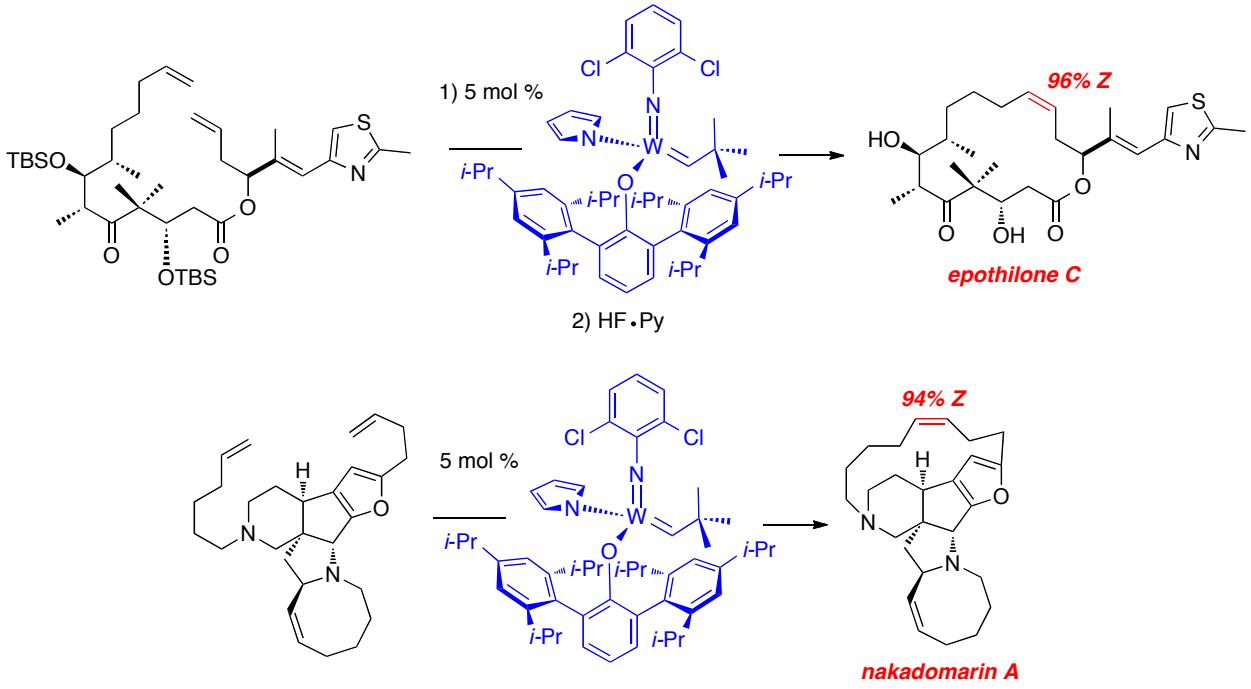
Synthesis of macrocyclic natural products by catalyst-controlled stereoselective ring-closing metathesis

Miao Yu,* Chenbo Wang,* Andrew F. Kyle,† Pavol Jakubec,† Darren J. Dixon,†
Richard R. Schrock,‡ & Amir H. Hoveyda*

*Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, Massachusetts 02467, USA
†Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Oxford OX1 3TA, UK
‡Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, USA

SUPPLEMENTARY INFORMATION



■ **General:** Unless otherwise noted, all reactions were performed with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) or flame-dried glassware with standard dry box or vacuum line techniques. All substrates were dried by azeotropic distillation with C_6H_6 prior to use in reactions with Mo- and W-based complexes. Substrate **3**[1], **11**[2], and the precursors to **13**[3] were prepared according to the previously reported procedures. Infrared (IR) spectra were recorded on a Bruker FTIR Alpha (ATR Mode) spectrometer, ν_{max} in cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), or weak (w). ^1H NMR spectra were recorded on a Varian Unity INOVA 400 (400 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance resulting from incomplete deuterium incorporation as the internal standard ($CDCl_3$: δ 7.26 ppm, C_6D_6: δ 7.16 ppm, CD_3OD: δ 3.31 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian Unity INOVA 400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.16 ppm, CD_3OD: δ 49.00 ppm). High-resolution mass spectrometry was performed on a Micromass LCT ESI-MS and JEOL Accu TOF Dart (positive mode) at the Boston College Mass Spectrometry Facility. *Z:E* ratios of **4**, **6** and **12** were determined by analysis of ^1H NMR spectra. The stereochemical identity of the macrocyclic alkenes was established by comparison with reported spectroscopic data (**4**[1], **12**[2]); the stereochemical identity of **6** was established by X-ray crystal structure of the major isomer. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Polarimeter.

Vacuum Pumps: Edwards RV8 two stage rotary vane pump generates a vacuum of 1.0 torr (glove box) or 0.02 torr (fume hood) at point of connection to the reaction vessel. KNF Laboport N840.3FTP diaphragm vacuum pump generates a vacuum of 7.0 torr at point of connection to the reaction vessel.

Solvents: Solvents were purged with Ar and purified under a positive pressure of dry Ar by a modified Innovative Technologies purification system. Toluene (Doe & Ingalls), dichloromethane (Fisher), benzene (Aldrich) and pentane[4] (J. T. Baker) were passed successively through activated copper and alumina columns. Tetrahydrofuran was purified by distillation from sodium benzophenone ketyl immediately prior to use. *N*,*N*-Dimethylformamide (Acros; extra dry with molecular sieves) was used as received. All work-up and purification procedures were carried out with reagent grade solvents (purchased from Fisher) under bench-top conditions.

---

(1) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 10073–10092.

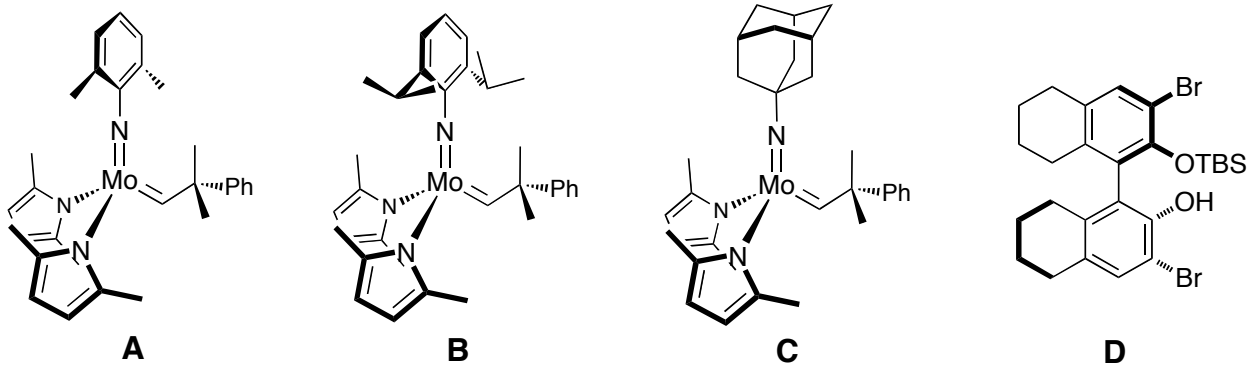
(2) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942–3943.

(3) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632–16633.

(4) *n*-Pentane was allowed to stir over concentrated H_2SO_4 for three days, washed with water, followed by a saturated aqueous solution of $NaHCO_3$, dried over $MgSO_4$, and filtered before use in a solvent purification system.

Metal-based Complexes: Mo-based bis(alkoxide) complex **1** was prepared according to a previously reported procedure[5]. Mo or W monopyrrolide-monoaryloxide complexes **7a**, **7b** and **8**[6] were prepared in situ according to published procedures from Mo bis(pyrrolide) complexes **A**, **B** and **C**, respectively, with chiral alcohol **D**[7]; **9** and **10**[8] were prepared and purified according to previously disclosed procedures[9]. Ru-based carbene complexes **2b-d** were obtained from Materia, Inc. and purified by silica gel column chromatography or by recrystallization (dichloromethane / pentane) prior to use. Unless otherwise noted, all Mo and W complexes were handled under an inert atmosphere of N_2 in a dry box. (As noted below, in some cases, catalysts can be manipulated and used outside a glove box).

Chart 1. **Mo Bis-pyrrolide Complexes and the Alcohol Used to Access Catalysts**



■ Reagents:

Acetic anhydride was purchased from Aldrich and used as received.

Azobisisobutyronitrile (AIBN) was purchased from Janssen Chimica and used as received.

***d_6*-Benzene** was purchased from Cambridge Isotope Laboratories and distilled from Na into activated 4 Å molecular sieves prior to use.

6-Bromo-1-hexene was purchased from Fluorochem and used as received.

***tert*-Butyldimethylsilyl trifluoromethanesulfonate (TBSOTf)** was purchased from TCI and used as received.

But-3-en-1-amine was purchased from Alfa Aesar and used as received.

But-3-en-1-ol was purchased from Aldrich and used as received.

(+)-Camphorsulfonic acid was purchased from Aldrich and used as received.

***d*-Chloroform** was purchased from Cambridge Isotope Laboratories and passed through basic alumina then stored in activated 4 Å molecular sieves prior to use.

---

(5) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886.

(6) Malcolmson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933–937.

(7) (a) Hock, A. S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 16373–16375. (b) Singh, R.; Czekelius, C.; Schrock, R. R.; Müller, P. M.; Hoveyda, A. H. *Organometallics* **2007**, *26*, 2528–2539.

(8) Jiang, A. J.; Zhao, Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 16630–16631.

(9) Jiang, A. J.; Simpson, J. H.; Muller, P.; Schrock, R. R. *J. Am. Chem. Soc.* **2009**, *131*, 7770–7780.

Dec-9-en-1-ol was purchased from Aldrich and used as received.

Dec-9-enoic acid was purchased from Aldrich and used as received.

Diisobutylaluminium hydride (DIBAL-H) was purchased from Strem and used as received.

Dimethyl sulfoxide (DMSO) was purchased from Acros and distilled over CaH_2 and dried over 4 Å activated molecular sieves prior to use.

Di-*tert*-Butyl dicarbonate was purchased from Alfa Aesar and used as received.

4-(*N*,*N*-Dimethylamino)pyridine (DMAP) was purchased from Aldrich and used as received.

***N*,*N*-Dimethylformamide (DMF)** was purchased from Acros and dried over 4 Å activated molecular sieves prior to use.

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) was purchased from Advanced Chem. Tech. and used as received.

Formaldehyde (37% solution in water) was purchased from Fisher Scientific and used as received.

Hex-5-enoic acid was purchased from Aldrich and used as received.

Hydrogen fluoride-pyridine complex was purchased from Aldrich and used as received.

1-Hydroxy-benzotriazole (HOBT) was purchased from Advanced Chem. Tech. and used as received.

2-Iodoxybenzoic acid (IBX) was purchased from Aldrich and used as received.

Lithium triethylborohydride (1.0 M solution in THF) was purchased from Aldrich and used as received.

2,6-Lutidine was purchased from Aldrich and distilled over CaH_2 prior to use.

Mesitylene was purchased from Aldrich and distilled over Na prior to use.

Methanol was purchased from Aldrich and dried over 4 Å activated molecular sieves prior to use.

***d*$_4$-Methanol** was purchased from Cambridge Isotope Laboratories and used as received.

Methyl triphenylphosphonium bromide was purchased from Alfa Aesar and used as received.

Oct-7-enoic acid was purchased from Aldrich and used as received.

Oxalyl chloride was purchased from Acros and distilled over CaH_2 prior to use.

Potassium *tert*-butyloxide was purchased from Alfa Aesar and used as received.

Tributyltin hydride was purchased from Alfa Aesar and used as received.

Triethylamine was purchased from Aldrich and distilled over CaH_2 prior to use.

Trifluoroacetic acid was purchased from Aldrich and used as received.

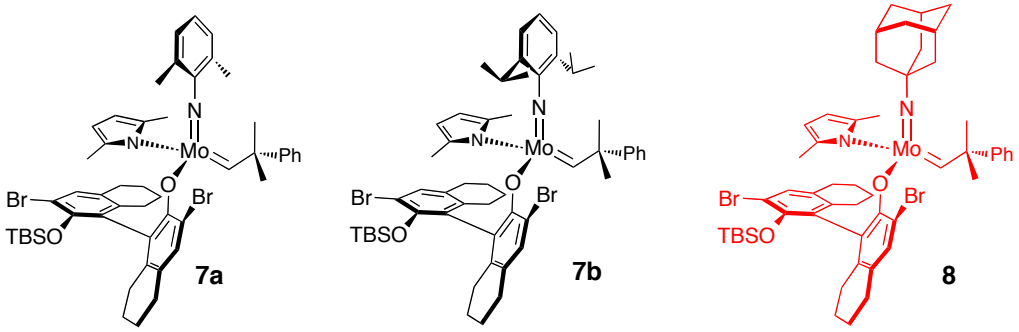
***p*-Toluenesulfonic acid (PTSA)** was purchased from Aldrich and used as received.

Undec-10-enoic acid was purchased from Aldrich and used as received.

Undec-10-en-1-amine was purchased from GFS Chemical and used as received.

■ Preparation of Mo Monoalkoxide-monopyrrolide Complexes

Chart 2. *In situ* Generated Mo Monoalkoxide-monopyrrolide Complexes



General procedure for the preparation of Mo complex 8: In an N_2-filled glove box, a 4-mL vial with a magnetic stir bar was charged with Mo bispyrrolide complex **C** (8.6 mg, 0.015 mmol), chiral alcohol **D** (8.5 mg, 0.015 mmol), and C_6D_6 (760 μL). The vial was tightly capped and the mixture was allowed to stir for one hour, at which time it was transferred to an NMR tube (screw cap NMR) by a pipette. The NMR tube was capped and sealed with Teflon tape. Please note that for *in situ*-generated complexes, only the diagnostic signals of the α carbon of the *syn*-alkylidenes are shown. ^{1}H NMR (400 MHz, C_6D_6): δ 12.94 (1H, s), 12.74 (1H, s), 12.46 (1H, s), 12.38 (1H, s); dr = 3:1 (entry 1, Table 1).

Representative procedure for preparation of Mo complex 8 (used *in situ*): In an N_2-filled glove box, a 4 mL vial containing a magnetic stir bar was charged with **C** (6.0 mg, 0.011 mmol), chiral alcohol **D** (6.0 mg, 0.011 mmol), and C_6H_6 (500 μL, 0.02 M), resulting in an orange solution. The vial was capped and the mixture was allowed to stir for one hour at 22 °C, after which the catalyst solution was transferred to the reaction mixture by a syringe (dried at 65 °C).

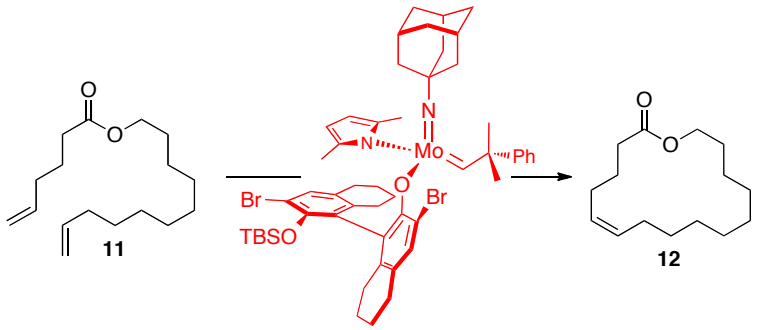
■ Synthesis of Macrocyclic Alkenes by *Z*-Selective Ring-Closing Metathesis (RCM)

General procedure for catalytic ring-closing metathesis (RCM) reactions with Mo or W-based catalyst: In an N_2-filled glove box, an oven-dried 35 mL vial equipped with a magnetic stir bar was charged with the diene substrate. A stock solution of the complex in C_6H_6 (or toluene), prepared as mentioned above, was added to the solution of substrate (0.005 M in toluene) by syringe. The resulting mixture was allowed to stir for two to three minutes to allow complete initiation of the catalyst. The vial was capped with a septum fitted with two 20-gauge needles and connected to a seven torr vacuum generated from a diaphragm vacuum pump. The resulting solution was allowed to stir for the required period of time under vacuum; toluene was added a few times to maintain the appropriate concentration. The reaction was then quenched by exposure of the solution to air and concentrated *in vacuo* (percent conversion determined by 400 MHz ^{1}H NMR analysis). Purification was performed by silica gel chromatography.

General procedure for catalytic ring-closing metathesis (RCM) reactions with Ru-based catalyst: A flame-dried 50 mL round bottom flask equipped with a magnetic stir bar, and fitted with a reflux condenser, was charged with a solution of diene substrate in dichloromethane or toluene. The Ru-based carbene was weighed and dissolved in the corresponding solvent. The solution of the catalyst was then added to the substrate through a syringe. The resulting mixture

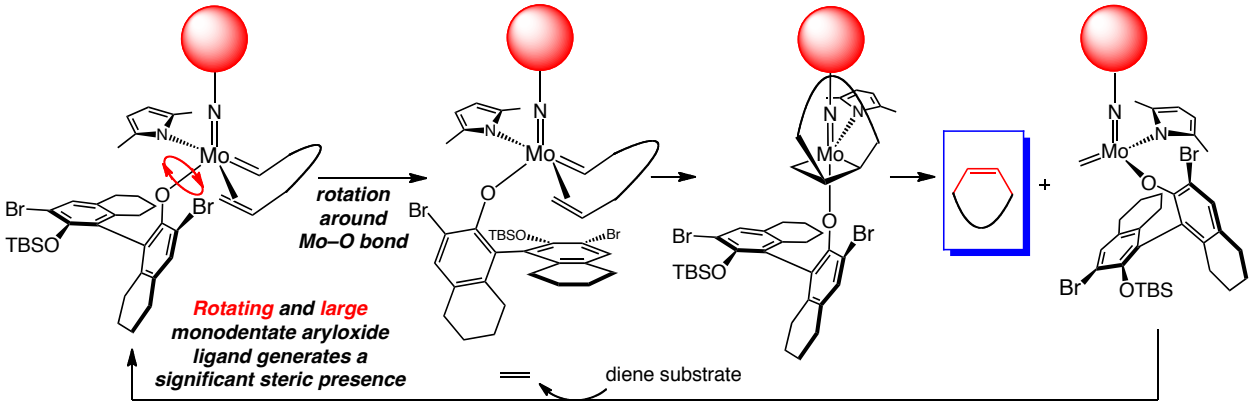
was allowed to stir at 40 °C for the required period of time. The reaction was quenched by the addition of excess ethyl vinyl ether and allowed to stir for two hours. Then the mixture was concentrated *in vacuo* (percent conversion determined by 400 MHz ^{1}H NMR analysis). Purification was performed by silica gel chromatography.

_Z_-selective Macrocyclic Ring-Closing Metathesis (RCM):

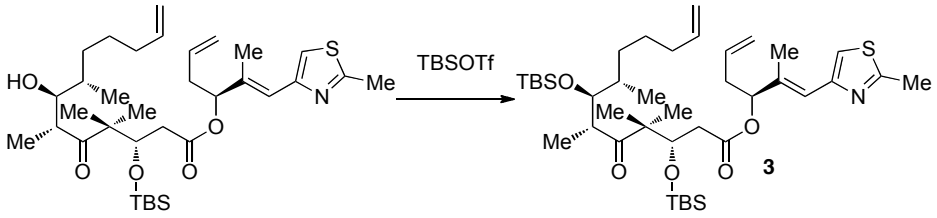


(*Z*)-Oxacyclohexadec-6-en-2-one (12). Following the general procedure for Mo-catalyzed RCM, with 1.2 mol % of **8**, diene **11** (12.4 mg, 0.0446 mmol) was transformed to **12** with 75% conversion in one hour. The resulting yellow oil was purified by silica gel chromatography (50:1 hexanes: diethyl ether) to afford the macrocyclic alkene **12** as a colorless oil (6.2 mg, 0.026 mmol, 56% yield, *Z*:*E* = 92:8). **IR (neat)**: 3003 (m), 2927 (s), 2856 (s), 1735 (s), 1459 (m), 1349 (m), 1239 (m), 1206 (m), 1167 (m), 1144 (m), 1045 (m), 715 (m); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 5.40-5.31 (2H, m), 4.15 (2H, dd, *J* = 5.2, 5.2 Hz), 2.35 (2H, dd, *J* = 6.6, 6.6 Hz), 2.13-2.01 (4H, m), 1.75-1.61 (4H, m), 1.44-1.27 (12H, m); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 174.0, 131.2, 129.0, 64.5, 34.3, 28.0, 27.9, 27.4, 27.0, 26.9, 26.8, 26.6, 26.2, 25.6, 25.5; **HRMS (ESI$^+$) [M+H]$^+$** calcd for $C_{15}H_{27}O_2$: 239.2011, found: 239.2010.

■ Model for Origin of *Z* Selectivity:

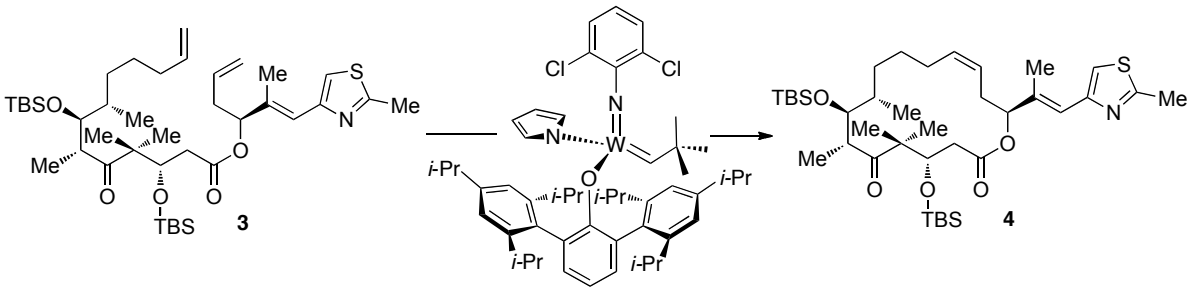


■ Synthesis of Epothilone C:



***(3S,6R,7S,8S)*-(*S,E*)-2-Methyl-1-(2-methylthiazol-4-yl)hexa-1,5-dien-3-yl 3,7-bis((*tert*-butyldimethylsilyl)oxy)-4,4,6,8-tetramethyl-5-oxotridec-12-enoate.** A solution of (*3S,6R,7S,8S*)-(*S,E*)-2-methyl-1-(2-methylthiazol-4-yl)hexa-1,5-dien-3-yl 3-((*tert*-butyldimethylsilyl)oxy)-7-hydroxy-4,4,6,8-tetramethyl-5-oxotridec-12-enoate[10] (0.326 g, 0.522 mmol) in CH_2Cl_2 (19.9 mL) at –50 °C was treated with 2,6-lutidine (1.82 mL, 15.7 mmol) followed by TBSOTf (3.60 mL, 15.7 mmol). The mixture was allowed to stir at the same temperature for 0.5 hour, after which the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The resulting mixture was washed with CH_2Cl_2 (three times). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification by chromatography on SiO_2 (hexanes:ethyl ether = 100:2 to 10:1) followed by the second chromatography (hexanes: diethyl ether = 100:4 to 100:6 to 10:1) to remove TBSOH, afforded the title compound (0.281 g, 0.383 mmol, 73% yield) as a colorless oil. The physical and spectral data were identical to those previously reported[1]. **IR (neat)** 3076 (w), 2954 (m), 2929 (m), 2886 (m), 2856 (m), 1736 (m), 1696 (m), 1641 (w), 1505 (w), 1471 (m), 1385 (s), 1292 (w), 1259 (m), 1177 (m), 1084 (m); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.95 (1H, s), 6.49 (1H, s), 5.85-5.65 (2H, m), 5.30 (1H, t, *J* = 6.8 Hz), 5.13-4.91 (4H, m), 4.34 (1H, dd, *J* = 6.0, 3.6 Hz), 3.73 (1H, dd, *J* = 6.8, 2.4 Hz), 3.15 (1H, dq, *J* = 14.0, 6.8 Hz), 2.70 (3H, s), 2.56-2.43 (3H, m), 2.39 (1H, dd, *J* = 16.8, 6.0 Hz), 2.07 (3H, d, *J* = 4.0 Hz), 2.05-1.98 (2H, m), 1.50-1.29 (3H, m), 1.24 (3H, s), 1.19-1.06 (2H, m), 1.06-1.02 (6H, m), 0.89 (3H, d, *J* = 6.8 Hz), 0.89 (9H, s), 0.87 (9H, s), 0.15 (3H, s), 0.05 (3H, s), 0.03 (6H, s); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 217.9, 171.4, 164.8, 152.7, 139.2, 137.0, 133.6, 121.3, 118.0, 116.6, 114.6, 78.9, 77.8, 74.3, 53.6, 45.4, 40.5, 39.1, 37.7, 34.5, 30.7, 27.3, 26.4, 26.3, 23.4, 20.5, 19.5, 18.7, 18.4, 17.8, 15.6, 14.8, –3.4, –3.6, –4.0, –4.5; **HRMS (ESI$^+$) [M+H]$^+$** calcd for $C_{40}H_{72}NO_5SSi_2$: 734.4670, found: 734.4652.

(10) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960–7973



(*4S,7R,8S,9S,16S,Z*)-4,8-Bis((*tert*-butyldimethylsilyl)oxy)-5,5,7,9-tetramethyl-16-((*E*)-1-(2-methylthiazol-4-yl)prop-1-en-2-yl)oxacyclohexadec-13-ene-2,6-dione.

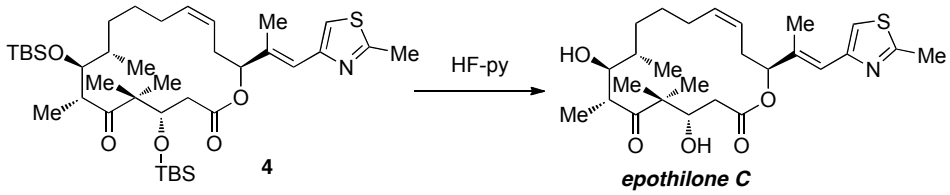
Reaction outside glovebox: A 250 mL Airfree® Schlenk flask (with a 24/40 joint, lubricated with Krytox® fluorinated grease) fitted with an Airfree® connecting adapter (Chemglass® item number AF-0506-03) and a rubber septum was connected to an argon (UHP) filled manifold, flame-dried and charged with diene **3** (0.219 g, 0.298 mmol). The diene was azeotroped with dry benzene three times (freeze-pump). The reaction apparatus was then charged with the solid tungsten complex (21.9 mg, 0.0224 mmol, weighed in air), evacuated, back-filled with argon and charged with mesitylene (50.0 mL, freshly distilled from sodium and transferred via a gas-tight syringe). The valve on the connecting adapter was closed to isolate the septum from reaction vessel. The resulting solution was exposed to vacuum (0.02 torr) and allowed to stir for 4 hours at 22 °C. The reaction mixture was then quenched by the addition of wet ethyl ether (~1 mL). Purification on SiO_2 (hexanes:Et_2O 20:1) afforded **4** (0.172 g, 0.243 mmol, 82% yield, 94:6 mixture of *Z*/*E* isomers as determined by 500MHz ^{1}H NMR) as a white foam along with recovered starting material (9.3 mg, 0.013 mmol, 3%).

Reaction inside glovebox: In an N_2-filled glovebox, diene (4.1 mg, 0.0056 mmol, azeotroped with benzene) in a 20-mL vial was dissolved in toluene (5.6 mL) and treated with a solution of the tungsten complex (0.028 mL, 0.020 M in benzene, 0.00056 mmol). The vial was capped with a septum fitted with one 20-gauge needles and a vacuum adapter. The mixture was exposed to vacuum (one torr) and allowed to stir at 22 °C for 2.5 hours. Additional toluene was added during the reaction (after 1.5 hours) to compensate for solvent loss due to vacuum. The reaction was quenched by the addition of ethyl ether and concentrated under reduced pressure. Purification on SiO_2 (hexanes: diethyl ether 20:1) afforded the title compound (3.4 mg, 0.0048 mmol, 85% yield, *Z:E* = 96:4) as a colorless solid. The physical and spectral data were identical to those previously reported[1,11,12]. **IR (neat)**: 2955 (m), 2924 (s), 2854 (m), 1743 (m), 1697 (w), 1462 (m), 1378 (w), 1254 (m), 1182 (w), 1158 (w), 1097 (w), 1066 (w), 1019 (w); **^{1}H NMR of *Z* isomer (400 MHz, $CDCl_3$)**: δ 6.96 (1H, s), 6.57 (1H, s) [diagnostic *E* isomer signal: 6.53 (1H, s)], 5.53 (1H, dt, *J* = 11.2, 4.2 Hz), 5.42-5.23 (1H, m), 5.02 (1H, d, *J* = 10.2 Hz), 4.03 (1H, dd, *J* = 10.2, 1.2 Hz), 3.89 (1H, d, *J* = 8.4 Hz), 3.05-2.96 (1H, m), 2.82 (1H, dd, *J* = 16.2, 1.2 Hz), 2.79-2.70 (2H, m), 2.70 (3H, s), 2.67 (1H, dd, *J* = 16.2, 10.2 Hz), 2.40-2.33 (1H, m), 2.11 (3H, d, *J* = 1.2 Hz), 2.10-2.06 (1H, m), 1.90-1.82 (1H, m), 1.62-1.46 (3H, m), 1.30-1.00 (1H, m), 1.19

(11) Storer R. I.; Takemoto, T.; Jackson, P. S.; Brown, D. S.; Baxendale, I. R.; Ley, S. V. *Chem. Eur. J.* **2004**, *10*, 2529–2547.

(12) Schinzer, D.; Bauer, A.; Bohm, O. M.; Limberg, A.; Cordes, M. *Chem. Eur. J.* **1999**, *5*, 2483–2491.

(3H, s), 1.14 (3H, s), 1.09 (3H, d, *J* = 6.6 Hz), 0.95 (3H, d, *J* = 6.6 Hz), 0.94 (9H, s), 0.84 (9H, s), 0.12 (3H, s), 0.10 (3H, s), 0.07 (3H, s), –0.10 (3H, s); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 215.2, 171.5, 164.8, 152.7, 138.8, 135.3, 123.0, 119.7, 116.3, 79.8, 79.5, 76.6, 53.6, 48.2, 39.1, 38.0, 32.0, 31.6, 29.4, 28.6, 26.6, 26.4, 25.2, 24.4, 19.4, 19.3, 18.9, 18.8, 17.9, 15.5, –3.0, –3.1, –3.5, –5.5. **HRMS (ESI$^+$) [M+H]$^+$** calcd for $C_{38}H_{67}NO_5SSi_2$: 706.4357, found: 706.4348.



