

Appendices

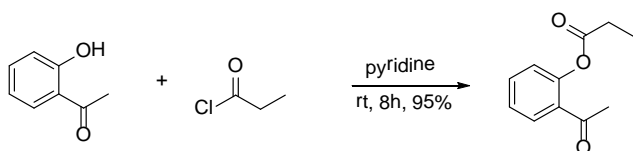
Appendix A: Experimental and supplementary data of chapter 3

Experimental

General

All melting points were taken on a Mel-Temp II melting point instrument. IR spectra were recorded on a Perkin-Elmer Spectrum RX1 spectrophotometer. NMR spectra were recorded at room temperature with a Jeol ECA 400 (400 MHz) or EX 270 (270MHz) NMR spectrometers with TMS as the internal standard unless specified. All chemical shifts are reported in ppm. The mixing time used in the NOESY spectra was 100 ms. ESI-TOF-MS spectra were recorded on a Agilent 6500 Accurate Mass Q-TOF system. Analytical thin-layer chromatography (TLC) was carried out on Merck precoated aluminum silica gel sheets (Kieselgel 60 F-254). Column chromatography was carried out with silica gel 60 (230-400 mesh) from Merck. All target compounds were characterized by ^1H , ^{13}C , 2D NMR and MS analyses. All reactions were carried out under nitrogen atmosphere unless specified. Anhydrous THF and toluene were distilled from sodium/benzophenone and CaH_2 , respectively before use. The other anhydrous solvents and reagents were purchased from Aldrich or Fisher.

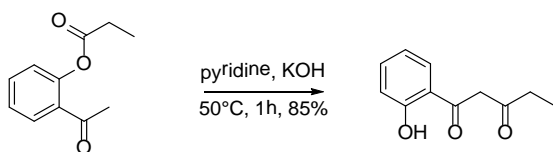
2'-propanoyloxyacetophenone



To a solution of 2'-hydroxyacetophenone (13.6 g, 0.1 mol) at rt in dry pyridine (150 mL) was added propanoyl chloride (8.7 mL, 0.1 mol). The mixture was stirred for 8 h. Afterwards the mixture was poured into ice-water acidified with 3 N HCl and extracted three times with dichloromethane. The organic phases were combined, washed with water, dried on Mg_2SO_4 , and evaporated. The crude residue was purified by column

chromatography (hexane:EtOAc=5:1) to afford 2'-propanoyloxyacetophenone (18.2 g, 95%) as pale yellow oil. ^1H NMR (270 MHz, CDCl_3): δ 7.64 (m, 1H), 7.34 (m, 1H), 7.12 (m, 1H), 6.96 (m, 1H), 2.50 (q, 15, 7.5, 2H), 2.35 (s, 3H), 1.11 (t, 7.5, 3H); ^{13}C NMR (67.9 MHz, CDCl_3): δ 197.15, 172.42, 148.73, 132.98, 130.32, 129.87, 125.53, 123.40, 28.88, 27.24, 8.34.

1-(2-hydroxyphenyl)-3-ethyl-1,3-propanedione **3-10d**



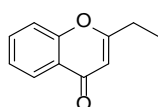
To a solution of 2'-propanoyloxyacetophenone (18.2 g, 0.095 mol) in dry pyridine (100 ml) was added KOH pellet (2.0 g, 0.036 mol). The mixture was warmed to 50°C and stirred for 2 h. Afterwards the mixture was poured into ice-water acidified with 3 N HCl and extracted three times with dichloromethane. The organic phases were combined, washed with water, dried on Mg_2SO_4 , and evaporated. The crude residue was purified by column chromatography (hexane:EtOAc=5:1) to afford **3-10d** (15.5 g, 85%) as pale yellow oil. ^1H NMR (270 MHz, CDCl_3): δ 14.94 (s, 0.3H), 12.02 (s, 1H), 7.58 (m, 1H), 7.36 (m, 1H), 6.91 (m, 1H), 6.80 (t, 7.6, 1H), 6.10 (s, 1.5H), 4.02 (s, 0.5H), 2.33 (q, 15, 7.5, 2H), 1.16 (t, 7.5, 3H); ^{13}C NMR (67.9 MHz, CDCl_3): δ 195.48, 187.34, 162.26, 135.54, 128.41, 119.19, 118.89, 118.44, 93.70, 53.08, 29.45, 10.43 (keto/enol-tautomeric ratio = 9/1 based on ^1H NMR integration).

General procedure for preparation of flavones **3-4a~3-4i** and 3-arylflavones **3-6a~3-6h**

To a solution of acetophenone in acetone (AR grade) (20mL/mmol) was added potassium carbonate (10 eq). The solution was stirred at room temperature for 10 min and aryl chloride (3 eq) was added. The mixture was stirred at reflux for 24 h. After cooling to room temperature, the acetone was evaporated and the crude mixture was

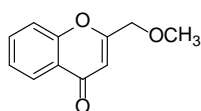
extracted with ethyl acetate, washed with water and brine afforded flavones **3-4a~3-4i** (51%-65%) and 3-arylflavones **3-6a~3-6h** (5%-23%) which were purified by column chromatography using hexane:ethyl acetate (4:1) as eluent. Heating the pure 3-arylflavones **3-6a~3-6h** in NaHCO₃ sat. MeOH for 2 h gave flavone **3-4a~3-4h** from 80%~quantitative yield.

2-ethyl-4*H*-chromen-4-one **3-4h**



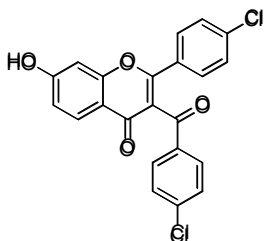
light yellow oil; ¹H NMR (270 MHz, CDCl₃): δ 8.15 (m, 1H), 7.62 (m, 1H), 7.36 (m, 2H), 6.16 (s, 1H), 2.62 (q, 15, 7.5, 2H), 1.31 (t, 7.5, 3H); ¹³C NMR (67.9 MHz, CDCl₃): δ 178.31, 170.72, 156.72, 133.27, 125.34, 124.66, 123.41, 117.63, 108.62, 27.27, 10.71.

2-methoxymethyl-4*H*-chromen-4-one **3-4i**



light yellow oil; ¹H NMR (CDCl₃, 270 MHz): δ 8.10 (dd, 8.0, 1.3 Hz, 1H), 7.58 (m, 1H), 7.35 (m, 2H), 6.34 (s, 1H), 4.29 (s, 2H), 3.42 (s, 3H); ¹³C NMR: 178.12, 164.89, 156.22, 133.73, 125.70, 125.15, 123.93, 117.93, 109.51, 70.67, 59.16.

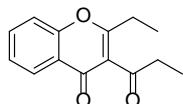
3-(4-chlorobenzoyl)-2-(4-chlorophenyl)-7-hydroxy-4*H*-chromen-4-one **3-6d**



Pale yellow amorphous solid; ¹H NMR (270 MHz, DMSO-D₆): δ 7.87 (m, 3H), 7.65 (m, 4H), 7.49 (d, 8.0, 2H), 6.98 (m, 2H); ¹³C NMR (67.9 MHz, CDCl₃): δ 192.74, 174.86, 163.57, 160.60, 157.72, 135.67, 132.20, 132.02, 131.18, 130.73, 130.31, 128.52, 126.89,

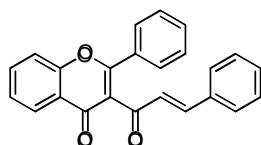
125.27, 121.58, 115.81, 115.32, 102.69; HRMS (ESI) calcd. C₂₂H₁₁Cl₂O₄ [M]
409.0040; found 409.0049

2-ethyl-3-propanoyl-4*H*-chromen-4-one 3-6h



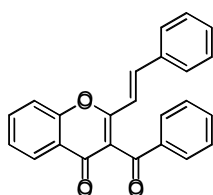
light yellow oil; ¹H NMR (270 MHz, CDCl₃): δ 8.01 (d, 8.0, 1H), 7.52 (m, 1H), 7.22-7.29 (m, 2H), 2.82 (q, 15, 7.5, 2H), 2.56 (q, 15, 7.5, 2H), 1.19 (t, 7.5, 3H), 1.03 (t, 7.5, 3H); ¹³C NMR (67.9 MHz, CDCl₃): δ 203.90, 175.88, 170.63, 155.43, 133.80, 125.55, 125.20, 123.39, 123.26, 117.59, 37.37, 26.09, 11.94, 7.84; HREIMS calcd. C₁₄H₁₅O₃ [M+H]⁺ 231.1016; found 231.1028

(*E*)-3-cinnamoyl-2-phenyl-4*H*-chromen-4-one 3-6k



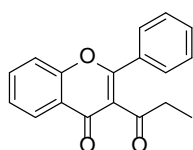
Pale yellow solid; ¹H NMR (270 MHz, CDCl₃): δ 8.26 (dd, 8.1, 1.2, 1H), 7.74 (m, 1H), 7.72 (dd, 7.8, 1.6, 2H), 7.56 (d, 16.2, 1H), 7.46 (m, 5H), 7.43 (m, 2H), 7.35 (m, 3H), 6.93 (d, 16.2, 1H); ¹³C NMR (67.9 MHz, CDCl₃): δ 192.62, 176.21, 162.88, 155.93, 145.50, 134.28, 134.22, 131.82, 131.49, 130.72, 128.78, 128.76, 128.57, 128.54, 127.52, 126.04, 125.59, 123.37, 122.97, 118.09; m.p.=245°C; HRMS (ESI) calcd. C₂₄H₁₇O₃ [M+H]⁺ 353.1172; found 353.1177

(*E*)-3-benzoyl-2-styryl-4*H*-chromen-4-one 3-6l



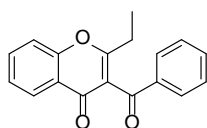
Pale yellow solid; ^1H NMR (270 MHz, CDCl_3): δ 8.06 (dd, 8.0, 1.4, 1H), 7.87 (d, 7.3, 2H), 7.64 (d, 15.8, 1H), 7.60 (m, 1H), 7.47 (m, 2H), 7.35 (m, 5H), 7.21 (m, 3H), 6.71 (d, 15.8, 1H); ^{13}C NMR (67.9 MHz, CDCl_3): δ 193.78, 176.18, 159.81, 155.36, 139.16, 137.28, 134.56, 134.22, 133.78, 130.13, 129.39, 128.79, 128.65, 127.91, 125.79, 125.26, 123.49, 121.99, 117.75, 117.35; m.p.=225°C; HRMS (ESI) calcd. $\text{C}_{24}\text{H}_{17}\text{O}_3$ $[\text{M}+\text{H}]^+$ 353.1172; found 353.1169

2-phenyl-3-propanoyl-4*H*-chromen-4-one 3-6m



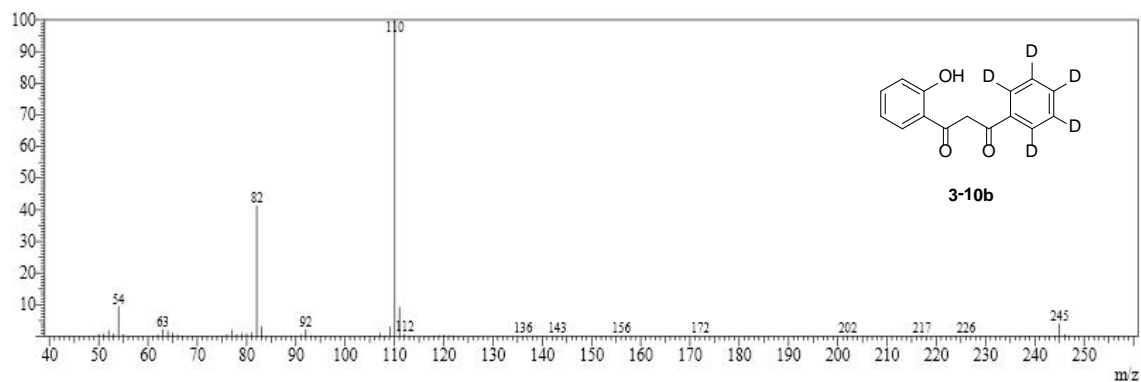
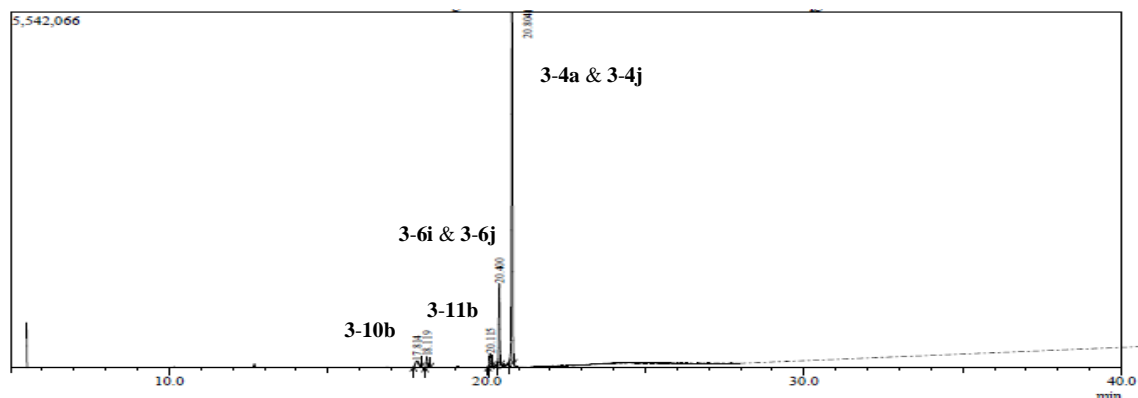
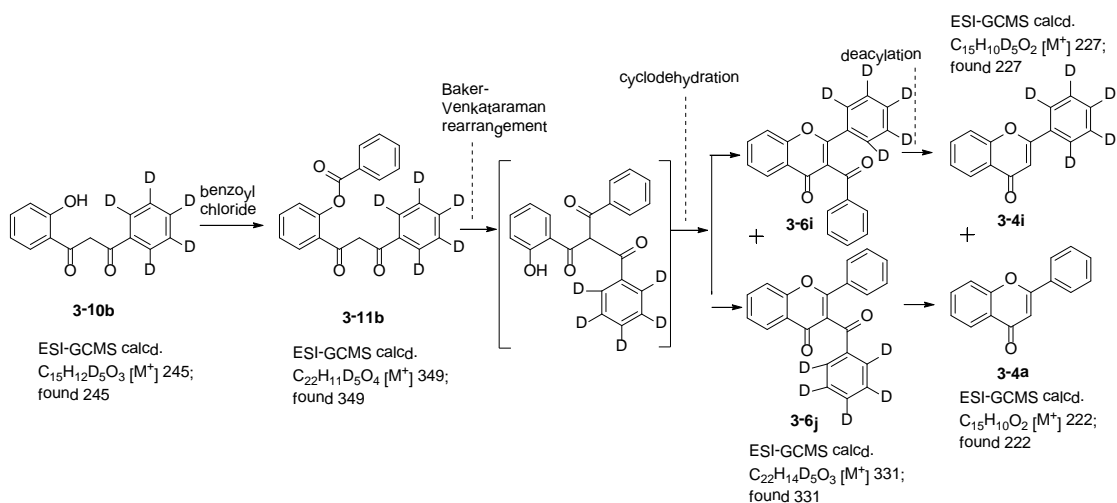
light yellow oil; ^1H NMR (270 MHz, CDCl_3): δ 7.94 (d, 7.9, 1H), 7.82 (d, 7.9, 1H), 7.09-7.53 (m, 7H), 2.35 (q, 15, 7.5, 2H), 0.86 (t, 7.5, 3H); ^{13}C NMR (67.9 MHz, CDCl_3): δ 197.87, 164.46, 163.19, 152.71, 148.42, 133.64, 131.34, 130.11, 129.88, 128.39, 128.25, 126.31, 123.66, 117.40, 37.27, 7.58; HREIMS calcd. $\text{C}_{18}\text{H}_{15}\text{O}_3$ $[\text{M}+\text{H}]^+$ 279.1016; found 279.1039

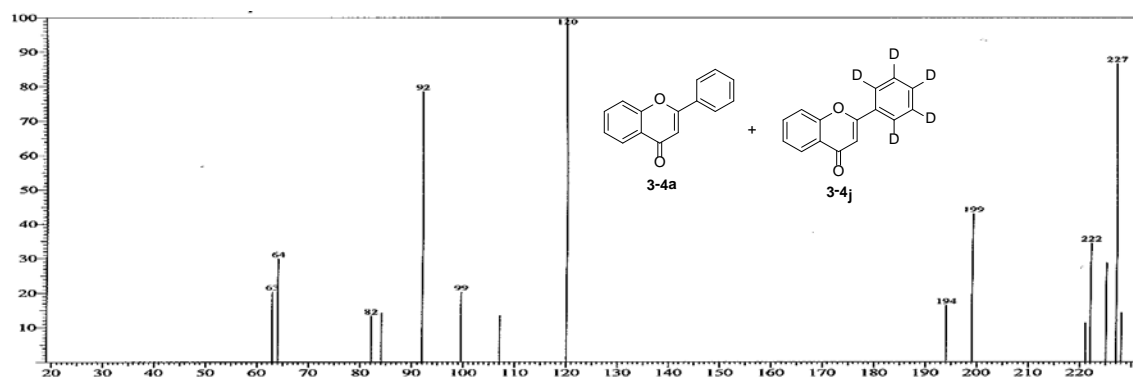
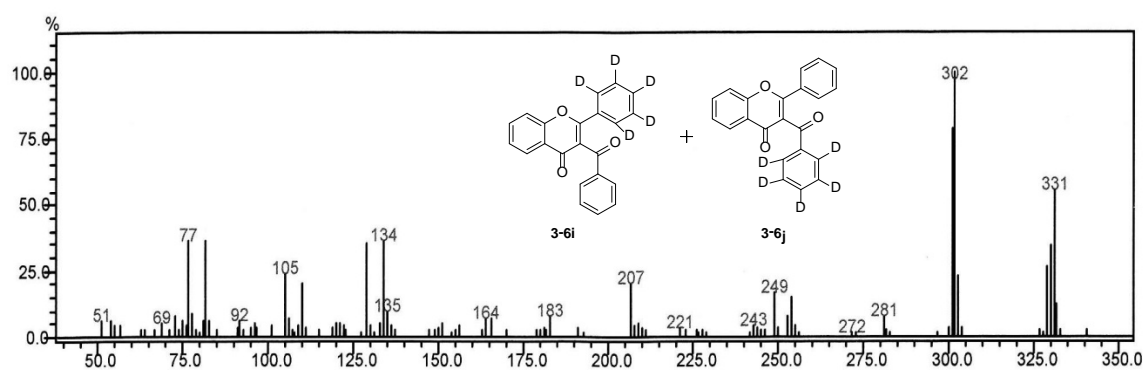
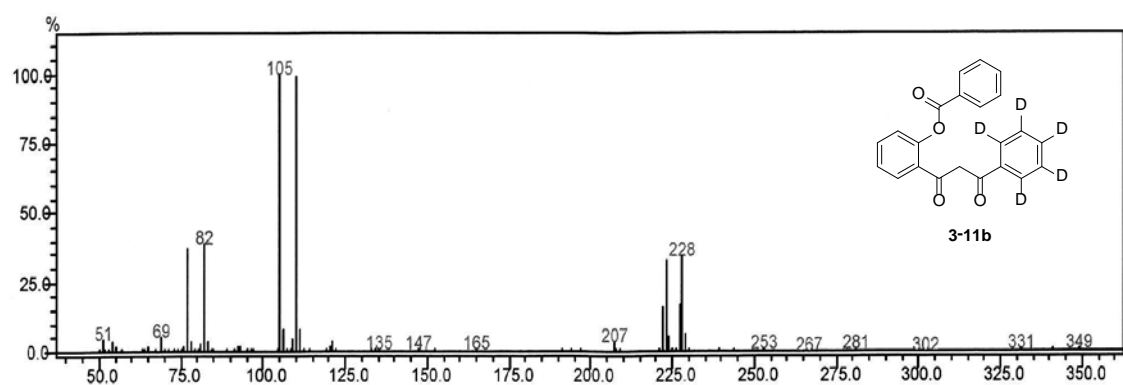
2-ethyl-3-benzoyl-4*H*-chromen-4-one 3-6n



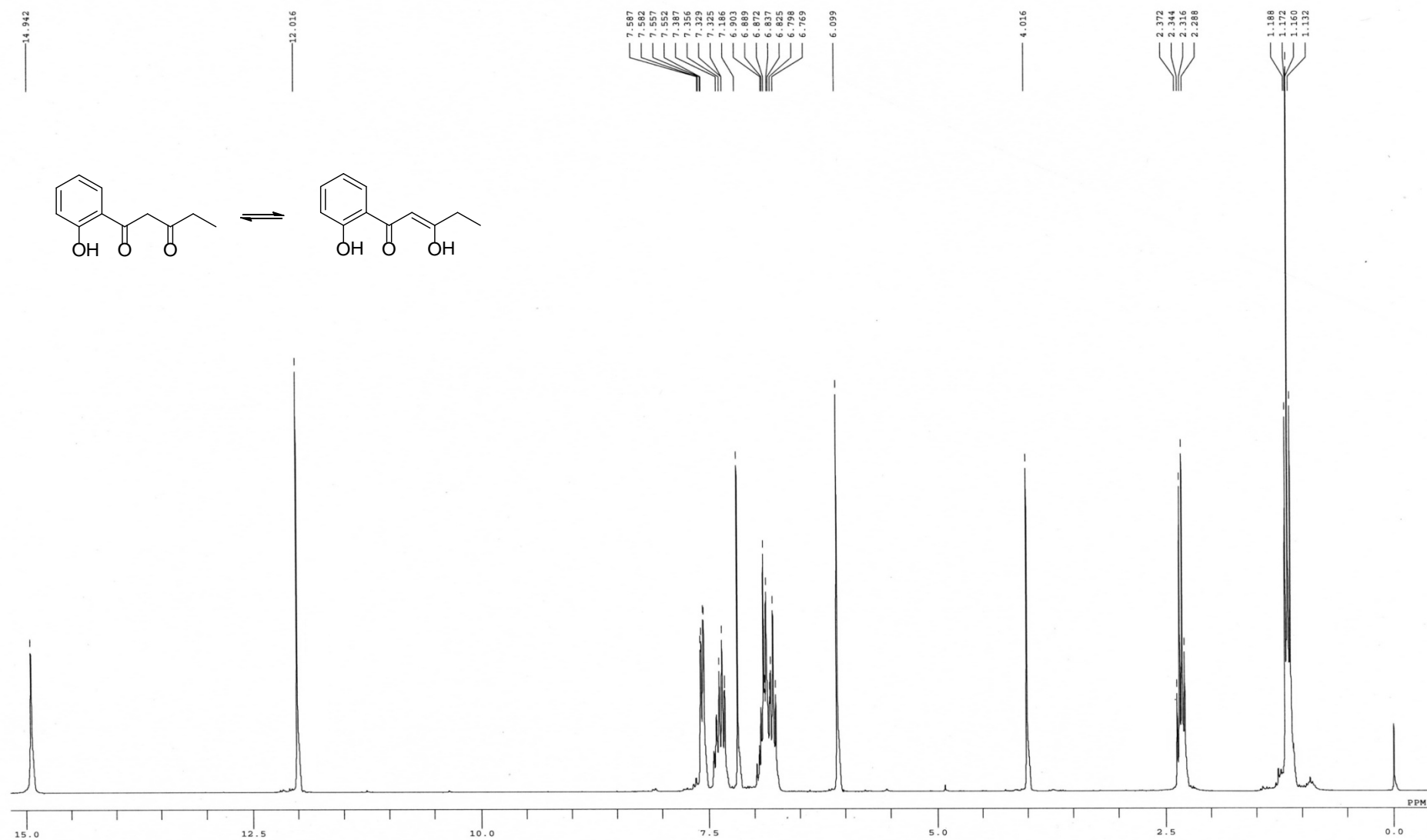
light yellow oil; ^1H NMR (270 MHz, CDCl_3): δ 8.16 (d, 8.2, 1H), 7.92 (m, 2H), 7.67 (m, 1H), 7.34-7.55 (m, 6H), 2.60 (q, 15, 7.5, 2H), 1.29 (t, 7.5, 3H); ^{13}C NMR (67.9 MHz, CDCl_3): δ 193.49, 175.78, 168.81, 155.75, 136.77, 133.81, 133.53, 129.04, 128.42, 125.45, 125.10, 123.03, 122.02, 117.65, 25.99, 11.45; HREIMS calcd. $\text{C}_{18}\text{H}_{15}\text{O}_3$ $[\text{M}+\text{H}]^+$ 279.1016; found 279.1020

GCMS analysis of the one pot BV reaction between 3-10b and benzoyl chloride in K_2CO_3 /acetone system. Sample was taken after 8 hours of reaction.

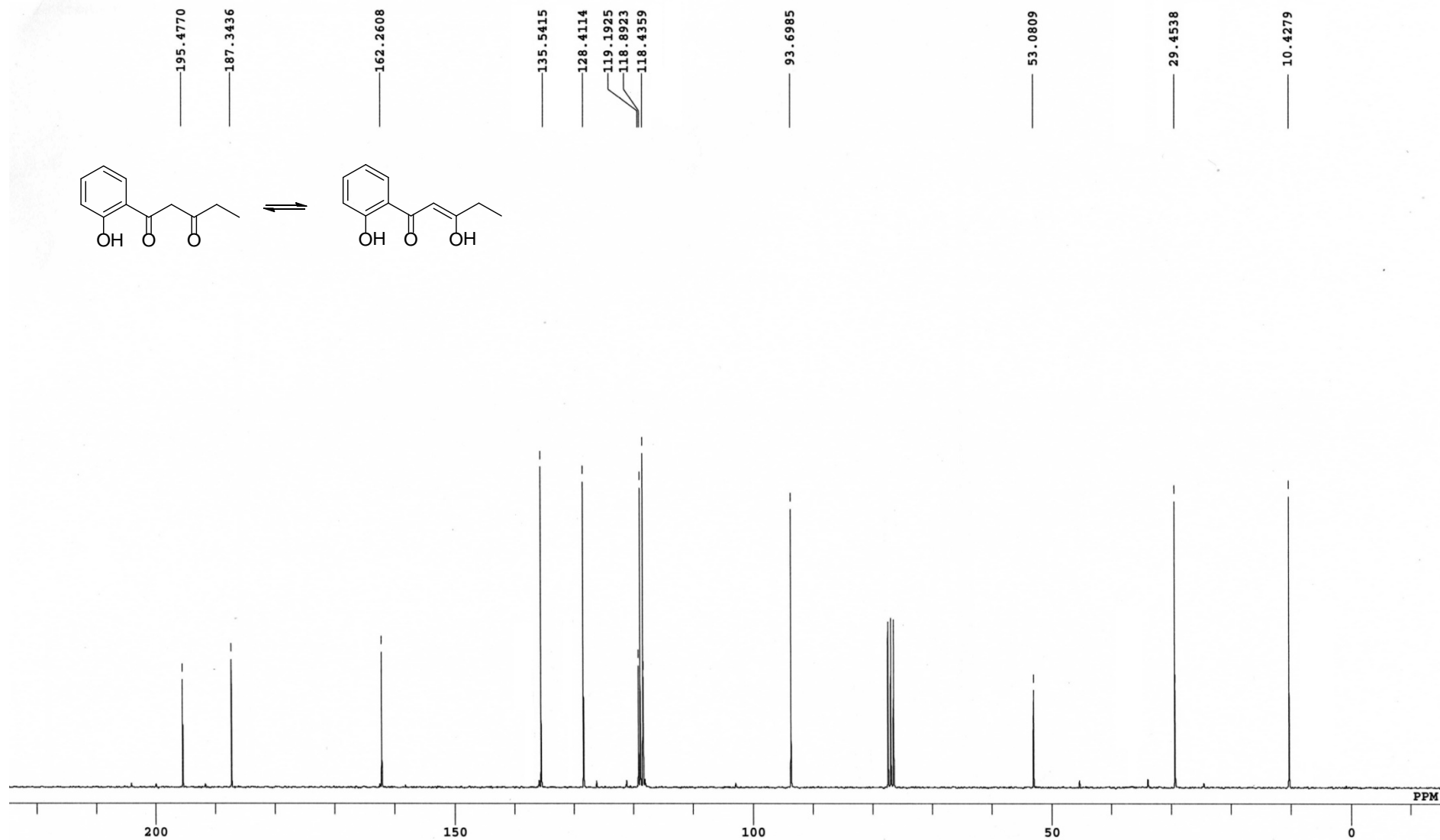
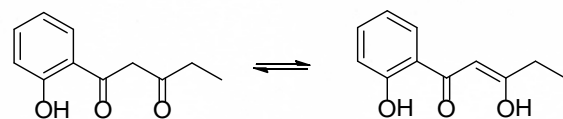




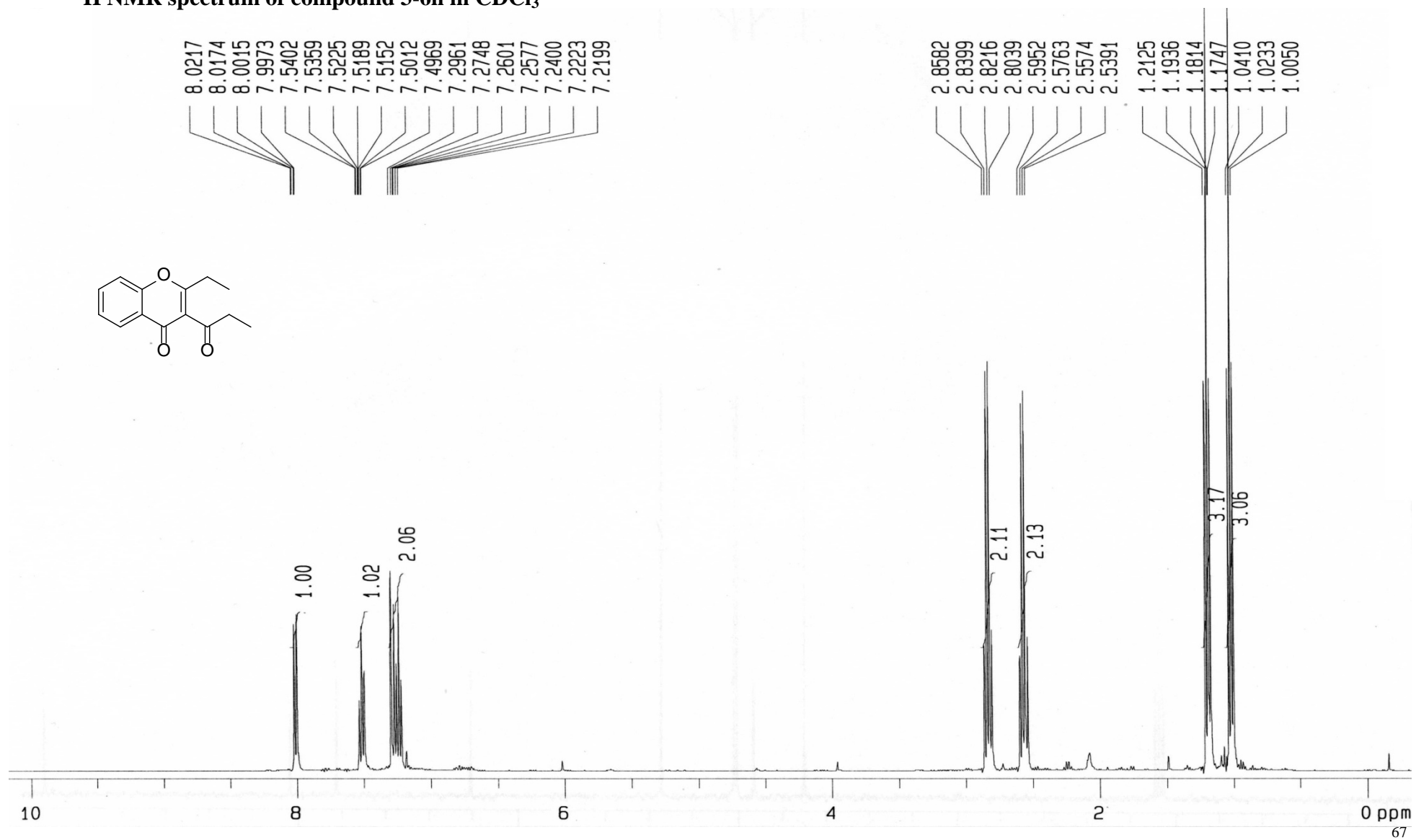
¹H NMR spectrum of compound 3-10d in CDCl₃



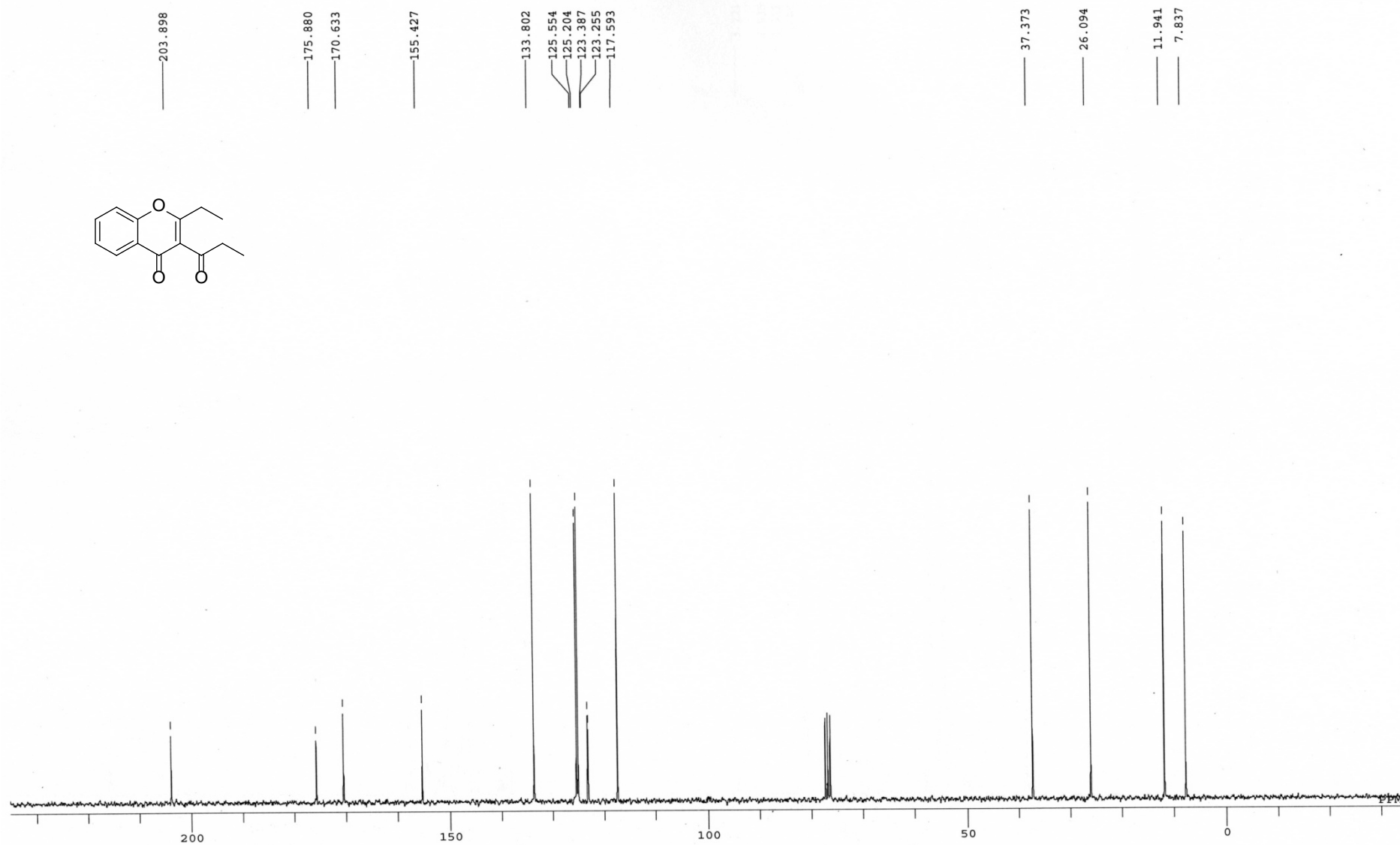
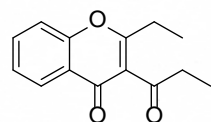
¹³C NMR spectrum of compound 3-10d in CDCl₃



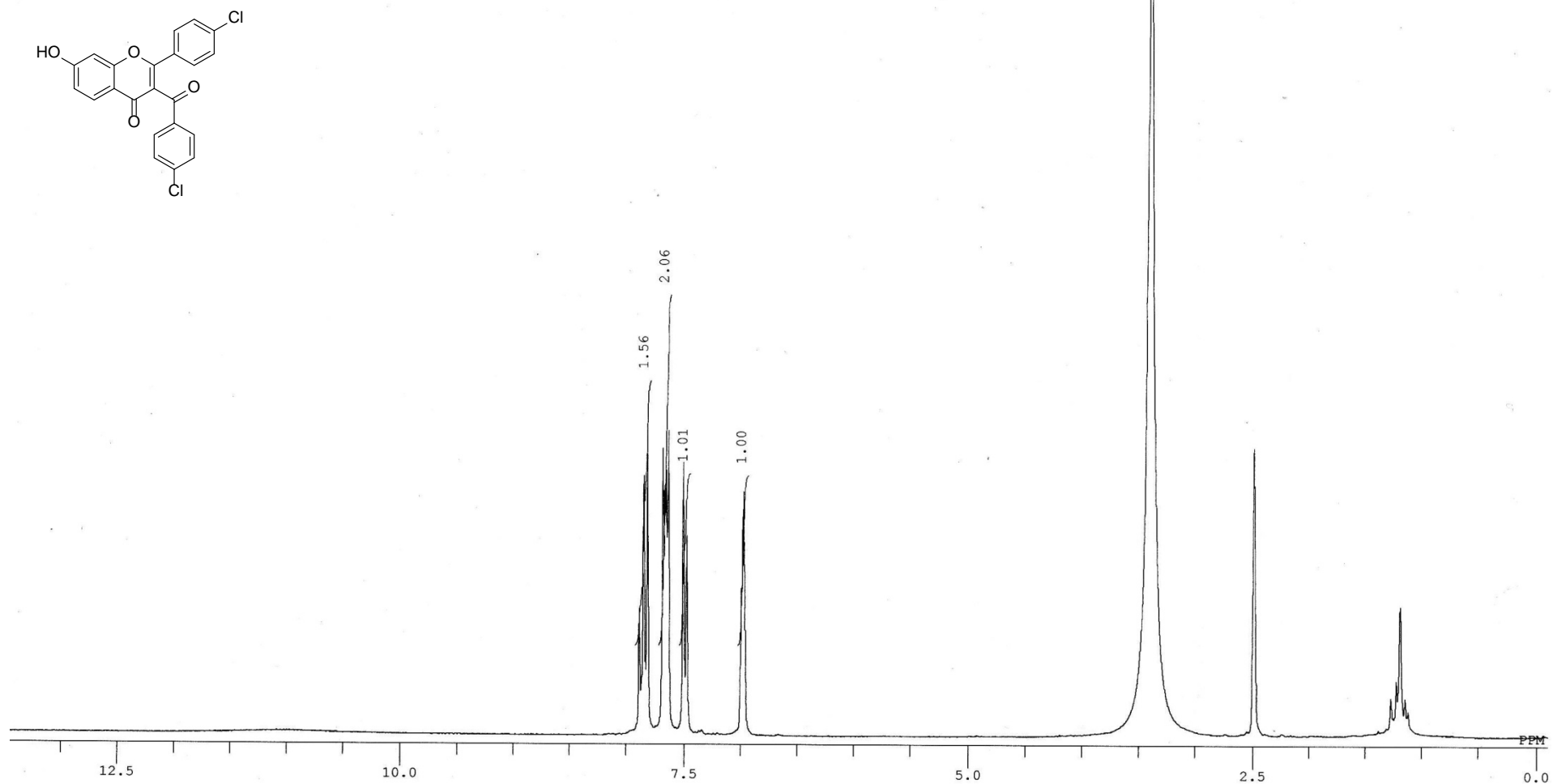
¹H NMR spectrum of compound 3-6h in CDCl₃



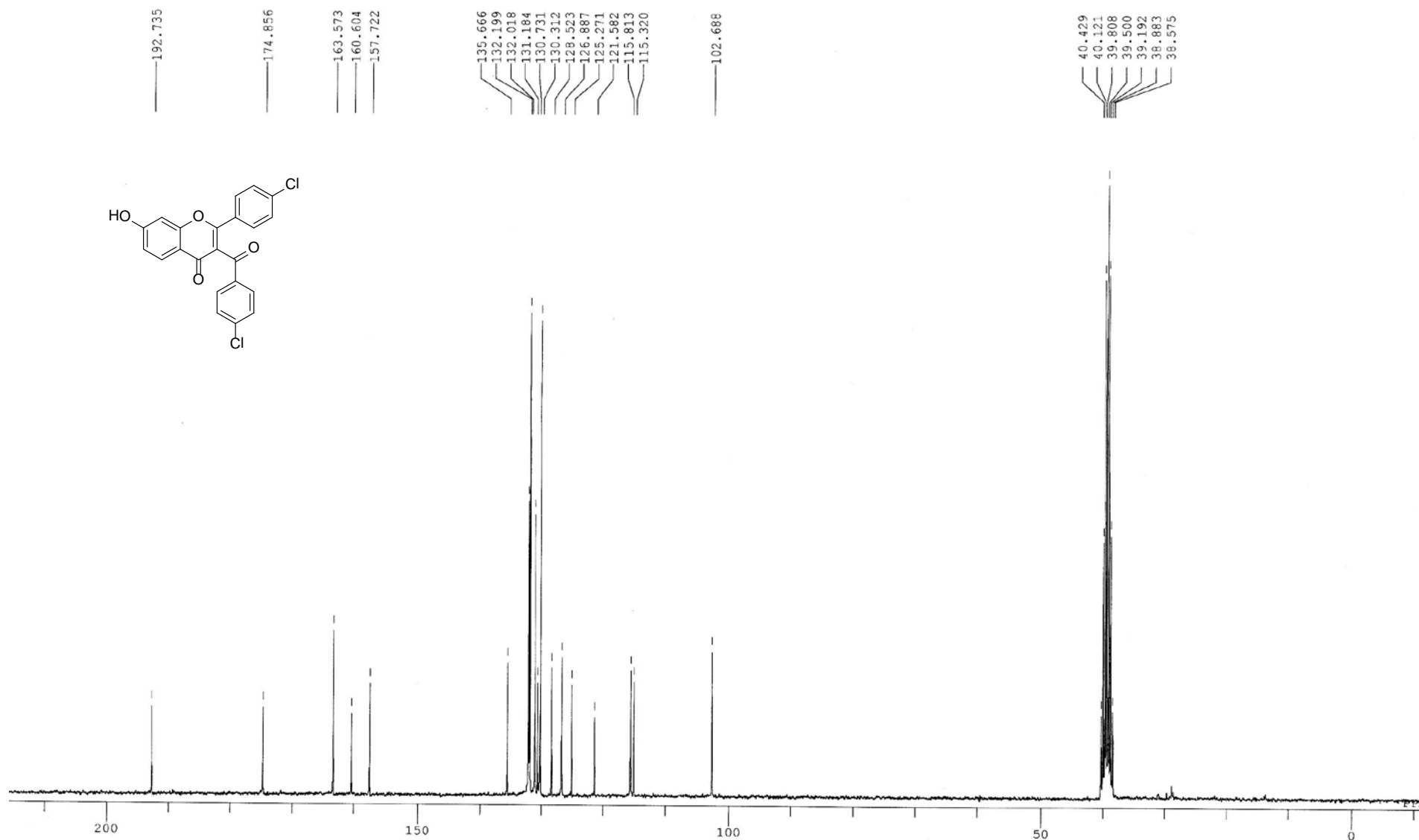
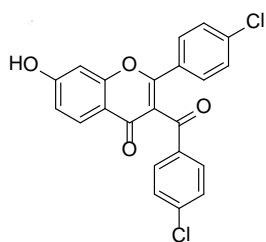
^{13}C NMR spectrum of compound 3-6h in CDCl_3



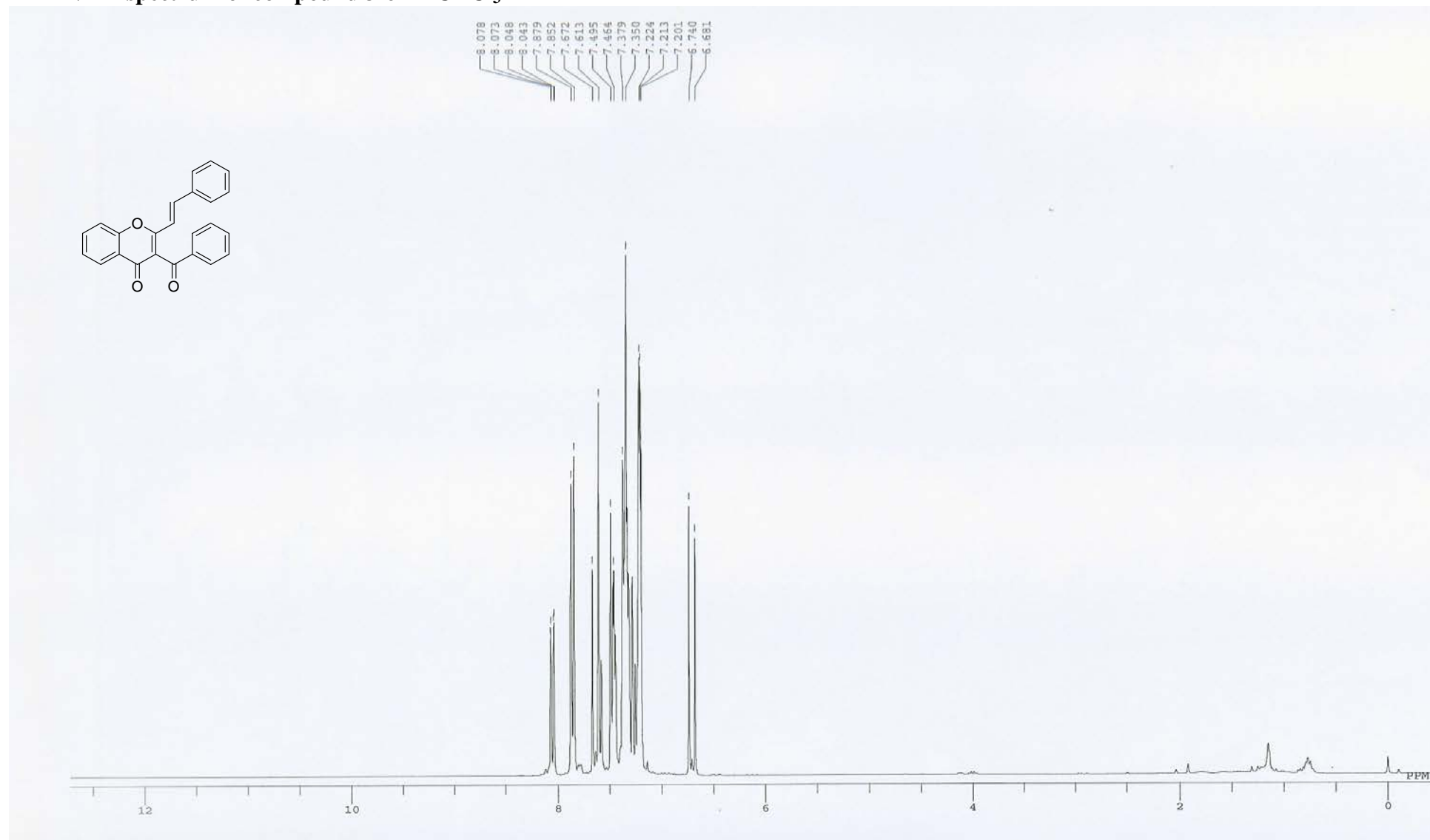
¹H NMR spectrum of compound 3-6d in DMSO-d₆



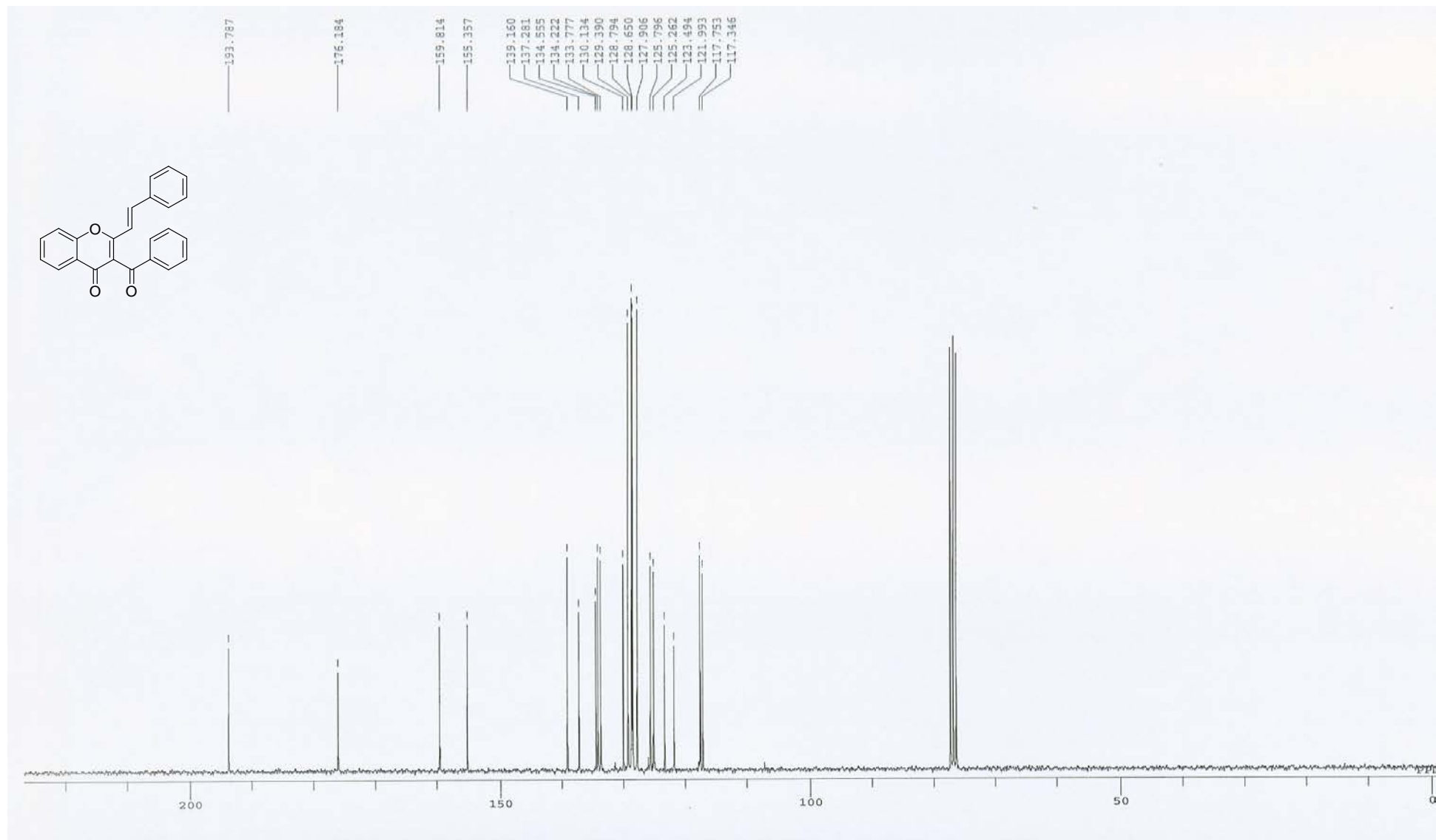
^{13}C NMR spectrum of compound 3-6d in DMSO- d_6



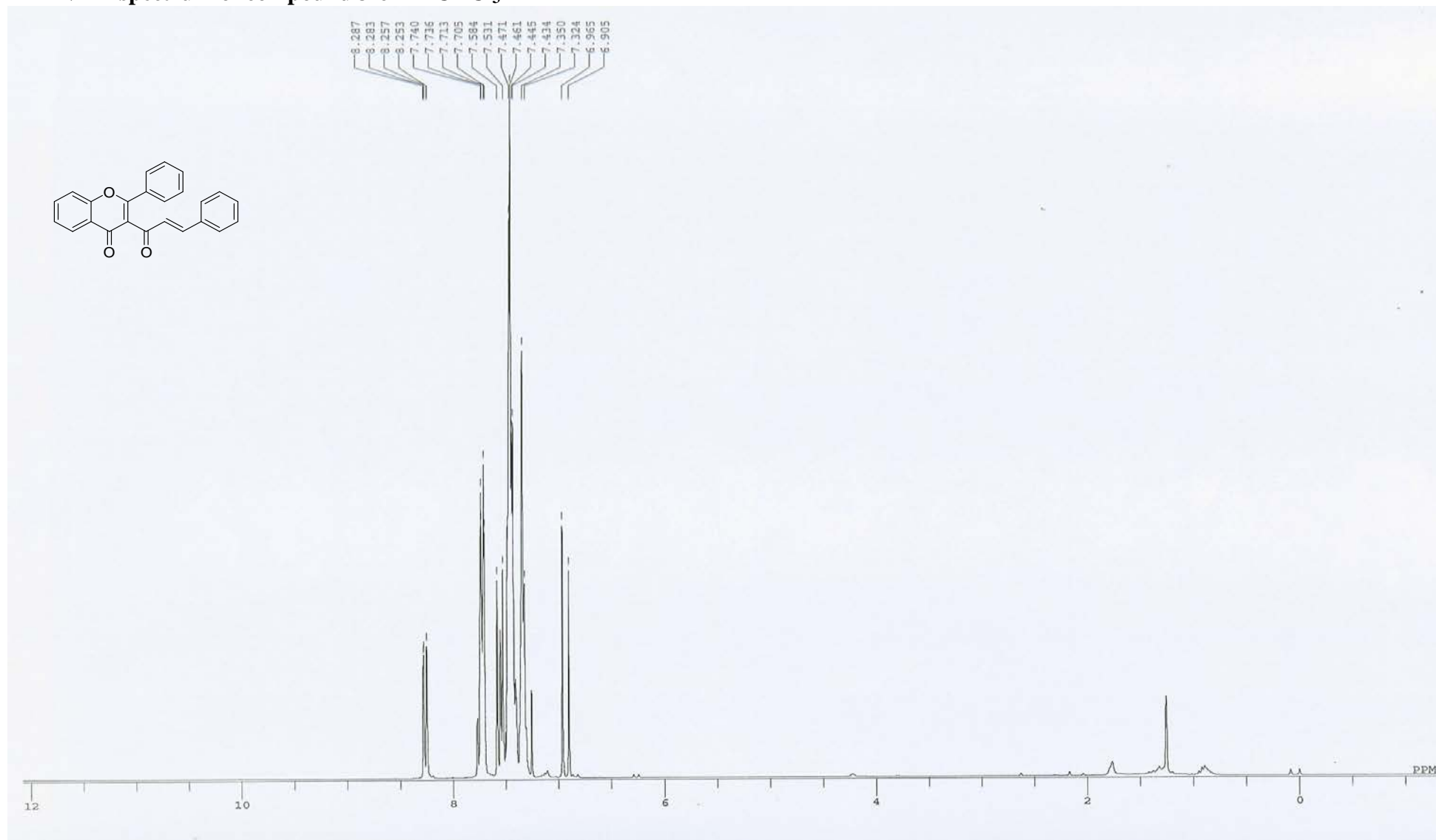
^1H NMR spectrum of compound 3-6l in CDCl_3



