

**Differentiation of Diastereotopic Bromine Atoms in S_N2 Reactions
of *gem*-Dibromides**

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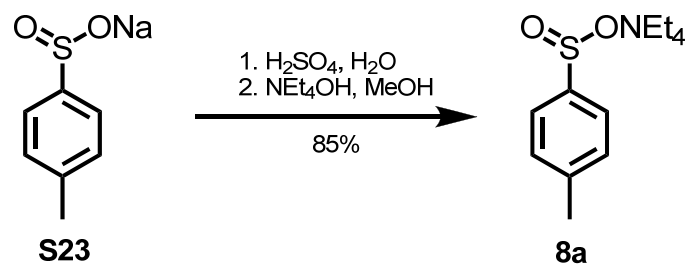
SUPPORTING INFORMATION

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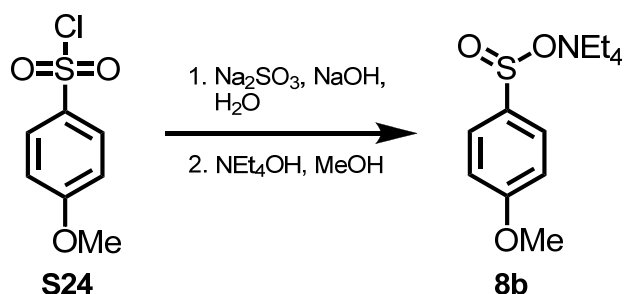
General Methods and Materials

All non-aqueous reactions were carried out using flame-dried glassware under argon atmosphere. All solvents were distilled by rotary evaporation. Solvents for non-aqueous reactions were dried as follows prior to use: THF and Et₂O were dried with KOH and subsequently distilled from sodium/benzophenone (THF), respectively from Solvona® (Et₂O). CH₂Cl₂ was distilled from CaH₂. MeOH was dried by refluxing with Mg-turnings (5g/L) and subsequent distillation. All commercially available reagents and reactants were used without purification unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) using Merck Silica Gel 60 F₂₄₅-plates and visualized by fluorescence quenching under UV-light. In addition, TLC-plates were stained using a cerium sulfate/phosphomolybdic acid stain. Chromatographic purification of products was performed on Merck Silica Gel 60 (230-400 mesh) unless otherwise noted using a forced flow of eluents. Concentration under reduced pressure was performed by rotary evaporation at 40 °C and appropriate pressure and by exposing to high vacuum at room temperature if necessary. IR spectra were recorded on a Bruker IFS 200 spectrometer. The absorption bands are given in wave numbers (cm⁻¹), intensities are reported as follows: s = strong, m = medium, w = weak, br = broad band. NMR-spectra were recorded on a Bruker AV300B, DRX400 or DRX500 spectrometer at room temperature. Chemical shifts are reported in ppm with the solvent resonance as internal standard. Data are reported as follows: s = singlet, d = doublet, t = triplet. Mass spectra were recorded on a Finnigan LTG-FT or QStar-Pulsar i (both mass service of Philipps-Universität Marburg).



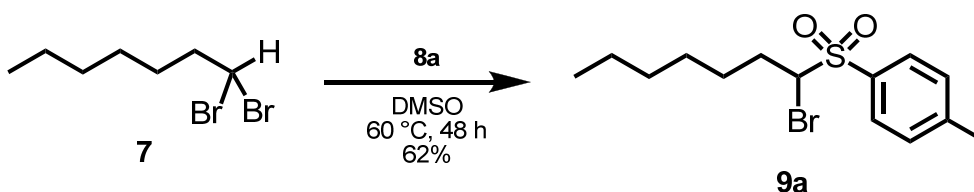
To a solution of sodium *p*-toluenesulfonate (**S23**) (4.00 g, 22.3 mmol, 1.00 eq) in water (10 mL) was added aq. H₂SO₄ (8%, 40mL) at 0 °C. After 30min the solution was extracted with Et₂O (2 x 40mL) and the combined organic layers were washed with water (2 x 10mL). The solvent was removed under reduced pressure to give *p*-toluenesulfonic acid (2.97 g, 19.0mmol, 85%) as a colourless solid. The *p*-toluenesulfonic acid was dissolved in MeOH (20mL) and NEt₄OH in MeOH (12.7mL, 19.0 mmol, 1.00 eq) was added dropwise at r.t. until

the reaction was neutral. The solvent was removed under reduced pressure to give crude sulfinate **8a** as a colourless oil. It was dried 24 h in high vacuum at r.t. to give sulfinate **8a** (5.42 g, 19.0 mmol, 85% over 2 steps) as a colourless solid. **¹H-NMR** (300 MHz, DMSO-*d*₆): δ = 1.15 (t, J = 7.3 Hz, 12H, N(CH₂CH₃)₄), 2.27 (s, 3H, CH₃), 3.20 (q, J = 7.3 Hz, 8H, N(CH₂CH₃)₄), 7.08 (d, J = 7.6 Hz, 2H, 3,5-H_{Ar}), 7.30 (d, J = 7.6 Hz, 2H, 2,6-H_{Ar}). **¹³C-NMR** (75 MHz, DMSO-*d*₆): δ = 7.0 (N(CH₂CH₃)₄), 20.7 (CH₃) 51.4 ((N(CH₂CH₃)₄), 124.3 (2C: C3,5), 127.9 (2C: C2,6), 136.1 (C1), 158.1 (C4). **FT-IR** (neat): $\tilde{\nu}$ = 2987 (m), 1457 (m), 1183 (m), 1052 (s), 977 (s), 807 (m), 713 (w), 610 (m), 562 (s), 441 (m). **HR-MS** (ESI): m/z calcd. for C₇H₇O₂S (M): 155.0172, found: 155.0174.



To a solution of sodium sulfite (3.71 g, 29.4 mmol, 1.50 eq) in water (50 mL) was added 4-methoxybenzenesulfonyl chloride (**S24**) (5.00 g, 24.2 mmol, 1.00 eq). The mixture was stirred at 70 °C, with periodic addition of NaOH to maintain an alkaline solution (pH 14). After complete dissolution of sulfonyl chloride, the reaction mixture was heated to 100 °C for 5 min. The reaction mixture was cooled to 0 °C and strongly acidified with conc. HCl (10 mL). Thereby, 4-methoxybenzenesulfinic acid precipitated as colourless solid. The reaction mixture was extracted with Et₂O (2 x 50 mL) and the combined organic layers were washed with water (2 x 10 mL) and brine (1 x 10 mL). The solvent was removed under reduced pressure to give 4-methoxybenzenesulfinic acid (3.63 g, 21.1 mmol, 87%) as a colourless solid. The 4-methoxybenzenesulfinic acid was dissolved in MeOH (10 mL). NEt₄OH in MeOH (14.1 mL, 21.1 mmol, 1.00 eq) was added dropwise at r.t. until the reaction mixture was neutral. The solvent was removed under reduced pressure to give crude sulfinate **8b** as a colourless oil. It was dried 24 h in high vacuum at r.t. to give sulfinate **8b** (6.36 g, 21.1 mmol, 87% over 2 steps) as a colourless solid. **¹H-NMR** (300 MHz, CDCl₃): δ = 1.15 (t, J = 7.0 Hz, 12H, N(CH₂CH₃)₄), 3.19 (q, J = 7.2 Hz, 8H, N(CH₂CH₃)₄), 3.73 (s, 3H, OCH₃), 6.80 (d, J = 8.5 Hz, 3,5-H_{Ar}), 7.56 (d, J = 8.5 Hz, 2,6-H_{Ar}). **¹³C-NMR** (75 MHz,

CDCl₃): δ = 7.7 (N(CH₂CH₃)₄), 52.6 ((N(CH₂CH₃)₄), 55.4 (OCH₃), 113.2 (2C: C3,5), 126.1 (2C: C2,6), 152.3 (C1), 159.7 (C4). **FT-IR** (neat): $\tilde{\nu}$ = 2982 (w), 1587 (m), 1486 (s), 1391 (m), 1297 (w), 1237 (s), 1173 (s), 1048 (s), 973 (s), 836 (m), 790 (s), 611 (w), 575 (s), 473 (w), 445 (m). **HR-MS** (ESI): m/z calcd. for C₇H₇O₃S (M⁻): 171.0121, found: 171.0122.

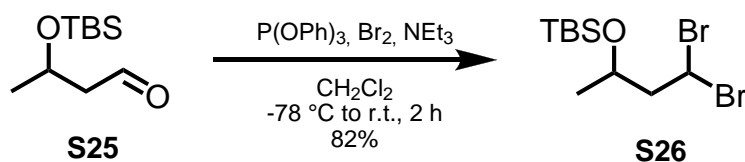


1,1-Dibromoheptane (7)¹ (100 mg, 0.39 mmol, 1.00 eq) and tetraethylammonium *p*-toluenesulfonate (8a) (331 mg, 1.16 mmol, 3.00 eq) were dissolved in DMSO (2.0 mL). The solution was stirred at 60 °C for 48 h. The reaction mixture was poured into EtOAc (10 mL) and washed with water (5 mL) and brine (5 mL). The organic layer was dried with MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (*n*-pentane - MTBE, 4:1) to give bromosulfone 9a (81 mg, 0.24 mmol, 62%) as a colourless solid. **TLC** (CH₂Cl₂): R_f = 0.56. **m.p.** (CHCl₃): 59 °C. **¹H-NMR** (300 MHz, CDCl₃): δ = 0.87 (t, J = 6.6 Hz, 3H, H-7), 1.26-1.45 (m, 7H, 6-H; 5-H; 4-H; 3-H_a), 1.58-1.69 (m, 1H, 3-H_b), 1.80-1.93 (m, 1H, 2-H_a), 2.34-2.44 (m, 1H, 2-H_b), 2.47 (s, 3H, CH₃), 4.68 (dd, J = 11.1, 2.9 Hz, 1-H), 7.37 (d, J = 8.0 Hz, 2H, 3,5-H_{Ar}), 7.84 (d, J = 8.3 Hz, 2H, 2,6-H_{Ar}). **¹³C-NMR** (75 MHz, CDCl₃): δ = 14.1 (C7), 21.9 (Ph-CH₃), 22.6 (C4-6), 27.2 (C3), 28.3 (C4-6), 31.5 (2C: C2 + C4-6), 66.3 (C1), 129.8 (2C: C_{Ar}3,5), 130.2 (2C: C_{Ar}2,6), 132.5 (C_{Ar}1), 145.8 (C_{Ar}4). **FT-IR** (neat): $\tilde{\nu}$ = 2967 (w), 2953 (w), 2941 (w), 2919 (m), 2857 (w), 1738 (w), 1595 (w), 1463 (w), 1451 (w), 1389 (w), 1318 (s), 1290 (m), 1261 (w), 1181 (w), 1147 (s), 1114 (m), 1100 (m), 1083 (s), 1018 (m), 973 (m), 817 (m), 802 (m), 769 (s), 741 (w), 727 (w), 703 (w), 664 (s), 635 (m), 567 (s), 536 (s), 478 (m), 409 (m). **HR-MS** (ESI): m/z calcd. for C₁₄H₂₂BrO₂S (M+H⁺): 335.0498, found: 335.0497.

¹ R. W. Hoffmann, P. Bovicelli, *Synthesis*, 1990, 657.



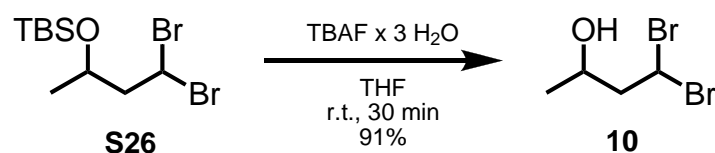
1,1-Dibromoheptane (**7**) (40 mg, 0.16 mmol, 1.00 eq) and sulfinate **8b** (144 mg, 0.48 mmol, 3.00 eq) were dissolved in DMSO (1.0 mL). The solution was stirred at 60 °C for 64 h. The reaction mixture was poured into EtOAc (10 mL) and washed with water (5 mL) and brine (5 mL). The organic layer was dried with MgSO₄ and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (*n*-pentane - MTBE, 4:1) to give bromosulfone **9b** (41 mg, 0.12 mmol, 76%) as a colourless solid. **TLC** (*n*-hexane – MTBE, 4:1): R_f = 0.44. **m.p.** (CHCl₃): 39 °C. **¹H-NMR** (400 MHz, CDCl₃): δ = 0.87 (t, *J* = 6.8 Hz, 3H, CH₃), 1.23-1.36 (m, 6H, 6-H; 5-H; 4-H), 1.37-1.43 (m, 1H, 3-H_a), 1.58-1.67 (m, 1H, 3-H_b), 1.80-1.90 (m, 1H, 2-H_a), 2.33-2.41 (m, 1H, 2-H_b), 3.89 (s, 3H, OCH₃), 4.67 (dd, *J* = 11.1, 2.9 Hz, 1H, 1-H), 7.03 (d, *J* = 9.0 Hz, 2H, 3,5-H_{Ar}), 7.88 (d, *J* = 9.0 Hz, 2H, 2,6-H_{Ar}). **¹³C-NMR** (100 MHz, CDCl₃): δ = 14.1 (C7), 22.6 (C6), 27.2 (C3), 28.3 (C5), 31.5 (C4), 31.6 (C2), 55.9 (OCH₃), 66.7 (C1), 114.4 (2C: C_{Ar}3,5), 126.7 (C_{Ar}1), 132.4 (2C: C_{Ar}2,6), 164.5 (C_{Ar}1). **FT-IR** (neat): $\tilde{\nu}$ = 2969 (w), 2955 (m), 2942 (m), 2915 (m), 2847 (w), 1595 (m), 1575 (w), 1495 (m), 1456 (m), 1321 (m), 1310 (m), 1293 (m), 1265 (m), 1181 (w), 1140 (s), 1105 (m), 1085 (m), 1019 (m), 971 (w), 837 (m), 822 (m), 806 (m), 772 (m), 729 (m), 666 (w), 633 (m), 573 (s), 540 (s), 508 (m), 495 (m), 472 (m). **HR-MS** (APCI): *m/z* calcd. for C₁₄H₂₂BrO₃S (M+H⁺): 349.0468, found: 349.0467.



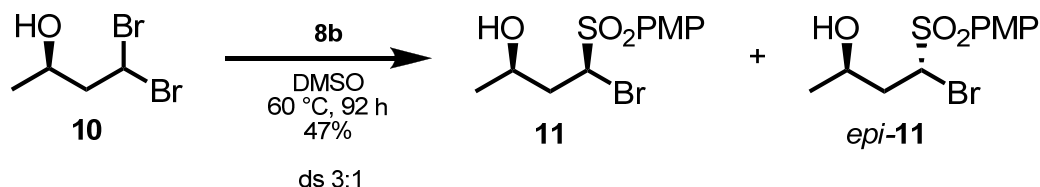
In an argon atmosphere triphenylphosphite (7.80 mL, 23.8 mmol, 1.50 eq) was dissolved in CH₂Cl₂ (250 mL) and cooled to -78 °C. Bromine (1.2 mL, 23.8 mmol, 1.20 eq) was added dropwise, followed by addition of triethylamine (8.20 mL, 59.4 mmol, 3.00 eq) and TBS-aldehyde **S25**² (4.02 g, 19.8 mmol, 1.00 eq). The mixture was allowed to warm to r.t. and was

² D. Romo, R. M. Rzasa, H. A. Shea, K. Park, J. M. Langenhan, L. Sun, A. Akhiezer, and J. O. Liu, *J. Am. Chem. Soc.*, 1998, **120**, 12237.

stirred for 2 h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (*n*-pentane) to give TBS-dibromide **S26** (5.62 g, 16.1 mmol, 82%) as a colourless oil. **TLC** (*n*-hexane): $R_f = 0.24$. **$^1\text{H-NMR}$** (300 MHz, CDCl_3): $\delta = 0.08$ (s, 3H, Si- CH_3), 0.11 (s, 3H, Si- CH_3), 0.89 (s, 9H, Si- $\text{C}(\text{CH}_3)_3$), 1.18 (d, $J = 4.5$ Hz, 3H, 4-H), 2.41 (ddd, $J = 14.3, 10.5, 3.3$ Hz, 2- H_a), 2.53 (ddd, $J = 14.3, 9.2, 3.6$ Hz, 2- H_b), 3.96-4.06 (m, 1H, 3-H), 5.72 (dd, $J = 7.5, 2.7$ Hz, 1-H). **$^{13}\text{C-NMR}$** (75 MHz, CDCl_3): $\delta = -4.6$ (Si- CH_3), -4.0 (Si- CH_3), 18.1 (Si- $\text{C}(\text{CH}_3)_3$), 23.6 (CH_3), 26.0 (Si- $\text{C}(\text{CH}_3)_3$), 43.5 (CHBr_2), 55.3 (CH_2), 67.2 (CHOTBS). **FT-IR** (neat): $\tilde{\nu} = 2955$ (m), 2929 (m), 2886 (w), 2857 (w), 1471 (m), 1462 (m), 1375 (m), 1361 (m), 1254 (s), 1159 (m), 1133 (s), 1098 (m), 1085 (m), 1045 (s), 1006 (w), 966 (s), 937 (m), 902 (m), 888 (m), 834 (s), 824 (s), 806 (s), 774 (s), 718 (m), 683 (s), 657 (m), 566 (m), 469 (m).



