Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Synthesis and Biological Evaluation of α-Tubulin-binding Pironetin Analogues Lacking Alkyl Pendants in the Side Chain or the Pyrone Ring

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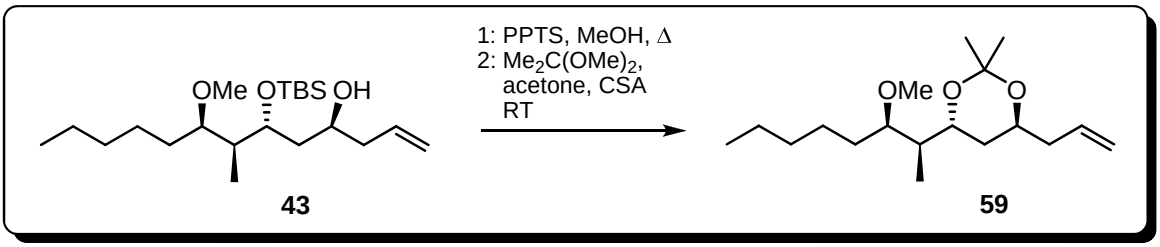
Supporting Information

Contents:

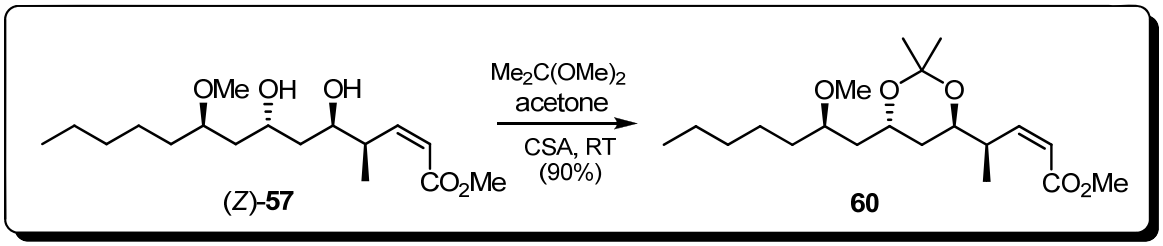
Synthesis and analytical data of intermediate compounds



(4*S*,6*R*)-4-Allyl-6-[(2*S*,3*R*)-3-methoxyoctan-2-yl]-2,2-dimethyl-1,3-dioxane (59). Compound **43** (19 mg, 0.051 mmol) was desilylated with 48% aq HF in MeCN under the reaction conditions described in the paper. Standard work-up (EtOAc) and column chromatography on silica gel (hexanes-EtOAc mixtures) afforded the expected 1,3-diol (13 mg, 98%), which was then dissolved in 1 mL of a 4:1 mixture of dry acetone and 2,2-dimethoxypropane. After addition of 3Å molecular sieves (5 mg) and camphorsulfonic acid (1.2 mg, 0.005 mmol), the mixture was stirred at room temperature for 1 h. After filtration through a pad of Celite and removal of volatiles under reduced pressure, the oily residue was chromatographed on silica gel (hexanes-EtOAc, 9:1) to yield acetonide **59** (6 mg, 40%): oil, $[\alpha]_D$ +45.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR δ 5.81 (1H, m), 5.10 (1H, br d, *J* ~ 17.3 Hz), 5.05 (1H, br d, *J* ~ 10.3 Hz), 3.85-3.75 (2H, m), 3.45 (1H, m), 3.36 (3H, s), 2.32 (1H, m), 2.21 (1H, m), 1.65-1.50 (2H, br m), 1.38 (3H, s), 1.35 (3H, s), 1.35-1.20 (7H, br m), 0.95-0.85 (5H, m, overlapping a 3H triplet), 0.78 (3H, d, *J* =7.2 Hz); ^{13}C NMR δ 100.4 (C), 134.7, 79.7, 67.3, 66.4, 37.1 (CH), 116.7, 41.9, 40.3, 32.2, 31.3, 25.8, 22.7 (CH_2), 58.1, 24.8, 24.6, 14.1, 7.9 (CH_3); HR ESMS *m/z* 321.2405 ($M+Na^+$), calcd. for $C_{18}H_{34}NaO_3$, 321.2406.

The position of the acetonide signals (δ 100.4, 24.8, 24.6) in the ^{13}C NMR spectrum of **59** indicates that **43** is the TBS derivative of an *anti*-1,3-diol,[1] thus confirming the relative configuration of the two oxygen-bearing carbon atoms.

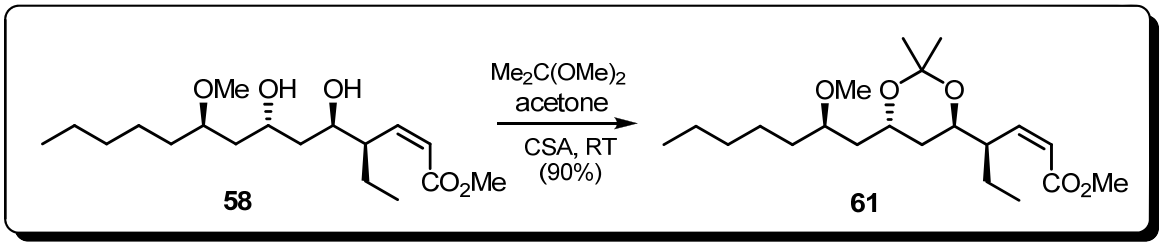
[1] S. D. Rychnovsky, B. N. Rogers and T. I. Richardson, *Acc. Chem. Res*., 1998, **31**, 9-17.



Methyl (4*R*,*Z*)-4-[(4*R*,6*S*)-6-[(*R*)-2-methoxyheptyl]-2,2-dimethyl-1,3-dioxan-4-yl]pent-2-enoate (60). Compound (*Z*)-**57** (19 mg, 0.060 mmol) was dissolved in 2 mL of a 4:1 mixture of dry acetone and 2,2-dimethoxypropane. After addition of 3Å molecular sieves (2 mg) and camphorsulfonic acid (2 mg), the mixture was stirred overnight at room temperature. Filtration through a pad of Celite and removal of volatiles under reduced pressure provided an oily residue which was chromatographed on silica gel (hexanes-EtOAc, 9:1) to yield acetonide **60** (90%): oil, $[\alpha]_D$ –51.7 (*c* 0.9, $CHCl_3$); IR ν_{max} 1727 (C=O) cm^{-1}; ^1H NMR δ 6.07 (1H, dd, *J* = 11.3, 10.3 Hz), 5.77 (1H, br d, *J* ~ 11.3 Hz), 3.99 (1H, m), 3.72 (3H, s), 3.62 (1H, m), 3.56 (1H, m), 3.34 (3H, s), 3.33 (1H, m, overlapped by the OMe singlet), 1.72 (1H, ddd, *J* = 12.5, 9.3, 5.9 Hz), 1.55-1.40 (5H, br m), 1.36 (3H, s), 1.33 (3H, s), 1.35-1.20 (6H, br m), 1.06 (3H, d, *J* =6.5 Hz), 0.89 (3H, t, *J* =7 Hz); ^{13}C NMR δ 166.6, 100.4 (C), 151.5, 119.2, 77.4, 69.6, 63.7, 37.6 (CH), 41.0, 36.7, 33.8, 32.3, 24.5, 22.7 (CH_2), 57.0, 51.1, 24.6, 24.4, 15.4, 14.0 (CH_3); HR ESMS *m/z* 379.2466 ($M+Na^+$), calcd. for $C_{20}H_{36}NaO_5$, 379.2461.

The position of the acetonide signals (δ 100.4, 24.6, 24.4) in the ^{13}C NMR spectrum of **60** indicates that (*Z*)-**57** is an *anti*-1,3-diol,[1] thus confirming the relative configuration of the oxygen-bearing carbon atoms.

[1] S. D. Rychnovsky, B. N. Rogers and T. I. Richardson, *Acc. Chem. Res.*, 1998, **31**, 9-17.



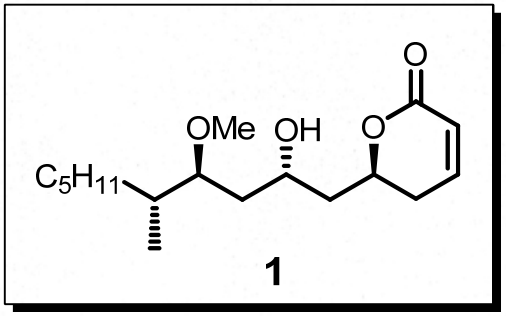
Methyl (4*R*,*Z*)-4-[(4*R*,6*S*)-6-[(*R*)-2-methoxyheptyl]-2,2-dimethyl-1,3-dioxan-4-yl]hex-2-enoate (61). Compound **58** was converted into acetonide **61** under the same conditions used for the preparation of **60**: oil, $[\alpha]_D$ –13.6 (*c* 1,3, $CHCl_3$); IR ν_{max} 1727 (C=O) cm^{-1}; ^1H NMR δ 5.93 (1H, dd, *J* = 11.6, 10

Hz), 5.89 (1H, br d, *J* ~ 11.6 Hz), 4.00 (1H, m), 3.72 (3H, s), 3.66 (1H, m), 3.48 (1H, m), 3.34 (3H, s), 3.33 (1H, m, overlapped by the OMe singlet), 1.86 (1H, m), 1.73 (1H, ddd, *J* = 13, 9.5, 5.8 Hz), 1.50-1.40 (5H, br m), 1.36 (3H, s), 1.33 (3H, s), 1.40-1.20 (7H, br m), 0.90 (3H, t, *J* =7 Hz), 0.86 (3H, t, *J* =7.5 Hz); ^{13}C NMR δ 166.7, 100.4 (C), 149.9, 121.2, 77.4, 68.9, 63.7, 44.6 (CH), 41.0, 37.1, 33.8, 32.2, 24.5, 23.3, 22.7 (CH_2), 57.0, 51.1, 24.6, 24.4, 14.0, 11.2 (CH_3); HR ESMS *m/z* 393.2620 ($M+Na^+$), calcd. for $C_{21}H_{38}NaO_5$, 393.2617.

The position of the acetonide signals (δ 100.4, 24.6, 24.4) in the ^{13}C NMR spectrum of **61** indicates that **58** is an *anti*-1,3-diol,[1] thus confirming the relative configuration of the oxygen-bearing carbon atoms.

[1] S. D. Rychnovsky, B. N. Rogers and T. I. Richardson, *Acc. Chem. Res*., 1998, **31**, 9-17.