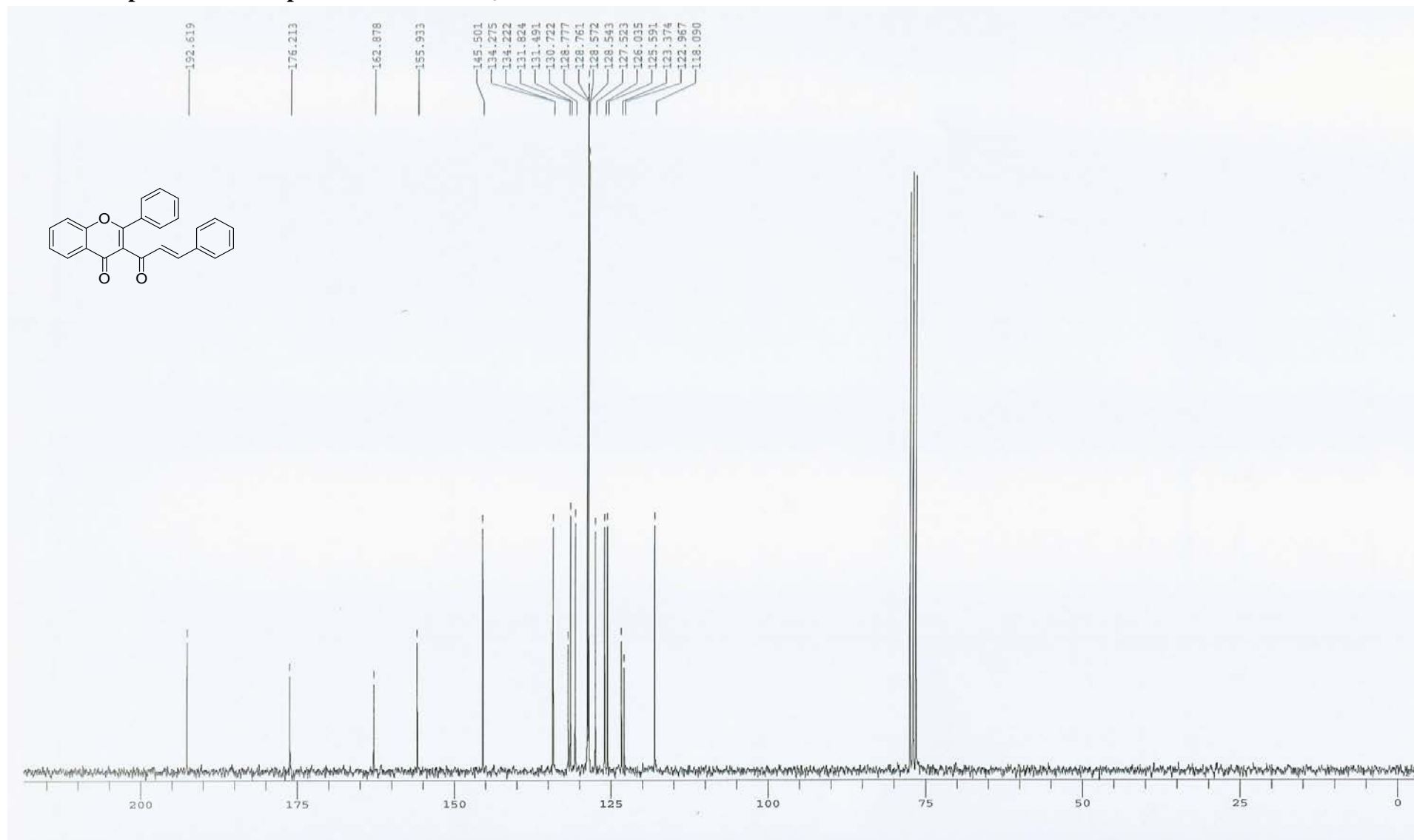
^{13}C NMR spectrum of compound 3-6l in CDCl_3



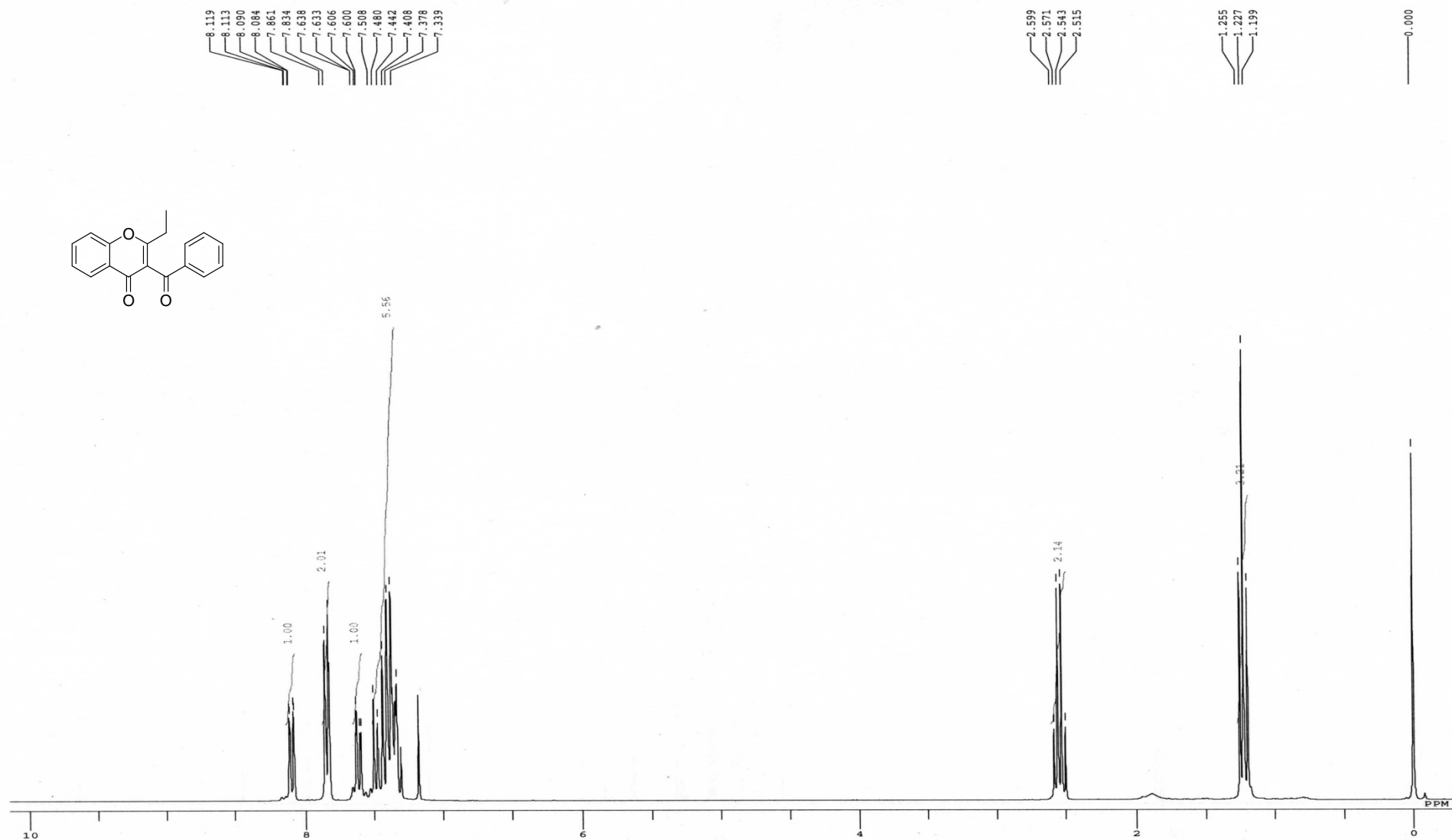
^1H NMR spectrum of compound 3-6k in CDCl_3



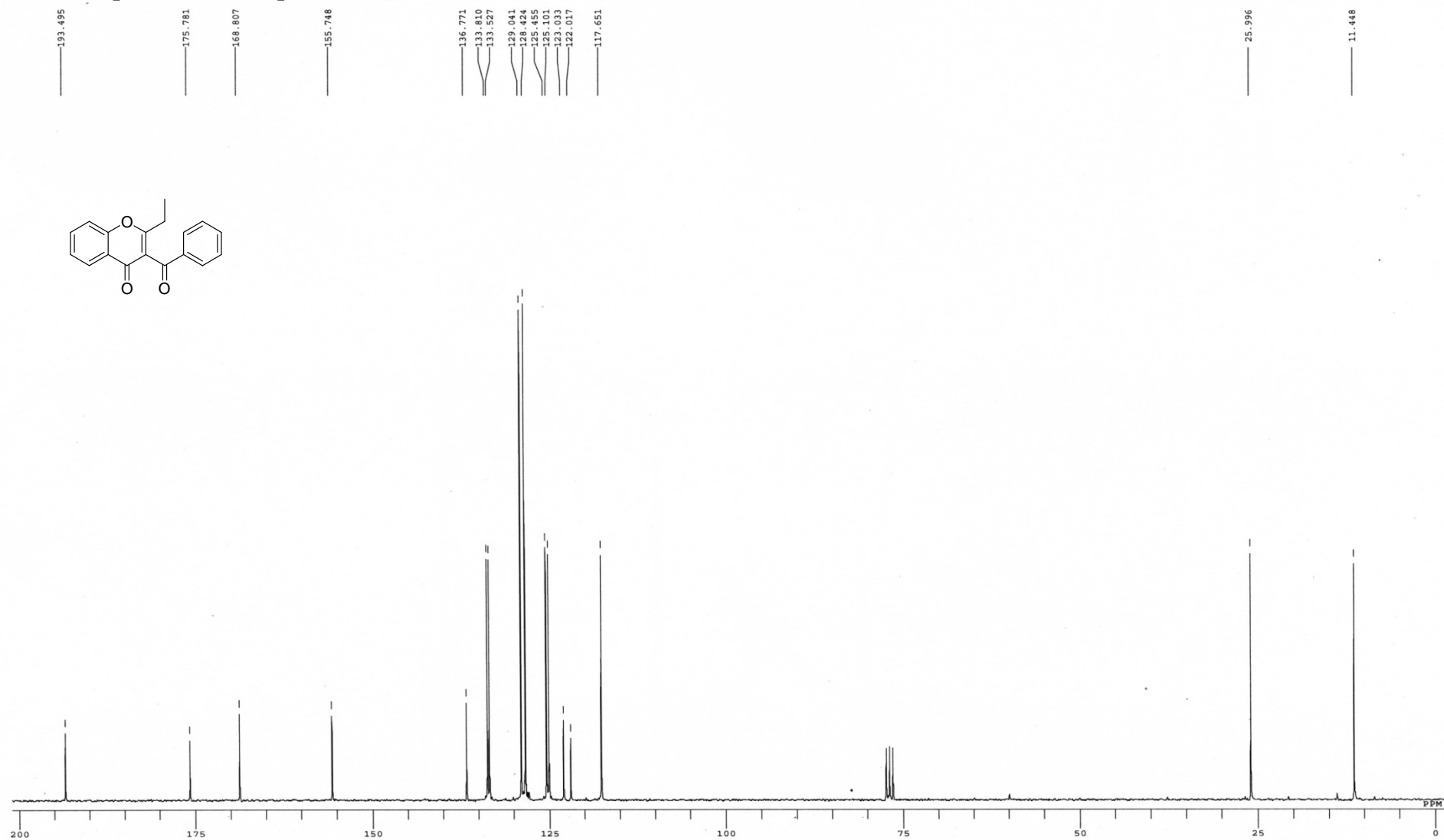
^{13}C NMR spectrum of compound 3-6k in CDCl_3



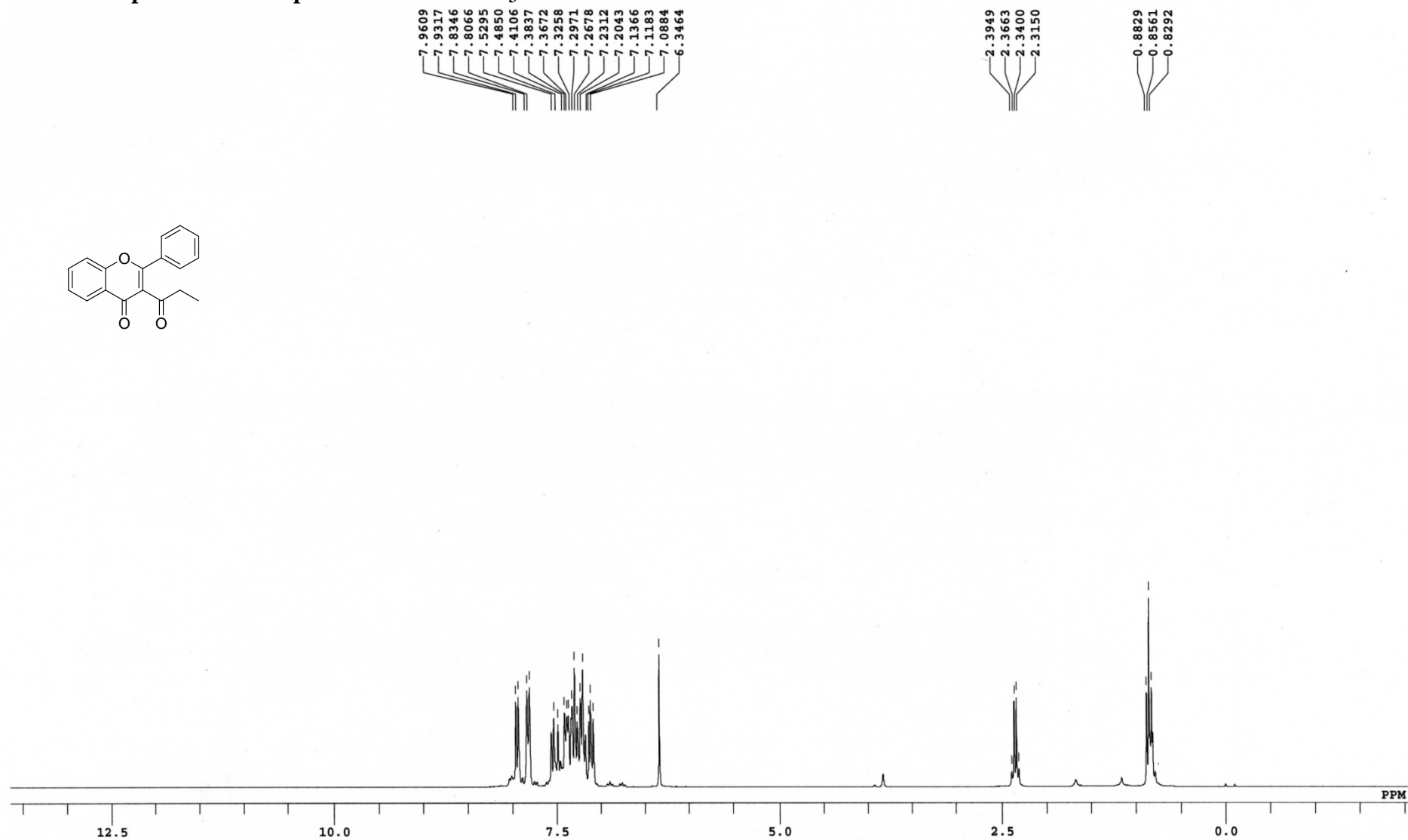
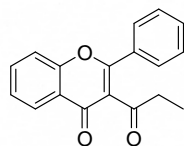
^1H NMR spectrum of compound 3-6n in CDCl_3



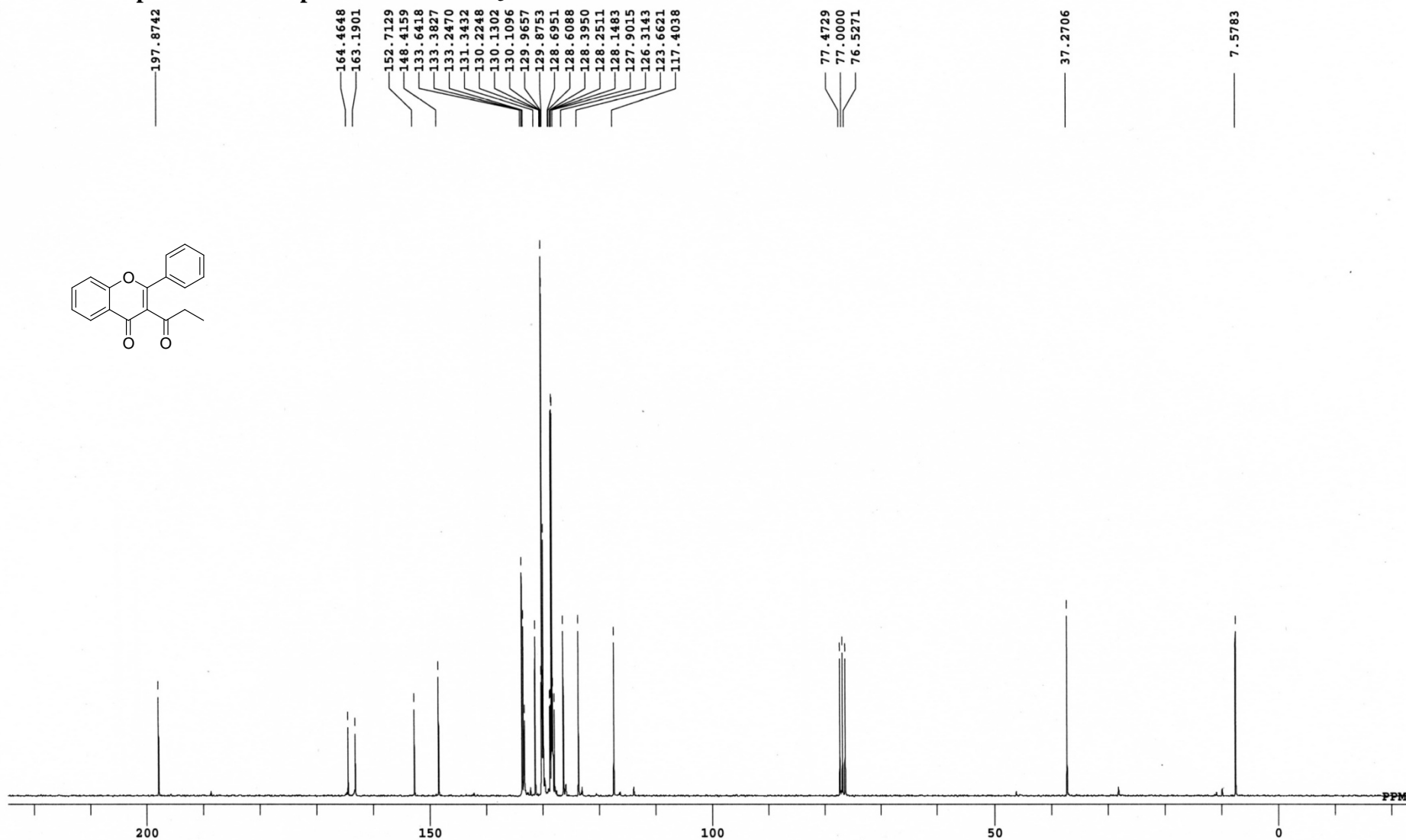
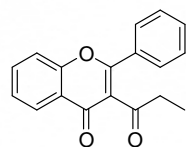
^{13}C NMR spectrum of compound 3-6n in CDCl_3



¹H NMR spectrum of compound 3-6m in CDCl₃



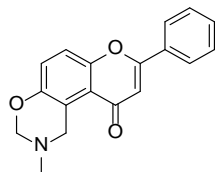
^{13}C NMR spectrum of compound 6m in CDCl_3



Appendix B: Experimental and supplementary data of chapter 4

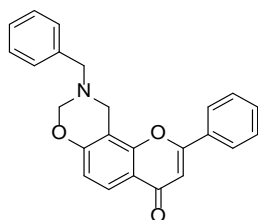
Experimental

2-methyl-8-phenyl-2,3-dihydro-1*H*,10*H*-chromeno[5,6-*e*][1,3]oxazin-10-one **N1**



To a solution of methylamine (0.1 mL, 11.85 M solution in water, 1.185 mmol) in methanol (2 mL) was added paraformaldehyde (0.5 ml, 36 % in water, 6.5 mmol). The mixture was heated at 65 °C for 1 h. Afterwards a solution of 6-hydroxyflavone (238 mg, 1 mmol) in methanol (10 mL) was added. The mixture was refluxed for additional 4 h. After completion of the reaction judged by TLC, the mixture was cooled and the solvent was removed under reduced pressure to give a yellow oil. The crude residue was purified by column chromatography (hexane:EtOAc=7:3) to afford **N1** (176 mg, 60%) as a pale yellow solid. Mp = 242 °C. ¹H NMR (270 MHz, CDCl₃): δ 7.80 (m, 2H), 7.43 (m, 3H), 7.28 (d, 8.1 Hz, 1H), 7.07 (d, 8.1 Hz, 1H), 6.60 (s, 1H), 4.72 (s, 2H), 4.58 (s, 2H), 2.52 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 180.95, 162.26, 152.45, 151.23, 131.96, 131.79, 129.37, 126.51, 123.55, 122.33, 120.05, 117.76, 108.34, 83.76, 52.62, 40.33; HRMS (ESI) calcd for C₁₈H₁₆NO₃ [M+H]⁺ = 294.1125 Found 294.1130

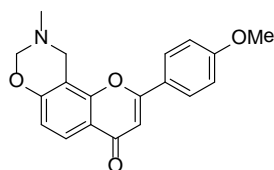
9-benzyl-2-phenyl-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one **N2**



To a solution of benzylamine (0.11 mL, 1 mmol) in methanol (2 mL) was added paraformaldehyde (0.5 ml, 36 % in water, 6.5 mmol). The mixture was heated at 65 °C for 1 h. Afterwards a solution of 7-hydroxyflavone (238 mg, 1 mmol) in methanol (10

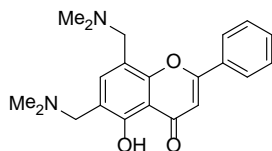
mL) was added. The mixture was refluxed for additional 4 h. After completion of the reaction judged by TLC, the mixture was cooled and the solvent was removed under reduced pressure to give a yellow oil. The crude residue was purified by column chromatography (hexane:EtOAc=7:3) to afford **N2** (240 mg, 65%) as a pale yellow solid. Mp = 265 °C. ¹H NMR (270 MHz, CDCl₃): δ 7.95 (d, 7.8 Hz, 1H), 7.90 (m, 2H), 7.42 (m, 3H), 7.30 (m, 5H), 6.83 (d, 7.8 Hz, 1H), 6.68 (s, 1H), 4.88 (s, 2H), 4.24 (s, 2H), 3.87 (s, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 178.34, 162.83, 159.28, 155.10, 137.89, 132.27, 131.85, 129.49, 129.44, 129.00, 128.08, 126.38, 125.09, 117.92, 115.68, 108.21, 108.01, 82.77, 56.33, 45.75; HRMS (ESI) calcd for C₂₄H₂₀NO₃ [M+H]⁺ = 370.1438 Found 370.1440

2-(4-methoxyphenyl)-9-methyl-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one **N3**



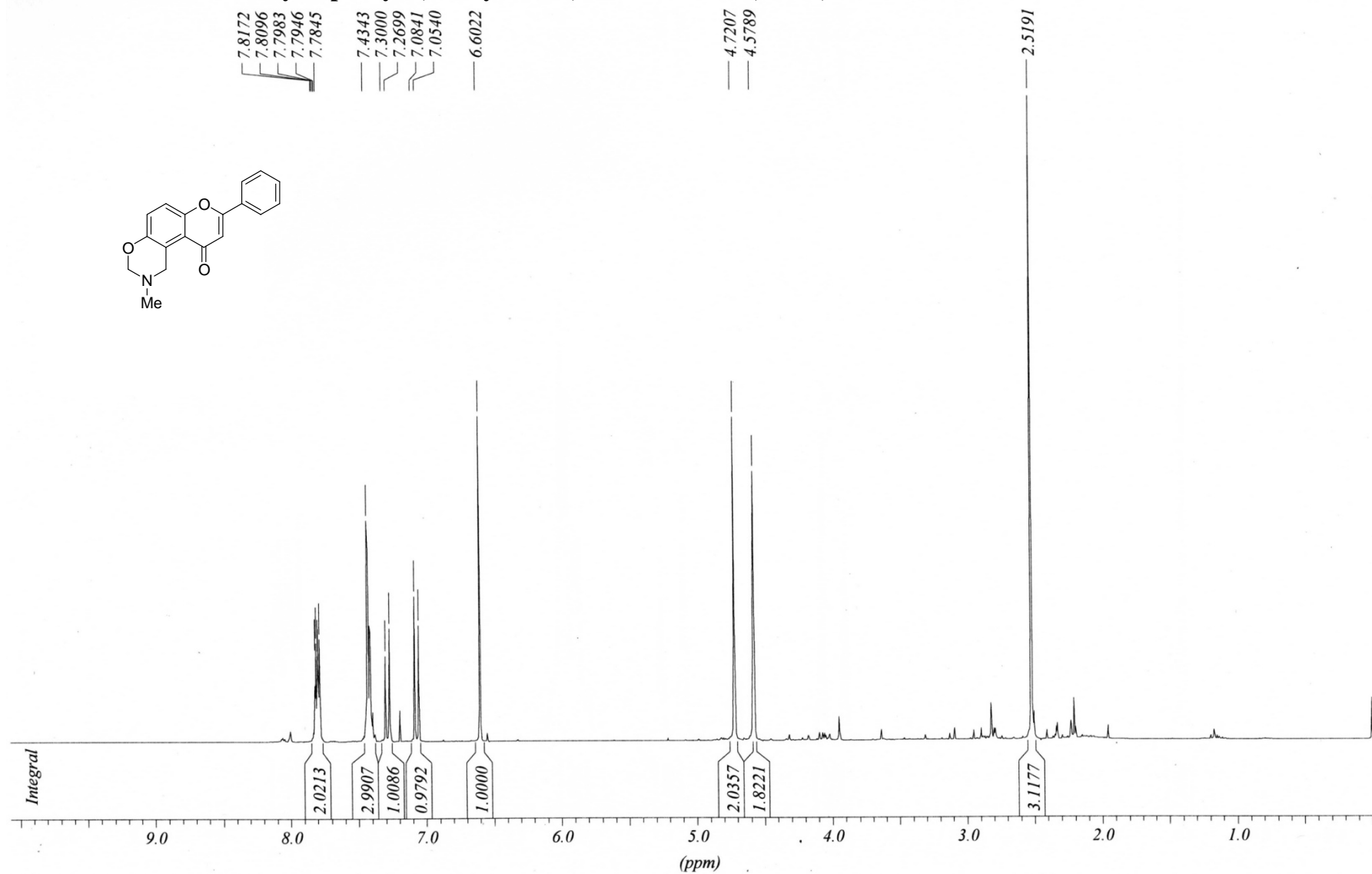
To a solution of methylamine (0.1 mL, 11.85 M solution in water, 1.185 mmol) in methanol (2 mL) was added paraformaldehyde (0.5 ml, 36 % in water, 6.5 mmol). The mixture was heated at 65 °C for 1 h. Afterwards a solution of 4'-methoxy-7-hydroxyflavone (268 mg, 1 mmol) in methanol (10 mL) was added. The mixture was refluxed for additional 10 h. Afterwards the solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane:EtOAc=7:3) to afford **N3** (200 mg, 62%) as a pale yellow solid. Mp = 272 °C. ¹H NMR (270 MHz, CDCl₃): δ 7.87 (d, 8.1 Hz, 1H), 7.69 (d, 8.1 Hz, 2H), 6.92 (d, 8.1 Hz, 2H), 6.75 (d, 8.1 Hz, 1H), 6.56 (s, 1H), 4.82 (s, 2H), 4.16 (s, 2H), 3.79 (s, 3H), 2.58 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 176.80, 161.28, 161.23, 157.21, 153.54, 126.57, 123.45, 123.03, 116.35, 113.90, 113.47, 106.52, 105.00, 83.38, 54.47, 46.18, 39.19; HRMS (ESI) calcd for C₁₉H₁₈NO₄ [M+H]⁺ = 324.1230 Found 324.1235

6,8-bis((dimethylamino)methyl)-5-hydroxyflavone **N4**

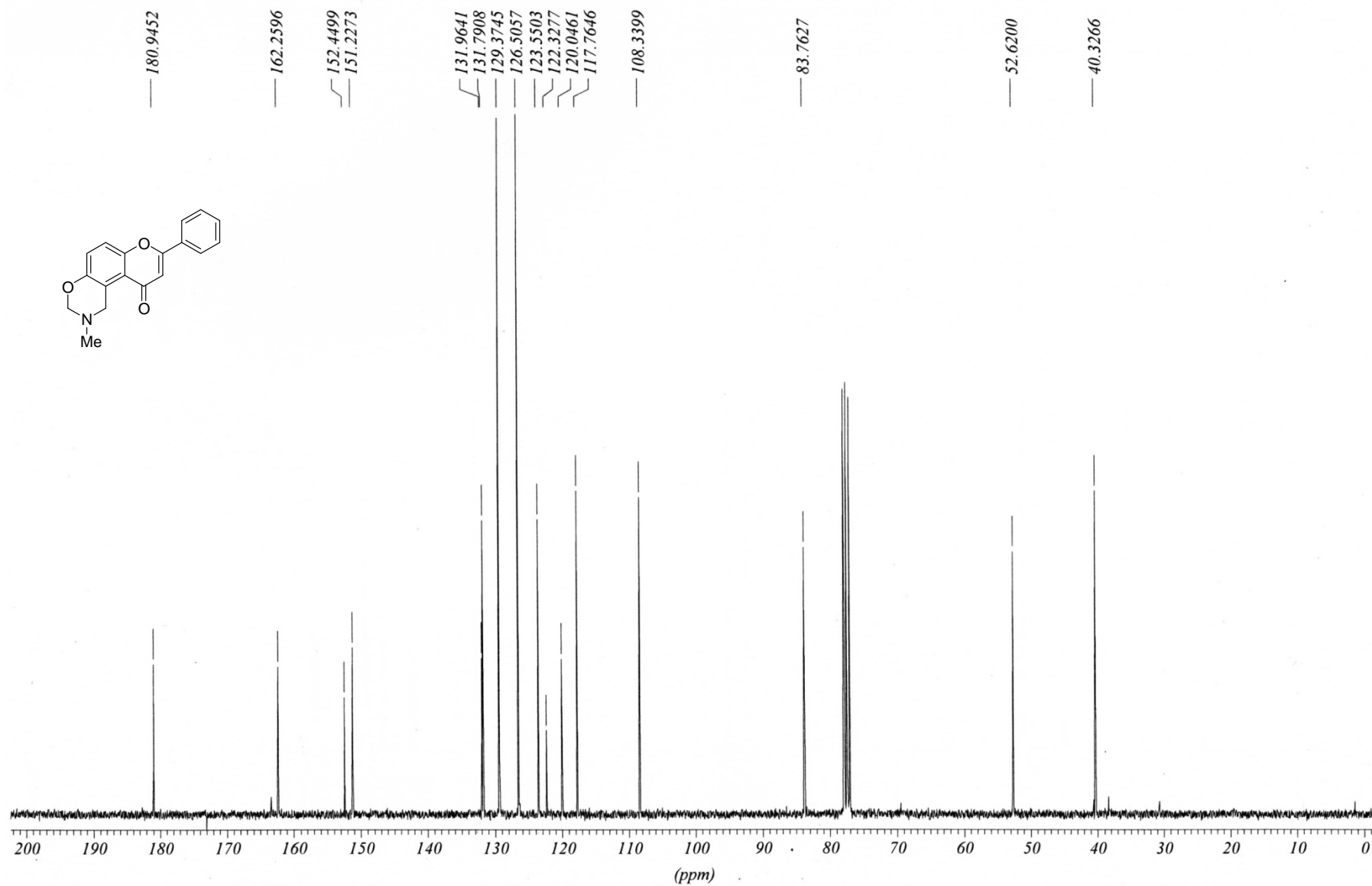


A mixture of 238 mg (1.0 mmol) of 5-hydroxyflavone, 2 mL (2.0 M in methanol, 2 mmol) of dimethylamine and 0.5 mL (36 % in water, 6.5 mmol) of paraformaldehyde in 15 mL of methanol was heated to 65 °C for 10 h. Afterwards the solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane:EtOAc=7:3) to afford **N4** (194 mg, 55%) as a grey white solid. Mp = 245 °C. ¹H NMR (270 MHz, CDCl₃): δ 7.85 (m, 2H), 7.54 (s, 1H), 7.48 (m, 3H), 6.68 (s, 1H), 3.61 (s, 2H), 3.46 (s, 2H), 2.25 (s, 6H), 2.23 (s, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 182.94, 163.19, 157.18, 152.63, 137.76, 130.97, 130.50, 128.16, 125.39, 119.27, 115.10, 109.31, 104.83, 56.26, 55.32, 44.43, 44.32; HRMS (ESI) calcd for C₂₁H₂₅N₂O₃ [M+H]⁺ = 353.1860 Found 353.1868

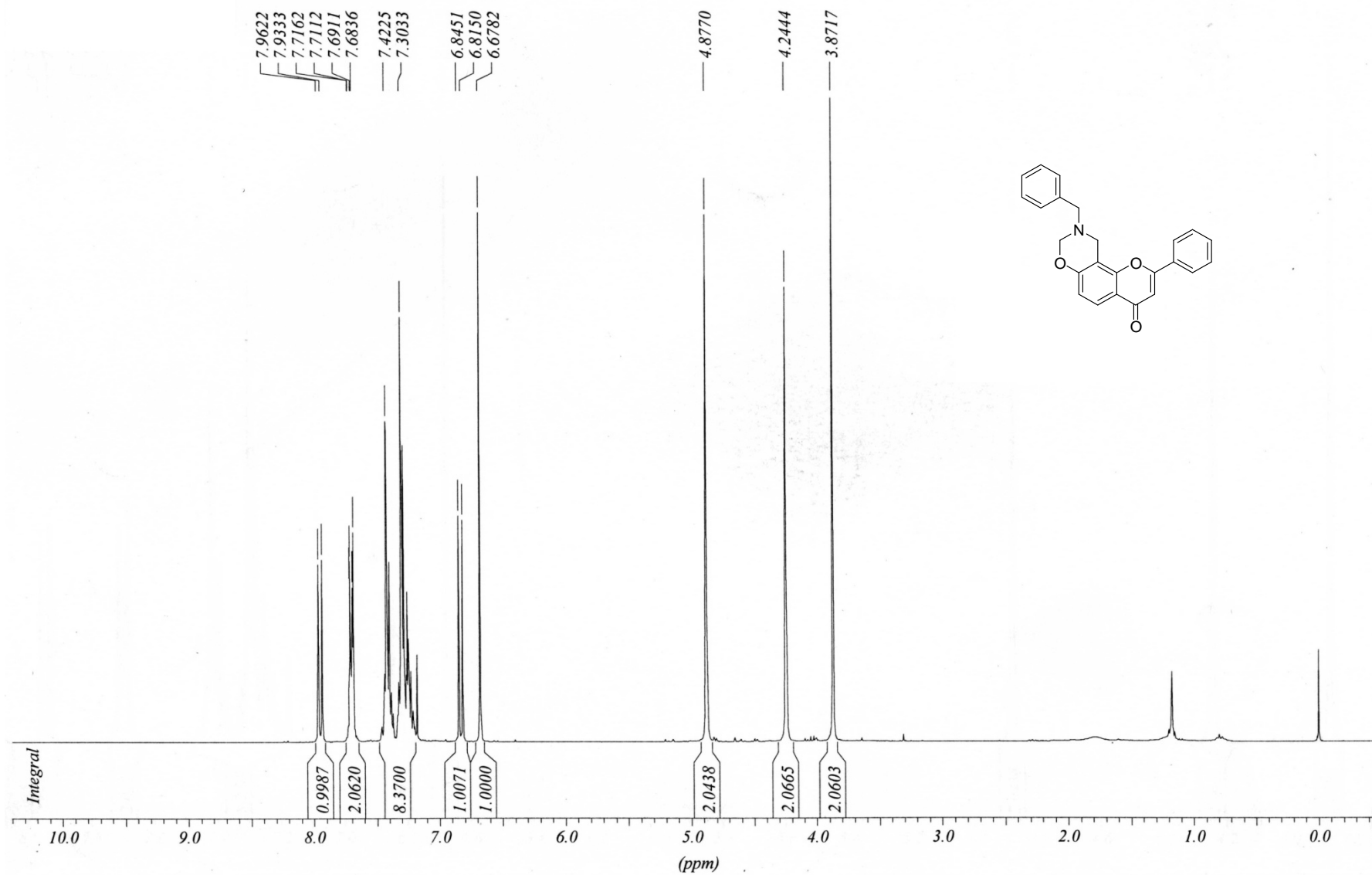
¹H NMR of 2-methyl-8-phenyl-2,3-dihydro-1*H*,10*H*-chromeno[5,6-*e*][1,3]oxazin-10-one N1



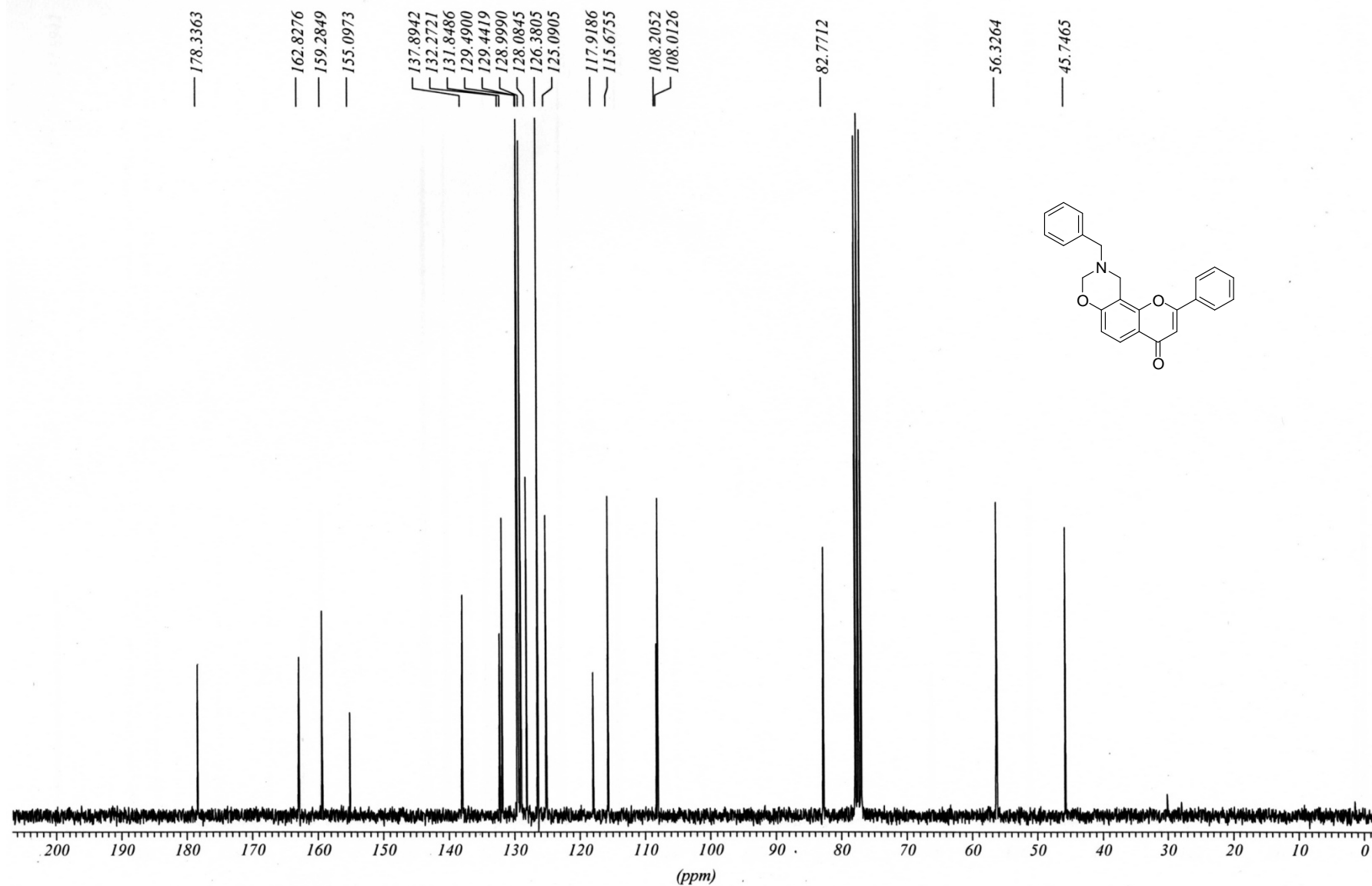
^{13}C NMR of 2-methyl-8-phenyl-2,3-dihydro-1*H*,10*H*-chromeno[5,6-*e*][1,3]oxazin-10-one N1



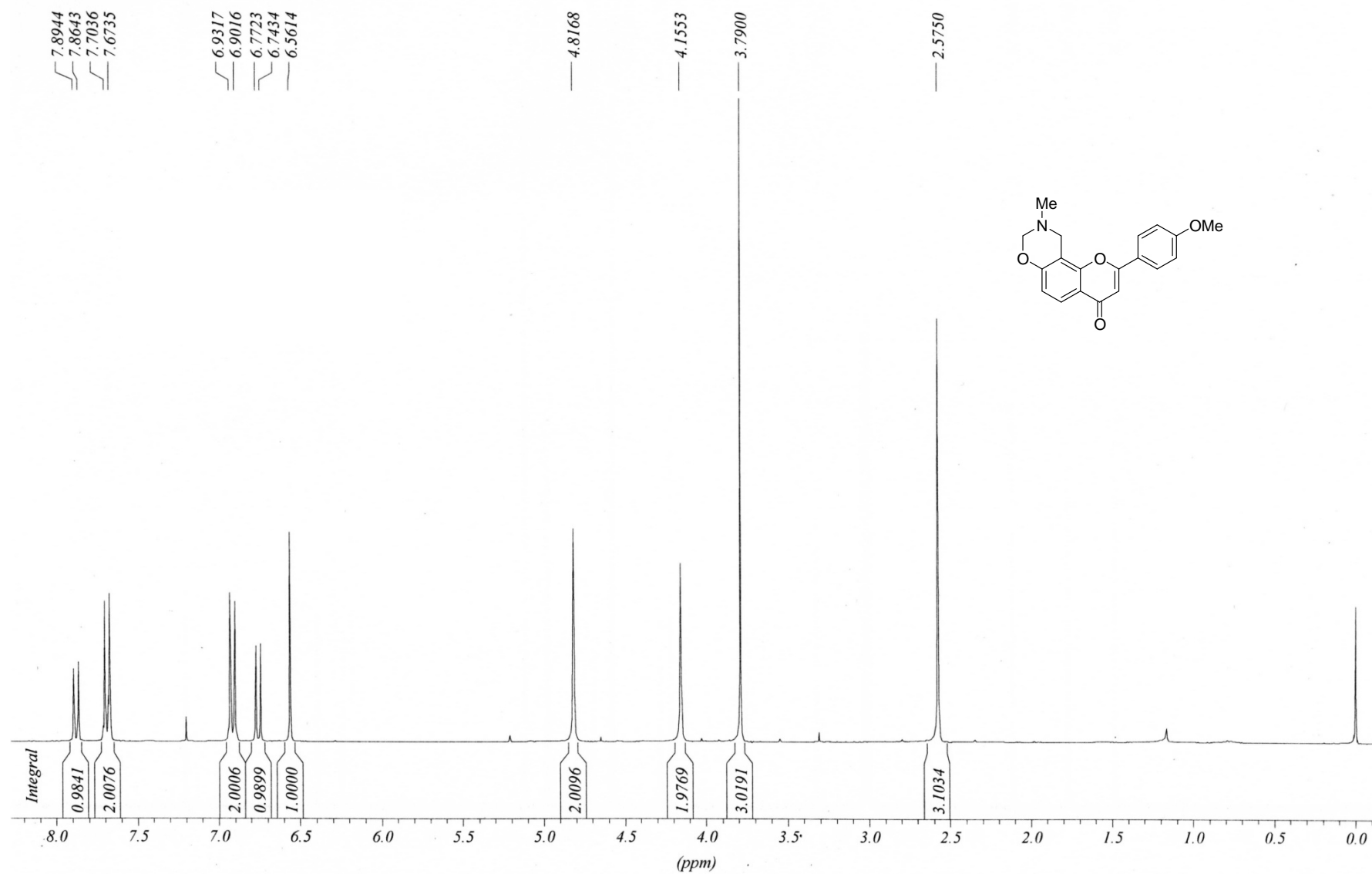
¹H NMR of 9-benzyl-2-phenyl-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one N2



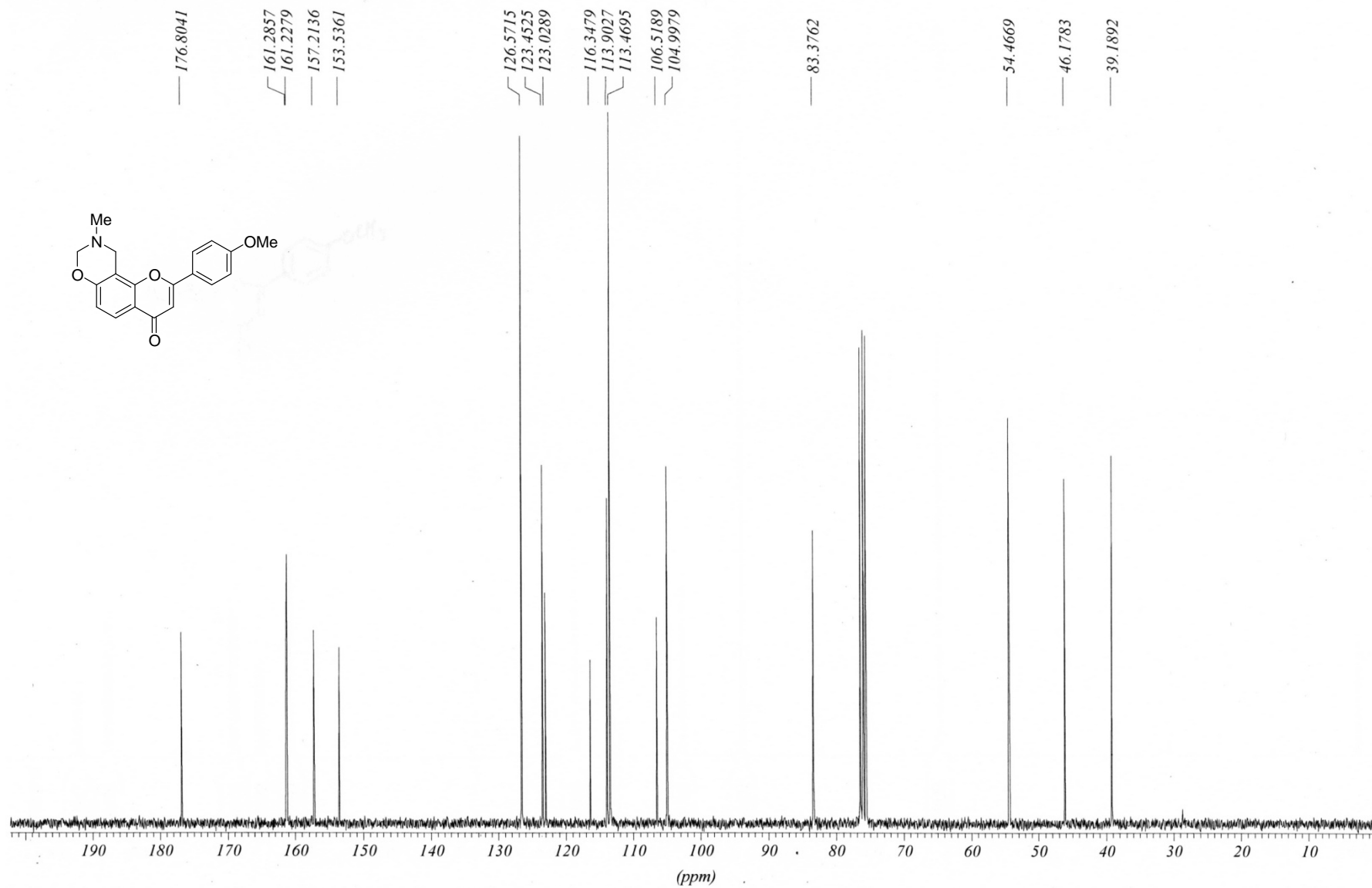
^{13}C NMR of 9-benzyl-2-phenyl-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one N2



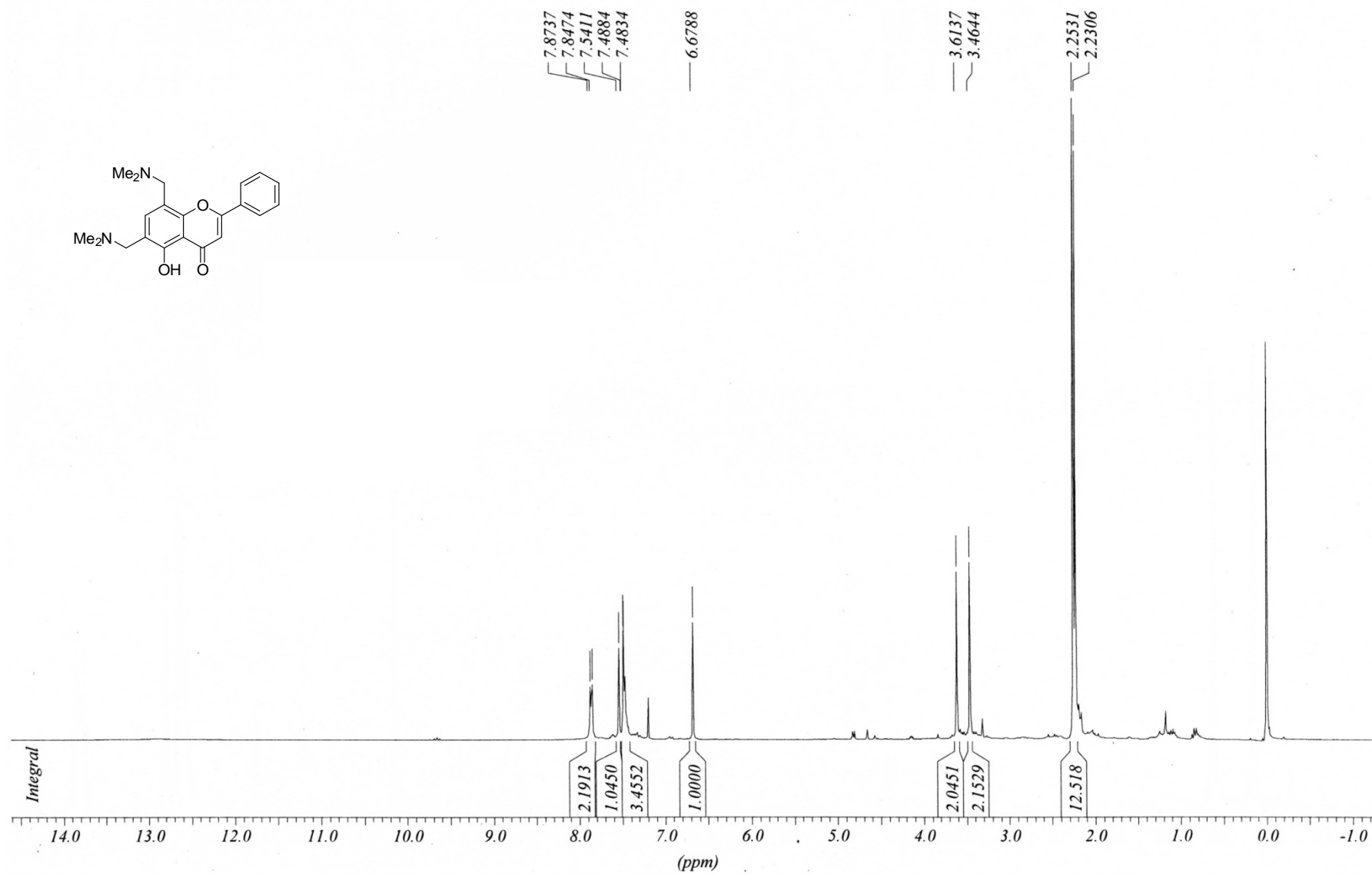
¹H NMR of 2-(4-methoxyphenyl)-9-methyl-9,10-dihydro-4*H*,8*H*-chromeno[8,7-*e*][1,3]oxazin-4-one N3



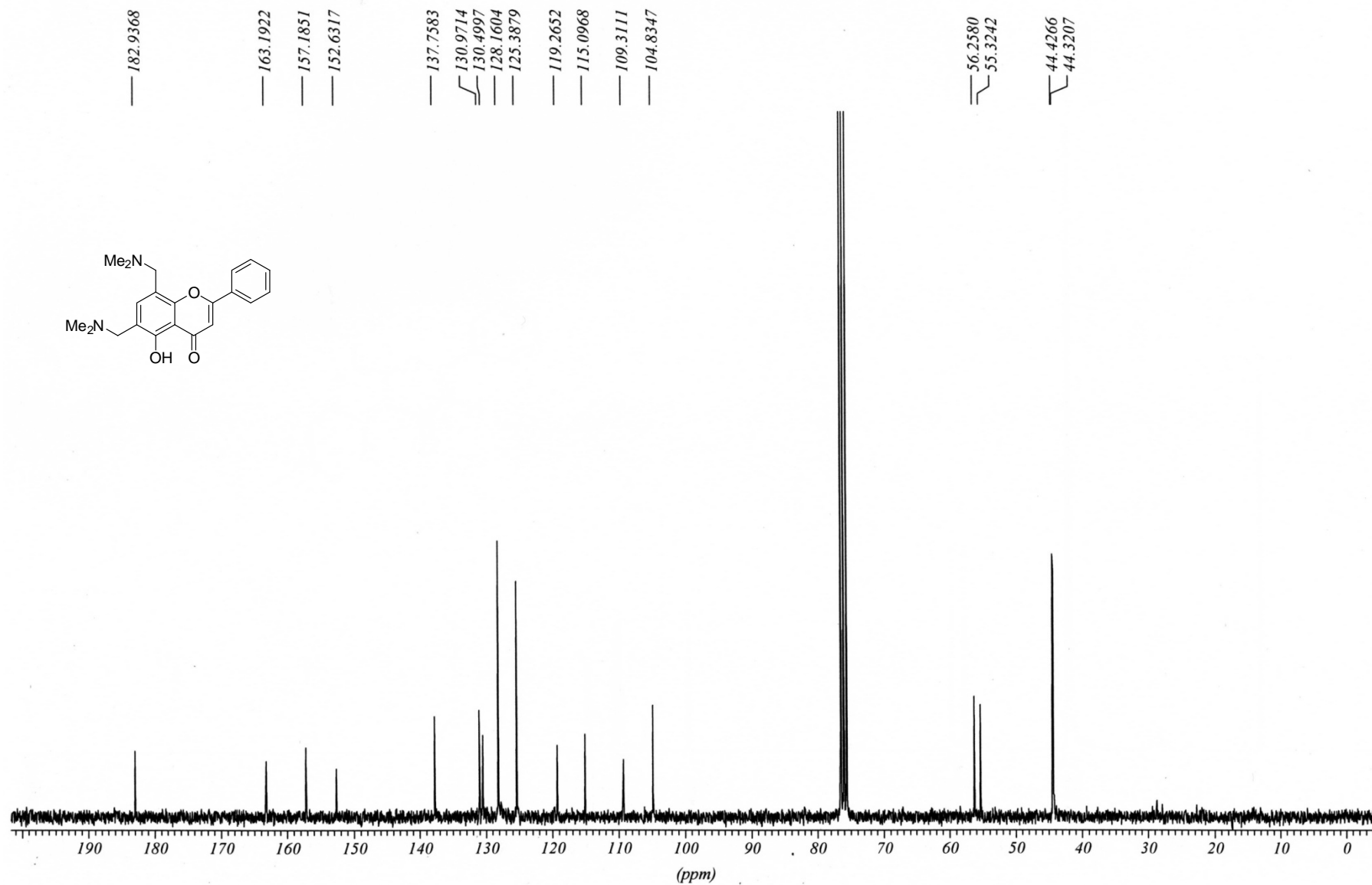
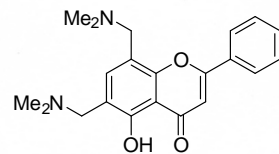
^{13}C NMR of 2-(4-methoxyphenyl)-9-methyl-9,10-dihydro-4H,8H-chromeno[8,7-e][1,3]oxazin-4-one N3



¹H NMR of 6,8-bis((dimethylamino)methyl)-5-hydroxyflavone N4



^{13}C NMR of 6,8-bis((dimethylamino)methyl)-5-hydroxyflavone N4



Appendix C: Experimental and supplementary data of chapter 5

Experimental

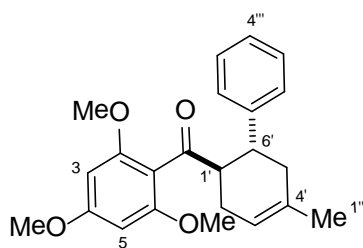
Preparation of substrates

Chalcones **5-1** & **5-9** were prepared according to literature procedures. Chalcones **5-2** & **5-3** were synthesised via Claisen-Schmidt condensation of the corresponding acetophenones and benzaldehyde under basic conditions.

General procedure for preparation of cycloadducts **5-4**, **5-4a**, **5-5**, **5-6**, **5-6a**, **5-7**, **5-7a**, **5-8** & **5-8a**.

To a screw-capped pressure tube (Ace Glass Inc, USA) equipped with a magnetic stirrer was added the corresponding chalcone (2 mmol) and the diene (1 ml). The resulting mixture was heated at the temperature reported and left under magnetic stirring for the period specified. After silica-gel column chromatography of the final mixture cycloadducts **5-4**, **5-4a**, **5-5**, **5-6**, **5-6a**, **5-7**, **5-7a**, **5-8** & **5-8a** were isolated.

