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A concise synthesis of methyl dihydrojasmonate and methyl (5-methylidene-4-oxocyclopent-2-en-1-yl)acetate from D-glucose

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Experimental

General

Instruments: Synthesized compounds were characterized by using nuclear magnetic resonance (NMR), and High-resolution mass spectra (HRMS). ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 and 100 MHz (Bruker AVANCE–400 III) spectrometer, respectively, and calibrated using residual deuterated solvent ($CDCl_3$ at δ 7.26 ppm for ^{1}H, δ 77.16 for ^{13}C NMR) and tetramethylsilane as internal reference. High–resolution mass spectrometry (HR–MS) was performed using a Bruker MicrOTOF–Q II–S1 using electrospray ionization (ESI) technique.

Materials: 2,6-lutidine, anhydrous magnesium sulfate ($MgSO_4$), sodium hydrogen carbonate ($NaHCO_3$), propionic acid, Zn powder, 1-iodobutane, cuprous iodide (CuI), palladium on carbon (10% Pd/C), methanol (MeOH), ethanol (EtOH), sulfuric acid (H_2SO_4) and anhydrous solvents for organic synthesis, including CH_2Cl_2, tetrahydrofuran (THF) and acetonitrile (MeCN) were purchased from FUJIFILM Wako Pure Chemical Co. Triisopropylsilyl trifluoromethanesulfonate (TIPSOTf), scandium(III) trifluoromethanesulfonate ($Sc(OTf)_3$) and pivalic acid were purchased from Tokyo Chemical Industry Co. Trimethylamine (Et_3N), *tert*-butyldimethylsilyl chloride (TBSCl), trimethyl orthoacetate ($CH_3C(OCH_3)_3$), were purchased from Sigma-Aldrich Co. Reactions were monitored by analytical thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254). Visualization of the developed chromatograms was performed by UV absorbance and aqueous cerium ammonium molybdate. All reagents and solvents were used without further purification.

Synthesis of 2-[(*tert*-butyldimethylsilyloxy)methyl]-4-hydroxycyclopent-2-en-1-one (10)

The primary -OH group of 4-hydroxy-2-(hydroxymethyl)cyclopentenone (**9**) was protected with *tert*-butyldimethylsilyl chloride (TBSCl) [S1]. In brief, compound **9** (1 g, 7.8 mmol) and TBSCl (1.76 g, 11.7 mmol) were dissolved in anhydrous THF (25 mL) under an argon atmosphere, and Et_3N (2.2 mL) was added to the solution while stirring. The reaction mixture was stirred at room temperature for 20 h. Completion of reaction was monitored with TLC. Saturated aqueous solution of NH_4Cl was added after completion of the reaction followed by extraction with ethyl acetate (3 × 25 mL). The extracts were combined and dried with $MgSO_4$. The extract was concentrated under vacuum to get a residue, which was purified by column chromatography (hexane: ethyl acetate = 75:25) to give **10** (1.74 g, 92 %) as colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 2.0, 4.4 Hz, 1H), 5.00-4.94 (m, 1H), 4.35 (t, J = 2.1 Hz, 2H), 2.83 (dd, J = 6.0, 18.6 Hz, 1H), 2.46 (d, J = 6.4 Hz, 1H), 2.34 (dd, J = 2.0, 18.6 Hz, 1H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 156.7, 147.9, 68.6, 57.9, 45.7, 25.9 (3C), 18.4, -5.35, -5.37; HRMS (ESI–TOF): m/z $C_{12}H_{23}O_3Si$ ($[M + H]^+$) calcd. for 243.1411, found 243.1415.

Synthesis of 2-[(*tert*-butyldimethylsilyloxy)methyl]-4-(triisopropylsilyloxy)-cyclopent-2-en-1-one (11)

The secondary -OH group of **10** was protected with triisopropylsilyl chloride (TIPSCl) [S1]. In brief, compound **10** (1.52 g, 6.27 mmol) was dissolved in anhydrous CH_2Cl_2 (25 mL) under an argon atmosphere. 2,6-Lutidine (1.1 mL, 9.41 mmol) and TIPSOTf (2.02 mL, 7.53 mmol) were added to the solution. The reaction mixture was stirred at room temperature for 1.5 h. Completion of reaction was monitored with TLC. Saturated aqueous solution of NH_4Cl was added after completion of the reaction, the mixture was extracted with ethyl acetate (3 × 25 mL). The extracts were combined and dried with $MgSO_4$. The extract was concentrated under vacuum to get a residue, which was purified by column chromatography (hexane: ethyl acetate = 5:95) to give **11** (2.44 g, 98 %) as a light-yellow viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J = 2.0, 4.2 Hz, 1H), 5.02-4.99 (m, 1H), 4.37 (t, J = 2.1 Hz, 2H), 2.81 (dd, J = 5.8, 18.2 Hz, 1H), 2.38 (dd, J = 2.0, 18.2 Hz, 1H), 1.10-1.04 (m, 21H), 0.91 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0, 157.2, 147.2, 69.2, 58.0, 46.8, 26.0 (3C), 18.4, 18.1 (6C), 12.2 (3C), -5.3 (2C); HRMS (ESI–TOF): m/z $C_{21}H_{43}O_3Si_2$ ($[M + H]^+$) calcd. for 399.2745, found 399.2742.

Synthesis of 2-hydroxymethyl-4-(triisopropylsilyloxy)cyclopent-2-en-1-one (12)

Compound **11** (2.42 g, 6.07 mmol) was dissolved in mixture of MeCN-water (24:1, 62.5 mL), then $Sc(OTf)_3$ (150 mg, 5 mol%) was added. The reaction mixture was stirred at room temperature for 6.5 h. Completion of reaction was monitored with TLC. Saturated aqueous solution of $NaHCO_3$ was added after completion of the reaction followed by extraction with ethyl acetate (3 × 25 mL). The extracts were combined and dried with $MgSO_4$. The extract was concentrated under vacuum to get a residue, which was purified by column chromatography (hexane: ethyl acetate = 75:25) to give **12** (1.38 g, 80 %) as a colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.31 (m, 1H), 5.04-5.00 (m, 1H), 4.41-4.33 (m, 2H), 2.82 (dd, J = 5.8, 18.3 Hz, 1H), 2.44 (broad s, 1H), 2.38 (dd, J = 2.1, 18.3 Hz, 1H), 1.15-1.06 (m, 21H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.2, 157.8, 145.5, 69.3, 57.5, 46.5, 18.05 (2C), 18.02 (4C), 12.2 (3C); HRMS (ESI–TOF): m/z $C_{15}H_{29}O_3Si$ ($[M + H]^+$) calcd. for 285.1886, found 285.1878.

Synthesis of methyl 2-[2-methylidene-3-oxo-5-(triisopropylsilyloxy)cyclopentyl]-acetate (13)

Compound **12** (505 mg, 1.78 mmol) was mixed with $CH_3C(OCH_3)_3$ (2.4 mL, 17.8 mmol) under an argon atmosphere. Pivalic acid (182 mg, 1.78 mmol) was added to the solution. The reaction mixture was stirred at 140 °C for 15 min followed by lowering the temperature to 110 °C and stirring for next 45 min. Completion of the reaction was monitored with TLC. Saturated aqueous solution of $NaHCO_3$ was added to the reaction mixture after cooling to room temperature. The resulting mixture was extracted with ethyl acetate (3 × 15 mL). The extracts were combined and washed with brine (30 mL) then dried with $MgSO_4$. The extract was concentrated under vacuum afforded a residue, which was purified by column chromatography (hexane: ethyl acetate = 95:5 to 90:10) to give **13** (410 mg, 68 %) as a light-yellow viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11-6.09 (m, 1H), 5.34-5.27 (m, 1H), 4.74-4.30 (m, 1H), 3.71-3.70 (two singlets, 3H), 3.32-3.18 (m, 1H), 2.87-2.32 (m, 4H), 1.07-1.02 (m, 21H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 203.3, 173.0, 172.0, 159.3, 146.5, 146.2, 118.9, 118.0, 72.0, 69.7, 69.3, 57.7, 51.9, 51.8, 47.8, 47.6, 47.1, 46.2, 44.3, 36.7, 32.7, 18.1, 18.1, 18.1, 18.0, 12.6, 12.3, 12.2; HRMS (ESI–TOF): m/z $C_{18}H_{33}O_4Si$ ($[M + H]^+$) calcd. for 341.2148, found 341.2130.

