CHEMBIOCHEM

Supporting Information

Chemoenzymatic Total Synthesis of Sorbicatechol Structural Analogues and Evaluation of Their Antiviral Potential

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SUPPORTING INFORMATION

1. General Information

Chemistry: All solvents used in the reactions were p.A. grade. Solvents for chromatography were technical grade and distilled prior to use. Anhydrous dichloromethane and THF were obtained from an MBraun MB-SPS 800 solvent purification system. Commercial materials were purchased at the highest commercial quality from the providers abcr, Acros, Organics, Alfa Aesar, Carbolution, Carl Roth, Merck, Sigma Aldrich, VWR, Jena Biosciences and Thermo Fisher Scientific. These chemicals were used without further purification. Silica gel Geduran® Si 60 (particle size 0.40–0.60 mm) purchased from Merck, was used for flash column chromatography. Solvent mixtures are understood as volume/volume. For TLC analysis, TLC-silica gel 60 F254 plates were purchased from Merck. Applied substances were observed using a UV lamp at 254 nm. For UV-inactive substances, dyeing reagents, such as 0.36% ninhydrin solution in ethanol were used. NMR spectra were recorded on Bruker AVHD300, Bruker AVHD400, Bruker AVHD500 (only ^{1}H NMR spectra), Bruker AV500-cryo, or Bruker Avance600 spectrometers. The chemical shifts δ are listed as parts per million [ppm] and refer to δ(TMS) = 0. The spectra were calibrated using residual undeuterated solvent as an internal reference (δ($CDCl_3$) = 7.26 ppm, δ(methanol-d_4) = 3.31 ppm for ^{1}H NMR; δ($CDCl_3$) = 77.0 ppm, δ(methanol-d_4) = 49.0 ppm for ^{13}C NMR). The following abbreviations are used to explain the multiplicities: bs = broad signal, s = singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublets of doublets, t = triplet, dt = doublet of triplets, m = multiplet.

For High Performance Liquid Chromatography (HPLC) analyses, a computer controlled Jasco system was used (UV-1575 Intelligent UV/VIS Detector, DG-2080-53 3-Line Degaser, two PU-1580 Intelligent HPLC Pumps, AS-1550 Intelligent Sampler, HG-1580-32 Dynamic Mixer). The analyses of the recorded chromatograms were performed using Galaxie- Chromatography-Software provided by Jasco. A Eurosphere II 100-3 C18 A (150 x 4.6 mm) column with integrated precolumn manufactured by Knauer was used for analytical separations with the following composition of the eluent: A = H_2O + 0.05% TFA and B = ACN + 0.05% TFA. The analytical method consisted of the following gradient: 0–1 min 5% B, 1–15 min to 95% B, 15–18 min 95% B, 18–18.5 min to 5% B, 18.5–20 min 5% B with a flowrate of 1 mL/min. This method was used for all analyses. Isolation of the products was carried out by semi-preparative HPLC controlled by a Jasco HPLC system consisting of an UV-1575 Intelligent UV/VIS Detector, two PU-2068 Intelligent prep. Pumps, a MIKA 1000 Dynamic Mixing Chamber (1000 µL Portmann Instruments AG Biel-Benken), a LC-NetII/ ADC, and a Rheodyne injection valve. The system was controlled by the Galaxie-Software and the eluent system consisted of: A = H_2O + 0.05% TFA and B = ACN + 0.05% TFA. A Eurosphere II 100-5 C18 A (250 x 16 mm) column with precolumn (30 x 16 mm) provided by Knauer was used as the stationary phase. General HPLC condition: gradient: 0–1 min 95% H2O + 0.05% TFA (A) / 5% acetonitrile + 0.05% TFA (B), 1–40 min 5% A / 95% B, 40–41 min 5% A / 95% B, 41–43 min 95% A / 5% B, 43–45 min 95% A / 5% B, flow rate: 12 mL/min, running time: 45 min The individual gradient compositions are given below. After preparative separation of the product, the collected fractions containing the desired product were combined and the ACN was removed under reduced pressure. The remaining aqueous phases were freeze-dried in liquid nitrogen and the water removed by lyophilization (Alpha 2-4 *Christ* with Chemistry-Hybrid-Pump-RC6 pump). For medium pressure liquid chromatography (MPLC) the Reveleris® X2 MPLC system (Grace) was used together with Reverleris® Reverse Phase (RP) C18 columns (Grace) using UV-detection at 220 nm, 254 nm, and 280 nm. General MPLC conditions: gradient: isocratic, H_2O + 0.05% TFA /acetonitrile + 0.05% TFA, proportion: 50:50, flow rate: 40 mL/min, running time: 20.0 min The eluent system was composed as follows: A= H_2O + 0.05% TFA and B= ACN + 0.05% TFA.

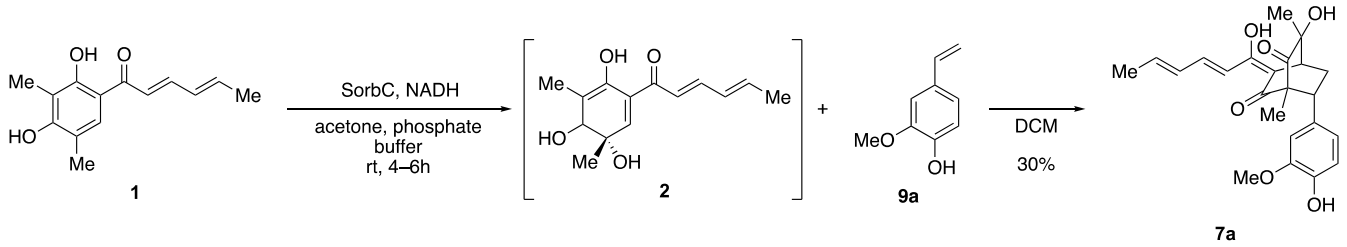
For Electrospray ionization mass spectrometry (ESI-MS) a LCQ Fleet Ion Trap mass spectrometer attached to a UltiMate 3000 HPLC system (both *Thermo Scientific*) and controlled by Xcalibur software was used. The analyses of the recorded spectra were performed using Thermo Xcalibur Qual Browser 2.2 SP1.48 Software. For High resolution mass spectrometry (HRMS) a Thermo LTQ FT Ultra mass spectrometer was used and analyses of the recorded spectra were again performed using Thermo Xcalibur Qual Browser 2.2 SP1.48 Software. The specific rotation was measured with a PerkinElmer Model 341 LLC Polarimeter at 20 °C. The concentration for the specific rotation measurements are given in mg/mL.

Biochemistry/Molecular Biology: PD-10 columns, and Vivaspin 2 Hydrosart membrane columns (30,000 MWCO) were purchased from VWR. Recombinant production and purification of SorbC was conducted as reported previously.[1] Final protein concentrations were determined photometrically using the Nanophotometer 330 (Implen) at 280 nm using the extinction coefficient of SorbC ε(280 nm) = 50920 M^{-1} cm^{-1}. Protein production, enrichment and purification were monitored by SDS-PAGE analysis (BioRad Mini Protean® Tetra System) using Unstained Protein MW Marker (Thermo Scientific). All buffers consisted of 50 mM Tris/Cl at pH 7.5, 150 mM NaCl, and 5% glycerol) with changing concentrations of imidazole (buffer A: 20 mM; buffer B: 250 mM; buffer C: no imidazole). The enzymatic oxidative dearomatization reactions were performed in phosphate buffer (50 mM, pH 8.0).

Anti-viral assays were performed using plate reader (Infinite M200 Pro, Tecan), multispeed vortex (Kisker Biotech) and HeraSafe Laminar Flow Bank. Cell culture flask were provided by Sarstedt and CELLSTAR 96 well plates from Greiner Bio-one. For cell culture media, like antibiotic-antimycotic 100x, DMEM, fetal bovine serum, sodium pyruvate and trypsin-EDTA were obtained from Gibco.

2. Chemo-Enzymatic Synthesis

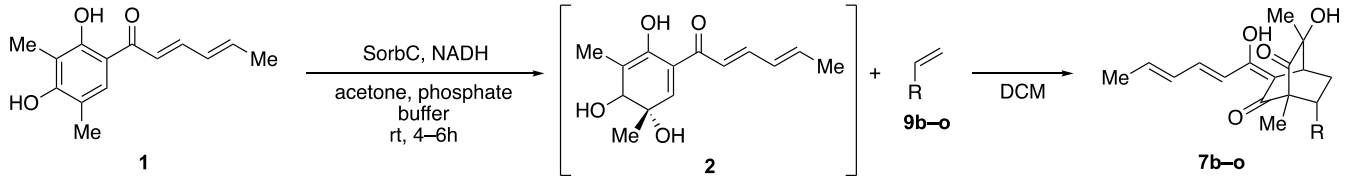
2.1. Enzymatic Synthesis of Sorbicatechol A (**7a**)[2]



Scheme S1. Synthesis of sorbicatechol A (**7a**).

Sorbicillin (**1**) (40.0 mg, 172.4 µmol, 1.0 eq.) was dissolved in acetone (8 mL) and added to phosphate buffer (40 mL, 50 mM, pH = 8) with the enzyme SorbC (1.75 mL, 13.0 mg/mL in Tris buffer). The reaction was started by addition of NADH (150.0 mg, 227.8 µmol, 1.3 eq.) and incubated for 6 h at rt. The reaction mixture was extracted with dichloromethane (3 x 100 mL), 2-methoxy-4-vinylphenol (**9a**) (72.3 mg, 482.0 µmol, 2.8 eq.) was added and the solvent was evaporated under reduced pressure, to increase the concentration of the dienophile slowly over time. Purification by preperative HPLC (retention time – analytical HPLC: 10.66 min). The desired product sorbicatechol A (**7a**) was obtained in 30 % isolated yield (20.6 mg, 51.7 µmol, 30%). ^{1}H NMR (600 MHz, $CDCl_3$) δ = 14.33 (s, 1 H), 7.37 (dd, *J* = 14.9, 10.9 Hz, 1 H), 6.78 (d, *J* = 8.1 Hz, 1 H), 6.48 (dd ,*J* = 8.1, 2.0 Hz,1 H), 6.44 (d, *J* = 2.0 Hz, 1 H), 6.36–6.19 (m, 3 H), 3.78 (s, 3 H), 3.29 (t, *J* = 2.6 Hz, 1 H), 3.08–2.98 (m, 2 H), 1.92 (d, *J* = 6.6 Hz, 3 H), 1.84 (ddd, *J* = 12.8, 4.4, 2.9 Hz 1 H), 1.26 (s, 3 H), 0.92 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 212.0, 198.0, 167.2, 146.6, 145.0, 142.6, 140.1, 133.3, 131.0, 121.6, 118.1, 114.4, 112.2, 110.4, 75.0, 65.2, 55.8, 47.8, 40.6, 31.5, 24.4, 19.1, 10.7. HRMS (ESI+): m/z 399.1802 $[M+H]^+$, calc.: 399.1802. $[\alpha]_D$ = –62.4° (c = 3.5 in MeOH). The physical and spectroscopic data were in agreement with that described in the literature.[3]

2.2. Enzymatic Synthesis of Derivatives **7b–o**



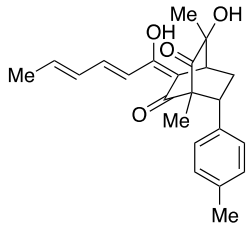
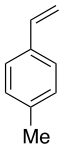
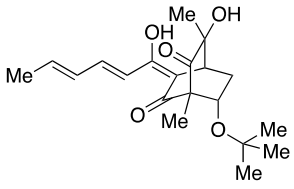
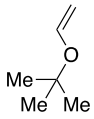
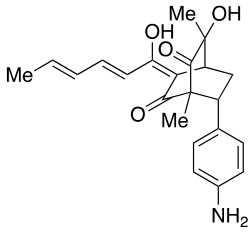
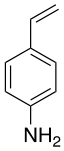
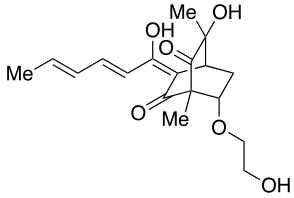
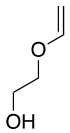
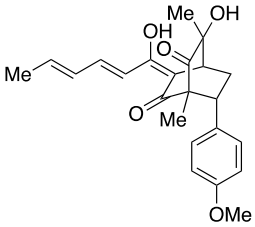
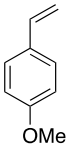
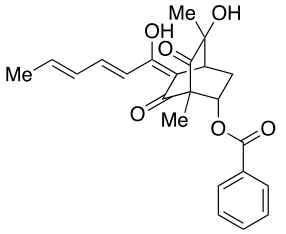
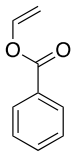
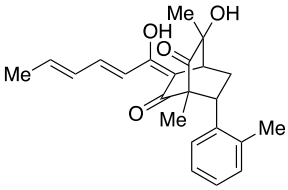
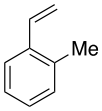
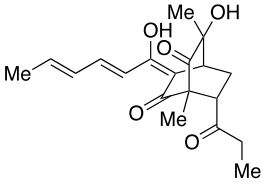
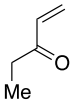
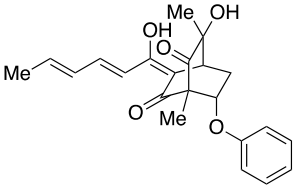
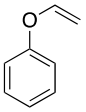
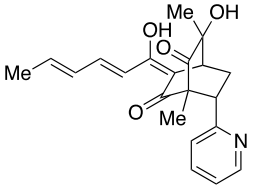
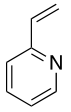
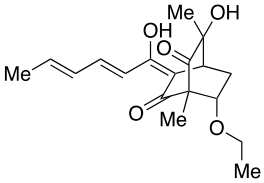
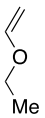
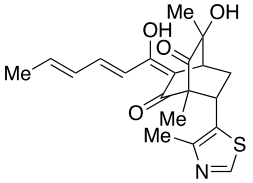
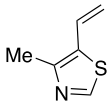
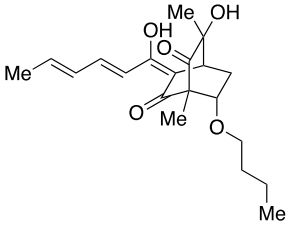
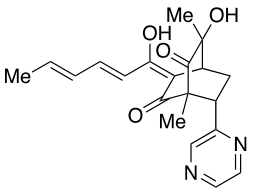
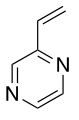
Scheme S2. Synthesis of sorbicatechol derivatives.[2]

Sorbicillin (**1**) (40.0 mg, 172.4 µmol, 1.0 eq.) was dissolved in acetone (8 mL), and added to phosphate buffer (50 mL, 50 mM, pH = 8) with the enzyme SorbC (3.0 mL, 8.2 mg/mL in Tris buffer). The reaction was started by addition of NADH (150.0 mg, 227.8 µmol, 1.3 eq.) and incubated for 4–6 h at rt. The reaction mixture was extracted with dichloromethane (3 x 100 mL), vinyl compound **9b–o** (1.0 mL / in excess) was added and the solvent was evaporated under reduced pressure. Purification by preperative HPLC (retention time: R_t). The desired products **7b–o** were obtained in 21–32% isolated yield.

7b: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.31 (bs, 1 H), 7.38 (dd, *J* = 15.0, 10.9 Hz, 1 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 6.84 (d, *J* = 8.1 Hz, 2 H), 6.44–6.16 (m, 3 H), 3.29 (t, *J* = 2.9 Hz, 1 H), 3.09 (dd, *J* = 10.7, 5.7 Hz, 1 H), 3.00 (ddd, *J* = 13.6, 10.7, 3.0 Hz, 1 H), 2.29 (s, 3 H), 1.91 (d, *J* = 6.7 Hz, 3 H), 1.85 (ddd, *J* = 13.4, 5.7, 2.8 Hz ,1 H), 1.26 (s, 3 H), 0.90 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 211.9, 197.9, 167.2, 142.5, 139.9, 138.4, 137.2, 131.0, 129.5, 129.5, 128.3, 128.3, 118.2, 112.2, 74.9, 64.9, 47.6, 40.6, 31.4, 24.5, 21.1, 19.1, 10.7. HRMS (ESI+): m/z 367.1905 $[M+H]^+$, calc.: 367.1904. $[\alpha]_D$ = –35.1° (c = 2.15 in MeOH)

SUPPORTING INFORMATION

Table S1. Yield and retention time of synthesized sorbicatechol derivatives.

Product			Starting material	Product			Starting material
7b		Yield: 22% R_f: 12.01 min	 **9b**	**7i**		Yield: 21% R_f: 10.57 min	 **9i**
7c		Yield: 24% R_f: 8.90 min	 **9c**	**7j**		Yield: 28% R_f: 8.47 min	 **9j**
7d		Yield: 27% R_f: 11.70 min	 **9d**	**7k**		Yield: 21% R_f: 11.82 min	 **9k**
7e		Yield: 22% R_f: 11.89 min	 **9e**	**7l**		Yield: 29% R_f: 10.29 min	 **9l**
7f		Yield: 30% R_f: 11.79 min	 **9f**	**7m**		Yield: 32% R_f: 8.47 min	 **9m**
7g		Yield: 29% R_f: 10.70 min	 **9g**	**7n**		Yield: 31% R_f: 10.43 min	 **9n**
7h		Yield: 32% R_f: 10.89 min	 **9h**	**7o**		Yield: 28% R_f: 10.24 min	 **9o**

7c: ^{1}H NMR (500 MHz, MeOD) δ = 7.39 (dd, *J* = 14.9, 11.0 Hz, 1 H), 7.30 (d, *J* = 8.6 Hz, 2 H), 7.17 (d, *J* = 8.6 Hz, 2 H), 6.49 (d, *J* = 15.0 Hz, 1 H), 6.43 (dd, *J* = 15.0, 11.0 Hz, 1 H), 6.25 (dd, *J* = 14.8, 7.1 Hz, 1 H), 3.36–3.33 (m, 1 H), 3.29 (d, *J* = 6.2 Hz, 1 H), 3.05 (ddd, *J* = 13.7, 10.6, 3.1 Hz, 1 H), 1.90 (d, *J* = 6.8 Hz ,3 H), 1.82 (ddd, *J* = 13.5, 6.1, 2.7 Hz, 1 H), 1.23 (s, 3 H), 0.79 (s, 3 H). ^{13}C NMR (125 MHz, MeOD) δ = 210.6, 199.1, 168.4, 161.7, 161.4, 144.7, 143.8, 140.6, 132.3, 131.3, 131.2, 124.2, 119.5, 113.6, 75.1, 65.8, 47.3, 42.2, 32.6, 23.9, 18.9, 11.3. HRMS (ESI+): m/z 368.1856 $[M+H]^+$, calc.: 368.1856. $[\alpha]_D$= –9.2° (c = 5.55 in MeOH).

7d: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.31 (bs, 1 H), 7.38 (dd, *J* = 15.0, 10.8 Hz, 1 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 6.39–6.17 (m, 3 H), 3.76 (s, 3 H), 3.28 (t, *J* = 2.9 Hz, 1 H), 3.09 (dd, *J* = 10.8, 5.5 Hz, 1 H), 3.00 (ddd, *J* = 13.5, 10.7, 2.9 Hz, 1 H), 1.91 (d, *J* = 6.7 Hz, 3 H), 1.84 (ddd, *J* = 13.3, 5.6, 2.8 Hz ,1 H), 1.26 (s, 3 H), 0.90 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 211.9, 197.9, 167.2, 158.9, 142.6, 139.9, 133.4, 131.0, 129.5, 129.5, 118.2, 114.1, 114.1, 112.1, 74.9, 65.1, 55.4, 47.3, 40.6, 31.5, 24.5, 19.1, 10.7. HRMS (ESI+): m/z 383.1854 $[M+H]^+$, calc.: 383.1853. $[\alpha]_D$= –66.2°(c = 2.7 in MeOH).

7e: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 14.39 (bs, 1 H), 7.38 (dd, *J* = 14.9, 10.8 Hz, 1 H), 7.15–7.07 (m, 3 H), 6.87 (d, *J* = 7.7 Hz, 1 H), 6.37–6.19 (m, 3 H), 3.56 (dd, *J* = 10.6, 6.5 Hz, 1 H), 3.29 (t, *J* = 2.6 Hz, 1 H), 3.01 (ddd, *J* = 13.5, 10.8, 3.0 Hz, 1 H), 2.29 (s, 3 H), 1.91 (d, *J* = 7.0 Hz, 3 H), 1.77 (ddd, *J* = 13.4, 6.6, 2.3 Hz, 1 H), 1.28 (s, 3 H), 0.94 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 211.6, 198.0, 167.3, 142.6, 140.4, 139.9, 136.4, 131.0, 130.5, 127.1, 127.0, 127.0, 118.2, 112.2, 74.8, 65.1, 41.2, 40.5, 32.0, 24.5, 20.4, 19.1, 9.7. HRMS (ESI+): m/z 367.1902 $[M+H]^+$, calc.: 367.1904. $[\alpha]_D$ = +84.2° (c = 2.6 in MeOH).

