

Enantioselective Synthesis of the [6,6] Spiroketal Core of Reveromycin A

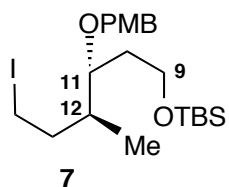
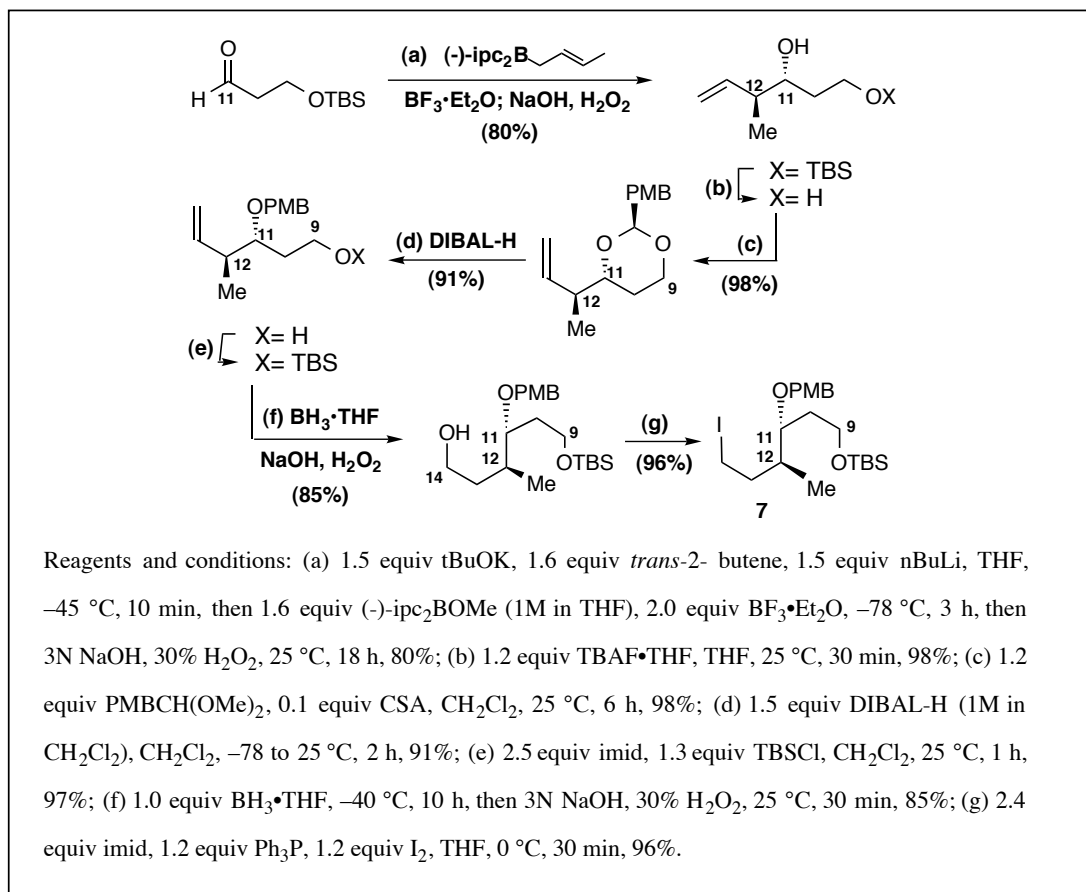
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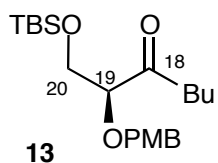
Supporting Information

General techniques. Organic solutions were concentrated by rotary evaporation below 45 °C at about 20 mmHg. All nonaqueous reactions were carried out using flame-dried glassware, under an argon atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. THF and Et₂O were distilled from sodium/benzophenone; CH₂Cl₂ and toluene from calcium hydride; and benzene from potassium. Pyridine, triethylamine and boron trifluoride etherate were distilled from calcium hydride prior to use. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on a Varian 400 MHz instrument and calibrated using residual undeuterated solvent as an internal reference. IR spectra were recorded on a Perkin-Elmer Model 781 spectrometer. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter. High resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions.

Preparation of iodide 7

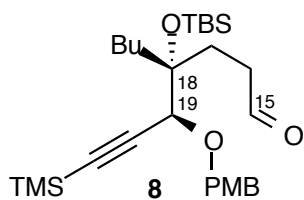


Iodide 7. light yellow oil; $R_f = 0.55$ (10% ether in hexanes); $[\alpha]^{25}_{\text{D}}: +16.1$ ($c = 1.0$, CH_2Cl_2); IR (film) ν_{max} 2957, 2936, 2863, 1614, 1515, 1254, 1092, 836; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.27 (d, 2H, $J = 8.0$ Hz), 6.88 (d, 2H, $J = 8.0$ Hz), 4.50 (d, 1H, $J = 11.5$ Hz), 4.42 (d, 1H, $J = 11.5$ Hz), 3.80 (s, 3H), 3.69-3.66 (m, 2H), 3.47-3.45 (m, 1H), 3.28-3.27 (m, 1H), 3.18-3.15 (m, 1H), 1.98-1.86 (m, 2H), 1.71-1.55 (m, 3H), 0.91 (d, 3H, $J = 7.0$ Hz), 0.88 (s, 9H), 0.035 (s, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 159.2, 131.1, 129.4, 113.8, 78.2, 71.3, 59.8, 55.2, 36.5, 36.0, 33.3, 25.9, 18.2, 13.9, 5.5, -5.4, -5.5; HRMS, calcd for $\text{C}_{21}\text{H}_{37}\text{IO}_3\text{Si}$ ($\text{M}+\text{Cs}^+$) 625.0609, found 625.0631.



Ketone 13. A solution of oxalyl chloride (8.0 ml, 91.8 mmol) in CH_2Cl_2 (150 ml) was cooled to $-78\text{ }^\circ\text{C}$ and treated with dimethylsulfoxide (7.8 ml, 110.1 mmol) added dropwise over 10 minutes. After stirring for 15 minutes, a solution of alcohol **18** (14.0 g, 36.7 mmol) in CH_2Cl_2 (30 ml) was slowly

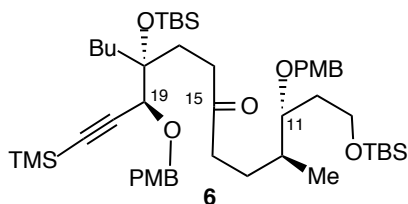
introduced. After additional stirring for 2 h at $-78\text{ }^\circ\text{C}$ the reaction was quenched with Et_3N (18.6 g, 183.5 mmol) and allowed to warm slowly to $25\text{ }^\circ\text{C}$. The reaction mixture was diluted with brine (300 ml) and CH_2Cl_2 (200 ml) and the aqueous layer was extracted with Et_2O (3 x 400 ml), dried (MgSO_4), filtered concentrated, and chromatographed (0-5% ether in hexanes) to afford ketone **13** (12.6 g, 33.0 mmol, 90%). **13**: light yellow oil; $R_f = 0.45$ (silica, 20% ether in hexanes); $[\alpha]_D^{25}$: -22.6 ($c = 1.1$, CH_2Cl_2); IR (film) ν_{max} 2956, 2858, 1717, 1514, 1250, 837; ^1H NMR (400 MHz, CDCl_3) δ 7.28 (d, 2H, $J = 8.5$ Hz), 6.88 (d, 2H, $J = 8.5$ Hz), 4.50 (d, 2H, $J = 4.8$ Hz), 3.87-3.84 (m, 3H), 3.83 (s, 3H), 2.58-2.53 (m, 2H), 1.54-1.50 (m, 2H), 1.32-1.27 (m, 2H), 0.91 (t, 3H, $J = 6.0$ Hz), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 211.6, 159.1, 129.4, 129.3, 113.7, 84.8, 72.2, 64.1, 55.3, 39.6, 25.9, 25.1, 22.5, 18.4, 14.1, -5.3 ; HRMS, calcd for $\text{C}_{21}\text{H}_{36}\text{O}_4\text{Si}$ ($\text{M}+\text{Cs}^+$) 513.1435, found 513.1442.



Aldehyde 8. A solution of the alkene **24** (5.20 g, 10.3 mmol) in $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{pyridine}$ (100 ml/100 ml/20 ml) at $-78\text{ }^\circ\text{C}$ was subjected to ozone over a period of 30 min. The reaction mixture was then flushed with argon, treated with triphenylphosphine (5.40 g, 20.6

mmol) and allowed to warm slowly to $25\text{ }^\circ\text{C}$. After stirring for 2 h, the reaction mixture was concentrated, and subjected to flash chromatography (0-15% ether in hexanes) to afford aldehyde **8** (4.42 g, 8.76 mmol, 85% yield). **8**: colorless oil; $R_f = 0.40$ (silica, 15% ether in hexanes); $[\alpha]_D^{25}$: $+28.1$ ($c = 1.25$, CH_2Cl_2); IR (film) ν_{max} 2957, 2931, 1729, 1520, 1259, 1097, 841; ^1H NMR (400 MHz, CDCl_3) δ 9.72 (d, 1H, $J = 1.0$ Hz), 7.26 (d, 2H, $J = 7.5$ Hz), 6.88 (d, 2H, $J = 7.5$ Hz), 4.75 (d, 1H, $J = 11.5$ Hz), 4.34 (d, 1H, $J = 11.0$ Hz), 3.91 (s, 1H), 3.80 (s, 3H), 2.43

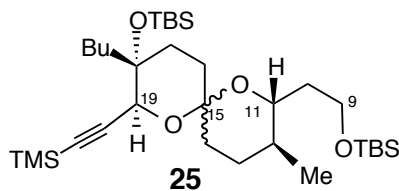
(m, 2H), 2.08-1.98 (m, 1H), 1.80-1.76 (m, 2H), 1.57-1.19 (m, 5H), 0.88 (t, 3H, $J= 6.5$ Hz), 0.84 (s, 9H), 0.18 (s, 9H), 0.055 (s, 3H), 0.035 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 203.0, 159.3, 129.9, 129.8, 113.7, 102.9, 93.1, 78.8, 74.4, 70.1, 55.2, 38.6, 36.9, 28.7, 26.0, 25.6, 23.2, 18.6, 13.9, -0.27, -2.25, -2.40; HRMS, calcd for $\text{C}_{28}\text{H}_{48}\text{O}_4\text{Si}_2$ ($\text{M}+\text{Cs}^+$) 637.2144, found 637.2161.



Ketone 6. A solution of the iodide **7** (4.83 g, 9.81 mmol) in Et_2O (50 ml) was cooled to -78 °C and treated with tert-butyllithium (11.5 ml of 1.7 M solution in pentane, 19.6 mmol). After stirring for 20 min, a solution of the aldehyde **8**

(3.07 g, 6.08 mmol) in Et_2O (30 ml) was added and the mixture was stirred for an additional 0.5 h. The reaction was quenched with aqueous saturated ammonium chloride (10 ml) and the mixture was warmed to 25 °C and diluted with Et_2O (50 ml). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 x 50 ml). The organic layers were combined, dried (MgSO_4), filtered, and concentrated under reduced pressure. The residue was subjected to flash chromatography (0-15% ether in hexanes) to afford the C15-alcohol as a colorless oil. This alcohol was redissolved in CH_2Cl_2 (100 ml) and treated at 25 °C with Dess-Martin periodinane (3.87 g, 9.12 mmol). After stirring for 1 h, the reaction was quenched with aqueous saturated sodium thiosulfate (50 ml) and aqueous saturated sodium bicarbonate (50 ml) and diluted with Et_2O (100 ml). The aqueous layer was extracted with Et_2O (3 x 100 ml), the organic layers were combined, dried (MgSO_4), filtered, and concentrated. The residue was subjected to flash chromatography (0-10% ether in hexanes) to afford ketone **6** (4.1 g, 4.74 mmol, 79% over two steps). **6**: colorless oil; $R_f= 0.50$ (20% ether in hexanes); $[\alpha]_D^{25}$: +51.5 ($c= 1.0$, CH_2Cl_2); IR (film) ν_{max} 2962, 2931, 1719, 1614, 1510, 1468, 1254, 1087, 836; ^1H NMR (400 MHz, CDCl_3) δ 7.26 (d, 2H, $J= 8.5$ Hz), 7.25 (d, 2H, $J= 8.5$ Hz), 6.87 (d, 2H, $J= 8.5$ Hz), 6.86 (d, 2H, $J= 8.5$ Hz), 4.75 (d, 1H, $J= 11.5$ Hz), 4.47 (d, 1H, $J= 10.5$ Hz), 4.37 (d, 1H, $J= 11.0$ Hz),

4.36 (d, 1H, J= 11.0 Hz), 3.90 (s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.70-3.67 (m, 2H), 3.43 (m, 1H), 2.46-2.33 (m, 4H), 1.98-1.92 (m, 1H), 1.78-1.63 (m, 3H), 1.63-1.55 (m, 3H), 1.54-1.50 (m, 1H), 1.40-1.34 (m, 1H), 1.28-1.19 (m, 4H), 0.88-0.84 (m, 24H), 0.19 (s, 9H), 0.057 (s, 3H), 0.034-0.027 (m, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 211.3, 159.3, 159.1, 131.2, 129.9, 129.8, 129.3, 113.7, 113.6, 103.2, 92.7, 79.0, 78.9, 74.5, 71.2, 70.1, 59.9, 55.2, 55.1, 40.7, 37.1, 36.8, 34.7, 33.0, 30.4, 26.8, 26.0, 25.9, 25.7, 23.3, 18.6, 18.2, 14.2, 13.9, -0.24, -2.26, -2.39, -5.42, -5.46; HRMS, calcd for $\text{C}_{49}\text{H}_{84}\text{O}_7\text{Si}_3$ ($\text{M}+\text{Cs}^+$) 1001.4579, found 1001.4599.

