

Further Investigation of Pyranone Activation

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Supporting Information

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GENERAL METHODS

Reactions were carried out in sealed vials or round bottoms flasks under atmospheric conditions unless otherwise noted. Diethyl ether (Et₂O) was dried over pressed Na. All other commercially available anhydrous solvents and reagents were used as received. Thin layer chromatography was performed with glass or aluminum plates (silica gel F₂₅₄, Art 5715, 0.25 mm), visualized by fluorescence quenching under UV light, and stained with potassium permanganate. Flash column chromatography was performed with silica gel 60 (200-400 mesh) as described by Still.¹ Mass spectral data was acquired using positive mode Electrospray Ionization (ESI+) and a high resolution Time of Flight (TOF) mass spectrometer. Infrared spectra were acquired on a FTIR spectrometer and were reported as wavenumbers (cm⁻¹). ¹H NMR spectra were acquired at 400 or 500 MHz and ¹³C NMR spectra were acquired at 100 MHz or 125 MHz where noted. ¹H and ¹³C NMR chemical shifts are reported as in ppm, (δ) relative to the residual solvent peaks. ¹H NMR coupling constants (*J*) are reported in Hertz (Hz), and multiplicities are indicated as follows: s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), td (triplet of doublets), ddt (doublet of doublet of triplets), dq (doublet of quartets), qq (quartet of quartets), m (multiplet), app. (apparent). Based on intensity in the ¹³C spectra, both magnetic and chemical shift equivalent peaks are noted in parentheses.

¹ Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

GENERAL PROCEDURES FOR ACID-MEDIATED REACTIONS (TABLES 1 & 2)

General Procedures for Acid Screening (Table 1):

To a 1 dram vial was added the appropriate pyranone² (0.1 mmol, 1.0 equiv.) as a stock solution in 1:1 CH₃CN:H₂O or 1:1 CH₃CN:CH₃OH where noted (0.1 M). Next, the appropriate acid was added (0.1 mmol, 1.0 equiv.). The vial capped and stirred at the appropriate temperature.

General Procedure for Acid-Mediated Exchange Studies (Table 2): To a 1 dram vial was added the appropriate pyranone (0.1 mmol, 1.0 equiv.) as a stock solution in 1:1 CH₃CN:H₂O or 1:1 CH₃CN:CH₃OH as appropriate (0.1 M). Next, acid was added (0.1 mmol, 1.0 equiv.). The vial capped and stirred at room temperature. At various time points throughout the reaction 200 μ L aliquots were removed, concentrated *via* rotary evaporation, and re-dissolved in 0.7 mL of a stock solution of 1,3,5-trimethoxybenzene in CDCl₃ (0.00286 M, 0.002 mmol per aliquot) as an internal standard. This solution was transferred to an NMR tube for analysis and determination of yield.

² Hydroxypyranone **1a** and acetoxy pyranone **1b** were both synthesized according to previous reports: (a) Sammes, P. G.; Street, L. J. *J. Chem. Soc. Perkin. Trans. 1*, **1983**, 2729. (b) Woodall, E. L.; Simanis, J. A.; Hamaker, C. H.; Goodell, J. R.; Mitchell, T. A. *Org. Lett.* **2013**, *15*, 3270.

CHARACTERIZATION OF CYCLOADDUCT 2 AND BY-PRODUCTS 3 & 4 (TABLE 1)

Cycloadduct 2: Cycloadduct isolated from a reaction unrelated to this report. $^1\text{H NMR}$: (400 MHz, CDCl_3) δ 7.13 (dd, $J = 9.8, 4.4$ Hz, 1H), 5.96 (d, $J = 9.8$, 1H), 4.88 (dd, $J = 6.6, 4.4$ Hz, 1H), 2.45-2.38 (m, 1H), 2.35-2.28 (m, 1H), 2.16 (dd, $J = 12.0, 8.8$ Hz, 1H), 1.98-1.76 (m, 4H), 1.73-1.68 (m, 1H), 1.63-1.57 (m, 1H). Spectral data is consistent with that of previously reported data.^{2,3}

Ketone by-product 3: By product isolated from a reaction unrelated to this report. $^1\text{H NMR}$: (400 MHz, CDCl_3) δ 7.57 (dd, $J = 1.7, 0.8$ Hz, 1H), 7.18 (dd, $J = 3.6, 0.8$ Hz, 1H), 6.52 (dd, $J = 3.6, 1.7$ Hz, 1H), 5.81 (ddt, $J = 17.0, 10.3, 6.7$ Hz, 1H), 5.07-4.98 (m, 2H), 2.83 (m, 2H), 2.14 (m, 2H), 1.83 (m, 2H) ppm; $^{13}\text{C NMR}$: (100 MHz, CDCl_3) δ 189.6, 153.0, 146.3, 138.1, 116.9, 115.5, 112.3, 37.8, 33.3, 23.4 ppm. Spectral data is consistent with that of previously reported data.⁴

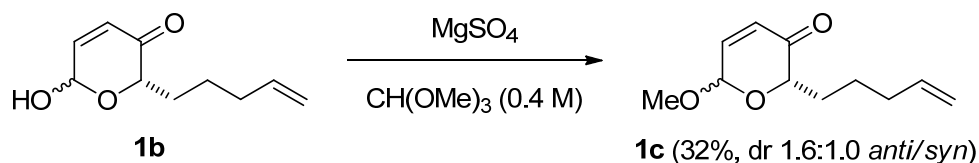
Butenolide By-Product 4: By product isolated as a ~4:1 mixture of geometrical stereoisomers from a reaction unrelated to this report. $^1\text{H NMR}$: (400 MHz, CDCl_3) δ 7.61 (dd, $J = 5.6, 0.7$ Hz, 0.25 H), 7.32 (d, $J = 5.4$ Hz, 1H), 6.19 (dd, $J = 5.6, 1.8$ Hz, 0.25 H), 6.15 (dd, $J = 5.4, 0.5$ Hz, 1H), 5.85-5.73 (m, 1.5 H), 5.30 (t, $J = 7.8$ Hz, 1H), 5.05-4.99 (m, 2.5 H), 2.45-2.39 (m, 2H), 2.33-2.27 (m, 0.5 H), 2.14-2.08 (m, 2.5 H), 1.62-1.55 (m, 2.5 H). Spectral peaks associated with the butenolide core are consistent with that of similar butenolides synthesized in a previously published report.⁵

³ Burns, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 14578.

⁴ Singh V.; Singh. V. *Synth. Commun.* **2010**, *40*, 1280-1291.

⁵ Curti, C.; et. al. *Org. Lett.*, **2011**, *13*, 4738-4741.

PREPARATION AND CHARACTERIZATION OF PYRANONE **1c**



Alternative Conditions⁶ toward Pure Diastereomers of Methoxypyranone **1c:** To a solution of crude hydroxypyranone **1a** (7.61 g, 41.8 mmol, 1.0 equiv) was added trimethyl orthoformate (111 mL) followed by MgSO₄ (12.6 g, 105 mmol, 2.5 equiv). The resulting solution was stirred under reflux for 19 h. The solution was warmed to room temperature and diluted with CH₂Cl₂. The reaction was washed with sat. aq. NaCl (2 x 50 mL), dried with MgSO₄, filtered, and concentrated to provide crude **1c** as a mixture of diastereomers (dr 1.6:1.0 *anti/syn*). Purification by flash column chromatography (hexanes:Et₂O 90:10) delivered *anti-1c*/*syn-1c* mixture as a yellow oil (45.7 mg, 0.23 mmol, 28%, dr 3.5:1.0) and *syn-1c* as a yellow oil (6.6 mg, 0.03 mmol, 4%, dr >19:1). A second purification by flash column chromatography (heptane:Et₂O 80:20) afforded a single diastereomer (dr >19:1) of *anti-1c* for characterization. *anti-1c*: **R_f** = 0.72 (heptane:Et₂O 70:30 (x3)); ¹H NMR (500 MHz, CDCl₃) δ 6.83 (dd, *J* = 10.4, 3.5 Hz, 1H), 6.08 (dd, *J* = 10.4, 0.5 Hz, 1H), 5.85-5.78 (m, 1H), 5.10 (dd, *J* = 3.5, 0.5 Hz, 1H), 5.05-5.00 (m, 1H), 4.98-4.95 (m, 1H), 4.39 (dd, *J* = 8.5, 3.6 Hz, 1H), 3.52 (s, 3H), 2.13-2.08 (m, 2H), 2.00-1.96 (m, 1H), 1.73-1.52 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 196.7, 143.3, 138.6, 127.9, 114.9, 94.3, 74.0, 56.6, 33.7, 29.1, 24.6; **IR (film)** ν_{max} 1687, 1641, 1047 cm⁻¹; **EI-HRMS** calculated for C₁₁H₁₆O₃ [M]⁺ 196.10095, found 196.11026. *syn-1c*: **R_f** = 0.67 (heptane:Et₂O 70:30 (x3)); ¹H NMR (500 MHz, CDCl₃) δ 6.86 (dd, *J* = 10.4, 1.9 Hz, 1H), 6.12 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.84-5.77 (m, 1H), 5.23-5.21 (m, 1H), 5.04-5.00 (m, 1H), 4.97-4.94 (m, 1H), 4.05 (m, 1H), 3.56 (s, 3H), 2.13-2.07 (m, 2H), 1.99-1.92 (m, 1H), 1.85-1.78 (m, 1H), 1.68-1.51 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 196.6, 146.5, 138.5, 128.8, 114.9, 96.9, 79.0, 56.4, 33.6, 31.0, 24.9; **IR (film)** ν_{max} 1692, 1641, 1050 cm⁻¹; **ESI-HRMS** calculated for C₁₁H₁₆O₃ [M+H]⁺ 197.1178, found 197.1183.

