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Lead tetraacetate assisted formation of bis(acetoxy)acetic acid derivative from carvone

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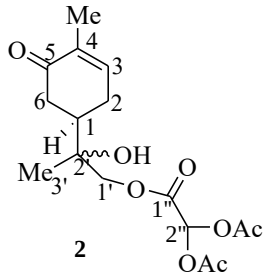
Experimental

General

Solvents were purified and dried before used by standard procedures. Reagents were generally the best quality commercial grade and used without further purification unless otherwise indicated. All reactions were carried in oven-dried glassware. TLC was performed using Sorbfil STC-1A 110 μm layer, silica gel 5–17 mesh precoated foil plates. Column chromatography was carried out using 210–280 mesh silica gel. Optical rotations were measured using the sodium D line at 589 nm on a Perkin Elmer, Model 241 MC polarimeter. IR (infrared spectra) was recorded on a Shimadzu IRPrestige-21 spectrometer as a nujol mull. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker AM-300 (300 MHz for ^{1}H and 500 MHz for ^{13}C) as solutions in $CDCl_3$, CD_6CO (Aldrich Chemical Company; spectra grade). Mass spectra were recorded in ethanol on a Shimadzu LCMS-2010 EV spectrometer. Elemental analyses were carried on a Euro EA 3000 CHNS-analyzer.

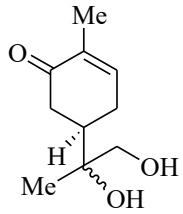


2

(2*RS*)-2-hydroxy-2-[(1*S*)-4-methyl-5-oxocyclohex-3-en-1-yl)]prop-1-yl bis(acetoxy)acetate (2)

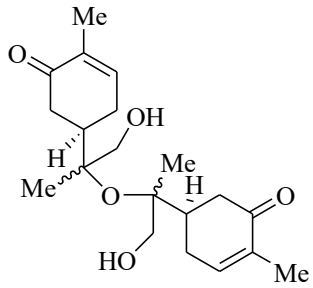
Lead tetraacetate (1 equiv., 1.18 g, 2.6 mmol) was added in an argon atmosphere to a stirred solution of *R*-carvone (0.1 g, 0.66 mmol) in benzene (5 ml). The mixture was refluxed for 48 h under stirring with gradual addition of the remaining 3 equiv. $Pb(OAc)_4$. Once *R*-carvone was consumed, an aqueous solution of $NaHCO_3$ was added, the organic layer was separated, and the aqueous layer was extracted with EtOAc (2×10 ml). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated. The residue was chromatographed on SiO_2 (eluent: 25% EtOAc/petroleum ether) to afford 0.13 g (59%) of product **2** as an oil, R_f (50% EtOAc/petroleum ether) 0.32, $[\alpha]_D^{20}$ -7.6, (*c* 0.675, CH_2Cl_2). IR, ν, cm^{-1}: 3509, 2980, 2998, 1766, 1660, 1374, 1200, 1103, 1052. ^{1}H NMR (300 MHz, $CDCl_3$), δ (*J*, Hz): 1.20 s (2'-C<u>H</u>$_3$), 1.75 s (4-C<u>H</u>$_3$), 2.15 s (6H, 2OAc), 2.20-2.46 m (4H), 2.53dd(0.5

H, *J*=1.2, 14.4 Hz, 6-CH_2), 2.63 d (0.5 H, *J*=14.4 Hz, 6-CH_2), 4.12 d (*J*=11.2 Hz), 4.15 and 4.16 s (1H, OH), 4.22 ddt (1H, *J*=11.3 Hz, CH_2O), 6.23 d (0.5 H, *J*=5.8 Hz), 6.28 d (0.5 H, *J*=5.7 Hz, 3-H) (2-H), 6.30 s (1H, $CH(OAc)_2$). ^{13}C NMR (125 MHz, $CDCl_3/CHCl_3$), δ: 15.56 (4-CH_3), 20.44 ($2CH_3CO_2$), 21.30 and 21.50 (3'-C), 26.36 and 27.06 (2-C), 38.61 and 39.12 (6-C), 41.93 and 42.18 (1-C), 72.18 and 72.22 (2-Cq), 70.86 (CH_2O), 84.48 ($CH(OAc)_2$), 135.28 and 135.44 (4-C), 144.36 and 144.91 (3-C), 164.80 and 164.82 (1″-C), 168.67 (OAc), 199.28 and 199.54 (5-C). Mass spectrum, m/z(Irel, %): 343 $[M+H+MeCN]^+$(100%). Found, %: C 56.26; H 6.55; O 37.32. $C_{16}H_{22}O_8$. Calculated, %: C 56.13; H 6.48; O 37.39. *M* 342.34.



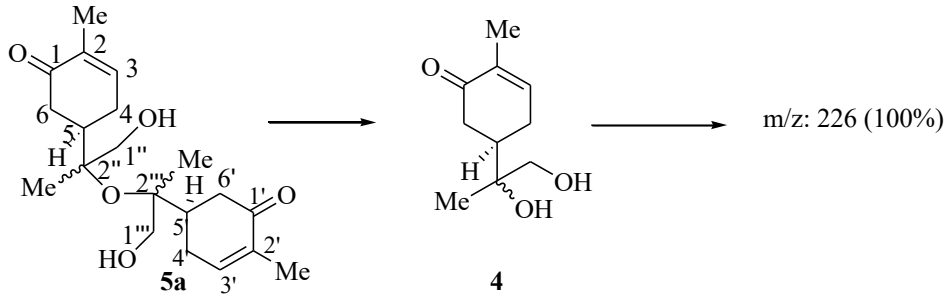
(5*R*,1'*RS*)-5-(1,2-dihydroxy-1-methylethyl)-2-methylcyclohex-2-en-1-one (4)

Potassium carbonate (0.02 g, 0.146 mmol) was added to a stirred solution of compound **2** (0.05 g, 0.146 mmol) in MeOH (5 ml). Once reactant **2** was consumed, MeOH was evaporated, then saturated solution of NH_4Cl (10 ml) and ethyl acetate were added to the residue. The organic layer was separated, and the aqueous one was extracted with ethyl acetate (3×10 ml). The combined organic extracts were dried with $MgSO_4$, filtered, evaporated and concentrated *in vacuo*. The residue was chromatographed on SiO_2 (eluent:50% EtOAc/petroleum ether) to afford 0.020 g (74%) of diol **4** as a light yellow oil, R_f (EtOAc) 0.29, $[\alpha]_D^{20}$ -10.1, (*c* 0.6, CH_2Cl_2). IR, ν, cm^{-1}: 3420, 2971, 2940, 2886, 1662, 1654, 1374, 1193, 1110, 1055. ^{1}HNMR (300 MHz, $CDCl_3$), δ (*J*, Hz): 1.14 s (3H, C<u>H</u>$_3$), 1.15 s (3H, C<u>H</u>$_3$), 1.75 s (3H, 2-C<u>H</u>$_3$), 2.20-2.70 m (5H, 2O<u>H</u>), 3.45 d (1H, *J*=10.7 Hz, C<u>H</u>$_2$O), 3.60 d (1H, *J*=10.8 Hz, C<u>H</u>$_2$O), 6.75 d (1H, *J*=5.6 Hz, 3-<u>H</u>), 6.85 d (1H, *J*=5.8 Hz, 3-<u>H</u>). ^{13}CNMR (125 MHz, $CDCl_3/CHCl_3$), δ: 14.84 (2-CH_3), 21.50 and 21.74 (1'-CH_3), 27.62 (C-4), 39.32 and 39.92 (C-5), 43.70 and 43.73 (C-5), 72.08 and 72.10 (C-2'), 81.65 and 81.78 (C-1'), 134.65 and 134.72 (C-2), 144.1 and 144.58 (C-3), 198.33 and 197.91 (C-1). Mass spectrum, m/z (Irel, %): 185 $[M+H]^+$(60%), 167 $[MH-H_2O]^+$(100%). *M* 184.23.

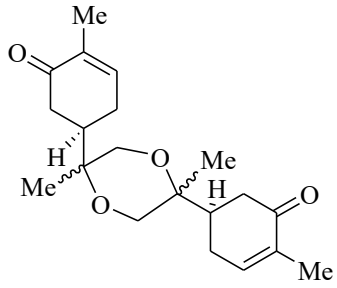


5,5'-[Oxybis(1-hydroxypropane-2,2-diyl)]-bis(2-methylcyclohex-2-en-1-one) (5a)

Yield 0.005 g (15%), colorless oily liquid, R_f (EtOAc) 0.38, $[\alpha]_D^{20}$ -27, (*c* 0.22, CH_2Cl_2). IR, ν, cm^{-1}: 3430, 2973, 2926, 2888, 1661, 1652, 1456, 1373, 1050. ^{1}HNMR (500 MHz, $CDCl_3$), δ (*J*, Hz): 1.13 s (6H, 2C<u>H</u>$_3$), 1.68 s (6H, 2C<u>H</u>$_3$), 2.20-2.60 m (1H, 5-<u>H</u>,), 3.35 d (1H, *J*=1.9 Hz), 3.45 m (C<u>H</u>$_2$O), 3.75-3.80 m (2H, 6-<u>H</u>), 6.82 d (1H, *J*=6.2 Hz, 3-<u>H</u>, 3'-<u>H</u>), 6.78 d (1H, *J*=6.2 Hz, 3-<u>H</u>, 3'-<u>H</u>). ^{13}CNMR (125 MHz, $CDCl_3$/$CHCl_3$), δ: 15.71 ($2CH_3$), 21.58 (CH_3) and 21.78 (CH_3), 39.53 and 40.20 (C-4 and C-4'), 42.64 and 43.57 (C-6 and C-6'), 68.54 and 68.61 ($2CH_2O$), 73.39 q(C-2'' and C-2'''), 135.34 and 135.45 (C-2 and C-2'), 145.49 and 146.00 (C-3 and C-3'), 199.61 and 199.97 (CO). Mass spectrum, m/z (Irel, %): 185 [**4**+H]$^+$ (85%), 226 [**4**+H+MeCN]$^+$(100%). *M* 350.45. No molecular ion is observed. Decomposition of **5a** to diol **4** occurs.



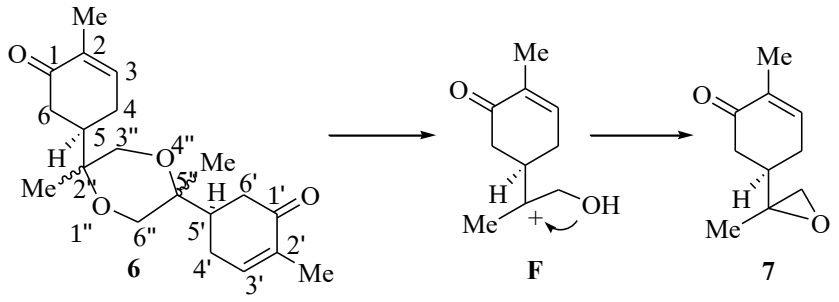
Scheme S1



5,5'-(2,5-Dimethyl-1,4-dioxane-2,5-diyl)-bis(2-methylcyclohex-2,5-en-1-one) (6)

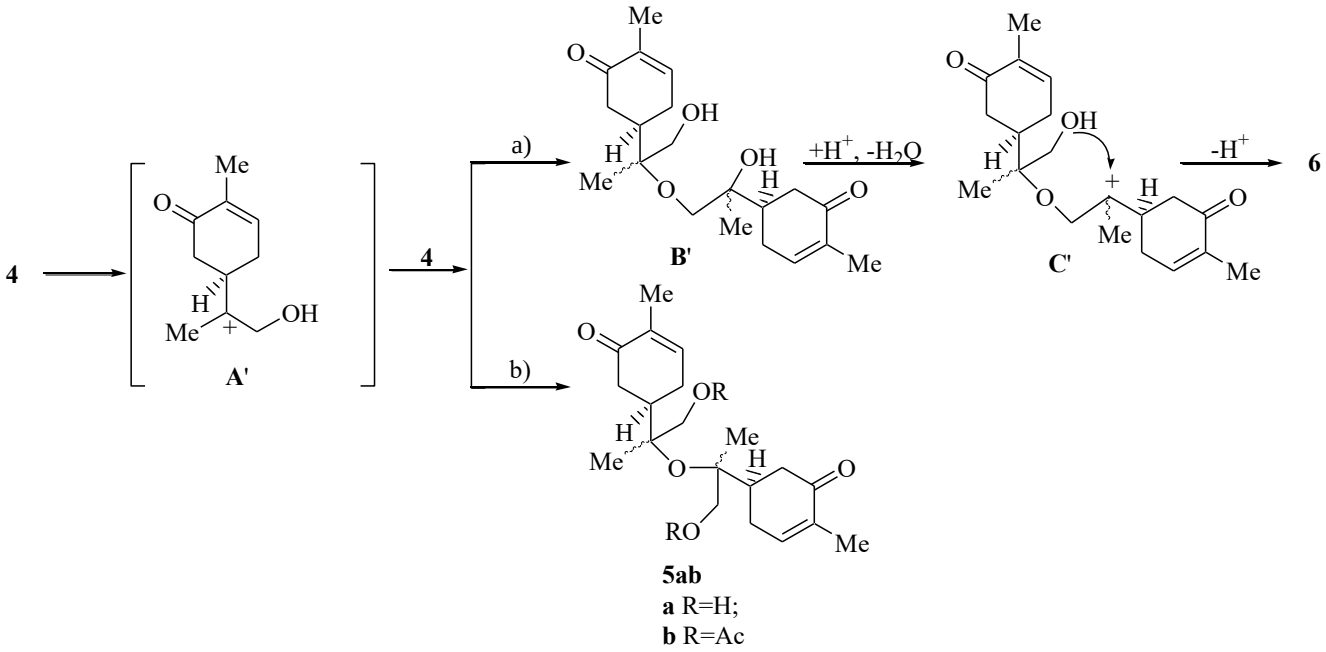
Yield 0.017 g (53%), colorless oily liquid, R_f (EtOAc) 0.44, $[\alpha]_D^{20}$ -25.8, (*c* 0.74, CH_2Cl_2). IR, ν, cm^{-1}: 2977, 2925, 2887, 2875, 2739, 1676, 1451, 1380, 1252, 1205, 1080, 1039, 1031. ^{1}HNMR (500 MHz, $CDCl_3$), δ (*J*, Hz): 1.23 s (3H, C<u>H</u>$_3$), 1.27 s (3H, C<u>H</u>$_3$), 1.68 s (6H, 2-C<u>H</u>$_3$), 2.15-2.27m (6H), 2.33-2.40m (2H), 2.45-2.52m (2H), 4.70 d (2H, *J*=8.7 Hz, C<u>H</u>$_2$O), 4.94 dd (2H, *J*=8.7, 3.7 Hz, C<u>H</u>$_2$O), 6.79 d (1H, *J*=6.2 Hz, 3-<u>H</u>), 6.81 d (1H, *J*=6.3 Hz, 3-<u>H</u>). ^{13}CNMR (125 MHz, $CDCl_3$/$CHCl_3$), δ: 14.82 (2-CH_3, 2'-CH_3), 21.49 and 21.73 (2''-CH_3), 27.14 and 27.61 (C-4, C-4'), 39.32 and 39.93 (C-5, C-5'),

43.73 and 43.76 (C-6, C-6'), 72.11 and 72.10 (CH_2O), 81.77 q and 81.65 q (C-2", C-5"), 134.65 and 134.73 (C-2, C-2'), 144.01 and 144.49 (C-3, C-3'), 197.73 and 197.80 (CO). Mass spectrum, m/z (Irel, %): 167 $[M+H]^+$ 40% (B), 208 $[M+H+MeCN]^+$(100%). *M* 332.43. No molecular ion is observed. Molecule **6** is decomposed by the scheme below *via* carbonium ion **F** to give **7**.