7f: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 14.01 (bs, 1 H), 7.32 (dd, *J* = 14.9, 10.8 Hz, 1 H), 7.26–7.22 (m, 2 H), 6.95 (t, *J* = 7.4 Hz, 1 H), 6.80 (d, *J* = 8.6 Hz, 2 H), 6.34–6.14 (m, 3 H), 4.42 (dd, *J* = 8.2, 2.1 Hz,1 H), 3.21 (t, *J* = 2.8 Hz,1 H), 3.01 (ddd, *J* = 14.1, 8.2, 2.4 Hz, 1 H), 1.89 (d, *J* = 6.6 Hz, 3 H), 1.79 (dt, *J* = 14.1, 3.0 Hz, 1 H), 1.37 (s, 3 H), 1.26 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 210.3, 195.9, 167.1, 157.0, 142.5 139.8, 130.9, 129.7, 129.7, 121.6, 117.9, 115.7, 115.7, 110.2, 77.3, 74.7, 66.4, 39.9, 31.0, 24.5, 19.1, 9.2 . HRMS (ESI+): m/z 369.1695 $[M+H]^+$, calc.: 369.1697. $[\alpha]_D$ = +258.7 (c = 5.6 in MeOH).

7g: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 13.95 (bs, 1 H), 7.29 (dd, *J* = 14.9, 10.8 Hz, 1 H), 6.33–6.09 (m, 3 H), 3.59–3.51 (m, 2 H), 3.36 (dd, *J* = 9.6, 7.0 Hz, 1 H), 3.15 (t, *J* = 3.0 Hz, 1 H), 2.78 (ddd, *J* = 13.8, 8.4, 2.6 Hz, 1 H), 1.89 (d, *J* = 6.8 Hz, 3 H), 1.68 (dt, *J* = 13.8, 3.0 Hz, 1 H), 1.31 (s, 3 H), 1.20 (s, 3 H), 1.12 (t, *J* = 7.0 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 211.1, 196.6, 166.6, 142.0, 139.4, 131.0, 118.1, 110.5, 79.3, 74.7, 67.1, 65.8, 39.9, 30.8, 24.5, 19.0, 15.2, 9.1. HRMS (ESI+): m/z 321.1695 $[M+H]^+$, calc.: 321.1696. $[\alpha]_D$= +334.0° (c = 4.15 in MeOH). The physical and spectroscopic data were in agreement with that described in the literature.[4]

7h: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 13.94 (bs, 1 H), 7.29 (dd, *J* = 14.2, 10.0 Hz, 1 H), 6.37–6.06 (m, 3 H), 3.54 (dd, *J* = 8.3, 2.5 Hz, 1 H), 3.48 (dt, *J* = 9.4, 6.4 Hz, 1 H), 3.32–3.23 (m, 1 H), 3.15 (t, *J* = 3.0 Hz, 1 H), 2.76 (ddd, *J* = 13.8, 8.3, 2.6 Hz, 1 H), 1.89 (d, *J* = 6.7 Hz, 3 H), 1.67 (dt, *J* = 13.7, 3.1 Hz, 1 H), 1.51–1.41 (m, 2 H), 1.32 (s, 3 H), 1.35–1.25 (m, 2 H), 1.20 (s, 3 H), 0.86 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 211.1, 196.6, 166.4, 141.9, 139.3, 131.0, 118.2, 110.5, 79.6, 74.8, 70.1, 67.3, 39.9, 31.8, 30.6, 24.5, 19.4, 19.0, 14.0, 9.1. HRMS (ESI+): m/z 349.2008 $[M+H]^+$, calc.: 349.2010. $[\alpha]_D$ = +376.0° (c = 3.2 in MeOH). The physical and spectroscopic data were in agreement with that described in the literature.[5]

7i: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.00 (bs, 1 H), 7.31 (dd, *J* = 14.9, 10.7 Hz, 1 H), 6.30–6.14 (m, 3 H), 3.73 (dd, *J* = 8.5, 2.6 Hz, 1 H), 3.11 (t, *J* = 3.0 Hz, 1 H), 2.81 (ddd, *J* = 13.7, 8.5, 2.6 Hz, 1 H), 1.89 (d, *J* = 6.8 Hz, 3 H), 1.64 (dt, *J* = 13.7, 3.1 Hz, 1 H), 1.24 (s, 3 H), 1.19 (s, 3 H), 1.11 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 211.8, 197.0, 166.2, 141.8, 139.2, 131.0, 118.2, 110.7, 74.7, 72.2, 66.9, 40.0, 34.9, 28.6, 28.6, 28.6, 28.5, 24.4, 19.0, 9.6. HRMS (ESI+): m/z 349.2011 $[M+H]^+$, calc.: 349.2010. $[\alpha]_D$ = +287.9° (c = 3.75 in MeOH).

7j: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 13.93 (bs, 1 H), 7.31 (dd, *J* = 14.9, 10.8 Hz, 1 H), 6.32–6.16 (m, 3 H), 3.69–3.59 (m, 4 H), 3.43 (ddd, *J* = 9.5, 5.7, 3.4 Hz, 1 H), 3.17 (t, *J* = 3.2 Hz, 1 H), 2.82 (ddd, *J* = 13.9, 8.3, 2.6 Hz, 1 H), 1.89 (d, *J* = 6.5 Hz, 3 H), 1.70 (dt, *J* = 13.8, 3.0 Hz, 1 H), 1.34 (s, 3 H), 1.21 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 210.5, 196.3, 166.9, 142.4, 139.8, 131.0, 117.9, 110.4, 80.0, 74.6, 71.4, 67.1, 61.9, 39.8, 30.5, 24.4, 19.1, 9.2. HRMS (ESI+): m/z 337.1646 $[M+H]^+$, calc.: 337.1646. $[\alpha]_D$ = +342.9° (c = 3.20 in MeOH).

7k: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 14.06 (bs, 1 H), 7.93 (dd, *J* = 8.3, 1.2 Hz, 2 H), 7.56 (t, *J* = 7.5 Hz, 1 H), 7.47–7.40 (m, 2 H), 7.34 (dd, *J* = 14.8, 10.9 Hz, 1 H), 6.36–6.18 (m, 3 H), 5.27 (dd, *J* = 8.7, 2.4 Hz, 1 H), 3.22 (t, *J* = 2.8 Hz, 1 H), 3.14 (ddd, *J* = 14.7, 8.7, 2.4 Hz, 1 H), 1.90 (dd, *J* = 6.8, 1.4 Hz, 3 H), 1.72 (dt, *J* = 14.6, 3.0 Hz, 1 H), 1.32 (s, 3 H), 1.27 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 205.3, 197.0, 190.7, 165.5, 165.2, 148.0, 144.5, 130.3, 130.0, 130.0, 129.9, 129.2, 128.8, 128.8, 121.3, 74.5, 73.0, 67.6, 46.5, 27.2, 24.3, 19.3, 9.8. HRMS (ESI+): m/z 397.1646 $[M+H]^+$, calc.: 397.1646. $[\alpha]_D$ = +89.9° (c = 1.35 in MeOH).

7l: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.08 (bs, 1 H), 7.30 (dd, *J* = 14.9, 10.7 Hz, 1 H), 6.29–6.13 (m, 3 H), 3.20 (t, *J* = 2.8 Hz, 1 H), 3.04 (dd, *J* = 10.9, 5.8 Hz, 1 H), 2.74 (ddd, *J* = 13.8, 11.0, 3.0 Hz, 1 H), 2.42 (dd, *J* = 11.4, 7.2 Hz, 2 H), 1.89 (d, *J* = 6.8 Hz, 3 H), 1.58 (ddd, *J* = 12.8, 5.8, 2.8 Hz, 1 H), 1.21 (s, 3 H), 1.20 (s, 3 H), 1.01 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 210.6, 210.0, 196.4, 167.0, 142.3, 139.6, 131.0, 118.0, 110.8, 74.9, 61.7, 50.7, 40.3, 37.6, 26.3, 24.3, 19.0, 10.4, 7.5. HRMS (ESI+): m/z 333.1698 $[M+H]^+$, calc.: 333.1697. $[\alpha]_D$ = +554.5° (c = 1.05 in MeOH).

7m: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.25 (bs, 1 H), 8.77 (d, *J* = 4.1 Hz, 1 H), 8.14 (t, *J* = 7.5 Hz ,1 H), 7.67–7.65 (m, 1 H), 7.41 (dd, *J* = 14.8, 10.6 Hz, 1 H), 7.35 (d, *J* = 7.9 Hz ,1 H), 6.36–6.23 (m, 3 H), 4.00 (dd, *J* = 10.2, 5.3 Hz, 1 H), 3.39–3.37 (m, 1 H), 3.23 (t, *J* = 11.6 Hz, 1 H), 1.92 (d, *J* = 6.4 Hz ,3 H), 1.87–1.83 (m, 1 H), 1.31 (s, 3 H), 0.97 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 208.0, 195.9, 168.8, 158.5, 143.9, 143.7, 143.6, 141.2, 131.0, 124.8, 124.7, 117.7, 111.8, 74.5, 63.2, 44.4, 40.6, 30.8, 24.2, 19.2, 10.4. HRMS (ESI+): m/z 354.1701 $[M+H]^+$, calc.: 354.1700. $[\alpha]_D$ = +52.6° (c = 5.40 in MeOH).

7n: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.32 (bs, 1 H), 8.97 (s, 1 H), 7.42 (dd, *J* = 14.8, 10.1 Hz, 1 H), 6.32–6.22 (m, 3 H), 3.60 (dd, *J* = 10.6, 4.8 Hz, 1 H), 3.27 (t, *J* = 2.9 Hz, 1 H), 3.16 (ddd, *J* = 13.4, 10.7, 2.5 Hz, 1 H), 2,45 (s, 3 H), 1.92 (d, *J* = 6.0 Hz ,3 H), 1.71 (ddd, *J* = 13.8, 4.9, 3.1 Hz, 1 H), 1.27 (s, 3 H), 1.01 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 210.5, 196.0, 169.0, 152.8, 147.7, 143.9, 141.2, 135.6, 130.9, 117.6, 111.4, 74.8, 64.7, 40.3, 39.8, 33.4, 24.5, 19.2, 14.3, 10.1. HRMS (ESI+): m/z 374.1422 $[M+H]^+$, calc.: 374.1421. $[\alpha]_D$ = +140.1° (c = 5.20 in MeOH).

7o: ^{1}H NMR (500 MHz, $CDCl_3$) δ = 14.10 (bs, 1 H), 8.57 (s, 1 H), 8.43 (d, *J* = 2.5 Hz ,1 H), 8.33 (d, *J* = 1.6 Hz ,1 H), 7.36 (dd, *J* = 14.9, 10.8 Hz, 1 H), 6.38–6.16 (m, 3 H), 3.37 (dd, *J* = 10.5, 6.0 Hz, 1 H), 3.33 (t, *J* = 3.0 Hz, 1 H), 2.94 (ddd, *J* = 13.4, 10.5, 3.2 Hz, 1 H), 2.05 (ddd, *J* = 13.1, 6.1, 2.7 Hz, 1 H), 1.91 (d, *J* = 6.7 Hz, 3 H), 1.30 (s, 3 H), 0.93 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 210.7, 196.4, 167.0, 157.1, 145.4, 143.7, 142.4, 142.3, 139.7, 131.0, 118.2, 111.9, 74.9, 63.5, 45.7, 40.5, 29.4, 24.4, 19.1, 10.7. HRMS (ESI+): m/z 355.1652 $[M+H]^+$, calc.: 355.1652. $[\alpha]_D$ = +25.0° (c = 0.50 in MeOH).

3. Anti-Viral Screening

3.1. HIV-Tests

HIV Full virus Screening (EASY-HIT). The EASY-HIT assay is based on HIV-1 susceptible reporter cells (LC5-RIC) that contain a stably integrated fluorescent reporter gene that is activated upon successful HIV-1 infection and expression of the early viral protein HIV-Rev and HIV-Tat. Briefly, LC5-RIC cells were seeded into black 96-well plates at a density of 10,000 cells per well 24 hours before infection and treatment of the cells. Compounds stocks dissolved at 100 mM in DMSO were screened at multiple concentrations from 3 to 10 µM at a final DMSO concentration of 0.1% to establish IC_{50} curves. After compound addition, LC5-RIC cells were infected by adding HIV-1_{LAI} inoculum at an MOI of 0.5 to each well of the plate. Cells were incubated at 37 °C, 5% CO_2 for 48 hours after infection and then measured for reporter expression. Reporter expression was determined by measuring the total fluorescent signal intensity of each well using a fluorescence microplate reader at an excitation filter wavelength of 552 nm and an emission filter wavelength of 596 nm.

Cell viability assays. Cell viability of LC5-RIC cultures exposed to HIV-1_{LAI} inoculum and test compounds was determined by performing a CellTiter-Blue® cell viability assay (Promega) and monitoring the ability of metabolically active cells to convert the redox dye resazurin into the fluorescent product resorufin. LC5-RIC cells were seeded into black 96-well plates at a density of 10,000 cells per well followed by overnight incubation at 37 °C, 5% CO_2. Compounds stocks dissolved at 100 mM in DMSO were screened at multiple concentrations from 3 to 100 µM at a final DMSO concentration of 0.1% followed by an additional 48 hours incubation. After the designated incubation time, CTB reagent (1:5 in cell culture medium) was added to each well. CTB containing plates were incubated for an additional hour after which fluorescence signal of resorufin was measured using a fluorescence microplate reader at an excitation filter wavelength of 550 nm and an emission filter wavelength of 600 nm.

3.2. Influenza-Tests

Influenza A inhibition and cell viability assay: A549 cells were seeded into 96-well-plates at a density of 20,000 cells per well 24 hours before infection and treatment on the cells. Compounds stocks (**5**, **5b**, **5m**, **5k**) dissolved at 500 mM in DMSO were screened at multiple concentrations from 5 mM serially diluted in DMEM to 0,25 µM (1:3). After compound addition, A549 cells were infected with Influenza A virus (strain SC35M) encoding Gaussia luciferase (PMID: 26068081) at an MOI of 0.01.

SUPPORTING INFORMATION

Cells were incubated at 37 °C, 5% CO_2 and gaussia luciferase accumulation was evaluated after 24, 48 and 72 hours. For testing cell viability, a reazurine reduction assay was performed at 48h post drug treatment (Citea PMID: 29255269).

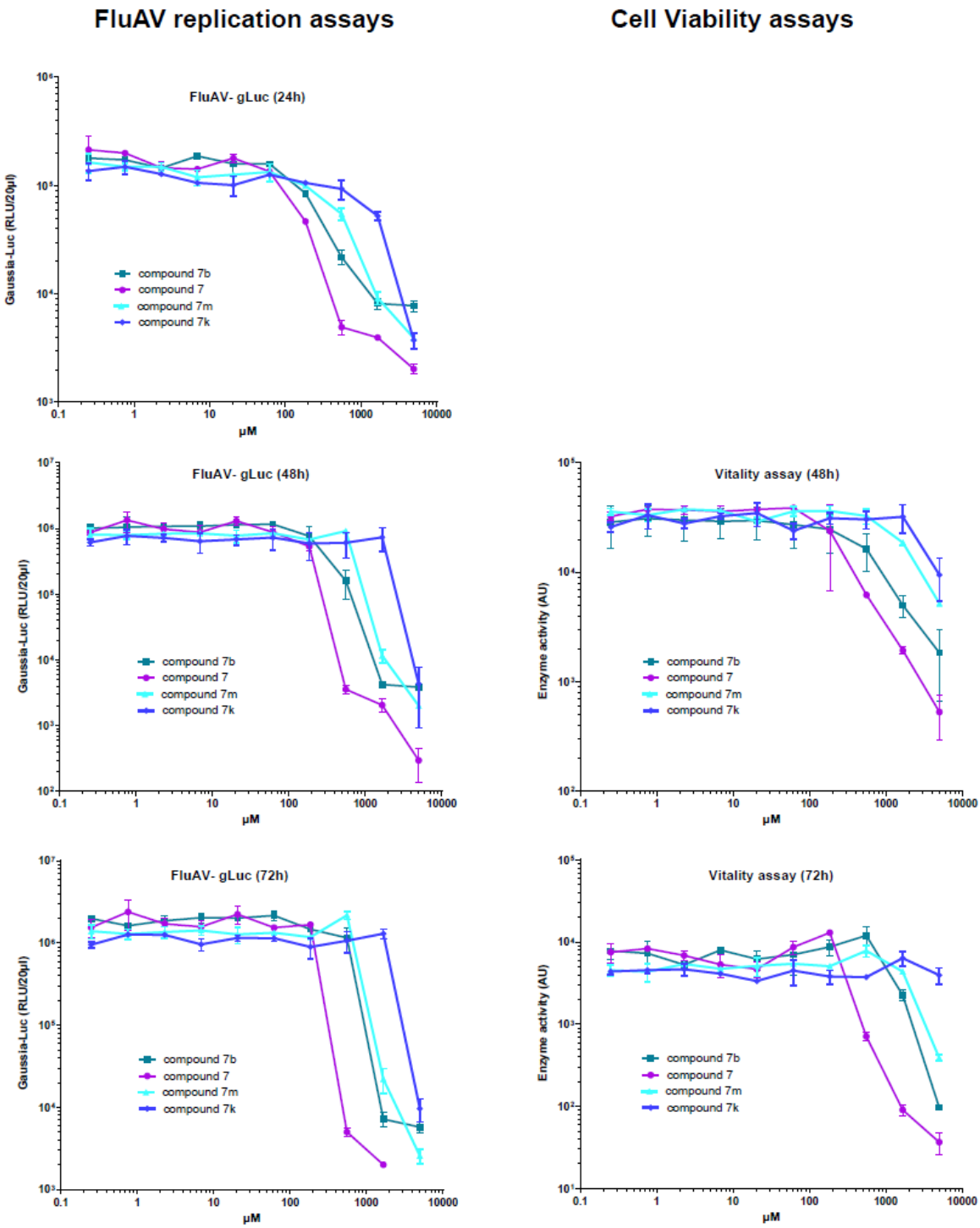


Figure S1. Activity of compounds on influenza A virus replication. Cells were treated with the indicated concentration of compound and infected with influenza A virus expressing gaussia luciferase. 24h, 48h and 72h later the supernatant was assayed for accumulation of gaussia luciferase (left). At 48h and 72h a resazurine conversion assay was used to test cell viability. Graph show representative experiments. Error bars: SD of duplicate measurements.

