14	87:13	85:15	85:15
6	*LB*	24:76	*RML*		*SMG*	
			24:76	25:75	25:75	25:75
7	*SMG*	89:11	*RML*		*LB*	
			88:12	87:13	87:13	88:12
8	*SMG*	53:47	*RML*		*LB*	
			52:48	53:47	52:48	54:46
9	*SMG*	16:84	*RML*		*LB*	
			18:82	17:83	17:83	17:83

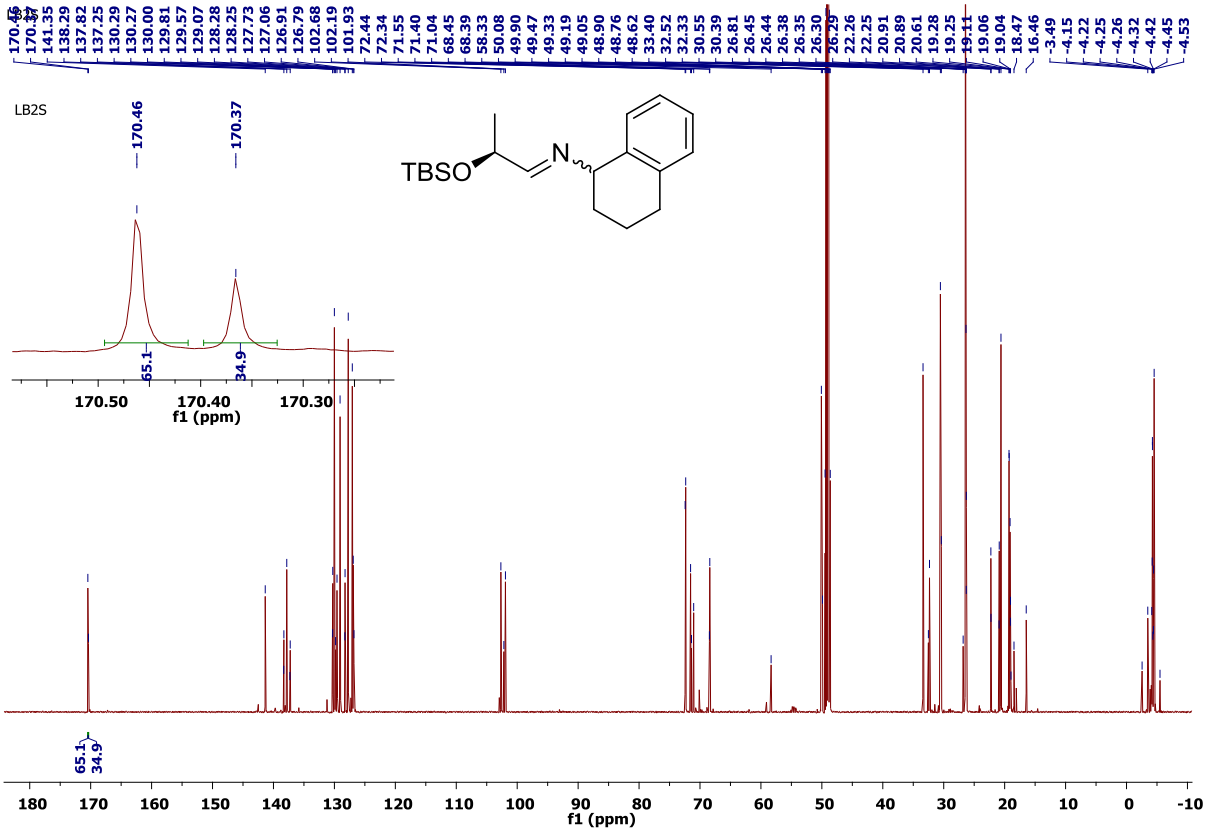
Sample 1 (LB)


LB1R
169.2
169.0
70.2
29.8
169.3
169.1
168.9
f1 (ppm)
TBSO
N
70.2
29.8
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

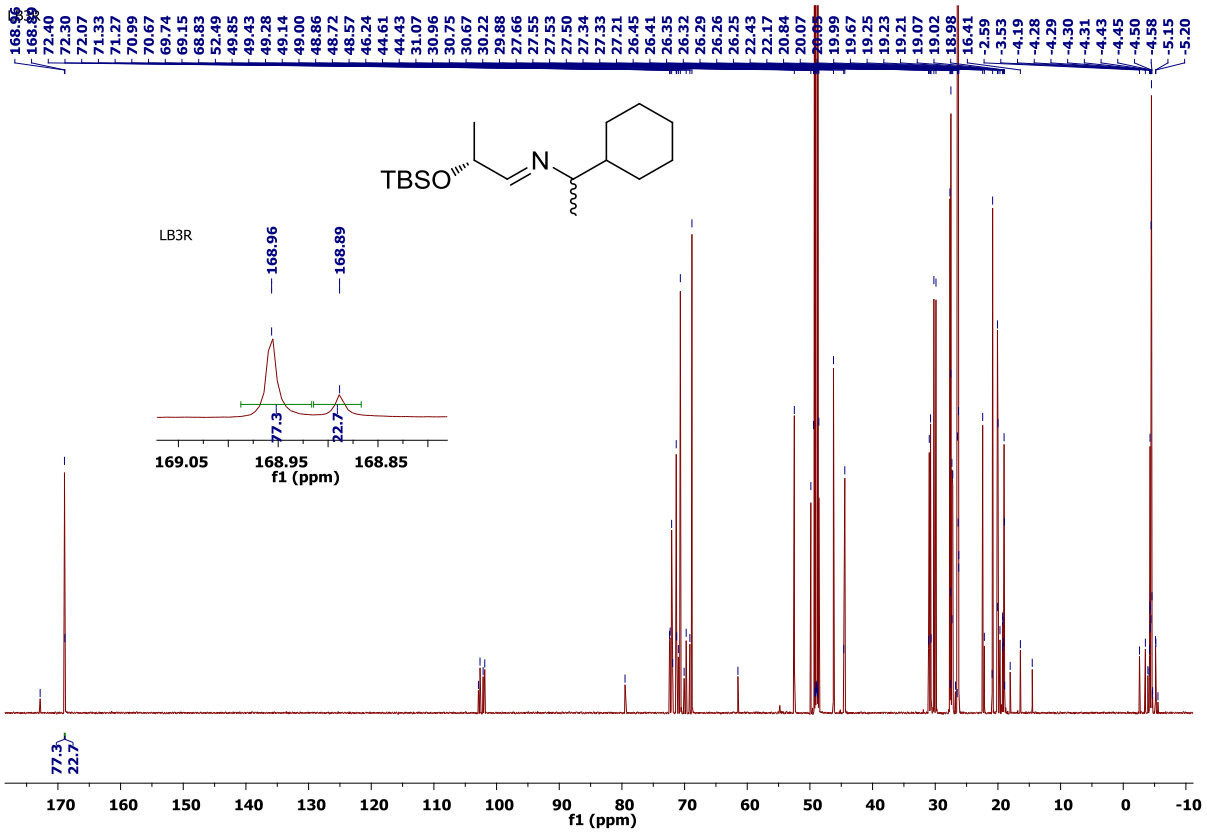

LB1S
169.20
169.06
31.0
69.0
169.3
169.2
169.1
169.0
168.9
168.8
f1 (ppm)
TBSO
N
31.0
69.0
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

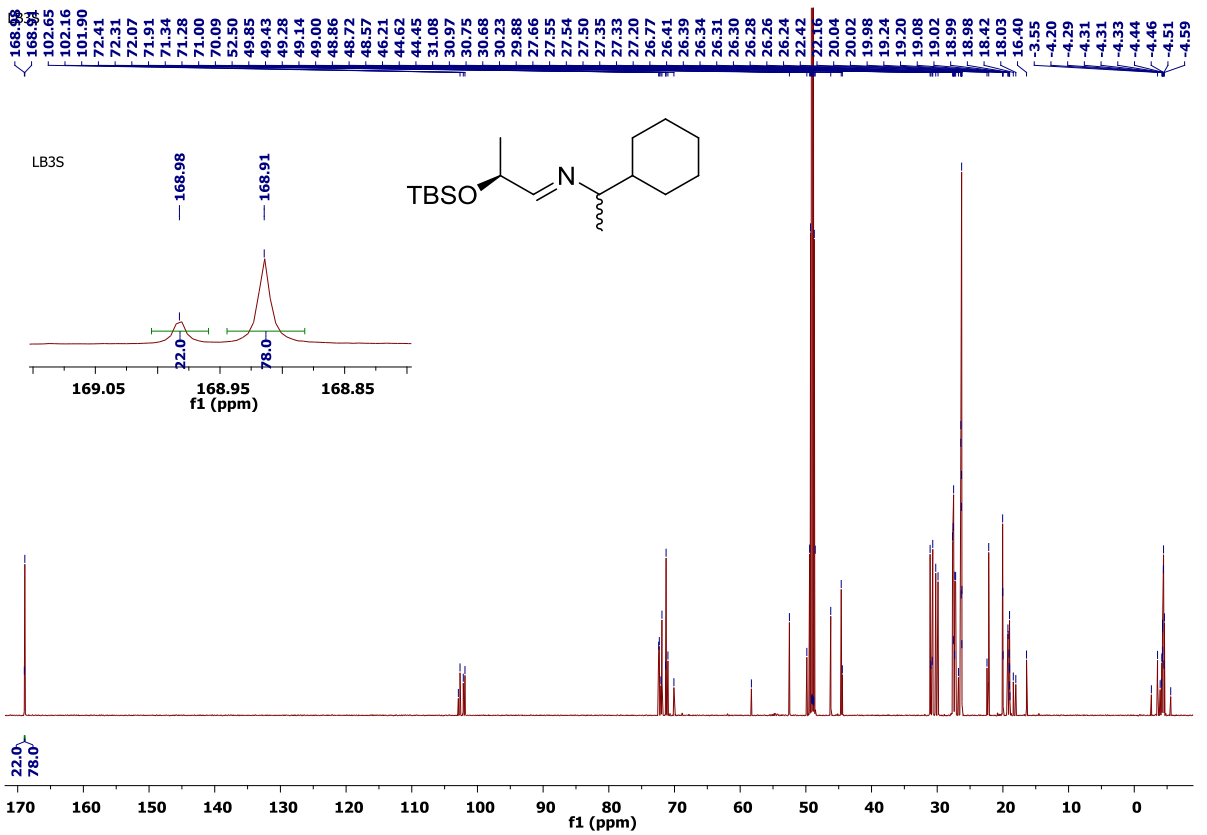
Sample 2 (LB)


LB2R
170.40
170.31
TBSO
N
34.5
65.5
170.5
170.4
170.3
170.2
170.1
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

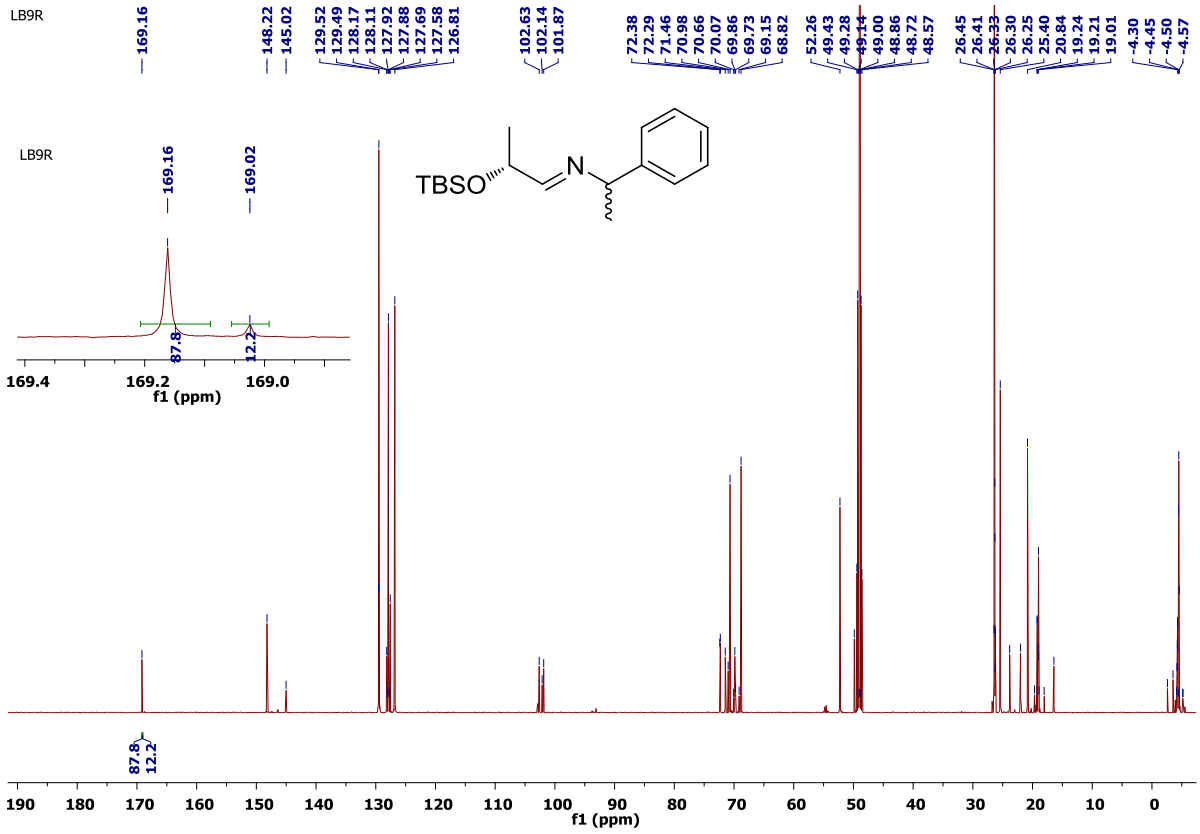

LB2S
170.46
170.37
TBSO
N
65.1
34.9
170.50
170.40
170.30
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

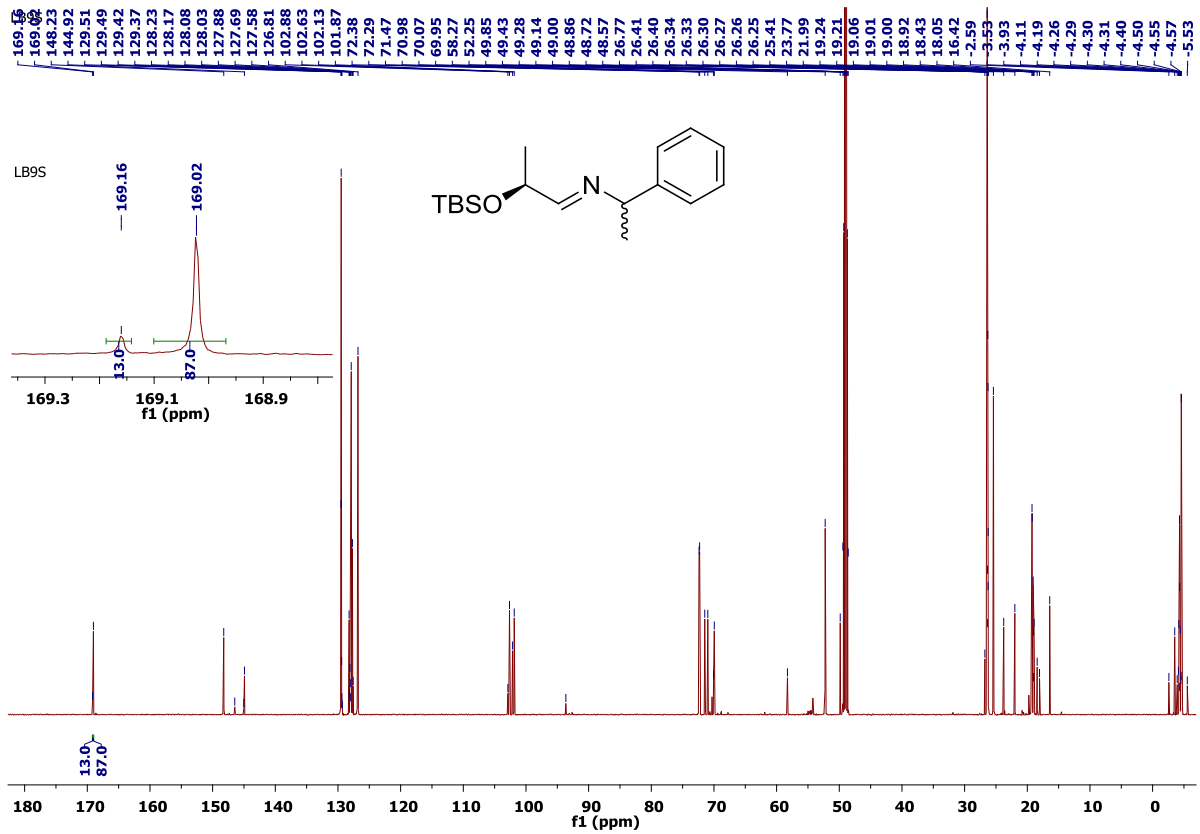
Sample 3 (LB)


TBSO
N
LB3R
168.96
168.89
77.3
22.7
169.05
168.95
168.85
f1 (ppm)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

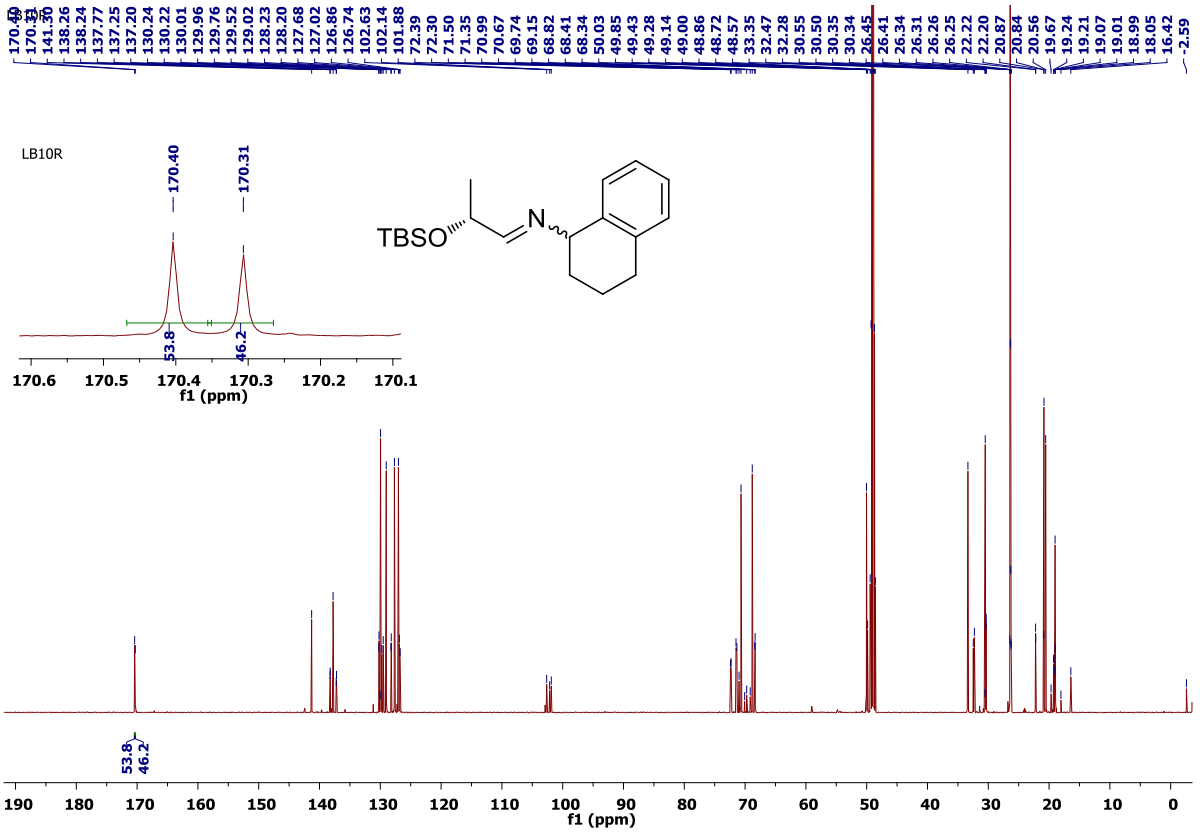

TBSO
N
LB3S
168.98
168.91
22.0
78.0
169.05
168.95
168.85
f1 (ppm)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

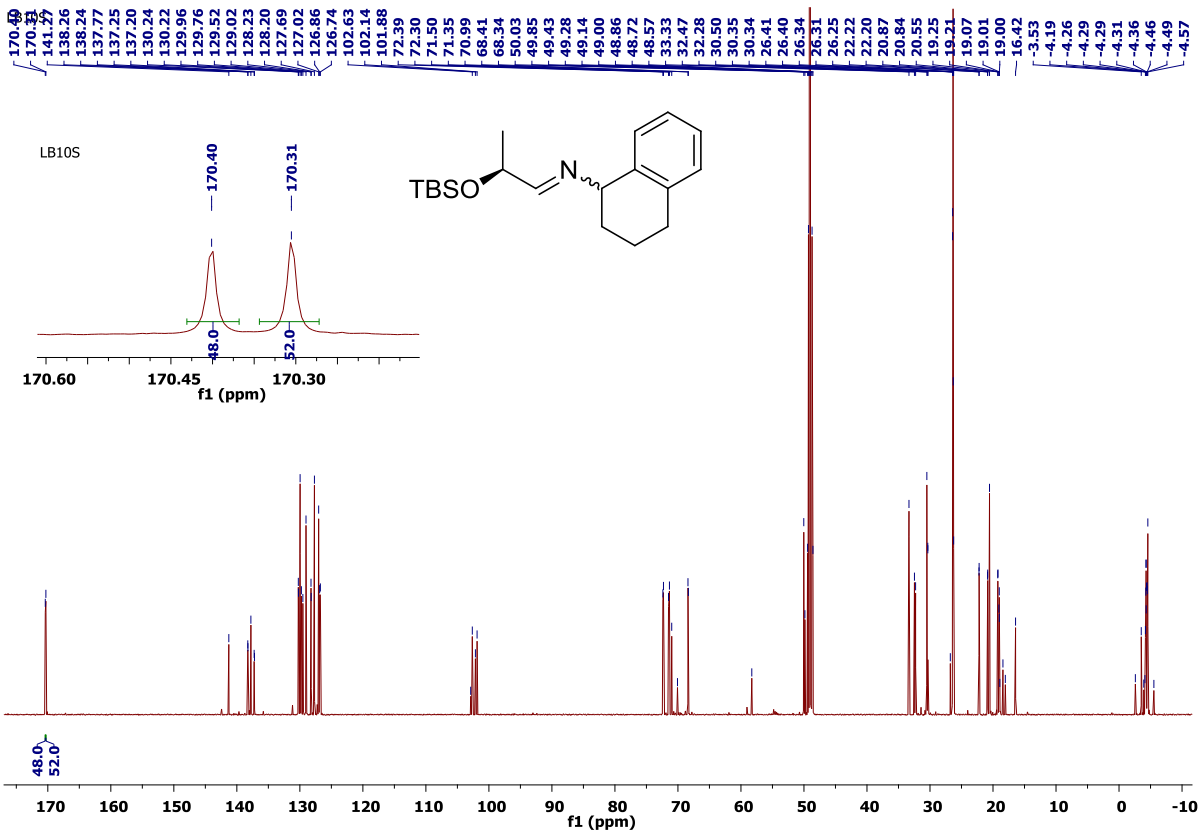
Sample 7 (LB)


LB9R
169.16
148.22
145.02
129.52
129.49
128.17
128.11
127.92
127.88
127.69
127.58
126.81
102.63
102.14
101.87
72.38
72.29
71.46
70.98
70.66
70.07
69.86
69.73
69.15
68.82
52.26
49.43
49.28
49.14
49.00
48.86
48.72
48.57
26.45
26.41
26.33
26.30
26.25
25.40
20.84
19.24
19.21
19.01
-4.30
-4.45
-4.50
-4.57
LB9R
169.16
169.02
87.8
12.2
169.4
169.2
169.0
f1 (ppm)
TBSO
N
87.8
12.2
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