The TBS-dibromide **S26** (2.53 g, 7.31 mmol, 1.00 eq) was dissolved in THF (50 mL). TBAF x H_2O (3.00 g, 10.3 mmol, 1.41 eq) was added and the solution was stirred at r.t. After 30 min the reaction mixture was poured into a mixture of MTBE (100 mL) and water (100 mL) and extracted. The layers were separated and the aqueous layer was extracted with MTBE (3 x 100 mL). The combined organic layers were dried with MgSO_4 . The solvents were removed under reduced pressure. The remaining crude product was purified by flash chromatography on silica gel (*n*-pentane - MTBE, 4:1) to give dibromide **10** (1.55 g, 6.68 mmol, 91%) as a colourless solid. **TLC** (*n*-hexane - MTBE, 3:1): $R_f = 0.13$. **m.p.** (CHCl_3): 54 °C. **$^1\text{H-NMR}$** (500 MHz, CDCl_3): $\delta = 1.27$ (d, $J = 4.5$ Hz, 3H, CH_3), 1.64 (s, 1H, OH), 2.42-2.57 (m, 2H, 3-H), 4.03-4.10 (m, 1H, 2-H), 5.85 (dd, $J = 9.6, 4.1$ Hz, CHBr_2). **$^{13}\text{C-NMR}$** (125 MHz, CDCl_3): $\delta = 23.6$ (C1), 43.0 (C4), 54.2 (C3), 66.6 (C2). **FT-IR** (neat): $\tilde{\nu} = 3196$ (s), 3015 (w), 2968 (m), 2925 (w), 1455 (w), 1417 (m), 1373 (m), 1360 (m), 1329 (m), 1255 (m), 1154 (s), 1125 (s), 1095 (m), 1076 (m), 1023 (s), 930 (m), 892 (m), 839 (s), 674 (s), 570 (s), 461 (m), 404 (m).

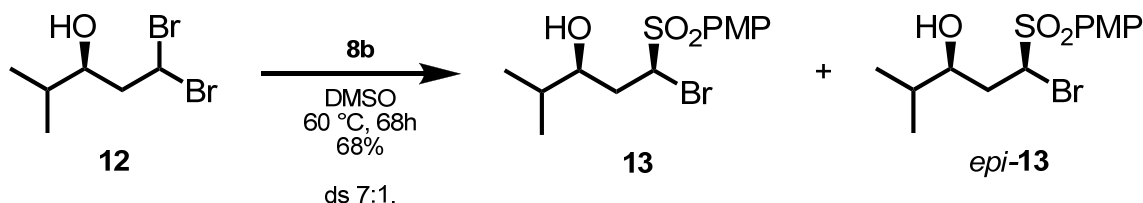


To a solution of sulfinate **8b** (776 mg, 2.58 mmol, 3.00 eq) in DMSO (3.0 mL) was added 4,4-dibromobutan-2-ol (**10**) (200 mg, 0.86 mmol, 1.00 eq). The reaction mixture was stirred at 60 °C for 92 h. The solution was diluted with EtOAc (15 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was dried with MgSO₄. The solvents were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (*n*-pentane - EtOAc, 2:1) to give sulfones **11** and *epi*-**11** (123 mg, 0.38 mmol, 47%) as a 2.8:1.0 mixture as a colourless oil. An analytical pure sample of both diastereomers was obtained by HPLC (Dynamax Microsorb SI-60 250x21.4 mm; *n*-hexane - MTBE, 1.9:1.0; flow rate 0.5 mL/min; detection at 220 nm; *t*₁ = 37.3 min (**11**); *t*₂ = 39.8 min (*epi*-**11**)).

Analytical data for (2R,4S*)-4-bromo-4-((4-methoxyphenyl)sulfonyl)butan-2-ol (11):* **TLC** (*n*-hexane – EtOAc, 1:1): R_f = 0.31. **¹H-NMR** (500 MHz, CDCl₃): δ = 1.31 (d, *J* = 6.2 Hz, 3H, CH₃), 1.61 (s, 1H, OH), 1.97 (ddd, *J* = 14.3, 11.8, 2.3 Hz, 1H, 3-H_a), 2.42 (ddd, *J* = 14.3, 10.4, 2.3 Hz, 1H, 3-H_b), 3.90 (s, 3H, OCH₃), 4.01-4.08 (m, 1H, 2-H), 5.05 (dd, *J* = 11.8, 2.3 Hz, 4-H), 7.04 (d, *J* = 8.9 Hz, 2H, 3,5-H_{Ar}), 7.89 (d, *J* = 8.9 Hz, 2H, 2,6-H_{Ar}). **¹³C-NMR** (125 MHz, CDCl₃): δ = 24.2 (C1), 40.2 (C3), 55.9 (OCH₃), 63.9 (C4), 65.1 (C2), 114.5 (2C: C_{Ar}3,5), 126.8 (C_{Ar}1), 132.4 (2C: C_{Ar}2,6), 164.6 (C_{Ar}4). **FT-IR** (neat): $\tilde{\nu}$ = 3518 (br w), 2969 (w), 2926 (w), 2844 (w), 1593 (s), 1577 (m), 1497 (m), 1459 (m), 1441 (w), 1416 (w), 1377 (w), 1323 (m), 1298 (s), 1262 (s), 1177 (w), 1141 (s), 1085 (s), 1021 (m), 932 (m), 896 (m), 836 (m), 806 (m), 773 (w), 735 (m), 702 (w), 667 (m), 627 (w), 571 (s), 545 (m), 510 (w), 480 (w), 447 (w), 423 (w). **HR-MS** (APCI): *m/z* calcd. for C₁₁H₁₆BrO₄S (M+H⁺): 324.9927, found: 324.9924.

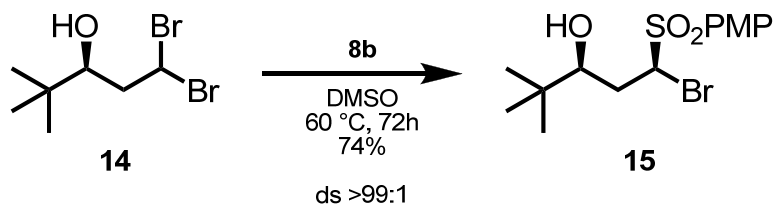
Analytical data for (2R,4R*)-4-bromo-4-((4-methoxyphenyl)sulfonyl)butan-2-ol (epi-11):* **TLC** (*n*-hexane – EtOAc, 1:1): R_f = 0.31. **¹H-NMR** (500 MHz, CDCl₃): δ = 1.25 (d, *J* = 6.2Hz, 3H, CH₃), 2.04 (s, 1H, OH), 2.20-2.26 (m, 1H, 3-H_a), 2.52 (ddd, *J* = 14.8, 6.0, 5.4Hz, 1H, 3-H_b), 3.91 (s, 3H, OCH₃), 4.19-4.25 (m, 1H, 2-H), 4.88 (dd, *J* = 7.6, 6.3Hz, 4-H), 7.04 (d, *J* = 9.0Hz, 2H, 3,5-H_{Ar}), 7.89 (d, *J* = 9.0Hz, 2H, 2,6-H_{Ar}). **¹³C-NMR** (125 MHz, CDCl₃): δ = 23.1 (C1), 42.0 (C3), 55.9 (OCH₃), 61.8 (C4), 66.0 (C2), 114.5 (2C: C_{Ar}3,5), 126.6 (C_{Ar}1), 132.5 (2C: C_{Ar}2,6), 164.7 (C_{Ar}4). **FT-IR** (neat): $\tilde{\nu}$ = 3516 (br w), 2924 (m), 2849 (w), 2361 (w), 1594 (s), 1577 (m), 1497 (m), 1460 (w), 1442 (w), 1415 (w), 1378 (w), 1322 (m), 1299

(m), 1263 (s), 1206 (w), 1143 (s), 1086 (m), 1022 (m), 943 (w), 836 (m), 806 (m), 768 (w), 701 (w), 668 (w), 627 (w), 569 (m), 548 (m), 510 (w). **HR-MS** (APCI): m/z calcd. for $C_{11}H_{16}BrO_4S$ ($M+H^+$): 324.9927, found: 324.9924.



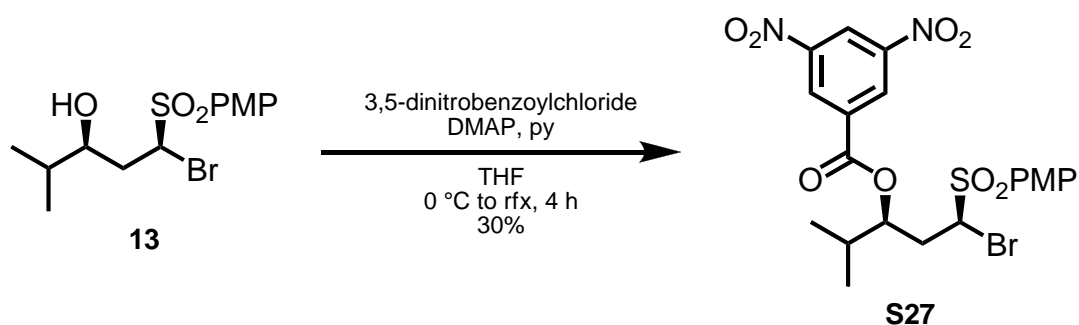
To a solution of sulfinate **8b** (368 mg, 1.14 mmol, 3.00 eq) in DMSO (2.0 mL) was added 1,1-dibromo-4-methyl-3-pentanol (**12**)³ (100 mg, 0.38 mmol, 1.00 eq). The reaction mixture was stirred at 60 °C for 68 h. The solution was diluted with EtOAc (15 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried with $MgSO_4$. The solvents were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (*n*-pentane - EtOAc, 2:1) to give mixture of sulfones **13** and *epi-13* (7.1:1.0; 91 mg, 0.26 mmol, 68%) in form of a colourless oil. *Analytical data for mixture of diastereomers*: **TLC** (*n*-hexane – EtOAc, 2:1): R_f = 0.30. **HR-MS** (APCI): m/z calcd. for $C_{13}H_{20}BrO_4S$ ($M+H^+$): 353.0240, found: 353.0238. **FT-IR** (neat): $\tilde{\nu}$ = 3558 (m), 2963 (m), 2947 (w), 2933 (w), 2894 (w), 2872 (w), 1590 (s), 1574 (m), 1495 (m), 1461 (m), 1443 (w), 1416 (w), 1315 (s), 1297 (s), 1192 (s), 1172 (m), 1147 (m), 1117 (s), 1085 (s), 1015 (s), 963 (w), 953 (w), 875 (m), 834 (s), 822 (m), 802 (w), 763 (w), 660 (m), 601 (m), 568 (s), 537 (s), 503 (m), 458 (m), 436 (m), 419 (m). *Analytical data for (1R*,3S*)-1-bromo-1-((4-methoxyphenyl)sulfonyl)-4-methylpentan-3-ol (13)*: **¹H-NMR** (500 MHz, $CDCl_3$): δ = 0.93 (d, J = 7.1 Hz, 3H, CH_3), 0.95 (d, J = 7.1 Hz, 3H, CH_3), 1.67-1.75 (m, 1H, 4-H), 1.82 (s, 1H, OH), 2.01 (ddd, J = 14.3, 11.8, 2.1 Hz, 1H, 2- H_a), 2.42 (ddd, J = 14.3, 10.5, 2.2 Hz, 1H, 2- H_b), 3.60 (ddd, J = 10.5, 5.6, 2.1 Hz, 1H, 3-H), 3.90 (s, 3H, OCH_3), 5.06 (dd, J = 11.8, 2.2 Hz, 1H, 1-H), 7.04 (d, J = 9.0 Hz, 2H, 3,5- H_{Ar}), 7.90 (J = 9.0 Hz, 2H, 2,6- H_{Ar}). **¹³C-NMR** (125 MHz, $CDCl_3$): δ = 17.7 (CH_3), 18.6 (CH_3), 34.3 (C_4), 35.6 (C_2), 55.9 (OCH_3), 64.6 (C_1), 73.6 (C_3), 114.5 (2C: $C_{Ar}3,5$), 127.0 ($C_{Ar}1$), 132.3 (2C: $C_{Ar}2,6$), 164.6 ($C_{Ar}4$).

³ R. W. Hoffmann, M. Bewersdorf, M. Krüger, W. Mikolajski, R. Stürmer, *Chem. Ber.*, 1991, **124**, 1243.

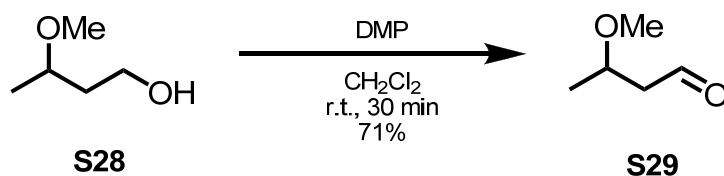


To a solution of sulfinate **8b** (175 mg, 0.54 mmol, 3.00 eq) in DMSO (1.0 mL) was added 1,1-dibromo-4,4-dimethyl-3-pentanol (**14**)⁴ (50 mg, 0.18 mmol, 1.00 eq). The reaction mixture was stirred at 60 °C for 72 h. The solution was diluted with EtOAc (10 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried with MgSO₄. The solvents were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (*n*-pentane - EtOAc, 3:1) to give sulfone **15** (49 mg, 0.13 mmol, 74%) as colourless solid. **TLC** (*n*-hexane - EtOAc, 2:1): R_f = 0.30. **m.p.** (CHCl₃): 82 °C. **¹H-NMR** (500 MHz, CDCl₃): δ = 0.92 (s, 9H, 3 x CH₃), 1.64 (s, 1H, OH), 2.04 (ddd, *J* = 14.2, 11.8, 2.0 Hz, 1H, 2-H_a), 2.40 (ddd, *J* = 14.2, 10.6, 2.1 Hz, 1H, 2-H_b), 3.49 (dd, *J* = 10.6, 2.0 Hz, 1H, 3-H), 3.90 (s, 3H, OCH₃), 5.05 (dd, *J* = 11.8, 2.1 Hz, 1H, 1-H), 7.04 (d, *J* = 9.0 Hz, 2H, 3,5-H_{Ar}), 7.90 (*J* = 9.0 Hz, 2H, 2,6-H_{Ar}). **¹³C-NMR** (125 MHz, CDCl₃): δ = 25.7 (3C: 3 x CH₃), 33.1 (C2), 35.0 (C4), 55.9 (OCH₃), 65.1 (C1), 76.6 (C3), 114.5 (2C: C_{Ar}3,5), 127.1 (C_{Ar}1), 132.3 (2C: C_{Ar}2,6), 164.6 (C_{Ar}4). **FT-IR** (neat): $\tilde{\nu}$ = 3509 (br m), 2964 (m), 2947 (m), 2869 (w), 1595 (m), 1577 (m), 1496 (m), 1465 (w), 1439 (w), 1360 (w), 1322 (m), 1296 (s), 1264 (s), 1218 (w), 1177 (m), 1136 (s), 1113 (m), 1086 (s), 1065 (s), 1016 (s), 979 (m), 936 (w), 919 (m), 855 (w), 832 (s), 806 (s), 746 (m), 670 (m), 625 (w), 577 (s), 556 (s), 530 (m), 491 (m), 475 (m), 417 (w). **HR-MS** (APCI): *m/z* calcd. for C₁₄H₂₁BrO₄SNa (M+Na⁺): 389.0215, found: 389.0212.

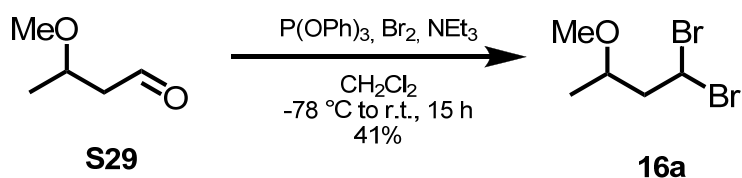
⁴ R. W. Hoffmann, M. Bewersdorf, M. Krüger, W. Mikolajski, R. Stürmer, *Chem. Ber.*, 1991, **124**, 1243.



