Catalytic, Asymmetric Transannular Aldolizations: Total Synthesis of (+)-Hirsutene

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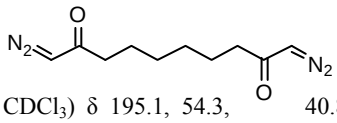
Supporting Information

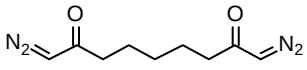
General: All reactions were carried out under argon atmosphere in oven-dried and/or flame-dried glassware with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents employed in the reactions were distilled from appropriate drying agent prior to use. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Reactions were monitored by thin layer chromatography using 0.25 mm E. Merck silica gel precoated glass plates (0.25 mm thickness, 60F-254, E. Merck) using UV light to visualize the course of reaction. Flash column chromatography was performed using E. Merck siliga gel 60 (particle size 0.040–0.063 mm) following the general protocol of Still.[1] Chemical yields refer to pure isolated substances. ^{1}H and ^{13}C NMR spectra were recorded at 25 °C on Bruker spectrometers at 500, 400 or 300 and 125, 100 or 75 MHz, respectively, using CDCl3 as the solvent and internal reference. The following abbreviations were used to designate chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, b = broad. MS (EI): Finnigan MAT 8200 (70 eV), ESI-MS: Finnigan MAT 95, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet).

General Procedure for Preparation of bis-α-Diazocarbonyl Compounds[2]

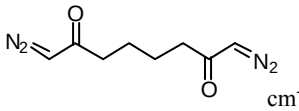
A stirred suspension of the corresponding dicarboxylic acid (1 equiv) in dry CH_2Cl_2 (0.5 M) under argon was cooled to 0 °C. Oxalyl chloride (2.2 equiv) was added to the solution followed by a catalytic amount of DMF (10 µL/1 g of substrate). After gas evolution had ceased and the solution became homogeneous, excess reagent and solvent were removed under reduced pressure. The residue was dissolved in a solution of dry 1:1 THF: CH_3CN (0.6 M in diacid) under argon. In a different flask, a solution of TMS-diazomethane (4.05 equiv, 2 M soln in Et_2O) in dry 1:1 THF:CH_3CN (0.6 M in diacid) was cooled to 0 °C. The above solution of the diacid chloride was added dropwise to the prepared reagent solution. Immediate $N_{2\,(g)}$ evolution was observed and the reaction stirred at 0 °C for 4 h. Excess reagent and solvent were removed under reduced pressure. The crude oil was subjected to column chromatography [silica gel; gradient 30%-50% EtOAc:Hex] to provide the pure products. Characterization of the diazo compounds en route to diones **5**, **7**, **13**, **15**, **17**, **19** and **21** is given below.



1,10-Bis-diazodecane-2,9-dione: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (bs, 2H), 2.29 (bm, 4H), 1.60 (p, *J* = 6.7 Hz, 4H), 1.31 (p, *J* = 3.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.1, 54.3, 40.8, 28.8, 24.9; IR (thin film, cm^{-1}): 2098, 1618, 1352. HRMS (*m/z*): $[MNa]^+$ calcd for $C_{10}H_{14}N_4NaO_2$, 245.1009; found 245.1008. yield: 76%



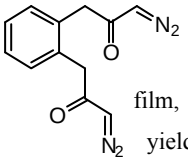
1,9-Bis-diazononane-2,8-dione: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.22 (bs, 2H), 2.28 (bm, 4H), 1.60 (p, *J* = 7.5 Hz, 4H), 1.32 (p, *J* = 7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5, 54.4, 40.4, 24.5; IR (thin film, cm^{-1}): 2098, 1619, 1350. HRMS (*m/z*): $[MNa]^+$ calcd for $C_9H_{12}N_4NaO_2$, 231.0852; found 231.0852. yield: 72%



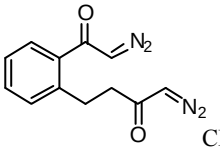
1,8-Bis-diazooctane-2,7-dione: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (bs, 2H), 2.33 (bm, 4H), 1.64 (p, *J* = 3.5 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5, 54.4, 40.4, 24.5; IR (thin film, cm^{-1}): 2097, 1618, 1367. HRMS (*m/z*): $[MH]^+$ calcd for $C_8H_{11}N_4O_2$, 195.0882; found

[1] Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
[2] Makhey, D.; Dajie, L.; Zhao, B.; Sim, S.-P.; Li, T.-K.; Liu, A.; Liu, L. F.; La Voie, E. J. *Bioorg. Med. Chem.***2003**, *11*, 1809.

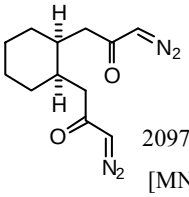
195.0880. yield: 82%



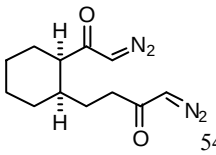
3,3'-(1,2-Phenylene)bis(1-diazopropan-2-one): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.22 (m, 4H), 5.25 (bs, 2H), 3.67 (bs, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.2, 133.7, 131.1, 127.9, 54.9, 45.3; IR (thin film, cm^{-1}): 2098, 1621, 1598, 1339. HRMS (*m/z*): $[MH]^+$ calcd for $C_{12}H_{11}N_4O_2$, 243.0882; found 243.0882. yield: 85%



1-Diazo-4-(2-(2-diazoacetyl)phenyl)butan-2-one: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.13 (m, 4H), 5.55 (bs, 1H), 5.24 (bs, 1H), 3.00 (t, *J* = 7.8 Hz, 2H), 2.60 (bm, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 139.7, 137.0, 131.1, 127.3, 126.3, 56.3, 54.3, 43.0, 29.2; IR (thin film, cm^{-1}): 2106, 1624, 1602, 1334. HRMS (*m/z*): $[MH]^+$ calcd for $C_{12}H_{11}N_4O_2$, 243.0882; found 243.0880. yield: 65%



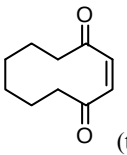
3,3'-((1*R*,2*S*)-cyclohexan-1,2-diyl)bis(1-diazopropan-2-one): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7-13 (m, 4H), 5.55 (bs, 1H), 5.24 (bs, 1H), 3.00 (t, *J* = 7.8 Hz, 2H), 2.60 (bm, 2H); IR (thin film, cm^{-1}): 2097, 1627, 1355. ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6, 54.8, 42.0, 36.2, 28.8, 23.2; HRMS (*m/z*): $[MNa]^+$ calcd for $C_{12}H_{16}N_4$ Na O_2, 271.1165; found 271.1162. yield: 70%



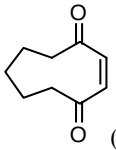
1-Diazo-4-(2-(2-diazoacetyl)cyclohexyl)butan-2-one: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (bs, 1H), 5.27 (bs, 1H), 2.53-2.15 (bm, 4H), 1.48-1.34 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4, 194.9, 54.2, 50.6, 39.0, 37.1, 282., 25.1, 24.8, 23.8, 22.1; IR (thin film, cm^{-1}): 2096, 1628, 1339. HRMS (*m/z*): $[MNa]^+$ calcd for $C_{12}H_{16}N_4NaO_2$, 271.1165; found 271.1162. yield: 68%

General Procedure for Preparation of 1,4-Enediones[3]

A stirred catalyst solution under argon containing $Ru[(\eta^5\text{-}C_5H_5)(PPh_3)_2]Cl$ (0.03 equiv) in dry CH_2Cl_2 (0.0006 M) was heated to 55 °C in a round-bottom flask equipped with a reflux condenser and an addition funnel. The substrate was added slowly dropwise as a solution in CH_2Cl_2 (0.005 M). After the addition was complete, the reaction mixture was refluxed for an additional 0.5 h. The solution was concentrated under reduced pressure and purified by column chromatography [silica gel; 10% EtOAc:Hex] to provide the pure products. Characterization of the ene-diones en route to diones **5**, **7**, **13**, **15**, **17**, **19** and **21** is given below.

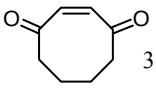


(*Z*)-Cyclodec-2-ene-1,4-dione (9): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (s, 2H), 2.53 (t, *J* = 6.5 Hz, 4H), 1.75 (p, *J* = 6.3 Hz, 4H), 1.42 (p, *J* = 3.1 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 136.4, 41.3, 23.7, 22.2; IR (thin film, cm^{-1}): 1686. HRMS (*m/z*): [M] calcd for $C_{10}H_{14}O_2$, 166.0993; found 166.0993. yield: 77%

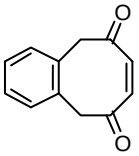


(*Z*)-Cyclonon-2-ene-1,4-dione (11): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.33 (bs, 2H), 2.56 (t, *J* = 6.4 Hz, 4H), 1.82 (p, *J* = 6.1 Hz, 4H), 1.65 (p, *J* = 5.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 136.6, 42.0, 26.1, 25.4; IR (thin film, cm^{-1}): 1668. HRMS (*m/z*): [M] calcd for $C_9H_{12}O_2$, 152.1902; found 152.1902. yield: 76%

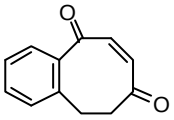
[3] Del Zotto, A.; Baratta, W.; Verardo, G.; Rigo, P. *Eur. J. Org. Chem.* **2000**, 2795.



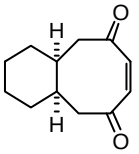
(*Z*)-Cyclooct-2-ene-1,4-dione: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (s, 2H), 2.59-2-54 (m, 4H), 1.89 (p, *J* = 3.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.7, 136.8, 40.3, 23.3; IR (thin film, cm^{-1}): 1642. HRMS (*m/z*): [M] calcd for $C_8H_{12}O_2$, 138.0681; found 138.0682. yield: 82%



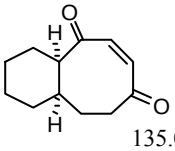
(*Z*)-Benzo[8]annulene-6,9(5*H*, 10*H*)-dione: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.16 (m, 4H), 6.10 (s, 2H), 3.87 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 134.3, 133.0, 130.8, 129.4, 128.3, 127.1, 126.7, 125.6, 81.4, 48.5, 36.9; IR (thin film, cm^{-1}): 1662. HRMS (*m/z*): [M] calcd for $C_{12}H_{10}O_2$, 186.0681; found 186.0679. yield: 79%



9,10-Dihydrobenzo[8]annulene-5,8-dione: ^{1}H NMR (400 MHz, $CDCl_3$) *characterized as a mixture of cis:trans isomers (10:1)* δ 7.74 (d, *J* = 5.6 Hz, 1H), 7.52-7.16 (m, 8H), 6.62 (d, *J* = 13.8 Hz), 6.55 (d, *J* = 13.7 Hz), 6.10 (d, *J* = 5.6 Hz, 1H), 3.47-3.40 (m, 2H), 3.26-3.23 (m, 2H), 3.15-3.03 (m, 2H), 2.87-2.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 194.6, 162.9, 137.6, 137.4, 136.8, 134.9, 133.0, 132.5, 130.4, 129.9, 129.1, 127. 6, 127.5, 125.7, 123.9, 57.1, 48.3, 31.8, 28.4; IR (thin film, cm^{-1}): 1691, 1635. HRMS (*m/z*): [M] calcd for $C_{12}H_{10}O_2$, 186.0681; found 186.0680. yield: 70%



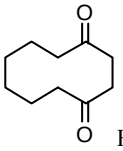
(4a*R*,10a*S*,*Z*)-1,2,3,4,4a,5,10,10a-Octahydrobenzo[8]annulene-6,9-dione: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 2H), 2.76-2.69 (m, 4H), 2.23-2.19 (m, 2H), 1.60-1.36 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 137.1, 44.9, 35.2, 29.5, 23.1; IR (thin film, cm^{-1}): 16691. HRMS (*m/z*): [M] calcd for $C_{12}H_{16}O_2$, 192.1150; found 192.1148. yield: 75%



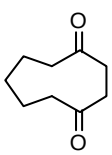
(4a*R*,10a*R*,*Z*)-2,3,4,4a,10,10a-Hexahydrobenzo[8]annulene-5,8(1H,9H)-dione: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.43 (d, *J* = 13.2 Hz, 1H), 6.30 (d, *J* = 13.2 Hz, 1H), 2.59-2.44 (m, 3H), 2.30-2.17 (m, 1H), 2.02-1.92 (m, 2H), 1.79 (bm, 1H), 1.68-1.25 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 204.0, 138.6, 135.0, 49.0, 40.0, 35.5, 31.1, 27.2, 24.0, 22.7, 22.4; IR (thin film, cm^{-1}): 1669. HRMS (*m/z*): [M] calcd for $C_{12}H_{16}O_2$, 192.1150; found 192.1152. yield: 76%

General Procedure for Preparation of 1,4-Diones from 1,4-Ene-Diones

To stirred solution of the substrate in wet EtOAc (0.5 M) was added palladium on carbon (10 % by wt.). The flask was evacuated and filled with hydrogen (x 3), equipped with a hydrogen-filled balloon and left to stir 3 h. The mixture was filtered through a plug of celite and the solvent was removed under reduced pressure. The resulting crude product was purified by column chromatography [silica gel; 10% EtOAc:Hex] to provide the pure products. Characterization of diones **5**, **7**, **13**, **15**, **17**, **19** and **21** is given below.

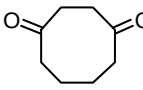


Cyclodecane-1,4-dione (5): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (bm, 4H), 2.46-2.42 (m, 4H), 1.69-1.62 (m, 4H), 1.33-1.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8, 40.8, 39.5, 23.4, 22.5; IR (thin film, cm^{-1}): 1699. HRMS (*m/z*): [M] calcd for $C_{10}H_{16}O_2$, 168.1150; found 168.1150. yield: 67%

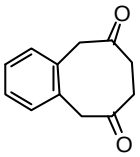


Cyclononane-1,4-dione (7): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.66 (bm, 4H), 2.39-2.34 (m, 4H), 1.78-1.70 (m, 4H), 1.62-1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.9, 44.7, 38.5, 28.7, 21.1; IR (thin film, cm^{-1}): 1696.

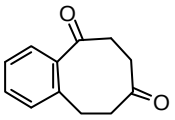
HRMS (*m/z*): [M] calcd for $C_9H_{14}O_2$, 154.0993; found 154.0992. yield: 69%



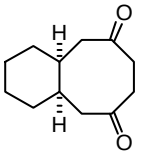
Cyclooctane-1,4-dione (13): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (m, 4H), 2.42-2.38 (m, 4H), 1.85-1.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.9, 41.4, 40.8, 24.6; IR (thin film, cm^{-1}): 1697. HRMS (*m/z*): [M] calcd for $C_8H_{12}O_2$, 140.0837; found 140.0837. yield: 72%



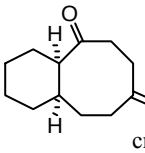
7,8-Dihydrobenzo[8]annulene-6,9(5*H*,10*H*)-dione (15): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (bm, 4H), 3.78 (s, 4H), 2.58 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.6, 133.0, 128.4, 49.2, 38.8; IR (thin film, cm^{-1}): 1662, 1608. HRMS (*m/z*): [M] calcd for $C_{12}H_{12}O_2$, 188.0837; found 188.0838. yield: 88%



6,7,9,10-Tetrahydrobenzo[8]annulene-5,8-dione (17): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.20 (m, 4H), 3.15-3.07 (m, 4H), 2.86-2.80 (m, 2H), 2.71-2.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.6, 206.1, 139.3, 136.6, 131.5, 130.0, 127.5, 127.2, 45.4, 40.9, 38.7, 29.5; IR (thin film, cm^{-1}): 1688, 1669. HRMS (*m/z*): [M] calcd for $C_{12}H_{12}O_2$, 188.0837; found 188.0838. yield: 75%



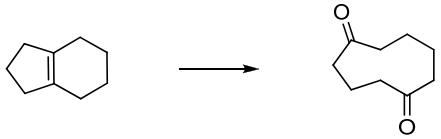
(4a*R*,10a*S*)-Decahydrobenzo[8]annulene-6,9-dione (19): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71-2.52 (m, 6H), 2.21 (bm, 2H), 2.14-2.10 (m, 2H), 1.49-1.34 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9, 46.2, 40.7, 36.2, 30.1, 23.3; IR (thin film, cm^{-1}): 1718. HRMS (*m/z*): [M] calcd for $C_{12}H_{18}O_2$, 194.1306; found 194.1305. yield: 89%



(4a*R*,10a*R*)-Octahydrobenzo[8]annulene-5,8(1*H*,9*H*)-dione (21): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86-2.75 (m, 2H), 2.45-2.30 (m, 4H), 2.21-2.14 (m, 1H), 2.11-2.02 (m, 1H), 1.82-1.16 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.9, 213.4, 51.6, 42.0, 40.3, 38.3, 35.2, 31.4, 27.2, 23.8, 22.4, 21.9; IR (thin film, cm^{-1}): 1695. HRMS (*m/z*): [M] calcd for $C_{12}H_{18}O_2$, 194.1307; found 194.1305. yield: 88%

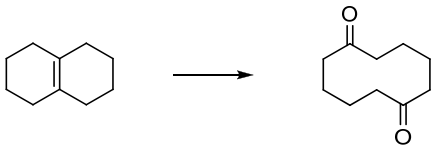
General Procedure for Preparation of 1,5- and 1,6- Diones by Oxidative Cleavage[4]

To a stirred mixture of the appropriate olefin[5] (6.0 mmol, 1 equiv) in CCl_4 (30 mL), CH_3CN (30 mL) and H_2O (43 mL) were added $NaIO_4$ (5.4 g, 25.2 mmol, 4.2 equiv) and RuO_2•H_2O (16.0 mg, 0.12 mmol, 0.02 equiv). The resulting mixture was stirred vigorously for 30 min. The reaction was diluted with H_2O (150 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by column chromatography [silica gel; 10% EtOAc:Hex] to afford the pure products. Characterization of diones **1** and **3** is given below.



Cyclononane-1,5-dione (1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46-2.43 (m, 4H), 2.34-2.31 (m, 4H), 2.14-2.08 (m, 2H), 1.86-1.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.1, 42.1, 40.7, 23.4, 21.5; IR (thin film, cm^{-1}): 1695. HRMS (*m/z*): [M] calcd for $C_9H_{14}O_2$, 154.0994; found 154.0995. yield: 93%

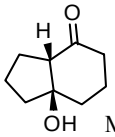
[4] Piers, E.; Skupinska, K. A.; Wallace, D. J. *Synlett* **1999**, *12*, 1867.
[5] House, H. O.; Lee, J. H.; VanDerveer, D.; Wissinger, J. E. *J. Org. Chem.* **1983**, *48*, 5285.



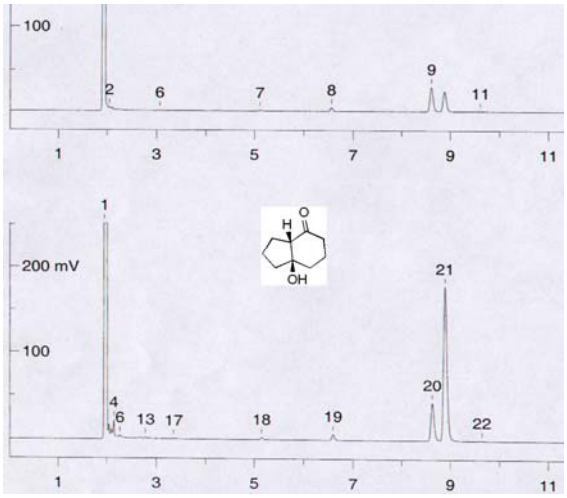
Cyclodecane-1,6-dione (3): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31-2.28 (m, 8H), 1.79-1.76 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.9, 42.1, 233.3; IR (thin film, cm^{-1}): 1685. HRMS (*m/z*): [M] calcd for $C_{10}H_{16}O_2$, 168.1150; found 168.1148. yield: 91%

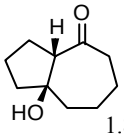
General Procedure for the Organocatalytic Transannular Aldol Reaction

To a dried vial under argon was added the diketone substrate followed by DMSO (0.5 M). *Trans*-4-fluoro-proline (20 mol%) was then added to the stirred solution and the reaction was allowed to continue for 24 h. At this time, the solution was diluted with CH_2Cl_2 and poured into a separatory funnel containing H_2O. After thorough mixing, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (x 2). The combined organics were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography [silica gel; gradient 20%-60% EtOAc:Hex] to afford the pure products. Characterization of aldols **2, 4, 10, 12, 14, 16, 18, 20** and **22** is given below.

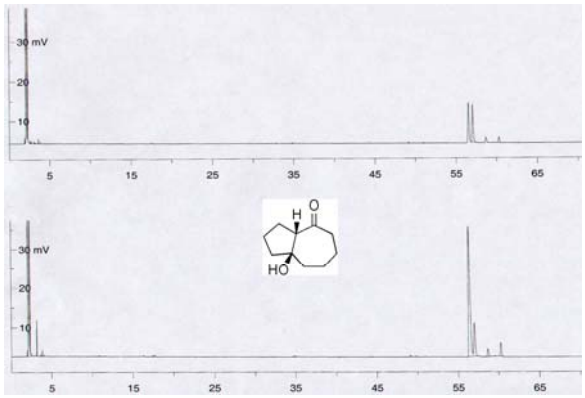


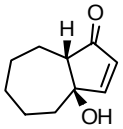
(3a*S*,7a*R*)-7a-Hydroxyhexahydro-1*H*-inden-4(2*H*)-one (2): $[\alpha]_D^{20}$ = + 41.9 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.55-2.50 (m, 1H), 2.39-2.25 (m, 2H), 2.20-2.12 (m, 1H), 2.09-1.53 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2, 84.5, 60.9, 39.5, 38.0, 34.9, 24.4, 21.3, 21.1; IR (thin film, cm^{-1}): 3418 (b), 1696. HRMS (*m/z*): [M] calcd for $C_9H_{14}O_2$, 154.0994; found 154.0994. yield: 57% (84% based on recovered diketone) The enantiomeric ratio was determined to be 97:3 by chiral-GC using BGB-178/BGB-15 column 29m (10 min at 150 °C, 6 °C/min until 220 °C). Major enantiomer: t_R = 8.90 min, minor enantiomer: t_R = 8.64 min.



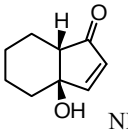


(3a*S*,8a*S*)-8a-Hydroxyoctahydroazulen-4(5*H*)-one (4): $[\alpha]_D^{20}$ = - 28.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.11 (t, *J* = 7.9 Hz, 1H), 2.60-2.54 (m, 1H), 2.47-2.41 (m, 1H), 2.19-2.01 (m, 2H), 1.98-1.89 (m, 2H), 1.81-1.34 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.8, 81.8, 62.4, 44.0, 43.2, 38.1, 25.9, 23.7, 23.5, 22.2; IR (thin film, cm^{-1}): 3434 (b), 1687. HRMS (*m/z*): [M] calcd for $C_{10}H_{16}O_2$, 168.1150; found 168.1150. yield: 57% (84% based on recovered diketone) The enantiomeric ratio of the major diastereomer (dr = 7:1) was determined to be 82:18 by chiral-GC using BGB-176/SE-52 column 29.5m (80 °C, 1.2 °C/min until 220 °C, 10 min at 220 °C). Major enantiomer: t_R = 49.88 min, minor enantiomer: t_R = 50.39 min. The peaks at 51.89 min and 53.25 min represent the minor diastereomer.

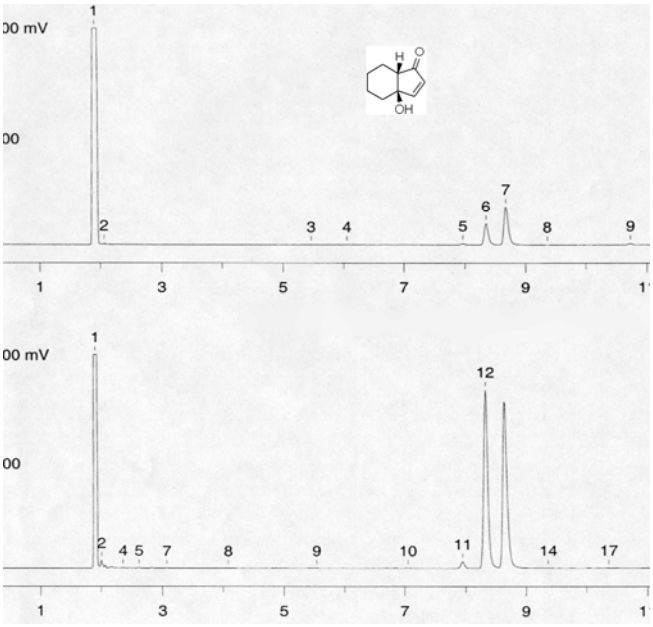


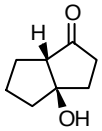


(3a*R*,8a*S*)-3a-Hydroxy-4,5,6,7,8,8a-hexahydroazulen-1(3a*H*)-one (10): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 5.7 Hz, 1H), 6.13 (d, *J* = 5.7 Hz, 1H), 2.46-2.43 (m, 1H), 2.36 (bs, 1H) 2.03-1.93 (m, 2H), 1.81-1.72 (m, 2H) 1.64-1.30 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.0, 166.5, 132.3, 82.9, 59.2, 37.7, 31.1, 27.3, 27.1, 23.0; IR (thin film, cm^{-1}): 3400 (b), 1682. HRMS (*m/z*): [M] calcd for $C_{10}H_{14}O_2$, 166.0993; found 166.0994. yield: 67% (92% based on recovered diketone)

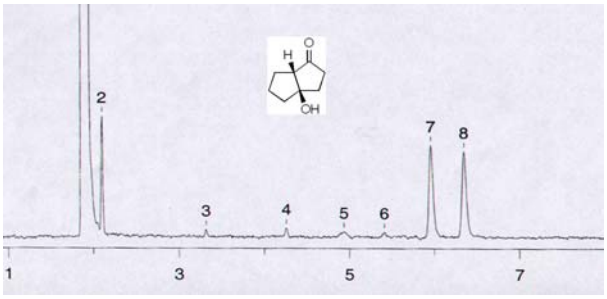


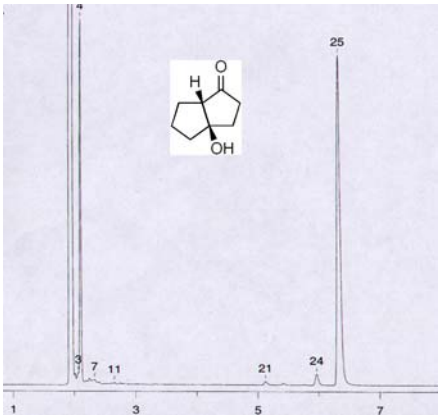
(3a*R*,7a*S*)-3a-Hydroxy-3a,4,5,6,7,7a-hexahydro-1*H*-inden-1-one (12): $[\alpha]_D^{20}$ = - 19.0 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 5.8 Hz, 1H), 6.15 (d, *J* = 5.8 Hz, 1H), 2.40-2.38 (m, 1H), 2.08-1.99 (m, 1H) 1.86 (bs, 1H), 1.81-1.73 (m, 2H) 1.63-1.52 (m, 2H), 1.49-1.41 (m, 2H), 1.21-1.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 166.0, 131.7, 78.0, 54.5, 36.1, 20.9, 20.5, 19.1; IR (thin film, cm^{-1}): 3424 (b), 1679. HRMS (*m/z*): [M] calcd for $C_9H_{12}O_2$, 152.1902; found 152.1902. yield: 67% (92% based on recovered diketone) The enantiomeric ratio was determined to be 71:39 by chiral-GC using BGB-178/BGB-15 column 29m (12 min at 150 °C, 8 °C/min until 230 °C, 5 min at 230 °C). Major enantiomer: t_R = 8.89 min, minor enantiomer: t_R = 8.68 min.

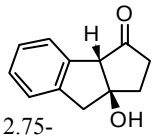




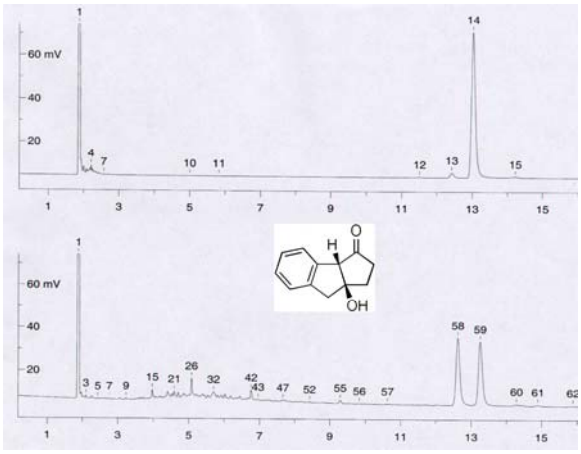
(3a*R*,6a*S*)-3a-Hydroxyhexahydropentalen-1(2*H*)-one (14): $[\alpha]_D^{20}$ = + 41.9 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.65-2.58 (m, 1H), 2.46-2.44 (bm, 1H), 2.36-2.29 (m, 1H), 2.13-2.05 (m, 3H), 1.91-1.71 (m, 5H) 1.64-1.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.8, 87.5, 59.9, 40.9, 38.5, 34.4, 28.0, 25.6; IR (thin film, cm^{-1}): 3344 (b), 1728. HRMS (*m/z*): [M] calcd for $C_8H_{12}O_2$, 140.0837; found 140.0836. yield: 53% (95% based on recovered diketone) The enantiomeric ratio was determined to be 97:3 by chiral-GC using BGB-178/BGB-15 column 29m (7 min at 150 °C, 12 °C/min until 230 °C, 5 min at 230 °C). Major enantiomer: t_R = 6.32 min, minor enantiomer: t_R = 5.97 min.

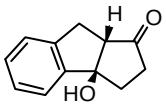






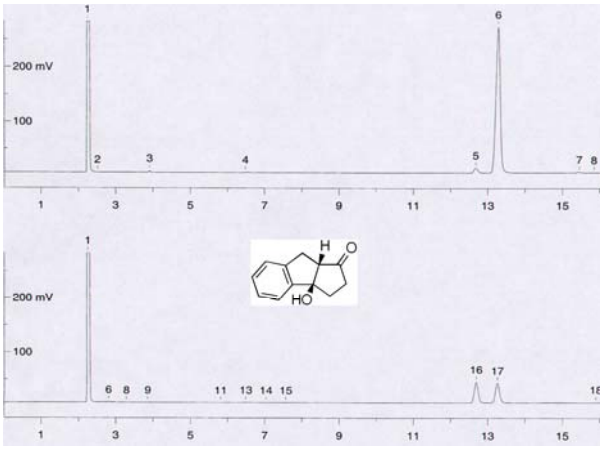
(3a*S*,8a*S*)-8a-Hydroxy-1,2,8,8a-tetrahydrocyclopenta[a]inden-3(3a*H*)-one (16): $[\alpha]_D^{20}$ = + 93.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.39 (m, 1H), 7.25-7.19 (m, 3H), 3.66 (bs, 1H), 3.24 (bs, 2H), 2.75-2.65 (m, 1H), 2.36-2.26 (m, 2H), 2.18-2.08 (m, 1H), 2.01 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.3, 141.1, 137.3, 128.0, 127.4, 125.2, 124.8, 87.0, 65.6, 46.4, 38.0, 35.2; IR (thin film, cm^{-1}): 3421 (b), 1734. HRMS (*m/z*): [M] calcd for $C_{12}H_{12}O_2$, 188.0837; found 188.0835. yield: 67% (93% based on recovered diketone) The enantiomeric ratio was determined to be 97:3 by chiral-GC using BGB-178/BGB-15 column 29m (20 min at 180 °C). Major enantiomer: t_R = 13.03 min, minor enantiomer: t_R = 12.42 min.

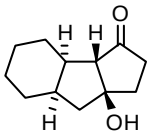




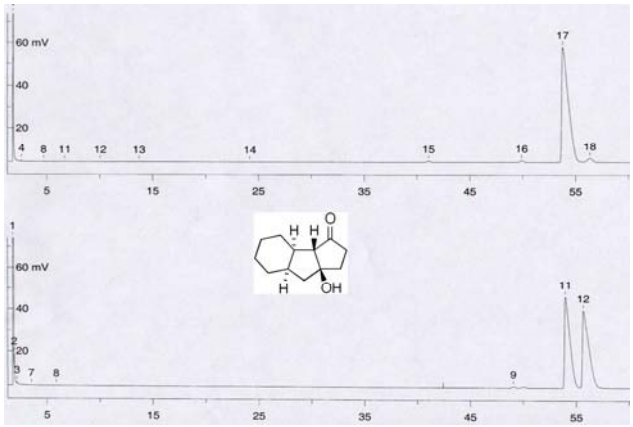
(3a*R*,8a*S*)-3a-Hydroxy-3,3a,8,8a-tetrahydrocyclopenta[a]inden-1(2*H*)-one (18): $[\alpha]_D^{20}$ = + 219.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.45 (m, 1H), 7.34-7.29 (m, 2H), 7.25-7.22 (m, 1H), 3.40-3.34 (m, 1H), 3.12-3.07 (m, 1H), 2.87-2.85 (m, 1H), 2.65-2.56 (m, 2H), 2.51-2.43 (m, 1H), 2.05-1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.0, 144.5, 142.7, 129.5, 127.8, 125.2, 123.0, 88.5, 59.2, 38.8, 33.7, 33.2; IR (thin film, cm^{-1}): 3400 (b), 1734, 1665. HRMS (*m/z*): [M] calcd for $C_{12}H_{12}O_2$, 188.0837; found 188.0836. yield: 80% The enantiomeric ratio was determined to be 97:3 by chiral-GC using BGB-178/BGB-15 column 29m (17 min at 180 °C). Major enantiomer: t_R = 13.30

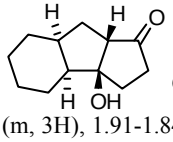
min, minor enantiomer: t_R = 12.68 min.



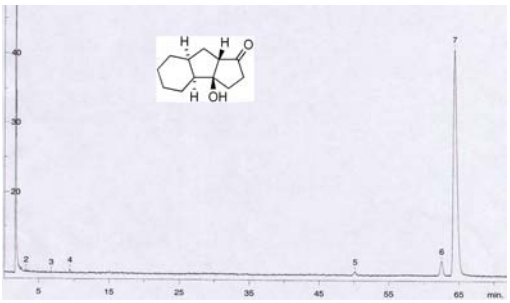


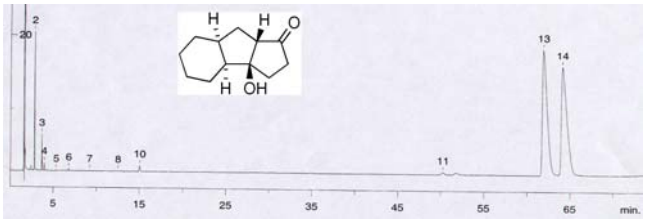
(3a*S*,3b*R*,7a*R*,8a*S*)-8a-Hydroxydecahydrocyclopenta[a]inden-3(3a*H*)-one (20): $[\alpha]_D^{20}$ = + 78.2 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62-2-56 (m, 1H), 2.30-2.24 (m, 2H), 2.15-1.90 (m, 6H), 1.75 (bs, 1H), 1.65-1.23 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.6, 86.8, 65.0, 45.6, 39.0, 38.8, 37.7, 27.7, 27.1, 24.0, 22.0; IR (thin film, cm^{-1}): 3434, 1726. HRMS (*m/z*): [M] calcd for $C_{12}H_{18}O_2$, 194.1307; found 194.1308. yield: 68% (95% based on recovered diketone) The enantiomeric ratio was determined to be 97:3 by chiral-GC using B-PM-CD column 29m (60 min at 140 °C). Major enantiomer: t_R = 53.77 min, minor enantiomer: t_R = 56.32 min.





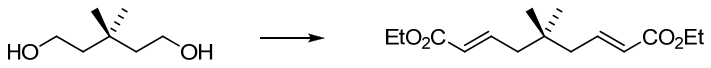
(3a*S*,3b*S*,7a*S*,8a*S*)-3a-Hydroxydecahydrocyclopenta[a]inden-1(2*H*)-one (22): $[\alpha]_D^{20}$ = + 24.1 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.75-2.67 (m, 1H), 2.22 (bm, 1H), 2.32-2.28 (m, 1H), 2.12-2.03 (m, 3H), 1.91-1.84 (m, 1H), 1.80-1.69 (m, 2H), 1.62 (bs, 1H) 1.60-1.05 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 221.3, 89.4, 58.2, 48.4, 38.6, 37.3, 35.7, 29.0, 26.7, 24.7, 23.0, 20.7; IR (thin film, cm^{-1}): 3385 (b), 1718. HRMS (*m/z*): [M] calcd for $C_{12}H_{18}O_2$, 194.1307; found 194.1305. yield: 42% The enantiomeric ratio was determined to be 95:5 by chiral-GC using B-PM-CD column 30m (70 min at 140 °C, 8 °C/min until 230 °C, 5 min at 230 °C). Major enantiomer: t_R = 64.22 min, minor enantiomer: t_R = 62.43 min.





Experimental Procedures for a Total Synthesis of (+)-Hirsutene:

(2*E*,7*E*)-Diethyl 5,5-dimethylnona-2,7-dienedioate, (26)

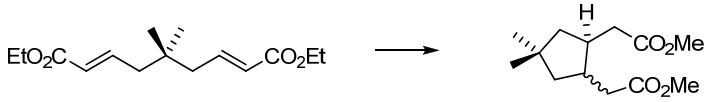


To a stirred solution of DMSO (20 mL, 280.0 mmol, 5 equiv) in dry CH_2Cl_2 (224 mL) at -78 °C was added oxalyl chloride (14.5 mL, 168.0 mmol, 3 equiv) slowly dropwise. The resulting solution was allowed to stir for 20 min. A solution of 3,3-dimethylpentane-1,5-diol[6] (7.4 g, 56.0 mmol, 1 equiv) in CH_2Cl_2 (56 mL) was then added dropwise, slowly and the mixture continued to stir for 1 h at -78 °C. Freshly distilled triethylamine (55 mL, 392.0 mmol, 7 equiv) was added slowly, dropwise to the solution and the mixture stirred for 1 h before being warmed to 0 °C. After the solution stirred at 0 °C for 15 min, it was poured into a separatory funnel containing saturated $NaHCO_{(aq)}$ (300 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The organics were combined, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude oil thus obtained was used immediately for the next reaction.

To a stirred solution of crude 3,3-dimethylpentanedialdehyde (56.0 mmol, 1 equiv) in dry CH_2Cl_2 (280 mL) at 0 °C was added ethoxycarbonylmethylene triphenylphosphorane (43 g, 123.2 mmol, 2.2 equiv) and the resulting mixture was allowed to stir for 3 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography [silica gel; 5% EtOAc:Hex] to afford the diester (11.4 g, yield: 76%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-6.91 (m, 2H), 5.83 (d, J = 3.6 Hz, 2H), 4.19 (q, J = 7.1 Hz, 4H), 2.12 (dd, J = 1.32, 6.6 Hz, 4H), 1.29 (t, J = 7.1 Hz, 6H), 0.96 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 47.1, 45.5, 40.2, 40.0, 36.5, 31.8, 31.5; IR (thin film, cm^{-1}): 1716, 1652. HRMS (*m/z*): [M] calcd for $C_{13}H_{20}O_2$, 208.1463; found 208.1461.