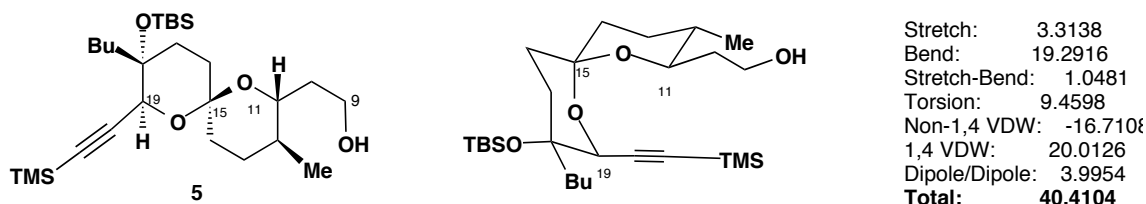


Spiroketal 25. A solution of ketone **6** (3.17 g, 3.64 mmol) in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (25 ml/1 ml) was treated with 2,3-dichloro-4,5-dicyanobenzoquinone (2.48 g, 10.9 mmol) at 25 °C. After

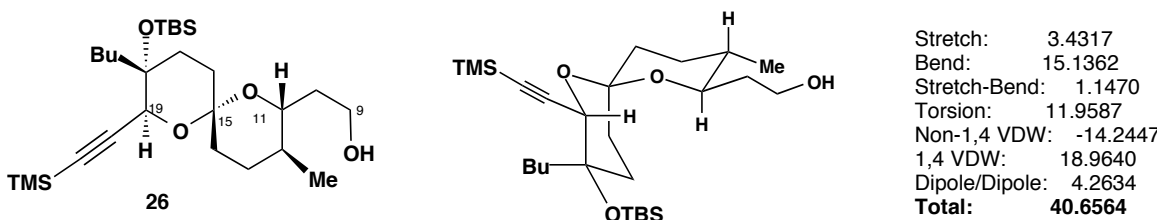
stirring for 2 h, the mixture was diluted with aqueous saturated sodium bicarbonate (100 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The organic layer was collected, dried (MgSO_4), filtered and concentrated. The residue was subjected to flash chromatography (0-2% ether in hexanes) to afford spiroketal **25** as a mixture of diastereomers at the C15 carbon center (1.78 g, 2.91 mmol, 81% combined yield). **25** (top diastereomer): colorless gum; R_f = 0.50 (4% ether in hexanes); $[\alpha]_D^{25}$: +21.1 (c = 1.25, CH_2Cl_2); IR (film) ν_{max} 2962, 2857, 1719, 1614, 1510, 1468, 1254, 836; ^1H NMR (400 MHz, CDCl_3) δ 4.24 (s, 1H), 3.80-3.70 (m, 3H), 2.04-1.67 (m, 6H), 1.55-1.24 (m, 11H), 0.91-0.90 (m, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.85-0.84 (m, 3H), 0.11 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 105.1, 95.9, 88.9, 74.8, 73.2, 70.9, 59.0, 37.8, 35.0, 34.3, 33.2, 32.1, 28.4, 27.8, 25.9, 25.8, 24.3, 23.2, 18.5, 18.2, 17.7, 14.0, -0.2, -2.3, -2.5; HRMS, calcd for $\text{C}_{33}\text{H}_{66}\text{O}_4\text{Si}_3$ ($\text{M}+\text{Cs}^+$) 743.3323, found 743.3341. **25** (bottom diastereomer): colorless gum; R_f = 0.45 (4% ether in hexanes); $[\alpha]_D^{25}$: +38.2 (c = 1.0, CH_2Cl_2); IR (film) ν_{max} 2964, 2931, 2857, 1718, 1612, 1510, 1468, 1251, 1085; ^1H NMR (400 MHz, CDCl_3) δ 4.73 (s, 1H), 3.80 (t, 2H, J = 7.0 Hz), 3.26-3.19 (m, 1H), 2.19-2.17 (m, 1H), 1.84-1.60 (m, 8H), 1.43-1.17 (m, 8H), 0.91 (t, 3H, J = 7.5 Hz),

0.88 (s, 9H), 0.87 (s, 9H), 0.82 (d, 3H, J= 6.5 Hz), 0.13 (s, 9H), 0.80 (s, 3H), 0.06 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 103.0, 97.2, 90.6, 75.5, 74.0, 70.3, 59.7, 36.7, 35.8, 34.6, 31.2, 29.6, 29.3, 26.5, 25.81, 25.80, 24.8, 23.1, 18.3, 18.0, 17.4, 14.0, -0.3, -2.0, -2.1; HRMS, calcd for $\text{C}_{33}\text{H}_{66}\text{O}_4\text{Si}_3$ ($\text{M}+\text{Cs}^+$) 743.3323, found 743.3346.

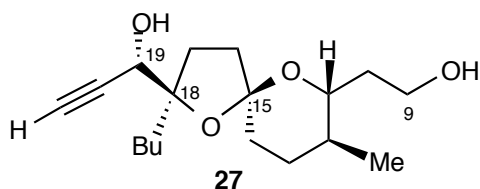
Spiroketal 5 and 26. A solution of spiroketal **25** (mixture of diastereomers at C15) (0.202 g, 0.328 mmol) in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (2.5/0.5 ml) at 25 °C was treated with camphorsulphonic acid (8 mg, 0.035 mmol) for 1 h. The reaction mixture was quenched with triethylamine (0.5 ml) and the residue concentrated and subjected to flash chromatography (5-20% ether in hexanes) to afford spiroketals **5** and **26** as a 1.5:1 mixture of diastereomers in favor of **5** (161 mg, 0.321 mmol, 98% combined yield).



Spiroketal 5 (major diastereomer, 96 mg, 0.193 mmol, 59%); white solid; $R_f = 0.25$ (33% ether in hexanes); $[\alpha]_D^{25}$: +41.2 ($c = 1.1$, CH_2Cl_2); IR (film) ν_{max} 3364, 2953, 2857, 1719, 1614, 996; ^1H NMR (500 MHz, C_6D_6) δ 4.53 (s, 1H), 4.12-4.10 (m, 1H), 3.94-3.90 (m, 2H), 2.75 (bs, 1H), 2.09-2.06 (m, 2H), 1.86-1.66 (m, 6H), 1.49-1.29 (m, 9H), 0.97 (s, 12H), 0.65 (t, 3H, J= 6.5 Hz), 0.22 (s, 9H), 0.10 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 105.9, 96.1, 89.9, 76.4, 75.1, 71.3, 60.0, 38.9, 35.5, 34.4, 33.5, 32.2, 28.1, 27.6, 26.3, 26.0, 24.6, 23.5, 18.6, 17.6, 14.1, -0.24, -2.42, -2.55; HRMS, calcd for $\text{C}_{27}\text{H}_{52}\text{O}_4\text{Si}_2$ ($\text{M}+\text{Cs}^+$) 629.2455, found 629.2478.

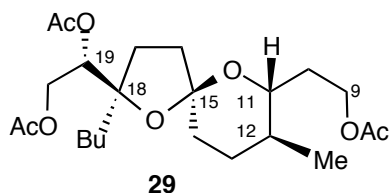


Spiroketal 26 (minor diastereomer, 64 mg, 0.129 mmol, 39%); white solid; $R_f = 0.22$ (33% ether in hexanes); $[\alpha]_D^{25}$: +30.1 (c= 1.1, CH₂Cl₂); IR (film) ν_{\max} 3364, 2953, 2858, 1719, 1615, 996; ¹H NMR (400 MHz, C₆D₆) δ 5.05 (s, 1H), 3.73-3.70 (m, 1H), 3.61-3.55 (m, 1H), 3.02-2.98 (m, 1H), 2.16-2.00 (m, 2H), 1.85-1.60 (m, 7H), 1.50-1.30 (m, 9H), 1.09 (s, 9H), 1.01 (t, 3H, J= 7.2 Hz), 0.56 (d, 3H, J= 6.8 Hz), 0.36 (s, 3H), 0.28 (s, 3H), 0.14 (s, 9H); ¹³C NMR (100 MHz, C₆D₆) δ 104.4, 97.3, 90.4, 76.8, 74.7, 70.8, 60.0, 36.7, 36.1, 35.3, 32.4, 30.2, 29.7, 27.2, 26.4, 25.7, 24.0, 19.0, 17.7, 14.7, 0.19, -1.3, -1.4; HRMS, calcd for C₂₇H₅₂O₄Si₂ (M+C_s⁺) 629.2455, found 629.2484.

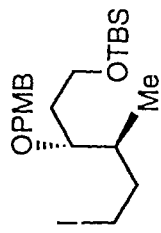


Spiroketal 27. A solution of spiroketal **25** (mixture of diastereomers at C15) (0.35 g, 0.573 mmol) in CH₂Cl₂ (3 ml) at 0 °C was treated with a solution of HF in pyridine (3.0 ml) and allowed stir for 1 h. The reaction was quenched with Et₃N (2 ml) and diluted with aqueous saturated sodium bicarbonate (20 ml). The reaction mixture was extracted with CH₂Cl₂ (3 x 30 ml) and the organic layer was separated, combined, dried (MgSO₄), filtered and concentrated. The crude residue was carried to the next reaction. A solution of the crude 5,6-spiroketal (18 mg, 0.047 mmol) in THF (0.30 ml) was treated with a 1M solution of TBAF in THF (100 μ l) and stirred at 25 °C for 15 minutes. The reaction mixture was quenched with saturated NH₄Cl (5 ml), diluted with Et₂O (10 ml). The layers were partitioned and the aqueous layer was extracted with Et₂O (2x5 ml). The organic layers were combined, washed with brine (5 ml), dried over MgSO₄, filtered, and subjected to flash chromatography (10-25% ether in hexanes) to afford the 5,6-spiroketal **27** (14 mg, 0.046 mmol, 80%). **27**: colorless oil; $R_f = 0.30$ (70% ether in hexanes); $[\alpha]_D^{25}$: +67.8 (c= 0.33, CH₂Cl₂); IR (film) ν_{\max} 3366, 2953, 2929, 2867, 1470, 1377, 1051, 996; ¹H NMR (400 MHz, CDCl₃) δ 4.39 (d, 1H, J= 2.0 Hz), 3.83-3.79 (m, 1H), 3.72-3.65 (m, 2H), 2.54 (bs, 2H), 2.45-2.41 (m, 1H), 2.39 (d, 1H, J= 2.0 Hz), 2.05-1.83 (m, 3H), 1.76-1.50 (m, 7H), 1.41-1.20 (m, 6H), 0.91 (t, 3H, J= 6.5 Hz), 0.86 (d, 3H, J= 6.0