To a solution of bromosulfones **13a** and **epi-13** (7.1:1.0; 49 mg, 0.14 mmol, 1.00 eq) in THF (3.0 mL) were added 3,5-dinitrobenzoylchloride (64 mg, 0.28 mmol, 2.00 eq), pyridine (0.05 mL, 0.56 mmol, 4.00 eq) and DMAP (4 mg, 0.03 mmol, 0.20 eq) at 0 °C. The reaction mixture was heated to reflux for 4 h. The mixture was diluted with EtOAc (10 mL) and washed with sat. aq. NH₄Cl (1 x 10 mL), sat. aq. NaHCO₃ (1 x 10 mL) and brine (1 x 10 mL). The organic layer was dried with MgSO₄ and the solvents were removed under reduced pressure to give the crude product. Recrystallization from MTBE/THF (10:1) gave dinitrobenzoate **S27** (23 mg, 0.04 mmol, 30%) as a colourless solid. NMR-analysis confirmed the presence of the main diastereomer in the crystal. **TLC** (*n*-hexane – EtOAc, 2:1): R_f = 0.61. **m.p.** (CHCl₃): 169 °C. **¹H-NMR** (400 MHz, CDCl₃): δ = 1.02 (d, *J* = 6.8 Hz, 6H, 2 x CH₃), 2.08-2.17 (m, 1H, 4-H), 2.29 (ddd, *J* = 15.2, 11.7, 1.8 Hz, 1H, 2-H_a), 2.92 (ddd, *J* = 15.2, 9.8, 2.3 Hz, 1H, 2-H_b), 3.90 (s, 3H, OCH₃), 4.71 (dd, *J* = 11.7, 2.3 Hz, 1H, 1-H), 5.34 (ddd, *J* = 9.8, 5.4, 1.8 Hz, 1H, 3-H), 7.03 (d, *J* = 9.0 Hz, 2H, 3,5-H_{Anisole}), 7.88 (d, *J* = 9.0 Hz, 2H, 2,6-H_{Anisole}), 9.10 (d, *J* = 2.1 Hz, 2H, 2,6-H_{Ar}), 9.24 (d, *J* = 2.1 Hz, 1H, 4-H_{Ar}). **¹³C-NMR** (100 MHz, CDCl₃): δ = 18.1 (CH₃), 18.2 (CH₃), 32.3 (C4), 33.7 (C2), 55.9 (OCH₃), 62.8 (C1), 78.8 (C3), 114.6 (2C: C_{Anisole}3,5), 122.8 (C_{Ar}4), 126.1 (C_{Anisole}1), 129.6 (2C: C_{Ar}2,6), 132.4 (2C: C_{Anisole}2,6), 133.6 (C_{Ar}1), 148.9 (2C: C_{Ar}3,5), 162.3 (CO₂Ar), 164.8 (C_{Anisole}4). **FT-IR** (neat): $\tilde{\nu}$ = 3095 (w), 2956 (w), 1733 (m), 1629 (w), 1592 (m), 1573 (w), 1547 (s), 1497 (m), 1474 (w), 1460 (w), 1445 (w), 1414 (w), 1389 (w), 1371 (w), 1344 (s), 1319 (m), 1309 (m), 1298 (m), 1273 (s), 1209 (m), 1167 (m), 1140 (m), 1128 (m), 1084 (m), 1019 (m), 978 (w), 957 (w), 943 (w), 924 (m), 842 (m), 826 (m), 809 (m), 778 (m), 739 (m), 719 (s), 656 (m), 630 (w), 610 (w), 580 (s), 535 (s), 519 (m), 504 (m), 485 (m), 471 (w), 447 (w). **HR-MS** (ESI): *m/z* calcd. for C₂₀H₂₁BrN₂O₉SNa (M+Na⁺): 596.0025, found: 569.0021.

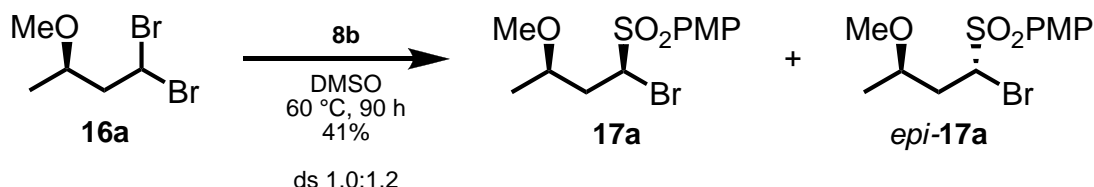


3-Methoxy-1-butanol (**S28**) (175 mg, 1.68 mmol, 1.00 eq) was dissolved in CH₂Cl₂ (17 mL). DMP (1.00 g, 2.36 mmol, 1.40 eq) was added. The reaction mixture was stirred at r.t. for 30 min. The reaction mixture was poured into sat. aq. NaHCO₃. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 25mL). The combined organic layers were dried with MgSO₄. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (Et₂O - *n*-pentane, 1:1) to give 3-methoxybutanal (**S29**) (112 mg, 1.19 mmol, 71%) as a colourless liquid. **TLC** (Et₂O - *n*-pentane, 1:1): R_f = 0.35. **¹H-NMR** (300 MHz, CDCl₃): δ = 1.23 (d, *J* = 6.2 Hz, 3H, CH₃), 2.48 (ddd, *J* = 16.3, 5.1, 1.9 Hz, 1H, 2-H_a), 2.63 (ddd, *J* = 16.3, 7.0, 2.3 Hz, 2-H_b), 3.34 (s, 3H, OCH₃), 3.80-3.90 (m, 1H, 3-H), 9.79 (1H, *J* = 2.13 Hz, 1-H). **¹³C-NMR** (75 MHz, CDCl₃): δ = 19.4 (C4), 50.4 (C2), 56.4 (OCH₃), 72.3 (C3), 201.5 (C1). **FT-IR** (neat): $\tilde{\nu}$ = 2976 (w), 1722 (s), 1375 (m), 1088 (s), 998 (m), 449 (w). **HR-MS** (APCI): *m/z* calcd. for C₁₄H₂₂BrO₃S (M+H⁺):, found:.



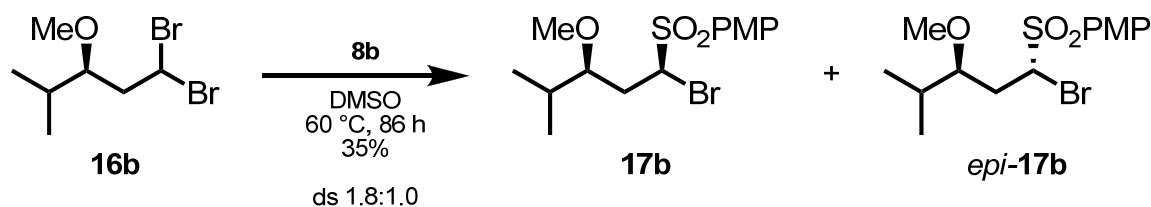
Under argon atmosphere triphenylphosphite (3.20 mL, 9.04 mmol, 1.50 eq) was dissolved in CH₂Cl₂ (90 mL) and cooled to -78 °C. Bromine (0.47 mL, 12.3 mmol, 1.10 eq) was added dropwise, followed by addition of triethylamine (2.86 mL, 20.6 mmol, 2.50 eq) and 3-methoxybutanal (**S29**) (849 mg, 8.22 mmol, 1.00 eq). The mixture was allowed to warm to r.t. and was stirred for 15 h at that temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (*n*-pentane - Et₂O, 5:1) to give the crude product as a pale yellow liquid. Distillation gave dibromide **16a** (822 mg, 3.39 mmol, 41%) as a colourless liquid. **TLC** (*n*-hexane - Et₂O, 2:1): R_f = 0.80. **¹H-NMR** (300 MHz, CDCl₃): δ = 1.18 (d, *J* = 6.0 Hz, 3H, 4-H), 2.481 (ddd, *J* = 14.7, 10.2, 3.3 Hz, 1H, 2-H_a), 2.63 (ddd, *J* = 14.7, 9.4, 3.6 Hz, 2-H_b), 3.34 (s, 3H, OCH₃), 3.48-3.58 (m,

1H, 3-H), 5.84 (dd, $J = 10.2, 3.6$ Hz, CHBr₂). ¹³C-NMR (75 MHz, CDCl₃): $\delta = 18.3$ (C4), 43.1 (C2), 53.0 (C1), 56.6 (OCH₃), 75.1(C3). FT-IR (neat): $\tilde{\nu} = 2978$ (m), 2930 (m), 2824 (w), 1595 (w), 1500 (w), 1462 (m), 1420 (w), 1374 (m), 1351 (m), 1266 (w), 1213 (m), 1168 (s), 1133 (s), 1096 (s), 1073 (s), 1006 (m), 920 (w), 888 (m), 804 (m), 754 (m), 682 (s), 596 (s), 514 (m), 475 (m), 400 (m).



To a solution of sulfinate **8b** (370 mg, 1.23 mmol, 3.00 eq) in DMSO (2.0 mL) was added 1,1-dibromo-3-methoxybutane (**16a**) (100 mg, 0.41 mmol, 1.00 eq). The reaction mixture was stirred at 60 °C for 90 h. The solution was diluted with ethyl acetate (15 mL) and washed with water (10 ml) and brine (10 mL). The organic layer was dried with MgSO₄. The solvents were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (*n*-pentane - EtOAc, 5:1) to give an inseparable mixture of sulfones **17a** and *epi-17a* (1.0:1.2; 59 mg, 0.17 mmol, 41%) as a colourless oil. *Analytical data for mixture of diastereomers*: TLC (*n*-hexane – EtOAc, 2:1): $R_f = 0.39$. HR-MS (APCI): m/z calcd. for C₁₂H₁₈BrO₄S (M+H⁺): 339.0083, found: 339.0081. FT-IR (neat): $\tilde{\nu} = 2971$ (w), 2931 (w), 2840 (w), 2358 (w), 1724 (w), 1591 (s), 1577 (m), 1543 (w), 1495 (m), 1460 (w), 1441 (w), 1415 (w), 1375 (w), 1323 (m), 1299 (m), 1259 (s), 1208 (w), 1172 (m), 1135 (s), 1083 (s), 1021 (m), 919 (w), 892 (w), 833 (m), 804 (m), 770 (m), 731 (w), 715 (w), 700 (w), 660 (m), 626 (w), 574 (m), 535 (m). *Analytical data for 1-(((1S*,3R*)-1-bromo-3-methoxybutyl)sulfonyl)-4-methoxybenzene (17a)*: ¹H-NMR (300 MHz, CDCl₃): $\delta = 1.20$ (d, $J = 6.1$ Hz, 3H, 4-H), 1.90 (ddd, $J = 14.4, 11.9, 2.5$ Hz, 1H, 2-H_a), 2.39-2.50 (m, 1H, 2-H_b), 3.30 (s, 3H, OCH₃), 3.49-3.59 (m, 1H, 3-H), 3.90 (s, 3H, ArOCH₃), 5.03 (dd, $J = 11.9, 2.3$ Hz, 1H, 1-H), 7.04 (d, $J = 8.9$ Hz, 2H, 3,5-H_{Ar}), 7.89 (d, $J = 8.9$ Hz, 2H, 2,6-H_{Ar}). ¹³C-NMR (75 MHz, CDCl₃): $\delta = 18.8$ (C4), 38.8 (C2), 55.9 (ArOCH₃), 56.4 (OCH₃), 63.9 (C1), 73.3 (C3), 114.5 (2C: C_{Ar}3,5), 126.7 (C_{Ar}1), 132.4 (2C: C_{Ar}2,6), 164.4 (C_{Ar}4). *Analytical data for 1-(((1R*,3R*)-1-bromo-3-methoxybutyl)sulfonyl)-4-methoxybenzene (epi-17a)*: ¹H-NMR (300 MHz, CDCl₃): $\delta = 1.16$ (d, $J = 6.2$ Hz, 3H, 4-H), 2.20 (ddd, $J = 14.7, 8.4, 6.4$ Hz, 1H, 2-H_a), 2.39-2.50 (m, 1H, 2-H_b), 3.33 (s, 3H, OCH₃), 3.59-3.69 (m, 1H, 3-H), 3.90 (s, 3H, ArOCH₃), 4.82 (dd, $J = 8.4, 5.3$ Hz, 1H, 1-H), 7.04 (d, $J = 8.9$ Hz, 2H, 3,5-H_{Ar}), 7.89 (d,

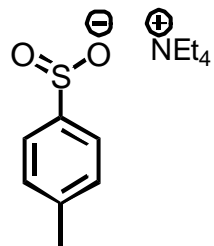
$J = 8.9$ Hz, 2H, 2,6- H_{Ar}). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): $\delta = 18.7$ (C4), 38.3 (C2), 55.9 (ArOCH_3), 56.4 (OCH_3), 61.7 (C1), 74.7 (C3), 114.5 (2C: $C_{Ar3,5}$), 126.7 (C_{Ar1}), 132.4 (2C: $C_{Ar2,6}$), 164.4 (C_{Ar4})



To a solution of sulfinate **8b** (162 mg, 0.54 mmol, 3.00 eq) in DMSO (1.0 mL) was added 1,1-dibromo-3-methoxy-4-methylpentane (**16b**)⁵ (49 mg, 0.18 mmol, 1.00 eq). The reaction mixture was stirred at 60 °C for 86 h. The solution was diluted with EtOAc (15 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was dried with MgSO_4 . The solvents were removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (*n*-pentane - EtOAc, 5:1) to give an inseparable mixture of sulfones **17b** and *epi-17b* (1.8:1.0; 23 mg, 0.06 mmol, 35%) as a colourless oil. *Analytical data for mixture of diastereomers*: TLC (*n*-hexane – MTBE, 5:1): $R_f = 0.17$. HR-MS (APCI): m/z calcd. for $\text{C}_{14}\text{H}_{22}\text{BrO}_4\text{S}$ ($\text{M}+\text{H}^+$): 367.0397, found: 367.0396. FT-IR (neat): $\tilde{\nu} = 2961$ (m), 1593 (m), 1577 (m), 1496 (m), 1462 (m), 1442 (w), 1323 (m), 1309 (m), 1300 (m), 1261 (s), 1207 (w), 1173 (w), 1142 (s), 1110 (m), 1084 (s), 1023 (m), 976 (w), 911 (m), 882 (w), 834 (m), 804 (m), 765 (w), 729 (s), 670 (m), 649 (w), 627 (w), 568 (s), 536 (s), 500 (m), 480 (w), 457 (w). *Analytical data for 1-(((1S*,3S*)-1-bromo-3-methoxy-4-methylpentyl)sulfonyl)-4-methoxybenzene (17b)*: $^1\text{H-NMR}$ (500 MHz, CDCl_3): $\delta = 0.88$ -0.90 (m, 6H, 2 x CH_3), 1.89 (ddd, $J = 14.3, 11.9, 2.3$ Hz, 1H, 2- H_a), 1.99-2.05 (m, 1H, 4-H), 2.42 (ddd, $J = 14.3, 10.7, 2.2$ Hz, 1H, 2- H_b), 3.25 (ddd, $J = 10.7, 4.7, 2.3$ Hz, 1H, 3-H), 3.34 (s, 3H, OCH_3), 3.90 (s, 3H, ArOCH_3), 4.98 (dd, $J = 11.9, 2.2$ Hz, 1H, 1-H), 7.03 (d, $J = 8.9$ Hz, 2H, 3,5- H_{Ar}), 7.89 (d, $J = 8.9$ Hz, 2H, 2,6- H_{Ar}). $^{13}\text{C-NMR}$ (125 MHz, CDCl_3): $\delta = 16.8$ (C3), 18.5 (C3), 29.6 (C4), 32.2 (C2), 55.9 (ArOCH_3), 57.9 (OCH_3), 64.8 (C1), 82.2 (C3), 114.5 (2C: $C_{Ar3,5}$), 127.1 (C_{Ar1}), 132.4 (2C: $C_{Ar2,6}$), 164.5 (C_{Ar4}). *Analytical data for 1-(((1R*,3S*)-1-bromo-3-methoxy-4-methylpentyl)sulfonyl)-4-methoxybenzene (epi-17b)*: $^1\text{H-NMR}$ (500 MHz, CDCl_3): $\delta = 0.87$ -0.89 (m, 6H, 2 x CH_3), 1.85 (ddd, $J = 13.5, 6.6, 5.0$ Hz, 1H, 2- H_a), 2.10-2.16 (m, 1H, 4-H), 2.51 (ddd, $J = 15.1, 5.6, 5.6$ Hz, 1H, 2- H_b), 3.31-

⁵ R. W. Hoffmann, K. Brumm, M. Bewersdorf, W. Mikolajski, A. Kusche, *Chem. Ber.*, 1992, **125**, 2741.

3.33 (m, 1H, 3-H), 3.36 (s, 3H, OCH₃), 3.90 (s, 3H, ArOCH₃), 4.85 (dd, $J = 7.2, 5.6$ Hz, 1H, 1-H), 7.03 (d, $J = 8.9$ Hz, 2H, 3,5-H_{Ar}), 7.89 (d, $J = 8.9$ Hz, 2H, 2,6-H_{Ar}). **¹³C-NMR** (125 MHz, CDCl₃): $\delta = 17.4$ (C3), 17.8 (C3), 30.1 (C4), 34.3 (C2), 55.9 (ArOCH₃), 57.9 (OCH₃), 62.0 (C1), 83.3 (C3), 114.5 (2C: C_{Ar}3,5), 127.1 (C_{Ar}1), 132.4 (2C: C_{Ar}2,6), 164.5 (C_{Ar}4).