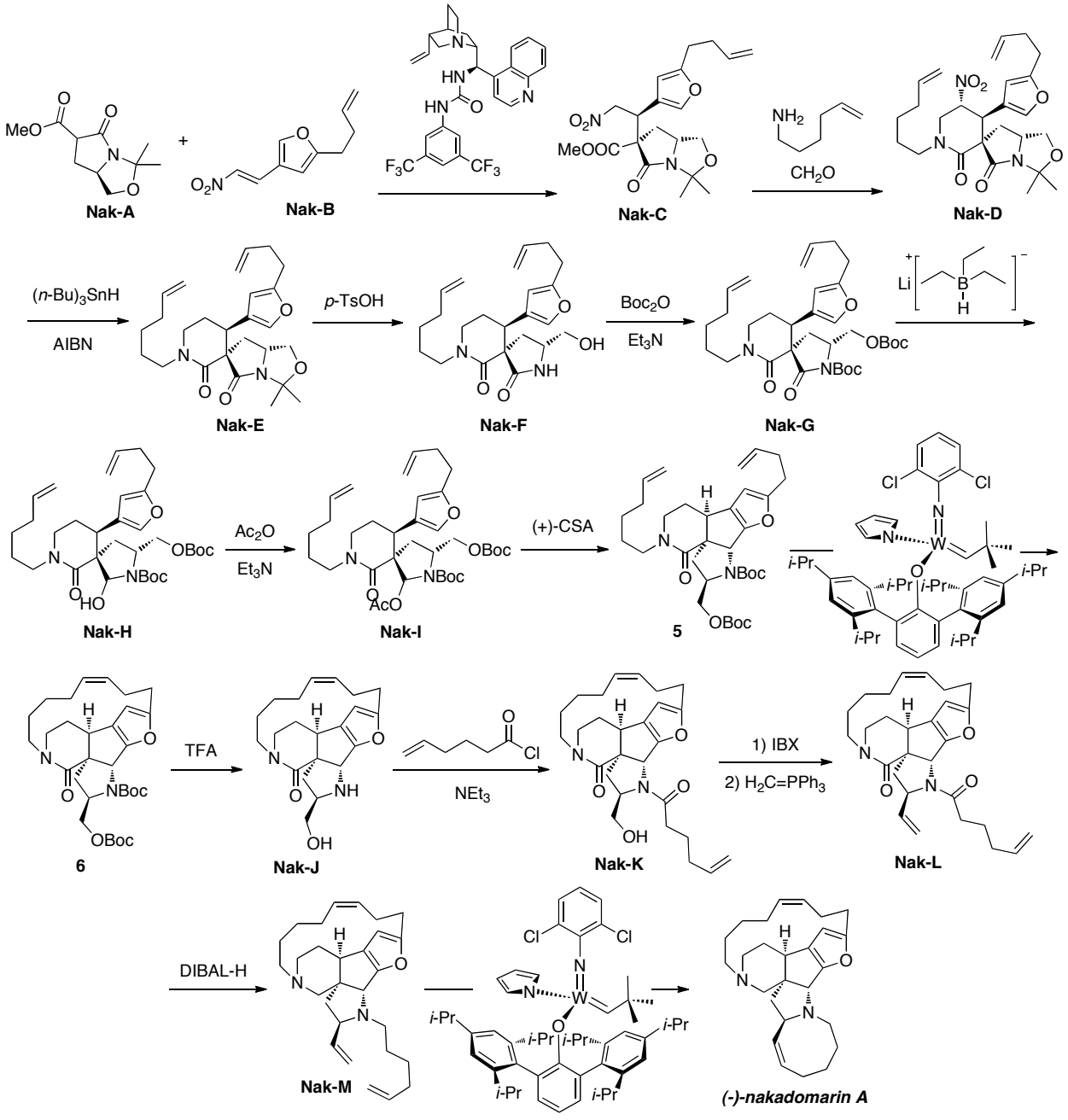
Epothilone C. A solution of (*4S,7R,8S,9S,16S,Z*)-4,8-Bis((*tert*-butyldimethylsilyl)oxy)-5,5,7,9-tetramethyl-16-((*E*)-1-(2-methylthiazol-4-yl)prop-1-en-2-yl)oxacyclohexadec-13-ene-2,6-dione (26.2 mg, 0.0371 mmol) in THF (3.60 mL) in a plastic vial was treated with HF-pyridine complex (70% HF, 1.09 mL). The mixture was allowed to stir at 22 °C for 36 hours, diluted with CH_2Cl_2 and quenched by the addition of a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Purification on SiO_2 (hexanes: diethyl ether 2:1 to 1:1) afforded epothilone C (15.2 mg, 0.0301 mmol, 81% yield, *Z:E* = 95:5) as a colorless solid together with 2.6 mg of mono-desilylated product. The physical and spectral data were identical to those previously reported[12, 13]. **IR (neat)**: 3503 (br), 2928 (s), 1732 (s), 1686 (s), 1506 (m), 1465 (m), 1405 (m), 1376 (m), 1331 (m), 1293 (m), 1249 (m), 1184 (m), 1150 (m), 1090 (m), 1047 (m), 1006 (m); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.96 (1 H, s), 6.59 (1 H, s) [diagnostic *E* isomer signal: 6.56 (1 H, s)], 5.49-5.34 (2 H, m), 5.29 (1 H, dd, *J* = 10.0, 2.0 Hz), 4.22 (1 H, d, *J* = 10.4 Hz), 3.74 (1 H, dd, *J* = 4.0, 2.0 Hz), 3.22 (1 H, br s), 3.14 (1 H, dq, *J* = 13.6, 2.4 Hz), 3.02 (1 H, br s), 2.74-2.64 (1 H, m), 2.70 (3 H, s), 2.50 (1 H, dd, *J* = 15.2, 11.2 Hz), 2.36 (1 H, dd, *J* = 15.2, 2.8 Hz), 2.30-2.15 (2 H, m), 2.09 (3 H, d, *J* = 1.6 Hz), 2.06-1.98 (1 H, m), 1.80-1.1.61 (2 H, m), 1.41-1.30 (1 H, m), 1.33 (s, 3 H), 1.28-1.16 (2 H, m), 1.18 (3 H, d, *J* = 6.8 Hz), 1.08 (3 H, s), 1.00 (3 H, d, *J* = 7.2 Hz); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 220.8, 170.6, 165.2, 152.2, 138.9, 133.6, 125.2, 119.6, 116.0, 78.6, 74.3, 72.5, 53.6, 41.9, 39.5, 38.8, 32.6, 32.0, 27.8, 27.7, 23.0, 19.3, 18.7, 16.1, 15.7, 13.7. **HRMS (ESI$^+$) [M+H]$^+$** calcd for $C_{26}H_{40}NO_5S$: 478.2627, found: 478.2625.

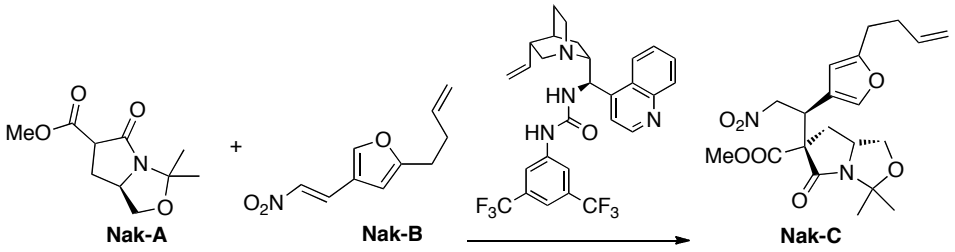
---

(13) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960–7973.

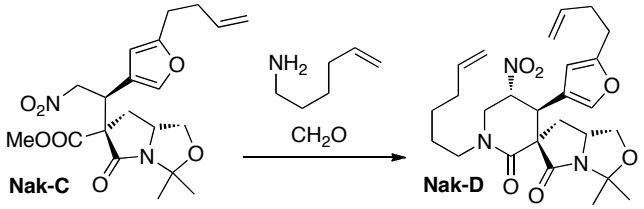
■ Synthesis of Nakadomarin A:

Chart 3. **Synthesis of (-)-Nakadomarin A**





Nitro ester Nak-A. To a solution of methyl ester **Nak-A**[14] (8.28 g, 38.8 mmol) and nitroalkene **Nak-B**[4] (4.95 g, 25.6 mmol) in toluene (82 mL) was added organocatalyst[4] (4.26 g, 7.77 mmol) in one portion. The mixture was allowed to stir for three days at 30 °C before being concentrated *in vacuo* and purified by silica gel chromatography (7:3 to 3:7 petroleum ether: diethyl ether). **Nak-C** was obtained as a yellow crystalline solid, which was further purified by recrystallization from diethyl ether and cooled to –20 °C. Further purification of the mother liquors were also required in a similar manner to give the desired compound as a colorless crystalline solid (7.50 g, 18.4 mmol, 72% yield, single diastereoisomer). M.p. 90-92 °C; **IR (neat)**: 2984 (w), 2935 (w), 1738 (s), 1690 (s), 1554 (s), 1413 (m), 1380 (m), 1278 (m), 1224 (m), 1038 (w), 923 (w), 819 (w); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.30 (1H, d, *J* = 0.8 Hz), 6.03 (1H, d, *J* = 0.8 Hz), 5.78 (1H, ddt, *J* = 17.0, 10.3, 6.6 Hz), 5.06-4.86 (4H, m), 4.07 (1H, dd, *J* = 10.6, 3.8 Hz), 3.94-3.88 (1H, m), 3.82 (3H, s), 3.43-3.30 (2H, m), 2.67 (2H, t, *J* = 7.5 Hz), 2.40-2.31 (2H, m), 2.21-2.17 (2H, m), 1.68 (3H, s), 1.43 (3H, s); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 171.7, 167.3, 157.1, 140.3, 137.0, 119.6, 115.6, 105.0, 91.9, 76.8, 69.9, 63.5, 58.7, 53.4, 38.8, 33.4, 31.9, 27.5, 26.3, 23.3; **HRMS (ESI$^+$) [M+Na]$^+$** calcd for $C_{20}H_{26}N_2NaO_7$: 429.1632, found: 429.1637; $[\alpha]_D^{21}$ + 0.9 (c = 0.67, $CHCl_3$).

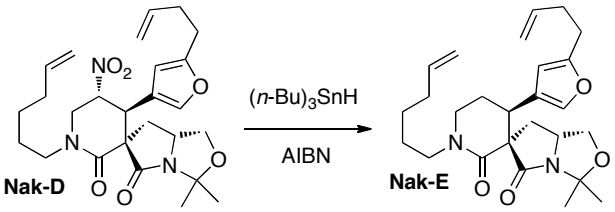


Nitro lactam Nak-D. A mixture of 6-bromo-1-hexene (11.4 g, 69.9 mmol) and NaN_3 (6.82 g, 105 mmol) in DMSO (82 mL) was allowed to stir at 22 °C for two hours. The mixture was poured into water (160 mL) and washed three times with diethyl ether (50 mL). The combined organic layers were washed with brine and water was added. Triphenylphosphine (36.7 g, 140 mmol) was added over ten minutes. The resulting solution was stirred for 16 hours and then washed with a solution of aqueous 1.0 M HCl three times. The aqueous phase was washed with diethyl ether and the aqueous layer was basified with solid sodium hydroxide while cooling in an ice-bath and then washed three times with diethyl ether (50 mL). The combined organic layers were washed with brine, dried and concentrated with a stream of nitrogen, to afford the desired amine as a colorless oil. A solution of nitro ester **Nak-C** (5.30 g, 13.0 mmol), hex-5-en-1-amine

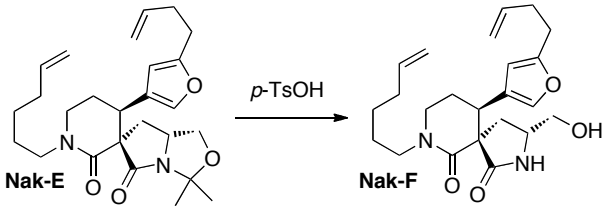
---

(14) Kyle, A. F., Jakubec, P.; Cockfield, D. M.; Cleator, E.; Skidmore, J.; Dixon, D. J. *Chem. Commun.* **2011**, DOI: 10.1039/c1cc13665h.

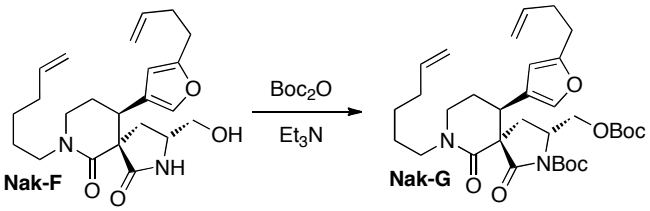
(1.94 g, 19.6 mmol) and formaldehyde (37% solution in water) (1.59 g, 1.46 mL, 19.6 mmol) in MeOH (100 mL) was allowed to heat at 65 °C for five hours. The solution was allowed to cool to 22 °C and concentrated *in vacuo* before being purified by silica gel chromatography (1:1 to 2:8 petroleum ether: diethyl ether) to afford the nitroamide **Nak-D** as a brown oil (4.15 g, 8.58 mmol, 66% yield). **IR (neat)**: 2982 (w), 2933 (w), 2858 (w), 1693 (s), 1650 (s), 1556 (s), 1411 (m), 1350 (m), 1259 (m), 1134 (w), 916 (w), 821 (w); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.28 (1H, d, *J* = 1.0 Hz), 6.06 (1H, d, *J* = 1.0 Hz), 5.89 (1H, ddd, *J* = 12.0, 9.5, 6.5 Hz), 5.84-5.72 (2H, m), 5.06-4.93 (4H, m), 4.01 (1H, dd, *J* = 12.0, 6.4 Hz), 3.90 (1H, dd, *J* = 8.0, 5.4 Hz), 3.79 (1H, dd, *J* = 12.1, 9.1 Hz), 3.57-3.47 (3H, m), 3.46-3.34 (2H, m), 3.01 (1H, dd, *J* = 13.3, 7.2 Hz), 2.66 (2H, t, *J* = 7.5 Hz), 2.38-2.30 (2H, m), 2.13-2.05 (2H, m), 1.90 (1H, dd, *J* = 13.1, 7.3 Hz), 1.70-1.56 (2H, m), 1.58 (3H, s), 1.47-1.37 (2H, m), 1.35 (3H, s); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 168.4, 167.2, 157.2, 139.9, 138.3, 137.0, 118.8, 115.7, 114.9, 104.9, 91.6, 81.5, 69.7, 62.8, 58.7, 49.4, 48.3, 42.9, 33.3, 31.9, 31.6, 27.6, 26.3, 26.2, 25.8, 23.3; **HRMS (ESI$^+$) [M+Na]$^+$** calcd for $C_{26}H_{35}N_3NaO_6$: 508.2418, found: 508.2412; $[\alpha]_D^{21}$ +97.3 (*c* = 0.640, $CHCl_3$).



Spirolactam Nak-E. Nitroamide Nak-D (5.60 g, 11.5 mmol) was dissolved in mesitylene (160 mL). To this solution was added AIBN (0.380 g, 2.31 mmol) and tributyltin hydride (16.8 g, 15.3 mL, 57.7 mmol); the mixture was degassed by repeated cycles of vacuum/nitrogen purge. The solution was heated rapidly to 160 °C in a pre-heated oil bath for 2.5 hours before being cooled to 22 °C. The mixture was loaded directly onto silica gel; the mesitylene and excess tin compounds eluted with petroleum ether before ramping the solvent system (9:1 to 1:8 petroleum ether: diethyl ether), to afford the spirolactam **Nak-E** as pale yellow oil (2.95 g, 6.67 mmol, 58% yield). **IR (neat)**: 2982 (w), 2932 (w), 2863 (w), 1691 (s), 1638 (s), 1548 (w), 1491 (w), 1442 (w), 1406 (m), 1261 (w), 914 (w); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.24 (1H, br. s), 6.05 (1H, br. s), 5.87-5.74 (2H, m), 5.08-4.91 (4H, m), 3.88 (1H, dd, *J* = 7.7, 5.2 Hz), 3.54-3.31 (6H, m), 2.99 (1H, dd, *J* = 12.8, 7.5 Hz), 2.95-2.87 (2H, m), 2.70-2.63 (2H, m), 2.40-2.32 (2H, m), 2.14-2.03 (2H, m), 1.84 (1H, dd, *J* = 12.6, 7.1 Hz), 1.78-1.71 (1H, m), 1.67-1.53 (5H, m), 1.48-1.36 (2H, m), 1.29 (3H, s); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 169.5, 168.6, 156.2, 138.6, 137.8, 137.2, 124.7, 115.4, 114.6, 105.6, 91.2, 69.9, 63.3, 58.6, 48.3, 47.4, 40.0, 33.4, 33.0, 32.0, 27.6, 26.3, 26.3, 26.0, 25.3, 23.4; **HRMS (ESI$^+$) [M+Na]$^+$** calcd for $C_{26}H_{36}N_2NaO_4$: 463.2567, found: 463.2578; $[\alpha]_D^{21}$ +94.1 (*c* = 2.30, $CHCl_3$).

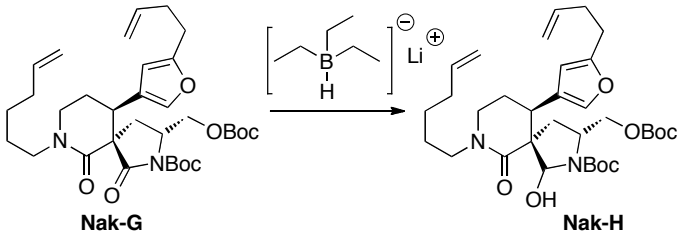


Alcohol Nak-F. *p*-Toluenesulfonic acid (63.0 mg, 0.330 mmol) was added to a solution of spirolactam **Nak-E** (2.91 g, 6.61 mmol) in methanol (150 mL) and the mixture was heated to 65 °C and allowed to stir at that temperature for four hours. Additional amount of *p*-toluenesulfonic acid (10.0 mg, 0.0500 mmol) was then introduced. After heating at reflux for an additional hour, the solution was cooled to 22 °C, concentrated and purified by silica gel chromatography (ethyl acetate to 98:2 ethyl acetate: methanol) to afford **Nak-F** as a colorless oil (2.11 g, 5.29 mmol, 80% yield). **IR (neat)**: 3406 (m), 3270 (m), 2929 (m), 2858 (m), 1695 (s), 1618 (s), 1494 (w), 1435 (m), 1348 (w), 1272 (m), 1125 (w), 1062 (w), 912 (m), 734 (w); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.22 (1H, d, *J* = 0.8 Hz), 6.28 (1H, br. s), 6.06 (1H, d, *J* = 0.8 Hz), 5.87-5.73 (2H, m), 5.08-4.91 (4H, m), 4.47 (1H, t, *J* = 5.4 Hz), 3.59 (2H, t, *J* = 4.9 Hz), 3.52-3.37 (3H, m), 3.37-3.22 (2H, m), 3.15-3.02 (1H, m), 2.84 (1H, dd, *J* = 13.4, 2.8 Hz), 2.71-2.60 (3H, m), 2.41-2.32 (2H, m), 2.16-2.03 (3H, m), 1.84-1.72 (1H, m), 1.67-1.54 (2H, m), 1.45-1.35 (2H, m); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 175.6, 170.5, 156.2, 138.5, 138.1, 137.4, 124.4, 115.3, 114.7, 105.7, 65.7, 55.6, 52.9, 48.5, 47.6, 40.4, 34.0, 33.4, 32.0, 27.6, 26.3, 26.0, 25.3; **HRMS (ESI$^+$) [M+Na]$^+$** calcd for $C_{23}H_{32}N_2NaO_4$: 423.2254, found: 423.2258; $[\alpha]_D^{21}$ +112.0 (*c* = 0.700, $CHCl_3$).



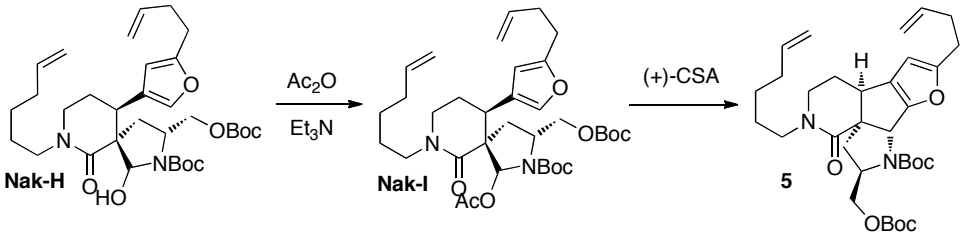
Bis-Boc-protected lactam Nak-G. To a solution of **Nak-F** (1.75 g, 4.37 mmol) in CH_2Cl_2 (75 mL) was added DMAP (53.0 mg, 0.430 mmol) and triethylamine (2.21 g, 3.04 mL, 21.9 mmol) before the portionwise addition of di-*tert*-butyl dicarbonate (4.77 g, 21.9 mmol). The solution was allowed to stir at 22 °C for 15 hours. The resulting dark yellow solution was concentrated and purified by silica gel chromatography (4:1 to 3:7 petroleum ether: ethyl acetate), to give the bis-Boc-protected lactam **Nak-G** as a colorless oil (2.55 g, 4.24 mmol, 97% yield). **IR (neat)**: 2979 (w), 2934 (w), 1781 (m), 1744 (s), 1640 (s), 1491 (w), 1455 (w), 1369 (m), 1278 (s), 1254 (s), 1158 (s), 914 (w), 856 (w); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.17 (1H, br, s), 5.93 (1H, br, s), 5.85-5.73 (2H, m), 5.06-4.92 (4H, m), 4.44 (1H, dd, *J* = 10.0, 4.4 Hz), 4.19 (1H, dd, *J* = 9.9, 8.6 Hz), 3.82 (1H, tt, *J* = 8.9, 4.5 Hz), 3.52-3.40 (3H, m), 3.29 (1H, ddd, *J* = 13.1, 8.7, 6.4 Hz), 3.06-2.92 (1H, m), 2.84 (1H, dd, *J* = 13.4, 2.8 Hz), 2.73 (1H, dd, *J* = 13.8, 4.7 Hz), 2.65-2.58 (2H, m), 2.37-2.29 (2H, m), 2.13-2.03 (3H, m), 1.79-1.71 (1H, m), 1.66-1.52 (2H, m), 1.48 (9H, s), 1.46 (9H, s), 1.45-1.36 (2H, m); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 172.8, 167.7, 156.7, 153.1, 149.4, 138.5, 138.3, 137.2, 123.9, 115.4, 114.7, 105.1, 83.3, 82.1, 68.2, 57.0, 53.4, 48.3,

47.4, 41.6, 33.5, 32.0, 31.3, 27.9, 27.8, 27.6, 26.4, 26.1, 25.2; **HRMS (ESI$^+$) [M+Na]$^+$** calcd for $C_{33}H_{48}N_2NaO_8$: 623.3303, found: 623.3312; $[\alpha]_D^{21}$ +120.0 (c = 0.700, $CHCl_3$).



Nak-G **Nak-H**

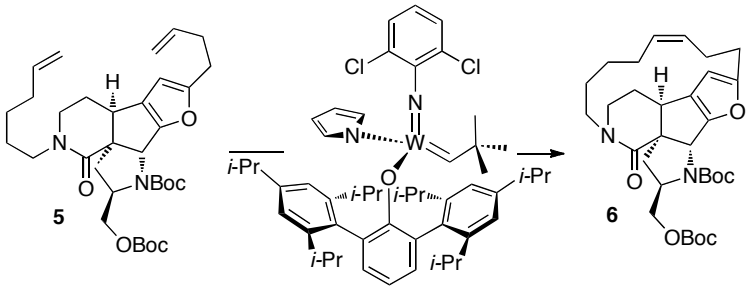
Boc-protected hemiaminol Nak-H. To a solution of **Nak-G** (2.50 g, 4.16 mmol) in THF (105 mL) was added dropwise lithium triethylborohydride (11.2 mL, 11.2 mmol, 1.0 M solution in THF) at –78 ºC and the solution was allowed to stir at this temperature for three hours. The reaction was then quenched by the addition of a saturated aqueous solution of NH_4Cl (100 mL). The reaction was allowed to warm to 22 ºC over one hour and then diluted by the addition of diethyl ether (150 mL). The aqueous layer was washed and the combined organics were dried (Na_2SO_4) and concentrated. The resulting oil was purified by silica gel chromatography (4:1 to 7:3 petroleum ether: ethyl acetate) to afford **Nak-H** as a colorless oil (2.04 g, 3.37 mmol, 81% yield): The ^{1}H NMR spectrum of the title compound suffers from considerable broadening due to rotamers when run in $CDCl_3$ at 298 K. Attempts to improve this spectrum by collecting the data in toluene-d_8 at 363 K resulted in decomposition of the compound. The material was used in the next step without full characterization.



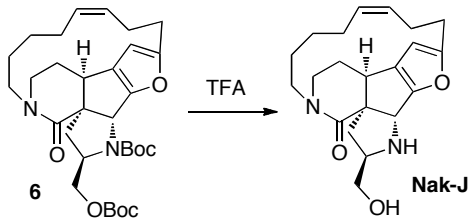
Nak-H **Nak-I** **5**

Diene 5. To a solution of **Nak-H** (300 mg, 0.498 mmol) in CH_2Cl_2 (10 ml) was added triethylamine (280 mg, 0.390 mL, 2.79 mmol), acetic anhydride (290 mg, 0.260 mL, 2.79 mmol) and DMAP (3.0 mg, 0.025 mmol). The reaction was allowed to stir at 22 ºC for six hours, followed by the addition of a second portion of DMAP (20.0 mg, 0.164 mmol). The mixture was allowed to stir for 15 hours, before being filtered through a short pad of silica, which was washed with diethyl ether. The filtrate was concentrated and the resulting residue was dissolved in CH_2Cl_2 (10 ml), (+)-camphorsulfonic acid (21.0 mg, 0.0900 mmol) was added and the mixture was allowed to stir at 22 ºC for one hour. The resulting solution was concentrated *in vacuo* and the resulting oil was purified by column chromatography (9:1 to 6:4 petroleum ether: ethyl acetate), to give diene **5** as colorless oil (268 mg, 0.458 mmol, 92% yield). The ^{1}H NMR spectrum of the title compound suffers from broadening due to the presence of rotamers when performed in $CDCl_3$ at 22 °C. The major rotamer has been assigned. **IR (neat)**: 2978 (m), 2931 (m), 1743 (s), 1699 (s), 1640 (s), 1483 (w), 1454 (w), 1380 (s), 1369 (s), 1279 (s), 1255 (s), 1162 (s), 1099 (w), 913 (w), 863 (w); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 5.91-5.68 (3H, m), 5.08-4.90

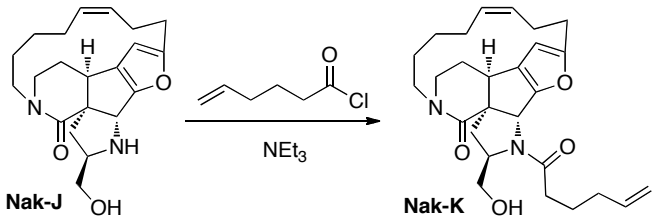
(5H, m), 4.72 (1H, dd, *J* = 9.6, 3.5 Hz), 4.35 (1H, t, *J* = 9.5 Hz), 4.13-4.04 (1H, m), 3.37 (2H, t, *J* = 7.3 Hz), 3.27-3.12 (2H, m), 3.02 (1H, t, *J* = 6.1 Hz), 2.69 (2H, t, *J* = 7.6 Hz), 2.59 (1H, dd, *J* = 13.4, 4.5 Hz), 2.38 (2H, q, *J* = 7.1 Hz), 2.16-1.99 (4H, m), 1.71-1.60 (1H, m), 1.56-1.43 (20H, m), 1.40-1.30 (2H, m); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 172.2, 161.1, 155.0, 153.9, 153.2, 138.4, 137.3, 128.2, 115.4, 114.8, 102.2, 81.7, 80.0, 67.0, 65.9, 63.9, 56.8, 48.0, 45.1, 43.5, 40.5, 33.4, 32.0, 29.2, 28.5, 28.3, 27.8, 26.7, 26.0; **HRMS (ESI$^+$) [M+Na]$^+$** calcd for $C_{33}H_{48}N_2NaO_7$: 607.3354, found: 607.3349; $[\alpha]_D^{21}$ +28.9 (*c* = 3.40, $CHCl_3$).



Boc-protected pentacycle 6. In an N_2-filled glove box, a 100 mL round bottom flask was charged with diene (107 mg, 0.186 mmol). Toluene (37 mL) was added and W complex **10** (9.1 mg, 0.0093 mmol, 0.05 equivalent) was subsequently introduced. The resulting mixture was allowed to stir for three minutes to allow complete initiation of the catalyst. The flask was capped with a septum fitted with two 20-gauge needles and connected to a seven torr vacuum generated from a diaphragm vacuum pump. After it was allowed to stir at 22 °C for two hours, the mixture was removed from the glovebox and exposed to air. The resulting solution was concentrated to deliver a yellow oil, which was then purified by silica gel chromatography (2:1 to 1:2 hexanes: diethyl ether) to afford the macrocyclic alkene **6** as a white solid (94.1 mg, 0.168 mmol, 90% yield, *Z:E* = 97:3). M.p. 184-187 °C; **IR (neat)**: 2978 (s), 2938 (s), 2868 (m), 1742 (s), 1694 (s), 1634 (s), 1488 (m), 1453 (m), 1393 (s), 1367 (s), 1351 (s), 1277 (s), 1254 (s), 1155 (s), 1106 (s), 953 (m), 859 (m), 792 (m), 761 (m), 732 (m); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 5.82 (1H, s), 5.44 (1H, dt, *J* = 5.6, 6.1 Hz), 5.26 (1H, dt, *J* = 5.6, 6.0 Hz), 4.81-4.72 (2H, m), 4.46 (1H, dt, *J* = 8.8, 2.4 Hz), 4.28-4.25 (1H, m), 4.17 (1H, dd, *J* = 6.6, 5.4 Hz), 3.27 (1H, s), 3.14 (1H, dt, *J* = 7.6, 2.4 Hz), 2.90 (1H, dd, *J* = 8.0, 2.8 Hz), 2.75 (1H, t, *J* = 8.4 Hz), 2.59-2.41 (4H, m), 2.19 (2H, dd, *J* = 8.8, 4.0 Hz), 2.10 (1H, d, *J* = 8.4 Hz), 1.93-1.88 (2H, m), 1.62-1.59 (1H, m), 1.53-1.40 (19H, m), 1.28-1.23 (1H, m), 0.99-0.96 (1H, m), 0.03-–0.05 (1H, m); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 171.6, 159.9, 157.0, 154.2, 153.4, 130.5, 128.7, 128.5, 103.0, 82.1, 80.2, 69.0, 67.7, 67.6, 58.3, 46.8, 43.5, 39.5, 36.0, 28.8, 28.3, 27.9, 27.6, 26.6, 26.3, 25.6, 22.3; **HRMS (ESI$^+$) [M+H]$^+$** calcd for $C_{31}H_{45}N_2O_7$: 557.3227, found: 557.3218; $[\alpha]_D^{20}$ –63.17 (c = 0.640, $CHCl_3$).