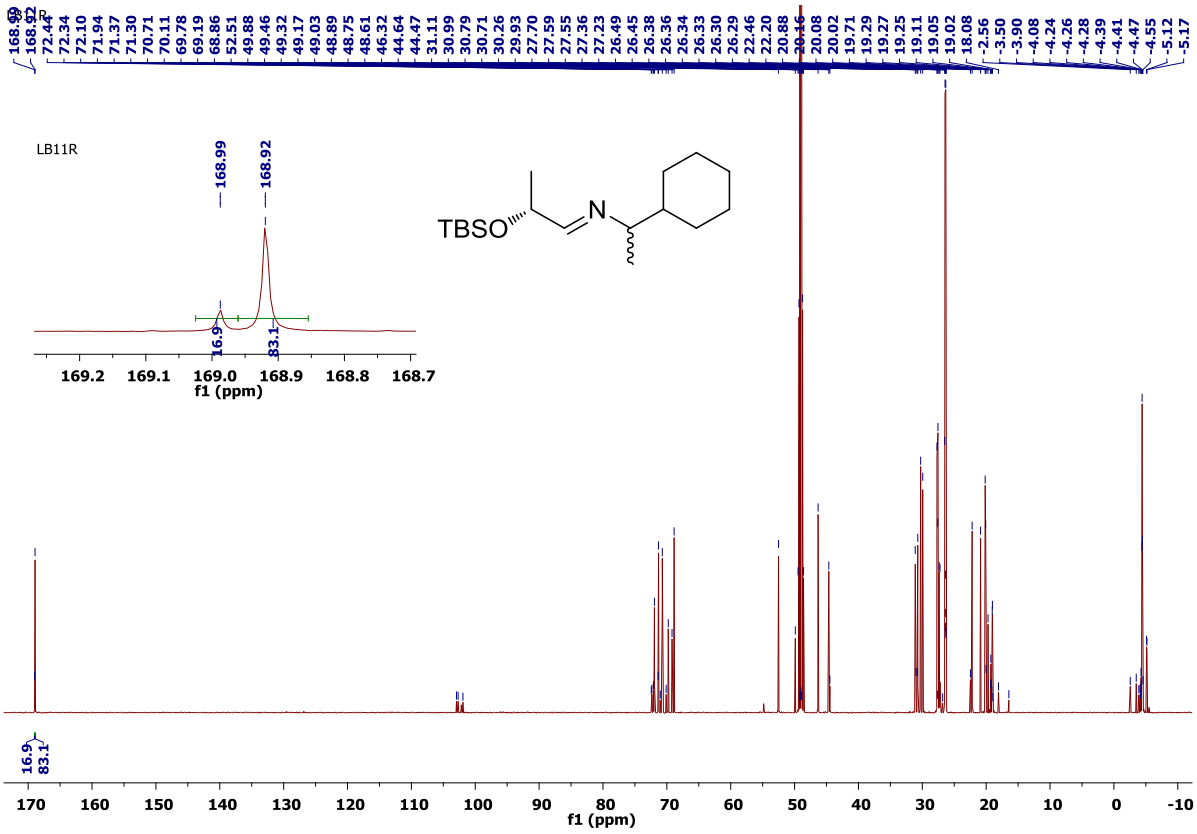

LB9S
169.16
169.02
13.0
87.0
169.3
169.1
168.9
f1 (ppm)
TBSO
N
13.0
87.0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

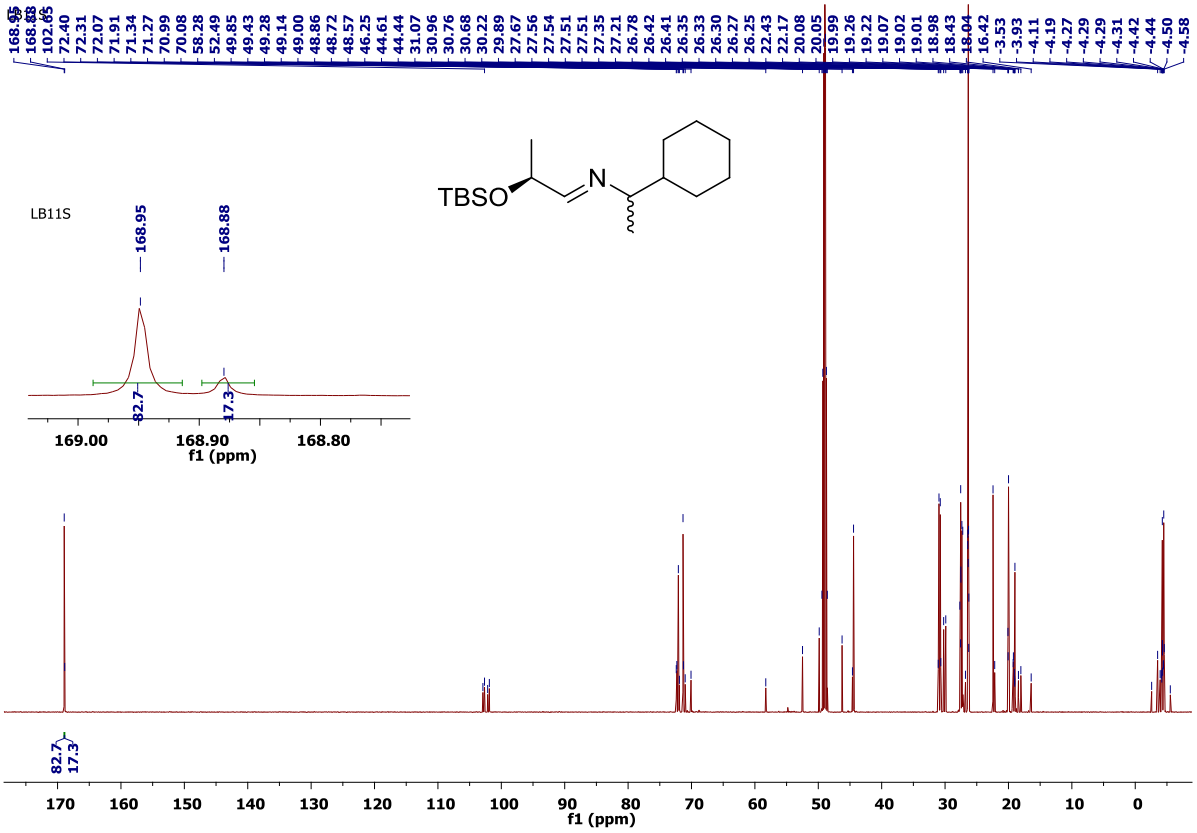
Sample 8 (LB)


LB10R
170.40
170.31
TBSO
N
53.8
46.2
170.6
170.5
170.4
170.3
170.2
170.1
f1 (ppm)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

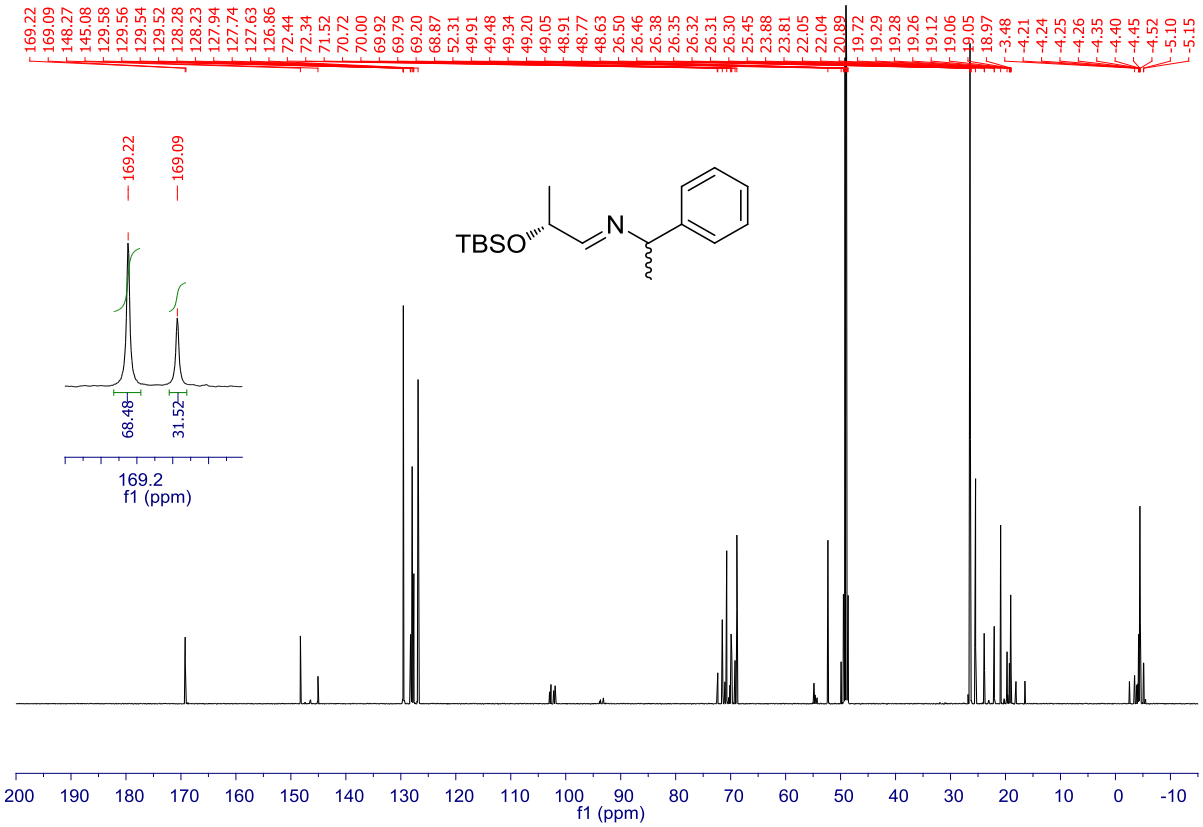

LB10S
170.40
170.31
TBSO
N
48.0
52.0
170.60
170.45
170.30
f1 (ppm)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

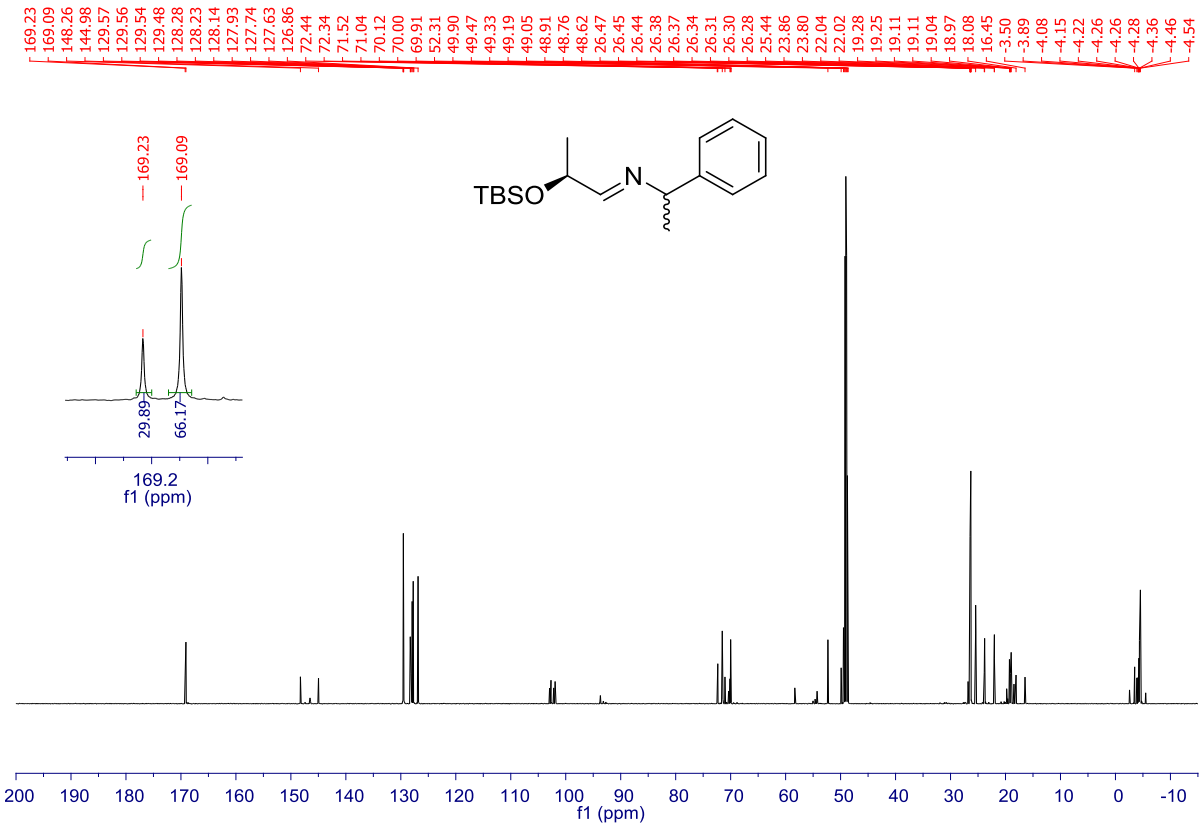
Sample 9 (LB)


LB11R
168.99
168.92
TBSO
N
16.9
83.1
f1 (ppm)

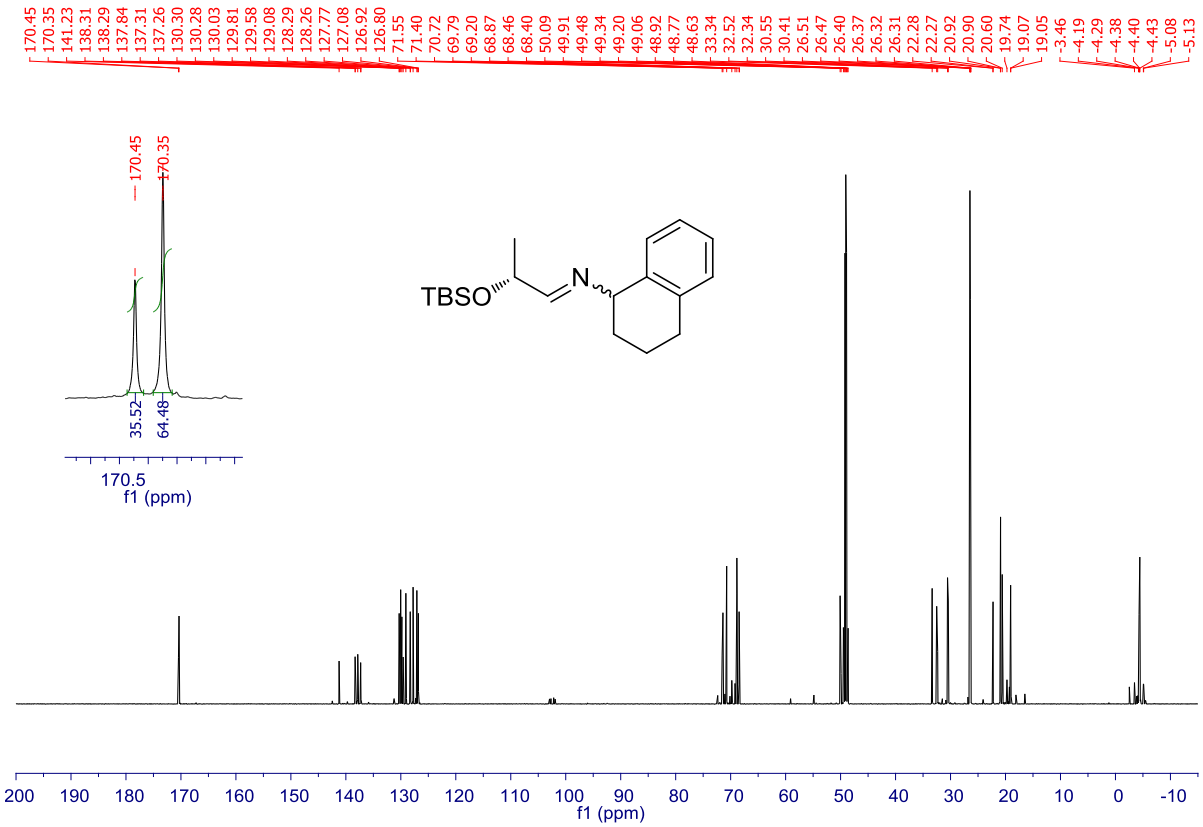

LB11S
168.95
168.88
TBSO
N
82.7
17.3
f1 (ppm)

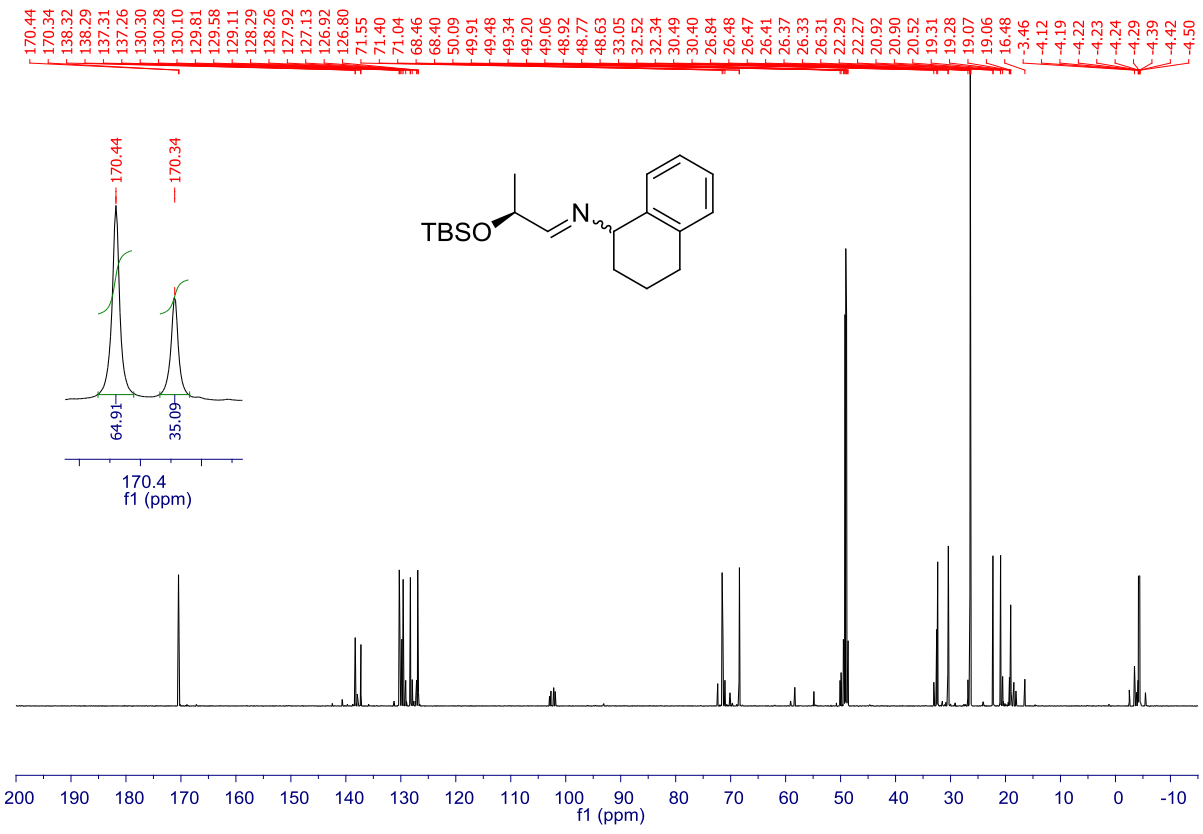
Sample 1 (SMG)


169.22
169.09
148.27
145.08
129.58
129.56
129.54
129.52
128.28
128.23
127.94
127.74
127.63
126.86
72.44
72.34
71.52
70.72
70.00
69.92
69.79
69.20
68.87
52.31
49.91
49.48
49.34
49.20
49.05
48.91
48.77
48.63
26.50
26.46
26.38
26.35
26.32
26.31
26.30
25.45
23.88
23.81
22.05
22.04
20.89
19.72
19.29
19.28
19.26
19.12
19.06
19.05
18.97
-3.48
-4.21
-4.24
-4.25
-4.26
-4.35
-4.40
-4.45
-4.52
-5.10
-5.15
169.22
169.09
68.48
31.52
169.2
f1 (ppm)
TBSO
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

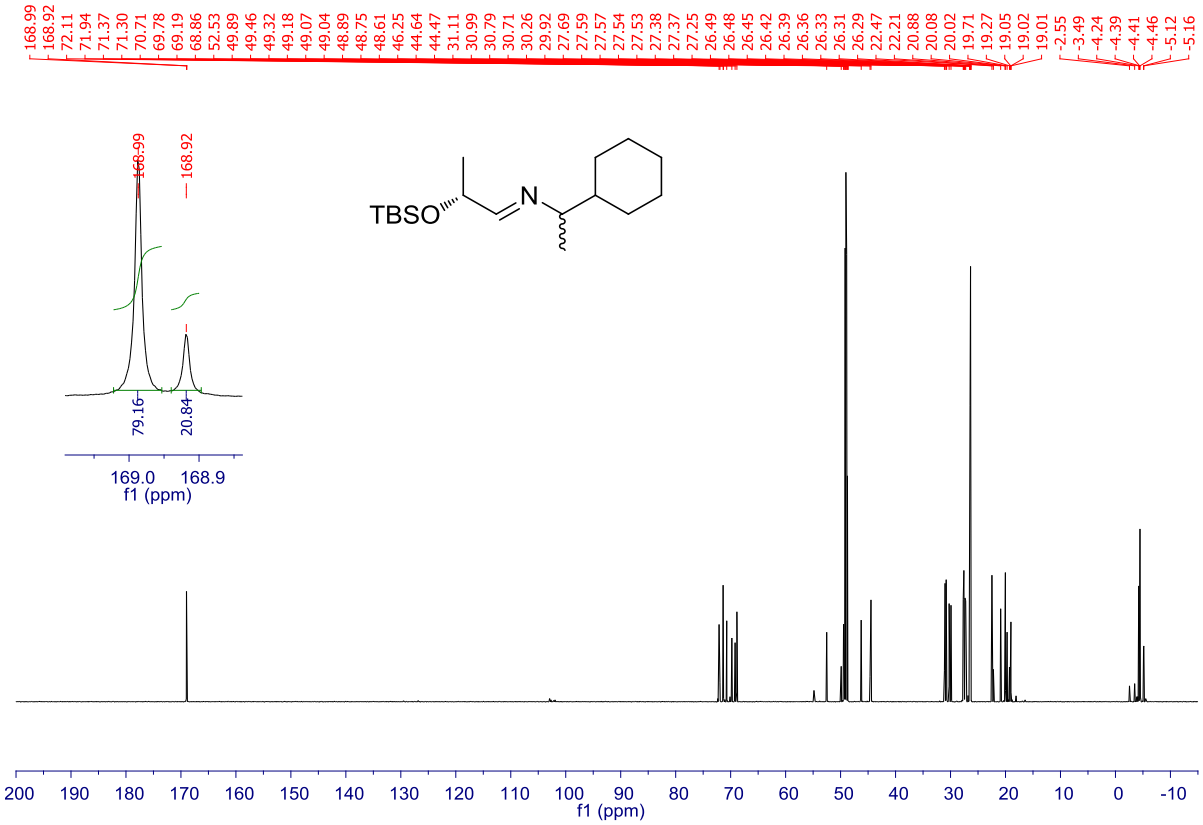

169.23
169.09
148.26
144.98
129.57
129.56
129.54
129.48
128.28
128.23
128.14
127.93
127.74
127.63
126.86
72.44
72.34
71.52
71.04
70.12
70.00
69.91
52.31
49.90
49.47
49.33
49.19
49.05
48.91
48.76
48.62
26.47
26.45
26.44
26.38
26.37
26.34
26.31
26.30
26.28
25.44
23.86
23.80
22.04
22.02
19.28
19.25
19.11
19.11
19.04
18.97
18.08
16.45
-3.50
-3.89
-4.08
-4.15
-4.22
-4.26
-4.26
-4.28
-4.36
-4.46
-4.54
169.23
169.09
29.89
66.17
169.2
f1 (ppm)
TBSO
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

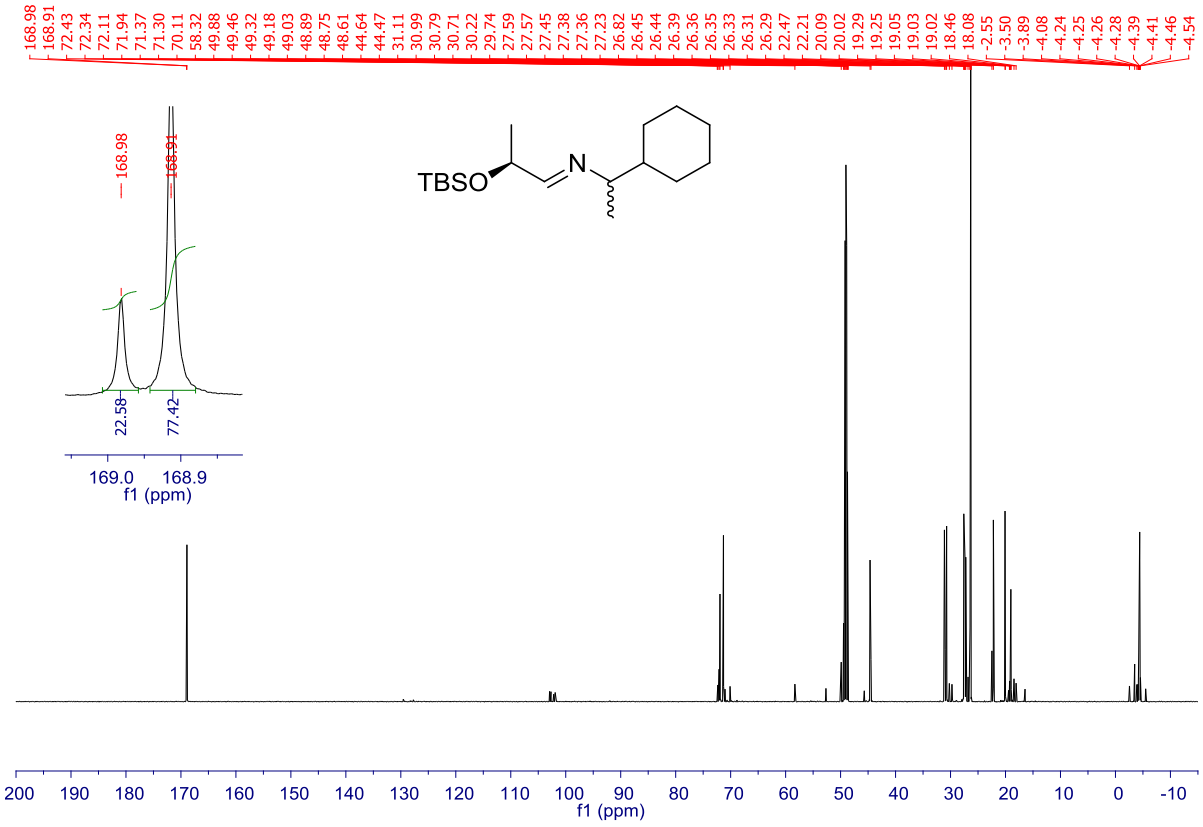
Sample 2 (SMG)