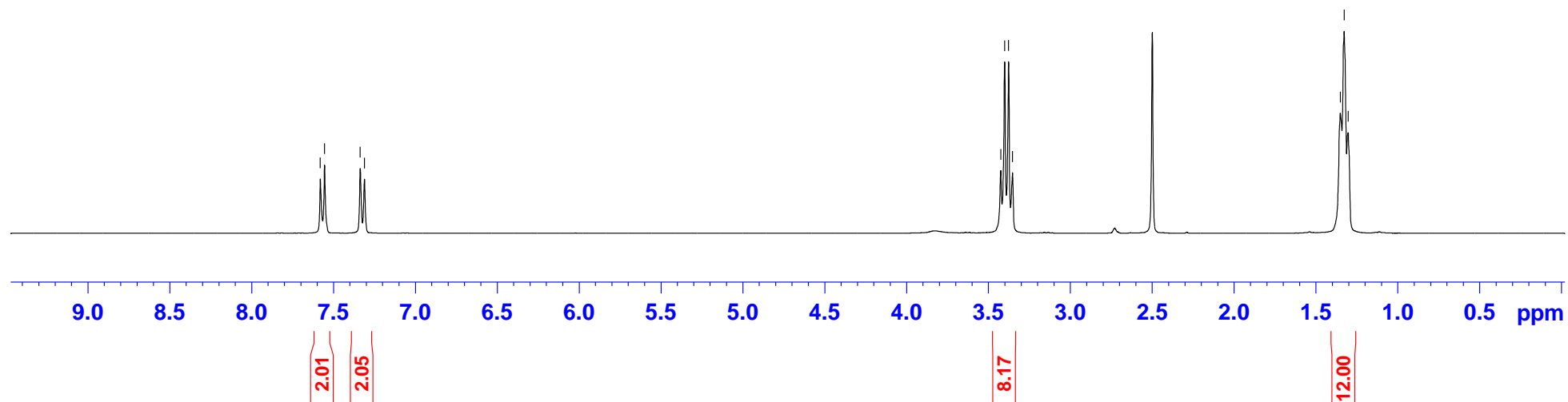
8a

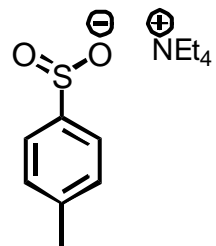
300 MHz, DMSO-*d*₆

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7.556
7.338
7.312

3.426
3.402
3.377
3.354

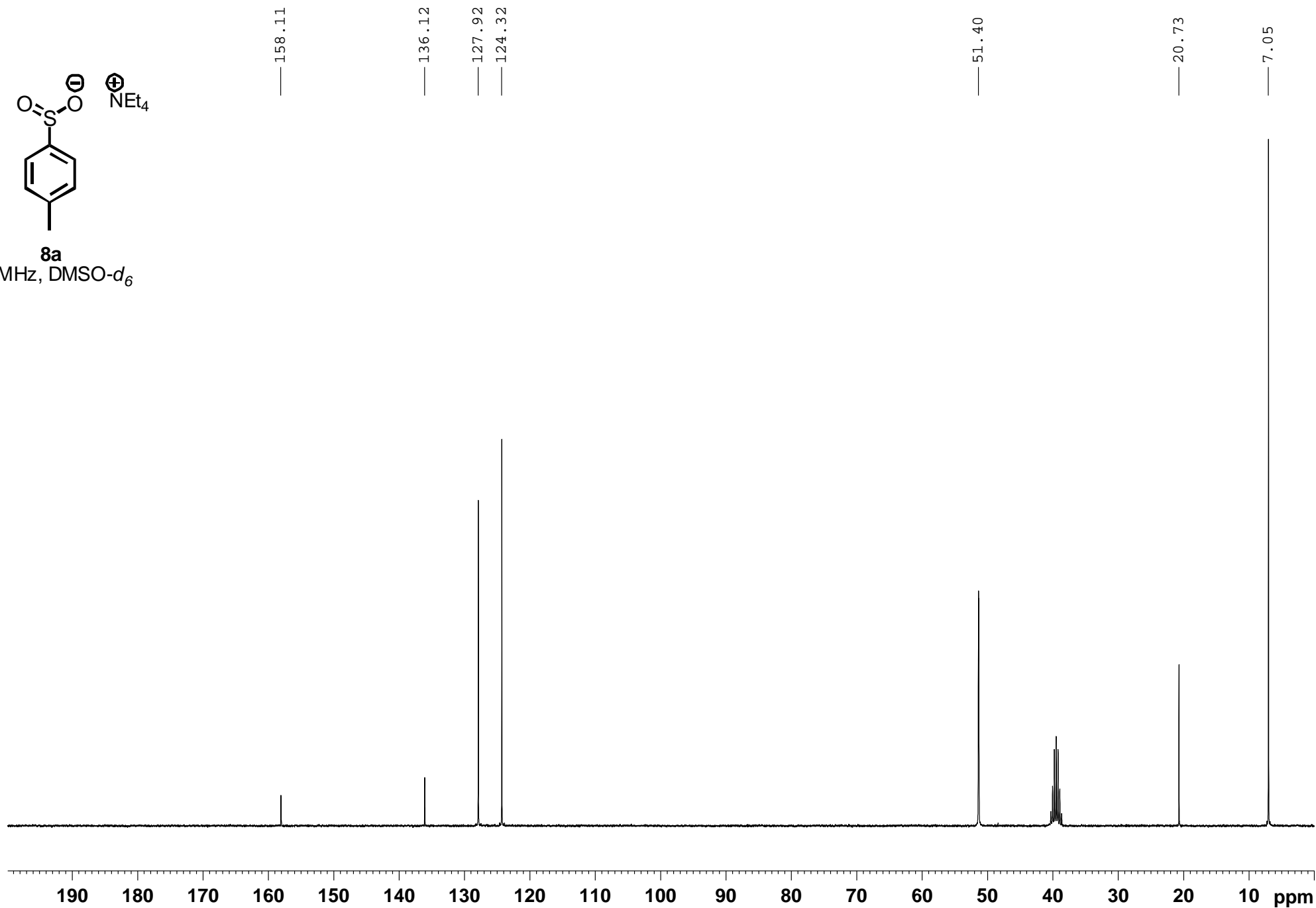
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1.328
1.304

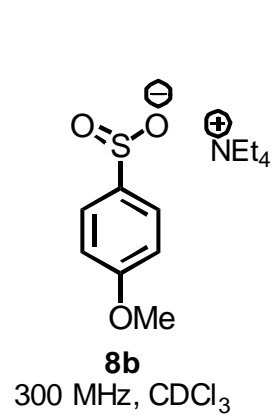




8a

75 MHz, DMSO- d_6





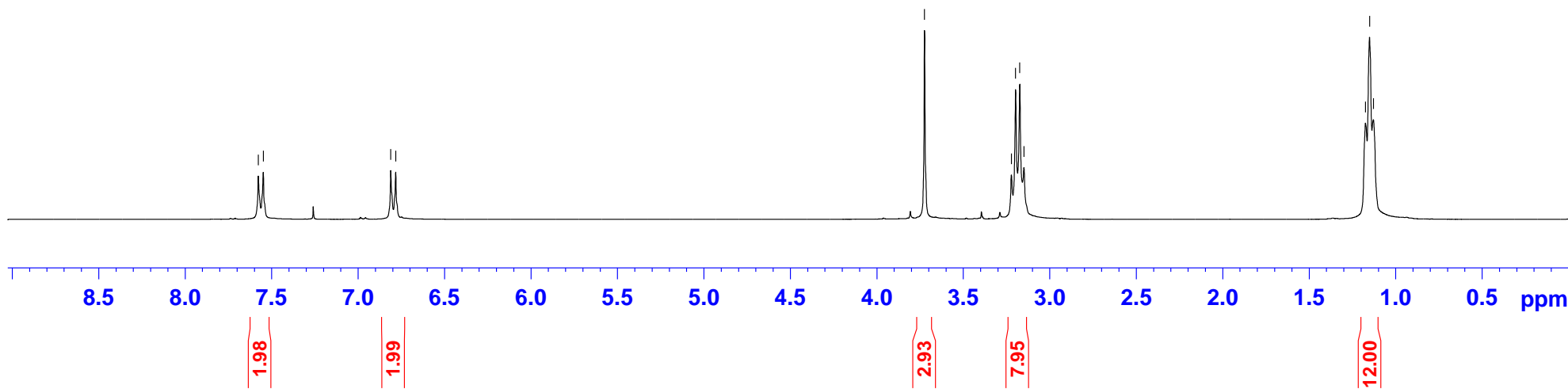
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7.549

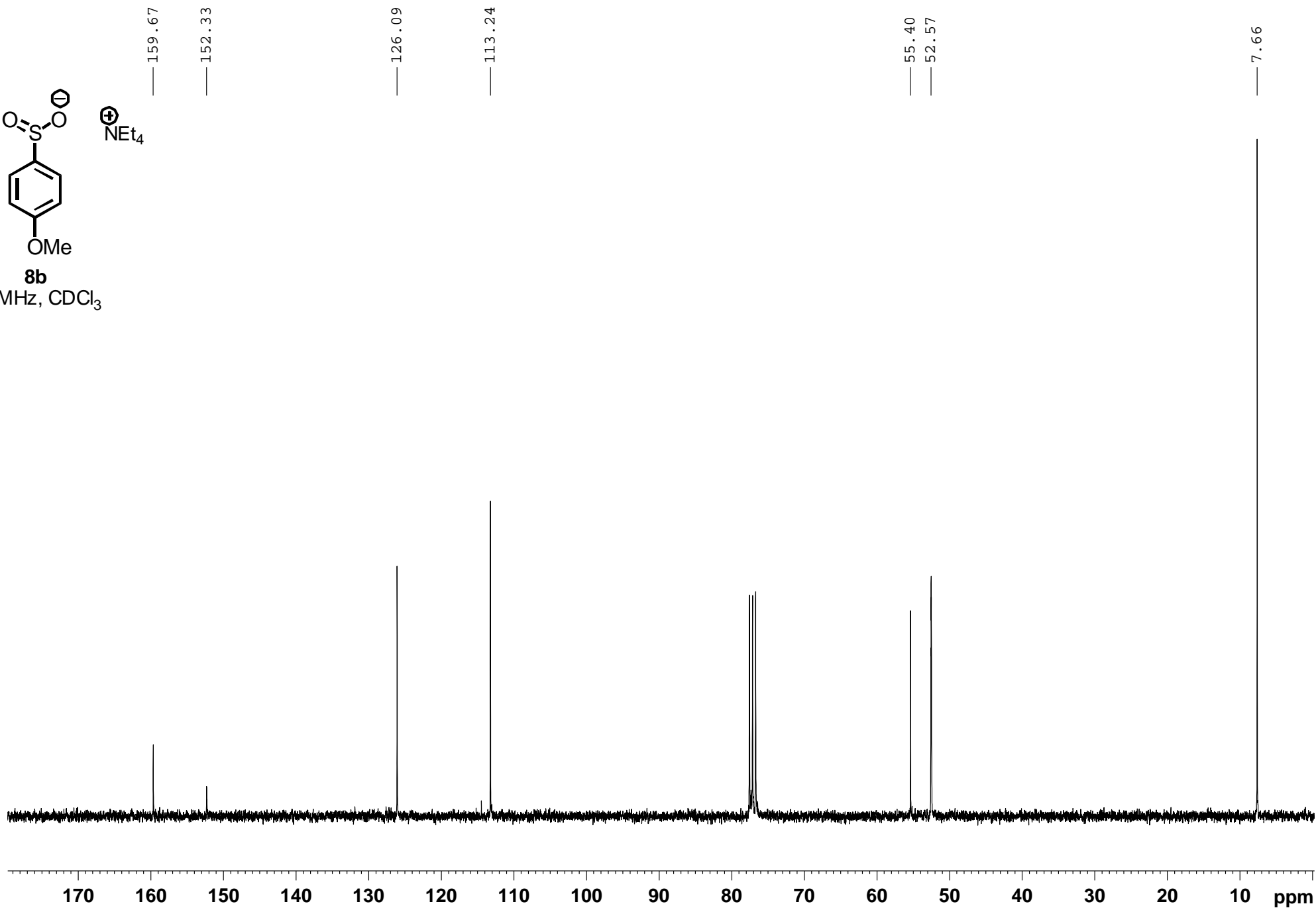
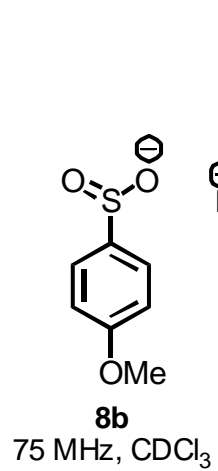
6.812
6.783

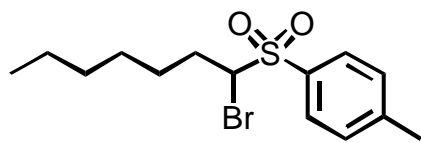
3.726

3.223
3.199
3.175
3.151

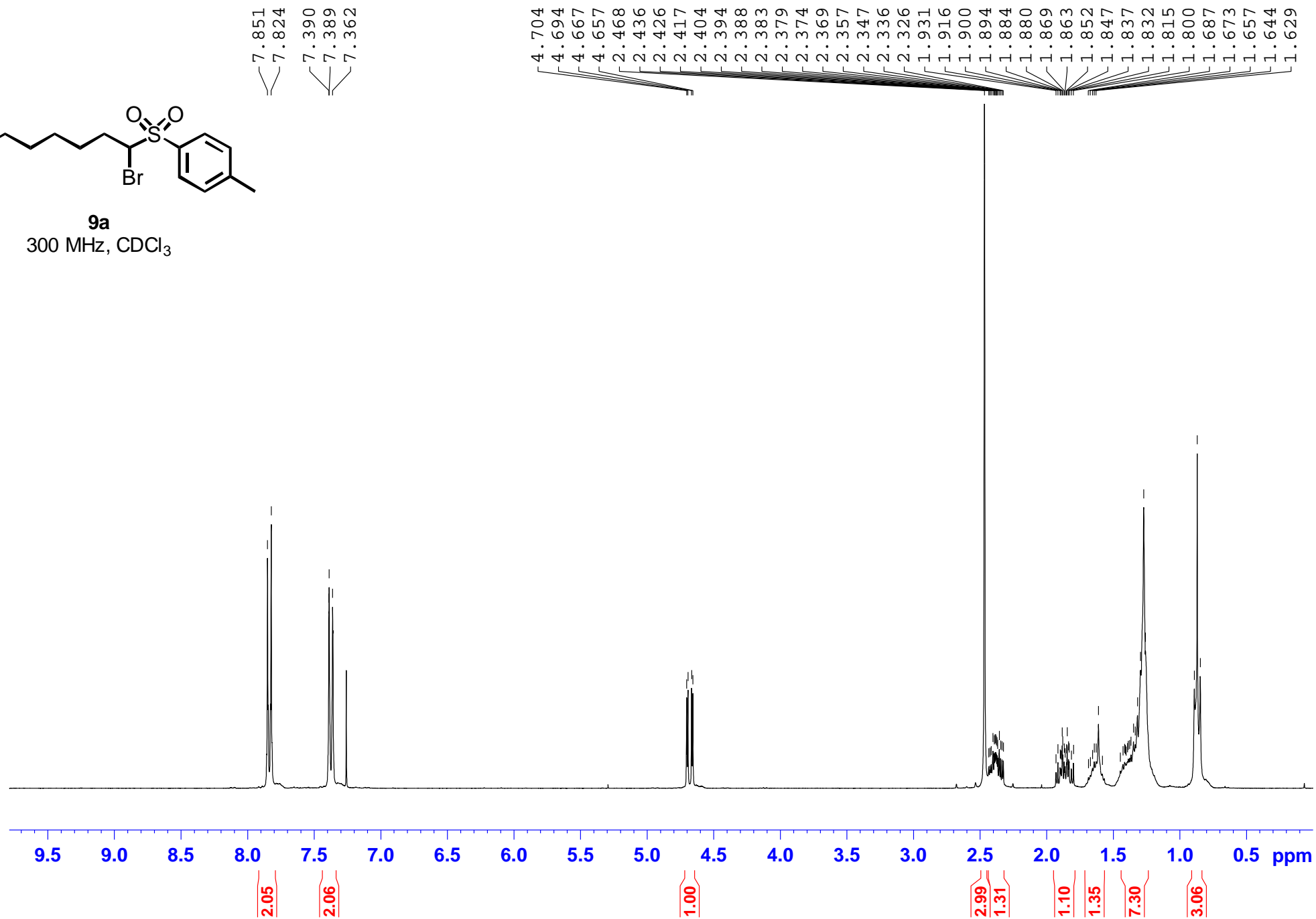
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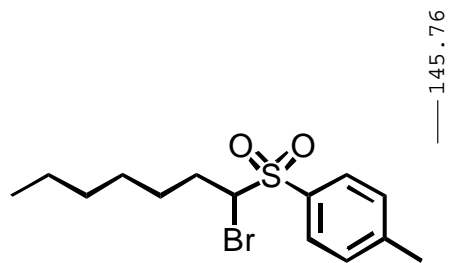