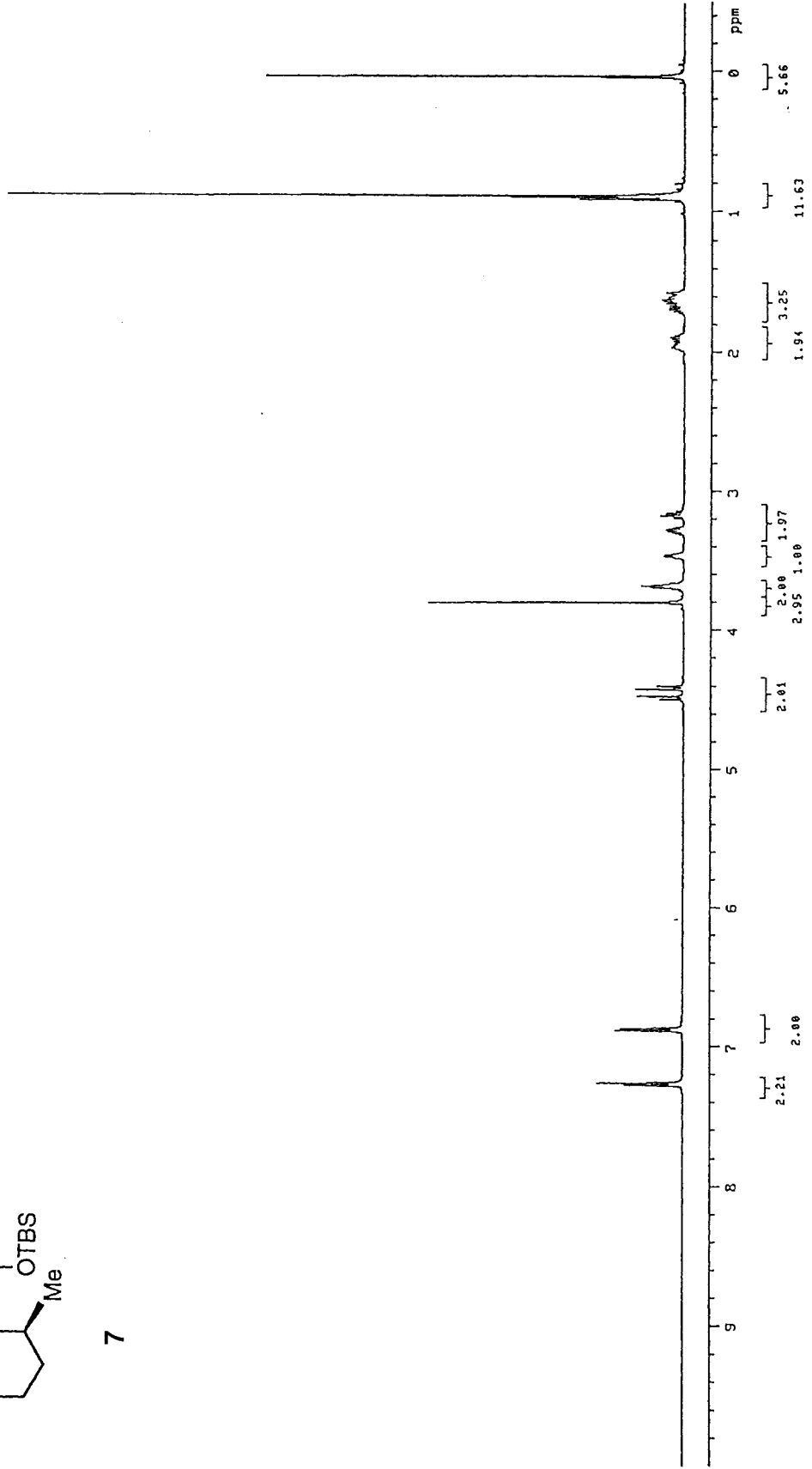
Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 107.4, 90.7, 82.6, 75.3, 73.4, 67.1, 59.1, 39.1, 36.6, 35.0, 34.4, 28.8, 28.1, 25.3, 23.1, 17.6, 14.0; HRMS, calcd for $\text{C}_{18}\text{H}_{30}\text{O}_4$ ($\text{M}+\text{Cs}^+$) 443.1195, found 443.1211.

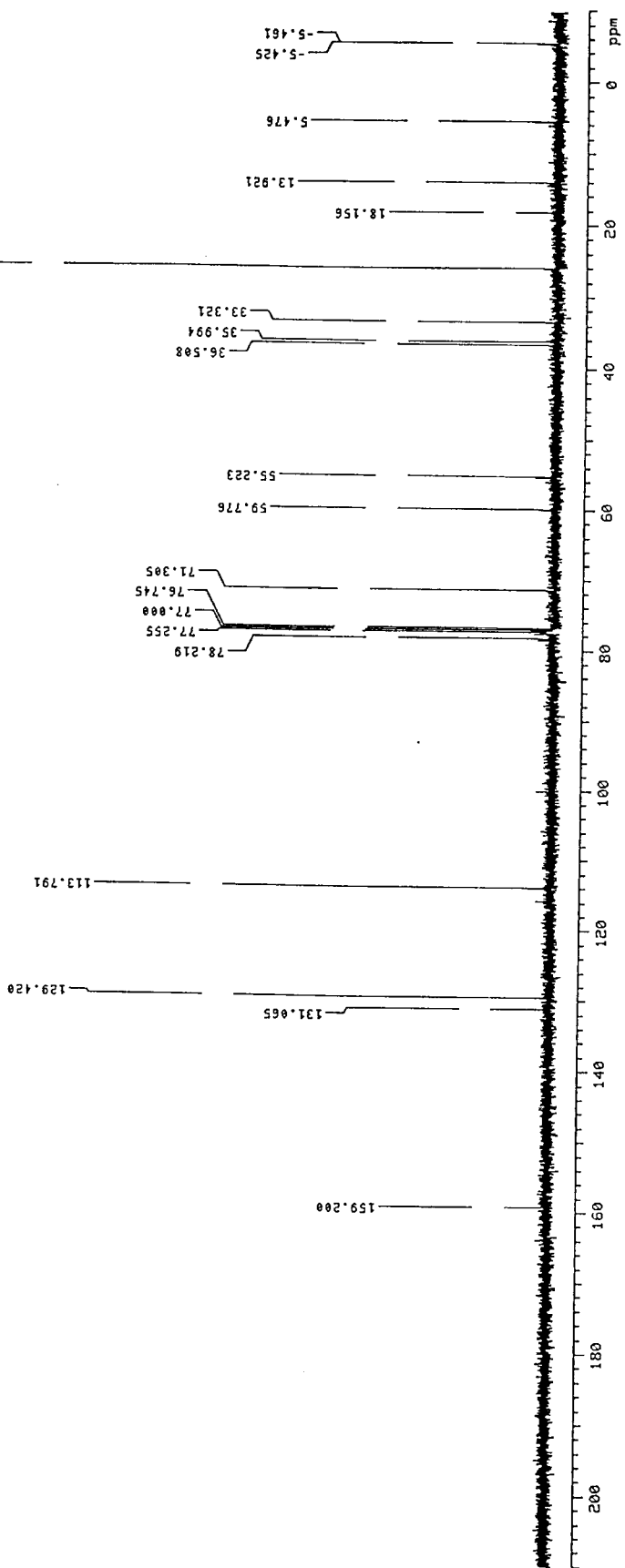
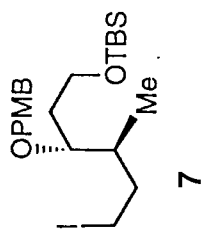


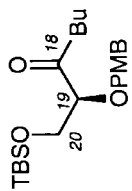
Triacetate 29. A solution of the alkene **28** (6 mg, 0.019 mmol) in MeOH (2 ml) was cooled to $-78\text{ }^\circ\text{C}$ and treated with ozone until the starting material was consumed (tlc test, ca 2 min). The mixture was then purged with oxygen (2 min) and argon (1 min). The reaction mixture was treated with NaBH_4 (4 mg, 0.010 mmol) at $-78\text{ }^\circ\text{C}$ and stirred to $25\text{ }^\circ\text{C}$. After 1.5 h. the mixture was diluted with a saturated solution of NH_4Cl (4 ml), CH_2Cl_2 (10 ml), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 5 ml), dried (MgSO_4), concentrated and taken on crude to the next step. A solution of the crude triol in CH_2Cl_2 (500 μl) was treated with pyridine (10 μl , 0.12 mmol) and acetic anhydride (6 μl , 66 mmol) at $25\text{ }^\circ\text{C}$ for 2 hours. The reaction mixture was diluted with ether (10 ml) and washed with a saturated solution of NaHCO_3 (2 x 5 ml). The organic layer was dried (MgSO_4), concentrated and subjected to flash chromatography (silica, 0-25% ether in hexanes) to afford triacetate **29** (7.4 mg, 0.017 mmol, 83% yield). **29**: colorless liquid; $R_f = 0.45$ (silica, 30% ether in hexanes); $[\alpha]_D^{25}$: +37.5 ($c = 1.0$, CHCl_3); IR (film) ν_{max} 2931, 2868, 1745, 1463, 1369, 1238, 1050, 1083, 993, 923; ^1H NMR (400 MHz, CDCl_3) δ 5.19 (dd, 1H, $J = 9.0, 2.5$ Hz), 4.52 (dd, 1H, $J = 12.0, 2.0$ Hz), 4.34-4.26 (m, 1H), 4.24 (dd, 1H, $J = 12.0, 8.5$ Hz), 4.18-4.13 (m, 1H), 3.49 (ddd, 1H, $J = 10.8, 8.0, 2.8$ Hz), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.96-1.50 (m, 11H), 1.31-1.25 (m, 6H), 0.91 (t, 3H, $J = 7.0$ Hz), 0.87 (d, 3H, $J = 6.5$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 171.27, 171.25, 170.4, 107.0, 86.2, 73.6, 63.9, 61.7, 38.4, 34.5, 34.4, 34.2, 32.1, 31.3, 29.6, 29.0, 25.4, 23.1, 21.0, 20.9, 20.7, 17.6, 14.0; HRMS, calcd for $\text{C}_{23}\text{H}_{38}\text{O}_8$ ($\text{M}+\text{Cs}^+$) 575.1619, found 575.1632.



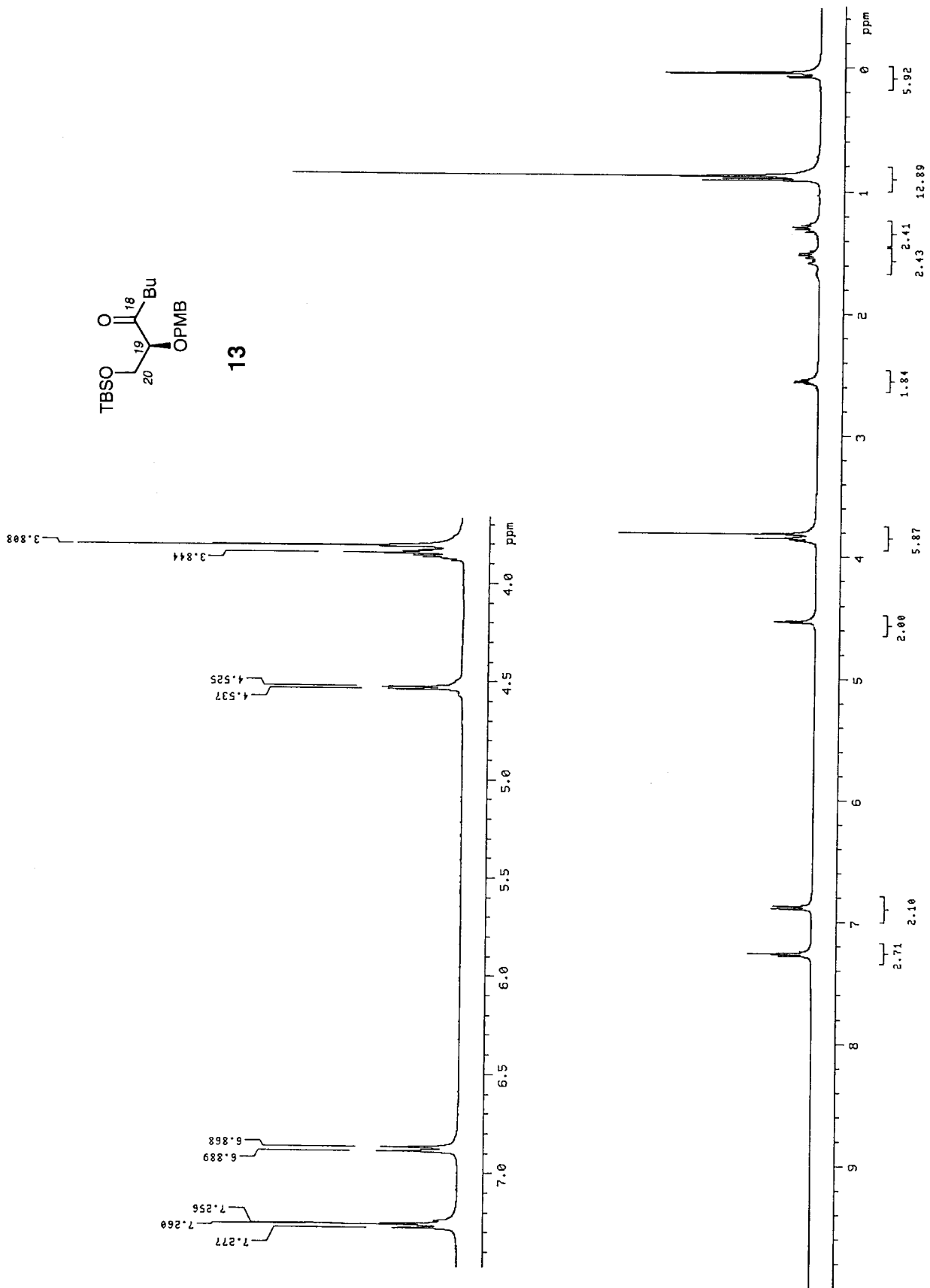
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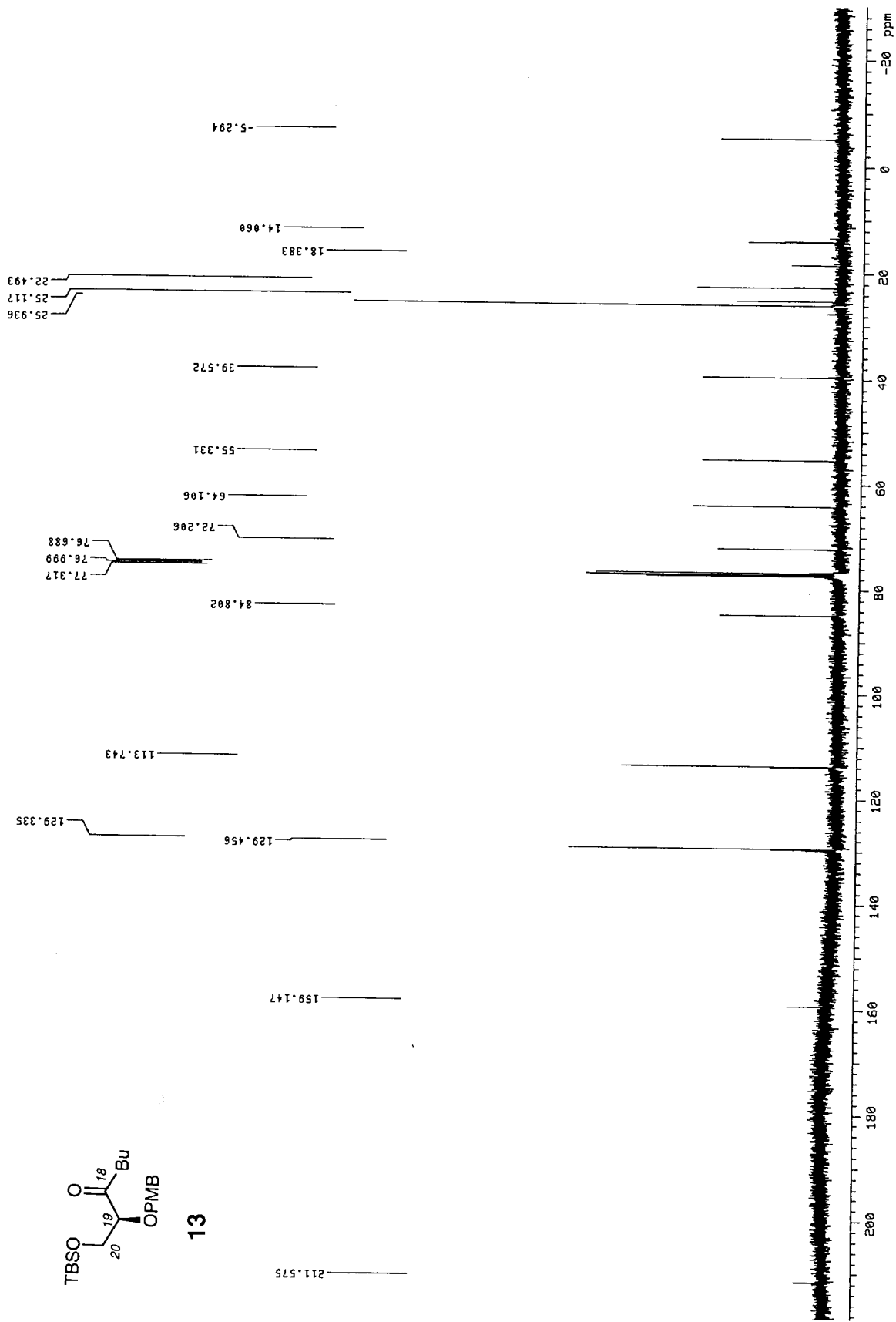


