Electronic Supplementary Information(ESI)

Co(III)(salen)-Catalyzed HKR of Two Stereocentered Alkoxy- and Azido Epoxides: A Concise Enantioselective Synthesis of (S,S)-Reboxetine and (+)- *epi*- Cytoxazone

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1. 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 Shimadzu Class-VPV6.10 with variable wavelength detector. N-bromosuccinimide was recrystallized before use.

2. Experimental Section

2.1. A general experimental procedure for the preparation of racemic alkoxy epoxides (2a-k & 10a):

A mixture of allyl alcohol (13 mmol), BnOH or MeOH (1.4 g, 13 mmol) was taken in CH_3CN (30 mL) and NBS (2.3 g, 15.6 mmol) was added slowly *via* solid addition funnel, with stirring at 25 °C and progress of reaction was monitored by TLC. After completion of the reaction, it was diluted with EtOAc (30 ml) and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by column chromatography [silica gel (60-120 mesh) and petroleum ether:EtOAc (80:20) as an eluent] to afford pure product. Which was taken in THF (20 mL) and NaOH powder (624 mg, 15.6 mmol) was added slowly with stirring at 0 °C for 2h (monitored by TLC). The reaction mixture was diluted with EtOAc (25 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts

were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude products which was purified by column chromatography [silica gel (60-120 mesh) and petroleum ether:EtOAc (90:10) as an eluent] gave **2a-k and 10a** in 80-86% yields.

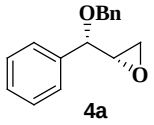
2.1. A general experimental procedure for the preparation of racemic azido epoxides (3a-b & 11a):

A mixture of allyl alcohol (13 mmol), NaN_3 (1.6 g, 26 mmol) was taken in CH_3CN: H_2O (30:10 mL) and NBS (2.3 g, 15.6 mmol) was added slowly *via* solid addition funnel, with stirring at 0 °C and progress of reaction was monitored by TLC. After completion of the reaction, it was diluted with EtOAc (30 ml) and washed with water and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by column chromatography [silica gel (60-120 mesh) and petroleum ether:EtOAc (90:10) as an eluent] to afford pure product. Which was taken in THF:H_2O (20:5 mL) and LiOH powder (375 mg, 15.6 mmol) was added slowly with stirring at 0 °C for 2h (monitored by TLC). The reaction mixture was diluted with EtOAc (25 mL) and water (30 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine and dried over anhyd. Na_2SO_4 and concentrated under reduced pressure to give crude products which was purified by column chromatography [silica gel (60-120 mesh) and petroleum ether:EtOAc (90:10) as an eluent] gave **3a-b & 11a** in 70-76% yields.

2.3. A general experimental procedure for Hydrolytic Kinetic Resolution (HKR) of racemic alkoxy epoxides :

To a solution of (*R*,*R*)-**1** or (S,S)-**1** (0.043 g, 0.07 mmol) in toluene (2.0 mL) was added acetic acid (0.04 g, 7.3 mmol). It was allowed to stir at 25 °C in open air for 30 min. over which time the color changed from orange-red to a dark brown and it was then concentrated in vaccuo to get the Co-salen complex as brown colored solid.

To solution of Co-salen complex -**1** (0.004 g, 0.5 mol%) and alkoxy and azido epoxide (1.41 mmol) in THF (0.5 mL) at 0 °C was added H_2O (0.012 g, 0.7 mmol) drop wise over 5 min. The reaction was allowed to warm to 25 °C and stirred for 14 h. After completion of reaction (monitored by TLC), solvent was removed *in vaccuo*. The crude product was purified by column chromatography over silica gel to give chiral alkoxy and azido epoxides **4a-k, 5a-b, 12a and 13a-b** (solvent system; pet ether: EtOAc = 90:10) and chiral alkoxy and azido diols **6a-k, 7a-b, 14a and 15a-b** (solvent system; pet ether: EtOAc = 70:30) in pure form.

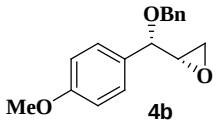


4a

(*S*)-2-((*S*)-(benzyloxy)(phenyl)methyl)oxirane (4a):

Yield: 45%; liquid; $[\alpha]^{D}_{25}$ +59.72 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$): 628, 757, 1043, 1242, 1654, 2989, 3094 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.58 (dd, 1H, *J* = 2.55, 2.25 Hz), 2.73 (dd, 1H, *J* = 0.8, 4.2 Hz), 3.22-3.27 (m, 1H), 4.8 (d, 1H, *J* = 6.7 Hz), 4.56 (dd, 2H, *J* = 10.06, 11.98 Hz), 7.30-7.38 (m, 10H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 43.62, 54.96, 70.30, 82.25, 126.77, 127.21, 127.32, 128.00, 128.30, 137.91 ppm; ESI-

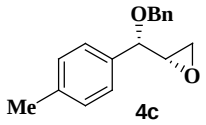
MS: *m*/*z* 263.2 $[M+Na]^+$ **Analysis**: $C_{16}H_{16}O_2$ requires: C, 79.97; H, 6.71; found: C, 79.58; H, 6.63 %.



4b

(*S*)-2-((*S*)-(benzyloxy)(4-methoxyphenyl)methyl)oxirane (4b):

Yield: 49%; liquid, $[\alpha]^D_{25}$ +57.25 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$): 667, 756, 1155, 1215, 1278, 1371, 1496, 1608, 2980, 2999, 3018 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.55 (dd, 1H, *J* = 2.20, 2.7 Hz), 2.73 (t, 1H, *J* = 4.28 Hz), 3.16-3.23 (m, 1H), 3.91 (s, 3H), 4.02 (d, 1H, *J* = 6.20 Hz), 4.55 (dd, 2H, *J* = 11.08, 11.98 Hz), 6.89(d, 1H, *J* = 8.69 Hz), 7.24-7.34 (m, 7H), 7.53 (d, 1H, *J* = 2.8 Hz) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 43.93, 55.01, 56.07, 70.57, 81.07, 111.77, 127.12, 127.57, 127.61, 128.28, 131.59, 131.89, 137.69, 155.74 ppm; **Analysis**: $C_{17}H_{18}O_3$ requires: C, 75.53; H, 6.71; found: C, 75.45; H, 6.57%.

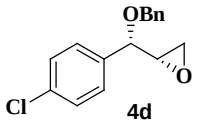


4c

(*S*)-2-((*S*)-(benzyloxy)(p-tolyl)methyl)oxirane (4c):

Yield: 48%; liquid, $[\alpha]^D_{25}$ +58..28 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 756, 850, 1155, 1208, 1273, 1329, 1453, 1614, 2985, 3018, 3085 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.37(s, 3H), 2.59 (dd, 1H, *J* = 2.12, 3.07 Hz), 2.73 (t, 1H, *J* = 4.95 Hz), 3.22-3.29 (m, 1H), 4.07 (d, 1H, *J* = 7.43 Hz), 4.55 (dd, 2H, *J* = 11.13, 11.68 Hz), 7.12-7.22 (m, 4H), 7.30-7.36 (m, 5H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 21.11, 44.18, 55.29, 70.48,

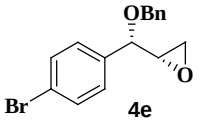
82.39, 126.88, 127.01, 127.49, 127.65, 128.27, 128.68, 129.28, 134.94, 138.02 ppm; **Analysis**: $C_{17}H_{18}O_2$ requires: C, 80.28; H, 7.13; found: C, 80.19; H, 7.05%.



4d

(*S*)-2-((*S*)-(benzyloxy)(4-chlorophenyl)methyl)oxirane (4d):

Yield: 45%; liquid, $[\alpha]^{D}_{25}$ +58.48 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 721, 848, 1124, 1210, 1278, 1496, 1630, 2988, 3018, 3089 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.54-2.58 (m, 1H), 2.73 (t, 1H, *J* = 4.49 Hz), 3.16-3.22 (m, 1H), 4.09 (d, 1H, *J* = 5.48 Hz), 4.55 (dd, 2H, *J* = 9.13, 11.40 Hz), 7.28-7.45 (m, 9H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 43.94, 55.03, 70.86, 81.49, 127.72, 128.45, 128.41, 128.85, 129.04, 129.28, 134.21, 136.59, 137.73 ppm; **Analysis**: $C_{16}H_{15}ClO_2$ requires: C, 69.95; H, 5.50; Cl, 12.90; found: C, 69.86; H, 5.35; Cl, 12.79%.

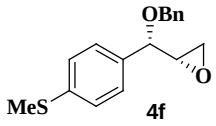


4e

(*S*)-2-((*S*)-(benzyloxy)(4-bromophenyl)methyl)oxirane (4e):

Yield: 44%; liquid, $[\alpha]^{D}_{25}$ +58.02 (*c* 1.1, $CHCl_3$); **IR** ($CHCl_3$): 667, 756, 850, 1125, 1215, 1253, 1325, 1608, 2950, 2998, 3018, 3051 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.56 (dd, 1H, *J* = 2.21, 2.42 Hz), 2.72 (t, 1H, *J* = 4.21 Hz), 3.18-3.22 (m, 1H), 4.09 (d, 1H, *J* = 7.96 Hz), 4.47-4.63 (m, 2H), 7.23-7.27 (m, 2H), 7.31-7.34 (m, 5H), 7.49-7.53 (m, 2H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 43.95, 54.95, 70.83, 81.49, 122.32, 127.71,

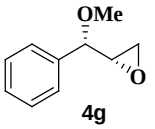
128.40, 128.77, 131.78, 137.06, 137.66 ppm; **Analysis**: $C_{16}H_{15}BrO_2$ requires: C, 60.21; H, 4.74, Br, 25.03; found: C, 49.39; H, 4.38; Br, 24.98%.



4f

(*S*)-2-((*S*)-(benzyloxy)(4-(methylthio)phenyl)methyl)oxirane (4f):

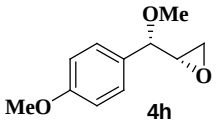
Yield: 48%; liquid, $[\alpha]^{D}_{25}$ +58.84 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 628, 765, 848, 1015, 1150, 1263, 1357, 1640, 2946, 2998, 3018, 3068 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.49 (s, 3H), 2.55 (dd, 1H, *J* = 2.05, 2.89 Hz), 2.71 (t, 1H, *J* = 4.46 Hz), 3.17-3.24 (m, 1H), 4.05 (d, 1H, *J* = 6.77 Hz), 4.55 (dd, 2H, *J* = 10.71, 12.30 Hz), 7.22-7.27 (m, 5H), 7.30-7.34 (m, 4H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 15.22, 43.61, 54.83, 70.23, 81.68, 126.20, 127.27, 127.32, 128.01, 134.50, 137.72, 138.44 ppm; **Analysis**: $C_{17}H_{18}O_2S$ requires: C, 71.30; H, 6.34; S, 11.20; found: C, 71.26; H, 6.29; S, 11.12%.



4g

(*S*)-2-((*S*)-methoxy(phenyl)methyl)oxirane (4g):

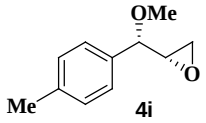
Yield: 48%; liquid; $[\alpha]^{D}_{25}$ +59.68 (*c* 0.8, $CHCl_3$); IR ($CHCl_3$): 685, 757, 1035, 1215, 1620, 2978, 3018, 3069 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.57 (dd, 1H, *J* = 2.22, 2.94 Hz), 2.68 (t, 1H, *J* = 4.71 Hz), 3.14-3.15 (m, 1H), 3.35 (s,3H), 3.85 (d, 1H, *J* = 7.60 Hz), 7.29-7.37 (m, 5H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 43.82, 55.02, 55.82, 85.02, 126.77, 128.12, 128.42, 137.80 ppm; ESI-MS: *m*/*z* 187.08 $[M+Na]^+$**Analysis**: $C_{10}H_{12}O_2$ requires: C, 73.15; H, 7.37; found: C, 73.08; H, 7.21 %.



4h

(*S*)-2-((*S*)-methoxy(4-methoxyphenyl)methyl)oxirane (4h):

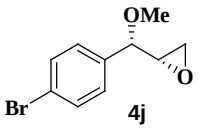
Yield: 47%; liquid; $[\alpha]^{D}_{25}$ +58.72 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$): 735, 845, 1065, 1120, 1215, 1620, 2980, 3010, 3098 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.57 (dd, 1H, *J* = 2.51, 2.82 Hz), 2.73 (t, 1H, *J* = 5.02 Hz), 3.09-3.16 (m, 1H), 3.36 (s,3H), 3.80 (d, 1H, *J* = 6.28 Hz), 3.91 (s, 3H), 6.89 (d, 1H, *J* = 8.50 Hz), 7.22 (d, 1H, *J* = 2.25 Hz), 7.26 (d, 1H, *J* = 2 Hz), 7.52 (d, 1H, *J* = 2.25 Hz) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 43.86, 54.89, 56.05, 56.92, 83.77, 111.73, 126.96, 131.46, 131.74, 155.71 ppm; **Analysis**: $C_{11}H_{14}O_3$ requires: C, 68.02; H, 7.27; found: C, 67.94; H, 7.19 %.



4i

(*S*)-2-((*S*)-methoxy(p-tolyl)methyl)oxirane (4i):

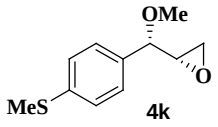
Yield: 44%; liquid, $[\alpha]^{D}_{25}$ +59.21 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 635, 764, 865, 1075, 1125, 1253, 1358, 1624, 2998, 3018, 3089 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 2.60 (dd, 1H, *J* = 2.16, 3.03 Hz), 2.73 (t, 1H, *J* = 4.75 Hz), 3.15-3.22 (m, 1H), 3.35 (s, 3H), 3.84 (d, 1H, *J* = 6.61 Hz), 7.17-7.26 (m, 4H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 20.94, 43.96, 55.08, 56.70, 84.90, 126.74, 129.12, 134.73, 137.87 ppm; **Analysis**: $C_{11}H_{14}O_2$ requires: C, 74.13; H, 7.92; found: C, 74.09; H, 7.84%.



4j

(*S*)-2-((*S*)-(4-bromophenyl)(methoxy)methyl)oxirane (4j):

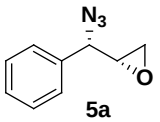
Yield: 45%; liquid, $[\alpha]^{D}_{25}$ +58.43 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$): 668, 750, 850, 1055, 1235, 1275, 1480, 1635, 2988, 3018, 3098 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.56 (dd, 1H, *J* = 2.28, 2.65 Hz), 2.72 (t, 1H, *J* = 4.43 Hz), 3.08-3.15 (m, 1H), 3.37 (s, 3H), 3.87 (d, 1H, *J* = 7.07 Hz), 7.19-7.23 (m, 2H), 7.48-7.52 (m, 2H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 43.75, 54.76, 57.08, 84.17, 122.18, 128.55, 131.67, 136.92 ppm; **Analysis**: $C_{10}H_{11}BrO_2$ requires: C, 49.41; H, 4.56; Br; 32.87; found: C, 49.39; H, 4.38; Br, 32.75%.



4k

(*S*)-2-((*S*)-methoxy(4-(methylthio)phenyl)methyl)oxirane (4k):

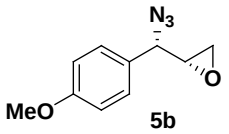
Yield: 47%; liquid, $[\alpha]^{D}_{25}$ +57.85 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 680, 785, 850, 1055, 1130, 1260, 1496, 1634, 2918, 2998, 3018, 3080 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.49 (s, 3H), 2.57 (dd, 1H, *J* = 2.16, 2.76 Hz), 2.72 (t, 1H, *J* = 4.42 Hz), 3.10-3.17 (m, 1H), 3.36 (s, 3H), 3.83 (d, 1H, *J* = 6.72 Hz), 7..24 (s, 4H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 15.52, 43.80, 54.92, 56.84, 84.5, 126.47, 127.31, 134.58, 138.61 ppm; **Analysis**: $C_{11}H_{14}O_2S$ requires: C, 62.83; H, 6.71; S, 15.25; found: C, 62.56; H, 6.59; S, 15.19%.



5a

(2R,3S)-2-(azido-phenyl-methyl)-oxirane (5a):

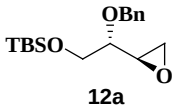
Yield: (48%); yellow liquid; **$[\alpha]^{25}_{D}$**: + 120 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 758, 860, 1125, 1250, 1460, 1493, 1602, 2105, 2932, 3025; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.73-2.84 (m, 2H), 3.23-3.29 (m, 1H), 4.25 (d, *J* = 6.10, 1H), 7.35-7.47 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 44.68, 54.61, 66.82, 127.26, 128.80, 128.91, 135.77; **Analysis:** $C_9H_9N_3O$ requires C, 61.70; H, 5.18; N, 23.99%; found C, 61.79; H, 5.14; N, 23.90%.



5b

(2R,3S)-2-(azido-4-Methoxyphenyl-methyl)oxirane (5b):

Yield: 48%; yellow liquid; **$[\alpha]^{25}_{D}$**: +82 (*c* 0.9, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 1039, 1250, 1516, 1609, 2106, 2932, 3025; **^{1}H NMR** (200 MHz, $CDCl_3$) δ = : 2.72-2.73 (m, 1H), 2.78-2.80 (m, 1H), 3.21-3.24 (m, 1H), 3.82 (s, 1H), 4.21(d, *J* = 5.10 Hz, 1H), 6.91 (d, *J* = 8.6, Hz, 2H) 7.30 (d, *J* = 8.6 Hz, 2H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$) δ = : 44.60, 54.62, 55.10, 66.13, 114.21, 127.77, 128.54, 159.84 ppm; **Analysis:** $C_{10}H_{11}N_3O_2$ requires C, 58.53; H, 5.40; N, 20.48%; found C, 58.48; H, 5.45; N, 20.56%.

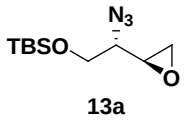


12a

((*R*)-2-(benzyloxy)-2-((*S*)-oxiran-2-yl)ethoxy)(tert-butyl)dimethylsilane (12a):

Yield: 47%; liquid, $[\alpha]^{D}_{25}$ +28.25 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$): 645, 785, 828, 1085, 1145, 1253, 1496, 1608, 2925, 2996, 3016, 3088 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 0.09 (s, 6H), 0.94 (s, 9H), 2.72-2.75 (m, 2H), 3.05-3.07 (m, 1H), 3.39-3.41 (m, 1H), 3.74-

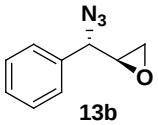
3.76 (m, 2H), 4.62-4.67 (m, 2H), 7.29-7.32 (m, 5H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): δ = -5.21, 18.03, 25.71, 44.99, 51.47, 64.01, 64.94, 72.71, 78.28, 127.67, 128.30, 138.42 ppm; **Analysis**: $C_{17}H_{28}O_3Si$ requires: C, 66.19; H, 9.15; found: C, 66.09; H, 8.98%.



13a

(2*S*,3*S*)-3-Azido-4-*tert*-butyldimethylsilyloxy-1,2-epoxybutane (13a):

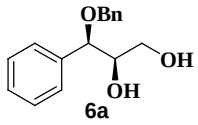
Yield: (48%); yellow liquid; **[α]$^{25}_{D}$**: +26 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 740, 839, 1127, 1250, 1463, 1493, 1602, 2106, 2932, 3025; **^{1}H NMR** (200 MHz, $CDCl_3$) δ = : 0.09 (s, 6H), 0.90 (s, 9H), 2.73 (dd, *J* = 5.0, 2.6 Hz, 1H), 2.80(dd, *J* = 5.0, 3.6 Hz, 1H), 3.01-3.07 (m, 1H), 3.21-3.29 (m, 1H), 3.74-3.90 (m, 2H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$) δ = : -5.55, 18.22, 25.76, 45.22, 50.27, 63.59, 63.93 ppm; **Analysis:** $C_{10}H_{21}N_3O_2Si$ requires C, 49.35; H, 8.70; N, 17.27; found C, 49.20; H, 8.75; N, 17.30%.



13b

(2*S*,3*S*)-2-(azido-phenyl-methyl)-oxirane (13b)

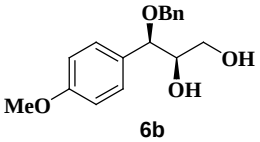
Yield: (48%); yellow liquid; **[α]$^{25}_{D}$**: +170 (*c* 1.5, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 758, 862, 1127, 1250, 1463, 1493, 1602, 2106, 2932, 3025; **^{1}H NMR** (200 MHz, $CDCl_3$) δ: 2.82-2.84 (m, 1H), 2.86-2.88 (m, 1H), 3.21-3.23 (m, 1H), 4.59 (d, *J* = 4.50, 1H), 7.34-7.40 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 44.50, 53.69, 64.91, 127.23, 128.69, 128.75, 135.73 ppm; **Analysis:** $C_9H_9N_3O$ requires C, 61.70; H, 5.18; N, 23.99%; found C, 61.79; H, 5.14; N, 23.90%.



6a

(2*R*,3*R*)-3-(benzyloxy)-3-phenylpropane-1,2-diol (6a):

Yield: 44%; gum; $[\alpha]^{D}_{25}$ -89.65 (*c* 1, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 12.351 (1.08%) and 13.599 (98.92%); IR ($CHCl_3$): 720, 845, 1045, 1125, 1654, 2985, 3085, 3465 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.13 (br s, 1H), 3.16 (br s, 1H), 3.34 (dd, 1H, *J* = 4.33, 6.07 Hz), 3.54 (dd, 1H, *J* = 2.88, 9.08 Hz), 3.73-3.83 (m, 1H), 4.27 (d, 1H, *J* = 12.45 Hz), 4.41-4.52 (m, 2H), 7.29-7.38 (m, 10H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 62.27, 70.67, 75.65, 82.09, 127.62, 127.98, 128.43, 128.65, 137.64, 137.95 ppm; ESI-MS: *m*/*z* 281.13 $[M+Na]^+$ **Analysis**: $C_{16}H_{18}O_3$ requires: C, 74.39; H, 7.02; found: C, 74.28; H, 6.97 %.

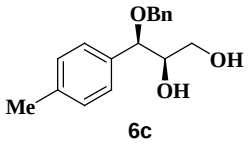


6b

(2*R*,3*R*)-3-(benzyloxy)-3-(4-methoxyphenyl)propane-1,2-diol (6b):

Yield: 47%; gum; $[\alpha]^{D}_{25}$ -89.45 (*c* 1.2, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 17.624 (1.05%) and 19.298 (98.89%); **IR** ($CHCl_3$): 635, 765, 840, 1045, 1215, 1353, 1371, 1496, 1634, 2980, 3068, 3446 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.02 (br s, 1H), 3.03 (br s, 1H), 3.25 (d, 1H, *J* = 12.70 Hz), 3.53 (d, 1H, *J* = 12.68 Hz), 3.63-3.70 (m, 1H), 3.91 (s, 3H), 4.21-4.36 (m, 2H), 4.47 (d, 1H, *J* = 11.92 Hz), 6.87(d, 1H, *J* = 8.06 Hz), 7.22-7.35 (m,

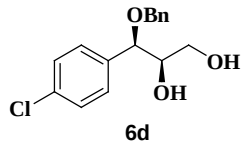
7H), 7.55 (d, 1H, *J* = 2.14 Hz) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 56.12, 62.17, 70.61, 75.43, 80.94, 111.79, 127.84, 127.91, 128.40, 131.49, 132.24, 137.38, 155.80 ppm; **Analysis**: $C_{17}H_{20}O_4$ requires: C, 70.81; H, 6.99; found: C, 70.57; H, 6.78%.



6c

(2*R*,3*R*)-3-(benzyloxy)-3-p-tolylpropane-1,2-diol (6c):

Yield: 45%; liquid, $[\alpha]^{D}_{25}$ -89..2 (*c* 1.2, $CHCl_3$); 96% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 12.570 (2.10%) and 13.692 (98.24%); **IR** ($CHCl_3$): 650, 756, 850, 1055, 1230, 1360, 1485, 1644, 2958, 3058, 3425 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.18 (br s, 1H), 2.36 (s, 3H), 3.35 (br s, 1H), 3.55-3.66 (m, 2H), 3.74-3.84 (m, 1H), 3.90 (dd, 1H, *J* = 3.43, 5.54 Hz), 4.18-4.31 (m, 1H), 4.35-4.47 (m, 2H), 7.28-7.36 (m, 9H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 21.02, 62.17, 69.99, 75.58, 84.55, 127.46, 127.53, 127.67, 128.39, 128.49, 128.65, 137.50, 137.81, 138.21 ppm; **Analysis**: $C_{17}H_{20}O_3$ requires: C, 74.97; H, 7.40; found: C, 74.89; H, 7.31%.

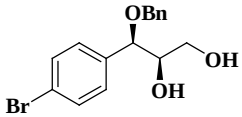


6d

(2*R*,3*R*)-3-(benzyloxy)-3-(4-chlorophenyl)propane-1,2-diol (6d):

Yield: 42%; liquid, $[\alpha]^{D}_{25}$ -89.25 (*c* 0.8, $CHCl_3$); **IR** ($CHCl_3$): 665, 720, 850, 1044, 1215, 1253, 1371, 1498, 1638, 2990, 3078, 3454 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.16 (br s, 1H), 3.12 (br s, 1H), 3.29 (dd, 1H, *J* = 4.93, 8.81 Hz), 3.54 (dd, 1H, *J* = 3.88,

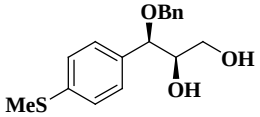
8.81 Hz), 3.68 (m, 1H), 4.26 (d, 1H, *J* = 11.5 Hz), 4.42-4.48 (m, 2H), 7.25-7.38 (m, 9H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 62.21, 70.95, 75.50, 81.38, 128.04, 128.60, 129.02, 134.44, 136.51, 137.34 ppm; **Analysis**: $C_{16}H_{17}ClO_3$ requires: C, 65.64; H, 5.85; Cl, 12.11; found: C, 65.56; H, 5.77; Cl, 12.05%.