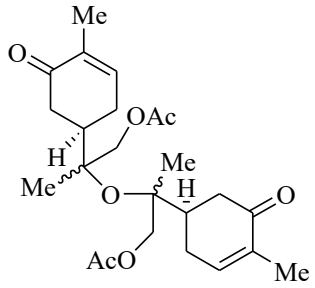


Scheme S2

The possible pathways for the formation of 5a and 6 from diol 4 in the $CDCl_3$-HCl (cat.) medium. Here the carbocation **A'** that is generated can trap one of the hydroxy groups of diol **4**. In the case (a), the cationic center in **A'** attacks the more accessible primary hydroxyl **4**, tertiary carbocation **C'** is generated again in the resulting diol **B'**, and intramolecular cyclo-closure in **C'** gives **6**. Hindered pathway (b) gives minor symmetric diol **5a**.



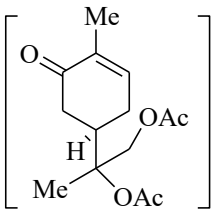
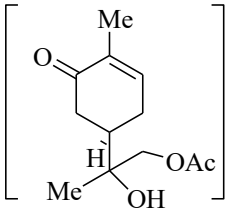
Scheme S3

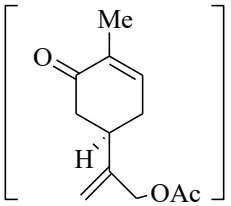
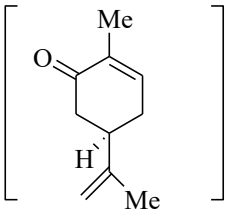


(1*R*')-Oxybis[2-*RS*-(4-methyl-5-oxocyclohex-3-en-1-yl)-propane-2,1-diyl] diacetate (5b)

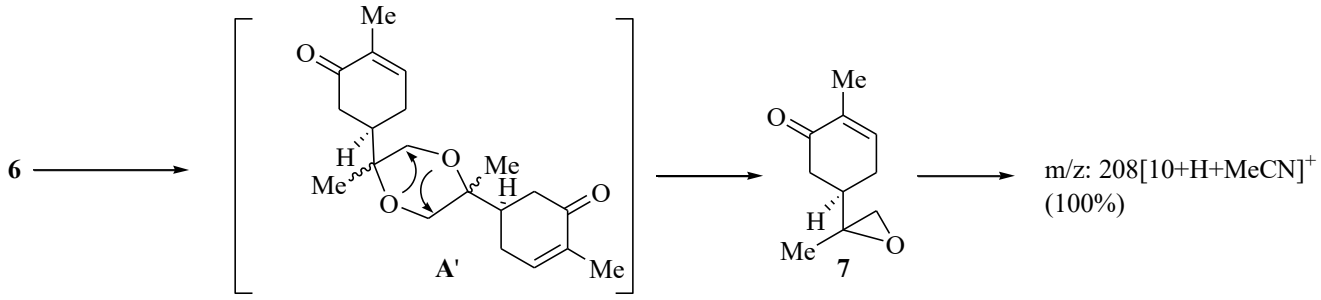
Triethylamine (0.0013 g, 0.0094 mmol) was added to a stirred solution of compound **5a** (0.0044 g, 0.012 mmol) in anhydrous CH_2Cl_2 (3 ml). The mixture was stirred for 10 min, then acetyl chloride (0.0018 ml, 0.026 mmol) was added. The mixture was stirred until the starting compound was consumed, then washed with a saturated NaCl solution, dried with $MgSO_4$, filtered and concentrated. The residue was chromatographed on SiO_2 (eluent: 50% EtOAc/petroleum ether). Yield 0.004 g (61%), colorless oily liquid, Rf (EtOAc) 0.48, $[\alpha]_D^{20}$ -15, (*c* 0.12, CH_2Cl_2). IR, ν, cm^{-1}: 3461, 3446, 2954, 2925, 2849, 1738, 1667, 1372, 1242, 1043. ^{1}H NMR (500 MHz, $CDCl_3$), δ (*J*, Hz): 1.20 s (6H, 2-C$\underline{H}_3$), 1.60 broad (1H, H_2O), 1.80 s (6H, 4'-C$\underline{H}_3$), 1.90 broad (1H, H_2O), 2.10 s (6H, 2OAc), 2.25-2.50 (2H), 2.55 d (1H, *J*=12.4 Hz), 2.65 d (1H, *J*=14.7 Hz), 4.00 d (1H, ^2J=11.4 Hz, H_A-CH_2), 4.02 d (1H, ^2J=11.4 Hz, $\underline{H}_A$-CH_2), 4.06 d (1H, ^2J=11.4 Hz, $\underline{H}_B$-CH_2), 4.00 d (1H, ^2J=11.4 Hz, $\underline{H}_B$-CH_2). ^{13}C NMR (125 MHz, $CDCl_3$/$CHCl_3$), δ: 15.61 (CH_3), 20.85 (CH_3), 21.38 (CH_3), 21.46 (CH_3), 26.40 (CH_2), 27.19 (CH_2), 38.68 (CH_2), 39.35 (CH_2), 41.90 (C-1'), 42.22 (C-1'), 69.40 and 69.48 (CH_2O), 72.36q and 72.44q (C-2), 171.01 and 171.09 (CO_2), 199.30 and 199.56 (CO). Found, %: s 66.42; H7.94; O 25.68. $C_{24}H_{34}O_7$. Calculated, %: s 66.34; H 7.89; O 25.77. *M* 434.

Diacetate **5b** gives a molecular ion. Subsequent decomposition gives fragment ions.

5b → 453 $[M+H_2O+H]^+$(5%), 350[**6**+H_2O](27%), 268  (100%), 227  (60%),

209  (85%), 148  (30%)

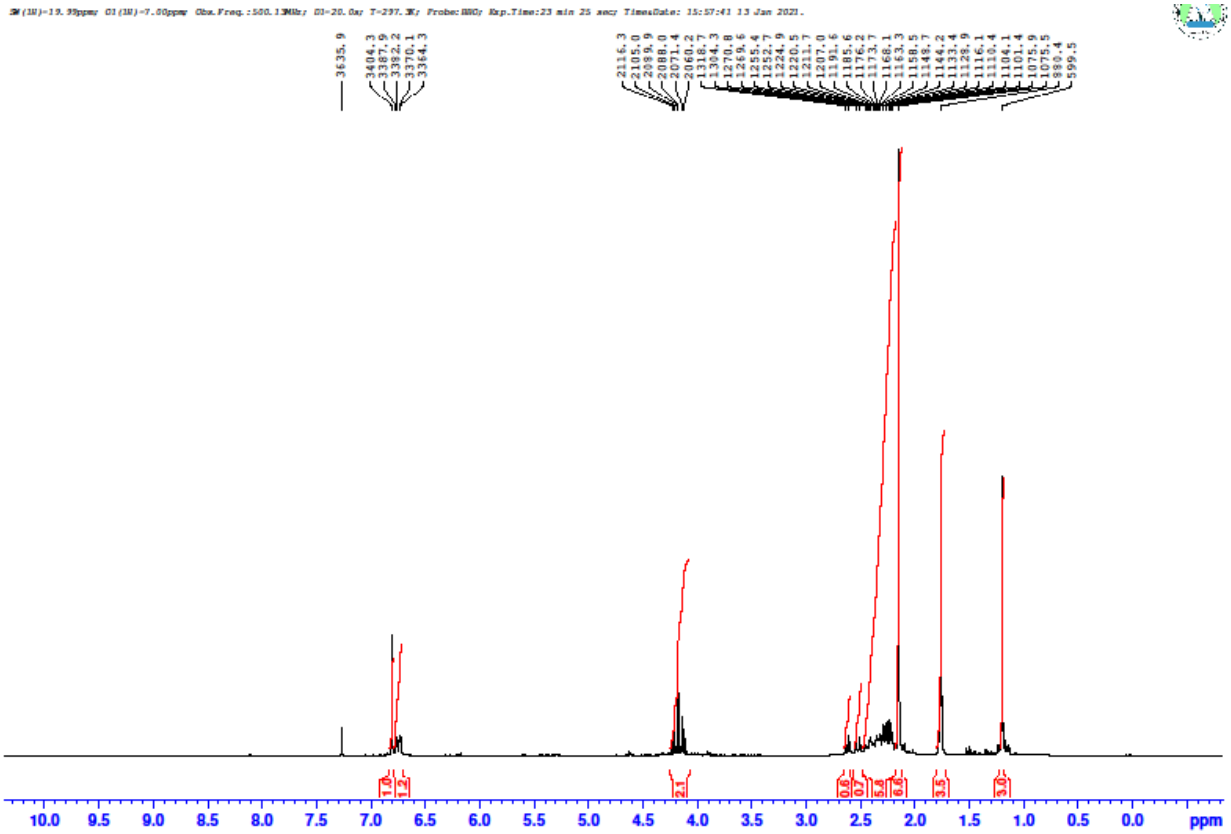
Of interest are the decomposition channels of molecules **4**-**6** in the mass spectra (Scheme S3). No molecular ions are observed in the case of **5a** and **6**. In the case of **5a**, hydration-fragmentation gives a stable molecule of diol **4**, which also gives a molecular ion with m/z: [**4**+H+MeCN]$^+$(100%). The resonance capture of an electron by molecule **4** initiates a disproportionation reaction (see A'). The resulting epoxide **7** adds a proton and MeCN to give molecular ion [**5b**+H+MeCN]$^+$ (100%). The mass spectrum of diacetate **5b** contains a low-intensity molecular ion peak.

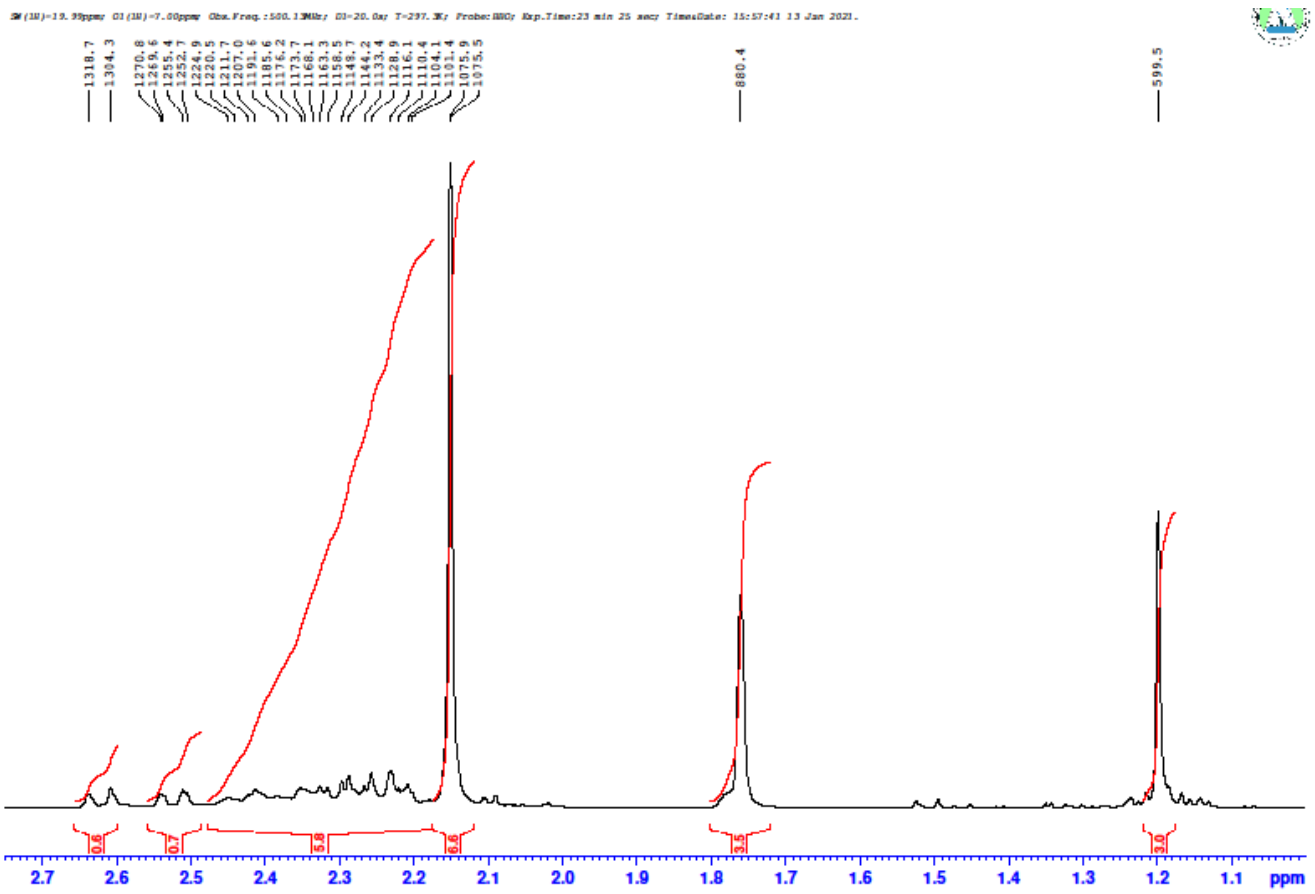


Scheme S4

(2*RS*)-2-Hydroxy-2-[(1*S*)-4-methyl-5-oxocyclohex-3-en-1-yl]prop-1-yl bis(acetoxy)acetate (2)