Dimethyl 2,2'-(4,4-dimethylcyclopentane-1,2-diyl)diacetate, (27)



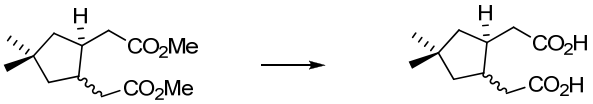
To a stirred solution of diester **26** (8.0 g, 29.8 mmol, 1 equiv) in dry MeOH (445 mL) at 0 °C in a round bottom flask equipped with a reflux condenser was added magnesium powder (10.7 g, 15 equiv). After 15-20 min the reaction mixture exothermed and continued to stir for an additional 3 h. The reaction was quenched by pouring into 1 N HCl (300 mL) at 0 °C. The solution was stirred for 20 min and then extracted with EtOAc (3 x 200 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The residue was purified by column chromatography [silica gel;

[6] Berglund, R. A.; Braish, T. F.; Jakubowshi, J. A.; Fuchs, P. L. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 649.

5% EtOAc:Hex] to afford cyclopentane **27** (6.36 g, yield: 88%).

^{1}H NMR (400 MHz, $CDCl_3$) *characterized as a mixture of cis:trans isomers (1.1:1)* δ 3.67 (s, 6H), 3.66 (s, 6H), 2.63-2.58 (m, 2H), 2.49 (dd, *J* = 4.2, 10.7 Hz, 2H), 2.35 (dd, *J* = 6.0, 9.1 Hz, 2H), 2.22-2.01 (m, 6H), 1.76 (dd, *J* = 5.6, 7.2 Hz, 2H), 1.66 (dd, *J* = 6.0, 7.3 Hz, 2H), 1.25-1.15 (m, 4H), 1.06 (s, 3H), 1.01 (s, 6H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 173.5, 51.5, 51.4, 47.7, 46.7, 41.8, 38.9, 37.7, 37.2, 37.0, 35.7, 31.2, 30.9, 30.2; IR (thin film, cm^{-1}): 1733. HRMS (*m/z*): $[MNa]^+$ calcd for $C_{13}H_{22}NaO_4$, 265.1410; found 265.1407.

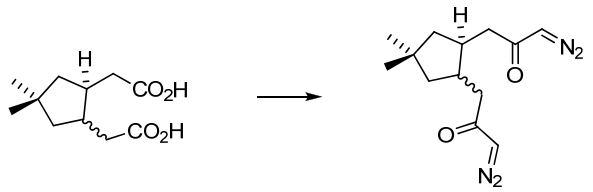
2,2'-(4,4-Dimethylcyclopentane-1,2-diyl)diacetic acid, (28)



To a stirred solution of diester **27** (6.36 g, 23.5 mmol, 1 equiv) in EtOH (40 mL) at 0 °C was added a cooled solution of KOH (6 N, 40 mL, 10 equiv). The reaction was brought to room temperature and was allowed to stir 24 h. The mixture was cooled to 0 °C, acidified with 6 N HCl and extracted with EtOAc (3 x 100 mL). The solvent was removed under reduced pressure and the residue was purified by recrystallization with hot hexanes to obtain the diacid as a white solid (2.86 g, 57%). The mother liquor contained **28** (1.03 g, 20%).

^{1}H NMR (400 MHz, acetone d^6) *characterized as a mixture of cis:trans isomers (1.1:1)* δ 11.19-7.00 (bs, 4H), 2.57 (dd, *J* = 3.8, 11.3 Hz, 4H), 2.41 (dd, *J* = 5.8, 9.5 Hz, 2H), 2.22-2.13 (m, 6H), 1.80 (dd, *J* = 5.6, 7.1 Hz, 2H), 1.68 (dd, *J* = 5.9, 7.3 Hz, 2H), 1.31 (dd, *J* = 5.3, 7.8 Hz, 2H), 1.21 (dd, *J* = 3.5, 9.5 Hz, 2H), 1.08 (s, 3H), 1.03 (s, 6H), 1.01 (s, 3H); ^{13}C NMR (100 MHz, acetone d^6) δ 175.2, 175.0, 49.3, 48.1, 43.1, 39.9, 39.3, 38.4, 38.1, 36.6, 33.2, 32.0, 31.3; IR (thin film, cm^{-1}): 2950 (b), 1694 HRMS (*m/z*): $[MNa]^+$ calcd for $C_{11}H_{18}NaO_4$, 237.1097; found 237.1095.

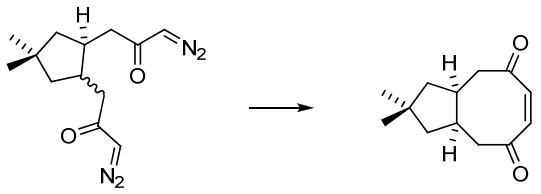
(S)-3,3'-(4,4-dimethylcyclopentane-1,2-diyl)bis(1-diazopropan-2-one), (29)



Bis-α-diazo compound **29** was prepared from diacid **28** (2 g, 9.3 mmol) according to the general procedure to afford 1.79 g (yield: 73%).

^{1}H NMR (400 MHz, $CDCl_3$) *characterized as a mixture of cis:trans isomers (1.1:1)* δ 5.23 (bs, 4H), 2.63-2.53 (bm, 2H), 2.49-2.29 (bm, 4H), 2.21-1.98 (bm, 6H), 1.72 (dd, *J* = 5.9, 7.0 Hz, 2H), 1.61 (dd, *J* = 6.1, 7.2 Hz, 2H), 1.19 (dd, *J* = 5.3, 7.8 Hz, 2H), 1.09 (dd, *J* = 3.4, 9.3 Hz, 2H), 1.02 (s, 3H), 0.97 (s, 6H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 54.7, 54.5, 47.6, 46.4, 45.8, 42.6, 42.0, 38.0, 37.2, 37.0, 31.1, 30.8, 30.0; IR (thin film, cm^{-1}): 2095, 1628, 1345, 1320, 1139. HRMS (*m/z*): $[MNa]^+$ calcd for $C_{13}H_{18}N_4NaO_2$, 285.1322; found 285.1321.

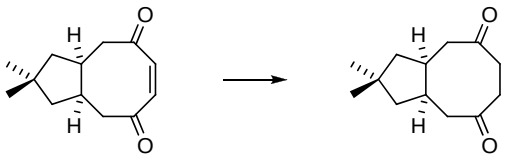
(3a*R*,9a*S*,*Z*)-2,2-Dimethyl-2,3,3a,4-tetrahydro-1*H*-cyclopenta[8]annulene-5,8(9*H*,9a*H*)-dione, (30)



Ene-dione **30** was prepared from bis-α-diazo compound **29** (950 mg, 3.62 mmol) according to the general procedure to afford 386 mg (yield: 52%) of the *cis*-isomer and 170 mg (yield: 22%) of the *trans*-isomer.

cis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (s, 2H), 2.68-2.61 (m, 2H), 2.55-2.48 (m, 2H), 2.43-2.40 (m, 2H), 1.71 (dd, *J* = 6.3, 7.1 Hz, 2H), 1.38 (dd, *J* = 6.6, 6.7 Hz, 2 H), 1.11 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.3, 136.6, 46.4, 44.3, 38.7, 36.6, 31.8, 31.7; IR (thin film, cm^{-1}): 1677, 1665. HRMS (*m/z*): [M] calcd for $C_{13}H_{18}O_2$, 206.1307; found 206.1304. (*trans*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 2H), 2.71 (dd, *J* = 4.6, 9.7 Hz, 2H), 2.39 (dd, *J* = 6.6, 7.6 Hz, 2H), 2.03-1.97 (m, 2H), 1.66-1.61 (m, 2H), 1.29-1.23 (m, 2H), 1.00 (s, 6H)).

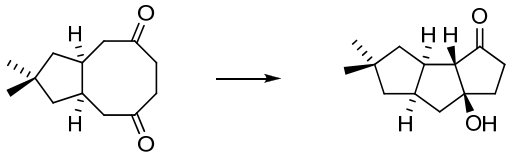
(3a*R*,9a*S*)-2,2-Dimethylhexahydro-1*H*-cyclopenta[8]annulene-5,8(9*H*,9a*H*)-dione, (23)



Diketone **23** was prepared from ene-dione **30** (386 mg, 1.87 mmol) according to the general procedure to afford 354 mg (yield: 91%).

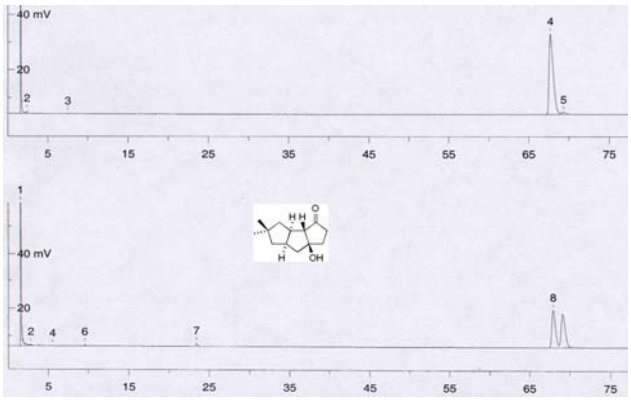
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74-2.44 (m, 8H), 2.30-2.26 (m, 2H), 1.71-1.66 (m, 2H), 1.36-1.31 (m, 2H), 1.08 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 47.1, 45.5, 40.2, 40.0, 36.5, 31.8, 31.5;IR (thin film, cm^{-1}): 1694. HRMS (*m/z*): [M] calcd for $C_{13}H_{20}O_2$, 208.1463; found 208.1461.

(+)-(3a*S*,3b*R*,6a*R*,7a*S*)-7a-Hydroxy-5,5-dimethyl-decahydro-cyclopenta[*a*]pentalen-3-one, (24)

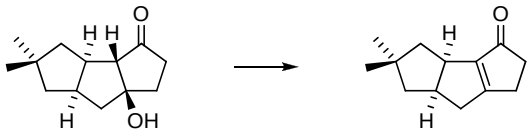


Aldol **24** was prepared from diketone **23** (45 mg, 0.216 mmol) according to the general procedure to afford 37.8 mg (yield: 84%) of the aldol adduct.

$[\alpha]_D^{20}$ = +67.6 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73-2.53 (m, 3H), 2.36-2.28 (m, 2H), 2.16-2.08 (m, 1H), 2.06-1.98 (m, 2H), 1.86-1.81 (m, 1H), 1.75-1.69 (m, 2H), 1.65 (bs, 1H), 1.48-1.38 (m, 2H), 1.08 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.4, 90.0, 66.4, 48.9, 48.5, 46.1, 45.5, 43.2, 42.3, 37.5, 34.2, 29.0, 26.9; IR (thin film, cm^{-1}): 3423 (b), 1711. HRMS (*m/z*): [M] calcd for $C_{13}H_{20}O_2$, 208.1463; found 208.1461. The enantiomeric ratio was determined to be 97.5:2.5 by chiral-GC using B-PM column 30m (80 min at 130 °C, 8 °C/min until 230 °C, 5 min at 230 °C). Major enantiomer: t_R = 67.68 min, minor enantiomer: t_R = 69.33 min.

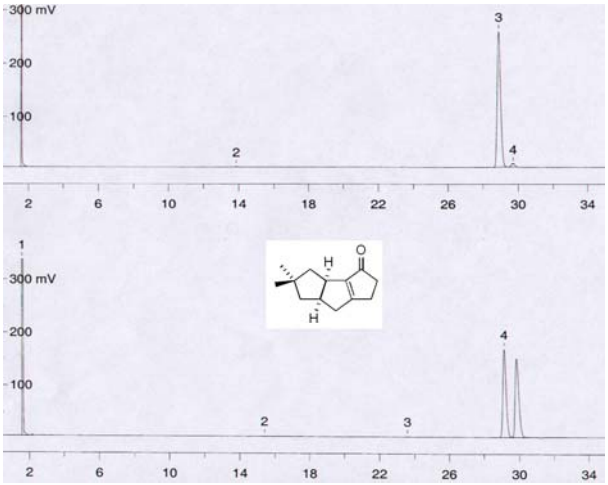


(-)-(3b*R*,6a*R*)-5,5-Dimethyl-1,2,3b,4,5,6,6a,7-octahydro-cyclopenta[*a*]pentalen-3-one, (32)

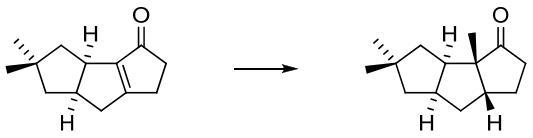


To a stirred solution of beta-hydroxy ketone **24** (58.0 mg, 0.28 mmol, 1 equiv) in Et_2O (1.2 mL) was added 2 N NaOH (1.2 mL, 10 equiv). The reation was allowed to stir for 24 h and then was poured into a separatory funnel containing saturated $NH_4Cl_{(aq)}$ (25 mL). The aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography [silica gel; 15% EtOAc:Hex] to afford enone **32** (52.0 mg, yield: 99%).

$[\alpha]_D^{20}$ = - 120.8 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34-3.18 (m, 2H), 2.77-2.70 (m, 3H), 2.49-2.46 (m, 2H), 2.22 (bm, 1H), 1.91-1.77 (m, 2H), 1.21-1.12 (m, 2H), 1.02 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.3, 184.7, 151.7, 49.2, 47.3, 44.9, 42.8, 41.4, 41.1, 38.6, 28.7, 26.9, 25.7; IR (thin film, cm^{-1}): 1691, 1634. HRMS (*m/z*): [M] calcd for $C_{13}H_{18}O_1$, 190.1358; found 190.1356. The enantiomeric ratio was determined to be 97.5:2.5 by chiral-GC using B-PM-CD column 30m (35 min at 130 °C, 8 °C/min until 230 °C, 5 min at 230 °C). Major enantiomer: t_R = 28.88 min, minor enantiomer: t_R = 29.71 min.



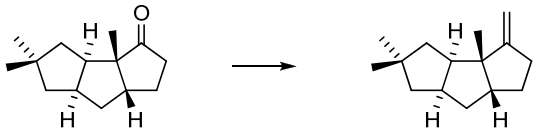
(+)-(3a*R*,3b*R*,6a*S*,7a*R*)-3a,5,5-Trimethyl-decahydro-cyclopenta[*a*]pentalen-3-one (hirsutene norketone), (33)



$NH_{3(g)}$ (200 µL) was condensed into a flask containing THF (30 µL) at -78 °C. A freshly cut piece of Li (0.30 mg, 0.046 mmol, 1.1 equiv) was added and the solution turned immediately dark blue. After the Li completely dissolved (5-10 min) enone **32** (8.0 mg, 0.042 mmol, 1 equiv) was added dropwise as a solution in THF (85 µL). The mixture was stirred vigorously for 10 min upon which MeI (10 µL, 0.084 mmol, 2 equiv) was added as a solution in THF (85 µL). The reaction was allowed to stir for 10 min and was then quenched with solid NH_4Cl. The mixture was diluted with Et_2O (5 mL) and poured into a separatory funnel containing H_2O (10 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The resulting residue was purified by column chromatography [silica gel; 2.5% EtOAc:Hex] to afford hirustene norketone (**33**) (6.5 mg, yield: 75%).

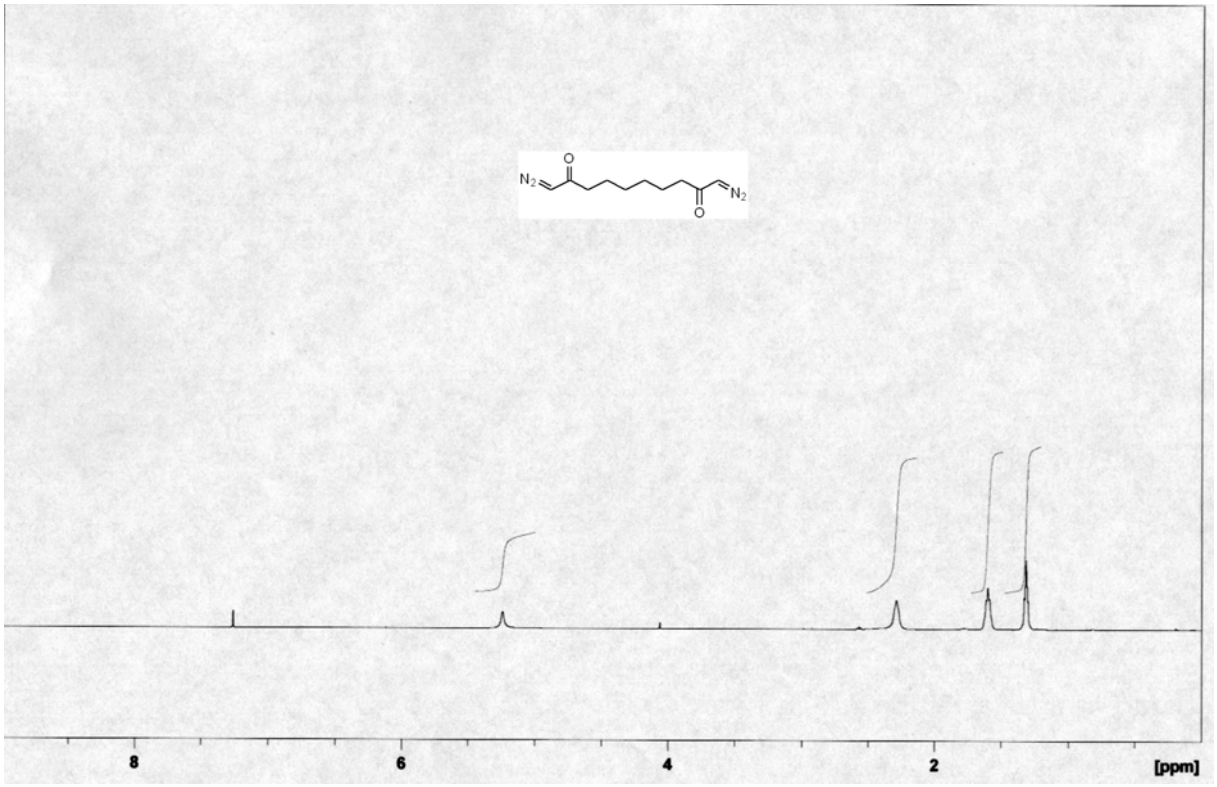
$[\alpha]_D^{20} = +41.0$ (*c* 0.1, hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.78 (dt, *J* = 10.6, 8.8 Hz, 1H), 2.50 (dq, *J* = 3.4, 9.0 Hz, 1H) 2.41-2.23 (m, 2H), 2.02-1.95 (m, 1H), 1.74-1.68 (m, 1H), 1.65-1.54 (m, 3H), 1.46-1.35 (m, 2H), 1.19-1.13 (m, 1H), 1.03 (s, 3H), 1.06-0.96 (m, 1H), 0.93 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 224.7, 59.3, 48.9, 48.8, 46.7, 43.3, 41.8, 41.1, 37.6, 34.2, 30.9, 29.7, 29.2, 26.5, 22.4, 17.3; HRMS (*m/z*): [M] calcd for $C_{14}H_{22}O$, 206.1671; found 206.1671.

(+)-Hirsutene, (34)



To a stirred solution of methyl triphenyl phosphonium bromide (35 mg, 0.098 mmol, 2.05 equiv) in $PhCH_3$ (100 µL) at 0 °C was added potassium *tert*-butoxide (11.0 mg, 0.096 mmol, 2.0 equiv). The resulting mixture was allowed to stir for 40 min. A solution of hirsutene norketone (**33**) (10.0 mg, 0.048 mmol, 1 equiv) in $PhCH_3$ (200 µL) was added dropwise at 0 °C. The solution was brought to reflux (115 °C) for 2.5 h. The reaction was cooled to room temperature, diluted with EtOAc (10 mL) and poured into a separatory funnel containing saturated $NH_4Cl_{(aq)}$ (25 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 x 15 mL). The combined organics were dried ($MgSO_4$), filtered and the solvent was removed *in vacuo*. The crude residue was purified by column chromatography [silica gel; 2% EtOAc:Hex] to afford hirsutene (**34**) (9.3 mg, yield: 87%).

