Supporting Information

Total Synthesis of (*ent*)-linderolide E and (*ent*)-15-hydroxy- and 15-acetoxyisogermafurenolides, and structural revision of (*ent*)-linderolide E

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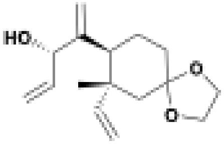
Supporting Information

General Experimental Section:

All reactions were carried out under an inert atmosphere (N2). Unless otherwise noted, all starting materials and reagents were obtained from commercial suppliers and used after further purification as detailed. Anhydrous dichloromethane, diethyl ether, and toluene were obtained from MBraun MBSPS-5 Solvent Purification Systems. Dry THF was obtained by distillation over Na wires using benzophenone ketyl as an indicator. Other solvents (e.g., MeOH) were dried by conventional methods prior to use.[1] The solvent was evaporated with a Buchi Rotavapor-R. Column chromatography was performed using silica gel (100–200 mesh) with indicated solvents. IR spectra were recorded with JASCO V-570 spectrophotometers, and only the significant transmittance values for each compound have been reported in cm−1. Mass spectra were obtained with a Bruker ESI-QTOF spectrometer (maXis impact 282001.00081). 1H NMR and 13C spectra were recorded on Bruker 400 or 500 MHz spectrometers. Optical rotation: Rudolph AUTOPOL IV polarimeter with a path length of 1 dm (sodium D line, 589 nm).

Experimental Section:

Synthesis of 2-((7*R*,8*S*)-7-methyl-7-vinyl-1,4-dioxaspiro [4.5] decan-8-yl) penta-1,4-dien-3-ol [11]:



11

To a stirred solution of compound **17** in THF (900 mg, 3.766 mmol, 1 equiv.) was added a 1M solution of vinyl magnesium bromide in THF (15.06 mL, 15.06 mmol, 4 equiv) at -35 °C under a N_2 atmosphere. The reaction mixture was allowed to stir at -35 °C for 1 h. The completion of the reaction was monitored using thin-layer chromatography (TLC). The reaction was quenched using saturated NH_4Cl. Separated the organic layer and the aqueous phase was extracted using Et_2O (20 mL x 3). The combined organic layer was dried using anhydrous

Na_2SO_4, filtered, and concentrated *in vacuo.* The crude was purified using silica gel column chromatography to afford compound **11** in a 73% yield.

R_f: 0.4 (25% EA/PE)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.80 – 5.66 (m, 2H), 5.40 (s, 1H), 5.28 (d, *J* = 17.1 Hz, 1H), 5.16 (d, *J* = 10.1 Hz, 1H), 4.97 (d, *J* = 2.2 Hz, 1H), 4.93 (d, *J* = 7.5 Hz, 2H), 4.46 (d, *J* = 7.1 Hz, 1H), 4.00 (dd, *J* = 9.4, 3.5 Hz, 2H), 3.90 (dd, *J* = 9.6, 3.9 Hz, 2H), 2.00 – 1.91 (m, 1H), 1.87 (dd, *J* = 14.7, 2.3 Hz, 1H), 1.68 (d, *J* = 13.7 Hz, 2H), 1.61 – 1.56 (m, 2H), 1.56 – 1.47 (m, 2H), 1.13 (s, 3H).

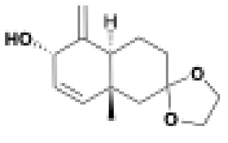
^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 149.0, 139.3, 116.3, 111.0, 110.7, 108.5, 76.9, 64.6, 63.6, 47.7, 45.9, 41.1, 35.8, 26.5, 17.1.

IR ν (neat, cm^{-1}): 3447, 2933, 1637, 1121, 1086, 1053, 970, 913, 748, 737.

$[\alpha]_{D}^{25}$: + 71.889 (c = 1.0; CH_2Cl_2)

HRMS (ESI-QTOF): *m/z* for $C_{16}H_{24}NaO_3$, $[M+Na]^+$ calcd. 287.1618, found. 287.1619

Synthesis of (6*S*,8a*R*) - 8a – methyl – 5 – methylene - 3,4,4a,5,6,8a – hexahydro - 1*H* -spiro [naphthalene - 2,2' -[1,3]dioxolan] – 6 – ol [18]:



18

To a stirred solution of compound **11** (100 mg, 0.378 mmol, 1 equiv) in dry toluene under N_2 atmosphere was added Grubbs' II catalyst (32 mg, 0.038 mmol, 0.1 equiv). The reaction mixture was kept for stirring overnight at room temperature for 12 h. The completion of the reaction was monitored using TLC. The reaction mixture was concentrated *in vacuo* and the crude was purified using silica gel column chromatography to obtain compound **18** in 90% yield.

R_f: 0.2 (25% EtOAc/ Pet ether)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.75 (d, *J* = 9.7 Hz, 1H), 5.64 (dd, *J* = 9.7, 3.9 Hz, 1H), 5.19 (s, 1H), 4.87 (s, 1H), 4.42 (d, *J* = 3.9 Hz, 1H), 4.01 – 3.97 (m, 2H), 3.93 – 3.88 (m, 2H), 2.40 – 2.35 (m, 1H), 1.96 – 1.91 (m, 1H), 1.76 – 1.63 (m, 6H), 0.90 (s, 3H).

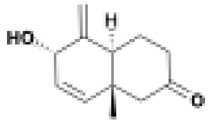
^{13}C NMR (100 MHz, CDCl$_3$): δ 149.9, 143.7, 124.2, 111.4, 109.2, 69.7, 64.6, 63.6, 45.2, 43.7, 38.8, 35.5, 21.3, 19.1.

IR ν (neat, cm^{-1}): 3444, 2932, 2874, 1656, 1437, 1429, 1357, 1263, 1239, 1159, 1138, 1088, 1031, 1017, 1000, 905, 837, 753.

$[\alpha]_D^{25}$: +84.014 (c = 1.0; CH_2Cl_2)

HRMS (ESI-QTOF): *m/z* for $C_{14}H_{20}NaO_3$, $[M+Na]^+$ calcd. 259.1305, found 259.1304.

Synthesis of (6*S*,8a*R*) – 6 – hydroxy - 8a – methyl – 5 – methylene - 3,4,4a,5,6,8a - hexahydronaphthalen - 2(1*H*) – one [19]:



19

To a solution of compound **18** (135 mg, 0.571 mmol, 1 equiv) in 9:1 mixture of acetone: H_2O was added *p*TsOH (54 mg, 0.286 mmol, 0.5 equiv.) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. Upon completion, the reaction was quenched using Sat. $NaHCO_3$ at 0 °C. The aqueous layer was separated and extracted using EtOAc (20 mL x 3). The combined organic layers were dried using anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude was purified using silica gel column chromatography to obtain compound **19** in 88% overall yield.

R*f*: 0.6 (50% EtOAc/Pet ether)

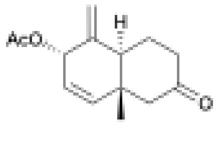
^{1}H NMR (400 MHz, CDCl$_3$): δ 6.27 (d, *J* = 9.7 Hz, 1H), 5.90 (dd, *J* = 9.6, 5.7 Hz, 1H), 5.08 (d, *J* = 25.9 Hz, 2H), 3.57 (d, *J* = 5.6 Hz, 1H), 3.06 (d, *J* = 13.6 Hz, 1H), 2.82 (dd, *J* = 12.0, 3.3 Hz, 1H), 2.50 – 2.36 (m, 3H), 2.02 (d, *J* = 13.5 Hz, 1H), 1.86 – 1.73 (m, 2H), 0.70 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 212.7, 143.7, 133.1, 126.4, 114.8, 72.1, 49.4, 42.8, 40.6, 36.8, 25.0, 17.7.

IR ν (neat, cm^{-1}): 3402, 3029, 2956,1699, 1601, 1423, 1383, 1263, 1193, 1108, 1027, 975, 942, 894, 793, 733, 700, 675.

HRMS (ESI-QTOF): *m/z* for $C_{12}H_{16}NaO_2$, $[M+Na]^+$ calcd. 215.1043, found 215.1040.

Synthesis of (2*S*,4a*R*,8a*S*)-4a-methyl-1-methylene-6-oxo-1,2,4a,5,6,7,8,8a-octahydronaphthalen-2-yl acetate [20]:



20

To a 50 mL oven-dried two-neck RB was added compound **19** (100 mg, 0.52 mmol, 1 equiv) dissolved in dry CH_2Cl_2. To this, Et_3N (0.2 mL, 1.56 mmol, 3 equiv.) and DMAP (6.35 mg, 0.052 mmol, 1 equiv.) were added, followed by Ac_2O (0.05 mL, 0.572 mmol, 1.1 equiv.) at 0 ^{o}C after 5 min. The reaction was stirred at rt for 1 h, until the starting material was completely consumed. The reaction was quenched with water, and the aqueous layer was extracted with dichloromethane (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture obtained was purified using silica gel column chromatography to afford product **20** in 99% overall yield.

R_f: 0.6 (25% EtOAc/Pet ether)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (d, *J* = 9.7 Hz, 1H), 5.86 (dd, *J* = 9.7, 5.6 Hz, 1H), 5.15 (dd, *J* = 2.3, 0.7 Hz, 1H), 5.08 (s, 1H), 4.76 (d, *J* = 5.6 Hz, 1H), 2.89 (ddd, *J* = 9.3, 3.6, 1.8 Hz, 1H), 2.71 (d, *J* = 13.4 Hz, 1H), 2.47 (dd, *J* = 10.3, 5.3 Hz, 2H), 2.43 – 2.35 (m, 1H), 2.09 (s, 3H), 2.01 (dd, *J* = 13.4, 1.0 Hz, 1H), 1.85 – 1.72 (m, 1H), 0.77 (s, 3H).

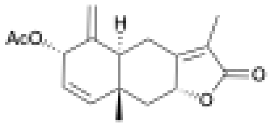
^{13}C NMR (100 MHz, $CDCl_3$): δ 211.03, 170.29, 143.30, 134.51, 122.73, 115.44, 73.82, 49.21, 41.16, 40.51, 37.74, 24.72, 21.13, 17.72.

IR ν (neat, cm^{-1}): 2946, 1716, 1602, 1430, 1371, 1309, 1233, 1016, 991, 968, 903, 797, 732, 632.

$[\alpha]_D^{25}$: -159.140 (c = 1.0; CH_2Cl_2)

HRMS (ESI-QTOF): *m/z* for $C_{14}H_{19}O_3$, $[M+H]^+$ calcd. 235.1330, found 235.1330.

Synthesis of (4a*S*,6*S*,8a*R*,9a*R*)-3,8a-dimethyl-5-methylene-2-oxo-2,4,4a,5,6,8a,9,9a-octahydronaphtho[2,3-*b*]furan-6-yl acetate [21]:



21

$TiCl_4$ (0.62 mL, 0.624 mmol, 1.5 equiv.) and Bu_3N (0.2 mL, 0.832 mmol, 2 equiv.) in dry CH_2Cl_2 were added successively to a stirred solution of ketone **20** (120 mg, 0.416 mmol, 1 equiv.) in dry CH_2Cl_2 at -78 ^oC under N_2 atmosphere, followed by stirring for 0.5 h. To the reaction mixture, a,a'-dimethoxyacetone (0.07 mL, 0.832 mmol, 2 equiv.) in dry CH_2Cl_2 was added. Then, the mixture was allowed to warm to rt and was stirred for 17 h. Water was added to the mixture, which was extracted with diethyl ether. The combined organic phase was washed with water, brine, and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The obtained crude product was purified by silica gel column chromatography to give compound **21** in 57% overall yield.

R*f*: 0.4 (25% EtOAc/Pet ether)

^{1}H NMR (400 MHz, CDCl$_3$) δ 6.37 (d, *J* = 9.7 Hz, 1H), 5.85 (dd, *J* = 9.6, 5.6 Hz, 1H), 5.20 (s, 1H), 5.13 (s, 1H), 4.92 (d, *J* = 5.7 Hz, 1H), 4.90 – 4.85 (m, 1H), 3.13 (dd, *J* = 14.0, 4.4 Hz, 1H), 2.52 (d, *J* = 10.0 Hz, 1H), 2.33 (t, *J* = 13.1 Hz, 1H), 2.16 (dd, *J* = 12.3, 6.2 Hz, 1H), 2.06 (s, 3H), 1.91 (d, *J* = 1.1 Hz, 3H), 1.52 (t, *J* = 12.0 Hz, 1H), 0.97 (s, 3H).

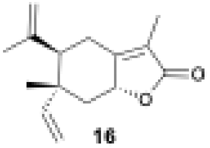
^{13}C NMR (100 MHz, CDCl$_3$): δ 174.63, 170.35, 160.68, 143.12, 133.80, 123.03, 120.95, 114.86, 77.95, 73.36, 40.80, 39.69, 37.67, 24.82, 21.06, 16.85, 8.40.

IR ν (neat, cm^{-1}): 2927, 1750, 1730, 1686, 1603, 1440, 1371, 1233, 1134, 1091, 1035, 1016, 980, 930, 900, 852, 798, 767, 661, 634, 589.

$[\alpha]_D^{25}$: -222.314 (c = 1.0; CH_2Cl_2)

HRMS (ESI-QTOF): *m/z* for $C_{17}H_{21}O_4$, $[M+H]^+$ calcd. 289.1440, found 289.1439.

Synthesis of (5*R*,6*R*,7a*R*)-3,6-dimethyl-5-(prop-1-en-2-yl)-6-vinyl-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one [16]:



16

$TiCl_4$ (9.3 mL, 9.265 mmol, 1.5 equiv.) and Bu_3N (2.9 mL, 12.35 mmol, 2 equiv.) in dry CH_2Cl_2 were added successively to a stirred solution of ketone **12** (1.1 g, 6.177 mmol, 1 equiv.) in dry CH_2Cl_2 at -78 °C under N_2 atmosphere, followed by stirring for 0.5 h. To the reaction mixture, a,a'-dimethoxyacetone (1 mL, 12.35 mmol, 2 equiv.) in dry CH_2Cl_2 was added. Then, the mixture was allowed to warm to rt and was stirred for 17 h. Water was added to the mixture, which was extracted with diethyl ether. The combined organic phase was washed with water, brine, and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The obtained crude product was purified by silica gel column chromatography to give compound **16** as a white solid in 56% overall yield.

R*f*: 0.4 (25% EtOAc/Pet ether)

^{1}H NMR (500 MHz, CDCl$_3$) δ 5.74 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.00 (dd, *J* = 17.5, 14.0 Hz, 3H), 4.84 (dd, *J* = 11.7, 6.0 Hz, 1H), 4.75 (s, 1H), 2.69 (dd, *J* = 14.3, 4.1 Hz, 1H), 2.57 (t, *J* = 13.8 Hz, 1H), 2.21 (dd, *J* = 12.3, 6.1 Hz, 1H), 2.06 (dd, *J* = 13.2, 4.1 Hz, 1H), 1.84 (s, 3H), 1.78 (s, 3H), 1.35 (t, *J* = 12.0 Hz, 1H), 1.18 (s, 3H).

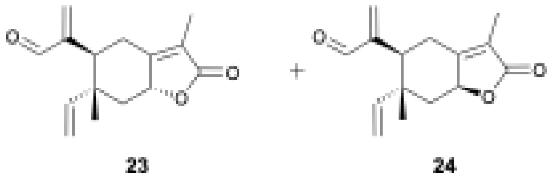
^{13}C NMR (101 MHz, CDCl$_3$) δ 174.82, 162.00, 146.55, 144.85, 120.05, 113.90, 111.81, 77.93, 52.94, 45.74, 40.80, 28.37, 24.70, 17.00, 8.24

IR ν (neat, cm^{-1}): 3082, 2927, 2858, 1748, 1686, 1639, 1444, 1380, 1325, 1217, 1123, 1089, 1032, 904, 761, 703, 657, 593.

$[\alpha]_D^{25}$: -24.631 (c = 1.0; CH_2Cl_2)

HRMS (ESI-QTOF): *m/z* for $C_{15}H_{20}O_2$, $[M+H]^+$ calcd. 233.1535, found 233.1534

Synthesis of 2-((5*S*,6*R*,7a*R*)-3,6-dimethyl-2-oxo-6-vinyl-2,4,5,6,7,7a-hexahydrobenzofuran-5-yl)acrylaldehyde [23] & 2-((5*R*,6*R*,7a*R*)-3,6-dimethyl-2-oxo-6-vinyl-2,4,5,6,7,7a-hexahydrobenzofuran-5-yl) acryl aldehyde [24]:



23 + 24

To a solution of compound **16** (596 mg, 2.56 mmol, 1 equiv.) in CH_2Cl_2 at 0 °C was added ^{t}BuOOH (0.67 mL, 5.13 mmol, 2 equiv.) and SeO_2 (142 mg, 1.28 mmol, 0.5 equiv.). Then the reaction mixture was allowed to warm to room temperature and was stirred for 16 h before it was quenched with sat. $Na_2S_2O_3$ solution at 0 °C. The reaction mixture was extracted with CH_2Cl_2, and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture obtained was purified using silica gel column chromatography to afford products **23** in 47% and **24** in 10% yields.

R*f*: 0.2 (25% EtOAc/Pet ether) for **23**

^{1}H NMR (400 MHz, CDCl$_3$) for 23: δ 9.42 (s, 1H), 6.28 (s, 1H), 6.20 (s, 1H), 5.55 (dd, *J* = 17.4, 10.7 Hz, 1H), 4.87 (dd, *J* = 25.3, 14.1 Hz, 3H), 2.92 (dd, *J* = 10.6, 7.1 Hz, 1H), 2.69 – 2.58 (m, 2H), 2.23 (dd, *J* = 12.4, 6.1 Hz, 1H), 1.81 (s, 3H), 1.42 (t, *J* = 12.1 Hz, 1H), 1.11 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) for 23: δ 193.55, 174.50, 160.47, 149.55, 145.28, 135.82, 121.02, 112.62, 77.63, 45.40, 41.67, 40.76, 27.48, 15.38, 8.37

IR ν (neat, cm^{-1}) for 23: 2929, 1687, 1629, 1442, 1380, 1328, 1219, 1090, 1031, 957, 912, 843, 763, 700, 631, 590.

$[\alpha]_D^{25}$ for 23: -22.920 (c = 1.0; CH_2Cl_2)

HRMS (ESI-QTOF) for 23: *m/z* for $C_{15}H_{18}O_3$, $[M+H]^+$ calcd. 247.1335, found 247.1335

R*f*: 0.3 (25% EtOAc/Pet ether) for **24**

^{1}H NMR (400 MHz, CDCl$_3$) for 24: δ 9.43 (s, 1H), 6.25 (s, 1H), 6.05 (s, 1H), 5.94 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.28 (dd, *J* = 22.5, 14.3 Hz, 2H), 4.92 (dd, *J* = 11.5, 6.2 Hz, 1H), 3.52 (d, *J* = 6.9 Hz, 1H), 2.72 (dd, *J* = 14.9, 7.0 Hz, 1H), 2.57 (d, *J* = 14.8 Hz, 1H), 2.34 (dd, *J* = 13.1, 6.2 Hz, 1H), 1.80 (s, 3H), 1.51 – 1.43 (m, 1H), 0.80 (s, 3H).