NMR spectra of intermediate and final compounds



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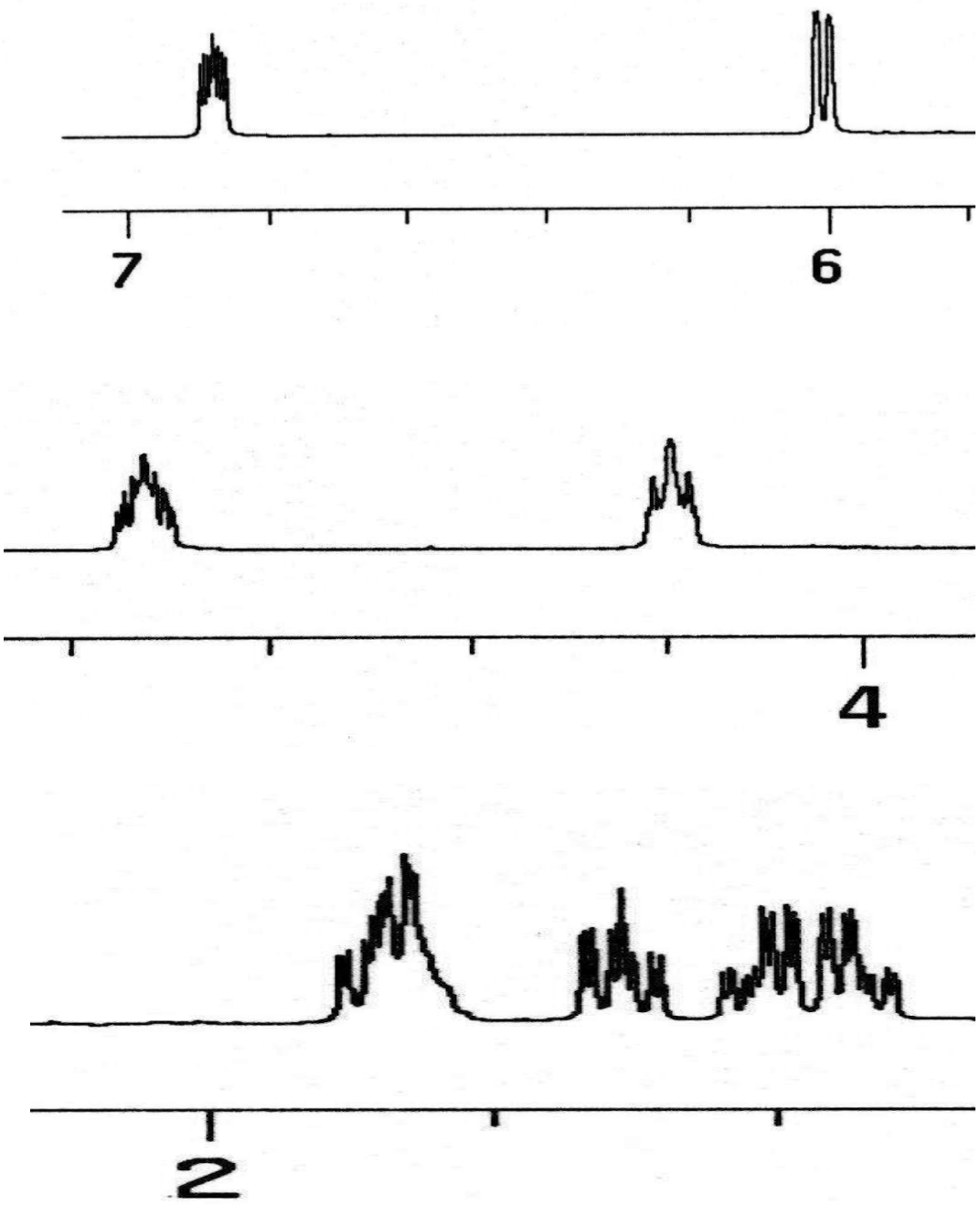

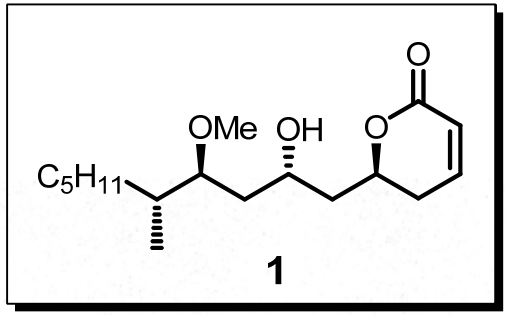

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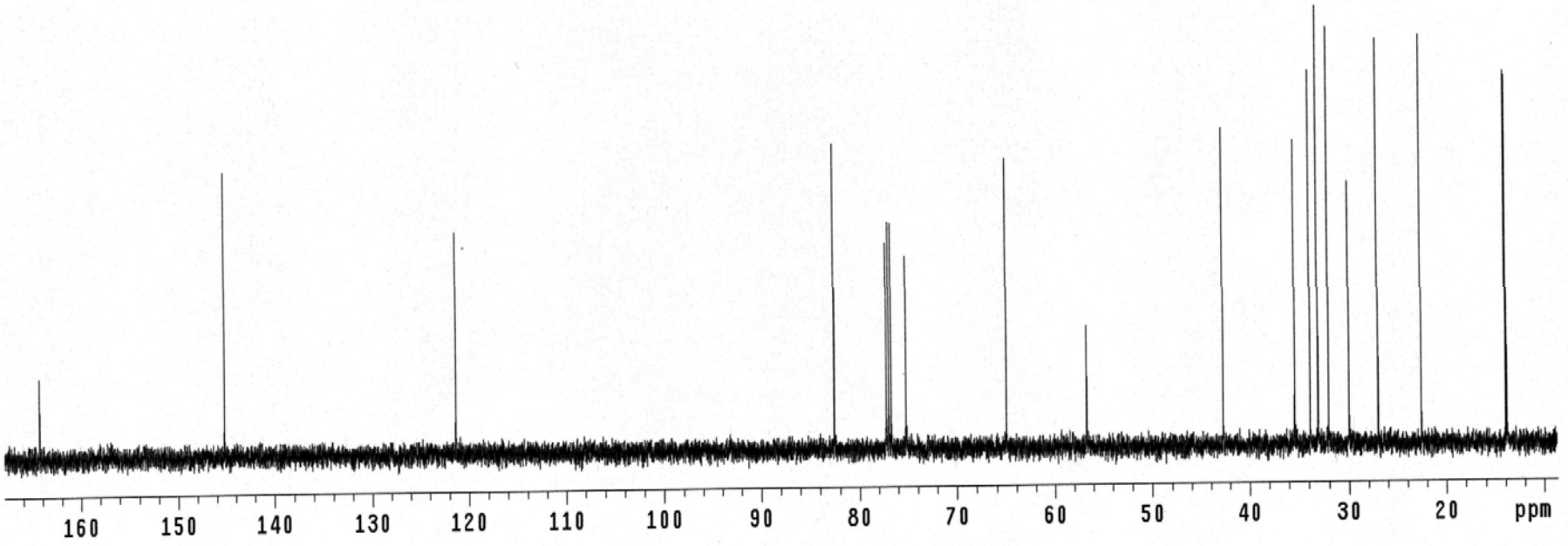

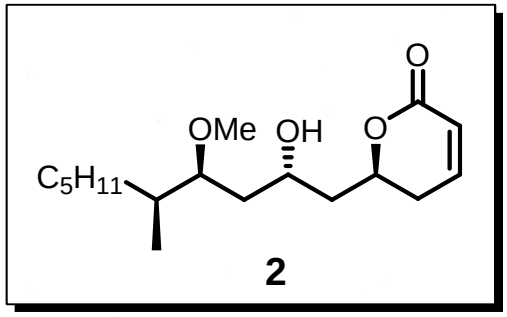

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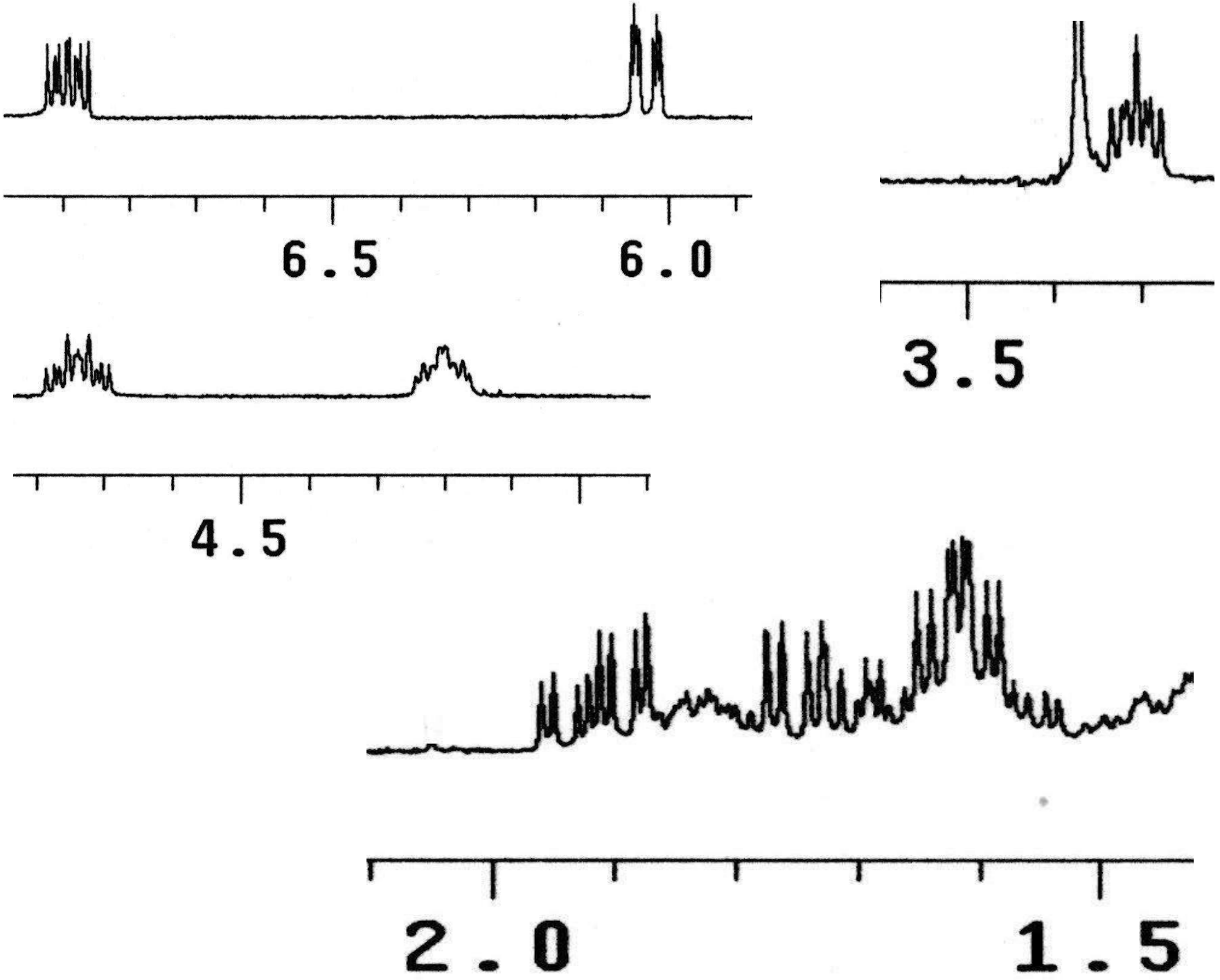

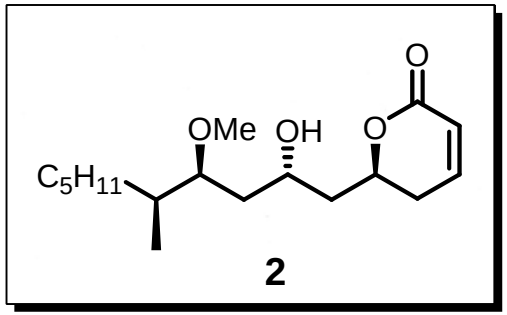

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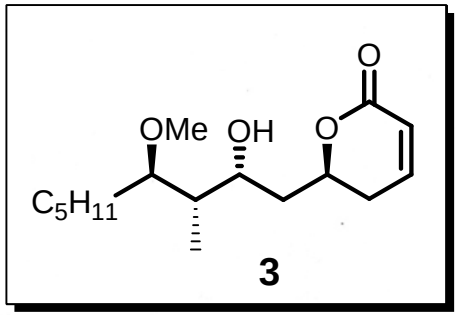