4. NMR Spectra

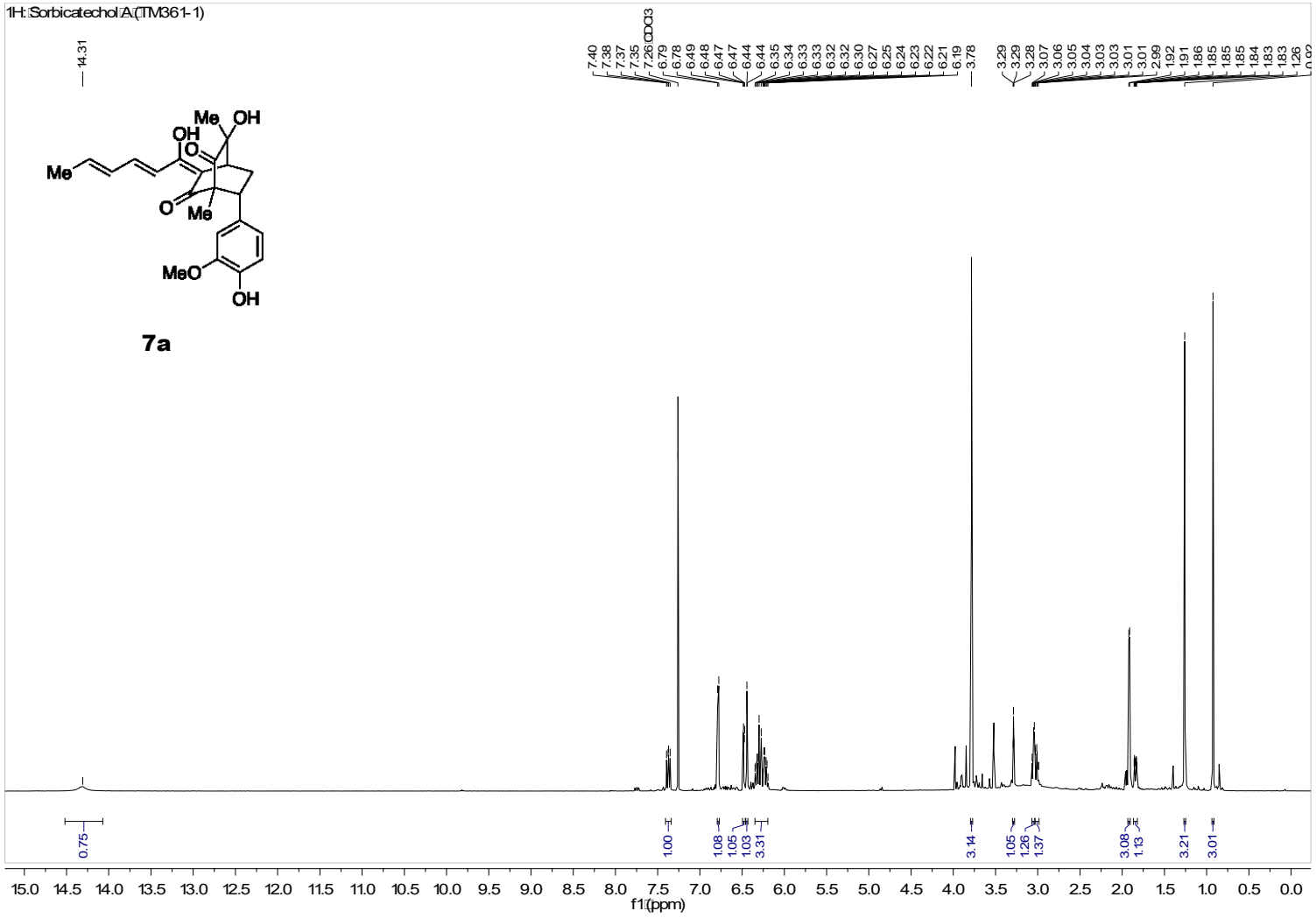


Figure S2. ^{1}H-NMR spectrum of sorbicatechol A (**7a**) in $CDCl_3$.

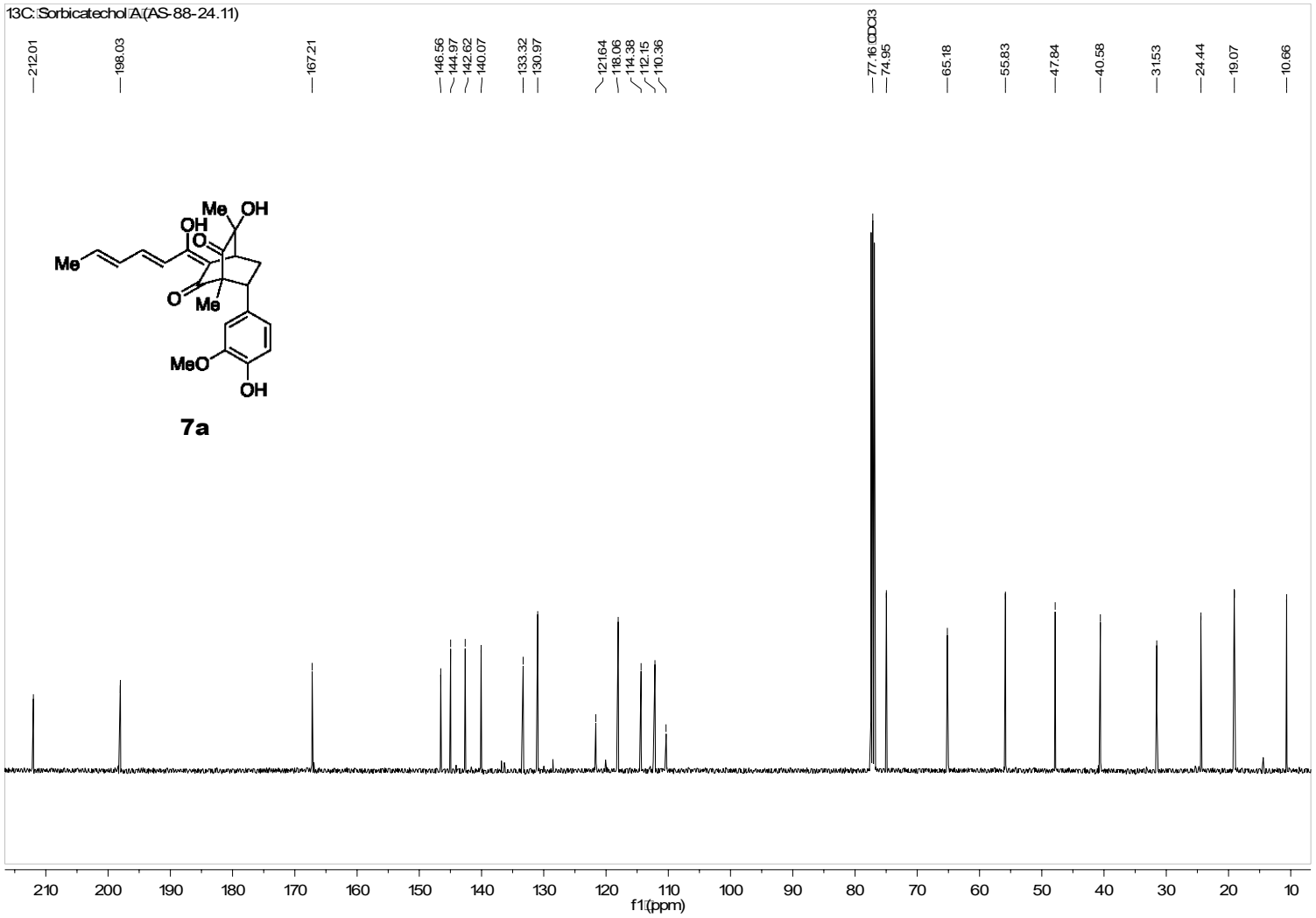
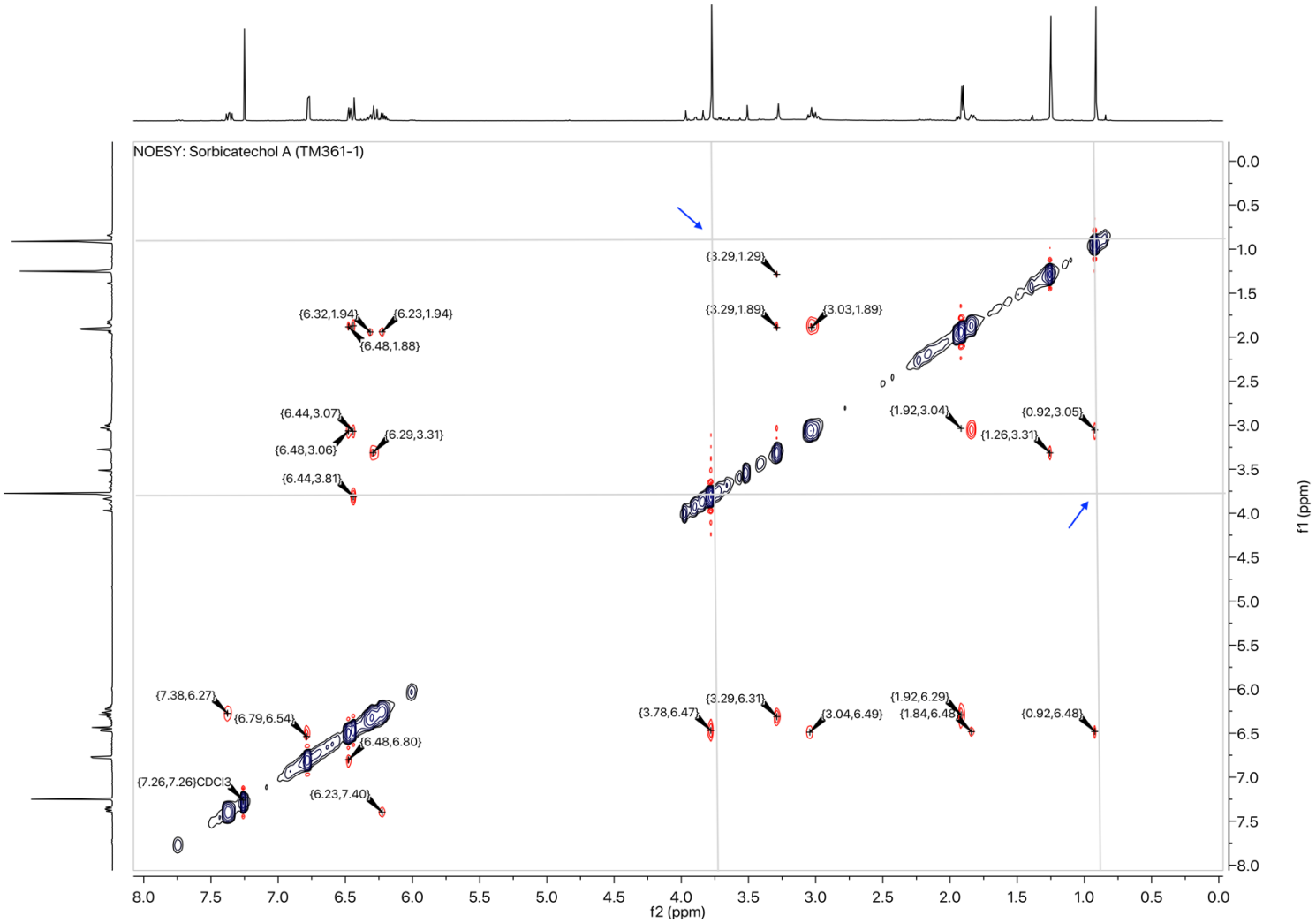
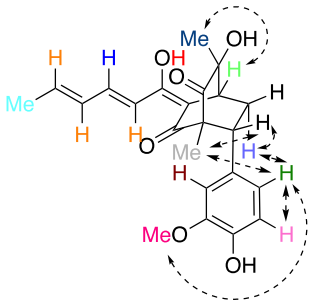


Figure S3. ^{13}C-NMR spectrum of sorbicatechol A (**7a**) in $CDCl_3$.





14.32 (s, 1H)
7.37 (dd, J = 14.9, 10.9 Hz, 1H)
6.78 (d, J = 8.1 Hz, 1H)
6.48 (dd ,J = 8.1, 2.0 Hz,1H)
6.44 (d, J = 2.0 Hz, 1H)
6.36–6.19 (m, 3H)
3.78 (s, 3H)
3.29 (t, J = 2.6 Hz, 1H)
3.08–2.98 (m, 2H),
1.92 (d, J = 6.6 Hz, 3H)
1.84 (ddd, J = 12.8, 4.4, 2.9 Hz, 1H)
1.26 (s, 3H)
0.92 (s, 3H)

Figure S4. NOESY spectrum of sorbicatechol A (**7a**) in $CDCl_3$. Blue arrows illustrate missing correlation between 1-CH_3 and 17-OCH_3 which would be necessary for *exo*-orientation.[3]

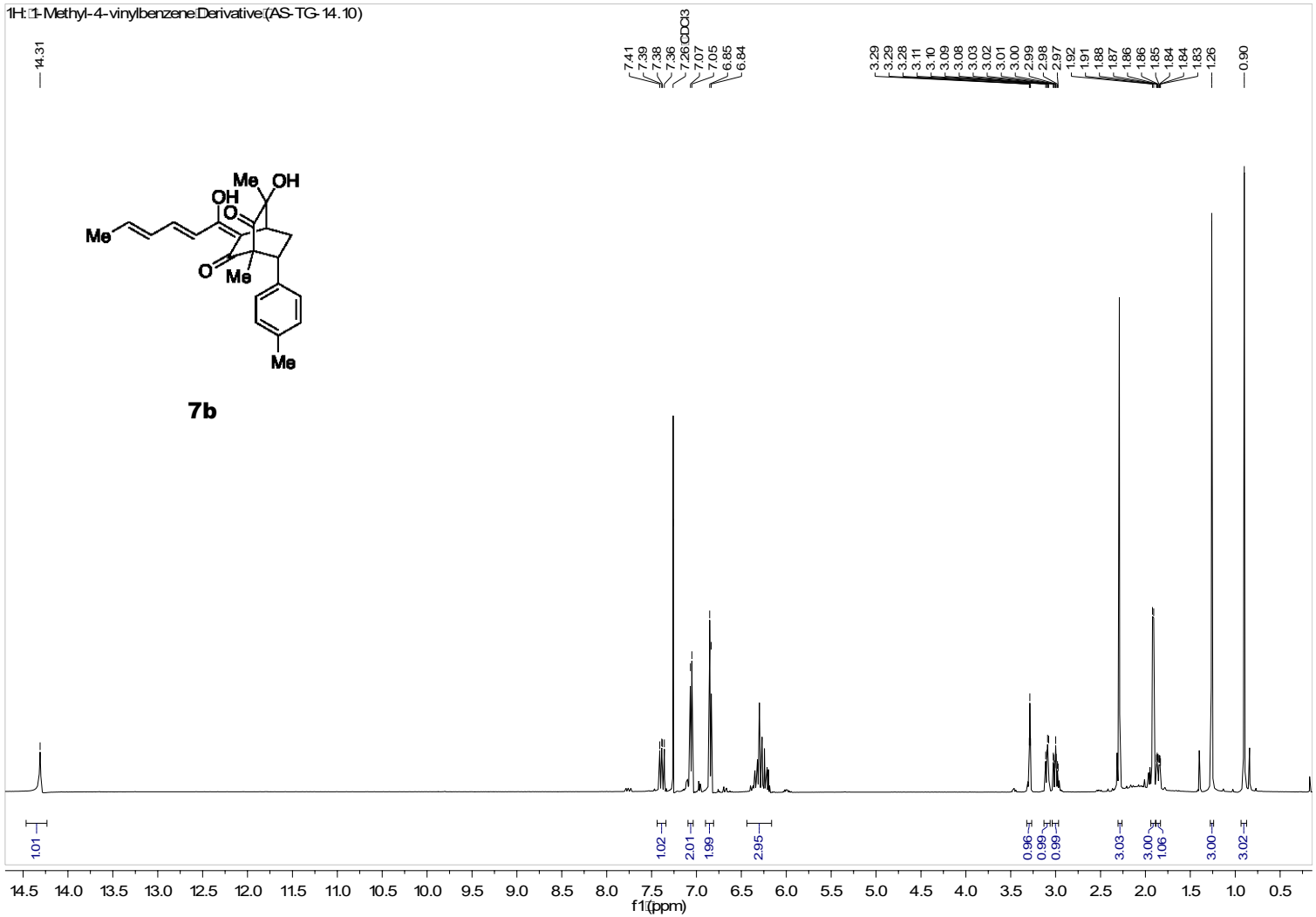


Figure S5. ^{1}H-NMR spectrum of 1-methyl-4-vinylbenzene derivative (**7b**) in $CDCl_3$.

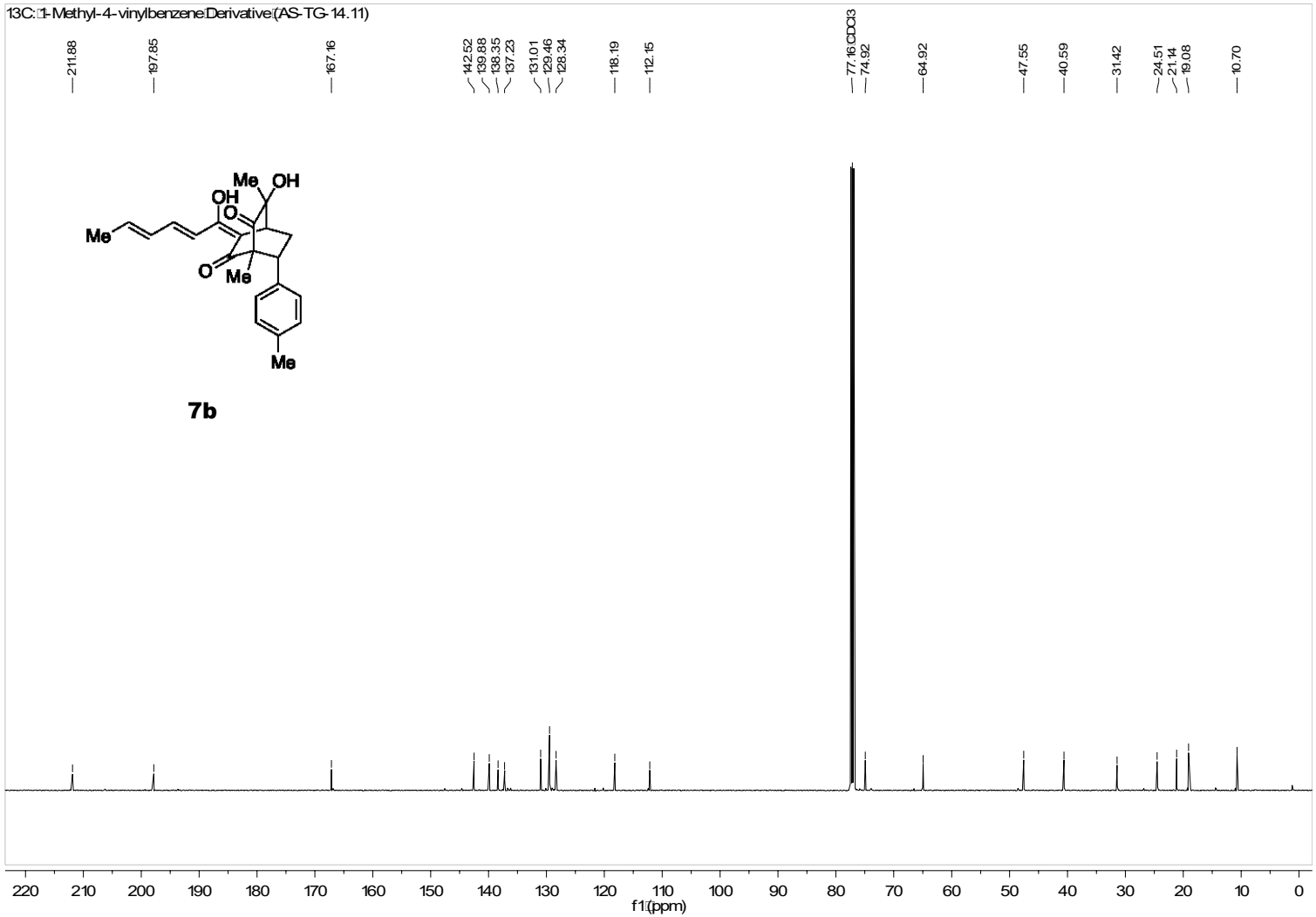


Figure S6. ^{13}C-NMR spectrum of 1-methyl-4-vinylbenzene derivative (**7b**) in $CDCl_3$.

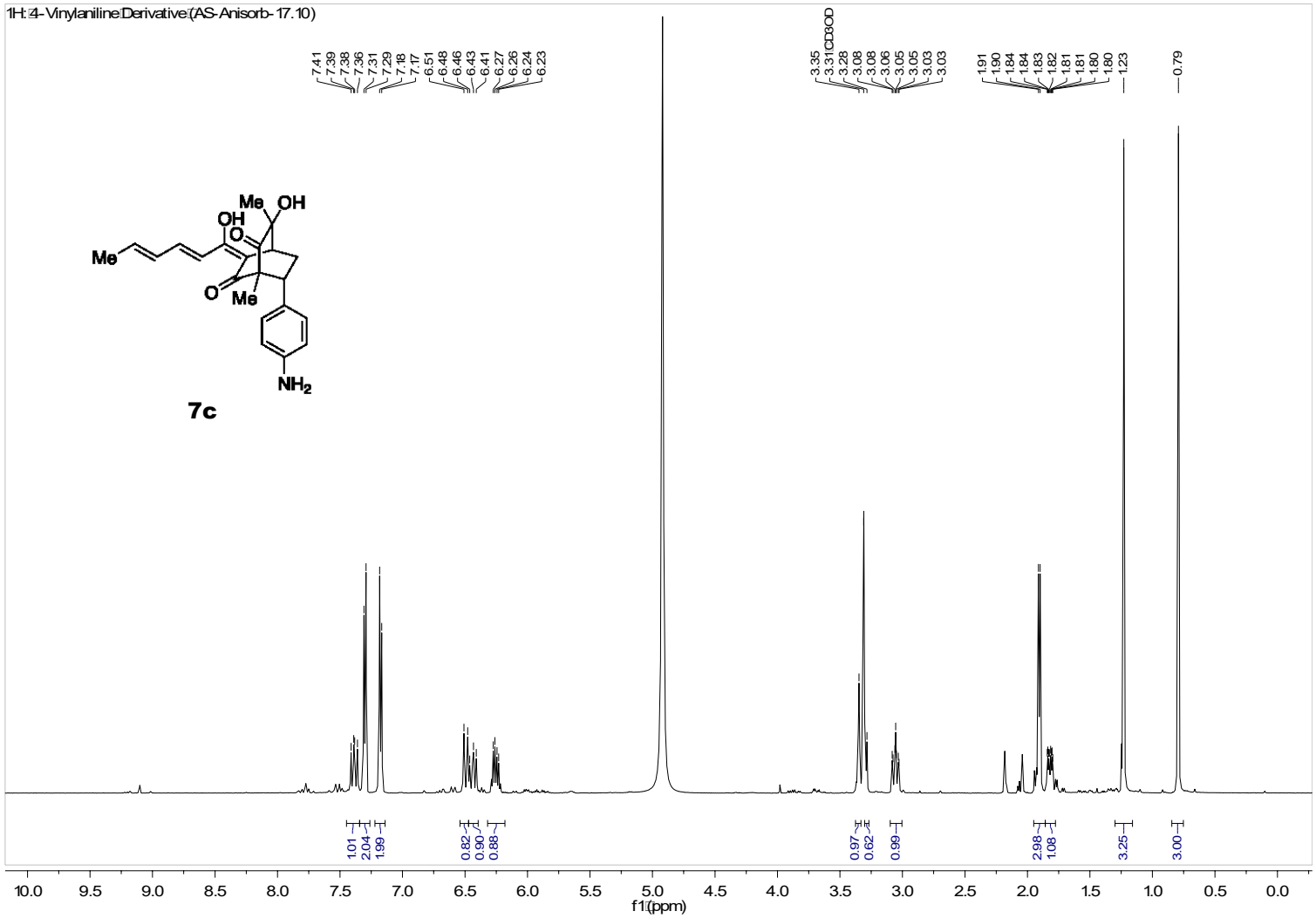


Figure S7. ^{1}H-NMR spectrum of 4-vinylaniline derivative (**7c**) in MeOD-d_4.