9a
300 MHz, CDCl₃





9a

75 MHz, CDCl₃

— 145.76

— 132.53

— 130.22

— 129.82

— 66.34

— 31.51

— 31.49

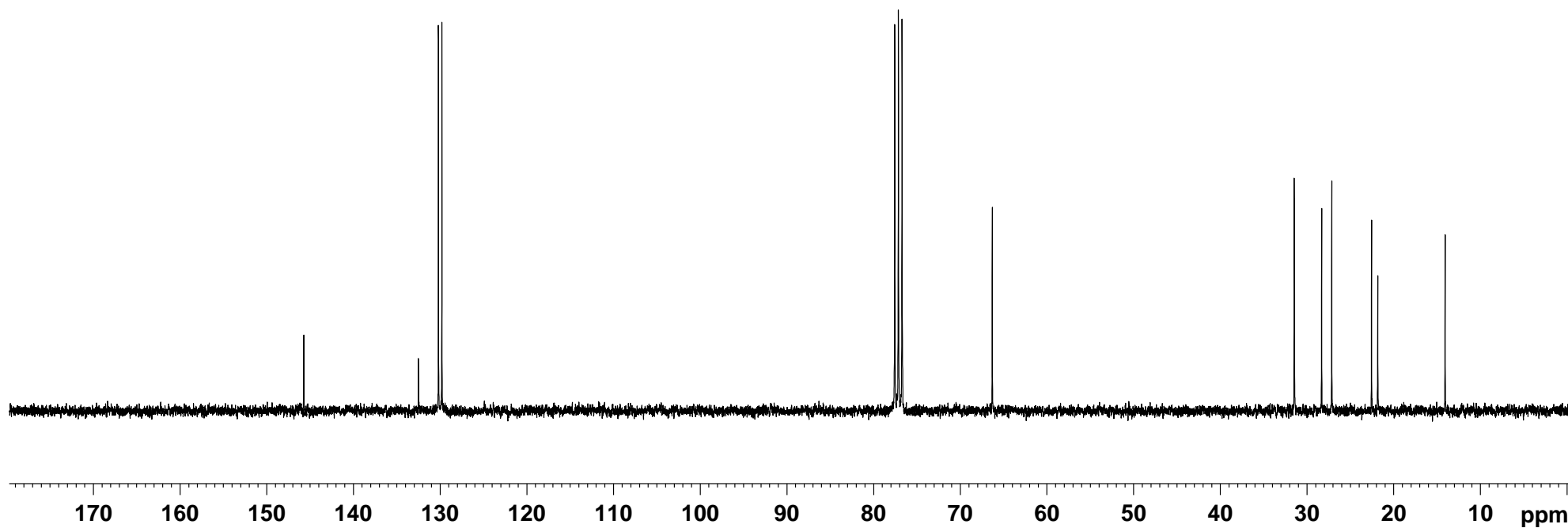
— 28.34

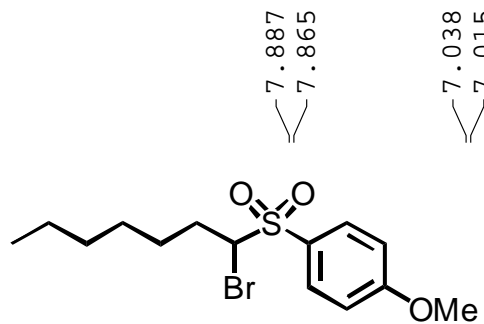
— 27.18

— 22.58

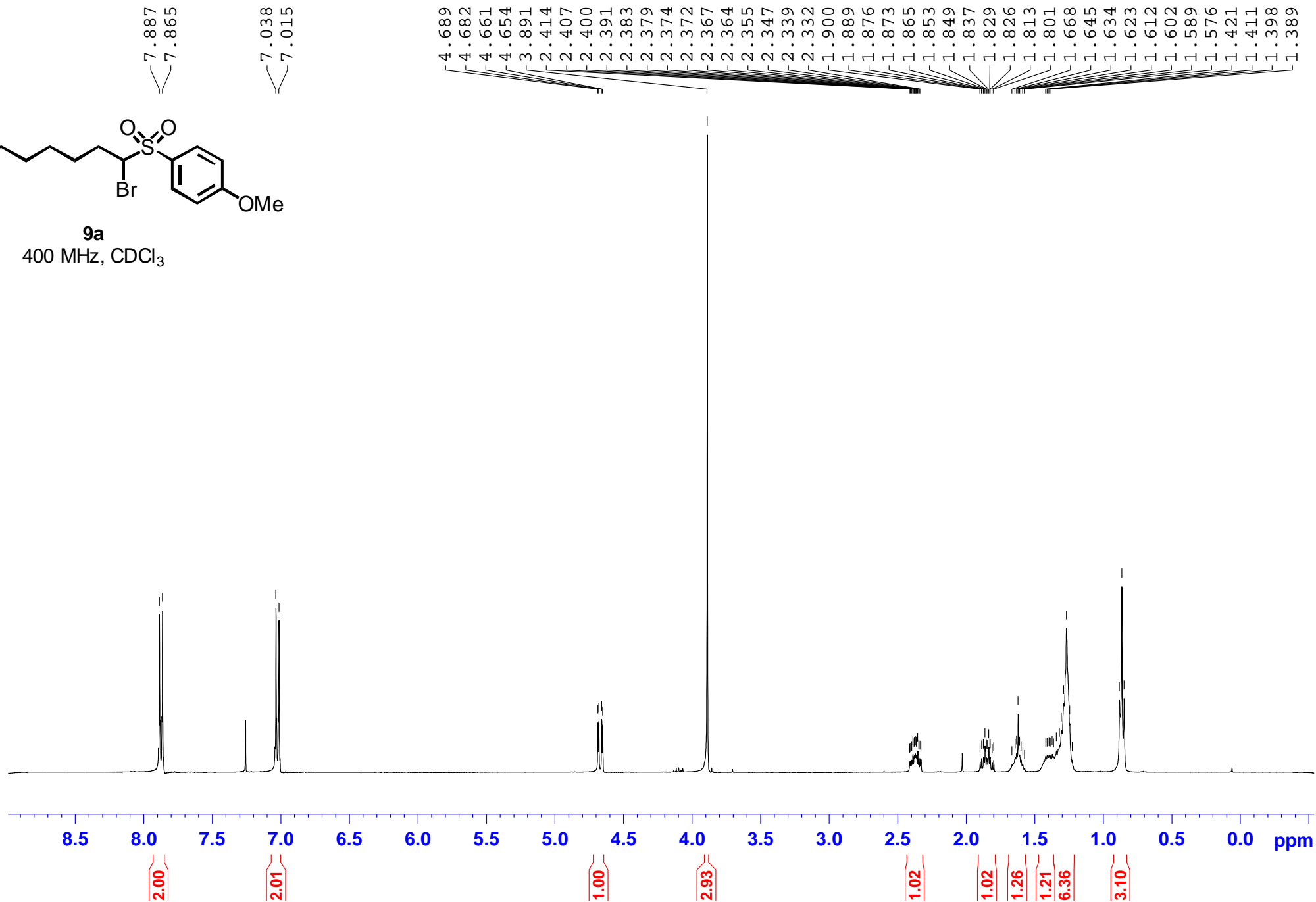
— 21.86

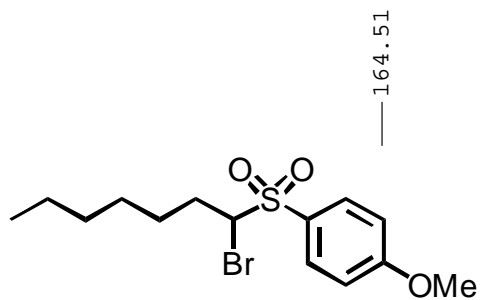
— 14.09



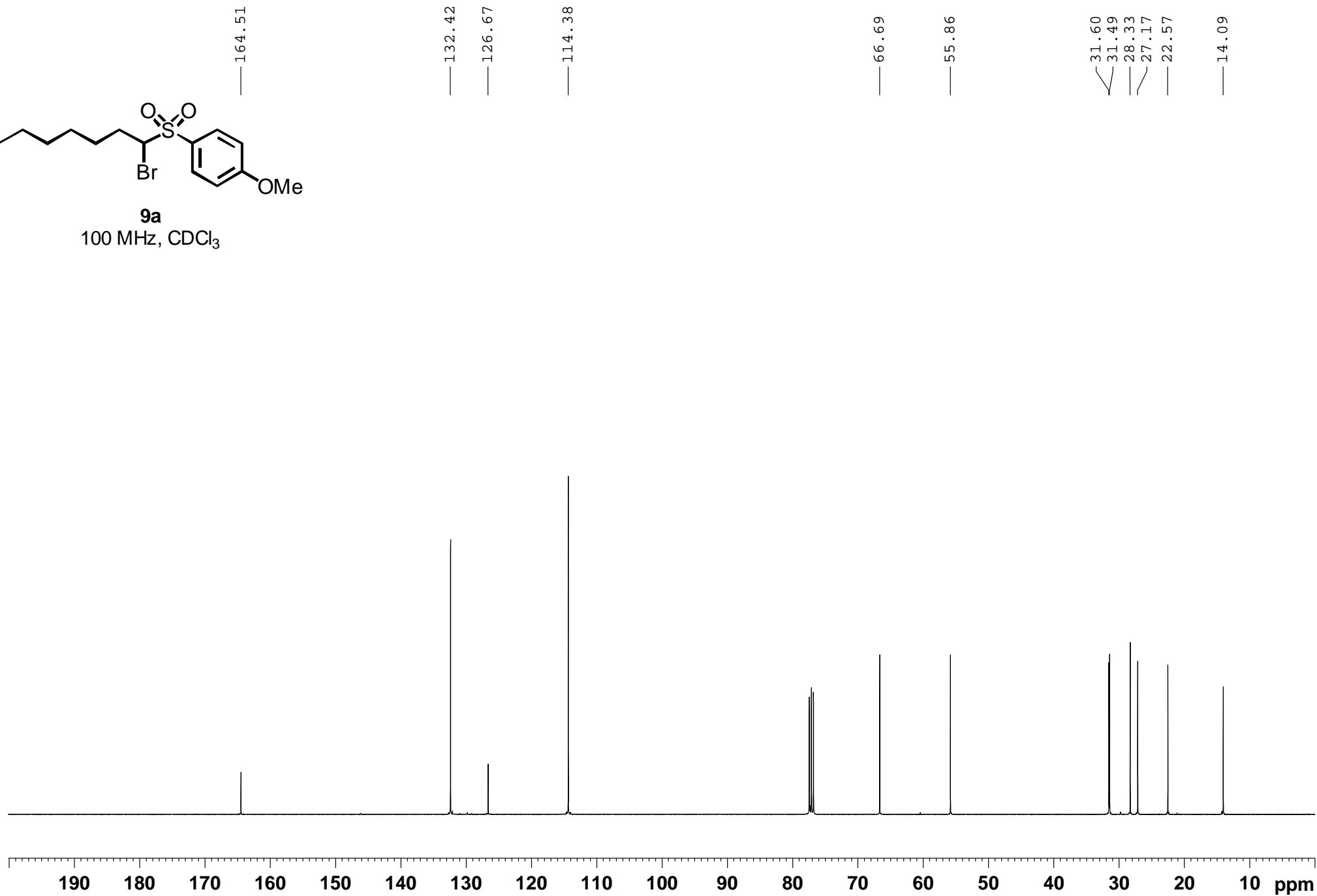


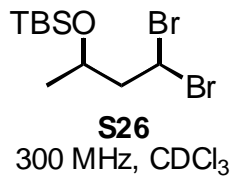
9a
400 MHz, CDCl₃





9a
100 MHz, CDCl₃





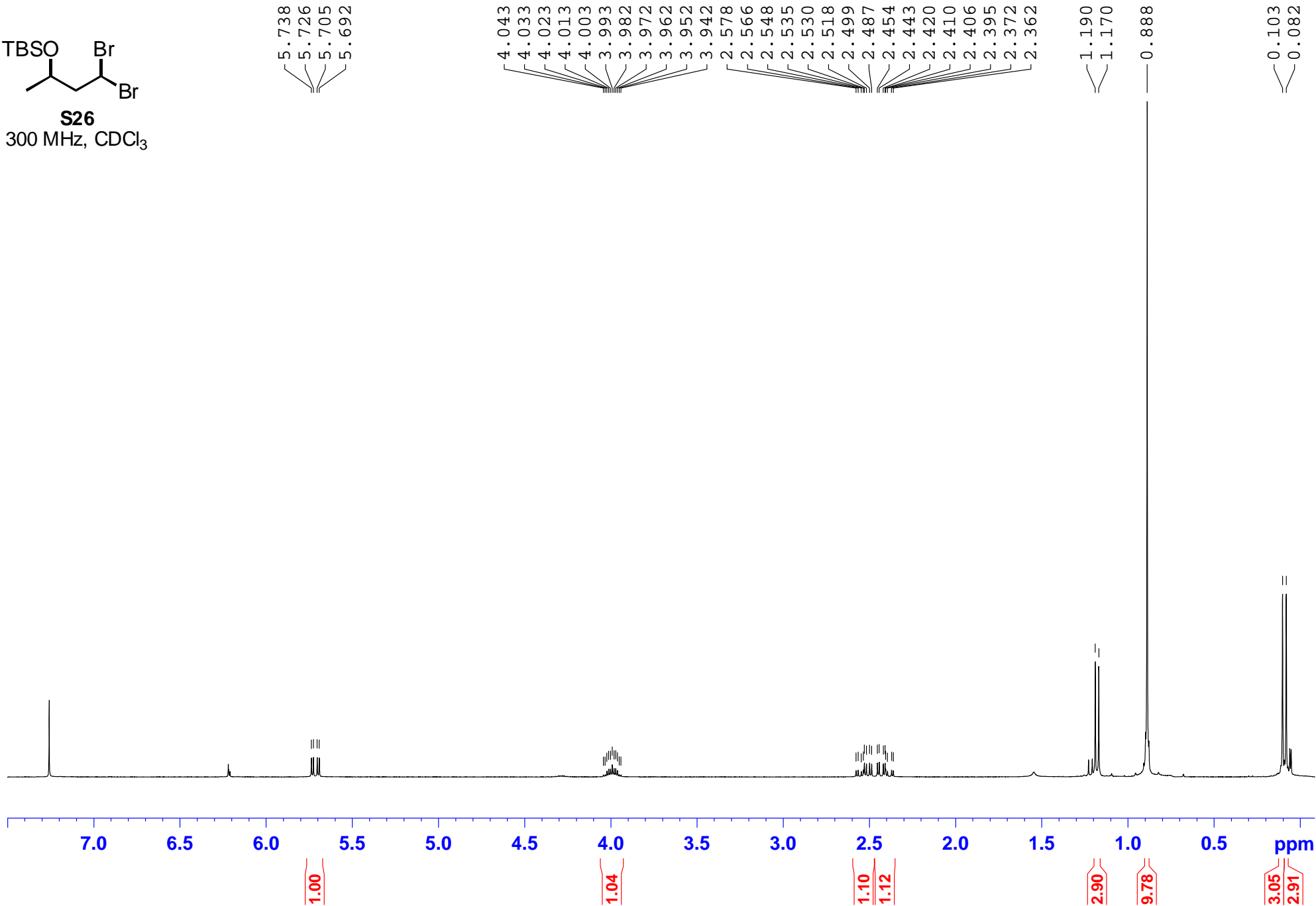
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5.726
5.705
5.692

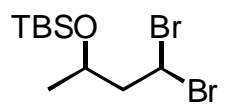
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2.566
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2.535
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2.362

