Synthesis and Antibiotic Potential of Myxocoumarin-Inspired Chromene Dione Analogs

Antonia Behnsen,[‡,a] Gesa Hertrampf,[‡,a] Sandra Vojnovic,[,b] Jasmina Nikodinovic-Runic,[b] and Tobias A. M. Gulder[ac,*]*

[a] Chair of Technical Biochemistry, Technical University of Dresden, Bergstraße 66, 01069 Dresden, Germany

[b] Institute of Molecular Genetics and Genetic Engineering, University of Belgrade, Vojvode Stepe 444a, Belgrade, 11000, Serbia

[c] Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Department of Natural Product Biotechnology, Helmholtz Centre for Infection Research (HZI) and Department of Pharmacy at Saarland University, Campus E8.1, 66123, Saarbrücken, Germany.

[‡] These authors contributed equally.

Supporting Information

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1. General Information

Commercial materials were purchased from the providers abcr, Acros Organics, Alfa Aesar, BLDpharm, Carbolution, Carl Roth, Merck, Sigma Aldrich, Thermo Fisher Scientific and Tokyo Chemical Industry at the highest commercial quality and used without further purification. All solvents used in reactions were p.A. grade. If required, reactions were performed under inert atmosphere in anhydrous solvents, which were purchased or prepared by distillation and dried over appropriate molecular sieves (3 Å, 4 Å). Solvents for column chromatography, purchased at technical grade, were distilled prior to use. Reactions under high pressure were conducted in Ace pressure glass tubes sealed with Teflon screw caps. For column chromatography, Silica gel Geduran® Si 60 (particle size 0.40-0.60 mm) from Merck was used. Solvent mixtures are understood as volume/volume. TLC analysis was performed using precoated TLC-silica gel 60 F254 plates purchased from Merck. Applied substances were detected using a UV lamp at 254 nm. UV-inactive substances could be observed after staining the plates with $KMnO_4$ solution. NMR spectra were recorded on a Bruker AC 300 P spectrometer. The chemical shifts δ are reported as parts per million [ppm]. The spectra were calibrated on the residual peak of the deuterated solvent (δ($(CD_3)_2CO$) = 2.05 ppm, δ($(CD_3)_2SO$) = 2.50 ppm for ^{1}H-NMR; δ($(CD_3)_2CO$) = 29.8 ppm, δ($(CD_3)_2SO$) = 39.5 ppm for ^{13}C-NMR). The following abbreviations (or combinations thereof) are used for the assignment of signal multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The following abbreviations for chemicals are used: Ac_2O = acetic anhydride, DCM = dichloromethane, DIPA = diisopropylamine, DMP = Dess-Martin periodinane, EtOAc = ethyl acetate, LDA = lithium diisopropylamide, *n*-BuLi = *n*-butyl lithium, $Pd_2(dba)_3$ = tris(dibenzylidene-acetone)dipalladium(0), *t*-BuBrettPhos = 2-(di-*t*-butylphosphino)-2',4',6'-triisopropyl-3,6-dimethoxy-1,1'-biphenyl, *t*-BuOH = *t*-butanol, TDA = tris-(3,5-dioxaheptyl)-amine, Tf_2O = triflic anhydride, THF = tetrahydrofuran, TLC = thin layer chromatography, rt = room temperature. For high resolution mass spectrometry (HRMS) a Bruker Impact II ultra-high-resolution Q-TOF mass spectrometer with electrospray ionization (ESI) was used.

2. Biological Activity Tests

2.1 Minimal inhibitory concentration (MIC) assay

MIC values against different gram-positive and gram-negative bacteria and *Candida* spp. were determined using microdilution assays according to standardized methodology, recommended by the National Committee for Clinical Laboratory Standards (M07-A8) for bacteria and Standards of European Committee on Antimicrobial Susceptibility Testing (v 7.3.1: method for the determination of broth dilution minimum inhibitory concentrations of antifungal agents for yeasts) for *Candida* spp. Test organisms included: *Staphylococcus aureus* NCTC 6571, *S. aureus* MRSA ATCC 43300, *Bacillus subtilis* NCTC 5398, *Enterococcus faecalis* ATCC 29212, *Listeria monocytogenes* NCTC 1194, *Klebsiella pneumoniae* ATCC BAA 2146 and *Acinetobacter baumannii* ATCC 19606 as bacterial strains, while *Candida* strains were: *C. auris* ATCC 21092 and *C. albicans* ATCC 10231. Luria-Bertani (LB) Broth (10 g/L of tryptone, 5 g/L of yeast extract, 10 g of NaCl, all media components from Biolife Italiana, Milano, Italy) was used to grow the bacterial strains, whereas *Candida* spp. were grown in RPMI (Roswell Park Memorial Institute) medium (Gibco™ by Thermo Fischer Scientific CE) supplemented with 2% of glucose (Biolife Italiana, Milano, Italy). All compounds tested were dissolved in DMSO at concentration of 50 mg/mL. Each sample was analyzed in duplicate and the highest tested concentration was 100 µg/mL. The inoculum for bacteria was 5×10^5 CFU/mL, while for *Candida* it was 1×10^5 CFU/mL. All MIC values were read after 24 h of incubation at 37 °C, using the Tecan Infinite 200 Pro multiplate reader (Tecan Group Ltd., Männedorf, Switzerland).

2.2 MTT assay

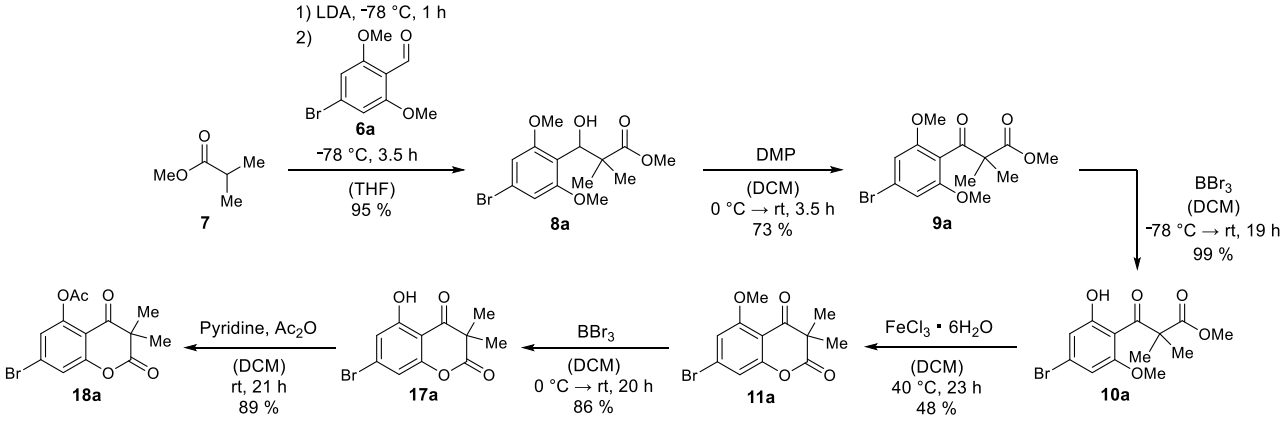
In vitro cytotoxicity in respect of antiproliferative effects was tested by the standard 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay with normal human lung fibroblasts (MRC-5),[1] obtained from American Type Culture Collection (ATCC). In a 96-well flat-bottom plate (Sarstedt, Nümbrecht, Germany), the cells, cultured in RMPI 1640 medium supplemented with 10 % FBS (Fetal Bovine Serum), 100 U/mL penicillin, and 100 µg/mL streptomycin (all media components from Gibco™ by Thermo Fischer Scientific CE) as a monolayer of 1×10^4 cells per well, were incubated with the investigated compounds in humidified atmosphere of 95 % air and 5 % CO2 at 37 °C. Each tested compound (diluted in DMSO and serially diluted further) was added to the cells in decreasing concentrations, starting with 100 µg/mL. The cell viability was measured after 48 h of incubation. Cytotoxicity is expressed as the concentration of the compound inhibiting cell growth by 50 % (IC_{50}) in comparison to DMSO-treated control. The extent of MTT reduction was measured spectrophotometrically at 540.0 nm using Tecan Infinite 200 Pro multiplate reader (Tecan Group Ltd., Männedorf, Switzerland).

2.3 Biological Results

Compound	*S. aureus* NCTC 6571	*S. aureus* MRSA ATCC 43300	*B. subtilis* NCTC 5398	*E. faecalis* ATCC 29212	*L. monocytogenes* NCTC 1194	*K. pneumoniae* ATCC BAA 2146	*A. Baumannii* ATCC 19606	*C. auris* ATCC 21092	*C. albicans* ATCC 10231	MRC5 IC_{50}
11a	>100	-	-	-	-	-	-	>100	-	-
11b	>100	-	-	-	-	-	-	>100	-	-
11c	>100	-	-	-	-	-	-	100	-	-
11d	>100	-	-	-	-	-	-	>100	-	-
11e	>100	-	-	-	-	-	-	>100	-	-
11f	6.25	3.125	12.5	6.25	>100	6.25	>100	100	25	20.0
16a	>100	-	-	-	-	-	-	>100	-	-
16b	>100	-	-	-	-	-	-	>100	-	-
16c	>100	-	-	-	-	-	-	>100	-	-
16e	>100	-	-	-	-	-	-	>100	-	-
16f	>100	-	-	-	-	-	-	>100	-	-
17a	3.125	1.563	1.563	12.5	12.5	12.5	6.25	3.125	12.5	13.5
17b	50	-	-	-	-	-	-	>100	-	-
17c	100	-	-	-	-	-	-	>100	-	-
17d	3.125	3.125	3.125	50	6.25	25	12.5	25	50	11.0
17e	>100	-	-	-	-	-	-	>100	-	-
17f	0.195	0.098	0.312	6.25	25	6.25	6.25	12.5	3.125	6.5
18a	3.125	1.563	3.125	12.5	12.5	12.5	6.25	3.125	12.5	13.5
18b	50	-	-	-	-	-	-	100	-	-
18d	3.125	3.125	6.25	50	25	50	12.5	25	50	17.0
18e	>100	-	-	-	-	-	-	>100	-	-
18f	0.195	0.195	0.625	12.5	25	12.5	12.5	50	25	8.0
19f	0.195	0.195	0.625	12.5	>50	12.5	>50	>100	>100	8.5

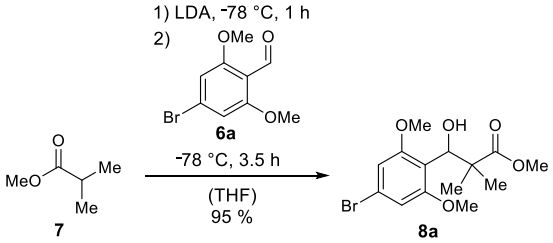
NCTC = National Collection of Type Cultures (NCTC, Culture Collection of Public Health, Salisbury, UK). ATCC = American Type Culture Collection (Manassas, Virginia, USA). "-" = no data collected.

3. Chemical Procedures



Scheme 1: Synthetic route towards chromene diones **11a**, **17a** and **18a** using 4-bromo-2,6-dimethoxybenzaldehyde (**6a**).[2]

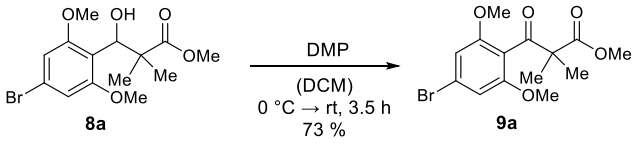
3.1 Methyl 3-(4-bromo-2,6-dimethoxyphenyl)-3-hydroxy-2,2-dimethylpropanoate (**8a**).



Following a previously reported procedure by Gulder *et al*.,[2] LDA was freshly prepared by the addition of *n*-BuLi (14.7 mL, 36.72 mmol, 2.5 M in hexane, 1.5 eq.) to a solution of DIPA (5.2 mL, 3.72 g, 36.72 mmol, 1.5 eq.) in THF (28.9 mL) at −78 °C under argon atmosphere. After stirring for 1 h, methyl isobutyrate (**7**, 2.8 mL, 2.50 g, 24.48 mmol, 1.0 eq.) was added and the reaction solution was stirred for 1 h at −78 °C. To this solution was added 4-bromo-2,6-dimethoxybenzaldehyde (**6a**, 6.60 g, 26.93 mmol, 1.1 eq.). After stirring for 3.5 h, the reaction solution was quenched by adding sat. NH_4Cl solution. The aqueous phase was extracted with Et_2O (3x) and the combined organic layers were washed with brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.25) afforded **8a** (8.03 g, 23.14 mmol, 95 %) as a white-yellow solid. Data consistent with that given in the literature.[2]

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 6.87 (s, 2H), 5.25 (d, *J* = 11.9 Hz, 1H), 4.29 (d, *J* = 11.9 Hz, 1H), 3.88 (s, 6H), 3.63 (s, 3H), 1.12 (s, 3H), 1.07 (s, 3H). HRMS (ESI): *m/z* calc. for $C_{14}H_{19}BrO_5$ $[M + Na]^+$ 369.0308, found 369.0309.

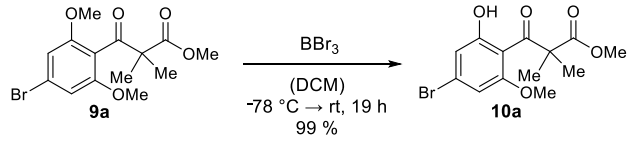
3.2 Methyl 3-(4-bromo-2,6-dimethoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**9a**).



Following a previously reported procedure by Gulder *et al*.,[2] **8a** (6.72 g, 19.35 mmol, 1.0 eq.) was dissolved in dry DCM (161.3 mL) and DMP (9.03 g, 21.29 mmol, 1.1 eq.) was added at 0 °C under argon atmosphere. The reaction solution was stirred for 3.5 h at room temperature and quenched by adding a 1:1 mixture of sat. $NaHCO_3$ solution and sat. $Na_2S_2O_3$ solution. The aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with sat. $NaHCO_3$ solution (2x) and water (2x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.32) to give **9a** (4.85 g, 14.05 mmol, 73 %) as a yellow solid. Data consistent with that given in the literature.[2]

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 6.88 (s, 2H), 3.81 (s, 6H), 3.59 (s, 3H), 1.38 (s, 6H). HRMS (ESI): *m/z* calc. for $C_{14}H_{17}BrO_5$ $[M + H]^+$ 345.0332, found 345.0333.

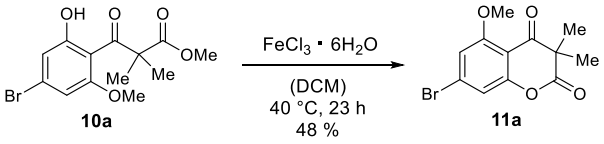
3.3 Methyl 3-(4-bromo-2-hydroxy-6-methoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**10a**).



Following a previously reported procedure by Gulder *et al*.,[2] BBr_3 (15.9 mL, 15.92 mmol, 1.0 M in DCM, 1.1 eq.) was added to a solution of **9a** (4.99 g, 14.47 mmol, 1.0 eq.) in dry DCM (90.5 mL) at −78 °C under argon atmosphere. The solution was allowed to warm up to room temperature overnight. The reaction was quenched by adding water at 0 °C. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with water (2x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.5) afforded **10a** (4.73 g, 14.28 mmol, 99 %) as a yellow oil. Data consistent with that given in the literature.[2]

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 12.45 (s, 1H), 6.78 (d, *J* = 1.8 Hz, 1H), 6.67 (t, *J* = 1.7 Hz, 1H), 3.86 (s, 3H), 3.62 (s, 3H), 1.42 (s, 6H). HRMS (ESI): *m/z* calc. for $C_{13}H_{15}BrO_5$ $[M + H]^+$ 331.0176, found 331.0179.

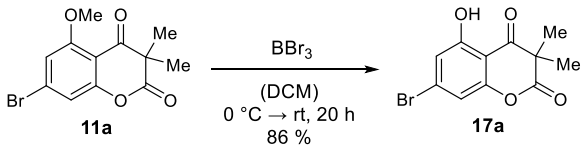
3.4 7-bromo-5-methoxy-3,3-dimethylchromane-2,4-dione (**11a**).



Following a previously reported procedure by Gulder *et al*.,[2] $FeCl_3 \cdot 6H_2O$ (1.74 g, 6.45 mmol, 0.5 eq.) was added to a solution of **10a** (4.27 g, 12.89 mmol, 1.0 eq.) in DCM (64.5 mL) at room temperature. After stirring for 23 h at 40 °C, water was added to the reaction solution. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.25) afforded **11a** (1.85 g, 6.18 mmol, 48 %) as a yellow solid and reisolated starting material **10a** (2.01 g, 6.07 mmol, 47 %). Data consistent with that given in the literature.[2]

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.15 (d, *J* = 1.7 Hz), 7.03 (d, *J* = 1.7 Hz, 1H), 3.96 (s, 3H), 1.46 (s, 6H). HRMS (ESI): *m/z* calc. for $C_{12}H_{11}BrO_4$ $[M + H]^+$ 298.9913, found 298.9909.

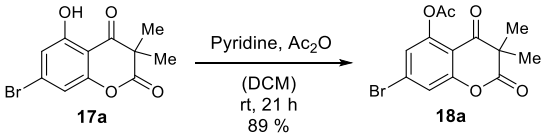
3.5 7-bromo-5-hydroxy-3,3-dimethylchromane-2,4-dione (**17a**).



Following a previously reported procedure by Gulder *et al*.,[2] **11a** (1.47 g, 4.91 mmol, 1.0 eq.) was dissolved in dry DCM (27.3 mL) under argon atmosphere and BBr_3 (5.41 mL, 5.41 mmol, 1.0 M in DCM, 1.1 eq.) was added at 0 °C. The reaction solution was allowed to warm up to room temperature overnight. The reaction was quenched by adding water at 0 °C. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with water (1x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.60) to give **17a** (1.21 g, 4.23 mmol, 86%) as a white solid. Data consistent with that given in the literature.[2]

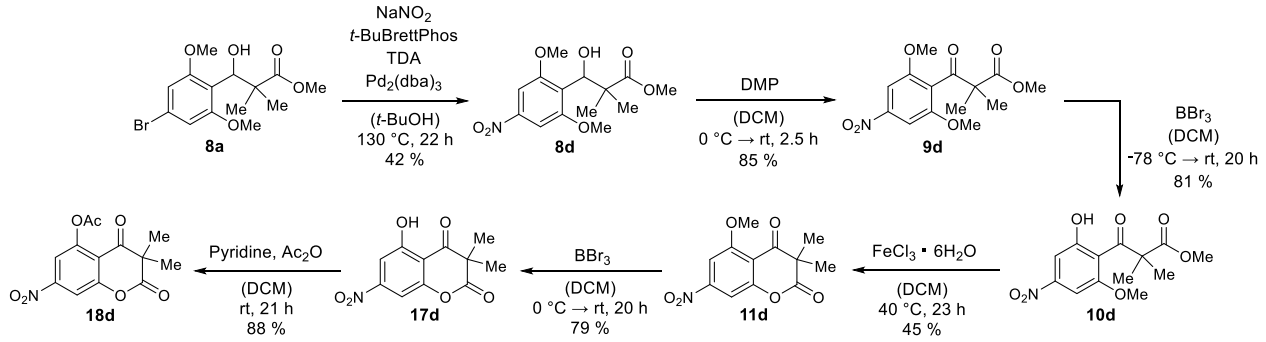
^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 11.60 (s, 1H), 7.00 (d, *J* = 1.7 Hz, 1H), 6.96 (d, *J* = 1.7 Hz, 1H), 1.59 (s, 6H). HRMS (ESI): *m/z* calc. for $C_{11}H_9BrO_4$ $[M + H]^+$ 284.9757, found 284.9758.

3.6 7-Bromo-3,3-dimethyl-2,4-dioxochroman-5-yl acetate (**18a**).



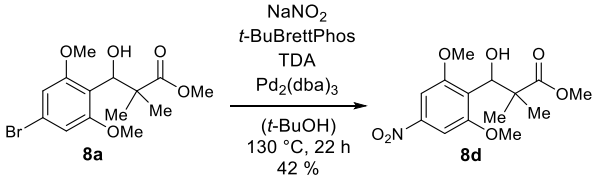
17a (0.62 g, 2.16 mmol, 1.0 eq.) was dissolved in dry DCM (35.9 mL) and dry pyridine (31.7 mL, 31.1 g, 345.2 mmol, 160 eq.) under argon atmosphere. Ac_2O (31.3 mL, 33.8 g, 291.2 mmol, 135 eq.) was added and the reaction mixture was stirred at room temperature for 21 h. The reaction solution was diluted with EtOAc and quenched by adding 10 % aqueous HCl. The organic layer was washed with 10 % aqueous HCl (2x), water (2x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.39) to give **18a** (0.63 g, 1.92 mmol, 89 %) as a white-brown solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.47 (d, *J* = 1.9 Hz, 1H), 7.30 (d, *J* = 1.9 Hz, 1H), 2.32 (s, 3H), 1.49 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 192.0, 170.6, 169.1, 156.5, 151.6, 129.3, 123.7, 119.1, 112.2, 54.0, 22.8, 20.8. HRMS (ESI): *m/z* calc. for $C_{13}H_{11}BrO_5$ $[M + H]^+$ 326.9863, found 326.9864.



Scheme 2: Synthetic route towards chromene diones **11d**, **17d** and **18d** *via* nitration of **8a**.

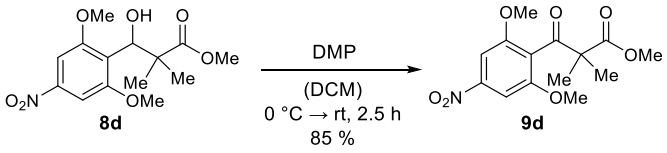
3.7 Methyl 3-(2,6-dimethoxy-4-nitrophenyl)-3-hydroxy-2,2-dimethyl-propanoate (**8d**)



An oven-dried glass pressure tube was charged with **8a** (100 mg, 0.29 mmol, 1.0 eq.), $NaNO_2$ (40.0 mg, 0.58 mmol, 2.0 eq.), *t*-BuBrettPhos (8.40 mg, 17.3 µmol, 6.0 mol%) and $Pd_2(dba)_3$ (6.60 mg, 7.20 µmol, 2.5 mol%) under argon atmosphere. TDA (4.60 µL, 4.70 mg, 14.4 µmol, 5.0 mol%) and dry *t*-BuOH (0.60 mL) were added, the tube was sealed with a Teflon screw cap and the reaction mixture was stirred for 22 h at 130 °C. After cooling to room temperature, the reaction mixture was diluted with EtOAc and washed with water (2x). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.23) afforded **8d** (38.0 mg, 0.12 mmol, 42 %) as a yellow solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.53 (s, 2H), 5.34 (d, *J* = 12.1 Hz, 1H), 4.39 (d, *J* = 12.1 Hz, 1H), 4.01 (s, 6H), 3.65 (s, 3H), 1.17 (s, 3H), 1.10 (s, 3H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 176.6, 159.6, 149.5, 124.1, 100.5, 74.0, 56.8, 52.0, 49.9, 23.8, 21.0. HRMS (ESI): m/z calc. for $C_{14}H_{19}NO_7$ $[M + Na]^+$ 336.1054, found 336.1028.

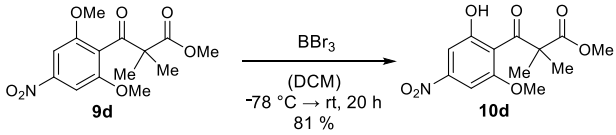
3.8 Methyl 3-(2,6-dimethoxy-4-nitrophenyl)-2,2-dimethyl-3-oxopropanoate (**9d**)



8d (0.36 g, 1.15 mmol, 1.0 eq.) was dissolved in dry DCM (13.0 mL) under argon atmosphere and DMP (0.54 g, 1.26 mmol, 1.1 eq.) was added at 0 °C. The reaction solution was stirred for 2.5 h at room temperature and quenched by adding a 1:1 mixture of sat. $NaHCO_3$ solution and sat. $Na_2S_2O_3$ solution. The aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with sat. $NaHCO_3$ solution (1x) and water (2x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 3:1, R_f = 0.35) to give **9d** (0.30 g, 0.97 mmol, 85 %) as a yellow solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.54 (s, 2H), 3.94 (s, 6H), 3.61 (s, 3H), 1.42 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 201.7, 173.0, 157.7, 150.8, 124.9, 100.7, 57.5, 57.0, 52.5, 23.0. HRMS (ESI): m/z calc. for $C_{14}H_{17}NO_7$ $[M + Na]^+$ 334.0897, found 334.0873.

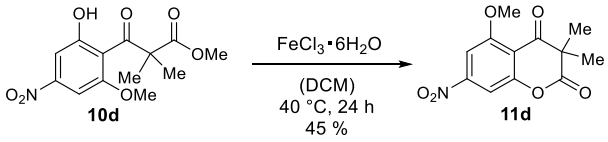
3.9 Methyl 3-(2-hydroxy-6-methoxy-4-nitrophenyl)-2,2-dimethyl-3-oxopropanoate (**10d**)



To a solution of **9d** (0.55 g, 1.77 mmol, 1.0 eq.) in dry DCM (11.0 mL) was added BBr_3 (1.95 mL, 1.95 mmol, 1.0 M in DCM, 1.1 eq.) at −78 °C under argon atmosphere. The solution was allowed to warm up to room temperature overnight. The reaction was quenched by adding water at 0 °C. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with water (1x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 3:1, R_f = 0.33) to give **10d** (0.43 g, 1.43 mmol, 81 %) as a yellow solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 10.82 (s, 1H), 7.40 - 7.36 (m, 2H), 3.95 (s, 3H), 3.62 (s, 3H), 1.45 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 203.5, 173.4, 159.4, 159.4, 151.4, 120.2, 105.5, 98.3, 57.5, 56.6, 52.5, 23.1. HRMS (ESI): m/z calc. for $C_{13}H_{15}NO_7$ $[M + Na]^+$ 320.0741, found 320.0716.

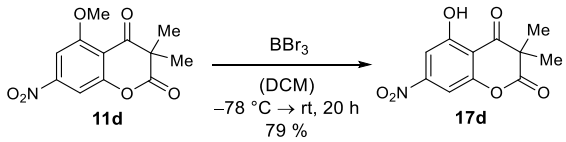
3.10 5-Methoxy-3,3-dimethyl-7-nitrochromane-2,4-dione (**11d**)



To a solution of **10d** (0.69 g, 2.30 mmol, 1.0 eq.) in DCM (12.0 mL) was added $FeCl_3 \cdot 6H_2O$ (0.31 g, 1.15 mmol, 0.5 eq.) at room temperature. After stirring for 24 h at 40 °C, water was added to the reaction solution. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was washed with cyclohexane and a 3:1 mixture of cyclohexane and acetone (R_f = 0.32) to give **11d** (0.28 g, 1.04 mmol, 45 %) as a yellow solid.

^{1}H-NMR (300 MHz, DMSO-d_6) δ (ppm): 7.67 (d, *J* = 2.1 Hz, 1H), 7.66 (d, *J* = 2.1 Hz, 1H), 3.99 (s, 3H), 1.38 (s, 6H). ^{13}C-NMR (75 MHz, DMSO-d_6) δ (ppm): 189.9, 169.9, 160.3, 155.5, 151.3, 112.1, 104.2, 102.8, 57.1, 52.8, 21.9. HRMS (ESI): m/z calc. for $C_{12}H_{11}NO_6$ $[M + H]^+$ 266.0659, found 266.0639.

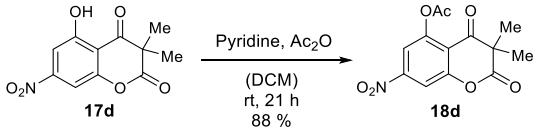
3.11 5-hydroxy-3,3-dimethyl-7-nitrochromane-2,4-dione (**17d**).



11d (99.0 mg, 0.37 mmol, 1.0 eq.) was dissolved in dry DCM (2.1 mL) under argon atmosphere and BBr_3 (0.41 mL, 0.41 mmol, 1.0 M in DCM, 1.1 eq.) was added at –78 °C. The reaction solution was allowed to warm up to room temperature overnight. The reaction was quenched by adding water at 0 °C. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with water (1x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 3:1, R_f = 0.37) to give **17d** (74.1 mg, 0.29 mmol, 79 %) as a yellow solid.

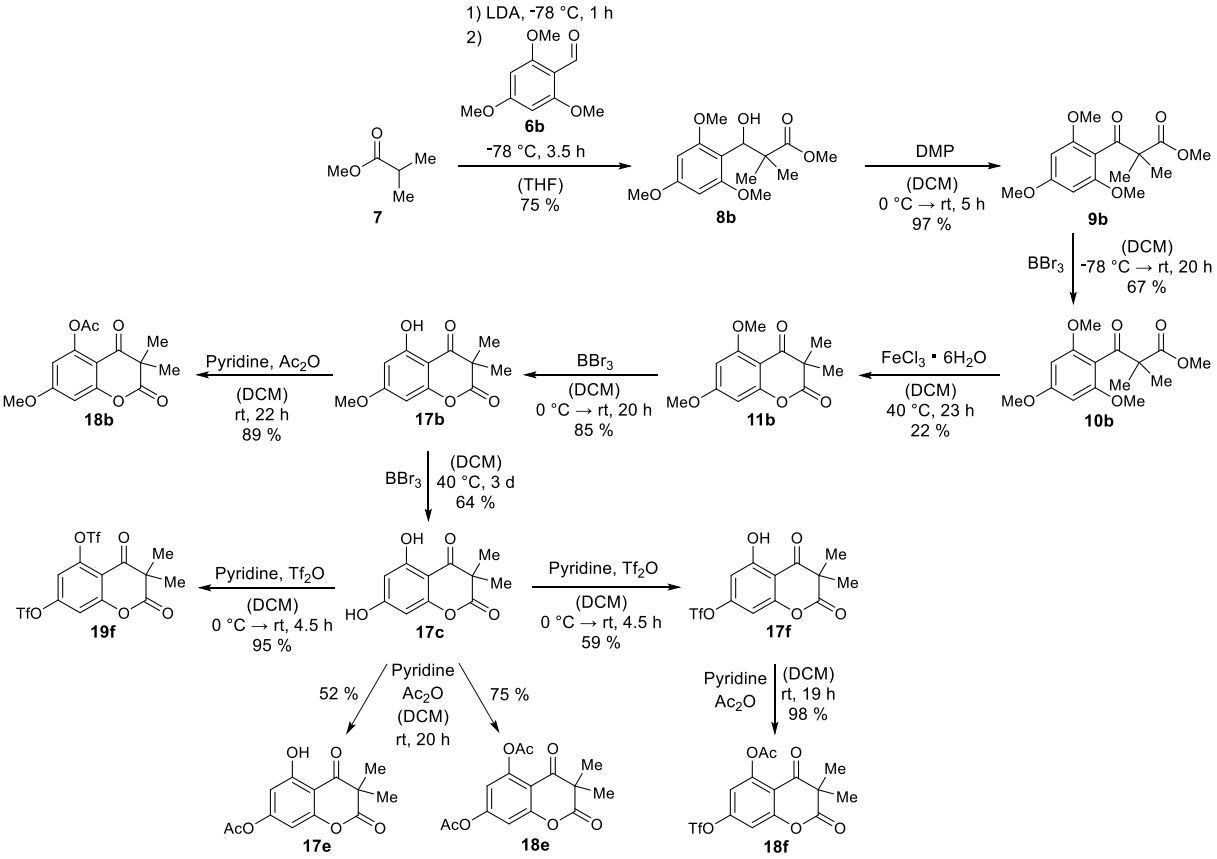
^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 11.49 (s, 1H), 7.39 (dd, *J* = 2.1, 0.6 Hz, 1H), 7.36 (dd, *J* = 2.1, 1.0 Hz, 1H), 1.50 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d6): δ (ppm) = 201.6, 170.1, 162.8, 156.4, 154.0, 109.0, 108.2, 103.1, 53.3, 23.6. HRMS (ESI): *m/z* calc. for $C_{11}H_9NO_6$ $[M + H]^+$ 252.0508, found 252.0504.

3.12 3,3-Dimethyl-7-nitro-2,4-dioxochroman-5-yl acetate (**18d**).



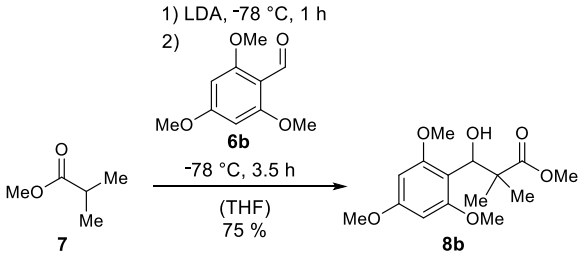
17d (38.0 mg, 0.15 mmol, 1.0 eq.) was dissolved in dry DCM (2.5 mL) and dry pyridine (2.0 mL, 2.02 g, 24.20 mmol, 160 eq.) under argon atmosphere. Ac_2O (2.0 mL, 2.20 g, 20.42 mmol, 135 eq.) was added and the reaction mixture was stirred at room temperature for 21 h. The reaction solution was diluted with EtOAc and quenched by adding 10 % aqueous HCl. The organic layer was washed with 10 % aqueous HCl (2x), water (2x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.34) to give **18d** (38.9 mg, 0.13 mmol, 88 %) as a white-yellow solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.99 (d, *J* = 2.2 Hz, 1H), 7.86 (d, *J* = 2.2 Hz, 1H), 2.36 (s, 3H), 1.52 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 191.9, 170.0, 169.1, 156.6, 152.2, 151.8, 117.3, 115.3, 111.3, 54.4, 22.5, 20.8. HRMS (ESI): *m/z* calc. for $C_{13}H_{11}NO_7$ $[M + H]^+$ 294.0614, found 294.0604.



Scheme 3: Synthetic route towards chromene diones **11b**, **17b,c,e,f, 18b,e,f** and **19f** using 2,4,6-trimethoxybenzaldehyde (**6b**).[2]

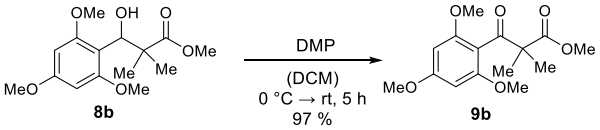
3.13 Methyl 3-hydroxy-2,2-dimethyl-3-(2,4,6-trimethoxyphenyl)propanoate (**8b**).



Following a previously reported procedure by Gulder *et al*.,[2] LDA was freshly prepared by the addition of *n*-BuLi (14.7 mL, 36.72 mmol, 2.5 M in hexane, 1.5 eq.) to a solution of DIPA (5.2 mL, 3.72 g, 36.72 mmol, 1.5 eq.) in THF (28.9 mL) at −78 °C under argon atmosphere. After stirring for 1 h, methyl isobutyrate (**7**, 2.8 mL, 2.50 g, 24.48 mmol, 1.0 eq.) was added and the reaction solution was stirred for 1 h at −78 °C. To this solution was added 2,4,6-trimethoxybenzaldehyde (**6b**, 5.28 g, 26.93 mmol, 1.1 eq.). After stirring for 3.5 h, the reaction solution was quenched by adding sat. NH_4Cl solution. The aqueous phase was extracted with Et_2O (3x) and the combined organic layers were washed with brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/acetone = 3:1, R_f = 0.31) afforded **8b** (5.46 g, 18.30 mmol, 75 %) as a white solid. Data consistent with that given in the literature.[2]

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 6.27 (s, 2H), 5.24 (d, *J* = 11.7 Hz, 1H), 4.30 (d, *J* = 11.7 Hz, 1H), 3.83 (s, 6H), 3.81 (s, 3H), 3.62 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H). HRMS (ESI): *m/z* calc. for $C_{15}H_{22}O_6$ $[M + Na]^+$ 321.1309, found 321.1305.

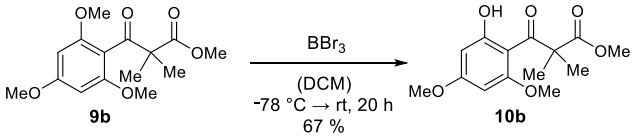
3.14 methyl 2,2-dimethyl-3-oxo-3-(2,4,6-trimethoxyphenyl)propanoate (**9b**).



Following a previously reported procedure by Gulder *et al*.,[2] **8b** (4.67 g, 15.65 mmol, 1.0 eq.) was dissolved in dry DCM (156.5 mL) and DMP (7.30 g, 17.22 mmol, 1.1 eq.) was added at 0 °C under argon atmosphere. The reaction solution was stirred for 5 h at room temperature and quenched by adding a 1:1 mixture of sat. $NaHCO_3$ solution and sat. $Na_2S_2O_3$ solution. The aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with sat. $NaHCO_3$ solution (2x) and water (2x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 3:1, R_f = 0.32) to give **9b** (4.51 g, 15.22 mmol, 97 %) as a yellow solid. Data consistent with that given in the literature.[2]

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 6.24 (s, 2H), 3.83 (s, 3H), 3.75 (s, 6H), 3.58 (s, 3H), 1.36 (s, 6H). HRMS (ESI): *m/z* calc. for $C_{15}H_{20}O_6$ $[M + H]^+$ 297.1333, found 297.1333.

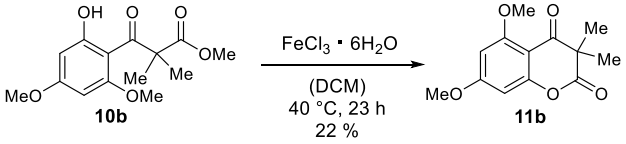
3.15 methyl 3-(2-hydroxy-4,6-dimethoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**10b**).



Following a previously reported procedure by Gulder *et al*.,[2] BBr_3 (22.8 mL, 12.8 mmol, 1.0 M in DCM, 1.1 eq.) was added to a solution of **9b** (4.51 g, 15.22 mmol, 1.0 eq.) in dry DCM (84.6 mL) at −78 °C under argon atmosphere. The solution was allowed to warm up to room temperature overnight. The reaction was quenched by adding water at 0 °C. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with water (2x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.38) afforded **10b** (2.86 g, 10.13 mmol, 67 %) as a yellow oil. Data consistent with that given in the literature.[2]

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 13.50 (s, 1H), 6.10 (d, *J* = 2.4 Hz, 1H), 6.06 (d, *J* = 2.4 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.59 (s, 3H), 1.40 (s, 6H). HRMS (ESI): *m/z* calc. for $C_{14}H_{18}O_6$ $[M + Na]^+$ 305.0996, found 305.0995.