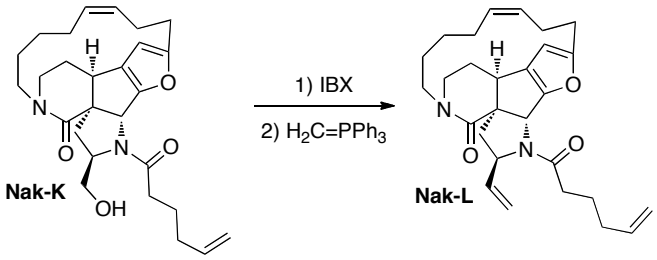


Aminol Nak-J. In a 35-mL vial equipped with a magnetic stir bar, the macrocyclic alkene **6** (130 mg, 0.233 mmol) was treated with trifluoroacetic acid (1.0 mL, 13 mmol), and allowed to stir for five minutes at 22 °C. The trifluoroacetic acid was removed by vacuum. The resulting yellow oil was treated with a saturated aqueous solution of $NaHCO_3$ (6.0 mL) and dichloromethane (6.0 mL). Layers were partitioned and the aqueous layer was washed with a 4:1 solution of chloroform/isopropanol (6.0 mL x 3). The combined organic layers were dried and concentrated. The resulting yellow oil was purified by silica gel chromatography (9:1 dichloromethane: methanol) to afford the aminol **Nak-J** as a white solid (80.0 mg, 0.225 mmol, 95% yield, *Z:E* = 95:5). M.p. 182–185 °C; **IR (neat)**: 3368 (br, s), 3004 (m), 2925 (s), 2856 (s), 1676 (s), 1604 (s), 1494 (m), 1443 (s), 1361 (m), 1201 (s), 1181 (s), 1131 (s), 1035 (m), 840 (m), 800 (m), 722 (m); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 5.82 (1H, s), 5.46 (1H, dt, *J* = 8.8, 7.4 Hz), 5.26 (1H, dt, *J* = 8.8, 8.0 Hz), 4.80-4.37 (4H, m), 3.82-3.69 (3H, m), 3.29 (1H, s), 3.08 (1H, dt, *J* = 12.4, 3.6 Hz), 2.91 (1H, dd, *J* = 12.0, 4.0 Hz), 2.82-2.78 (1H, m), 2.62-2.46 (3H, m), 2.32 (1H, dd, *J* = 12.4, 9.6 Hz), 2.16-2.09 (2H, m), 2.00-1.88 (3H, m), 1.64-1.46 (2H, m), 1.30-1.25 (1H, m), 1.05-0.99 (1H, m), 0.06-–0.05 (1H, m); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 173.6, 161.7, 155.8, 130.4, 129.6, 128.7, 103.4, 71.7, 69.0, 63.7, 63.0, 46.8, 43.4, 41.1, 37.1, 28.8, 27.6, 26.4, 26.0, 25.3, 23.2; **HRMS (ESI$^+$) [M+H]$^+$** calcd for $C_{21}H_{29}N_2O_3$: 357.2178, found: 357.2171; $[\alpha]_D^{20}$ –78.41 (c = 0.700, $CHCl_3$).



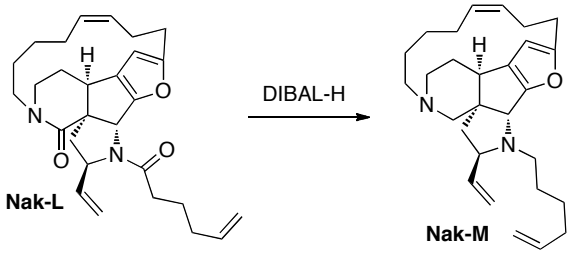
Alcohol Nak-K. In a 4-mL vial equipped with a magnetic stir bar, DMF (20 μL) was added to 5-hexenoic acid (40.0 mg, 0.351 mmol) and the mixture was allowed to cool to 0 °C. Oxalyl chloride (53.0 mg, 0.421 mmol) was added and the solution was allowed to stir for 15 minutes at 22 °C. Diethyl ether (1.0 mL) was added and the mixture was filtered through a cotton plug and concentrated with a stream of nitrogen to deliver 5-hexenyl chloride. In another 50-mL round bottom flask, aminol (120 mg, 0.337 mmol) and triethylamine (170 mg, 0.217 mL, 1.69 mmol) were dissolved in dichloromethane (15 mL) and allowed to cool to –20 °C; a pre-cooled solution of 5-hexenyl chloride in dichloromethane was then introduced by syringe. The mixture was allowed to slowly warm to 22 °C over 30 minutes and allowed to stir for three hours. The resulting mixture was concentrated by vacuum to afford a yellow oil, which was purified by silica gel chromatography (1:1 hexanes: ethyl acetate to 9:1 ethyl acetate: methanol) to afford primary alcohol **Nak-K** as a white solid (84.0 mg, 0.283 mmol, 84% yield, *Z:E* = 95:5). M.p.

147-149 °C; **IR (neat)**: 3350 (br, m), 2923 (s), 2854 (s), 1628 (s), 1549 (m), 1490 (m), 1440 (s), 1353 (m), 1326 (m), 1218 (m), 1203 (m), 1099 (m), 1080 (m), 911 (m), 805 (m), 750 (m); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 6.04 (1H, d, *J* = 9.2 Hz), 5.87 (1H, s), 5.84-5.76 (1H, m), 5.46 (1H, dt, *J* = 8.8, 9.2 Hz), 5.26 (1H, dt, *J* = 8.0, 9.0 Hz), 5.07-4.95 (2H, m), 4.91 (1H, s), 4.45 (1H, dt, *J* = 12.8, 4.0 Hz), 4.26-4.19 (1H, m), 3.75-3.62 (2H, m), 3.32 (1H, t, *J* = 2.8 Hz), 3.11 (1H, dt, *J* = 12.0, 4.0 Hz), 2.93 (1H, dd, *J* = 12.4, 4.8 Hz), 2.78-2.67 (1H, m), 2.60-2.39 (5H, m), 2.30-2.11 (5H, m), 2.02-1.89 (3H, m), 1.81-1.43 (4H, m), 1.33-1.22 (1H, m), 1.05-0.95 (1H, m), –0.01-–0.12 (1H, m); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 174.8, 171.2, 161.1, 155.4, 138.2, 130.5, 130.5, 128.5, 115.2, 103.6, 68.9, 68.2, 66.6, 66.4, 46.8, 43.2, 39.2, 35.1, 34.5, 33.4, 28.7, 27.5, 26.5, 26.3, 25.4, 24.3, 22.3; **HRMS (ESI$^+$) [M+H]$^+$** calcd for $C_{27}H_{37}N_2O_4$: 453.2753, found: 453.2739; $[\alpha]_D^{20}$ –48.67 (c = 0.260, $CHCl_3$).

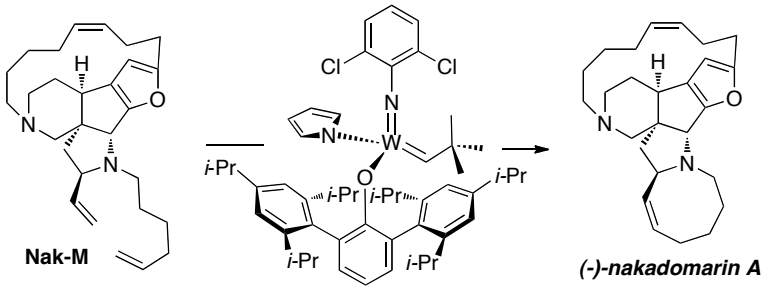


Triene Nak-L. In a 50-mL round bottom flask equipped with a magnetic stir bar, 2-iodoxybenzoic acid (413 mg, 1.47 mmol) was added to a solution of the alcohol (148 mg, 0.327 mmol) in DMSO (20 mL). The reaction mixture was allowed to stir at 22 °C for 24 hours, at which time it was poured into a saturated aqueous solution of $NaHCO_3$ (60 mL) and washed with diethyl ether (4 x 60 mL). The combined organic layers were washed with water (30 mL), dried with Na_2SO_4 and concentrated to afford the desired aldehyde as a yellow oil, which was used directly for the next step without purification. In a 50-mL round bottom flask, KO*t*-Bu (172 mg, 1.54 mmol) was added to $MePPh_3Br$ (700 mg, 1.96 mmol) in toluene (10 mL). The resulting mixture was placed in a sonication bath until a homogenous bright yellow solution formed. The mixture was allowed to stir at 22 °C for 90 minutes. The unpurified aldehyde was dissolved in THF (10 mL) and the solution was rapidly added to the aforementioned freshly prepared ylide solution. After 15 minutes, the mixture was concentrated; 30 mL water and 30 mL ethyl acetate were added. Layers were partitioned and the aqueous layer was washed three times with ethyl acetate (30 mL). The combined organic layers were dried with Na_2SO_4 and concentrated by vacuum to afford a colorless oil, which was purified by silica gel chromatography (3:2 to 2:3 hexanes: ethyl acetate) to afford the triene **Nak-L** as a white foam (122 mg, 0.272 mmol, 83% yield, *Z:E* = 95:5). **IR (neat)**: 2934 (s), 2863 (s), 1633 (s), 1488 (m), 1440 (s), 1406 (s), 1355 (s), 1287 (s), 1206 (s), 1168 (m), 992 (m), 953 (m), 912 (m), 732 (m); **^{1}H NMR (400 MHz, $CDCl_3$)**: (characterized as a mixture of two rotamers) δ 5.96-5.68 (3H, m), 5.48 (1H, dt, *J* = 9.2, 9.0 Hz), 5.28 (1H, dt, *J* = 8.8, 8.2 Hz), 5.20-4.89 (5H, m), 4.67-4.44 (2H, m), 3.34 (1H, s), 3.21-3.12 (1H, m), 3.00-2.69 (2H, m), 2.59-2.32 (5H, m), 2.20-1.92 (7H, m), 1.79-1.43 (5H, m), 1.34-1.18 (1H, m), 1.06-0.98 (1H, m), 0.04-–0.08 (1H, m); **^{13}C NMR (100 MHz, $CDCl_3$)**: (characterized as a mixture of two rotamers) δ 173.1, 172.5, 171.5, 171.3, 160.6, 160.1, 157.6, 156.0, 140.3, 139.6, 138.6, 138.6, 130.5, 130.3, 129.9, 129.1, 128.6, 128.2, 115.5, 114.9, 114.9, 113.9, 103.5, 103.0,

70.4, 68.3, 67.6, 67.0, 63.5, 63.3, 46.9, 43.4, 39.9, 39.6, 39.1, 38.3, 34.5, 34.4, 33.4, 33.3, 28.8, 28.7, 27.5, 27.2, 26.6, 26.4, 26.2, 25.5, 25.3, 24.3, 24.2, 22.4, 22.2; **HRMS (ESI$^+$) [M+H]$^+$** calcd for $C_{28}H_{37}N_2O_3$: 449.2804, found: 449.2790; $[\alpha]_D^{20}$ –76.61 (c = 0.110, $CHCl_3$).

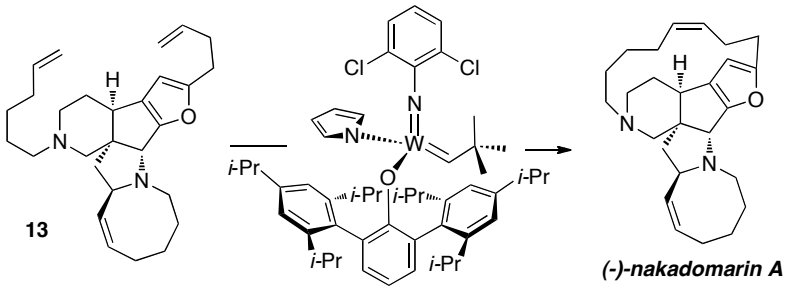


Diamine Nak-M. In a 25-mL round bottom flask equipped with a magnetic stir bar, DIBAL–H (159 μL, 0.893 mmol) was added to a solution of amide (20.0 mg, 0.0446 mmol) in 5.0 mL diethyl ether at 0 °C and allowed to stir for four hours. A second portion of DIBAL-H (159 μL, 0.893 mmol) was added and the mixture was allowed to warm to 22 °C and stir for two hours. A saturated aqueous solution of Rochelle salt (5 ml) was added at –78 °C and the mixture was allowed to warm to 22 °C and stir for six hours. The layers were partitioned and the aqueous fraction was washed three times with diethyl ether (10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated by vacuum to afford a colorless oil, which was purified by neutral alumina chromatography (10:1 to 2:1 hexanes: diethyl ether) to afford diamine **Nak-M** as a colorless oil (14.0 mg, 0.0333 mmol, 75% yield, *Z:E* = 95:5). **IR (neat)**: 3075 (m), 3003 (m), 2921 (s), 2856 (s), 2974 (s), 1641 (s), 1556 (m), 1445 (s), 1385 (m), 1359 (m), 1342 (m), 1172 (s), 1129 (s), 1100 (m), 1084 (m), 992 (s), 910 (s), 857 (m), 793 (m), 726 (m); **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 5.94-5.83 (1H, m), 5.78 (1H, s), 5.69-5.60 (1H, m), 5.48 (1H, dt, *J* = 8.0, 9.0 Hz), 5.26 (1H, dt, *J* = 7.6, 9.2 Hz), 5.14-4.94 (4H, m), 4.16 (1H, s), 3.14-3.08 (1H, m), 3.00 (1H, d, *J* = 10.8 Hz), 2.78-2.70 (2H, m), 2.65-2.43 (4H, m), 2.41 (1H, dt, *J* = 11.6, 3.2 Hz), 2.32-2.09 (6H, m), 2.00-1.84 (3H, m), 1.77 (1H, ddd, *J* = 14.0, 7.2, 2.4 Hz), 1.70-1.53 (3H, m), 1.50-1.38 (2H, m), 1.36-1.25 (2H, m), 1.08-0.96 (2H, m), 0.94-0.78 (2H, m); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ 160.6, 156.2, 140.9, 139.5, 133.6, 131.7, 128.1, 116.8, 114.2, 103.3, 71.0, 66.8, 62.6, 59.6, 58.4, 49.9, 45.1, 42.7, 41.4, 33.8, 28.9, 28.3, 27.9, 27.7, 27.2, 26.5, 26.3, 22.3; **HRMS (ESI$^+$) [M+H]$^+$** calcd for $C_{28}H_{41}N_2O$: 421.3219, found: 421.3207; $[\alpha]_D^{20}$ –30.14 (c = 0.067, methanol).



Nakadomarin A through a W-catalyzed RCM. In an N_2-filled glove box, diamine (8.0 mg, 0.019 mmol) was charged to an 8-mL vial, which was dissolved in toluene (3.8 mL) and treated

with a stock solution of W complex **10** (93 μL, 0.00095 mmol, 1 mg/mL, 0.05 equivalent). The resulting mixture was allowed to stir for three minutes to allow complete initiation of the catalyst. The vial was capped with a septum fitted with two 20-gauge needles and connected to a one torr vacuum generated from the Edwards RV8 two-stage rotary vane pump. The solution was allowed to stir at 22 °C for eight hours; it was then removed from the glovebox and exposed to air. The resulting oil was purified by silica gel chromatography (19:1 diethyl ether: ammonium hydroxide) to afford nakadomarin A as a white foam (4.2 mg, 0.011 mmol, 56% yield, *Z:E* = 91:9) together with recovered diamine starting material (1.0 mg, 0.0023 mmol, 12% recovery). The physical and spectral data of the desired product were identical to those previously reported[15]. **IR (neat)**: 3005 (m), 2923 (s), 2856 (s), 2790 (s), 2742 (s), 1444 (s), 1357 (m), 1330 (m), 1309 (m), 1276 (m), 1238 (m), 1196 (m), 1132 (s), 1080 (m), 953 (m), 937 (s), 725 (m); **^{1}H NMR (400 MHz, CD_3OD)**: δ 5.86 (1H, s), 5.79 (1H, dd, *J* = 17.6, 9.4 Hz), 5.51-5.40 (2H, m), 5.28-5.21 (1H, m), 3.92 (1H, s), 3.74-3.69 (1H, m), 3.08-2.98 (1H, m), 3.03 (1H, d, *J* = 12.4 Hz), 2.83 (1H, br, s), 2.80-2.68 (2H, m), 2.64-2.57 (2H, m), 2.52-2.44 (1H, m), 2.40 (1H, dd, *J* = 11.6, 3.6 Hz), 2.34-2.26 (3H, m), 2.18-1.95 (4H, m), 1.90 (2H, dd, *J* = 12.4, 4.8 Hz), 1.81 (1H, ddd, *J* = 14.0, 7.2, 2.6 Hz), 1.74-1.56 (4H, m), 1.47 (1H, dd, *J* = 12.4, 10.0 Hz), 1.42-1.27 (2H, m), 1.11-1.00 (2H, m), 0.92-0.88 (1H, m); **^{13}C NMR (100 MHz, CD_3OD)**: δ 162.3, 156.7, 135.1, 134.4, 132.2, 131.6, 129.3, 104.7, 74.7, 63.6, 60.7, 59.3, 58.2, 50.9, 46.1, 43.5, 43.1, 29.5, 29.2, 29.2, 28.8, 27.2, 27.1, 26.0, 26.0, 23.0; **HRMS (ESI$^+$) [M+H]$^+$** calcd for $C_{26}H_{37}N_2O$: 393.2906, found: 393.2899; $[\alpha]_D^{20}$ –73.59 (c = 0.040, methanol).



Nakadomarin A through a W-catalyzed macrocyclic RCM of 13. In an N_2-filled glove box, diamine **13** (8.0 mg, 0.019 mmol) was charged to a 35-mL vial, which was dissolved in toluene (19 mL) and treated with a stock solution of W complex **10** (93 μL, 0.00095 mmol, 1.0 mg/mL, 0.05 equivalent). The resulting mixture was allowed to stir for three minutes to allow complete initiation of the catalyst. The vial was capped with a septum fitted with two 20-gauge needles and connected to a one torr vacuum generated from a mechanic pump. The solution was allowed to stir at 22 °C for six hours; it was then removed from the glovebox and exposed to air. The resulting oil was purified by silica gel chromatography (19:1 diethyl ether: ammonium hydroxide) to afford nakadomarin A as a white foam (4.7 mg, 0.012 mmol, 63% yield, *Z:E* = 95:5) together with recovered diamine starting material **13** (0.7 mg, 0.002 mmol, 9% recovery).

---

(15) (a) Ono, K.; Nakagawa, M.; Nishida, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2020–2023. (b) Ref 4. (c) Nilson, M. G.; Funk, R. L. *Org. Lett.* **2010**, *12*, 4912–4915.

■ **Proof of Stereochemistry:** The identity of the major isomer **6** from W-catalyzed macrocyclic RCM was established through X-ray crystallography (see below).

X-ray structure of RCM product 6

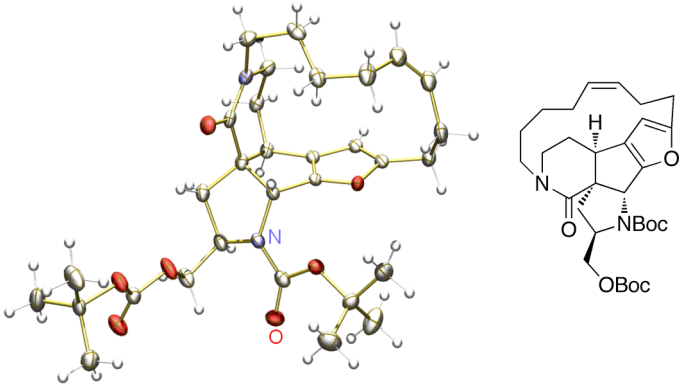


Table 1. **Crystal data and structure refinement for $C_{31}H_{44}N_2O_7$**

Identification code	C31H44N2O7	
Empirical formula	$C_{31}H_{44}N_2O_7$	
Formula weight	556.68	
Temperature	100(2) K	
Wavelength	1.54178 ≈	
Crystal system	Monoclinic	
Space group	P 2(1)	
Unit cell dimensions	a = 10.342(3) ≈	α= 90∞.
	b = 9.907(3) ≈	β= 93.895(12)∞.
	c = 14.462(5) ≈	γ = 90∞.
Volume	1478.2(8) ≈^{3}	
Z	2	
Density (calculated)	1.251 Mg/m^3	
Absorption coefficient	0.716 mm^{-1}	
F(000)	600	
Crystal size	0.20 x 0.12 x 0.05 mm^3	
Theta range for data collection	3.06 to 67.47∞.	
Index ranges	-12<=h<=12, -11<=k<=11, -17<=l<=10	
Reflections collected	15917	
Independent reflections	5100 [R(int) = 0.0382]	
Completeness to theta = 67.47∞	98.0 %	

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9651 and 0.8701
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5100 / 1 / 367
Goodness-of-fit on F^2	1.097
Final R indices [I>2sigma(I)]	R1 = 0.0293, wR2 = 0.0787
R indices (all data)	R1 = 0.0778, wR2 = 0.0915
Absolute structure parameter	0.02(14)
Extinction coefficient	na
Largest diff. peak and hole	0.365 and -0.302 e.$\approx^{-3}$

Table 2. **Atomic coordinates (x10^4) and equivalent isotropic displacement parameters (≈^{2}x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor**

	x	y	z	U(eq)
O(1)	4527(1)	8673(1)	8644(1)	20(1)
O(2)	4447(1)	6117(1)	5694(1)	27(1)
O(3)	1883(1)	7772(1)	8390(1)	26(1)
O(4)	1069(1)	5782(2)	8899(1)	31(1)
O(5)	1230(1)	4069(1)	6696(1)	32(1)
O(6)	-222(1)	2376(2)	6662(1)	35(1)
O(7)	-91(1)	3894(2)	5490(1)	30(1)
N(1)	6478(2)	6505(2)	6312(1)	22(1)
N(2)	2747(2)	5852(2)	7953(1)	22(1)
C(1)	6779(2)	7403(2)	5541(1)	27(1)
C(2)	6893(2)	8881(2)	5860(1)	29(1)
C(3)	5723(2)	9348(2)	6349(1)	29(1)
C(4)	5740(2)	10823(2)	6691(1)	34(1)
C(5)	6858(2)	11124(2)	7363(1)	32(1)
C(6)	6840(2)	11362(2)	8270(1)	32(1)
C(7)	5721(2)	11376(2)	8878(1)	30(1)
C(8)	5813(2)	10236(2)	9610(1)	27(1)
C(9)	5670(2)	8874(2)	9191(1)	22(1)
C(10)	4644(2)	7410(2)	8283(1)	19(1)
C(11)	3803(2)	6648(2)	7584(1)	20(1)
C(12)	2944(2)	4399(2)	7883(1)	24(1)
C(13)	3983(2)	4279(2)	7177(1)	25(1)
C(14)	4793(2)	5559(2)	7293(1)	21(1)
C(15)	5259(2)	6058(2)	6358(1)	21(1)
C(16)	7503(2)	6364(2)	7050(1)	25(1)
C(17)	7213(2)	5242(2)	7712(1)	25(1)
C(18)	5898(2)	5477(2)	8100(1)	21(1)
C(19)	5761(2)	6825(2)	8568(1)	20(1)
C(20)	6436(2)	7770(2)	9180(1)	21(1)
C(21)	1826(2)	6417(2)	8457(1)	24(1)

C(22)	1049(2)	8661(2)	8908(1)	25(1)
C(23)	1480(2)	10064(2)	8651(2)	34(1)
C(24)	1278(3)	8410(3)	9943(2)	46(1)
C(25)	-350(2)	8446(3)	8567(2)	41(1)
C(26)	1735(2)	3589(2)	7596(1)	28(1)
C(27)	236(2)	3339(2)	6309(1)	24(1)
C(28)	-1180(2)	3327(2)	4880(1)	25(1)
C(29)	-2425(2)	3474(2)	5351(1)	32(1)
C(30)	-902(2)	1884(2)	4637(2)	38(1)
C(31)	-1173(2)	4238(3)	4038(1)	43(1)

Table 3. ***Bond lengths [≈] and angles [∞]***

O(1)-C(10)	1.365(2)
O(1)-C(9)	1.391(2)
O(2)-C(15)	1.232(2)
O(3)-C(21)	1.347(3)
O(3)-C(22)	1.473(2)
O(4)-C(21)	1.220(2)
O(5)-C(27)	1.347(2)
O(5)-C(26)	1.450(2)
O(6)-C(27)	1.195(2)
O(7)-C(27)	1.328(2)
O(7)-C(28)	1.493(2)
N(1)-C(15)	1.342(3)
N(1)-C(16)	1.459(2)
N(1)-C(1)	1.476(2)
N(2)-C(21)	1.359(2)
N(2)-C(12)	1.457(3)
N(2)-C(11)	1.476(2)
C(1)-C(2)	1.537(3)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-C(3)	1.514(3)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.542(3)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.489(3)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(6)	1.334(3)
C(5)-H(5)	0.9500
C(6)-C(7)	1.501(3)
C(6)-H(6)	0.9500

C(7)-C(8)	1.547(3)
C(7)-H(7A)	0.9900
C(7)-H(7B)	0.9900
C(8)-C(9)	1.482(3)
C(8)-H(8A)	0.9900
C(8)-H(8B)	0.9900
C(9)-C(20)	1.352(3)
C(10)-C(19)	1.332(3)
C(10)-C(11)	1.492(2)
C(11)-C(14)	1.565(3)
C(11)-H(11)	1.0000
C(12)-C(26)	1.519(3)
C(12)-C(13)	1.537(3)
C(12)-H(12)	1.0000
C(13)-C(14)	1.522(3)
C(13)-H(13A)	0.9900
C(13)-H(13B)	0.9900
C(14)-C(15)	1.547(2)
C(14)-C(18)	1.580(2)
C(16)-C(17)	1.510(3)
C(16)-H(16A)	0.9900
C(16)-H(16B)	0.9900
C(17)-C(18)	1.524(3)
C(17)-H(17A)	0.9900
C(17)-H(17B)	0.9900
C(18)-C(19)	1.508(3)
C(18)-H(18)	1.0000
C(19)-C(20)	1.437(3)
C(20)-H(20)	0.9500
C(22)-C(25)	1.512(3)
C(22)-C(23)	1.513(3)
C(22)-C(24)	1.519(3)
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-H(24A)	0.9800

C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800
C(25)-H(25A)	0.9800
C(25)-H(25B)	0.9800
C(25)-H(25C)	0.9800
C(26)-H(26A)	0.9900
C(26)-H(26B)	0.9900
C(28)-C(29)	1.504(3)
C(28)-C(30)	1.504(3)
C(28)-C(31)	1.517(3)
C(29)-H(29A)	0.9800
C(29)-H(29B)	0.9800
C(29)-H(29C)	0.9800
C(30)-H(30A)	0.9800
C(30)-H(30B)	0.9800
C(30)-H(30C)	0.9800
C(31)-H(31A)	0.9800
C(31)-H(31B)	0.9800
C(31)-H(31C)	0.9800

C(10)-O(1)-C(9)	104.77(14)
C(21)-O(3)-C(22)	121.99(15)
C(27)-O(5)-C(26)	114.50(15)
C(27)-O(7)-C(28)	120.47(15)
C(15)-N(1)-C(16)	124.74(15)
C(15)-N(1)-C(1)	118.93(15)
C(16)-N(1)-C(1)	115.49(15)
C(21)-N(2)-C(12)	123.39(16)
C(21)-N(2)-C(11)	122.40(16)
C(12)-N(2)-C(11)	113.14(15)
N(1)-C(1)-C(2)	111.27(14)
N(1)-C(1)-H(1A)	109.4
C(2)-C(1)-H(1A)	109.4
N(1)-C(1)-H(1B)	109.4
C(2)-C(1)-H(1B)	109.4
H(1A)-C(1)-H(1B)	108.0

C(3)-C(2)-C(1)	112.56(17)
C(3)-C(2)-H(2A)	109.1
C(1)-C(2)-H(2A)	109.1
C(3)-C(2)-H(2B)	109.1
C(1)-C(2)-H(2B)	109.1
H(2A)-C(2)-H(2B)	107.8
C(2)-C(3)-C(4)	116.55(18)
C(2)-C(3)-H(3A)	108.2
C(4)-C(3)-H(3A)	108.2
C(2)-C(3)-H(3B)	108.2
C(4)-C(3)-H(3B)	108.2
H(3A)-C(3)-H(3B)	107.3
C(5)-C(4)-C(3)	112.98(19)
C(5)-C(4)-H(4A)	109.0
C(3)-C(4)-H(4A)	109.0
C(5)-C(4)-H(4B)	109.0
C(3)-C(4)-H(4B)	109.0
H(4A)-C(4)-H(4B)	107.8
C(6)-C(5)-C(4)	128.0(2)
C(6)-C(5)-H(5)	116.0
C(4)-C(5)-H(5)	116.0
C(5)-C(6)-C(7)	129.8(2)
C(5)-C(6)-H(6)	115.1
C(7)-C(6)-H(6)	115.1
C(6)-C(7)-C(8)	112.36(18)
C(6)-C(7)-H(7A)	109.1
C(8)-C(7)-H(7A)	109.1
C(6)-C(7)-H(7B)	109.1
C(8)-C(7)-H(7B)	109.1
H(7A)-C(7)-H(7B)	107.9
C(9)-C(8)-C(7)	112.61(15)
C(9)-C(8)-H(8A)	109.1
C(7)-C(8)-H(8A)	109.1
C(9)-C(8)-H(8B)	109.1
C(7)-C(8)-H(8B)	109.1
H(8A)-C(8)-H(8B)	107.8

C(20)-C(9)-O(1)	110.71(16)
C(20)-C(9)-C(8)	134.36(18)
O(1)-C(9)-C(8)	114.84(16)
C(19)-C(10)-O(1)	112.20(15)
C(19)-C(10)-C(11)	116.28(17)
O(1)-C(10)-C(11)	131.29(17)
N(2)-C(11)-C(10)	115.93(14)
N(2)-C(11)-C(14)	103.99(14)
C(10)-C(11)-C(14)	99.74(15)
N(2)-C(11)-H(11)	112.1
C(10)-C(11)-H(11)	112.1
C(14)-C(11)-H(11)	112.1
N(2)-C(12)-C(26)	115.14(17)
N(2)-C(12)-C(13)	103.29(15)
C(26)-C(12)-C(13)	112.16(16)
N(2)-C(12)-H(12)	108.7
C(26)-C(12)-H(12)	108.7
C(13)-C(12)-H(12)	108.7
C(14)-C(13)-C(12)	105.49(15)
C(14)-C(13)-H(13A)	110.6
C(12)-C(13)-H(13A)	110.6
C(14)-C(13)-H(13B)	110.6
C(12)-C(13)-H(13B)	110.6
H(13A)-C(13)-H(13B)	108.8
C(13)-C(14)-C(15)	111.84(15)
C(13)-C(14)-C(11)	103.83(15)
C(15)-C(14)-C(11)	105.25(14)
C(13)-C(14)-C(18)	113.81(15)
C(15)-C(14)-C(18)	114.16(15)
C(11)-C(14)-C(18)	106.86(13)
O(2)-C(15)-N(1)	122.51(16)
O(2)-C(15)-C(14)	117.37(17)
N(1)-C(15)-C(14)	119.91(15)
N(1)-C(16)-C(17)	111.67(16)
N(1)-C(16)-H(16A)	109.3
C(17)-C(16)-H(16A)	109.3