6e

(2*R*,3*R*)-3-(benzyloxy)-3-(4-bromophenyl)propane-1,2-diol (6e):

Yield: 47%; gum, $[\alpha]^{D}_{25}$ -89.08 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 658, 780, 810, 1055, 1155, 1278, 1371, 1496, 1638, 2998, 3018, 3450 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.72 (br s, 1H), 3.24-3.27 (m, 2H), 3.49-3.52 (m, 2H), 3.67-3.69 (m, 2H), 4.24 (d, 1H, *J* = 8.95 Hz), 4.38-4.46 (m, 2H), 7.23-7.34 (m, 7H), 7.50 (d, 2H, *J* = 8.85 Hz) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 62.17, 70.88, 75.47, 81.38, 122.45, 128.00, 128.53, 129.31, 131.87, 137.03, 137.30 ppm; **Analysis**: $C_{16}H_{17}BrO_3$ requires: C, 56.99; H, 5.08; Br, 23.70; found: C, 56.79; H, 4.99; Br, 23.62%.

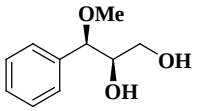


6f

(2*R*,3*R*)-3-(benzyloxy)-3-(4-(methylthio)phenyl)propane-1,2-diol (6f):

Yield: 47%; liquid, $[\alpha]^{D}_{25}$ -88.92 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$): 685, 780, 885, 1065, 1075, 1265, 1371, 1485, 1638, 2940, 3018, 3089, 3456 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.12 (br s, 1H), 2.50 (s, 3H), 3.13 (br s, 1H), 3.24-3.36 (m, 1H), 3.49-3.58 (m, 1H), 3.71-3.75 (m, 1H), 4.26 (d, 1H, *J* = 11.63 Hz), 4.37-4.51 (m, 2H), 7.23-7.38 (m,

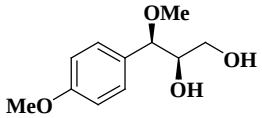
9H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 15.57, 62.24, 70.61, 75.51, 81.64, 126.53, 127.86, 127.95, 128.10, 128.45, 134.61, 137.58, 138.89 ppm; **Analysis**: $C_{17}H_{23}O_3S$ requires: C, 67.08; H, 6.62; S, 10.53; found: C, 66.98; H, 6.58; S, 10.45%.



6g

(2*R*,3*R*)-3-methoxy-3-phenylpropane-1,2-diol (6g):

Yield: 47%; liquid, $[\alpha]^{D}_{25}$ -89.68 (*c* 1.2, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 11.168 (0.99%) and 11.963 (99.01%); **IR** ($CHCl_3$): 675, 745, 865, 1045, 1145, 1278, 1371, 1485, 1608, 2960, 3018, 3085, 3458 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.50 (br s, 1H), 3.26 (s, 3H), 3.29-3.40 (m, 2H), 3.52-3.61 (m, 1H), 3.71-3.75 (m, 1H), 4.20 (d, 1H, *J* = 9.19 Hz), 7.33-7.36 (m, 5H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 56.61, 62.22, 75.67, 84.47, 127.44, 128.19, 128.43, 137.88 ppm; ESI-MS: *m*/*z* 205.09 $[M+Na]^+$**Analysis**: $C_{10}H_{14}O_3$ requires: C, 65.91; H, 7.74; found: C, 65.88; H, 7.35%.

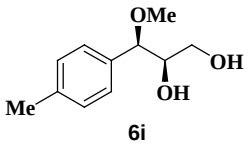


6h

(2*R*,3*R*)-3-methoxy-3-(4-methoxyphenyl)propane-1,2-diol (6h):

Yield: 46%; liquid, $[\alpha]^{D}_{25}$ -89.58 (*c* 0.8, $CHCl_3$); 97% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 16.629 (1.88%) and 18.290 (98.90%); **IR** ($CHCl_3$): 670, 748, 840, 1075, 1275, 1278, 1385, 1494, 1644, 2920, 3018, 3088, 3458 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.18 (br s, 1H), 3.14 (br

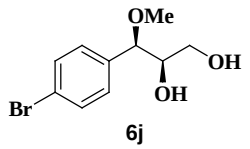
s, 1H), 3.25 (s, 4H), 3.51-3.64 (m, 2H), 3.90 (s, 3H), 4.13 (d, 1H, *J* = 7.87 Hz), 6.85 (d, 1H, *J* = 8.42 Hz), 7.19-7.24 (m, 2H), 7.49 (d, 1H, *J* = 2.02 Hz) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 56.33, 56.84, 62.35, 75.63, 83.44, 111.90, 127.95, 131.46, 132.20, 155.91 ppm; **Analysis**: $C_{11}H_{16}O_4$ requires: C, 62.25; H, 7.60; found: C, 62.18; H, 7.45%.



6i

(2*R*,3*R*)-3-methoxy-3-p-tolylpropane-1,2-diol (6i):

Yield: 45%; liquid, $[\alpha]^{D}_{25}$ -89.25 (*c* 1.2, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 12.572 (1.06%) and 13.690 (98.94%); **IR** ($CHCl_3$): 650, 785, 850, 1055, 1215, 1371, 1496, 1645, 2925, 3018, 3098, 3450 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.27 (br s, 1H), 2.36 (s, 3H), 3.24 (s, 4H), 3.30-3.36 (m, 1H), 3.47-3.57 (m, 1H), 3.65-3.74 (m, 1H), 4.15 (d, 1H, *J* = 8.45 Hz), 7.18-7.22 (m, 4H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 21.10, 56.46, 62.27, 75.65, 84.32, 127.40, 129.15, 134.80, 137.80 ppm; **Analysis**: $C_{11}H_{16}O_3$ requires: C, 67.32; H, 8.22; found: C, 67.25; H, 8.17%.

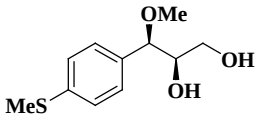


6j

(2*R*,3*R*)-3-(4-bromophenyl)-3-methoxypropane-1,2-diol (6j):

Yield: 42%; liquid, $[\alpha]^{D}_{25}$ -89.44 (*c* 1.2, $CHCl_3$); **IR** ($CHCl_3$): 620, 750, 850, 1040, 1275, 1375, 1494, 1645, 2910, 3018, 3440 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 2.26 (br s, 1H), 3.20 (br s, 1H), 3.25 (s, 3H), 3.32 (m, 1H), 3.52-3.68 (m, 2H), 4.20 (d, 1H, *J* =

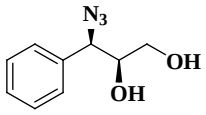
8.65 Hz), 7.21 (d, 2H, *J* = 8.74 Hz), 7.50 (d, 2H, *J* = 8.74 Hz), ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): δ = 56.87, 62.11, 75.56, 83.84, 122.35, 129.20, 131.76, 136.93 ppm; **Analysis**: $C_{10}H_{13}BrO_3$ requires: C, 46.00; H, 5.02; Br, 30.60; found: C, 45.85; H, 4.95; Br, 30.54%.



6k

(2*R*,3*R*)-3-methoxy-3-(4-(methylthio)phenyl)propane-1,2-diol (6k):

Yield: 46%; liquid, $[\alpha]^{D}_{25}$ -89.32 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 650, 765, 850, 1055, 1260, 1275, 1374, 1496, 1645, 2950, 3018, 3098, 3446 cm^{-1}; **^{1}H NMR** (200 MHz, $CDCl_3$): δ = 2.49 (s, 3H), 3.12 (brs, 1H), 3.25 (s, 3H), 3.34 (brs, 1H), 3.52-3.71 (m, 2H), 4.17 (d, 1H, *J* = 10.01 Hz), 7.23-7.25 (m, 4H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$): δ = 15.61, 56.70, 62.21, 75.63, 84.05, 126.53, 128.00, 134.49, 138.84 ppm; **Analysis**: $C_{11}H_{16}O_3S$ requires: C, 57.87; H, 7.06; found: C, 57.78; H, 6.95%.

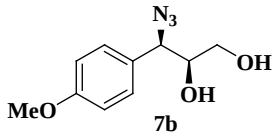


7a

(2*S*, 3*R*)-3-Azido-3-phenyl-propane-1,2diol (7a):

Yield: 47%; yellow liquid; **$[\alpha]^{25}_{D}$**: -188 (*c* 1, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 13.020 (0.90%) and 13.512 (99.20%); **IR** ($CHCl_3$, cm^{-1}): 859, 828, 1039, 1100, 1384, 1454, 1493, 1602, 2099, 2932, 3052, 3392 (broad); **^{1}H NMR** (200 MHz, $CDCl_3$) δ =: 3.30 (dd , *J* = 11.54,

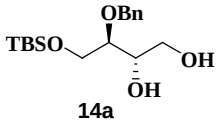
6.01 Hz, 1H), 3.44 (d, *J* = 11.54 Hz, 1H), 3.80 (br s, 1H), 3.62-3.94 (m, 1H), 4.52 (d, *J* = 8.10 Hz, 1H), 7.28-7.35 (m, 5H); **^{13}C NMR** (50 MHz, $CDCl_3$) δ =: 62.8, 68.1, 75.0, 127.5, 128.7, 128.9, 136.22; **Analysis:** $C_9H_{11}N_3O_2$ requires C, 55.95; H, 5.74; N, 21.75%; found C, 56.10; H, 5.65; N, 21.60%.



7b

(2*S*, 3*R*)-3-Azido-3-(4-methoxyphenyl)-propane-1,2diol (7b):

Yield: 48%; yellow liquid; **[α]$^{25}_{D}$**: -190 (*c* 1, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 15.97 (1.50%) and 17.73 (98.50%); **IR** ($CHCl_3$, cm^{-1}): 1035, 1195, 1513, 1616, 2100, 2920, 3050, 3368 (broad); **^{1}H NMR** (200 MHz, $CDCl_3$) δ = : 2.09 (br s , 1H), 2.81 (br s , 1H), 3.35 (dd, *J* = 11.2, 4.8 Hz, 1H), 3.55 (dd, *J* = 11.6, 2.3 Hz, 1H), 3.75-3.86 (m, 1H), 3.82 (s, 3H), 4.58 (d, *J* = 8.4 Hz, 1H), 6.92 (dd, *J* = 8.7, 2.1 Hz, 2H) 7.27 (dd, *J* = 6.0, 2.1 Hz, 2H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$) δ = : 55.16, 62.78, 67.87, 75.01, 114.33, 128.05, 128.84, 159.87 ppm; **Analysis:** $C_{10}H_{13}N_3O_3$ requires C, 55.95; H, 5.74; N, 21.75%; found C, 56.10; H, 5.65; N, 21.60%.

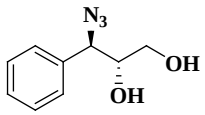


14a

(2*R*,3*S*)-3-(benzyloxy)-4-tert-butyl) dimethylsilyloxybutane-1,2-diol (14a):

Yield: 49%; liquid, $[\alpha]^{D}_{25}$ -29.24 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$): 640, 750, 850, 1040,1075, 1238, 1375, 1485, 1640, 2980, 3018, 3089, 3445 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ =

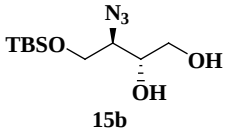
0.07 (s, 6H), 0.90 (s, 9H), 2.65 (br s, 1H), 2.33 (br s, 1H), 2.69-2.81 (m, 1H), 3.37-3.53 (m, 1H), 3.57-3.88 (m, 3H), 4.04-4.30 (m, 2H), 4.56-4.73 (m, 2H), 7.34 (m, 5H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$): δ = -5.32, 18.26, 25.90, 63.10, 71.25, 72.29, 72.63, 78.66, 127.94, 128.57, 137.94 ppm; **Analysis**: $C_{17}H_{30}O_4Si$ requires: C, 62.54; H, 9.26; found: C, 62.38; H, 9.12%.



15a

(2*R*, 3*R*)-3-Azido-3-phenyl-propane-1,2diol (15a)

Yield: 46%; yellow liquid; **[α]$^{25}_{D}$**: -180 (*c* 0.35, $CHCl_3$); 98% ee by chiral HPLC analysis (Chiralpak OD-H, *n*-hexane/*i*PrOH, 90:10, 0.5 mL/min) retention time 14.68 (0.80%) and 15.89 (99.14%); **IR** ($CHCl_3$, cm^{-1}): 859, 828, 875, 1039, 1101, 1386, 1456, 1493, 1602, 2099, 2934, 3032, 3392; **^{1}H NMR** (200 MHz, $CDCl_3$) δ =: 2.59 (br s, 1H), 2.77 (br s, 1H), 3.58-3.71 (m, 2H), 3.72-3.86 (m, 1H), 4.57 (d, *J* = 7.0 Hz, 1H), 7.30-7.44 (m, 5H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$) δ =: 62.83, 66.99, 74.03, 127.80, 128.77, 128.94, 136.13 ppm; **Analysis:** $C_9H_{11}N_3O_2$ requires C, 55.95; H, 5.74; N, 21.75%; found C, 56.08; H, 5.66; N, 21.61%.

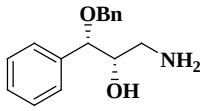


15b

(2*R*,3*R*)-3-Azido-4-(*tert*-butyldimethylsilyloxy)butane-1,2-diol (15b):

Yield: (47%); yellow liquid; **[α]$^{25}_{D}$**: -29 (*c* 1, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 740, 839, 1109, 1265, 1471, 2100, 2931, 3390; **^{1}H NMR** (200 MHz, $CDCl_3$) δ = : 0.12 (s, 6H),

0.90 (s, 9H), 2.92 (br s, 1H), 3.39-3.48 (m, 2H), 3.61-3.81 (m, 3H), 3.81-3.97 (m, 2H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$) δ = : -5.58, 18.19, 25.79, 63.54, 63.61, 63.81, 71.44, ppm; **Analysis:** $C_{10}H_{23}N_3O_3Si$ requires C, 45.95; H, 8.87; N, 16.08; found C, 45.90; H, 8.92; N, 16.13%.

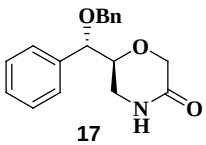


16

(1*S*,2*S*)-3-amino-1-(benzyloxy)-1-phenylpropan-2-ol (16):

To a stirred solution of epoxide **4a** (793 mg, 3 mmol) in MeOH (10 mL) was added 30% NH_4OH (15 mL) and the mixture was stirred at 25 °C for 12 h. After completion of the reaction, the solvent was distilled off under reduced pressure and crude product was purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (70:30) to give the aminoalcohol **16** in 83% yield.

Yield: 83%; gum; **[α]$^{25}_{D}$**: +48.99 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 735, 837, 910, 1097, 1256, 1389, 1472, 1605, 1655, 2929, 3371, 3410, 3426; **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 2.53-2.69 (m, 2H), 3.86-4.00 (m, 1H), 4.16-4.22 (m, 2H), 4.41 (d, 1H, *J* = 11.01 Hz) 7.24-7.28 (m, 10H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$) δ: 41.64, 70.61, 70.88, 82.48, 127.71, 127.99, 128.38, 128.59, 137.52, 137.71 ppm; **Analysis:** $C_{16}H_{19}NO_2$ requires C, 74.68; H, 7.44; N, 5.44; found C, 74.58; H, 7.39; N, 5.35%.

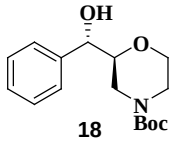


17

(*S*)-6-((*S*)-(benzyloxy)(phenyl)methyl)morpholin-3-one (17):

To a stirred solution of amine **16** (1.47g, 5.24 mmol) and Et_3N (1.60 mL, 11.5 mmol) in CH_2Cl_2 (40 mL), was added drop-wise at –10 °C, a solution of chloro acetylchloride (0.45 mL, 5.66 mmol) in CH_2Cl_2 (10 mL). After stirring for 0.5 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with water followed by saturated brine. The combined organic phase was dried over anhyd. Na_2SO_4 and solvent distilled off under reduced pressure to give the crude product which was dissolved in *t*-BuOH (20 mL) and added to a stirred solution of KO^tBu (1.18 g, 10.44 mmol) in *t*-BuOH (6 mL). The reaction mixture was stirred for 3 h at 25 °C and quenched by the addition of water. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 30 mL). The combined organic phase was washed with water and brine, dried over anhyd. Na_2SO_4, the solvent distilled off under reduced pressure and crude product purified by column chromatography over silica gel using EtOAc/Pet. ether as eluent (25:75) to give the lactam **17** in 72% yield.

Yield: 72% for 2 steps; gum; $[\alpha]^{25}_{D}$: +36.34 (*c* 1.0, $CHCl_3$); **IR** ($CHCl_3$, cm^{-1}): 669, 700, 777, 860, 1029, 1105, 1251, 1362, 1462, 1541, 1684, 2856, 2885, 2927, 2954, 3219; **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 2.79 (td, 1H, *J*=12.0, 3.67 Hz), 3.20 (t, 1H *J*=13.02 Hz), 3.88-3.98 (m, 1H), 4.19-4.27 (m, 2H), 4.33-4.41 (m, 2H), 4.77 (d, *J* = 12.59 Hz, 1H), 7.56 (br s, 1H), 7.28-7.40 (m, 10H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$) δ = 42.90, 67.48, 70.59, 75.80, 80.80, 127.51, 127.85, 128.36, 128.69, 137.04, 137.52, 169.26 ppm; **Analysis:** $C_{18}H_{19}NO_3$ requires C, 72.71; H, 6.44; N, 4.71; found C, 72.59; H, 6.39; N, 4.62%.

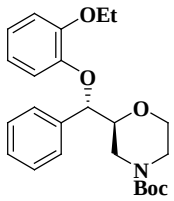


18

(*S*)-tert-butyl 2-((*S*)-hydroxy(phenyl)methyl)morpholine-4-carboxylate (18):

A solution of Red Al (3.5 mL, 10.48 mmol) in dry toluene (10 mL) was slowly added to a stirred solution of amide **17** (964 mg, 3 mmol) in dry toluene (40 mL) at 25 °C. The reaction mixture was stirred for 4 h and the excess Red Al was quenched by the addition of 2N NaOH (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 30 mL). The combined organic layer was washed with water, brine, dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product obtained was dissolved in CH_2Cl_2 (15 mL). The mixture was cooled to 0 °C and Et_3N (460 µL, 3 mmol) and $(Boc)_2O$ (654 mg, 3 mmol) were added to it. After 1 h the reaction mixture was quenched by the addition of aqueous $NaHCO_3$ (10%). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried over anhyd. Na_2SO_4, solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using Pet. Ether/EtOAc as eluent (85:15) to give morpholine derivative in 75% yield. To a solution of morpholine derivative (0.53 g, 2 mmol) in MeOH (20 mL) was added catalytic amount of 10% Pd/C and the resulting heterogeneous mixture was stirred for 12 h at 25 °C. The reaction mixture was then filtered through a pad of celite and the solvent was removed under reduced pressure to give the crude product, which was then purified by column chromatography over silica gel using petroleum ether/EtOAc (80:20) to give **18** in 88% yield.

Yield: 88% **mp:** 105-106 °C; **[α]$^{25}_{D}$**: +33.62 (*c* 1.0, $CHCl_3$); {lit.[12] **[α]$^{20}_{D}$**: +34.0 (*c* 1.24, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 669, 721, 862, 1068, 1114, 1181, 1241, 1323, 1456, 1610, 1701, 2861, 3214; **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 1.37 (s, 9H), 2.67 (br s, 1H), 2.87-2.99 (m, 2H), 3.37-3.61 (m, 3H), 3.79 (d, 1H, *J* = 13.9 Hz), 3.94 (d, 1H, *J* = 12.19 Hz), 4.49 (d, 1H, *J* = 6.96 Hz), 7.27-7.34 (m, 5H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$) δ = 28.37, 43.94, 44.60, 66.41, 75.06, 79.45, 79.89, 126.95, 128.32, 128.49, 139.35, 154.37 ppm; **Analysis**: $C_{16}H_{23}NO_4$ requires C, 65.51; H, 7.90; N, 4.77%; found C, 65.46; H, 7.79; N, 4.72%.



(*S*)-2-((*S*)-(2-ethoxyphenoxy)(phenyl)methyl)morpholine (19):

To a stirred solution of morpholine **18** (300 mg, 1.13 mmol), PPh_3 (449 mg, 1.356 mmol) and imidazole (355 mg, 1.356 mmol) in CH_2Cl_2 was added CBr_4 (449 mg, 1.356 mmol) at 0 °C and the mixture was stirred at 25 °C for 2 h. The reaction mixture was quenched by the addition of 10% $Na_2S_2O_3$ solution and the organic phase was separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, the solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using Pet. ether/EtOAc as eluent (90:10) to give bromo derivative as colorless solid in 81% yield. To a stirred suspension of sodium hydride (60% oil dispersion, 60 mg, 1.5 mmol) and ethoxy phenol (50.5 mg, 0.356 mmol) in DMF (5 mL) at 0 °C bromo derivative (100 mg, 0.305 mmol)

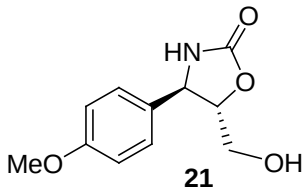
in DMF (4 mL) was added drop wise and the mixture was stirred at 25 °C for 2 h under nitrogen atmosphere. The reaction mixture was quenched by the addition of aqueous solution of water and the organic phase was separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over anhyd. Na_2SO_4, the solvent distilled off under reduced pressure and the crude product purified by column chromatography over silica gel using Pet. ether/EtOAc as eluent (90:10) to provide *N*-Boc amide as colorless oil in 72% yield.

Yield: 72%; gum; **$[\alpha]^{25}_{D}$**: +50.4 (*c* 1.0, $CHCl_3$); {lit.[1] $[\alpha]^{20}_{D}$: +51.0 (*c* 1.01, $CHCl_3$)}; **IR** ($CHCl_3$, cm^{-1}): 761, 986, 1123, 1134, 1251, 1456, 1499, 1543, 1690, 2915, 2923; **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 1.45 (s, 12H), 2.79-3.00 (m, 2H), 3.50-3.56 (m, 1H), 3.70-3.90 (m, 4H), 4.01-4.12 (m, 2H), 5.16 (d, 1H, *J*=3.5 Hz), 6.67-6.87 (m, 4H), 7.29-7.43 (m, 5H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$) δ = 15.00, 28.32, 43.85, 45.75, 64.57, 66.83, 74.92, 79.91, 82.16, 114.14, 118.60, 120.79, 122.45, 127.39, 128.24, 137.57, 147.89, 150.02, 154.79 ppm; **Analysis**: **$C_{24}H_{31}NO_5$** requires C, 69.71; H, 7.56; N, 3.39%; found C, 69.64; H, 7.61; N, 3.34%.

To a stirred solution of *N*-Boc amide (100 mg, 0.242 mmol) in CH_2Cl_2 (4 mL), trifluoroacetic acid (0.74 mL, 3.6 mmol) was added dropwise at 0 °C. The reaction mixture was allowed to reach 25 °C and stirred for 1.5 h. The reaction mixture was cooled to 0 °C and quenched by the addition of 1M NaOH solution (15 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc/MeOH (95:5, 3 x 30 mL). The combined organic phase was dried over anhyd. Na_2SO_4, solvent evaporated under reduced pressure and the crude product purified by column chromatography over

silica gel using MeOH/$CHCl_3$ (10:90) as eluent to provide (*S*,*S*)-reboxetine **19** as colorless oil.

Yield: 98%; gum; **$[\alpha]^{25}_D$**: +12.59 (*c* 1.1, MeOH); {lit.[1] $[\alpha]^{20}_D$: +13.0 (*c* 1.03, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): 750, 997, 1119, 1154, 1251, 1453, 1499, 1593, 2915, 3031; **^{1}H NMR** (200 MHz, $CDCl_3$) δ = 1.44 (t, *J*=7.5 Hz, 3H), 2.98-2.80 (m, 4H), 3.77-3.68 (m, 1H), 4.13-3.97 (m, 4H), 5.26 (d, *J*=5.5 Hz, 1H), 6.71-6.79 (m, 2H), 6.84-6.97 (m, 2H), 7.27-7.43 (m, 5H) ppm; **^{13}C NMR** (50 MHz, $CDCl_3$) δ = 15.3, 45.1, 46.8, 65.7, 67.0, 78.8, 83.4, 115.5, 118.9, 121.9, 123.5, 128.6, 129.3, 138.6, 148.7, 150.9 ppm; **Analysis**: **$C_{19}H_{23}NO_3$** requires C, 72.82; H, 7.40; N, 4.47%; found C, 72.69; H, 7.37; N, 4.44%.



21

(4*S*, 5*S*)-5-(Hydroxymethyl)-4-(4-methoxyphenyl)oxazolidin-2-one:
(+)-*epi*-cytoxazone (21):

To a solution of amino diol **20** (0.3g, 1.0 mmol) in dry THF (10 mL) was added sodium hydride (0.05 g, 60% w/w, 2.0 mmol) at room temperature, and the mixture was stirred under nitrogen atmosphere for 2.5 h. The reaction mixture was concentrated, ethyl acetate (10 mL) was added, and washed with saturated aq. NH_4Cl (5 mL) and brine solution (5 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography to give **21** as a white solid (0.216 g, 96% yield).

