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Supporting Information

The Affinity of RSK for Cylitol analogues of SL0101 is Critically Dependent on the B-Ring C-4'-Hydroxy

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Section A: General Information

Section B: Experimental Procedure

Section C: ^{1}H, ^{13}C Spectra

General chemistry methods and materials

^{1}H and ^{13}C spectra were recorded on 400 MHz and 500 MHz spectrometers. Chemical shifts were reported relative to $CDCl_3$ (δ 7.26 ppm), CD_3OD (δ 3.31 ppm), acetone-d_6 (δ 2.05 ppm) for ^{1}H, and $CDCl_3$ (δ 77.0 ppm), CD_3OD (δ 49.15 ppm), acetone-d_6 (δ 29.92 ppm) for ^{13}C. Optical rotations were measured with a digital polarimeter at sodium D line (589 nm) and were reported in concentration of g/100 mL at 25 ºC in the solvent specified. Infrared (IR) spectra were obtained on a FT-IR spectrometer. Flash chromatography was performed using the indicated solvent system on silica gel standard grade 60 (230-400 mesh). R_f values are reported for analytical TLC using the specified solvents and 0.25 mm silica gel 60 F254 plates that were visualized by UV

irradiation (254 nm and 365 nm) or by staining with $KMnO_4$ stain or *p*-anisaldehyde stain. Ethyl ether, tetrahydrofuran, methylene chloride, toluene, and triethylamine were dried by passing through activated alumina (8 x 14 mesh) column with argon gas pressure. Commercial reagents were used without purification unless otherwise noted. Air and/or moisture-sensitive reactions were carried out under an atmosphere of argon/nitrogen using oven/flamed-dried glassware and standard syringe/septum techniques. Melting points are uncorrected. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectra were obtained using α-cyano-4-hydroxycinnamic acid (CCA) as the matrix on a MALDI-TOF mass spectrometer.

In vitro kinase assay

Purified recombinant RSK2

His-tagged RSK2 cDNA was generated using the Bac-to-Bac Baculovirus Expression System (Thermo Fisher Scientific). RSK2 expressed in Sf9 cells was activated with phorbol 12-myristate 13-acetate (20 min). Recombinant protein was purified using a Ni-NTA Spin Kit (Qiagen).

RSK2 in vitro kinase assay

IC_{50} determination was performed as previously described[1]. Briefly, a fusion protein consisting of glutathione S-transferase and the amino acid sequence RRRLA**S**TNDKG (1 μg/well) was adsorbed to MaxiSorp-treated LumiNunc 96-well white polystyrene plates (Thermo Fisher Scientific). The wells were blocked with 3% tryptone in phosphate-buffered saline. Kinase (0.3 nM) in kinase buffer (25 mM HEPES pH 7.4), 150 mM NaCl, 5 mM β-glycerophosphate, 1.5 mM DTT, 30 mM $MgCl_2$, 1% BSA) was added. Reactions were incubated with or without inhibitor. Reactions were initiated by the addition of ATP (10 μM) for 15 min, which is in the linear range of the assay. The reactions were terminated by addition of EDTA (500 mM, pH 8.0). The plates were washed and phosphorylation was measured using rabbit polyclonal anti- LApSTND[1] and horseradish peroxidase (HRP)-conjugated donkey anti-rabbit (Jackson ImmunoResearch Laboratories) antibodies. Western Lightning Enhanced Chemiluminescent Reagent Plus (PerkinElmer Technology Corporation) was used to measure HRP activity. To determine IC_{50} values, non-linear regression analysis was performed using GraphPad Prism version 6.0a.

Further validation of inhibitor activity for RSK2 (RPS6KA3, Thermo Fisher Scientific) was determined using the LanthaScreen® Eu kinase binding assay for according to the manufacturer's instructions (Thermo Fisher Scientific). Inhibitors were pre-incubated with purified kinase before addition of kinase tracer 236 for two h. Excitation fluorescence was 330 ± 80 nm, background emission from Eu tag 620 ± 10 nm and fluorescence resonance energy transfer (FRET) emission 665 ± 8 nm. Fluorescence was

[1] Li M,; Li Y,; Mrozowski RM,; et al. *ACS Med Chem Lett*. **2015**, *6*, 95–99.

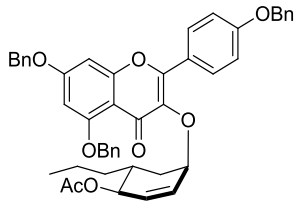
measured using a Synergy Neo (BioTek Instruments). FRET was calculated as the ratio of emission at 665 divided by emission at 620.

Cell proliferation assay

The MCF-7 line was obtained and cultured as direct by ATCC. Stocks were authenticated based on growth rate, morphology, molecular markers and absence of mycoplasma. For proliferation assays 10^3 cells/well were plated in a 96-well. Inhibitor or vehicle was added, and luciferase measured at 42 h using CellTiterGlo reagent (Promega Corp.) with a GLoMax Discover luminometer (Promega Corp.).

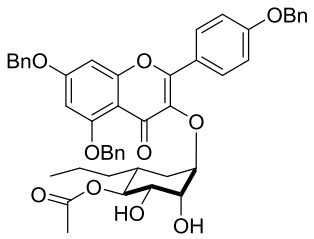
Compounds characterization:

(1S,4R,6R)-4-((5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yl)oxy)-6-propylcyclohex-2-en-1-yl acetate (7f)



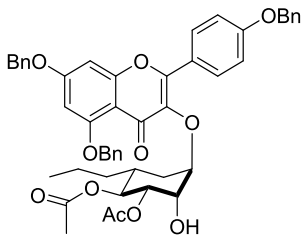
To a solution of cyclitol **8** (100 mg, 0.29 mmol) in dichloromethane (1.5 mL) added aglycone **9f** (106.8 mg, 0.19 mmol), $Pd_2(dba)_3$•$CHCl_3$ (7.5 mg, 2.5 mol%), triphenylphosphine (6.6 mg, 10 mol%) and DBU (58 μM, 0.56 mmol) at 0 ºC successively, the resulting mixture was stirred for overnight at room temperature. Then reaction solution was concentrated on rotary evaporator and loaded onto chromatography directly. Product **7f** was given by flash chromatography with solvent (Hexane: Ethyl Acetate = 6 : 1) to afford yellow solid (168 mg, 80%): m.p. 84 – 86 ℃; R_f = 0.38 (Hexane: Ethyl Acetate = 2 : 1); $[\alpha]_D^{20}$: – 32 (c = 0.6, CH_2Cl_2); IR (thin film, cm^{-1}) 2956, 2873, 1730, 1603, 1508, 1372, 1244, 1142, 1014, 833, 733, 696; ^1H (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.9 Hz, 2H), 7.59 (d, *J* = 7.4 Hz, 2H), 7.26 – 7.49 (m, 13H), 7.07 (d, *J* = 9.0 Hz, 2H), 6.57 (d, *J* = 2.1 Hz, 1H), 6.44 (d, *J* = 2.1 Hz, 1H), 6.15 (dd, *J* = 9.9, 3.9 Hz, 1H), 5.71 (dd, *J* = 10.0, 1.6 Hz, 1H), 5.27 (s, 2H), 5.13 (s, 2H), 5.08 (s, 2H), 4.96 (d, *J* = 8.5 Hz, 1H), 4.88 (d, *J* = 3.2 Hz, 1H), 2.09 (s, 3H), 1.91 (d, *J* = 14.0 Hz, 1H), 1.77 – 1.86 (m, 1H), 1.40 (td, *J* = 16.1, 4.4 Hz, 1H), 1.22 - 1.28 (m, 2H), 1.01 – 1.17 (m, 1H), 0.82 – 1.01 (m, 3H), 0.79 (t, *J* = 6.8 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 174.2, 171.3, 162.9, 160.5, 160.0, 159.0, 153.9, 139.4, 136.7, 136.7, 135.9, 131.0, 130.9, 130.8, 129.8, 129.0 (2C), 128.9 (2C), 128.9 (2C), 128.7, 128.4, 127.9, 127.9 (2C), 127.7 (2C), 126.9 (2C), 124.0, 114.7 (2C), 110.2, 98.4, 94.1, 73.9, 73.3, 71.0, 70.7, 70.3, 34.4, 34.3, 31.5, 21.6, 19.6, 14.7; HRMS (MALDI-TOF/CCA): Calcd. $[C_{47}H_{43}O_{82}+Na]^+$: 737.3109, Found: 737.3110.

(1S,2S,3R,4R,6R)-4-((5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yl)oxy)-2,3-dihydroxy-6-propylcyclohexyl acetate (13f)



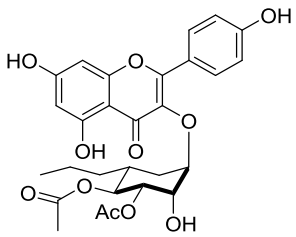
Acetate alkene **7f** (300 mg, 0.41 mmol) was dissloved in 0.81 mL of a mixture of acetone and *t*-butyl alcohol (1: 1), then at 0 ^{o}C added osmium tetroxide (1.35 mg, 1.3 mol%) and 50% *N*-methylmorpholine *N*-oxide water solution (85 μL, 0.41 mmol) dropwise successively. The resulting mixture was stirred at room temperature for 3 hrs. After reaction completed, reaction mixture was washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, then concentrated on rotary evaporator. The resulting crude was purified by chromatography and flash with solvent (Hexane: Ethyl Acetate = 1: 1) to afford product **13f** as light yellow solid (226 mg, 72%): m.p. 94 – 96 ^{o}C; R_f = 0.1 (Hexane: Ethyl Acetate = 1: 1); $[\alpha]_D^{20}$: – 47 (c = 0.4, CH_2Cl_2); IR (thin film, cm^{-1}) 3410, 2925, 1727, 1603, 1173, 1014, 832, 735, 696; ^{1}H (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 7.4 Hz, 2H), 7.50 – 7.27 (m, 13H), 7.09 (d, *J* = 8.9 Hz, 2H), 6.58 (d, *J* = 2.1 Hz, 1H), 6.47 (d, *J* = 2.1 Hz, 1H), 5.27 (s, 2H), 5.15 (s, 2H), 5.09 (s, 2H), 4.90 (t, *J* = 6.0 Hz, 1H), 4.23 (s, 1H), 4.15 (d, *J* = 2.3 Hz, 1H), 3.91 (dd, *J* = 5.9, 3.4 Hz, 1H), 2.08 (s, 3H), 1.59– 1.75 (m, 2H), 1.41– 1.31 (m, 3H), 1.26 (t, *J* = 7.2 Hz, 1H), 1.16 – 0.94 (m, 4H), 0.92 – 0.82(m, 1H), 0.75 (t, *J* = 6.9 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 174.7, 171.2, 163.3, 160.8, 160.0, 159.1, 154.8, 139.4, 136.5, 136.4, 135.7, 130.9, 129.0 (3C), 128.9 (3C), 128.9 (3C), 128.7, 128.5, 128.0, 127.8 (2C), 127.7 (2C), 126.9 (2C), 123.5, 114.8 (2C), 109.8, 98.5, 94.1, 72.3, 72.1, 71.0, 70.7, 70.4, 36.4, 33.5, 30.5, 21.5, 20.3, 14.5; HRMS (MALDI-TOF/CCA): Calcd. $[C_{47}H_{45}O_{10}+Na]^+$: 793.2983, Found: 793.2998

(1S,2S,3S,4R,6R)-4-((5,7-bis(benzyloxy)-2-(4-(benzyloxy)phenyl)-4-oxo-4H-chromen-3-yl)oxy)-3-hydroxy-6-propylcyclohexane-1,2-diyl diacetate (14f)



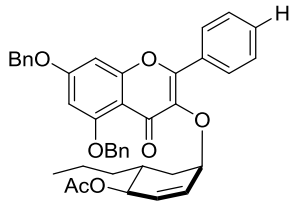
To a solution of compound acetate diol **13f** (190 mg, 0.25 mmol) in 0.5 mL acetonitrile, Taylor's borinate catalyst (5.5mg, 10 mol%), acetic chloride (21 μL, 0.3 mmol) and Hunig's base (85 μL, 0.5 mmol) added successively at 0 ^{o}C. The resulting mixture was stirred at room temperature for 10 hrs. Then reaction mixture was washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, then concentrated on rotary evaporator. The resulting crude was purified by HPLC and flash with solvent (Hexane: Ethyl Acetate = 1 : 1) to afford product **14f** as pale yellow solid (145 mg, 60%): m.p. 75–77 ^{o}C; R_f = 0.29 (Hexane: Ethyl Acetate = 1 : 1); $[\alpha]_D^{20}$: –75 (c = 1.2, CH_2Cl_2); IR (thin film, cm^{-1}) 3490, 3089, 2929, 1603, 1499, 1371, 1229, 1175, 835, 735, 697, 603; ^{1}H (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.8 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.48–7.23 (m, 13H), 7.10 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 2.0 Hz, 1H), 6.44 (d, *J* = 2.0 Hz, 1H), 5.25 (s, 2H), 5.23 (d, *J* = 3.0 Hz, 1H), 5.13 (s, 2H), 5.07 (s, 2H), 4.98 (t, *J* = 8.5 Hz, 1H), 4.47 (d, *J* = 3.4 Hz, 1H), 4.34 (s, 1H), 2.04 (s, 1H), 2.02 (s, 3H), 2.01 (s, 3H), 1.73 (m, 1H), 1.70–1.61 (m, 1H), 1.45–1.39 (m, 1H), 1.29–1.15 (m, 2H), 1.16 –1.03 (m, 1H), 1.03 – 0.83 (m, 2H), 0.73 (t, *J* = 7.0 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 174.1, 170.6, 169.9, 163.0, 160.7, 159.9, 159.0, 154.3, 139.2, 136.6, 136.5, 135.8, 130.8, 129.0 (3C), 128.9 (3C), 128.8 (3C), 128.7, 128.4, 127.9, 127.8 (2C), 127.7 (2C), 126.8 (2C), 123.5, 114.9 (2C), 110.1, 98.4, 94.1, 79.8, 73.7, 73.3, 70.9, 70.7, 70.3, 36.0, 33.7, 29.8, 21.3, 19.8, 14.5; HRMS (MALDI-TOF/CCA): Calcd. $[C_{49}H_{48}O_{11}+Na]^+$: 835.3089, Found: 835.3075.

(1S,2S,3S,4R,6R)-4-((5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-4H-chromen-3-yl)oxy)-3-hydroxy-6-propylcyclohexane-1,2-diyl diacetate (3a)



To a solution of bis-acetate compound **14a** (50 mg, 0.06 mmol) in 0.2 mL methanol added Pd/C (1.3 mg, 10 mol%) and resulting mixture was stirred under a H_2 atmosphere for 24 hrs. The reaction mixture was loaded onto silica gel and elution with Hexane-EtOAc (1: 1) to give product **3a** (23.3 mg, 74%): m.p.: 161–163 ^{o}C; R_f = 0.11 (Hexane: Ethyl Acetate = 1 : 2); $[\alpha]_D^{20}$: –116 (c = 0.5, MeOH); IR (thin film, cm^{-1}) 3376, 2959, 2360, 1723, 1657, 1608, 1511, 1462, 1367, 1261, 1175, 1042, 841; ^{1}H (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.38 (d, *J* = 4.0 Hz, 1H), 6.19 (d, *J* = 4.0 Hz, 1H), 5.08 (dd, *J* = 10.0, 2.8 Hz, 1H), 5.00 (t, *J* = 10.2 Hz, 1H), 4.56 (d, *J* = 3.1 Hz, 1H), 4.28 (t, *J* = 4.0 Hz, 1H), 2.03 (s, 3H), 1.98 (s, 3H), 1.72 (d, *J* = 14.4 Hz, 1H), 1.63 – 1.48 (m, 1H), 1.48 – 1.32 (m, 1H), 1.22 – 1.04 (m, 2H), 0.97 – 0.79 (m, 2H), 0.74 (t, *J* = 6.3 Hz, 3H); ^{13}C (100 MHz, $CDCl_3$) δ 178.6, 171.2, 170.8, 164.7, 162.0, 160.4, 157.8, 157.3, 135.5, 131.0 (2C), 121.5, 115.3 (2C), 104.6, 98.6, 93.5, 79.6, 73.9, 73.2, 69.3, 35.2, 33.7, 28.2, 19.7, 19.6, 19.1, 13.4; HRMS (MALDI-TOF/CCA): Calcd. $[C_{28}H_{29}O_{11}+Na]^+$: 565.1680, Found: 565.1689.

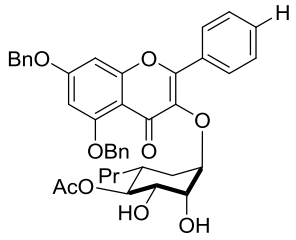
(1S,4R,6R)-4-((5,7-bis(benzyloxy)-4-oxo-2-phenyl-4H-chromen-3-yl)oxy)-6-propylcyclohex-2-en-1-yl acetate (7b)



To a solution of H-aglycone compound **9b** (150 mg, 0.33 mmol) and benzoate cyclitol **8** (231 mg, 0.66 mmol) in 3.0 mL dry CH_2Cl_2 added $Pd_2(dba)_3$•$CHCl_3$ (8.6 mg, 2.5 mol%), triphenylphosphine (8.7 mg, 10 mol%) and DBU (74.5 μM, 0.50 mmol) at 0 ^{o}C successively, the resulting mixture was stirred for

overnight at room temperature. Then reaction solution was concentrated on rotary evaporator and loaded onto chromatography directly. Product **7b** was given by flash chromatography with solvent (Hexane: Ethyl Acetate = 10 : 1) to afford yellow solid (157.62 mg, 75%), R_f = 0.40 (Hexanes : Ethyl Acetate = 3 : 1), $[\alpha]_D^{22}$: –53 (c = 0.9, CH_2Cl_2); m.p.: 50 – 52 ^oC; IR (thin film, cm^{-1}) 3064, 2956, 2929, 1731, 1605, 1496, 1446, 1371, 1172, 1111, 10299, 988, 951, 918, 821, 735, 696, 656; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.50 – 7.43 (m, 3H), 7.43 – 7.33 (m, 7H), 7.30 (t, *J* = 7.3 Hz, 1H), 6.59 (d, *J* = 2.0 Hz, 1H), 6.46 (d, *J* = 2.0 Hz, 1H), 6.12 (dd, *J* = 10.0, 4.0 Hz, 1H), 5.68 (dd, *J* = 10.0, 1.5 Hz, 1H), 5.29 (s, 2H), 5.09 (s, 2H), 4.93 (d, *J* = 8.9 Hz, 1H), 4.88 (d, *J* = 3.3 Hz, 1H), 2.07 (s, 3H), 1.86 (d, *J* = 14.2 Hz, 1H), 1.82 – 1.72 (m, 1H), 1.42 – 1.32 (m, 1H), 1.22 – 1.15 (m, 1H), 1.10 – 1.00 (m, 1H), 0.93 – 0.83 (m, 2H), 0.75 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 171.0, 162.8, 159.8, 158.9, 153.7, 139.8, 136.4, 130.9, 130.1, 129.3, 129.0, 128.8, 128.6, 128.4, 128.2, 127.7, 127.6, 126.6, 110.1, 98.2, 93.9, 73.6, 73.1, 70.8, 70.5, 34.1, 34.0, 31.3, 21.3, 19.2, 14.4; HRMS (MALDI-TOF/CCA) calcd. $[C_{40}H_{38}O_7+Na]^+$: 653.2510, Found: 653.2513

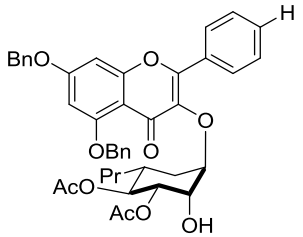
(1S,2S,3R,4R,6R)-4-((5,7-bis(benzyloxy)-4-oxo-2-phenyl-4H-chromen-3-yl)oxy)-2,3-dihydroxy-6-propylcyclohexyl acetate (13b)



Acetate alkene **7b** (132.4 mg, 0.21 mmol) was dissloved in 2 mL of a mixture of acetone and *t*-butyl alcohol (1: 1), then at 0 ^oC added osmium tetroxide (1.3 mol%) and 50% *N*-methylmorpholine *N*-oxide water solution (43 μL, 0.21 mmol) dropwise successively. The resulting mixture was stirred at room temperature for 3 hrs. After reaction completed, reaction mixture was washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, then concentrated on rotary evaporator. The resulting crude was purified by chromatography and flash with solvent (Hexane: Ethyl Acetate = 1: 1) to afford

product **13b** as light yellow solid (101 mg, 72%): R_f = 0.21 (Hexanes : Ethyl Acetate = 1 : 1); $[\alpha]_D^{23}$: –32 (c = 2.4, CH_2Cl_2); m.p. : 104 – 106 ^oC; IR (thin film, cm^{-1}) 3604 – 3228(br), 2956, 2925, 2870, 2854, 1733, 1608, 1486, 1447, 1373, 1301, 1244, 1174, 1108, 1074, 1032, 998, 823, 736, 696; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 6.4, 2.6 Hz, 2H), 7.55 (d, *J* = 7.4 Hz, 2H), 7.51 – 7.48 (m, 2H), 7.42 – 7.35 (m, 8H), 7.29 (d, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 1.5 Hz, 1H), 6.46 (d, *J* = 1.3 Hz, 1H), 5.26 (s, 2H), 5.08 (s, 2H), 4.86 (t, *J* = 7.2 Hz, 1H), 4.31 (s, 1H), 4.20 – 4.11 (m, 1H), 3.82 (dd, *J* = 6.7, 3.0 Hz, 1H), 2.06 (s, 3H), 1.66 (dt, *J* = 24.2, 7.9 Hz, 1H), 1.58 (dt, *J* = 12.9, 6.9 Hz, 1H), 1.33 – 1.27 (m, 1H), 1.13 – 1.04 (m, 1H), 1.04 – 0.96 (m, 1H), 0.96 – 0.88 (m, 1H), 0.86 (d, *J* = 6.1 Hz, 1H), 0.73 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 171.2, 163.1, 159.8, 158.9, 154.5, 139.6, 136.2, 135.5, 130.8, 130.6, 129.1, 129.0, 128.9, 128.9, 128.8, 128.8, 128.6, 128.6, 128.5, 128.5, 128.3, 127.8, 127.7, 127.7, 127.6, 126.8, 126.7, 126.6, 109.8, 98.4, 93.9, 80.7, 75.4, 72.0, 71.9, 71.9, 70.8, 70.5, 36.0, 33.4, 29.9, 29.70 21.2, 19.9, 14.2; HRMS (MALDI-TOF/CCA) calcd. $[C_{40}H_{40}O_9+Na]^+$: 687.2565, Found: 687.2565