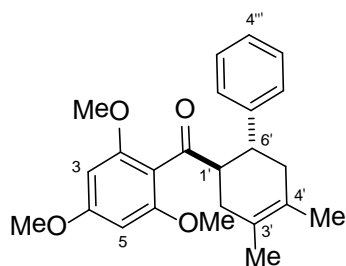
(2, 4, 6-trimethoxyphenyl)(4-methyl-6-phenylcyclohex-3-enyl)methanone (**5-4a**)



characterized in a para/meta regioisomers mixture: 3/2; chromatography on silica gel, eluent hex/EtOAc, 9/1 gradient; 86% overall yield; pale yellow needles; mp 132-134 °C (CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.09 (m, 4H, H-2''', 6''', H-3''', 5'''), 7.01 (m, 1H, H-4'''), 5.86 (s, 2H, H-3, 5), 5.39 (bs, 1H, H-3'), 3.69 (s, 3H, OCH₃), 3.50 (s, 6H, 2 x OCH₃), 3.41 (ddd, 1H, J=10.0, 9.5, 5.9 Hz, H-1'), 3.11 (ddd, 1H, J=10.2, 10.0, 5.9Hz, H-6'), 2.27 (m, 2H, H-2'), 2.07 (m, 2H, H-5'), 1.60 (s, 3H, 4'-CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 205.96 (C=O), 162.21 (C-4), 158.56 (C-2,6), 145.09 (C-1'''), 133.13

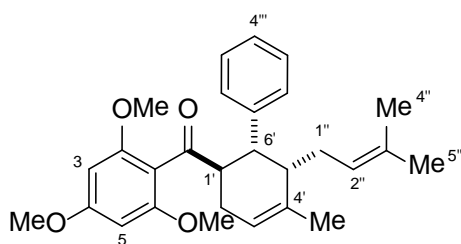
(C-4'), 127.91 (C-2''',6'''), 127.64 (C-3''',5'''), 125.67 (C-4'''), 119.97 (C-3'), 113.79 (C-1), 90.10 (C-3,5), 55.54, 55.25 (OCH₃), 52.31 (C-1'), 42.96 (C-6'), 39.04 (C-5'), 28.30 (C-2'), 23.12 (C-1''). FT-IR (KBr, cm⁻¹) ν : 2935, 1705, 1585, 1465, 1409, 1224, 1128; HRESIMS calcd. C₂₃H₂₇O₄ [M+H]⁺ 367.1904; found 367.1963.

(2, 4, 6-trimethoxyphenyl)(3, 4-dimethyl-6-phenylcyclohex-3-enyl)methanone (5-5)



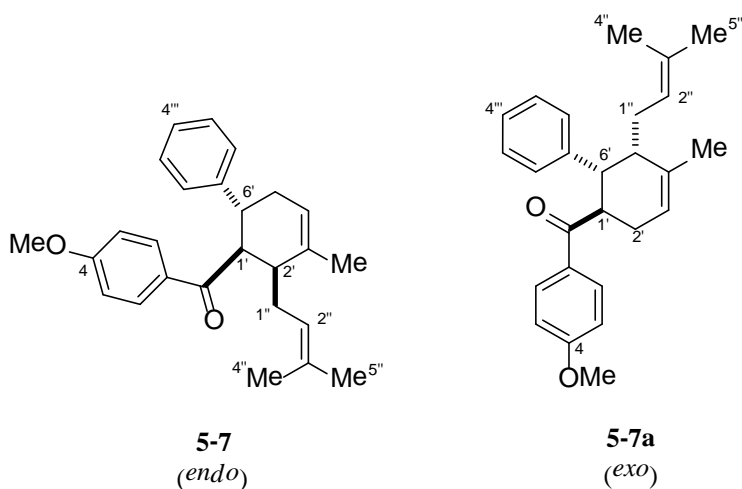
chromatography on silica gel, eluent hex/EtOAc, 9/1 gradient; 93% overall yield; yellow solid; mp 94-96 °C (CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.08 (m, 4H, H-2''', 6''', H-3''', 5'''), 7.00 (m, 1H, H-4'''), 5.86 (s, 2H, H-3, 5), 3.70 (s, 3H, OCH₃), 3.50 (s, 6H, 2 x OCH₃), 3.47 (m, overlapped, 1H, J can't estimated, H-1'), 3.05 (ddd, 1H, J=10.0, 9.7, 5.9Hz, H-6'), 2.30 (m, 2H, H-2'), 2.11 (m, 2H, H-5'), 1.58 (s, 3H, 3'-CH₃), 1.55 (s, 3H, 4'-CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 205.95 (C=O), 162.19 (C-4), 158.54 (C-2,6), 145.05 (C-1'''), 127.88 (C-2''',6'''), 127.59 (C-3''',5'''), 125.62 (C-4'''), 124.78 (C-3'), 124.67 (C-4'), 113.85 (C-1), 90.08 (C-3,5), 55.55, 55.26 (OCH₃), 53.15 (C-1'), 43.41 (C-6'), 40.92 (C-5'), 34.39 (C-2'), 18.77 (CH₃-3'), 18.57 (CH₃-4'). FT-IR (KBr, cm⁻¹) ν : 2925, 1675, 1603, 1457, 1412, 1234, 1130; HRESIMS calcd. C₂₄H₂₉O₄ [M+H]⁺ 381.2060; found 381.2089.

(2, 4, 6-trimethoxyphenyl)(4-methyl-5-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (5-6a).

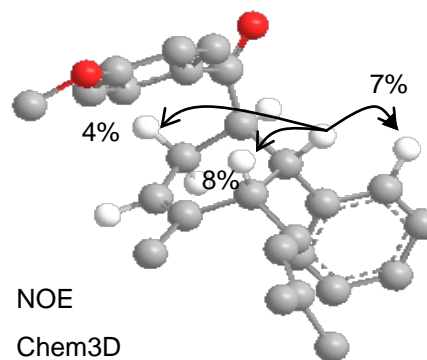
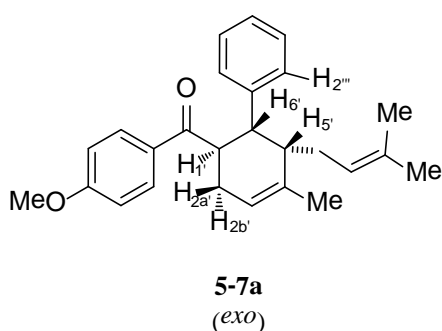


characterized in a p/m -regioisomers mixture: 3/2; oil; chromatography on silica gel, eluent hex/EtOAc, 8/2 gradient; 99% overall yield; ^1H NMR (400 MHz, CDCl_3): δ 7.15 (m, 5H, H-2'''-6'''), 6.04 (s, 2H, H-3, 5), 5.51 (bs, 1H, H-3'), 4.90 (t, 1H, H-2''), 3.80 (s, 3H, OCH_3), 3.64 (s, 6H, 2 x OCH_3), 3.69 (m, overlapped, 1H, J can't estimated, H-1'), 3.41 (dd, 1H, J=11, 6.2, H-6'), 2.34 (m, 2H, H-2'), 2.33 (m, 1H, H-5'), 2.03 (m, 2H, H-1''), 1.75 (s, 3H, 3'- CH_3), 1.57 (s, 3H, CH_3 -4''), 1.27 (s, 3H, CH_3 -5''); ^{13}C NMR (100 MHz, CDCl_3): δ 205.79 (C=O), 162.42 (C-4), 158.77 (C-2,6), 143.13 (C-1'''), 136.66 (C-4'), 130.85 (C-3''), 129.26 (C-2''',6'''), 127.61 (C-3''',5'''), 125.66 (C-4'''), 123.71 (C-2''), 121.22 (C-3'), 113.70 (C-1), 90.45 (C-3,5), 55.70, 55.41 (OCH_3), 48.48 (C-1'), 46.08 (C-6'), 43.46 (C-5'), 27.58 (C-1''), 27.13 (C-2'), 22.74 (C-4'-Me), 25.93 (C-4''), 17.73 (C-5''). FT-IR (CHCl_3 , cm^{-1}) ν : 3004, 1693, 1605, 1413, 1227, 1129; HRESIMS calcd. $\text{C}_{28}\text{H}_{35}\text{O}_4$ $[\text{M}+\text{H}]^+$ 435.2530; found 435.2540.

(4-methoxyphenyl)(3-methyl-2-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (**5-7**) & (4-methoxyphenyl)(4-methyl-5-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (**5-7a**).

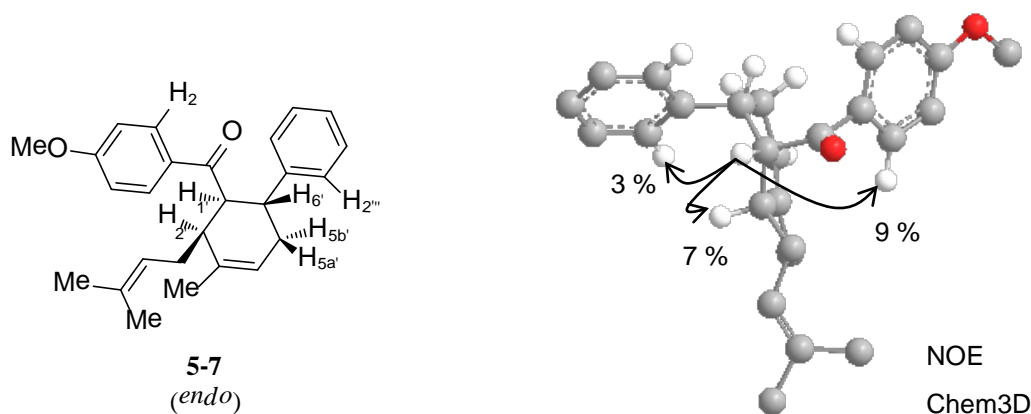


After chromatography on silica gel (15 % EtOAc in hexane), the desired mixture of compounds **5-7** & **5-7a** (719 mg, 96%) was isolated as a yellow oil which was shown in a p/m –regioisomeric ratio of 3/2 (determined by ^1H NMR integration). Pure sample of each regioisomer **5-7** & **5-7a** was obtained by further separation on silica gel chromatography (40 % CH_2Cl_2 in hexane).



^1H NMR (400 MHz, CDCl_3): δ 7.85 (d, 2H, $J=8.5$, H-1,6), 7.07 (m, 2H, H-3''',5'''), 7.05 (m, 3H, H-2''',4''',6'''), 6.84 (d, 2H, $J=8.5$, H-3, 5), 5.42 (bs, 1H, H-3'), 4.91 (t, 1H, H-2''), 4.25 (ddd, 1H, $J=10, 10, 6$, H-1'), 3.74 (s, 3H, OCH_3), 3.49 (dd, 1H, $J=10, 5.1$, H-6'), 2.38 (m, 1H, H-2'), 2.25 (q, 1H, H-5'), 2.14 (m, 1H, H-2'), 1.90 (m, 2H, H-1''), 1.69 (s, 3H, 3'- CH_3), 1.58 (s, 3H, CH_3 -4''), 1.29 (s, 3H, CH_3 -5''); NOE_Diff (400 MHz,

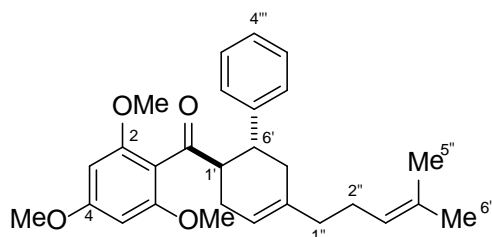
CDCl₃) Irradiation at δ 3.51 (H-6'): 8 % enhancement at H-5', 7 % enhancement at H-2''', 4 % enhancement at H-2'a ; H-1' collapsed to doublet of doublet ($J = 10, 6$ Hz); ¹³C NMR (100 MHz, CDCl₃): δ 201.99 (C=O), 163.27 (C-4), 142.81 (C-1'''), 137.37 (C-4'), 130.64 (C-3''), 130.20 (C-2,6), 127.95 (C-2''',6'''), 127.84 (C-3''',5'''), 125.71 (C-4'''), 123.62 (C-2''), 120.00 (C-3'), 113.72 (C-3,5), 112.82 (C-1), 55.31 (OCH₃), 46.02 (C-6'), 44.98 (C-5'), 39.47 (C-1'), 31.13 (C-2'), 27.38 (C-1''), 25.82 (C-4''), 22.67 (C-4'-Me), 17.88 (C-5''). FT-IR (KBr, cm⁻¹) ν : 2987, 1676, 1605, 1403, 1240, 1129; HRESIMS calcd. C₂₆H₃₁O₂ [M+H]⁺ 375.2319; found 375.2340.



¹H NMR (400 MHz, CDCl₃): δ 7.86 (d, 2H, $J=8.5$, H-1,6), 7.20 (m, 5H, H-2'''~6'''), 6.90 (d, 2H, $J=8.5$, H-3, 5), 5.49 (bs, 1H, H-4'), 4.87 (t, 1H, H-2''), 4.13 (dd, 1H, $J=10.4, 4.8$, H-1'), 3.81 (s, 3H, OCH₃), 3.46 (ddd, 1H, $J=10.5, 10.5, 6.3$, H-6'), 2.37 (m, 3H, H-2' & H-5';overlapped), 2.17 (m, 1H, H-1''), 2.00 (m, 1H, H-1''), 1.80 (s, 3H, 3'-CH₃), 1.50 (s, 3H, CH₃-4''), 1.48 (s, 3H, CH₃-5''); NOE_Diff (400 MHz, CDCl₃) Irradiation at δ 4.13 (H-1'): 9 % enhancement at H-2, 7 % enhancement at H-2', 3 % enhancement at H-2''' ; H-6' collapsed to doublet of doublet ($J = 10.5, 6.3$ Hz); ¹³C NMR (100 MHz, CDCl₃): δ 199.29 (C=O), 163.16 (C-4), 146.64 (C-1'''), 136.85 (C-3'), 131.86 (C-3''), 130.32 (C-2,6), 128.42 (C-3''',5'''), 127.20 (C-2''',6'''), 125.83 (C-4'''), 124.03 (C-2''), 121.45 (C-4'), 113.77 (C-3,5), 113.56 (C-1), 55.48 (OCH₃), 50.21 (C-

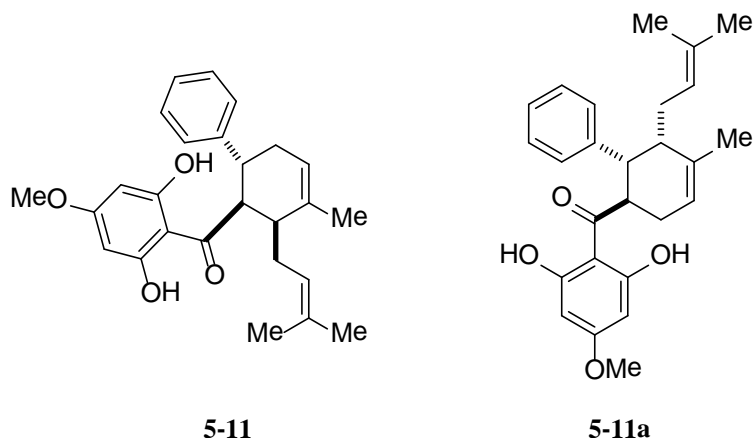
1'), 43.20 (C-2'), 37.18 (C-6'), 35.29 (C-5'), 29.03 (C-1''), 23.04 (C-2'-Me), 25.86 (C-4''), 17.92 (C-5''). FT-IR (KBr, cm^{-1}) ν : 2987, 1676, 1605, 1403, 1240, 1129; HRESIMS calcd. $\text{C}_{26}\text{H}_{31}\text{O}_2$ $[\text{M}+\text{H}]^+$ 375.2319; found 375.2340.

(2, 4, 6-trimethoxyphenyl)(4-(4-methylpen-3-enyl)-6-phenylcyclohex-3-enyl)methanone (5-8a).



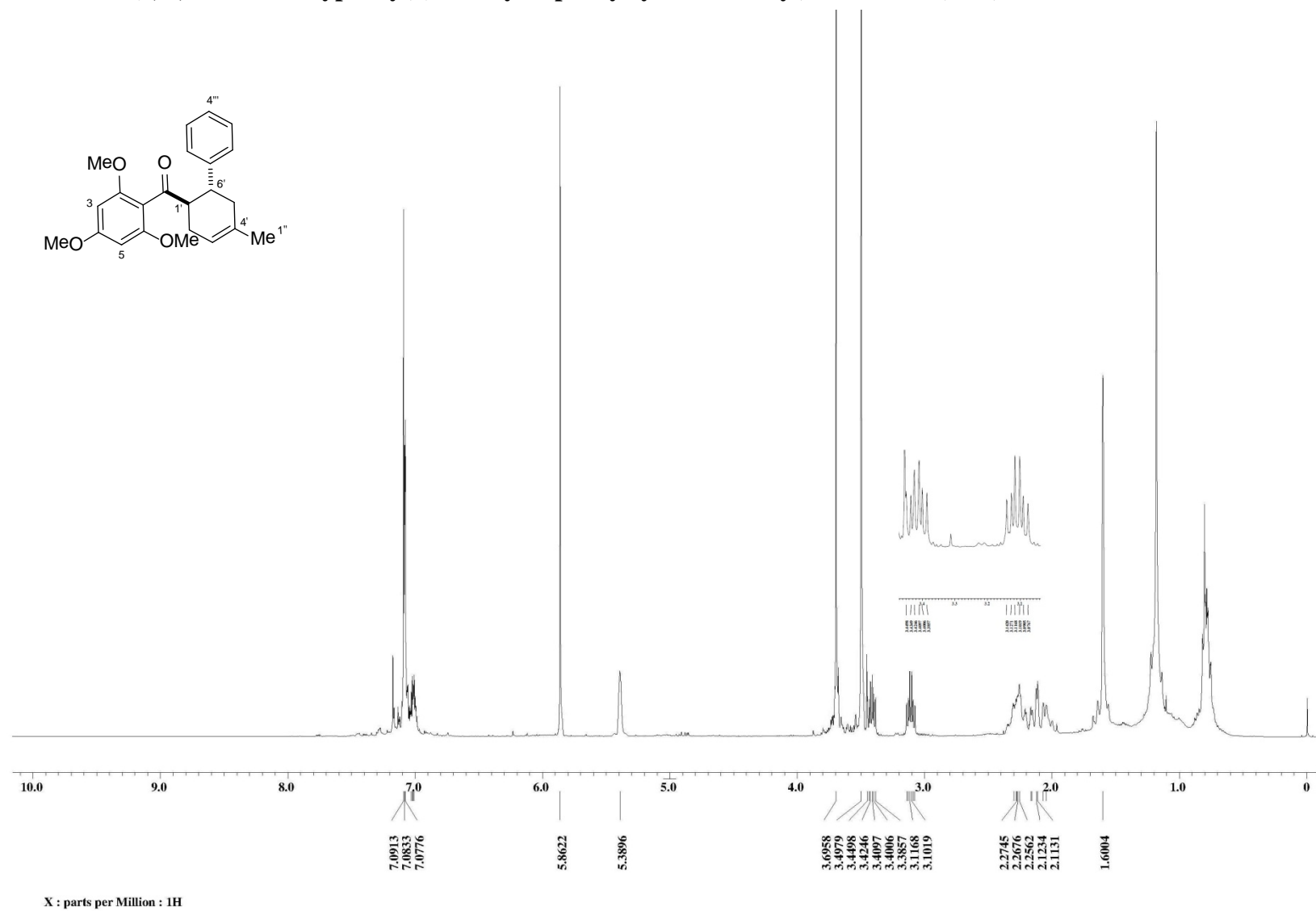
characterized in a p/m -regioisomers mixture: 3/2; chromatography on silica gel, eluent hex/EtOAc, 4/1 gradient; 89% overall yield; yellow solid; mp 108-110 °C (CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.15 (m, 5H, H-2'''-6'''), 5.94 (s, 2H, H-3, 5), 5.47 (bs, 1H, H-3'), 5.08 (t, 1H, H-3''), 3.77 (s, 3H, OCH_3), 3.57 (s, 6H, 2 x OCH_3), 3.47 (ddd, 1H, $J=10.0, 10.2, 5.9\text{Hz}$, H-1'), 3.14 (ddd, 1H, $J=10.2, 10.2, 5.4\text{Hz}$, H-6'), 2.36 (m, 2H, H-2'), 2.19 (m, 1H, H-5'), 2.07 (m, 2H, H-2''), 1.96 (m, 2H, H-1''), 1.66 (s, 3H, CH_3 -5''), 1.58 (s, 3H, CH_3 -6''); ^{13}C NMR (100 MHz, CDCl_3): δ 205.97 (C=O), 162.22 (C-4), 158.57 (C-2,6), 145.15 (C-1'''), 136.82 (C-4'), 131.44 (C-4''), 127.94 (C-2''',6'''), 127.65 (C-3''',5'''), 125.69 (C-4''), 124.22 (C-3''), 119.59 (C-3'), 113.82 (C-1), 90.11 (C-3,5), 55.55, 55.28 (OCH_3), 52.49 (C-1'), 43.05 (C-6'), 37.56 (C-1''), 37.28 (C-5'), 28.41 (C-1'), 26.35 (C-2''), 25.69 (C-5''), 17.68 (C-6''); FT-IR (KBr, cm^{-1}) ν : 2929, 1700, 1602, 1457, 1412, 1227, 1132; HRESIMS calcd. $\text{C}_{28}\text{H}_{35}\text{O}_4$ $[\text{M}+\text{H}]^+$ 435.2530; found 435.2548.

For total synthesis of panduratin A and panduratin A (5-11 & 5-11a).

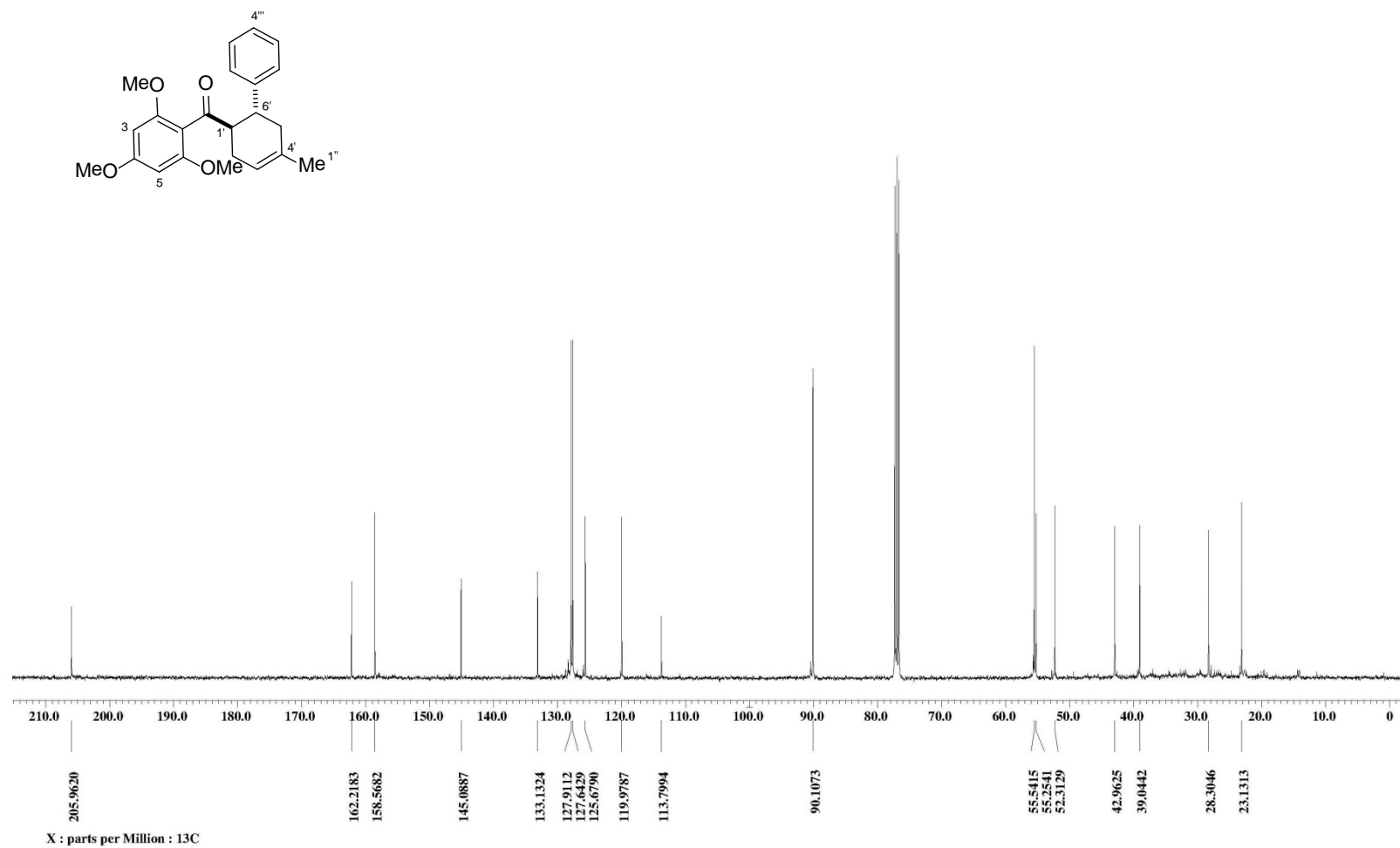


To a screw-capped pressure tube equipped with a magnetic stirrer was added 2'-hydroxy-4'-methoxy-6'-ethoxymethoxychalcone **5-9** (328 mg, 1 mmol) and ocimene (0.5 ml). The reaction mixture was heated at 150 °C for 24 hr. To the resulting orange residue was added 10 ml of MeOH and 4 ml of HCl (3M). The cloudy mixture was refluxed at 80°C for 10 min. The resulting yellow solution was cooled to room temperature, diluted with water, extracted with EtOAc, washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification on silica gel (15% EtOAc in hexane) afforded the mixture of panduratin A and isopanduratin A (162.4 mg, 89% for two steps) as a yellow solid. All spectroscopic data were identical with those of the natural product.²

^1H NMR of (2, 4, 6-trimethoxyphenyl)(4-methyl-6-phenylcyclohex-3-enyl)methanone (5-4a)



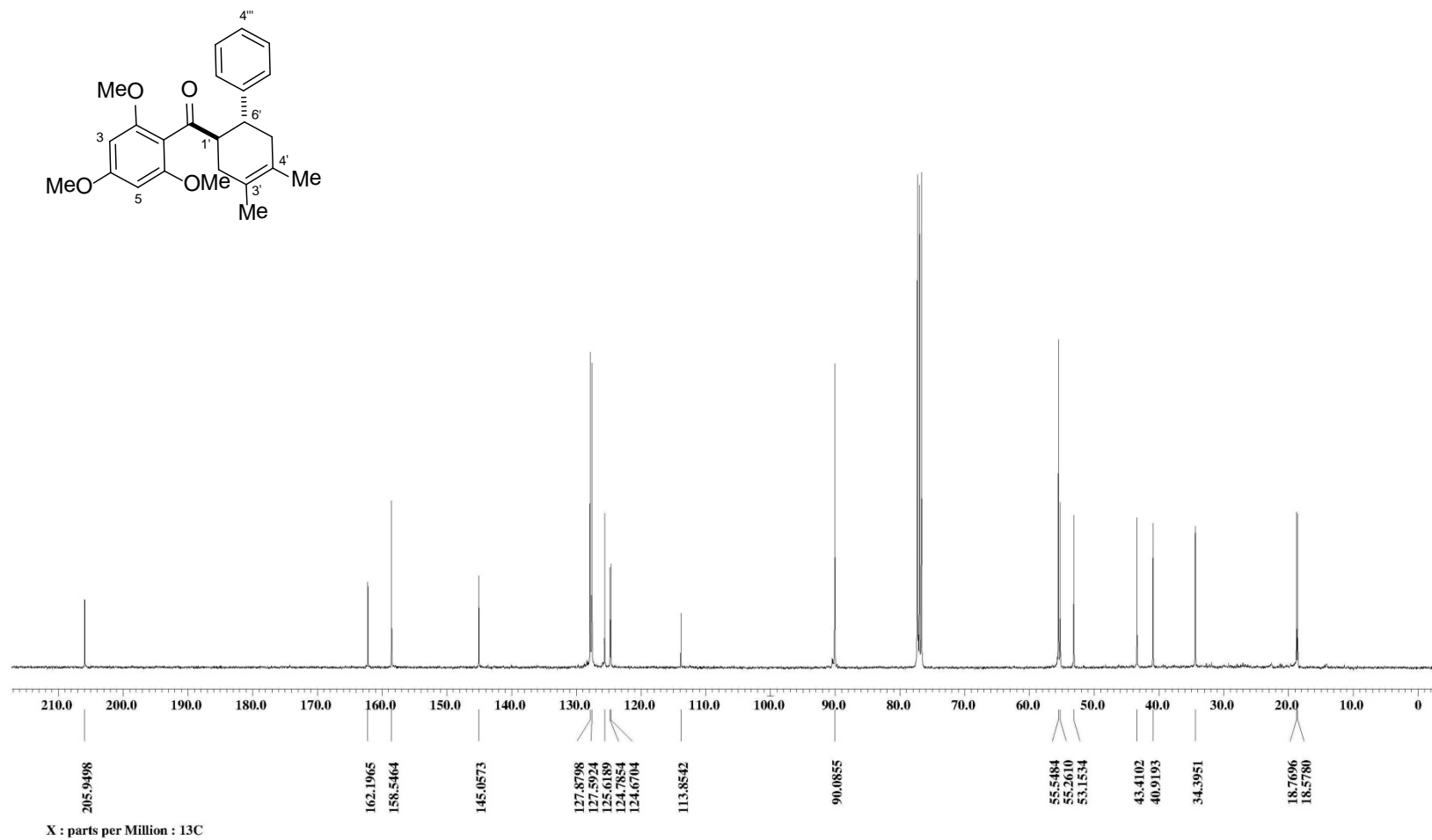
^{13}C NMR of (2, 4, 6-trimethoxyphenyl)(4-methyl-6-phenylcyclohex-3-enyl)methanone (5-4a)



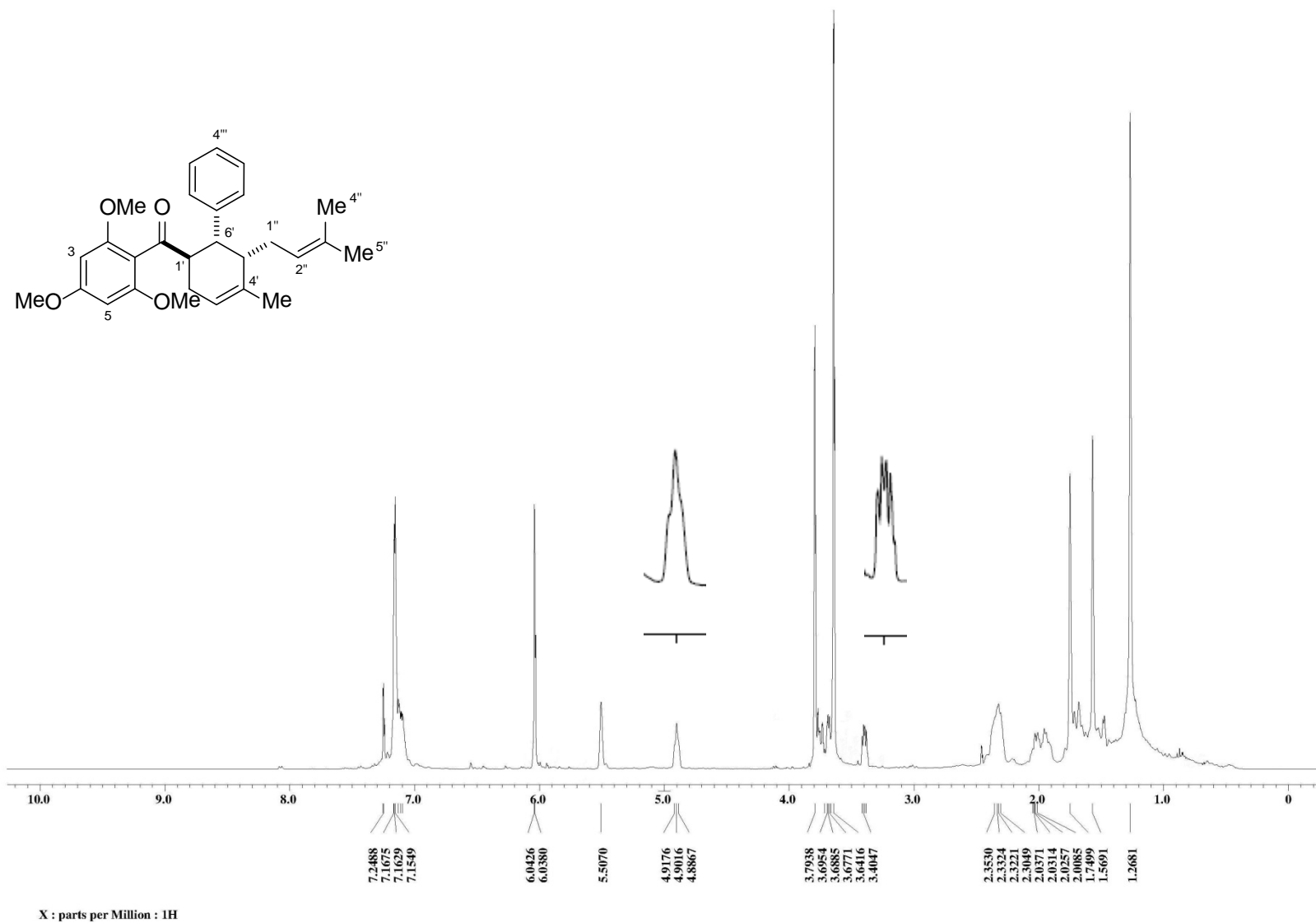
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100

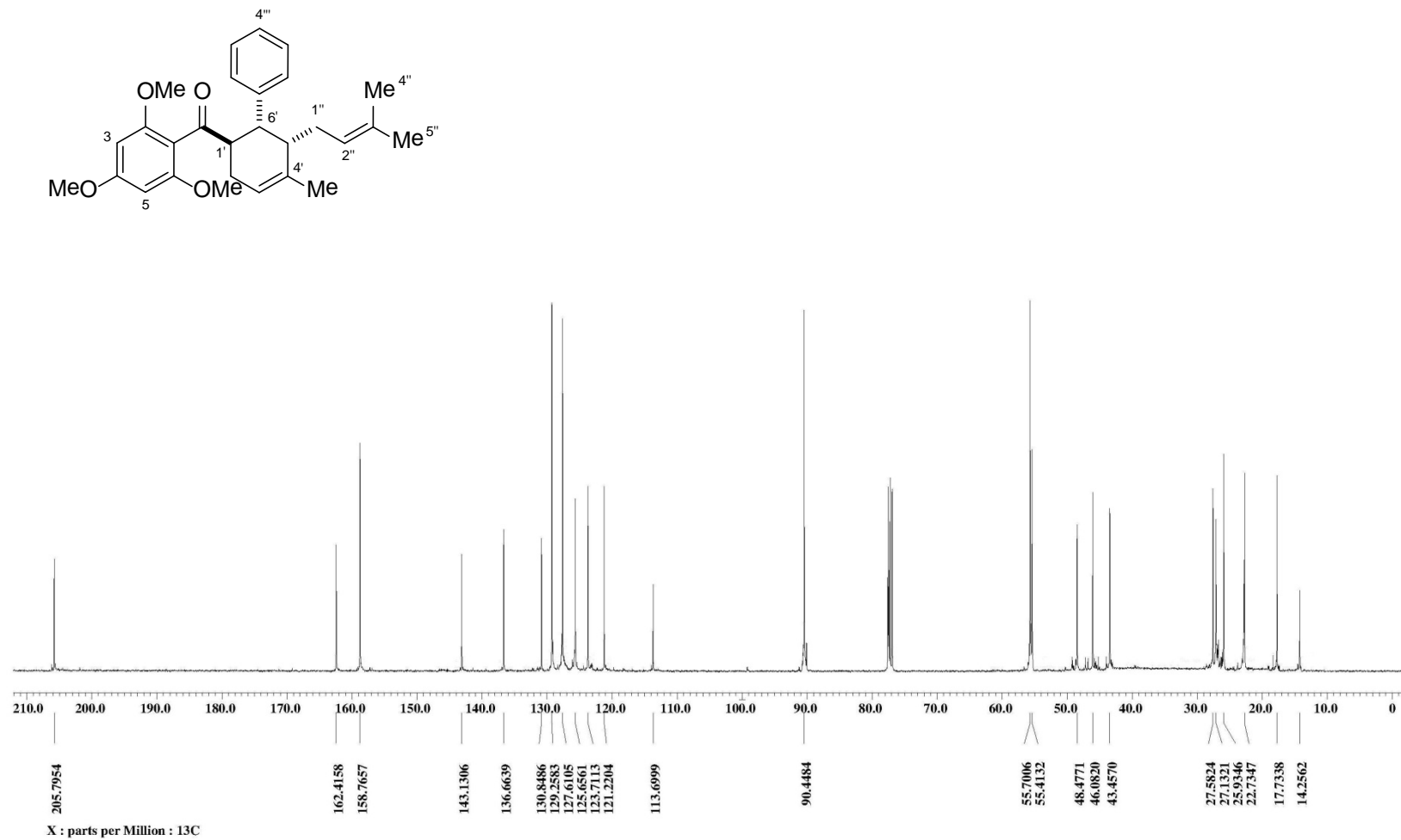
^{13}C NMR of (2, 4, 6-trimethoxyphenyl)(3, 4-dimethyl-6-phenylcyclohex-3-enyl)methanone (5-5)



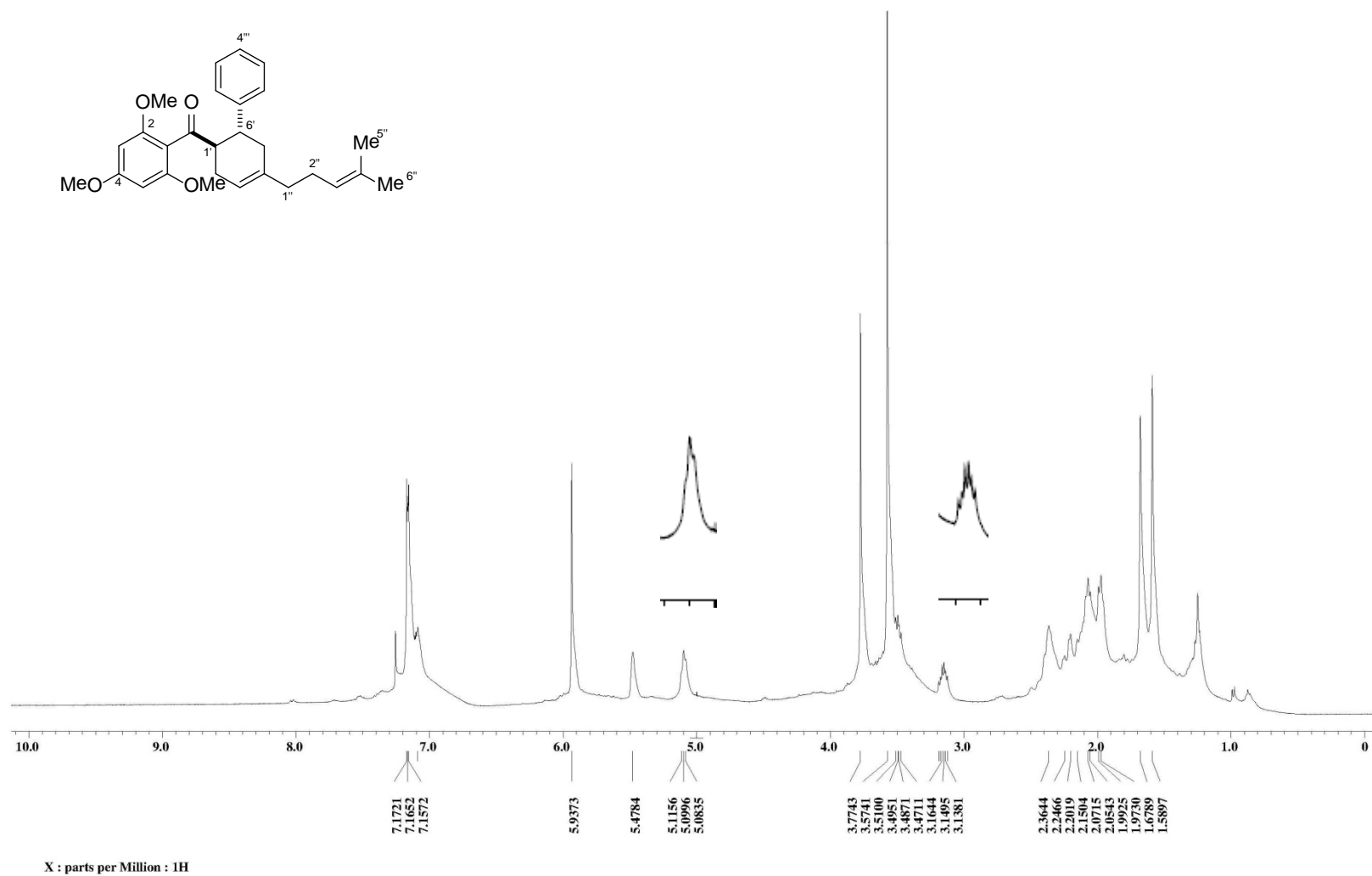
¹H NMR of (2, 4, 6-trimethoxyphenyl)(4-methyl-5-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (5-6a)



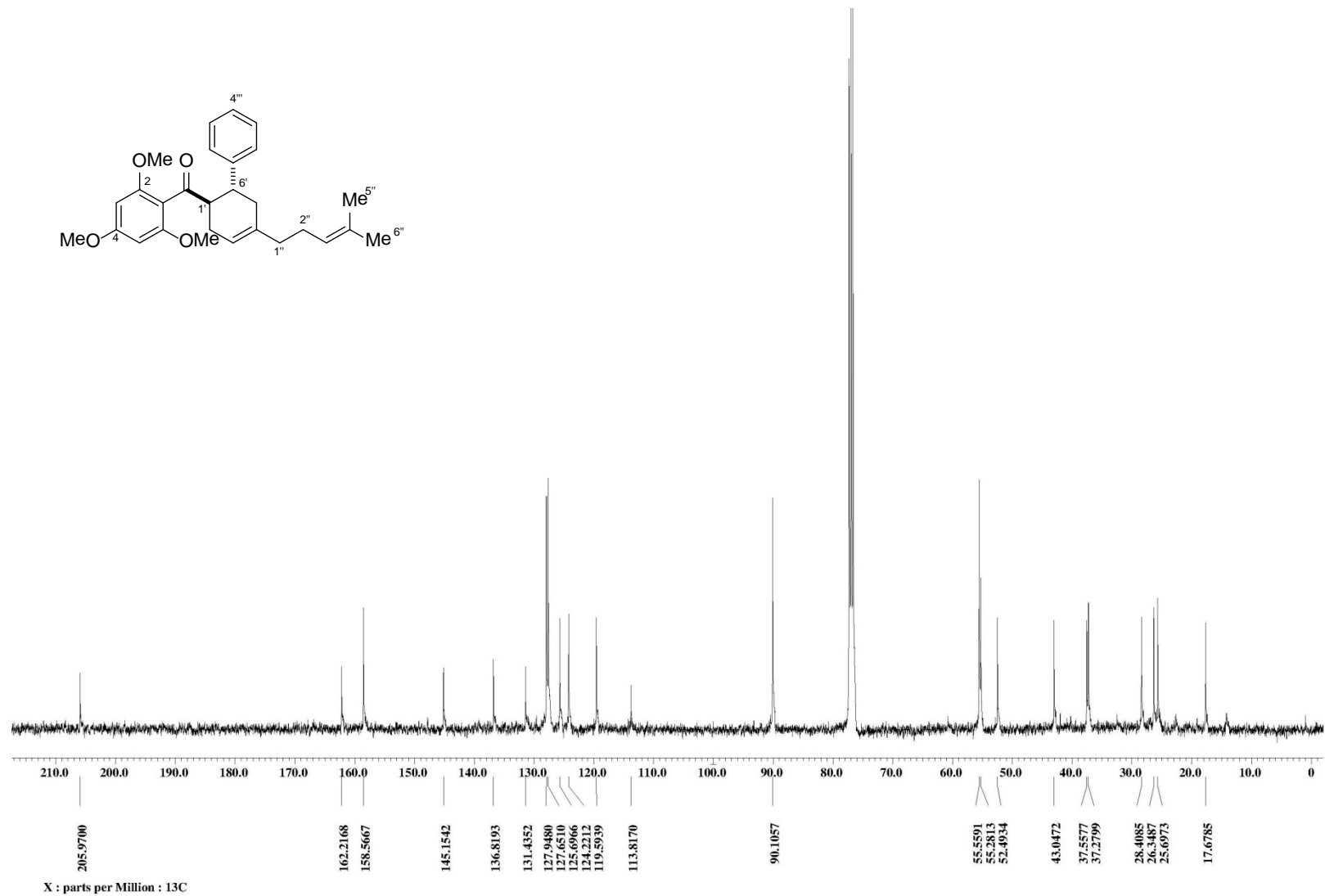
^{13}C NMR of (2, 4, 6-trimethoxyphenyl)(4-methyl-5-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (5-6a)



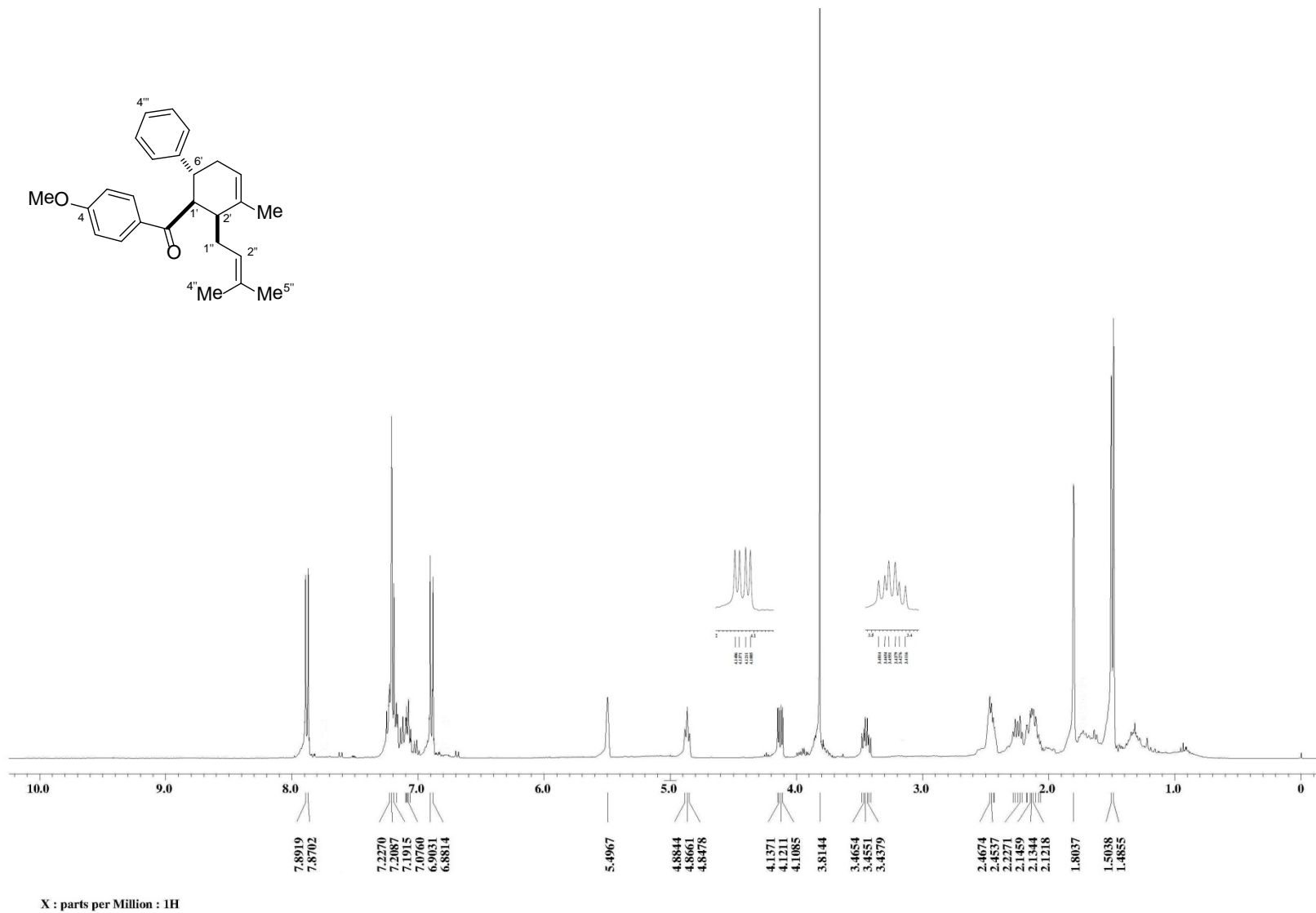
^1H NMR of (2, 4, 6-trimethoxyphenyl)(4-(4-methylpen-3-enyl)-6-phenylcyclohex-3-enyl)methanone (5-8a)



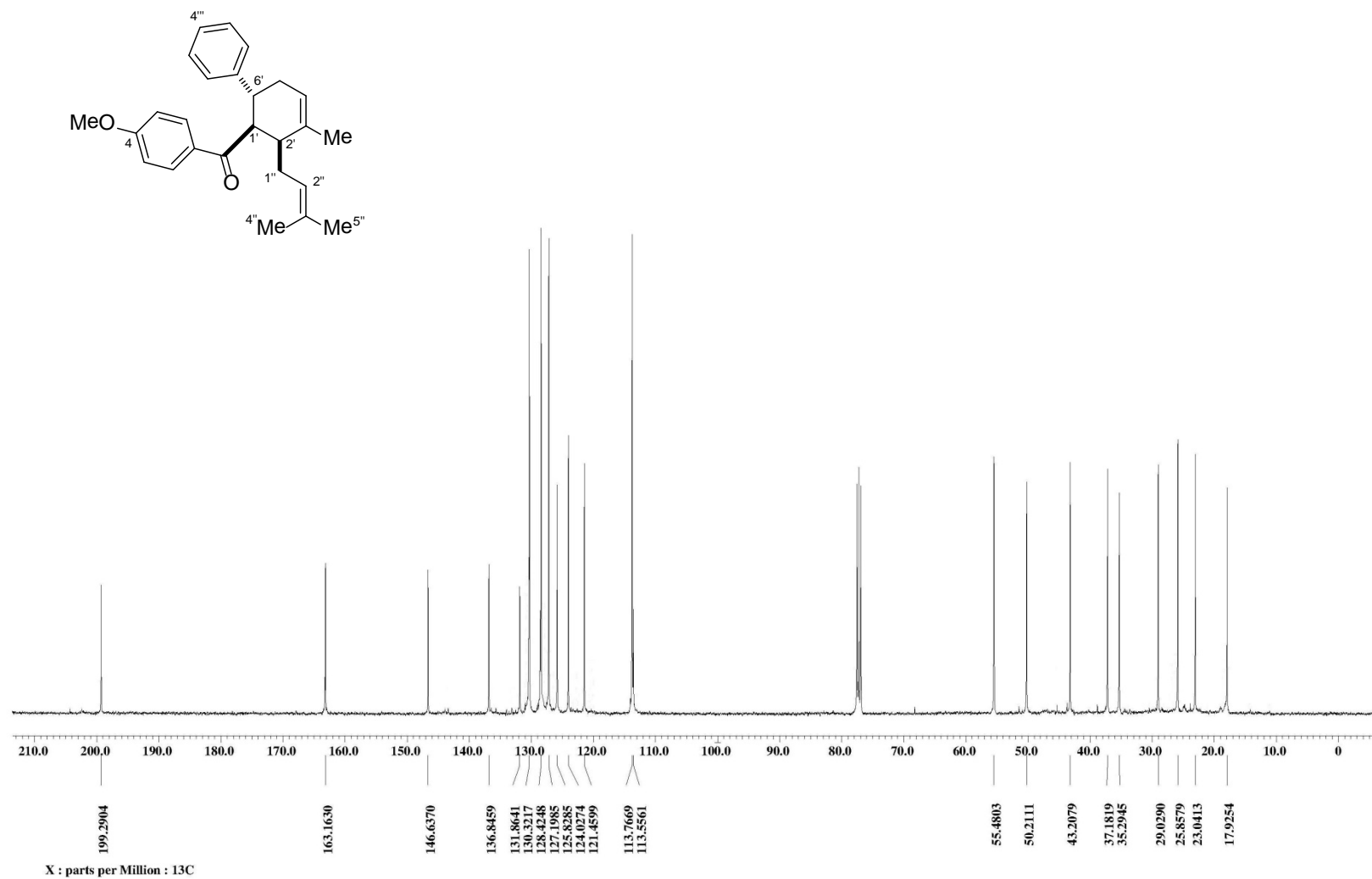
^{13}C NMR of (2, 4, 6-trimethoxyphenyl)(4-(4-methylpen-3-enyl)-6-phenylcyclohex-3-enyl)methanone (5-8a)



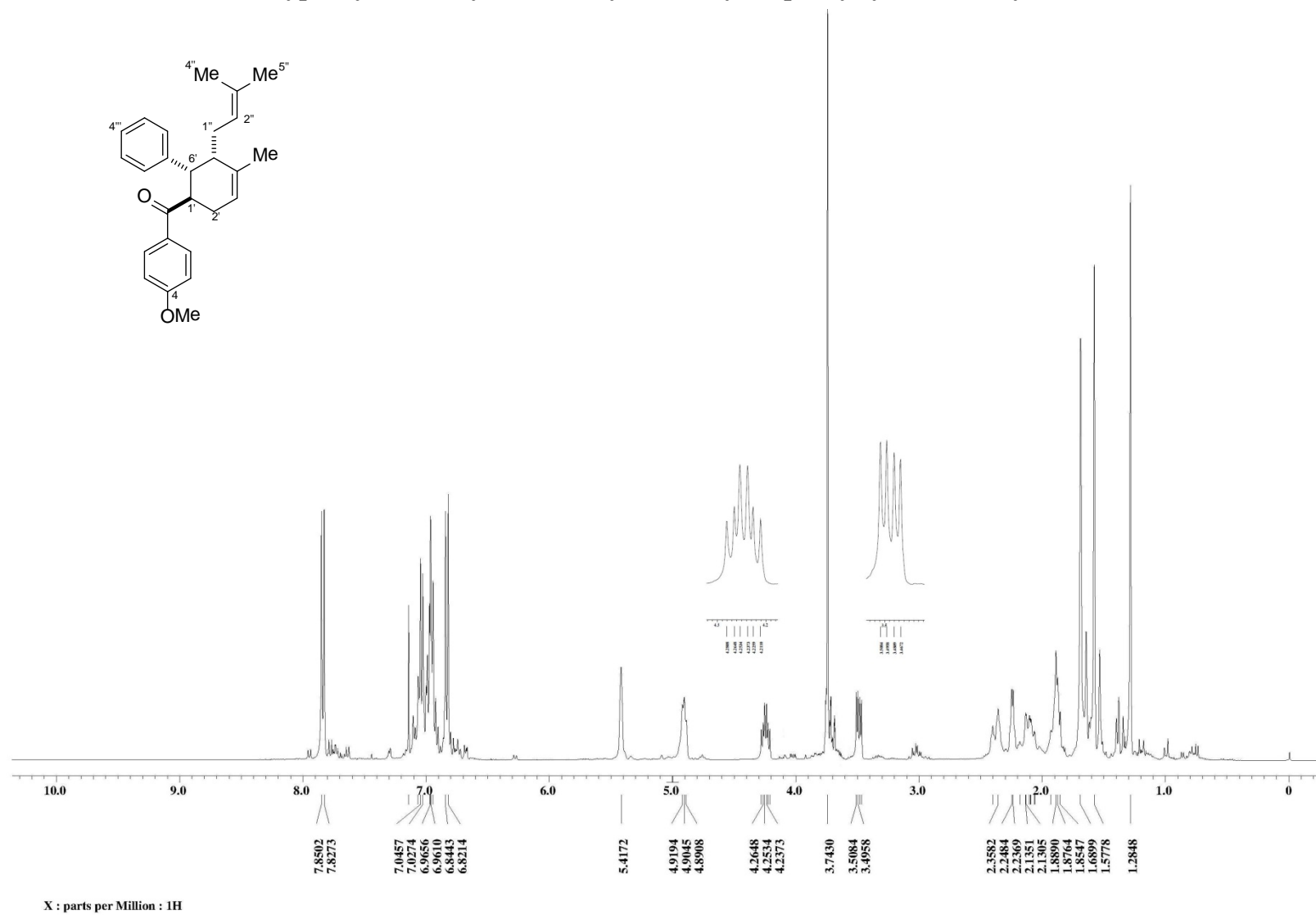
^1H NMR of (4-methoxyphenyl)(3-methyl-2-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (5-7)



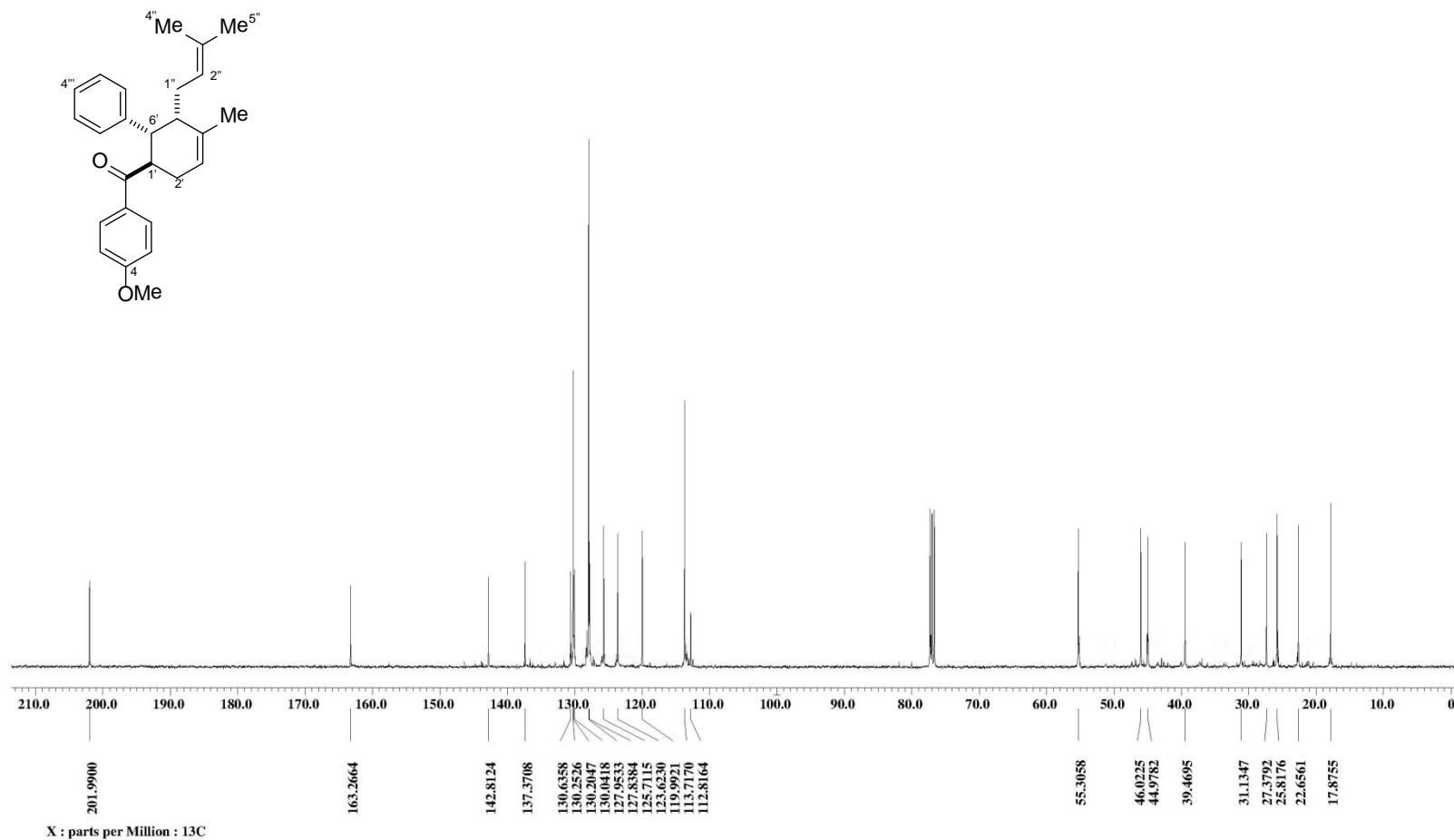
^{13}C NMR of (4-methoxyphenyl)(3-methyl-2-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (5-7)



^1H NMR of (4-methoxyphenyl)(4-methyl-5-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (5-7a)



^{13}C NMR of (4-methoxyphenyl)(4-methyl-5-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (5-7a)



Appendix C: Experimental and supplementary data of chapter 5

Experimental

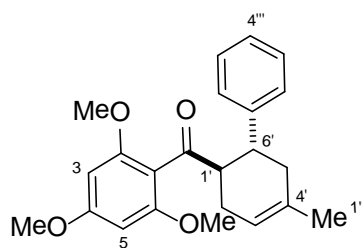
Preparation of substrates

Chalcones **5-1** & **5-9** were prepared according to literature procedures. Chalcones **5-2** & **5-3** were synthesised via Claisen-Schmidt condensation of the corresponding acetophenones and benzaldehyde under basic conditions.