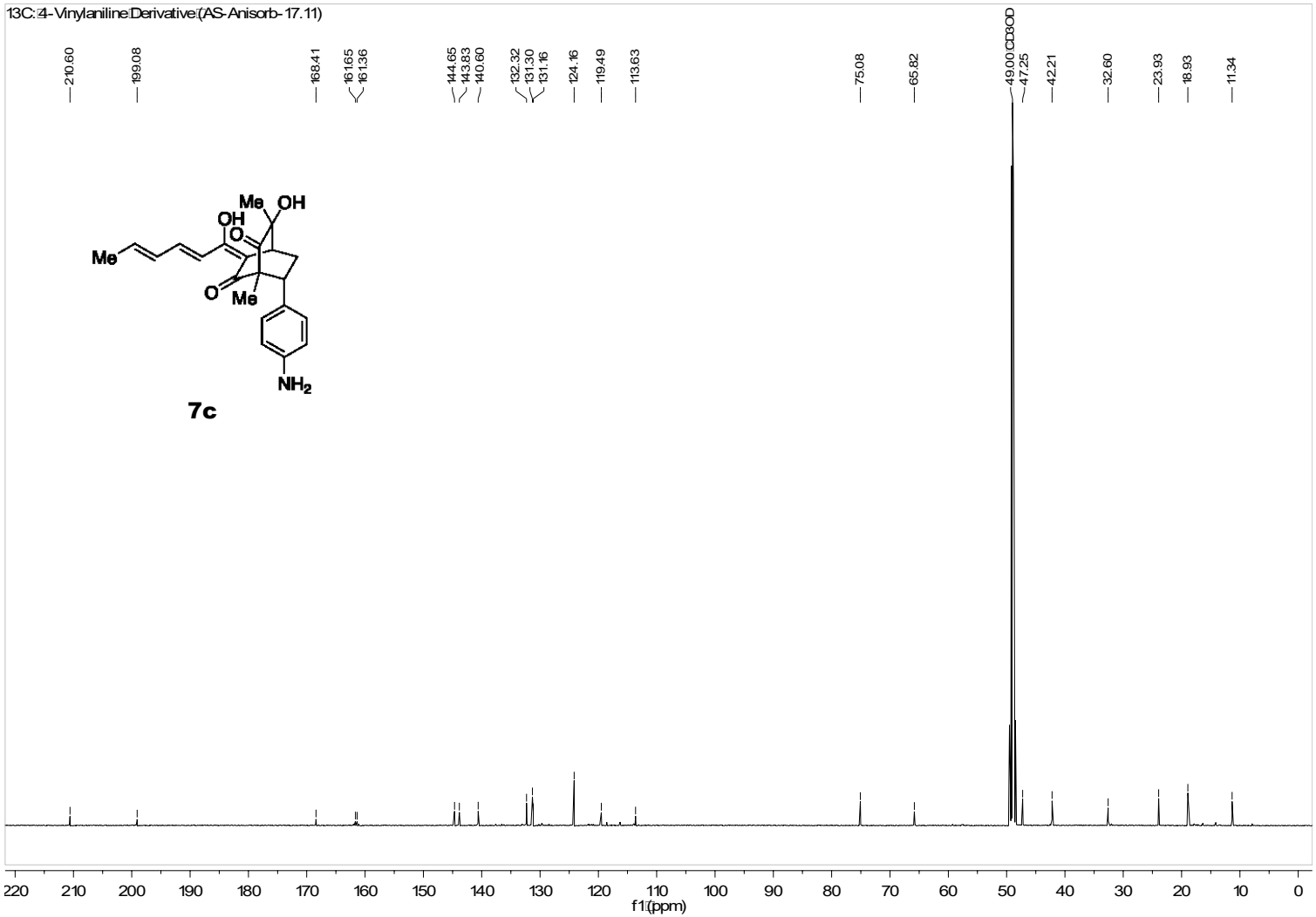


Figure S8. ^{13}C-NMR spectrum of 4-vinylaniline derivative (**7c**) in MeOD-d_4.

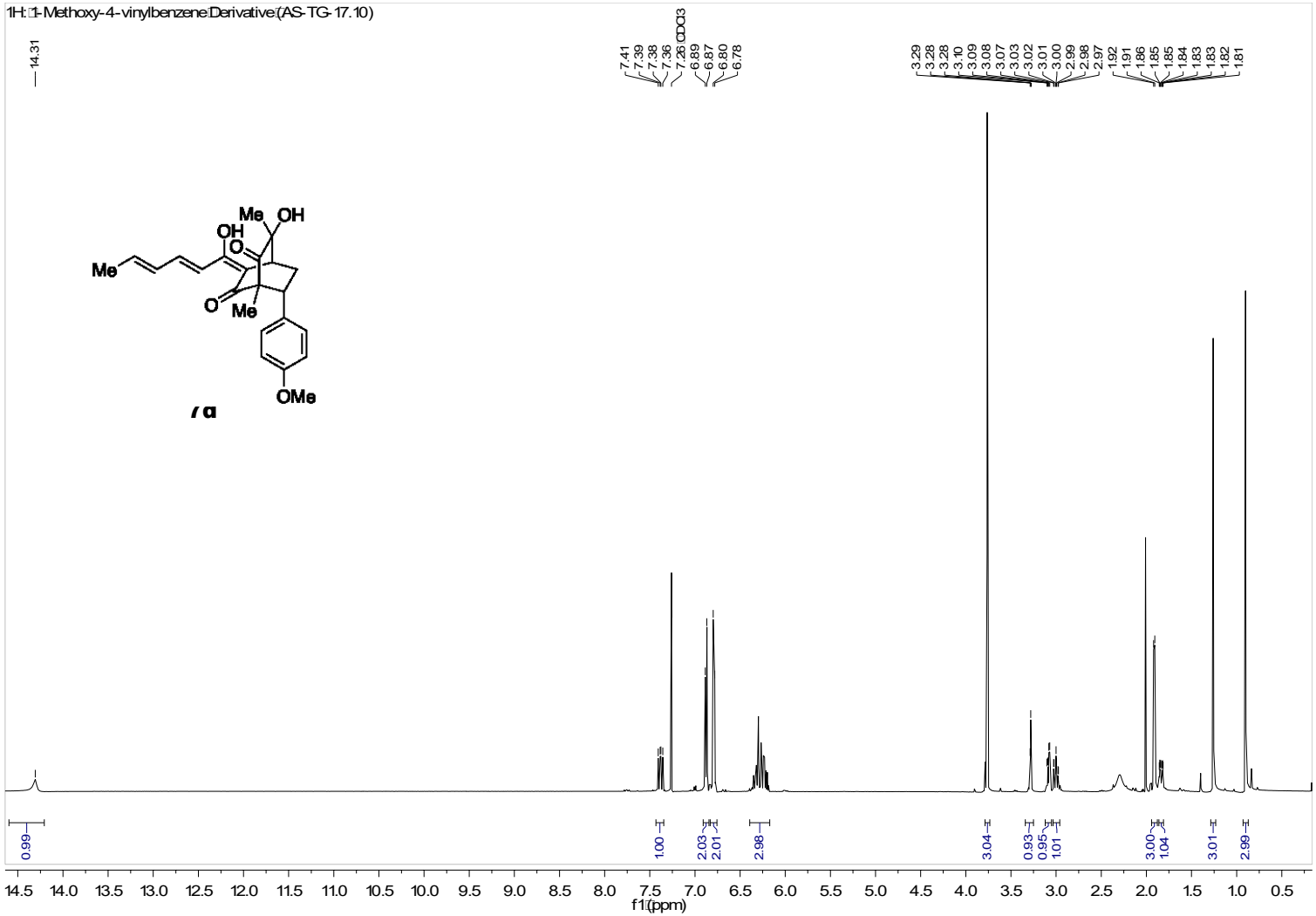


Figure S9. ^{1}H-NMR spectrum of 1-methoxy-4-vinylbenzene derivative (**7d**) in $CDCl_3$.

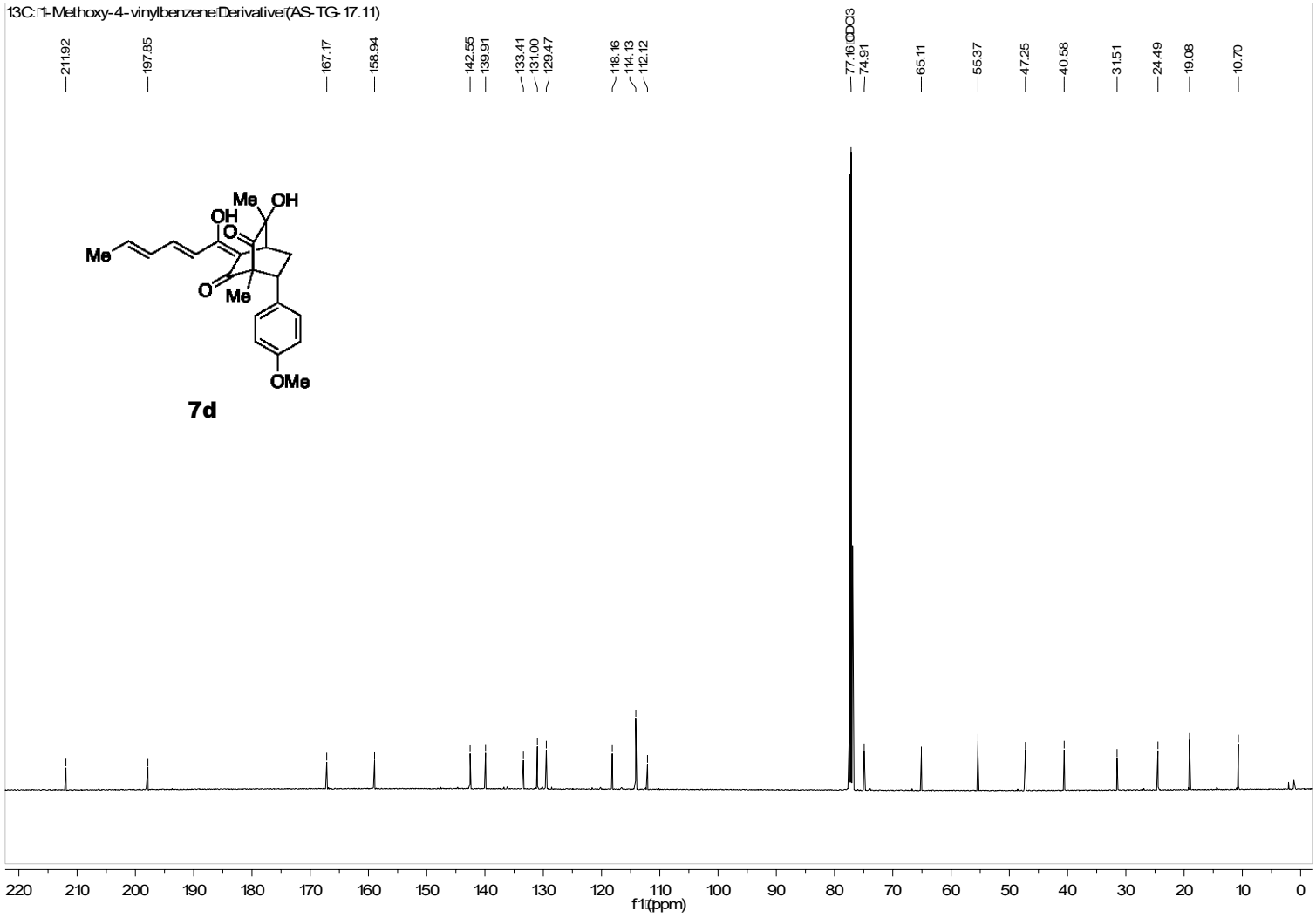


Figure S10. ^{13}C-NMR spectrum of 1-methoxy-4-vinylbenzene derivative (**7d**) in $CDCl_3$.

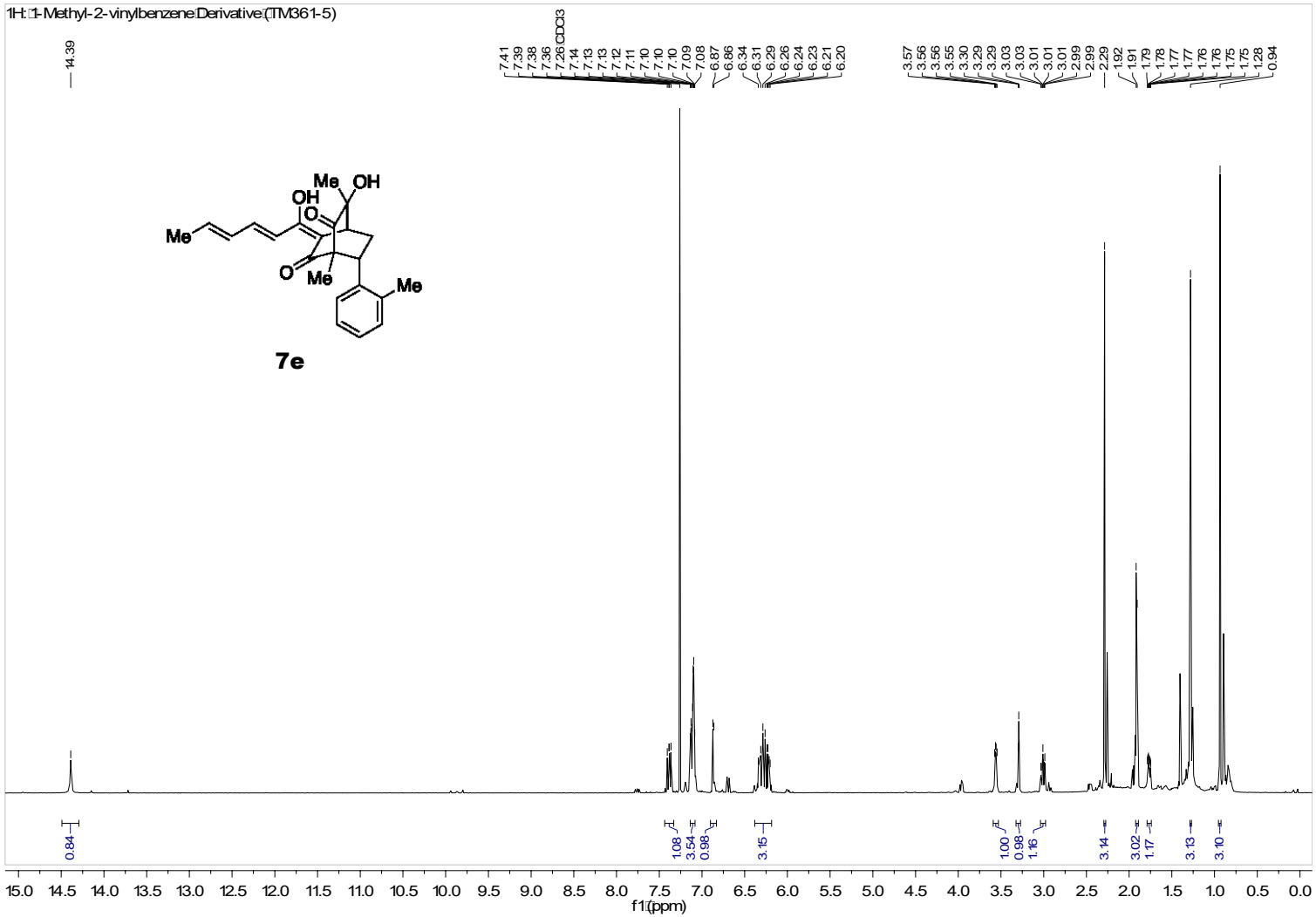


Figure S7. ^{1}H-NMR spectrum of 1-methyl-2-vinylbenzene derivative (**7e**) in $CDCl_3$.

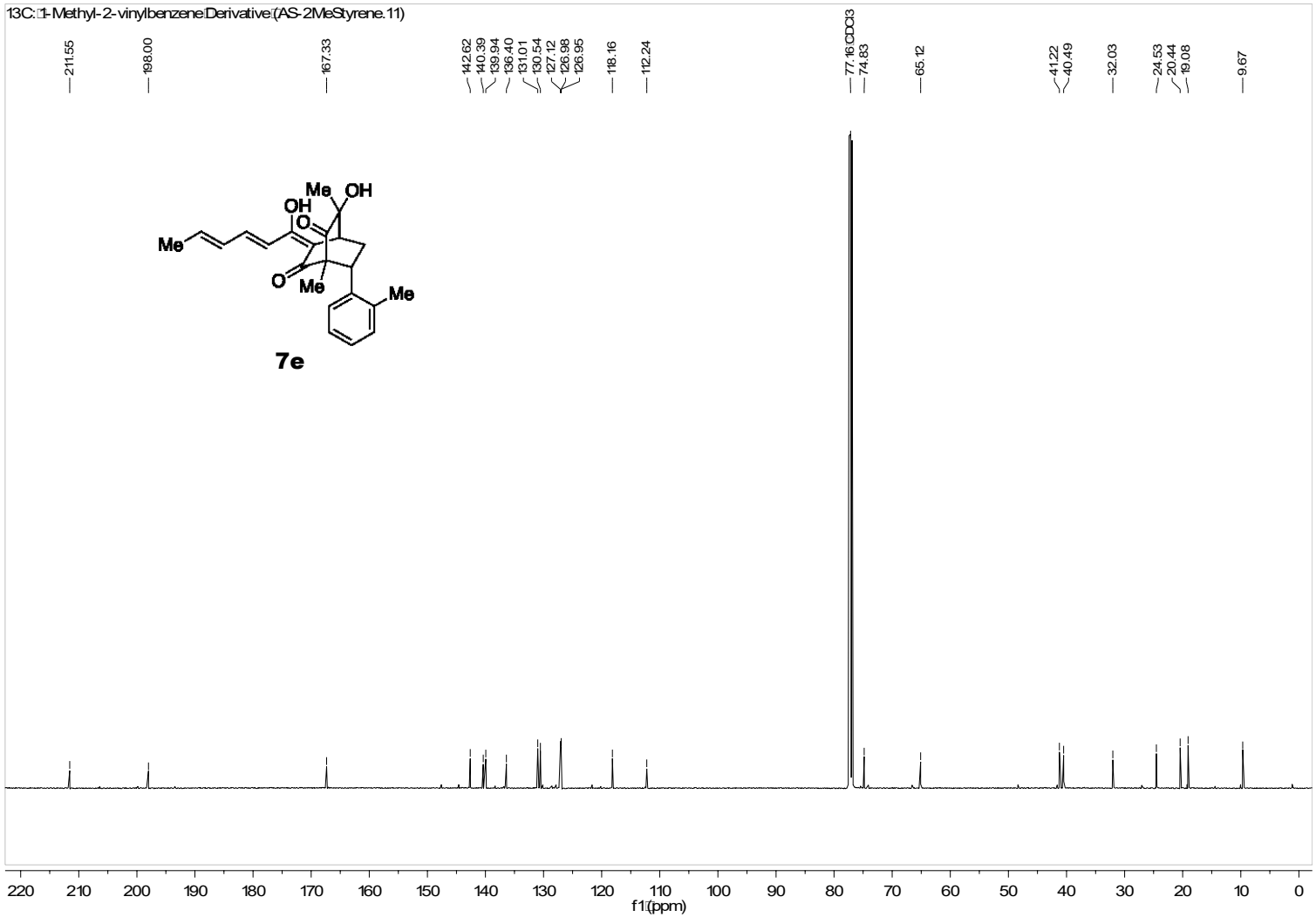


Figure S8. ^{13}C-NMR spectrum of 1-methyl-2-vinylbenzene derivative (**7e**) in $CDCl_3$.