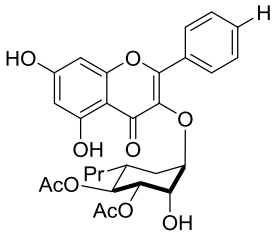
(1S,2S,3S,4R,6R)-4-((5,7-bis(benzyloxy)-4-oxo-2-phenyl-4H-chromen-3-yl)oxy)-3-hydroxy-6-propylcyclohexane-1,2-diyl diacetate (14b)



To a solution of diol **13b** (117.5 mg, 0.18 mmol) in 2 mL acetonitrile at 0 ^oC, was added Taylor's borinate catalyst (4 mg, 10 mol%), acetyl chloride (15 μL, 0.22 mmol) and Hunig's base (62 μL, 0.36 mmol) successively. The resulting mixture was stirred at room temperature for 6 hours. Crude material was filtered through a silica gel pad and loaded on HPLC to deliver pure *C*-3 acetyl substituted compound **14b** (74 mg, 60%) as light yellow solid, R_f = 0.40 (Hexanes : Ethyl Acetate = 1 : 1); $[\alpha]_D^{22}$:

–55 (c = 1.6, CH_2Cl_2); m.p.: 79 – 81 ^oC; IR (thin film, cm^{-1}) 3515 – 3230(br), 3030, 2956, 2871, 2690, 1806, 1736, 1606, 1576, 1484, 1437, 1371, 1209, 1197, 1175, 1143, 1110, 1074, 1042, 1003, 888, 768, 738, 697, 669, 651; ^1H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.1 Hz, 2H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.54 – 7.48 (m, 3H), 7.42 – 7.36 (m, 7H), 7.30 (t, *J* = 7.3 Hz, 1H), 6.58 (d, *J* = 1.7 Hz, 1H), 6.46 (d, *J* = 1.6 Hz, 1H), 5.27 (d, *J* = 6.8 Hz, 2H), 5.20 (dd, *J* = 8.5, 2.8 Hz, 1H), 5.08 (s, 2H), 4.98 (t, *J* = 8.8 Hz, 1H), 4.52 (d, *J* = 2.8 Hz, 1H), 4.36 (s, 1H), 2.02 (d, *J* = 6.4 Hz, 6H), 1.71 (d, *J* = 14.3 Hz, 1H), 1.66 – 1.52 (m, 1H), 1.43 (d, *J* = 11.2 Hz, 1H), 1.21 – 1.12 (m, 1H), 1.08 (dd, *J* = 18.7, 8.1 Hz, 1H), 1.03 – 0.91 (m, 1H), 0.89 – 0.81 (m, 1H), 0.72 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 170.4, 169.6, 163.0, 159.8, 158.9, 154.0, 139.5, 136.3, 135.6, 130.8, 130.4, 129.1, 129.1, 129.0, 129.0, 128.8, 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 127.7, 127.6, 126.7, 112.5, 110.0, 98.3, 93.9, 79.5, 73.5, 73.0, 70.8, 70.7, 70.5, 35.6, 33.5, 29.4, 20.9, 19.5, 14.2; HRMS (MALDI-TOF/CCA) calcd. $[C_{42}H_{42}O_{10}+Na]^+$: 729.2670, Found: 729.2694

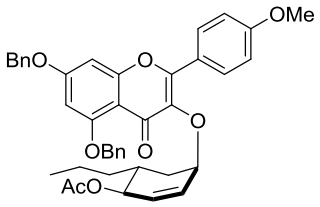
(1S,2S,3S,4R,6R)-4-((5,7-dihydroxy-4-oxo-2-phenyl-4H-chromen-3-yl)oxy)-3-hydroxy-6-propylcyclohexane-1,2-diyl diacetate (3b)



To a solution of compound **14b** (60 mg, 0.085 mmol) in 0.8 mL solvent mixture of THF and methanol (1 : 1) added Pd/C (9 mg, 10 mol%) and resulting mixture was stirred under a H_2 atmosphere for 12 hrs. The reaction mixture was flushed through celite column and recrystallized with acetone to give product **3b** (32 mg, 72%) as yellow solid. R_f = 0.12 (Hexanes : Ethyl Acetate = 1 : 2); m.p. : 97 – 99 ^oC; $[\alpha]_D^{23}$ = – 58 (c = 1.65, Acetone); IR (thin film, cm^{-1}) 3480 – 3214 (br), 2956, 2927, 2871, 1741, 1718, 1654, 1609, 1506, 1491, 1448, 1367, 1307, 1253, 1210, 1172, 1091, 1073, 1041, 1009, 838, 814, 768, 711, 693, 668; ^1H NMR (500 MHz, cd_3od-d4) δ 7.91 (dd, *J* = 6.0, 2.0 Hz, 2H), 7.52 (d, *J* = 3.5 Hz, 3H), 6.34

(s, 1H), 6.18 (s, 1H), 5.09 – 4.93 (m, 2H), 4.54 (d, *J* = 2.0 Hz, 1H), 4.28 (s, 1H), 2.01 (s, 3H), 1.97 (s, 3H), 1.68 (d, *J* = 14.1 Hz, 1H), 1.53 – 1.46 (m, 1H), 1.41 (t, *J* = 13.3 Hz, 1H), 1.33 – 1.26 (m, 1H), 1.10 (d, *J* = 6.7 Hz, 2H), 0.92 – 0.84 (m, 2H), 0.83 – 0.76 (m, 1H), 0.71 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, cd$_3$od-d4) δ 178.5, 171.0, 170.6, 164.6, 161.8, 157.2, 156.7, 136.5, 130.6, 130.6, 128.9, 128.3, 104.7, 98.5, 93.4, 79.7, 73.7, 73.0, 69.2, 35.1, 33.4, 28.1, 19.5, 19.5, 18.8, 13.2; HRMS (MALDI-TOF/CCA) calcd. $[C_{28}H_{30}O_{10}+Na]^+$: 549.1731, Found: 549.1722

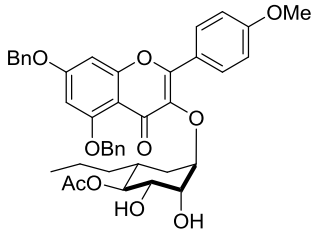
(1S,4R,6R)-4-((5,7-bis(benzyloxy)-2-(4-methoxyphenyl)-4-oxo-4H-chromen-3-yl)oxy)-6-propylcyclohex-2-en-1-yl acetate (7c)



To a solution of benzyl protected methoxyl-aglycone compound **9c** (50 mg, 0.104 mmol) and cyclitol benzoate **8** (72.3 mg, 0.208 mmol) in 1.0 mL dry CH_2Cl_2 added $Pd_2(dba)_3$•$CHCl_3$ (2.7 mg, 2.5 mol%), triphenylphosphine (2.9 mg, 10 mol%) and DBU (23.3 μM, 0.156 mmol) at 0 ^oC successively, the resulting mixture was stirred for overnight at room temperature. Then reaction solution was concentrated on rotary evaporator and loaded onto chromatography directly. Product **7c** was given by flash chromatography with solvent (Hexane: Ethyl Acetate = 8 : 1) to afford yellow oil (47 mg, 68%), R_f = 0.40 (Hexanes : Ethyl Acetate = 3 : 1), $[\alpha]_D^{21}$: –39 (c = 1.7, CH_2Cl_2); m.p.: 68 – 70 ^oC; IR (thin film, cm^{-1}) 2956, 2923, 2851, 1732, 1624, 1605, 1575, 1509, 1498, 1488, 1454, 1439, 1372, 1358, 1299, 1255, 1198, 1178, 1119, 1101, 1029, 835, 821, 736, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 7.5 Hz, 2H), 7.39 (dd, *J* = 17.3, 5.6 Hz, 9H), 7.30 (t, *J* = 7.2 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 2H), 6.57 (s, 1H), 6.44 (s, 1H), 6.12 (dd, *J* = 9.6, 2.8 Hz, 1H), 5.69 (d, *J* = 10.0 Hz, 1H), 5.27 (s, 2H), 5.08 (s, 2H), 4.94 (d, *J* = 8.6 Hz, 1H), 4.87 (s, 1H), 3.87 (s, 3H), 2.08 (s, 3H), 1.90 (d, *J* = 14.2 Hz, 1H), 1.86 – 1.79 (m, 1H), 1.42 – 1.36 (m, 1H), 1.11 – 1.05 (m, 1H), 0.94 – 0.88 (m, 1H), 0.94 – 0.86 (m,

2H), 0.77 (t, J = 6.8 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 171.0, 162.6, 161.1, 159.8, 158.7, 153.8, 139.1, 136.4, 135.7, 130.7, 130.6, 129.5, 128.7, 128.6, 128.4, 127.6, 127.6, 126.6, 123.5, 113.6, 110.0, 98.1, 93.9, 73.7, 73.0, 70.8, 70.5, 55.4, 34.2, 34.1, 31.3, 29.7, 21.3, 19.4, 14.4; HRMS (MALDI-TOF/CCA) calcd. $[C_{43}H_{40}O_8+Na]^+$: 683.2615, Found: 683.2630

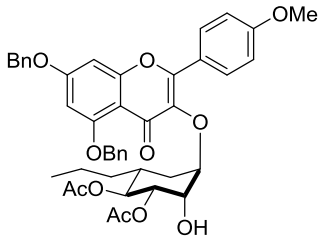
(1S,2S,3R,4R,6R)-4-((5,7-bis(benzyloxy)-2-(4-methoxyphenyl)-4-oxo-4H-chromen-3-yl)oxy)-2,3-dihydroxy-6-propylcyclohexyl acetate (13c)



Acetate alkene **7c** (47 mg, 0.071 mmol) was dissloved in 1 mL of a mixture of acetone and CH_2Cl_2 (1: 1), then at 0 ^oC added osmium tetroxide (1.3 mol%) and 50% *N*-methylmorpholine *N*-oxide water solution (23 μL, 0.071 mmol) dropwise successively. The resulting mixture was stirred at room temperature for 3 hrs. After reaction completed, reaction mixture was washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, then concentrated on rotary evaporator. The resulting crude was purified by chromatography and flash with solvent (Hexane: Ethyl Acetate = 1: 1) to afford product **13c** as light yellow oil (31 mg, 62%): R_f = 0.13 (Hexanes : Ethyl Acetate = 1 : 1); $[\alpha]_D^{23}$: –41 (c = 2.6, CH_2Cl_2); IR (thin film, cm^{-1}) 3554 – 3276(br), 2957, 2824, 2853, 1732, 1604, 1573, 1510, 1498, 1486, 1453, 1437, 1372, 1299, 1255, 1207, 1176, 1118, 1100, 1030, 913, 890, 836, 736, 697, 624, 607; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 7.5 Hz, 2H), 7.42 – 7.35 (m, 8H), 7.29 (t, J = 7.3 Hz, 1H), 7.01 (d, J = 8.6 Hz, 2H), 6.57 (s, 1H), 6.46 (s, 1H), 5.25 (s, 2H), 5.08 (s, 2H), 4.89 (t, J = 6.5 Hz, 1H), 4.27 (d, J = 1.5 Hz, 1H), 4.21 – 4.15 (m, 1H), 3.90 (s, 1H), 3.88 (s, 3H), 2.07 (s, 3H), 1.72 – 1.60 (m, 2H), 1.36 – 1.30 (m, 2H), 1.13 – 0.97 (m, 3H), 0.92 – 0.81 (m, 2H), 0.74 (t, J = 6.9 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.32 171.0, 163.0, 161.4, 159.8, 158.8, 154.6, 139.1, 136.2, 135.6, 130.6, 128.7, 128.6, 128.4, 127.7, 127.5, 126.7, 123.1, 113.8, 109.7, 98.4, 94.0, 80.7, 75.2, 72.1,

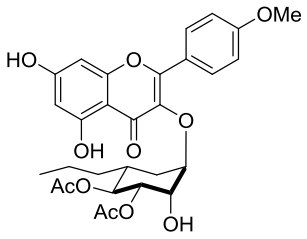
71.9, 70.9, 70.5, 55.4, 36.2, 33.4, 30.2, 29.7, 21.2, 20.1, 14.1; HRMS (MALDI-TOF/CCA) calcd. $[C_{43}H_{42}O_{10}+Na]^+$: 717.2670, Found: 717.2650

(1S,2S,3S,4R,6R)-4-((5,7-bis(benzyloxy)-2-(4-methoxyphenyl)-4-oxo-4H-chromen-3-yl)oxy)-3-hydroxy-6-propylcyclohexane-1,2-diyl diacetate (14c)



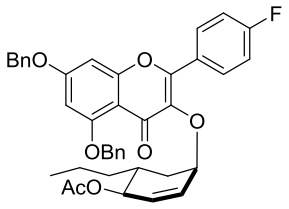
To a solution of diol **13c** (25.7 mg, 0.037 mmol) in 0.3 mL acetonitrile at 0 ^oC, was added Taylor's borinate catalyst (0.8 mg, 10 mol%), acetyl chloride (3.2 μL, 0.044 mmol) and Hunig's base (12.9 μL, 0.074 mmol) successively. The resulting mixture was stirred at room temperature for 6 hours. Crude material was filtered through a silica gel pad and loaded on HPLC to deliver pure *C*-3 acetyl substituted compound **14c** (15.8 mg, 58%) as light yellow oil, R_f = 0.40 (Hexanes : Ethyl Acetate = 1 : 1); $[\alpha]_D^{22}$: −57 (c = 1.8, CH_2Cl_2); IR (thin film, cm^{-1}) 2955, 2923, 2853, 1737, 1623, 1603, 1573, 1510, 1498, 1485, 1453, 1439, 1369, 1300, 1254, 1222, 11176, 1119, 1101, 1031, 973, 938, 918, 890, 836, 737, 698, 670, 647; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.39 (dd, *J* = 16.1, 5.6 Hz, 7H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.58 (s, 1H), 6.46 (s, 1H), 5.26 (s, 2H), 5.25 – 5.19 (m, 1H), 5.08 (s, 2H), 4.98 (t, *J* = 8.5 Hz, 1H), 4.49 (s, 1H), 4.32 (s, 1H), 3.89 (s, 3H), 2.02 (s, 6H), 1.77 (dt, *J* = 8.5, 4.5 Hz, 1H), 1.64 (ddd, *J* = 10.8, 9.6, 6.1 Hz, 1H), 1.44 (t, *J* = 13.7 Hz, 1H), 1.21 (ddd, *J* = 7.5, 5.7, 3.0 Hz, 1H), 1.16 – 1.07 (m, 1H), 1.03 – 0.96 (m, 1H), 0.94 – 0.87 (m, 2H), 0.74 (t, *J* = 7.0 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 170.3, 169.6, 162.8, 161.3, 159.8, 158.8, 154.1, 138.9, 136.3, 135.6, 130.5, 130.5, 130.5, 128.8, 128.6, 128.6, 128.4, 127.7, 127.6, 126.6, 126.6, 123.1, 113.9, 113.8, 109.9, 98.2, 93.9, 79.4, 73.5, 73.1, 70.8, 70.5, 55.4, 35.7, 33.5, 29.6, 21.0, 19.6, 14.2; HRMS (MALDI-TOF/CCA) calcd. $[C_{43}H_{44}O_{11}+Na]^+$: 759.2276, Found: 759.2773

(1S,2S,3S,4R,6R)-4-((5,7-dihydroxy-2-(4-methoxyphenyl)-4-oxo-4H-chromen-3-yl)oxy)-3-hydroxy-6-propylcyclohexane-1,2-diyl diacetate (3c)



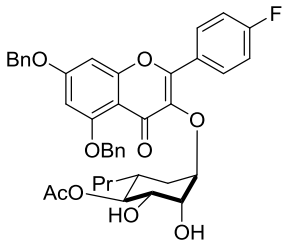
To a solution of compound **14c** (15 mg, 0.020 mmol) in 0.3 mL THF/CH_2Cl_2 (1 : 1) was added Pd/C(2 mg, 10 mol%) under H_2 atmosphere. The resulting suspension solution was stirred overnight at room temperature. Mixture was filtered through a celite column to remove Pd/C. Crude was purified by silica gel column chromatography and flushed with solvent (Hexanes : Ethyl Acetate = 1 : 1) to afford deprotected final product **3c** (7.8 mg, 72%); R_f = 0.12 (Hexanes : Ethyl Acetate = 1: 1); m.p.: 148 – 150 ^oC; $[\alpha]_D^{22}$: –43 (c = 0.4, Acetone); IR (thin film, cm^{-1}) 3464 – 3221(br), 2957, 2930, 2873, 1739, 1718, 1653, 1608, 1507, 1456, 1436, 1367, 1303, 1257, 1177, 1088, 1038, 838; ^1H NMR (500 MHz, acetone – d6) δ 7.97 (dd, *J* = 8.7, 2.3 Hz, 2H), 7.14 (dd, *J* = 9.0, 1.9 Hz, 2H), 6.49 (s, 1H), 6.27 (s, 1H), 5.13 – 5.01 (m, 2H), 4.55 (s, 1H), 4.35 (s, 1H), 3.92 (s, 4H), 1.96 (s, 7H), 1.78 (d, J = 14.7 Hz, 2H), 1.63 (dt, J = 11.7, 7.6 Hz, 1H), 1.51 – 1.44 (m, 1H), 1.35 – 1.26 (m, 1H), 1.22 – 1.12 (m, 2H), 0.90 (dddd, J = 10.5, 8.8, 3.8, 2.8 Hz, 3H), 0.73 (t, J = 6.4 Hz, 3H).6.49 (s, 1H), 6.27 (s, 1H), 5.13 – 5.01 (m, 2H), 4.55 (s, 1H), 4.35 (s, 1H), 3.92 (s, 3H), 1.96 (s, 6H), 1.78 (d, *J* = 14.7 Hz, 1H), 1.59 – 1.67 (m, 1H), 1.47 (t, *J* = 1.4 Hz, 1H), 1.35 – 1.26 (m, 1H), 1.22 – 1.12 (m, 2H), 0.93 – 0.87 (m, 3H), 0.73 (t, *J* = 6.4 Hz, 3H).; ^{13}C NMR (100 MHz, acetone – d6) δ 178.6, 169.6, 169.4, 164.1, 162.4, 161.9, 157.1, 136.2, 130.8, 122.8, 114.1, 114.0, 98.6, 93.7, 93.6, 80.1, 73.6, 72.6, 69.4, 55.0, 35.3, 33.6, 20.0, 19.9, 19.1, 13.7; HRMS (MALDI-TOF/CCA) calcd. $[C_{29}H_{32}O_{11}+H]^+$: 557.2017, Found: 557.1997

(1S,4R,6R)-4-((5,7-bis(benzyloxy)-2-(4-fluorophenyl)-4-oxo-4H-chromen-3-yl)oxy)-6-propylcyclohex-2-en-1-yl acetate (7d)



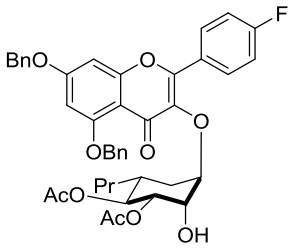
To a solution of fluoro-aglycone compound **9d** (135.1 mg, 0.29 mmol) and benzoate cyclitol **8** (200 mg, 0.58 mmol) in 0.6 mL dry CH_2Cl_2 added $Pd_2(dba)_3$•$CHCl_3$ (7.5 mg, 2.5 mol%), triphenylphosphine (7.7 mg, 10 mol%) and DBU (65 μM, 0.43 mmol) at 0 ^oC successively, the resulting mixture was stirred for overnight at room temperature. Then reaction solution was concentrated on rotary evaporator and loaded onto chromatography directly. Product **7d** was given by flash chromatography with solvent (Hexane: Ethyl Acetate = 8 : 1) to afford yellow oil (123 mg, 66%), R_f = 0.38 (Hexanes : Ethyl Acetate = 3 : 1), $[\alpha]_D^{21}$: −19 (c = 1.7, CH_2Cl_2); IR (thin film, cm^{-1}) 2932, 1736, 1606, 1507, 1499, 1452, 1436, 1412, 1371, 1352, 1284, 1236, 1197, 1173, 1096, 1024, 824, 736, 700, 454; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (dd, *J* = 8.1, 6.0 Hz, 2H), 7.58 (d, *J* = 7.7 Hz, 2H), 7.42 – 7.37 (m, 7H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.16 (t, J = 8.6 Hz, 2H), 6.58 (s, 1H), 6.46 (s, 1H), 6.07 (d, *J* = 10.1 Hz, 1H), 5.67 (d, *J* = 10.0 Hz, 1H), 5.28 (s, 2H), 5.09 (s, 2H), 4.94 (s, 1H), 4.93 (s, 1H), 2.08 (s, 3H), 1.90 (d, *J* = 14.3 Hz, 1H), 1.81 – 1.71 (m, 1H), 1.44 – 1.35 (m, 1H), 1.22 – 1.28 (m, 1H), 1.16 – 1.07 (m, 1H), 1.00 – 0.87 (m, 3H), 0.78 (t, *J* = 6.9 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 171.0, 162.8, 163.7 (d, *J* = 200 Hz, 1C), 159.8, 158.7, 152.8, 139.5, 136.3, 135.6, 131.2, 131.1, 131.0, 129.1, 128.8, 128.6, 128.6, 128.5, 127.7, 127.6, 126.6, 115.3 (d, *J* = 17.2 Hz, 2C), 110.0, 98.2, 93.8, 73.6, 72.9, 70.8, 70.5, 34.1, 34.0, 31.3, 21.3, 19.4, 14.3; HRMS (MALDI-TOF/CCA) calcd. $[C_{40}H_{37}FO_7+Na]^+$: 671.2416, found:671.2428