General procedure for preparation of cycloadducts **5-4**, **5-4a**, **5-5**, **5-6**, **5-6a**, **5-7**, **5-7a**, **5-8** & **5-8a**.

To a screw-capped pressure tube (Ace Glass Inc, USA) equipped with a magnetic stirrer was added the corresponding chalcone (2 mmol) and the diene (1 ml). The resulting mixture was heated at the temperature reported and left under magnetic stirring for the period specified. After silica-gel column chromatography of the final mixture cycloadducts **5-4**, **5-4a**, **5-5**, **5-6**, **5-6a**, **5-7**, **5-7a**, **5-8** & **5-8a** were isolated.

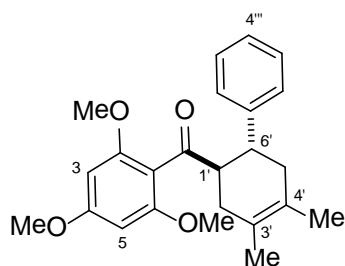
(2, 4, 6-trimethoxyphenyl)(4-methyl-6-phenylcyclohex-3-enyl)methanone (**5-4a**)



characterized in a para/meta regioisomers mixture: 3/2; chromatography on silica gel, eluent hex/EtOAc, 9/1 gradient; 86% overall yield; pale yellow needles; mp 132-134 °C (CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.09 (m, 4H, H-2''', 6''', H-3''', 5'''), 7.01 (m, 1H, H-4'''), 5.86 (s, 2H, H-3, 5), 5.39 (bs, 1H, H-3'), 3.69 (s, 3H, OCH₃), 3.50 (s, 6H, 2 x OCH₃), 3.41 (ddd, 1H, J=10.0, 9.5, 5.9 Hz, H-1'), 3.11 (ddd, 1H, J=10.2, 10.0, 5.9Hz, H-6'), 2.27 (m, 2H, H-2'), 2.07 (m, 2H, H-5'), 1.60 (s, 3H, 4'-CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 205.96 (C=O), 162.21 (C-4), 158.56 (C-2,6), 145.09 (C-1'''), 133.13

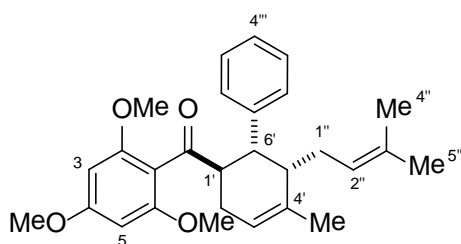
(C-4'), 127.91 (C-2''',6'''), 127.64 (C-3''',5'''), 125.67 (C-4'''), 119.97 (C-3'), 113.79 (C-1), 90.10 (C-3,5), 55.54, 55.25 (OCH₃), 52.31 (C-1'), 42.96 (C-6'), 39.04 (C-5'), 28.30 (C-2'), 23.12 (C-1''). FT-IR (KBr, cm⁻¹) ν : 2935, 1705, 1585, 1465, 1409, 1224, 1128; HRESIMS calcd. C₂₃H₂₇O₄ [M+H]⁺ 367.1904; found 367.1963.

(2, 4, 6-trimethoxyphenyl)(3, 4-dimethyl-6-phenylcyclohex-3-enyl)methanone (5-5)



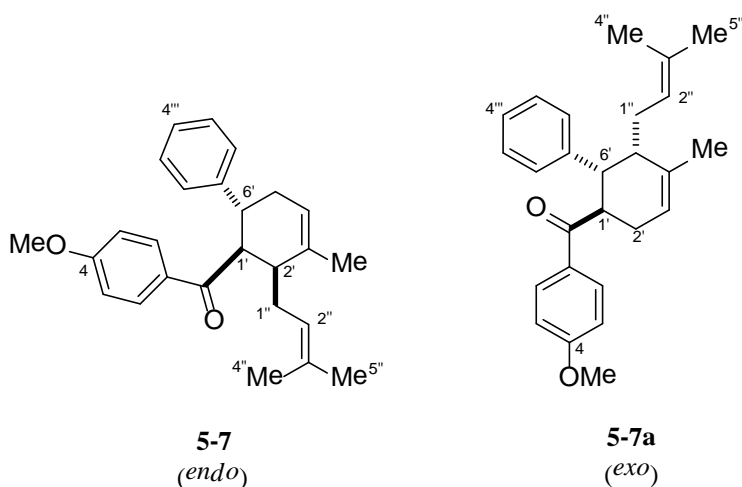
chromatography on silica gel, eluent hex/EtOAc, 9/1 gradient; 93% overall yield; yellow solid; mp 94-96 °C (CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 7.08 (m, 4H, H-2''', 6''', H-3''', 5'''), 7.00 (m, 1H, H-4'''), 5.86 (s, 2H, H-3, 5), 3.70 (s, 3H, OCH₃), 3.50 (s, 6H, 2 x OCH₃), 3.47 (m, overlapped, 1H, J can't estimated, H-1'), 3.05 (ddd, 1H, J=10.0, 9.7, 5.9Hz, H-6'), 2.30 (m, 2H, H-2'), 2.11 (m, 2H, H-5'), 1.58 (s, 3H, 3'-CH₃), 1.55 (s, 3H, 4'-CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 205.95 (C=O), 162.19 (C-4), 158.54 (C-2,6), 145.05 (C-1'''), 127.88 (C-2''',6'''), 127.59 (C-3''',5'''), 125.62 (C-4'''), 124.78 (C-3'), 124.67 (C-4'), 113.85 (C-1), 90.08 (C-3,5), 55.55, 55.26 (OCH₃), 53.15 (C-1'), 43.41 (C-6'), 40.92 (C-5'), 34.39 (C-2'), 18.77 (CH₃-3'), 18.57 (CH₃-4'). FT-IR (KBr, cm⁻¹) ν : 2925, 1675, 1603, 1457, 1412, 1234, 1130; HRESIMS calcd. C₂₄H₂₉O₄ [M+H]⁺ 381.2060; found 381.2089.

(2, 4, 6-trimethoxyphenyl)(4-methyl-5-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (5-6a).

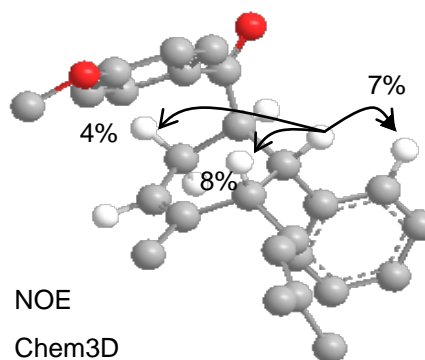
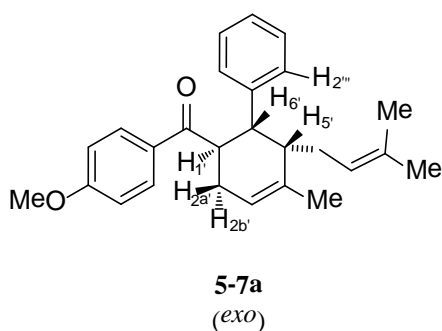


characterized in a p/m -regioisomers mixture: 3/2; oil; chromatography on silica gel, eluent hex/EtOAc, 8/2 gradient; 99% overall yield; ^1H NMR (400 MHz, CDCl_3): δ 7.15 (m, 5H, H-2'''-6'''), 6.04 (s, 2H, H-3, 5), 5.51 (bs, 1H, H-3'), 4.90 (t, 1H, H-2''), 3.80 (s, 3H, OCH_3), 3.64 (s, 6H, 2 x OCH_3), 3.69 (m, overlapped, 1H, J can't estimated, H-1'), 3.41 (dd, 1H, J=11, 6.2, H-6'), 2.34 (m, 2H, H-2'), 2.33 (m, 1H, H-5'), 2.03 (m, 2H, H-1''), 1.75 (s, 3H, 3'- CH_3), 1.57 (s, 3H, CH_3 -4''), 1.27 (s, 3H, CH_3 -5''); ^{13}C NMR (100 MHz, CDCl_3): δ 205.79 (C=O), 162.42 (C-4), 158.77 (C-2,6), 143.13 (C-1'''), 136.66 (C-4'), 130.85 (C-3'''), 129.26 (C-2''',6'''), 127.61 (C-3''',5'''), 125.66 (C-4'''), 123.71 (C-2''), 121.22 (C-3'), 113.70 (C-1), 90.45 (C-3,5), 55.70, 55.41 (OCH_3), 48.48 (C-1'), 46.08 (C-6'), 43.46 (C-5'), 27.58 (C-1''), 27.13 (C-2'), 22.74 (C-4'-Me), 25.93 (C-4''), 17.73 (C-5''). FT-IR (CHCl_3 , cm^{-1}) ν : 3004, 1693, 1605, 1413, 1227, 1129; HRESIMS calcd. $\text{C}_{28}\text{H}_{35}\text{O}_4$ $[\text{M}+\text{H}]^+$ 435.2530; found 435.2540.

(4-methoxyphenyl)(3-methyl-2-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (**5-7**) & (4-methoxyphenyl)(4-methyl-5-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (**5-7a**).

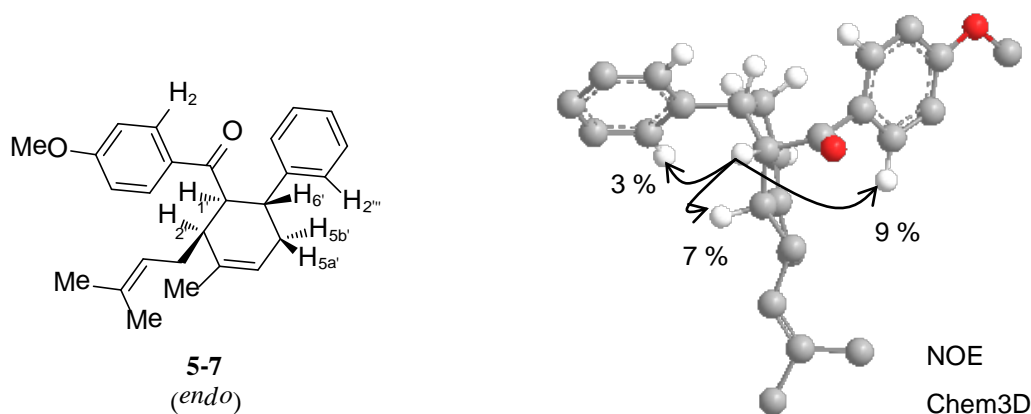


After chromatography on silica gel (15 % EtOAc in hexane), the desired mixture of compounds **5-7** & **5-7a** (719 mg, 96%) was isolated as a yellow oil which was shown in a p/m –regioisomeric ratio of 3/2 (determined by ^1H NMR integration). Pure sample of each regioisomer **5-7** & **5-7a** was obtained by further separation on silica gel chromatography (40 % CH_2Cl_2 in hexane).



^1H NMR (400 MHz, CDCl_3): δ 7.85 (d, 2H, $J=8.5$, H-1,6), 7.07 (m, 2H, H-3''',5'''), 7.05 (m, 3H, H-2''',4''',6'''), 6.84 (d, 2H, $J=8.5$, H-3, 5), 5.42 (bs, 1H, H-3'), 4.91 (t, 1H, H-2''), 4.25 (ddd, 1H, $J=10, 10, 6$, H-1'), 3.74 (s, 3H, OCH_3), 3.49 (dd, 1H, $J=10, 5.1$, H-6'), 2.38 (m, 1H, H-2'), 2.25 (q, 1H, H-5'), 2.14 (m, 1H, H-2'), 1.90 (m, 2H, H-1''), 1.69 (s, 3H, 3'- CH_3), 1.58 (s, 3H, CH_3 -4''), 1.29 (s, 3H, CH_3 -5''); NOE_Diff (400 MHz,

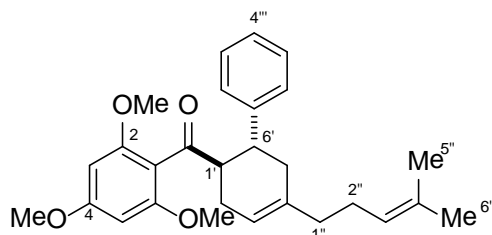
CDCl₃) Irradiation at δ 3.51 (H-6'): 8 % enhancement at H-5', 7 % enhancement at H-2''', 4 % enhancement at H-2'a ; H-1' collapsed to doublet of doublet ($J = 10, 6$ Hz); ¹³C NMR (100 MHz, CDCl₃): δ 201.99 (C=O), 163.27 (C-4), 142.81 (C-1'''), 137.37 (C-4'), 130.64 (C-3''), 130.20 (C-2,6), 127.95 (C-2''',6'''), 127.84 (C-3''',5'''), 125.71 (C-4'''), 123.62 (C-2''), 120.00 (C-3'), 113.72 (C-3,5), 112.82 (C-1), 55.31 (OCH₃), 46.02 (C-6'), 44.98 (C-5'), 39.47 (C-1'), 31.13 (C-2'), 27.38 (C-1''), 25.82 (C-4''), 22.67 (C-4'-Me), 17.88 (C-5''). FT-IR (KBr, cm⁻¹) ν : 2987, 1676, 1605, 1403, 1240, 1129; HRESIMS calcd. C₂₆H₃₁O₂ [M+H]⁺ 375.2319; found 375.2340.



¹H NMR (400 MHz, CDCl₃): δ 7.86 (d, 2H, $J=8.5$, H-1,6), 7.20 (m, 5H, H-2'''~6'''), 6.90 (d, 2H, $J=8.5$, H-3, 5), 5.49 (bs, 1H, H-4'), 4.87 (t, 1H, H-2''), 4.13 (dd, 1H, $J=10.4, 4.8$, H-1'), 3.81 (s, 3H, OCH₃), 3.46 (ddd, 1H, $J=10.5, 10.5, 6.3$, H-6'), 2.37 (m, 3H, H-2' & H-5';overlapped), 2.17 (m, 1H, H-1''), 2.00 (m, 1H, H-1''), 1.80 (s, 3H, 3'-CH₃), 1.50 (s, 3H, CH₃-4''), 1.48 (s, 3H, CH₃-5''); NOE_Diff (400 MHz, CDCl₃) Irradiation at δ 4.13 (H-1'): 9 % enhancement at H-2, 7 % enhancement at H-2', 3 % enhancement at H-2''' ; H-6' collapsed to doublet of doublet ($J = 10.5, 6.3$ Hz); ¹³C NMR (100 MHz, CDCl₃): δ 199.29 (C=O), 163.16 (C-4), 146.64 (C-1'''), 136.85 (C-3'), 131.86 (C-3''), 130.32 (C-2,6), 128.42 (C-3''',5'''), 127.20 (C-2''',6'''), 125.83 (C-4'''), 124.03 (C-2''), 121.45 (C-4'), 113.77 (C-3,5), 113.56 (C-1), 55.48 (OCH₃), 50.21 (C-

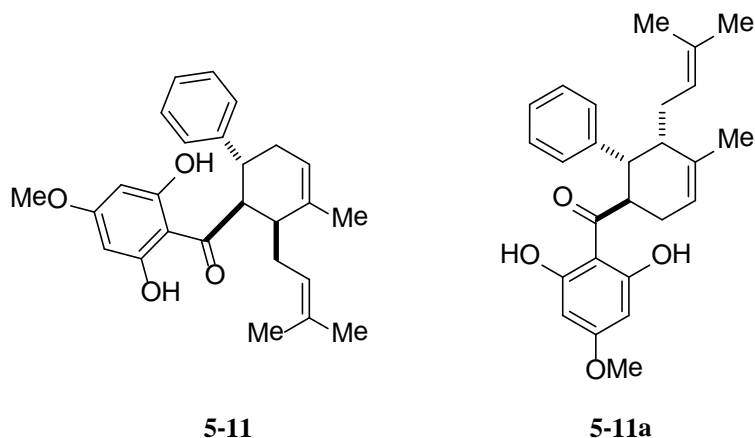
1'), 43.20 (C-2'), 37.18 (C-6'), 35.29 (C-5'), 29.03 (C-1''), 23.04 (C-2'-Me), 25.86 (C-4''), 17.92 (C-5''). FT-IR (KBr, cm^{-1}) ν : 2987, 1676, 1605, 1403, 1240, 1129; HRESIMS calcd. $\text{C}_{26}\text{H}_{31}\text{O}_2$ $[\text{M}+\text{H}]^+$ 375.2319; found 375.2340.

(2, 4, 6-trimethoxyphenyl)(4-(4-methylpen-3-enyl)-6-phenylcyclohex-3-enyl)methanone (5-8a)



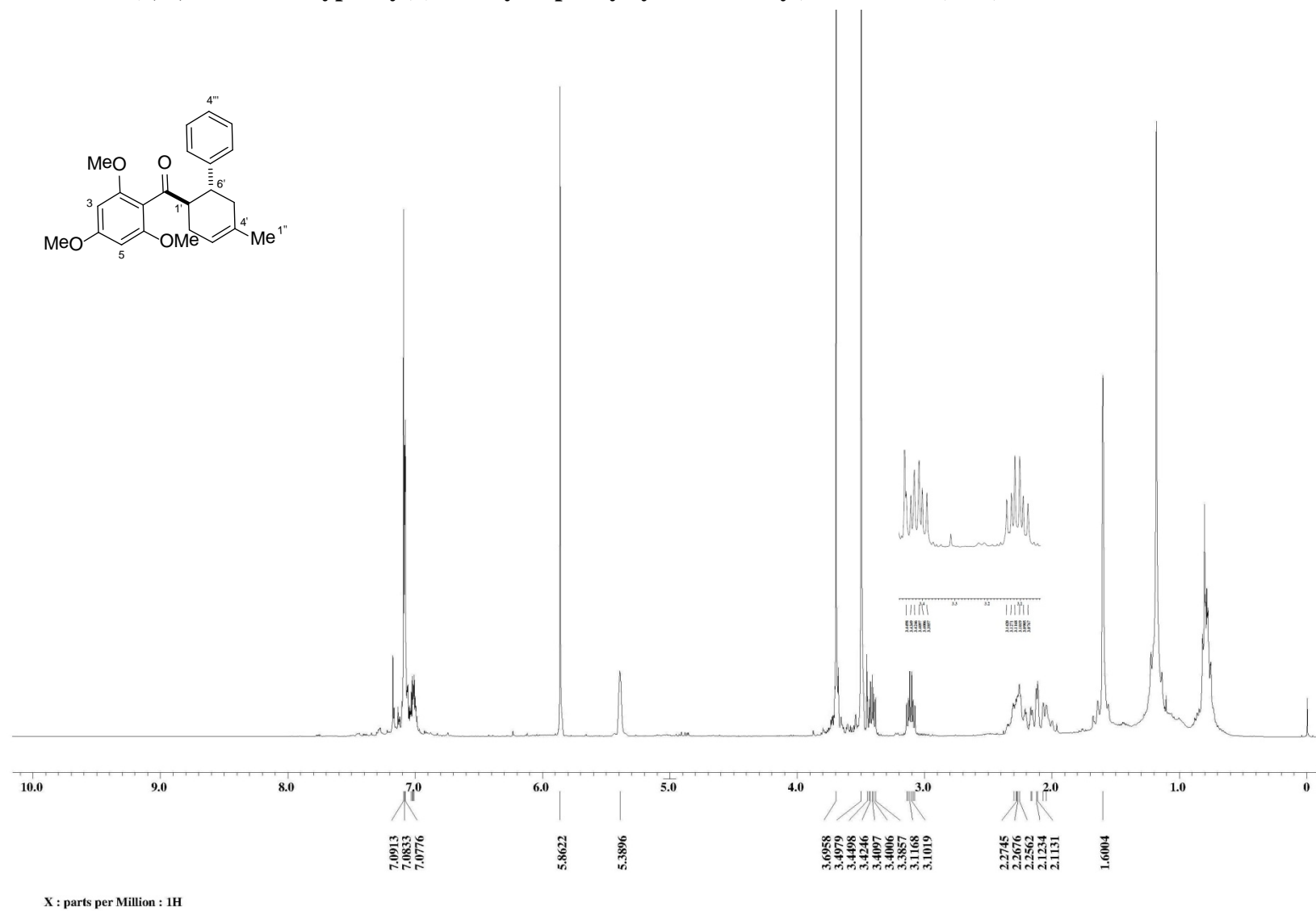
characterized in a p/m -regioisomers mixture: 3/2; chromatography on silica gel, eluent hex/EtOAc, 4/1 gradient; 89% overall yield; yellow solid; mp 108-110 °C (CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.15 (m, 5H, H-2'''-6'''), 5.94 (s, 2H, H-3, 5), 5.47 (bs, 1H, H-3'), 5.08 (t, 1H, H-3''), 3.77 (s, 3H, OCH_3), 3.57 (s, 6H, 2 x OCH_3), 3.47 (ddd, 1H, $J=10.0, 10.2, 5.9\text{Hz}$, H-1'), 3.14 (ddd, 1H, $J=10.2, 10.2, 5.4\text{Hz}$, H-6'), 2.36 (m, 2H, H-2'), 2.19 (m, 1H, H-5'), 2.07 (m, 2H, H-2''), 1.96 (m, 2H, H-1''), 1.66 (s, 3H, CH_3 -5''), 1.58 (s, 3H, CH_3 -6''); ^{13}C NMR (100 MHz, CDCl_3): δ 205.97 (C=O), 162.22 (C-4), 158.57 (C-2,6), 145.15 (C-1'''), 136.82 (C-4'), 131.44 (C-4''), 127.94 (C-2''',6'''), 127.65 (C-3''',5'''), 125.69 (C-4'''), 124.22 (C-3''), 119.59 (C-3'), 113.82 (C-1), 90.11 (C-3,5), 55.55, 55.28 (OCH_3), 52.49 (C-1'), 43.05 (C-6'), 37.56 (C-1''), 37.28 (C-5'), 28.41 (C-1'), 26.35 (C-2''), 25.69 (C-5''), 17.68 (C-6''); FT-IR (KBr, cm^{-1}) ν : 2929, 1700, 1602, 1457, 1412, 1227, 1132; HRESIMS calcd. $\text{C}_{28}\text{H}_{35}\text{O}_4$ $[\text{M}+\text{H}]^+$ 435.2530; found 435.2548.

For total synthesis of panduratin A and panduratin A (5-11 & 5-11a)

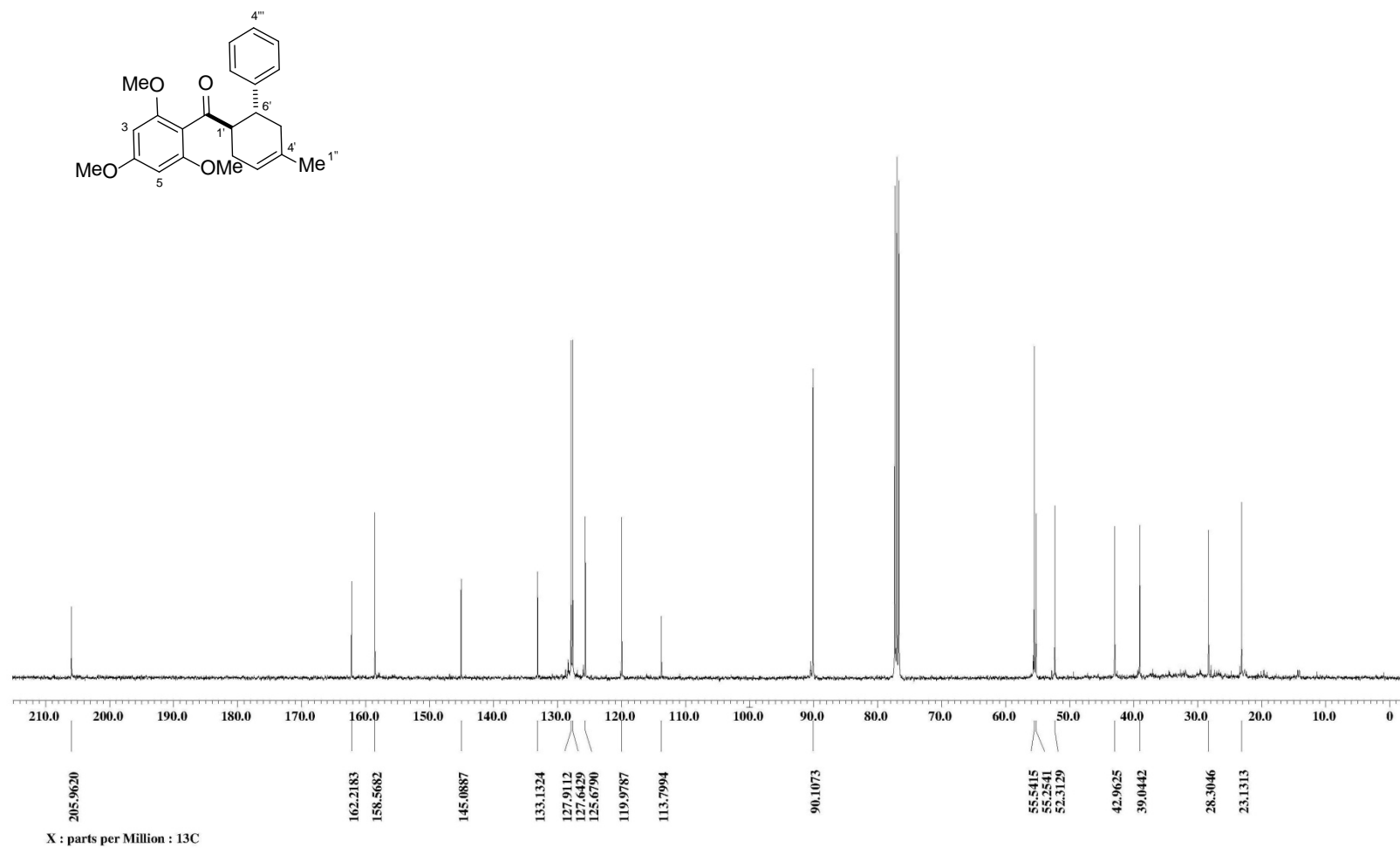


To a screw-capped pressure tube equipped with a magnetic stirrer was added 2'-hydroxy-4'-methoxy-6'-ethoxymethoxychalcone **5-9** (328 mg, 1 mmol) and ocimene (0.5 ml). The reaction mixture was heated at 150 °C for 24 hr. To the resulting orange residue was added 10 ml of MeOH and 4 ml of HCl (3M). The cloudy mixture was refluxed at 80°C for 10 min. The resulting yellow solution was cooled to room temperature, diluted with water, extracted with EtOAc, washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification on silica gel (15% EtOAc in hexane) afforded the mixture of panduratin A and isopanduratin A (162.4 mg, 89% for two steps) as a yellow solid. All spectroscopic data were identical with those of the natural product.

^1H NMR of (2, 4, 6-trimethoxyphenyl)(4-methyl-6-phenylcyclohex-3-enyl)methanone (5-4a)



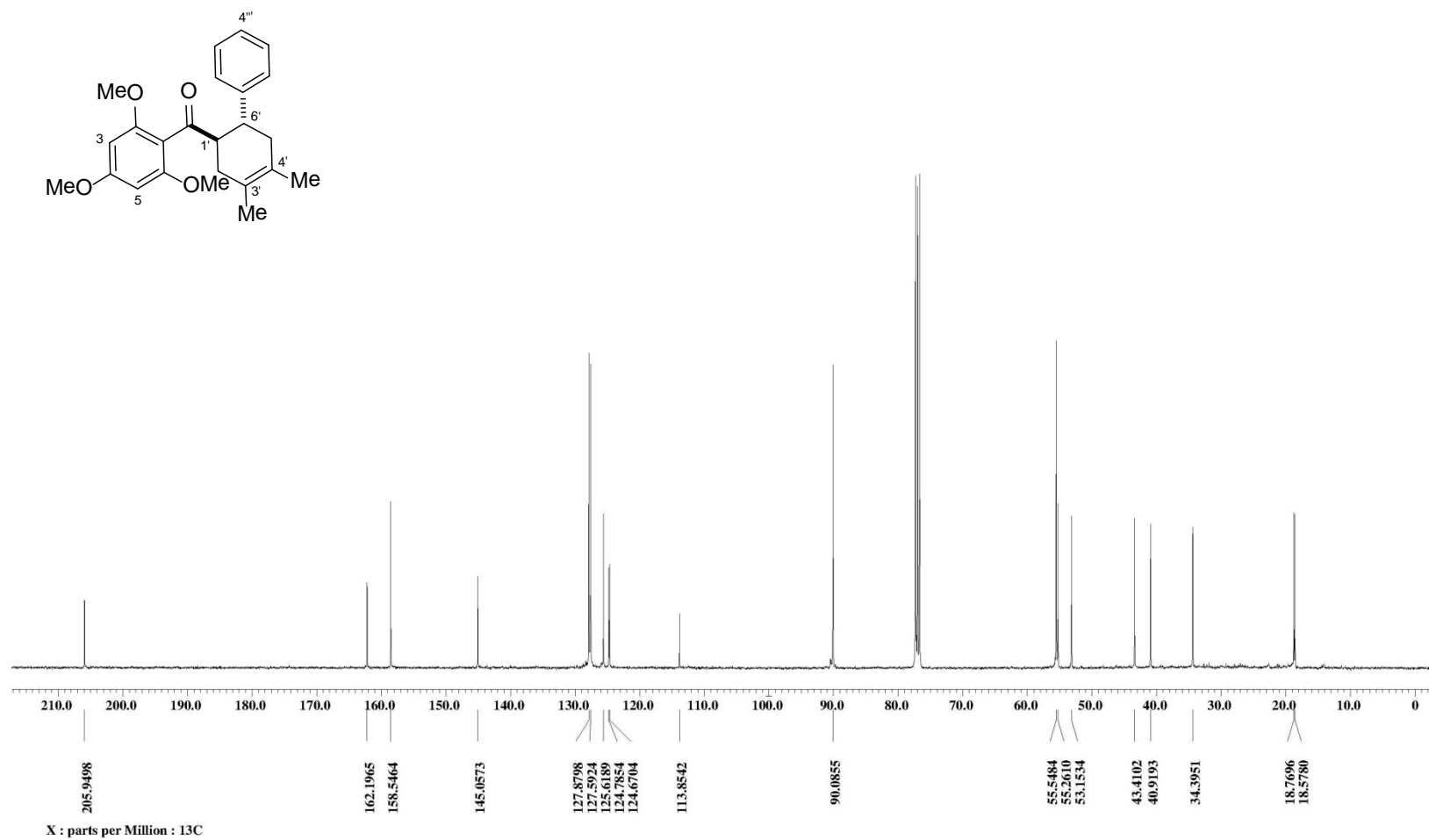
^{13}C NMR of (2, 4, 6-trimethoxyphenyl)(4-methyl-6-phenylcyclohex-3-enyl)methanone (5-4a)



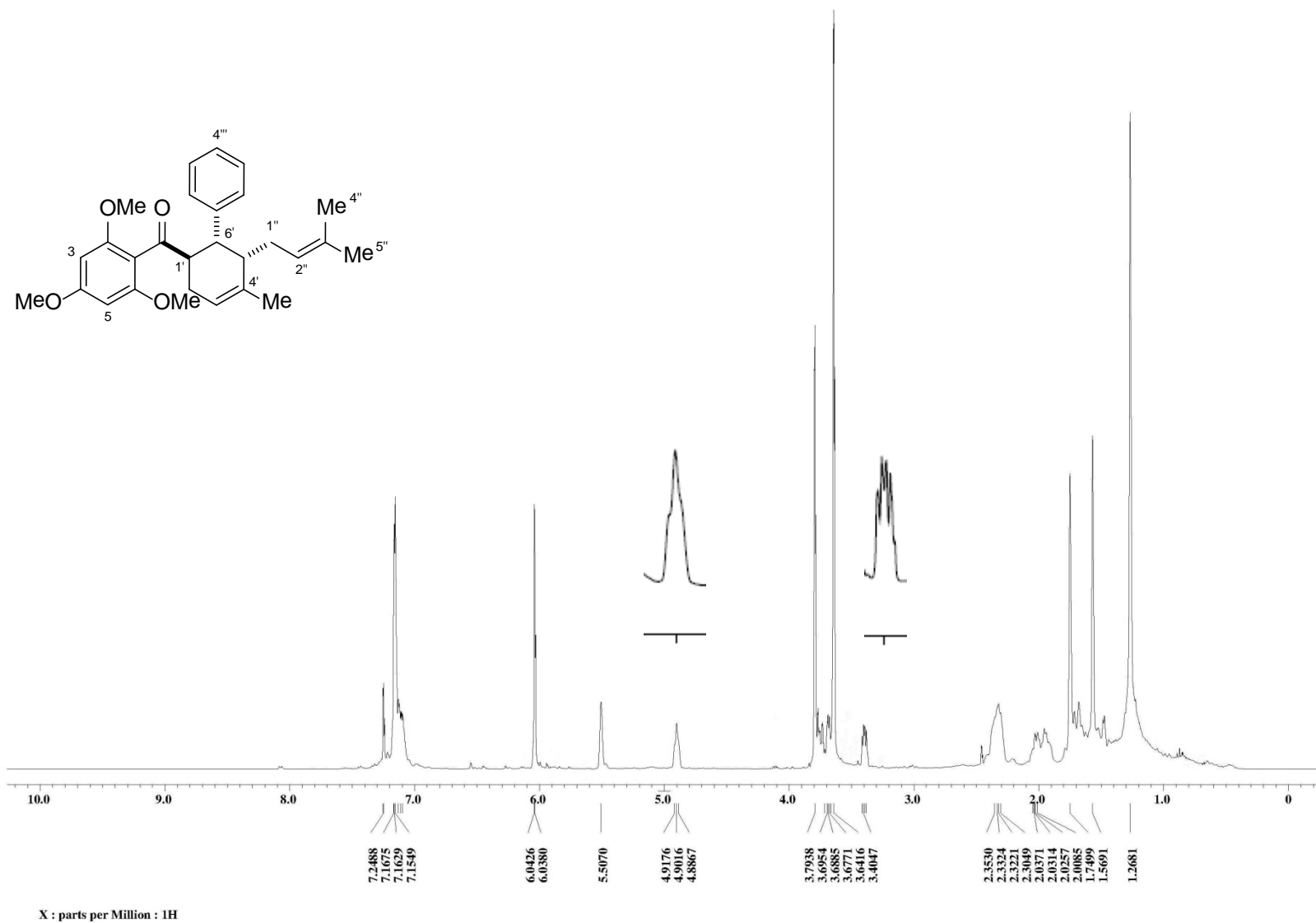
Chemical structure of the compound is shown above the spectrum. The structure is a substituted cyclohexene derivative. It features a cyclohexene ring with a methyl group (Me) at C4, a methoxy group (OMe) at C3, and a carbonyl group (C=O) at C1. The carbonyl group is attached to a phenyl ring (C6H5) at C1'. The cyclohexene ring also has a methyl group (Me) at C3' and a methoxy group (OMe) at C5. The chemical shift values (ppm) are indicated below the spectrum: 7.0821, 7.0718, 7.0158, 5.8645, 3.7027, 3.5002, 3.4704, 3.4601, 3.4464, 3.0790, 3.0699, 3.0550, 3.0447, 2.3065, 2.2814, 2.1555, 2.1108, 2.0719, 1.5856, 1.5524.

100

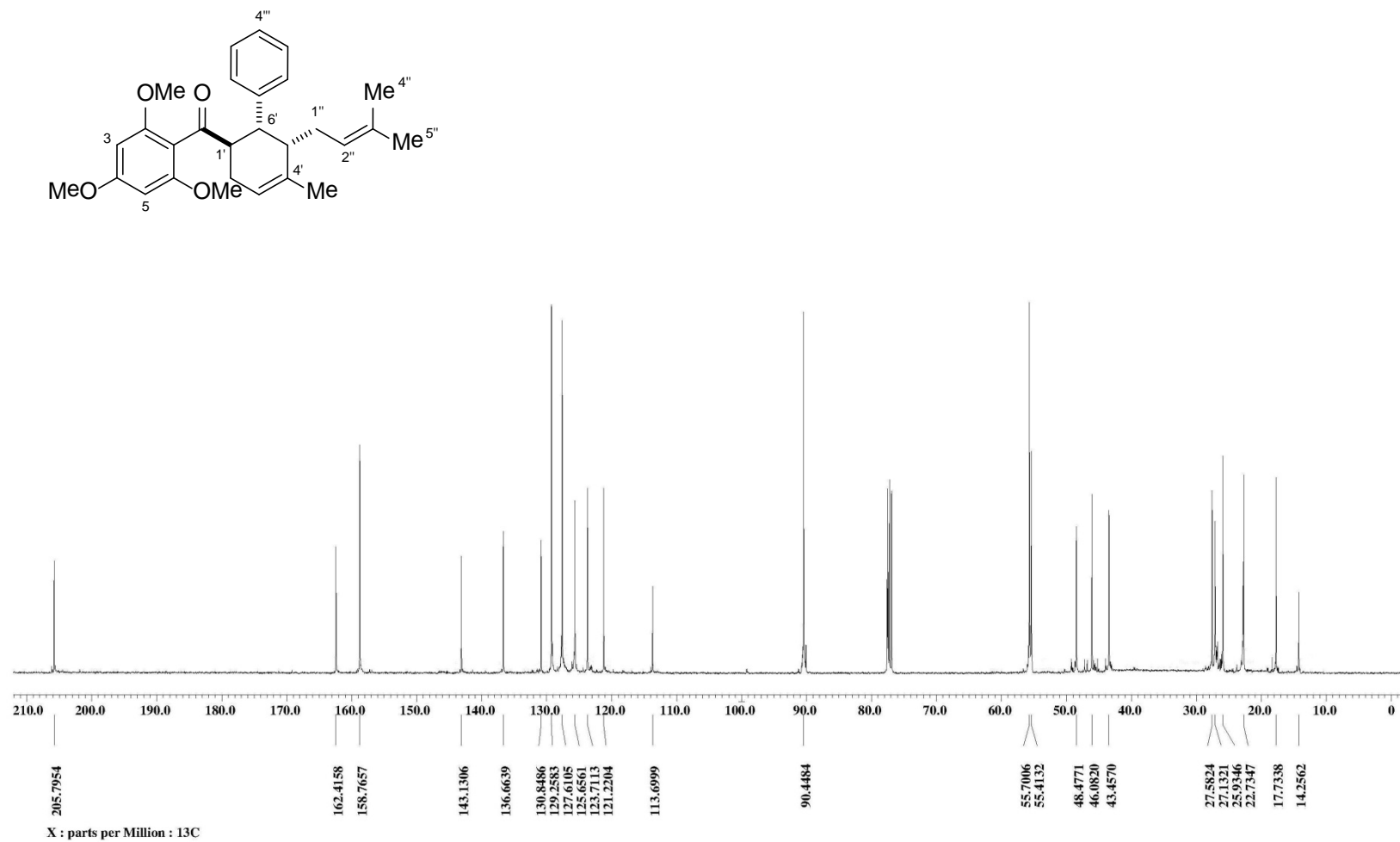
^{13}C NMR of (2, 4, 6-trimethoxyphenyl)(3, 4-dimethyl-6-phenylcyclohex-3-enyl)methanone (5-5)



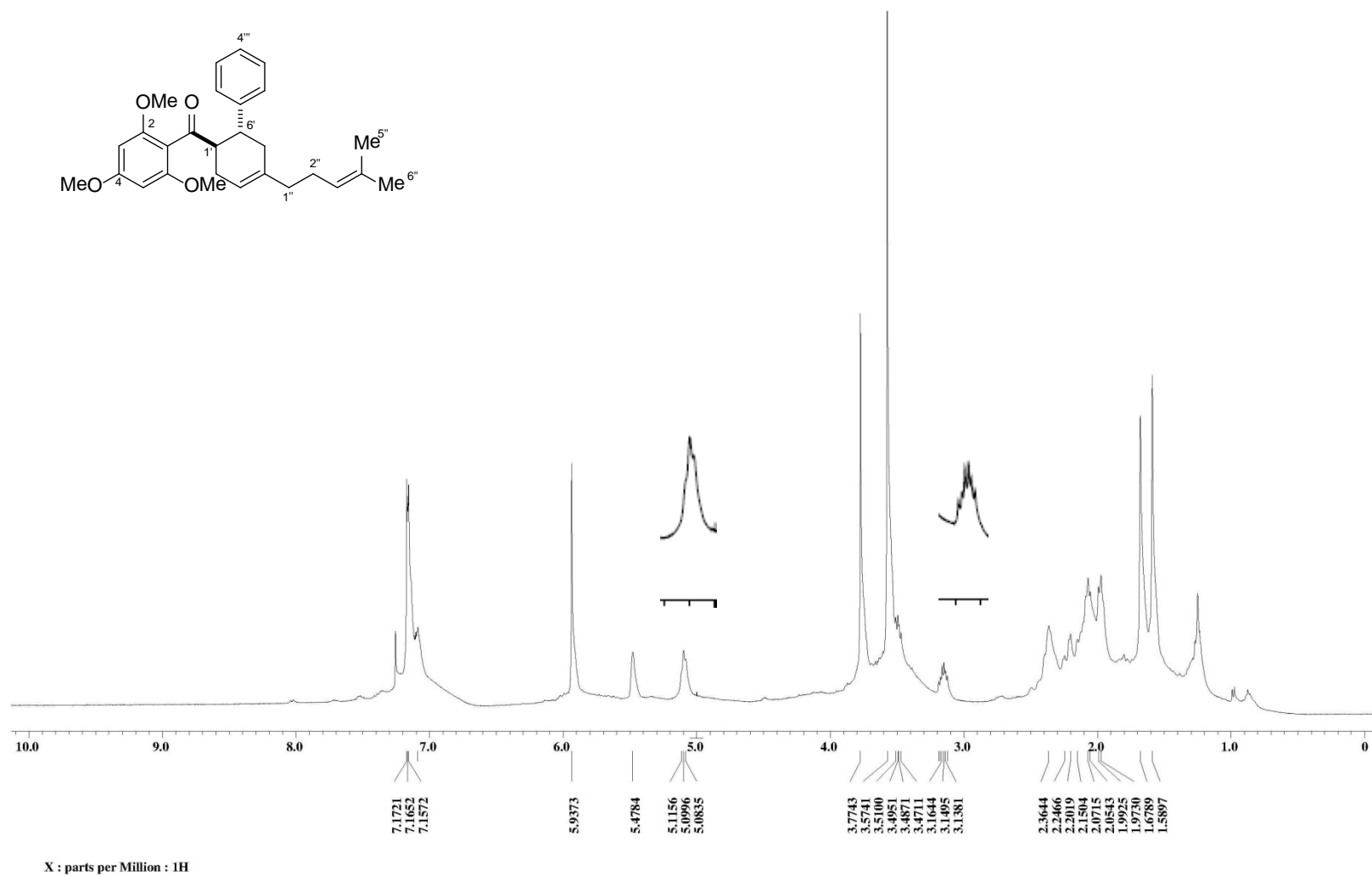
¹H NMR of (2, 4, 6-trimethoxyphenyl)(4-methyl-5-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (5-6a)



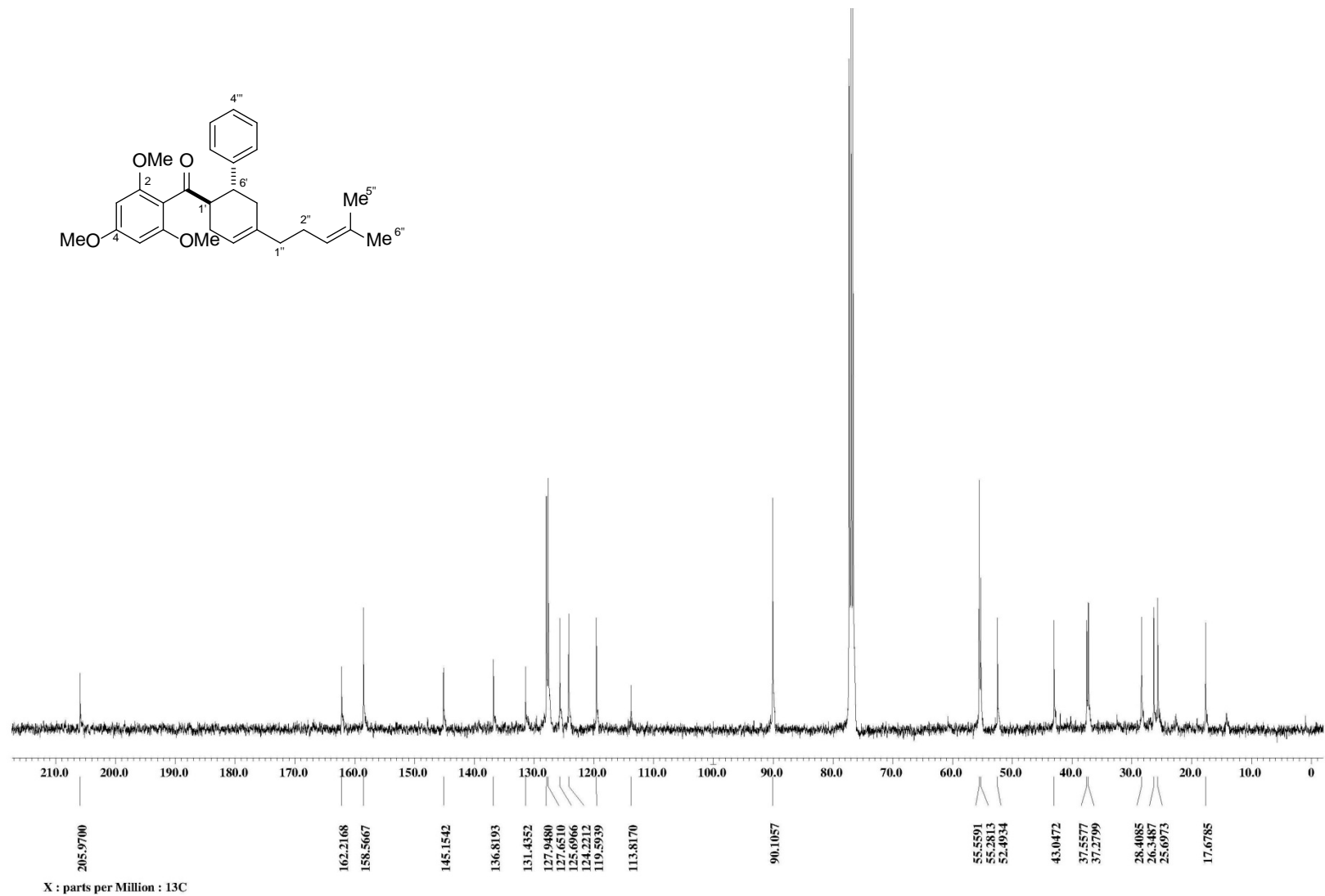
^{13}C NMR of (2, 4, 6-trimethoxyphenyl)(4-methyl-5-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (5-6a)



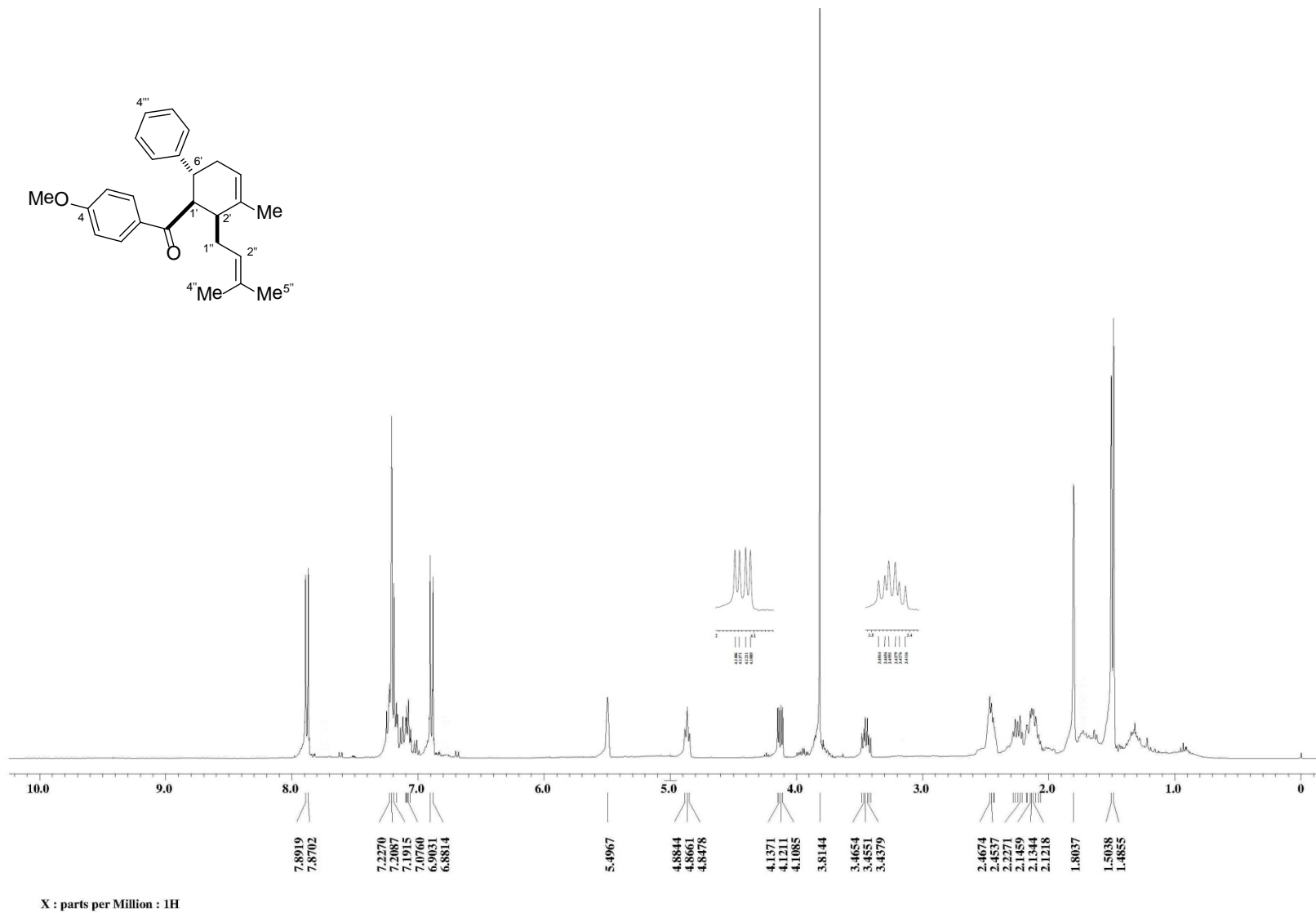
^1H NMR of (2, 4, 6-trimethoxyphenyl)(4-(4-methylpen-3-enyl)-6-phenylcyclohex-3-enyl)methanone (5-8a)



