Synthesis of Enantioenriched Propargylic Alcohols Related to Polyketide Natural Products. A Comparison of Methodologies

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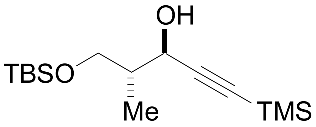
Supporting Information

Experimental procedures for all intermediates and selected ^{1}H NMR spectra.

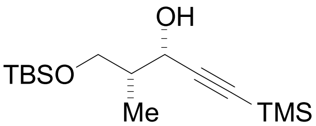


(3*R*, 4*R*)-5-(t-Butyldimethylsilyloxy)-4-methyl-1-trimethylsilyl-1-pentyn-3-ol (2a). A. Addition with *(S)*-BINOL as the Chiral Ligand.

The standard procedure for TMS acetylene addition was employed (see below) using aldehyde **1a** (0.10 g, 0.49 mmol), TMS acetylene (0.28 mL, 2.0 mmol), Et$_2$Zn (0.20 mL, 2.0 mmol), Ti(OiPr)$_4$ (0.15 mL, 0.49 mmol), and (*S*)-BINOL (0.056 g, 0.20 mmol), affording alcohol **2a** (0.11 g, 73% yield, 10:1 mixture of diastereomers) as a clear oil. R$_f$ = 0.3 (10% EtOAc/ hexanes); $[\alpha]^{D}_{20}$ = - 6.0 (c = 1.47, CHCl$_3$); IR (film) 3432, 2174 cm^{-1}; ^{1}H NMR (CDCl$_3$, major diastereomer) δ 4.39 (t, J = 5.5 Hz, 1H), 3.93 (dd, J = 4.0 Hz, 10.0 Hz, 1H), 3.57 (dd, J = 6.5 Hz, 10.0 Hz, 1H), 3.43 (d, J = 5.5 Hz, 1H), 1.96-1.88 (m, 1H), 1.01 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.17 (s,9H), 0.08 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 105.72, 89.76, 67.14, 66.78, 40.44, 25.81, 18.15, 12.91, -0.12, -5.63, -5.66; Anal. Calcd for C$_{15}$H$_{32}$O$_2$Si$_2$: C, 59.94, H, 10.73, Found: C, 59.97, H, 10.54.

B. Without BINOL

The standard procedure for TMS acetylene addition was employed using aldehyde **1a** (0.10 g, 0.49 mmol), TMS acetylene (0.28 mL, 2.0 mmol), Et$_2$Zn (0.20 mL, 2.0 mmol), and Ti(OiPr)$_4$ (0.15 mL, 0.49 mmol), affording alcohol **3a** (0.072 g, 48% yield, 1.5:1 mixture of diastereomers favoring the 3*R* diastereomer) as a clear oil. All analytical data was consistent with the BINOL directed cases.

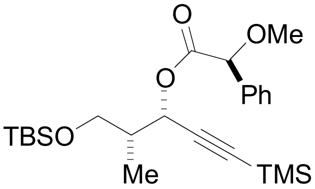


(3*S*, 4*R*)-5-(t-Butyldimethylsilyloxy)-4-methyl-1-trimethylsilyl-1-pentyn-3-ol (3a)

Standard Procedure for TMS Acetylide Addition to Aldehydes

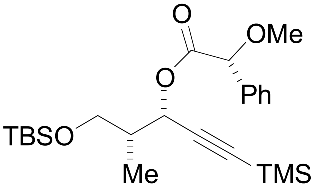
TMS acetylene (0.28 mL, 2.7 mmol) was taken up in 2 mL of toluene. Et$_2$Zn (0.20 mL, 2.0 mmol) was added to the solution carefully. The mixture was heated to reflux for 1 h, during which time a large amount of grey precipitate formed in the reaction flask. The mixture was cooled to room temperature, and (*R*)-BINOL (0.056 g, 0.20 mmol), Et$_2$O (8 mL), and Ti(OiPr)$_4$ (0.15 mL, 0.49 mmol) were added. After 1 h, aldehyde **2a** (0.050 mL, 0.42 mmol) was added, and the mixture was stirred overnight. The reaction was quenched with 1.0 M tartaric acid and the mixture was stirred for 30 min. The mixture was partitioned in a separatory funnel, and the aqueous portion was extracted three times with Et$_2$O. The combined organic extracts were washed with brine and dried over MgSO$_4$. Filtration and concentration, followed by flash chromatography on silica gel (2.5% EtOAc/ hexanes to 5% EtOAc/ hexanes gradient), afforded propargylic alcohol **3a** (0.10 g, 67% yield) as a light yellow oil. R$_f$ = 0.3 (10% EtOAc/ hexanes); $[\alpha]^{D}_{20}$ = - 24.1 (c = 1.21, CHCl$_3$); IR (film) 3441, 2183 cm^{-1}; ^{1}H NMR (CDCl$_3$, major diastereomer) δ 4.42 (dd, J = 3.5 Hz, 8.0

Hz, 1H), 3.93 (d, J = 7.5 Hz, 1H), 3.86 (t, J = 9.5 Hz, 1H), 3.67 (dd, J = 4.5 Hz, 9.5 Hz, 1H), 2.18-2.11 (m, 1H), 0.91 (s, 9H), 0.88 (d, J =7.0 Hz, 3H), 0.18 9s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 104.91, 90.08, 67.62, 66.73, 39.59, 25.82, 18.14, 12.48, -0.08, -5.58, -5.72.



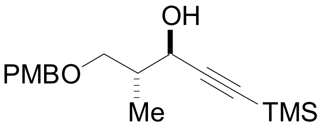
(*S*)-O-Methyl Mandelic Ester of 3a

Alcohol **3a** (0.010 g, 0.033 mmol) was taken up in 1 mL of CH_2Cl_2. (*S*)-O-methyl mandelic acid (0.011 g, 0.066 mmol), DCC (0.014 g, 0.066 mmol), and a few crystals of DMAP were added, and the mixture was stirred for 15 min. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (100% hexanes), affording the desired ester (0.008 g, 53%) yield as a clear oil. ^{1}H NMR ($CDCl_3$) δ 7.47-7.26 (m, 5H), 5.46 (d, J = 5.4 Hz, 1H), 4.79 (s, 1H), 3.56-3.43 (m, 2H), 3.45 (s, 3H), 2.05-1.95 (m, 1H), 0.96 (d, J = 6.9 Hz, 3H), 0.86 (s, 9H), 0.08 (s, 9H), -0.01 (s, 3H), -0.03 (s, 3H).



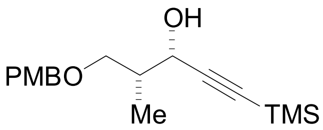
(*R*)-O-Methyl Mandelic Ester of 3a

Alcohol **3a** (0.010 g, 0.033 mmol) was taken up in 1 mL of CH_2Cl_2. (*R*)-O-methyl mandeliwc acid (0.011 g, 0.066 mmol), DCC (0.014 g, 0.066 mmol), and a few crystals of DMAP were added, and the mixture was stirred for 15 min. The solvent was removed under vacuum, and the residue was purified by flash chromatography on silica gel (100% hexanes), affording the desired ester (0.008 g, 53%) yield as a clear oil. ^{1}H NMR ($CDCl_3$) δ7.45-7.30 (m, 5H), 5.50 (d, J = 5.1 Hz, 1H), 4.80 (s, 1H), 3.43 (s, 3H), 3.31 (A of ABX, J = 6.3 Hz, 9.9 Hz, 1H), 3.12 (B of ABX, J = 6.3 Hz, 9.9 Hz, 1H), 1.98-1.85 (m, 1H), 0.82 (d, J = 6.3 Hz, 3H), 0.81 (s, 9H), 0.15 (s, 9H), -0.09 (s, 3H), -0.12 (s, 3H).



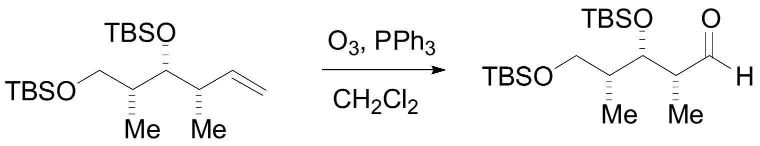
(3*R*, 4*R*)-5-(*p*-Methoxybenzyl)-4-methyl-1-trimethylsilyl-1-pentyn-3-ol (2b)

The standard procedure for TMS acetylene addition was employed using aldehyde **1b** (0.090 g, 0.44 mmol), TMS acetylene (0.25 mL, 1.8 mmol), Et_2Zn (0.18 mL, 1.8 mmol), $Ti(OiPr)_4$ (0.13 mL, 0.44 mmol), and *S*-BINOL (0.052 g, 0.18 mmol). During the workup, the organic extracts were washed with 10% NaOH before the brine wash to remove the BINOL residue, which co-spotted with the product. Flash chromatography on silica gel (2.5% EtOAc/ hexanes to 10% EtOAc/ hexanes gradient) afforded alcohol **2b** (0.090 g, 69% yield, 6:1 mixture of diastereomers) as a clear oil. R_f = 0.05 (20% EtOAc/ hexanes); ^{1}H NMR ($CDCl_3$, major diastereomer) δ 7.24 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.45 (d, J = 3.0 Hz, 2H), 4.38 (t, J = 6.3 Hz, 1H), 2.80 (s, 3H), 3.68 (dd, J = 4.2 Hz, 9.3 Hz, 1H), 3.42 (dd, J = 6.9 Hz, 9.3 Hz, 1H), 3.13 (d, J = 5.4 Hz, 1H), 2.09-2.02 (m, 1H), 1.03 (d, J = 6.6 Hz, 3H), 0.17 (s, 9H); Anal. Calcd for $C_{17}H_{26}O_3Si$: C, 66.62, H, 8.55, Found: C, 66.69, H, 8.72.



(3*S*, 4*R*)-5-(*p*-Methoxybenzyl)-4-methyl-1-trimethylsilyl-1-pentyn-3-ol (3b)

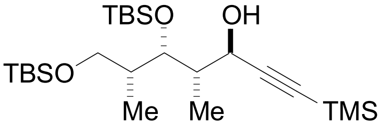
The standard procedure for TMS acetylene addition was employed using aldehyde **1b** (0.090 g, 0.44 mmol), TMS acetylene (0.25 mL, 1.8 mmol), Et_2Zn (0.18 mL, 1.8 mmol), $Ti(OiPr)_4$ (0.13 mL, 0.44 mmol), and *R*-BINOL (0.052 g, 0.18 mmol). During the workup, the organic extracts were washed with 10% NaOH before the brine wash to remove the BINOL residue, which co-spotted with the product. Flash chromatography on silica gel (2.5% EtOAc/ hexanes to 10% EtOAc/ hexanes gradient) afforded alcohol **3b** (0.10 g, 77% yield, 7:1 mixture of diastereomers) as a clear oil. R_f = 0.05 (20% EtOAc/ hexanes); ^{1}H NMR ($CDCl_3$, major diastereomer) δ 7.25 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 4.45 (d, J = 2.7 Hz, 2H), 4.42-4.36 (m, 1H), 3.80 (s, 3H), 3.68 (t, J = 9.0 Hz, 1H), 3.50 (dd, J = 4.2 Hz, 9.3 Hz, 1H), 2.30-2.18 (m, 1h), 0.90 (d, J = 7.2 Hz, 3H), 0.17 (s, 9H); Anal. Calcd for $C_{17}H_{26}O_3Si$: C, 66.62, H, 8.55, Found: C, 66.48, H, 8.48.



(2*R*, 3*S*, 4*R*)-3,5-Bis(*t*-butyldimethylsilyloxy)-2,4-dimethylpentanal (4)

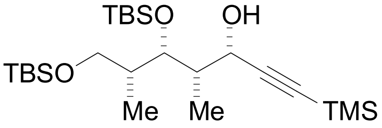
The above alkene[1] (0.30 g, 0.81 mmol) was taken up in 8 mL of CH_2Cl_2 and chilled to –78 °C. O_3 was bubbled through the solution until a blue color persisted. Ar was then bubbled through the reaction mixture for 15 min. PPh_3 (0.32 g, 1.21 mmol) was then added, and the mixture was warmed to room temperature for 3 h. The solvent was removed under reduced pressure and the residue was triturated with 10% EtOAc/ hexanes and filtered through Celite to remove triphenylphosphine oxide. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (1% EtOAc/ hexanes to 2.5% EtOAC/ hexanes gradient), affording aldehyde **4** (0.21 g, 70% yield) as a clear oil. R_f = 0.20 (5% EtOAc/ hexanes); $[\alpha]^D_{20}$ = - 40.9 (c = 1.45, $CHCl_3$); IR (film) 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.87 (d, J = 0.6 Hz, 1H), 4.23 (dd, J = 3.6 Hz, 5.4 Hz, 1H), 3.47 (A of ABX, J = 7.5 Hz, 10.2 Hz, 1H), 3.40 (B of ABX, J = 5.7 Hz, 10.2 Hz, 1H), 2.64-2.55 (m, 1H), 1.82-1.70 (m, 1H), 1.05 (d, J = 7.2 Hz, 3H), 0.89

(s, 9H), 0.88 (s, 9H), 0.81 (d, J = 6.9 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 205.41, 72.06, 65.25, 51.60, 39.13, 25.92, 25.85, 18.23, 18.16, 11.54, 9.44, -4.11, -4.54, -5.40.



(3*R*, 4*R*, 5*S*, 6*R*)-5,7-Bis(t-butyldimethylsilyloxy)-4,6-dimethyl-1-trimethylsilyl-1-heptyn-3-ol (5)

The standard procedure for TMS acetylene addition was employed using aldehyde **4** (0.10 g, 0.27 mmol), TMS acetylene (0.15 mL, 1.1 mmol), Et_2Zn (0.11 mL, 1.1 mmol), $Ti(OiPr)_4$ (0.080 mL, 0.27 mmol), and (*S*)-BINOL (0.031 g, 0.11 mmol), affording alcohol **5** (0.12 g, 92% yield, 1.6:1 mixture of diastereomers) as a clear oil. R_f = 0.1 (5% EtOAc/ hexanes); ^{1}H NMR ($CDCl_3$, major diastereomer) δ 4.34 (dd, J = 3.5 Hz, 8.5 Hz, 1H), 4.04 (t, J = 3.0 Hz, 1H), 3.43 (A of ABX, J = 7.5 Hz, 10.0 Hz, 1H), 3.38 (B of ABX, J = 7.0 Hz, 9.5 Hz, 1H), 3.17 (d, J = 3.5 Hz, 1H), 2.00-1.80 (m, 2H), 0.97 (d, J = 7.0 Hz, 3H), 0.92-0.88 (m, 21 H), 0.17 (s, 9H), 0.12 (s, 3H), 0.08 (s, 3H), 0.04 (s, 6H); Anal. Calcd for $C_{24}H_{52}O_3Si_3$: C, 60.95, H, 11.08, Found: C, 61.18, H, 11.28.

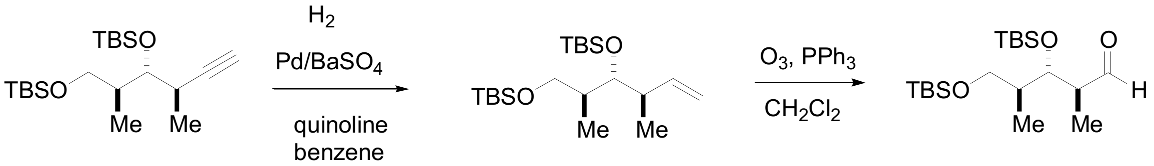


(3*S*, 4*R*, 5*S*, 6*R*)-5,7-Bis(t-butyldimethylsilyloxy)-4,6-dimethyl-1-trimethylsilyl-1-heptyn-3-ol (6). A. With *(R)*-BINOL as the Chiral Ligand.

The standard procedure for TMS acetylene addition was employed using aldehyde **4** (0.10 g, 0.27 mmol), TMS acetylene (0.15 mL, 1.1 mmol), Et_2Zn (0.11 mL, 1.1 mmol), $Ti(OiPr)_4$ (0.080 mL, 0.27 mmol), and (*R*)-BINOL (0.031 g, 0.11 mmol), affording alcohol **6** (0.11 g, 85% yield, 7:1 mixture of diastereomers) as a clear oil. R_f = 0.1 (5% EtOAc/ hexanes); $[\alpha]^D{}_{20}$ = - 1.7 (c = 1.30, $CHCl_3$); IR (film) 3450, 2174 cm^{-1}; ^{1}H NMR ($CDCl_3$, major diastereomer) δ 4.31 (d, J = 7.0 Hz, 1H), 3.94 (t, J = 4.0 Hz, 1H), 3.55 (A of ABX, J = 6.5 Hz, 10.0 Hz, 1H), 3.40 (B of ABX, J = 7.0 Hz, 9.5 Hz, 1H), 2.09 (broad s, 1H), 1.92-1.82 (m, 2H), 1.02 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.90 (s, 9H), 0.17 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 106.51, 90.44, 73.91, 66.02, 65.67, 43.25, 40.50, 26.10, 25.93, 18.41, 18.25, 12.73, 10.78, -0.15, -4.00, -4.06, -5.37; Anal. Calcd for $C_{24}H_{52}O_3Si_3$: C, 60.95, H, 11.08, Found: C, 61.20, H, 11.18.

B. Without BINOL

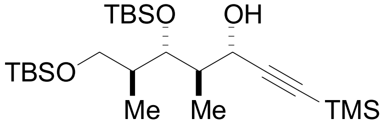
The standard procedure for TMS acetylene addition was employed using aldehyde **4** (0.064 g, 0.17 mmol), TMS acetylene (0.14 mL, 1.0 mmol), Et_2Zn (0.10 mL, 1.0 mmol), and $Ti(OiPr)_4$ (0.050 mL, 0.17 mmol), affording alcohol **6** (0.10 g, 77% yield, 2:1 mixture) as a clear oil. All analytical data matched the previously characterized material.



