An Asymmetric Synthesis of 1,2,4-Trioxane Anticancer Agents via Desymmetrization of Peroxyquinols through a Brønsted Acid Catalysis Cascade

David M. Rubush[†], Michelle A. Morges[‡], Barbara J. Rose[‡], Douglas H. Thamm[‡], and Tomislav Rovis[†*]

[†]*Colorado State University, Department of Chemistry, Fort Collins, Colorado 80523, United States*

[‡]*Colorado State University, Animal Cancer Center, Department of Clinical Sciences, Fort Collins, Colorado 80523*

*rovis@lamar.colostate.edu

Supporting Information

General Methods:

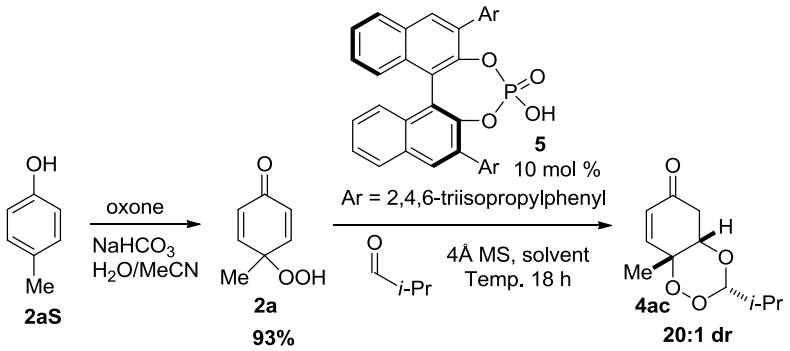
All reactions were carried out in oven-dried glassware with magnetic stirring. Dichloroethane (DCE) was distilled from CaH_2 under an atmosphere of argon. Dichloromethane was degassed with argon and passed through two columns of neutral alumina. Toluene was degassed with argon and passed through one column of neutral alumina and one column of Q5 reactant. Column chromatography was performed on Silicycle Inc. silica gel 60 (230-400 mesh). Thin layer chromatography was performed on Silicycle Inc. 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light (254 nm) and $KMnO_4$ followed by heating.

^{1}H NMR and ^{13}C NMR spectra were obtained on Varian 300 or 400 MHz spectrometers in $CDCl_3$ at ambient temperature and chemical shifts are expressed in parts per million (δ, ppm). Proton chemical shifts are referenced to 7.26 ppm ($CHCl_3$) and carbon chemical shifts are referenced to 77.0 ppm ($CDCl_3$). NMR data reporting uses the following abbreviations: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and *J*, coupling constant in Hz.

Aldehydes were either purchased from Aldrich or synthesized according to literature procedures. 4-Peroxyquinols **2a**-**2e** were synthesized according to the literature procedure.[1] Thiourea was purchased from Aldrich. Catalysts **5** and **6a** were synthesized as previously reported.[15b]

Reaction Optimization: Solvents and Temperatures

A screen of solvents and temperatures found that DCE at 50 °C gave the highest yield and enantioselectivity.



Entry	Solvent	Temperature	Yield (%)	ee%
1	THF	25 °C	< 5%	NA
2	Dioxane	25 °C	< 5%	NA
3	Toluene	25 °C	29%	49%
4	CH_2Cl_2	25 °C	38%	85%
5	DCE	25 °C	40%	85%
6	DCE	0 °C	10%	85%
7	DCE	50 °C	**88%**	**85%**
8	DCE	65 °C	85%	85%

Reaction Optimization: Catalyst Loading

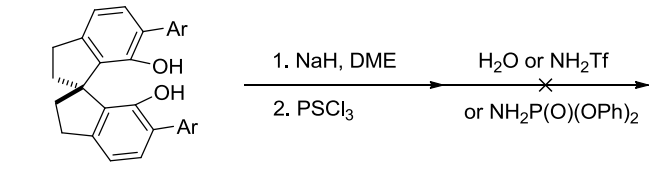
The enantioselectivity and yield dropped off if the catalyst loading was below 10 mol % presumably due to the background reaction.

Entry	Catalyst Loading	Yield (%)	ee%
1	1 mol %	13%	69%
2	2.5 mol %	20%	73%
3	5 mol %	33%	76%
4	10 mol %	**92%**	**86%**
5[a]	10 mol %	90%	74%
6	25 mol %	40%	86%

[a] No 4Å MS

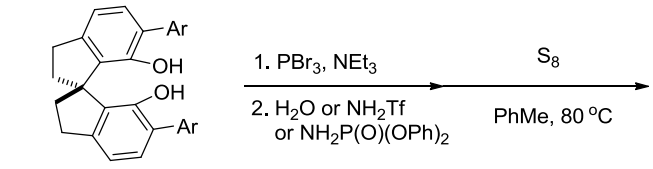
Reaction Optimization: Catalyst Synthesis

The procedure developed by Birman was used to synthesize the SPINOL diol and List's procedure was employed for the synthesis of phosphoric acid **6a**. The variants of **6a** were synthesized using procedures that have previously been reported for BINOL analogs.



Ar = 2,4,6-triisopropylphenyl

X= O **0%**
X = NTf **0%**
22 X = $NP(O)(OPh)_2$ **0%**

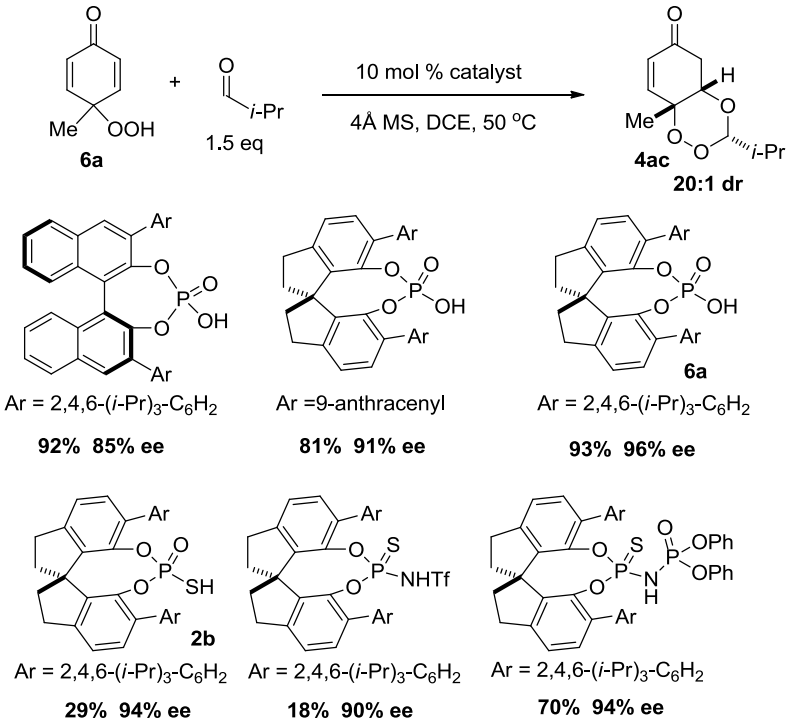


Ar = 2,4,6-triisopropylphenyl

2b X= O **66%**
X = NTf **53%**
X = $NP(O)(OPh)_2$ **64%**

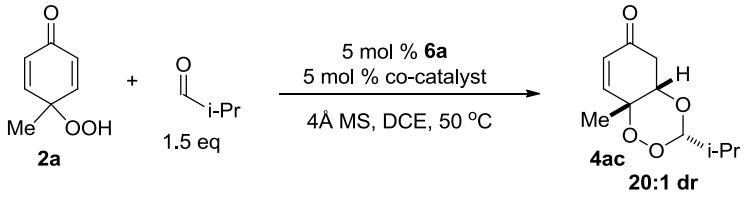
Reaction Optimization: Catalyst Screen

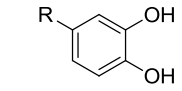
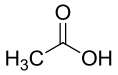
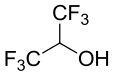
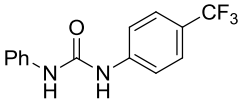
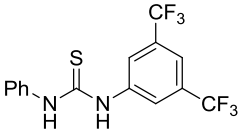
A catalyst screen including commercially available **6a**[15b] and other derivatives[2], found that SPINOL derived catalyst **6a** gave the highest yield and enantioselectivity.



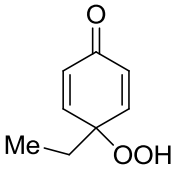
Reaction Optimization: Co-Catalyst Screen

A screen of additives found that biaryl thiourea improved the yield while maintaining the enantioselectivity.

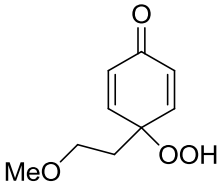


Entry	Co-catalyst	Yield (%)	ee (%)
1	None	46%	95%
2	 R = H, *t*-Bu, CN, CO_2Et	< 5%	NA
3		25%	96%
4		31%	95%
5		24%	96%
6		**92%**	**96%**

Synthesis of Starting Materials:

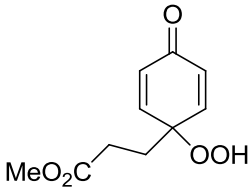


4-ethyl-4-hydroperoxycyclohexa-2,5-dienone (2b). Prepared according to the literature procedure for 2a: 68% yield; white solid; recrystallized from EtOAc (mp: 75-77); R_f = 0.11 (85:15 Hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.77, (s, 1H), 6.86 (d, *J* = 10.2 Hz, 2H), 6.35, (d, *J* = 10.2 Hz, 2H), 1.74 (q, *J* = 7.6 2H), 0.85 (t, *J* = 7.6, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 186.0, 149.3 (2C), 131.3 (2C), 82.3, 28.9, 7.7; **IR** (NaCl, neat): 3284, 3057, 2981, 2942, 2883, 1671, 1623, 1402, 1182, 1059, 993, 864 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_8H_9O_3]^-$ ([M - H]$^-$): 153.0557; found: 153.0056.



4-hydroperoxy-4-(2-methoxyethyl)cyclohexa-2,5-dienone (2d). Prepared according to the literature procedure for 2a: 55% yield; yellow oil; R_f = 0.19 (50:50 Hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.65, (s, 1H), 6.95 (d, *J* = 10.2, 2H), 6.28, (d, *J* = 10.2, 2H), 3.44 (t, *J* = 5.7 Hz 2H), 3.29 (s, 3H), 2.01 (t, *J* = 5.9 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 185.7, 148.5 (2C), 130.1 (2C), 79.6, 67.3,

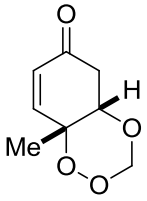
58.7, 36.1; **IR** (NaCl, neat): 3284, 2929, 2878, 2834, 1671, 1626, 1397, 1264, 1178, 1114, 862 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_9H_{12}O_4]^-$ ($[M - H]^-$): 183.0657; found: 183.0657.



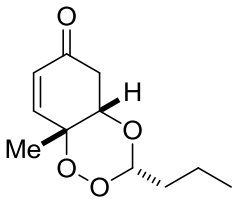
methyl 3-(1-hydroperoxy-4-oxocyclohexa-2,5-dien-1-yl)propanoate (2e). Prepared according to the literature procedure for 2a: 72% yield; white solid; recrystallized from EtOAc (mp: 85-86); R_f = 0.14 (67:33 Hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.25 (s, 1H), 6.89 (d, *J* = 10.2 Hz, 2H), 6.32 (d, *J* = 10.2 Hz, 2H), 3.66 (s, 3H), 2.33 (t, *J* = 7.5 Hz, 2H), 2.08 (t, *J* = 7.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 185.4, 173.2, 147.9 (2C), 131.2 (2C), 80.4, 52.1, 30.5, 28.2; **IR** (NaCl, neat): 3320, 3053, 3006, 2958, 2851, 1736, 1672, 1627, 1439, 1205, 1082, 865 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{10}H_{11}O_5]^-$ ($[M - H]^-$): 213.0606; found: 211.0612.

General Procedure for Peroxyquinol Desymmetrization and Characterization

To an oven dried 1 mL vial, with a magnetic stir bar, was added 4-methyl-4-hydroperoxycyclohexa-2,5-dienone **1** (0.1 mmol, 1.0 equiv), phosphoric acid **6a** (3.6 mg, 0.005 mmol, 0.05 equiv), thiourea **7** (1.8 mg, 0.005 mmol, 0.05 equiv), aldehyde (0.15 mmol, 1.25 equiv), activated 4Å molecular sieves (25 mg) and 1,2-dichloroethane (0.4 mL). The vial was then sealed, heated to 45 °C and stirred until the starting material disappeared by TLC (12-48h). The reaction was concentrated *in vacuo*. Column chromatography 10-20%(hexanes:ethyl acetate) of the resulting yellow residue gave the analytically pure 1,2,4-trioxane as a white solid or clear oil.

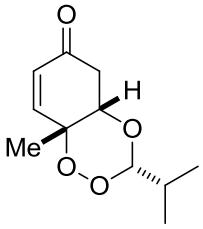


(4aS,8aR)-8a-methyl-4a,5-dihydrobenzo[e][1,2,4]trioxin-6(8aH)-one (4aa). Prepared according to the general procedure: 89% yield; >20:1 dr; 94% ee; white solid; R_f = 0.16 (80:20 Hexanes:EtOAc); $[\alpha]^{20}_D$ = -108.5, c = 0.0024 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IA column, 95:5 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 11.59 min, RT_{major} = 12.69 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.88 (dd, *J* = 10.4, 2.7 Hz, 1H), 6.11 (d, *J* = 10.4 Hz, 1H), 5.42 (d, *J* = 8.5 Hz, 1H), 5.16 (d, *J* = 8.5 Hz, 1H), 4.15 (q, *J* = 2.9 Hz, 1H), 2.71 (d, *J* = 3.0 Hz, 2H), 1.34, (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.5, 150.6, 129.8, 95.8, 79.1, 75.8, 40.8, 20.9; **IR** (NaCl, neat): 3043, 2987, 2921, 2865, 1674, 1625, 1388, 1149, 817 cm^{-1}; **HRMS** (ESI-APCI) *m/z* $[C_8H_{11}O_4]^+$ ($[M + H]^+$): calcd 170.0652, found 170.0653.

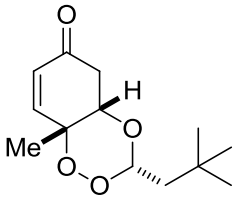


(3S,4aS,8aR)-8a-methyl-3-propyl-4a,5-dihydrobenzo[e][1,2,4]trioxin-6(8aH)-one (4ab). Prepared according to the general procedure: 90% yield; >20:1 dr; 95% ee; clear oil; R_f = 0.27 (80:20 Hexanes:EtOAc); $[\alpha]^{20}_D$ = -67.0, c = 0.0031 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IA column, 99:1 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 17.57 min, RT_{major} = 23.80 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.84 (dd, *J* = 10.4, 3.0 Hz, 1H), 6.07 (d, *J* = 10.4 Hz, 1H), 5.25 (t, *J* = 5.2

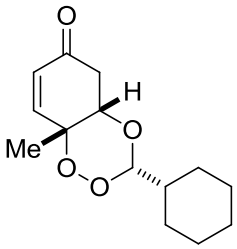
Hz, 1H), 4.15 (q, *J* = 2.9 Hz, 1H), 2.69, (d, *J* = 3.0 Hz, 2H), 1.53-1.45 (m, 2H), 1.44-1.33 (m, 2H), 1.33 (s, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.9, 151.0, 129.6, 104.0, 77.7, 76.3, 41.0, 33.7, 20.6, 16.8, 13.8; **IR** (NaCl, neat): 3055, 2936, 2878, 1683, 1460, 1385, 1231, 1094, 835, 783 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{11}H_{17}O_4]^+$ ($[M + H]^+$): 213.1121, found 213.1120.



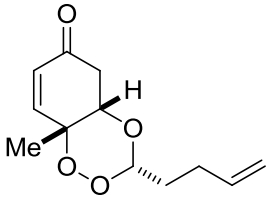
(3S,4aS,8aR)-3-isopropyl-8a-methyl-4a,5-dihydrobenzo[e][1,2,4]trioxin-6(8aH)-one (4ac). Prepared according to the general procedure: 92% yield; >20:1 dr; 96% ee; white solid; R_f = 0.29 (80:20 Hexanes:EtOAc); $[\alpha]^{20}_D$ = -49.5, c = 0.0123 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IC column, 97:3 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 7.92 min, RT_{major} = 9.60 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.84 (dd, *J* = 10.4 Hz, 2.7 Hz, 1H) 6.06 (d, *J* = 10.4 Hz, 1H), 5.01 (d, *J* = 5.1 Hz, 1H), 4.14 (q, *J* = 2.9 Hz, 1H), 2.72-2.69 (m, 2H), 1.84-1.71 (m, 1H), 1.33, (s, 3H), 0.88 (d, *J* = 3.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 195.1,151.1, 129.5, 101.1, 77.7, 76.3, 41.0, 30.9, 20.5, 16.7, 16.6; **IR** (NaCl, neat): 3041, 2971, 2935, 2880, 1684, 1473, 1388, 1289, 1081, 843 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{11}H_{17}O_4]^+$ ($[M + H]^+$): 213.1121; found: 213.1119.



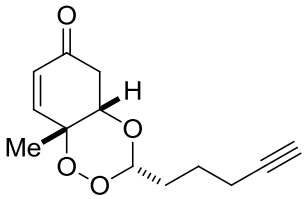
(3S,4aS,8aR)-8a-methyl-3-neopentyl-4a,5-dihydrobenzo[e][1,2,4]trioxin-6(8aH)-one (4ad). Prepared according to the general procedure: 84% yield; >20:1 dr; 96% ee; white solid; R_f = 0.30 (80:20 Hexanes:EtOAc); $[\alpha]^{20}_D$ = -120.0, c = 0.0047 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IC column, 97:3 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 12.32 min, RT_{major} = 18.11 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.84 (dd, *J* = 10.4, 2.8 Hz, 1H), 6.06 (d, *J* = 10.4 Hz, 1H), 5.25 (t, *J* = 4.9 Hz, 1H), 4.16 (q, *J* = 2.9 Hz, 1H), 2.68, (d, *J* = 3.0 Hz, 2H), 1.46-1.36 (m, 2H), 1.33 (s, 3H), 0.92 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.9, 151.1, 129.6, 103.2, 77.5, 76.3, 45.4, 41.0, 29.8 (3C), 29.2, 20.6; **IR** (NaCl, neat): 3057, 2959, 2902, 2877, 1683, 1452, 1367, 1235, 1108, 1070, 792, 740 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{13}H_{21}O_4]^+$ ($[M + H]^+$): 241.1434, found 241.1423.



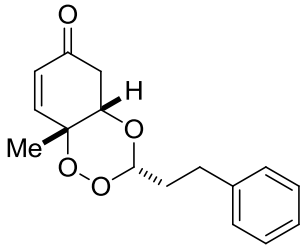
(3S,4aS,8aR)-3-cyclohexyl-8a-methyl-4a,5-dihydrobenzo[e][1,2,4]trioxin-6(8aH)-one (4ae). Prepared according to the general procedure: 77% yield; >20:1 dr; 98% ee; white solid; R_f = 0.32 (80:20 Hexanes:EtOAc); $[\alpha]^{20}_D$ = -91.8, c = 0.0073 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IA column, 97:3 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 8.30min, RT_{major} = 8.97 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.83 (dd, *J* = 10.4, 2.7 Hz, 1H), 6.06 (d, *J* = 10.4 Hz, 1H), 5.01 d, *J* = 5.4 Hz, 1H), 4.13 (q, *J* = 2.9 Hz, 1H), 2.60-2.68, (m, 2H), 1.72-1.42 (m, 6H), 1.32 (s, 3H), 1.20-0.97 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 195.2, 151.1, 129.5, 106.5, 77.8, 76.3, 41.0, 40.3, 26.83, 26.75, 26.1, 25.48, 25.47, 20.5; **IR** (NaCl, neat): 2932, 2855, 1684, 1450, 1230, 1115, 1065, 780 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{14}H_{21}O_4]^+$ ($[M + H]^+$): 253.1434, found 253.1440.



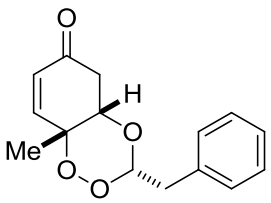
(3S,4aS,8aR)-3-(but-3-en-1-yl)-8a-methyltetrahydrobenzo[e][1,2,4]trioxin-6(7H)-one (4af). Prepared according to the general procedure: 95% yield; >20:1 dr; 97% ee; clear oil; R_f = 0.40 (67:33 Hexanes:EtOAc); $[\alpha]^{20}_D$ = -44.5, c = 0.0046 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IC column, 97:3 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 15.27 min, RT_{major} = 20.12 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.85 (dd, *J* = 10.4, 2.8 Hz, 1H), 6.08 (d, *J* = 10.9 Hz, 1H), 5.75 (dddd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H), 5.28, (t, *J* = 5.3 Hz, 1H), 5.05-4.95 (m, 2H), 4.17 (q, *J* = 2.9 Hz, 1H), 2.73-2.69 (m, 2H), 2.15-2.08 (m, 2H), 1.66-1.59, (m, 2H), 1.34, (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.9, 151.0, 137.1, 129.7, 115.4, 103.5, 77.8, 76.4, 41.0, 30.9, 27.5, 20.6; **IR** (NaCl, neat): 3077, 2980, 2934, 2886, 1684, 1642, 1387, 1112, 1063, 915, 782 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{12}H_{19}O_4]^+$ ($[M + H]^+$): 225.1121, found 225.1124.



(3S,4aS,8aR)-8a-methyl-3-(pent-4-yn-1-yl)-4a,5-dihydrobenzo[e][1,2,4] trioxin-6(8aH)-one (4ag). Prepared according to the general procedure: 83% yield; >20:1 dr; 97% ee; clear oil; R_f = 0.38 (67:33 Hexanes:EtOAc); $[\alpha]^{20}_D$ = -54.3, c = 0.0124 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IA column, 95:5 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 17.52 min, RT_{major} = 25.04 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.85 (dd, *J* = 10.4, 2.8 Hz, 1H), 6.08 (d, *J* = 10.4 Hz, 1H), 5.30 (dd, *J* = 4.8, 4.8 Hz, 1H), 4.17 (dd, *J* = 5.9, 3.0 Hz, 1H), 2.76-2.65 (m, 2H), 2.18 (ddd, *J* = 7.0, 7.0, 2.7 Hz, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.71-1.55 (m, 4H), 1.34 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.8, 150.9, 129.7, 103.5, 83.5, 77.8, 76.4, 68.9, 40.9, 30.7, 22.3, 20.6, 18.1; **IR** (NaCl, neat): 3291, 2963, 2935, 2884, 2116, 1683, 1387, 1231, 1115, 783 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{13}H_{17}O_4]^+$ ($[M + H]^+$): 237.1121, found 237.1110.

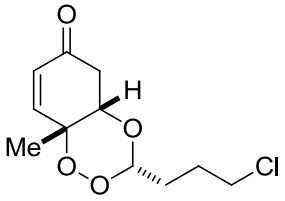


(3S,4aS,8aR)-8a-methyl-3-phenethyl-4a,5-dihydrobenzo[e][1,2,4]trioxin-6 (8aH)-one (4ah). Prepared according to the general procedure: % yield; 93% ee; white solid; R_f = 0.21 (80:20 hexanes:EtOAc); $[\alpha]^{20}_D$ = -92.4, c = 0.0093 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IC column, 97:3 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 21.64 min, RT_{major} = 32.11 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.28-7.10 (m, 5 H), 6.84 (dd, *J* = 2.7, 10.4 Hz, 1H), 6.07 (d, *J* = 10.4 Hz, 1H), 5.22 (t, *J* = 5.3 Hz, 1H), 4.12 (q, *J* = 2.9 Hz, 1H), 2.71-2.62 (m, 4H), 1.86-1.78 (m, 2H), 1.30 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.9, 151.0, 140.7, 129.6, 128.4, 128.3, 126.1, 103.1, 77.8, 76.3, 40.9, 33.1, 29.5, 20.5; **IR** (NaCl, neat): 3062, 3028, 2963, 2934, 2887, 1683, 1604, 1497, 1455, 1387, 1202, 1113, 898, 701 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{16}H_{19}O_4]^+$ ($[M + H]^+$): calcd 275.1287, found 275.1275.

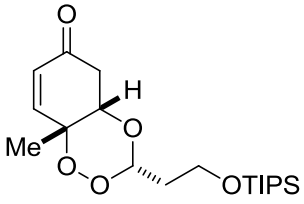


(3S,4aS,8aR)-3-benzyl-8a-methyl-4a,5-dihydrobenzo[e][1,2,4]trioxin-6(8aH)-one (4ai). Prepared according to the general procedure: 83% yield; >20:1 dr; 90% ee; white solid; R_f = 0.20 (80:20 Hexanes:EtOAc); $[\alpha]^{20}_D$ = -

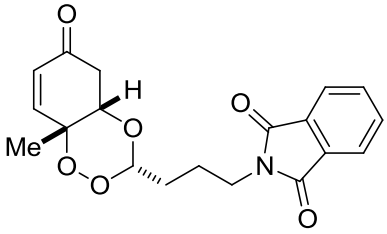
125.0, c = 0.0075 g/ml CH_2Cl_2; HPLC analysis: Chiralcel OC column, 80:20 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 8.14 min, RT_{major} = 9.53 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.29-7.14, (m, 5H), 6.84 (dd, *J* = 10.4, 2.7 Hz, 1H), 6.07 (d, *J* = 10.4 Hz, 1H), 5.41 (d, *J* = 5.4 Hz, 1H), 4.14 (d, *J* = 2.9 Hz, 1H), 2.81 (d, *J* = 5.4 Hz, 2H), 2.68, (dd, *J* = 5.4, 3.0 Hz, 2H), 1.31, (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.9, 150.8, 134.6, 129.68, 129.58 (2C), 128.3 (2C), 126.8, 104.3, 77.8, 76.5, 40.9, 38.5, 20.5; **IR** (NaCl, neat): 3063, 3032, 2982, 2888, 1684, 1497, 1455, 1385, 1350, 1281, 1173, 1110, 897, 700 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{15}H_{17}O_4]^+$ ($[M + H]^+$): 261.1121, found 261.1119.



(3S,4aS,8aR)-3-(3-chloropropyl)-8a-methyl-4a,5-dihydrobenzo[e][1,2,4] trioxin-6(8aH)-one (4aj). Prepared according to the general procedure: 97% yield; >20:1 dr; 97% ee; clear oil; R_f = 0.36 (67:33 Hexanes:EtOAc); $[\alpha]^{20}_D$ = -91.0, c = 0.0208 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IA column, 97:3 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 18.97 min, RT_{major} = 20.00 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.85 (dd, *J* = 10.4, 2.8 Hz, 1H), 6.08 (d, *J* = 10.4 Hz, 1H), 5.31 (t, *J* = 5.1 Hz, 1H), 4.18 (q, *J* = 2.9 Hz, 1H), 3.50 (t, *J* = 6.4 Hz, 2H), 2.70 (d, *J* = 3.0 Hz, 2H), 1.88-1.80 (m, 2H), 1.74-1.68 (m, 2H), 1.34 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.8, 150.8, 129.7, 103.1, 77.8, 76.4, 44.4, 40.9, 29.1, 26.3, 20.5; **IR** (NaCl, neat): 3040, 2966, 2935, 2886, 1683, 1445, 1386, 1231, 1150, 1083, 783 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{11}H_{17}O_4Cl]^+$ ($[M + H]^+$): 247.0732, found 247.0734.

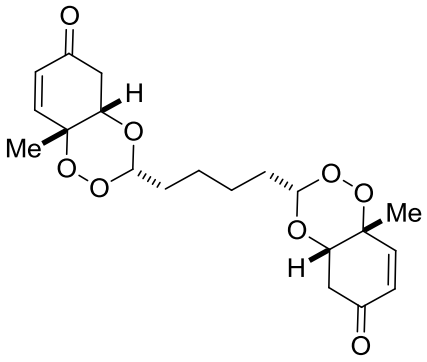


(3S,4aS,8aR)-8a-methyl-3-(2-((triisopropylsilyl)oxy)ethyl)-4a,5-dihydro benzo[e][1,2,4]trioxin-6(8aH)-one (4ak). Prepared according to the general procedure: 71% yield; >20:1 dr; 94% ee; clear oil; R_f = 0.25 (80:20 Hexanes:EtOAc; $[\alpha]^{20}_D$ = -92.4, c = 0.0091 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IA column, 97:3 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 10.01 min, RT_{major} = 14.93 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.86 (dd, *J* = 10.4, 2.7 Hz, 1H), 6.08 (d, *J* = 10.4 Hz, 1H), 5.48 (t, *J* = 5.4 Hz, 1H), 4.16 (q, *J* = 2.9 Hz, 1H), 3.83-3.69 (m, 2H), 2.71 (d, *J* = 2.9 Hz, 2H), 1.83-1.74 (m, 1H), 1.73-1.64 (m, 1H), 1.35 (s, 3H), 1.13-1.01 (m, 19H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 195.0, 151.1, 129.7, 101.9, 77.9, 76.4, 58.0, 41.0, 35.0, 20.6, 17.95 (3C), 17.93 (3C), 11.9 (3C); **IR** (NaCl, neat): 2943, 2867, 1686, 1463, 1385, 1230, 1108, 1071, 883, 681 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{19}H_{35}O_5Si]^+$ ($[M + H]^+$): 371.2248, found 371.2250.