Yield: 96%; **mp**: 159-160 °C {lit.[2] **mp**: 161-162 °C}; **$[\alpha]^{25}_D$**: +32.60 (*c* 1, MeOH) {lit.[2] **$[\alpha]^{25}_D$**: +32.8 (c 0.6, MeOH)}; **IR** ($CHCl_3$, cm^{-1}): 772, 832, 1104, 1252, 1522, 1570,

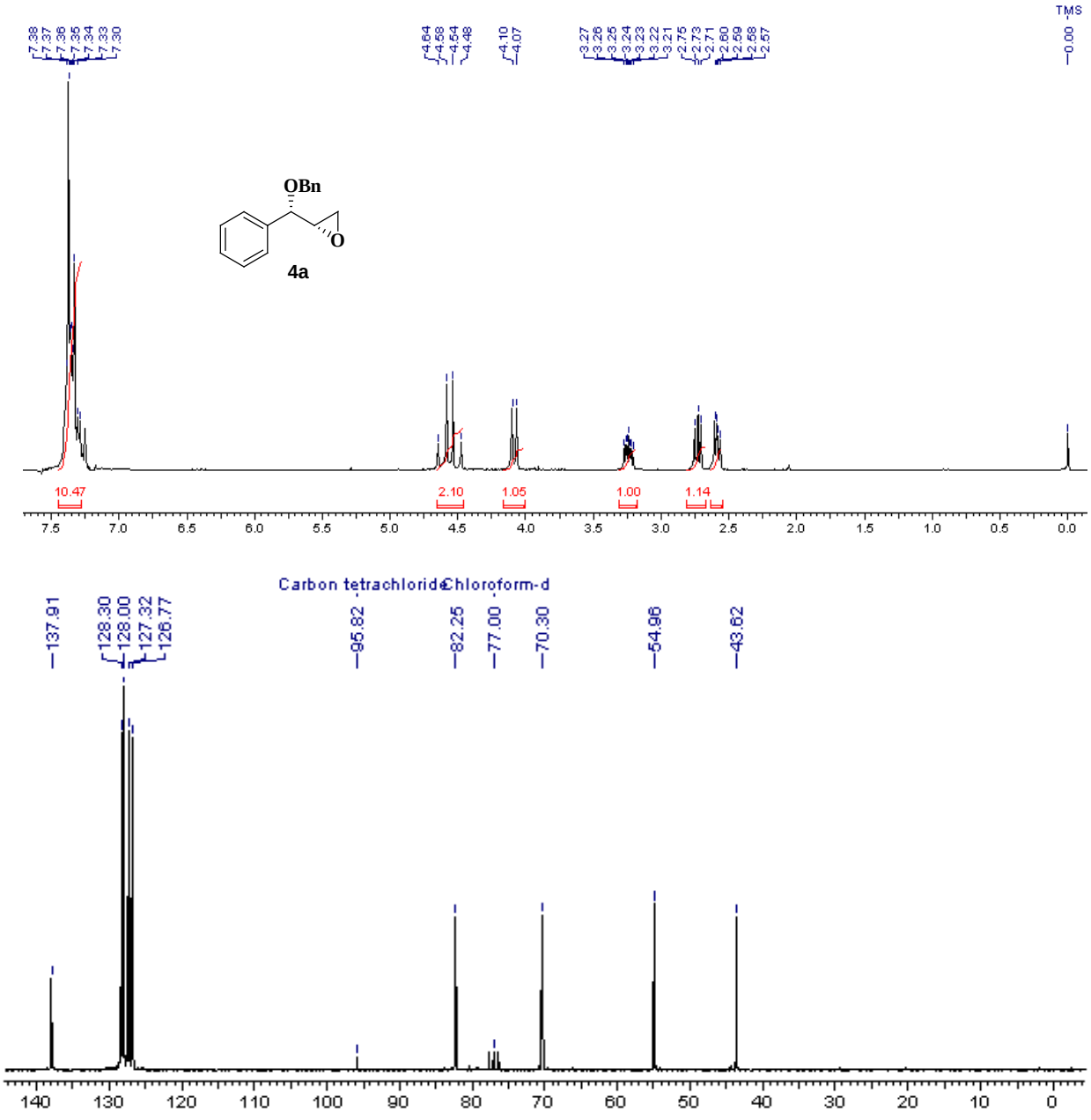
1724, 3244; **^{1}H NMR** (200 MHz, DMSO-D_6) δ = : 3.43-3.50 (m, 1H), 3.56-3.59 (m, 1H), 3.70 (s, 3H), 4.03-4.17 (m, 1H), 4.58(d, *J* = 5.8 Hz, 1H), 5.17 (t, *J* = 5.56 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 2H), 7.22(d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (50 MHz, $DMSOD_6$) δ: 55.37, 56.43, 61.20, 84.44, 114.37, 127.72, 133.14, 158.41, 159.27; **Analysis**: $C_{11}H_{13}NO_4$ requires C, 59.19; H, 5.87; N, 6.27%; found C, 59.20; H, 5.80; N, 6.23%.

References:

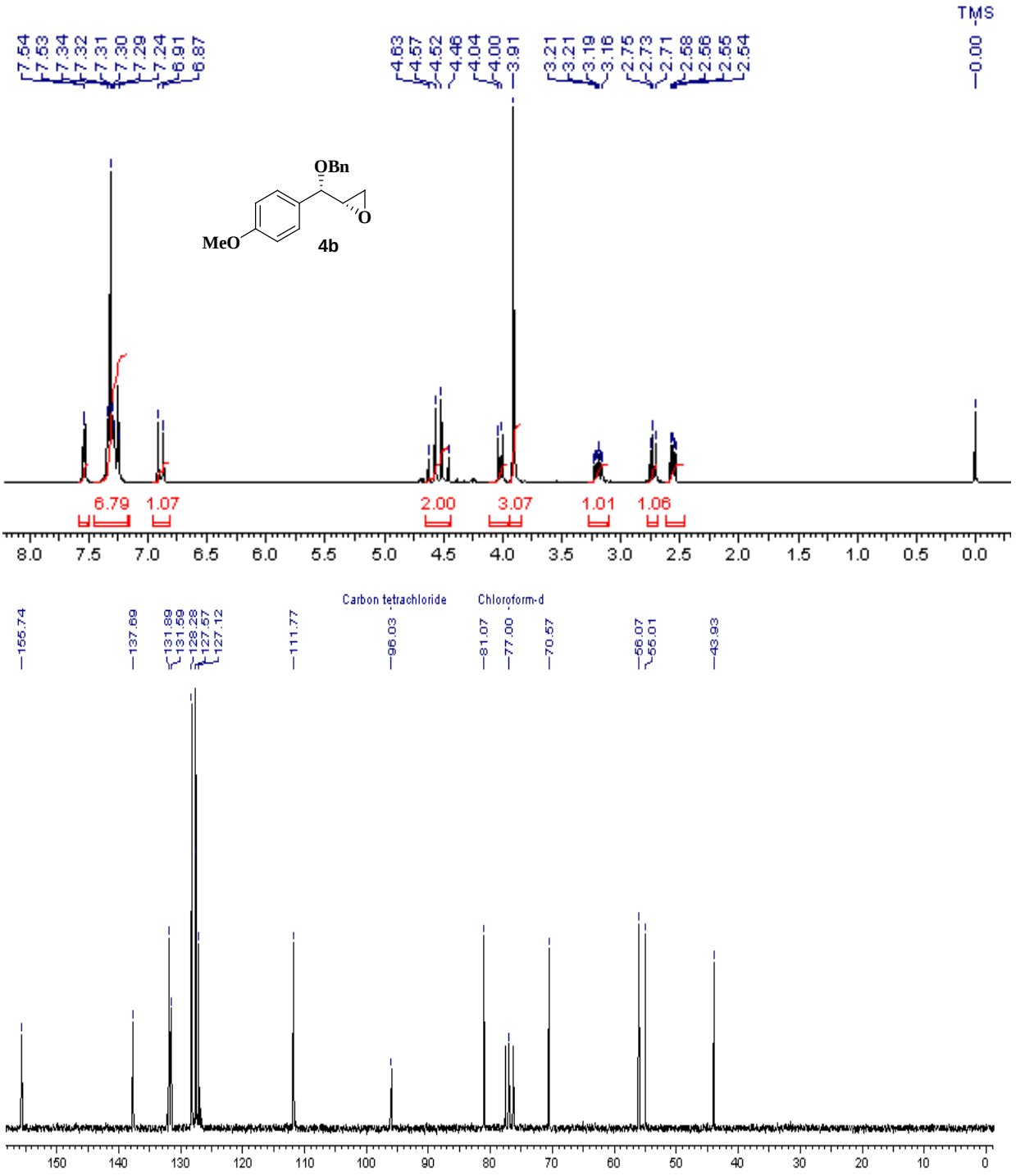
1. E. Brenner, R. M. Baldwin, G. Tamagnan, *Org. Lett.*, 2005, **7**, 937-939

2. S-G. Kim, T-H Park, *Tetrahedron: Asymmetry*, 2008, **19,** 1626–1629

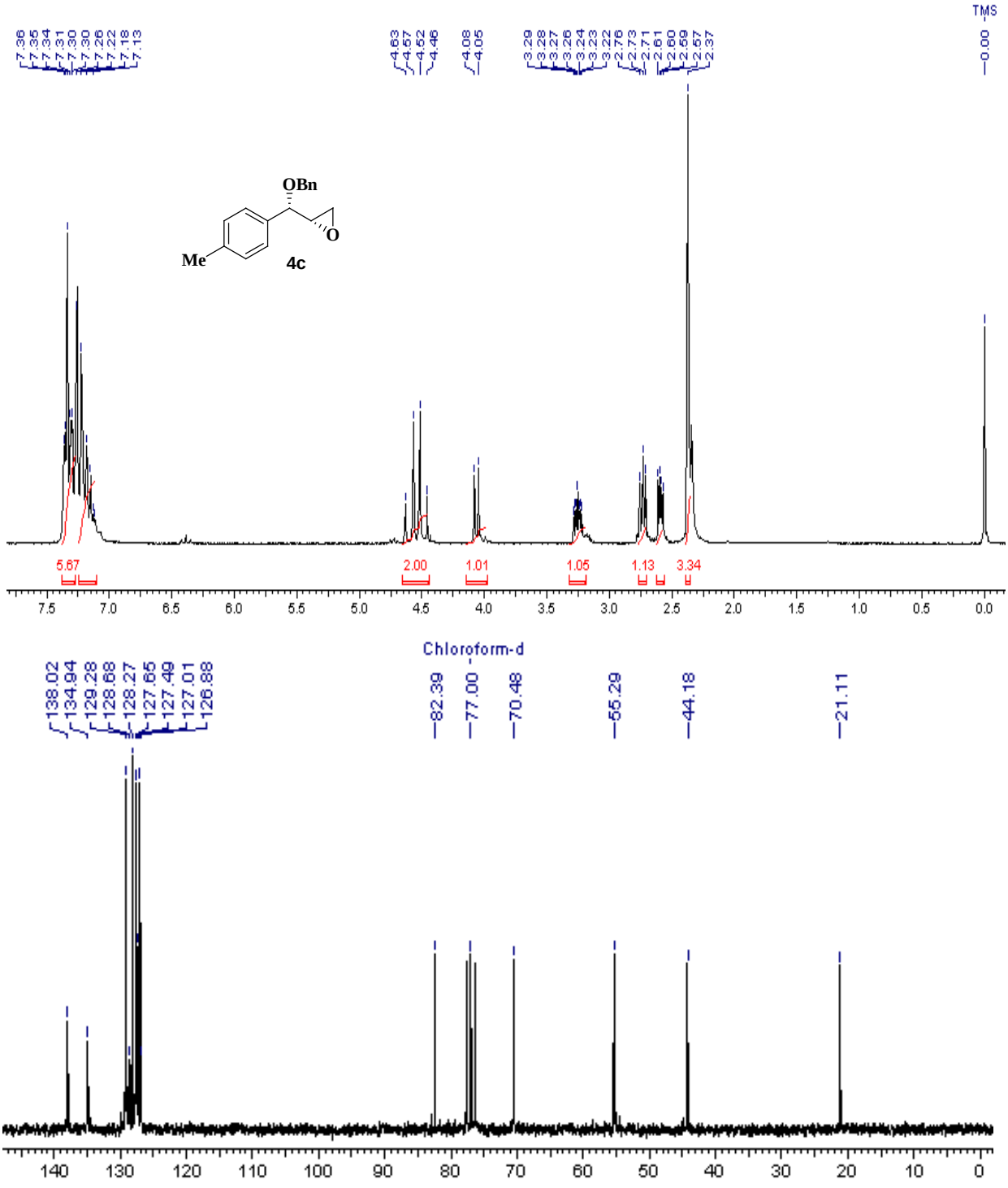
2. Spectra



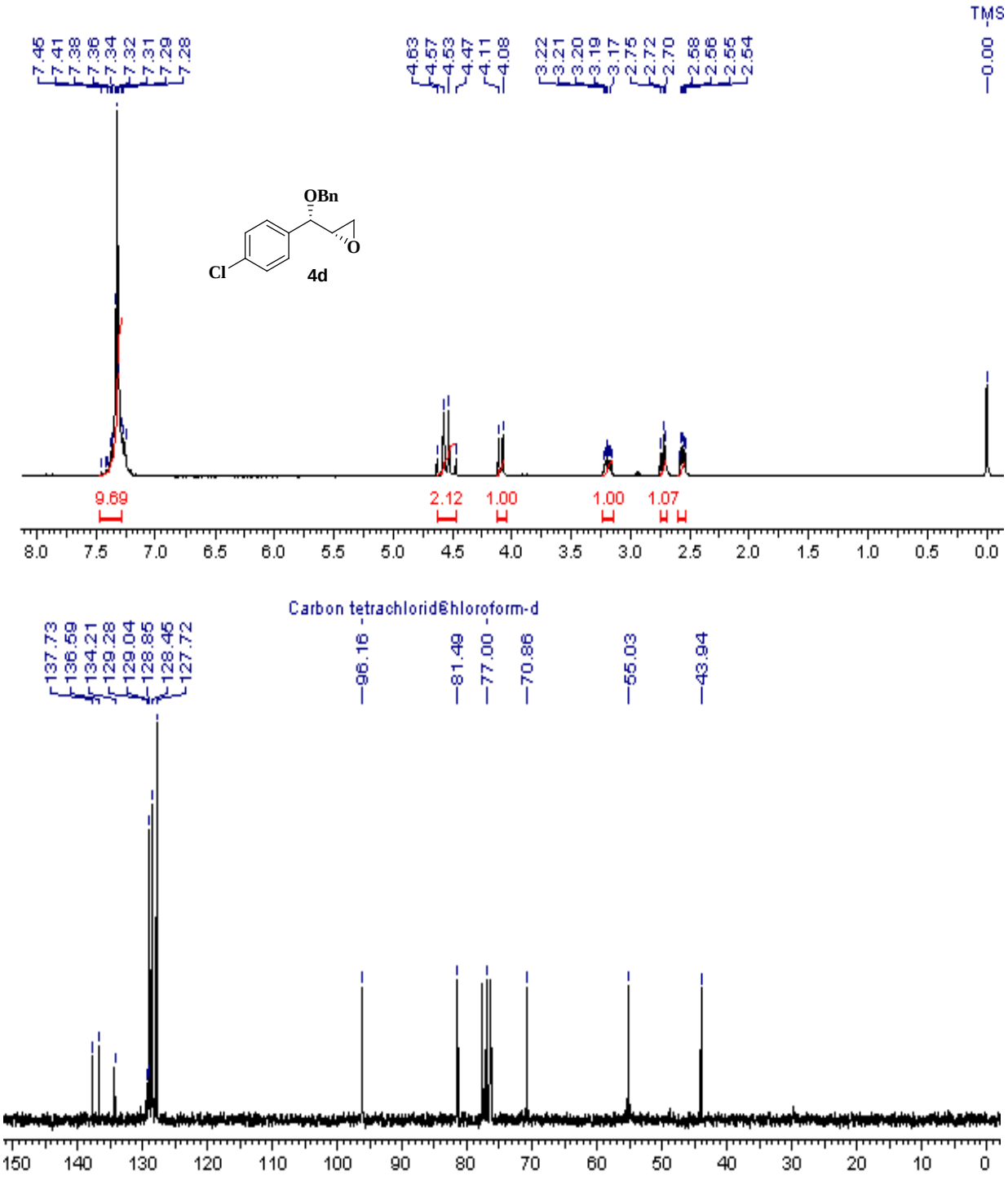
^{1}H and ^{13}C NMR spectra of 4a



^{1}H and ^{13}C NMR spectra of 4b



^{1}H and ^{13}C NMR spectra of 4c



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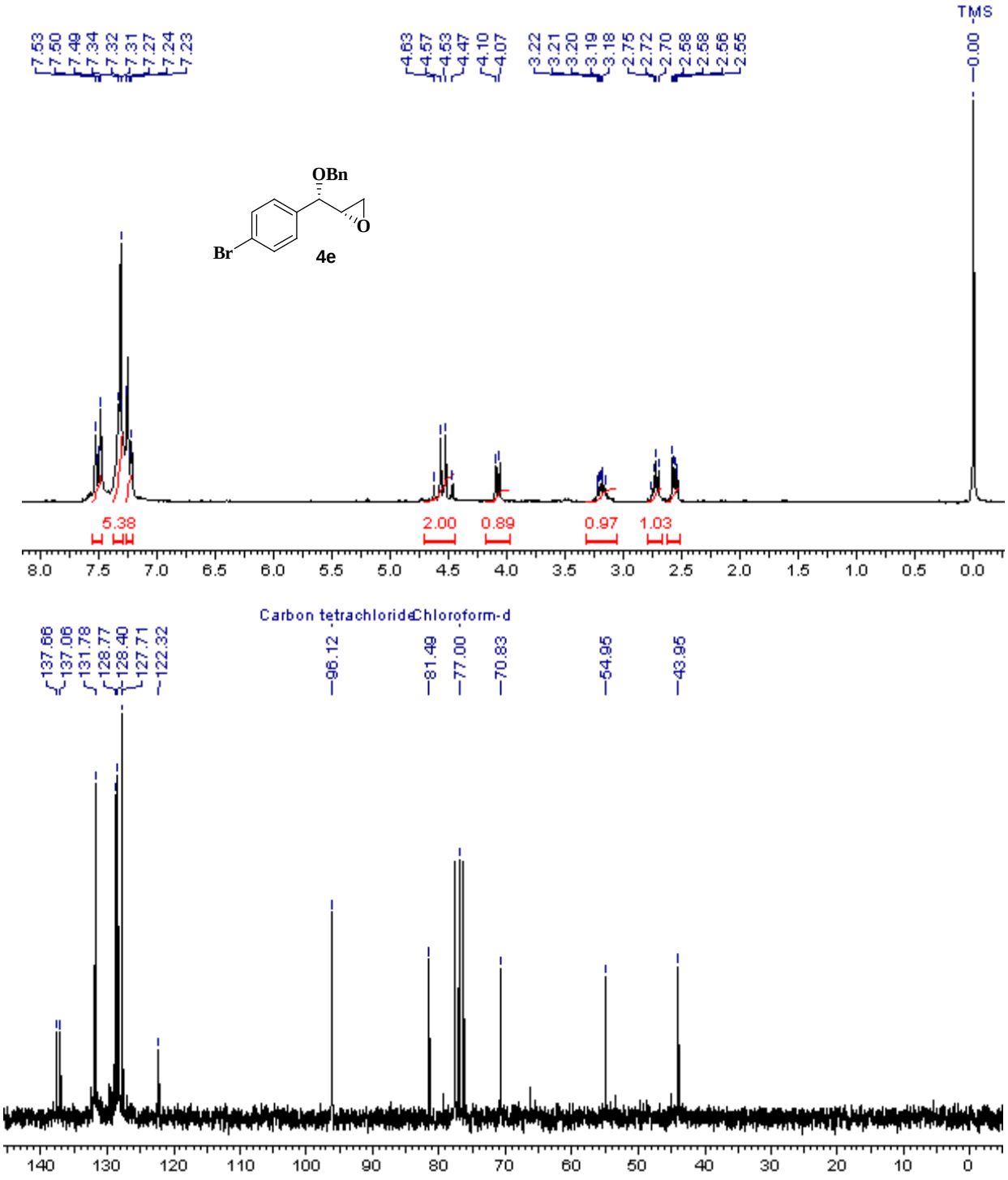
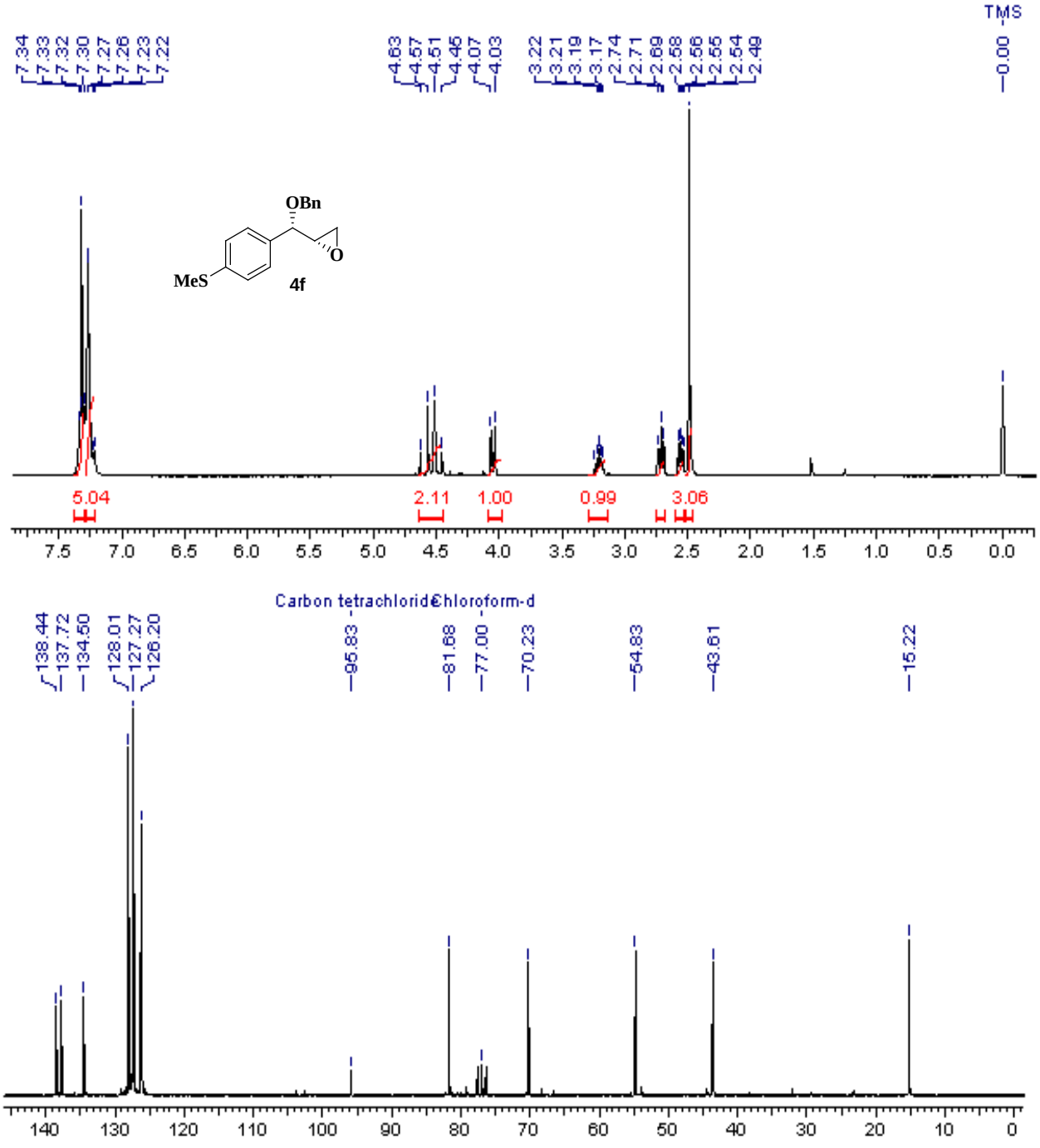
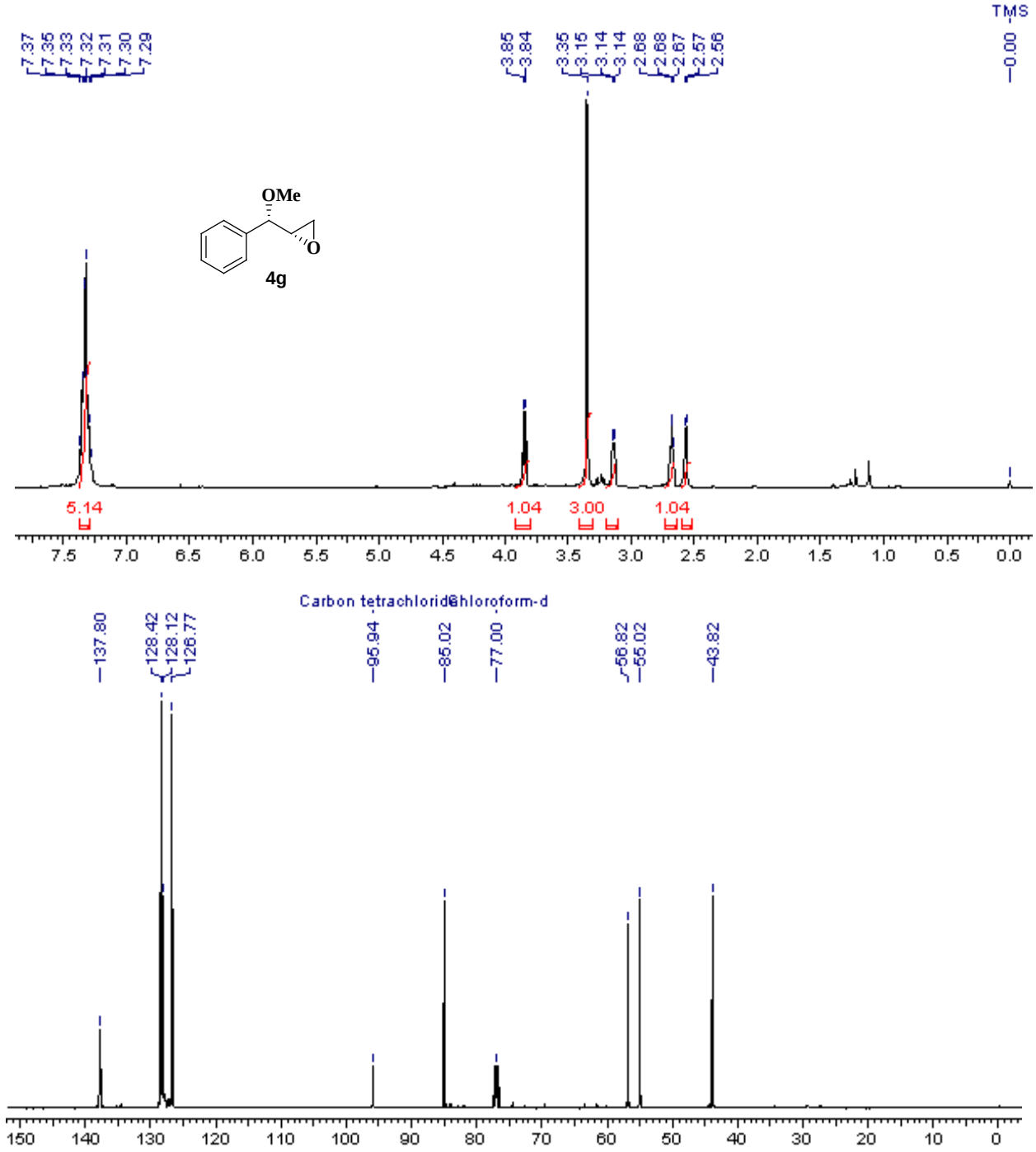


