Suppremental Information

Managing the Retro-Pathway in Direct Catalytic Asymmetric Aldol Reactions of Thioamides

Youmei Bao, Naoya Kumagai,* and Masakatsu Shibasaki*

Institute of Microbial Chemistry (BIKAKEN), Tokyo, Japan

mshibasa@bikaken.or.jp, nkumagai@bikaken.or.jp

1. General

The catalytic asymmetric aldol reaction was performed in a flame-dried 20 mL glass test tubes with a 3-way glass stopcock under Ar atmosphere unless otherwise noted. Air- and moisture-sensitive liquids were transferred via a gas-tight syringe and a stainless-steel needle. All work-up and purification procedures were carried out with reagent-grade solvents under ambient atmosphere.

2. Instrumentation

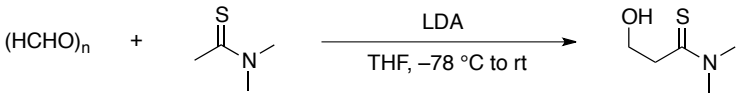
Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR was recorded on JEOL ECS-400. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and referenced to residual protium in the NMR solvent ($CDCl_3$: δ 7.24 ppm). For ^{13}C NMR chemical shifts are reported in the scale relative to NMR solvent ($CDCl_3$: δ 77.0 ppm) as an internal reference. NMR data are reported as follows: chemical shifts, multiplicity (s: singlet, d: doublet, dd: doublet of doublets, t: triplet, q: quartet, m: multiplet, br: broad signal), coupling constant (Hz), and integration. Optical rotation was measured using a 2 mL cell with a 1.0 dm path length on a JASCO polarimeter P-1030. High resolution mass spectra (ESI Orbitrap (+)) were measured on ThermoFisher Scientific LTQ Orbitrap XL. HPLC analysis was conducted on a JASCO HPLC system equipped with Daicel chiral-stationary-phase columns (ϕ 0.46 cm x 25 cm).

3. Materials

Unless otherwise noted, materials were purchased from commercial suppliers and were used without further purification. THF, CH_2Cl_2 and diethyl ether were purified by passing through a solvent purification system (Glass Contour). Mesitylcopper was purchased from Strem chemicals or prepared by following the literature procedure,[1] and handled in a glove box. (*S*,*S*)- and (*R*,*R*)-Ph-BPE and 2,2,5,7,8-pentamethylchromanol (ArOH) were purchased from Aldrich. ArOH was used after recrystallization from *n*-hexane. *N*,*N*-diallylpropiothioamide (**1a**) was prepared from the corresponding *N*,*N*-diallylpropioamide by following the reported procedure.[2] The same procedure was used to synthesize *N*,*N*-diallylbutanethioamide (**1b**) and *N*,*N*-diallylethanethioamide (**1c**). Column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM) or Kanto Chemical 60N (neutral, spherial, 50–60 μM)

4. General Procedure

4.1 Synthesis of 3-hydroxy-*N*,*N*-dimethylpropanethioamide (additive 8).

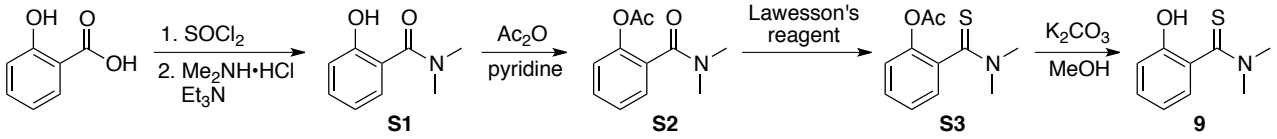


To a 200 mL flame-dried flask containing *N*,*N*-dimethylethanethioamide (1.0 g, 9.7 mmol) at –78 °C, lithium diisopropylamide (LDA, 11 mL, 1.09 M in THF, 1.2 eq.) was added slowly and the resulting reaction mixture was warmed to 0 °C. After stirring for 30 min, the reaction mixture was cooled down to –78 °C and paraformaldehyde (1.5 g, 5 eq.) dispersed in 30 mL THF was added. After 10 min of stirring at –78 °C, the reaction mixture was warmed to room temperature and stirred for overnight. The reaction was quenched with 50 mL of sat. NH_4Cl aq. and the biphasic mixture was extracted with $CHCl_3$, and the combined organic extracts were dried over Na_2SO_4. Volatiles were removed under reduced pressure and the resulting crude mixture was purified by silica gel column chromatography to give **8** as a pale yellow oil (570 mg, 44% yield).

^1H NMR ($CDCl_3$, 400 Hz): δ 4.02–3.98 (m, 2H), 3.83 (t, *J* = 7.1 Hz, 1H), 3.49 (s, 3H), 3.29 (s, 3H), 2.74 (t, *J* = 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 Hz): δ 201.4, 59.9, 44.1, 43.0, 41.5.

[1]Tsuda, T.; Yazawa, T.; Watanabe, K.; Fujii, T.; Saegusa, T. *J. Org. Chem.* **1981**, *46*, 192.
[2]Iwata, M.; Yazaki, R.; Chen, H.; Sureshkumar, D.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5554.

4.2 Synthesis of 2-hydroxy-*N*,*N*-dimethylbenzothioamide (additive 9)



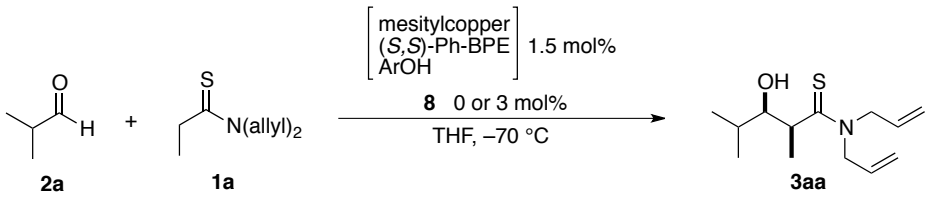
To a 300 mL flask, 50 mL $SOCl_2$ and salicylic acid (10 g, 72.5 mmol) were added. The reaction mixture was heated to 80 °C for 1 h. After cooling, $SOCl_2$ was carefully evaporated. The resulting mixture was dissolved in 100 mL toluene, and $Me_2NH{\cdot}HCl$ (17.7 g, 217.5 mmol, 3 eq.) and triethylamine (40.4 mL, 290 mmol, 4 eq.) were added. After stirring at room temperature for overnight, the reaction mixture was heated to 100 °C for 1 h. After cooling to room temperature, 170 mL sat. NH_4Cl aq. was added and the mixture was extracted with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4. The filtrate was concentrated and recrystallized from EtOAc/*n*-hexane to givie **S1** as a white to orange crystal (11.2 g, 94% yield).

To the flask containing **S1** (5 g, 30.2 mmol) in 150 mL CH_2Cl_2 at 0 °C, pyridine (4.8 mL, 60.4 mmol, 2 eq.) and acetic anhydride (4.3 mL, 45.5 mmol, 1.5 eq.) were added and the reaction mixture was warmed to room temperature. After stirring for overnight, the reaction was quenched with 50 mL 0.5 N HCl aq. and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over Na_2SO_4. Filtration and evaporation gave an orange oil of **S2**, which were used directly for the next step. To a stiired solution of **S2** (5 g, 24.1 mmol) in 240 mL THF, Lawesson's reagent (5.4 g, 13.3 mmol, 0.55 eq.) was added and the reaction mixture was refluxed for 1 h. After cooling to room temperature, the mixture was concentrated and loaded onto silica gel for silica gel column chromatography to give **S3** as a pale yellow crystal (4.4 g, 81% yield).

To a stirred solution of **S3** (3.6 g, 16.2 mmol) in 60 mL MeOH, K_2CO_3 (2.2 g, 16.2 mmol, 1 eq.) was added and the reaction mixture was stirred at room temperature for overnight. After removal of volatiles, 150 mL of sat. NH_4Cl aq. was added and the resulting mixture was extracted with ether. The combined organic extracts were washed with brine and dried over Na_2SO_4. The filtrate was concentrated and purified by silica gel column chromatography to give **9** as a pale pink solid (2.7 g, 92% yield). ^1H NMR ($CDCl_3$, 400 Hz): δ 8.35 (s, 1H), 7.51–7.47 (m, 1H), 7.26–7.23 (m, 2H), 7.14–7.10 (m, 1H), 3.84 (s, 3H), 3.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 Hz): δ 196.5, 153.7, 130.9, 127.0, 126.1, 119.5, 118.3, 44.7, 42.9.

4.3 Direct catalytic asymmetric aldol reaction (Table 1 and 2).

4.3.1 General procedure for the catalytic asymmetric aldol reaction

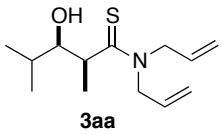


To a flame-dried 20 mL test tube equipped with a magnetic striring bar and a 3-way glass stopcock were charged with (*S*,*S*)-Ph-BPE (6.1 mg, 0.012 mmol), 2,2,5,7,8-pentamethylchromanol (ArOH, 2.6 mg, 0.012 mmol) and mesitylcopper (2.2 mg, 0.012 mmol) in a dry box. To the mixture was added dry THF (240 μL, 0.05 M) *via* syringe at room temperature, after 5 min of stirring at the same temperature, yellow-green solution of (*S*,*S*)-Ph-BPE/mesitylcopper/ArOH solution was obtained, which was used within 15 min.

To a flame-dried 20 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock were charged with *N*,*N*-diallylthiopropionamide (**1a**, 40 μL, 0.24 mmol, 1.2 eq.), dry THF (882 μL or 822 μL, 0.2 M), **2a** (18 μL, 0.2 mmol) and additive **8** (60 μL, 0.1 M in THF, 6 μmol) if any. The reaction mixture was cooled to –70 °C. To the resulting cooled solution was added (*S*,*S*)-Ph-BPE/mesitylcopper/ArOH solution (60 μL, 3 μmol) prepared above dropwise to run the reaction. After certain time at the same temperature, the precooled solution of acetic acid in THF (0.1 M in THF, 1 mL, 0.1 mmol), then saturated aq. NH_4Cl were added to quench the reaction. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was

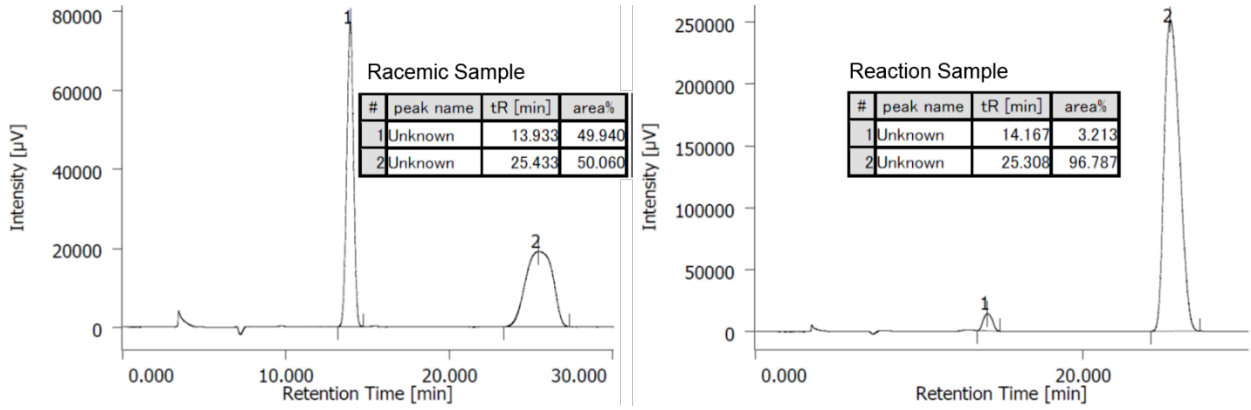
concentrated under reduced pressure. The chemical yield and diastereomeric ratio were determined by ^{1}H NMR of the crude mixture. The crude product was purified by silica gel column chromatography to give the desired product as a colorless oil.

(2*S*,3*R*)-*N*,*N*-Diallyl-3-hydroxy-2,4-dimethylpentanethioamide (3aa)

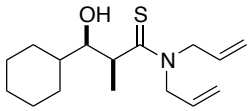


3aa

Colorless oil, IR ($CHCl_3$ solution) ν 3402, 3019, 1710, 1488, 1412, 1362, 1210, 1089, 929, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.90–5.73 (m, 2H), 5.28–5.09 (m, 4H), 4.85–4.80 (m, 2H), 4.24 (dd, *J* = 6.0, 14.7 Hz, 1H), 4.20 (dd, *J* = 4.6, 15.6 Hz, 1H), 4.09 (dd, *J* = 4.6, 17.4 Hz, 1H), 3.31 (d, *J* = 8.9 Hz, 1H), 3.16 (q, *J* = 6.9 Hz, 1H), 1.68 (m, 1H), 1.18 (d, *J* = 6.9 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 210.9, 130.8, 130.4, 118.6, 117.7, 77.9, 55.6, 52.6, 42.8, 31.1, 19.7, 19.2, 13.8; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{13}H_{23}ONNaS$ *m*/*z* 264.1393 [M+Na]$^+$, found 264.1386; $[\alpha]_D^{26}$ 128.8 (*c* 1.21, $CHCl_3$, 94% ee sample); HPLC: CHIRALCEL OZ-H (ϕ 0.46 cm x 25 cm), 2-propanol/*n*-hexane = 1/99, flow rate 1.0 mL/min, detection 254 nm, t_R = 14.2 min (minor), 25.3 min (major).

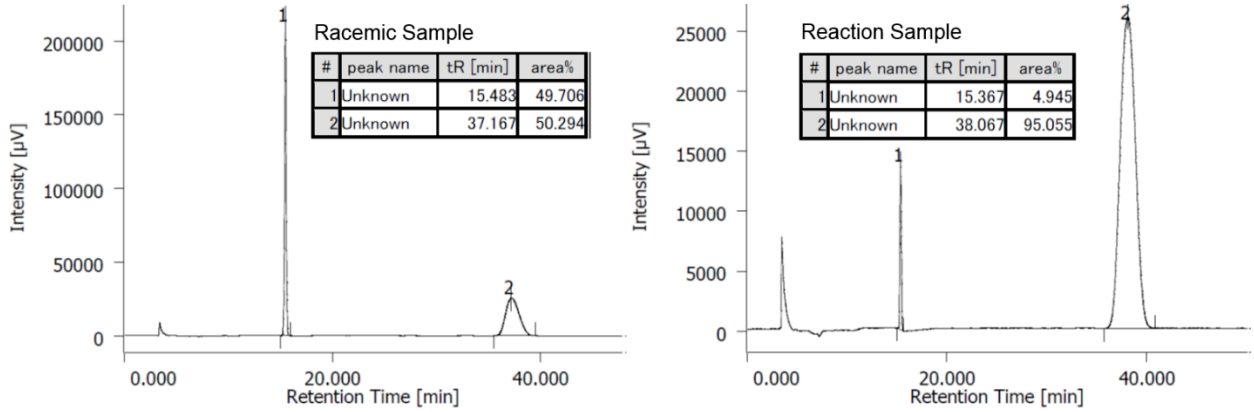


(2*S*,3*R*)-*N*,*N*-Diallyl-3-cyclohexyl-3-hydroxy-2-methylpropanethioamide (3ab)

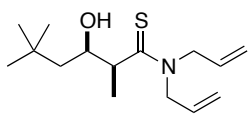


3ab

Colorless oil, IR ($CHCl_3$ solution) ν 3335, 2990, 2927, 2853, 1643, 1489, 1449, 1412, 1221, 1205, 1143, 930 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.85–5.74 (m, 2H), 5.28–5.12 (m, 4H), 4.82–4.76 (m, 2H), 4.36 (dd, *J* = 5.9, 14.6 Hz, 1H), 4.2–4.0 (m, 2H), 3.36 (d, *J* = 8.7 Hz, 1H), 3.15 (q, *J* = 6.6 Hz, 1H), 2.09 (d, *J* = 13.0 Hz, 1H), 1.72–1.69 (m, 2H), 1.64–1.54 (m, 2H), 1.39–1.34 (m, 1H), 1.21–1.07 (m, 6H), 0.93–0.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 210.8, 130.8, 130.4, 118.5, 117.6, 76.5, 55.5, 52.6, 42.4, 40.5, 29.8, 29.2, 26.4, 26.0, 25.9, 13.8; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{16}H_{27}ONNaS$ *m*/*z* 304.1706 [M+Na]$^+$, found 304.1705; $[\alpha]_D^{25}$ 119.9 (*c* 2.80, $CHCl_3$, 90% ee sample); HPLC: CHIRALCEL OZ-H (ϕ 0.46 cm x 25 cm), 2-propanol/*n*-hexane = 1/99, flow rate 1.0 mL/min, detection 254 nm, t_R = 15.4 min (minor), 38.1 min (major).



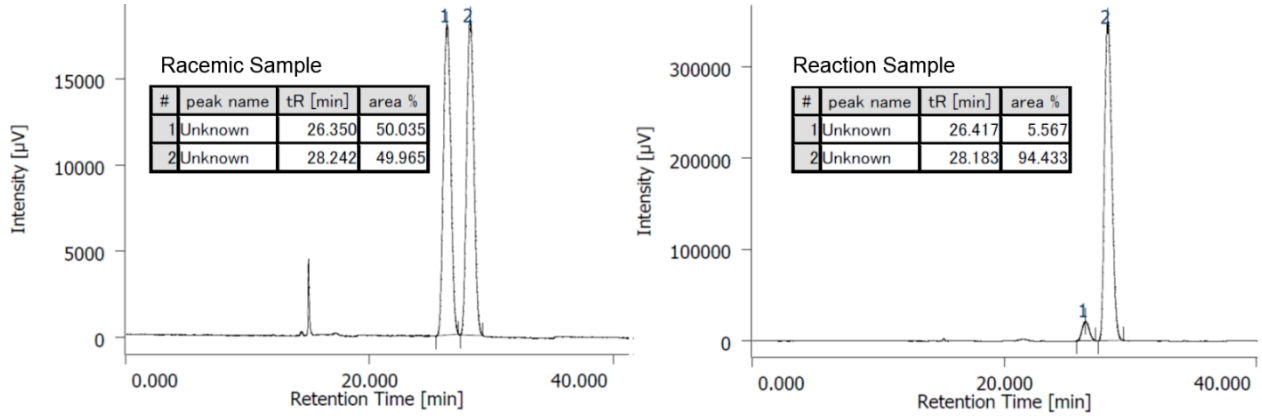
(2*S*,3*R*)-*N*,*N*-Diallyl-3-hydroxy-2,5,5-trimethylhexanethioamide (3ac)



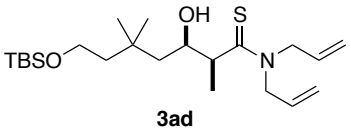
3ac

Colorless oil, IR ($CHCl_3$ solution) ν 3407, 3018, 1709, 1415, 1363, 1217, 1090, 926, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.88–5.73 (m, 2H), 5.27–5.09 (m, 4H), 4.94 (dd, *J* = 5.0, 14.7 Hz, 1H), 4.59 (s, 1H), 4.25–4.17 (m, 2H), 4.05 (dt, *J* = 2.3, 17.6 Hz, 1H), 3.91 (dd, *J* = 1.6, 8.5 Hz, 1H) 2.75

(qd, *J* = 1.6, 6.9 Hz, 1H), 1.48 (q, *J* = 8.5 Hz, 1H), 1.21 (d, *J* = 6.6 Hz, 3H), 1.03 (d, *J* = 14.0 Hz, 1H), 0.91 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 210.8, 131.0, 130.5, 118.5, 117.6, 70.0, 55.3, 52.6, 49.4, 48.2, 30.3, 30.0, 14.0; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{15}H_{28}ONS$ *m*/*z* 270.1886 $[M+H]^+$, found 270.1884; $[\alpha]_D^{26}$ 127.2 (*c* 1.54, $CHCl_3$, 90% ee sample); HPLC: CHIRALCEL OD-H (ϕ 0.46 cm x 25 cm) and OD-H (ϕ 0.46 cm x 25 cm), 2-propanol/*n*-hexane = 1/99, flow rate 0.5 mL/min, detection 254 nm, t_R = 26.4 min (minor), 28.2 min (major).

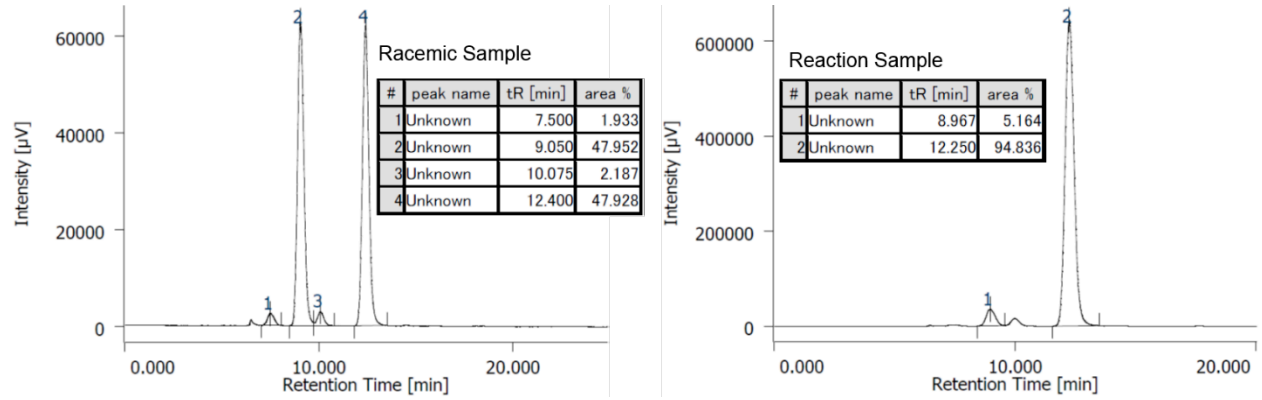


(2*S*,3*R*)-*N*,*N*-Diallyl-7-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2,5,5-trimethylheptanethioamide (3ad)

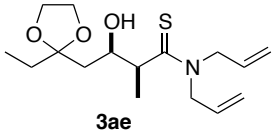


3ad

Colorless oil, IR ($CHCl_3$ solution) *ν* 3368, 3019, 1710, 1211, 1083, 929, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.85–5.72 (m, 2H), 5.27–5.09 (m, 4H), 4.88 (dd, *J* = 5.3, 14.9 Hz, 1H), 4.53 (s, 1H), 4.31 (dd, *J* = 5.2, 13.7 Hz, 1H), 4.20–4.06 (m, 2H), 3.95 (d, *J* = 8.7 Hz, 1H), 3.71–3.61 (m, 2H), 2.76–2.74 (m, 1H), 1.70–1.63 (m, 1H), 1.52–1.38 (m, 2H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.12 (d, *J* = 14.2 Hz, 1H), 0.93 (s, 3H), 0.90 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 210.5, 131.1, 130.6, 118.5, 117.6, 70.4, 60.2, 55.3, 52.6, 48.7, 47.4, 44.4, 32.2, 28.1, 28.0, 25.9, 18.2, 15.1, –5.3, –5.4; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{22}H_{44}O_2NSSi$ *m*/*z* 414.2857 $[M+H]^+$, found 414.2852; $[\alpha]_D^{26}$ 82.0 (*c* 1.11, $CHCl_3$, 90% ee sample); HPLC: CHIRALCEL OZ-H (ϕ 0.46 cm x 25 cm), 2-propanol/*n*-hexane = 2/98, flow rate 0.5 mL/min, detection 254 nm, t_R = 9.0 min (minor), 12.2 min (major).

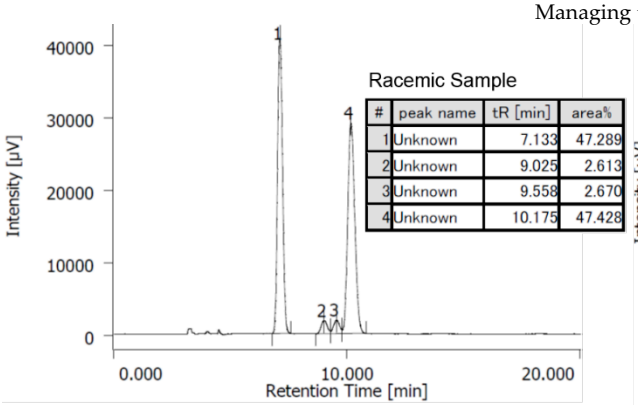


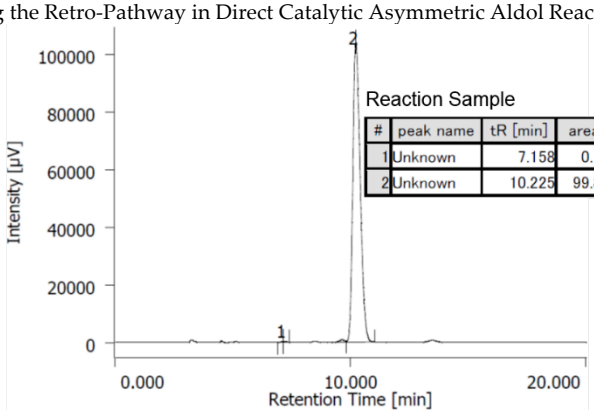
(2*S*,3*R*)-*N*,*N*-Diallyl-4-(2-ethyl-1,3-dioxolan-2-yl)-3-hydroxy-2-methylbutanethioamide (3ae)



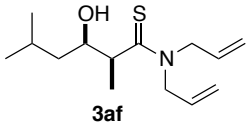
3ae

Colorless oil, IR ($CHCl_3$ solution) *ν* 3501, 3019, 1486, 1411, 1061, 930, 669 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.88–5.73 (m, 2H), 5.27–5.11 (m, 4H), 4.68 (dd, *J* = 5.8, 14.9 Hz, 1H), 4.50 (dd, *J* = 6.0, 14.9 Hz, 1H), 4.28–4.20 (m, 2H), 4.16–4.10 (m, 2H), 3.93–3.90 (m, 4H), 3.02–2.96 (m, 1H), 1.88 (dd, *J* = 2.5, 14.2 Hz, 1H), 1.68 (q, *J* = 8.0 Hz, 2H), 1.60 (dd, *J* = 8.7, 14.2 Hz, 1H), 1.28 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 208.9, 131.3, 130 .7, 118.3, 117.7, 112.0, 71.3, 64.8, 64.5, 55.4, 52.6, 47.7, 40.1, 29.7, 17.0, 8.0; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{16}H_{27}O_3NNaS$ *m*/*z* 336.1604 $[M+Na]^+$, found 336.1600; $[\alpha]_D^{26}$ 91.1 (*c* 0.91, $CHCl_3$, >99% ee sample); HPLC: CHIRALCEL OZ-H (ϕ 0.46 cm x 25 cm), 2-propanol/*n*-hexane = 10/90, flow rate 1.0 mL/min, detection 254 nm, t_R = 7.2 min (minor), 10.2 min (major).



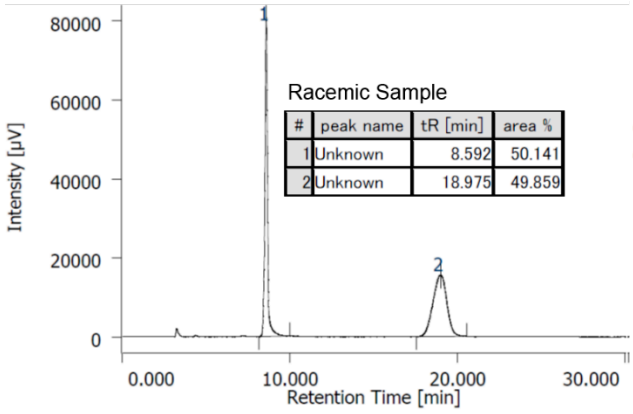


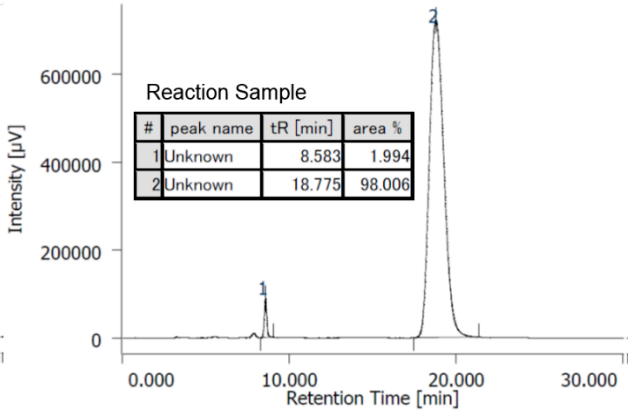
(2*S*,3*R*)-*N*,*N*-Diallyl-3-hydroxy-2,5-dimethylhexanethioamide (3af)



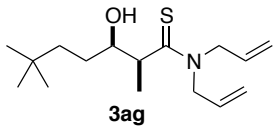
3af

Colorless oil, IR ($CHCl_3$ solution) ν 3400, 3019, 1710, 1488, 1413, 1363, 1213, 930, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.87–5.73 (m, 2H), 5.26–5.07 (m, 4H), 4.93 (dd, J = 5.3, 14.9 Hz, 1H), 4.64 (s, 1H), 4.24–4.17 (m, 2H), 4.07–4.02 (m, 1H), 3.87–3.84 (m, 1H), 2.81 (qd, J = 1.6, 6.6 Hz, 1H), 1.80–1.70 (m, 1H), 1.51–1.43 (m, 1H), 1.19 (d, J = 6.9 Hz, 3H), 1.00–0.97 (m, 1H), 0.87 (d, J = 3.2 Hz, 3H), 0.85 (d, J = 3.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 210.9, 131.0, 130.4, 118.5, 117.5, 70.4, 55.3, 52.7, 46.4, 44.0, 24.4, 23.4, 21.9, 13.9; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{14}H_{26}ONS$ m/z 256.1730 $[M+H]^+$, found 256.1728; $[\alpha]_D^{26}$ 140.8 (c 1.94, $CHCl_3$, 96% ee sample); HPLC: CHIRALCEL OZ-H (ϕ 0.46 cm x 25 cm), 2-propanol/n-hexane = 2/98, flow rate 1.0 mL/min, detection 254 nm, t_R = 8.6 min (minor), 18.8 min (major).



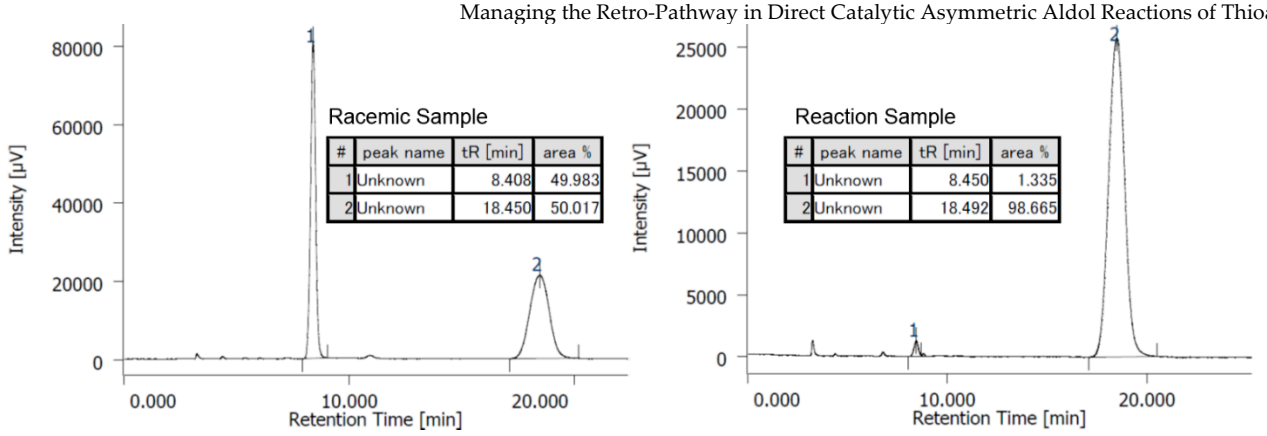


(2*S*,3*R*)-*N*,*N*-Diallyl-3-hydroxy-2,6,6-trimethylheptanethioamide (3ag)

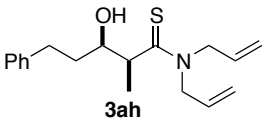


3ag

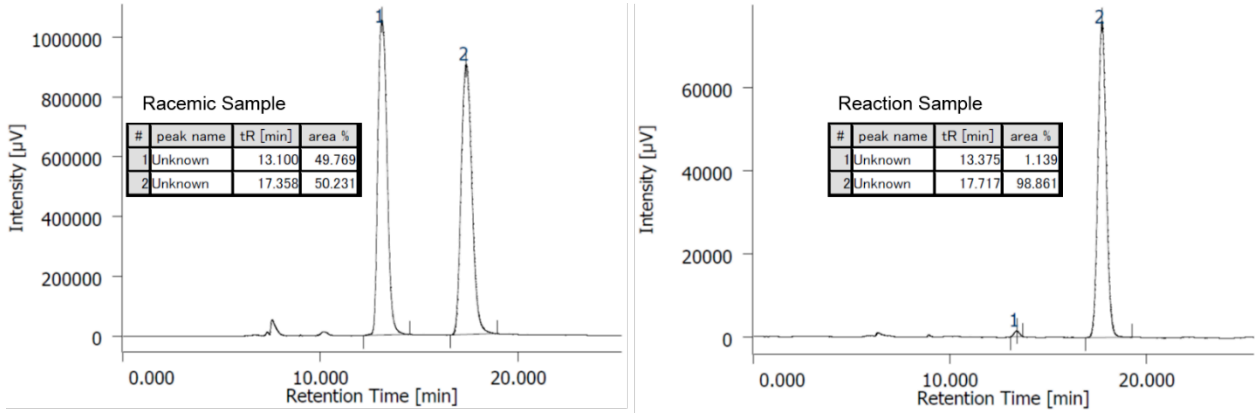
Colorless oil, IR ($CHCl_3$ solution) ν 3352, 2957, 1710, 1489, 1412, 1364, 930, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.89–5.75 (m, 2H), 5.30–5.11 (m, 4H), 4.87 (dd, J = 5.3, 14.9 Hz, 1H), 4.72 (s, 1H), 4.32 (dd, J = 6.2, 14.9 Hz, 1H), 4.20 (dd, J = 3.6, 17.4 Hz, 1H), 4.09 (dd, J = 4.6, 17.4 Hz, 1H), 3.70 (t, J = 6.9 Hz, 1H), 2.93 (q, J = 6.6 Hz, 1H), 1.53–1.50 (m, 1H), 1.36 (dt, J = 4.1, 12.8 Hz, 1H), 1.27–1.21 (m, 4H), 1.08 (dt, J = 4.1, 12.8 Hz, 1H), 0.86 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 210.8, 131.0, 130.4, 118.6, 117.7, 73.5, 55.4, 52.7, 45.8, 40.3, 30.1, 29.8, 29.3, 13.8; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{16}H_{30}ONS$ m/z 284.2043 $[M+H]^+$, found 284.2042; $[\alpha]_D^{22}$ 120.0 (c 1.05, $CHCl_3$, 97% ee sample); HPLC: CHIRALCEL OZ-H (ϕ 0.46 cm x 25 cm), 2-propanol/n-hexane = 2/98, flow rate 1.0 mL/min, detection 254 nm, t_R = 8.4 min (minor), 18.5 min (major).