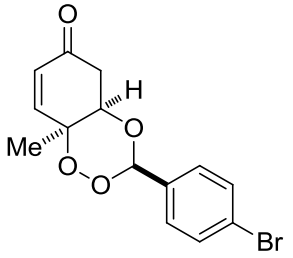


2-(3-((3S,4aS,8aR)-8a-methyl-6-oxo-4a,5,6,8a-tetrahydrobenzo [e][1,2,4]trioxin-3-yl)propyl)isoindoline-1,3-dione (4al). Prepared according to the general procedure: 81% yield; >20:1 dr; 98% ee; white solid; R_f = 0.16 (67:33 Hexanes:EtOAc); $[\alpha]^{20}_D$ = -103.0, c = 0.0026 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IC column, 70:30 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 27.10 min, RT_{major} = 28.20 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.83-7.78 (m,

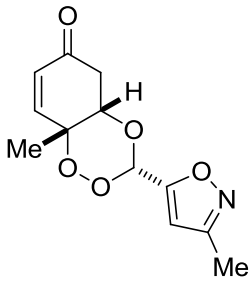
2H), 7.72-7.66 (m, 2H), 6.83 (dd, *J* = 10.4, 2.8 Hz, 1H), 6.06 (d, *J* = 10.4 Hz, 1H), 5.30 (t, *J* = 5.1 Hz, 1H), 4.16 (q, *J* = 2.9 Hz, 1H), 3.64 (t, *J* = 7.2 Hz, 2H), 2.67 (d, *J* = 2.8 Hz, 2H), 1.79-1.70, (m, 2H), 1.62-1.55 (m, 2H), 1.32 (s 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.7, 168.2 (2C), 150.8, 133.9 (2C), 132.0 (2C), 129.7, 123.2 (2C), 103.2, 77.8, 76.3, 40.8, 37.4, 29.1, 22.6, 20.5; **IR** (NaCl, neat): 3061, 2937, 2884, 1772, 1716, 1615, 1398, 1049, 721 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{19}H_{19}NO_6Na]^+$ ([M + Na]$^+$): 380.1105, found 380.1102.



(3S,3'S,4aS,4a'S,8aR,8a'R)-3,3'-(butane-1,4-diyl)bis(8a-methyl-4a,5-dihydrobenzo[e][1,2,4]trioxin-6(8aH)-one) (4am). Prepared according to the general procedure: 79% yield; 96% ee; clear oil; R_f = 0.15 (60:40 hexanes:ethyl acetate); $[\alpha]^{20}_D$ = -117.8, c = 0.0026 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IA column, 60:40 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 8.26 min, RT_{major} = 9.95 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.84 (dd, *J* = 2.7, 10.4 Hz, 2H), 6.07 (d, *J* = 10.4 Hz, 2H), 5.23 (t, *J* = 5.2 Hz, 2H), 4.15 (q, *J* = 2.9 Hz, 2H), 2.69 (d, *J* = 3.1 Hz, 4H), 1.53-1.45 (m, 4H), 1.37-1.30 (m, 4H), 1.33 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.9, 151.0, 129.6, 103.9, 77.8, 76.3, 41.0, 31.5, 23.1, 20.6; **IR** (NaCl, neat): 3056, 2949, 2877, 1683, 1463, 1387, 1232, 1144, 1036, 780, 733 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{20}H_{27}O_8]^+$ ([M + H]$^+$): calcd 395.1700, found 395.1697.

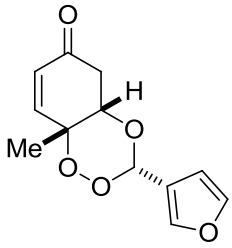


(3R,4aR,8aS)-3-(4-bromophenyl)-8a-methyl-4a,5-dihydrobenzo[e][1,2,4] trioxin-6(8aH)-one (4an). Prepared according to the general procedure using the **opposite** antipode of catalyst **6a**: 66% yield; 91% ee; white solid; R_f = 0.1 (80:20 hexanes:EtOAc); $[\alpha]^{20}_D$ = +113.7, c = 0.0097 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IA column, 97:3 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 26.89 min, RT_{major} = 31.31 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = Hz, 2H), 7.20 (dd, *J* = Hz, 2H), 6.85 (dd, *J* = 2.8, 10.4 Hz, 1H), 6.11 (s, 1H), 6.08 (dd, *J* = 0.9, 10.4 Hz, 1H), 4.32 (q, *J* = 3.0 Hz, 1H), 2.77 (ddd, *J* = 0.9, 3.0, 17.5 Hz, 1H), 2.71 (dd, *J* = 3.1, 17.5 Hz, 1H), 1.36 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.6, 150.7, 132,4, 131.7, 129.8, 128.7, 124.5, 102.8, 78.0, 77.0, 40.9, 20.6; **IR** (NaCl, neat): 2906, 1680, 1601, 1500, 1346,cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{14}H_{14}O_4Br]^+$ ([M + H]$^+$): calcd 325.0070, found 325.0084.



(3S,4aS,8aR)-8a-methyl-3-(3-methylisoxazol-5-yl)-4a,5-dihydrobenzo[e] [1,2,4]trioxin-6(8aH)-one (4ao). Prepared according to the general procedure: 53% yield; 91% ee; white solid; R_f = 0.21 (67:33 hexanes:EtOAc); $[\alpha]^{20}_D$ = -84.0, c = 0.0054 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IA column, 90:10 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 14.23 min, RT_{major} = 15.84 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.91 (dd, *J* = 2.8, 10.4 Hz, 1H), 6.37 (s,

1H), 6.13 (d, *J* = 10.4 Hz, 1H), 5.98 (s, 1H) 4.39 (q, *J* = 2.9 Hz, 1H), 2.79-2.76 (m, 2H), 2.39 (s, 3H), 1.42 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.2, 170.4, 158.1, 129.8, 99.8, 97.6, 40.7, 20.6, 12.2; **IR** (NaCl, neat): 3142, 2983, 2903, 1682, 1604, 1496, 1347, 1232, 1173, 1087, 1041, 900, cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{12}H_{14}NO_5]^+$ ($[M + H]^+$): calcd 252.0866, found 252.0866.



(3S,4aS,8aR)-3-(furan-3-yl)-8a-methyl-4a,5-dihydrobenzo[e][1,2,4]trioxin-6 (8aH)-one (4ap). Prepared according to the general procedure: 45% yield; 91% ee; clear oil; R_f = 0.36 (60:40 hexanes:EtOAc); $[\alpha]^{20}_D$ = -102.3, c = 0.0046 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IA column, 90:10 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 12.2 min, RT_{major} = 14.1 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.53-7.51 (m, 1H), 7.37 (t, *J* = 1.7 Hz, 1H), 6.91 (dd, *J* = 2.8, 10.4 Hz, 1H), 6.40-6.38 (m, 1H), 6.23 (s, 1H), 6.14 (dd, *J* = 0.8, 10.4 Hz, 1H), 4.35 (q, *J* = 3.0 Hz, 1H), 2.82 (ddd, *J* = 0.8, 3.0, 17.5 Hz, 1H), 2.76 (dd, *J* = 3.0, 17.5 Hz, 1H), 1.41 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.6, 150.8, 141.9, 129.8, 119.7, 108.4, 99.83, 78.0, 76.8, 40.9, 20.6; **IR** (NaCl, neat): 3148, 2892, 1681, 1604, 1504, 1344, 1160, 1064, 986, 876, 811 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{12}H_{13}O_5]^+$ ($[M + H]^+$): calcd 237.0757, found 237.0753.

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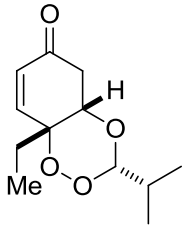
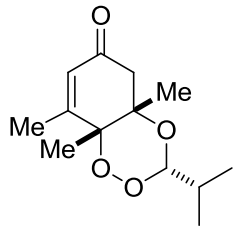
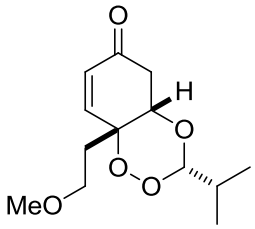


(3S,4aS,8aR)-8a-ethyl-3-isopropyl-4a,5-dihydrobenzo[e][1,2,4]trioxin-6(8aH)-one (2cb). Prepared according to the general procedure: 79% yield; >20:1 dr; 96% ee; clear oil; R_f = 0.36 (80:20 Hexanes:EtOAc); $[\alpha]^{20}_D$ = -57.7, c = 0.0034 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IA column, 99:1 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 13.10 min, RT_{major} = 15.71 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.90 (dd, *J* = 10.5, 2.7 Hz, 1H), 6.10 (d, *J* = 10.5 Hz, 1H), 4.98 (d, *J* = 5.4 Hz, 1H), 4.20 (q, *J* = 3 Hz, 1H), 2.69 (d, *J* = 3 Hz, 2H), 1.63-1.88 (m, 3H), 1.00 (t, *J* = 7.5 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 195.2, 150.7, 129.9, 107.0, 79.8, 75.2, 40.8, 30.9, 28.6, 16.64, 16.62, 7.1; **IR** (NaCl, neat): 2972, 2941, 2881, 1689, 1463, 1389, 1194, 1159, 957, 665 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{12}H_{19}O_4]^+$ ($[M + H]^+$): 227.1278, found 227.1275.

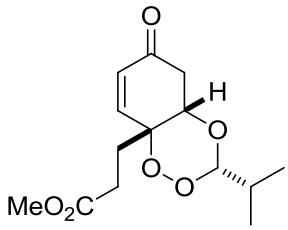


(3S,4aS,8aR)-3-isopropyl-4a,8,8a-trimethyl-4a,5-dihydrobenzo[e][1,2,4] trioxin-6(8aH)-one (2cc). Prepared according to the general procedure: 63% yield; 90% ee; white solid; R_f = 0.50 (67:33 Hexanes:EtOAc); $[\alpha]^{20}_D$ = -67.6, c = 0.0011 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IC column, 97:3 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 17.59 min, RT_{major} = 21.30 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.94-5.92 (m, 1H), 5.21 (d, *J* = 4.5 Hz, 1H), 2.61 (d, *J* = 17.1 Hz, 1H), 2.50 (d, *J* = 17.0 Hz, 1H), 2.04 (s, 3H), 1.77-1.60 (m, 1H), 1.44, (s, 3H), 1.20, (s,

3H) 0.81 (dd, *J* = 1.1, 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 195.1, 161.7, 127.8, 101.4, 82.3, 75.6, 48.0, 30.9, 19.0, 18.29, 18.27, 16.39, 16.28; **IR** (NaCl, neat): 2968, 2933, 2880, 1677, 1460, 1393, 1282, 1081, 957 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{13}H_{21}O_4]^+$ ($[M + H]^+$): 241.1434, found 241.1434.

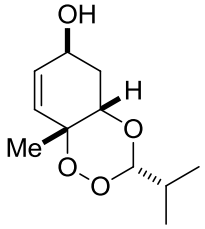


(3S,4aS,8aR)-3-isopropyl-8a-(2-methoxyethyl)-4a,5-dihydrobenzo[e][1,2,4] trioxin-6(8aH)-one (2cd). Prepared according to the general procedure: 66% yield; >20:1 dr; 96% ee; clear oil; R_f = 0.21 (67:33 Hexanes:EtOAc); $[\alpha]^{20}_D$ = -86.2, c = 0.0021 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IA column, 95:5 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 7.78 min, RT_{major} = 12.69 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.85 (dd, J = 10.4, 2.8 Hz, 1H), 6.05 (dd, *J* = 10.4 Hz, 0.9 Hz 1H), 4.97 (d, *J* = 5.1 Hz, 1H), 4.27 (q, *J* = 2.9 Hz, 1H), 3.50 (ddd, *J* = 5.6, 6.9, 9.8 Hz,1H), 3.43 (ddd, *J* = 5.6, 6.6, 9.8 Hz,1H), 3.28 (s, 3H), 2.75 (dd, *J* = 3.0, 17.6 Hz, 1H), 2.65 (ddd, *J* = 1.0, 3.0, 17.6 Hz, 2H), 1.99 (ddd, *J* = 5.6, 6.6, 15.0 Hz, 1H) 1.88 (ddd, *J* = 5.6, 6.8, 15.0 Hz, 1H), 1.80-1.76 (m, 1H), 0.86 (d, *J* = 7.0 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ ; **IR** (NaCl, neat): 2968, 2929, 2879, 1687, 1473, 1392, 1191, 1116, 1082, 1015, 772 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{13}H_{21}O_5]^+$ ($[M + H]^+$): 257.1384, found 257.1357.



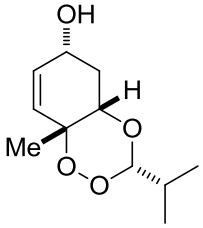
methyl 3-((3S,4aS,8aR)-3-isopropyl-6-oxo-4a,5,6,8a-tetrahydrobenzo[e] [1,2,4]trioxin-8a-yl)propanoate (2ce). Prepared according to the general procedure: 67% yield; 95% ee; clear oil; R_f = 0.40 (67:33 Hexanes:EtOAc); $[\alpha]^{20}_D$ = -104.0, c = 0.0037 g/ml CH_2Cl_2; HPLC analysis: Chiralcel IA column, 80:20 Hexanes:*i*so-propanol, 1.0 ml/min, RT_{minor} = 7.38 min, RT_{major} = 13.80 min, 210 nm. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.83 (dd, *J* = 10.5, 2.8 Hz, 1H), 6.09 (*d*, J = 10.5 Hz, 1H), 4.97 (d, *J* = 5.1 Hz, 1H), 4.16 (d, *J* = 2.9 Hz, 1H), 3.66 (s, 3H), 2.75 (dd, *J* = 17.7, 3.1 Hz, 1H), 2.68 (dd, *J* = 17.7, 3.0 Hz, 1H), 2.52 (ddd, *J* = 6.2, 9.9, 16.4 Hz, 1H), 2.40 (ddd, *J* = 6.1, 9.9, 16.1 Hz, 1H), 2.10 (ddd *J* = 6.0, 9.9, 14.8 Hz, 1H), 2.00 (ddd, *J* = 6.2, 9.9, 14.8 Hz, 1H), 1.80-1.67 (m, 1H), 0.86 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 194.7, 172.7, 149.1, 130.5, 107.0, 78.8, 75.1, 51.9, 40.7, 30.8, 27.1, 16.59, 16.51; **IR** (NaCl, neat): 2969, 2880, 1738, 1688, 1439, 1260, 1175, 1083, 1016, 794 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{14}H_{21}O_6]^+$ ($[M + H]^+$): 285.1333, found 285.1318.

Trioxane Derivatives.

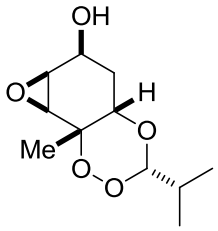


3-isopropyl-8a-methyl-4a,5,6,8a-tetrahydrobenzo[e][1,2,4]trioxin-6-ol (9s). Trioxane **4ac** (233 mg, 1.1 mmol, 1 eq) was added to a solution of $CeCl_3{\cdot}(H_2O)_7$ (450 mg, 1.2 mmol 1.1 eq) in 3.5 mL of methanol (0.3M). After the mixture was cooled to 0 °C, $NaBH_4$ was added portionwise. The reaction was stirred at 0 °C for 1 h and then for an 1 h at room temperature. The reaction was quenched with sat. NH_4Cl and the aqueous layer was extracted using EtOAc. The organic extracts were dried with $MgSO_4$ and concentrated *in vacuo*. Column chromatography on SiO_2 with 25% (hexanes:ethyl acetate) of the residue gave analytically pure **9s** as a clear oil. 96% yield; 4:1 dr; clear oil;

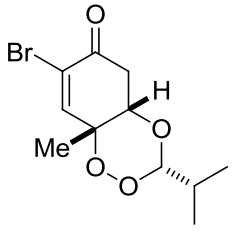
R_f (major) = 0.29 (67:33 Hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.87 (dt, *J* = 1.9, 10.4 Hz, 1H), 5.70 (dt *J* = 2.2, 10.4 Hz, 1H), 4.94 (d, *J* = 4.9 Hz, 1H), 4.53 (ddt, *J* = 2.1, 5.9, 8.1 Hz, 1H), 3.9 (dt, *J* = 1.9, 4.2 Hz, 1H), 2.43 (dddd, *J* = 1.7, 4.4, 6.0, 13.5 Hz, 1H), 1.81-1.70 (m, 2H), 1.63 (bs, 1H), 1.19 (s, 3H), 0.90 (dd, *J* = 1.9, 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 133.0, 131.1, 106.4, 77.2 75.8, 64.7, 36.1, 31.0, 22.5, 16.70, 16.68; **IR** (NaCl, neat): 3364, 3030, 2968, 2936, 2877, 1471, 1395, 1171, 1079, 896 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{12}H_{21}O_4]^+$ 229.1434 ($[M - OH + HOCH_3]^+$): 229.1434, found 229.1428.



R_f (minor) = 0.51 (67:33 Hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.03 (ddd, *J* = 1.7, 4.7, 10.2 Hz, 1H), 5.75 (dd, *J* = 1.7, 10.2 Hz, 1H), 4.93 (d, *J* = 5.2 Hz, 1H), 4.04-3.97 (bm, 1H), 3.99 (dt, *J* = 2.0, 4.0 Hz, 1H), 2.96 (bd, *J* = 10.2 Hz, 1H), 2.28 (ddt, *J* = 1.6, 3.9, 15.3 Hz, 1H), 2.06 (ddd, *J* = 1.9, 5.2, 15.3 Hz, 1H), 1.86-1.73 (m, 1H), 1.10 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 131.5, 130.8, 107.3, 77.8, 75.2, 62.4, 32.9, 30.9, 21.4, 17.00, 16.92; **IR** (NaCl, neat): 3557, 3033, 2970, 2935, 2879, 1472, 1409, 1369, 1171, 1073, 895,809 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{12}H_{21}O_4]^+$ 229.1434 ($[M - OH + HOCH_3]^+$): 229.1434, found 229.1429.

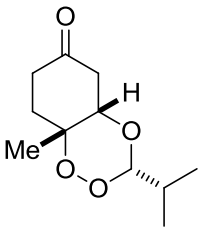


3-isopropyl-7b-methylhexahydrooxireno[2',3':3,4]benzo[1,2-e][1,2,4]trioxin-6-ol (9). To a solution of **9s** (43 mg, 0.2 mmol, 1 eq) dissolved in 2 mL of dichloromethane (0.1M) at 0 ºC was added *m*-chloroperoxybenzoic (92 mg, (75% pure), 0.4 mmol, 2 eq) The reaction was stirred at 0 °C for 1hour and then allowed to stir at room temperature for 4 hours. The reaction mixture was concentrated *in vacuo* and purified using column chromatography on SiO_2 with 20% (hexanes:ethyl acetate) to afford analytically pure **9s** as a white solid.: 91% yield; white solid; R_f = 0.27 (67:33 Hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.92 (d, *J* = 4.7 Hz, 1H), 4.41 (ddd, *J* = 1.2, 5.9, 10.4 Hz, 1H), 3.64 (d, *J* = 5.3 Hz, 1H), 3.49-3.46 (m, 2H), 2.11 (dt, *J* = 5.7, 13.6 Hz, 1H), 1.85-1.74 (m, 1H), 1.71 (s, 1H), 1.39 (ddd, *J* = 1.1, 10.4, 13.6 Hz, 1H), 1.21 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 6H) ; **^{13}C NMR** (100 MHz, $CDCl_3$): δ 106.0, 75.6, 74.8, 65.2, 59.3, 55.9, 31.1, 29.6, 18.3, 16.62, 16.47; **IR** (NaCl, neat): 3407, 2970, 2939, 2878, 1462, 1396, 1268, 1184, 1089, 1001, 939, 874, 820, 672 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{11}H_{22}NO_5]^+$ ($[M + NH_4]^+$): calcd 248.1492, found 248.1438.

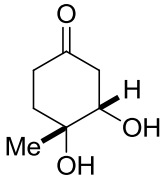


7-bromo-3-isopropyl-8a-methyl-4a,5-dihydrobenzo[e][1,2,4]trioxin-6(8aH)-one (10). To a solution of **4ac** (238 mg, 1.12 mmol, 1 eq) in 8 mL CCl_4 (0.14M) at 0 ºC was added Br_2 (75 µL, 1.46 mmol, 1.3 eq). The reaction was allowed to stir for 30 minutes at 0 ºC and then 0.5 mL of NEt_3 was added and the reaction was warmed to room temperature. The reaction mixture was concentrated *in vacuo* and purified using column chromatography on SiO_2 with 15% (hexanes:ethyl acetate) to afford analytically pure **10** as an off white solid (245 mg, 0.84 mmol). Note: The dibromide intermediate can be isolated in 4:1 dr if no NEt_3 is added. 75% yield; off white solid; R_f = 0.28 (80:20 Hexanes:EtOAc); **^{1}H**

NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 2.6 Hz, 1H), 5.01 (d, *J* = 5.1 Hz, 1H), 4.17 (q, *J* = 2.9 Hz, 1H), 2.95 (dd, *J* = 3.1, 17.3 Hz, 1H), 2.78 (dd, *J* = 2.9, 17.3 Hz, 1H), 1.84-1.71 (m, 1H), 1.37 (s, 3H), 0.88 (dd, *J* = 1.6, 7.0 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 187.2, 151.2, 123.7. 107.1, 79.6, 76.0, 40.5, 30.8, 20.2, 16.65, 16.50; **IR** (NaCl, neat): 3047, 2971, 2935, 2880, 1702, 1612, 1472, 1268, 1082, 1032, 968, 796, 687 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{11}H_{19}NO_4Br]^+$ ($[M + NH_4]^+$): calcd 308.0492, found 310.0484.



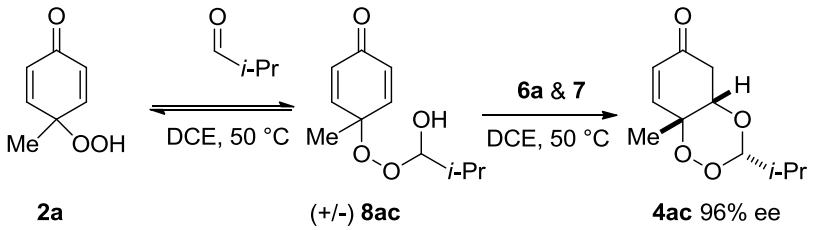
3-isopropyl-8a-methyltetrahydrobenzo[e][1,2,4]trioxin-6(7H)-one (11). Trioxane **4ac** (51.4 mg, 0.242 mmol, 1 eq), 5% Rh/Al_2O_3 (25 mg, 0.012 mmol, 0.05 eq) and PtO_2 (2.7 mg, 0.012, 0.05 eq) were placed in a round bottom flask and dissolved in 2.5 mL of ethyl acetate (0.1M). A balloon of H_2 was placed on the reaction vessel and it was stirred at room temperature for 1 h. The crude mixture was filtered through a plug of Celite and concentrated *in vacuo*. Column chromatography on SiO_2 with 15% (hexanes:ethyl acetate) of the residue gave analytically pure **11** as a clear oil. Note: If the reaction is left longer the trioxane will reduce to **12**. : 81% yield; clear oil; R_f = 0.50 (67:33 Hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.93 (d, *J* = 5.0 Hz), 3.96-3.93 (m, 1H), 3.00, (td, *J* = 5.8, 13.6 Hz, 1H), 2.64 (dd, *J* = 3.8, 15.9 Hz, 1H), 2.57-2.36 (m, 3H), 1.88-1.75 (m, 1H), 1.36 (s, 3H), 0.93 (d, *J* = Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 206.8, 107.9, 78.56, 78.24, 43.6, 37.7, 30.9, 28.1, 19.8, 16.72, 16.60; **IR** (NaCl, neat): 2970, 2879, 1717, 1472, 1219, 1144, 1079, 954 cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_{11}H_{19}O_4]^+$ ($[M + H]^+$): 229.1434, found 229.1434.



3,4-dihydroxy-4-methylcyclohexanone (12). To a solution of **11** (12.8 mg, 0.06 mmol, 1 eq) dissolved in 0.3 mL of acetic acid (0.2M), was added zinc dust (19.5 mg, 0.299 mmol, 5 eq). The solution was stirred for 6 h and then filtered through a pad of SiO_2 to afford the product as a clear oil in 75% yield. Notes: The reaction proceeds by reducing **11** to the dioxolane which is cleaved under acidic conditions to afford the diol. If **4ac** is reacted under these conditions then *p*-cresol is the only product. 85% yield; clear oil; R_f = 0.20 (50:50 Hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 3.74 (dd, *J* = 14.7, 3.8 Hz, 1H), 2.70-2.53 (m, 2H), 2.56, (dd, *J* = 1.8, 5.7 Hz, 1H), 2.30-1.95 (bs, 2H), 2.25 (dddd, *J* = 14.7, 4.9, 4.9, 1.8 Hz, 1H), 2.11 (ddd, *J* = 14.0, 4.9, 1.2 Hz, 1H), 1.66 (dddd, *J* = 16.7, 14.0, 11.6, 5.1 Hz, 1H), 1.40 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 209.0, 74.5, 70.4, 46.0, 36.9, 33.9, 25.6; **IR** (NaCl, neat): 3414, 2970, 2933, 1709, 1417, 1260, 1129, 1066, 921cm^{-1}; **HRMS** (ESI-APCI) *m/z* calcd $[C_7H_9O_2]^-$ ($[M - H]^-$): calcd 125.0608, found 125.0607.

Mechanistic Studies

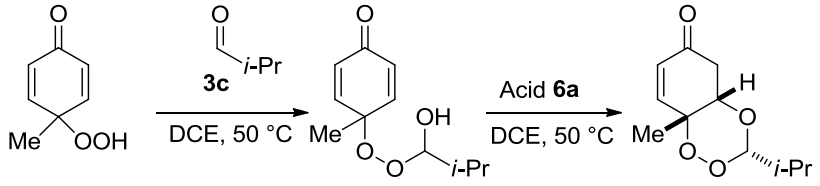
The reaction was carried out using the general procedure and it was monitored by chiral HPLC by taking aliquots from the reaction at 5 min, 1h, 6h, and 18 h. The ee of **8ac** was always 0% and the ee for **4ac** was 96% throughout the course of the reaction.



2a (+/-) **8ac** **4ac** 96% ee

Entry	Time	ee **8ac**	ee **4ac**
1	5 min	0%	> 92% trace
2	1 h	0%	96%
3	4 h	0%	96%
4	8 h	0%	96%
5	18 h	trace	96%

HPLC analysis: Chiralcel IC column, 90:10 Hexanes:*i*so-propanol, 1.0 ml/min, 210nm. **4ac** (96% ee) RT_{minor} = 8.33 min, RT_{major} = 9.31 min, **8ac** (0% ee) RT = 10.11 min, RT = 11.69 min, **2a** RT = 20.00 min.



2a (+/-) **8ac** **4ac** 94% ee

4-((1-hydroxy-2-methylpropyl)peroxy)-4-methylcyclohexa-2,5-dienone (8ac)

(+/-) 8ac was synthesized by heating **2a** and **3c** in DCE at 50 °C. The reaction was concentrated *in vacuo* to remove any excess **3c. 2a** was not removed because it co-elutes with **(+/-) 8ac** and **(+/-) 8ac** decomposes slowly on SiO_2. **(+/-) 8ac** was analyzed by chiral HPLC and found to be racemic. The mixture of **(+/-) 8ac** and **2a** were subject to the standard reaction conditions and reaction went to complete conversion in 94% ee.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96-6.84 (m, 2H), 6.11 (m, 2H), 4.88 (d, *J* = 5.8 Hz, 1H), 3.25 (bs, 1H), 1.77-1.68 (m, 1H), 1.37 (s, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H).