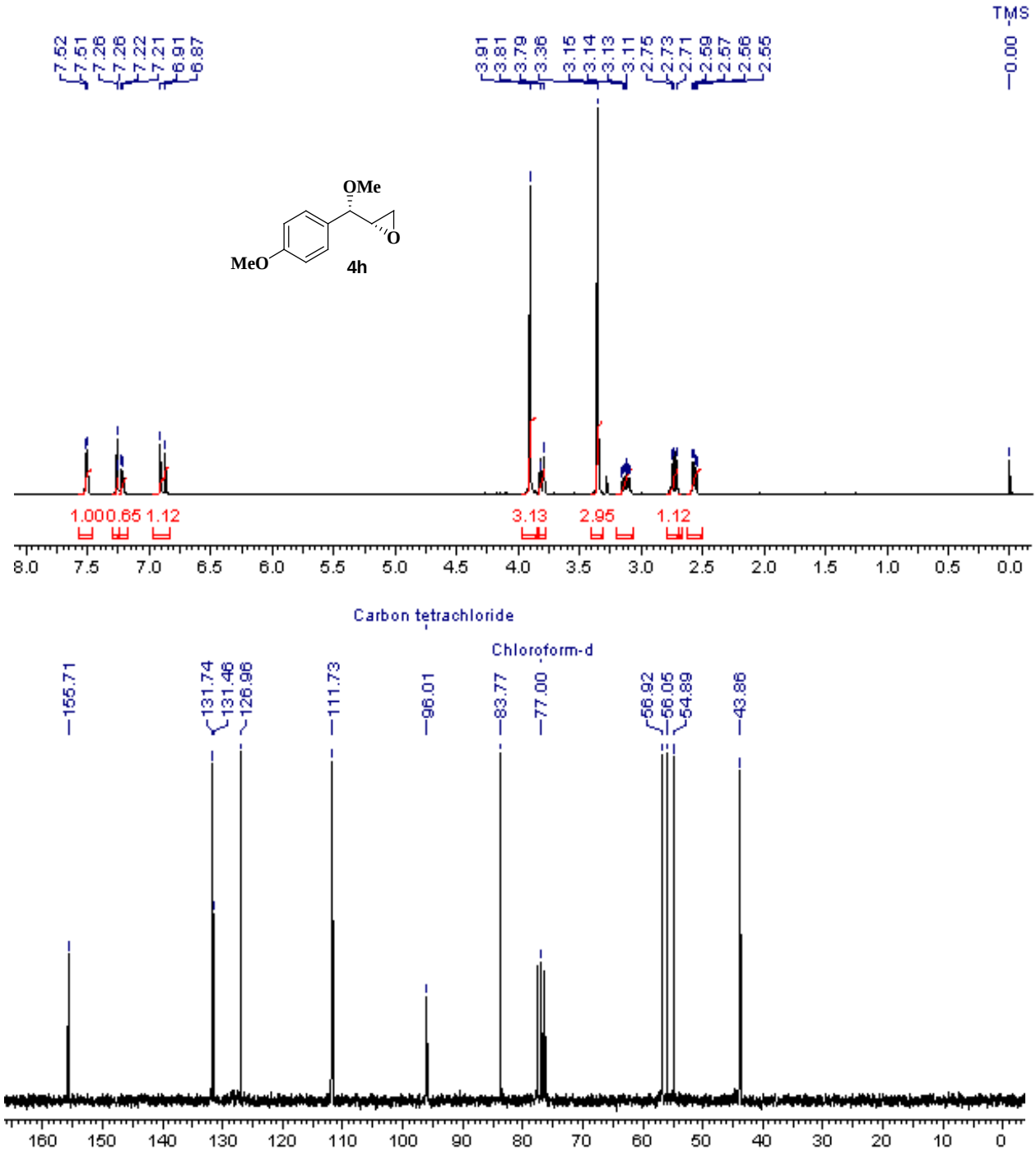
^{1}H and ^{13}C NMR spectra of 4d



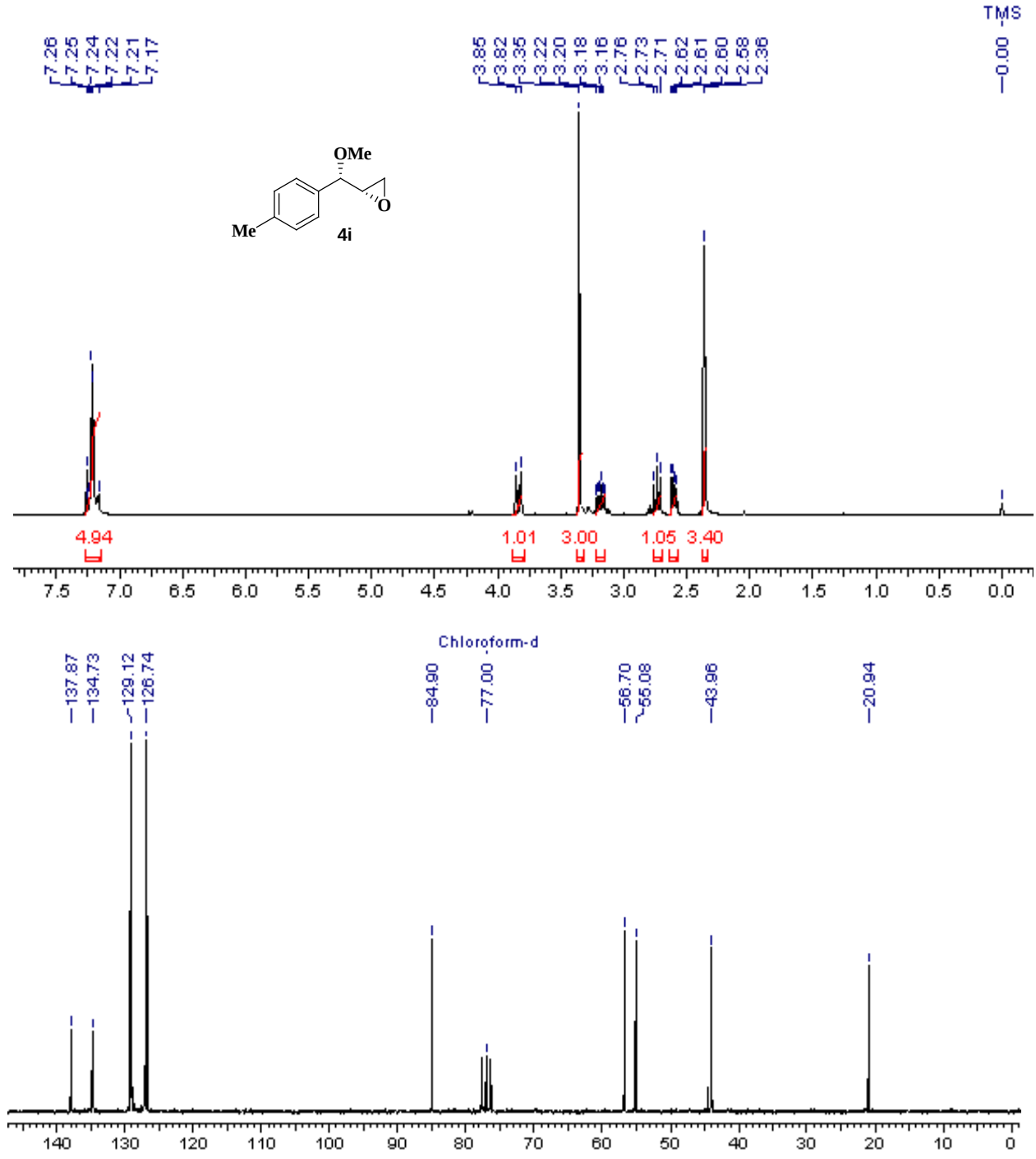
^{1}H and ^{13}C NMR spectra of 4f



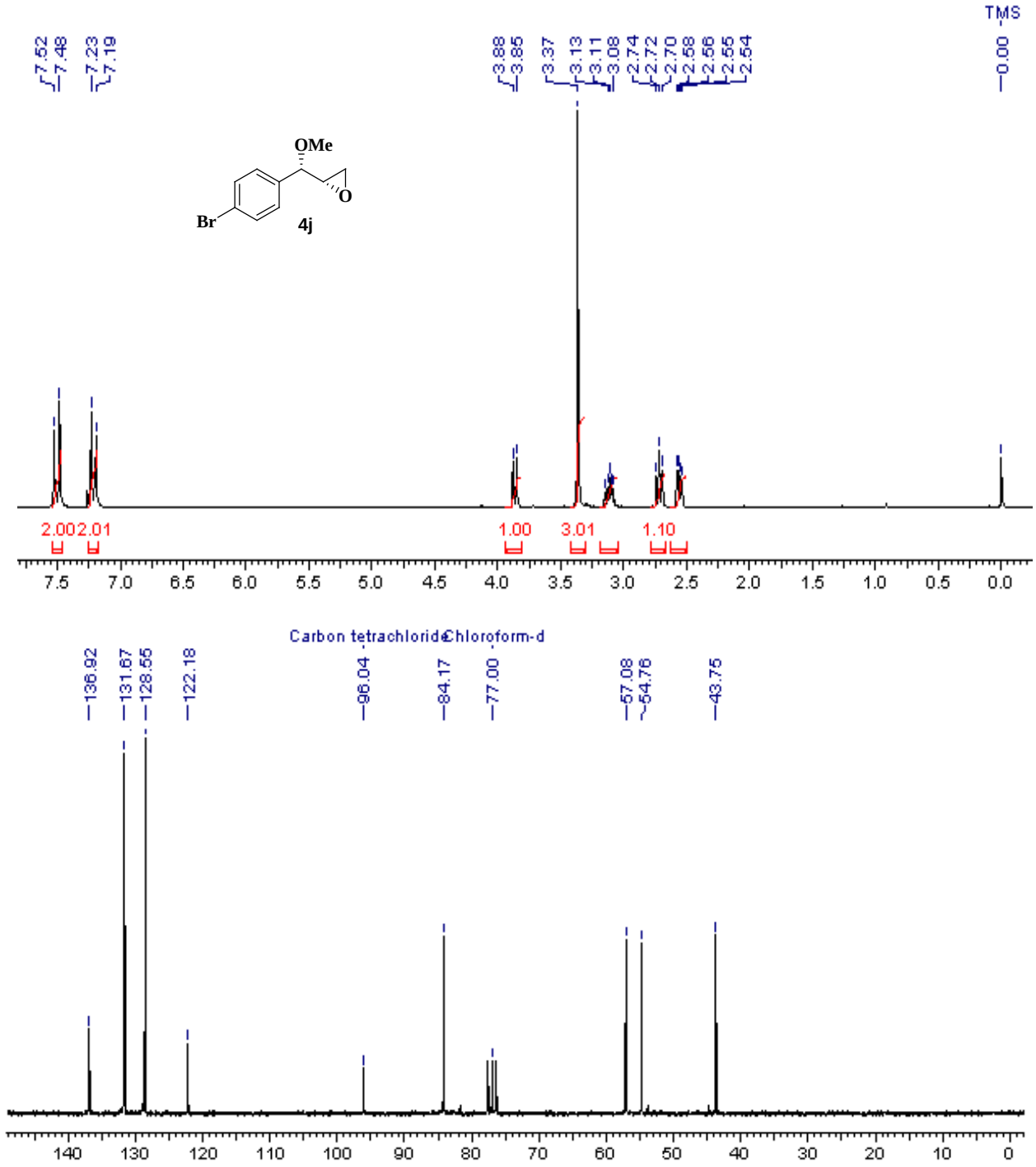
^{1}H and ^{13}C NMR spectra of 4g



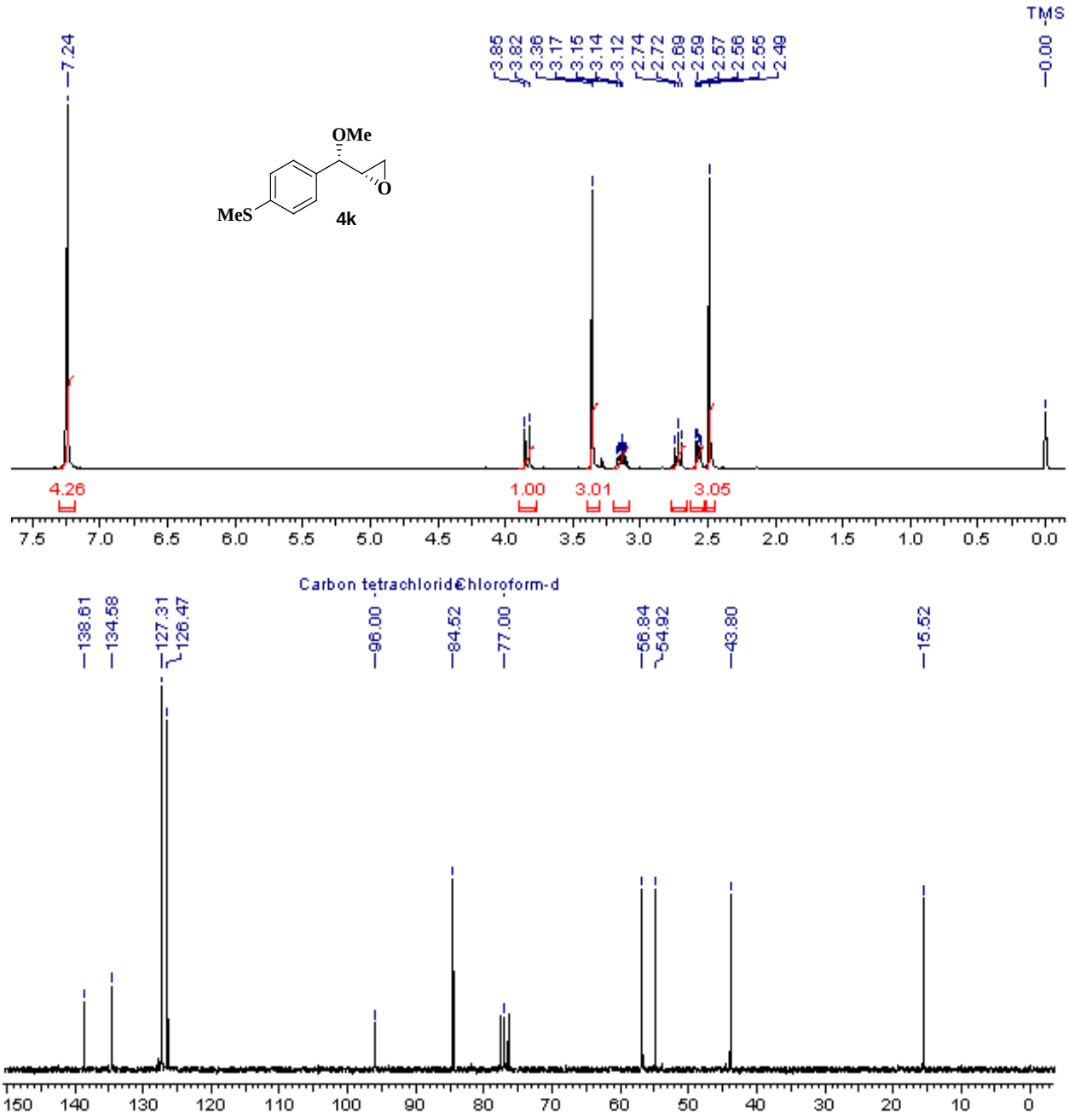
^{1}H and ^{13}C NMR spectra of 4h



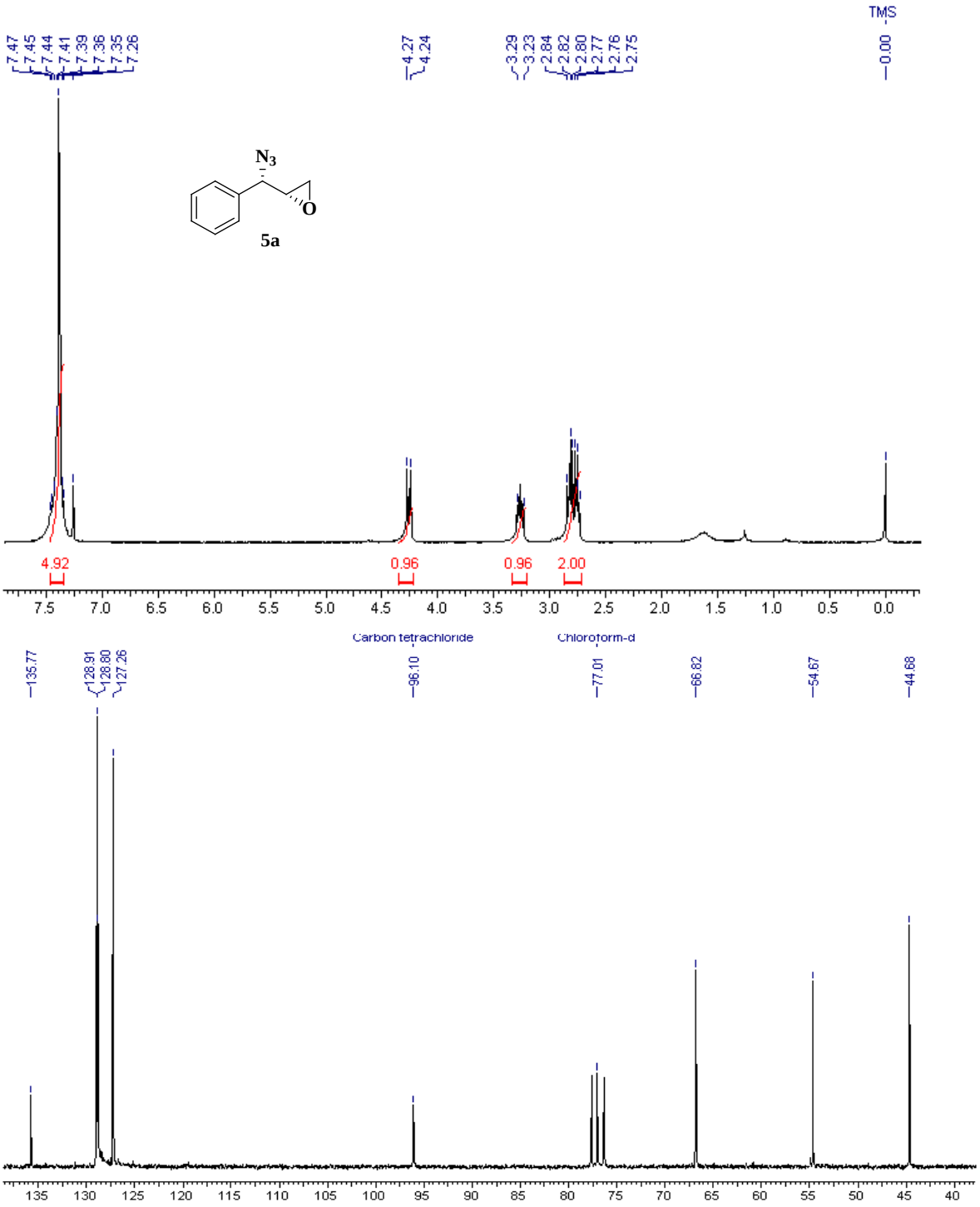
^{1}H and ^{13}C NMR spectra of 4i



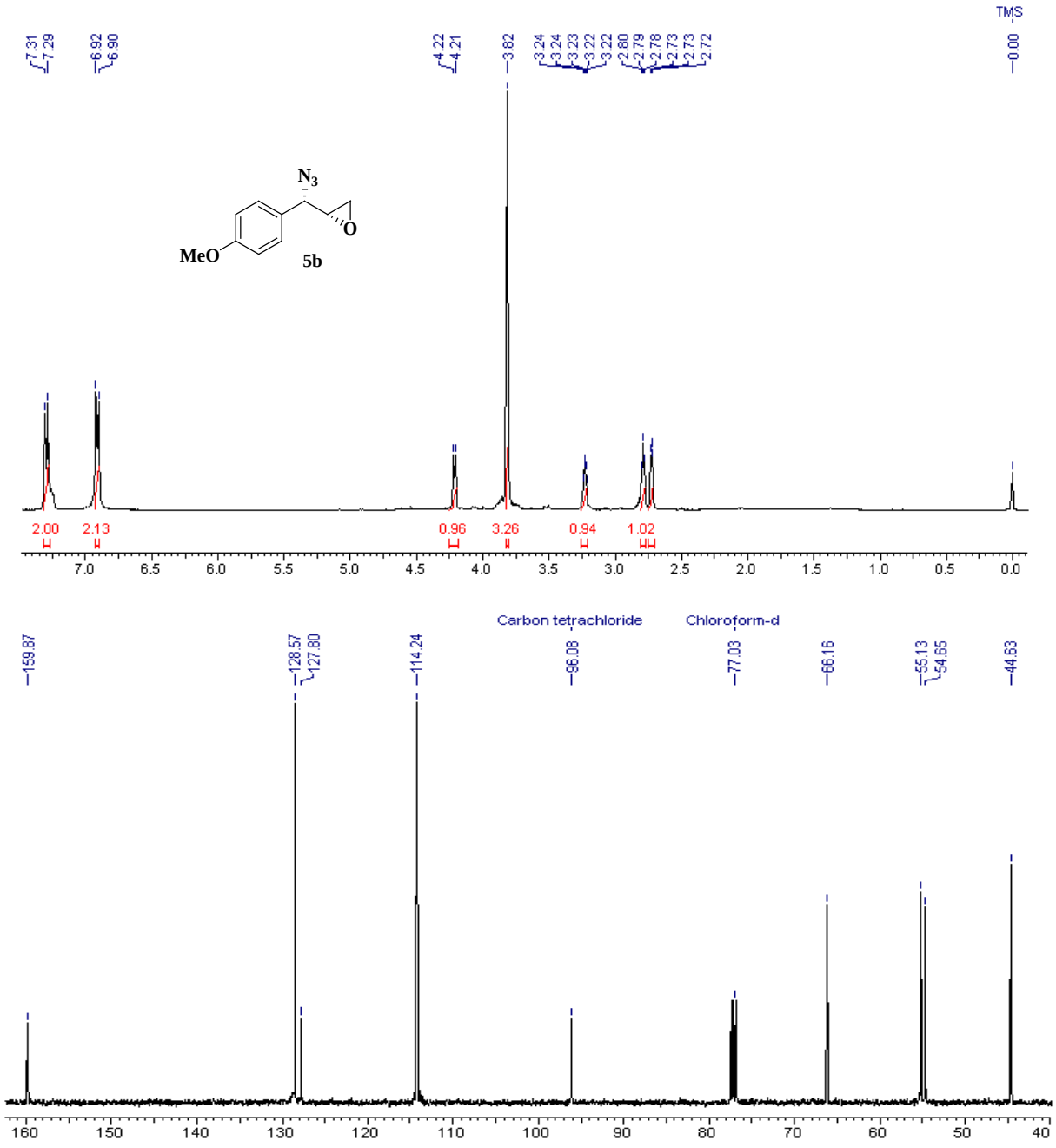
^{1}H and ^{13}C NMR spectra of 4j



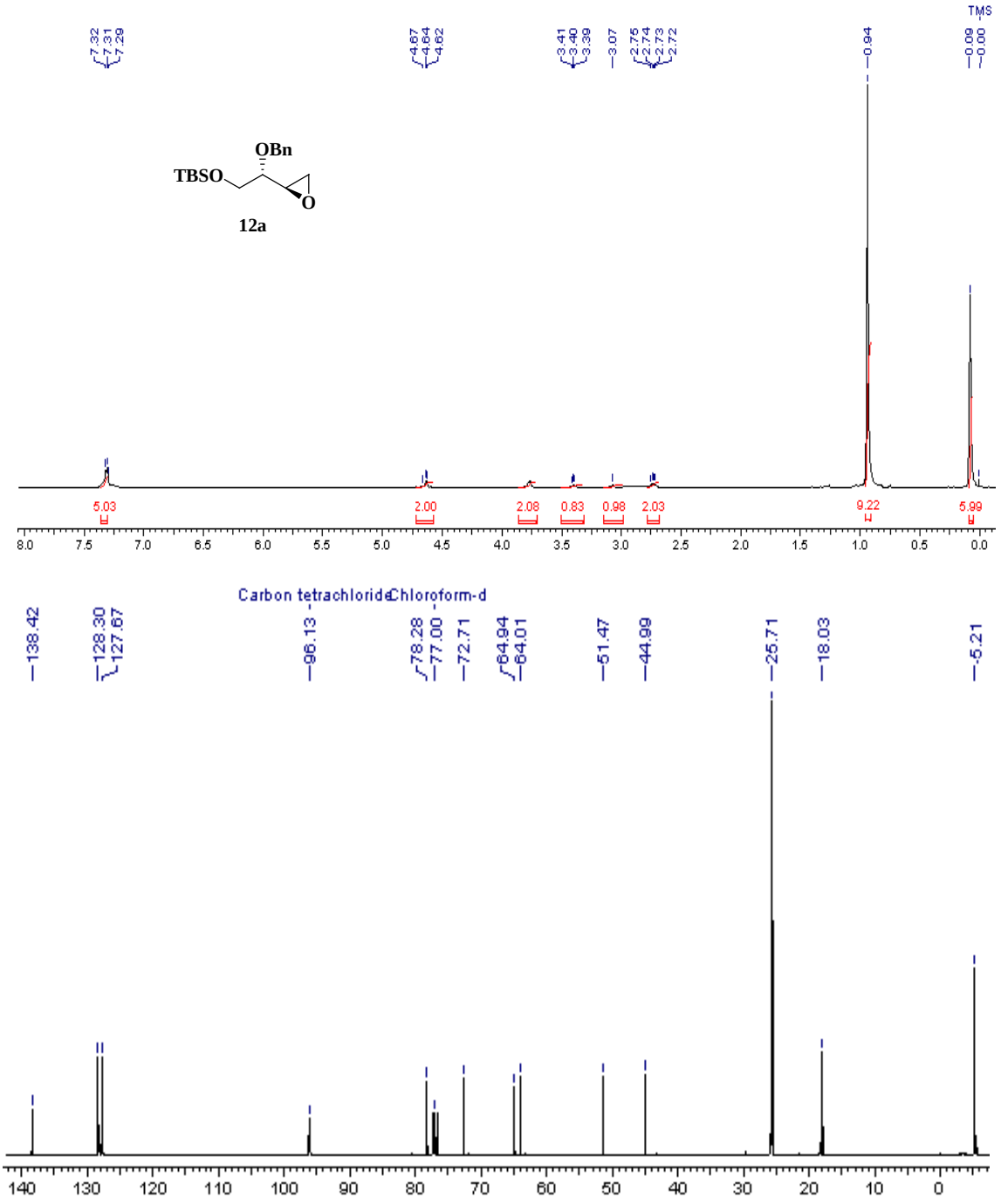
^{1}H and ^{13}C NMR spectra of 4k



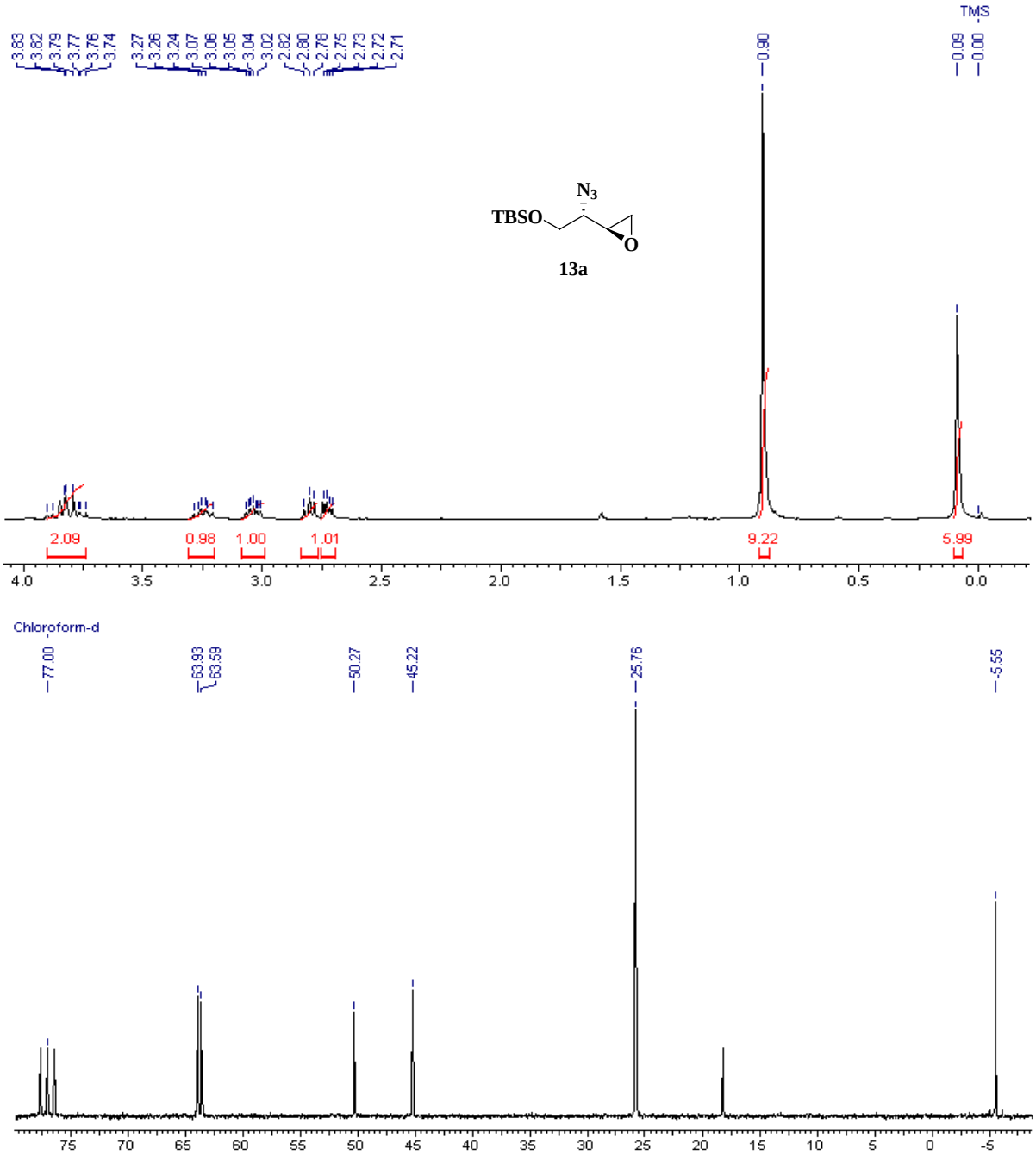
^{1}H and ^{13}C NMR spectra of 5a