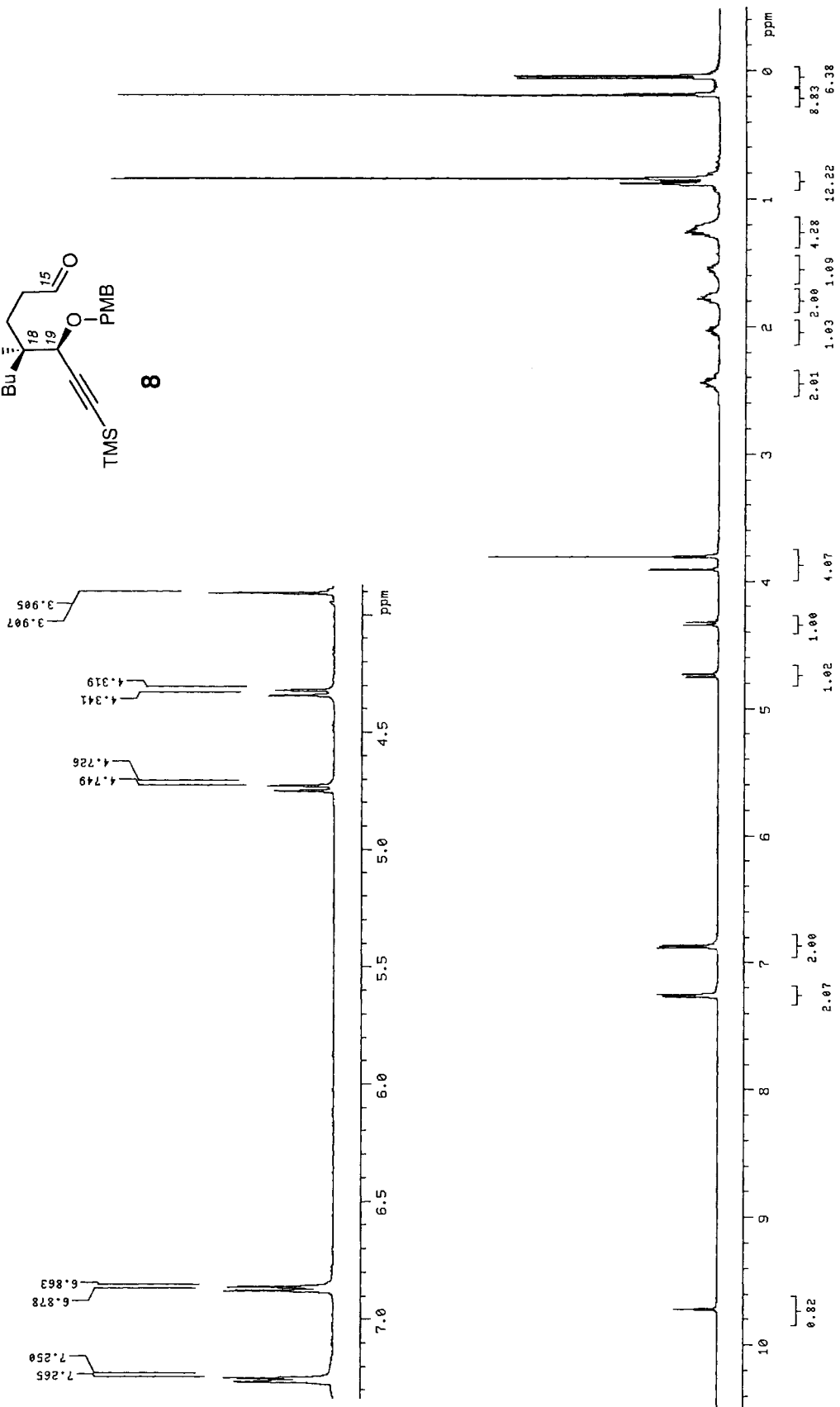
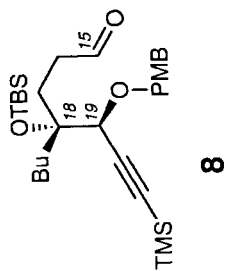