170.45
170.35
141.23
138.31
138.29
137.84
137.31
137.26
130.30
130.28
130.03
129.81
129.58
129.08
128.29
128.26
127.77
127.08
126.92
126.80
71.55
71.40
70.72
69.79
69.20
68.87
68.46
68.40
50.09
49.91
49.48
49.34
49.20
49.06
48.92
48.77
48.63
33.34
32.52
32.34
30.55
30.41
26.51
26.47
26.40
26.37
26.32
26.31
22.28
22.27
20.92
20.90
20.60
19.74
19.07
19.05
-3.46
-4.19
-4.29
-4.38
-4.40
-4.43
-5.08
-5.13
170.45
170.35
35.52
64.48
170.5
f1 (ppm)
TBSO
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

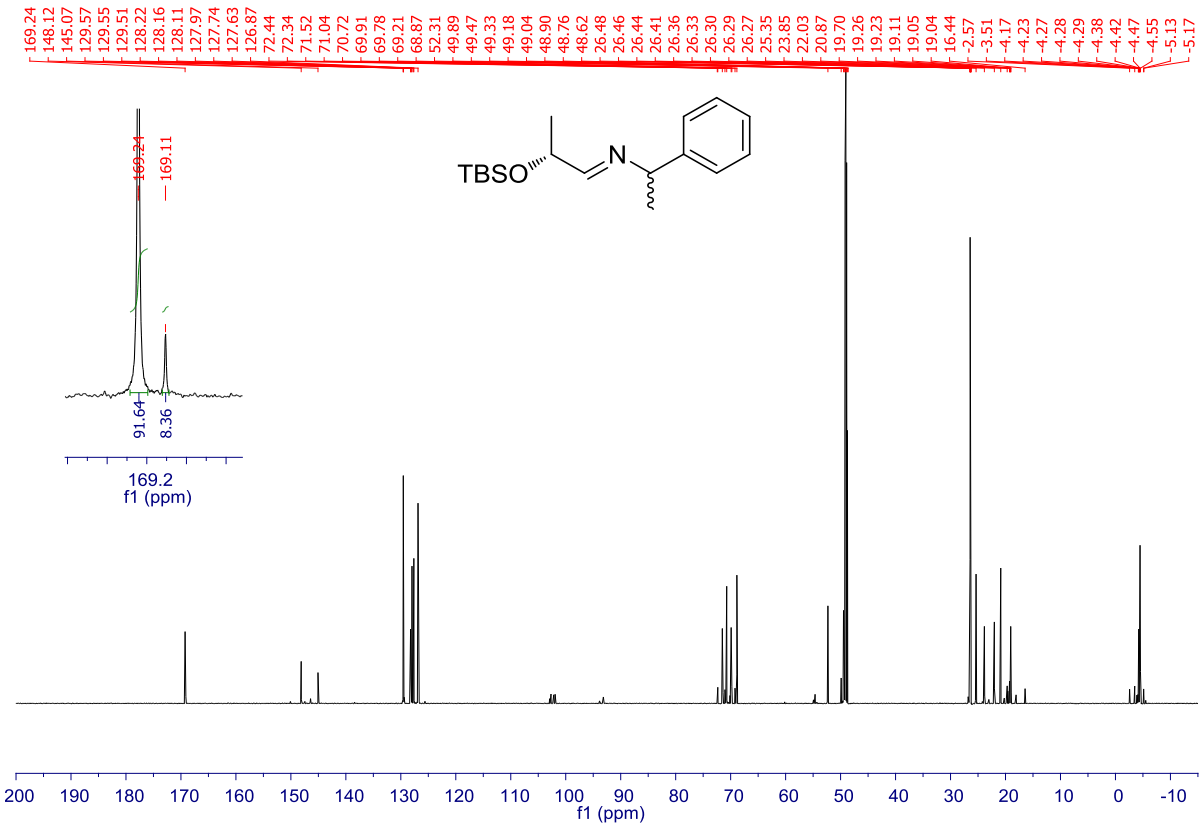

170.44
170.34
138.32
138.29
137.31
137.26
130.30
130.28
130.10
129.81
129.58
129.11
128.29
128.26
127.92
127.13
126.92
126.80
71.55
71.40
71.04
68.46
68.40
50.09
49.91
49.48
49.34
49.20
49.06
48.92
48.77
48.63
33.05
32.52
32.34
30.49
30.40
26.84
26.48
26.47
26.41
26.37
26.33
26.31
22.29
22.27
20.92
20.90
20.52
19.31
19.28
19.07
19.06
16.48
-3.46
-4.12
-4.19
-4.22
-4.23
-4.24
-4.29
-4.39
-4.42
-4.50
170.44
170.34
64.91
35.09
170.4
f1 (ppm)
TBSO
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

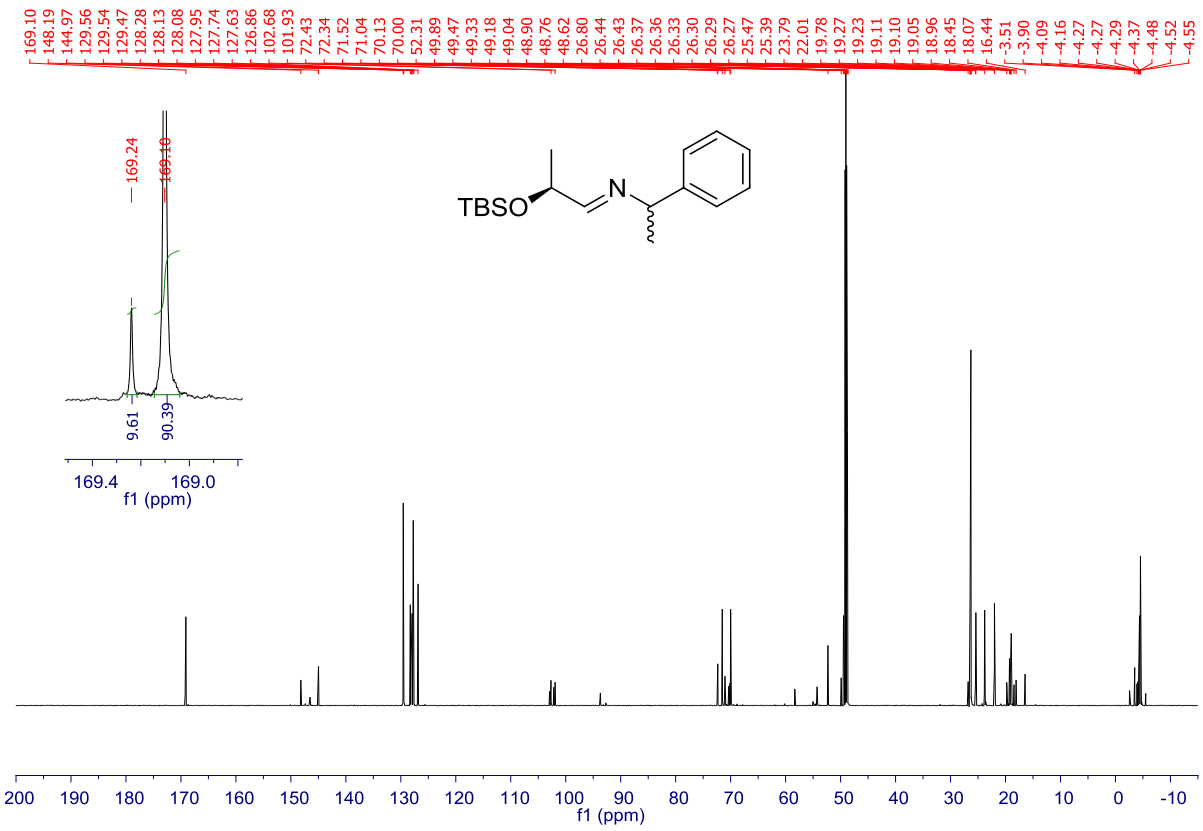
Sample 3 (SMG)


168.99
168.92
72.11
71.94
71.37
71.30
70.71
69.78
69.19
68.86
52.53
49.89
49.46
49.32
49.18
49.07
49.04
48.89
48.75
48.61
46.25
44.64
44.47
31.11
30.99
30.79
30.71
30.26
29.92
27.69
27.59
27.57
27.54
27.53
27.38
27.37
27.25
26.49
26.48
26.45
26.42
26.39
26.36
26.33
26.31
26.29
22.47
22.21
20.88
20.08
20.02
19.71
19.27
19.05
19.02
19.01
-2.55
-3.49
-4.24
-4.39
-4.41
-4.46
-5.12
-5.16
168.99
168.92
79.16
20.84
169.0
168.9
f1 (ppm)
TBSO
N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

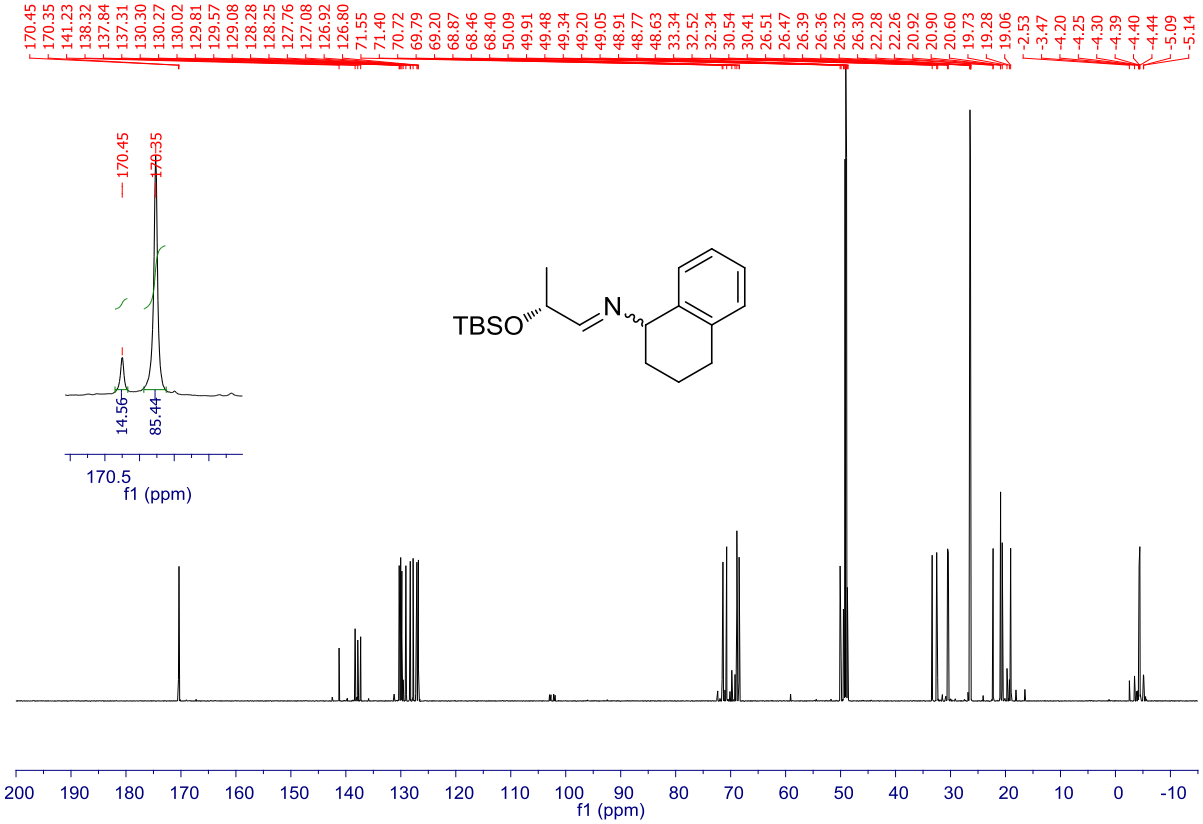

168.98
168.91
72.43
72.34
72.11
71.94
71.37
71.30
70.11
58.32
49.88
49.46
49.32
49.18
49.03
48.89
48.75
48.61
44.64
44.47
31.11
30.99
30.79
30.71
30.22
29.74
27.59
27.57
27.45
27.38
27.36
27.23
26.82
26.45
26.44
26.39
26.36
26.35
26.33
26.31
26.29
22.47
22.21
20.09
20.02
19.29
19.25
19.05
19.03
19.02
18.46
18.08
-2.55
-3.50
-3.89
-4.08
-4.24
-4.25
-4.26
-4.28
-4.39
-4.41
-4.46
-4.54
168.98
168.91
22.58
77.42
169.0
168.9
f1 (ppm)
TBSO
N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

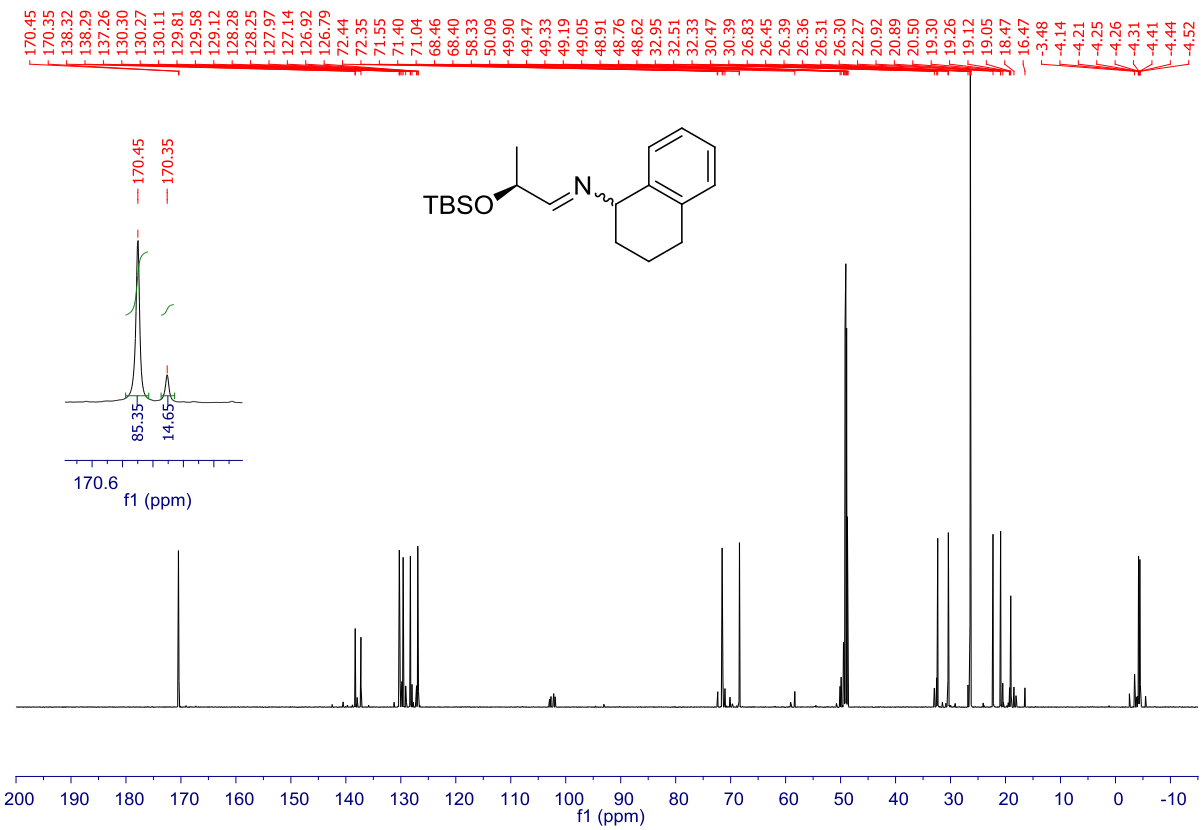
Sample 4 (SMG)


TBSO
N
169.24
169.11
91.64
8.36
169.2
f1 (ppm)
f1 (ppm)

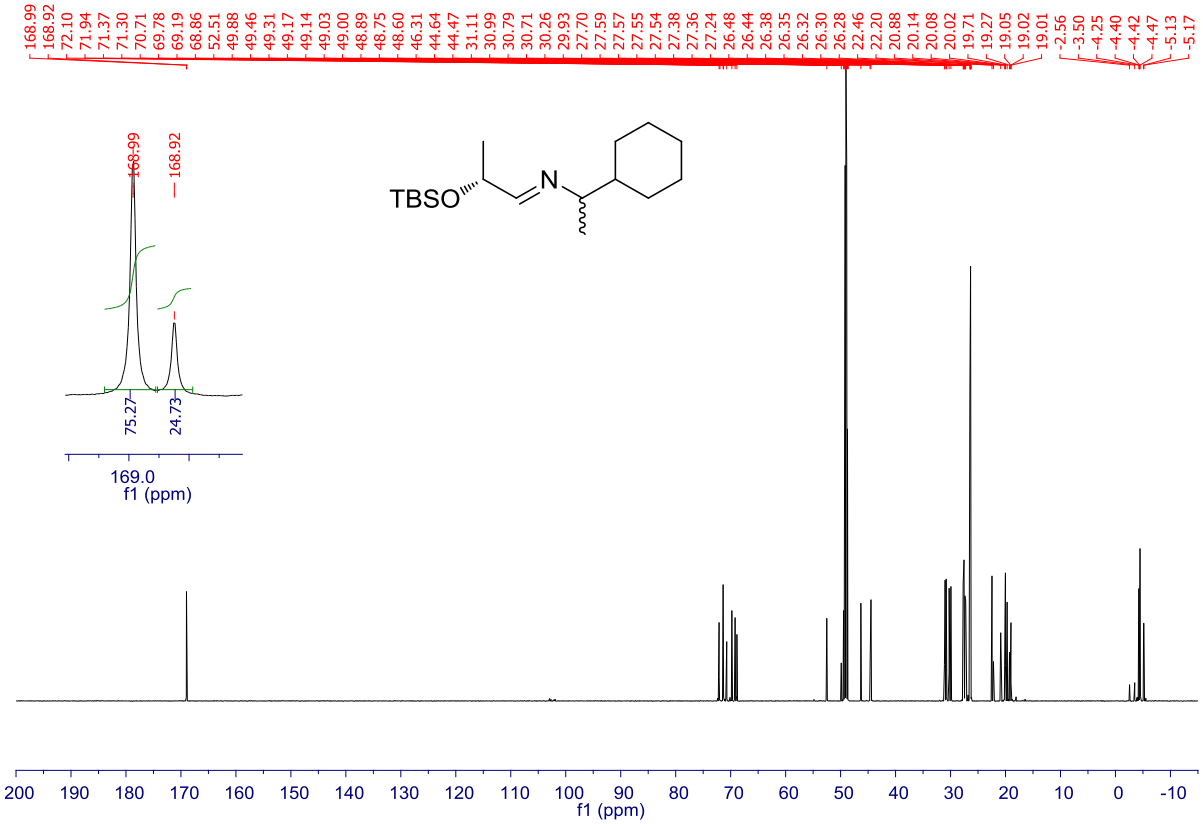

TBSO
N
169.24
169.10
9.61
90.39
169.4
169.0
f1 (ppm)
f1 (ppm)

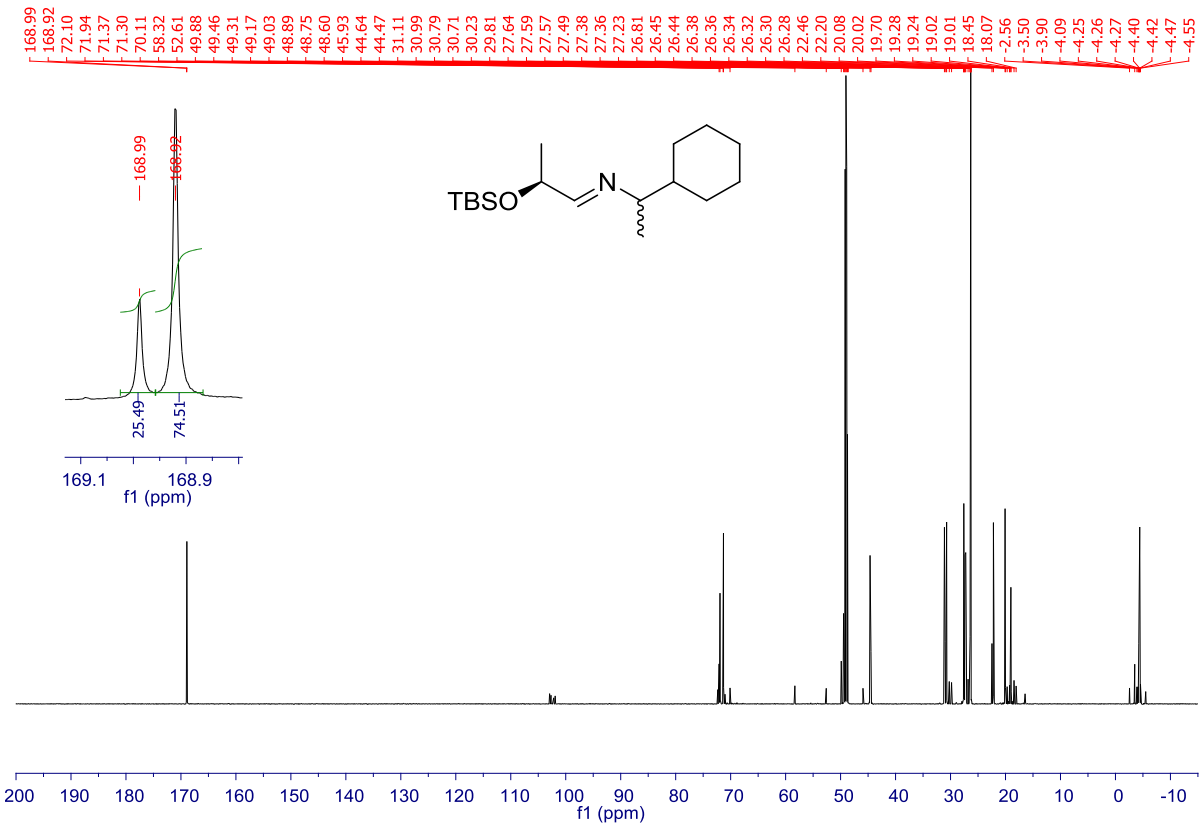
Sample 5 (SMG)


170.45
170.35
141.23
138.32
137.84
137.31
130.30
130.27
130.02
129.81
129.57
129.08
128.28
128.25
127.76
127.08
126.92
126.80
71.55
71.40
70.72
69.79
69.20
68.87
68.46
68.40
50.09
49.91
49.48
49.34
49.20
49.05
48.91
48.77
48.63
33.34
32.52
32.34
30.54
30.41
26.51
26.47
26.39
26.36
26.32
26.30
22.28
22.26
20.92
20.90
20.60
19.73
19.28
19.06
-2.53
-3.47
-4.20
-4.25
-4.30
-4.39
-4.40
-4.44
-5.09
-5.14
170.45
170.35
14.56
85.44
170.5
f1 (ppm)
TBSO
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

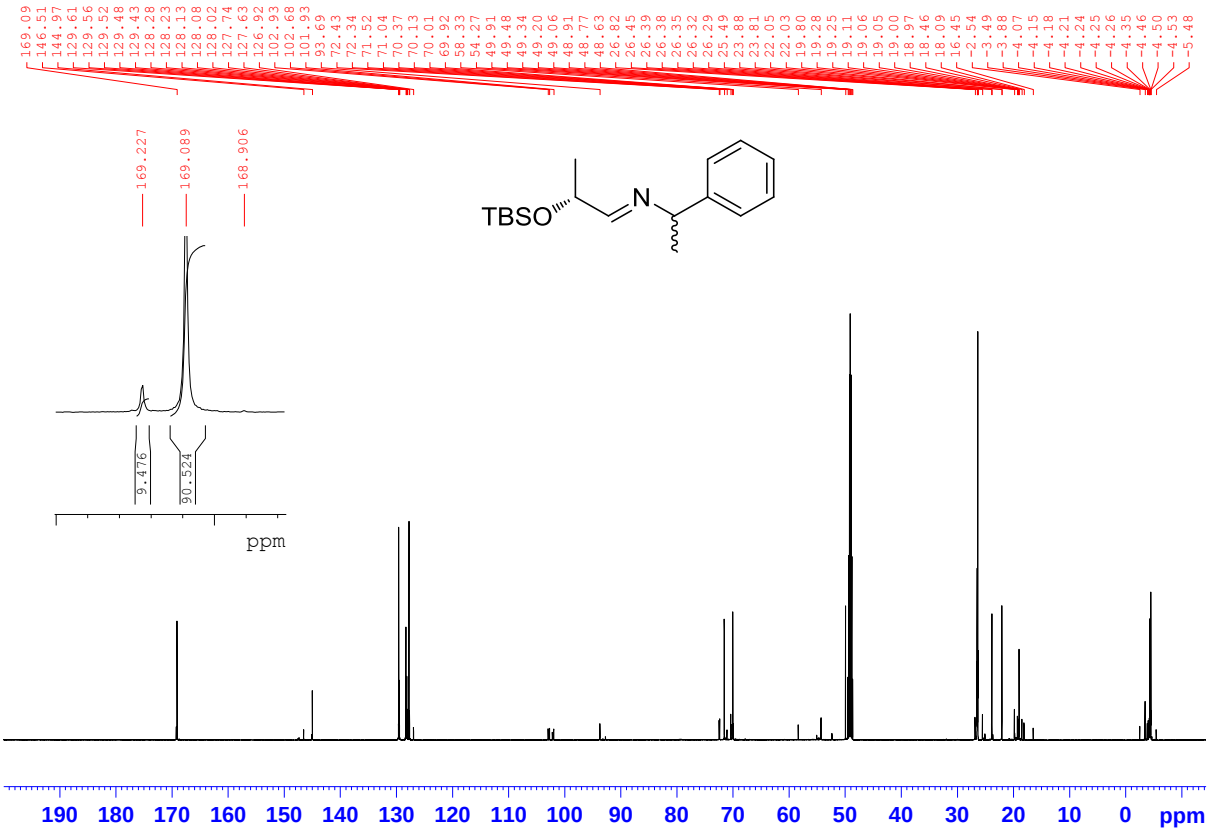

170.45
170.35
138.32
138.29
137.26
130.30
130.27
130.11
129.81
129.58
129.12
128.28
128.25
127.97
127.14
126.92
126.79
72.44
72.35
71.55
71.40
71.04
68.46
68.40
58.33
50.09
49.90
49.47
49.33
49.19
49.05
48.91
48.76
48.62
32.95
32.51
32.33
30.47
30.39
26.83
26.45
26.39
26.36
26.31
26.30
22.27
20.92
20.89
20.50
19.30
19.26
19.12
19.05
18.47
16.47
-3.48
-4.14
-4.21
-4.25
-4.26
-4.31
-4.41
-4.44
-4.52
170.45
170.35
85.35
14.65
170.6
f1 (ppm)
TBSO
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