^{1}H NMR

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1168.1
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1144.2
1133.4
1128.9
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1110.4
1104.1
1101.4
1075.9
1075.5
880.4
599.5
0.6
0.7
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6.6
3.5
3.0
2.7
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2.4
2.3
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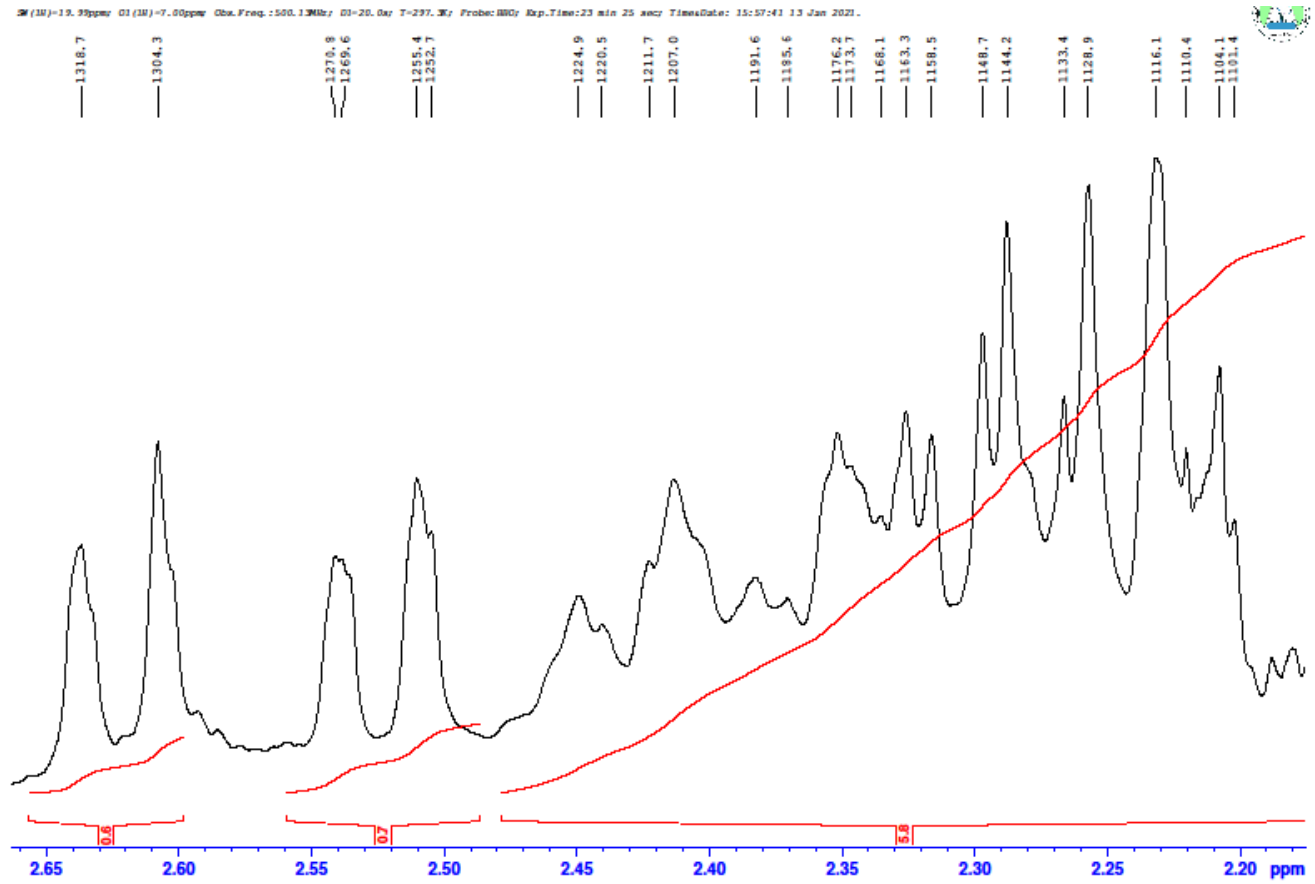
1.4
1.3
1.2
1.1
ppm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1269.6
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1185.6
1176.2
1173.7
1168.1
1163.3
1158.5
1148.7
1144.2
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1116.1
1110.4
1104.1
1101.4
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2.25
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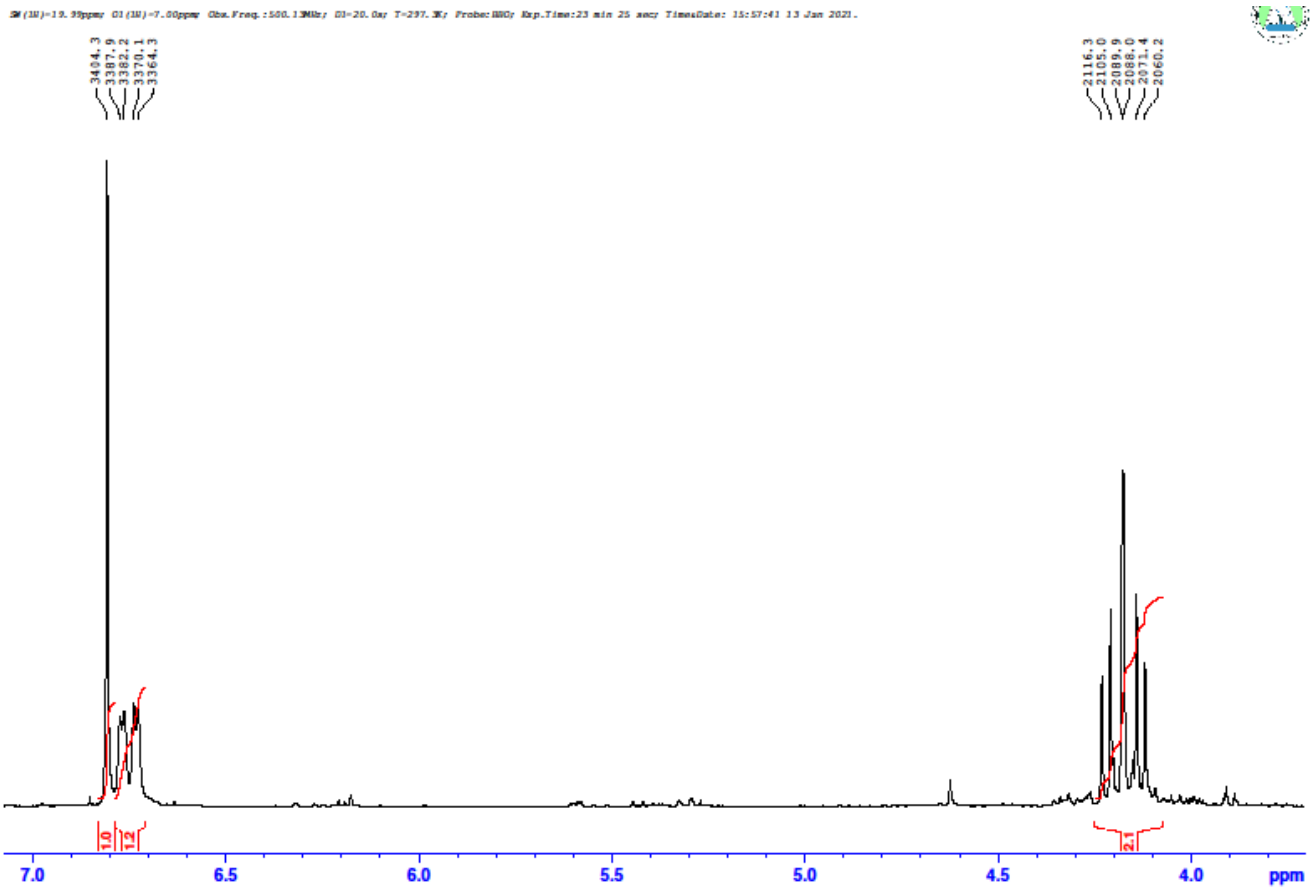
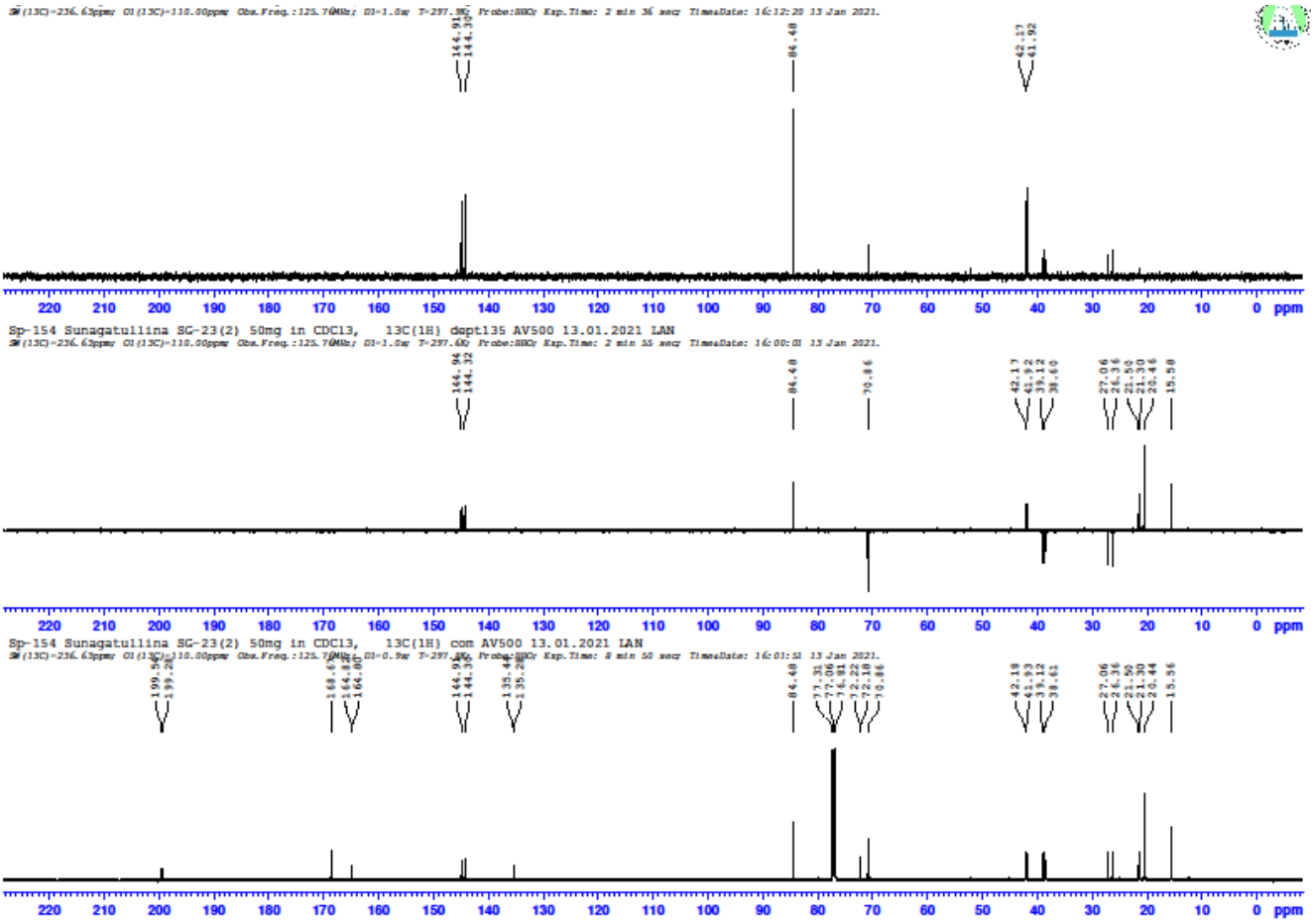
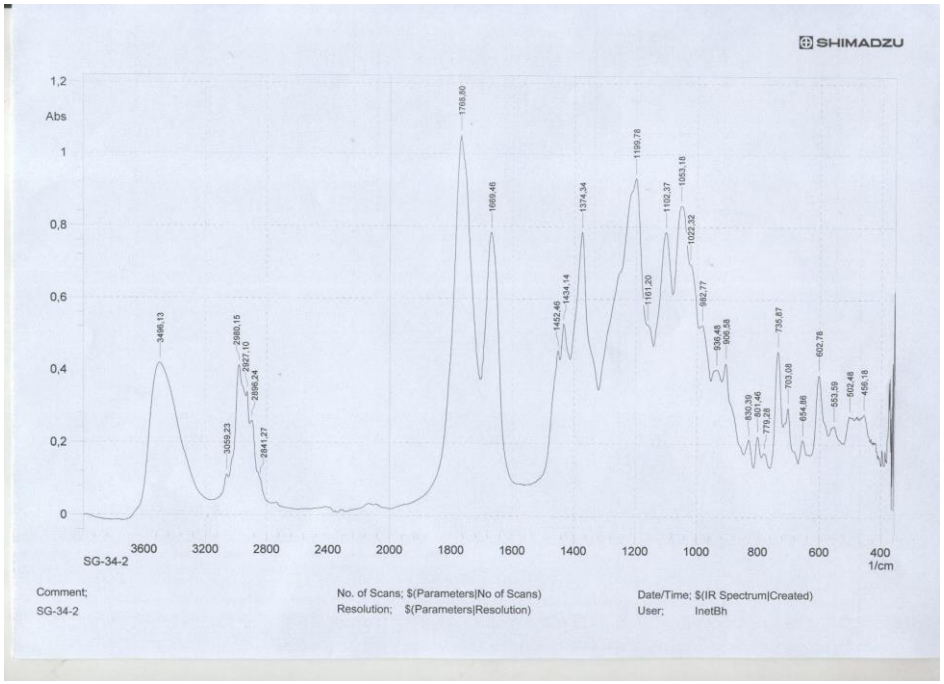
ppm