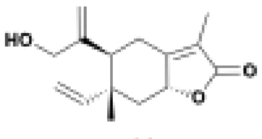
^{13}C NMR (101 MHz, CDCl$_3$) for 24: δ 194.20, 174.37, 161.25, 151.76, 144.78, 135.53, 121.25, 114.21, 77.99, 40.94, 38.62, 37.16, 28. 15, 27.46, 8.21

IR ν (neat, cm^{-1}) for 24: 2931, 1746, 1684, 1631, 1457, 1374, 1304, 1219, 1088, 1039, 925, 765, 670.

$[\alpha]_D^{25}$ for 24: +13.009 (c = 1.0; CH_2Cl_2)

HRMS (ESI-QTOF) for 24: *m/z* for $C_{15}H_{18}O_3$, $[M+H]^+$ calcd. 247.1330, found 247.1329

Synthesis of (5*S*,6*R*,7a*R*)-5-(3-hydroxyprop-1-en-2-yl)-3,6-dimethyl-6-vinyl-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one [14]:



14

NaBH$_4$ (31 mg, 0.812 mmol, 2 equiv.) was added in one portion to a solution of enone **23** (100mg, 0.406 mmol, 1 equiv.) and CeCl$_3$·7H$_2$O (227 mg, 0.609 mmol, 1.5 equiv.) in MeOH (20 mL) at -78 °C. The resulting mixture was warmed up slowly to rt over 12 h. The reaction was quenched by the addition of 15 mL of acetone and then 15 mL of H$_2$O. The solvents were evaporated *in vacuo*. The residue was partitioned between Et$_2$O and H$_2$O. Separated the organic layer. Extracted the aqueous layer with Et$_2$O (20 mL x 3). The combined organic layer was washed with brine. The combined organic layer was dried using anhydrous Na$_2$SO$_4$, filtered and concentrated *in vacuo.* The obtained crude product was purified by silica gel column chromatography to give compound **14** in 95% overall yield.

R$_f$: 0.3 (50% EtOAc/Pet ether)

^{1}H NMR (400 MHz, CDCl$_3$) δ 5.67 (dd, J = 17.4, 10.8 Hz, 1H), 5.33 (s, 1H), 4.98 (dd, J = 16.5, 12.4 Hz, 3H), 4.84 (dd, J = 11.1, 5.8 Hz, 1H), 4.10 – 4.04 (m, 1H), 3.98 (d, J = 14.2 Hz, 1H), 2.68 (dd, J = 14.4, 4.2 Hz, 1H), 2.58 (t, J = 13.8 Hz, 1H), 2.21 (dd, J = 12.4, 6.1 Hz, 1H), 2.09 (dd, J = 14.4, 5.4 Hz, 1H), 1.80 (s, 3H), 1.34 (t, J = 12.0 Hz, 1H), 1.16 (s, 3H).

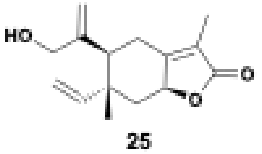
^{13}C NMR (100 MHz, CDCl$_3$): δ 174.78, 161.62, 148.78, 145.91, 120.35, 112.67, 112.61, 77.80, 67.15, 47.88, 45.51, 40.75, 28.90, 16.44, 8.29.

IR ν (neat, cm^{-1}): 3437, 2926, 1740, 1683, 1640, 1441, 1383, 1330, 1221, 1093, 1031, 913, 769, 658, 591.

$[\alpha]_D^{25}$: -54.821 (c = 1.0; CH$_2$Cl$_2$)

HRMS (ESI-QTOF): *m/z* for C$_{15}$H$_{21}$O$_3$, [M+H]$^+$ calcd. 249.1486, found 249.1486.

Synthesis of (5*S*,6*R*,7a*S*)-5-(3-hydroxyprop-1-en-2-yl)-3,6-dimethyl-6-vinyl-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one [25]:



25

$NaBH_4$ (31 mg, 0.812 mmol, 2 equiv.) was added in one portion to a solution of enone **24** (100mg, 0.406 mmol, 1 equiv.) and $CeCl_3\cdot7H_2O$ (227 mg, 0.609 mmol, 1.5 equiv.) in MeOH (20 mL) at -78 °C. The resulting mixture was warmed up slowly to rt over 12 h. The reaction was quenched by the addition of 15 mL of acetone and then 15 mL of H_2O. Evaporate the solvent *in vacuo*. Partition the residue between Et_2O and H_2O. Separated the organic layer. Extracted the aqueous layer with Et_2O (20 mL x 3). The combined organic layer was washed with brine. The combined organic layer was dried using anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The obtained crude product was purified by silica gel column chromatography to give compound **25** in 94% overall yield.

R_f: 0.3 (50% EtOAc/Pet ether)

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (dd, J = 17.6, 11.0 Hz, 1H), 5.14 (dd, J = 27.7, 16.7 Hz, 3H), 4.86 – 4.80 (m, 1H), 4.79 (s, 1H), 3.96 (s, 2H), 2.63 – 2.59 (m, 2H), 2.53 – 2.46 (m, 1H), 2.29 – 2.22 (m, 1H), 1.72 (s, 3H), 1.67 – 1.58 (m, 2H), 0.92 (s, 3H).

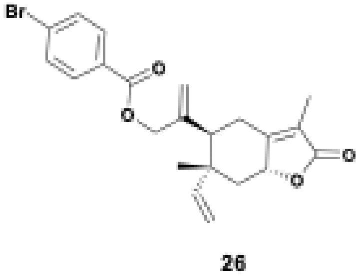
^{13}C NMR (100 MHz, $CDCl_3$): δ 174.69, 161.51, 150.61, 145.77, 121.26, 113.63, 111.71, 78.08, 68.16, 44.17, 41.21, 38.82, 29.71, 29.10, 27.57, 8.20.

IR ν (neat, cm^{-1}): 3437, 2925, 1736, 1683, 1637, 1461, 1343, 1303, 1222, 1039, 1015, 914, 768, 673.

$[\alpha]_D^{25}$: +32.247 (c = 1.0; CH_2Cl_2)

HRMS (ESI-QTOF): *m/z* for $C_{15}H_{21}O_3$, $[M+H]^+$ calcd. 249.1486, found 249.1485.

Synthesis of 2-((5*S*,6*R*,7a*R*)-3,6-dimethyl-2-oxo-6-vinyl-2,4,5,6,7,7a-hexahydrobenzofuran-5-yl)allyl 4-bromobenzoate [26]:



26

To a 50 mL round-bottomed flask were added 4-nitrobenzoic acid (67.3 mg, 0.403 mmol, 1 equiv.), compound **14** (100 mg, 0.403 mmol, 1 equiv.), DCC (83.1 mg, 0.403 mmol, 1 equiv.), and DMAP (15 mg, 0.121 mmol, 0.3 equiv.) in CH_2Cl_2. The reaction was stirred at room temperature for 24 h. Upon completion, the reaction mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography to give compound **26** in 71% overall yield.

R*f*: 0.4 (25% EtOAc/Pet ether)

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 5.72 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.38 (s, 1H), 5.05 (dd, *J* = 26.1, 15.0 Hz, 3H), 4.84 (dd, *J* = 11.0, 5.8 Hz, 1H), 4.71 (q, *J* = 13.8 Hz, 2H), 2.73 (dd, *J* = 14.4, 4.0 Hz, 1H), 2.60 (t, *J* = 13.8 Hz, 1H), 2.23 (dd, *J* = 12.4, 6.0 Hz, 1H), 2.14 (dd, *J* = 13.2, 3.9 Hz, 1H), 1.79 (s, 3H), 1.36 (t, *J* = 12.0 Hz, 1H), 1.20 (s, 3H).

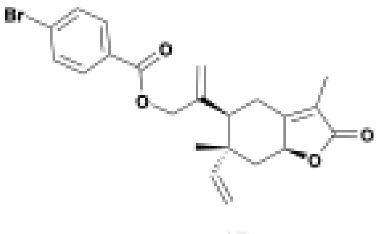
^{13}C NMR (100 MHz, CDCl$_3$): δ 174.54, 165.31, 161.11, 145.45, 143.62, 131.87, 131.08, 128.83, 128.39, 120.59, 115.24, 113.15, 77.64, 68.40, 48.68, 45.47, 40.81, 28.76, 16.53, 8.26.

IR ν (neat, cm^{-1}): 2938, 1748, 1719, 1643, 1588, 1527, 1393, 1264, 1173, 1096, 1032, 1008, 913, 846, 755

$[\alpha]_D^{25}$: -18.384 (c = 1.0; CH$_2$Cl$_2$)

HRMS (ESI-QTOF): *m/z* for C$_{22}$H$_{24}$BrO$_4$, [M+H]$^+$ calcd. 433.0835, found 433.0834.

Synthesis of 2-((5*S*,6*R*,7a*S*)-3,6-dimethyl-2-oxo-6-vinyl-2,4,5,6,7,7a-hexahydrobenzofuran-5-yl)allyl 4-bromobenzoate [27]:



27

To a 50 mL round-bottomed flask were added 4-nitrobenzoic acid (67.3 mg, 0.403 mmol, 1 equiv.), compound **25** (100 mg, 0.403 mmol, 1 equiv.), DCC (83.1 mg, 0.403 mmol, 1 equiv.), and DMAP (15 mg, 0.121 mmol, 0.3 equiv.) in CH$_2$Cl$_2$. The reaction was stirred at room temperature for 24 h. Upon completion, the reaction mixture was filtered through a pad of Celite. The solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography to give compound **27** in 51% overall yield.

R*f*: 0.4 (25% EtOAc/Pet ether)

^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.5 Hz, 2H), 7.62 (d, *J* = 7.5 Hz, 2H), 5.93 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.24 (dd, *J* = 14.5, 11.1 Hz, 3H), 4.98 (s, 1H), 4.91 (dd, *J* = 10.8, 6.8 Hz, 1H), 4.73 (s, 2H), 2.82 – 2.68 (m, 2H), 2.63 (d, *J* = 6.3 Hz, 1H), 2.37 (dd, *J* = 13.0, 6.4 Hz, 1H), 1.82 (s, 3H), 1.70 (t, *J* = 12.4 Hz, 1H), 1.07 (s, 3H).

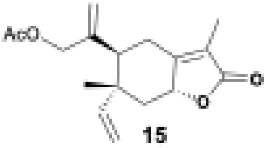
^{13}C NMR (100 MHz, $CDCl_3$): δ 174.48, 165.34, 160.91, 145.55, 145.47, 131.92, 131.13, 128.73, 128.46, 121.57, 114.34, 113.79, 77.91, 68.95, 44.88, 41.26, 38.87, 28.87, 27.62, 8.24.

IR ν (neat, cm^{-1}): 2929, 1749, 1721, 1644, 1589, 1527, 1394, 1265, 1172, 1099, 1040, 1008, 916, 848, 756

$[\alpha]_D^{25}$: + 52.748 (c = 1.0; CH_2Cl_2)

HRMS (ESI-QTOF): *m/z* for $C_{22}H_{24}BrO_4$, $[M+H]^+$ calcd. 433.0840, found 433.0839.

Synthesis of 2-((5*S*,6*R*,7a*R*)-3,6-dimethyl-2-oxo-6-vinyl-2,4,5,6,7,7a-hexahydrobenzofuran-5-yl)allyl acetate [15]:



15

To a 50 mL oven-dried two-neck RB was added compound **14** (100 mg, 0.403 mmol, 1 equiv.) dissolved in dry CH_2Cl_2. To this, Et_3N (0.17 mL, 1.209 mmol, 3 equiv.) and DMAP (5 mg, 0.0403 mmol, 0.1 equiv.) were added, followed by Ac_2O (0.04 mL, 0.443 mmol, 1.1 equiv.) at 0 °C after 5 min. The reaction was stirred at rt for 1 h, until the starting material was completely consumed. The reaction was quenched with water, and the aqueous layer was extracted with dichloromethane (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude mixture obtained was purified using silica gel column chromatography to afford product **15** in 99% overall yield.

R_f: 0.4 (25% EtOAc/Pet ether)

^1H NMR (400 MHz, $CDCl_3$) δ 5.67 (dd, *J* = 17.4, 10.7 Hz, 1H), 5.29 (s, 1H), 5.00 (dd, *J* = 17.4, 13.9 Hz, 3H), 4.83 (dd, *J* = 11.2, 5.9 Hz, 1H), 4.46 (s, 2H), 2.69 (dd, *J* = 14.4, 3.8 Hz, 1H), 2.57 (t, *J* = 13.8 Hz, 1H), 2.20 (dd, *J* = 12.4, 6.0 Hz, 1H), 2.06 (t, *J* = 4.5 Hz, 4H), 1.80 (s, 3H), 1.33 (t, *J* = 12.0 Hz, 1H), 1.16 (s, 3H).

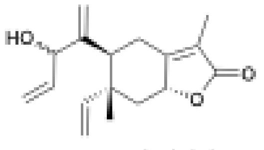
^{13}C NMR (101 MHz, $CDCl_3$): δ 174.57, 170.50, 161.27, 145.54, 143.70, 120.46, 115.04, 112.91, 77.64, 67.76, 48.46, 45.43, 40.74, 28.61, 20.92, 16.43, 8.25.

IR ν (neat, cm^{-1}): 2943, 1740, 1686, 1642, 1438, 1378, 1326, 1225, 1123, 1089, 1028, 913, 844, 768, 703, 658, 593.

$[\alpha]^{21}_{D}$: -56.693 (c = 1.0; CH_2Cl_2)

HRMS (ESI-QTOF): *m/z* for $C_{17}H_{23}O_4$, $[M+H]^+$ calcd 291.1592, found 291.1591.

Synthesis of (5*S*,6*R*,7a*R*)-5-(3-hydroxypenta-1,4-dien-2-yl)-3,6-dimethyl-6-vinyl-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one [28]:



28 dr=1.1:1

To a stirred solution of compound **23** in THF (100 mg, 0.406 mmol, 1 equiv.) was added 1.6 M solution of vinyl magnesium chloride in THF (0.3 mL, 0.487 mmol, 1.2 equiv.) at -50 °C under an N_2 atmosphere. The reaction mixture was allowed to stir at -50 °C for 1 h. The completion of the reaction was monitored using thin-layer chromatography (TLC). The reaction was quenched using saturated NH_4Cl. The organic layer was separated, and the aqueous phase was extracted using EtOAc (20 mL x 3). The combined organic layer was dried using anhydrous Na_2SO_4, filtered, and concentrated *in vacuo.* The crude was purified using silica gel column chromatography to afford compound **28** in 80% yield as an inseparable diastereomeric mixture in a 1.1:1 ratio.

R_f: 0.5 (50% EtOAc/Pet ether)

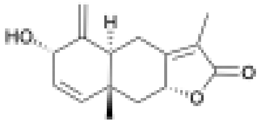
^{1}H NMR (400 MHz, CDCl$_3$): δ 5.92 – 5.82 (m, 1H), 5.77 (dd, *J* = 14.8, 8.0 Hz, 1H), 5.74 – 5.69 (m, 1H), 5.69 – 5.64 (m, 1H), 5.56 (d, *J* = 1.1 Hz, 1H), 5.34 (dt, *J* = 17.3, 1.6 Hz, 1H), 5.30 (s, 1H), 5.25 (ddt, *J* = 10.4, 8.1, 1.4 Hz, 2H), 5.19 (ddd, *J* = 10.1, 1.2, 0.8 Hz, 1H), 5.09 – 5.05 (m, 3H), 5.03 (dd, *J* = 3.6, 2.8 Hz, 2H), 5.00 – 4.97 (m, 1H), 4.87 (dd, *J* = 11.3, 5.7 Hz, 2H), 4.57 (d, *J* = 4.5 Hz, 1H), 4.42 (d, *J* = 7.4 Hz, 1H), 2.68 (dd, *J* = 14.1, 4.0 Hz, 1H), 2.58 (d, *J* = 6.2 Hz, 2H), 2.40 (dd, *J* = 13.2, 4.0 Hz, 1H), 2.26 (ddd, *J* = 12.4, 7.6, 6.1 Hz, 2H), 1.93 (dd, *J* = 11.2, 6.2 Hz, 1H), 1.82 (t, *J* = 1.6 Hz, 3H), 1.80 – 1.79 (m, 3H), 1.38 (q, *J* = 11.9 Hz, 2H), 1.22 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 174.75, 174.69, 161.58, 161.55, 150.30, 150.27, 146.28, 145.67, 138.82, 138.35, 120.38, 120.33, 117.04, 115.27, 115.10, 112.66, 112.63, 111.59, 77.75, 77.74, 76.96, 76.29, 48.06, 46.65, 45.84, 45.37, 40.91, 40.87, 30.19, 29.17, 16.65, 16.56, 8.23, 8.12.

IR ν (neat, cm^{-1}): 3446, 3085, 2979, 2868, 1737, 1682, 1639, 1415, 1383, 1327, 1221, 1095, 1032, 915, 844, 766, 736, 698, 659, 600.

HRMS (ESI-QTOF): *m/z* for $C_{17}H_{23}O_3$, $[M+H]^+$ calcd. 275.1638, found 275.1638

Synthesis of (4a*S*,6*R*,8a*R*,9a*R*)-6-hydroxy-3,8a-dimethyl-5-methylene-4a,5,6,8a,9,9a-hexahydronaphtho[2,3-*b*]furan-2(4*H*)-one [22]:



22

To a stirred solution of compound **28** (263 mg, 0.958 mmol, 1 equiv.) in dry toluene under N_2 atmosphere was added Grubbs' I catalyst (78 mg, 0.0958, 0.1 equiv.). The reaction mixture was kept stirring for 16 h at room temperature. The completion of the reaction was monitored using TLC. The reaction mixture was concentrated *in vacuo* and was purified using silica gel column chromatography to obtain compound **22** in 52% yield.

R$_f$: 0.4 (50% EtOAc/Pet ether)

^{1}H NMR (400 MHz, CDCl$_3$) ^{1}H NMR (400 MHz, CDCl$_3$) δ 5.75 (d, *J* = 9.8 Hz, 1H), 5.71 (dd, *J* = 9.8, 3.5 Hz, 1H), 5.28 (s, 1H), 4.96 (s, 1H), 4.85 (dd, *J* = 11.2, 6.5 Hz, 1H), 4.46 (d, *J* = 3.1 Hz, 1H), 2.81 (d, *J* = 10.0 Hz, 1H), 2.47 – 2.35 (m, 3H), 1.82 (s, 3H), 1.29 (dd, *J* = 25.1, 13.3 Hz, 1H), 0.92 (s, 3H).