(2*S*, 3*S*, 4*S*)-3,5-Bis(*t*-butyldimethylsilyloxy)-2,4-dimethylpentanal (7)

The above alkyne[2] (0.32 g, 0.86 mmol) was taken up in 10 mL of benzene. 5% Pd/ $BaSO_4$ (reduced, 0.32 g) and quinoline (0.10 mL) were added, and the mixture was stirred for 5 min. H_2 was bubbled through the mixture for 1 h. The mixture was then filtered through Celite and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (100% hexanes), affording the corresponding alkene (0.31 g, 97% yield) as a yellow oil. $R_f = 0.50$ (2.5% EtOAc/ hexanes); IR (film) 1641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.95-5.87 (m, 1 H), 5.00-4.94 (m, 2H), 3.67 (A of ABX, J = 5.0 Hz, 10.0 Hz, 1H), 3.53 (dd, J = 3.5 Hz, 6.5 Hz, 1H), 3.42 (B of ABX, J = 7.5 Hz, 10.0 Hz, 1H), 2.42-2.36 (m, 1H), 1.82-1.76 (m, 1H), 1.03 (d, J = 7.0 Hz, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.87 (d, J = 7.0 Hz, 3H), 0.05 (s, 6H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 141.54, 113.69, 77.44, 65.42, 41.66, 40.47, 26.12, 25.96, 18.38, 18.30, 14.12, -3.99, -5.28, -5.39; Anal. Calcd for $C_{20}H_{44}O_2Si_2$: C, 64.45, H, 11.90, Found: C, 64.71, H, 11.91.

The aforementioned alkene (0.23 g, 0.62 mmol) was taken up in 10 mL of CH_2Cl_2 and chilled to –78 °C. O_3 was bubbled through the solution until a blue color persisted. Ar was then bubbled through the reaction mixture for 15 min. PPh_3 (0.24 g, 0.93 mmol) was then added, and the mixture was warmed to room temperature for 3 h. The solvent was removed under reduced pressure and the residue was triturated with 10% EtOAc/ hexanes and filtered through Celite to remove triphenylphosphine oxide. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (1% EtOAc/ hexanes to 2.5% EtOAC/ hexanes gradient), affording aldehyde **7** (0.20 g, 87% yield) as a clear oil. $R_f = 0.20$ (5% EtOAc/ hexanes); $[\alpha]^{D}_{20} = + 26.1$ (c = 1.38, $CHCl_3$); IR (film) 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.79 (d, J = 3.0 Hz, 1H), 4.01 (dd, J = 3.0 Hz, 5.5 Hz, 1H), 3.58 (A of ABX, J = 6.0 Hz, 10.5 Hz, 1H), 3.51 (B of ABX, J = 6.0 Hz, 9.5 Hz, 1H), 2.60-2.54 (m, 1H), 1.98-1.90 (m, 1H), 1.13 (d, J = 7.0 Hz, 3H), 0.89 (s, 18H), 0.86 (d, J = 7.5 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 205.07, 75.38, 64.89, 49.30, 41.03, 25.87, 18.14, 12.81, 11.99, -4.33, -4.56, -5.41, -5.55.



(3*S*, 4*S*, 5*S*, 6*S*)-5,7-Bis(t-butyldimethylsilyloxy)-4,6-dimethyl-1-trimethylsilyl-1-heptyn-3-ol (8) A. From TMS Acetylene Addition to Aldehyde 7 with *(S)*-Binol as the Chiral Ligand.

The standard procedure for TMS acetylene addition was employed using aldehyde **7** (0.075g, 0.20 mmol), TMS acetylene (0.11 mL, 0.80 mmol), Et_2Zn (0.082 mL, 0.080mmol), $Ti(OiPr)_4$ (0.059 mL, 0.20 mmol), and (*R*)-BINOL (0.023 g, 0.080 mmol), affording alcohol **8** (0.055 g, 59% yield, 6:1 mixture of diastereomers) as a clear oil. $R_f = 0.1$ (5% EtOAc/ hexanes); ^1H NMR ($CDCl_3$, major diastereomer) δ 4.44

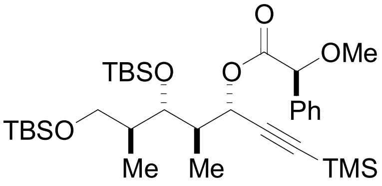
(d, J = 7.5 Hz, 1H), 3.78 (dd, J = 3.6 Hz, 6.6 Hz, 1H), 3.60 (A of ABX, J = 7.5 Hz, 10.2 Hz, 1H), 3.43 (B of ABX, J = 6.6 Hz, 10.2 Hz, 1H), 3.09 (s, 1H), 2.04-1.96 (m, 2H), 1.01 (d, J = 6.9 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.17 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.04 (s, 6H).

B. Without BINOL

The standard procedure for TMS acetylene addition was employed using aldehyde 7 (0.10 g, 0.21 mmol), TMS acetylene (0.18 mL, 1.3 mmol), Et_2Zn (0.13 mL, 1.3 mmol), and $Ti(OiPr)_4$ (0.062 mL, 0.21 mmol), affording alcohol **8** (0.10 g, 77% yield, 1.3:1 mixture in favor the 3*(S)* diastereomer) as a clear oil. All analytical data matched the previously characterized material.

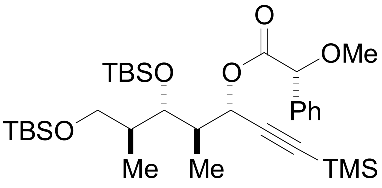
C. From Noyori reduction of ketone 13

Ketone **13** (0.052 g, 0.11 mmol) was taken up in 1.5 mL iPrOH. Catalyst *ent*-**14** (0.0032 g, 0.0055 mmol) was added, and the mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (1% EtOAc/ hexanes to 2.5% EtOAc/ hexanes gradient), affording alcohol **8**(0.038 g, 73% yield) as a light yellow oil. R_f = 0.2 (5% EtOAc/ hexanes). The NMR spectra of this material were identical to those of the material prepared in part A.



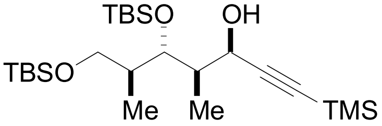
(*S*)-O-Methyl Mandelic Ester of 8

Alcohol **8** (0.010 g, 0.021 mmol) was taken up in 1 mL of CH_2Cl_2. (*S*)-O-Methyl mandelic acid (0.0070 g, 0.042 mmol), DCC (0.0087 g, 0.042 mmol), and a few crystals of DMAP were added. The mixture was stirred for 15 min, and the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel (100% hexanes), affording the desired ester (0.008 g, 62%) yield as a clear oil. ^1H NMR ($CDCl_3$) δ 7.46-7.31 (m, 5H), 5.67 (d, J = 4.8 Hz, 1H), 4.76 (s, 1H), 3.70-3.58 (m, 2H), 3.44 (s, 3H), 3.36 (B of ABX, J = 7.2 Hz, 9.9 Hz, 1H), 2.16-1.88 (m, 2H), 0.98 (d, J = 6.9 Hz, 3H), 0.92-0.86 (m, 21 H), 0.14 (s, 3H), 0.14 (s, 3H) 0.08 (s, 9H), 0.02 (s, 3H), 0.02 (s, 3H).



(*R*)-O-Methyl Mandelic Ester of 8

Alcohol **8** (0.010 g, 0.021 mmol) was taken up in 1 mL of CH_2Cl_2. (*S*)-O-Methyl mandelic acid (0.0070 g, 0.042 mmol), DCC (0.0087 g, 0.042 mmol), and a few crystals of DMAP were added. The mixture was stirred for 15 min, and the solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel (100% hexanes), affording the desired ester (0.009 g, 69%) yield as a clear oil. ^{1}H NMR (CDCl$_3$) δ 7.45-, 7.30 (m, 5H), 5.70 (d, J = 5.1 Hz, 1H), 4.78 (s, 1H), 3.56 (A of ABX, J = 6.6 Hz, 10.2 Hz, 1H), 3.50 (dd, J = 2.7 Hz, 8.4 Hz, 1H), 3.42 (s, 9H), 3.26 (B of ABX, J = 7.2 Hz, 9.9 Hz, 1H), 1.94-1.70 (m, 2H), 0.89-0.85 (m, 21H), 0.80 (d, J = 7.2 Hz, 3H), 0.15 (s, 9H), 0.12 (s, 3H), 0.03 (s, 3H), -0.01 (s, 3H), -0.03 (s, 3H).

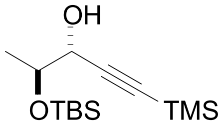


(3*R*, 4*S*, 5*S*, 6*S*)-5,7-Bis(t-butyldimethylsilyloxy)-4,6-dimethyl-1-trimethylsilyl-1-heptyn-3-ol (9) A. From TMS Acetylene Addition to Aldehyde 7.

The standard procedure for TMS acetylene addition was employed using aldehyde **7** (0.075g, 0.20 mmol), TMS acetylene (0.11 mL, 0.80 mmol), Et$_2$Zn (0.082 mL, 0.080mmol), Ti(OiPr)$_4$ (0.059 mL, 0.20 mmol), and (*S*)-BINOL (0.023 g, 0.080 mmol), affording alcohol **9** (0.063 g, 67% yield, 6:1 mixture of diastereomers) as a clear oil. R$_f$ = 0.2 (5% EtOAc/ hexanes); $[\alpha]^D_{20}$ = + 9.9 (c = 1.62, CHCl$_3$); IR (film) 3441, 2182 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 4.73 (3.0 Hz, 1H), 3.90 (t, J = 5.0 Hz, 1H), 3.61 (A of ABX, J = 3.5 Hz, 10 Hz, 1H), 3.50-3.47 (m, 2H), 2.00-1.95 (m, 2H), 1.13 (d, J = 7.5 Hz, 3H), 0.94 (d, J =7.0 Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.16 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (CDCl$_3$) δ 106.03, 89.19, 77.78, 64.92, 64.72, 40.92, 39.85, 26.07, 25.89, 18.24, 18.20, 13.14, 13.12, -0.08, -4.09, -4.25, -5.40, -5.50; Anal. Calcd for C$_{24}$H$_{52}$O$_3$Si$_3$: C, 60.95, H, 11.08, Found: C, 60.91, H, 11.23.

B: From Noyori Reduction of Ketone 13

Ketone **13** (0.054 g, 0.11 mmol) was taken up in 1.5 mL of iPrOH. Catalyst **14** (0.0034 g, 0.0057 mmol) was added, and the mixture was stirred overnight. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (1% EtOAc/ hexanes to 2.5% EtOAc/ hexanes), affording alcohol **9** (0.041 g, 76% yield) as a light yellow oil. R$_f$ = 0.2 (5% EtOAc/ hexanes); The NMR spectra of this material were superimposable with those of material prepared in part A.



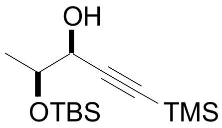
(3*R*, 4*S*)-4-(t-Butyldimethylsilyloxy)-1-trimethylsilyl-1-pentyn-3-ol (11). A With *(R)*-BINOL as the Chiral Ligand.

The standard procedure for TMS acetylene addition was employed using aldehyde **10** (0.10 g, 0.53 mmol), TMS acetylene (0.30 mL, 2.1 mmol), Et$_2$Zn (0.22 mL, 2.1 mmol), Ti(OiPr)$_4$ (0.16 mL, 0.53 mmol), and (*R*)-BINOL (0.061 g, 0.21 mmol), affording alcohol **11** (0.090 g, 60% yield, 11:1 mixture of diastereomers) as a clear oil. R$_f$ = 0.5 (20% EtOAc/ hexanes); $[\alpha]^D_{20}$ = + 2.1 (c = 1.25, CHCl$_3$); IR (film) 3214, 2174 cm^{-1}; ^{1}H NMR (CDCl$_3$, major diastereomer) δ 4.24 (d, J = 3.0 Hz, 1H), 3.92-3.89 (m, 1H), 2.33

(broad s, 1H), 1.22 (dd, J = 1.0 Hz, 6.0 Hz, 3H), 0.90 (s, 9H), 0.17 (s, 9H), 0.10 (s, 3H), 0.10 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 103.65, 90.70, 70.99, 67.42, 25.73, 18.17, 18.00, -0.20, -4.45, -4.81.

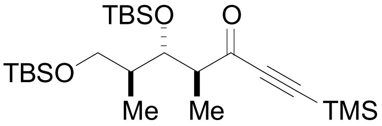
B. Without BINOL.

The standard procedure for TMS acetylene addition was employed using aldehyde **10** (0.10 g, 0.49 mmol), TMS acetylene (0.28 mL, 2.0 mmol), Et_2Zn (0.20 mL, 2.0 mmol), and $Ti(OiPr)_4$ (0.15 mL, 0.49 mmol), affording alcohol **11** (0.10 g, 66% yield, 6:1 mixture of diastereomers favoring the 3(*R)* diastereomer) as a clear oil. All analytical data was consistent with the BINOL directed cases.



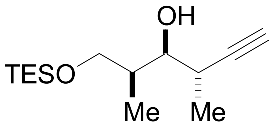
(3*S*, 4*S*)-4-(t-Butyldimethylsilyloxy)-1-trimethylsilyl-1-pentyn-3-ol (12)

The standard procedure for TMS acetylene addition was employed using aldehyde **10** (0.10 g, 0.53 mmol), TMS acetylene (0.30 mL, 2.1 mmol), Et_2Zn (0.22 mL, 2.1 mmol), $Ti(OiPr)_4$ (0.16 mL, 0.53 mmol), and (*S*)-BINOL (0.061 g, 0.21 mmol), affording alcohol **12** (0.083 g, 55% yield, 1.3:1 mixture of diastereomers) as a clear oil. R_f = 0.5 (20% EtOAc/ hexanes); ^{1}H NMR ($CDCl_3$, major diastereomer) δ 4.06 (d, J = 5.0 Hz, 1H), 3.89-3.95 (m, 1H), 1.12 (d, J = 6.5 Hz, 3H), 0.91 (s, 9H), 0.17 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H).



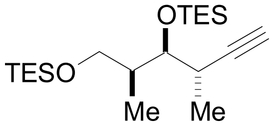
(4*S*, 5*S*, 6*S*)-5,7-Bis(t-butyldimethylsilyloxy)-4,6-dimethyl-1-trimethylsilyl-1-heptyn-3-one (13)

To a solution of alcohol **8** (0.085 g, 0.18 mmol) in 2 mL of CH_2Cl_2 was added $NaHCO_3$ (0.16 g, 1.8 mmol) and Dess-Martin periodinane (0.11 g, 0.27 mmol). The heterogeneous mixture was stirred for 30 min and quenched with equal volumes of aq. $NaHCO_3$ and aq. $Na_2S_2O_3$. After 30 min, the biphasic mixture was partitioned in a separatory funnel and the aqueous portion was extracted three times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and filtered. Concentration under reduced pressure, followed by flash chromatography on silica gel (1% EtOAc/ hexanes) afforded ketone **13** (0.058 g, 68% yield) as a light yellow oil. R_f = 0.2 (5% EtOAc/ hexanes); $[\alpha]^{D}_{20}$ = + 37.4 (c = 1.38, $CHCl_3$); IR (film) 1684 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.29 (t, J = 5.5 Hz, 1H), 3.65 (A of ABX, J = 4.5 Hz, 9.5 Hz, 1H), 3.51 (B of ABX, J = 6.5 Hz, 9.5 Hz, 1H), 2.88-2.82 (m, 1H), 1.86-1.79 (m, 1H), 1.14 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.81 (d, J = 7.0 Hz, 3H), 0.25 (s, 9H), 0.10 (s, 3H), 0.10 (s, 3H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 189.39, 101.99, 98.65, 74.41, 64.80, 54.37, 39.36, 25.97, 25.93, 18.29, 18.17, 13.78, 10.14, -0.77, -4.50, -5.36, -5.47.



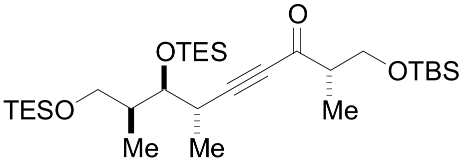
(2*S*, 3S, 4*S*)-2,4-Dimethyl-1-(triethylsilyloxy)-5-hexyn-3-ol (16)

Pd(OAc)$_2$ (0.13g, 0.59 mmol) was taken up in 120 mL of THF and chilled to -78 °C. PPh$_3$ (0.15g, 0.59 mmol) was added and the mixture was stirred for 5 min. Aldehyde **15**(2.4 g, 12 mmol) and mesylate **16** (2.3 g, 15 mmol) were added in 5 mL of THF. After 5 min, Et$_2$Zn (35 mL, 1.0 M in THF) was added slowly. The mixture was stirred for five minutes, then warmed to –20 °C and stirred overnight. Within five minutes of being warmed to –20 °C, the reaction mixture turned a dark brown color. The reaction was quenched by slow addition of aq. NH$_4$Cl and partitioned in a separatory funnel. The aqueous portion was extracted three times with Et$_2$O and the combined organic extracts were washed with brine and dried over MgSO$_4$ with activated charcoal. Filtration through Celite and concentration under reduced pressure, followed by flash chromatography on silica gel (5% EtOAc/ hexanes) afforded stereotriad **17** (2.3 g, 76% yield) as a yellow oil. R$_f$ = 0.10 (5% EtOAc/ hexanes); $[\alpha]^D_{20}$ = - 4.8 (c = 1.66, CHCl$_3$); IR (film) 3475 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 3.68 (d, J = 5.0 Hz, 2H), 3.62 (dd, J = 3.5 Hz, 7.0 Hz, 1H), 2.77 (s, 1H), 2.68-2.62 (m, 1H), 2.13 (d, J = 2.0 Hz, 1H), 1.84-1.78 (m, 1H), 1.19 (d, J = 7.0 Hz, 3H), 0.96 (t, J = 8.5 Hz, 9H), 0.96 (d, J = 7.0 Hz, 3H), 0.60 (q, J = 8.0 Hz, 6H); ^{13}C NMR (CDCl$_3$) δ 86.30, 75.86, 70.02, 66.75, 37.32, 30.43, 17.40, 10.09, 6.57, 4.12; Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.57, H, 11.00, Found: C, 65.39, H, 11.02.



