Organocatalytic Sequential α-Amination-Horner-Wadsworth-Emmons Olefination of Aldehydes: Enantioselective Synthesis of γ-Amino-α,β-Unsaturated Esters

Shriram P. Kotkar, Vilas B. Chavan and Arumugam Sudalai

Chemical Engineering and Process Development Division, National Chemical Laboratory, Pashan Road, Pune 411008, India
a.sudalai@ncl.res.in

Supporting Information

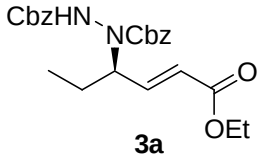
General Information

Solvents were purified and dried by standard procedures before use; petroleum ether of boiling range 60–80 ^{o}C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a JASCO-181 digital polarimeter. Infrared spectra were recorded on Shimadzu FTIR-8400 spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on Bruker AV-200 and AV-400 NMR spectrometers, respectively. Elemental analysis was carried on a Carlo Erba CHNS-O analyzer. HPLC was performed on Dionex P680 with variable wavelength detector using Chiracel OD-H column from Diacel.

General experimental procedure for sequential α-amination/ Horner-Wodsworth-Emmons olefination:

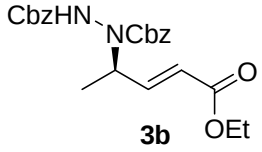
To a cooled solution of dibenzyl azodicarboxylate (DBAD) (328 mg, 1 mmol) and L-proline (11.5 mg, 10 mol%) in CH_3CN (10 mL) at 0 °C was added *n*-butyraldehyde (87 mg, 1.2 mmol) and the mixture was stirred for 2h at 0 °C and further for 1 h at 10 °C. This was followed by addition of lithium bromide (130 mg, 1.5 mmol), triethyl phosphonoacetate (336 mg, 1.5 mmol) and DBU (152 mg, 1 mmol) in that sequence and the whole mixture was stirred at 5 °C for 45 min. It was then quenched with aq. ammonium chloride solution and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4 and concentrated under

reduced pressure to give the crude product **3a**, which was then purified by flash column chromatography (packed with silica gel 60-120 mesh) using petroleum ether and ethyl acetate as eluents to afford the pure product.



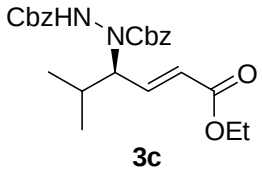
3a

3a, Viscous liquid; Yield: 84%; HPLC: Chiracel OD-H column (2-Propanol: *n*-Hexane = 4:96, flow rate 1.0 mL/min, λ = 260 nm). Retention time (min): 40.15 (major) and 54.95 (minor). The racemic standard was prepared in the same way with DL-proline as a catalyst, ee 99%; $[\alpha]^{25}_{D}$ +10 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) ν 3389, 3020, 2926, 2852, 1758, 1715, 1289, 1215, 1041, 757 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) δ 0.94 (m, 3H), 1.25 (t, *J* = 7 Hz, 3H), 1.62 (m, 2H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.64 (m, 1H), 5.11 (m, 4H), 5.85 (d, *J* = 15.5 Hz, 1H), 6.86 (m, 2H), 7.28 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 10.42, 13.90, 23.88, 60.32, 64.70, 67.45, 68.01, 122.25, 127.48, 127.87, 128.25, 144.77, 155.53, 156.56, 166.09; Analysis: $C_{24}H_{28}N_2O_6$ requires C, 65.44; H, 6.41; N, 6.36; found C, 65.25; H, 6.28; N, 6.59%.



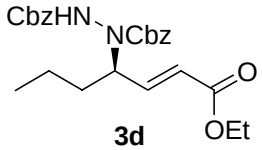
3b

3b, Colorless solid; mp: 80 °C; Yield: 83%; HPLC: Chiracel OD-H column (2-Propanol: *n*-Hexane = 6:94, flow rate 1.0 mL/min, λ = 260 nm). Retention time (min): 24.39 (minor) and 31.49 (major), ee 92%; $[\alpha]^{25}_{D}$ +5 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) ν 3301, 3020, 1750, 1713, 1407, 1285, 1216, 1029, 758 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.2 Hz, 3H), 1.30 (d, *J* = 6.8 Hz, 3H), 4.11 (q, *J* = 7.2 Hz, 2H), 5.12 (m, 5H), 5.83 (d, *J* = 16.1 Hz, 1H), 6.85-6.96 (dd, *J* = 15.7, 5.3 Hz, 1H), 7.08 (s, 1H), 7.29 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.02, 16.25, 54.21, 60.40, 66.55, 68.14, 121.84, 127.72, 127.95, 128.14, 128.35, 135.57, 146.50, 152.21, 156.61,166.11; Analysis: $C_{23}H_{26}N_2O_6$ requires C, 64.78; H, 6.15; N, 6.57; found C, 64.59; H, 6.27; N, 6.59%.



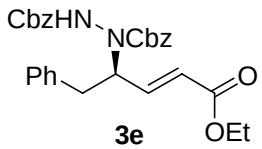
3c

3c, Viscous liquid; Yield: 80%; HPLC: Chiracel OD-H column (2-Propanol: *n*-Hexane = 3:97, flow rate 1.0 mL/min, λ = 260 nm). Retention time (min): 43.39 (major) and 47.94 (minor), ee 92%; $[\alpha]^{25}_{D}$ +2 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) ν 3584, 3295, 3020, 2964, 1753, 1713, 1406, 1286, 1216, 1043, 756 cm^{-1}; 1H NMR (200 MHz, $CDCl_3$) δ 0.84 (d, *J* = 6.7, 3H), 1.0 (m, 3H), 1.27 (t, *J* = 7 Hz, 3H), 1.98 (m, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.33 (m, 1H), 5.14 (m, 4H), 5.90 (d, *J* = 15.6 Hz, 1H), 6.45 (s, 1H), 6.77-6.89 (dd, *J* = 15.7, 9.1 Hz, 1H), 7.31 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.19, 19.55, 20.00, 29.31, 60.53, 65.52, 67.79, 68.32, 124.26, 127.85, 128.52, 135.73, 143.62, 155.84, 156.54, 166.20; Analysis: $C_{25}H_{30}N_2O_6$ requires C, 66.06; H, 6.65; N, 6.16; found C, 66.17; H, 6.61; N, 6.31%.



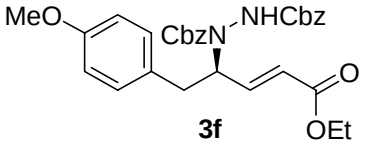
3d

3d, Colorless solid; mp: 72 °C; Yield: 85%; HPLC: Chiracel OD-H column (2-Propanol: *n*-Hexane = 3:97, flow rate 1.0 mL/min, λ = 260 nm). Retention time (min): 25.79 (minor) and 28.42 (major), ee 95%; $[\alpha]^{25}_{D}$ +8 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) ν 3295, 2936, 2962, 1714, 1407, 1281, 1216, 1042, 756 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.90 (m, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.53-1.77 (m, 4H), 4.13 (q, *J* = 7.2 Hz, 2H), 4.77 (m, 1H), 5.11 (m, 4H), 5.85 (d, *J* = 15.5 Hz, 1H), 6.74 (s, 1H), 6.78-6.86 (dd, *J* = 16.1, 7.2 Hz, 1H), 7.28 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.61, 13.99, 19.01, 32.77, 58.38, 60.26, 67.43, 68.02, 122.59, 127.63, 127.79, 128.26, 135.58, 145.16, 155.42, 156.51, 166.01; Analysis: $C_{25}H_{30}N_2O_6$ requires C, 66.06; H, 6.65; N, 6.16; found C, 66.27; H, 6.46; N, 6.35%.