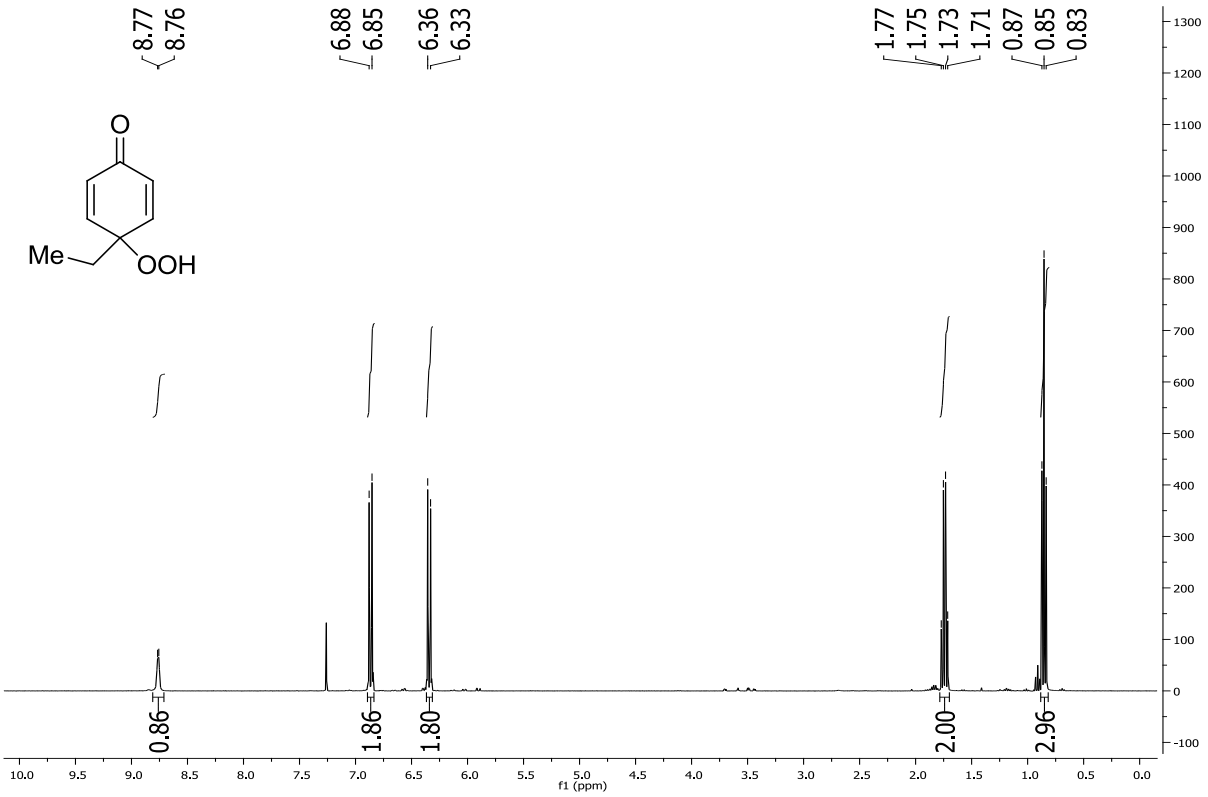
Cell Lines and Conditions

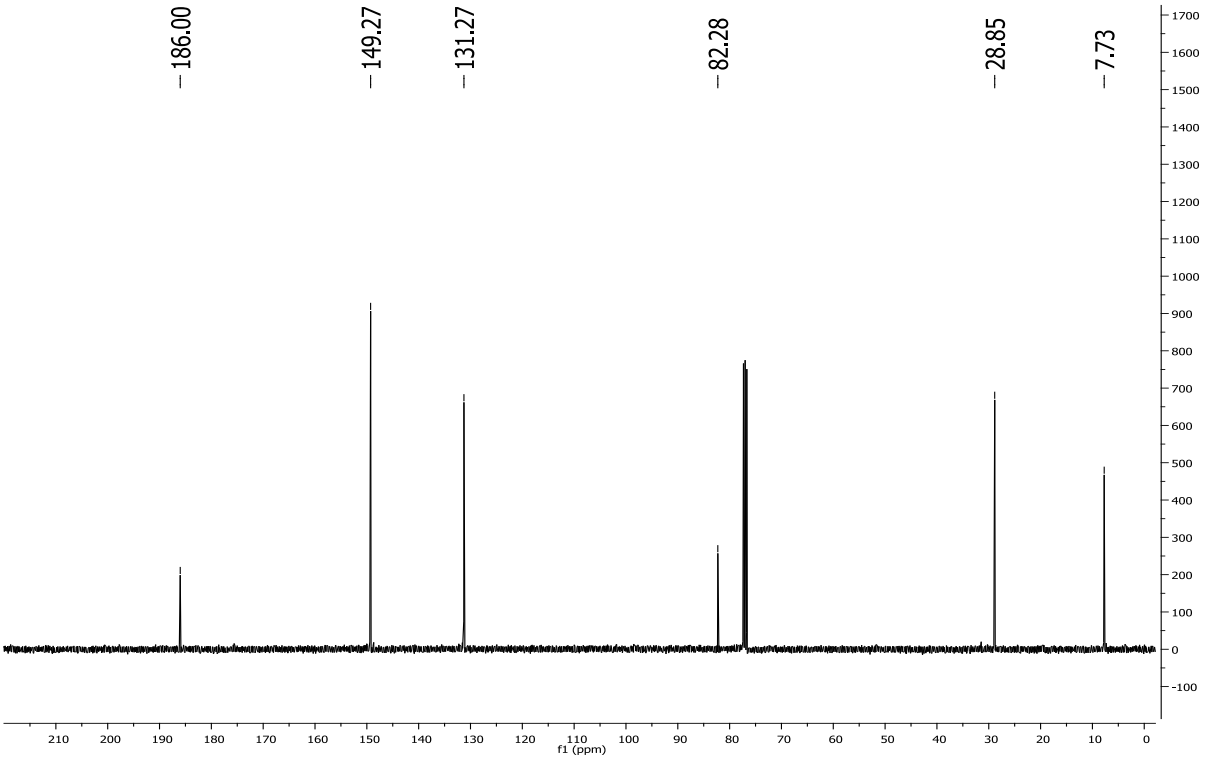
The D17 canine osteosarcoma cell line was obtained from American Type Culture Collection, (Manassas, VA). The M21 human melanoma cell line was generously provided by Dr. M. Albertini (University of Wisconsin-Madison). The human MDA-MB231 breast, A549 lung, and PC3 prostate carcinoma cell lines were generously provided by Dr. D. Gustafson (Colorado State University). All cells were grown in minimal essential medium supplemented with 5% heat-inactivated fetal bovine serum (HyClone, Logan, UT), 5% heat-inactivated newborn calf serum (HyClone), 100 units/ml penicillin-streptomycin (Mediatech, Herndon, VA), 2 mM L-glutamine (Mediatech), 1 mM sodium pyruvate (Mediatech), and 1X nonessential amino acid solution (Sigma, St. Louis, MO) at 37°C in a humidified atmosphere containing 5% CO_2. All cell lines were serially passaged by trypsinization.

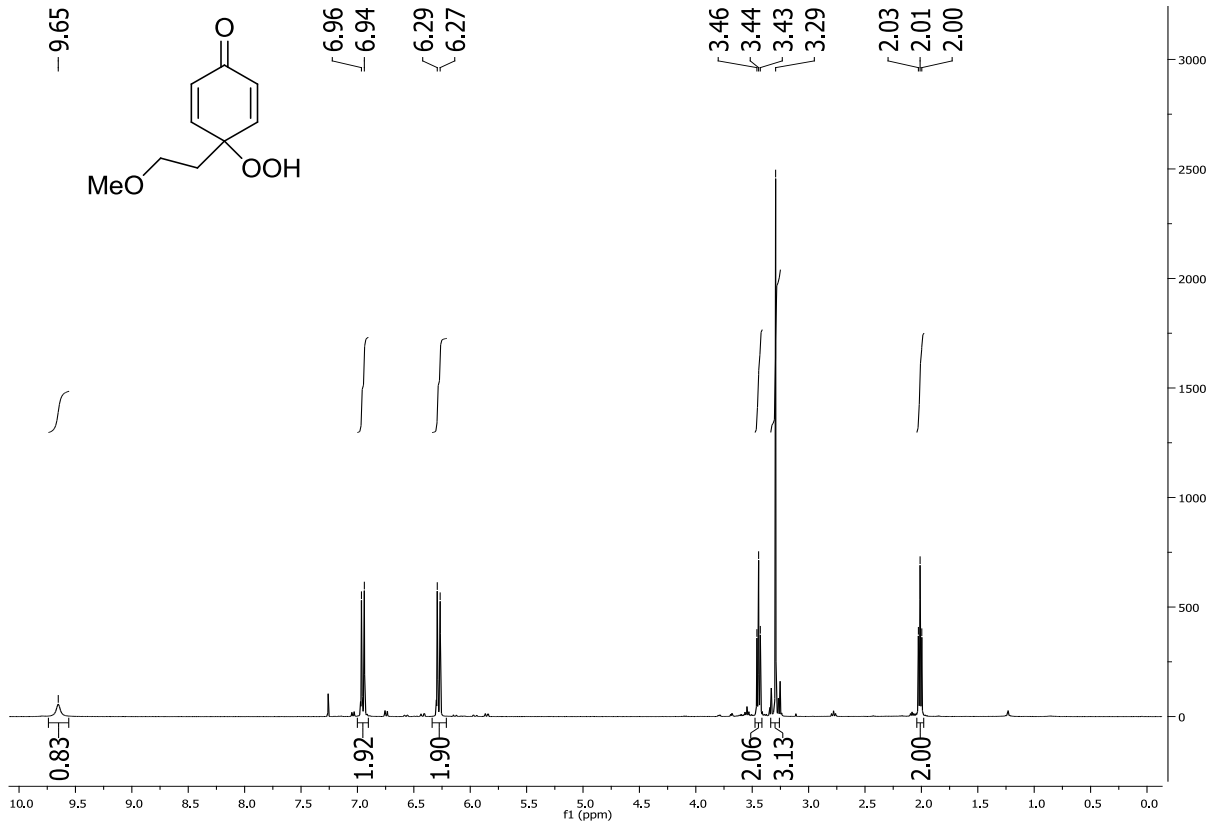
Growth Inhibition

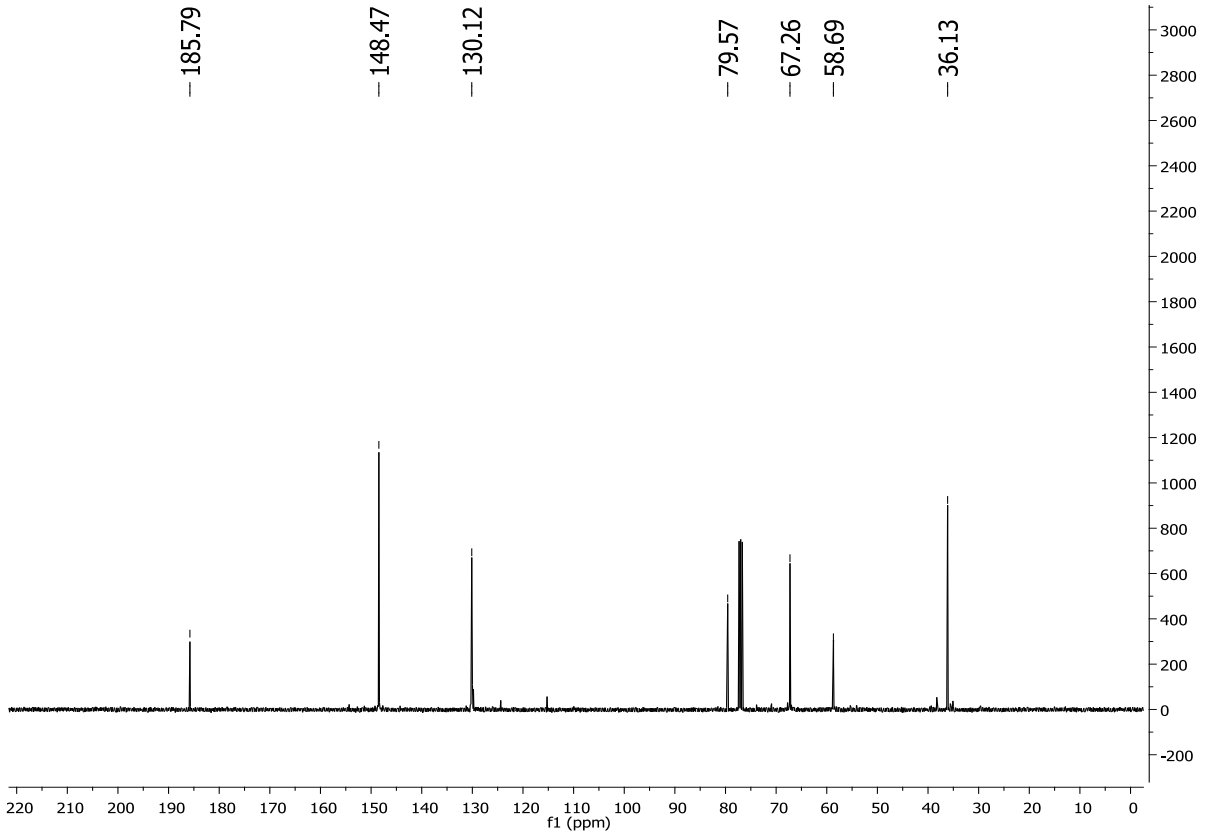
Stocks of artemisinin derivatives and synthetic trioxanes were stored in DMSO. Cells were plated at 2,000 cells/well in 200 μL medium in 96-well plates and allowed to adhere overnight. The plates were then washed and the medium replaced with medium containing varying concentrations of trioxane in quintuplicate. The final concentration of DMSO never exceeded 1%. After 72 h, the relative viable cell number was assessed using Alamar Blue™ (Promega, Madison, WI) according to the manufacturer's instructions. Relative fluorescence was expressed as a percentage of untreated cells and the IC_{50} was then calculated for each cell line by nonlinear regression analysis fitting to a sigmoidal dose-response curve, using Prism v4.0b for Macintosh (GraphPad Software, Inc., San Diego, CA). For conditions where a regression curve could not be fit, IC_{50} was estimated from the plotted growth inhibition curve.

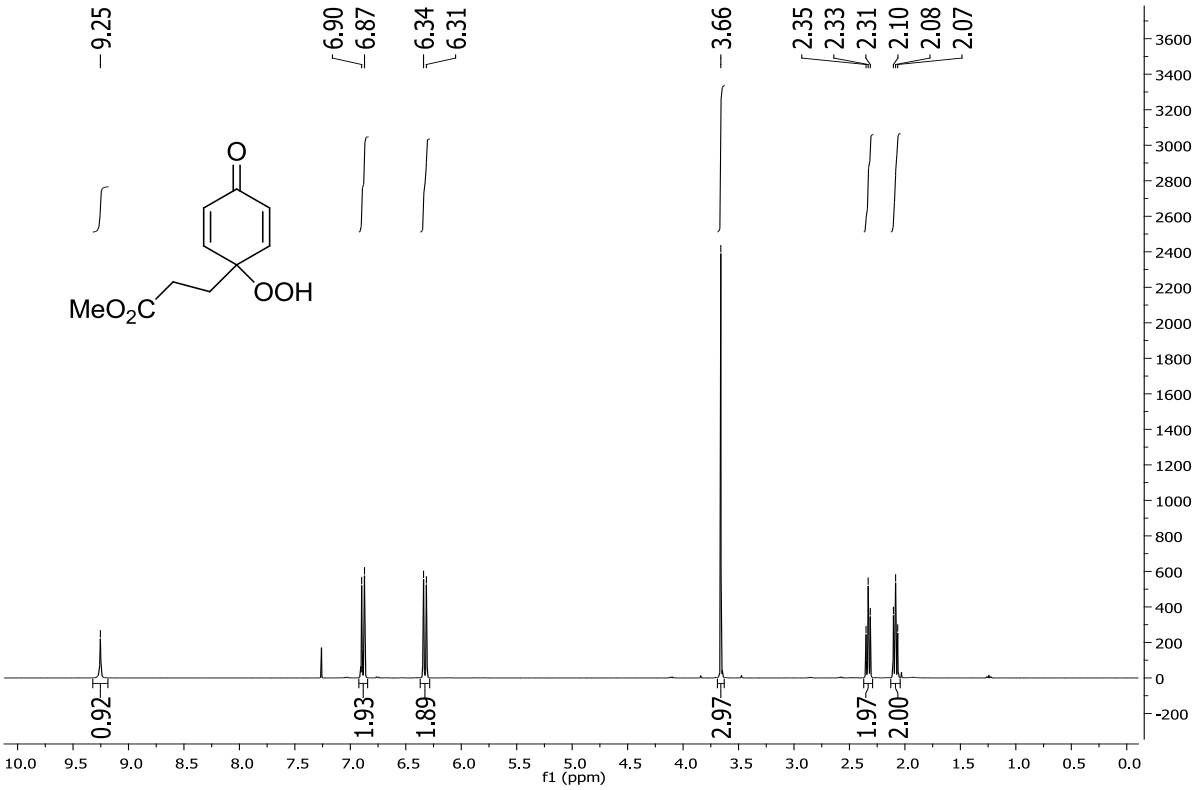
^{1}H NMR and ^{13}C NMR Spectra of New Compounds

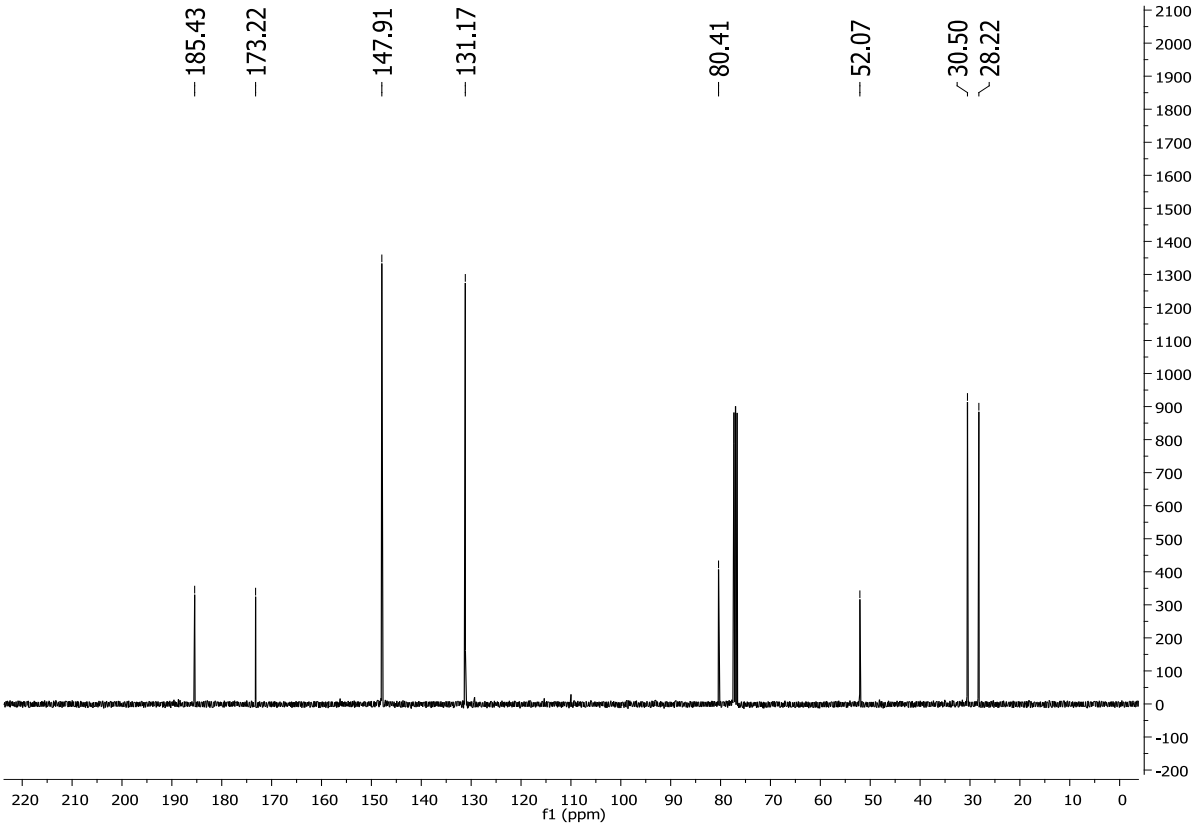





9.65
6.96
6.94
6.29
6.27
3.46
3.44
3.43
3.29
2.03
2.01
2.00
O
MeO
OOH
0.83
1.92
1.90
2.06
3.13
2.00
f1 (ppm)


185.79
148.47
130.12
79.57
67.26
58.69
36.13
f1 (ppm)


9.25
6.90
6.87
6.34
6.31
3.66
2.35
2.33
2.31
2.10
2.08
2.07
O
OOH
MeO2C
0.92
1.93
1.89
2.97
1.97
2.00
f1 (ppm)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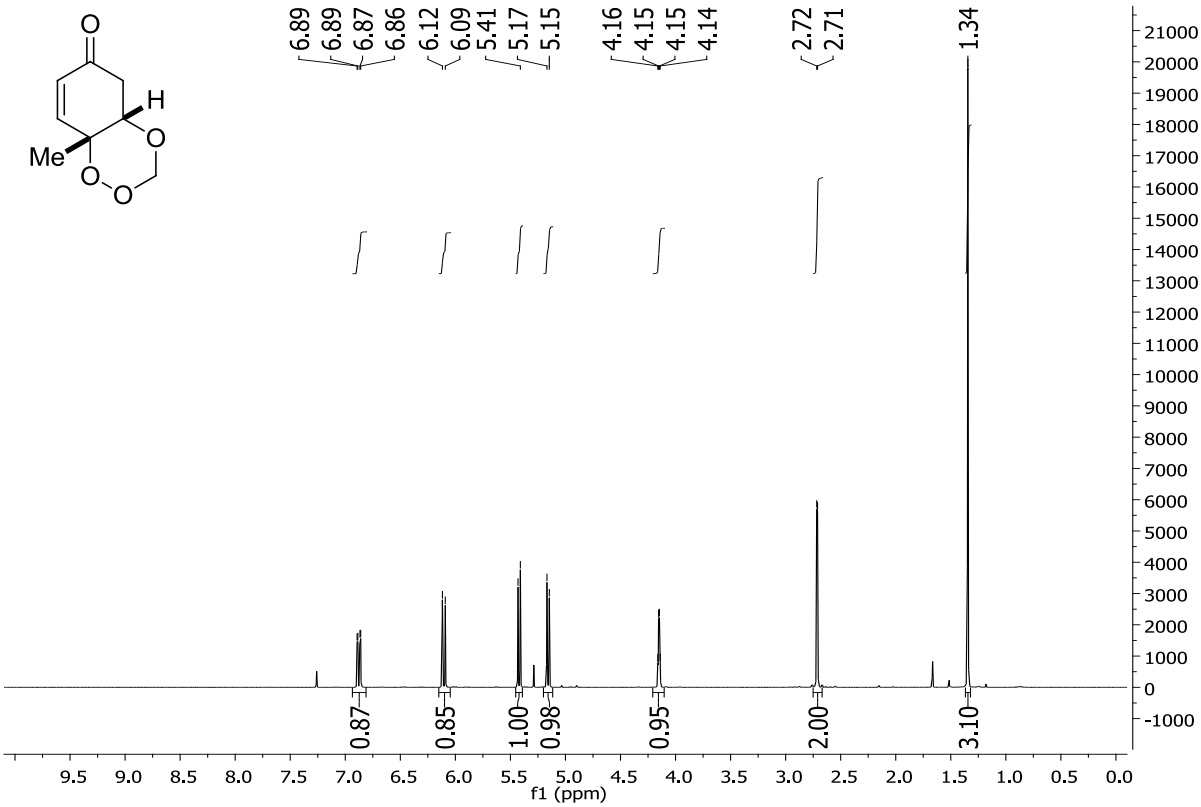
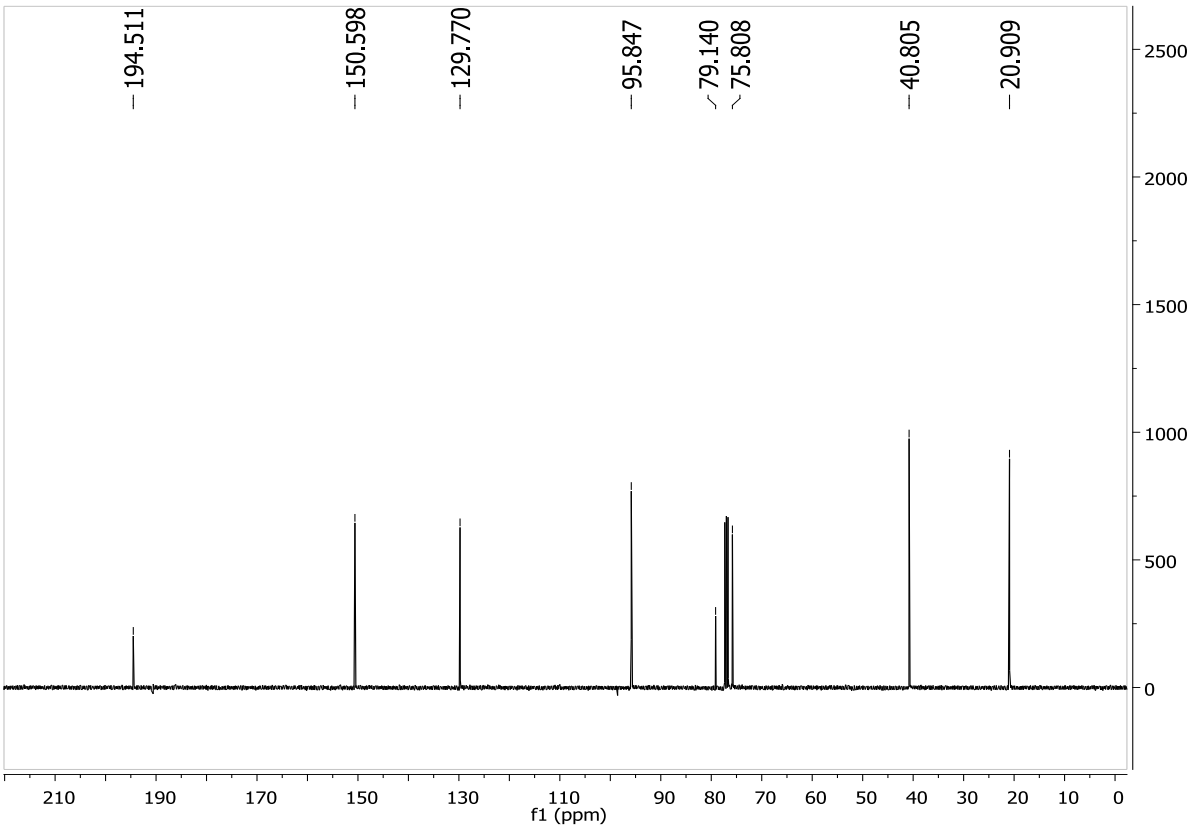
173.22
147.91
131.17
80.41
52.07
30.50
28.22
f1 (ppm)


6.89
6.89
6.87
6.86
6.12
6.09
5.41
5.17
5.15
4.16
4.15
4.15
4.14
2.72
2.71
1.34
0.87
0.85
1.00
0.98
0.95
2.00
3.10
f1 (ppm)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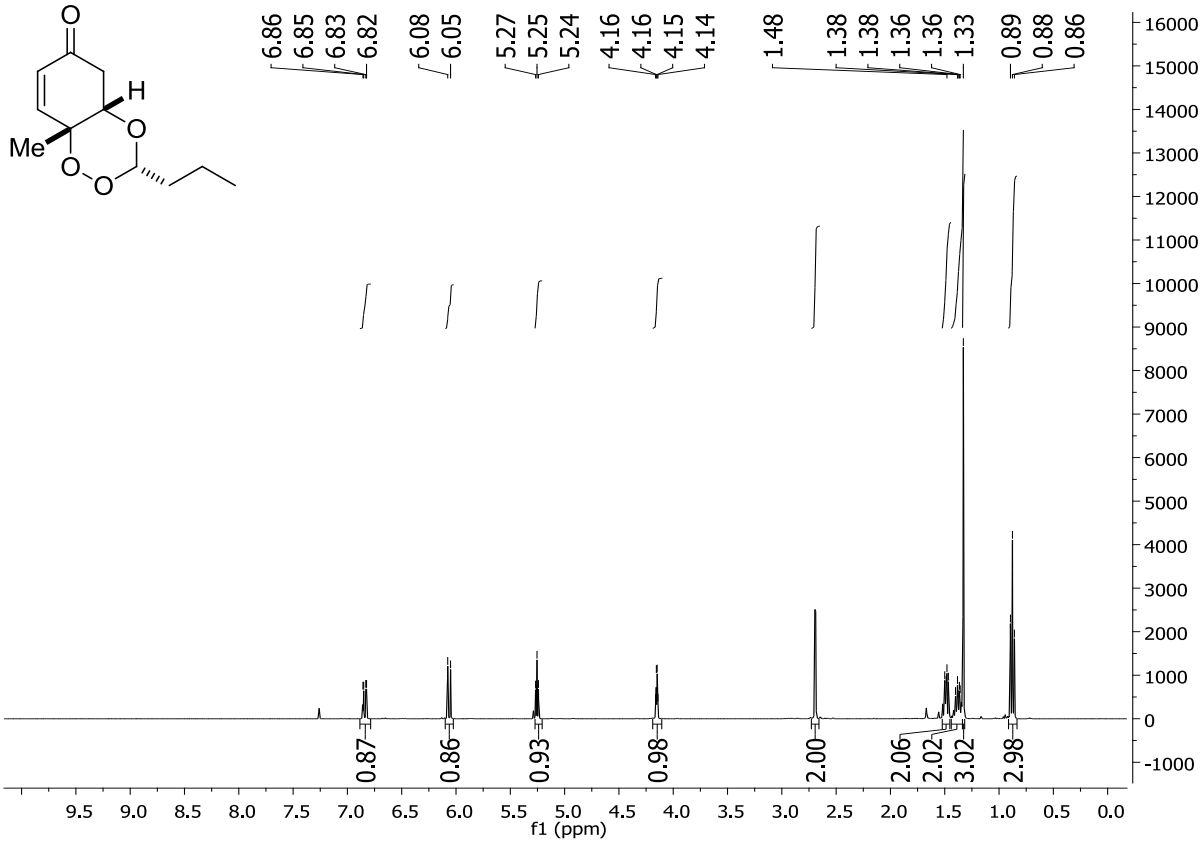
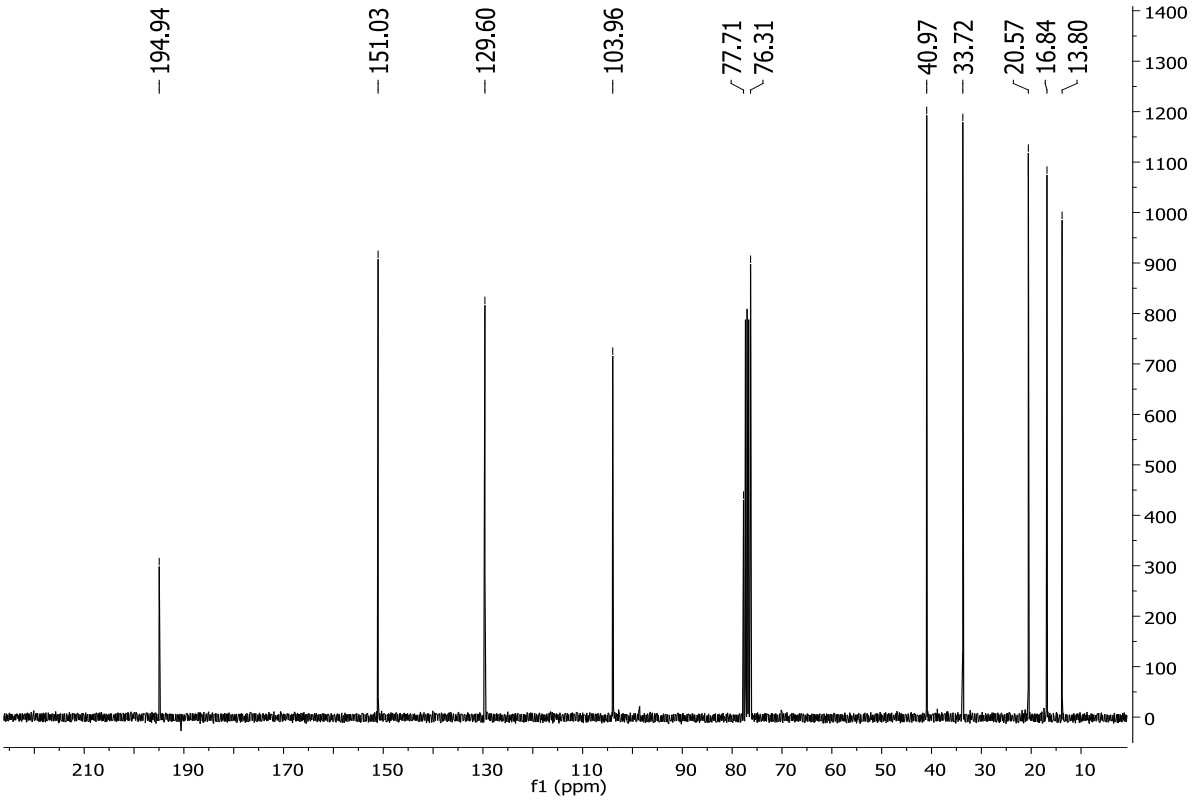
79.140
75.808
40.805
20.909
f1 (ppm)