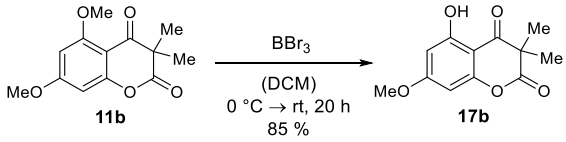
3.16 5,7-dimethoxy-3,3-dimethylchromane-2,4-dione (**11b**).



Following a previously reported procedure by Gulder *et al*.,[2] $FeCl_3 \cdot 6H_2O$ (1.37 g, 5.07 mmol, 0.5 eq.) was added to a solution of **10b** (2.86 g, 10.13 mmol, 1.0 eq.) in DCM (50.7 mL) at room temperature. After stirring for 18 h at 40 °C, water was added to the reaction solution. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/acetone = 3:1, R_f = 0.25) afforded **11b** (0.55 g, 2.20 mmol, 22 %) as a white solid and reisolated starting material **10b** (1.77 g, 6.27 mmol, 62 %). Data consistent with that given in the literature.[2]

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 6.46 (d, *J* = 2.3 Hz, 1H), 6.36 (d, *J* = 2.3 Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 1.43 (s, 6H). HRMS (ESI): *m/z* calc. for $C_{13}H_{14}O_5$ $[M + H]^+$ 251.0919, found 251.0917.

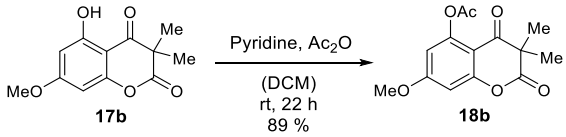
3.17 5-hydroxy-7-methoxy-3,3-dimethylchromane-2,4-dione (**17b**).



Following a previously reported procedure by Gulder *et al*.,[2] **11b** (0.55 mg, 2.20 mmol, 1.0 eq.) was dissolved in dry DCM (36.6 mL) under argon atmosphere and BBr_3 (5.5 mL, 5.49 mmol, 1.0 M in DCM, 2.5 eq.) was added at 0 °C. The reaction solution was allowed to warm up to room temperature overnight. The reaction was quenched by adding water at 0 °C. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with water (1x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 3:1, R_f = 0.42) to give **17b** (0.44 g, 1.87 mmol, 85 %) and the dihydroxy compound **17c** (27.3 mg, 0.12 mmol, 6 %) as white solids. Data consistent with that given in the literature.[2]

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 11.87 (s, 1H), 6.30 (d, *J* = 2.3 Hz, 1H), 6.28 (d, *J* = 2.3 Hz, 1H), 3.93 (s, 3H), 1.56 (s, 6H). HRMS (ESI): *m/z* calc. for $C_{12}H_{12}O_5$ $[M + H]^+$ 237.0763, found 237.0755.

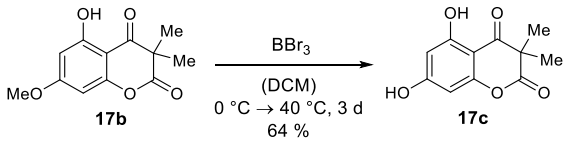
3.18 7-methoxy-3,3-dimethyl-2,4-dioxochroman-5-yl acetate (**18b**).



17b (0.20 g, 0.85 mmol, 1.0 eq.) was dissolved in dry DCM (21.2 mL) and dry pyridine (16.1 mL, 15.74 g, 198.97 mmol, 235 eq.) under argon atmosphere. Ac_2O (16.0 mL, 17.29 g, 196.33 mmol, 200 eq.) was added and the reaction mixture was stirred at room temperature for 22 h. The reaction solution was diluted with EtOAc and quenched by adding 10 % aqueous HCl. The organic layer was washed with 10 % aqueous HCl (2x), water (2x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 3:1, R_f = 0.39) to give **18b** (0.21 g, 0.75 mmol, 89 %) as a white solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 6.71 (d, *J* = 2.4 Hz, 1H), 6.59 (d, *J* = 2.4 Hz, 1H), 3.96 (s, 3H), 2.28 (s, 3H), 1.45 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 191.3, 171.4, 169.1, 166.4, 157.9, 152.9, 107.5, 106.3, 100.3, 56.9, 53.3, 23.2, 20.9. HRMS (ESI): *m/z* calc. for $C_{14}H_{14}O_6$ $[M + H]^+$ 279.0869, found 279.0865.

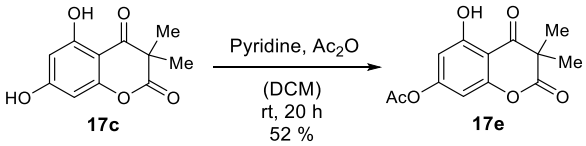
3.19 5,7-dihydroxy-3,3-dimethylchromane-2,4-dione (**17c**).



Following a previously reported procedure by Gulder *et al*.,[2] **17b** (0.24 mg, 1.02 mmol, 1.0 eq.) was dissolved in dry DCM (16.9 mL) under argon atmosphere and BBr_3 (5.1 mL, 5.08 mmol, 1.0 M in DCM, 5.0 eq.) was added at 0 °C. The reaction solution was stirred at 40 °C for 3 d. The reaction was quenched by adding water at 0 °C. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with water (1x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 3:1, R_f = 0.18) to give **17c** (0.15 g, 0.65 mmol, 64 %) as a white solid. Data consistent with that given in the literature.[2]

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 11.88 (s, 1H), 10.04 (s, 1H), 6.17 (s, 2H), 1.55 (s, 6H). HRMS (ESI): *m/z* calc. for $C_{11}H_{10}O_5$ $[M + H]^+$ 223.0606, found 223.0597.

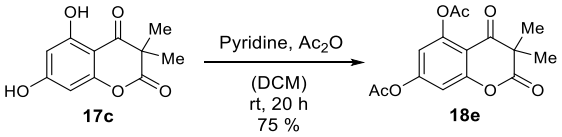
3.20 5-hydroxy-3,3-dimethyl-2,4-dioxochroman-7-yl acetate (**17e**).



17c (80.0 mg, 0.36 mmol, 1.0 eq.) was dissolved in dry DCM (2.0 mL) and dry pyridine (31 µL, 29.9 mg, 0.38 mmol, 1.05 eq.) under argon atmosphere. Ac_2O (36 µL, 38.6 mg, 0.38 mmol, 1.05 eq.) was added and the reaction mixture was stirred at room temperature for 20 h. The reaction solution was diluted with EtOAc and quenched by adding 10 % aqueous HCl. The organic layer was washed with 10 % aqueous HCl (2x), water (2x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 3:1, R_f = 0.35) to give **17e** (49.1 mg, 0.19 mmol, 52 %) as a white solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 11.69 (s, 1H), 6.57 (d, *J* = 2.1 Hz, 1H), 6.55 (d, *J* = 2.1 Hz, 1H), 2.30 (s, 3H), 1.60 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 200.9, 170.8, 168.7, 163.6, 159.4, 156.5, 106.8, 103.4, 102.5, 52.4, 23.9, 21.0. HRMS (ESI): *m/z* calc. for $C_{13}H_{12}O_6$ $[M + H]^+$ 265.0712, found 265.0705.

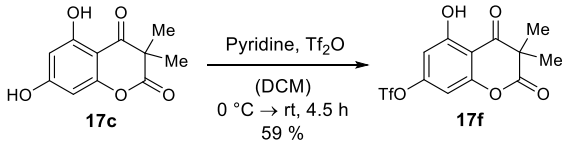
3.21 3,3-dimethyl-2,4-dioxochromane-5,7-diyl diacetate (**18e**).



17c (35.0 mg, 0.16 mmol, 1.0 eq.) was dissolved in dry DCM (4.0 mL) and dry pyridine (3.0 mL, 2.96 g, 37.35 mmol, 235 eq.) under argon atmosphere. Ac_2O (3.0 mL, 3.25 g, 31.79 mmol, 200 eq.) was added and the reaction mixture was stirred at room temperature for 20 h. The reaction solution was diluted with EtOAc and quenched by adding 10 % aqueous HCl. The organic layer was washed with 10 % aqueous HCl (2x), water (2x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 3:1, R_f = 0.34) to give **18e** (36.6 mg, 0.12 mmol, 75 %) as a white solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.02 (d, *J* = 2.2 Hz, 1H), 6.87 (d, *J* = 2.2 Hz, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 1.48 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 191.9, 170.9, 169.1, 168.7, 157.0, 156.9, 152.0, 114.5, 110.5, 109.4, 53.8, 22.9, 21.0, 20.9. HRMS (ESI): *m/z* calc. for $C_{15}H_{14}O_7$ $[M + H]^+$ 307.0818, found 307.0812.

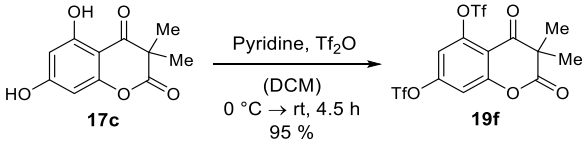
3.22 5-hydroxy-3,3-dimethyl-2,4-dioxochroman-7-yl trifluoromethanesulfonate (**17f**).



Following a previously reported procedure by Gulder *et al.*,[2] **17c** (0.12 g, 0.52 mmol, 1.0 eq.) was dissolved in dry DCM (3.7 mL) and dry pyridine (44 µL, 43.4 mg, 0.55 mmol, 1.05 eq.) under argon atmosphere. Tf_2O (92 µL, 0.15 g, 0.55 mmol, 1.05 eq.) was added at 0 °C. After stirring for 30 min at 0 °C, the reaction solution was allowed to warm up to room temperature and was stirred for further 4 h. The reaction solution was diluted with EtOAc and quenched by adding 10% aqueous HCl. The organic layer was washed with 10% aqueous HCl (1x), water (1x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 3:1, R_f= 0.39) to give **17f** (0.11 g, 0.31 mmol, 59 %) as a white solid. Data consistent with that given in the literature.[2]

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 11.78 (s, 1H), 6.89 (s, 2H), 1.63 (s, 6H). HRMS (ESI): *m/z* calc. for $C_{12}H_9F_3O_7S$ $[M + H]^+$ 355.0099, found 355.0092.

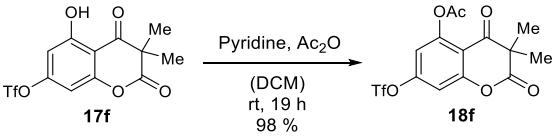
3.23 3,3-dimethyl-2,4-dioxochromane-5,7-diyl bis(trifluoromethanesulfonate) (**19f**).



17c (72.0 mg, 0.32 mmol, 1.0 eq.) was dissolved in dry DCM (2.3 mL) and dry pyridine (58 µL, 56.0 mg, 0.71 mmol, 2.2 eq.) under argon atmosphere. Tf_2O (0.12 mL, 0.20 g, 0.71 mmol, 2.2 eq.) was added at 0 °C. After stirring for 30 min at 0 °C, the reaction solution was allowed to warm up to room temperature and was stirred for further 4 h. The reaction solution was diluted with EtOAc and quenched by adding 10 % aqueous HCl. The organic layer was washed with 10% aqueous HCl (1x), water (1x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 3:1, R_f = 0.47) to give **19f** (0.11 g, 0.31 mmol, 95 %) as a white solid.

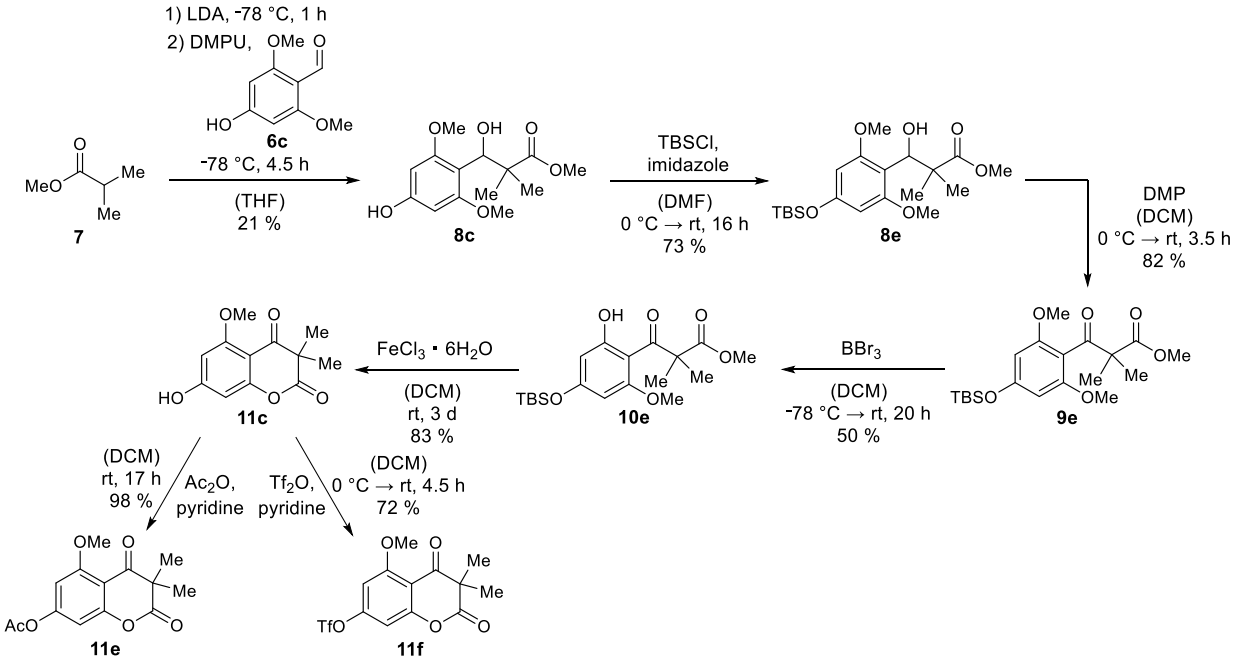
^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.71 (d, *J* = 2.3 Hz, 1H), 7.66 (d, *J* = 2.3 Hz, 1 H), 1.58 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 191.3, 169.7, 157.6, 153.4, 148.8, 119.5 (q, *J* = 319.7 Hz), 114.1, 113.8, 113.2, 54.4, 22.6. HRMS (ESI): m/z calc. for $C_{13}H_8F_6O_9S_2$ $[M + H]^+$ 486.9592, found 486.9583.

3.24 3,3-dimethyl-2,4-dioxo-7-(((trifluoromethyl)sulfonyl)oxy)chroman-5-yl acetate (**18f**).



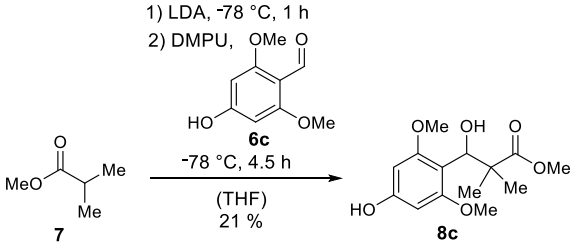
17f (45.0 mg, 0.13 mmol, 1.0 eq.) was dissolved in dry DCM (2.8 mL) and dry pyridine (2.4 mL, 2.36 g, 29.85 mmol, 235 eq.) under argon atmosphere. Ac_2O (2.4 mL, 2.59 g, 25.41 mmol, 200 eq.) was added and the reaction mixture was stirred at room temperature for 19 h. The reaction solution was diluted with EtOAc and quenched by adding 10 % aqueous HCl. The organic layer was washed with 10 % aqueous HCl (2x), water (2x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 3:1, R_f = 0.47) to give **18f** (49.2 mg, 0.12 mmol, 98 %) as a white solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.41 (d, *J* = 2.4 Hz, 1H), 7.25 (d, *J* = 2.4 Hz, 1H), 2.33 (s, 3H), 1.51 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 191.6, 170.3, 168.9, 157.3, 153.5, 152.6, 119.5 (q, *J* = 319.1 Hz), 114.2, 113.3, 109.8, 54.1, 22.7, 20.8. HRMS (ESI): *m/z* calc. for $C_{14}H_{11}F_3O_8S$ $[M + Na]^+$ 419.0024, found 419.0019.



Scheme 4: Synthetic route towards chromene diones **11c,e,f** using 4-hydroxy-2,6-dimethoxybenzaldehyde (**6c**).

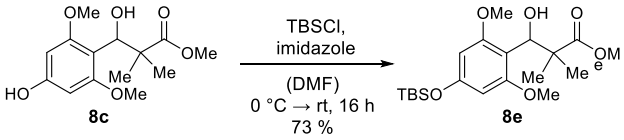
3.25 methyl 3-hydroxy-3-(4-hydroxy-2,6-dimethoxyphenyl)-2,2-dimethylpropanoate (**8c**).



LDA was freshly prepared by the addition of n-BuLi (13.2 mL, 32.93 mmol, 2.5 M in hexane, 3.0 eq.) to a solution of DIPA (4.6 mL, 3.33 g, 32.93 mmol, 3.0 eq.) in THF (117.6 mL) at −78 °C under argon atmosphere. After stirring for 1 h, methyl isobutyrate (**7**, 2.5 mL, 2.24 g, 21.95 mmol, 2.0 eq.) was added and the reaction solution was stirred for 1 h at −78 °C. To this solution was added 4-hydroxy-2,6-dimethoxybenzaldehyde (**6c**, 2.00 g, 10.98 mmol, 1.0 eq.) and DMPU (8.0 mL, 8.44 g, 65.86 mmol, 6.0 eq.). After stirring for 4.5 h, the reaction solution was quenched by adding sat. NH_4Cl solution. The aqueous phase was extracted with Et_2O (3x) and the combined organic layers were washed with brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/acetone = 1:1, R_f = 0.50) afforded **8c** (0.65 g, 2.30 mmol, 21 %) as a yellow oil.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 8.41 (s, 1H), 6.17 (s, 2H), 5.22 (d, *J* = 11.7 Hz, 1H), 4.28 (d, *J* = 11.7 Hz, 1H), 3.77 (s, 6H), 3.62 (s, 3H), 1.08 (s, 3H), 1.05 (s, 3H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 177.4, 160.1, 159.3, 107.9, 93.1, 74.0, 55.8, 51.7, 50.4, 24.0, 20.6. HRMS (ESI): *m/z* calc. for $C_{14}H_{20}O_6$ $[M + H]^+$ 307.1152, found 307.1148.

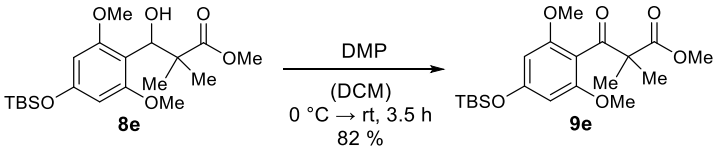
3.26 methyl 3-(4-((tert-butyldimethylsilyl)oxy)-2,6-dimethoxyphenyl)-3-hydroxy-2,2-dimethylpropanoate (**8e**).



To a solution of **8c** (0.65 g, 2.30 mmol, 1.0 eq.) in DMF (3.0 mL) was added TBSCl (0.36 g, 2.42 mmol, 1.05 eq.) and imidazole (0.16 g, 2.42 mmol, 1.05 eq.) at 0 °C. After stirring for 16 h at room temperature, water was added to the reaction solution. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with water (2x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/acetone = 2:1, R_f = 0.57) afforded **8e** (0.67 g, 1.67 mmol, 73 %) as a yellow oil.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 6.20 (s, 2H), 5.24 (d, *J* = 11.7 Hz, 1H), 4.30 (d, *J* = 11.7 Hz, 1H), 3.80 (s, 6H), 3.62 (s, 3H), 1.09 (s, 3H), 1.06 (s, 3H), 1.00 (s, 9H), 0.25 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 177.3, 159.9, 157.4, 110.0, 97.6, 73.3, 55.9, 51.7, 50.3, 26.0, 23.9, 20.6, 18.8, –4.3. HRMS (ESI): *m/z* calc. for $C_{20}H_{34}O_6Si$ [M + Na]$^+$ 421.2017, found 421.2017.

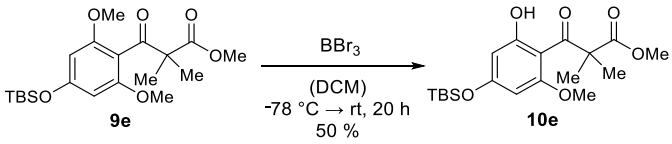
3.27 methyl 3-(4-((tert-butyldimethylsilyl)oxy)-2,6-dimethoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**9e**).



8e (0.67 g, 1.67 mmol, 1.0 eq.) was dissolved in dry DCM (20.9 mL) and DMP (0.78 g, 1.84 mmol, 1.1 eq.) was added at 0 °C under argon atmosphere. The reaction solution was stirred for 3.5 h at room temperature and quenched by adding a 1:1 mixture of sat. $NaHCO_3$ solution and sat. $Na_2S_2O_3$ solution. The aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with sat. $NaHCO_3$ solution (2x) and water (2x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.39) to give **9e** (0.54 g, 1.37 mmol, 82 %) as a white-red solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 6.17 (s, 2H), 3.72 (s, 6H), 3.57 (s, 3H), 1.36 (s, 6H), 1.00 (s, 9H), 0.26 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 202.6, 173.6, 159.1, 158.4, 113.3, 97.3, 57.4, 56.1, 52.2, 26.0, 23.3, 18.8, –4.3. HRMS (ESI): m/z calc. for $C_{20}H_{32}O_6Si$ [M + Na]$^+$ 419.1860, found 419.1864.

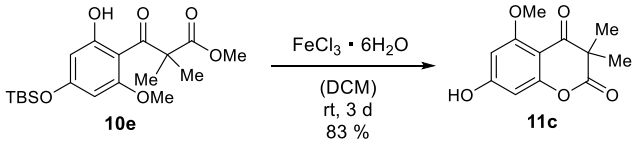
3.28 methyl 3-(4-((tert-butyldimethylsilyl)oxy)-2-hydroxy-6-methoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**10e**).



To a solution of **9e** (0.29 g, 0.74 mmol, 1.0 eq.) in dry DCM (4.1 mL) was added BBr_3 (0.81 mL, 0.81 mmol, 1.0 M in DCM, 1.1 eq.) at −78 °C under argon atmosphere. The solution was allowed to warm up to room temperature overnight. The reaction was quenched by adding water at 0 °C. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with water (2x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.57) afforded **10e** (98.2 mg, 0.28 mmol, 35 %) as a yellow oil.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 13.28 (s, 1H), 6.04 - 6.01 (m, 2H), 3.78 (s, 3H), 3.60 (s, 3H), 1.40 (s, 6H), 1.00 (s, 9H), 0.30 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 203.9, 174.5, 167.7, 163.9, 162.2, 105.7, 101.7, 95.9, 56.7, 55.0, 52.1, 25.9, 23.9, 18.8, –4.3. HRMS (ESI): *m/z* calc. for $C_{19}H_{30}O_6Si$ $[M + H]^+$ 383.1884, found 383.1883.

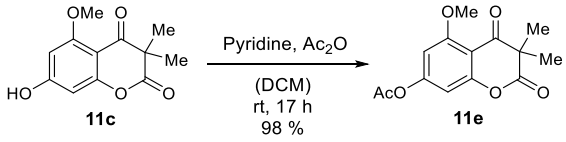
3.29 7-hydroxy-5-methoxy-3,3-dimethylchromane-2,4-dione (**11c**).



To a solution of **10e** (98.2 mg, 0.26 mmol, 1.0 eq.) in DCM (1.1 mL) was added $FeCl_3 \cdot 6H_2O$ (48.6 mg, 0.18 mmol, 0.7 eq.) at room temperature. After stirring for 3 d at room temperature, water was added to the reaction solution. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/acetone = 1:1, R_f = 0.50) afforded **11c** (50.3 mg, 0.21 mmol, 83 %) as a white-brown solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 9.76 (s, 1H), 6.37 (d, *J* = 2.2 Hz, 1H), 6.23 (d, *J* = 2.2 Hz, 1H), 3.85 (s, 3H), 1.42 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 189.8, 172.1, 165.2, 163.4, 158.3, 102.5, 96.7, 96.5, 56.4, 53.0, 23.5. HRMS (ESI): *m/z* calc. for $C_{12}H_{12}O_5$ $[M + H]^+$ 237.0763, found 237.0757.

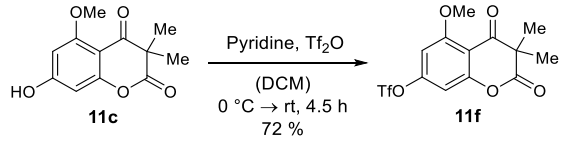
3.30 5-methoxy-3,3-dimethyl-2,4-dioxochroman-7-yl acetate (**11e**).



11c (20.0 mg, 84.7 µmol, 1.0 eq.) was dissolved in dry DCM (2.1 mL) and dry pyridine (10.0 µL, 10.0 mg, 0.13 mmol, 1.5 eq.) under argon atmosphere. Ac_2O (8.8 µL, 9.51 mg, 93.1 µmol, 1.1 eq.) was added and the reaction mixture was stirred at room temperature for 17 h. The reaction solution was diluted with EtOAc and quenched by adding 10 % aqueous HCl. The organic layer was washed with 10 % aqueous HCl (2x), water (2x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 1:1, R_f = 0.62) to give **11e** (23.0 mg, 82.7 µmol, 98 %) as an orange oil.

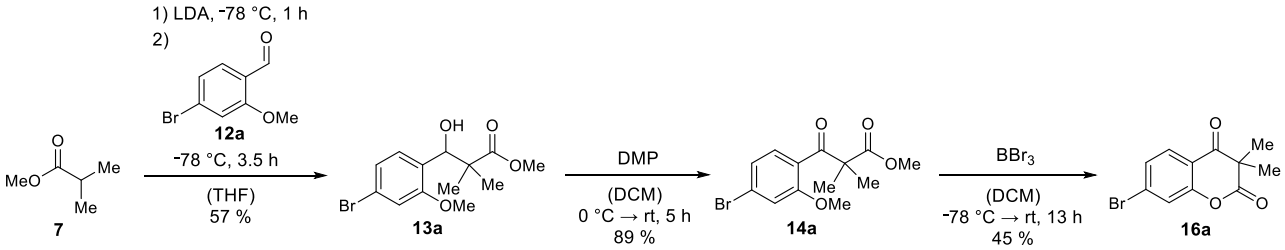
^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 6.76 (d, *J* = 2.1 Hz, 1H), 6.63 (d, *J* = 2.1 Hz, 1H), 3.90 (s, 3H), 2.30 (s, 3H), 1.46 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 190.6, 171.4, 168.9, 162.3, 157.7, 157.3, 107.0, 103.6, 103.1, 56.9, 53.6, 23.2, 21.0. HRMS (ESI): *m/z* calc. for $C_{14}H_{14}O_6$ $[M + H]^+$ 279.0869, found 279.0864.

3.31 5-methoxy-3,3-dimethyl-2,4-dioxochroman-7-yl trifluoromethanesulfonate (**11f**).



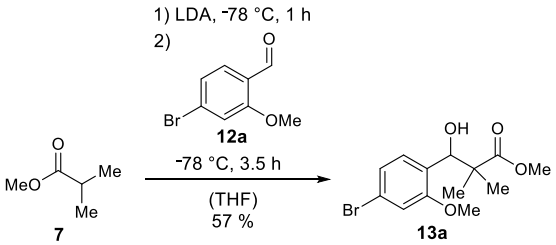
11c (20.0 mg, 84.7 µmol, 1.0 eq.) was dissolved in dry DCM (0.65 mL) and dry pyridine (10.0 µL, 10.0 mg, 0.13 mmol, 1.5 eq.) under argon atmosphere. Tf_2O (13.9 µL, 23.3 mg, 93.1 µmol, 1.1 eq.) was added at 0 °C. After stirring for 30 min at 0 °C, the reaction solution was allowed to warm up to room temperature and was stirred for further 4 h. The reaction solution was diluted with EtOAc and quenched by adding 10 % aqueous HCl. The organic layer was washed with 10% aqueous HCl (1x), water (1x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 1:1, R_f = 0.75) to give **11f** (22.3 mg, 60.6 µmol, 72 %) as an orange oil.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.10 (d, *J* = 2.3 Hz, 1H), 6.95 (d, *J* = 2.3 Hz, 1H), 4.01 (s, 3H), 1.48 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 190.4, 170.8, 162.8, 157.7, 154.5, 121.7, 109.3, 103.3, 102.9, 57.6, 53.9, 22.9. HRMS (ESI): *m/z* calc. for $C_{13}H_{11}F_3O_7S$ $[M + H]^+$ 369.0256, found 369.0251.



Scheme 5: Synthetic route towards chromene dione **16a** using 4-bromo-2-methoxybenzaldehyde (**12a**).

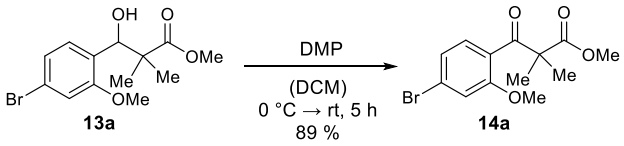
3.32 Methyl 3-(4-bromo-2-methoxyphenyl)-3-hydroxy-2,2-dimethylpropanoate (**13a**).



LDA was freshly prepared by the addition of *n*-BuLi (6.3 mL, 15.90 mmol, 2.5 M in hexane, 1.5 eq.) to a solution of DIPA (2.2 mL, 1.60 g, 15.90 mmol, 1.5 eq.) in THF (13.0 mL) at −78 °C under argon atmosphere. After stirring for 1 h, methyl isobutyrate (**7**, 1.2 mL, 1.08 g, 10.60 mmol, 1.0 eq.) in THF (1.40 mL) was added and the reaction solution was stirred for 1 h at −78 °C. To this solution was added 4-bromo-2-methoxybenzaldehyde (**12a**, 2.50 g, 11.60 mmol, 1.1 eq.). After stirring for 3.5 h, the reaction solution was quenched by adding sat. NH_4Cl solution. The aqueous phase was extracted with Et_2O (3x) and the combined organic layers were washed with brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.32) to give **13a** (1.92 g, 6.06 mmol, 57 %) as a yellow oil.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.40 - 7.35 (m, 1H), 7.16 - 7.10 (m, 2H), 5.44 (d, *J* = 4.8 Hz, 1H), 4.38 (d, *J* = 4.9 Hz, 1H), 3.86 (s, 3H), 3.65 (s, 3H), 1.11 (s, 3H), 0.99 (s, 3H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 177.5, 158.5, 131.6, 130.3, 123.7, 121.9, 114.5, 71.0, 56.1, 51.9, 49.2, 22.9, 19.1. HRMS (ESI): m/z calc. for $C_{13}H_{17}BrO_4$ $[M + Na]^+$ 339.0202, found 339.0158.

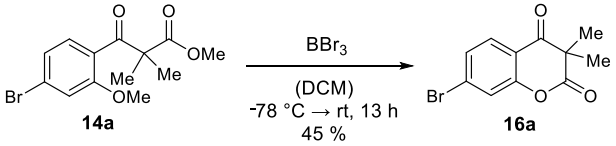
3.33 Methyl 3-(4-bromo-2-methoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**14a**).



13a (1.90 g, 5.99 mmol, 1.0 eq.) was dissolved in dry DCM (50.0 mL) and DMP (2.80 g, 6.59 mmol, 1.1 eq.) was added at 0 °C. The reaction solution was stirred for 5 h at room temperature and quenched by adding a 1:1 mixture of sat. $NaHCO_3$ solution and sat. $Na_2S_2O_3$ solution. The aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with sat. $NaHCO_3$ solution (2x) and water (2x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.47) to give **14a** (1.69 g, 5.35 mmol, 89 %) as a yellow solid.

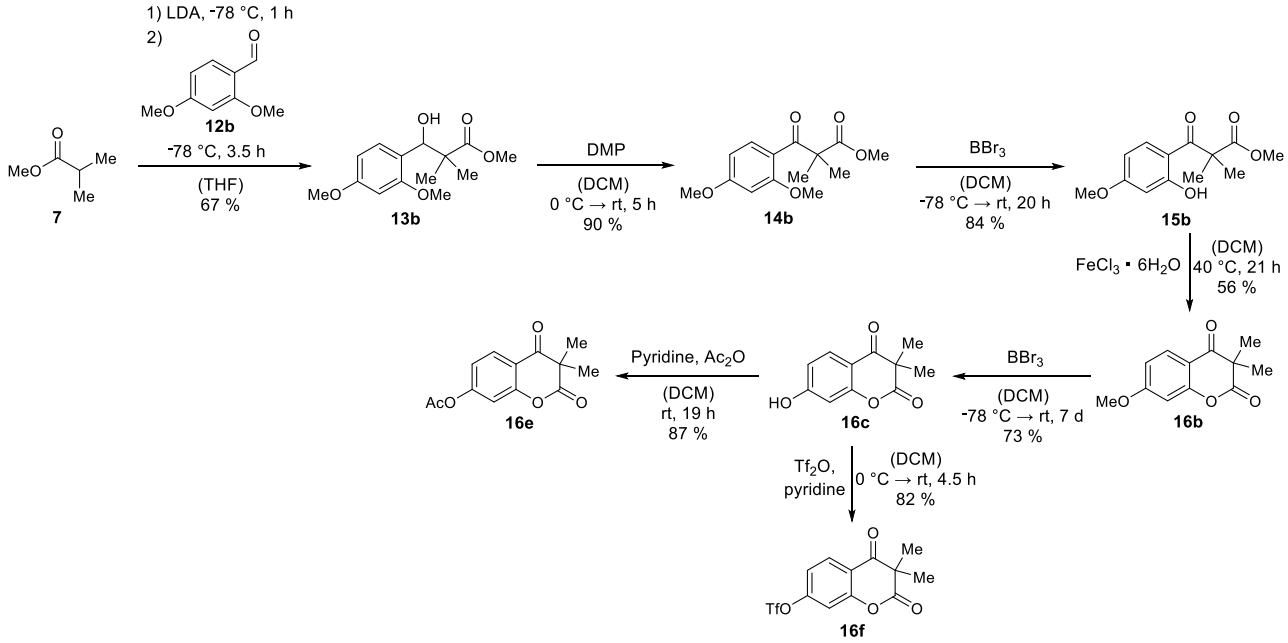
^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.51 (d, *J* = 8.3 Hz, 1H), 7.31 (d, *J* = 1.8 Hz, 1H), 7.23 (dd, *J* = 8.3, 1.7 Hz, 1H), 3.89 (s, 3H), 3.63 (s, 3H), 1.38 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 199.7, 174.3, 158.5, 132.8, 127.5, 127.2, 124.8, 116.0, 55.89, 55.86, 52.3, 23.3. HRMS (ESI): m/z calc. for $C_{13}H_{15}BrO_4$ $[M + H]^+$ 315.0226, found 315.0209.

3.34 7-Bromo-3,3-dimethylchromane-2,4-dione (**16a**)



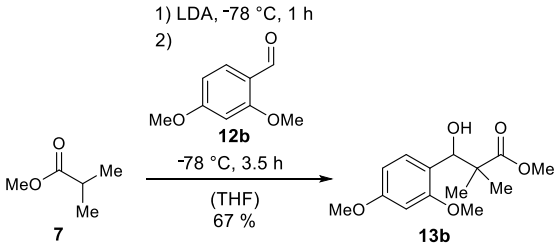
To a solution of **14a** (1.77 g, 5.61 mmol, 1.0 eq.) in dry DCM (35.0 mL) was added BBr_3 (6.2 mL, 6.17 mmol, 1.0 M in DCM, 1.1 eq.) at −78 °C under argon atmosphere. The solution was allowed to warm up to room temperature overnight. The reaction was quenched by adding water at 0 °C. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with water (2x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was washed with cyclohexane to give **16a** (0.68 g, 2.53 mmol, 45 %) as a white solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.82 - 7.78 (m, 1H), 7.56 - 7.51 (m, 2H), 1.52 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 193.8, 171.4, 156.1, 130.5, 129.4, 128.9, 121.2, 118.4, 53.6, 23.3. HRMS (ESI): m/z calc. for $C_{11}H_9BrO_3$ $[M + H]^+$ 268.9808, found 268.9790.



Scheme 6: Synthetic route towards chromene dione **16b,c,e,f** using 2,4-dimethoxybenzaldehyde (**12b**).

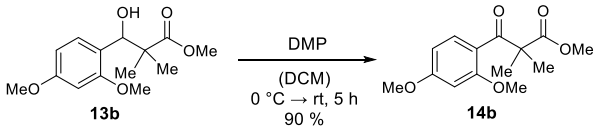
3.35 methyl 3-(2,4-dimethoxyphenyl)-3-hydroxy-2,2-dimethylpropanoate (**13b**).



LDA was freshly prepared by the addition of *n*-BuLi (5.0 mL, 12.48 mmol, 2.5 M in hexane, 1.5 eq.) to a solution of DIPA (1.8 mL, 1.26 g, 12.48 mmol, 1.5 eq.) in THF (44.6 mL) at −78 °C under argon atmosphere. After stirring for 1 h, methyl isobutyrate (**7**, 0.95 mL, 0.85 g, 8.32 mmol, 1.0 eq.) was added and the reaction solution was stirred for 1 h at −78 °C. To this solution was added 2,4-dimethoxybenzaldehyde (**12b**, 1.52 g, 9.15 mmol, 1.1 eq.). After stirring for 3 h, the reaction solution was quenched by adding sat. NH_4Cl solution. The aqueous phase was extracted with Et_2O (3x) and the combined organic layers were washed with brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (pentane/Et_2O = 3:1, R_f = 0.14) to give **13b** (1.64 g, 6.12 mmol, 67 %) as a yellow oil.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.34 - 7.30 (m, 1H), 6.54 - 6.51 (m, 2H), 5.38 (d, *J* = 5.1 Hz, 1H), 4.12 (d, *J* = 5.1, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.64 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 177.8, 161.1, 158.7, 130.6, 122.8, 105.1, 98.31, 71.53, 55.6, 55.5, 51.8, 49.4, 23.1, 19.0. HRMS (ESI): *m/z* calc. for $C_{14}H_{20}O_5$ $[M + H]^+$ 269.1383, found 269.1382.