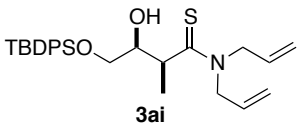
(2*S*,3*R*)-*N*,*N*-Diallyl-3-hydroxy-2-methyl-5-phenylpentanethioamide (3ah)



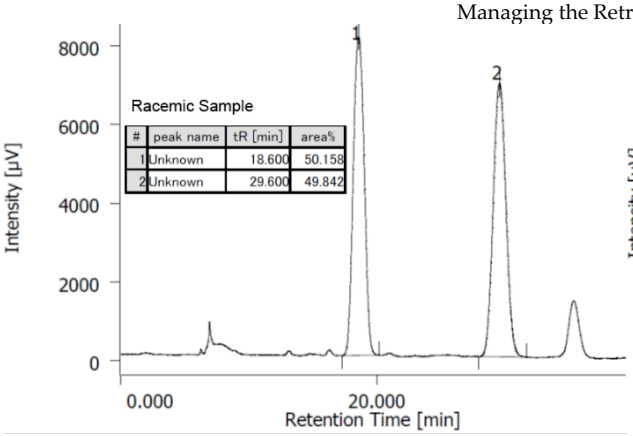
Colorless oil, IR ($CHCl_3$ solution) ν 3348, 3007, 1710, 1492, 1453, 1412, 930, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.18 (m, 5H), 5.92–5.74 (m, 2H), 5.29–5.09 (m, 4H), 4.94 (dd, J = 5.3, 14.9 Hz, 1H), 4.82 (s, 1H), 4.30 (dd, J = 6.4, 14.9 Hz, 1H), 4.20 (dd, J = 4.2, 17.4 Hz, 1H), 4.08 (dd, J = 4.4, 17.4 Hz, 1H), 3.86 (dd, J = 3.0, 9.4 Hz, 1H), 2.93–2.87 (m, 2H), 2.70–2.66 (m, 1H), 1.96–1.90 (m, 1H), 1.59–1.56 (m, 1H), 1.27 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 210.5, 142.0, 130.9, 130.4, 128.4, 128.3, 125.7, 118.6, 117.6, 71.9, 55.3, 52.7, 46.3, 36.7, 32.4, 14.0; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{18}H_{26}ONS$ m/z 304.1730 $[M+H]^+$, found 304.1730; $[\alpha]_D^{22}$ 145.1 (c 1.76, $CHCl_3$, 98% ee sample); HPLC: CHIRALCEL OZ-H (ϕ 0.46 cm x 25 cm), 2-propanol/n-hexane = 10/90, flow rate 0.5 mL/min, detection 254 nm, t_R = 13.4 min (minor), 17.7 min (major).

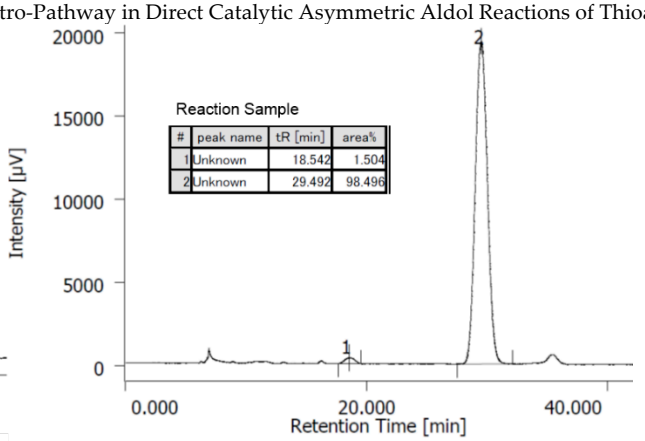


(2*S*,3*S*)-*N*,*N*-Diallyl-4-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxy-2-methylbutanethioamide (3ai)

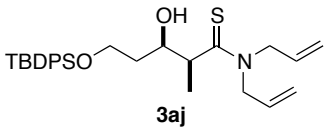


Colorless oil, IR ($CHCl_3$ solution) ν 3342, 2932, 2859, 1710, 1488, 1428, 1363, 1226, 1112, 996, 823, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.61–7.59 (m, 4H), 7.41–7.36 (m, 6H), 5.87–5.67 (m, 2H), 5.24–5.06 (m, 4H), 4.62 (dd, J = 5.0, 15.4 Hz, 1H), 4.52 (dd, J = 5.2, 14.9 Hz, 1H), 4.38 (s, 1H), 4.23 (dd, J = 3.2, 17.4 Hz, 1H), 4.09 (dd, J = 1.8, 17.4 Hz, 1H), 3.97–3.95 (m, 1H), 3.70–3.68 (m, 1H), 3.57–3.55 (m, 1H), 3.40 (q, J = 6.6 Hz, 1H), 1.16 (d, J = 6.8 Hz, 3H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 209.7, 135.48, 135.45, 133.0, 130.9, 130.5, 129.80, 129.78, 127.7, 118.5, 117.7, 73.2, 64.1, 55.2, 52.6, 42.3, 26.9, 19.0, 14.0; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{27}H_{37}O_2NNaSSi$ m/z 490.2206 $[M+Na]^+$, found 490.2198; $[\alpha]_D^{25}$ 35.9 (c 2.24, $CHCl_3$, 97% ee sample); HPLC: CHIRALCEL OD-H (ϕ 0.46 cm x 25 cm) and OZ-H (φ 0.46 cm x 25 cm), 2-propanol/n-hexane = 1/99, flow rate 1.0 mL/min, detection 254 nm, t_R = 18.5 min (minor), 29.5 min (major).



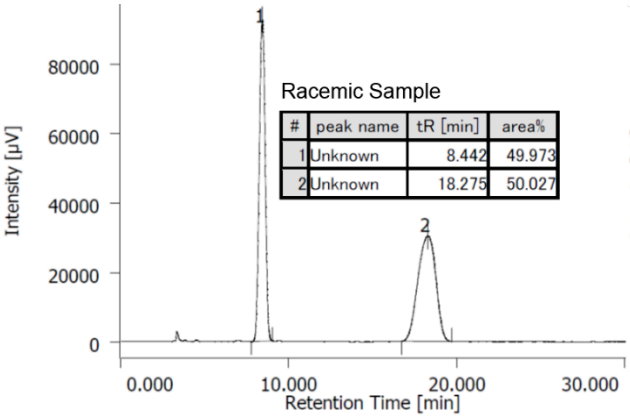


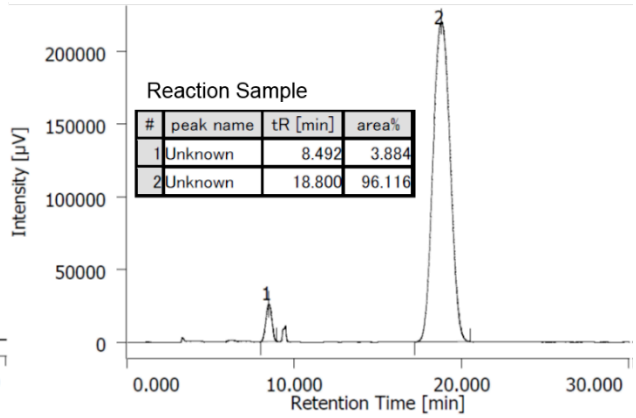
(2*S*,3*R*)-*N*,*N*-Diallyl-5-((*tert*-butyldiphenylsilyl)oxy)-3-hydroxy-2-methylpentanethioamide (3aj)



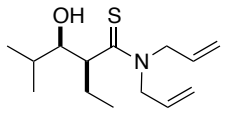
3aj

Colorless oil, IR ($CHCl_3$ solution) ν 3488, 3405, 3019, 1709, 1416, 1362, 1210, 1110, 908, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.66–7.62 (m, 4H), 7.41–7.34 (m, 6H), 5.87–5.69 (m, 2H), 5.23– 5.09 (m, 4H) 4.75 (dd, J = 5.5, 14.9 Hz, 1H), 4.56 (s, 1H), 4.42 (dd, J = 6.2, 14.9 Hz, 1H), 4.14–4.09 (m, 3H), 3.81 (t, J = 6.0 Hz, 2H), 2.95 (m, 1H), 1.76–1.68 (m, 1H), 1.64–1.58 (m, 1H), 1.26 (d, J = 6.6 Hz, 3H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 209.9, 135.53, 135.50, 133.4, 131.1, 130.6, 129.7, 127.68, 127.67, 118.4, 117.6, 72.0, 62.2, 55.3, 52.6, 46.8, 37.0, 26.8, 19.1, 15.3; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{28}H_{39}O_2NNaSSi$ m/z 504.2363 $[M+Na]^+$, found 504.2359; $[\alpha]_D^{26}$ 44.1 (c 2.37, $CHCl_3$, 92% ee sample); HPLC: CHIRALCEL OZ-H (ϕ 0.46 cm x 25 cm), 2-propanol/n-hexane = 2/98, flow rate 1.0 mL/min, detection 254 nm, t_R = 8.5 min (minor), 18.8 min (major)



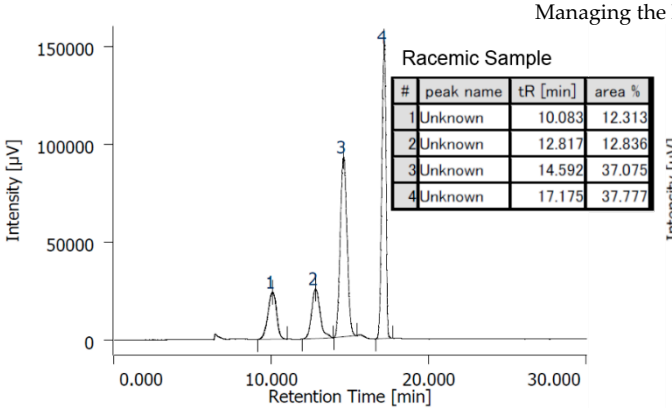


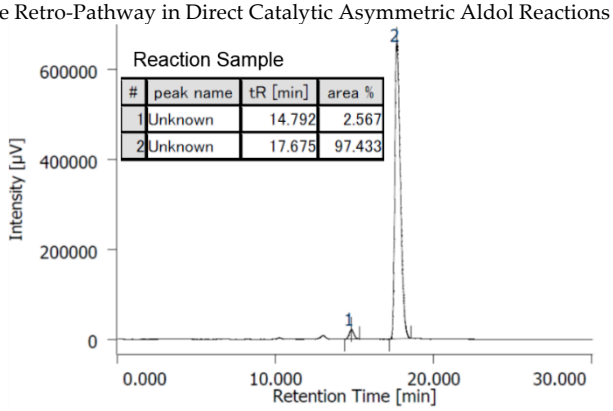
(2*S*,3*R*)-*N*,*N*-Diallyl-2-ethyl-3-hydroxy-4-methylpentanethioamide (3ba)



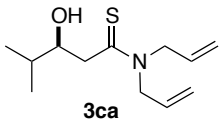
3ba

Colorless oil, IR ($CHCl_3$ solution) ν 3405, 3019, 1710, 1413, 1363, 1213, 1090, 929, 669 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.90–5.72 (m, 2H), 5.29–5.11 (m, 4H), 4.81 (dd, J = 5.5, 14.6 Hz, 1H), 4.72 (s, 1H), 4.43 (dd, J = 6.2, 14.6 Hz, 1H), 4.29–4.24 (m, 1H), 4.10 (dd, J = 4.8, 17.4 Hz, 1H), 3.15–3.08 (m, 2H), 2.12–2.04 (m, 1H), 1.77–1.68 (m, 2H), 0.99 (d, J = 6.6 Hz, 3H), 0.84–0.78 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 209.4, 130.9, 130.5, 118.8, 118.2, 78.4, 55.9, 52.5, 50.1, 31.5, 22.0, 20.0, 19.2, 12.2; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{14}H_{26}ONS$ m/z 256.1730 $[M+H]^+$, found 256.1726; $[\alpha]_D^{26}$ 148.0 (c 1.54, $CHCl_3$, 95% ee sample); HPLC: CHIRALCEL OZ-H (ϕ 0.46 cm x 25 cm), 2-propanol/n-hexane = 2/98, flow rate 0.5 mL/min, detection 254 nm, t_R = 14.8 min (minor), 17.7 min (major).



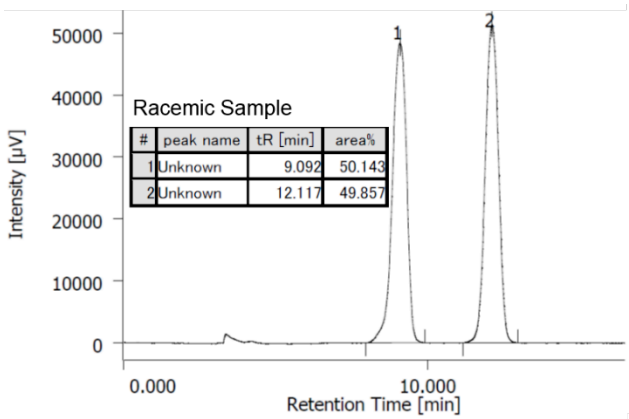


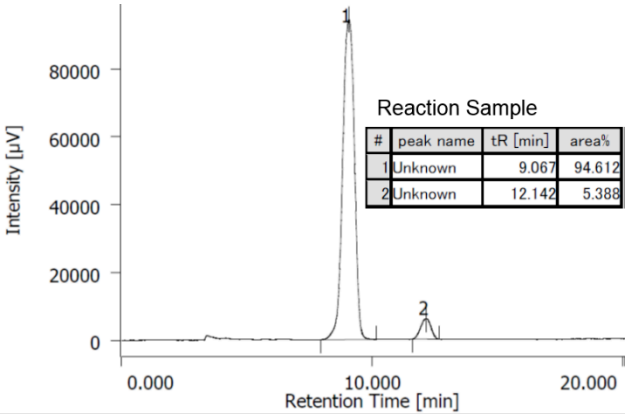
(*S*)-*N*,*N*-Diallyl-3-hydroxy-4-methylpentanethioamide (3ca)



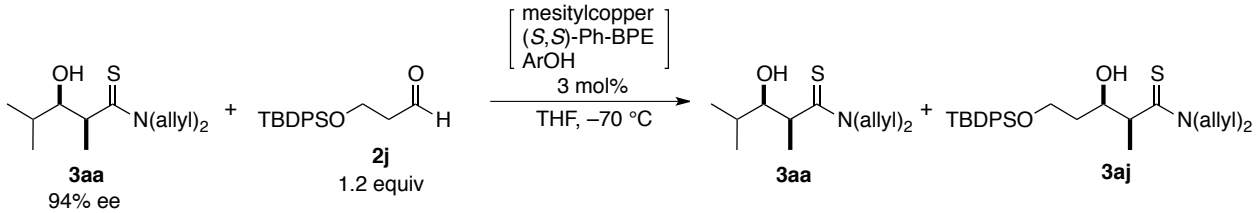
3ca

Colorless oil, IR ($CHCl_3$ solution) ν 3414, 2965, 1642, 1491, 1411, 1297, 1204, 994, 931, 684 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.90–5.72 (m, 2H), 5.29–5.11 (m, 4H), 4.69 (dd, *J* = 6.0, 14.9 Hz, 1H), 4.56 (dd, *J* = 6.0, 14.9 Hz, 1H), 4.24 (dt, *J* = 2.5, 17.2 Hz, 1H), 4.09 (dt, *J* = 2.5, 17.4 Hz, 1H), 3.96–3.89 (m, 2H), 2.79 (dd, *J* = 1.8, 15.6 Hz, 1H), 2.64 (dd, *J* = 9.8, 15.6 Hz, 1H), 1.78–1.70 (m, 1H), 0.94 (t, *J* = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 203.4, 130.53, 130.49, 118.7, 117.9, 74.6, 55.8, 52.8, 45.1, 33.3, 18.5, 17.8; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{12}H_{21}ONNaS$ *m*/*z* 250.1236 $[M+Na]^+$, found 250.1235; $[\alpha]_D^{25}$ –84.8 (*c* 0.92, $CHCl_3$, 89% ee sample); HPLC: CHIRALCEL OD-H (ϕ 0.46 cm x 25 cm), 2-propanol/*n*-hexane = 1/99, flow rate 1.0 mL/min, detection 254 nm, t_R = 9.1 min (major), 12.1 min (minor).





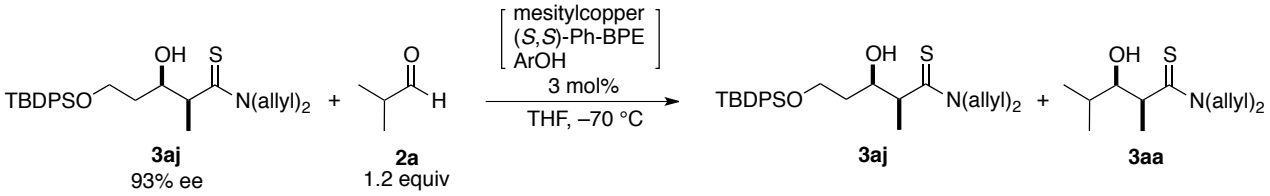
4.3.2 Crossover experiment.



To a flame-dried 20 mL test tube equipped with a magnetic striring bar and a 3-way glass stopcock were charged with (*S*,*S*)-Ph-BPE (3.0 mg, 6 μmol), 2,2,5,7,8-pentamethylchromanol (ArOH, 1.3 mg, 6 μmol) and mesitylcopper (1.1 mg, 6 μmol) in a dry box. To the mixture was added THF (120 μL, 0.05 M) *via* syringe at room temperature, after 5 min of stirring at the same temperature, yellow-green solution of (*S*,*S*)-Ph-BPE/mesitylcopper/ArOH solution was obtained, which was used within 15 min.

To a flame-dried 20 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock were charged with **3aa** (24.1 mg, 0.1 mmol, 94% ee sample), **2j** (37.4 mg, 0.12 mmol, 1.2 eq.), dry THF (440 μL, 0.2 M), the reaction mixture was cooled to –70 °C. To the resulting cooled solution was added (*S*,*S*)-Ph-BPE/mesitylcopper/ArOH solution (60 μL, 3 μmol) prepared above dropwise to run the reaction. After specified time at the same temperature, the

precooled solution of acetic acid in THF (0.1 M in THF, 1 mL, 0.1 mmol), then saturated aq. NH_4Cl were added to quench the reaction. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure. The product distribution was determined by crude ^1H NMR. The enantiomeric excess was determined by HPLC analysis.

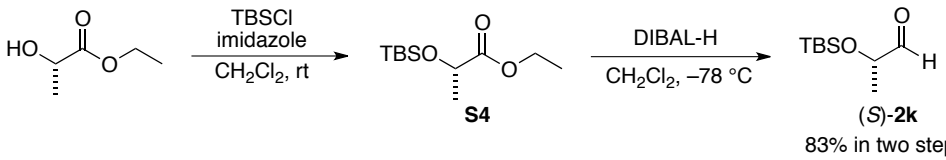


To a flame-dried 20 mL test tube equipped with a magnetic striring bar and a 3-way glass stopcock were charged with (*S,S*)-Ph-BPE (3.0 mg, 6 μmol), 2,2,5,7,8-pentamethylchromanol (ArOH, 1.3 mg, 6 μmol) and mesitylcopper (1.1 mg, 6 μmol) in a dry box. To the mixture was added THF (120 μL, 0.05 M) *via* syringe at room temperature, after 5 min of stirring at the same temperature, yellow-green solution of (*S,S*)-Ph-BPE/mesitylcopper/ArOH solution was obtained, which was used within 15 min.

To a flame-dried 20 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock were charged with **3aj** (48.1 mg, 0.1 mmol, 93% ee sample), **2a** (11 μL, 0.12 mmol, 1.2 eq.), dry THF (440 μL, 0.2 M), the reaction mixture was cooled to –70 °C. To the resulting cooled solution was added (*S,S*)-Ph-BPE/mesitylcopper/ArOH solution (60 μL, 3 μmol) prepared above dropwise to run the reaction. After 48 h at the same temperature, the precooled solution of acetic acid in THF (0.1 M in THF, 1 mL, 0.1 mmol), then saturated aq. NH_4Cl were added to quench the reaction. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure. The product distribution was determined by crude ^1H NMR. The enantiomeric excess was determined by HPLC analysis.

4.4. Direct catalytic asymmetric aldol reaction with chiral aldehyde (Table 3 and 4).

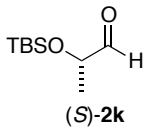
4.4.1 Synthesis of (*S*)-2-((*tert*-butyldimethylsilyl)oxy)propanal ((*S*)-2k).



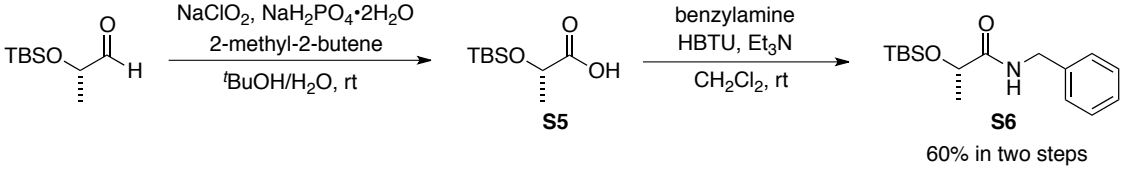
(*S*)-2-((*tert*-Butyldimethylsilyl)oxy)propanal was synthesized from ethyl L-lactate by following literature.[3] To a 500 mL flask containing ethyl L-lactate (14.2 g, 120 mmol) and imidazole (16.4 g, 240 mmol, 2 eq.), CH_2Cl_2 (250 mL) was added and the resulting solution was cooled to 0 °C. TBSCl (23.6 g, 156 mmol, 1.3 eq.) in CH_2Cl_2 (50 mL) was added via a cannula and the reaction mixture was warmed to room temperature. After stirring for overnight, the reaction mixture was washed with 1N HCl aq., sat. $NaHCO_3$ aq. and brine, and dried over Na_2SO_4. Filtration and concentration gave a crude product of **S4** as a colorless oil, which was used for the next step without purification. The crude **S4** (2.2 g, 9 mmol) was dissolved in 50 mL CH_2Cl_2 and the solution was cooled to –78 °C. Diisobutylaluminium hydride (DIBAL-H, 11 mL, 1.04 M in *n*-hexane, 10.6 mmol, 1.2 eq.) was added dropwise via a cannula. After stirring at the same temperature for 1 h, 5 mL of methanol was added dropwise via a cannula to the reaction mixture at –78 °C. After stirring at the same temperature for 20 min, the reaction mixture was warmed to 0 °C, and 20 mL sat. potassium sodium tartrate aq. was added. The reaction mixture was further warmed to room temperature and stirred for 3 h until clear phase separation was observed. The mixture was extracted with CH_2Cl_2, and combined organic extracts were washed with brine and dired over Na_2SO_4. Filtration and concentration gave the crude product, which was distilled to give (*S*)-**2k** as a colorless oil (83% in two steps). All data matched the reported data.[3]

[3]Kim, D.; Lee, J.; Shim, P.; Lim, J.; Doi, T.; Kim, A. *J. Org. Chem.* **2002**, *67*, 772.

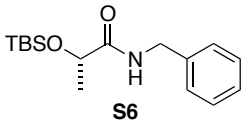
Colorless oil, ^{1}H NMR ($CDCl_3$, 400 Hz): δ 9.59 (d, J = 1.4 Hz, 1H), 4.07 (qd, J = 1.4, 6.9 Hz, 1H), 1.05 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 Hz): δ 204.2, 73.8, 25.7, 18.5, 18.2, –4.8; $[\alpha]_D^{24}$ –14.8 (c 0.84, $CHCl_3$). The enantiopurity of the aldehyde was determined to be >99% by HPLC analysis after transforming the aldehyde to *N*-benzyl-2-((*tert*-butyldimethylsilyl)oxy)-propanamide (**S6**) by following procedures.



(*S*)-**2k**

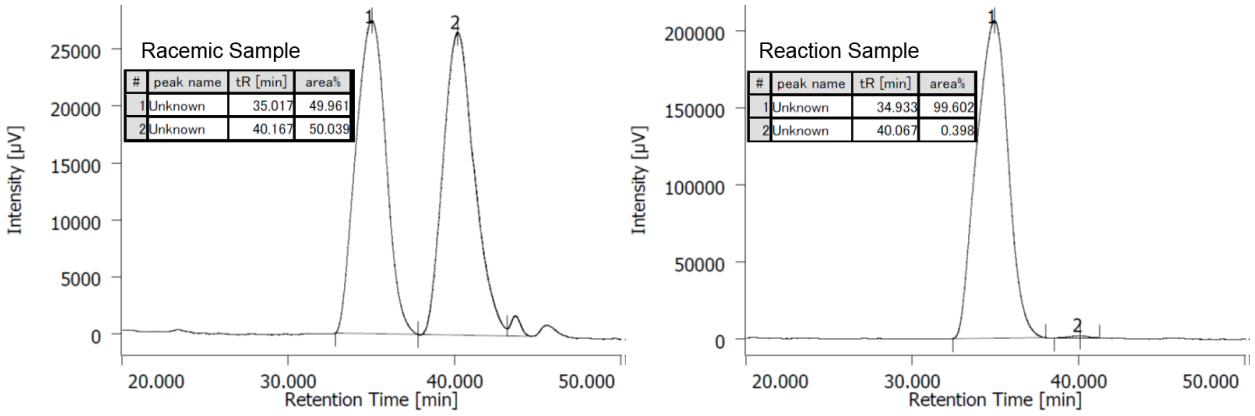


To a stirred solution of (*S*)-**2k** (188 mg, 1 mmol) in ^{t}BuOH/H_2O (1.2 mL, 5:1), 2-methyl-2-butene (1.06 mL, 10 mmol, 10 eq.), $NaClO_2$ (271 mg, 3 mmol, 3 eq.) and NaH_2PO_4·$2H_2O$ (468 mg, 3 mmol, 3 eq.) were added. After stirring at room temperature for 30 min, the reaction mixture was diluted with ethyl acetate, and the resulting mixture was washed with 1N HCl aq. and brine, and dried over Na_2SO_4. Filtration and concentration gave crude acid **S5**, which was directly used for the next step. **S5** (102 mg, 0.5 mmol) was dissolved in 5 mL CH_2Cl_2 and HBTU (379 mg, 1 mmol, 2 eq.), benzylamine (109 μL, 1 mmol, 2 eq.), and Et_3N (140 μL, 1 mmol, 2 eq.) were added to the solution. After stirring at room temperature for 2 h, the reaction mixture was concentrated and directly loaded onto silica gel column chromatography to give **S6** as a colorless oil (87 mg, 60% in two steps).

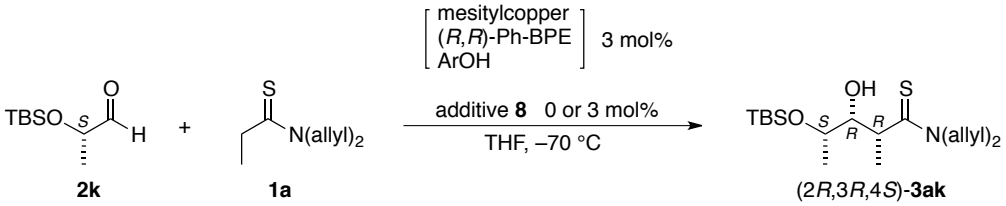


S6

Colorless oil; IR ($CHCl_3$ solution) ν 3420, 3008, 2955, 2930, 2858, 1710, 1666, 1524, 1363, 1260, 1121, 945, 838 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 Hz): δ 7.32–7.22 (m, 5H), 6.93 (br, 1H), 4.49 (dd, J = 6.4, 14.9 Hz, 1H), 4.38 (dd, J = 5.6, 14.7 Hz, 1H), 4.24 (q, J = 6.9 Hz, 1H), 1.38 (d, J = 6.6 Hz, 3H), 0.82 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 Hz): δ 174.3, 138.1, 128.7, 127.5, 127.4, 70.0, 42.9, 25.7, 22.0, 17.9; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{16}H_{28}O_2NSi$ m/z 294.1884 $[M+H]^+$, found 294.1882; $[\alpha]_D^{26}$ –17.2 (c 2.52, $CHCl_3$); HPLC: CHIRALCEL AD-H (ϕ 0.46 cm x 25 cm) and AD-H (ϕ 0.46 cm x 25 cm), 2-propanol/*n*-hexane = 2/98, flow rate 0.5 mL/min, detection 220 nm, t_R = 34.9 min (major), 40.0 min (minor).



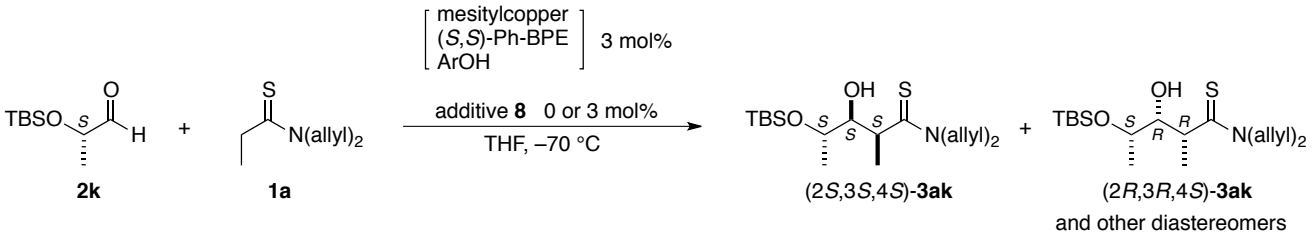
4.4.2 Experimental procedure.



To a flame-dried 20 mL test tube equipped with a magnetic striring bar and a 3-way glass stopcock were charged with (*R*,*R*)-Ph-BPE (6.1 mg, 0.012 mmol), 2,2,5,7,8-pentamethylchromanol (ArOH, 2.6 mg, 0.012 mmol) and mesitylcopper (2.2 mg, 0.012 mmol) in a dry box. To the mixture was added THF (240 μL, 0.05 M) *via* syringe at room temperature, after 5 min of stirring at the same temperature, yellow-green solution of (*R*,*R*)-Ph-BPE/mesitylcopper/ArOH solution

was obtained, which was used within 15 min.

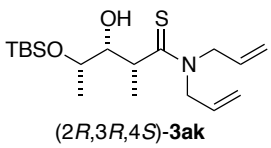
To a flame-dried 20 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock were charged with *N*,*N*-diallylthiopropionamide (**1a**, 40 μL, 0.24 mmol, 1.2 eq.), dry THF (1.8 mL or 1.86 mL, 0.1 M), and (*S*)-**2k** (44 μL, 0.2 mmol) and additive **8** (60 μL, 0.1 M in THF, 6 μmol) if any, the reaction mixture was cooled to –70 °C. To the resulting cooled solution was added (*R*,*R*)-Ph-BPE/mesitylcopper/ArOH solution (120 μL, 6 μmmol) prepared above dropwise to run the reaction. After certain time at the same temperature, the precooled solution of acetic acid in THF (0.1 M in THF, 1 mL, 0.1 mmol), then saturated aq. NH_4Cl were added to quench the reaction. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure. The chemical yield and diastereomeric ratio were determined by ^1H NMR of the crude mixture. The crude product was purified by silica gel column chromatography, giving the desired product as a colorless oil.



To a flame-dried 20 mL test tube equipped with a magnetic striring bar and a 3-way glass stopcock were charged with (*S*,*S*)-Ph-BPE (10.1 mg, 0.02 mmol), 2,2,5,7,8-pentamethylchromanol (ArOH, 4.4 mg, 0.02 mmol) and mesitylcopper (3.6 mg, 0.02 mmol) in a dry box. To the mixture was added THF (0.4 mL, 0.05 M) *via* syringe at room temperature, after 5 min of stirring at the same temperature, yellow-green solution of (*S*,*S*)-Ph-BPE/mesitylcopper/ArOH solution was obtained, which was used within 15 min.

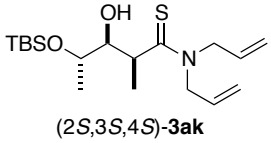
To a flame-dried 20 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock were charged with *N*,*N*-diallylthiopropionamide (**1a**, 40 μL, 0.24 mmol, 1.2 eq.), dry THF (1.6 mL or 1.7 mL, 0.1 M), and (*S*)-**2k** (44 μL, 0.2 mmol) and additive **8** (100 μL, 0.1 M in THF, 0.01 mmol) if any, and the reaction mixture was cooled to –78 °C. To the resulting cooled solution was added (*S*,*S*)-Ph-BPE/mesitylcopper/ArOH solution (0.2 mL, 0.01 mmol) prepared above dropwise to run the reaction. After certain time at the same temperature, the precooled solution of acetic acid in THF (0.1 M in THF, 1 mL, 0.1 mmol), then saturated aq. NH_4Cl were added to quench the reaction. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure. The chemical yield and diastereomeric ratio were determined by ^1H NMR of the crude mixture. The crude product was purified by silica gel column chromatography to give the desired product as a colorless oil.

(2*R*,3*R*,4*S*)-*N*,*N*-Diallyl-4-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2-methylpentanethioamide (2*R*,3*R*,4*S*-3ak)



Less polar product, colorless oil, IR ($CHCl_3$ solution) ν 3338, 2957, 2931, 2857, 1710, 1489, 1412, 1257, 1224, 1088, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 400 Hz): δ 5.89–5.71 (m, 2H), 5.27–5.08 (m, 4H), 4.68–4.63 (m, 2H), 4.50 (dd, *J* = 6.0, 14.7 Hz, 1H), 4.26 (dd, *J* = 3.9, 17.4 Hz, 1H), 4.10 (dd, *J* = 2.3, 17.2 Hz, 1H), 3.65 (m, 1H), 3.52 (q, *J* = 6.9 Hz, 1H), 3.36 (d, *J* = 8.0 Hz, 1H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.19 (d, *J* = 6.6 Hz, 3H), 0.85 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 Hz): δ 210.1, 130.9, 130.4, 118.5, 117.7, 76.7, 68.6, 55.1, 52.4, 41.0, 25.7, 21.2, 17.8, 13.6, –4.3, –4.7; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{18}H_{36}O_2NSSi$ *m*/*z* 358.2231 $[M+H]^+$, found 358.2230; $[\alpha]_D^{28}$ –68.0 (*c* 2.18, $CHCl_3$).

(2*S*,3*S*,4*S*)-*N*,*N*-Diallyl-4-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-2-methylpentanethioamide (2*S*,3*S*,4*S*-3ak)

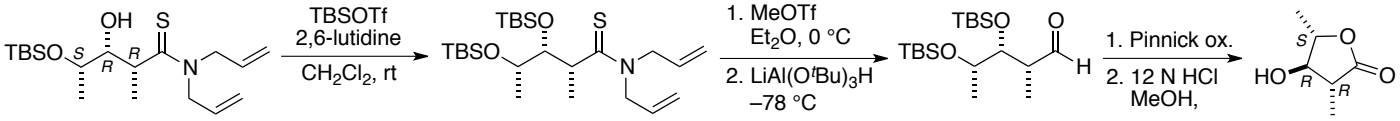


More polar product, colorless oil, IR ($CHCl_3$ solution) ν 3336, 2956, 2931, 2858, 1644, 1488, 1410, 1256, 1138, 1088, 987, 933, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 400 Hz): δ 5.90–5.72 (m, 2H), 5.28–5.12 (m, 4H), 4.85 (dd, *J* = 5.5, 14.7 Hz, 1H), 4.38 (dd, *J* = 6.2, 14.9 Hz, 2H), 4.08–4.01 (m, 1H), 3.94–3.89 (m, 1H), 3.77–3.76 (m, 1H), 3.38 (d, *J* = 5.7 Hz, 1H), 3.18–3.13 (m, 1H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.18 (d, *J* = 6.4 Hz, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 Hz): δ 210.1, 131.2, 130.7,

118.6, 118.2, 77.6, 69.9, 55.2, 52.8, 44.0, 16.0, 20.5, 18.2, 17.6, –3.9, –4.5; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{18}H_{35}O_2NNaSSi$ *m*/*z* 380.2050 $[M+Na]^+$, found 380.2043; $[\alpha]_D^{27}$ 13.2 (*c* 0.28, $CHCl_3$).