⁶ Torii, S.; Tanaka, H.; Anoda, T.; Simizu, Y. *Chem. Lett.* **1976**, *5*, 495.

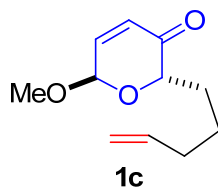
GENERAL PROCEDURE FOR MICROWAVE-ASSISTED REACTIONS (TABLE 3)

To a 10 mL microwave reactor vial was added the appropriate pyranone (0.1 mmol, 1.0 equiv.) as a stock solution in 1:1 CH₃CN:CH₃OH (0.1 M). To the vessel was added a stir bar and a silicone/PFTE vial cap. The resulting solution was heated via microwave with stirring at various temperatures. A ramp time of 2 minutes was used to achieve the appropriate temperatures, and after reaching the desired temperature solutions were stirred for 10 minutes. Upon completion of heating 200 μ L aliquots were removed, concentrated *via* rotary evaporation, and re-dissolved in 0.7 mL of a stock solution of 1,3,5-trimethoxybenzene in CDCl₃ (0.00286 M, 0.002 mmol per aliquot) as an internal standard. This solution was transferred to an NMR tube for analysis and determination of yield.

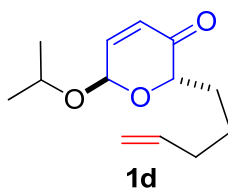
GENERAL PROCEDURE FOR MICROWAVE-ASSISTED REACTIONS (TABLE 4)

To a 10 mL microwave vessel was added acetoxypyranone *anti*-**1b** (1.0 equiv.) and alcohol (2.0 equiv.) dissolved in acetonitrile (1 M). To the vessel was added a stir bar and a silicone/PFTE vial cap. The resulting solution was heated via microwave for 1 h at 160 °C with an 8 min ramp time. The solution was then concentrated, and purified by flash column chromatography. Yields represent the combination of diastereomers, while spectral information represents the specific diastereomer shown.

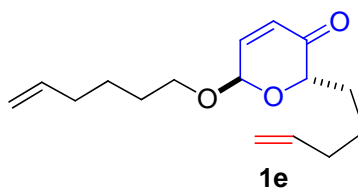
PREPARATION AND CHARACTERIZATION OF PYRANONES **1c-1g**



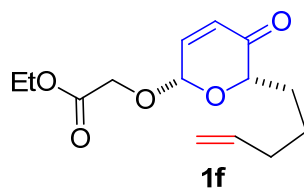
Prepared according to the general procedure with *anti-1b* (208 mg, 0.927 mmol), MeOH (75 μ L, 1.85 mmol), and CH₃CN (925 μ L). Purification by flash column chromatography (hexanes:EtOAc 90:10) delivered *anti-1c* as a white solid (35 mg, 0.18 mmol, 20%, dr >19:1), and *anti-1c/syn-1c* mixture as a yellow oil (89 mg, 0.45 mmol, 49%, dr 1.4:1.0). Spectral data matched that obtained from the alternative conditions toward pure diastereomers of methoxypyranone **1c** (*vide supra*).



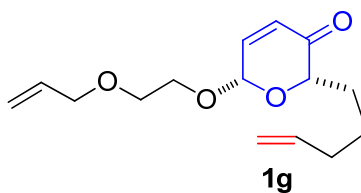
Prepared according to the general procedure with *anti-1b* (200 mg, 0.892 mmol), *i*PrOH (107 mg, 1.78 mmol), and CH₃CN (890 μ L). Purification by flash column chromatography (hexanes:EtOAc 90:10) delivered *anti-1d* as a pale yellow oil (49 mg, 0.22 mmol, 25%, dr >19:1), *anti-1d/syn-1d* mixture as a yellow oil (76 mg, 0.34 mmol, 38%, dr 1.7:1.0), and *anti-1d/syn-1d* mixture as a yellow oil (11 mg, 0.05 mmol, 5%, dr 0.13:1.0); Characterization data for *anti-1d*: R_f = 0.49 (hexanes:EtOAc 85:15); ¹H NMR (500 MHz, CDCl₃) δ 6.80 (dd, J = 10.2, 3.6 Hz, 1H), 6.06 (dd, J = 10.2, 0.6 Hz, 1H), 5.85-5.77 (m, 1H), 5.30 (dd, J = 3.6, 0.6 Hz, 1H), 5.03-4.99 (m, 1H), 4.97-4.94 (m, 1H), 4.44 (dd, J = 8.4, 3.6 Hz, 1H), 4.05 (qq, J = 6.3, 6.1 Hz, 1H), 2.15-2.05 (m, 2H), 2.01-1.95 (m, 1H), 1.72-1.64 (m, 1H), 1.60-1.49 (m, 2H), 1.27 (d, J = 6.3 Hz, 3H), 1.23 (d, J = 6.1 Hz, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 196.9, 144.0, 138.4, 127.5, 114.7, 91.3, 73.8, 70.8, 33.5, 29.1, 24.5, 23.3, 21.8; IR (film) ν_{\max} 1700, 1049 cm⁻¹; ESI-HRMS calculated for C₁₃H₂₀O₃ [M+Li]⁺ 231.1567, found 231.1560.



Prepared according to the general procedure with *anti*-**1b** (224 mg, 1.00 mmol, 1.0 equiv.), 5-hexen-1-ol (93.5 mg, 2.00 mmol, 2.0 equiv.), and CH₃CN (925 μ L). Purification by flash column chromatography (hexanes:Et₂O 85:15) delivered *anti*-**1e** as a pale yellow oil (112 mg, 0.42 mmol, 42%, dr >19:1), and *anti*-**1e**/*syn*-**1e** mixture as a yellow oil (54 mg, 0.20 mmol, 20%, dr 0.21:1.0); Characterization data for *anti*-**1e**: R_f = 0.26 (hexanes:Et₂O 85:15); ¹H NMR (500 MHz, CDCl₃) δ 6.83 (dd, J = 10.2, 3.5 Hz, 1H), 6.07 (dd, J = 10.2, 0.6 Hz, 1H), 5.86-5.76 (m, 2H), 5.19 (dd, 3.5, 0.6 Hz, 1H), 5.04-4.99 (m, 2H), 4.98-4.95 (m, 2H), 4.40 (dd, J = 8.4, 3.6 Hz, 1H), 3.85-3.80 (m, 1H), 3.6-3.56 (m, 1H), 2.15-2.04 (m, 4H), 2.02-1.95 (m, 1H), 1.68-1.46 (m, 7H); ¹³C NMR (400 MHz, C₆D₆) δ 195.4, 142.9, 138.31, 138.30, 127.1, 114.6, 114.5, 93.1, 73.8, 68.7, 33.5, 33.4, 29.13, 29.05, 25.4, 24.5; IR (film) ν_{\max} 1700, 1034 cm⁻¹; ESI-HRMS calculated for C₁₆H₂₄O₃ [M+Li]⁺ 271.1880, found 271.1892.