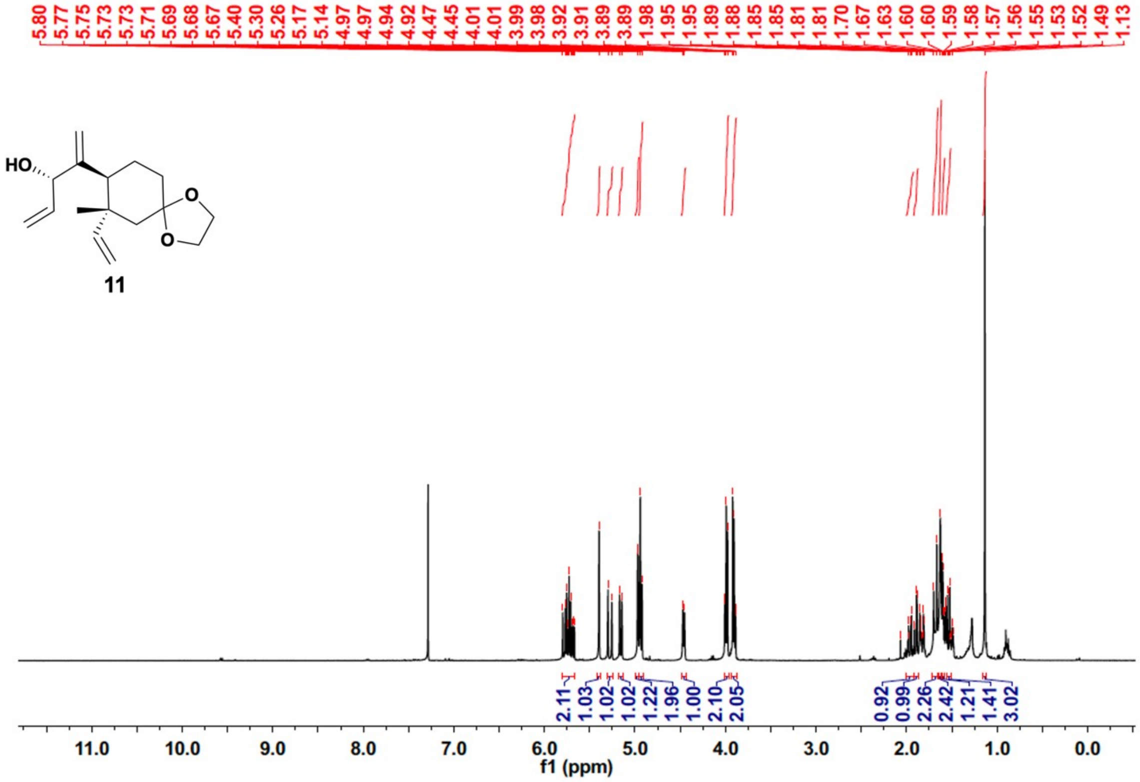
^{13}C NMR (100 MHz, CDCl$_3$): δ 174.60, 161.72, 148.19, 141.01, 125.68, 121.04, 112.17, 77.96, 69.37, 44.18, 44.13, 38.85, 24.77, 18.27, 8.40.

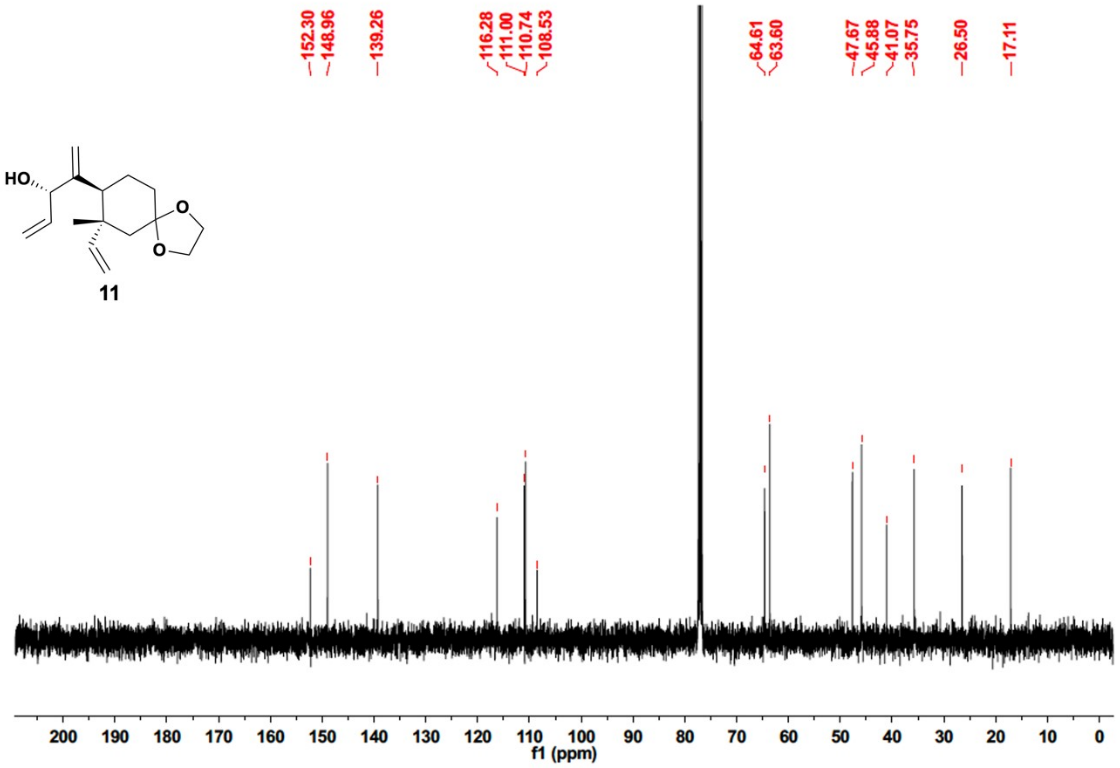
IR ν (neat, cm^{-1}): 3448, 3020, 2933, 2864, 1734, 1681, 1456, 1377, 1320, 1244, 1123, 1094, 1032, 1003, 907, 847, 764, 655, 586.

$[\alpha]_D^{21}$: -86.143 (c = 1.0; MeOH)

HRMS (ESI-QTOF): *m/z* for $C_{15}H_{18}NaO_3$, $[M+Na]^+$ calcd 269.1149, found 269.1148.

Spectra


5.80 5.77 5.75 5.73 5.71 5.69 5.68 5.67 5.40 5.30 5.26 5.17 5.14 4.97 4.97 4.94 4.92 4.47 4.45 4.01 4.01 3.99 3.98 3.92 3.91 3.89 3.89 1.98 1.95 1.95 1.89 1.88 1.85 1.85 1.81 1.81 1.70 1.67 1.63 1.60 1.60 1.59 1.58 1.57 1.56 1.55 1.53 1.52 1.49 1.13
HO
O
O
11
2.11 1.03 1.02 1.02 1.22 1.96 1.00 2.10 2.05
0.92 0.99 2.26 2.42 1.21 1.41 3.02
11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)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63.60
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45.88
41.07
35.75
26.50
17.11
200
190
180
170
160
150
140
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120
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100
90
80
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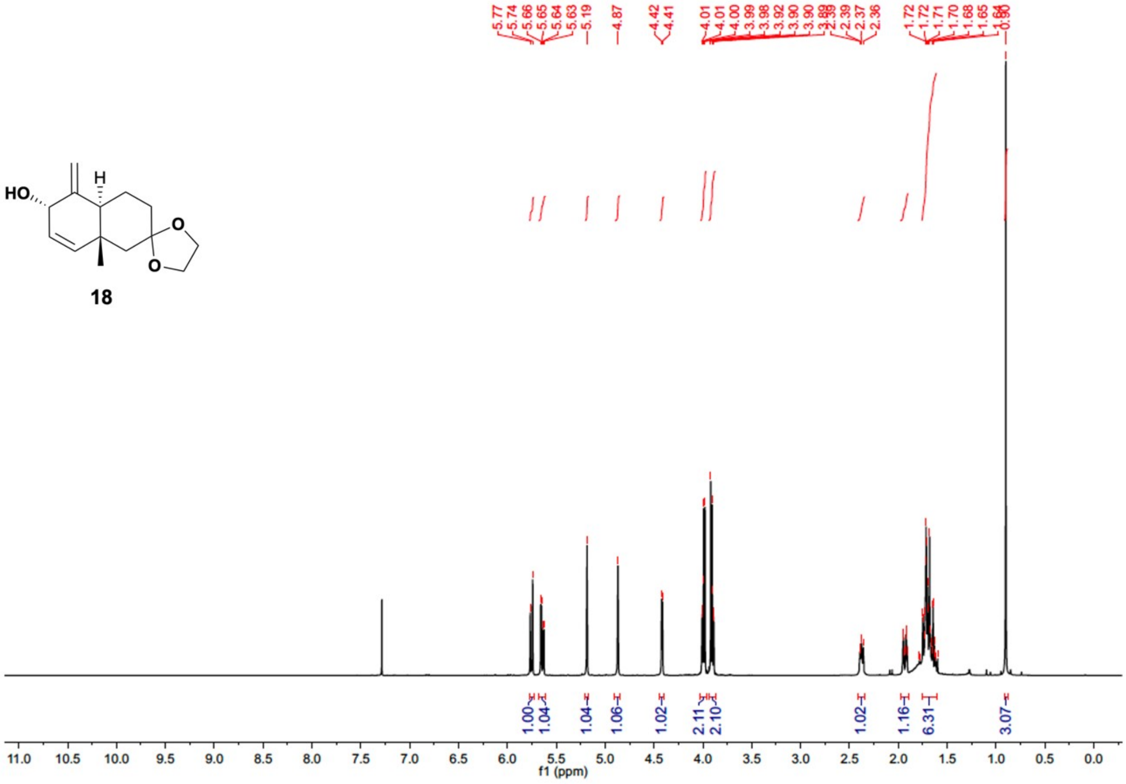
40
30
20
10
0
f1 (ppm)

11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4.01
4.00
3.99
3.98
3.92
3.90
3.90
3.89
2.39
2.39
2.37
2.36
1.72
1.72
1.71
1.70
1.68
1.65
1.64
0.90
1.00
1.04
1.04
1.06
1.02
2.11
2.10
1.02
1.16
6.31
3.07
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
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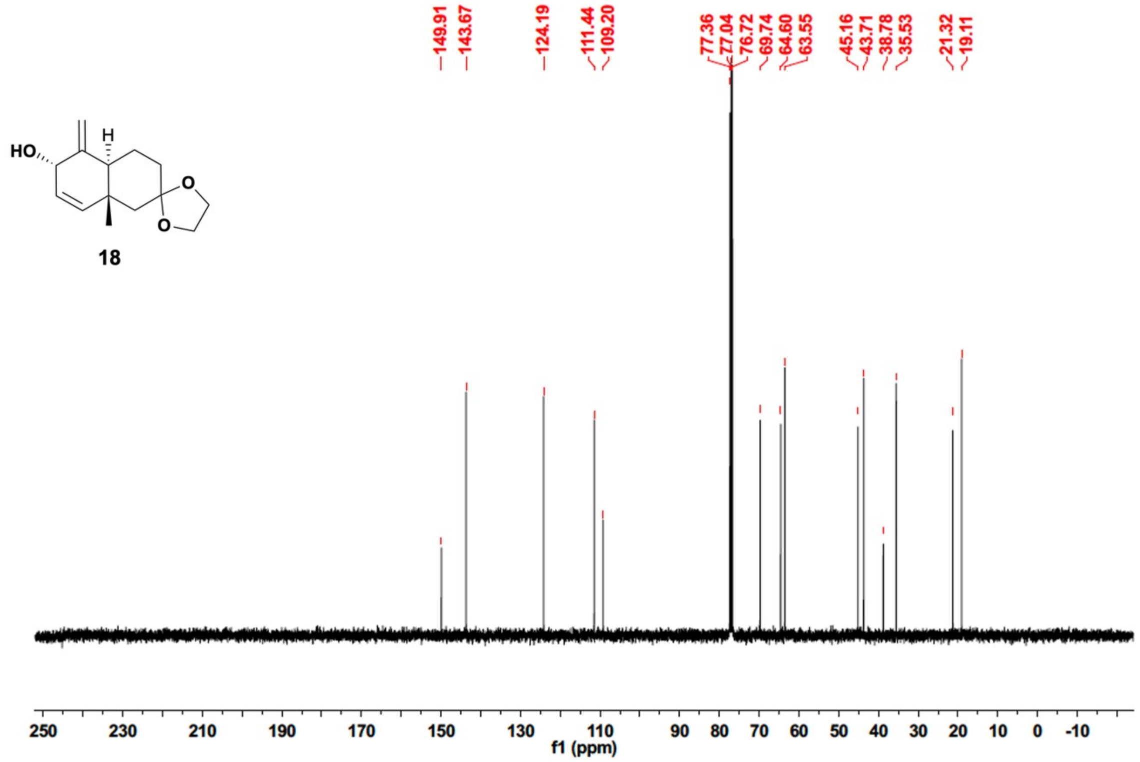
1.0
0.5
0.0
f1 (ppm)

18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76.72
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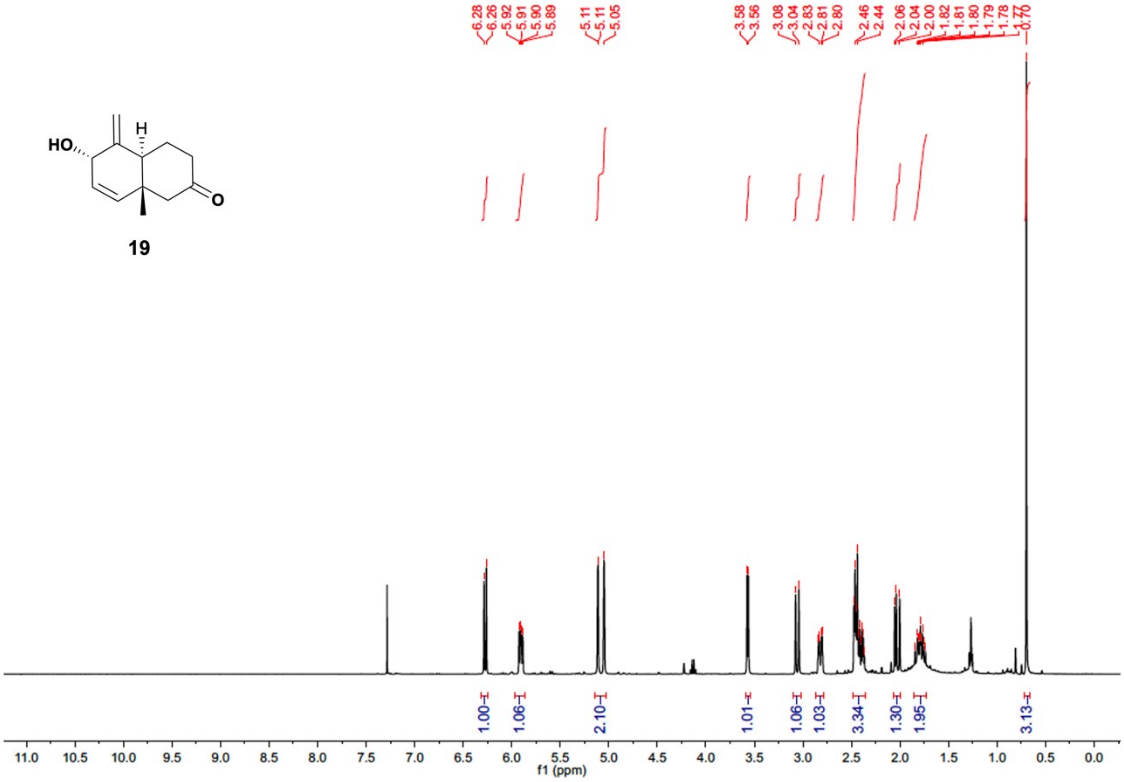
45.16
43.71
38.78
35.53
21.32
19.11
250
230
210
190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

18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H
O
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5.91
5.90
5.89
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5.11
5.05
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3.04
2.83
2.81
2.80
2.46
2.44
2.06
2.04
2.00
1.82
1.81
1.80
1.79
1.78
0.77
0.70
1.00
1.06
2.10
1.01
1.06
1.03
3.34
1.30
1.95
3.13
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10.5
10.0
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9.0
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7.5
7.0
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5.0
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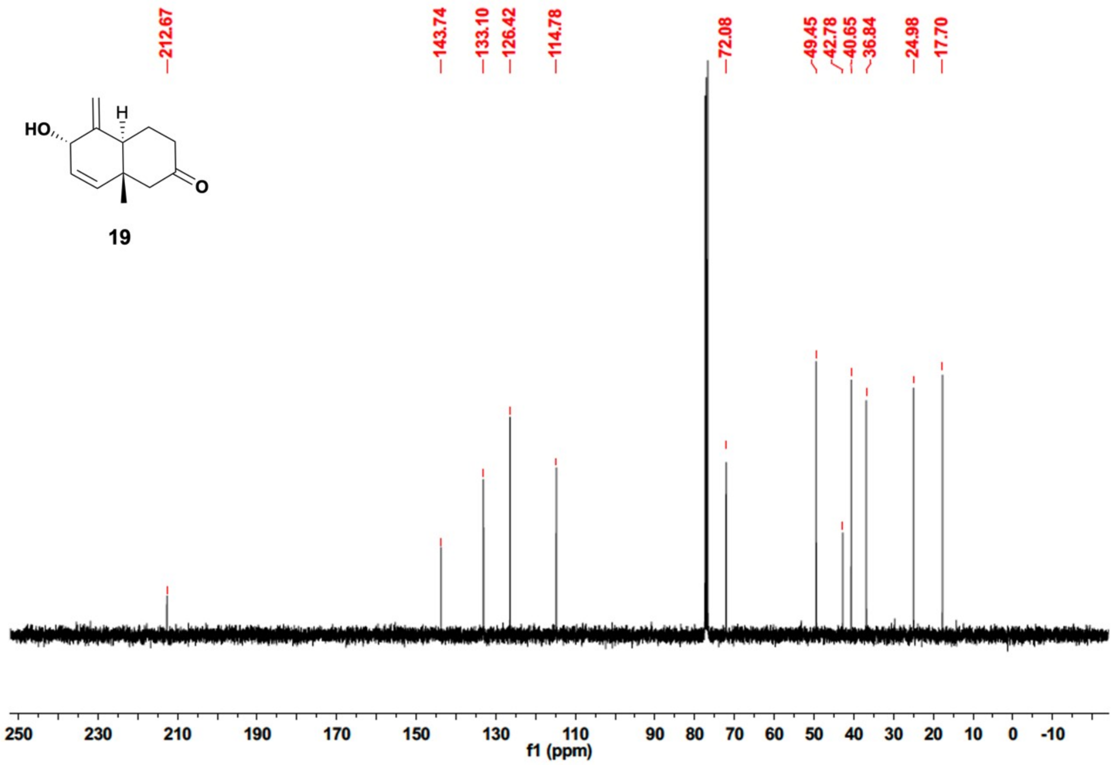
0.0
f1 (ppm)