$[\alpha]_D^{20} = +13.0$ (*c* 0.1 , hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (bs, 1H), 4.78 (bs, 1H) 2.64-2.45 (m, 4H), 2.18-2.13 (m, 1H), 1.77-1.70 (m, 1H), 1.66-1.62 (m, 1H), 1.51-1.41 (m, 4H), 1.22 (t, *J* = 11.7 Hz, 1H) 1.06 (s, 3H), 1.11-0.99 (m, 1H), 0.96 (s, 3H), 0.92 (s, 3H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 103.5, 56.0, 53.4, 49.9, 49.0, 44.3, 41.9, 40.9, 38.6, 30.9, 29.8, 27.2, 26.8, 23.2; IR (thin film, cm^{-1}): 1461. HRMS (*m/z*): [M] calcd for $C_{15}H_{24}$, 204.1878; found 204.1877.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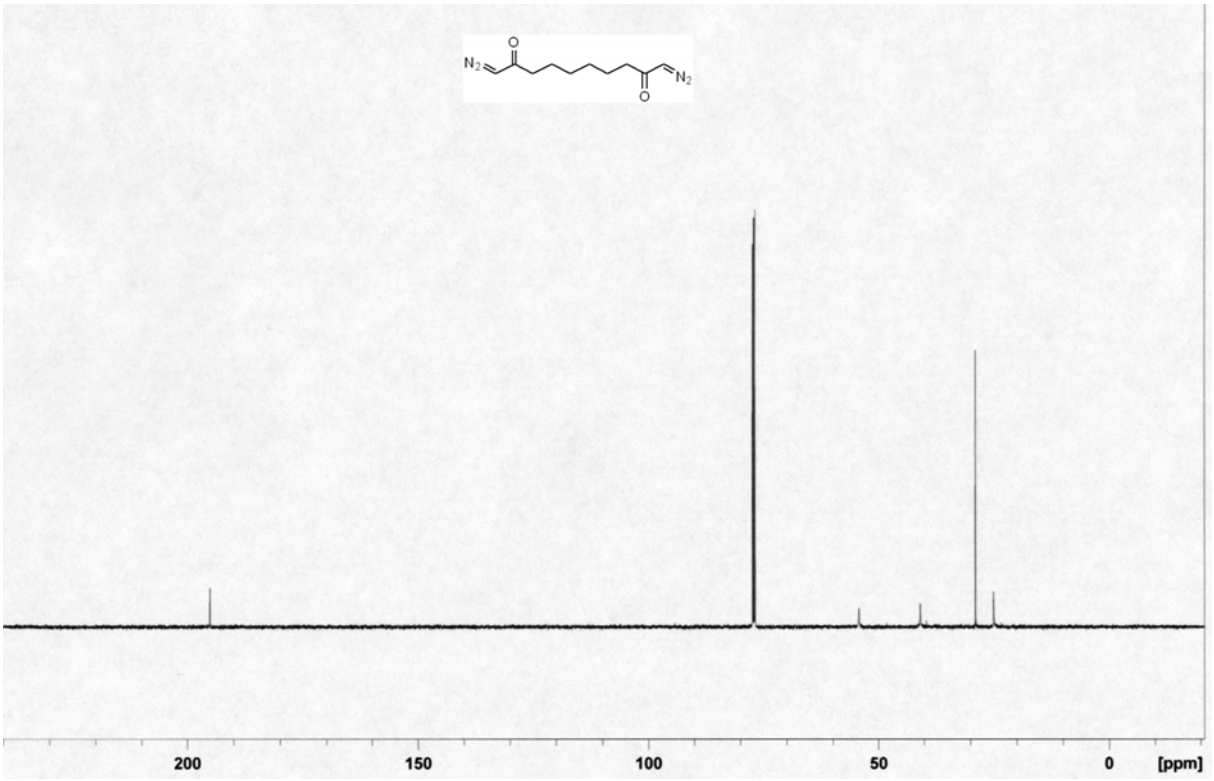
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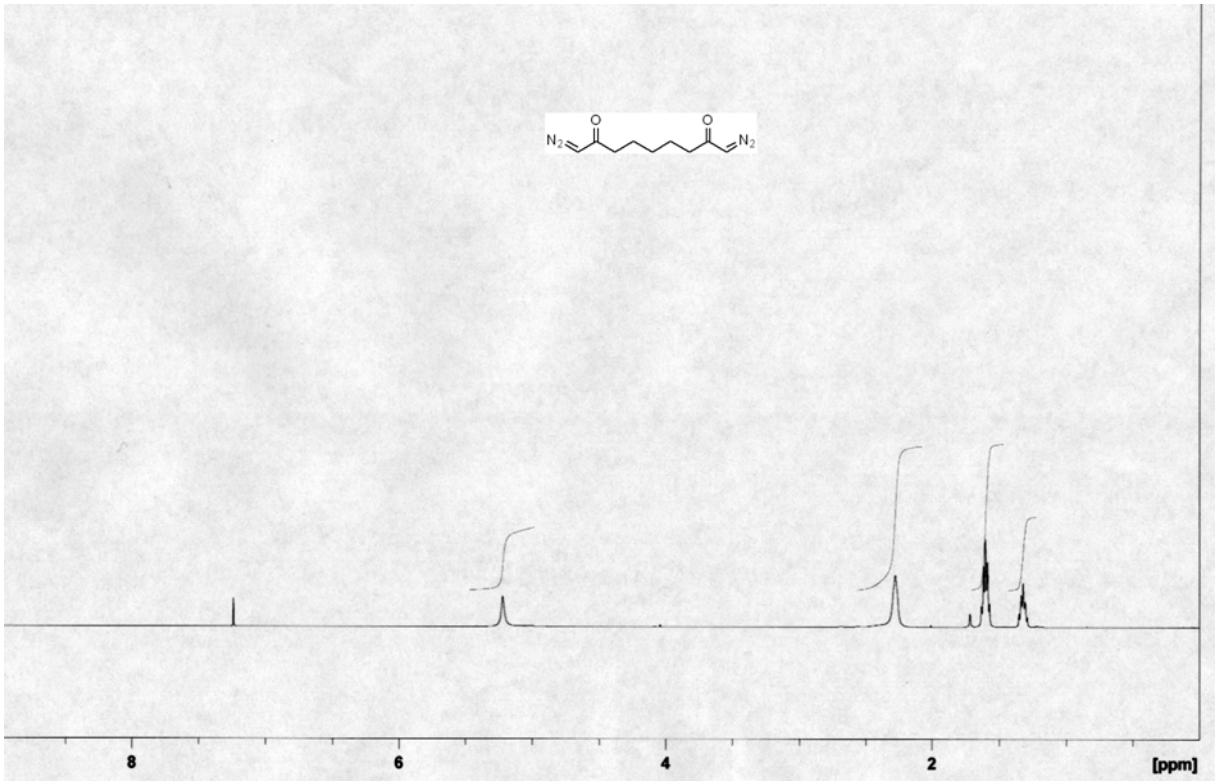
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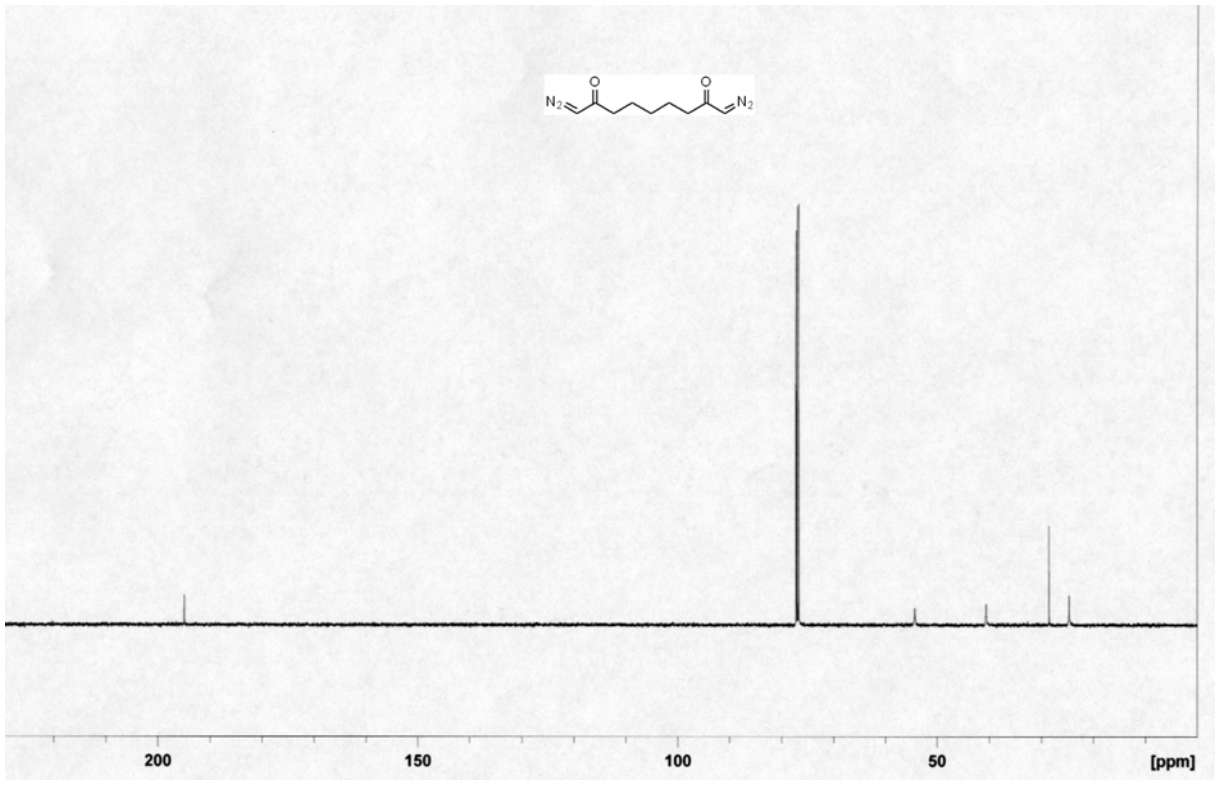
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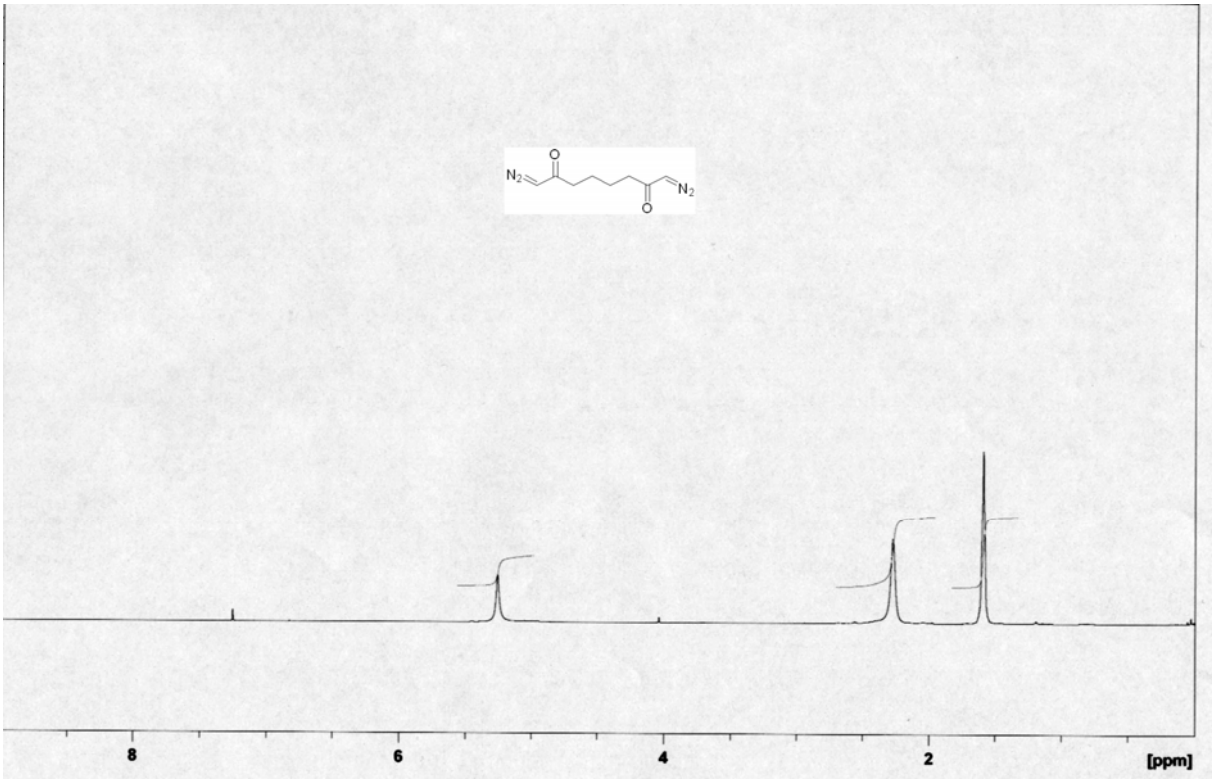
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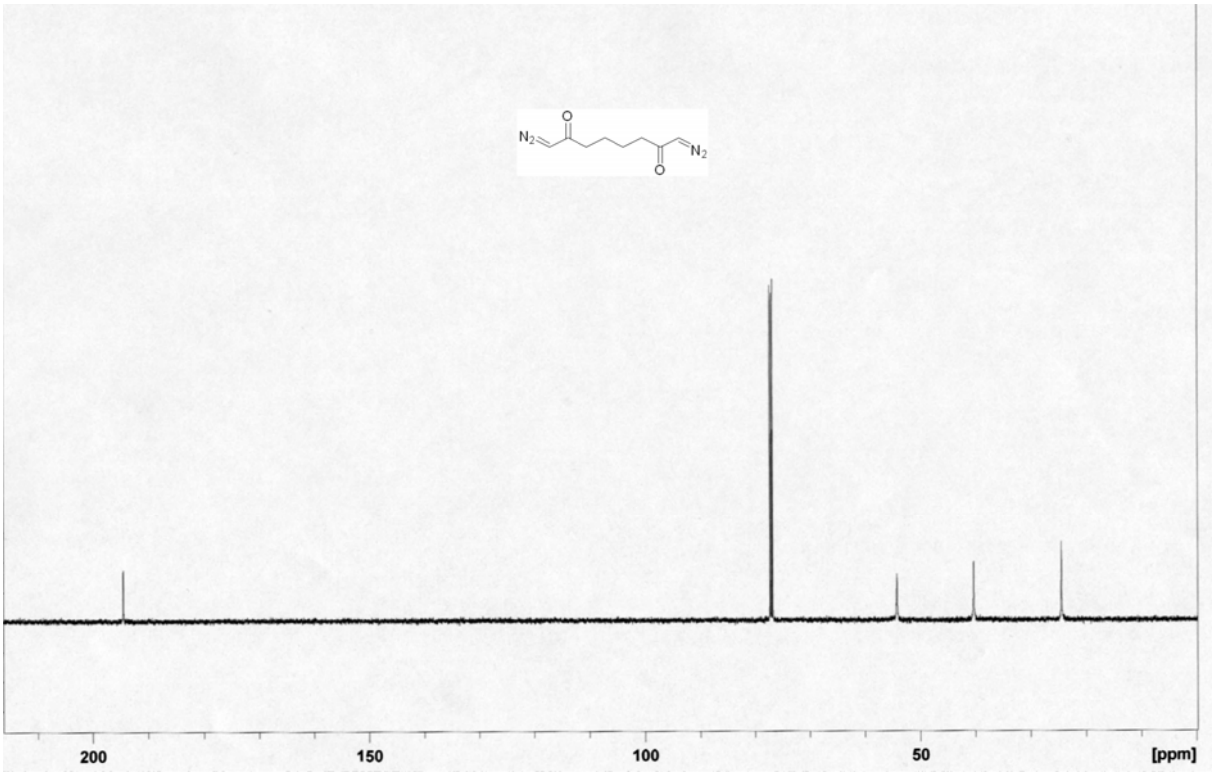
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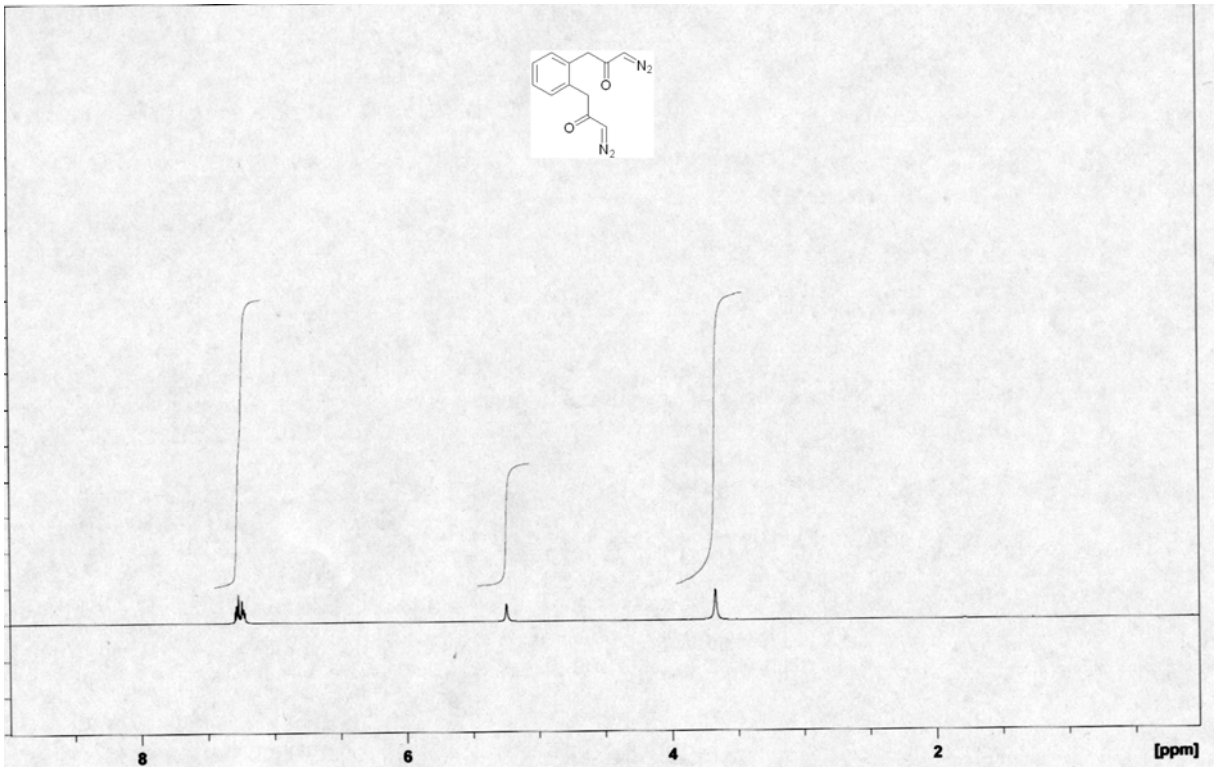
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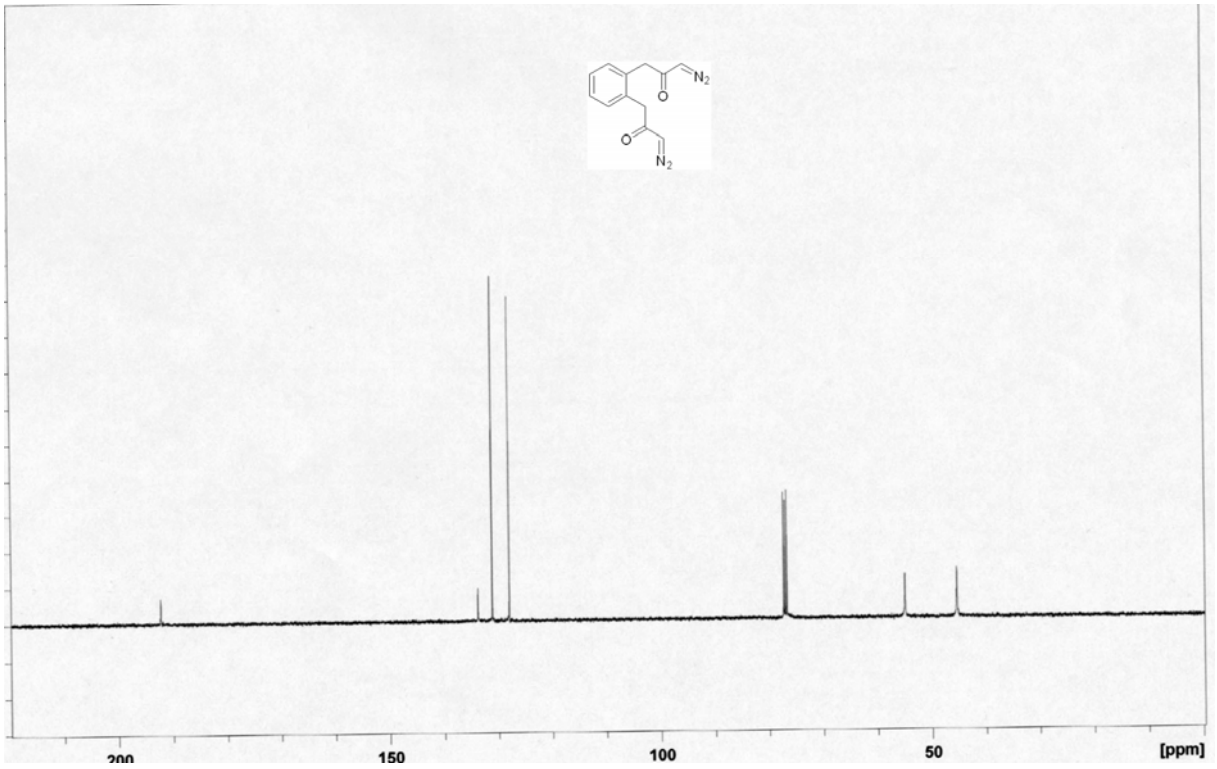
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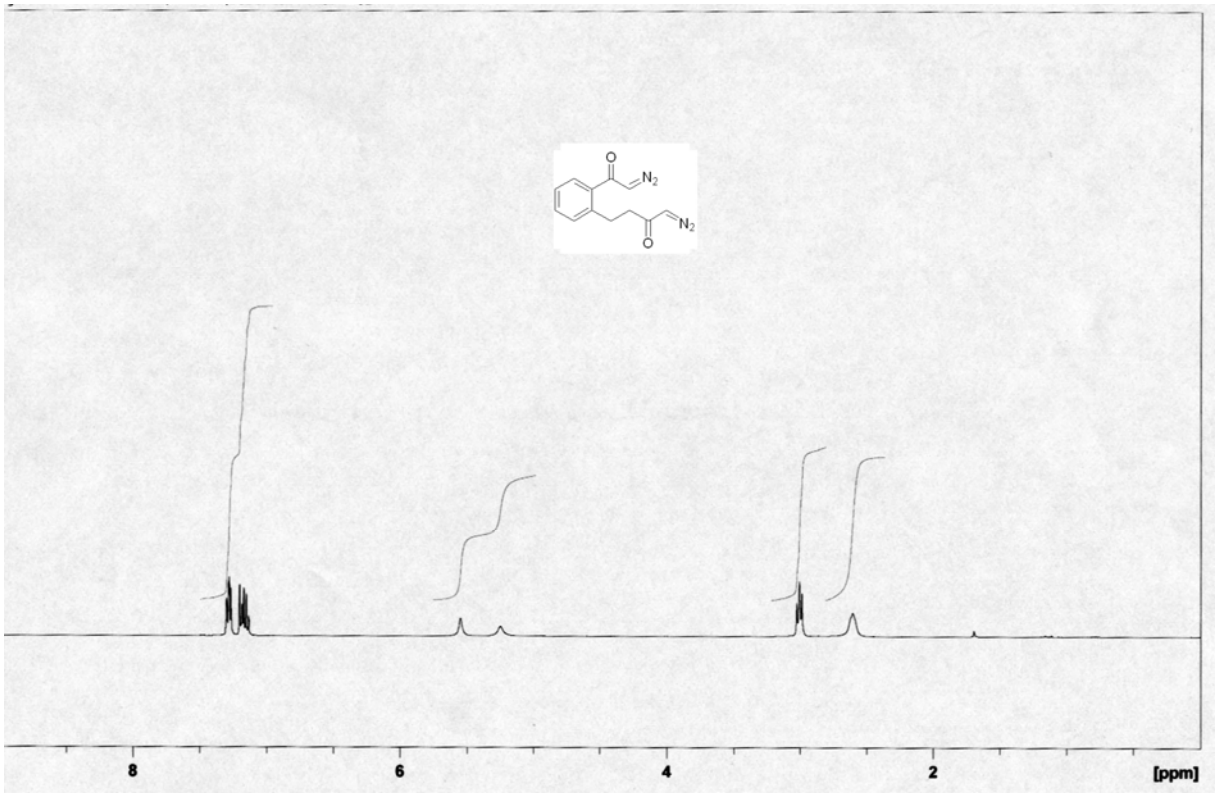
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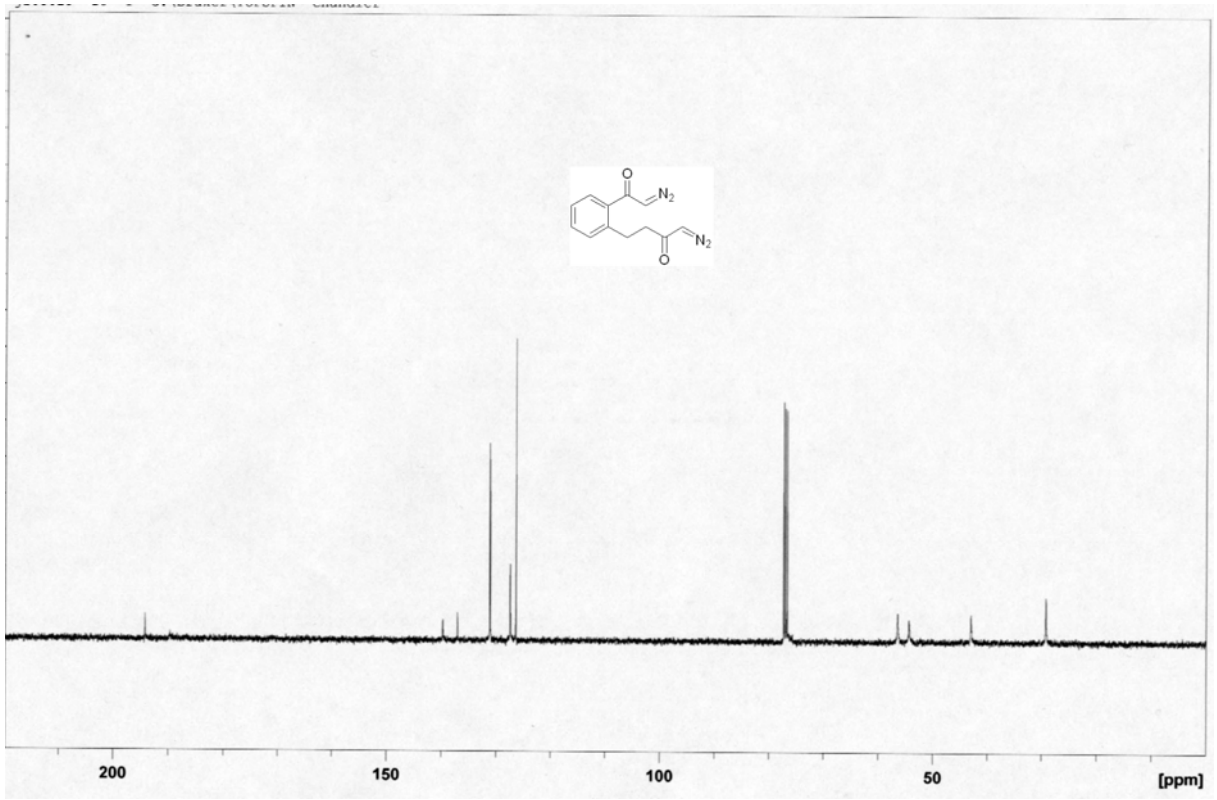