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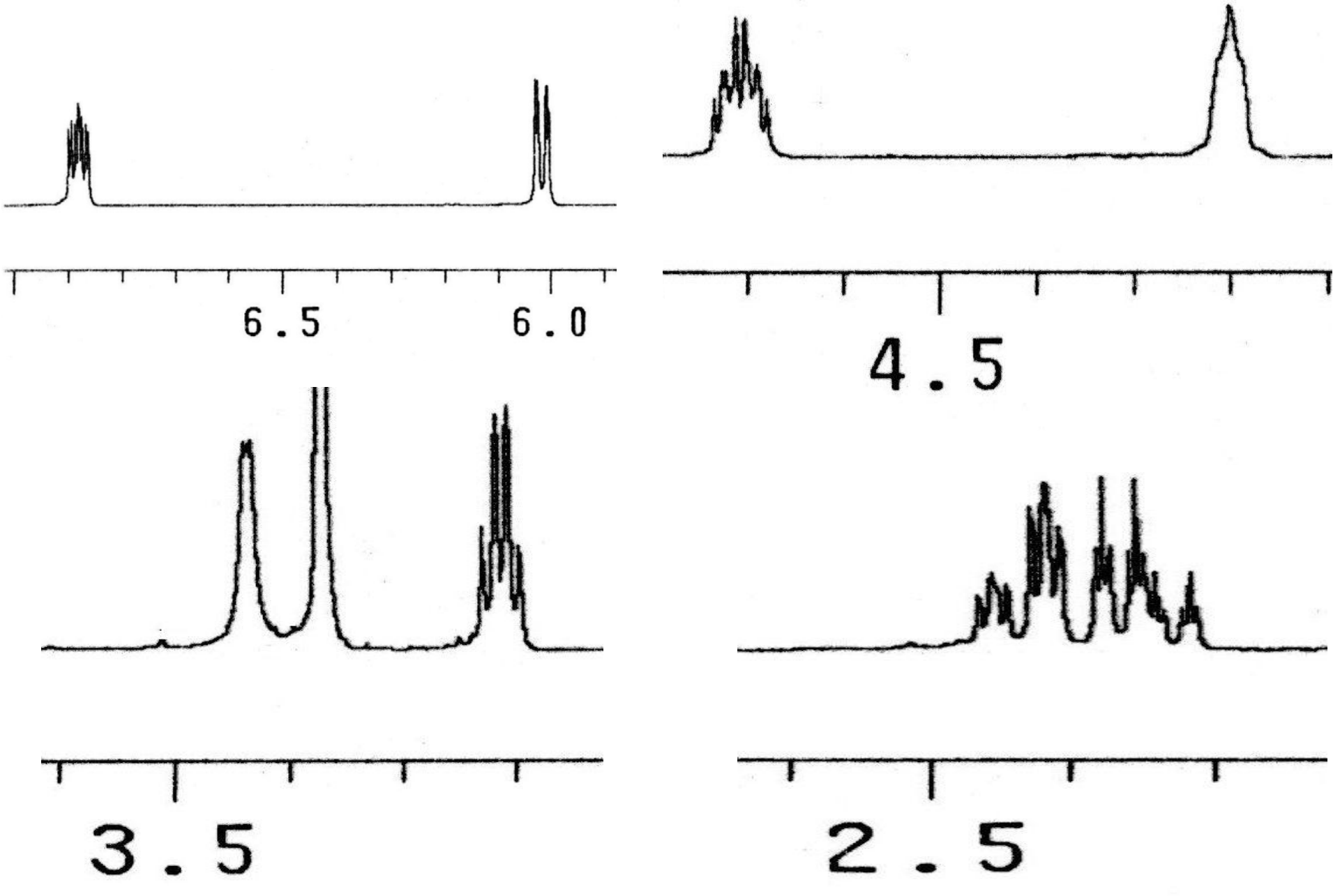

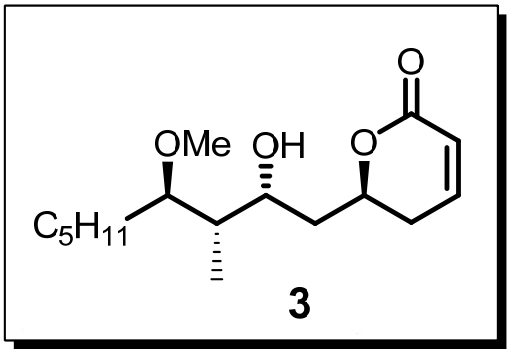

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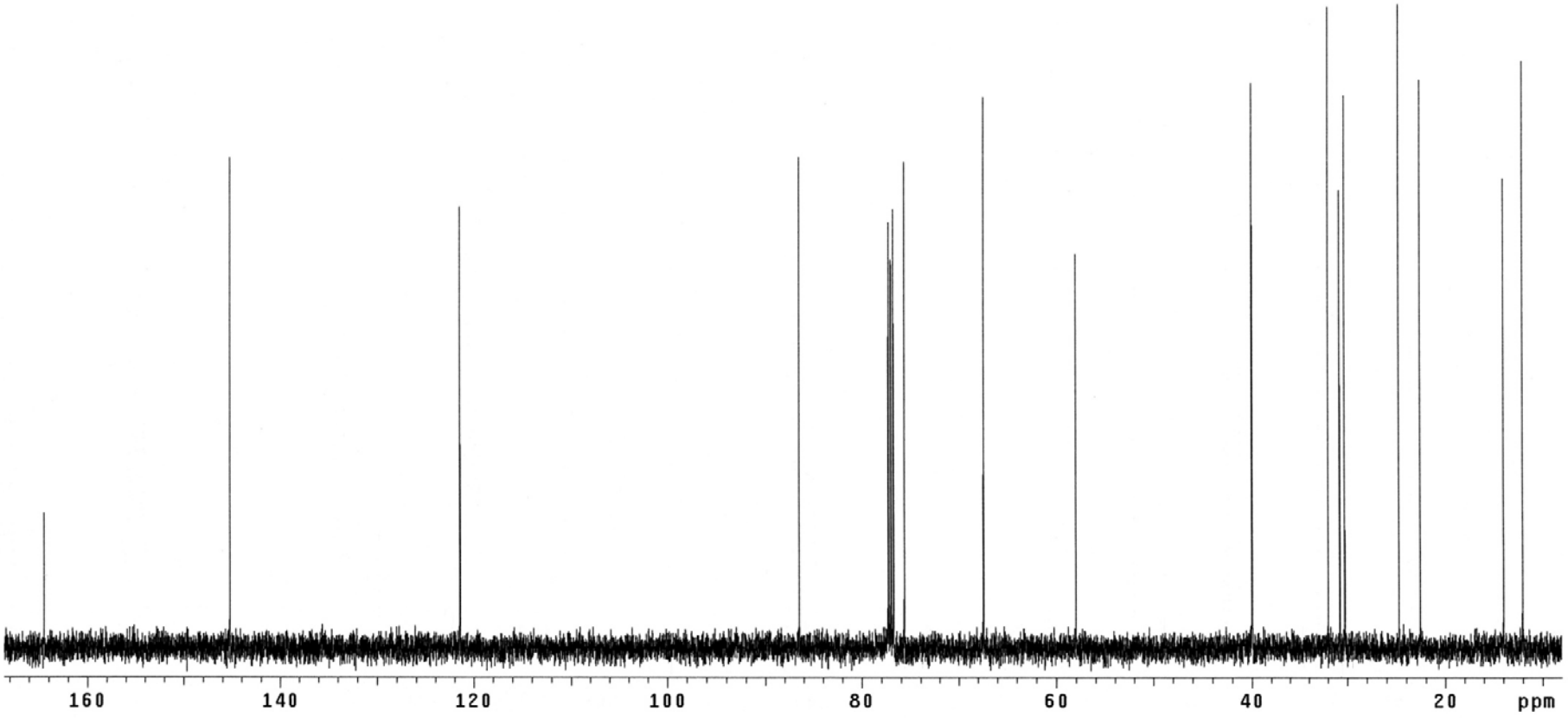

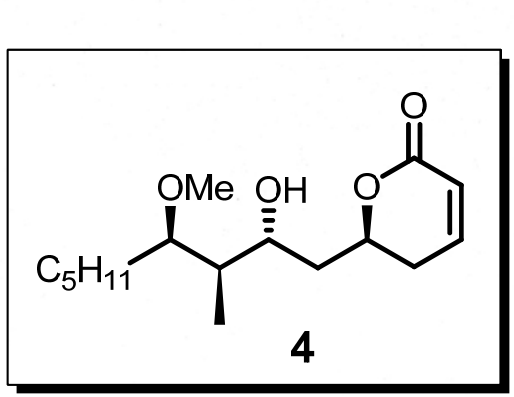

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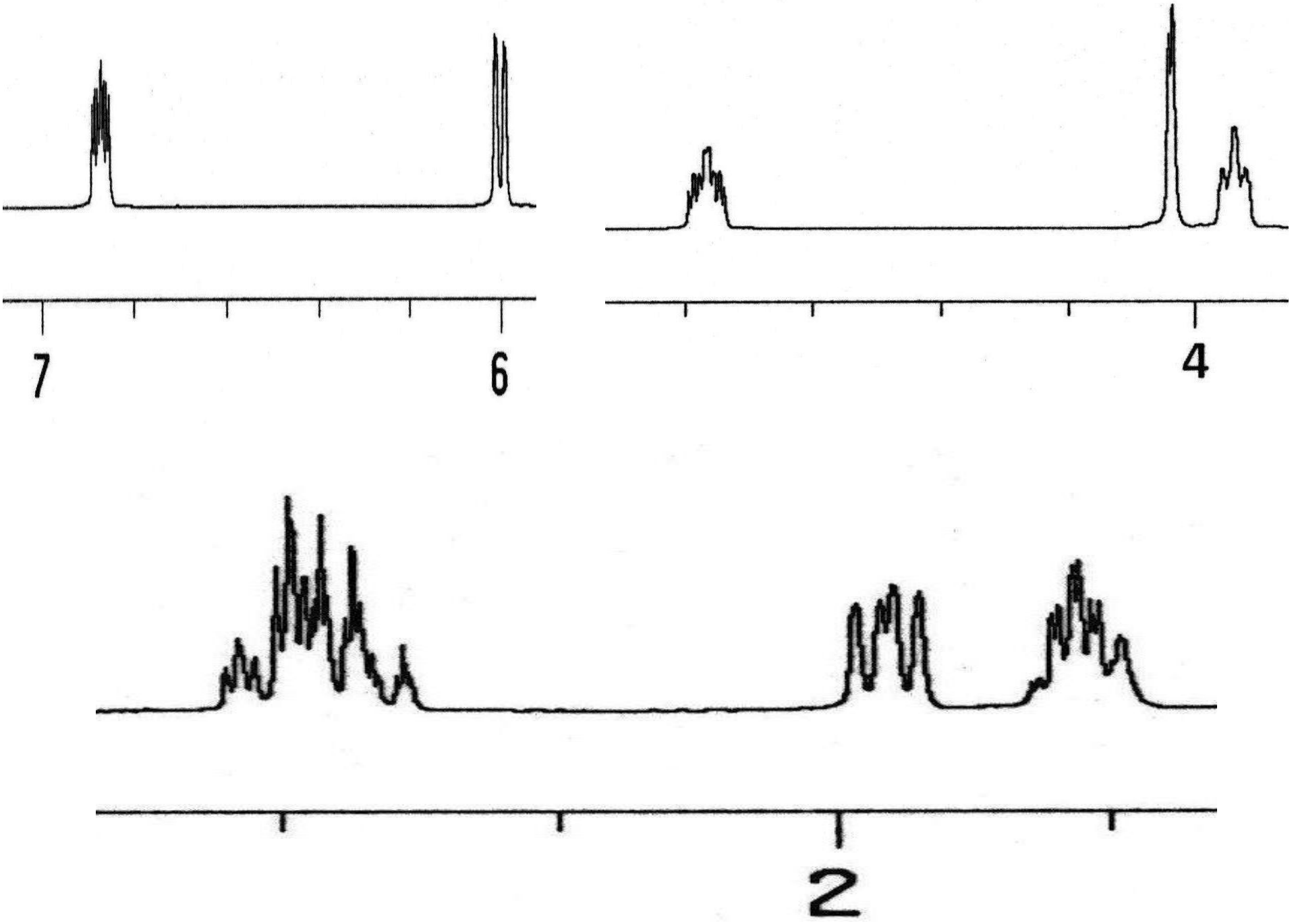