(1S,2S,3R,4R,6R)-4-((5,7-bis(benzyloxy)-2-(4-fluorophenyl)-4-oxo-4H-chromen-3-yl)oxy)-2,3-dihydroxy-6-propylcyclohexyl acetate (13d)



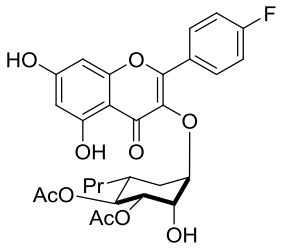
Acetate alkene **7d** (42 mg, 0.065 mmol) was dissloved in 0.2 mL of a mixture of acetone and *t*-butyl alcohol (1: 1), then at 0 ^{o}C added osmium tetroxide (1.3 mol%) and 50% *N*-methylmorpholine *N*-oxide water solution (13 μL, 0.065 mmol) dropwise successively. The resulting mixture was stirred at room temperature for 3 hrs. After reaction completed, reaction mixture was washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, then concentrated on rotary evaporator. The resulting crude was purified by chromatography and flash with solvent (Hexane: Ethyl Acetate = 1: 1) to afford product **13d** as light yellow solid (31 mg, 63%): R_f = 0.23 (Hexanes : Ethyl Acetate = 1 : 1); $[\alpha]_D^{22}$: –42 (c = 2.1, CH_2Cl_2); m.p. : 82 -85 ^{o}C. ; IR (thin film, cm^{-1}) 3573 – 3242(br), 2927, 2872, 2852, 1731, 1607, 1508, 1453, 1435, 1229, 1210, 1174, 1144, 1110, 1095, 1079, 1037, 842, 824, 737, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.0, 5.5 Hz, 2H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.39 (dd, *J* = 17.4, 5.9 Hz, 8H), 7.29 (t, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 8.4 Hz, 2H), 6.57 (s, 1H), 6.48 (s, 1H), 5.26 (s, 2H), 5.09 (s, 2H), 4.87 (t, *J* = 6.8 Hz, 1H), 4.33 (s, 1H), 4.17 (s, 1H), 3.86 – 3.77 (m, 1H), 2.07 (s, 3H), 1.70 – 1.62 (m, 1H), 1.58 (dd, *J* = 12.1, 5.5 Hz, 1H), 1.35 – 1.29 (m, 2H), 1.15 – 1.07 (m, 1H), 1.07 – 0.93 (m, 2H), 0.93 – 0.81 (m, 2H), 0.74 (t, *J* = 7.0 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 171.1, 163.2, 163.9 (d, *J* = 251.2 Hz, 1C), 159.9, 158.8, 153.4, 139.4, 136.1, 135.5, 131.2, 131.1, 128.9, 128.8, 128.6, 128.5, 127.8, 127.5, 127.0, 126.9, 126.7, 126.6, 115.5 (d, *J* = 21.7 Hz, 2C), 109.7, 98.5, 94.0, 80.7, 75.2, 72.0, 71.9, 70.9, 70.6, 36.1, 33.4, 30.1, 29.7, 21.2, 20.0, 14.1; HRMS (MALDI-TOF/CCA) calcd. $[C_{40}H_{39}FO_9+Na]^+$: 705.2470, found: 705.2476.

(1S,2S,3S,4R,6R)-4-((5,7-bis(benzyloxy)-2-(4-fluorophenyl)-4-oxo-4H-chromen-3-yl)oxy)-3-hydroxy-6-propylcyclohexane-1,2-diyl diacetate (14d)



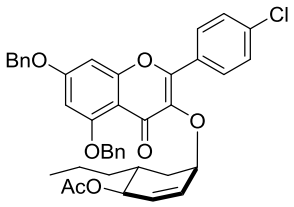
To a solution of diol **13d** (31 mg, 0.045 mmol) in 4.5 mL acetonitrile at 0 ^{o}C, was added Taylor's borinate catalyst (10 mg, 10 mol%), acetyl chloride (38.7 μL, 0.054 mmol) and Hunig's base (158 μL, 0.09 mmol) successively. The resulting mixture was stirred at room temperature for 6 hours. Crude material was filtered through a silica gel pad and loaded on HPLC to deliver pure *C*-3 acetyl substituted compound **14d** (18 mg, 55%) as light yellow solid, R_f = 0.41 (Hexanes : Ethyl Acetate = 1 : 1); $[\alpha]_D^{23}$: –46 (c = 0.7, CH_2Cl_2); m.p.: 89 – 91 ^{o}C; IR (thin film, cm^{-1}) 3477 – 3208, 2932, 2872, 2662, 2493, 1735, 1630, 1606, 1569, 1438, 1371, 1230, 1197, 1176, 1112, 1094, 1042, 843, 823, 740, 702; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.53 (d, *J* = 7.5 Hz, 2H), 7.43 – 7.30 (m, 7H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.19 (t, *J* = 8.6 Hz, 2H), 6.52 (d, *J* = 2.0 Hz, 1H), 6.40 (d, *J* = 1.9 Hz, 1H), 5.21 (s, 2H), 5.14 (dd, *J* = 9.1, 2.8 Hz, 1H), 5.05 (s, 2H), 5.01 (t, *J* = 9.2 Hz, 1H), 4.66 (d, *J* = 2.3 Hz, 1H), 4.41 (s, 1H), 2.00 (s, 3H), 1.98 (s, 3H), 1.67 (d, *J* = 13.8 Hz, 1H), 1.51 – 1.47 (m, 1H), 1.41 (t, *J* = 11.5 Hz, 1H), 1.20 – 1.11 (m, 1H), 1.11 – 1.04 (m, 1H), 0.96 – 0.89 (m, 1H), 0.88 – 0.75 (m, 1H), 0.71 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 170.4, 169.6, 163.8 (d, *J* = 250.8 Hz, 1C), 163.1, 163.0, 159.9, 158.8, 153.0, 139.1, 136.2, 135.5, 131.2, 131.1, 128.8, 128.7, 128.6, 128.5, 127.7, 127.6, 126.9, 126.6, 115.6 (d, *J* = 22 Hz, 2C), 109.9, 98.3, 93.9, 79.1, 73.4, 72.9, 70.8, 70.6, 70.5, 35.7, 33.5, 29.3, 20.9, 19.6, 14.2 ; HRMS (MALDI-TOF/CCA) calcd. $[C_{42}H_{41}FO_{10}+Na]^+$; 747.2576, found:747.2586

(1S,2S,3S,4R,6R)-4-((2-(4-fluorophenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)-3-hydroxy-6-propylcyclohexane-1,2-diyl diacetate (3d)



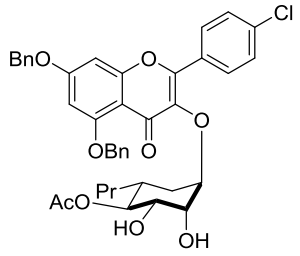
To a solution of compound **14d** (18 mg, 0.025 mmol) in 0.3 mL THF/MeOH (1 : 1) was added Pd/C(2.6 mg, 10 mol%) under H_2 atmosphere. The resulting suspension solution was stirred overnight at room temperature. Mixture was filtered through a celite column to remove Pd/C. Crude was purified by silica gel column chromatography and flushed with solvent (Hexanes : Ethyl Acetate = 1 : 1) to afford deprotected final product **3d** (9.7 mg, 71%); R_f = 0.10 (Hexanes : Ethyl Acetate = 1: 2); m.p.: 113 – 115 ^oC; IR (thin film, cm^{-1}) 3550 – 3191(br), 2960, 2932, 2873, 1741, 1716, 1655, 1612, 1506, 1466, 1455, 1368, 1308, 1212, 1173, 1087, 1041, 1009, 996, 892, 843, 812, 562, 512; ^1H NMR (500 MHz, acetone-d6) δ 8.06 (t, *J* = 7.0 Hz, 2H), 7.35 (t, *J* = 8.4 Hz, 2H), 6.47 (s, 1H), 6.27 (s, 1H), 5.05 (q, *J* = 10.1 Hz, 2H), 4.61 (s, 1H), 4.34 (s, 1H), 1.96 (s, 6H), 1.78 (d, *J* = 13.5 Hz, 1H), 1.58 – 1.47 (m, 2H), 1.22 – 1.12 (m, 2H), 0.97 – 0.84 (m, 2H), 0.73 (t, *J* = 6.6 Hz, 3H).; ^{13}C NMR (100 MHz, acetone-d6) δ 205.4, 178.66, 169.7, 169.5, 164.0 (d, *J* = 249.4 Hz, 1C), 164.2, 162.3, 157.1, 155.7, 136.7, 131.8, 131.7, 127.1, 115.6 (d, *J* = 22 Hz, 2C), 105.1, 98.8, 93.7, 80.1, 73.5, 72.5, 69.3, 35.3, 33.6, 29.5, 29.4, 29.2, 29.0, 28.8, 28.6, 28.4, 20.0, 19.9, 19.0, 13.7; ^{13}C NMR (100 MHz, CD_3OD) δ 178.4, 171.0, 170.6, 164.6, 164.1 (d, *J* = 250 Hz, 1C), 161.8, 157.0, 155.6, 136.2, 131.5, 131.4, 126.9, 126.8, 115.3 (d, *J* = 22 Hz, 2C), 104.7, 98.5, 93.4, 79.6, 73.6, 73.0, 69.1, 35.1, 33.4, 28.1, 19.5, 18.9, 13.2.; HRMS (MALDI-TOF/CCA) calcd. $[C_{28}H_{29}FO_{10}+Na]^+$; 567.1637, found:567.1608

(1S,4R,6R)-4-((5,7-bis(benzyloxy)-2-(4-chlorophenyl)-4-oxo-4H-chromen-3-yl)oxy)-6-propylcyclohex-2-en-1-yl acetate (7e)



To a solution of chloro-aglycone compound **9e** (150 mg, 0.31 mmol) and benzoate cyclitol **8** (215 mg, 0.062 mmol) in 6.0 mL dry CH_2Cl_2 added $Pd_2(dba)_3$•$CHCl_3$ (8.0 mg, 2.5 mol%), triphenylphosphine (8.3 mg, 10 mol%) and DBU (70 μM, 0.47 mmol) at 0 ^oC successively, the resulting mixture was stirred for overnight at room temperature. Then reaction solution was concentrated on rotary evaporator and loaded onto chromatography directly. Product **7e** was given by flash chromatography with solvent (Hexane: Ethyl Acetate = 10 : 1) to afford yellow oil (122 mg, 60%), R_f = 0.38 (Hexanes : Ethyl Acetate = 3 : 1), $[\alpha]_D^{22}$: −16 (c = 4.1, CH_2Cl_2); IR (thin film, cm^{-1}) 2955, 2928, 2865, 1732, 1607, 1488, 1453, 1436, 1397, 1372, 1240, 1211, 1198, 1173, 1092, 1028, 1014, 951, 834, 823, 775, 738, 698; ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 6.8 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.46 – 7.27 (m, 10H), 6.58 (d, *J* = 2.2 Hz, 1H), 6.46 (d, *J* = 2.2 Hz, 1H), 6.08 (dd, *J* = 10.1, 4.0 Hz, 1H), 5.68 (dd, *J* = 10.2, 2.0 Hz, 1H), 5.28 (s, 2H), 5.09 (s, 2H), 4.93 (dd, *J* = 9.1, 6.8 Hz, 2H), 2.09 (s, 3H), 1.89 (dt, *J* = 14.5, 3.1 Hz, 1H), 1.81 – 1.70 (m, 2H), 1.44 – 1.35 (m, 1H), 1.27 (dd, *J* = 10.0, 3.9 Hz, 2H), 1.13 – 1.04 (m, 1H), 0.99 – 0.83 (m, 4H), 0.79 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.82, 171.01, 162.90, 159.82, 158.74, 152.47, 139.83, 136.28, 136.19, 135.58, 131.10, 130.26, 129.62, 129.08, 128.76, 128.62, 128.46, 127.71, 127.58, 126.62, 110.00, 98.22, 93.83, 73.57, 73.06, 70.77, 70.50, 34.19, 34.04, 31.41, 21.29, 19.42, 14.37; HRMS (MALDI-TOF/CCA) calcd. $[C_{40}H_{37}ClO_7+Na]^+$: 687.2120, found: 687.2092

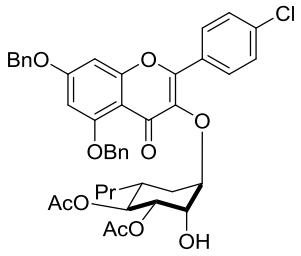
(1S,2S,3R,4R,6R)-4-((5,7-bis(benzyloxy)-2-(4-chlorophenyl)-4-oxo-4H-chromen-3-yl)oxy)-2,3-dihydroxy-6-propylcyclohexyl acetate (13e)



Acetate alkene **7e** (110 mg, 0.17 mmol) was dissloved in 2 mL of a mixture of acetone and CH_2Cl_2 (1: 1), then at 0 ^oC added osmium tetroxide (1.3 mol%) and 50% *N*-methylmorpholine *N*-oxide water solution (34 μL, 0.17 mmol) dropwise successively. The resulting mixture was stirred at room

temperature for 3 hrs. After reaction completed, reaction mixture was washed with saturated sodium bicarbonate and brine, dried over sodium sulfate, then concentrated on rotary evaporator. The resulting crude was purified by chromatography and flash with solvent (Hexane: Ethyl Acetate = 1: 1) to afford product **13e** as light yellow solid (65 mg, 56%): R_f = 0.17 (Hexanes : Ethyl Acetate = 1 : 1); $[\alpha]_D^{22}$: –43 (c = 1.8, CH_2Cl_2); m.p.: 84 – 86 ^oC. ; IR (thin film, cm^{-1}) 3607 – 3238 (br), 2955, 2926, 2870, 2855, 1728, 1605, 1571, 1487, 1435, 11401, 1372, 1300, 1245, 1208, 1173, 1143, 1112, 1091, 1039, 888, 833, 735, 697, 604, 484; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.6 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.49 (d, *J* = 8.6 Hz, 2H), 7.42 – 7.37 (m, 7H), 7.31 (t, *J* = 7.4 Hz, 1H), 6.59 (d, *J* = 2.0 Hz, 1H), 6.49 (d, *J* = 2.0 Hz, 1H), 5.27 (s, 2H), 5.10 (s, 2H), 4.88 (t, *J* = 6.3 Hz, 1H), 4.31 (s, 1H), 4.16 (dd, *J* = 6.1, 3.5 Hz, 1H), 3.85 (dd, *J* = 6.0, 3.4 Hz, 1H), 2.09 (s, 3H), 1.70 – 1.56 (m, 2H), 1.42 – 1.24 (m, 2H), 1.16 – 0.95 (m, 3H), 0.76 (t, *J* = 7.0 Hz, 3H).; 13C NMR (100 MHz, $CDCl_3$) δ 174.2, 171.1, 163.3, 159.9, 158.9, 153.2, 139.7, 136.7, 136.1, 135.5, 130.3, 129.3, 128.9, 128.9, 128.8, 128.8, 128.7, 128.6, 128.5, 127.8, 127.5, 126.6, 109.7, 98.5, 93.9, 80.9, 75.0, 72.1, 72.0, 70.9, 70.6, 36.3, 33.3, 30.2, 21.2, 20.2, 14.1; HRMS (MALDI-TOF/CCA) calcd. $[C_{40}H_{39}ClO_9+Na]^+$: 721.2175, found: 721.2172

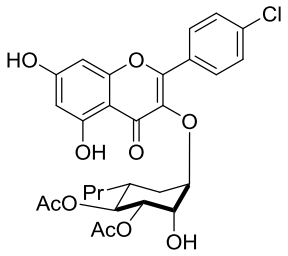
(1S,2S,3S,4R,6R)-4-((5,7-bis(benzyloxy)-2-(4-chlorophenyl)-4-oxo-4H-chromen-3-yl)oxy)-3-hydroxy-6-propylcyclohexane-1,2-diyl diacetate (14e)



To a solution of diol **13e** (40 mg, 0.057 mmol) in 0.9 mL acetonitrile at 0 ^oC, was added Taylor's borinate catalyst (1.2 mg, 10 mol%), acetyl chloride (4.8 μL, 0.068 mmol) and Hunig's base (20 μL, 0.114 mmol) successively. The resulting mixture was stirred at room temperature for 6 hours. Crude material was filtered through a silica gel pad and loaded on HPLC to deliver pure *C*-3 acetyl substituted compound **14e** (17 mg, 40%) as light yellow solid, R_f = 0.40 (Hexanes : Ethyl Acetate = 1 : 1); $[\alpha]_D^{23}$:

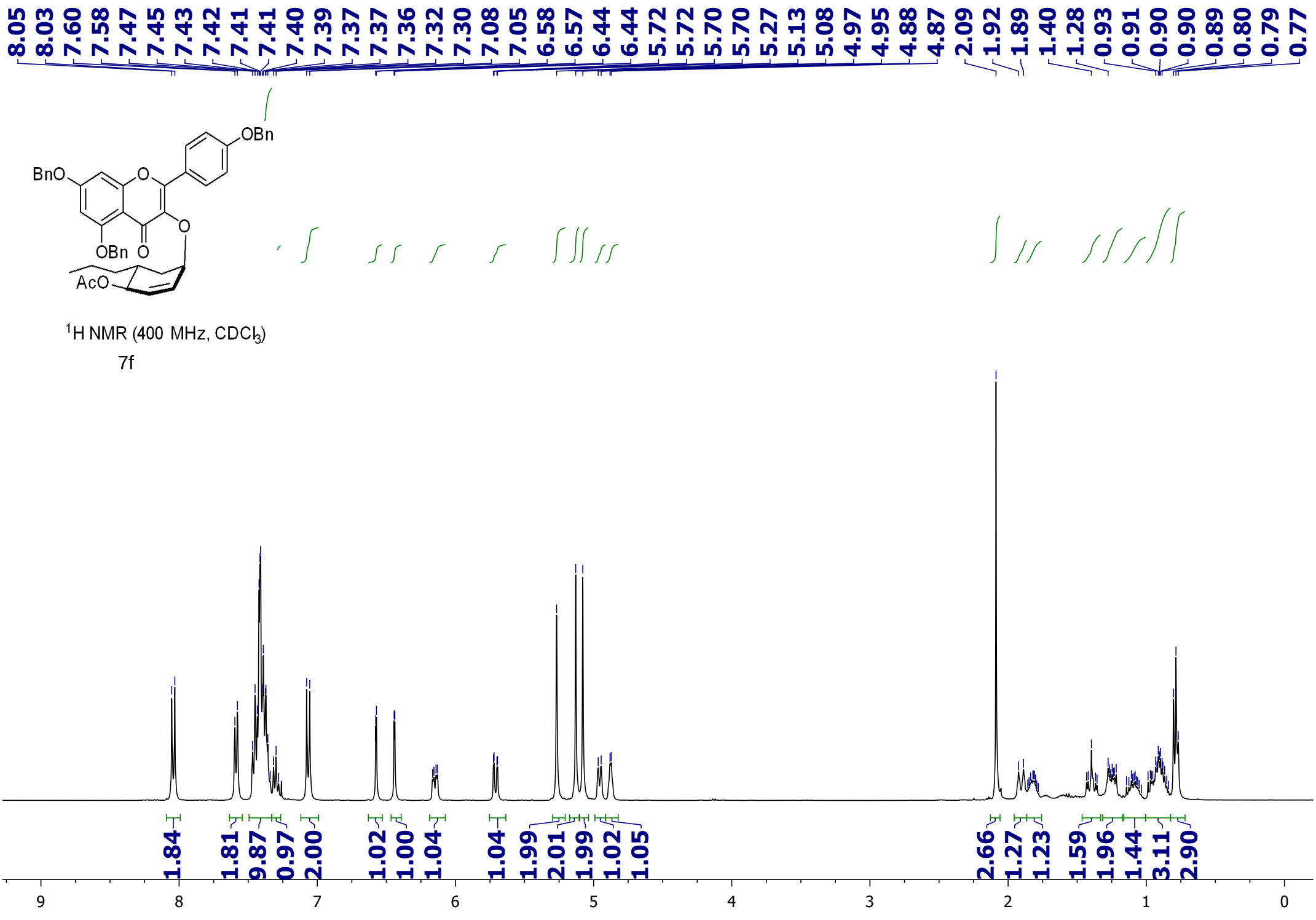
–38 (c = 0.8, CH_2Cl_2); m.p.: 93 – 95 ^oC; IR (thin film, cm^{-1}) 3499 – 3180(br), 3055, 2956, 2871, 2855, 2570, 1731, 1627, 1605, 1570, 1439, 1370, 1317, 1296, 1175, 1143, 1090, 1069, 1043, 1090, 1029, 1016, 869, 834, 805, 701, 648; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 10.3 Hz, 2H), 7.49 (dk, *J* = 13.1 Hz, 2H), 7.43 – 7.33 (m, 7H), 7.29 (t, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 1.7 Hz, 1H), 6.46 (d, *J* = 1.6 Hz, 1H), 5.26 (s, 2H), 5.16 (dd, *J* = 9.3, 4.6 Hz, 1H), 5.10 (s, 2H), 4.98 (t, *J* = 8.8 Hz, 1H), 4.60 (d, *J* = 2.8 Hz, 1H), 4.34 (s, 1H), 2.03 (s, 6H), 1.72 (d, *J* = 14.5 Hz, 1H), 1.58 – 1.51 (m, 1H), 1.47 – 1.41 (m, 1H), 1.23 – 1.17 (m, 2H), 1.13 – 1.06 (m, 1H), 1.01 – 0.93 (m, 1H), 0.90 – 0.85 (m, 1H), 0.74 (t, *J* = 7.1 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 170.4, 169.7, 163.1, 159.9, 158.8, 152.7, 139.4, 136.5, 136.2, 135.5, 130.3, 129.3, 128.8, 128.8, 128.8, 128.7, 128.6, 128.6, 128.5, 128.5, 127.7, 127.5, 126.6, 109.9, 98.3, 93.9, 79.3, 73.5, 73.0, 70.8, 70.5, 35.7, 33.5, 29.7, 29.3, 20.9, 19.6, 14.2; HRMS (MALDI-TOF/CCA) calcd. $[C_{42}H_{41}ClO_{10}+Na]^+$: 763.2280, found: 763.2286