4.4.3 Determination of the absolute configuration

Relative and absolute configuration of aldol adduct **3ak** was determined by converting into the reported 5-membered lactone **S9** by following procedures.



(2*R*,3*R*,4*S*)-**3ak** (2*R*,3*R*,4*S*)-**S7** (2*R*,3*R*,4*S*)-**S8** (2*R*,3*R*,4*S*)-**S9**

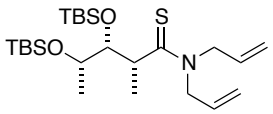
To a stirred solution of (2*R*,3*R*,4*S*)-**3ak** (357 mg, 1 mmol, obtained with the (*R*)-catalyst) in 10 mL of CH_2Cl_2, 2,6-lutidine (233 μL, 2 mmol, 2 eq.) and TBSOTf (459 μL, 2 mmol, 2 eq.) were added at 0 °C and the reaction mixture was stirred at room temperature for 2 h. Saturated NH_4Cl aq. was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the resulting residue was purified by column chromatography, giving (2*R*,3*R*,4*S*)-**S7** as a colorless oil (462 mg, 98% yield).

To a stirred solution of (2*R*,3*R*,4*S*)-**S7** (450 mg, 0.955 mmol) in 10 mL of ether, MeOTf (209 μL, 1.91 mmol, 2 eq.) was added at 0 °C and the reaction miture was stirred at room temperature for 5 h. The reaction mixture was cooled to –78 °C and $LiAlH(O^tBu)_3$ (1.91 mL, 1.0 M in THF, 1.91 mmol, 2 eq.) was added. After stirring at the same temperature for 4 h, silica gel (9.55 g, 10 g/1 mmol starting material) was added slowly with CH_2Cl_2 at –78 °C. The resulting mixture was slowly warmed to room temperature for 1.5 h, and filtered through a short pad of silica gel with ethyl acetate as eluent. The filtrate was concentrated under reduced pressure and the crude material was purified by column chromatography to give aldehyde (2*R*,3*R*,4*S*)-**S8** as a colorless oil (288 mg, 84% yield).

To a stirred solution of (2*R*,3*R*,4*S*)-**S8** (180 mg, 0.5 mmol) in ^{t}BuOH/H_2O (1.2 mL, 5:1), 2-methyl-2-butene (530 μL, 5 mmol, 10 eq.), $NaClO_2$ (136 mg, 1.5 mmol, 3 eq.), and $NaH_2PO_4{\cdot}2H_2O$ (234 mg, 1.5 mmol, 3 eq.) were added. After stirring at room temperature for 30 min, the reaction mixture was diluted with ethyl acetate, washed with 1N HCl aq. and brine, dried over Na_2SO_4. Filtartion and concentration gave crude acid, which was used directly for the next step. The crude acid was dissolved in 2 mL MeOH and several drops of 12 N HCl was added till the starting material was consumed in 30 min. Sat. $NaHCO_3$ aq. was added to neutralize. MeOH was removed under reduced pressure, and the resulting residue was dissolved in EtOAc, and the resulting mixture was washed with brine and dried over Na_2SO_4. The crude product was purified by silica gel column chromatography to give lactone (2*R*,3*R*,4*S*)-**S9** as a colorless oil (58 mg, 90% yield in two steps).

Configuration of (2*R*,3*R*,4*S*)-**S9** was confirmed by NOE analysis and reported NMR data.[4]

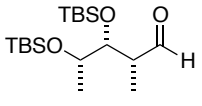
(2*R*,3*R*,4*S*)-*N*,*N*-Diallyl-3,4-bis((*tert*-butyldimethylsilyl)oxy)-2-methylpentanethioamide ((2*R*,3*R*,4*S*)-S7)



(2*R*,3*R*,4*S*)-**S7**

Colorless oil; IR ($CHCl_3$ solution) *ν* 2957, 2930, 2857, 1472, 1408, 1254, 1149, 1104, 1033, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 400 Hz): δ 5.91–5.71 (m, 2H), 5.26–5.09 (m, 4H), 4.88 (dd, *J* = 5.5, 14.6 Hz, 1H), 4.41–4.27 (m, 3H), 4.06 (dd, *J* = 4.8, 17.2 Hz, 1H), 3.80–3.76 (m, 1H), 2.95–2.87 (m, 1H), 1.24 (d, 3H), 0.97 (d, 3H), 0.89 (s, 9H), 0.85 (s, 9H), 0.12 (s, 6H), 0.06 (s, 3H), 0.01 (s, 3H) ; ^{13}C NMR ($CDCl_3$, 150 Hz): δ 209.0, 131.3, 131.0, 118.3, 117.9, 82.3, 70.6, 55.3, 52.5, 45.6, 26.3, 26.0, 20.8, 18.5, 18.1, 17.8, –3.5, –4.1, –4.6, –4.8; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{24}H_{50}O_2NSSi_2$ *m*/*z* 472.3095 $[M+H]^+$, found 472.3084; $[\alpha]_D^{28}$ –61.5 (*c* 1.10, $CHCl_3$).

(2*R*,3*R*,4*S*)-3,4-Bis((*tert*-butyldimethylsilyl)oxy)-2-methylpentanal ((2*R*,3*R*,4*S*)-S8)



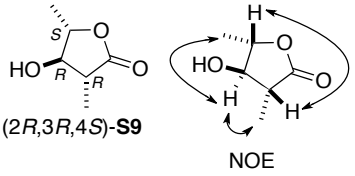
(2*R*,3*R*,4*S*)-**S8**

Colorless oil, IR ($CHCl_3$ solution) *ν* 2957, 2931, 2958, 1717, 1472, 1362, 1257, 1104, 839 cm^{-1}; ^1H NMR ($CDCl_3$, 400 Hz): δ 9.71 (s, 1H), 3.95 (dd, *J* = 2.7, 6.2 Hz, 1H), 3.70–3.64 (m, 1H), 2.72 (qd, *J* = 3.2, 6.9

[4]Nebot, J.; Figueras, S.; Romea, P.; Urpí, F.; Ji, Y. *Tetrahedron* **2006**, *62*, 11090.

Hz, 1H), 1.15 (d, *J* = 6.2 Hz, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 0.83 (s, 18H), 0.05 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), –0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 Hz): δ 205.2, 76.1, 70.0, 25.8, 20.7, 18.2, 18.0, 7.4, –4.1, –4.2, –4.9; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{18}H_{40}O_3NaSi_2$ *m*/*z* 383.2408 $[M+Na]^+$, found 383.2399; $[\alpha]_D^{28}$ –16.6 (*c* 1.96, $CHCl_3$).

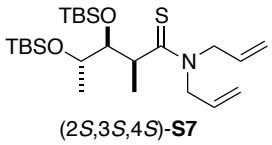
(2*R*,3*R*,4*S*)-4-Hydroxy-3,5-dimethyldihydrofuran-2(3H)-one ((2*R*,3*R*,4*S*)-S9)



Colorless oil, IR ($CHCl_3$ solution) *ν* 3615, 3399, 3025, 2982, 2935, 1780, 1455, 1213, 1180, 1064, 963 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 Hz): δ 4.22–4.16 (m, 1H), 3.71–3.66 (m, 1H), 2.79 (d, *J* = 5.3 Hz, 1H), 2.62–2.54 (m, 1H), 1.44 (d, *J* = 6.2 Hz, 3H), 1.28 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 Hz): δ 176.2, 80.6, 79.7, 43.9, 18.0, 12.5; HRMS (ESI-Orbitrap) Anal. calcd. for $C_6H_{10}O_3Na$ *m*/*z* 153.0522 $[M+Na]^+$, found 153.0519; $[\alpha]_D^{28}$ –30.4 (*c* 0.64, $CHCl_3$). The absolute configuration was determined by NOE experiment, and further confirmed by comparison with reported data. ($[\alpha]_D$ –23.5(c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.22 (dq, *J* = 7.6, 6.1 Hz, 1H), 3.76–3.67 (m, 1H), 2.75 (br, 1H), 2.60 (dq, *J* = 9.2, 7.2 Hz, 1H), 1.46 (d, *J* = 6.1 Hz, 3H), 1.31 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 176.7, 80.5, 80.0, 43.9, 18.0, 12.5.)[4]

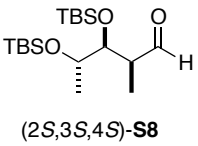
(2*S*,3*S*,4*S*)-**3ak** (the major diastereomer obtained with the (*S*)-catalyst) was converted to lactone (2*S*,3*S*,4*S*)-**S9** by following the identical procedure and its configuration was confirmed by comparing with the reported NMR data.[5]

(2*S*,3*S*,4*S*)-*N*,*N*-Diallyl-3,4-bis((*tert*-butyldimethylsilyl)oxy)-2-methylpentanethioamide ((2*S*,3*S*,4*S*)-S7)



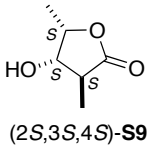
Colorless oil; IR ($CHCl_3$ solution) *ν* 2958, 2929, 2857, 1711, 1255, 1103, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 Hz): δ 5.92–5.80 (m, 2H), 5.23–5.14 (m, 4H), 4.65–4.47 (m, 3H), 4.43 (q, *J* = 4.4 Hz, 1H), 4.05–3.9 9 (m, 1H), 3.88–3.83 (m, 1H), 3.34–3.28 (m, 1H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.84 (s, 9H), 0.17 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), –0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 Hz): δ 211.1, 132.1, 131.6, 118.2, 118.0, 77.8, 71.6, 55.9, 53.0, 42.2, 26.0, 20.2, 18.5, 18.2, 17.6, –4.0, –4.4, –4.5, –4.7; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{24}H_{50}O_2NSSi_2$ *m*/*z* 472.3095 $[M+H]^+$, found 472.3093; $[\alpha]_D^{27}$ 38.8 (*c* 0.80, $CHCl_3$).

(2*S*,3*S*,4*S*)-3,4-Bis((*tert*-butyldimethylsilyl)oxy)-2-methylpentanal ((2*S*,3*S*,4*S*)-S8)



Colorless oil, IR ($CHCl_3$ solution) *ν* 2958, 2929, 2857, 1711, 1255, 1103, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 Hz): δ 9.57 (d, *J* = 3.2 Hz, 1H), 3.88–3.82 (m, 1H), 3.78–3.75 (m, 1H), 2.58–2.54 (m, 1H), 1.12 (d, *J* = 6.4 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.84 (s, 9H), 0.05 (d, 6H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 Hz): δ 202.5, 75.3, 70.7, 48.0, 25.7, 18.0, 17.4, 11.4, –4.5, –4.6, –4.7, –4.8; HRMS (ESI-Orbitrap) Anal. calcd. for $C_{18}H_{40}O_3NaSi_2$ *m*/*z* 383.2408 $[M+Na]^+$, found 383.2404; $[\alpha]_D^{28}$ –0.6 (*c* 0.71, $CHCl_3$).

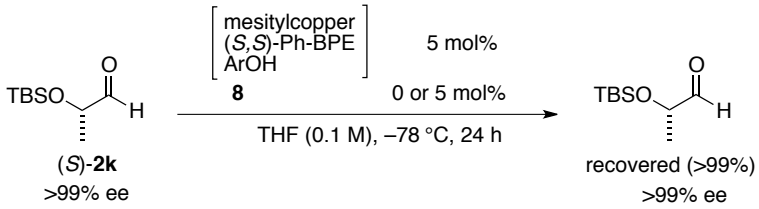
(2*S*,3*S*,4*S*)-4-Hydroxy-3,5-dimethyldihydrofuran-2(3H)-one ((2*S*,3*S*,4*S*)-S9)



colorless oil, IR ($CHCl_3$ solution) *ν* 3503, 3406, 3023, 3016, 1709, 1418, 1363, 1227, 1090, 902 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 Hz): δ 4.68–4.61 (m, 1H), 4.14–4.10 (m, 1H), 2.64–2.57 (m, 1H), 2.03 (dd, *J* = 1.8, 4.8 Hz, 1H), 1.38 (dd, *J* = 1.8, 6.4 Hz, 3H), 1.28 (dd, *J* = 2.0, 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 Hz): δ 177.9, 77.8, 75.4, 43.2, 13.8, 13.0; HRMS (ESI-Orbitrap) Anal. calcd. for $C_6H_{10}O_3Na$ *m*/*z* 153.0522 $[M+Na]^+$, found 153.0519; $[\alpha]_D^{28}$ –71.7 (*c* 0.30, $CHCl_3$). The absolute configuration was confirmed by comparison with the reported data (typical chemical shifts in ^{1}H NMR: δ = 4.12 (dd, *J* = 5.0, 5.0 Hz, 1H), 4.66 (dq, *J* = 6.6 Hz, 1H)).[5]

[5]Nakata, M.; Takao, H.; Ikeyama, Y.; Sakai, T.; Tatsuta, K.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1749.

4.4.4 Control experiment



To a flame-dried 20 mL test tube equipped with a magnetic striring bar and a 3-way glass stopcock were charged with (*S*,*S*)-Ph-BPE (10.1 mg, 0.02 mmol), 2,2,5,7,8-pentamethylchromanol (ArOH, 4.4 mg, 0.02 mmol) and mesitylcopper (3.6 mg, 0.02 mmol) in a dry box. To the mixture was added THF (0.4 mL, 0.05 M) *via* syringe at room temperature, after 5 min of stirring at the same temperature, yellow-green solution of (*S*,*S*)-Ph-BPE/mesitylcopper/ArOH solution was obtained, which was used within 15 min.

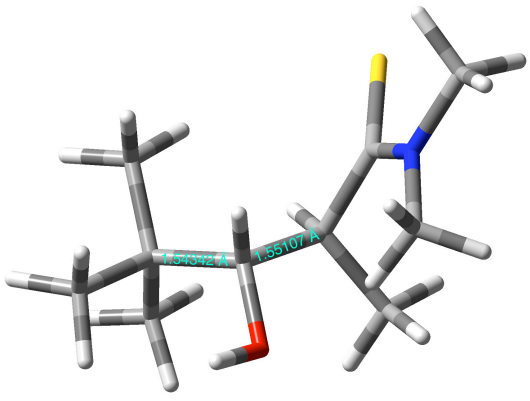
To a flame-dried 20 mL test tube equipped with a magnetic stirring bar and a 3-way glass stopcock were charged with (*S*)-**2k** (44 μL, 0.2 mmol), dry THF (1.76 mL, 0.1 M). The reaction mixture was cooled to –78 °C. To the resulting cooled solution was added Ph-BPE/mesitylcopper/ArOH solution (0.2 mL, 0.01 mmol) prepared above dropwise to run the reaction. After 24 h at the same temperature, the precooled solution of acetic acid in THF (0.1 M in THF, 1 mL, 0.1 mmol), then saturated aq. NH_4Cl were added to quench the reaction. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure. ^1H NMR of the crude mixture showed complete recovery of (*S*)-**2k**. The enantiopurity of the recovered aldehyde was determined to be >99% by HPLC analysis after transforming to *N*-benzyl-2-((*tert*-butyldimethylsilyl)oxy)propanamide as mentioned before.

5. Calculated Structure of Aldol Adducts

All calculations were performed using Gaussian 09.[6] Computed XYZ-coordinates are summarized in Table S1-9.

Table S1. XYZ-coordinates and the structure of **3al'** optimized at PM2 with a 6-31G(d,p) basis set.

Number	atom	X	Y	Z
1	C	2.226447	0.354306	-0.343339
2	C	3.205723	-0.336044	-1.299125
3	H	3.630872	-1.239154	-0.858702
4	H	2.718419	-0.596946	-2.241958
5	H	4.037235	0.329940	-1.530408
6	C	2.919521	0.563412	1.002891
7	H	.312801	1.157422	1.686001
8	H	3.133531	-0.395994	1.473194
9	H	3.861987	1.093603	0.857906
10	C	0.974272	-0.535103	-0.191164
11	C	-0.065366	0.033843	0.808077
12	C	1.410599	0.369493	0.172952
13	N	-2.121345	-0.612174	-0.428429
14	C	-3.426175	-0.289067	-0.994002
15	H	-3.820028	-1.180961	-1.474486
16	H	-4.107576	0.047721	-0.212955

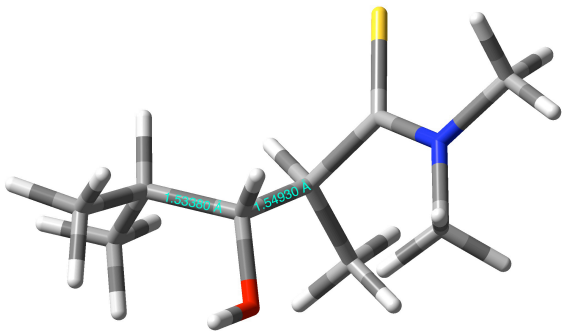


[6]M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

17	C	-1.754320	-2.023405	-0.487838
18	H	-0.752882	-2.190139	-0.115735
19	H	-2.460007	-2.613677	0.100579
20	S	-1.980614	1.930740	0.271028
21	C	-0.231274	-0.775613	2.101377
22	H	-0.910128	-0.233505	2.759309
23	H	-0.627604	-1.773182	1.936826
24	H	0.729687	-0.879650	2.601052
25	O	1.323414	-1.860061	0.244303
26	H	1.846808	-2.259783	-0.462102
27	H	0.512449	-0.595032	-1.187874
28	H	0.292664	1.009203	1.124130
29	C	1.816566	1.693855	-0.958601
30	H	1.376767	1.546210	-1.947137
31	H	1.087937	2.226898	-0.349442
32	H	2.694223	2.331592	-1.074432
33	H	-1.804622	-2.361644	-1.523963
34	H	-3.329376	0.516896	-1.719045

Table S2. XYZ-coordinates and the structure of **3aa'** optimized at PM2 with a 6-31G(d,p) basis set.

Number	atom	X	Y	Z
1	C	-2.308897	-0.571191	-0.540235
2	C	-3.224416	0.018893	-1.611792
3	H	-3.733804	0.912435	-1.244643
4	H	-2.667382	0.282354	-2.512374
5	H	-3.998133	-0.694483	-1.893132
6	C	-3.099863	-0.890196	0.725151
7	H	-2.495168	-1.414299	1.463722
8	H	-3.469766	0.029530	1.176635
9	H	-3.953923	-1.524743	0.488494
10	C	-1.120904	0.358308	-0.262322
11	C	-0.088531	-0.288419	0.694899
12	C	1.297880	-0.436404	0.076653
13	N	2.007236	0.673464	-0.232331
14	C	3.356524	0.520087	-0.763838
15	H	3.791342	1.509493	-0.880341
16	H	3.960058	-0.077681	-0.083440
17	C	1.534973	2.050848	-0.136469
18	H	0.496004	2.095921	0.159702
19	H	2.141569	2.601094	0.585337
20	S	1.911572	-1.964956	-0.165396
21	C	-0.035051	0.319680	2.101451
22	H	0.651813	-0.270659	2.707529
23	H	0.296163	1.353722	2.108499
24	H	-1.020749	0.286903	2.561148
25	O	-1.559096	1.603324	0.308069
26	H	-2.101330	2.043745	-0.359348
27	H	-0.630356	0.558014	-1.225461



28	H	-0.397170	-1.323763	0.825373
29	H	1.640924	2.531698	-1.110629
30	H	3.332566	0.005935	-1.724544
31	H	-1.875986	-1.496386	-0.935415

Table S3. XYZ-coordinates and the structure of **3ab'** optimized at PM2 with a 6-31G(d,p) basis set.

Number	atom	X	Y	Z
1	C	0.194026	-0.655602	-0.122301
2	C	-0.794310	0.124714	0.781314
3	C	-2.071889	0.535796	0.057791
4	N	-2.928621	-0.421683	-0.366210
5	C	-4.177191	-0.016935	-1.001591
6	H	-4.763688	-0.910356	-1.200157
7	H	-4.727761	0.656008	-0.347060
8	C	-2.705745	-1.862708	-0.306967
9	H	-1.721508	-2.098863	0.073625
10	H	-3.460969	-2.328277	0.329124
11	S	-2.390272	2.155756	-0.156833
12	C	-1.079084	-0.519005	2.143544
13	H	-1.706059	0.159222	2.722048
14	H	-1.582746	-1.477991	2.067739
15	H	-0.147779	-0.678492	2.683299
16	O	0.370316	-1.973667	0.424268
17	H	0.901429	-2.472085	-0.210646
18	H	-0.240265	-0.739829	-1.129060
19	H	-0.325598	1.083790	0.993404
20	H	-2.799774	-2.278754	-1.311735
21	H	-3.977961	0.514723	-1.932011
22	C	1.534524	0.072940	-0.266277
23	C	2.285447	0.205279	1.060176
24	C	2.429056	-0.597136	-1.313682
25	H	1.291886	1.079340	-0.632591
26	C	3.606910	0.953901	0.882171
27	H	2.476787	-0.797387	1.452491
28	H	1.669167	0.722891	1.798220
29	C	3.743613	0.159376	-1.500566
30	H	2.665978	-1.618011	-0.989977
31	H	1.894775	-0.675026	-2.265482
32	C	4.488187	0.291080	-0.174044
33	H	4.135528	1.009896	1.836346
34	H	3.395890	1.983831	0.577825
35	H	4.366960	-0.346084	-2.241561
36	H	3.527092	1.156771	-1.895106
37	H	5.410899	0.859029	-0.311363
38	H	4.778618	-0.705530	0.173878

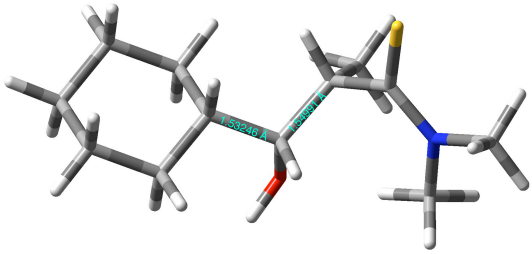


Table S4. XYZ-coordinates and the structure of **3ba'** optimized at PM2 with a 6-31G(d,p) basis set.

Number	atom	X	Y	Z
1	C	-2.423420	-0.301391	0.739594
2	C	-3.414940	-1.459521	0.637663
3	H	-3.899157	-1.476811	-0.341046
4	H	-2.924336	-2.420722	0.799551
5	H	-4.204597	-1.357279	1.381114
6	C	-3.120378	1.027623	0.463347
7	H	-2.463294	1.877959	0.640149
8	H	-3.457091	1.065159	-0.571986
9	H	-3.989042	1.142157	1.111815
10	C	-1.219995	-0.527939	-0.183800
11	C	-0.121275	0.547360	0.017330
12	C	1.209297	-0.050018	0.461089
13	O	1.939979	-0.759874	-0.431366
14	C	3.248044	-1.264852	-0.032956
15	H	3.748935	-1.645093	-0.920096
16	H	3.831085	-0.463341	0.413485
17	C	1.466951	-1.254189	-1.721079
18	H	0.436804	-0.978022	-1.900191
19	H	2.093937	-0.860374	-2.522911
20	S	1.736850	0.218557	2.015960
21	C	0.020853	1.558665	-1.132147
22	H	0.309522	1.068456	-2.059691
23	H	-0.963466	1.990779	-1.317946
24	O	-1.617792	-0.528329	-1.565831
25	H	-2.199426	-1.289734	-1.690157
26	H	-0.797612	-1.511396	0.066868
27	H	-0.418376	1.130035	0.888924
28	H	1.542070	-2.343676	-1.730700
29	H	3.149221	-2.059243	0.708517
30	H	-2.017582	-0.289524	1.756785
31	C	1.017920	2.663068	-0.796860
32	H	1.046021	3.406751	-1.593133
33	H	0.747599	3.167102	0.131028
34	H	2.023331	2.262836	-0.672609

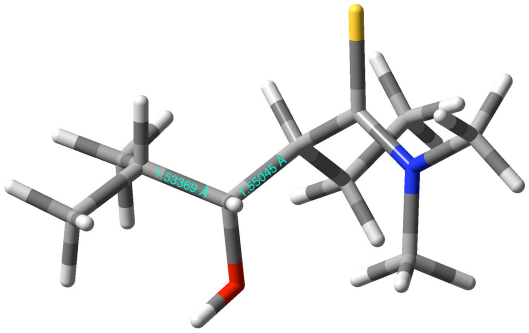
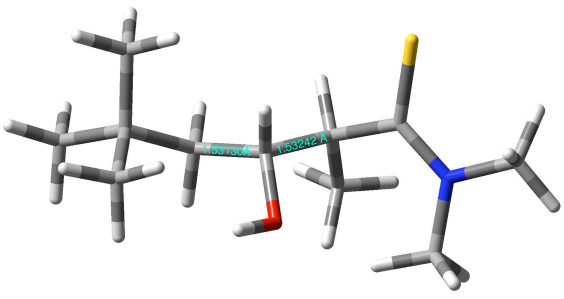


Table S5. XYZ-coordinates and the structure of **3ac'** optimized at PM2 with a 6-31G(d,p) basis set.

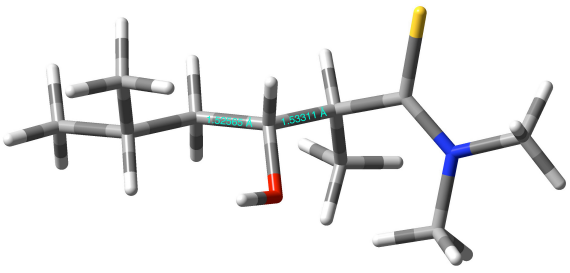
Number	atom	X	Y	Z
1	C	1.876078	-0.376656	0.616191
2	C	3.131396	0.143653	-0.109447
3	C	0.536275	-0.144995	-0.088184
4	C	-0.627726	-0.078824	0.906316
5	C	-1.904490	0.442083	0.239224
6	N	-2.861795	-0.412123	-0.187131
7	C	-4.135279	0.128305	-0.647599
8	H	-4.855689	-0.686035	-0.677810
9	H	-4.470770	0.903043	0.035996



10	C	-2.679959	-1.837855	-0.456299
11	H	-1.629701	-2.079736	-0.506008
12	H	-3.191482	-2.444736	0.292598
13	S	-2.079259	2.095094	0.113811
14	C	-0.750604	-1.328450	1.787006
15	H	-1.721627	-1.356433	2.280644
16	H	-0.615195	-2.253702	1.234614
17	H	0.011435	-1.296964	2.564845
18	O	0.244801	-1.204785	-1.013383
19	H	0.881035	-1.147502	-1.734934
20	H	0.543137	0.814154	-0.616849
21	H	-0.369516	0.749244	1.567359
22	H	3.114478	-2.051318	-1.432643
23	H	-4.035707	0.573382	-1.639048
24	H	1.852450	0.095094	1.603997
25	H	1.971292	-1.454297	0.780470
26	C	4.359463	-0.385661	0.634475
27	H	5.278219	-0.002163	0.187541
28	H	4.339129	-0.078744	1.681288
29	H	4.394533	-1.475836	0.601500
30	C	3.158662	1.673525	-0.086306
31	H	2.291628	2.103241	-0.588475
32	H	3.169612	2.042573	0.940370
33	H	4.053118	2.045916	-0.588507
34	C	3.188879	-0.340048	-1.560261
35	H	3.105877	-1.427397	-1.618893
36	H	2.401128	0.115000	-2.165336
37	H	4.137713	-0.055607	-2.017405

Table S6. XYZ-coordinates and the structure of **3af'** optimized at PM2 with a 6-31G(d,p) basis set.

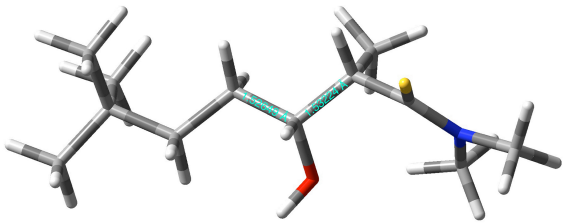
Number	atom	X	Y	Z
1	C	2.117108	-0.180179	0.585435
2	C	3.319272	-0.055162	-0.355549
3	H	3.230554	-0.840599	-1.114081
4	C	0.760989	0.005486	-0.088407
5	C	-0.405227	-0.155801	0.893606
6	C	-1.710647	0.386247	0.301892
7	N	-2.602427	-0.446769	-0.280468
8	C	-3.906325	0.076142	-0.670724
9	H	-4.566619	-0.768256	-0.855162
10	H	-4.303288	0.697797	0.126882
11	C	-2.323307	-1.795631	-0.770315
12	H	-1.259143	-1.966312	-0.817911
13	H	-2.816678	-2.545175	-0.149360
14	S	-1.999947	2.020804	0.451201
15	C	-0.466415	-1.532681	1.569478
16	H	-1.457696	-1.712160	1.984329
17	H	-0.220561	-2.347382	0.893828



18	H	0.242564	-1.564694	2.395386
19	O	0.585573	-0.950002	-1.146412
20	H	1.161913	-0.685784	-1.873876
21	H	0.683812	1.021399	-0.488977
22	H	-0.197658	0.573894	1.677120
23	H	-2.715764	-1.871534	-1.784289
24	H	-3.828353	0.690197	-1.569465
25	H	2.212310	0.563719	1.384264
26	H	2.145164	-1.167008	1.053694
27	C	4.613979	-0.305576	0.413869
28	H	5.477794	-0.275743	-0.250662
29	H	4.753336	0.458195	1.180881
30	H	4.597400	-1.278363	0.905636
31	C	3.370695	1.299830	-1.058780
32	H	2.506166	1.473136	-1.699815
33	H	3.403217	2.106774	-0.324638
34	H	4.262364	1.376373	-1.681438

Table S7. XYZ-coordinates and the structure of **3ag'** optimized at PM2 with a 6-31G(d,p) basis set.

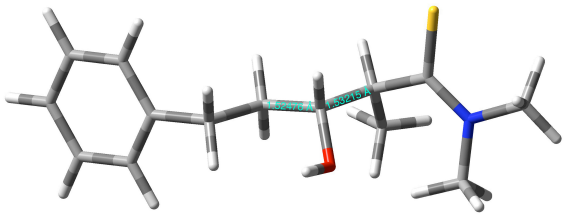
Number	atom	X	Y	Z
1	C	1.366547	-0.022164	0.408936
2	C	2.474408	0.004330	-0.642073
3	C	-0.021339	0.024985	-0.224885
4	C	-1.143492	0.066599	0.817609
5	C	-2.482078	0.460840	0.184964
6	N	-3.383815	-0.483222	-0.167304
7	C	-4.712417	-0.064191	-0.597623
8	H	-5.365536	-0.933466	-0.569762
9	H	-5.084709	0.708426	0.069233
10	C	-3.103458	-1.903162	-0.373718
11	H	-2.039843	-2.071040	-0.439938
12	H	-3.550974	-2.507612	0.416981
13	S	-2.793484	2.087774	0.001231
14	C	-1.149139	-1.137112	1.769843
15	H	-2.112464	-1.225145	2.271164
16	H	-0.932274	-2.076186	1.268174
17	H	-0.392680	-0.993566	2.540127
18	O	-0.237171	-1.120359	-1.063863
19	H	0.292325	-0.997633	-1.860925
20	H	-0.109813	0.942006	-0.820199
21	H	-0.916176	0.946384	1.420726
22	H	-3.544013	-2.196233	-1.326521
23	H	-4.684526	0.347530	-1.607858
24	H	1.459681	0.833003	1.083077
25	H	1.445714	-0.929261	1.009944
26	C	3.917095	0.108521	-0.117248
27	H	2.405811	-0.908656	-1.243365
28	H	2.298960	0.846888	-1.322244



29	C	4.862233	0.040214	-1.318961
30	H	5.902098	0.122313	-0.998841
31	H	4.746363	-0.905330	-1.851566
32	H	4.659486	0.851924	-2.019738
33	C	4.136109	1.437637	0.607391
34	H	3.896485	2.279790	-0.044248
35	H	3.521975	1.516467	1.504159
36	H	5.179258	1.534351	0.912573
37	C	4.231033	-1.050773	0.829556
38	H	3.630030	-1.002093	1.737429
39	H	4.040506	-2.010879	0.346054
40	H	5.281116	-1.025277	1.125150

Table S8. XYZ-coordinates and the structure of **3ah'** optimized at PM2 with a 6-31G(d,p) basis set.