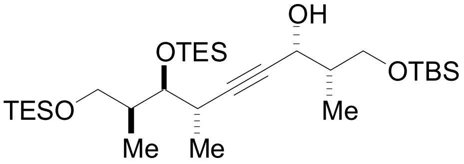
(3*S*, 4*S*, 5*S*)-3,5-Dimethyl-4,6-(triethylsilyloxy)-1-hexyne (18)

Alcohol **17** (2.7 g, 11 mmol) was taken up in 110 mL of CH$_2$Cl$_2$ and chilled to 0 °C. 2,6-lutidine (2.5 mL, 21 mmol) and TESOTf (3.6 mL, 16 mmol) were added sequentially, and the mixture was stirred for 90 min. The solvent was removed under vacuum and the residue was taken up in 100 mL of Et$_2$O and washed successively with aq NH$_4$Cl, aq. CuSO$_4$, and brine. The ethereal solution was dried over MgSO$_4$ and filtered. Concentration under reduced pressure, followed by flash chromatography on silica gel (100% hexanes) afforded bis TES ether **18** (3.1 g, 80% yield) as a pale yellow oil. R$_f$ = 0.5 (2.5% EtOAc/ hexanes); IR (film) 3301 cm^{-1}; $[\alpha]^D_{20}$ = + 3.9 (c = 1.36, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 3.76 (dd, J = 3.5 Hz, 6.0 Hz, 1H), 3.55 (A of ABX, J = 7.0 Hz, 10.0 Hz, 1H), 3.44 (B of ABX, J = 7.0 Hz, 10.0 Hz, 1H), 2.64-2.59 (m, 1H), 2.03 (d, J = 2.0 Hz, 1H), 1.89-1.82 (m, 1H), 1.16 (d, J = 7.0 Hz, 3H), 0.99-0.94 (m, 18 H), 0.87 (d, J = 7.0 Hz, 3H), 0.65 (q, J = 8.0 Hz, 6H), 0.59 (q, J = 8.0 Hz, 6H); ^{13}C NMR (CDCl$_3$) δ 87.71, 74.80, 69.53, 65.60, 39.03, 31.52, 16.46, 11.02, 7.05, 6.78, 5.42, 4.46.



(2*S*, 6*S*, 7*S*, 8*S*)-1-(t-Butyldimethylsilyloxy)-7,9-bis(triethylsilyloxy)-2,6,8-(trimethyl)-4-nonyn-3-one (21)

Alkyne **18** (0.93g, 2.5 mmol) was taken up in 19 mL of THF and chilled to –78 °C. BuLi (1.0 mL, 2.5 M in hexanes) was added slowly. After 5 min, the mixture was warmed to 0 °C and stirred for 40 min. The mixture was then chilled to –78 °C, and amide **20** (0.50 g, 1.9 mmol) in 3 mL of THF was added slowly. After 5 min, the solution was warmed to 0 °C and stirred for 30 min. The reaction was quenched with aq NH_4Cl and the mixture was partitioned in a separatory funnel. The aqueous portion was extracted three times with ether and the combined organic extracts were washed with brine and dried over $MgSO_4$. Filtration and concentration under reduced pressure, followed by flash chromatography on silica gel (100% hexanes to 1% EtOAc/ hexanes), afforded ynone **21** (1.1 g, 100% yield) as a yellow oil. R_f = 0.25 (5% EtOAc/ hexanes); $[\alpha]^{D}_{20}$ = +2.1 (c = 1.80, $CHCl_3$); IR (film) 2209, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.90 (dd, J = 6.5 Hz, 10.0 Hz, 1H), 3.81 (t, J = 5.0 Hz, 1H), 3.72 (dd, J = 6.0 Hz, 10.0 Hz, 1H), 3.52 (A of ABX, J = 7.0 Hz, 10.0 Hz, 1H), 3.45 (B of ABX, J = 6.0 Hz, 10.0 Hz, 1H), 2.85-2.80 (m, 1H), 2.76-2.69 (m, 1H), 1.86-1.82 (m, 1H), 1.23 (d, J = 7.5 Hz, 3H), 1.16 (d, J = 7.0 Hz, 3H), 0.97 (t, J = 8.0 Hz, 9H), 0.95 (t, J = 8.0 Hz, 9H), 0.89 (d, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.64 (q, J = 8.0 Hz, 6H), 0.58 (q, J = 8.0 Hz, 6H), 0.04 (d, J = 1.5 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 190.13, 97.55, 81.38, 74.72, 65.25, 64.51, 51.26, 39.76, 32.15, 25.78, 18.21, 17.26, 12.76, 11.49, 7.02, 6.77, 6.74, 5.37, 4.40, -5.51.



(2*S*, 3*R*, 6*S*, 7*S*, 8*S*)-1-(t-Butyldimethylsilyloxy)-7,9-bis(triethylsilyloxy)-2,6,8-trimethyl-4-nonyn-3-ol (22)

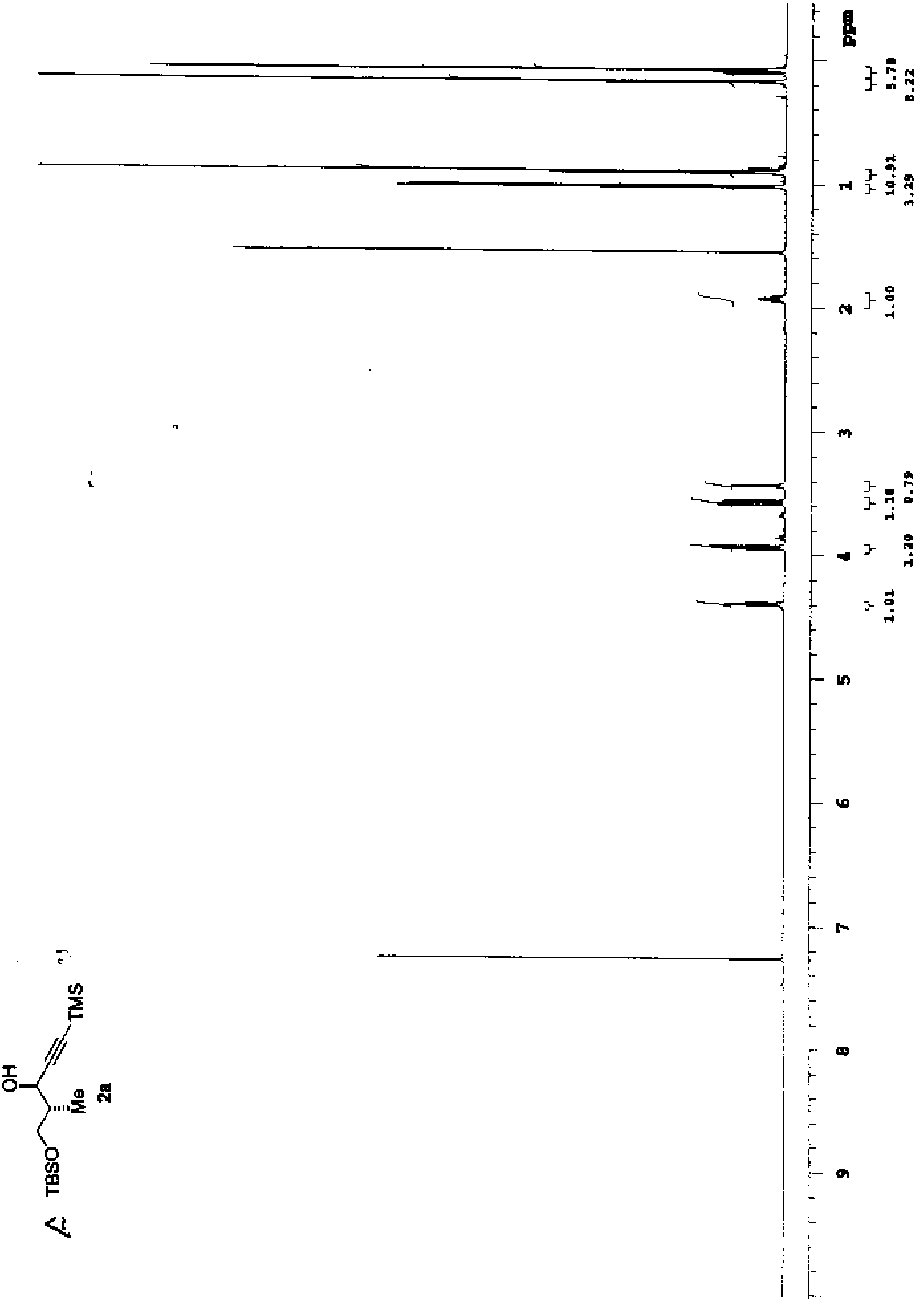
Ynone **21** (1.1 g, 1.9 mmol) was taken up in 19 mL of i-PrOH. Catalyst **14** (0.056 g, 0.096 mmol) was added in one portion, and the solution was stirred overnight. The solvent was removed under vacuum, and the crude residue was purified by flash chromatography on silica gel (2.5 % EtOAc/ hexanes), affording propargylic alcohol **22** (0.93 g, 85% yield) as a yellow oil. R_f = 0.20 (5% EtOAc/ hexanes); $[\alpha]^{D}_{20}$ = +10.2 (c = 1.36, $CHCl_3$); IR (film) 3501, 2235 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.44 (s, 1H), 3.85 (t, J = 9.5 Hz, 1H), 3.75 (t, J = 4.5 Hz, 1H), 3.63 (dd, J = 4.5 Hz, 10.0 Hz, 1H), 3.53 (A of ABX, J = 6.5 Hz, 9.5 Hz, 1H), 3.43 (B of ABX, J = 6.5 Hz, 10.0 Hz, 1H), 2.70-2.64 (m ,1H), 2.12-2.04 (m, 1H), 1.92-1.84 (m, 1H), 1.70 (d, J = 7.0 Hz, 3H), 0.99-0.94 (m, 18H), 0.90 (s, 9H), 0.88 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 7.0 Hz, 3H), 0.64 (q, J = 7.0 Hz, 6H), 0.58 (q, J = 7.5 Hz, 6H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$) δ

88.83, 80.61, 74.95, 67.14, 66.68, 65.69, 40.19, 39.32, 31.83, 25.82, 18.12, 17.84, 12.36, 11.56, 7.06, 6.79, 5.40, 4.43, -5.59, -5.65.

References

1) White, J. A.; Hanselmann, R.; Jackson, R. W.; Porter, W. J.; Okba, Y.; Tiller, T.; Wang, S. *J. Org. Chem.*, **2001**, *66*, 5217.

2) Marshall, J. A.; Schaaf, G. M. *J. Org. Chem.*, **2001**, *66*, 7825.



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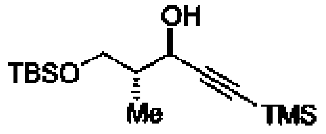
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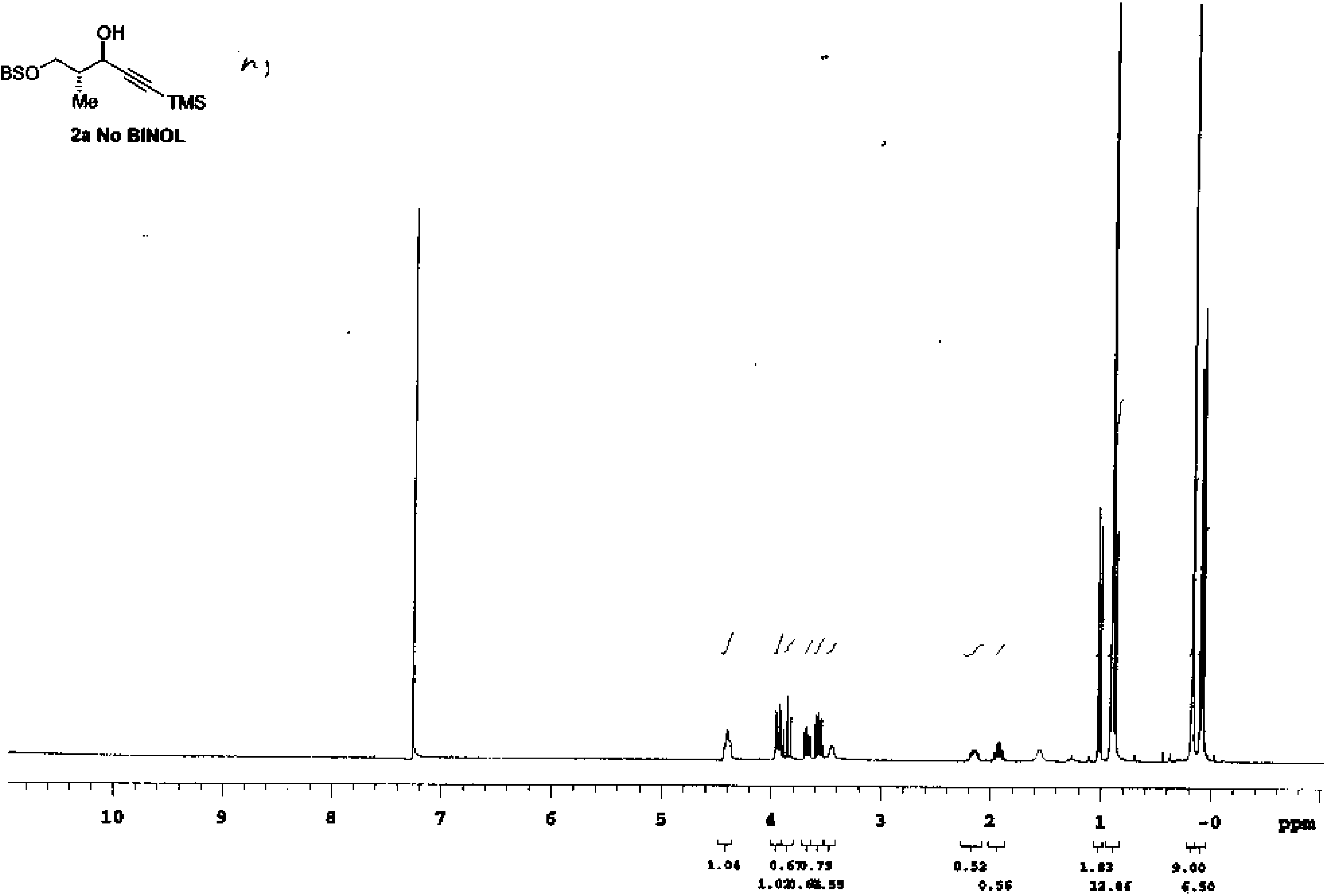
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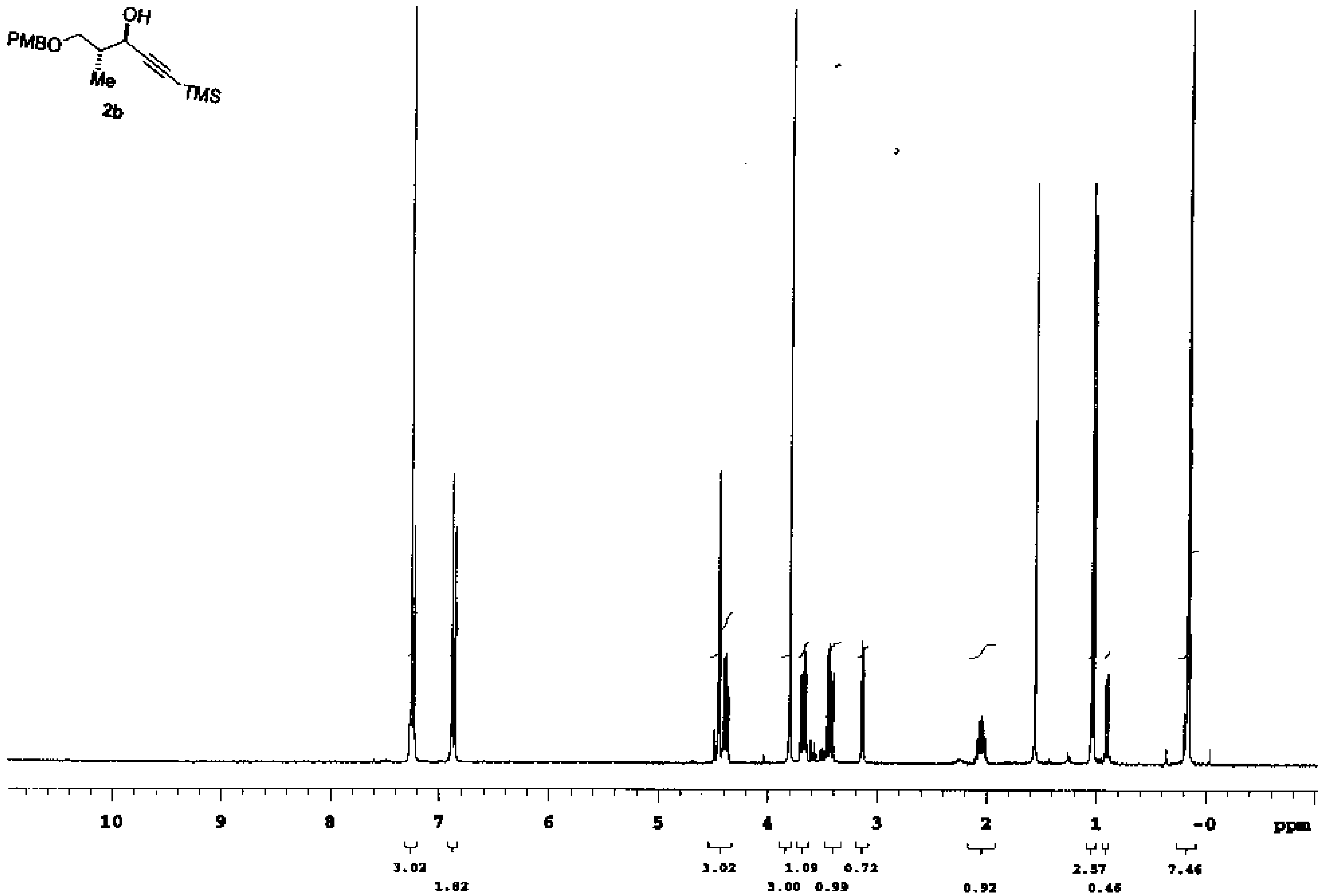OH
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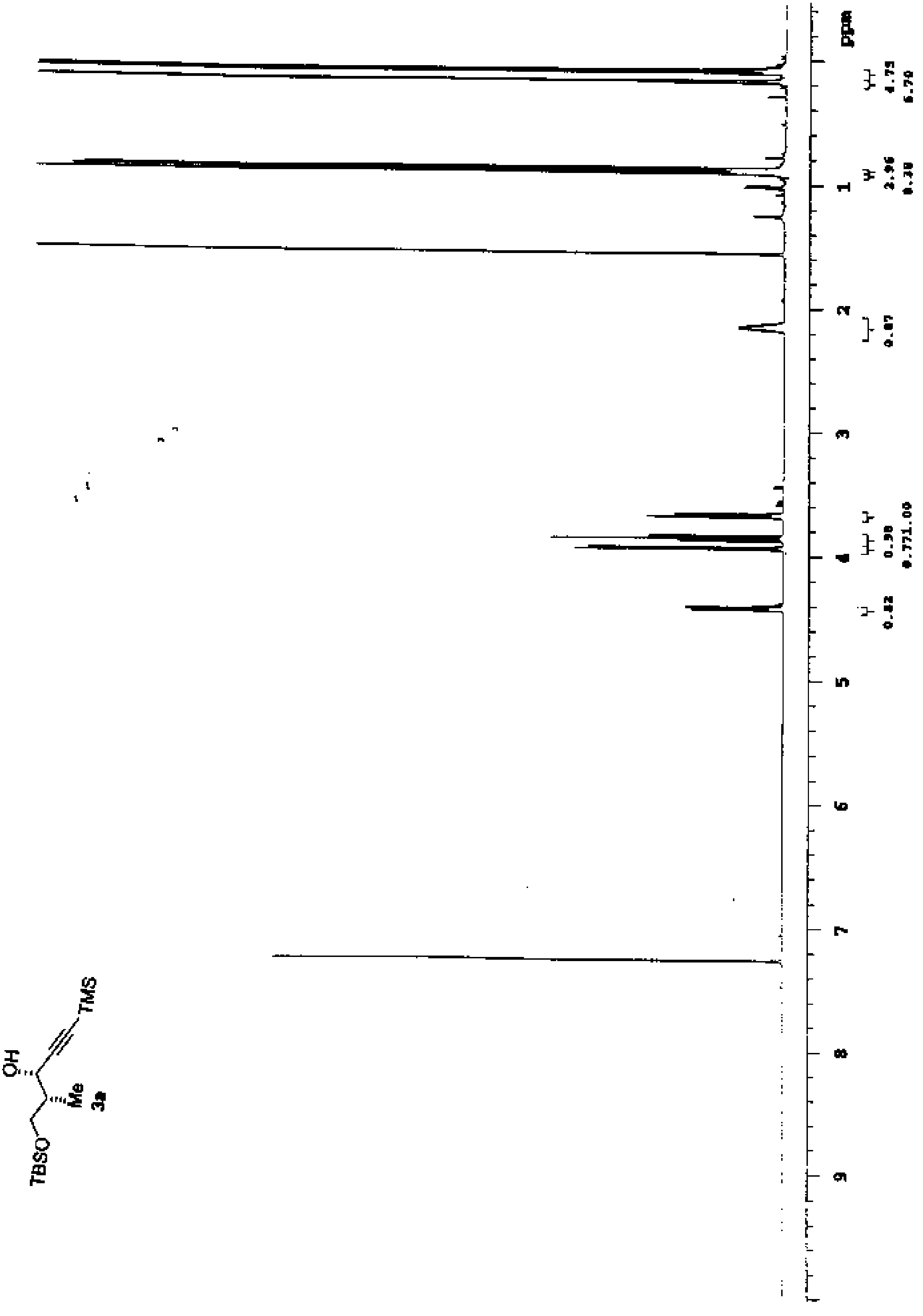