(1S,2S,3S,4R,6R)-4-((2-(4-chlorophenyl)-5,7-dihydroxy-4-oxo-4H-chromen-3-yl)oxy)-3-hydroxy-6-propylcyclohexane-1,2-diyl diacetate (3e)



To a solution of compound **14e** (15 mg, 0.02 mmol) in 0.3 mL THF/CH_2Cl_2 (1 : 1) was added Pd/C(1.1 mg, 5 mol%) under H_2 atmosphere. The resulting suspension solution was stirred overnight at room temperature. Mixture was filtered through a celite column to remove Pd/C. Crude was purified by silica gel column chromatography and flushed with solvent (Hexanes : Ethyl Acetate = 1 : 1) to afford deprotected final product **3e** (4.4 mg, 40%); R_f = 0.10 (Hexanes : Ethyl Acetate = 1: 2); m.p.: 110 – 112 ^oC; $[\alpha]_D^{23}$: –28 (c = 1.6, Acetone); IR (thin film, cm^{-1}): 3501 – 3265(br), 2959, 2926, 2854, 1740, 1716, 1654, 1609, 1559, 1507, 1489, 1464, 1456, 1436, 1368, 1308, 1259, 1215, 1173, 1088, 1044, 1015, 837, 802, 757, 735, 699; ^1H NMR (500 MHz, acetone-d6) δ 8.02 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 8.6 Hz,

2H), 6.50 (s, 1H), 6.29 (s, 1H), 5.17 – 4.93 (m, 2H), 4.62 (d, *J* = 2.9 Hz, 1H), 4.35 (s, 1H), 1.98 (t, *J* = 7.2 Hz, 6H), 1.77 (d, *J* = 13.4 Hz, 1H), 1.60 – 1.40 (m, 2H), 1.24 – 1.11(m, 2H), 1.05 – 0.80 (m, 2H), 0.74 (t, *J* = 7.0 Hz, 3H).; ^{13}C NMR (100 MHz, acetone-d6) δ 178.7, 169.6, 169.5, 164.4, 162.4, 157.2, 155.5, 153.4, 137.0, 136.4, 130.9, 129.5, 128.8, 105.2, 98.8, 96.8, 93.7, 80.2, 73.5, 72.5, 69.2, 35.3, 33.6, 20.0, 19.9, 19.1, 13.7; HRMS (MALDI-TOF/CCA) calcd. $[C_{42}H_{41}ClO_{10}+Na]^+$: 763.2280, found: 763.2286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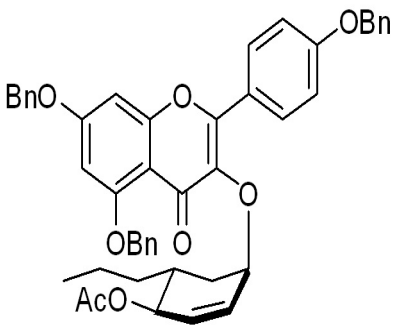
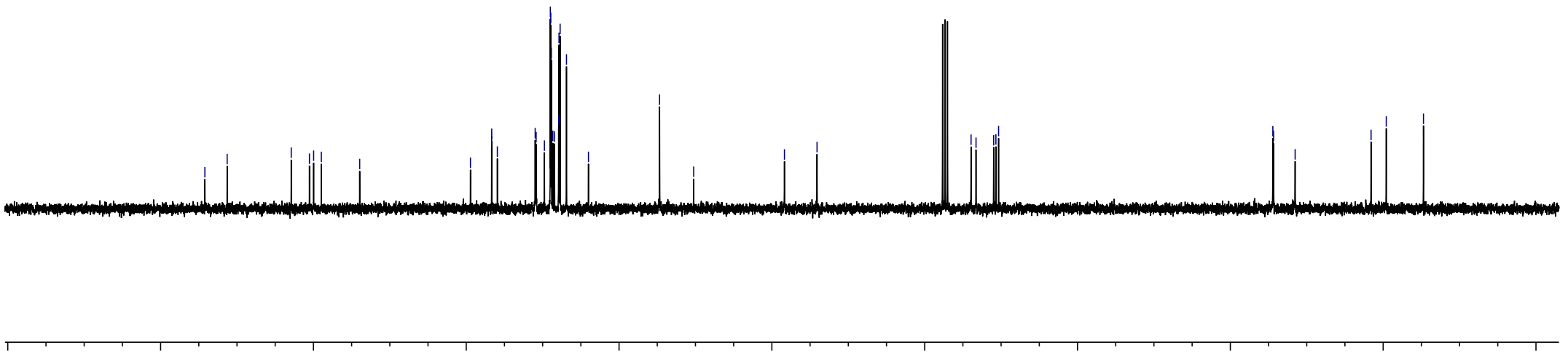
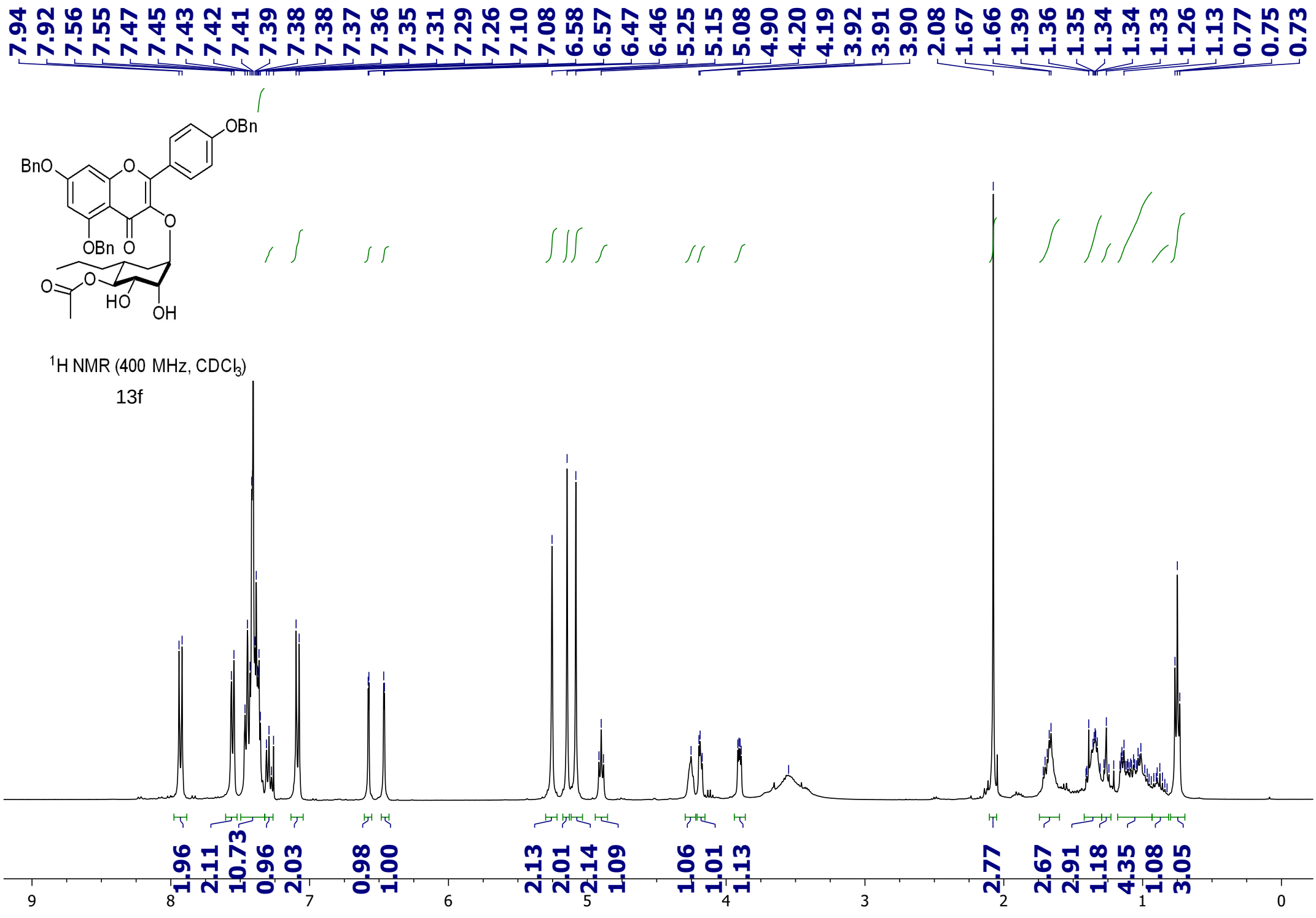
OBn
BnO
O
O
OBn
O
O
AcO
1H NMR (400 MHz, CDCl3)
7f
1.84 1.81 9.87 0.97 2.00 1.02 1.00 1.04 1.04 1.99 2.01 1.99 1.02 1.05 2.66 1.27 1.23 1.59 1.96 1.44 3.11 2.90
9 8 7 6 5 4 3 2 1 0



^{13}C NMR (100 MHz, $CDCl_3$)

7f

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OBn
BnO
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O
OBn
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HO
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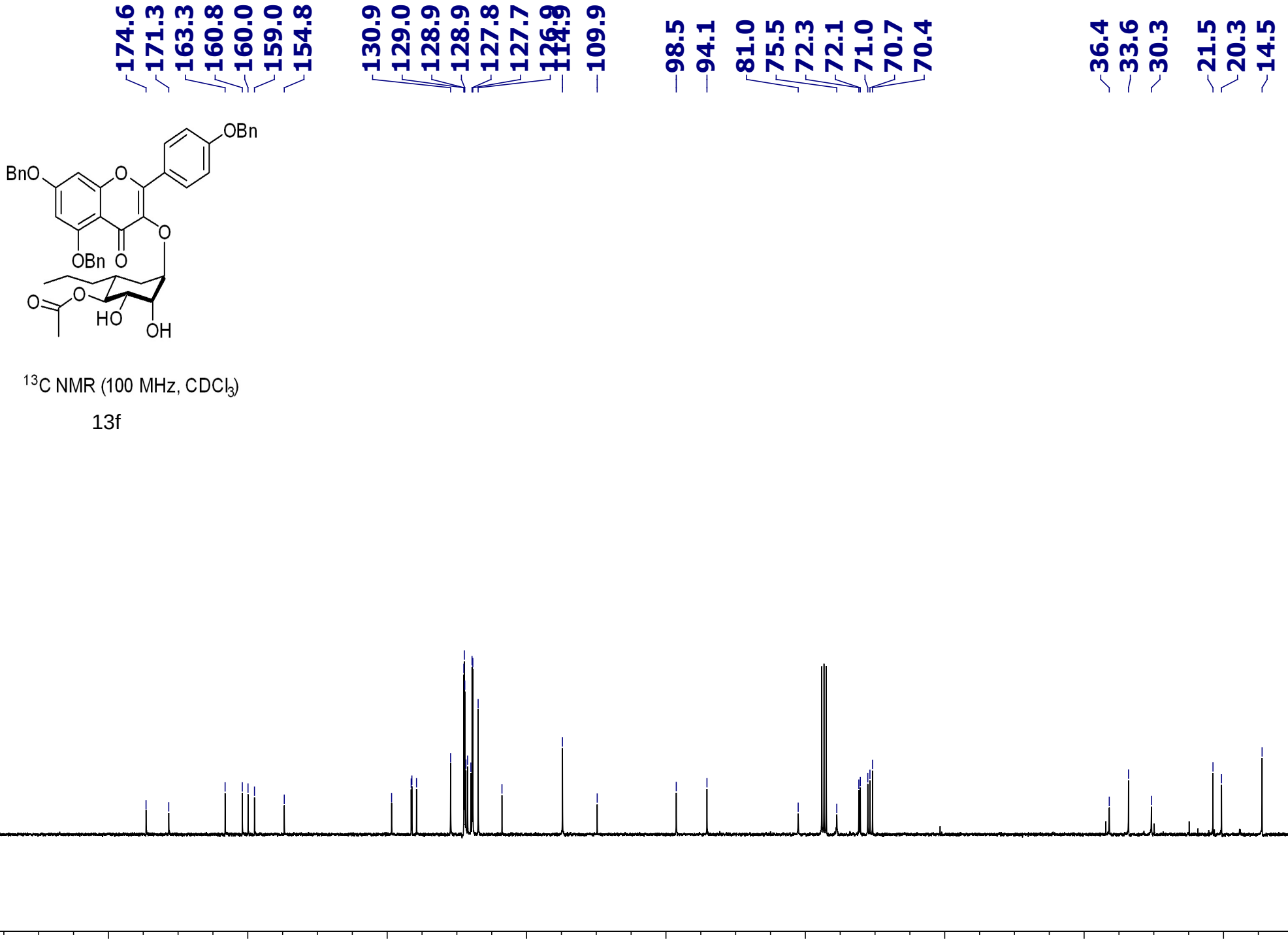
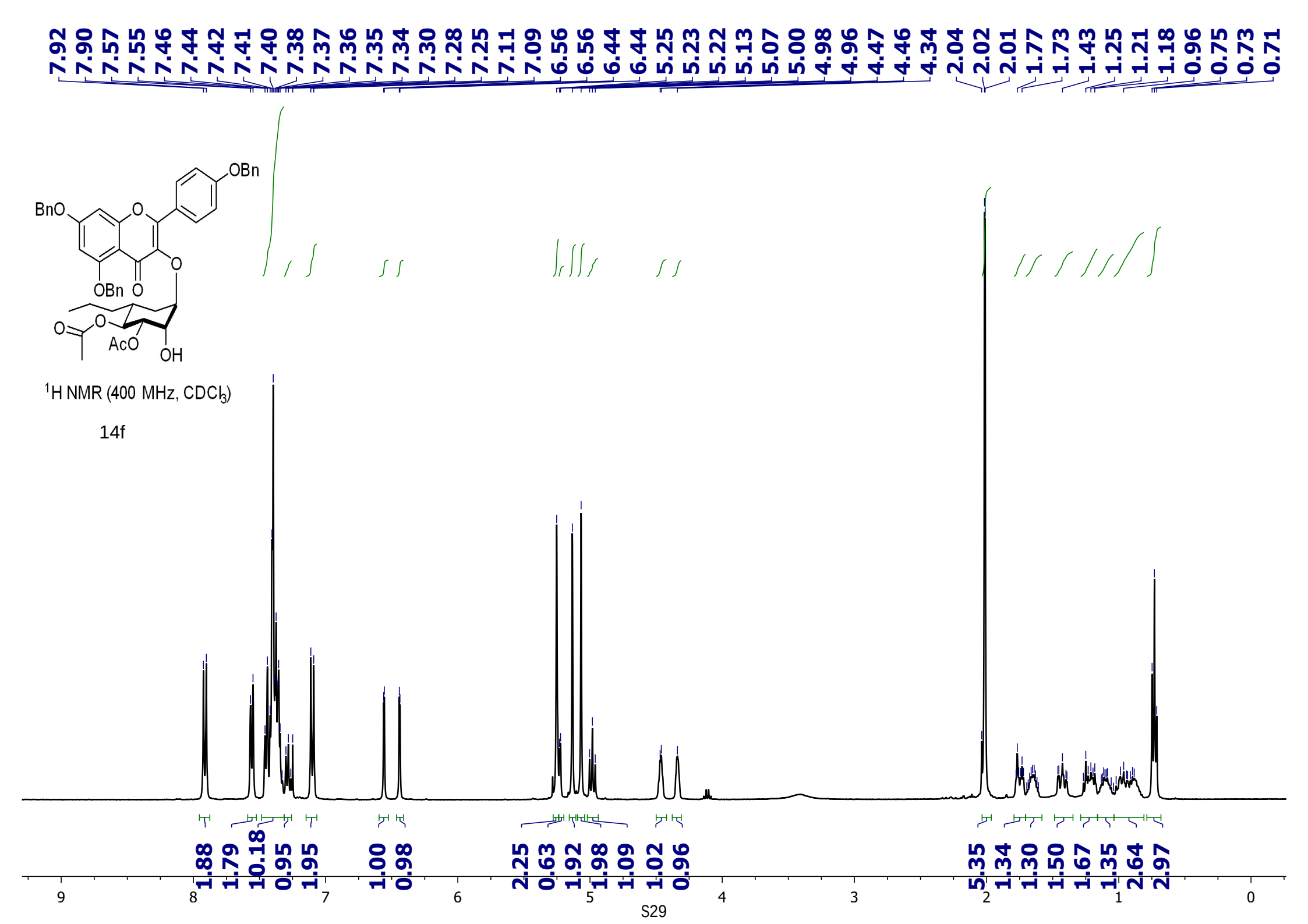
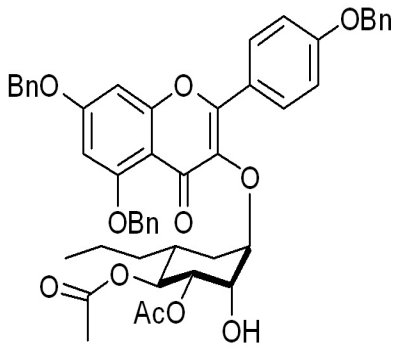
1H NMR (400 MHz, CDCl3)
13f
1.96 2.11 10.73 0.96 2.03 0.98 1.00 2.13 2.01 2.14 1.09 1.06 1.01 1.13 2.77 2.67 2.91 1.18 4.35 1.08 3.05
9 8 7 6 5 4 3 2 1 0



^{13}C NMR (100 MHz, $CDCl_3$)