19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24.98
17.70
250
230
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110
90
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70
60
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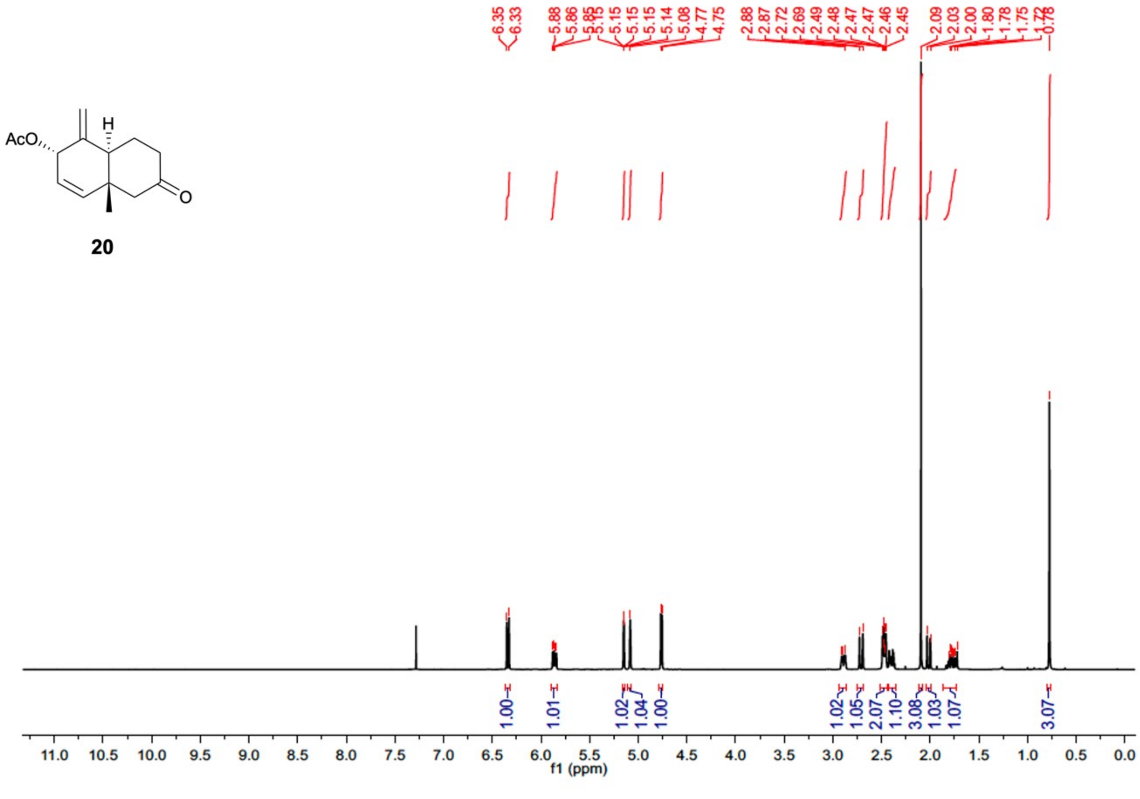
30
20
10
0
-10
f1 (ppm)

19


AcO
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O
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5.86
5.85
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5.15
5.15
5.14
5.08
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4.75
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2.72
2.69
2.49
2.48
2.47
2.47
2.46
2.45
2.09
2.03
2.00
1.80
1.78
1.75
1.72
0.78
1.00
1.01
1.02
1.04
1.00
1.02
1.05
2.07
1.10
3.08
1.03
1.07
3.07
11.0
10.5
10.0
9.5
9.0
8.5
8.0
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7.0
6.5
6.0
5.5
5.0
4.5
4.0
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3.0
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2.0
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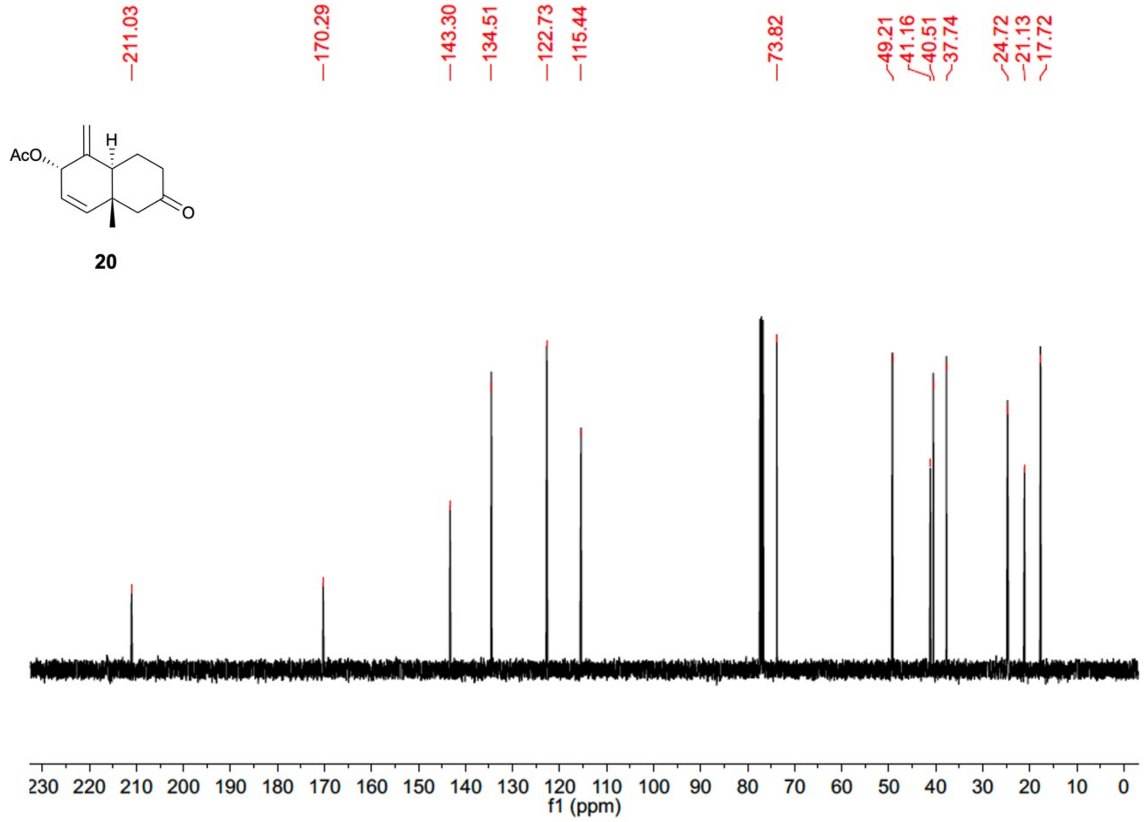
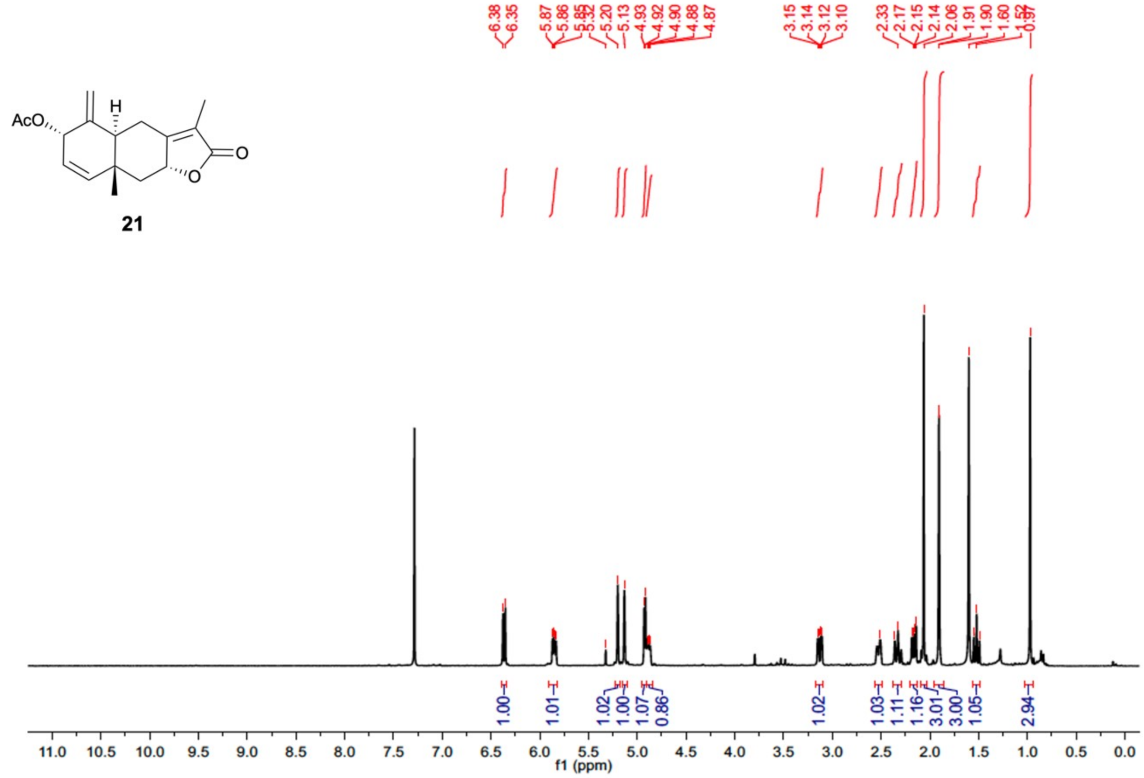
1.0
0.5
0.0
f1 (ppm)

20



211.03
170.29
143.30
134.51
122.73
115.44
73.82
49.21
41.16
40.51
37.74
24.72
21.13
17.72
AcO
H
O
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

20



6.38
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5.85
5.32
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5.13
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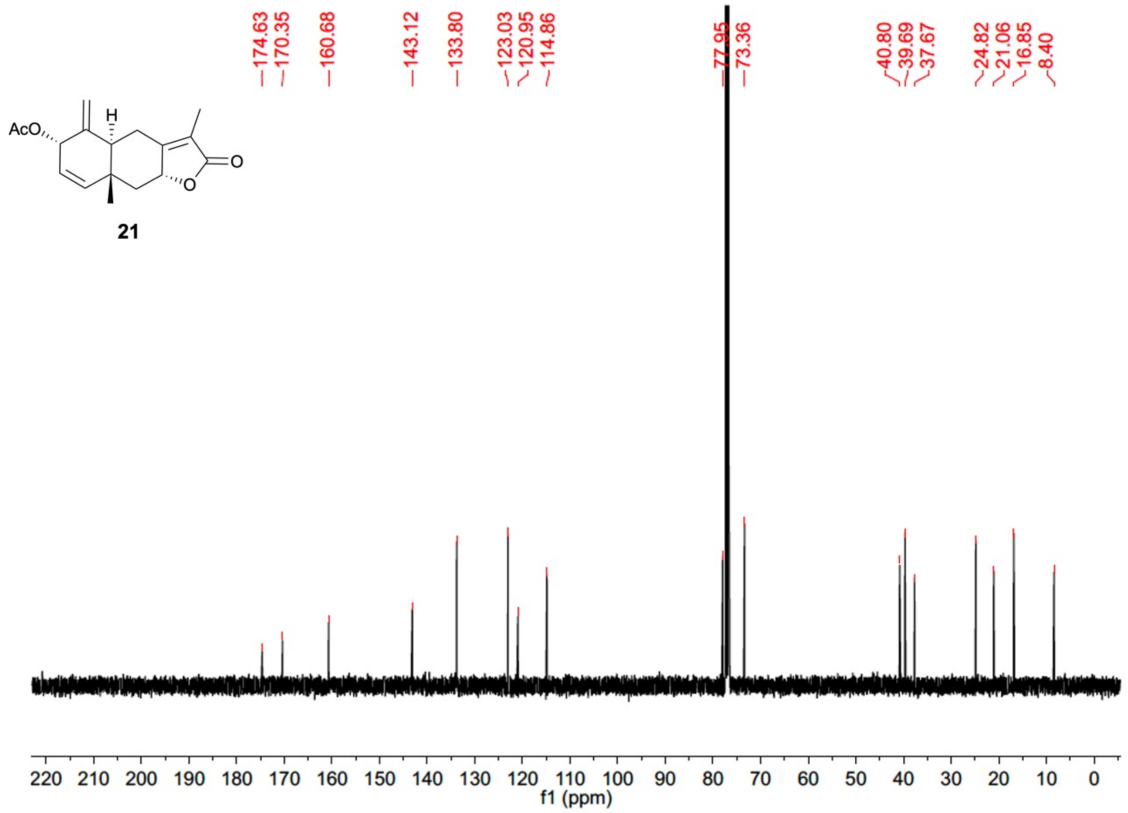
4.92
4.90
4.88
4.87
3.15
3.14
3.12
3.10
2.33
2.17
2.15
2.14
2.06
1.91
1.90
1.60
1.52
0.97
1.00
1.01
1.02
1.00
1.07
0.86
1.02
1.03
1.11
1.16
3.01
3.00
1.05
2.94
AcO
H
O
O
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

21



AcO
H
O
O
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160.68
143.12
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123.03
120.95
114.86
77.95
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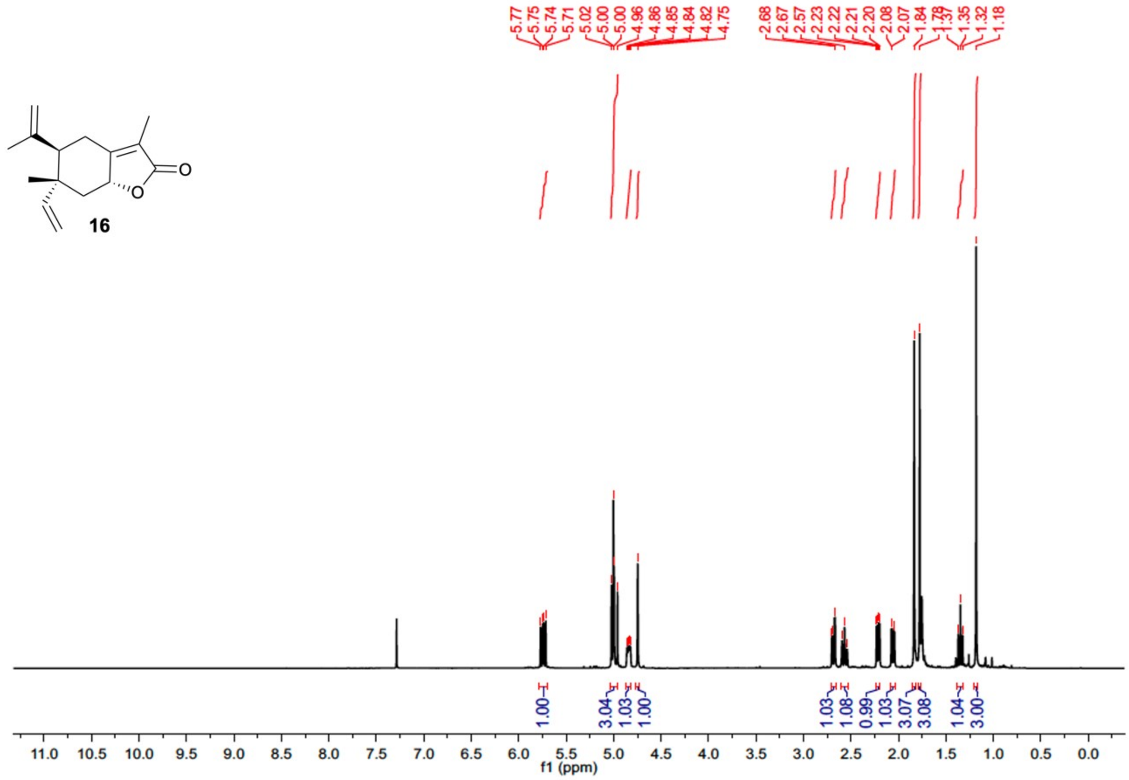
40.80
39.69
37.67
24.82
21.06
16.85
8.40
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

21



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4.75
2.68
2.67
2.57
2.23
2.22
2.21
2.20
2.08
2.07
1.84
1.78
1.37
1.35
1.32
1.18
1.00
3.04
1.03
1.00
1.03
1.08
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1.03
3.07
3.08
1.04
3.00
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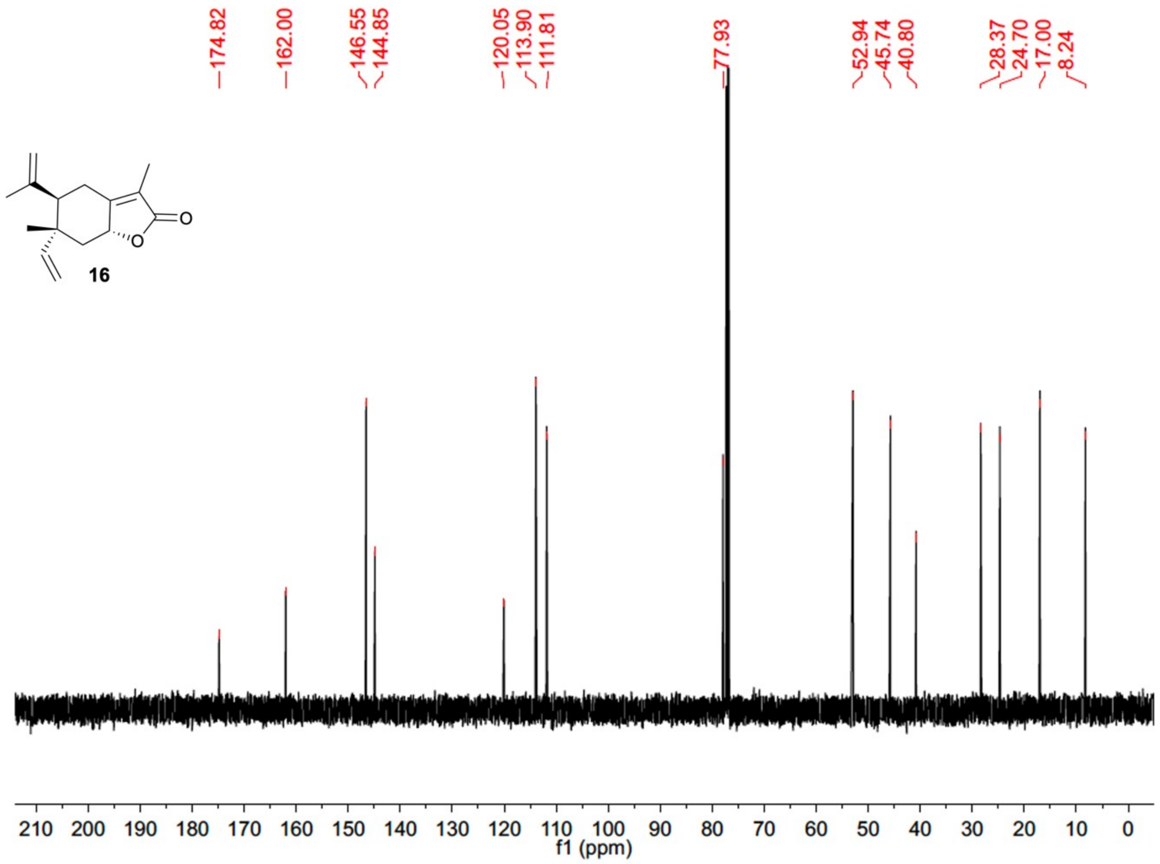
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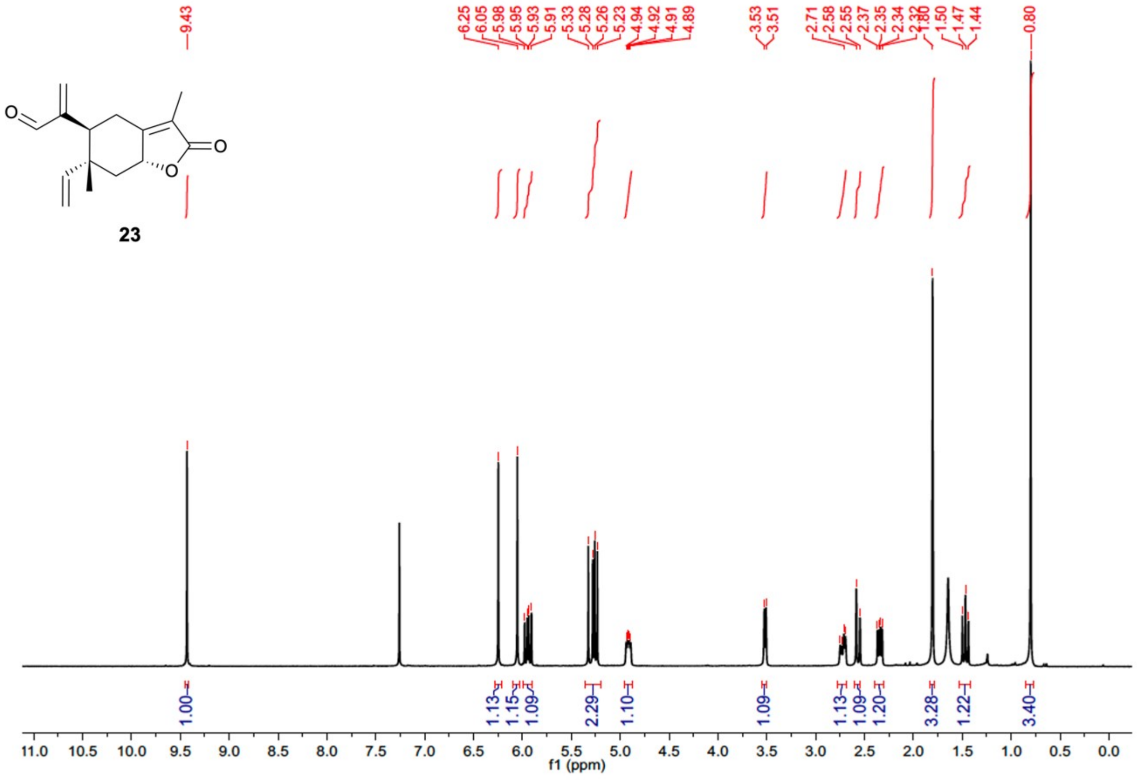
f1 (ppm)