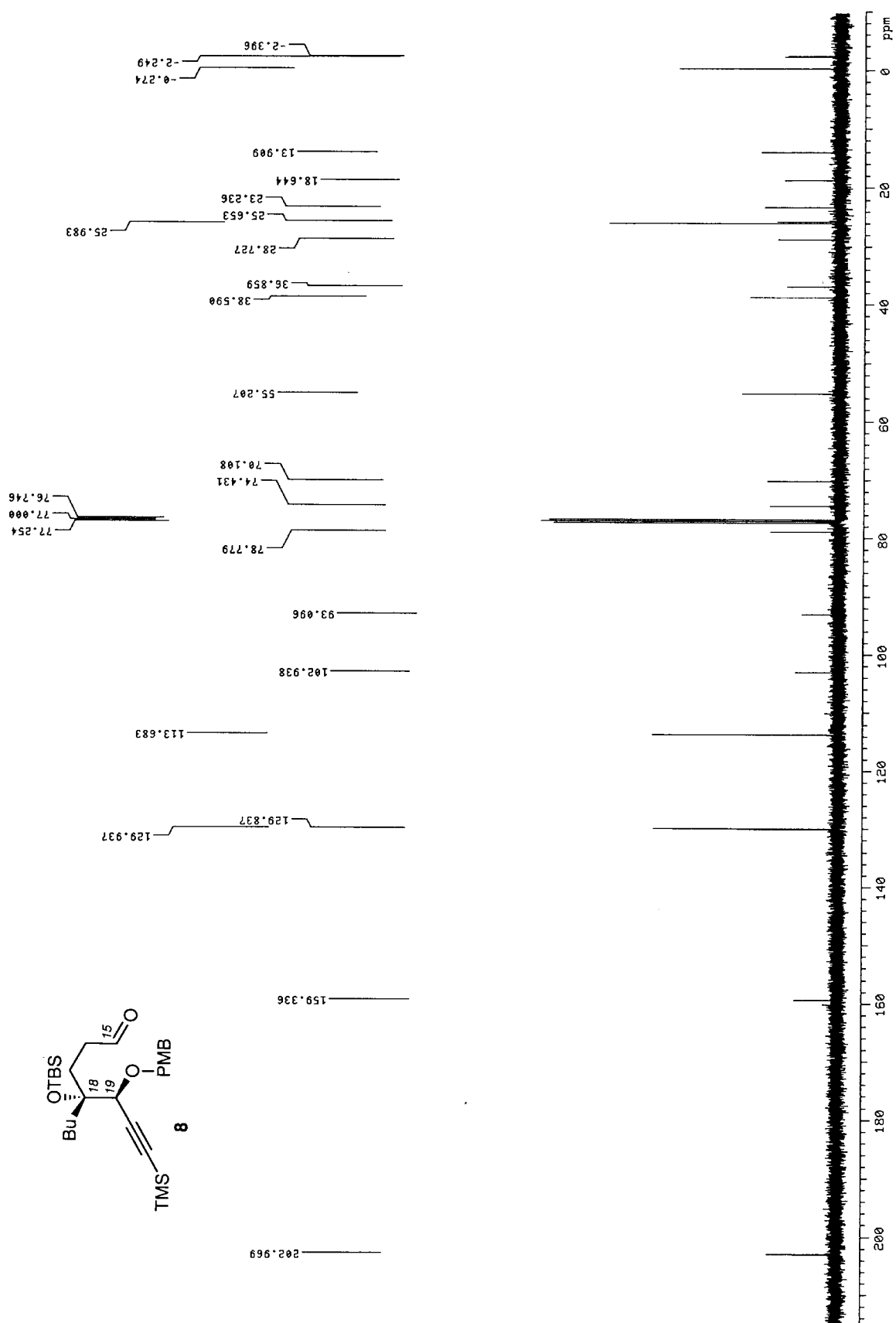


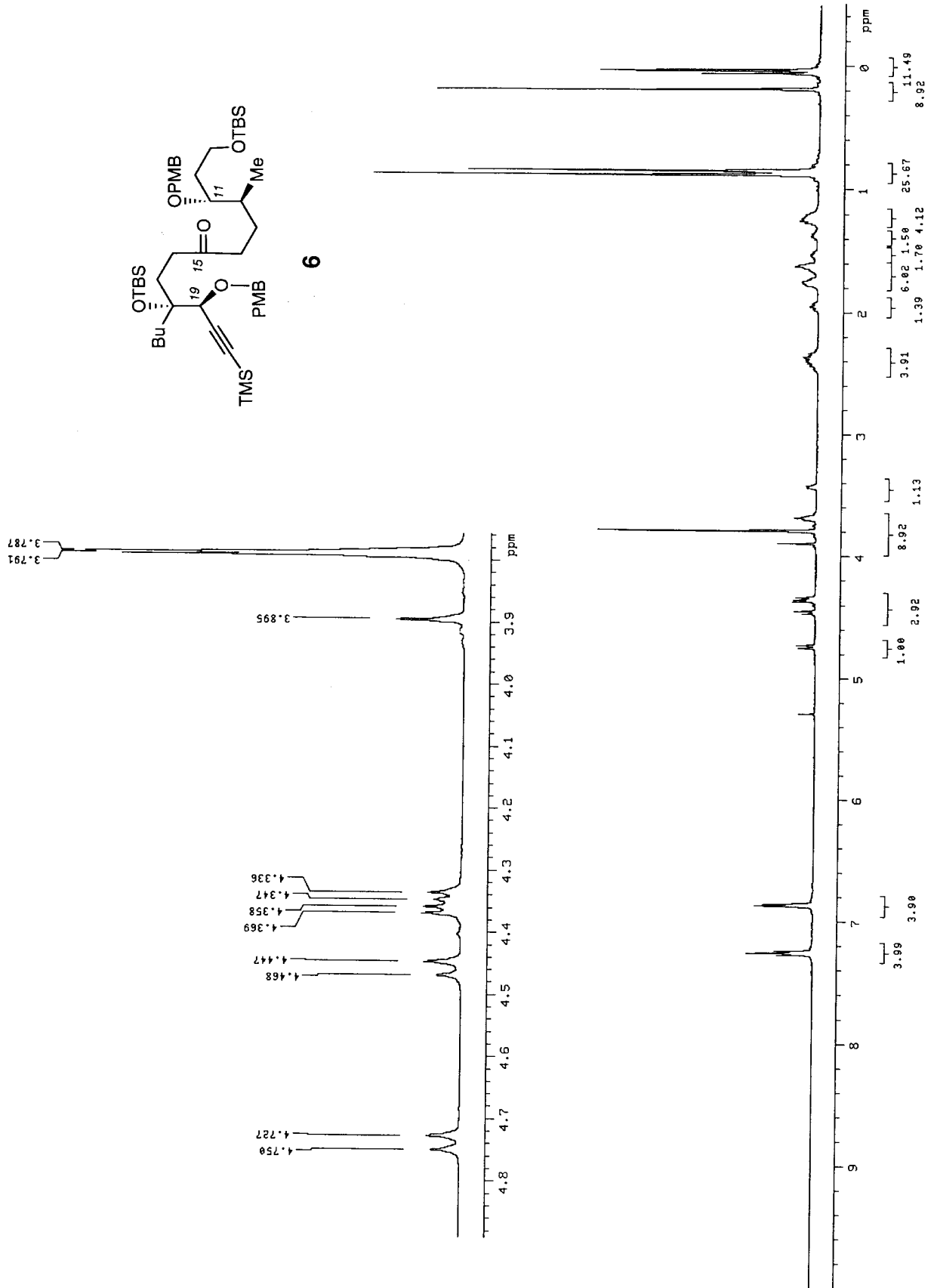
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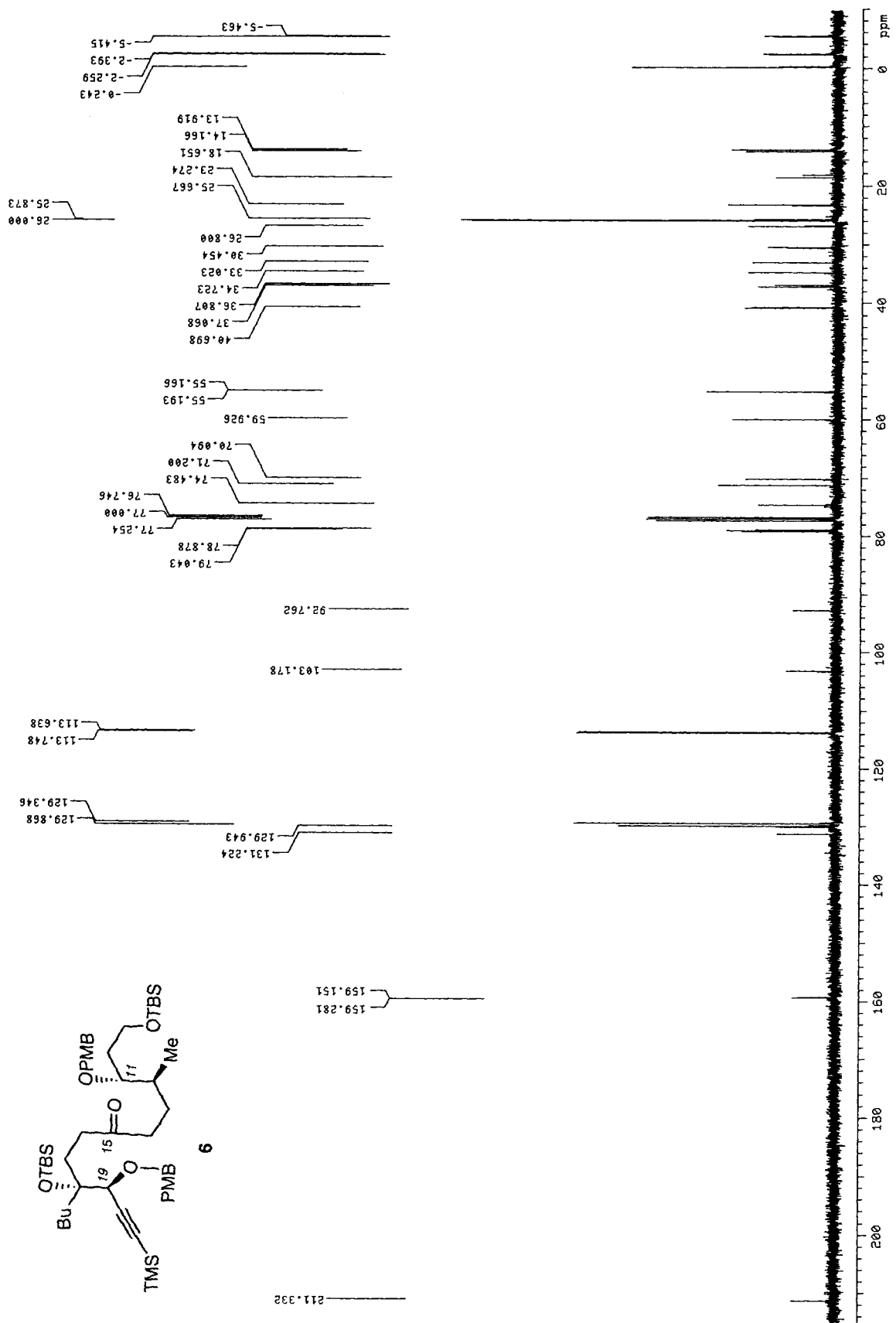