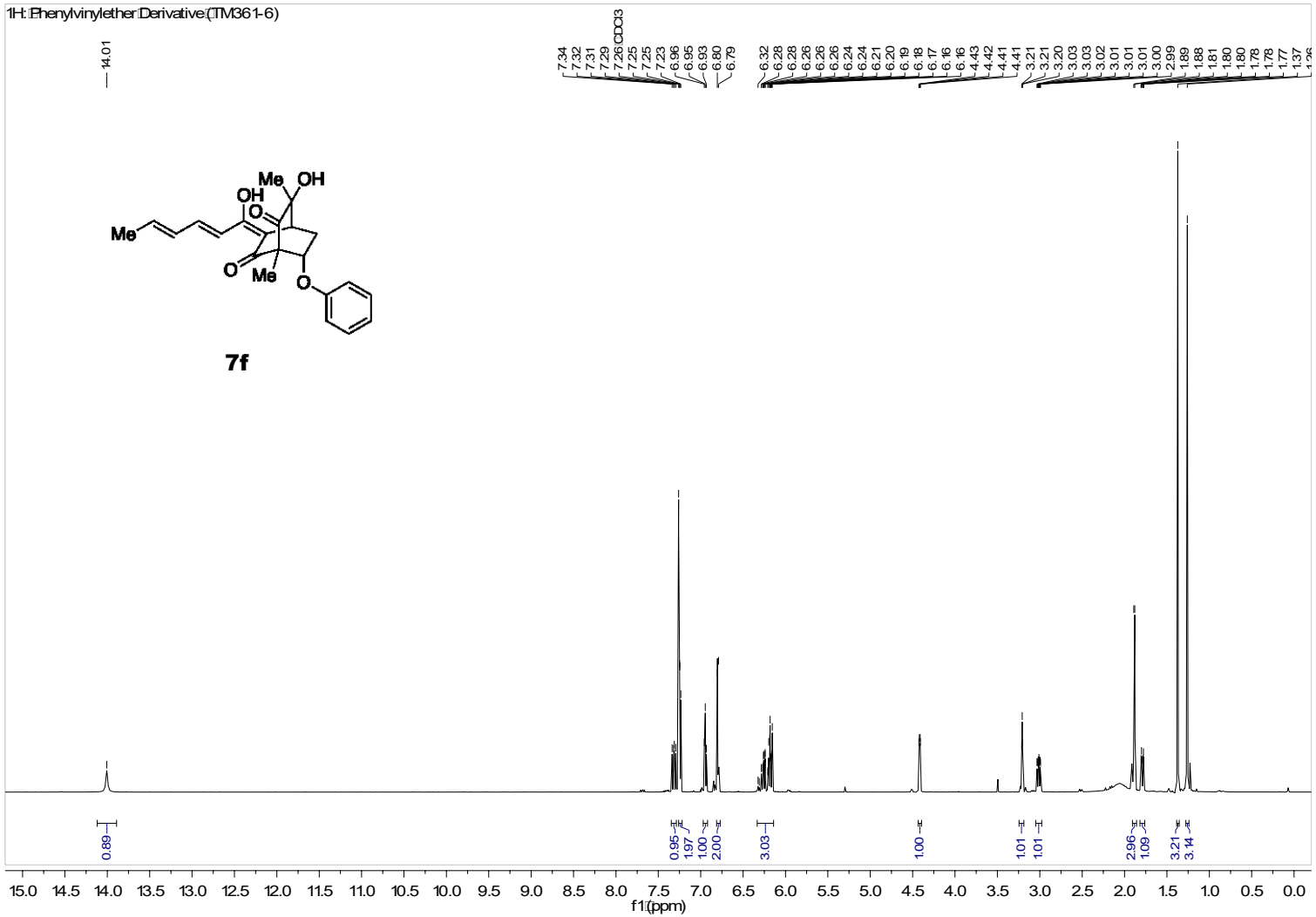


Figure S9. ^{1}H-NMR spectrum of phenylvinylether derivative (**7f**) in $CDCl_3$.

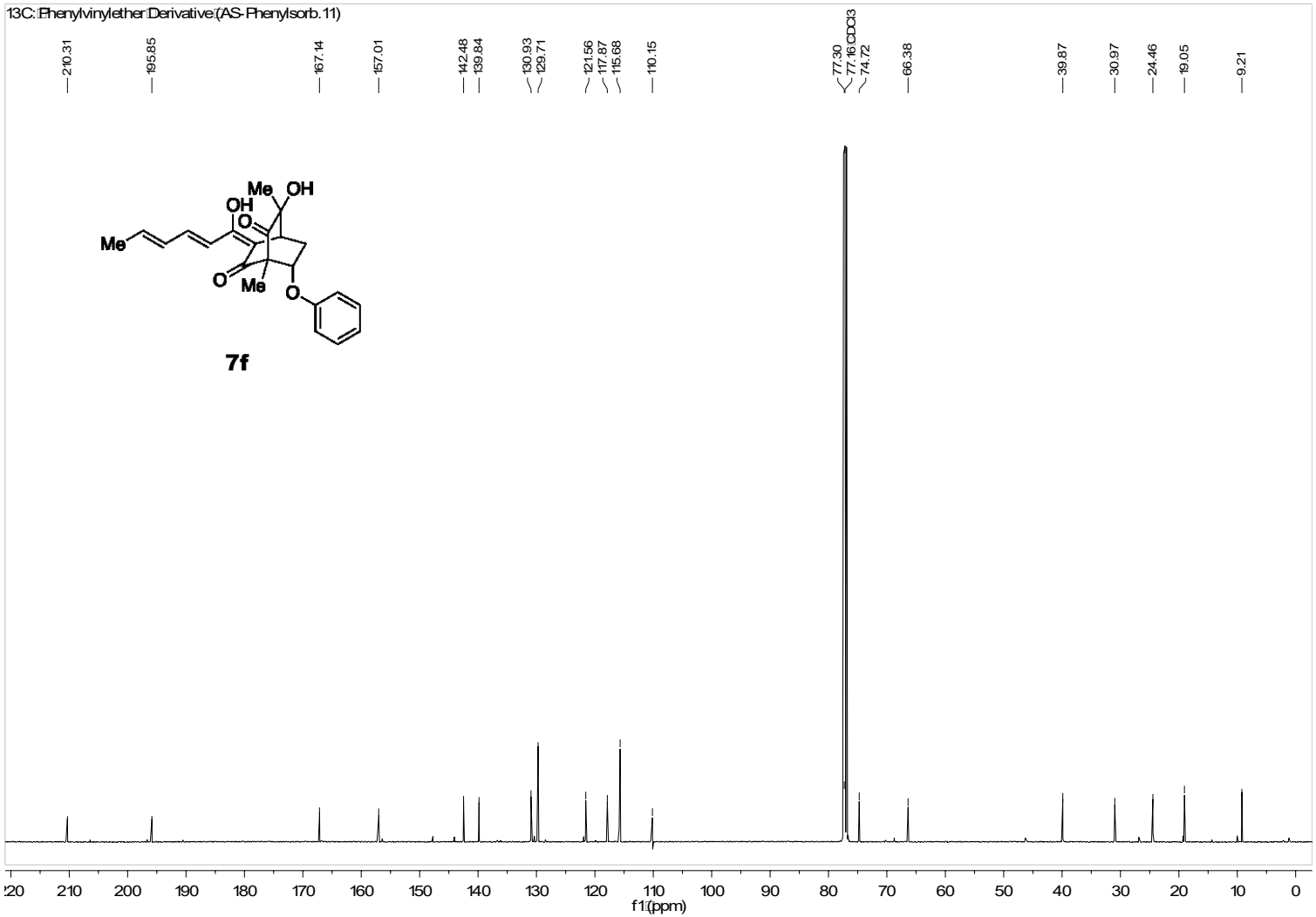


Figure S10. ^{13}C-NMR spectrum of phenylvinylether derivative (**7f**) in $CDCl_3$.

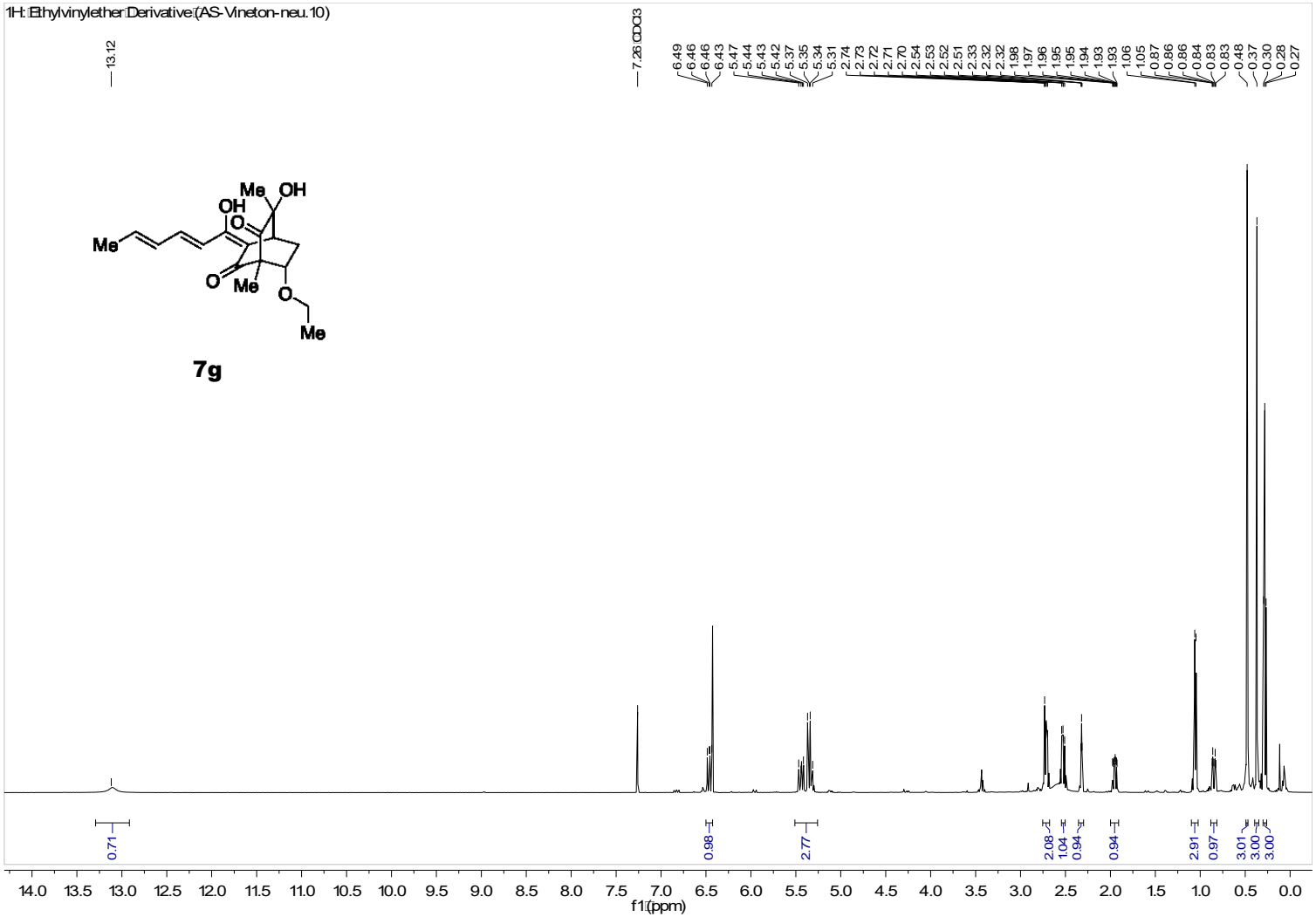


Figure S11. ^{1}H-NMR spectrum of ethylvinylether derivative (**7g**) in $CDCl_3$.

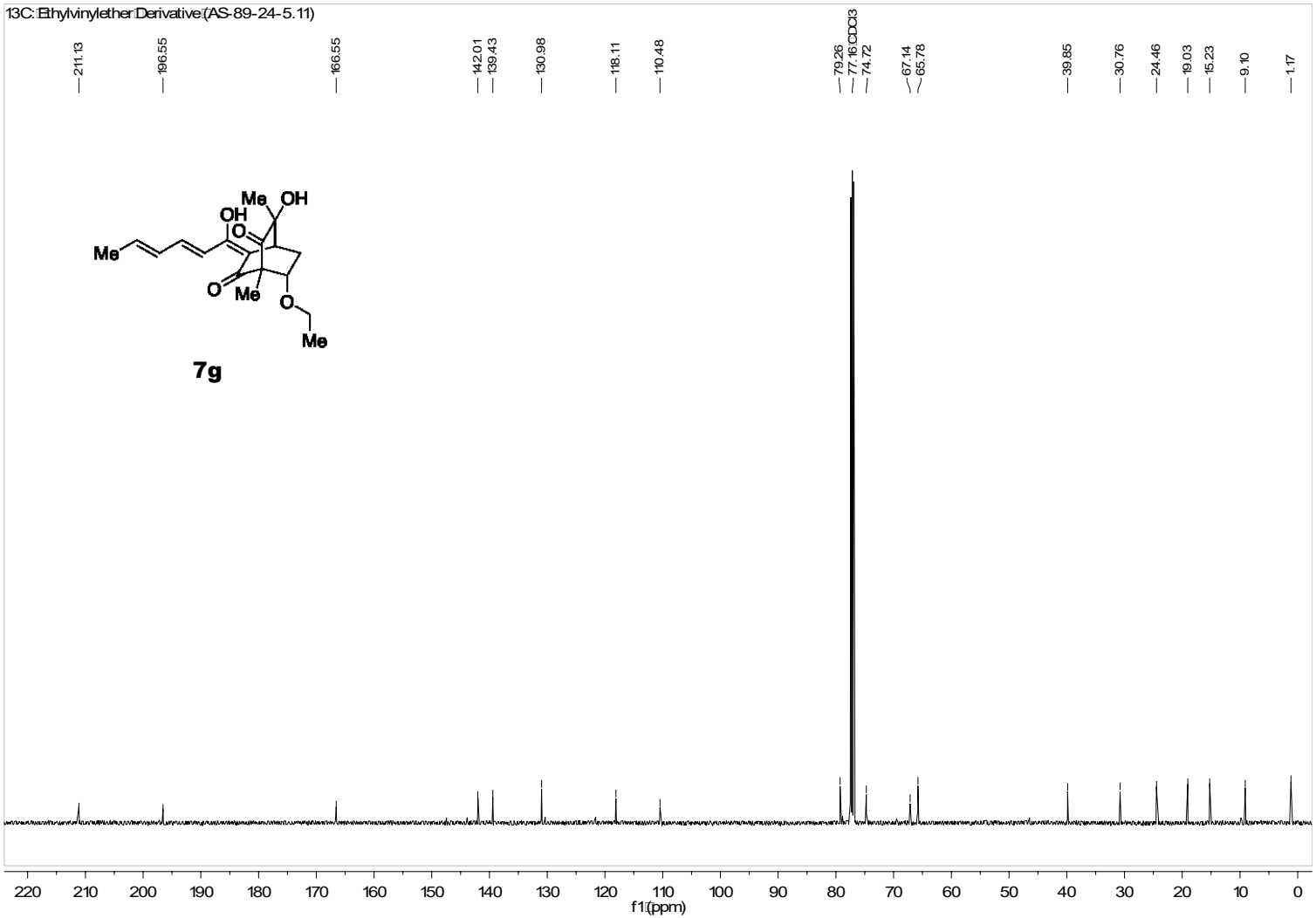


Figure S16. ^{13}C-NMR spectrum of ethylvinylether derivative (**7g**) in $CDCl_3$.

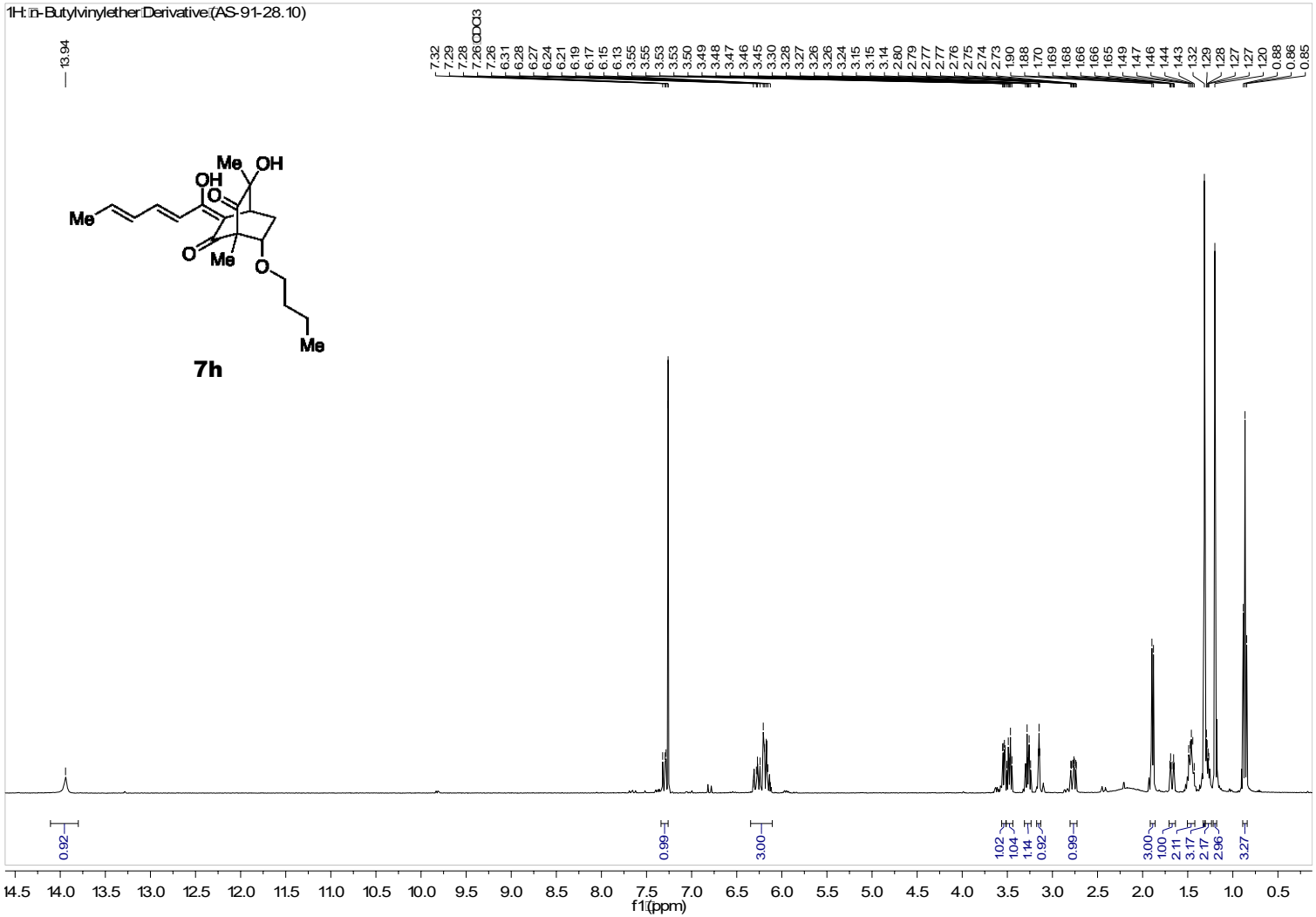


Figure S17. ^{1}H-NMR spectrum of *n*-butylvinylether derivative (**7h**) in $CDCl_3$.