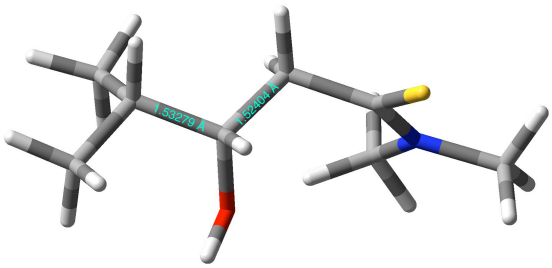
Number	atom	X	Y	Z
1	C	0.884852	0.013826	0.110681
2	C	1.901251	0.023952	-1.035123
3	C	-0.557332	0.039951	-0.383595
4	C	-1.570666	0.100753	0.763987
5	C	-2.967792	0.471300	0.255621
6	N	-3.894666	-0.485829	0.024595
7	C	-5.262867	-0.084336	-0.280309
8	H	-5.904530	-0.953933	-0.157721
9	H	-5.569268	0.708402	0.396321
10	C	-3.626154	-1.909838	-0.170453
11	H	-2.574564	-2.072682	-0.348804
12	H	-3.978023	-2.493925	0.681434
13	S	-3.304724	2.090821	0.052907
14	C	-1.470682	-1.079660	1.739643
15	H	-2.376753	-1.158711	2.339464
16	H	-1.301197	-2.030097	1.241119
17	H	-0.639691	-0.914574	2.423862
18	O	-0.839165	-1.128522	-1.171706
19	H	-0.477141	-0.978738	-2.053004
20	H	-0.712084	0.941272	-0.988696
21	H	-1.292312	0.996111	1.321123
22	H	-4.166537	-2.233065	-1.059983
23	H	-5.341326	0.294519	-1.300718
24	H	1.058388	0.882678	0.752057
25	H	1.046258	-0.880278	0.716524
26	H	1.757893	-0.868414	-1.649307
27	H	1.721311	0.894320	-1.673764
28	C	3.316237	0.053824	-0.522494
29	C	3.956657	1.272378	-0.264603
30	C	3.991268	-1.136612	-0.224529
31	C	5.247226	1.301994	0.264940
32	H	3.444822	2.201009	-0.492939
33	C	5.281598	-1.111850	0.305870



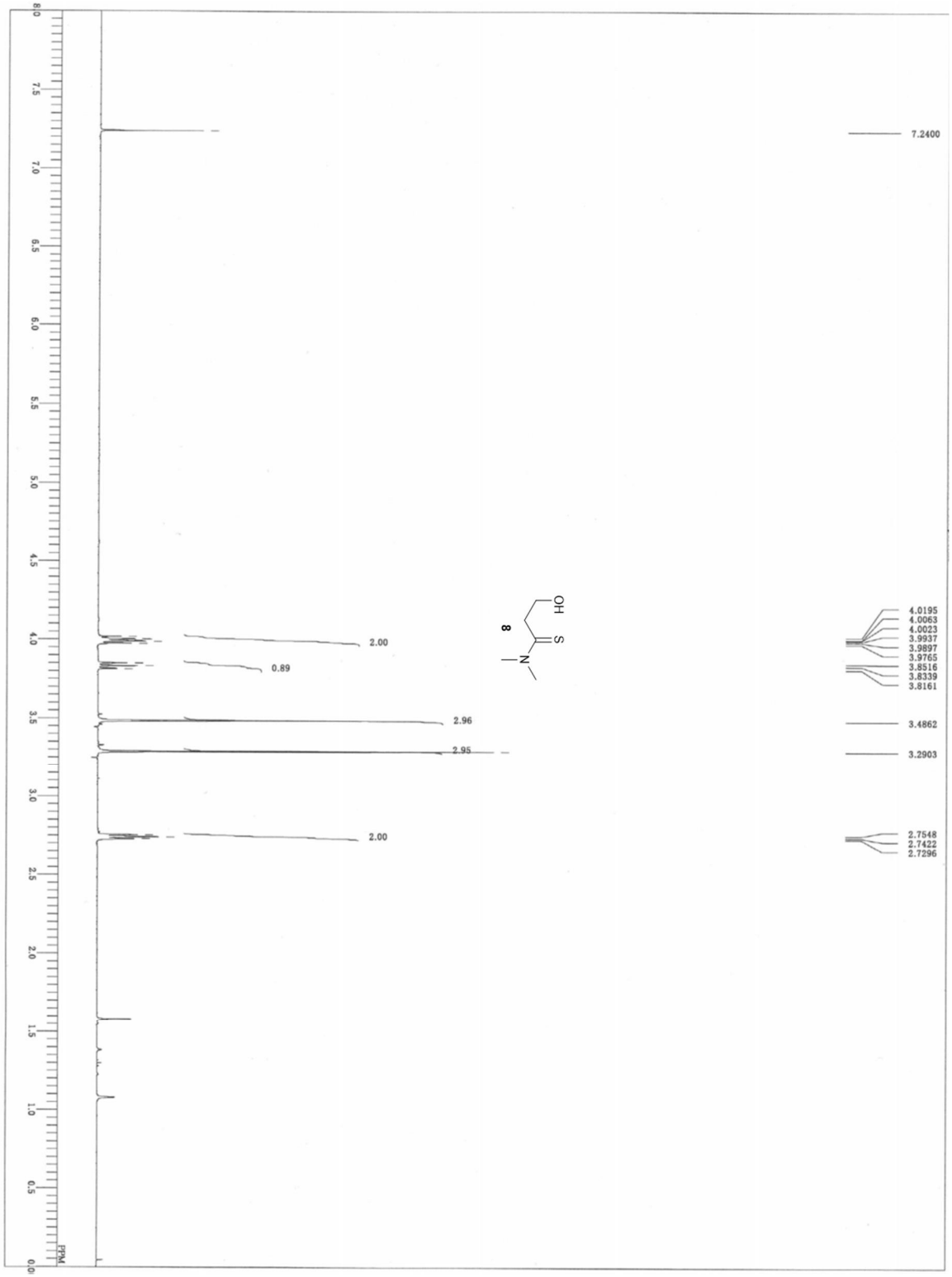
34	H	3.506225	-2.086594	-0.421796
35	C	5.911634	0.108856	0.555291
36	H	5.731855	2.252199	0.451627
37	H	5.793104	-2.040992	0.524395
38	H	6.913761	0.130103	0.964208

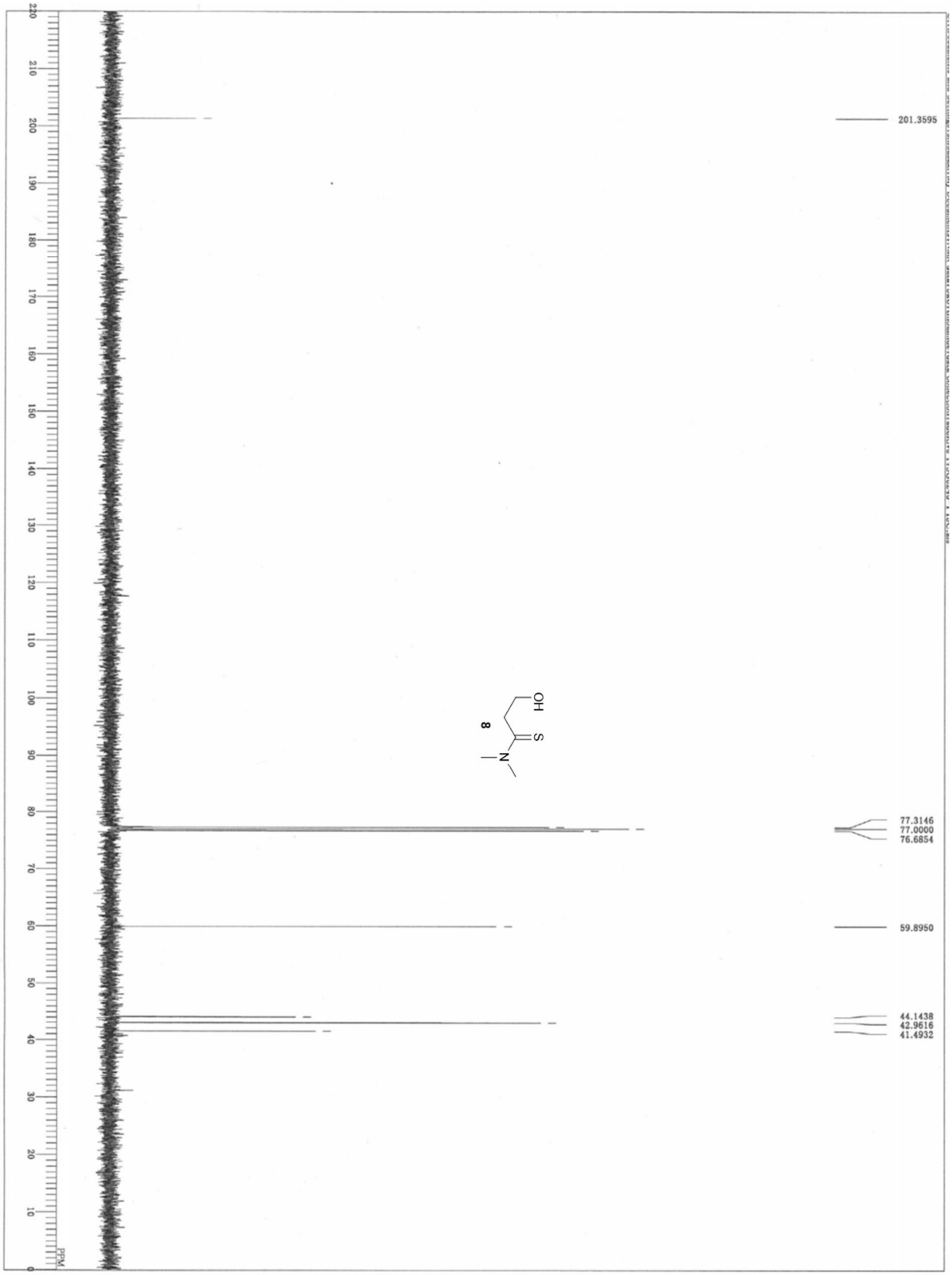
Table S9. XYZ-coordinates and the structure of **3ca'** optimized at PM2 with a 6-31G(d,p) basis set.

Number	atom	X	Y	Z
1	C	2.597478	-0.355521	-0.317029
2	C	3.573187	-0.656441	0.819081
3	H	3.593387	0.167971	1.533063
4	H	3.296165	-1.569281	1.349176
5	H	4.585632	-0.784645	0.437782
6	C	2.973577	0.946740	-1.018085
7	H	2.399206	1.100020	-1.930764
8	H	2.794673	1.790463	-0.352107
9	H	4.029085	0.943384	-1.290421
10	C	1.160257	-0.340201	0.215530
11	C	0.111199	-0.087476	-0.860717
12	C	-1.288147	-0.331018	-0.332940
13	N	-2.033743	0.747679	-0.012472
14	C	-3.409547	0.540579	0.424609
15	H	-3.900217	1.506610	0.496639
16	H	-3.931880	-0.092630	-0.289950
17	C	-1.529632	2.121553	-0.060856
18	H	-0.514303	2.160015	0.315836
19	H	-1.575685	2.528440	-1.073332
20	S	-1.836012	-1.892237	-0.165507
21	O	0.980943	0.688865	1.203632
22	H	1.341973	0.360259	2.035510
23	H	0.941089	-1.319347	0.656525
24	H	0.275173	-0.796289	-1.671727
25	H	-2.154552	2.732649	0.584164
26	H	-3.431507	0.036258	1.390833
27	H	2.650830	-1.178396	-1.038266
28	H	0.235553	0.916352	-1.264167



6. NMR Spectra of New Compounds

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S
N
8
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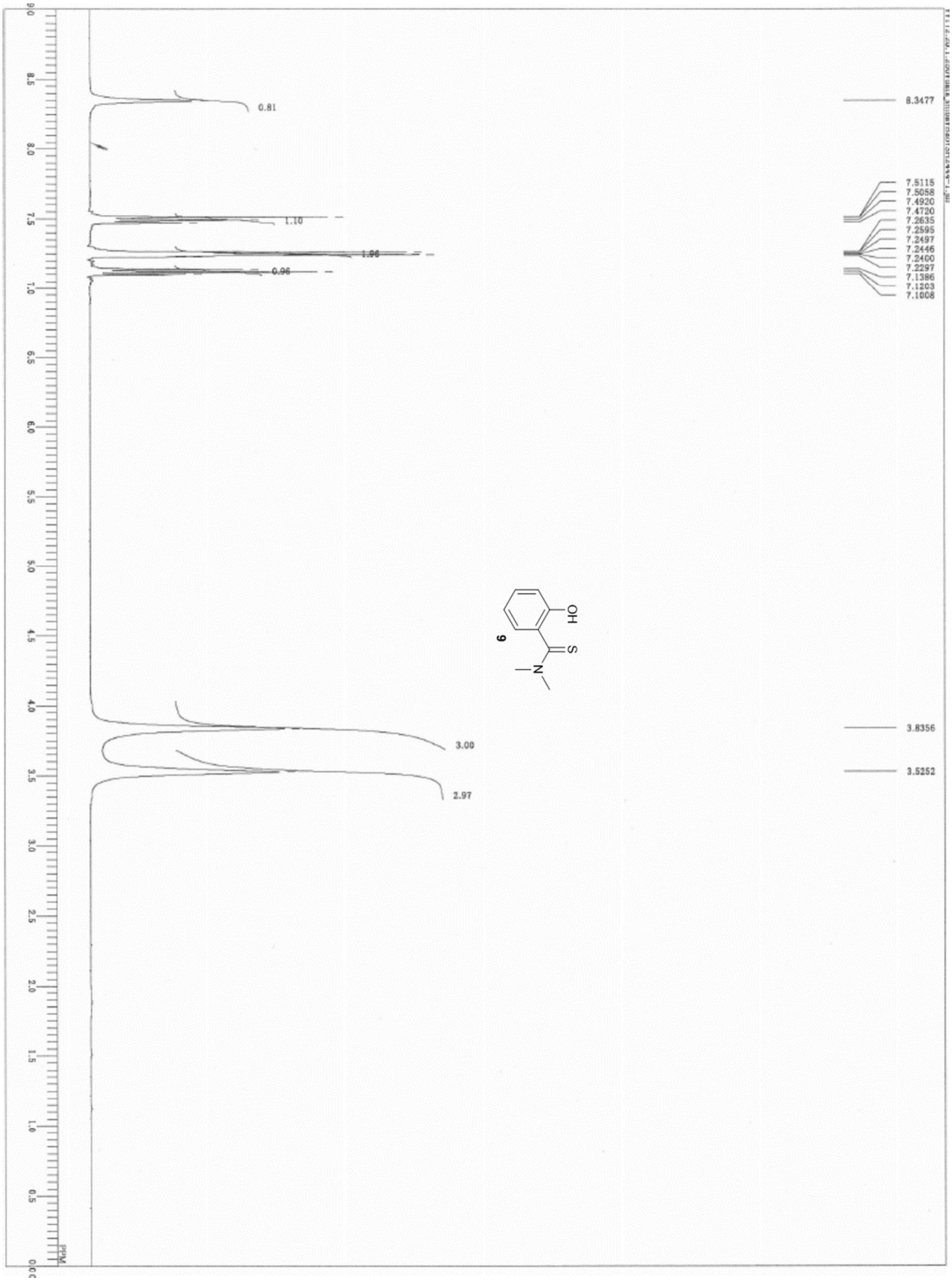
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7.2497
7.2446
7.2400
7.2297
7.1386
7.1203
7.1008
3.8356
3.5252
HO
S
N
9
PPM