^{13}C NMR



IR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1768.80
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1434.14
1374.34
1199.78
1161.20
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992.77
936.48
906.58
830.39
801.46
770.26
735.87
703.08
654.86
602.76
583.59
502.48
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3200
2800
2400
2000
1800
1600
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1200
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800
600
400
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Date/Time; $(IR Spectrum|Created)
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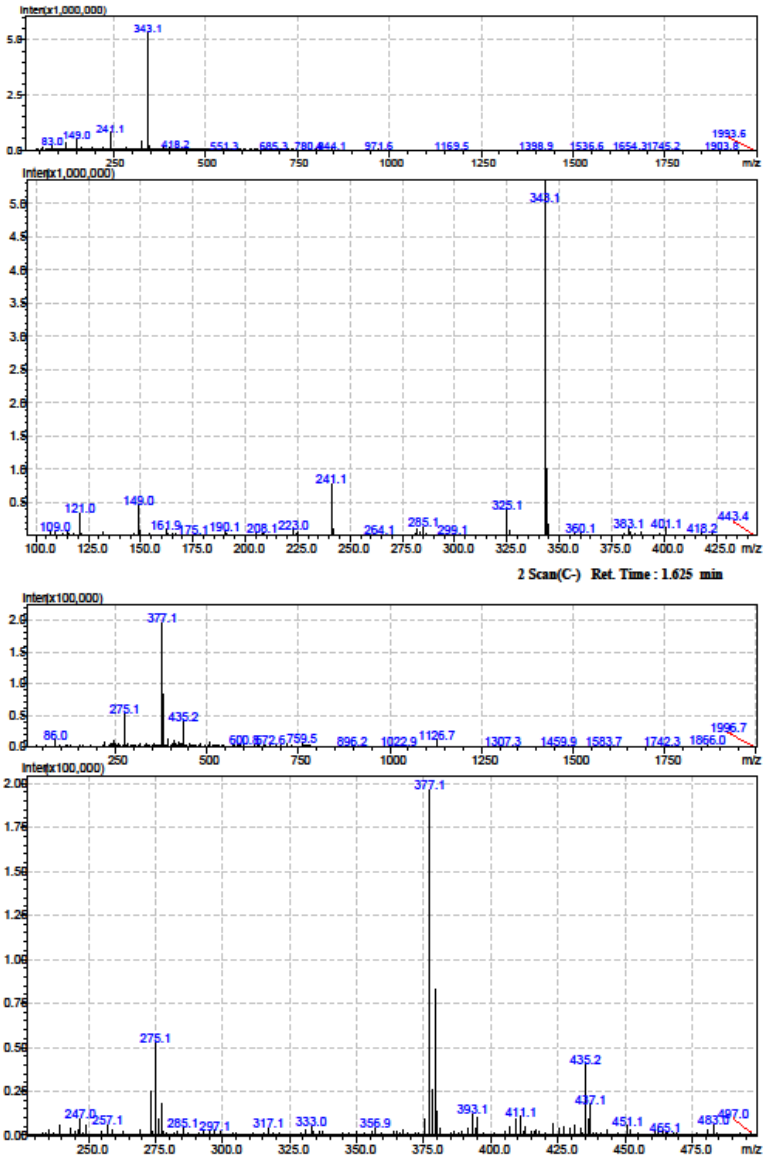
Mass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149.0
241.1
418.2
551.3
685.3
780.4
844.1
971.6
1169.5
1398.9
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1654.3
1745.2
1903.6
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m/z
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149.0
109.0
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175.1
190.1
208.1
223.0
264.1
285.1
299.1
325.1
360.1
383.1
401.1
418.2
443.4
m/z
2 Scan(C-) Ret. Time : 1.625 min
Inten(x100,000)
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275.1
435.2
86.0
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672.6
759.5
896.2
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411.1
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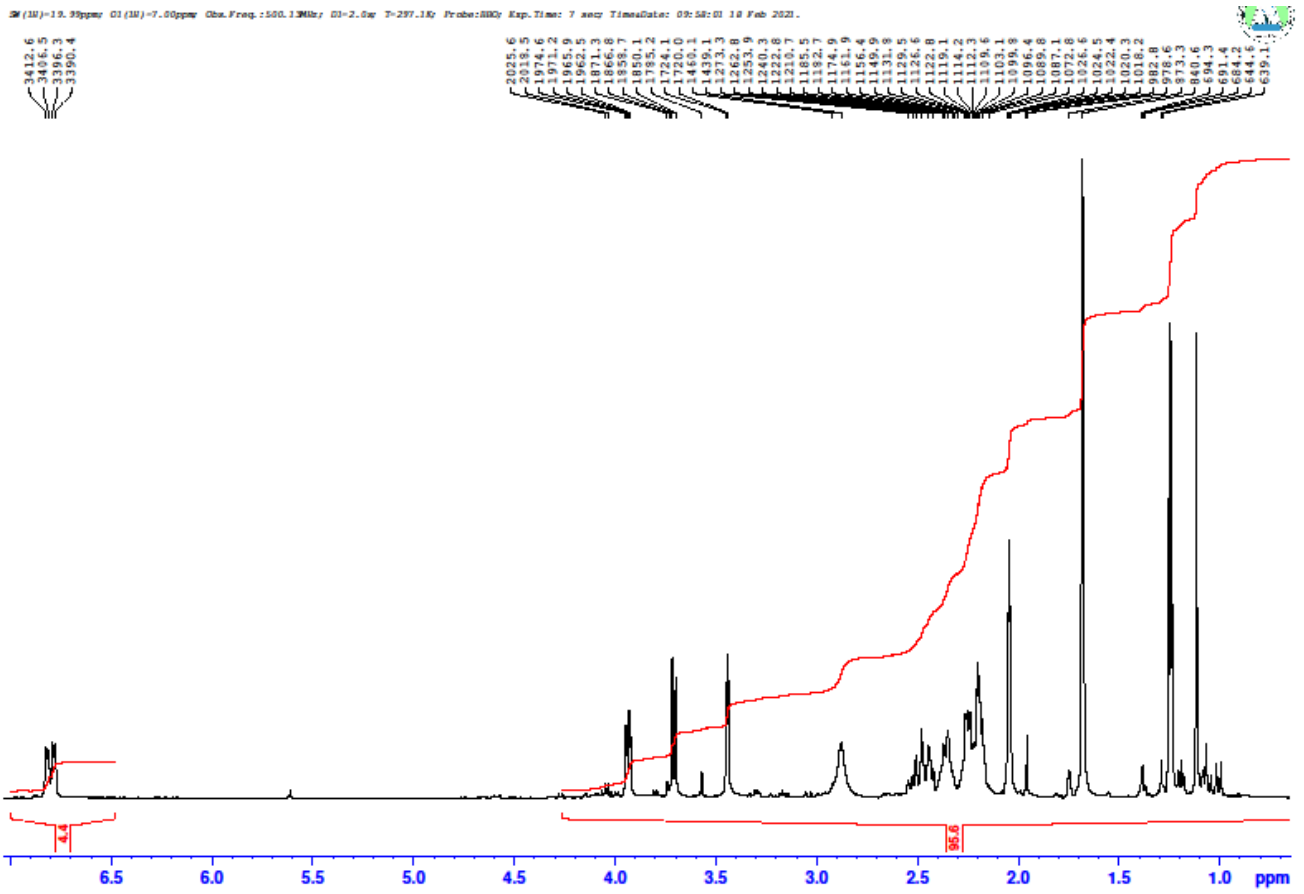
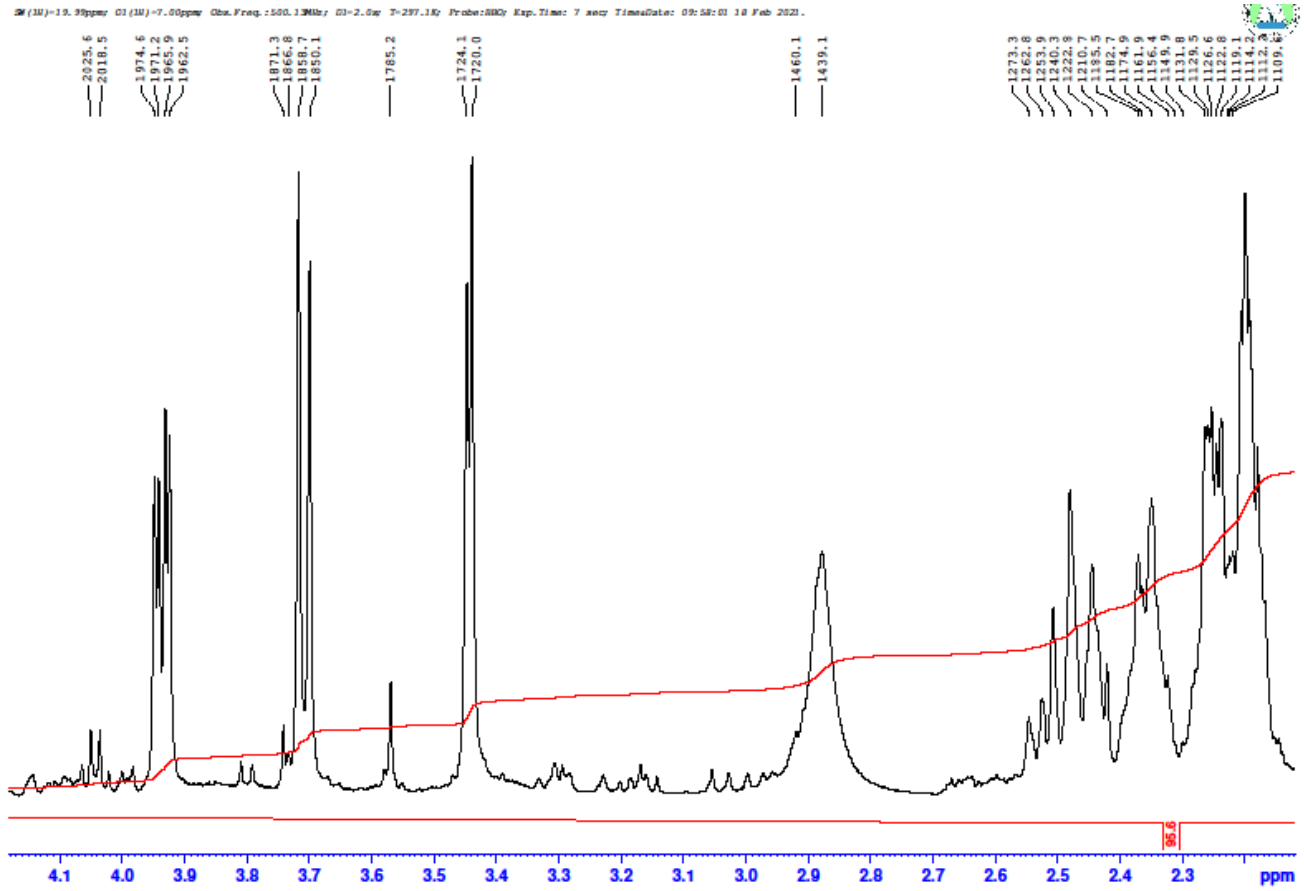
465.1
483.0
497.0
m/z

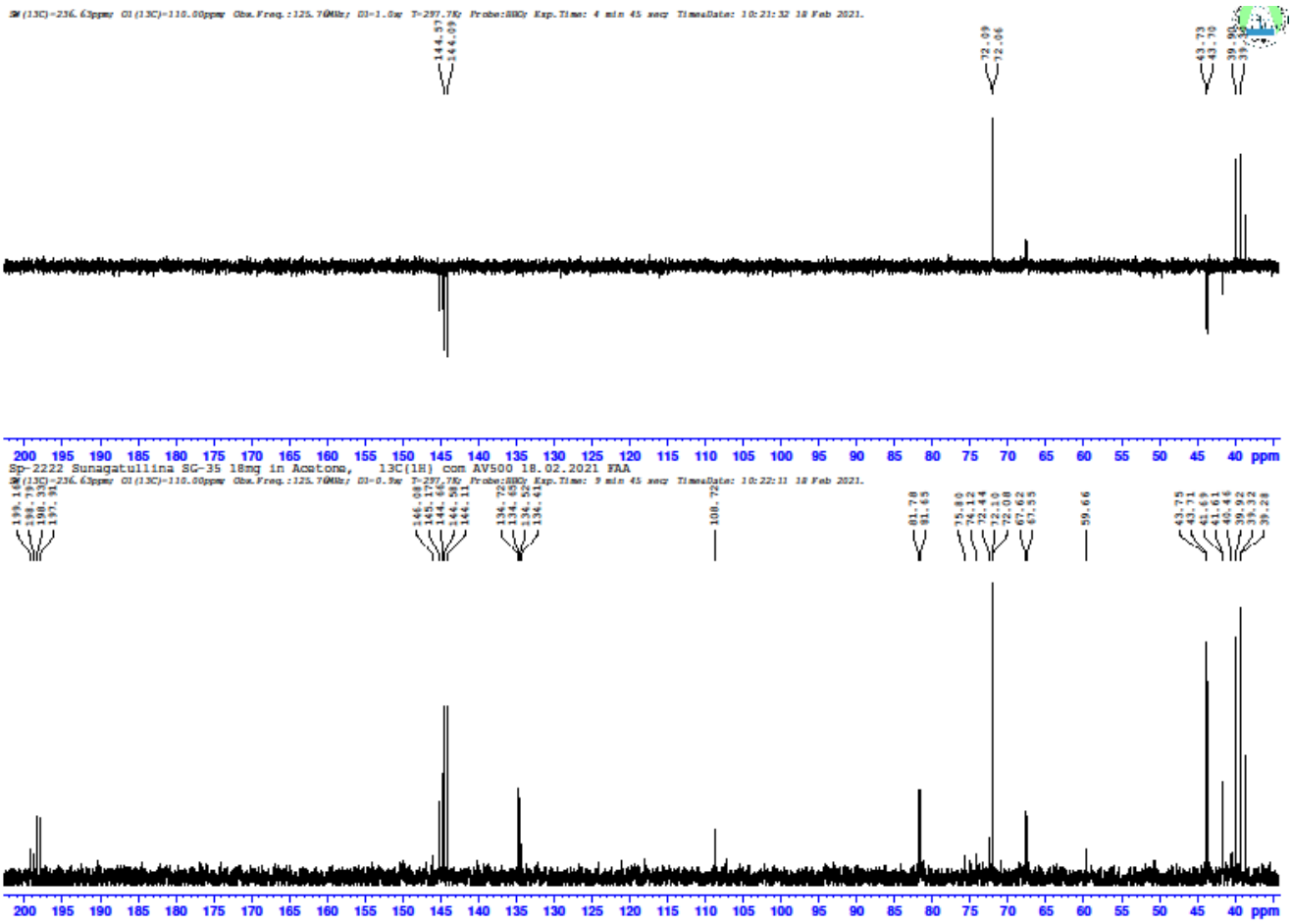
(5*R*,1'*RS*)5-(1,2-Dihydroxy-1-methylethyl)-2-methylcyclohex-2-en-1-one (4)