16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4.91
4.89
3.53
3.51
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2.58
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2.35
2.34
2.32
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1.47
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1.15
1.09
2.29
1.10
1.09
1.13
1.09
1.20
3.28
1.22
3.40
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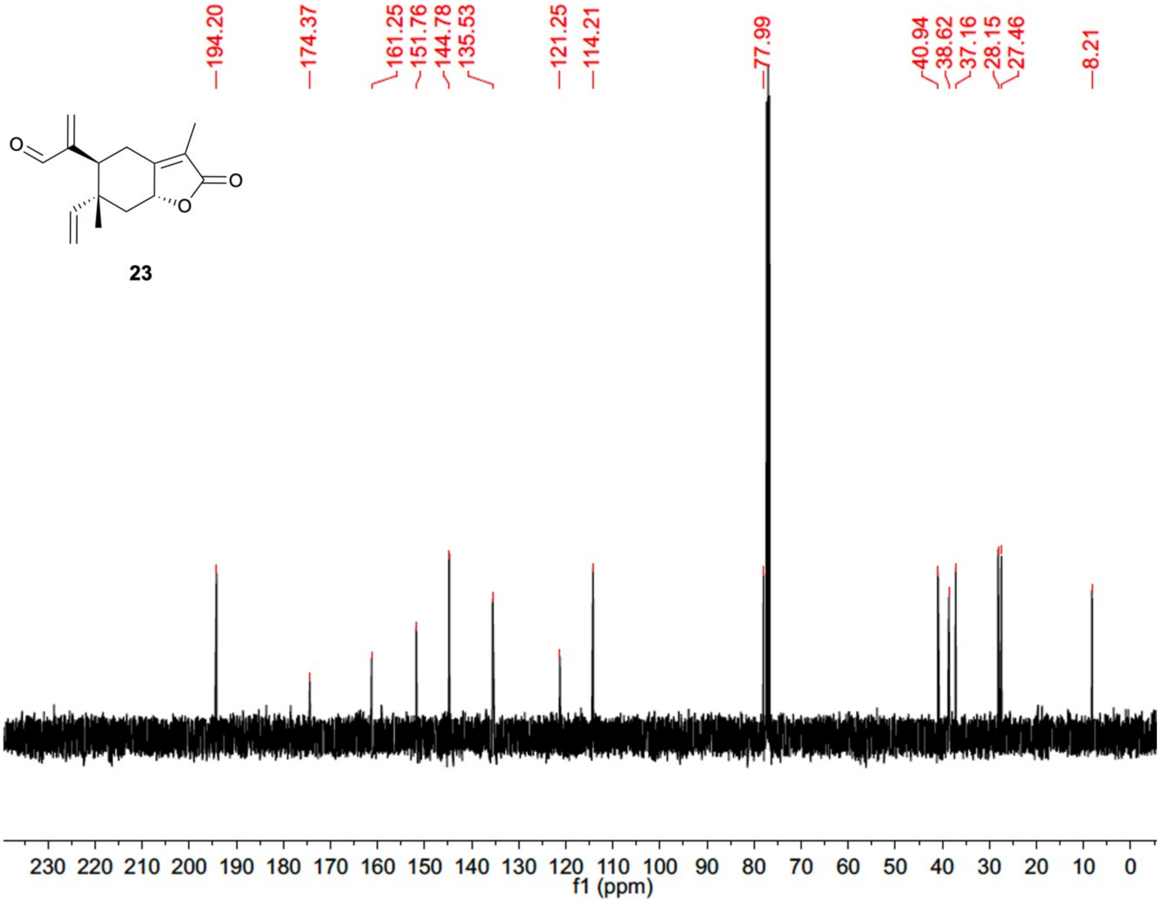
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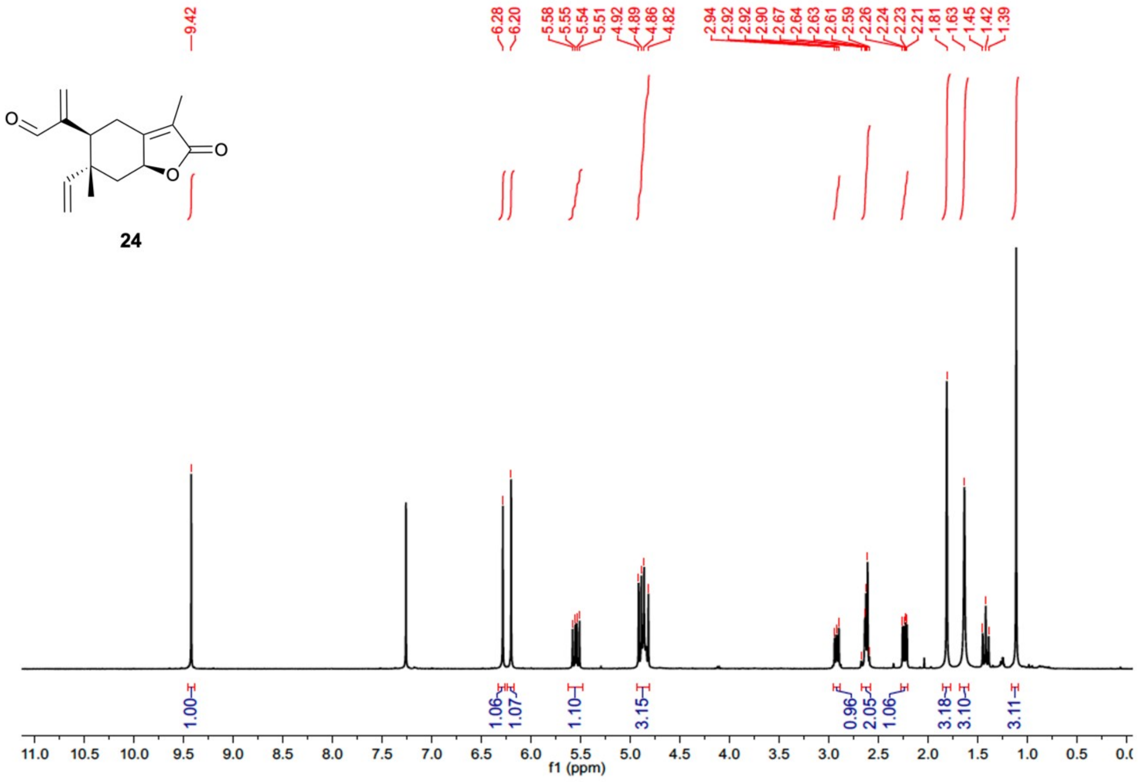
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2.92
2.90
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2.64
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2.26
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2.23
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1.42
1.39
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O
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1.06
1.07
1.10
3.15
0.96
2.05
1.06
3.18
3.10
3.11
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
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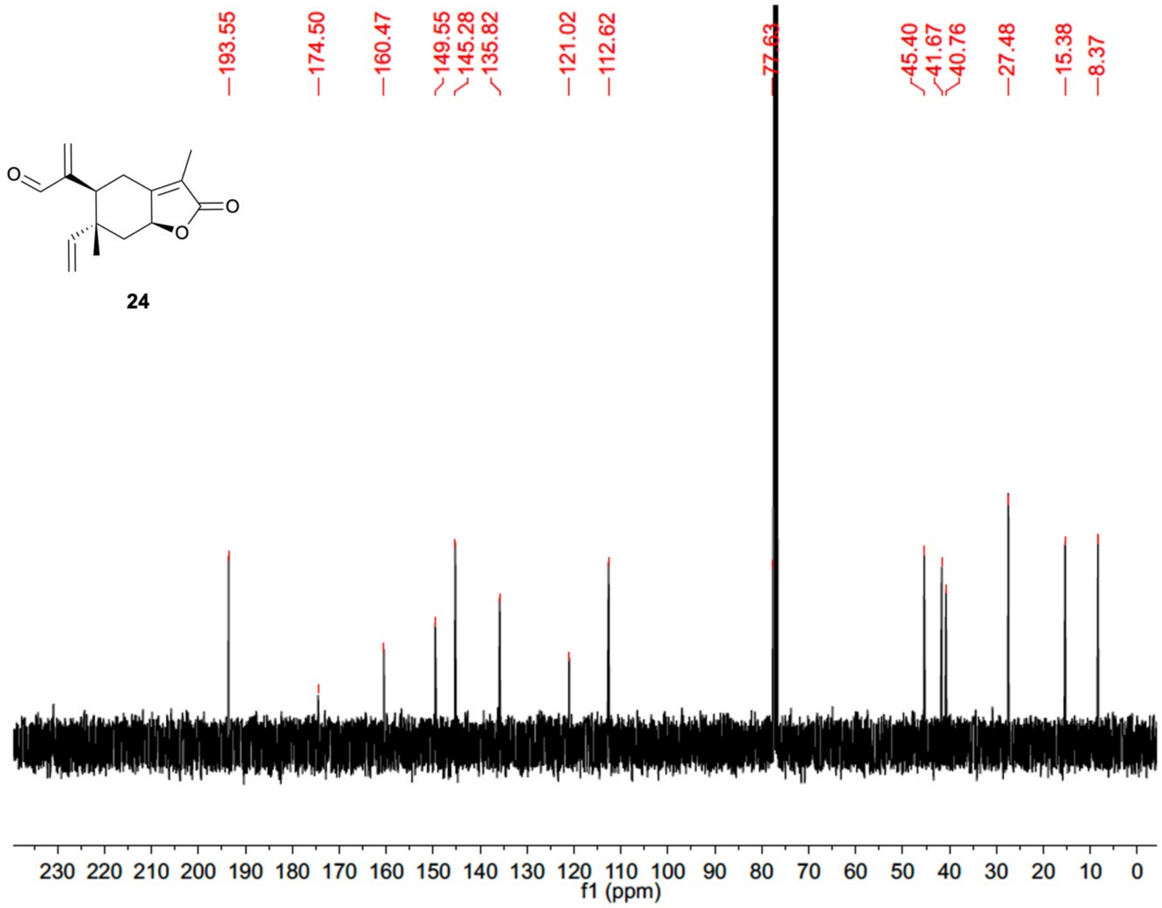
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112.62
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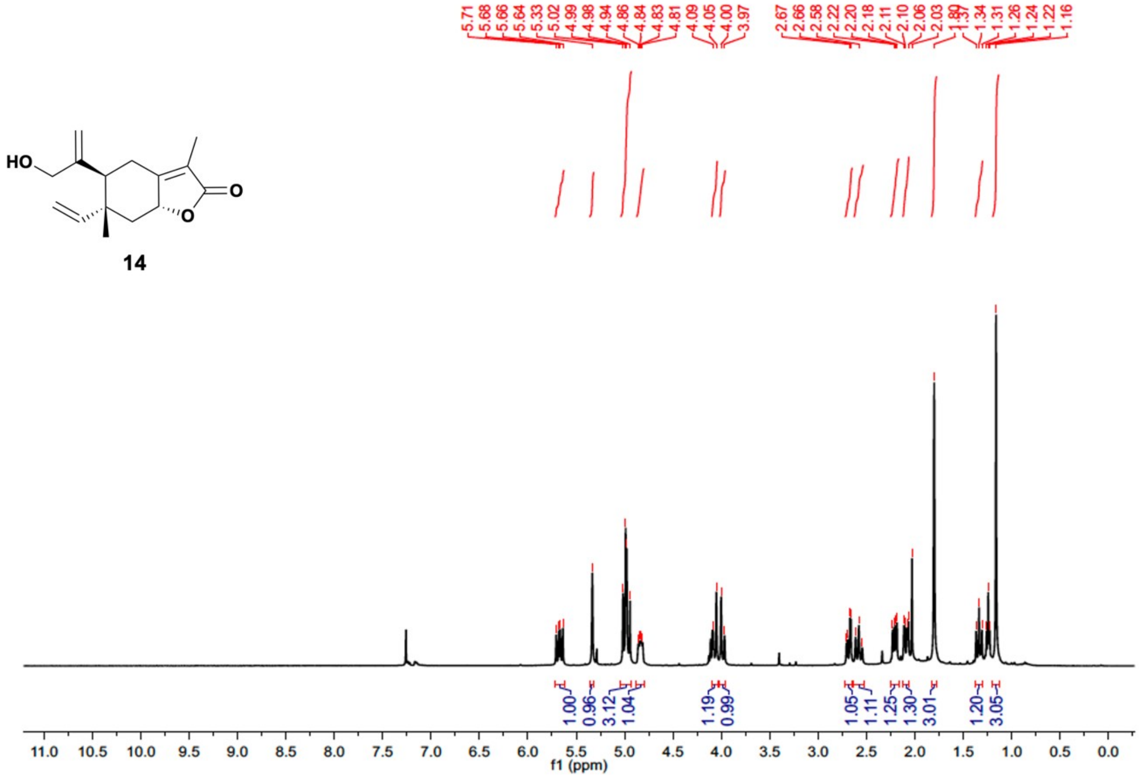
f1 (ppm)

24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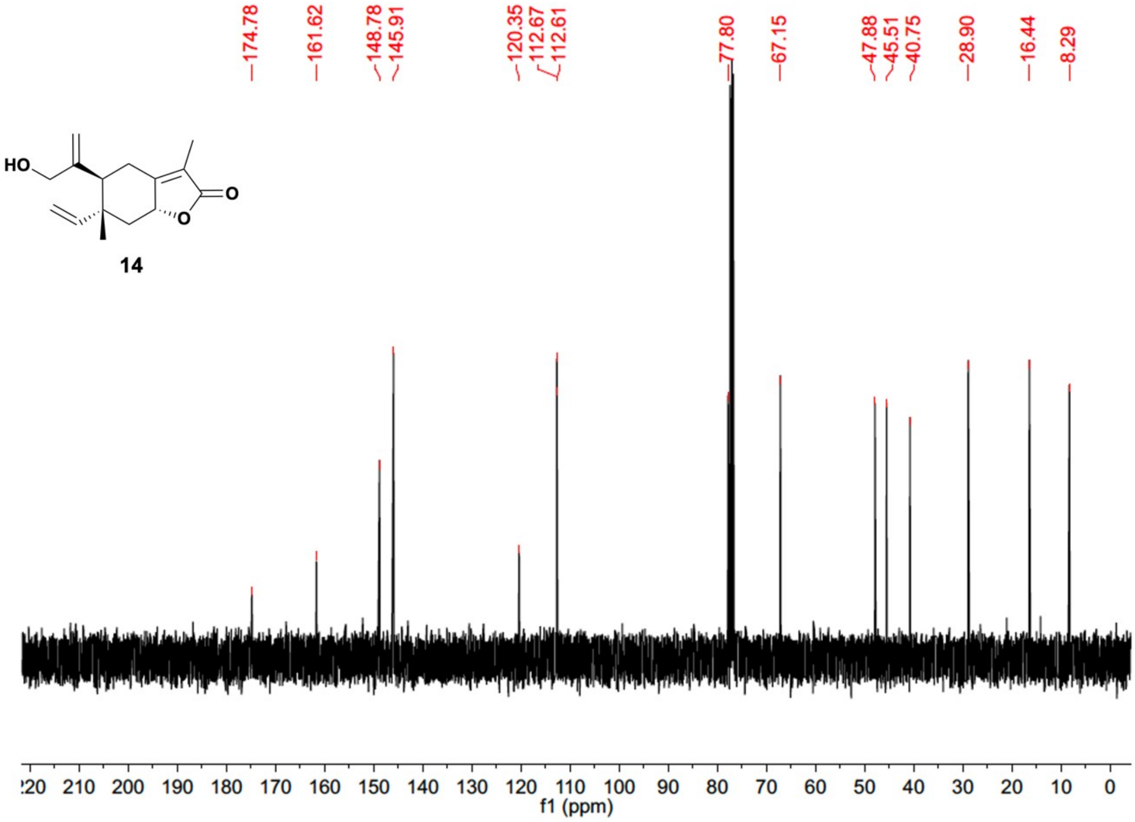
4.09
4.05
4.00
3.97
2.67
2.66
2.58
2.22
2.20
2.18
2.11
2.10
2.06
2.03
1.80
1.37
1.34
1.31
1.26
1.24
1.22
1.16
HO
O
O
1.00
0.96
3.12
1.04
1.19
0.99
1.05
1.11
1.25
1.30
3.01
1.20
3.05
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