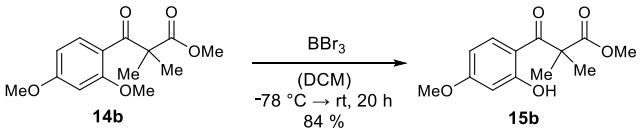
3.36 methyl 3-(2,4-dimethoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**14b**).



13b (1.64 g, 6.12 mmol, 1.0 eq.) was dissolved in dry DCM (51.0 mL) and DMP (2.86 g, 6.73 mmol, 1.1 eq.) was added at 0 °C. The reaction solution was stirred for 5 h at room temperature and quenched by adding a 1:1 mixture of sat. $NaHCO_3$ solution and sat. $Na_2S_2O_3$ solution. The aqueous phase was extracted with Et_2O (3x). The combined organic layers were washed with sat. $NaHCO_3$ solution (2x) and water (2x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.21) to give **14b** (1.47 g, 5.53 mmol, 90 %) as a yellow oil.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.74 - 7.71 (m, 1H), 6.63 - 6.59 (m, 2H), 3.88 (s, 3H), 3.82 (s, 3H), 3.60 (s, 3H), 1.35 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 197.6, 174.9, 165.5, 160.1, 134.0, 120.2, 107.0, 98.5, 56.0, 55.5, 55.0, 52.0, 23.6. HRMS (ESI): *m/z* calc. for $C_{14}H_{18}O_5$ $[M + K]^+$ 305.0786, found 305.0788.

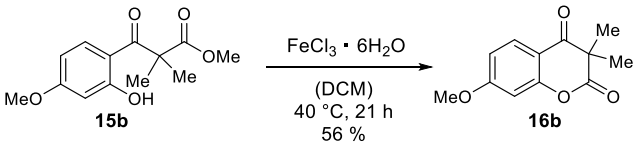
3.37 methyl 3-(2-hydroxy-4-methoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**15b**).



To a solution of **14b** (1.47 g, 5.53 mmol, 1.0 eq.) in dry DCM (34.6 mL) was added BBr_3 (6.1 mL, 6.08 mmol, 1.0 M in DCM, 1.1 eq.) at −78 °C under argon atmosphere. The solution was allowed to warm up to room temperature overnight. The reaction was quenched by adding water at 0 °C. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with water (2x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/acetone = 3:1, R_f = 0.50) afforded **15b** (1.17 g, 4.63 mmol, 84 %) as a yellow oil.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 12.67 (s, 1H), 7.48 (dd, *J* = 8.9, 0.5 Hz, 1H), 6.54 - 6.49 (m, 2H), 3.89 (s, 3H), 3.67 (s, 3H), 1.52 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 203.1, 176.1, 167.3, 166.8, 132.1, 111.9, 108.5, 102.2, 56.2, 53.9, 53.0, 24.5. HRMS (ESI): *m/z* calc. for $C_{13}H_{16}O_5$ $[M + H]^+$ 253.1070, found 253.1071.

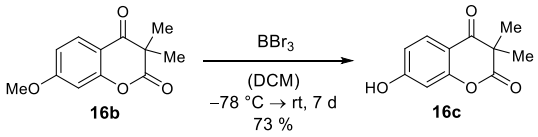
3.38 7-methoxy-3,3-dimethylchromane-2,4-dione (**16b**).



To a solution of **15b** (1.17 g, 4.63 mmol, 1.0 eq.) in DCM (23.1 mL) was added $FeCl_3 \cdot 6H_2O$ (0.63 g, 2.31 mmol, 0.5 eq.) at room temperature. After stirring for 21 h at 40 °C, water was added to the reaction solution. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.34) afforded **16b** (0.57 g, 2.59 mmol, 56 %) as a yellow oil.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.81 (d, *J* = 8.8 Hz, 1H), 6.89 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.76 (d, *J* = 2.4 Hz, 1H), 3.95 (s, 3H), 1.49 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 193.0, 172.2, 167.3, 157.6, 129.6, 113.1, 112.3, 101.8, 56.6, 52.8, 23.7. HRMS (ESI): *m/z* calc. for $C_{12}H_{12}O_4$ $[M + H]^+$ 221.0814, found 221.0808.

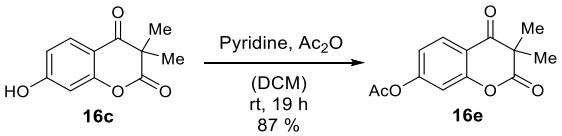
3.39 7-hydroxy-3,3-dimethylchromane-2,4-dione (**16c**).



16b (0.33 mg, 1.51 mmol, 1.0 eq.) was dissolved in dry DCM (9.5 mL) under argon atmosphere and BBr_3 (5.3 mL, 5.30 mmol, 1.0 M in DCM, 3.5 eq.) was added at –78 °C. The reaction solution was allowed to warm up to room temperature and was stirred for 7 d. The reaction was quenched by adding water at 0 °C. The aqueous phase was extracted with EtOAc (3x) and the combined organic layers were washed with water (1x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.09) to give **16c** (0.23 g, 1.11 mmol, 73 %) as a white/beige solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 9.81 (s, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 6.81 (dd, *J* = 8.6, 2.27 Hz, 1H), 6.61 (d, *J* = 2.3 Hz, 1H), 1.48 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 192.9, 172.4, 165.7, 157.6, 130.1, 113.9, 111.7, 103.6, 52.7, 24.3. HRMS (ESI): *m/z* calc. for $C_{11}H_{10}O_4$ $[M + H]^+$ 207.0657, found 207.0651.

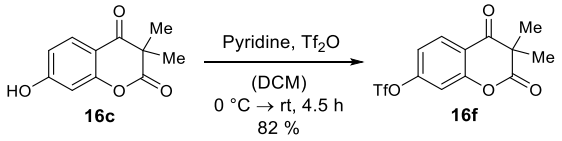
3.40 3,3-dimethyl-2,4-dioxochroman-7-yl acetate (**16e**).



16c (40.0 mg, 0.19 mmol, 1.0 eq.) was dissolved in dry DCM (4.9 mL) and dry pyridine (23.5 µL, 23.0 mg, 0.29 mmol, 1.5 eq.) under argon atmosphere. Ac_2O (20.2 µL, 21.8 mg, 0.21 mmol, 1.1 eq.) was added and the reaction mixture was stirred at room temperature for 17 h. The reaction solution was diluted with EtOAc and quenched by adding 10 % aqueous HCl. The organic layer was washed with 10 % aqueous HCl (2x), water (2x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.24) to give **16e** (42.0 mg, 0.17 mmol, 87 %) as a white-orange solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 7.92 (d, *J* = 8.5 Hz, 1H), 7.12 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 2.32 (s, 3H), 1.53 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 193.6, 171.7, 169.0, 157.8, 156., 129.2, 119.5, 116.8, 111.6, 53.4, 23.5, 21.0. HRMS (ESI): *m/z* calc. for $C_{13}H_{12}O_5$ $[M + H]^+$ 249.0763, found 249.0759.

3.41 3,3-dimethyl-2,4-dioxochroman-7-yl trifluoromethanesulfonate (**16f**).



16c (40.0 mg, 0.19 mmol, 1.0 eq.) was dissolved in dry DCM (1.4 mL) and dry pyridine (23.5 µL, 23.0 mg, 0.29 mmol, 1.5 eq.) under argon atmosphere. Tf_2O (35.9 µL, 30.2 mg, 0.21 mmol, 1.1 eq.) was added at 0 °C. After stirring for 30 min at 0 °C, the reaction solution was allowed to warm up to room temperature and was stirred for further 4 h. The reaction solution was diluted with EtOAc and quenched by adding 10% aqueous HCl. The organic layer was washed with 10% aqueous HCl (1x), water (1x) and brine (1x), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (cyclohexane/acetone = 5:1, R_f = 0.37) to give **16f** (54.1 mg, 0.16 mmol, 82 %) as a white solid.

^{1}H-NMR (300 MHz, acetone-d_6) δ (ppm): 8.09 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.47 - 7.43 (m, 2H), 1.56 (s, 6H). ^{13}C-NMR (75 MHz, acetone-d_6) δ (ppm): 193.4, 171.1, 156.7, 154.6, 130.4, 119.6 (q, *J* = 320.0 Hz), 119.5, 118.7, 112.0, 53.7, 23.3. HRMS (ESI): *m/z* calc. for $C_{12}H_9F_3O_6S$ $[M + H]^+$ 339.0150, found 339.0140.

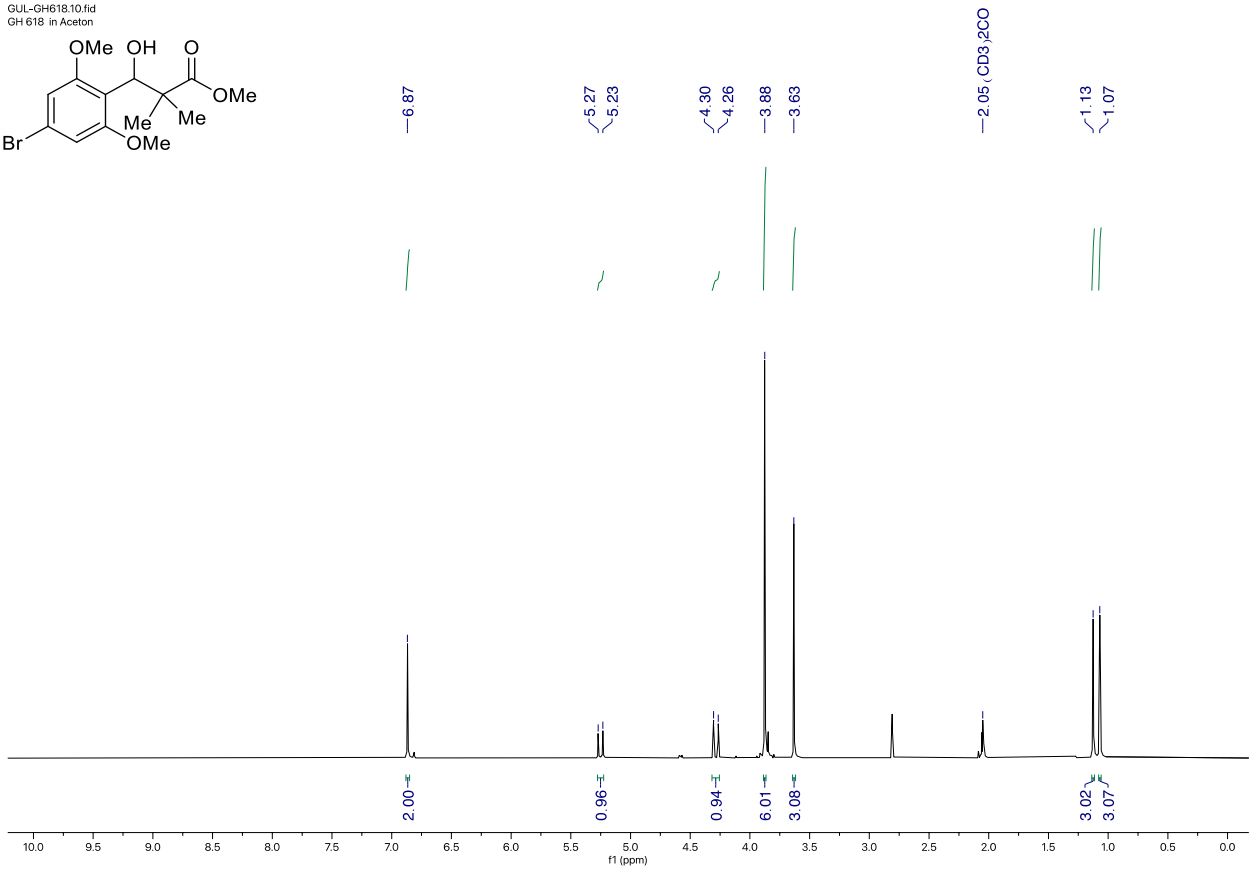
4. References

[1] M. B. Hansen, S. E. Nielsen, K. Berg, *J. Immunol. Methods* **1989**, *119*, 203-210.

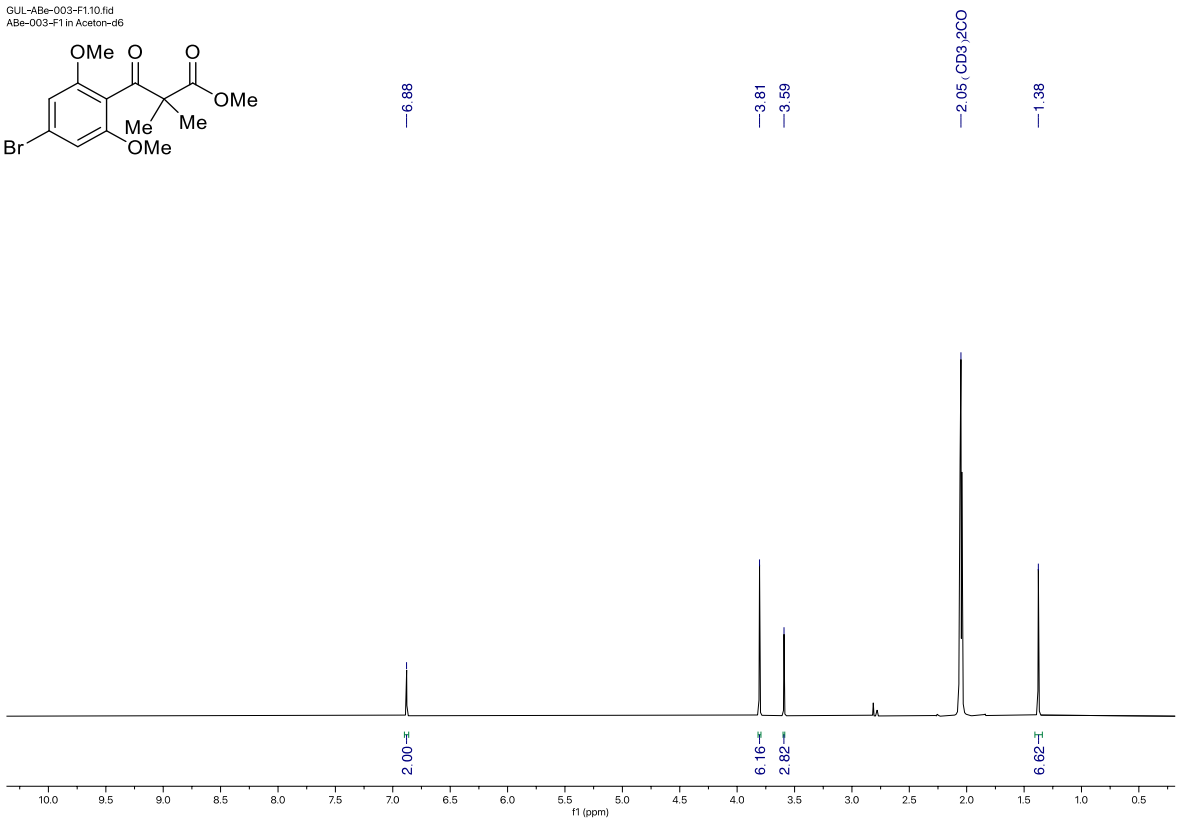
[2] G. Hertrampf, S. Vojnovic, J. I. Müller, C. Merten, J. Nikodinovic-Runic, T. A. M. Gulder, *J. Org. Chem.* **2023**, *19*, 14184 – 14188.

5. NMR Spectra

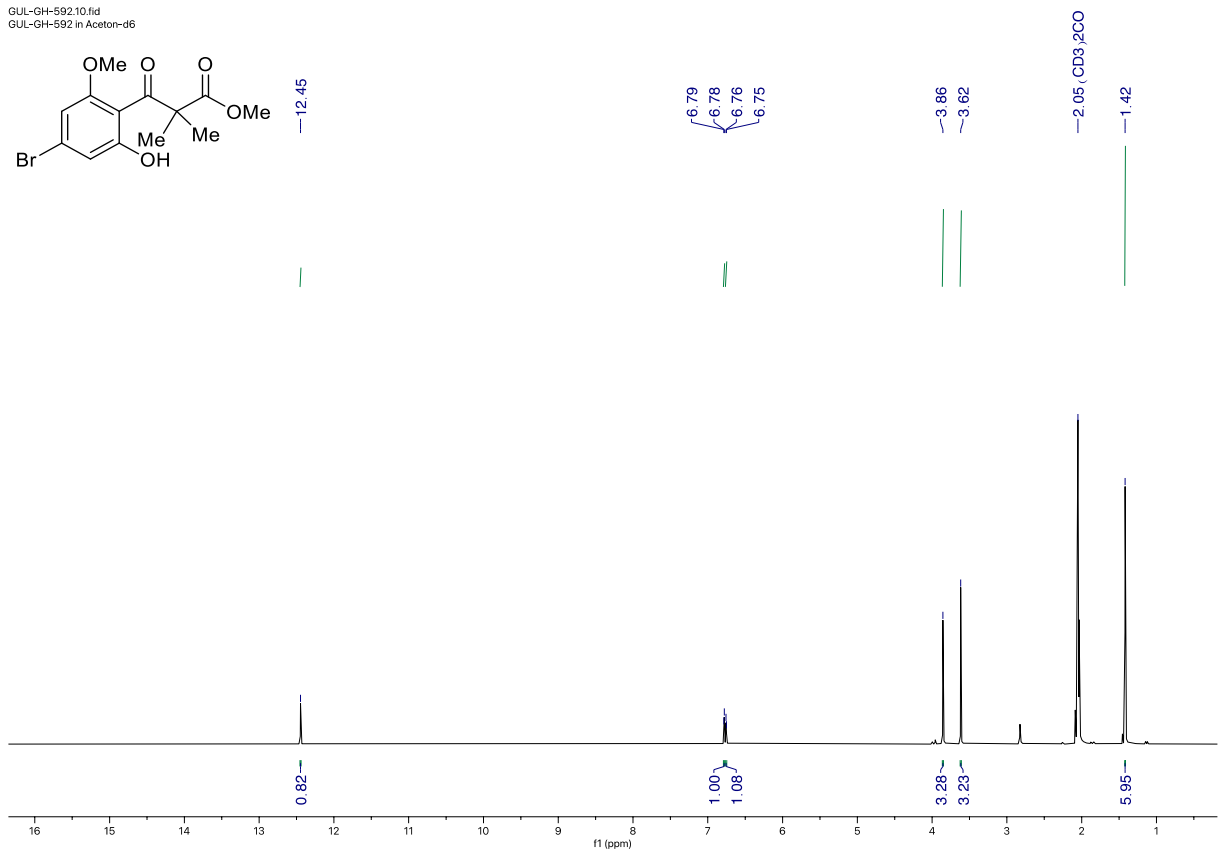
5.1 Methyl 3-(4-bromo-2,6-dimethoxyphenyl)-3-hydroxy-2,2-dimethylpropanoate (**8a**).



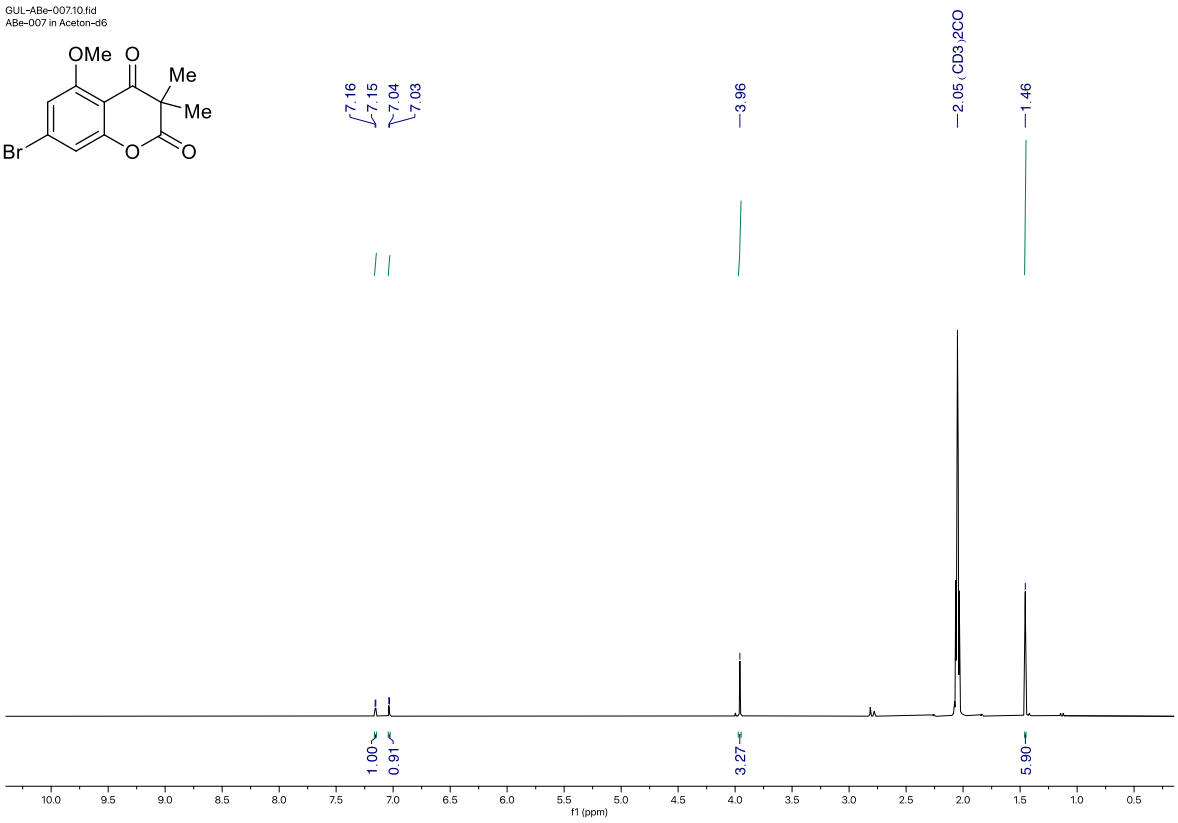
5.2 Methyl 3-(4-bromo-2,6-dimethoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**9a**).



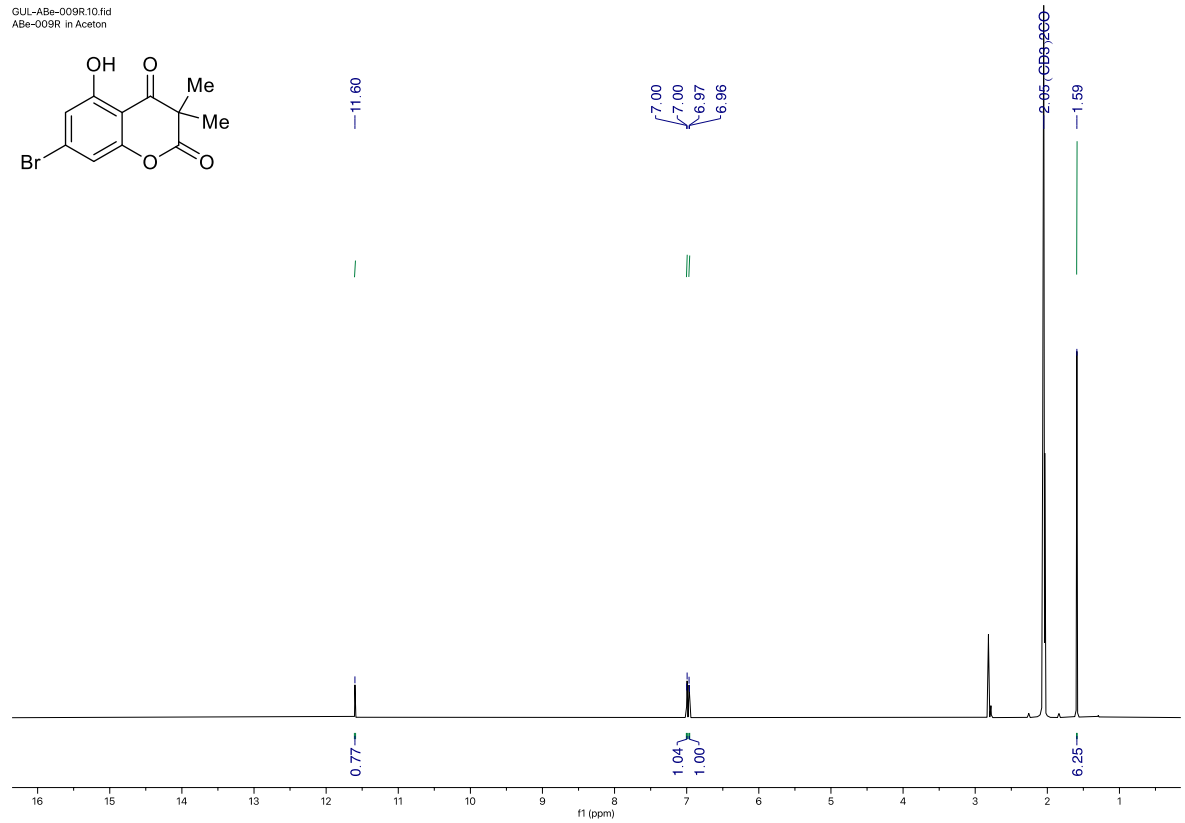
5.3 Methyl 3-(4-bromo-2-hydroxy-6-methoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**10a**).



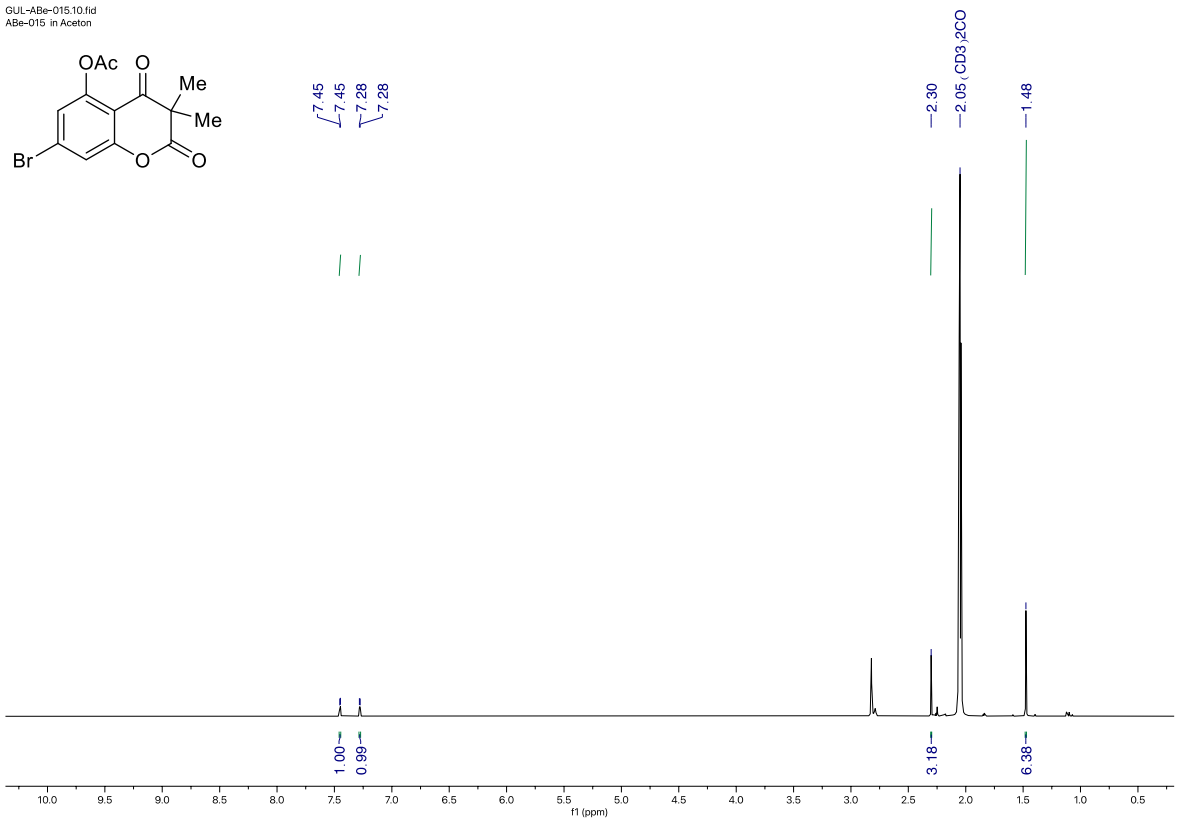
5.4 7-bromo-5-methoxy-3,3-dimethylchromane-2,4-dione (**11a**).

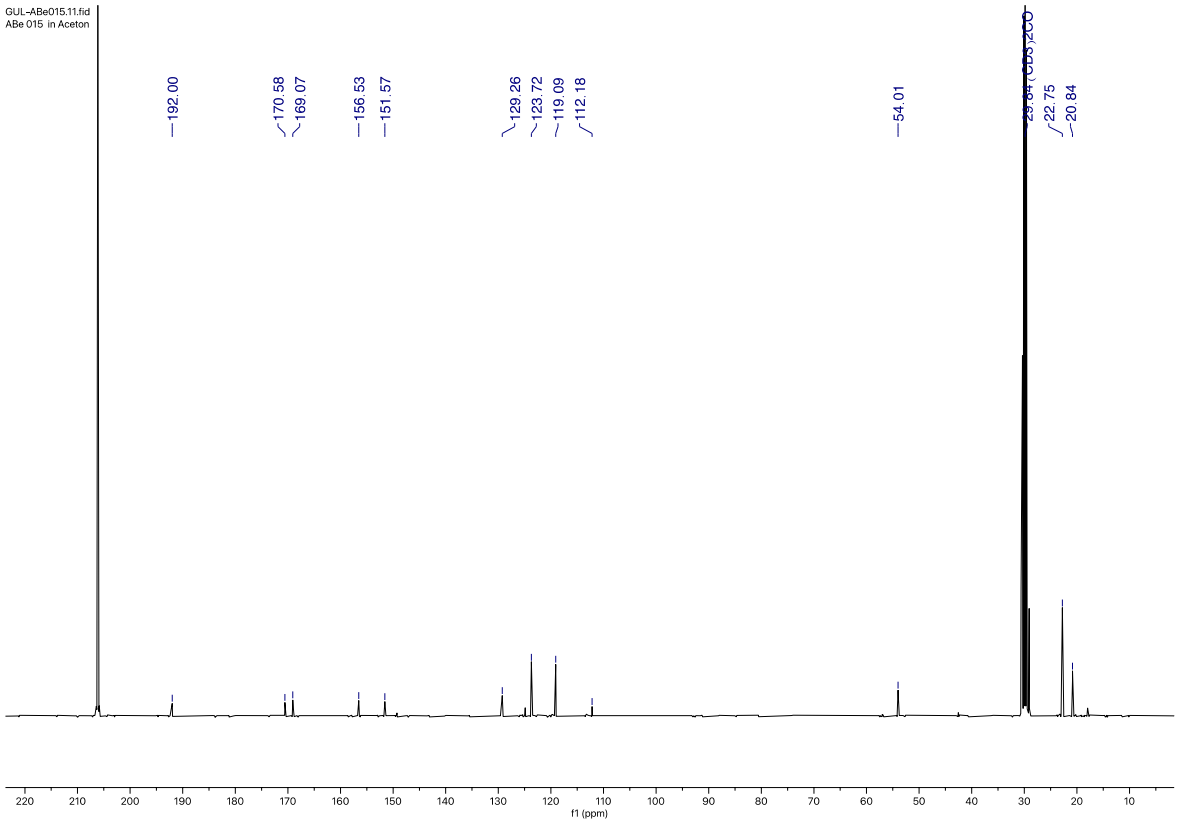


5.5 7-bromo-5-hydroxy-3,3-dimethylchromane-2,4-dione (**17a**).

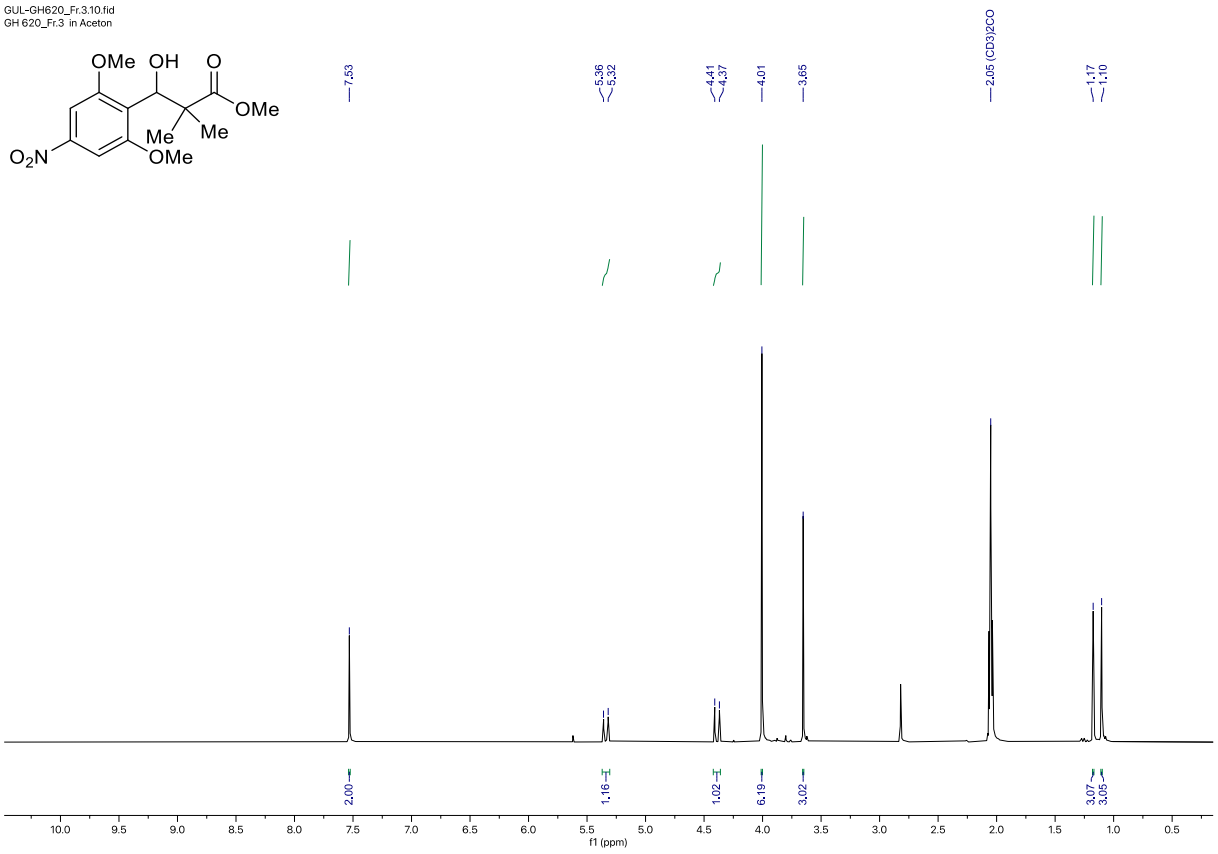


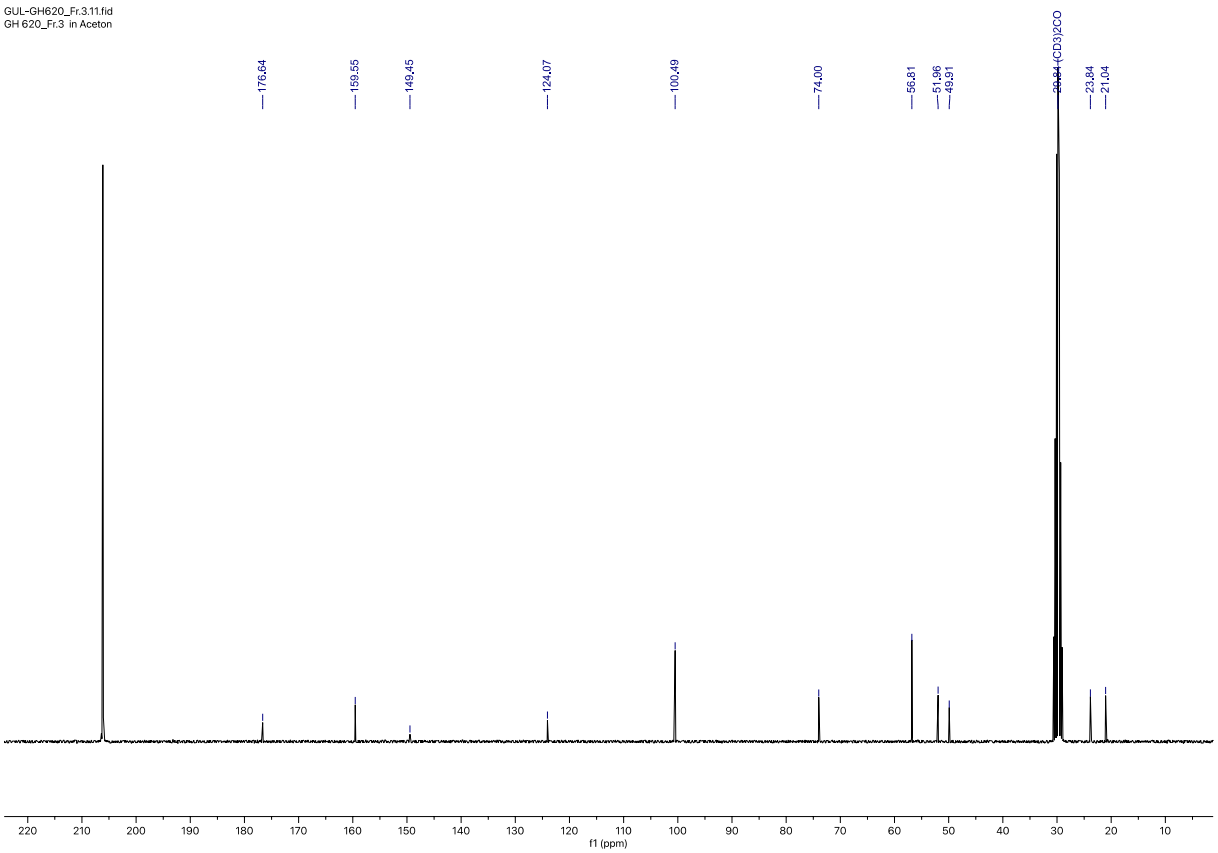
5.6 7-bromo-3,3-dimethyl-2,4-dioxochroman-5-yl acetate (**18a**).