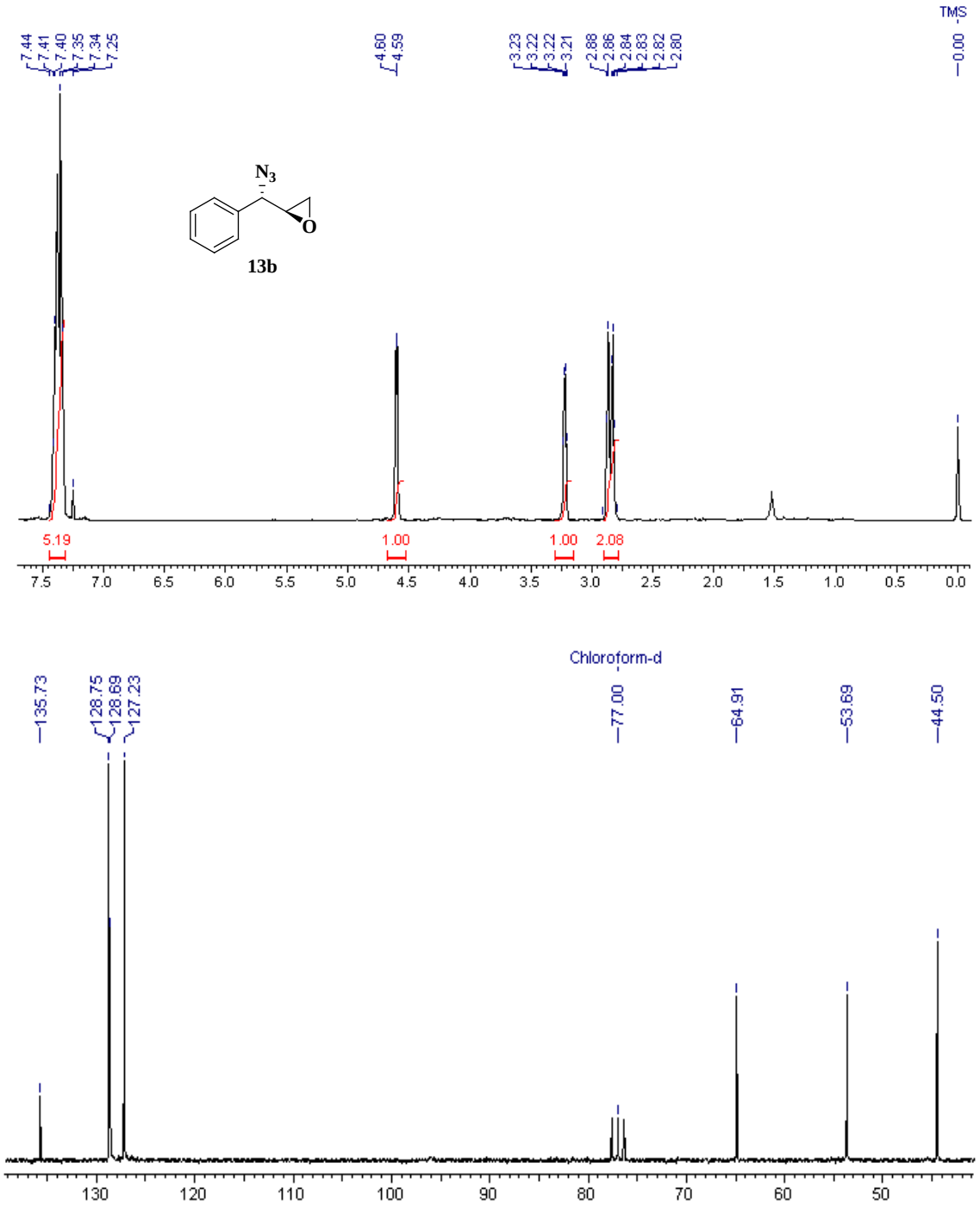
^{1}H and ^{13}C NMR spectra of 5b



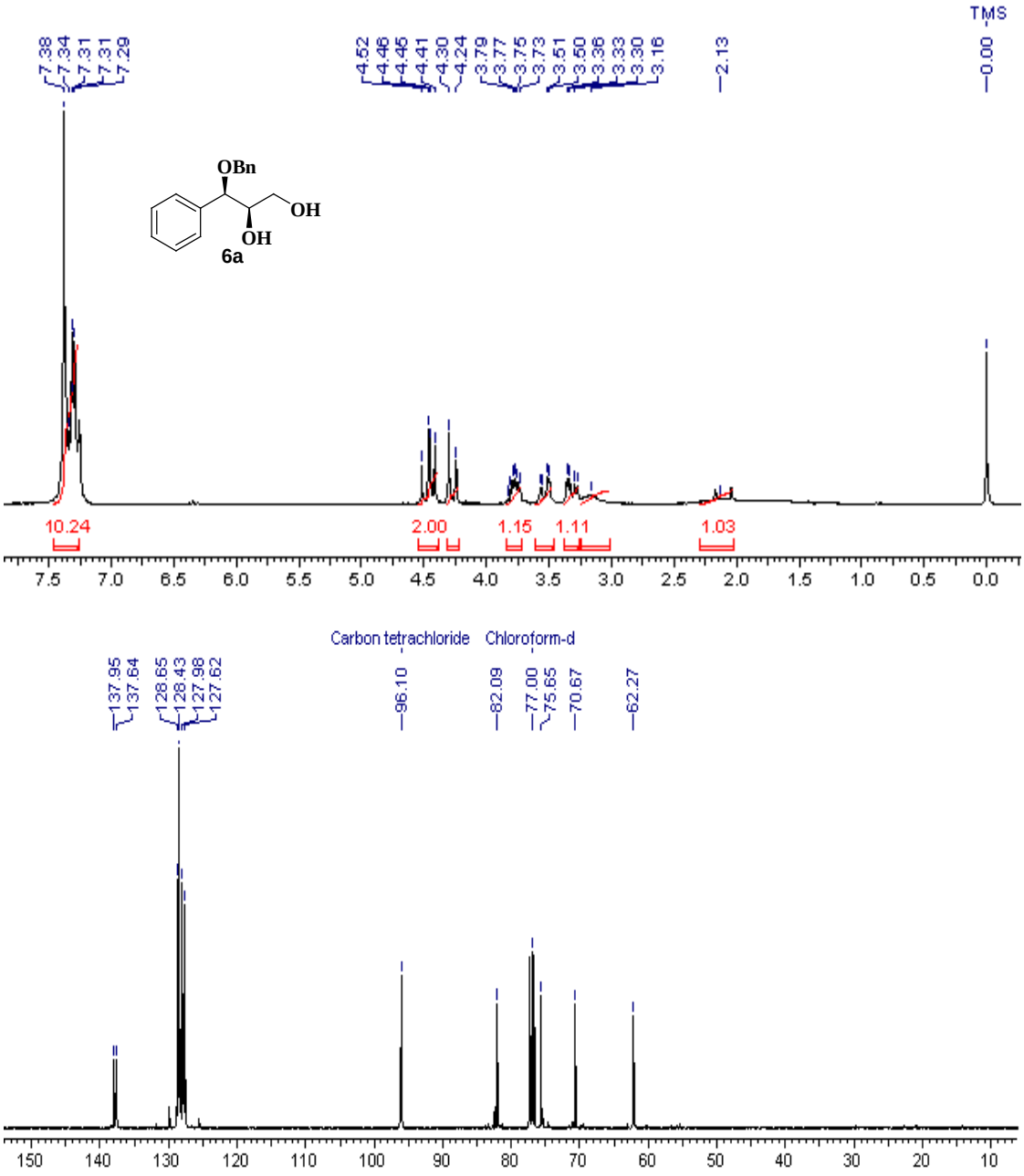
^{1}H and ^{13}C NMR spectra of 12a



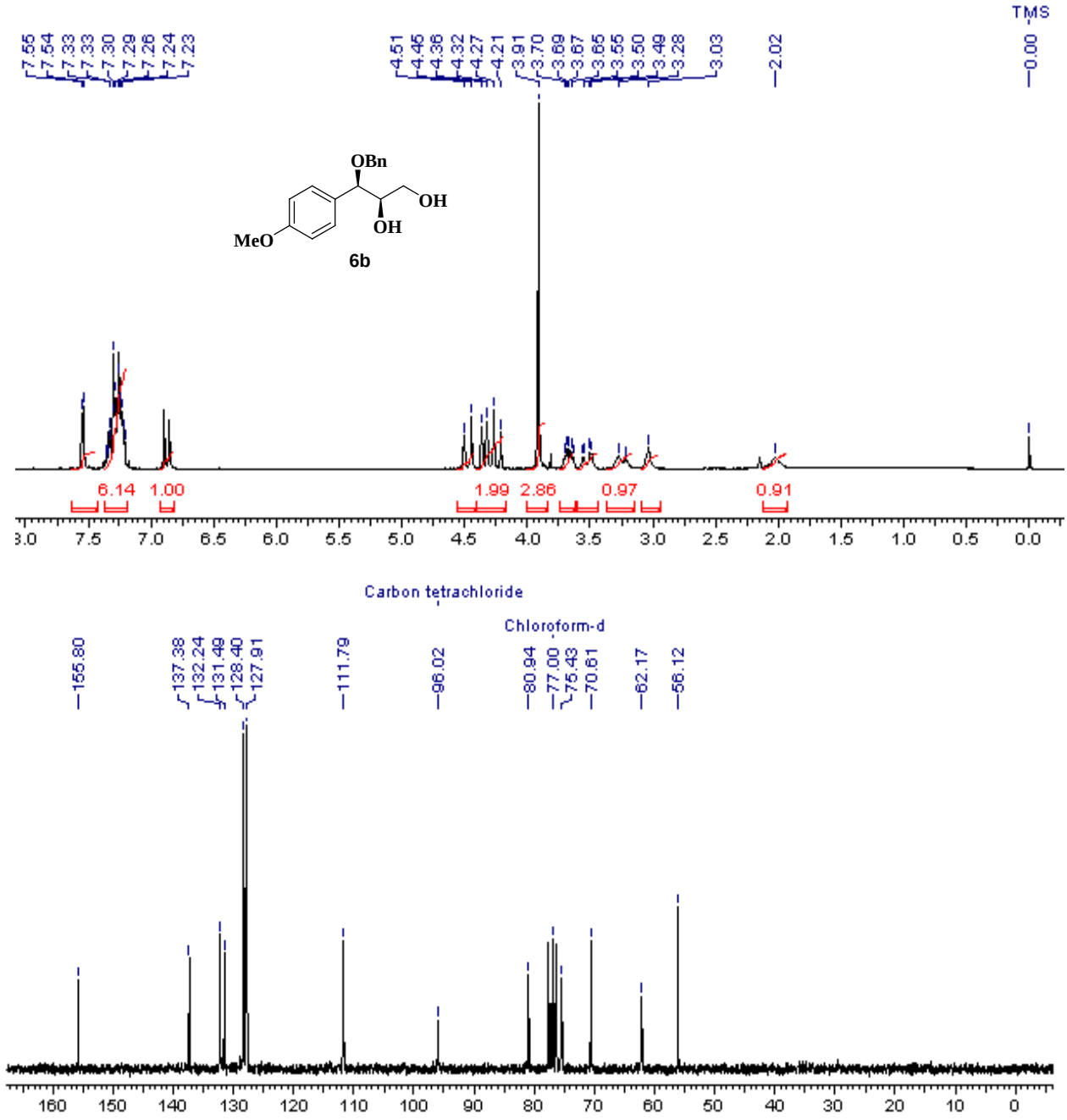
^{1}H and ^{13}C NMR spectra of 13a



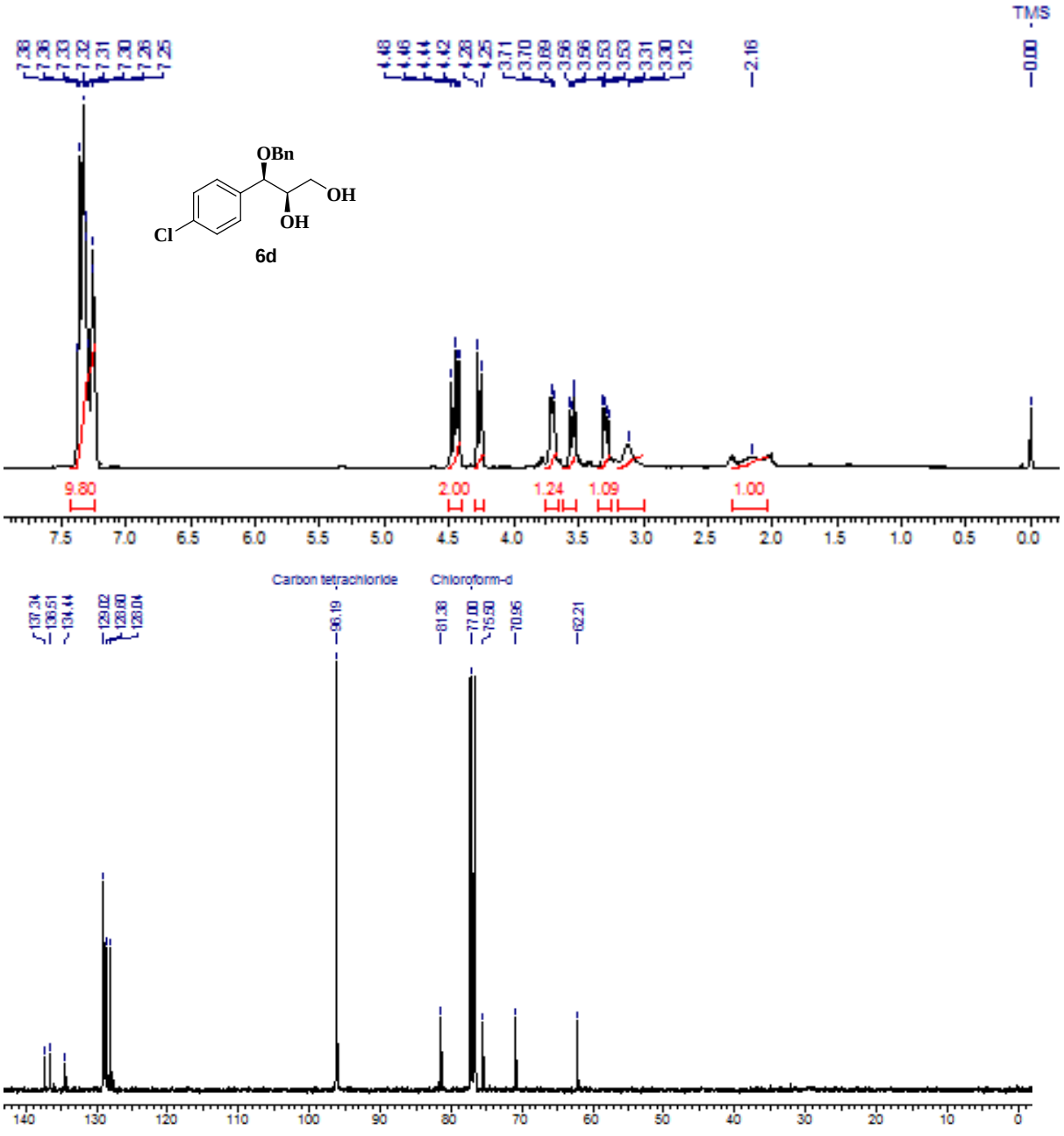
^{1}H and ^{13}C NMR spectra of 13b



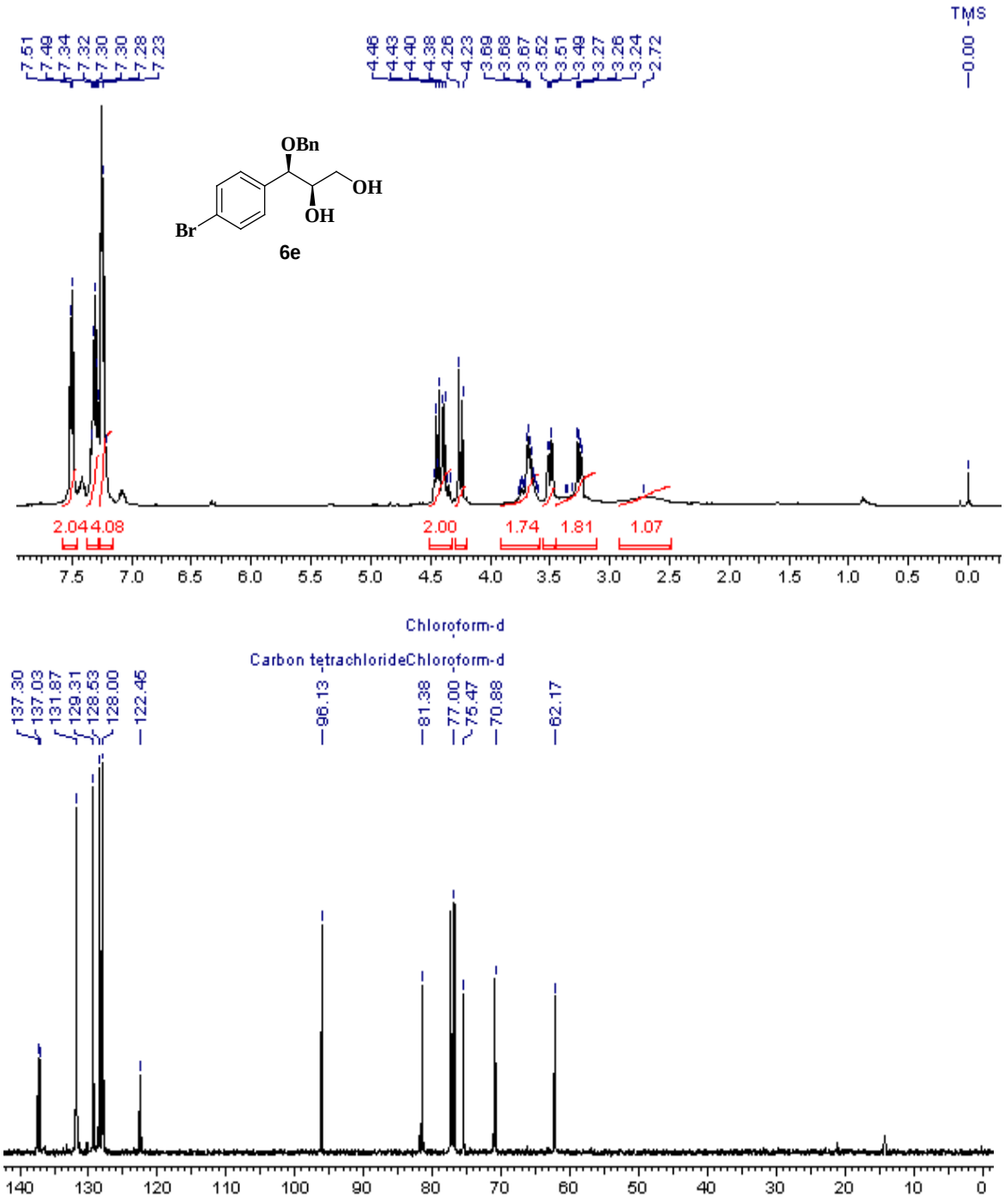
^{1}H and ^{13}C NMR spectra of 6a



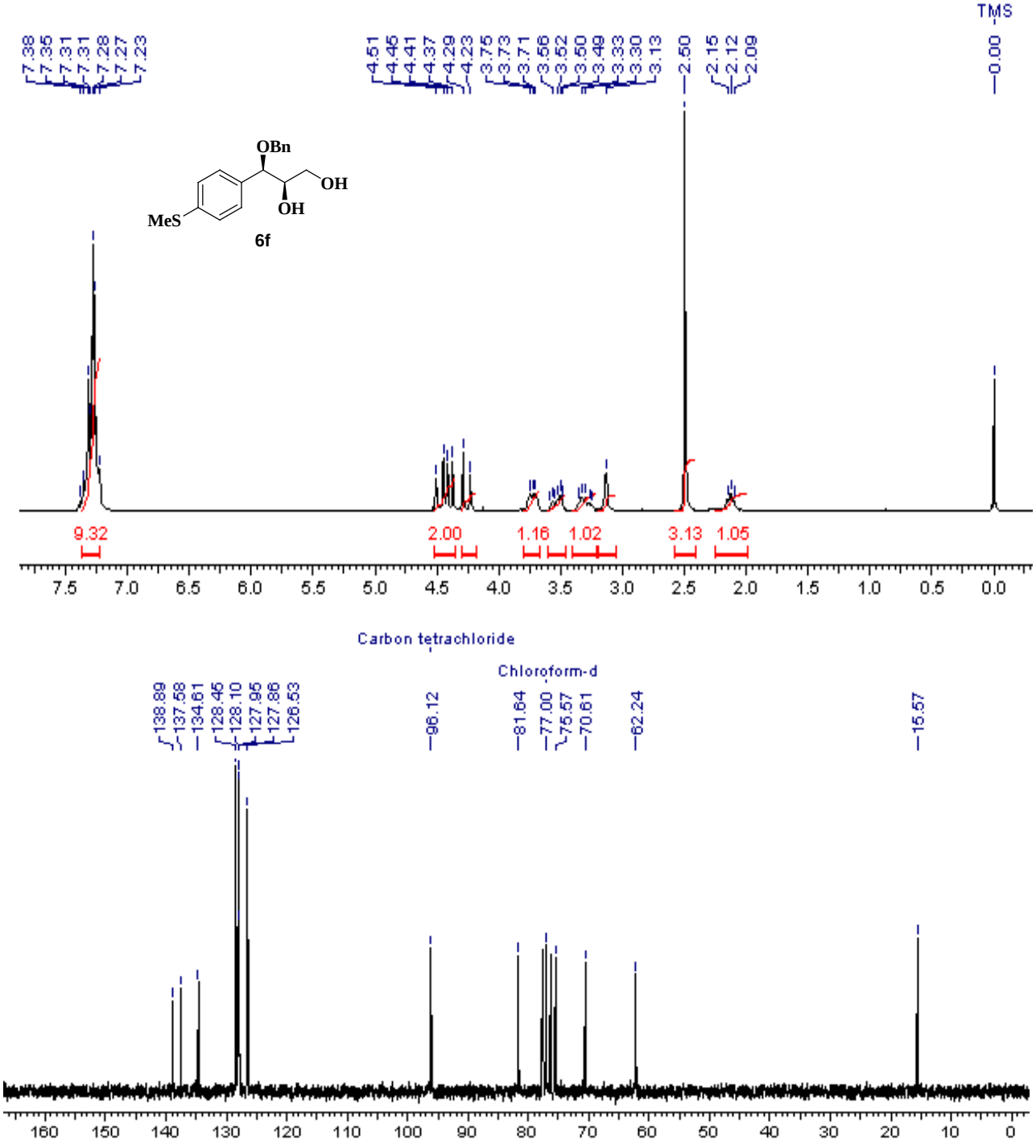
^{1}H and ^{13}C NMR spectra of 6b



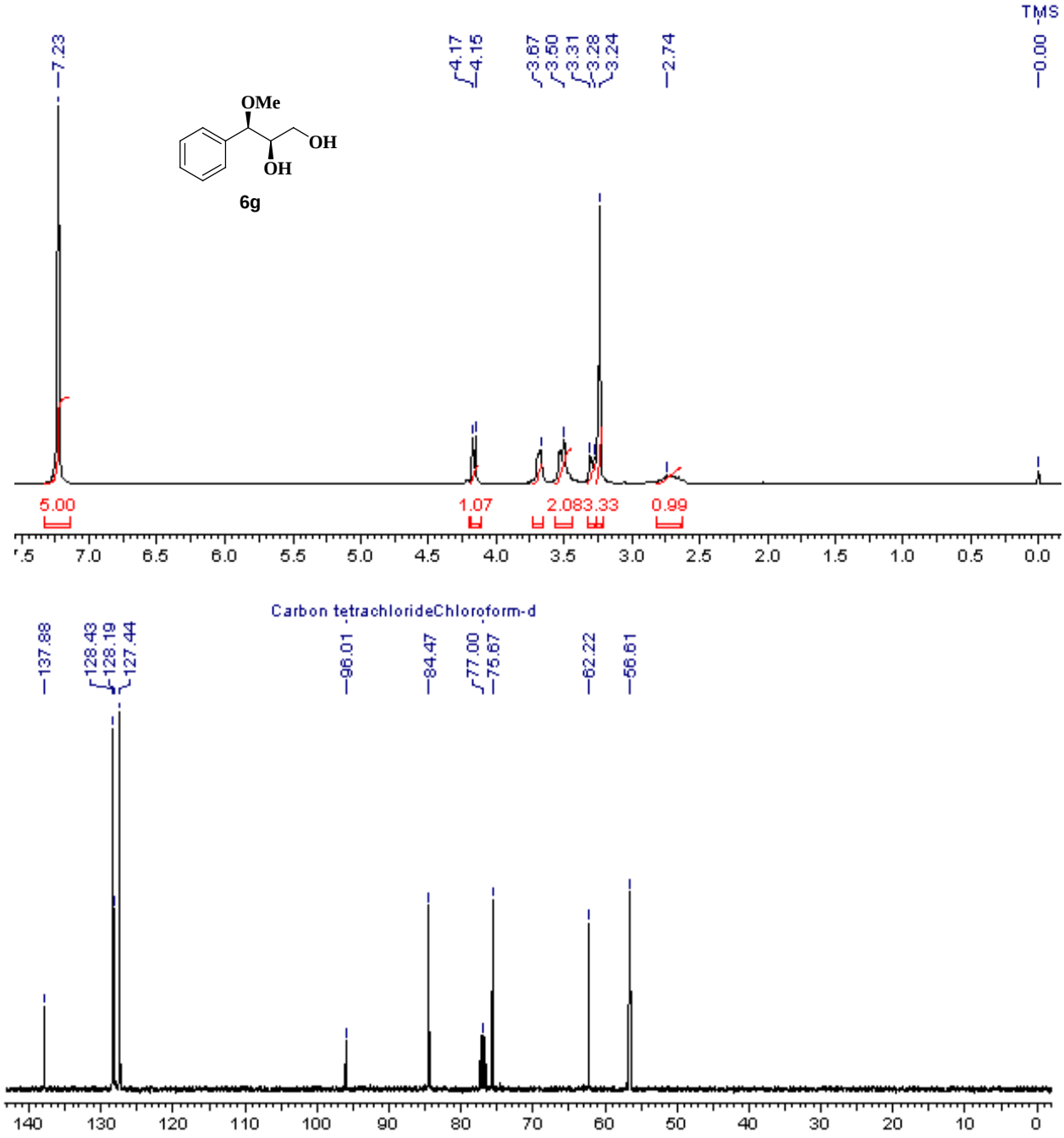
^{1}H and ^{13}C NMR spectra of 6d



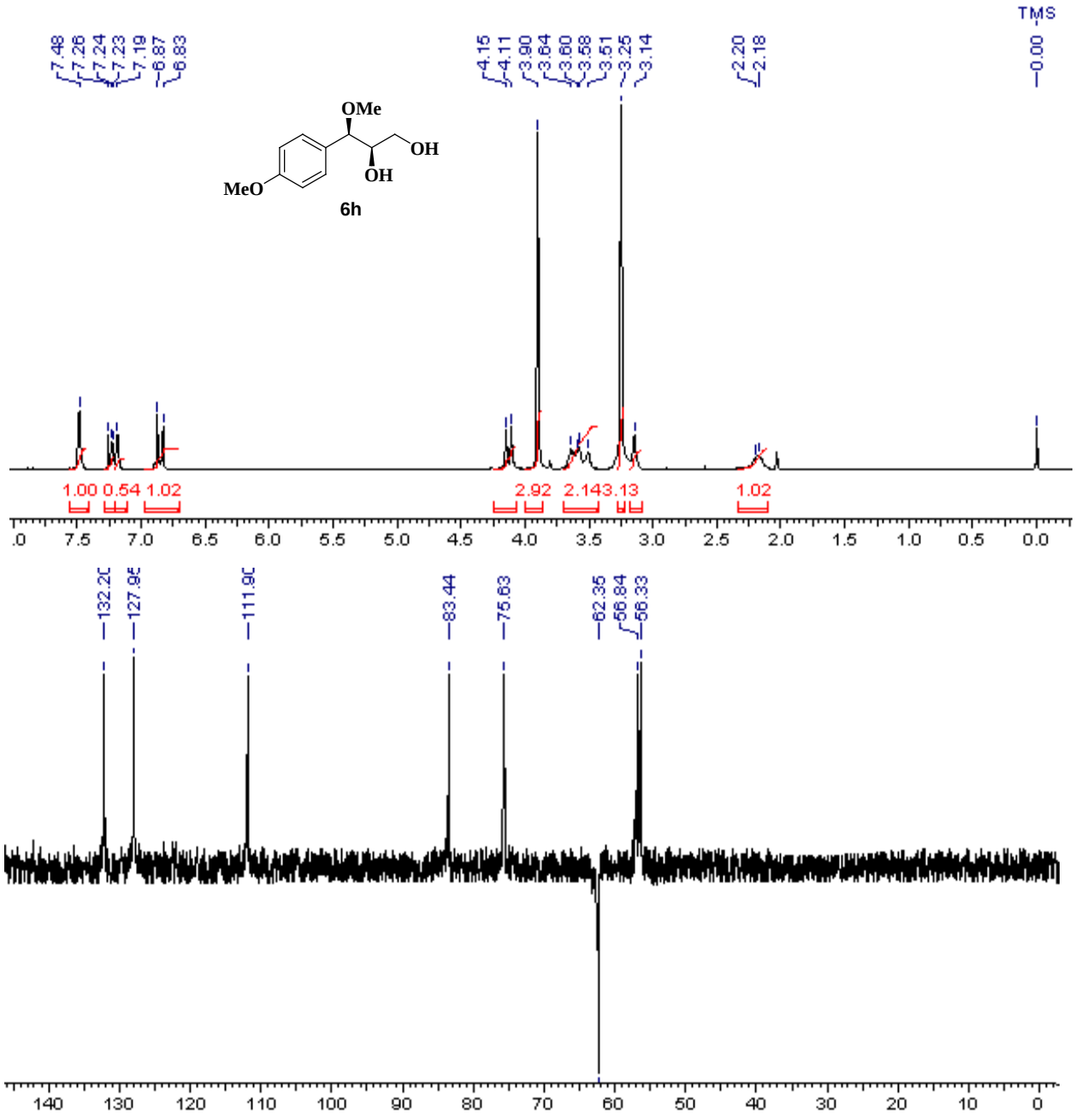
^{1}H and ^{13}C NMR spectra of 6e



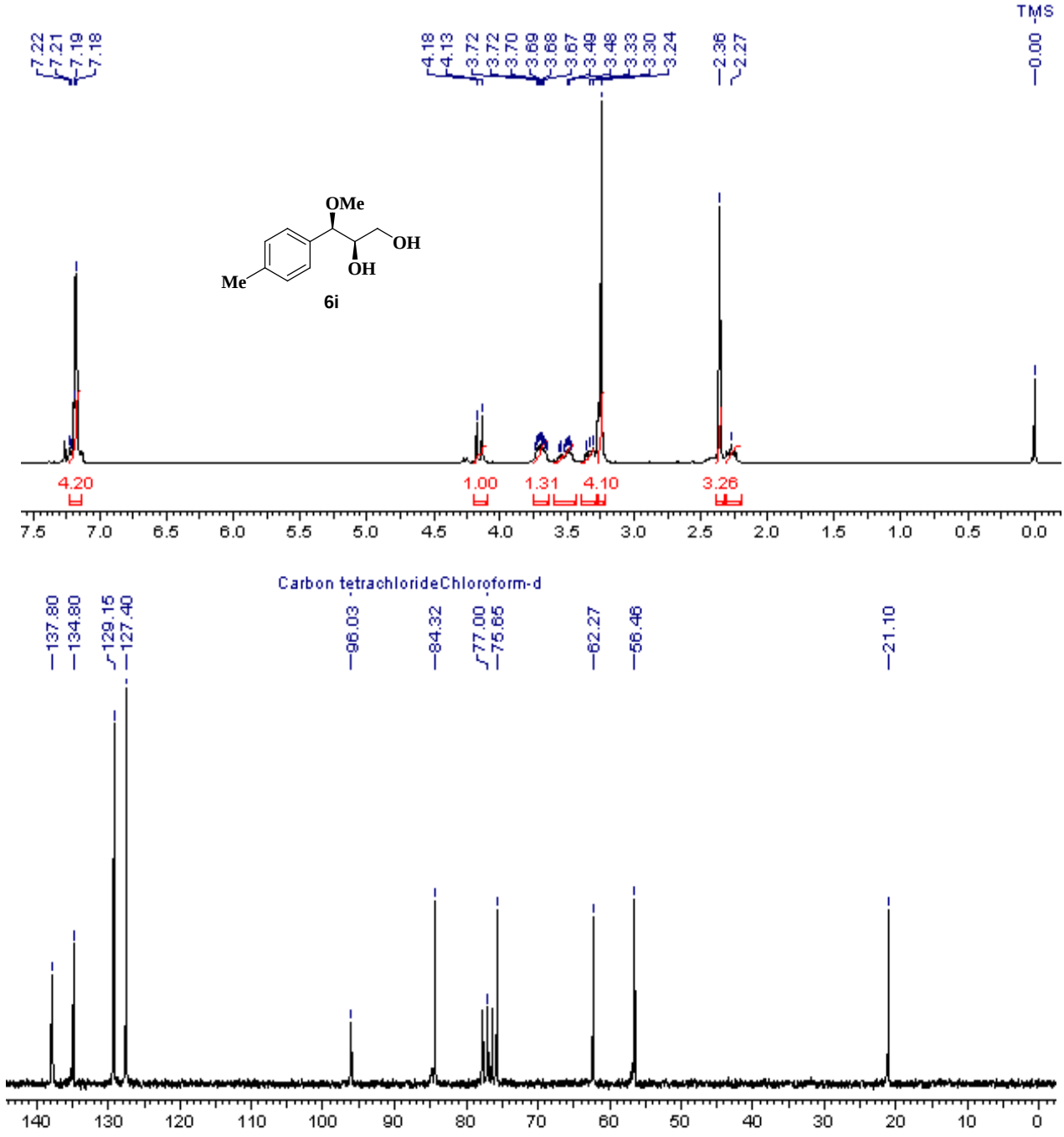