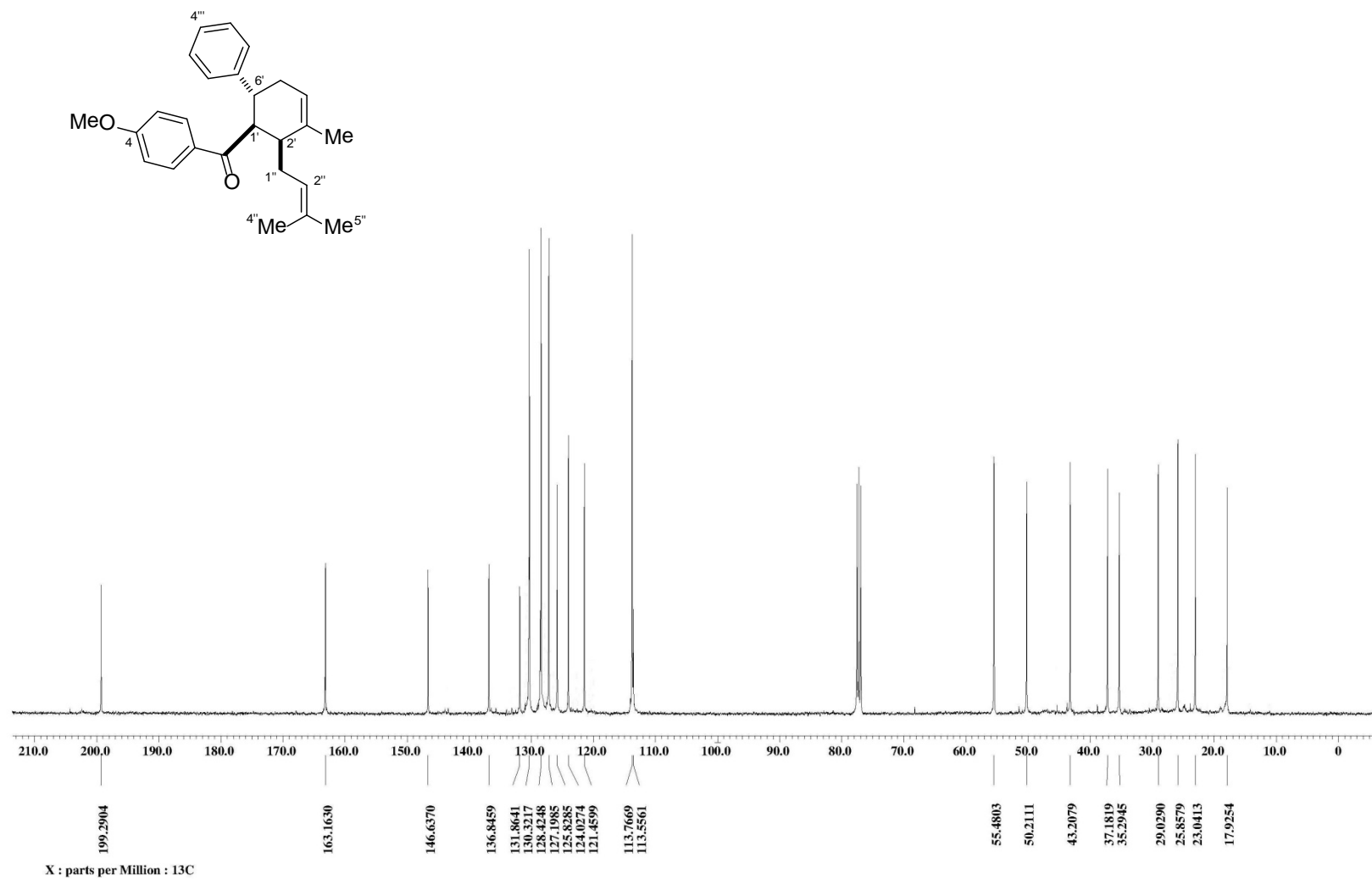
^{13}C NMR of (2, 4, 6-trimethoxyphenyl)(4-(4-methylpen-3-enyl)-6-phenylcyclohex-3-enyl)methanone (5-8a)



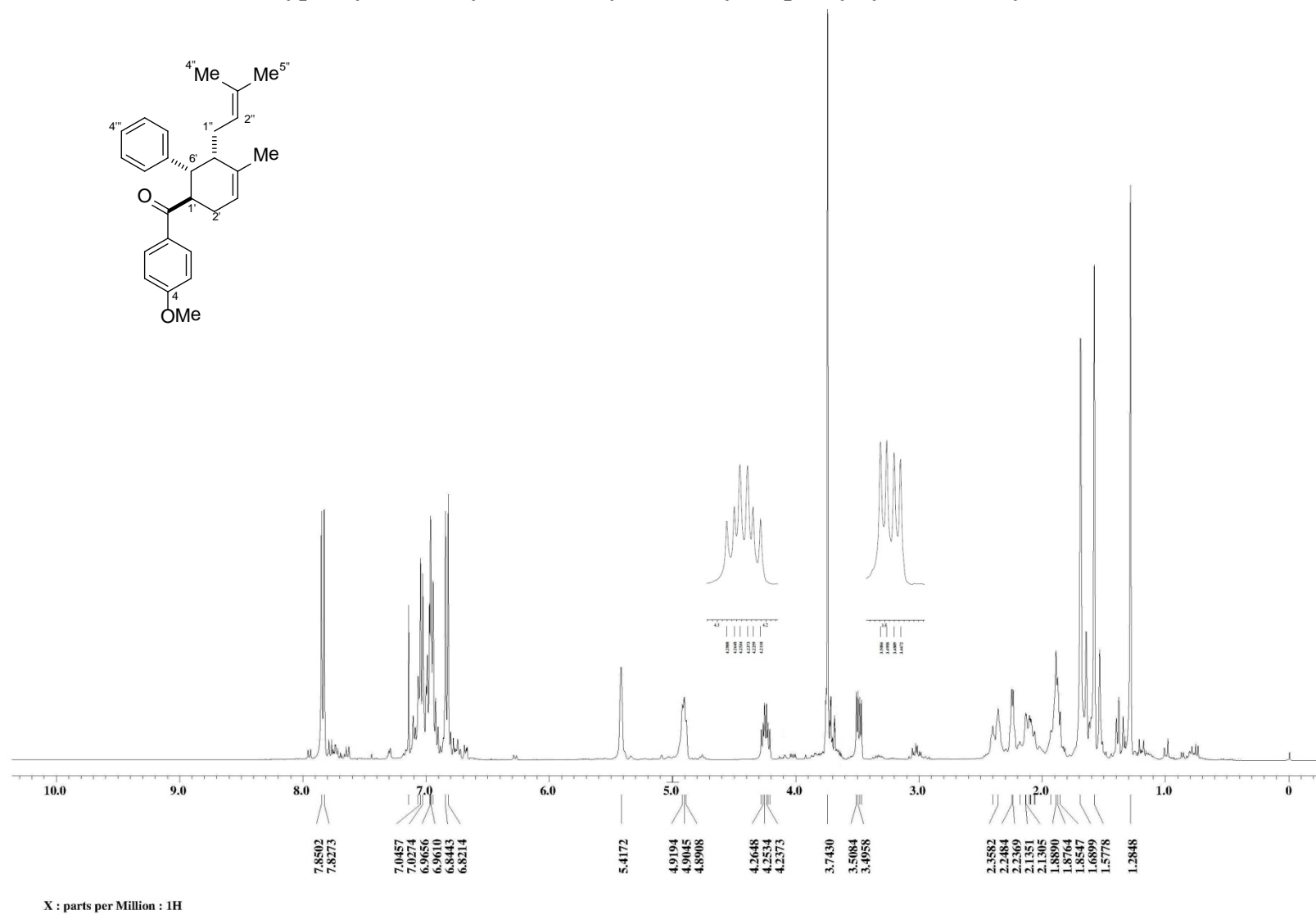
^1H NMR of (4-methoxyphenyl)(3-methyl-2-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (5-7)



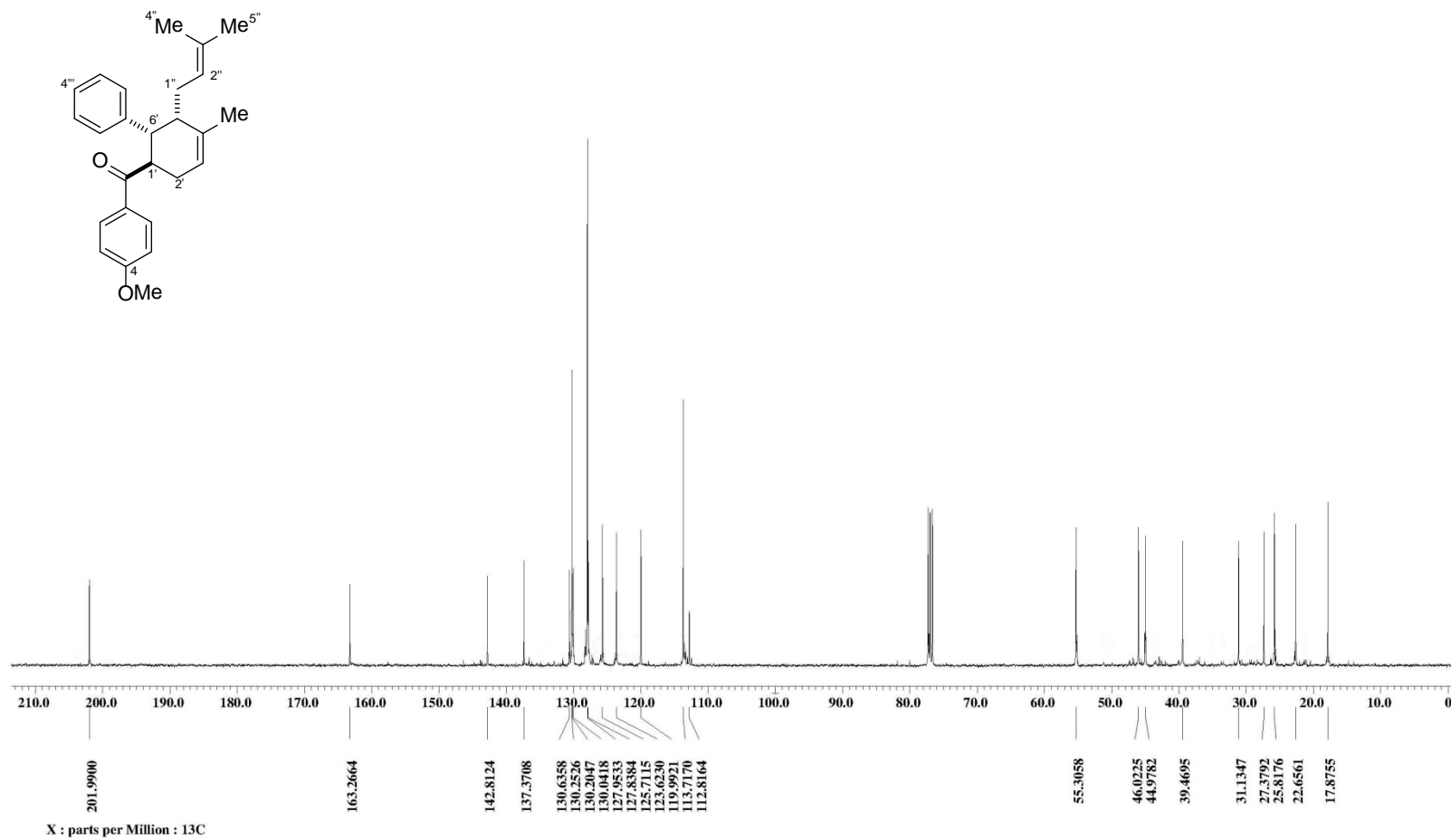
^{13}C NMR of (4-methoxyphenyl)(3-methyl-2-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (5-7)



^1H NMR of (4-methoxyphenyl)(4-methyl-5-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (5-7a)



^{13}C NMR of (4-methoxyphenyl)(4-methyl-5-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)methanone (5-7a)



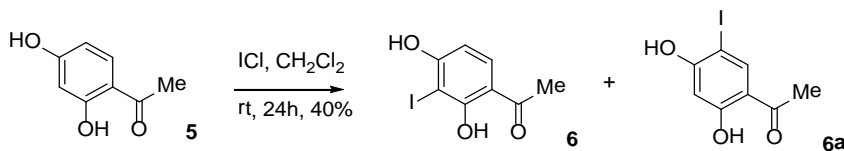
Appendix D: Experimental and supplementary data of chapter 6

Experimental

General

All melting points were taken on a Mel-Temp II melting point instrument. NMR spectra were obtained using a Jeol ECA 400 (400 MHz) and EX 270 (270MHz) NMR spectrometers with TMS as the internal standard. All chemical shifts are reported in ppm. Analytical thin-layer chromatography (TLC) was carried out on Merck precoated aluminum silica gel sheets (Kieselgel 60 F-254). Column chromatography was done with silica gel 60 (230-400 mesh) from Merck. All target compounds were characterized by ^1H , ^{13}C , 2D NMR and MS analyses. All reactions were carried out under nitrogen atmosphere unless specified. Anhydrous THF was distilled from sodium/benzophenone before use. The other anhydrous solvents and reagents were purchased from Aldrich or Fisher.

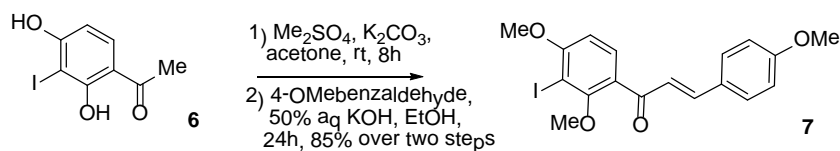
3'-iodo-2',4'-dihydroxyacetophenone **6**



To a solution of 2',4'-dihydroxyacetophenone **5** (15.2 g, 0.1 mol) at rt in CH₂Cl₂ (450 mL) was added iodine monochloride (55 mL, 2M in CH₂Cl₂, 1.1 equiv). The purple mixture was stirred for 24 h. Afterwards 100 mL of saturated sodium thiosulfate solution were added to remove excess of ICl, and the organic layer was washed with H₂O (50 mL), collected and concentrated. The crude residue was purified by column chromatography (hexane:EtOAc=4:1) to afford **6a** (12.5 g, 45%) and desired compound **6** (11.1 g, 40%) as a pale white solid. ^1H NMR (270 MHz, acetone-D₆): δ 12.46 (s, 1H), 7.39 (d, 8.8, 1H), 6.28 (d, 8.7, 1H), 2.47 (s, 3H); ^{13}C NMR (67.9 MHz, acetone-D₆): δ 203.24, 165.62, 6.28 (d, 8.7, 1H), 2.47 (s, 3H); ^{13}C NMR (67.9 MHz, acetone-D₆): δ 203.24, 165.62,

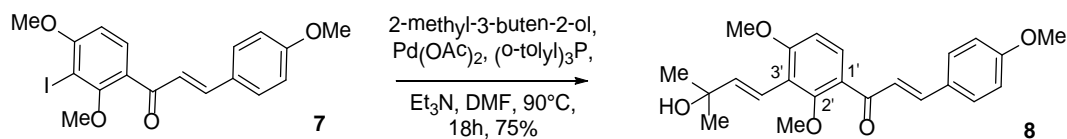
164.30, 142.85, 116.33, 103.30, 73.46, 26.63; m.p. = 165°C.

3'-iodo-2',4',4'-trimethoxychalcone **7**



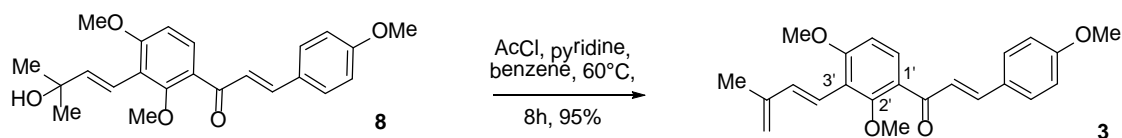
To a solution of 3'-iodo-2',4'-dihydroxyacetophenone **6** (2.78 g, 0.01 mol) in dry acetone (150 mL) was added K_2CO_3 (6.9 g, 5 equiv) and dimethyl sulfate (2.3 mL, 2.4 equiv). The mixture was stirred at rt for 8 h. Then, the pale white solution was filtered and the acetone was removed by vacuum evaporation to give 3'-iodo-2',4'-dimethoxyacetophenone for subsequent Claisen-Schmidt condensation reaction. To a solution of 3'-iodo-2',4'-dimethoxyacetophenone in ethanol (200 mL) was added 4-methoxybenzaldehyde (1.2 mL, 0.01 mol) and 50% aq KOH (10 mL). The red-yellowish mixture was stirred at rt for 24 h. Afterwards, the mixture was poured into ice-water acidified with 3 N HCl and extracted three times with ethyl acetate. The organic phases were combined, washed with water, dried on Mg_2SO_4 , and evaporated. The residue was subjected to column chromatography (hexane:EtOAc=4:1) to give chalcone **7** as a yellow solid (3.60 g, 85% over two steps). ^1H NMR (400 MHz, CDCl_3): δ 7.68 (d, 8.5, 1H), 7.67 (d, $J=16.3$, 1H), 7.53 (d, $J=8.8$, 2H), 7.39 (d, $J=15.8$, 1H), 6.87 (d, $J=8.8$, 2H), 6.65 (d, $J=8.5$, 1H), 3.89, 3.78, 3.74 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 190.49, 162.39, 161.75, 160.59, 143.99, 132.52, 130.43, 127.72, 127.20, 123.43, 114.47, 106.97, 85.16, 62.88, 56.97, 55.51; m.p.= 95.

2',4,4'-trimethoxy-3'-[(1E)-3-hydroxy-3-methylbut-1-en-1-yl]chalcone **8**



A mixture of 424 mg (1.00 mmol) of chalcone **7**, 430 mg (5 mmol) of 2-methyl-3-buten-2-ol, 170 μ L (1.25 mmol) of Et₃N, 11 mg (0.049 mmol) of Pd(OAc)₂, and 61 mg (0.20 mmol) of tri-*ortho*-tolylphosphine in 4 mL dry DMF was flushed with nitrogen and then heated to 90 °C for 18 h. Afterwards 30 mL of dichloromethane were added, and the reaction mixture was washed with H₂O (3 x 10 mL). The organic layer was dried over MgSO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (hexane:EtOAc=4:1), affording 287 mg of **8** as a yellow oil (75% yield). ¹H NMR (400 MHz, CDCl₃): δ 7.62 (d, 15.8, 1H), 7.53 (d, 8.7, 2H), 7.50 (d, 8.2, 1H), 7.34 (d, 15.8, 1H), 6.77 (d, 16.0, 1H), 6.86 (d, 8.5, 2H), 6.69 (d, 15.8, 1H), 6.70 (d, 8.0, 1H), 3.85, 3.78, 3.63 (s, 3H each), 1.41 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 191.72, 161.38, 161.05, 158.68, 143.14, 143.07, 130.04, 129.93, 127.65, 126.80, 124.18, 119.37, 115.86, 114.23, 106.71, 71.33, 62.99, 55.71, 55.21, 29.74; HRMS (ESI) calcd for C₂₃H₂₇O₅ [M+H]⁺ = 383.1853. Found 383.1845

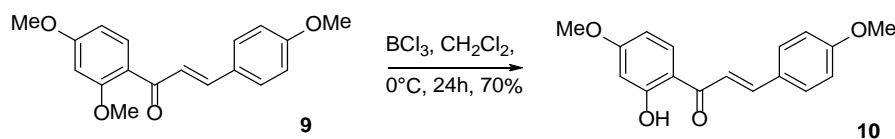
2',4,4'-trimethoxy-3'-[(1E)-3-methylbut-1,3-dien-1-yl]chalcone **3**



A mixture of 248 mg (0.65 mmol) of **8**, 65 μ L (0.90 mmol, 1.35 equiv) of acetyl chloride, and 70 μ L (2.6 mmol, 1.3 equiv) of pyridine in 10 mL benzene was heated to 60 °C for 8 h.

Then, 10 mL of 5% aqueous NaHCO_3 were poured into the reaction mixture. The aqueous layer was extracted with hexane (30 mL) and the organic layer was washed with brine and dried over MgSO_4 . After evaporation of the solvents, the residue was purified by column chromatography (hexane:EtOAc=4:1), affording 346 mg of diene **3** (95% yield) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 7.59 (d, 15.8, 1H), 7.49 (dd, 8.8, 1.7, 2H), 7.49 (d, 8.2, 1H), 7.32 (d, 15.8, 1H), 7.27 (d, 16.6, 1H), 6.83 (d, 8.5, 2H), 6.69 (d, 16.6, 1H), 6.68 (d, 8.3, 1H), 5.05 (s, 1H), 5.03 (s, 1H), 3.85, 3.76, 3.63 (s, 3H each), 1.94 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 191.84, 161.44, 161.20, 158.86, 143.20, 136.98, 130.15, 130.00, 127.82, 126.96, 124.31, 119.90, 119.07, 117.45, 114.33, 106.80, 62.33, 55.89, 55.35, 18.25; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{25}\text{O}_4$ $[\text{M}+\text{H}]^+ = 365.1747$ Found 365.1745

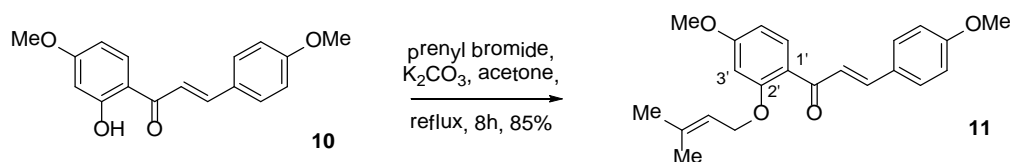
2'-hydroxy-4,4'-dimethoxychalcone **10**



To a solution of chalcone **9** (1.49 g, 5 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added boron trichloride (5 ml, 1.0 M in CH_2Cl_2). The reaction mixture was stirred for 24 h before addition of methanol (20 ml). The mixture was then poured into ice-water acidified and extracted three times with CH_2Cl_2 . The organic phases were combined, dried on Mg_2SO_4 , and evaporated. The residue was subjected to column chromatography (hexane:EtOAc=4:1) to give chalcone **10** as a yellow solid (1.0 g, 70%). ^1H NMR (270 MHz, CDCl_3): δ 13.49 (s, 1H), 7.64 (d, $J=15.1$, 1H), 7.61 (d, $J=7.9$, 1H), 7.38 (d, $J=8.6$, 2H), 7.23 (d, $J=15.1$, 1H), 6.73 (d, $J=8.6$, 2H), 6.31 (d, $J=7.8$, 1H), 6.28 (d, $J=2.4$, 1H), 3.64, 3.63 (s, 3H each); ^{13}C NMR (67.9 MHz, CDCl_3): δ 191.49, 166.32, 165.73, 161.53,

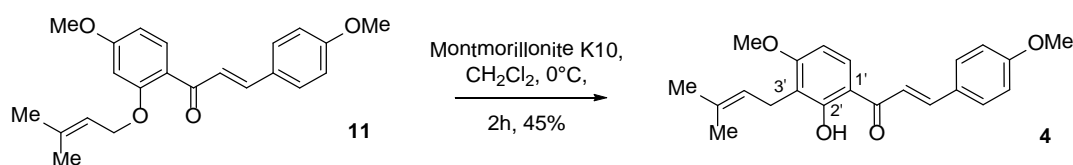
143.94, 130.92, 130.13, 127.15, 117.33, 114.16, 113.86, 107.21, 100.84, 55.22, 55.07; m.p = 110°C.

2'-prenyloxy-4,4'-dimethoxychalcone **11**



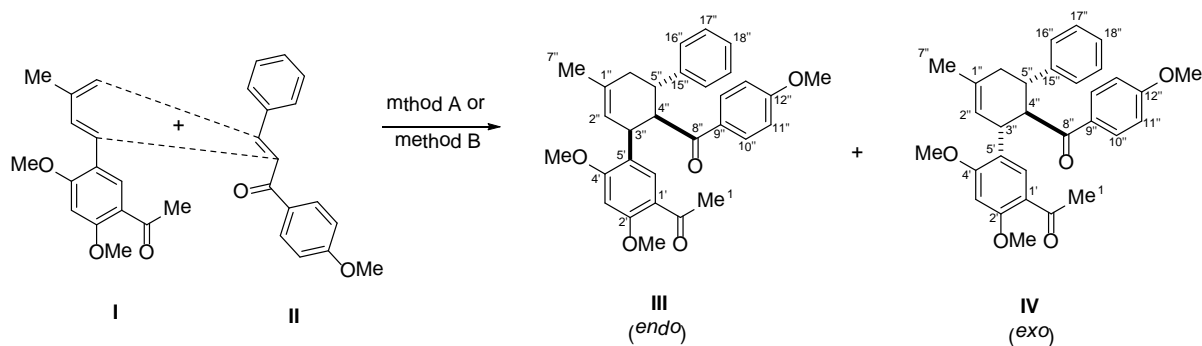
To a solution of chalcone **10** (284 mg, 1 mmol) in acetone (20 mL) was added K_2CO_3 (277 mg, 2 mmol) and prenyl bromide (298 mg, 2 mmol). The reaction mixture was heated under reflux for 8 h before the addition of water and CH_2Cl_2 . The aqueous phase was extracted with CH_2Cl_2 (2x). The organic layers were collected, washed with brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by column chromatography (hexane:EtOAc=4:1) to provide chalcone **11** (299 mg, 85%) as a yellow amorphous. 1H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 15.8, 1H), 7.50 (d, 8.8, 2H), 7.49 (d, 8.2, 1H), 7.32 (d, 15.8, 1H), 7.27 (d, 16.6, 1H), 6.83 (d, 8.5, 2H), 6.69 (d, 16.6, 1H), 6.68 (d, 8.3, 1H), 5.05 (s, 1H), 5.03 (s, 1H), 3.85, 3.76, 3.63 (s, 3H each), 1.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.84, 161.44, 161.20, 158.86, 143.20, 136.98, 130.15, 130.00, 127.82, 126.96, 124.31, 119.90, 119.07, 117.45, 114.33, 106.80, 62.33, 55.89, 55.35, 18.25; HRMS (ESI) calcd for $C_{23}H_{25}O_4$ $[M+H]^+ = 365.1747$ Found 353.1746

2'-hydroxy-3'-prenyl-4,4'-dimethoxychalcone **4**



To a solution of chalcone **11** (352 mg, 1 mmol) at 0°C in CH₂Cl₂ (20 mL) was added Montmorillonite K10 (352 mg, 1 weight equiv). The reaction mixture was stirred for 8 h before filtered through celite. The organic layers were collected and concentrated. The crude residue was purified by column chromatography (hexane:EtOAc=4:1) to provide chalcone **4** (158 mg, 45%) as a yellow amorphous. C5'-prenylated chalcone was also isolated in 40% yield. ¹H NMR (270 MHz, CDCl₃): δ 13.51 (s, 1H), 7.83 (d, 15.4, 1H), 7.77 (d, 9.2, 1H), 7.58 (d, 8.6, 2H), 7.45 (d, 15.5, 1H), 6.91 (d, 8.6, 2H), 6.46 (d, 8.9, 1H), 5.24 (t, 6.7, 1H), 3.88, 3.83 (s, 3H each), 3.38 (d, 7.0, 2H), 1.79, 1.68 (s, 3H each); ¹³C NMR (67.9 MHz, CDCl₃): δ 192.16, 163.09, 162.92, 161.63, 143.89, 131.77, 130.23, 129.03, 127.50, 122.03, 117.96, 117.39, 114.58, 114.35, 101.96, 55.67, 55.32, 25.76, 21.66, 17.76.

Model study of the [4+2] cycloaddition reaction using diene **I** and dienophile **II**



Preparation of cycloadducts **III** (*endo*) and **IV** (*exo*)

Method A: thermal condition.

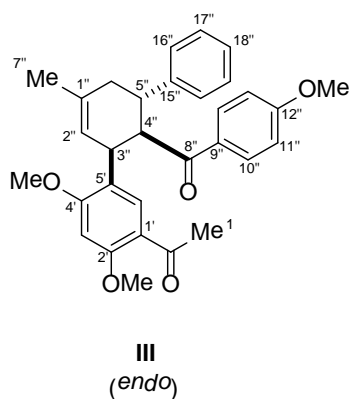
To a screw-capped pressure tube (Ace Glass Inc, USA) equipped with a magnetic stirrer was added the corresponding diene **I** (246 mg, 1 mmol), dienophile **II** (238mg, 1 mmol), and dry toluene (5 mL). The resulting mixture was heated at the 160°C and left under

magnetic stirring for 18h. After silica-gel column chromatography of the final mixture cycloadducts **III** and **IV** were isolated (290 mg, 60%).

Method B: catalytic cycloaddition.

To a screw-capped pressure tube (Ace Glass Inc, USA) equipped with a magnetic stirrer was added ZnI_2 (0.06 mmol, 60 mol%), Bu_4NBH_4 (0.01 mmol, 10 mol%), diene **I** (25 mg, 0.1 mmol), dienophile **II** (24 mg, 0.1 mmol), and dry CH_2Cl_2 (3 mL) in a N_2 glove bag (SigmaAldrich). The resulting mixture was heated at the 60°C and left under magnetic stirring for 18h. After silica-gel column chromatography of the final mixture cycloadducts **III** and **IV** were isolated (yield 30 mg, 62%).

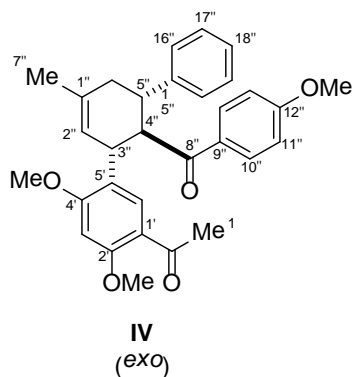
[(1S,2S,6S)-2-(5-acetyl-2,4-dimethoxyphenyl)-4-methyl-6-phenylcyclohex-3-en-1-yl](4-methoxyphenyl)methanone



Pale white solid; ^1H NMR (400 MHz, CDCl_3): δ 7.71 (s, 1H, H6'), 7.74 (d, 8.5, 2H, H11'',13''), 6.88-6.98 (m, 5H, H17''-19''), 6.79 (d, 8.5, 2H, H10'',14''), 6.09 (s, 1H, H3'), 5.40 (bs, 1H, H2''), 4.24 (bs, 1H, H3''), 4.23 (t, 5.3, 1H, H4''), 3.76, 2.96 (s, 3H each, OCH_3), 3.14 (ddd, 11.5,11.2,5.6, 1H, H5''), 2.52 (s, 3H, COCH_3), 2.22, 2.43 (m, 1H each, H6''), 1.78 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3): δ 198.32 (C8''), 198.14 (C=O), 161.98 (C12''), 162.67 (C4'), 160.62 (C2'), 145.30 (C15''), 135.92 (C1''), 132.24 (C9''), 133.31

(C6'), 129.67 (C10'',14''), 128.17 (C16'',20''), 127.54 (C17'',19''), 125.83 (C18''), 121.14 (C5'), 122.03 (C2''), 119.52 (C1'), 113.40 (C11'',13''), 93.69 (C3'), 55.44, 54.29 (C-OCH₃), 50.29 (C4''), 38.12 (C5''), 37.18 (C3''), 40.56 (C6''), 32.28 (-CO(CH₃)), 23.33 (C7''); m.p. 185°C; HRMS (ESI) calcd for C₃₁H₃₃O₅ [M+H]⁺ = 485.2323. Found 485.2325

[(1S,2R,6S)-2-(5-acetyl-2,4-dimethoxyphenyl)-4-methyl-6-phenylcyclohex-3-en-1-yl](4-methoxyphenyl)methanone



Pale white solid; ¹H NMR (400 MHz, CDCl₃): δ 7.78 (s, 1H, H6'), 7.22 (d, 8.7, 2H, H11'',13''), 7.07 (d, 7.3, 2H, H16'',20''), 7.00 (t, 7.8, 2H, H17'',19''), 6.91 (m, 1H, H18''), 6.44 (d, 8.5, 2H, H10'',14''), 5.91 (s, 1H, H3'), 5.26 (bs, 1H, H2''), 4.18 (bd, 10, 1H, H3''), 3.76 (t, 11, 1H, H4''), 3.68, 3.62, 3.44 (s, 3H each, OCH₃), 3.39 (ddd, 11.2,11.2,5.3, 1H, H5''), 2.48 (s, 3H, COCH₃), 2.26, 2.41 (m, 1H each, H6''), 1.71 (s, 3H, CH₃); ¹³C NMR (100 MHz, CDCl₃): δ 202.12 (C8''), 197.99 (C=O), 162.54 (C12''), 161.69 (C4'), 160.11 (C2'), 143.99 (C15''), 134.29 (C1''), 131.59 (C9''), 130.96 (C6'), 130.04 (C10'',14''), 128.25 (C16'',20''), 127.72 (C17'',19''), 126.21 (C18''), 125.15 (C5'), 124.52 (C2''), 120.24 (C1'), 112.78 (C11'',13''), 94.03 (C3'), 55.42, 55.14 (C-OCH₃), 53.44 (C4''), 44.66 (C5''), 39.66 (C3''), 39.01 (C6''), 32.12 (-CO(CH₃)), 23.45 (C7''); m.p. 180°C HRMS (ESI) calcd for C₃₁H₃₃O₅ [M+H]⁺ = 485.2323. Found 485.2320

Preparation of pentamethyl ethers of kuwanon V (1a) and dorsterone (2a)

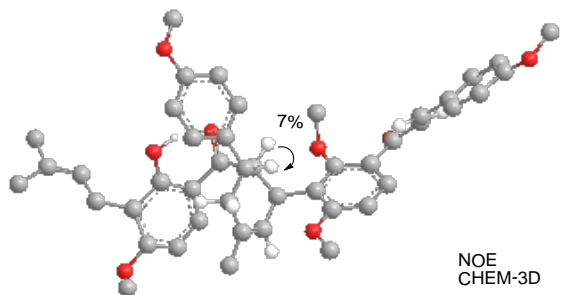
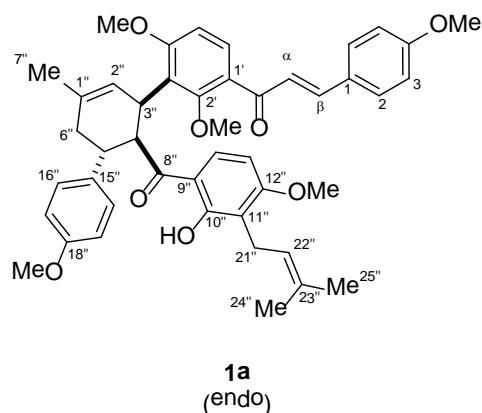
Method A: thermal condition.

To a screw-capped pressure tube (Ace Glass Inc, USA) equipped with a magnetic stirrer was added the corresponding diene **3** (38 mg, 0.1 mmol), dienophile **4** (40 mg, 0.1 mmol), and dry toluene (2 mL). The resulting mixture was heated at the 160°C and left under magnetic stirring for 18h. After silica-gel column chromatography of the final mixture cycloadducts **1a** and **2a** were isolated (yield 39 mg, 55%).

Method B: catalytic cycloaddition.

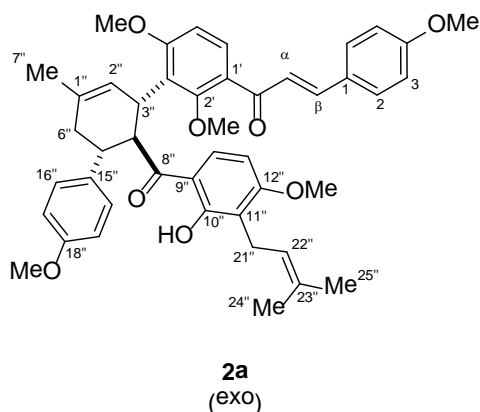
To a screw-capped pressure tube (Ace Glass Inc, USA) equipped with a magnetic stirrer was added AgOTf (0.06 mmol, 60 mol%), Bu₄NBH₄ (0.01 mmol, 10 mol%), diene **3** (36 mg, 0.1 mmol), dienophile **4** (35 mg, 0.1 mmol), and dry CH₂Cl₂ (5 mL) in a N₂ glove bag (SigmaAldrich). The resulting mixture was heated at the 60°C and left under magnetic stirring for 18h. After silica-gel column chromatography of the final mixture cycloadducts **1a** and **2a** were isolated (yield 44 mg, 65%).

(±)-kuwanon V pentamethyl ether 1a



Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 12.54 (s, 1H, OH), 7.80 (d, 8.6, 1H, H14"), 7.66 (d, 16.0, 1H, H $_{\beta}$), 7.63 (d, 8.6, 2H, H2,6), 7.32 (d, 8.6, 1H, H6'), 7.07 (d, 8.6, 2H, H16", 20"), 7.03 (d, 16.3, 1H, H $_{\alpha}$), 6.93 (d, 8.6, 2H, H3,5), 6.70 (d, 8.1, 2H, H17",19"), 6.44 (d, 8.6, 1H, H5')*, 6.44 (d, 8.6, 1H, H13")*, 5.49 (bs, 1H, H2"), 5.05 (t, 6.8, 1H, H22"), 4.60 (bs, 1H, H3"), 4.31 (t, 9.6, 6.8, 1H, H4"), 3.97 (ddd, 10.8, 10.8, 5.7, 1H, H5"), 3.87, 3.86, 3.72, 3.46 (s, OMe), 3.21 (bd, 5.9, 1H, H21"), 2.40, 2.19 (m, 2H, H6"), 1.78 (s, 3H, H7"), 1.67 (s, 3H, H24"), 1.58 (s, 3H, H25"); NOE_Diff (400 MHz, CDCl_3) Irradiation at δ 4.31 (H4") gave 3% enhancement at H3" while H5" collapsed to doublet of doublet (J = 10.8, 5.7 Hz); ^{13}C NMR (100 MHz, CDCl_3): δ 205.87 (C8"), 195.40 (C=O), 162.52 (C10"), 161.63 (C2')*, 161.63 (C4)*, 161.63 (C12")*, 160.02 (C4'), 157.73 (C18"), 138.41 (C1"), 133.29 (C15")*, 133.29 (C3')*, 131.73 (C23"), 130.63 (C2,6), 130.29 (C6'), 129.54 (C $_{\beta}$)*, 129.54 (C14")*, 128.52 (C16",20"), 128.01 (C1), 126.71 (C9"), 124.25 (C $_{\alpha}$), 122.20 (C2"), 122.11 (C22"), 116.89 (C11"), 115.52 (C1'), 114.41 (C3), 113.74 (C17",19"), 105.99 (C5'), 101.51 (C13"), 62.72, 54.99, 55.49, 55.81, 54.99 (C-OMe), 50.30 (C4"), 39.79 (C6"), 37.46 (C5"), 35.18 (C3"), 25.83 (C25"), 23.70 (C7"), 21.59 (C21"), 17.86 (C24"). *chemical shift overlapped. HRMS (ESI) calcd for $\text{C}_{45}\text{H}_{49}\text{O}_8$ $[\text{M}+\text{H}]^+ = 717.3422$. Found 717.3421

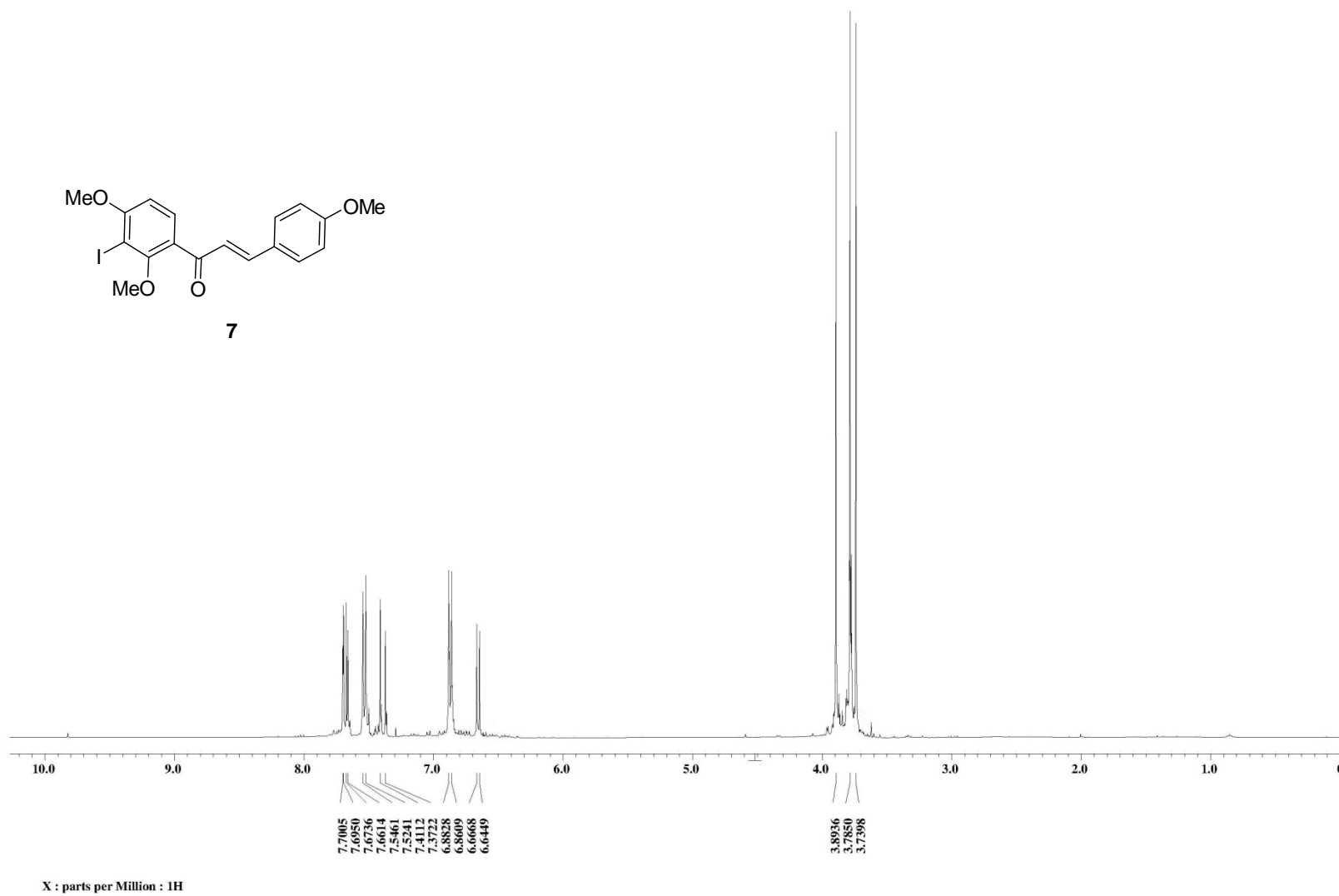
(±)-dorsterone pentamethyl ether 2a



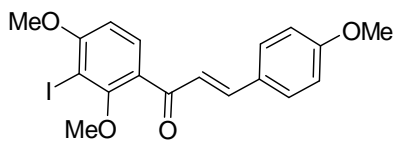
Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 12.80 (s, 1H, OH), 7.70 (d, 8.6, 1H, H14"), 7.57 (d, 16.0, 1H, H $_{\beta}$), 7.52 (d, 8.6, 2H, H2,6), 7.38 (d, 8.6, 1H, H6'), 7.15 (d, 8.6, 2H, H16", 20"), 7.18 (d, 16.3, 1H, H $_{\alpha}$), 6.97 (d, 8.6, 2H, H3,5), 6.71 (d, 8.1, 2H, H17",19"), 6.36 (d, 8.6, 1H, H5'), 6.07 (d, 8.6, 1H, H13"), 5.37 (bs, 1H, H2"), 5.00 (t, 6.8, 1H, H22"), 4.51 (bs, 1H, H3"), 4.55 (t, 9.99, 1H, H4"), 3.95 (m, 1H, H5")*, 3.97, 3.85, 3.75, 3.67, 3.51 (s, OMe), 3.11 (bd, 7.0, 1H, H21"), 2.41, 2.32 (m, 2H, H6"), 1.77 (s, 3H, H7"), 1.67 (s, 3H, H24"), 1.60 (s, 3H, H25"); ^{13}C NMR (100 MHz, CDCl_3): δ 208.15 (C8"), 191.87 (C=O), 162.42 (C10"), 161.54 (C2'), 161.34 (C4)*, 161.34 (C4')*, 160.55 (C12"), 157.77 (C18"), 136.18 (C1"), 132.08 (C15"), 131.56 (C3'), 130.82 (C23"), 130.02 (C2,6), 128.71 (C6'), 143.33 (C $_{\beta}$), 129.57 (C14"), 128.34 (C16",20"), 127.59 (C1), 126.34 (C9"), 124.69 (C $_{\alpha}$), 123.67 (C2"), 122.15 (C22"), 116.32 (C11"), 115.77 (C1'), 114.40 (C3), 113.65 (C17",19"), 105.84 (C5'), 101.06 (C13"), 63.18, 55.79, 55.33, 55.25, 54.98 (C-OMe), 49.24 (C4"), 39.25 (C6"), 38.63 (C5"), 36.55 (C3"), 25.65 (C25"), 23.65 (C7"), 21.35 (C21"), 17.59 (C24"). *chemical shift overlapped. HRMS (ESI) calcd for $\text{C}_{45}\text{H}_{49}\text{O}_8$ $[\text{M}+\text{H}]^+ = 717.3422$.

Found 717.3423

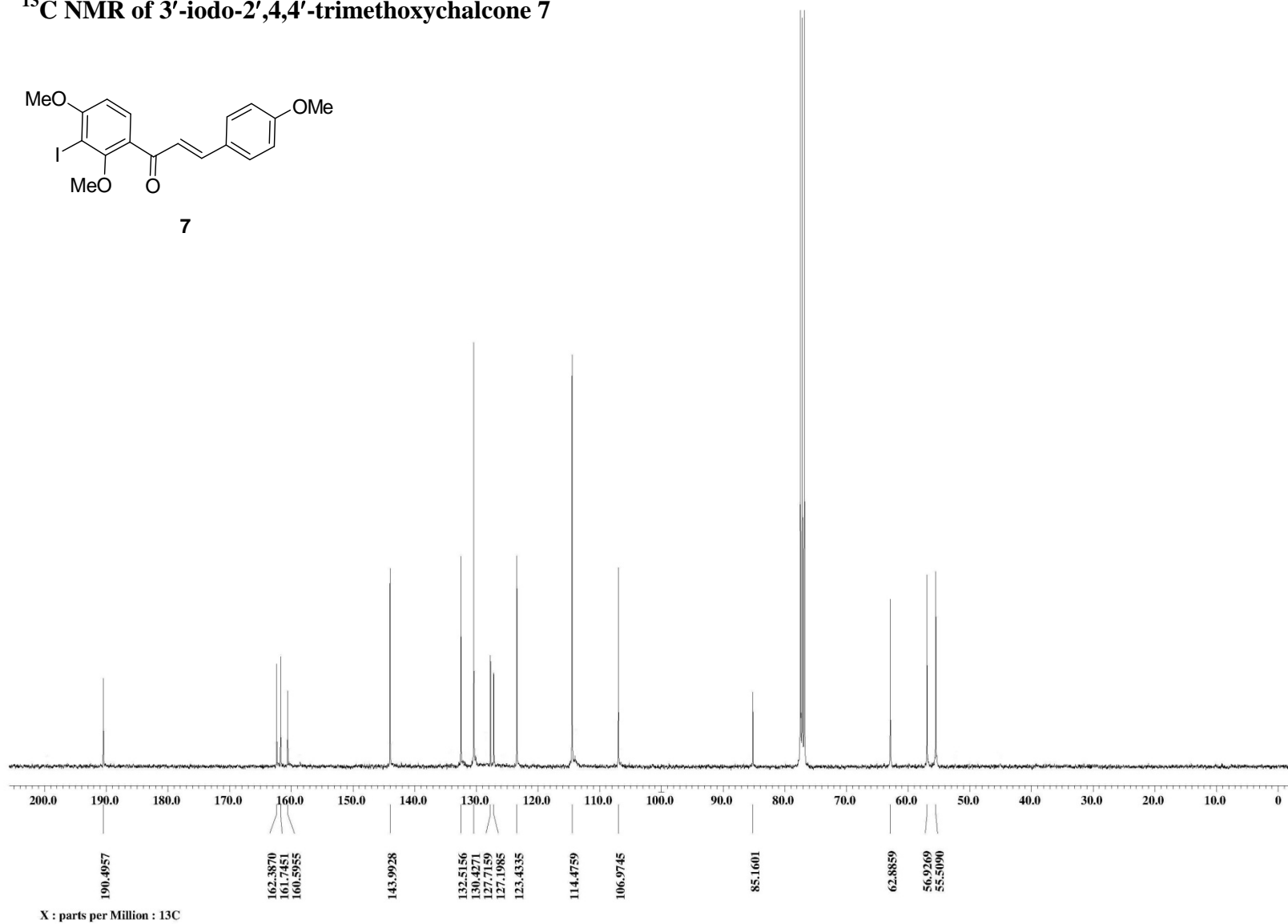
^1H NMR of 3'-iodo-2',4,4'-trimethoxychalcone 7



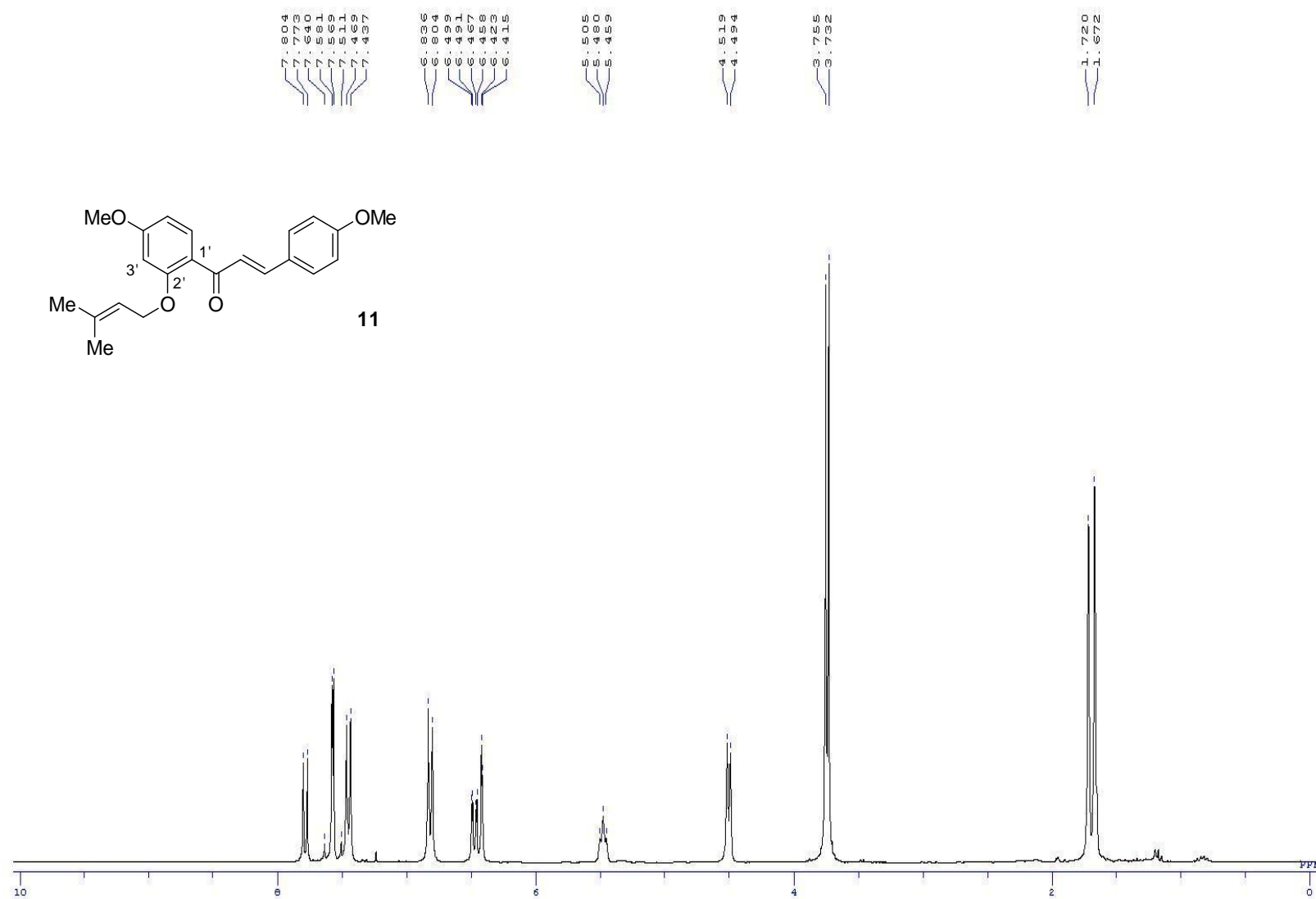
^{13}C NMR of 3'-iodo-2',4,4'-trimethoxychalcone 7



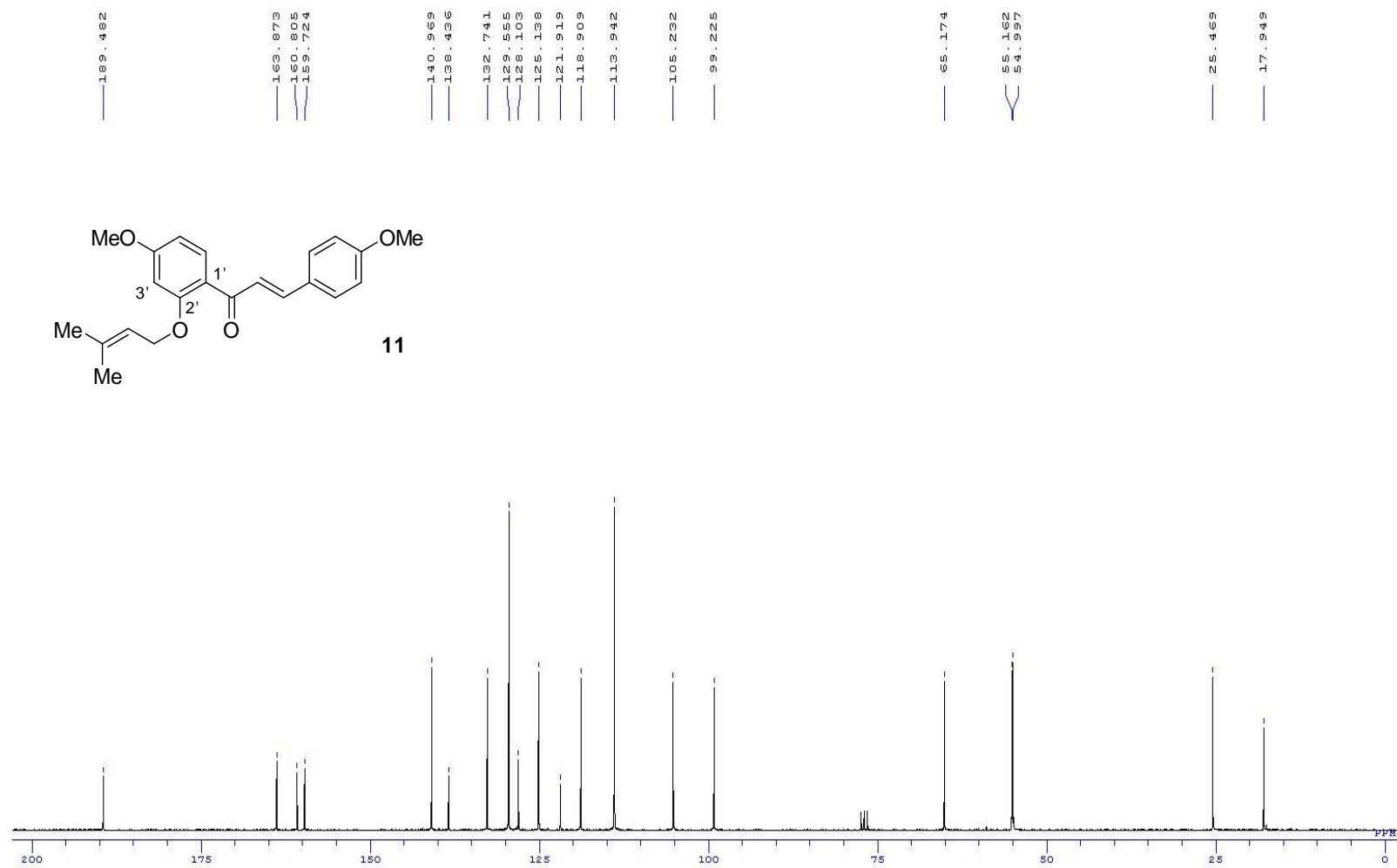
7



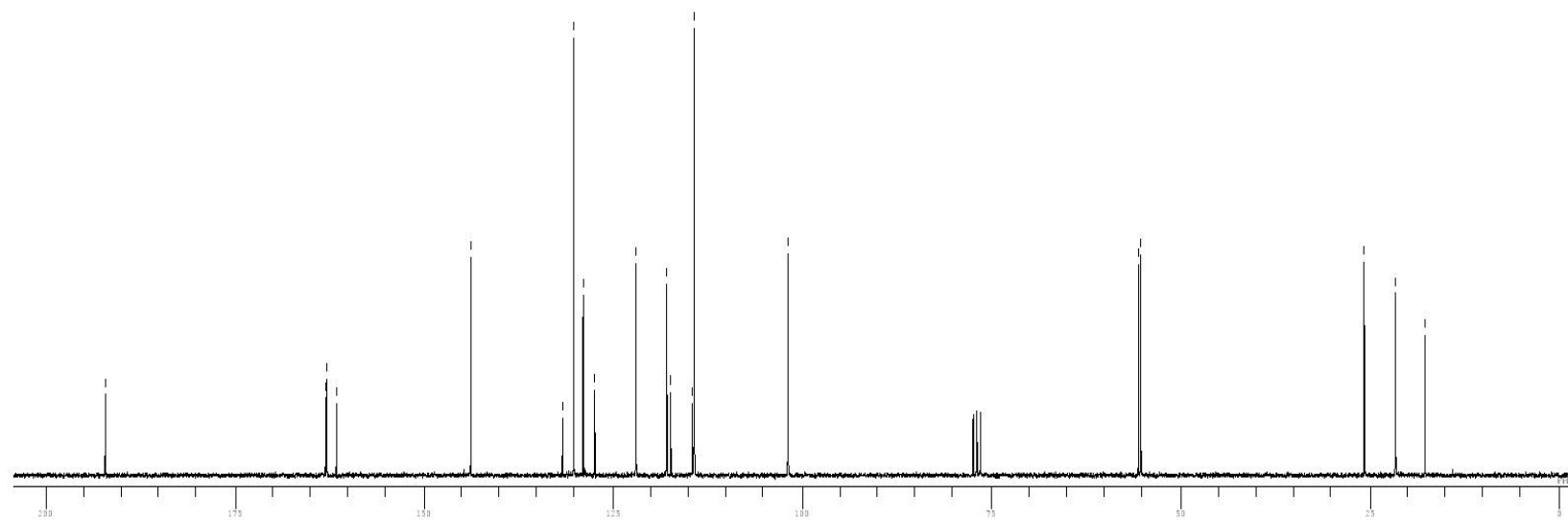
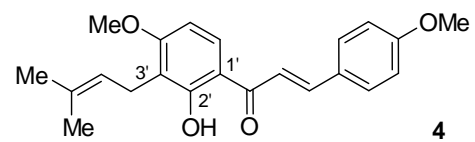
^1H NMR of 2'-prenyloxy-4,4'-dimethoxychalcone 11