N(1)-C(16)-H(16B)	109.3
C(17)-C(16)-H(16B)	109.3
H(16A)-C(16)-H(16B)	107.9
C(16)-C(17)-C(18)	109.94(16)
C(16)-C(17)-H(17A)	109.7
C(18)-C(17)-H(17A)	109.7
C(16)-C(17)-H(17B)	109.7
C(18)-C(17)-H(17B)	109.7
H(17A)-C(17)-H(17B)	108.2
C(19)-C(18)-C(17)	114.48(16)
C(19)-C(18)-C(14)	101.55(14)
C(17)-C(18)-C(14)	110.80(14)
C(19)-C(18)-H(18)	109.9
C(17)-C(18)-H(18)	109.9
C(14)-C(18)-H(18)	109.9
C(10)-C(19)-C(20)	106.40(16)
C(10)-C(19)-C(18)	110.67(15)
C(20)-C(19)-C(18)	142.80(18)
C(9)-C(20)-C(19)	105.88(16)
C(9)-C(20)-H(20)	127.1
C(19)-C(20)-H(20)	127.1
O(4)-C(21)-O(3)	125.78(19)
O(4)-C(21)-N(2)	124.54(19)
O(3)-C(21)-N(2)	109.68(16)
O(3)-C(22)-C(25)	109.26(17)
O(3)-C(22)-C(23)	103.45(15)
C(25)-C(22)-C(23)	109.91(18)
O(3)-C(22)-C(24)	110.22(17)
C(25)-C(22)-C(24)	112.3(2)
C(23)-C(22)-C(24)	111.32(19)
C(22)-C(23)-H(23A)	109.5
C(22)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(22)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5

C(22)-C(24)-H(24A)	109.5
C(22)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(22)-C(24)-H(24C)	109.5
H(24A)-C(24)-H(24C)	109.5
H(24B)-C(24)-H(24C)	109.5
C(22)-C(25)-H(25A)	109.5
C(22)-C(25)-H(25B)	109.5
H(25A)-C(25)-H(25B)	109.5
C(22)-C(25)-H(25C)	109.5
H(25A)-C(25)-H(25C)	109.5
H(25B)-C(25)-H(25C)	109.5
O(5)-C(26)-C(12)	108.14(15)
O(5)-C(26)-H(26A)	110.1
C(12)-C(26)-H(26A)	110.1
O(5)-C(26)-H(26B)	110.1
C(12)-C(26)-H(26B)	110.1
H(26A)-C(26)-H(26B)	108.4
O(6)-C(27)-O(7)	128.85(18)
O(6)-C(27)-O(5)	124.38(17)
O(7)-C(27)-O(5)	106.77(16)
O(7)-C(28)-C(29)	109.31(15)
O(7)-C(28)-C(30)	110.30(17)
C(29)-C(28)-C(30)	112.44(17)
O(7)-C(28)-C(31)	101.86(15)
C(29)-C(28)-C(31)	110.92(18)
C(30)-C(28)-C(31)	111.50(18)
C(28)-C(29)-H(29A)	109.5
C(28)-C(29)-H(29B)	109.5
H(29A)-C(29)-H(29B)	109.5
C(28)-C(29)-H(29C)	109.5
H(29A)-C(29)-H(29C)	109.5
H(29B)-C(29)-H(29C)	109.5
C(28)-C(30)-H(30A)	109.5
C(28)-C(30)-H(30B)	109.5
H(30A)-C(30)-H(30B)	109.5

C(28)-C(30)-H(30C)	109.5
H(30A)-C(30)-H(30C)	109.5
H(30B)-C(30)-H(30C)	109.5
C(28)-C(31)-H(31A)	109.5
C(28)-C(31)-H(31B)	109.5
H(31A)-C(31)-H(31B)	109.5
C(28)-C(31)-H(31C)	109.5
H(31A)-C(31)-H(31C)	109.5
H(31B)-C(31)-H(31C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. **Anisotropic displacement parameters ($\approx^2$x 10^3). 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}
O(1)	21(1)	19(1)	22(1)	-4(1)	4(1)	-1(1)
O(2)	30(1)	30(1)	20(1)	0(1)	-2(1)	-2(1)
O(3)	23(1)	23(1)	32(1)	0(1)	6(1)	-3(1)
O(4)	30(1)	31(1)	34(1)	5(1)	8(1)	-5(1)
O(5)	40(1)	27(1)	27(1)	6(1)	-11(1)	-17(1)
O(6)	34(1)	33(1)	35(1)	8(1)	-8(1)	-12(1)
O(7)	34(1)	30(1)	24(1)	3(1)	-6(1)	-13(1)
N(1)	24(1)	24(1)	18(1)	-1(1)	2(1)	3(1)
N(2)	23(1)	18(1)	24(1)	0(1)	1(1)	-5(1)
C(1)	27(1)	32(1)	21(1)	2(1)	4(1)	1(1)
C(2)	30(1)	30(1)	25(1)	9(1)	-3(1)	-8(1)
C(3)	36(1)	26(1)	25(1)	3(1)	-1(1)	-4(1)
C(4)	50(1)	25(1)	27(1)	2(1)	1(1)	-1(1)
C(5)	41(1)	24(1)	33(1)	1(1)	5(1)	-3(1)
C(6)	44(1)	22(1)	30(1)	0(1)	3(1)	-5(1)
C(7)	36(1)	20(1)	34(1)	-5(1)	1(1)	-4(1)
C(8)	32(1)	27(1)	22(1)	-6(1)	4(1)	-4(1)
C(9)	24(1)	26(1)	16(1)	-1(1)	3(1)	-7(1)
C(10)	22(1)	17(1)	18(1)	0(1)	5(1)	-5(1)
C(11)	21(1)	18(1)	21(1)	0(1)	0(1)	-3(1)
C(12)	31(1)	20(1)	22(1)	1(1)	-2(1)	-6(1)
C(13)	33(1)	19(1)	24(1)	-1(1)	1(1)	-2(1)
C(14)	26(1)	18(1)	18(1)	0(1)	0(1)	0(1)
C(15)	28(1)	18(1)	18(1)	-3(1)	0(1)	3(1)
C(16)	23(1)	30(1)	22(1)	-1(1)	2(1)	3(1)
C(17)	27(1)	26(1)	21(1)	-1(1)	-2(1)	6(1)
C(18)	27(1)	17(1)	18(1)	3(1)	1(1)	2(1)
C(19)	22(1)	21(1)	16(1)	2(1)	3(1)	-4(1)
C(20)	23(1)	25(1)	16(1)	1(1)	3(1)	-3(1)
C(21)	23(1)	27(1)	22(1)	2(1)	-3(1)	-5(1)
C(22)	21(1)	29(1)	26(1)	-2(1)	2(1)	4(1)

C(23)	28(1)	30(1)	46(1)	-5(1)	8(1)	4(1)
C(24)	63(2)	44(2)	30(1)	-3(1)	1(1)	16(1)
C(25)	23(1)	44(2)	57(1)	5(1)	0(1)	2(1)
C(26)	34(1)	27(1)	23(1)	6(1)	-6(1)	-9(1)
C(27)	26(1)	20(1)	25(1)	0(1)	1(1)	-2(1)
C(28)	25(1)	26(1)	22(1)	-5(1)	-4(1)	-5(1)
C(29)	31(1)	34(1)	30(1)	-4(1)	0(1)	2(1)
C(30)	30(1)	36(1)	45(1)	-18(1)	-7(1)	7(1)
C(31)	49(1)	55(2)	24(1)	4(1)	-11(1)	-24(1)

Table 5. **Hydrogen coordinates (x10^4) and isotropic displacement parameters (≈^{2}x 10 ^{3})**

	x	y	z	U(eq)
H(1A)	6087	7326	5036	32
H(1B)	7605	7116	5293	32
H(2A)	7678	8983	6285	34
H(2B)	6997	9465	5315	34
H(3A)	5628	8751	6889	35
H(3B)	4944	9221	5921	35
H(4A)	5774	11433	6151	41
H(4B)	4924	11010	6988	41
H(5)	7685	11149	7115	39
H(6)	7661	11551	8577	39
H(7A)	4903	11276	8487	36
H(7B)	5696	12259	9197	36
H(8A)	6662	10293	9968	32
H(8B)	5128	10369	10048	32
H(11)	3487	7231	7051	24
H(12)	3313	4057	8496	29
H(13A)	4527	3470	7306	30
H(13B)	3577	4214	6539	30
H(16A)	7599	7224	7396	30
H(16B)	8333	6173	6774	30
H(17A)	7896	5211	8226	30
H(17B)	7210	4364	7384	30
H(18)	5707	4733	8538	25
H(20)	7253	7644	9510	26
H(23A)	1343	10188	7979	52
H(23B)	2401	10177	8840	52
H(23C)	973	10736	8969	52
H(24A)	2200	8531	10128	69
H(24B)	1018	7486	10085	69
H(24C)	765	9050	10282	69
H(25A)	-445	8580	7895	62

H(25B)	-900	9094	8870	62
H(25C)	-613	7525	8716	62
H(26A)	1951	2617	7562	34
H(26B)	1078	3707	8056	34
H(29A)	-2577	4430	5480	48
H(29B)	-2364	2968	5935	48
H(29C)	-3145	3121	4946	48
H(30A)	-912	1323	5194	56
H(30B)	-47	1827	4385	56
H(30C)	-1565	1562	4172	56
H(31A)	-329	4178	3771	65
H(31B)	-1330	5173	4223	65
H(31C)	-1856	3953	3576	65

Table 6. Torsion angles [∞]

C(15)-N(1)-C(1)-C(2)	102.49(19)
C(16)-N(1)-C(1)-C(2)	-67.5(2)
N(1)-C(1)-C(2)-C(3)	-52.5(2)
C(1)-C(2)-C(3)-C(4)	-179.59(16)
C(2)-C(3)-C(4)-C(5)	-59.5(2)
C(3)-C(4)-C(5)-C(6)	-109.5(3)
C(4)-C(5)-C(6)-C(7)	1.1(4)
C(5)-C(6)-C(7)-C(8)	114.6(3)
C(6)-C(7)-C(8)-C(9)	-66.9(2)
C(10)-O(1)-C(9)-C(20)	-1.35(18)
C(10)-O(1)-C(9)-C(8)	175.83(14)
C(7)-C(8)-C(9)-C(20)	119.3(2)
C(7)-C(8)-C(9)-O(1)	-57.0(2)
C(9)-O(1)-C(10)-C(19)	0.20(18)
C(9)-O(1)-C(10)-C(11)	-174.12(17)
C(21)-N(2)-C(11)-C(10)	57.5(2)
C(12)-N(2)-C(11)-C(10)	-111.02(18)
C(21)-N(2)-C(11)-C(14)	165.87(15)
C(12)-N(2)-C(11)-C(14)	-2.66(18)
C(19)-C(10)-C(11)-N(2)	97.81(19)
O(1)-C(10)-C(11)-N(2)	-88.1(2)
C(19)-C(10)-C(11)-C(14)	-13.05(19)
O(1)-C(10)-C(11)-C(14)	161.08(16)
C(21)-N(2)-C(12)-C(26)	52.2(2)
C(11)-N(2)-C(12)-C(26)	-139.39(15)
C(21)-N(2)-C(12)-C(13)	174.83(15)
C(11)-N(2)-C(12)-C(13)	-16.77(19)
N(2)-C(12)-C(13)-C(14)	29.92(18)
C(26)-C(12)-C(13)-C(14)	154.50(16)
C(12)-C(13)-C(14)-C(15)	-144.67(15)
C(12)-C(13)-C(14)-C(11)	-31.69(17)
C(12)-C(13)-C(14)-C(18)	84.10(18)
N(2)-C(11)-C(14)-C(13)	21.20(16)
C(10)-C(11)-C(14)-C(13)	141.19(14)

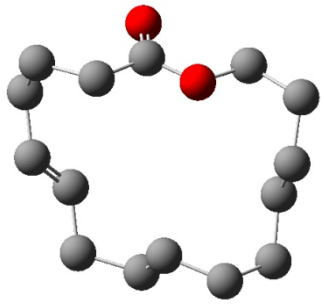
N(2)-C(11)-C(14)-C(15)	138.86(14)
C(10)-C(11)-C(14)-C(15)	-101.14(15)
N(2)-C(11)-C(14)-C(18)	-99.40(16)
C(10)-C(11)-C(14)-C(18)	20.59(17)
C(16)-N(1)-C(15)-O(2)	-174.93(18)
C(1)-N(1)-C(15)-O(2)	16.1(3)
C(16)-N(1)-C(15)-C(14)	10.5(3)
C(1)-N(1)-C(15)-C(14)	-158.51(17)
C(13)-C(14)-C(15)-O(2)	47.5(2)
C(11)-C(14)-C(15)-O(2)	-64.7(2)
C(18)-C(14)-C(15)-O(2)	178.50(16)
C(13)-C(14)-C(15)-N(1)	-137.69(18)
C(11)-C(14)-C(15)-N(1)	110.21(18)
C(18)-C(14)-C(15)-N(1)	-6.6(2)
C(15)-N(1)-C(16)-C(17)	21.2(2)
C(1)-N(1)-C(16)-C(17)	-169.47(16)
N(1)-C(16)-C(17)-C(18)	-55.6(2)
C(16)-C(17)-C(18)-C(19)	-55.87(19)
C(16)-C(17)-C(18)-C(14)	58.2(2)
C(13)-C(14)-C(18)-C(19)	-135.38(15)
C(15)-C(14)-C(18)-C(19)	94.55(17)
C(11)-C(14)-C(18)-C(19)	-21.37(17)
C(13)-C(14)-C(18)-C(17)	102.61(18)
C(15)-C(14)-C(18)-C(17)	-27.5(2)
C(11)-C(14)-C(18)-C(17)	-143.39(15)
O(1)-C(10)-C(19)-C(20)	0.93(19)
C(11)-C(10)-C(19)-C(20)	176.17(15)
O(1)-C(10)-C(19)-C(18)	-175.79(13)
C(11)-C(10)-C(19)-C(18)	-0.6(2)
C(17)-C(18)-C(19)-C(10)	133.26(16)
C(14)-C(18)-C(19)-C(10)	13.83(18)
C(17)-C(18)-C(19)-C(20)	-41.5(3)
C(14)-C(18)-C(19)-C(20)	-161.0(2)
O(1)-C(9)-C(20)-C(19)	1.89(19)
C(8)-C(9)-C(20)-C(19)	-174.52(18)
C(10)-C(19)-C(20)-C(9)	-1.71(19)

C(18)-C(19)-C(20)-C(9)	173.2(2)
C(22)-O(3)-C(21)-O(4)	3.6(3)
C(22)-O(3)-C(21)-N(2)	-176.35(14)
C(12)-N(2)-C(21)-O(4)	-0.1(3)
C(11)-N(2)-C(21)-O(4)	-167.48(17)
C(12)-N(2)-C(21)-O(3)	179.86(15)
C(11)-N(2)-C(21)-O(3)	12.5(2)
C(21)-O(3)-C(22)-C(25)	-65.1(2)
C(21)-O(3)-C(22)-C(23)	177.88(16)
C(21)-O(3)-C(22)-C(24)	58.8(2)
C(27)-O(5)-C(26)-C(12)	173.08(16)
N(2)-C(12)-C(26)-O(5)	59.4(2)
C(13)-C(12)-C(26)-O(5)	-58.3(2)
C(28)-O(7)-C(27)-O(6)	1.1(3)
C(28)-O(7)-C(27)-O(5)	-179.47(15)
C(26)-O(5)-C(27)-O(6)	0.6(3)
C(26)-O(5)-C(27)-O(7)	-178.88(16)
C(27)-O(7)-C(28)-C(29)	63.9(2)
C(27)-O(7)-C(28)-C(30)	-60.2(2)
C(27)-O(7)-C(28)-C(31)	-178.69(19)

Symmetry transformations used to generate equivalent atoms:

■ **DFT Calculations:** Geometry optimizations and frequency calculations performed with tight geometry and SCF convergence criteria at M052x/6-31G(d) level of theory in Gaussian 09, Revision A.02 with ultrafine grids[16, 17]. Single point energies of optimized structures calculated at M052x/6-311+G(2df,2p) level of theory. Initial conformer distributions for each molecule generated with Spartan '04 through the use of molecular mechanics[18].

Macrocyclic Alkene *E*-12



Coordinates (Angstroms):

Atom	X	Y	Z
C	-2.041708	-2.783364	-0.087092
H	-3.248809	-0.775619	-1.561592
C	1.434450	-1.736250	0.064960
C	2.148387	-1.009921	1.179184
O	0.143779	-1.950036	0.375029
H	1.498873	-0.203079	1.523890
H	2.240462	-1.714800	2.010906
H	1.208385	1.431329	-1.641266
H	-3.660516	-1.650248	0.762826
C	-3.391231	0.902272	-0.216310
C	-2.709037	-0.384102	-0.692519

(16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr., J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S. A.; Daniels, D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian 09, Revision A 02, Gaussian, Inc., Wallingford CT, 2009.

(17) Zhao, Y.; Schultz, N. E., Truhlar, D. G. *J. Chem. Theory and Comput.* **2006**, *2*, 364–382.

(18) Spartan '04, http://www.wavefun.com

H	-0.597620	-2.055377	-1.547839
O	1.932877	-2.107775	-0.970975
C	-2.708591	1.565021	0.988175
C	-1.215738	1.848534	0.791596
H	-0.819865	2.307681	1.704072
C	-0.931146	2.778849	-0.386836
H	-0.667540	0.910136	0.660548
H	-1.551169	3.676664	-0.293859
H	-1.222488	2.295173	-1.324932
C	0.543368	3.192393	-0.482163
H	0.852087	3.681876	0.446582
H	0.648060	3.932301	-1.283158
H	-3.222577	2.507572	1.203062
H	-3.433730	1.611981	-1.047144
H	-2.840065	0.936904	1.873297
H	-4.429301	0.678006	0.049405
C	1.454795	2.032342	-0.765832
C	3.443095	0.556016	-0.372037
H	2.779064	2.299576	0.827731
C	3.516455	-0.482467	0.758937
H	4.454949	0.930559	-0.557440
H	3.106587	0.065316	-1.285897
H	3.994477	-0.037026	1.635692
H	4.141210	-1.316014	0.433310
C	2.531412	1.705897	-0.051743
H	-1.697308	-0.148927	-1.036795
H	-2.061720	-1.100633	1.236835
C	-2.648621	-1.461217	0.390247
H	-2.656599	-3.217136	-0.881823
H	-2.032357	-3.497622	0.739771
C	-0.630266	-2.637565	-0.627031
H	-0.169471	-3.604730	-0.827829

Item	Value	Threshold	Converged?
Maximum Force	0.000001	0.000015	YES
RMS Force	0.000000	0.000010	YES
Maximum Displacement	0.000027	0.000060	YES

RMS Displacement 0.000003 0.000040 YES
Predicted change in Energy=-7.515763D-12
Optimization completed.
-- Stationary point found.

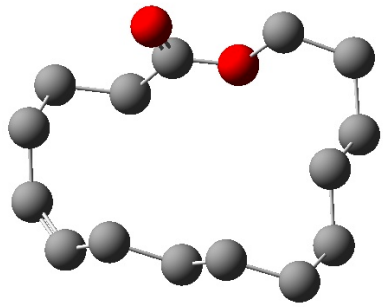
Thermochemistry:

Zero-point correction= 0.399952 (Hartree/Particle)
Thermal correction to Energy= 0.417444
Thermal correction to Enthalpy= 0.418388
Thermal correction to Gibbs Free Energy= 0.354845
Sum of electronic and zero-point Energies= -737.213951
Sum of electronic and thermal Energies= -737.196459
Sum of electronic and thermal Enthalpies= -737.195515
Sum of electronic and thermal Free Energies= -737.259058

Single Point Energy:

SCF Done: E(RM052X) = -737.868832888 A.U. after 13 cycles
Convg = 0.6081D-08 -V/T = 2.0045

Macrocyclic Alkene *Z*-12



Coordinates (Angstroms):

Atom	X	Y	Z
C	-2.629232	-2.507236	-0.082233
H	-1.699973	0.043343	0.500822
C	0.939670	-1.900343	0.190667
C	1.914422	-1.506325	-0.893789
O	-0.277416	-2.156199	-0.321825
H	1.905452	-2.307040	-1.637488
H	1.521176	-0.616297	-1.394541
C	2.373332	2.231374	-0.476291

H	-2.215442	-1.087816	-1.640503
C	-2.947137	1.356408	-0.649227
C	-2.717905	0.047423	0.104727
H	-1.052814	-3.543200	1.000582
O	1.193367	-1.992989	1.368328
C	-2.649440	2.607266	0.186044
C	-1.254438	2.622265	0.823993
H	-1.102534	3.586646	1.319103
C	-0.114420	2.390050	-0.167198
H	-1.198641	1.866503	1.613593
H	-0.145556	3.156062	-0.950474
H	-0.238104	1.426719	-0.671480
C	1.258851	2.402395	0.516339
H	1.286430	1.620319	1.277768
H	1.383977	3.357547	1.039320
H	-2.760816	3.489854	-0.451463
H	-2.319996	1.358344	-1.546374
H	-3.398531	2.698579	0.978689
H	-3.982329	1.397712	-1.001896
H	2.418005	2.999595	-1.245245
C	3.436224	0.081412	0.399855
C	3.282993	1.255696	-0.526166
C	3.318184	-1.253595	-0.352833
H	2.706377	0.100111	1.208086
H	4.426392	0.126634	0.864559
H	3.595008	-2.070577	0.315293
H	4.023016	-1.257990	-1.188788
H	4.010014	1.291009	-1.335298
H	-3.391290	-0.009351	0.968358
H	-3.912834	-1.188544	-1.200943
C	-2.898376	-1.175934	-0.791708
H	-2.676937	-3.322393	-0.808067
H	-3.401958	-2.698792	0.668668
C	-1.288123	-2.544877	0.629673
H	-1.253304	-1.859344	1.474594

Item	Value	Threshold	Converged?

Maximum Force	0.000001	0.000015	YES
RMS Force	0.000000	0.000010	YES
Maximum Displacement	0.000031	0.000060	YES
RMS Displacement	0.000008	0.000040	YES

Predicted change in Energy=-8.905519D-12

Optimization completed.

-- Stationary point found.

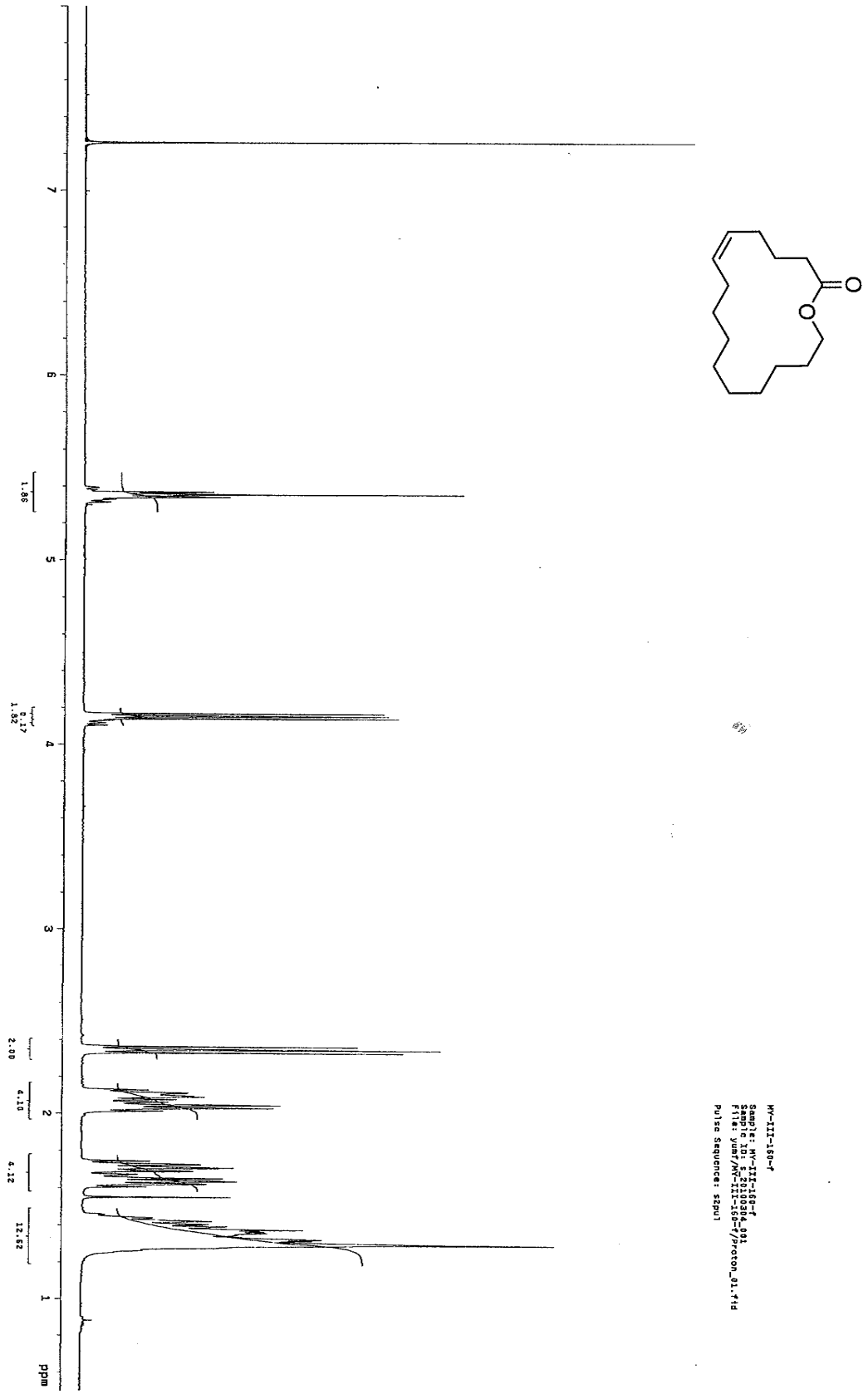
Thermochemistry:

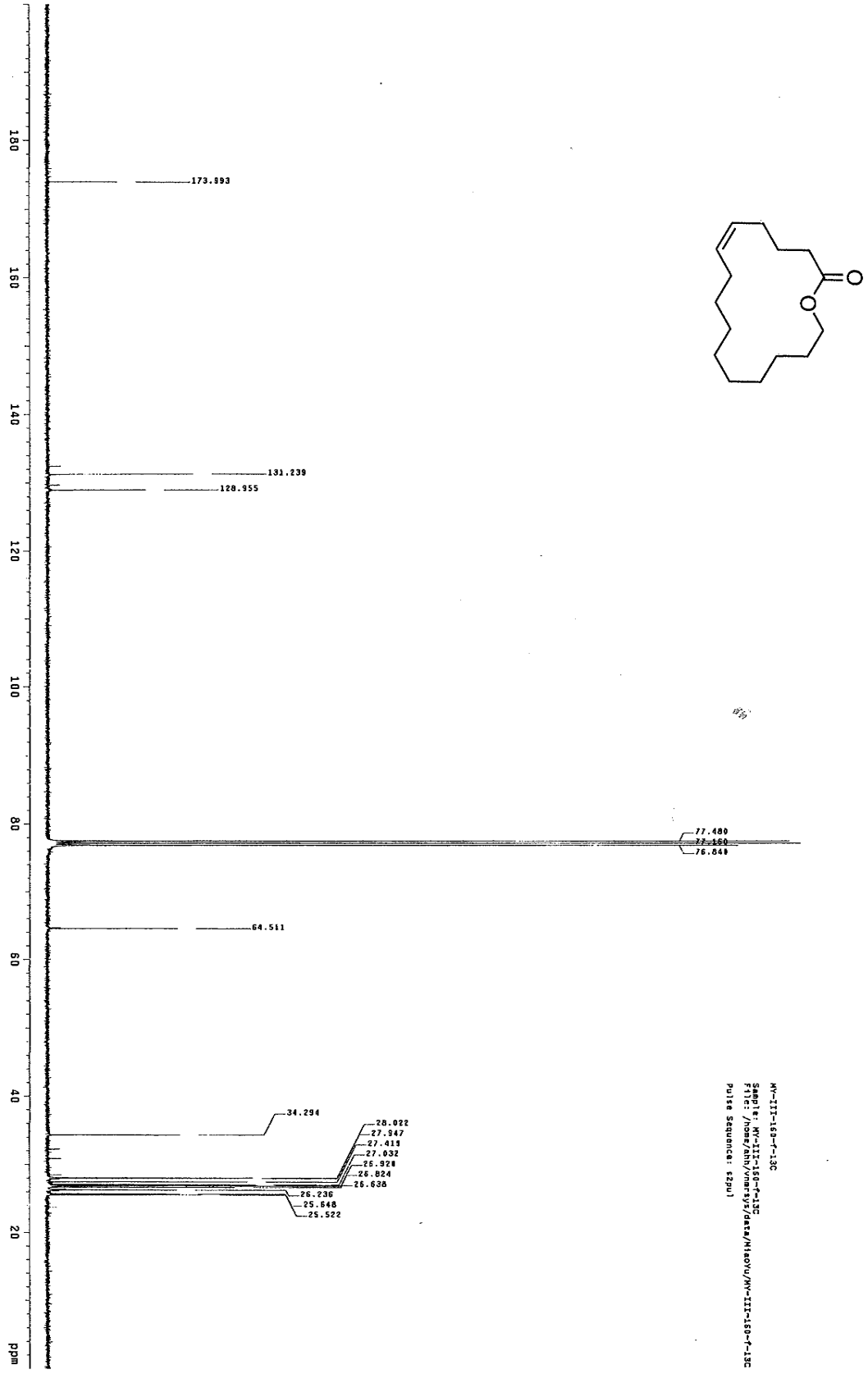
Zero-point correction=	0.399866 (Hartree/Particle)
Thermal correction to Energy=	0.417554
Thermal correction to Enthalpy=	0.418498
Thermal correction to Gibbs Free Energy=	0.353786
Sum of electronic and zero-point Energies=	-737.210337
Sum of electronic and thermal Energies=	-737.192648
Sum of electronic and thermal Enthalpies=	-737.191704
Sum of electronic and thermal Free Energies=	-737.256416