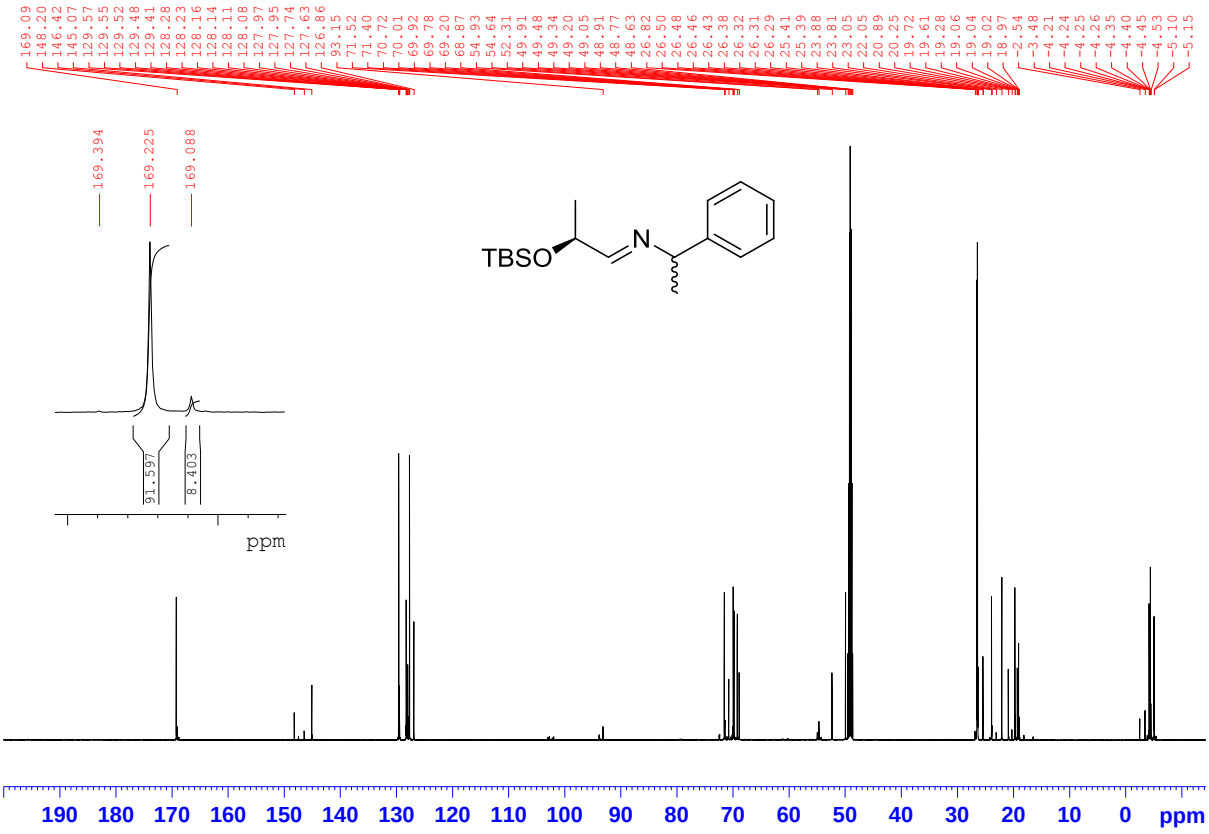
Sample 6 (SMG)


168.99
168.92
72.10
71.94
71.37
71.30
70.71
69.78
69.19
68.86
52.51
49.88
49.46
49.31
49.17
49.14
49.03
49.00
48.89
48.75
48.60
46.31
44.64
44.47
31.11
30.99
30.79
30.71
30.26
29.93
27.70
27.59
27.57
27.55
27.54
27.38
27.36
27.24
26.48
26.44
26.38
26.35
26.32
26.30
26.28
22.46
22.20
20.88
20.14
20.08
20.02
19.71
19.27
19.05
19.02
19.01
-2.56
-3.50
-4.25
-4.40
-4.42
-4.47
-5.13
-5.17
168.99
168.92
75.27
24.73
169.0
f1 (ppm)
TBSO
N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

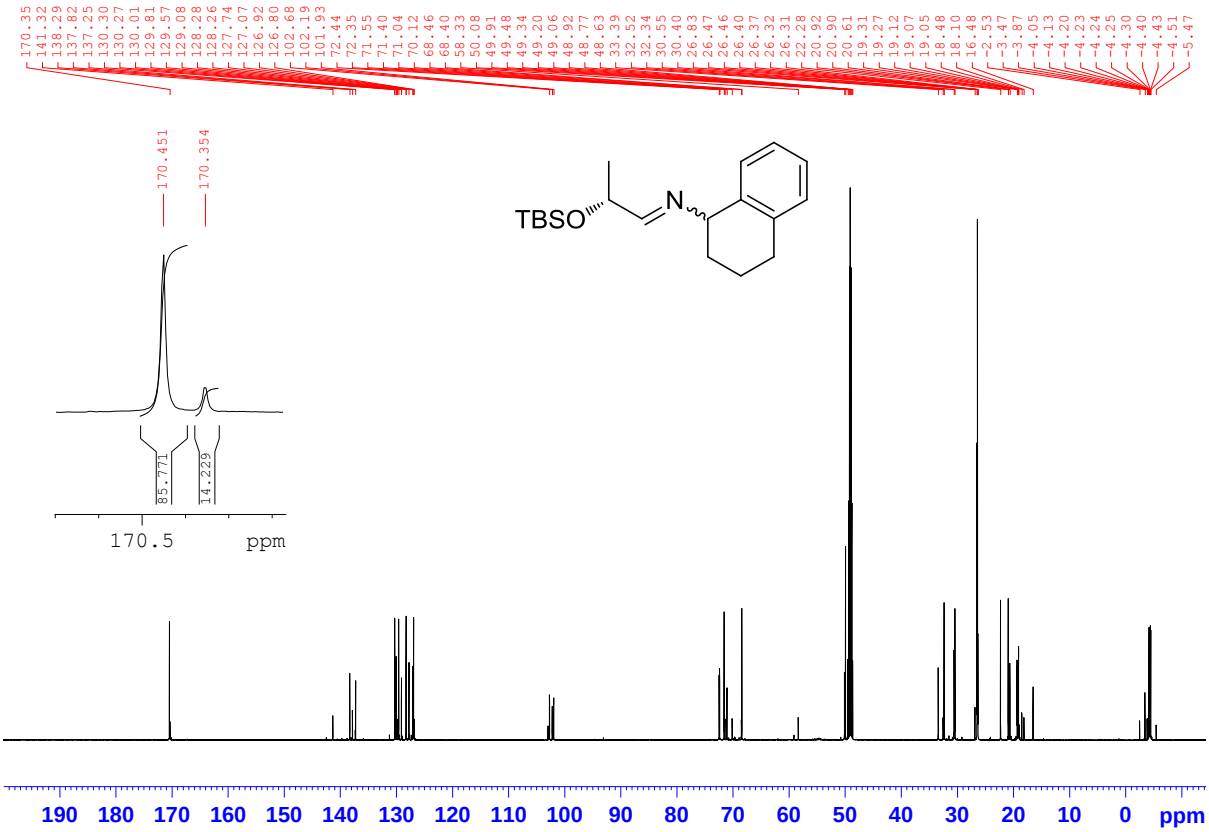

168.99
168.92
72.10
71.94
71.37
71.30
70.11
58.32
52.61
49.88
49.46
49.31
49.17
49.03
48.89
48.75
48.60
45.93
44.64
44.47
31.11
30.99
30.79
30.71
30.23
29.81
27.64
27.59
27.57
27.49
27.38
27.36
27.23
26.81
26.45
26.44
26.38
26.36
26.34
26.32
26.30
26.28
22.46
22.20
20.08
20.02
19.70
19.28
19.24
19.02
19.01
18.45
18.07
-2.56
-3.50
-3.90
-4.09
-4.25
-4.26
-4.27
-4.40
-4.42
-4.47
-4.55
168.99
168.92
25.49
74.51
169.1
168.9
f1 (ppm)
TBSO
N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

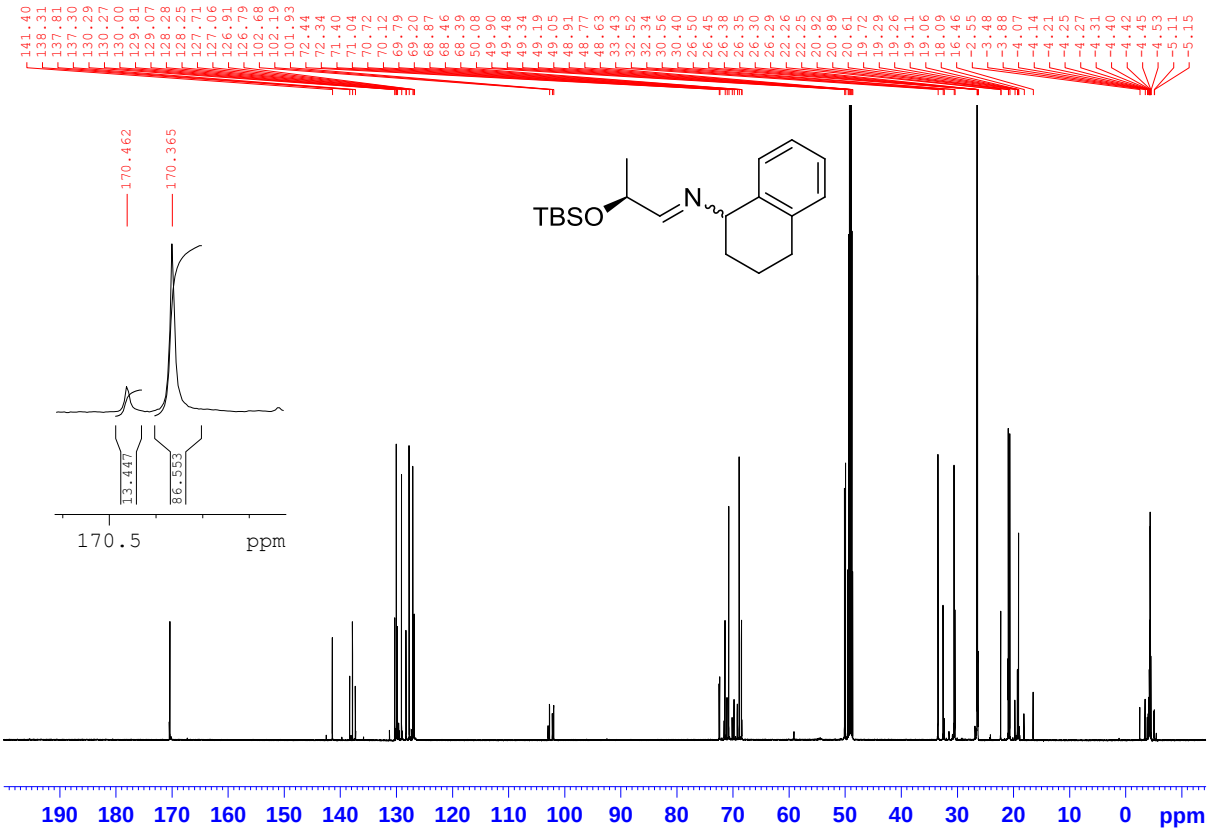
Sample 4 (RML)


TBSO
N
169.227
169.089
168.906
9.476
90.524
ppm
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

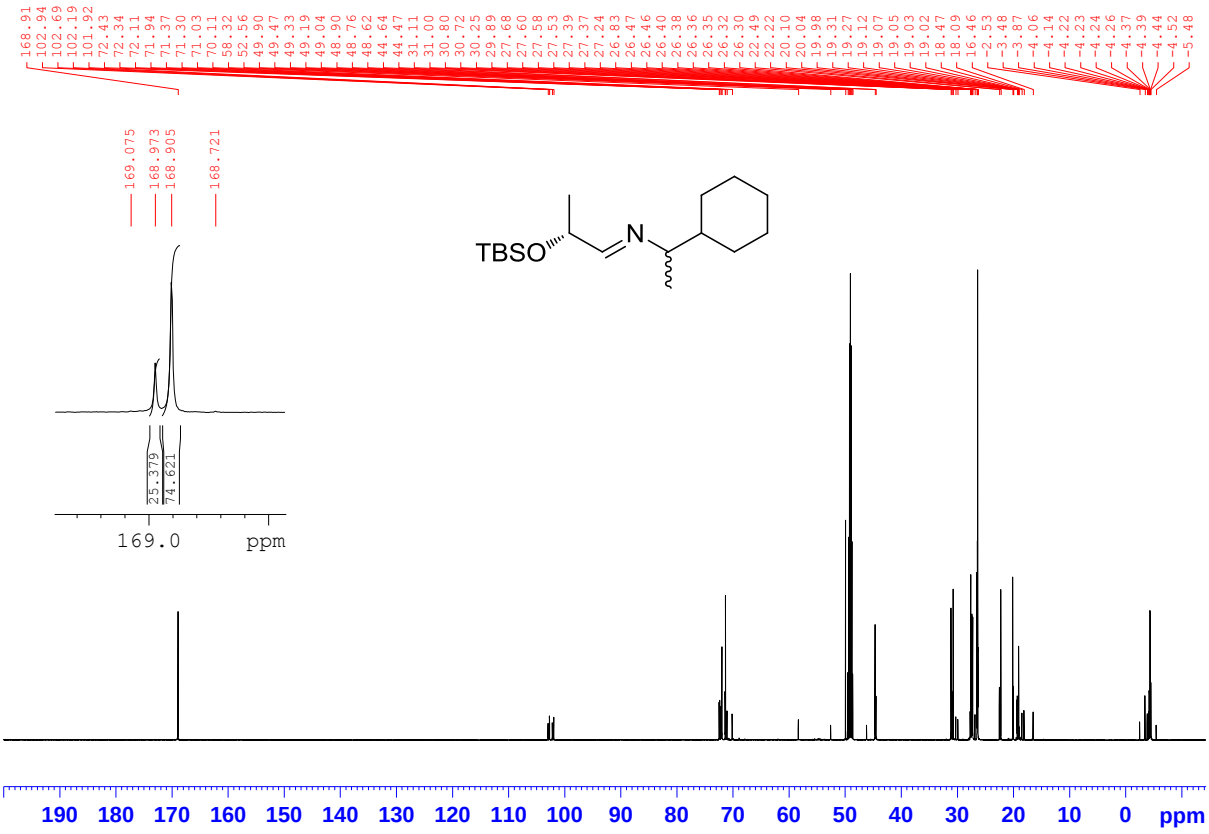

TBSO
N
169.394
169.225
169.088
91.597
8.403
ppm
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

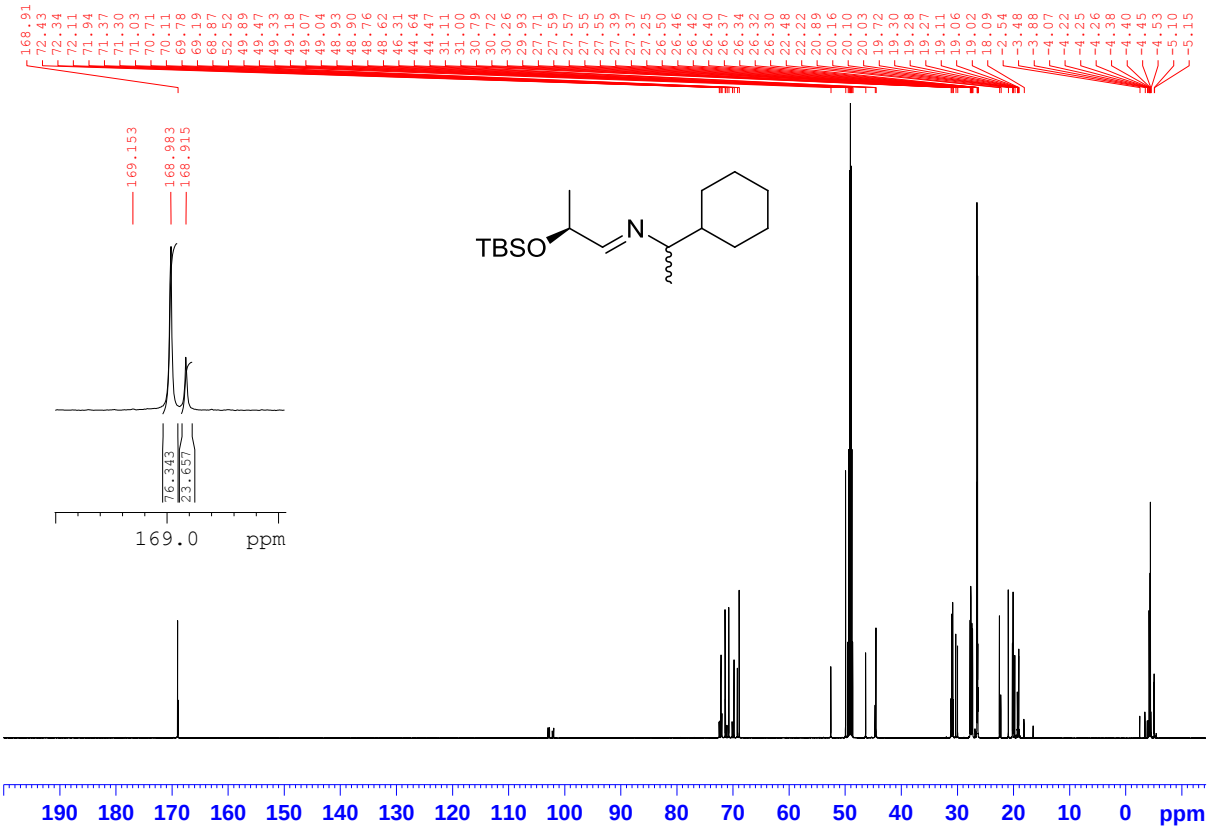
Sample 5 (RML)


170.35
141.32
138.29
137.82
137.25
130.30
130.27
130.01
129.81
129.57
129.08
128.28
128.26
127.74
127.07
126.92
126.80
102.68
102.19
101.93
72.44
72.35
71.55
71.40
71.04
70.12
68.46
68.40
68.33
58.33
50.08
49.91
49.48
49.34
49.20
49.06
48.92
48.77
48.63
33.39
32.52
32.34
30.55
30.40
26.83
26.47
26.46
26.40
26.37
26.32
26.31
22.28
20.92
20.90
20.61
19.31
19.27
19.12
19.07
19.05
18.48
18.10
16.48
-2.53
-3.47
-3.87
-4.05
-4.13
-4.20
-4.23
-4.24
-4.25
-4.30
-4.40
-4.43
-4.51
-5.47
170.451
170.354
85.771
14.229
170.5
ppm
TBSO
N
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

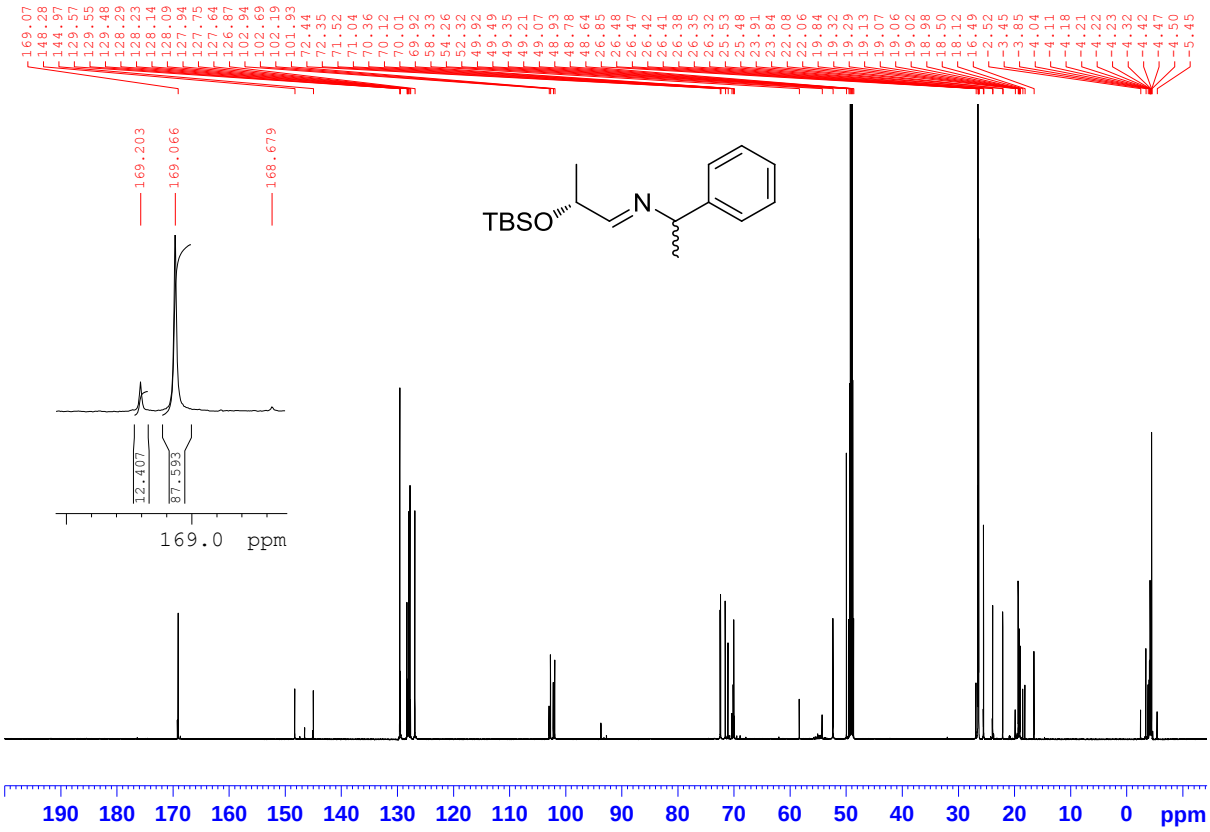

141.40
138.31
137.81
137.30
130.29
130.27
130.00
129.81
129.07
128.28
128.25
127.71
127.06
126.91
126.79
102.68
102.19
101.93
72.44
72.34
71.40
71.04
70.72
70.12
69.79
69.20
68.87
68.46
68.39
50.08
49.90
49.48
49.34
49.19
49.05
48.91
48.77
48.63
33.43
32.52
32.34
30.56
30.40
26.50
26.45
26.38
26.35
26.30
26.29
22.26
22.25
20.92
20.89
20.61
19.72
19.29
19.26
19.11
19.06
18.09
16.46
-2.55
-3.48
-3.88
-4.07
-4.14
-4.21
-4.25
-4.27
-4.31
-4.40
-4.42
-4.45
-4.53
-5.11
-5.15
170.462
170.365
13.447
86.553
170.5
ppm
TBSO
N
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

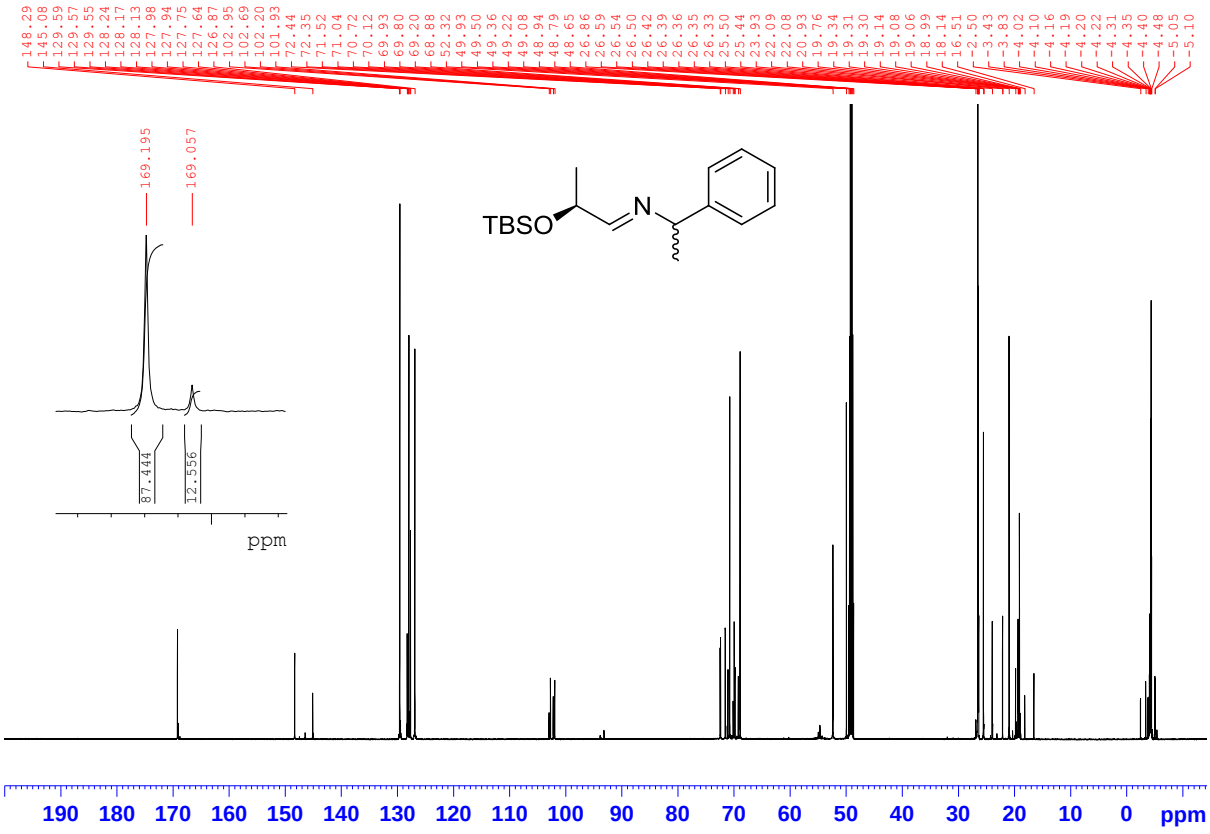
Sample 6 (RML)