Synthesis of methyl 2-(3-oxo-2-pentyl-5-(triisopropylsilyloxy)cyclopentyl)acetate (14)

Zinc powder (33 mg, 0.51 mmol) and cuprous iodide (CuI, 33 mg, 0.17 mmol) were suspended in ethanol: water (9:1) (4 mL). The resulting suspension was sonicated for 10 min, then 1-iodobutane (50 µL, 0.43 mmol) and compound **13** (58 mg, 0.17 mmol) were added simultaneously. The reaction mixture was sonicated for 1.5 h. Zinc powder (33 mg) and 1-iodobutane (50 µL) were added again to the reaction mixture, and sonication was continued for 1.5 h. The reaction mixture was filtered after completion of the reaction and diluted with water. The resulting mixture was extracted with ethyl acetate (3 × 15 mL), and the combined extracts were dried with $MgSO_4$. The resulting extract was concentrated under vacuum and purified by column chromatography (hexane: ethyl acetate = 95:5) to give **14** (44 mg, 65 %) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62-4.27 (m, 1H), 3.68-3.67 (two singlet, 3H), 3.00-1.97 (m, 6H), 1.75-1.37 (m, 2H), 1.37-1.22 (m, 6H), 1.07-1.02 (m, 21H), 0.89-0.85 (two triplet, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.3, 216.9, 173.6, 172.4, 72.9, 70.6, 53.2, 52.4, 51.8, 47.7, 46.8, 46.4, 42.0, 36.4, 32.1, 32.0, 29.6, 29.4, 27.7, 26.7, 25.9, 22.6, 22.5, 18.1, 18.1, 18.1, 14.2, 12.4, 12.3, 12.2; HRMS (ESI–TOF): m/z $C_{22}H_{43}O_4Si$ ($[M + H]^+$) calcd. for 399.2931, found 341.2912.

Synthesis of methyl 2-(4-oxo-5-pentylcyclopent-2-en-1-yl)acetate (15)

Sulfuric acid (1 M aq., 4 mL) was added to a solution of compound **14** (41 mg, 0.103 mmol) in methanol (8 mL). The mixture was stirred under reflux (90 °C in bath) for 45 min. Completion of the reaction was monitored with TLC. Saturated aqueous $NaHCO_3$ (20 mL) was added to the reaction mixture after completion of the reaction, and the mixture was extracted with ethyl acetate (3 × 25 mL). The extracts were combined, dried with $MgSO_4$, and concentrated under vacuum followed by purification with column chromatography (hexane: ethyl acetate = 80:20) to give **15** (20 mg, 85 %) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 2.5, 5.7 Hz, 1H), 6.15 (dd, J = 1.9, 5.7 Hz, 1H), 3.71 (s, 3H), 3.05-3.00 (m, 1H), 2.58 (dd, J = 6.6, 15.7 Hz, 1H), 2.46 (dd, J = 8.4, 15.7 Hz, 1H), 2.00 (ddd, J = 2.4, 4.9, 8.2 Hz, 1H), 1.77-1.69 (m, 1H), 1.53-1.44 (m, 1H), 1.37-1.25 (m, 6H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 172.0, 165.2, 133.9, 52.0, 51.4, 44.2, 38.6, 32.0, 30.9, 26.7, 22.6, 14.2; HRMS (ESI–TOF): m/z $C_{13}H_{21}O_3$ ($[M + H]^+$) calcd. for 225.1491, found 225.1477.

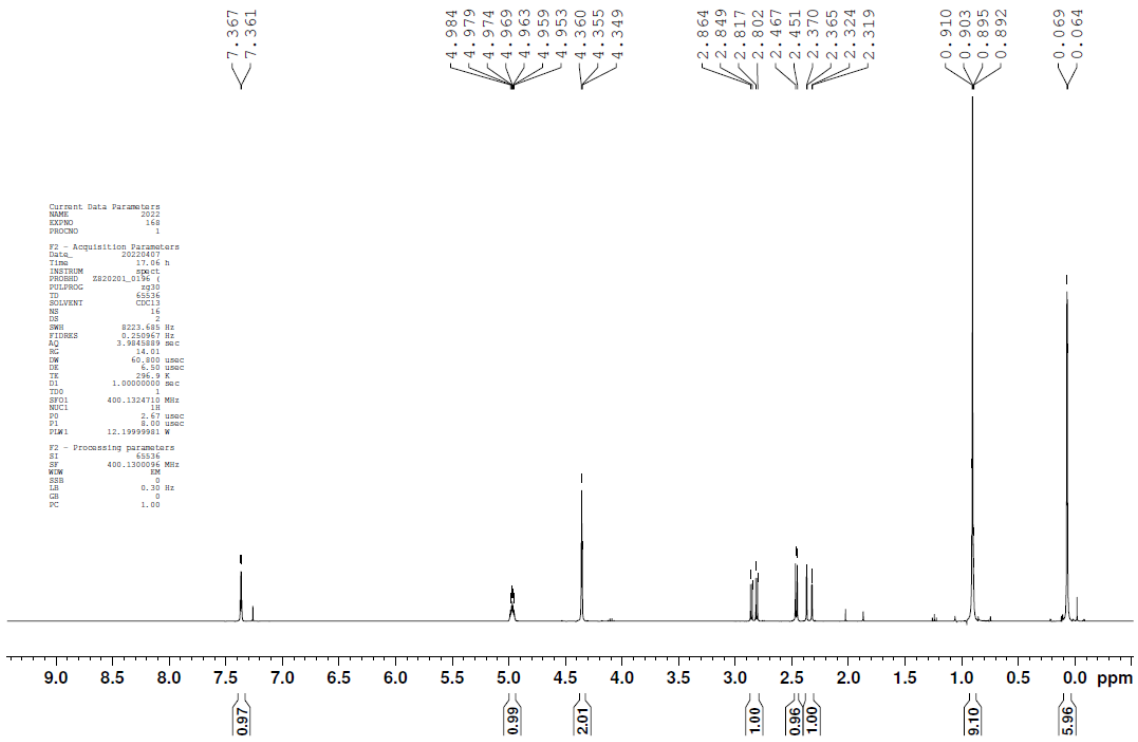
Synthesis of Hedione® (1)

Catalyst Pd/C (10%, 1.5 mg) was added to a solution of compound **15** (15 mg, 0.067 mmol) in methanol (6 mL) under hydrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was filtered through a pad of celite after completion of the reaction, concentrated under vacuum, and purified by column chromatography (hexane: ethyl acetate = 90:10) to give product **1** (15 mg, 99 %) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 2.66-2.59 (m, 1H), 2.38-2.19 (m, 4H), 2.16-2.07 (m, 1H), 1.81-1.76 (m, 1H), 1.59-1.36 (m, 4H), 1.30-1.22 (m, 5H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.8, 172.8, 54.4, 51.8, 39.1, 38.3, 37.8, 32.2, 28.0, 27.4, 26.5, 22.6, 14.2; HRMS (ESI–TOF): m/z $C_{13}H_{23}O_3$ ($[M + H]^+$) calcd. for 227.1647, found 227.1633.

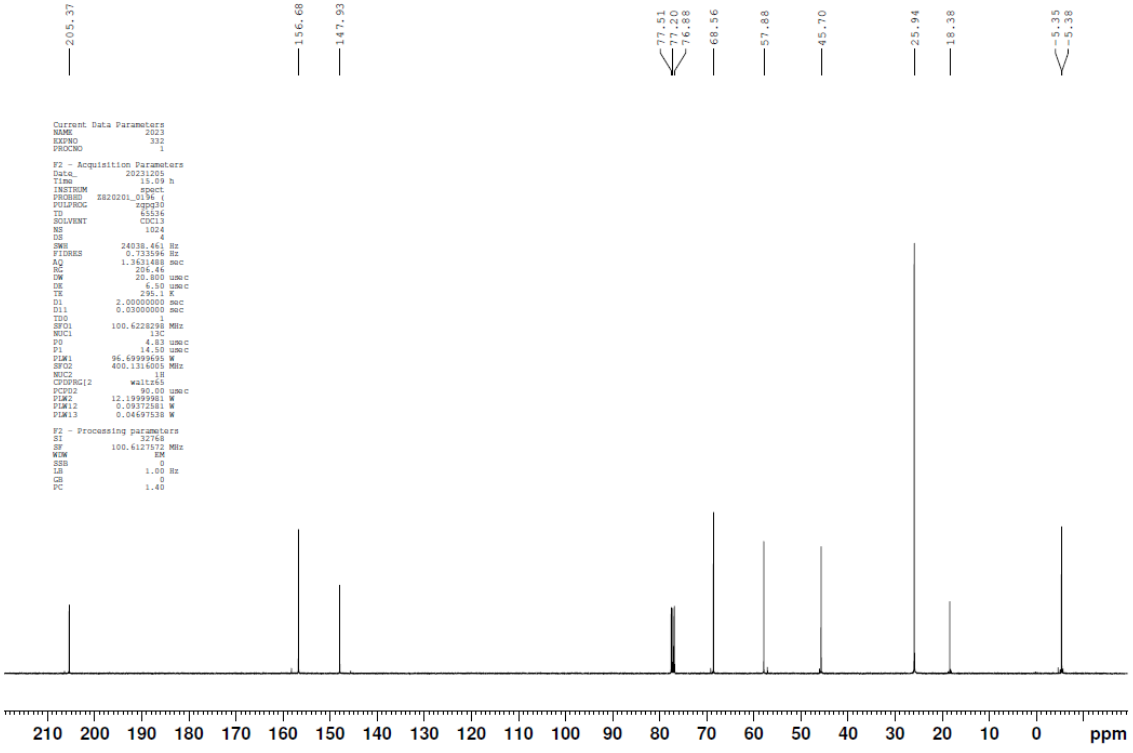
Synthesis of methyl (±)-2-(5-methylidene-4-oxocyclopent-2-en-1-yl)acetate (5)

Compound **5** was synthesized by using same method for the synthesis of **15**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (ddd, J = 1.0, 2.5, 6.0 Hz, 1H), 6.42 (ddd, J = 1.0, 2.4, 6.0 Hz, 1H), 6.16-6.15 (m, 1H), 5.48 (broad singlet, 1H), 3.86-3.80 (m, 1H), 3.73 (s, 3H), 2.67 (dd, J = 6.5, 16.3 Hz, 1H), 2.51 (dd, J = 8.4, 16.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4, 171.5, 161.1, 144.6, 135.7, 117.8, 52.1, 40.8, 37.8; HRMS (ESI–TOF): m/z $C_9H_{11}O_3$ ($[M + H]^+$) calcd. for 167.0703, found 167.0703.