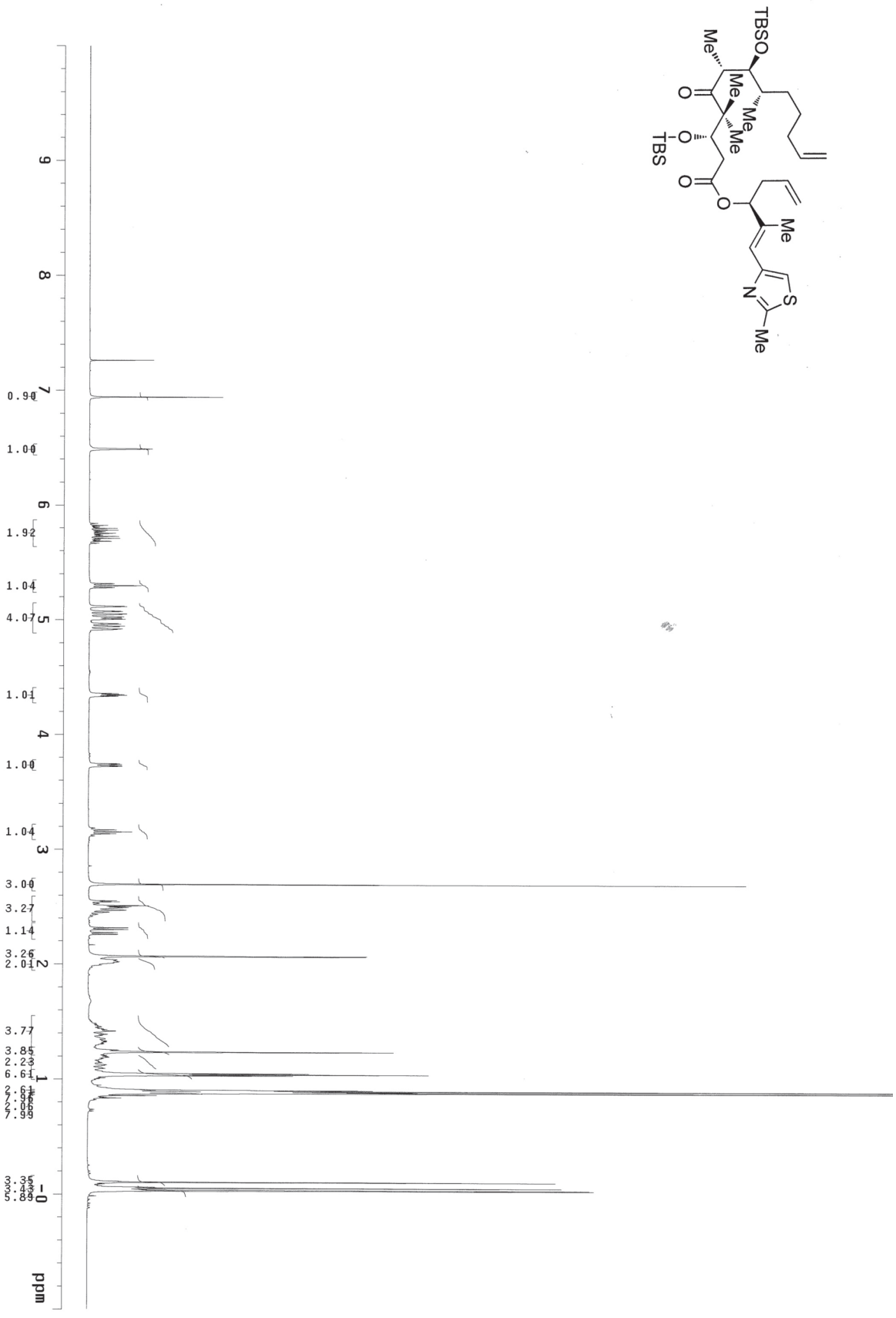
Single Point Energy:

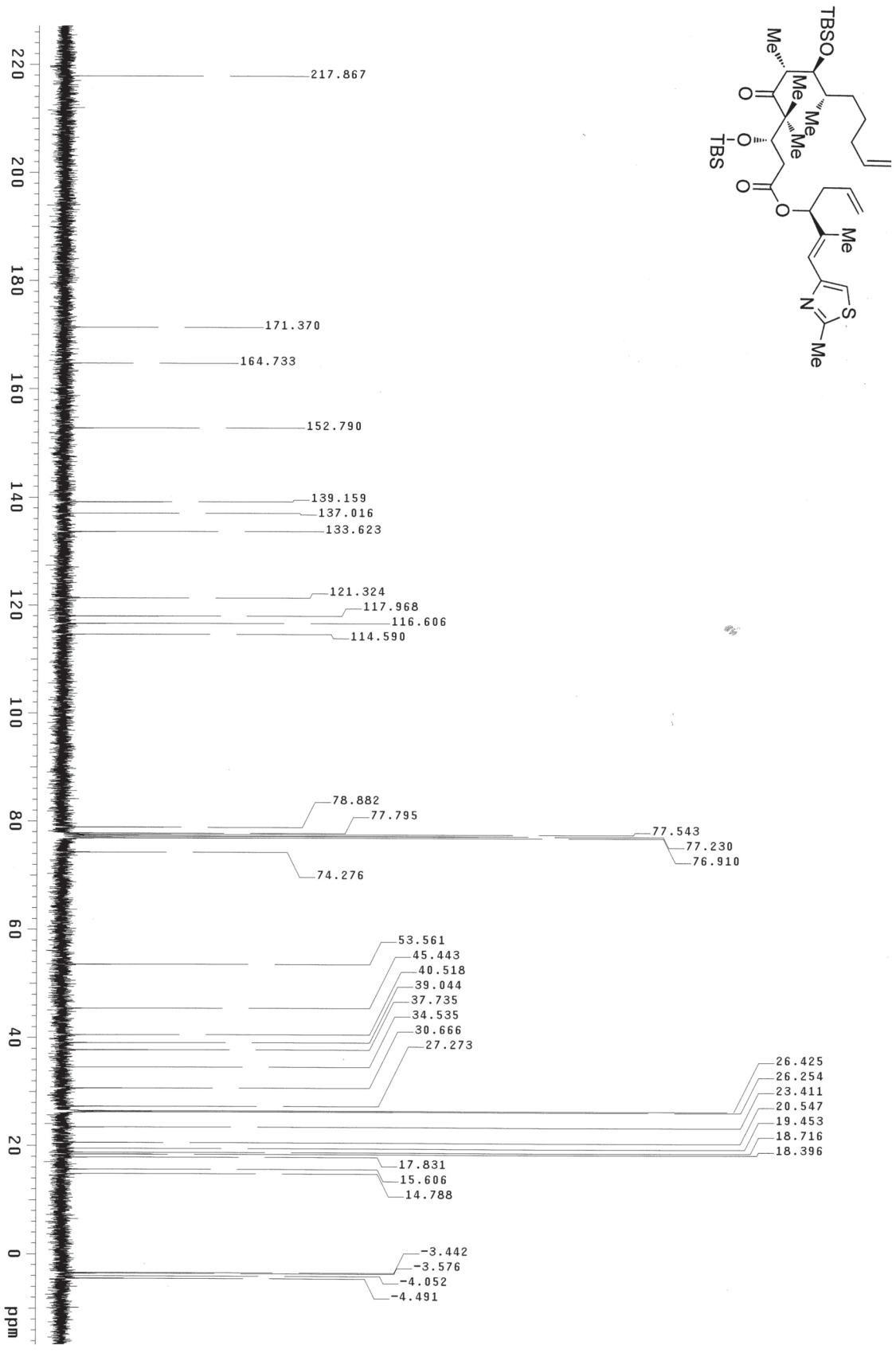
SCF Done: E(RM052X) = -737.865815613 A.U. after 14 cycles

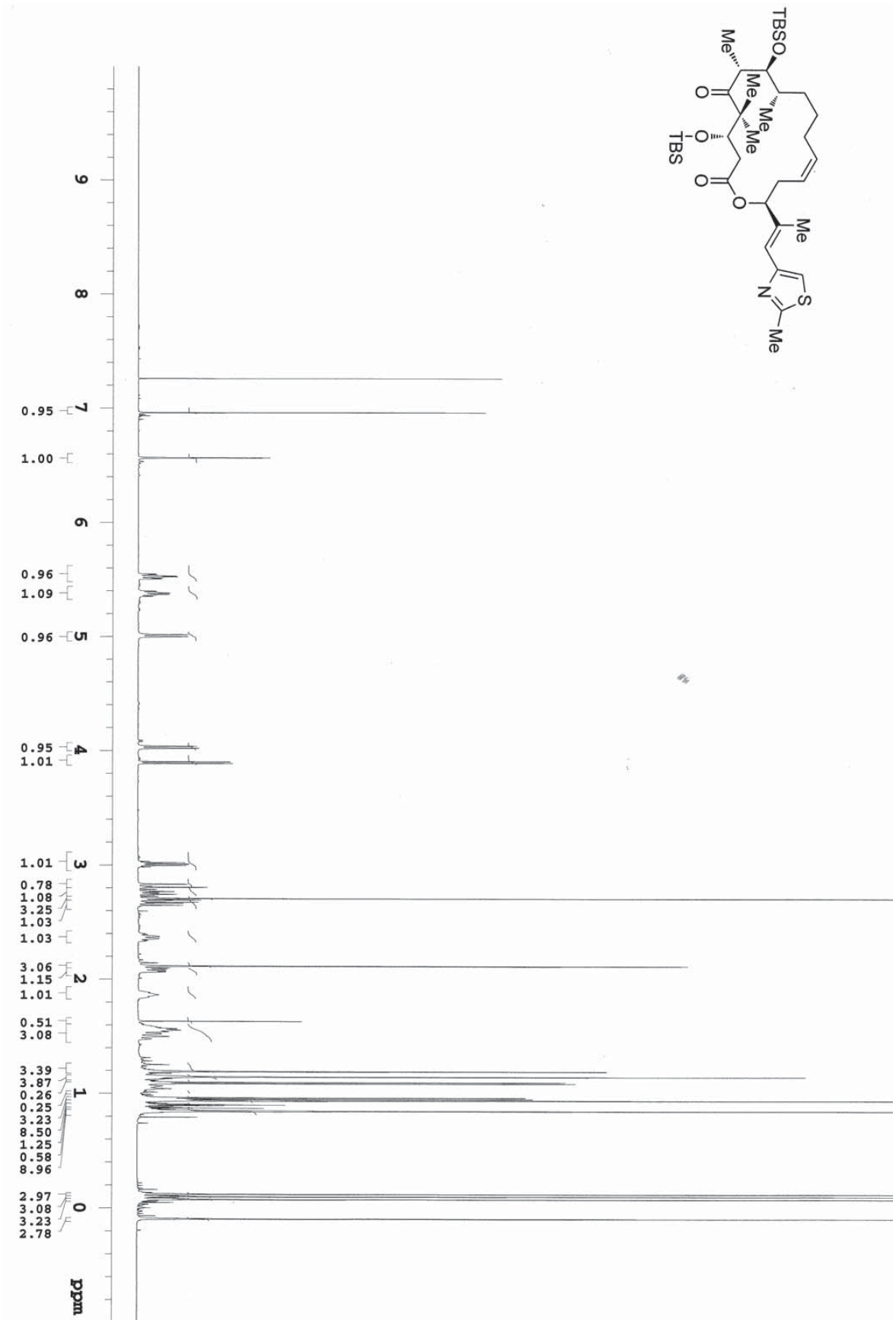
Convg = 0.1023D-08 -V/T = 2.0045

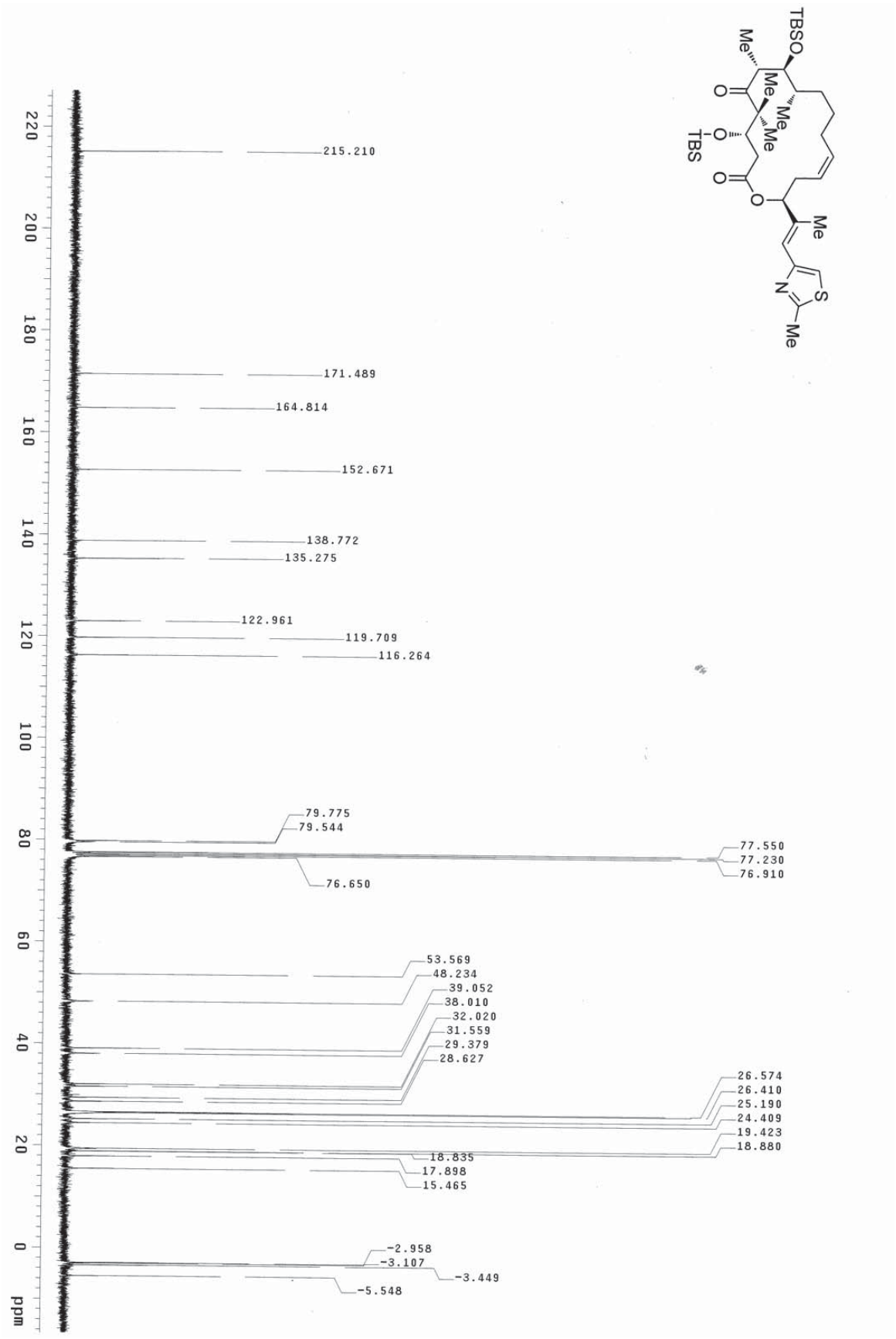

MY-III-169-f
Sample: MY-III-169-f
Sample ID: MY201003d_001
File: yumy/MY-III-169-f/Proton_01.fid
Pulse Sequence: s2pul
ppm
1.96
0.17
1.92
2.00
4.10
4.12
12.62

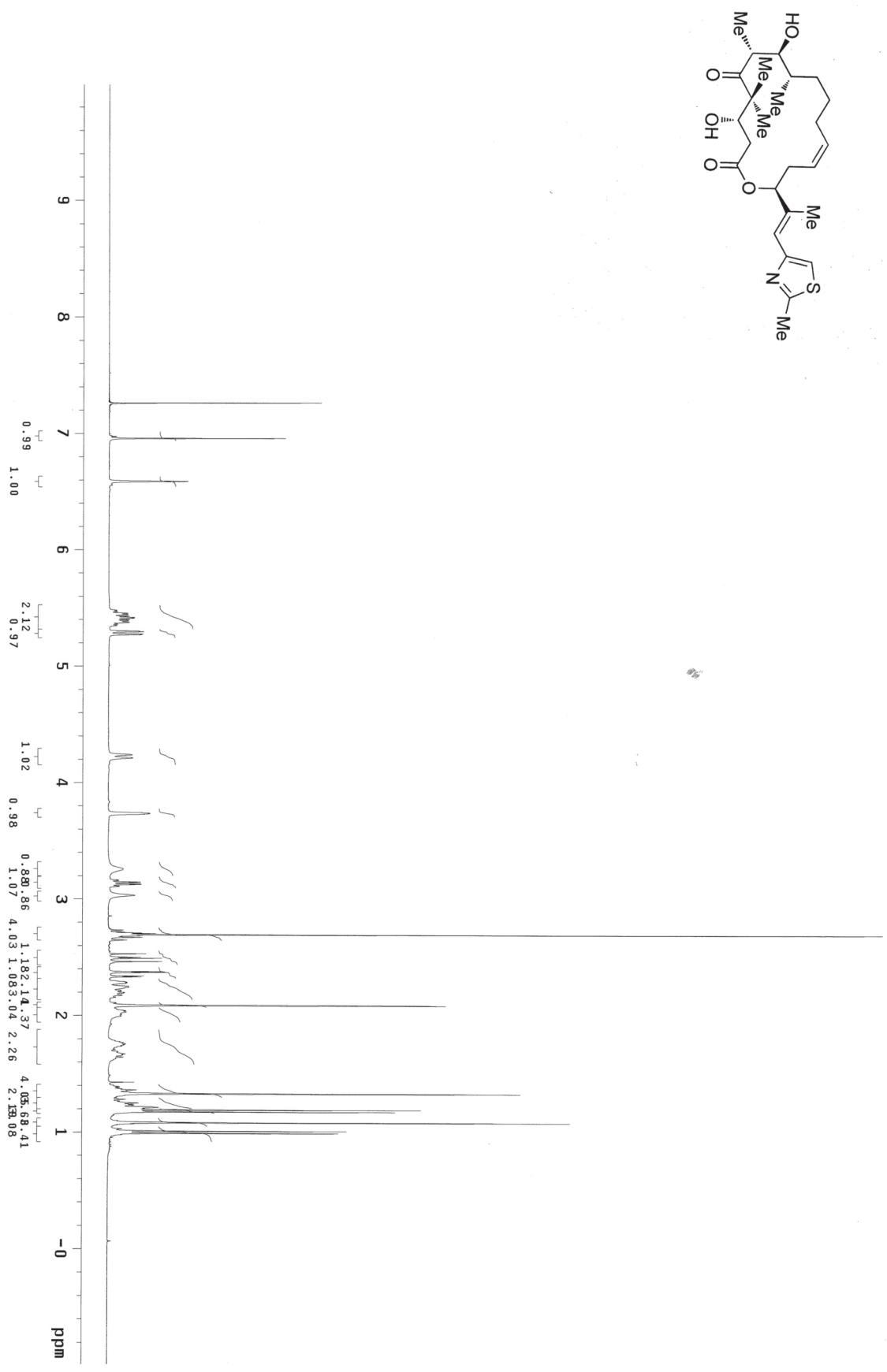

173.893
131.239
128.955
77.480
77.160
76.840
64.511
34.294
28.022
27.947
27.419
27.032
26.928
26.824
26.638
26.236
25.848
25.522
180
160
140
120
100
80
60
40
20
ppm
MY-III-169-f-13C
Sample: MY-III-169-f-13C
File: /home/nmr/vnmrsys/data/MiaoYu/MY-III-169-f-13C
Pulse Sequence: s2pul

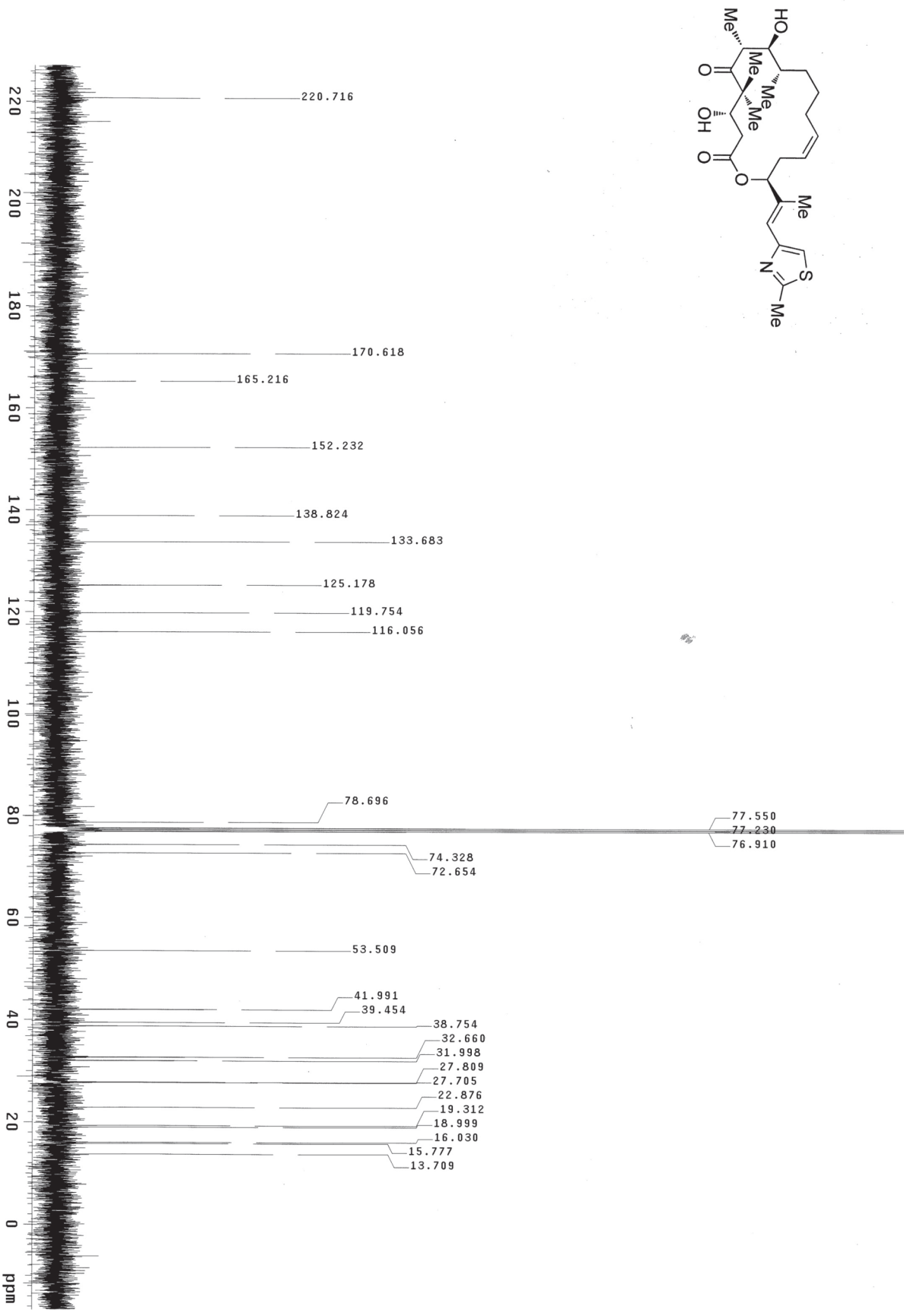

TBSO
Me
Me
Me
Me
O
O
O
TBS
O
O
Me
N
S
Me
0.90
1.00
1.92
1.04
4.07
1.01
1.00
1.04
3.00
3.27
1.14
3.26
2.01
3.77
3.85
2.23
6.61
2.61
7.99
5.80
ppm

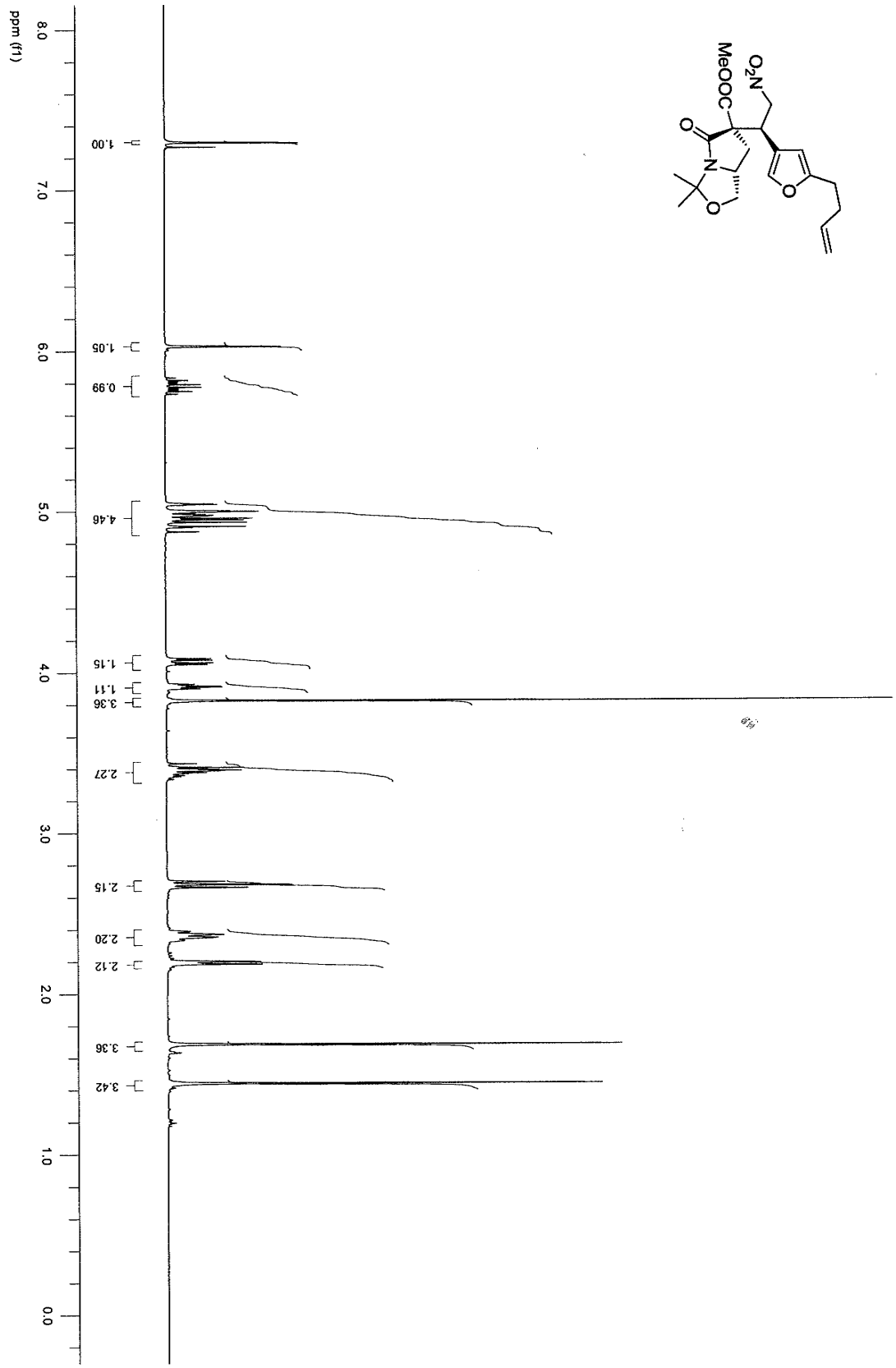

217.867
171.370
164.733
152.790
139.159
137.016
133.623
121.324
117.968
116.606
114.590
78.882
77.795
77.543
77.230
76.910
74.276
53.561
45.443
40.518
39.044
37.735
34.535
30.666
27.273
26.425
26.254
23.411
20.547
19.453
18.716
18.396
17.831
15.606
14.788
-3.442
-3.576
-4.052
-4.491
ppm
TBSO
Me
Me
Me
Me
O
O
O
TBS
O
Me
N
S
Me

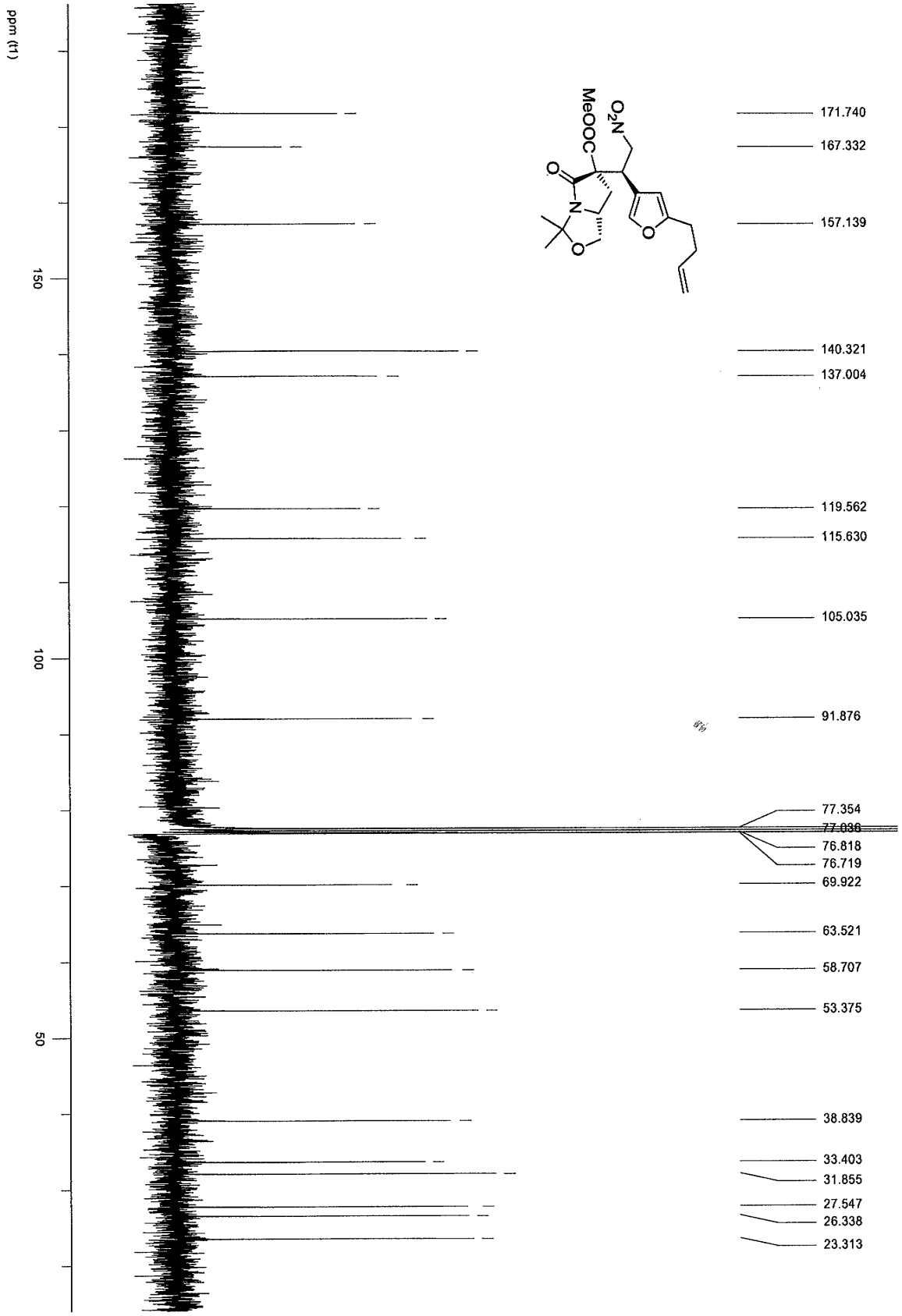

TBSO
Me
Me
Me
Me
O
O
O
TBS
O
O
Me
N
S
Me
0.95
1.00
0.96
1.09
0.96
0.95
1.01
1.01
0.78
1.08
3.25
1.03
1.03
3.06
1.15
1.01
0.51
3.08
3.39
3.87
0.26
0.25
3.23
8.50
1.25
0.58
8.96
2.97
3.08
3.23
2.78
ppm