TBSO
N
169.075
168.973
168.905
168.721
25.379
74.621
169.0
ppm
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

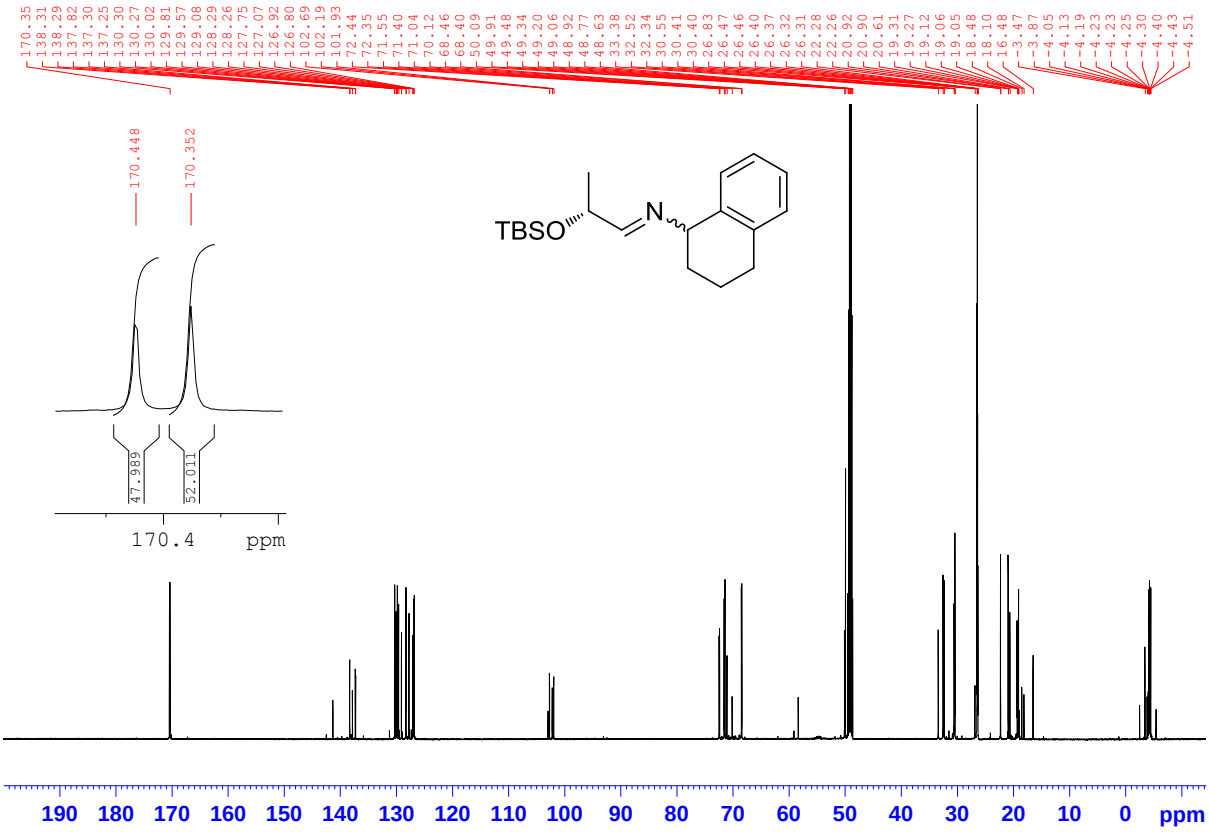

TBSO
N
169.153
168.983
168.915
76.343
23.657
169.0
ppm
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

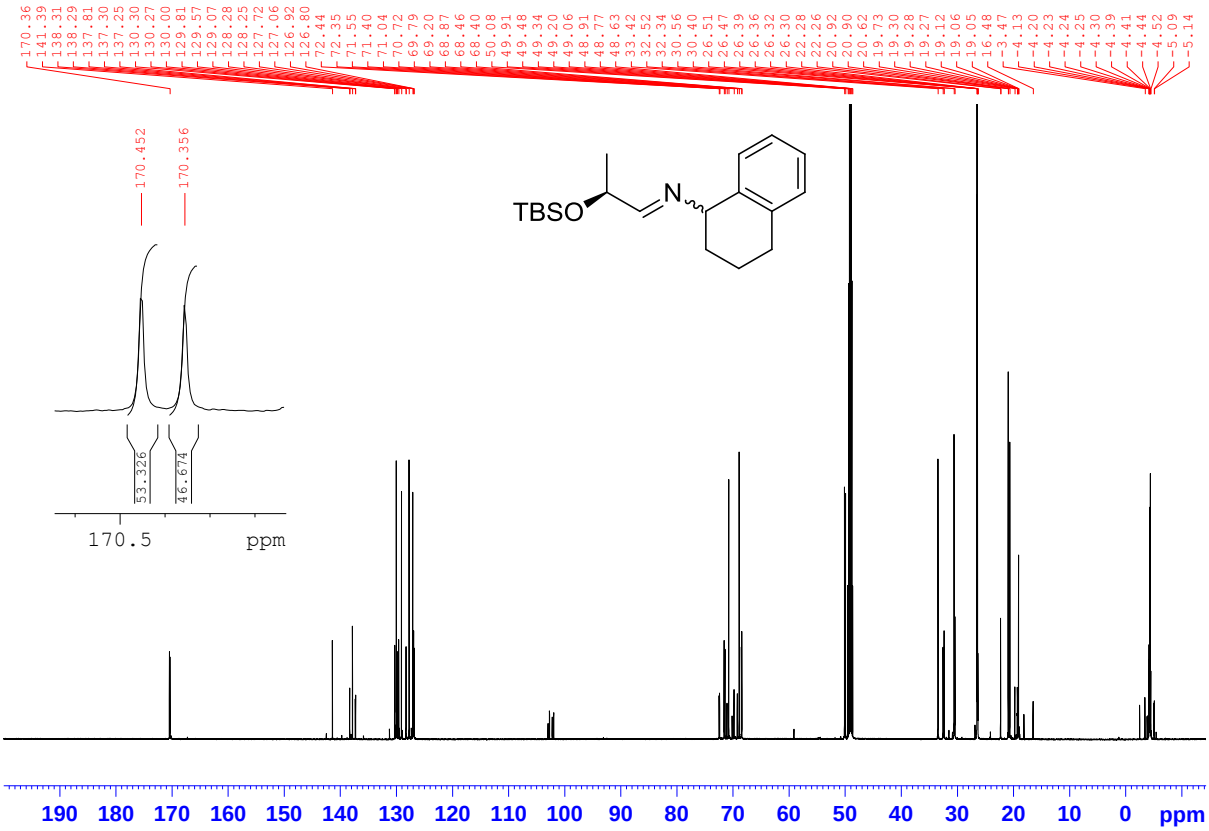
Sample 7 (RML)


TBSO
N
169.203
169.066
168.679
12.407
87.593
169.0 ppm
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

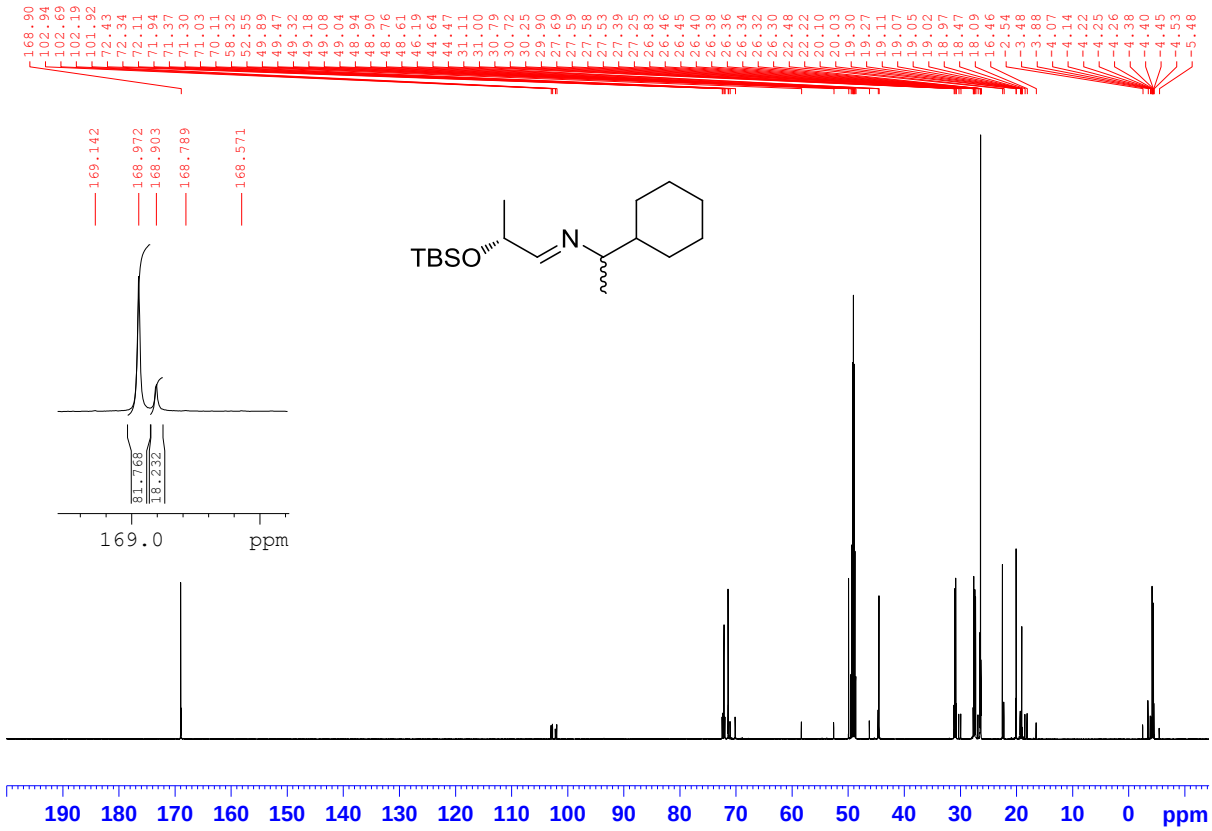

TBSO
N
169.195
169.057
87.444
12.556
ppm
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

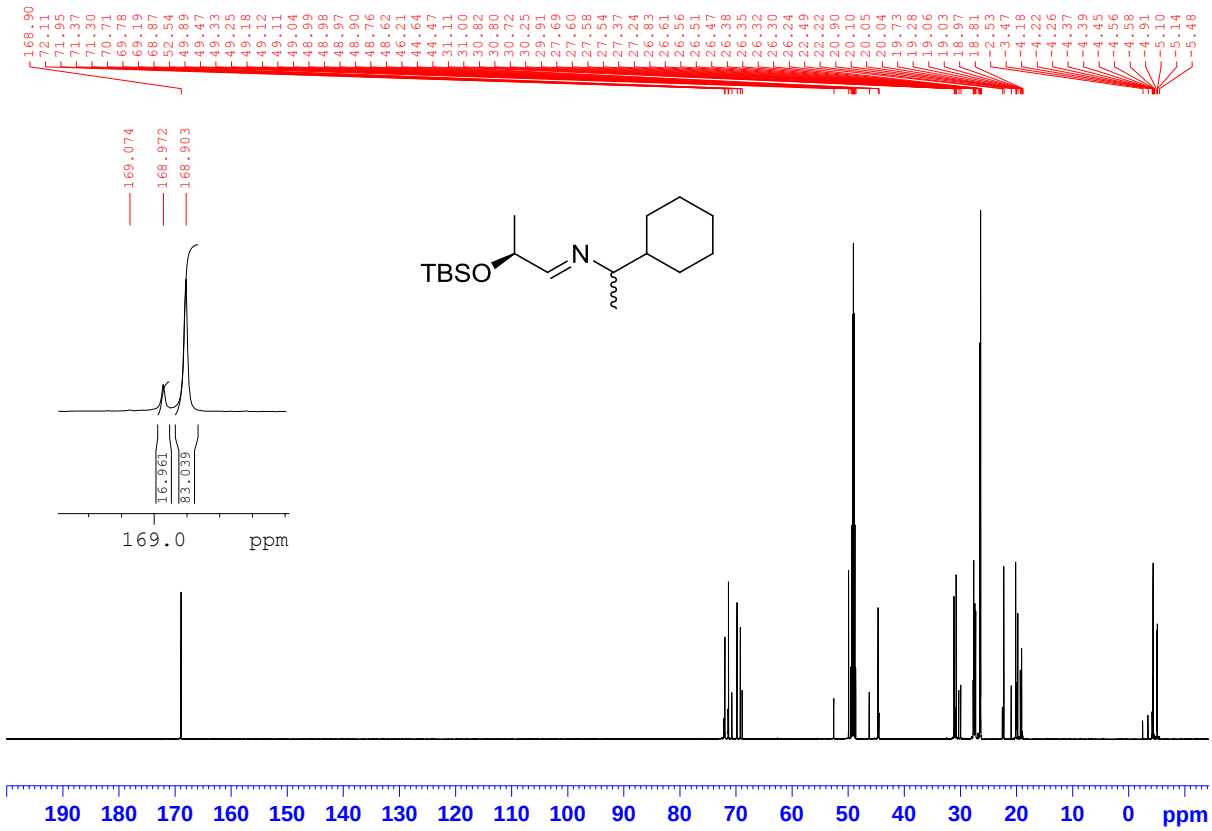
Sample 8 (RML)


TBSO
N
170.448
170.352
47.989
52.011
170.4
ppm
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

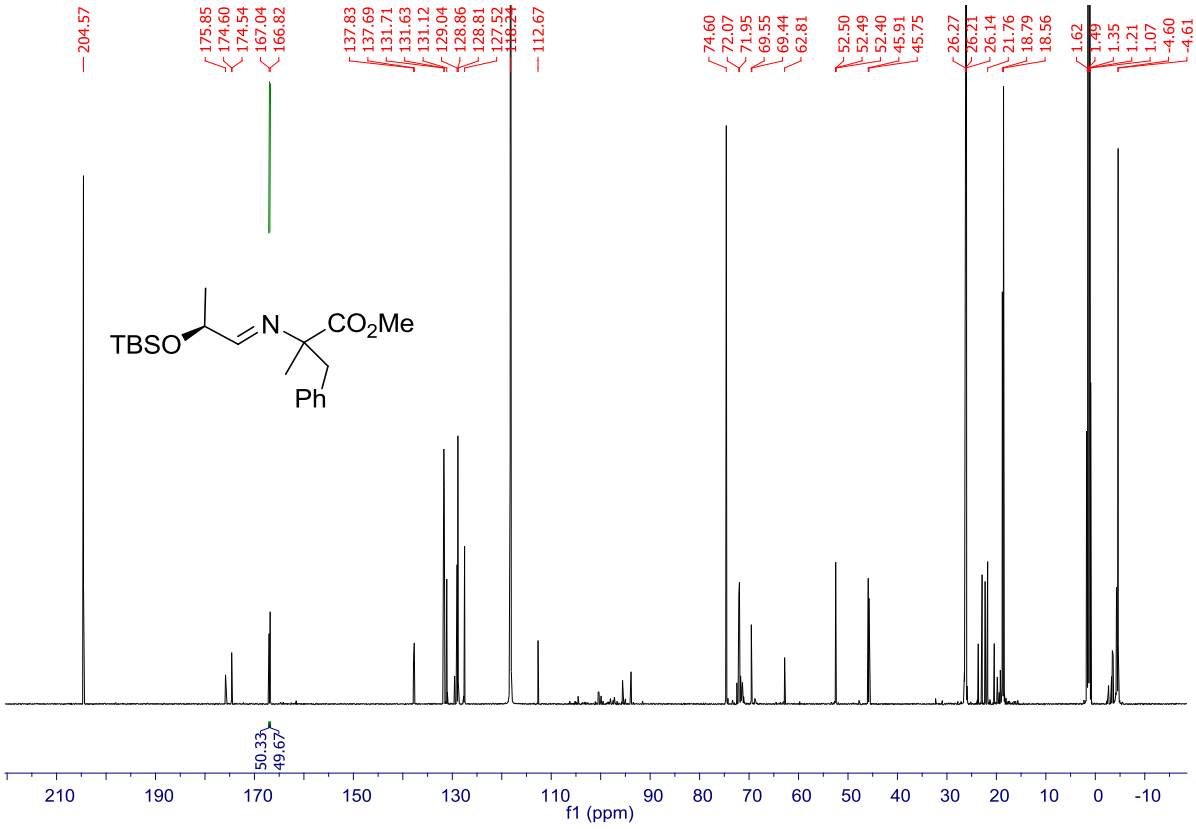

TBSO
N
170.452
170.356
53.326
46.674
170.5
ppm
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

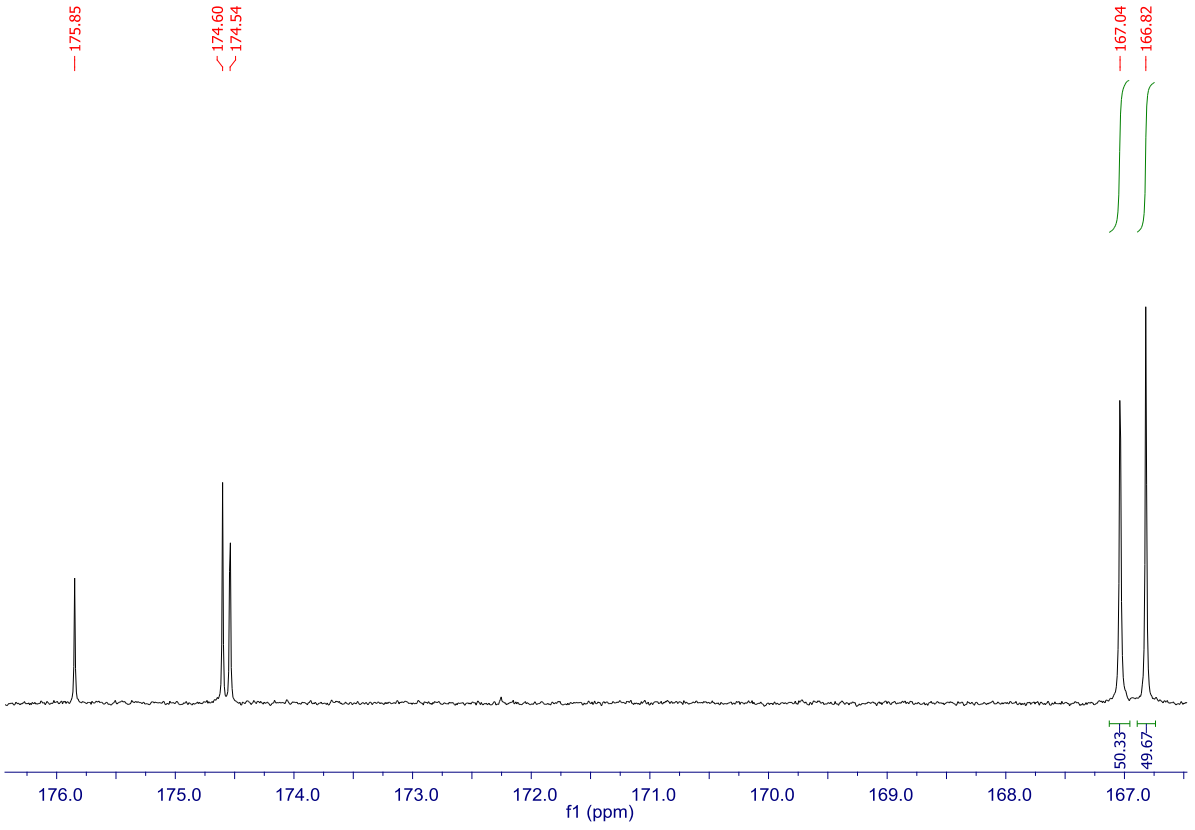
Sample 9 (RML)


TBSO
N
169.0
ppm
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

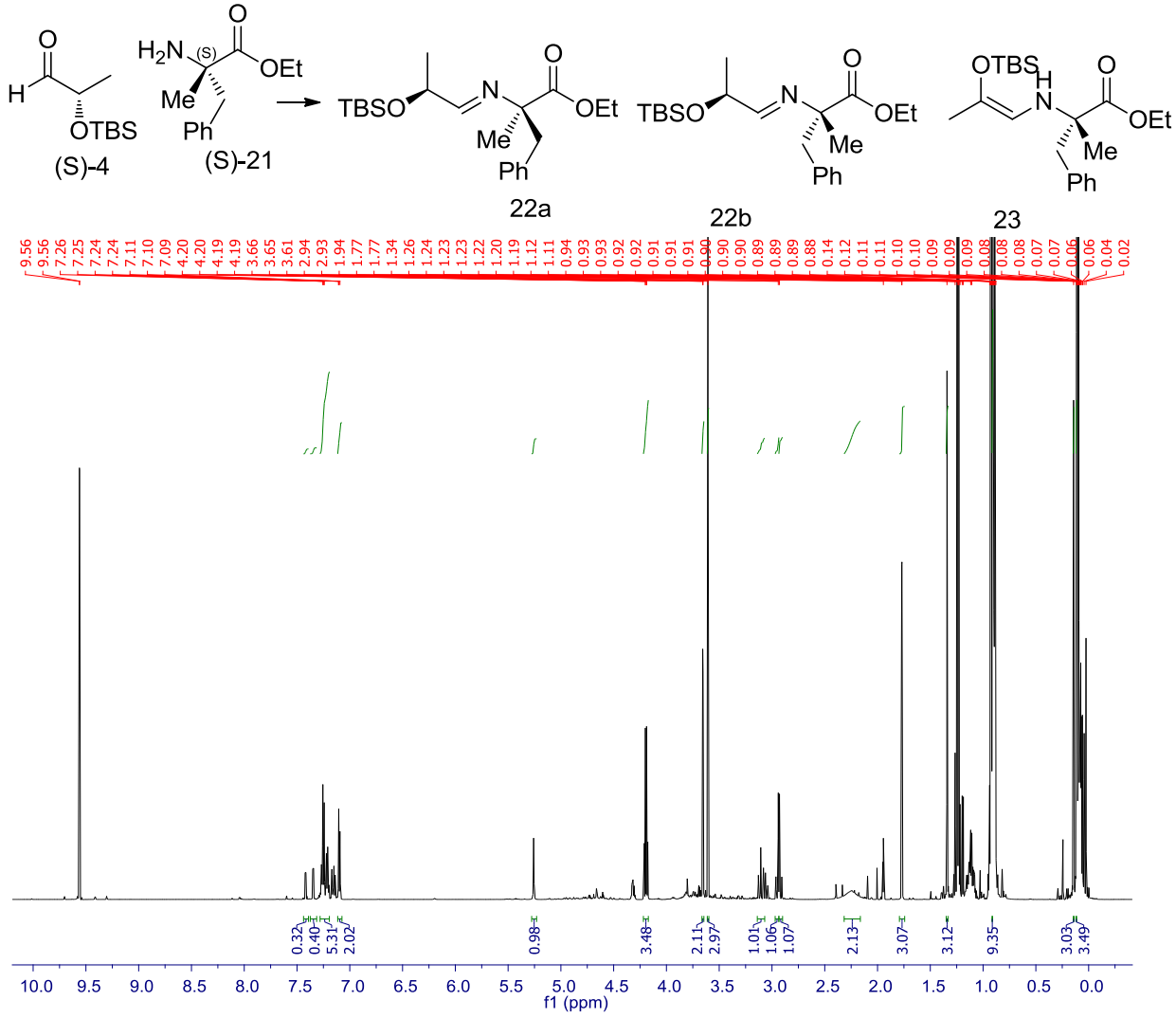

TBSO
N
169.0
ppm
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

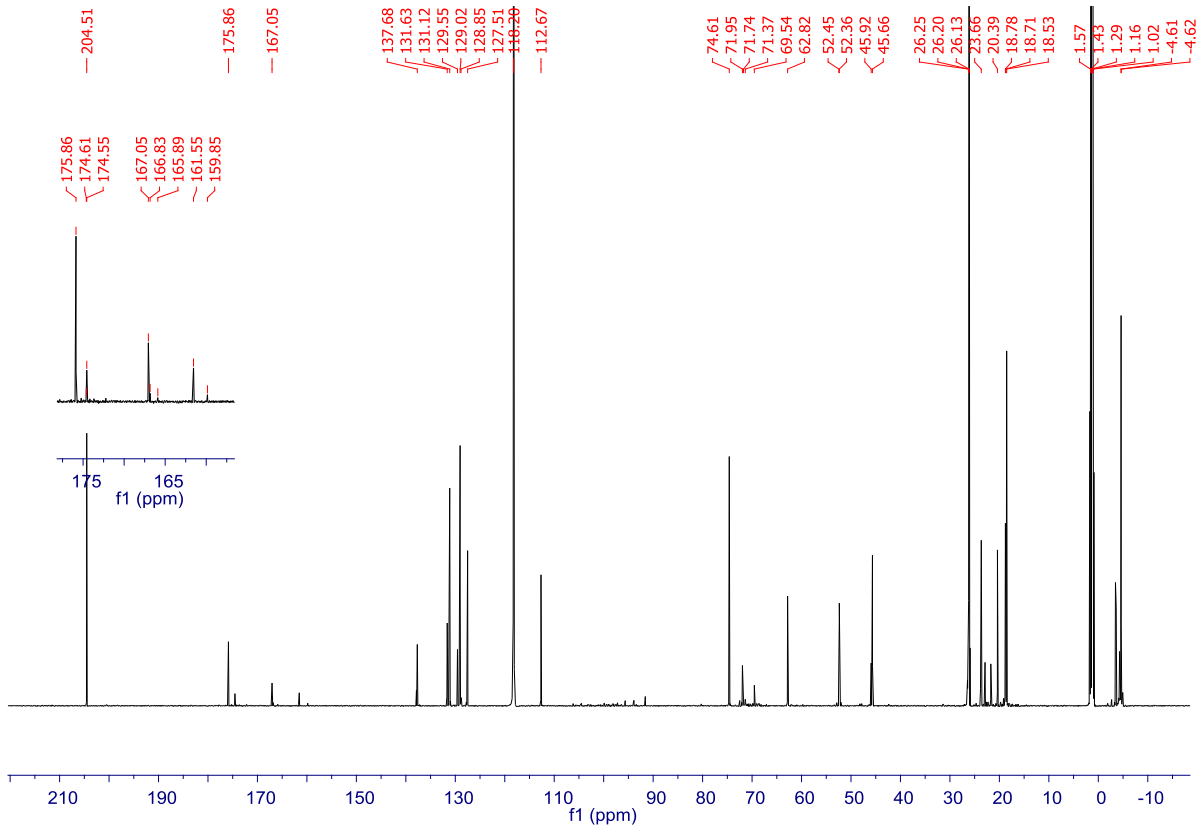
(±)-α-Methyl-DL-phenylalanine methyl ester-(21) and (*S*)-4, d_3-MeCN