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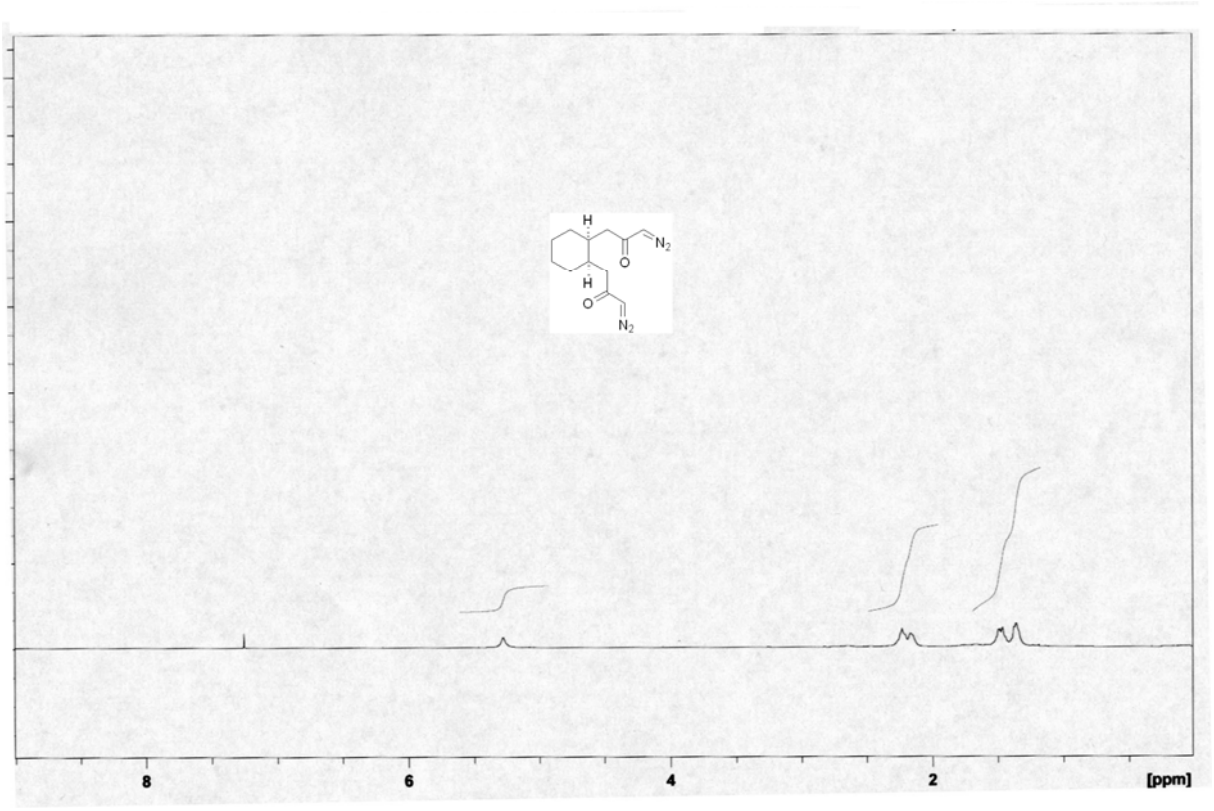
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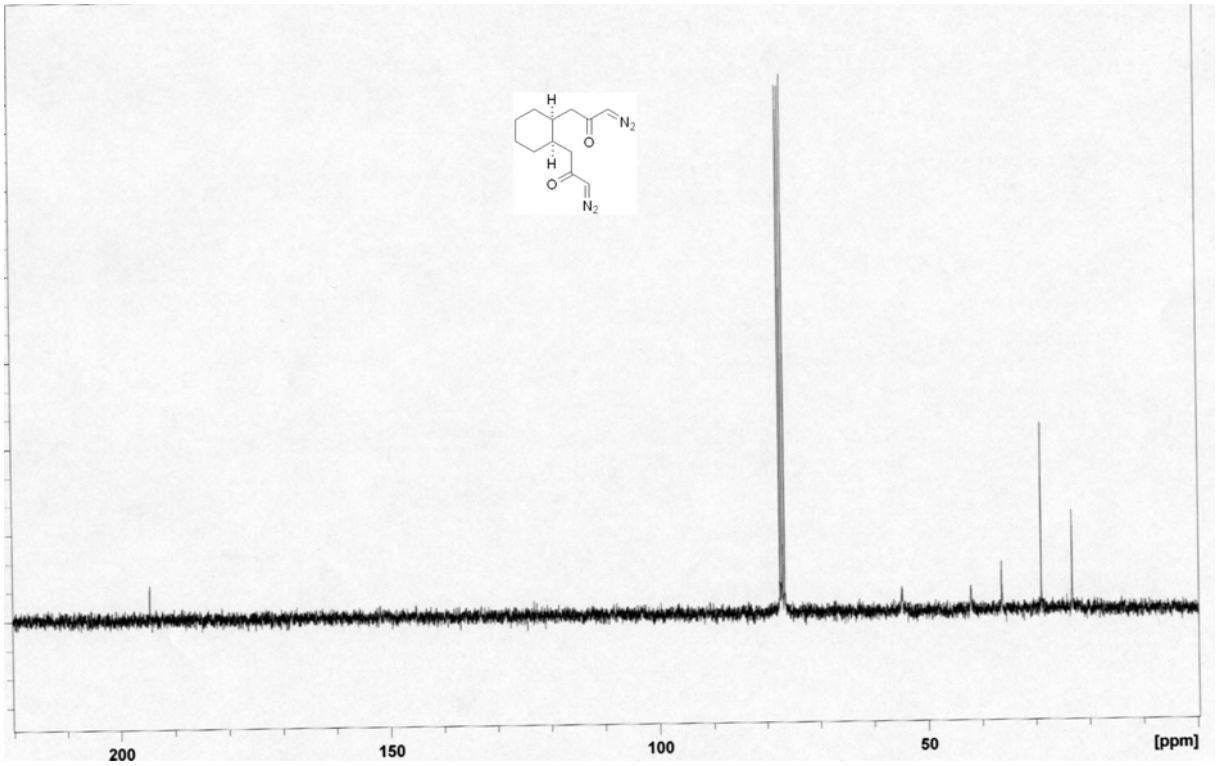
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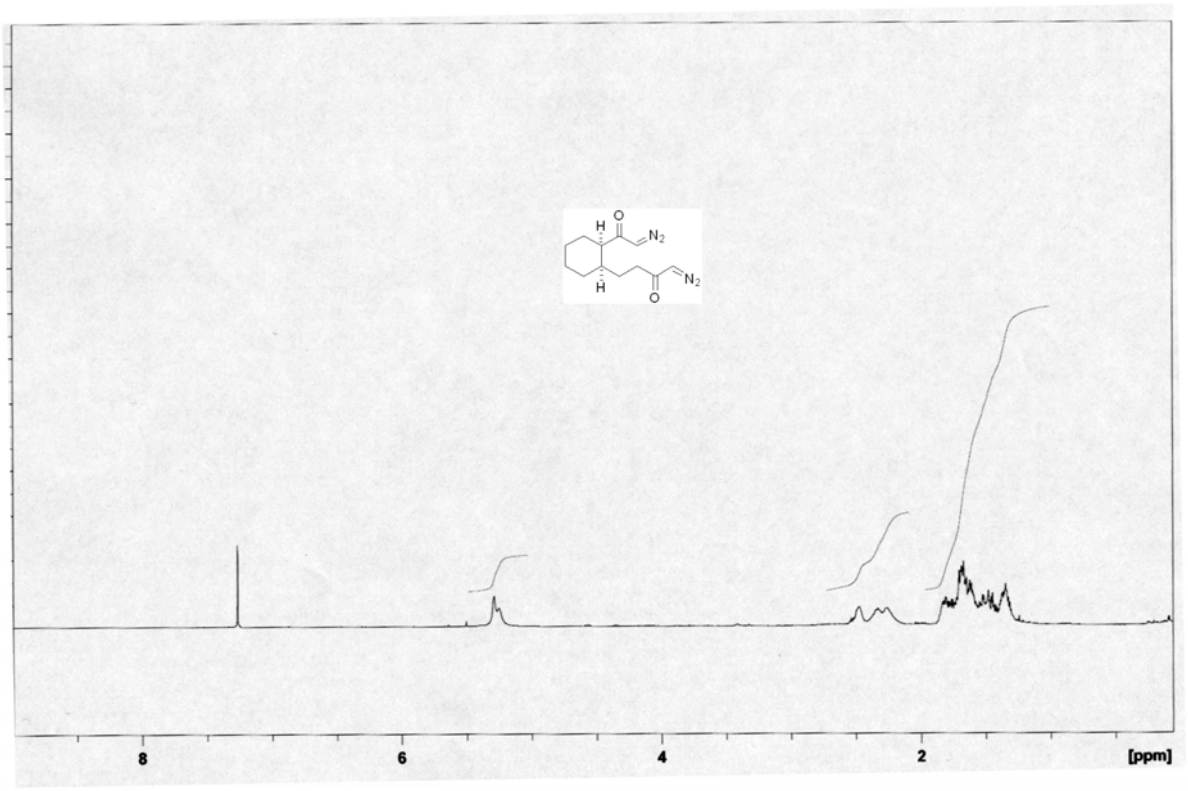
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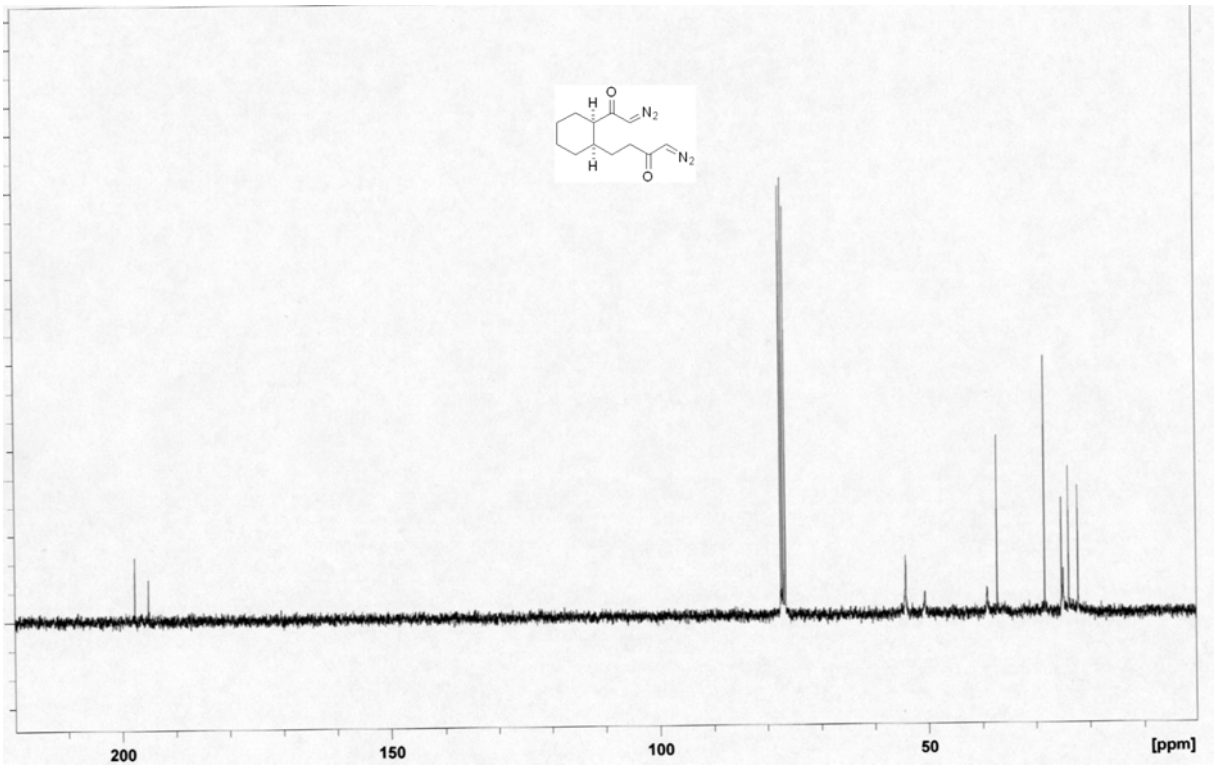
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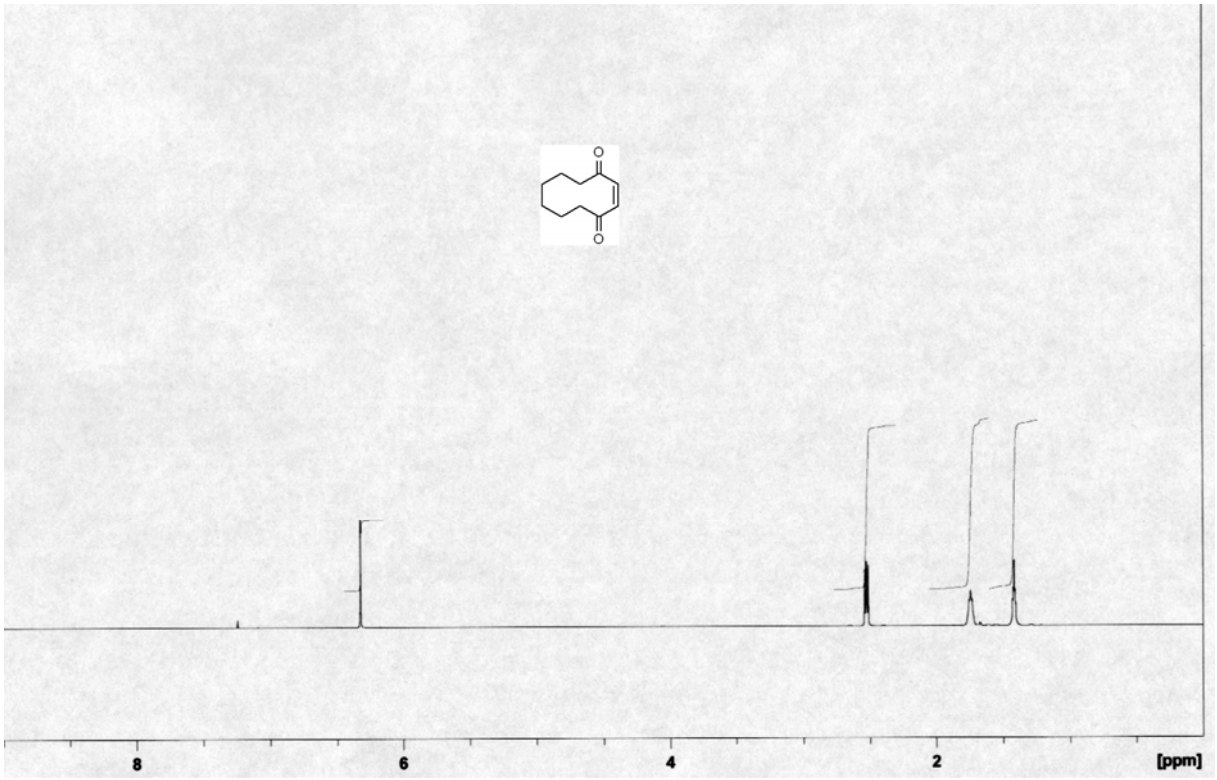
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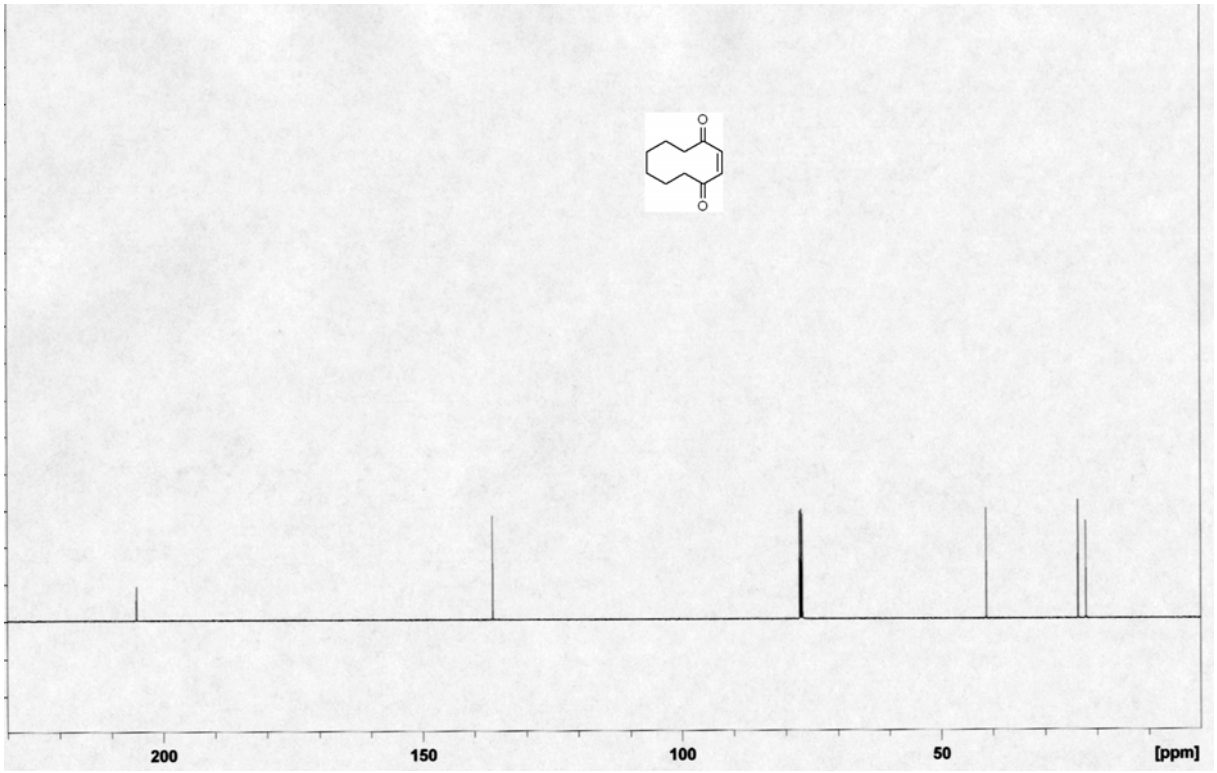
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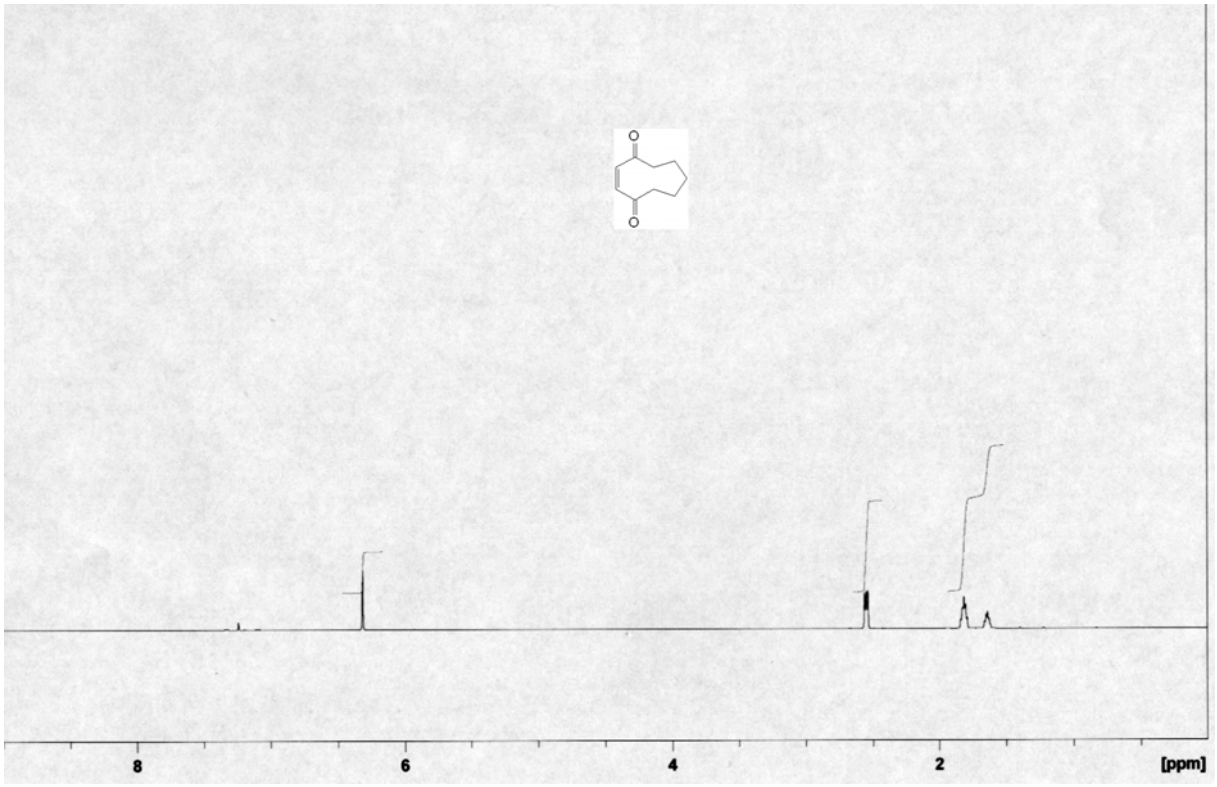
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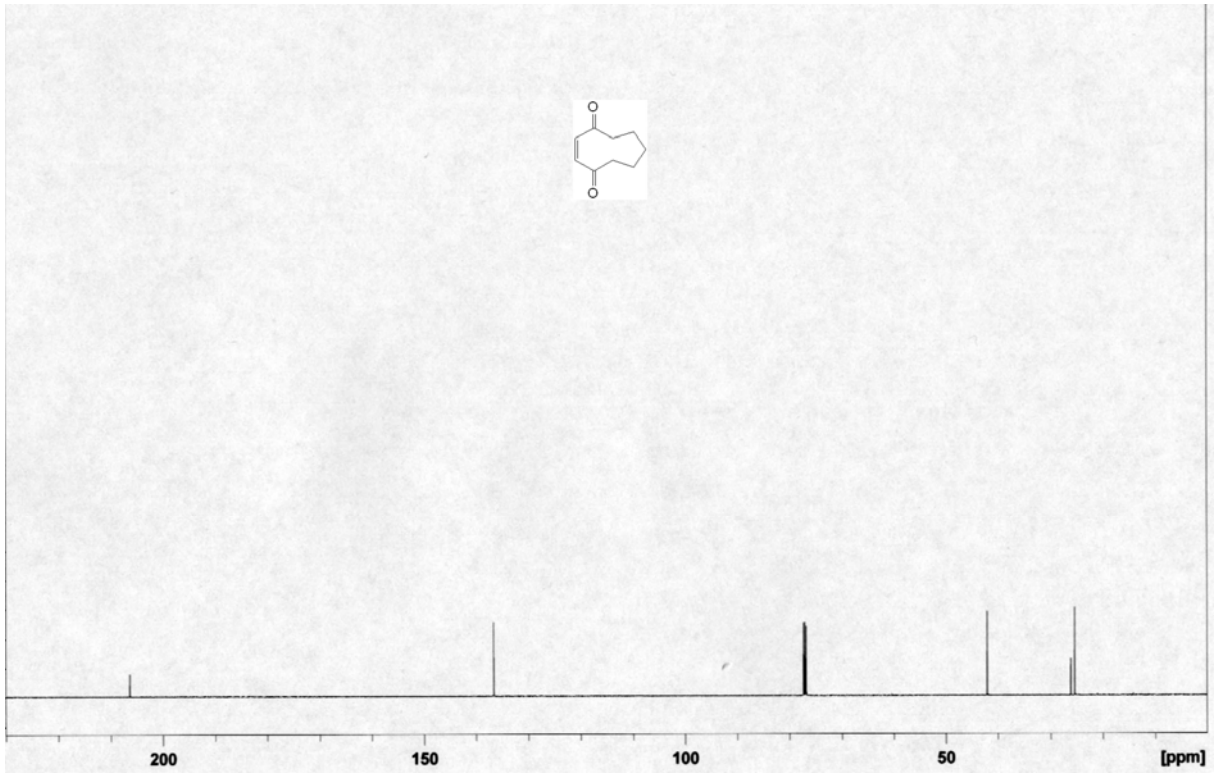
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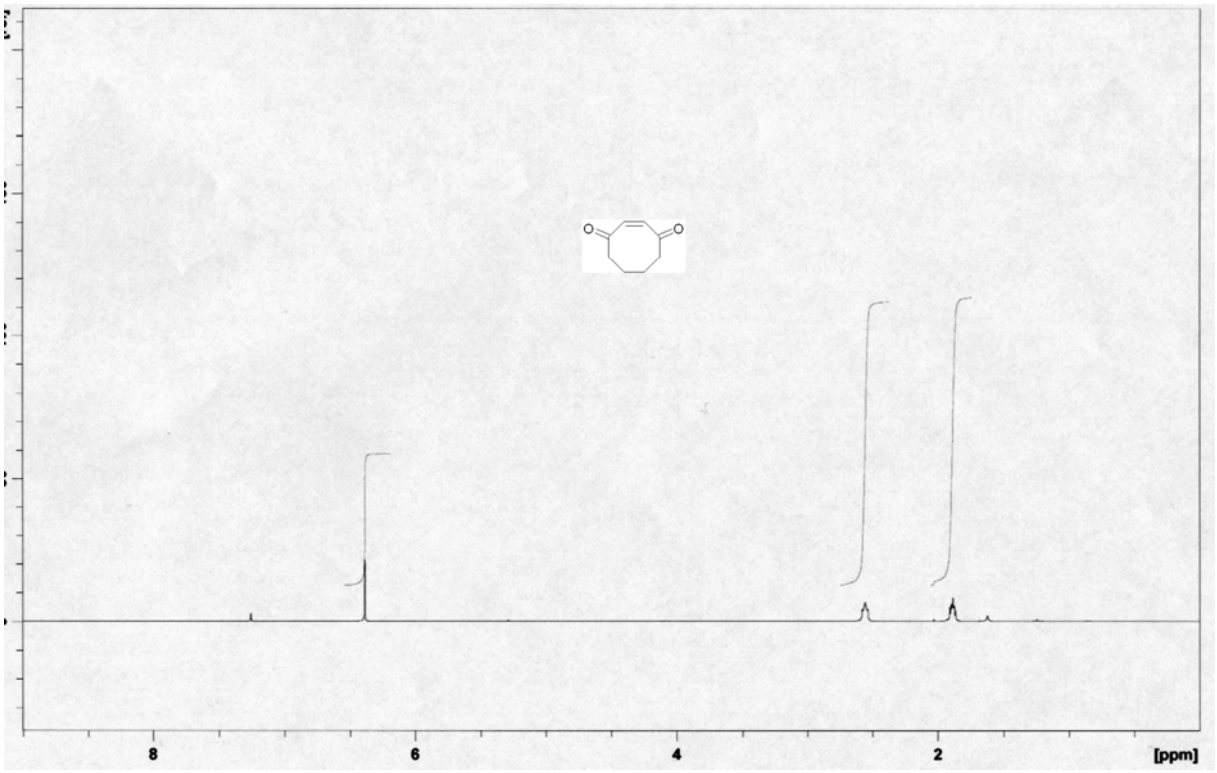
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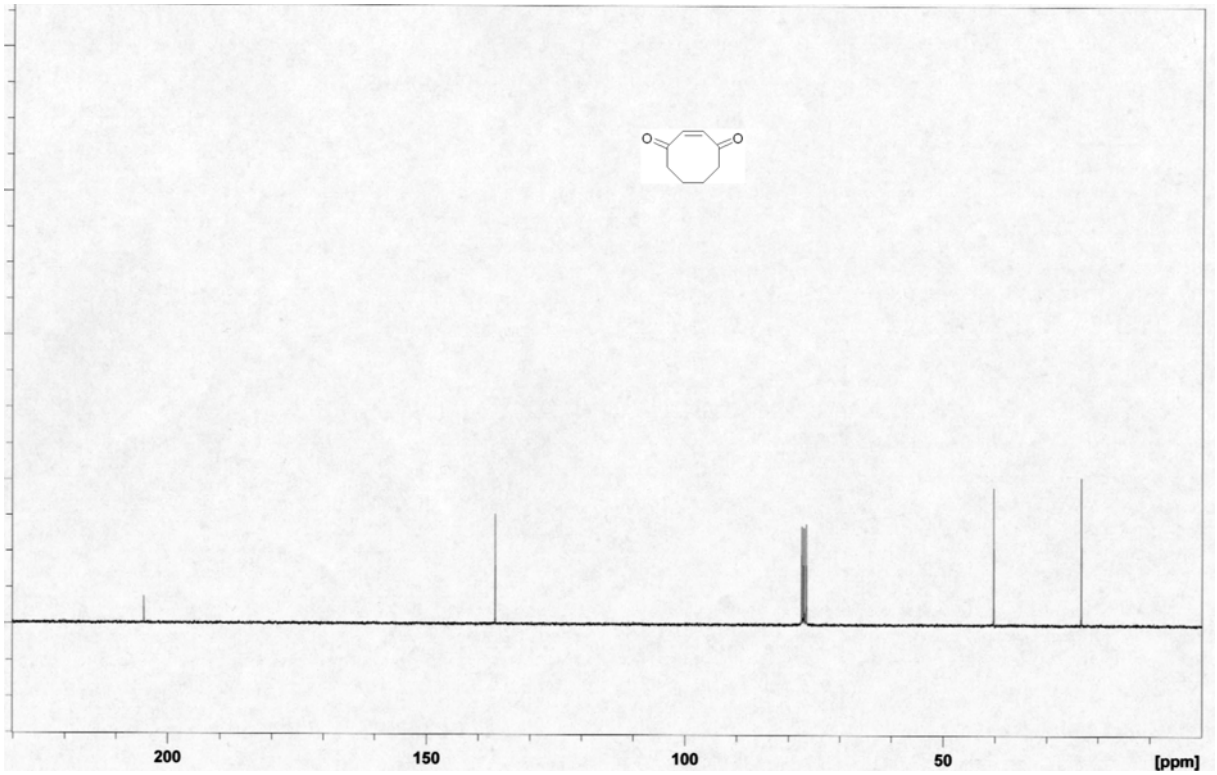
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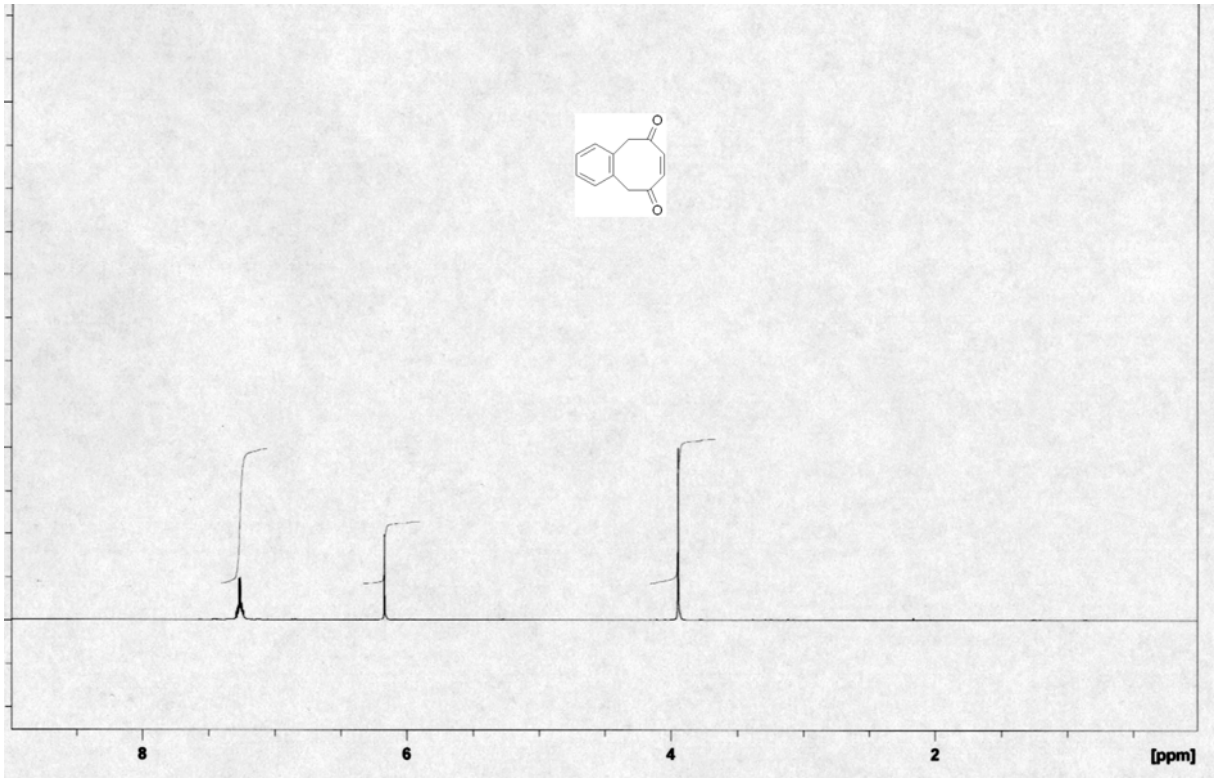
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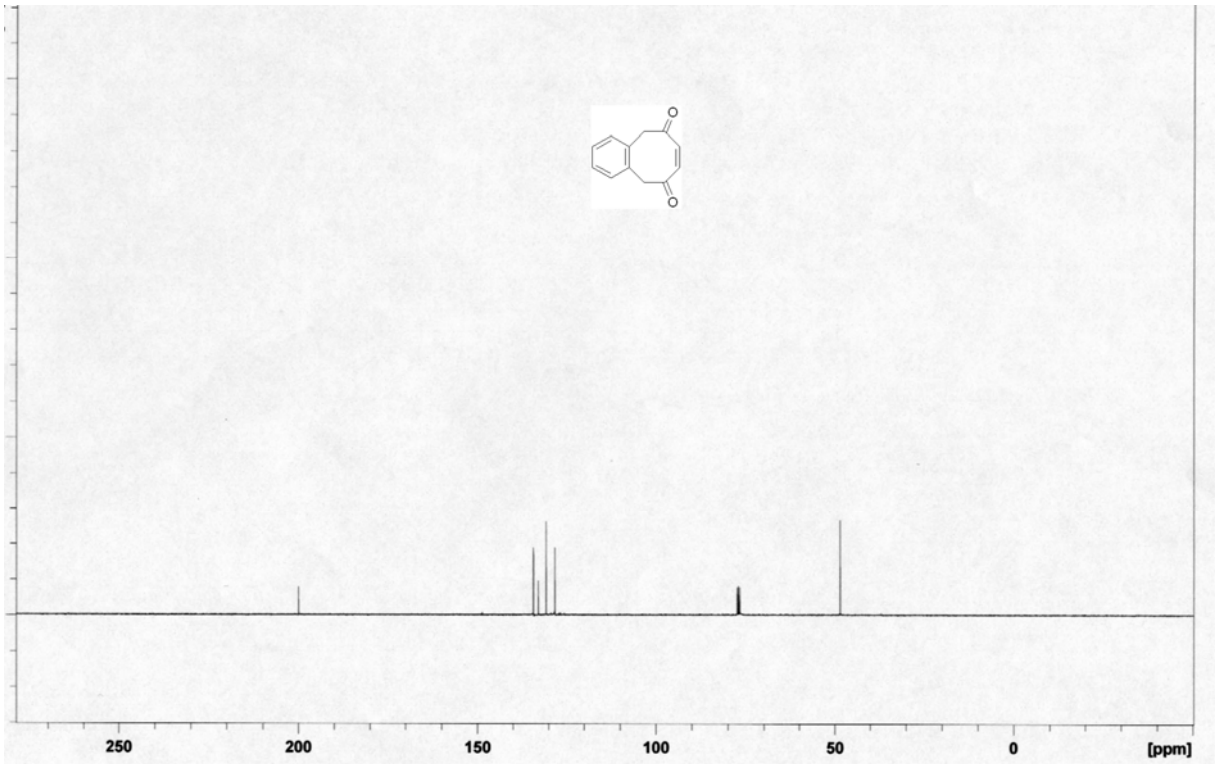
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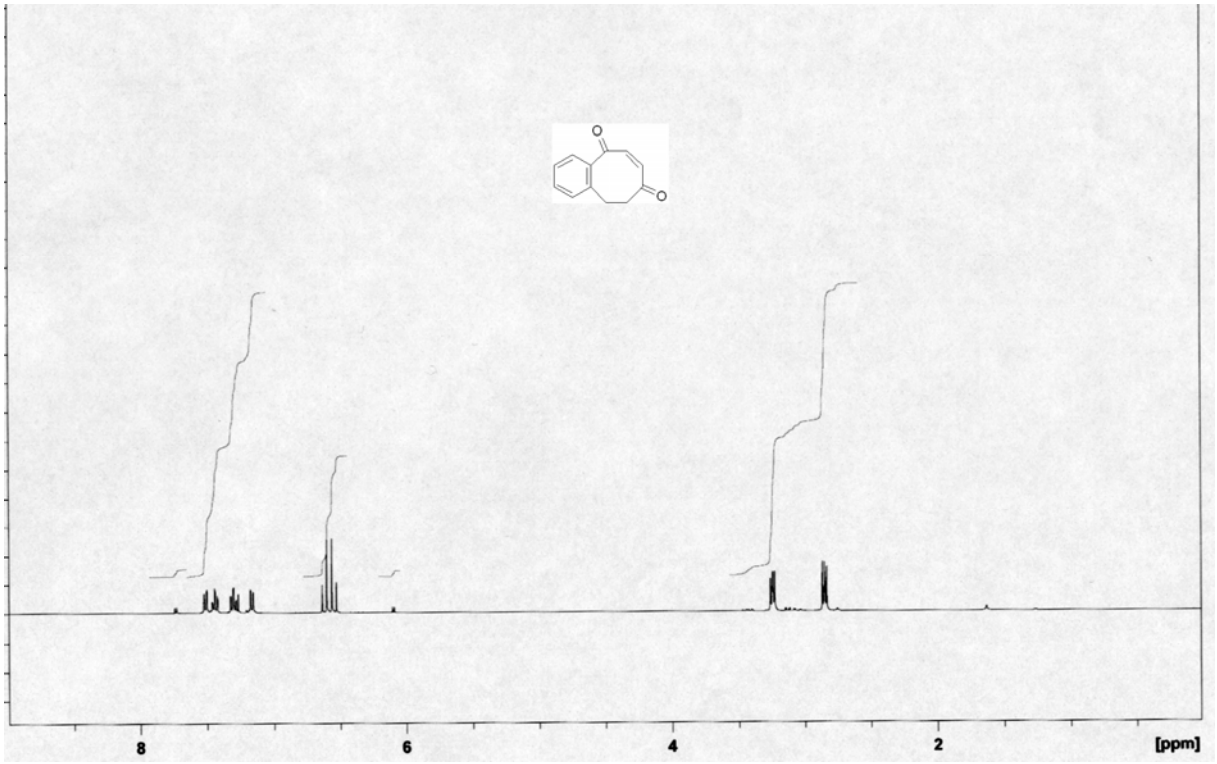
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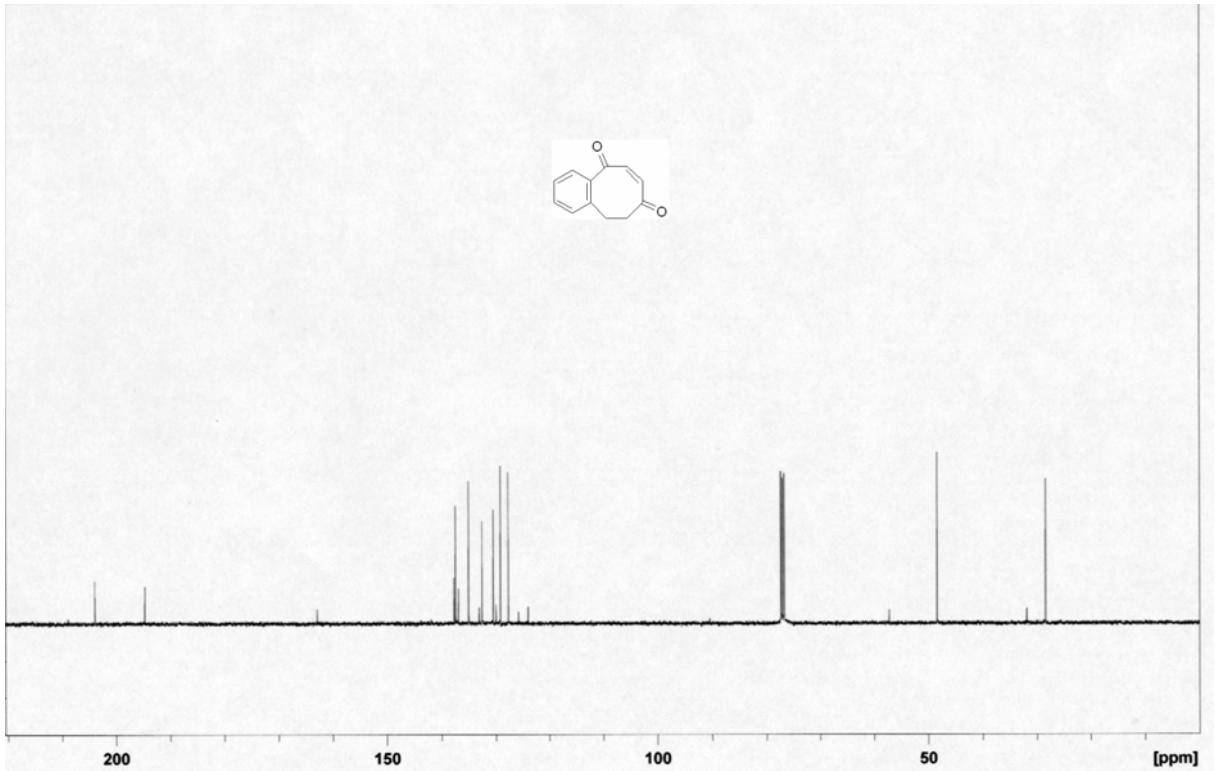
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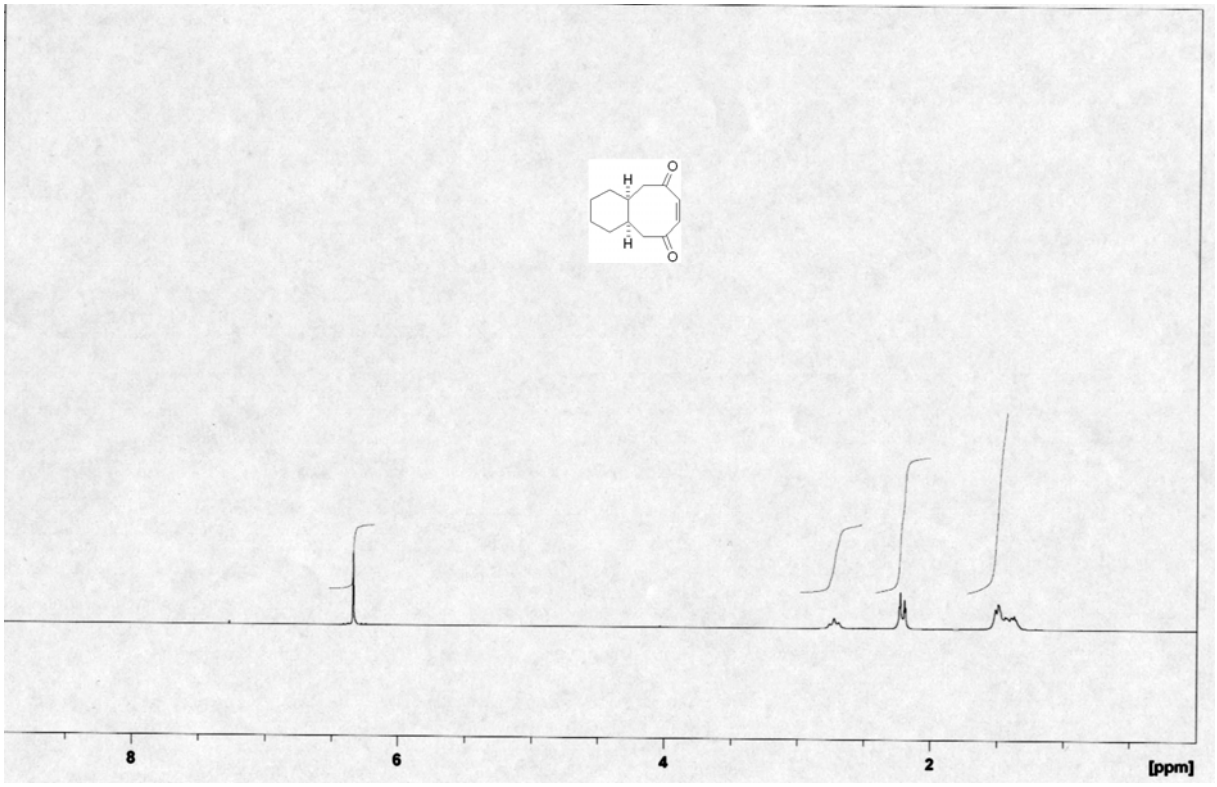