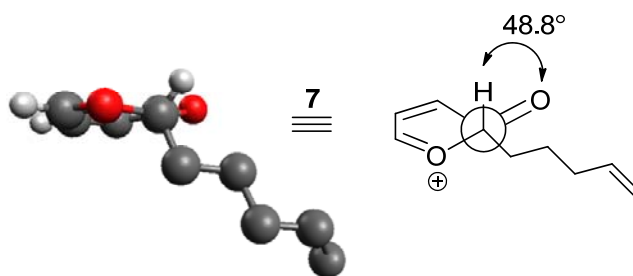
Prepared according to the general procedure with *anti*-**1b** (206 mg, 0.917 mmol), ethyl glycolate (191 mg, 1.83 mmol), and CH₃CN (915 μL). Purification by flash column chromatography (hexanes:EtOAc 85:15) delivered *anti*-**1f**/*syn*-**1f** mixture (111 mg) contaminated with cycloadduct **2** (13 mg) as a pale yellow oil (calc. 98 mg, 0.37 mmol, 40%, dr 1.49:1.0) and *syn*-**1f** as a yellow oil (11 mg, 0.045 mmol, 4%, dr >19:1); Characterization data for *syn*-**1f**: R_f = 0.21 (hexanes:EtOAc 85:15); ¹H NMR (400 MHz, CDCl₃) δ 6.98 (dd, J = 10.4, 2.1 Hz, 1H), 6.15 (dd, J = 10.4, 1.5 Hz, 1H), 5.84-5.74 (m, 1H), 5.46-5.45 (m, 1H), 5.04-4.99 (m, 1H), 4.98-4.94 (m, 1H), 4.37 (d, J = 16.4 Hz, 1H), 4.32 (d, J = 16.4 Hz, 1H), 4.27-4.21 (m, 2H), 4.08-4.04 (m, 1H), 2.15-2.01 (m, 2H), 1.97-1.78 (m, 2H), 1.65-1.48 (m, 2H), 1.30 (dd, J = 7.2, 7.1 Hz, 3H); ¹³C NMR (400 MHz, CDCl₃) δ 196.0, 169.7, 145.4, 138.2, 128.7, 114.9, 95.0, 79.0, 64.7, 61.2, 33.4, 31.1, 24.7, 14.2; IR (film) ν_{\max} 1751, 1699, 1063 cm⁻¹; ESI-HRMS calculated for C₁₄H₂₀O₅ [M+Li]⁺ 275.1466, found 275.1454.



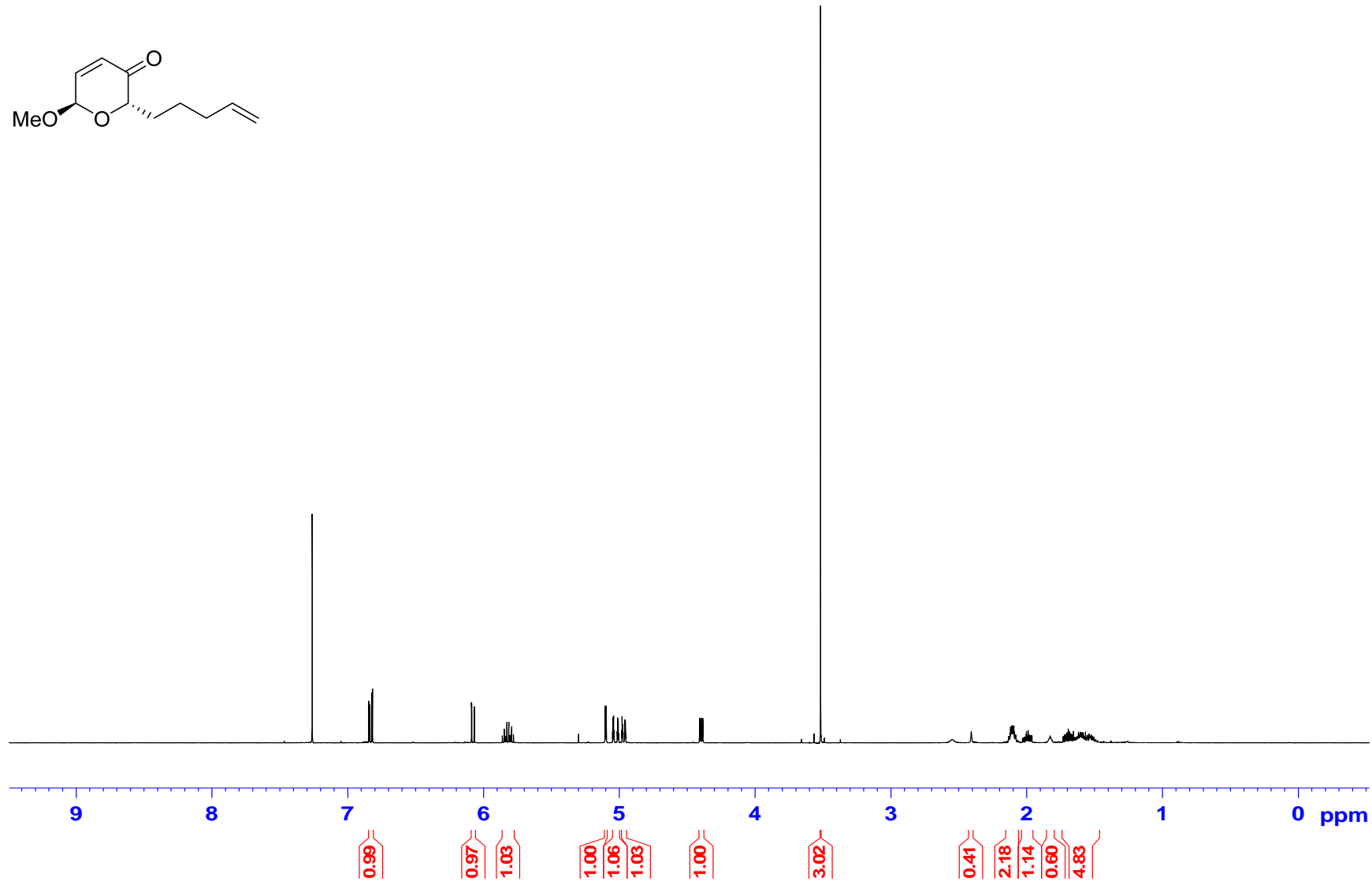
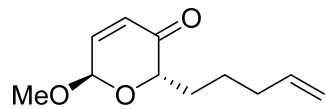
Prepared according to the general procedure with *anti*-**1b** (210 mg, 0.936 mmol), 2-allyloxyethanol (191 mg, 1.87 mmol) and CH₃CN (935 μL). Purification by flash column chromatography (hexanes:EtOAc 90:10) delivered *anti*-**1g**/*syn*-**1g** mixture (181 mg) contaminated with cycloadduct **2** (18 mg) as a pale yellow oil (calc. 163 mg, 0.61 mmol, 65%, dr 3.7:1.0) and *syn*-**1g** as a yellow oil (19 mg, 0.07 mmol, 8%, dr >19:1); Characterization data for *syn*-**1g**: $R_f = 0.15$ (hexanes:EtOAc 90:10); ¹H NMR (400 MHz, CDCl₃) δ 6.92 (dd, $J = 10.3, 1.9$, 1H), 6.12 (dd, $J = 10.3, 1.7$, 1H), 5.97-5.87 (m, 1H), 5.86-5.76 (m, 1H), 5.40-5.39 (m, 1H), 5.31-5.26 (m, 1H), 5.21-5.18 (m, 1H), 5.05-4.98 (m, 1H), 4.97-4.94 (m, 1H), 4.05-4.01 (m, 4H), 3.85-3.79 (m, 1H), 3.67-3.64 (m, 2H), 2.14-2.03 (m, 2H), 2.01-1.77 (m, 2H), 1.68-1.48 (m, 2H); ¹³C NMR (400 MHz, CDCl₃) δ 196.4, 146.6, 138.4, 134.6, 128.6, 117.3, 114.8, 96.0, 78.9, 72.3, 69.2, 68.1, 33.4, 30.7, 24.7; IR (film) ν_{\max} 1700, 1051 cm⁻¹; ESI-HRMS calculated for C₁₅H₂₂O₄ [M+H]⁺ 267.1596, found 267.1581.