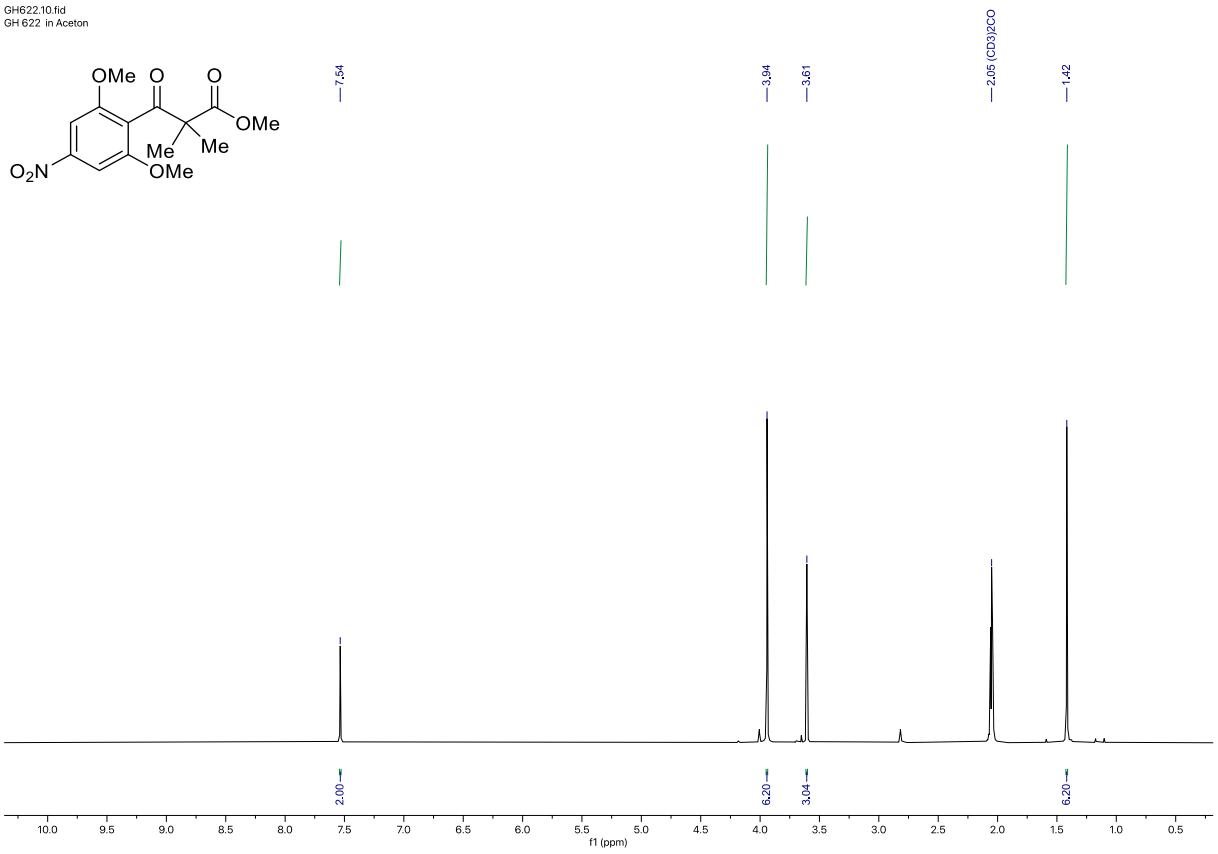


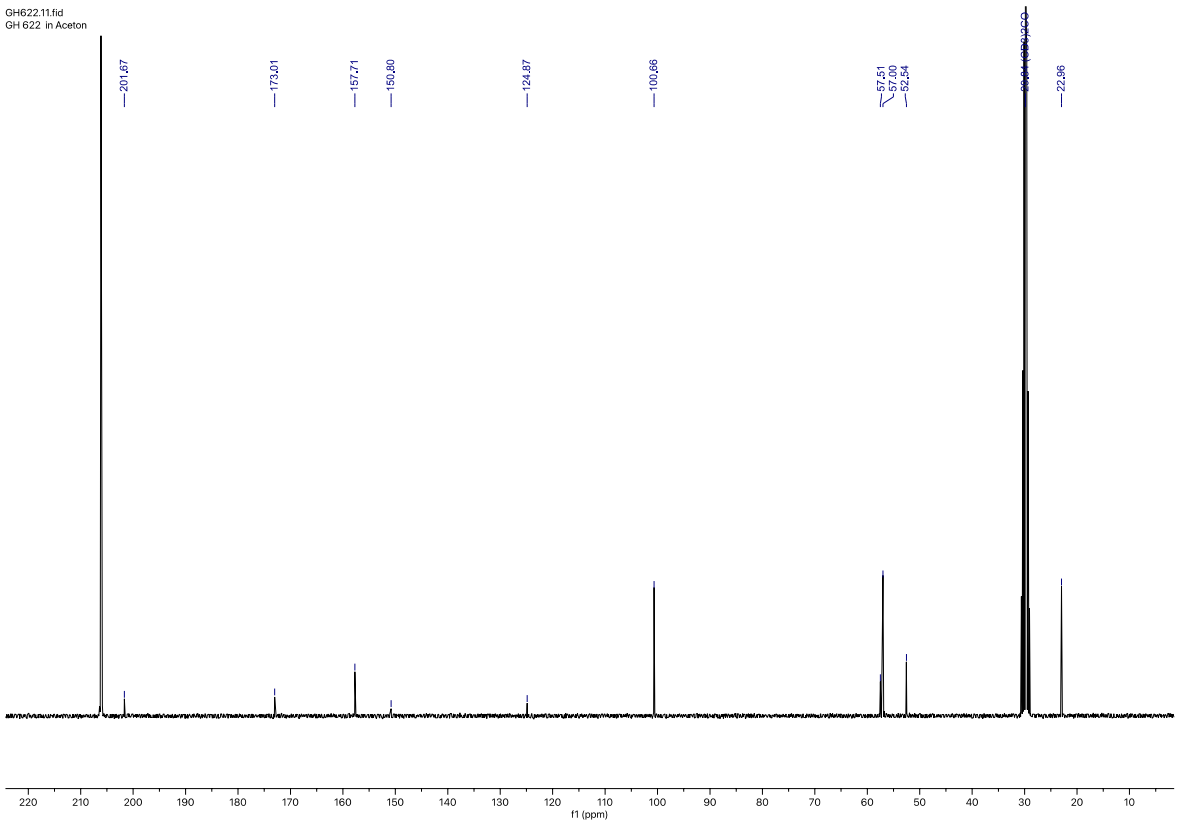
5.7 Methyl 3-(2,6-dimethoxy-4-nitrophenyl)-3-hydroxy-2,2-dimethyl-propanoate (**8d**)



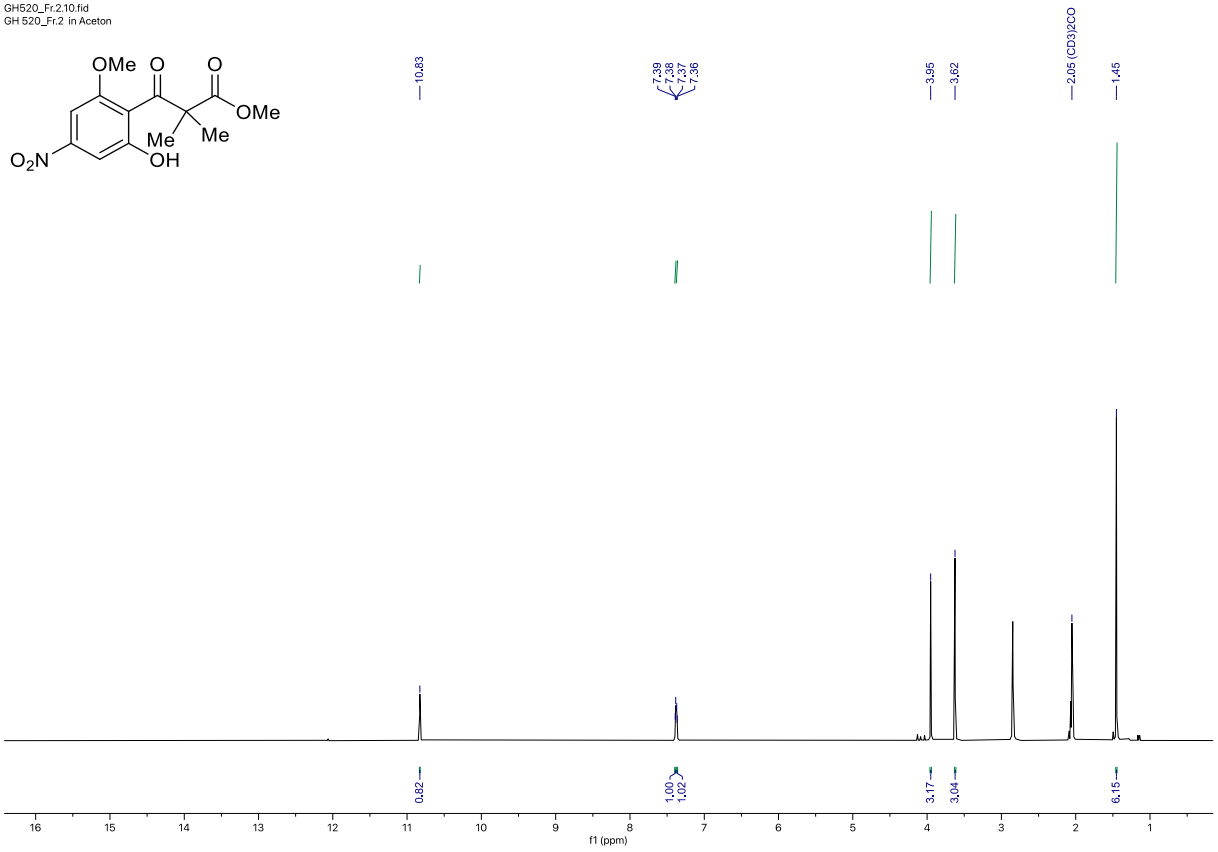


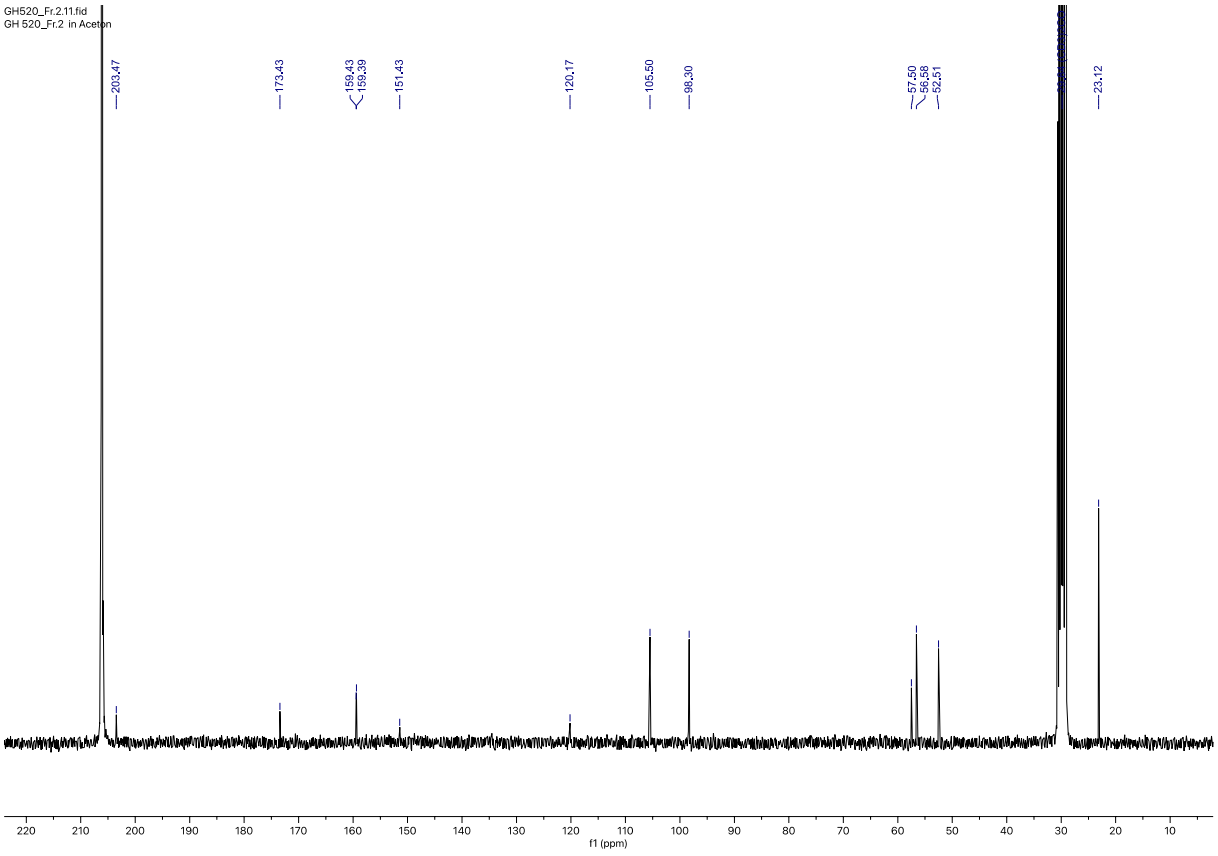
5.8 Methyl 3-(2,6-dimethoxy-4-nitrophenyl)-2,2-dimethyl-3-oxopropanoate (**9d**)



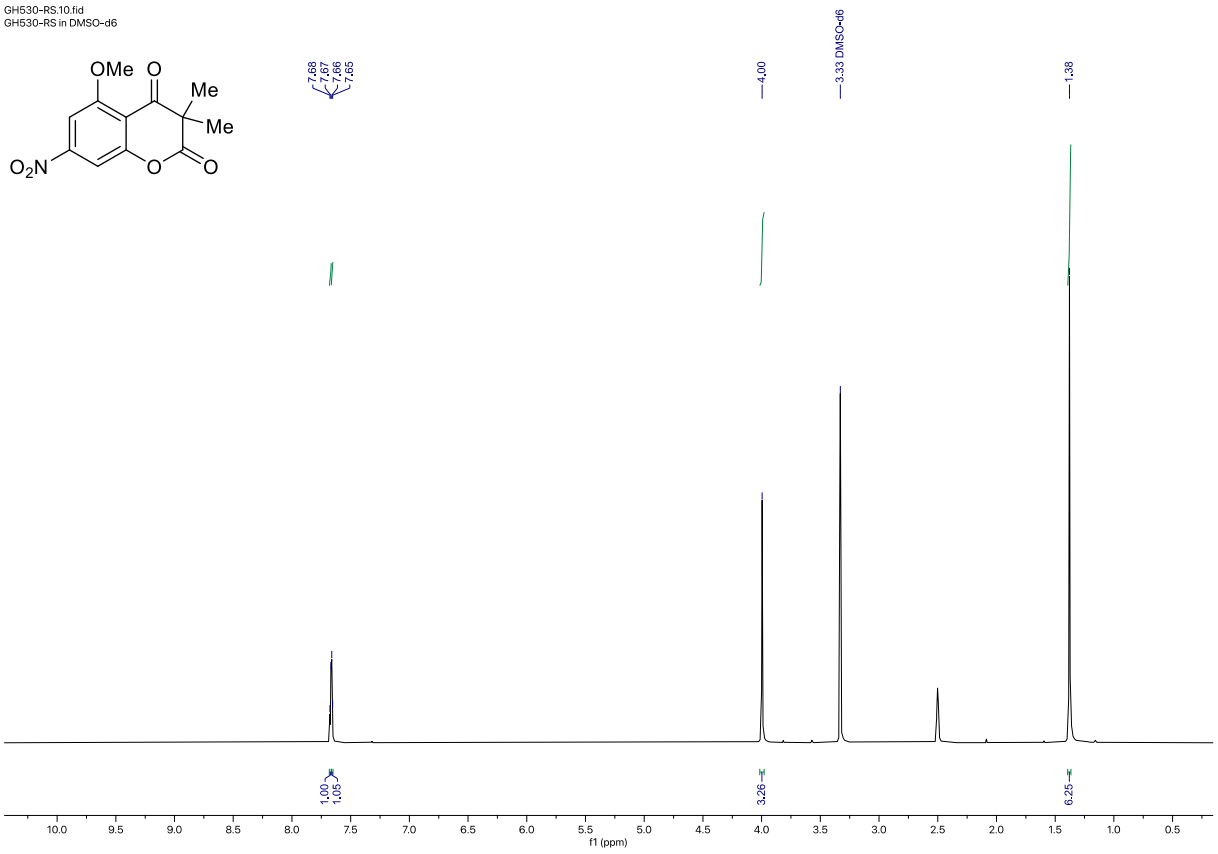


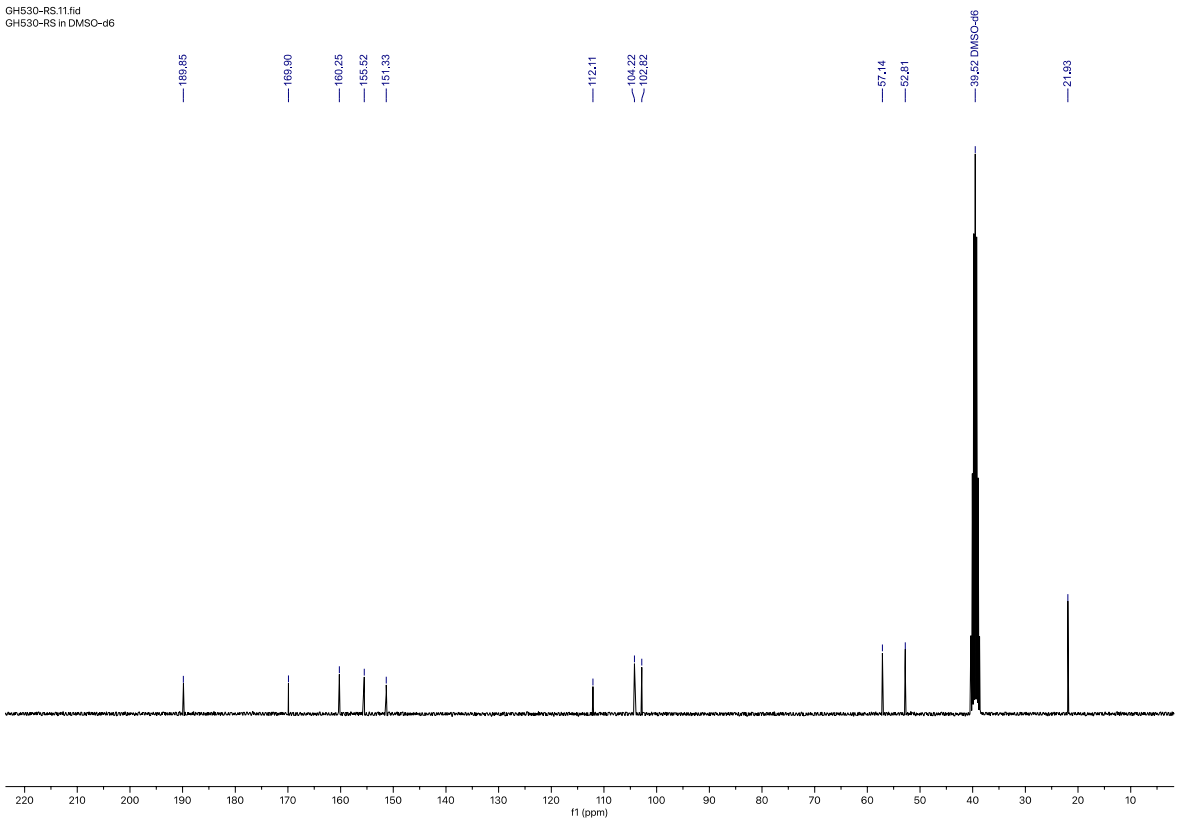
5.9 Methyl 3-(2-hydroxy-6-methoxy-4-nitrophenyl)-2,2-dimethyl-3-oxopropanoate (**10d**)



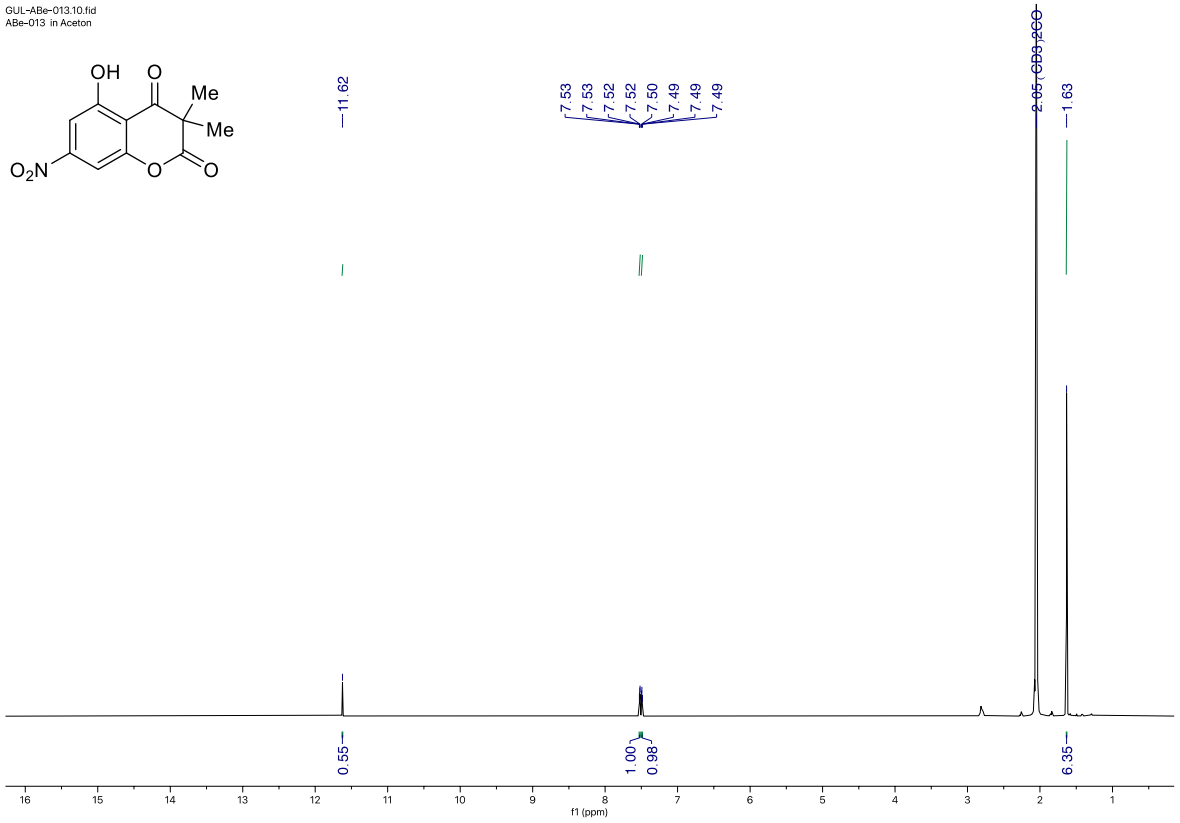


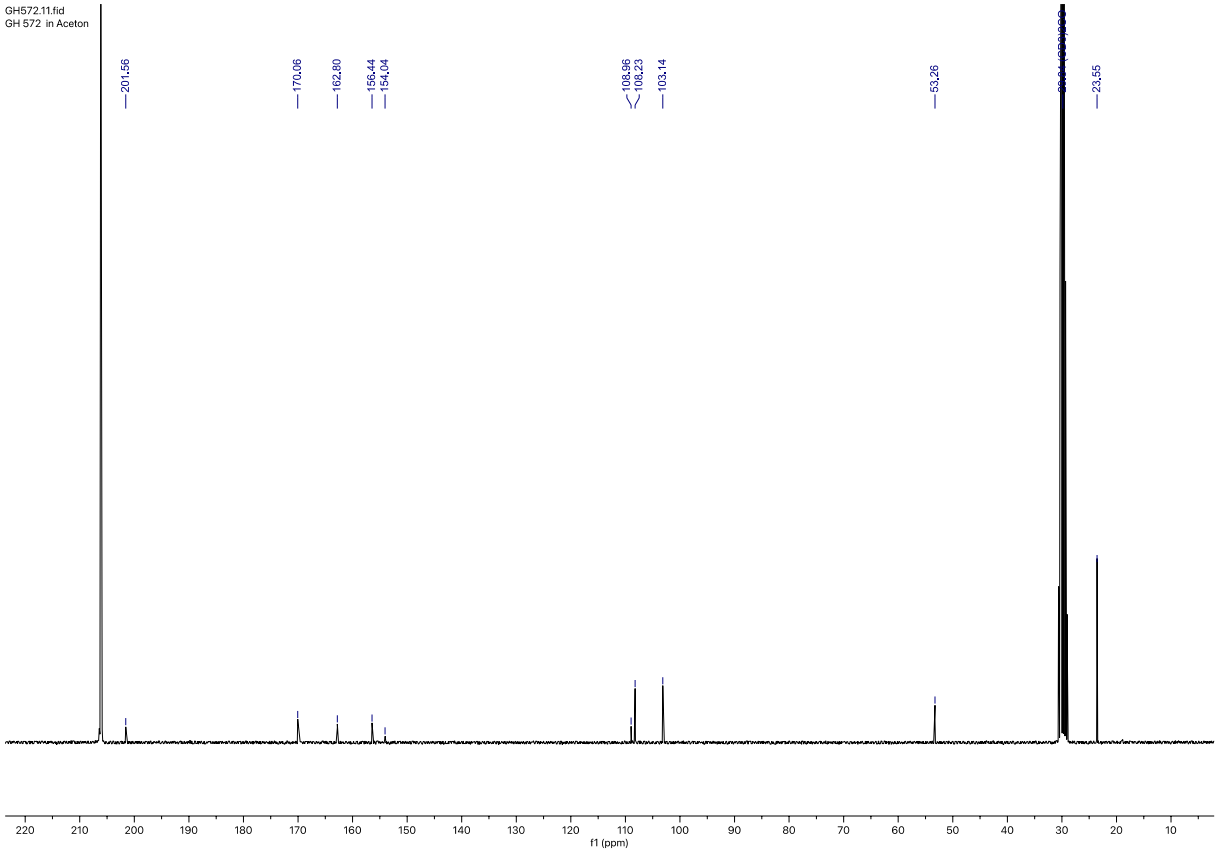
5.10 5-Methoxy-3,3-dimethyl-7-nitrochromane-2,4-dione (**11d**)



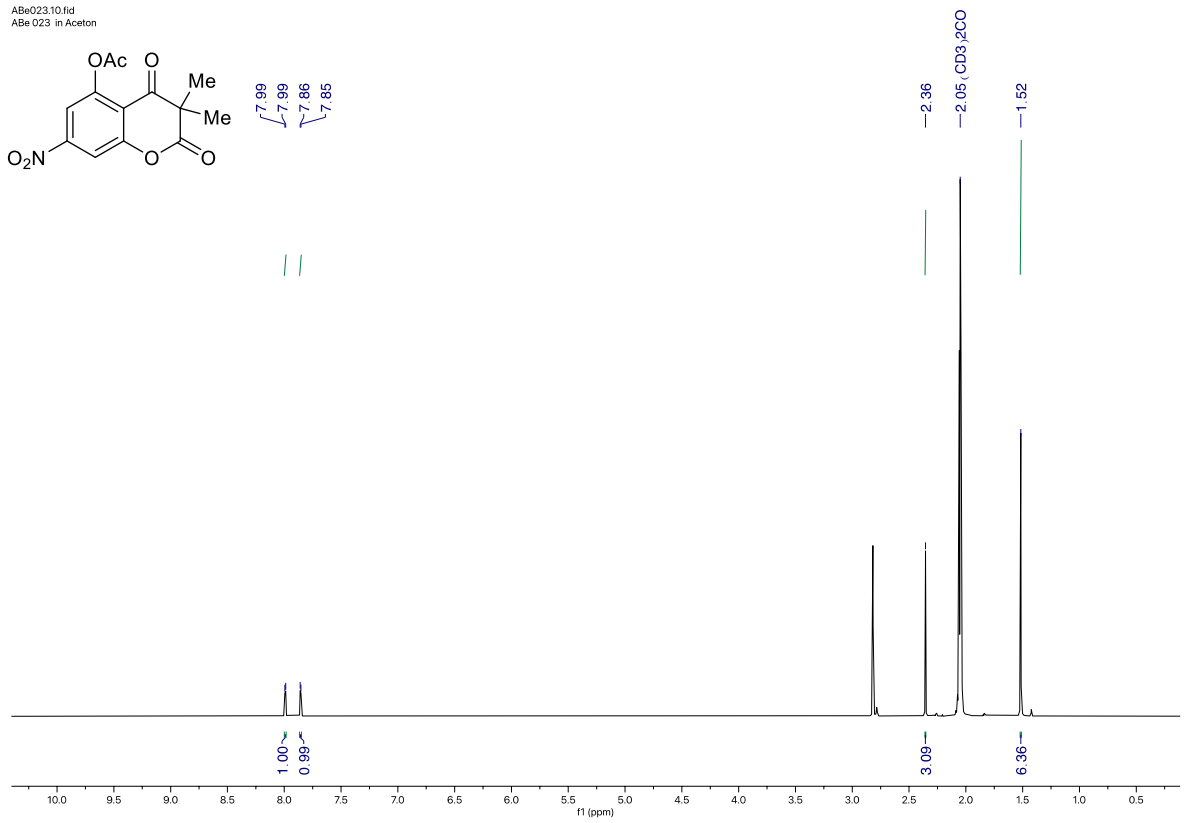


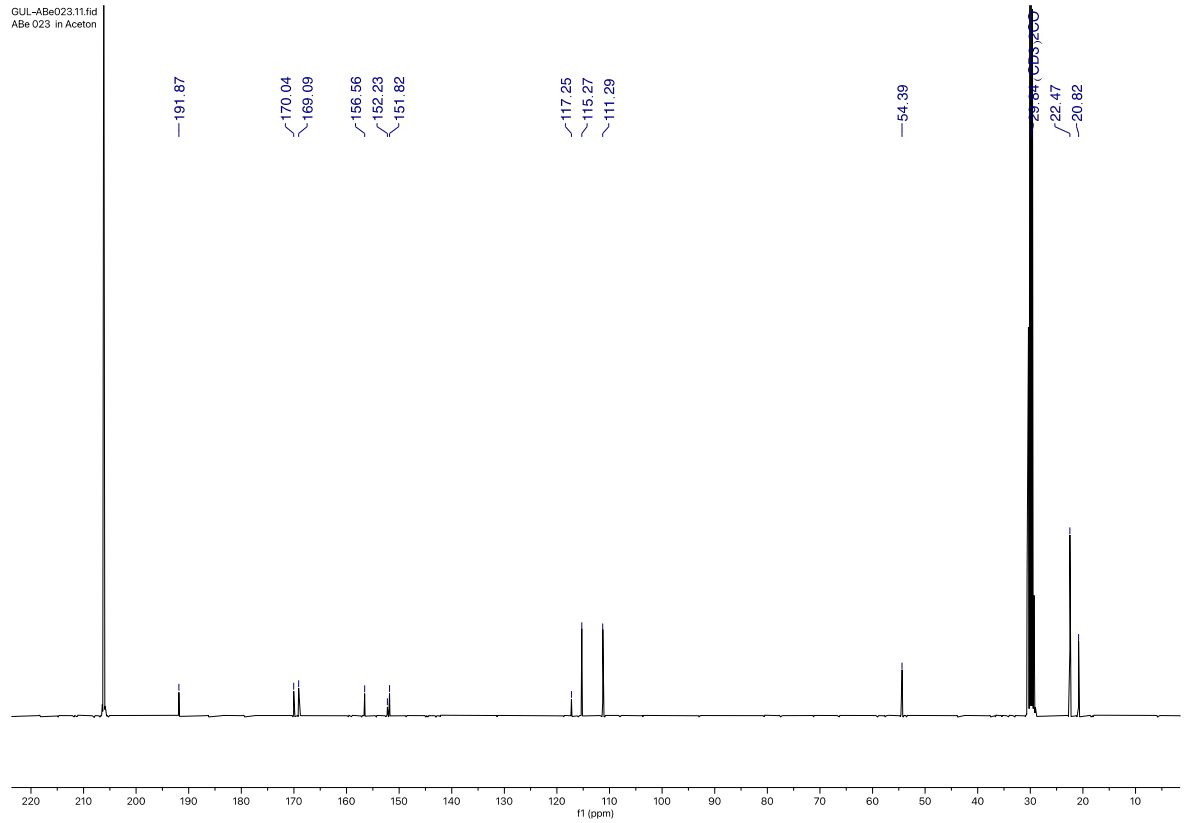
5.11 5-hydroxy-3,3-dimethyl-7-nitrochromane-2,4-dione (**17d**).



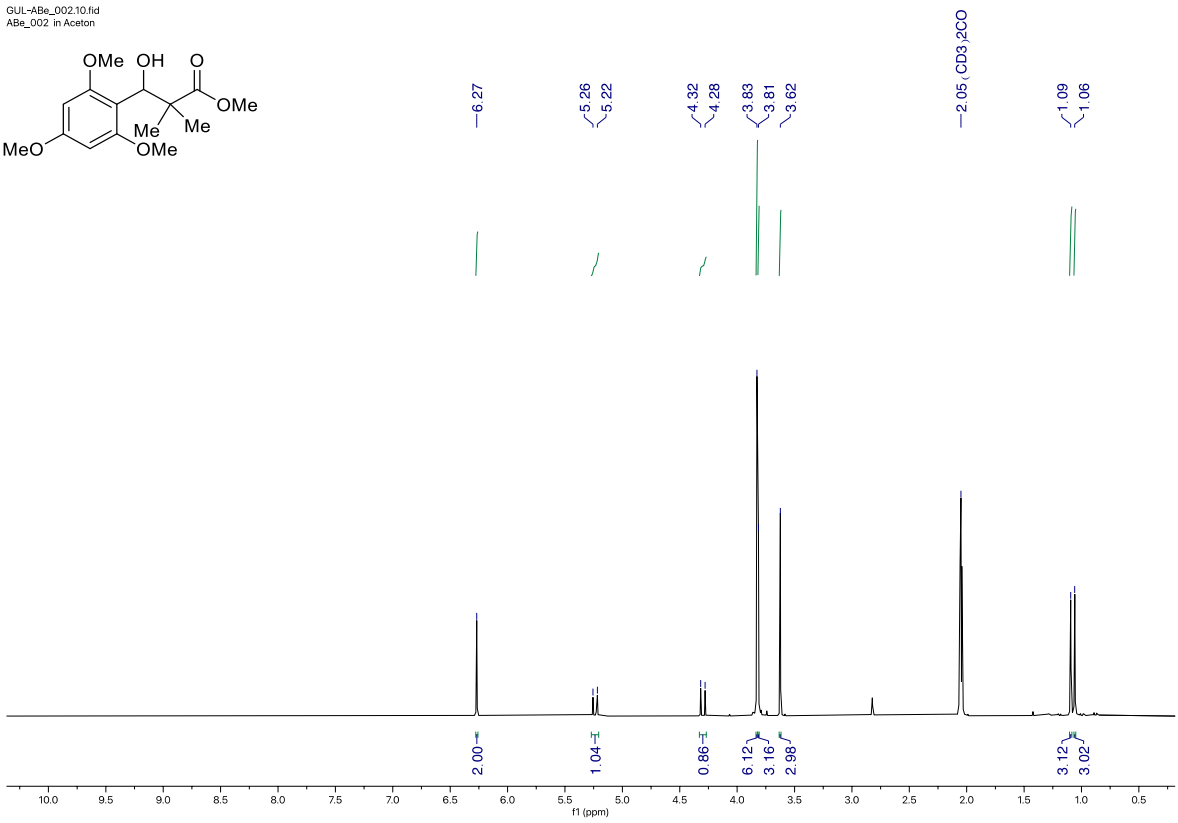


5.12 3,3-dimethyl-7-nitro-2,4-dioxochroman-5-yl acetate (**18d**).