1.190
1.170

0.888

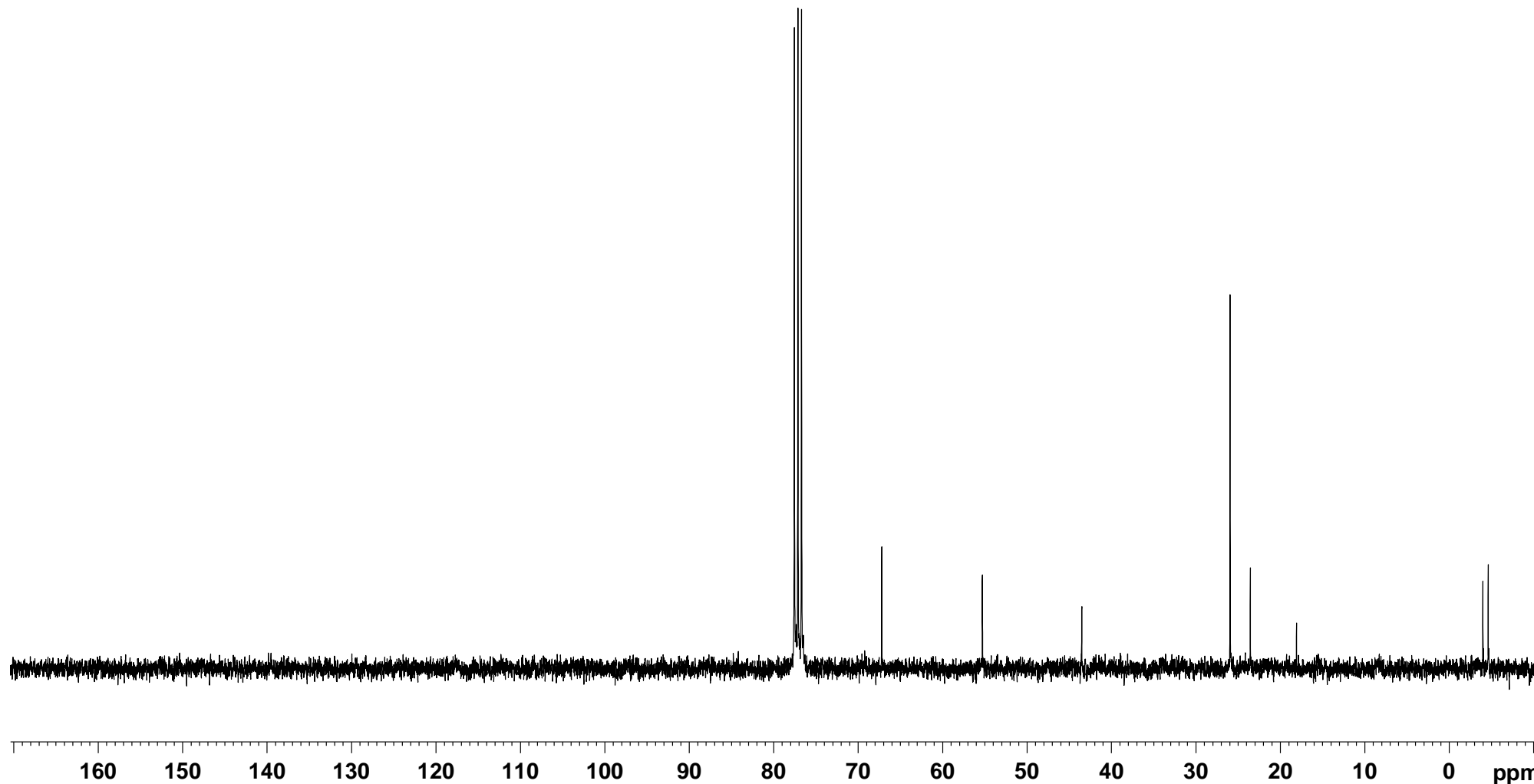
0.103
0.082

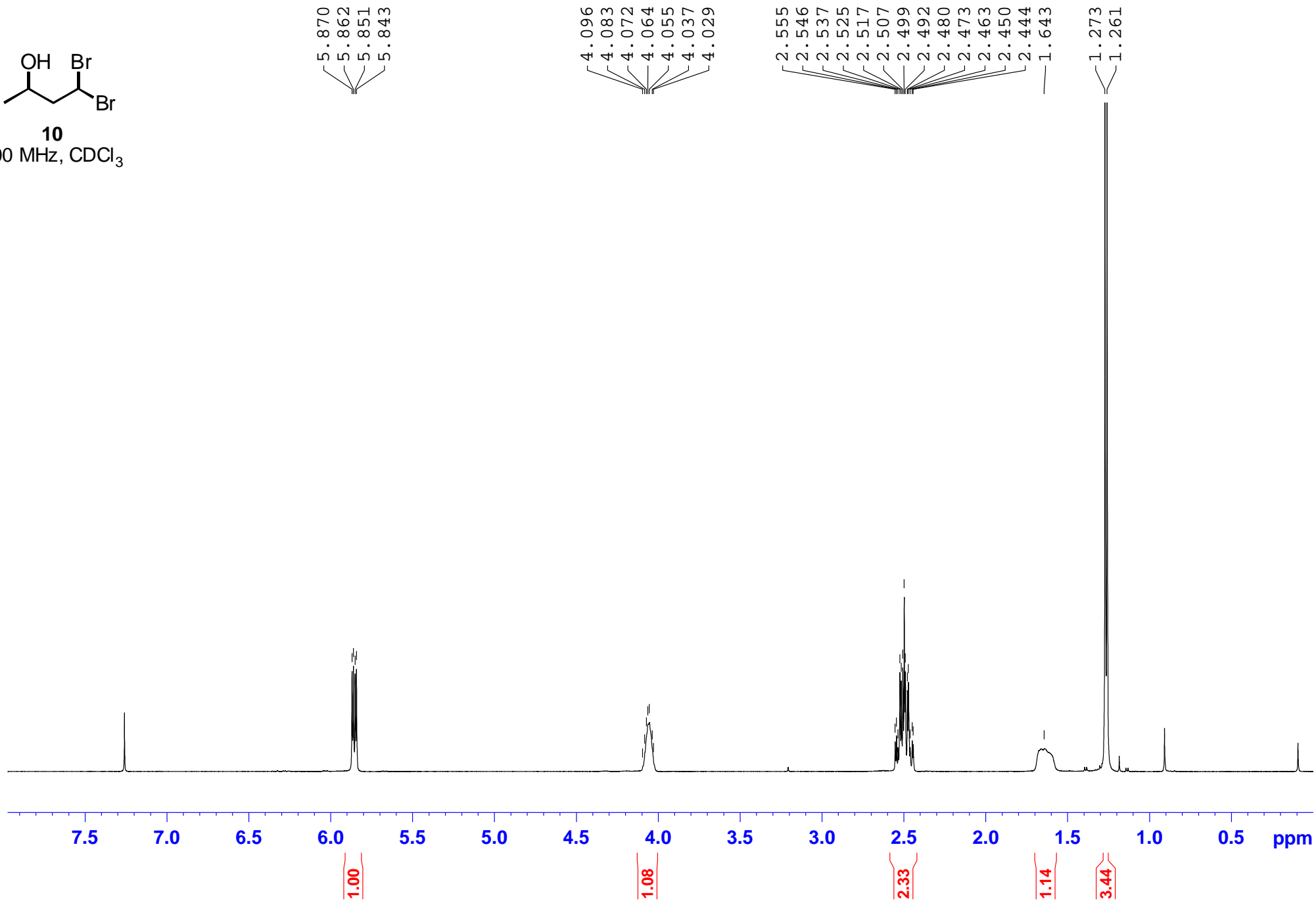
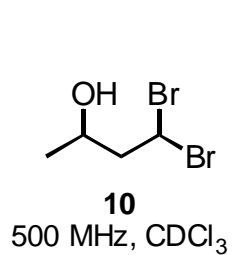