^{1}H NMR

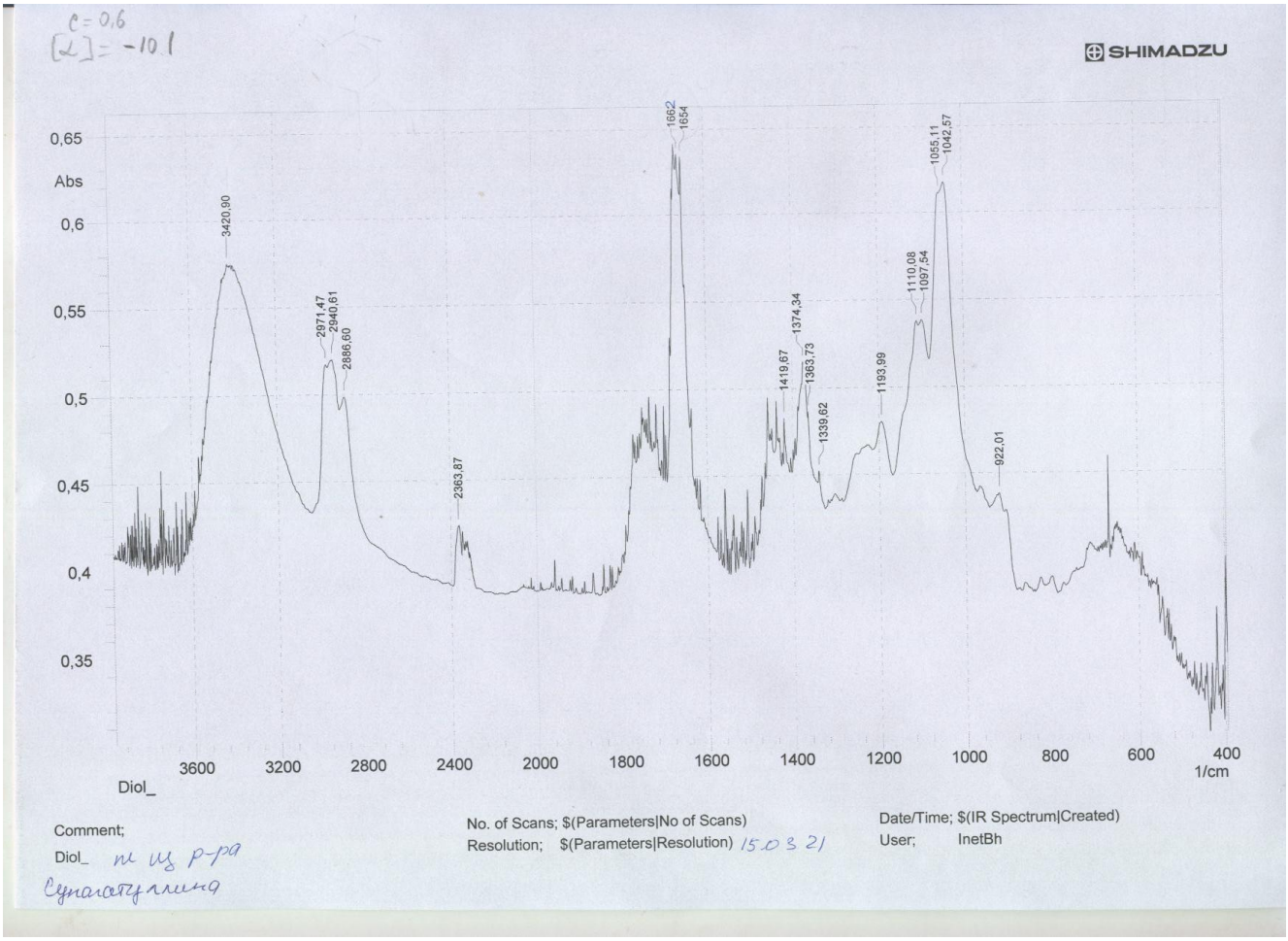




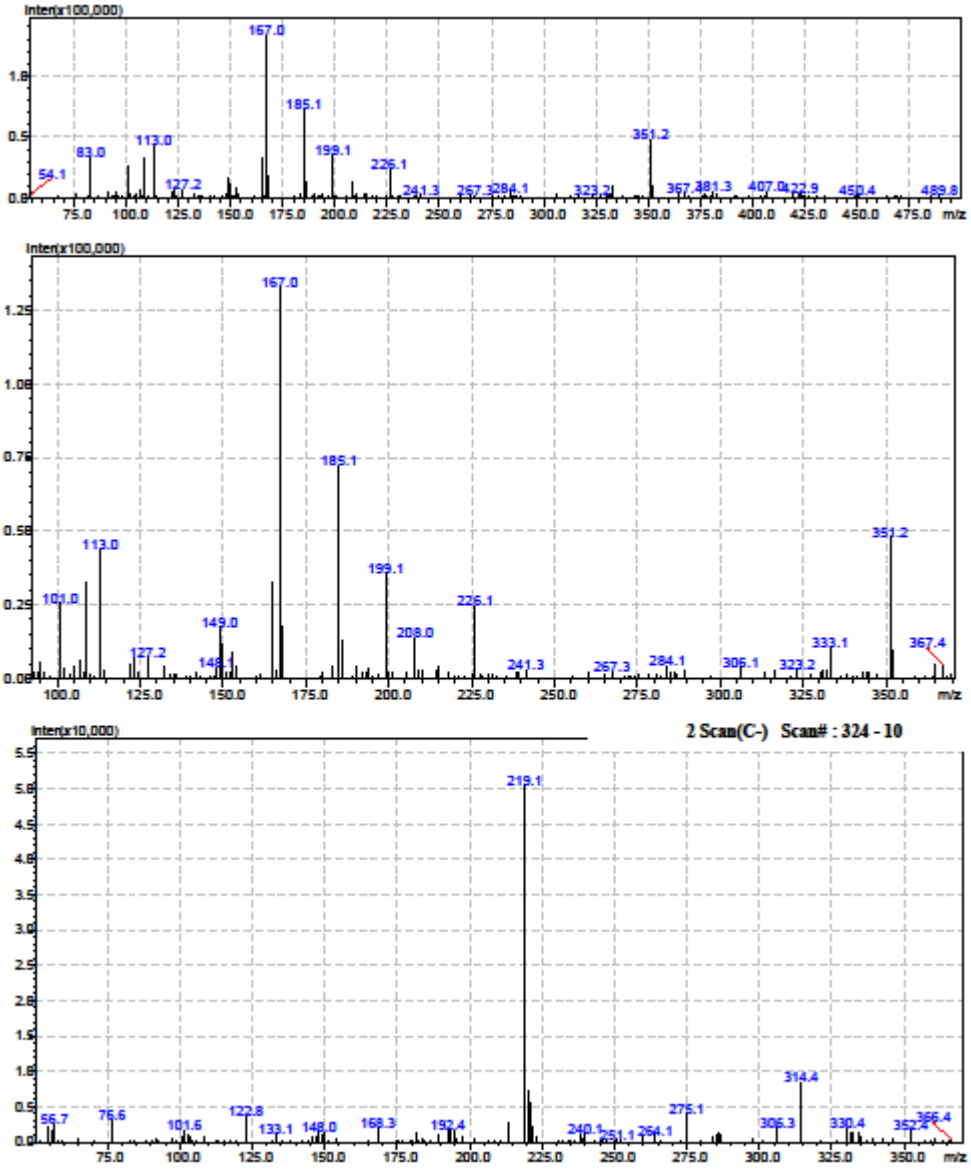
^{13}C NMR


Sp-2222 Sunagatullina SG-35 18mg in Acetone, 13C(1H) com AV500 18.02.2021 FAA

IR

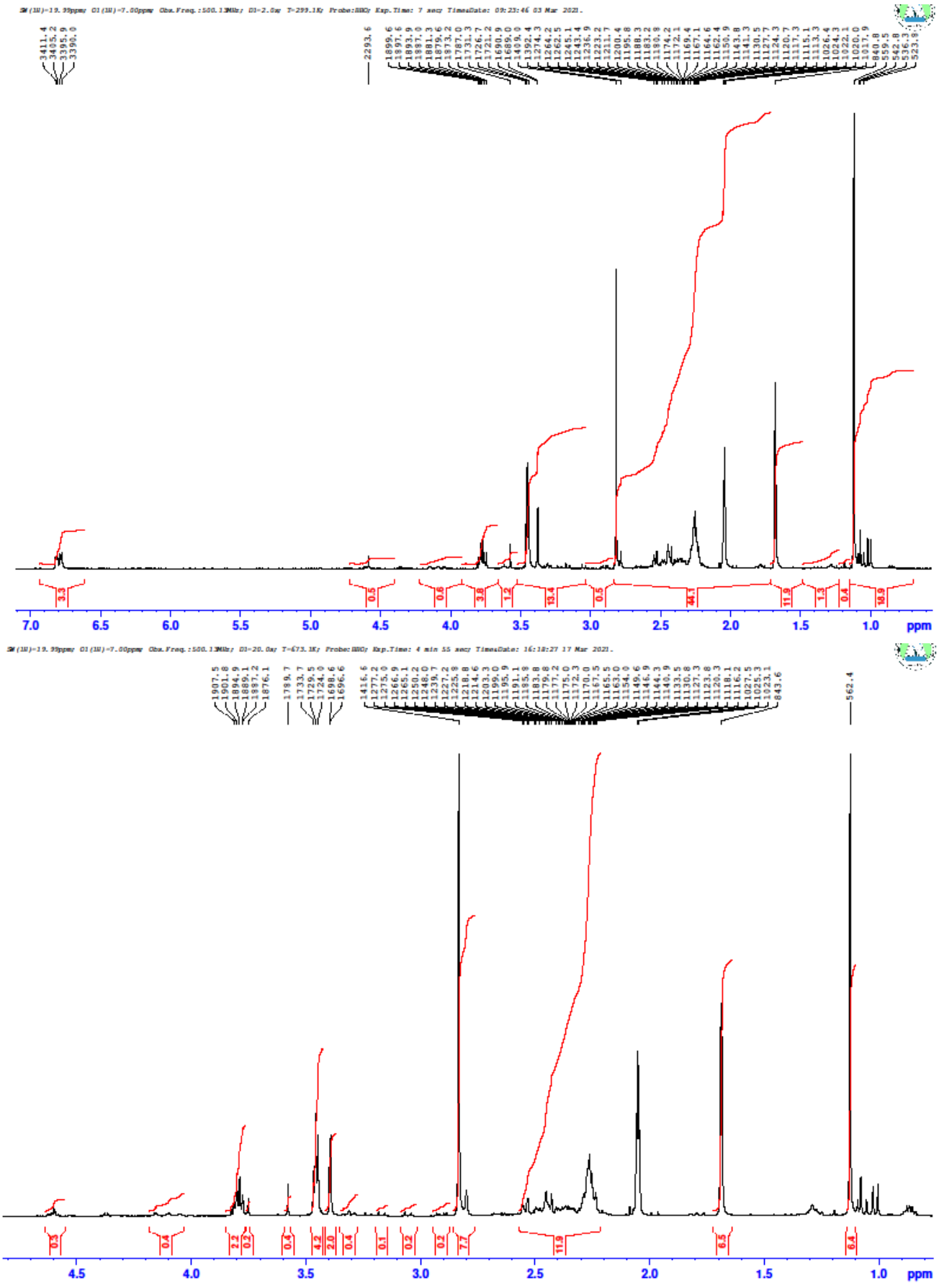

c = 0,6
[α] = -10,1
SHIMADZU
Abs
3420,90
2971,47
2940,61
2886,60
2363,87
1662
1654
1419,67
1374,34
1363,73
1339,62
1193,99
1110,08
1097,54
1055,11
1042,57
922,01
1/cm
Diol_
Comment;
Diol_ в ИЦ р-ра
Сунагатуллина
No. of Scans; $(Parameters|No of Scans)
Resolution; $(Parameters|Resolution) 15.03.21
Date/Time; $(IR Spectrum|Created)
User; InetBh

Mass

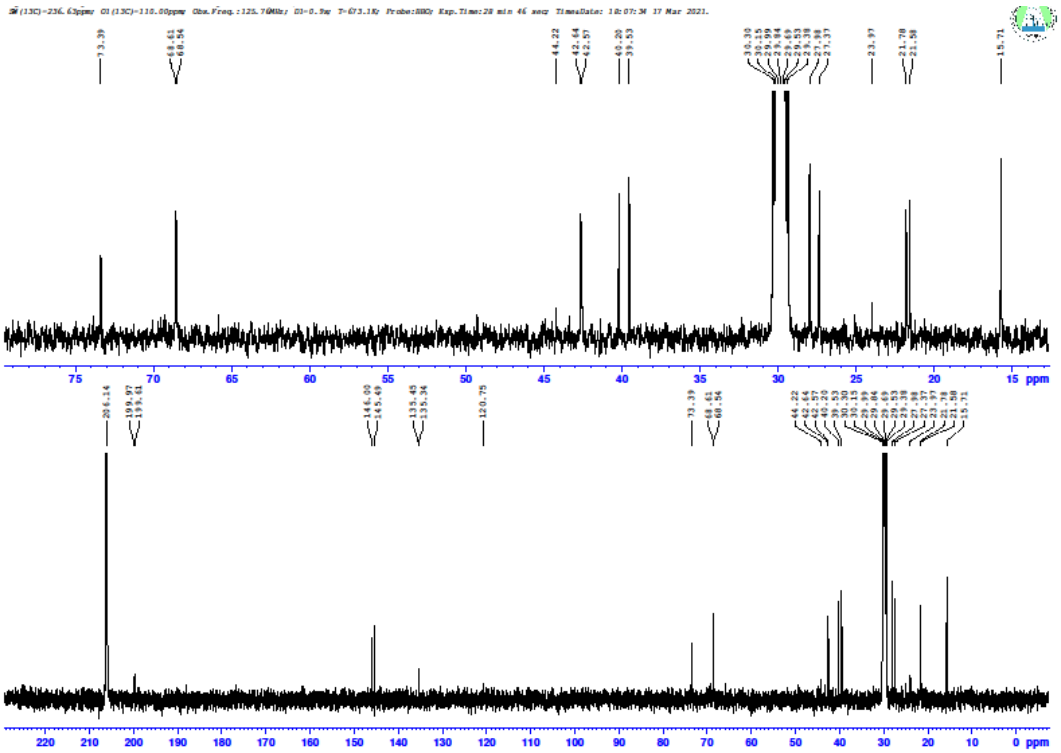

Inten(x100,000)
167.0
185.1
113.0
83.0
199.1
351.2
54.1
127.2
226.1
Inten(x100,000)
167.0
185.1
113.0
199.1
351.2
101.0
149.0
226.1
208.0
127.2
333.1
367.4
Inten(x10,000)
2 Scan(C-) Scan# : 324 - 10
219.1
314.4
56.7
76.6
101.6
122.8
133.1
148.0
168.3
192.4
275.1
305.3
330.4
366.4
m/z