COMPUTATIONAL METHODS AND EXPERIMENTAL PARAMETERS

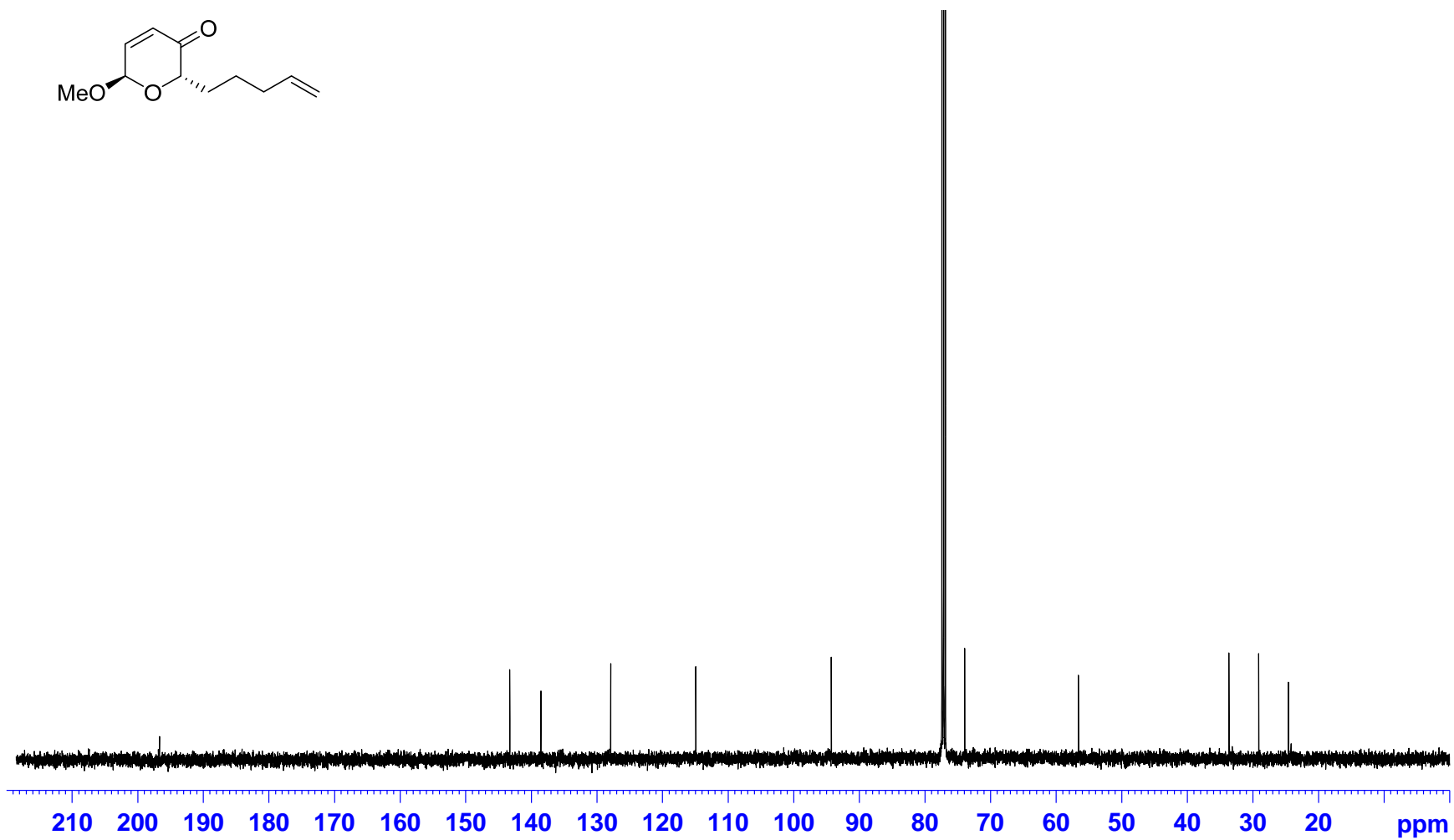
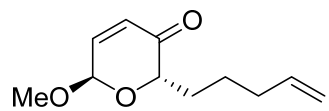
Conformation search of oxocarbenium **7** was performed. Initial structures were generated utilizing a systematic conformation searching approach, and minimized with the MMFF94 force field using the Spartan '02 software package (Wavefunction, Inc.). Multiple representative low energy conformers generated from the search were transferred to the Gaussian '03 software package (Gaussian, Inc.), and geometries were optimized using Density Functional Theory (DFT) at the B3LYP level of theory, and a 6-31G** basis set with d(6) Cartesian diffuse functions. Analysis of the optimized low energy conformer of **7** shows the α -hydrogen of oxocarbenium **7** at a dihedral angle of 48.8° with respect to the carbonyl.



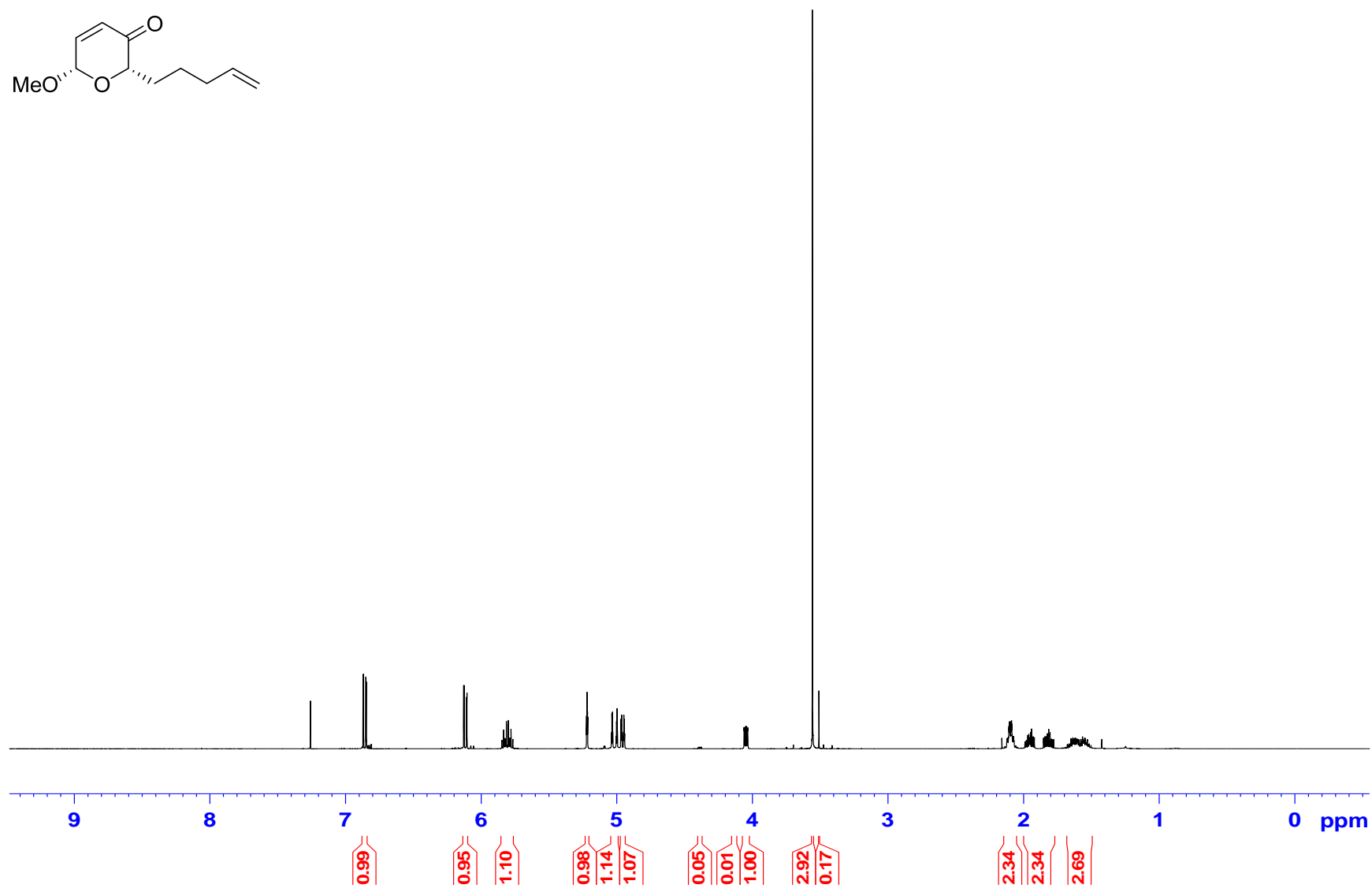
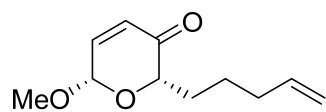
*hydrogens of the tether removed for simplicity