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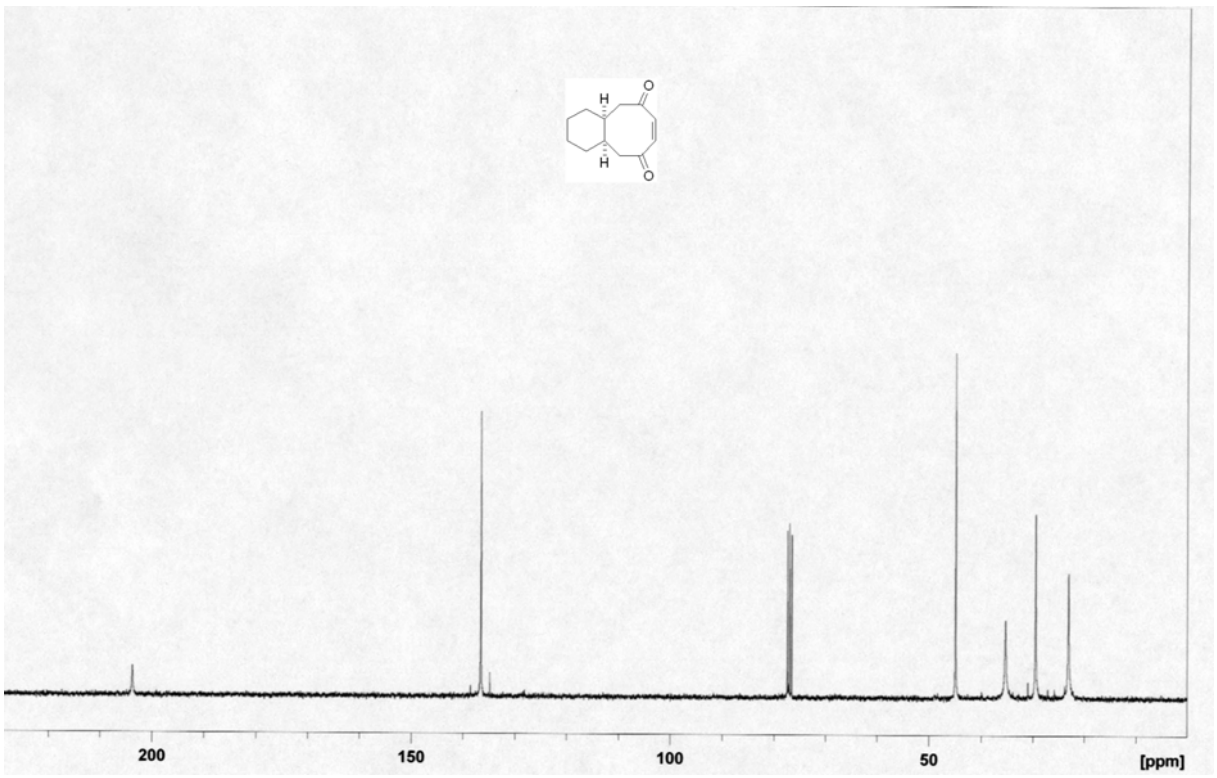
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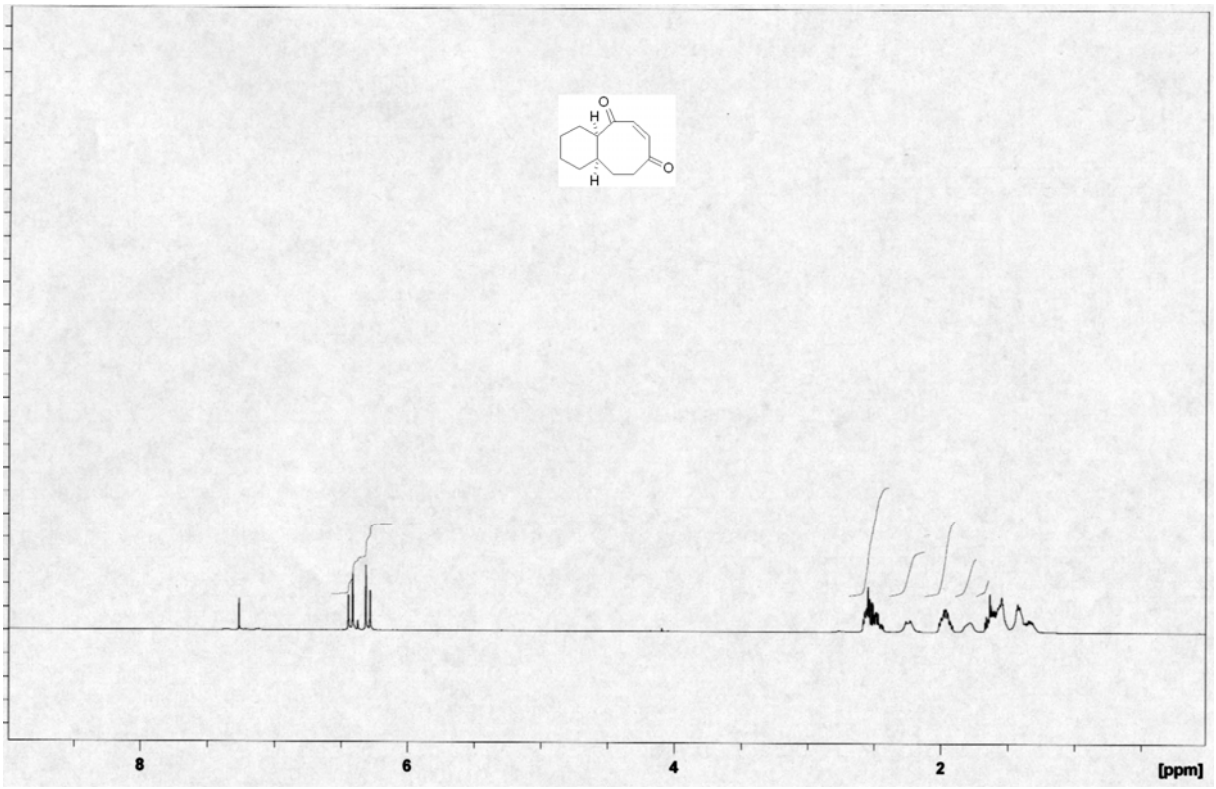
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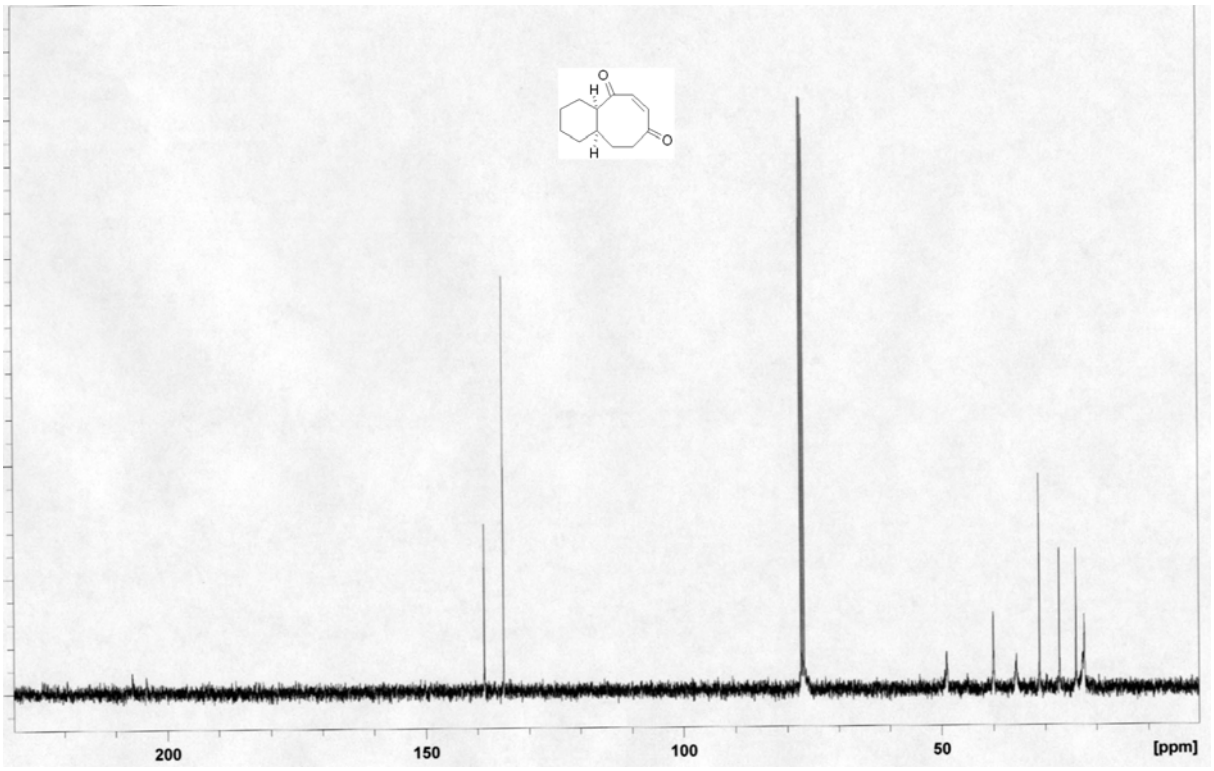
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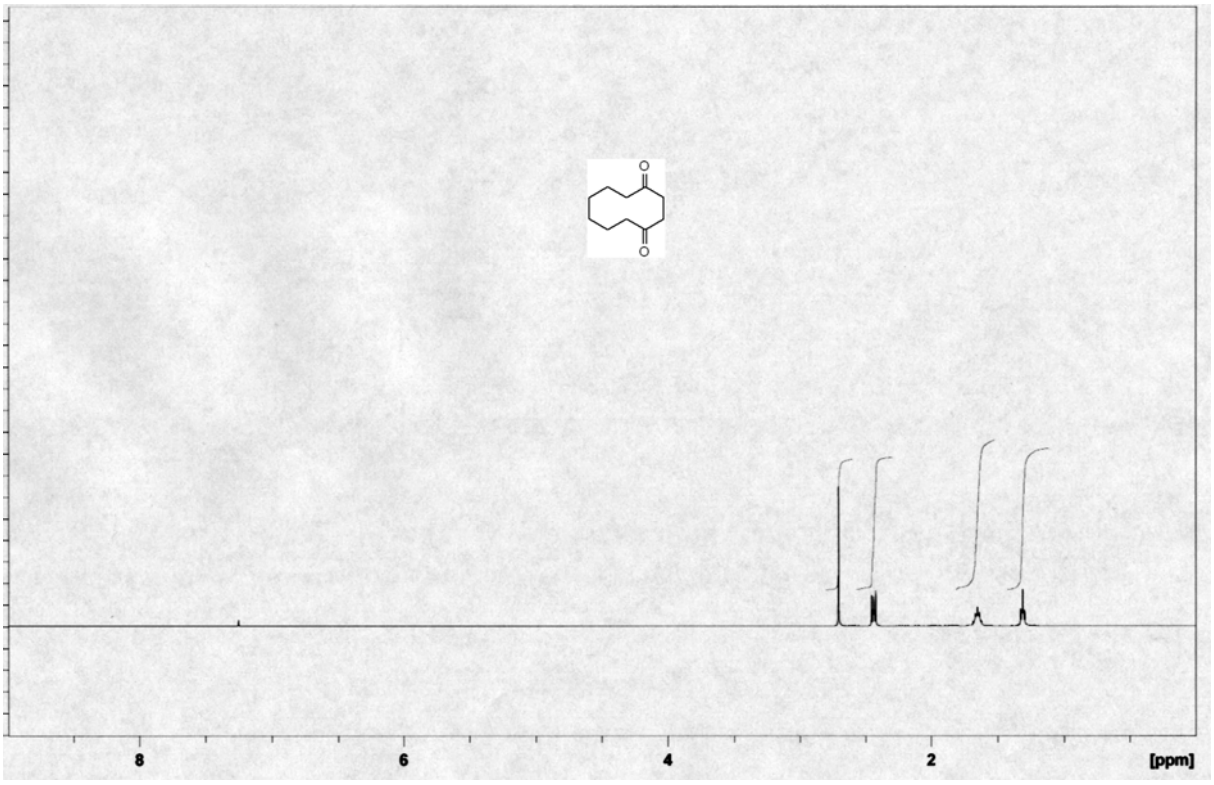
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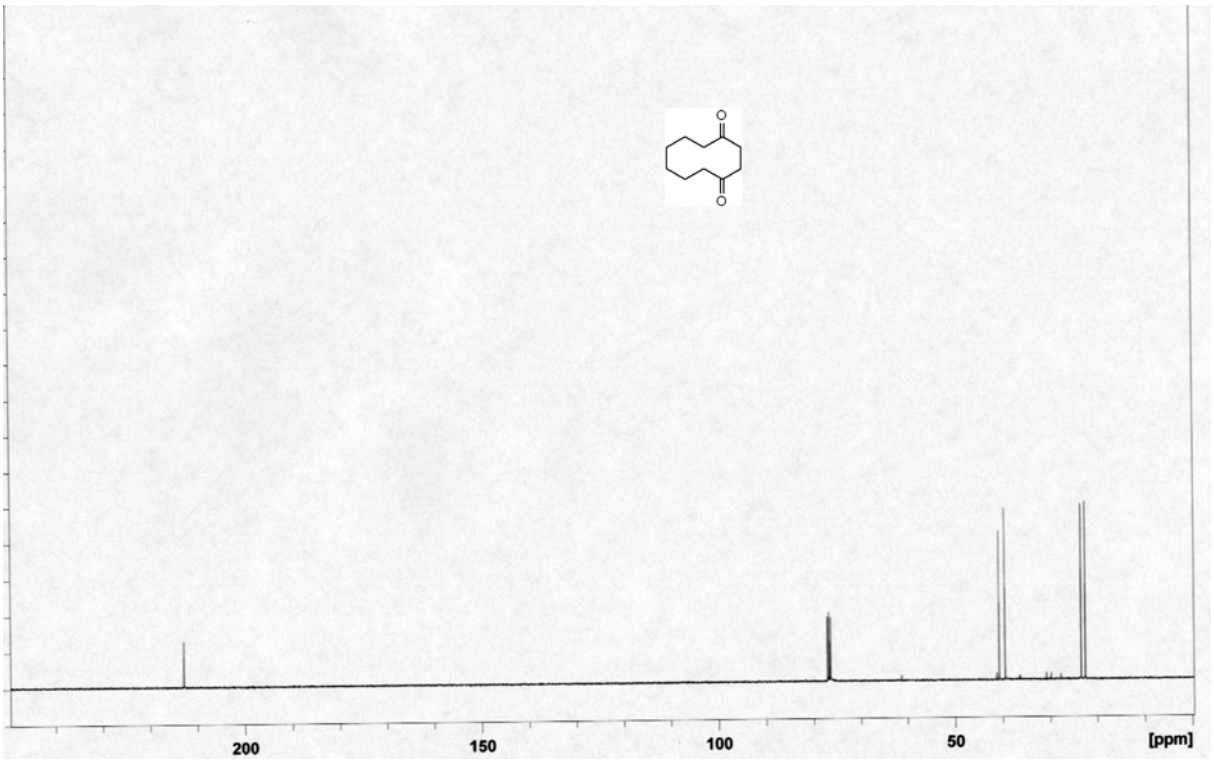
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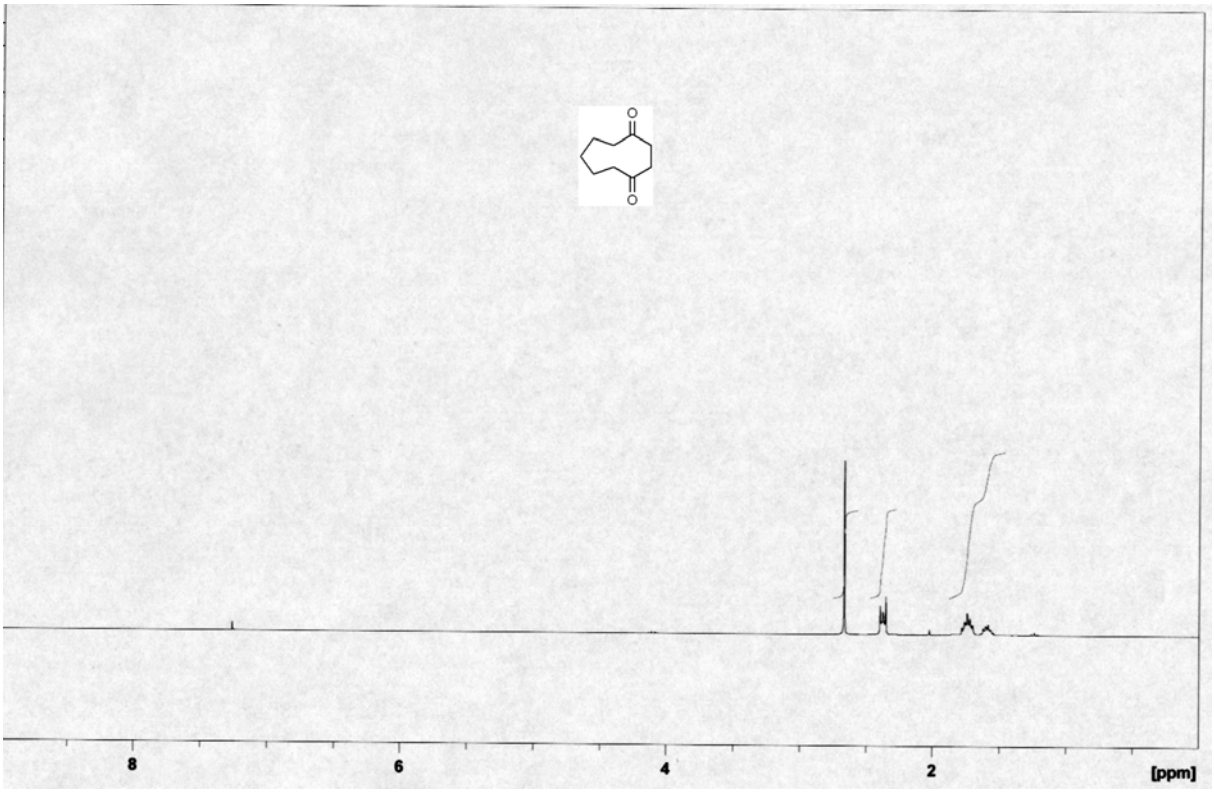
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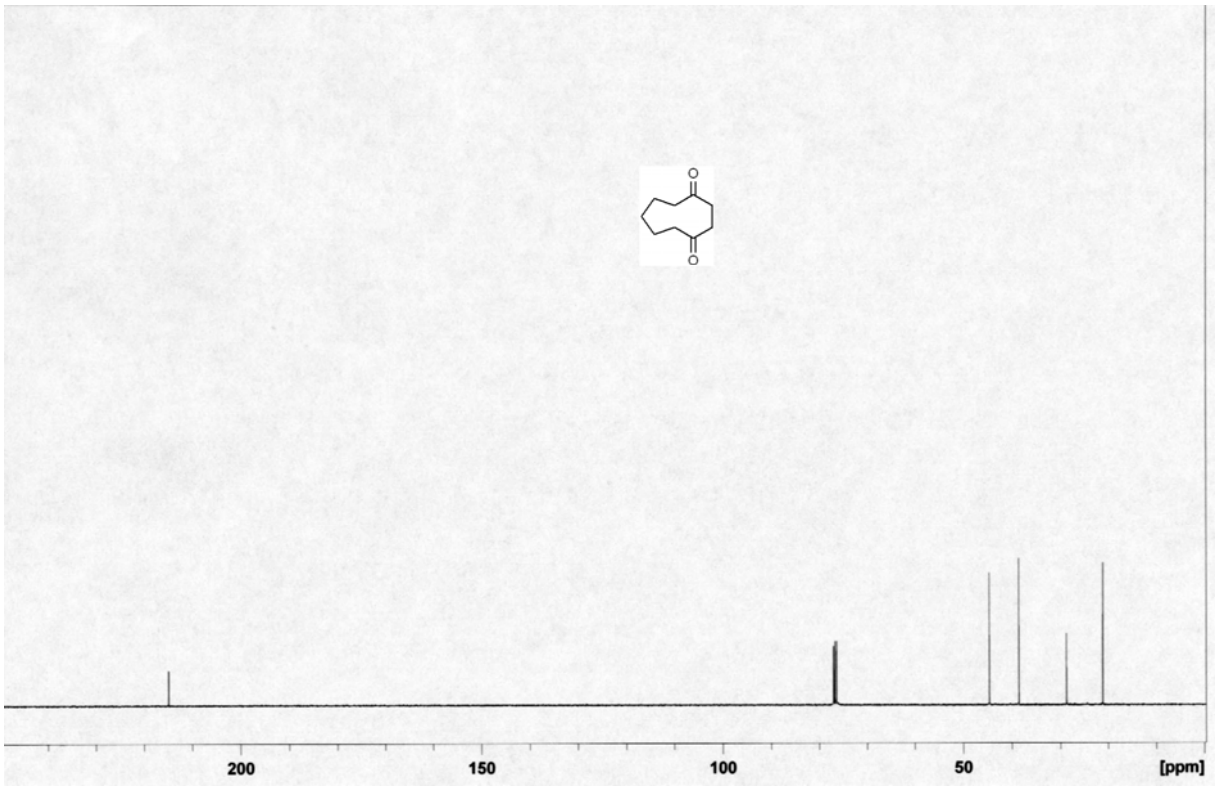
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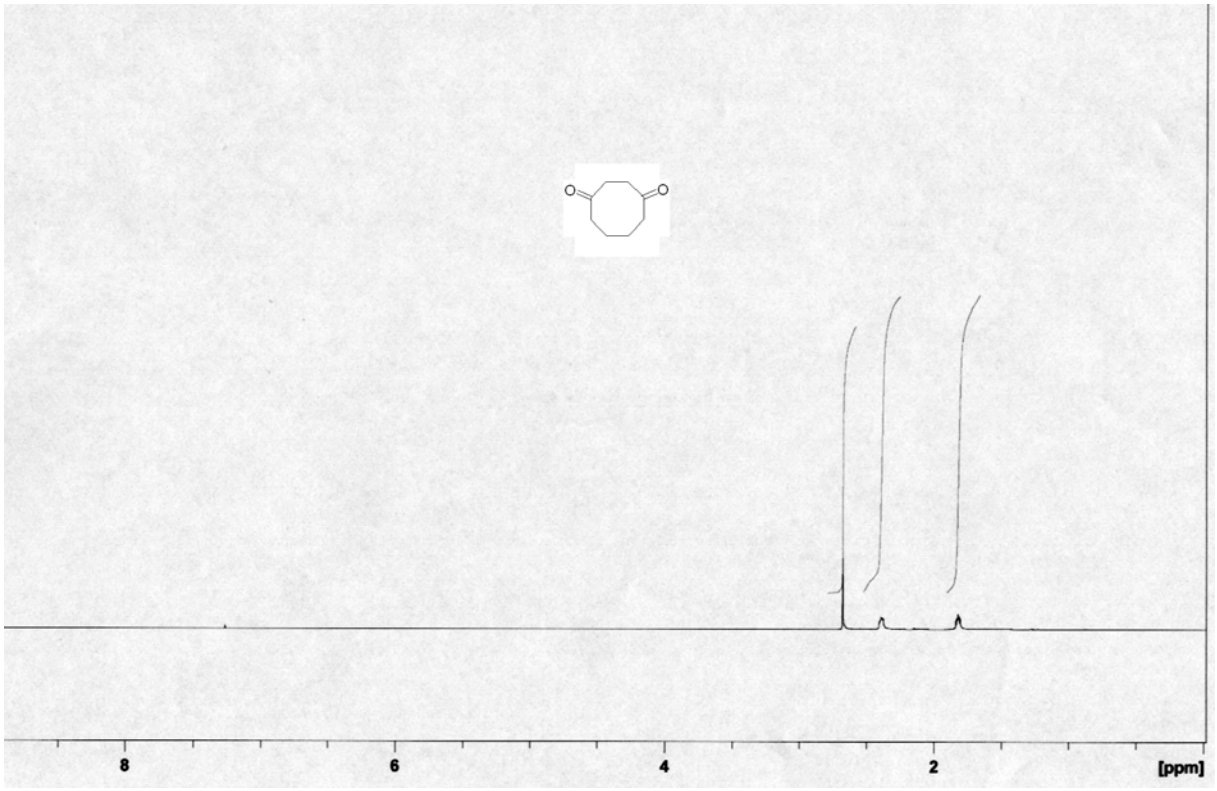
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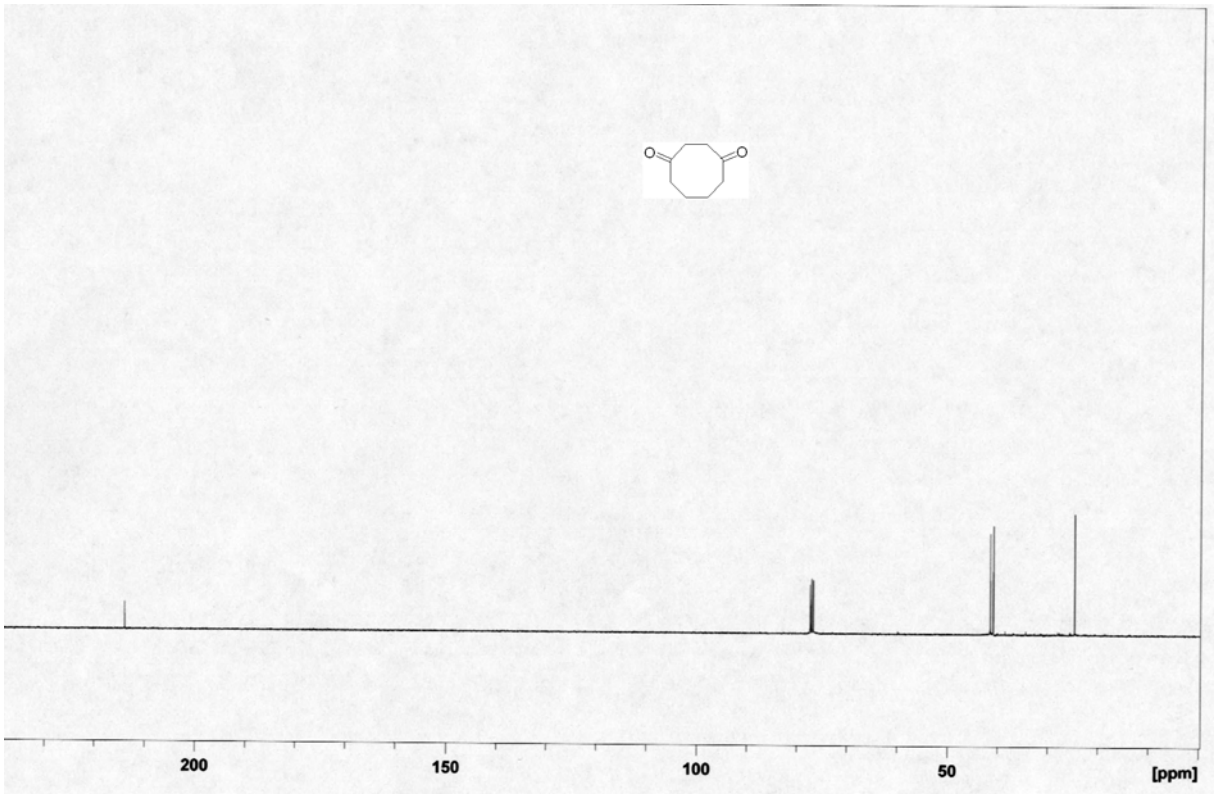
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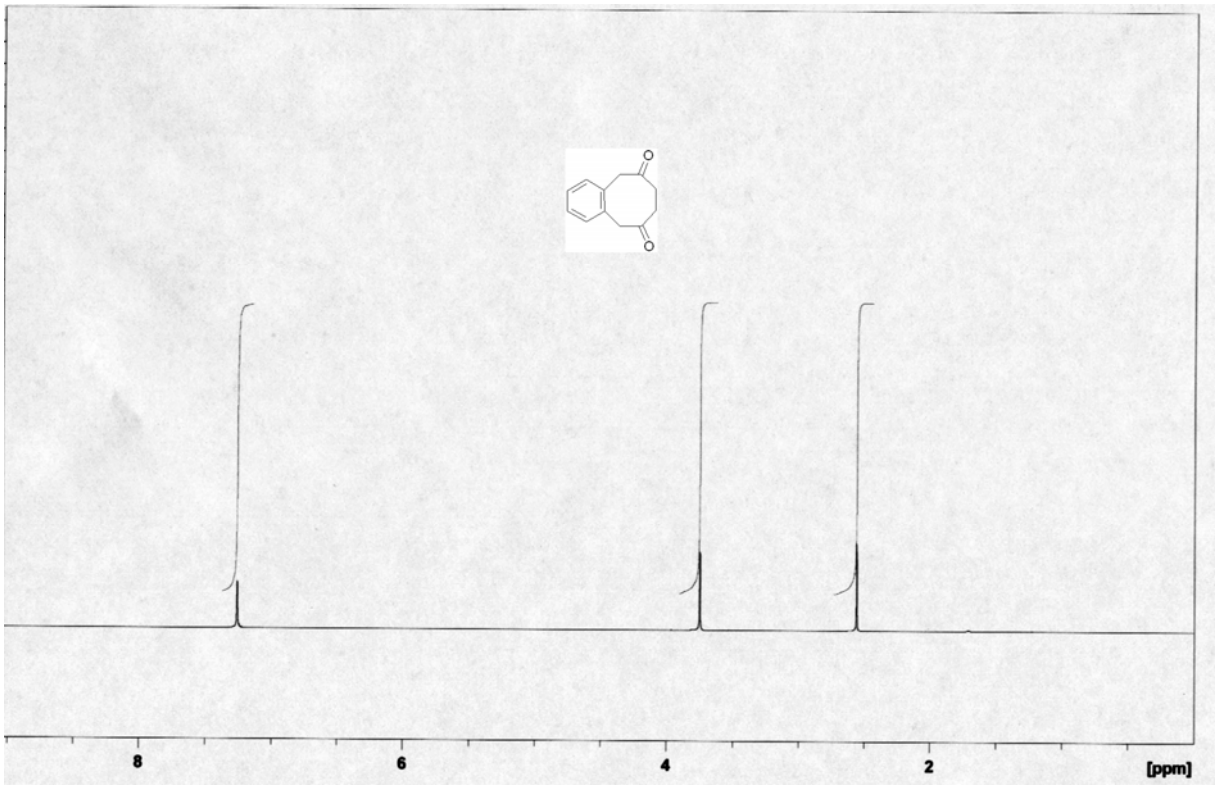
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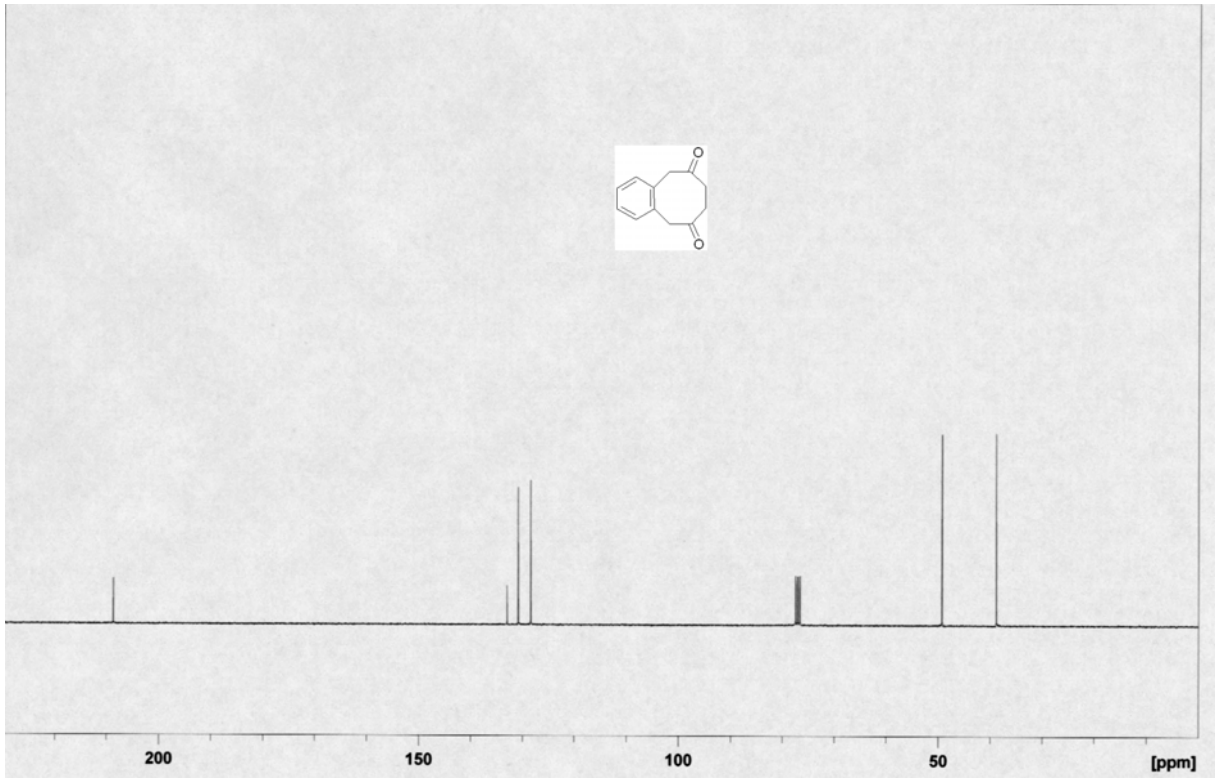
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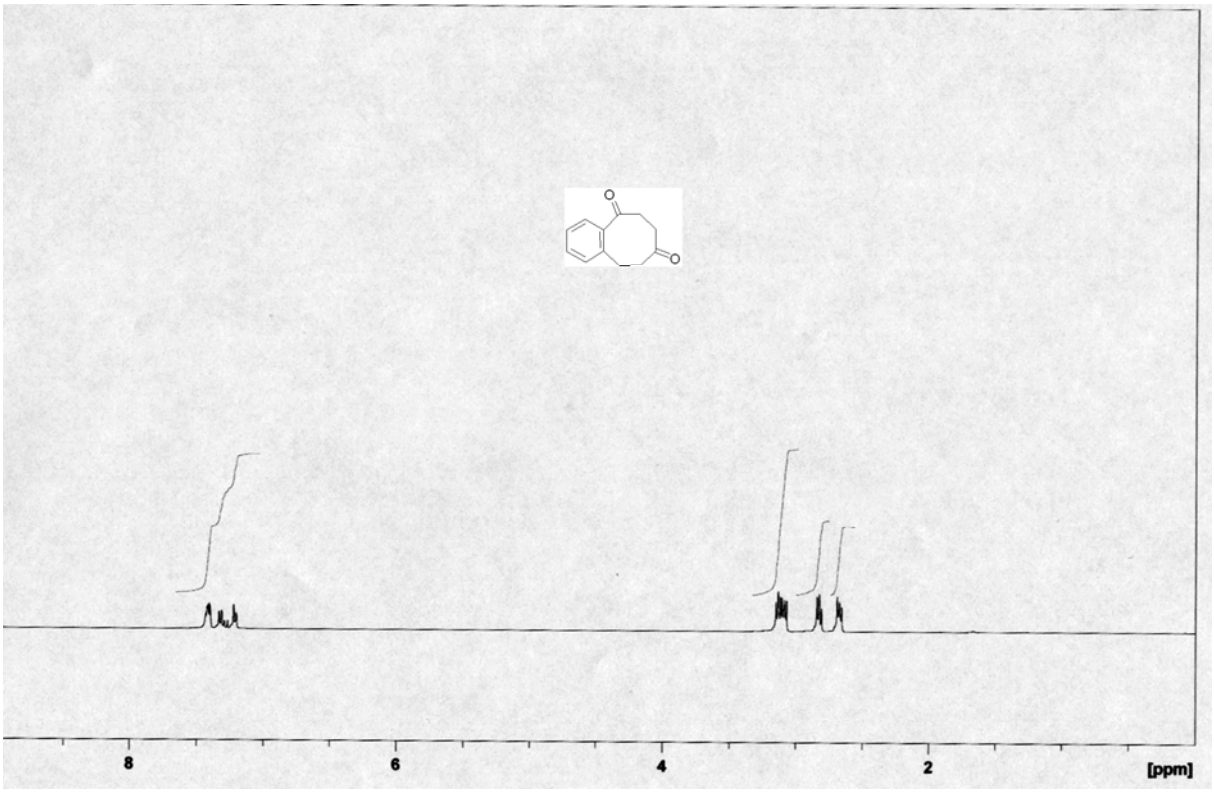
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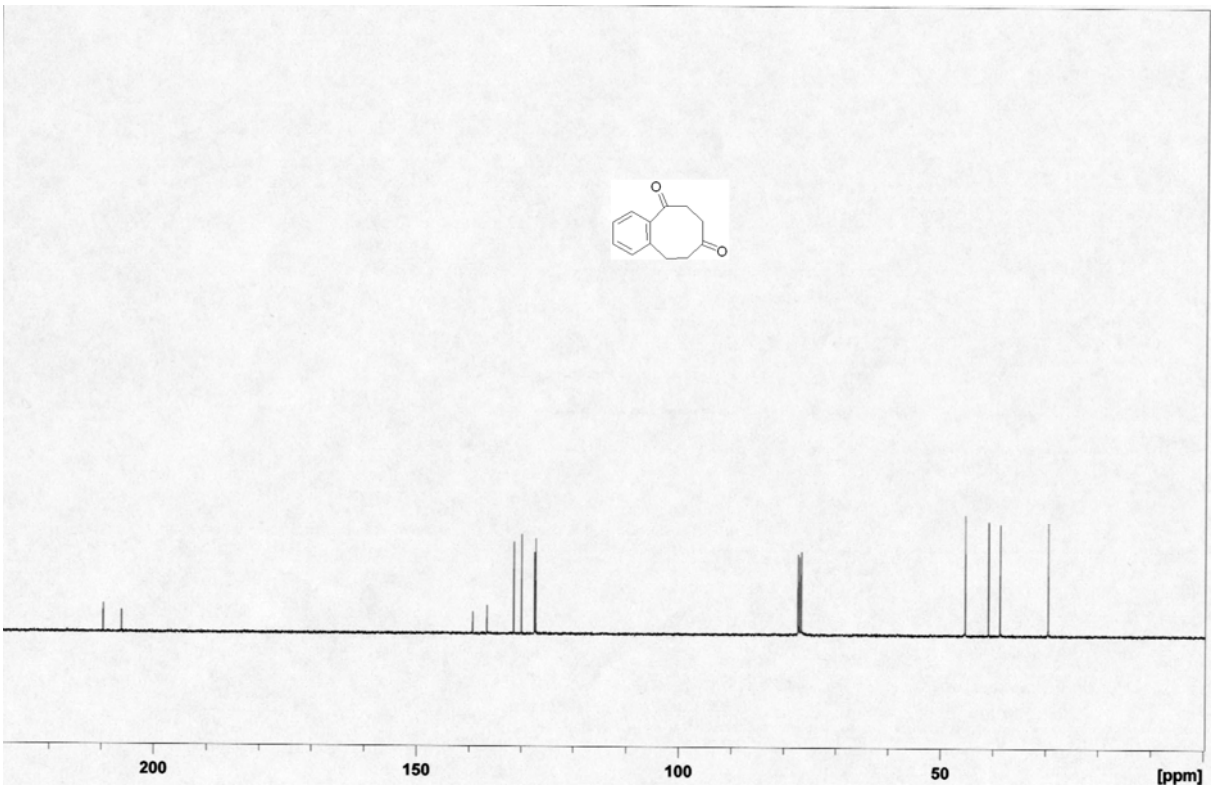
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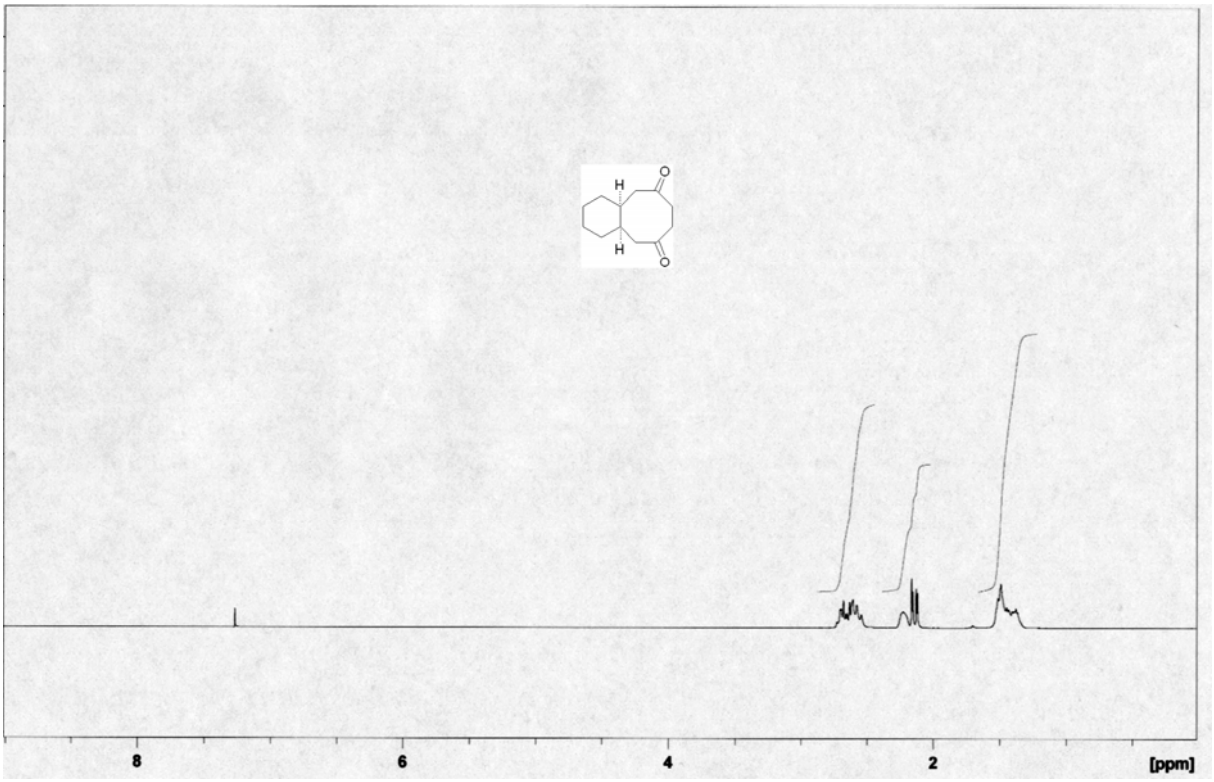
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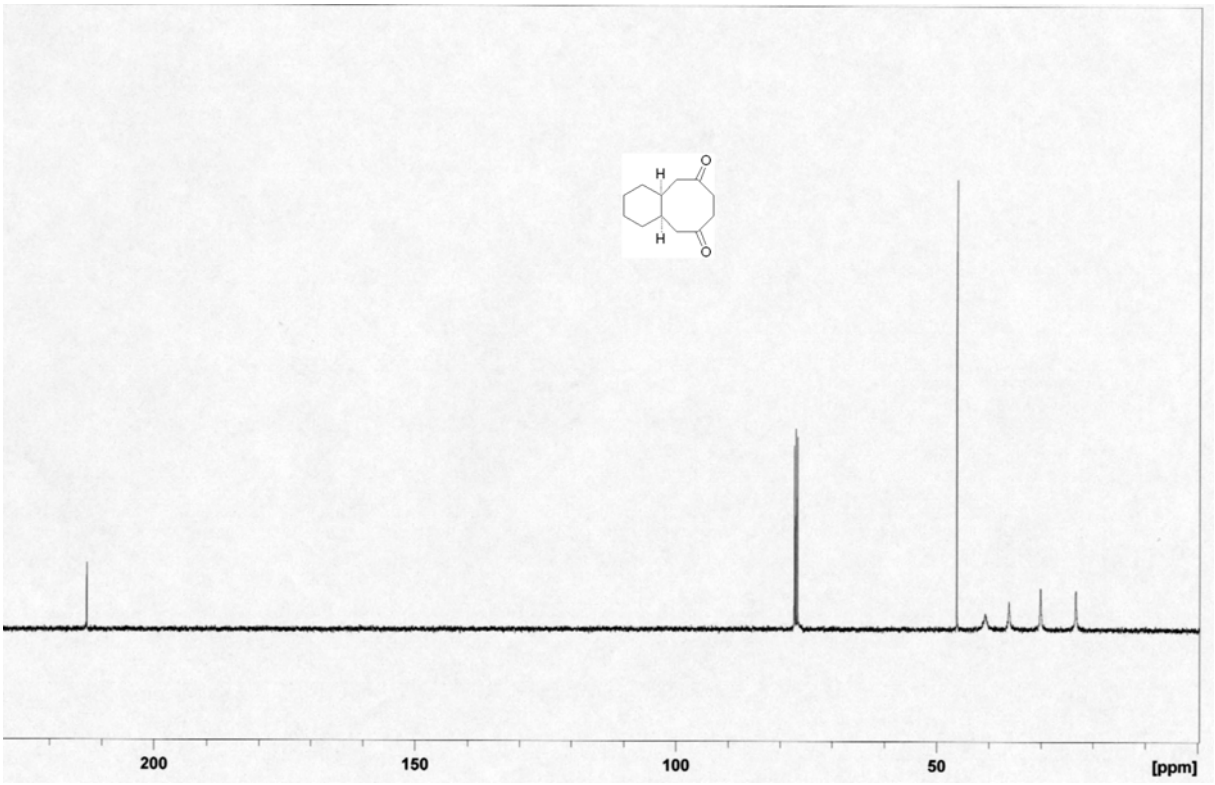