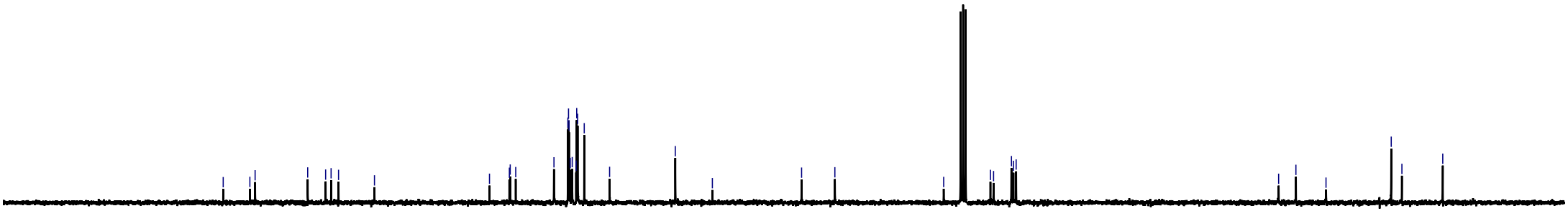
13f

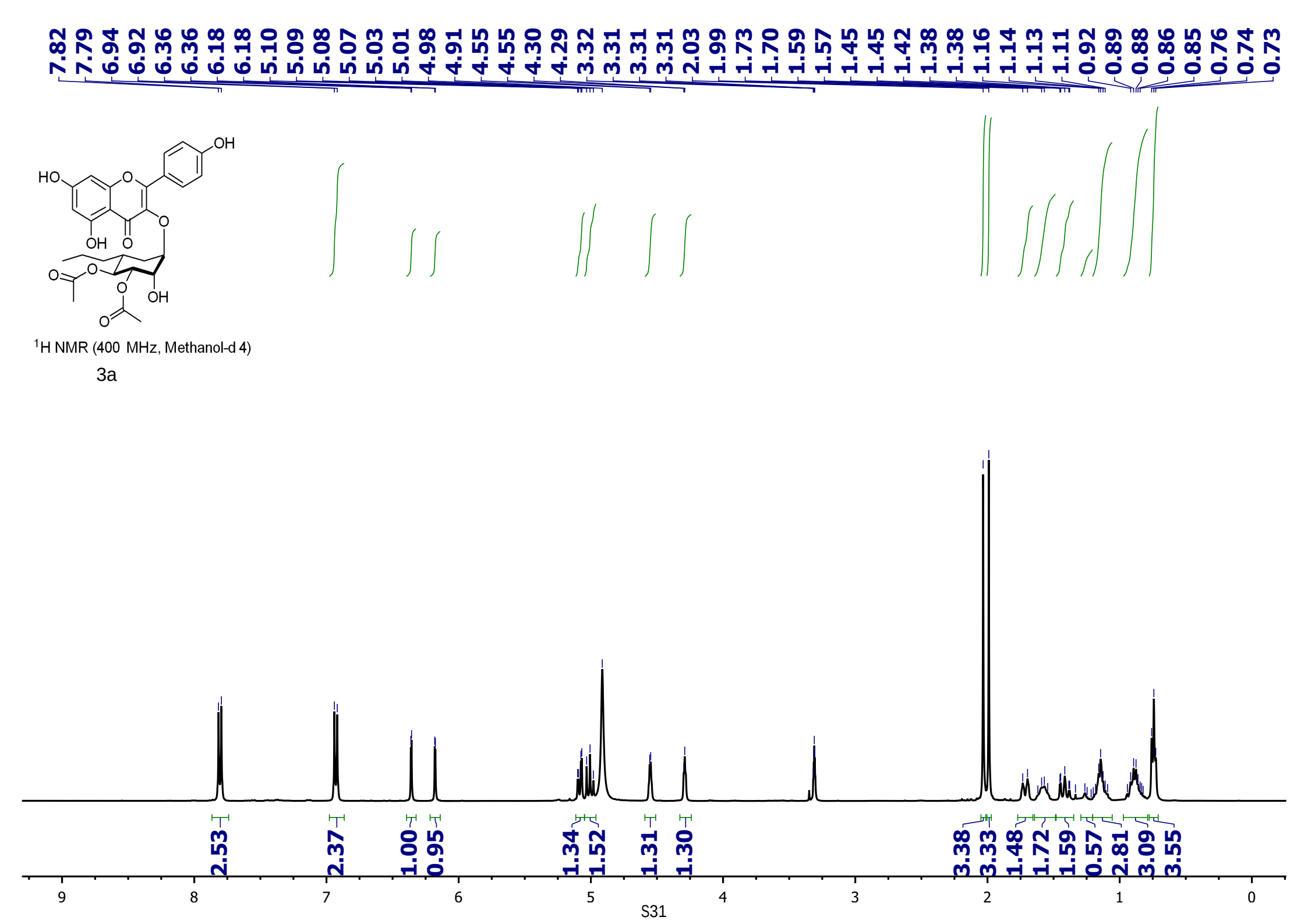

7.92 7.90 7.57 7.55 7.46 7.44 7.42 7.41 7.40 7.38 7.37 7.36 7.35 7.34 7.30 7.28 7.25 7.11 7.09 6.56 6.56 6.44 6.44 5.25 5.23 5.22 5.13 5.07 5.00 4.98 4.96 4.47 4.46 4.34 2.04 2.02 2.01 1.77 1.73 1.43 1.25 1.21 1.18 0.96 0.75 0.73 0.71
BnO
OBn
OBn
O
AcO
OH
^{1}H NMR (400 MHz, $CDCl_3$)
14f
1.88 1.79 10.18 0.95 1.95 1.00 0.98 2.25 0.63 1.92 1.98 1.09 1.02 0.96 5.35 1.34 1.30 1.50 1.67 1.35 2.64 2.97
9 8 7 6 5 4 3 2 1 0



^{13}C NMR (100 MHz, $CDCl_3$)

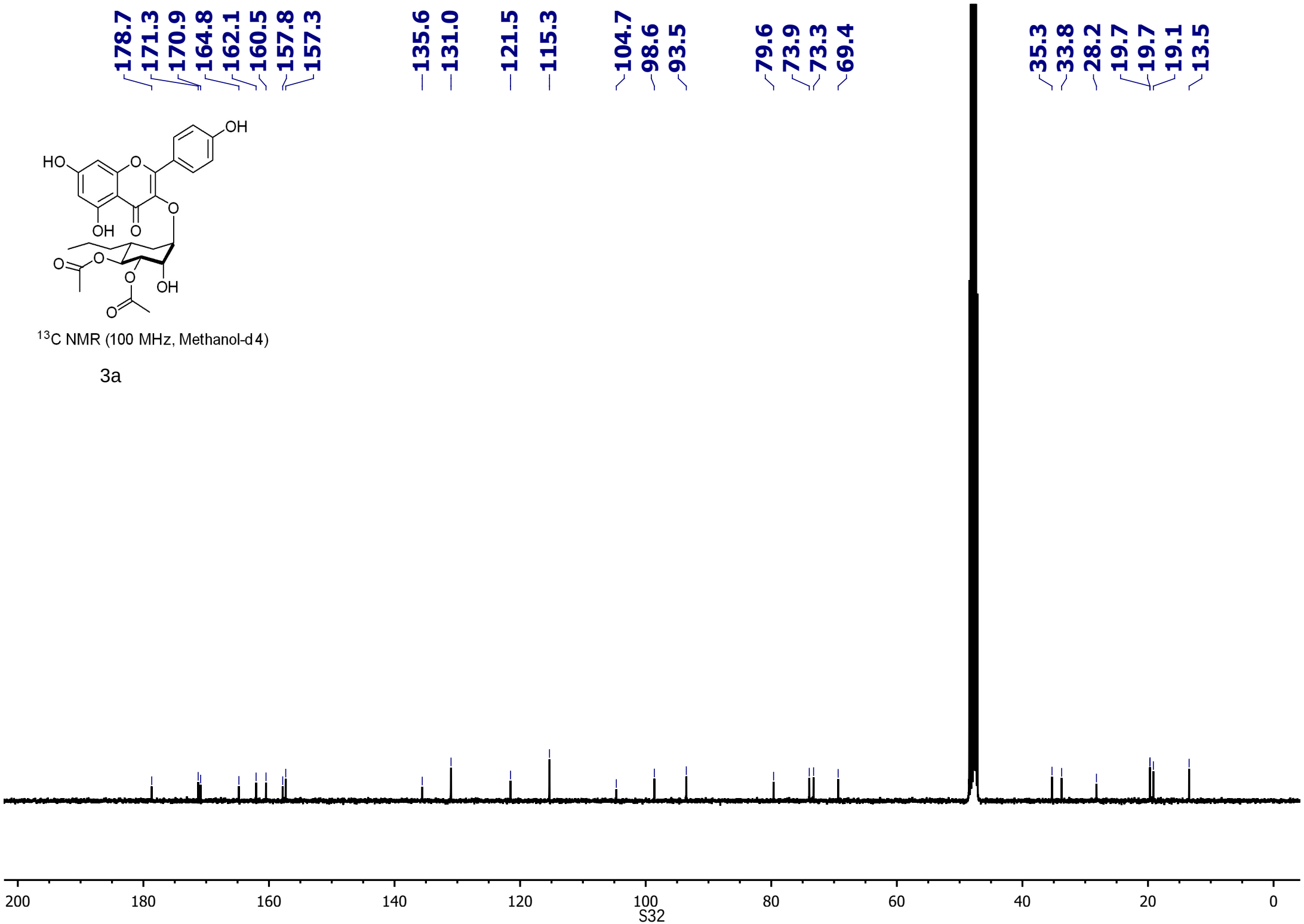
14f





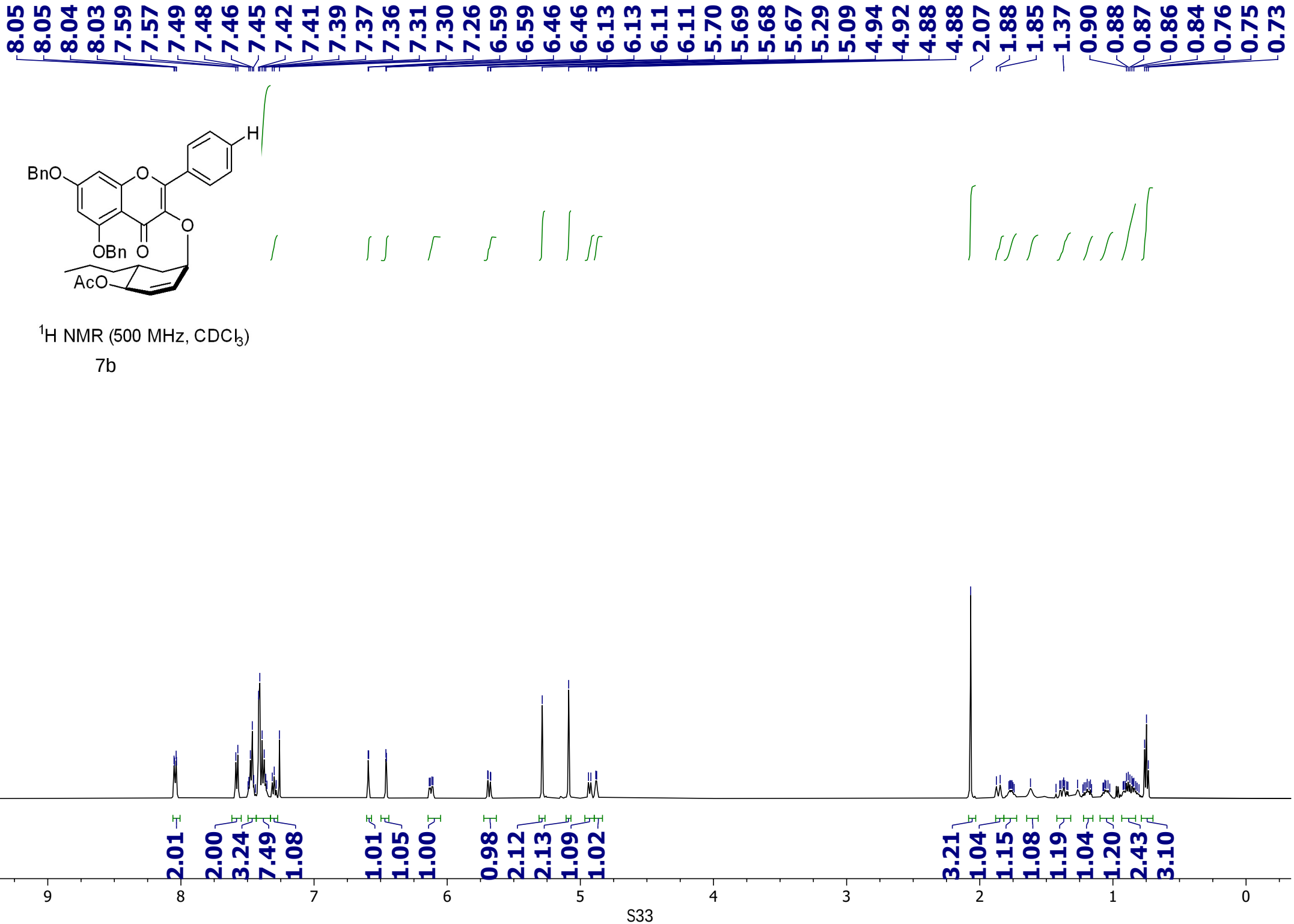
^{1}H NMR (400 MHz, Methanol-d 4)

3a



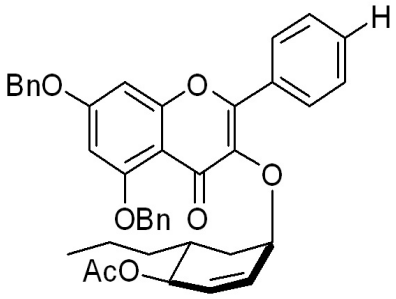
^{13}C NMR (100 MHz, Methanol-d4)

3a



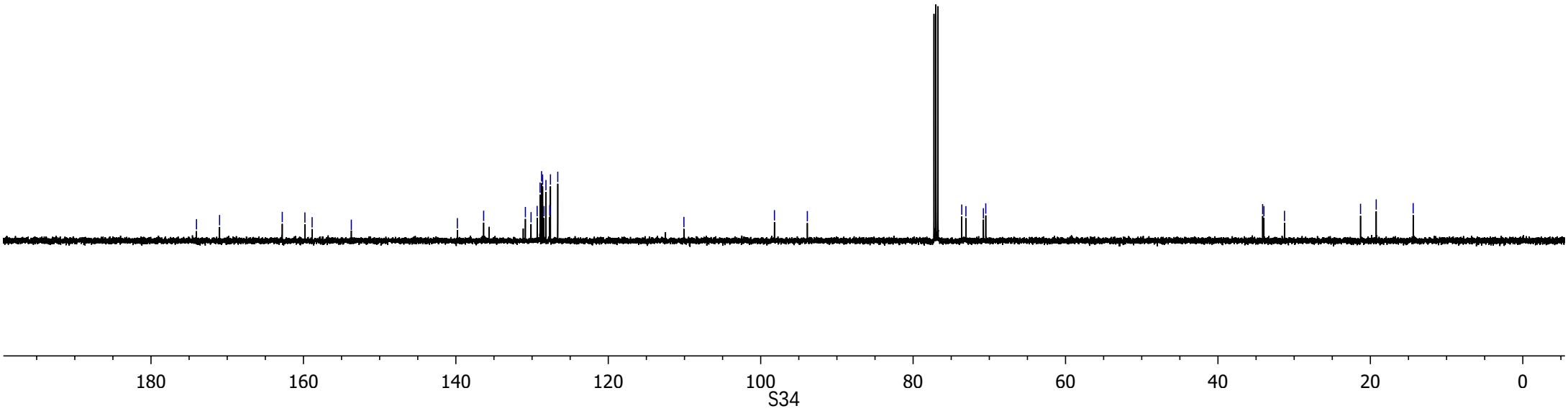
^{1}H NMR (500 MHz, $CDCl_3$)

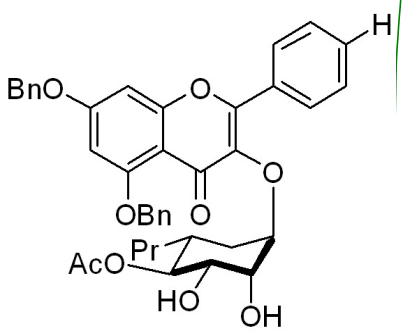
7b



^{13}C NMR (100 MHz, $CDCl_3$)

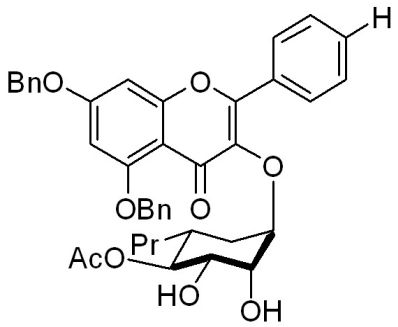
7b





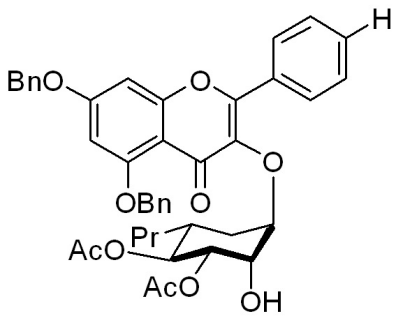
^{1}H NMR (500 MHz, $CDCl_3$)

13b



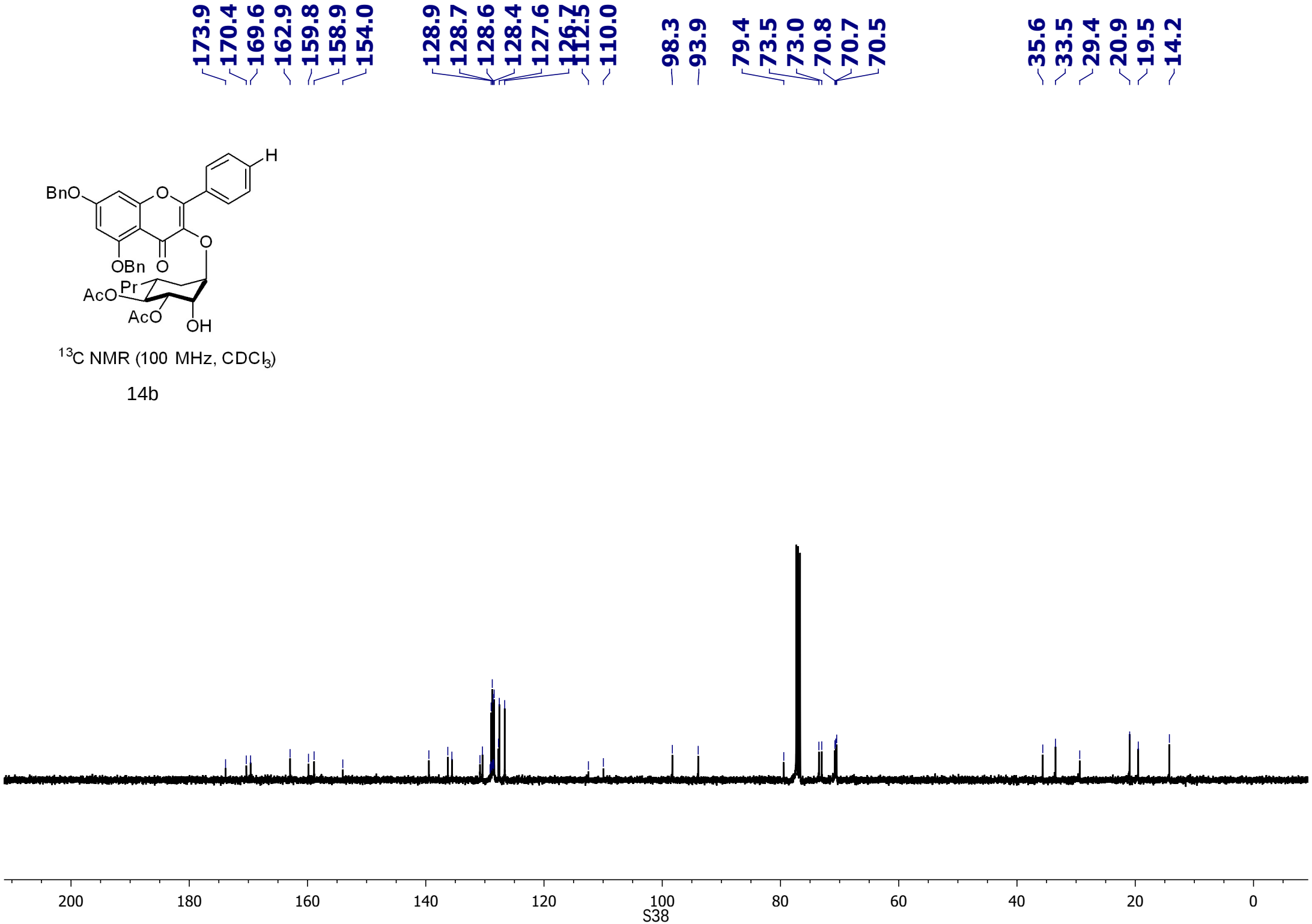
^{13}C NMR (100 MHz, $CDCl_3$)

13b



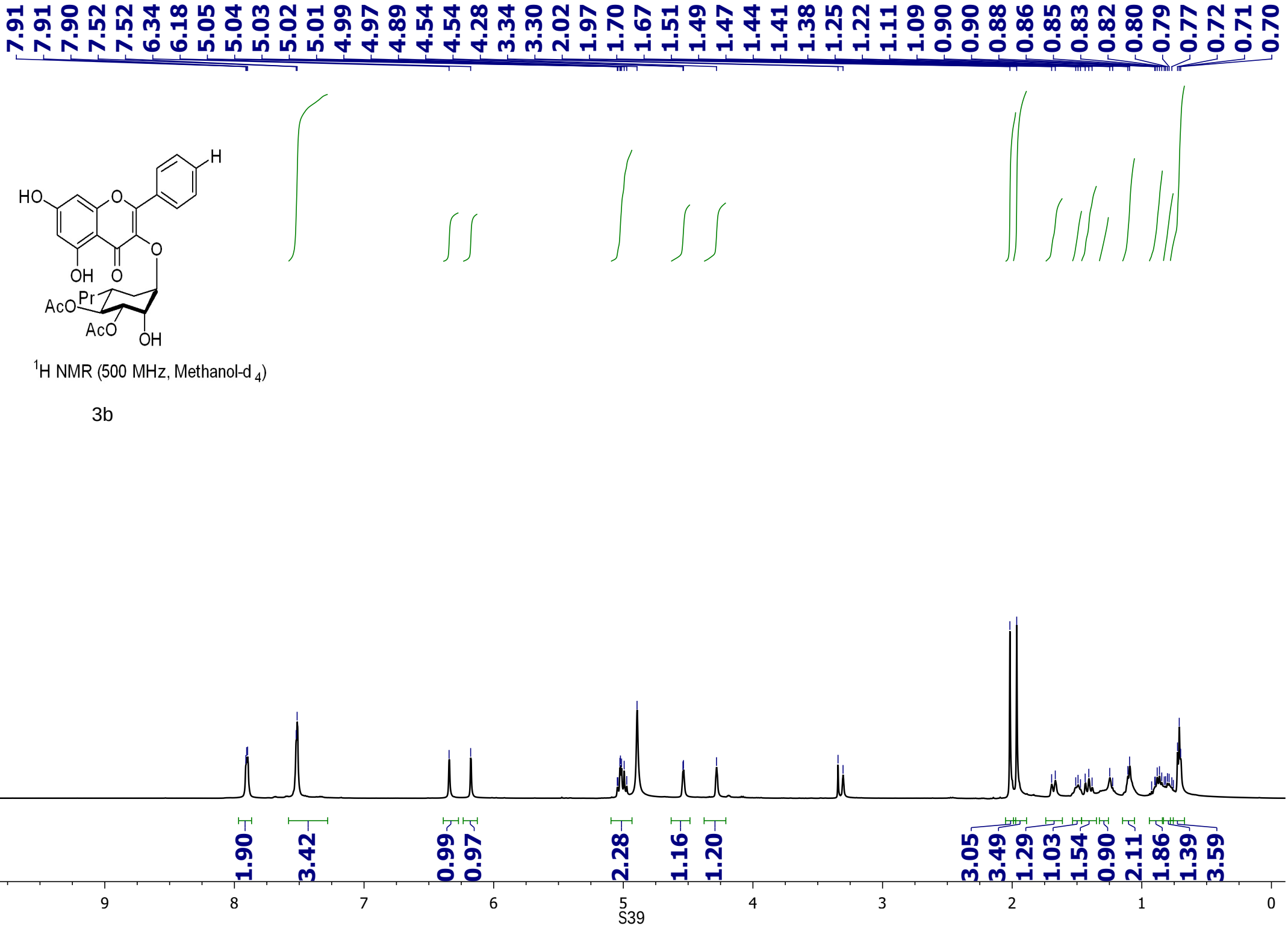
^{1}H NMR (500 MHz, $CDCl_3$)