3e

3e, Colorless solid; mp 92 °C; Yield: 88%; HPLC: Chiracel OD-H column (2-Propanol: *n*-Hexane = 6:94, flow rate 1.0 mL/min, λ = 260 nm). Retention time (min): 49.18 (minor) and 55.55 (major), ee 99%; $[\alpha]^{25}_{D}$ +8.5 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) ν 3387, 3020, 1759, 1715, 1285, 1215, 1044, 758 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H), 2.91-3.10 (m, 2H), 4.12 (q, *J* = 7.3 Hz, 2H), 5.16 (m, 5H), 5.83 (d, *J* = 15.4 Hz, 1H), 6.48 (s, 1H), 6.88-7.0 (dd, *J* = 15.7, 6.7 Hz, 1H), 7.21-7.29 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.09, 37.51, 60.32, 61.87, 67.76, 68.13, 123.11, 126.67, 127.77, 128.08, 128.36, 128.40, 128.53, 128.93, 135.51, 136.80, 143.99, 155.18, 156.55, 165.79; Analysis: $C_{29}H_{30}N_2O_6$ requires C, 69.31; H, 6.02; N, 5.57; found C, 69.25; H, 6.12; N, 5.43%.



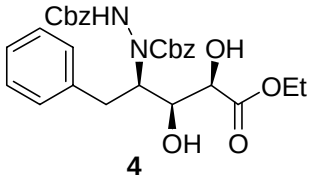
3f

3f, Colorless solid; mp: 78 °C; Yield: 88%; HPLC: Chiracel OD-H column (2-Propanol: *n*-Hexane = 3:97, flow rate 1.0 mL/min, λ = 260 nm). Retention time (min): 69.9 (minor) and 83.0 (major), ee 99%; $[\alpha]^{25}_{D}$ +4 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) ν 3384, 3020, 1753, 1715, 1513, 1249, 1216, 1038, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.90 (m, 2H), 3.76 (s, 3H), 4.13 (q, *J* = 7.2 Hz, 2H), 5.07 (m, 5H), 5.84 (d, *J* = 16.2 Hz, 1H), 6.30 (s, 1H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.87-6.99 (dd, *J* = 16.2, 7.1 Hz, 1H), 7.05 (m, 2H), 7.30 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.06, 36.64, 54.89, 60.26, 60.65, 67.69, 68.15, 113.92, 123.02, 127.73, 128.04, 128.32, 128.69, 129.87, 135.54, 144.12, 155.19, 156.52, 158.25, 165.79; Analysis: $C_{30}H_{32}N_2O_7$ requires C, 67.66; H, 6.06; N, 5.26; found C, 67.46; H, 6.16; N, 5.13%.

Experimental Procedure for Dihydroxylation:

To a solution of olefin **3e** (1 g, 2 mmol) and NMO (0.702 g, 6 mmol, 3 equiv.) in 20 mL THF-H_2O (1:1) at 0 °C, was added OsO_4 (25.4 mg, 0.1 M in toluene, 5 mol%) and the reaction mixture was stirred at the same temperature for 12 h and at 25 °C for 6 h. The reaction was quenched with sodium bisulfite (0.5 g), diluted with water and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude

product, which was then purified by flash column chromatography using petroleum ether: ethyl acetate (40:60) to afford pure diol **4**.

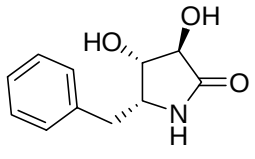


4

4, Colorless solid; mp: 80 °C; Yield: 92%; $[\alpha]^{25}_{D}$ +16 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) ν 3390, 3218, 3020, 2929, 2400, 1667, 1427, 1215, 1075, 923, 758 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7 Hz, 3H), 2.51-2.77 (m, 2H), 3.87 (m, 1H), 4.13-4.24 (q, *J* = 7 Hz, 2H), 4.30 (m, 1H), 4.62-4.96 (m, 5H), 6.94-7.38 (m, 15H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.62, 31.81, 58.89, 61.61, 65.38, 65.56, 69.38, 69.66, 124.32, 125.44, 125.55, 125.95, 126.07, 126.32, 126.55, 126.77, 127.57, 127.76, 134.35, 134.65, 154.61, 170.75; Analysis: $C_{29}H_{32}N_2O_8$ requires C, 64.91; H, 6.01; N, 5.22; found C, 64.55; H, 6.15; N, 5.18%.

Synthesis of (3*R*, 4*S*, 5*R*)-5-benzyl-3,4-dihydroxypyrrolidine-2-one (5):

5: The solution of diol **4** (0.804 mg, 1.5 mmol) in MeOH (20 mL) and acetic acid (10 drops) was treated with Raney nickel (3 g, excess) under H_2 (80 psig) atmosphere for 24 h. The reaction mixture was filtered over celite and concentrated to give crude aminodiol which on strirring in EtOH at 50 °C for 5h cyclized to product **5** (purified by flash chromatography using ethyl acetate as eluent).

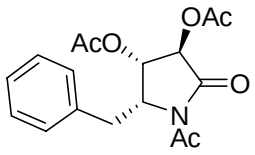


5

5, Colorless solid; mp: 180 °C; Yield: 65%; $[\alpha]^{25}_{D}$ +106 (*c* 1.0, $CHCl_3$). IR (nujol) ν 3320, 2918, 2854, 1668, 1461, 1377, 1112, 721 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$ + DMSO-d_6) δ 2.55 (m, 1H), 2.97-3.07 (dd, *J* = 4.6, 13.7 Hz, 1H), 3.71 (m, 1H), 3.79 (d, *J* = 7.4 Hz, 1H), 4.09 (t, *J* = 7.2 Hz, 1H), 7.24 (m, 5H), 7.61 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$+DMSO-d_6): δ 35.06, 54.82, 72.35, 73.64, 124.76, 124.91, 128.28, 137.43, 173.22;

Analysis: $C_{11}H_{13}NO_3$ requires C, 63.76; H, 6.32; N, 6.76; found C, 63.56; H, 6.67; N, 6.88%.

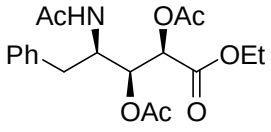
Synthesis of triacetate derivative (6): Acetylation was carried out by treating **5** (207 mg, 1 mmol) with triethyl amine (404 mg, 4 mmol), acetic anhydride (408 mg, 4 mmol) and cat. DMAP in CH_2Cl_2 (8 mL) for 2 h. The crude product was purified by flash column chromatography using pet ether: ethyl aceate (80:20) to afford pure **6**.



6

6, Colorless solid; mp: 105 °C; Yield: 94%; $[\alpha]^{25}_D$ +44 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) ν 3031, 1751, 1703, 1373, 1215, 1074, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.94 (s, 3H), 2.12 (s, 3H), 2.56 (s, 3H), 2.98 (dd, *J* = 14.2, 2.6 Hz 2H), 3.08 (dd, *J* = 14.2, 7.8, 2H), 4.97 (dt, *J* = 7.9, 2.8 Hz, 1H), 5.34 (d, *J* = 9.8 Hz, 1H), 5.41 (dd, *J* = 8, 9.7 Hz, 1H), 7.21-7.33 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.36, 25.72, 33.96, 54.57, 71.11, 72.31, 127.10, 128.58, 129.70, 135.94, 167.08, 169.50, 169.82, 170.08; Analysis: $C_{17}H_{19}NO_6$ requires C, 61.25; H, 5.75; N, 4.20; found C, 61.59; H, 5.40; N, 4.41%.

Synthesis of triacetate 7: Hydrogenation of **4** was carried out using the same procedure as described for **5**, followed by direct acetylation (as described for **6**) using acetic anhydride and triethyl amine gave crude **7** which was purified by flash column chromatography using ethyl aceate as eluent.