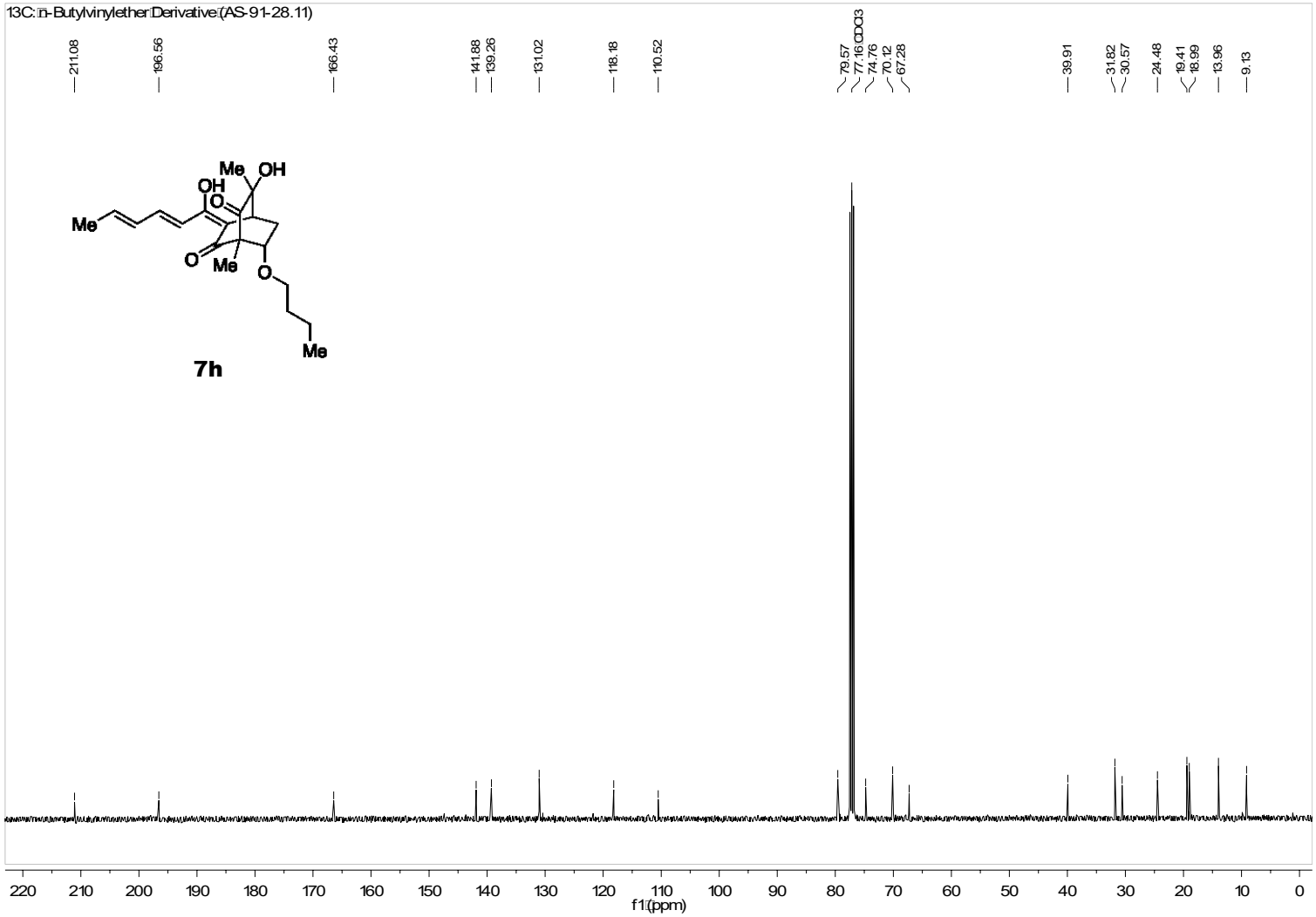


Figure S18. ^{13}C-NMR spectrum of *n*-butylvinylether derivative (**7h**) in $CDCl_3$.

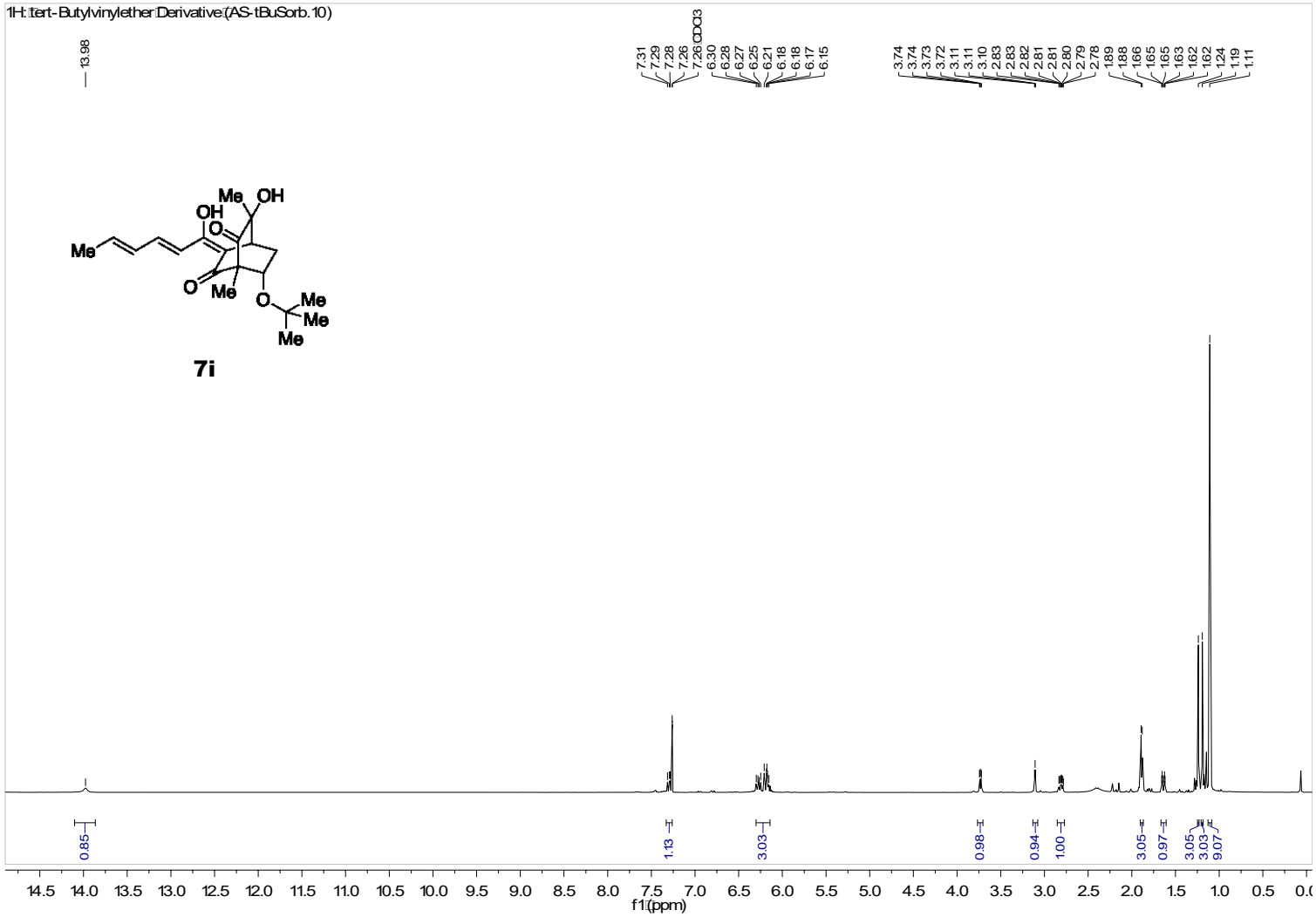


Figure S19. ^{1}H-NMR spectrum of *tert*-butylvinylether derivative (**7i**) in $CDCl_3$.

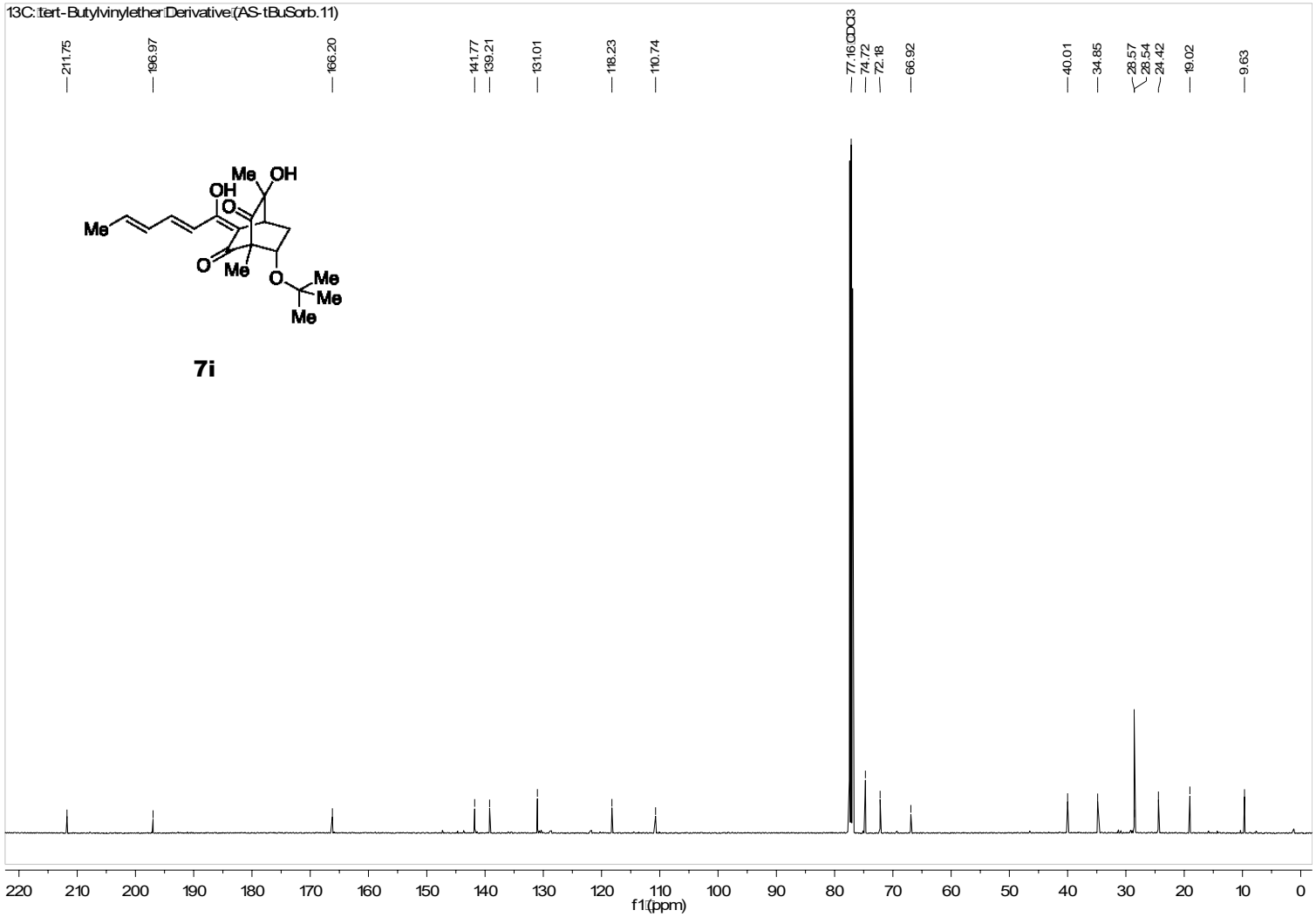


Figure S20. ^{13}C-NMR spectrum of *tert*-butylvinylether derivative (**7i**) in $CDCl_3$.

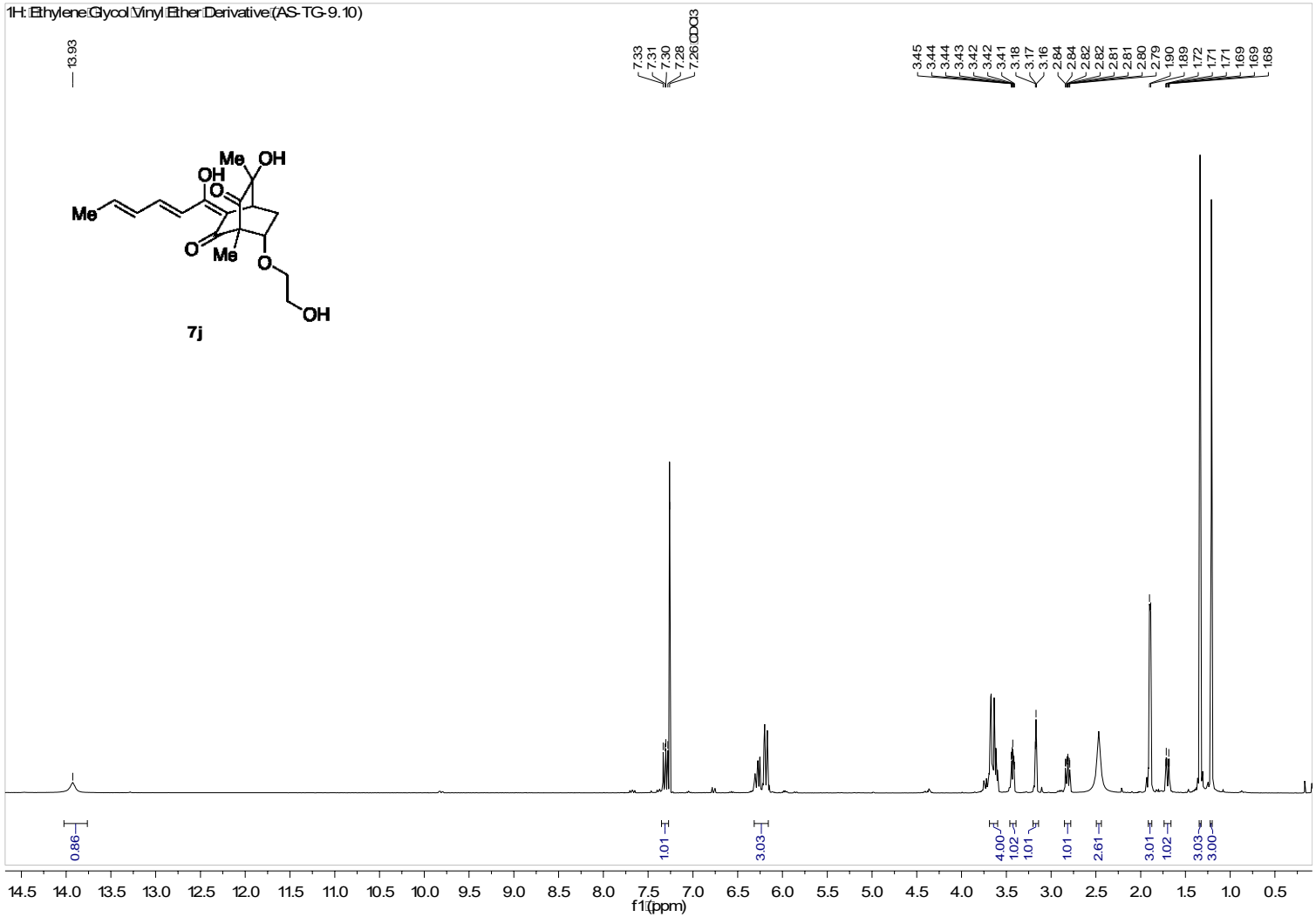


Figure S12. ^{1}H-NMR spectrum of ethylene glycol vinyl ether derivative (**7j**) in $CDCl_3$.

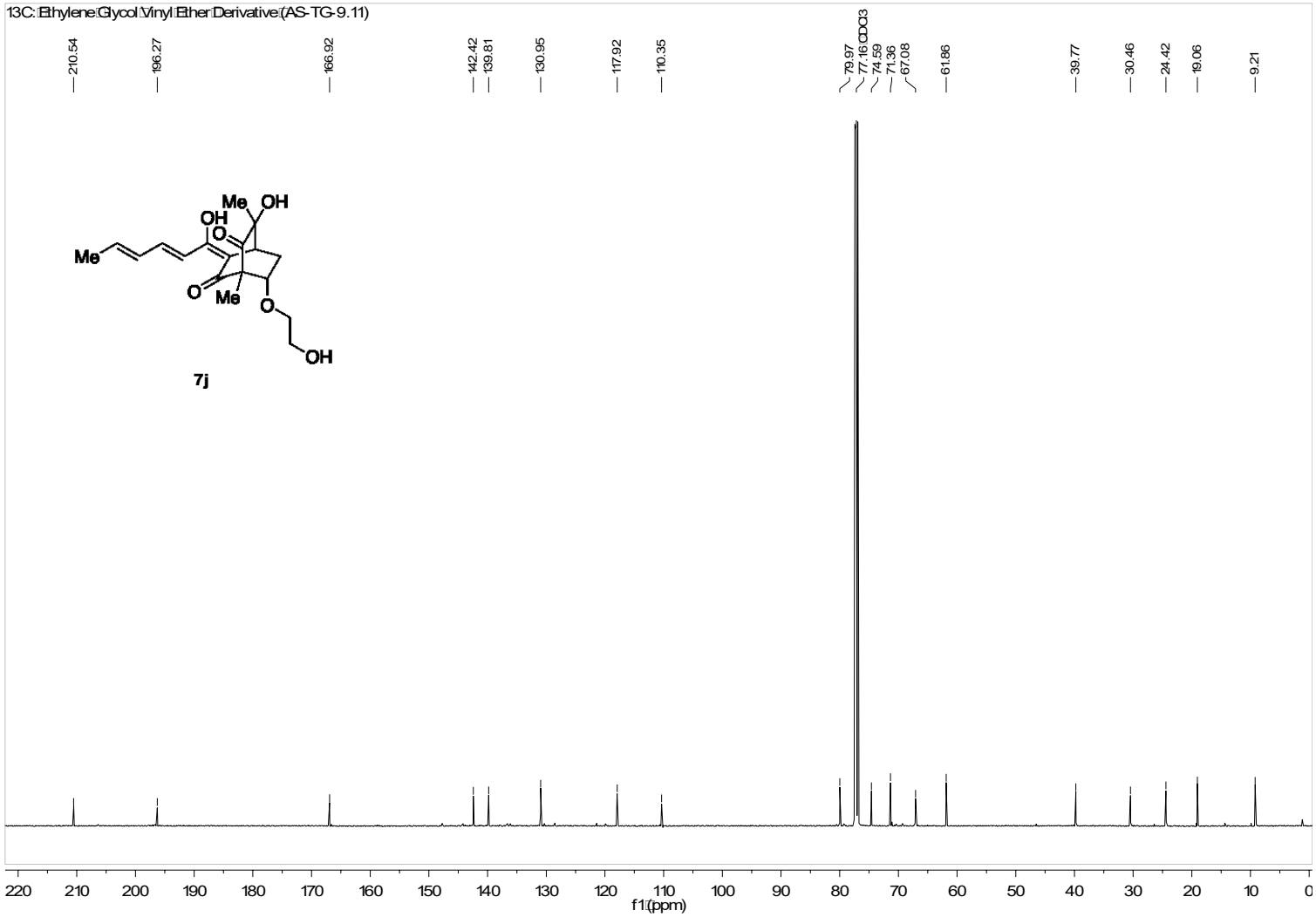


Figure S13. ^{13}C-NMR spectrum of ethylene glycol vinyl ether derivative (**7j**) in $CDCl_3$.