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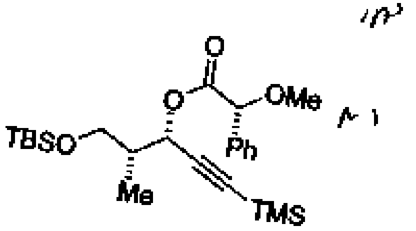

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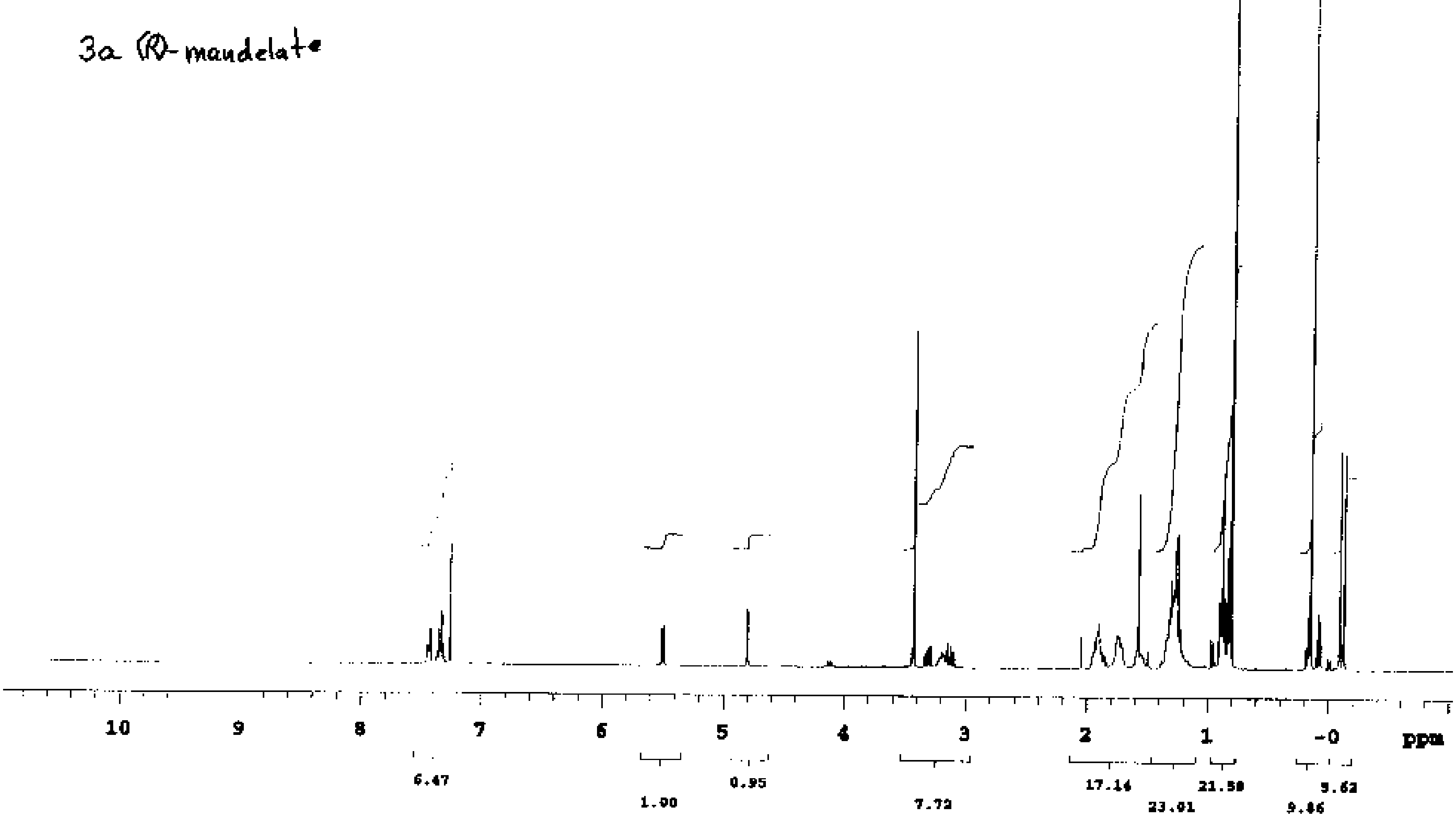

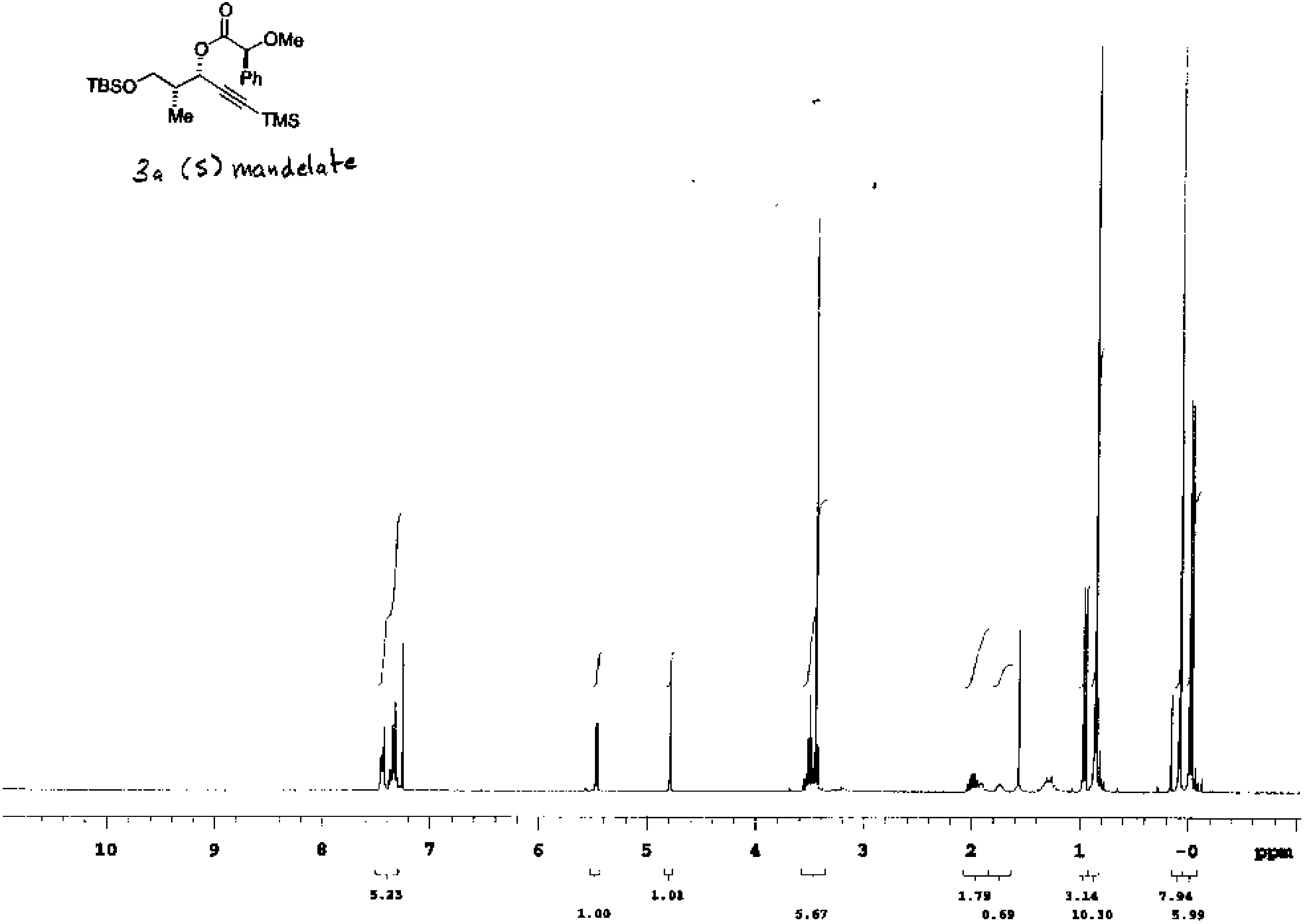

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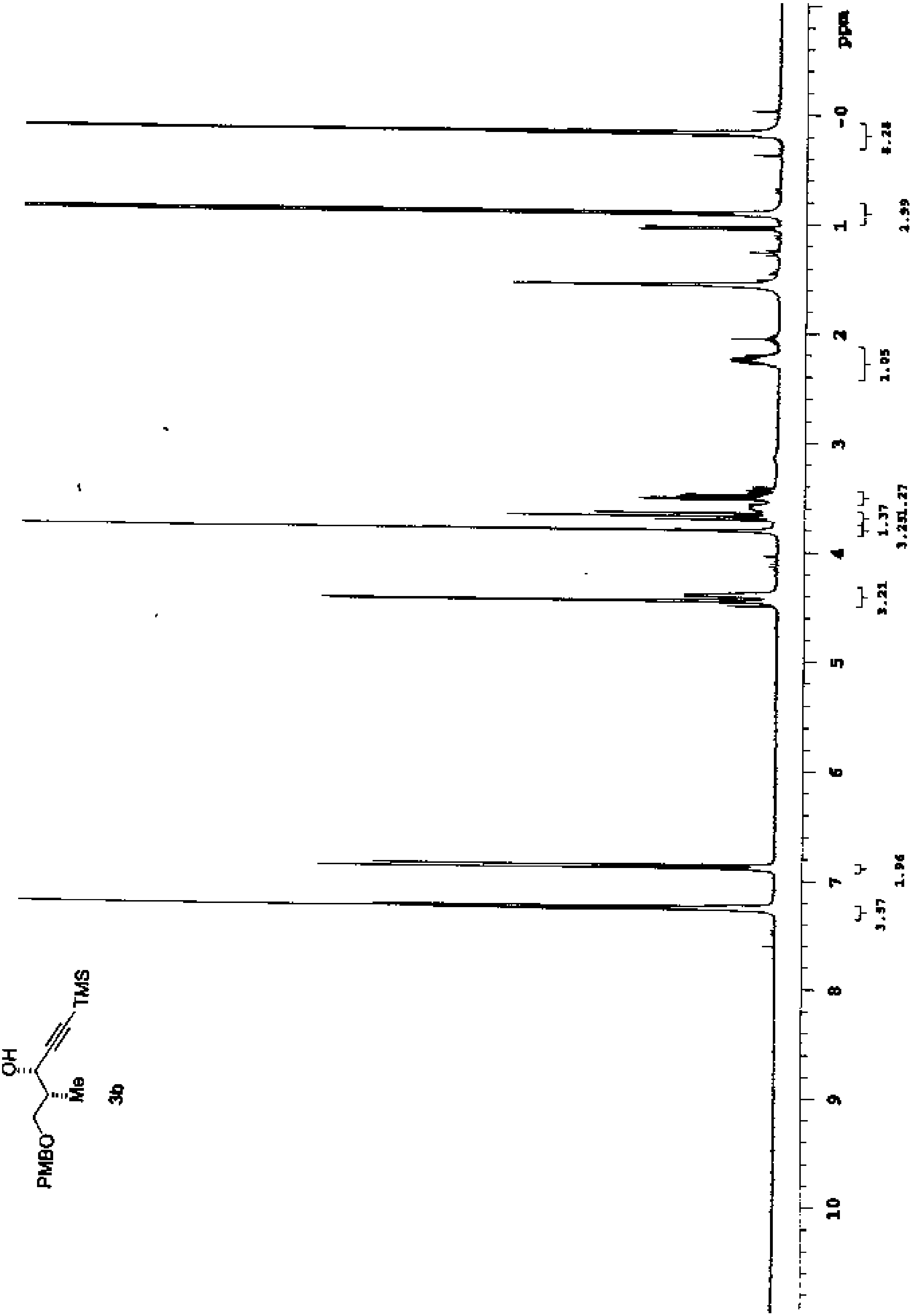