5,5'-[Oxybis(1-hydroxypropane-2,2-diyl)]bis(2-methylcyclohex-2-en-1-one) (5a)

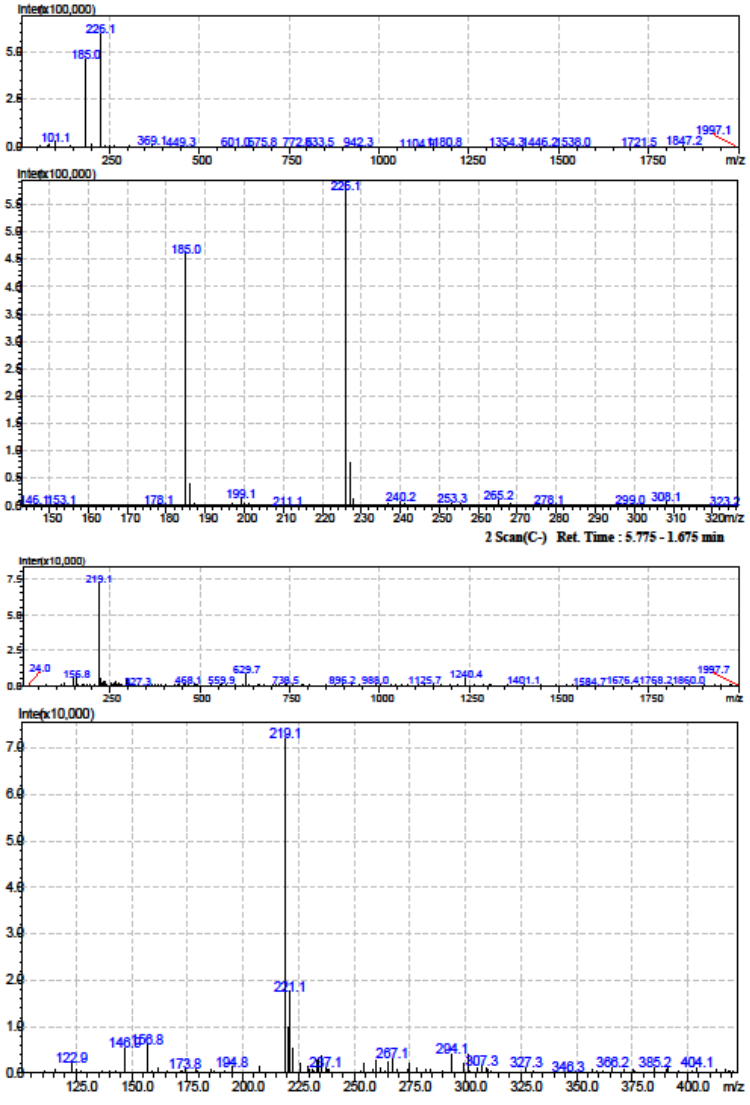
^{1}H NMR



^{13}C NMR

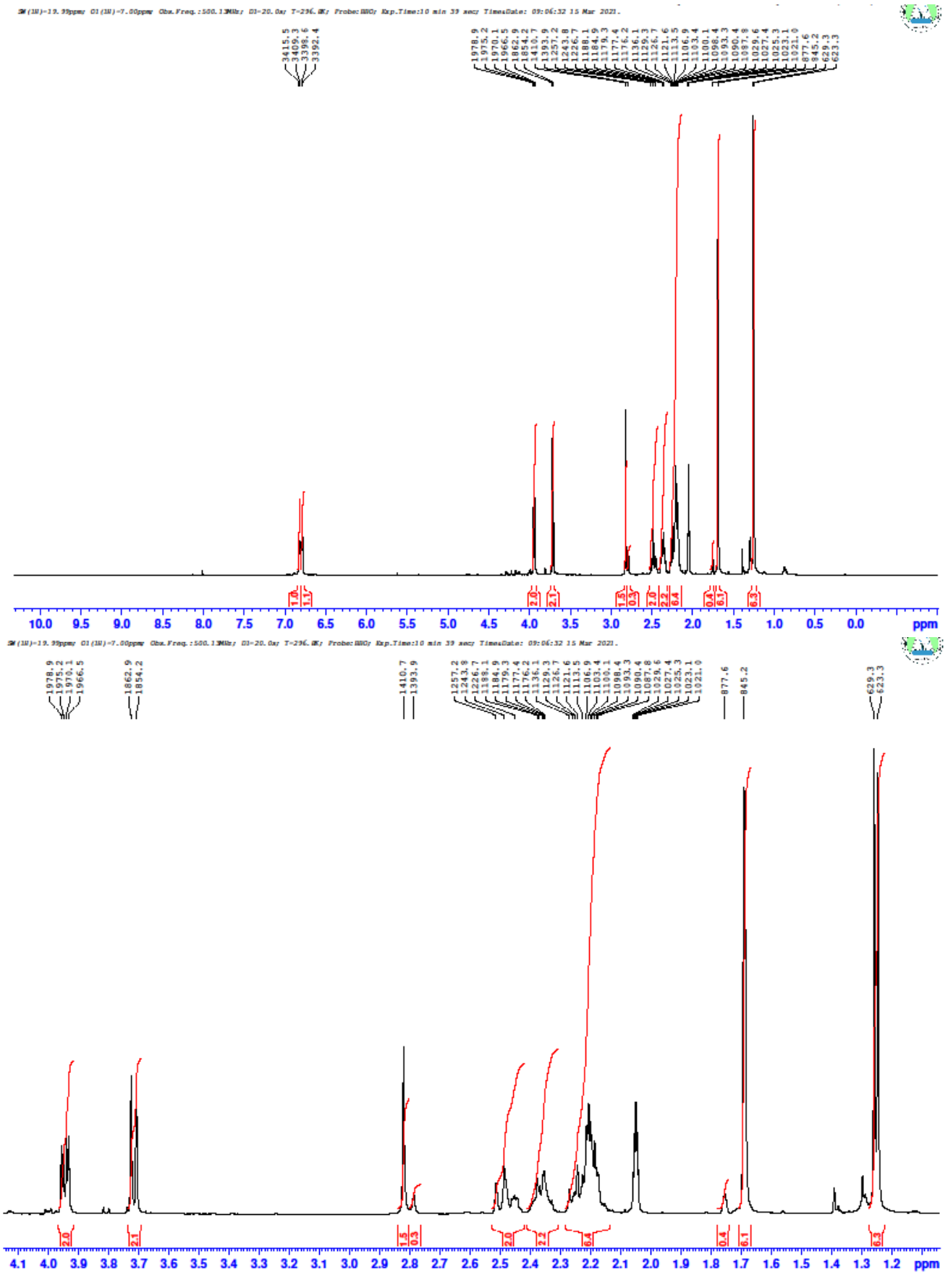


Mass

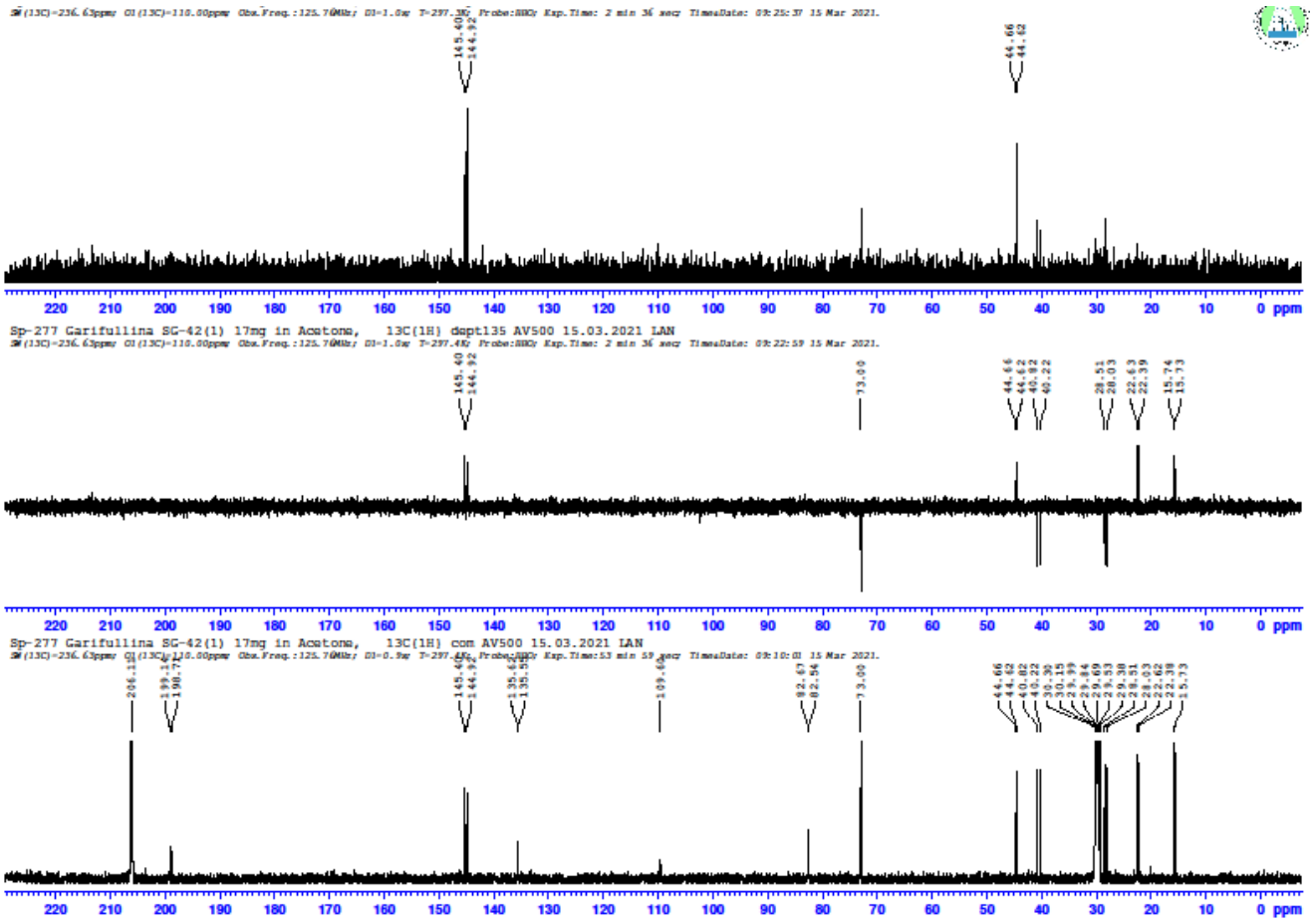


5,5'-(2,5-Dimethyl-1,4-dioxane-2,5-diyl)bis(2-methylcyclohex-2,5-en-1-one) (6)