O
H
Me
O
O
O
6.86
6.85
6.83
6.82
6.08
6.05
5.27
5.25
5.24
4.16
4.16
4.15
4.14
1.48
1.38
1.38
1.36
1.36
1.33
0.89
0.88
0.86
0.87
0.86
0.93
0.98
2.00
2.06
2.02
3.02
2.98
f1 (ppm)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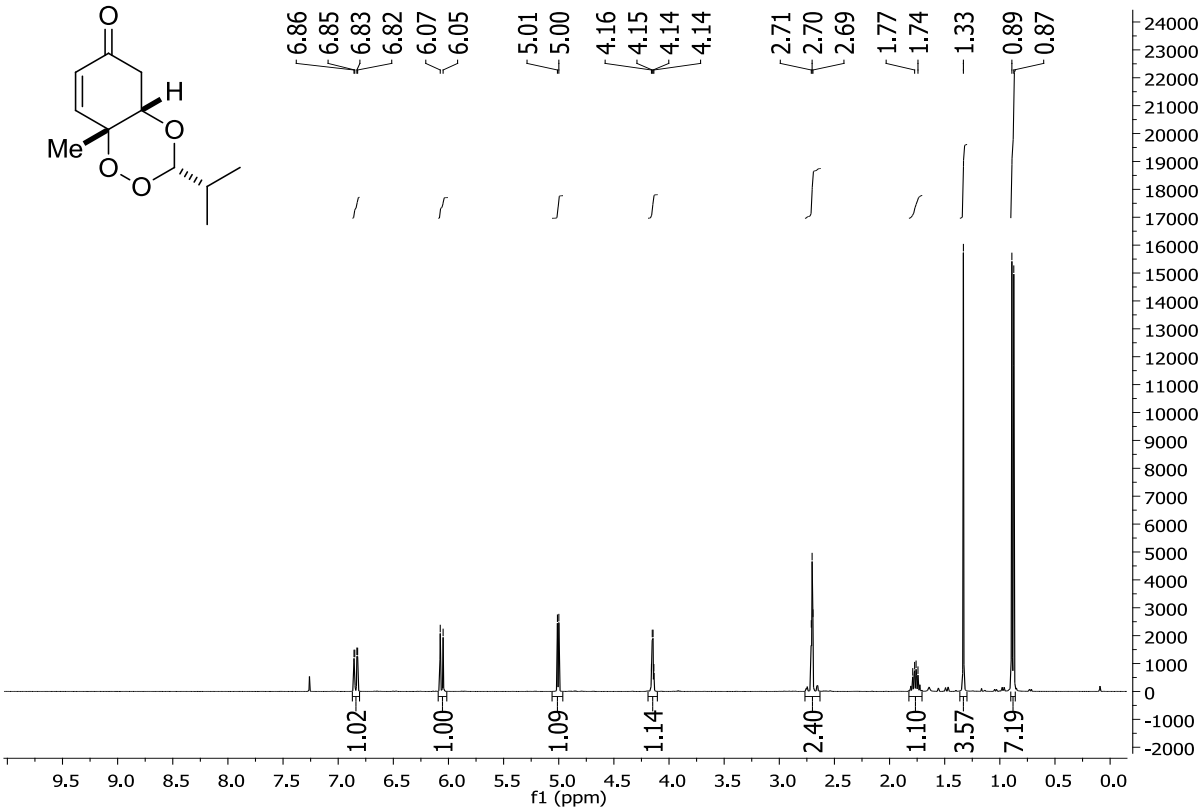
76.31
40.97
33.72
20.57
16.84
13.80
f1 (ppm)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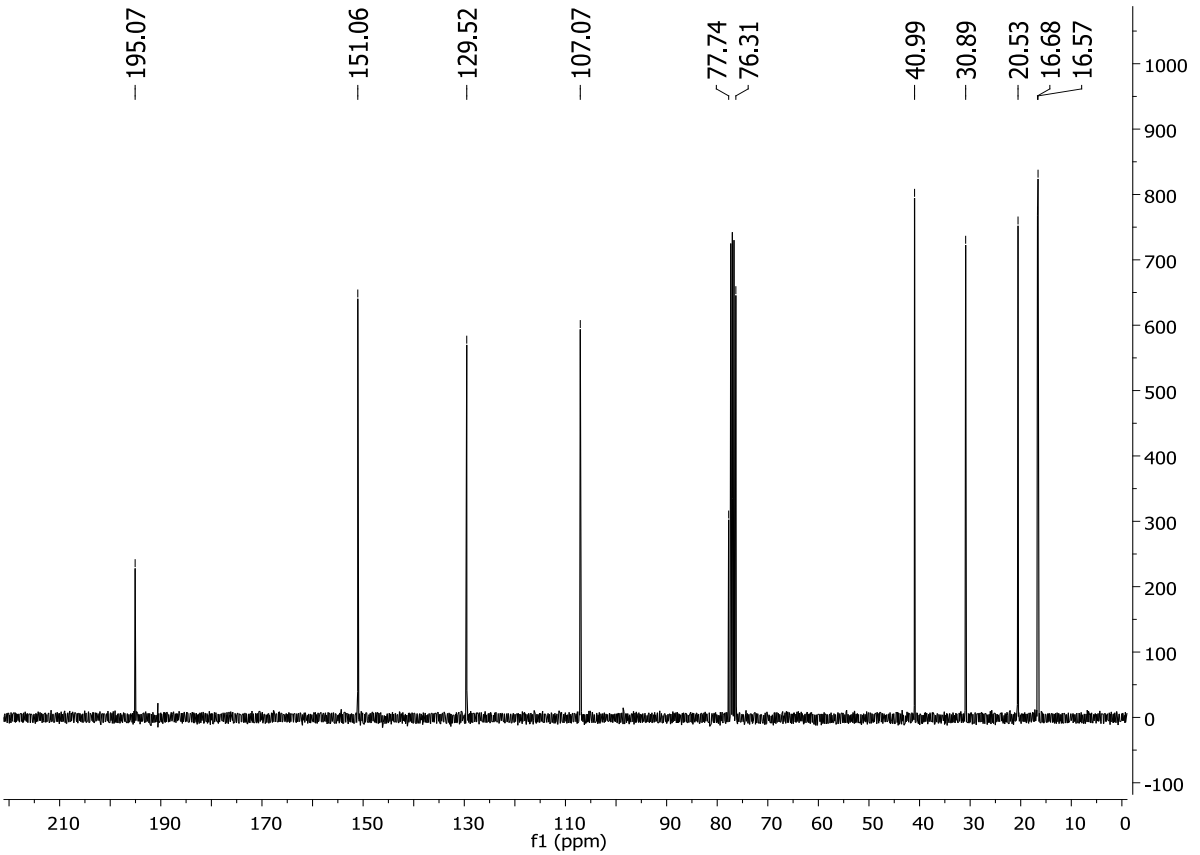
6.85
6.83
6.82
6.07
6.05
5.01
5.00
4.16
4.15
4.14
4.14
2.71
2.70
2.69
1.77
1.74
1.33
0.89
0.87
1.02
1.00
1.09
1.14
2.40
1.10
3.57
7.19
f1 (ppm)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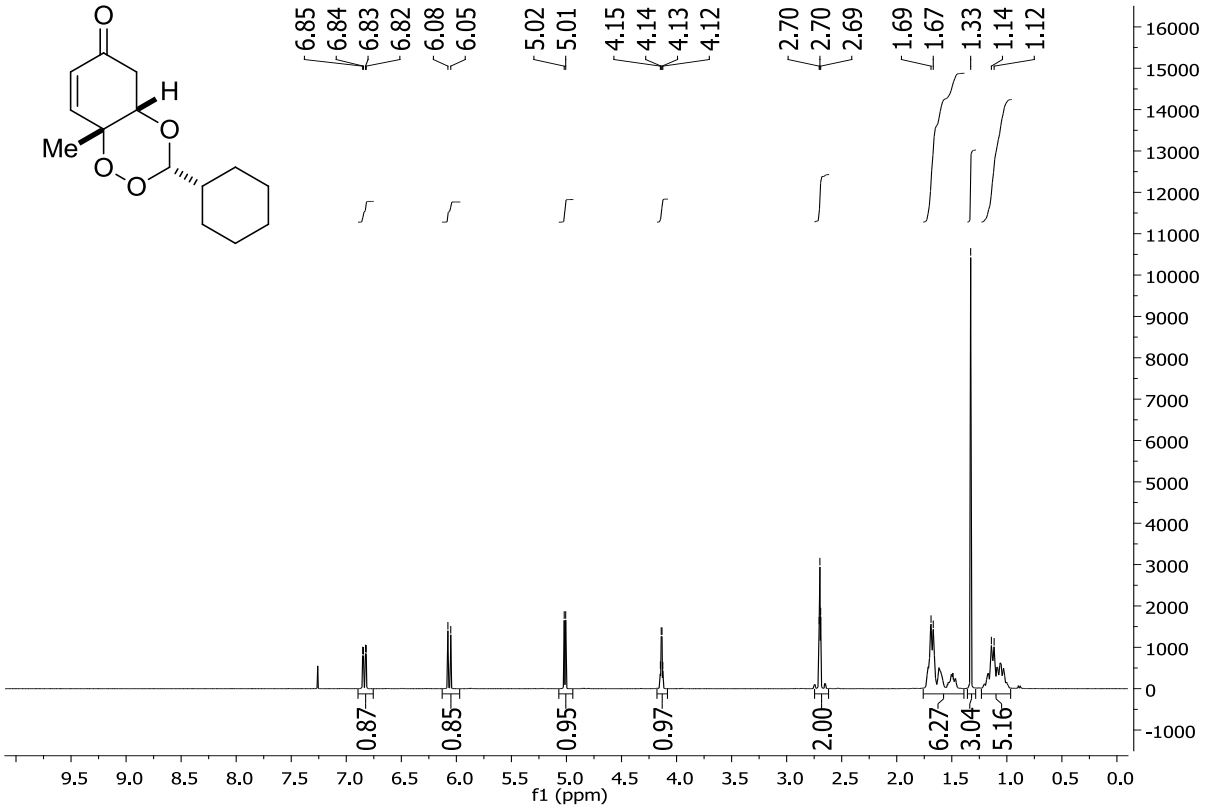
77.74
76.31
40.99
30.89
20.53
16.68
16.57
f1 (ppm)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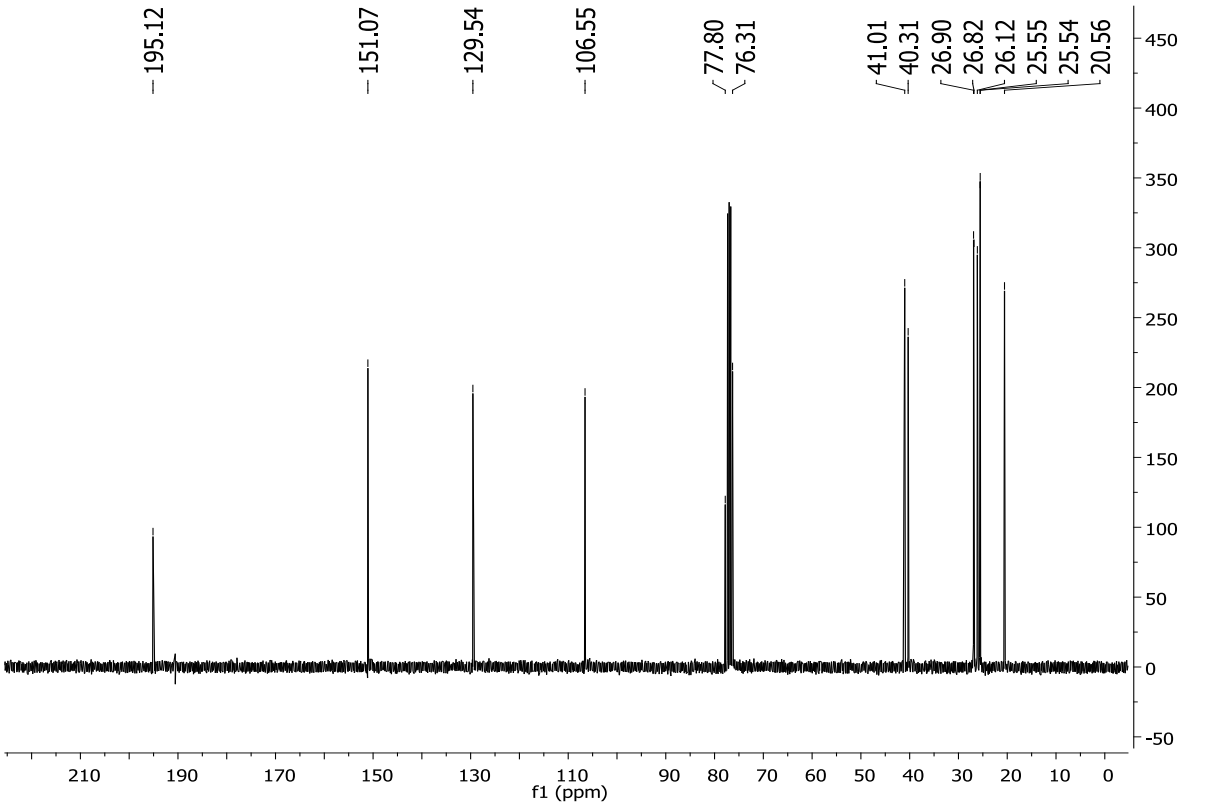
H
O
Me
O
O
6.85
6.84
6.83
6.82
6.08
6.05
5.02
5.01
4.15
4.14
4.13
4.12
2.70
2.70
2.69
1.69
1.67
1.33
1.14
1.12
0.87
0.85
0.95
0.97
2.00
6.27
3.04
5.16
f1 (ppm)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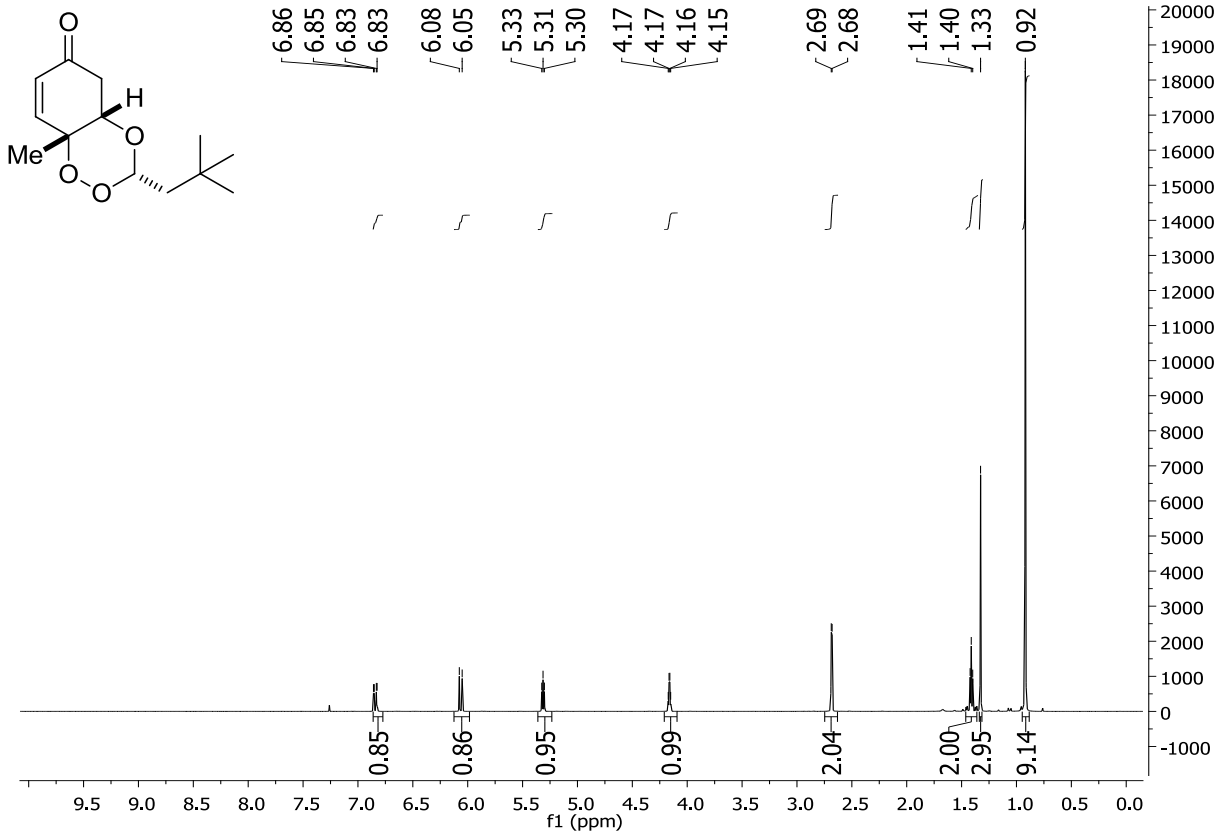
129.54
106.55
77.80
76.31
41.01
40.31
26.90
26.82
26.12
25.55
25.54
20.56
f1 (ppm)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6.85
6.83
6.83
6.08
6.05
5.33
5.31
5.30
4.17
4.17
4.16
4.15
2.69
2.68
1.41
1.40
1.33
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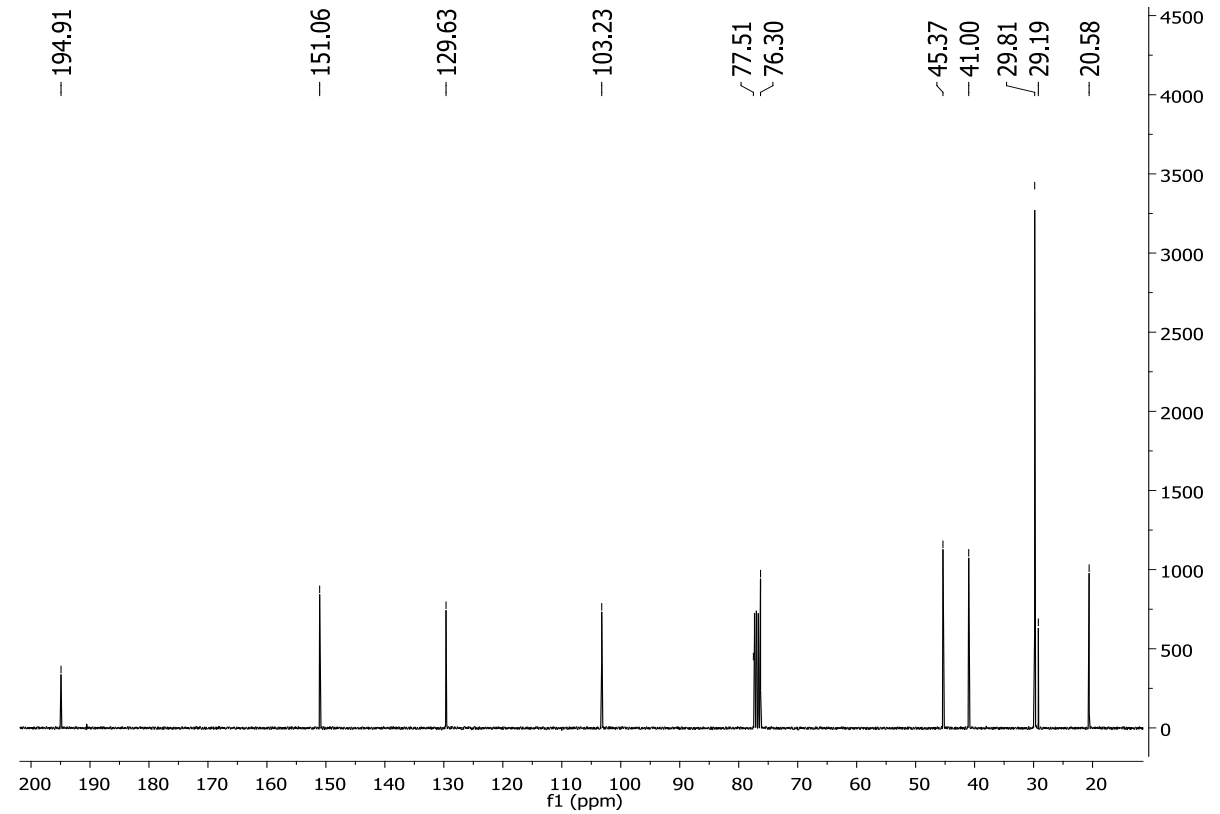
0.85
0.86
0.95
0.99
2.04
2.00
2.95
9.14
f1 (ppm)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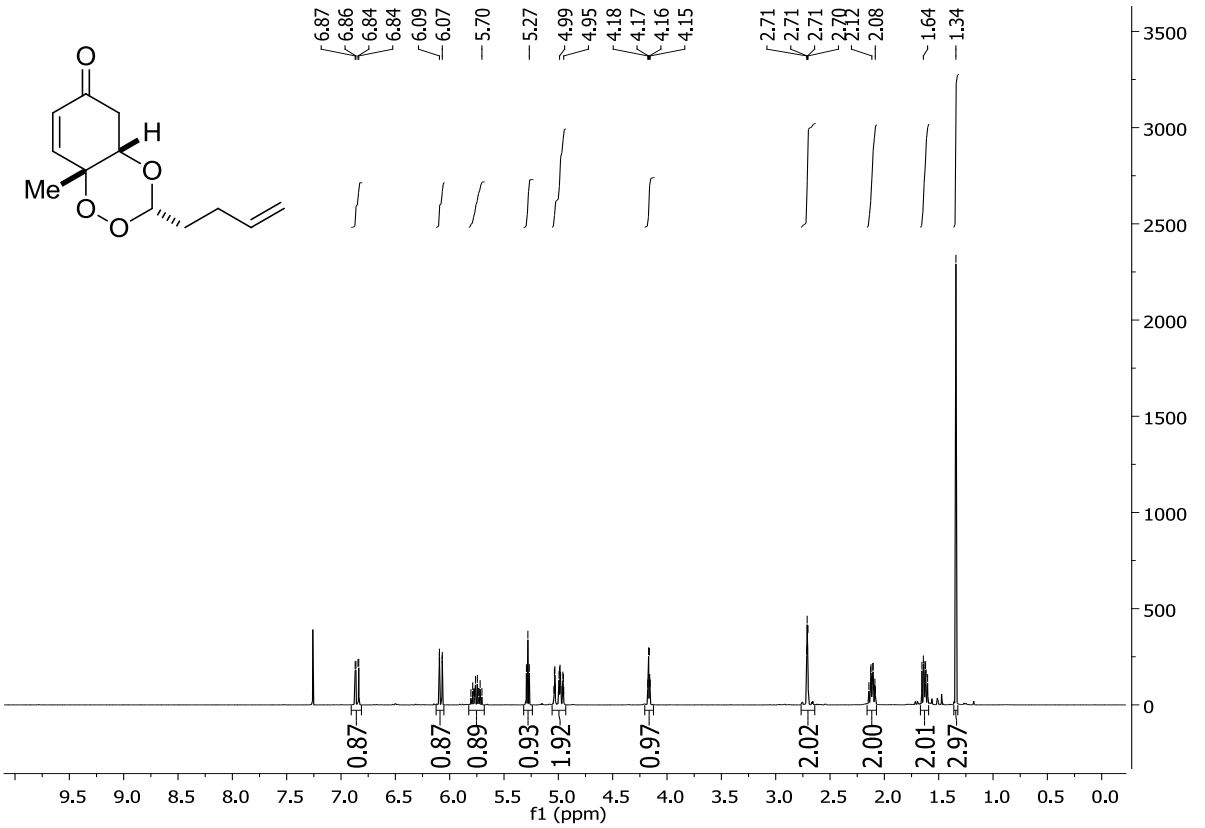
76.30
45.37
41.00
29.81
29.19
20.58
f1 (ppm)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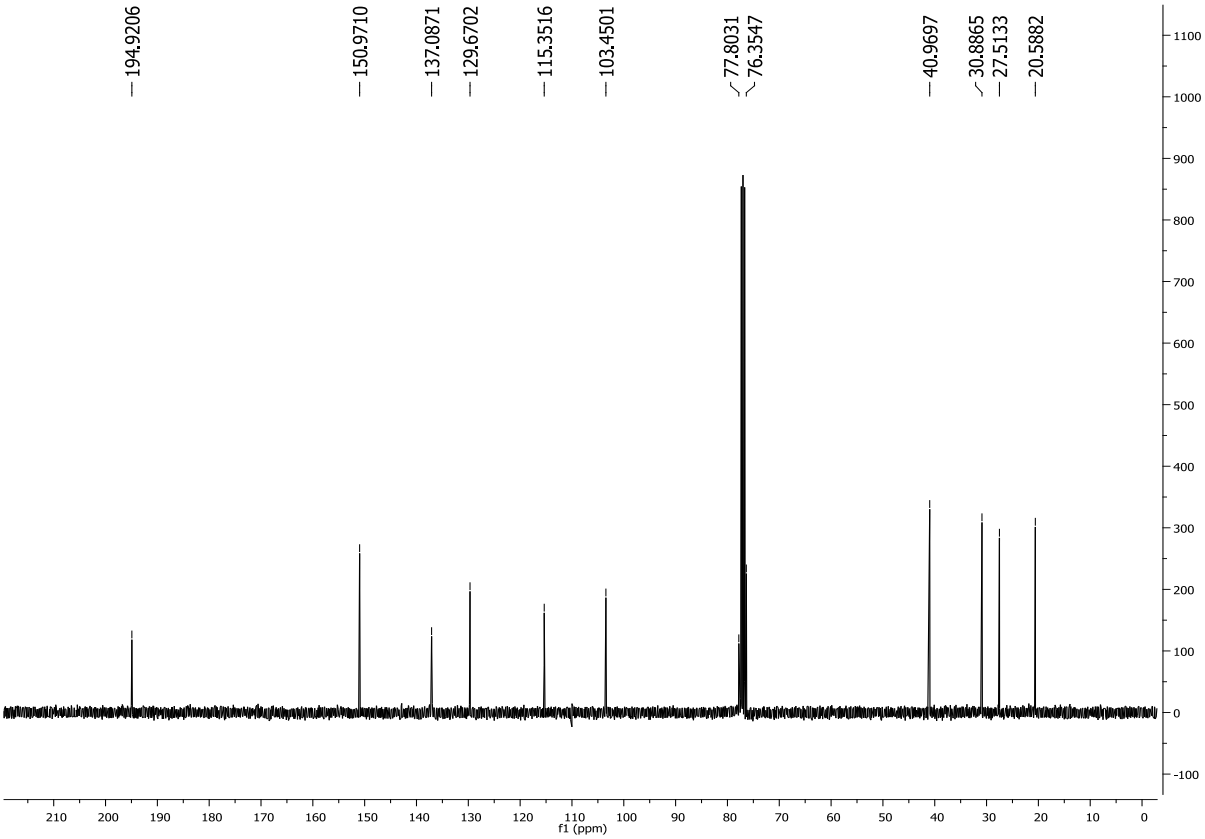
6.86
6.84
6.84
6.09
6.07
5.70
5.27
4.99
4.95
4.18
4.17
4.16
4.15
2.71
2.71
2.71
2.70
2.12
2.08
1.64
1.34
0.87
0.87
0.89
0.93
1.92
0.97
2.02
2.00
2.01
2.97
f1 (ppm)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137.0871
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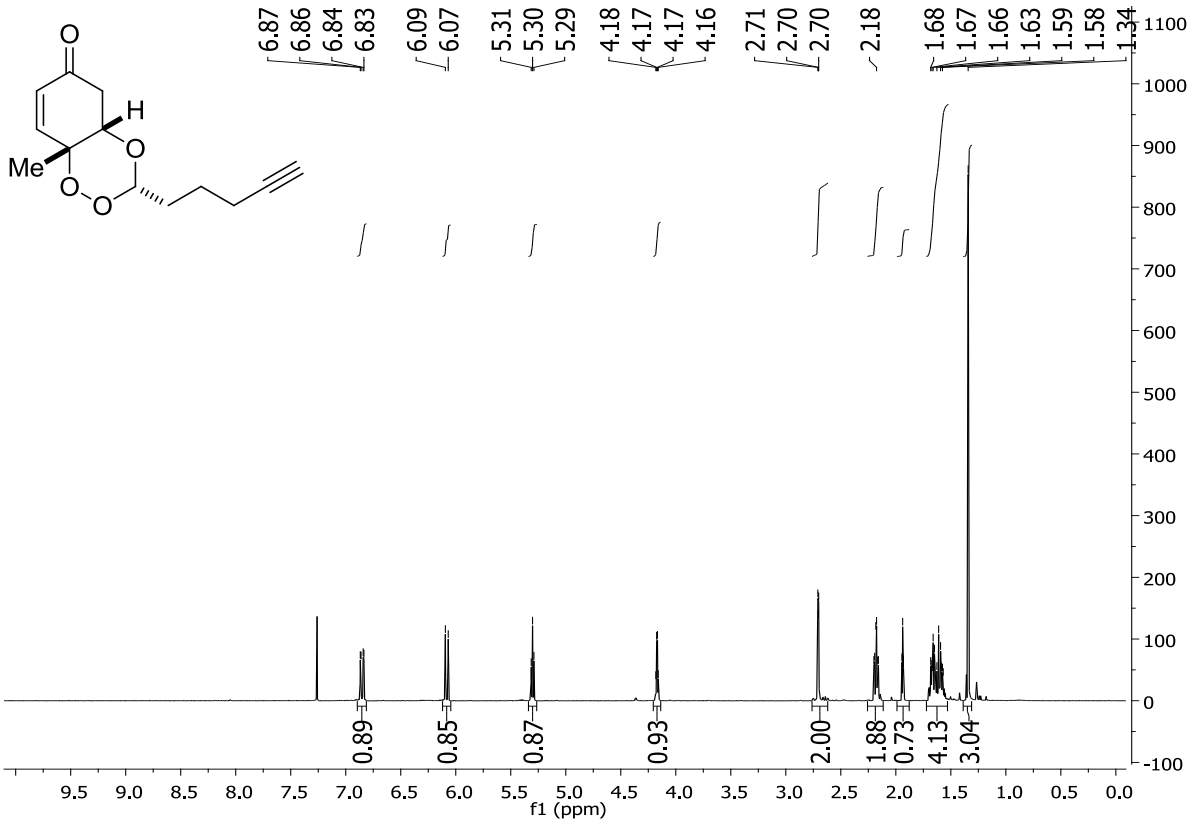
20.5882
f1 (ppm)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6.84
6.83
6.09
6.07
5.31
5.30
5.29
4.18
4.17
4.17
4.16
2.71
2.70
2.70
2.18
1.68
1.67
1.66
1.63
1.59
1.58
1.34
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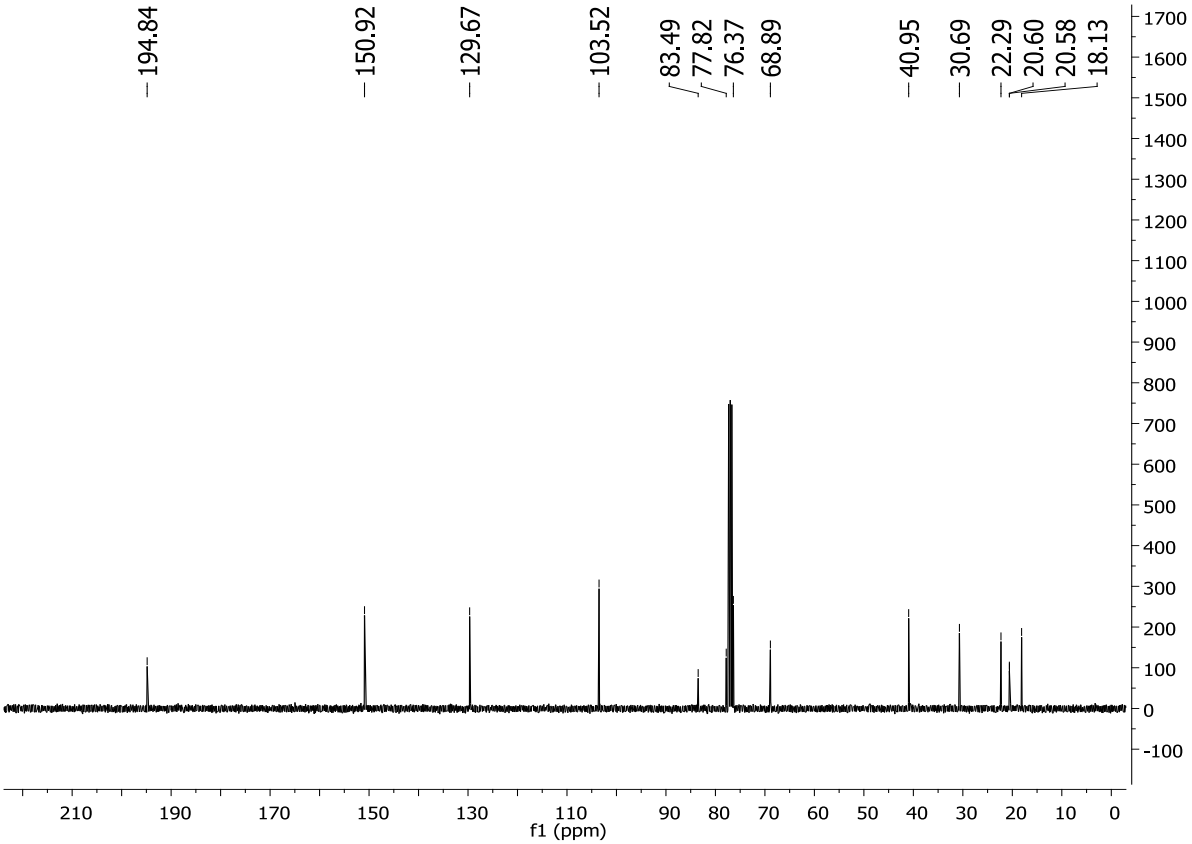
0.85
0.87
0.93
2.00
1.88
0.73
4.13
3.04
f1 (ppm)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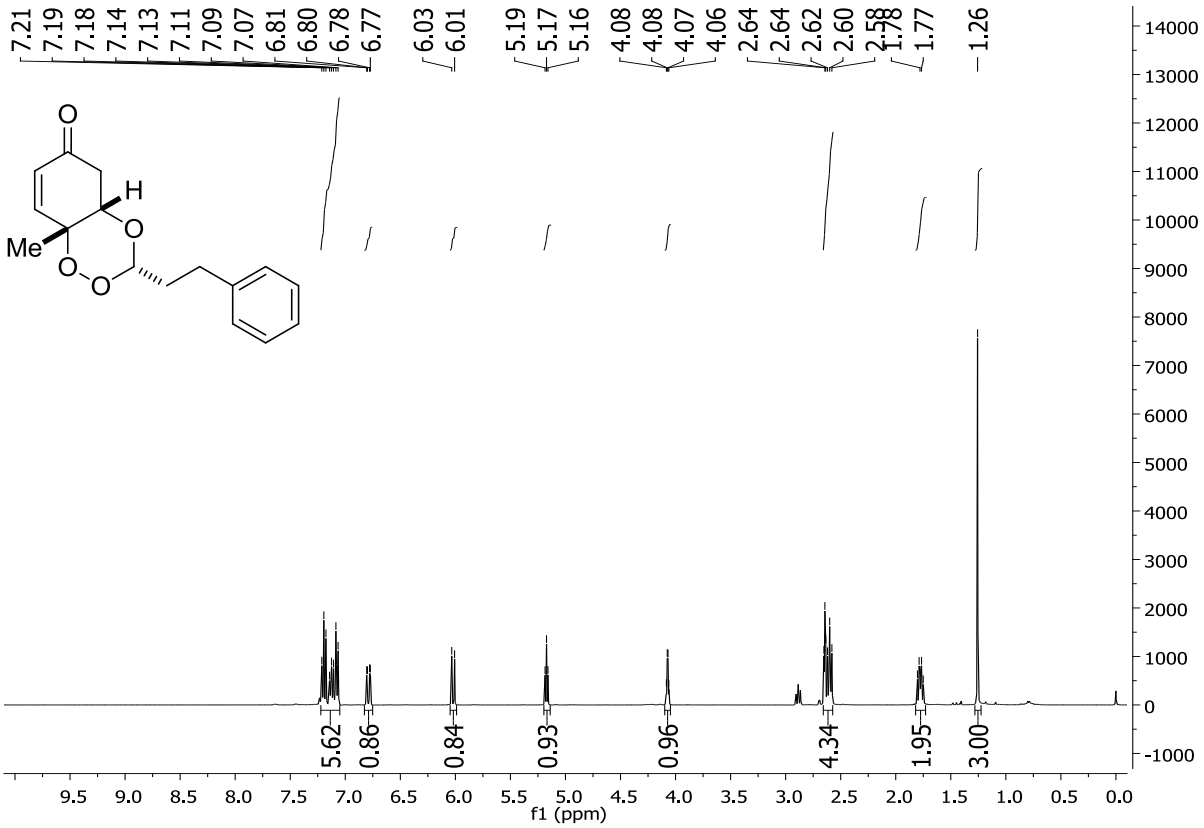
76.37
68.89
40.95
30.69
22.29
20.60
20.58
18.13
f1 (ppm)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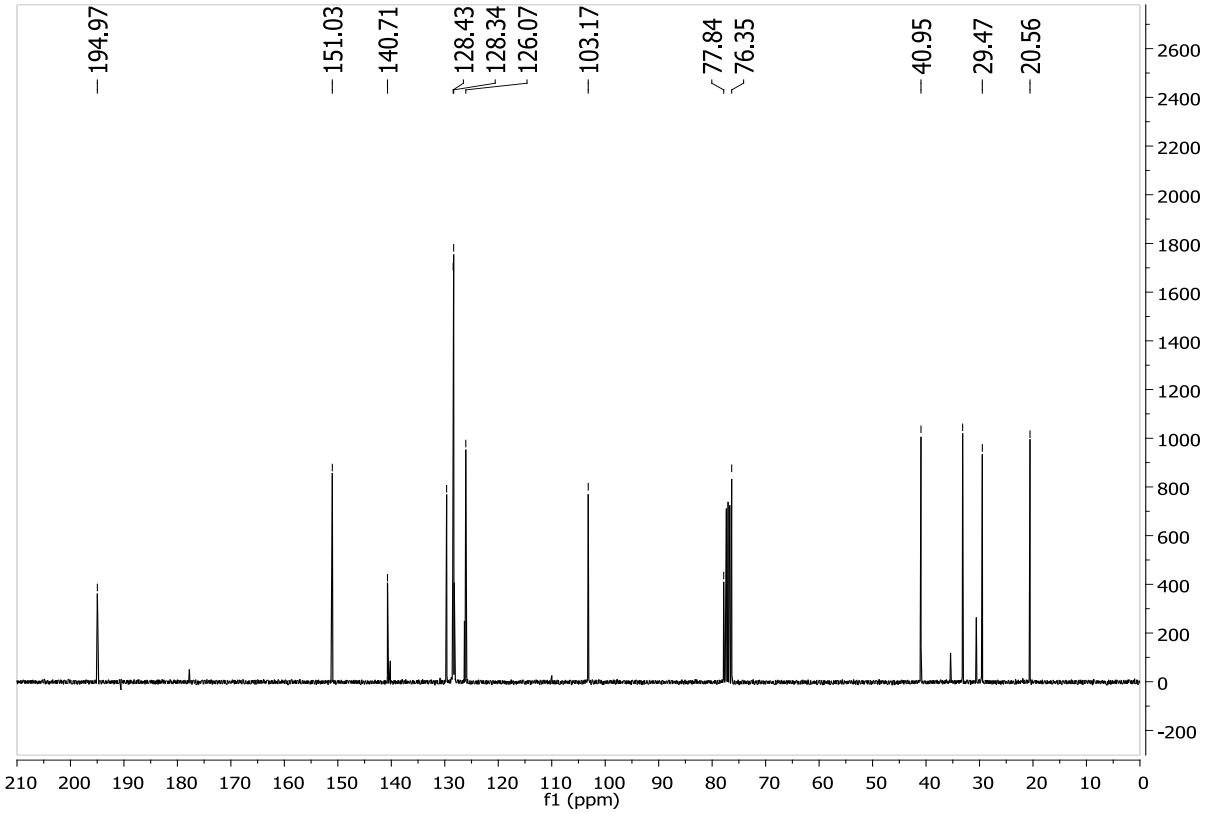
7.19
7.18
7.14
7.13
7.11
7.09
7.07
6.81
6.80
6.78
6.77
6.03
6.01
5.19
5.17
5.16
4.08
4.08
4.07
4.06
2.64
2.64
2.62
2.60
2.58
1.78
1.77
1.26
O
H
O
Me
O
O
5.62
0.86
0.84
0.93
0.96
4.34
1.95
3.00
f1 (ppm)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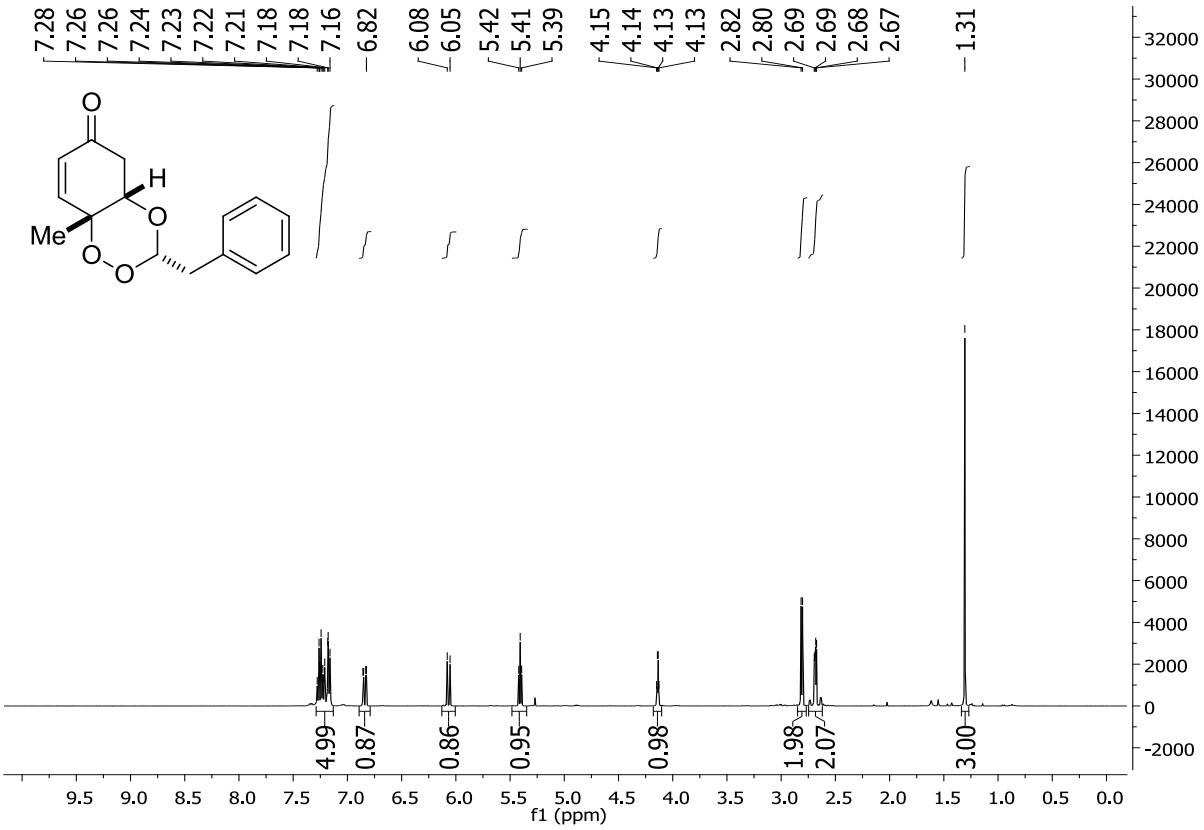
126.07
103.17
77.84
76.35
40.95
29.47
20.56
f1 (ppm)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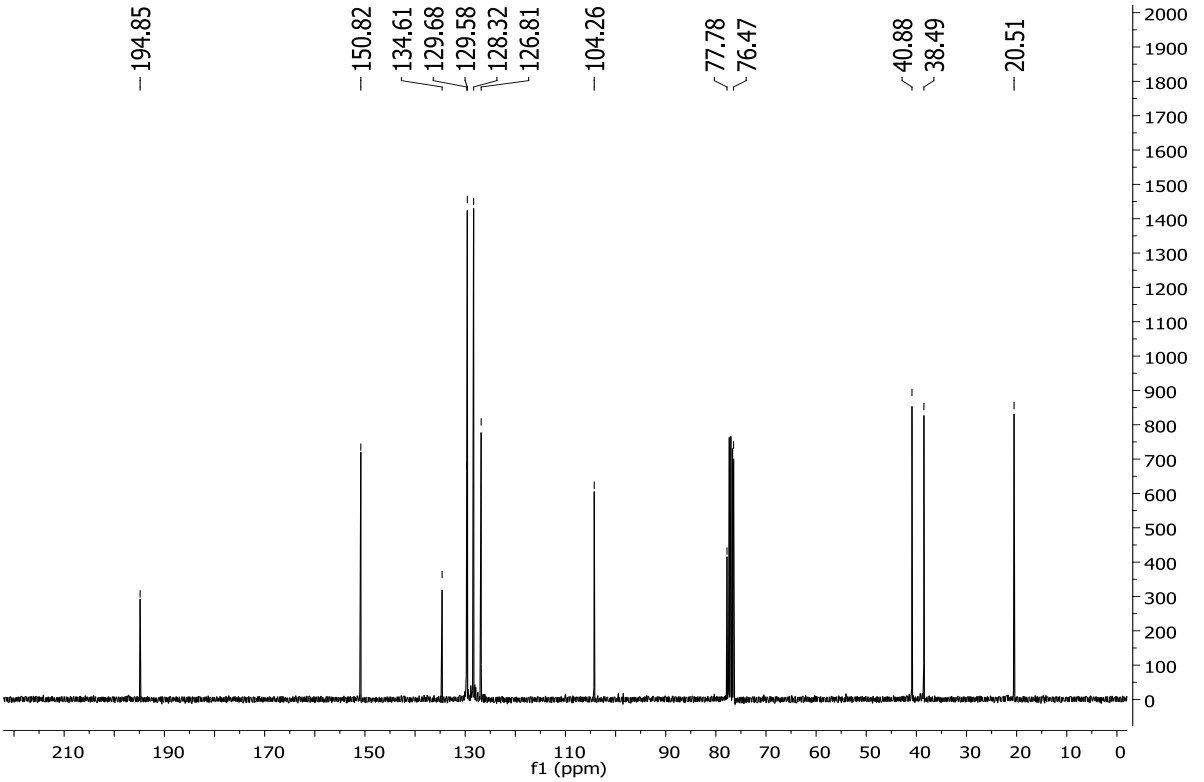
7.23
7.22
7.21
7.18
7.18
7.16
6.82
6.08
6.05
5.42
5.41
5.39
4.15
4.14
4.13
4.13
2.82
2.80
2.69
2.69
2.68
2.67
1.31
O
H
O
Me
O
O
4.99
0.87
0.86
0.95
0.98
1.98
2.07
3.00
f1 (ppm)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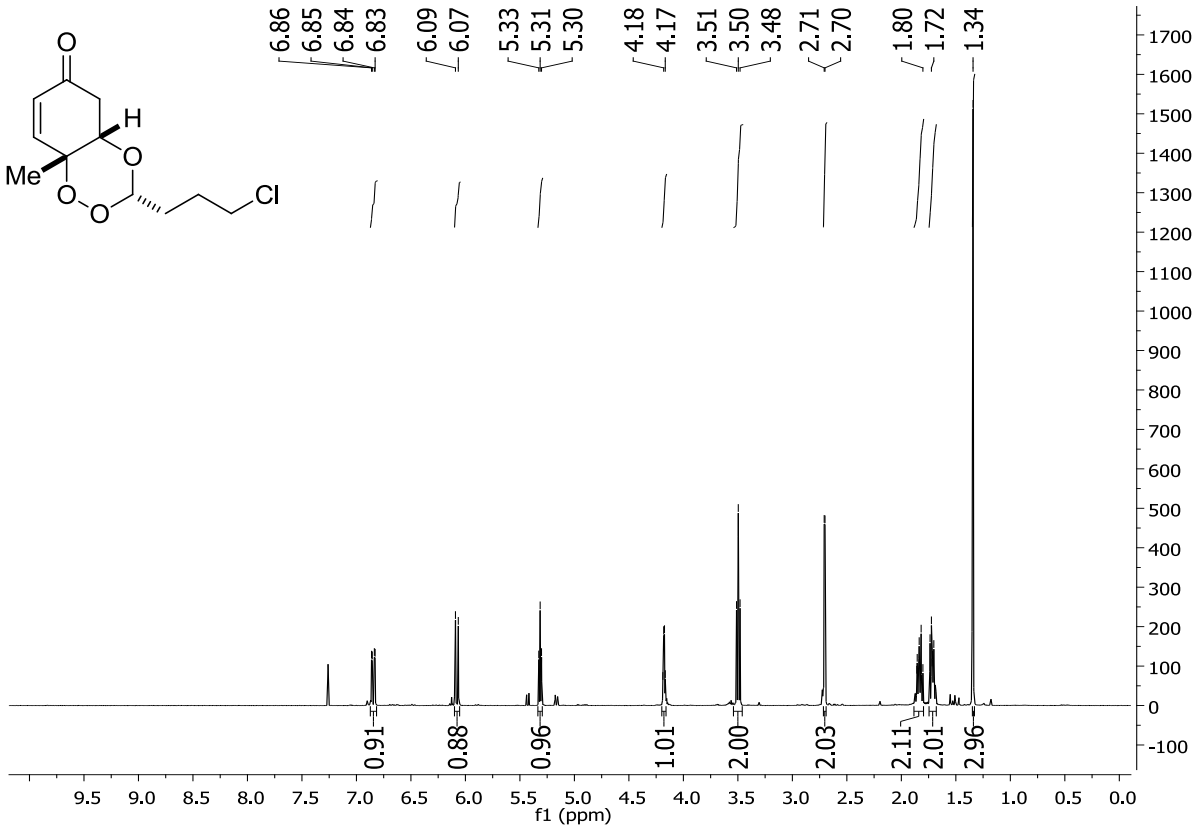
104.26
77.78
76.47
40.88
38.49
20.51
f1 (ppm)