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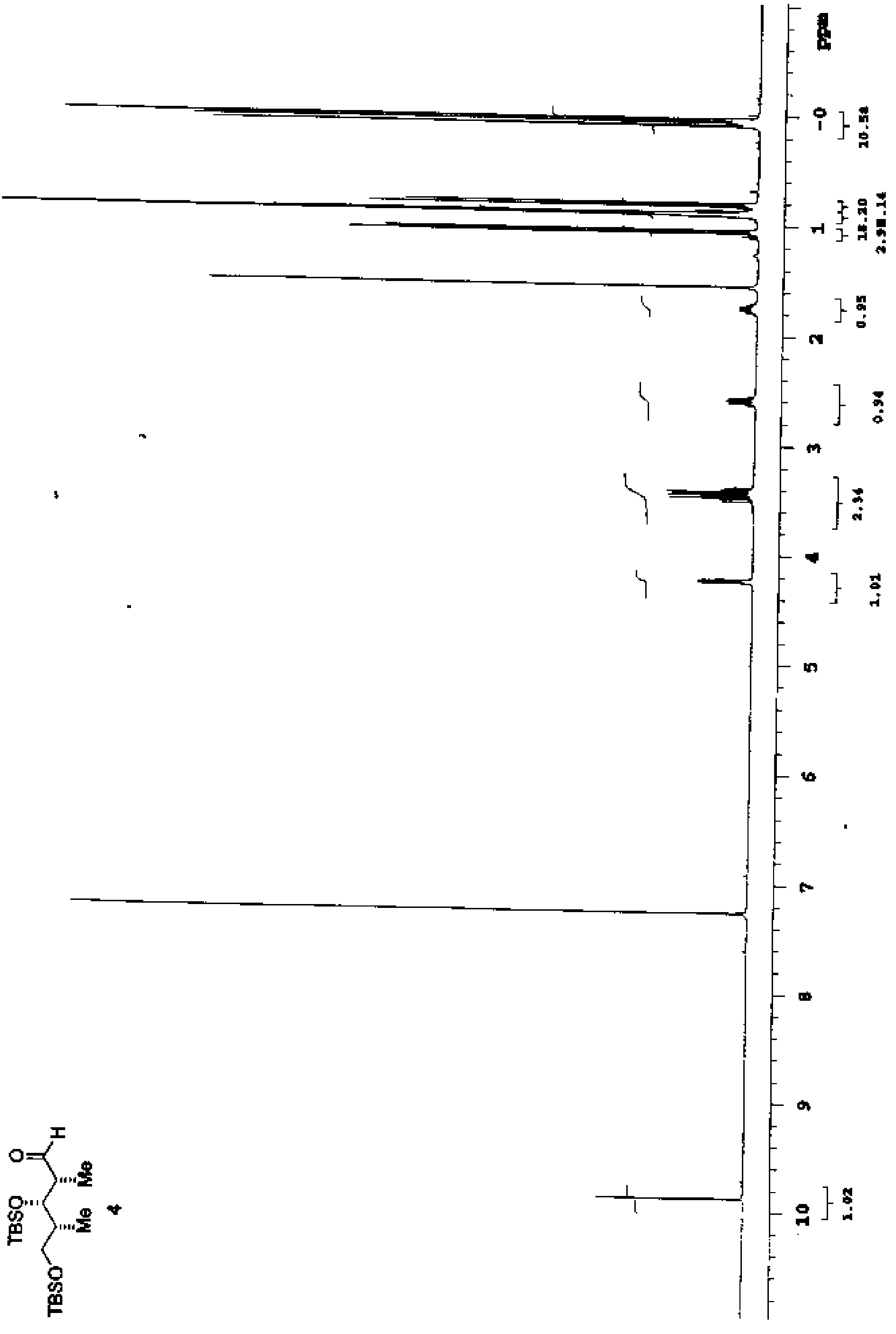
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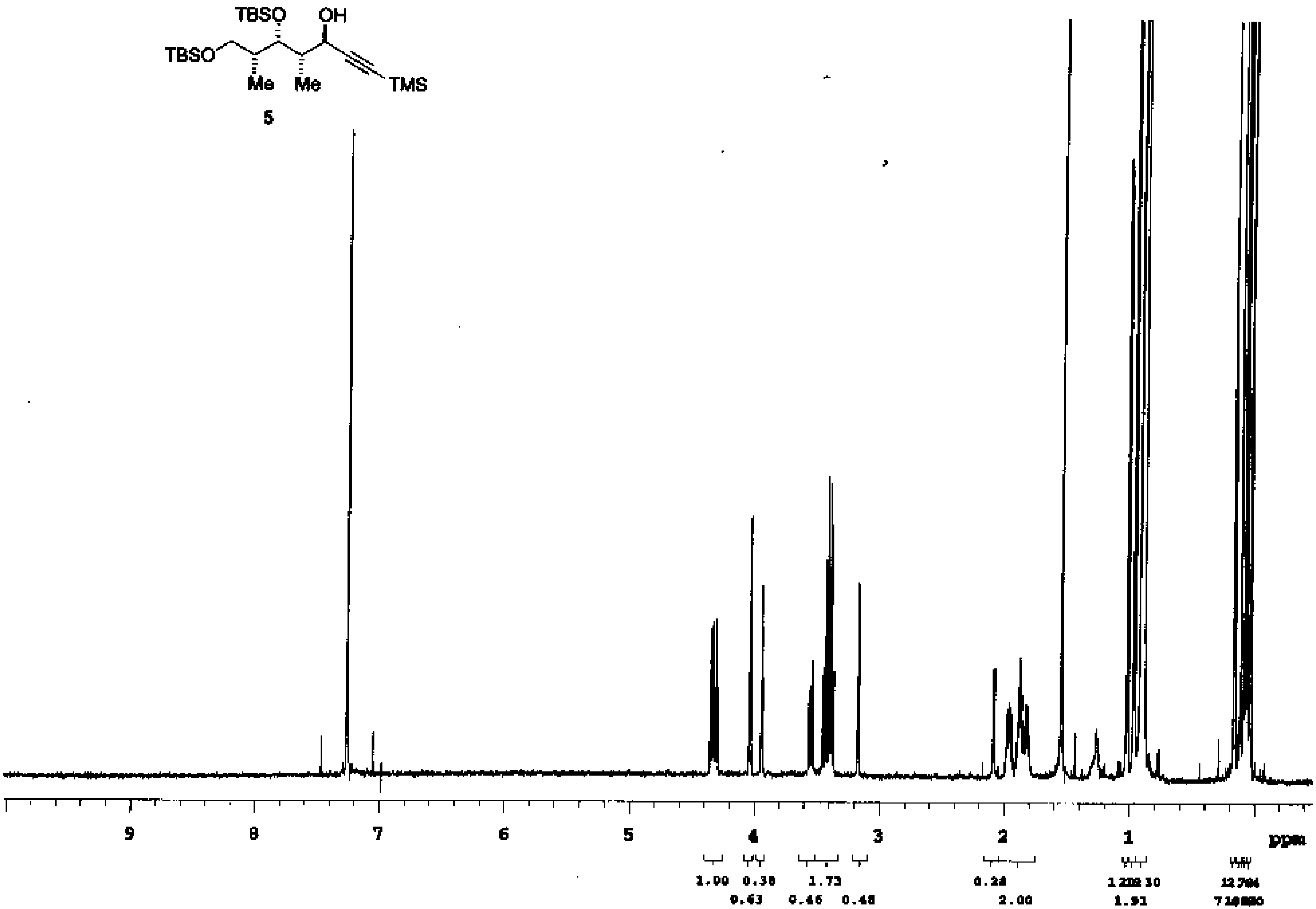
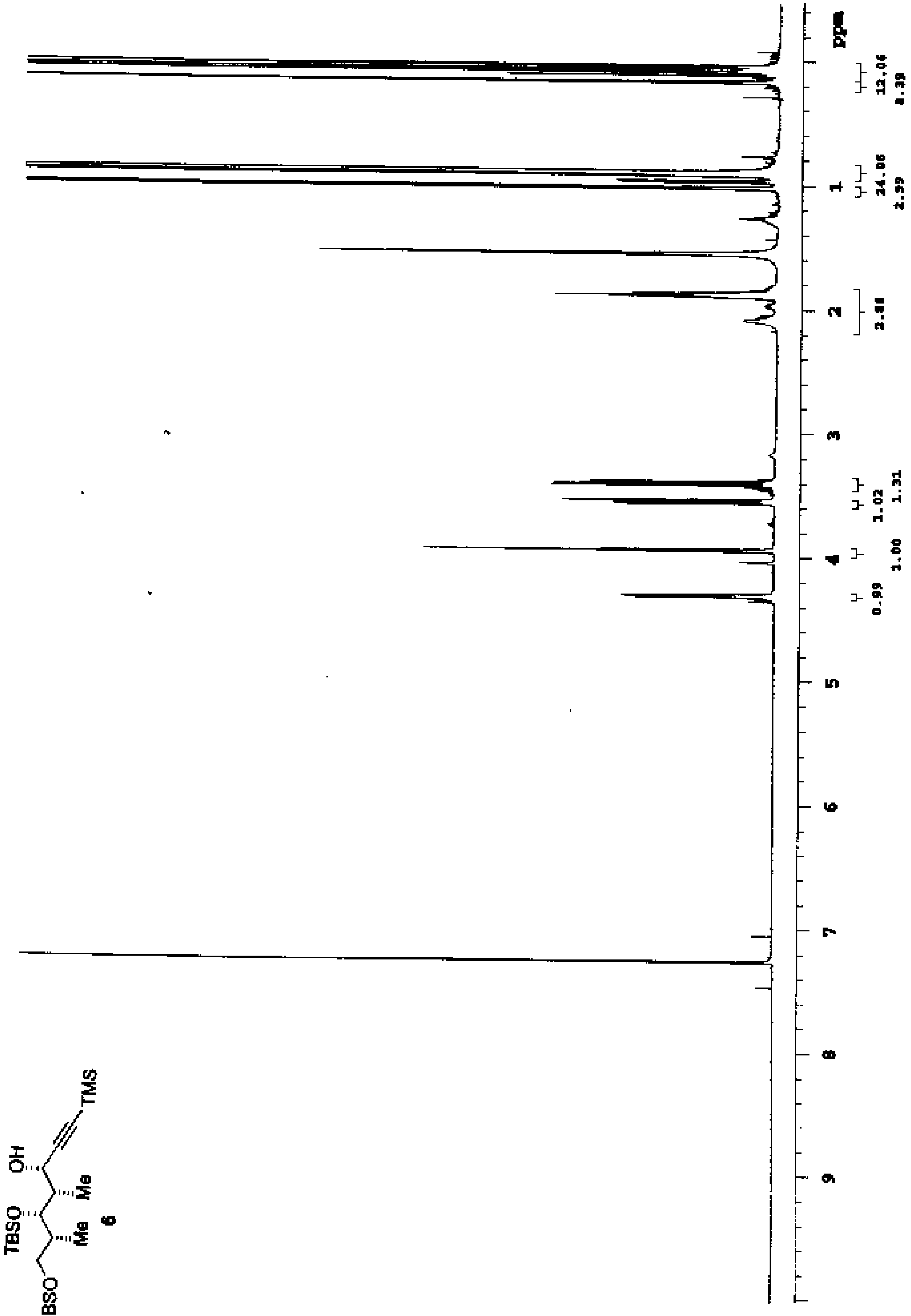
4

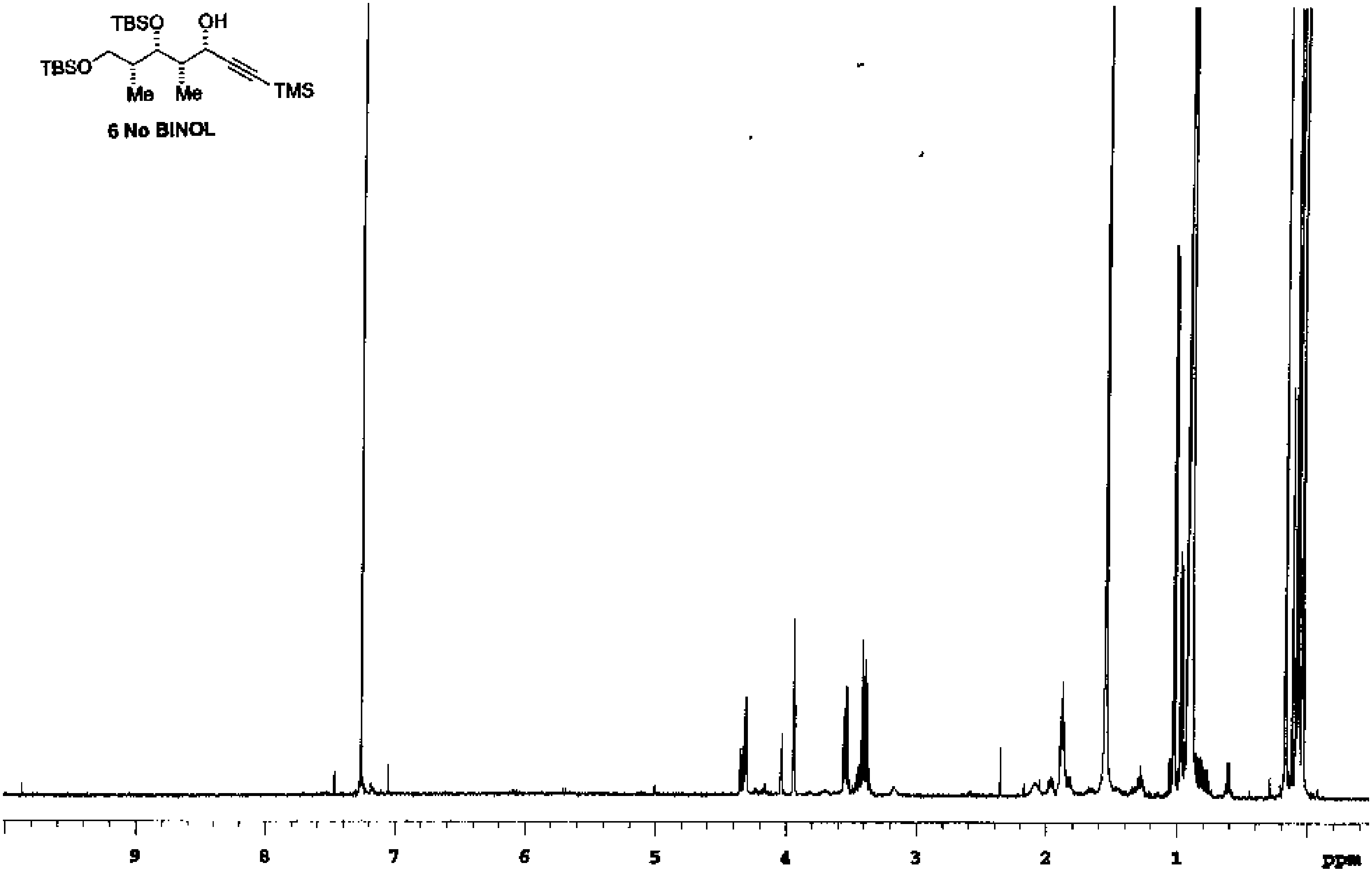


5

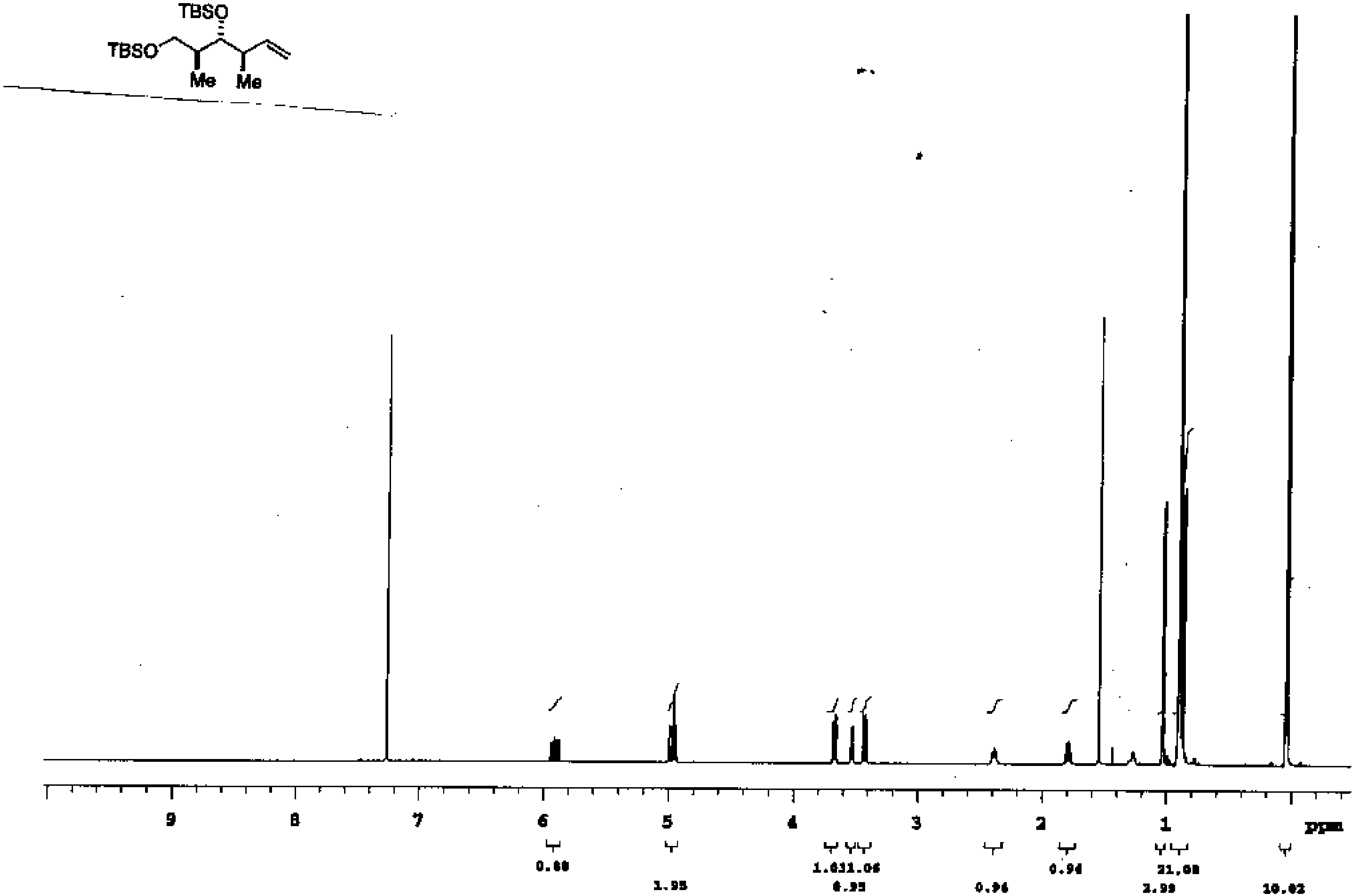
TBSO
TBSO
OH
Me
Me
TMS
9
8
7
6
5
4
3
2
1
ppm
1.00
0.38
0.63
1.73
0.46
0.48
0.28
2.00
1.91
12.704

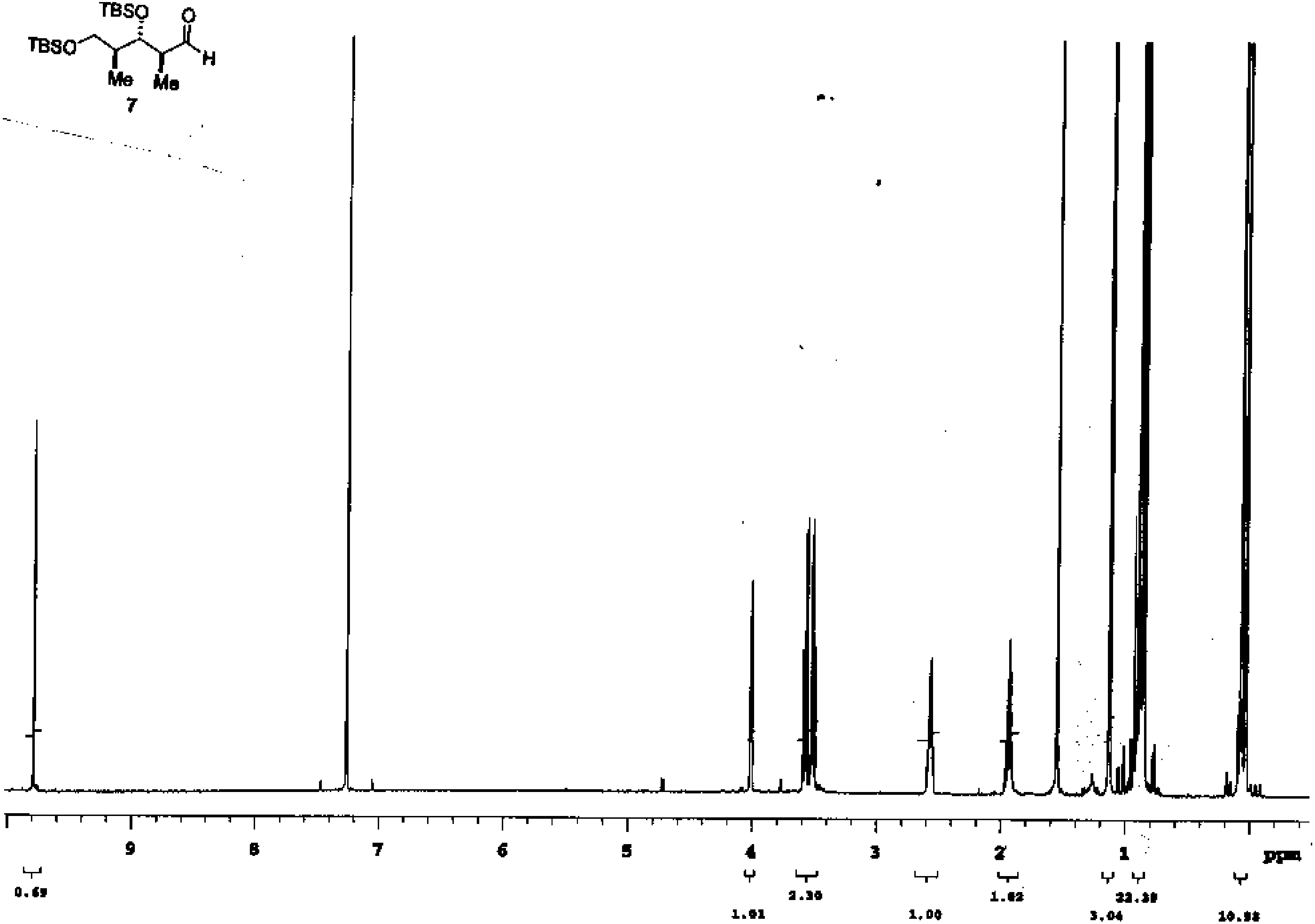

6

TBSO
TBSO
OH
Me
Me
TMS
ppm
1
2
3
4
5
6
7
8
9
12.06
8.39
24.06
2.59
2.88
1.31
1.02
1.00
0.99