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76.6854
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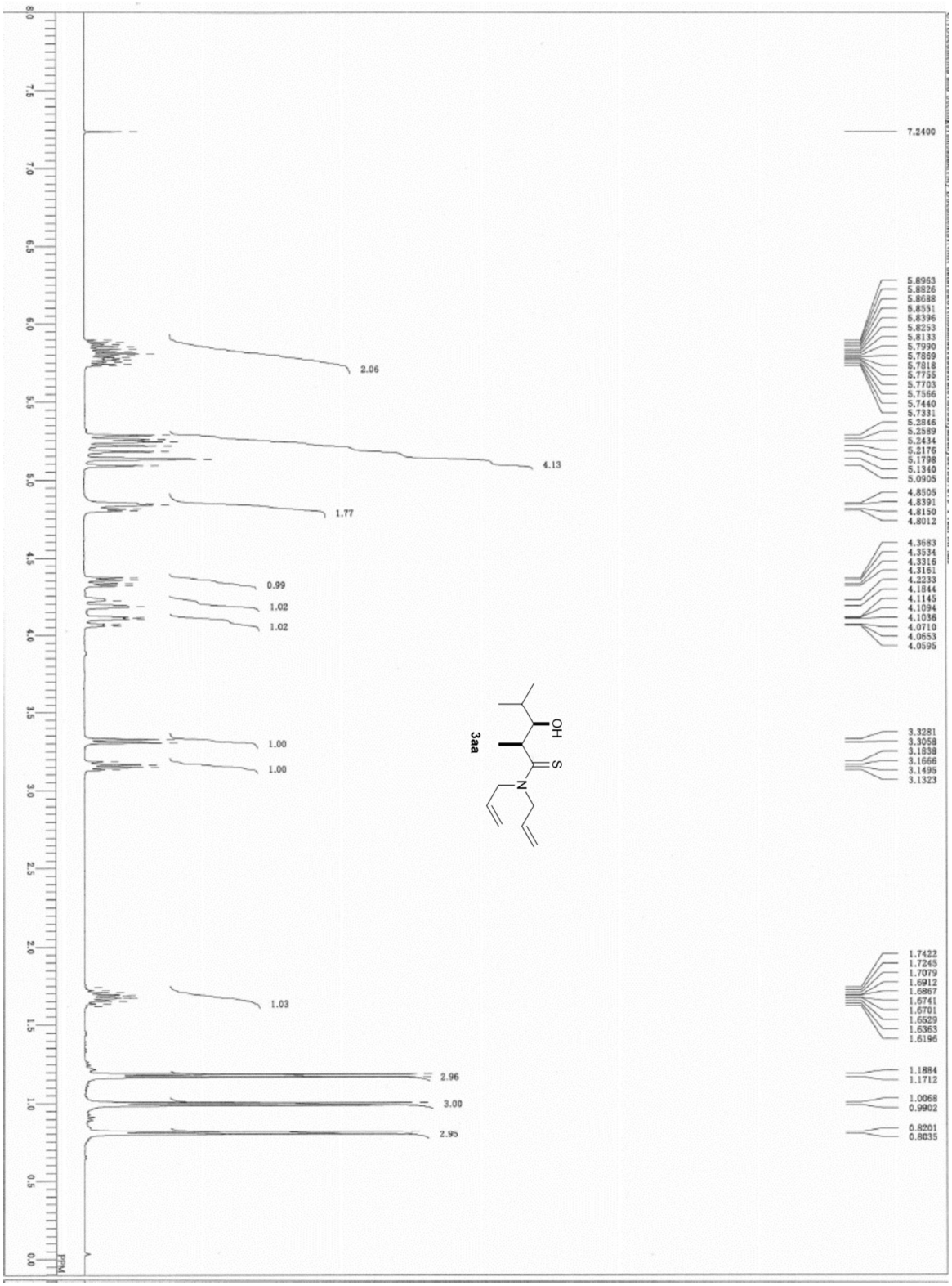
OH
S
N
9
PPM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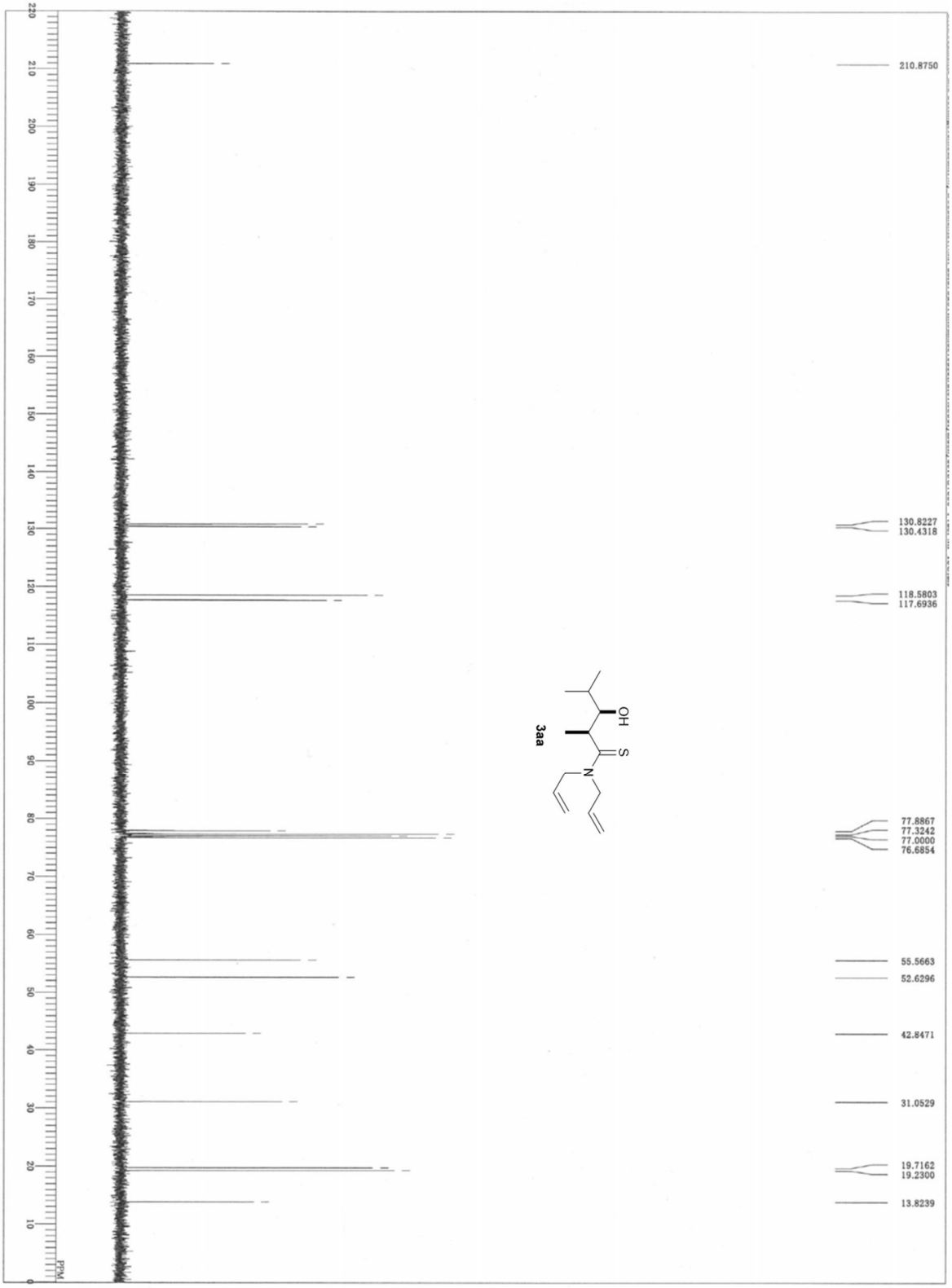
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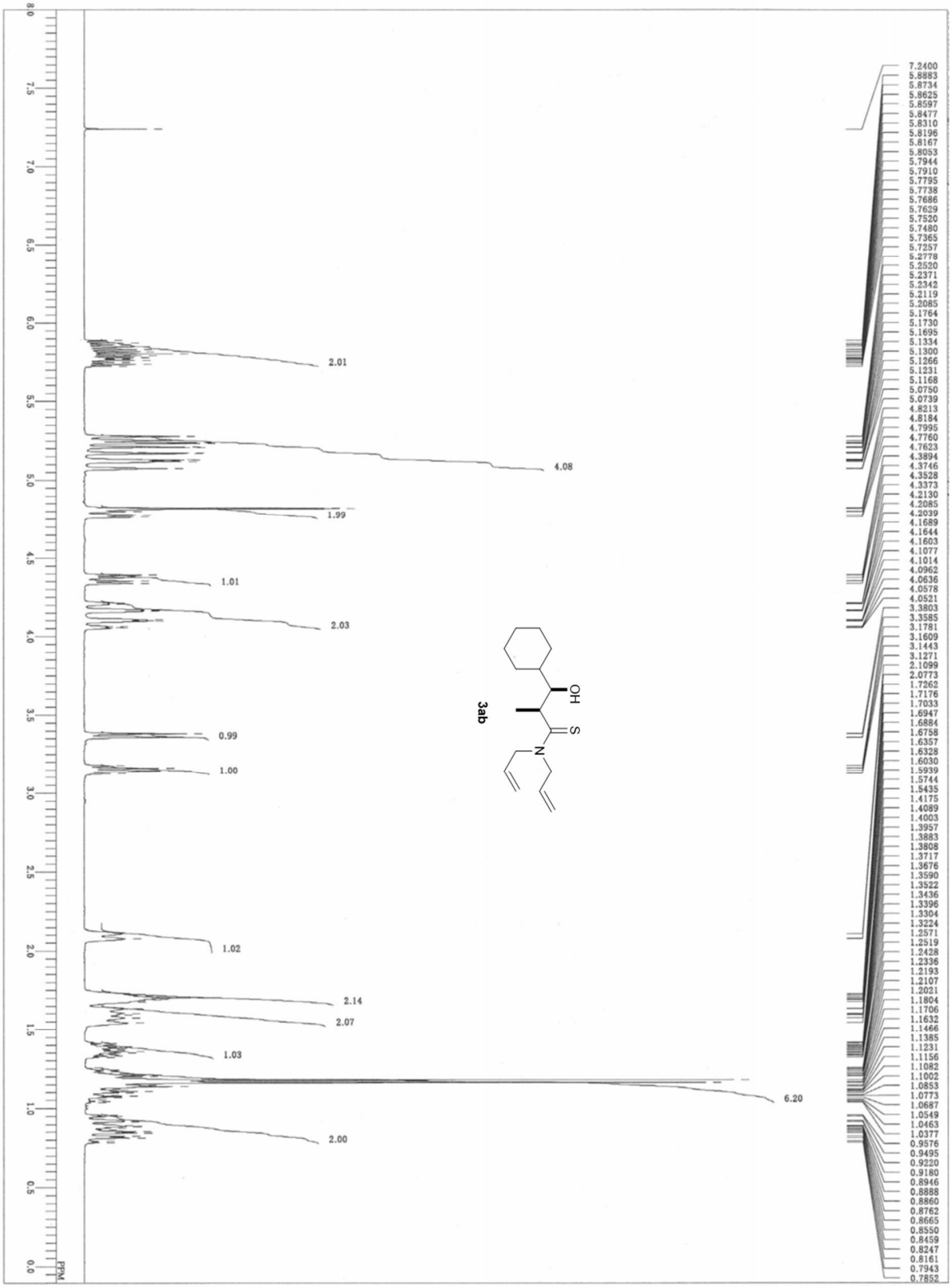
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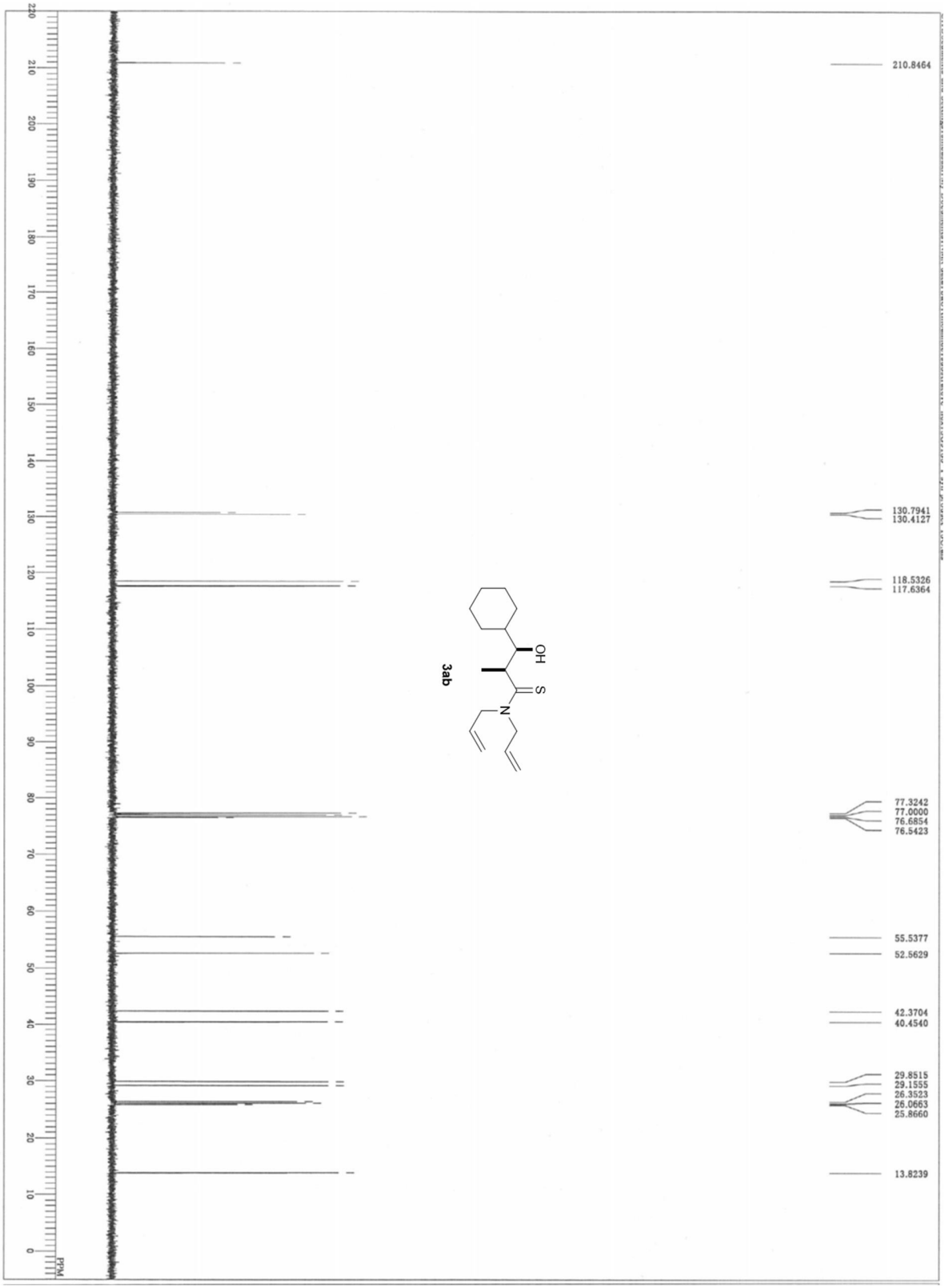
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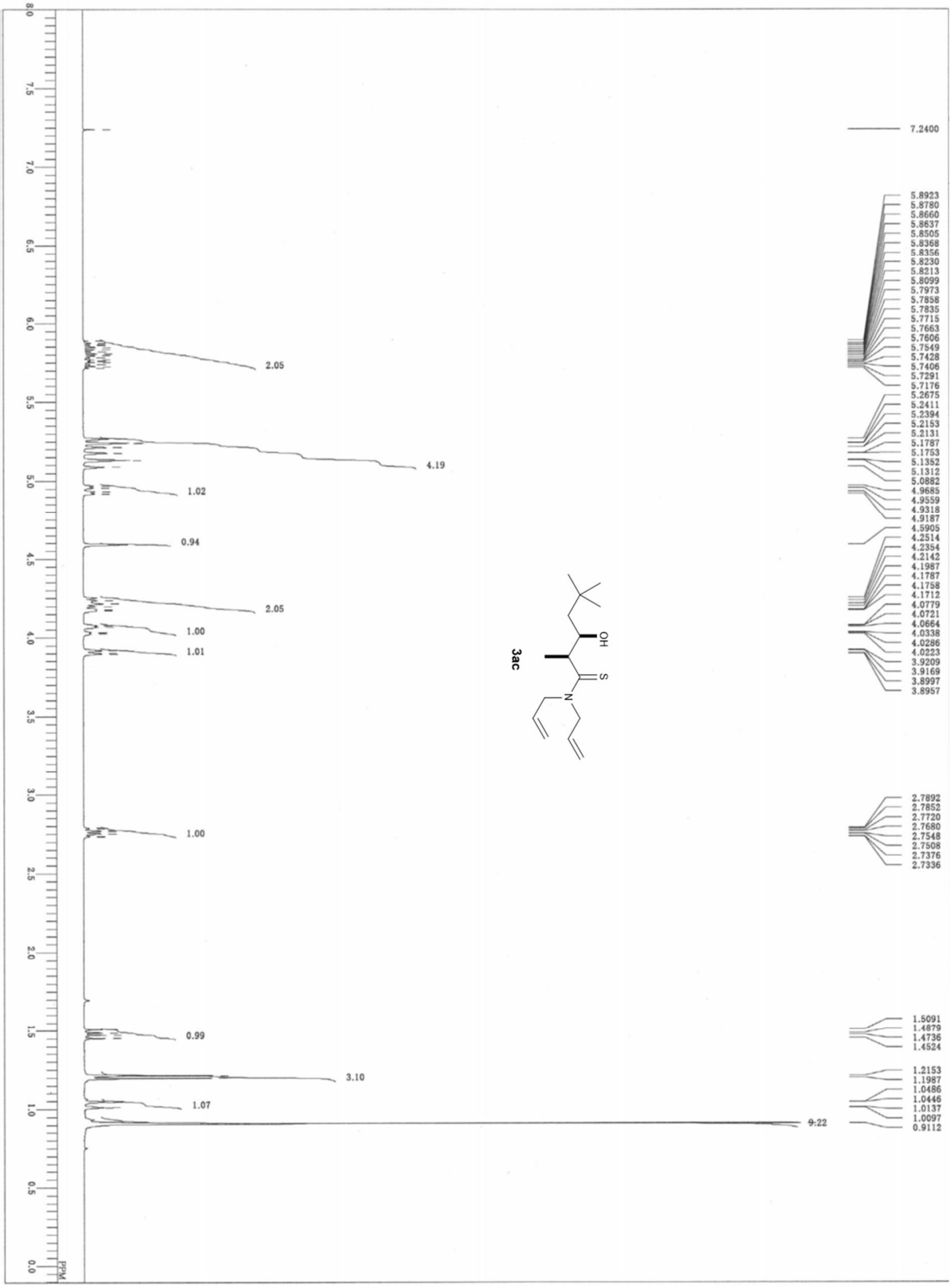
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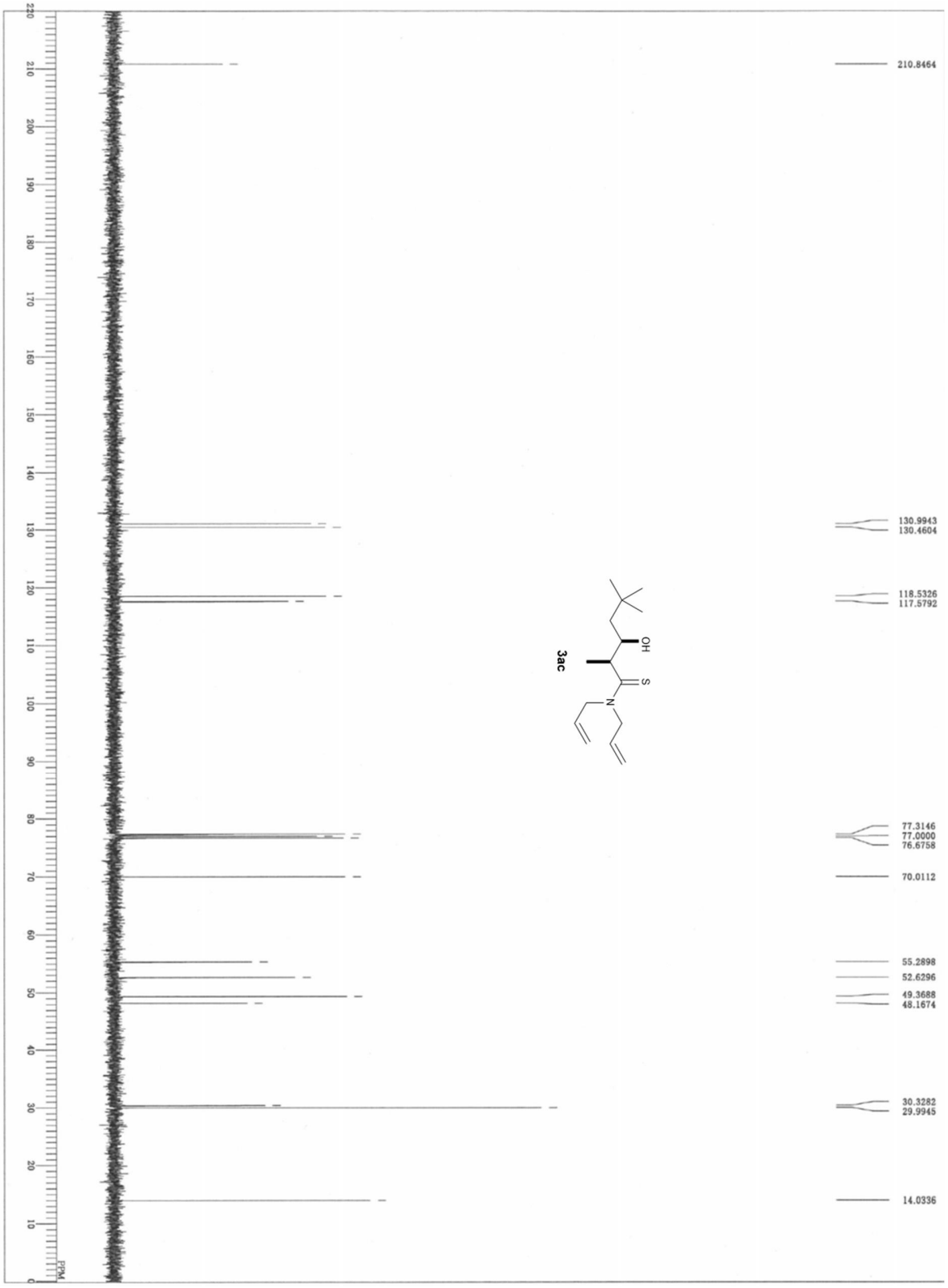
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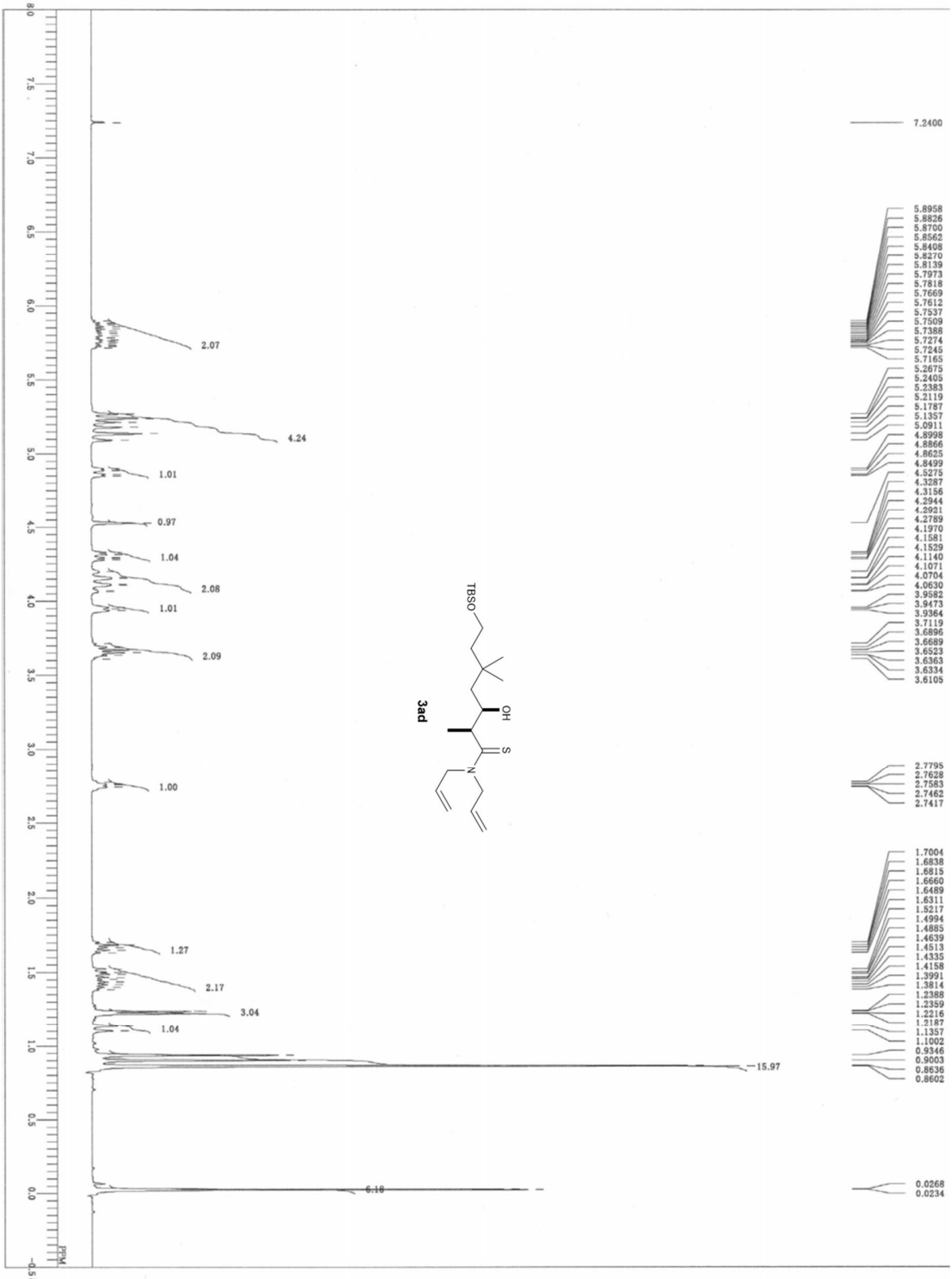
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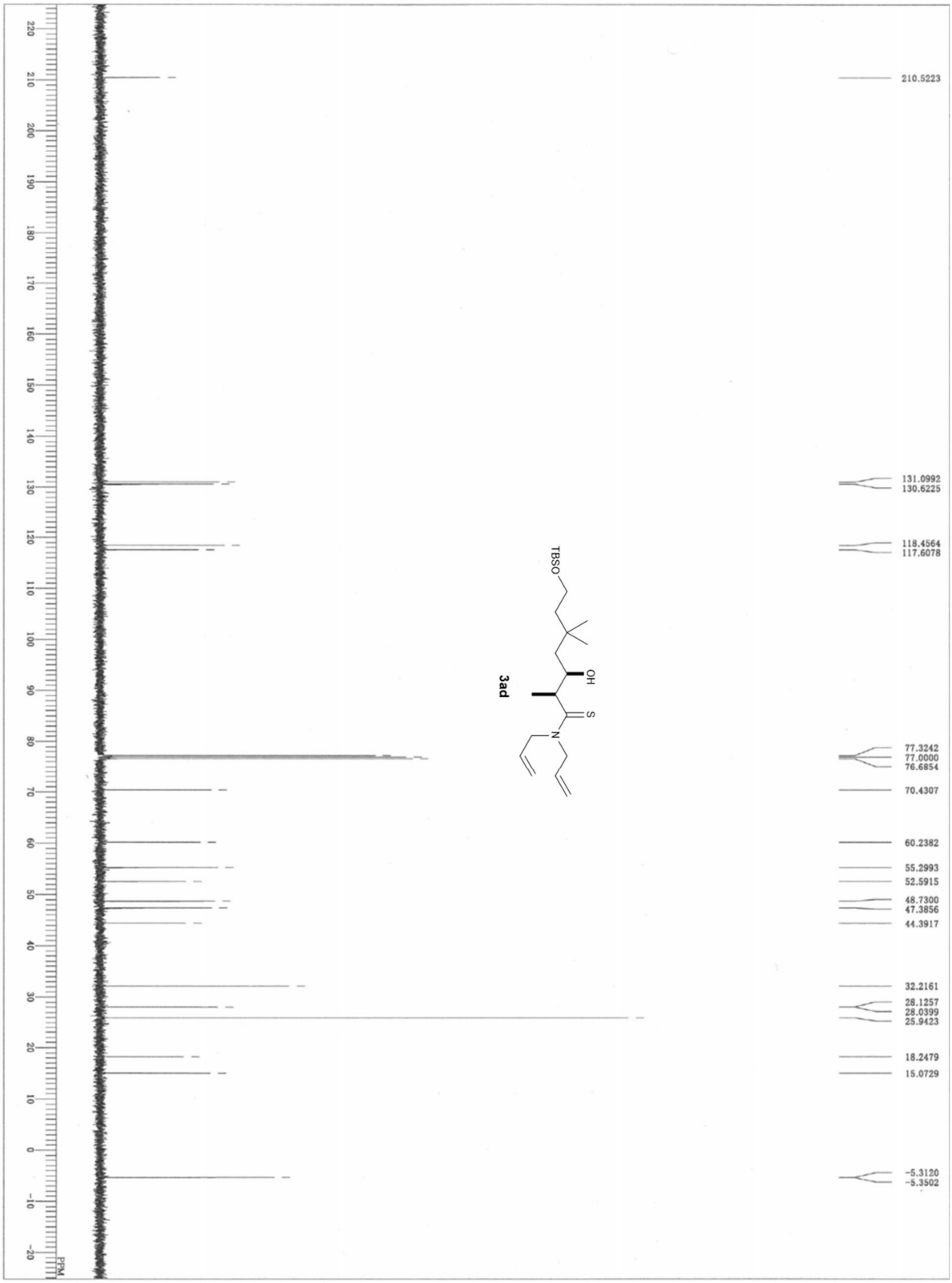
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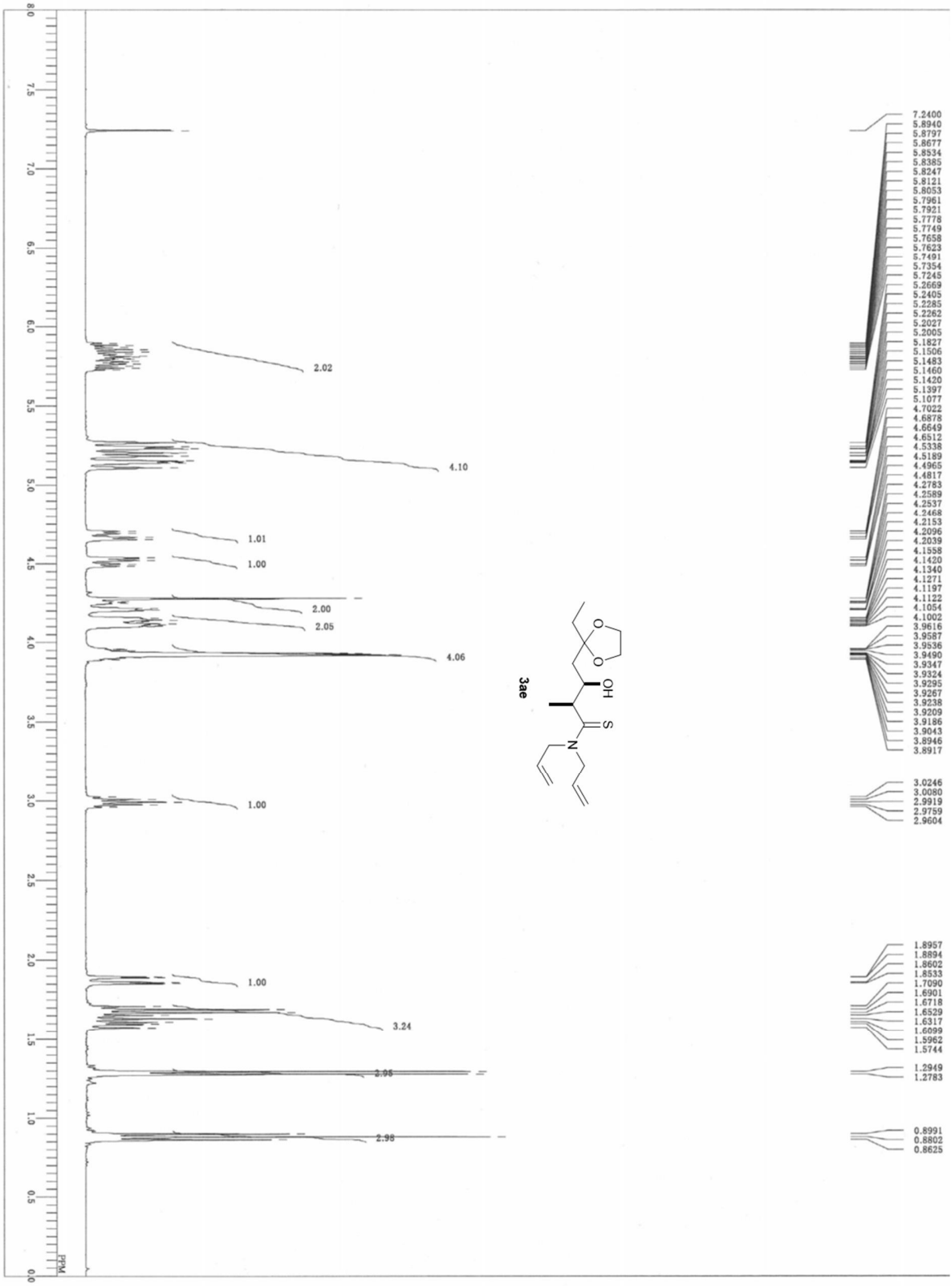
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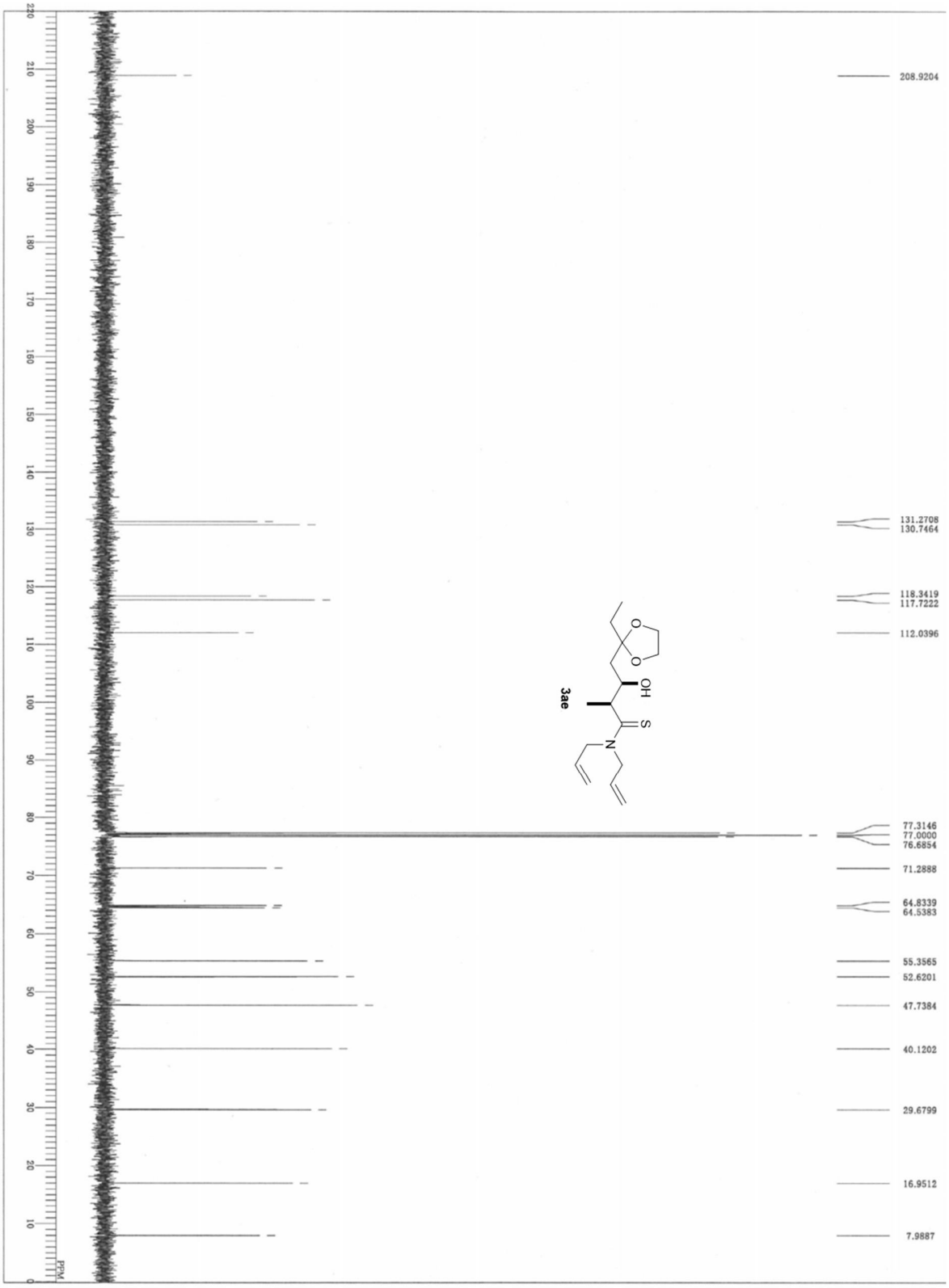
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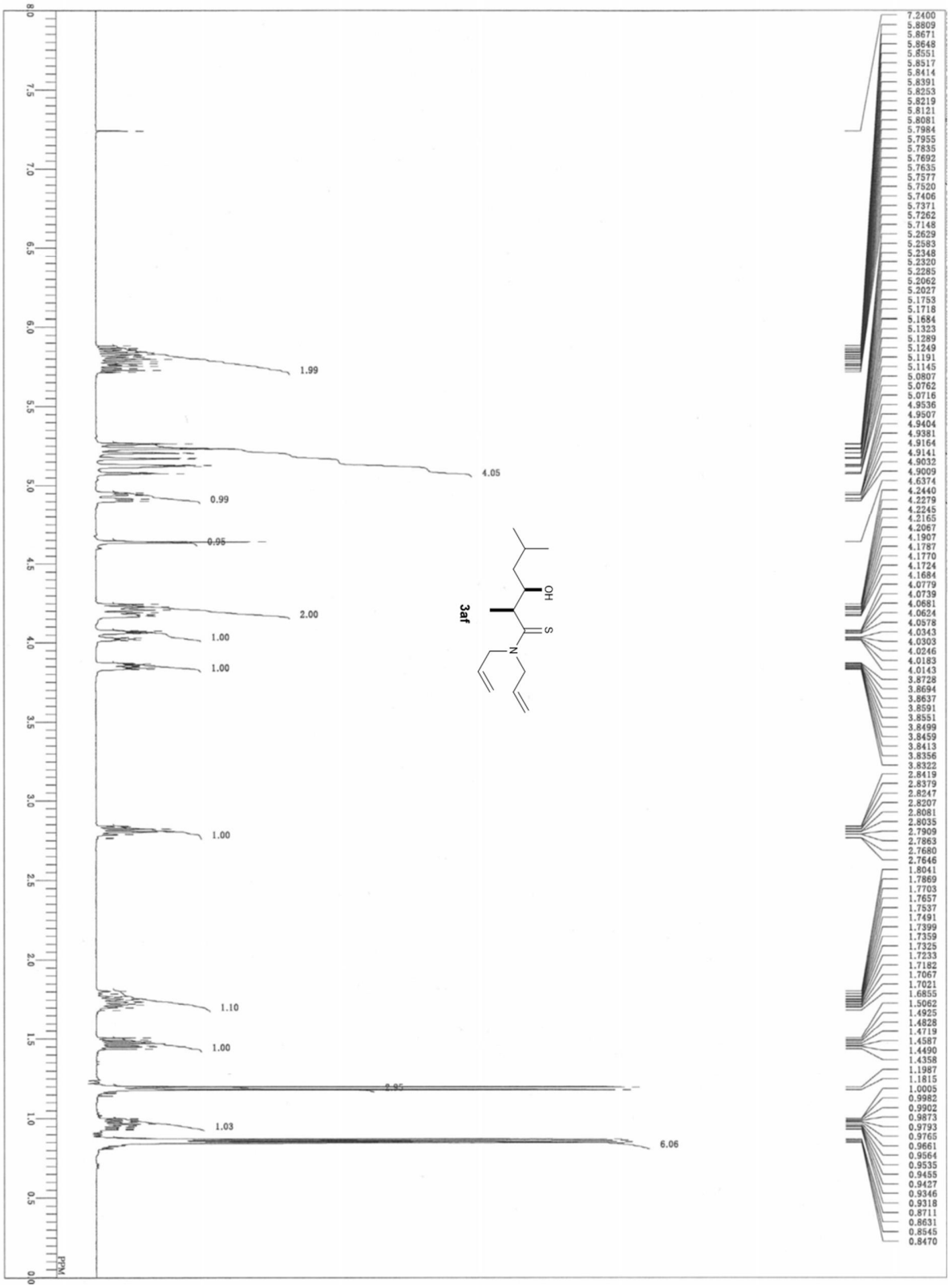
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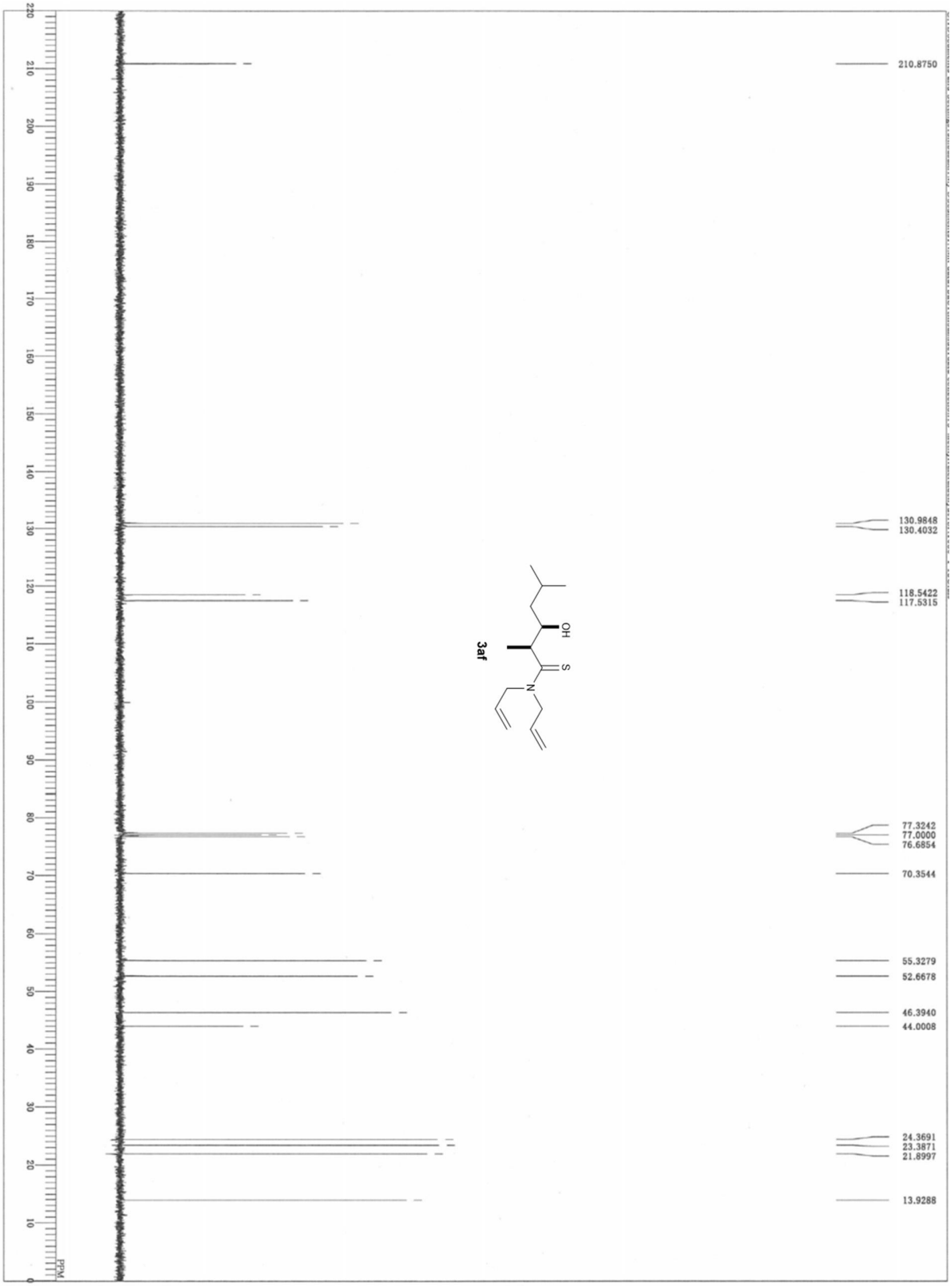
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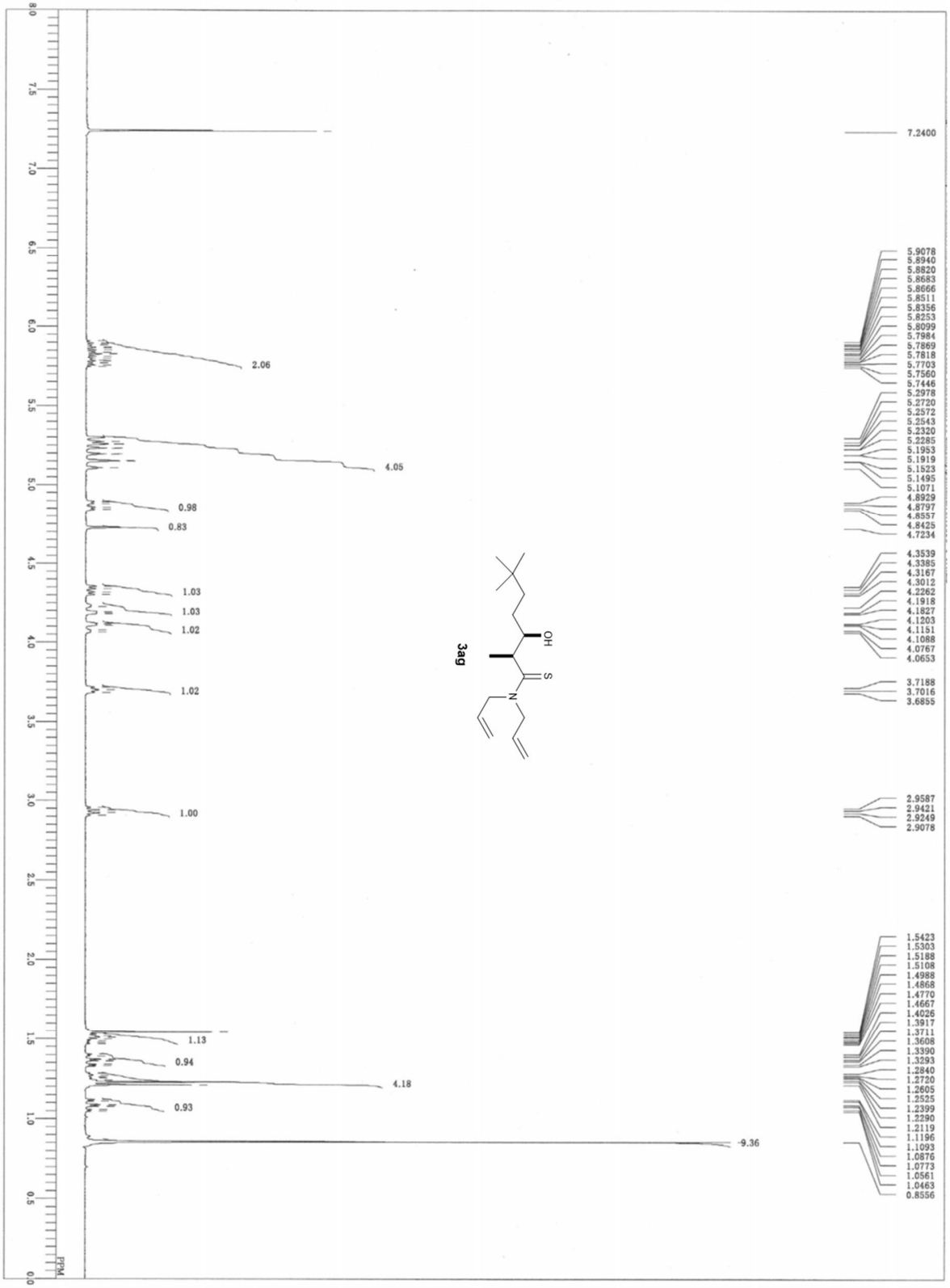
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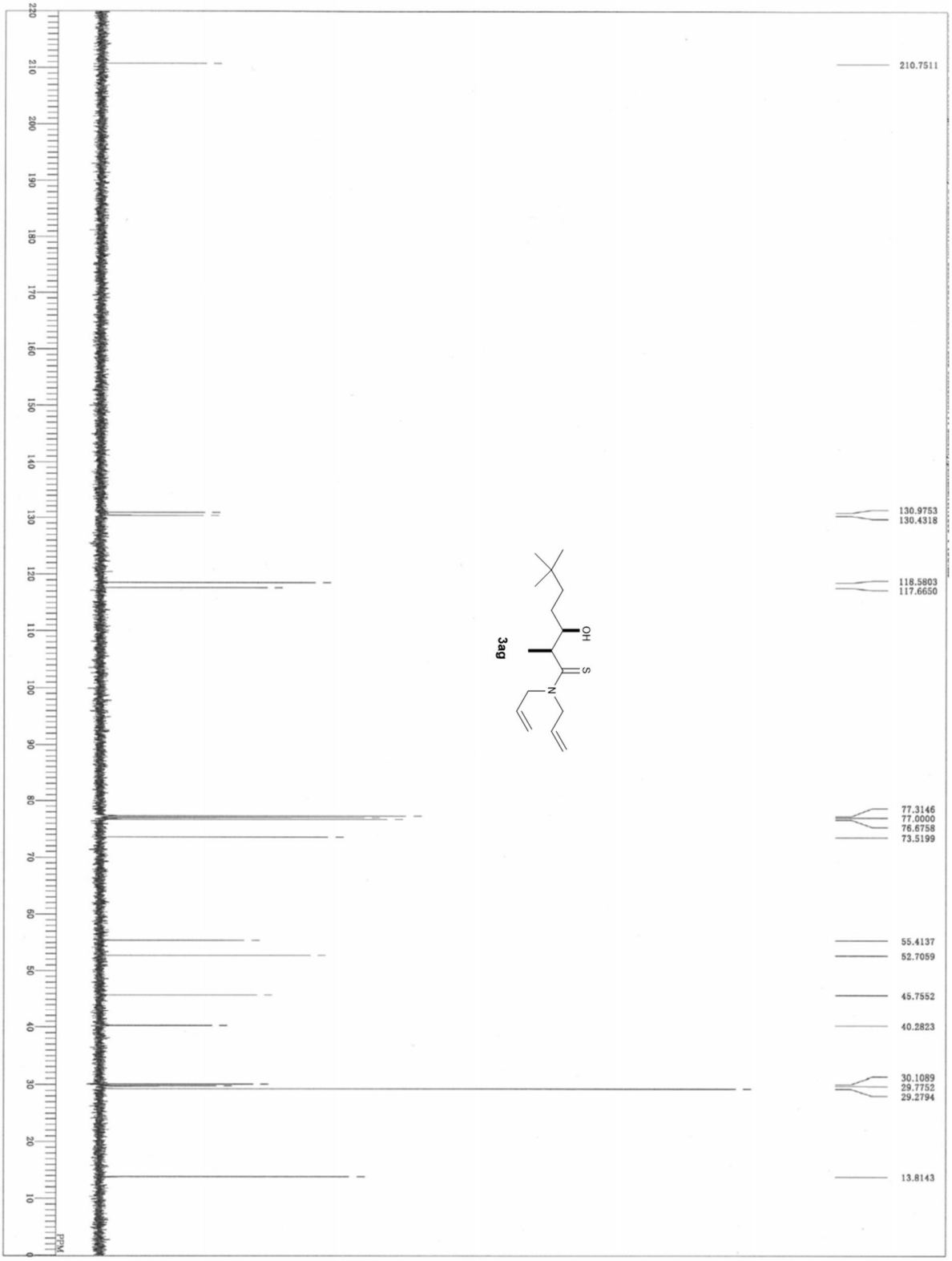
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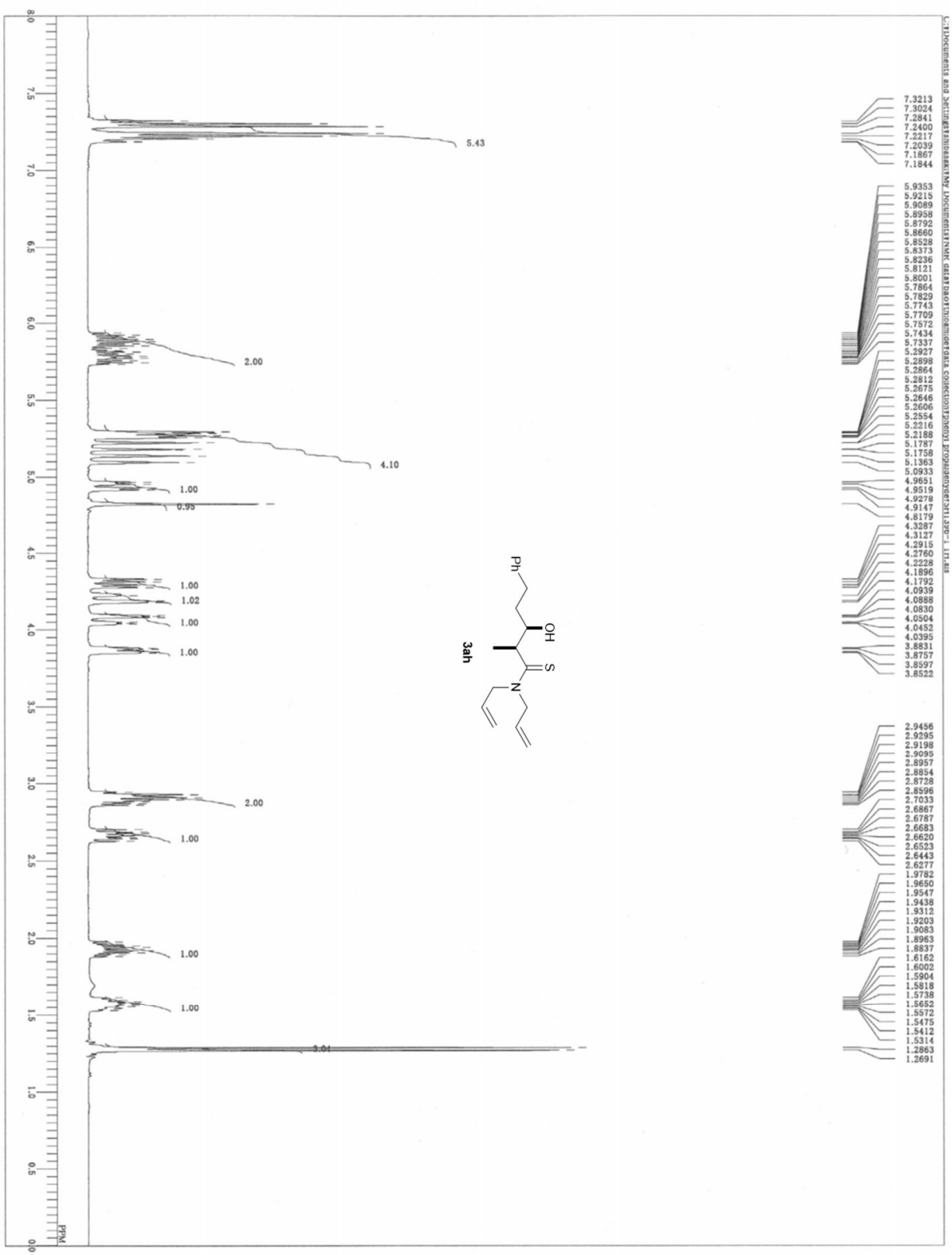
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PPM