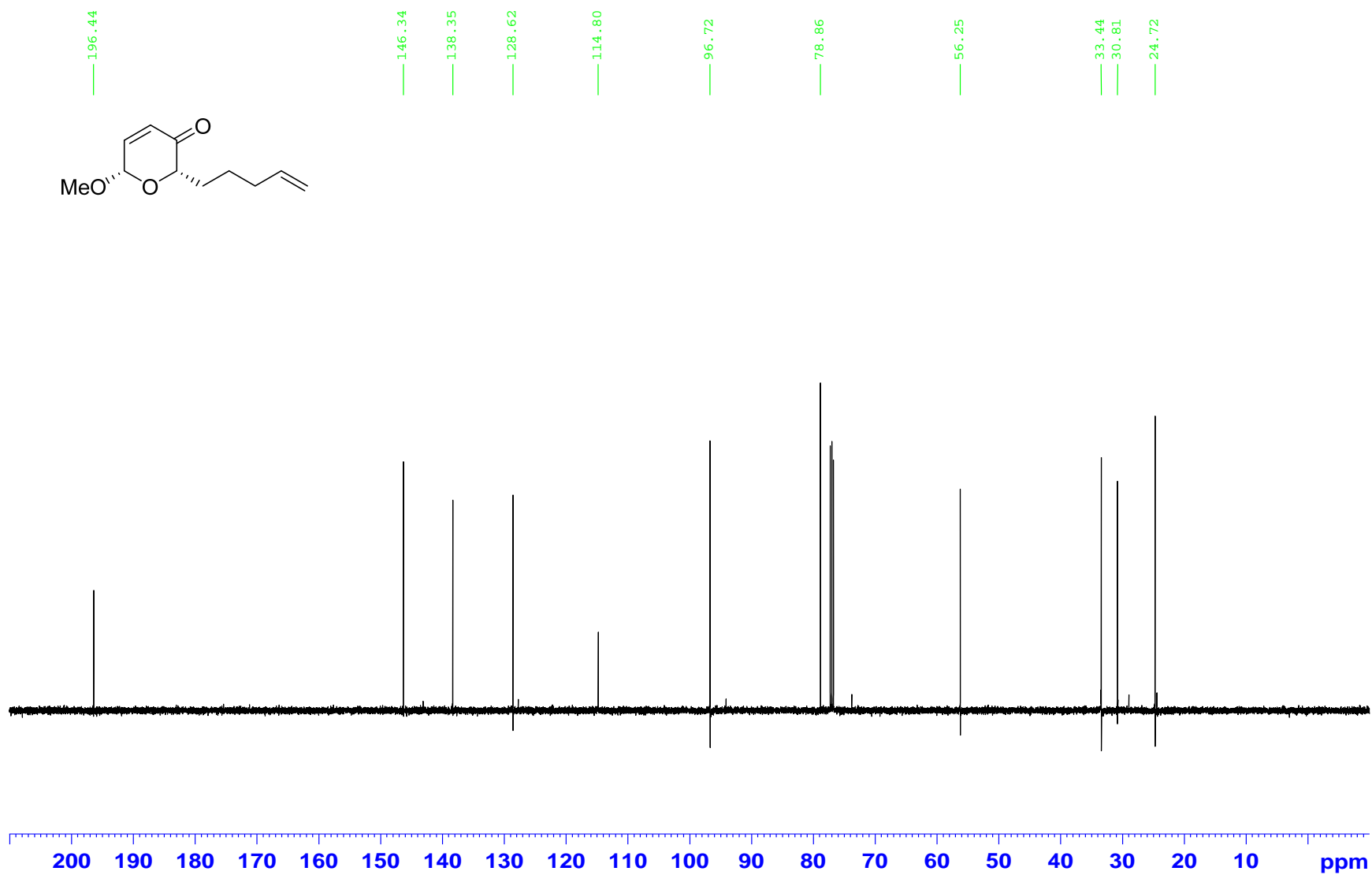
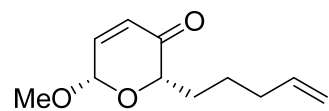
¹H NMR (500 MHz) of *anti*-Methoxypyranone 1c in CDCl₃



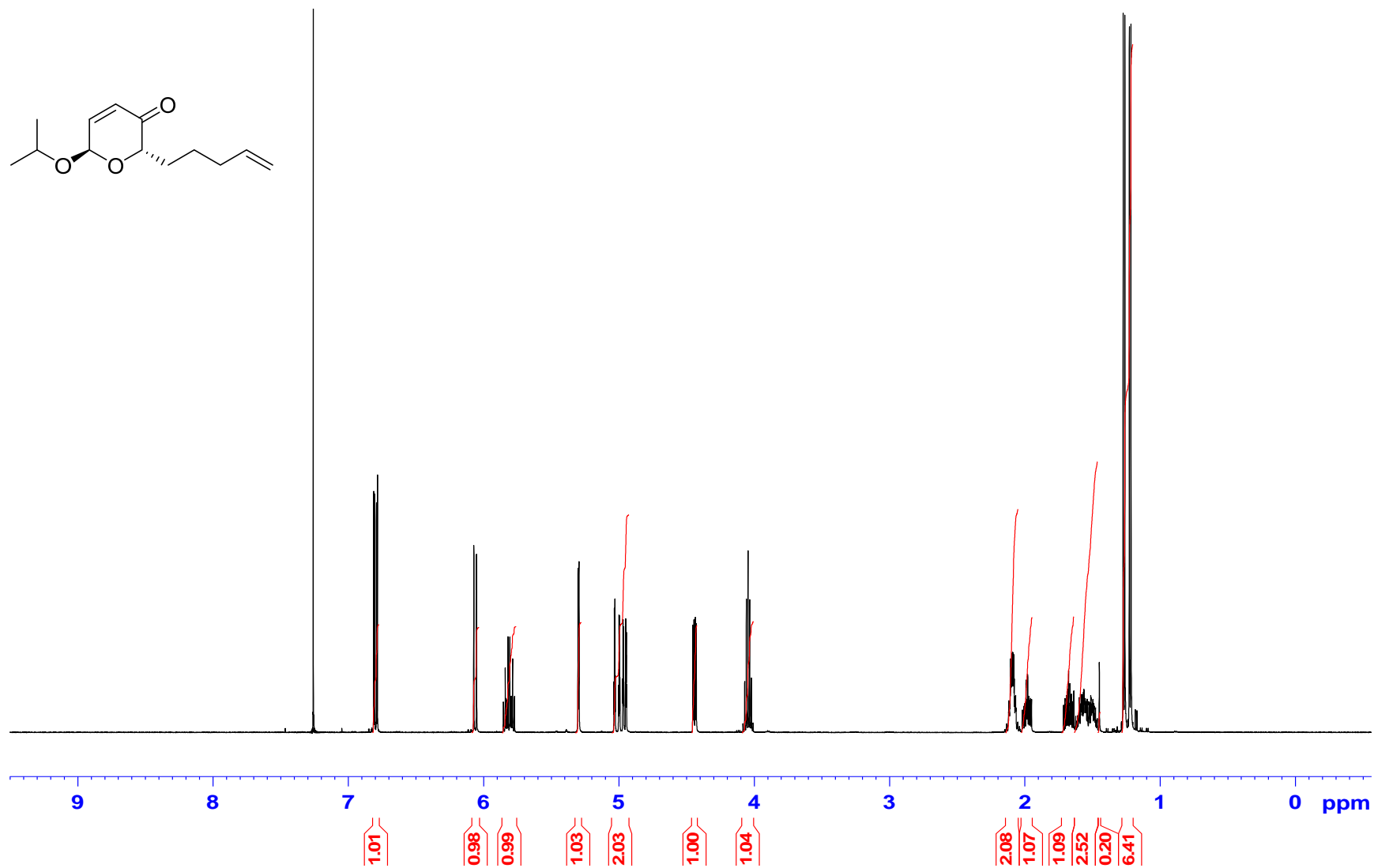
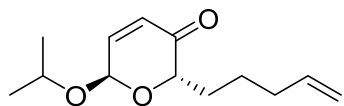
^{13}C NMR (125 MHz) of *anti*-Methoxypyranone 1c in CDCl_3



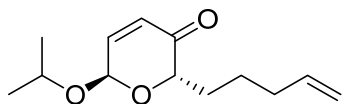
¹H NMR (500 MHz) of *syn*-Methoxypyranone 1c in CDCl₃