^{1}H ($CDCl_3$, 400 MHz) NMR of compound **10**



^{13}C ($CDCl_3$, 100 MHz) NMR of compound **10**



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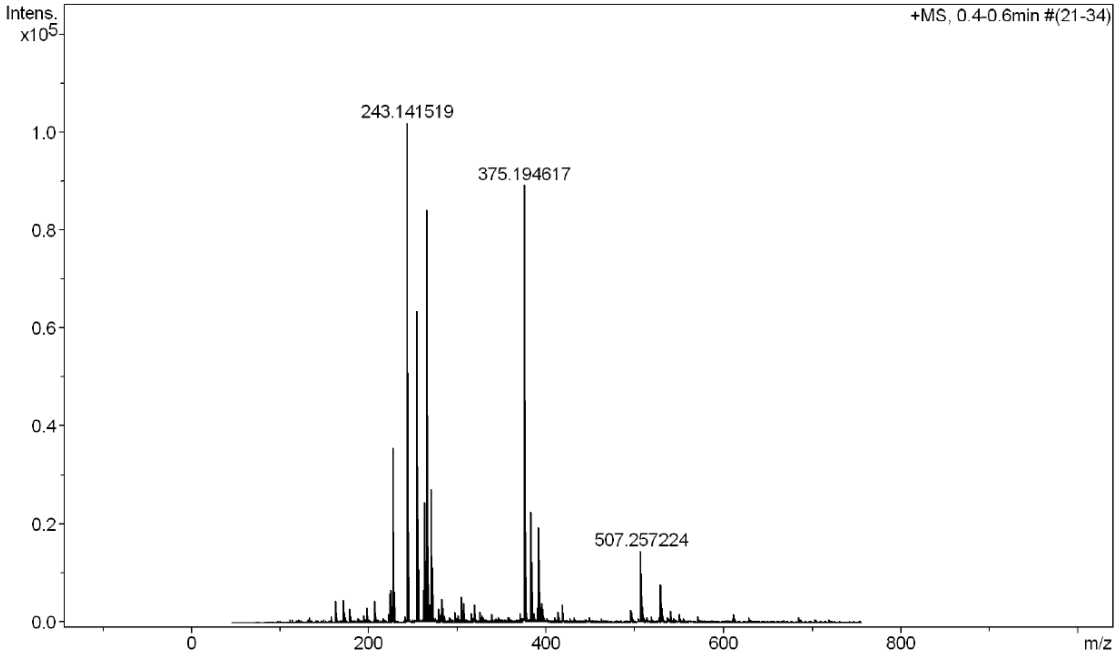
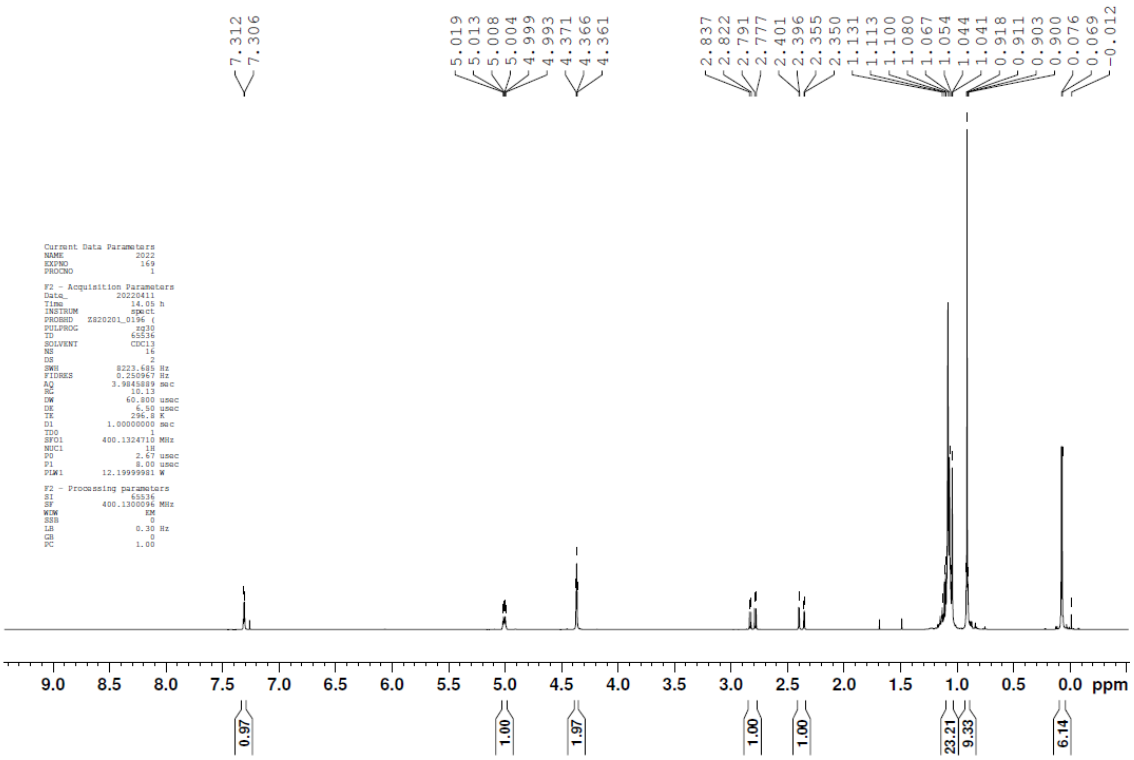
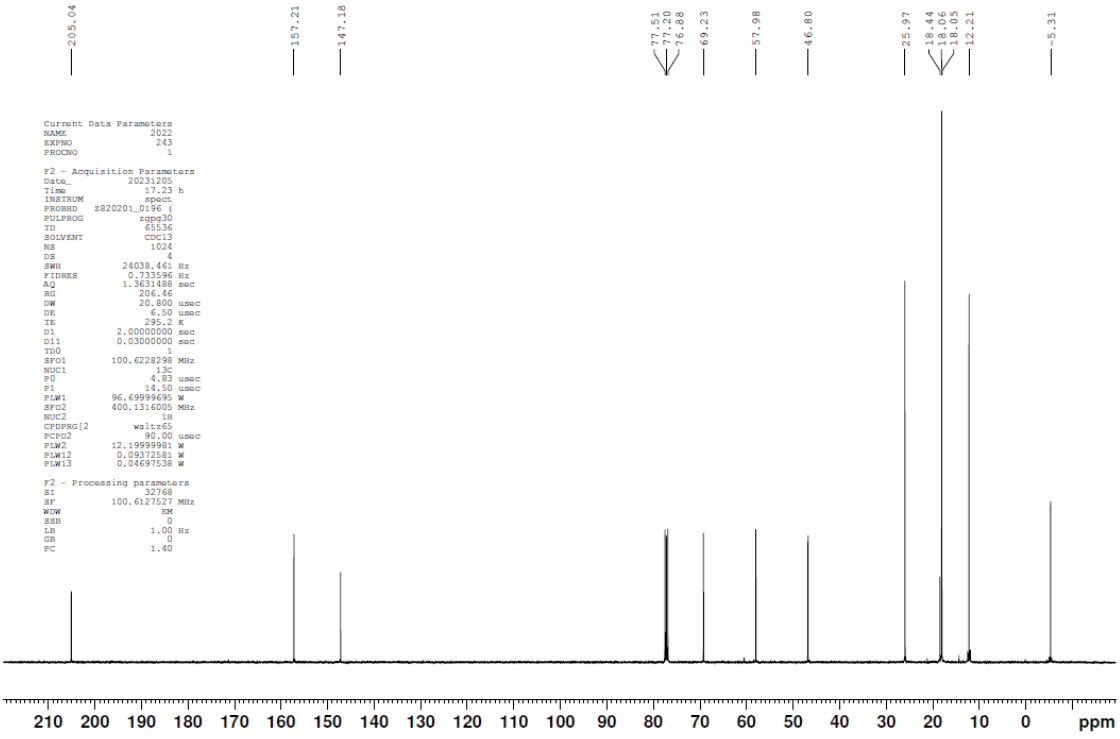