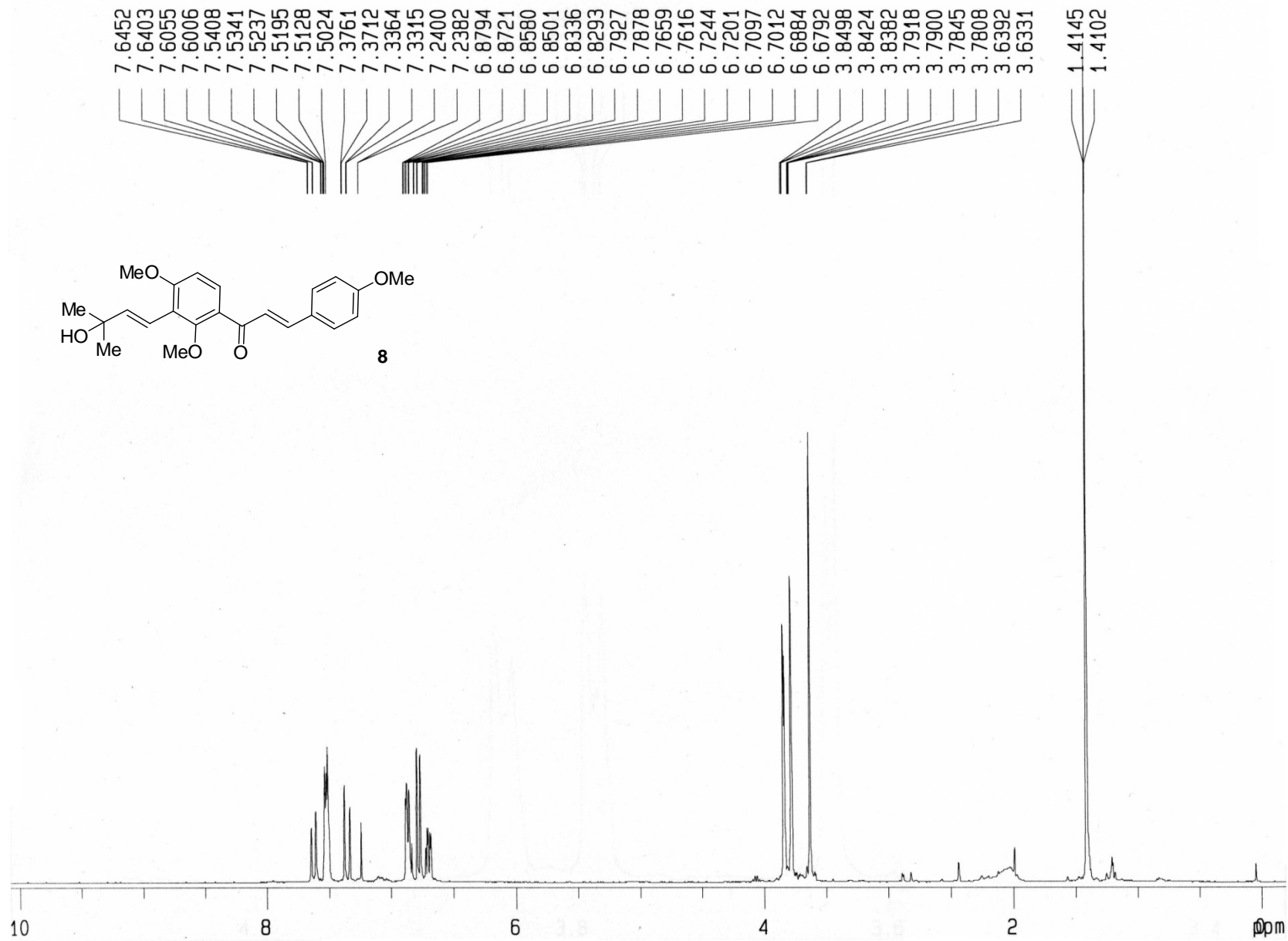
¹³C NMR of 2'-prenyloxy-4,4'-dimethoxychalcone 11



^{13}C NMR of 2'-hydroxy-3'-prenyl-4,4'-dimethoxychalcone **4**

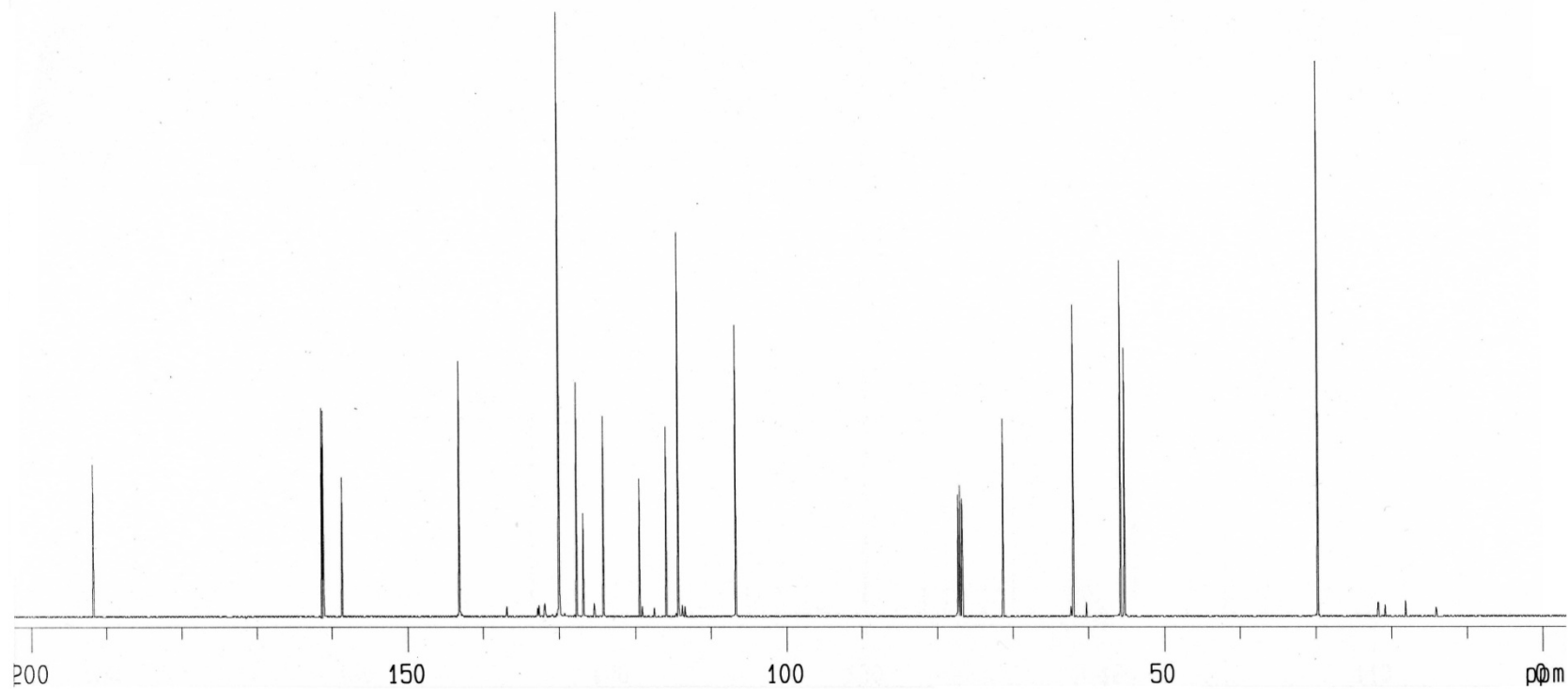
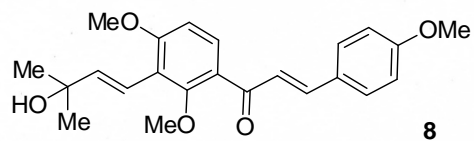
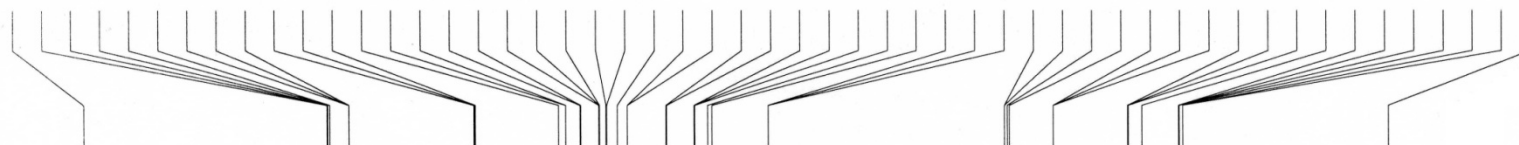


¹H NMR of 2',4,4'-trimethoxy-3'-[(1E)-3-hydroxy-3-methylbut-1-en-1-yl]chalcone 8

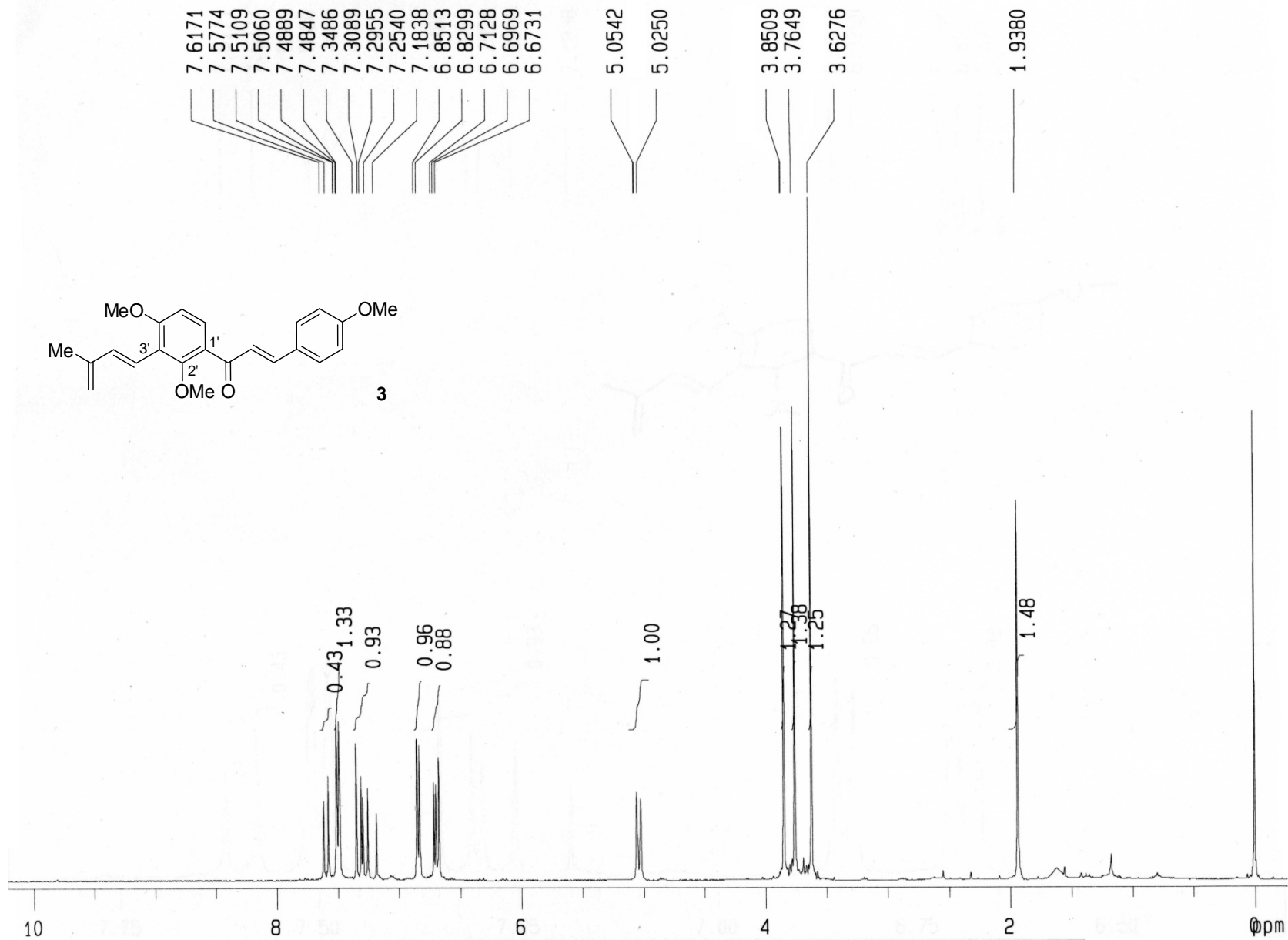


^{13}C NMR of 2',4,4'-trimethoxy-3'-[(1E)-3-hydroxy-3-methylbut-1-en-1-yl]chalcone 8

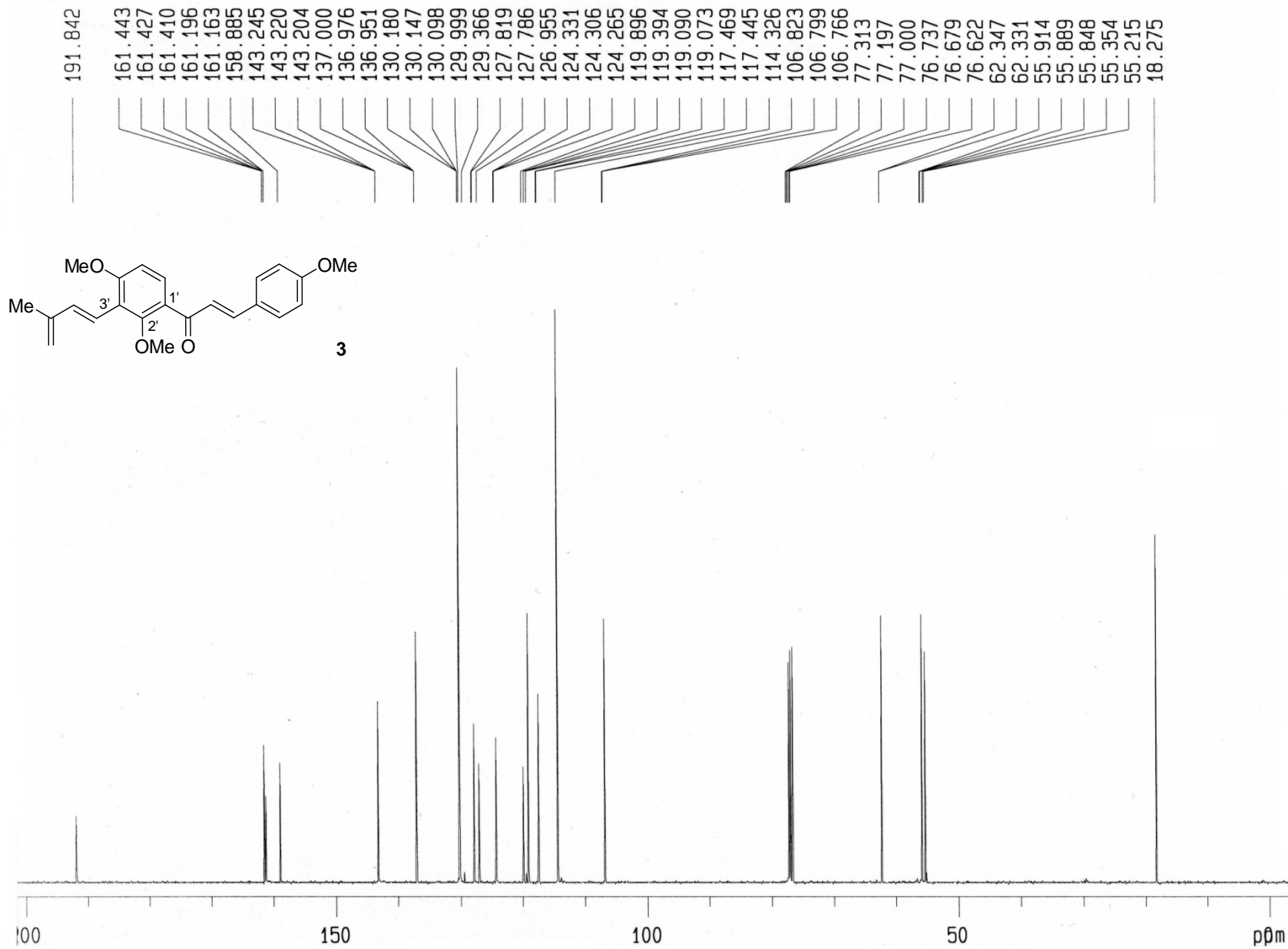
191.719
161.386
161.369
161.344
161.073
161.048
158.704
158.687
158.671
158.671
143.187
143.138
143.072
143.072
132.689
131.834
131.768
130.040
129.933
127.712
127.687
127.654
126.823
126.799
125.433
124.215
124.183
119.394
119.370
115.906
115.857
115.816
114.236
113.693
106.725
106.708
106.659
77.362
77.321
77.321
77.000
76.679
71.356
71.332
71.315
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55.741
55.708
55.256
55.206
29.743



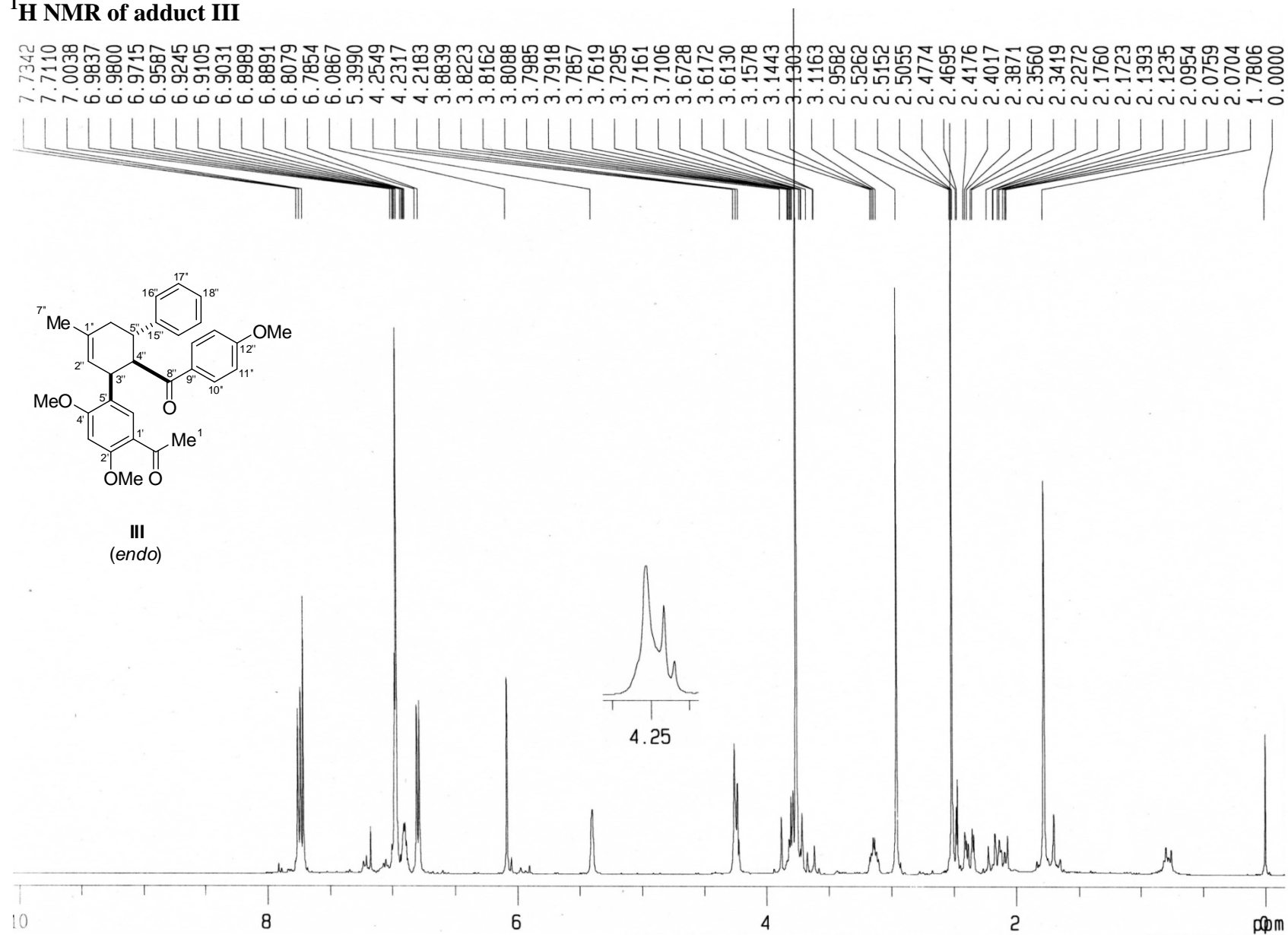
¹H NMR of 2',4,4'-trimethoxy-3'-[(1E)-3-methylbut-1,3-dien-1-yl]chalcone 3



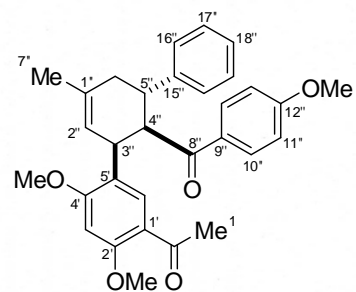
^{13}C NMR of 2',4,4'-trimethoxy-3'-[(1E)-3-methylbut-1,3-dien-1-yl]chalcone 3



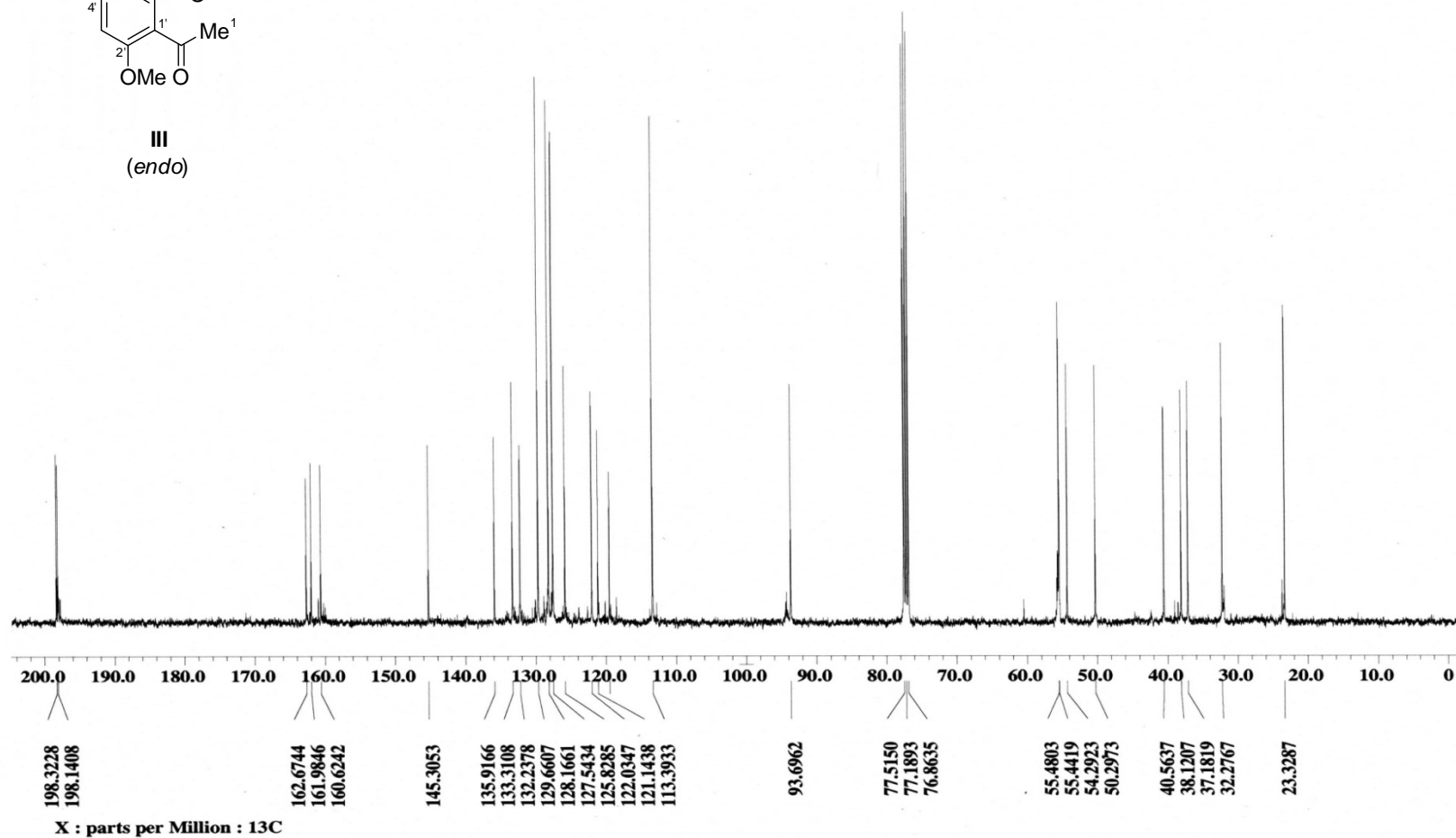
¹H NMR of adduct III



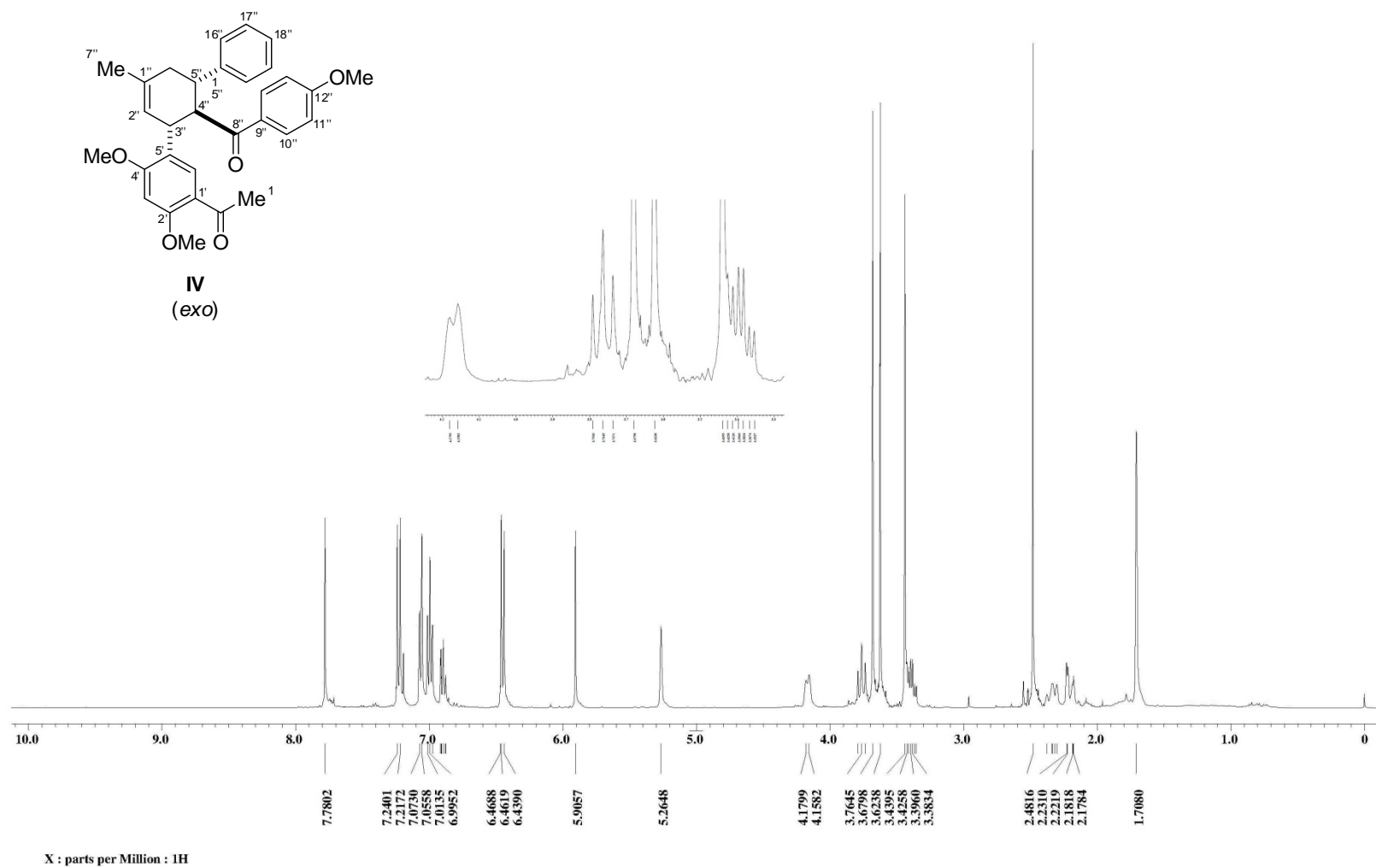
¹³C NMR of adduct III



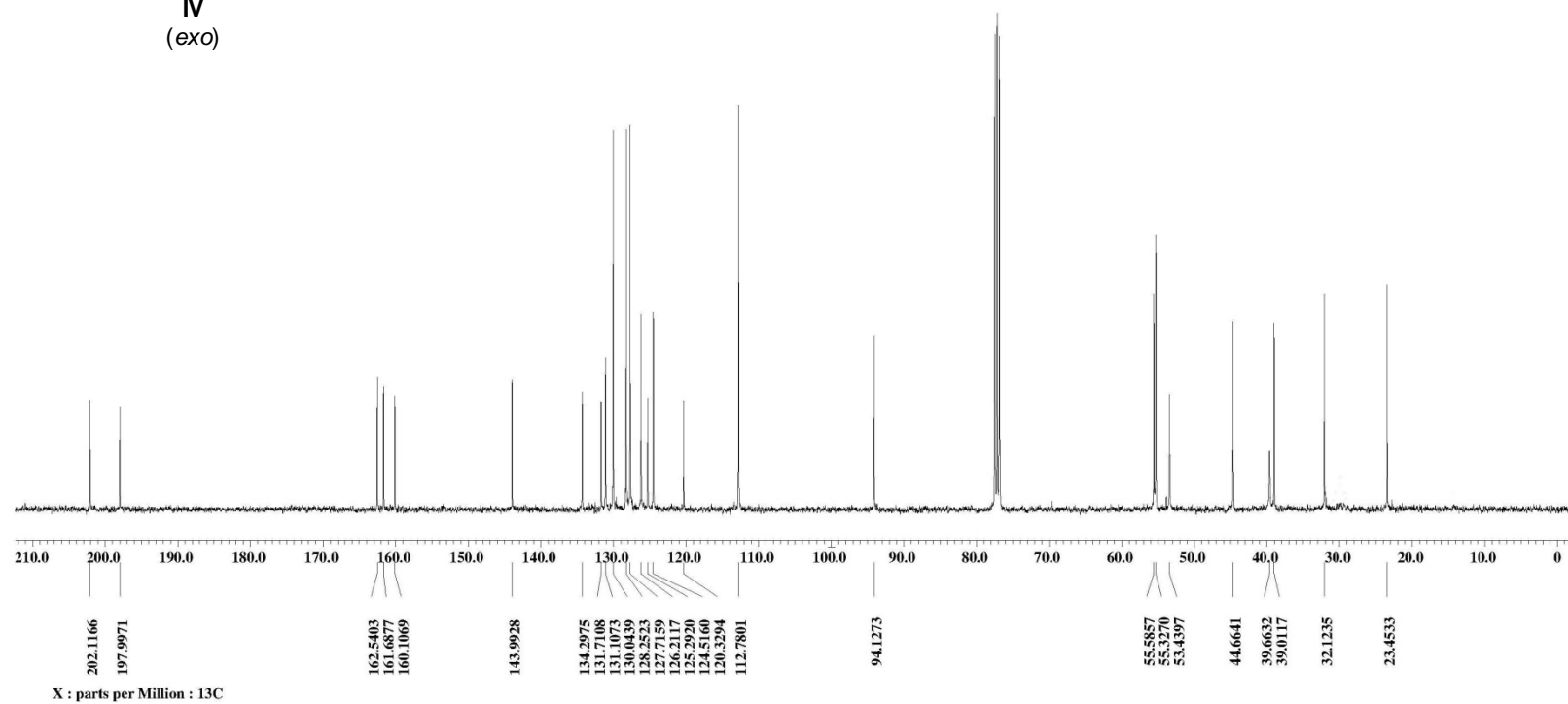
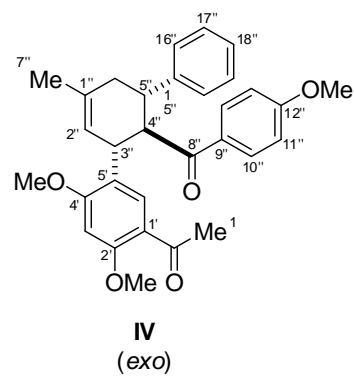
III
(endo)



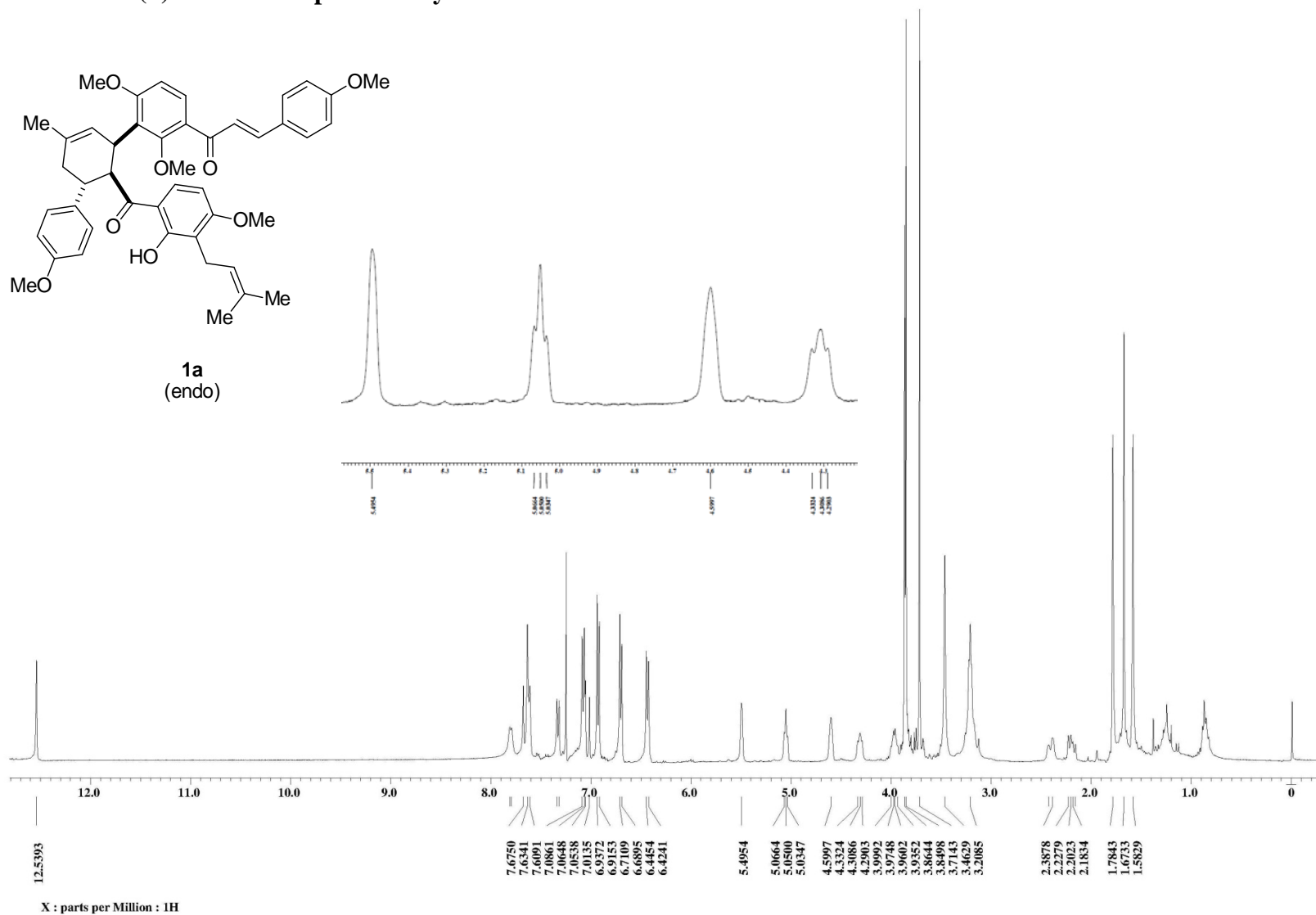
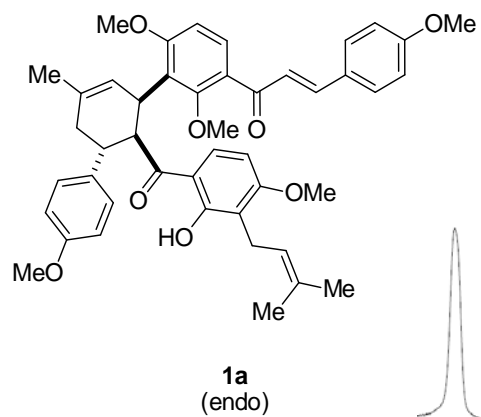
¹H NMR of adduct IV



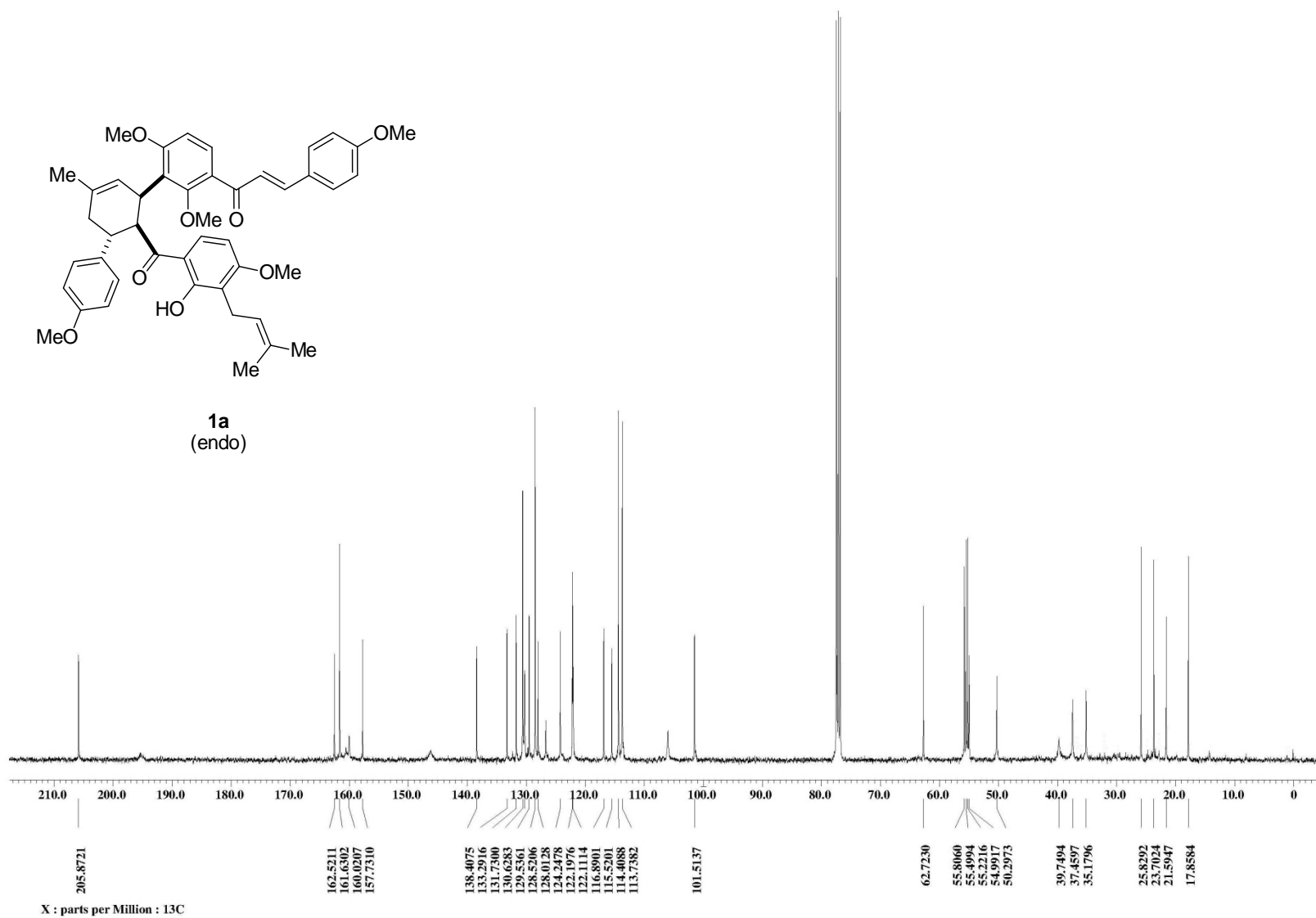
¹³C NMR of adduct IV



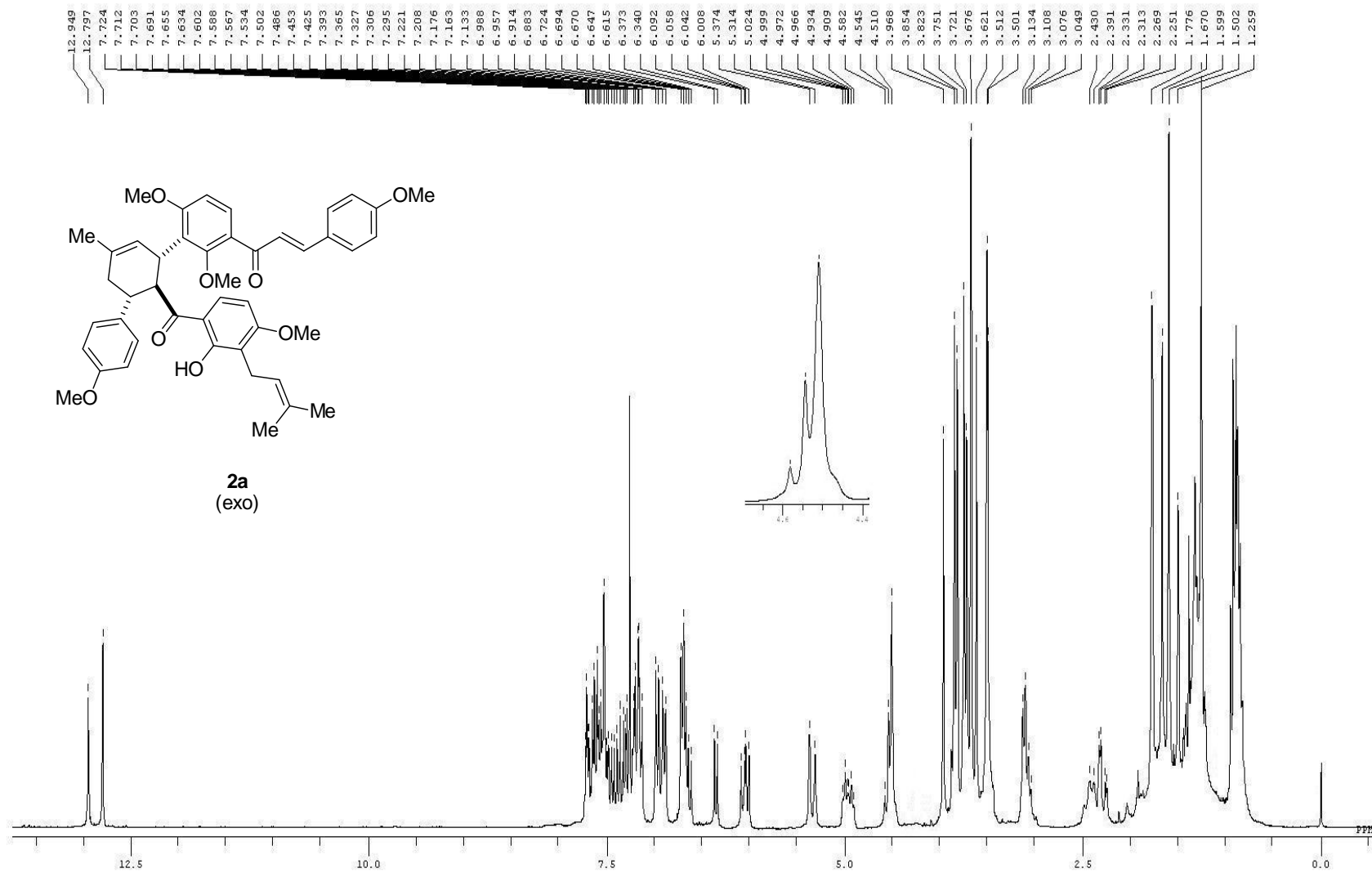
¹H NMR of (±)-kuwanon V pentamethyl ether **1a**



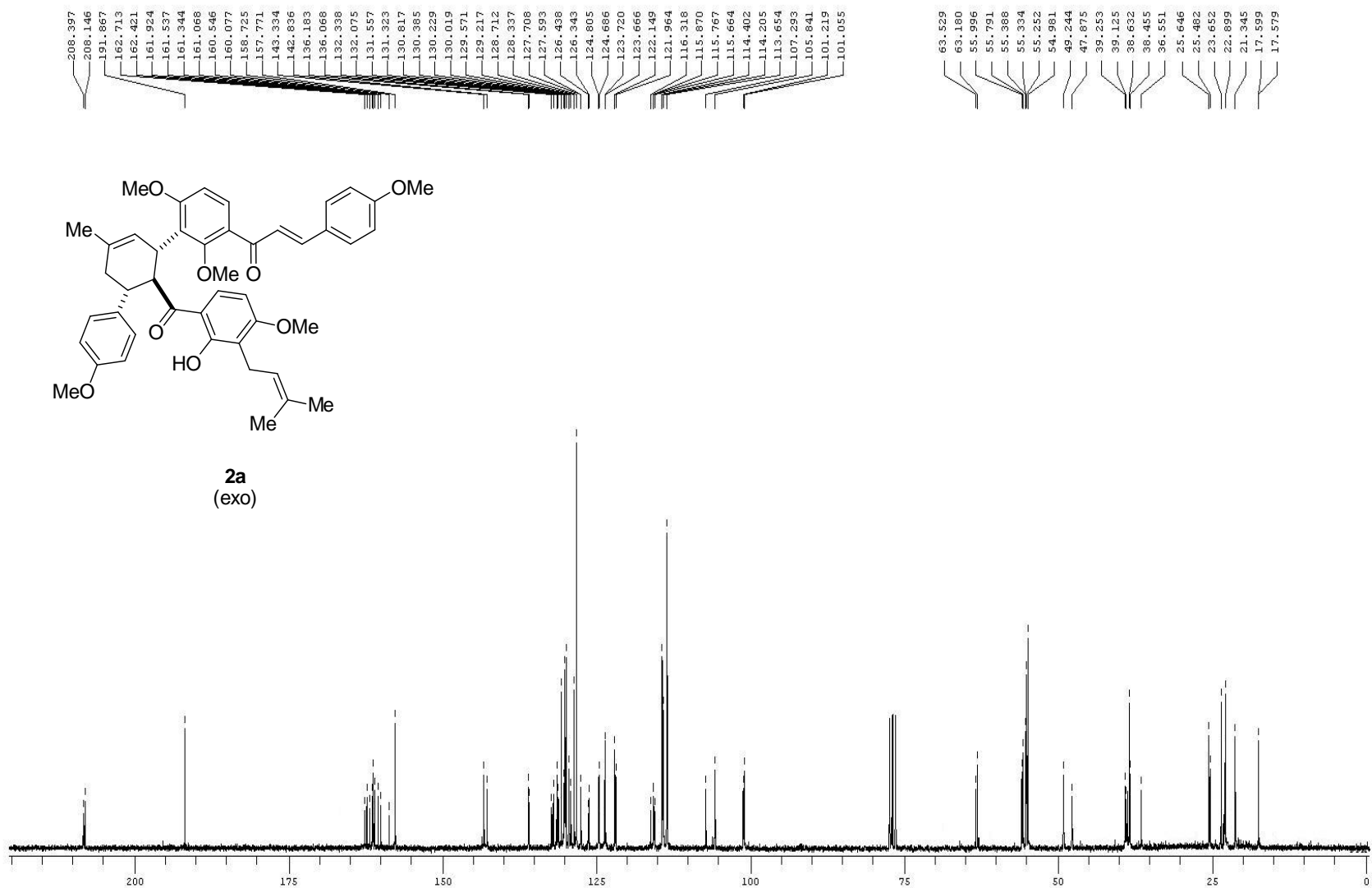
^{13}C NMR of (\pm)-kuwanon V pentamethyl ether 1a



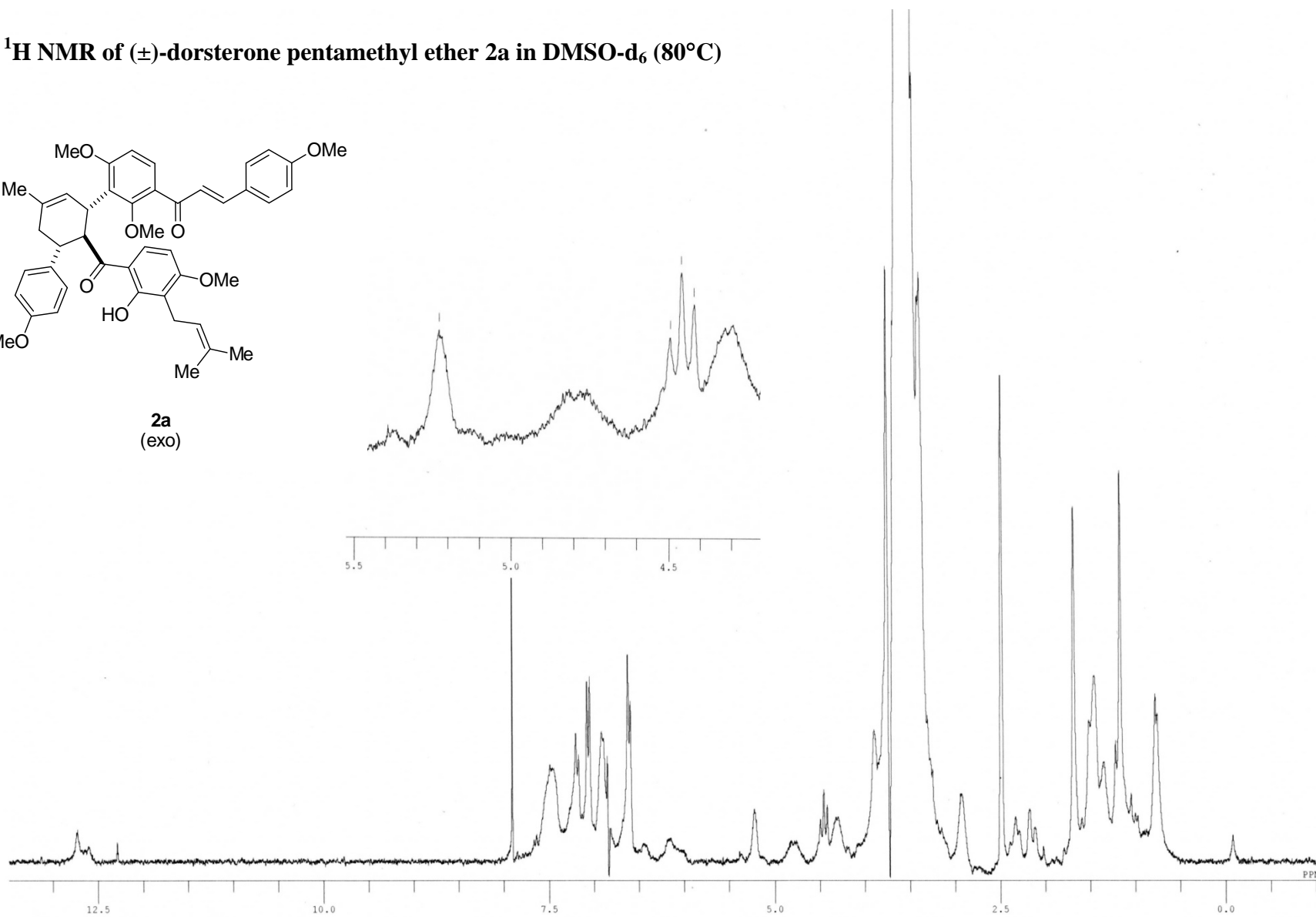
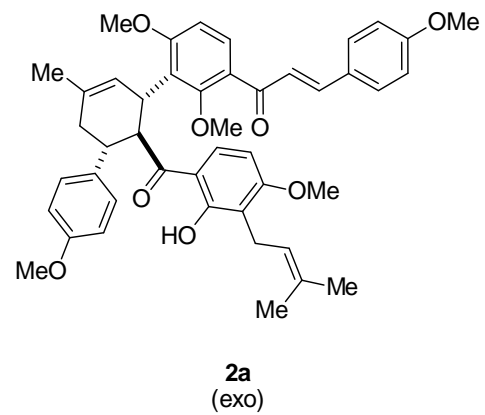
¹H NMR of (±)-dorsterone pentamethyl ether 2a (epimerization in CDCl₃ at 25 °C)



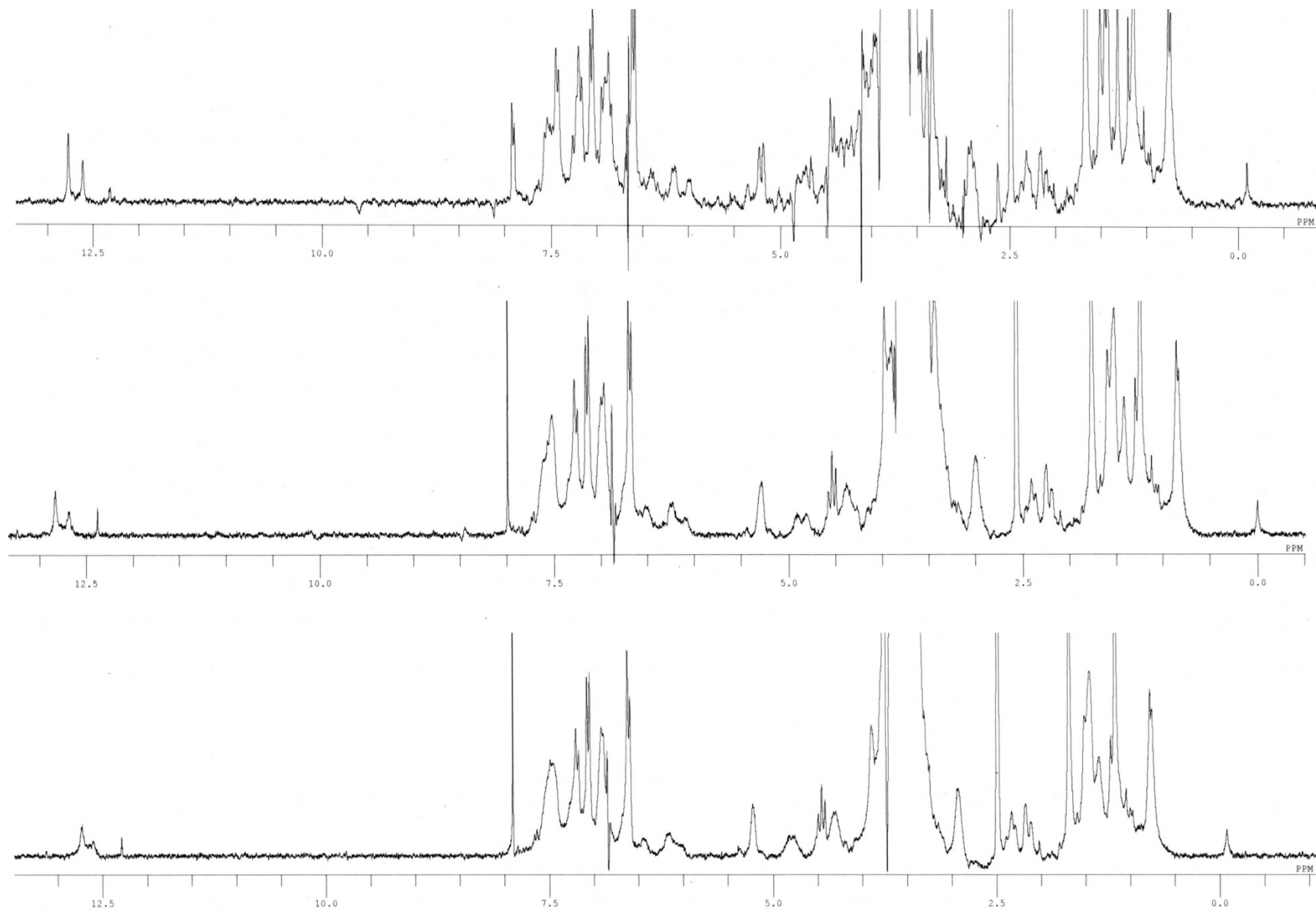
¹³C NMR of (±)-dorsterone pentamethyl ether 2a (epimerization in CDCl₃ at 25 °C)



^1H NMR of (\pm)-dorsterone pentamethyl ether **2a in DMSO-d_6 (80°C)**



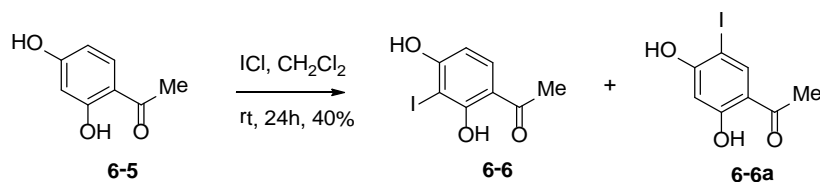
^1H NMR of (\pm)-dorsterone pentamethyl ether 2a in DMSO- d_6 at 50, 70, and 80°C, respectively.