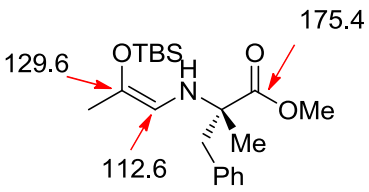
(±)-α-Methyl-DL-phenylalanine methyl ester-(21) and (*S*)-4, d_3-MeCN, 90 min



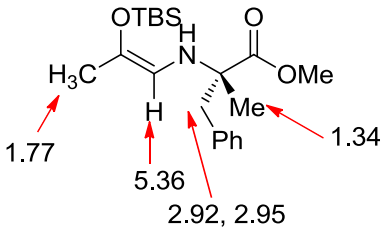


The diagnostic signals for the enamine **23** were assigned as follows:

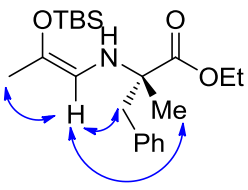
^{13}C shifts



^{1}H shifts

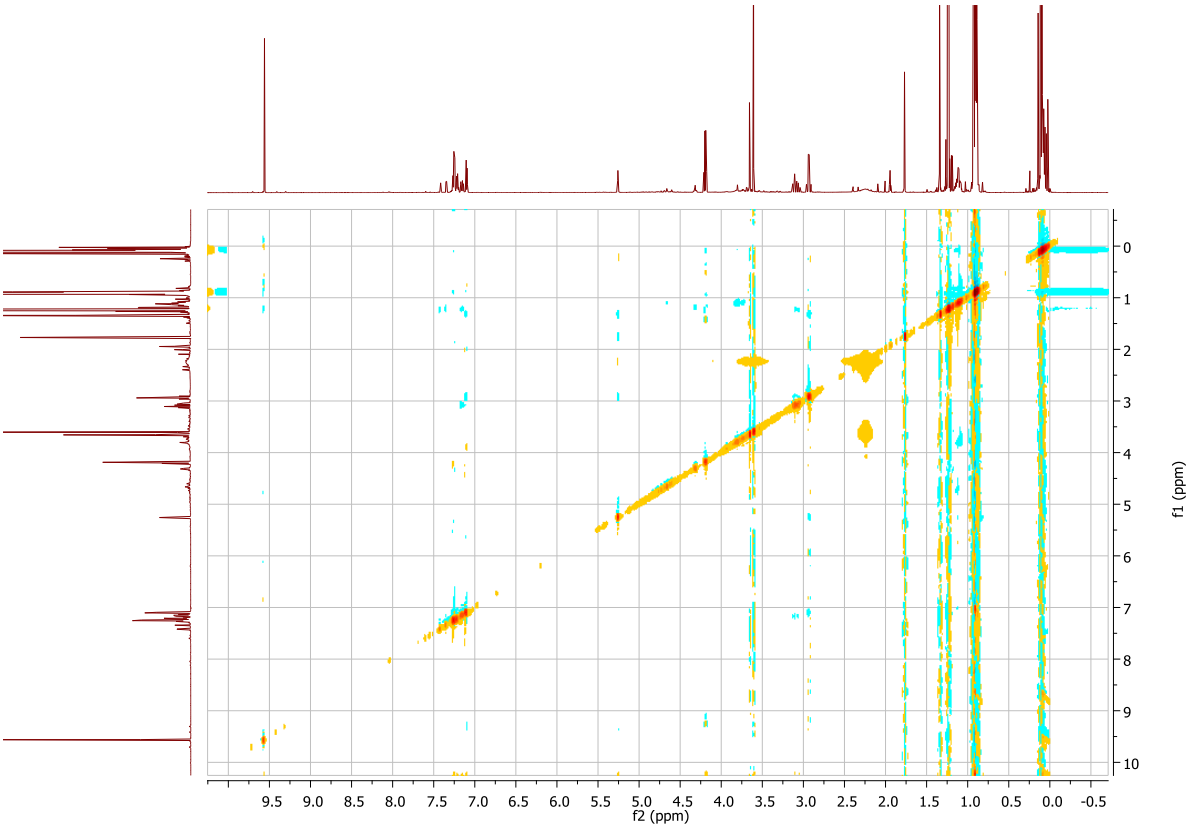


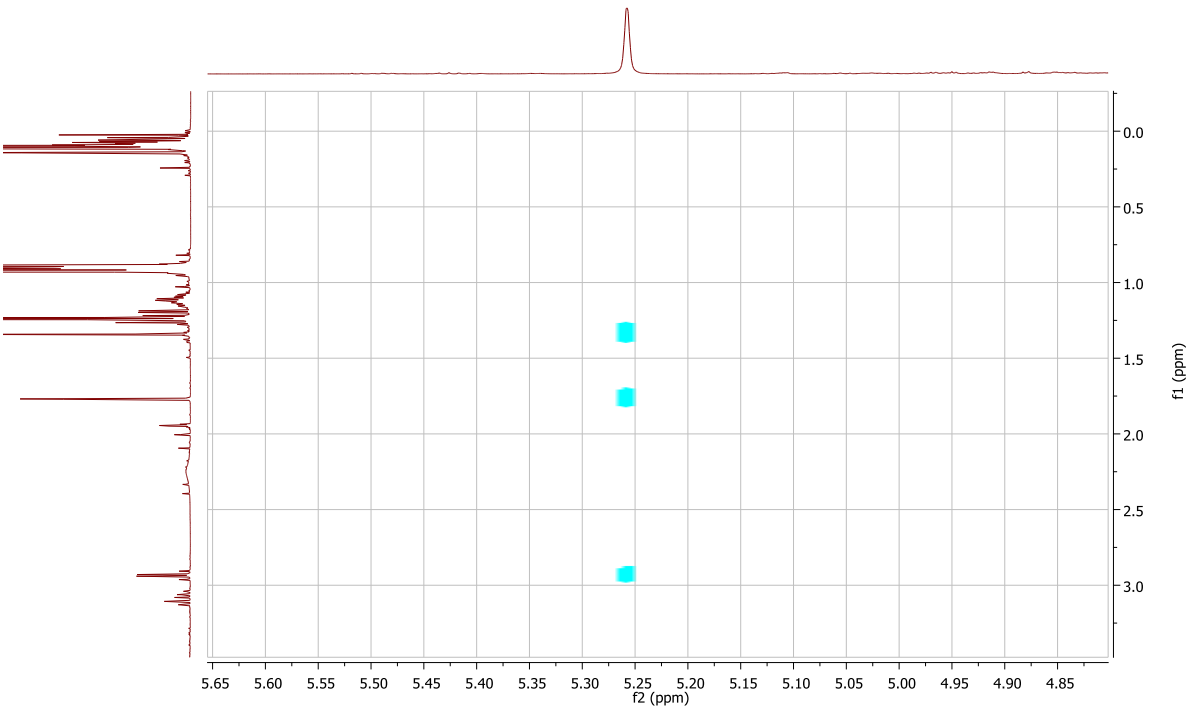
nOe crosspeaks



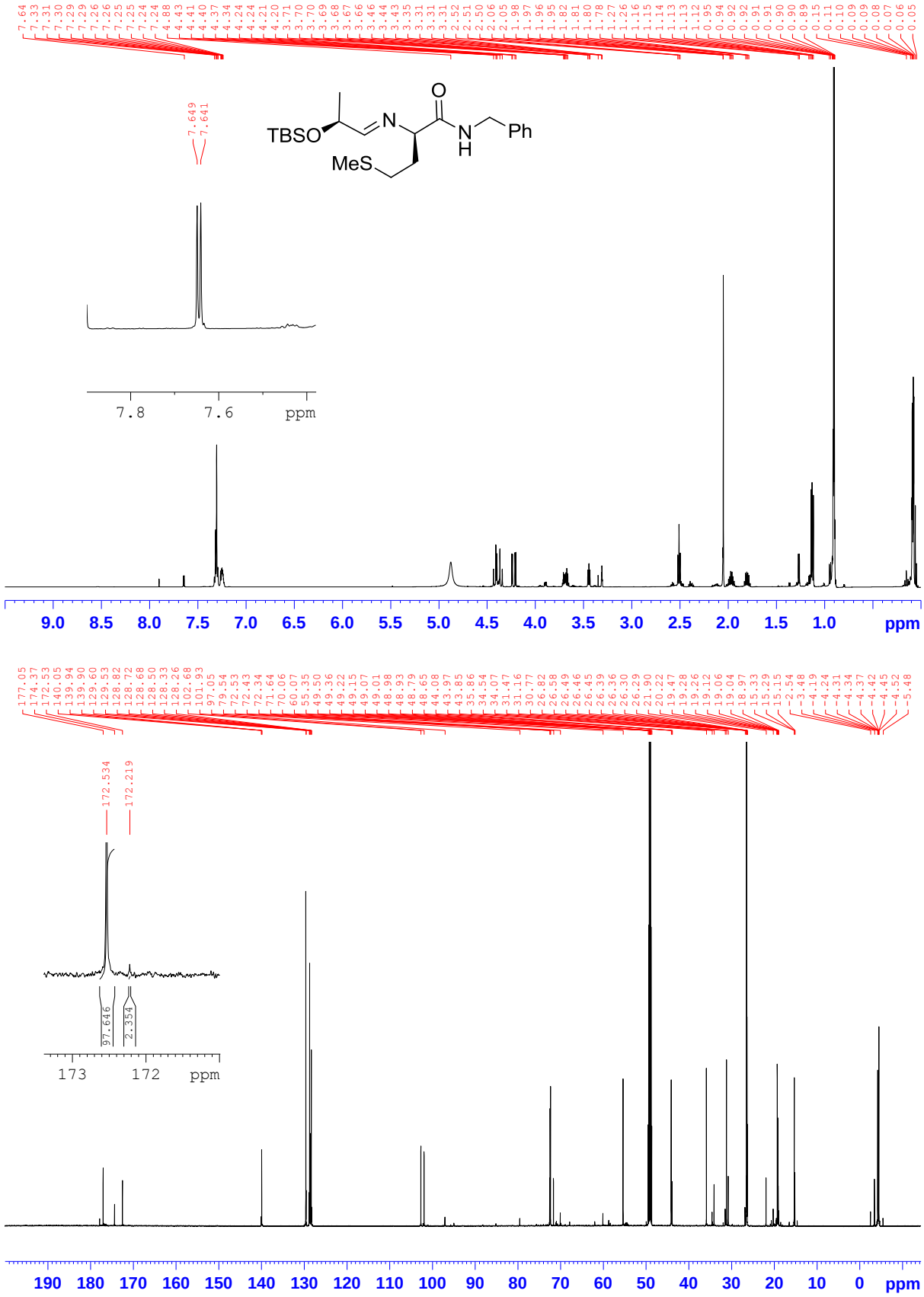
The geometry was determined from the nOe's shown. The NOESY spectrum is on the following page.

NOESY spectrum of mixture of imines 22 and enamine 23

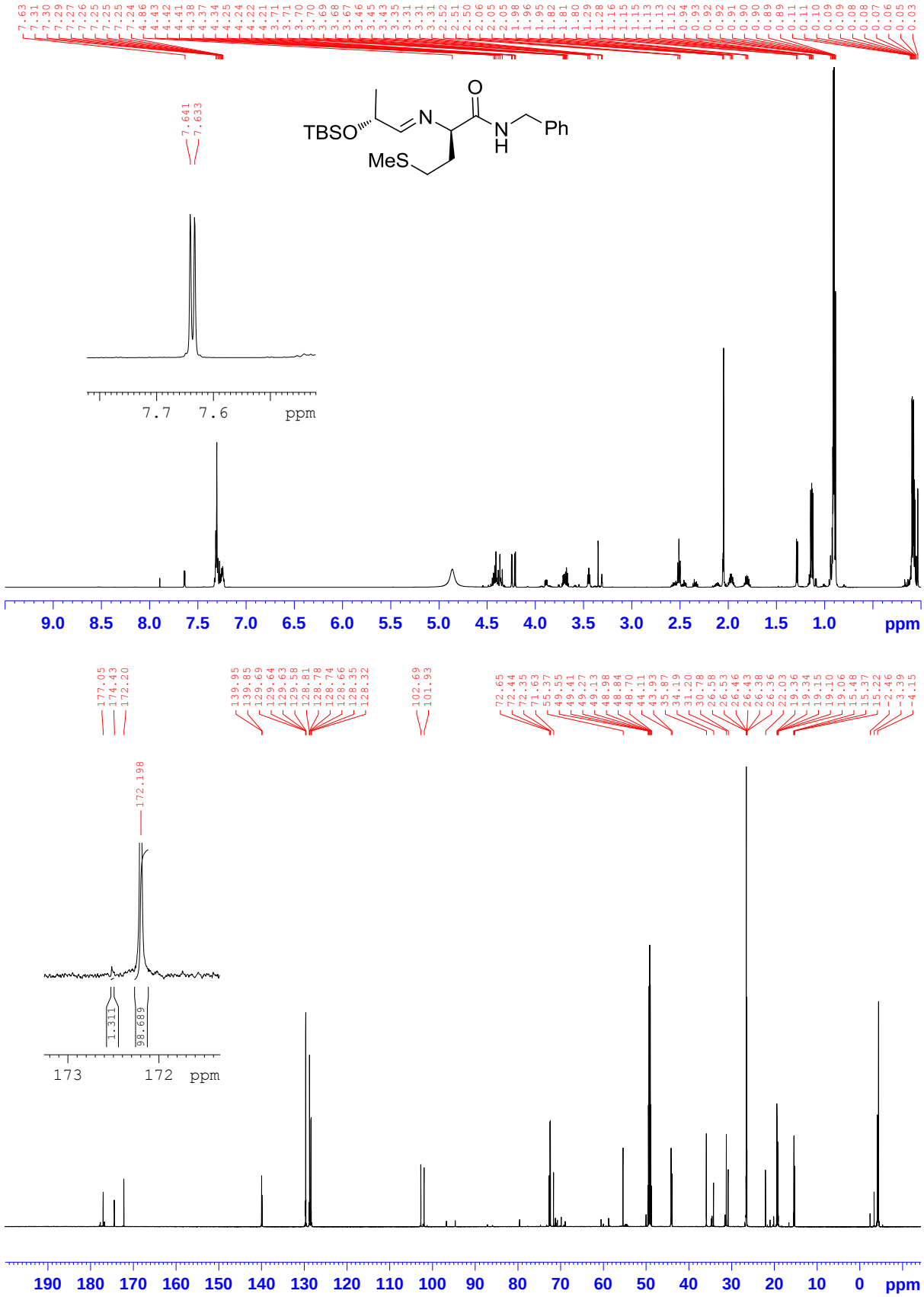




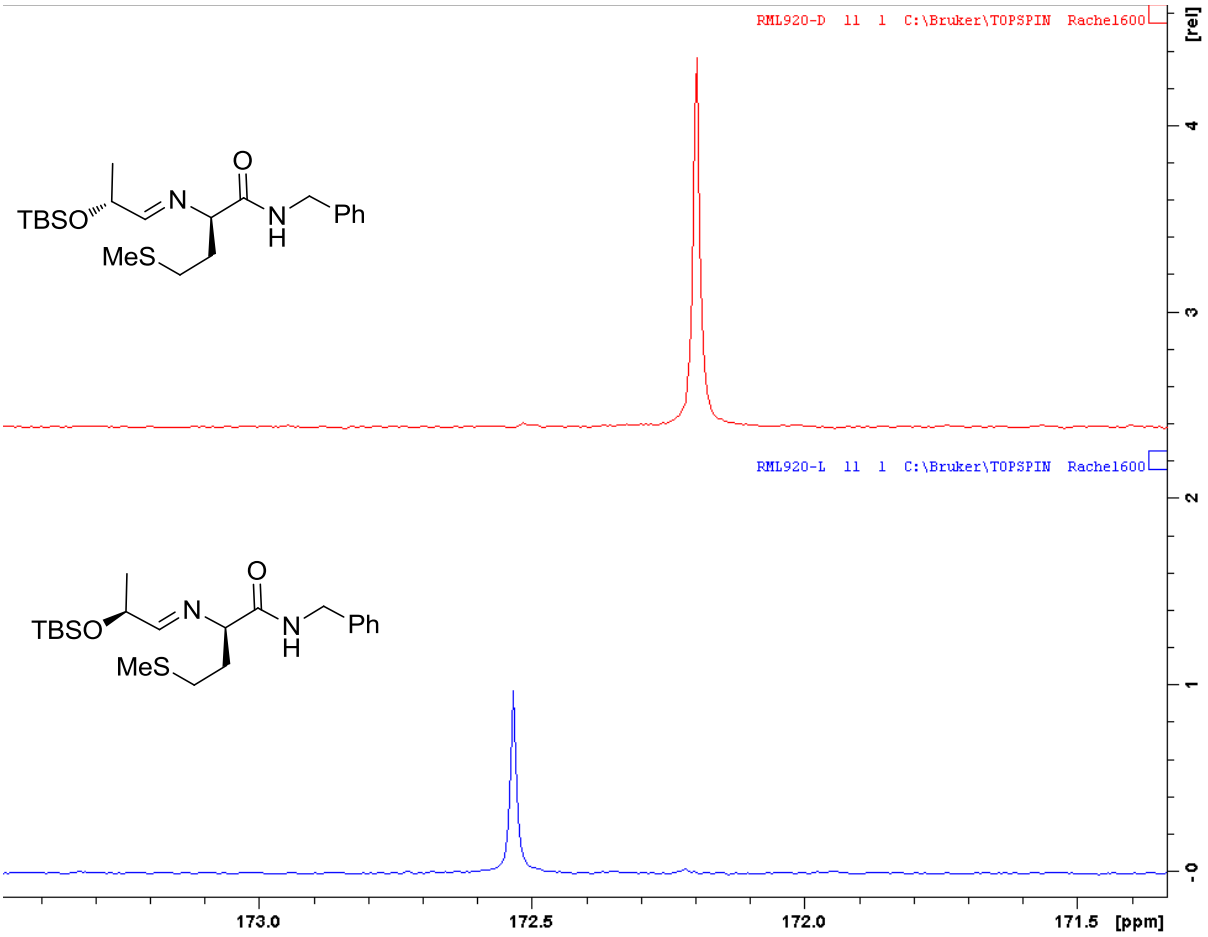
Amide 26a and (*S*)-4



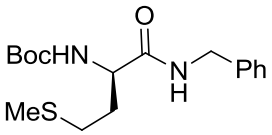
Amide 26a and (*R*)-4

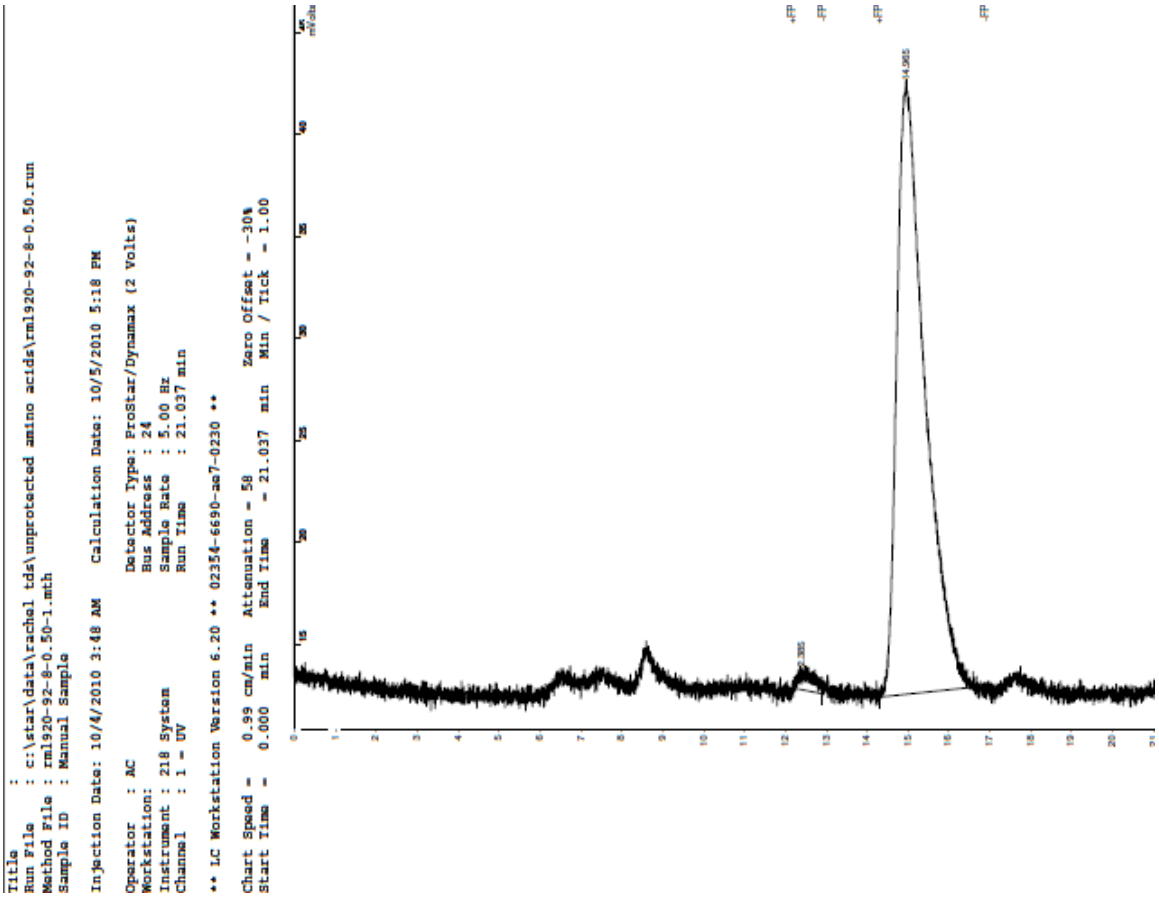


Amide 26a and (*S*)-4/Amide 26a and (*R*)-4 overlaid



Amide 25a chiral HPLC





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Title :
Run File : c:\star\data\rachel tds\unprotected amino acids\rml920-92-8-0.50.run
Method File : rml920-92-8-0.50-1.mth
Sample ID : Manual Sample

Injection Date: 10/4/2010 3:48 AM Calculation Date: 10/5/2010 5:18 PM

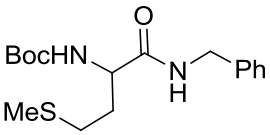
Operator : AC Detector Type: ProStar/Dynamax (2 Volts)
Workstation: Bus Address : 24
Instrument : 218 System Sample Rate : 5.00 Hz
Channel : 1 - UV Run Time : 21.037 min