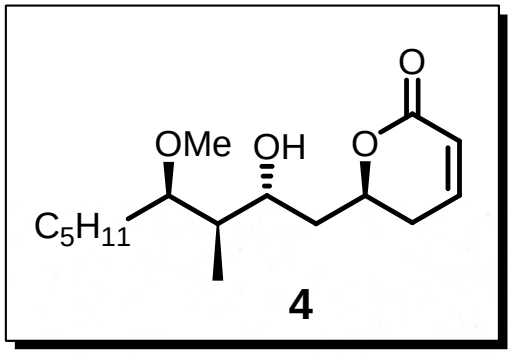

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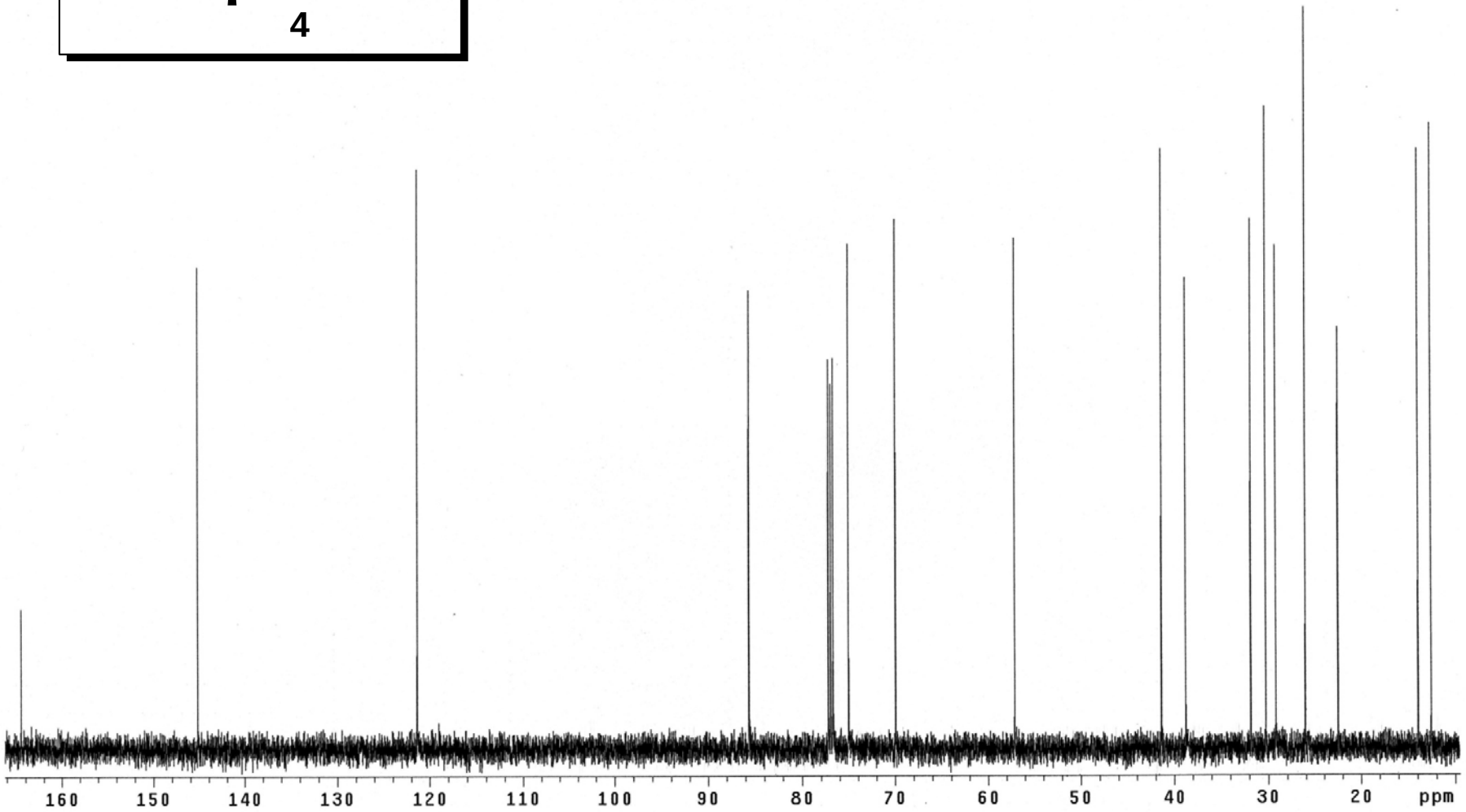

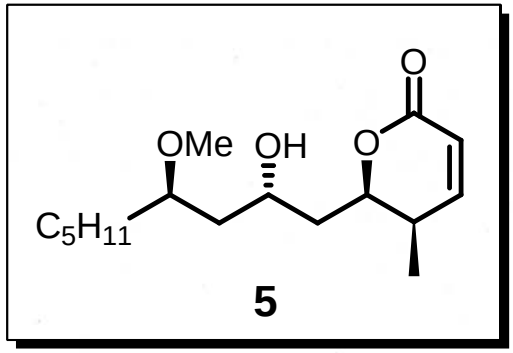

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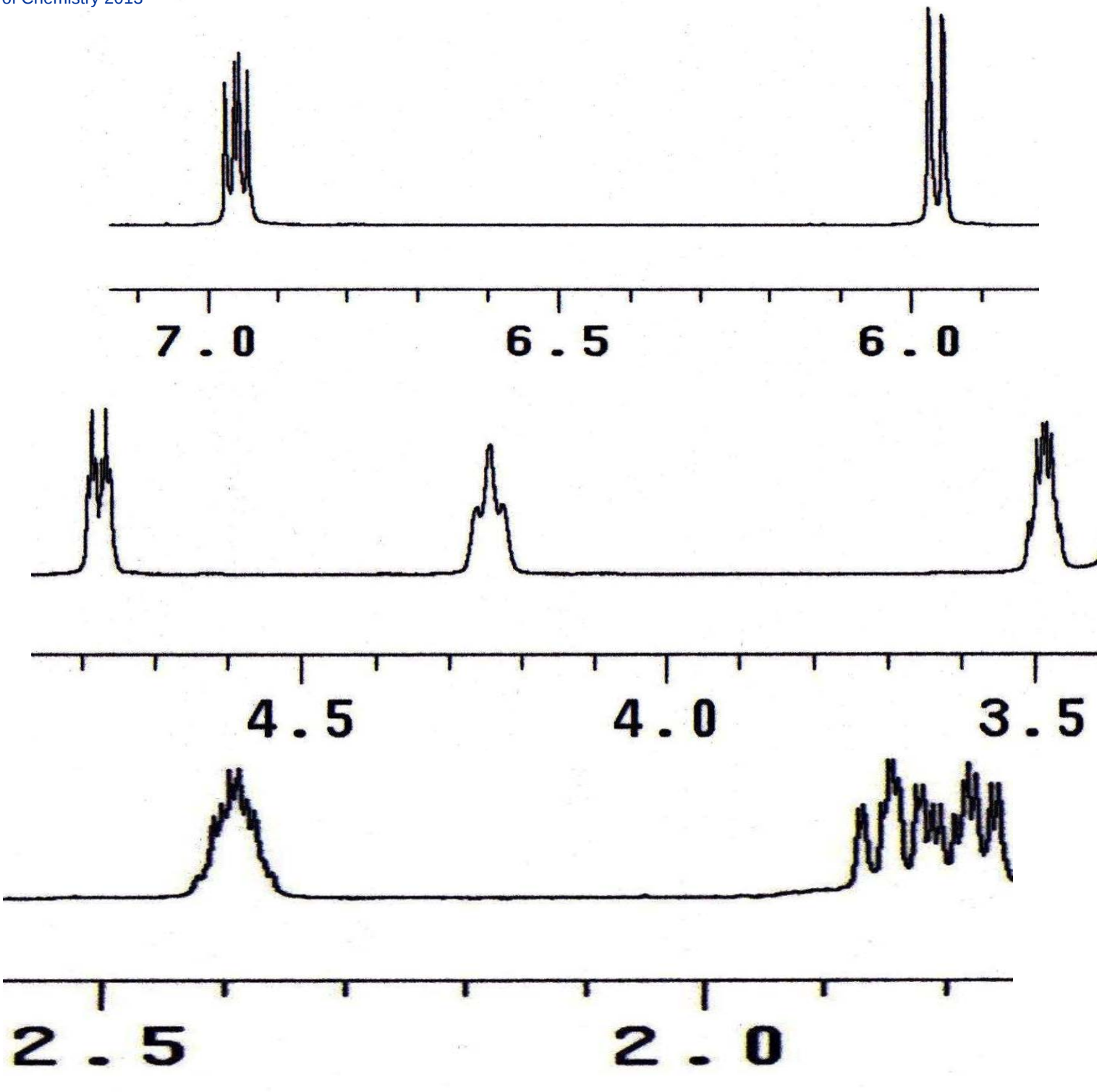

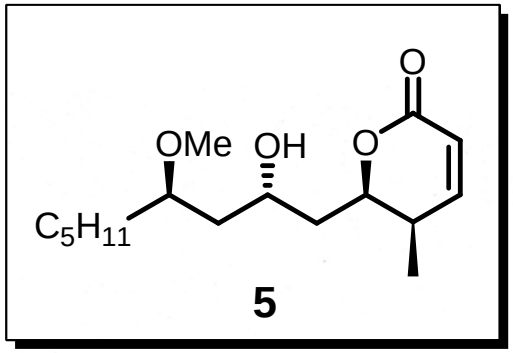

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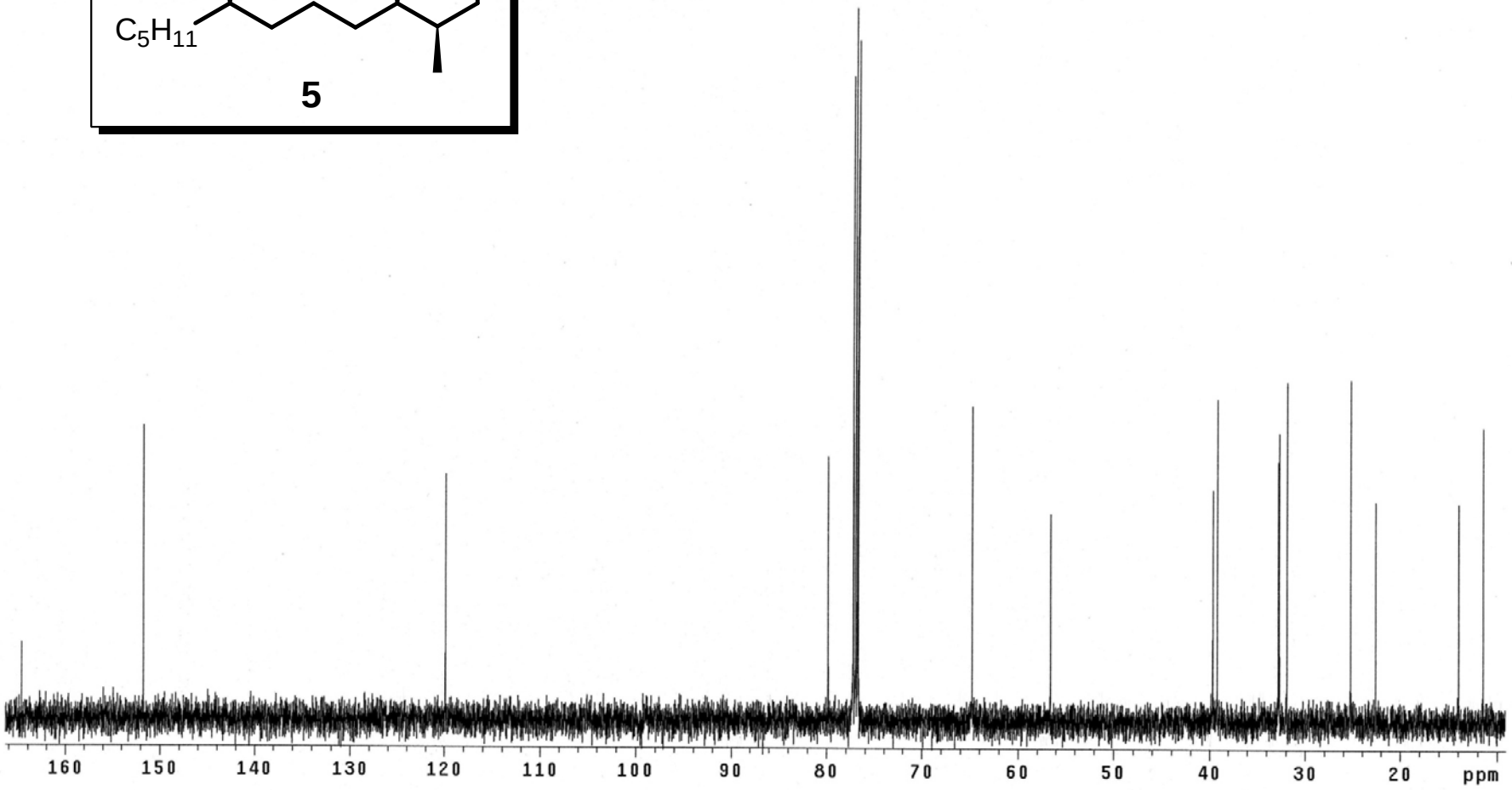