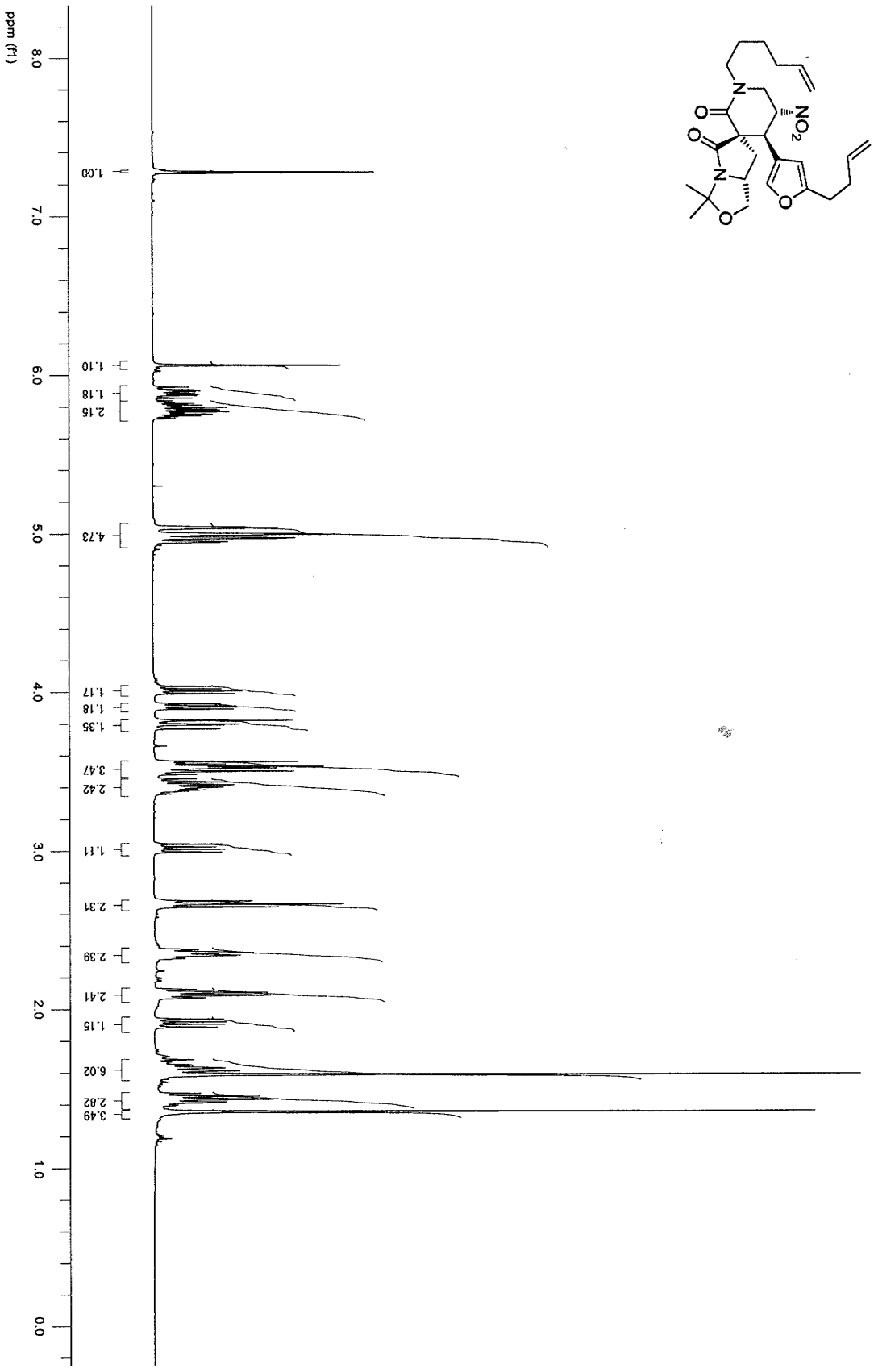

TBSO
Me
Me
Me
Me
O
O
O
TBS
O
O
Me
N
S
Me
215.210
171.489
164.814
152.671
138.772
135.275
122.961
119.709
116.264
79.775
79.544
77.550
77.230
76.910
76.650
53.569
48.234
39.052
38.010
32.020
31.559
29.379
28.627
26.574
26.410
25.190
24.409
19.423
18.880
18.835
17.898
15.465
-2.958
-3.107
-3.449
-5.548
220
200
180
160
140
120
100
80
60
40
20
0
ppm

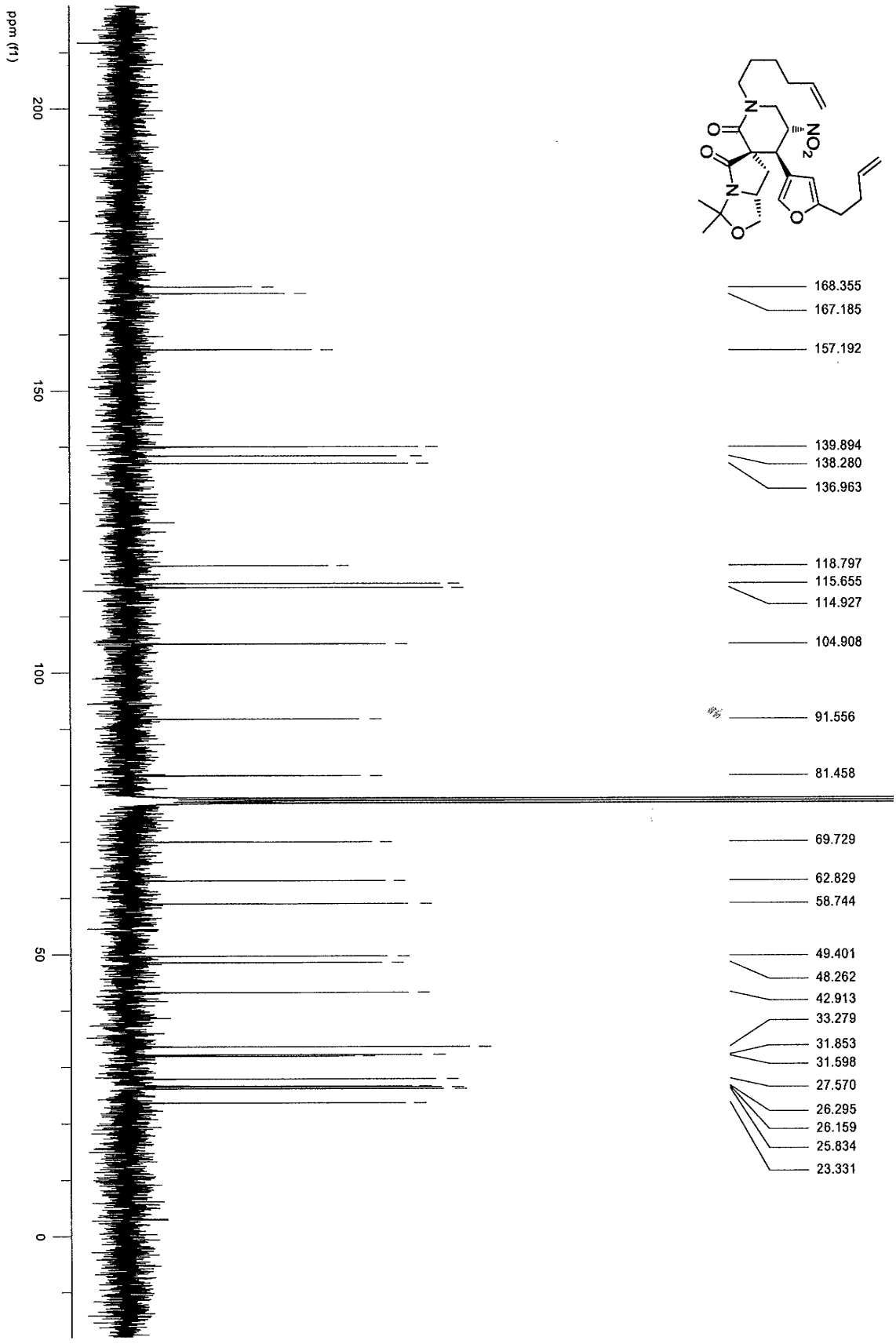

HO
Me
Me
Me
Me
Me
O
OH
O
O
Me
N
S
Me
ppm
9
8
7
6
5
4
3
2
1
0
0.99
1.00
2.12
0.97
1.02
0.98
0.88
0.86
1.07
4.03
1.18
2.14
1.08
3.04
4.37
2.26
4.05
5.68
8.41
2.13
3.08

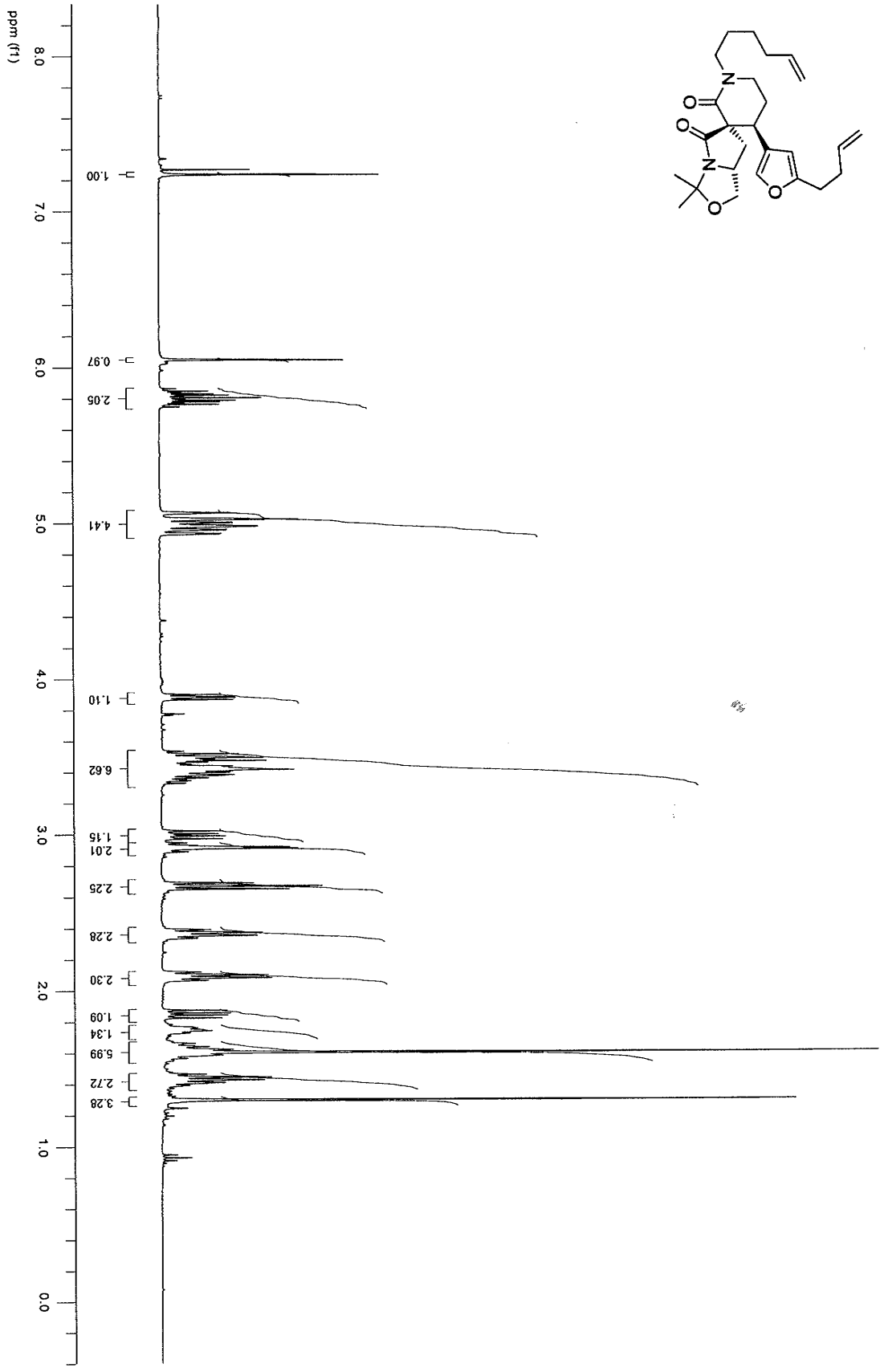

220.716
170.618
165.216
152.232
138.824
133.683
125.178
119.754
116.056
78.696
77.550
77.230
76.910
74.328
72.654
53.509
41.991
39.454
38.754
32.660
31.998
27.809
27.705
22.876
19.312
18.999
16.030
15.777
13.709
220
200
180
160
140
120
100
80
60
40
20
0
ppm

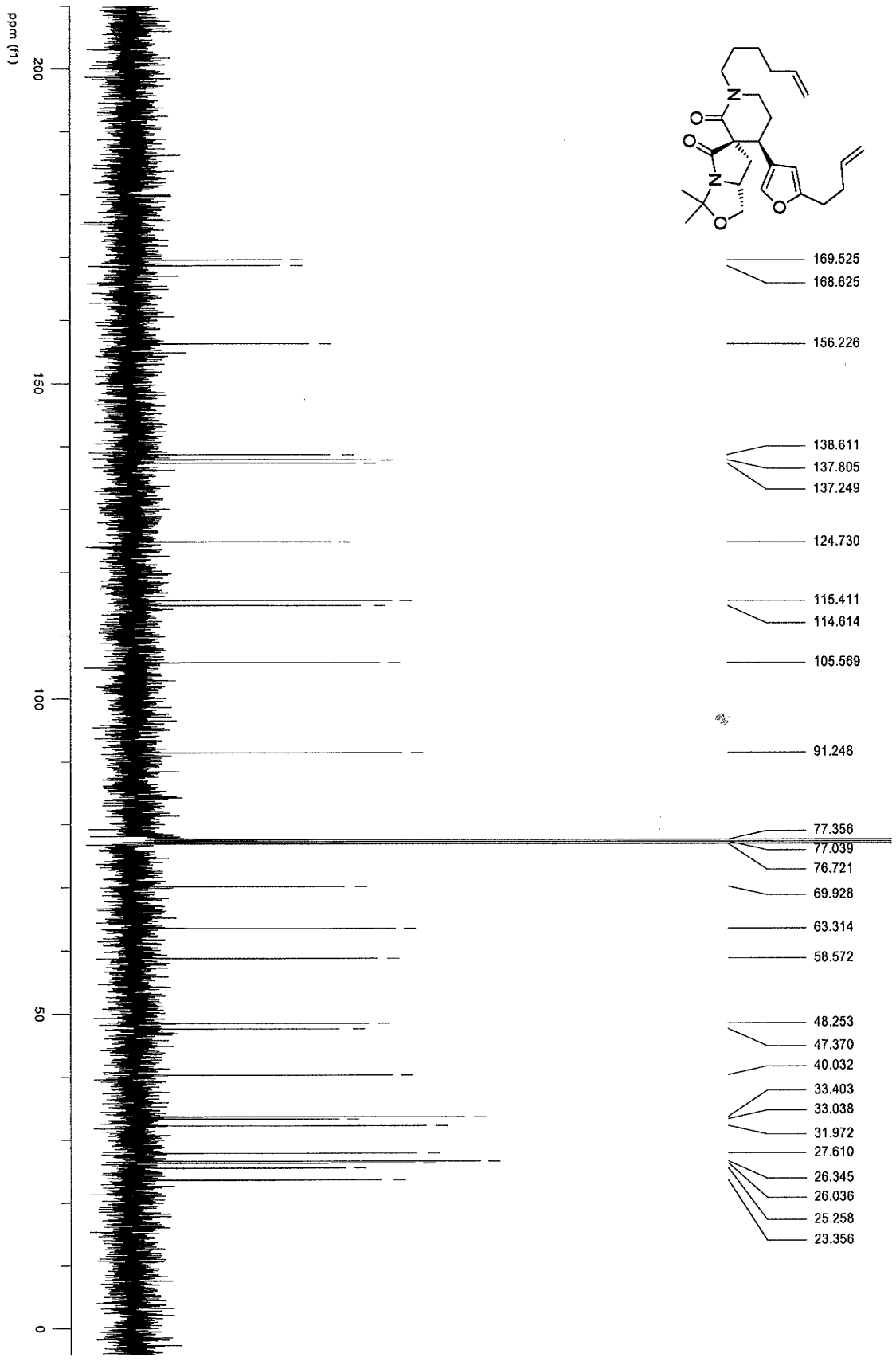

ppm (f1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.00
1.05
0.99
4.46
1.15
1.11
3.36
2.27
2.15
2.20
2.12
3.36
3.42
MeOOC
O_2N
O
N
O
O

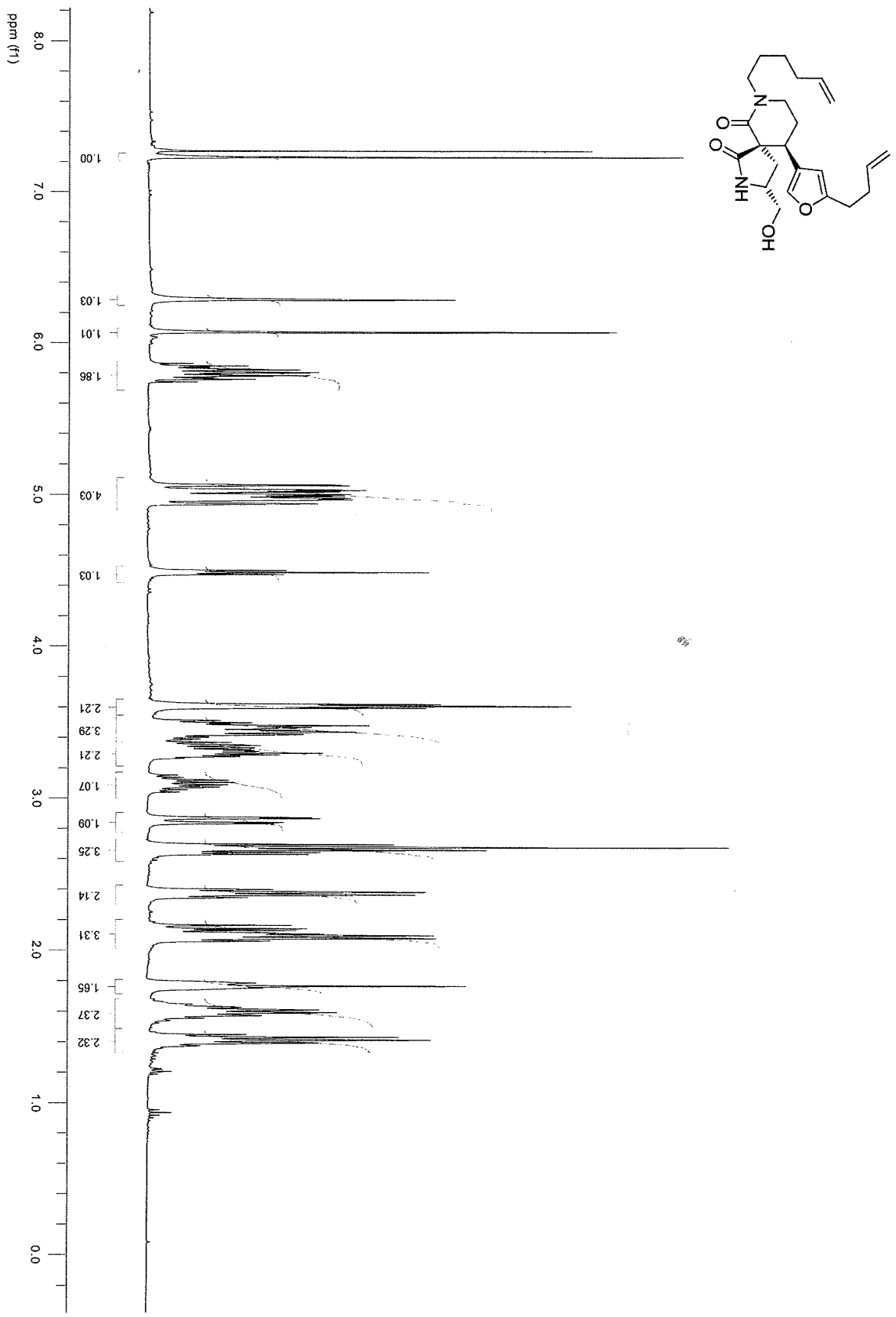

ppm (t1)
150
100
50
MeOOC
O2N
O
N
O
O
171.740
167.332
157.139
140.321
137.004
119.562
115.630
105.035
91.876
77.354
77.036
76.818
76.719
69.922
63.521
58.707
53.375
38.839
33.403
31.855
27.547
26.338
23.313

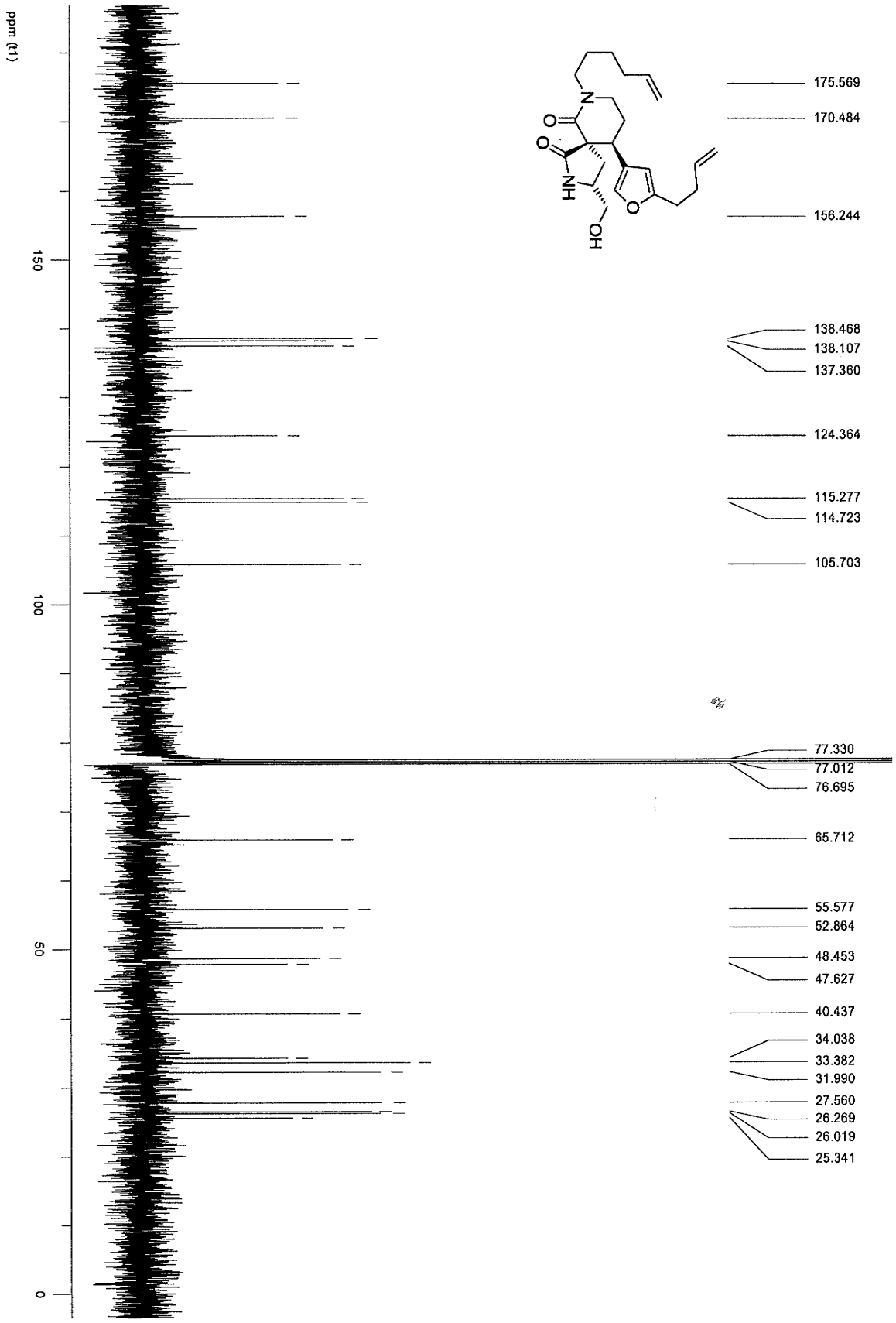

ppm (f1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.00
1.10
1.18
2.15
4.73
1.17
1.18
1.35
3.47
2.42
1.11
2.31
2.39
2.41
1.15
6.02
2.82
3.49
N
O
O
N
O
NO_2
N
O

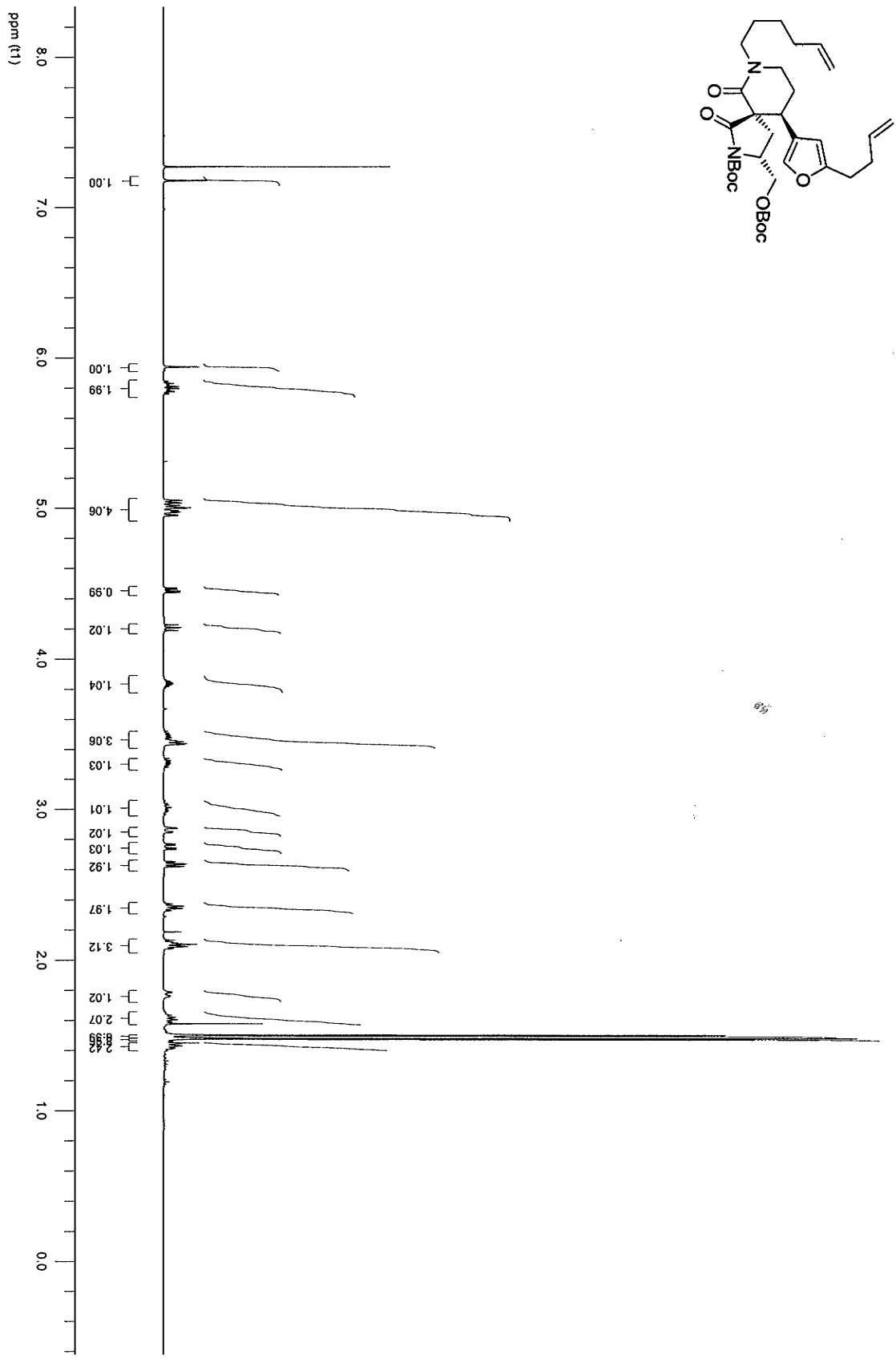

ppm (f1)
200
150
100
50
0
168.355
167.185
157.192
139.894
138.280
136.963
118.797
115.655
114.927
104.908
91.556
81.458
69.729
62.829
58.744
49.401
48.262
42.913
33.279
31.853
31.598
27.570
26.295
26.159
25.834
23.331