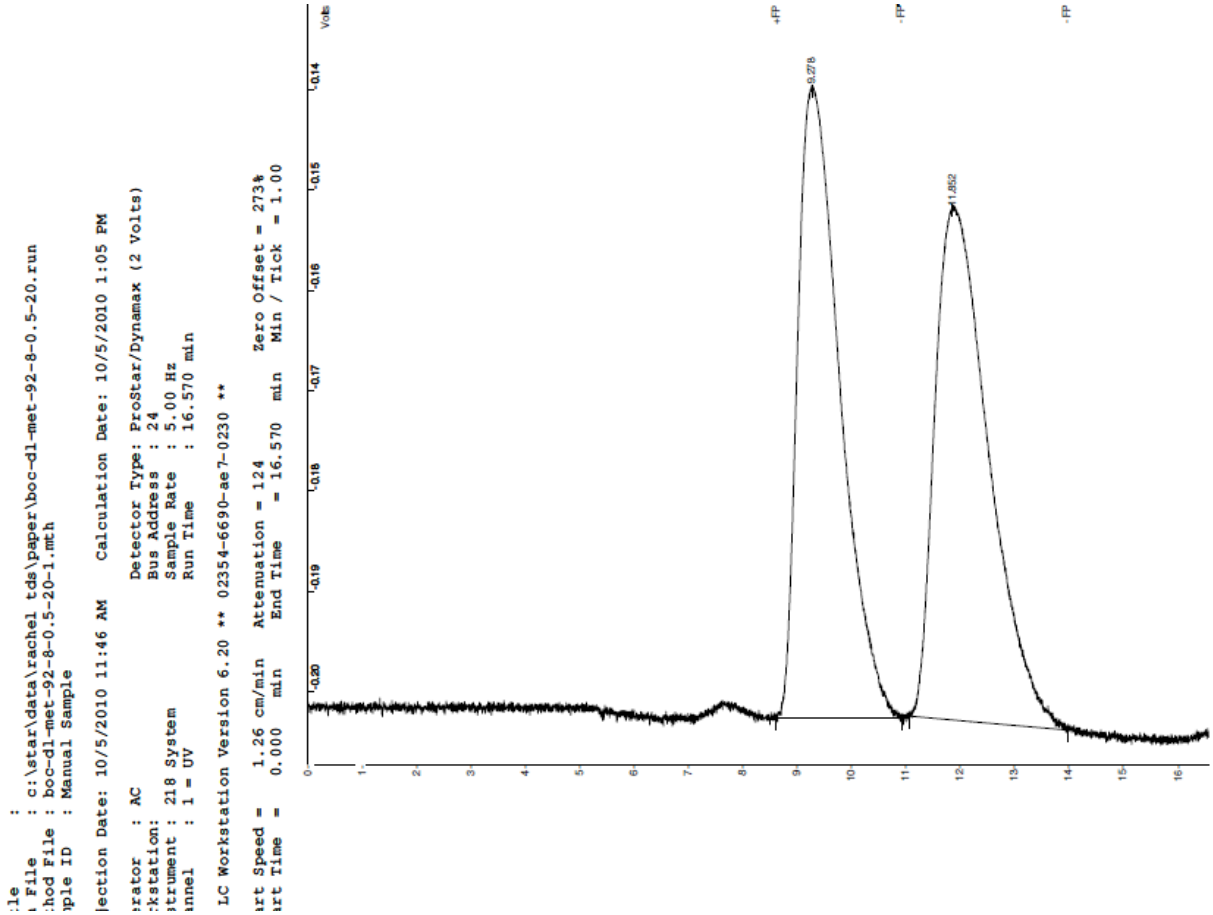
** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		1.6603	12.385	0.000	24171	BB	0.5	
2		98.3397	14.965	0.000	1431657	BB	43.2	
	Totals:	100.0000		0.000	1455828			

(±)-25a chiral HPLC



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Title        :
Run File     : c:\star\data\rachel tds\paper\boc-dl-met-92-8-0.5-20.run
Method File  : boc-dl-met-92-8-0.5-20-1.mth
Sample ID    : Manual Sample

Injection Date: 10/5/2010 11:46 AM     Calculation Date: 10/5/2010 1:05 PM

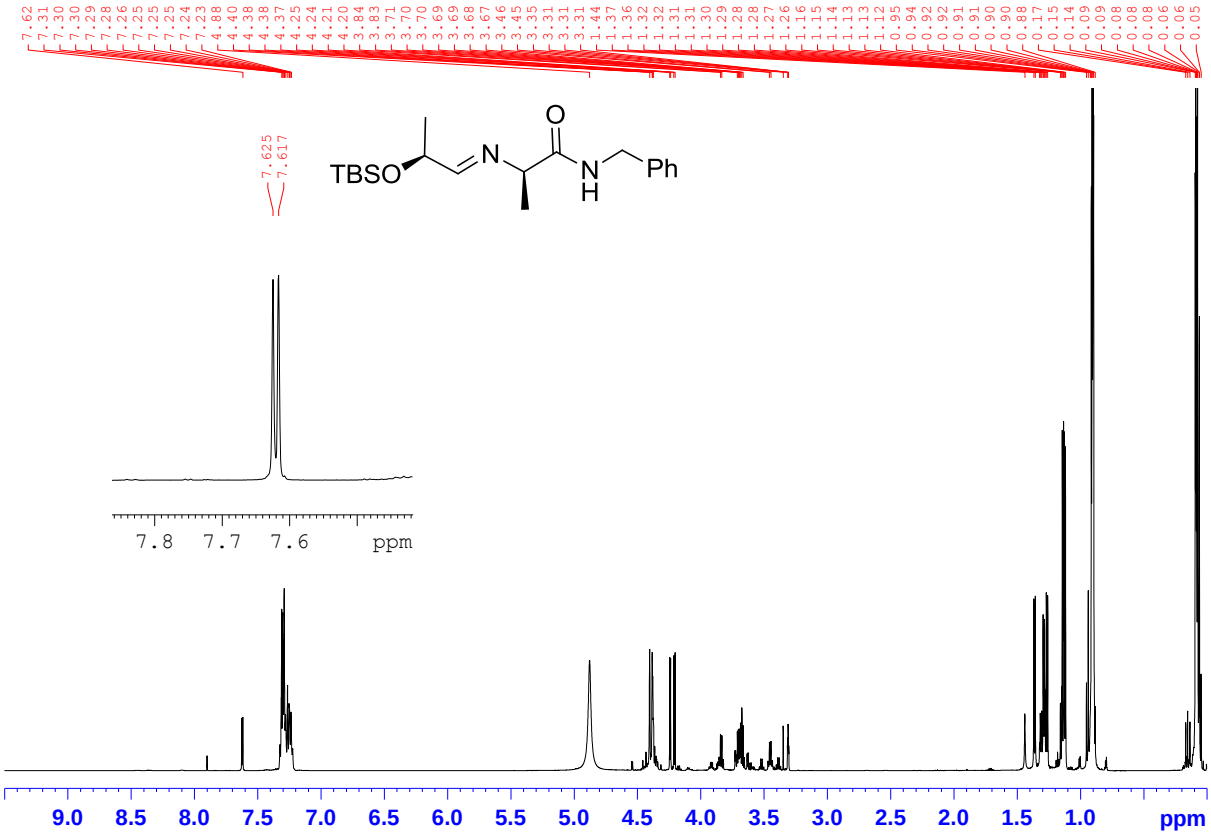
Operator     : AC                      Detector Type: ProStar/Dynamax (2 Volts)
Workstation:                           Bus Address  : 24
Instrument : 218 System                Sample Rate  : 5.00 Hz
Channel      : 1 - UV                  Run Time     : 16.570 min