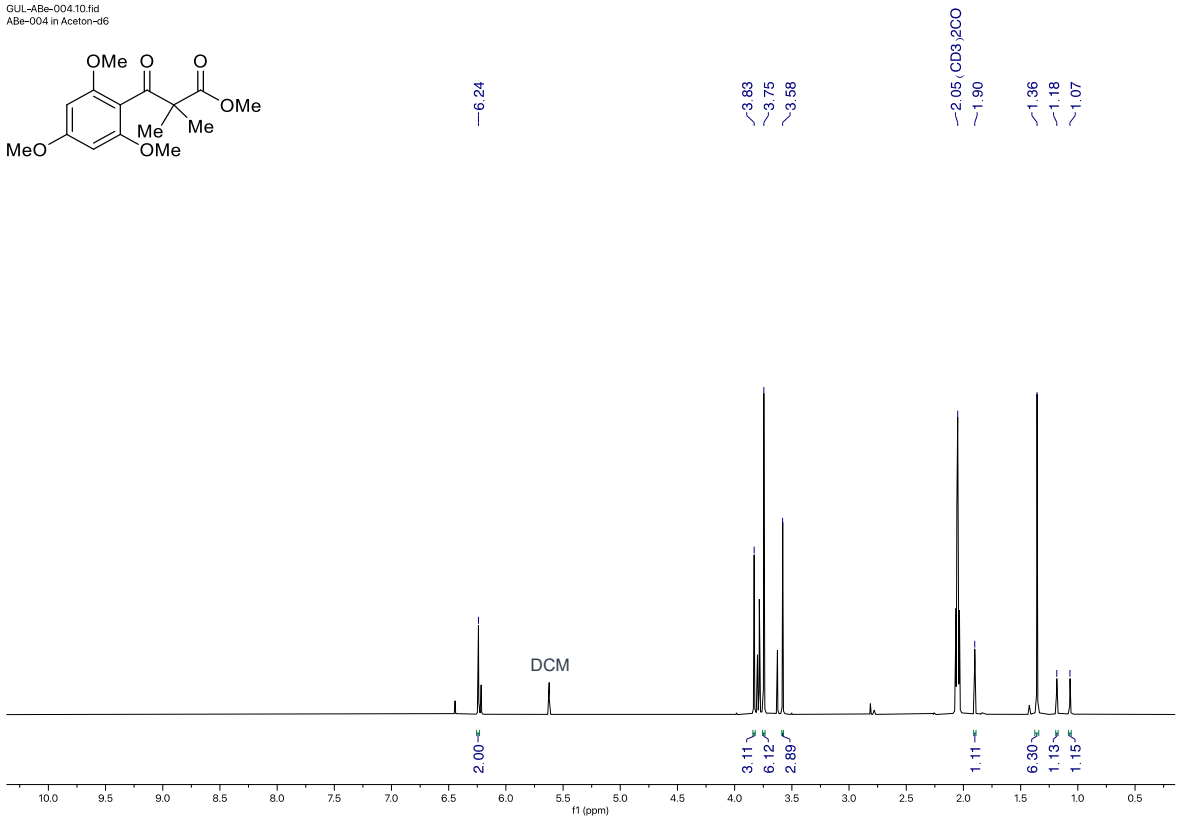




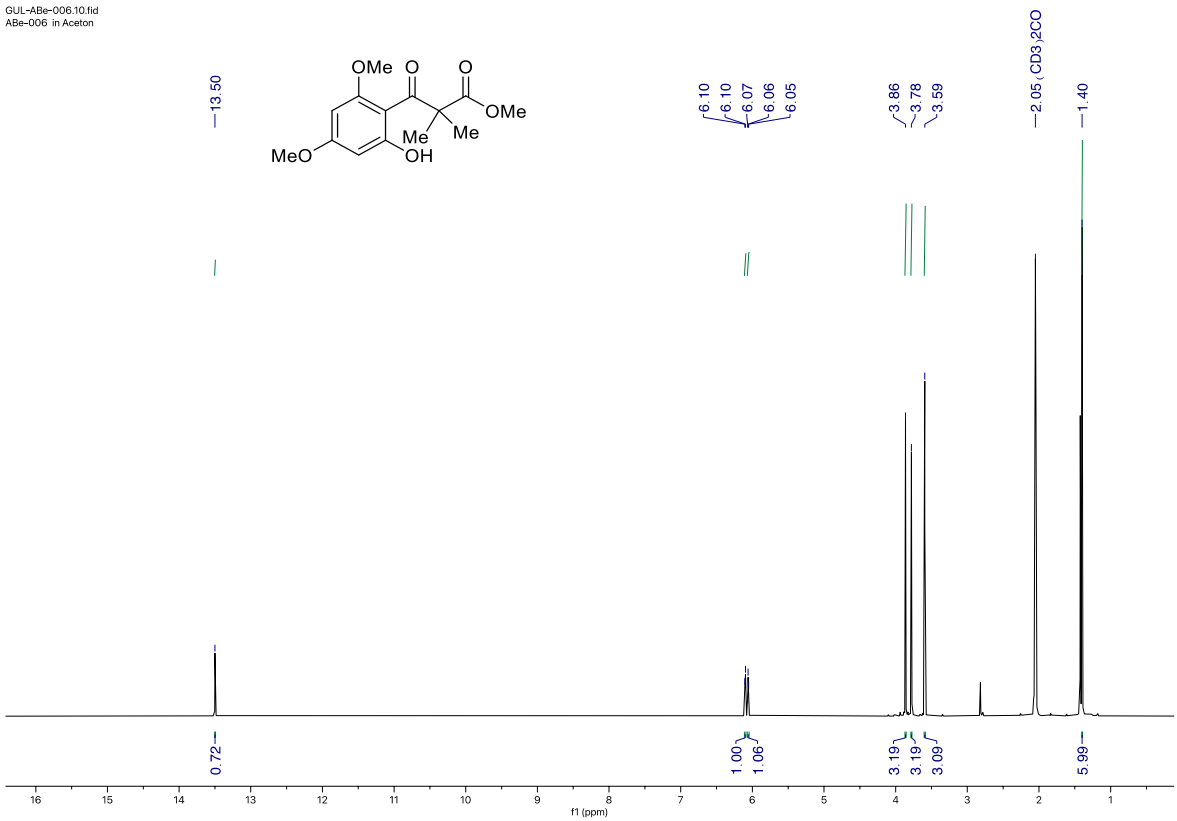
5.13 methyl 3-hydroxy-2,2-dimethyl-3-(2,4,6-trimethoxyphenyl)propanoate (**8b**).



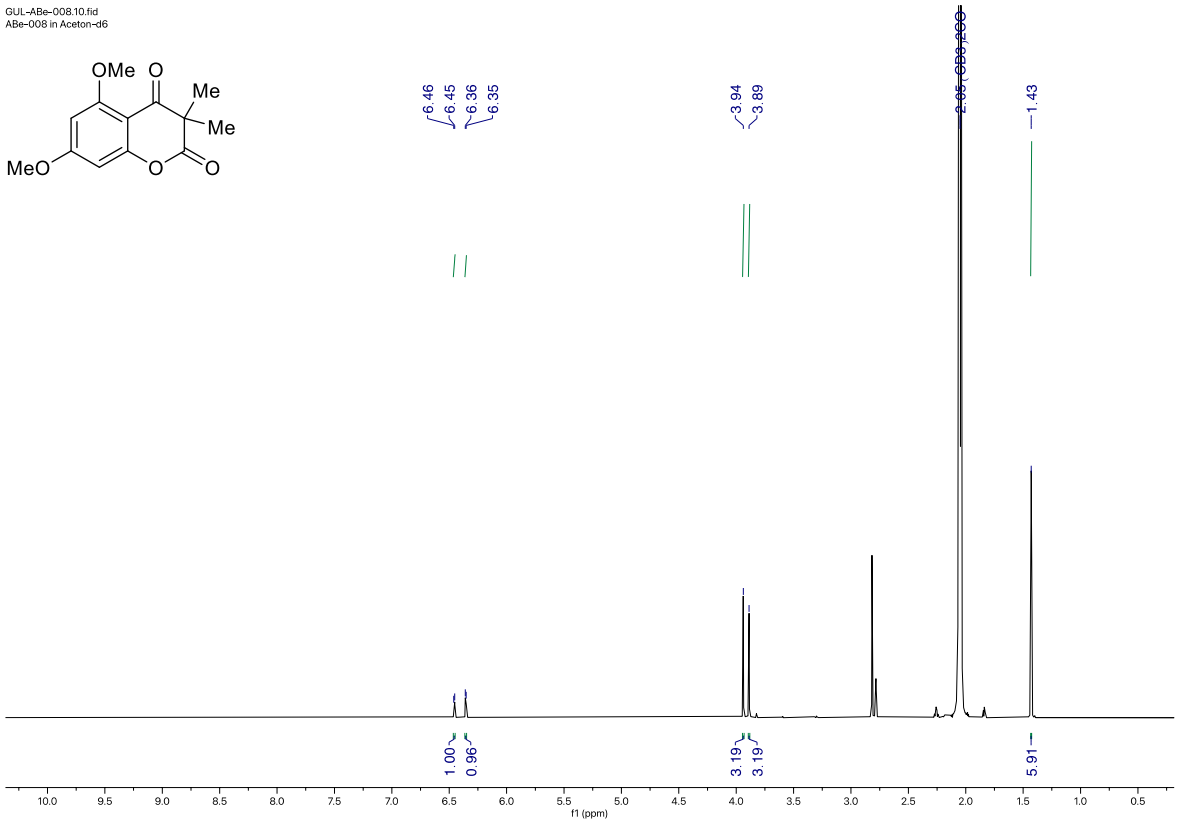
5.14 methyl 2,2-dimethyl-3-oxo-3-(2,4,6-trimethoxyphenyl)propanoate (**9b**).



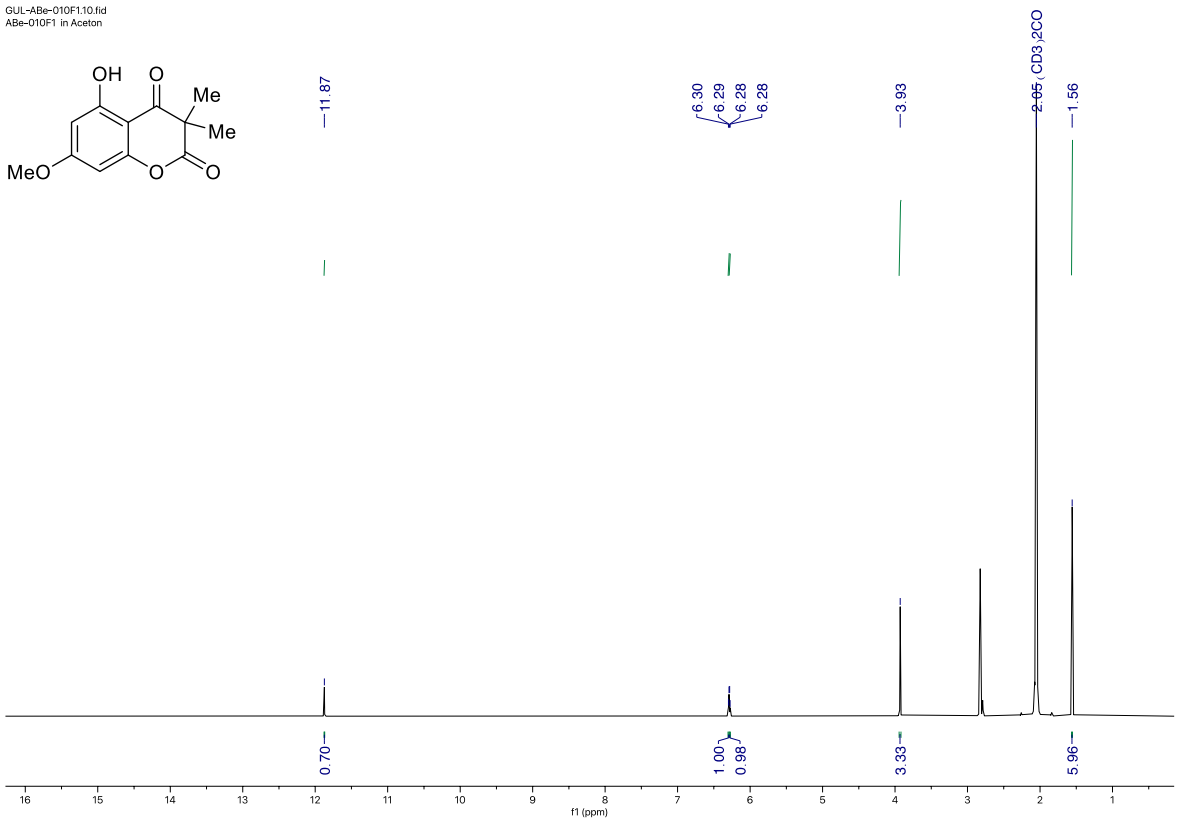
5.15 methyl 3-(2-hydroxy-4,6-dimethoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**10b**).



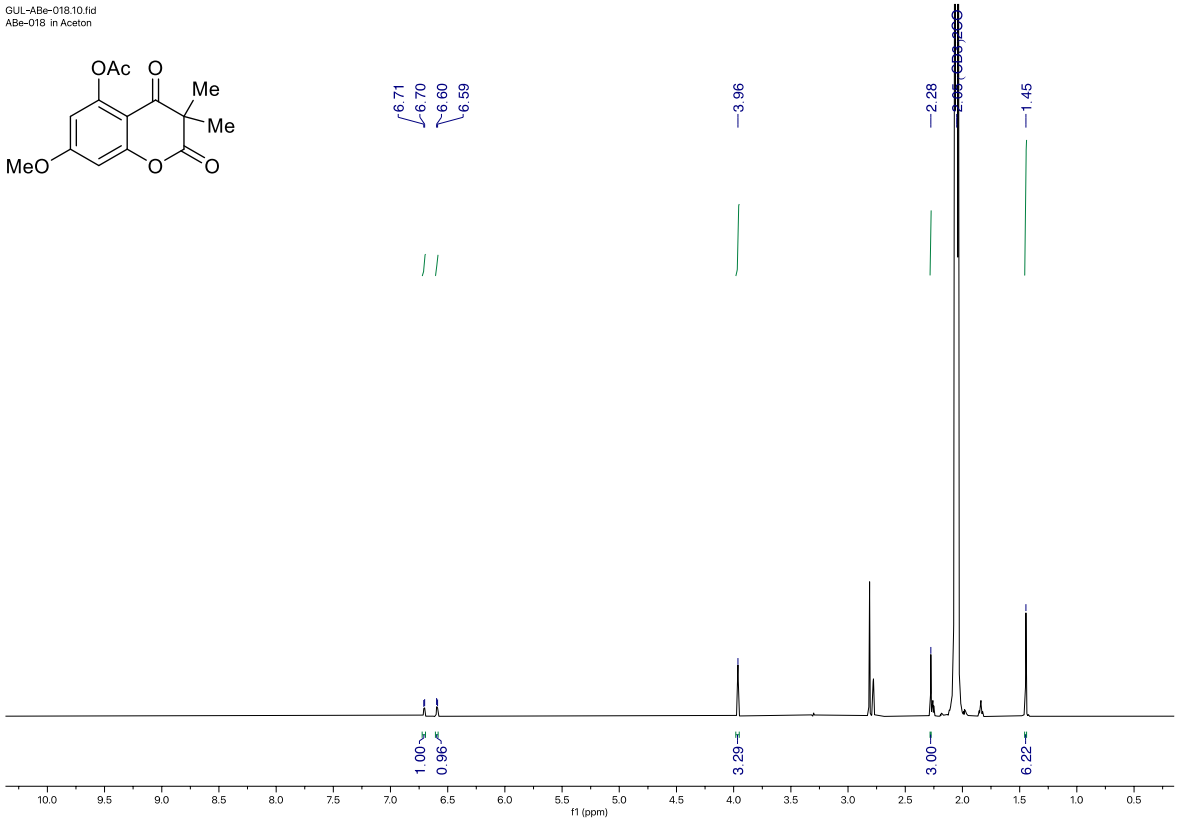
5.16 5,7-dimethoxy-3,3-dimethylchromane-2,4-dione (**11b**).

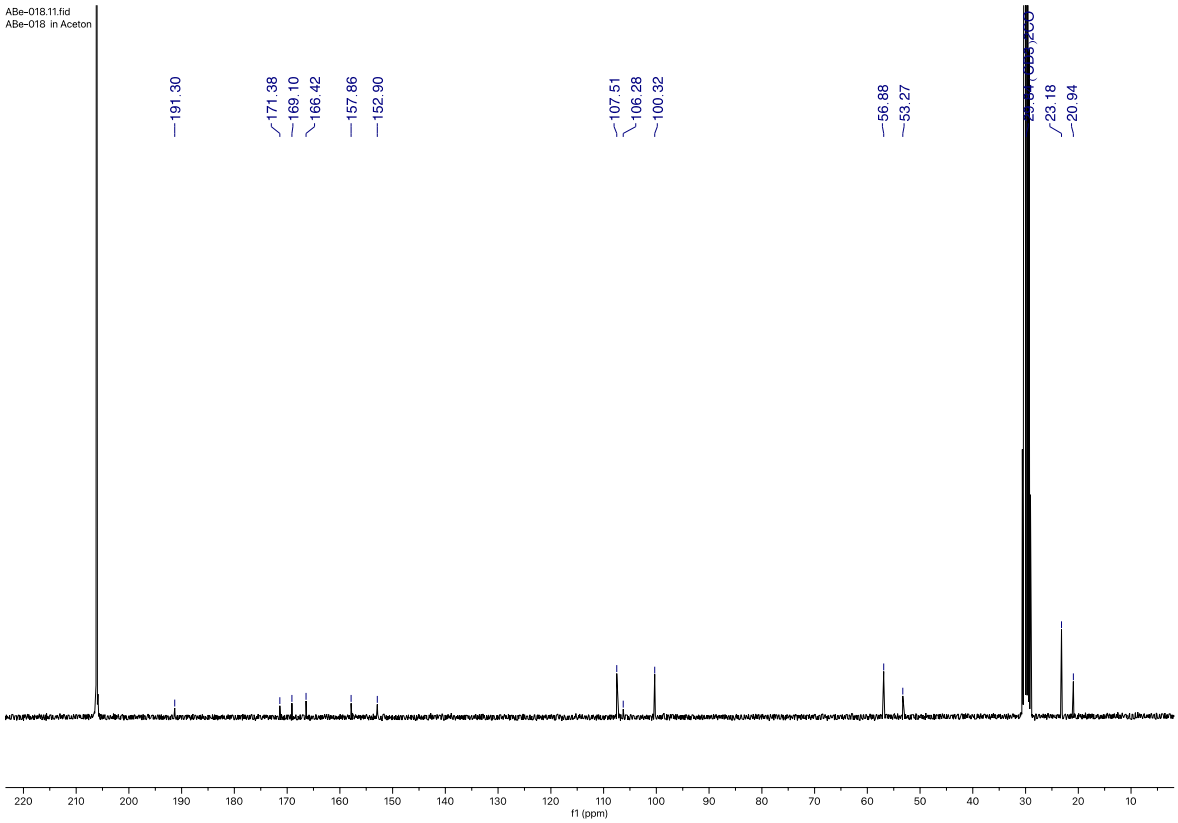


5.17 5-hydroxy-7-methoxy-3,3-dimethylchromane-2,4-dione (**17b**).

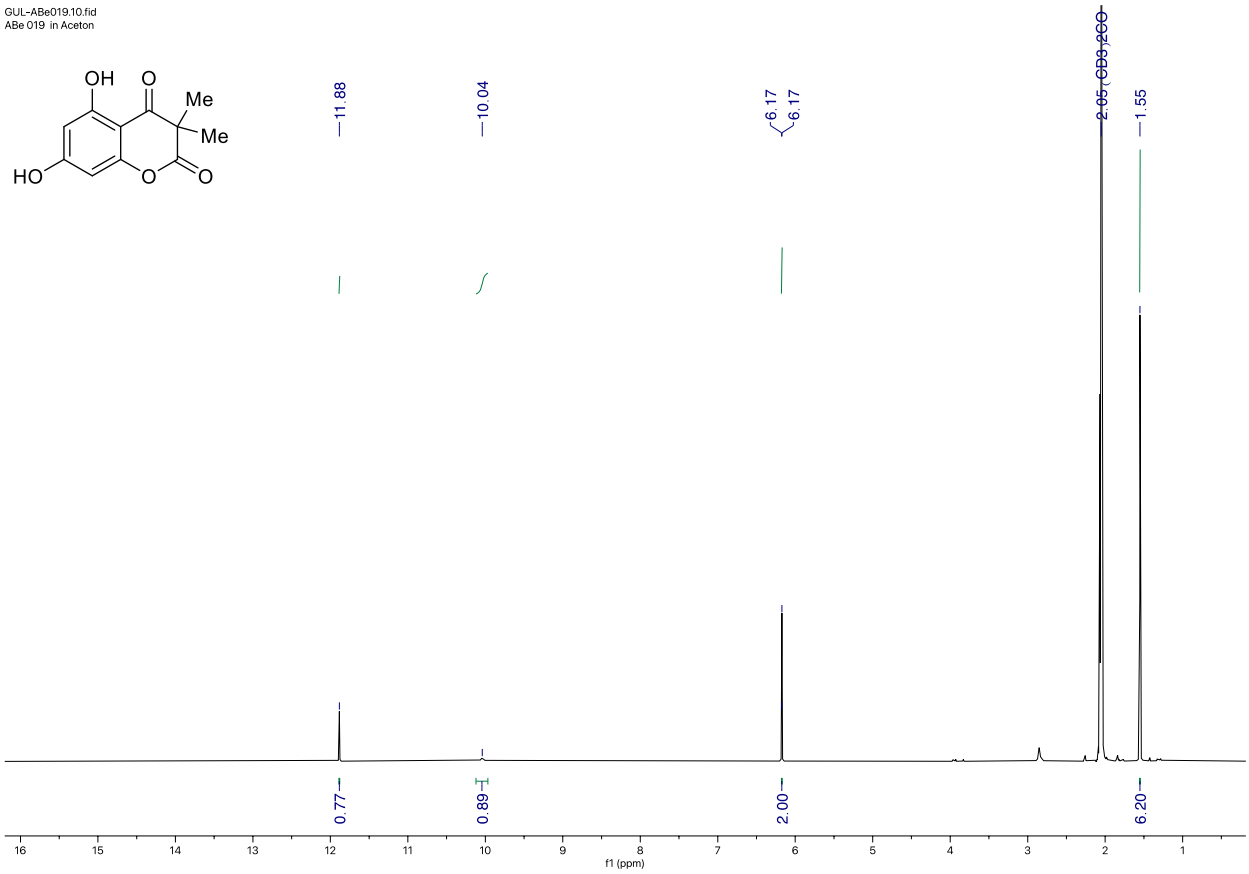


5.18 7-methoxy-3,3-dimethyl-2,4-dioxochroman-5-yl acetate (**18b**).

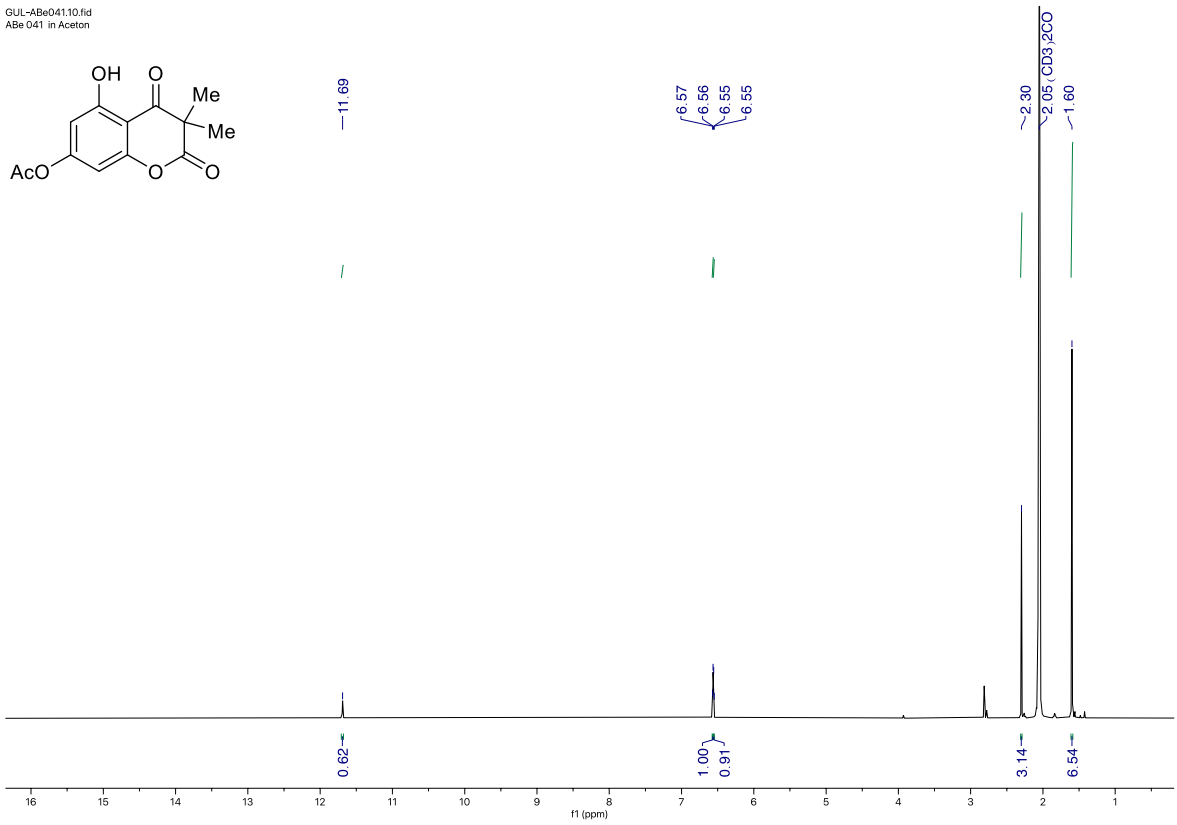


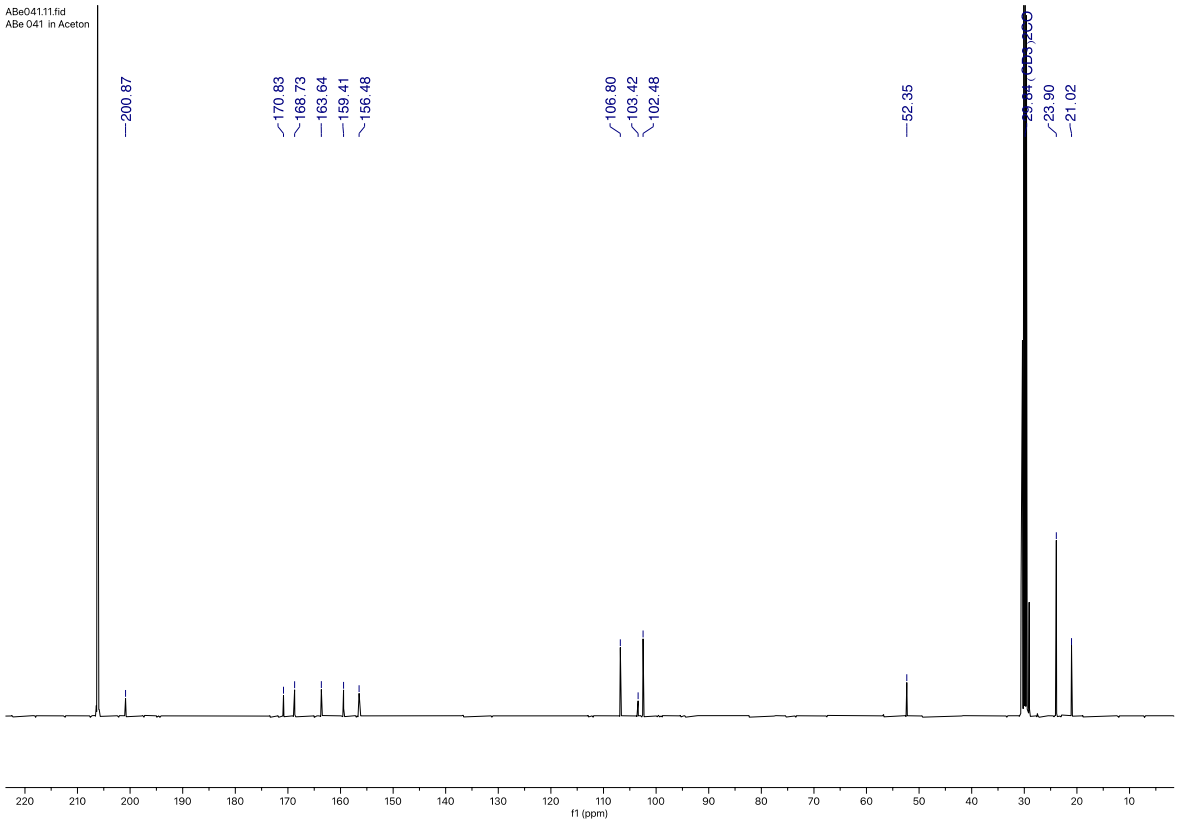


5.19 5,7-dihydroxy-3,3-dimethylchromane-2,4-dione (**17c**).

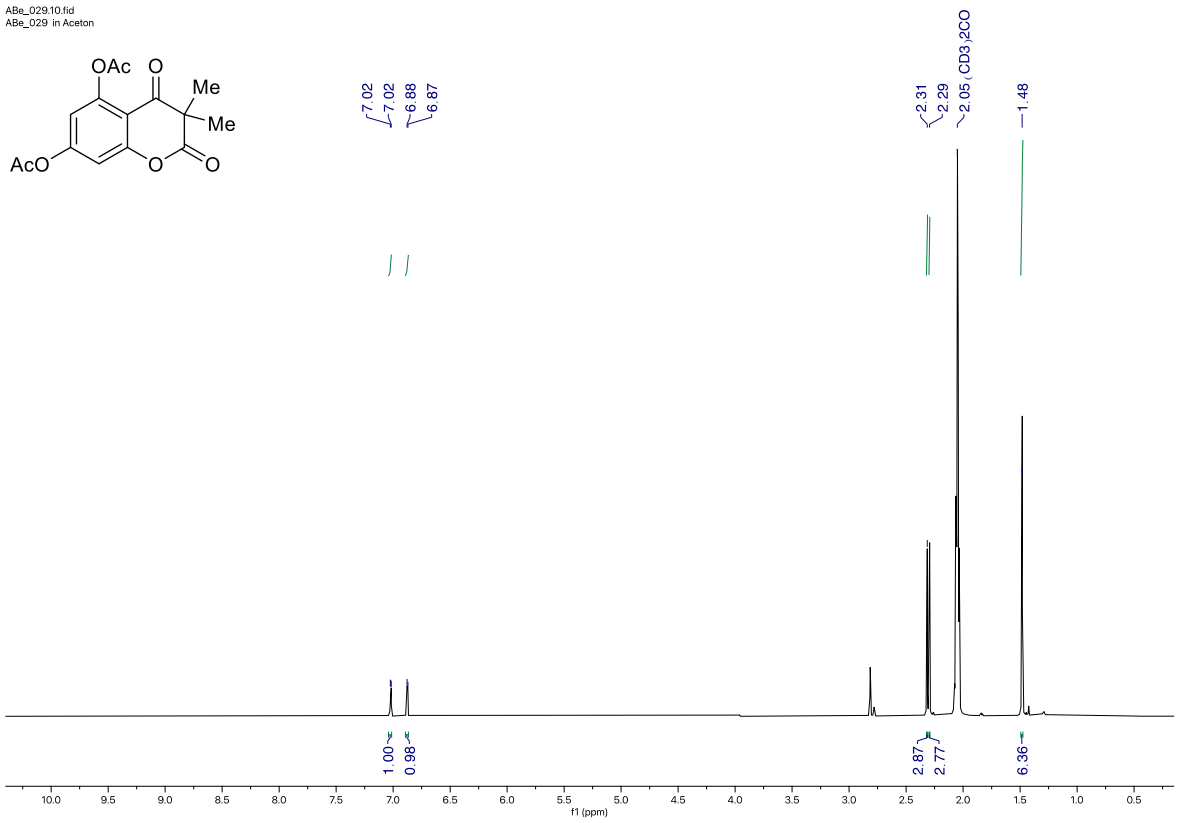


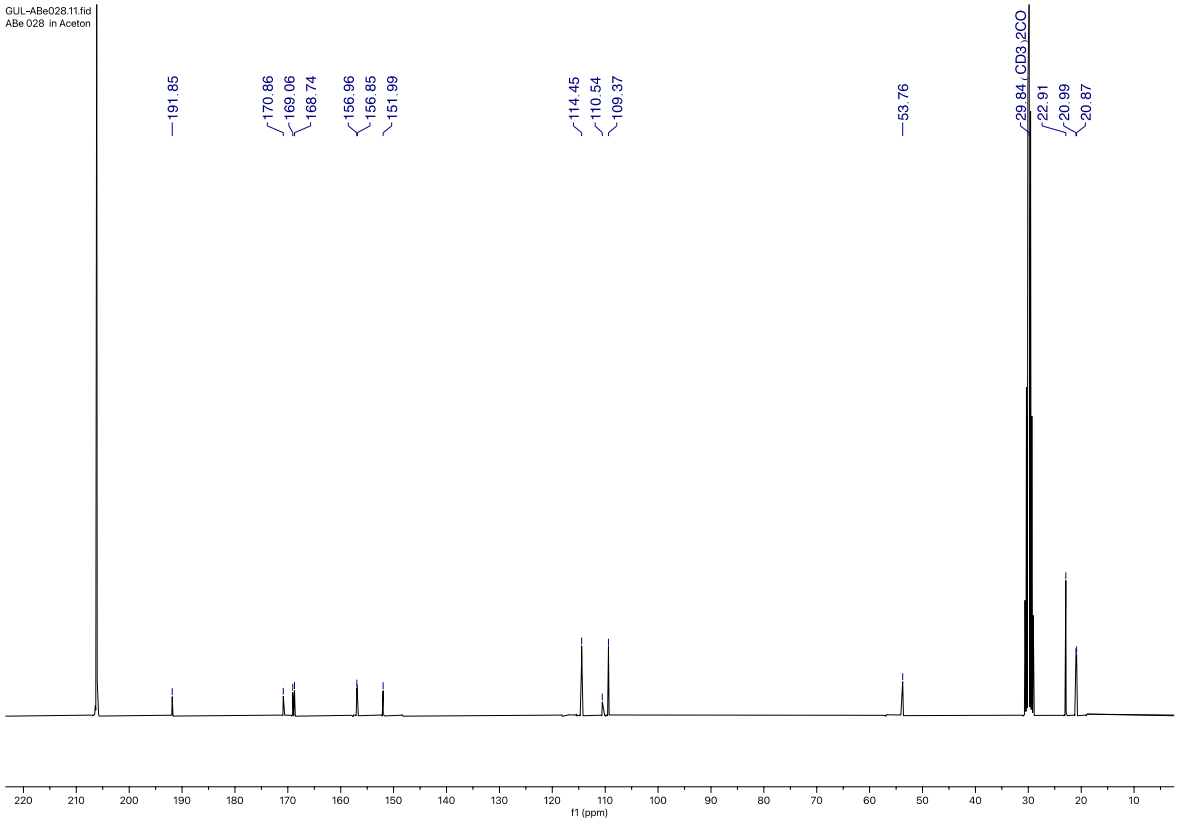
5.20 5-hydroxy-3,3-dimethyl-2,4-dioxochroman-7-yl acetate (**17e**).



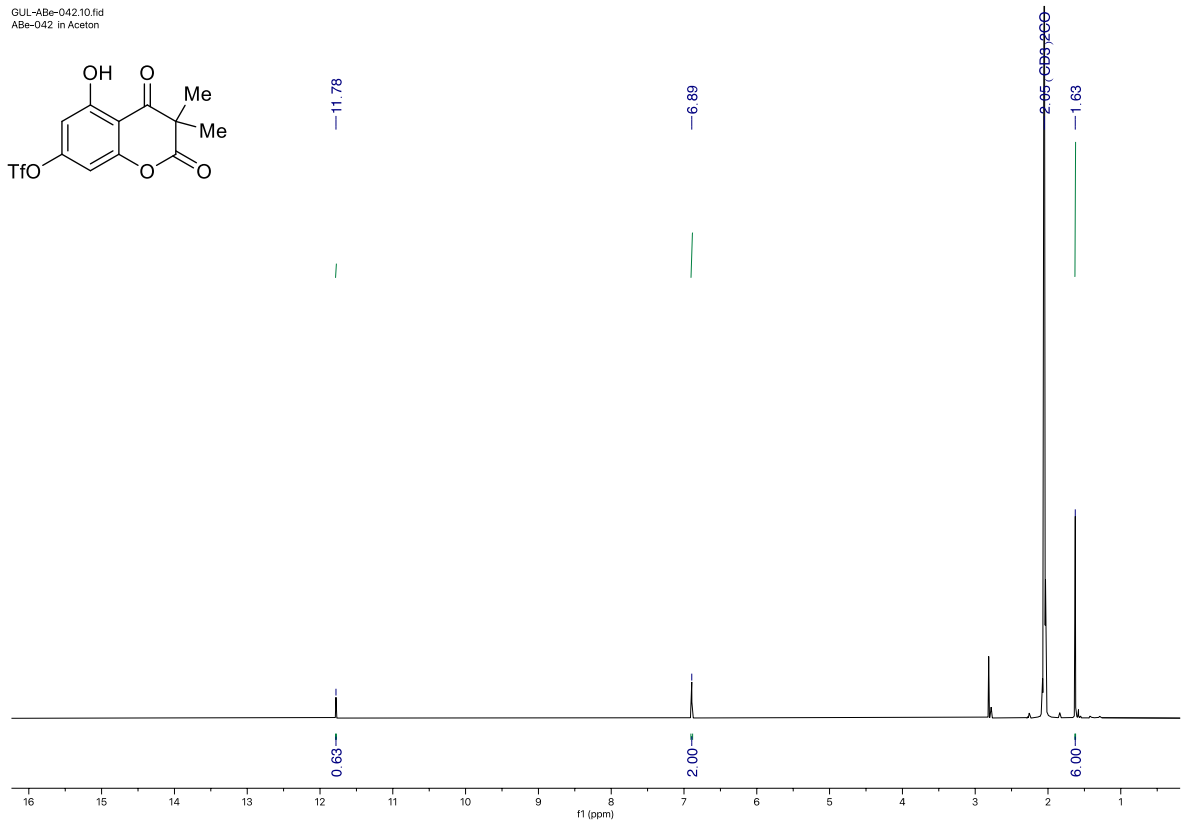


5.21 3,3-dimethyl-2,4-dioxochromane-5,7-diyl diacetate (**18e**).