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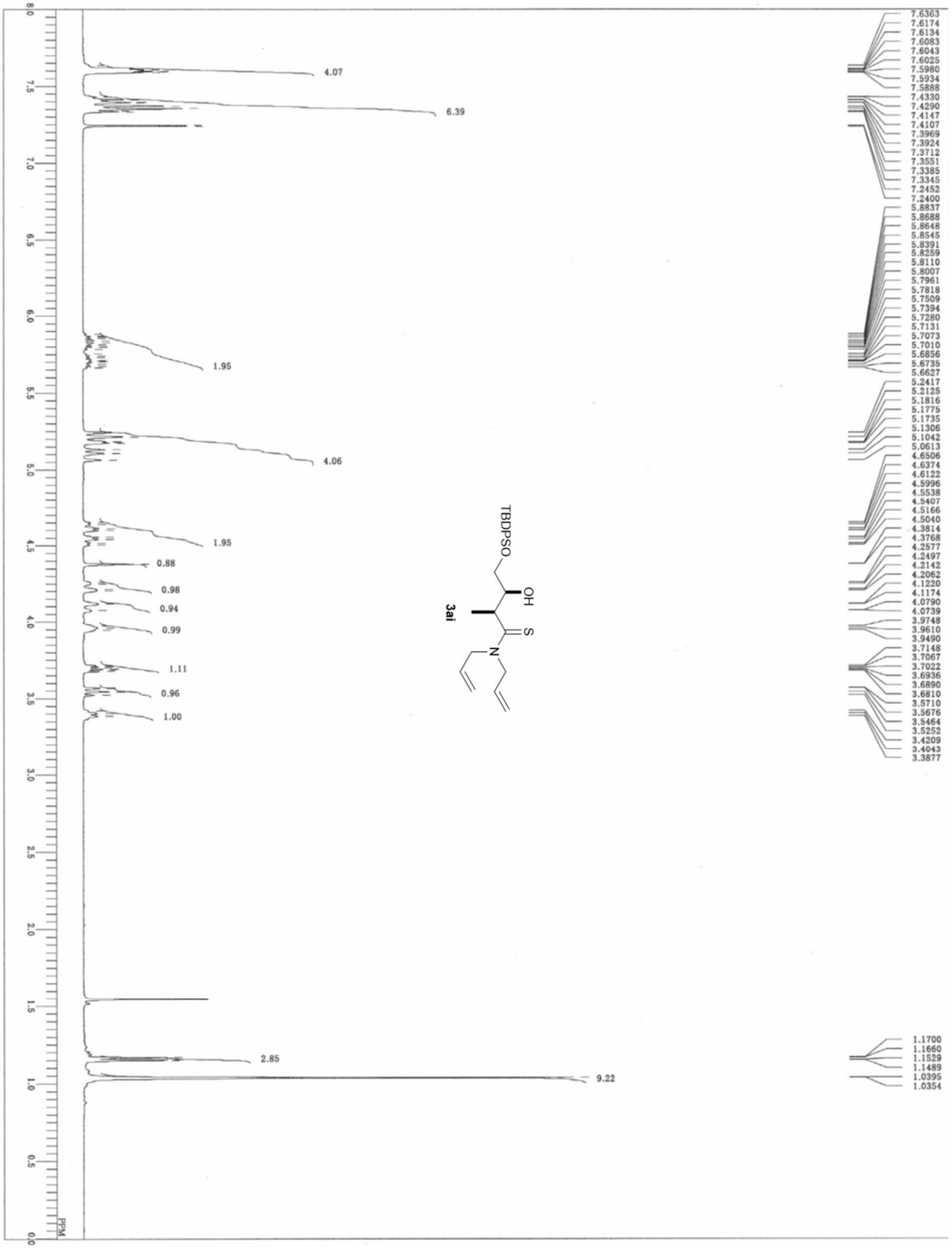
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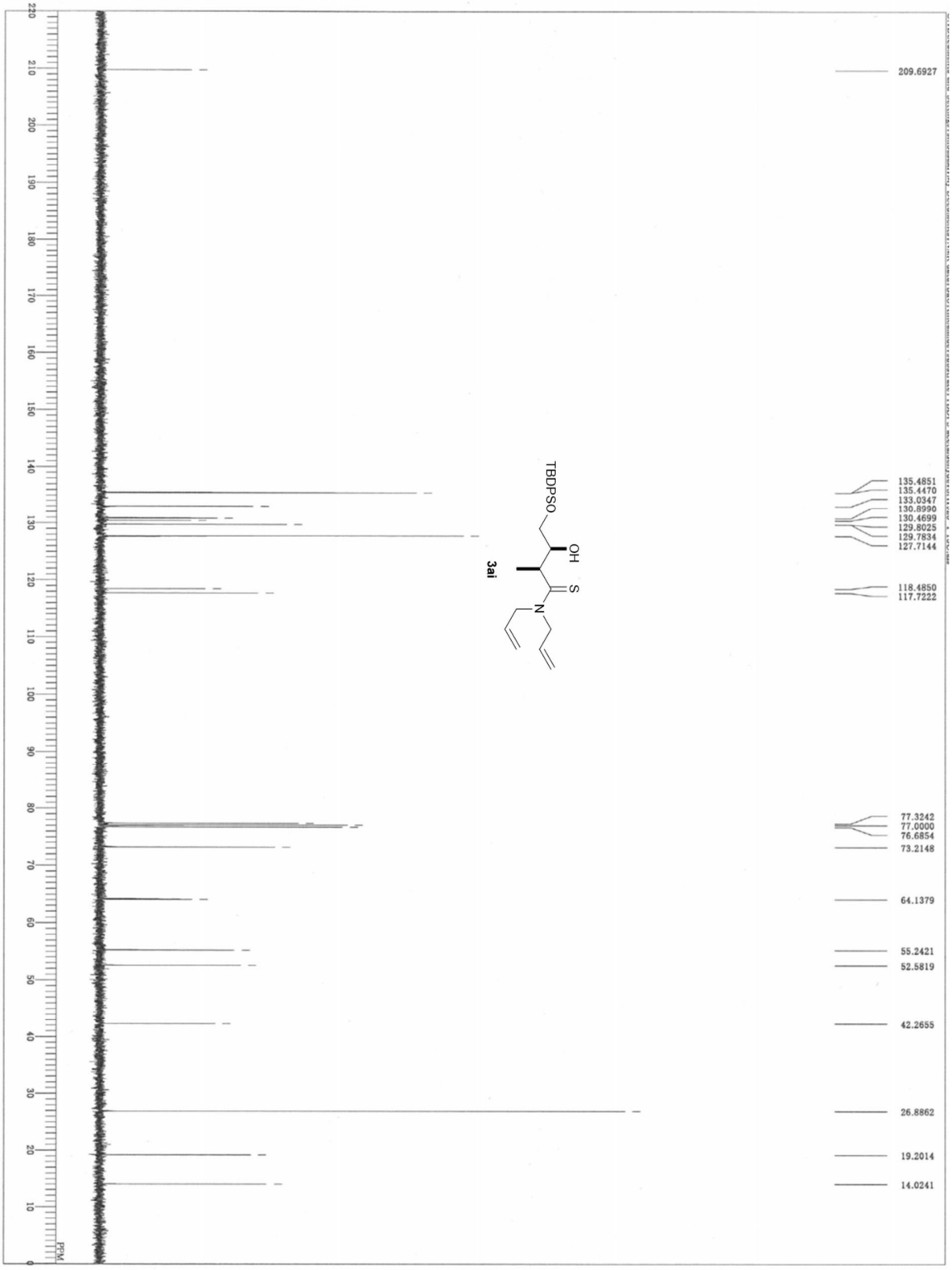
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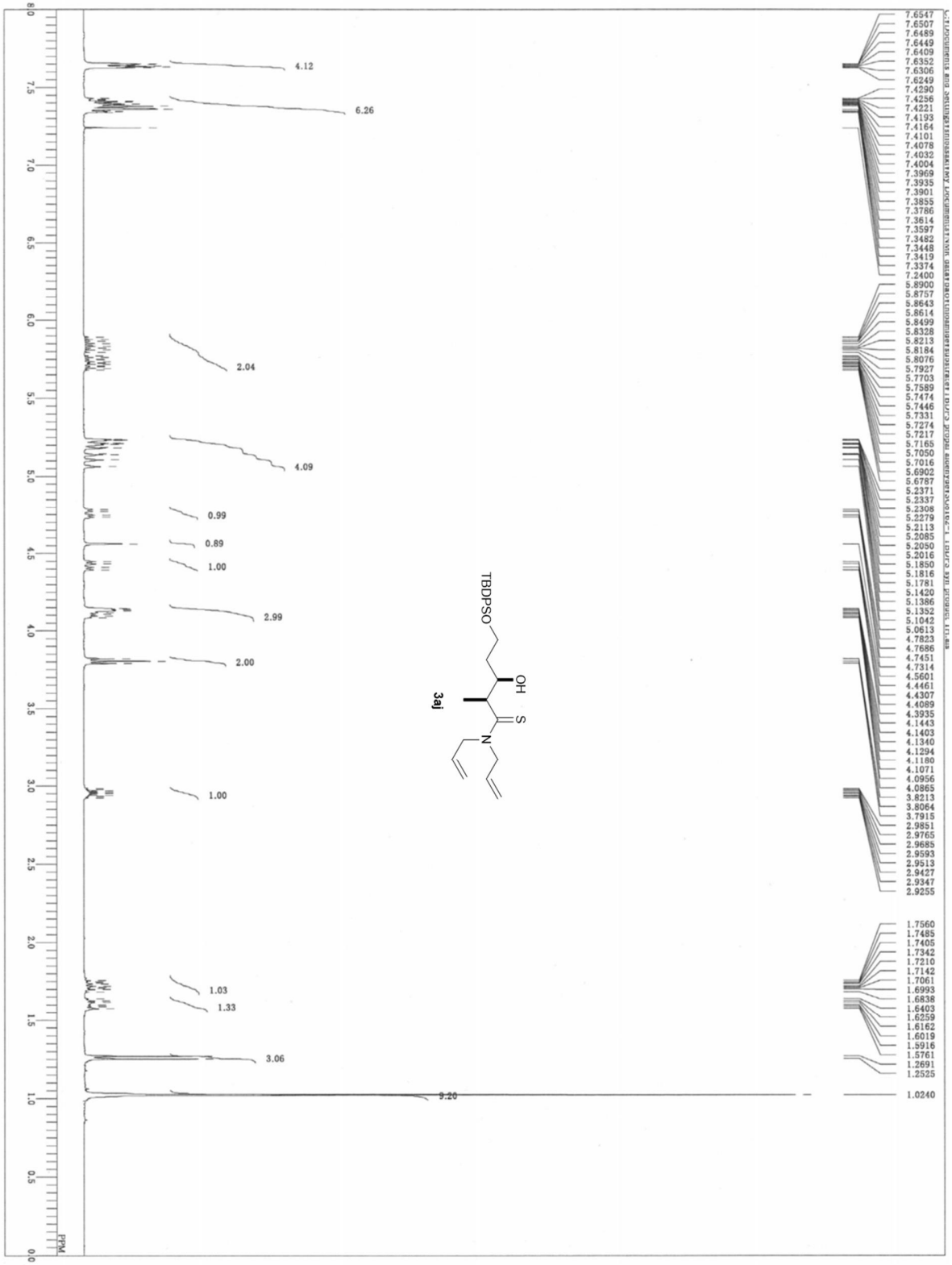
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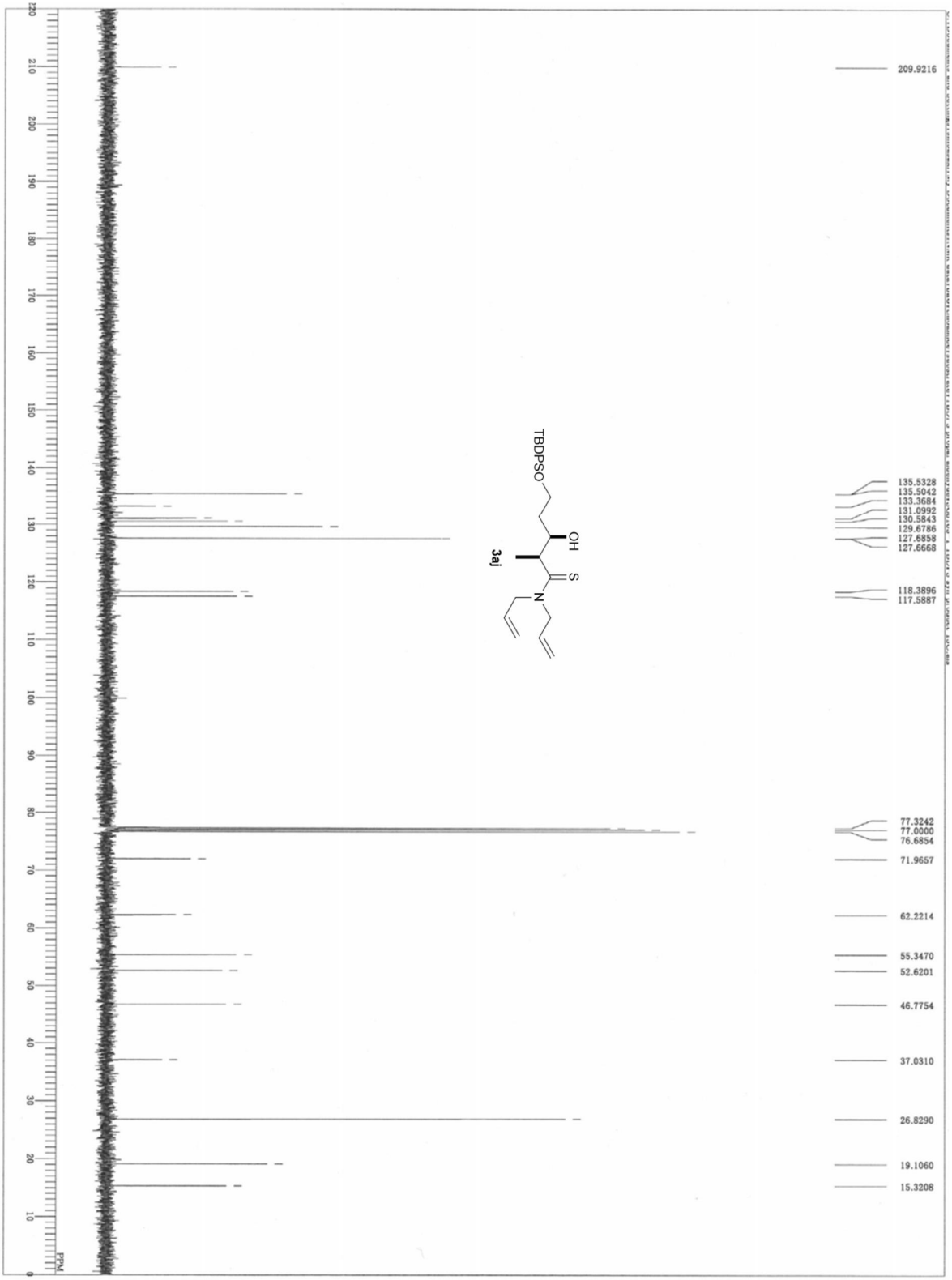
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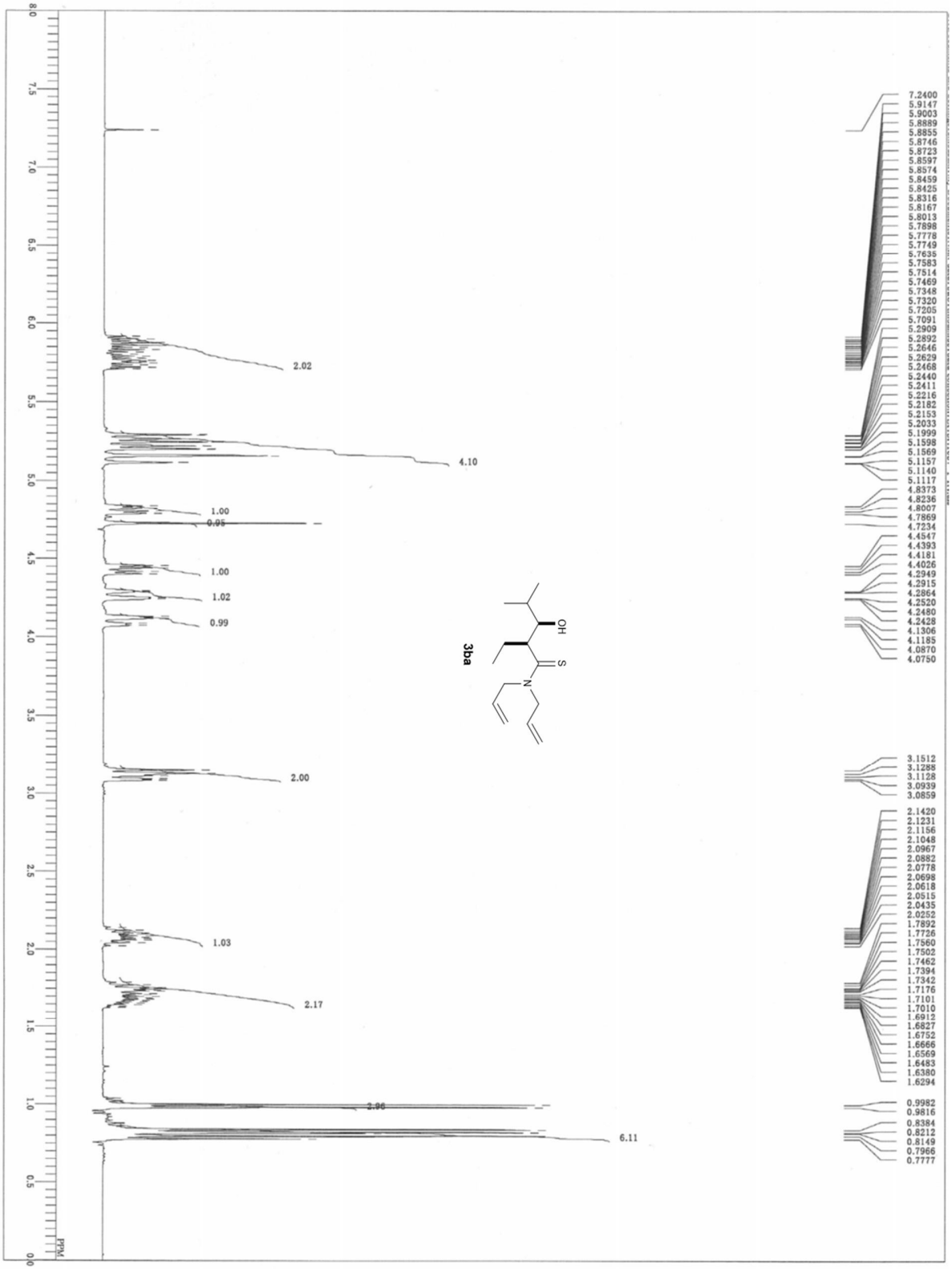
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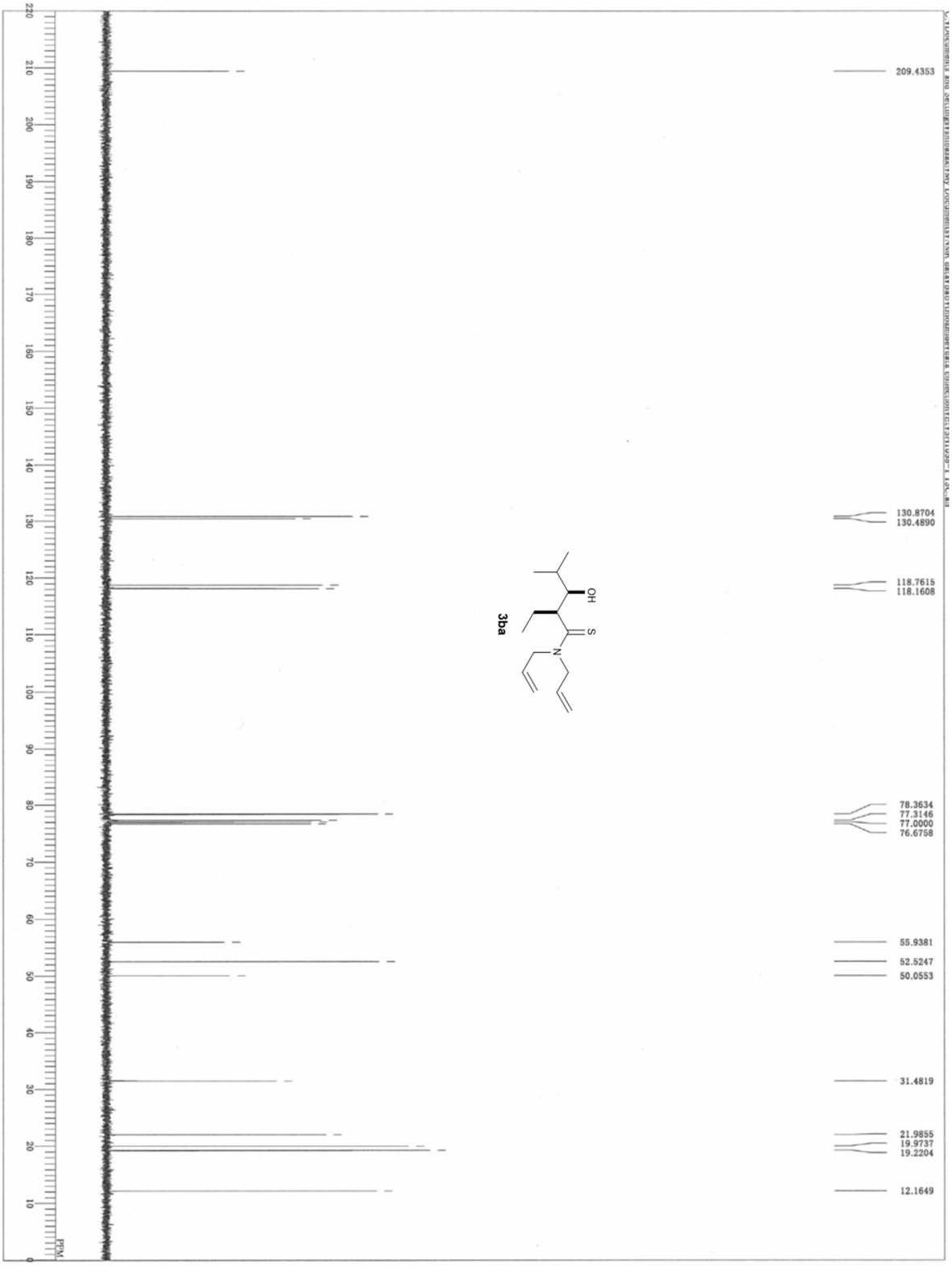
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N
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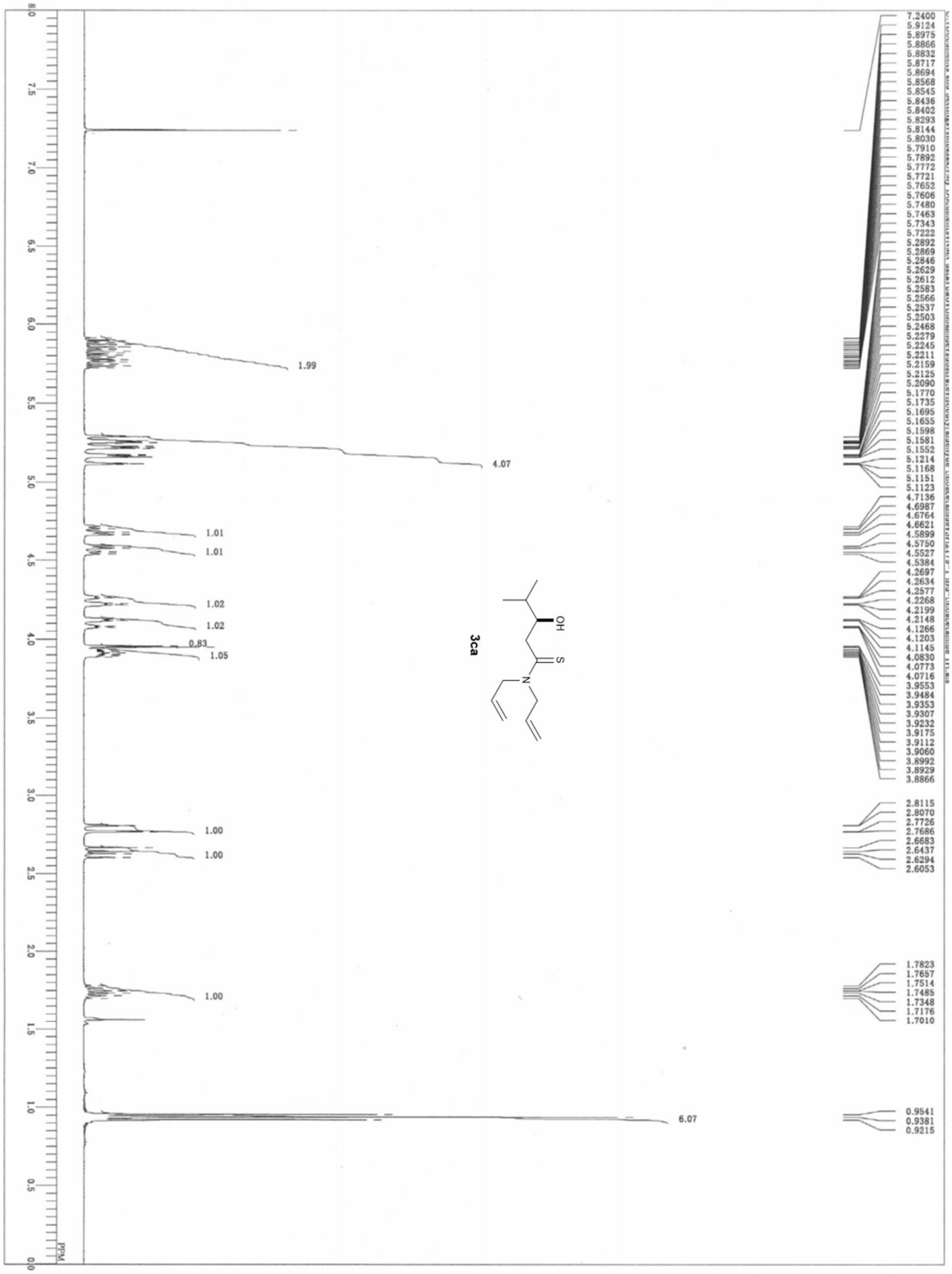
PPM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1.00
1.00
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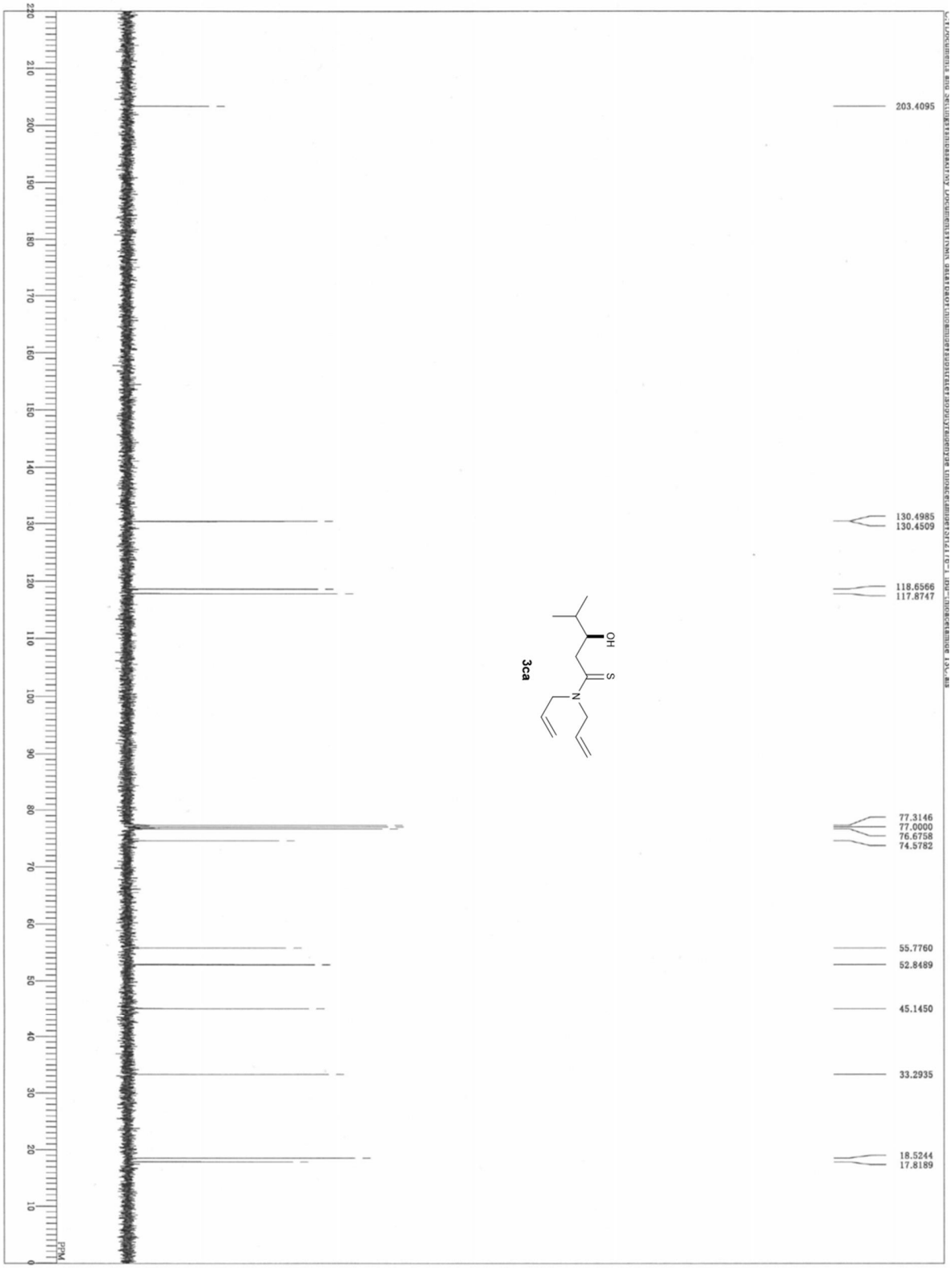
S
N
PPM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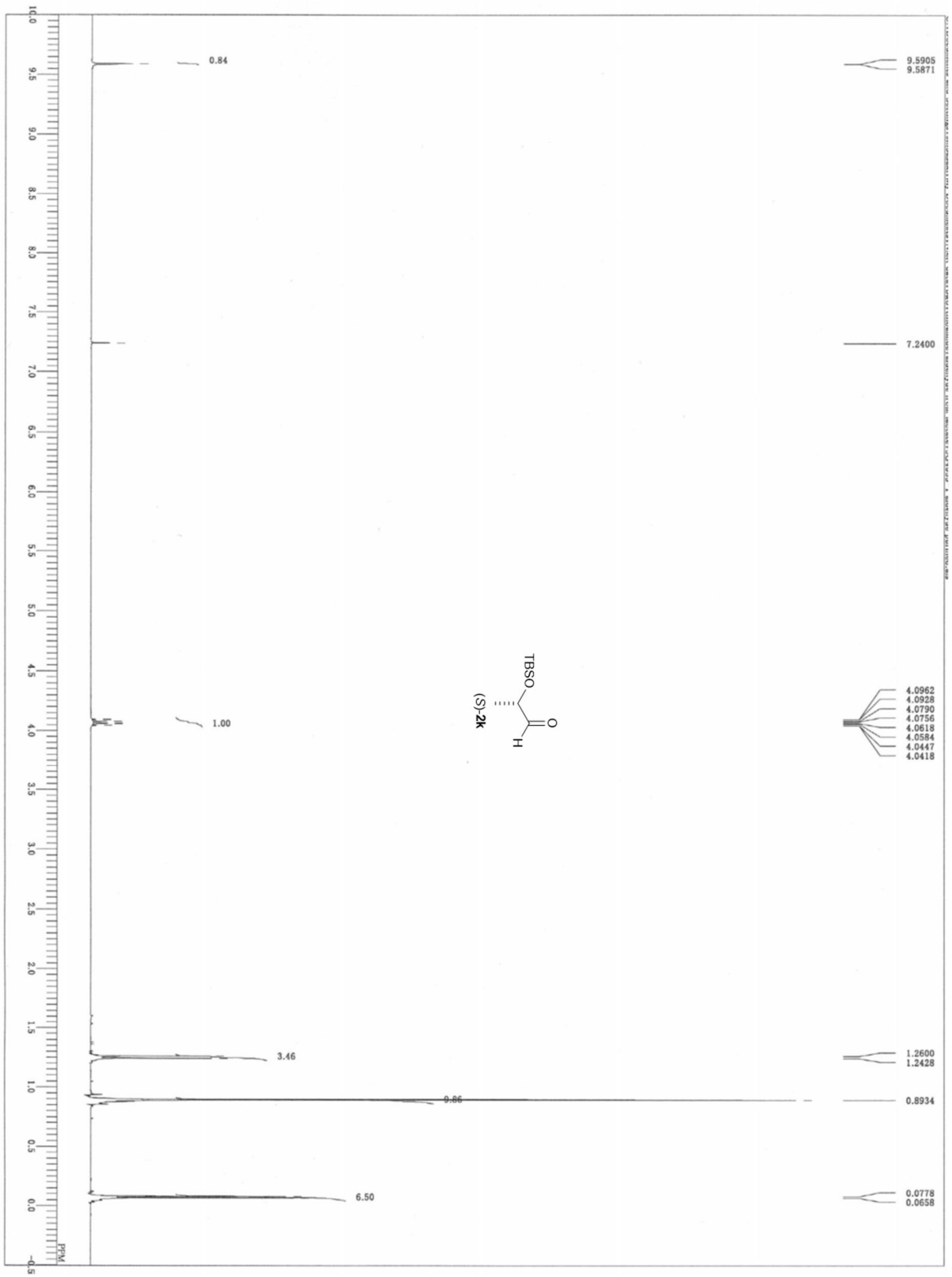
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4.0584
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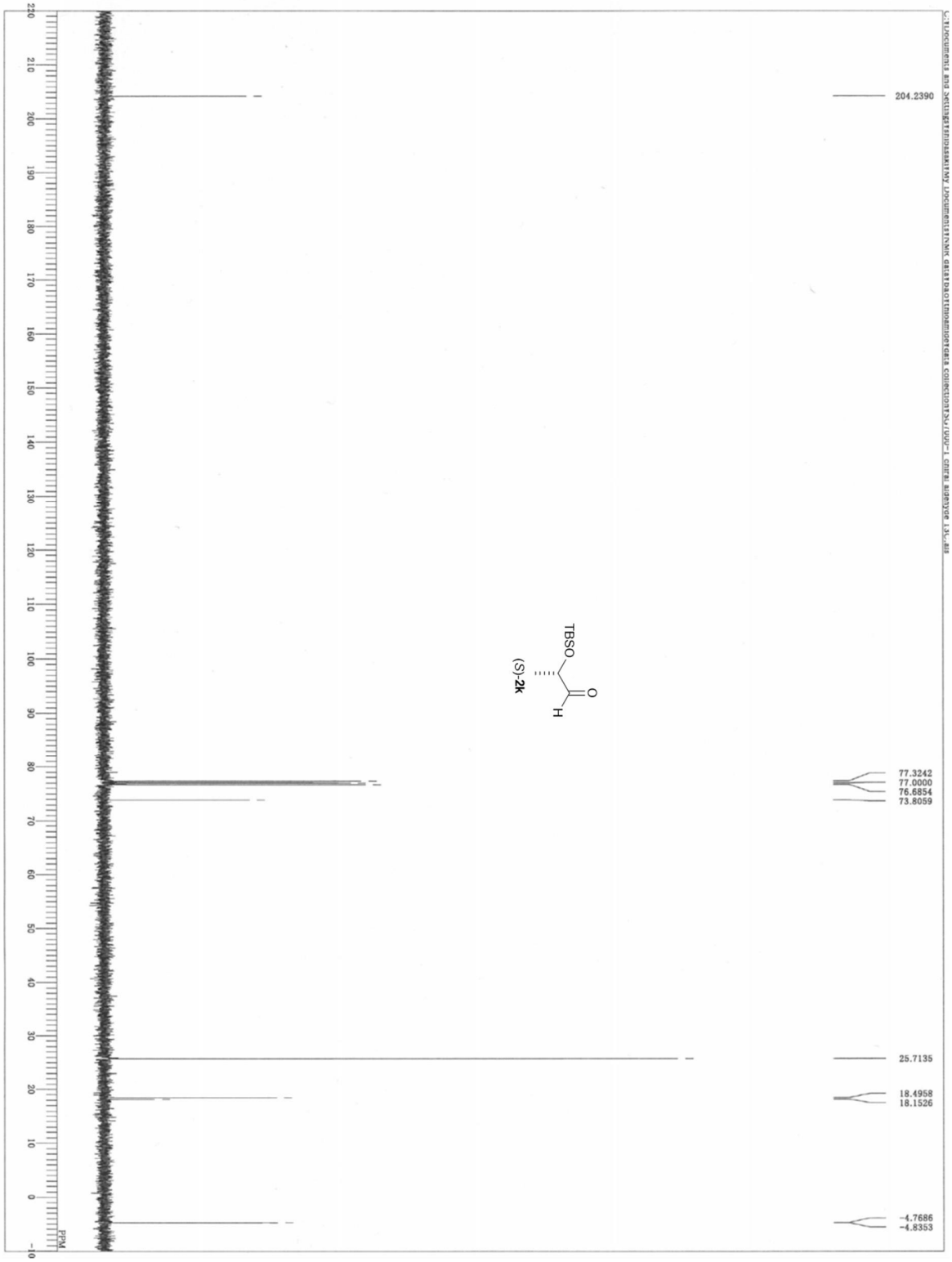
TBSO
O
H
(S)-2k