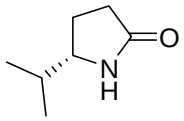
7

7, Colorless solid; mp: 85 °C; Yield: 77%; $[\alpha]^{25}_D$ +30.18 (*c* 1.0, MeOH); IR ($CHCl_3$) ν 3019, 1750, 1677, 1513, 1373, 1215, 1047, 756 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.1, 3H), 1.90 (s, 3H), 2.06 (s, 3H), 2.14 (s, 3H), 2.77 (m, 2H), 4.14 (m, 2H), 4.57 (m, 1H), 5.22 (d, *J* = 3.6 Hz, 1H), 5.33 (dd, *J* = 3.5, 5.7 Hz, 1H), 5.69 (d, *J* = 9.3 Hz, 1H), 7.14-7.29 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.98, 20.40, 20.51, 23.13, 38.08, 50.55, 61.89, 71.14, 71.66, 126.94, 128.62, 129.17, 136.31, 166.75, 169.18, 169.62,

169.89; Analysis: $C_{19}H_{25}NO_7$ requires C, 60.15; H, 6.64; N, 3.69; found C, 60.28; H, 6.78; N, 3.52%.

Synthesis of (*S*)-5-isopropylpyrrolidin-2-one (8):

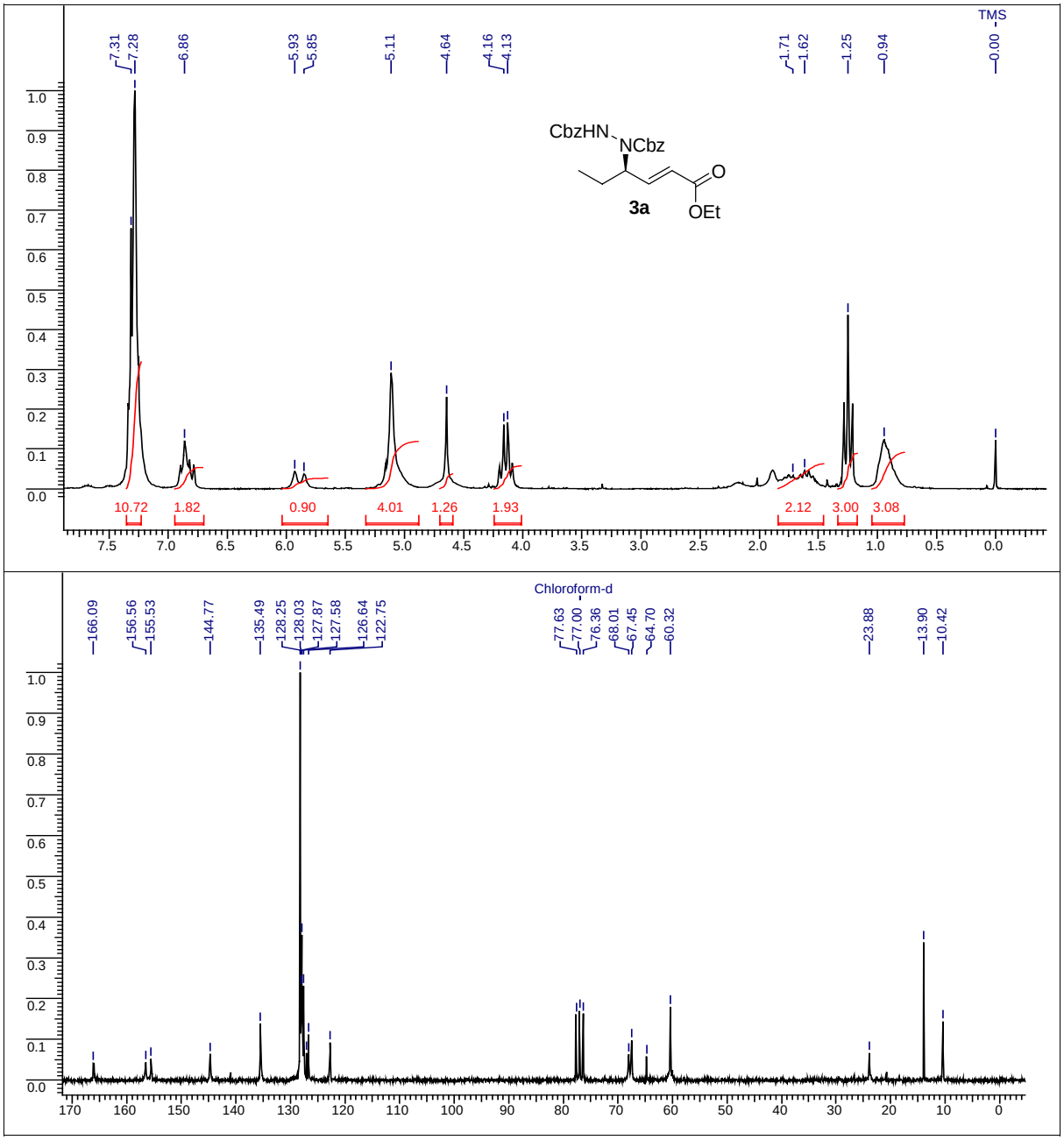
Hydrogenation of **3c** was carried out using the same procedure described for **5** followed by cyclization in EtOH furnished crude **8** which was purified by flash chromatography (ethyl acetate).