Appendix D: Experimental and supplementary data of chapter 6

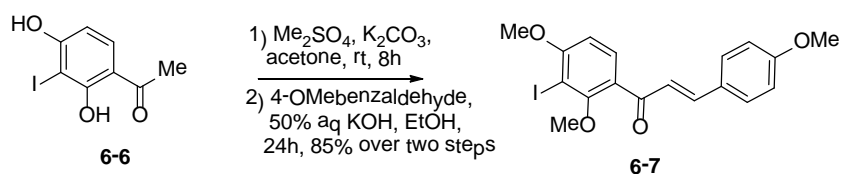
Experimental

3'-iodo-2',4'-dihydroxyacetophenone **6-6**



To a solution of 2',4'-dihydroxyacetophenone **6-5** (15.2 g, 0.1 mol) at rt in CH₂Cl₂ (450 mL) was added iodine monochloride (55 mL, 2M in CH₂Cl₂, 1.1 equiv). The purple mixture was stirred for 24 h. Afterwards 100 mL of saturated sodium thiosulfate solution were added to remove excess of ICl, and the organic layer was washed with H₂O (50 mL), collected and concentrated. The crude residue was purified by column chromatography (hexane:EtOAc=4:1) to afford **6-6a** (12.5 g, 45%) and desired compound **6-6** (11.1 g, 40%) as a pale white solid. ¹H NMR (270 MHz, acetone-D₆): δ 12.46 (s, 1H), 7.39 (d, 8.8, 1H), 6.28 (d, 8.7, 1H), 2.47 (s, 3H); ¹³C NMR (67.9 MHz, acetone-D₆): δ 203.24, 165.62, 164.30, 142.85, 116.33, 103.30, 73.46, 26.63; m.p. = 165°C.

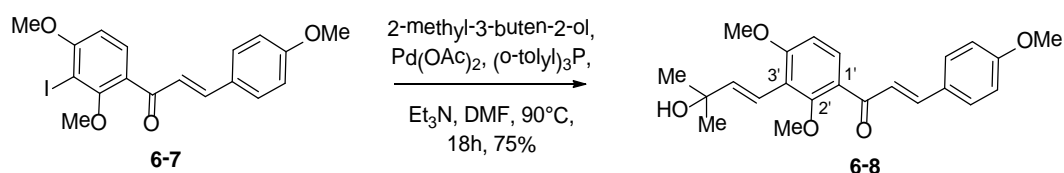
3'-iodo-2',4,4'-trimethoxychalcone **6-7**



To a solution of 3'-iodo-2',4'-dihydroxyacetophenone **6-6** (2.78 g, 0.01 mol) in dry acetone (150 mL) was added K₂CO₃ (6.9 g, 5 equiv) and dimethyl sulfate (2.3 mL, 2.4 equiv). The mixture was stirred at rt for 8 h. Then, the pale white solution was filtered and the acetone was removed by vacuum evaporation to give 3'-iodo-2',4'-

dimethoxyacetophenone for subsequent Claisen-Schmidt condensation reaction. To a solution of 3'-iodo-2',4'-dimethoxyacetophenone in ethanol (200 ml) was added 4-methoxybenzaldehyde (1.2 ml, 0.01 mol) and 50% aq KOH (10 ml). The red-yellowish mixture was stirred at rt for 24 h. Afterwards, the mixture was poured into ice-water acidified with 3 N HCl and extracted three times with ethyl acetate. The organic phases were combined, washed with water, dried on Mg₂SO₄, and evaporated. The residue was subjected to column chromatography (hexane:EtOAc=4:1) to give chalcone **6-7** as a yellow solid (3.60 g, 85% over two steps). ¹H NMR (400 MHz, CDCl₃): δ 7.68 (d, 8.5, 1H), 7.67 (d, *J*=16.3, 1H), 7.53 (d, *J*=8.8, 2H), 7.39 (d, *J*=15.8, 1H), 6.87 (d, *J*=8.8, 2H), 6.65 (d, *J*=8.5, 1H), 3.89, 3.78, 3.74 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 190.49, 162.39, 161.75, 160.59, 143.99, 132.52, 130.43, 127.72, 127.20, 123.43, 114.47, 106.97, 85.16, 62.88, 56.97, 55.51; m.p.= 95.

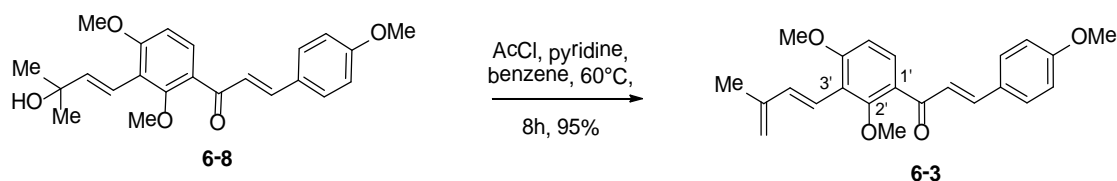
2',4,4'-trimethoxy-3'-[(1E)-3-hydroxy-3-methylbut-1-en-1-yl]chalcone **6-8**



A mixture of 424 mg (1.00 mmol) of chalcone **6-7**, 430 mg (5 mmol) of 2-methyl-3-buten-2-ol, 170 μL (1.25 mmol) of Et₃N, 11 mg (0.049 mmol) of Pd(OAc)₂, and 61 mg (0.20 mmol) of tri-*ortho*-tolylphosphine in 4 mL dry DMF was flushed with nitrogen and then heated to 90 °C for 18 h. Afterwards 30 mL of dichloromethane were added, and the reaction mixture was washed with H₂O (3 x 10 mL). The organic layer was dried over MgSO₄, filtered and concentrated under vacuum. The residue was purified by column chromatography (hexane:EtOAc=4:1), affording 287 mg of **6-8** as a yellow oil (75% yield). ¹H NMR (400 MHz, CDCl₃): δ 7.62 (d, 15.8, 1H), 7.53 (d, 8.7, 2H),

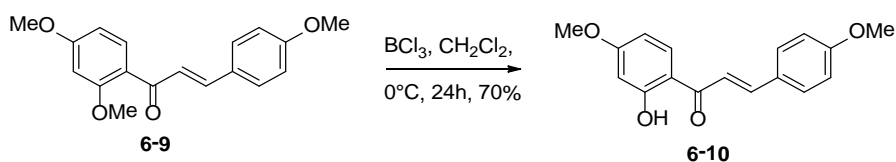
7.50 (d, 8.2, 1H), 7.34 (d, 15.8, 1H), 6.77 (d, 16.0, 1H), 6.86 (d, 8.5, 2H), 6.69 (d, 15.8, 1H), 6.70 (d, 8.0, 1H), 3.85, 3.78, 3.63 (s, 3H each), 1.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 191.72, 161.38, 161.05, 158.68, 143.14, 143.07, 130.04, 129.93, 127.65, 126.80, 124.18, 119.37, 115.86, 114.23, 106.71, 71.33, 62.99, 55.71, 55.21, 29.74; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{27}\text{O}_5$ $[\text{M}+\text{H}]^+ = 383.1853$. Found 383.1845

2',4,4'-trimethoxy-3'-[(1E)-3-methylbut-1,3-dien-1-yl]chalcone **6-3**



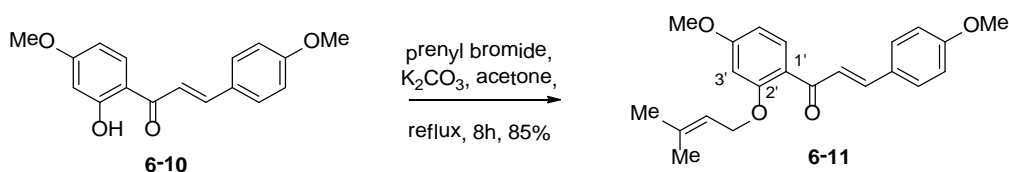
A mixture of 248 mg (0.65 mmol) of **6-8**, 65 μL (0.90 mmol, 1.35 equiv) of acetyl chloride, and 70 μL (2.6 mmol, 1.3 equiv) of pyridine in 10 mL benzene was heated to 60 $^\circ\text{C}$ for 8 h. Then, 10 mL of 5% aqueous NaHCO_3 were poured into the reaction mixture. The aqueous layer was extracted with hexane (30 mL) and the organic layer was washed with brine and dried over MgSO_4 . After evaporation of the solvents, the residue was purified by column chromatography (hexane:EtOAc=4:1), affording 346 mg of diene **6-3** (95% yield) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 7.59 (d, 15.8, 1H), 7.49 (dd, 8.8, 1.7, 2H), 7.49 (d, 8.2, 1H), 7.32 (d, 15.8, 1H), 7.27 (d, 16.6, 1H), 6.83 (d, 8.5, 2H), 6.69 (d, 16.6, 1H), 6.68 (d, 8.3, 1H), 5.05 (s, 1H), 5.03 (s, 1H), 3.85, 3.76, 3.63 (s, 3H each), 1.94 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 191.84, 161.44, 161.20, 158.86, 143.20, 136.98, 130.15, 130.00, 127.82, 126.96, 124.31, 119.90, 119.07, 117.45, 114.33, 106.80, 62.33, 55.89, 55.35, 18.25; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{25}\text{O}_4$ $[\text{M}+\text{H}]^+ = 365.1747$ Found 365.1745

2'-hydroxy-4,4'-dimethoxychalcone **6-10**



To a solution of chalcone **6-9** (1.49 g, 5 mmol) in CH_2Cl_2 (100 mL) at 0°C was added boron trichloride (5 mL, 1.0 M in CH_2Cl_2). The reaction mixture was stirred for 24 h before addition of methanol (20 mL). The mixture was then poured into ice-water acidified and extracted three times with CH_2Cl_2 . The organic phases were combined, dried on Mg_2SO_4 , and evaporated. The residue was subjected to column chromatography (hexane:EtOAc=4:1) to give chalcone **6-10** as a yellow solid (1.0 g, 70%). ^1H NMR (270 MHz, CDCl_3): δ 13.49 (s, 1H), 7.64 (d, $J=15.1$, 1H), 7.61 (d, $J=7.9$, 1H), 7.38 (d, $J=8.6$, 2H), 7.23 (d, $J=15.1$, 1H), 6.73 (d, $J=8.6$, 2H), 6.31 (d, $J=7.8$, 1H), 6.28 (d, $J=2.4$, 1H), 3.64, 3.63 (s, 3H each); ^{13}C NMR (67.9 MHz, CDCl_3): δ 191.49, 166.32, 165.73, 161.53, 143.94, 130.92, 130.13, 127.15, 117.33, 114.16, 113.86, 107.21, 100.84, 55.22, 55.07; m.p = 110°C .

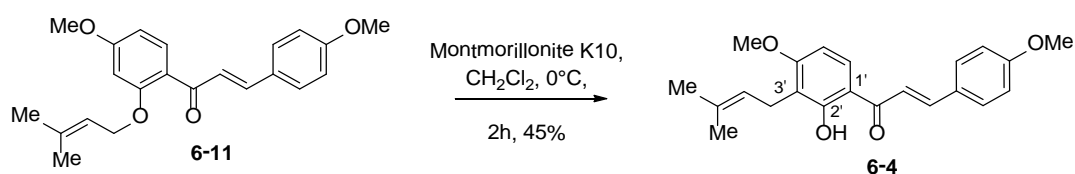
2'-prenyloxy-4,4'-dimethoxychalcone **6-11**



To a solution of chalcone **6-10** (284 mg, 1 mmol) in acetone (20 mL) was added K_2CO_3 (277 mg, 2 mmol) and prenyl bromide (298 mg, 2 mmol). The reaction mixture was heated under reflux for 8 h before the addition of water and CH_2Cl_2 . The aqueous phase was extracted with CH_2Cl_2 (2x). The organic layers were collected, washed with brine, dried over MgSO_4 and concentrated. The crude residue was purified by column chromatography (hexane:EtOAc=4:1) to provide chalcone **6-11** (299 mg, 85%) as a

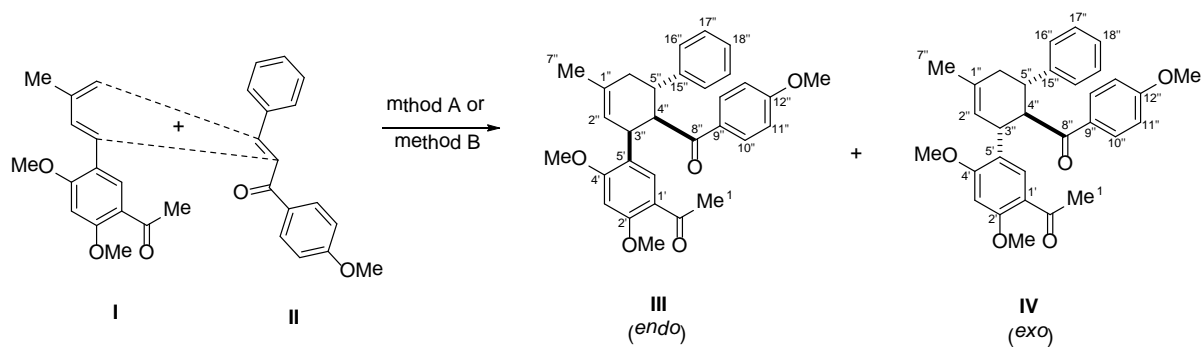
yellow amorphous. ^1H NMR (400 MHz, CDCl_3): δ 7.59 (d, 15.8, 1H), 7.50 (d, 8.8, 2H), 7.49 (d, 8.2, 1H), 7.32 (d, 15.8, 1H), 7.27 (d, 16.6, 1H), 6.83 (d, 8.5, 2H), 6.69 (d, 16.6, 1H), 6.68 (d, 8.3, 1H), 5.05 (s, 1H), 5.03 (s, 1H), 3.85, 3.76, 3.63 (s, 3H each), 1.94 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 191.84, 161.44, 161.20, 158.86, 143.20, 136.98, 130.15, 130.00, 127.82, 126.96, 124.31, 119.90, 119.07, 117.45, 114.33, 106.80, 62.33, 55.89, 55.35, 18.25; HRMS (ESI) calcd for $\text{C}_{23}\text{H}_{25}\text{O}_4$ $[\text{M}+\text{H}]^+ = 365.1747$ Found 353.1746

2'-hydroxy-3'-prenyl-4,4'-dimethoxychalcone **6-4**



To a solution of chalcone **6-11** (352 mg, 1 mmol) at 0°C in CH_2Cl_2 (20 mL) was added Montmorillonite K10 (352 mg, 1 weight equiv). The reaction mixture was stirred for 8 h before filtered through celite. The organic layers were collected and concentrated. The crude residue was purified by column chromatography (hexane:EtOAc=4:1) to provide chalcone **6-4** (158 mg, 45%) as a yellow amorphous. C5'-prenylated chalcone was also isolated in 40% yield. ^1H NMR (270 MHz, CDCl_3): δ 13.51 (s, 1H), 7.83 (d, 15.4, 1H), 7.77 (d, 9.2, 1H), 7.58 (d, 8.6, 2H), 7.45 (d, 15.5, 1H), 6.91 (d, 8.6, 2H), 6.46 (d, 8.9, 1H), 5.24 (t, 6.7, 1H), 3.88, 3.83 (s, 3H each), 3.38 (d, 7.0, 2H), 1.79, 1.68 (s, 3H each); ^{13}C NMR (67.9 MHz, CDCl_3): δ 192.16, 163.09, 162.92, 161.63, 143.89, 131.77, 130.23, 129.03, 127.50, 122.03, 117.96, 117.39, 114.58, 114.35, 101.96, 55.67, 55.32, 25.76, 21.66, 17.76.

Model study of the [4+2] cycloaddition reaction using diene I and dienophile II



Preparation of cycloadducts III (*endo*) and IV (*exo*)

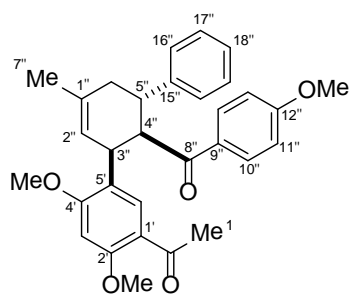
Method A: thermal condition.

To a screw-capped pressure tube (Ace Glass Inc, USA) equipped with a magnetic stirrer was added the corresponding diene **I** (246 mg, 1 mmol), dienophile **II** (238mg, 1 mmol), and dry toluene (5 mL). The resulting mixture was heated at the 160°C and left under magnetic stirring for 18h. After silica-gel column chromatography of the final mixture cycloadducts **III** and **IV** were isolated (290 mg, 60%).

Method B: catalytic cycloaddition.

To a screw-capped pressure tube (Ace Glass Inc, USA) equipped with a magnetic stirrer was added ZnI_2 (0.06 mmol, 60 mol%), Bu_4NBH_4 (0.01 mmol, 10 mol%), diene **I** (25 mg, 0.1 mmol), dienophile **II** (24 mg, 0.1 mmol), and dry CH_2Cl_2 (3 mL) in a N_2 glove bag (SigmaAldrich). The resulting mixture was heated at the 60°C and left under magnetic stirring for 18h. After silica-gel column chromatography of the final mixture cycloadducts **III** and **IV** were isolated (yield 30 mg, 62%).

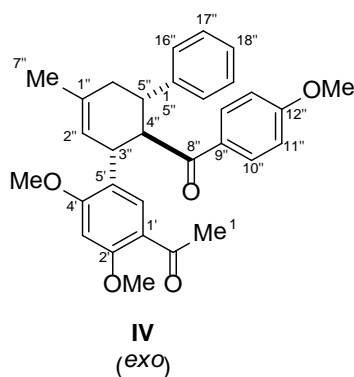
[(1S,2S,6S)-2-(5-acetyl-2,4-dimethoxyphenyl)-4-methyl-6-phenylcyclohex-3-en-1-yl](4-methoxyphenyl)methanone (III)



III
(*endo*)

Pale white solid; ^1H NMR (400 MHz, CDCl_3): δ 7.71 (s, 1H, H6'), 7.74 (d, 8.5, 2H, H11'',13''), 6.88-6.98 (m, 5H, H17''-19''), 6.79 (d, 8.5, 2H, H10'',14''), 6.09 (s, 1H, H3'), 5.40 (bs, 1H, H2''), 4.24 (bs, 1H, H3''), 4.23 (t, 5.3, 1H, H4''), 3.76, 2.96 (s, 3H each, OCH_3), 3.14 (ddd, 11.5,11.2,5.6, 1H, H5''), 2.52 (s, 3H, COCH_3), 2.22, 2.43 (m, 1H each, H6''), 1.78 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3): δ 198.32 (C8''), 198.14 (C=O), 161.98 (C12''), 162.67 (C4'), 160.62 (C2'), 145.30 (C15''), 135.92 (C1''), 132.24 (C9''), 133.31 (C6'), 129.67 (C10'',14''), 128.17 (C16'',20''), 127.54 (C17'',19''), 125.83 (C18''), 121.14 (C5'), 122.03 (C2''), 119.52 (C1'), 113.40 (C11'',13''), 93.69 (C3'), 55.44, 54.29 (C- OCH_3), 50.29 (C4''), 38.12 (C5''), 37.18 (C3''), 40.56 (C6''), 32.28 (- $\text{CO}(\text{CH}_3)$), 23.33 (C7''); m.p. 185°C; HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{33}\text{O}_5$ $[\text{M}+\text{H}]^+ = 485.2323$. Found 485.2325

[(1*S*,2*R*,6*S*)-2-(5-acetyl-2,4-dimethoxyphenyl)-4-methyl-6-phenylcyclohex-3-en-1-yl](4-methoxyphenyl)methanone (IV)



Pale white solid; ^1H NMR (400 MHz, CDCl_3): δ 7.78 (s, 1H, H6'), 7.22 (d, 8.7, 2H, H11'',13''), 7.07 (d, 7.3, 2H, H16'',20''), 7.00 (t, 7.8, 2H, H17'',19''), 6.91 (m, 1H, H18''), 6.44 (d, 8.5, 2H, H10'',14''), 5.91 (s, 1H, H3'), 5.26 (bs, 1H, H2''), 4.18 (bd, 10, 1H, H3''), 3.76 (t, 11, 1H, H4''), 3.68, 3.62, 3.44 (s, 3H each, OCH_3), 3.39 (ddd, 11.2,11.2,5.3, 1H, H5''), 2.48 (s, 3H, COCH_3), 2.26, 2.41 (m, 1H each, H6''), 1.71 (s, 3H, CH_3); ^{13}C NMR (100 MHz, CDCl_3): δ 202.12 (C8''), 197.99 (C=O), 162.54 (C12''), 161.69 (C4'), 160.11 (C2'), 143.99 (C15''), 134.29 (C1''), 131.59 (C9''), 130.96 (C6'), 130.04 (C10'',14''), 128.25 (C16'',20''), 127.72 (C17'',19''), 126.21 (C18''), 125.15 (C5'), 124.52 (C2''), 120.24 (C1'), 112.78 (C11'',13''), 94.03 (C3'), 55.42, 55.14 (C- OCH_3), 53.44 (C4''), 44.66 (C5''), 39.66 (C3''), 39.01 (C6''), 32.12 ($-\text{CO}(\text{CH}_3)$), 23.45 (C7''); m.p. 180°C HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{33}\text{O}_5$ $[\text{M}+\text{H}]^+ = 485.2323$. Found 485.2320

Preparation of pentamethyl ethers of kuwanon V (6-1a) and dorsterone (6-2a)

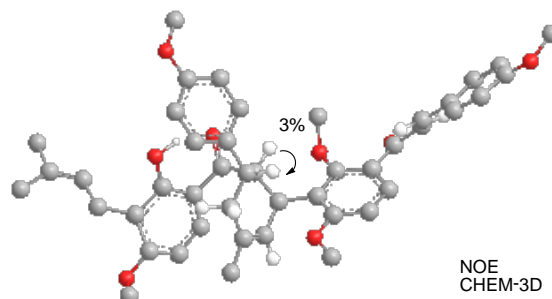
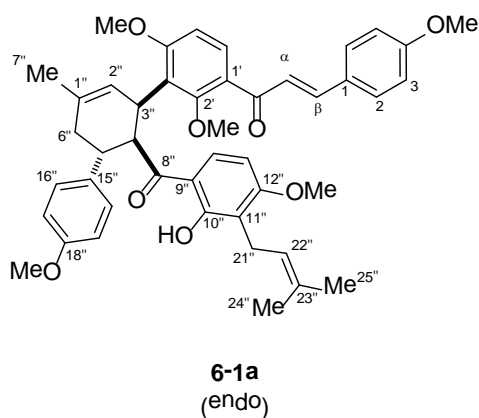
Method A: thermal condition.

To a screw-capped pressure tube (Ace Glass Inc, USA) equipped with a magnetic stirrer was added the corresponding diene **6-3** (38 mg, 0.1 mmol), dienophile **6-4** (40 mg, 0.1 mmol), and dry toluene (2 mL). The resulting mixture was heated at the 160°C and left under magnetic stirring for 18h. After silica-gel column chromatography of the final mixture cycloadducts **6-1a** and **6-2a** were isolated (yield 39 mg, 55%).

Method B: catalytic cycloaddition.

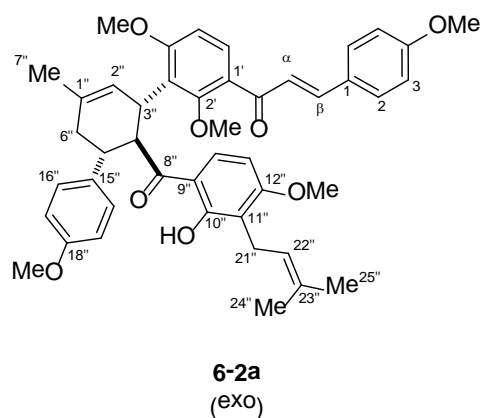
To a screw-capped pressure tube (Ace Glass Inc, USA) equipped with a magnetic stirrer was added AgOTf (0.06 mmol, 60 mol%), Bu₄NBH₄ (0.01 mmol, 10 mol%), diene **6-3** (36 mg, 0.1 mmol), dienophile **6-4** (35 mg, 0.1 mmol), and dry CH₂Cl₂ (5 mL) in a N₂ glove bag (SigmaAldrich). The resulting mixture was heated at the 60°C and left under magnetic stirring for 18h. After silica-gel column chromatography of the final mixture cycloadducts **6-1a** and **6-2a** were isolated (yield 44 mg, 65%).

(±)-kuwanon V pentamethyl ether 6-1a



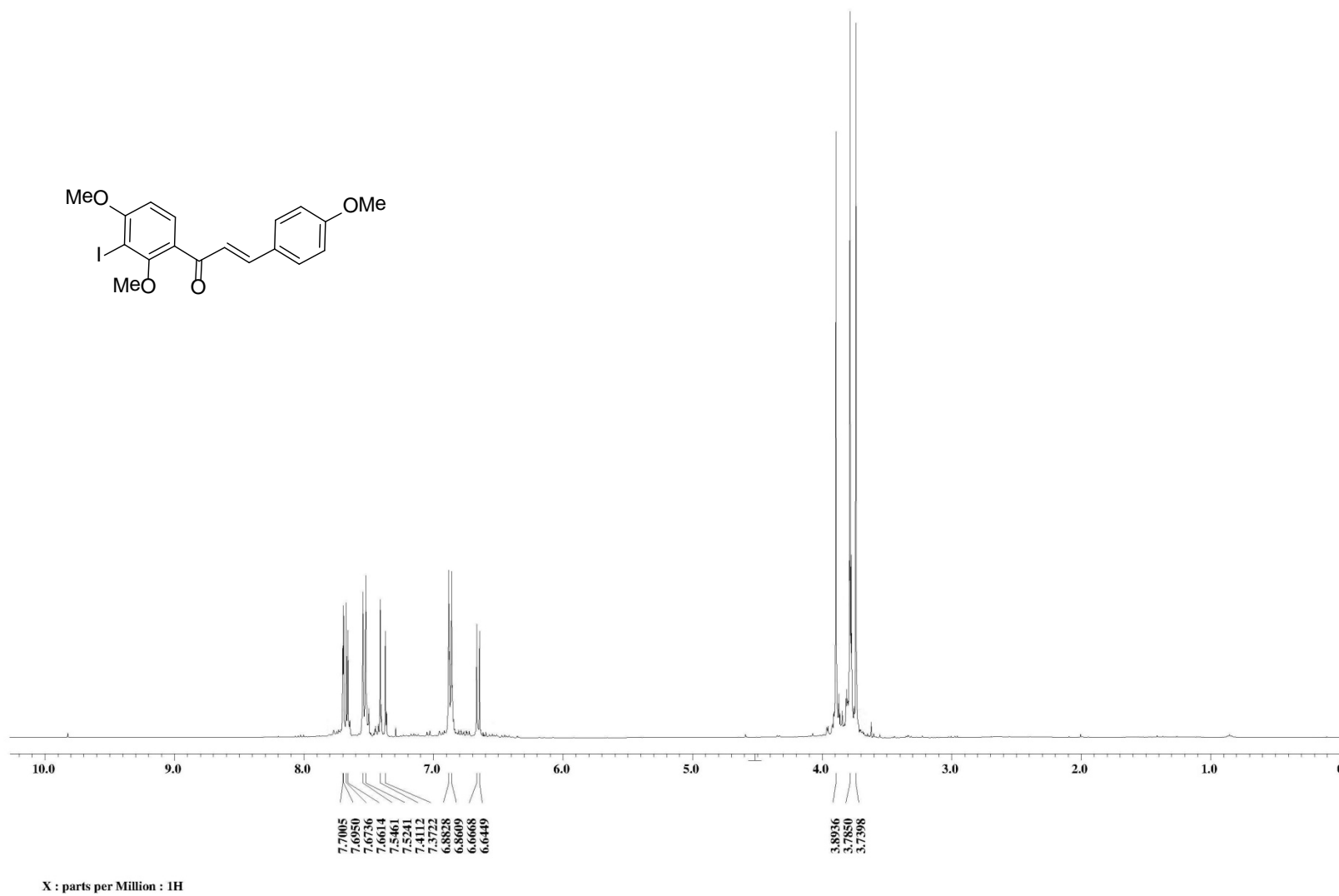
Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 12.54 (s, 1H, OH), 7.80 (d, 8.6, 1H, H14"), 7.66 (d, 16.0, 1H, H_β), 7.63 (d, 8.6, 2H, H2,6), 7.32 (d, 8.6, 1H, H6'), 7.07 (d, 8.6, 2H, H16", 20"), 7.03 (d, 16.3, 1H, H_α), 6.93 (d, 8.6, 2H, H3,5), 6.70 (d, 8.1, 2H, H17",19"), 6.44 (d, 8.6, 1H, H5')*, 6.44 (d, 8.6, 1H, H13")*, 5.49 (bs, 1H, H2"), 5.05 (t, 6.8, 1H, H22"), 4.60 (bs, 1H, H3"), 4.31 (t, 9.6, 6.8, 1H, H4"), 3.97 (ddd, 10.8, 10.8, 5.7, 1H, H5"), 3.87, 3.86, 3.72, 3.46 (s, OMe), 3.21 (bd, 5.9, 1H, H21"), 2.40, 2.19 (m, 2H, H6"), 1.78 (s, 3H, H7"), 1.67 (s, 3H, H24"), 1.58 (s, 3H, H25"); NOE_Diff (400 MHz, CDCl_3) Irradiation at δ 4.31 (H4") gave 3% enhancement at H3" while H5" collapsed to doublet of doublet ($J = 10.8, 5.7$ Hz); ^{13}C NMR (100 MHz, CDCl_3): δ 205.87 (C8"), 195.40 (C=O), 162.52 (C10"), 161.63 (C2')*, 161.63 (C4)*, 161.63 (C12")*, 160.02 (C4'), 157.73 (C18"), 138.41 (C1"), 133.29 (C15")*, 133.29 (C3')*, 131.73 (C23"), 130.63 (C2,6), 130.29 (C6'), 129.54 (C_β)*, 129.54 (C14")*, 128.52 (C16",20"), 128.01 (C1), 126.71 (C9"), 124.25 (C_α), 122.20 (C2"), 122.11 (C22"), 116.89 (C11"), 115.52 (C1'), 114.41 (C3), 113.74 (C17",19"), 105.99 (C5'), 101.51 (C13"), 62.72, 54.99, 55.49, 55.81, 54.99 (C-OMe), 50.30 (C4"), 39.79 (C6"), 37.46 (C5"), 35.18 (C3"), 25.83 (C25"), 23.70 (C7"), 21.59 (C21"), 17.86 (C24"). *chemical shift overlapped. HRMS (ESI) calcd for $\text{C}_{45}\text{H}_{49}\text{O}_8$ $[\text{M}+\text{H}]^+ = 717.3422$. Found 717.3421

(±)-dorsterone pentamethyl ether 6-2a

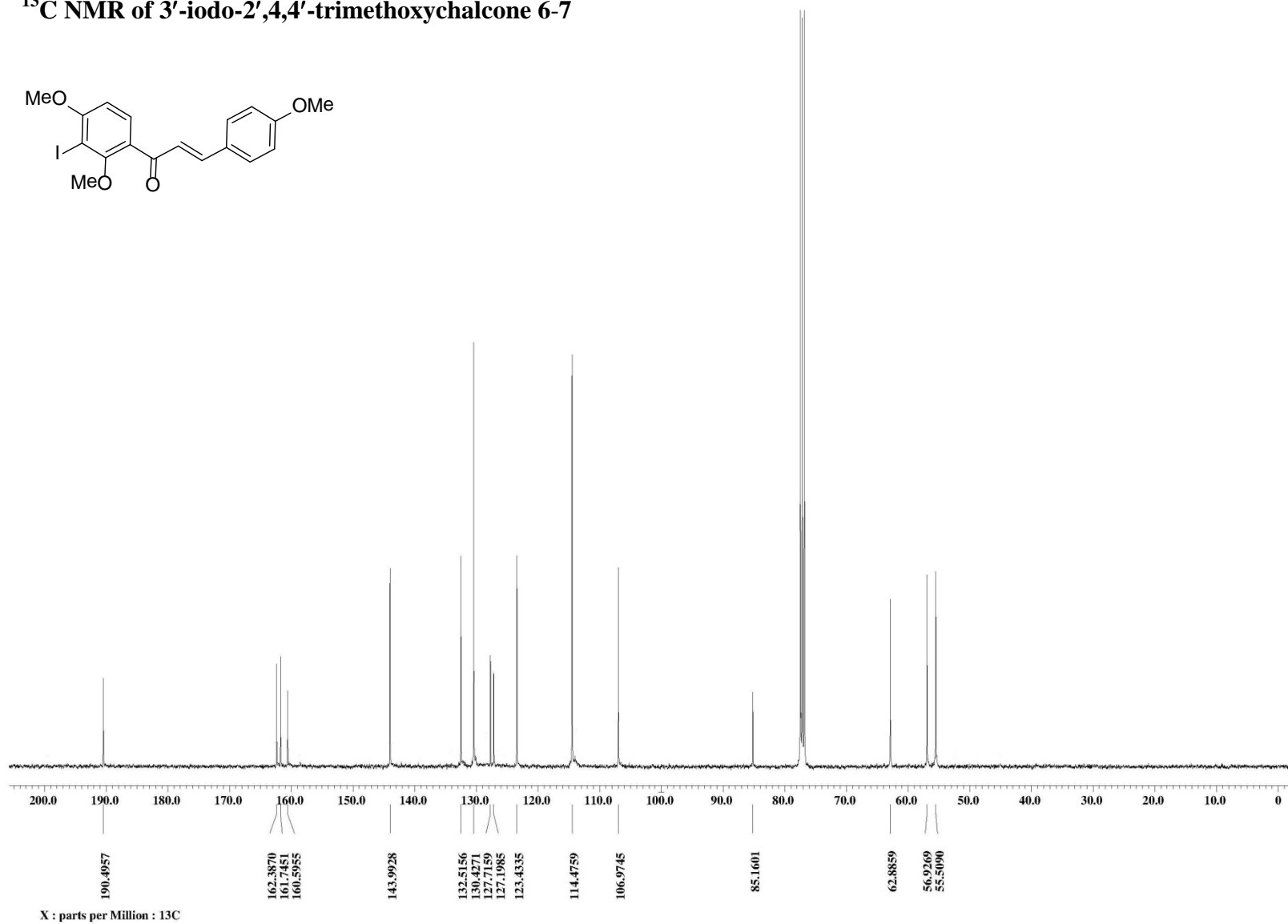


Yellow oil; ^1H NMR (400 MHz, CDCl_3): δ 12.80 (s, 1H, OH), 7.70 (d, 8.6, 1H, H14''), 7.57 (d, 16.0, 1H, H $_{\beta}$), 7.52 (d, 8.6, 2H, H2,6), 7.38 (d, 8.6, 1H, H6'), 7.15 (d, 8.6, 2H, H16'', 20''), 7.18 (d, 16.3, 1H, H $_{\alpha}$), 6.97 (d, 8.6, 2H, H3,5), 6.71 (d, 8.1, 2H, H17'',19''), 6.36 (d, 8.6, 1H, H5'), 6.07 (d, 8.6, 1H, H13''), 5.37 (bs, 1H, H2''), 5.00 (t, 6.8, 1H, H22''), 4.51 (bs, 1H, H3''), 4.55 (t, 9.99, 1H, H4''), 3.95 (m, 1H, H5'')*, 3.97, 3.85, 3.75, 3.67, 3.51 (s, OMe), 3.11 (bd, 7.0, 1H, H21''), 2.41, 2.32 (m, 2H, H6''), 1.77 (s, 3H, H7''), 1.67 (s, 3H, H24''), 1.60 (s, 3H, H25''); ^{13}C NMR (100 MHz, CDCl_3): δ 208.15 (C8''), 191.87 (C=O), 162.42 (C10''), 161.54 (C2''), 161.34 (C4'')*, 161.34 (C4'')*, 160.55 (C12''), 157.77 (C18''), 136.18 (C1''), 132.08 (C15''), 131.56 (C3''), 130.82 (C23''), 130.02 (C2,6), 128.71 (C6'), 143.33 (C $_{\beta}$), 129.57 (C14''), 128.34 (C16'',20''), 127.59 (C1), 126.34 (C9''), 124.69 (C $_{\alpha}$), 123.67 (C2''), 122.15 (C22''), 116.32 (C11''), 115.77 (C1'), 114.40 (C3), 113.65 (C17'',19''), 105.84 (C5'), 101.06 (C13''), 63.18, 55.79, 55.33, 55.25, 54.98 (C-OMe), 49.24 (C4''), 39.25 (C6''), 38.63 (C5''), 36.55 (C3''), 25.65 (C25''), 23.65 (C7''), 21.35 (C21''), 17.59 (C24''). *chemical shift overlapped. HRMS (ESI) calcd for $\text{C}_{45}\text{H}_{49}\text{O}_8$ $[\text{M}+\text{H}]^+ = 717.3422$. Found 717.3423

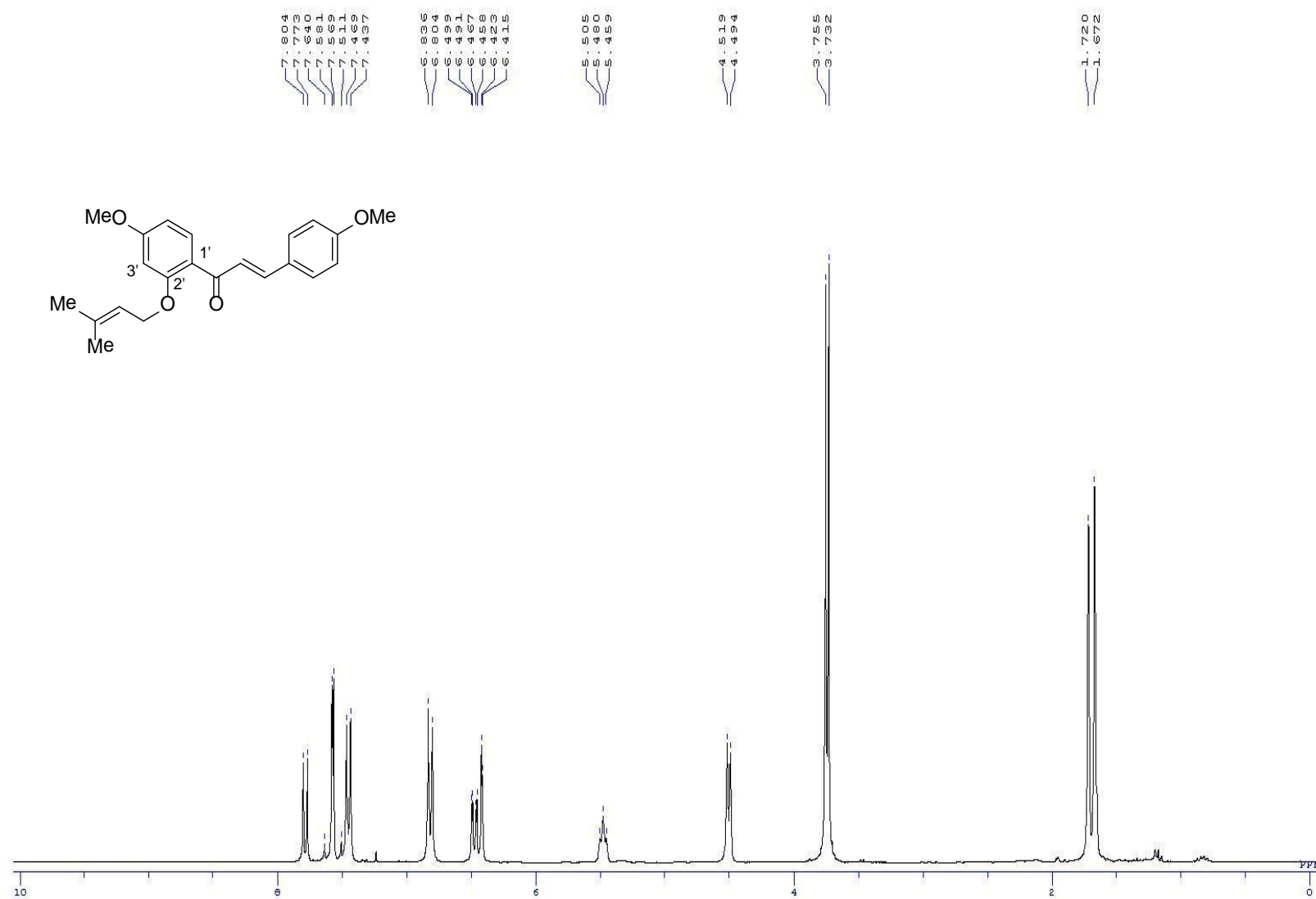
^1H NMR of 3'-iodo-2',4,4'-trimethoxychalcone 6-7



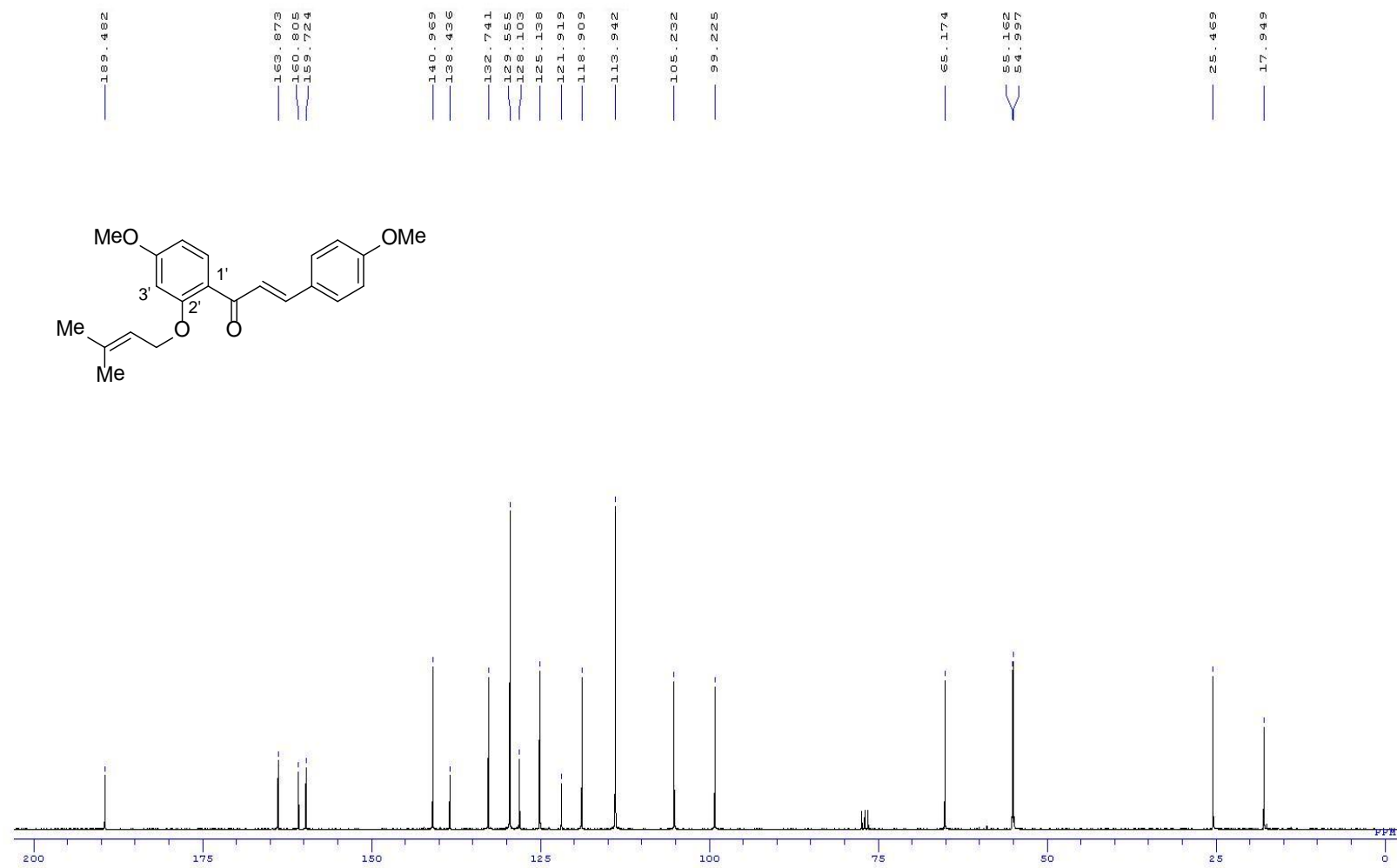
^{13}C NMR of 3'-iodo-2',4,4'-trimethoxychalcone 6-7



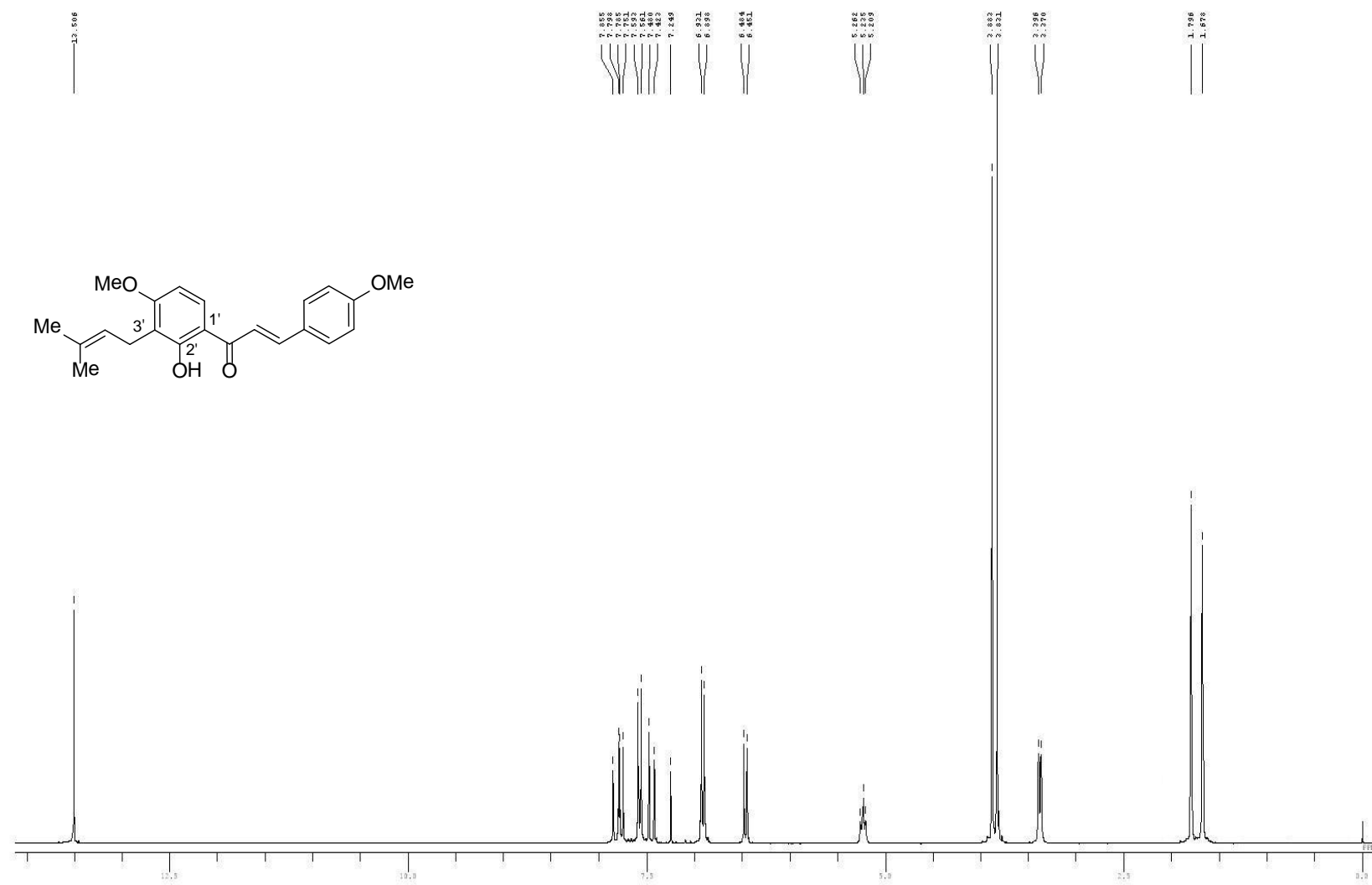
^1H NMR of 2'-prenyloxy-4,4'-dimethoxychalcone 6-11



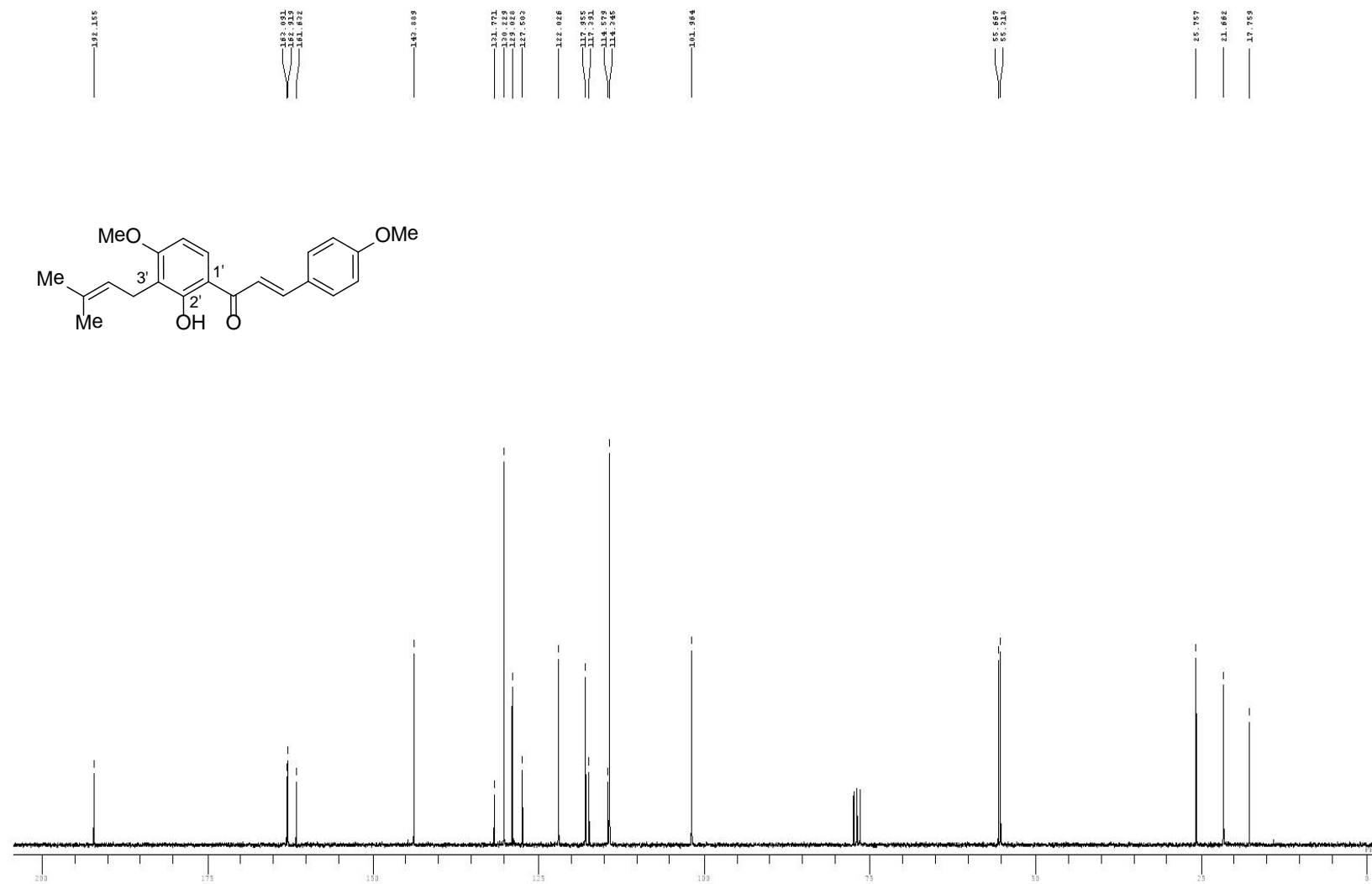
¹³C NMR of 2'-prenyloxy-4,4'-dimethoxychalcone 6-11



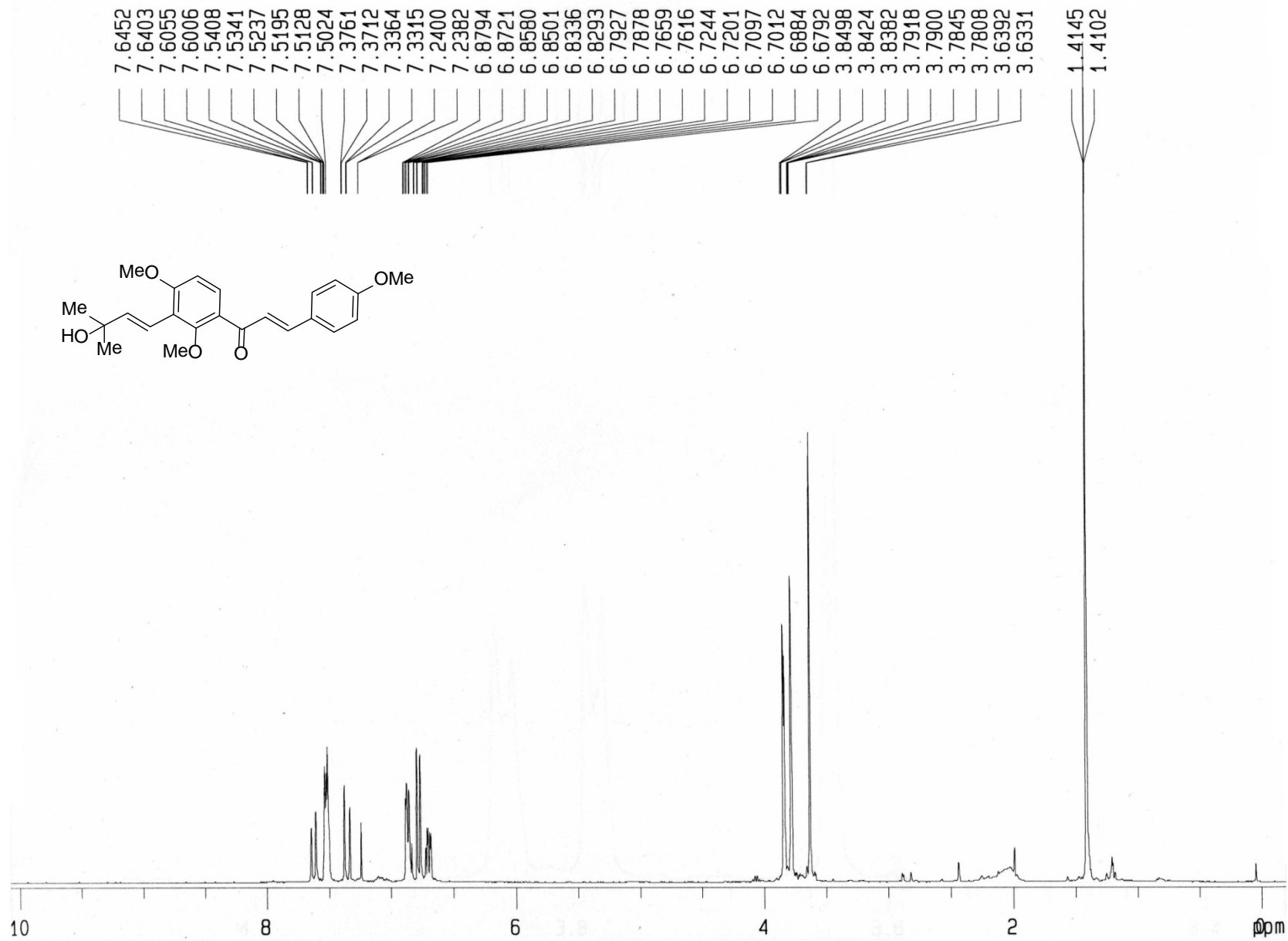
¹H NMR of 2'-hydroxy-3'-prenyl-4,4'-dimethoxychalcone 6-4