PPM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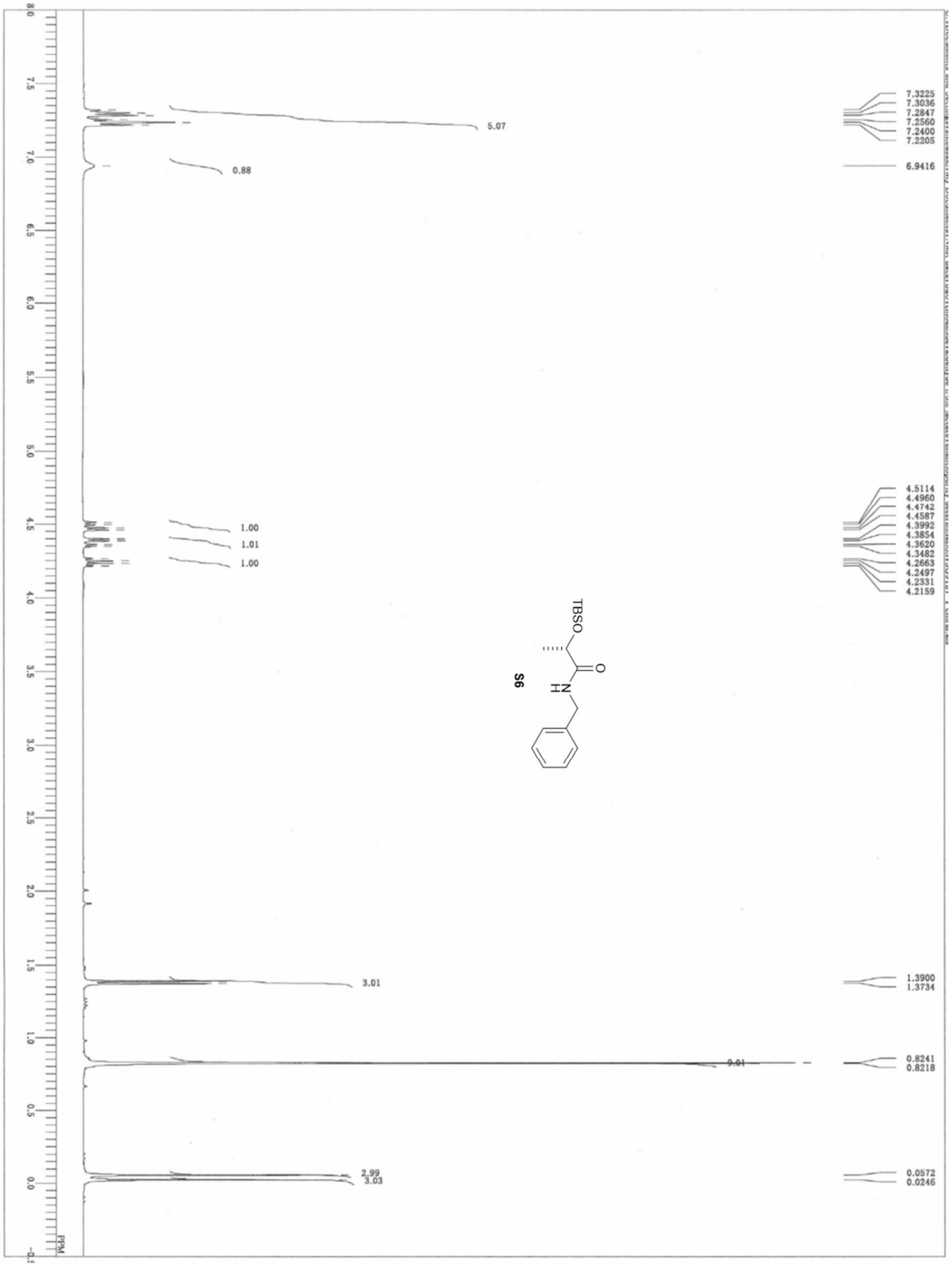
O
H
(S)-2k
PPM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7.2400
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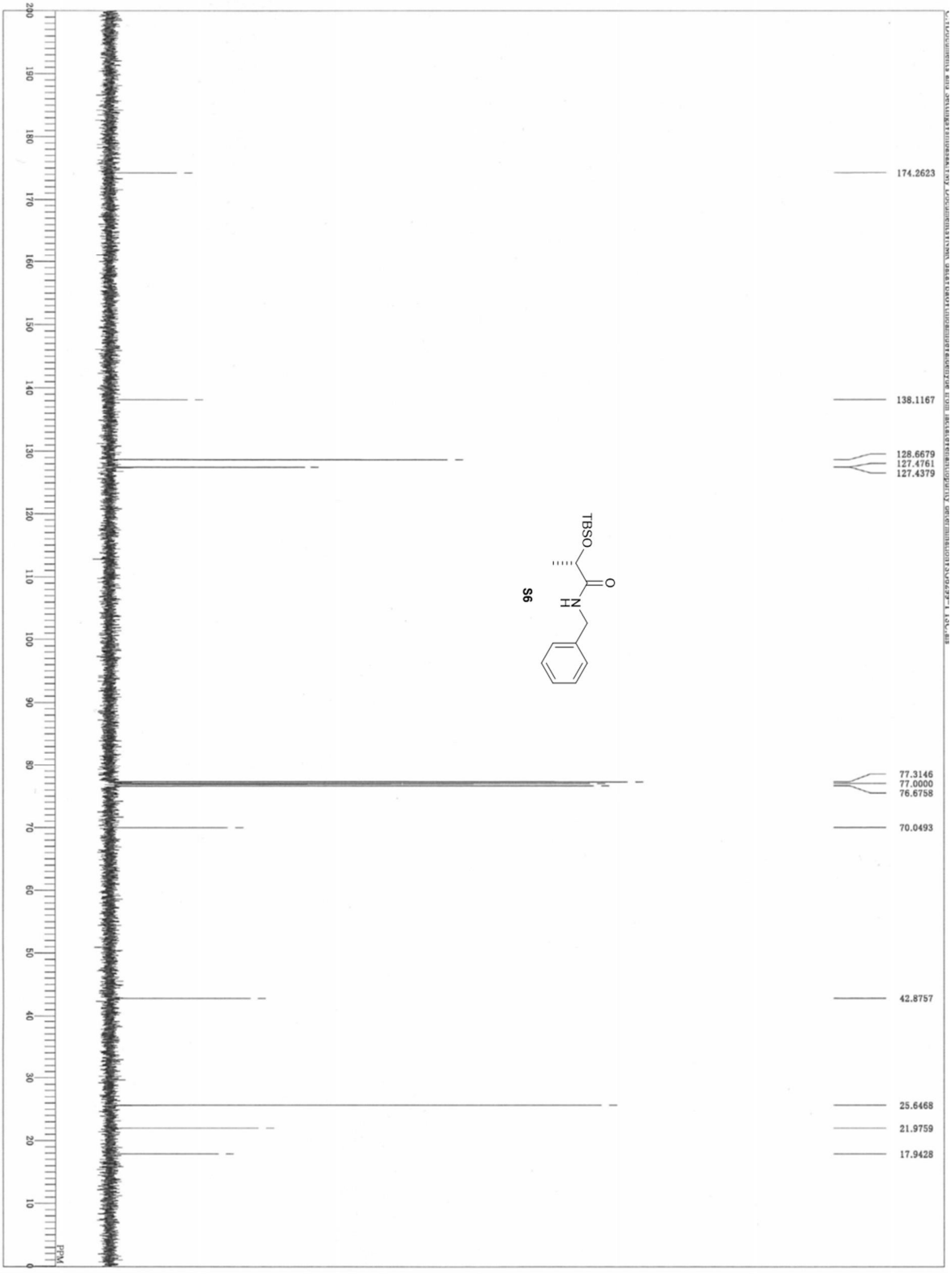
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H
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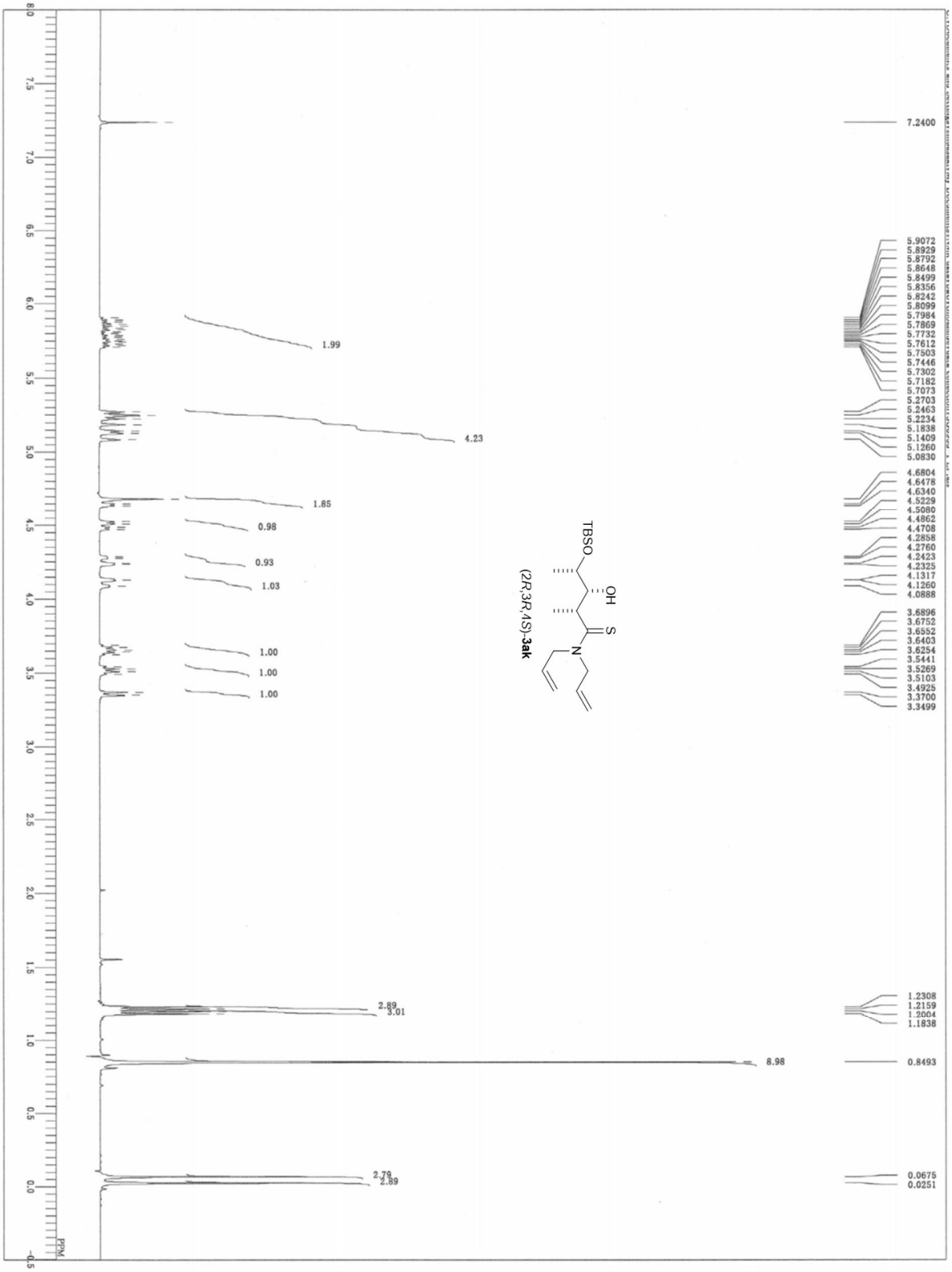
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5.8242
5.8099
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5.7869
5.7732
5.7612
5.7503
5.7446
5.7302
5.7182
5.7073
5.2703
5.2463
5.2234
5.1838
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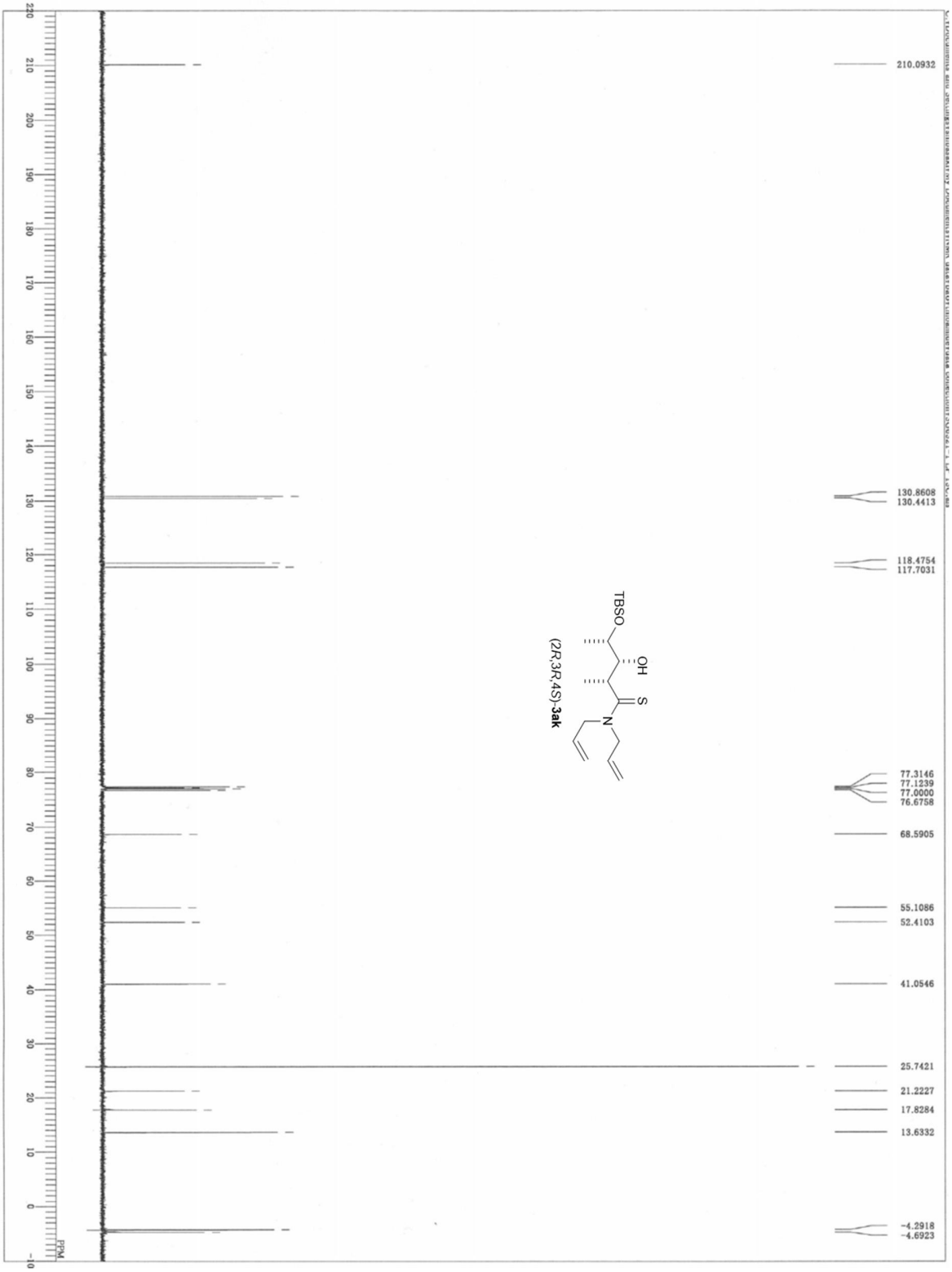
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S
N
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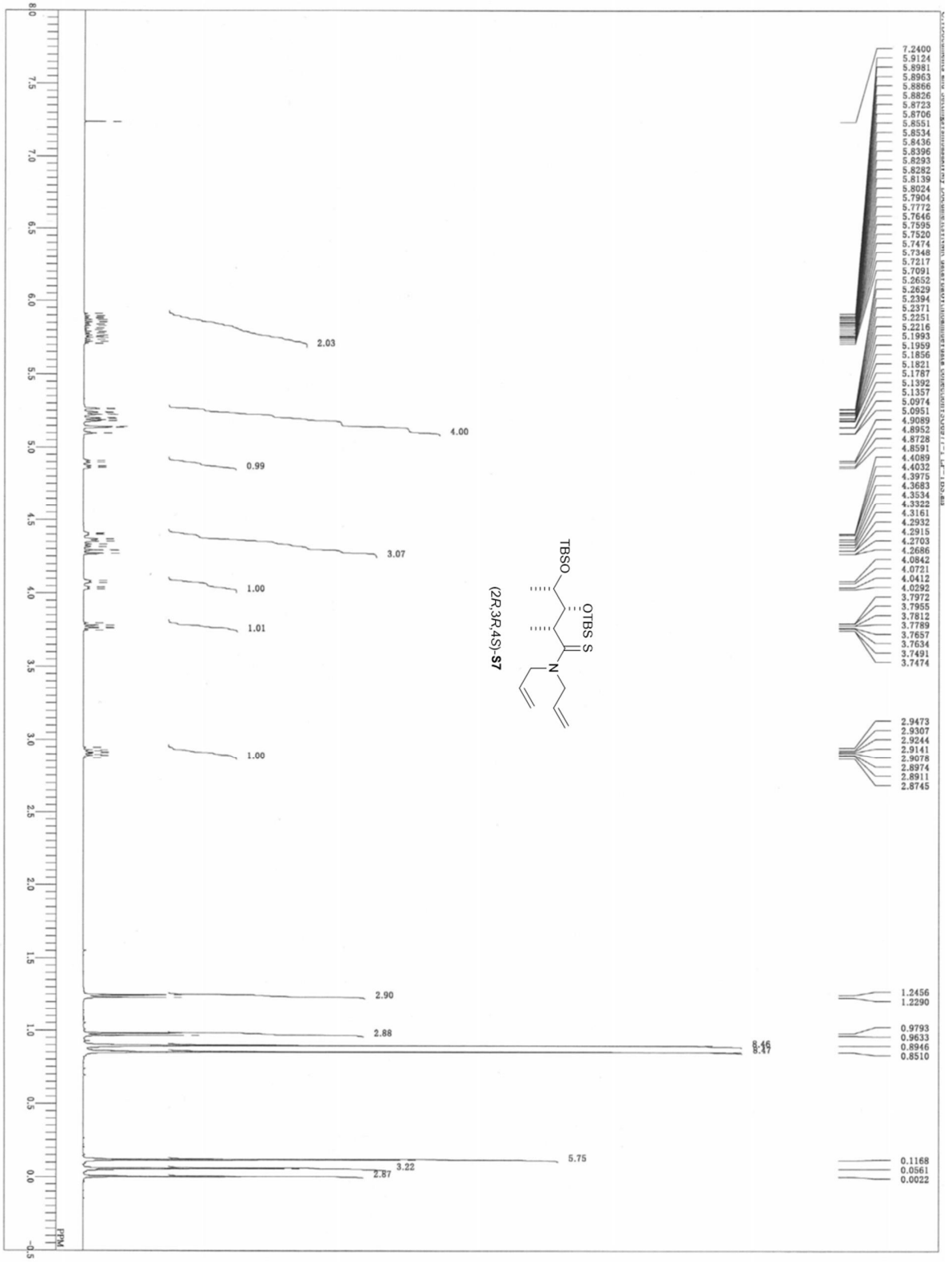
PPM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OTBS
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1.00
1.01
1.00
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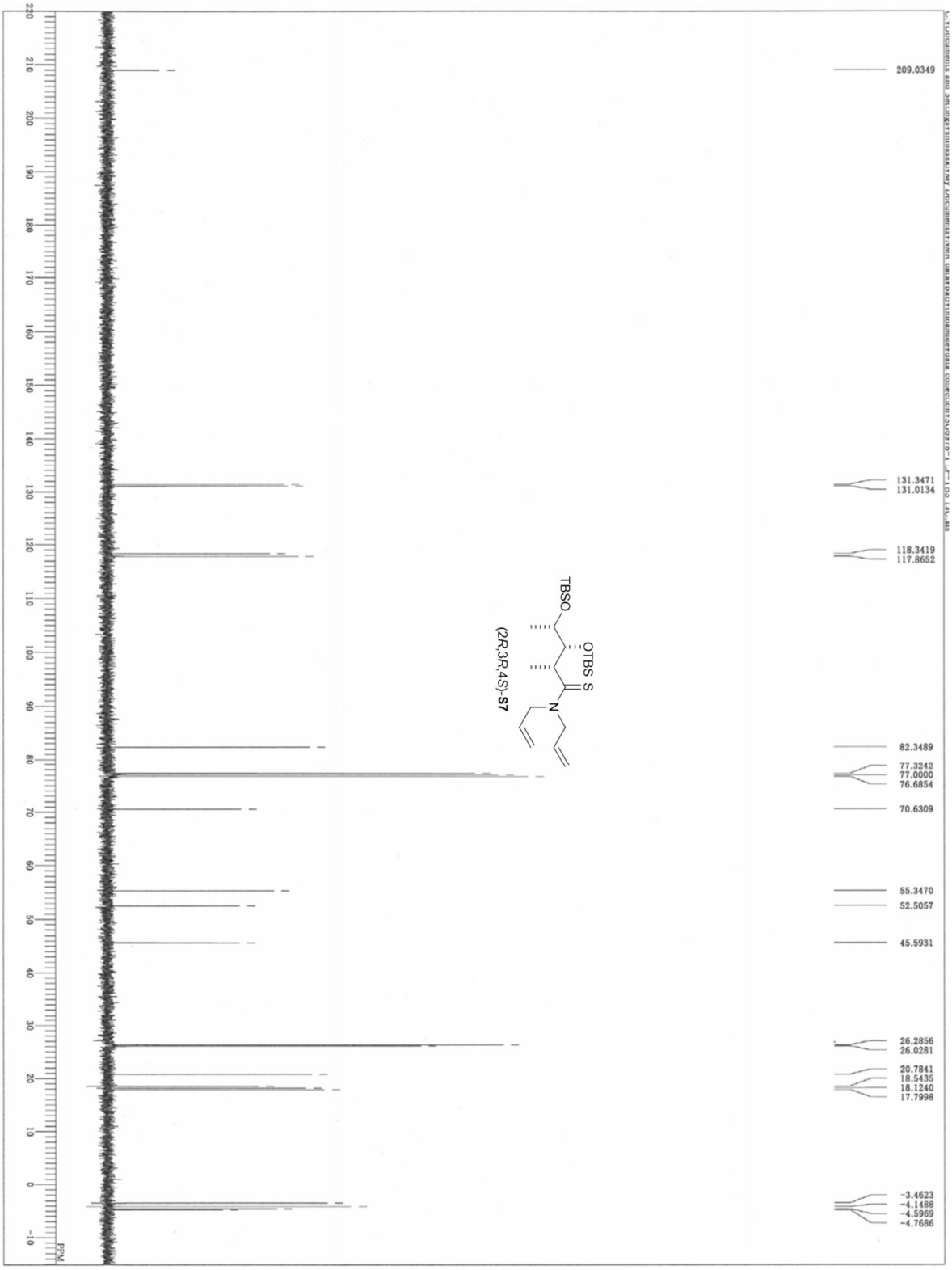
PPM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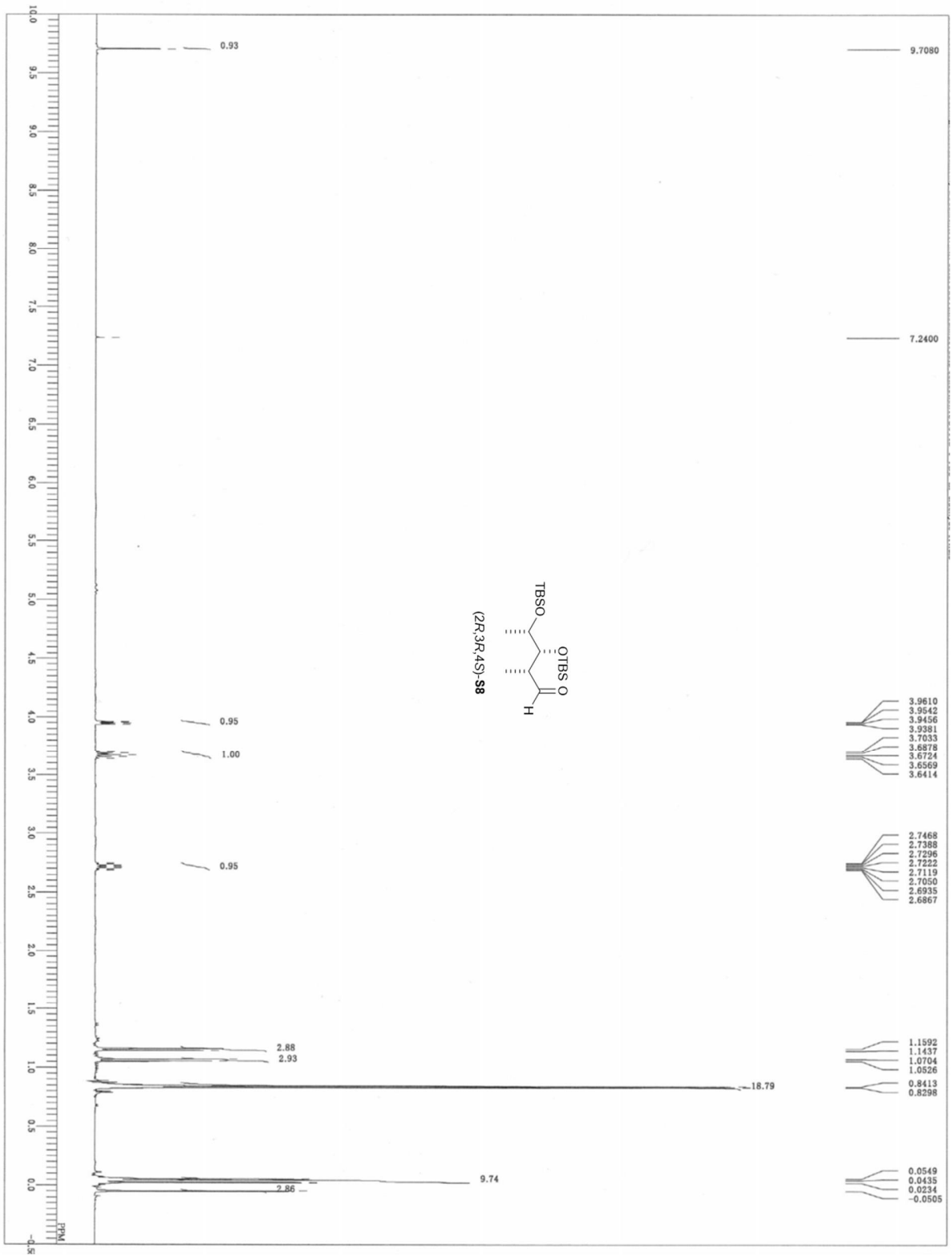
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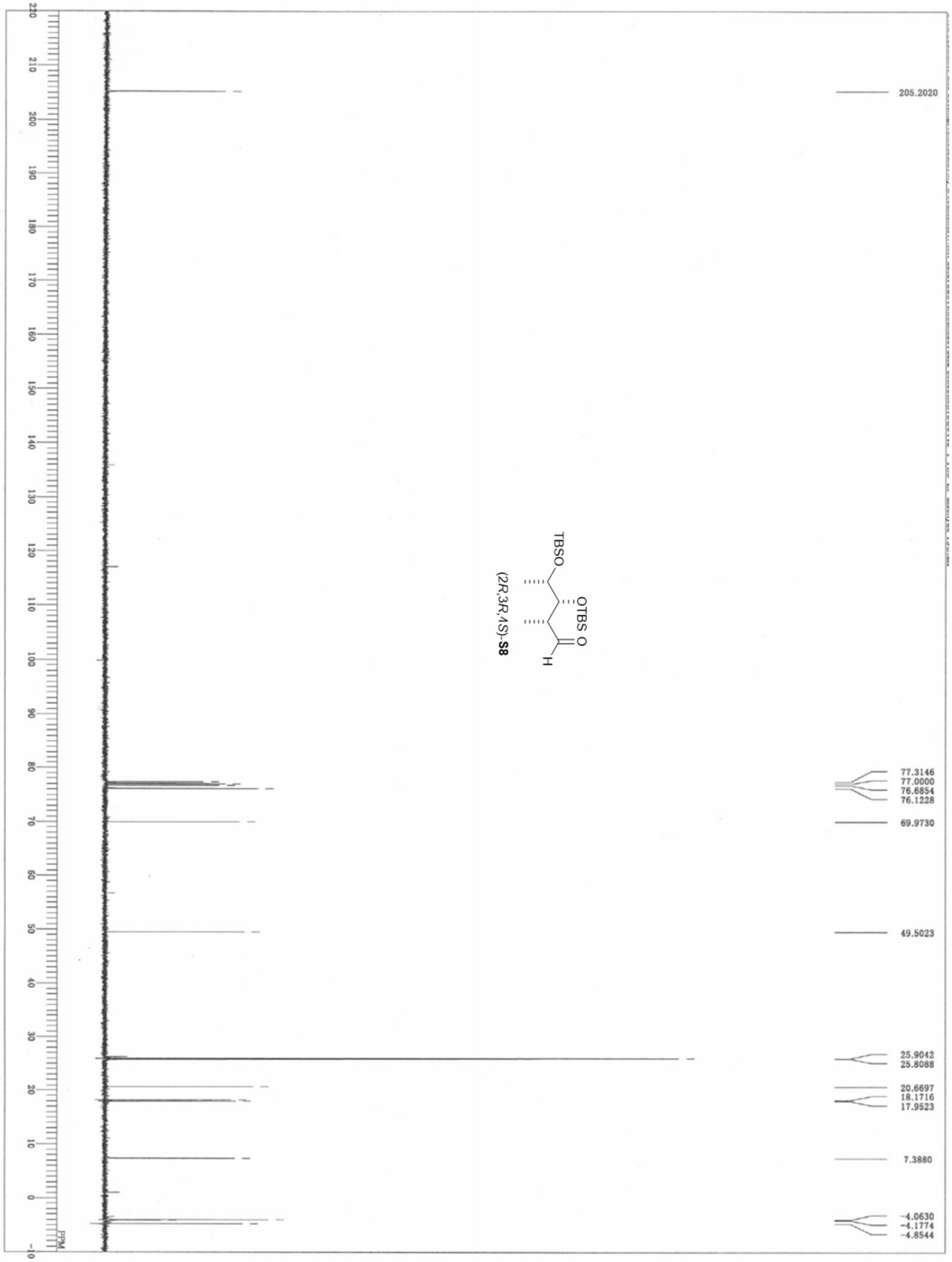