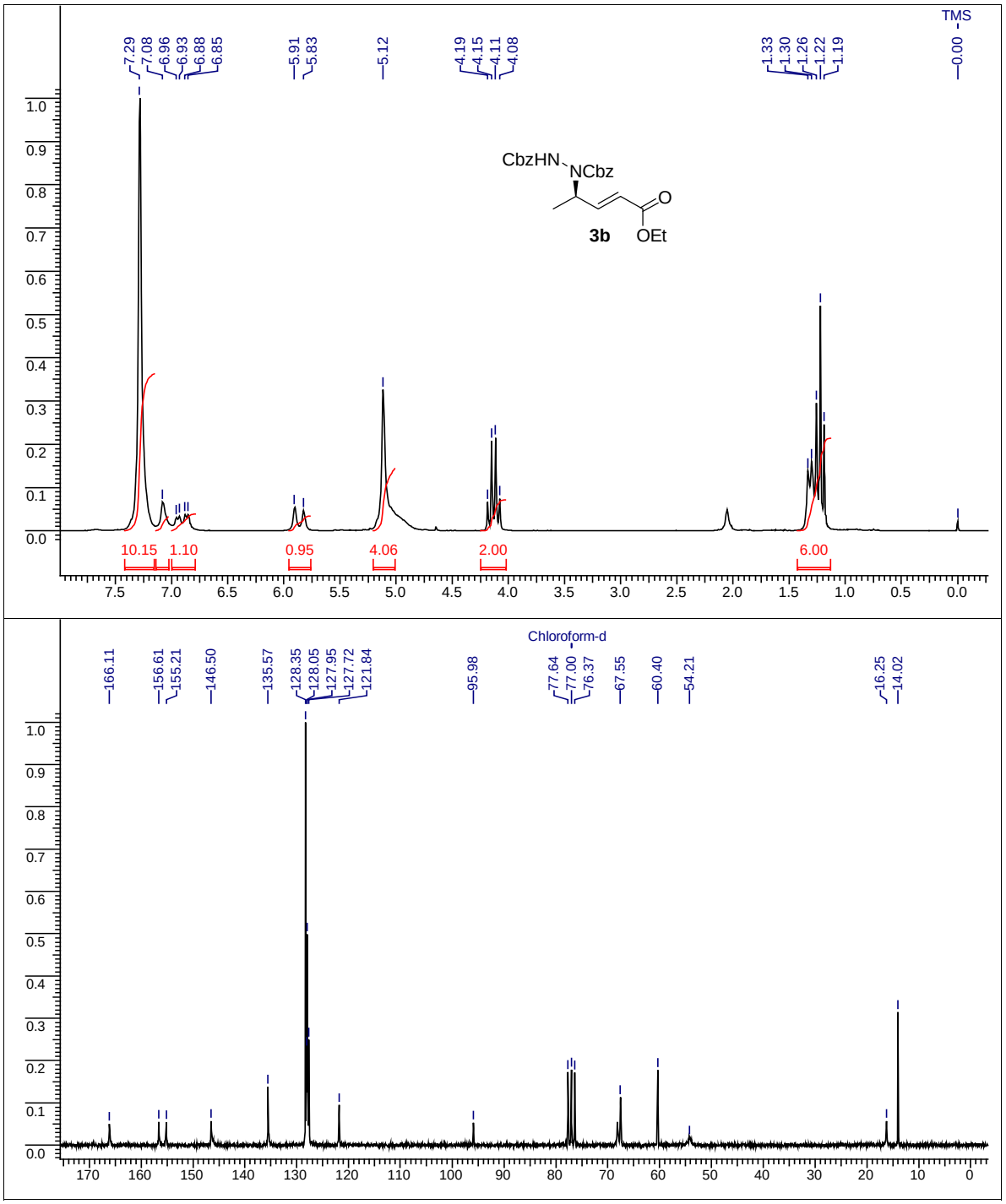


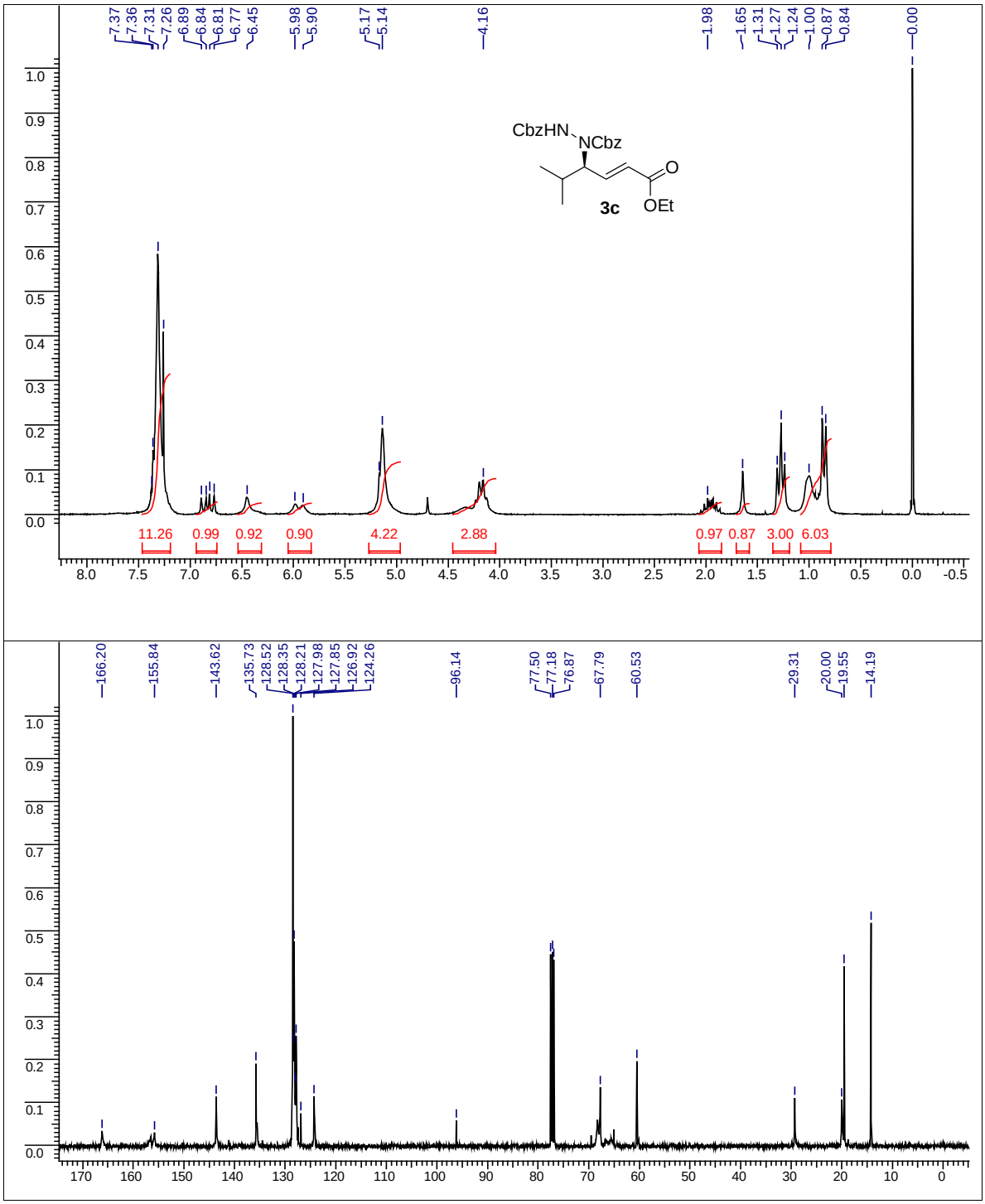
8

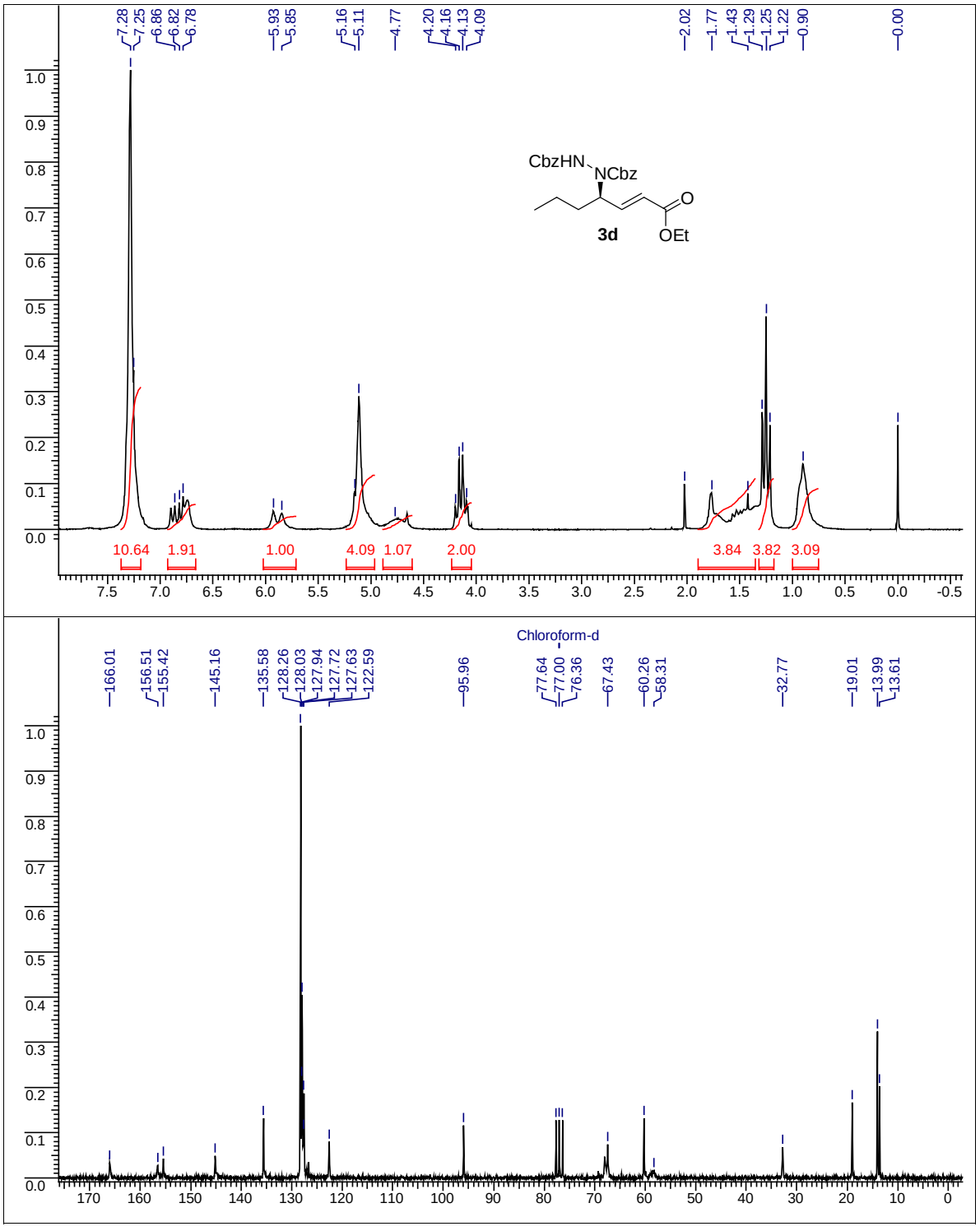
8, Colorless solid; mp: 65 °C; Yield: 70%; $[\alpha]^{25}_D$ -16.5 (*c* 2.0, CH_2Cl_2) [lit[21] $[\alpha]^{25}_D$ -18.2 (*c* 2.0, CH_2Cl_2)]. IR ($CHCl_3$) ν 3220, 2966, 1697, 1458, 1388, 1271, 754 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H), 1.62 (p, *J* = 6.8 Hz, 1H), 1.77 (m, 1H), 2.11-2.38 (m, 3H), 3.38 (q, *J* = 6.9 Hz, 1H), 7.53 (brs, 1H) ; ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.04, 18.65, 24.51, 30.58, 33.45, 60.79, 179.16; Analysis: $C_7H_{13}NO$ requires C, 66.10; H, 10.3; N, 11.01; found C, 65.57; H, 10.33; N, 11.4%.