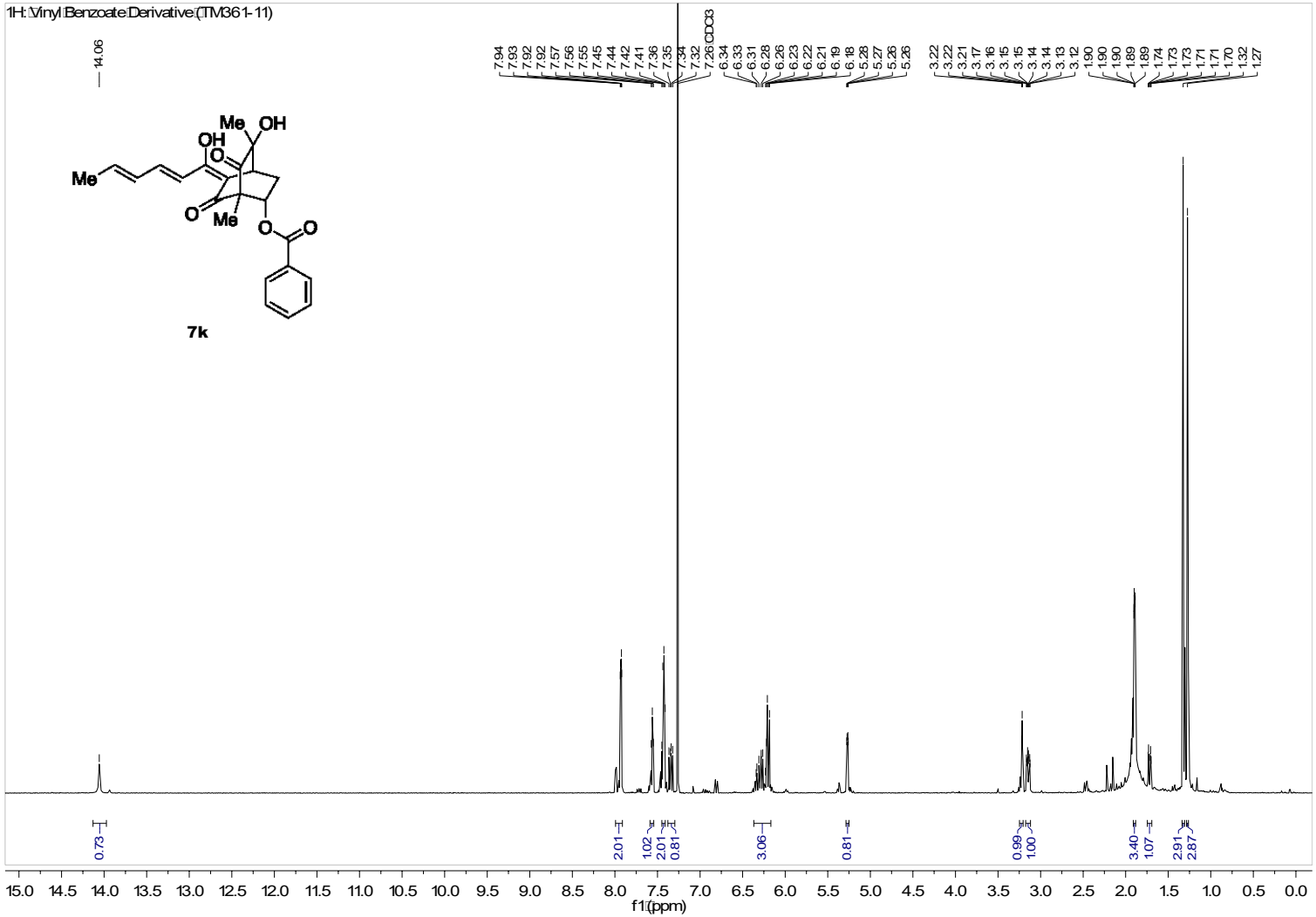


Figure S23. ^{1}H-NMR spectrum of vinyl benzoate derivative (**7k**) in $CDCl_3$.

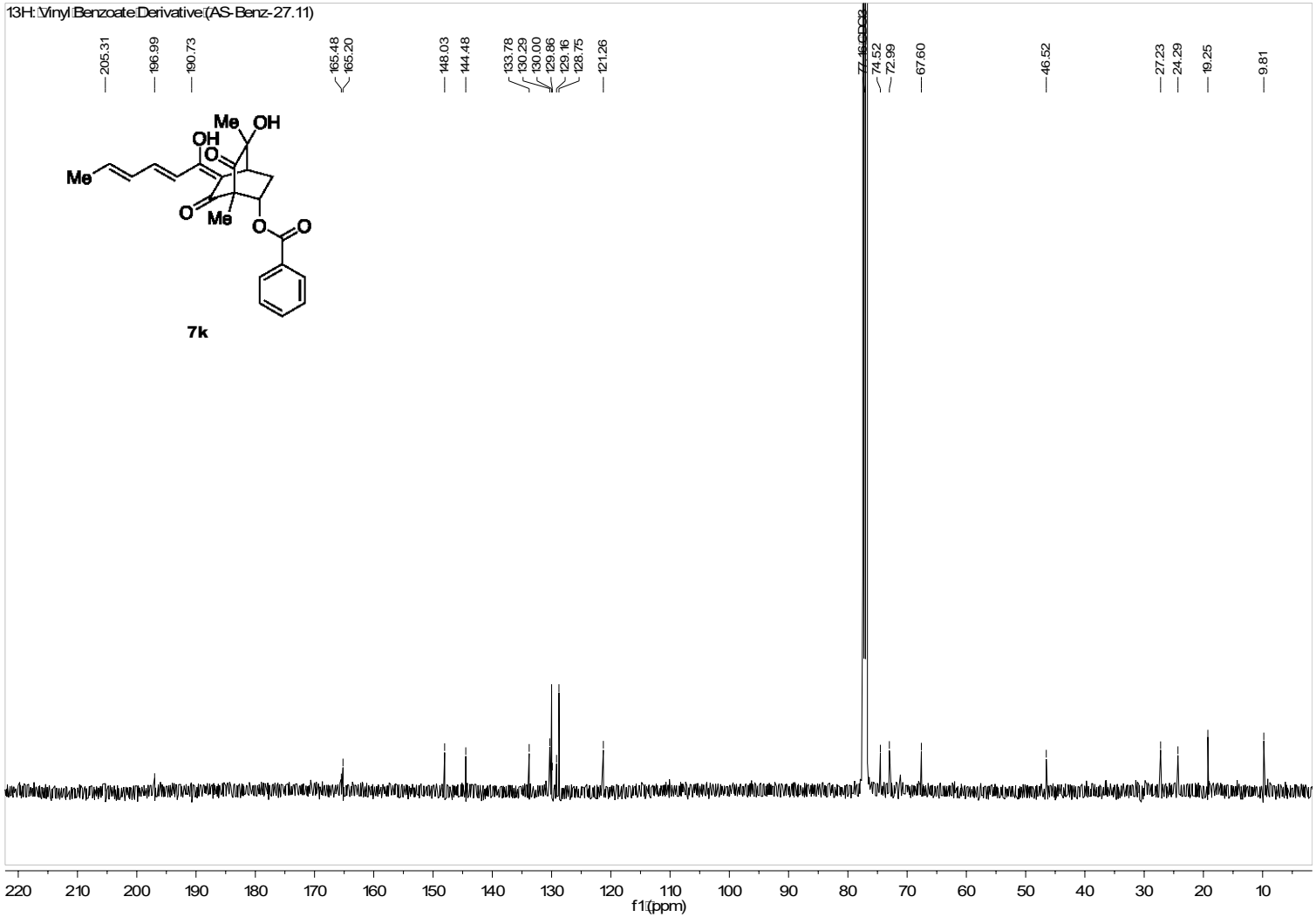


Figure S24. ^{13}C-NMR spectrum of vinyl benzoate derivative (**7k**) in $CDCl_3$.

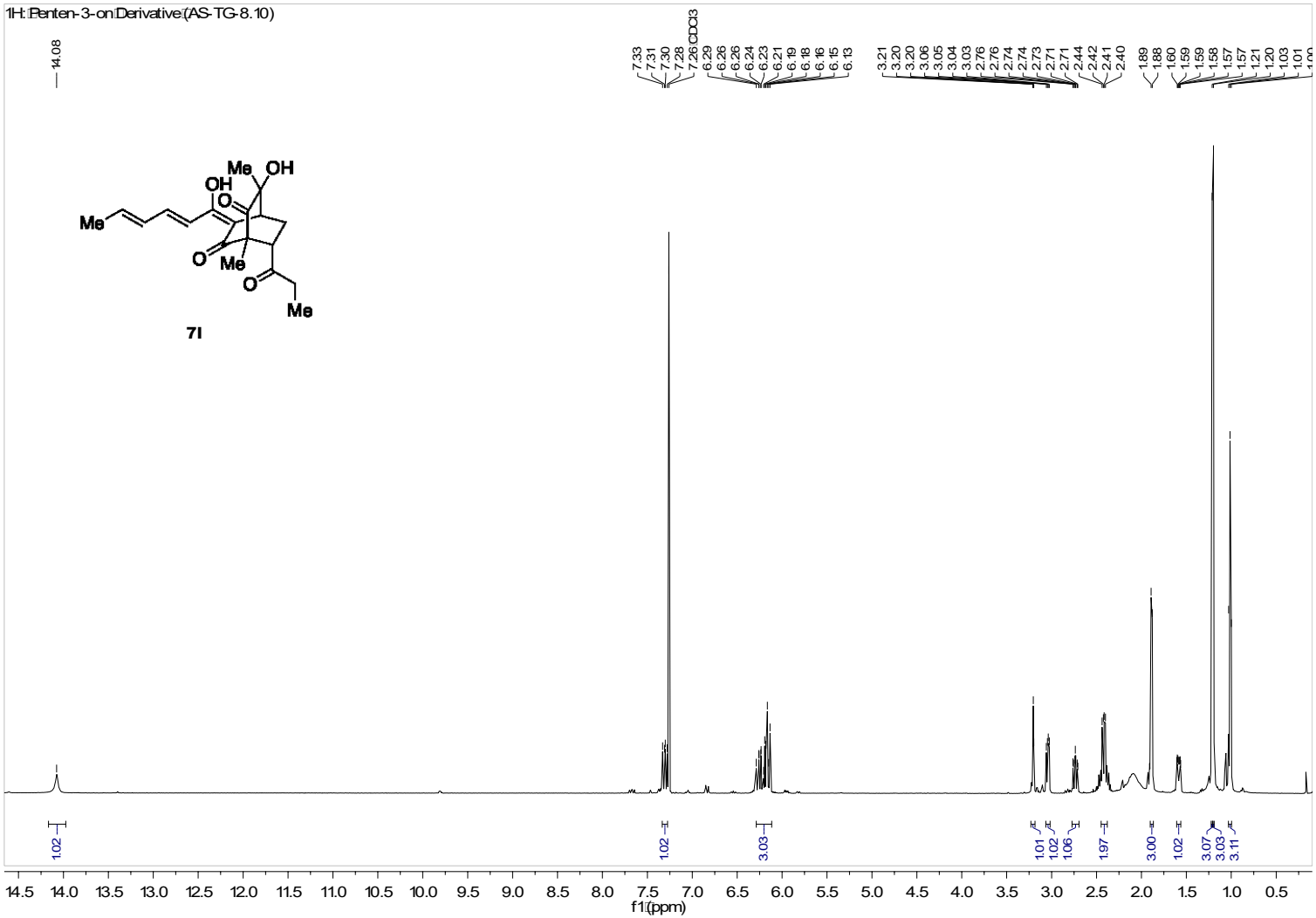


Figure S25. ^{1}H-NMR spectrum of penten-3-on derivative (**7I**) in $CDCl_3$.

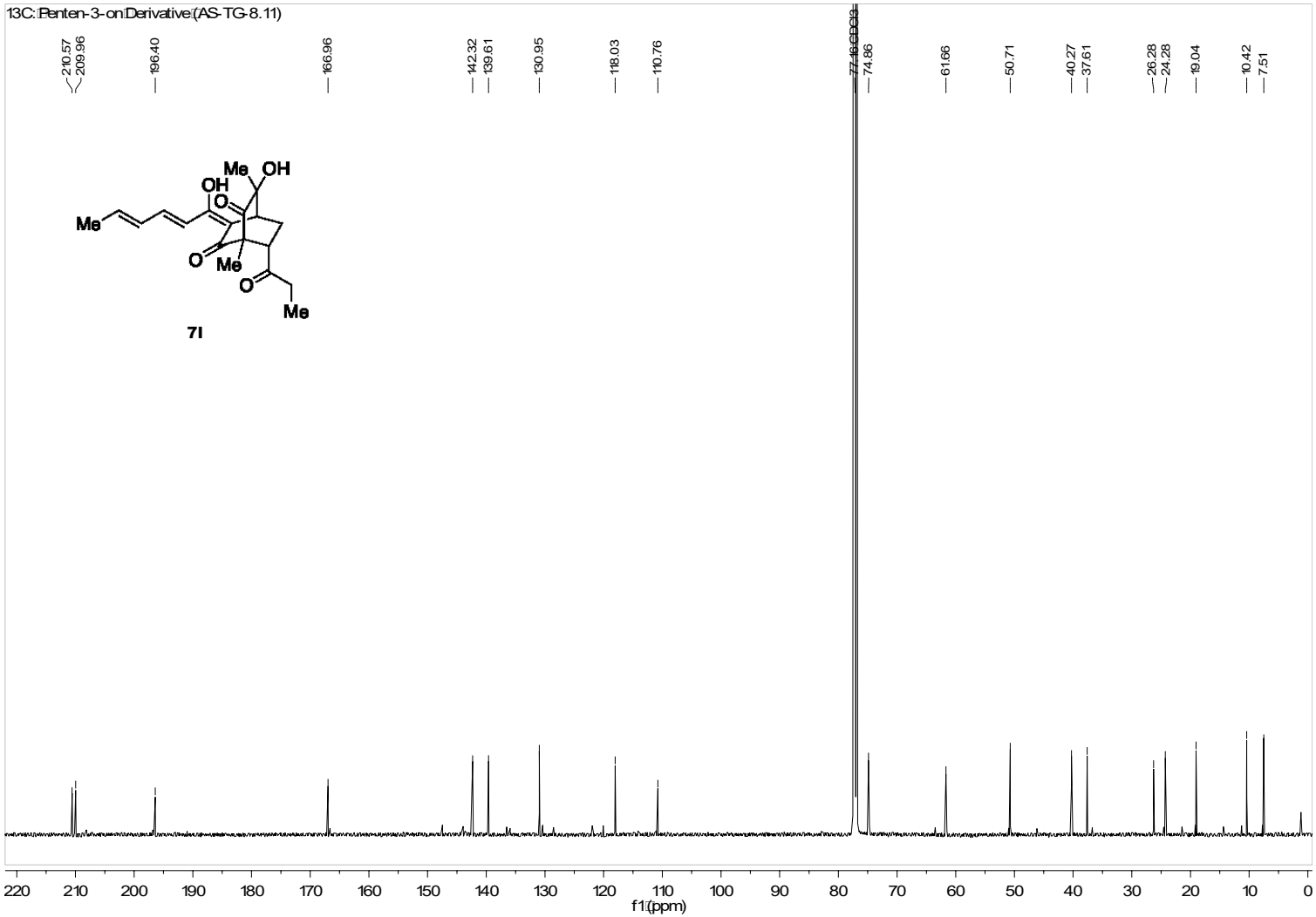


Figure S26. ^{13}C-NMR spectrum of penten-3-on derivative (**7l**) in $CDCl_3$.

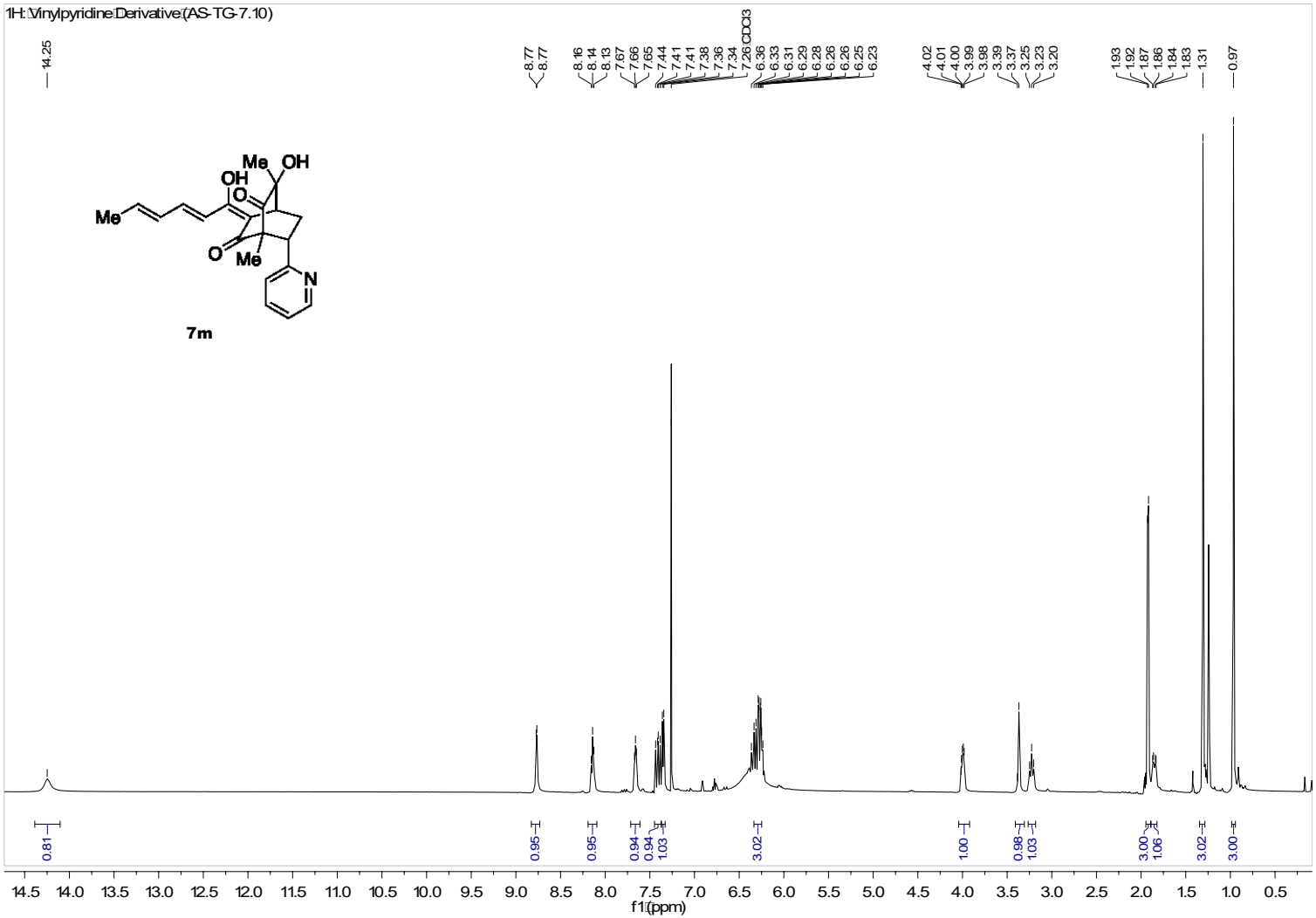


Figure S27. ^{1}H-NMR spectrum of vinylpyridine derivative (**7m**) in $CDCl_3$.

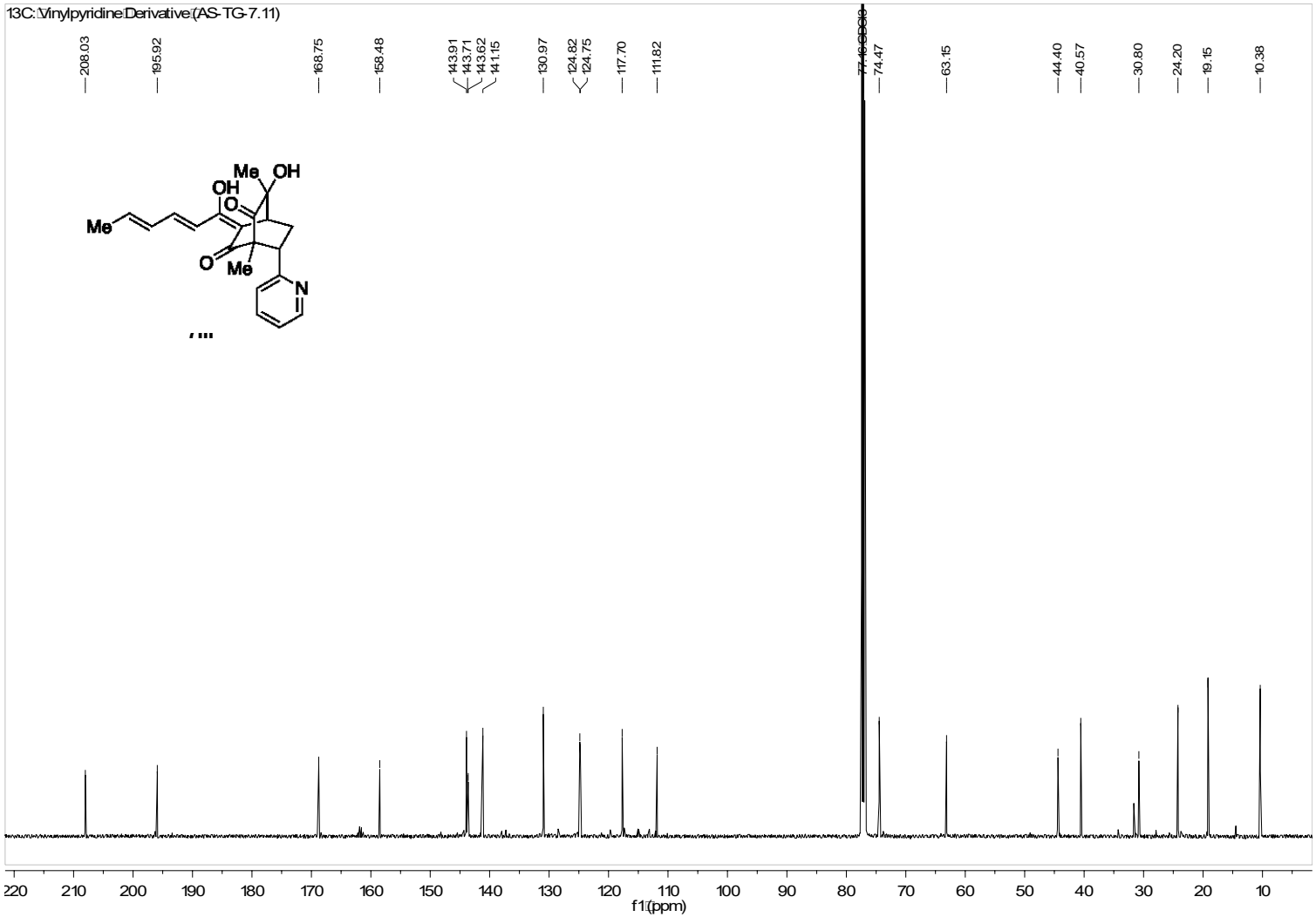


Figure S14. ^{13}C-NMR spectrum of vinylpyridine derivative (**7m**) in $CDCl_3$.