O
H
O
Me
O
O
Cl
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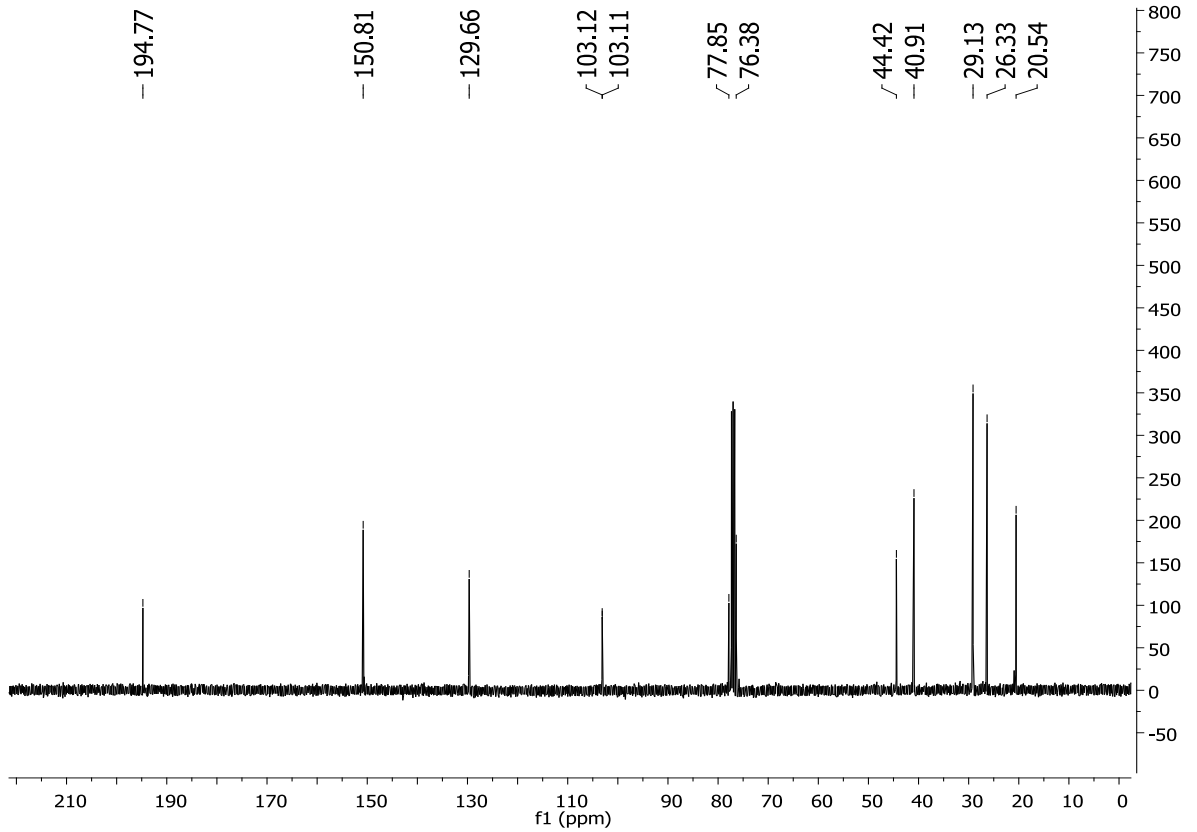
6.85
6.84
6.83
6.09
6.07
5.33
5.31
5.30
4.18
4.17
3.51
3.50
3.48
2.71
2.70
1.80
1.72
1.34
0.91
0.88
0.96
1.01
2.00
2.03
2.11
2.01
2.96
f1 (ppm)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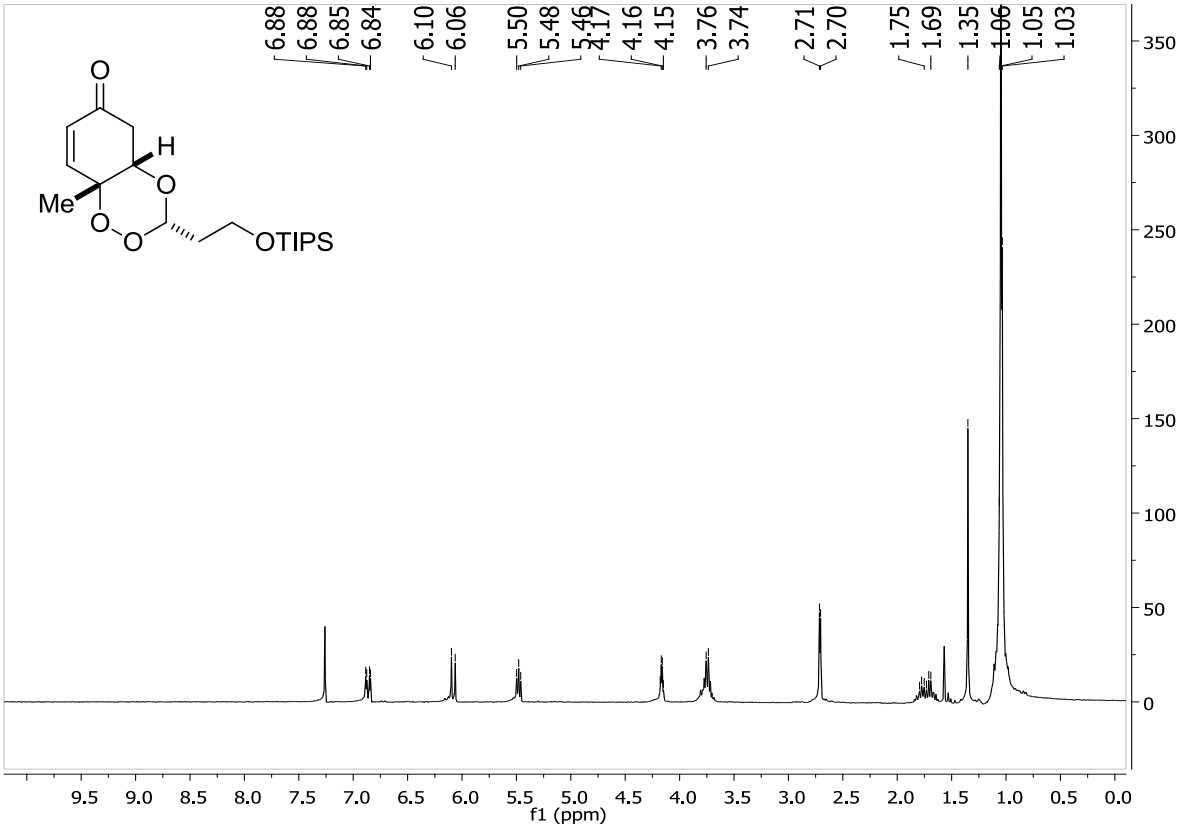
103.11
77.85
76.38
44.42
40.91
29.13
26.33
20.54
f1 (ppm)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6.88
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6.06
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5.48
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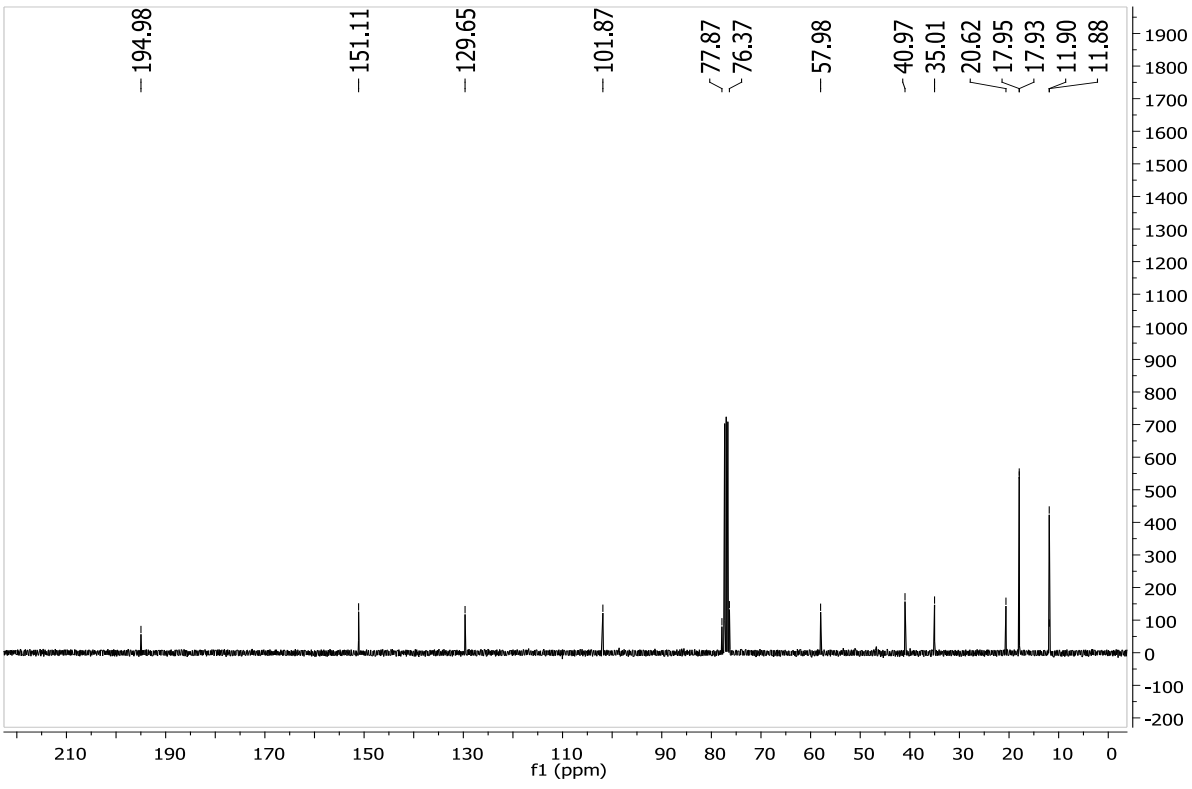
4.17
4.16
4.15
3.76
3.74
2.71
2.70
1.75
1.69
1.35
1.06
1.05
1.03
O
H
O
Me
O
O
OTIPS
f1 (ppm)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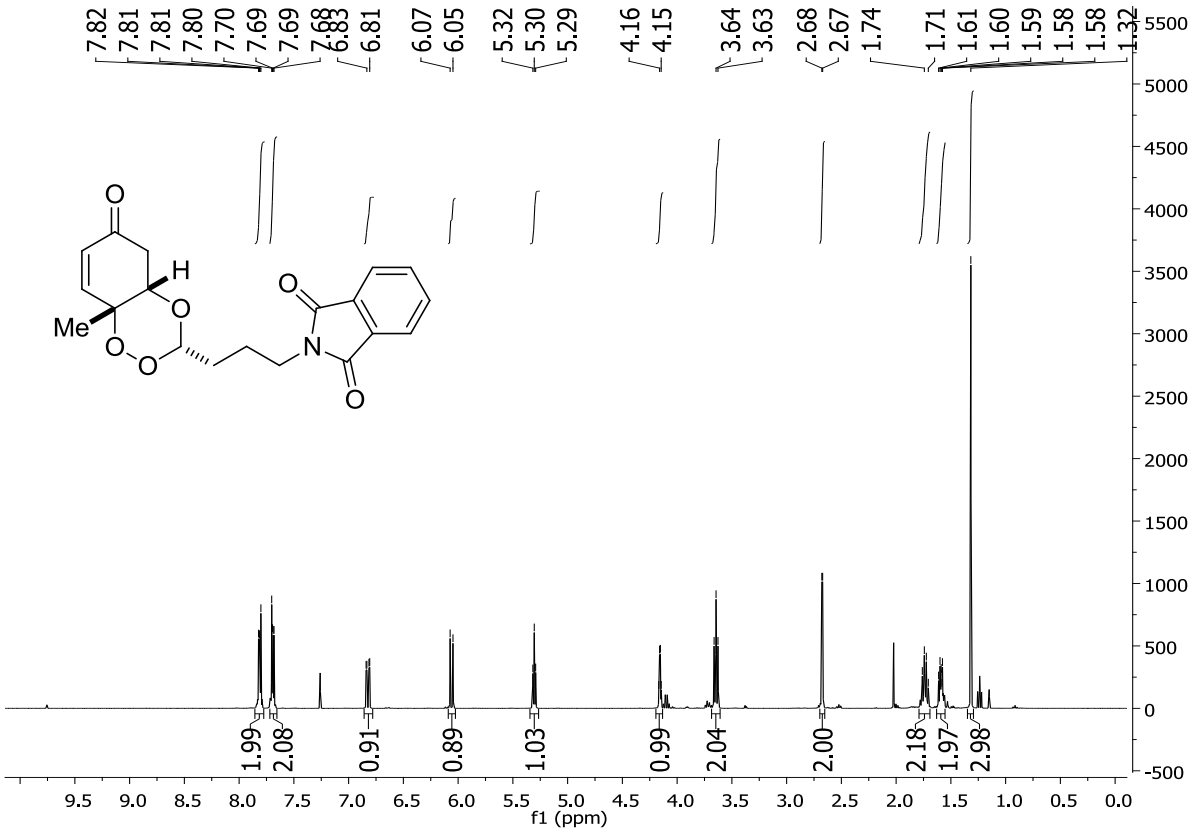
57.98
40.97
35.01
20.62
17.95
17.93
11.90
11.88
f1 (ppm)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7.81
7.80
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7.69
7.68
6.83
6.81
6.07
6.05
5.32
5.30
5.29
4.16
4.15
3.64
3.63
2.68
2.67
1.74
1.71
1.61
1.60
1.59
1.58
1.58
1.32
1.99
2.08
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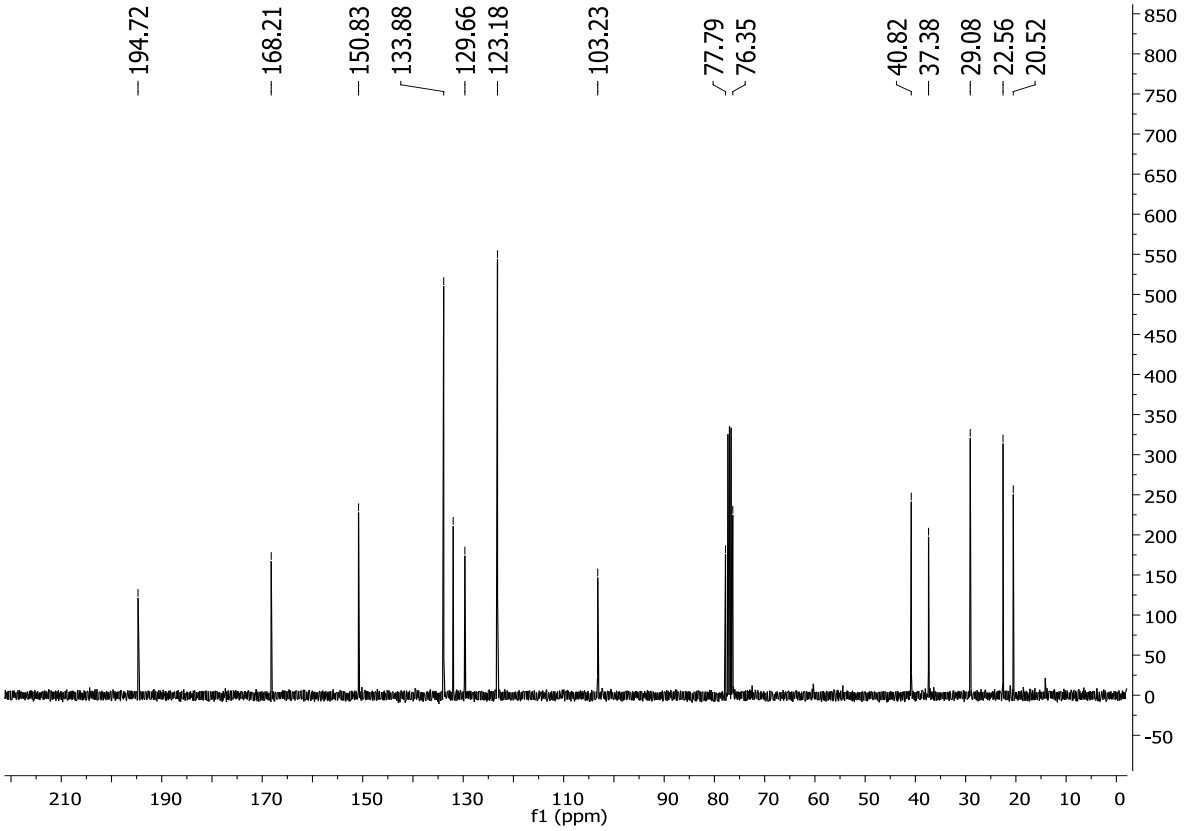
0.89
1.03
0.99
2.04
2.00
2.18
1.97
2.98
f1 (ppm)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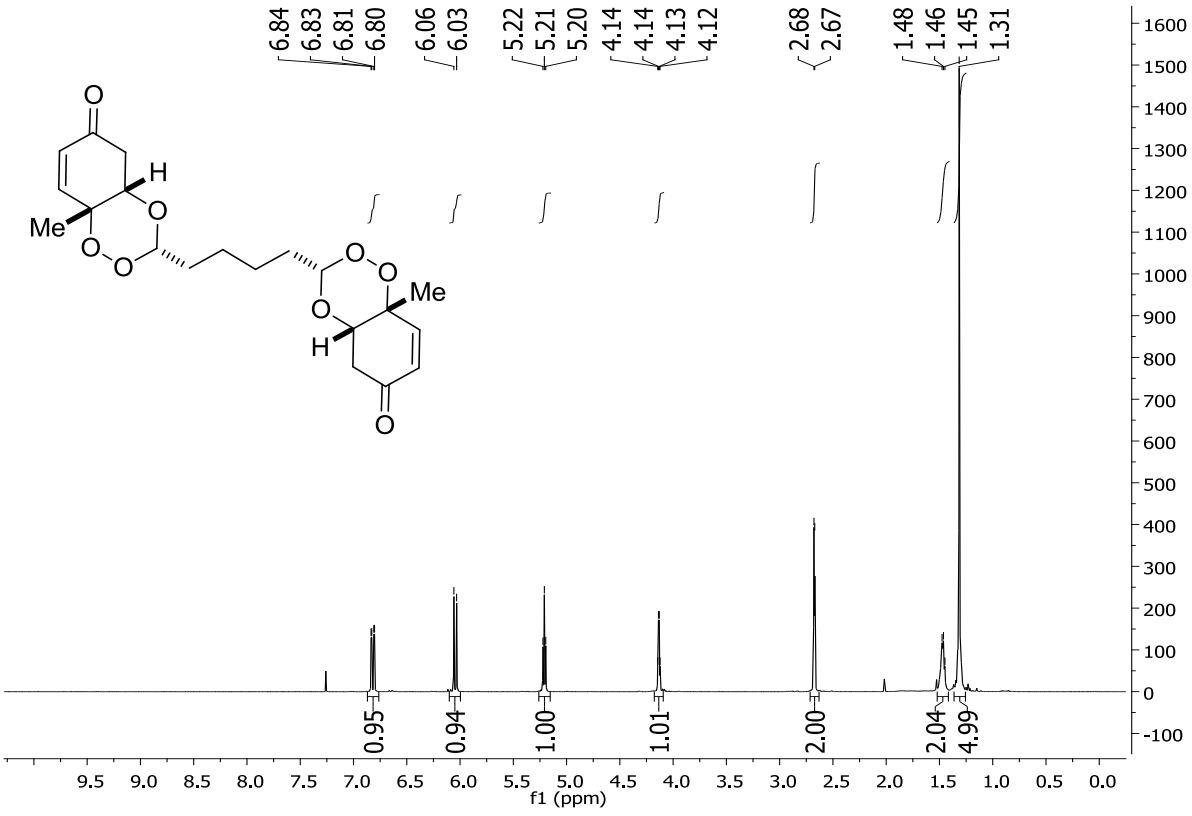
77.79
76.35
40.82
37.38
29.08
22.56
20.52
f1 (ppm)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6.03
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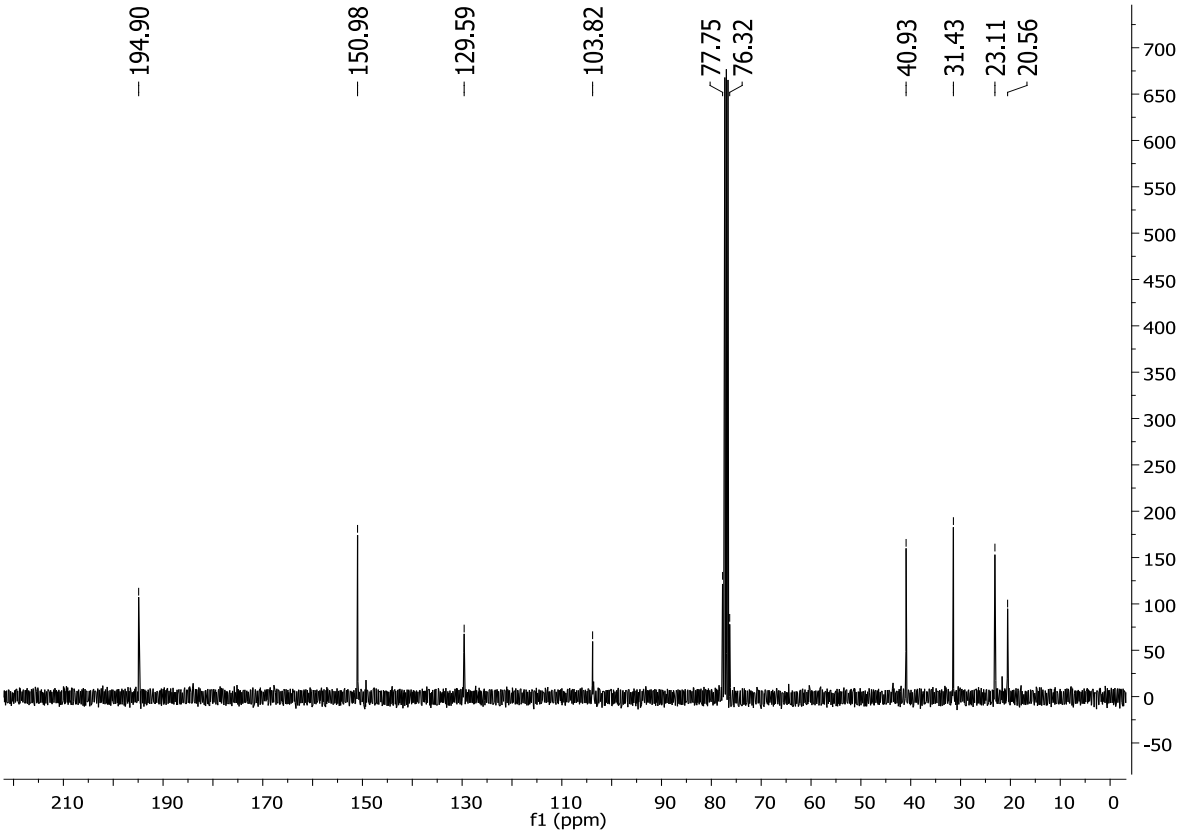
5.21
5.20
4.14
4.14
4.13
4.12
2.68
2.67
1.48
1.46
1.45
1.31
Me
Me
0.95
0.94
1.00
1.01
2.00
2.04
4.99
f1 (ppm)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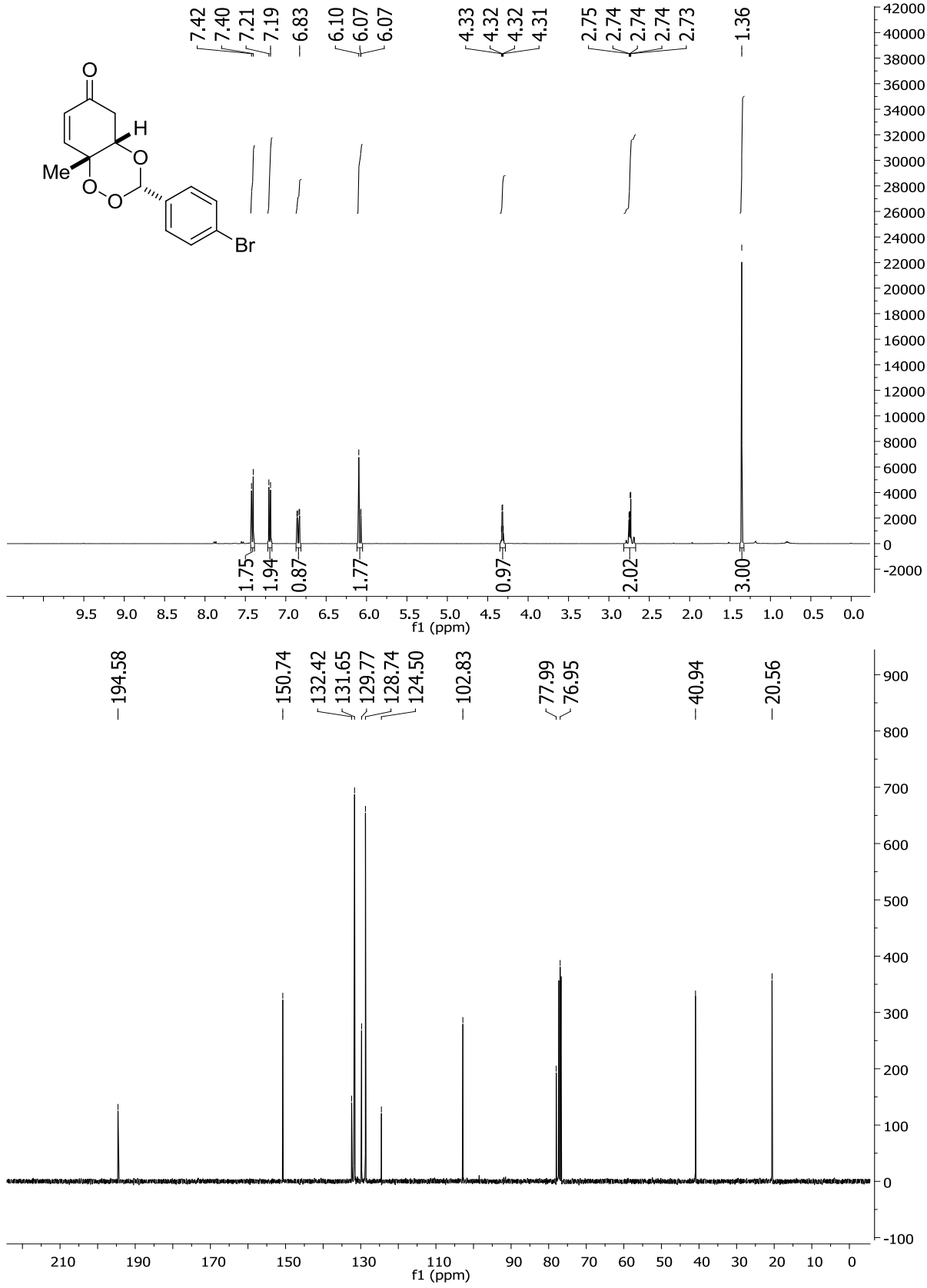
76.32
40.93
31.43
23.11
20.56
f1 (ppm)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6.10
6.07
6.07
4.33
4.32
4.32
4.31
2.75
2.74
2.74
2.74
2.73
1.36
O
H
Me
O
O
O
Br
1.75
1.94
0.87
1.77
0.97
2.02
3.00
f1 (ppm)
194.58
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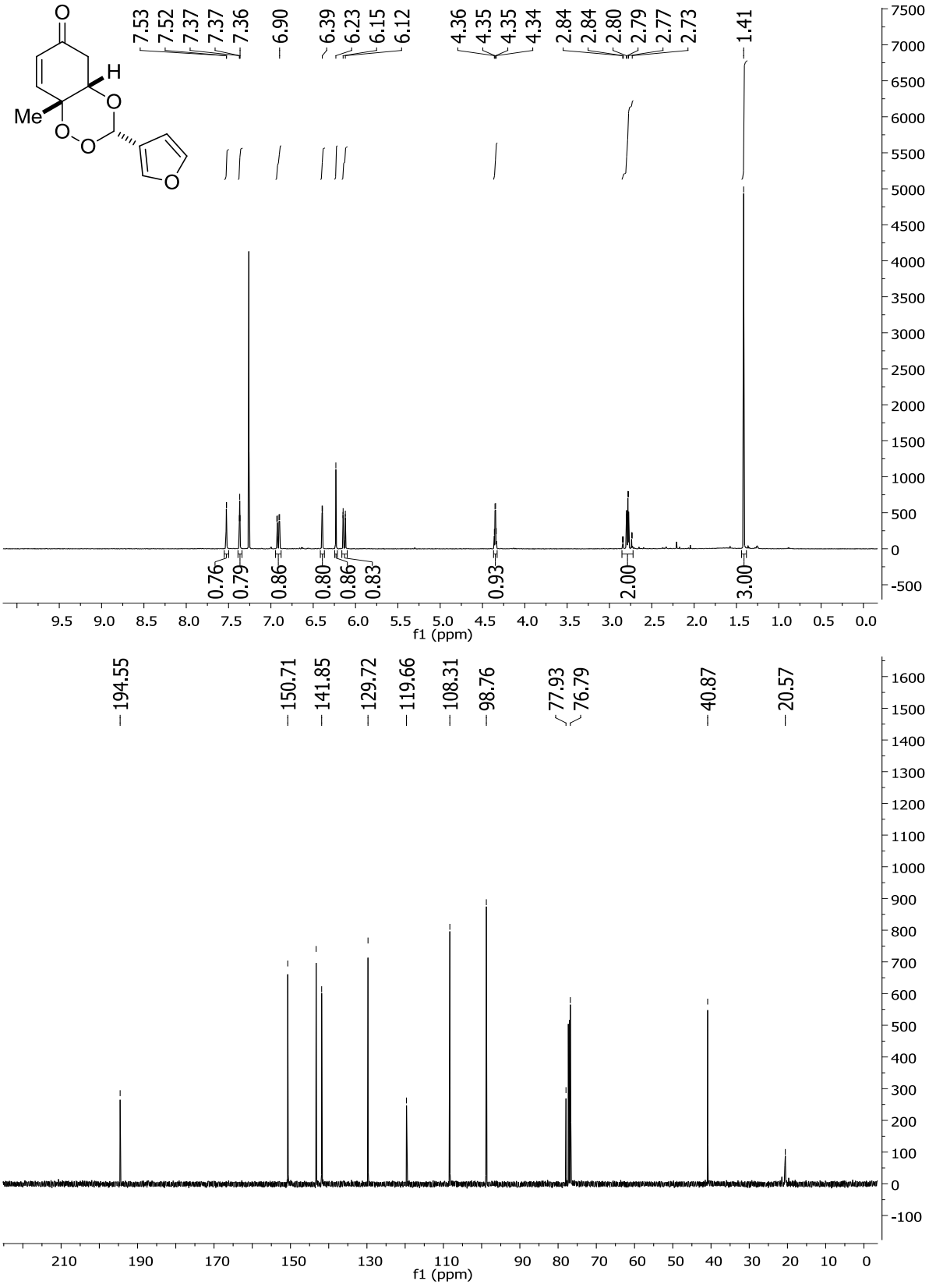
129.77
128.74
124.50
102.83
77.99
76.95
40.94
20.56
f1 (ppm)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7.37