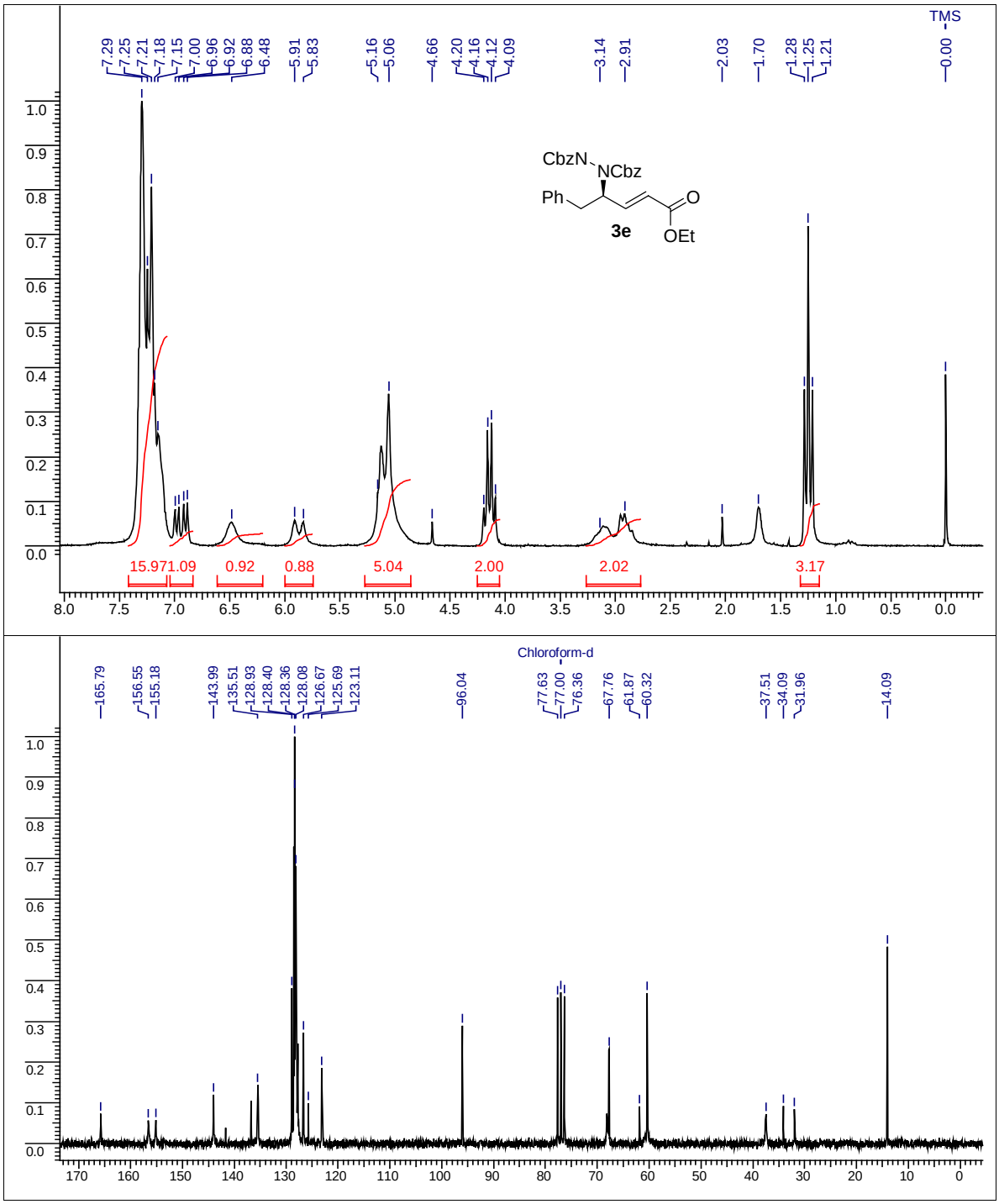
SPECTRA

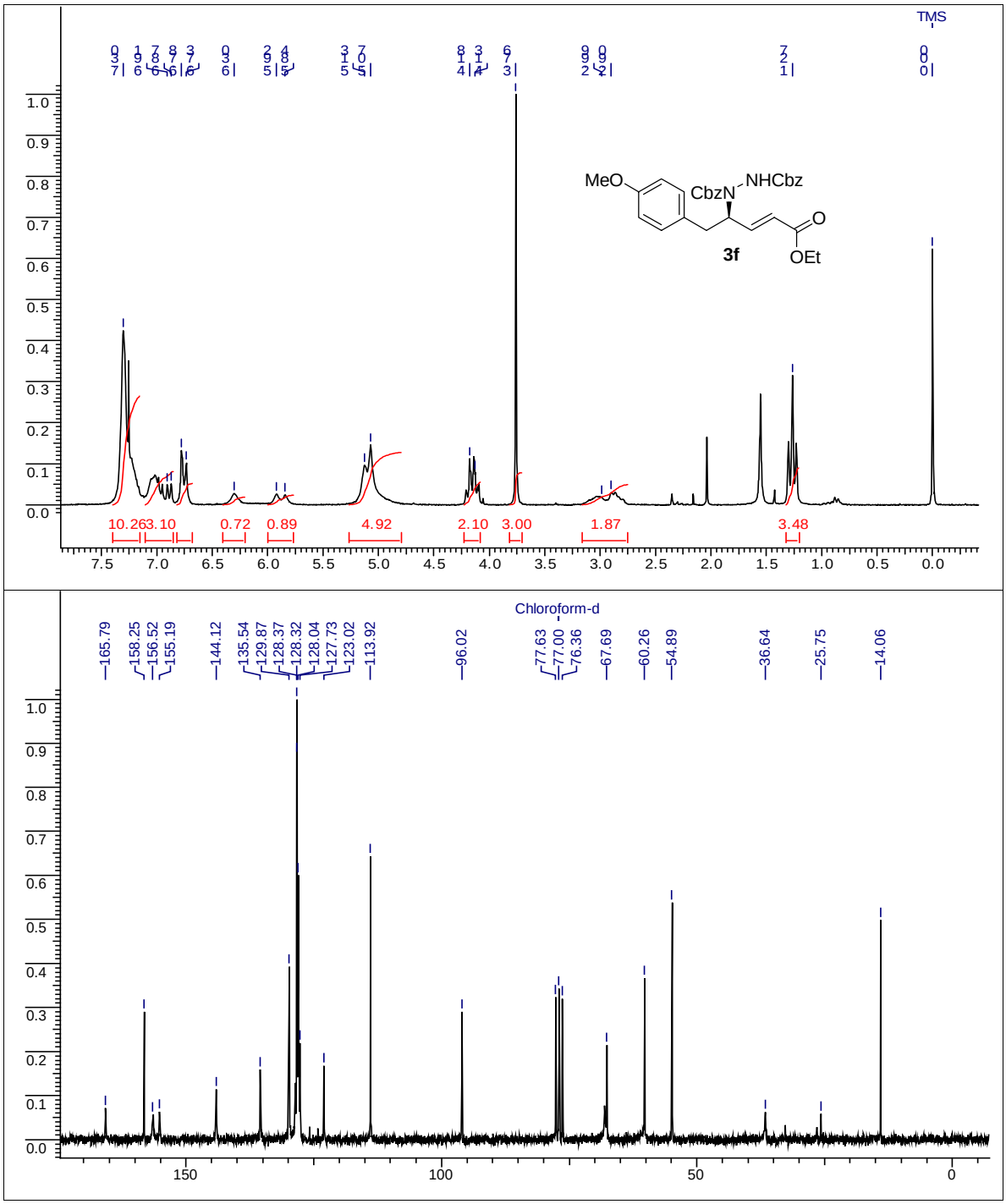

TMS
7.31
7.28
6.86
5.93
5.85
5.11
4.64
4.16
4.13
1.71
1.62
1.25
0.94
0.00
CbzHN
NCbz
O
OEt
3a
10.72
1.82
0.90
4.01
1.26
1.93
2.12
3.00
3.08
Chloroform-d
166.09
156.56
155.53
144.77
135.49
128.25
128.03
127.87
127.58
126.64
122.75
77.63
77.00
76.36
68.01
67.45
64.70