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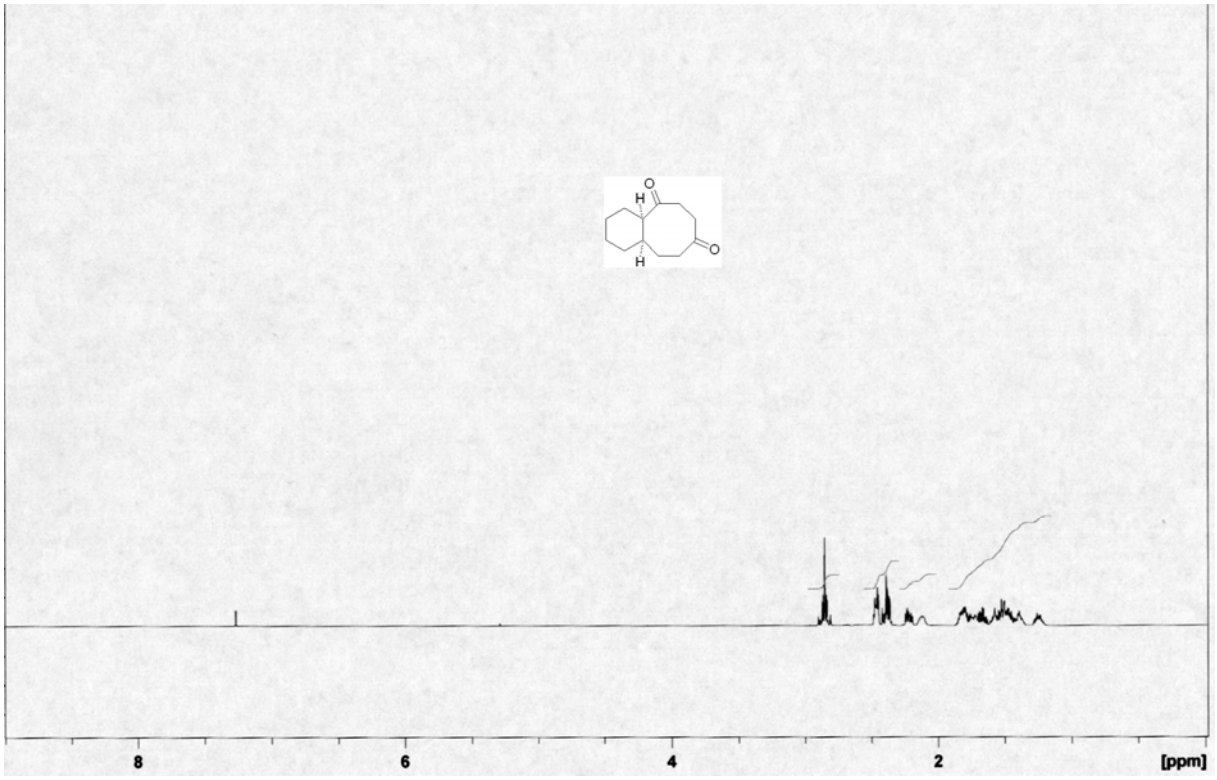
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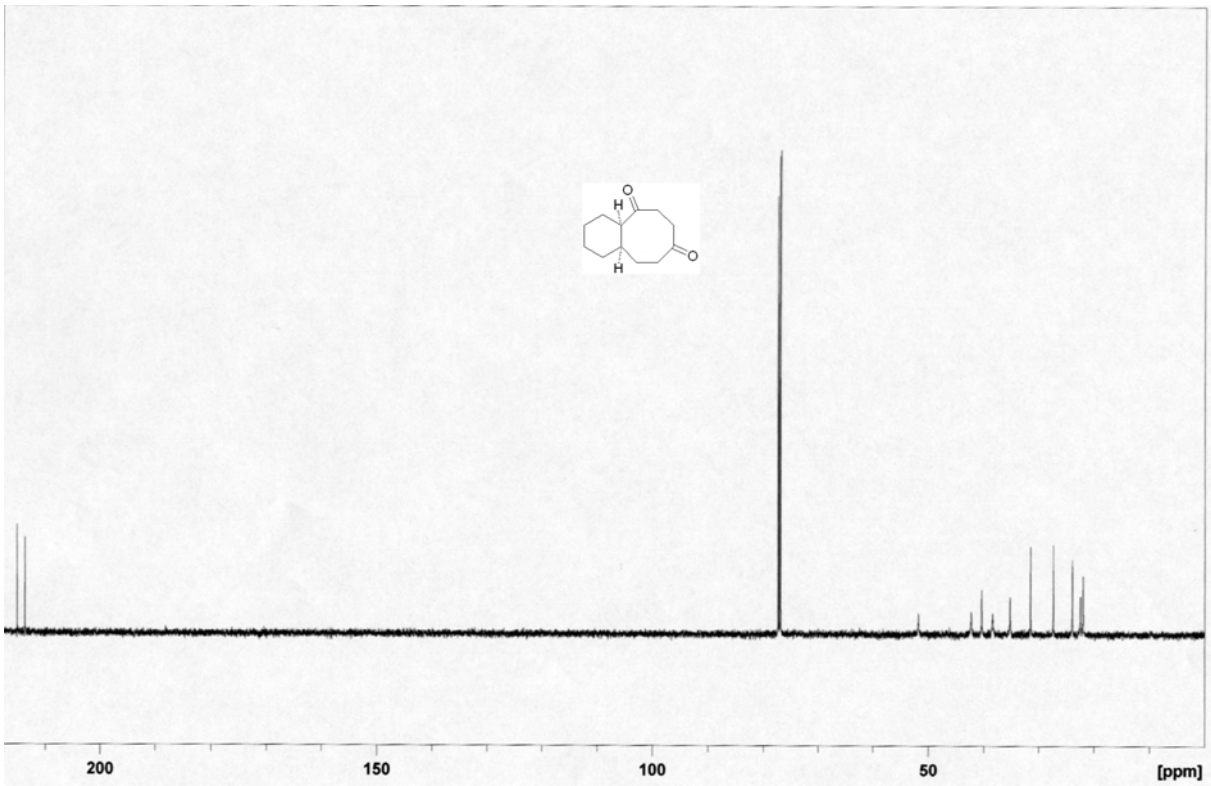
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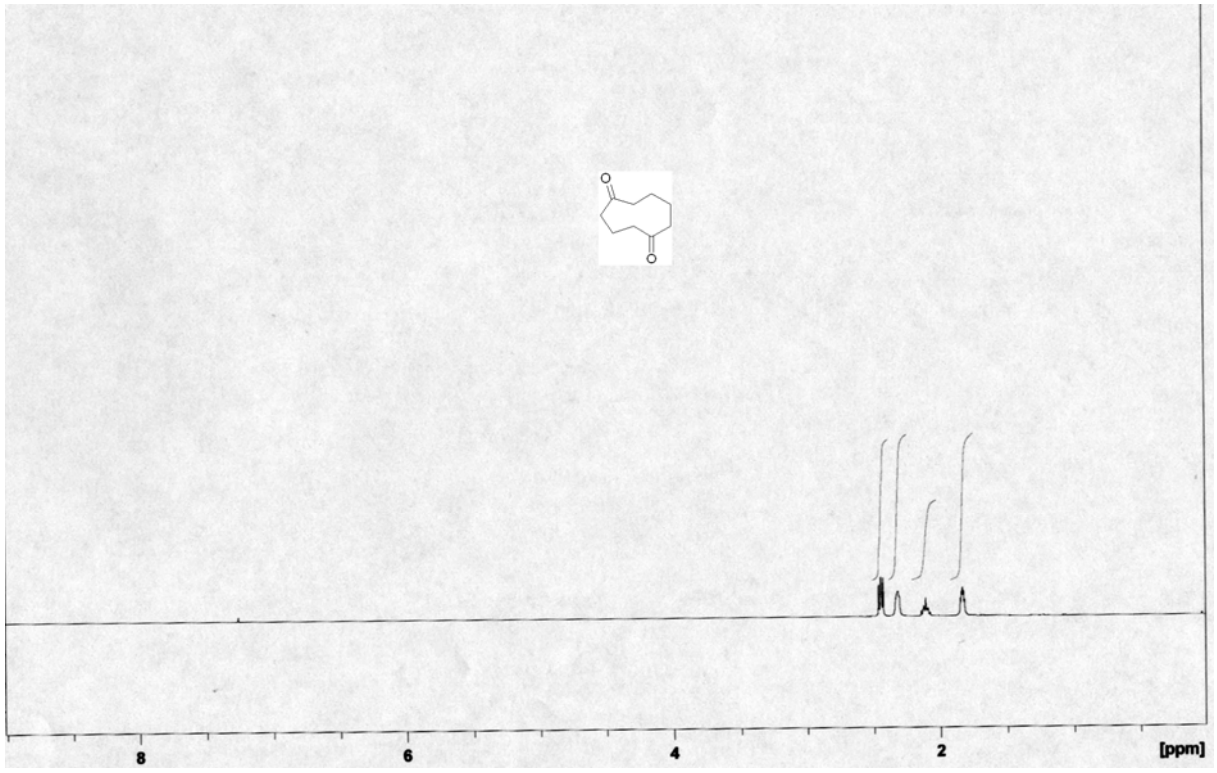
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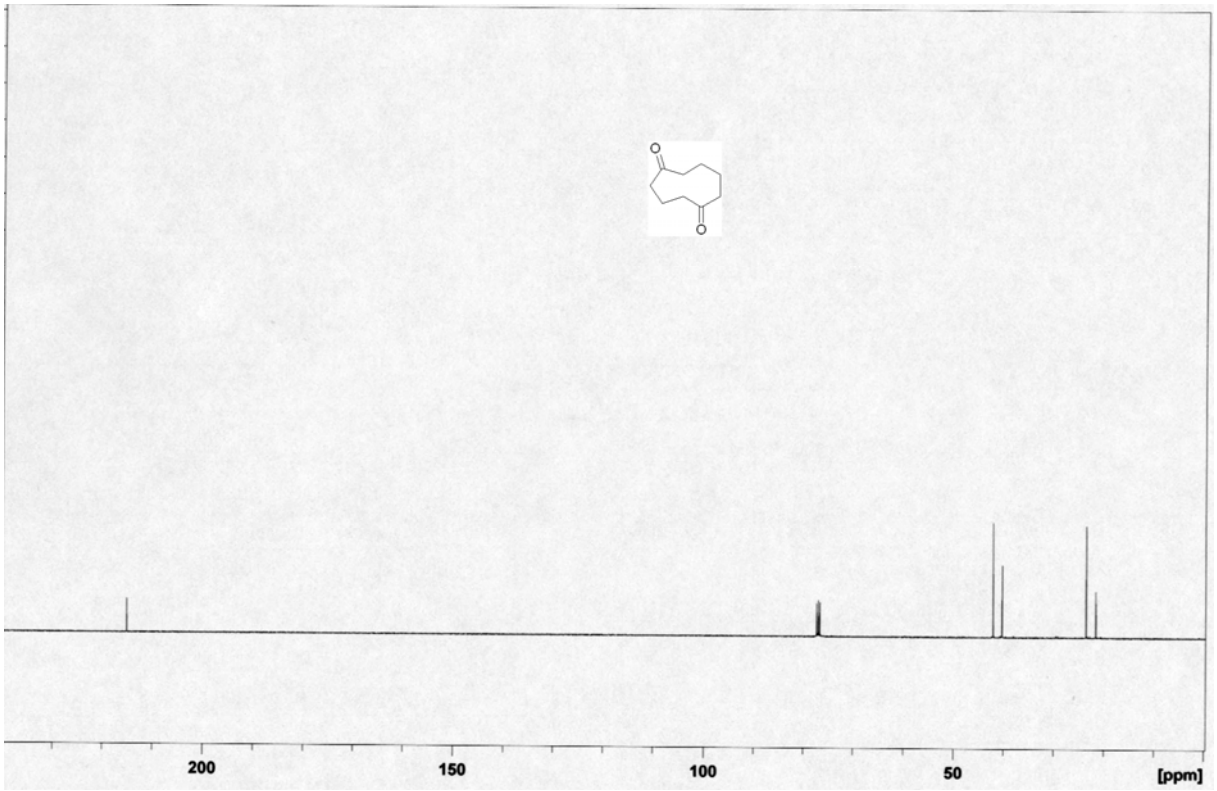
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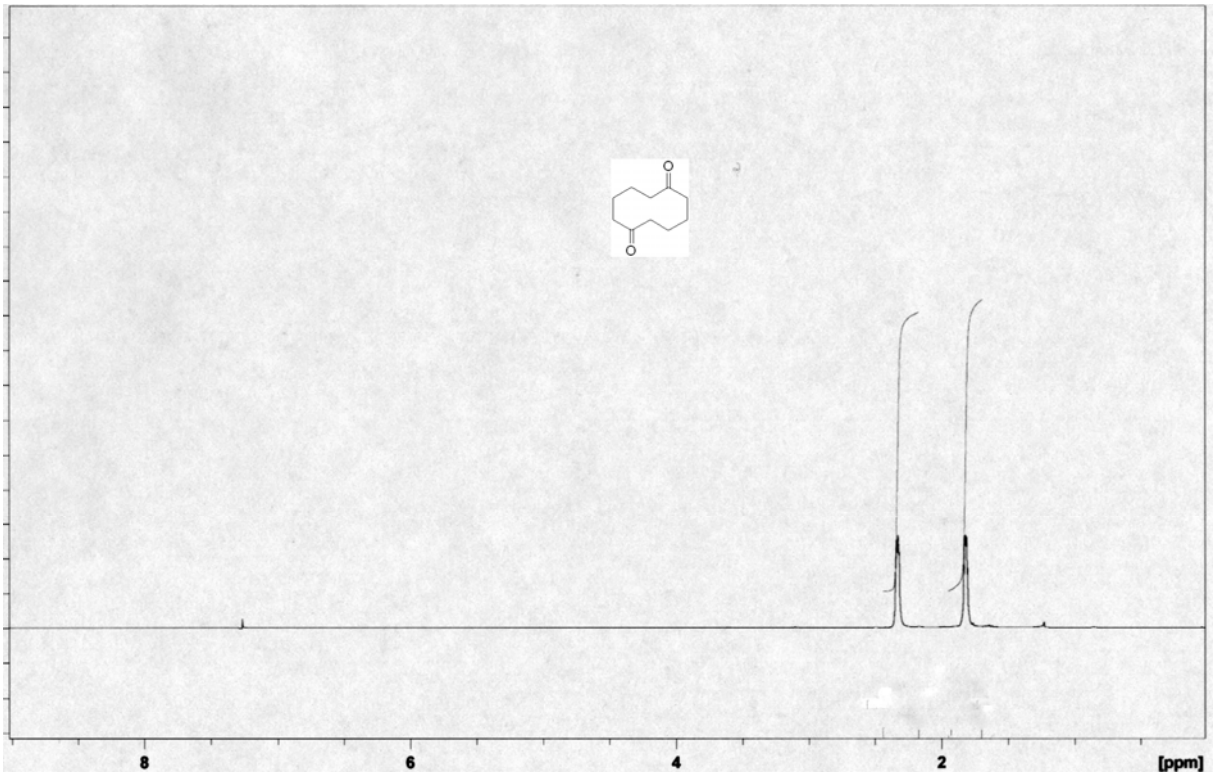
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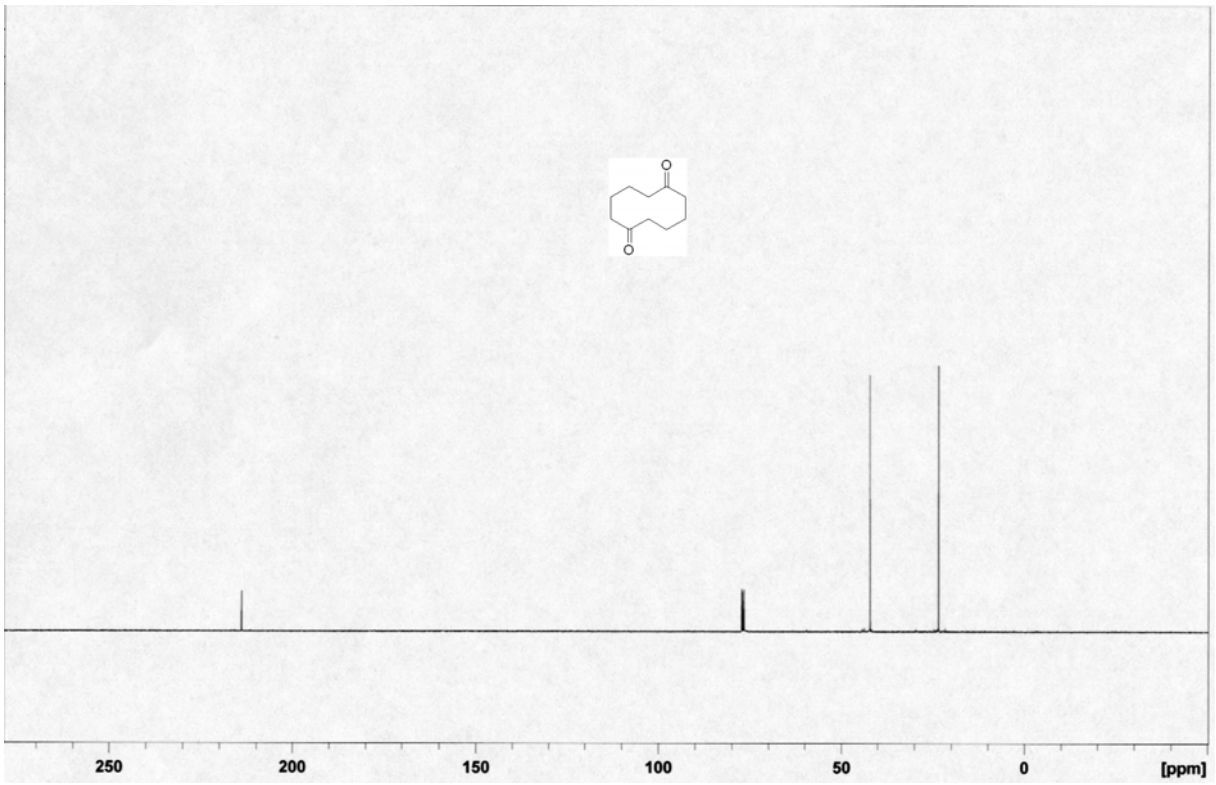
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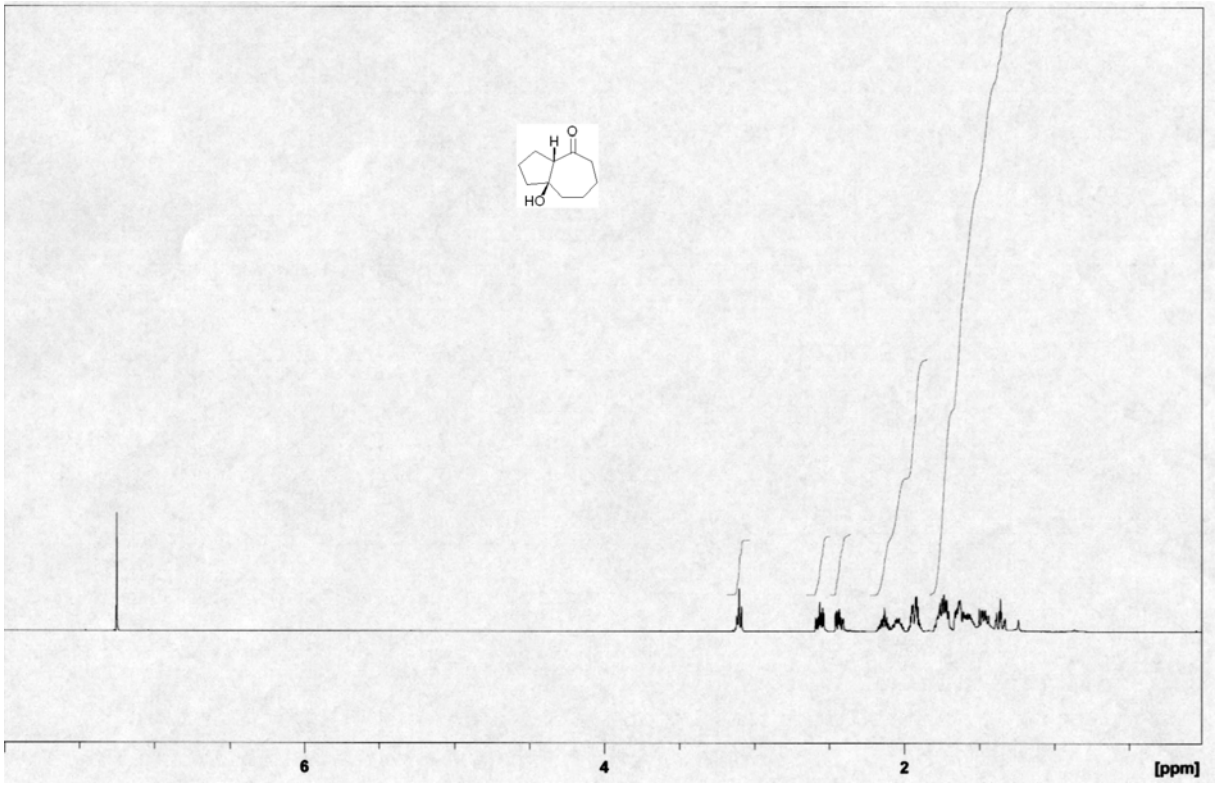
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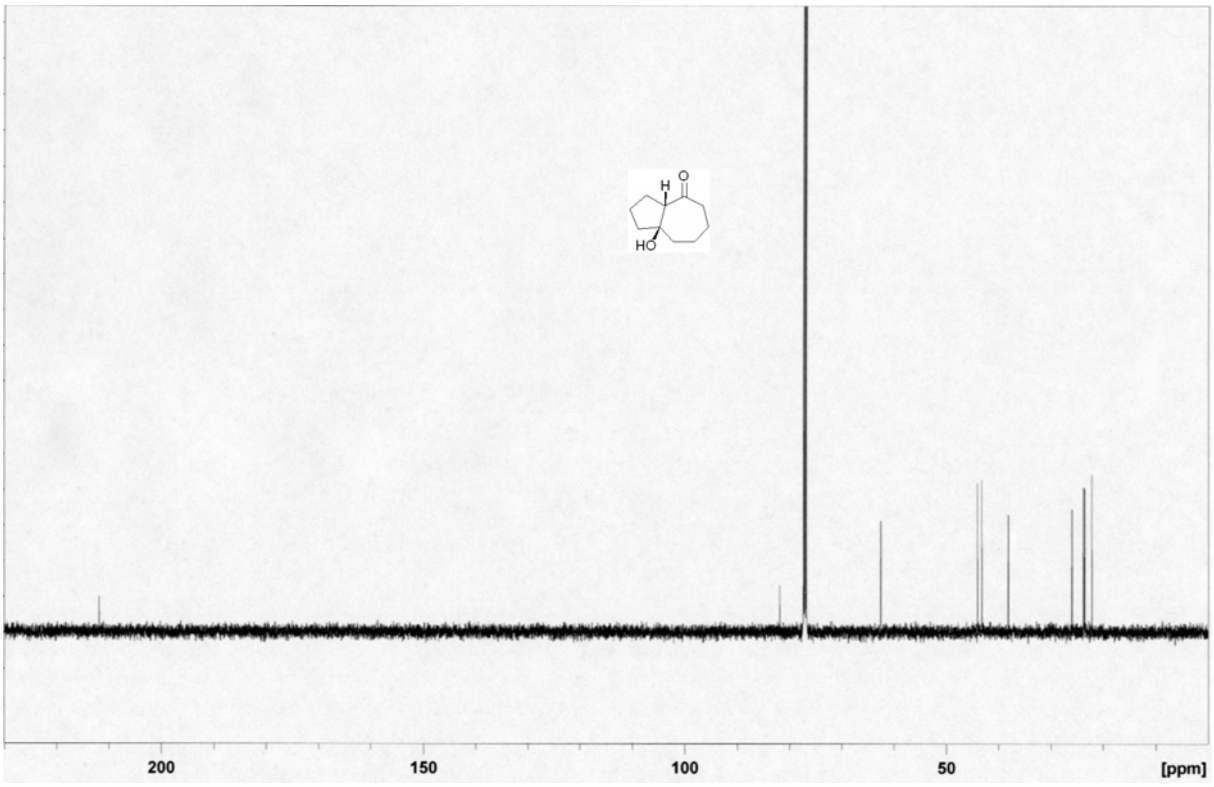
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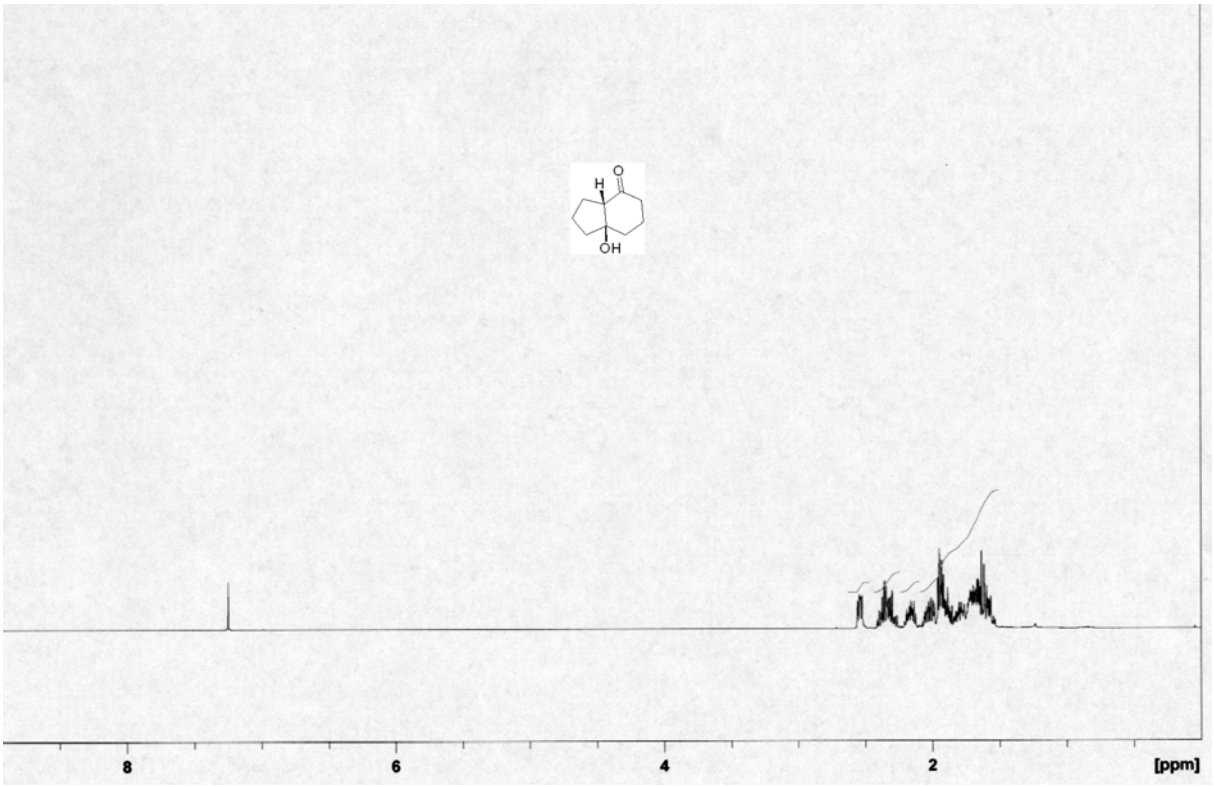
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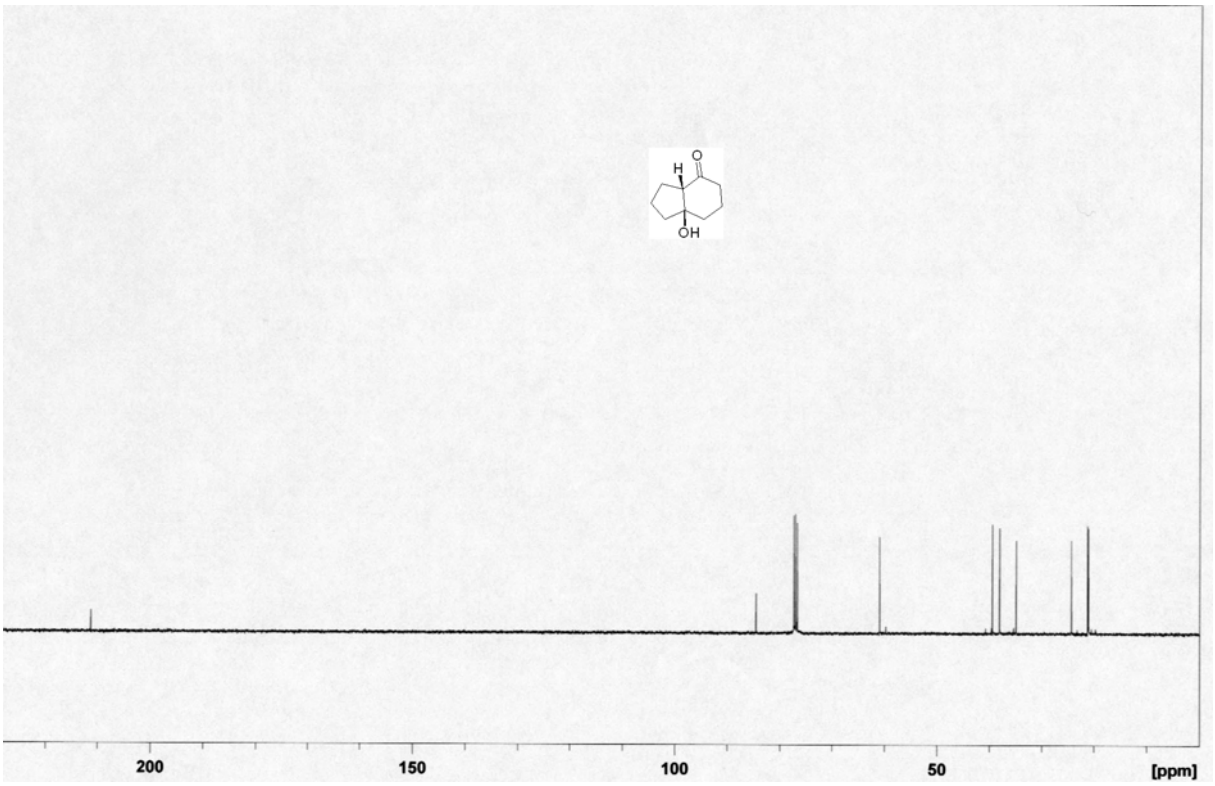
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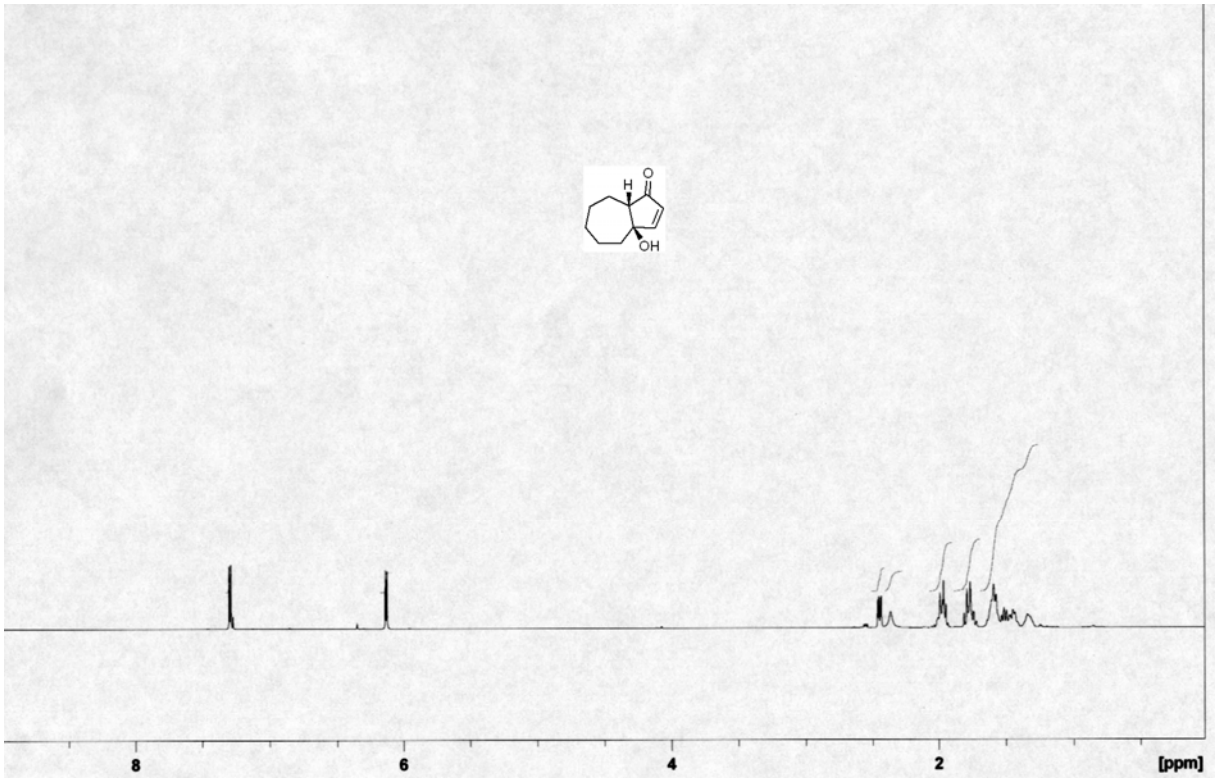
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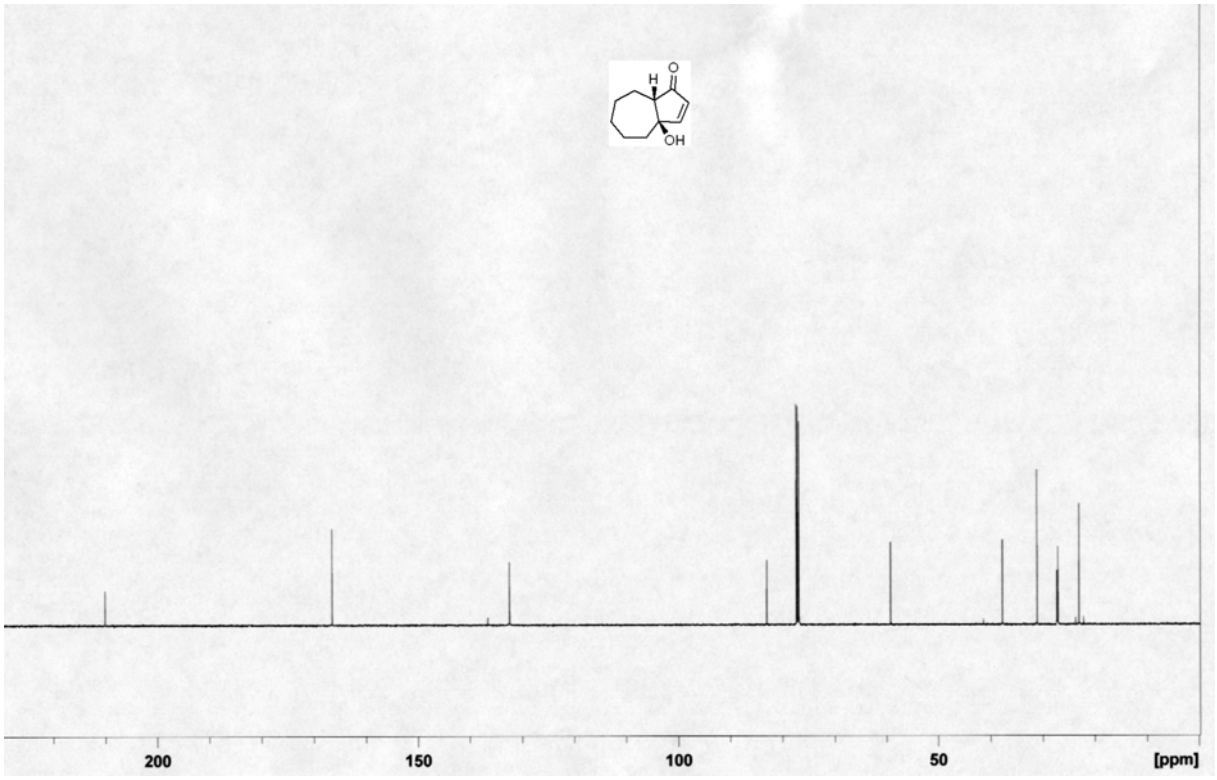
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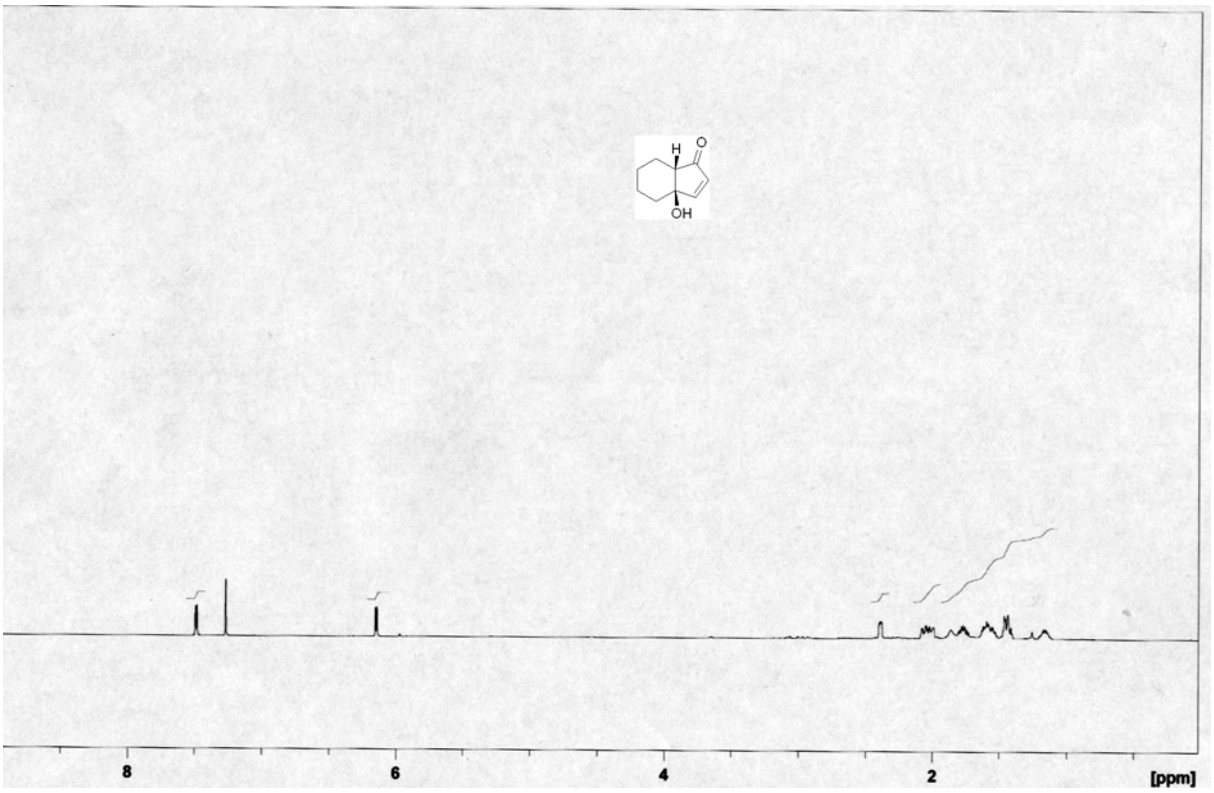
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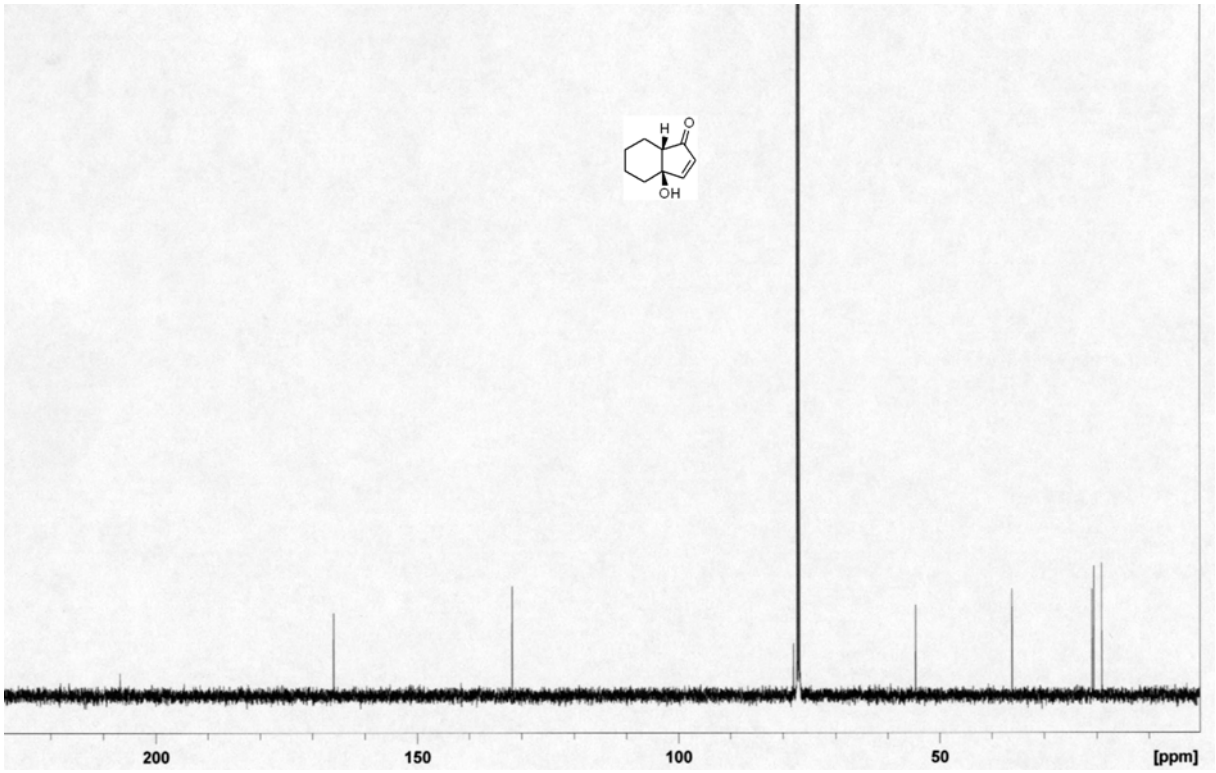
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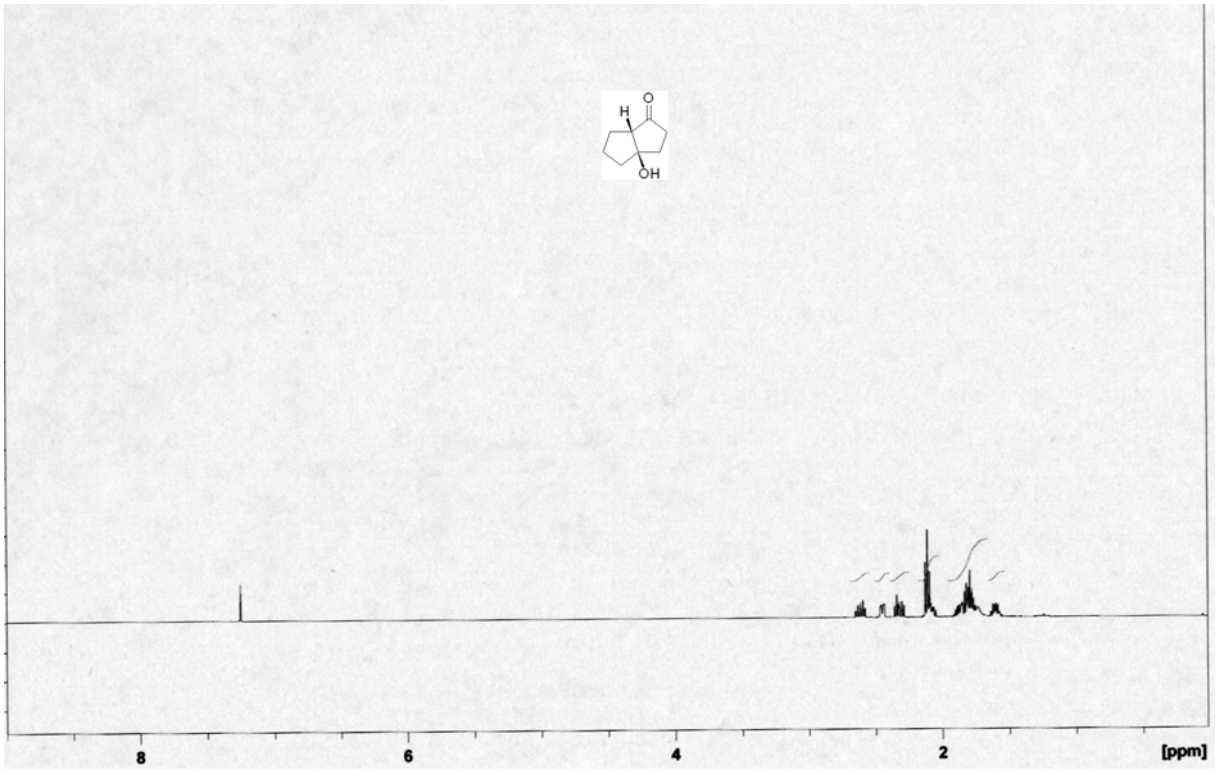