7.36
6.90
6.39
6.23
6.15
6.12
4.36
4.35
4.35
4.34
2.84
2.84
2.80
2.79
2.77
2.73
1.41
0.76
0.79
0.86
0.80
0.86
0.83
0.93
2.00
3.00
f1 (ppm)
194.55
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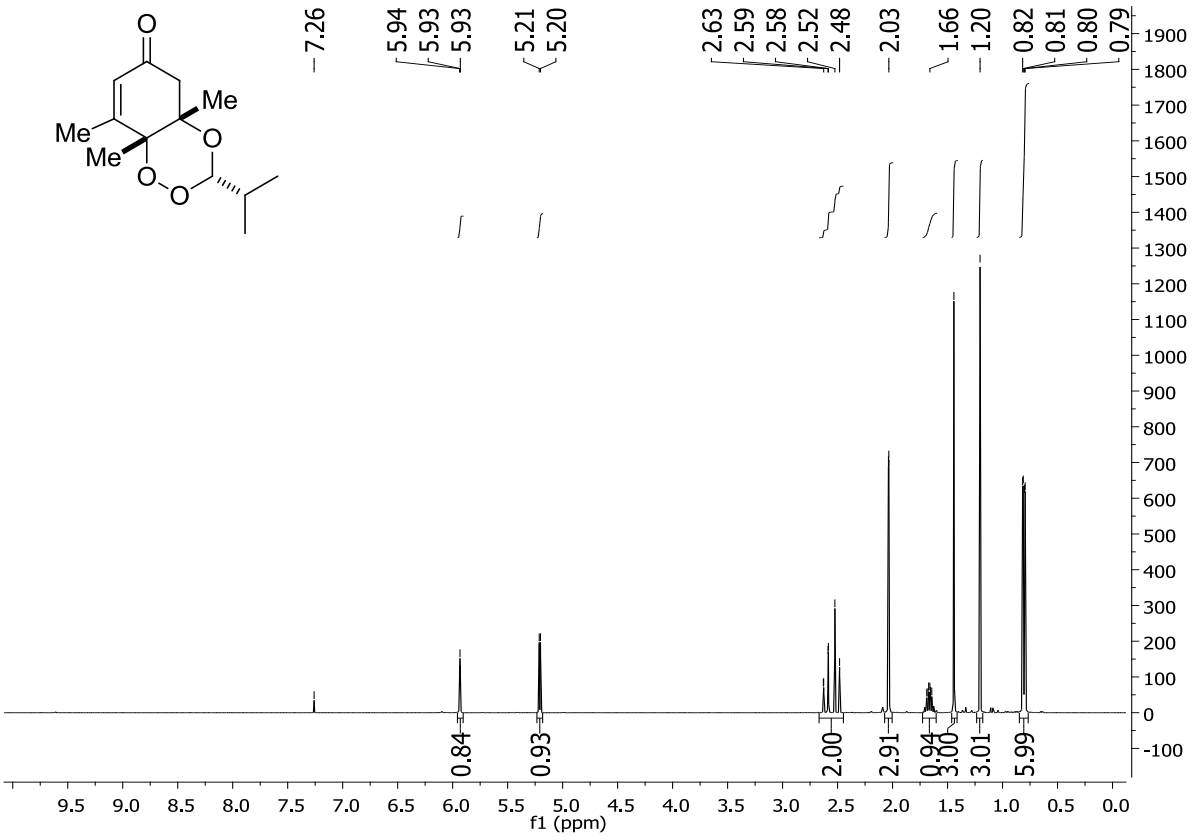
141.85
129.72
119.66
108.31
98.76
77.93
76.79
40.87
20.57
f1 (ppm)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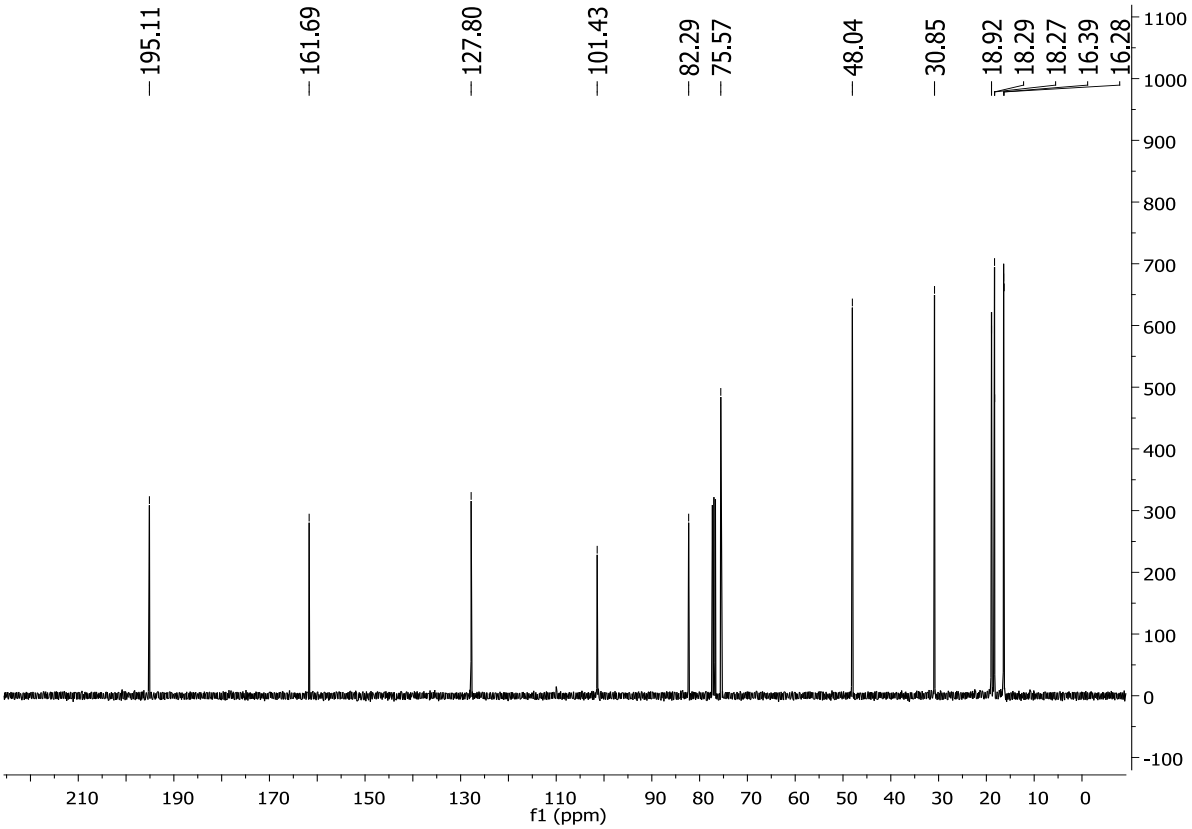
5.93
5.21
5.20
2.63
2.59
2.58
2.52
2.48
2.03
1.66
1.20
0.82
0.81
0.80
0.79
0.84
0.93
2.00
2.91
0.94
3.00
3.01
5.99
f1 (ppm)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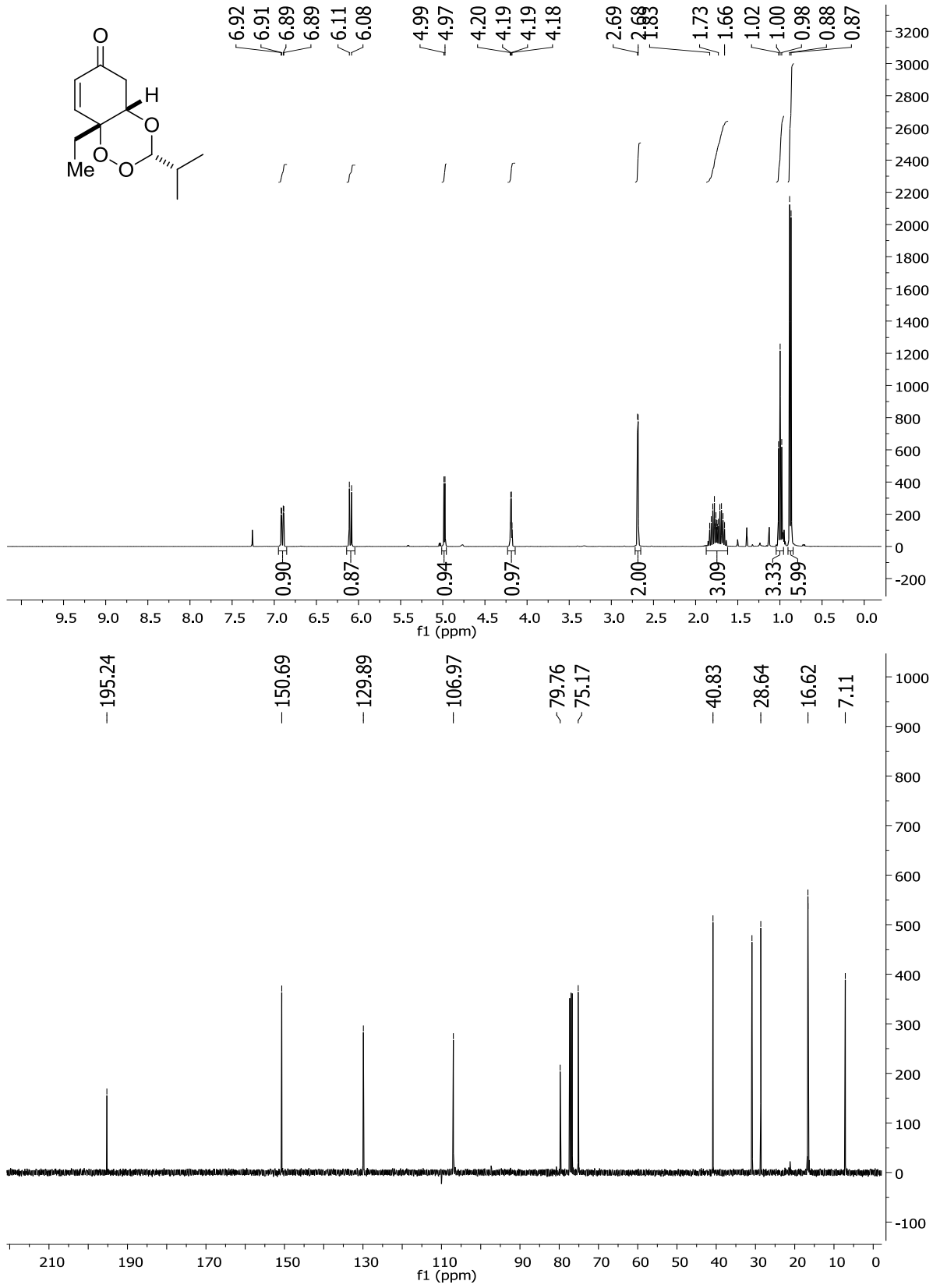
101.43
82.29
75.57
48.04
30.85
18.92
18.29
18.27
16.39
16.28
f1 (ppm)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6.89
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6.08
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4.97
4.20
4.19
4.19
4.18
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2.68
1.83
1.73
1.66
1.02
1.00
0.98
0.88
0.87
0.90
0.87
0.94
0.97
2.00
3.09
3.33
5.99
f1 (ppm)
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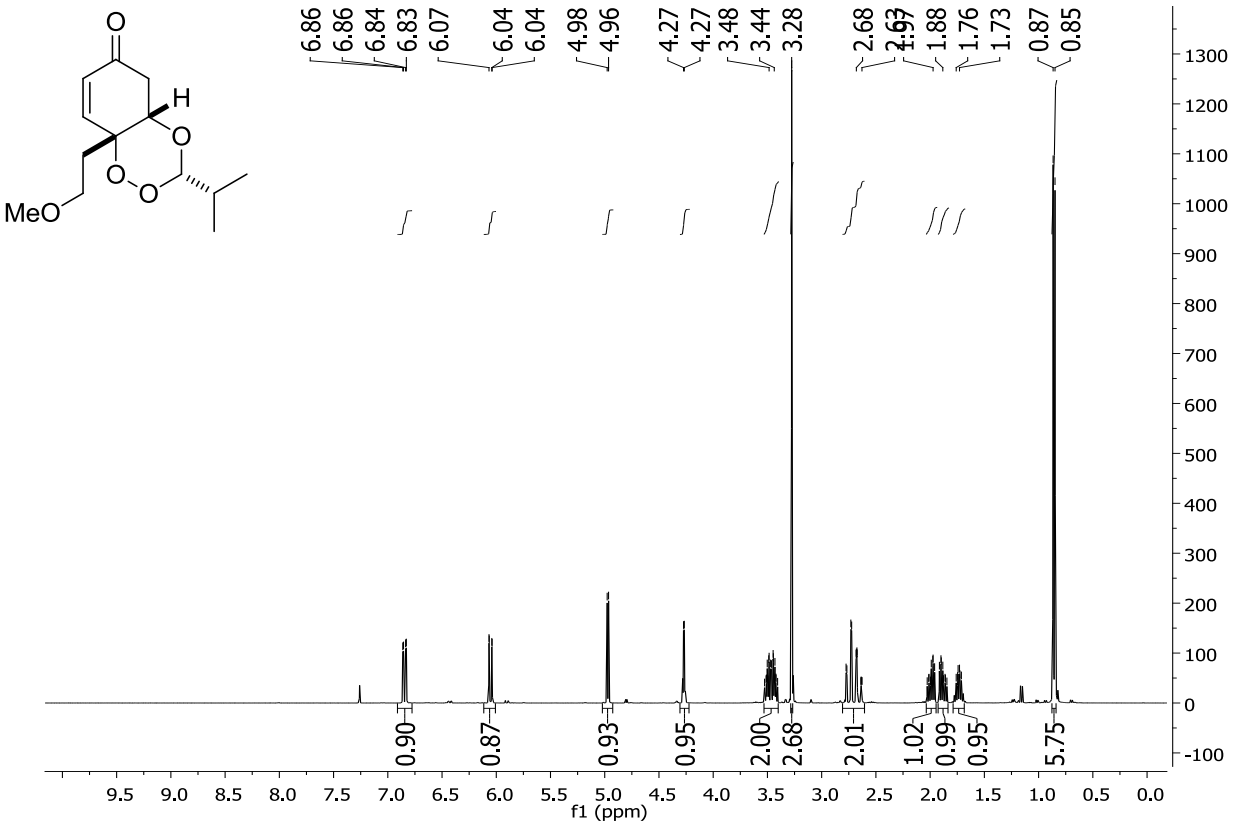
129.89
106.97
79.76
75.17
40.83
28.64
16.62
7.11
f1 (ppm)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O
O
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6.83
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6.04
6.04
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4.27
4.27
3.48
3.44
3.28
2.68
1.88
1.76
1.73
0.87
0.85
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1.02
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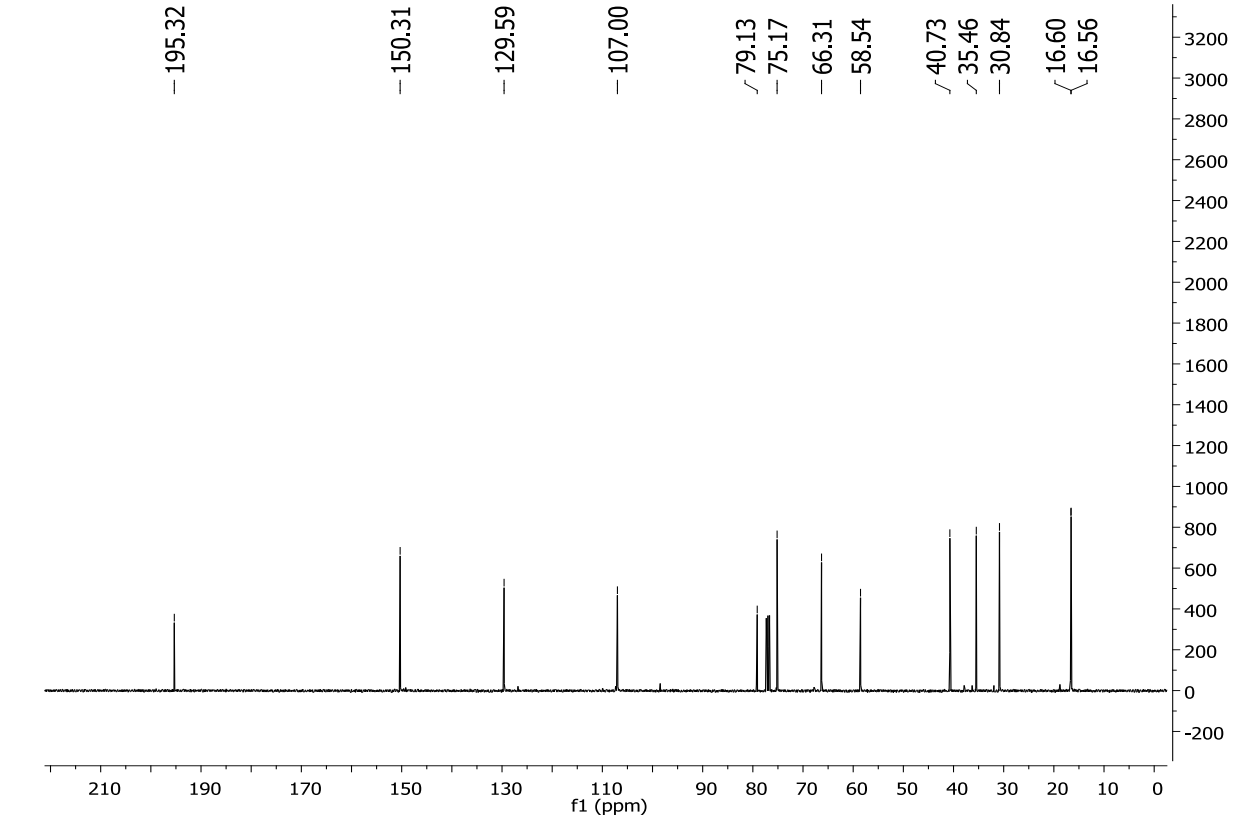
f1 (ppm)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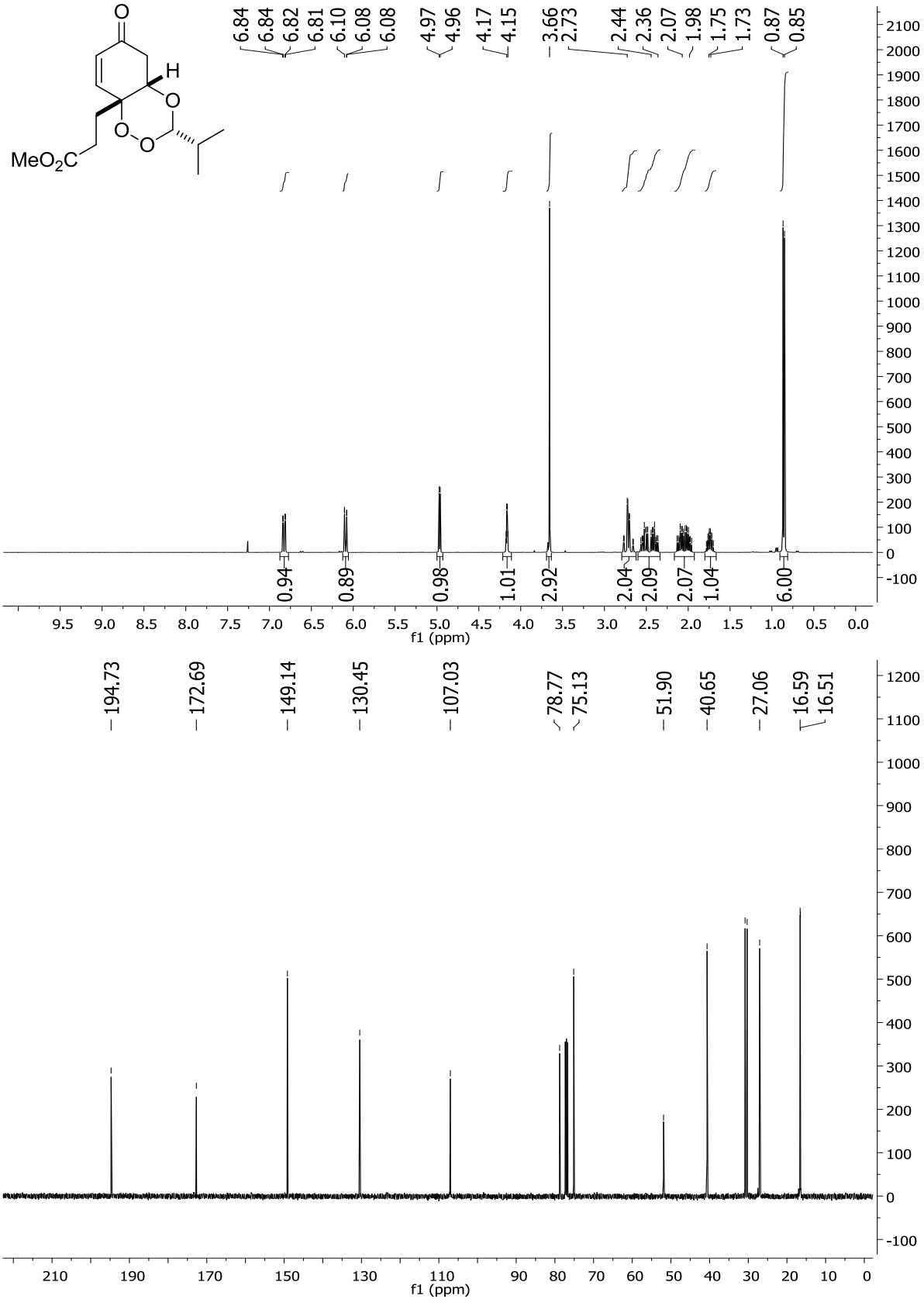
f1 (ppm)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2.44
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2.07
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1.75
1.73
0.87
0.85
0.94
0.89
0.98
1.01
2.92
2.04
2.09
2.07
1.04
6.00
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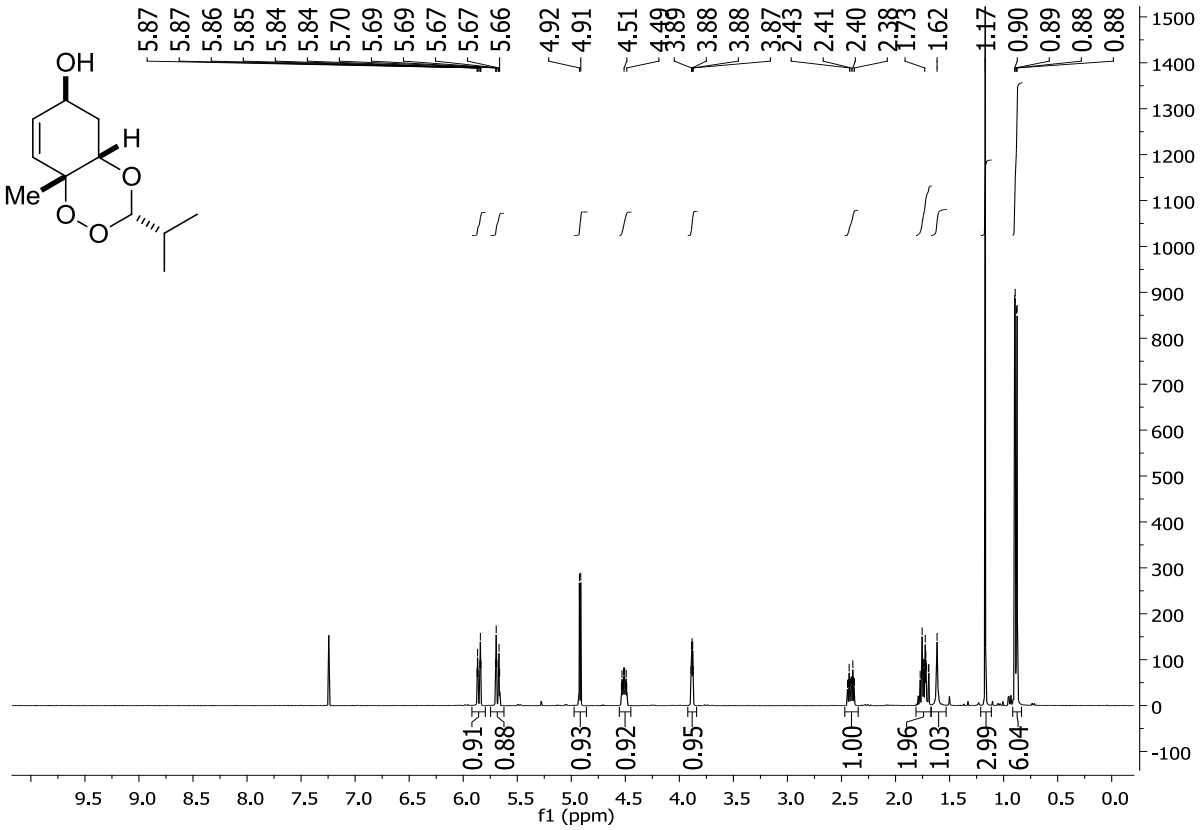
f1 (ppm)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5.69
5.67
5.67
5.66
4.92
4.91
4.51
4.49
3.89
3.88
3.88