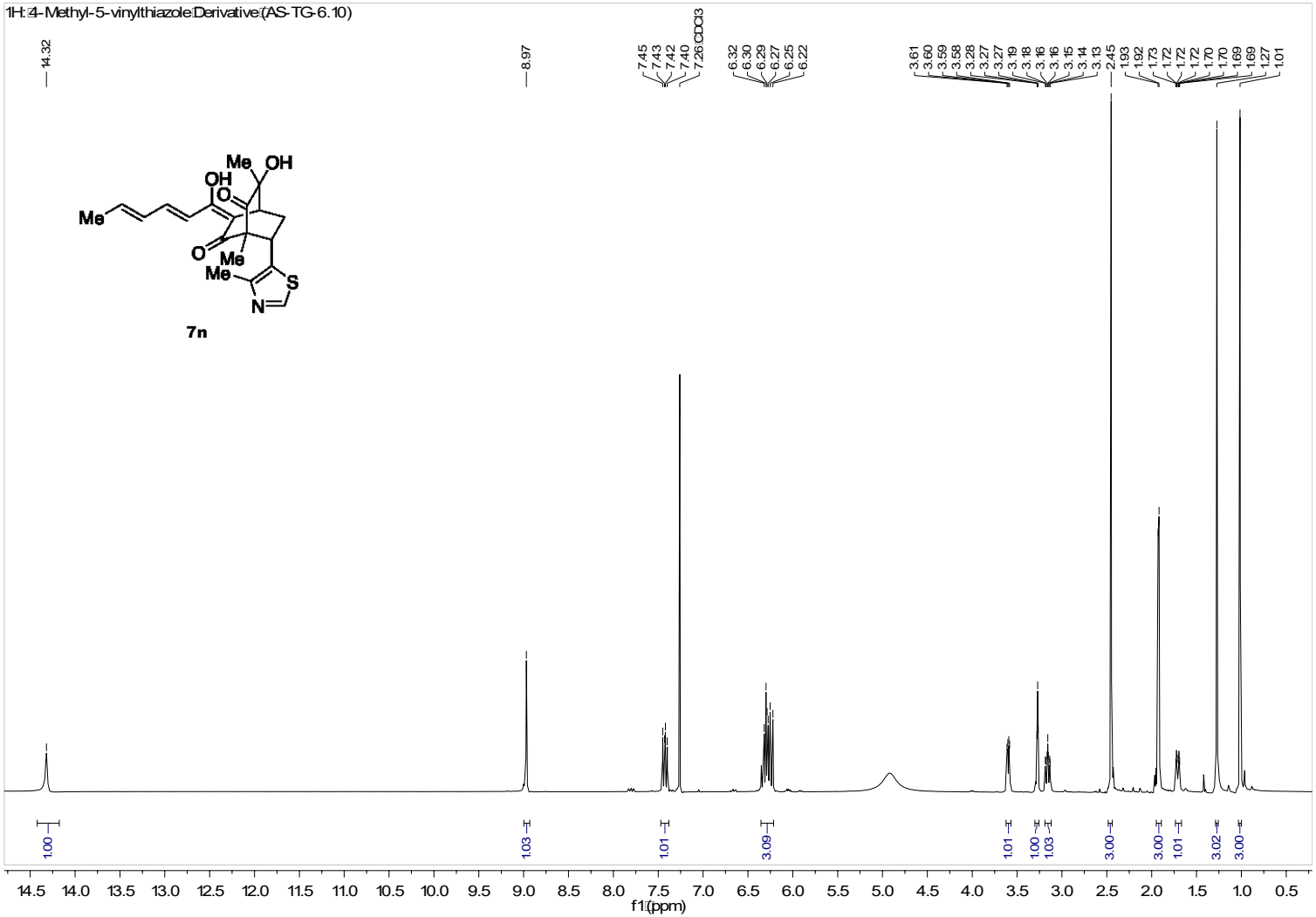


Figure S29. ^{1}H-NMR spectrum of 4-methyl-5-vinylthiazole derivative (**7n**) in $CDCl_3$.

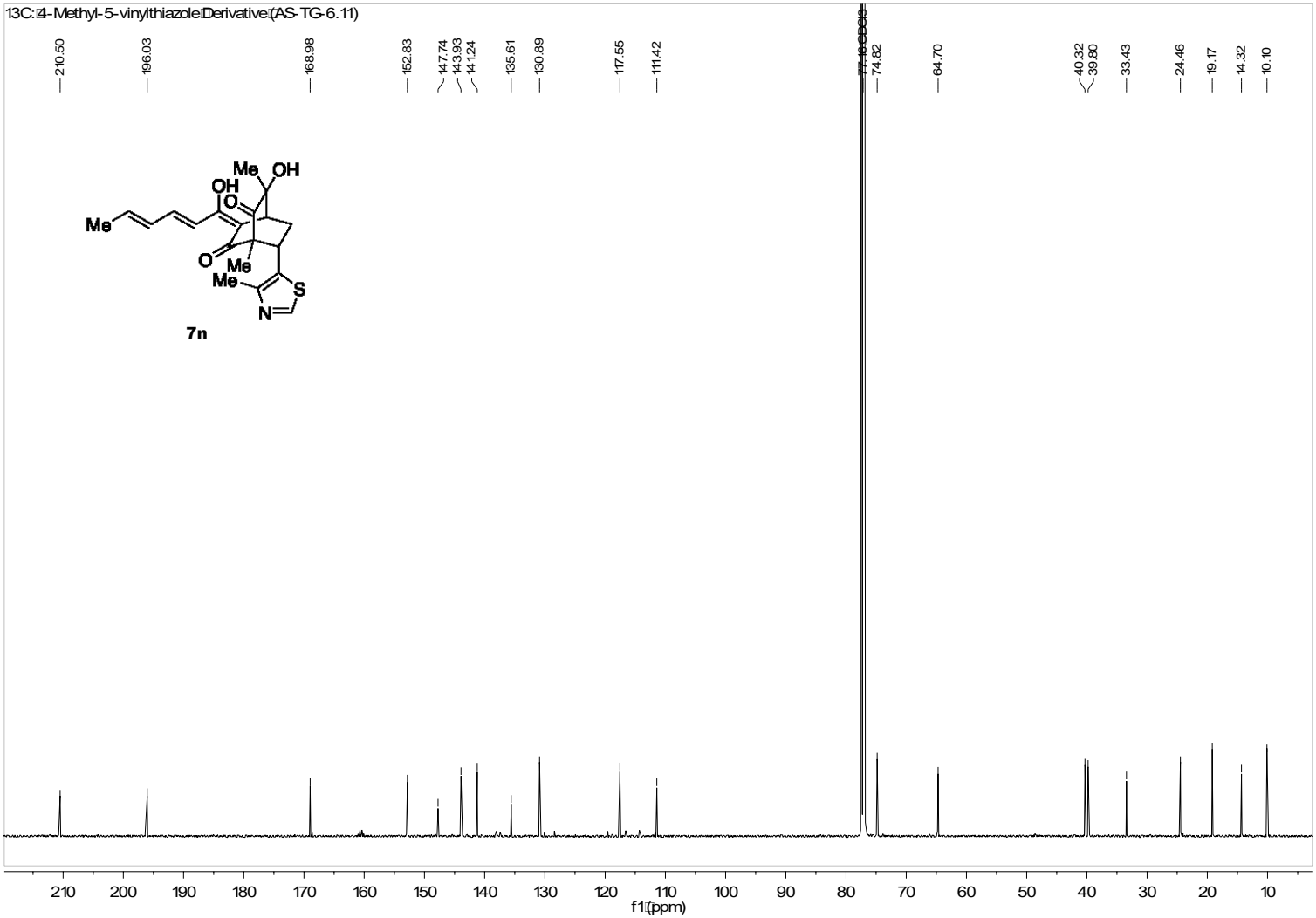


Figure S15. ^{13}C-NMR spectrum of 4-methyl-5-vinylthiazole derivative (**7n**) in $CDCl_3$.

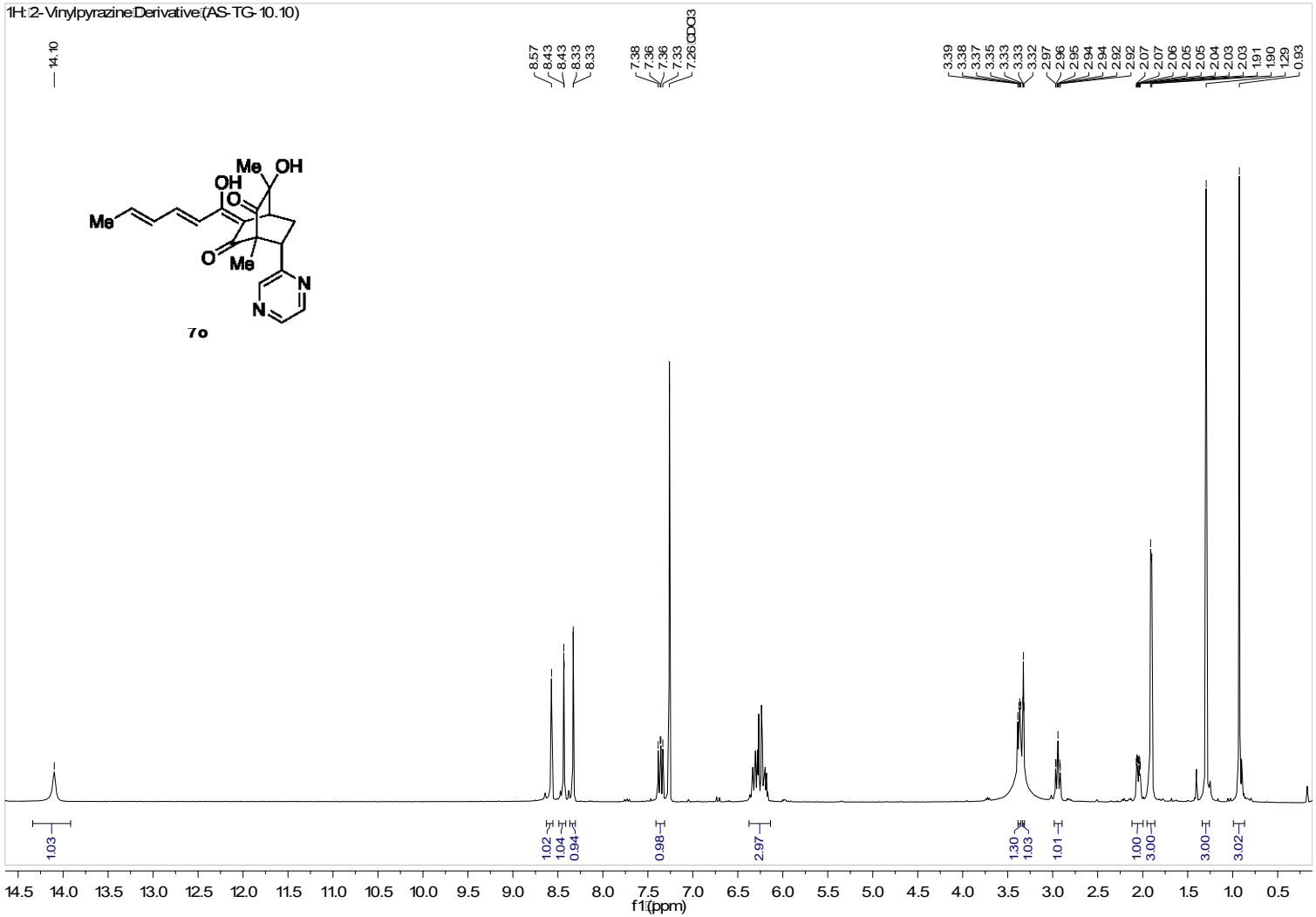


Figure S31. ^{1}H-NMR spectrum of 2-vinylpyrazine derivative (**7o**) in $CDCl_3$.

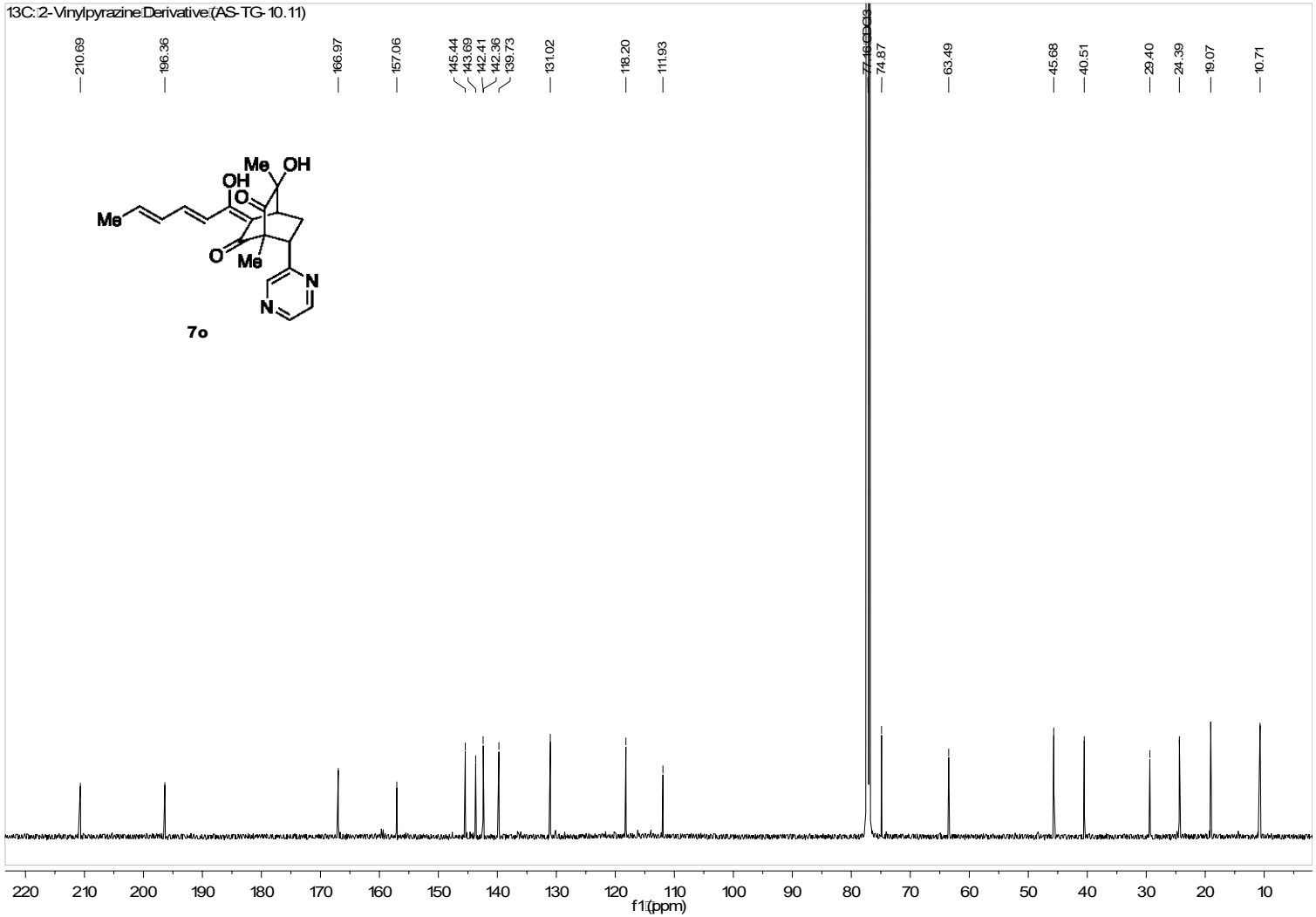


Figure S32. ^{13}C-NMR spectrum of 2-vinylpyrazine derivative (**7o**) in $CDCl_3$.

5. HPLC Chromatograms

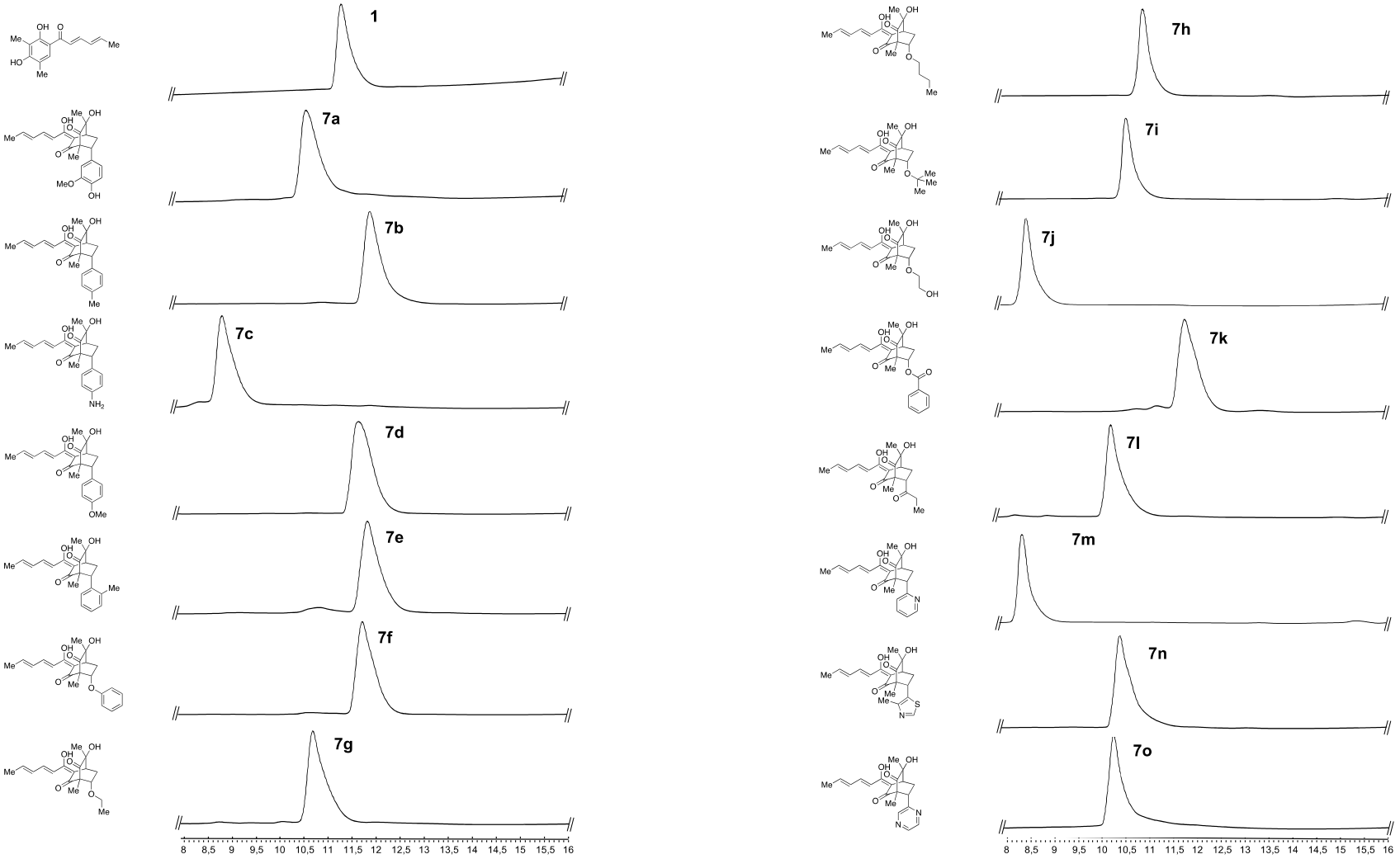


Figure S33. Chromatograms of products **7a**–**o**.

6. References

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