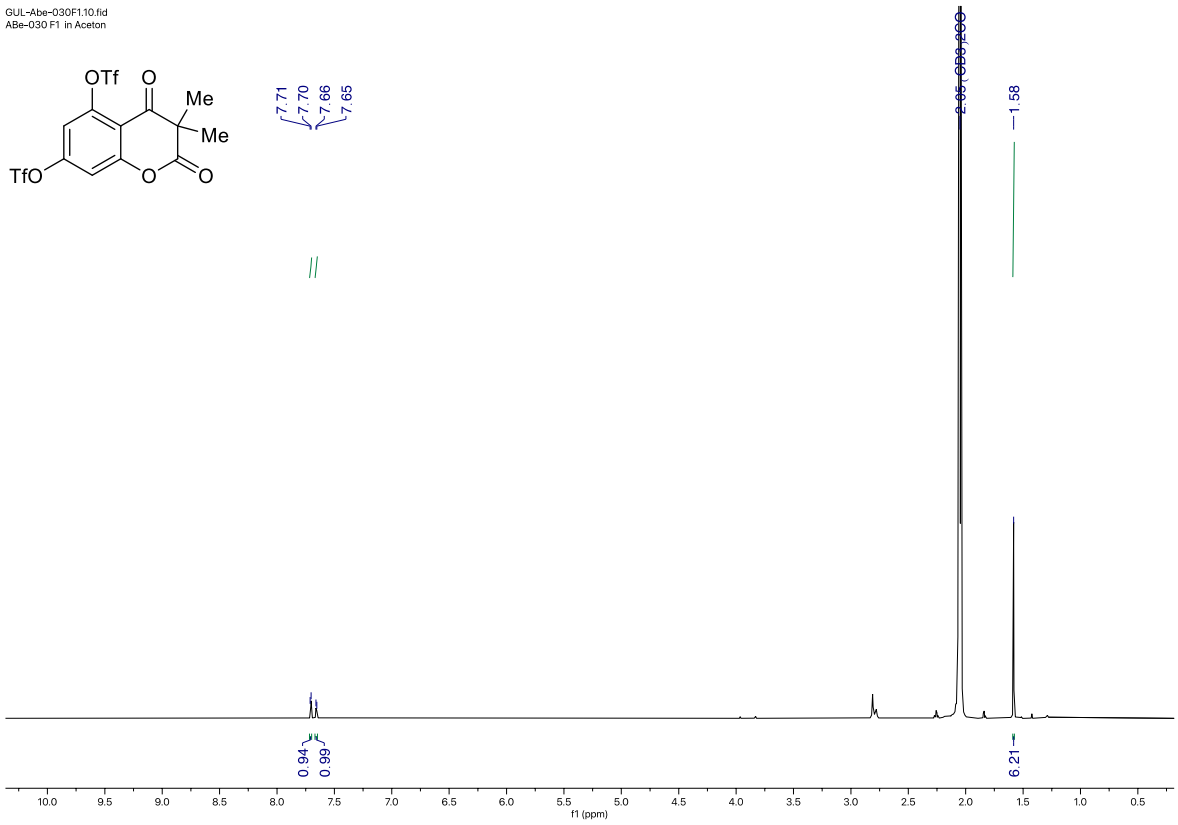


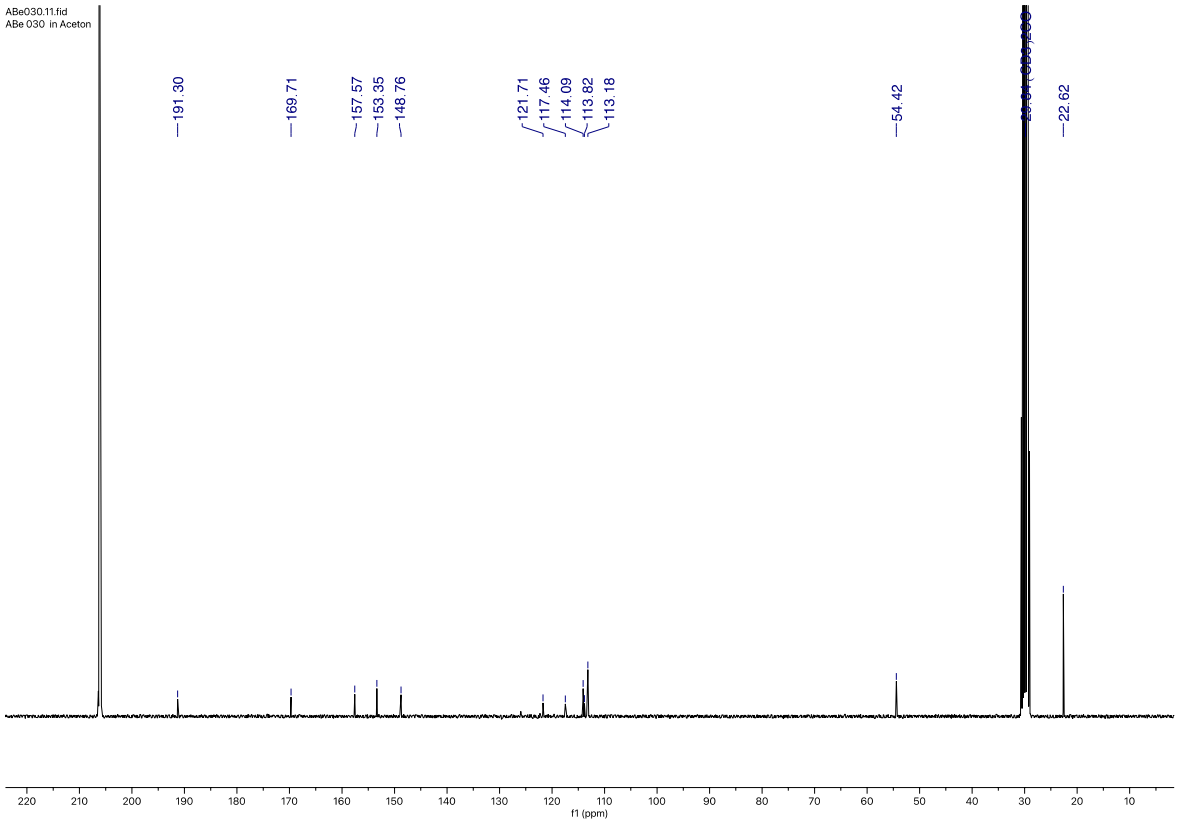


5.22 5-hydroxy-3,3-dimethyl-2,4-dioxochroman-7-yl trifluoromethanesulfonate (**17f**).

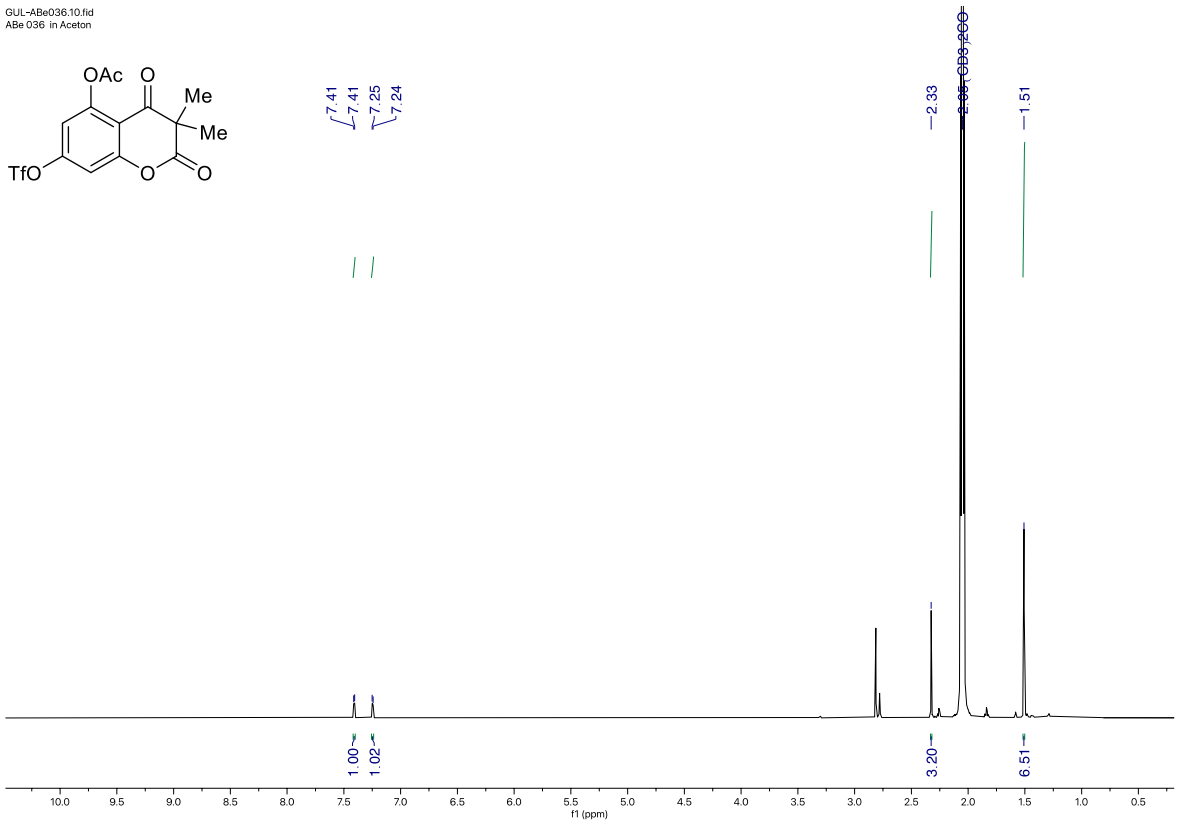


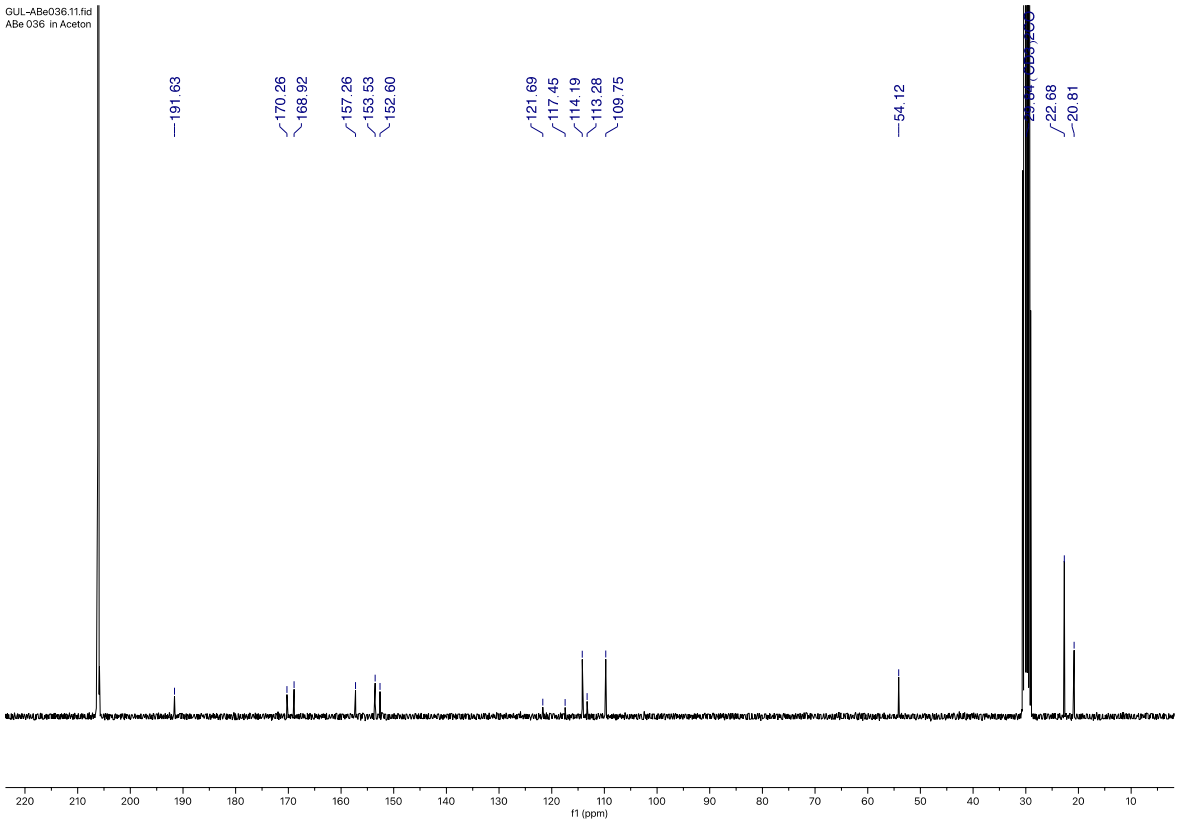
5.23 3,3-dimethyl-2,4-dioxochromane-5,7-diyl bis(trifluoromethanesulfonate) (**19f**).



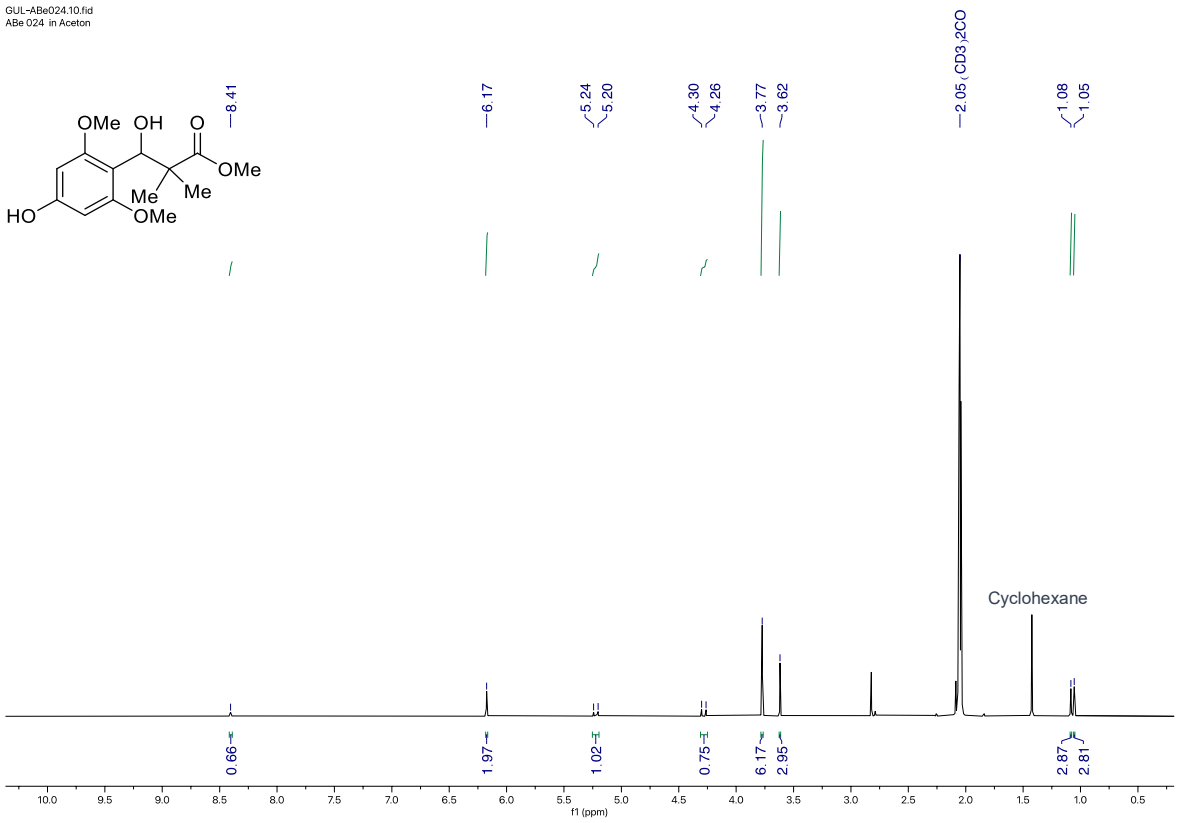


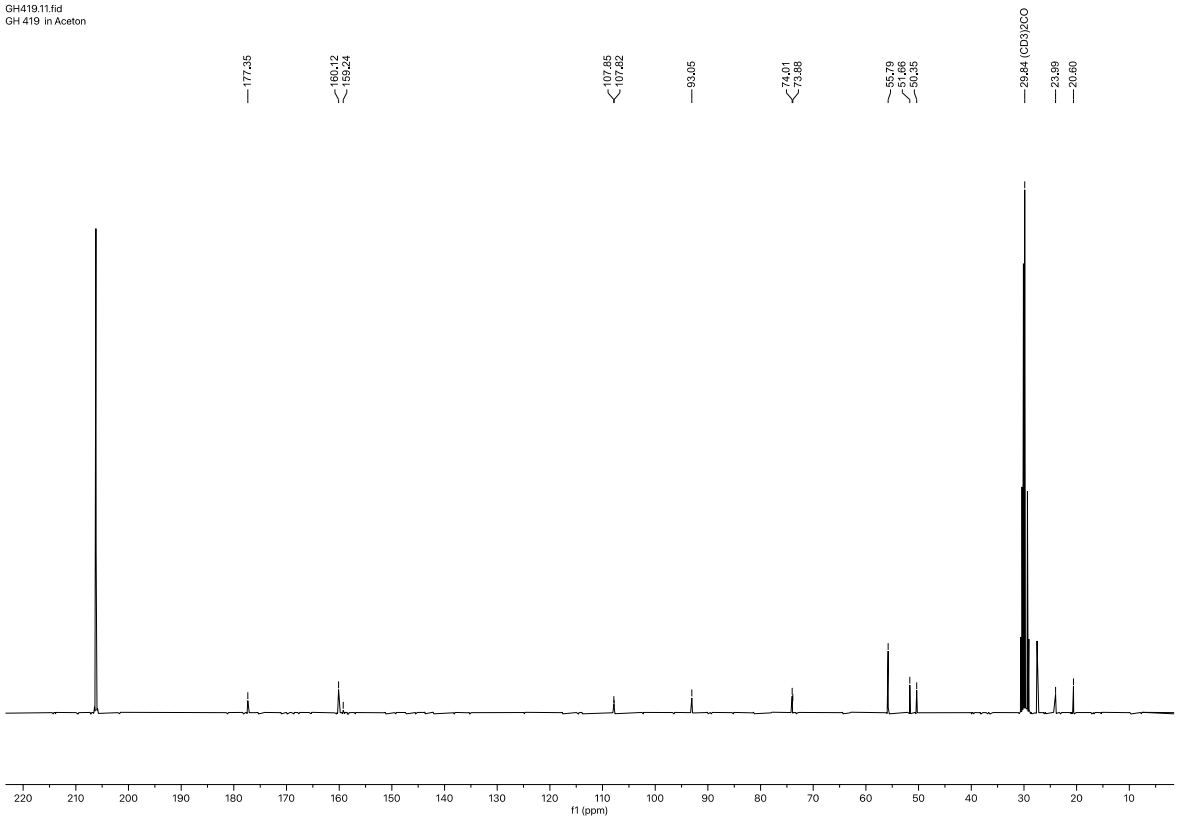
5.24 3,3-dimethyl-2,4-dioxo-7-(((trifluoromethyl)sulfonyl)oxy)chroman-5-yl acetate (**18f**).



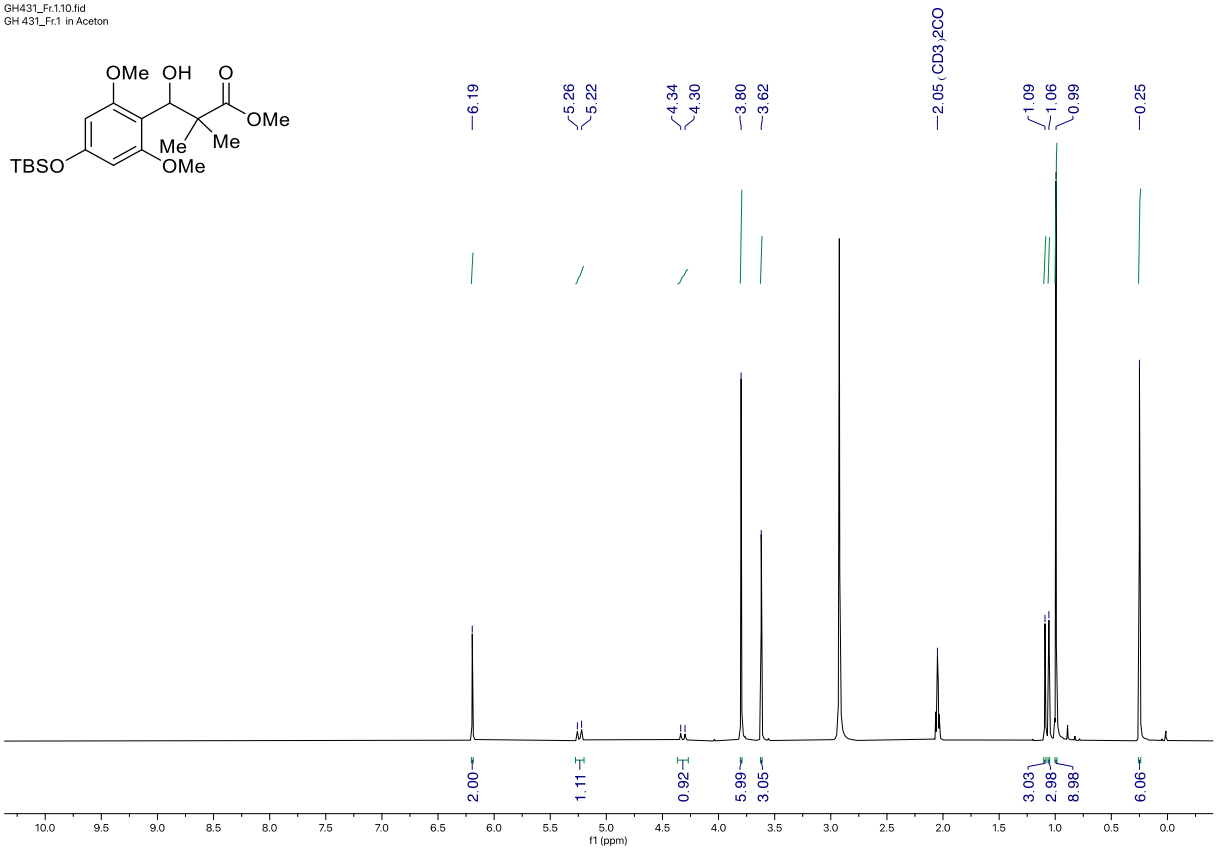


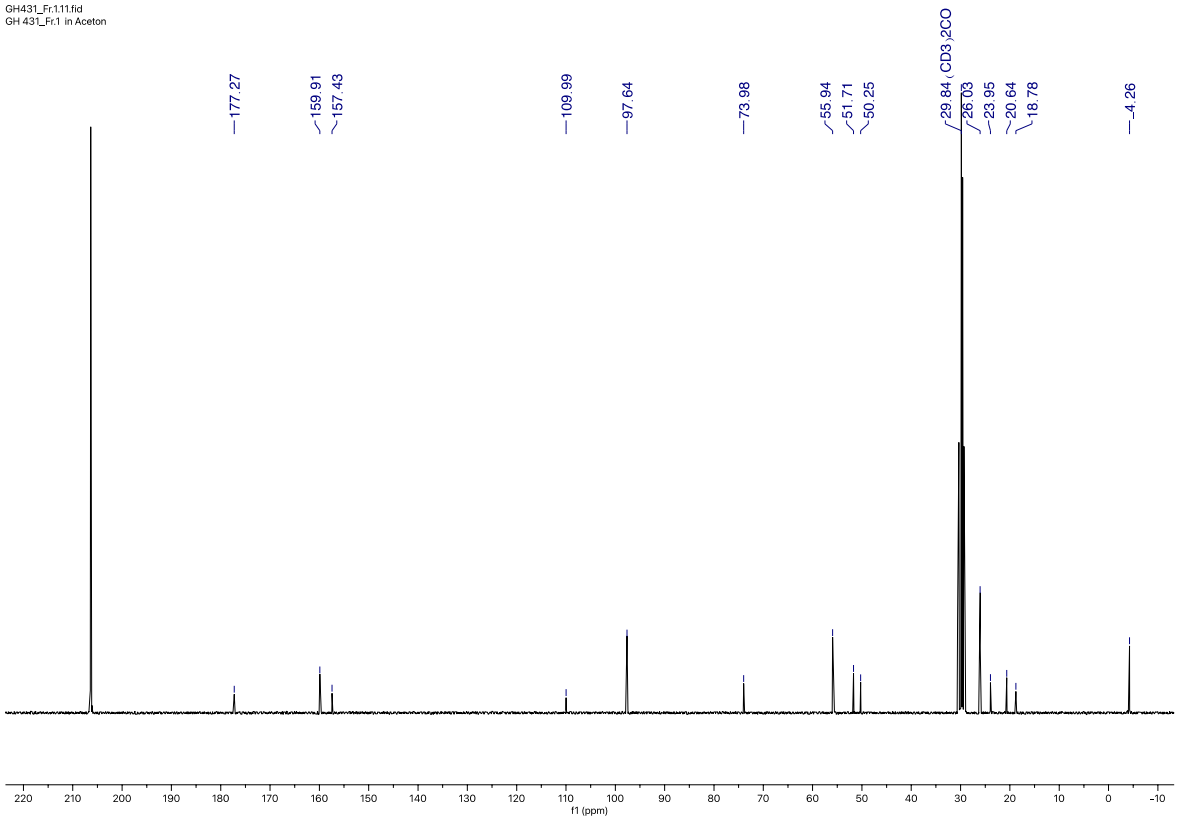
5.25 methyl 3-hydroxy-3-(4-hydroxy-2,6-dimethoxyphenyl)-2,2-dimethylpropanoate (**8c**).



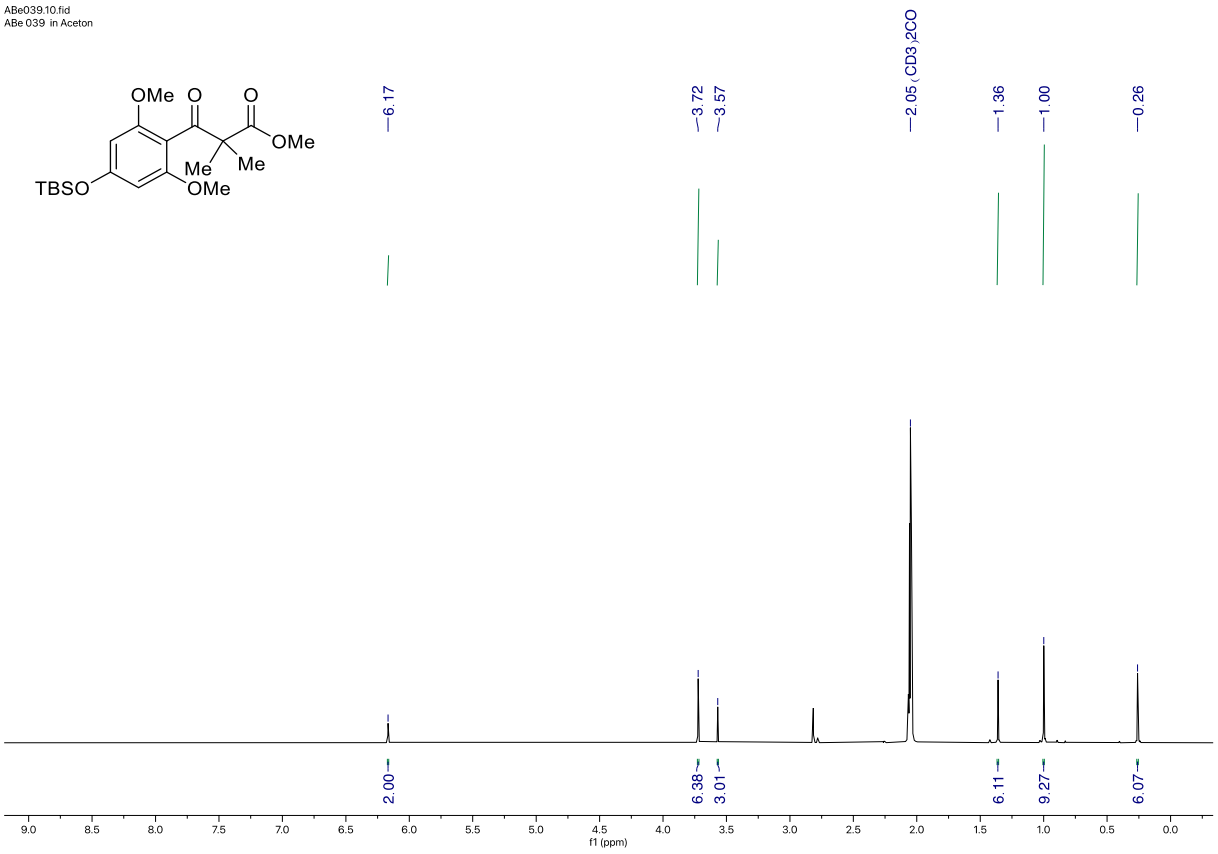


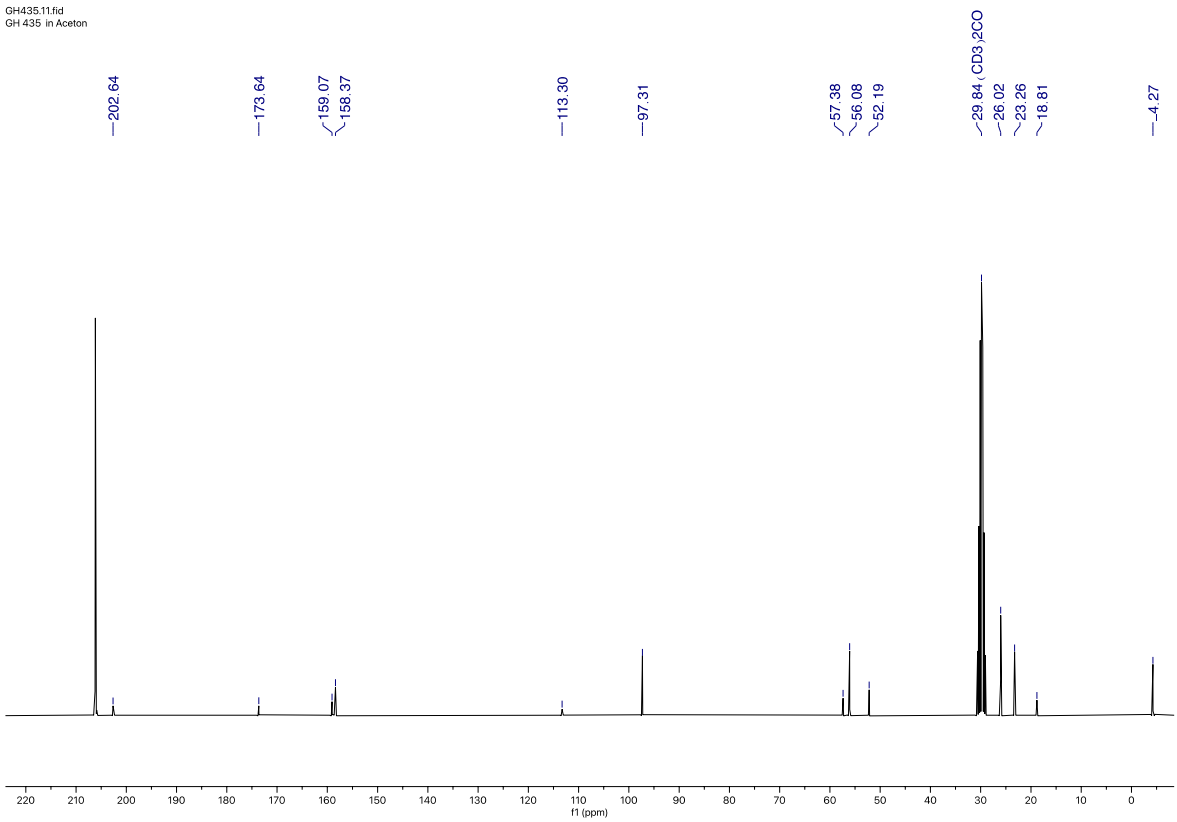
5.26 methyl 3-(4-((tert-butyldimethylsilyl)oxy)-2,6-dimethoxyphenyl)-3-hydroxy-2,2-dimethylpropanoate (**8e**).



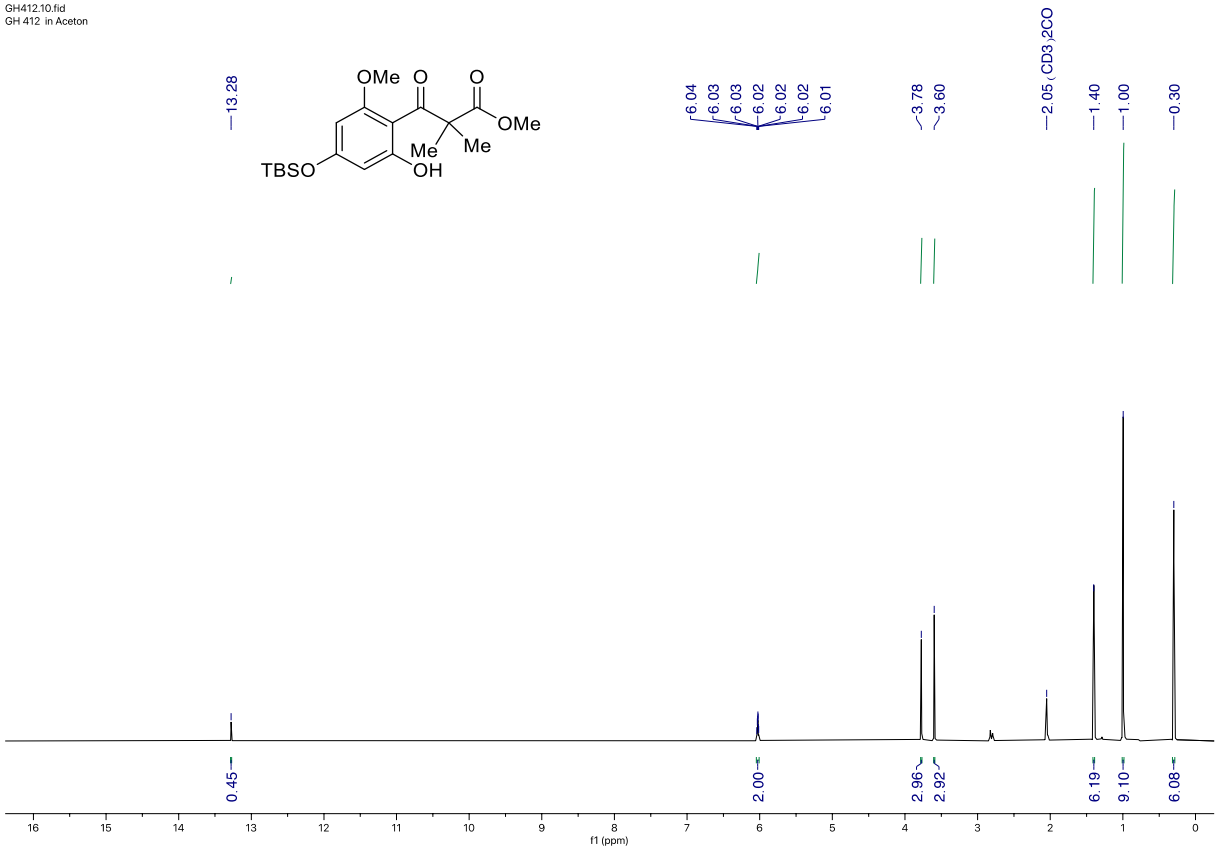


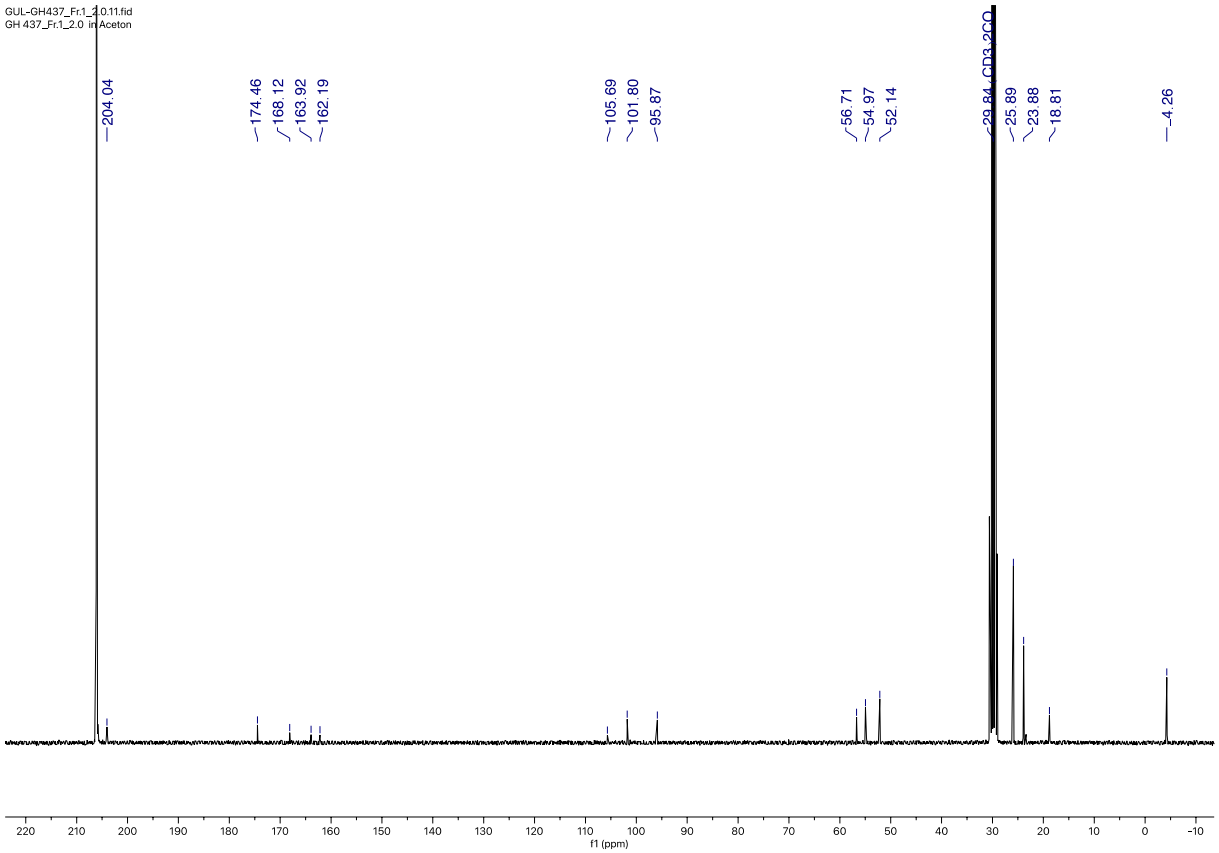
5.27 methyl 3-(4-((tert-butyldimethylsilyl)oxy)-2,6-dimethoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**9e**).