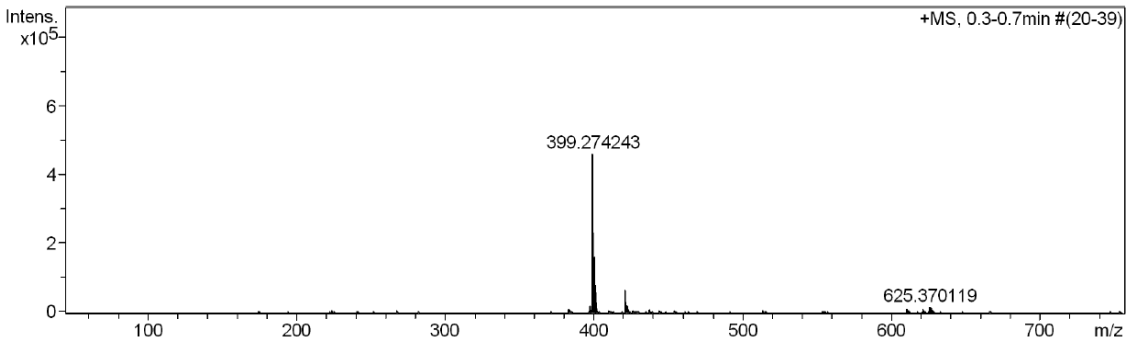
^{1}H ($CDCl_3$, 400 MHz) NMR of compound **11**



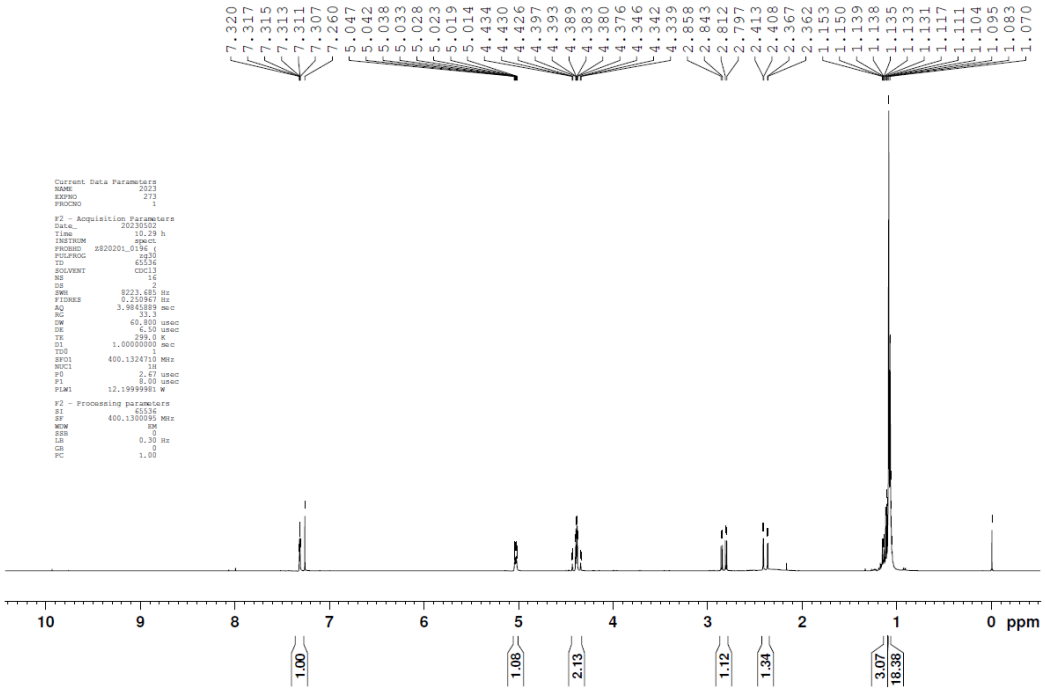
^{13}C ($CDCl_3$, 100 MHz) NMR of compound **11**