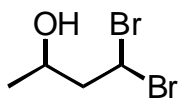


S26
75 MHz, CDCl₃

— 67.24
— 55.32
— 43.55
— 25.99
— 23.59
— 18.12





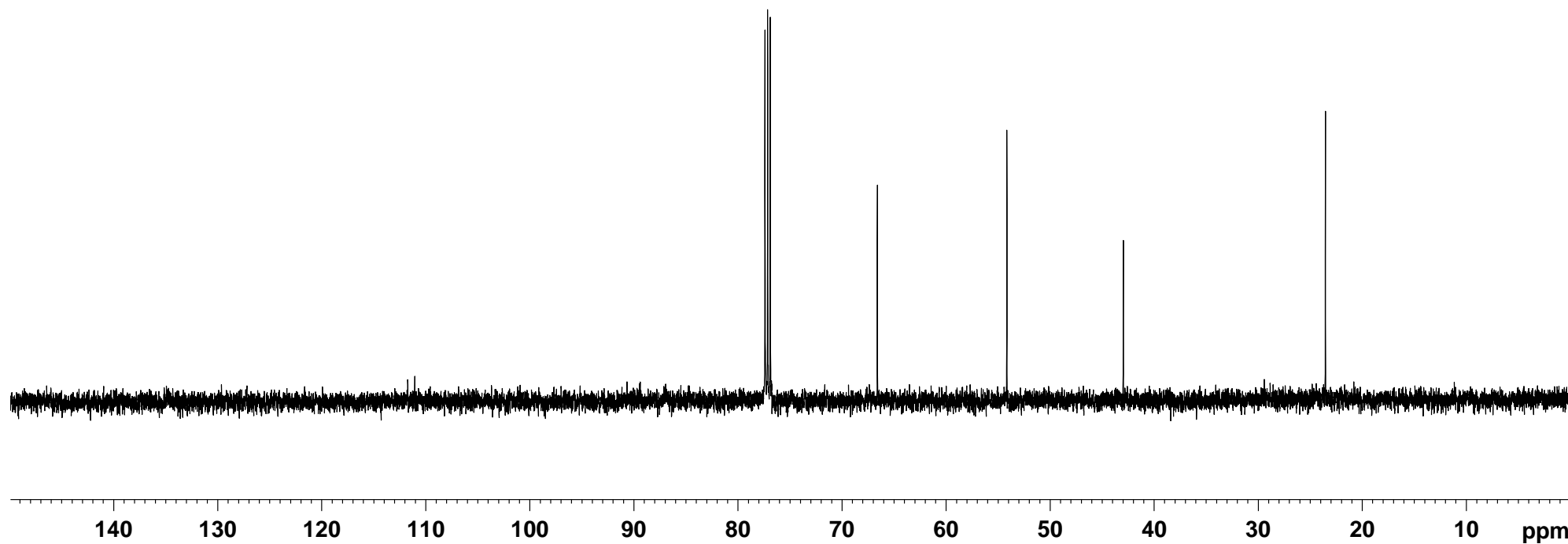
10
125 MHz, CDCl₃

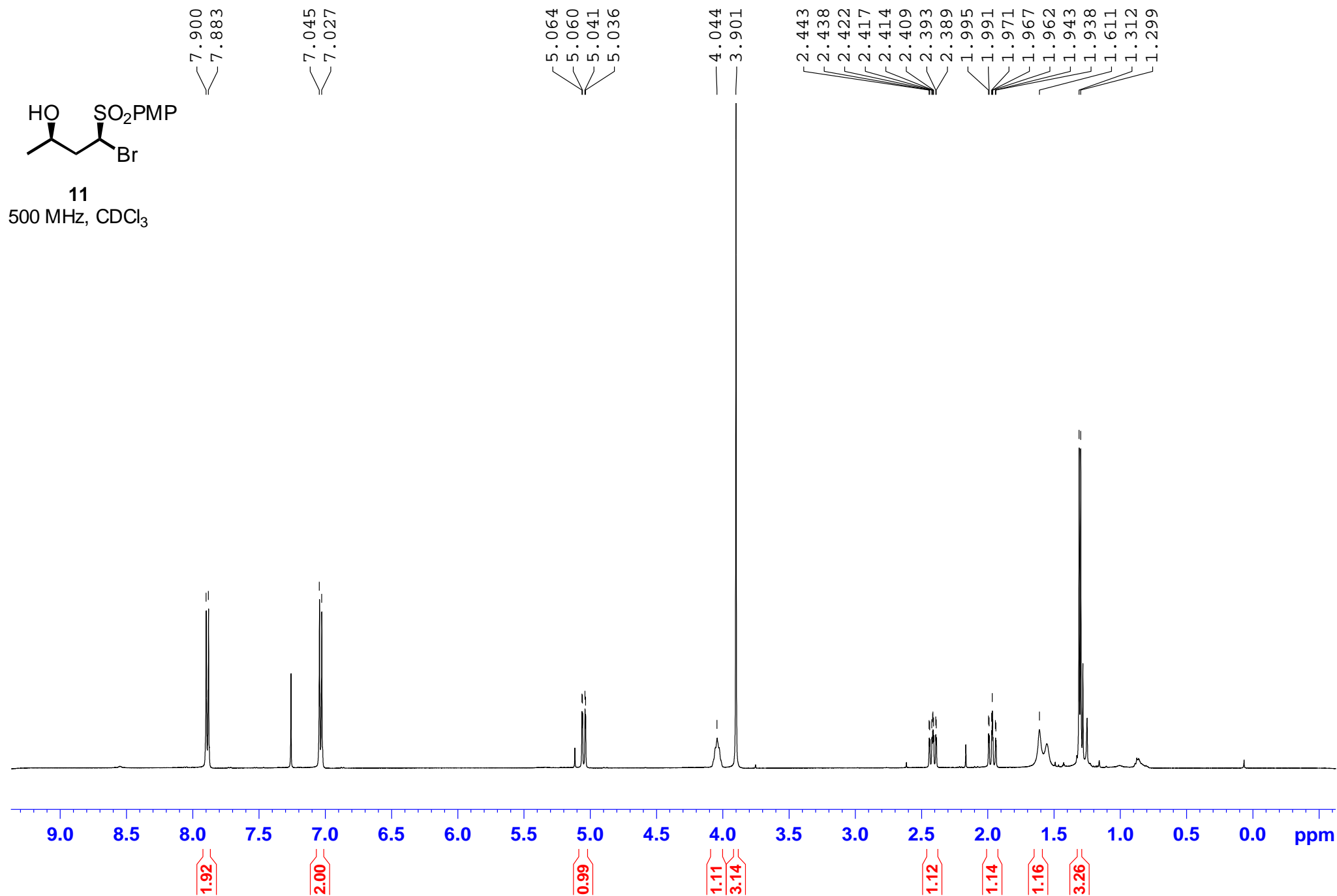
— 66.61

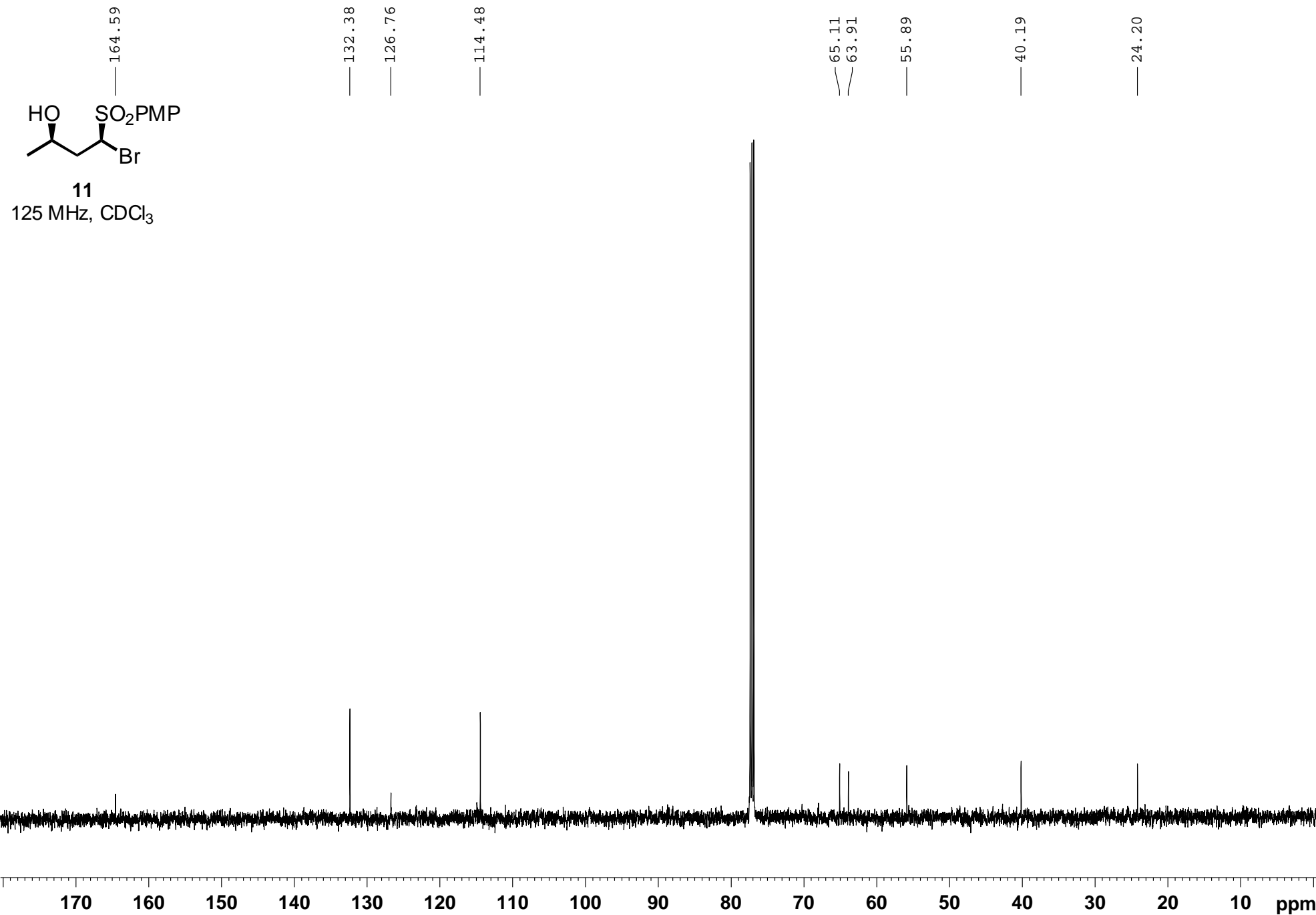
— 54.17

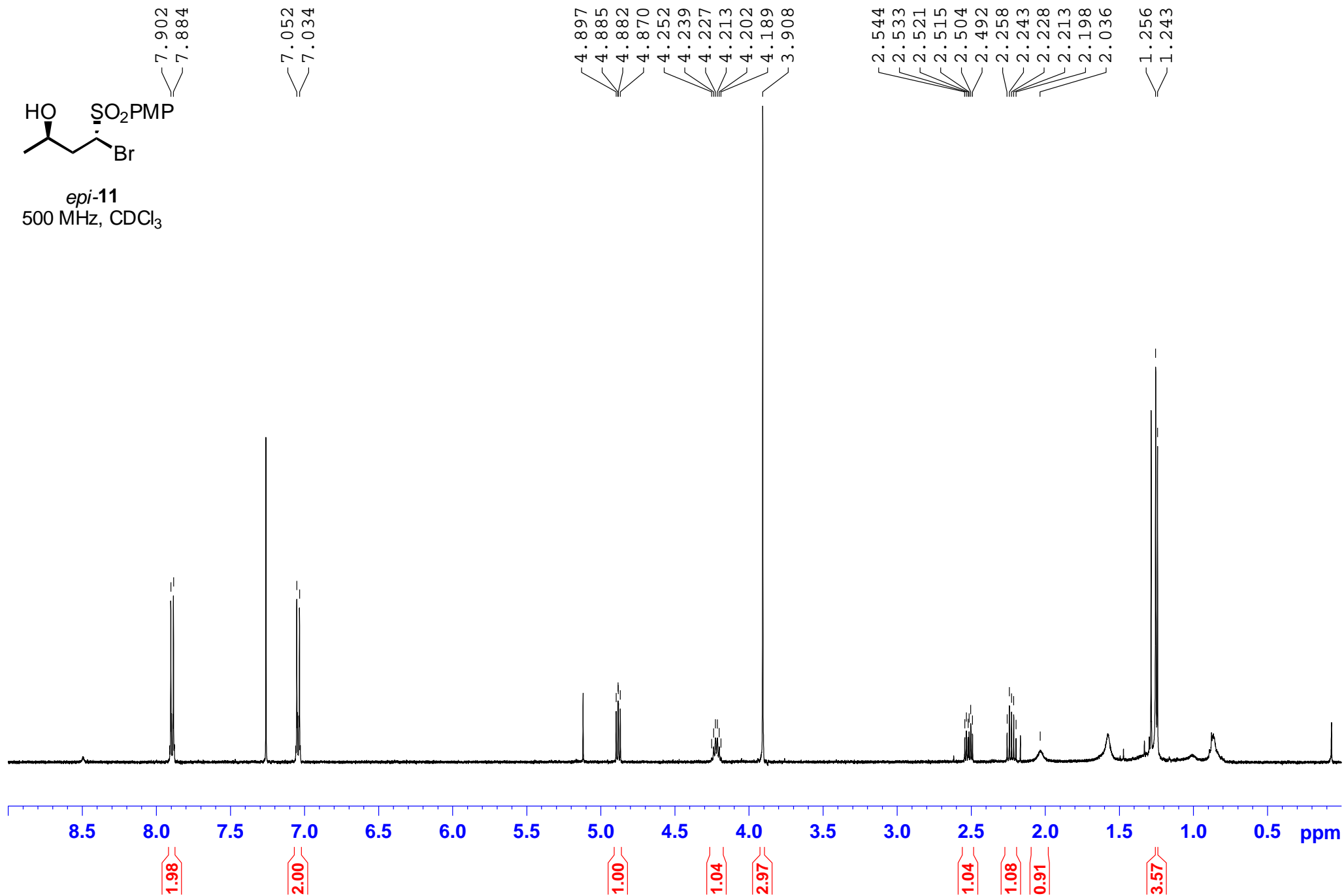
— 42.97

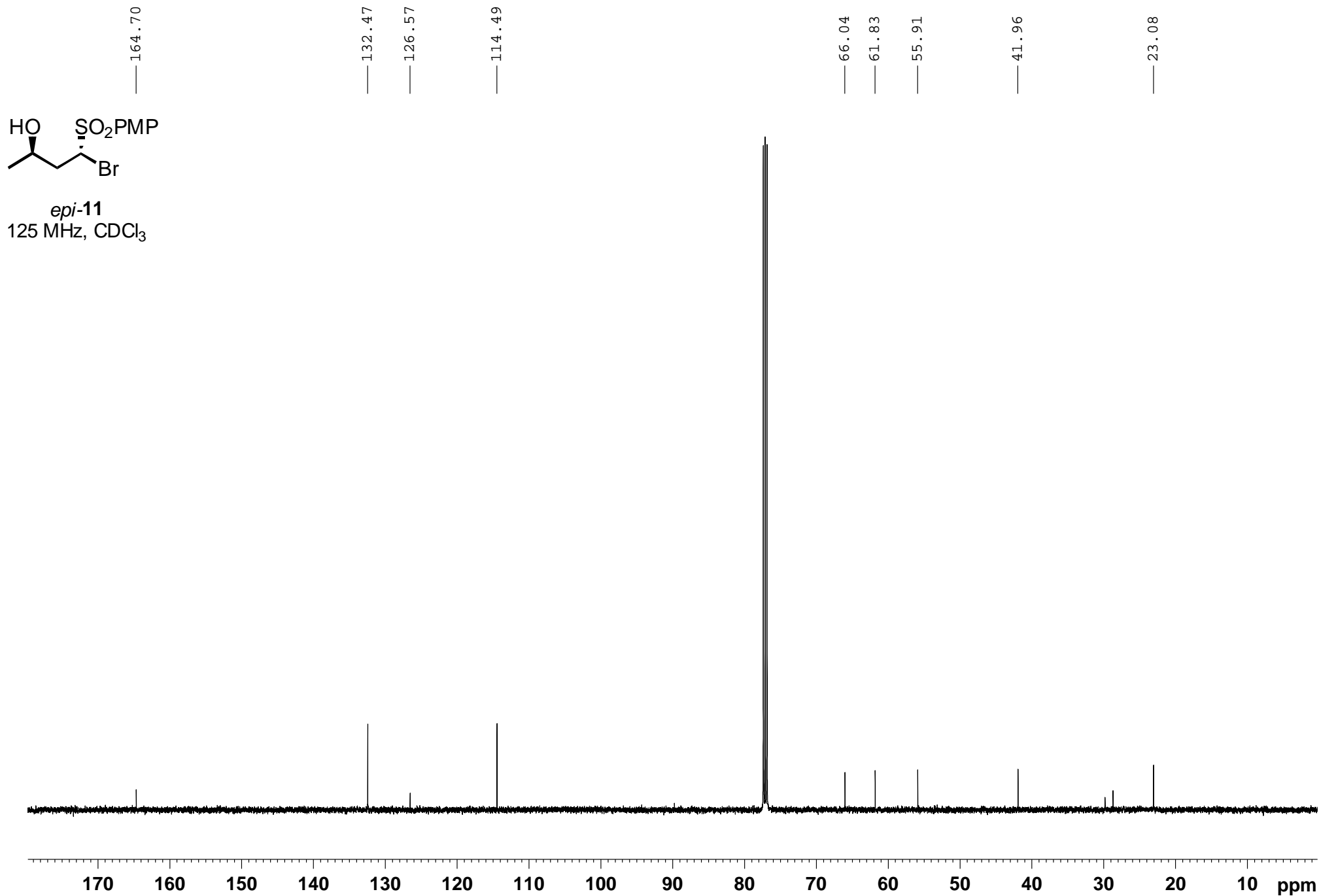
— 23.55

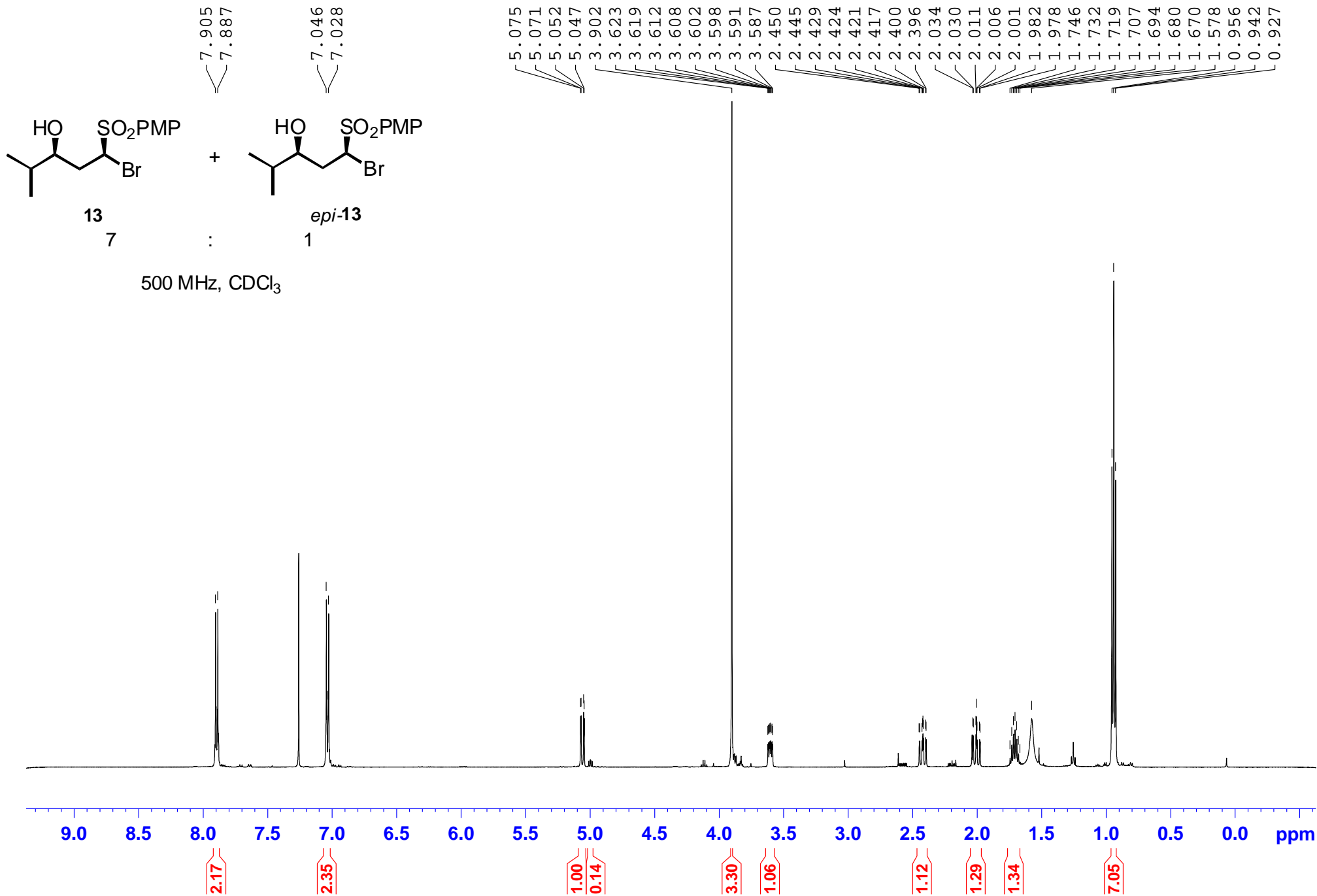


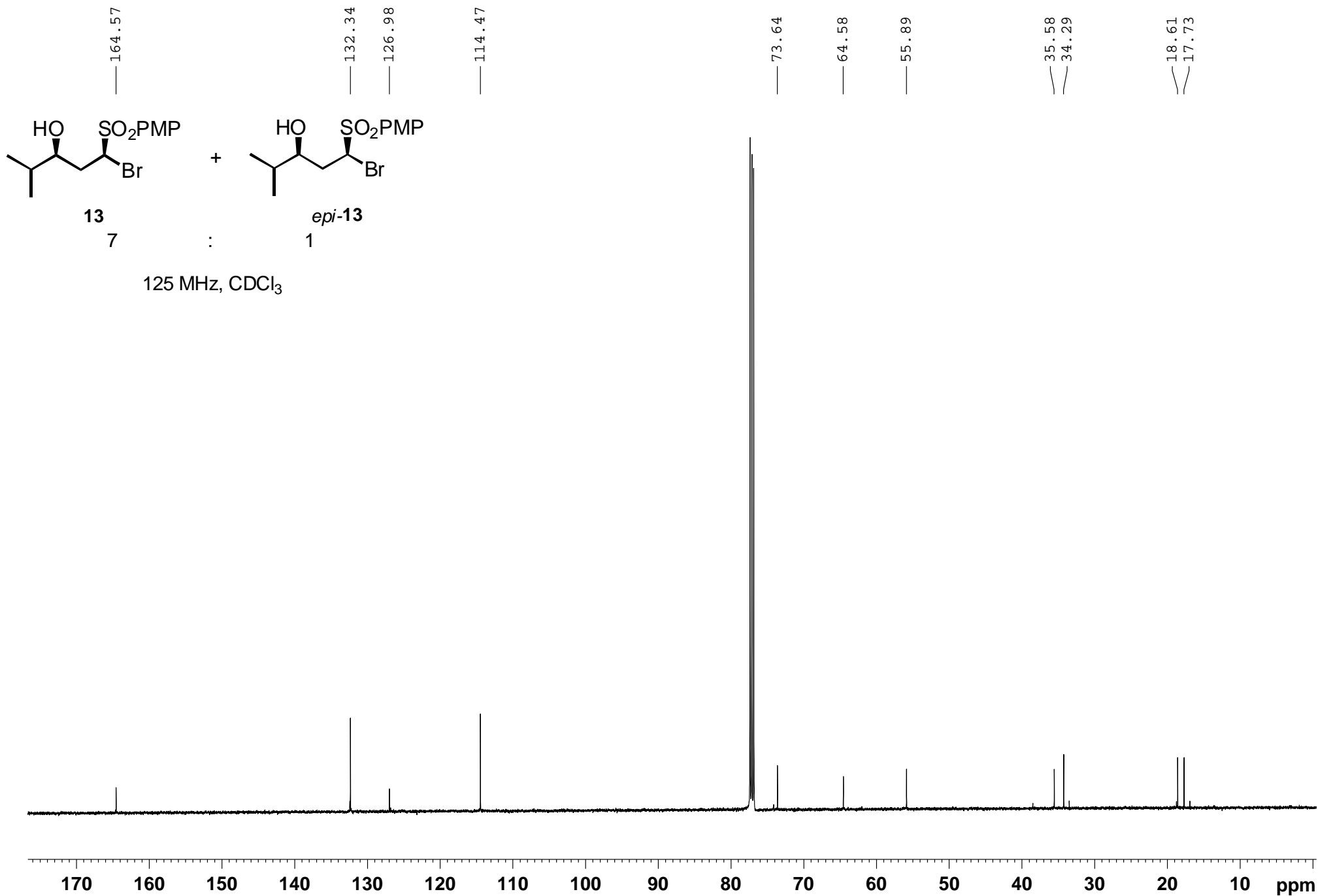












7.907
7.890
7.260
7.047
7.029

5.064
5.060
5.041
5.037

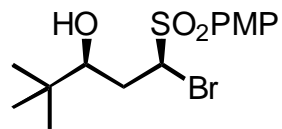
3.903

3.499
3.495
3.478
3.474

2.431
2.427
2.410
2.406
2.403
2.398
2.381
2.377

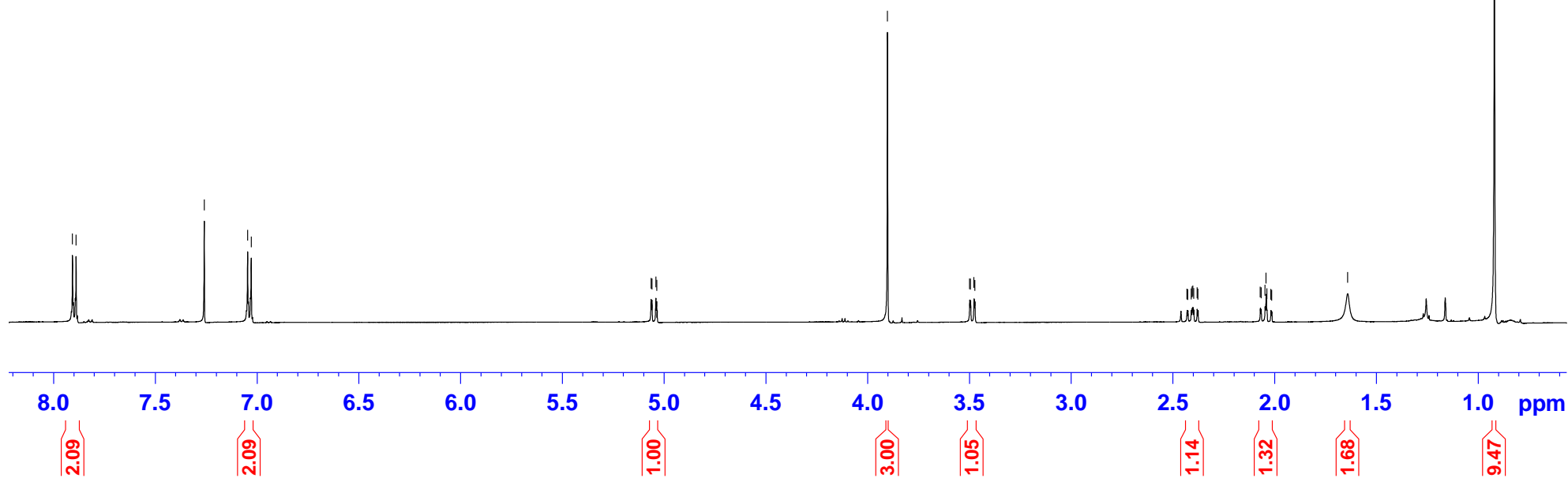
2.071
2.067
2.047
2.043
2.039
2.019
2.015
1.642