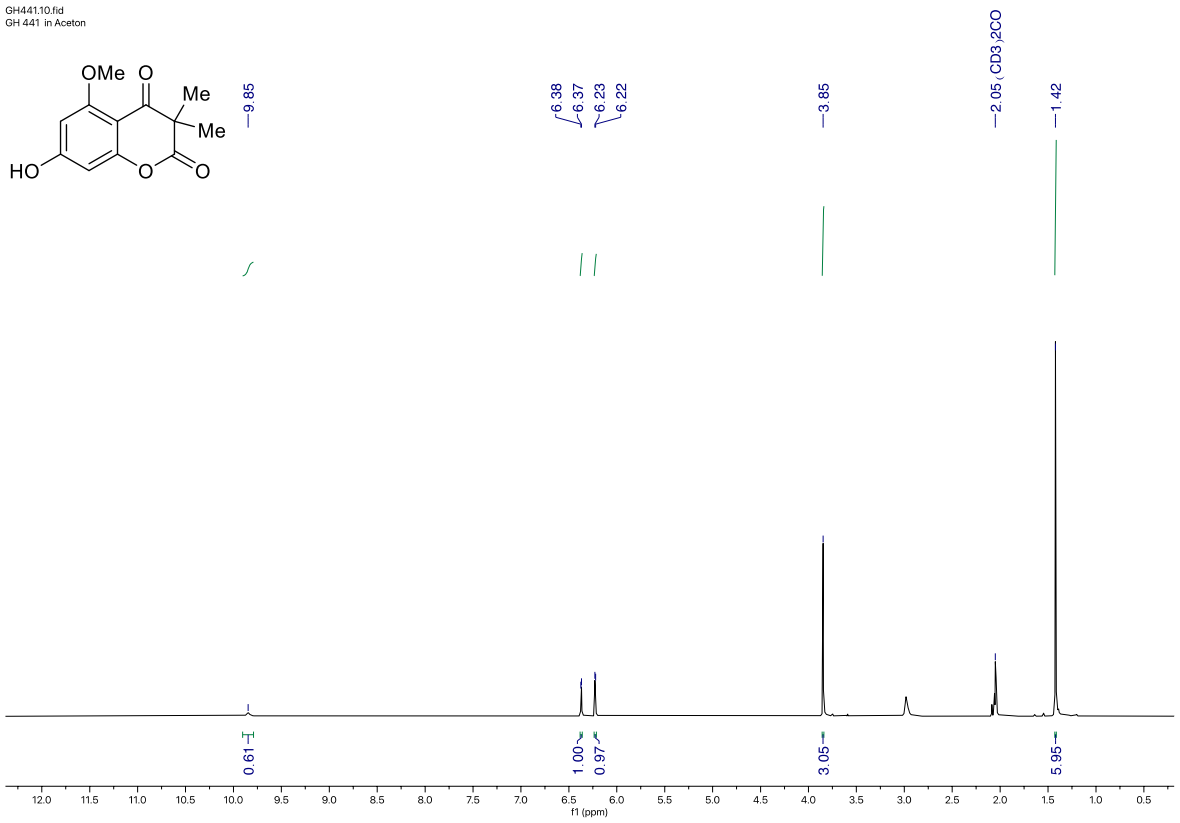


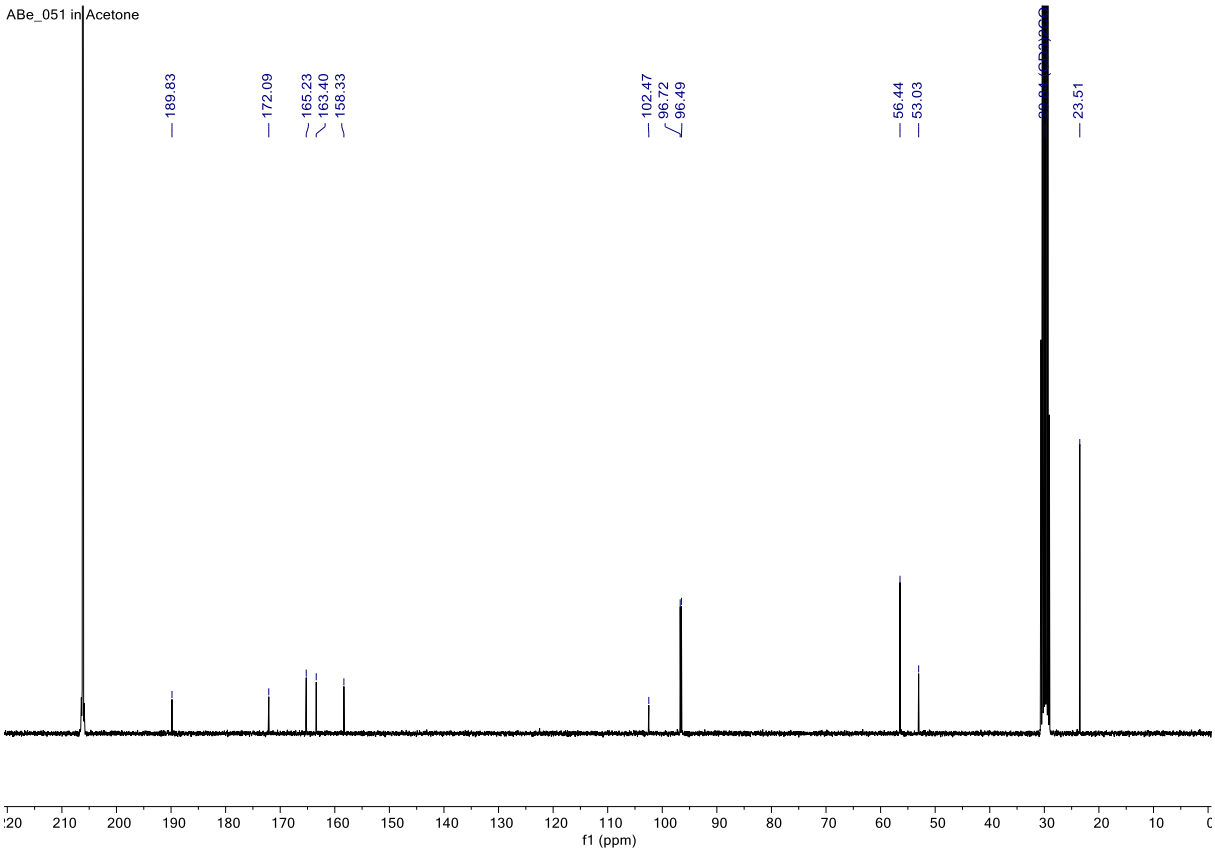
5.28 methyl 3-(4-((tert-butyldimethylsilyl)oxy)-2-hydroxy-6-methoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**10e**).



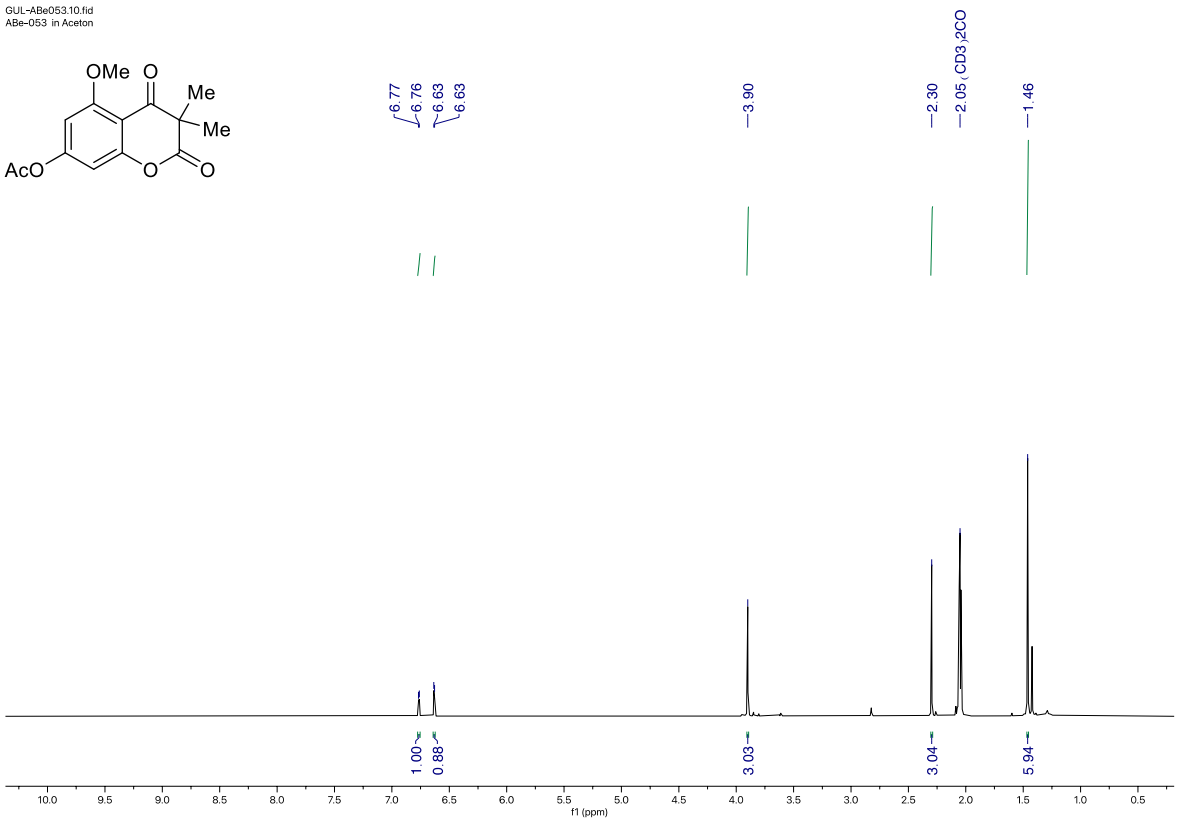


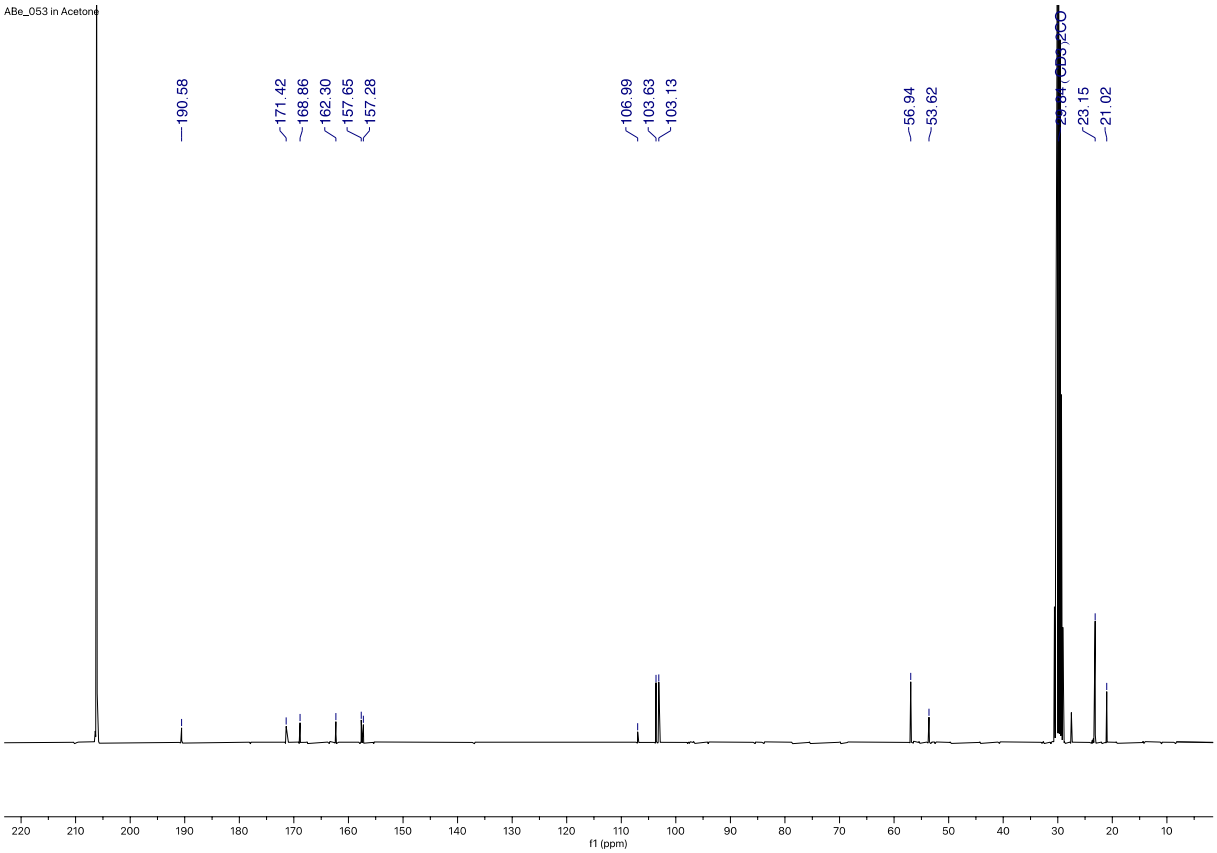
5.29 7-hydroxy-5-methoxy-3,3-dimethylchromane-2,4-dione (**11c**).



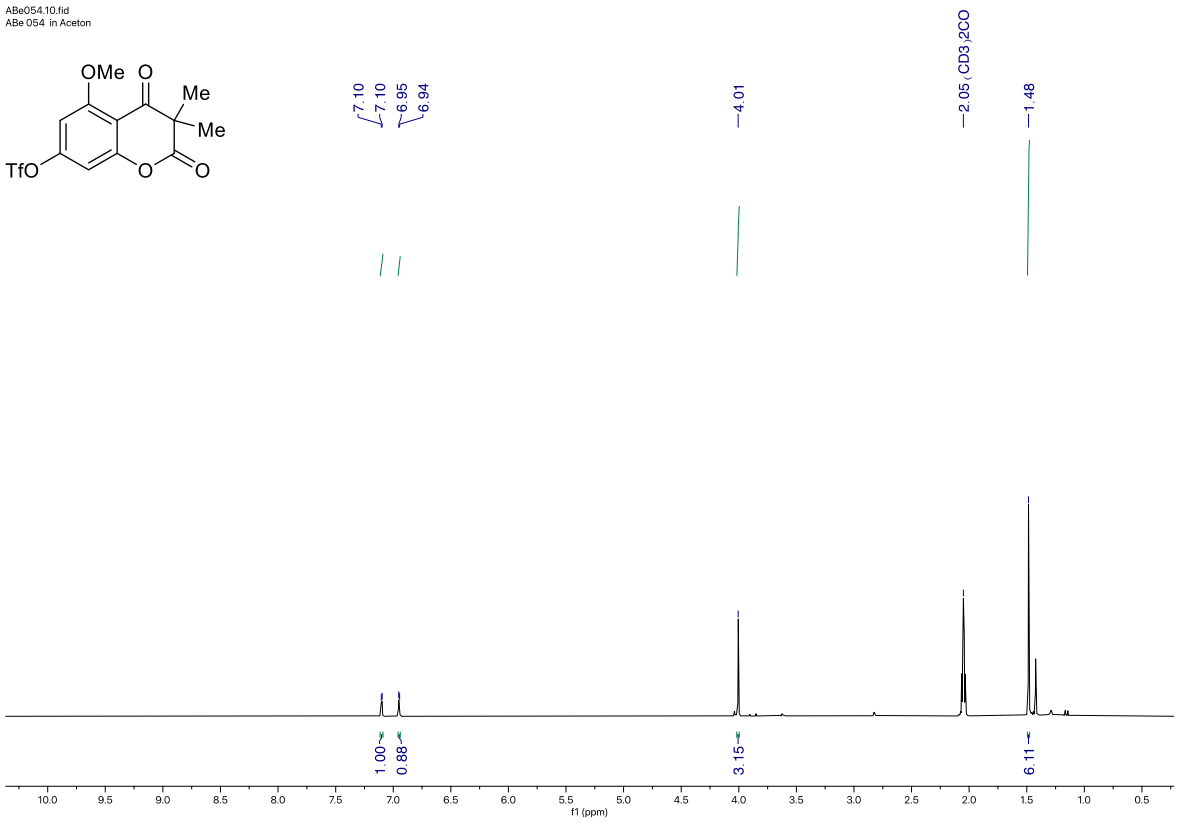


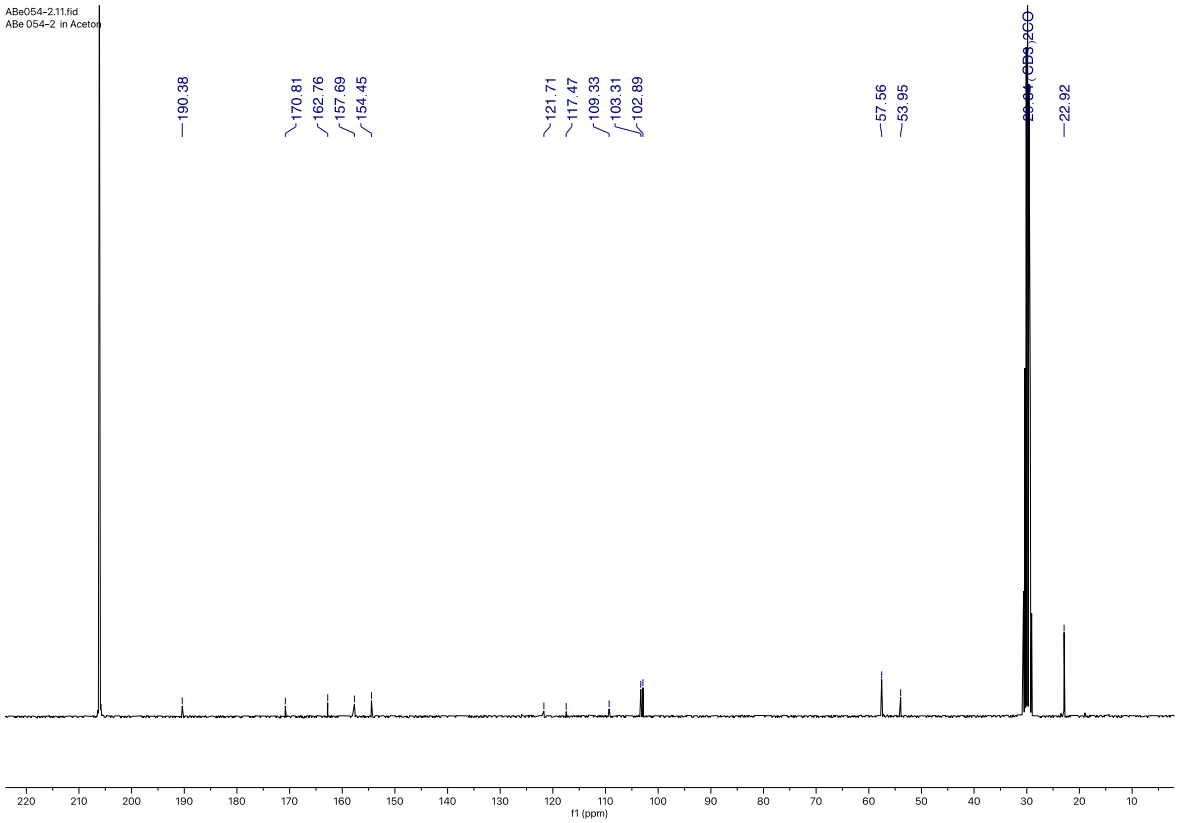
5.30 5-methoxy-3,3-dimethyl-2,4-dioxochroman-7-yl acetate (**11e**).



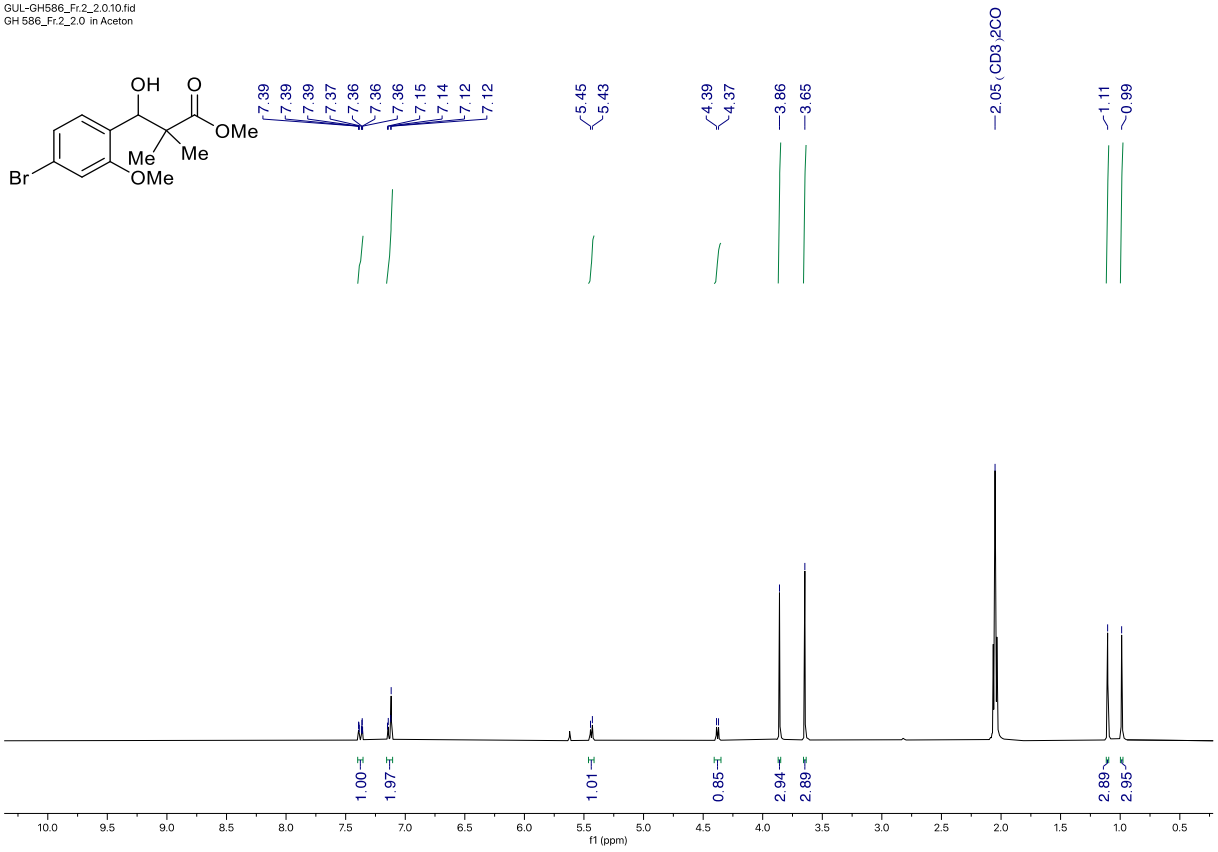


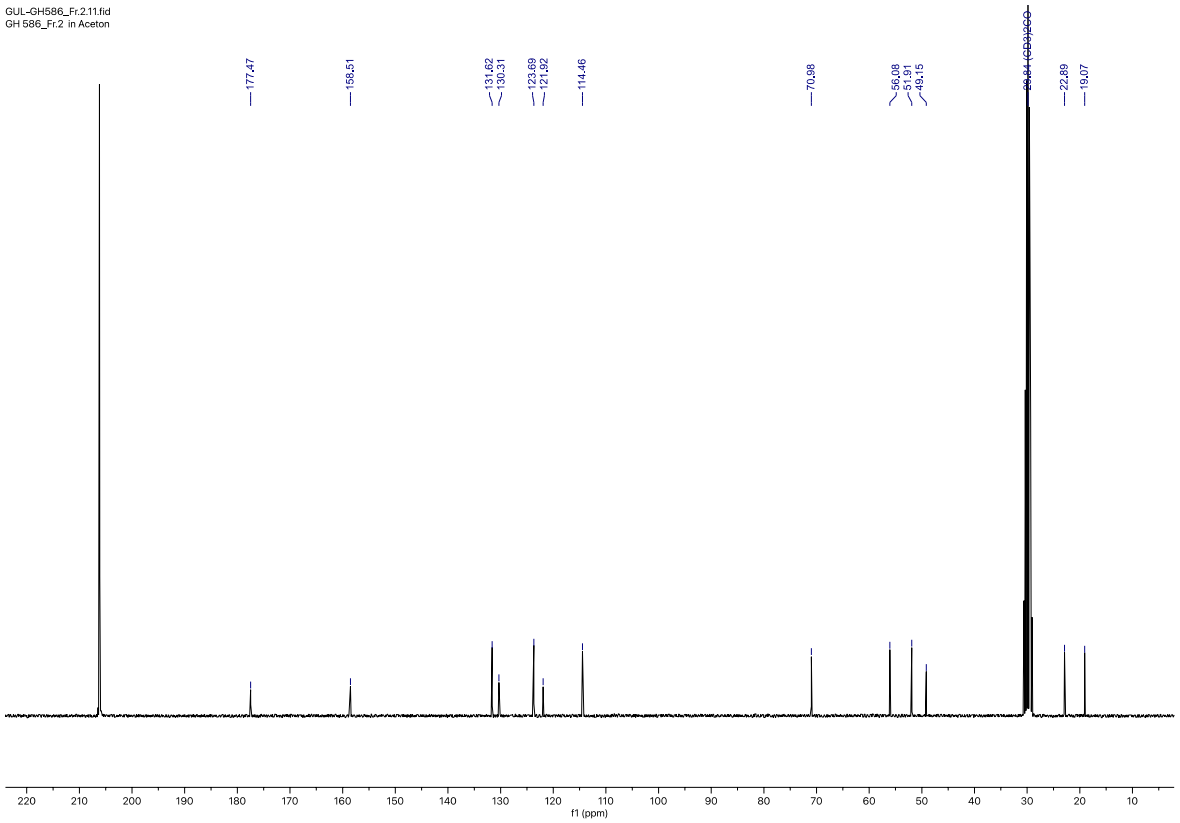
5.31 5-methoxy-3,3-dimethyl-2,4-dioxochroman-7-yl trifluoromethanesulfonate (**11f**).



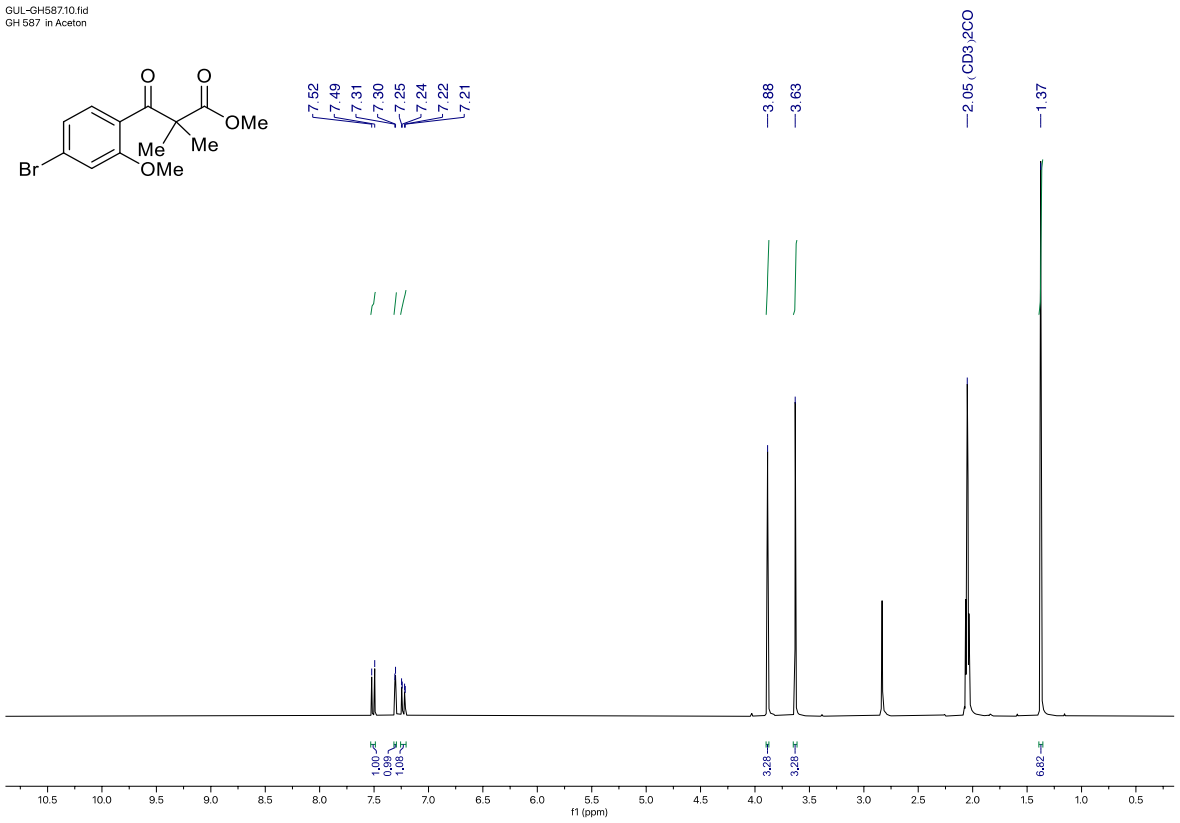


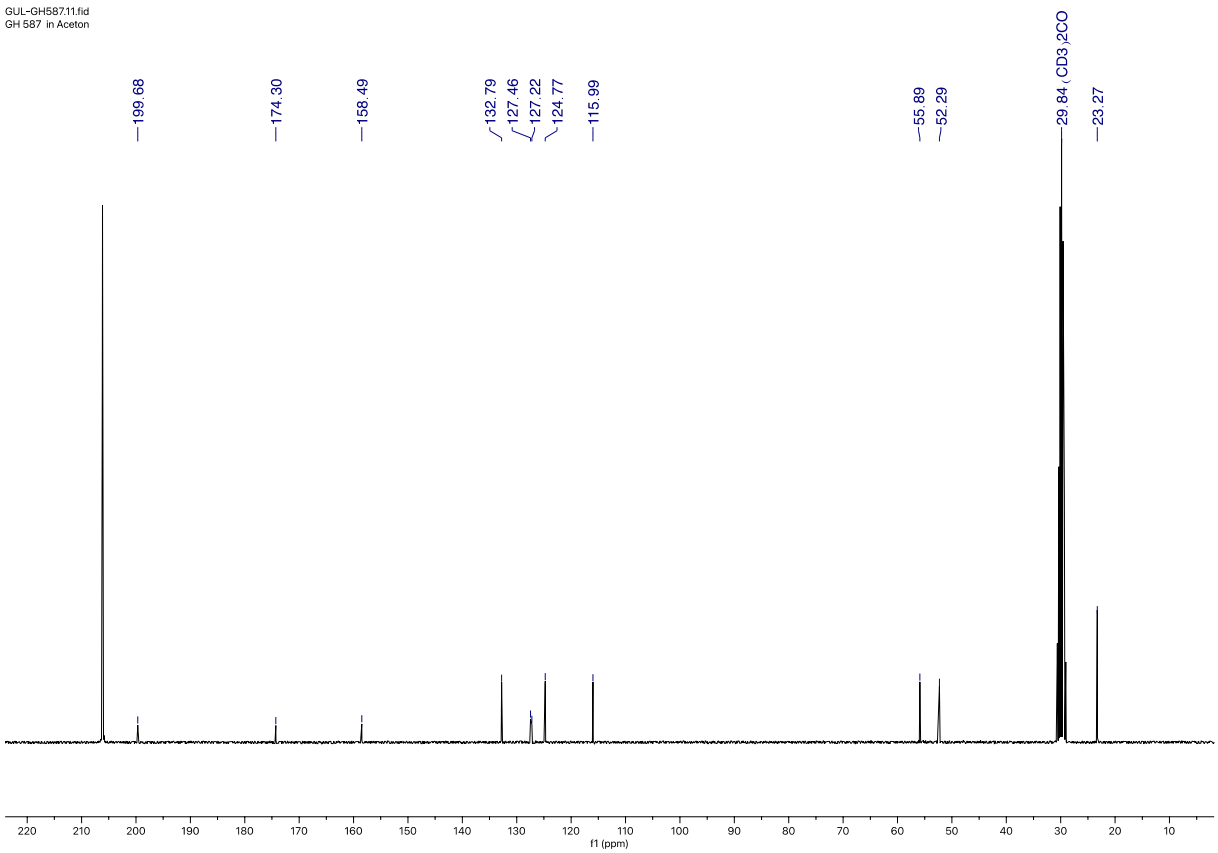
5.32 Methyl 3-(4-bromo-2-methoxyphenyl)-3-hydroxy-2,2-dimethylpropanoate (**13a**).



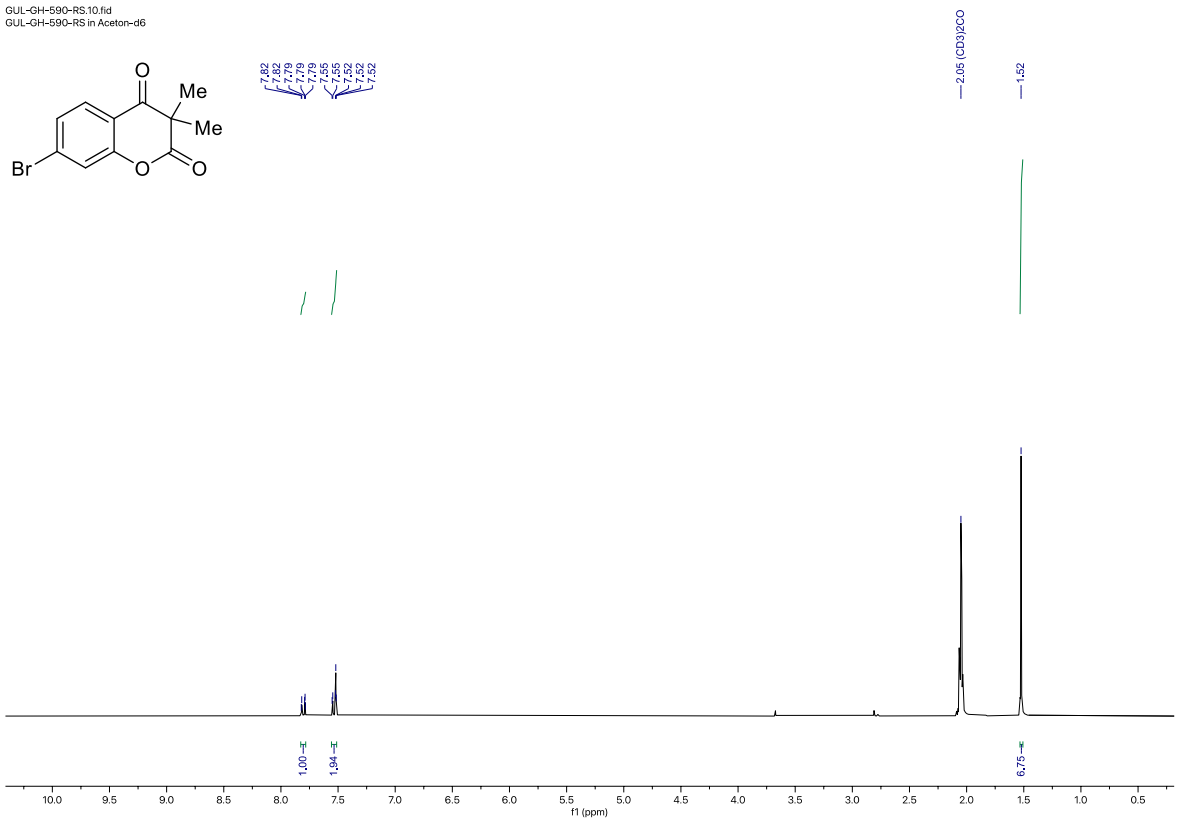


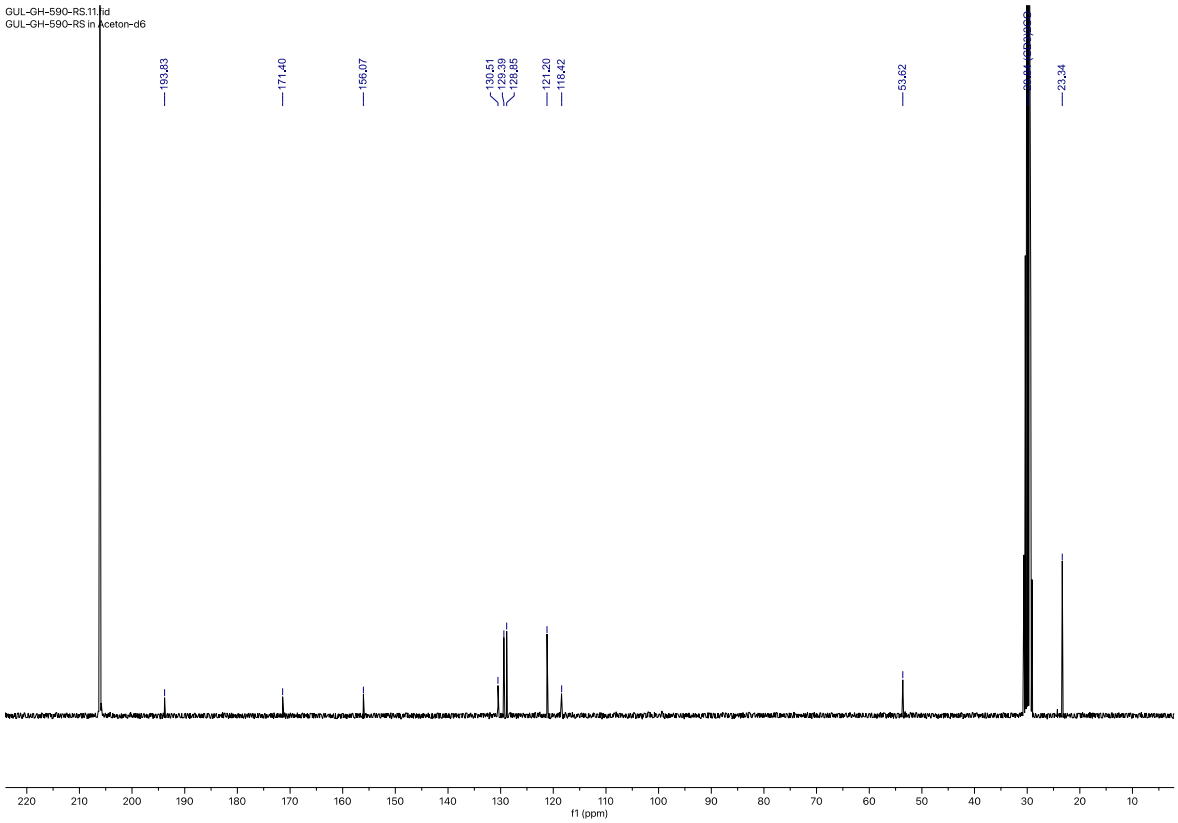
5.33 Methyl 3-(4-bromo-2-methoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**14a**).