^{1}H and ^{13}C NMR spectra of 6f



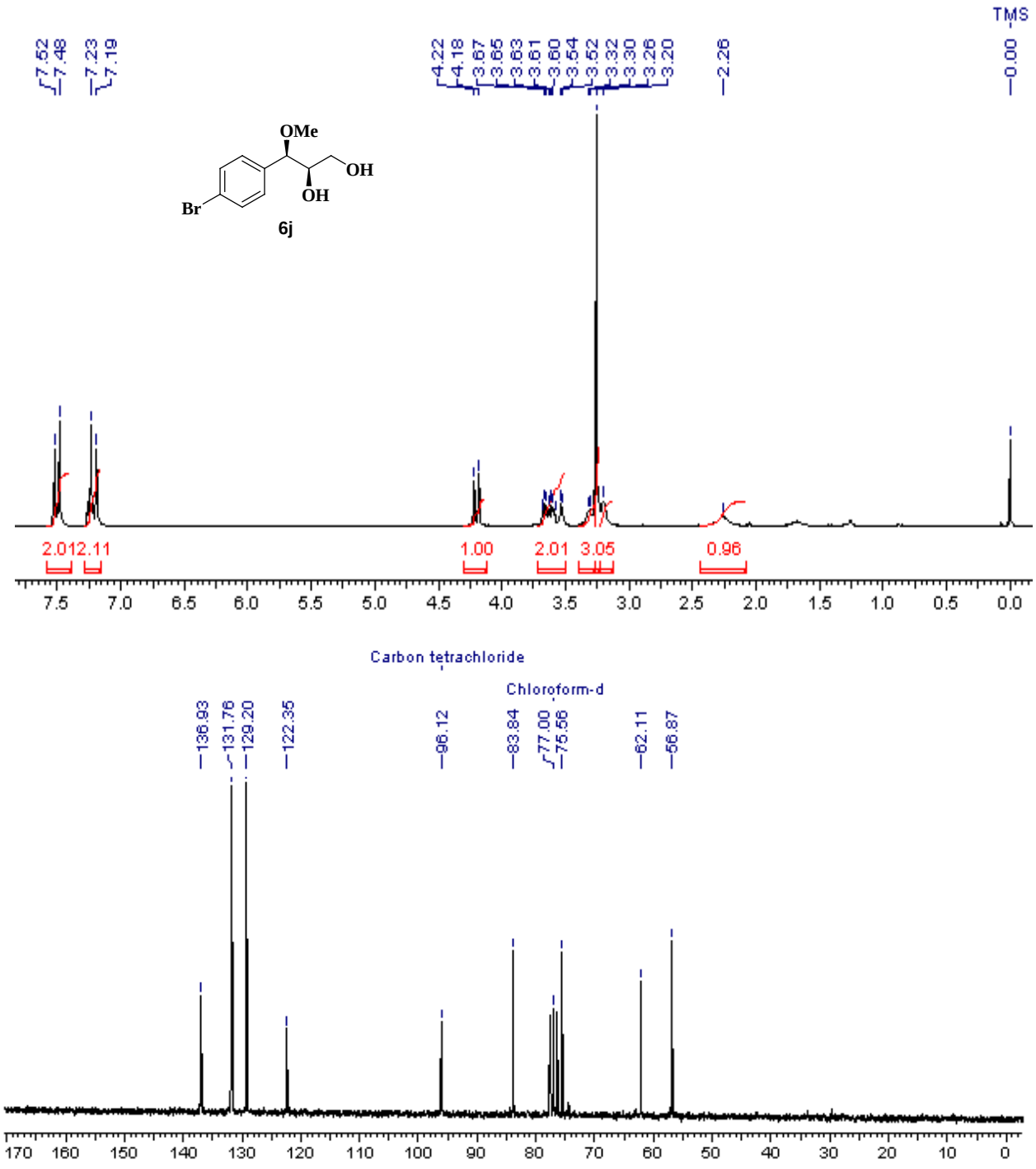
^{1}H and ^{13}C NMR spectra of 6g



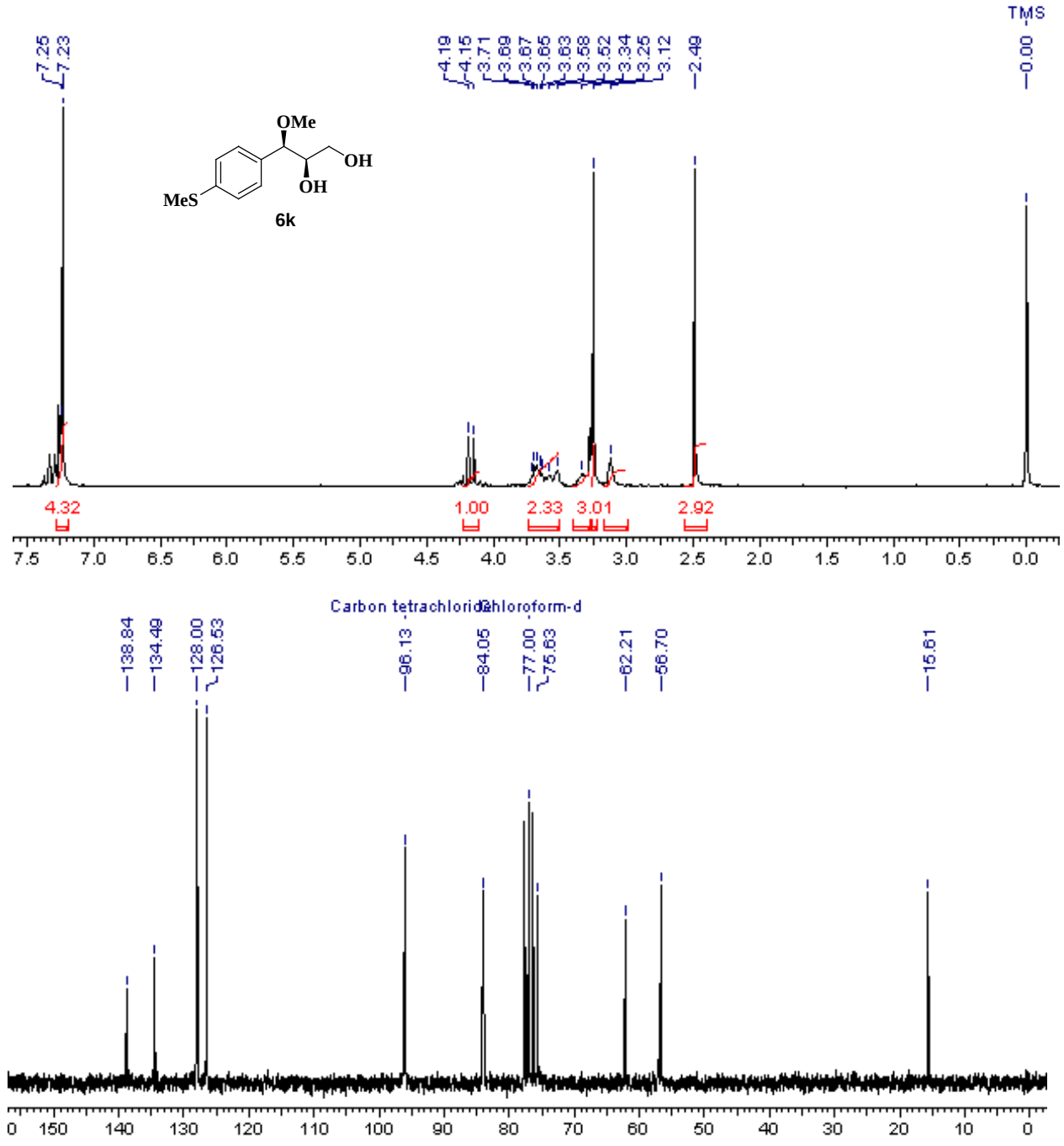
^{1}H and DEPT spectra of 6h



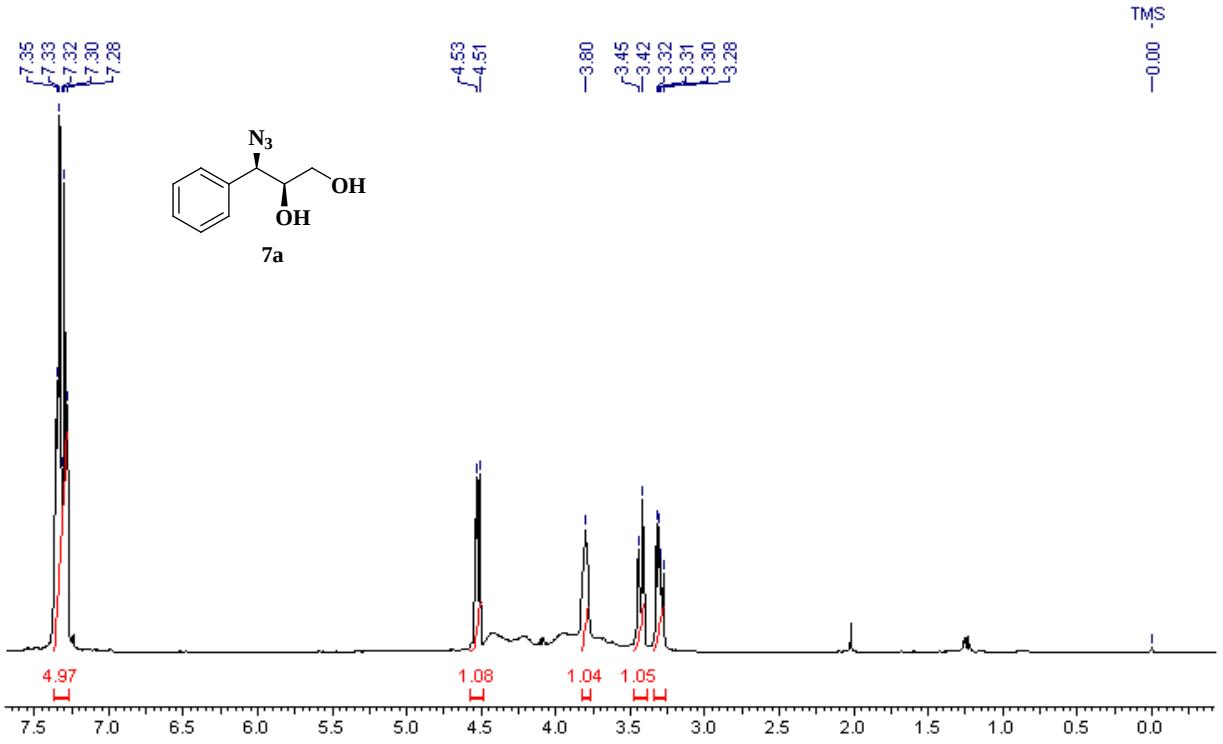
^{1}H and ^{13}C NMR spectra of 6i

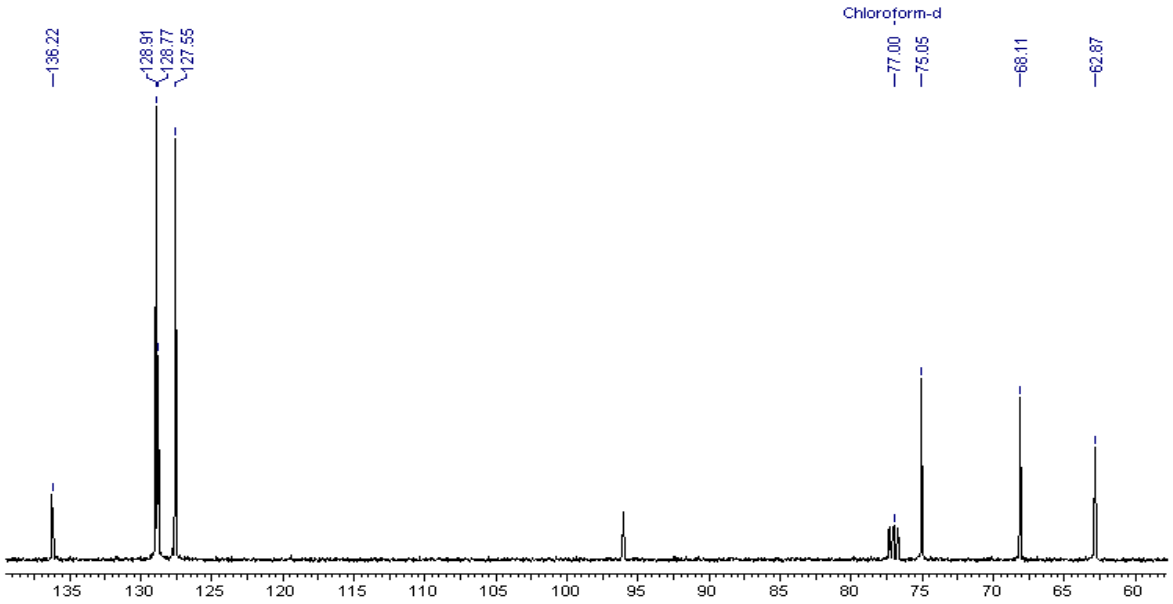


^{1}H and ^{13}C NMR spectra of 6j

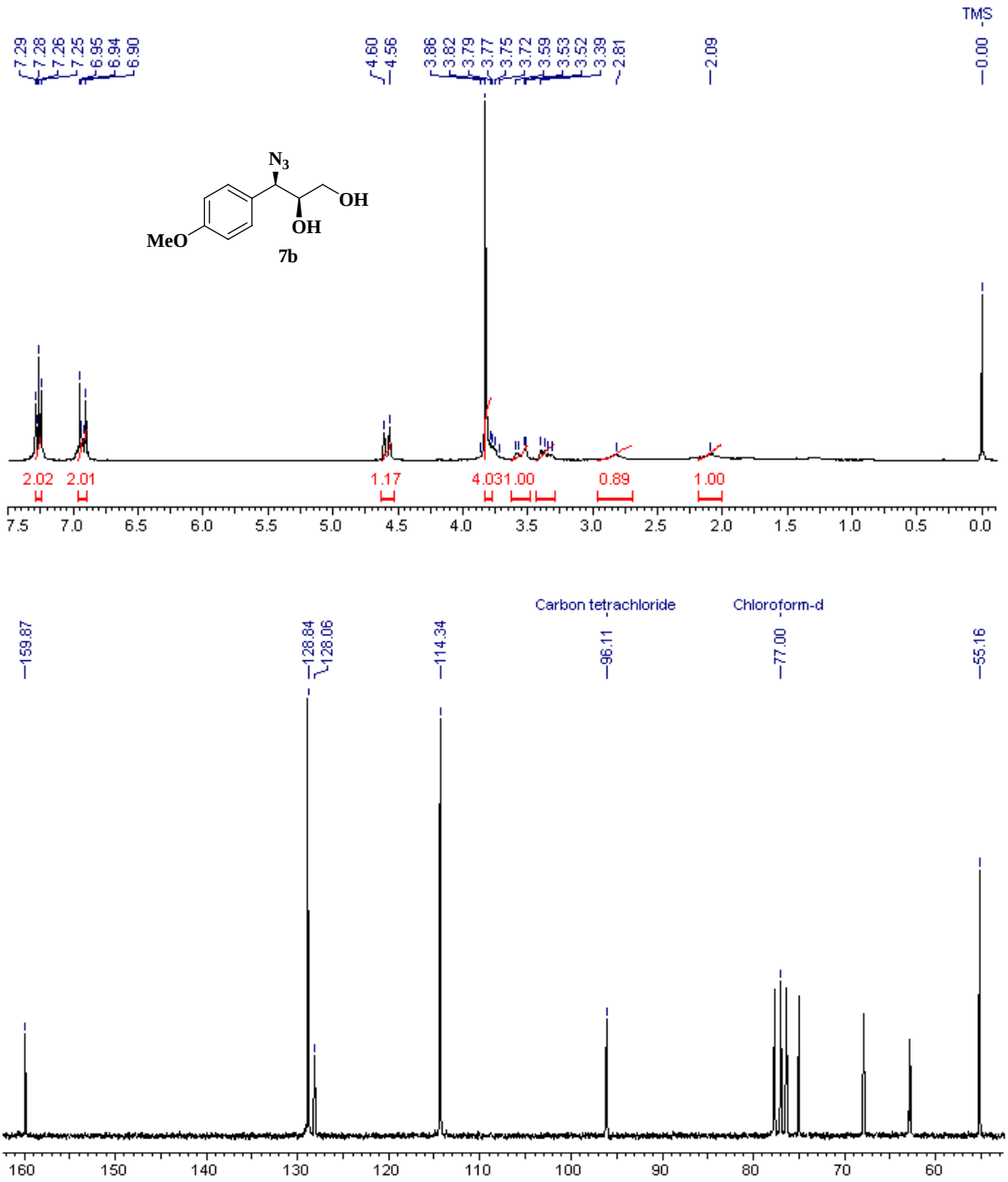


^{1}H and ^{13}C NMR spectra of 6k

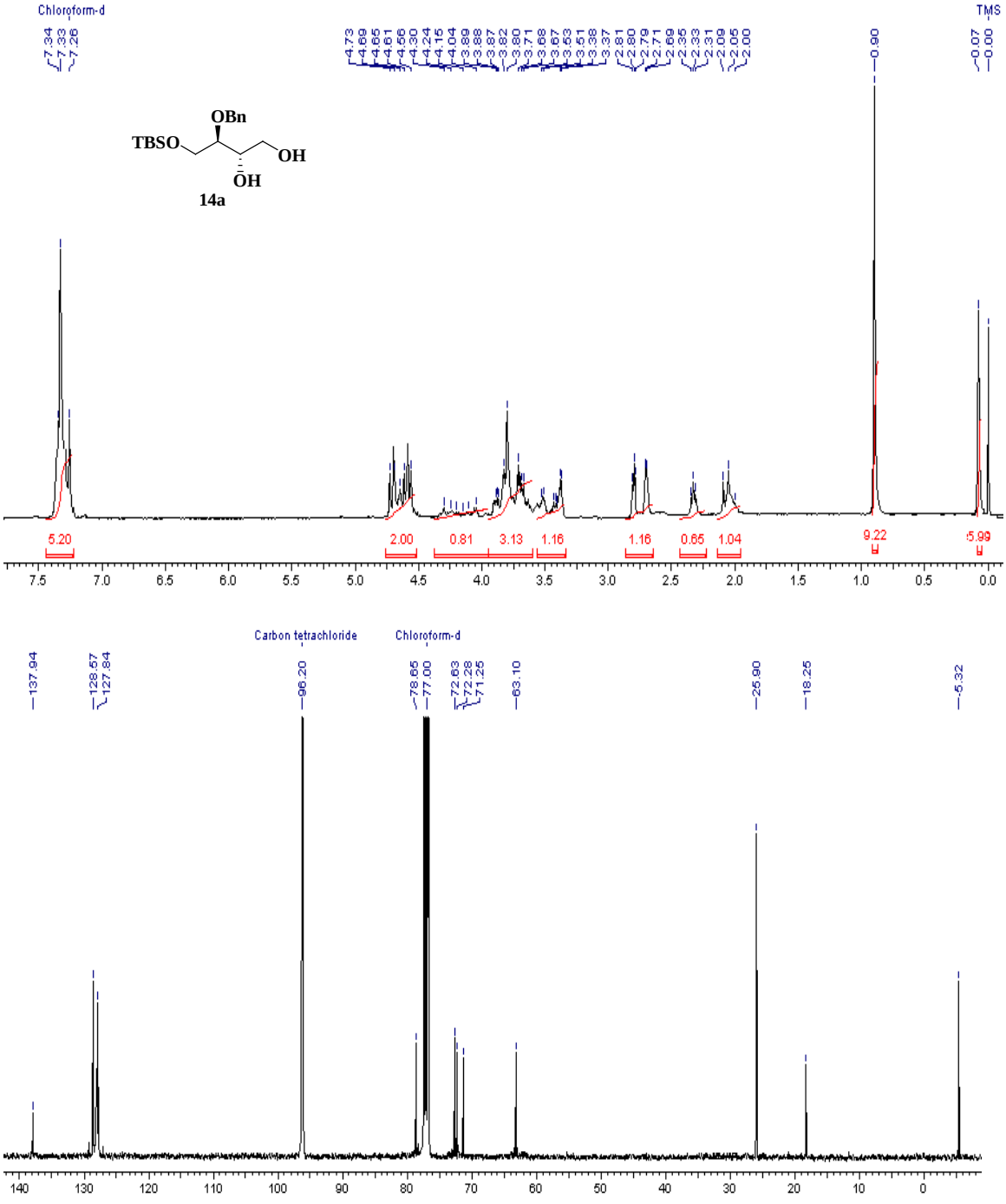




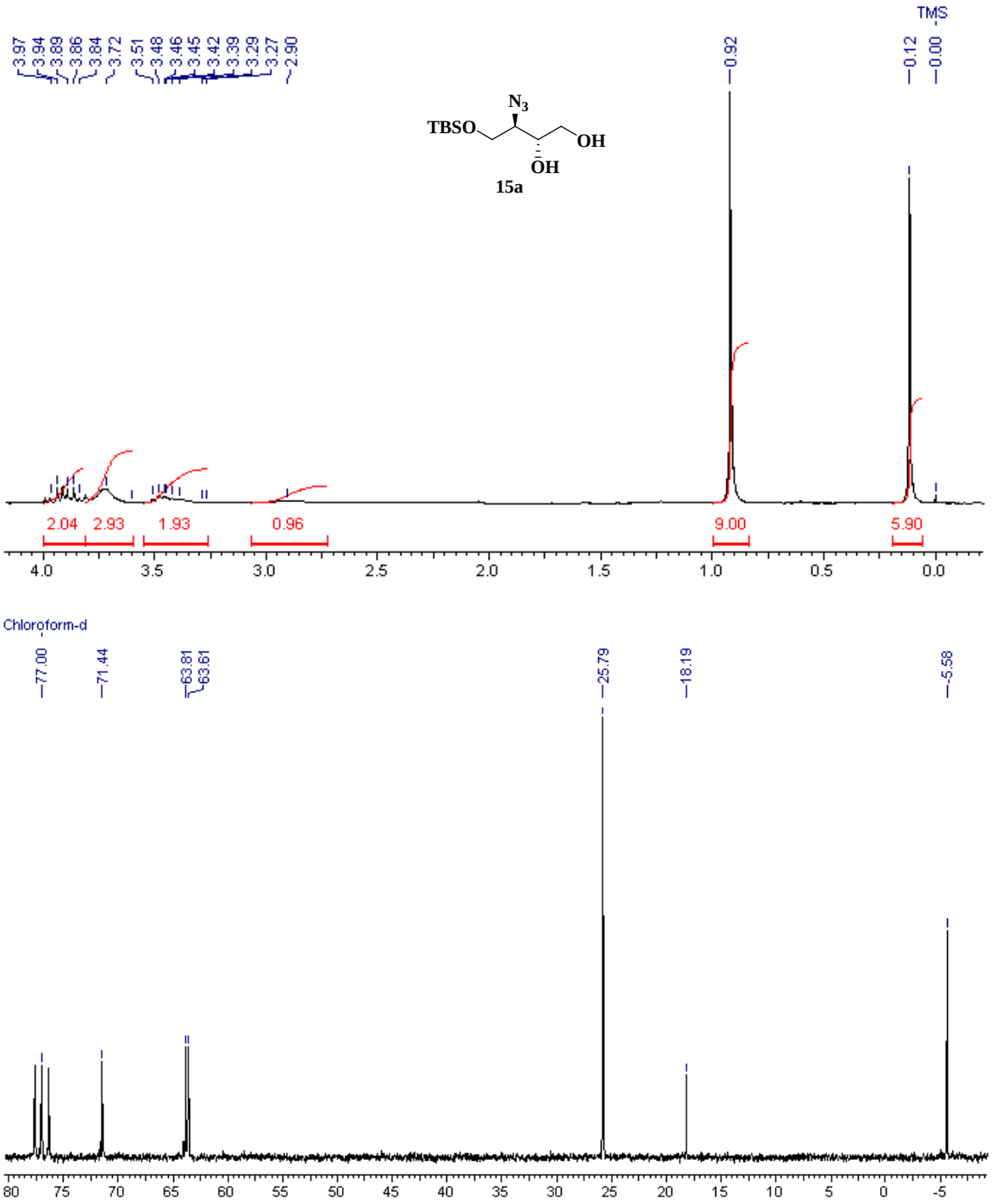
^{1}H and ^{13}C NMR spectra of 7a



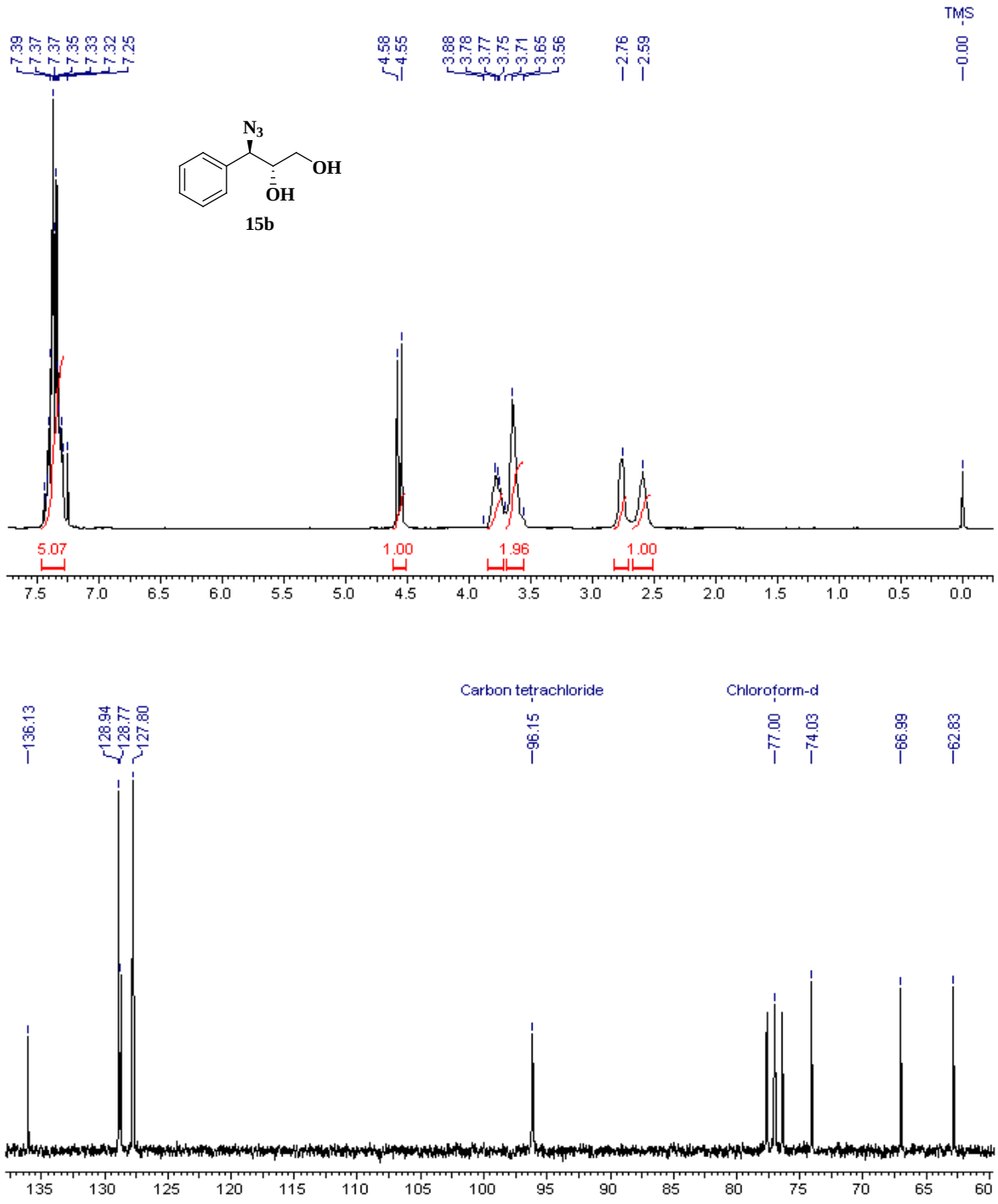
^{1}H and ^{13}C NMR spectra of 7b