14b



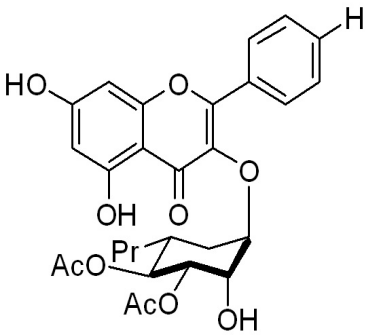
^{13}C NMR (100 MHz, $CDCl_3$)

14b



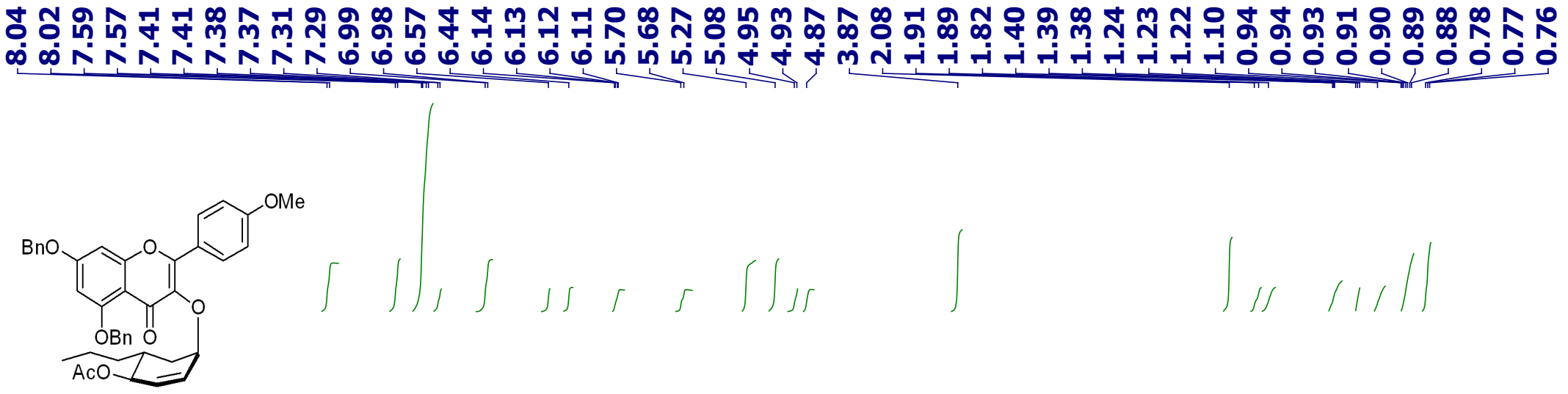
^{1}H NMR (500 MHz, Methanol-d $_{4}$)

3b



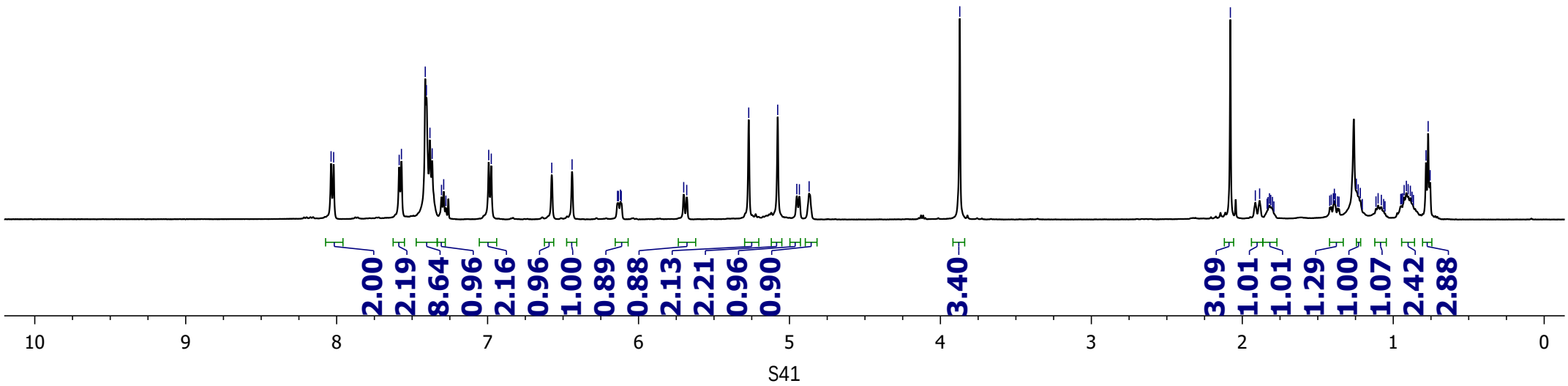
^{13}C NMR (100 MHz, Methanol-d $_4$)

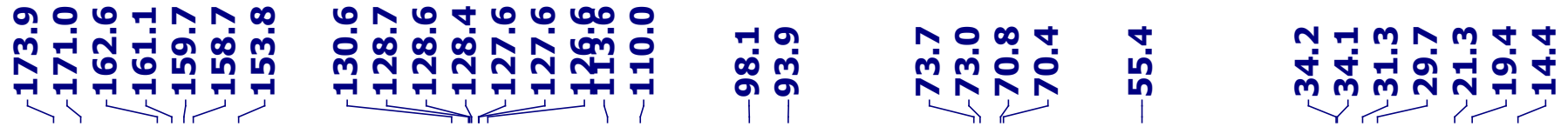
3b

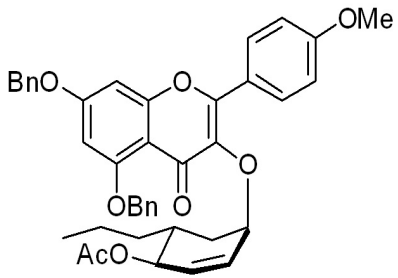


^{1}H NMR (500 MHz, $CDCl_3$)

7c

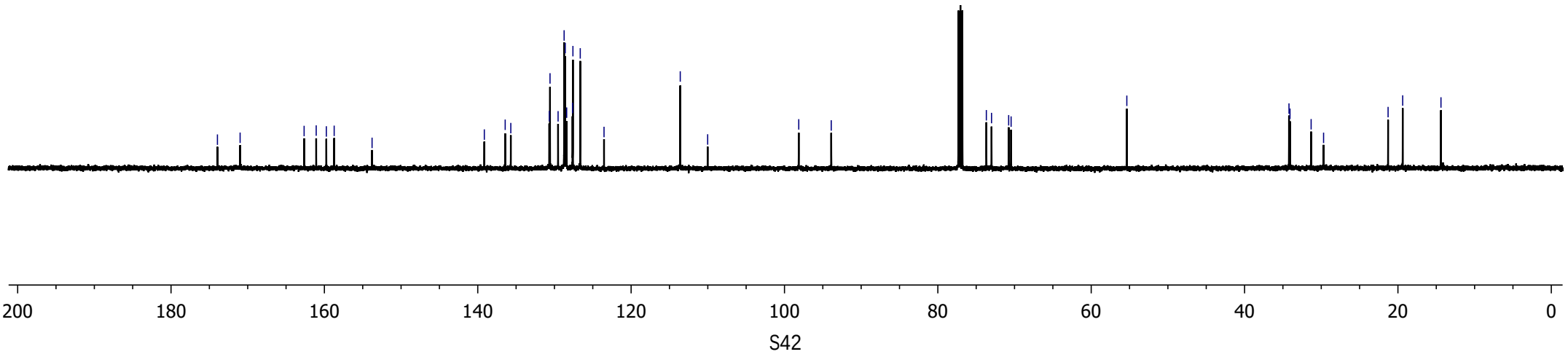


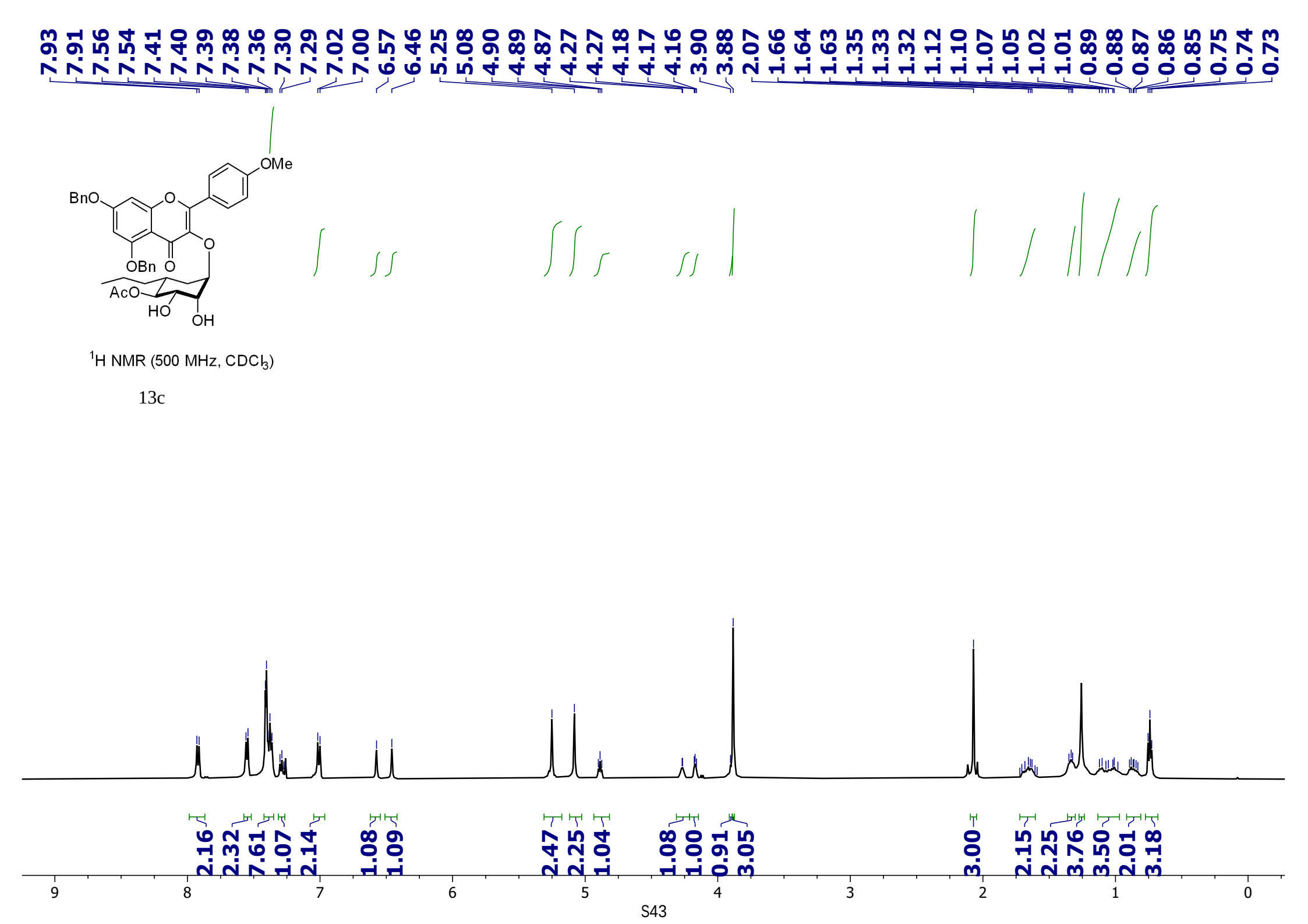




^{13}C NMR (100 MHz, $CDCl_3$)

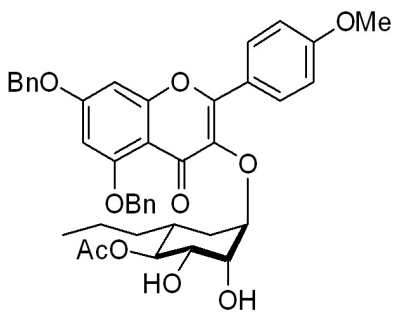
7c





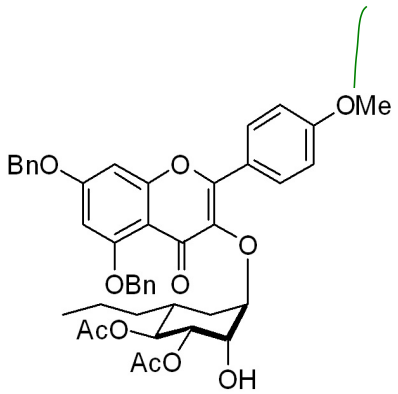
^{1}H NMR (500 MHz, $CDCl_3$)

13c



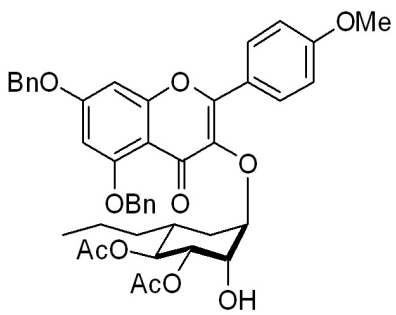
^{13}C NMR (100 MHz, $CDCl_3$)

13c



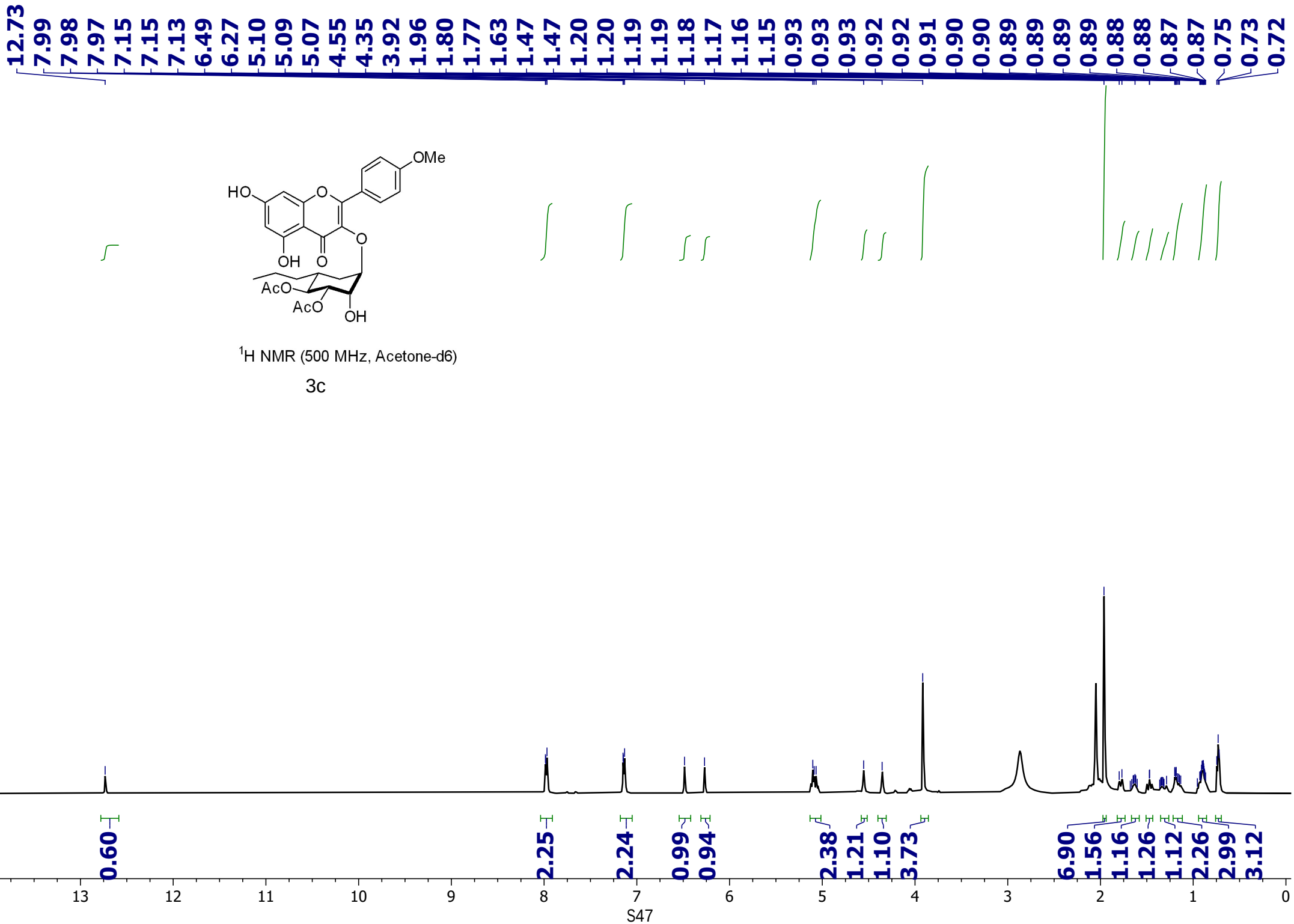
^{1}H NMR (500 MHz, $CDCl_3$)

14c



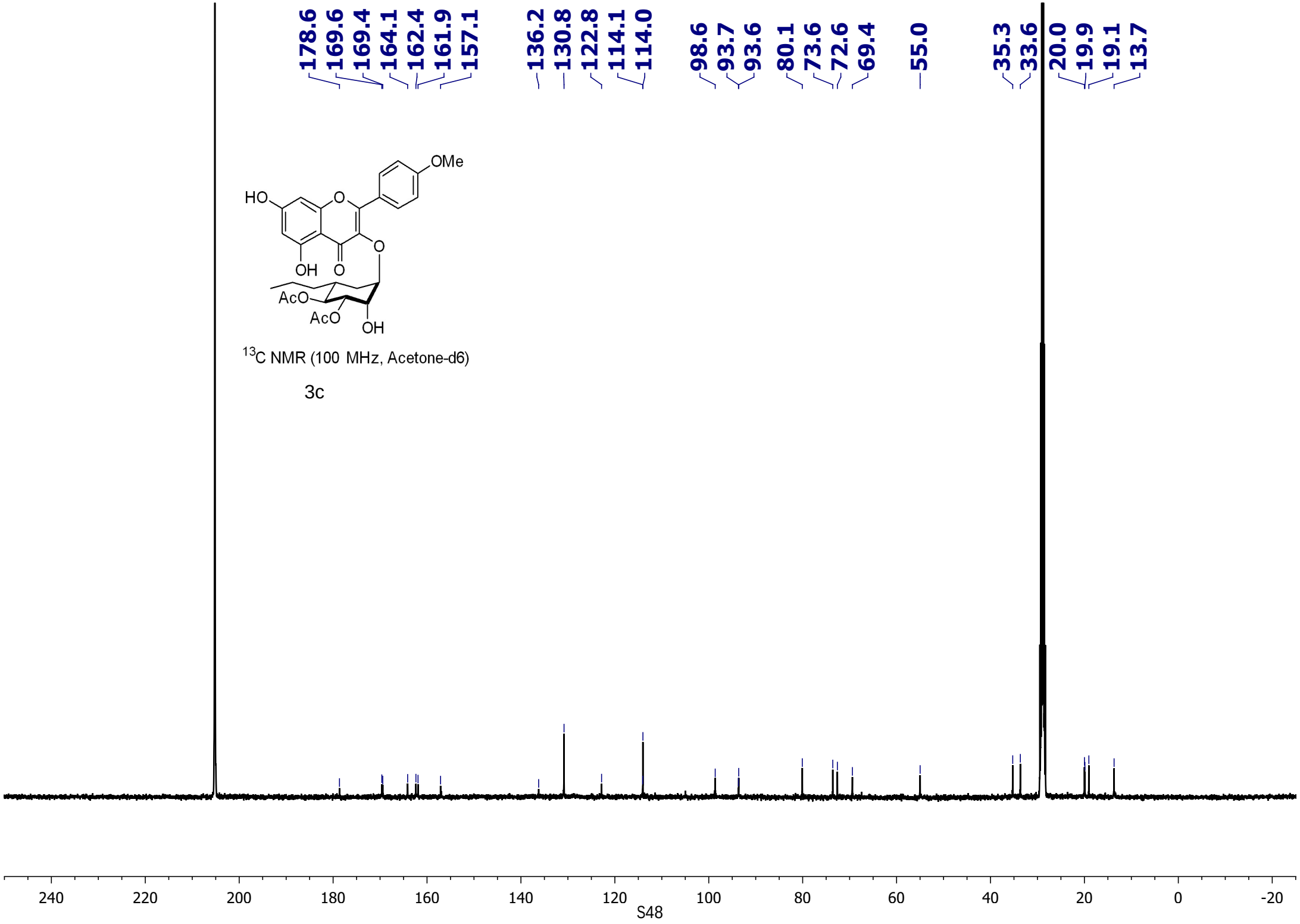
^{13}C NMR (100 MHz, $CDCl_3$)