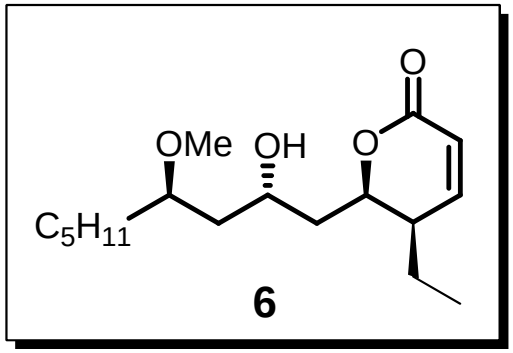

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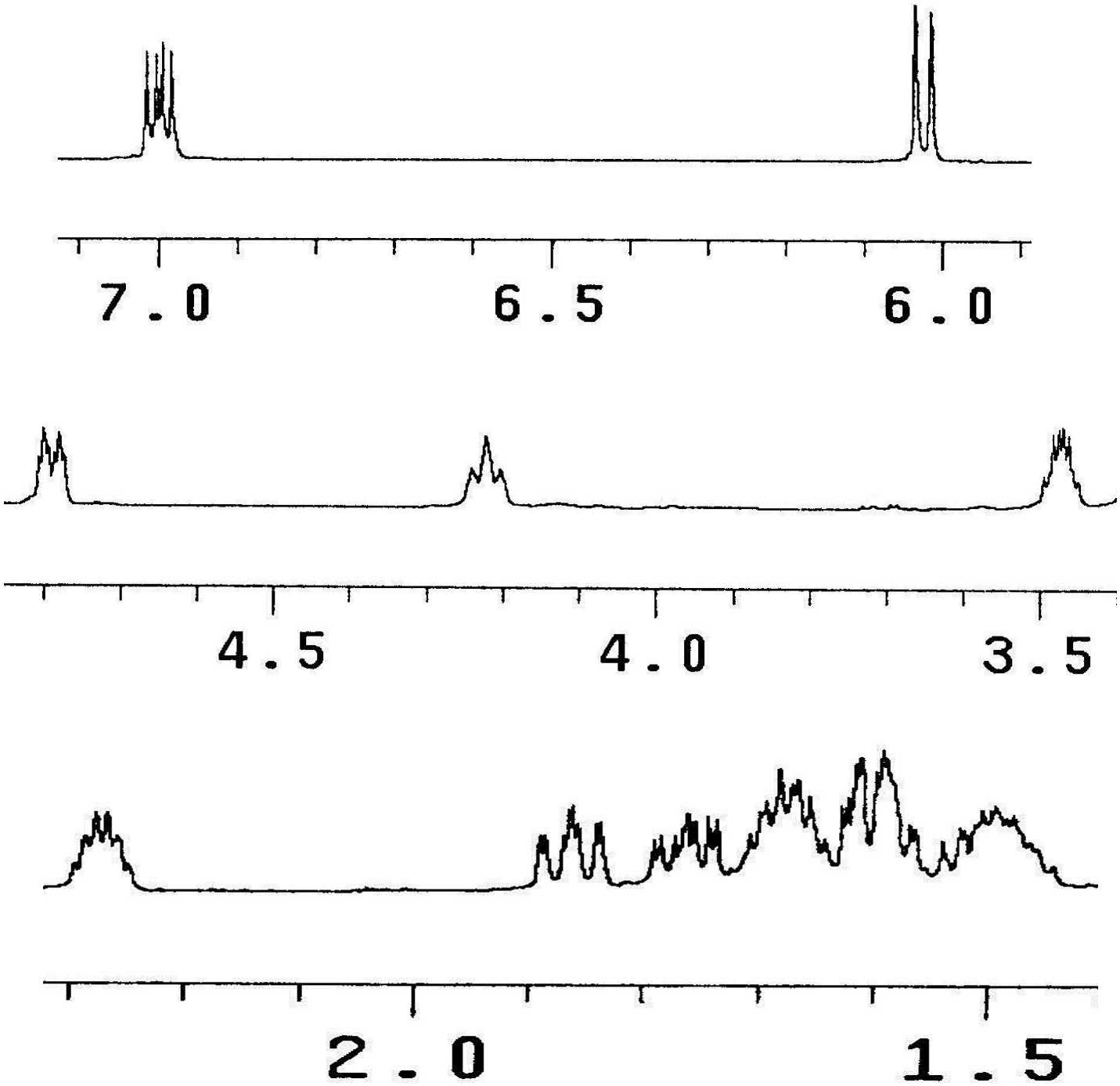

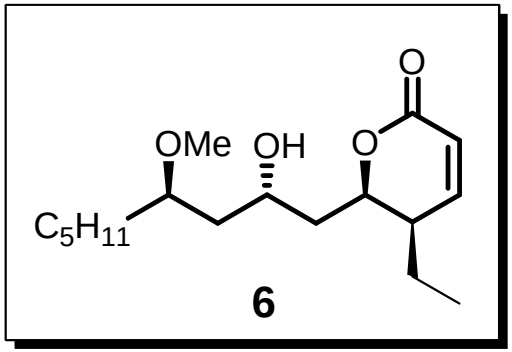

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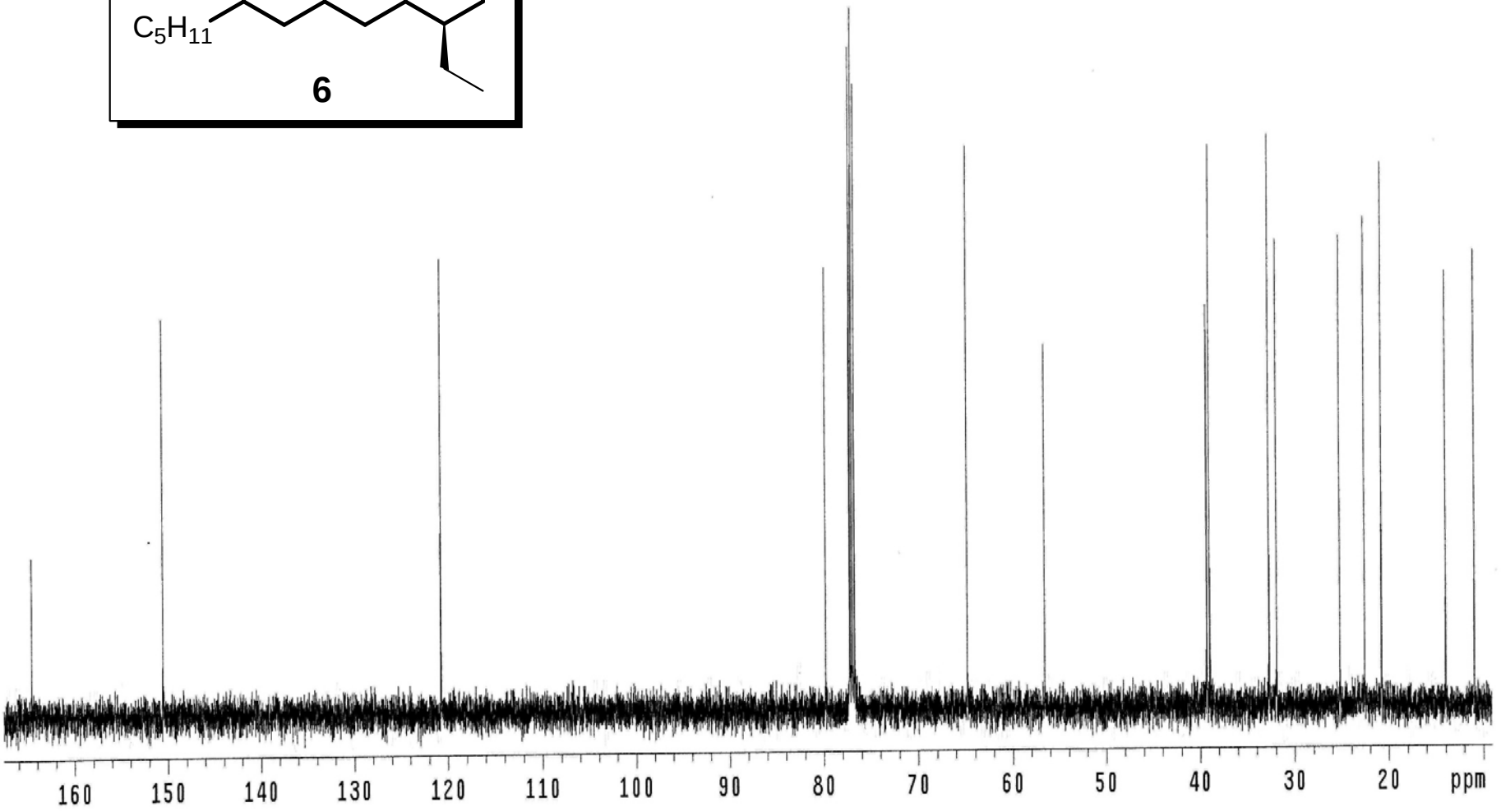

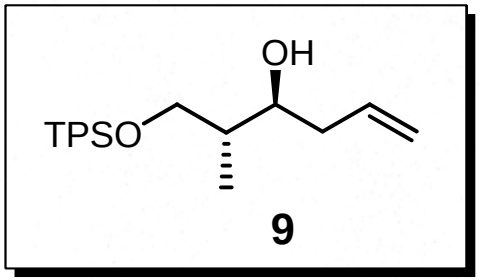

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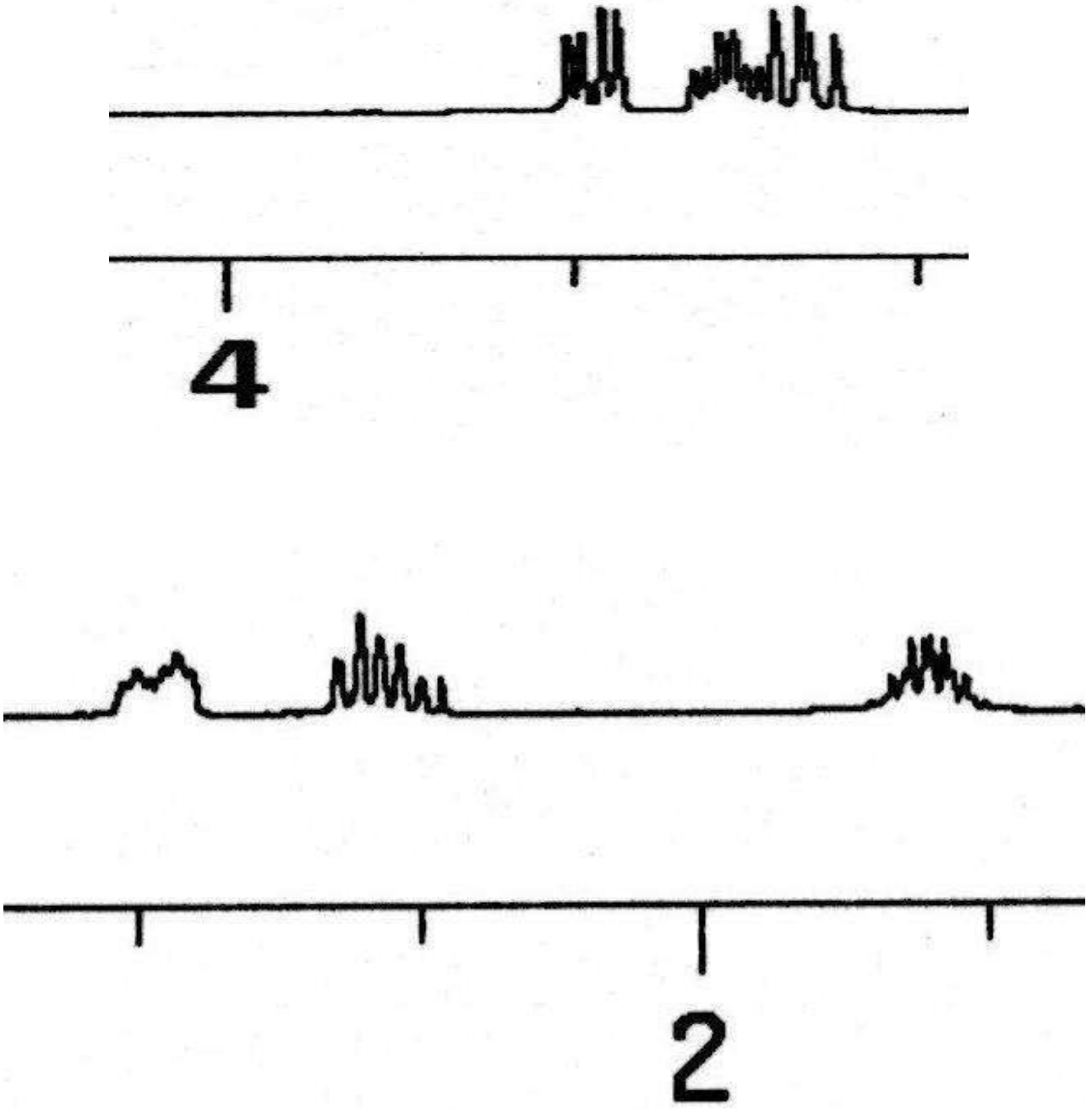