6 No BINOL


TBSO
TBSO
Me
Me
9
8
7
6
5
4
3
2
1
ppm
0.88
1.95
1.03
1.06
0.95
0.96
0.94
21.08
2.99
10.02

TBSO
TBSO
O
H
Me
Me
9
8
7
6
5
4
3
2
1
ppm
0.69
1.01
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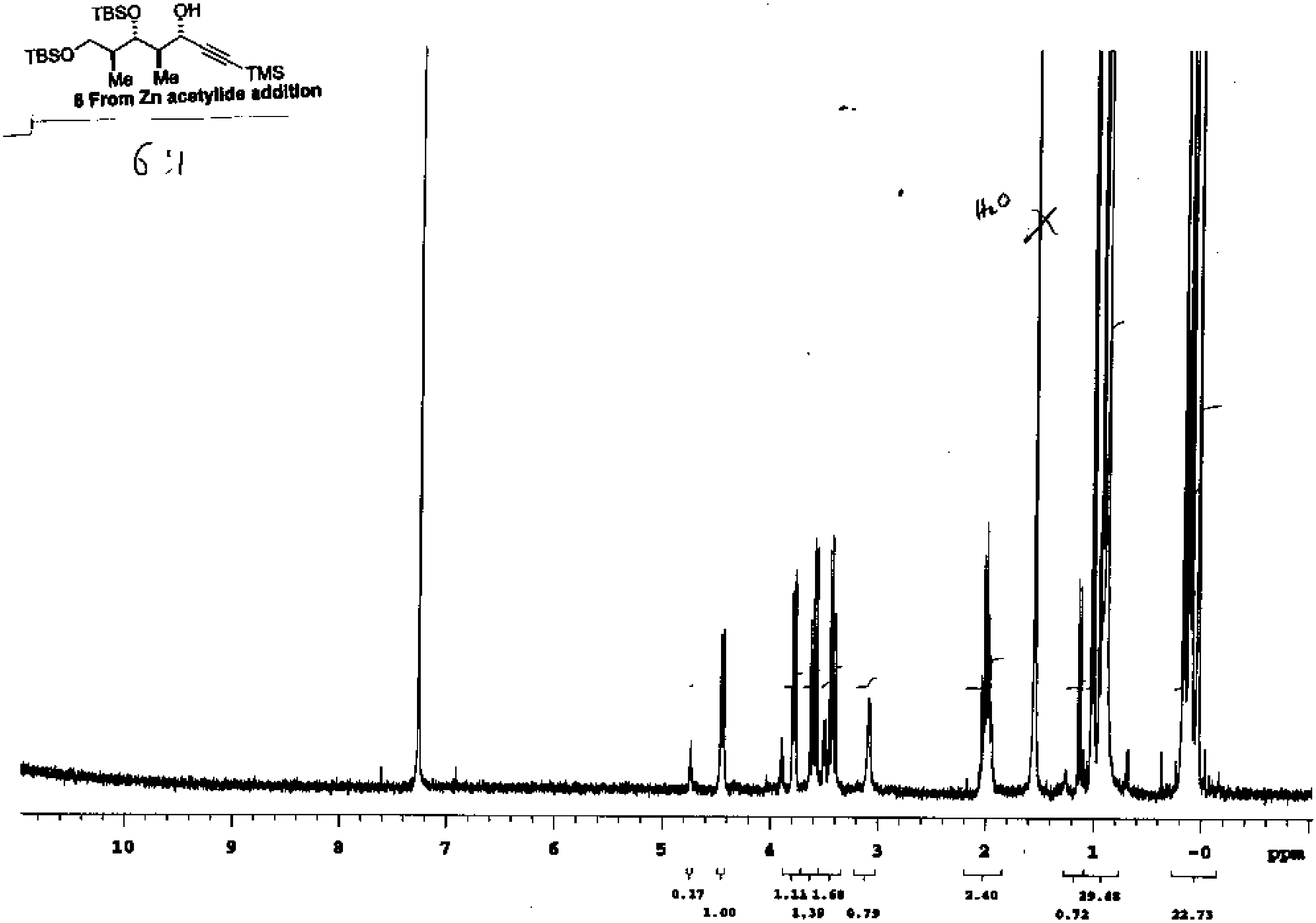
1.02
3.04
22.38
10.98