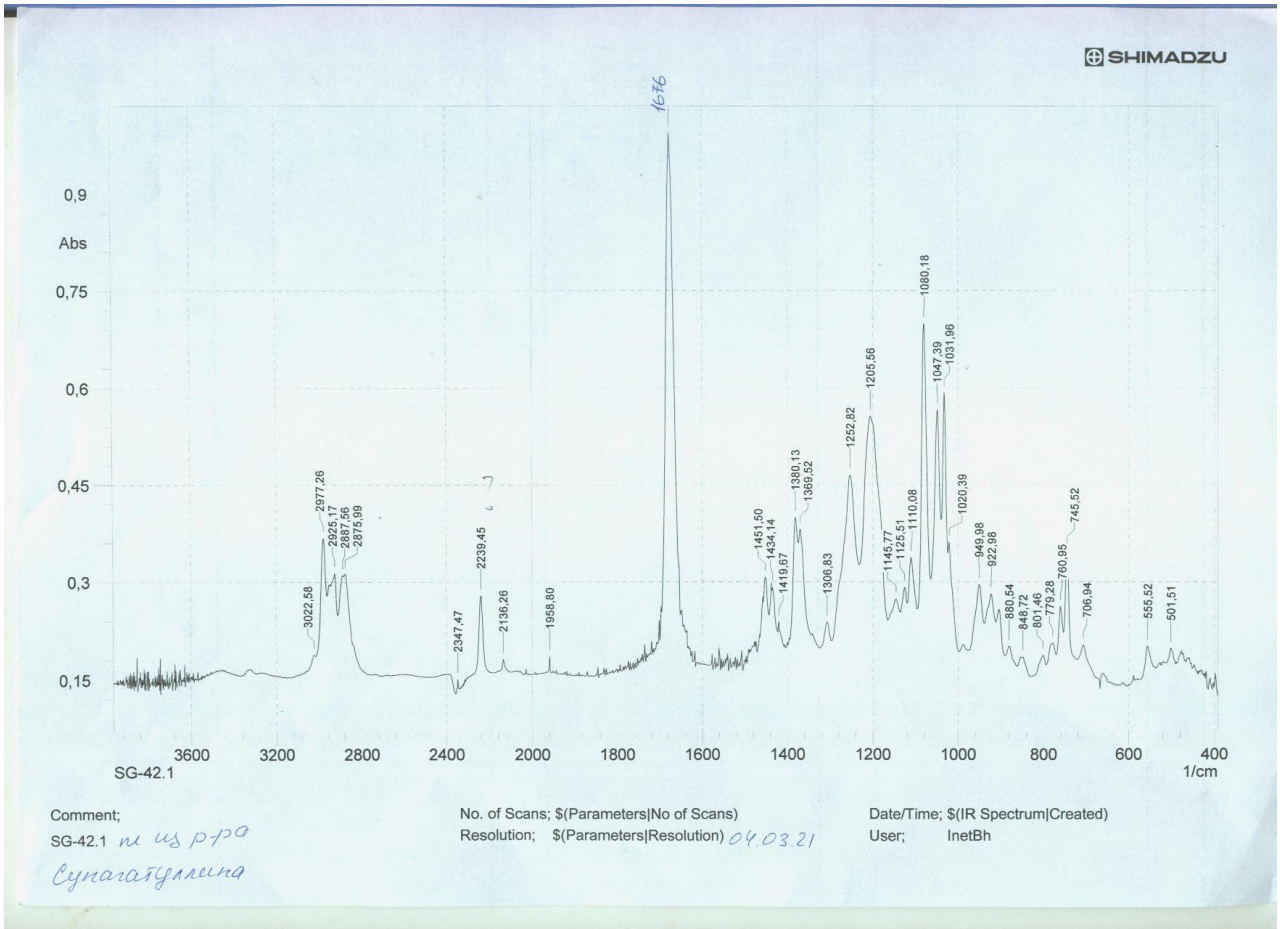
^{1}H NMR



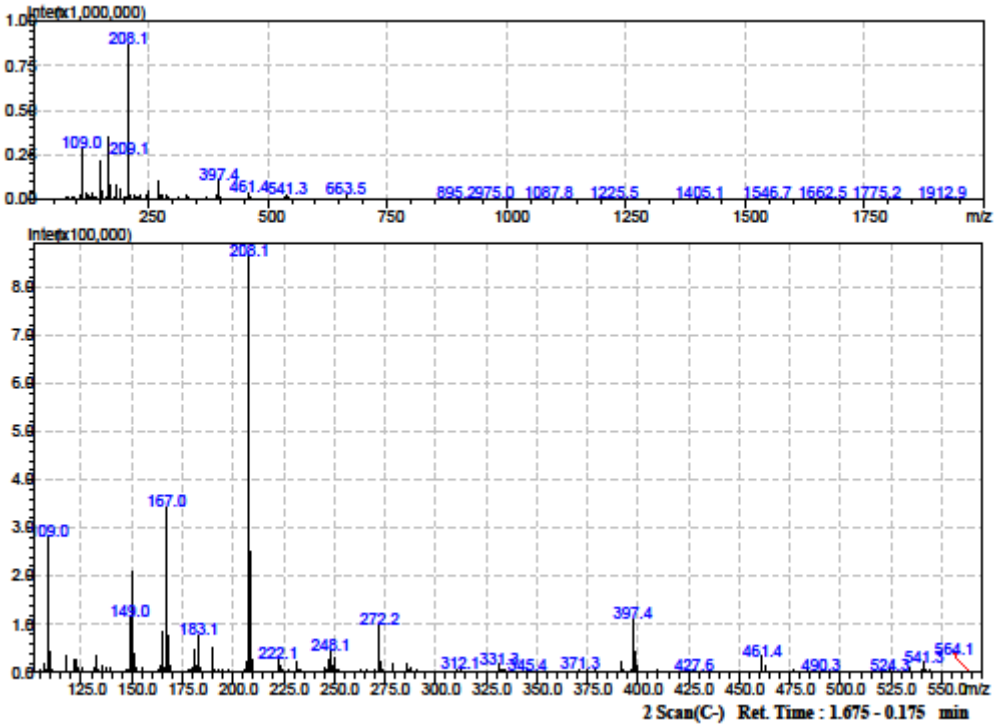
^{13}C NMR


Sp-277 Garifullina SG-42(1) 17mg in Acetona, 13C{1H} dept135 AV500 15.03.2021 LAN
Sp-277 Garifullina SG-42(1) 17mg in Acetona, 13C{1H} com AV500 15.03.2021 LAN
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

IR

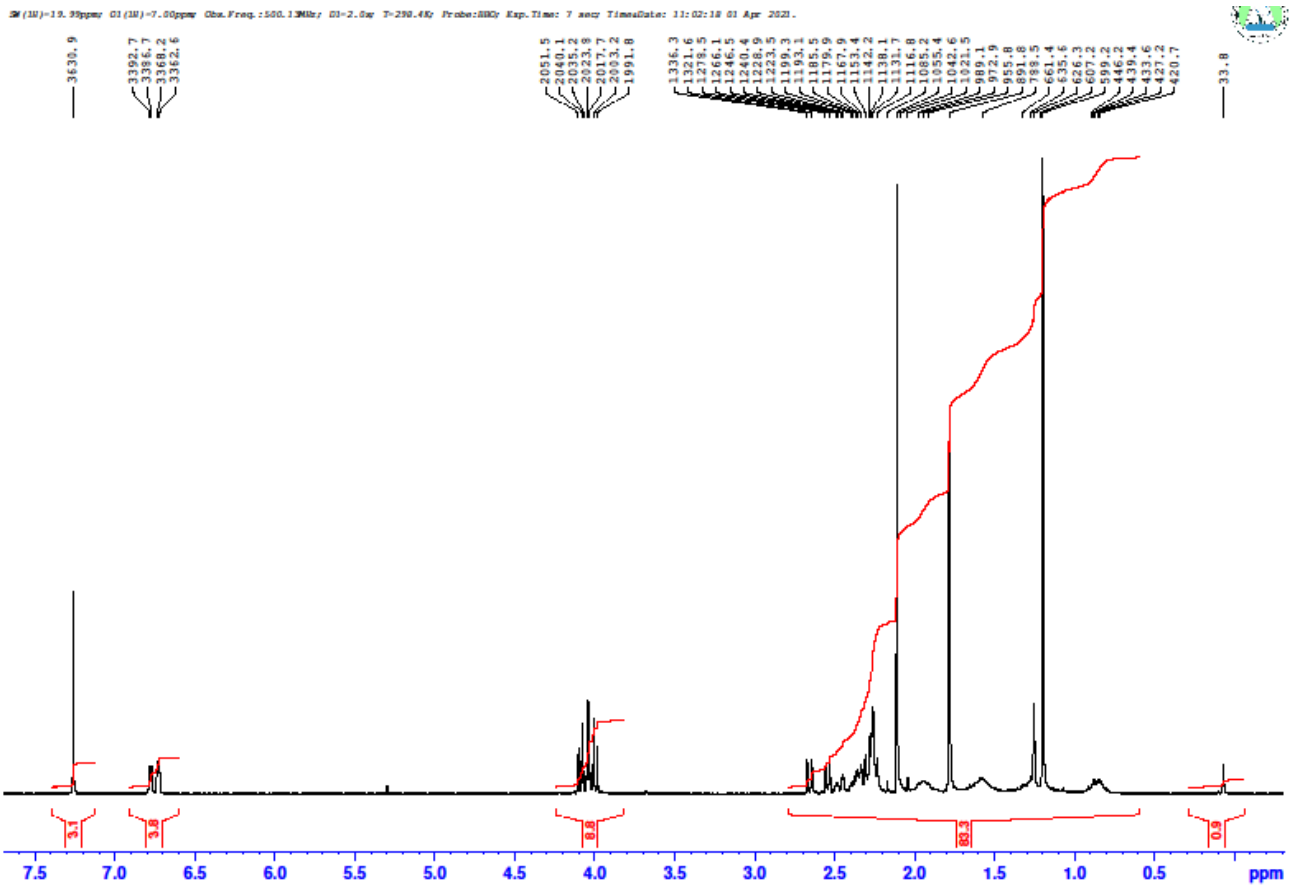

SHIMADZU
Abs
0,9
0,75
0,6
0,45
0,3
0,15
3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
1/cm
SG-42.1
1676
2977.26
2925.17
2887.56
2875.99
3022.58
2347.47
2239.45
2136.26
1958.80
1451.50
1434.14
1419.67
1380.13
1369.52
1306.83
1252.82
1205.56
1145.77
1125.51
1110.08
1080.18
1047.39
1031.96
1020.39
949.98
922.98
880.54
848.72
801.46
779.28
760.95
745.52
706.94
555.52
501.51
Comment;
SG-42.1
No. of Scans; $(Parameters|No of Scans)
Resolution; $(Parameters|Resolution) 04.03.21
Date/Time; $(IR Spectrum|Created)
User; InetBh

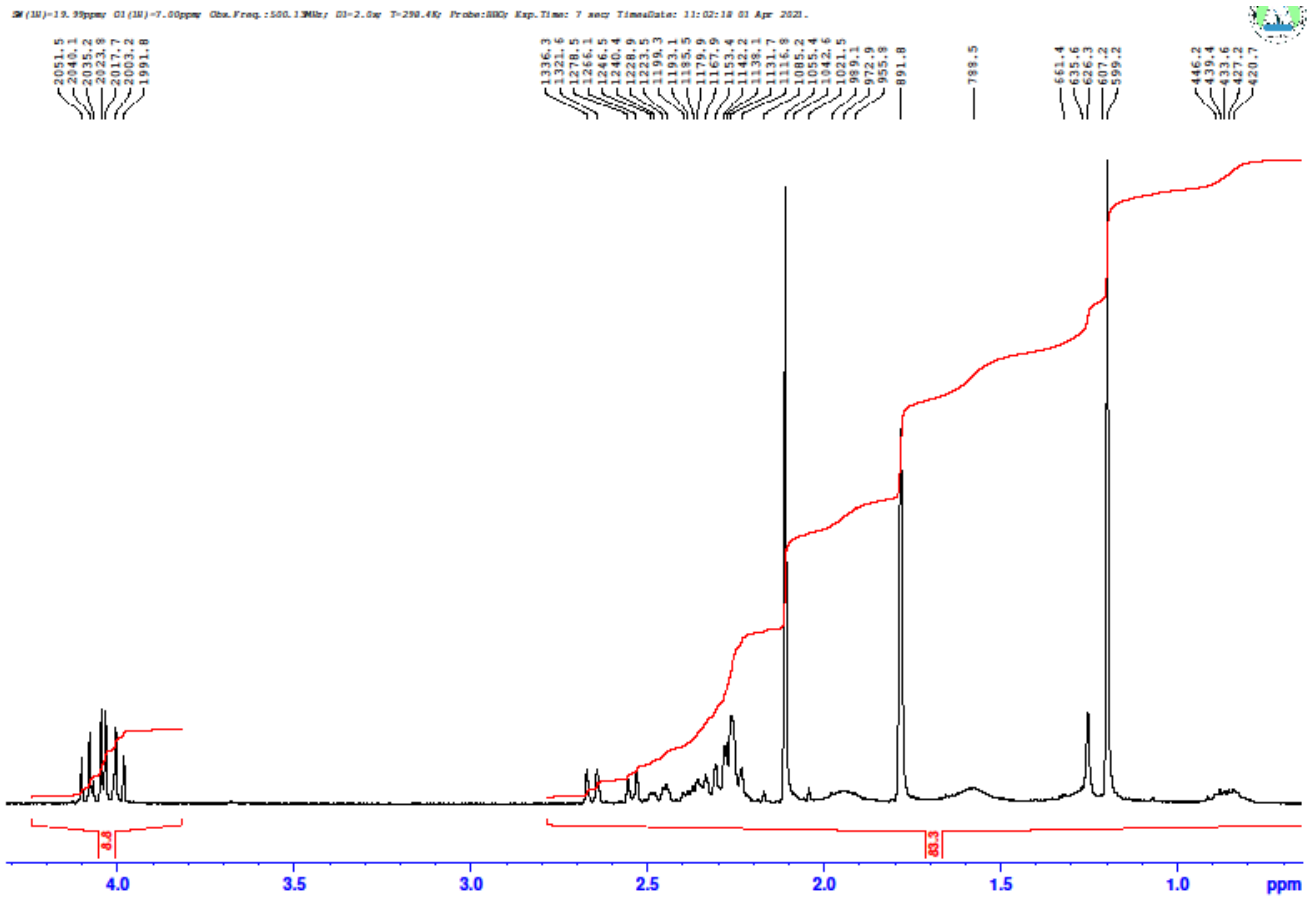
Mass



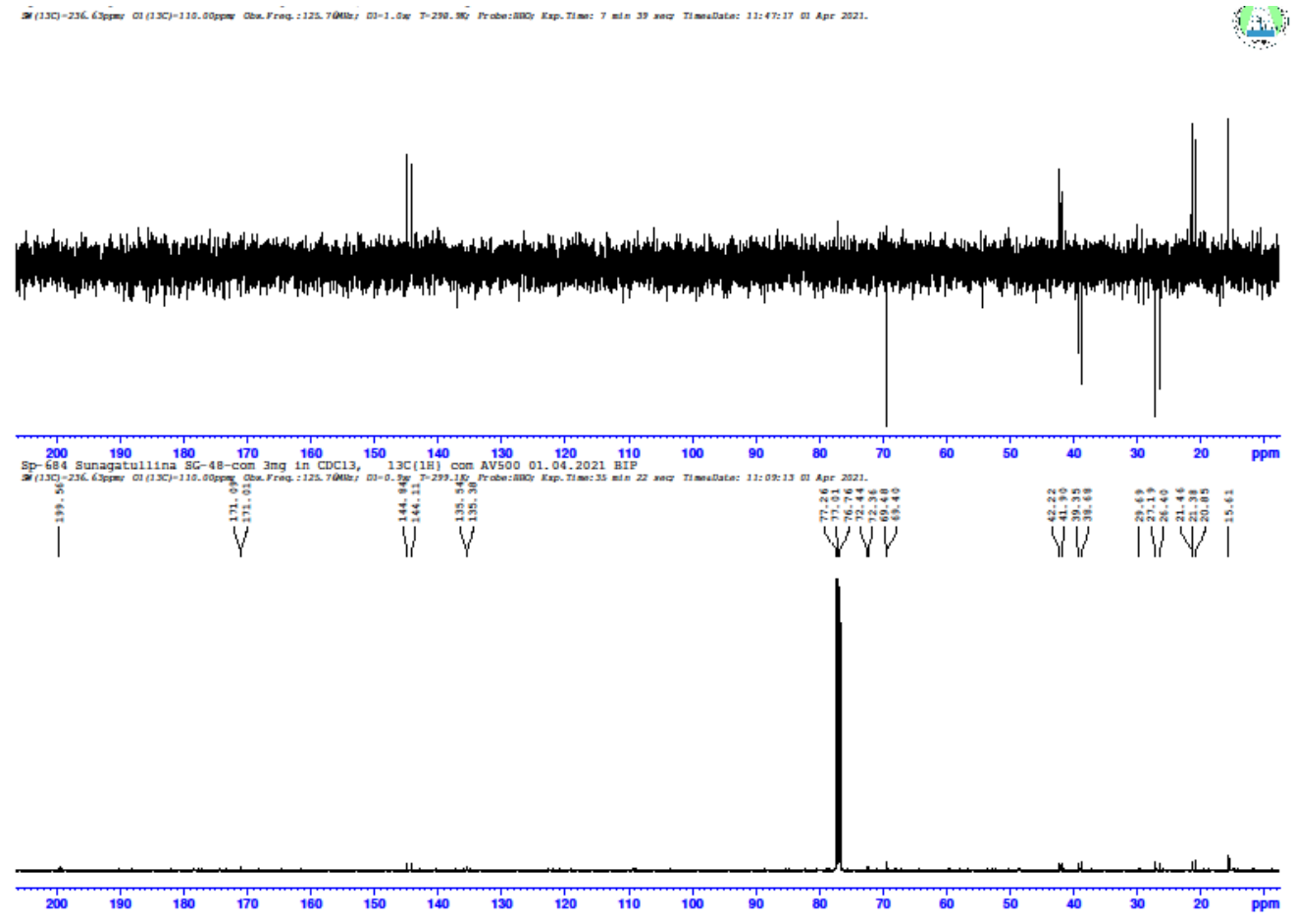
(1*R*')-Oxybis[2-*RS*-(4-methyl-5-oxocyclohex-3-en-1-yl)propane-2,1-diyl] diacetate (5b)