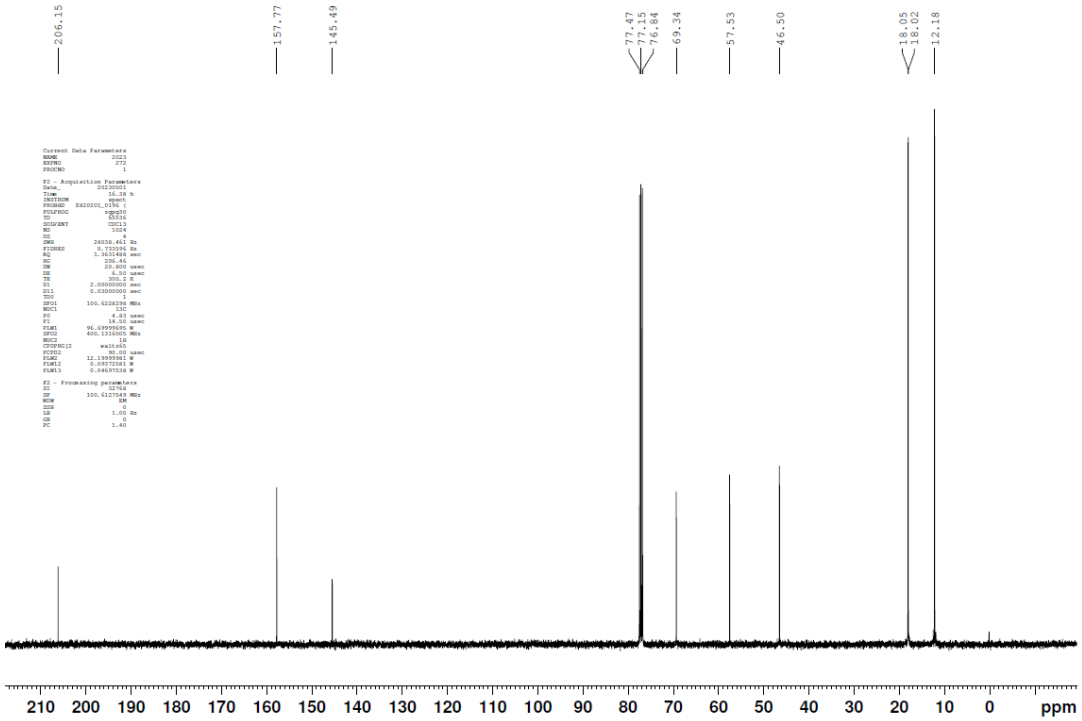
HRMS (ESI–TOF) of compound **11**



^{1}H ($CDCl_3$, 400 MHz) NMR of compound **12**



^{13}C ($CDCl_3$, 100 MHz) NMR of compound **12**



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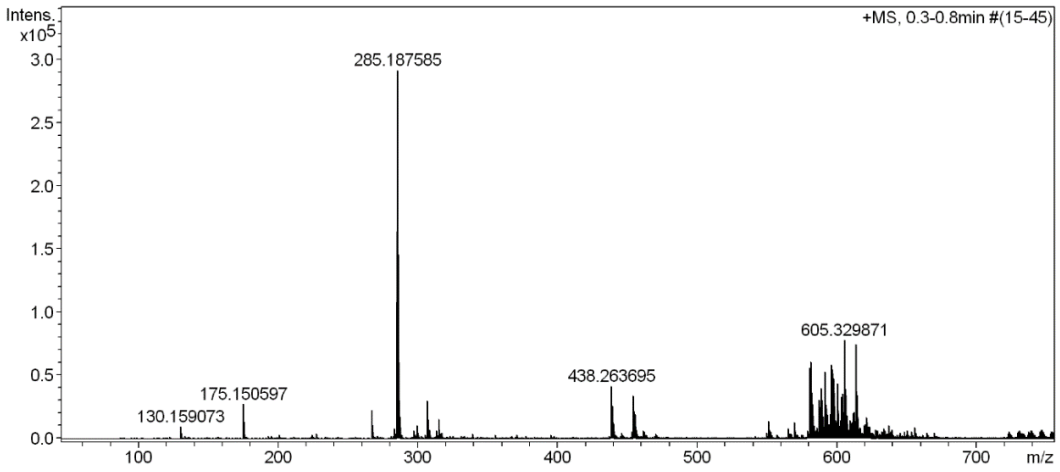
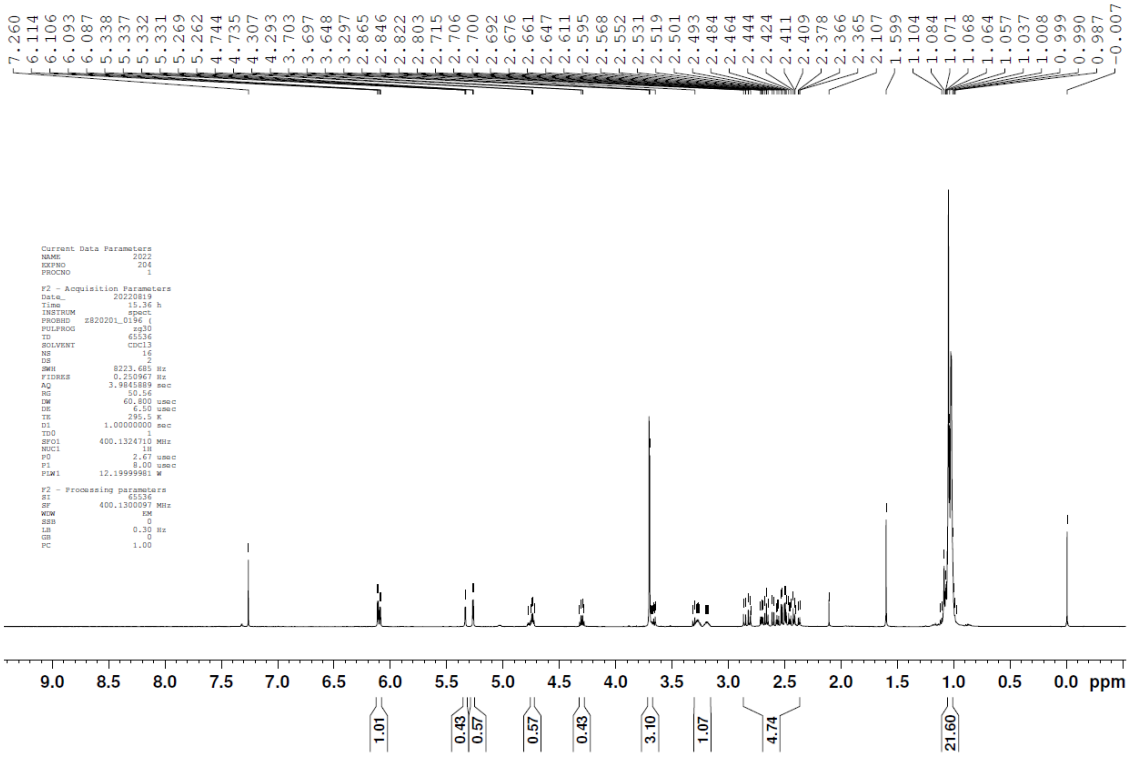
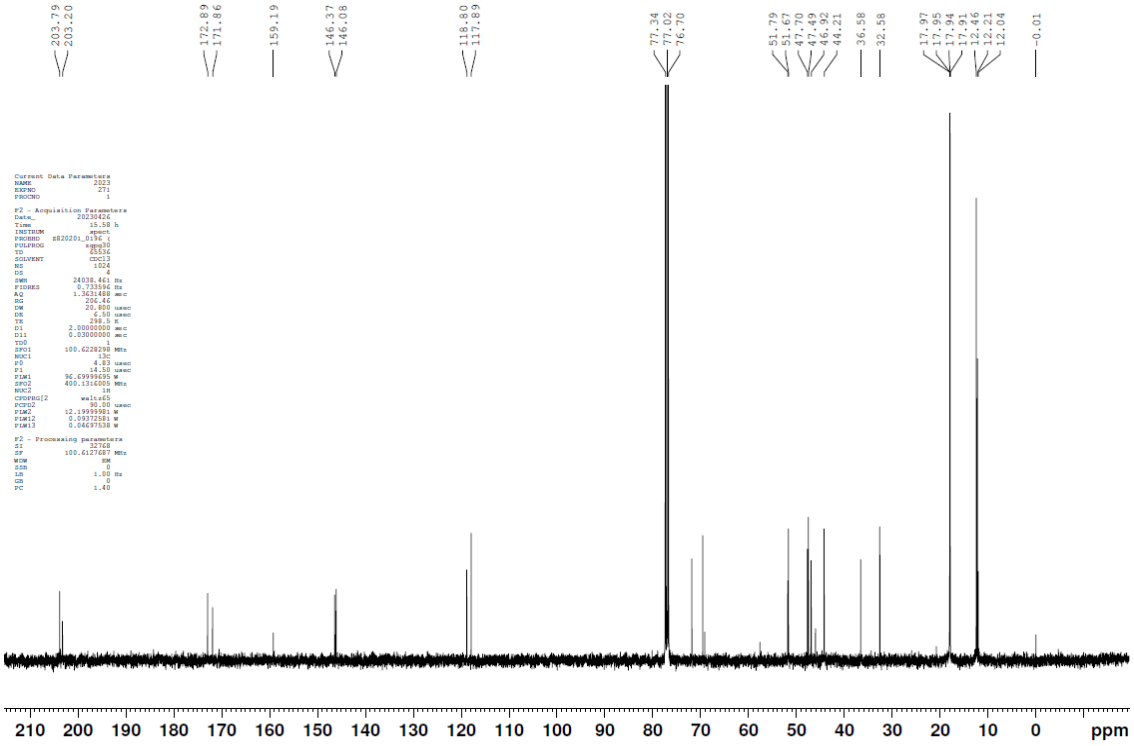


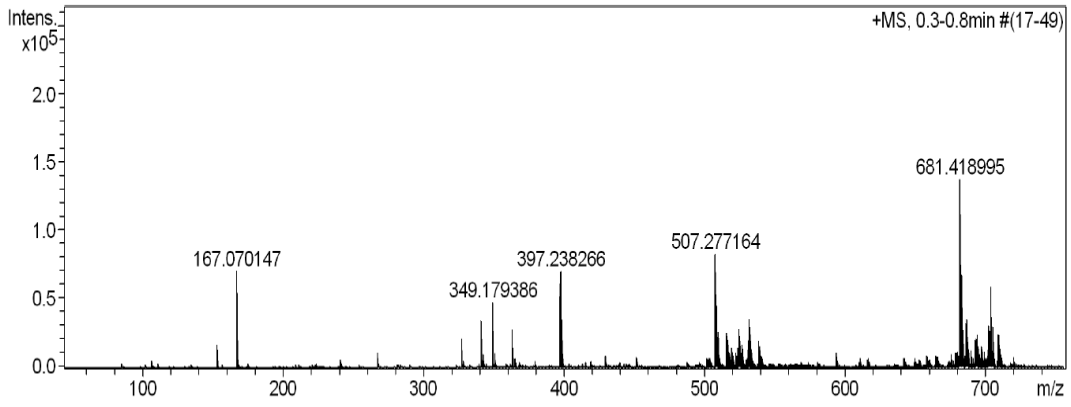
^{1}H ($CDCl_3$, 400 MHz) NMR of compound **13**