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OTBS O
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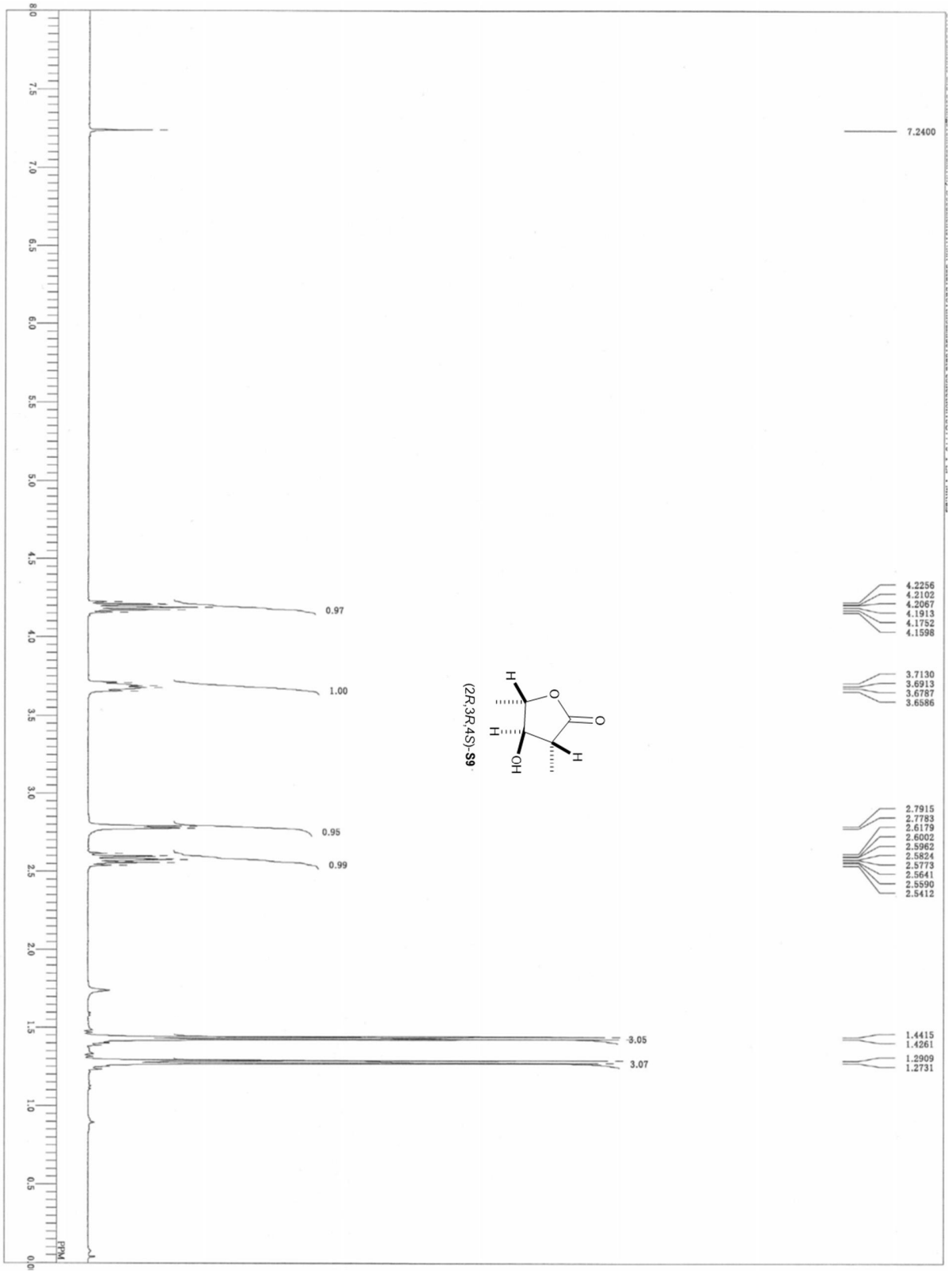
PPM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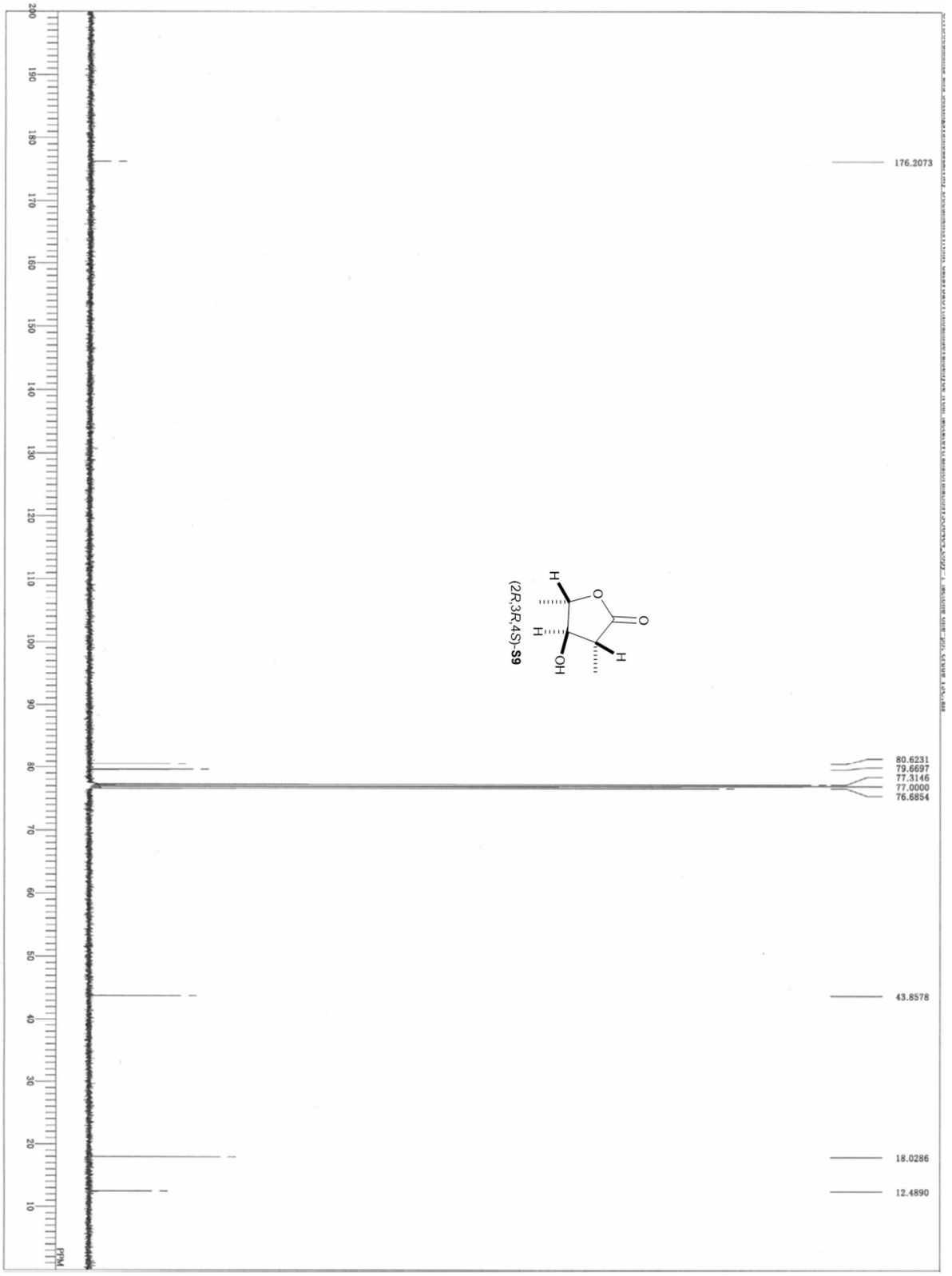
PPM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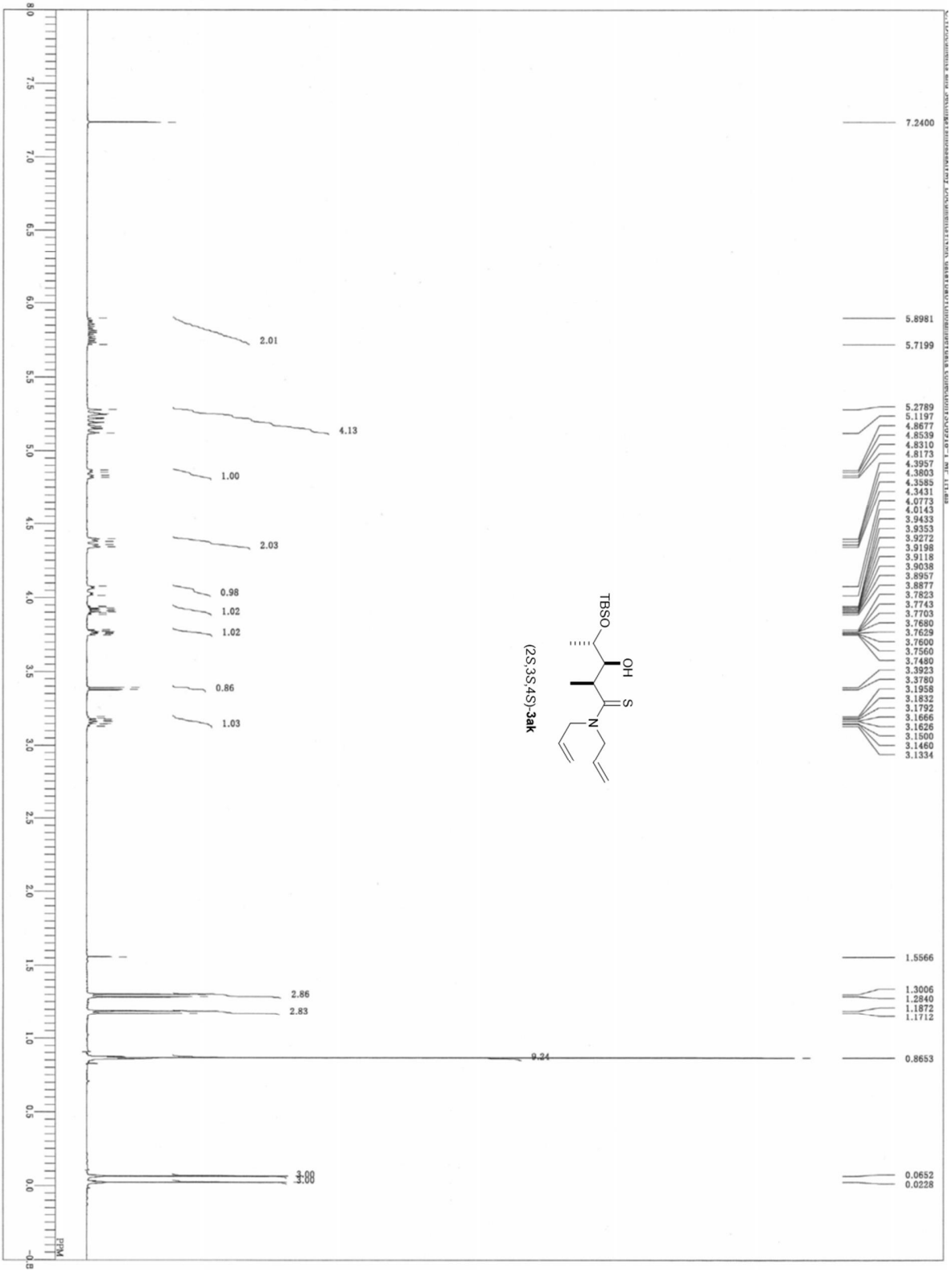
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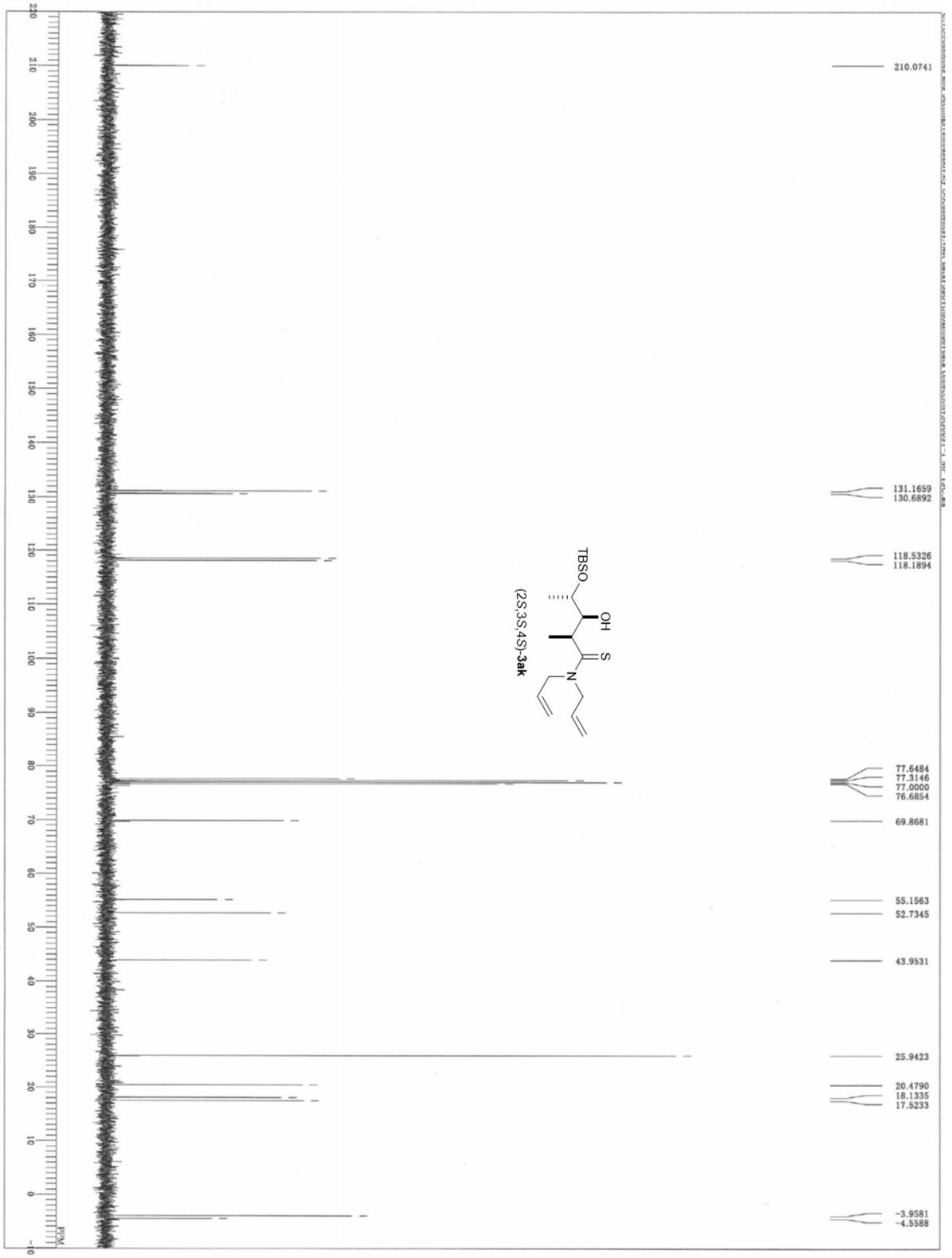
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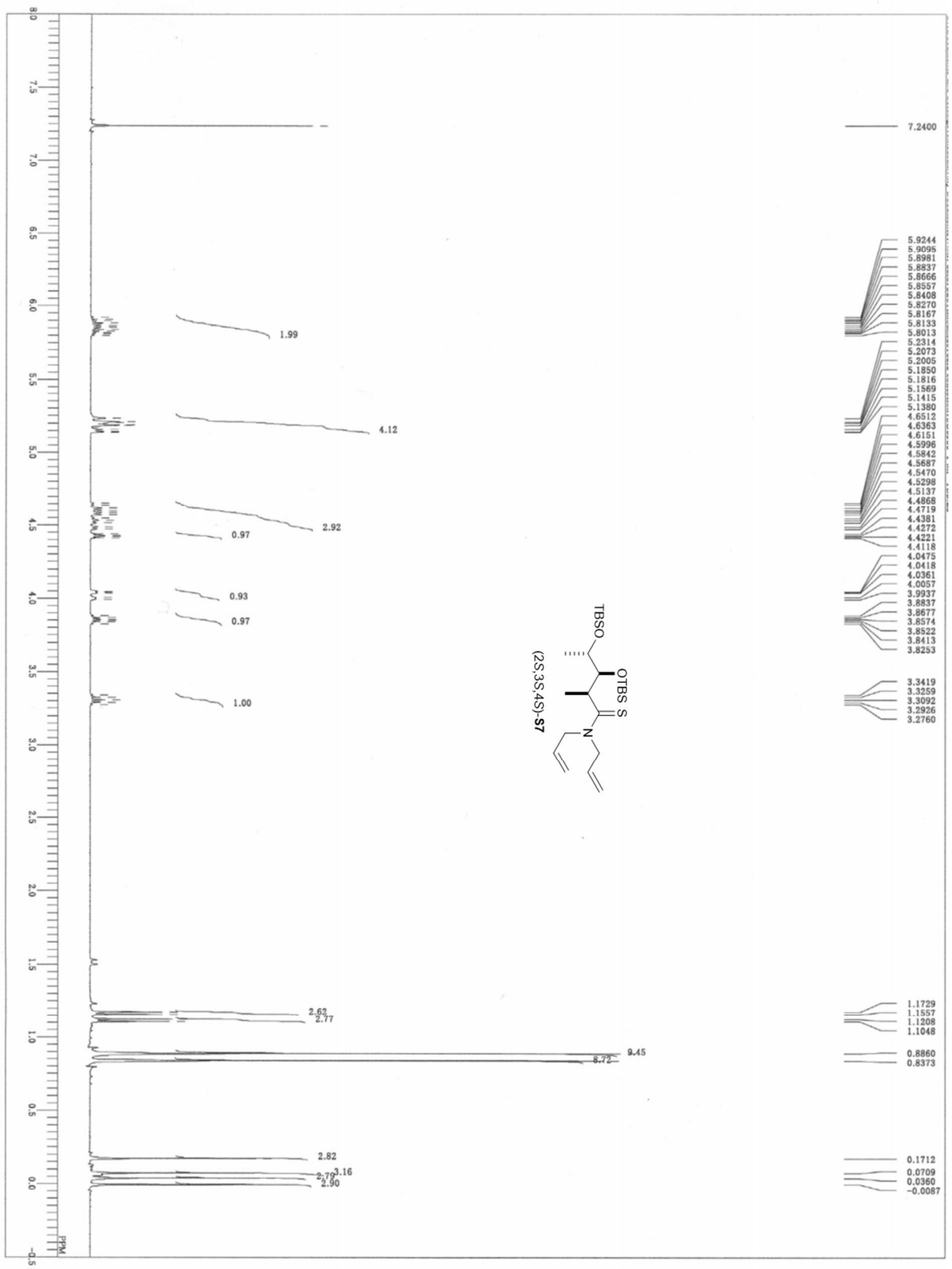
TBSO
OH
S
N
(2S,3S,4S)-3ak
PPM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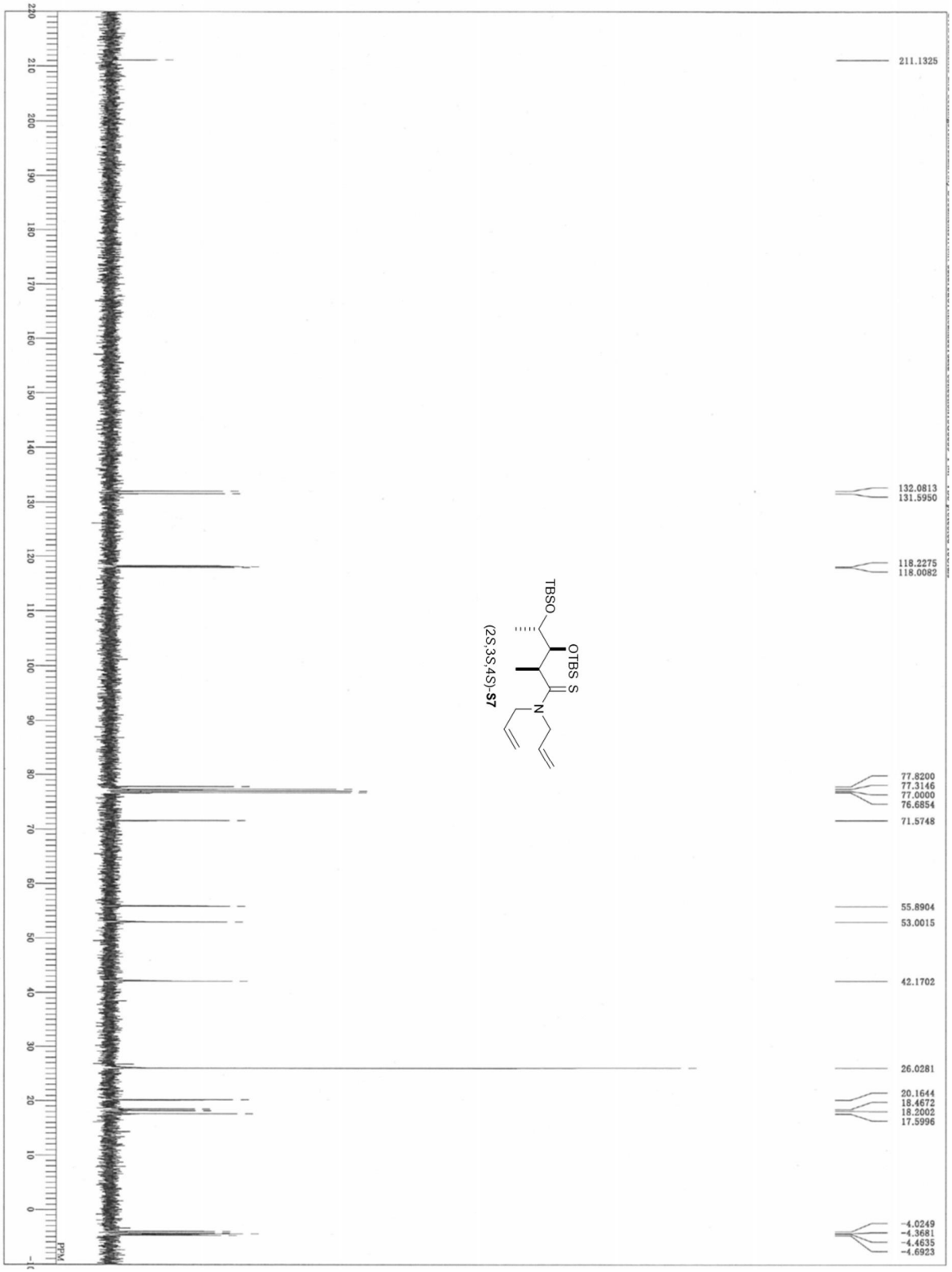
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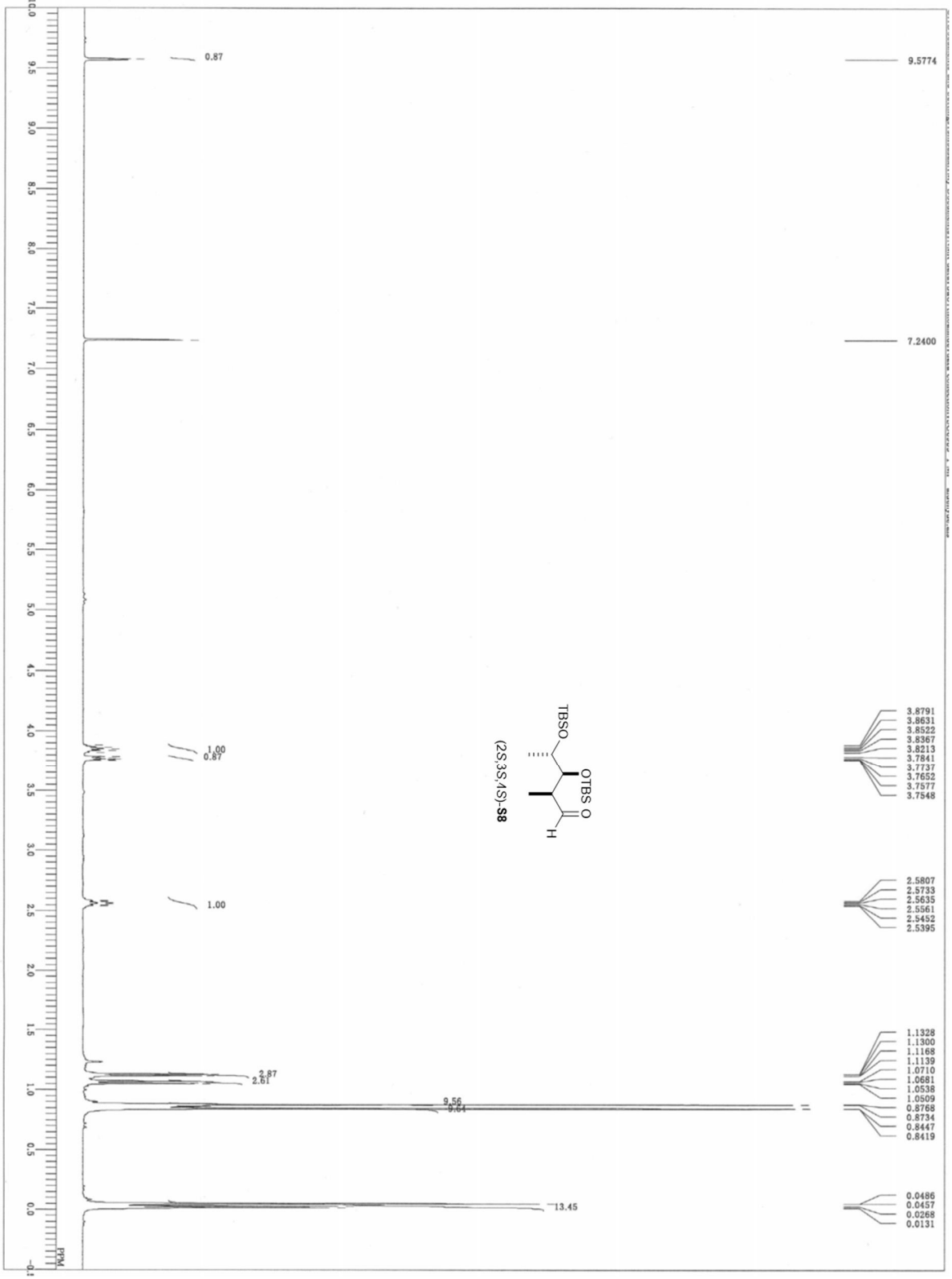
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(2S,3S,4S)-S8
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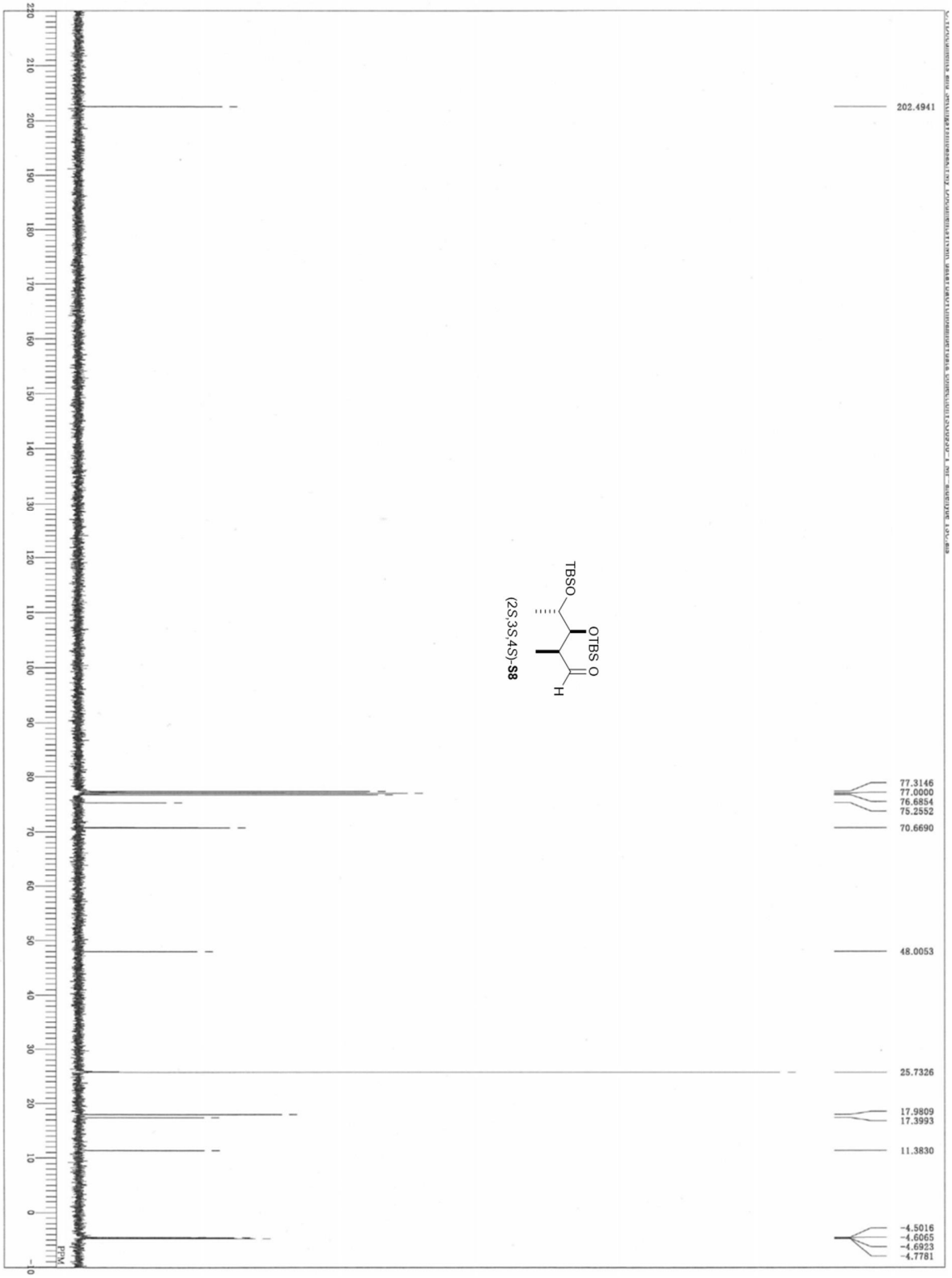
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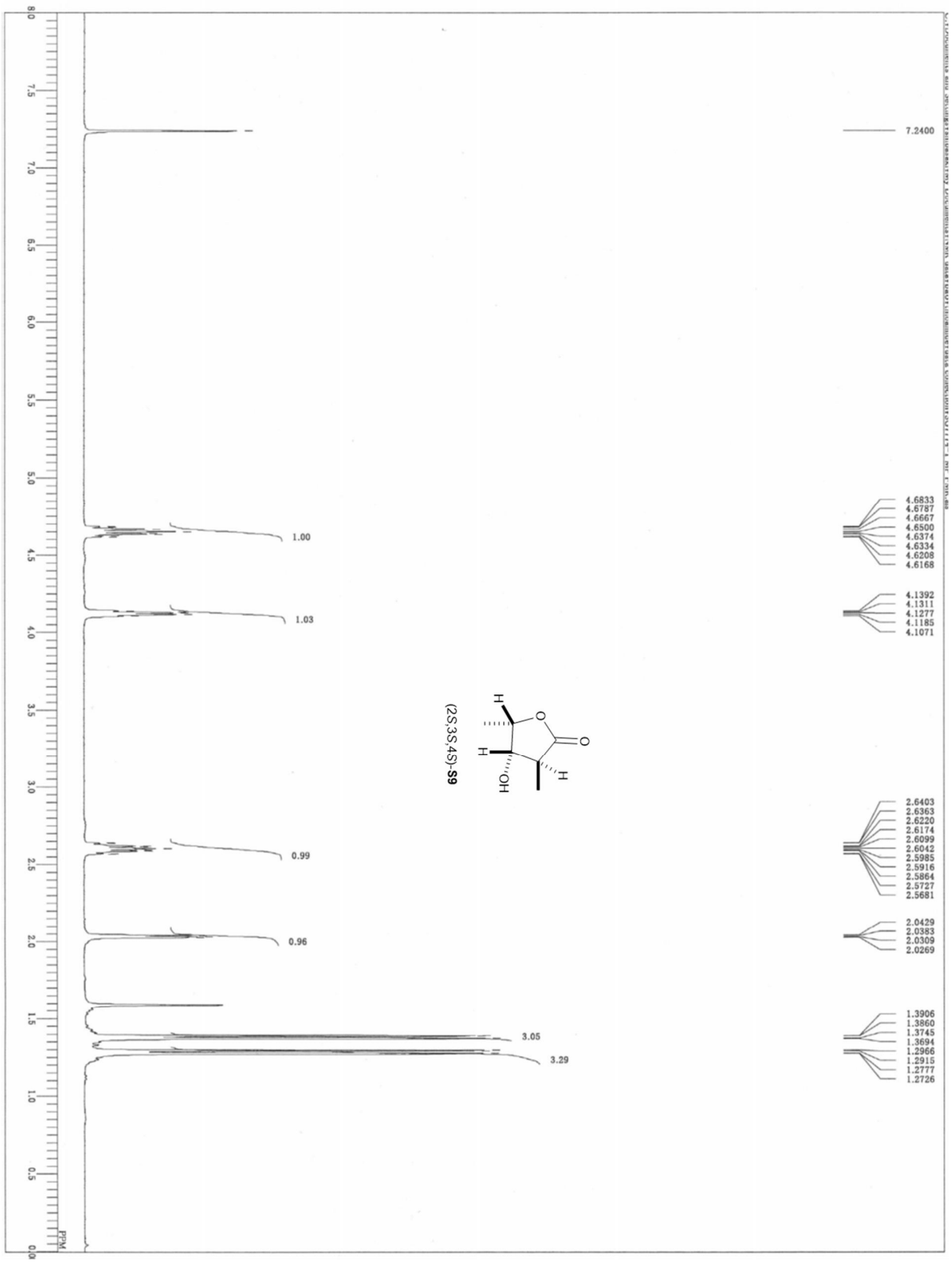
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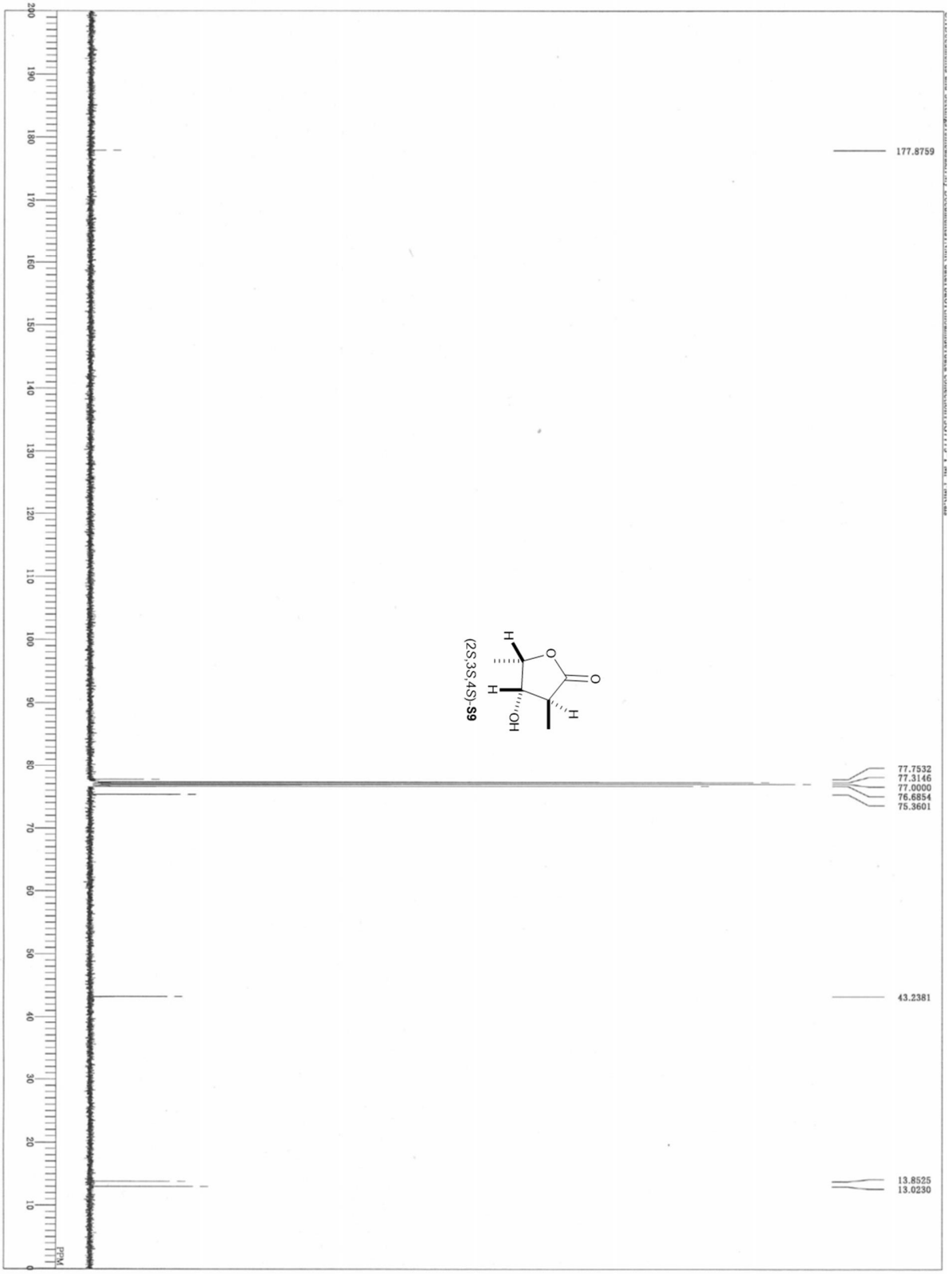
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