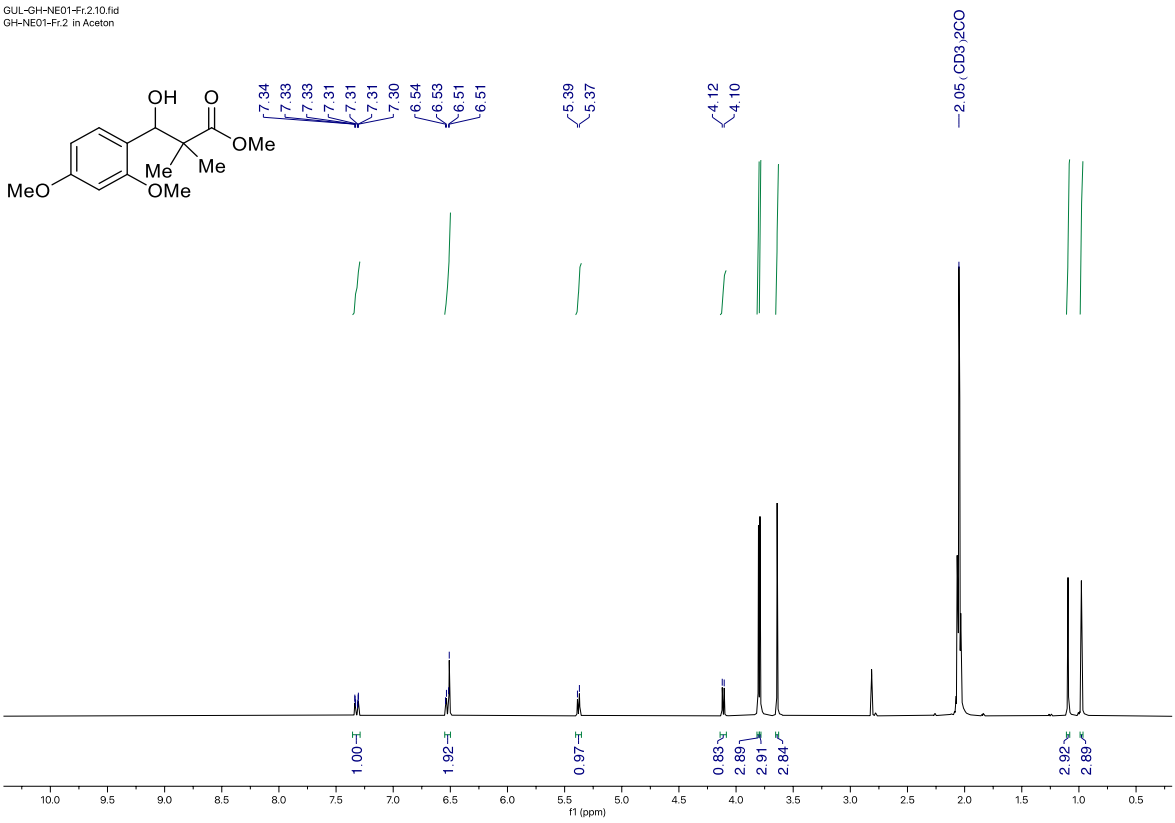


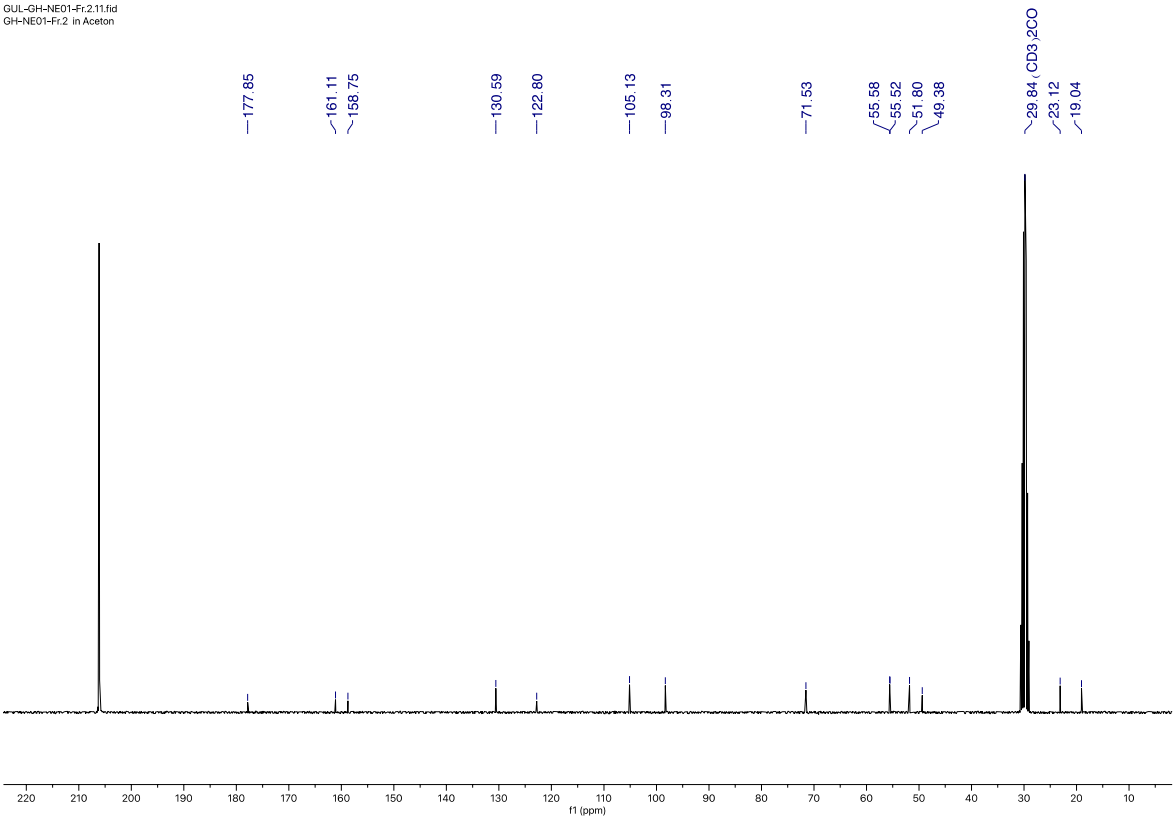
5.34 7-Bromo-3,3-dimethylchromane-2,4-dione (**16a**)



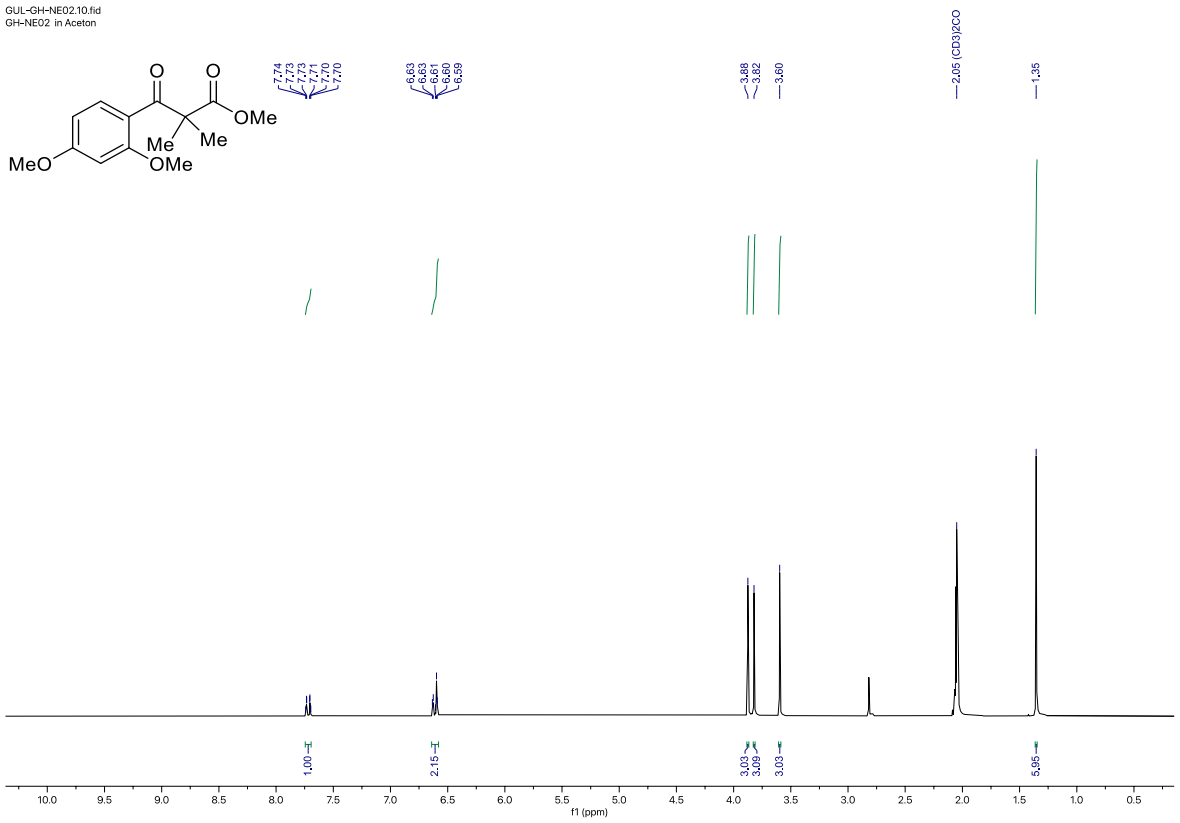


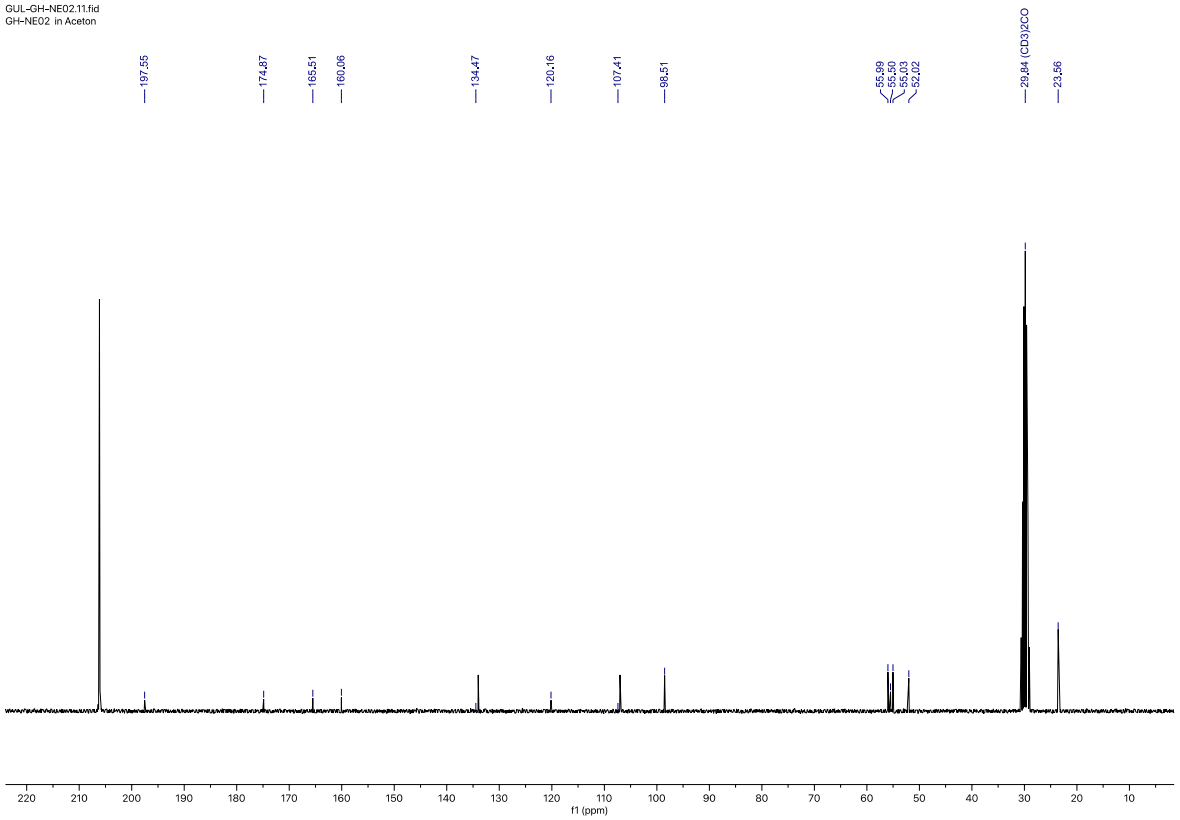
5.35 methyl 3-(2,4-dimethoxyphenyl)-3-hydroxy-2,2-dimethylpropanoate (**13b**).



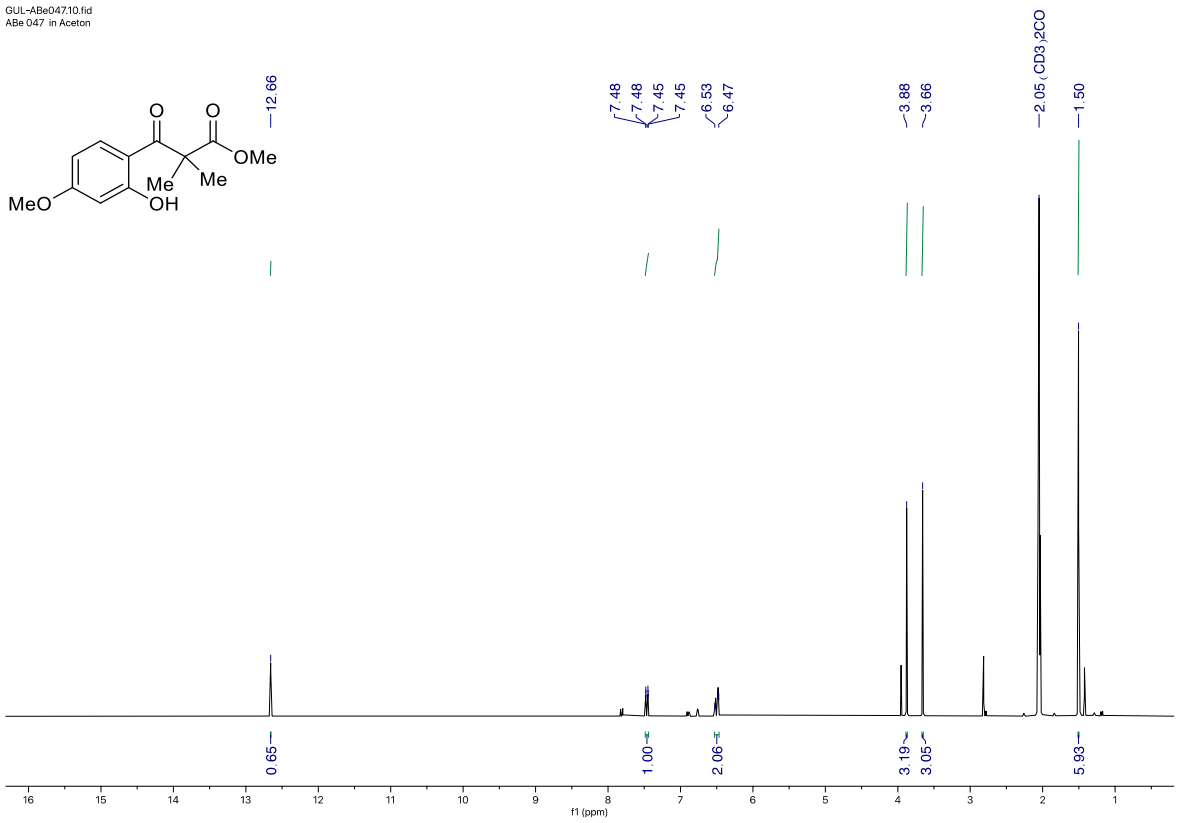


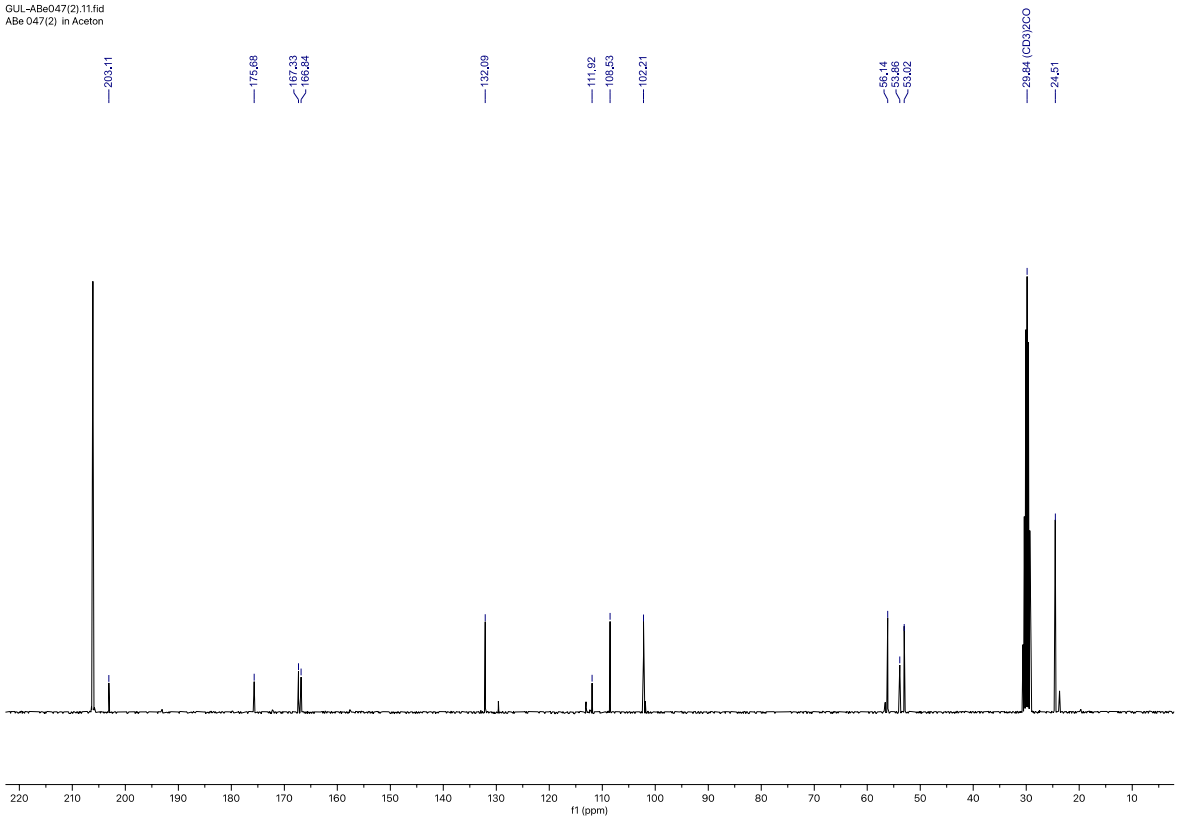
5.36 methyl 3-(2,4-dimethoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**14b**).



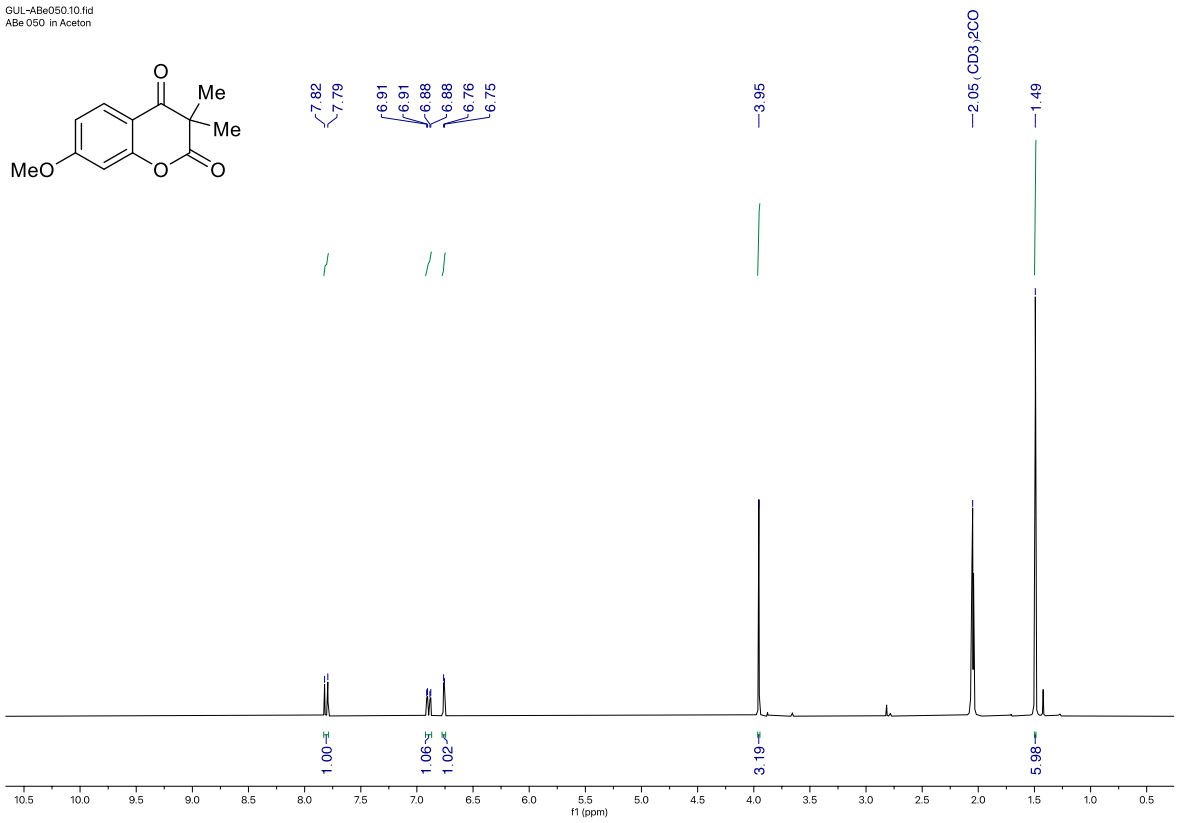


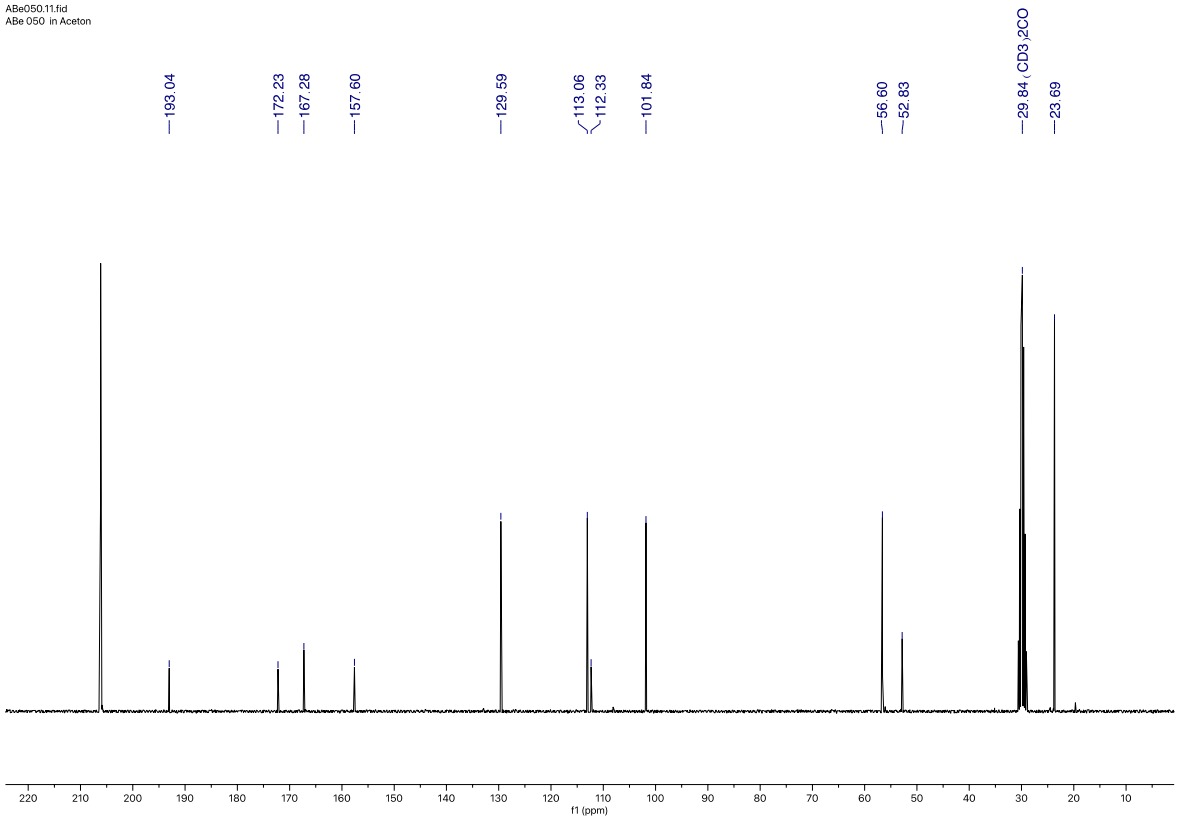
5.37 methyl 3-(2-hydroxy-4-methoxyphenyl)-2,2-dimethyl-3-oxopropanoate (**15b**).



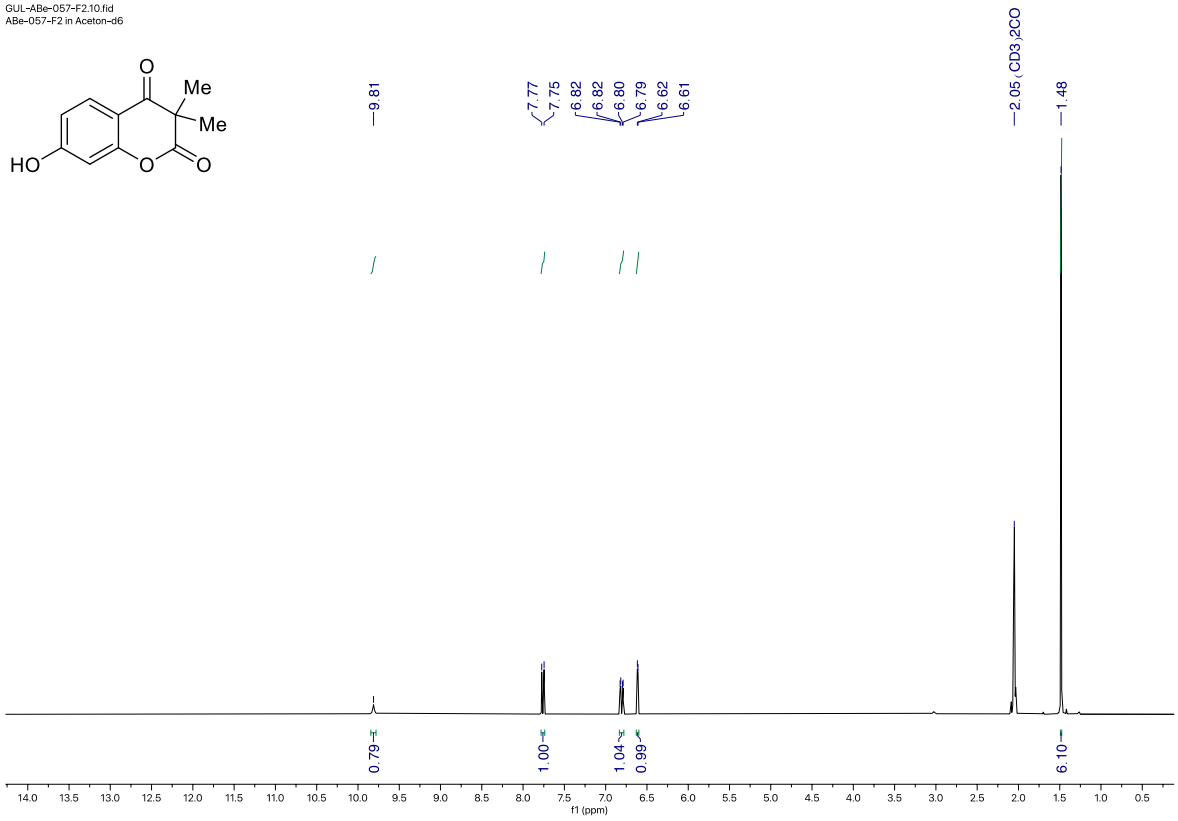


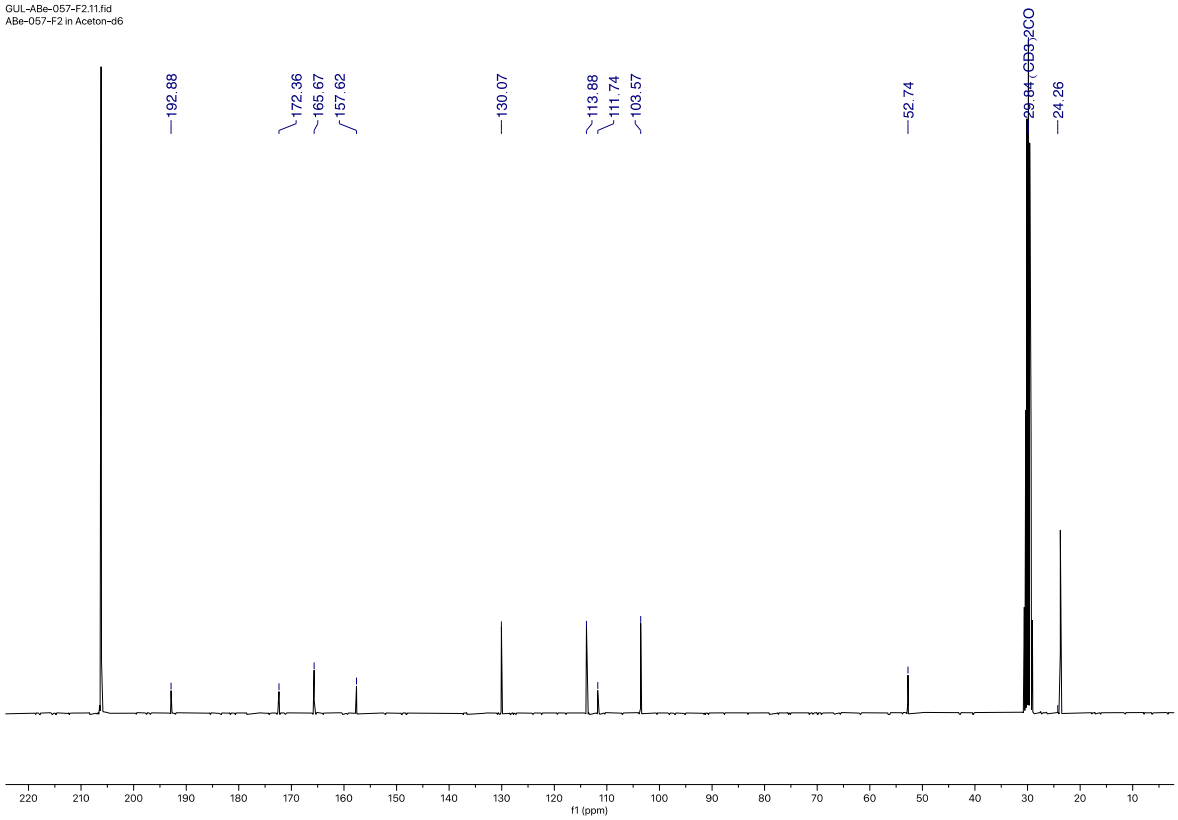
5.38 7-methoxy-3,3-dimethylchromane-2,4-dione (**16b**).



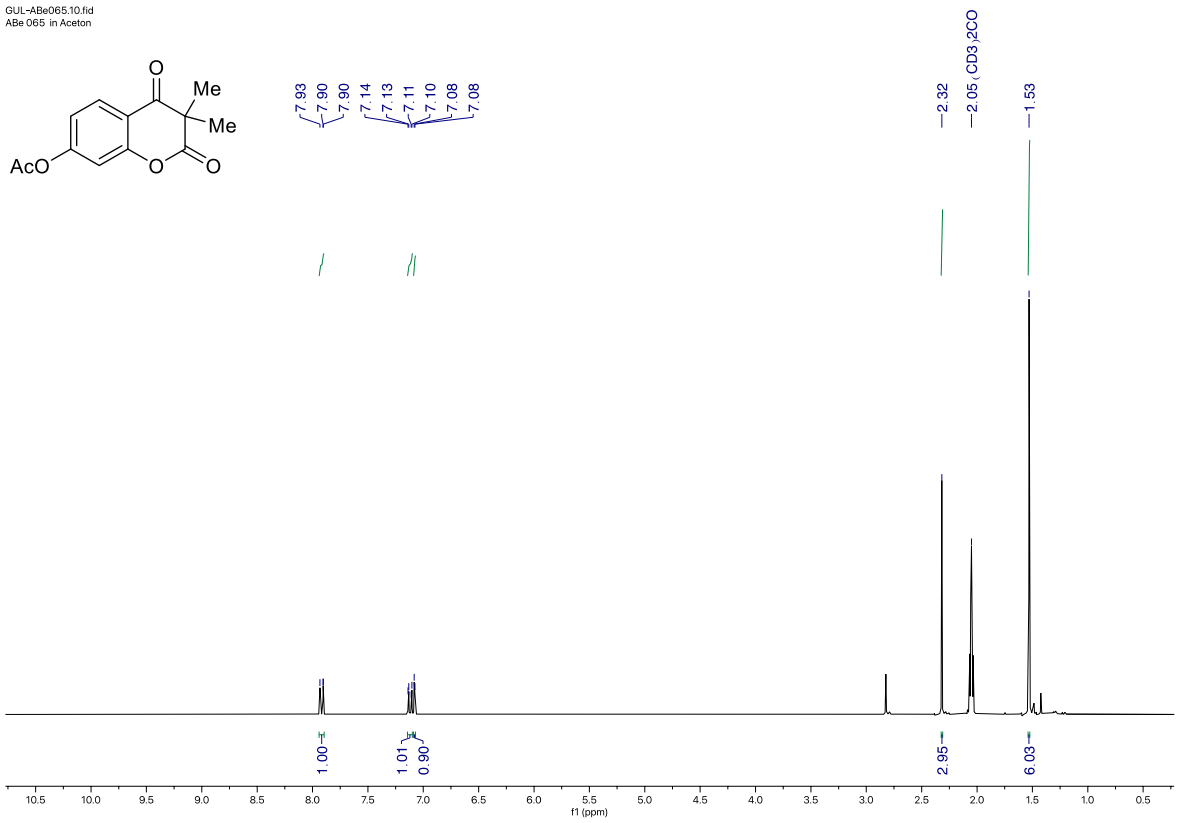


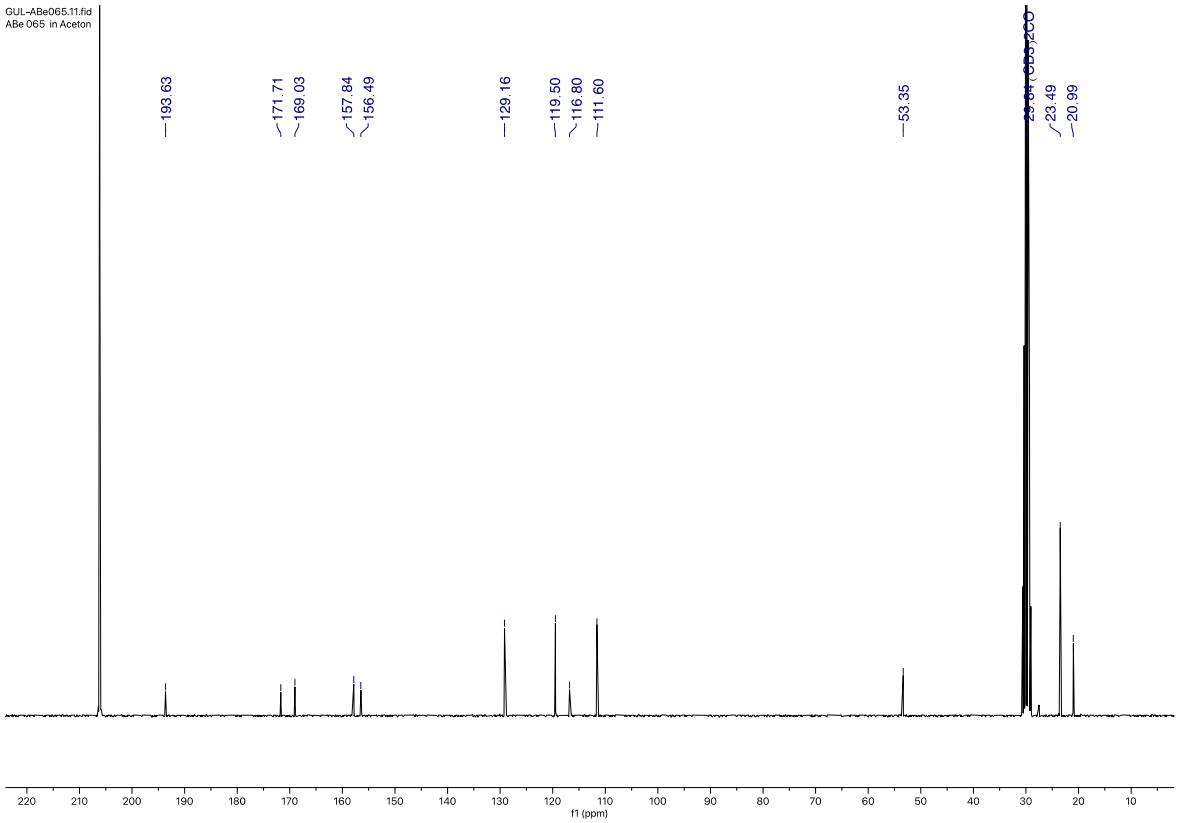
5.39 7-hydroxy-3,3-dimethylchromane-2,4-dione (**16c**).





5.40 3,3-dimethyl-2,4-dioxochroman-7-yl acetate (**16e**).





5.41 3,3-dimethyl-2,4-dioxochroman-7-yl trifluoromethanesulfonate (**16f**).