14c



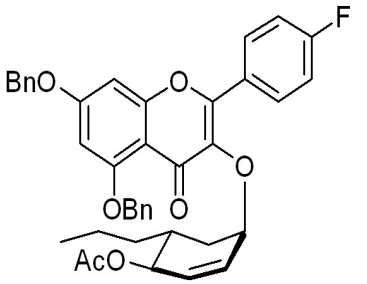
^{1}H NMR (500 MHz, Acetone-d6)

3c



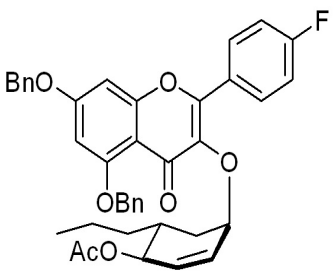
^{13}C NMR (100 MHz, Acetone-d6)

3c



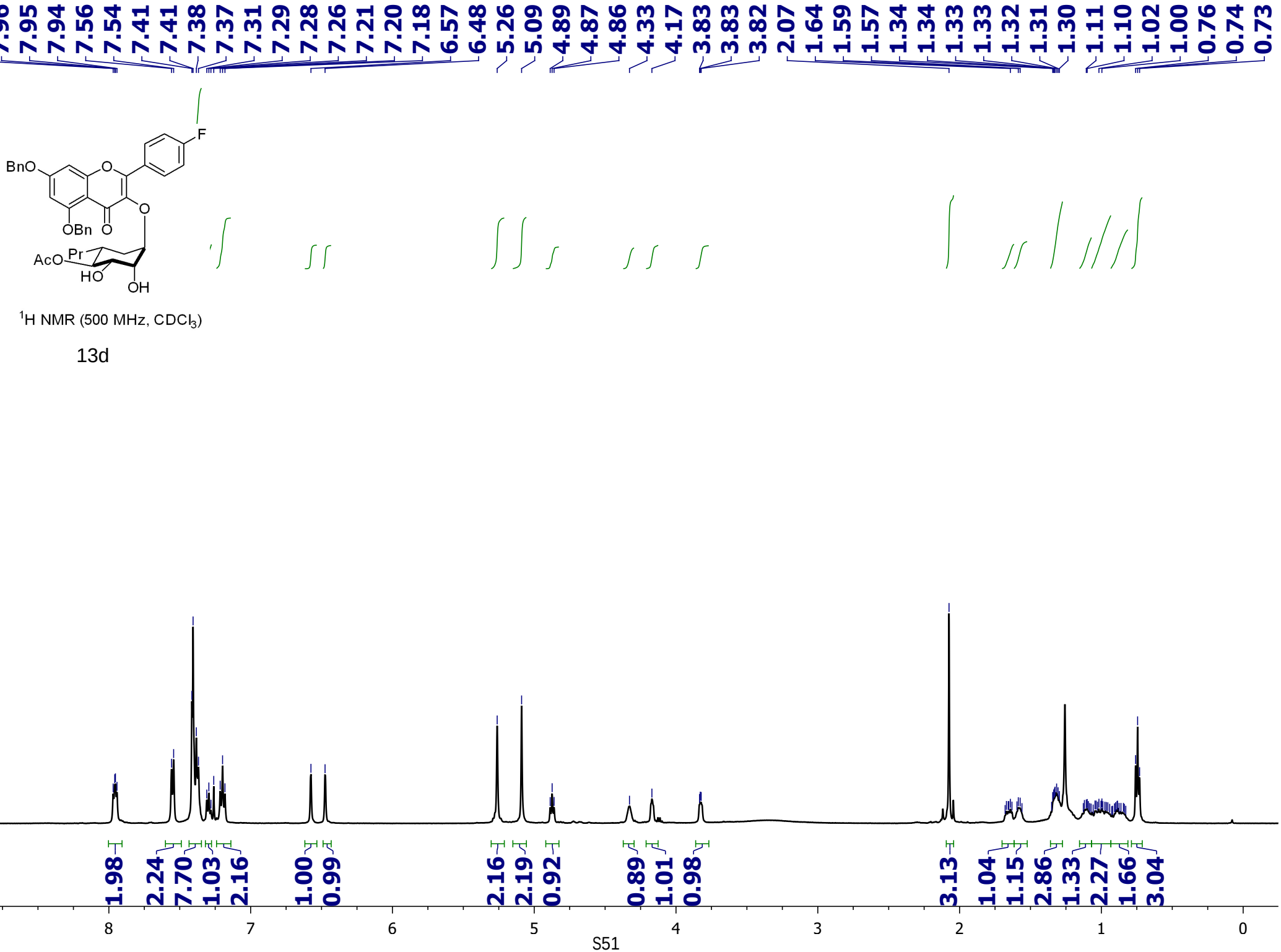
^{1}H NMR (500 MHz, $CDCl_3$)

7d



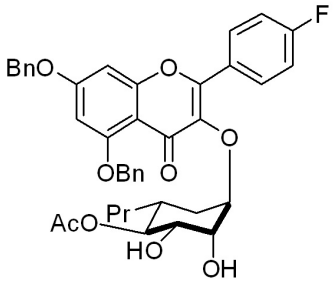
^{13}C NMR (100 MHz, $CDCl_3$)

7d



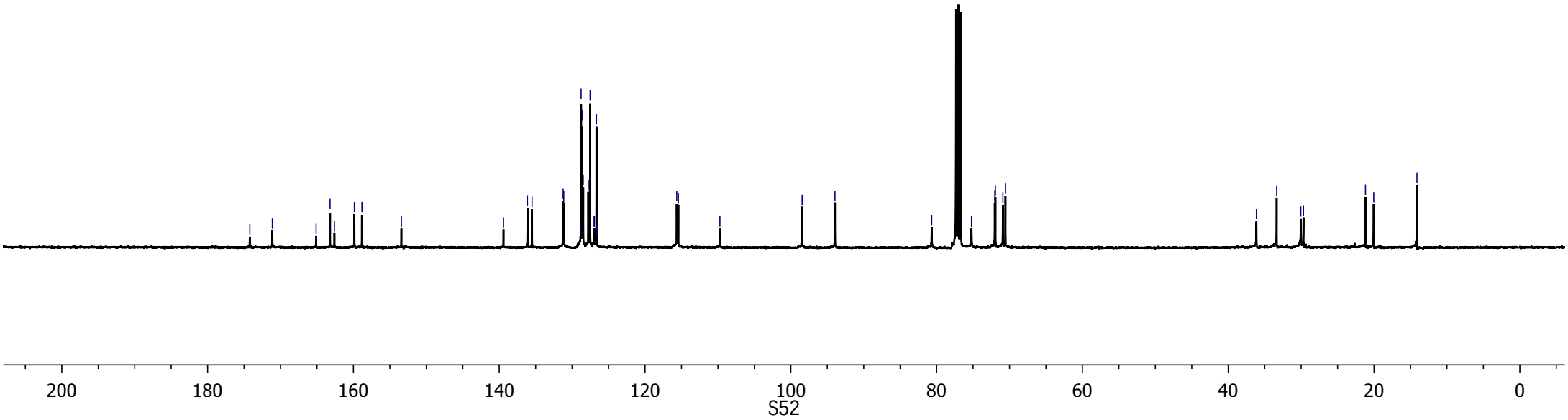
^{1}H NMR (500 MHz, $CDCl_3$)

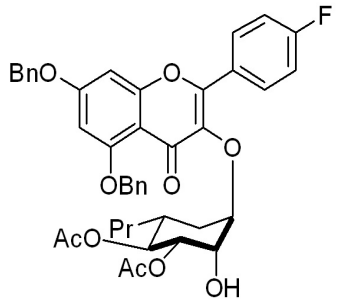
13d



^{13}C NMR (100 MHz, $CDCl_3$)

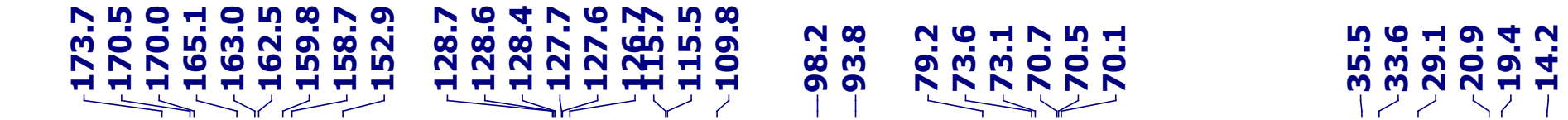
13d

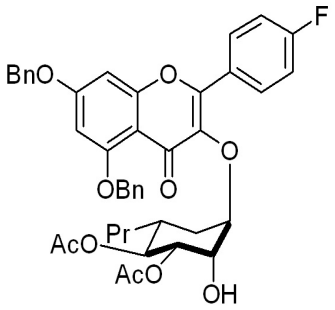




^{1}H NMR (500 MHz, $CDCl_3$)

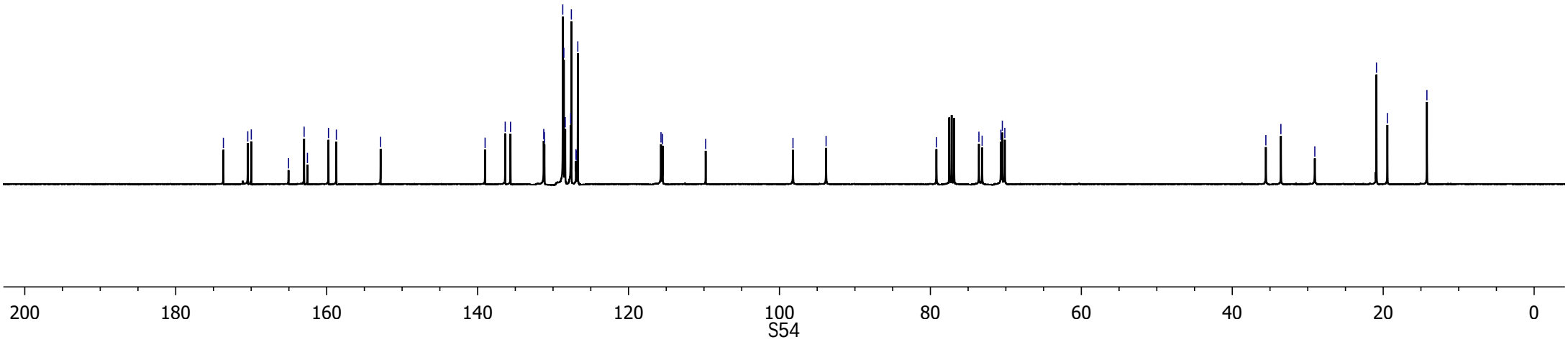
14d

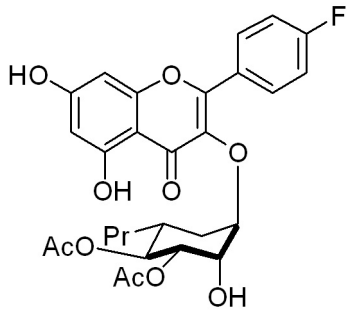




^{13}C NMR (100 MHz, $CDCl_3$)

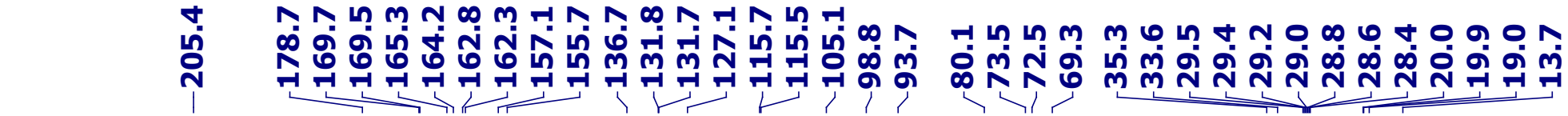
14d

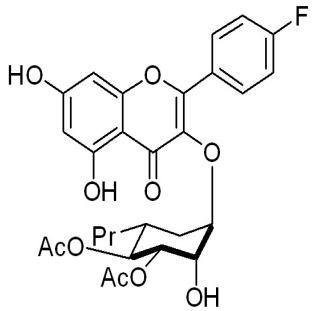




^{1}H NMR (500 MHz, Acetone-d$_6$)

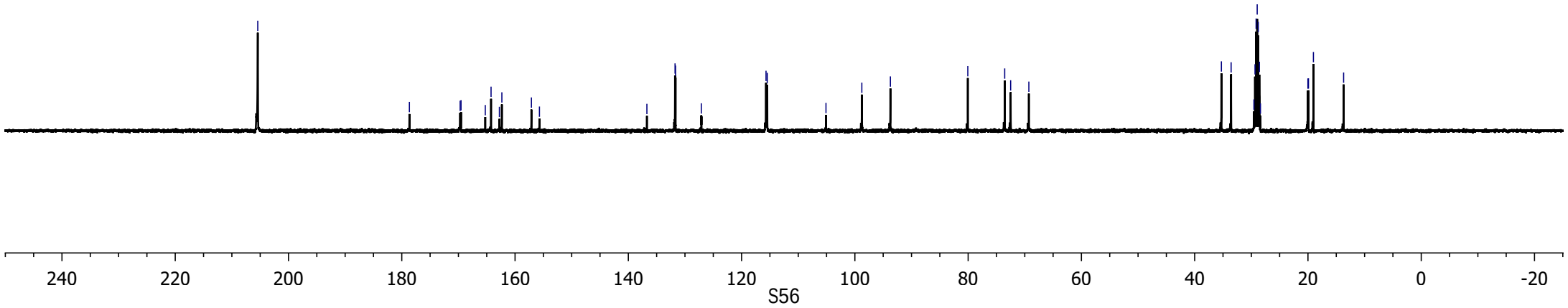
3d

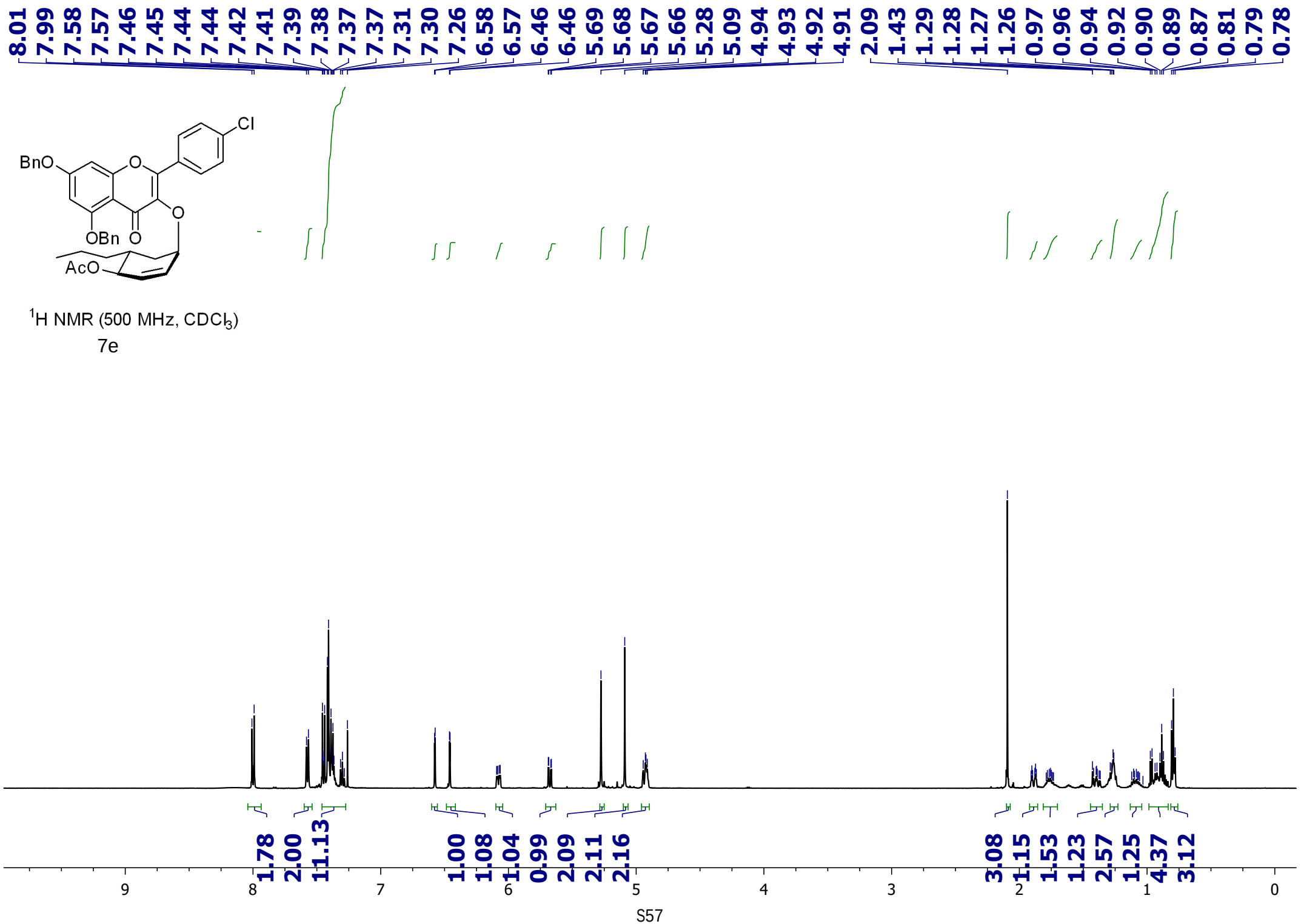




^{13}C NMR (100 MHz, acetone-d6)