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

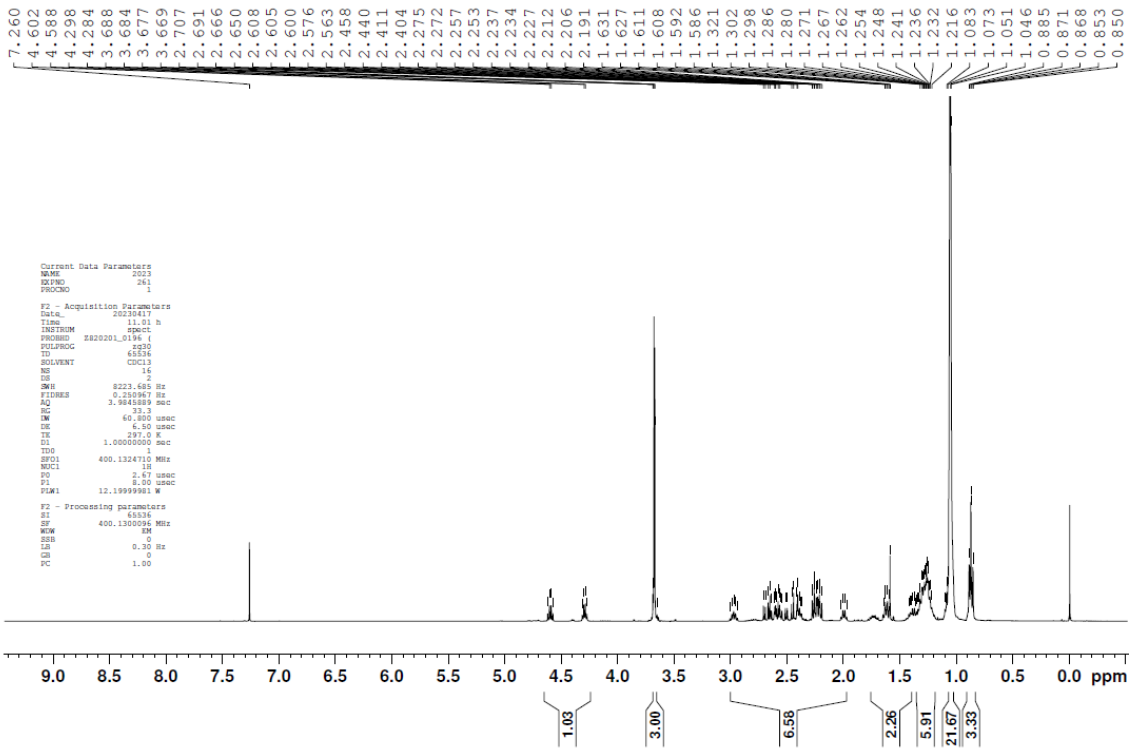


HRMS (ESI–TOF) of compound **13**

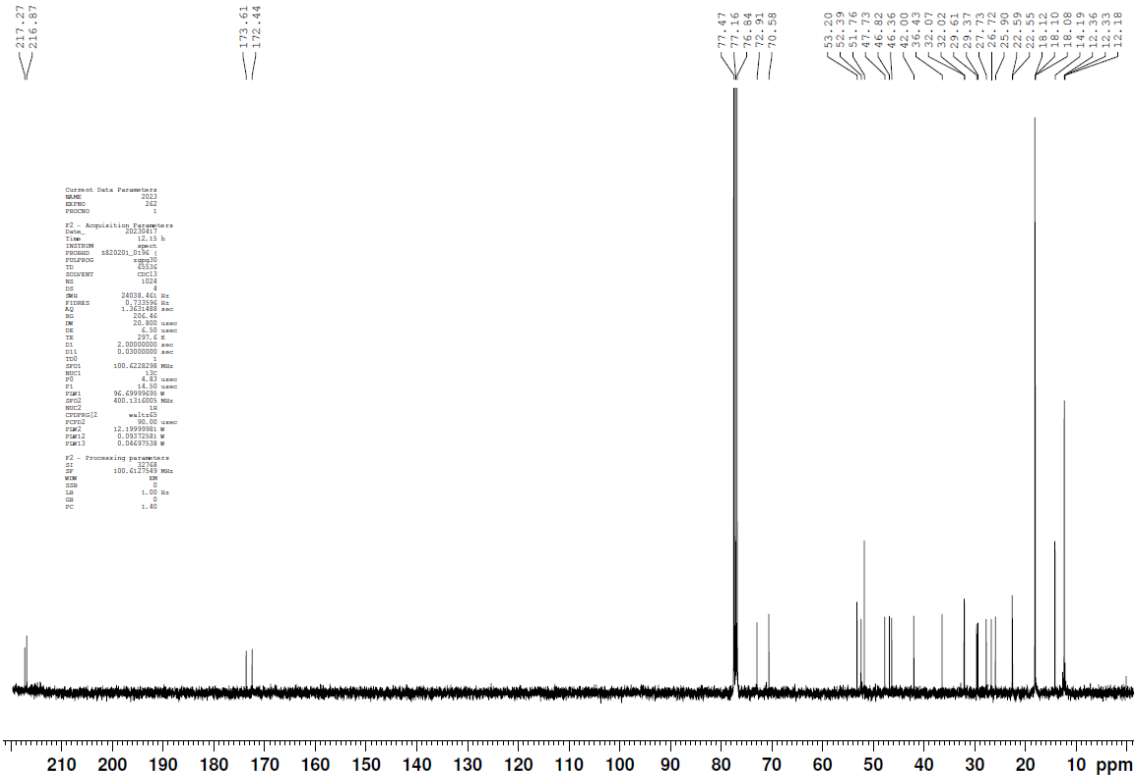


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
341.213043	1	C 18 H 33 O 4 Si	100.00	341.214263	1.220	3.574	32.7	3.5	even	ok

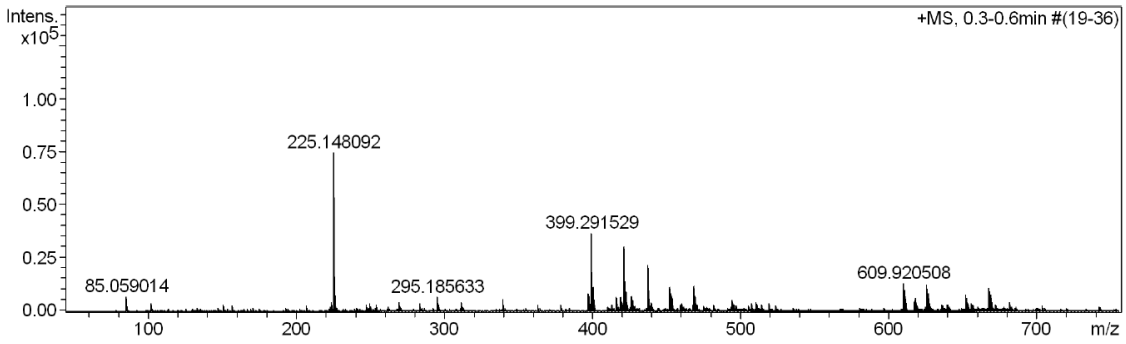
^{1}H ($CDCl_3$, 400 MHz) NMR of compound **14**