14



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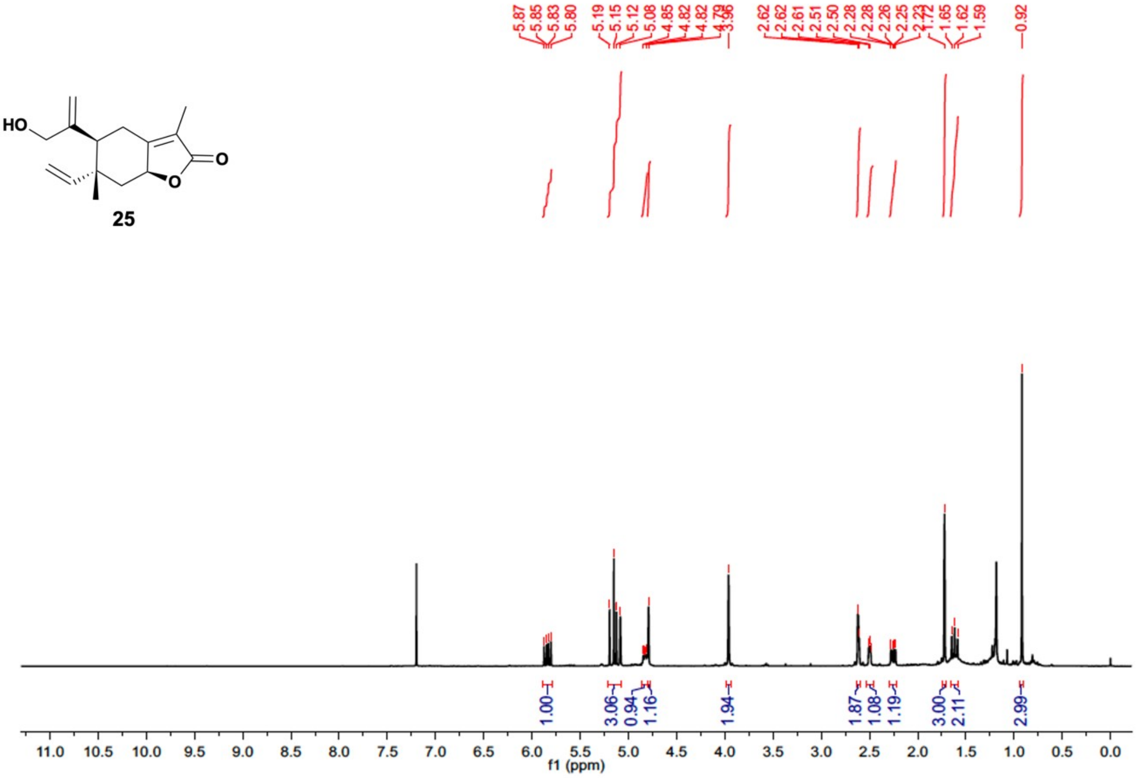
148.78
145.91
120.35
112.67
112.61
77.80
67.15
47.88
45.51
40.75
28.90
16.44
8.29
HO
O
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

14



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4.82
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2.61
2.51
2.50
2.28
2.28
2.26
2.25
2.23
1.72
1.65
1.62
1.59
0.92
HO
O
O
1.00
3.06
0.94
1.16
1.94
1.87
1.08
1.19
3.00
2.11
2.99
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
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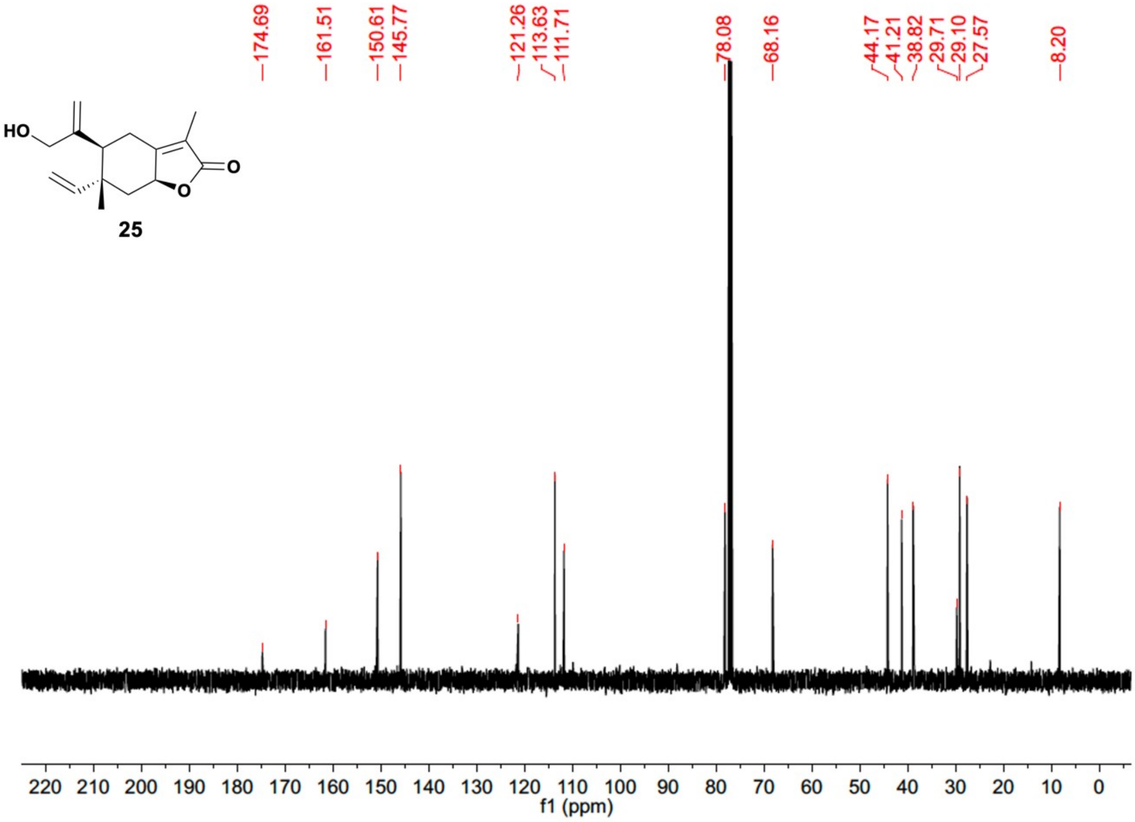
25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O
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113.63
111.71
78.08
68.16
44.17
41.21
38.82
29.71
29.10
27.57
8.20
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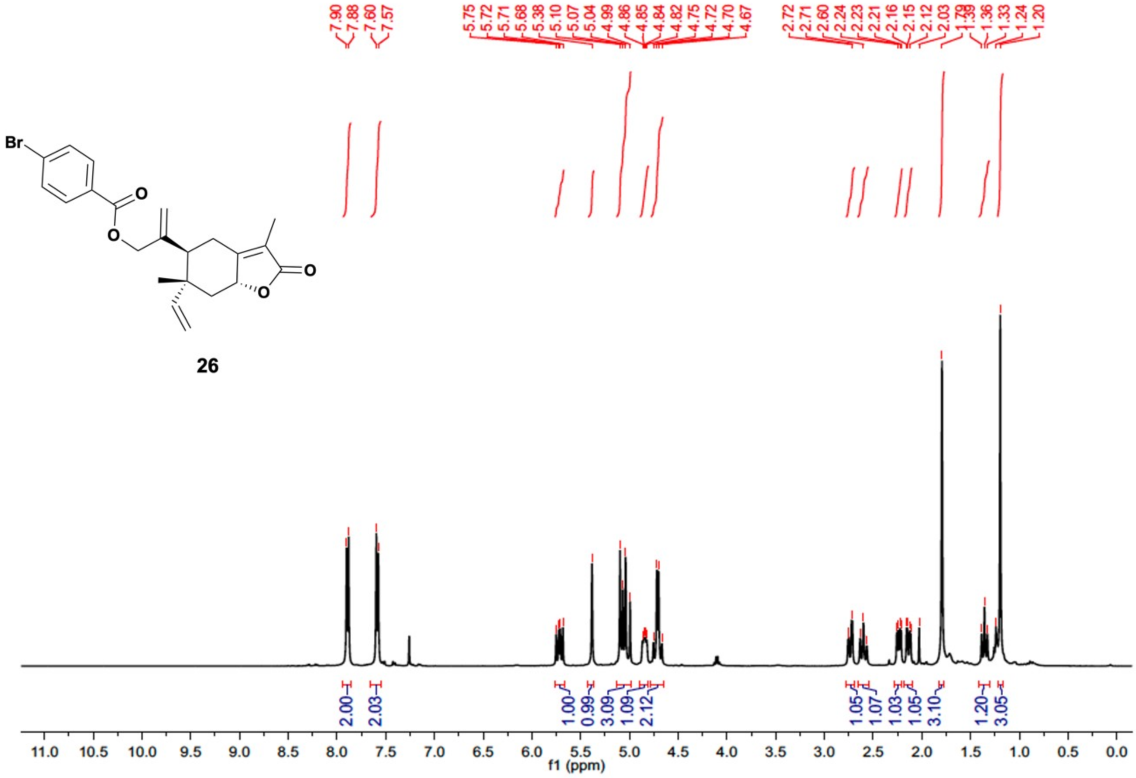
f1 (ppm)

25


Br
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O
O
O
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7.60
7.57
5.75
5.72
5.71
5.68
5.38
5.10
5.07
5.04
4.99
4.86
4.85
4.84
4.82
4.75
4.72
4.70
4.67
2.72
2.71
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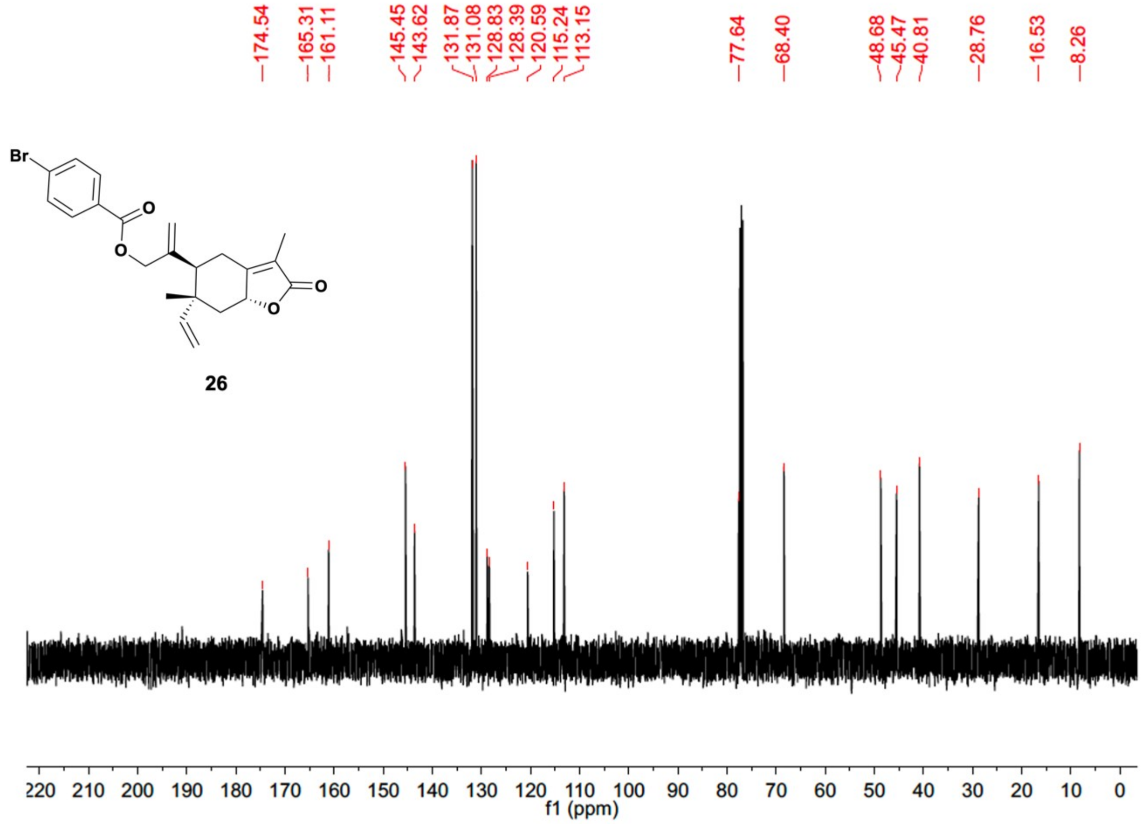
2.24
2.23
2.21
2.16
2.15
2.12
2.03
1.79
1.39
1.36
1.33
1.24
1.20
2.00
2.03
1.00
0.99
3.09
1.09
2.12
1.05
1.07
1.03
1.05
3.10
1.20
3.05
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

26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161.11
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131.08
128.83
128.39
120.59
115.24
113.15
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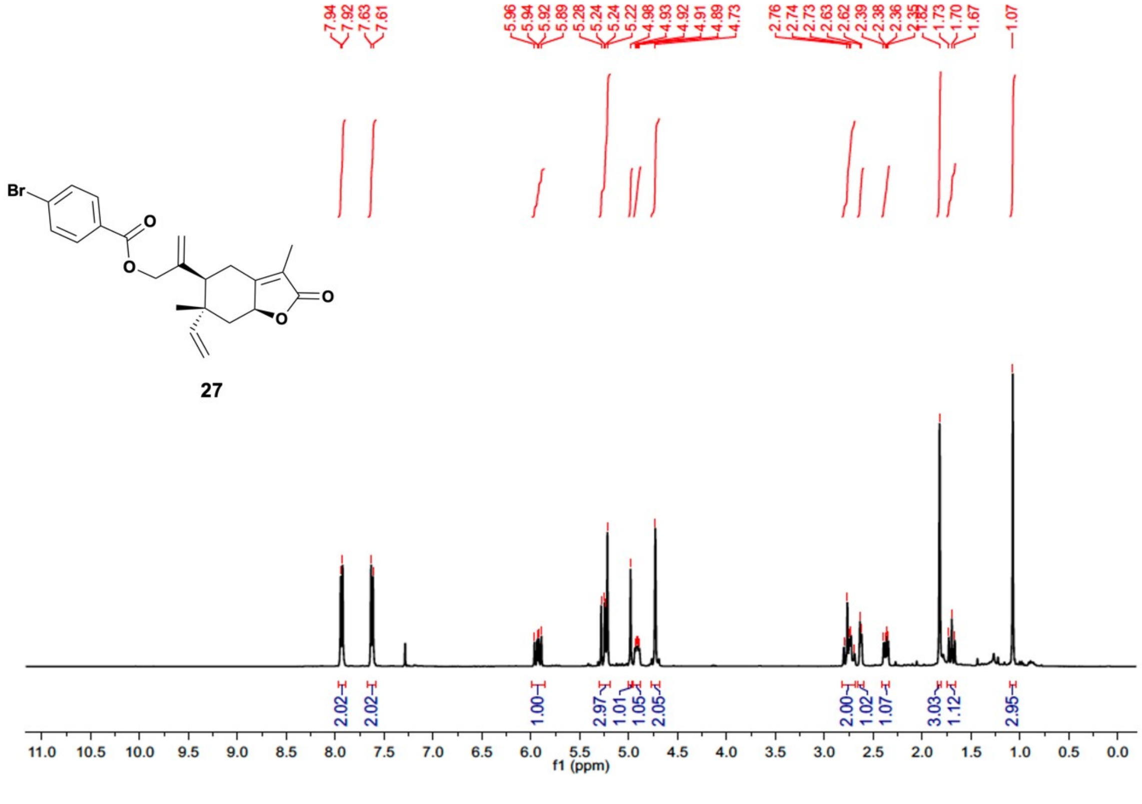
68.40
48.68
45.47
40.81
28.76
16.53
8.26
Br
O
O
O
O
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

26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5.92
5.89
5.28
5.24
5.24
5.22
4.98
4.93
4.92
4.91
4.89
4.73
2.76
2.74
2.73
2.63
2.62
2.39
2.38
2.36
2.35
1.82
1.73
1.70
1.67
1.07
Br
O
O
O
O
2.02
2.02
1.00
2.97
1.01
1.05
2.05
2.00
1.02
1.07
3.03
1.12
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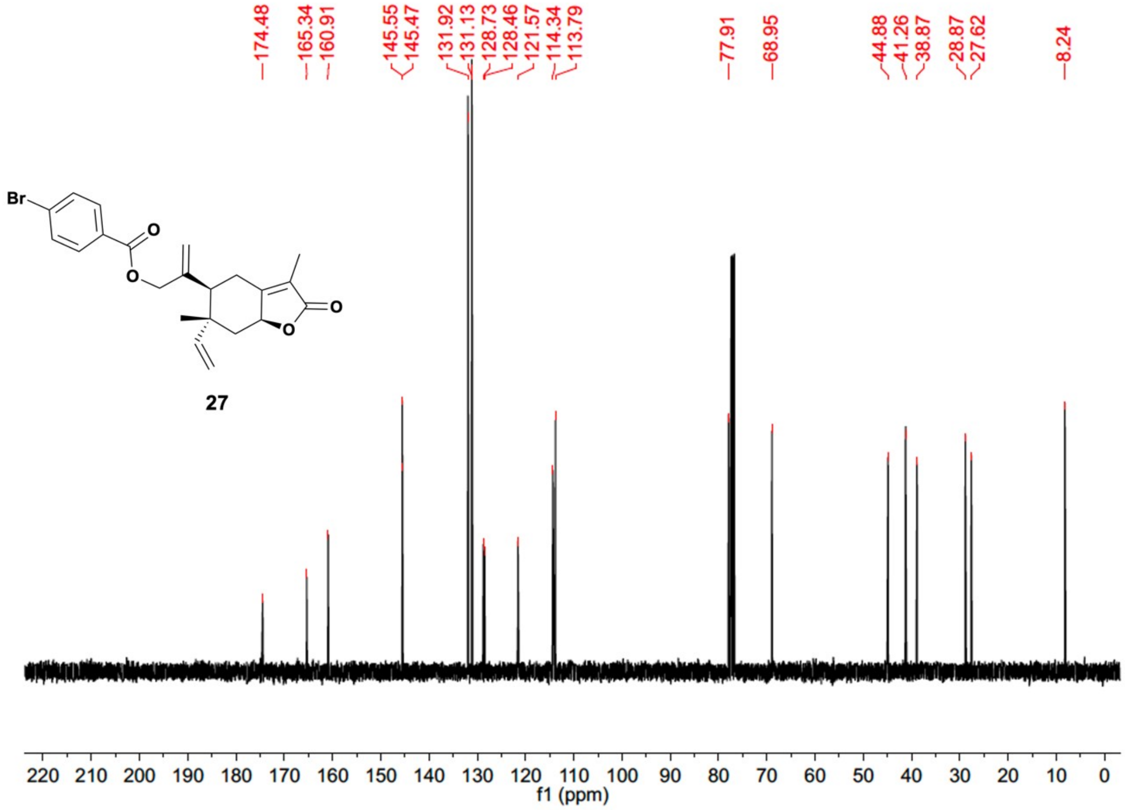
f1 (ppm)