¹³C NMR (125 MHz) of *syn*-Methoxypyranone 1c in CDCl₃



¹H NMR (500 MHz) of *anti*-Isopropoxy-pyranone 1d in CDCl₃



196.86

144.04

138.42

127.53

114.74

91.29

73.83

70.81

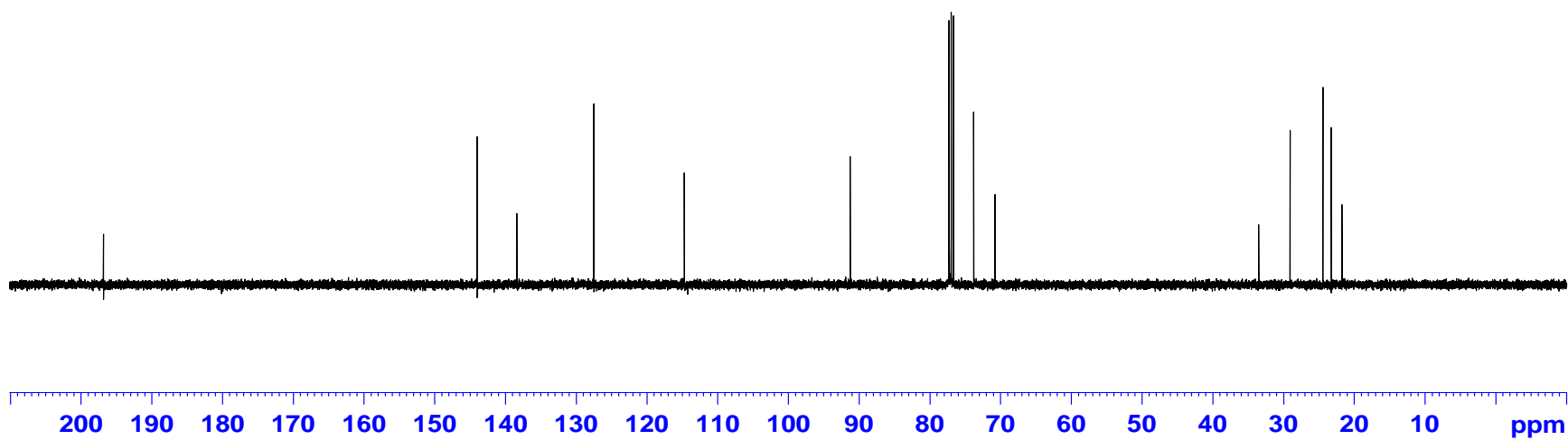
33.54

29.10

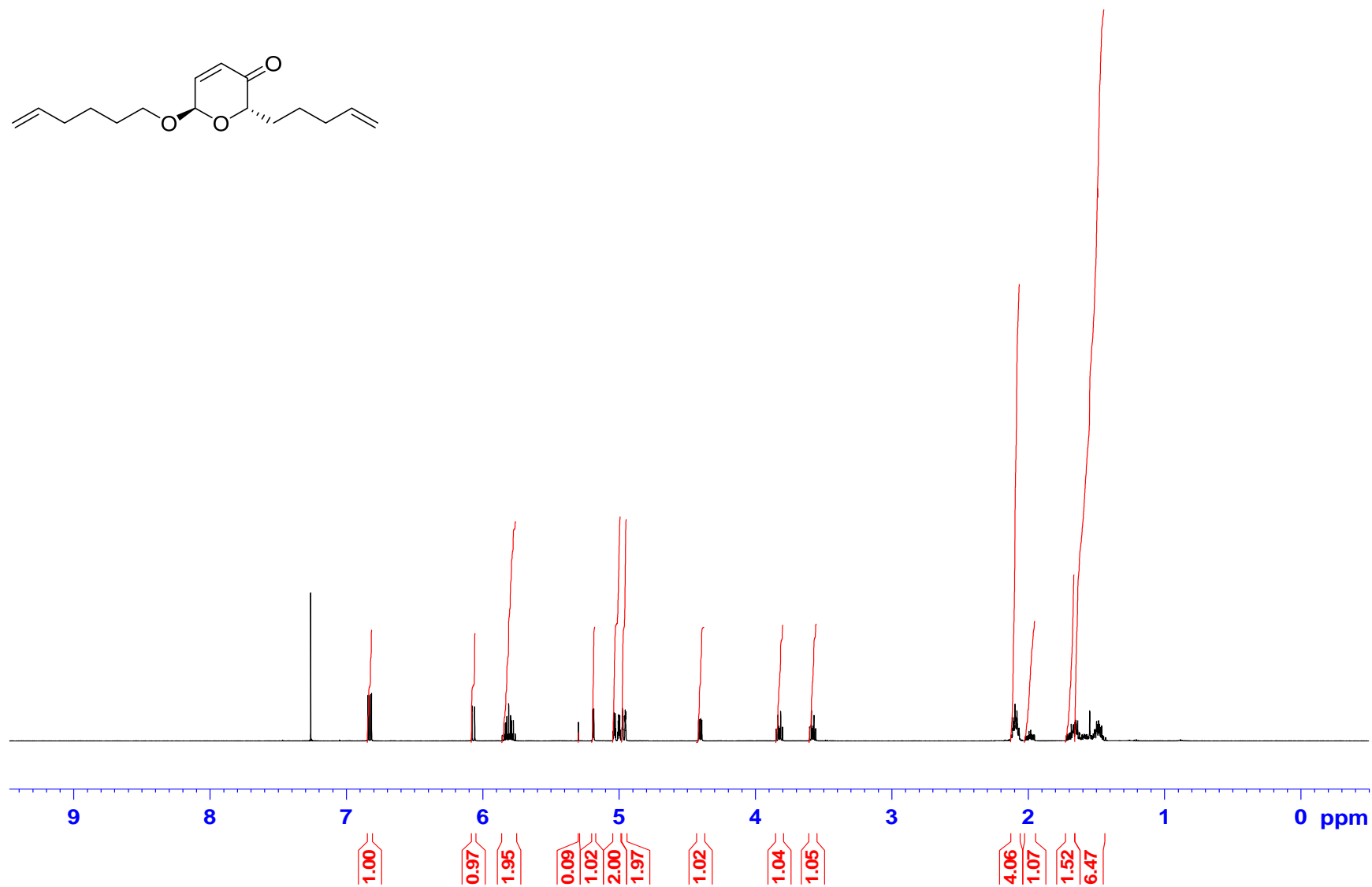
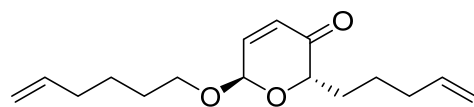
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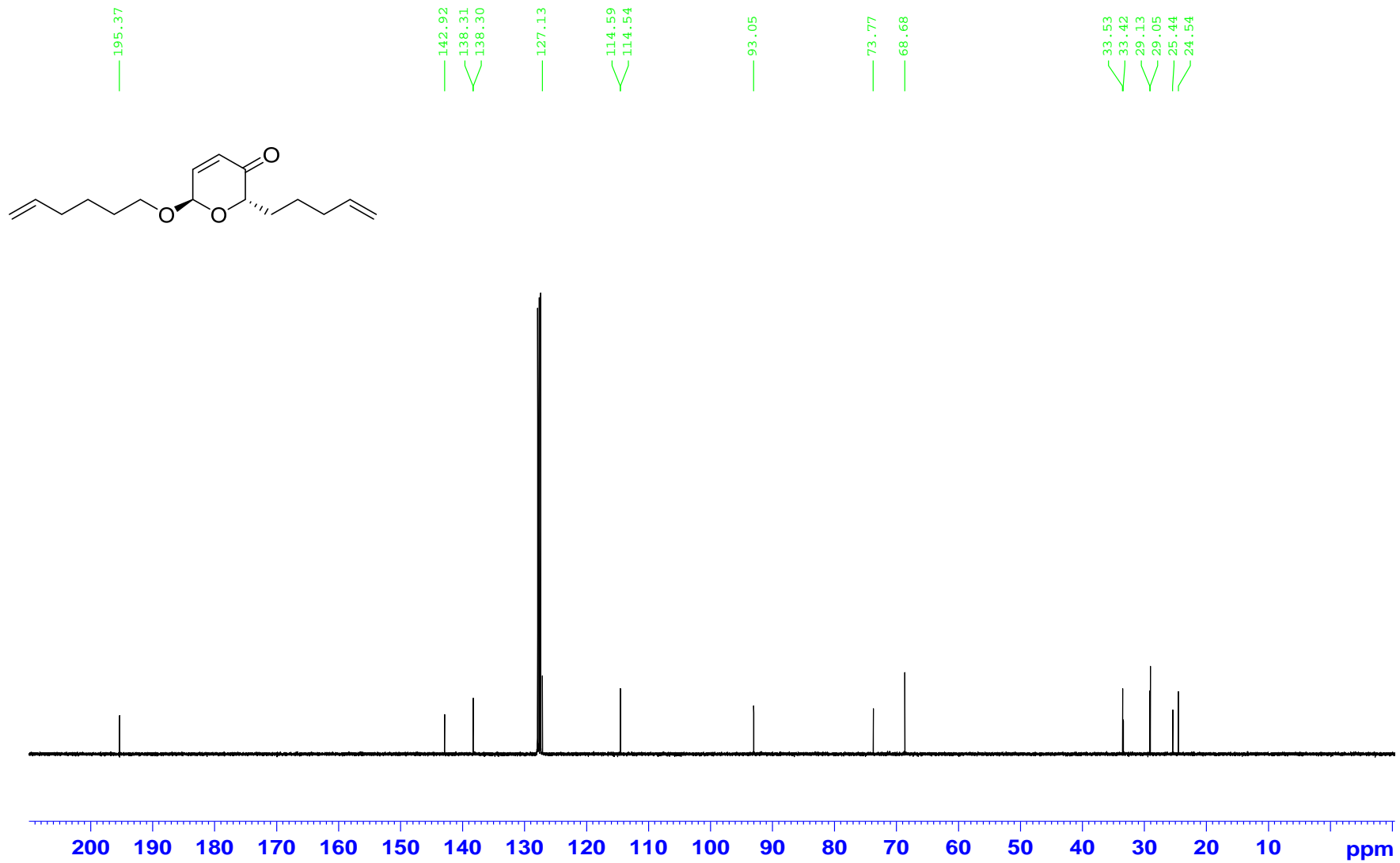
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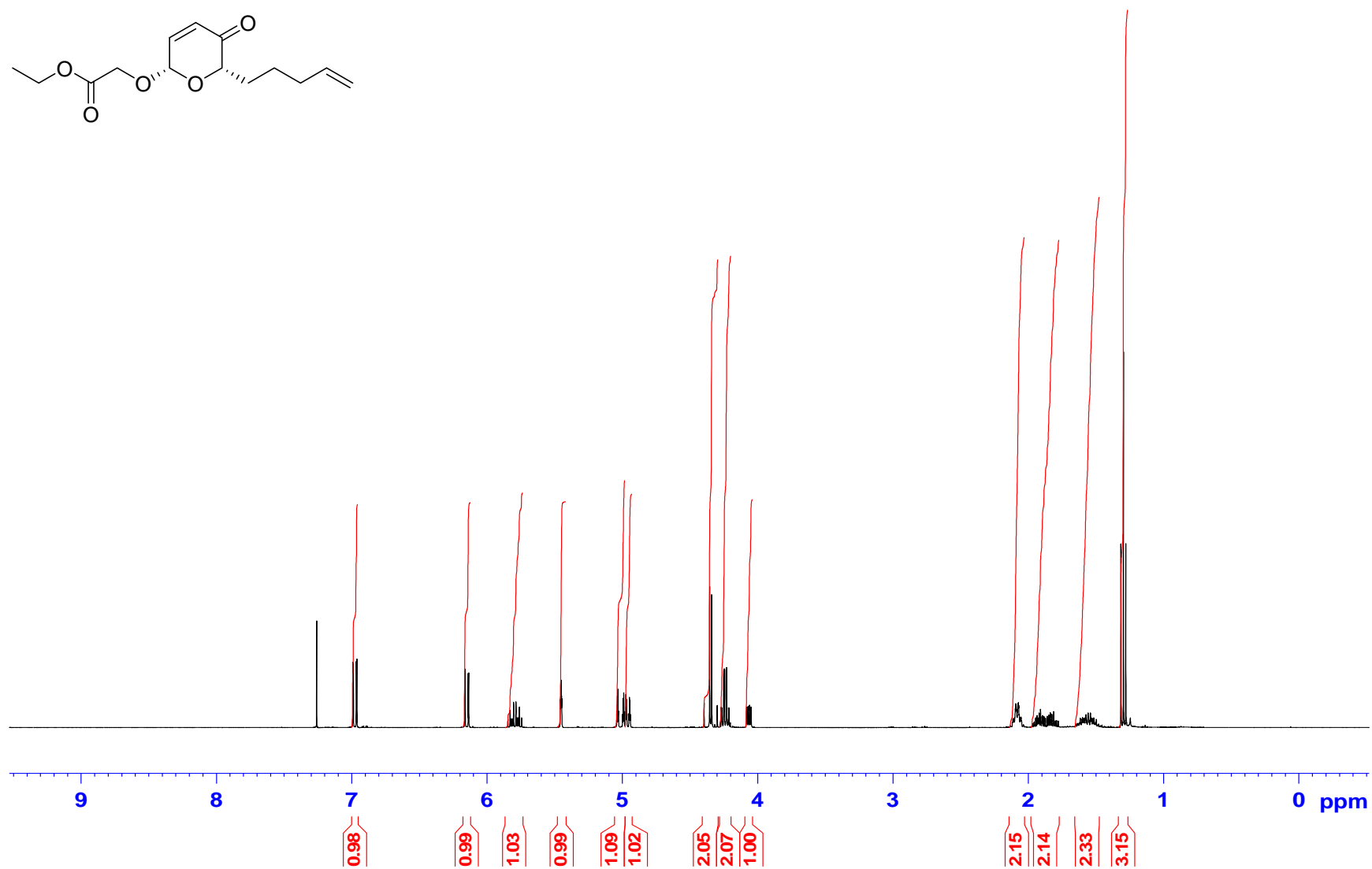
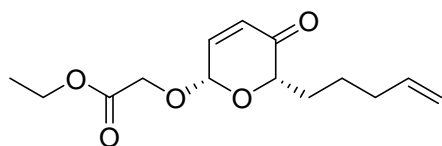
^{13}C NMR (125 MHz) of *anti*-Isopropoxypropanone 1d in CDCl_3