7

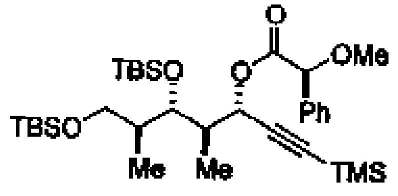


6 From Zn acetylide addition

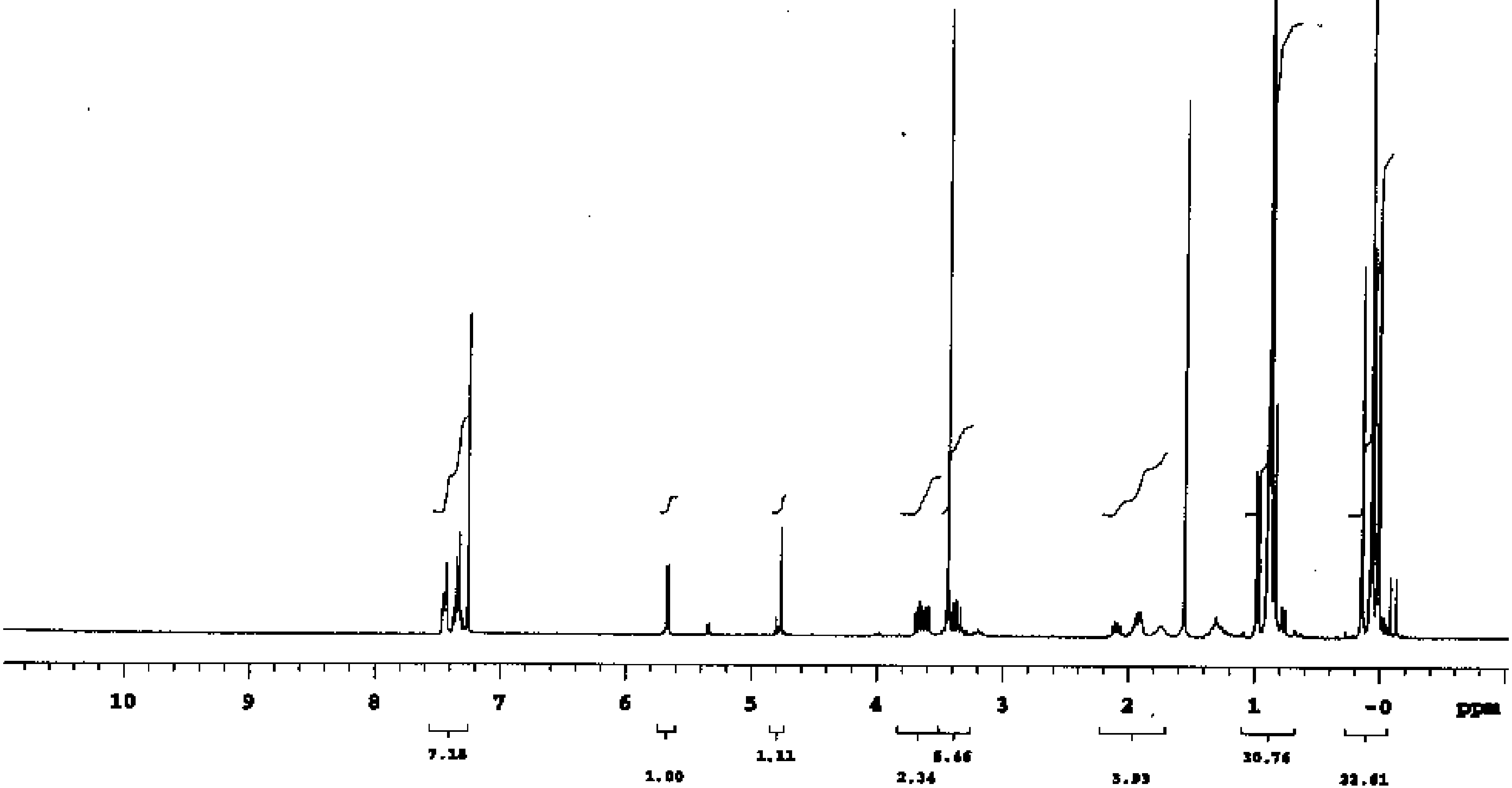
6:1

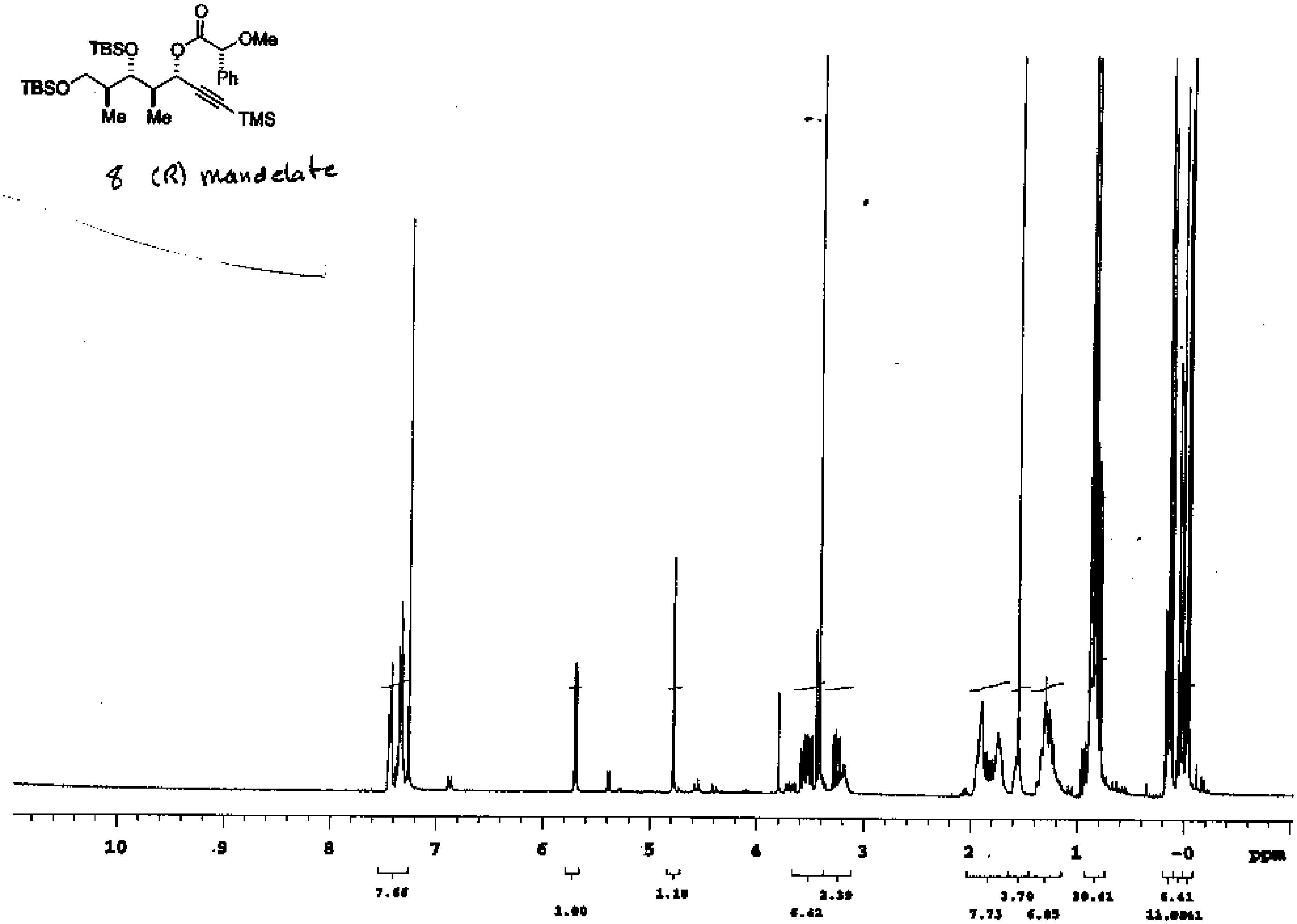
one

Pulse Sequence: s2pul

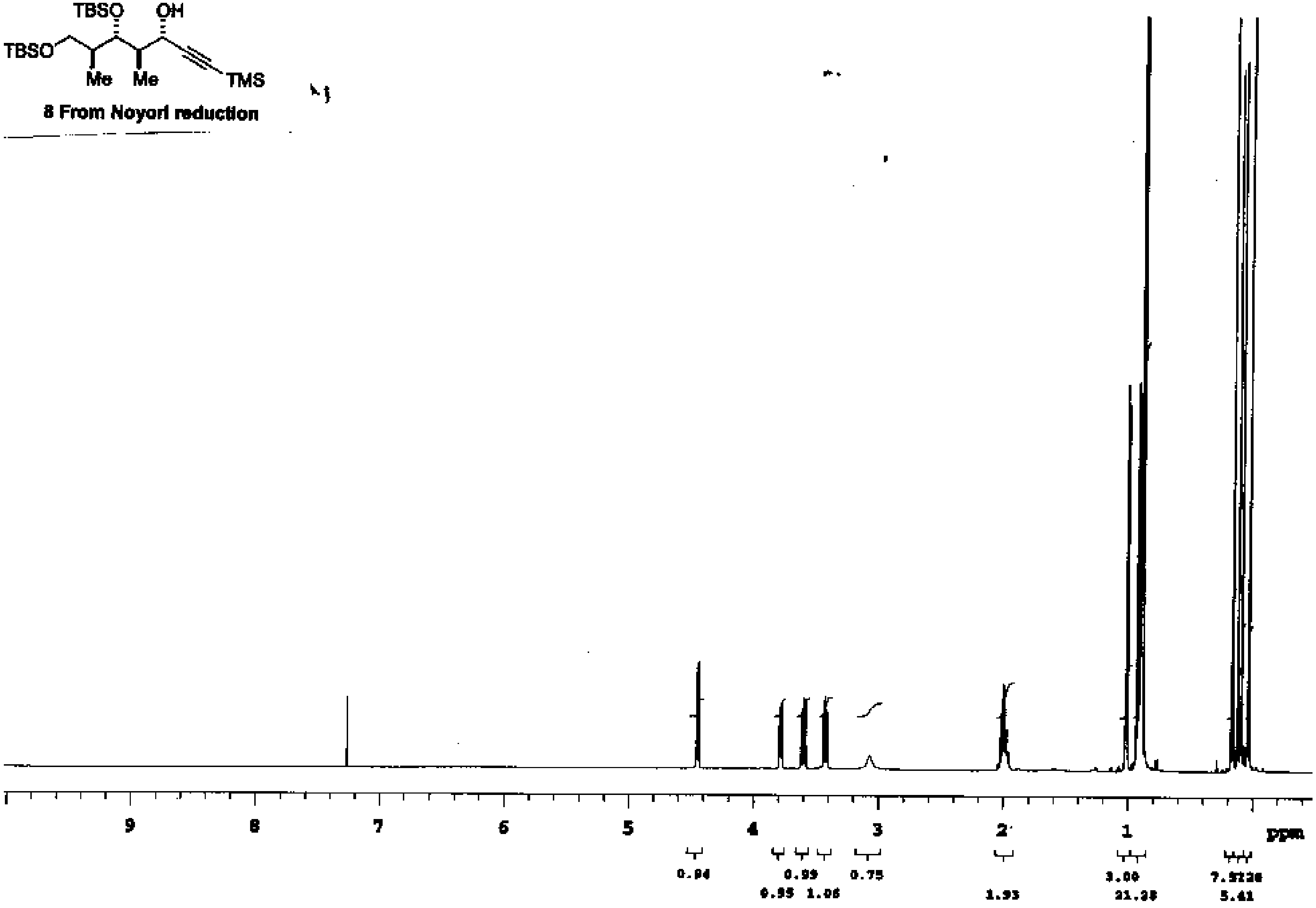


8 (S)-mandelate

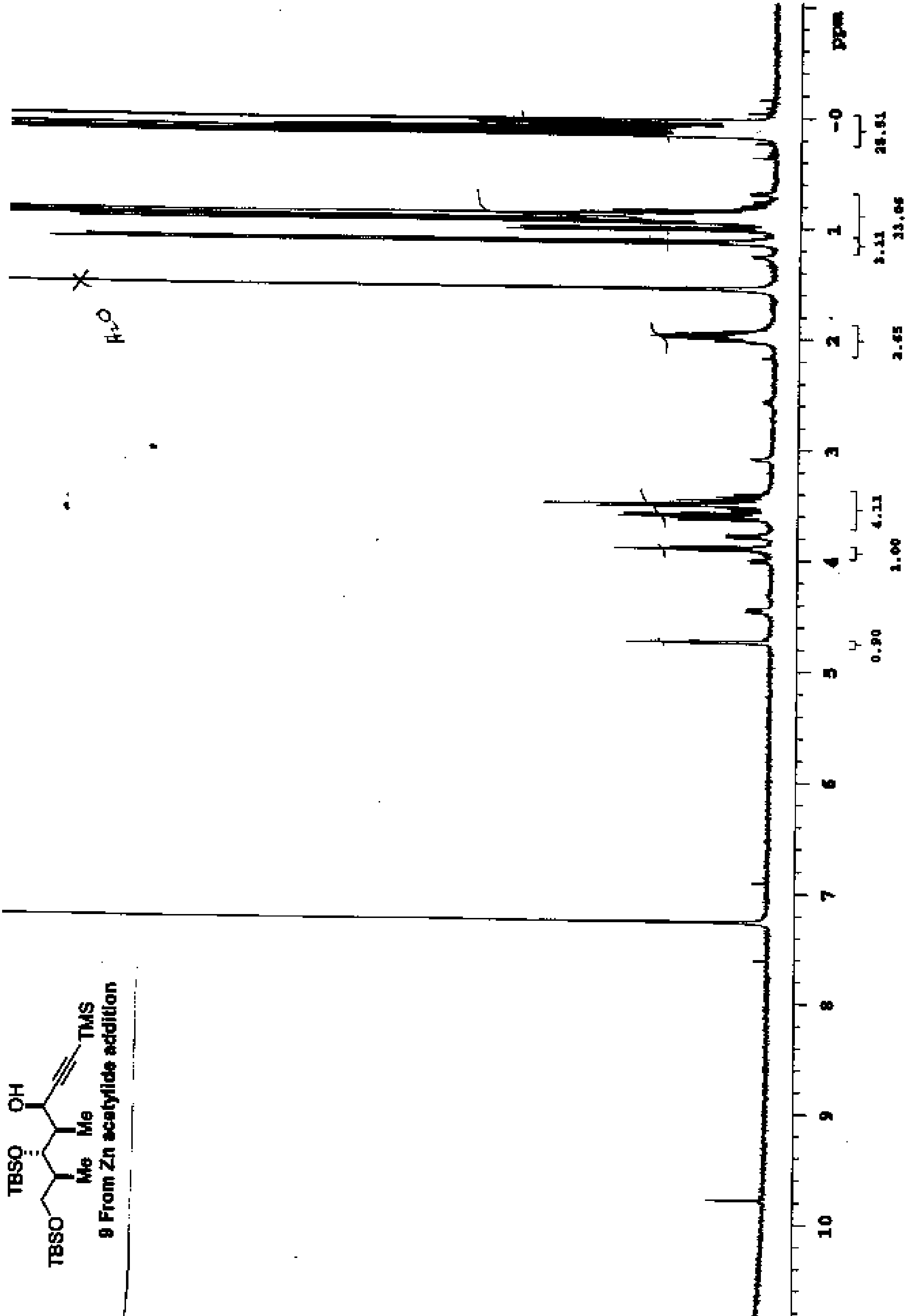




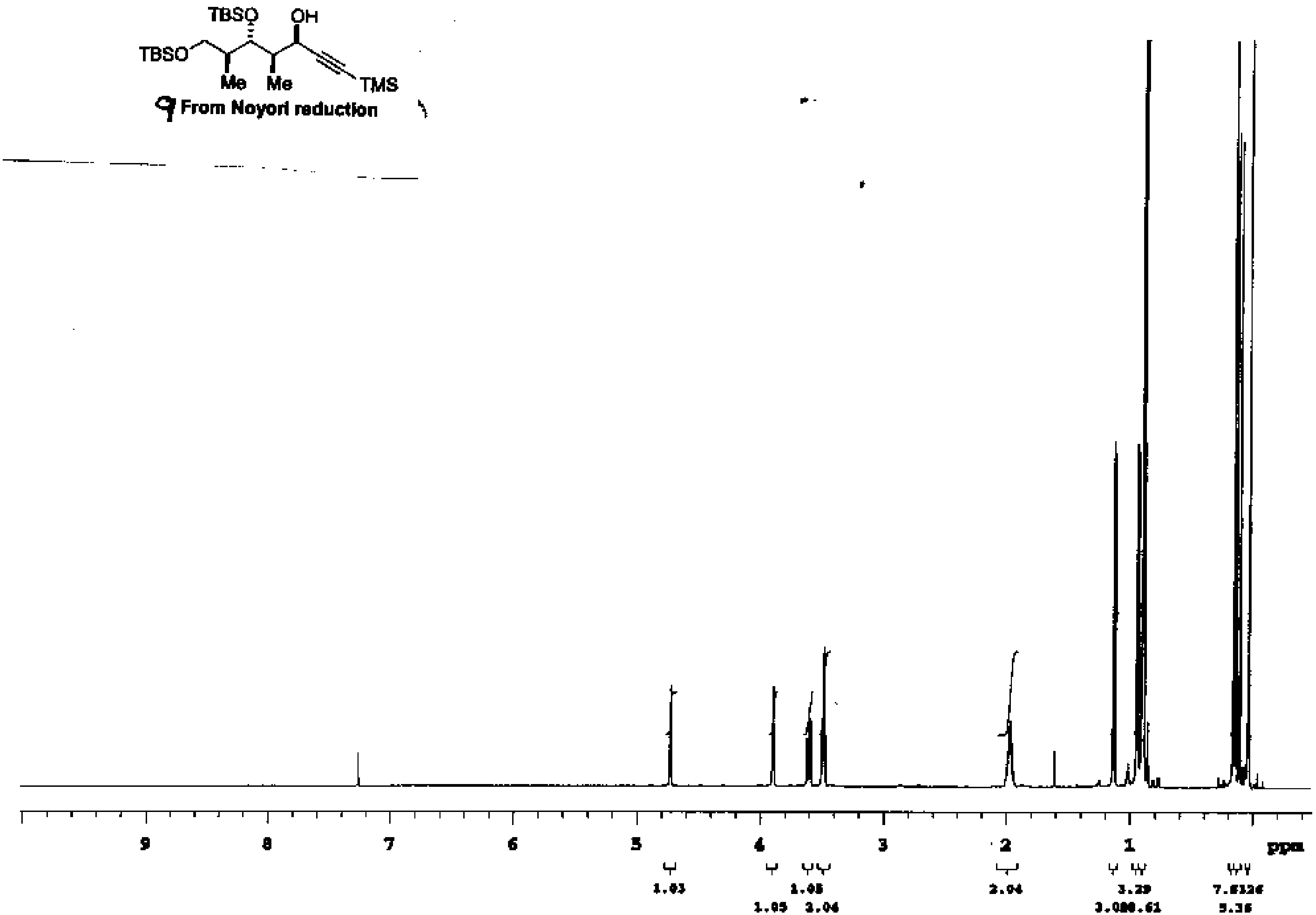
8 (R) mandelate



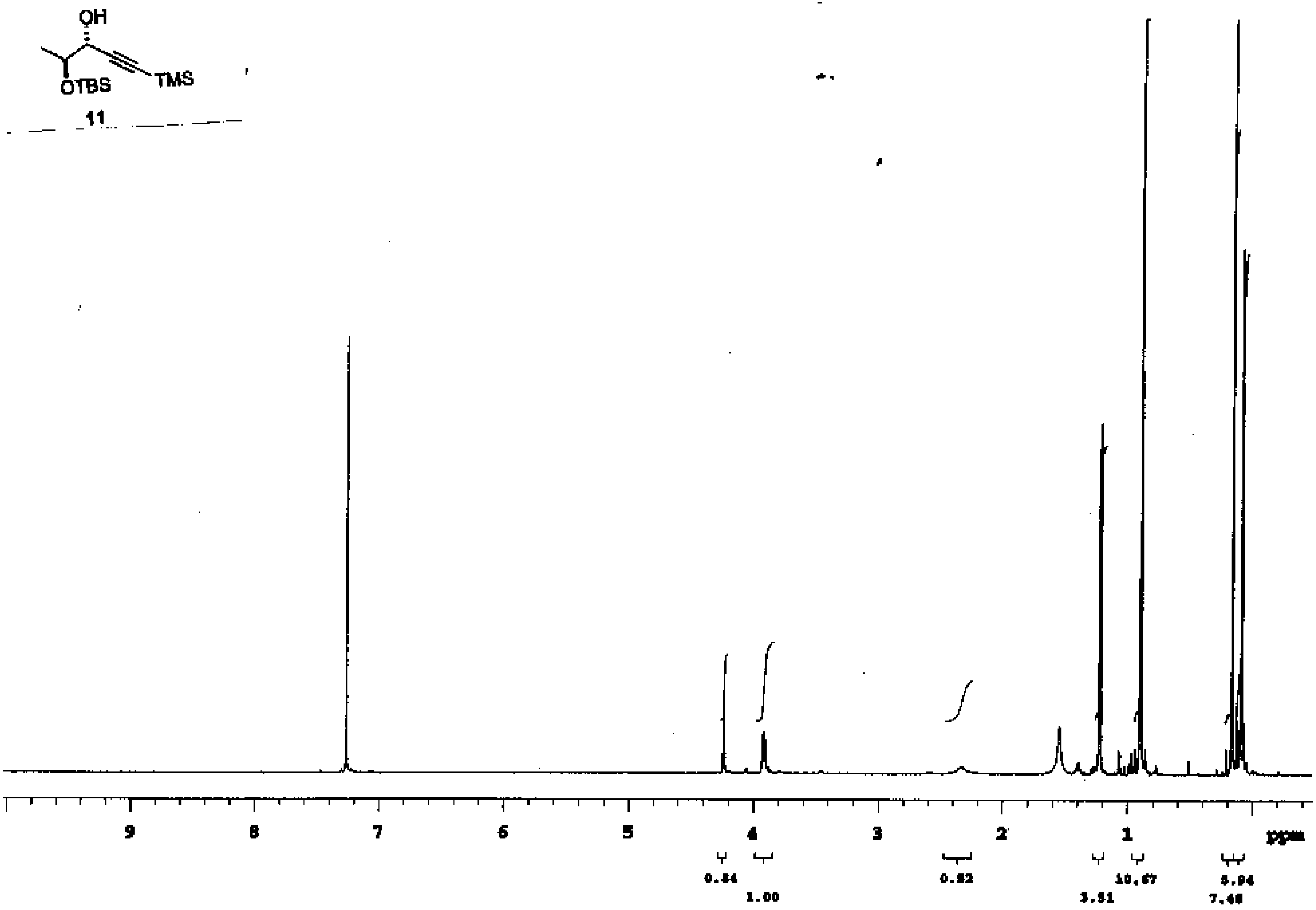
8 From Noyori reduction

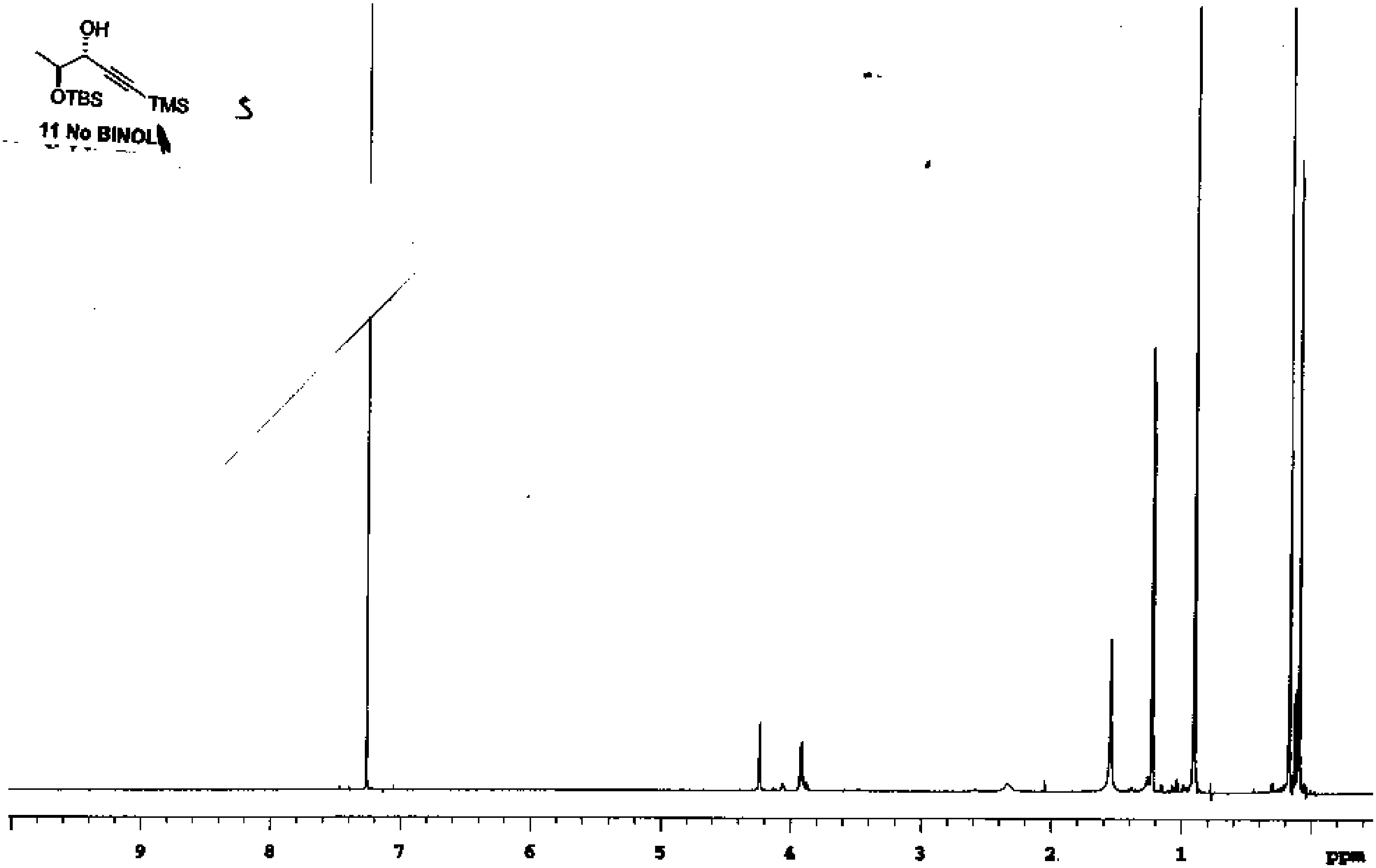


9 From Zn acetylide addition

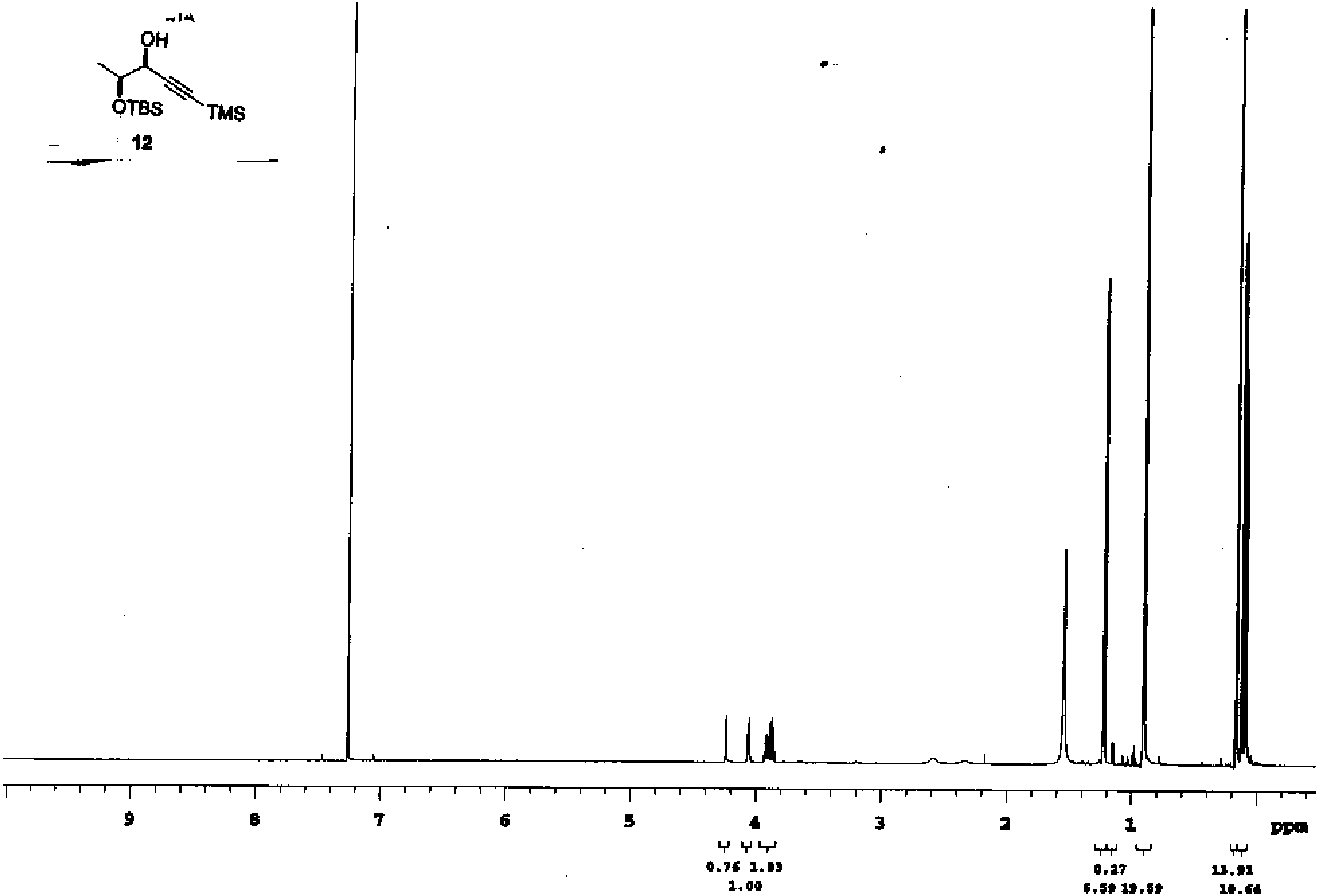


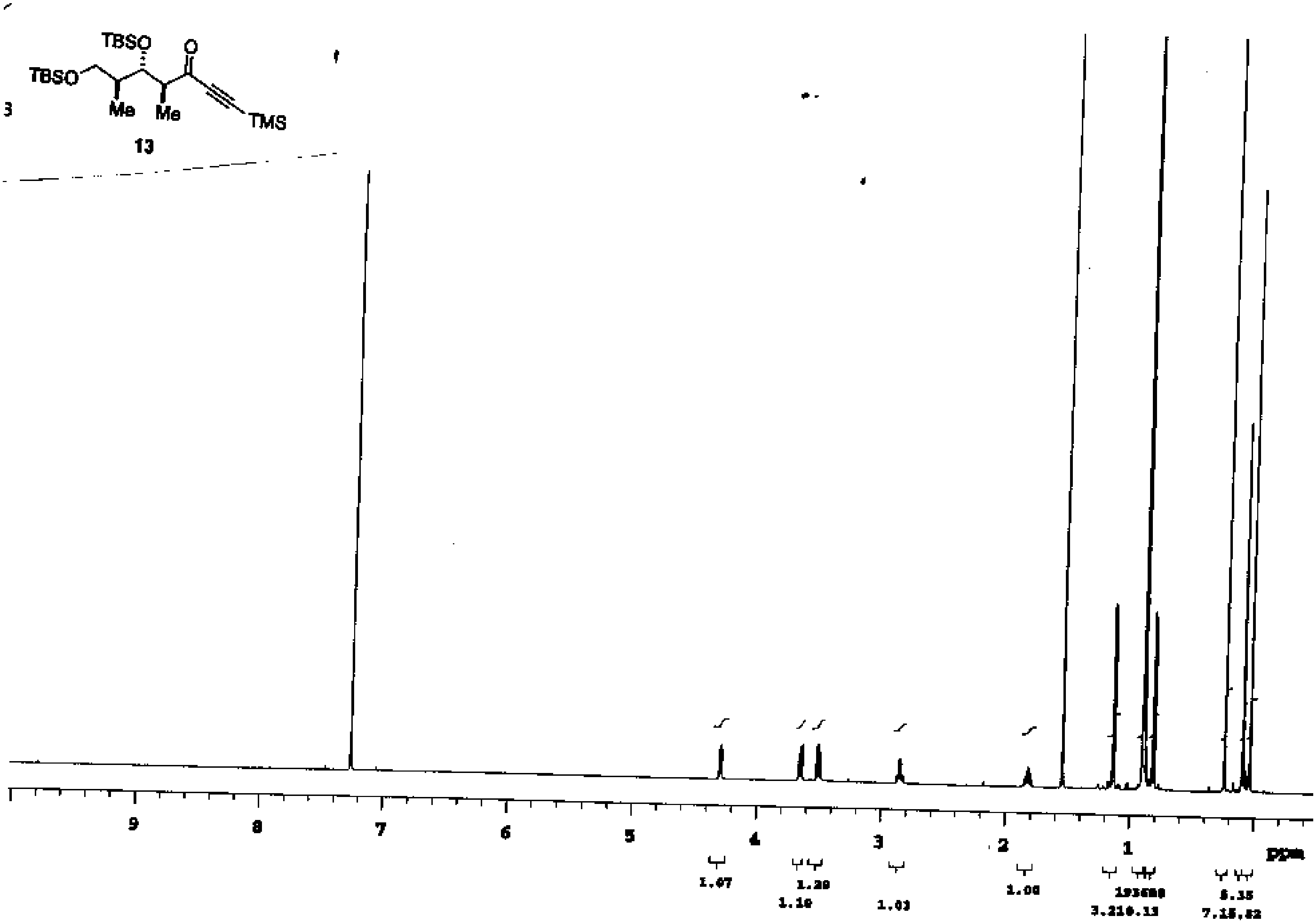
9 From Noyori reduction


11

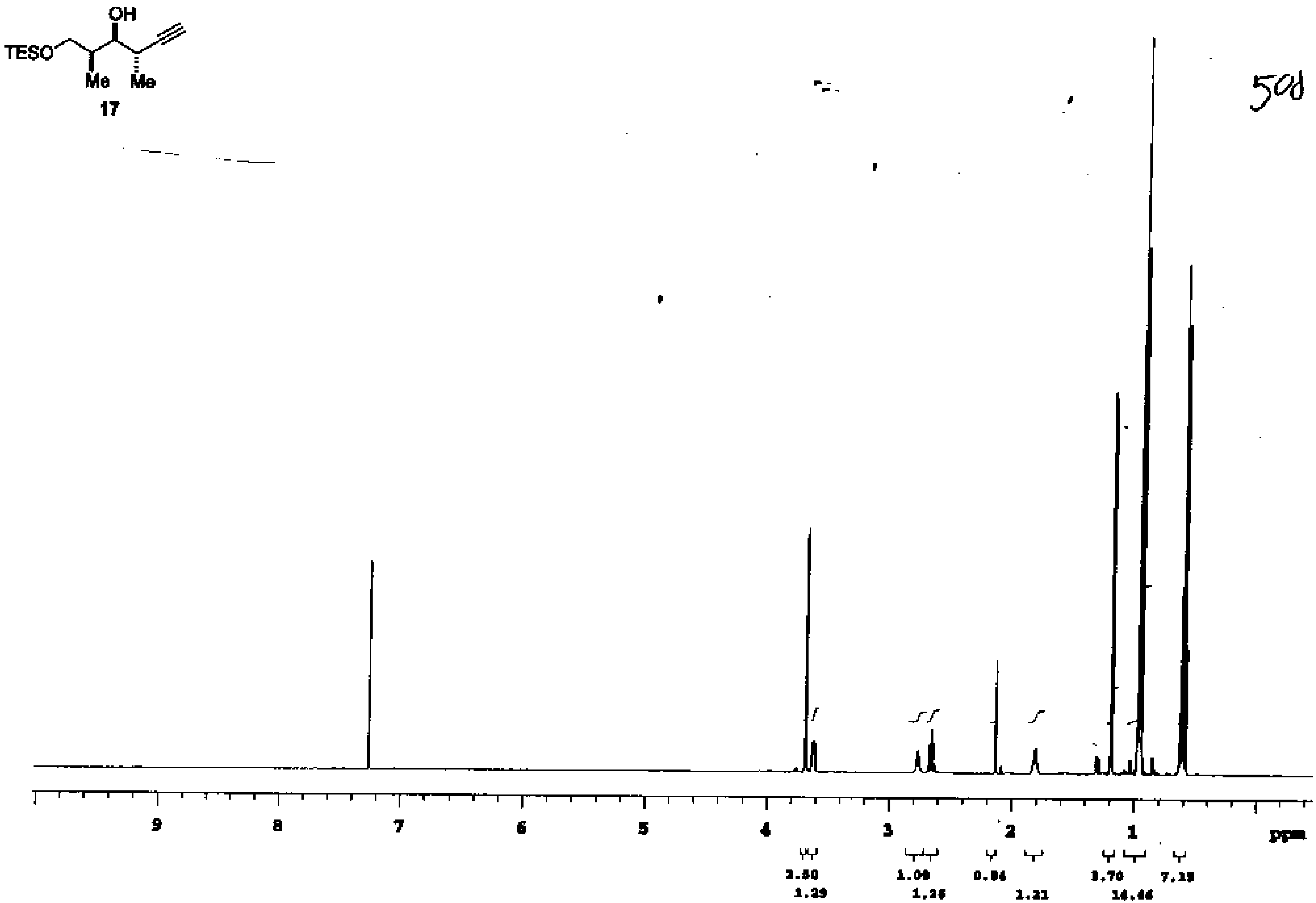


11 No BINOL


OH
OTBS
TMS
12
9
8
7
6
5
4
3
2
1
ppm
0.76 1.83
1.00
0.27
6.59 19.59