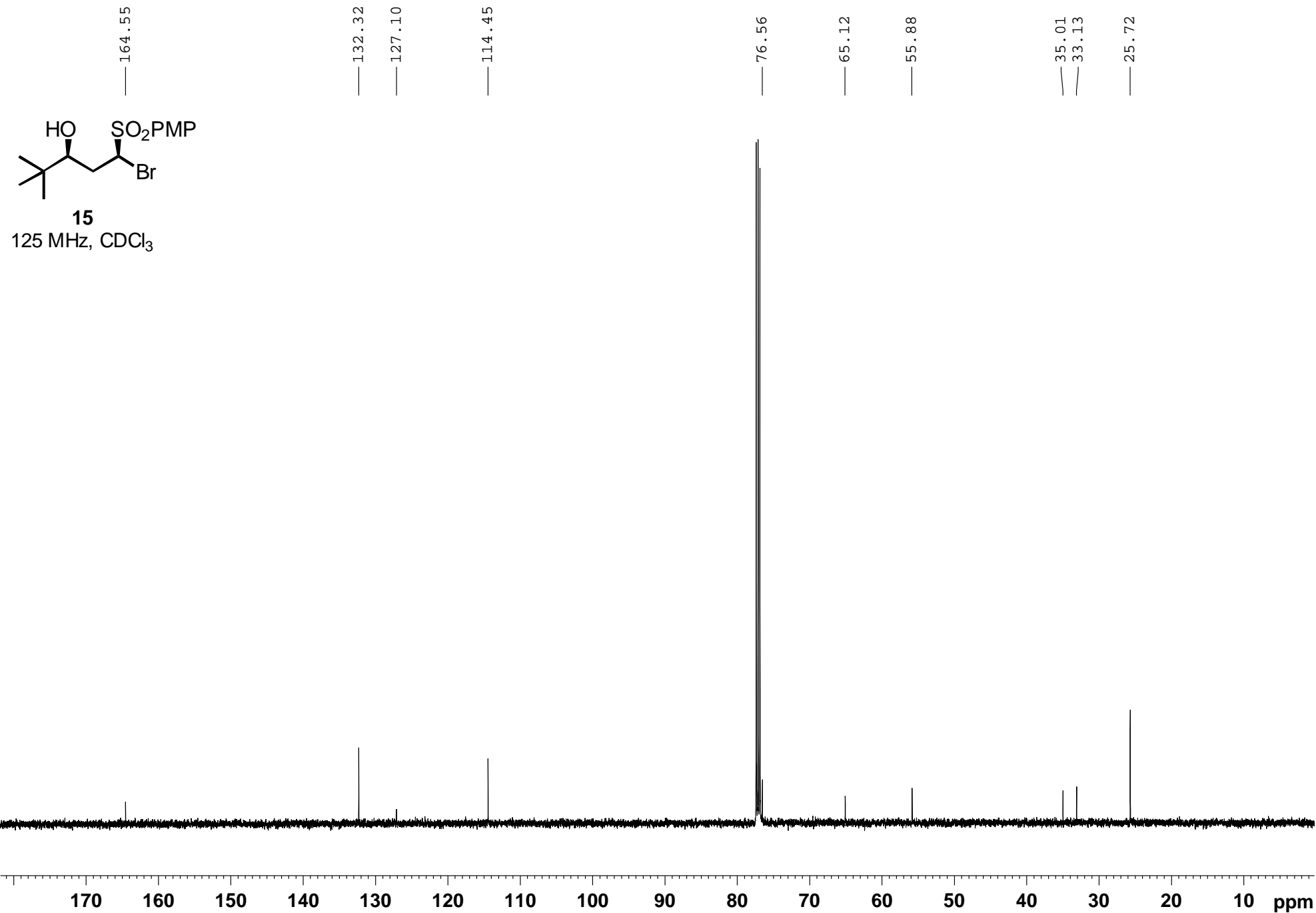
0.921

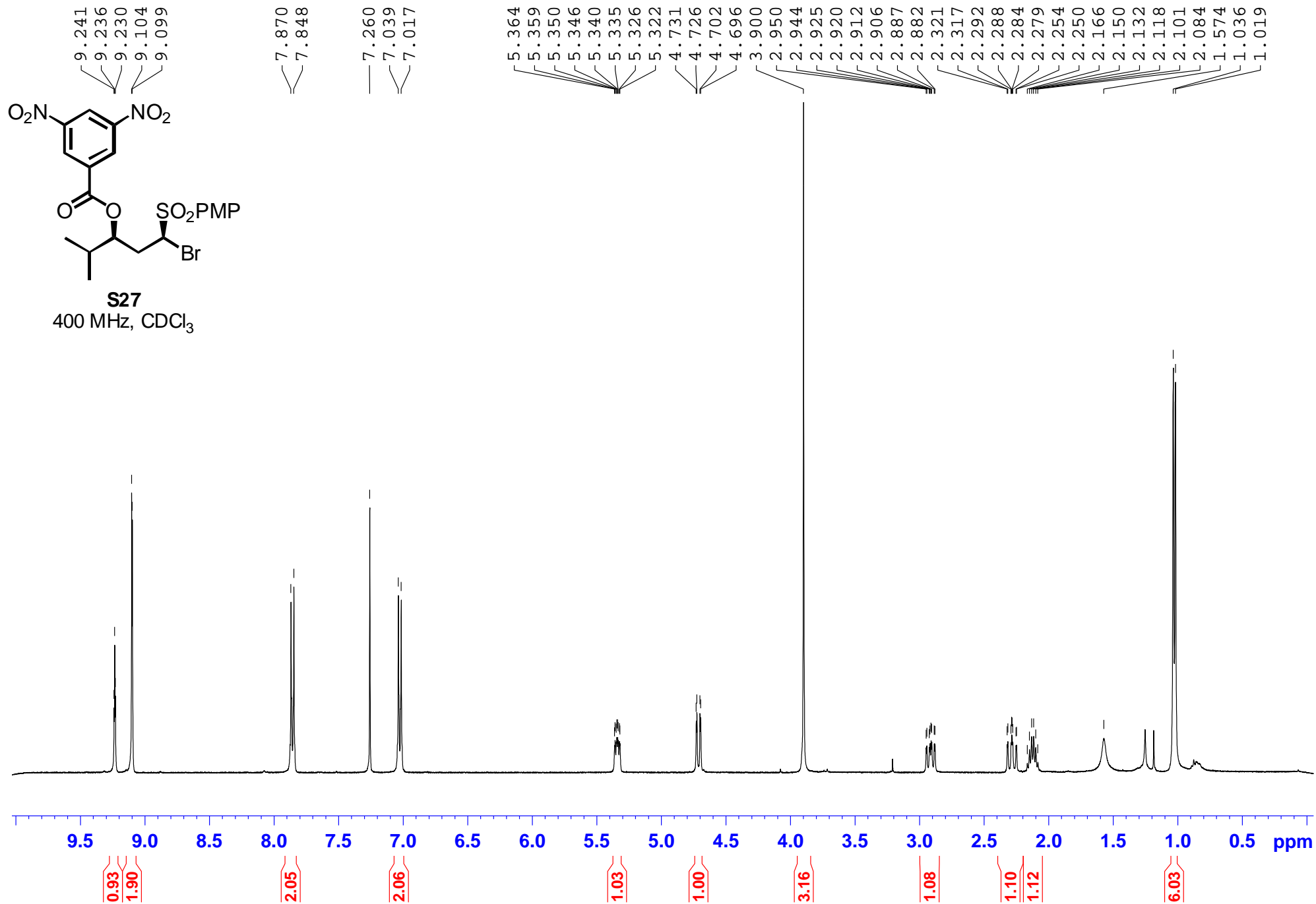


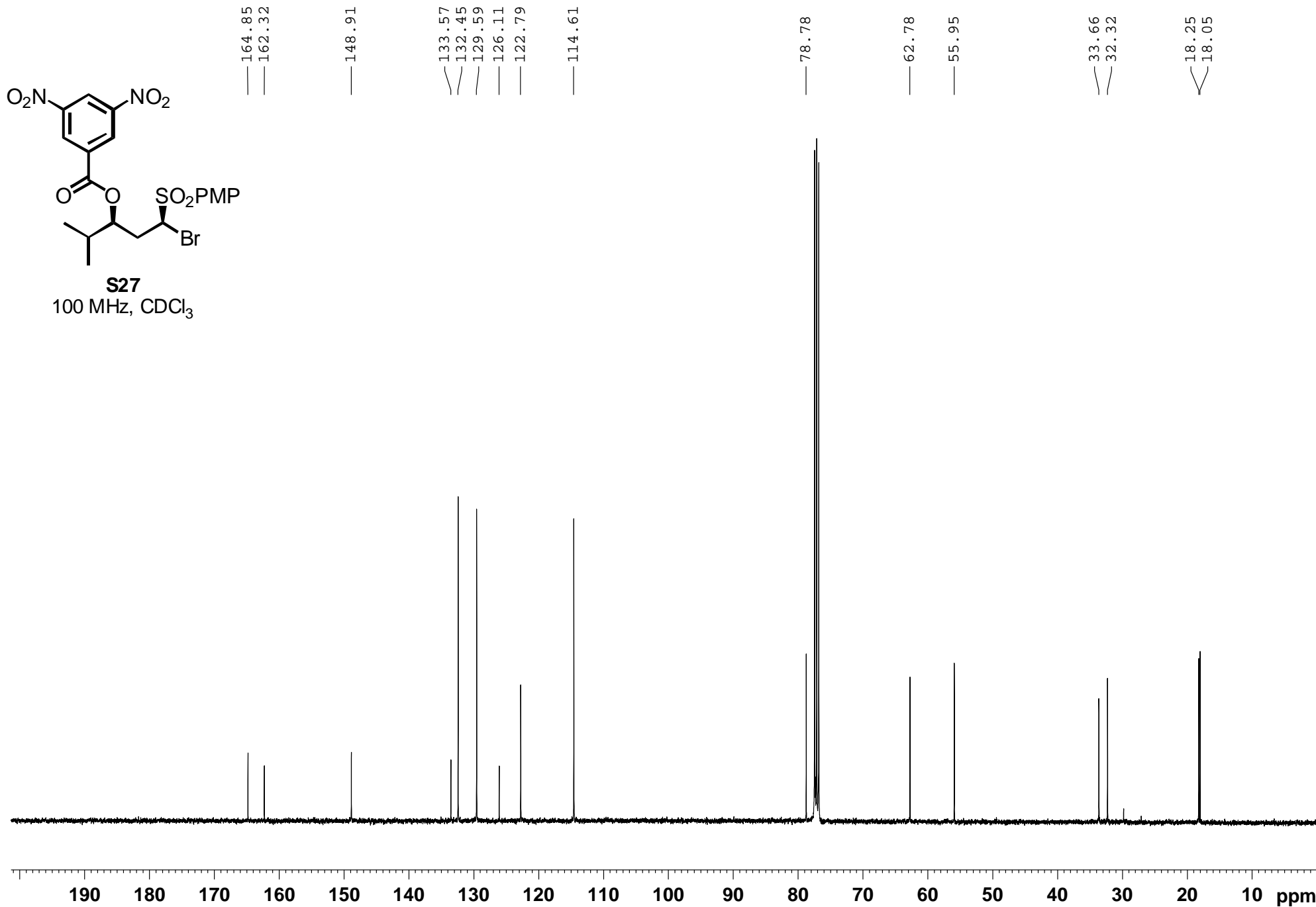
15

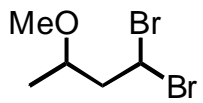
500 MHz, CDCl₃



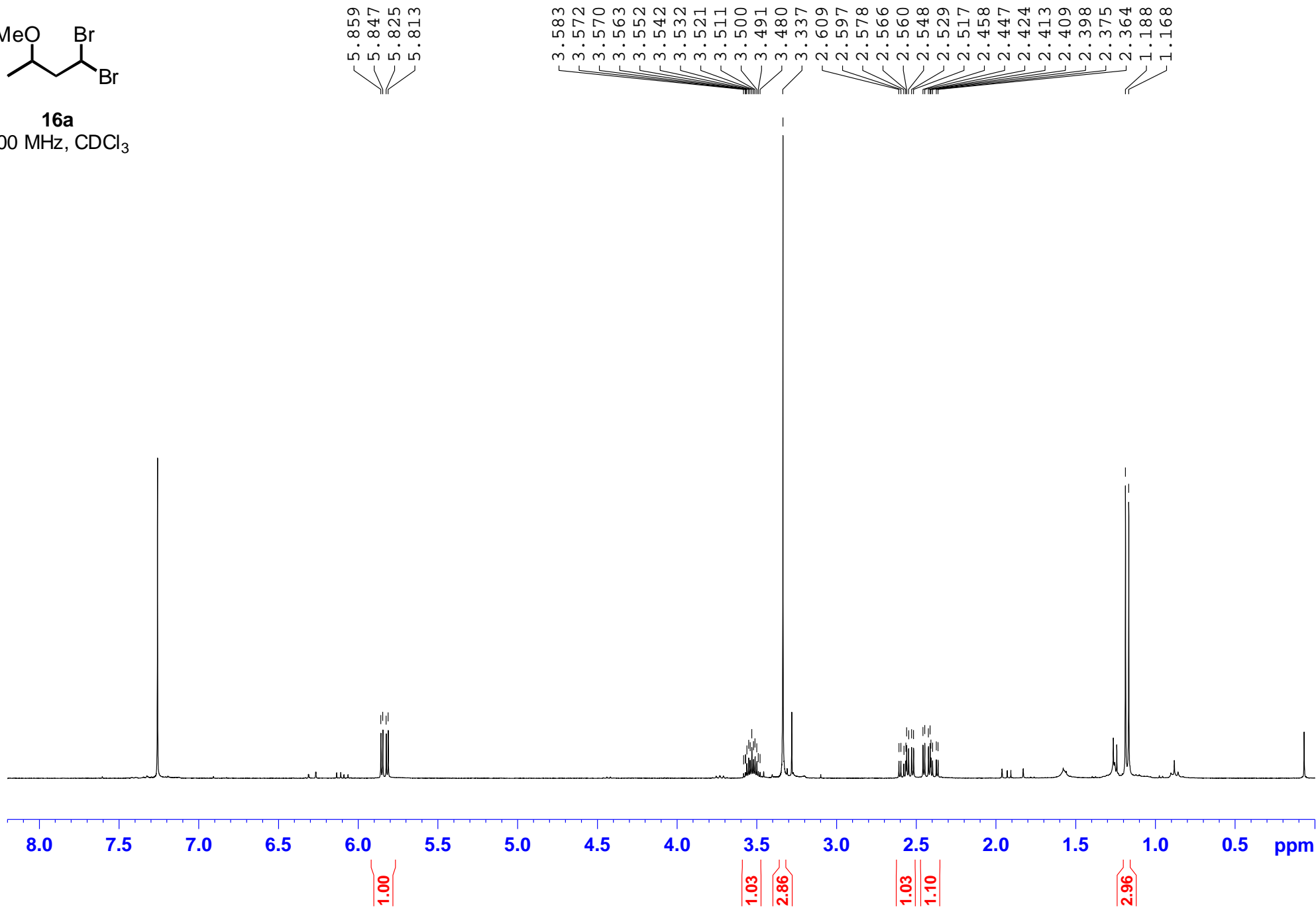


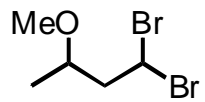




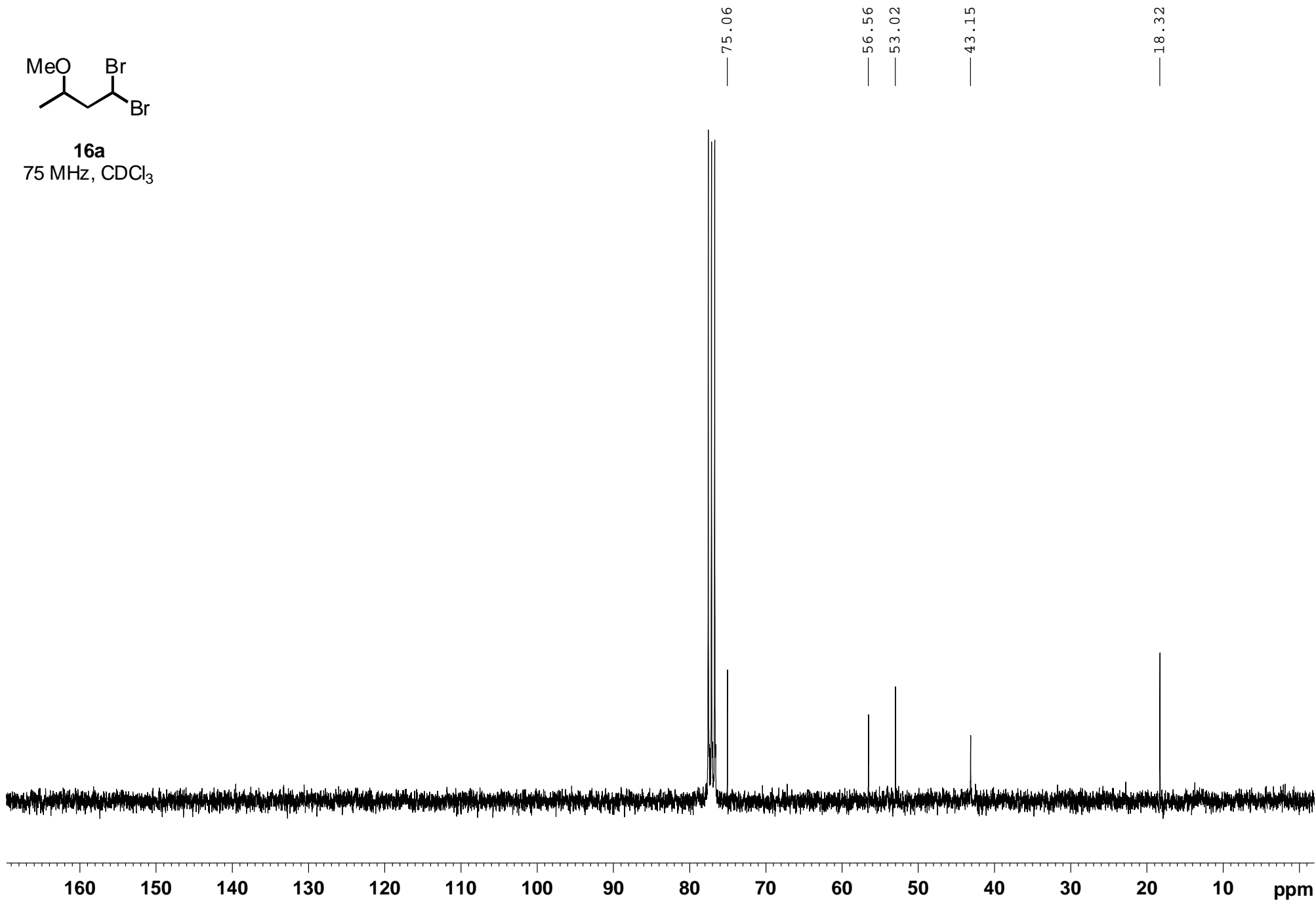


16a
300 MHz, CDCl₃

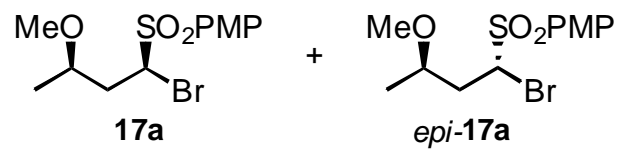




16a
75 MHz, CDCl₃



7.903
7.873
7.053
7.023
5.057
5.050
5.018
5.010
4.846
4.828
4.818
4.800
3.904
3.899
3.669
3.648
3.628
3.607
3.586
3.575
3.567
3.555
3.546
3.540
3.532
3.526
3.520
3.512
3.325
3.300
2.507
2.495
2.490
2.486
2.481
2.473
2.468
2.458
2.446
2.440
2.438
2.433
2.425
2.420
2.398
2.390
2.267
2.245
2.238
2.217
2.196
2.189
2.168
1.952
1.944
1.913
1.905
1.896
1.865
1.857
1.210
1.189
1.173
1.152



1.0 : 1.2

300 MHz, CDCl₃