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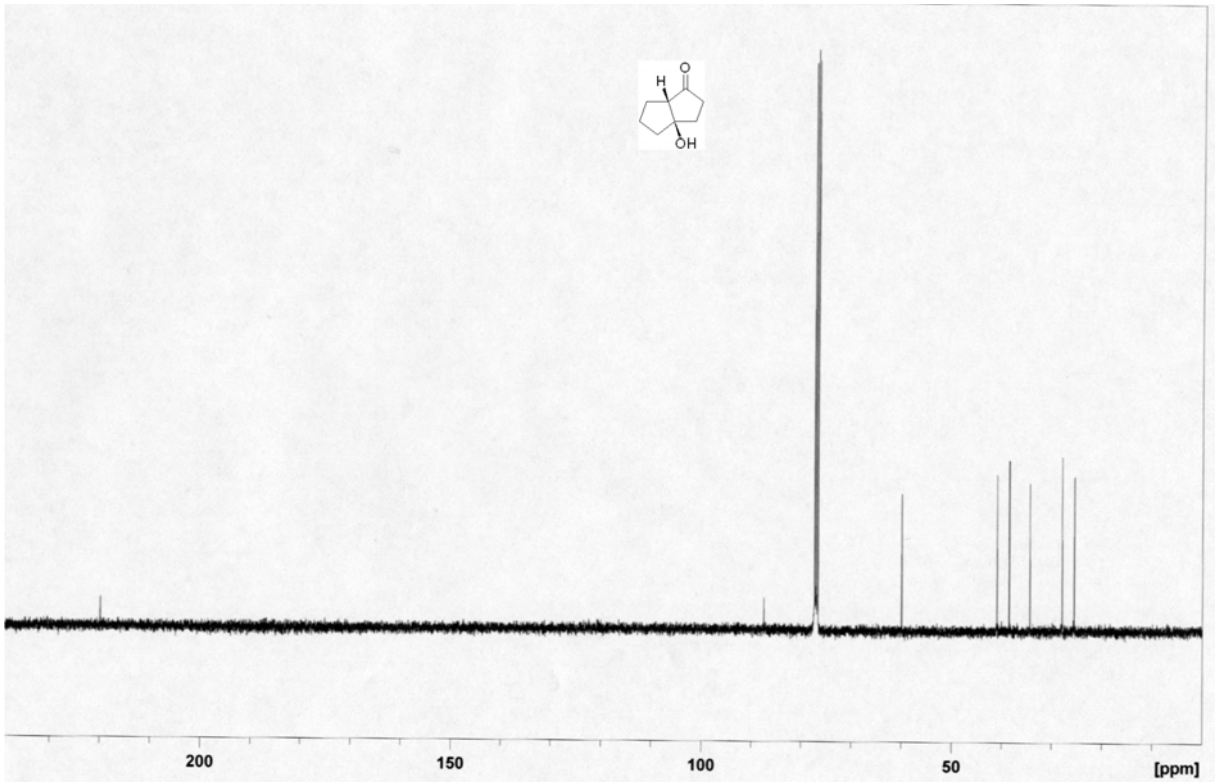
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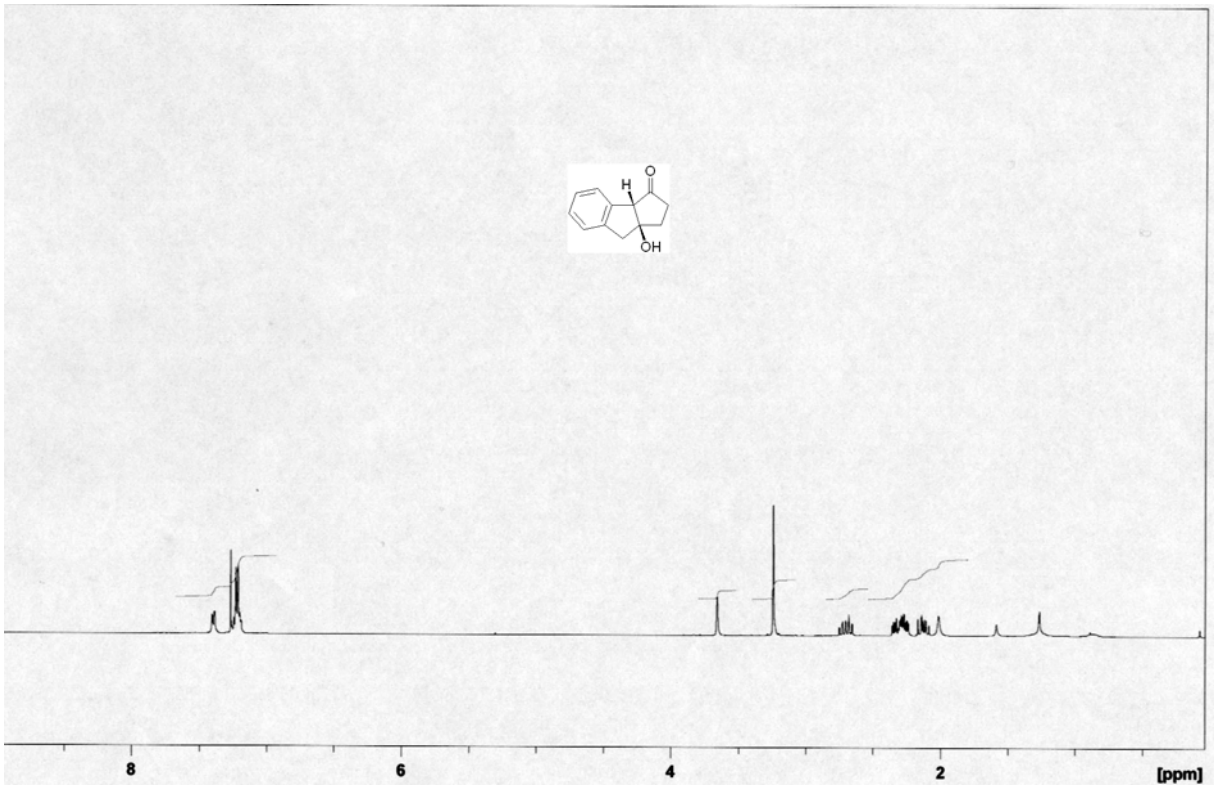
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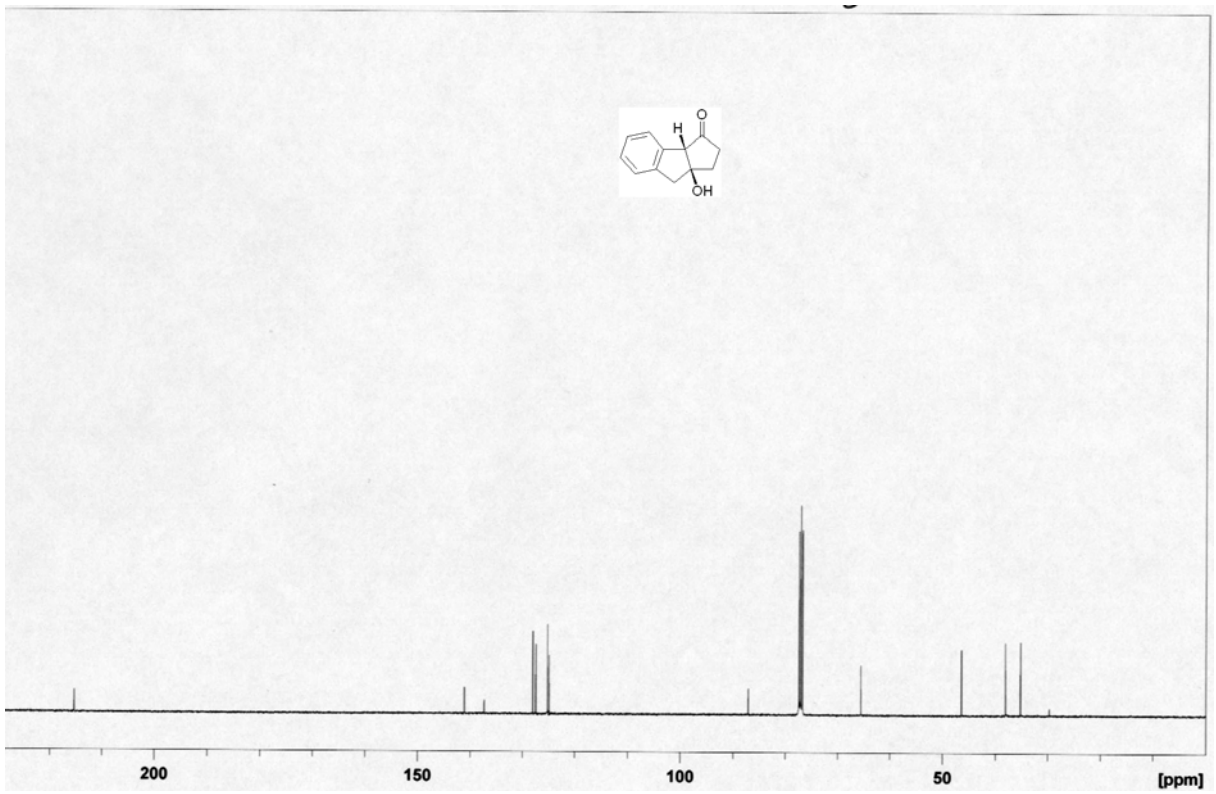
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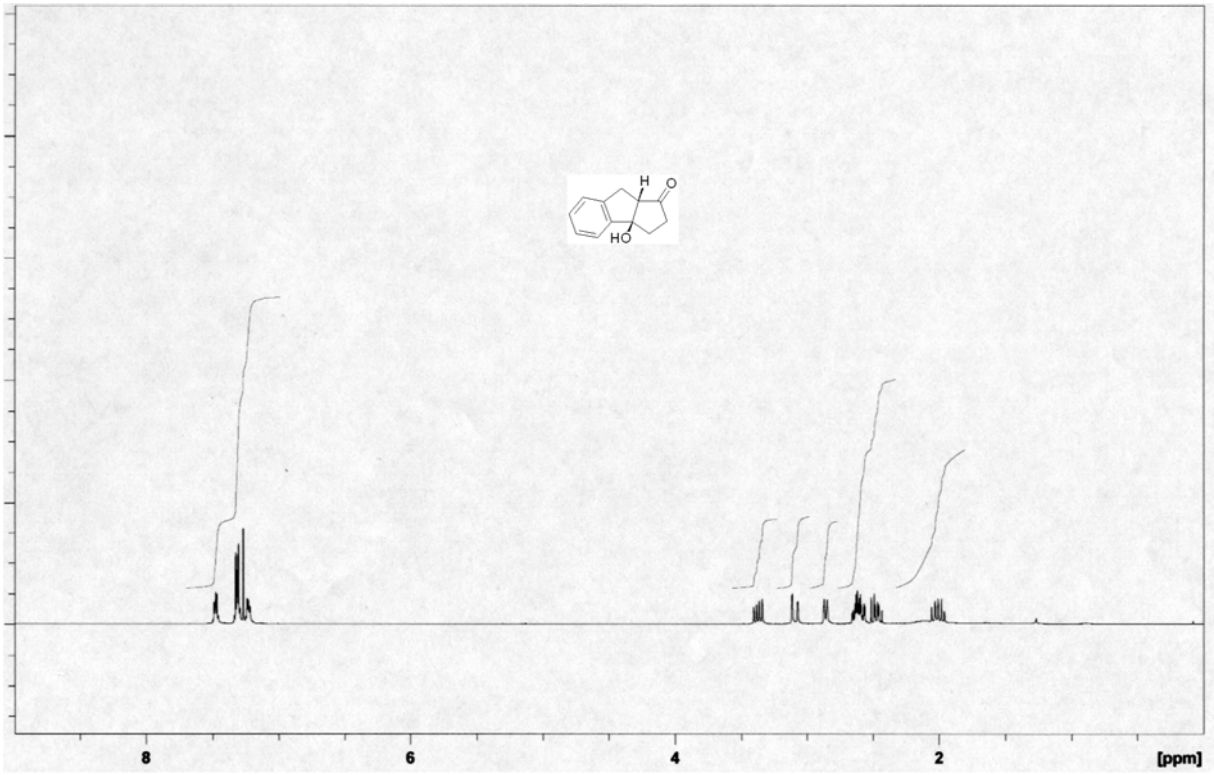
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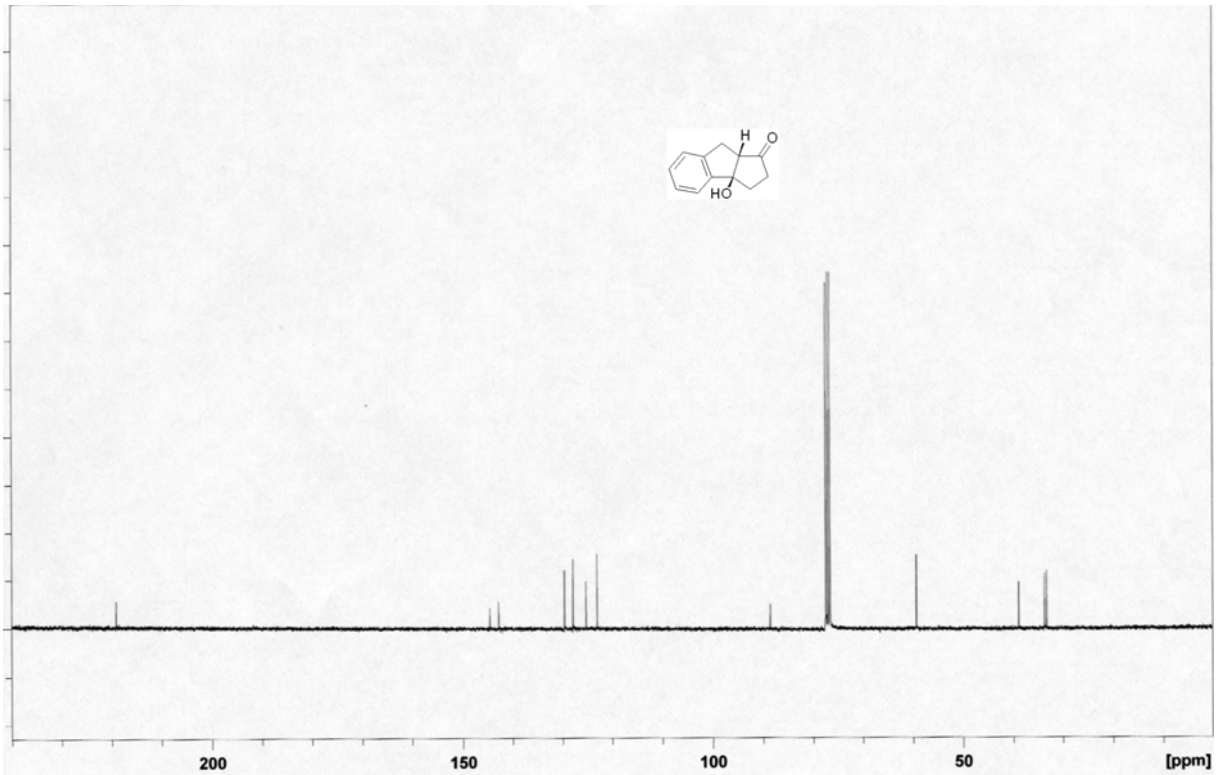
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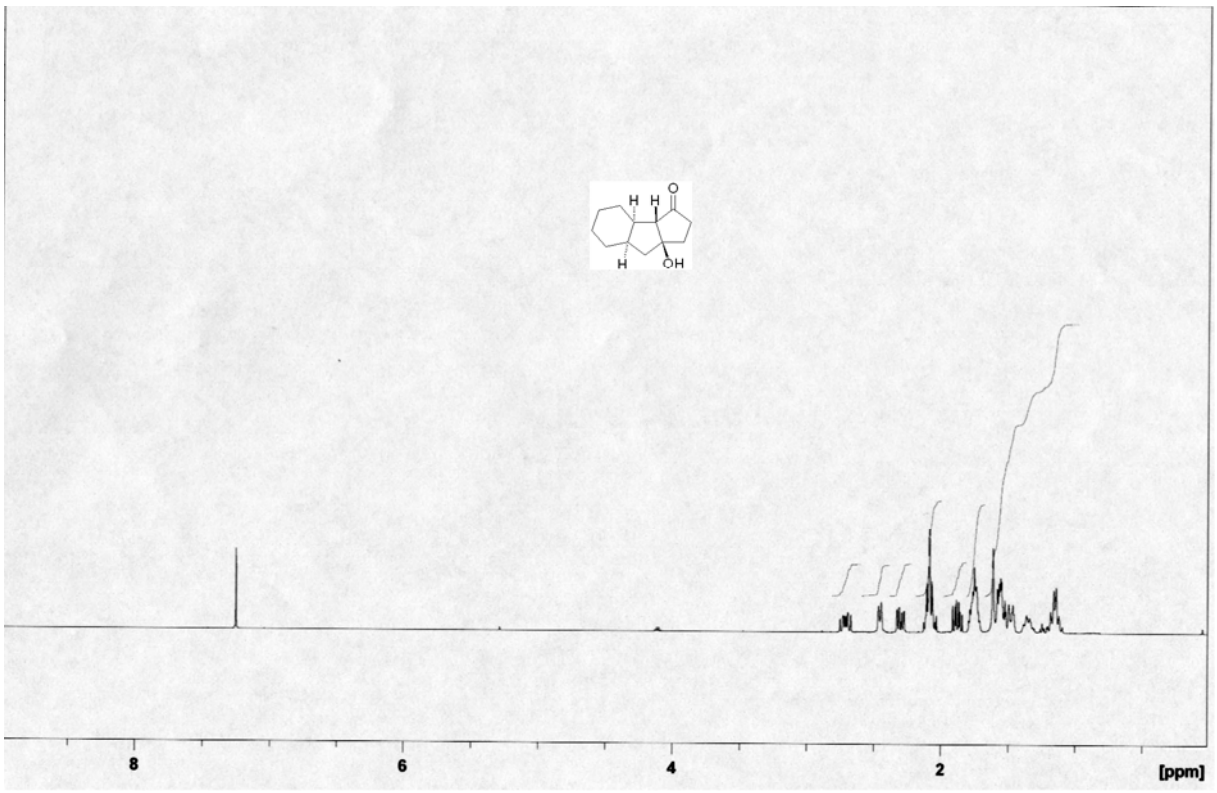
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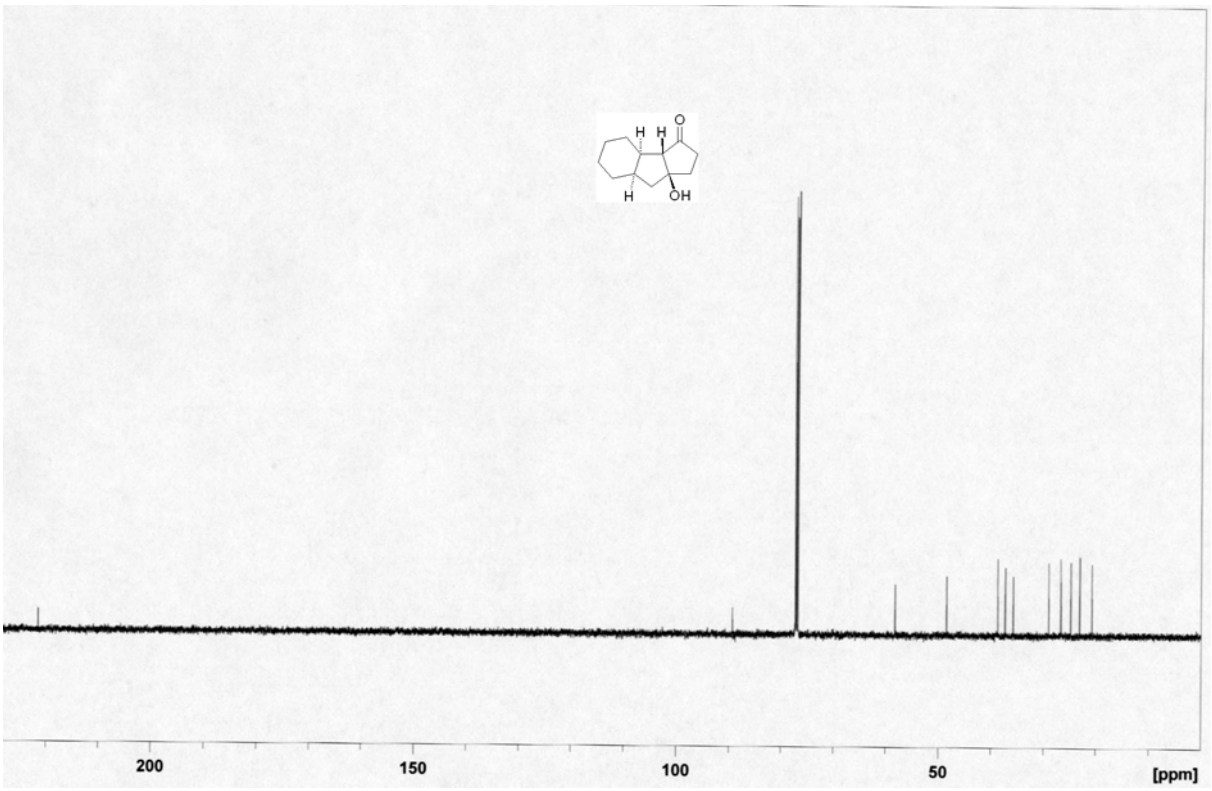
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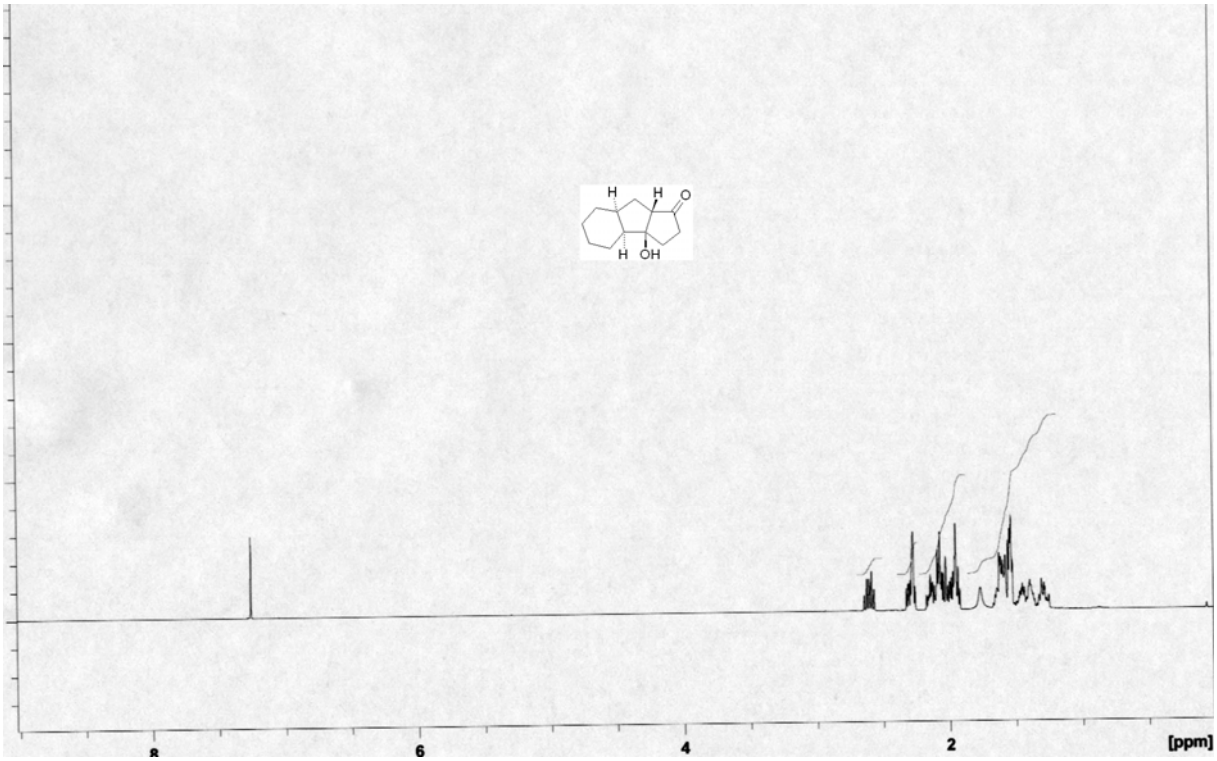
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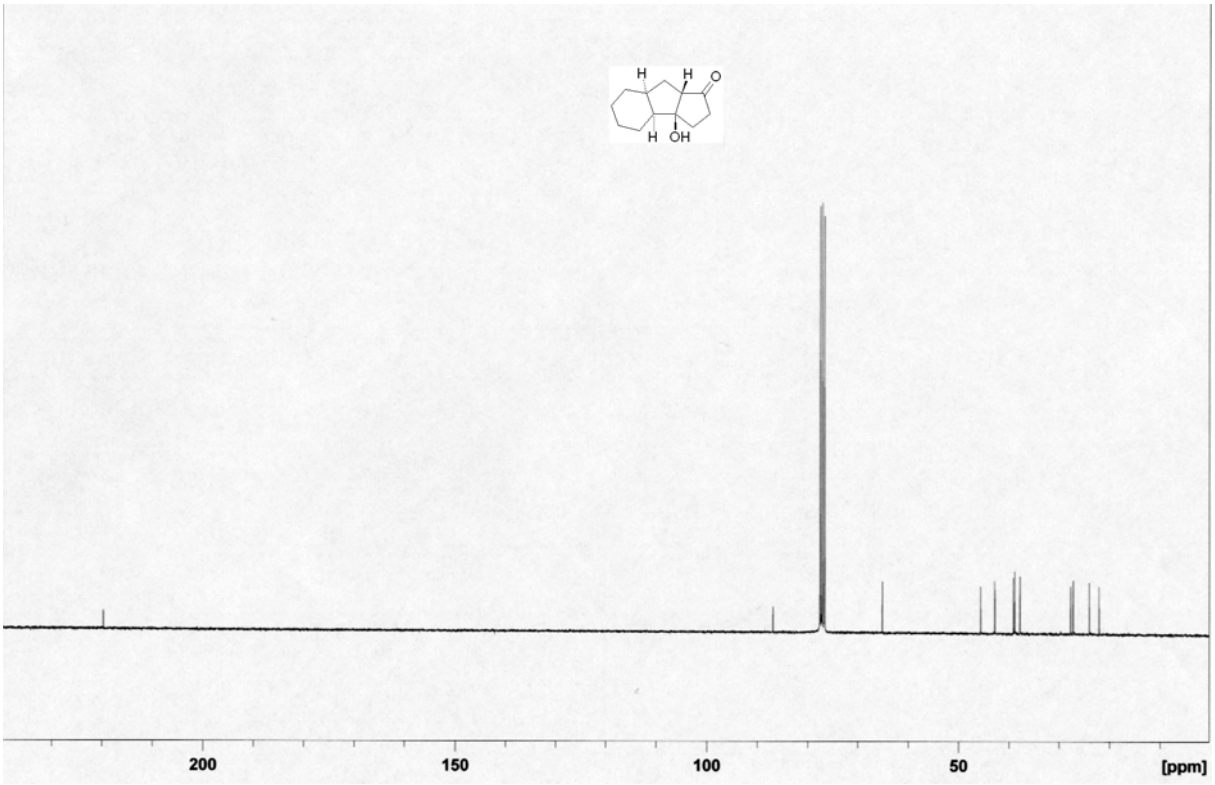
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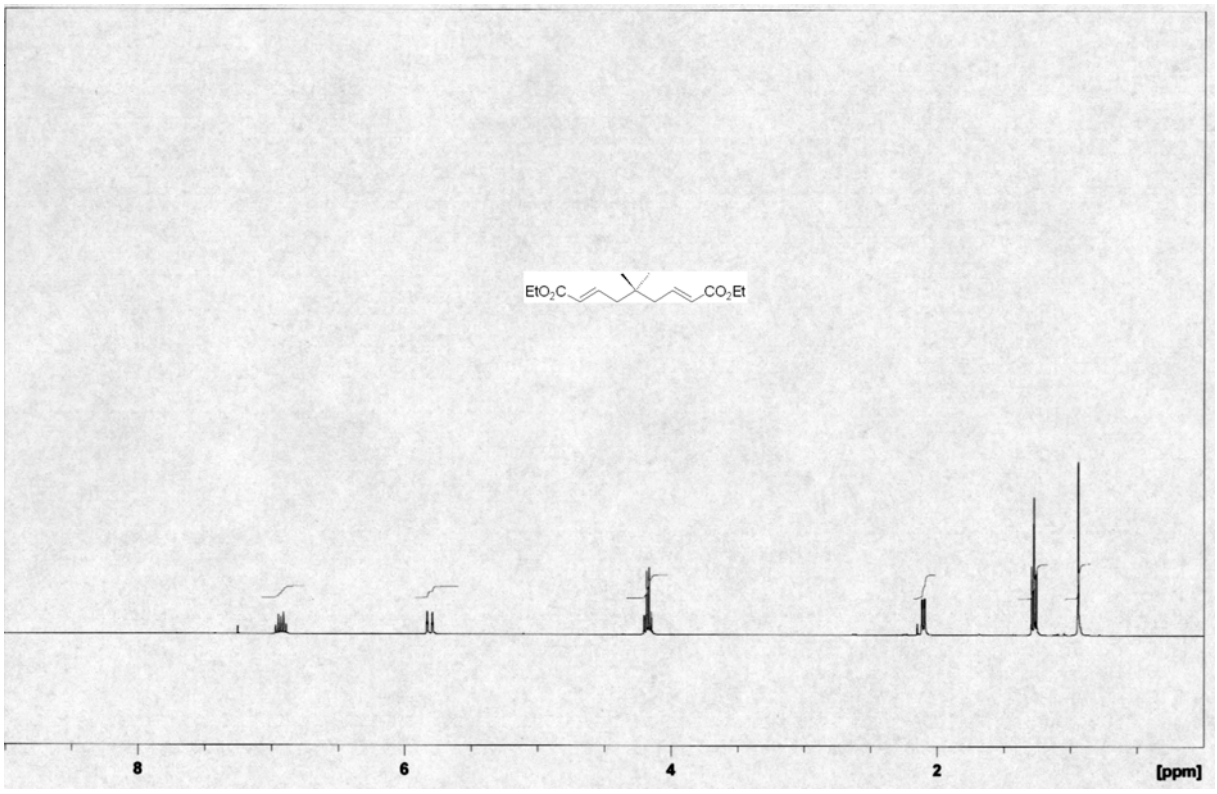
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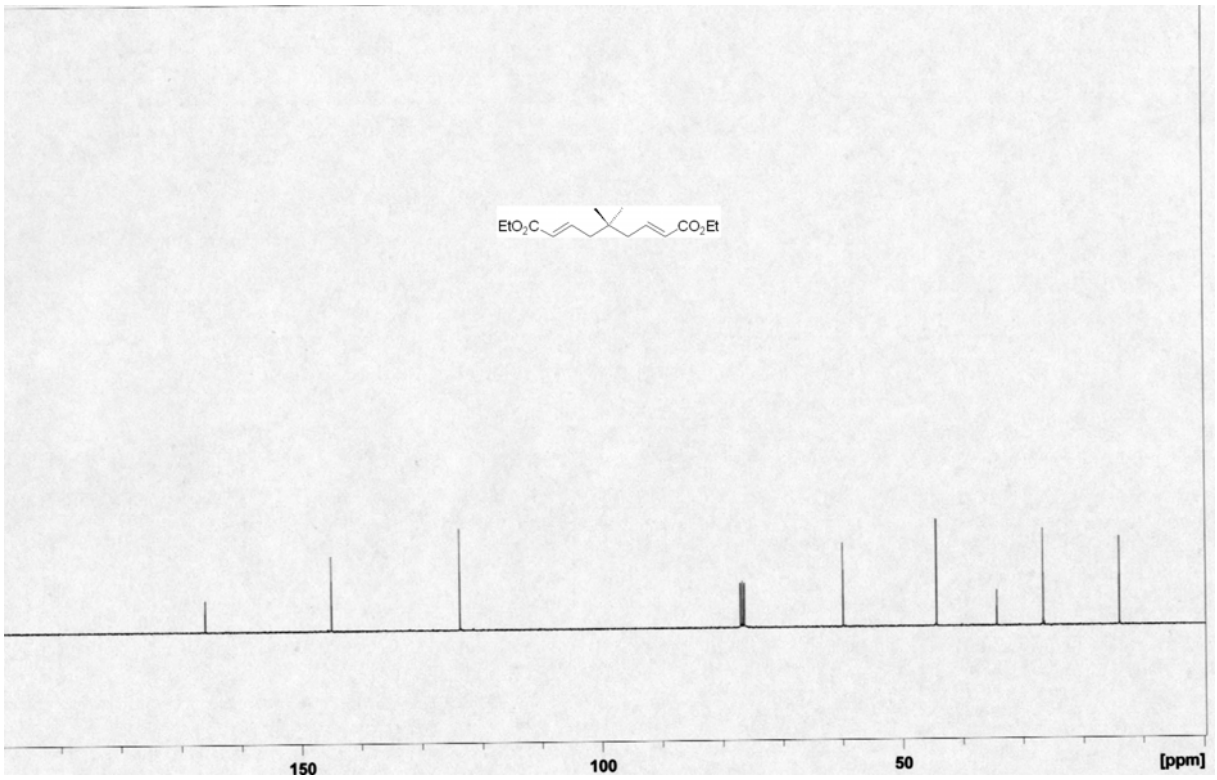
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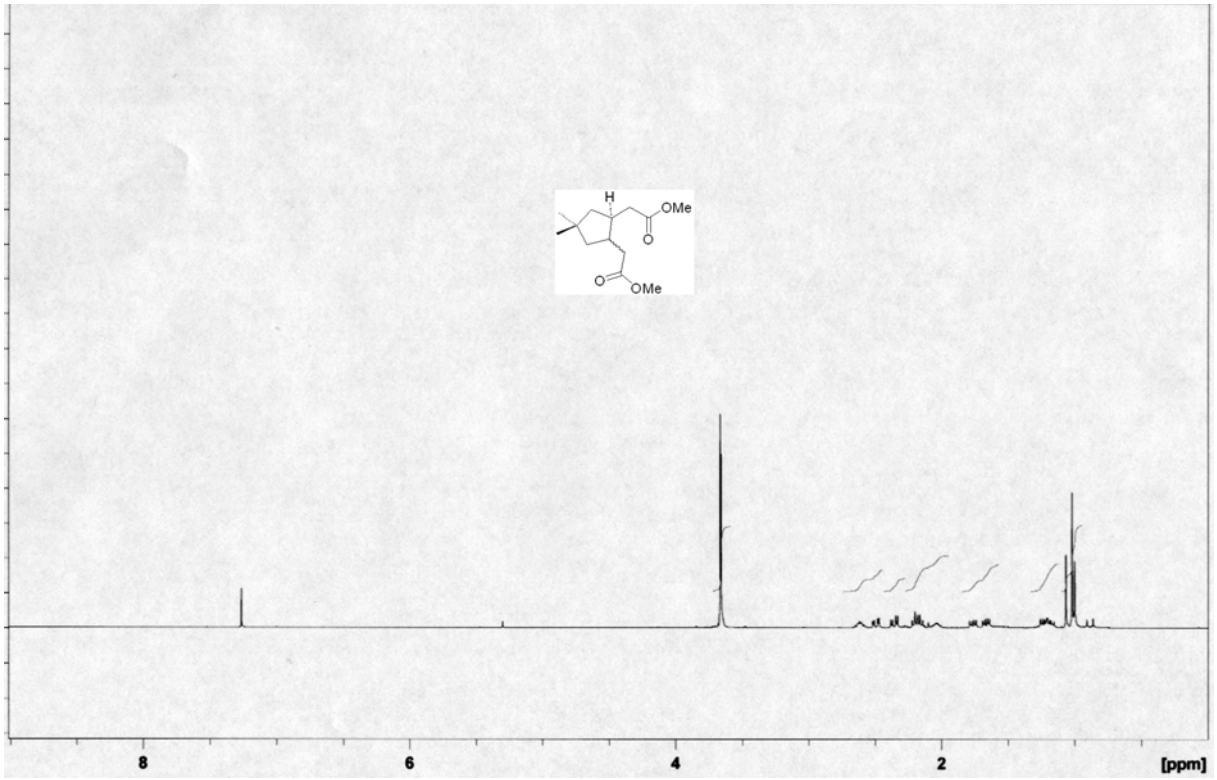
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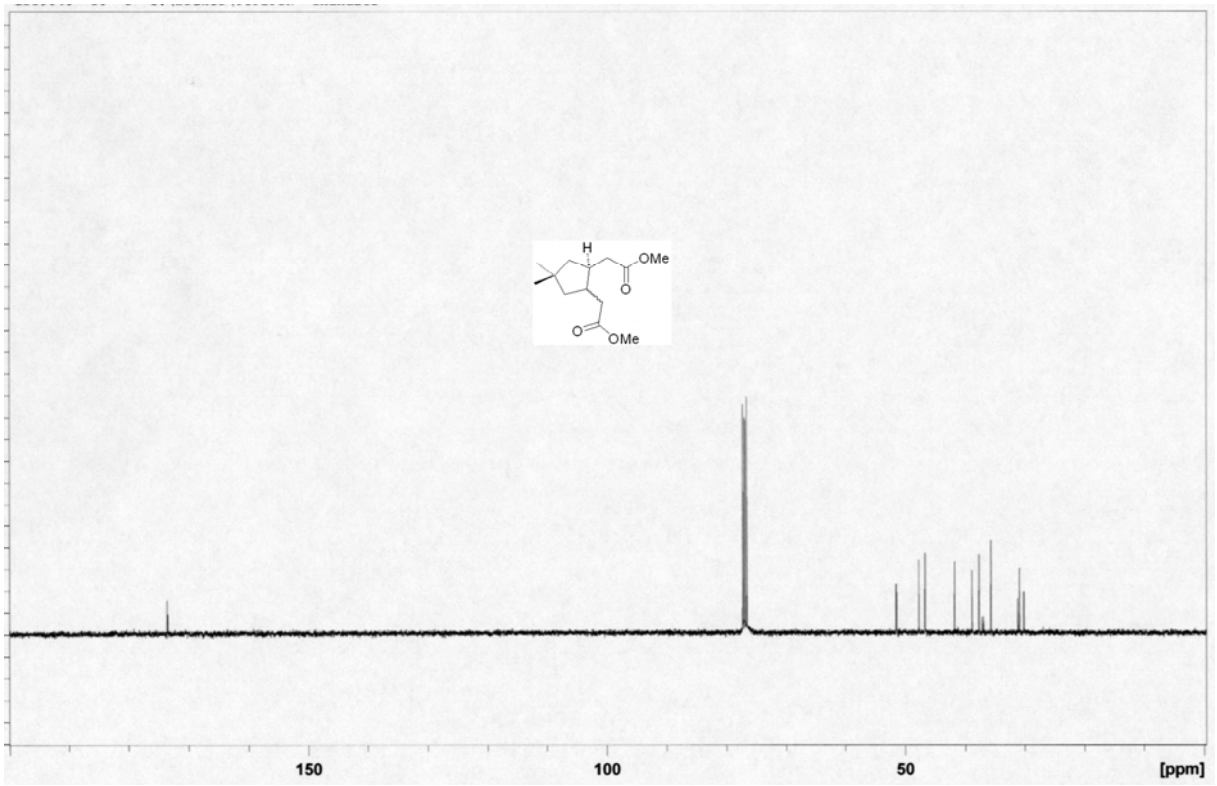
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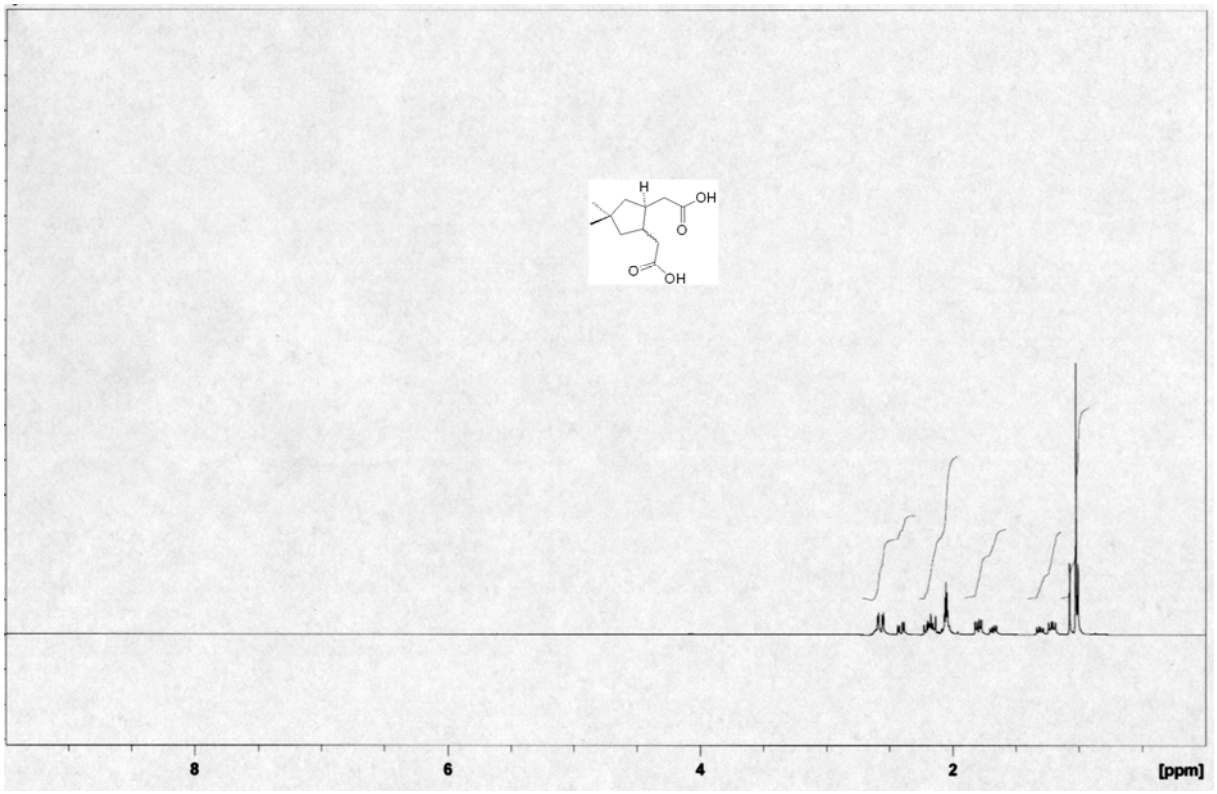
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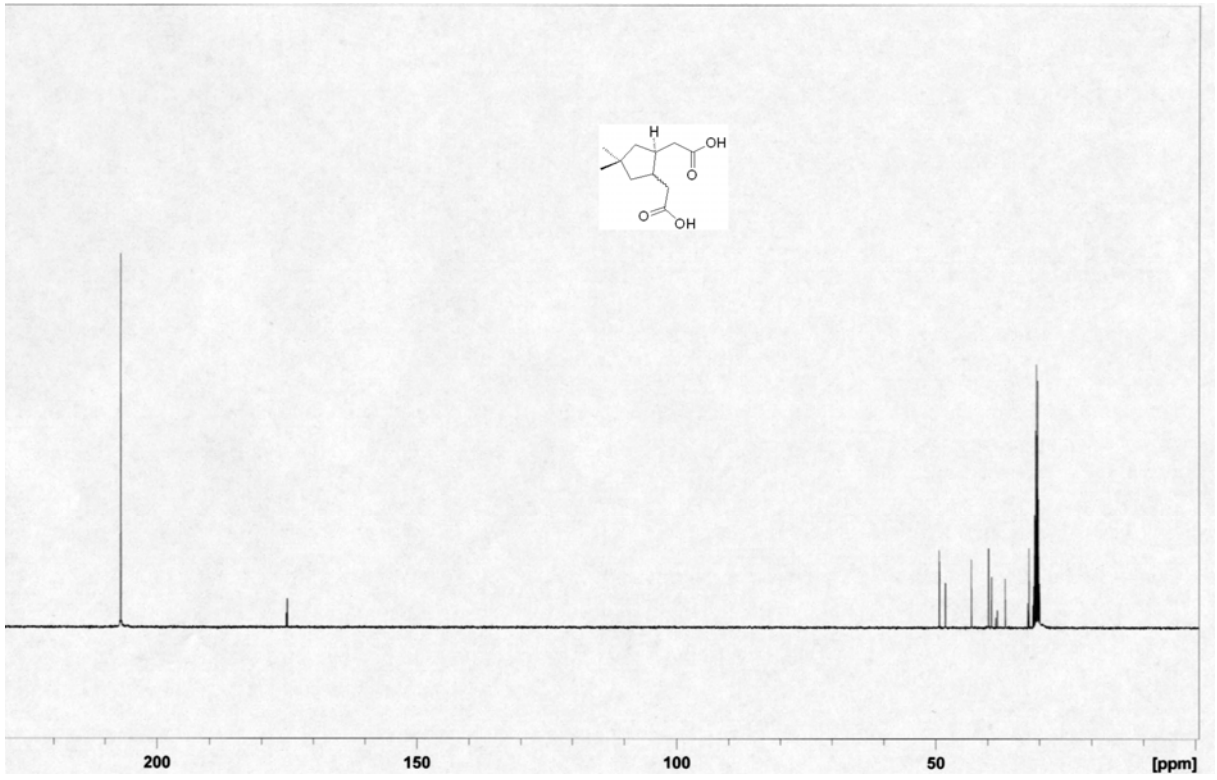