^{13}C ($CDCl_3$, 100 MHz) NMR of compound **14**

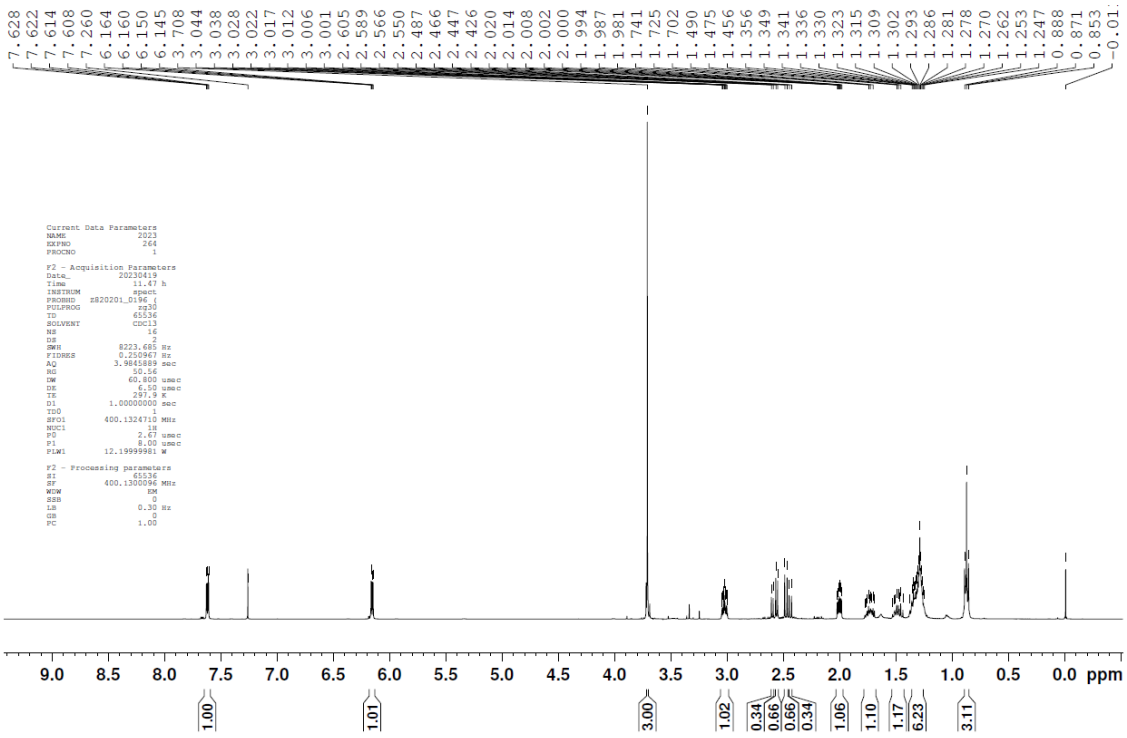


HRMS (ESI–TOF) of compound **14**

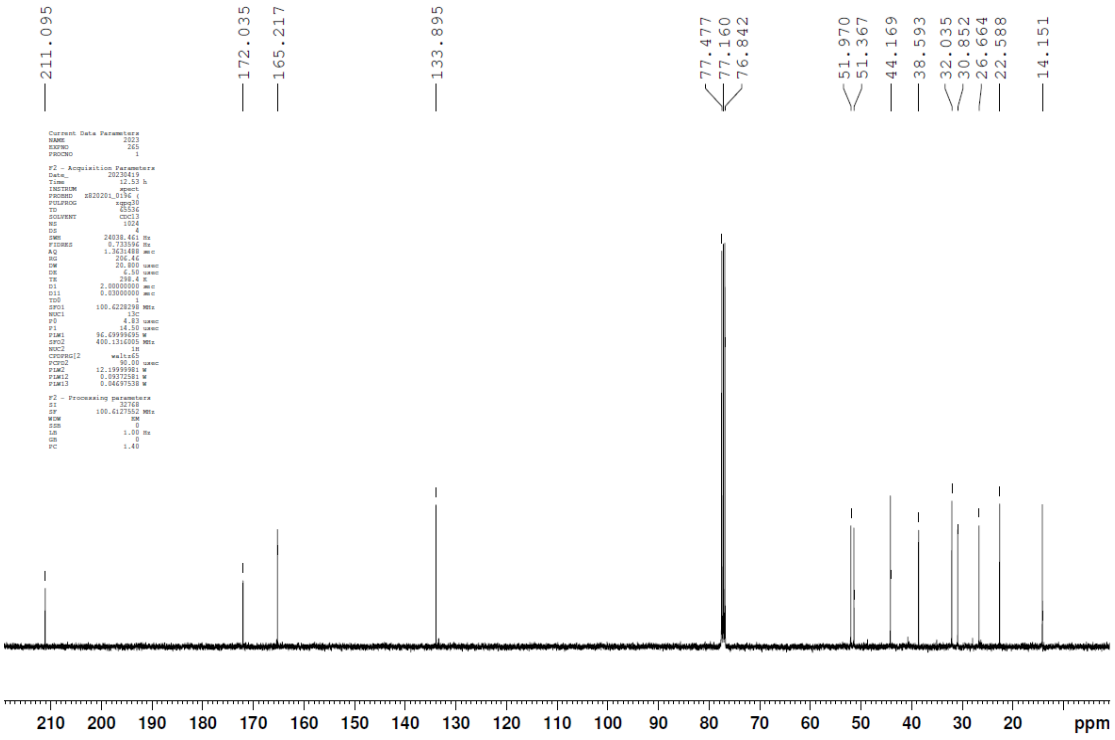


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
399.291529	1	C 22 H 43 O 4 Si	100.00	399.292513	0.983	2.463	4.8	2.5	even	ok

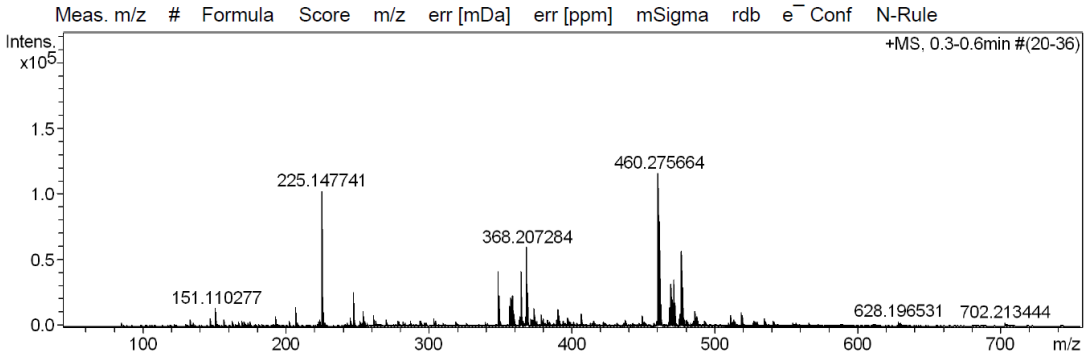
^{1}H ($CDCl_3$, 400 MHz) NMR of compound **15**



^{13}C ($CDCl_3$, 100 MHz) NMR of compound **15**

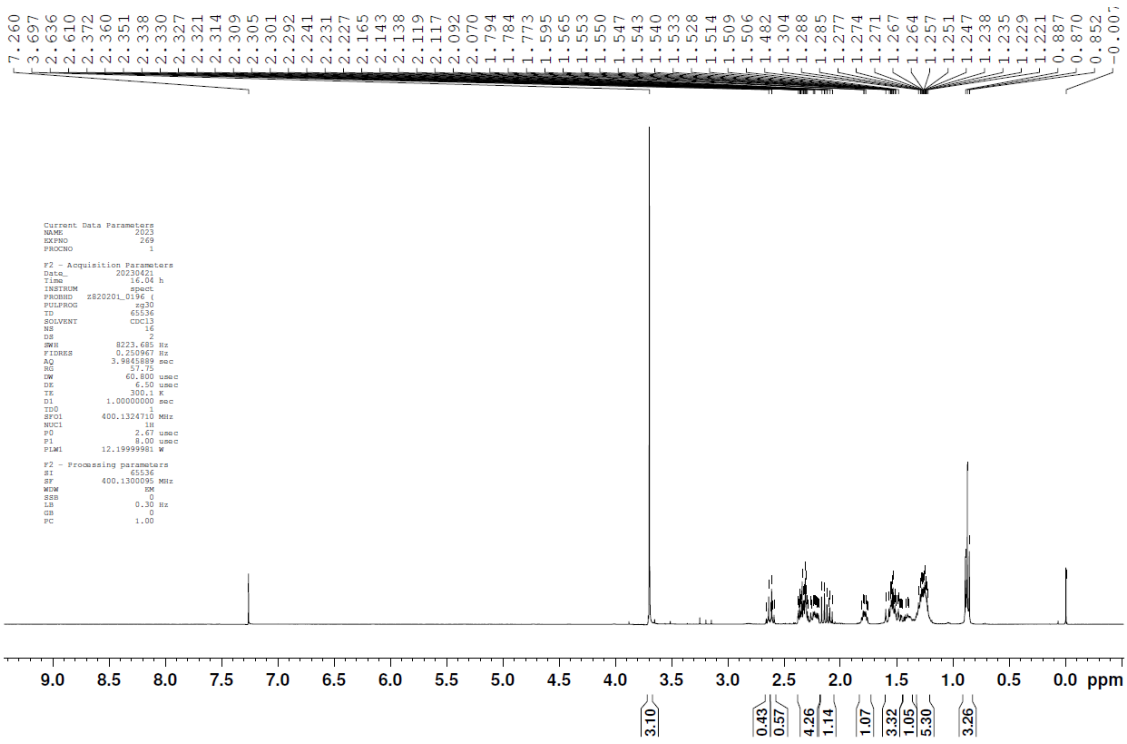


HRMS (ESI–TOF) of compound **15**

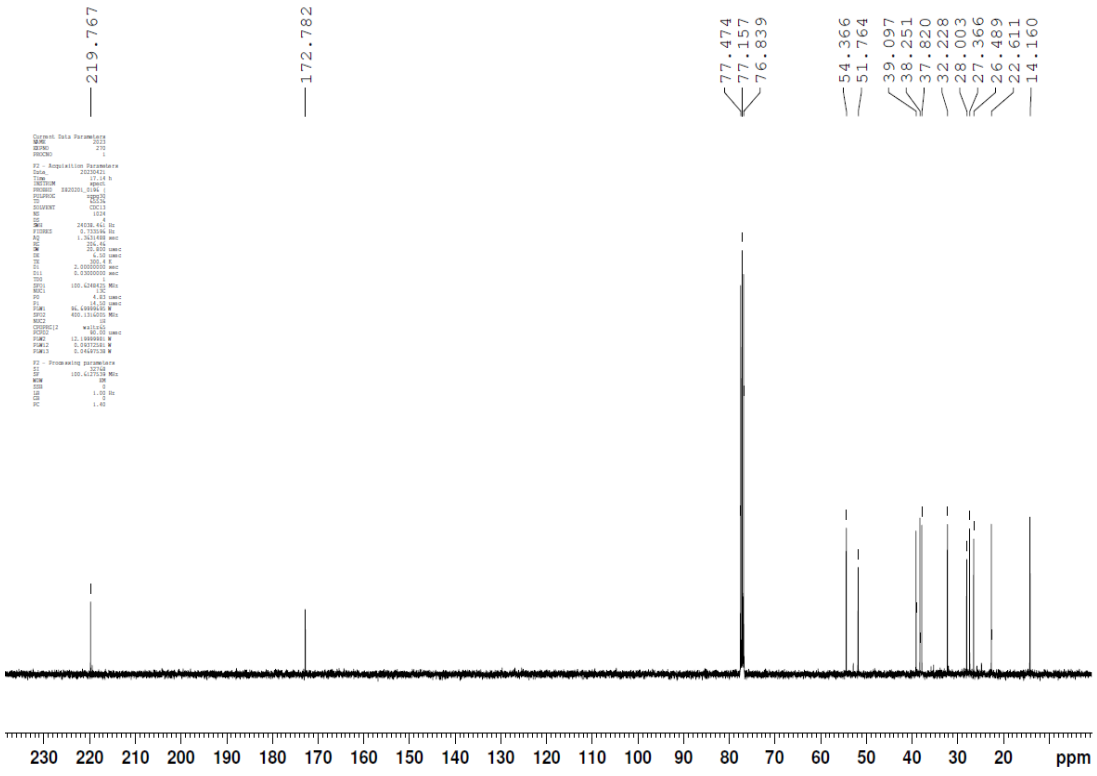


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e¯ Conf	N-Rule
225.147741	1	C 13 H 21 O 3	100.00	225.148521	0.780	3.463	3.8	3.5	even	ok