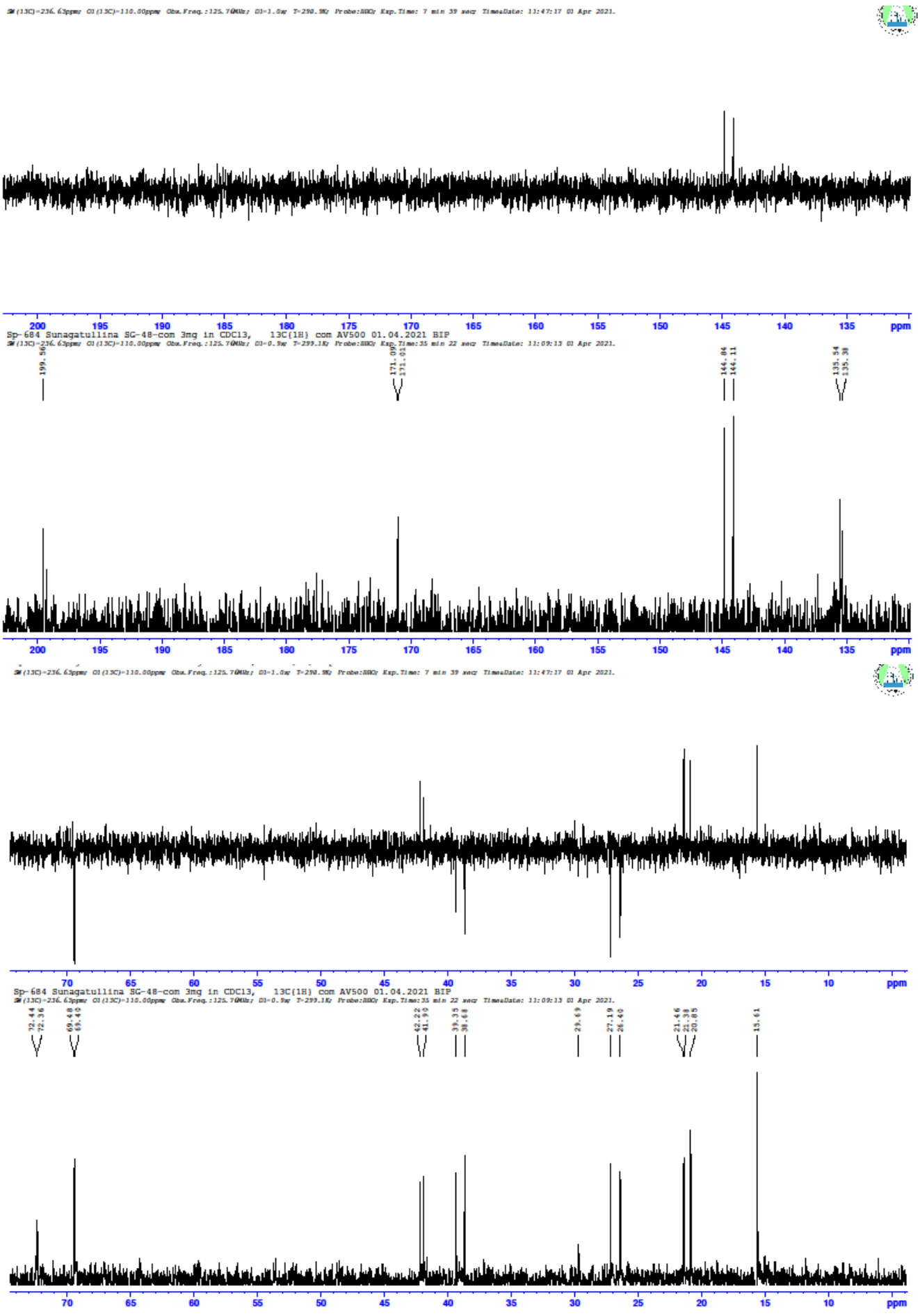
NMR ^{1}H



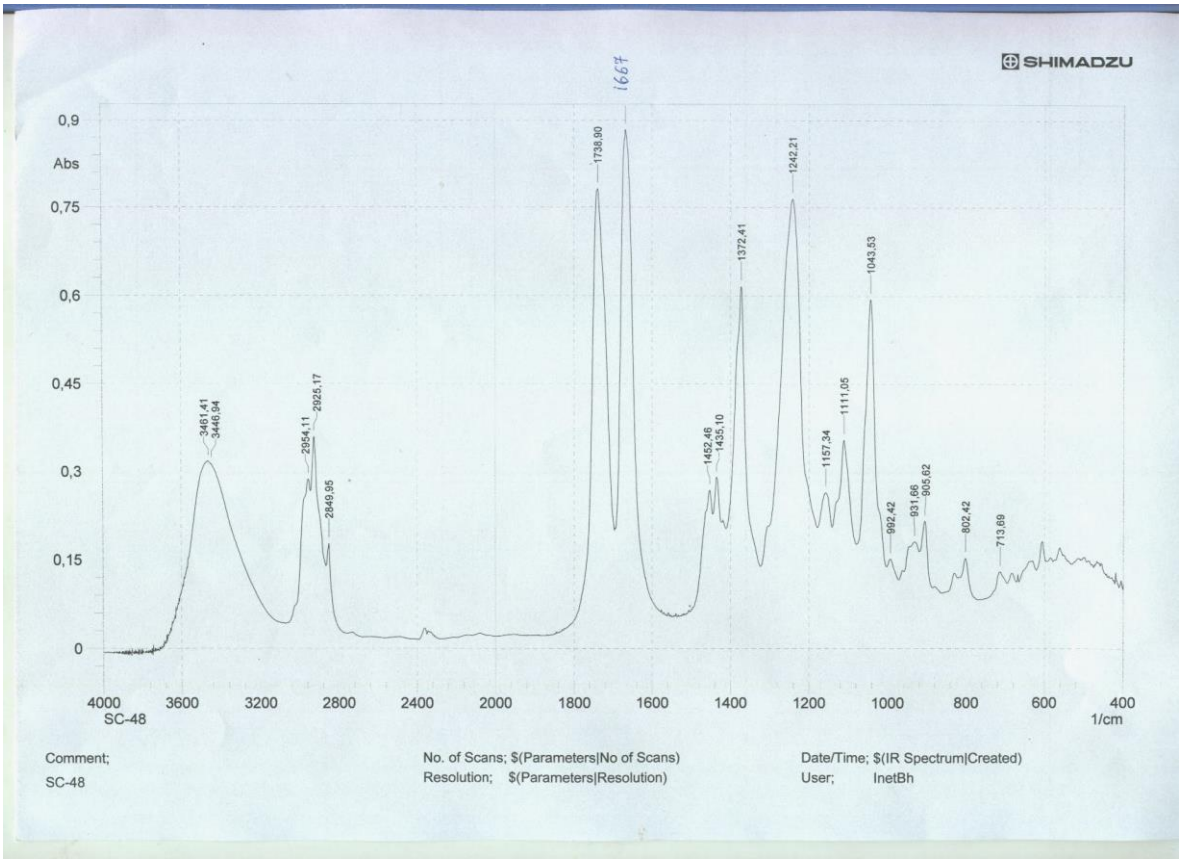

2051.5
2040.1
2035.2
2023.9
2017.7
2003.2
1991.8
1336.3
1321.6
1278.5
1266.1
1246.5
1240.4
1228.9
1223.5
1199.3
1193.1
1185.5
1179.9
1167.9
1153.4
1142.2
1138.1
1131.7
1116.8
1085.2
1055.4
1042.6
1021.5
999.1
972.9
955.8
891.8
788.5
661.4
635.6
626.3
607.2
599.2
446.2
439.4
433.6
427.2
420.7
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm

NMR ^{13}C

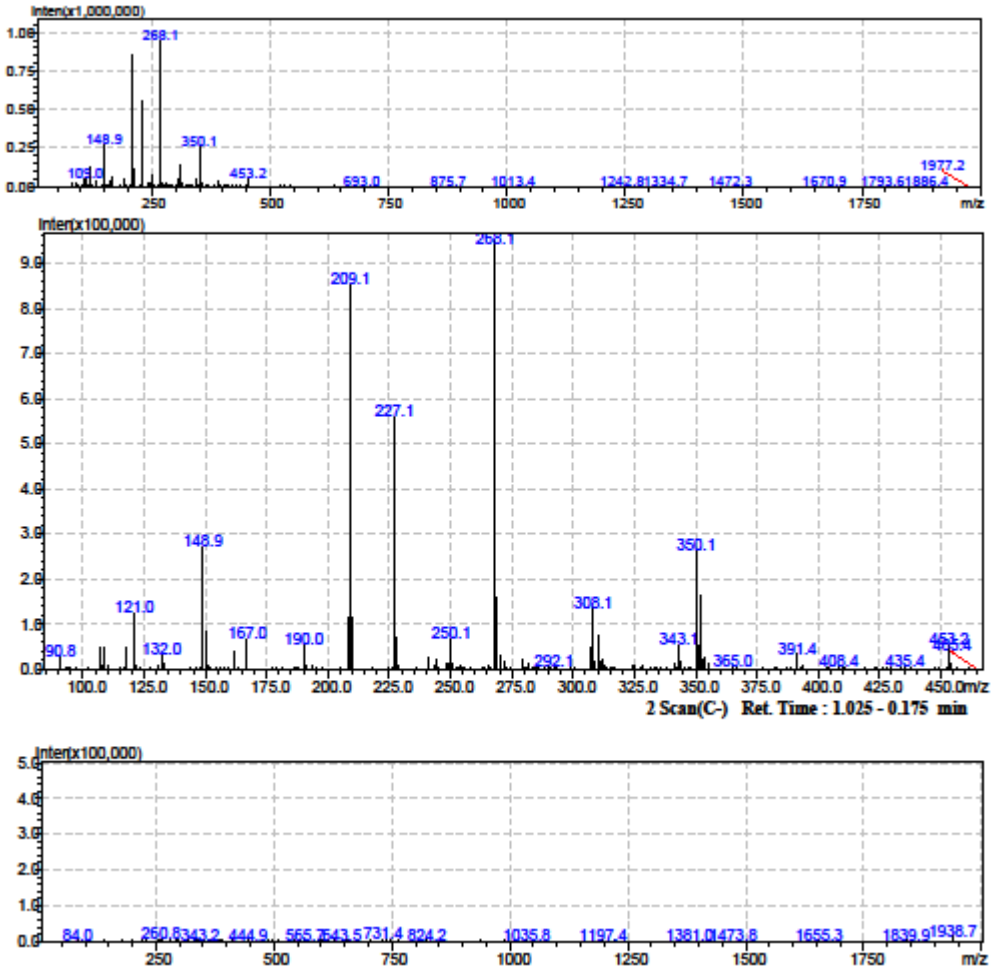

Sp-684 Sunagatullina SG-48-com 3mg in CDCl3, 13C(1H) com AV500 01.04.2021 BIP
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


Sp-684 Sunagatullina SG-48-com 3mg in CDCl3, 13C(1H) com AV500 01.04.2021 BIP
199.56
171.09
171.01
144.84
144.11
135.54
135.38
72.44
72.36
69.48
69.40
42.22
41.90
39.35
38.68
29.69
27.19
26.40
21.46
21.38
20.85
15.61
ppm

IR


SHIMADZU
1667
Abs
0,9
0,75
0,6
0,45
0,3
0,15
0
3461,41
3446,94
2954,11
2925,17
2849,95
1738,90
1452,46
1435,10
1372,41
1242,21
1157,34
1111,05
1043,53
992,42
931,66
905,62
802,42
713,69
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
1/cm
SC-48
Comment;
SC-48
No. of Scans; $(Parameters|No of Scans)
Resolution; $(Parameters|Resolution)
Date/Time; $(IR Spectrum|Created)
User; InetBh

Mass


Inten(x1,000,000)
268.1
148.9
350.1
121.0
453.2
693.0
875.7
1013.4
1242.8
1334.7
1472.3
1670.9
1793.6
1886.4
1977.2
m/z
Inten(x100,000)
268.1
209.1
227.1
148.9
350.1
308.1
121.0
167.0
190.0
250.1
90.8
132.0
292.1
343.1
365.0
391.4
408.4
435.4
453.2
2 Scan(C-) Ret. Time : 1.025 - 0.175 min
Inten(x100,000)
84.0
260.8
343.2
444.9
565.7
643.5
731.4
824.2
1035.8
1197.4
1381.0
1473.8
1655.3
1839.9
1938.7
m/z