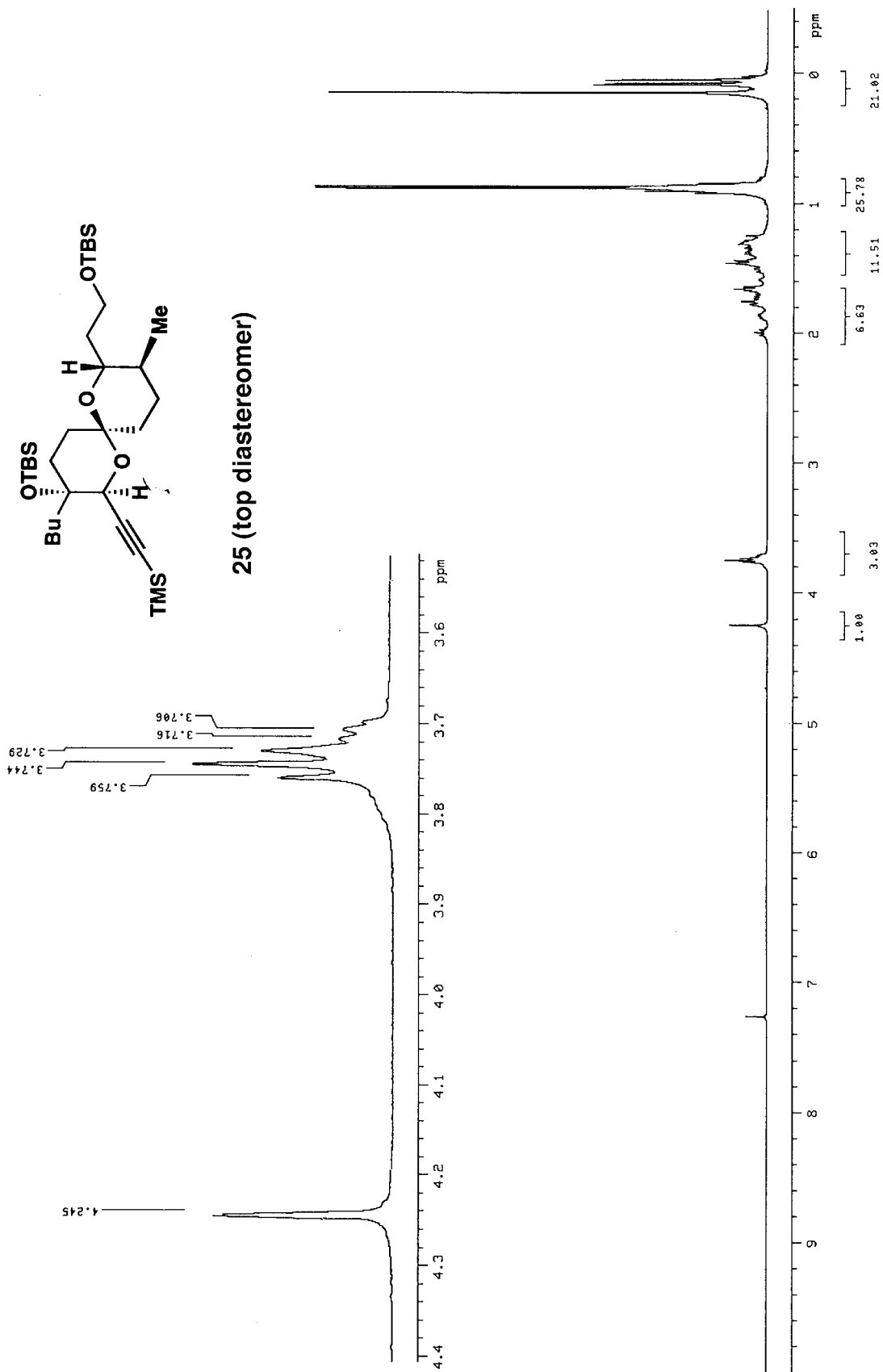


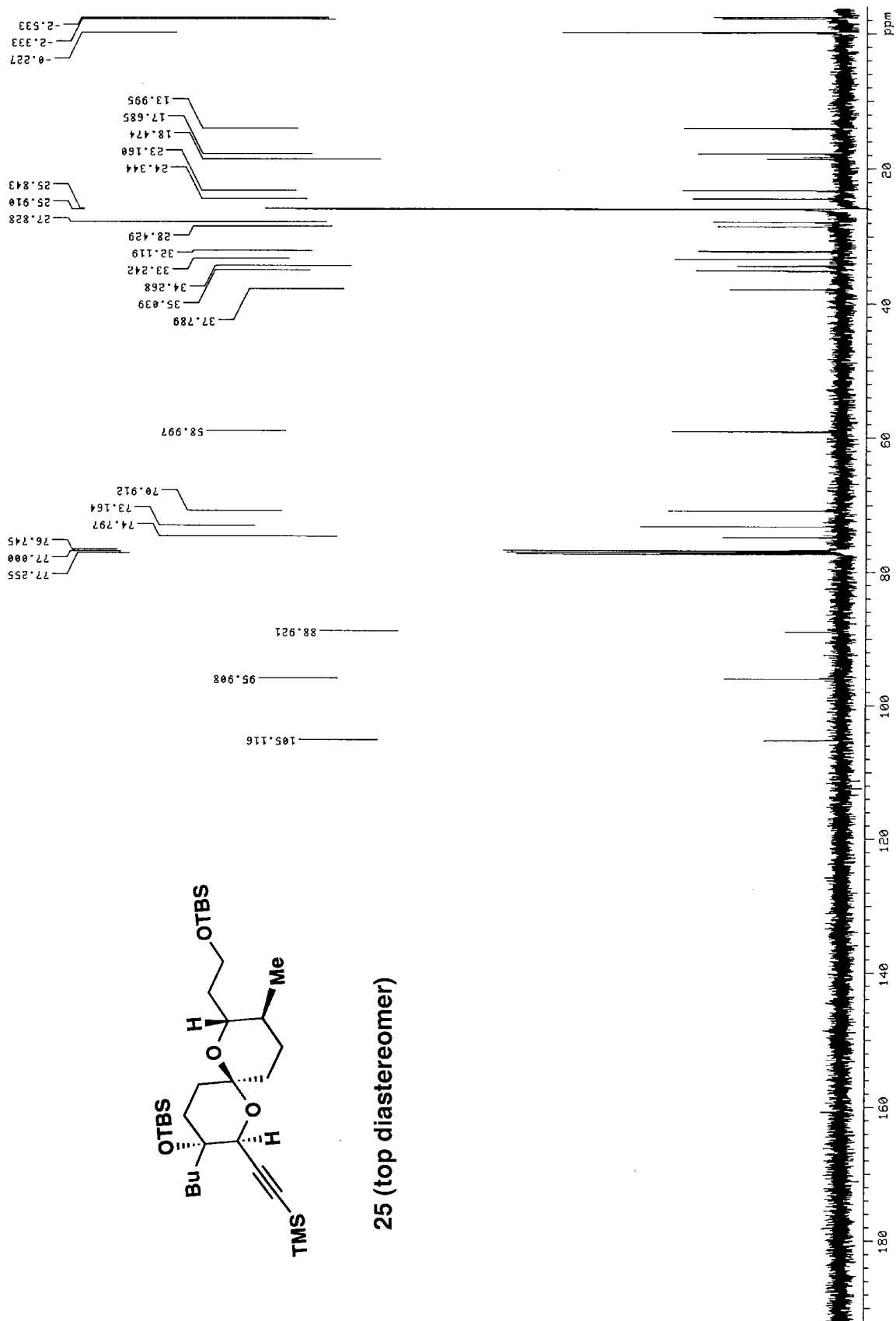




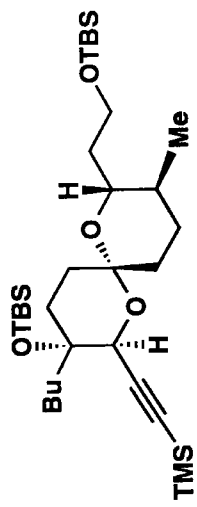




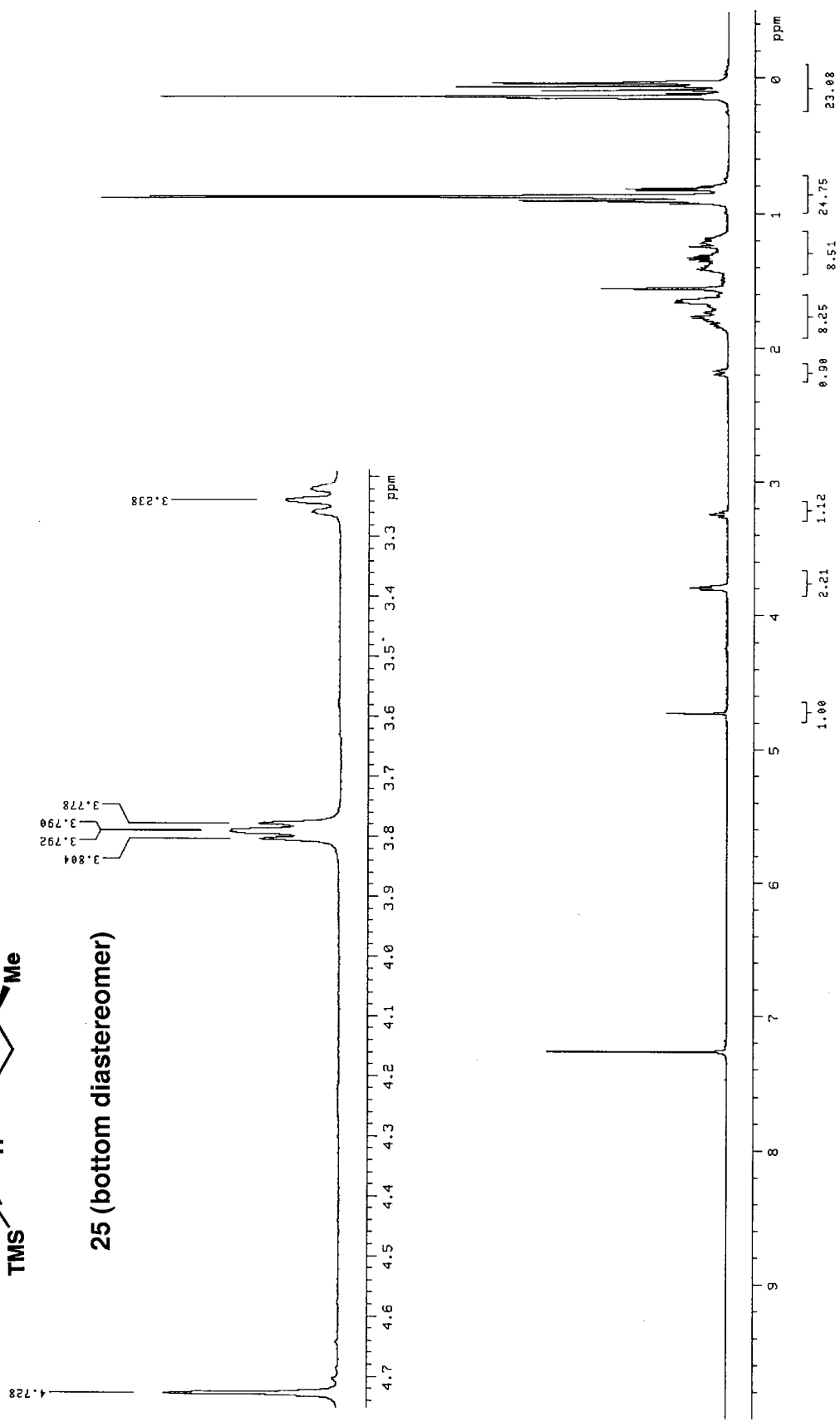


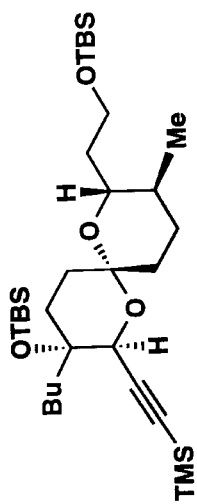


25 (top diastereomer)

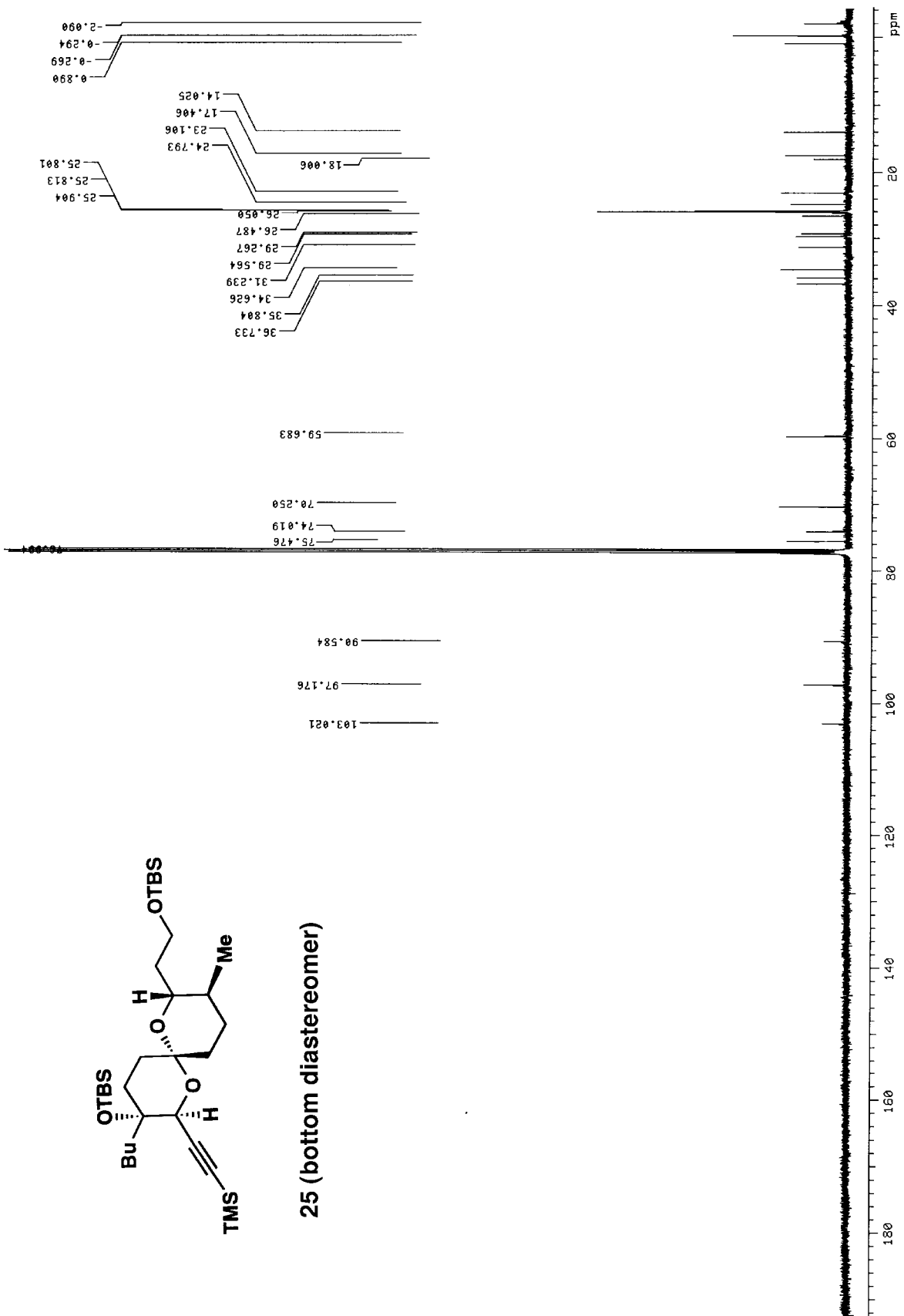


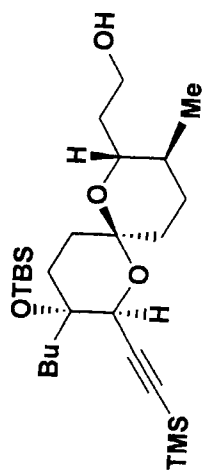
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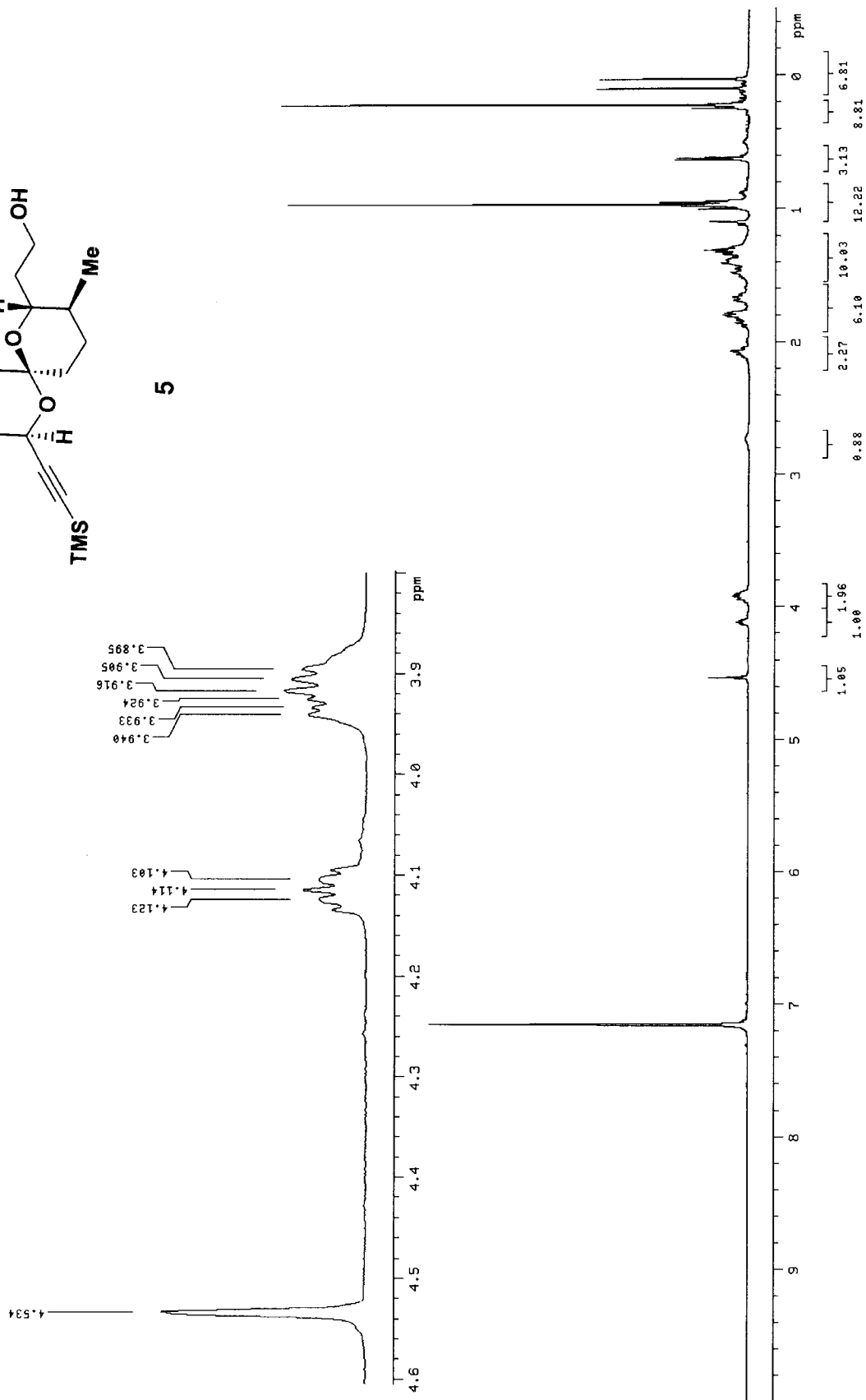