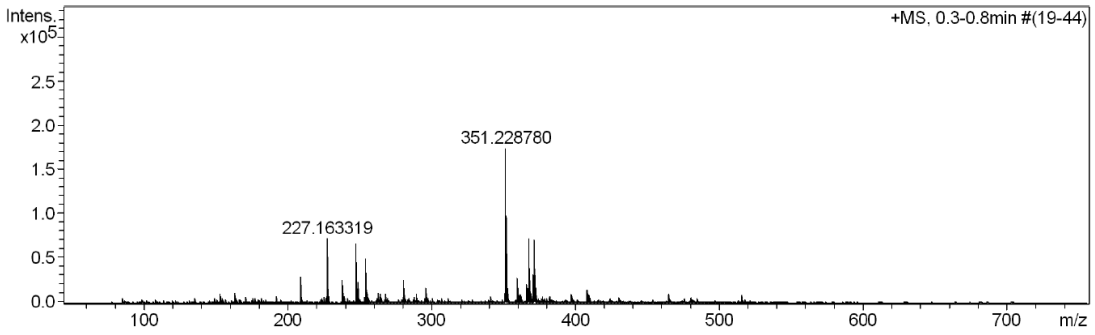
^{1}H ($CDCl_3$, 400 MHz) NMR of compound **1**



^{13}C ($CDCl_3$, 100 MHz) NMR of compound **1**

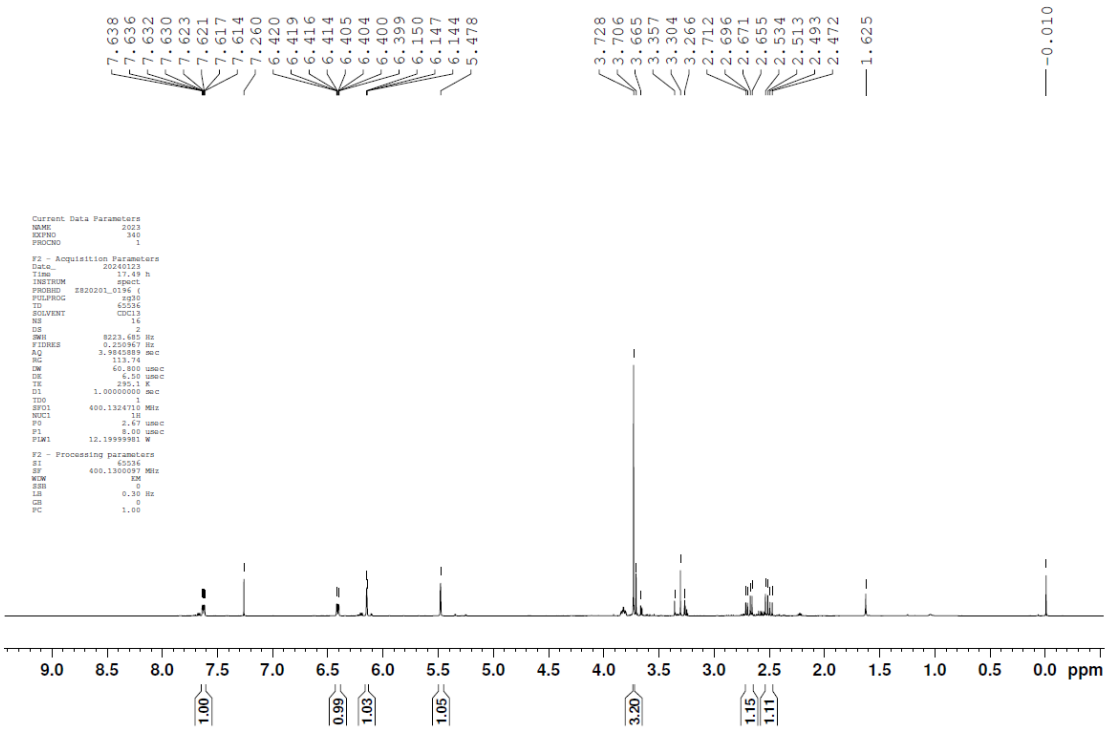


HRMS (ESI–TOF) of compound **1**

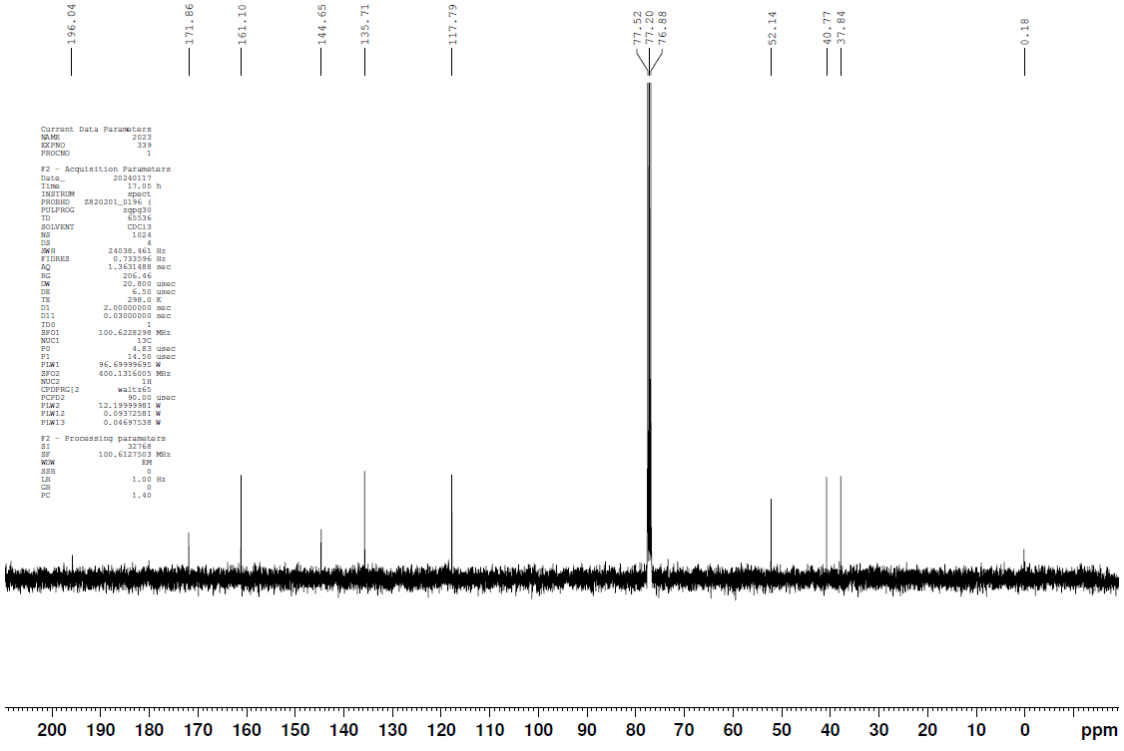


Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
227.163319	1	C 13 H 23 O 3	100.00	227.164171	0.852	3.752	6.5	2.5	even	ok

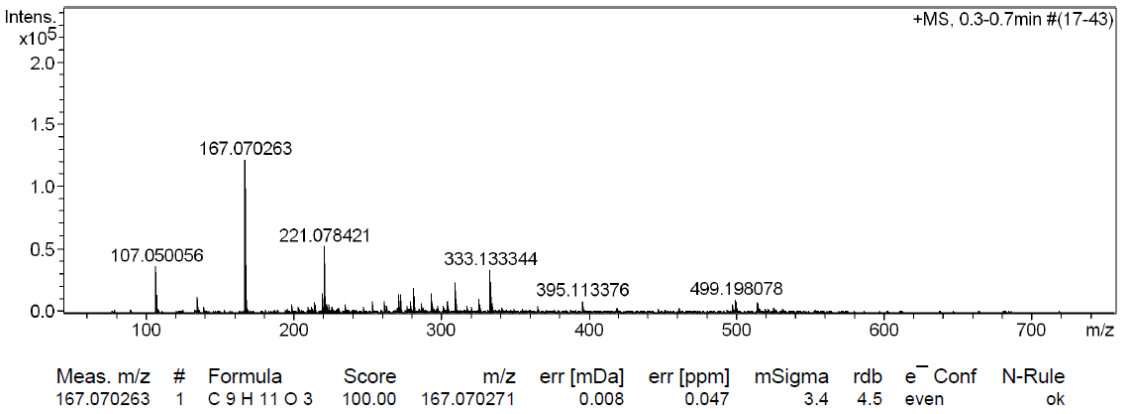
^{1}H ($CDCl_3$, 400 MHz) NMR of compound **5**



^{13}C ($CDCl_3$, 100 MHz) NMR of compound **5**



HRMS (ESI–TOF) of compound **5**



Meas. m/z	#	Formula	Score	m/z	err [mDa]	err [ppm]	mSigma	rdb	e⁻ Conf	N-Rule
167.070263	1	C 9 H 11 O 3	100.00	167.070271	0.008	0.047	3.4	4.5	even	ok

Reference

S1. T. Kamishima, M. Suzuki, K. Narita, Y. Koseki, T. Nonaka, H. Nakatsuji, H. Hattori and H. Kasai, *Sci. Rep.,* 2022, **12,** 1. https://doi.org/10.1038/s41598-022-11608-8.