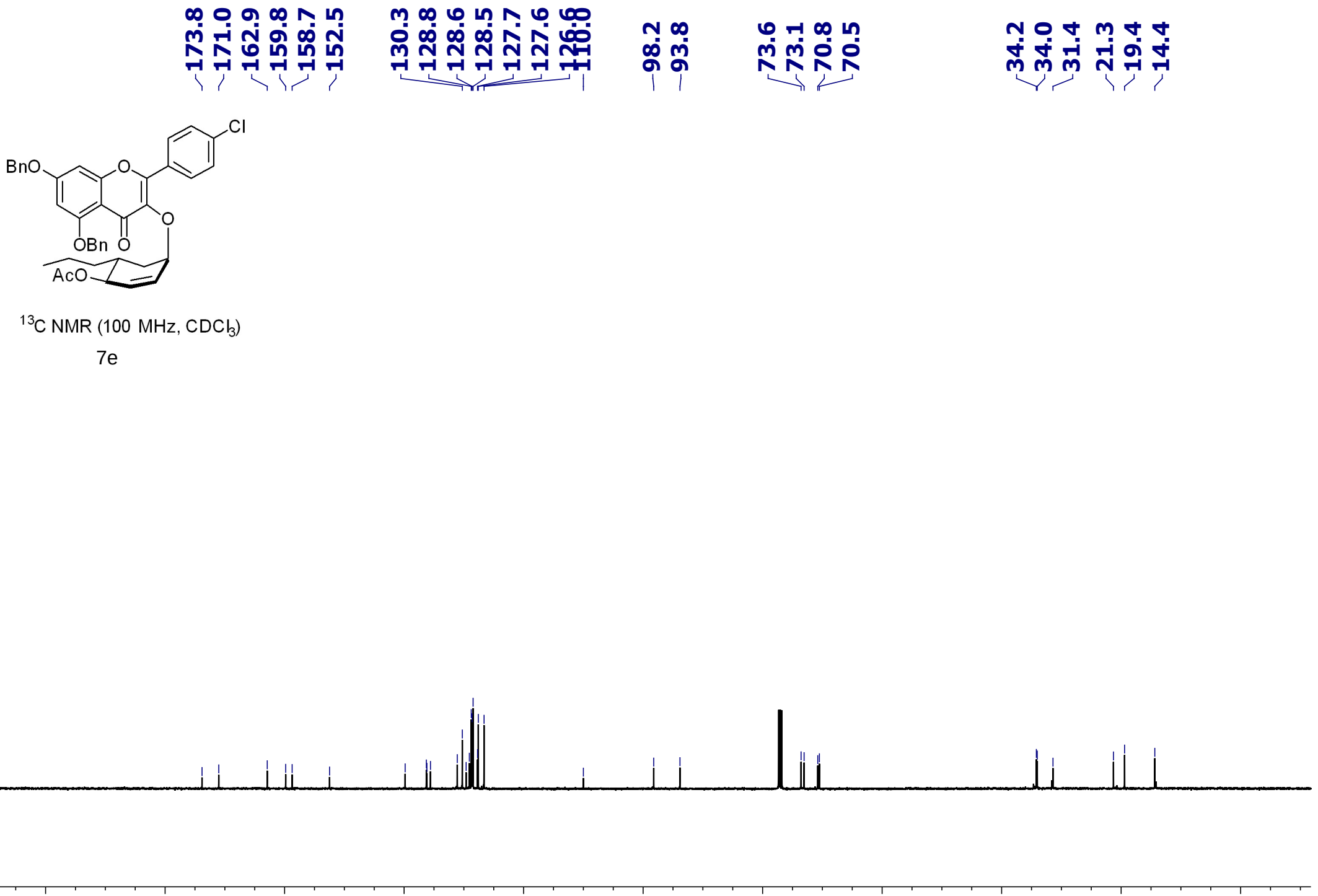
3d





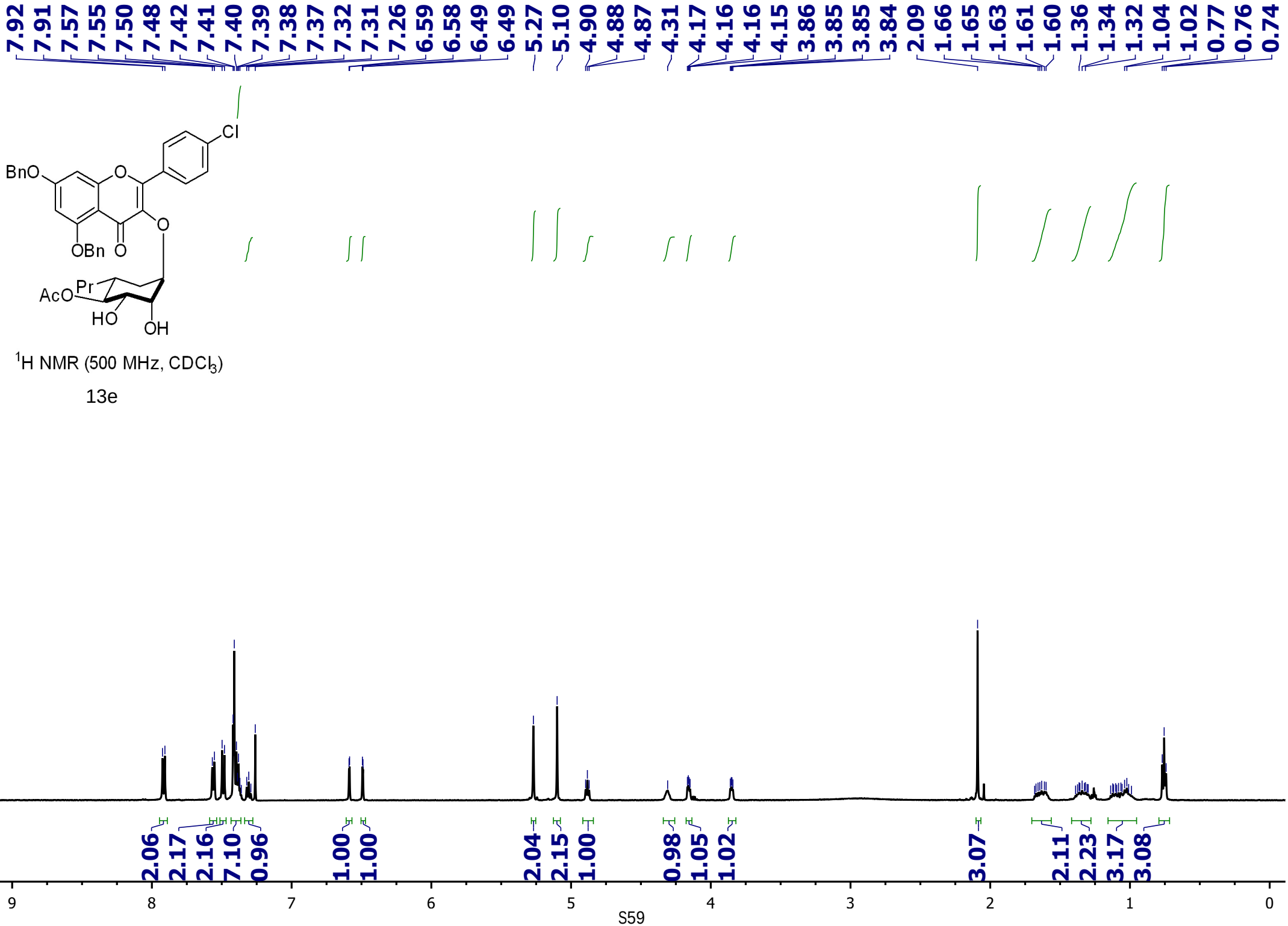
^{1}H NMR (500 MHz, $CDCl_3$)

7e



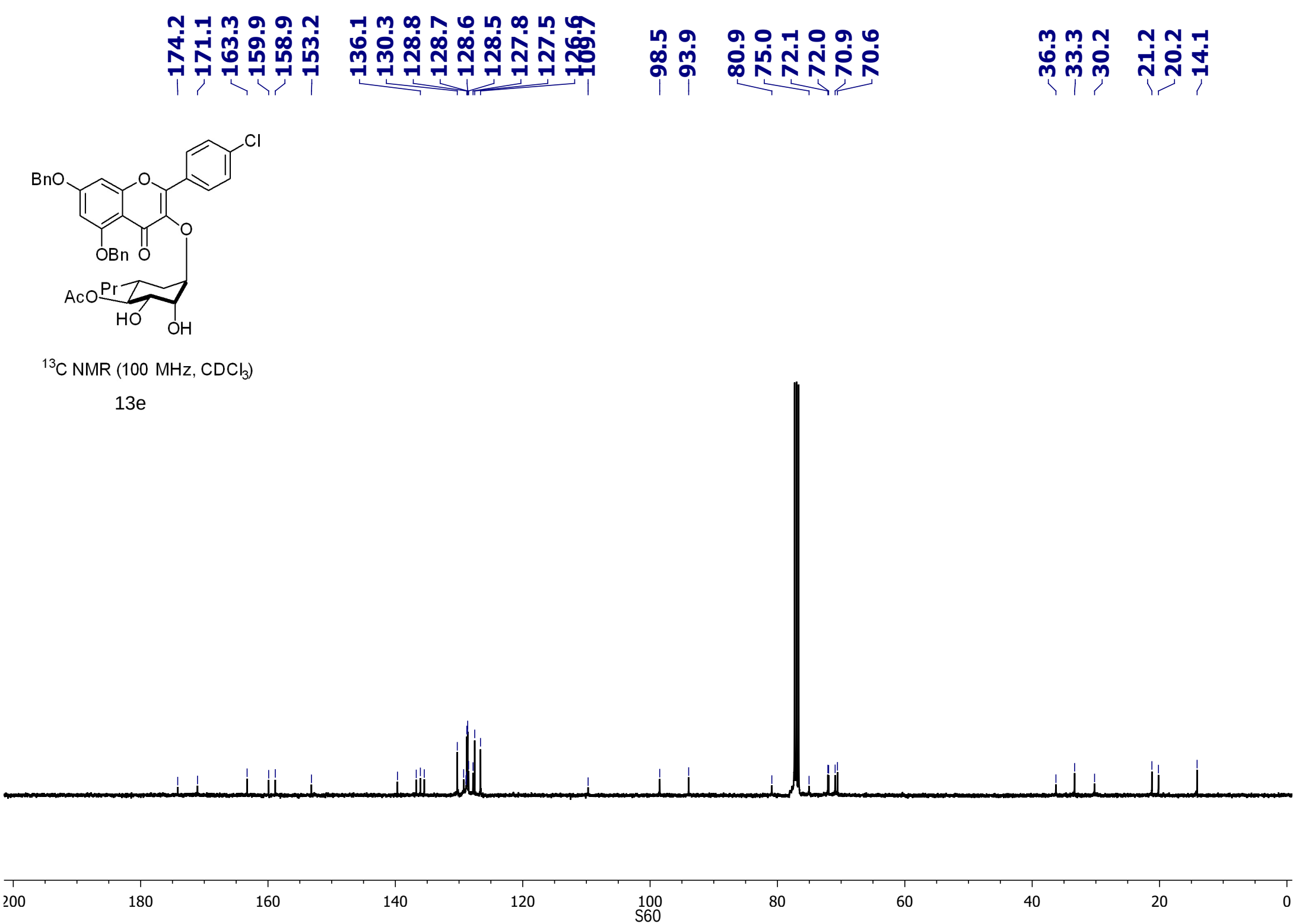
^{13}C NMR (100 MHz, $CDCl_3$)

7e



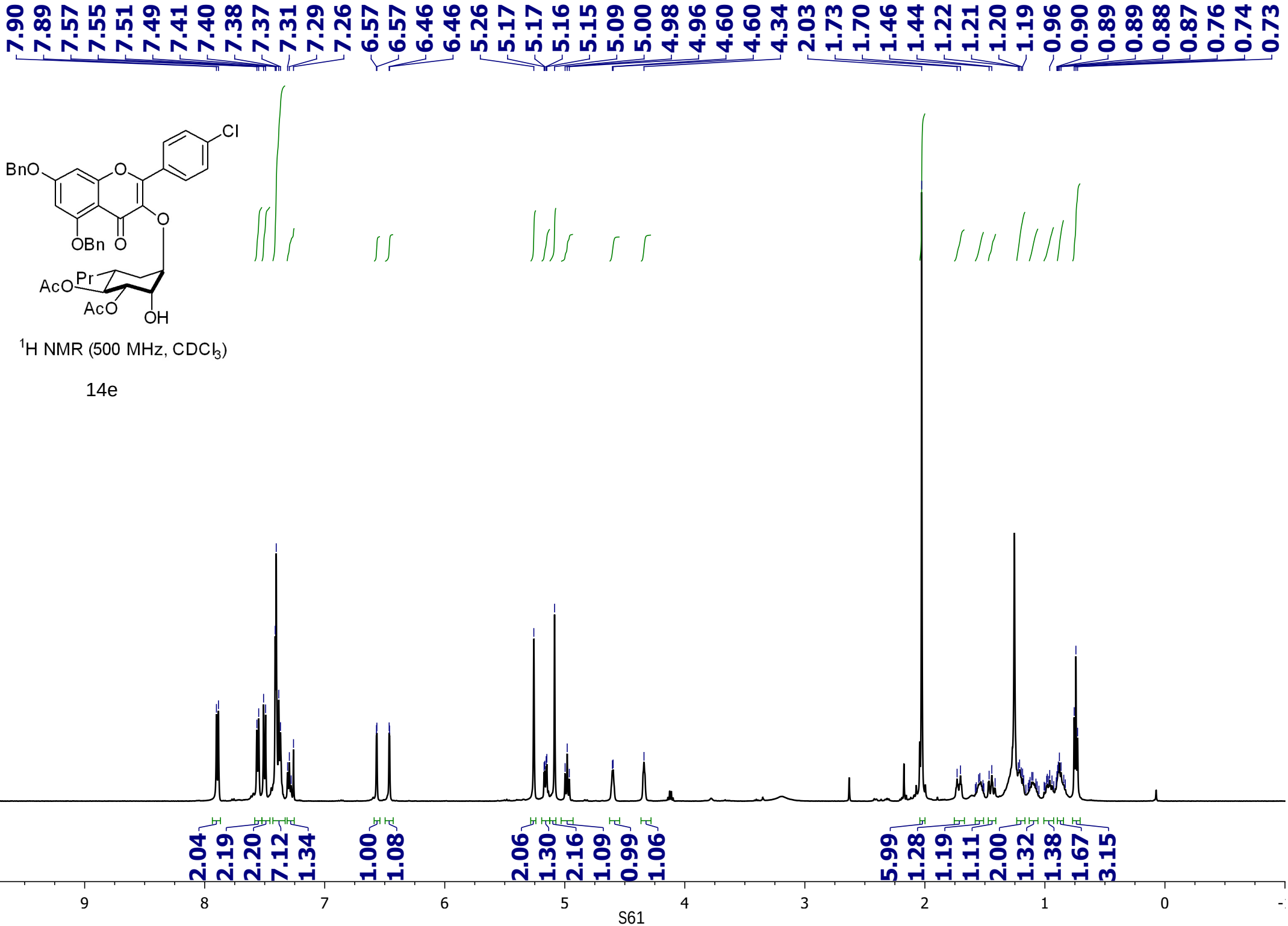
^{1}H NMR (500 MHz, $CDCl_3$)

13e



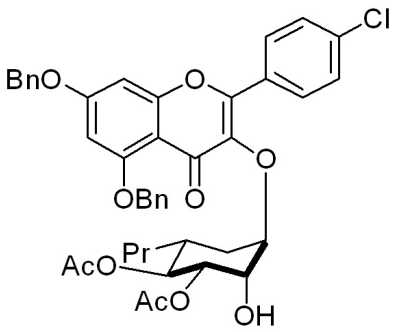
^{13}C NMR (100 MHz, $CDCl_3$)

13e



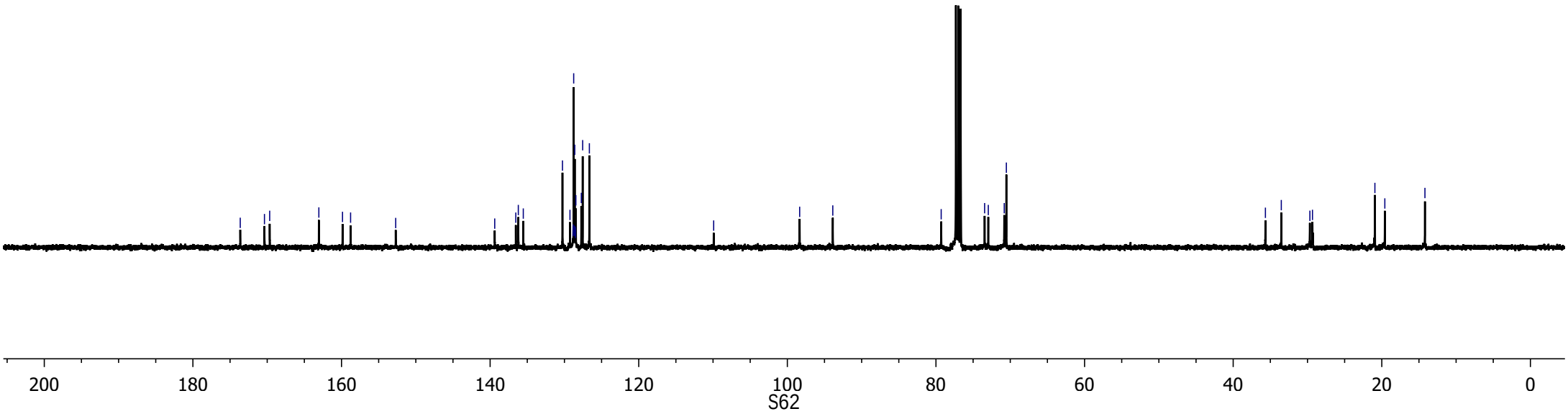
^{1}H NMR (500 MHz, $CDCl_3$)

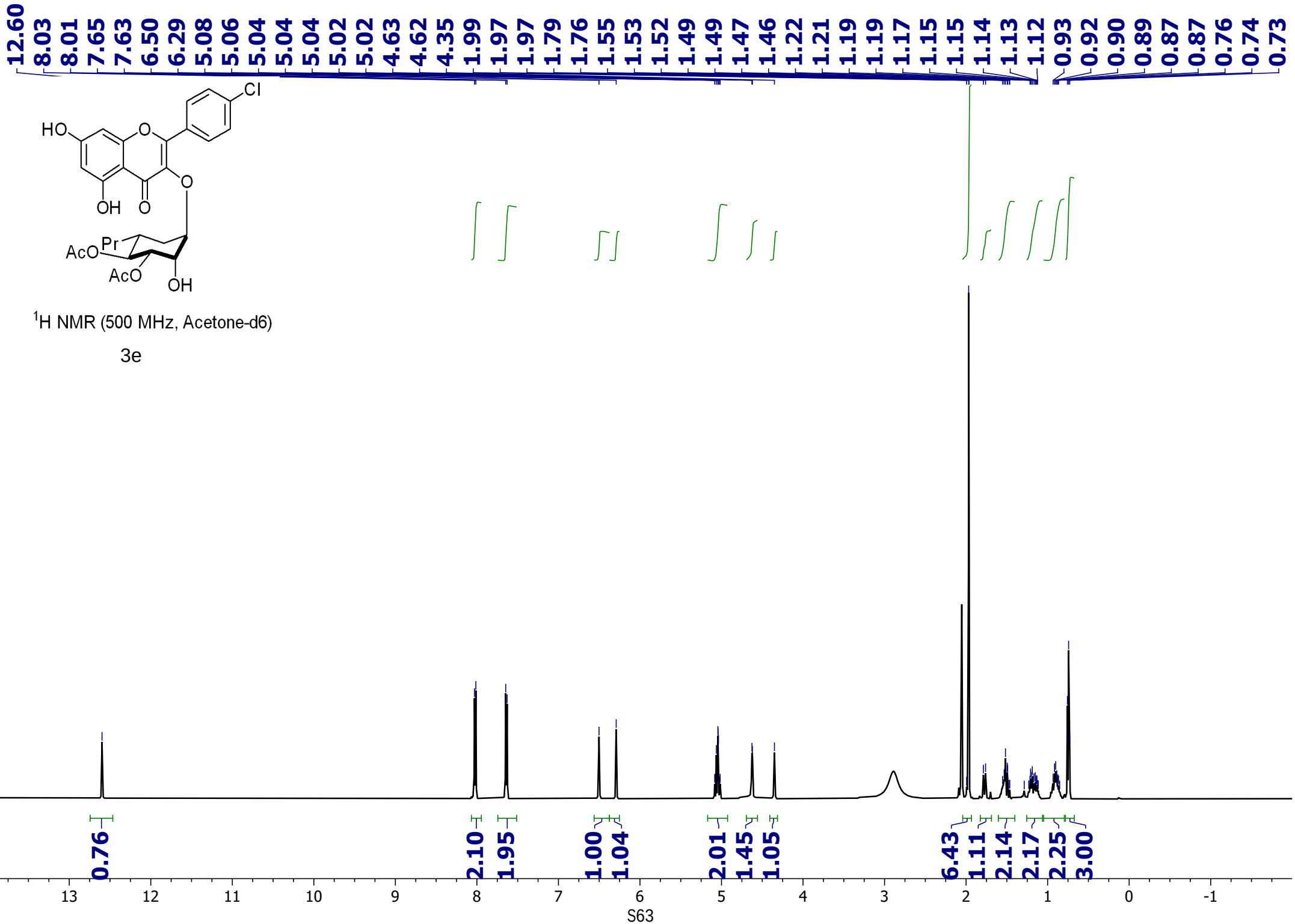
14e



^{13}C NMR (100 MHz, $CDCl_3$)

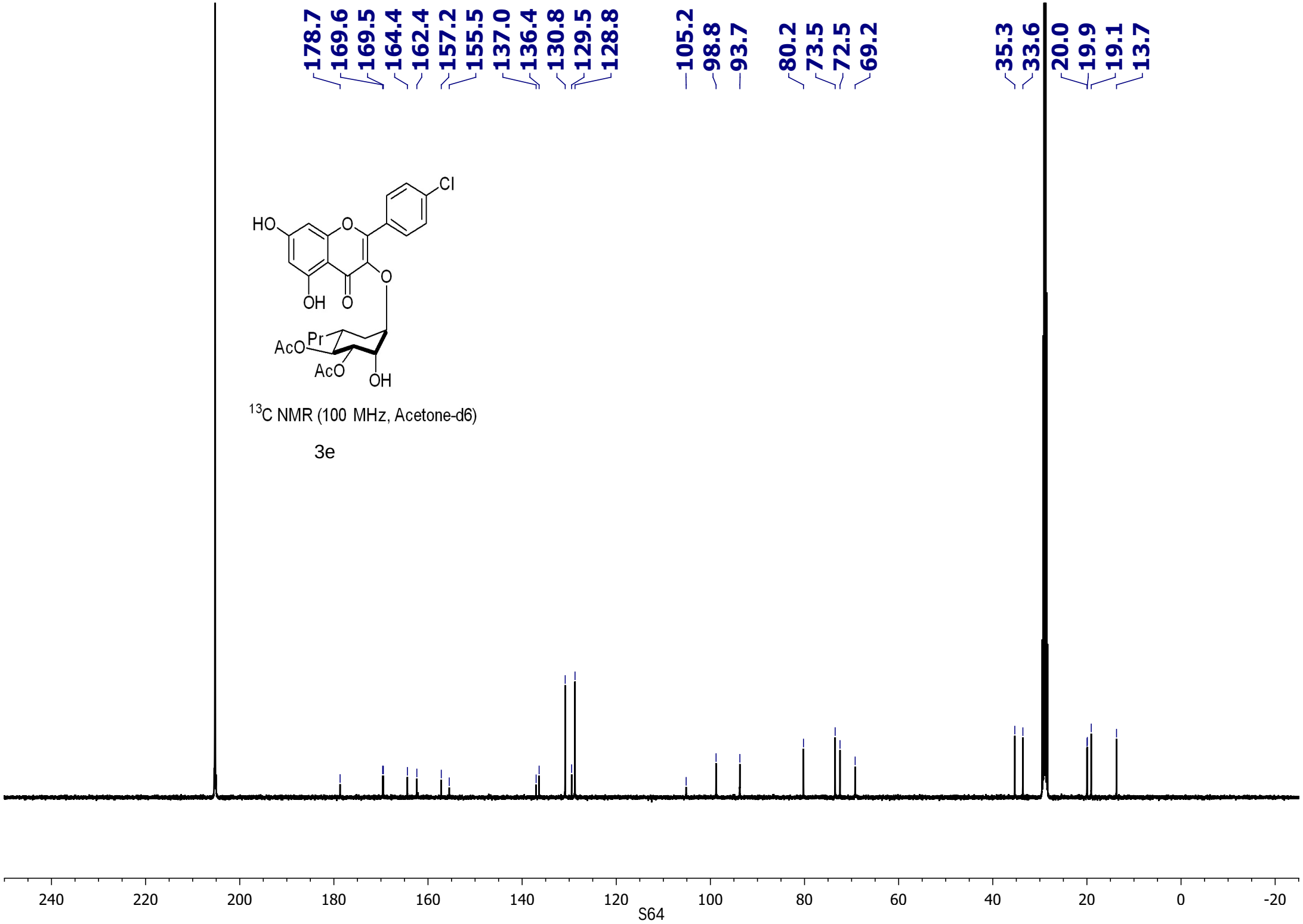
14e





^{1}H NMR (500 MHz, Acetone-d6)

3e



^{13}C NMR (100 MHz, Acetone-d6)

3e