13.91
10.66

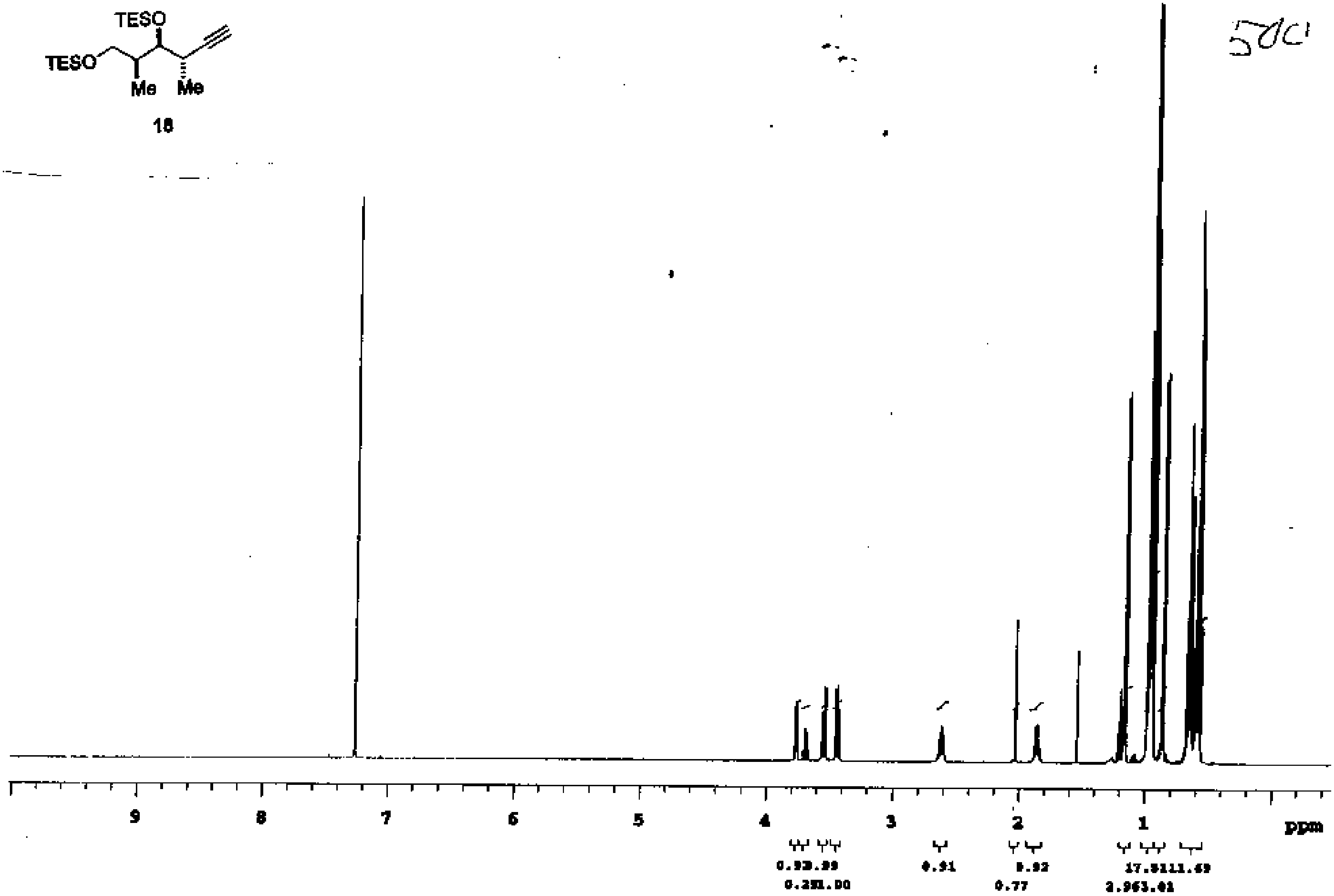

13

TBSO
TBSO
O
Me
Me
TMS
9
8
7
6
5
4
3
2
1
ppm
1.07
1.10
1.20
1.03
1.00
193680
3.210.13
6.15
7.15.82


TESO
OH
Me
Me
9
8
7
6
5
4
3
2
1
ppm
2.50
1.29
1.00
1.26
0.84
1.21
3.70
14.46
7.15

17

508


TESO
TESO
Me
Me

18

5dCl

9
8
7
6
5
4
3
2
1
ppm
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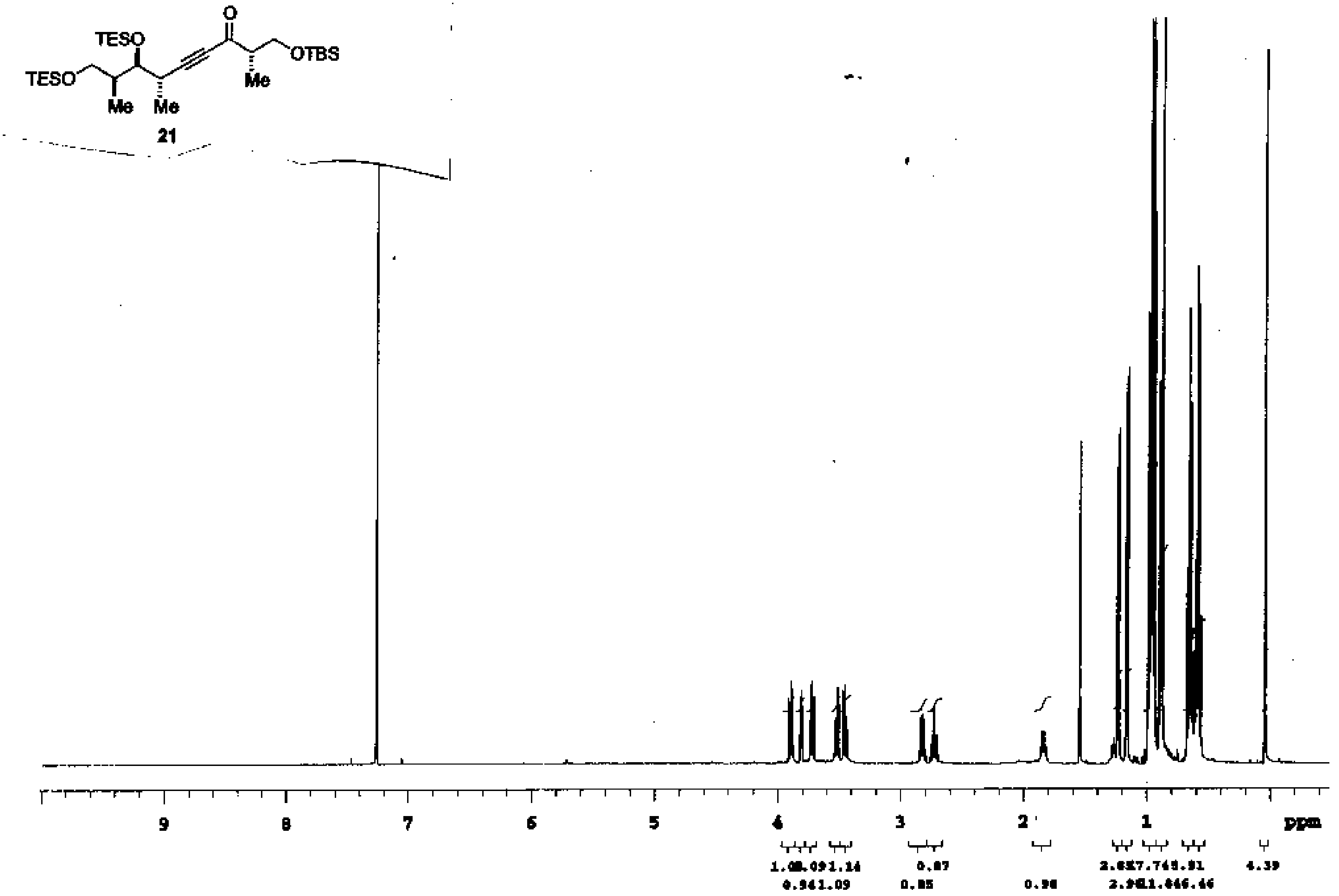
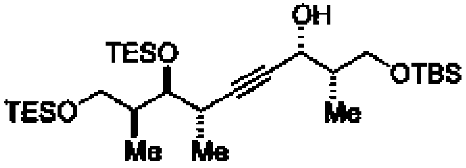
0.281.00
0.91
0.92
0.77
17.9111.69
2.963.01

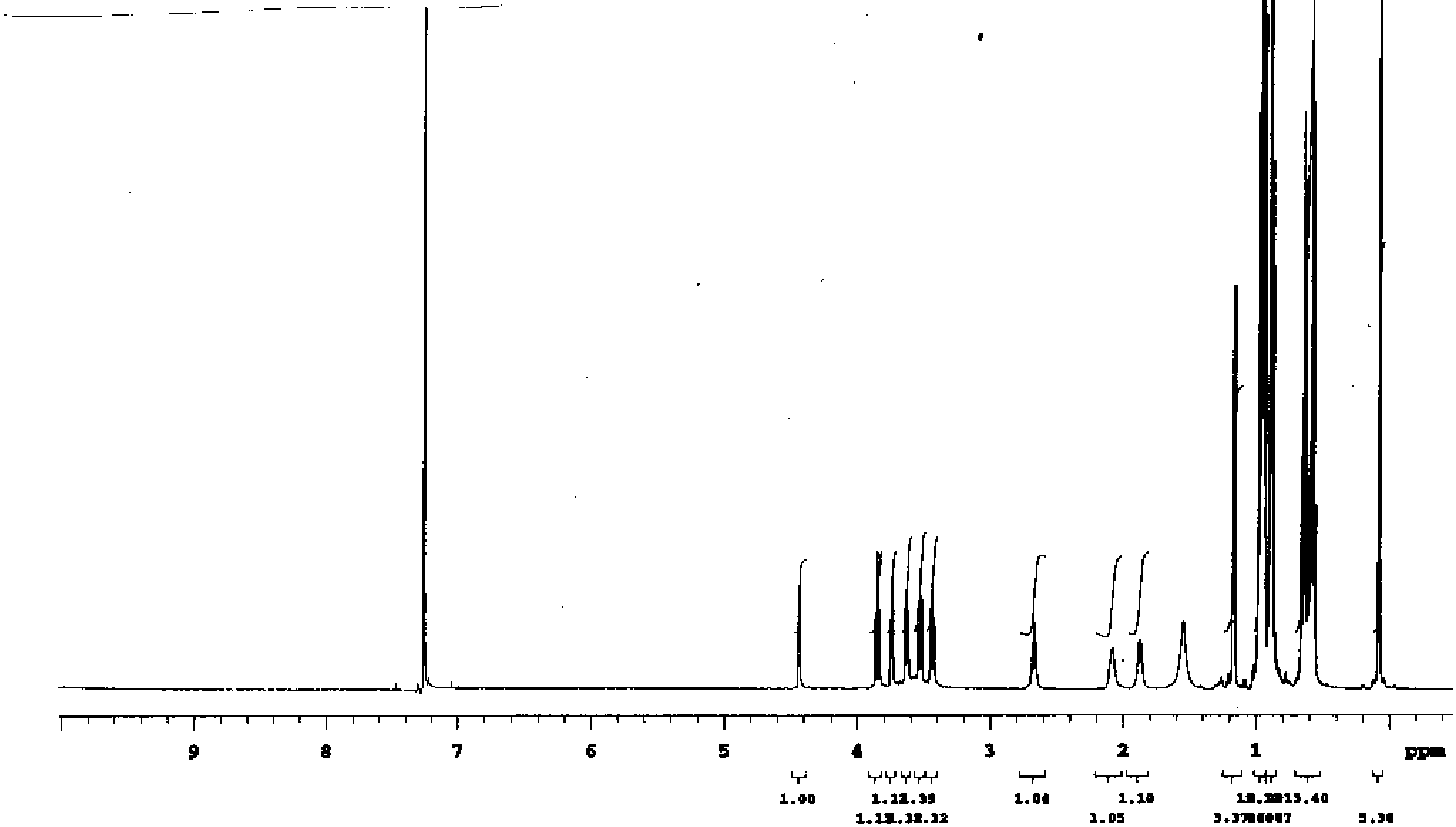

21

TESO
TESO
O
OTBS
Me
Me
Me
9
8
7
6
5
4
3
2
1
ppm
1.08.091.14
0.941.09
0.87
0.85
0.98
2.837.748.81
2.961.046.46
4.39



OH
TESO
TESO
OTBS
Me
Me
Me

22



9
8
7
6
5
4
3
2
1
ppm
1.00
1.04
1.05
1.10
13.40
5.36