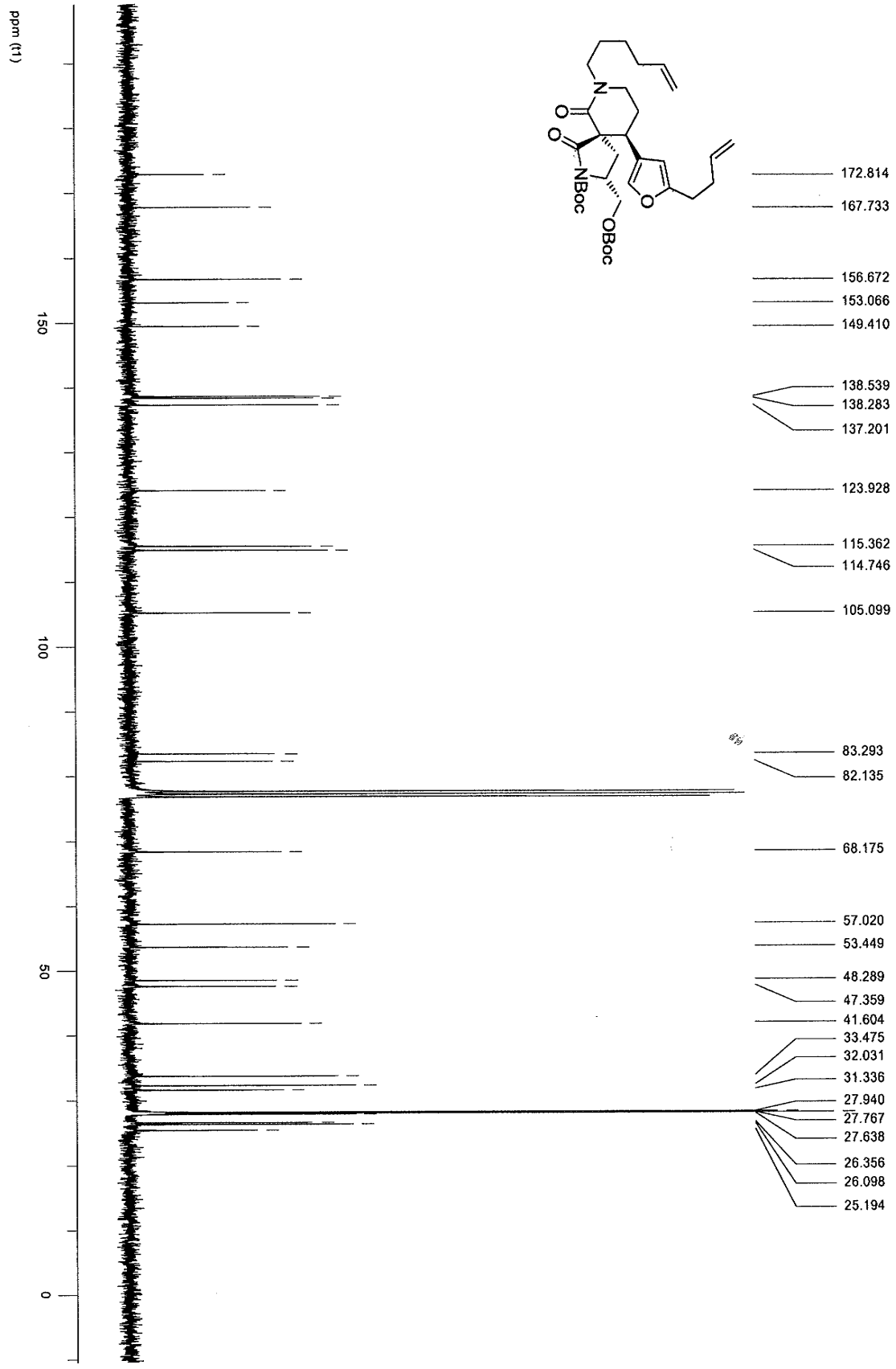

ppm (f1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.00
0.97
2.05
4.41
1.10
6.62
1.15
2.01
2.25
2.28
2.30
1.09
1.34
5.99
2.72
3.28
N
O
O
N
O
O

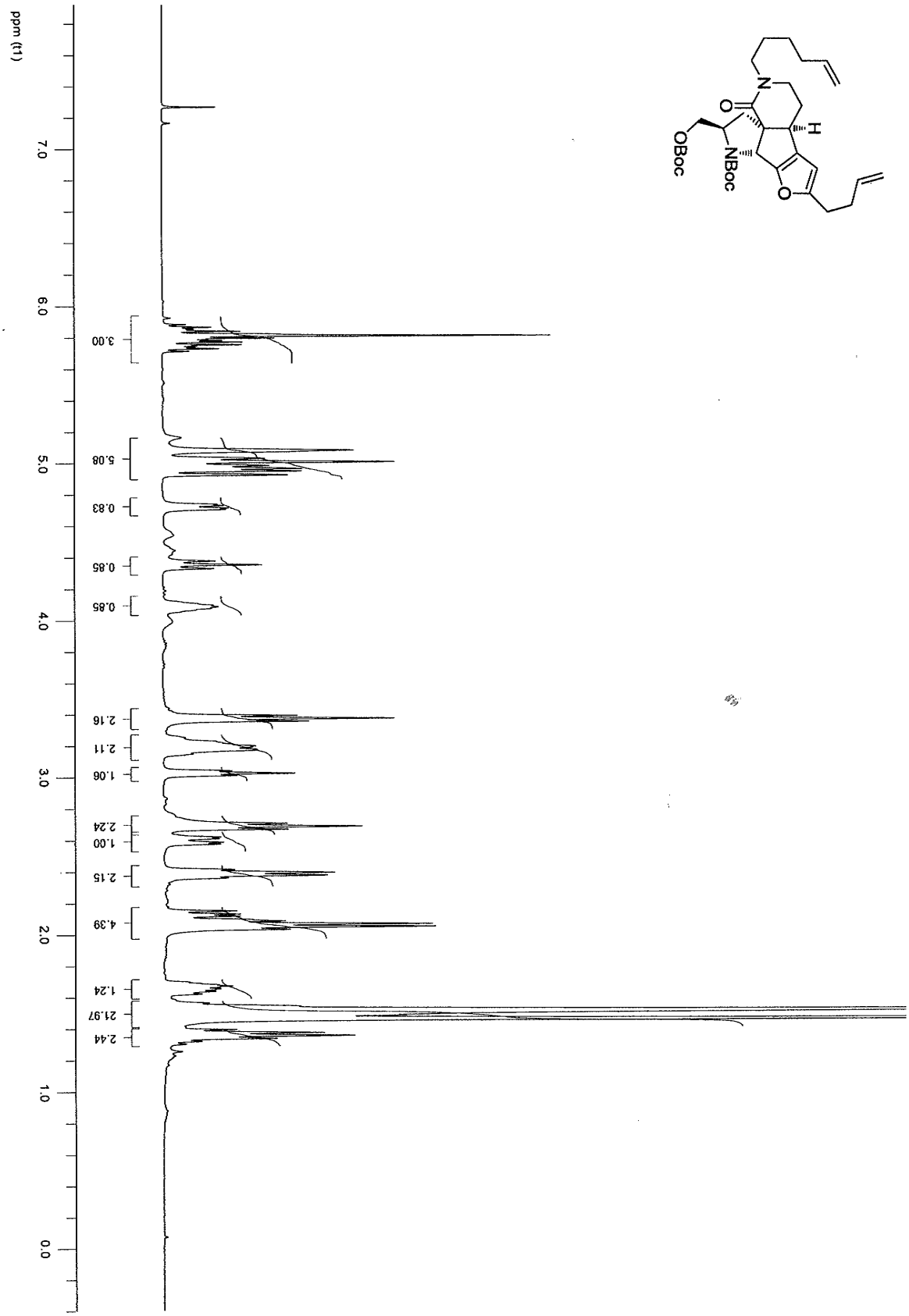

ppm (f1)
200
150
100
50
0
169.525
168.625
156.226
138.611
137.805
137.249
124.730
115.411
114.614
105.569
91.248
77.356
77.039
76.721
69.928
63.314
58.572
48.253
47.370
40.032
33.403
33.038
31.972
27.610
26.345
26.036
25.258
23.356

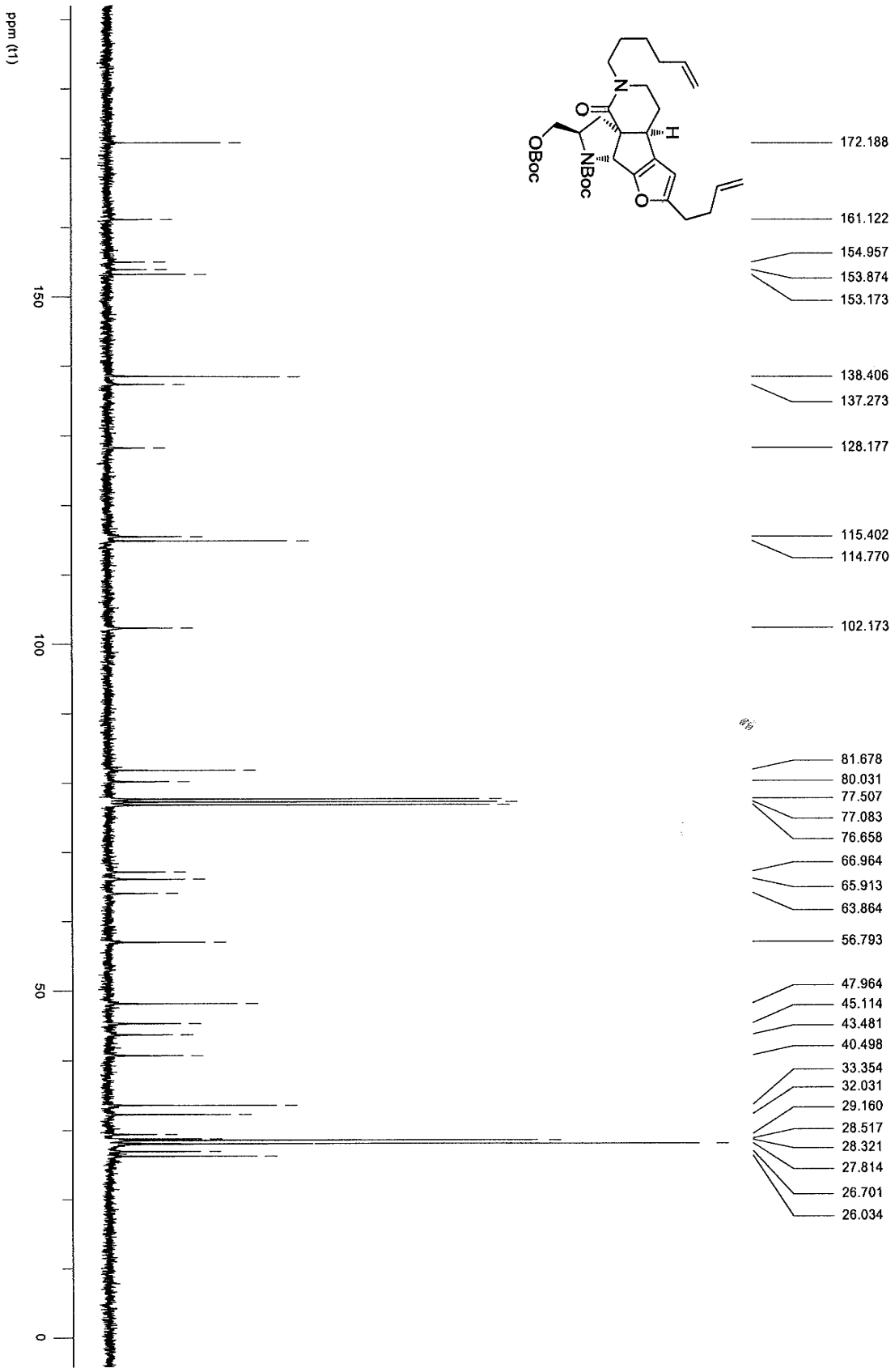

ppm (f1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.00
1.03
1.01
1.86
4.03
1.03
2.21
3.29
2.21
1.07
1.09
3.25
2.14
3.31
1.65
2.37
2.32
O
O
N
NH
OH
O

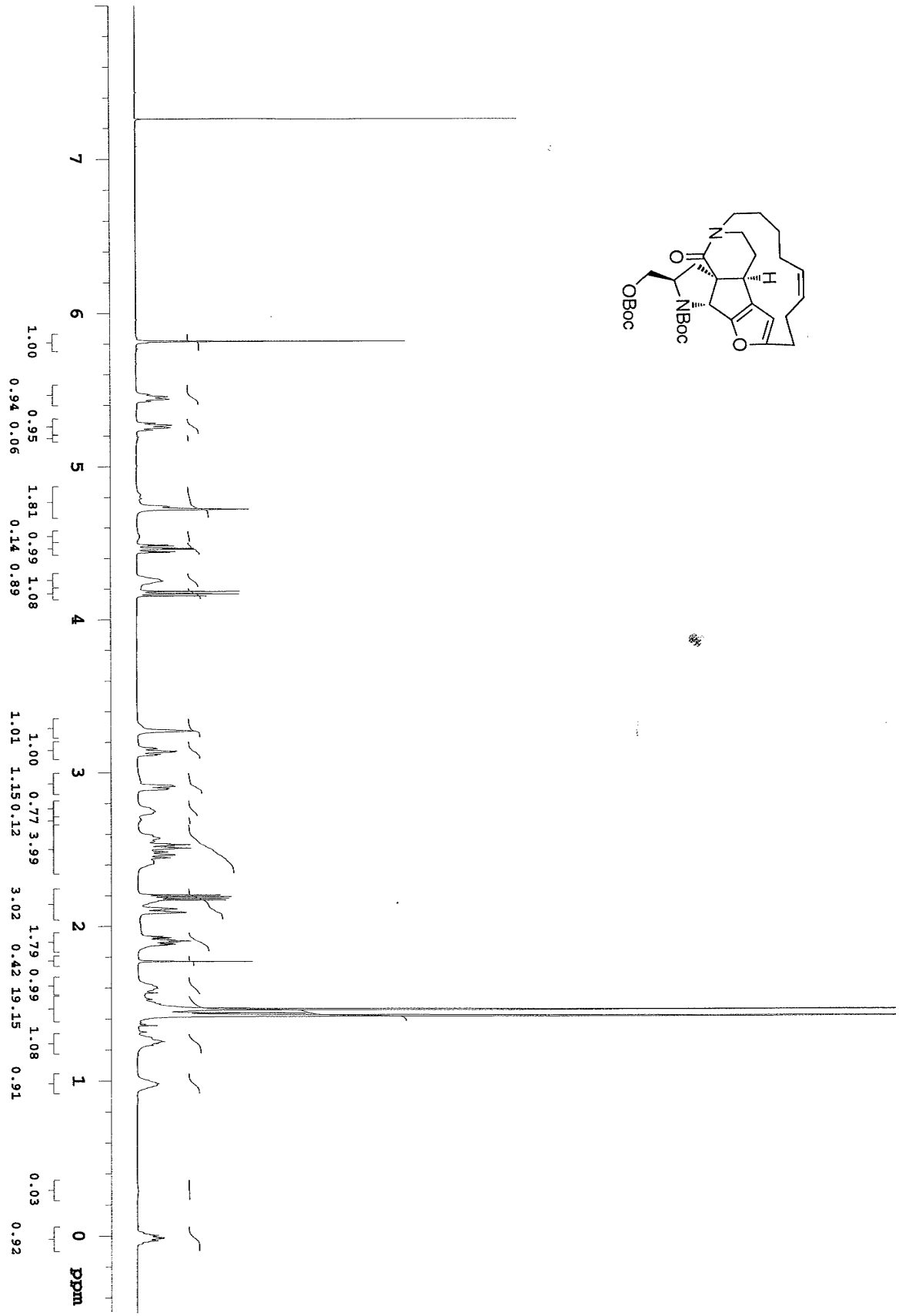

ppm (t1)
150
100
50
0
175.569
170.484
156.244
138.468
138.107
137.360
124.364
115.277
114.723
105.703
77.330
77.012
76.695
65.712
55.577
52.864
48.453
47.627
40.437
34.038
33.382
31.990
27.560
26.269
26.019
25.341
N
O
O
NH
OH
O

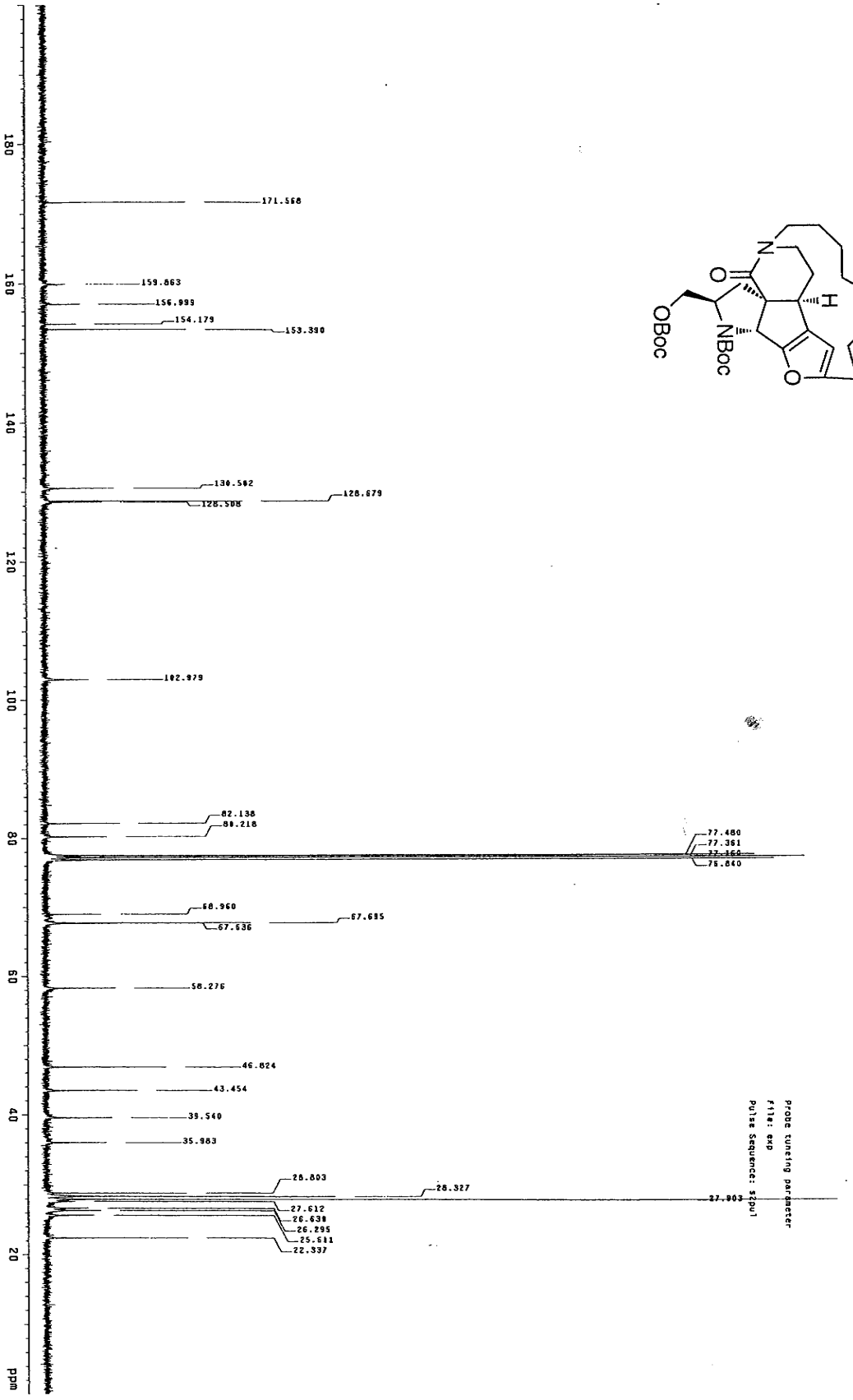

ppm (t1)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
1.00
1.00
1.99
4.06
0.99
1.02
1.04
3.06
1.03
1.01
1.02
1.03
1.92
1.97
3.12
1.02
2.07
8.99
2.42
N
O
O
NBoc
OBoc
O

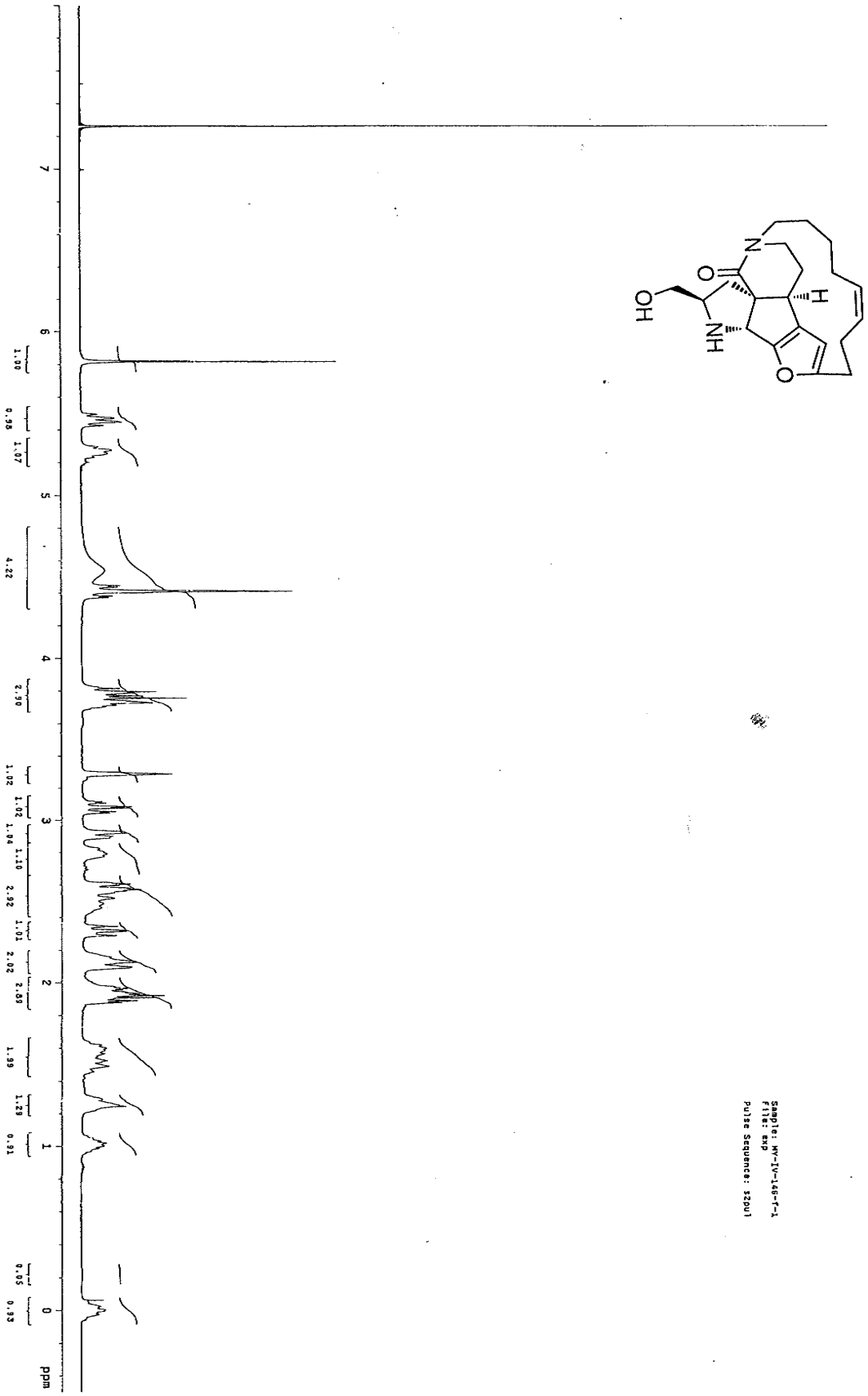

ppm (t1)
150
100
50
0
N
O
O
NBoc
OBoc
O
172.814
167.733
156.672
153.066
149.410
138.539
138.283
137.201
123.928
115.362
114.746
105.099
83.293
82.135
68.175
57.020
53.449
48.289
47.359
41.604
33.475
32.031
31.336
27.940
27.767
27.638
26.356
26.098
25.194

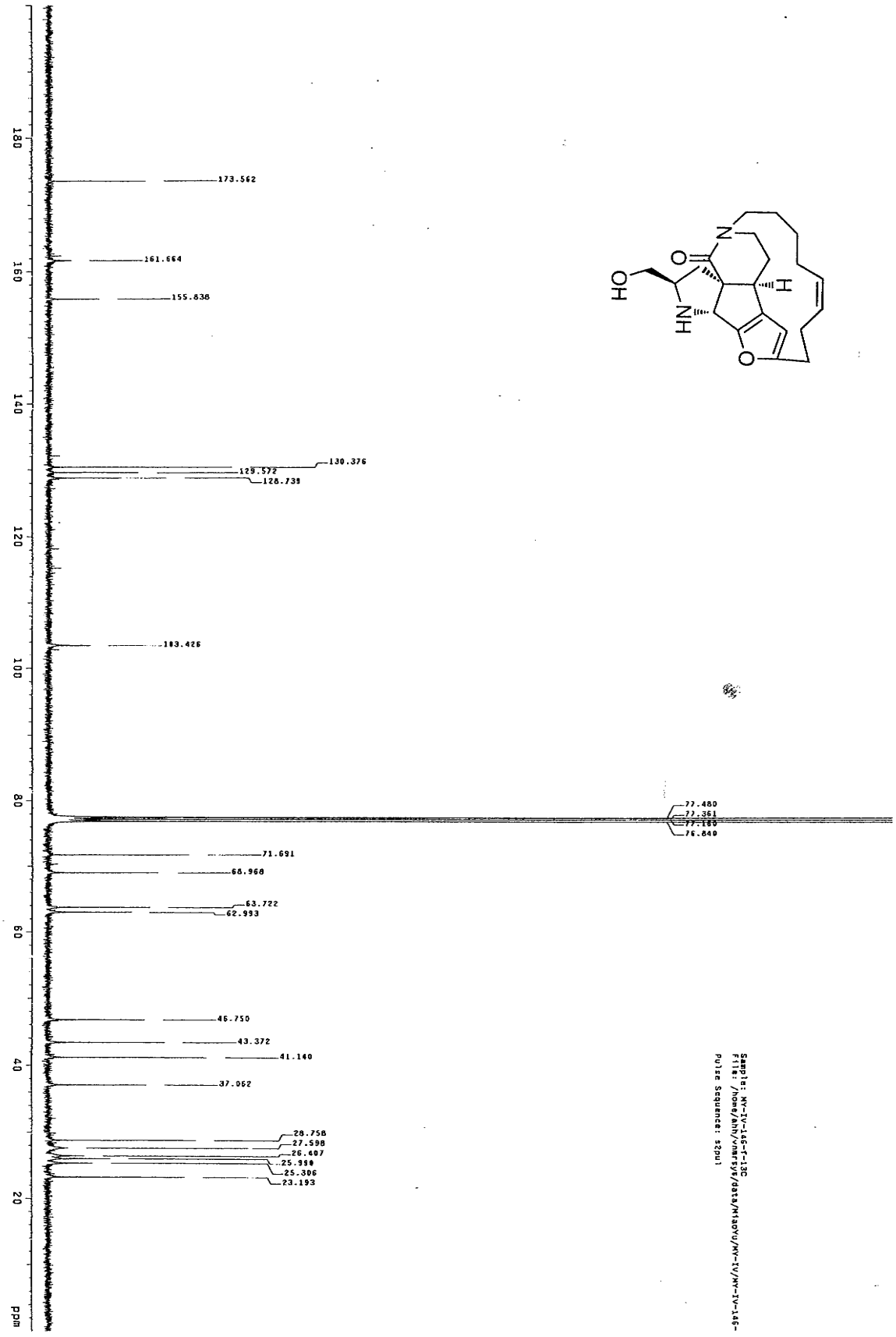

ppm (t1)
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
3.00
5.08
0.83
0.85
0.85
2.16
2.11
1.06
2.24
1.00
2.15
4.39
1.24
21.97
2.44
N
O
H
OBoc
NBoc
O

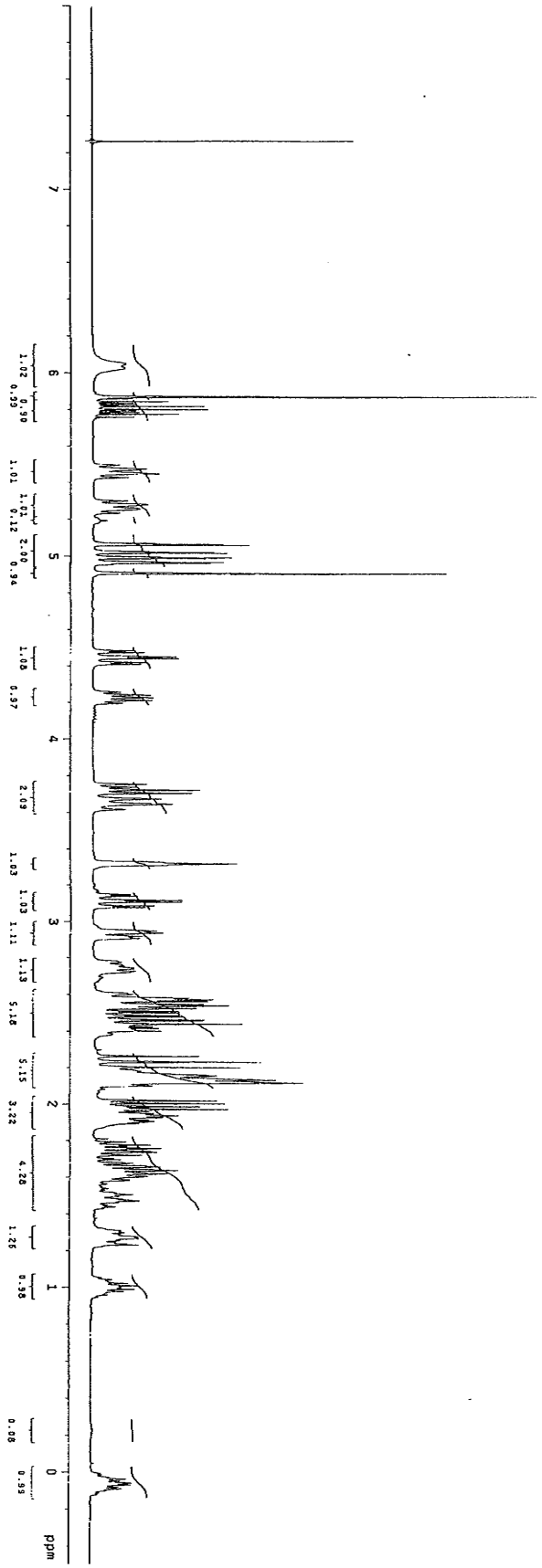

ppm (t1)
150
100
50
0
OBoc
NBoc
O
N
H
O
172.188
161.122
154.957
153.874
153.173
138.406
137.273
128.177
115.402
114.770
102.173
81.678
80.031
77.507
77.083
76.658
66.964
65.913
63.864
56.793
47.964
45.114
43.481
40.498
33.354
32.031
29.160
28.517
28.321
27.814
26.701
26.034