60.32
23.88
13.90
10.42

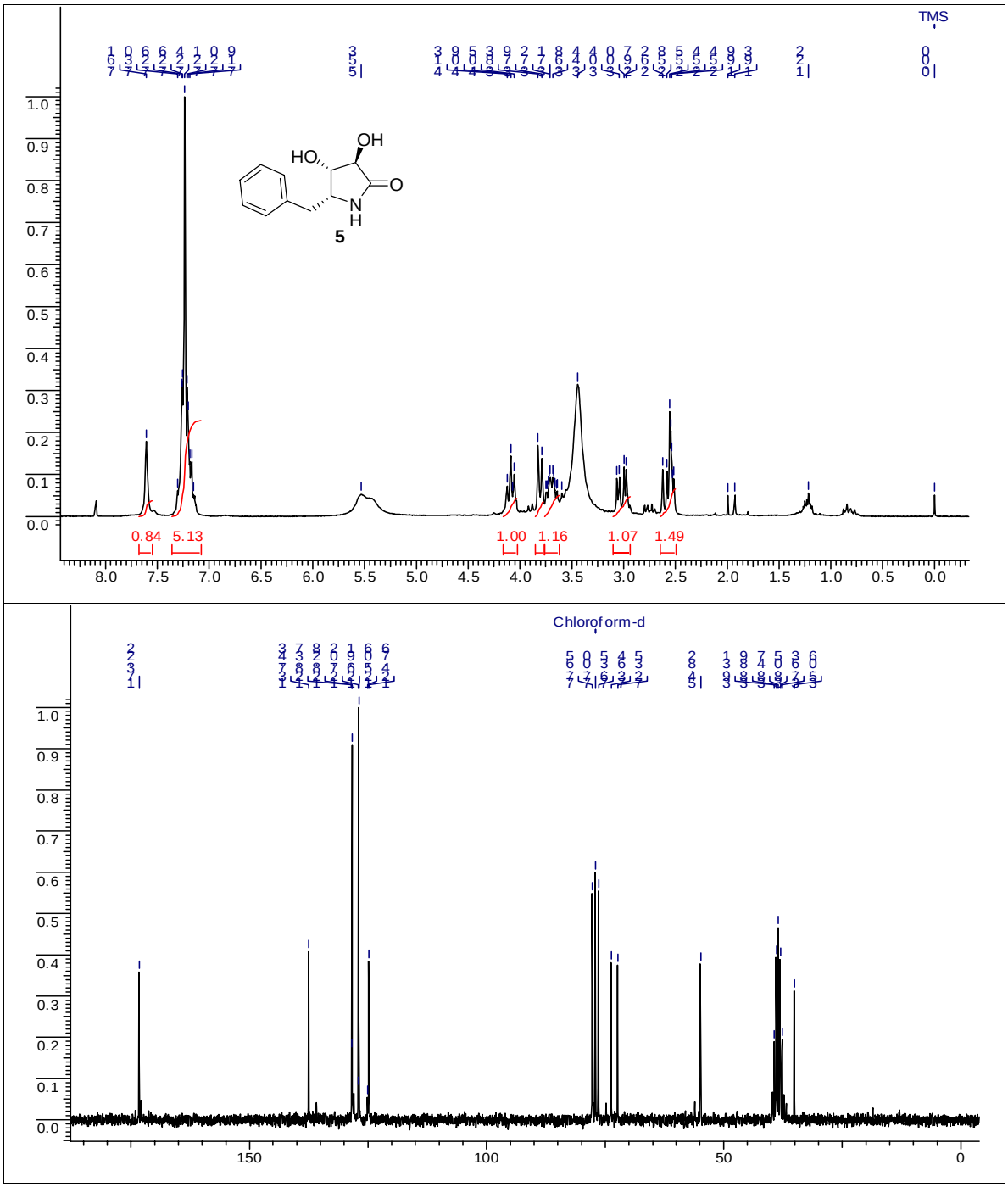

TMS
7.29
7.08
6.96
6.93
6.88
6.85
5.91
5.83
5.12
4.19
4.15
4.11
4.08
1.33
1.30
1.26
1.22
1.19
0.00
CbzHN
NCbz
O
3b
OEt
10.15
1.10
0.95
4.06
2.00
6.00
Chloroform-d
166.11
156.61
155.21
146.50
135.57
128.35
128.05
127.95
127.72
121.84
95.98
77.64
77.00
76.37
67.55
60.40
54.21
16.25
14.02