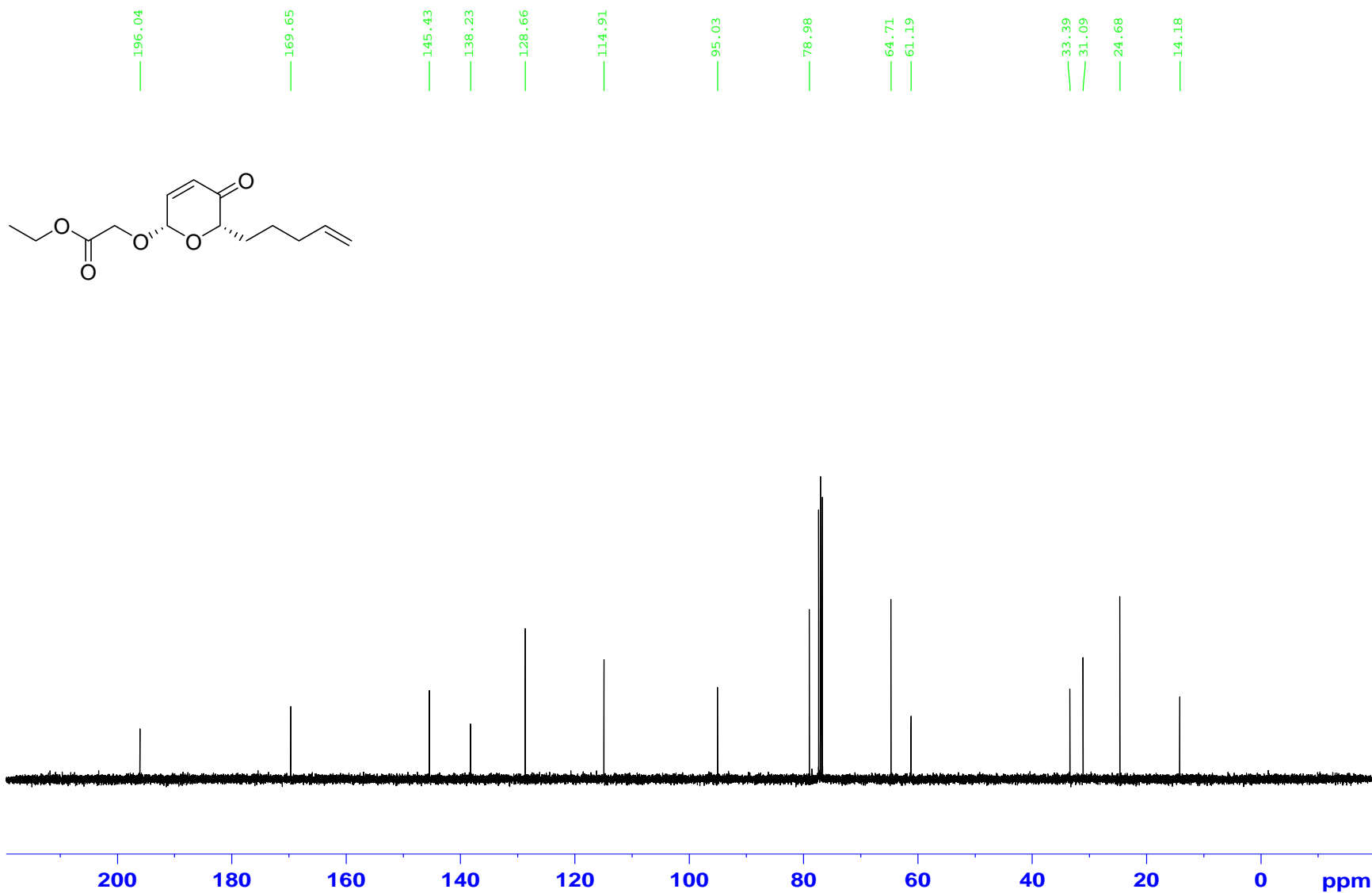
¹H NMR (500 MHz) of *anti*-Alkoxy pyranone 1e in CDCl₃