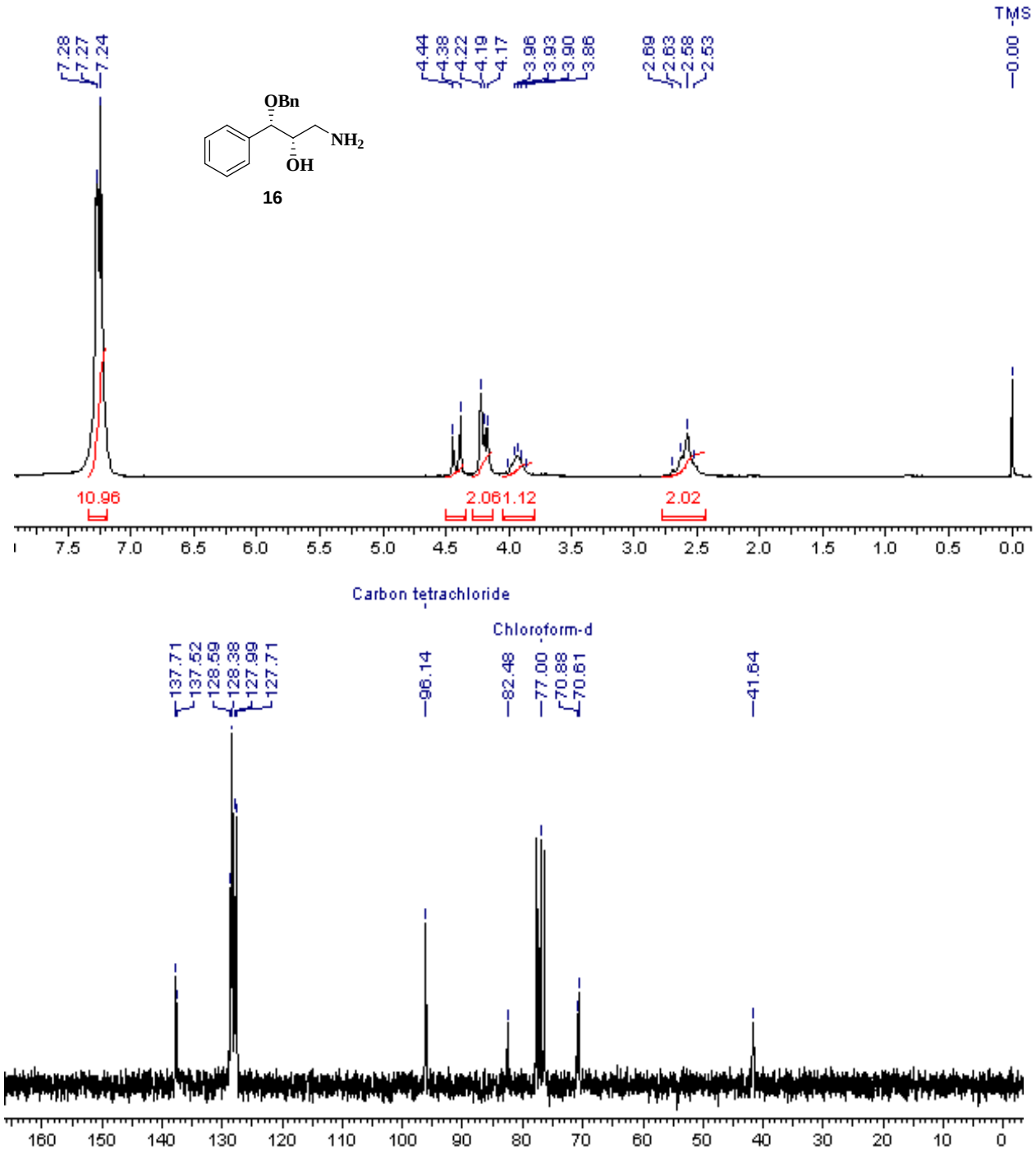
^{1}H and ^{13}C NMR spectra of 14a



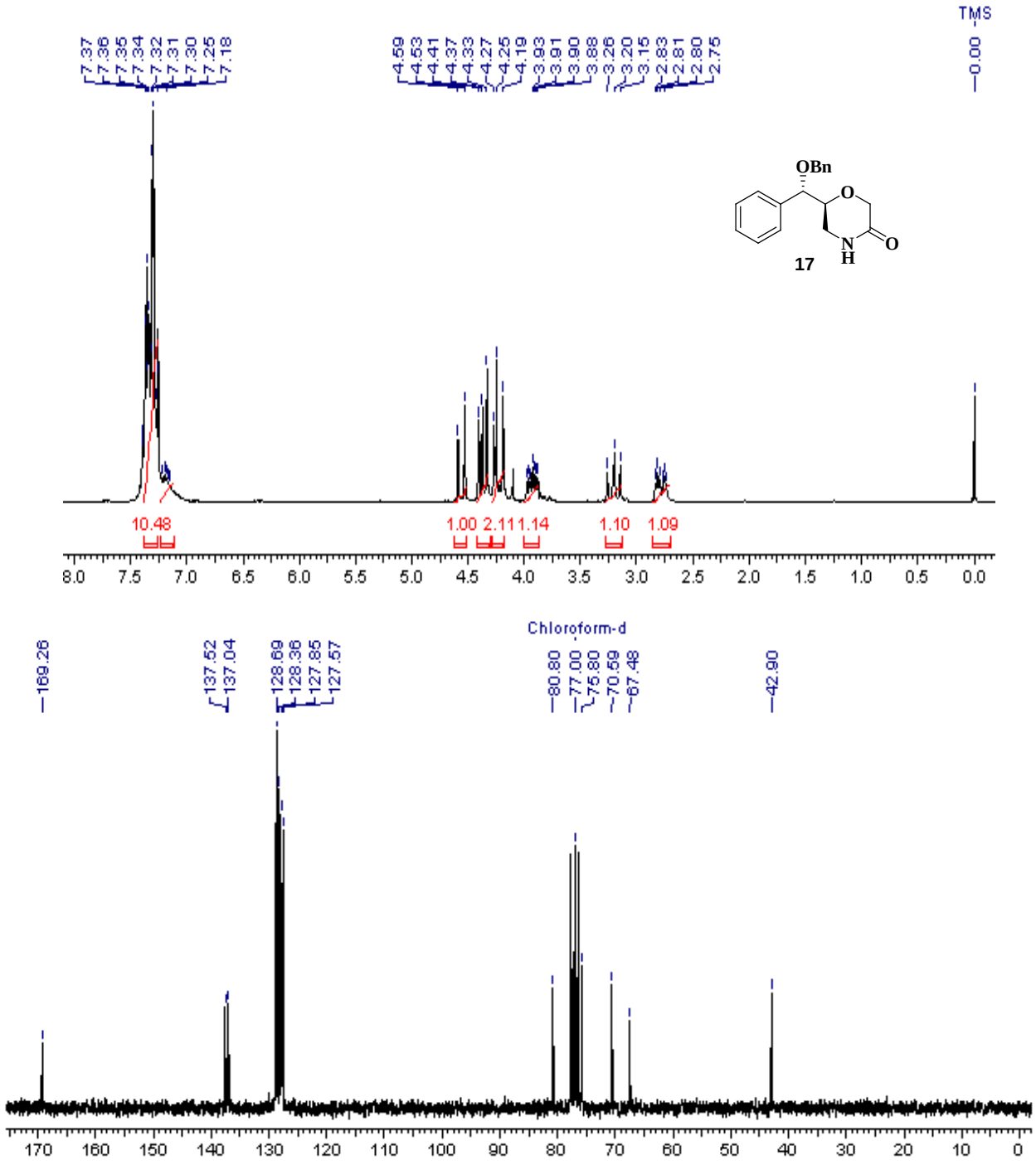
^{1}H and ^{13}C NMR spectra of 15a



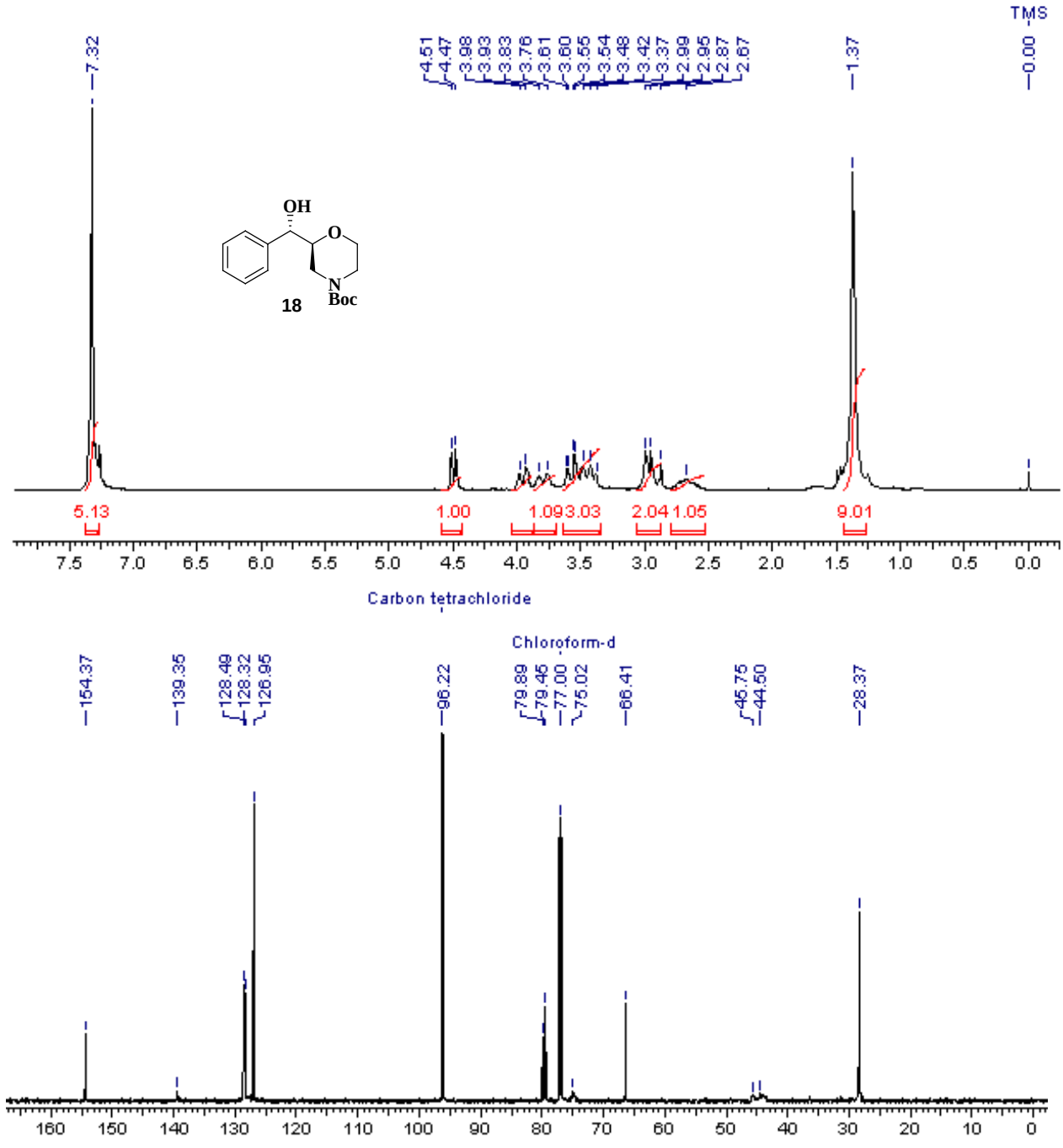
^{1}H and ^{13}C NMR spectra of 15b



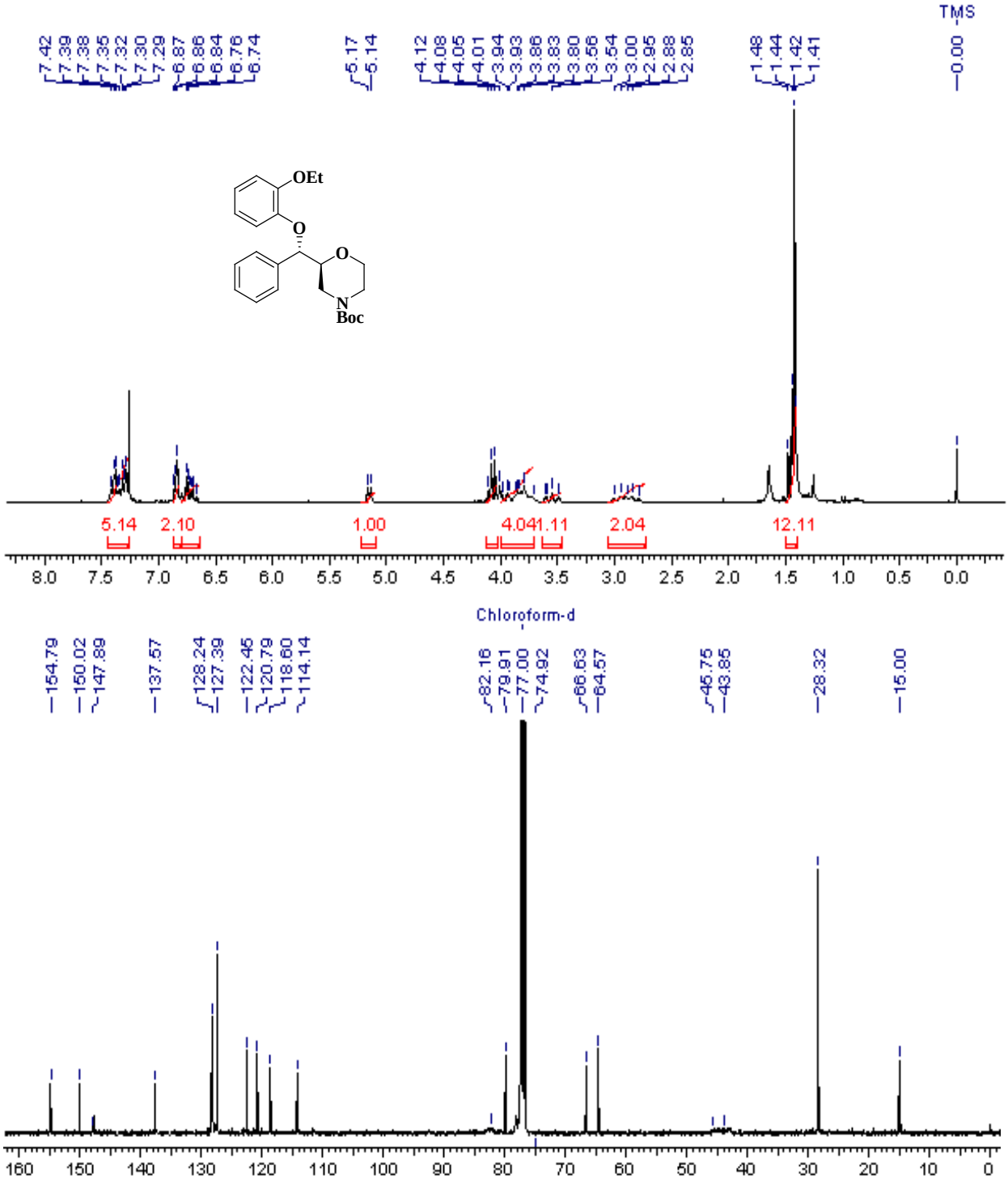
^{1}H and ^{13}C NMR spectra of 6k



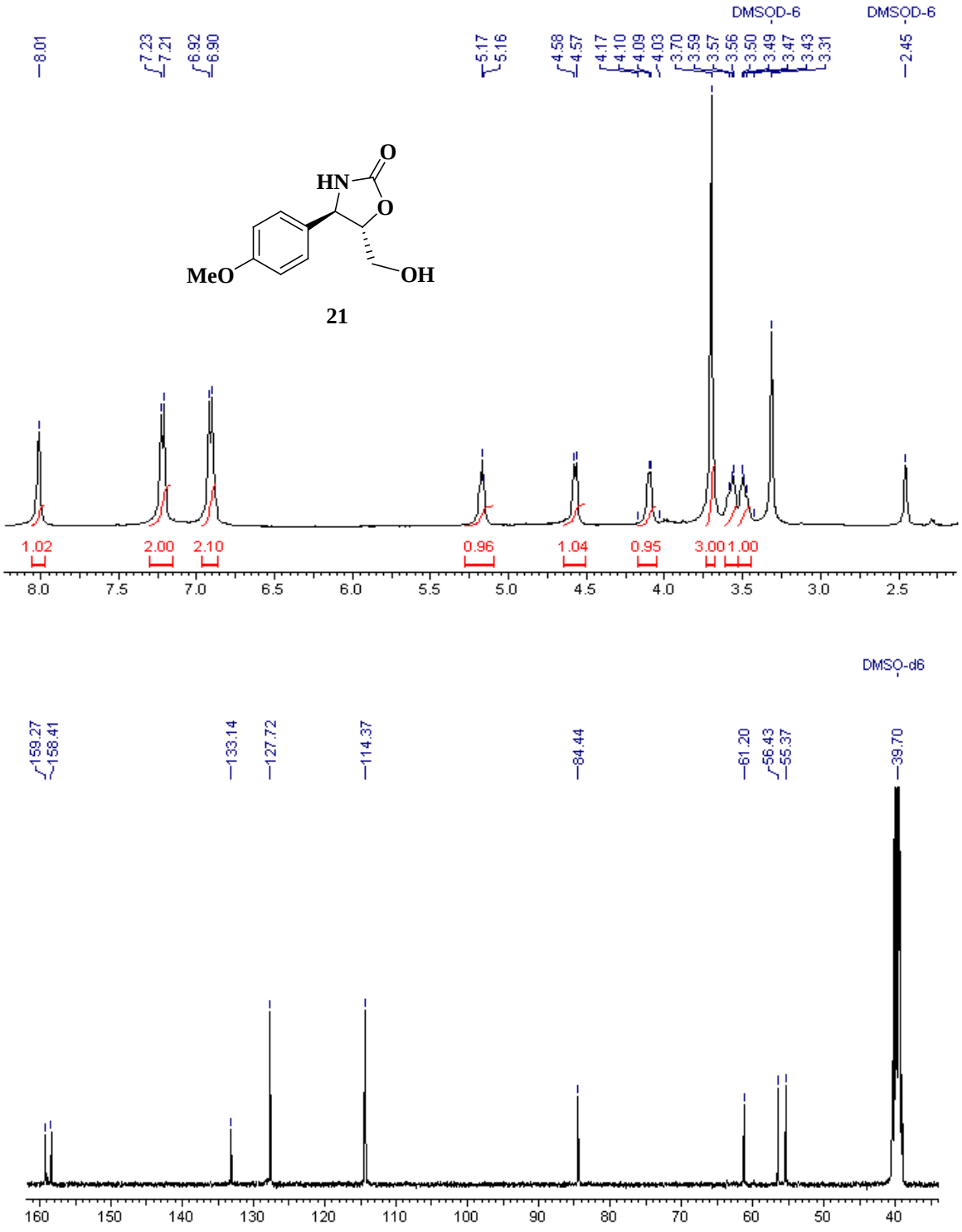
^{1}H and ^{13}C NMR spectra of 17



^{1}H and ^{13}C NMR spectra of 18

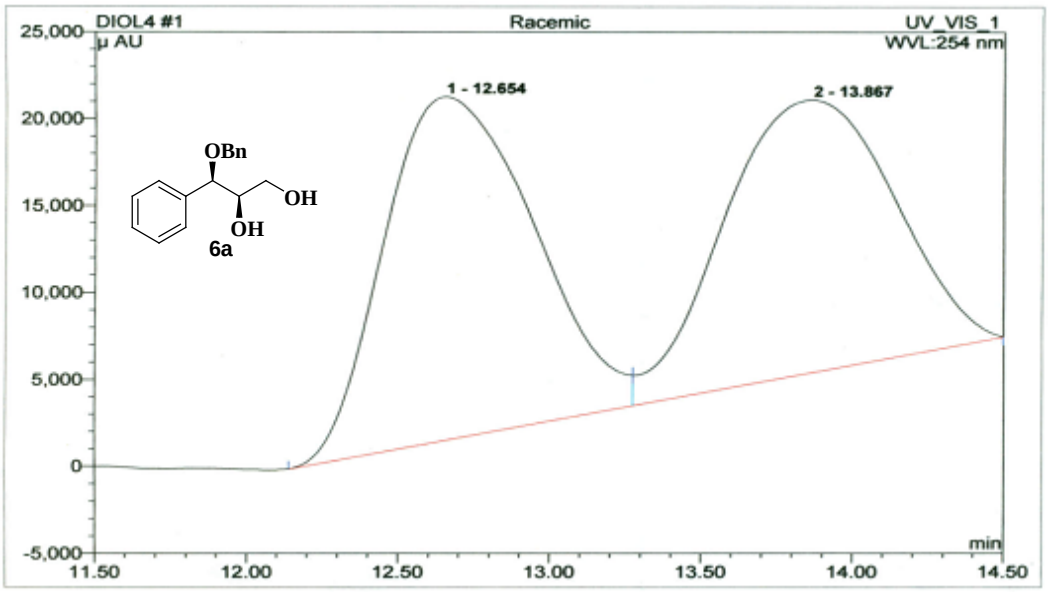


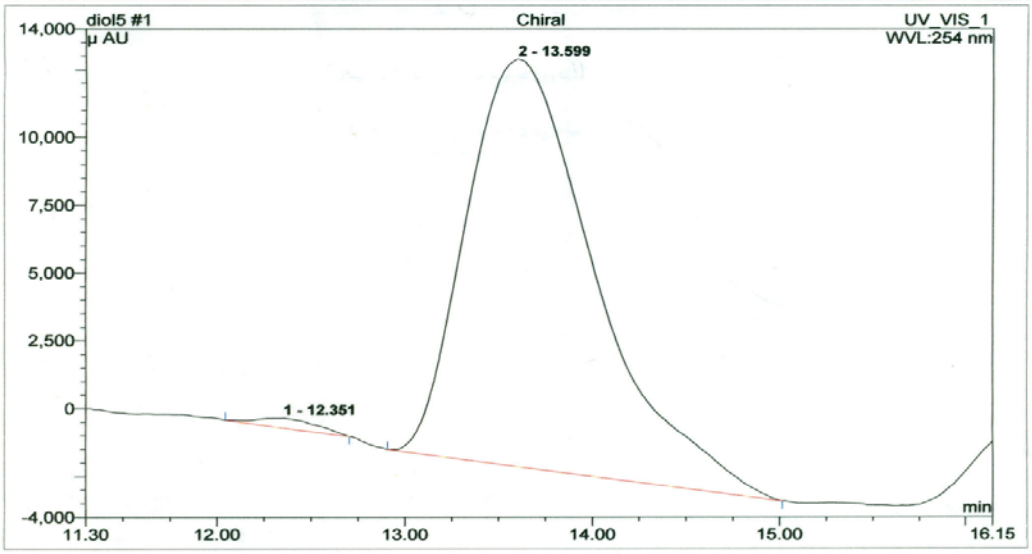
^{1}H and ^{13}C NMR spectra of Boc protected (*S*,*S*)-reboxetine 19



21

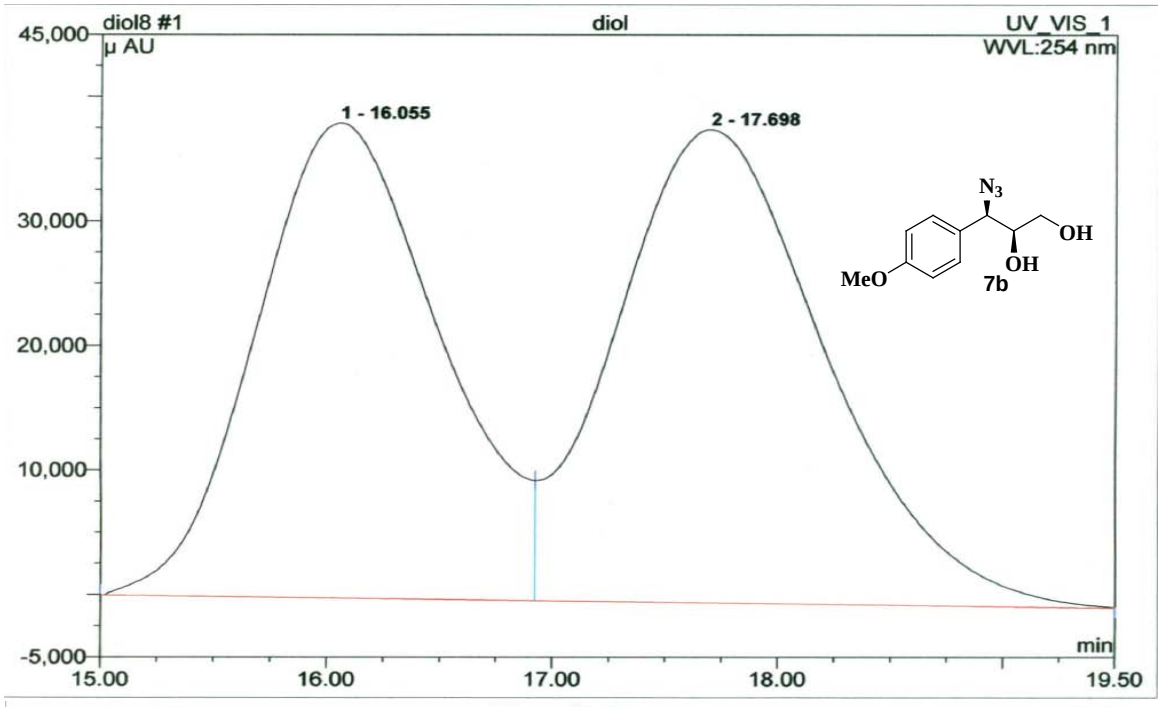
^{1}H and ^{13}C NMR spectra of 21