27


27

Br
O
O
O
O
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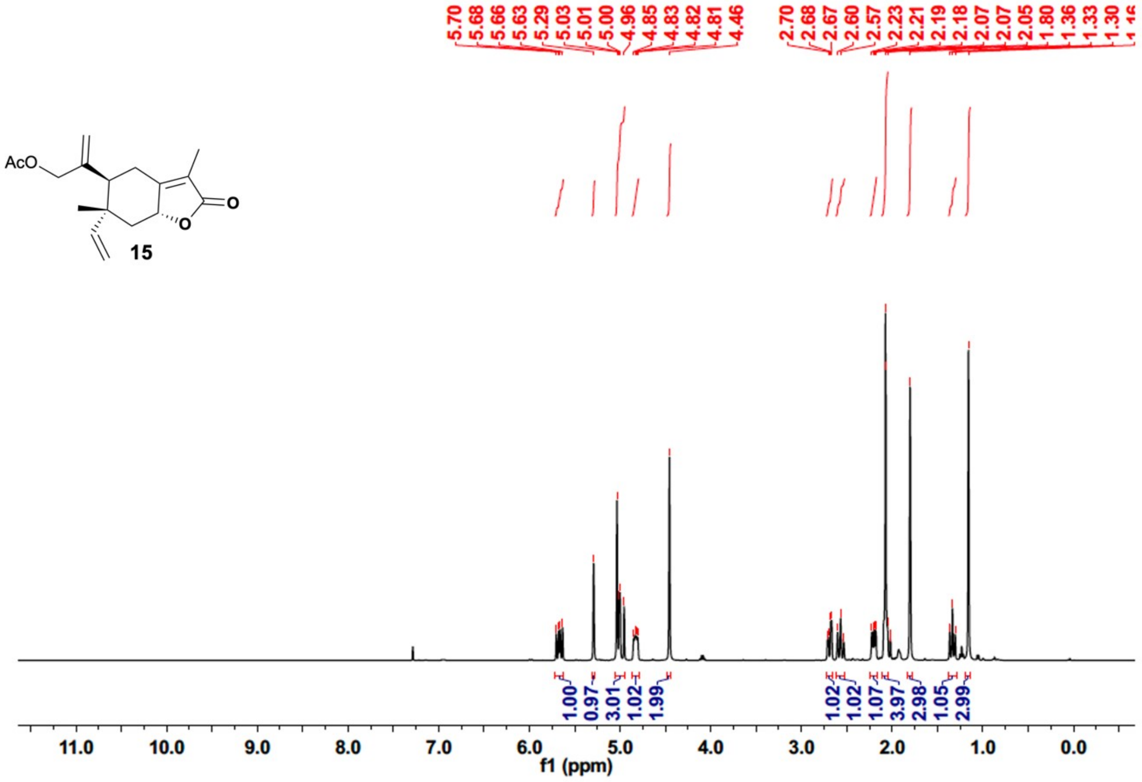
165.34
160.91
145.55
145.47
131.92
131.13
128.73
128.46
121.57
114.34
113.79
77.91
68.95
44.88
41.26
38.87
28.87
27.62
8.24
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


15

AcO
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O
5.70
5.68
5.66
5.63
5.29
5.03
5.01
5.00
4.96
4.85
4.83
4.82
4.81
4.46
2.70
2.68
2.67
2.60
2.57
2.23
2.21
2.19
2.18
2.07
2.07
2.05
1.80
1.36
1.33
1.30
1.00
0.97
3.01
1.02
1.99
1.02
1.02
1.07
3.97
2.98
1.05
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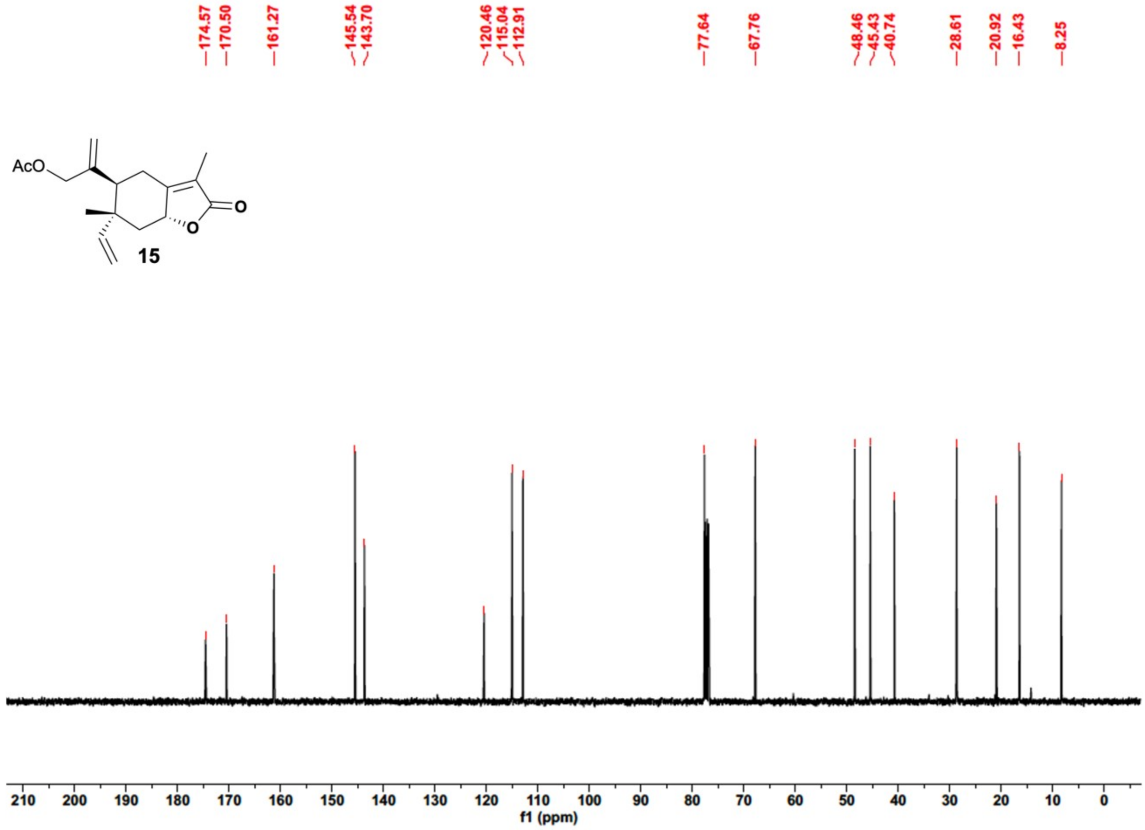
f1 (ppm)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67.76
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45.43
40.74
28.61
20.92
16.43
8.25
AcO
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O
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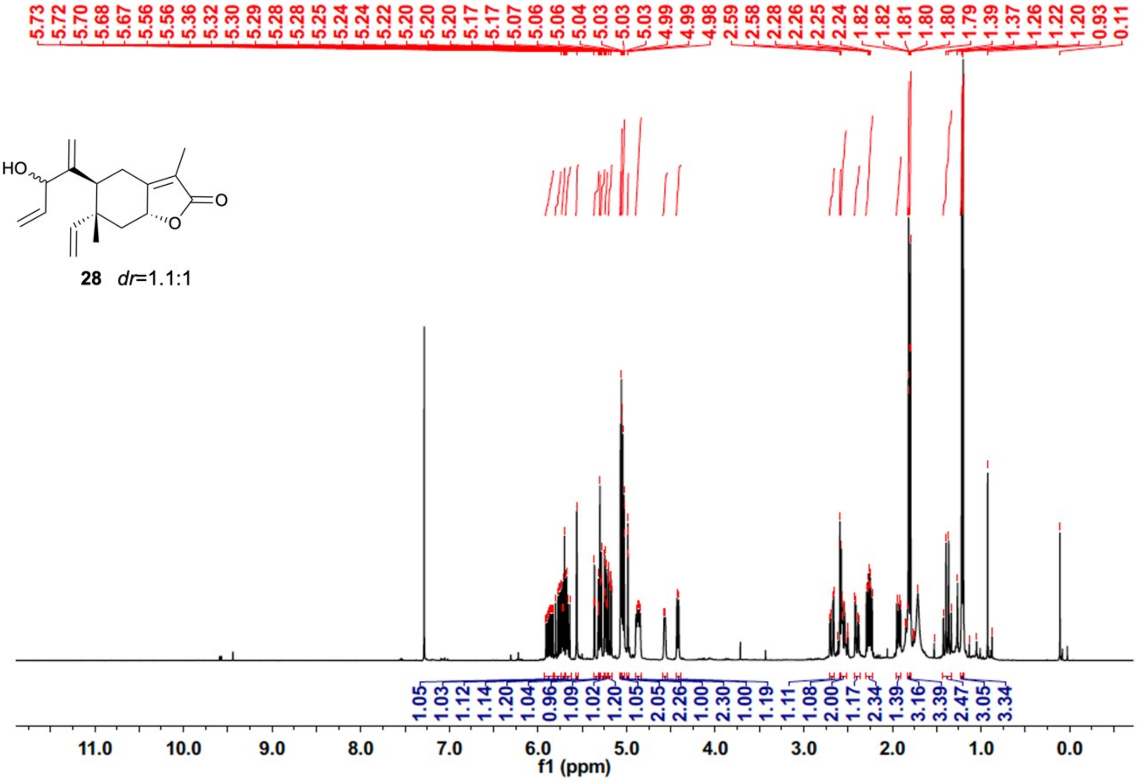
f1 (ppm)

15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5.36
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5.28
5.25
5.24
5.24
5.22
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5.20
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5.17
5.17
5.07
5.06
5.06
5.04
5.03
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1.80
1.80
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1.37
1.26
1.22
1.20
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0.11
HO
O
O
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1.03
1.12
1.14
1.20
1.04
0.96
1.09
1.02
1.20
1.05
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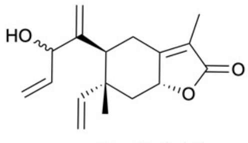
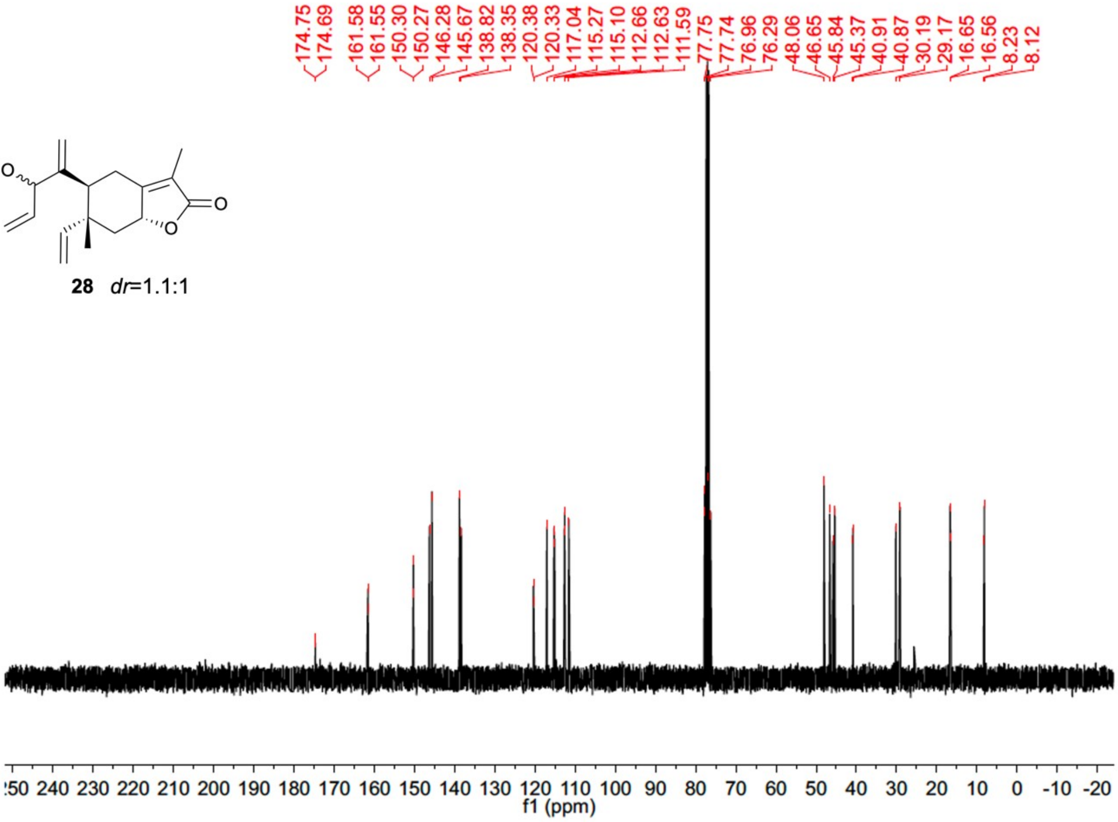
2.00
1.17
2.34
1.39
3.16
3.39
2.47
3.05
3.34
11.0 10.0 9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
f1 (ppm)

28 *dr*=1.1:1


HO
O
O

28 *dr*=1.1:1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115.27
115.10
112.66
112.63
111.59
77.75
77.74
76.96
76.29
48.06
46.65
45.84
45.37
40.91
40.87
30.19
29.17
16.65
16.56
8.23
8.12
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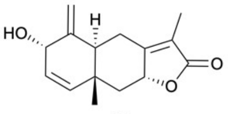
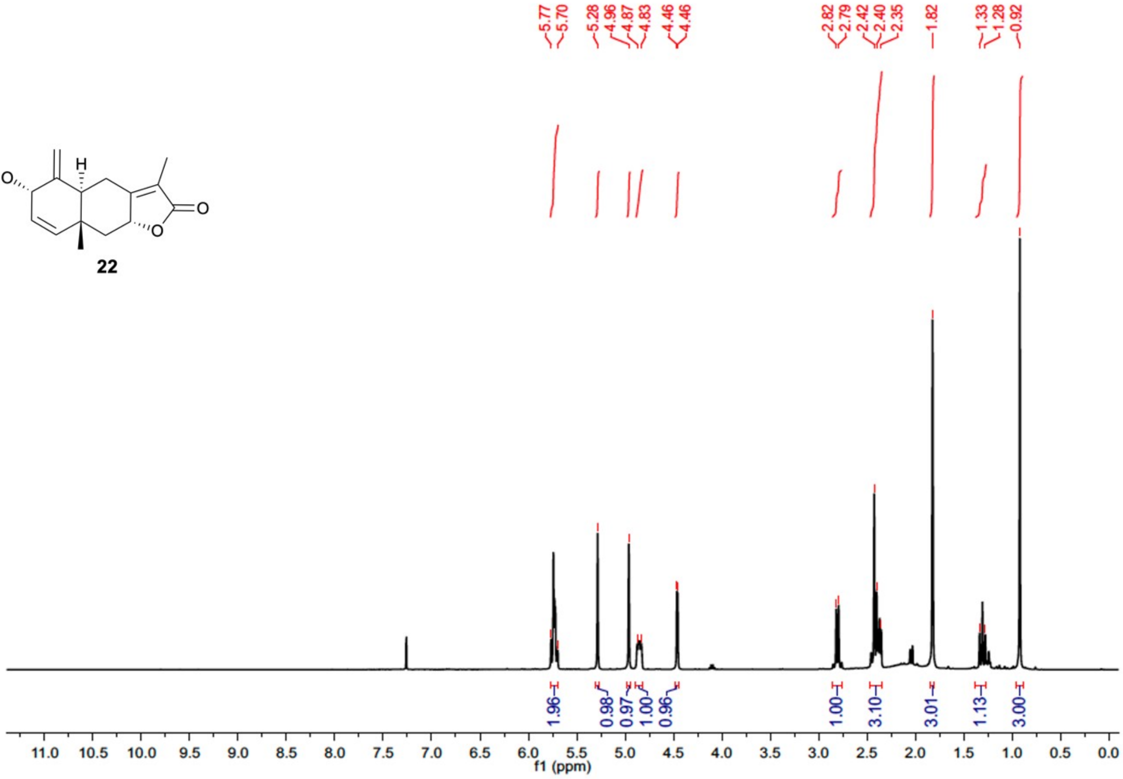
f1 (ppm)


H
HO
O
O

22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4.46
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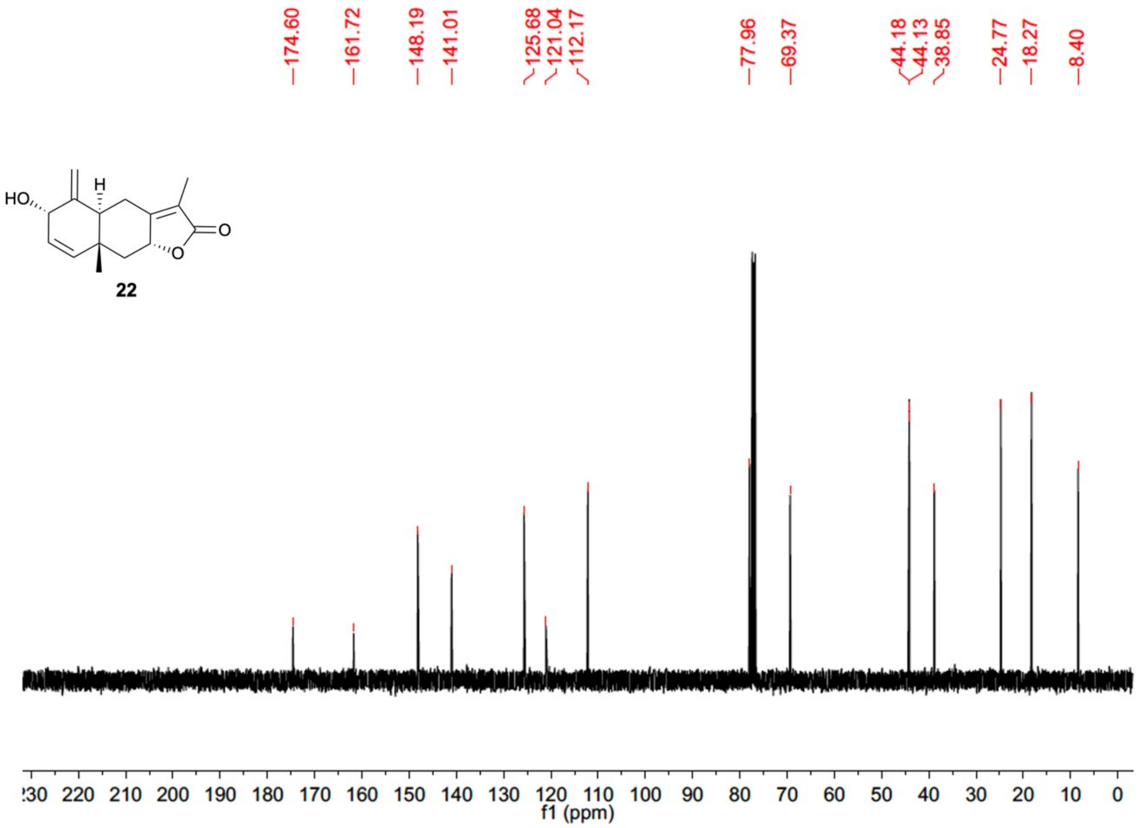
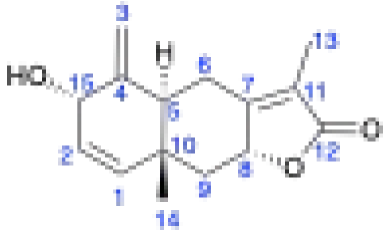
2.35
1.82
1.33
1.28
0.92
1.96
0.98
0.97
1.00
0.96
1.00
3.10
3.01
1.13
3.00
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)



Comparison of NMR spectroscopic Data

Table 1: Comparison of ^{1}H NMR spectroscopic data of isolated natural[2] linderolide E with our synthetic (*ent*)-linderolide E **22**.



22

H	**Natural Linderolide E (5)**	**Synthetic (*ent*)-Linderolide E (22)**	(N – S)^a Δδ (ppm)
1	5.77 d	5.75 d	0.02
2	5.73 dd	5.71 dd	0.02
3	4.98 br s 5.30 br s	4.96 s 5.28 s	0.02 0.02

4	-	-	-
5	2.42 d	2.47-2.35 m	-0.05
6	2.44 dd 2.82 dd	2.47-2.35 m 2.81 d	-0.03 0.01
7	-	-	-
8	4.85 m	4.85 dd	0
9	1.33 dd 2.39 dd	1.29 dd 2.47-2.35 m	0.04 -0.08
10	-	-	-
11	-	-	-
12	-	-	-
13	1.84 d	1.82 s	0.02
14	0.94 s	0.92 s	0.02
15	4.47 d	4.46 d	0.01

[a] Difference in chemical shift value between natural and synthetic one.