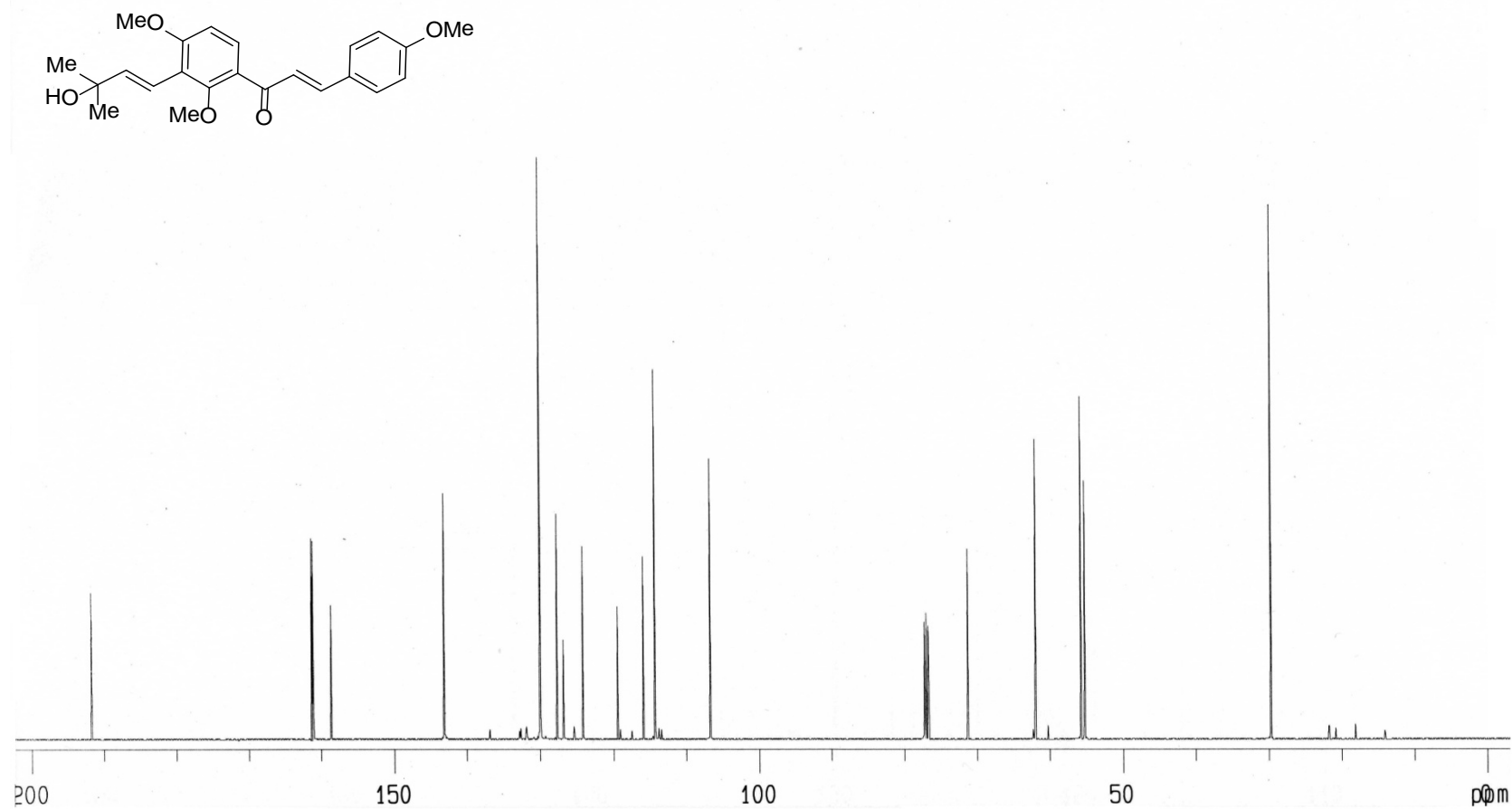
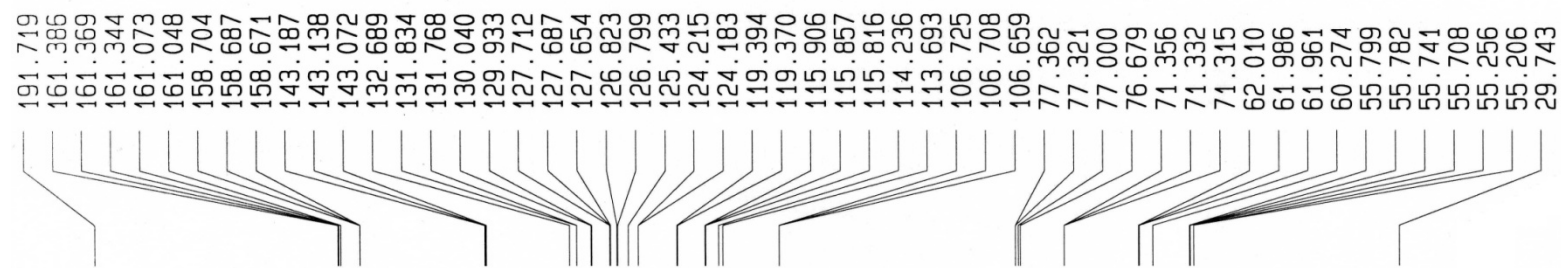
^{13}C NMR of 2'-hydroxy-3'-prenyl-4,4'-dimethoxychalcone 6-4



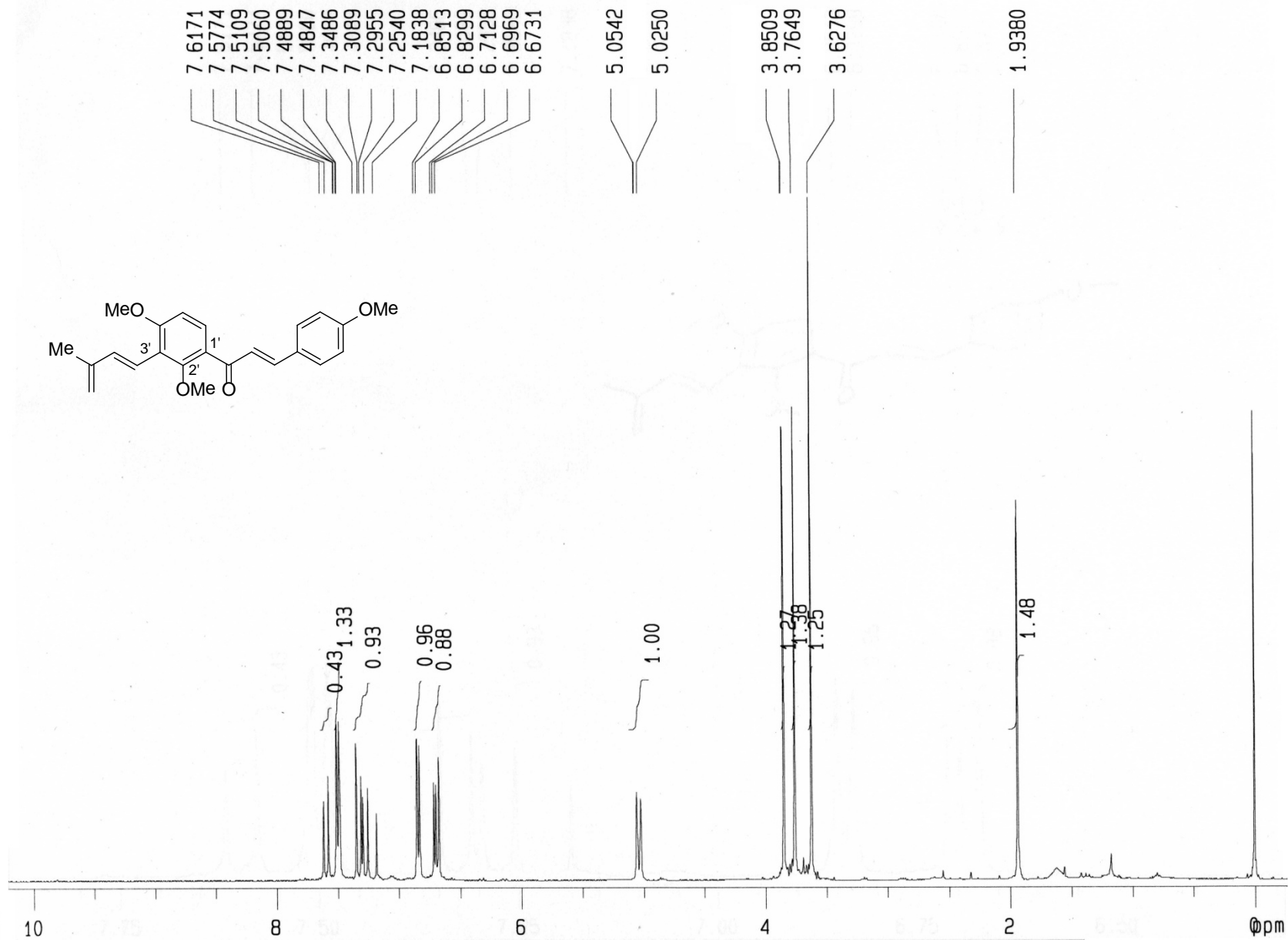
¹H NMR of 2',4,4'-trimethoxy-3'-[(1E)-3-hydroxy-3-methylbut-1-en-1-yl]chalcone 6-8



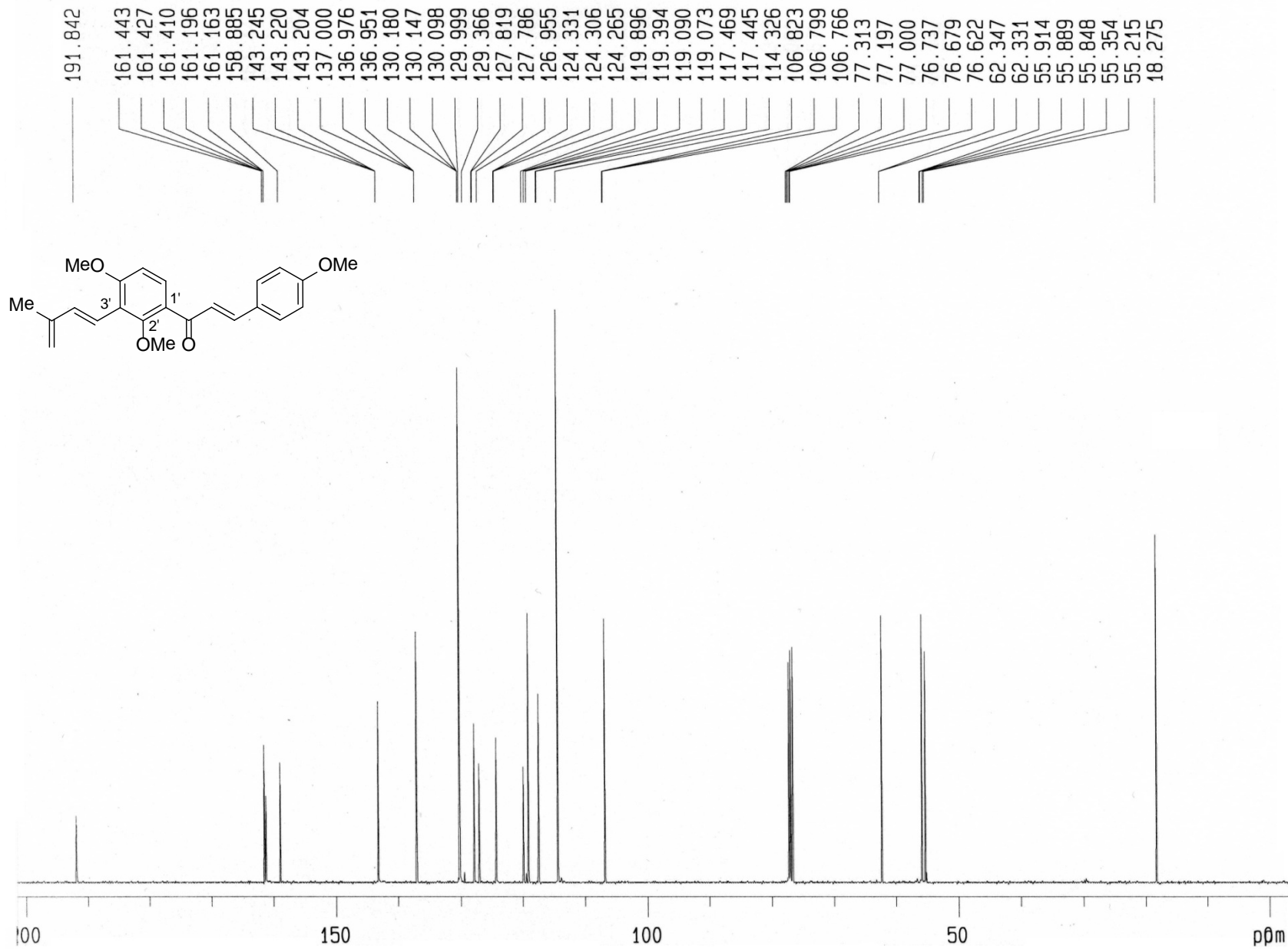
^{13}C NMR of 2',4,4'-trimethoxy-3'-[(1E)-3-hydroxy-3-methylbut-1-en-1-yl]chalcone 6-8



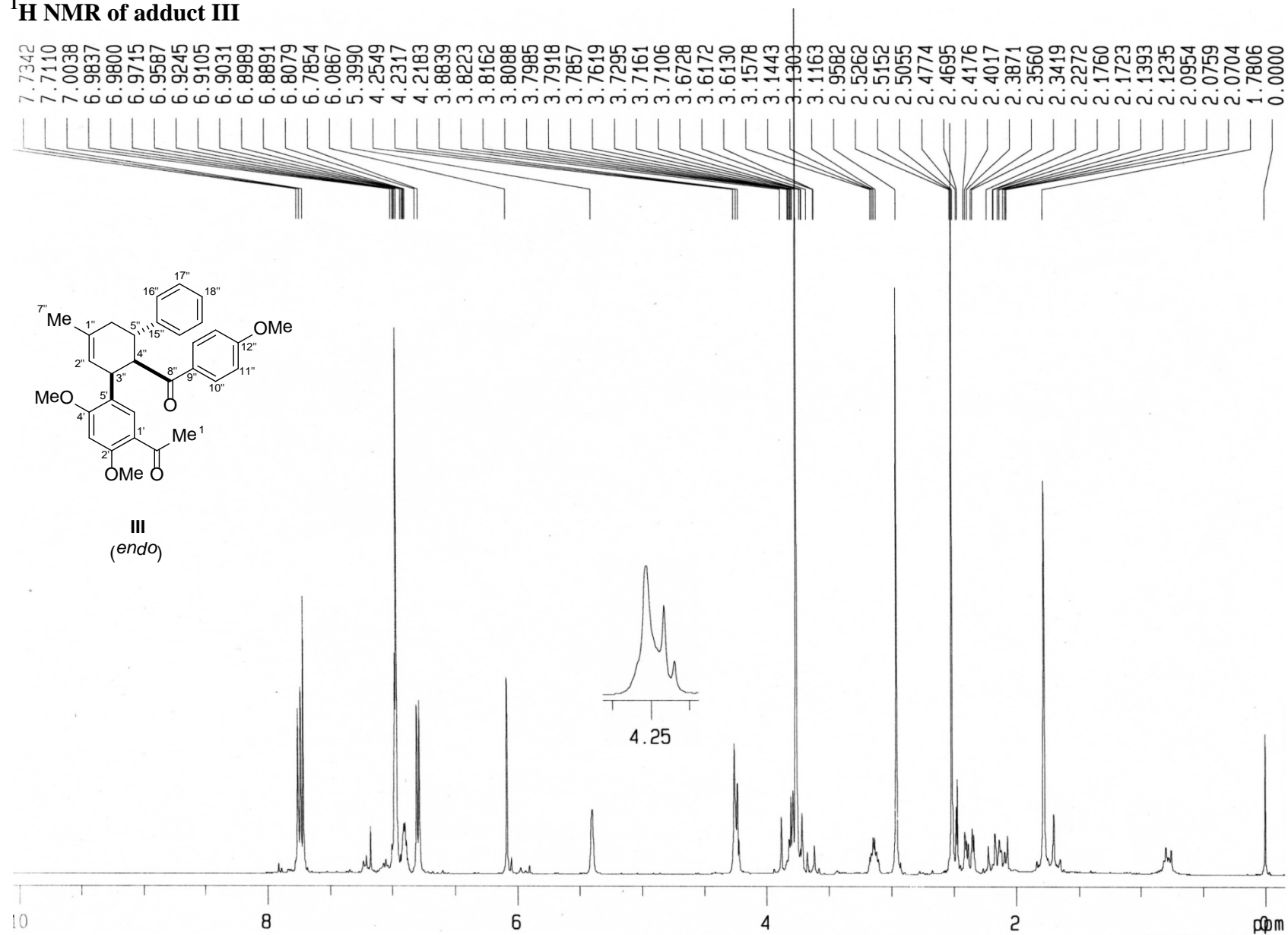
¹H NMR of 2',4,4'-trimethoxy-3'-[(1E)-3-methylbut-1,3-dien-1-yl]chalcone 6-3



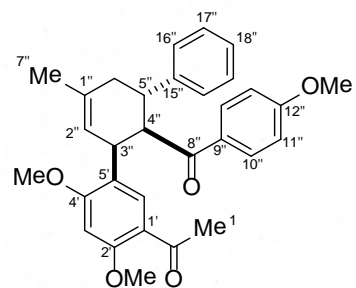
^{13}C NMR of 2',4,4'-trimethoxy-3'-[(1E)-3-methylbut-1,3-dien-1-yl]chalcone 6-3



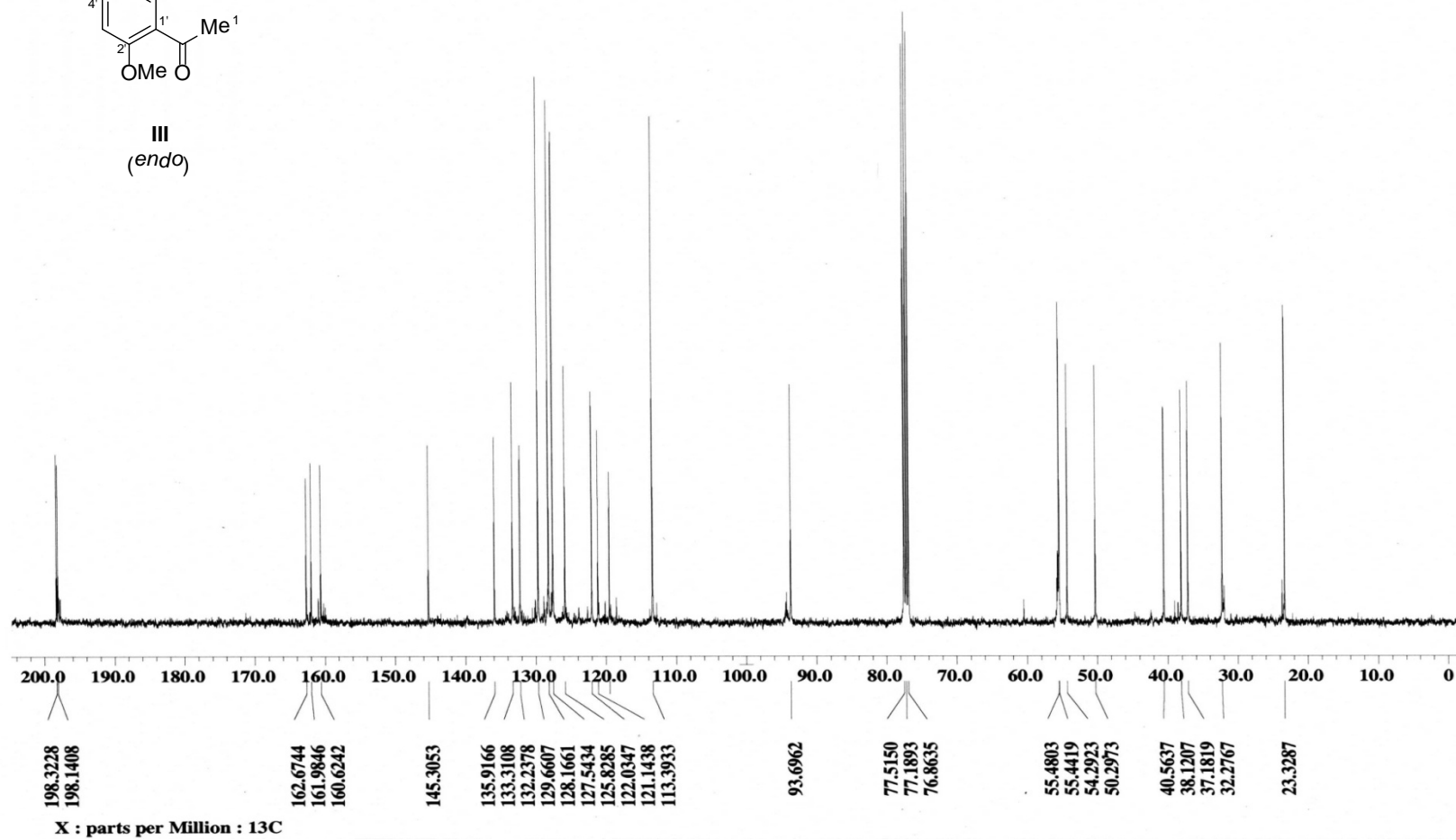
¹H NMR of adduct III



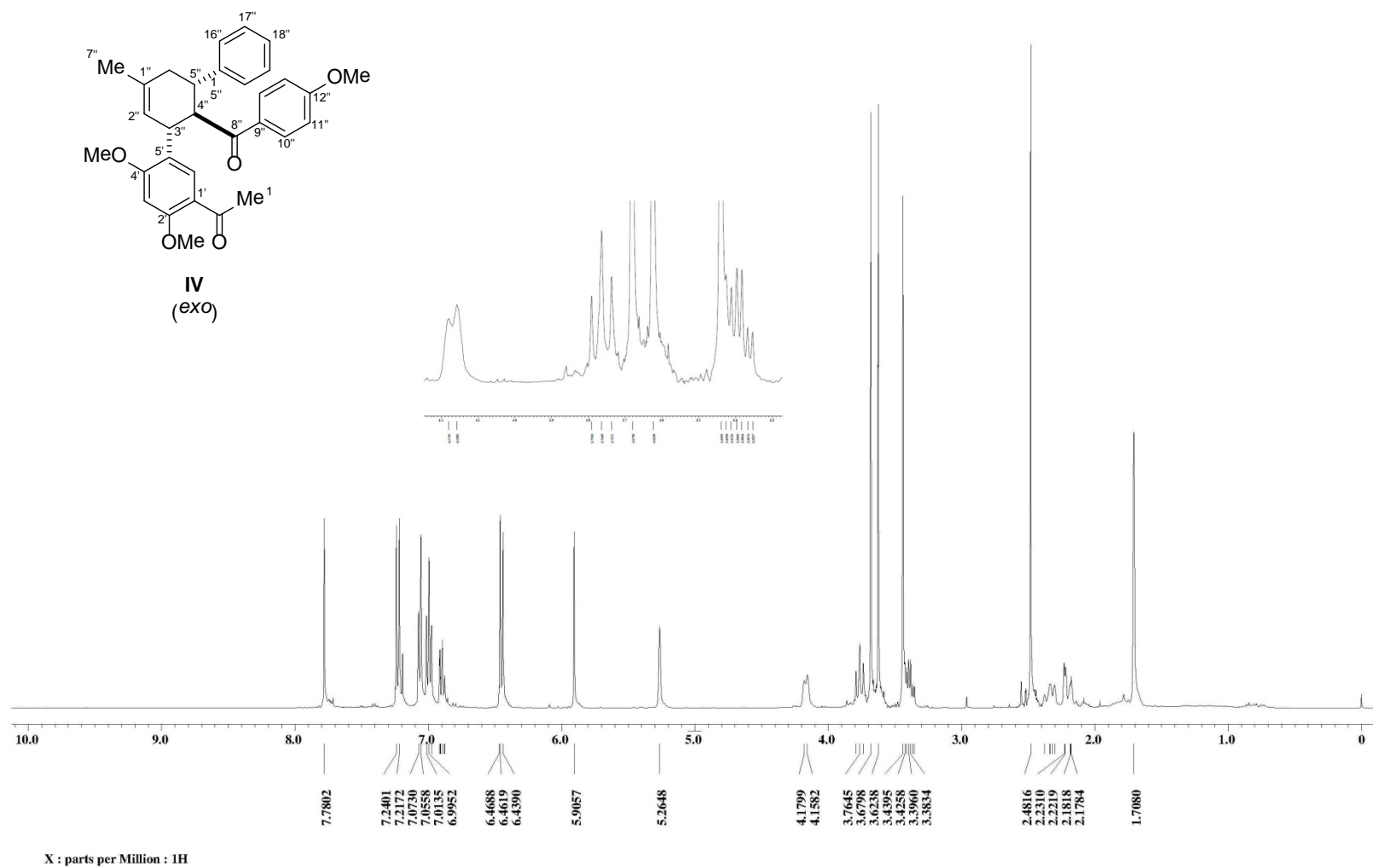
^{13}C NMR of adduct IV



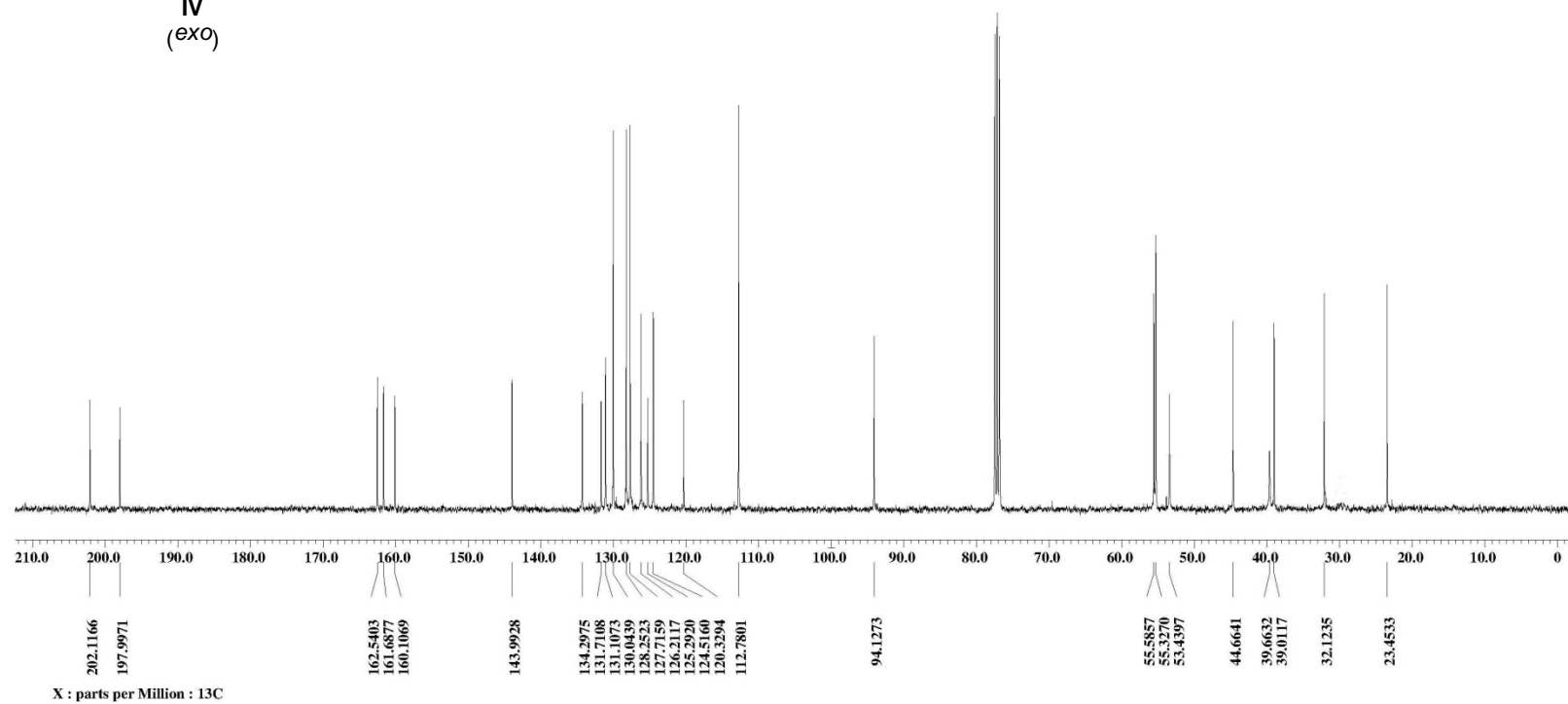
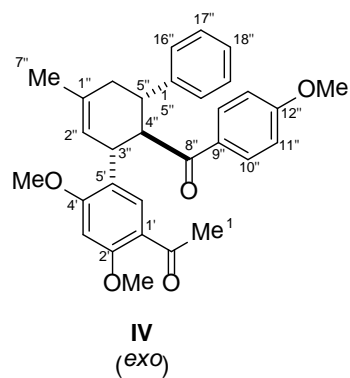
III
(endo)



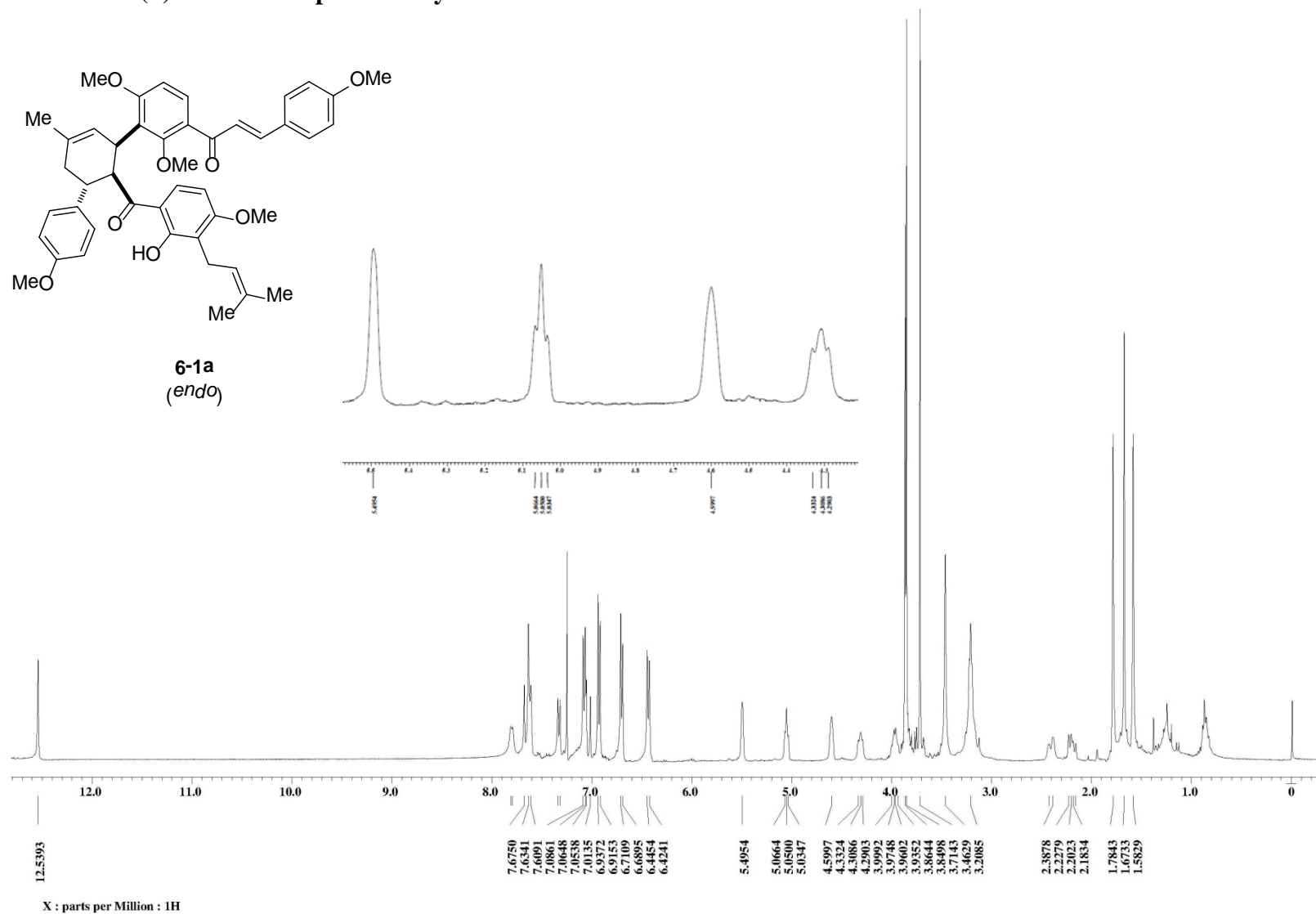
¹H NMR of adduct IV



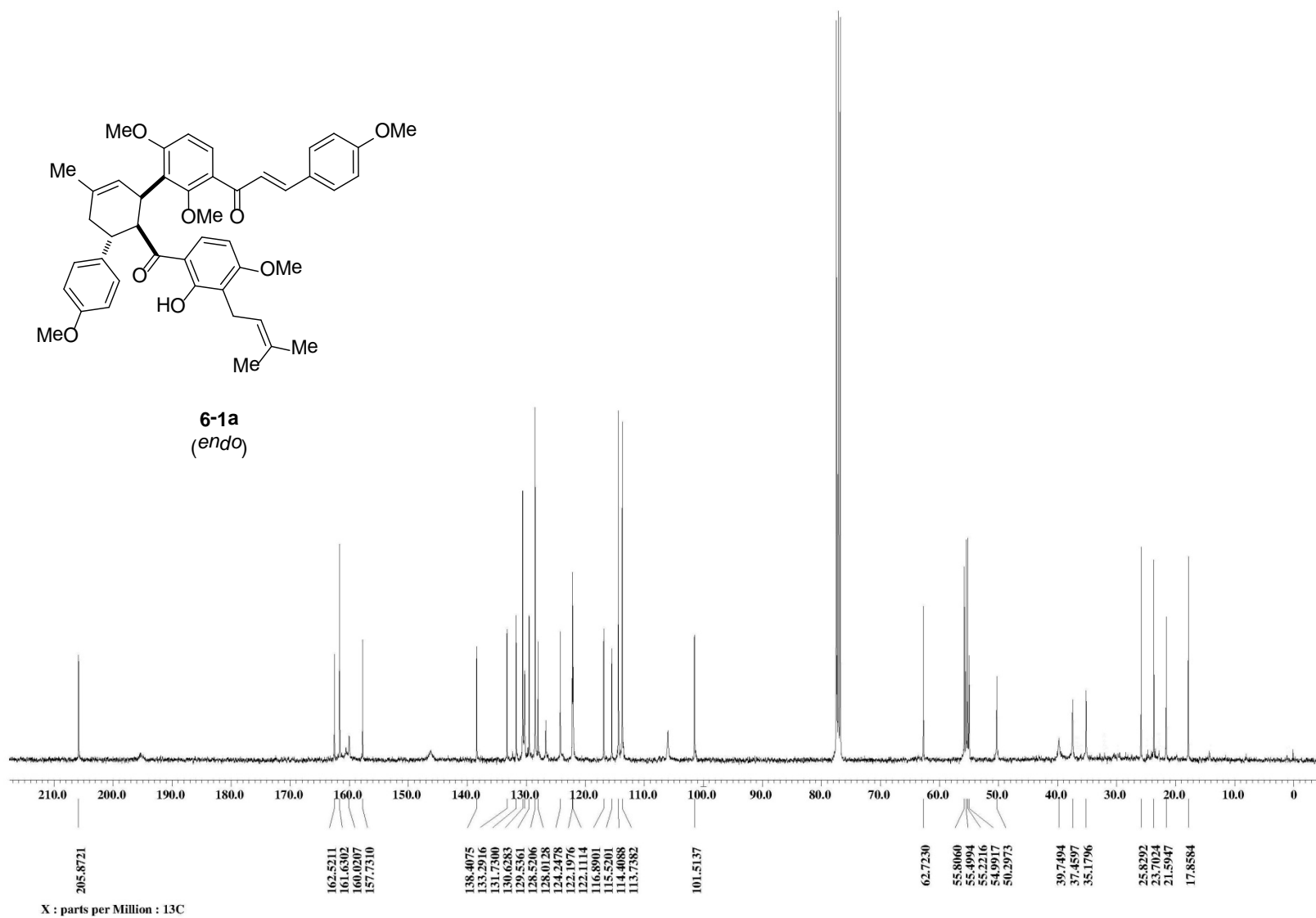
¹³C NMR of adduct IV



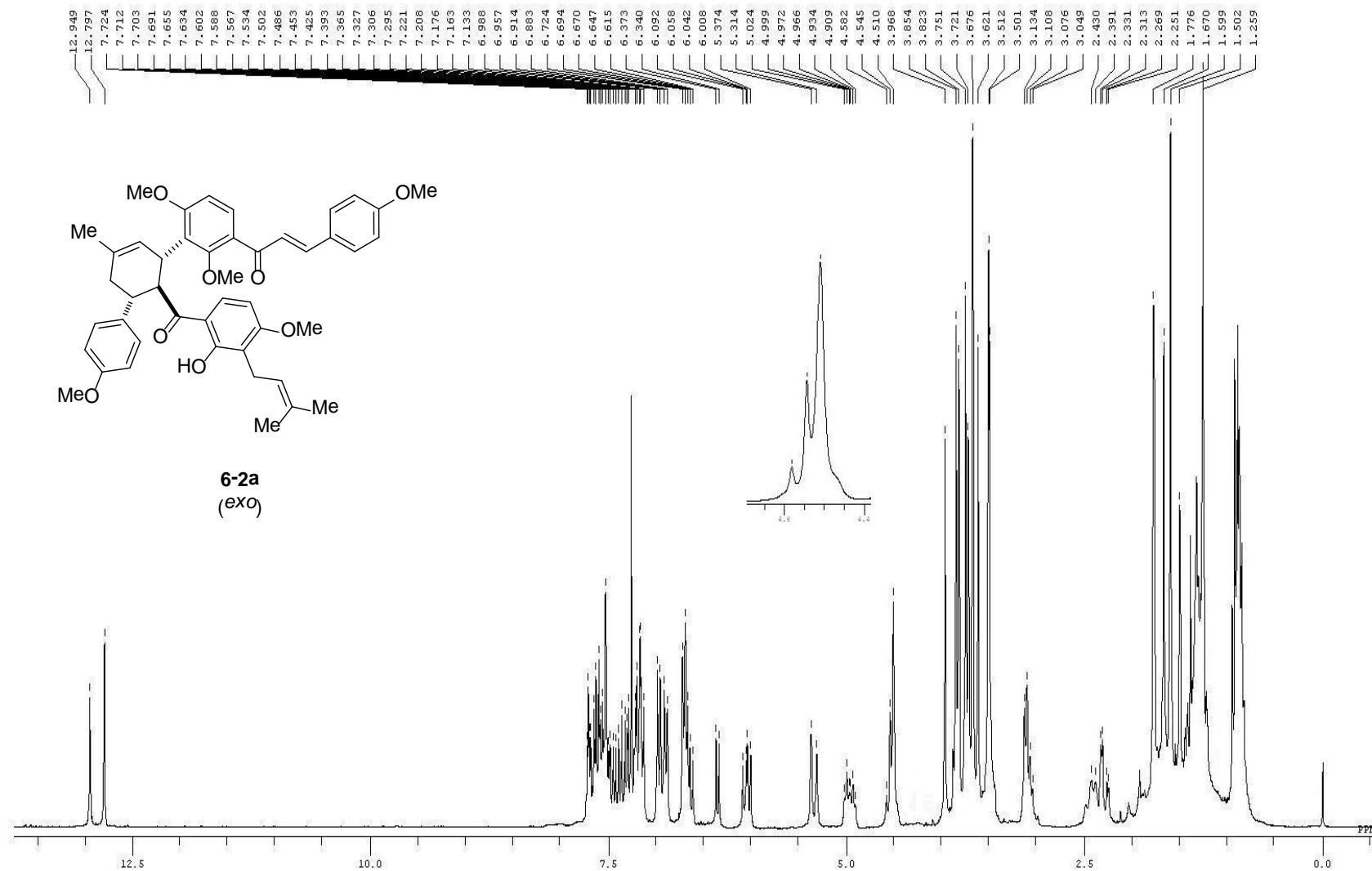
¹H NMR of (±)-kuwanon V pentamethyl ether 6-1a



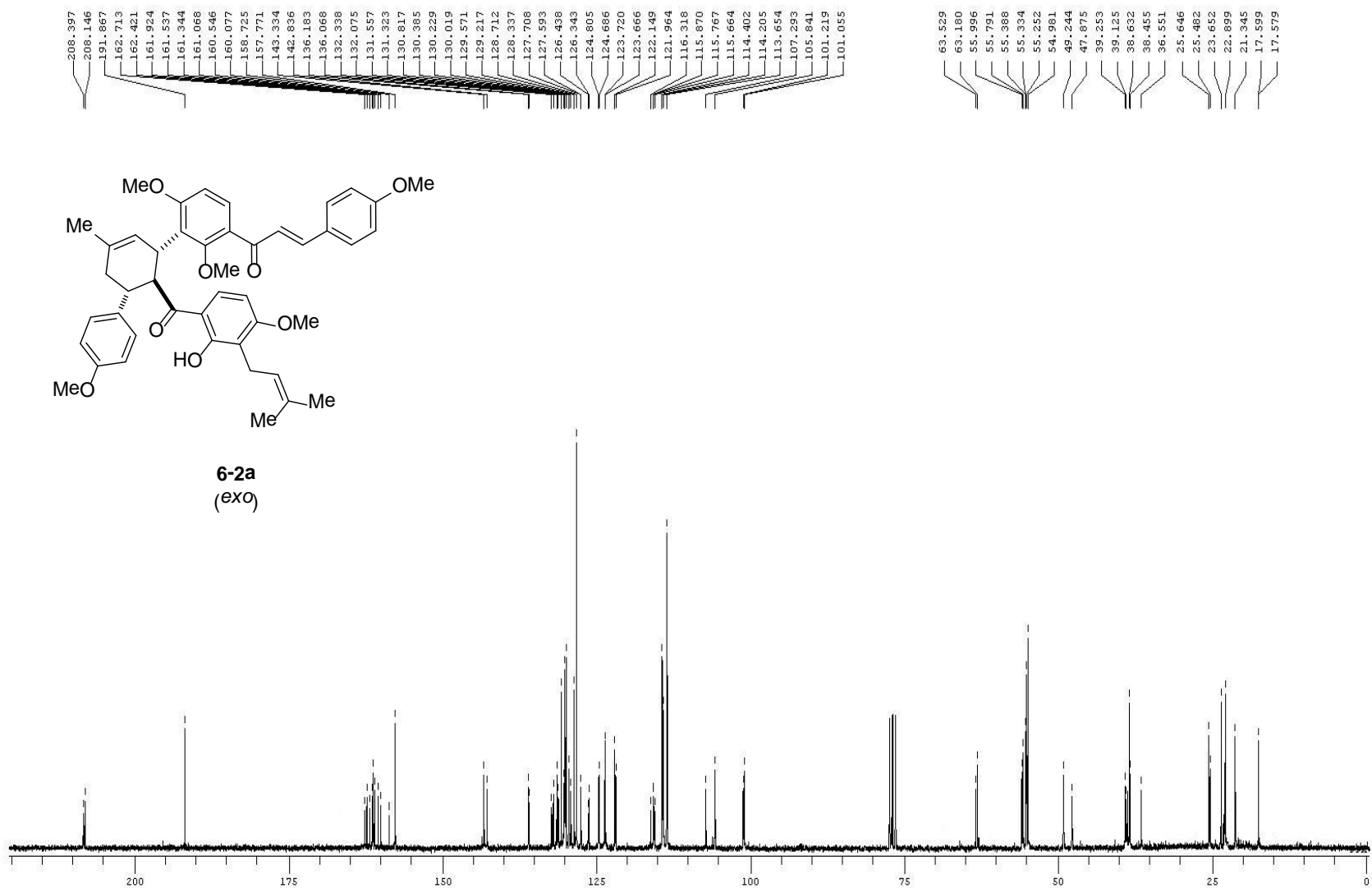
^{13}C NMR of (\pm)-kuwanon V pentamethyl ether 6-1a



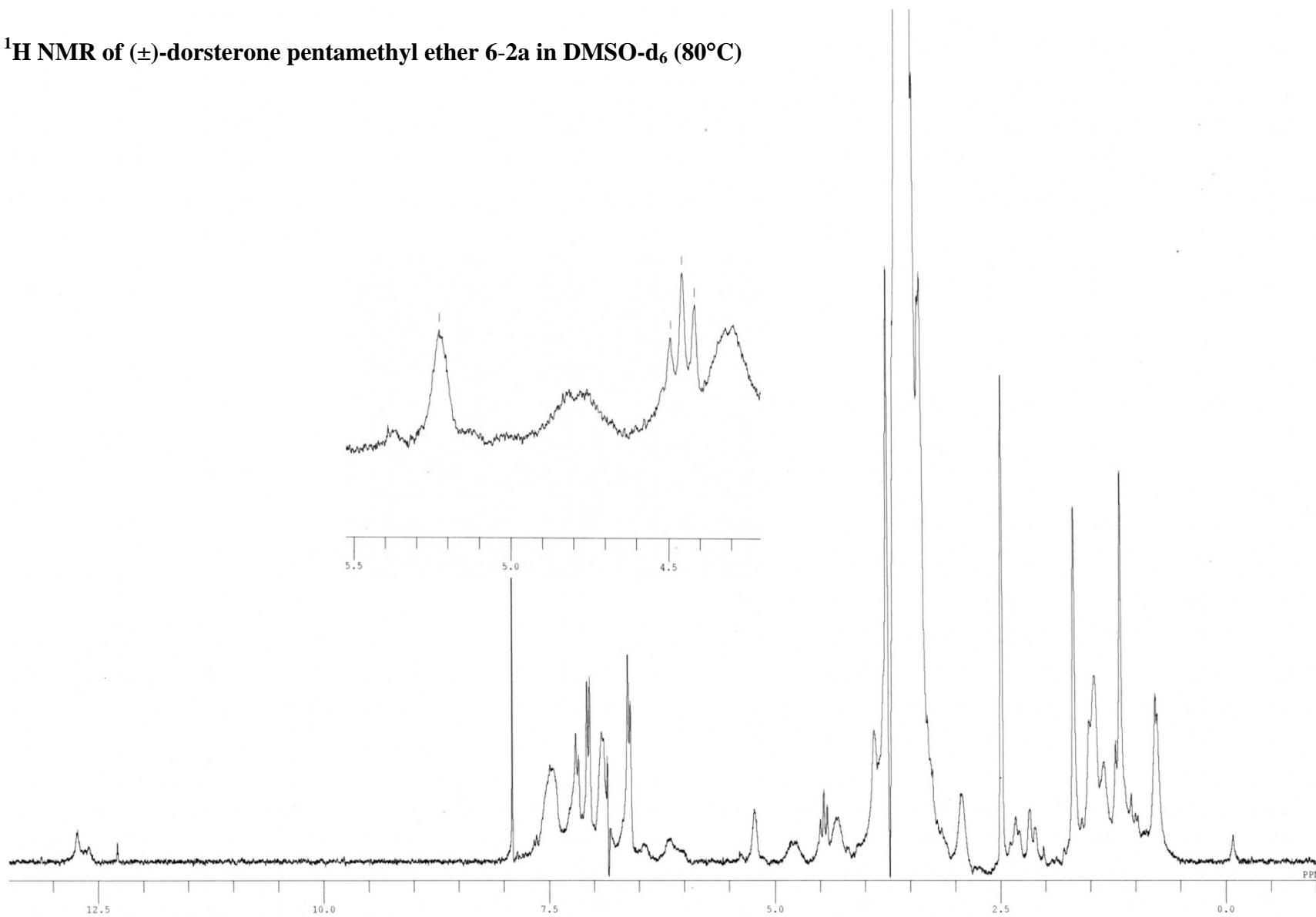
¹H NMR of (±)-dorsterone pentamethyl ether 6-2a (epimerization in CDCl₃ at 25 °C)



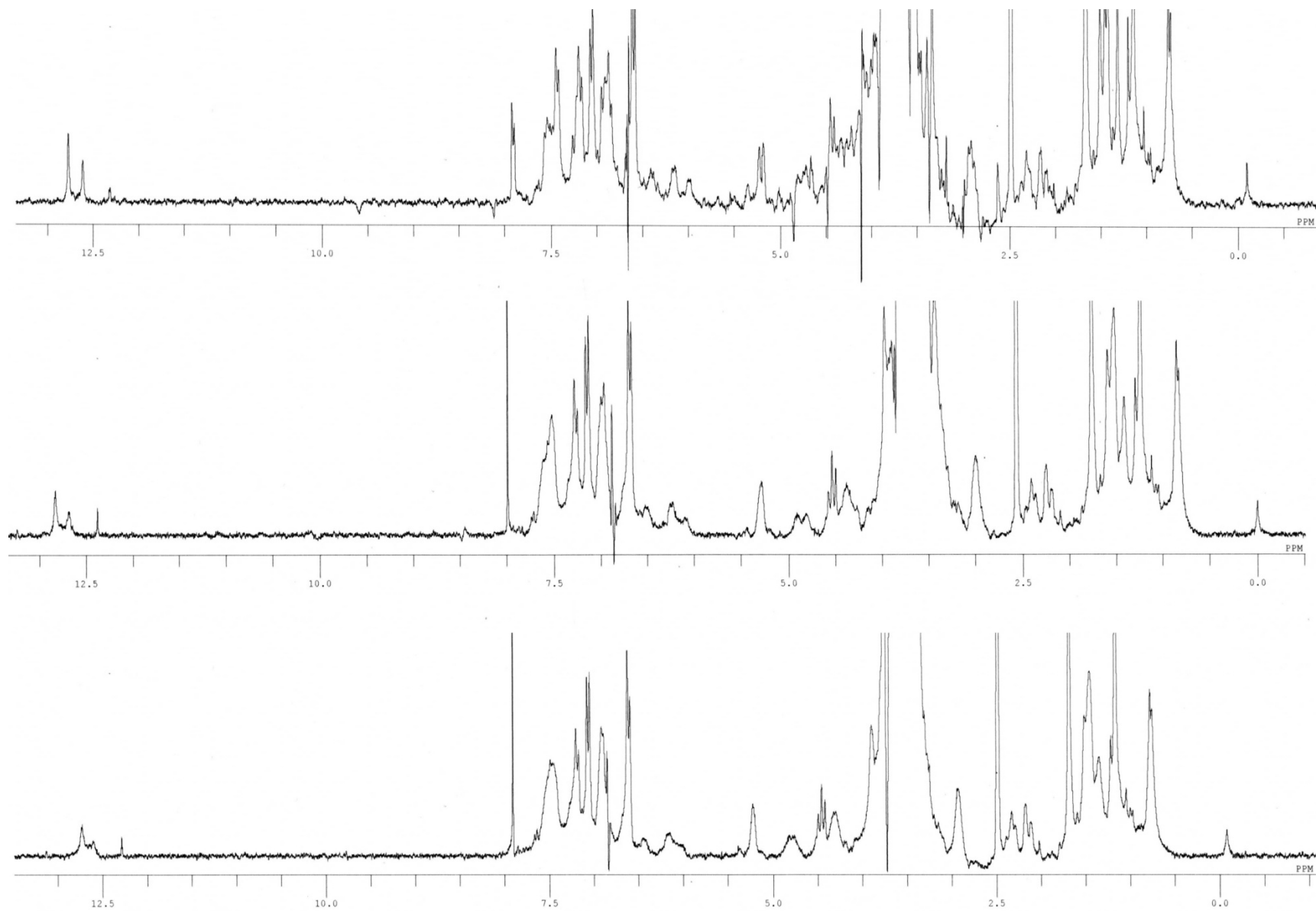
^{13}C NMR of (\pm)-dorsterone pentamethyl ether 6-2a (epimerization in CDCl_3 at 25 $^\circ\text{C}$)



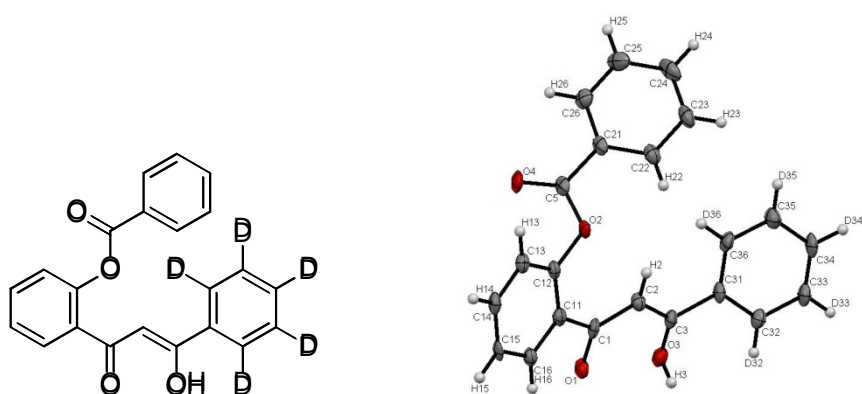
^1H NMR of (\pm)-dorsterone pentamethyl ether 6-2a in DMSO- d_6 (80°C)



^1H NMR of (\pm)-dorsterone pentamethyl ether 6-2a in DMSO- d_6 at 50, 70, and 80°C, respectively.



Appendix E: Crystal data and refinement details for 1-(2-benzoyloxyphenyl)-3-(²H₅)phenyl-1,3-propanedione 3-11b^a



Empirical formula	C ₂₂ H ₁₁ D ₅ O ₄
Formula weight	349.14
Crystal system	Monoclinic
Space group	P 2 ₁ /c
a (Å)	16.7173(12)
b (Å)	13.3236(9)
c (Å)	7.3084(5)
α (°)	90
β (°)	90
γ (°)	90
Volume (Å ³)	1627.83
Z value	4
Calculated density, D _{calc} (Mg/m ³)	1.503
Absorption coefficient, μ (mm ⁻¹)	1.039
Crystal size (mm)	0.50 x 0.13 x 0.12
F(000)	768
Cell determination, 2θ range (°)	2.44 - 28.25
Limiting indices	-21 ≤ h ≤ 22, -17 ≤ k ≤ 13, -9 ≤ l ≤ 5
Reflections collected/unique	6704/3279 [R _(int) =0.103]
Max. and min. transmission	0.831 and 0.571

Data/restraints/parameters	3279/36/236
Goodness-of-fit on F^2	0.947
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.042$, $wR_2 = 0.082$
R indices (all data)	$R_1 = 0.045$, $wR_2 = 0.086$
Largest diff. peak and hole ($e \text{ \AA}^{-3}$)	0.31 and -0.31

^aThe diffraction measurement was performed on a Bruker APEX-II CCD area-detector diffractometer (MoK α ; $\lambda=0.71073$) in temperature of 296 K. The crystal structure was solved using direct method. *SHELXL97* [Sheldrick, G.M. 1997. *SHELXS97* and *SHELXL97*. University of Göttingen, Germany] was used for the refinement of the structure.