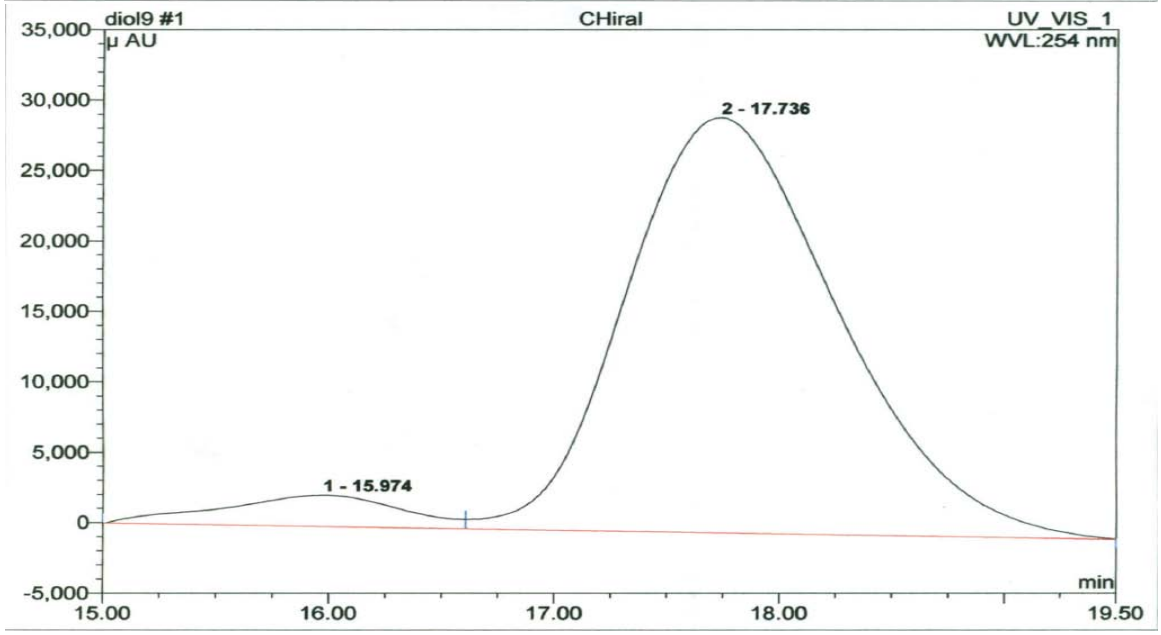




No.	Peak Name	Ret.Time (detected) min	Area µ AU*min	Rel.Area %	Height µ AU	Amount	Type
1	n.a.	12.35	130.443	1.08	349.879	n.a.	BMB
2	n.a.	13.60	11932.889	98.92	15012.384	n.a.	BMB

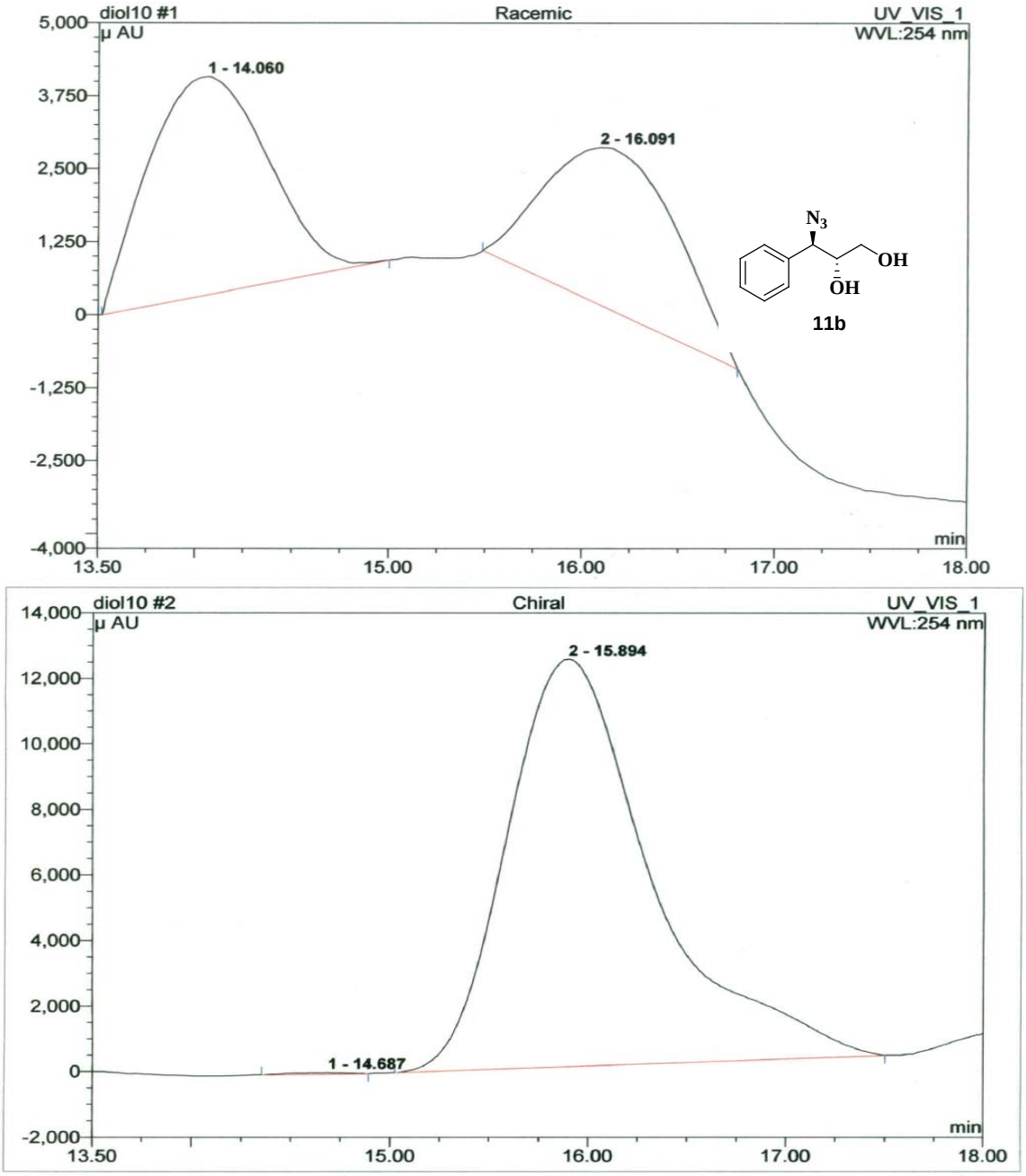
HPLC chromatogram of 6a





No	Ret. Time min	Height µ AU	Area µ AU* min	Rel. Area %	Amount	Type
1	15.97	560.800	512.360	1.50	n. a.	BMB
2	17.73	36825.916	33644.986	98.50	n. a.	BMB

HPLC chromatogram of 7b



No	Ret. Time min	Height µ AU	Area µ AU* min	Rel. Area %	Amount	Type
1	14.68	91.878	251.906	0.86	n.a.	BMB
2	15.89	10591.692	29039.522	99.14	n.a.	BMB

HPLC chromatogram of 11b