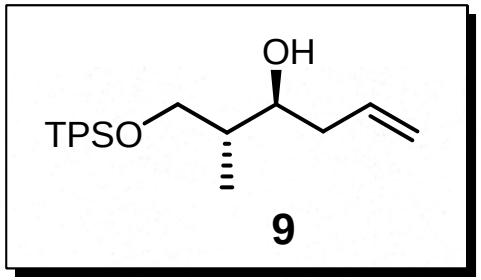

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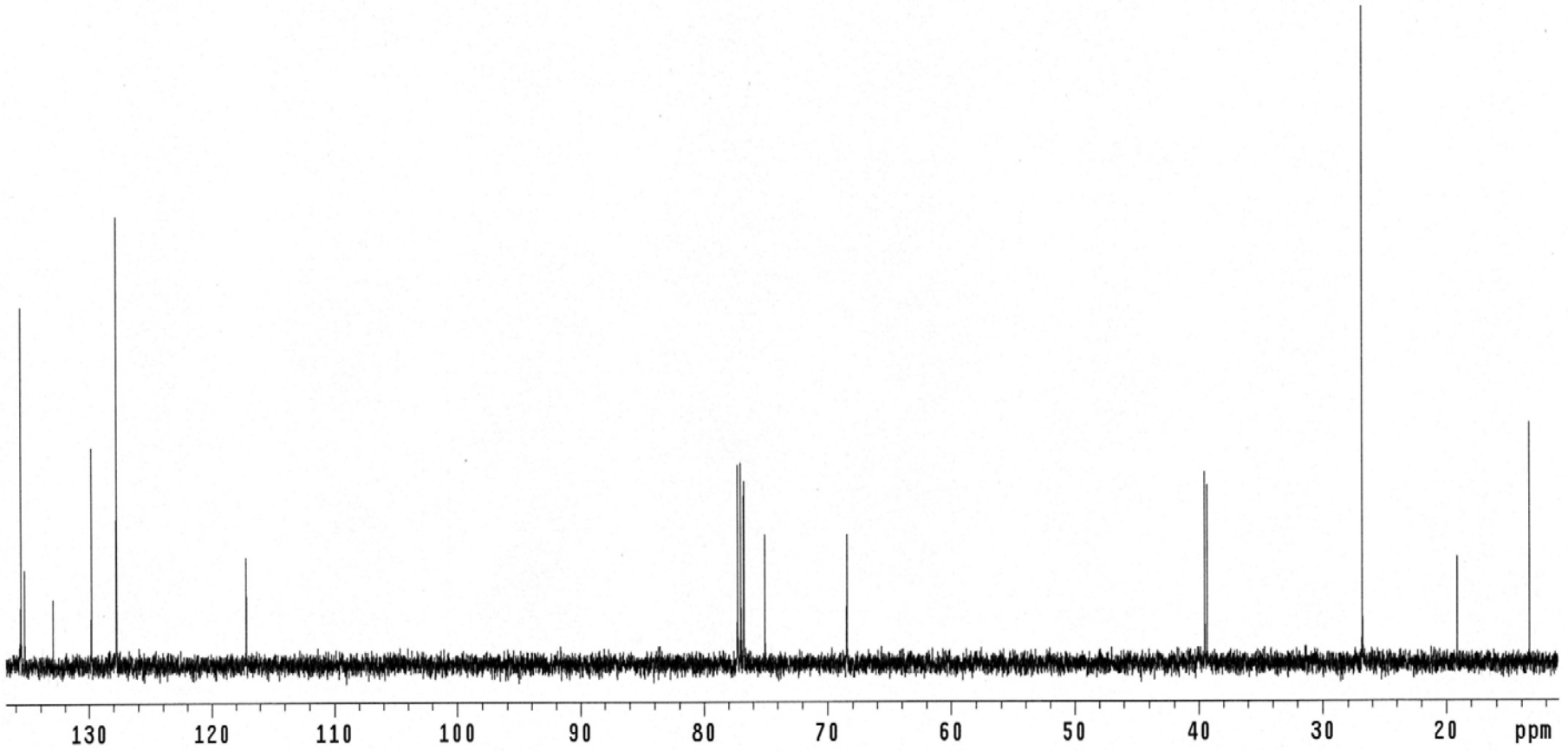

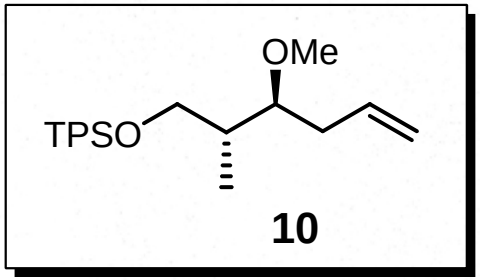

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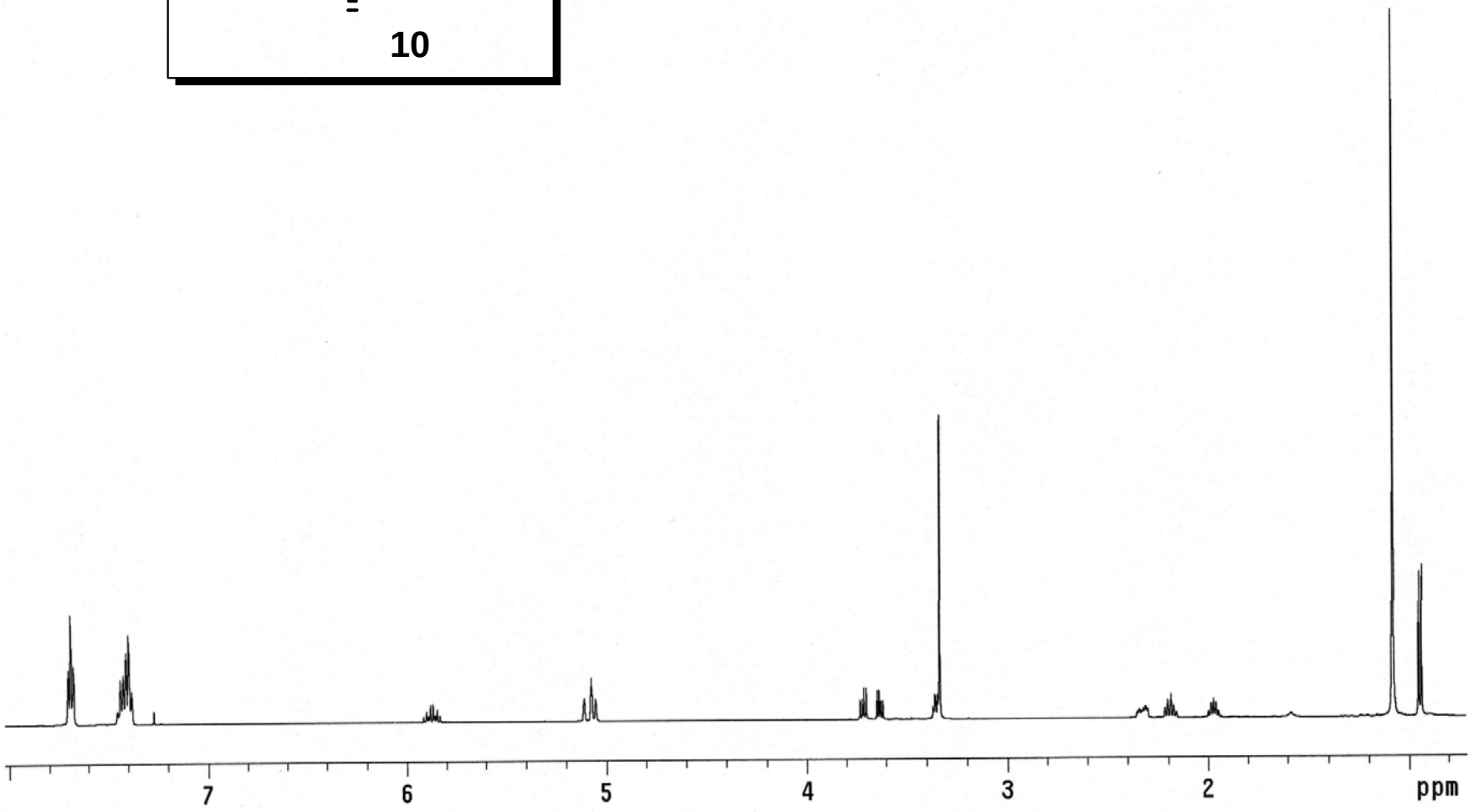