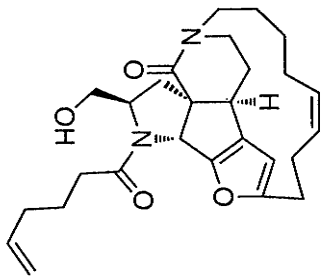

7
6
5
4
3
2
1
0
ppm
1.00
0.95
1.81
0.99
1.08
0.94
0.06
0.14
0.89
1.00
0.77
3.99
1.01
1.15
0.12
1.79
0.99
1.08
3.02
0.42
19.15
0.91
0.03
0.92
OBoc
NBoc
O
N
H
O


171.568
159.863
156.999
154.179
153.390
130.502
128.679
128.508
102.979
82.138
80.218
77.480
77.361
77.160
75.840
68.960
67.686
67.636
58.276
46.824
43.454
39.540
35.983
28.803
28.327
27.903
27.612
26.638
26.295
25.611
22.337
ppm
Probe tuning parameter
File: exp
Pulse Sequence: s2pul
OBoc
NBoc
N
O
H
O

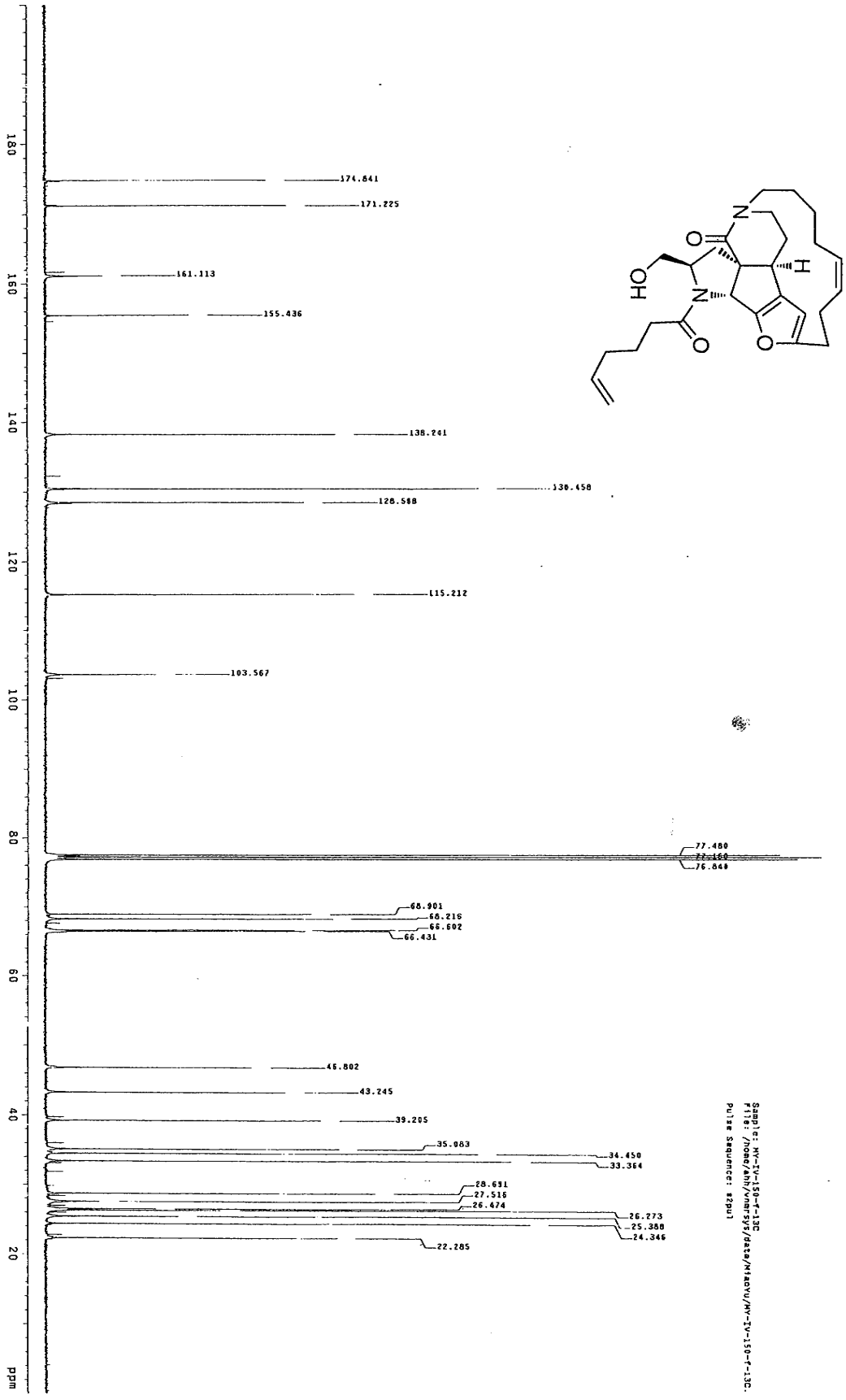

Sample: MY-LV-169-F-1
File: exp
Pulse Sequence: s2pul
1.00
0.99
1.07
4.22
2.90
1.02
1.02
1.04
1.10
2.92
1.01
2.02
2.69
1.99
1.29
0.91
0.95
0.93
ppm

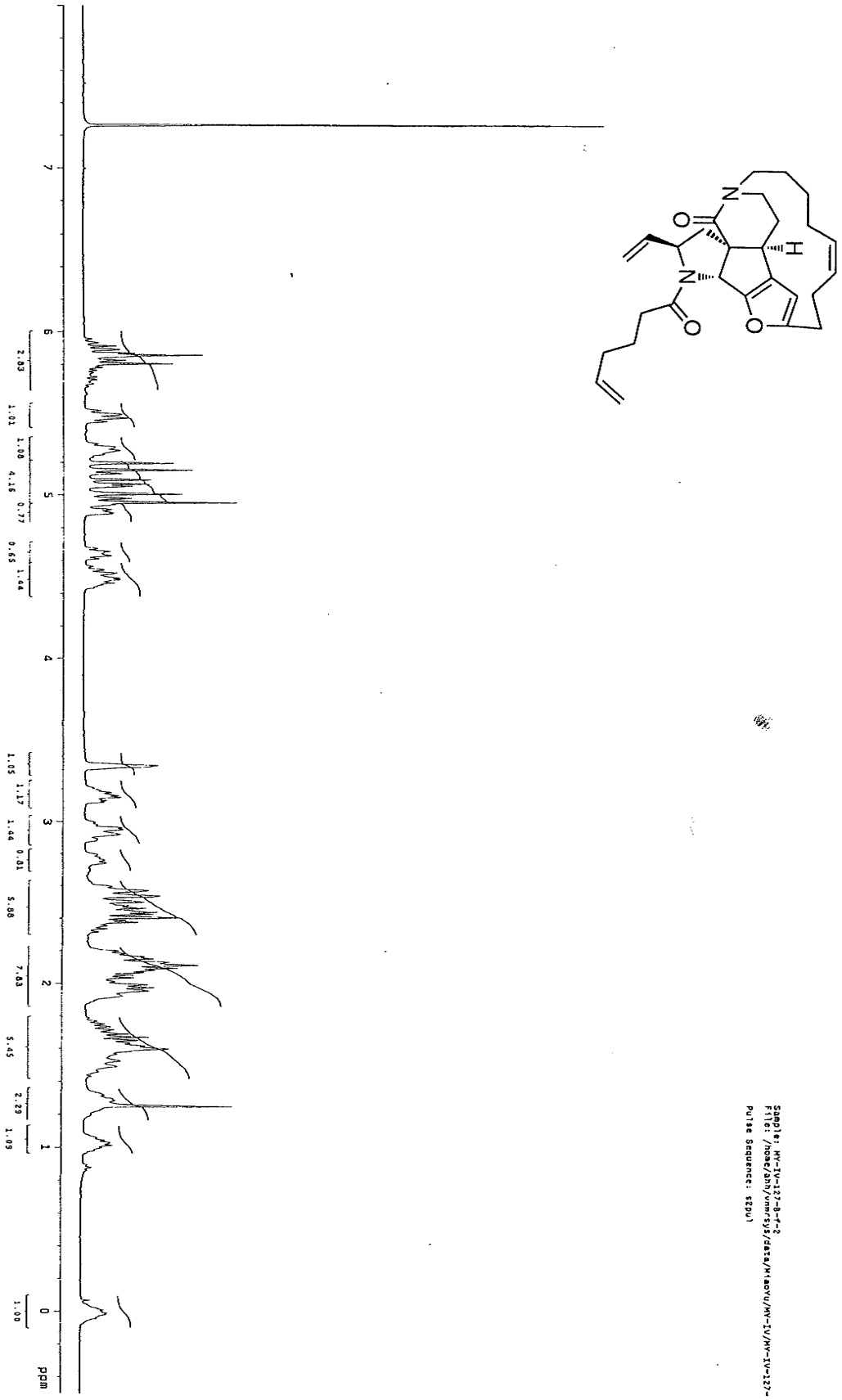

173.562
161.664
155.636
130.376
129.572
128.738
103.426
77.480
77.361
77.189
76.840
71.691
66.968
63.722
62.993
46.750
43.372
41.140
37.062
28.758
27.598
26.407
25.998
25.306
23.193
ppm
Sample: MY-IV-146-f-13C
File: /home/ahh/vnmrsys/data/MiaoYu/MY-IV/MY-IV-146-
Pulse Sequence: s2pul

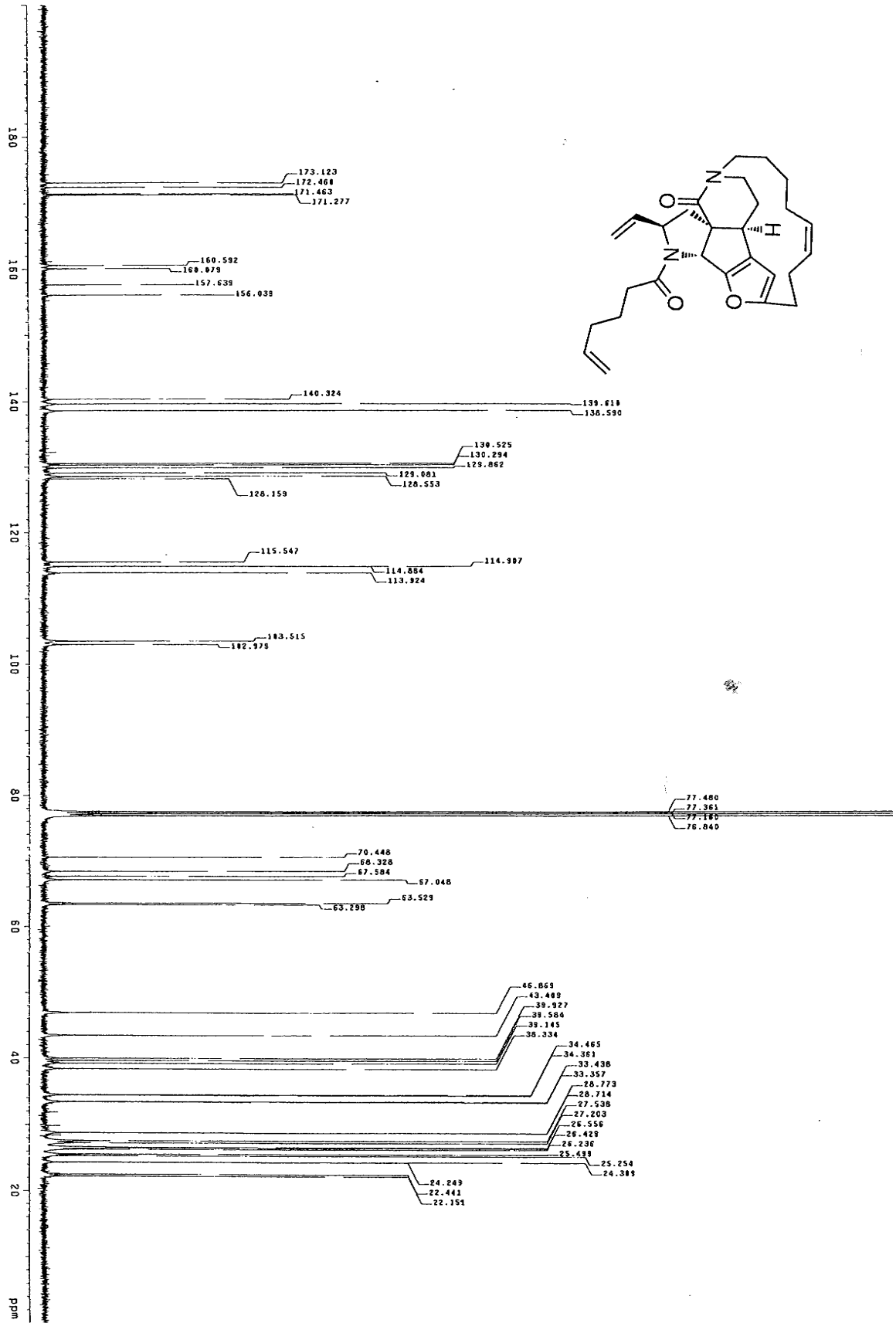


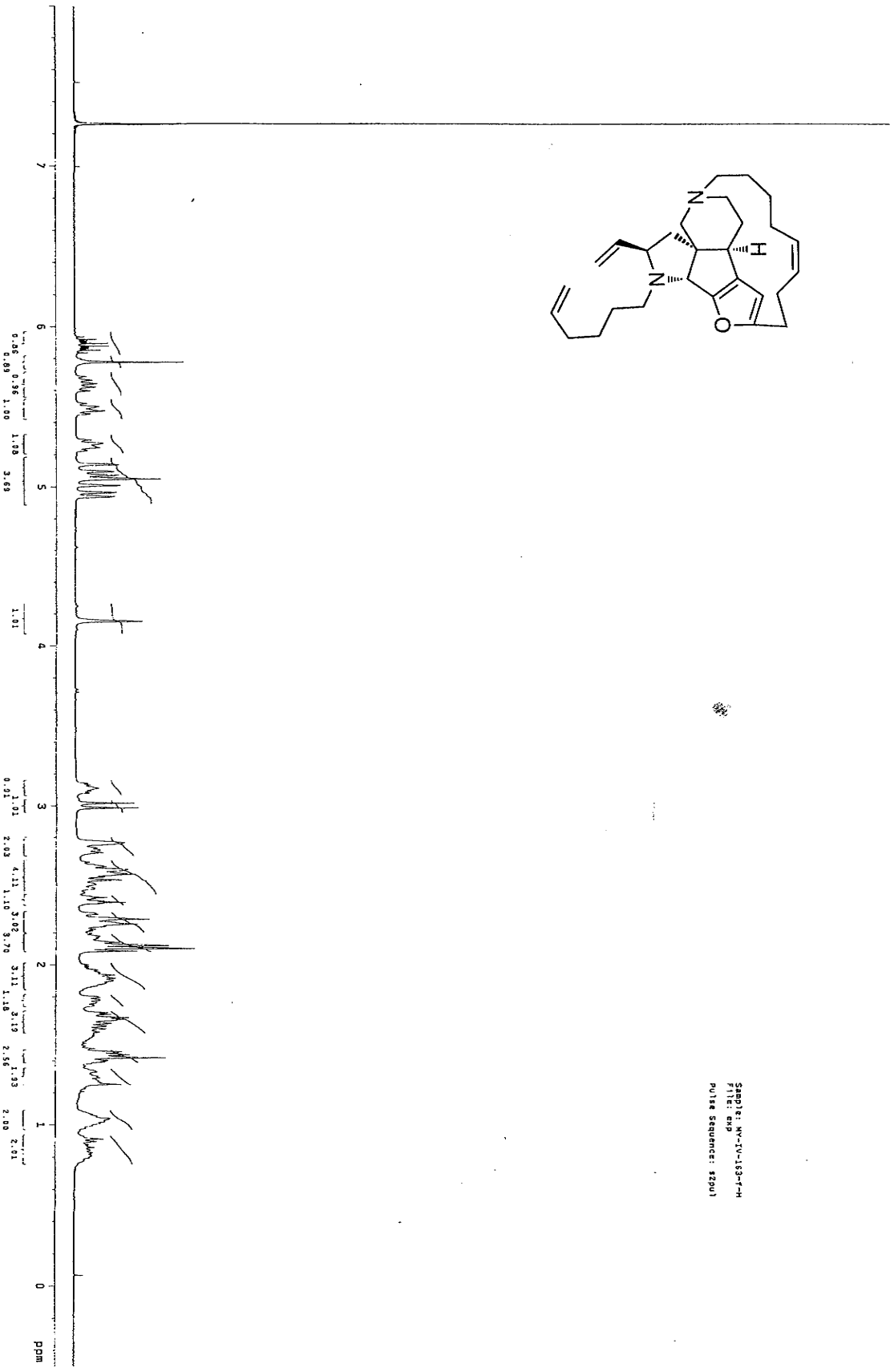


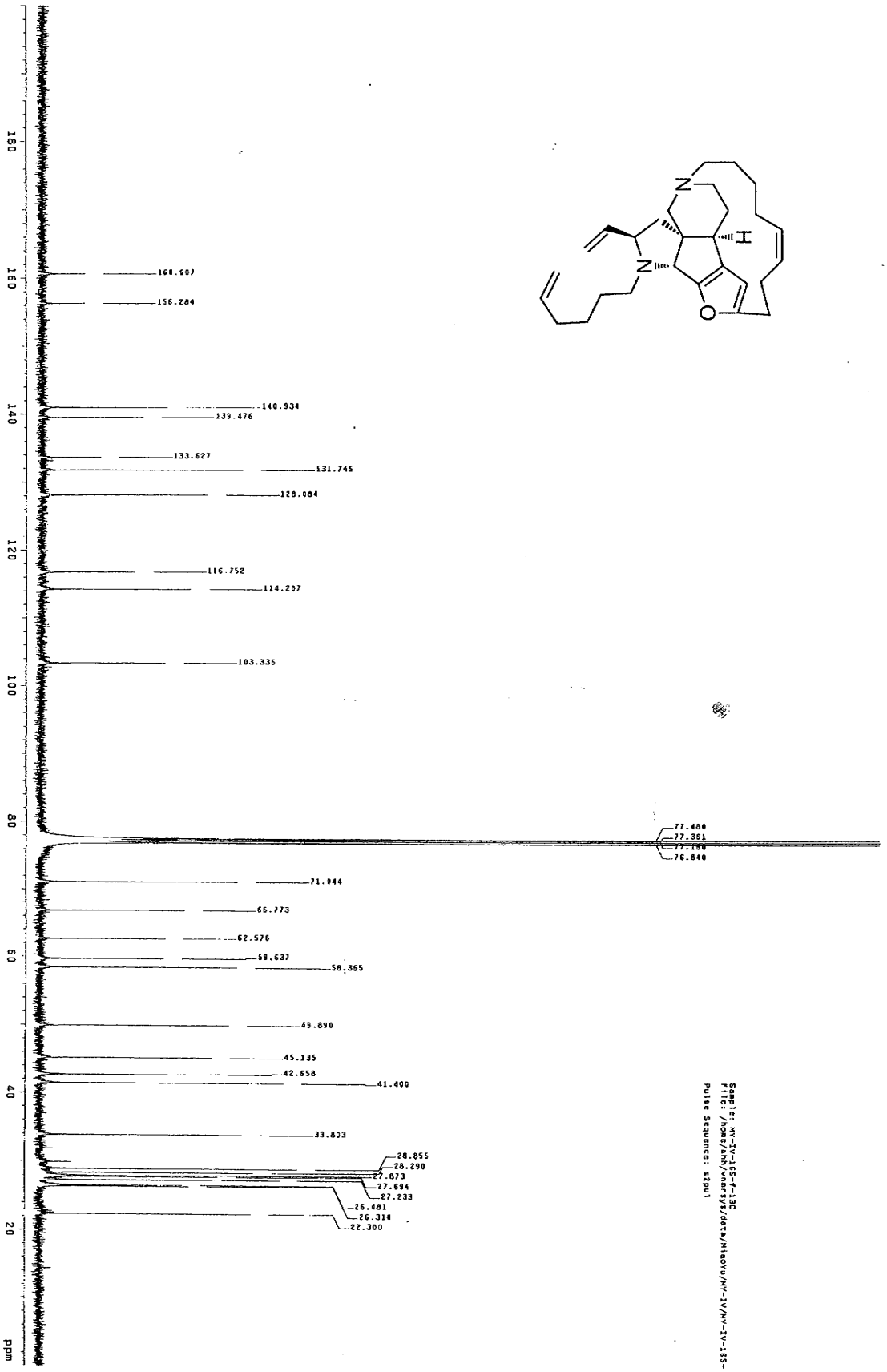
Sample: wy-IV-150-r
File: exp
Pulse Sequence: s2pul

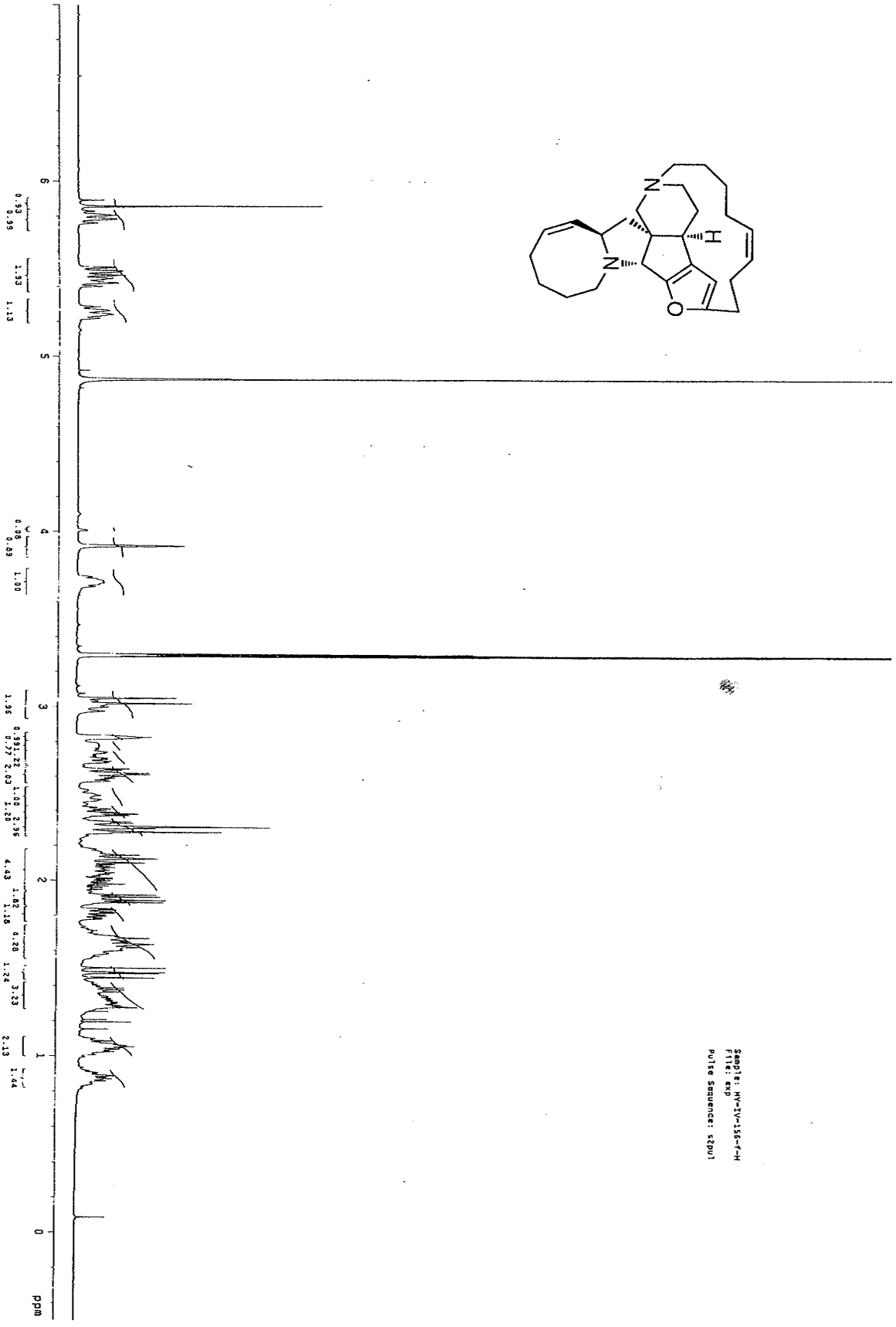

174.841
171.225
161.113
155.436
138.241
130.458
128.588
115.212
103.567
77.480
76.848
68.901
68.216
66.602
66.431
45.802
43.245
39.205
35.083
34.450
33.364
28.691
27.516
26.474
26.273
25.358
24.346
22.285
180
160
140
120
100
80
60
40
20
ppm
HO
N
O
H
O
N
O
O
Sample: AV-1-150-1-13C
File: /nmr/avh/avnmrsys/data/AV-1-150-1-13C/1/fid
Pulse Sequence: s2pul

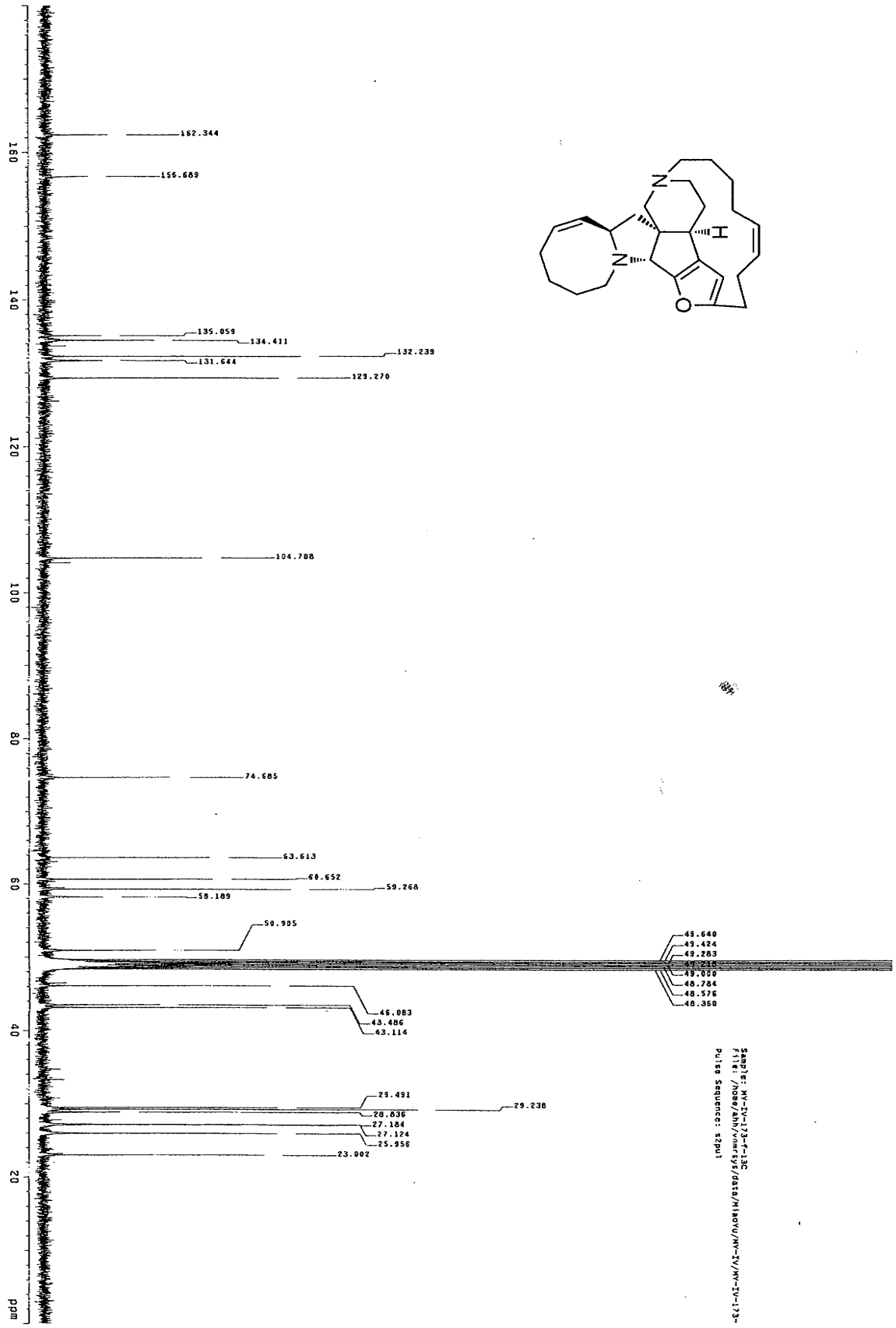

Sample: HY-IV-127-B-r-2
File: /home/ahj/vnmrsys/data/Hiaoyu/HY-IV/HY-IV-127-
Pulse Sequence: s2pul
ppm


173.123
172.468
171.463
171.277
160.592
160.079
157.639
156.038
140.324
139.618
138.590
130.525
130.294
129.862
129.081
128.553
128.159
115.547
114.987
114.884
113.924
103.515
102.975
77.480
77.361
77.160
76.840
70.448
68.328
67.584
67.048
63.529
63.298
46.869
43.489
39.927
39.584
39.145
38.334
34.465
34.361
33.438
33.357
28.773
28.714
27.538
27.203
26.556
26.429
26.236
25.439
25.254
24.389
24.249
22.441
22.151
ppm


Sample: NY-IV-163-1-H
File: exp
Pulse Sequence: szpul
ppm


160.507
156.284
140.934
139.476
133.627
131.745
128.084
116.752
114.207
103.336
77.480
77.381
77.180
76.840
71.044
66.773
62.576
59.637
58.365
49.890
45.135
42.658
41.409
33.803
28.855
28.290
27.873
27.694
27.233
26.481
26.314
22.300
ppm
Sample: MY-YU-1SS-F-13C
File: /home/anh/vnmrsys/data/HaoYu/MY-1/MY-YU-1SS-
Pulse Sequence: s2pul


Sample: HY-IV-155-f-H
File: exp
Pulse Sequence: s2pul
ppm


162.344
156.689
135.059
134.411
132.239
131.644
129.270
104.708
74.685
63.613
60.652
59.268
58.189
50.905
48.640
49.424
49.283
49.000
48.784
48.576
48.360
46.083
43.486
43.114
29.491
29.238
28.836
27.184
27.124
25.956
23.002
ppm
Sample: MV-IV-173-f-13C
File: /home/ahh/vnmrsys/data/HiaoYu/MV-IV/MV-IV-173-
Pulse Sequence: s2pul