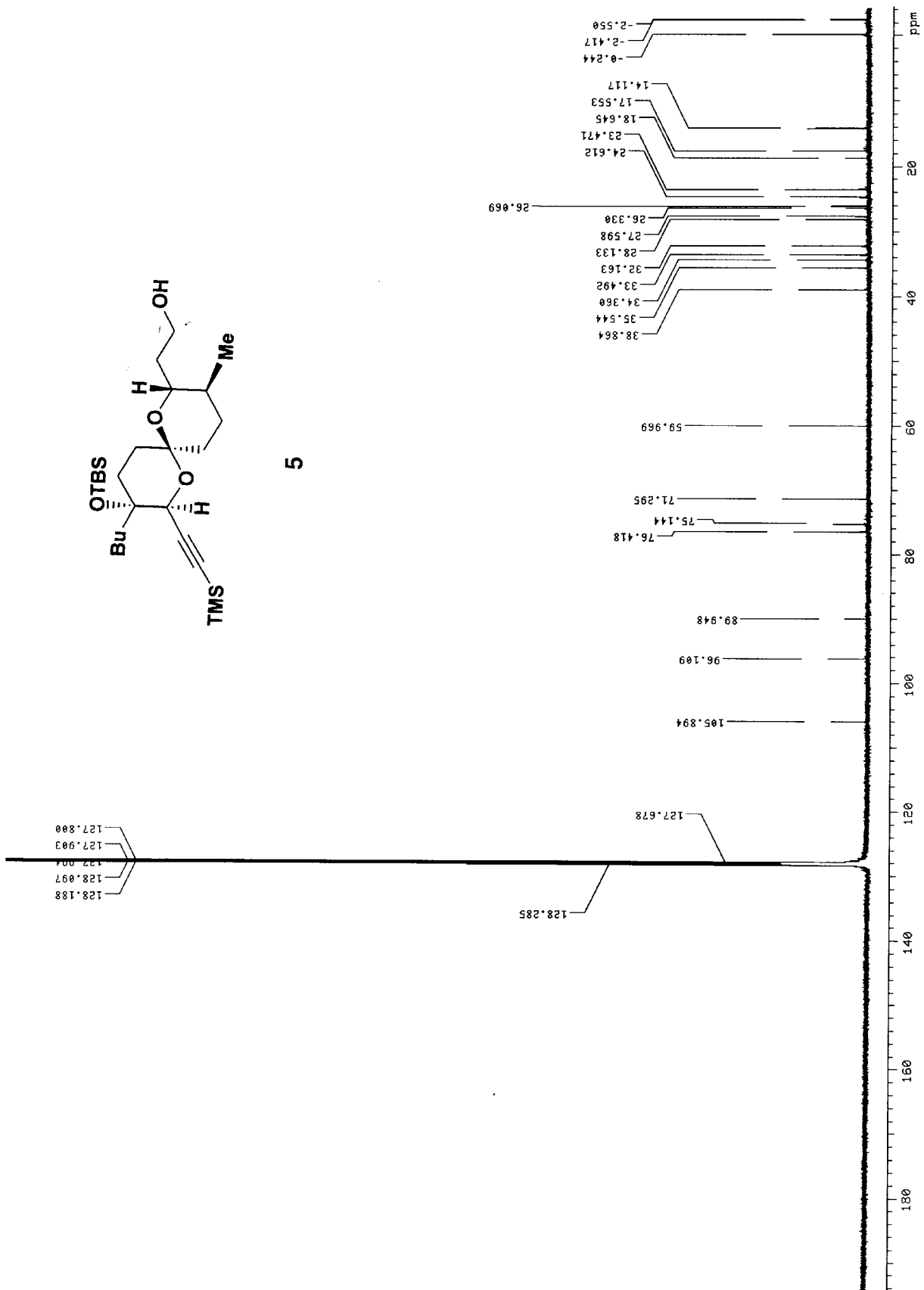
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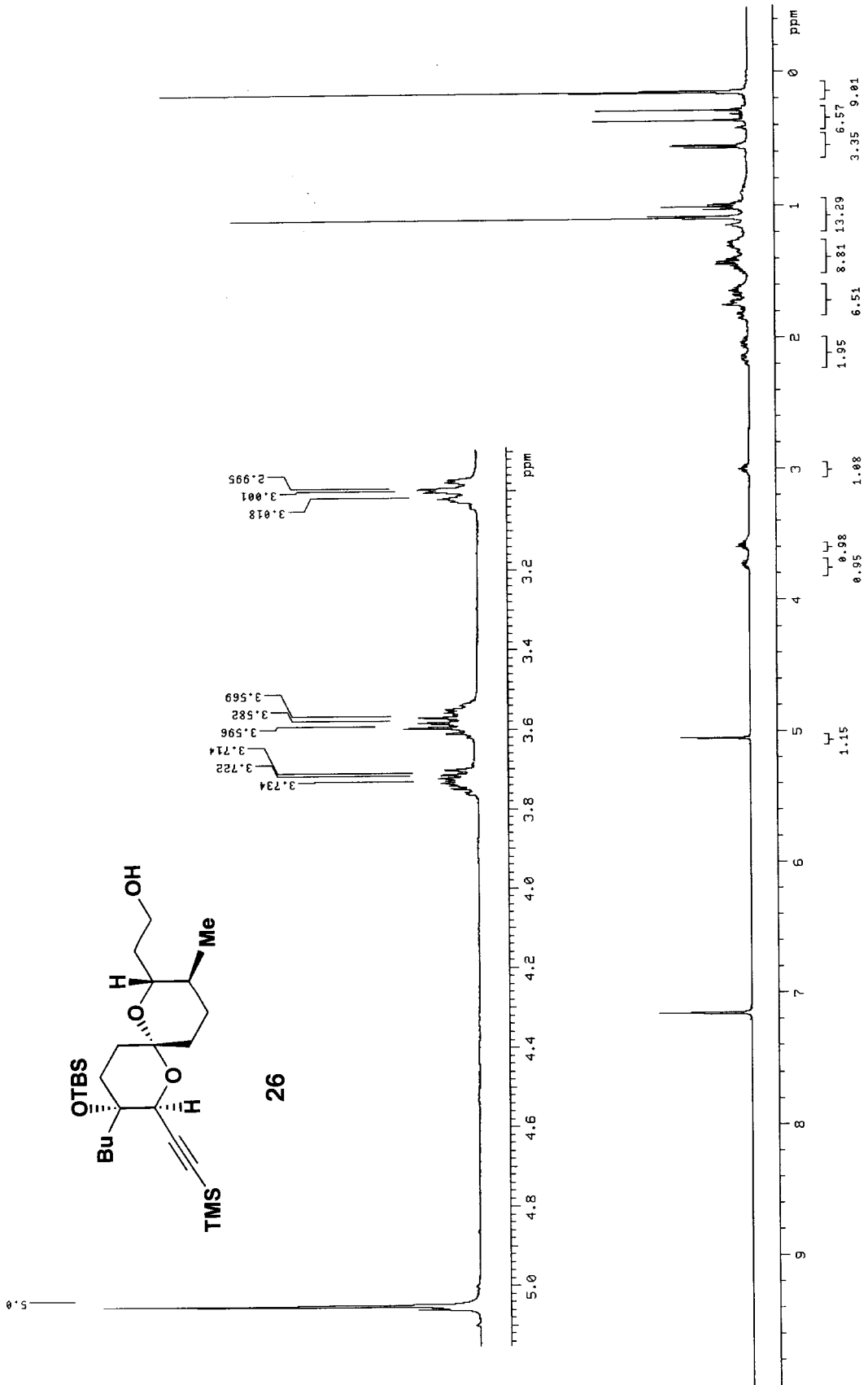


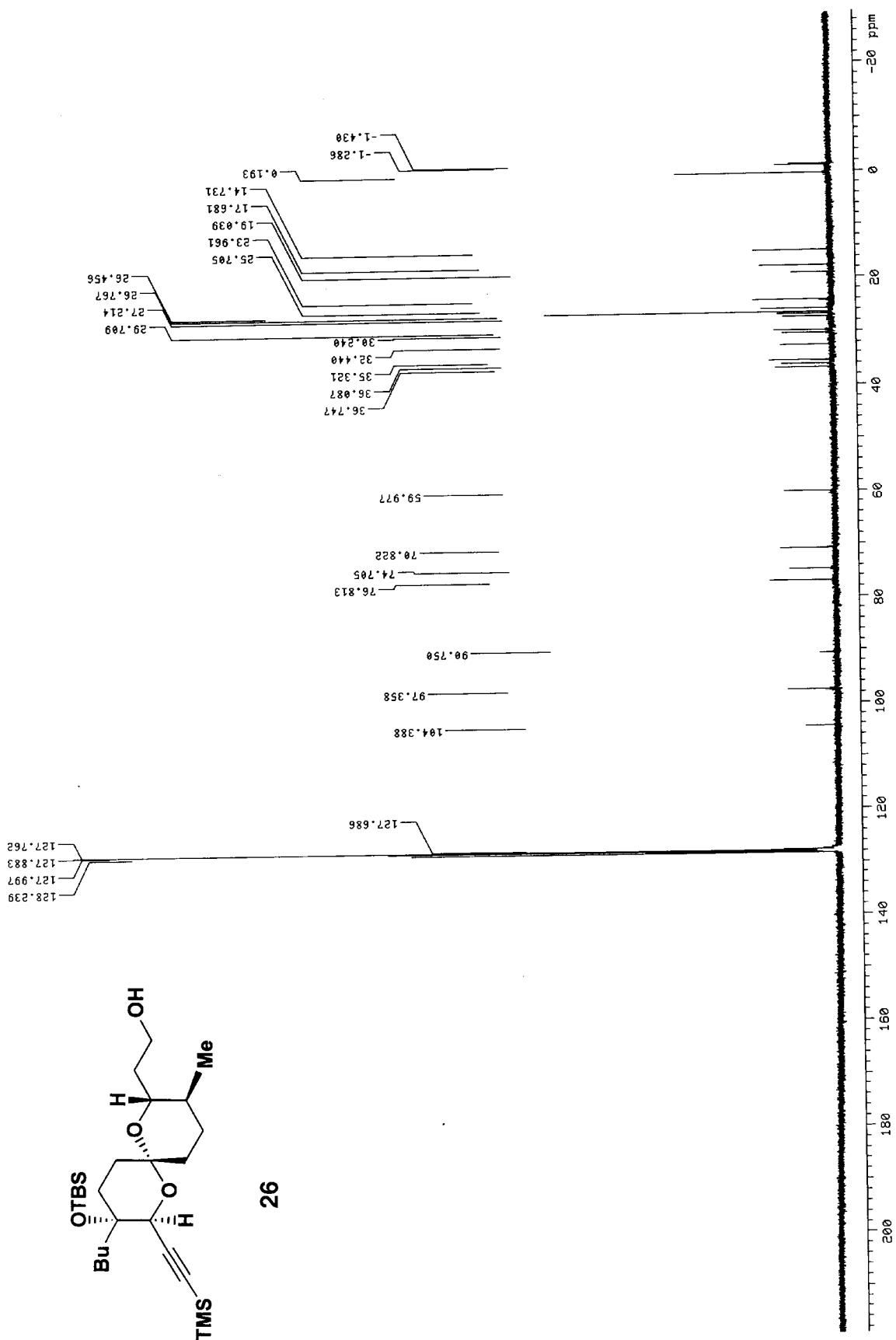


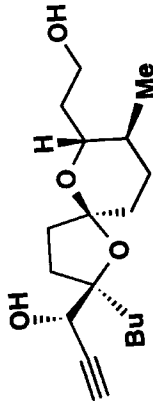
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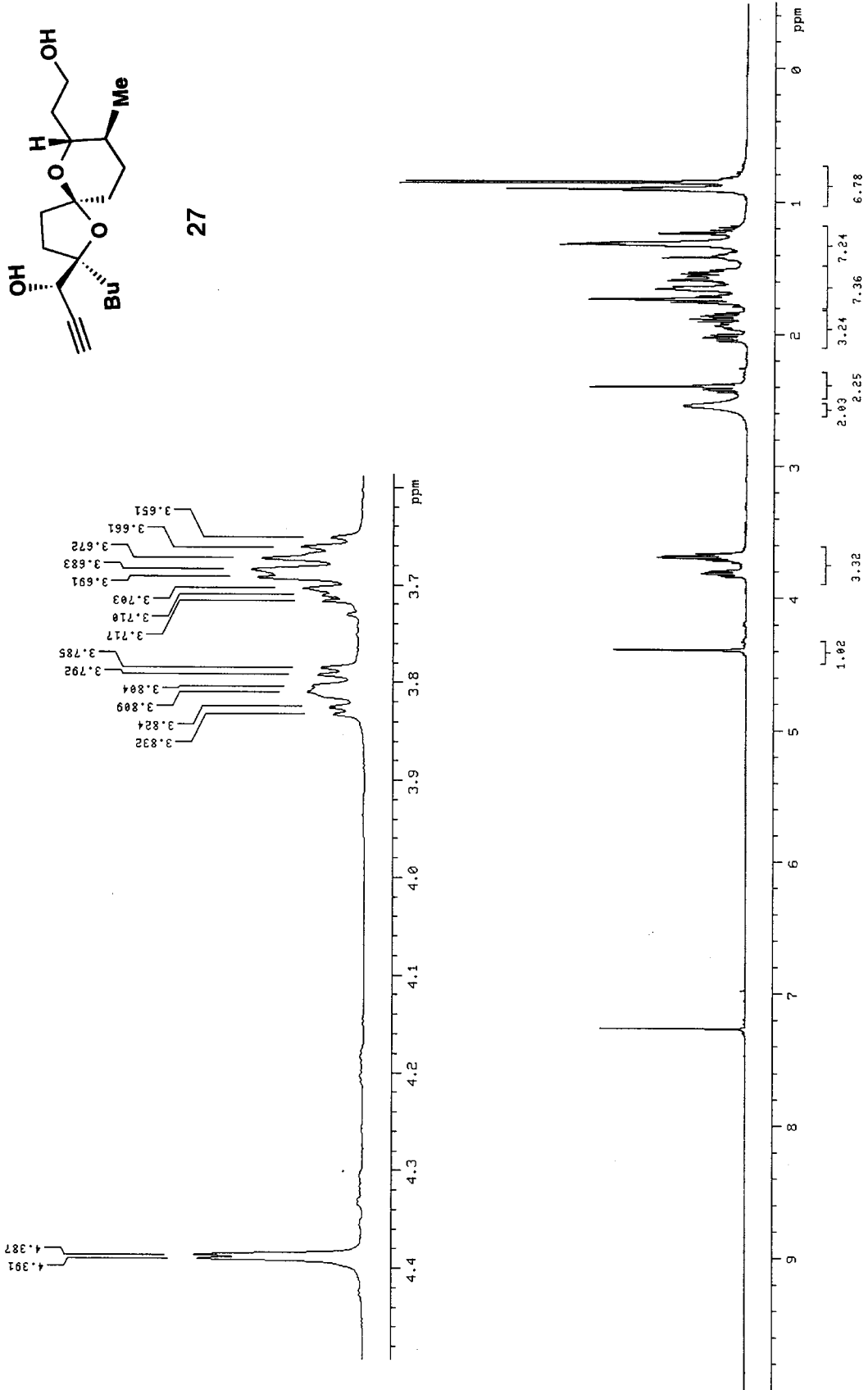