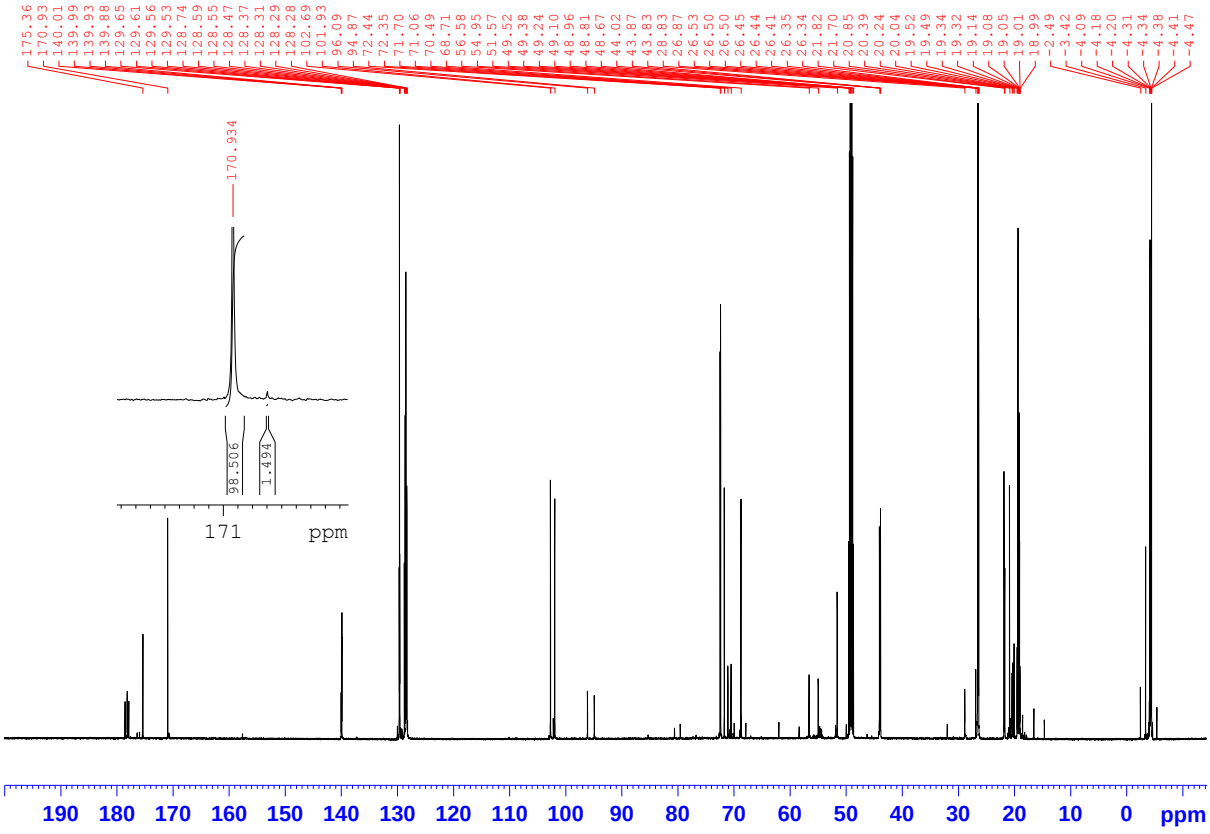
** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode         : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent
```

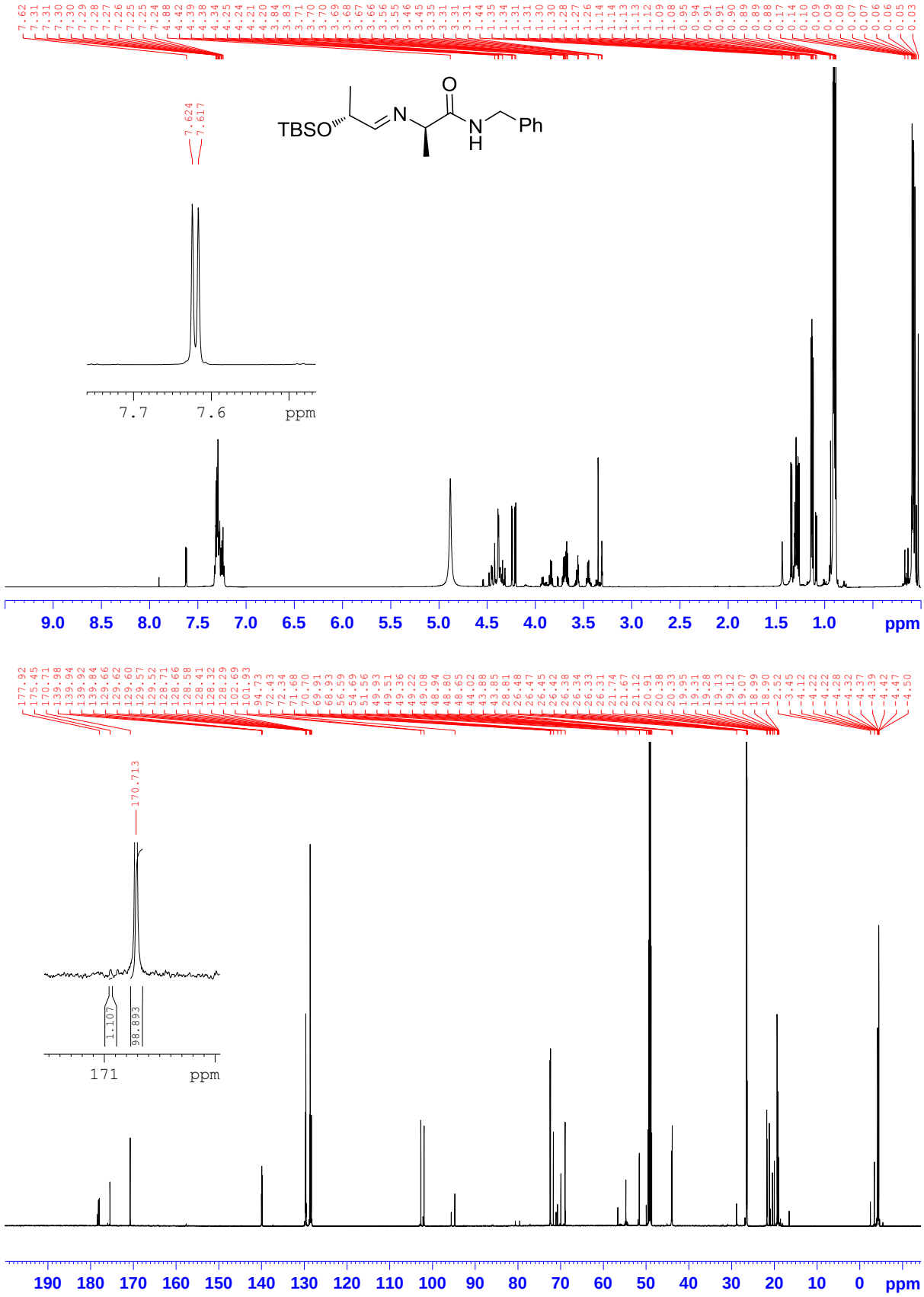
Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		49.0595	9.278	0.000	3391570	BB	49.7	
2		50.9406	11.852	0.000	3521614	BB	62.9	
	Totals:	100.0001		0.000	6913184			

Amide 26b and (*S*)-4

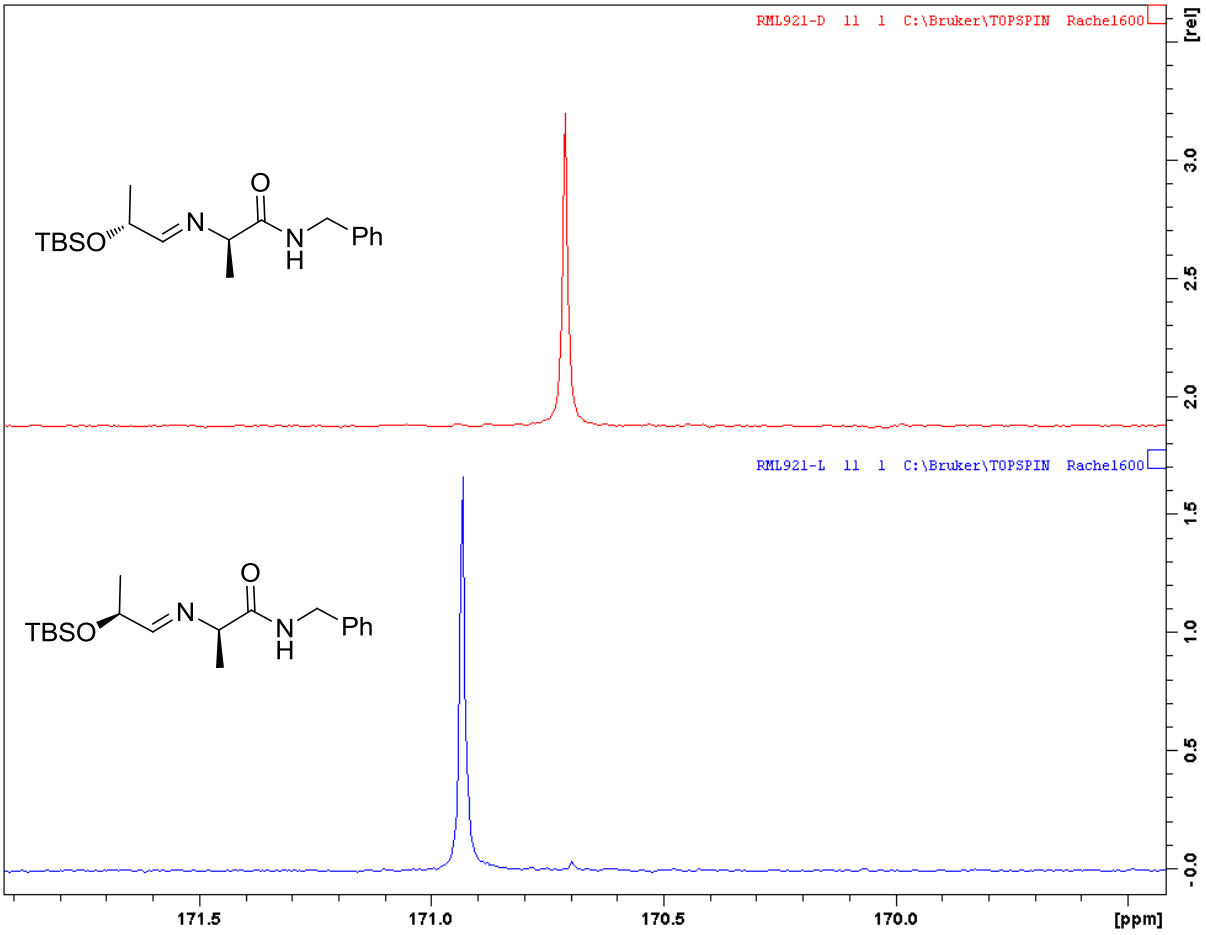




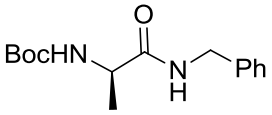
Amide 26b and (*R*)-4

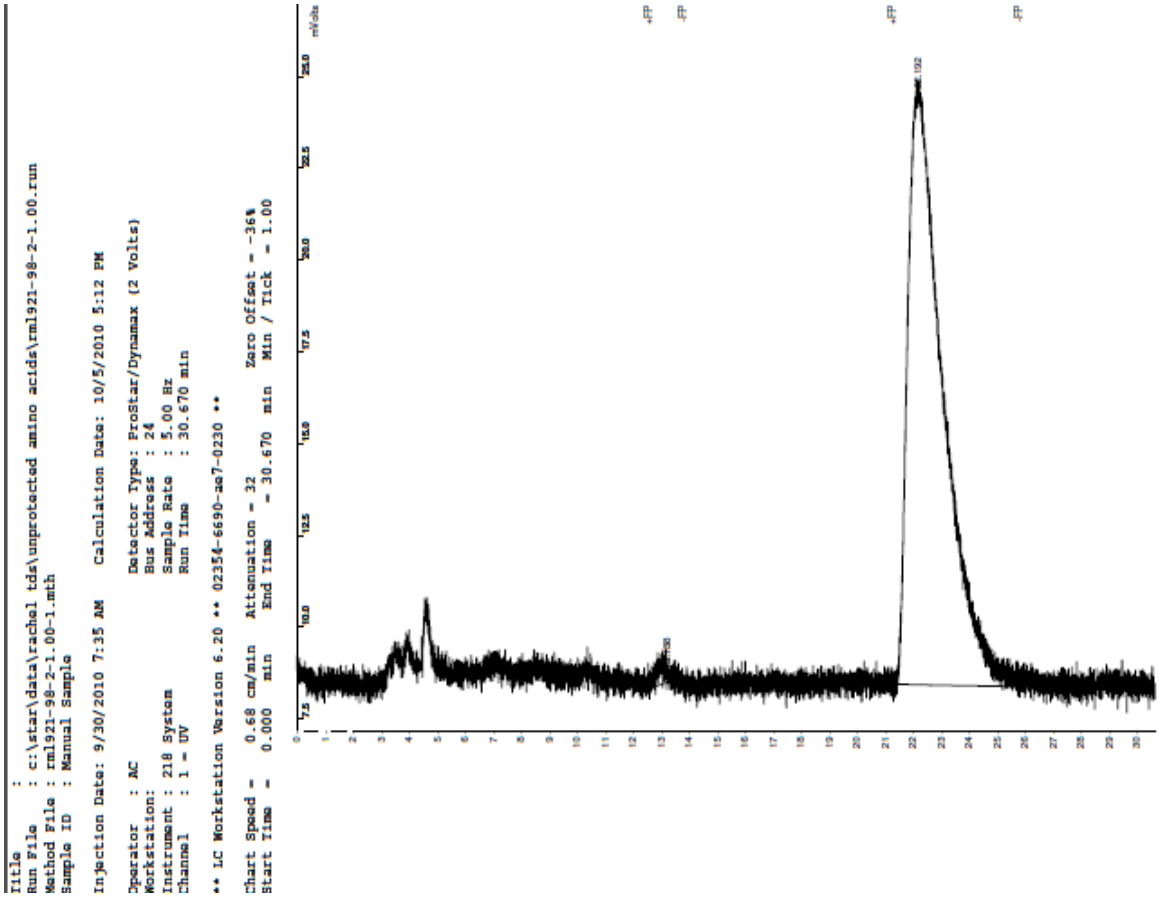


Amide 26b and (*S*)-4/Amide 26a and (*R*)-4 overlaid



Amide 25b Chiral HPLC





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Title :
Run File : c:\star\data\rachel tds\unprotected amino acids\rml921-98-2-1.00.run
Method File : rml921-98-2-1.00-1.mth
Sample ID : Manual Sample

Injection Date: 9/30/2010 7:35 AM Calculation Date: 10/5/2010 5:12 PM

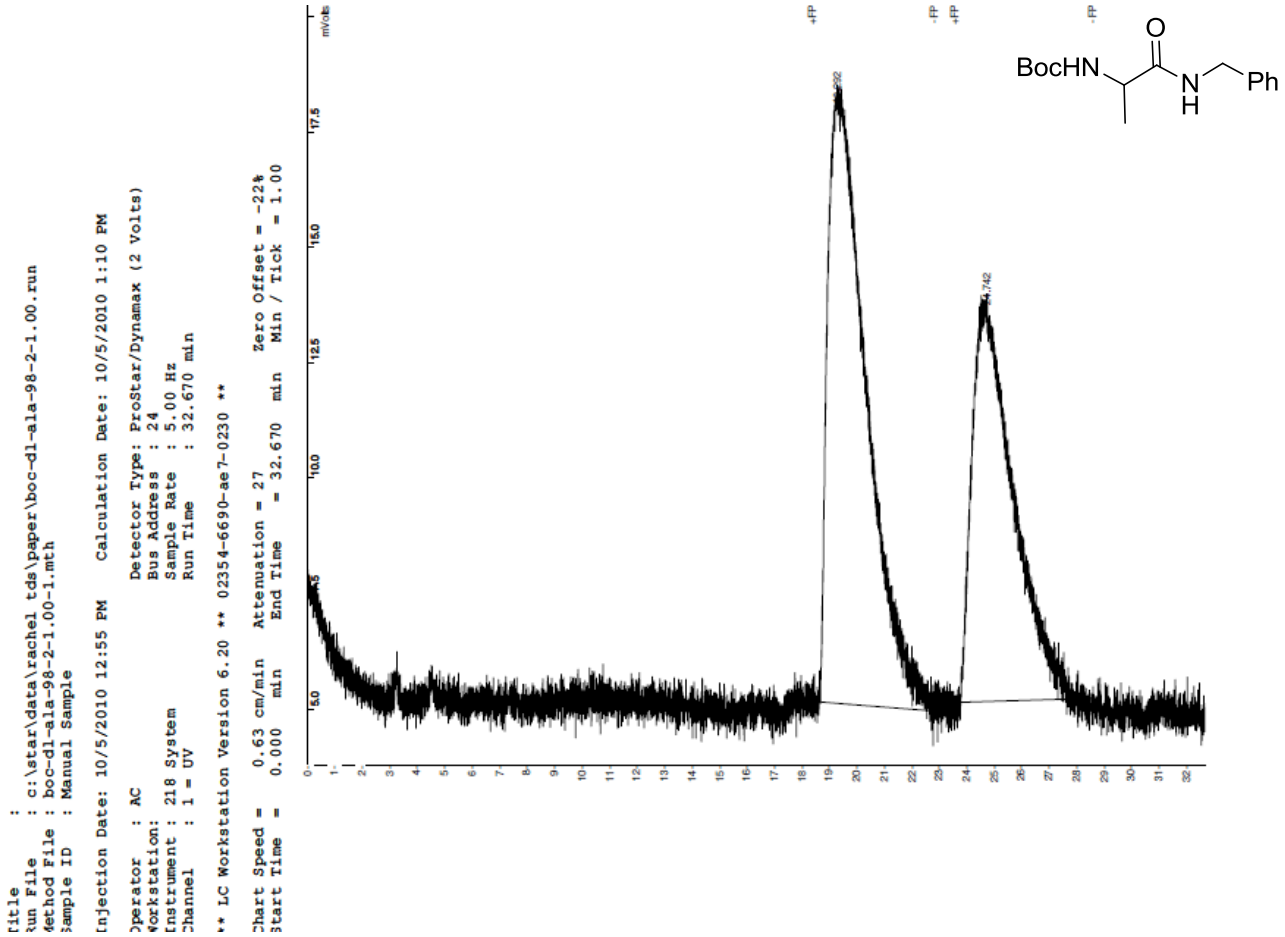
Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 - UV
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 30.670 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		0.9707	13.188	0.000	13881	BB	0.3	
2		99.0293	22.192	0.000	1416128	BB	76.2	
	Totals:	100.0000		0.000	1430009			

(±)-25b chiral HPLC



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Title :
Run File : c:\star\data\rachel tds\paper\boc-dl-ala-98-2-1.00.run
Method File : boc-dl-ala-98-2-1.00-1.mth
Sample ID : Manual Sample

Injection Date: 10/5/2010 12:55 PM Calculation Date: 10/5/2010 1:10 PM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 - UV

Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 32.670 min

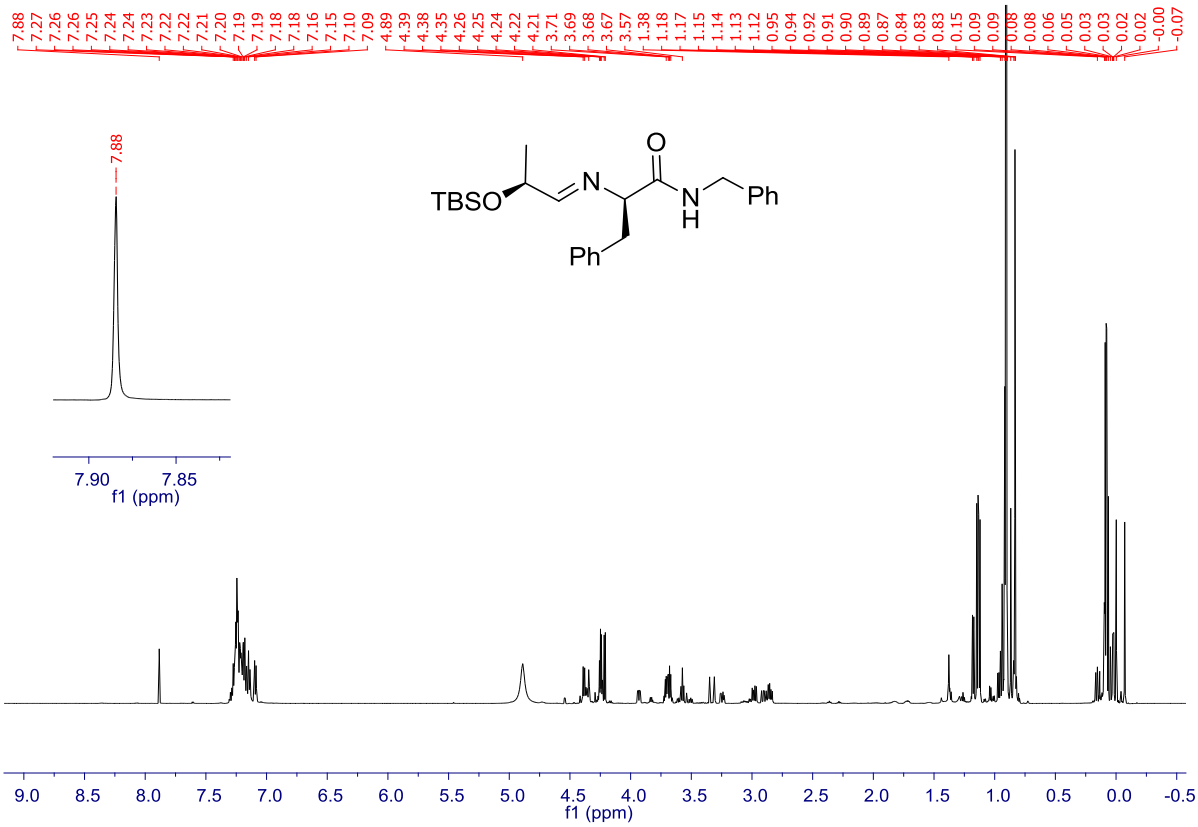
** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

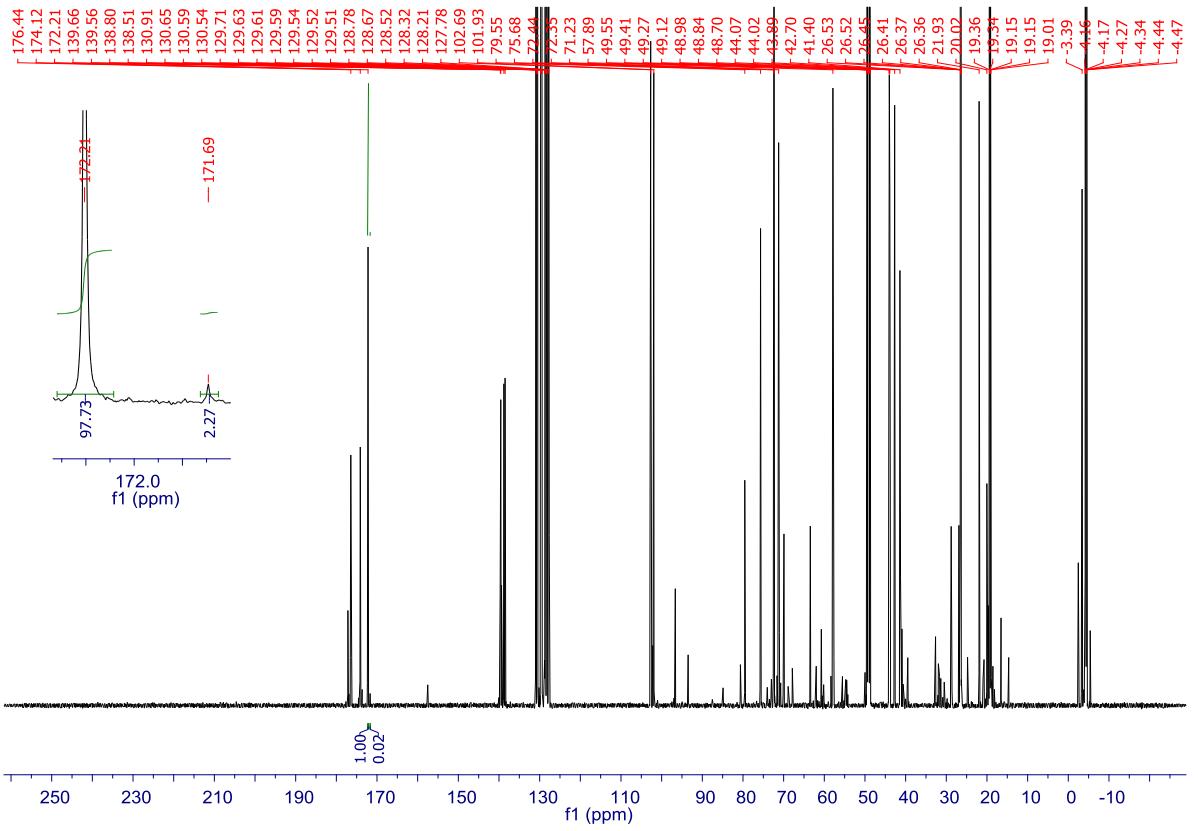
Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		59.1229	19.292	0.000	1295464	BB	85.5	
2		40.8771	24.742	0.000	895673	BB	89.4	
	Totals:	100.0000		0.000	2191137			

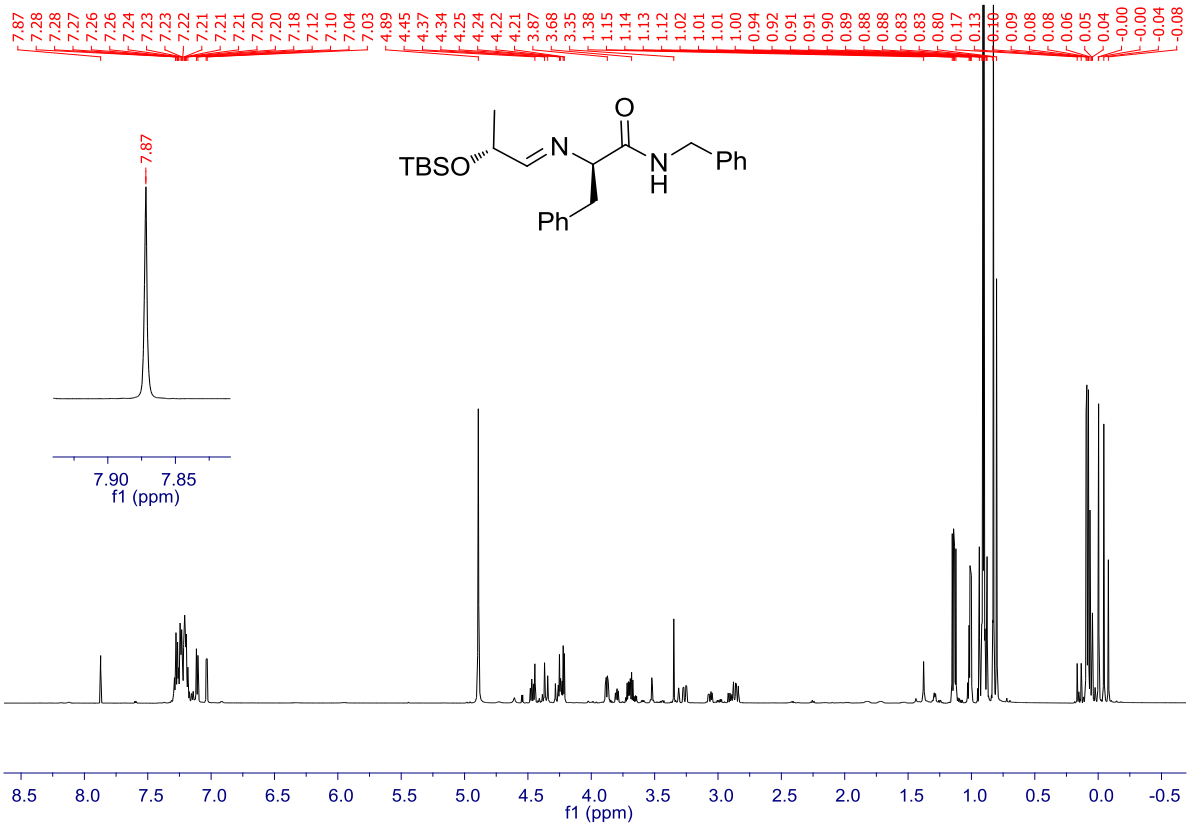
Total Unidentified Counts : 2191137 counts

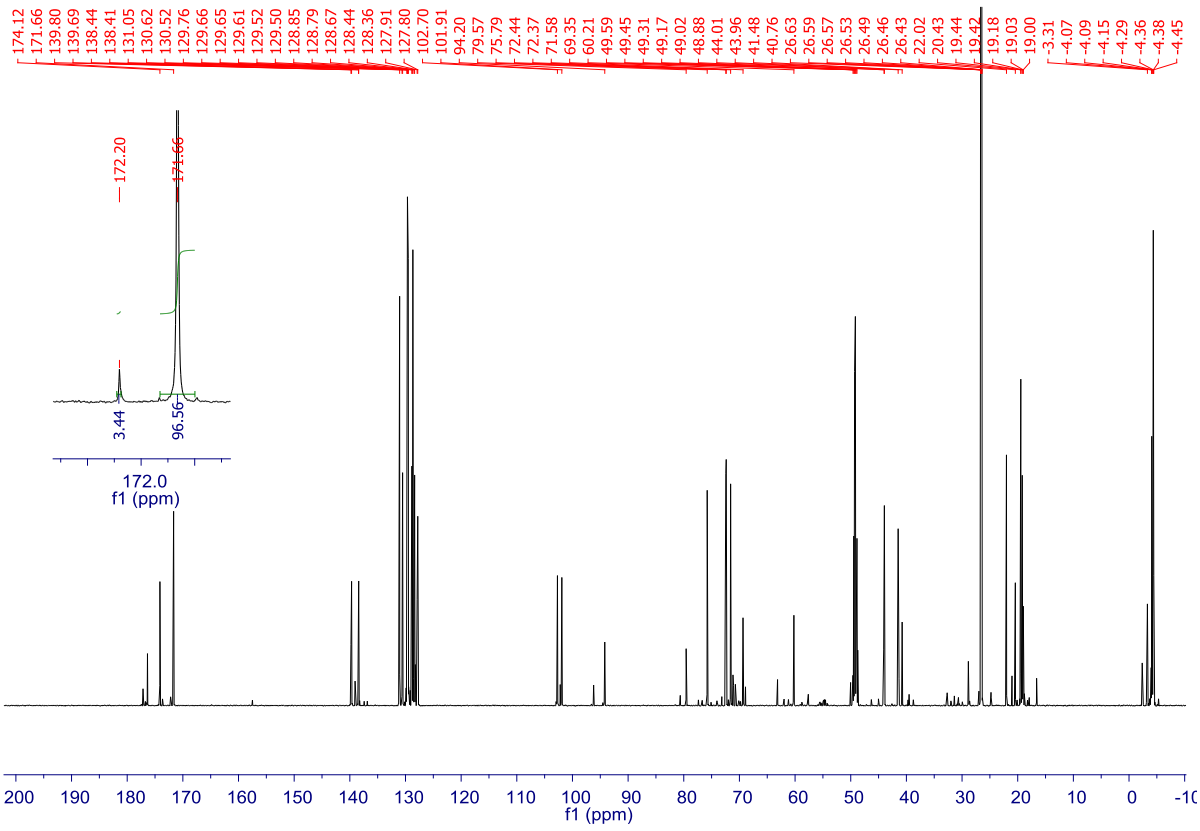
Amide 26c and (*S*)-4



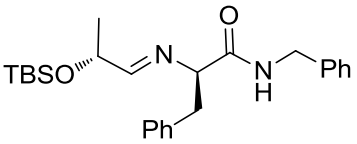


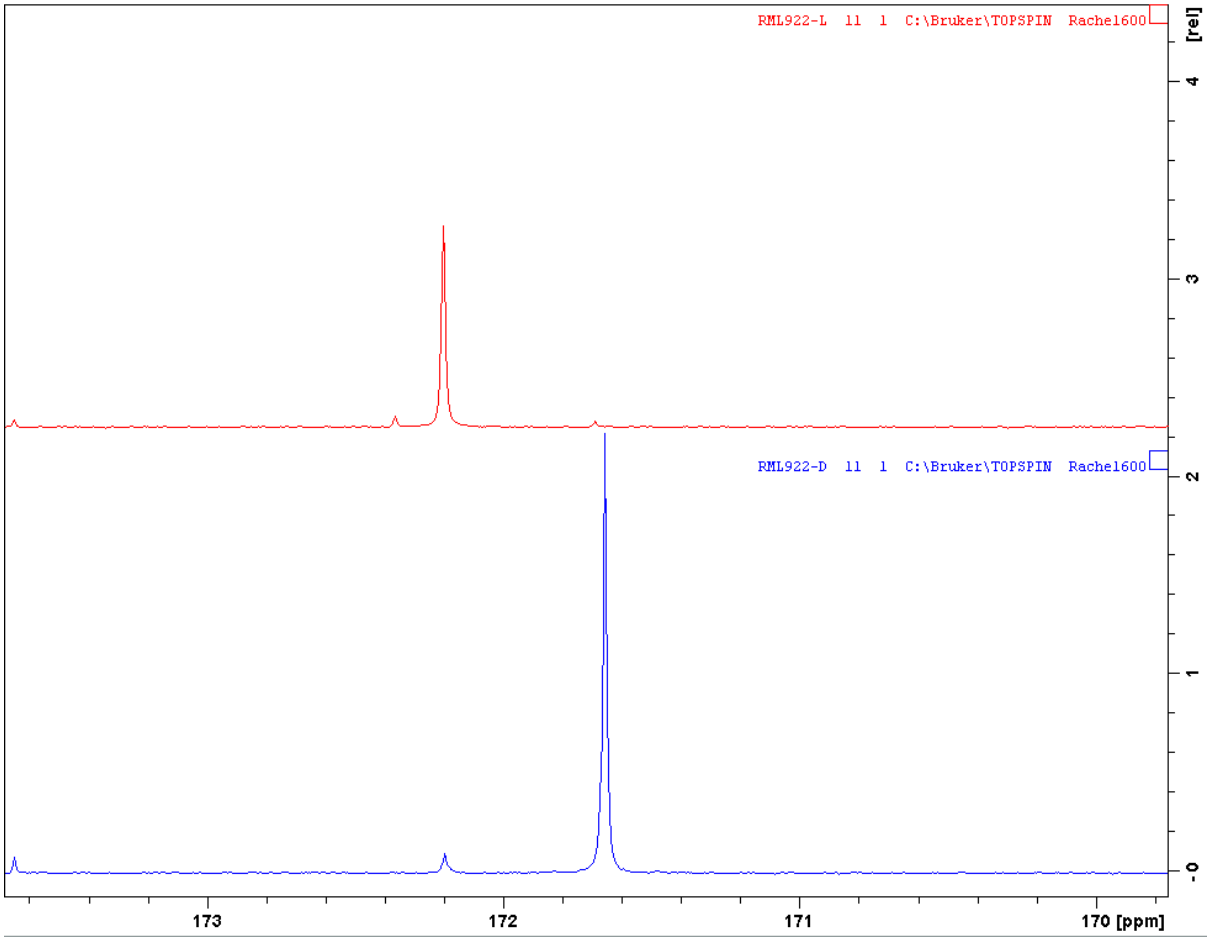
Amide 26c and (*R*)-4



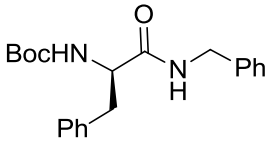


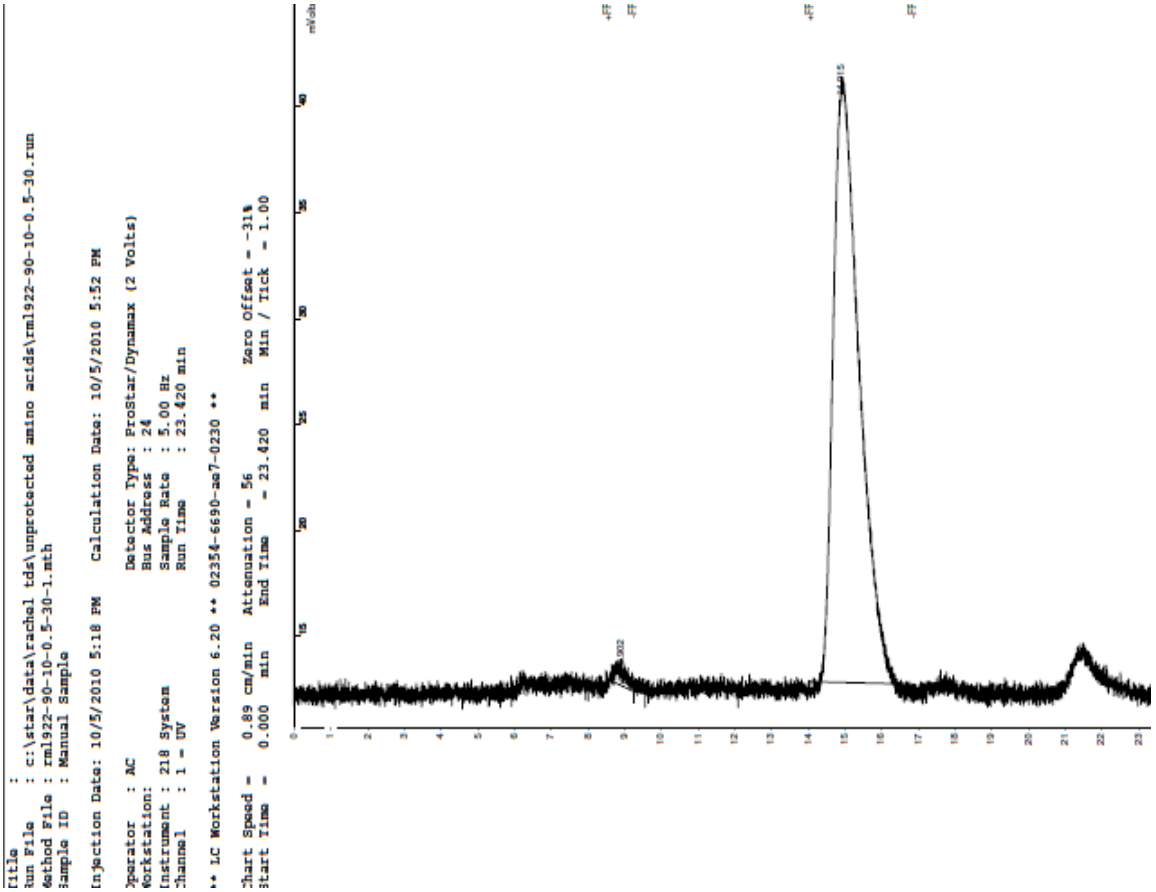
Amide 26c and (*S*)-4/Amide 26a and (*R*)-4 overlaid





Amide 25c Chiral HPLC





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Title :
Run File : c:\star\data\rachel tds\unprotected amino acids\rml922-90-10-0.5-30.run
Method File : rml922-90-10-0.5-30-1.mth
Sample ID : Manual Sample

Injection Date: 10/5/2010 5:18 PM Calculation Date: 10/5/2010 5:52 PM

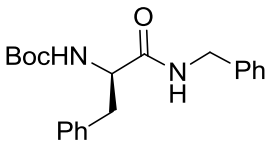
Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 = UV
Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 23.420 min

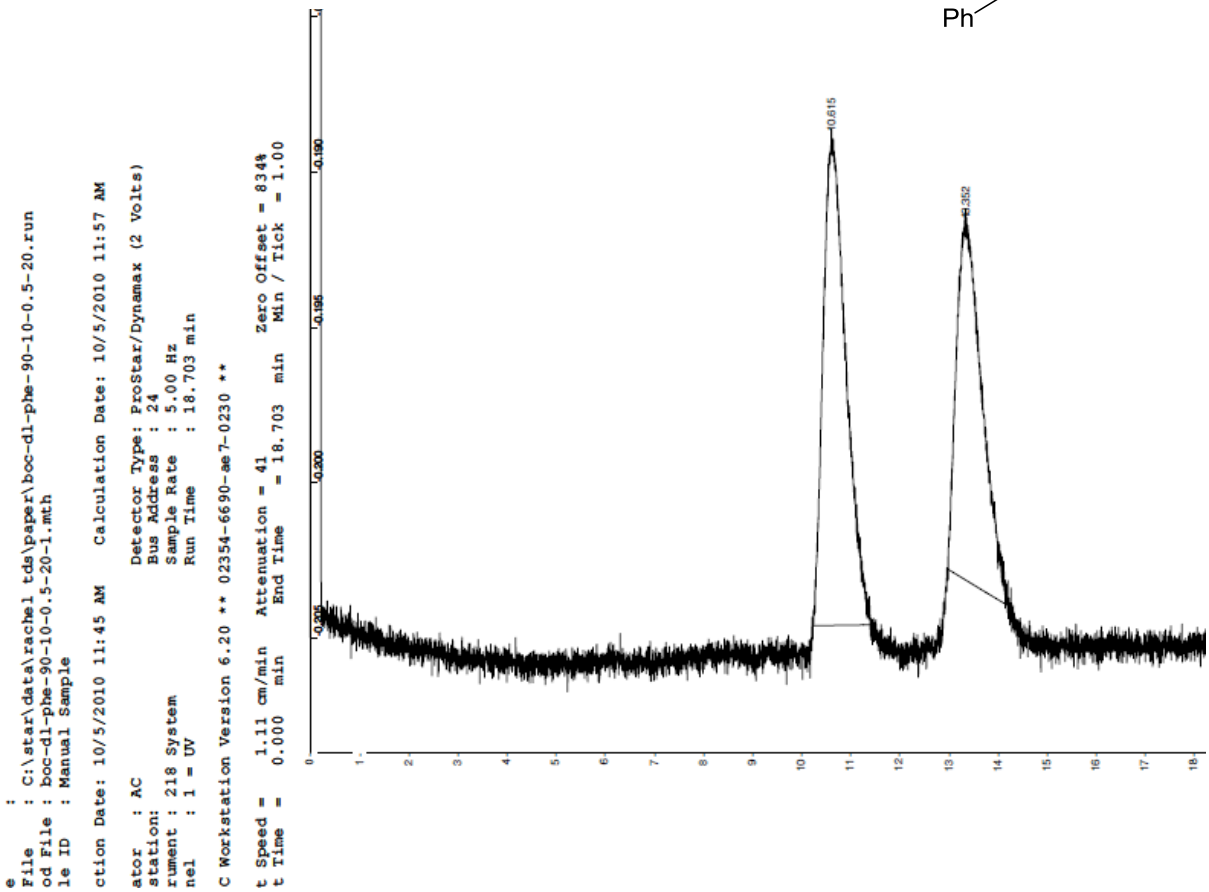
** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		1.2955	8.902	0.000	18165	BB	0.5	
2		98.7045	14.915	0.000	1384045	BB	44.7	
Totals:		100.0000		0.000	1402210			

(±)-Amide 25c Chiral HPLC





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Title :
Run File : C:\star\data\rachel tds\paper\boc-dl-phe-90-10-0.5-20.run
Method File : boc-dl-phe-90-10-0.5-20-1.mth
Sample ID : Manual Sample

Injection Date: 10/5/2010 11:45 AM Calculation Date: 10/5/2010 11:57 AM

Operator : AC
Workstation:
Instrument : 218 System
Channel : 1 - UV

Detector Type: ProStar/Dynamax (2 Volts)
Bus Address : 24
Sample Rate : 5.00 Hz
Run Time : 18.703 min

** LC Workstation Version 6.20 ** 02354-6690-ae7-0230 **

Run Mode : Analysis
Peak Measurement: Peak Area
Calculation Type: Percent

Peak No.	Peak Name	Result ()	Ret. Time (min)	Time Offset (min)	Area (counts)	Sep. Code	Width 1/2 (sec)	Status Codes
1		54.8020	10.615	0.000	505270	BB	29.9	
2		45.1980	13.352	0.000	416721	BB	31.0	
	Totals:	100.0000		0.000	921991			

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