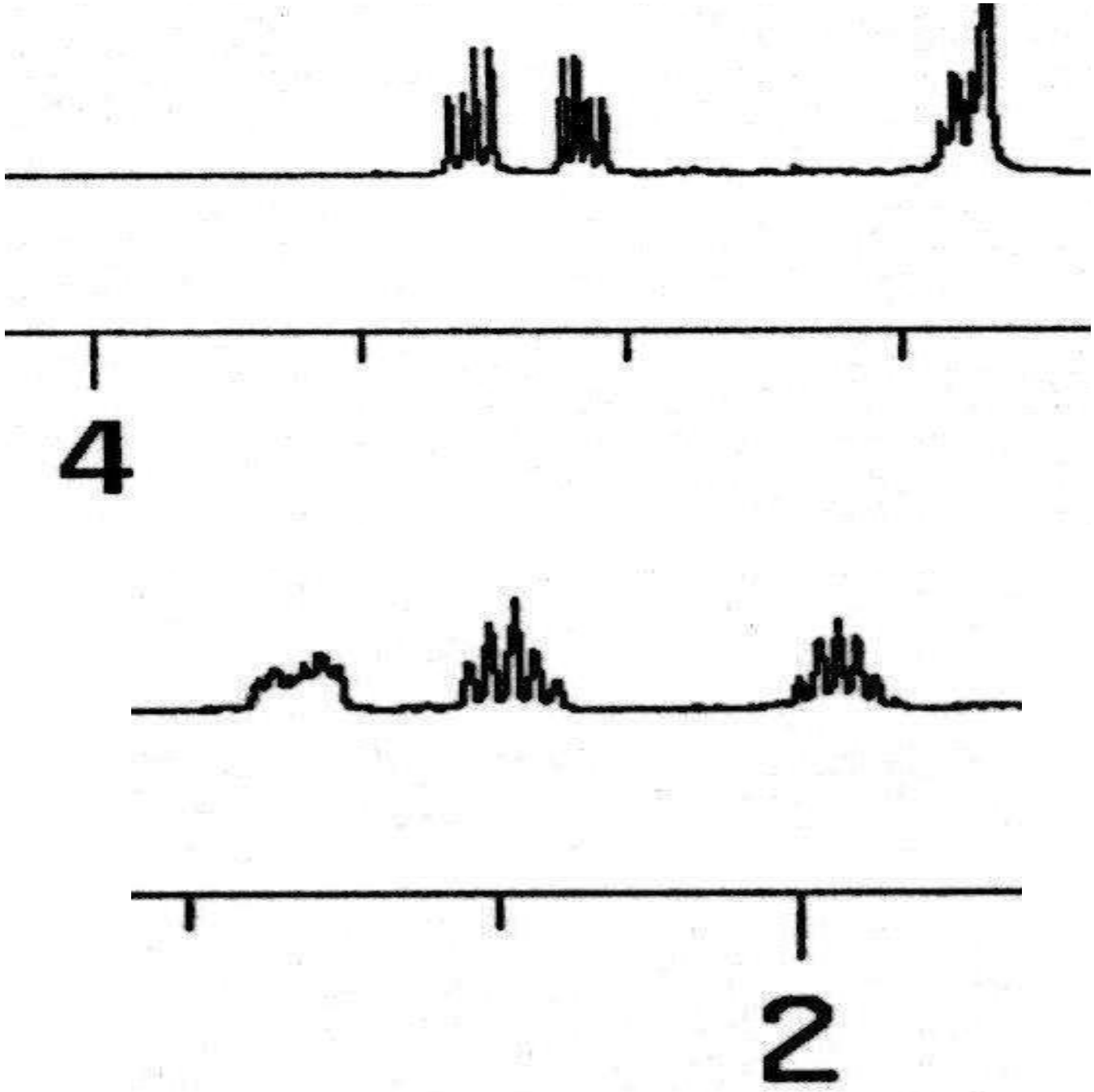

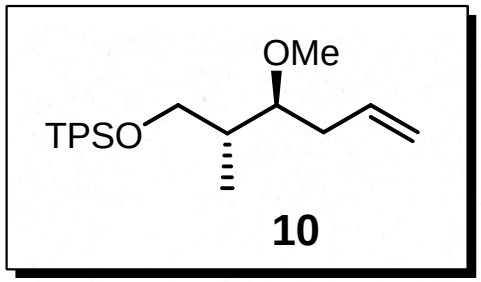

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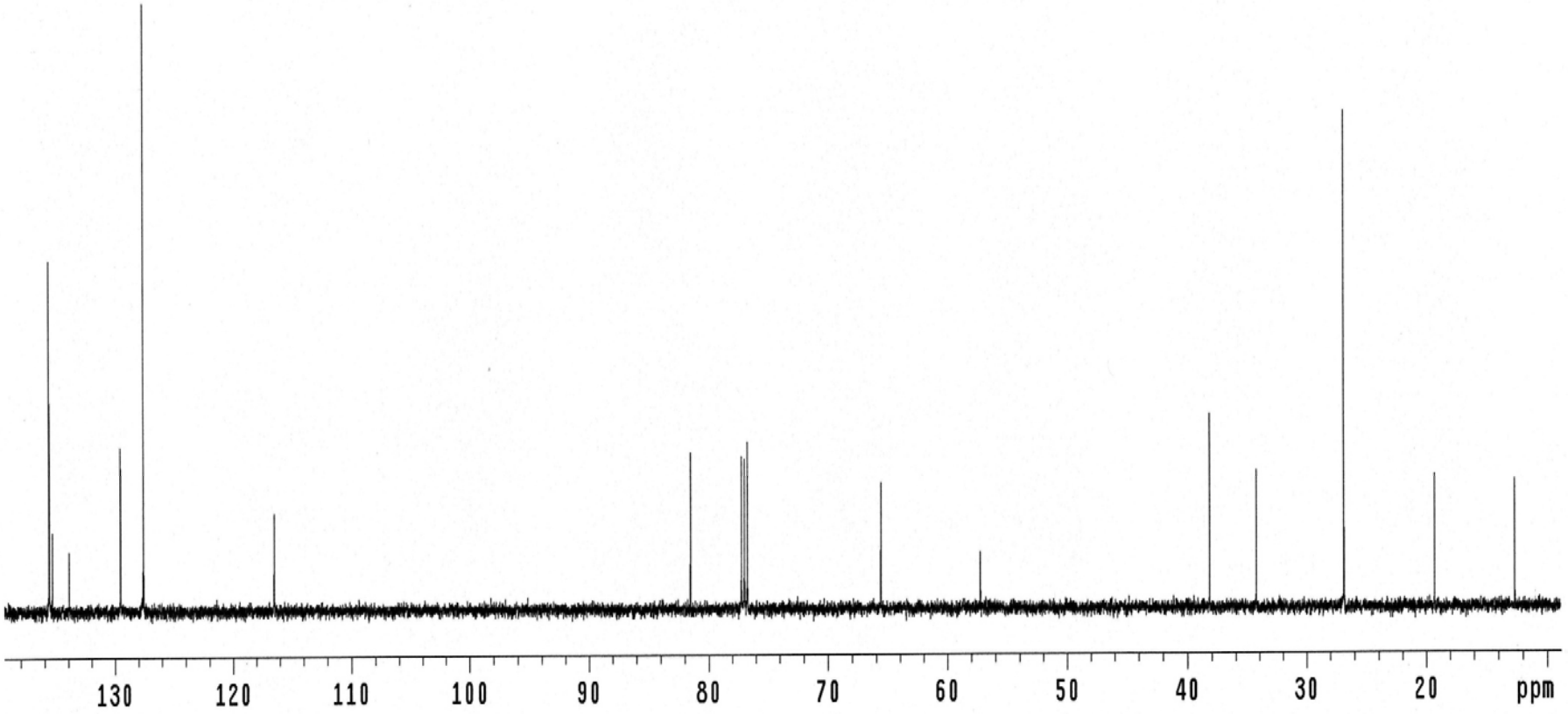