3.87
2.43
2.41
2.40
2.38
1.73
1.62
1.17
0.90
0.89
0.88
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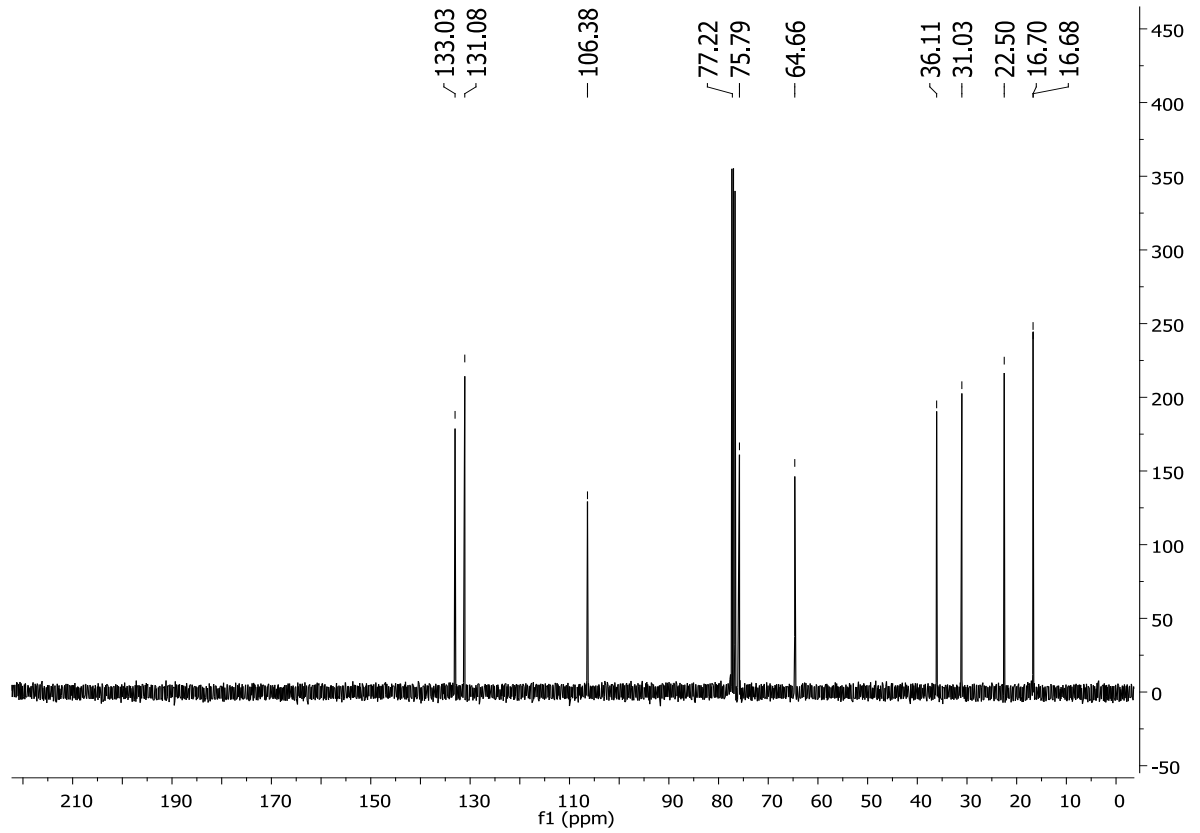
0.93
0.92
0.95
1.00
1.96
1.03
2.99
6.04
f1 (ppm)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36.11
31.03
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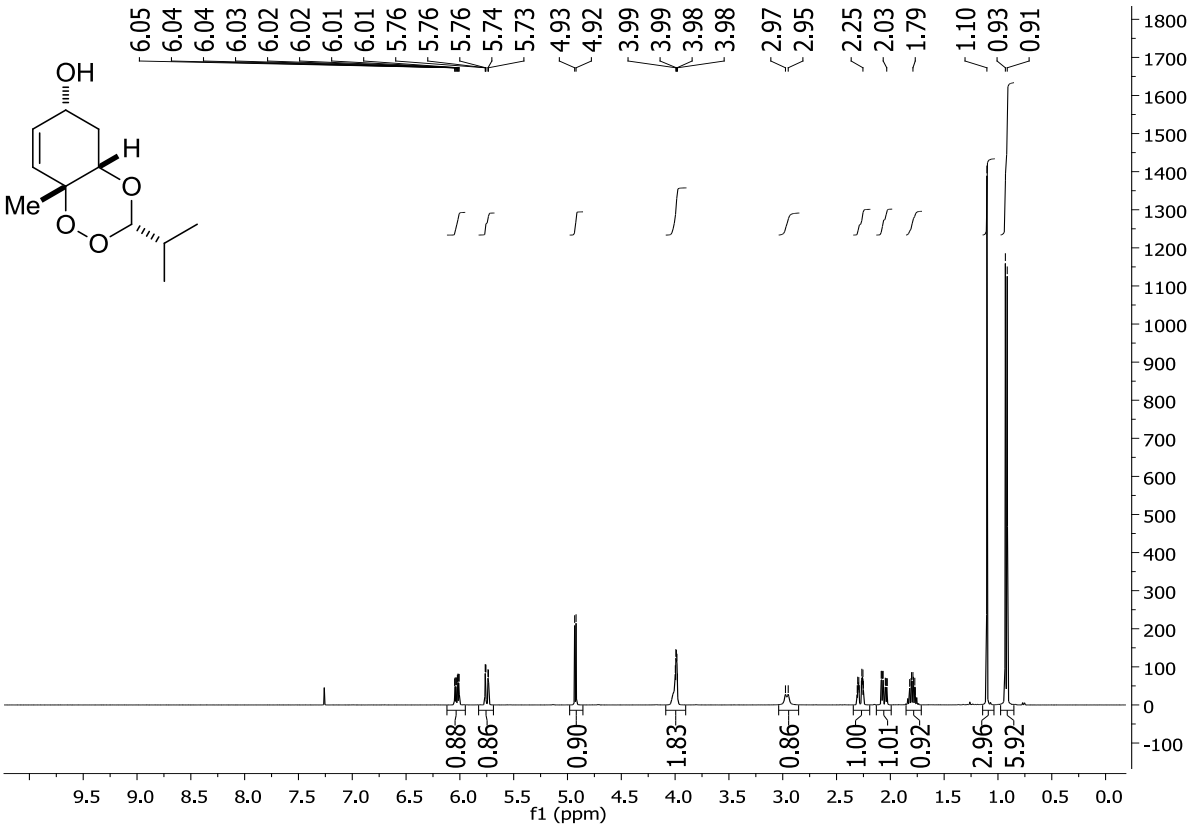
16.68
f1 (ppm)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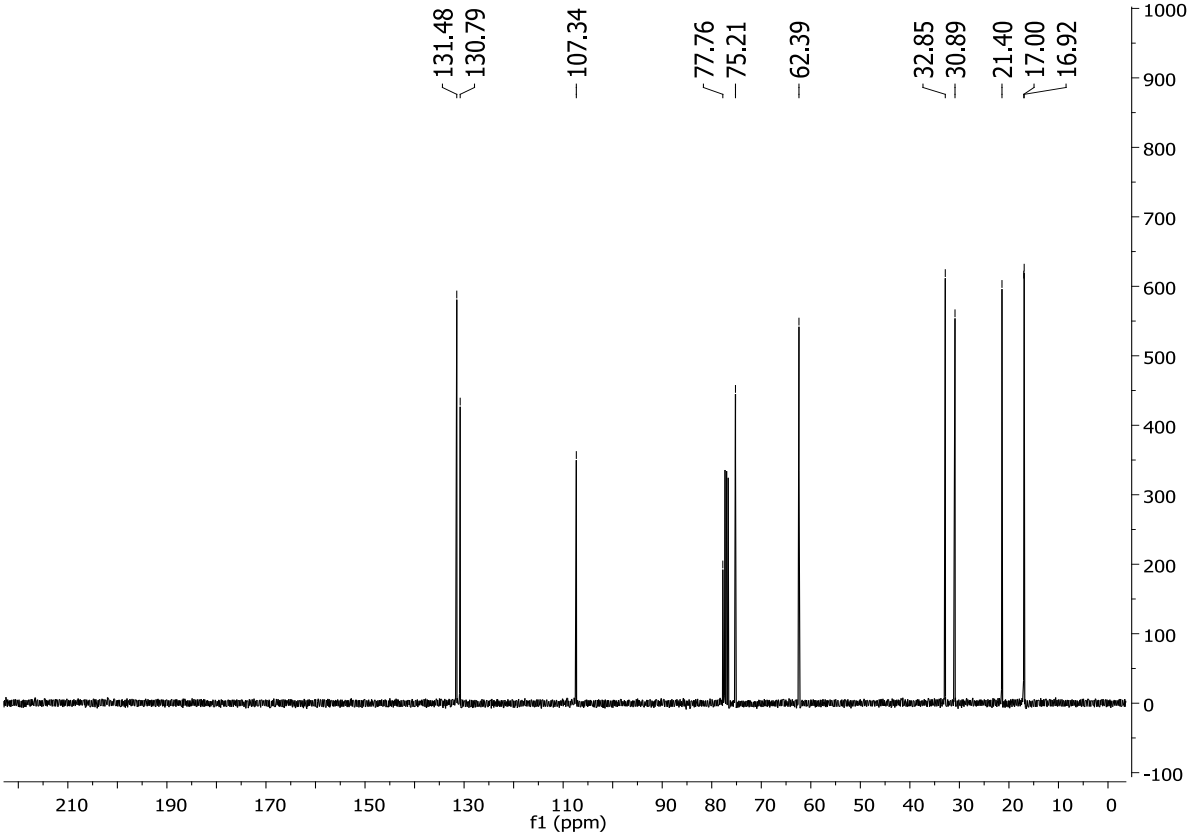
4.93 4.92
3.99 3.99 3.98 3.98
2.97 2.95
2.25 2.03 1.79
1.10 0.93 0.91
OH
H
O
Me
O
O
0.88 0.86 0.90 1.83 0.86 1.00 1.01 0.92 2.96 5.92
f1 (ppm)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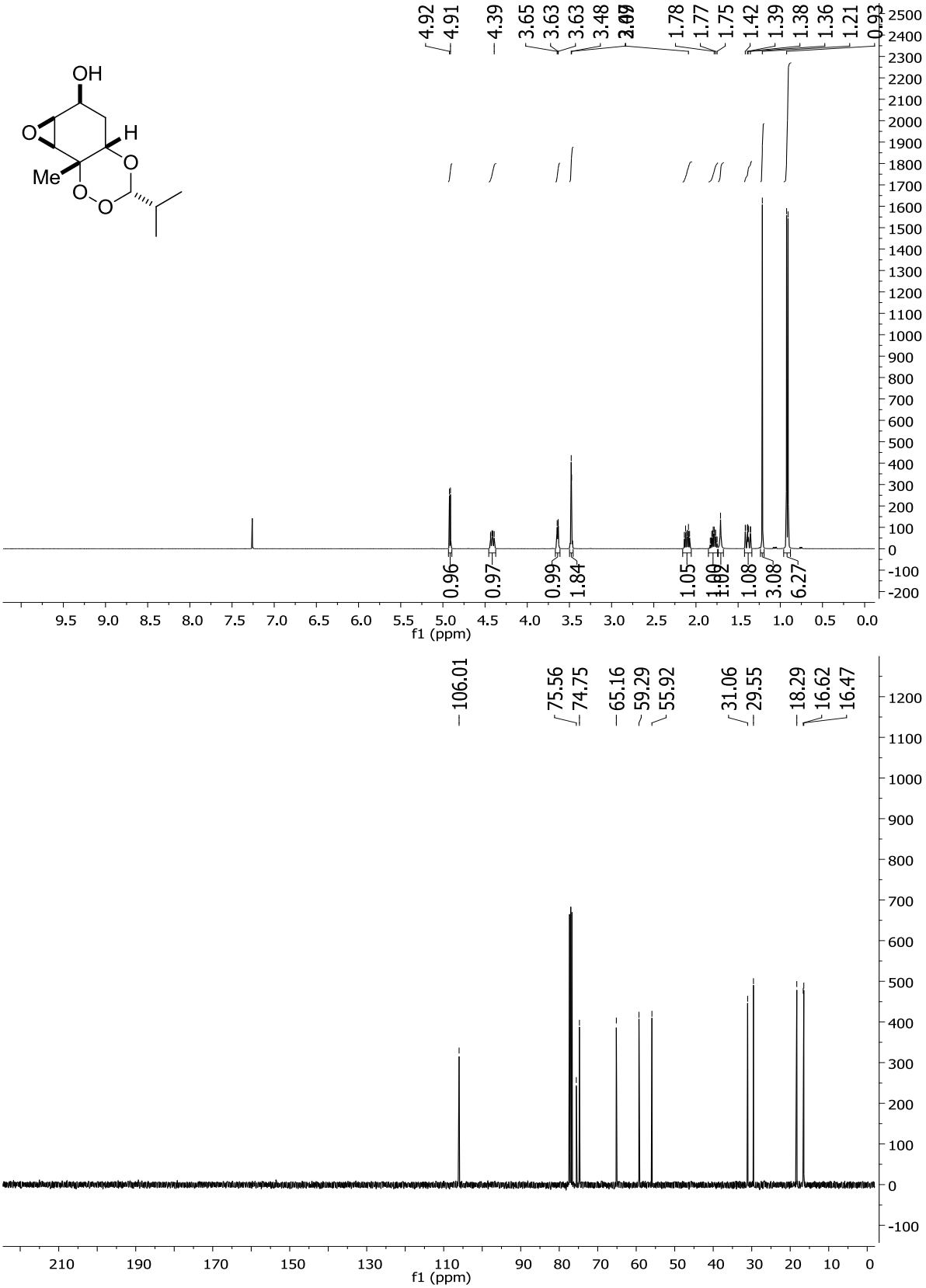
30.89
21.40
17.00
16.92
f1 (ppm)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H
O
Me
O
O
4.92
4.91
4.39
3.65
3.63
3.63
3.48
1.78
1.77
1.75
1.42
1.39
1.38
1.36
1.21
0.93
0.96
0.97
0.99
1.84
1.05
1.08
3.08
6.27
f1 (ppm)
106.01
75.56
74.75
65.16
59.29
55.92
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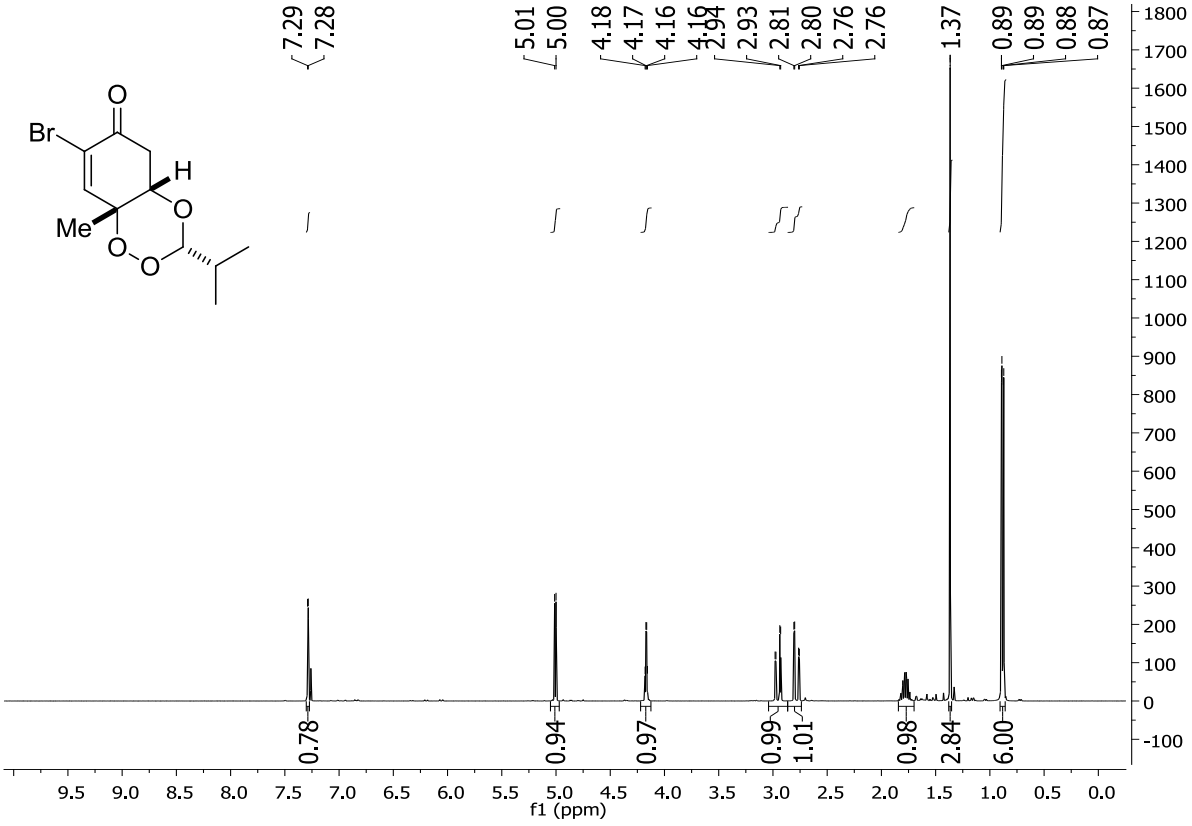
29.55
18.29
16.62
16.47
f1 (ppm)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2.93
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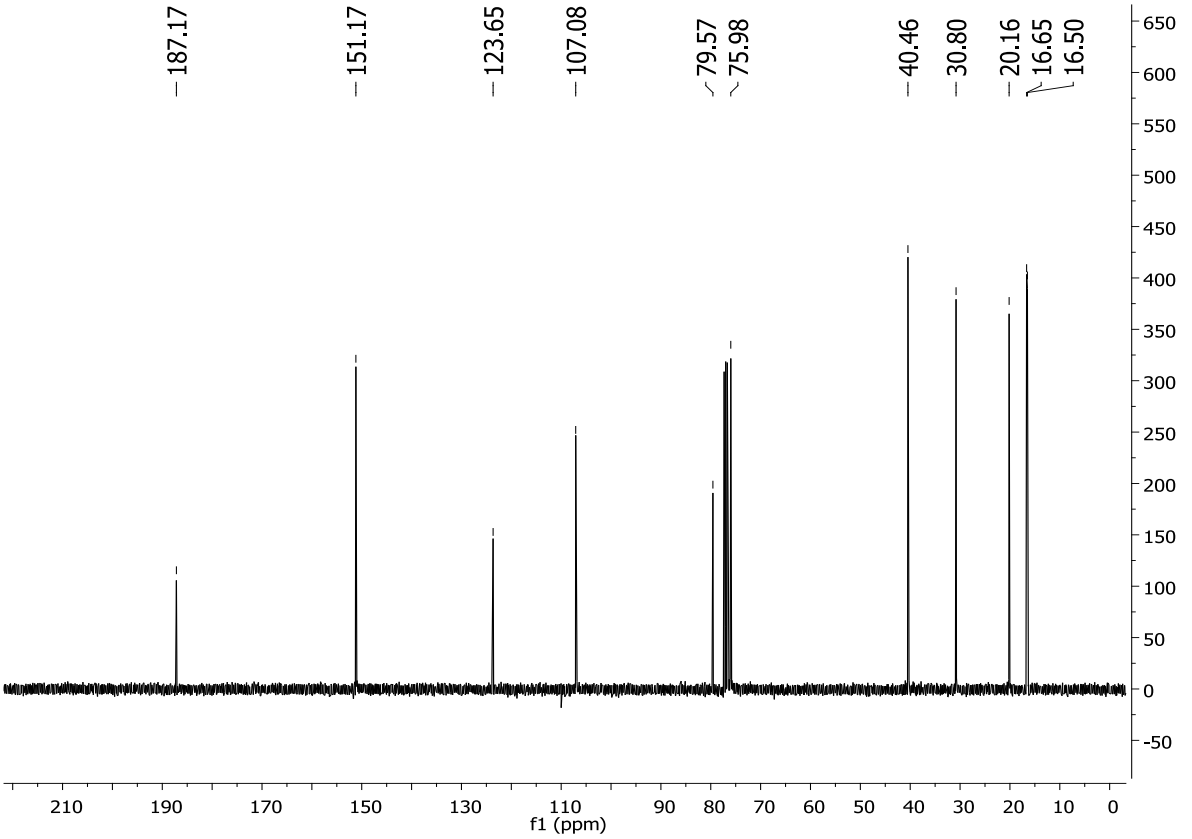
2.76
1.37
0.89
0.89
0.88
0.87
0.78
0.94
0.97
0.99
1.01
0.98
2.84
6.00
f1 (ppm)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79.57
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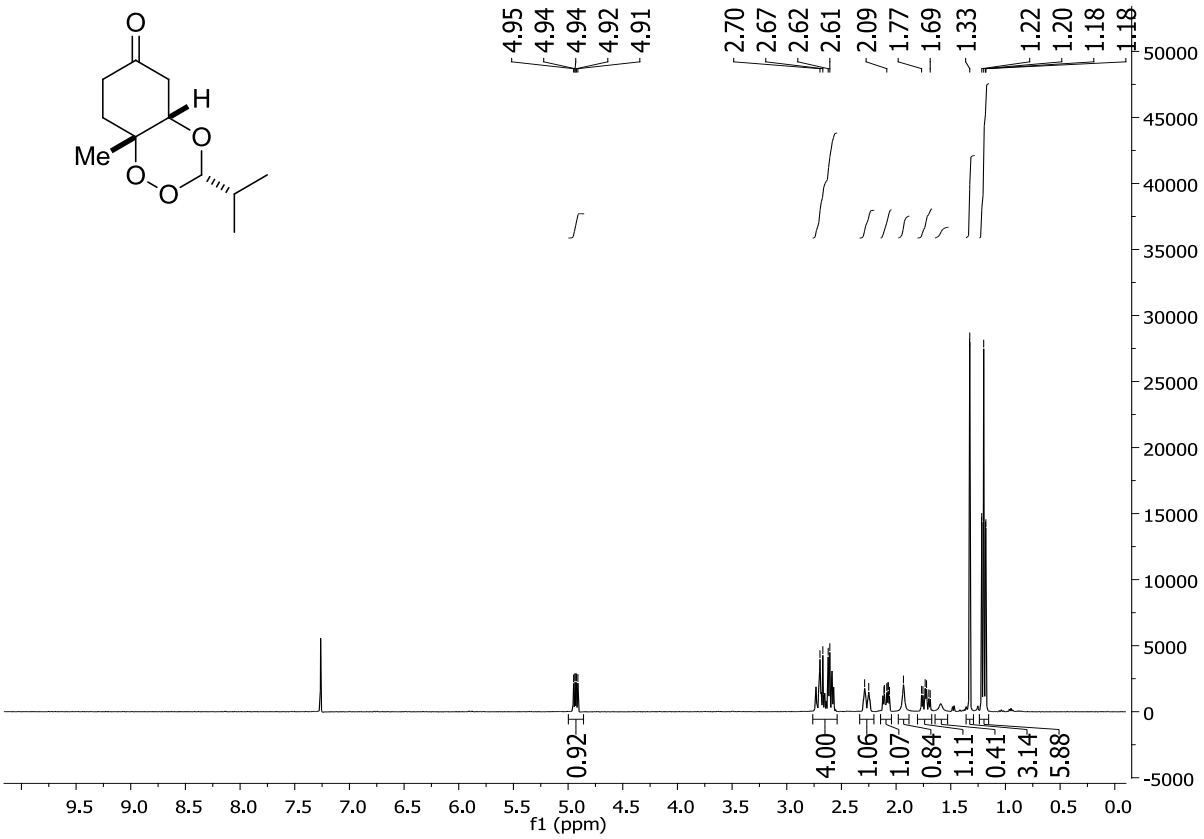
40.46
30.80
20.16
16.65
16.50
f1 (ppm)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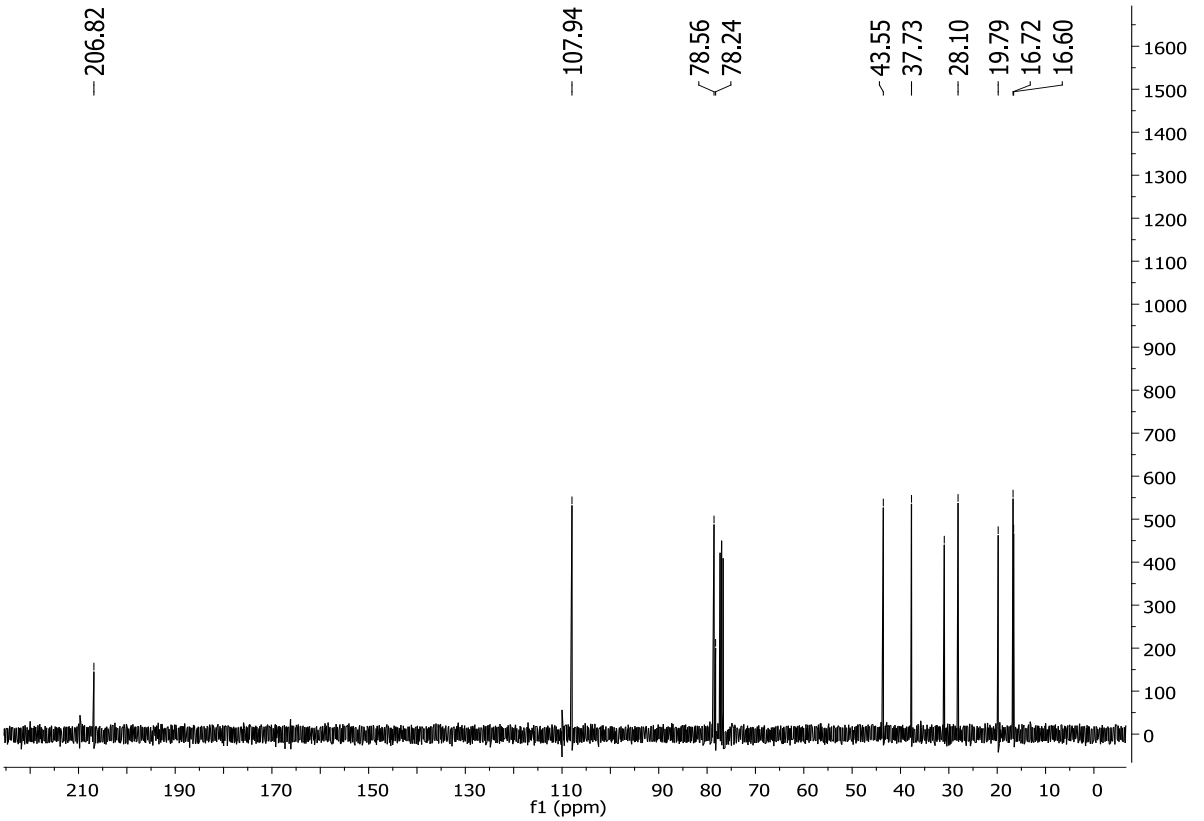
4.94
4.92
4.91
2.70
2.67
2.62
2.61
2.09
1.77
1.69
1.33
1.22
1.20
1.18
1.18
0.92
4.00
1.06
1.07
0.84
1.11
0.41
3.14
5.88
f1 (ppm)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107.94
78.56
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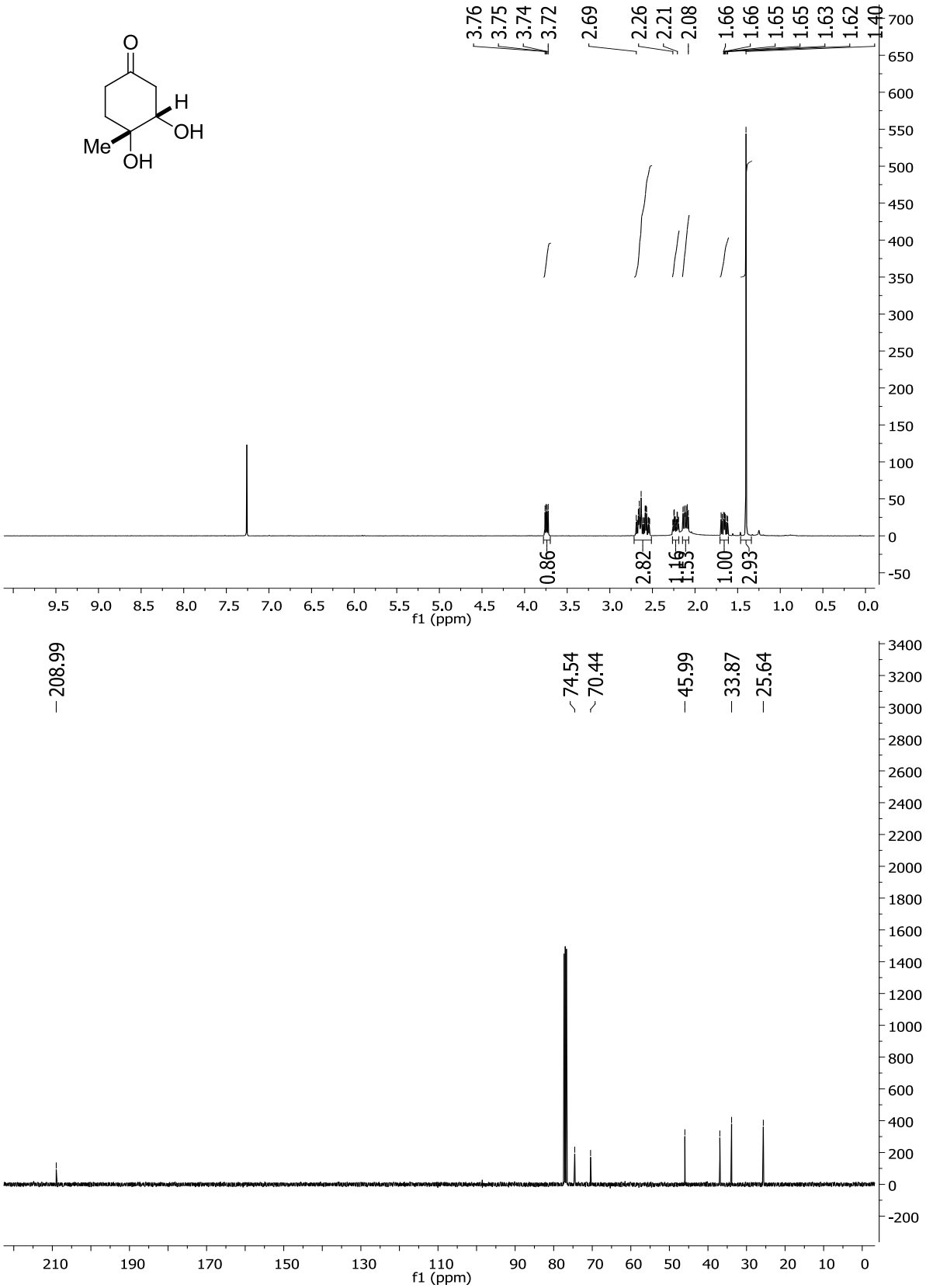
43.55
37.73
28.10
19.79
16.72
16.60
f1 (ppm)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OH
Me
OH
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3.75
3.74
3.72
2.69
2.26
2.21
2.08
1.66
1.66
1.65
1.65
1.63
1.62
1.40
0.86
2.82
1.16
1.53
1.00
2.93
f1 (ppm)
208.99
74.54
70.44
45.99
33.87
25.64
f1 (ppm)