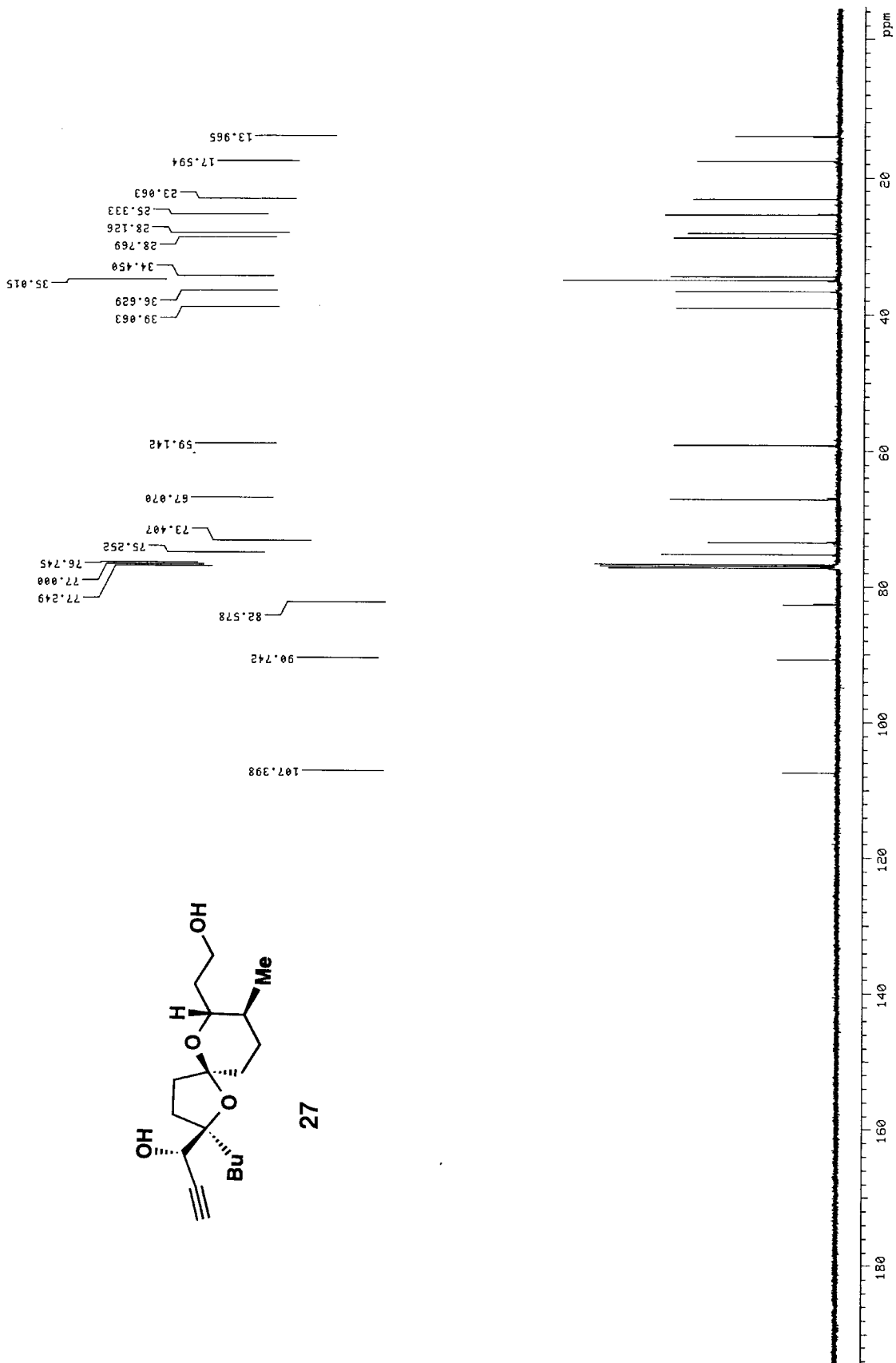


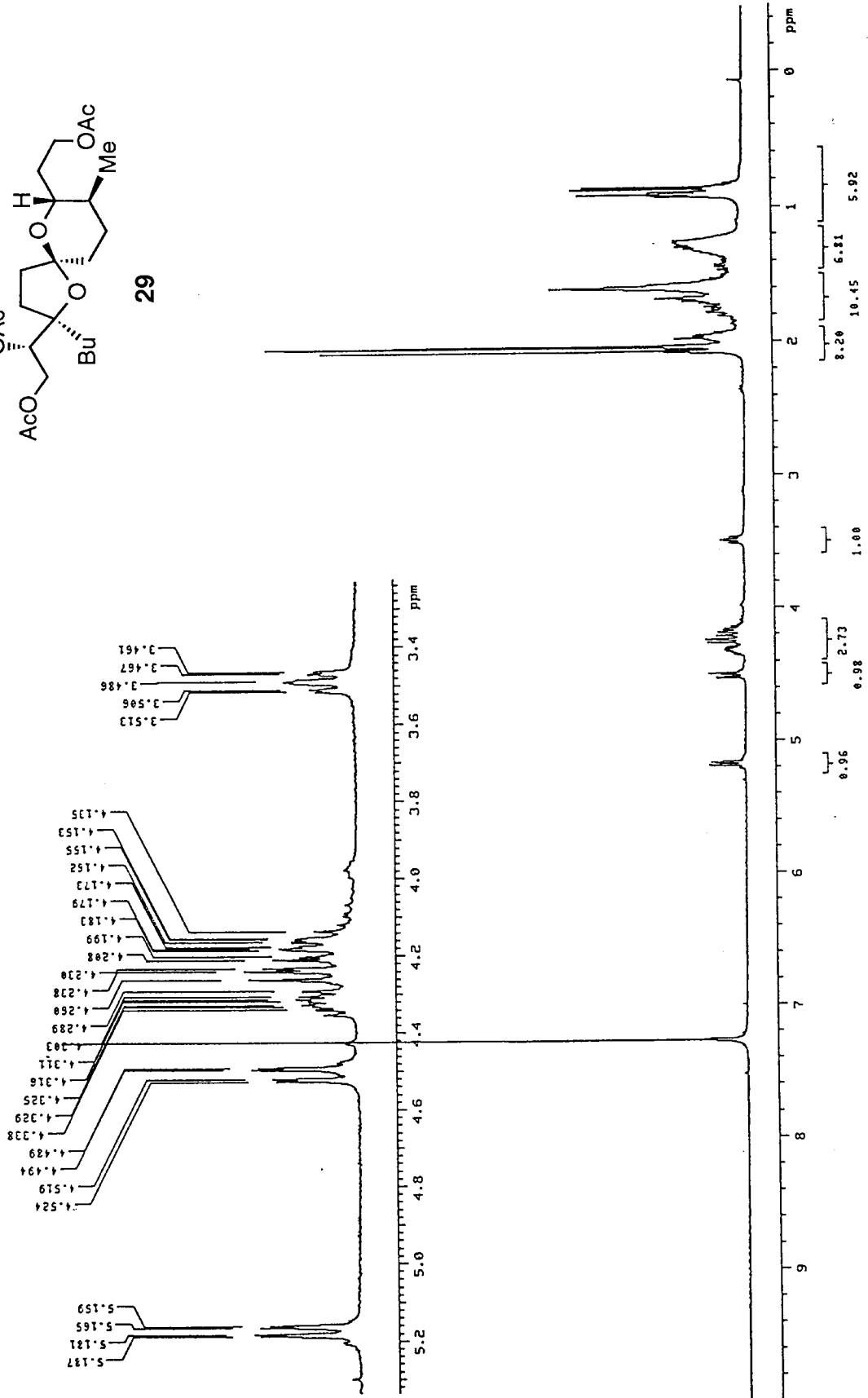
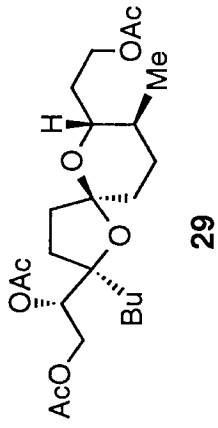


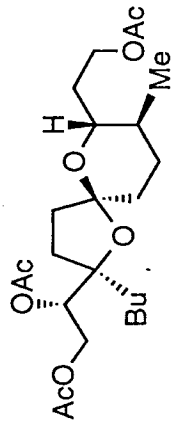
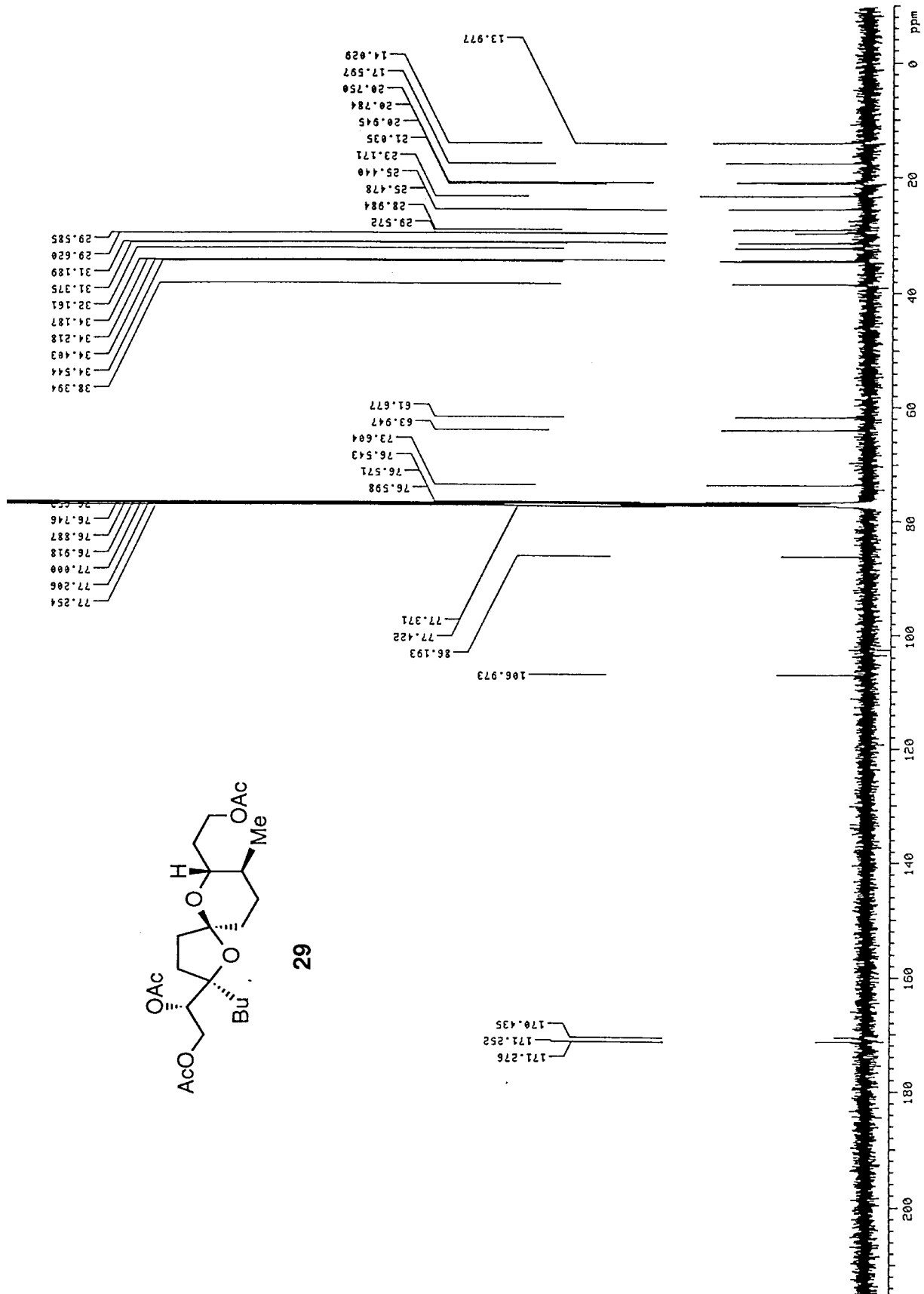


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