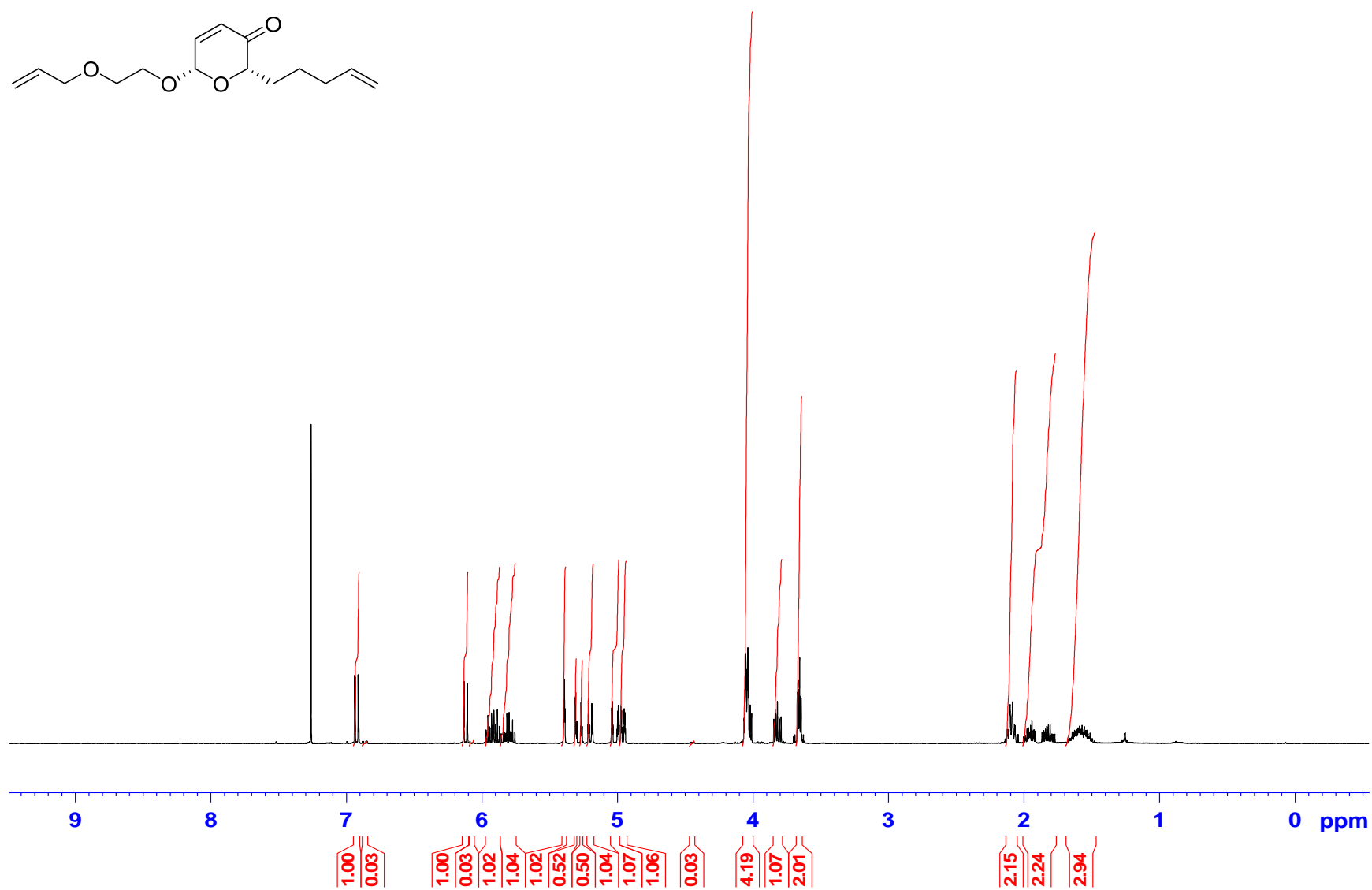
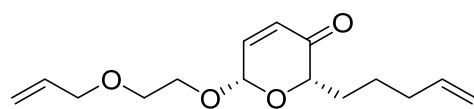
¹³C NMR (125 MHz) of *anti*-Alkoxy pyranone 1e in C₆D₆



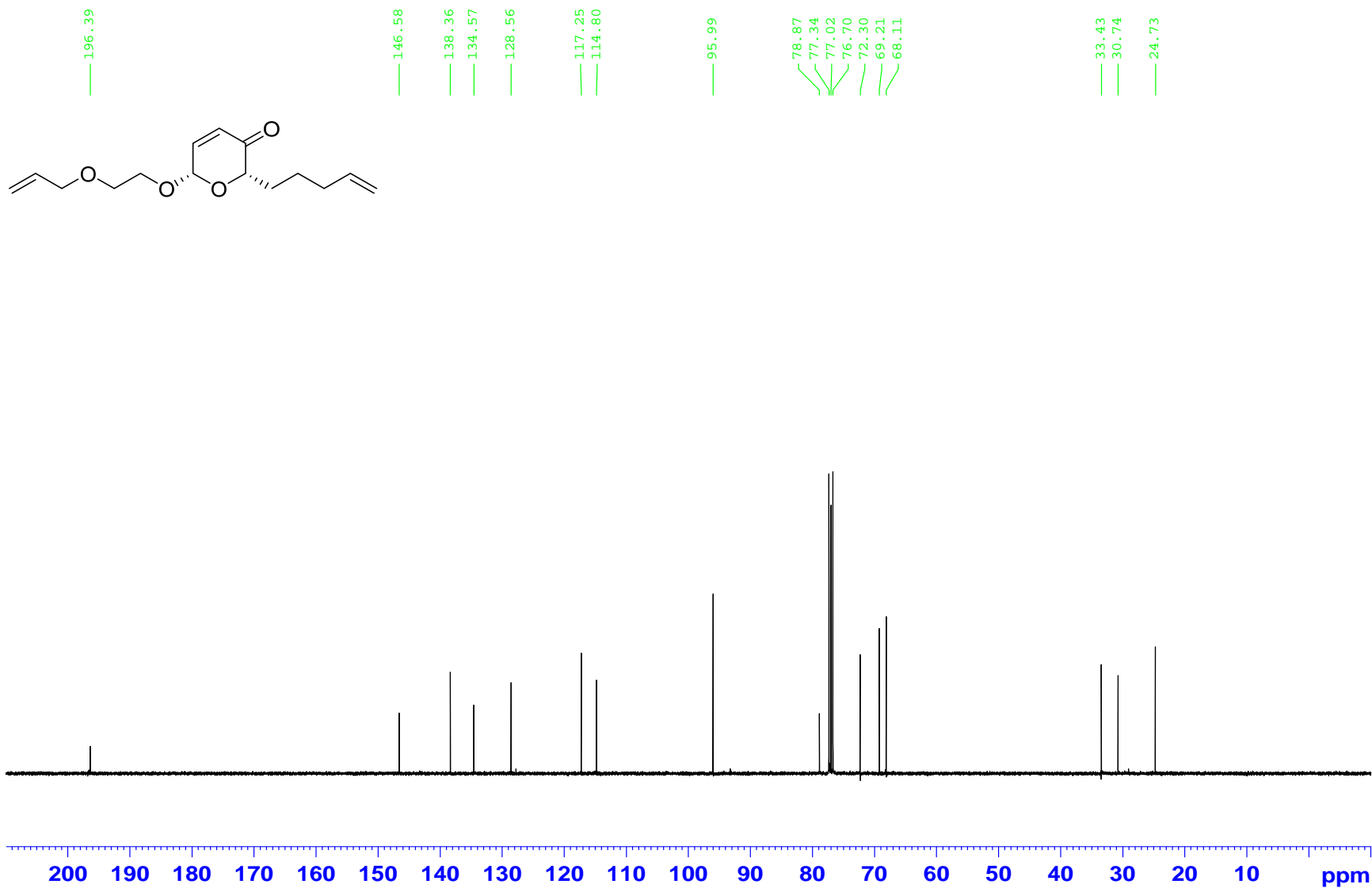
^1H NMR (400 MHz) of *syn*-Alkoxy pyranone 1f in CDCl_3



¹³C NMR (125 MHz) of *syn*-Alkoxy pyranone 1f in CDCl₃



¹H NMR (400 MHz) of *syn*-Alkoxy pyranone 1g in CDCl₃



¹³C NMR (125 MHz) of *syn*-Alkoxy pyranone 1g in CDCl₃