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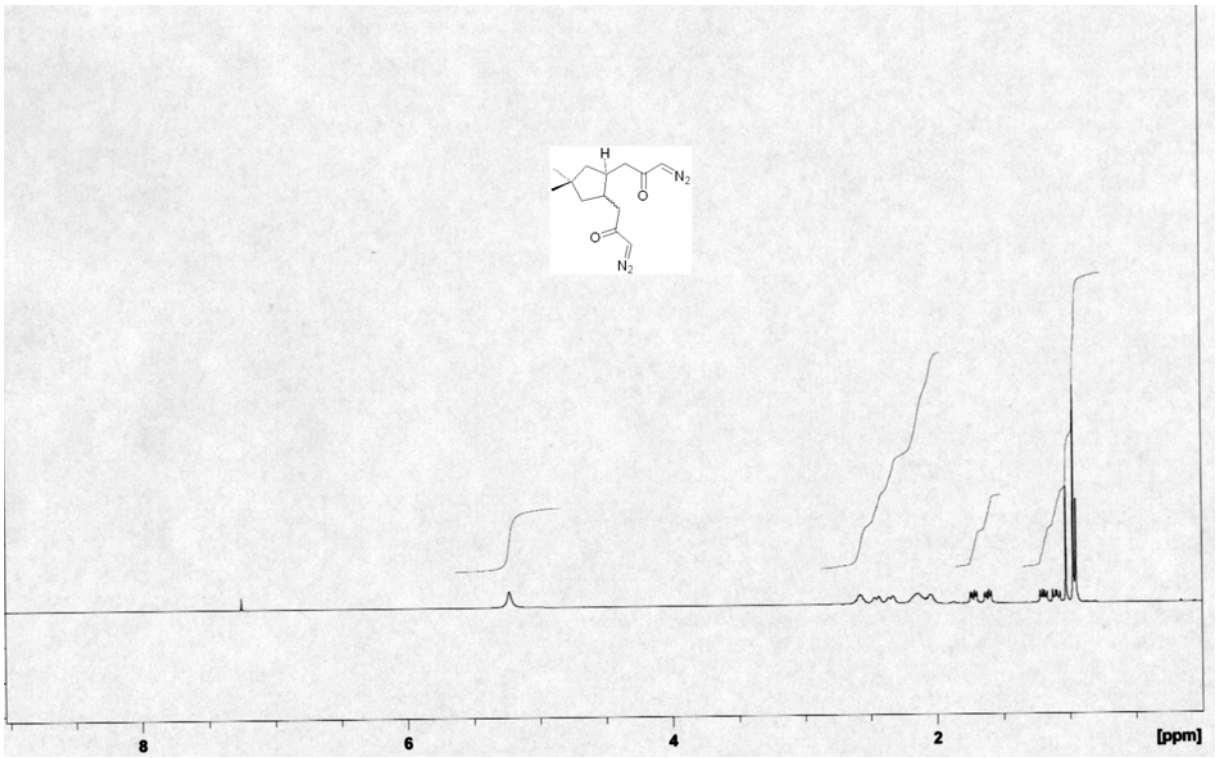
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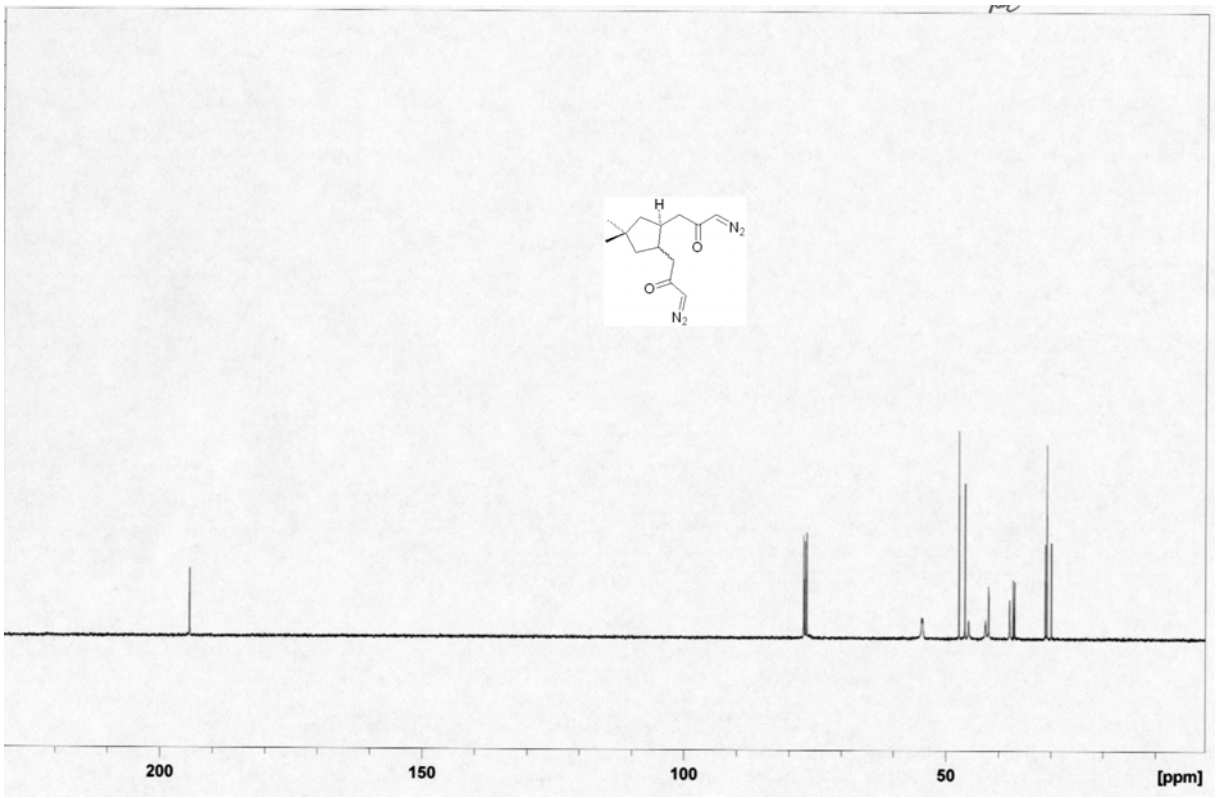
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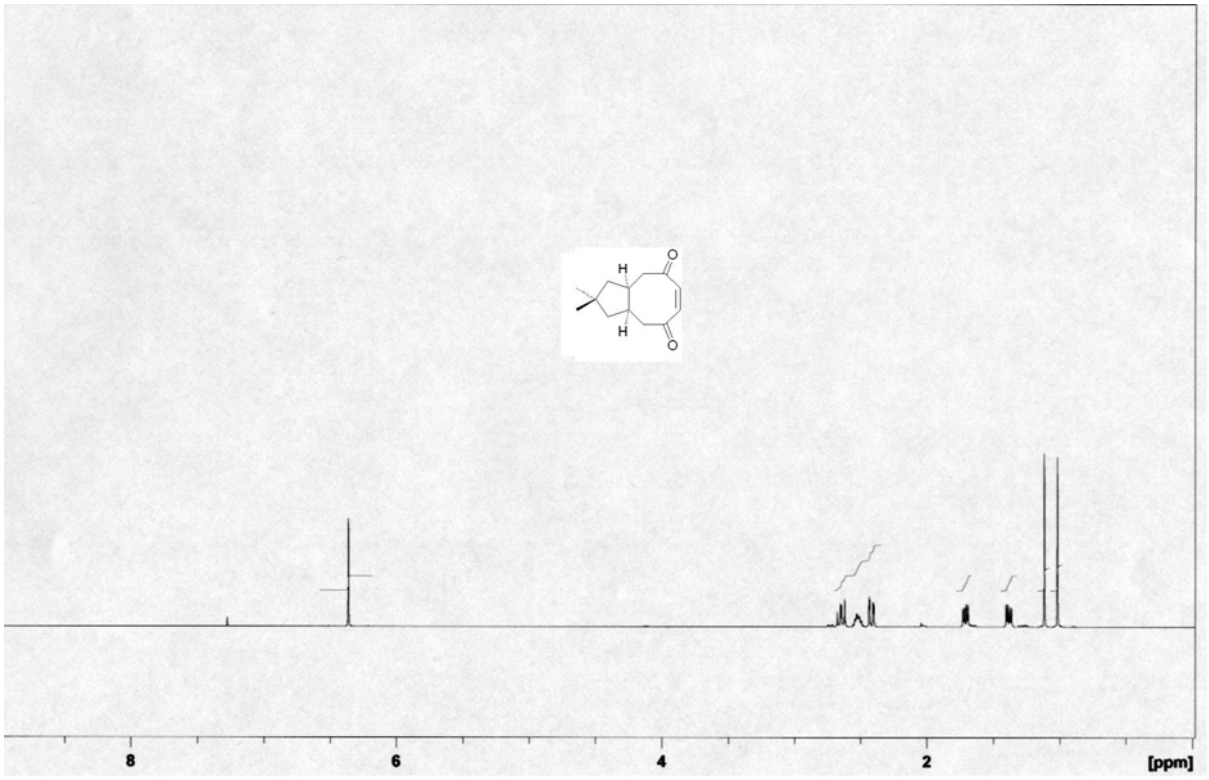
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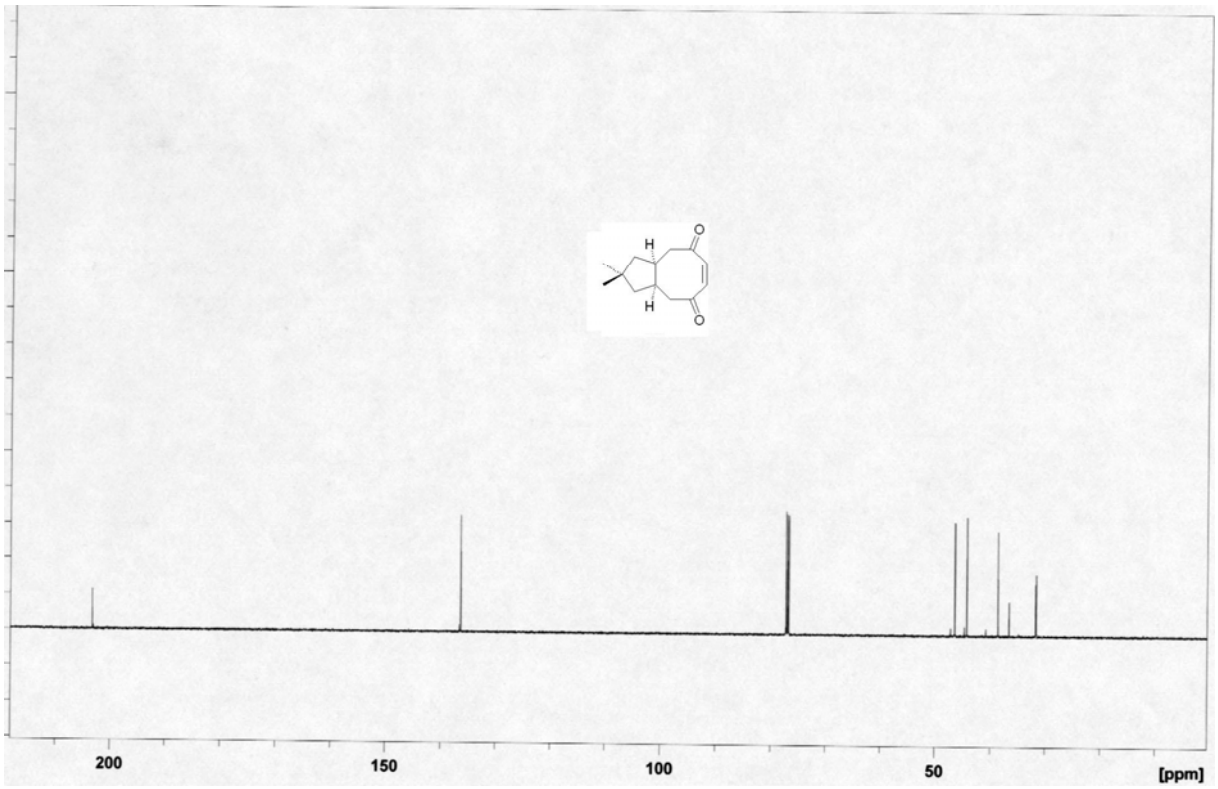
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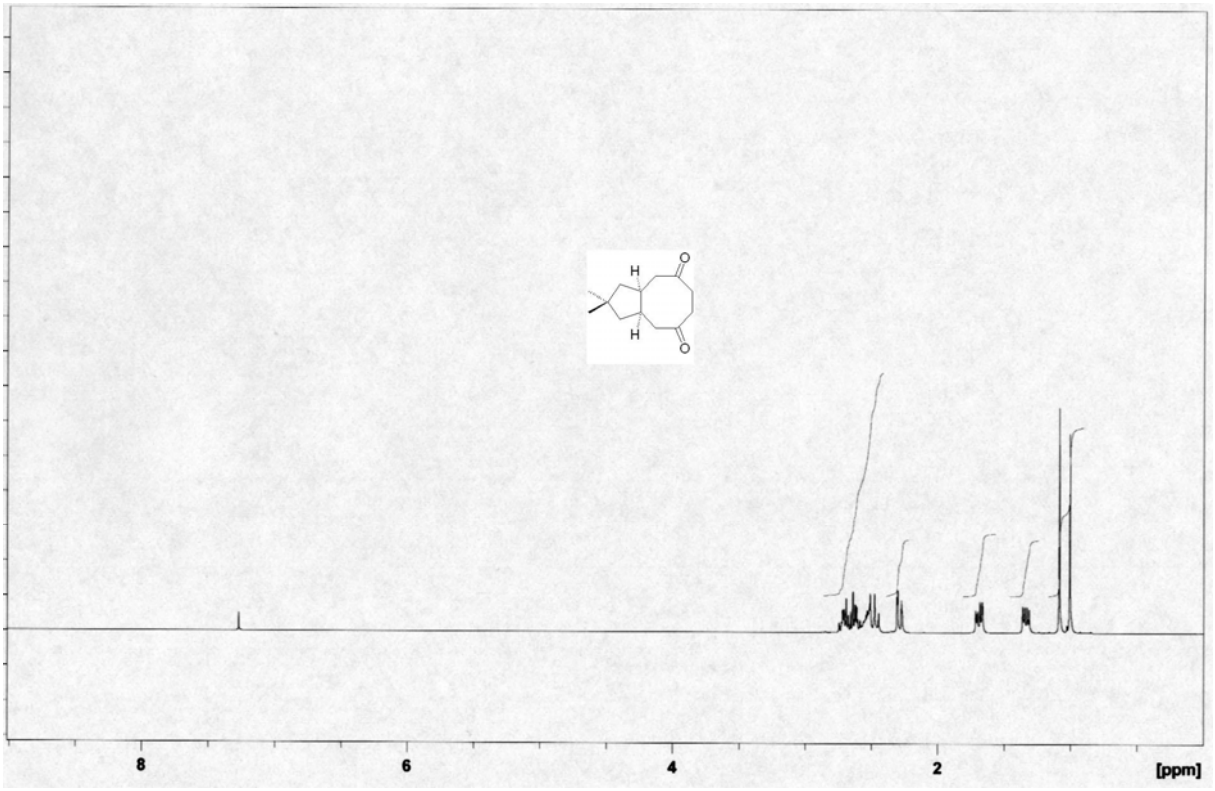
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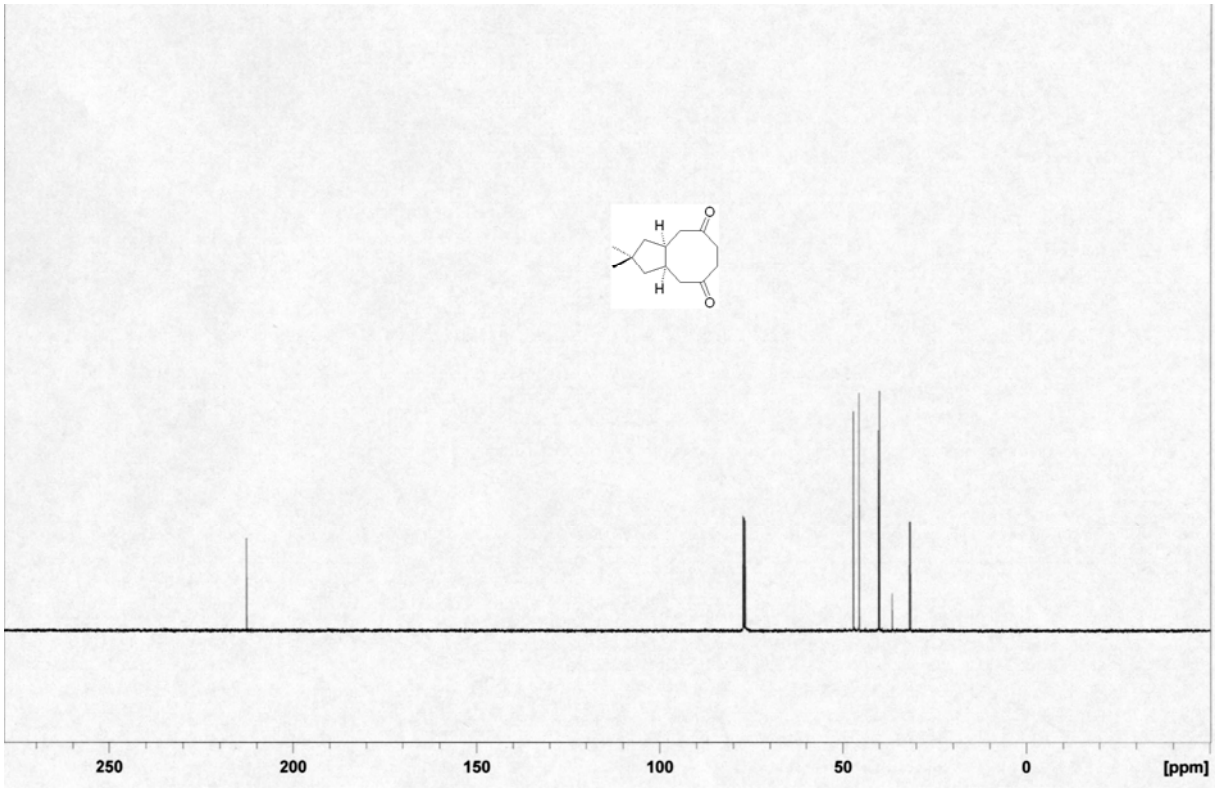
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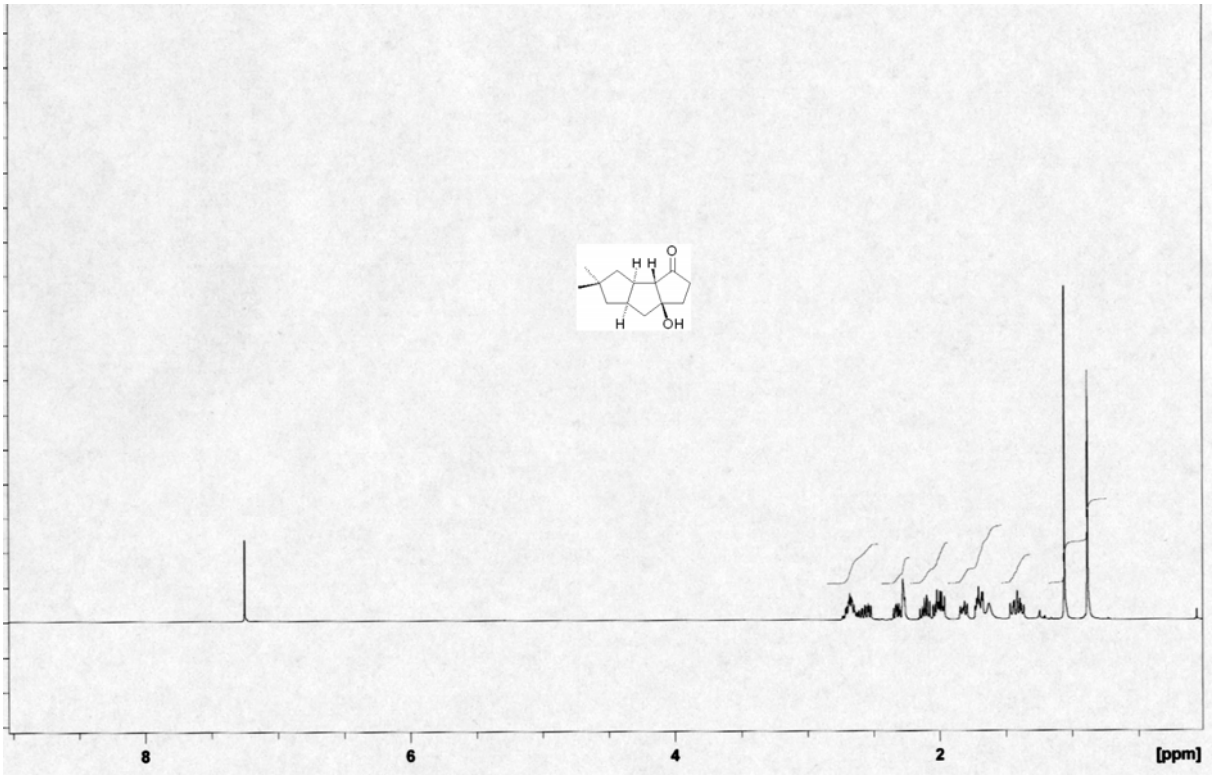
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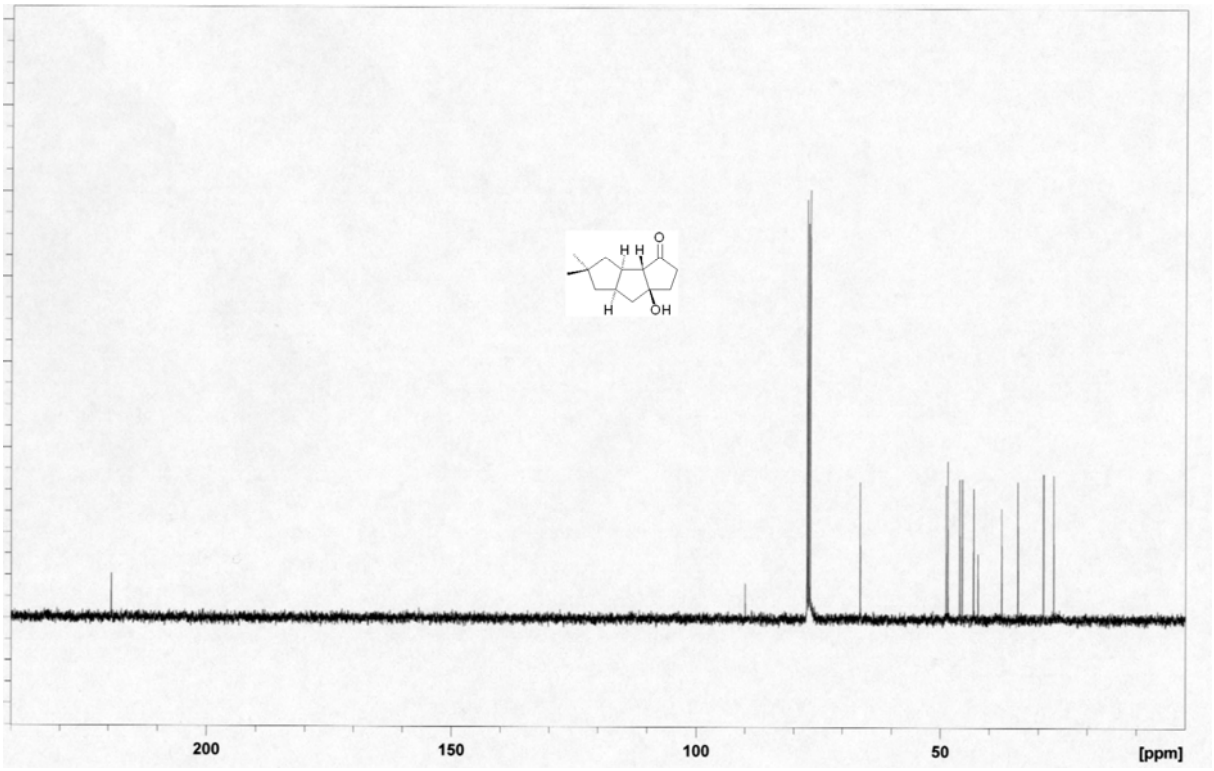
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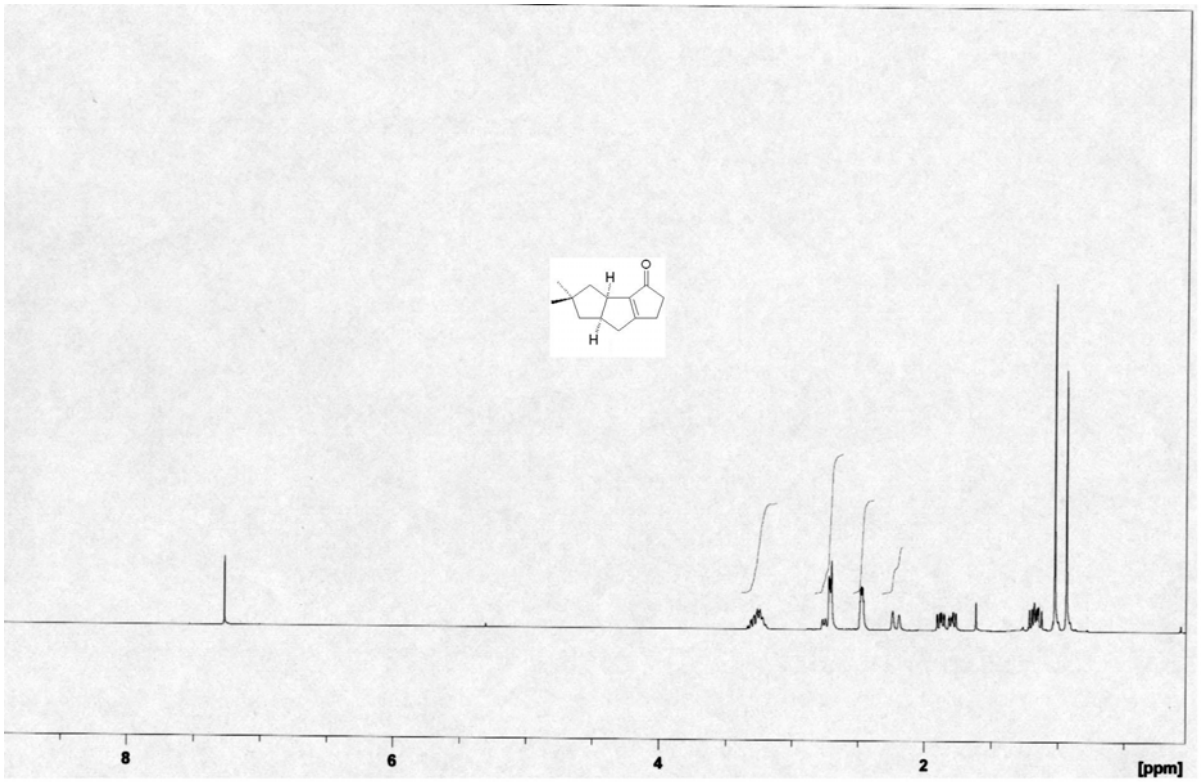
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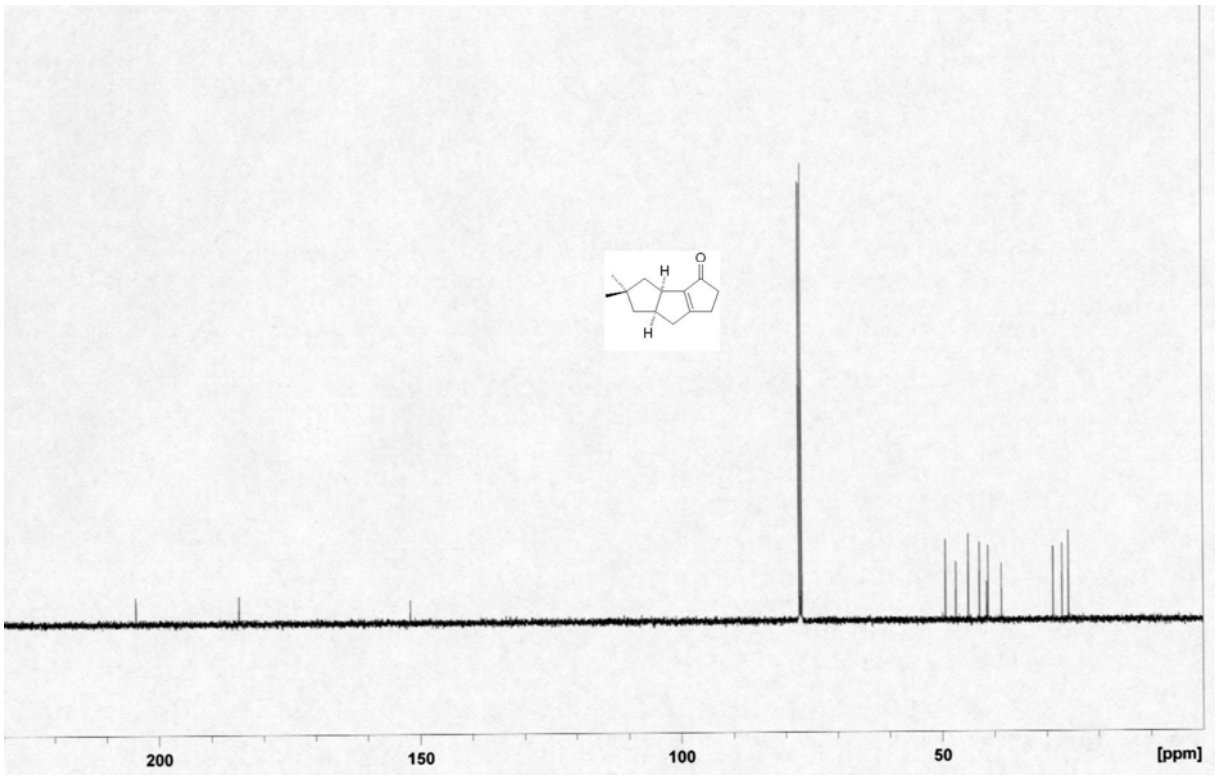
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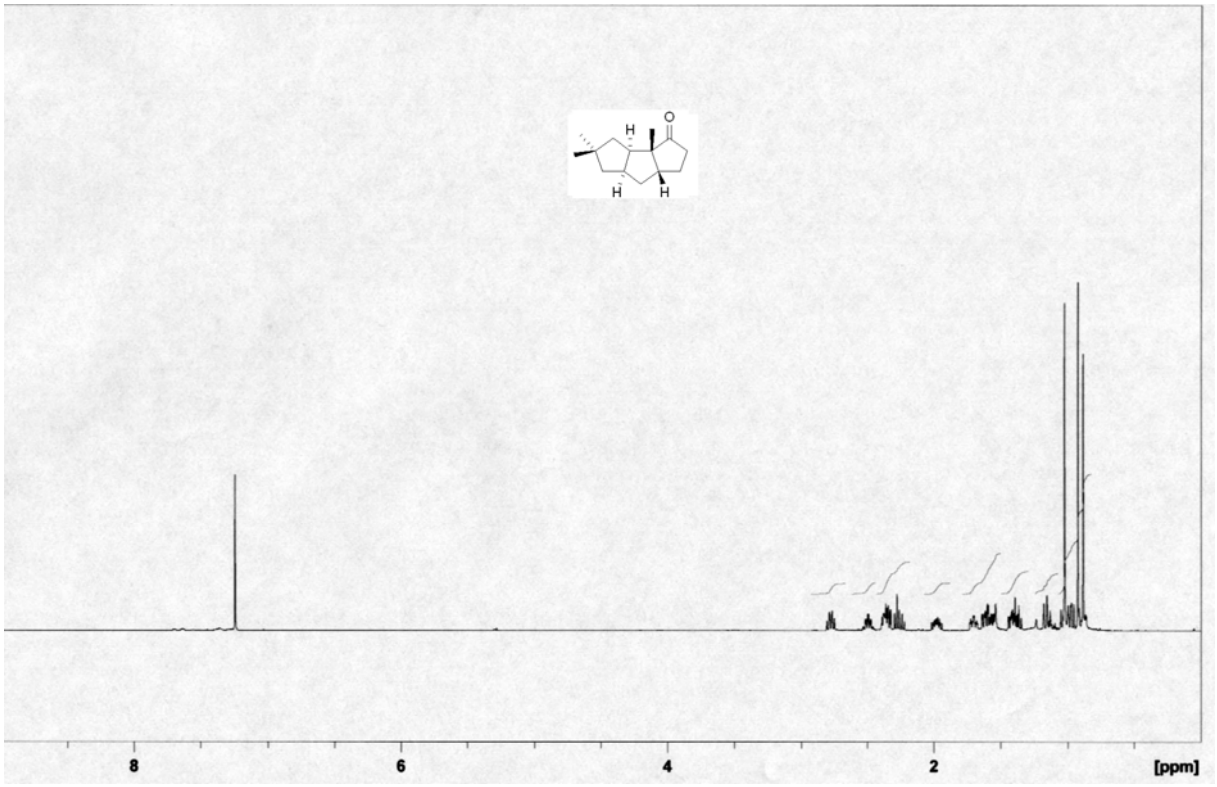
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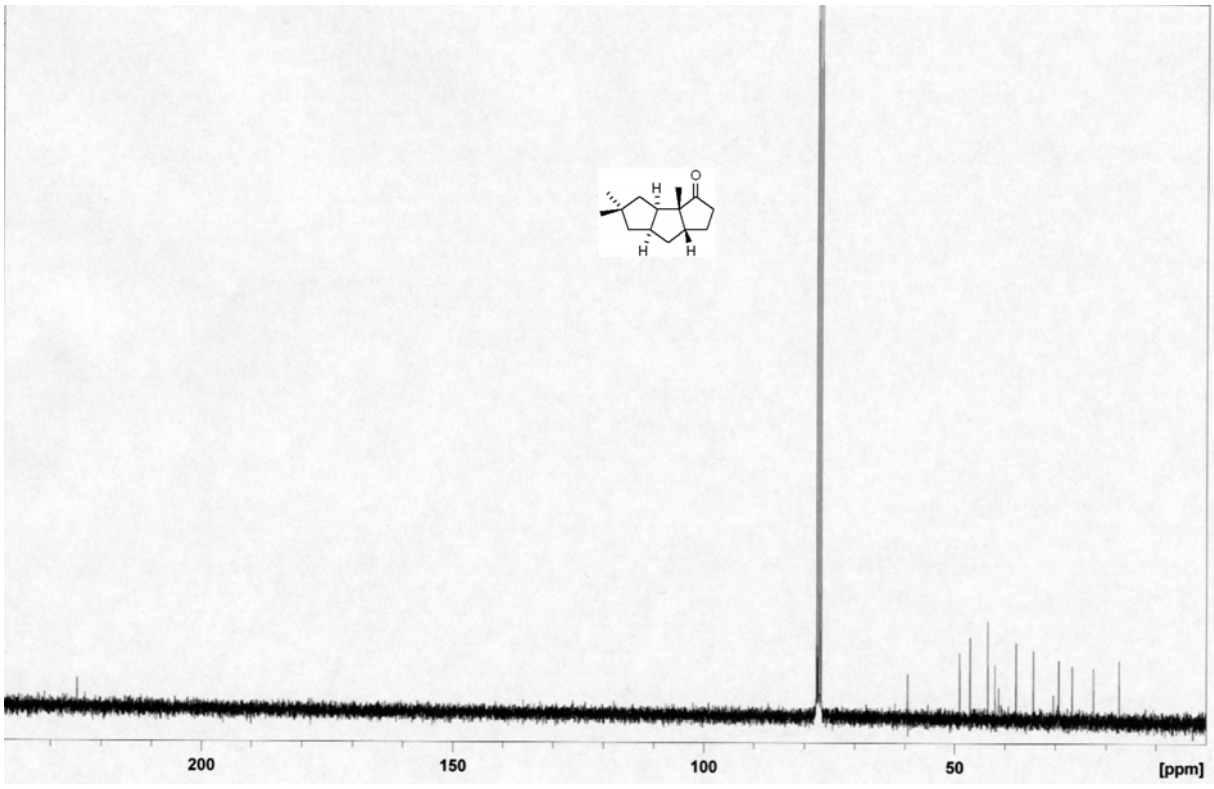
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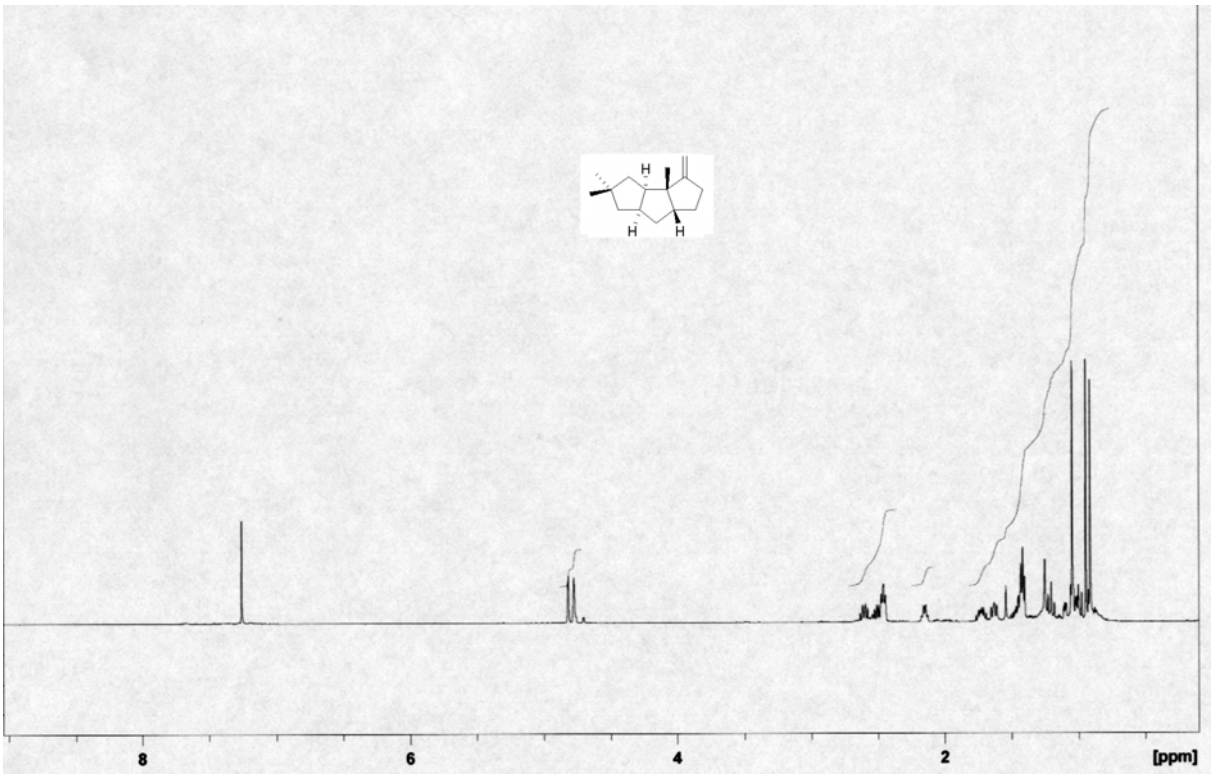
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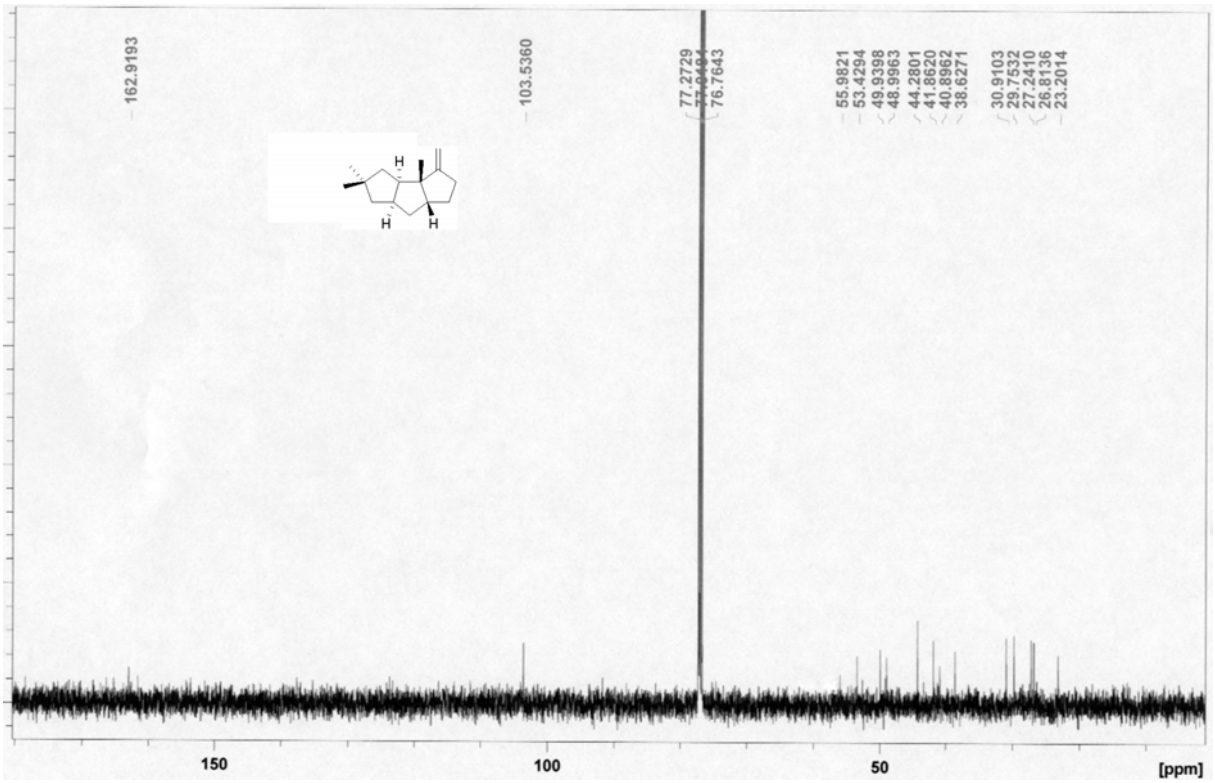
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