Crystal Structure Tables for 4an

Table 1. Crystal data and structure refinement for Rovis130_0m.

Identification code	rovis130_0m	
Empirical formula	$C_{14}H_{13}BrO_4$	
Formula weight	325.15	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.0393(3) Å	α= 90°.
	b = 10.7218(4) Å	β= 90°.
	c = 17.8586(7) Å	γ = 90°.
Volume	1347.86(9) Å^3	
Z	4	
Density (calculated)	1.602 Mg/m^3	
Absorption coefficient	3.056 mm^{-1}	
F(000)	656	
Crystal size	0.28 x 0.17 x 0.15 mm^3	
Theta range for data collection	2.22 to 29.13°.	
Index ranges	-9<=h<=9, -14<=k<=13, -24<=l<=24	
Reflections collected	29435	
Independent reflections	3638 [R(int) = 0.0420]	
Completeness to theta = 29.13°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.6639 and 0.4784	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3638 / 0 / 174	
Goodness-of-fit on F^2	1.096	
Final R indices [I>2sigma(I)]	R1 = 0.0318, wR2 = 0.0548	
R indices (all data)	R1 = 0.0493, wR2 = 0.0709	
Absolute structure parameter	0.009(9)	
Largest diff. peak and hole	0.698 and -0.443 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Rovis130_0m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	3192(1)	-2371(1)	8429(1)	43(1)
C(1)	5337(4)	-1314(3)	8579(2)	27(1)
C(2)	6892(5)	-1758(2)	8964(2)	29(1)
C(3)	8435(5)	-976(2)	9058(1)	25(1)
C(4)	8420(4)	232(2)	8773(1)	21(1)
C(5)	6819(4)	658(2)	8391(1)	25(1)
C(6)	5269(4)	-120(3)	8287(1)	27(1)
C(7)	10083(4)	1074(3)	8880(1)	23(1)
C(8)	11035(4)	3001(2)	9403(1)	20(1)
C(9)	10186(4)	4140(2)	9778(1)	22(1)
C(10)	8784(4)	4811(2)	9290(2)	24(1)
C(11)	9187(4)	4808(2)	8484(2)	27(1)
C(12)	10594(5)	4124(3)	8188(2)	28(1)
C(13)	13861(4)	3959(3)	8742(2)	32(1)
C(14)	11926(5)	3341(2)	8648(1)	24(1)
O(1)	9505(3)	2133(2)	9294(1)	20(1)
O(2)	10650(3)	1463(2)	8148(1)	28(1)
O(3)	12404(3)	2201(2)	8256(1)	30(1)
O(4)	7415(3)	5350(2)	9550(1)	33(1)

Table 3. Bond lengths [Å] and angles [°] for Rovis130_0m.

Br(1)-C(1)	1.907(3)
C(1)-C(2)	1.377(4)
C(1)-C(6)	1.383(4)
C(2)-C(3)	1.383(4)
C(3)-C(4)	1.391(4)
C(4)-C(5)	1.394(4)
C(4)-C(7)	1.491(4)
C(5)-C(6)	1.386(4)
C(7)-O(1)	1.415(3)
C(7)-O(2)	1.428(3)
C(8)-O(1)	1.437(3)
C(8)-C(9)	1.515(4)
C(8)-C(14)	1.531(3)
C(9)-C(10)	1.500(4)
C(10)-O(4)	1.216(3)
C(10)-C(11)	1.467(4)
C(11)-C(12)	1.341(4)
C(12)-C(14)	1.504(4)
C(13)-C(14)	1.524(4)
C(14)-O(3)	1.448(3)
O(2)-O(3)	1.479(3)

C(2)-C(1)-C(6)	122.4(3)
C(2)-C(1)-Br(1)	119.6(2)
C(6)-C(1)-Br(1)	118.0(2)
C(1)-C(2)-C(3)	118.4(3)
C(2)-C(3)-C(4)	120.9(3)
C(3)-C(4)-C(5)	119.3(3)
C(3)-C(4)-C(7)	120.7(3)
C(5)-C(4)-C(7)	119.9(2)
C(6)-C(5)-C(4)	120.3(2)
C(1)-C(6)-C(5)	118.7(3)
O(1)-C(7)-O(2)	108.9(2)

O(1)-C(7)-C(4)	109.1(2)
O(2)-C(7)-C(4)	106.2(2)
O(1)-C(8)-C(9)	106.7(2)
O(1)-C(8)-C(14)	110.0(2)
C(9)-C(8)-C(14)	111.0(2)
C(10)-C(9)-C(8)	112.8(2)
O(4)-C(10)-C(11)	121.9(3)
O(4)-C(10)-C(9)	121.8(2)
C(11)-C(10)-C(9)	116.2(2)
C(12)-C(11)-C(10)	122.1(3)
C(11)-C(12)-C(14)	123.4(2)
O(3)-C(14)-C(12)	110.6(2)
O(3)-C(14)-C(13)	102.3(2)
C(12)-C(14)-C(13)	112.0(2)
O(3)-C(14)-C(8)	108.7(2)
C(12)-C(14)-C(8)	111.0(2)
C(13)-C(14)-C(8)	111.9(2)
C(7)-O(1)-C(8)	112.0(2)
C(7)-O(2)-O(3)	105.71(19)
C(14)-O(3)-O(2)	108.70(18)

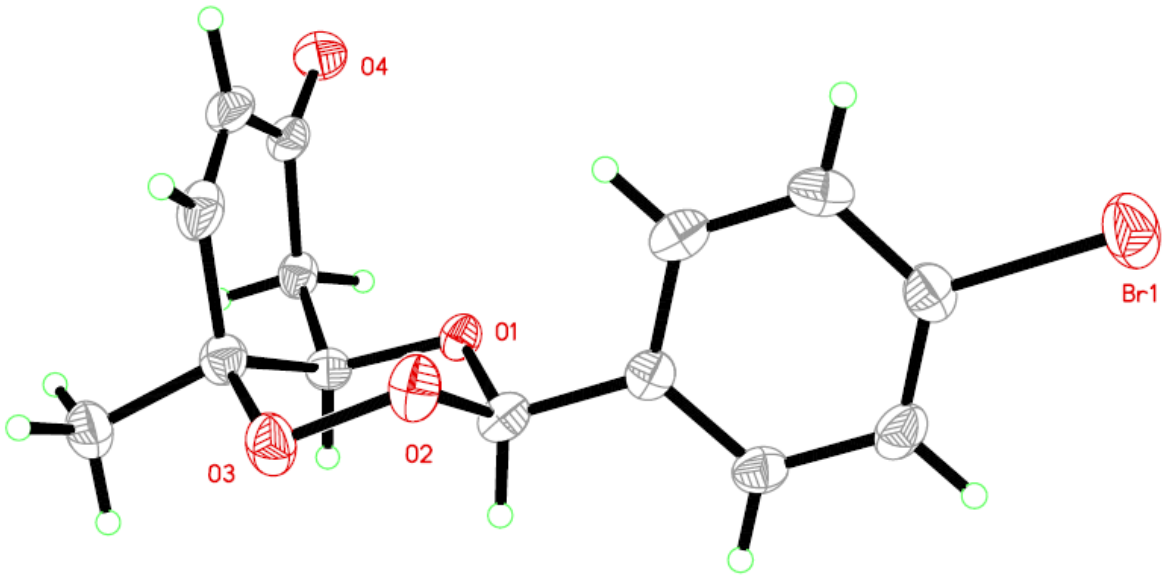
Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for Rovis130_0m. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	35(1)	37(1)	57(1)	-18(1)	0(1)	-6(1)
C(1)	25(2)	25(2)	31(2)	-12(1)	3(1)	0(1)
C(2)	34(2)	19(1)	34(2)	-3(1)	6(2)	3(2)
C(3)	27(2)	22(1)	27(1)	-3(1)	1(1)	5(1)
C(4)	24(2)	20(1)	18(1)	-4(1)	8(1)	3(1)
C(5)	34(2)	23(1)	18(1)	-1(1)	3(1)	6(1)
C(6)	27(2)	30(2)	23(1)	-8(1)	-3(1)	9(1)
C(7)	31(2)	20(1)	19(1)	0(1)	3(1)	3(1)
C(8)	22(2)	24(1)	16(1)	2(1)	-4(1)	0(1)
C(9)	25(2)	21(1)	19(1)	0(1)	-2(1)	-4(1)
C(10)	27(2)	16(1)	28(1)	1(1)	-1(1)	-1(1)
C(11)	30(2)	25(1)	26(1)	8(1)	-8(1)	-3(1)
C(12)	35(2)	29(2)	21(1)	6(1)	-3(1)	-9(1)
C(13)	26(2)	36(2)	34(2)	6(1)	4(1)	-5(1)
C(14)	25(2)	25(1)	21(1)	2(1)	2(1)	-1(1)
O(1)	24(1)	17(1)	19(1)	-1(1)	2(1)	-1(1)
O(2)	35(1)	27(1)	22(1)	-4(1)	8(1)	-5(1)
O(3)	28(1)	29(1)	32(1)	-3(1)	10(1)	-3(1)
O(4)	30(1)	27(1)	42(1)	0(1)	2(1)	5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for Rovis130_0m.

	x	y	z	U(eq)
H(2)	6903	-2581	9161	35
H(3)	9522	-1267	9320	30
H(5)	6790	1485	8201	30
H(6)	4183	161	8020	32
H(7)	11143	628	9140	28
H(8)	12019	2623	9736	24
H(9A)	9546	3880	10246	26
H(9B)	11223	4722	9914	26
H(11)	8428	5307	8162	32
H(12)	10757	4135	7659	34
H(13A)	14704	3403	9024	48
H(13B)	13712	4746	9015	48
H(13C)	14413	4125	8248	48



References

[1] Carreno, M. C.; Gonzalez-Lopez, M.; Urbano, A.; *Angew. Chem. Int. Ed.* **2006**, *45*, 2737.

[2] Xing, C.-H.; Liao, Y.-X.; Ng, J.; Hu, Q.-S. *J. Org. Chem.* **2011**, *76*, 4125-4131.