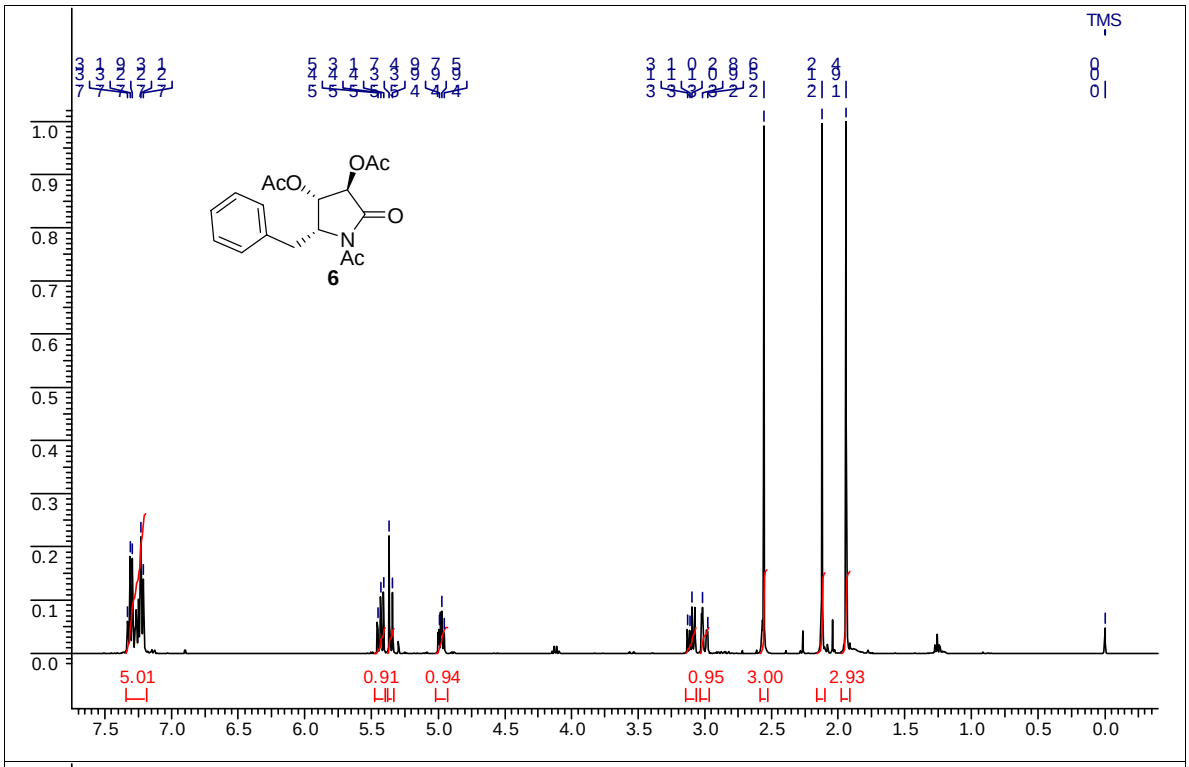

7.37
7.36
7.31
7.26
6.89
6.84
6.81
6.77
6.45
5.98
5.90
5.17
5.14
4.16
1.98
1.65
1.31
1.27
1.24
1.00
0.87
0.84
0.00
CbzHN
NCbz
O
OEt
3c
11.26
0.99
0.92
0.90
4.22
2.88
0.97
0.87
3.00
6.03
166.20
155.84
143.62
135.73
128.52
128.35
128.21
127.98
127.85
126.92
124.26
96.14
77.50
77.18
76.87
67.79
60.53
29.31
20.00
19.55
14.19

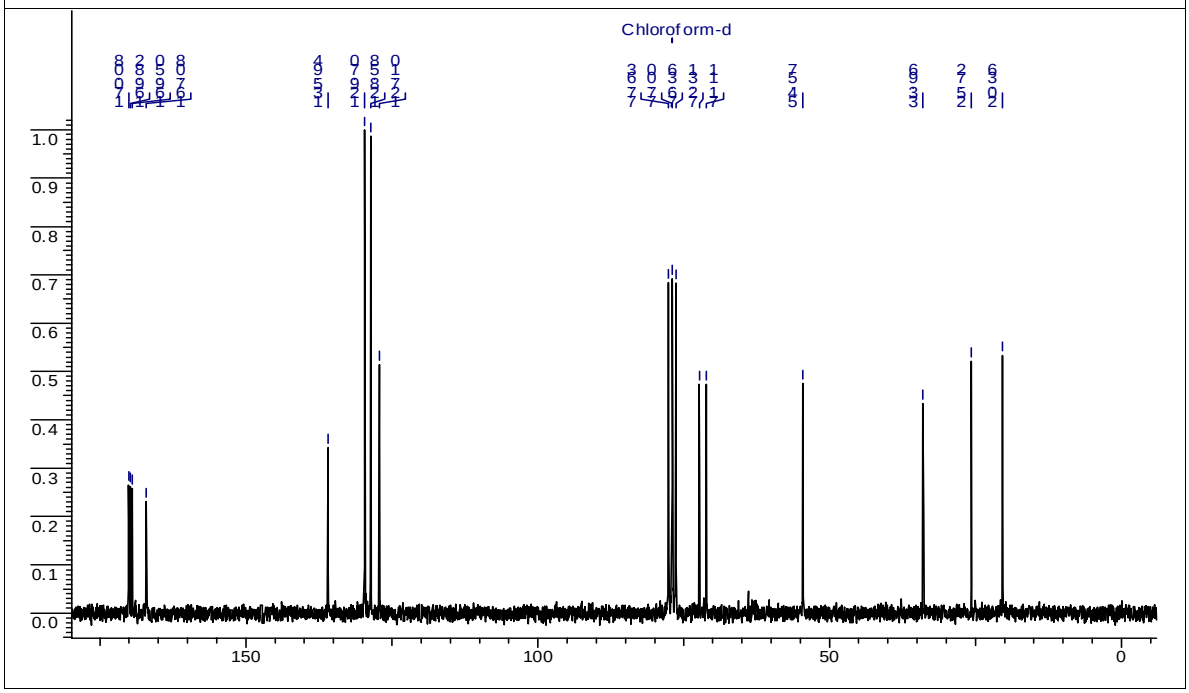

7.28
7.25
6.86
6.82
6.78
5.93
5.85
5.16
5.11
4.77
4.20
4.16
4.13
4.09
2.02
1.77
1.43
1.29
1.25
1.22
0.90
0.00
CbzHN
NCbz
O
OEt
3d
10.64
1.91
1.00
4.09
1.07
2.00
3.84
3.82
3.09
Chloroform-d
166.01
156.51
155.42
145.16
135.58
128.26
128.03
127.94
127.72
127.63
122.59
95.96
77.64
77.00
76.36
67.43
60.26
58.31
32.77
19.01
13.99
13.61