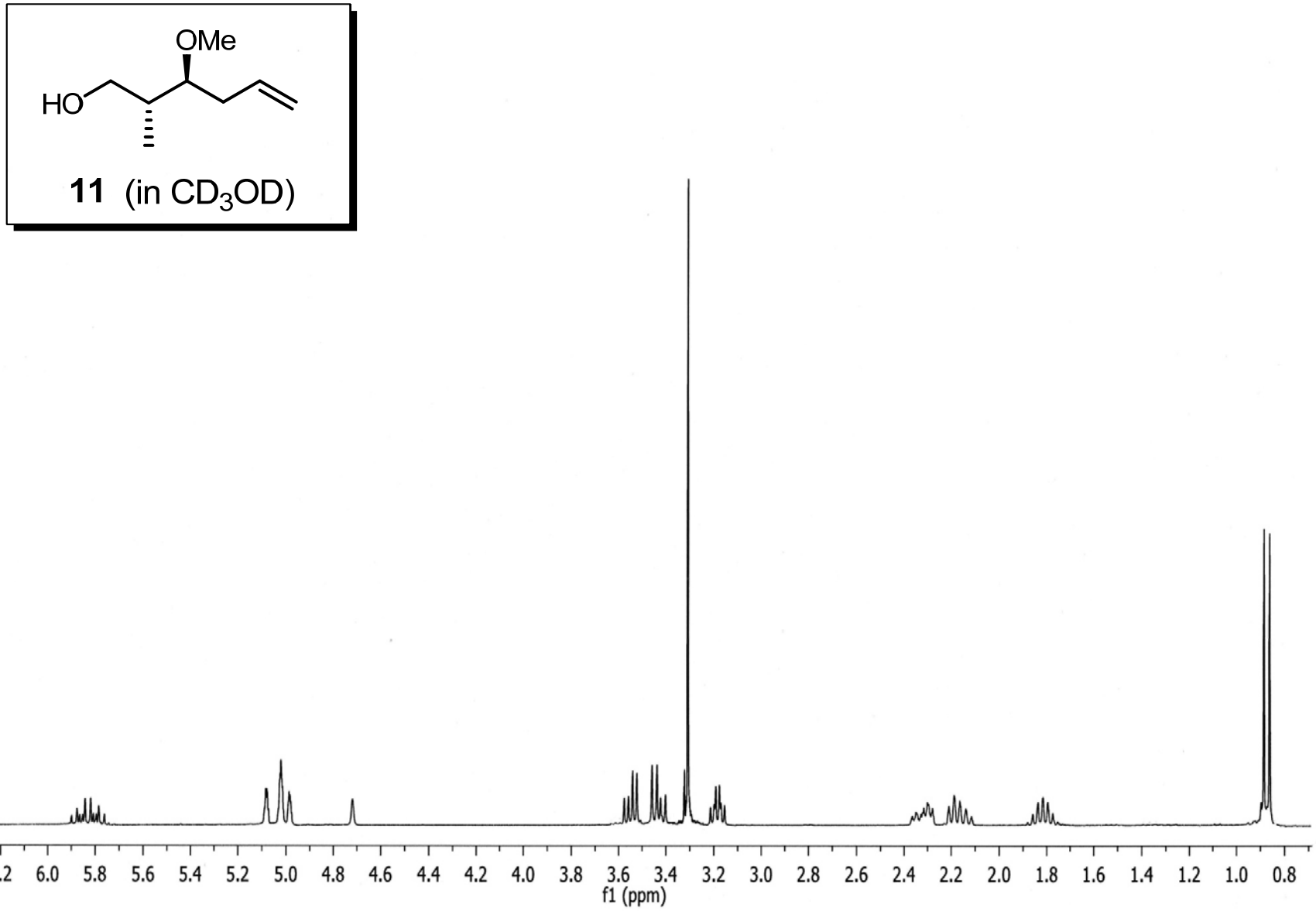

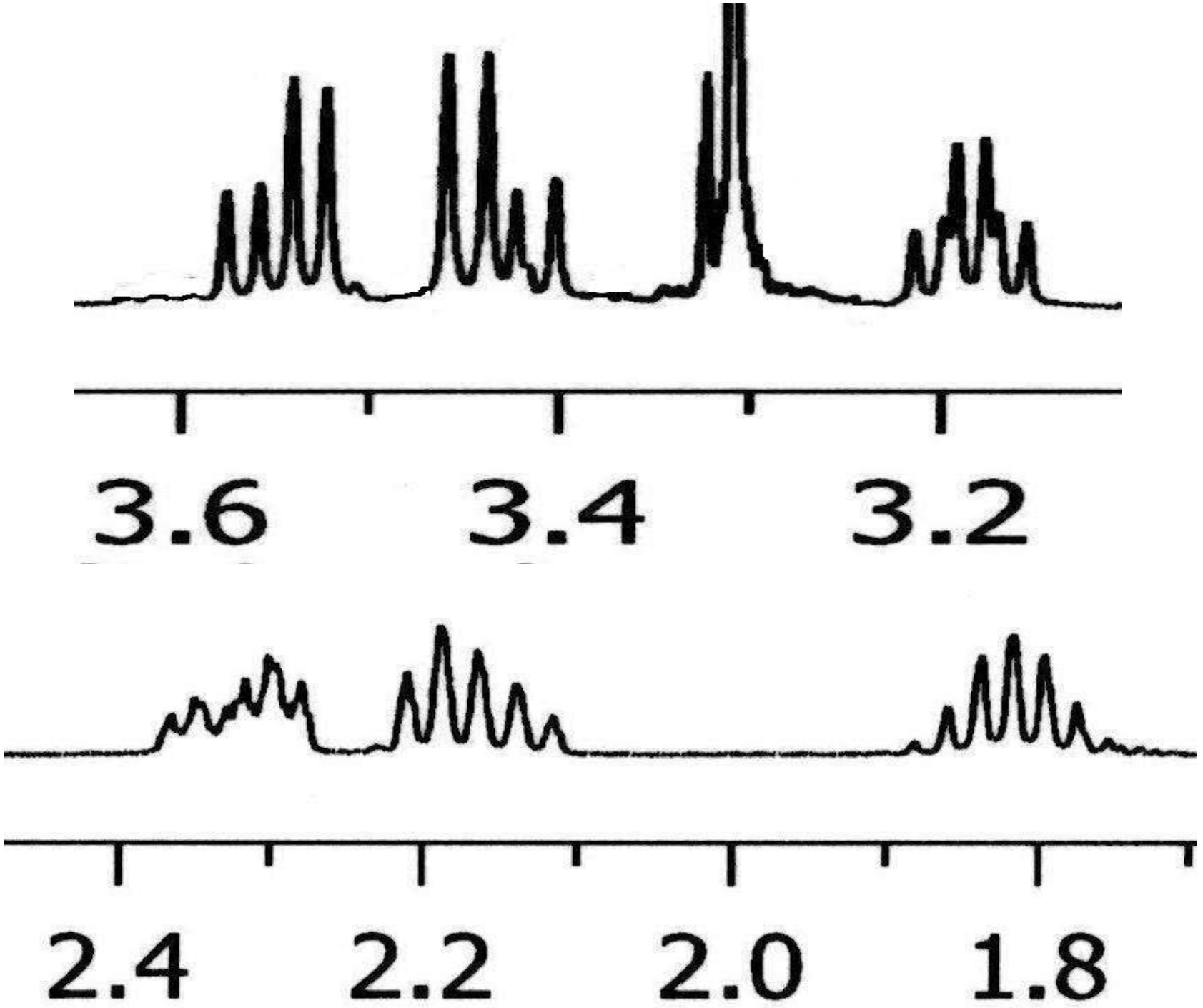

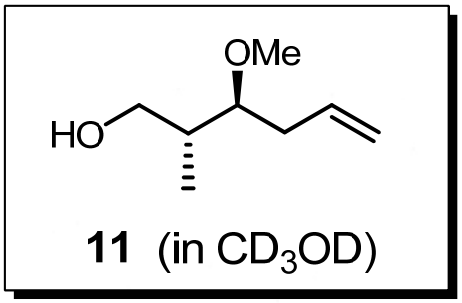

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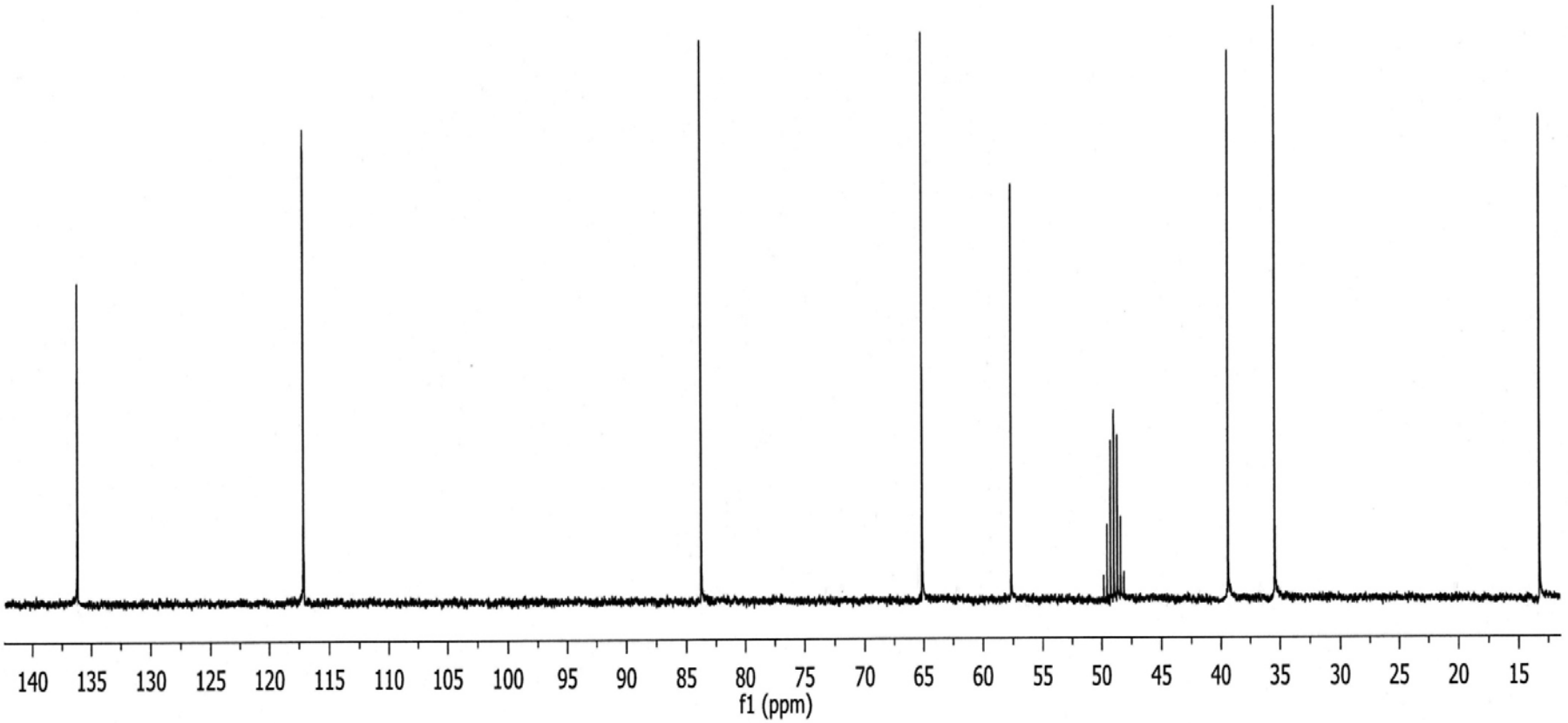

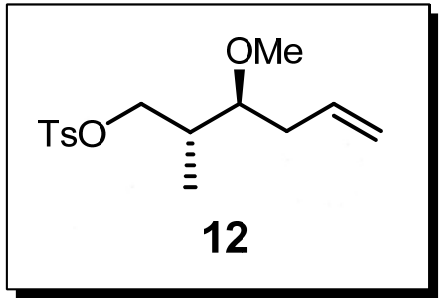

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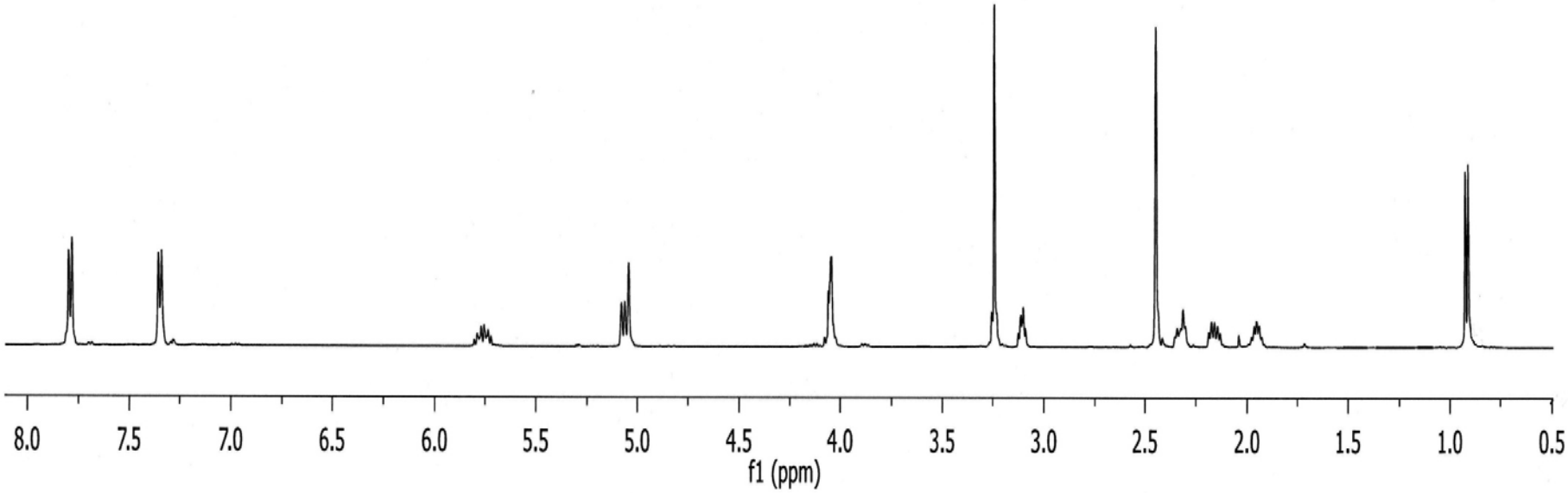

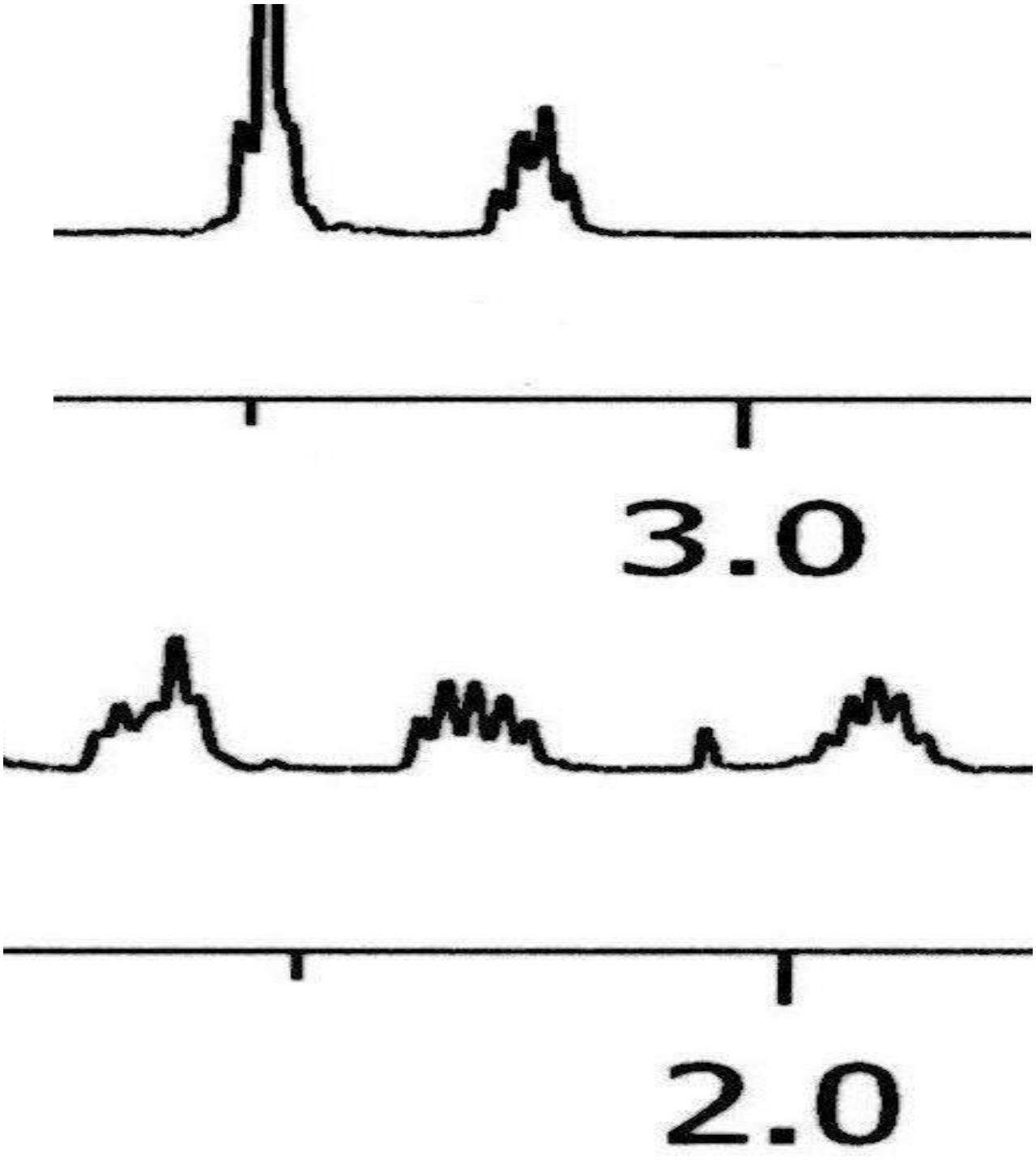

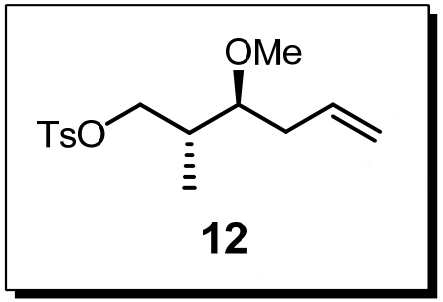

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