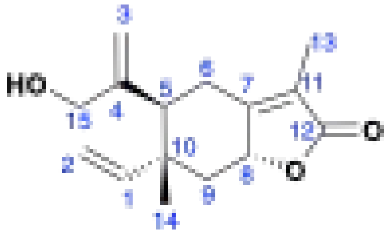
Table 2: Comparison of ^{13}C NMR spectroscopic data of isolated natural[2] linderolide E with our synthetic (*ent*)-linderolide E **22**.

C	**Natural Linderolide E (5)**	**Synthetic (*ent*)-Linderolide E (22)**	(N – S)[a] $\Delta\delta$ (ppm)
1	141.1	141.01	0.09
2	125.7	125.68	0.02
3	112.1	112.17	-0.07
4	148.3	148.19	0.11
5	44.2	44.13	0.07
6	24.8	24.77	0.03
7	161.5	161.72	-0.22
8	77.9	77.96	-0.06
9	44.3	44.18	0.12

10	38.9	38.85	0.05
11	121.2	121.04	0.16
12	174.3	174.6	-0.3
13	8.4	8.4	0
14	18.3	18.27	0.03
15	69.5	69.37	0.13

[a] Difference in chemical shift value between natural and synthetic one.

Table 3: Comparison of ^{1}H NMR spectroscopic data of isolated natural[2,3] 15-hydroxy isogermafurenolide with our synthetic (*ent*)-15-hydroxy isogermafurenolide **14**.



14

H	**Natural 15-hydroxy isogermafurenolide (14)**	**Synthetic (*ent*)-15 hydroxy isogermafurenolide (14)**	(N – S)[a] $\Delta\delta$ (ppm)
1	5.69 dd	5.67 dd	0.02
2	4.99 dd 5.03 dd	4.98 dd 4.98 dd	0.01 0.05
3	5.00 ddd	4.98 dd	0.02

	5.35 ddd	5.33 s	0.02
4	-	-	-
5	2.11 ddq	2.09 dd	0.02
6	2.60 ddqd 2.70 dd	2.58 t 2.68 dd	0.02 0.02
7	-	-	-
8	4.85 ddqd	4.84 dd	0.01
9	1.36 ddq 2.23 dd	1.34 t 2.21 dd	0.02 0.02
10	-	-	-
11	-	-	-
12	-	-	-
13	1.82 dd	1.80 s	0.02
14	1.18 dd	1.16 s	0.02
15	4.00 ddd 4.09 ddd	3.98 d 4.10-4.04 (m)	0.02 -0.01

[a] Difference in chemical shift value between natural and synthetic one.

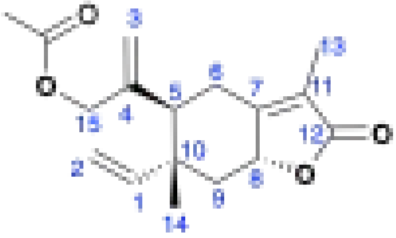
Table 4: Comparison of ^{13}C NMR spectroscopic data of isolated natural[2,3] 15-hydroxy isogermafurenolide with our synthetic (*ent*)-15-hydroxy isogermafurenolide **14**.

C	**Natural 15-hydroxy isogermafurenolide (14)**	**Synthetic (*ent*)-15 hydroxy isogermafurenolide (14)**	(N – S)[a] $\Delta\delta$ (ppm)
1	145.9	145.91	-0.01
2	112.7	112.67	0.03
3	112.6	112.61	-0.01
4	148.8	148.78	0.02
5	47.9	47.88	0.02
6	28.9	28.9	0
7	161.5	161.62	-0.12
8	77.8	77.8	0

9	45.5	45.51	-0.01
10	40.8	40.75	0.05
11	120.4	120.35	0.05
12	174.7	174.78	-0.08
13	8.3	8.29	0.01
14	16.5	16.44	0.06
15	67.2	67.15	0.05

[a] Difference in chemical shift value between natural and synthetic one.

Table 5: Comparison of ^{1}H NMR spectroscopic data of isolated natural[2,3] 15-acetoxy isogermafurenolide with our synthetic (*ent*)-15-acetoxy isogermafurenolide **15**.



15

H	Natural 15-acetoxy isogermafurenolide (15)	Synthetic (*ent*)-15 acetoxy isogermafurenolide (15)	(N – S)[a] Δ*δ* (ppm)
1	5.68 dd	5.67 dd	0.01
2	5.00 dd 5.05 dd	5.00 dd 5.00 dd	0 0.05
3	5.06 dd 5.32 dd	5.00 dd 5.29 s	0.06 0.03
4	-	-	-
5	2.09 ddq	2.06 t	0.03
6	2.58 ddqd 2.71 dd	2.57 t 2.69 dd	0.01 0.02
7	-	-	-
8	4.85 ddqd	4.83 dd	0.02

9	1.36 ddq 2.23 dd	1.33 t 2.20 dd	0.03 0.03
10	-	-	-
11	-	-	-
12	-	-	-
13	1.83 dd	1.80 s	0.03
14	1.18 dd	1.16 s	0.02
15	4.48 dd	4.46 d	0.02
CH$_3$COO-15	2.11 s	2.06 s	0.05

[a] Difference in chemical shift value between natural and synthetic one.

Table 6: Comparison of ^{13}C NMR spectroscopic data of isolated natural[2,3] 15-acetoxy isogermafurenolide with our synthetic (*ent*)-15-acetoxy isogermafurenolide **15**.

C	**Natural 15-acetoxy isogermafurenolide (15)**	**Synthetic (*ent*)-15 acetoxy isogermafurenolide (15)**	(N – S)[a] Δδ (ppm)
1	145.5	145.54	-0.04
2	113.1	112.91	0.19
3	115.3	115.04	0.26
4	143.7	143.70	0
5	48.6	48.46	0.14
6	28.7	28.61	0.09
7	161.7	161.27	0.43
8	77.9	77.64	0.26
9	45.5	45.43	0.07

10	40.7	40.74	-0.04
11	120.4	120.46	-0.06
12	175.1	174.57	0.53
13	8.3	8.25	0.05
14	16.5	16.43	0.07
15	67.9	67.76	0.14
CH$_3$COO**-15**	20.9	20.92	-0.02
CH$_3$**COO-15**	171.0	170.50	0.5

[a] Difference in chemical shift value between natural and synthetic one.

X-Ray Crystallographic Analysis

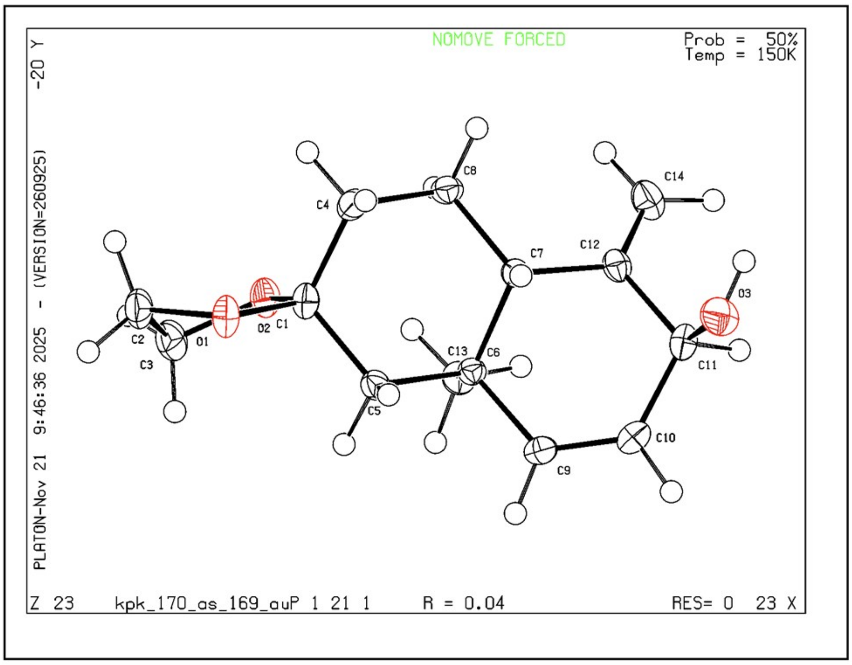


Figure 1: ORTEP drawing of **18** showing thermal ellipsoid at the 50% probability level

Table 7:

Datablock: kpk_170_as_169_autored

Bond precision: C-C = 0.0020 A Wavelength=0.71073

Cell: a=8.8535(2) b=8.0124(2) c=9.0131(2)
alpha=90 beta=104.910(3) gamma=90

Temperature: 150 K

	Calculated	Reported
Volume	617.84(3)	617.84(3)
Space group	P 21	P 1 21 1
Hall group	P 2yb	P 2yb
Moiety formula	C14 H20 O3	C14 H20 O3
Sum formula	C14 H20 O3	C14 H20 O3
Mr	236.30	236.30
Dx,g cm-3	1.270	1.270
Z	2	2
Mu (mm-1)	0.088	0.088
F000	256.0	256.0
F000'	256.13	
h,k,lmax	13,12,13	13,11,13
Nref	4828[2557]	4063
Tmin,Tmax	0.983,0.994	0.955,1.000
Tmin'	0.979	

Correction method= # Reported T Limits: Tmin=0.955 Tmax=1.000
AbsCorr = MULTI-SCAN

Data completeness= 1.59/0.84 Theta(max)= 33.462

R(reflections)= 0.0391(3307) wR2(reflections)= 0.0964(4063)

S = 1.083 Npar= 156

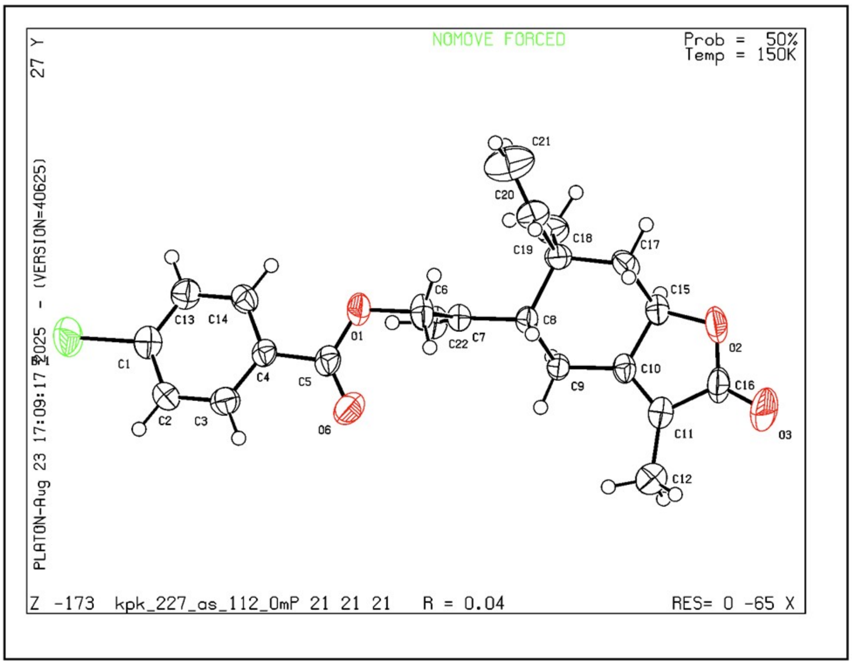


Figure 2: ORTEP drawing of **26** showing thermal ellipsoid at the 50% probability level

Table 8:
Datablock: kpk_227_as_112_0m

Bond precision: C-C = 0.0080 A Wavelength=0.71073

Cell: a=9.3798(15) b=10.7769(19) c=19.553(3)
alpha=90 beta=90 gamma=90

Temperature: 150 K

	Calculated	Reported
Volume	1976.5(6)	1976.5(6)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C22 H23 Br O4	C22 H23 Br O4
Sum formula	C22 H23 Br O4	C22 H23 Br O4
Mr	431.30	431.31
Dx,g cm-3	1.449	1.449
Z	4	4
Mu (mm-1)	2.104	2.104
F000	888.0	888.0
F000'	887.25	
h,k,lmax	11,12,23	11,12,23
Nref	3480[2002]	3477
Tmin,Tmax	0.430,0.604	0.442,0.746
Tmin'	0.397	

Correction method= # Reported T Limits: Tmin=0.442 Tmax=0.746

AbsCorr = NUMERICAL

Data completeness= 1.74/1.00 Theta(max)= 24.999

R(reflections)= 0.0434(2789) wR2(reflections)= 0.1068(3477)

S = 1.031 Npar= 246

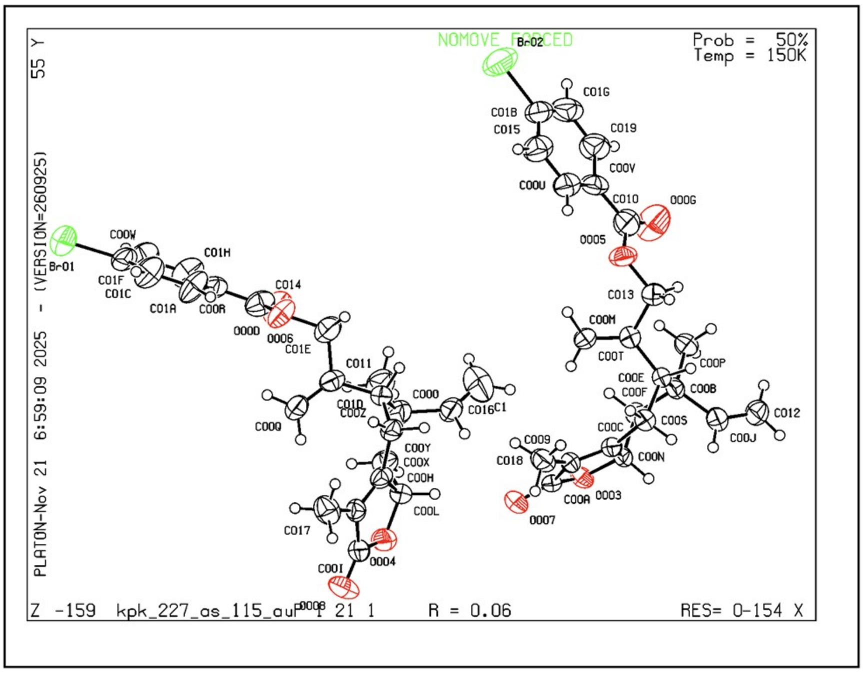


Figure 3: ORTEP drawing of **27** showing thermal ellipsoid at the 50% probability level

Table 9:
Datablock: kpk_227_as_115_autored

Bond precision: C-C = 0.0137 A Wavelength=0.71073
Cell: a=7.2933(3) b=14.1291(5) c=19.7449(6)
alpha=90 beta=95.884(3) gamma=90
Temperature: 150 K

	Calculated	Reported
Volume	2023.95(13)	2023.95(13)
Space group	P 21	P 1 21 1
Hall group	P 2yb	P 2yb
Moiety formula	C22 H23 Br O4	2(C22 H23 Br O4)
Sum formula	C22 H23 Br O4	C44 H46 Br2 O8
Mr	431.30	862.63
Dx,g cm-3	1.416	1.415
Z	4	2
Mu (mm-1)	2.055	2.055
F000	888.0	888.0
F000'	887.25	
h,k,lmax	8,16,23	8,16,23
Nref	7131[3724]	7130
Tmin,Tmax	0.744,0.840	0.256,1.000
Tmin'	0.663	

Correction method= # Reported T Limits: Tmin=0.256 Tmax=1.000
AbsCorr = MULTI-SCAN
Data completeness= 1.91/1.00 Theta(max)= 24.997
R(reflections)= 0.0591(4400) wR2(reflections)= 0.1516(

7130)

S = 1.031 Npar= 491

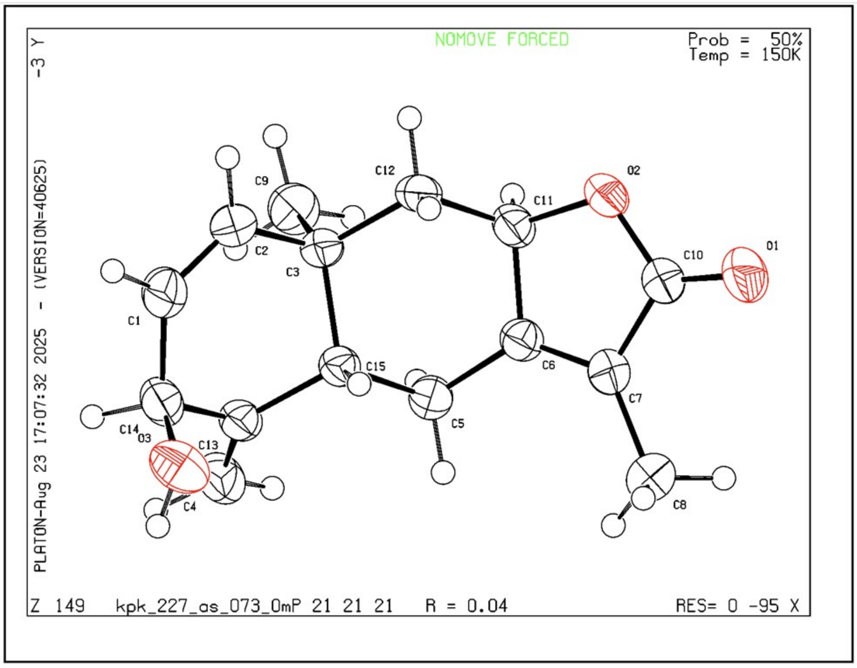


Figure 4: ORTEP drawing of **22** showing thermal ellipsoid at the 50% probability level

Table 10:
Datablock: kpk_227_as_073_0m

Bond precision: C-C = 0.0036 A Wavelength=0.71073

Cell: a=9.803(1) b=10.3295(12) c=12.6647(15)
alpha=90 beta=90 gamma=90

Temperature: 150 K

	Calculated	Reported
Volume	1282.4(2)	1282.4(2)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C15 H18 O3	C15 H18 O3
Sum formula	C15 H18 O3	C15 H18 O3
Mr	246.29	246.29
Dx,g cm-3	1.276	1.276
Z	4	4
Mu (mm-1)	0.088	0.088
F000	528.0	528.0
F000'	528.27	
h,k,lmax	11,12,15	11,12,15
Nref	2271[1324]	2265
Tmin,Tmax	0.957,0.970	0.505,0.745
Tmin'	0.957	

Correction method= # Reported T Limits: Tmin=0.505 Tmax=0.745

AbsCorr = NUMERICAL

Data completeness= 1.71/1.00 Theta(max)= 25.045

R(reflections)= 0.0379(1955) wR2(reflections)= 0.0909(2265)

S = 1.050 Npar= 166

References:

1 D. B. G. Williams and M. Lawton, *J. Org. Chem.*, **2010**, *75*, 8351–8354.

2 H. Sumioka, L. Harinantenaina, K. Matsunami, H. Otsuka, M. Kawahata and K. Yamaguchi, *Phytochemistry*, **2011**, *72*, 2165–2171.

3 S. K. S. Amoah, F. L. De Oliveira, A. C. H. Da Cruz, N. M. De Souza, F. R. Campos, A. Barison and M. W. Biavatti, *Phytochemistry*, **2013**, *87*, 126–132.