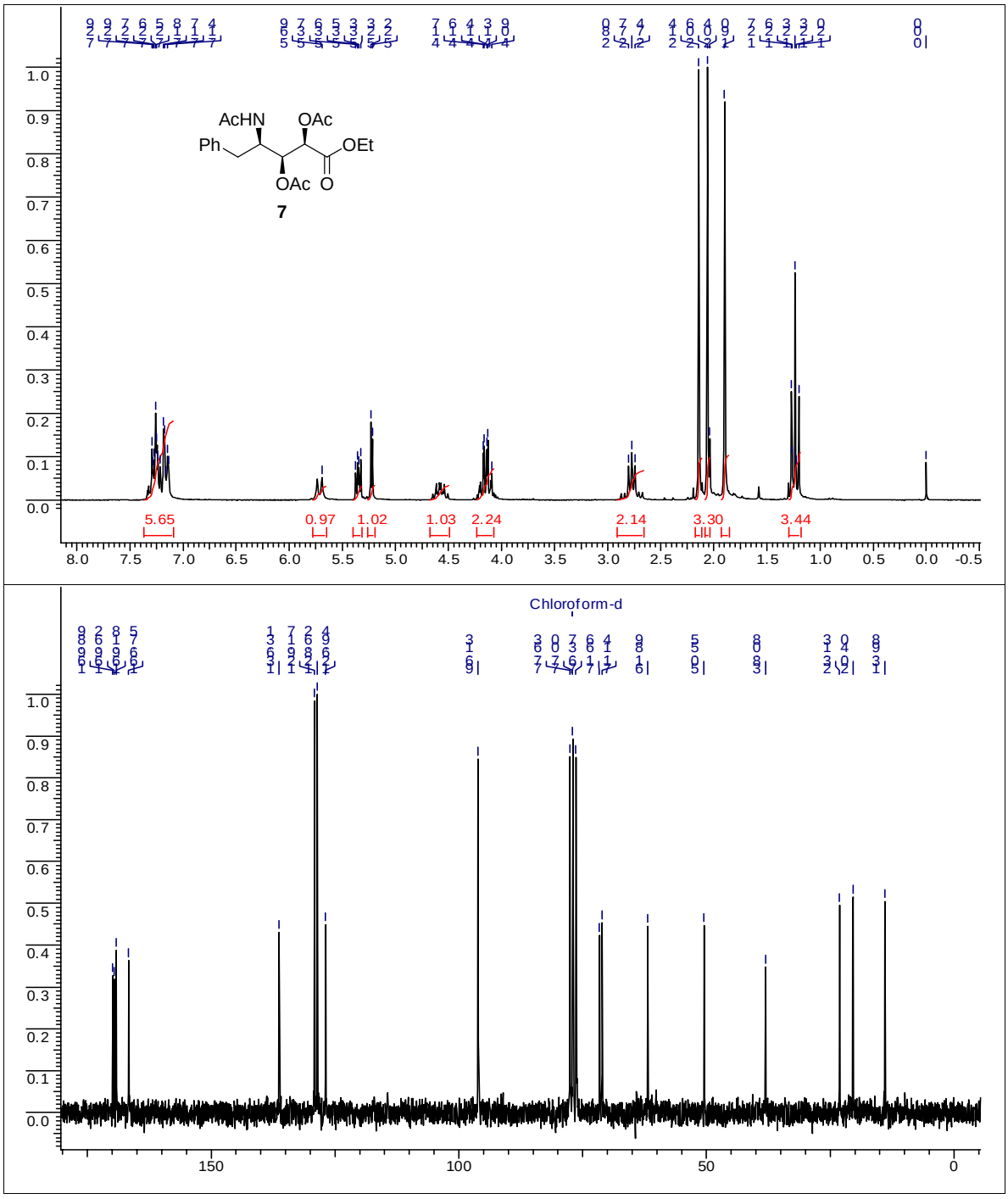

TMS
7.29
7.25
7.21
7.18
7.15
7.00
6.96
6.92
6.88
6.48
5.91
5.83
5.16
5.06
4.66
4.20
4.16
4.12
4.09
3.14
2.91
2.03
1.70
1.28
1.25
1.21
0.00
CbzN
NCbz
Ph
O
OEt
3e
15.97
1.09
0.92
0.88
5.04
2.00
2.02
3.17
Chloroform-d
165.79
156.55
155.18
143.99
135.51
128.93
128.40
128.36
128.08
126.67
125.69
123.11
96.04
77.63
77.00
76.36
67.76
61.87
60.32
37.51
34.09
31.96
14.09

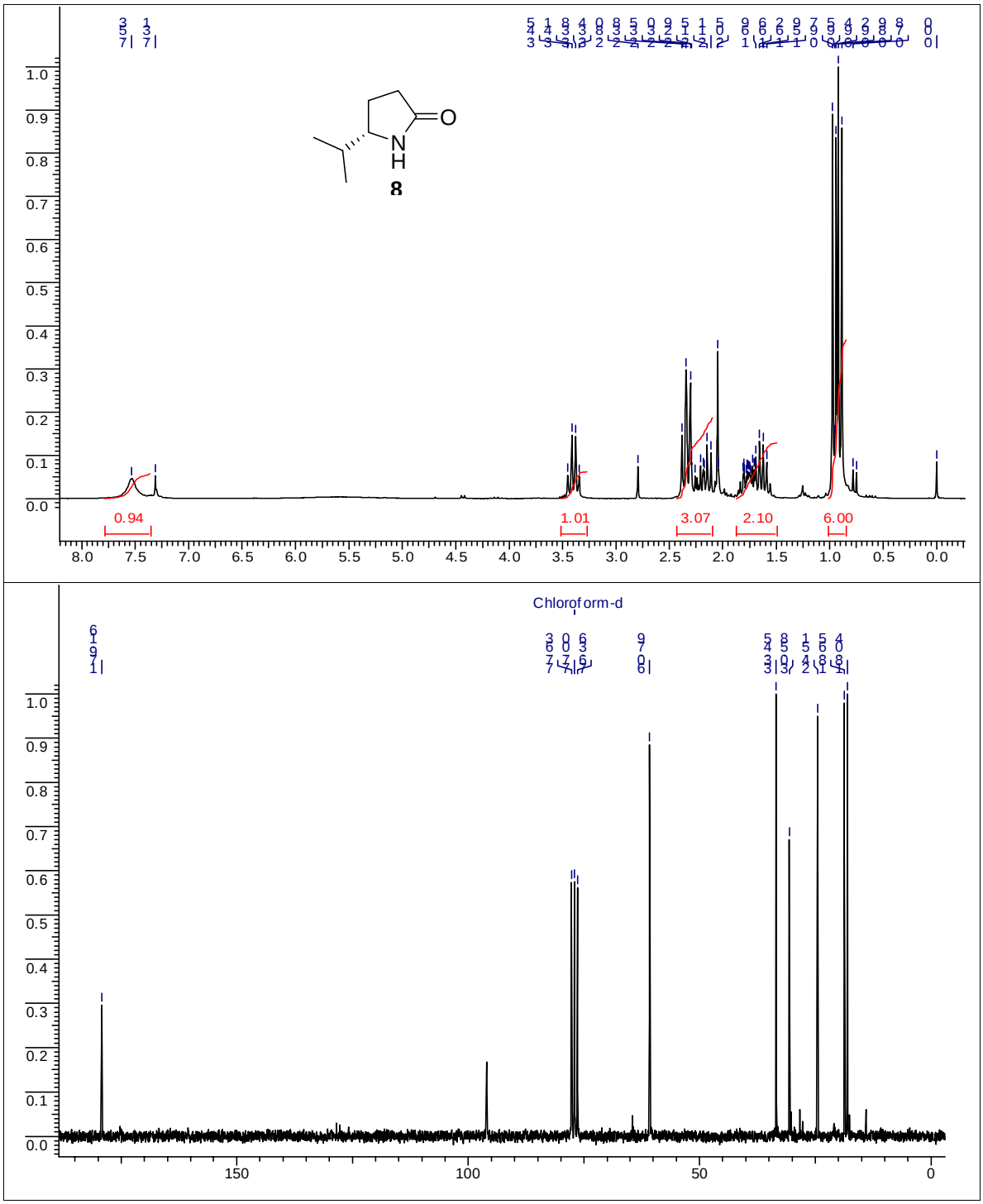

TMS
MeO
CbzN
NHCbz
O
OEt
3f
10.26
3.10
0.72
0.89
4.92
2.10
3.00
1.87
3.48
Chloroform-d
165.79
158.25
156.52
155.19
144.12
135.54
129.87
128.37
128.32
128.04
127.73
123.02
113.92
96.02
77.63
77.00
76.36
67.69
60.26
54.89
36.64
25.75
14.06


TMS
OH
HO
O
N
H
5
0.84
5.13
1.00
1.16
1.07
1.49
Chloroform-d


TMS
OAc
AcO
O
N
Ac
6
5.01
0.91
0.94
0.95
3.00
2.93


Chloroform-d


AcHN
OAc
Ph
OEt
OAc
O
7
5.65
0.97
1.02
1.03
2.24
2.14
3.30
3.44
Chloroform-d


O
N
H
8
0.94
1.01
3.07
2.10
6.00
Chloroform-d